# Selectivity of Aryl and Benzylic Bromination

**A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy**

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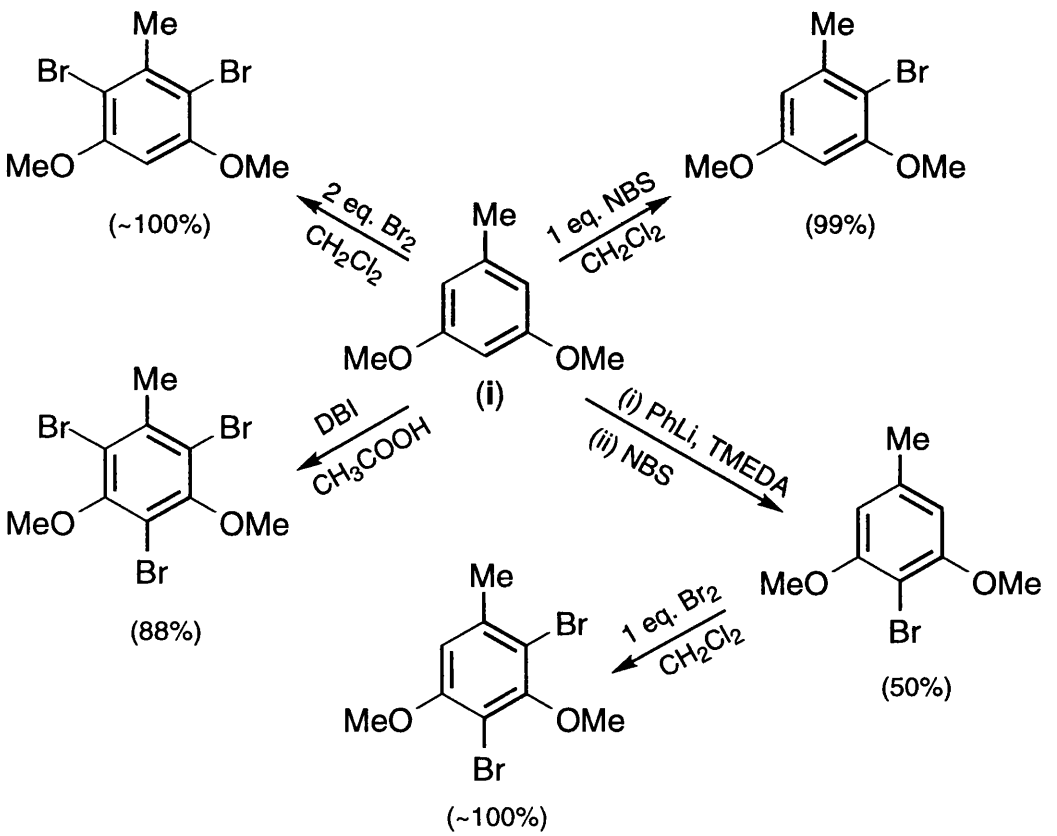
# Summary

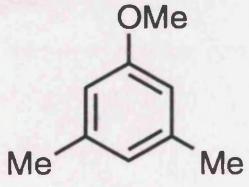
Bromination has historically been an important organic transformation. The organic bromides produced are extremely useful as intermediates in synthetic pathways and are utilised widely throughout synthesis for a variety of purposes. Organic bromides are also becoming increasingly important as the end products of synthesis as the field of organohalogen natural products expands and more of these compounds are shown to exhibit potentially useful biological activities.

During this research the selectivity of bromination in a variety of aromatic systems was studied. The aim being to build up an understanding of the factors involved such that we would be better able to predict and manipulate the selectivity of bromination.

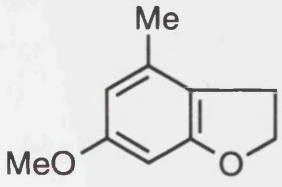
Initial studies centred upon the aryl bromination of anisoles. The aryl bromination of methyl 3,5-dimethoxybenzoate and 3,5-dimethoxytoluene was extensively studied. Conditions were found whereby all the aryl brominated derivatives could be obtained selectively in good yield. For 3,5-dimethoxytoluene (**i**) these conditions are summarised in the diagram below.



These results along with those obtained for the bromination of a range of other anisoles, including 3,5-dimethyl anisole (**ii**) and 6-methoxy-4-methyl-2,3-dihydrobenzofuran (**iii**), indicate that the most important factors in determining the selectivity of bromination for this type of compound are steric inhibition of resonance hindering bromination *ortho* to methoxy groups and whether the conditions used and reactivity of the substrate are such that a product distribution that is kinetic or thermodynamic in nature results.

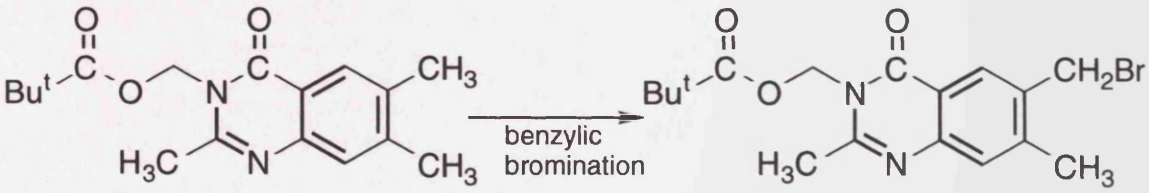



(**ii**)




(**iii**)

Another area of research centred upon the bromination steps involved in the synthetic pathway to ZD9331, a potential drug substance currently being developed by Zeneca Pharmaceuticals. In particular, the benzylic bromination of 2,6,7-trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**iv**) was studied extensively.




(**iv**) (**v**)

It was demonstrated that the use of more selective benzylic bromination conditions, namely a photo-initiated reaction with NBS in dichloromethane, rather than reaction with NBS in chlorobenzene initiated by the thermal decomposition of AIBN, resulted in an improvement from 47% to 80% in the obtained yield of the desired product, 6-bromomethyl-2,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**v**).

The C2-methyl group of quinazolinone (**iv**) was identified as being brominated *via* an ionic, rather than radical, route and this, combined with the selective C6-methyl group bromination methodology, allowed a range of brominated derivatives of quinazolinone (**iv**) to be prepared which aided the identification and quantitation of the brominated side products produced by the bromination of quinazolinone (**iv**) under various conditions.

# Acknowledgements

I would like to thank my supervisor Doctor R. A. Hill and industrial co-supervisor Doctor D. Adshead for their contibutions and encouragement throughout the course of this project.

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# Table of Contents


**1. Introduction**

**1.1 The Importance of Bromination..... 1**

1.1.1 Uses of Organic Bromides as Intermediates..... 1

1.1.2 Uses of Organic Bromides as End Products..... 3

**1.2 Conclusion..... 6**

**2. Introduction to Aryl Bromination**

**2.1 Mechanism of Electrophilic Aromatic Substitution..... 7**

**2.2 Evidence for Arenium Ion Mechanism..... 8**

2.2.1 Isotope Effects..... 8

2.2.2 Isolation of Arenium Ion Intermediates..... 9

**2.3 Regioselectivity and Reactivity of Electrophilic Aromatic Substitution..... 9**

2.3.1 Directing Influence of Inductive and Field Effects..... 11

2.3.2 Directing Influence of Resonance Effects..... 12

2.3.3 Classes of Substituent Groups..... 14

2.3.4 The Combined Effect of More than One Substituent..... 16

2.3.5 The Effect of Electrophile Reactivity..... 18

2.3.6 The Effect of Substrate Reactivity..... 20

2.3.7 Factors which Determine the *ortho/para* Ratio..... 20

**2.4 Reagents Used to Effect Aryl Bromination..... 24**

**3. Introduction to Benzylic Bromination**

**3.1 General Features of Free Radical Reactions..... 30**

**3.2 Mechanism of Benzylic Bromination with Bromine.. 32**

**3.3 Selectivity of Hydrogen Atom Abstraction..... 33**

**3.4 Polar Effects on the Selectivity of Hydrogen Atom Abstaction..... 34**

3.4.1 Substituent Effects on Benzyl Cation Stability and Transition State Polarity..... 34

3.4.2 Effect of Transition State Polarity on the Enthalpy and Entropy of Activation..... 36

**3.5 Mechanism of Benzylic Bromination with NBS..... 39**

**3.6 Evidence to Support the Goldfinger Mechanism..... 40**
3.6.1 Relative Rates of Bromination with $Br_2$ and NBS..... 40
3.6.2 The Hydrogen Atom Abstraction Selectivity of the Succinimidyl Radical..... 42
3.7.3 The Allylic Bromination of Alkenes using $Br_2$ in Low Concentration..... 43
**3.7 Conclusions about the NBS Mechanism..... 44**
**3.8 Other Reagents used to Effect Benzylic Bromination. 45**

**4. The Aryl Bromination of Methyl 3,5-Dimethoxybenzoate**
**4.1 Objectives of Research Project..... 49**
**4.2 The Use of $Br_2$ in the Aryl Bromination of Methyl 3,5-Dimethoxybenzoate..... 49**
**4.3 The Effect of Varying Reaction Parameters on the Selectivity of Bromination..... 50**
4.3.1 Varying the Number of Mole Equivalents of $Br_2$ used... 50
4.3.2 Varying the Reaction Temperature..... 51
4.3.3 Bromination Without Stirring of the Reaction Mixture... 53
4.3.4 Varying the Concentration of the Substrate Solution..... 53
**4.4 Conditions for Optimising Monobromination Selectivity using $Br_2$..... 53**
**4.5 Monodebromination *via* Metal-Halogen Exchange.... 54**
**4.6 Bromination using NBS..... 54**

**5. The Aryl Bromination of 3,5-Dimethoxytoluene**
**5.1 The Aryl Bromination of 3,5-Dimethoxytoluene using $Br_2$..... 56**
**5.2 The Aryl Bromination of 3,5-Dimethoxytoluene using NBS..... 57**
**5.3 Monodebromination *via* Grignard Formation..... 57**
**5.4 The Aryl Tribromination of 3,5-Dimethoxytoluene... 58**
5.4.1 Explanation of the Low Reactivity of the C-4 Position Towards Bromination..... 58
5.4.2 Preparations of 2,4,6-Tribromo-3,5-dimethoxytoluene. 65
**5.5 Attempted Preparations of 4-Bromo-3,5-dimethoxytoluene..... 66**
5.5.1 *via* C-4 Lithiation..... 66
5.5.2 Other Potential Routes Towards the Synthesis..... 68

**5.6 The Acid-Catalysed Migration of Bromine Atoms from C-4 to C-6..... 76**
**5.7 Does a Methoxy Group in an *ortho* Position, Relative to Two Bromine Substituents, Still Exert an Activating Influence on the Ring?..... 76**
**5.8 The Bromination of 3,5-Dimethylanisole..... 77**
**5.9 Studies on the Bromination of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran..... 79**
5.9.1 The Synthesis of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran..... 79
5.9.2 The Bromination of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran..... 81
5.9.3 Acid-Catalysed Bromine Atom Migration in the Brominated Derivatives of 6-Methoxy-4-Methyl-2,3-Dihydrobenzofuran..... 83
**5.10 Acid-Catalysed Bromine Atom Equilibration in the Brominated Derivatives of 3,5-Dimethoxytoluene..... 84**

**6. The Benzylic Bromination of 3,5-Diacetoxytoluene**
**6.1 Attempted Benzylic Bromination of 3,5-Dimethoxytoluene..... 89**
**6.2 The Benzylic Bromination of 3,5-Diacetoxytoluene..... 89**

**7. Zeneca Pharmaceuticals Bromination Projects**
**7.1 The C-6 Bromination of 3,4-Dimethylacetanilide..... 92**
**7.2 The C-4/C-6 Dibromination of 3-Methylacetanilide.. 94**
**7.3 The Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone..... 96**
7.3.1 Explanation of the Observed Selectivity of Bromination. 96
7.3.2 Importance of the Bromination Step in the Synthesis of ZD9331..... 97
7.3.3 Initial Experiments on the Benzylic Bromination..... 97
7.3.4 Determination of the Product Distribution Arising from Conditions Based on a Zeneca Pharmaceuticals Method. 99
7.3.5 Experiments to Investigate the Effect on the Product Distribution of Varying the Solvent and Mode of Initiation..... 100

7.3.6 Identification of Quinazolinone **69** ..... 101
7.3.7 Effect of Other Changes on the Product Distribution.... 102
7.3.8 The Synthesis of 2,6,7-Tri(bromomethyl)-*N*(3)-pivaloyloxymethylquinazolinone..... 103
7.3.9 Attempted Preparation of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone *N*-oxide..... 106
7.3.10 Attempted Benzylic Iodination and Chlorination..... 108

**8. Experimental to Chapters 4-7**

**8.1 General Experimental Section..... 109**
**8.2 Experimental Details for Chapter 4..... 110**
**8.3 Experimental Details for Chapter 5..... 116**
**8.4 Experimental Details for Chapter 6..... 152**
**8.5 Experimental Details for Chapter 7..... 156**

**References..... 177**

# Abbreviations

| | |
|---|---|
| **AIBN** | Azo-bis-isobutyronitrile |
| **b.p.** | boiling point |
| **br** | broad |
| **d** | doublet (NMR spectroscopy) |
| **DBI** | Dibromoisocyanuric acid |
| **DCM** | Dichloromethane |
| **DMF** | Dimethylformamide |
| **DMSO** | Dimethylsulfoxide |
| **h** | hours |
| **lit.** | literature value |
| **m** | multiplet (NMR spectroscopy) |
| **m.p.** | melting point |
| **min** | minute(s) |
| **ml** | millilitre(s) |
| **mmol** | millimole(s) |
| **mol** | mole(s) |
| **NBS** | N-Bromosuccinimide |
| **NOE** | nuclear Overhauser enhancement |
| **PPA** | Polyphosphoric acid |
| **q** | quartet (NMR spectroscopy) |
| **s** | singlet (NMR spectroscopy) |
| **t** | triplet (NMR spectroscopy) |
| **THF** | Tetrahydrofuran |
| **TMEDA** | N,N,N',N'-Tetramethylethylenediamine |
| **v. br** | very broad |

# 1

# Introduction

## 1.1 The Importance of Aryl and Benzylic Bromination

Bromination has historically been a very important organic transformation as the organic bromides produced have widespread use, both as intermediates in synthetic pathway and as end products in their own right.

### 1.1.1 Uses as Intermediates

The organic bromides produced as the products of benzylic and aryl bromination (the reactions with which this thesis is concerned) are extremely useful intermediates that have been used for a variety of purposes in synthetic pathways.

Perhaps, in synthesis, the most widespread use made of these bromides is as direct precursors to organometallic reagents such as Grignard reagents, aryl lithium reagents and lithium diaryl cuprates. The scope of use of such species is enormous and they are used extensively in synthesis, particularly in C-C bond forming reactions. These reactions include nucleophilic acyl addition reactions with ketones and aldehydes, conjugate addition to $\alpha,\beta$-unsaturated ketones, addition to $CO_2$, nucleophilic acyl substitution reactions with esters, $S_N2$ opening of epoxides and coupling reactions with alkyl, aryl, allylic, benzylic or vinylic halides.

Another major synthetic application of benzylic bromination is the general functionalisation of aromatic side chains that would be difficult by almost any other means. Chlorination can also be used in this regard but bromination has the advantage of being more selective. The benzyl bromides produced react readily by either $S_N1$ or $S_N2$ reactions and the bromine can easily be displaced by a large range of oxygen, nitrogen or carbon based nucleophiles. There are 2 main reasons for this high level of reactivity. Firstly, the bromide ion is a relatively good leaving group (being the conjugate base of a relatively strong acid) and secondly, there is unsaturation at the $\beta$-carbon in the substrate, which results in the stabilisation of benzylic cations by resonance thus lowering the activation energy for $S_N1$ reactions. Even for $S_N2$ reactions, where a full positive charge does not develop on the benzylic carbon in the transition state, the adjacent aromatic ring increases the rate of substitution at the benzylic position through resonance effects.

Aryl bromides can also undergo nucleophilic substitution reactions whereby the bromine can be replaced with a range of other substituents. There are 2 main mechanism in aromatic nucleophilic substitution when a bromide ion is the leaving group. These are the $S_NAr$ mechanism (see figure 1), which generally requires that the ring has other electron-withdrawing substituents *ortho* or *para* to the bromine, and the benzyne mechanism (see figure 2) which requires that there be a hydrogen atom *ortho* to the bromine and the use of a strong base such as $^-NH_2$.

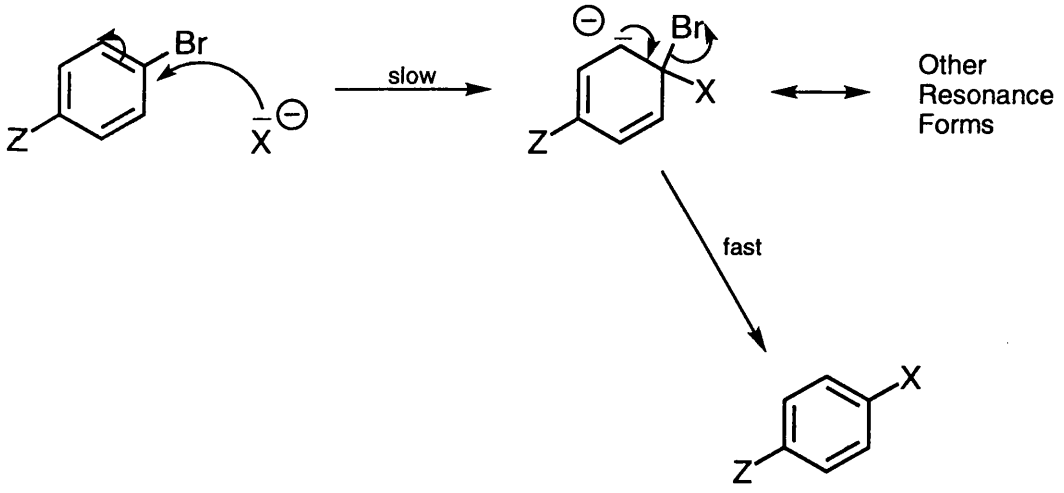



**Figure 1:** $S_NAr$ Mechanism of Nucleophilic Aryl substitution

It can be seen from figure that the $S_NAr$ mechanism involves initial attack by the nucleophile at the carbon bearing the leaving group resulting in the formation of an intermediate anion. This attack is only usually feasible if Z is electron withdrawing and able to stabilise the anion by further delocalisation of the negative charge on the ring.

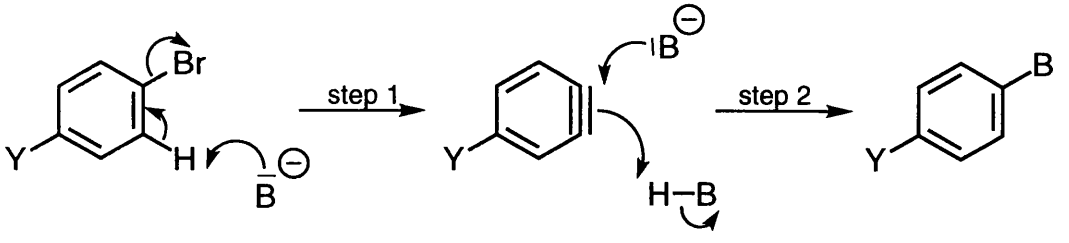



**Figure 2:** Benzyne Mechanism of Nucleophilic Aromatic Substitution

Though the bond-breaking and bond-forming reactions in the benzyne mechanism are shown to be synchromous in figure 2, this is not necessarily the case and for bromide as the leaving group the initial proton abstraction is the rate determining step, hence the need for a strong base. It should also be stated that the nucleophile can attack either side of the triple bond, depending upon whether Y is

electron-releasing or electron-withdrawing (attack at position *ortho* to the original bromine substituent is called cine substitution).

Though, there are therefore limitations on the use of aromatic nucleophilic substitution, it is still a valuable way of introducing different substituents (including -OH, -OR, $-NR_2$ and -CN) onto the ring and is particularly useful for ring closure reactions to form fused heterocycles.

### 1.1.2 Uses as End Products

Organic bromides have a broad range of application as end products. Examples of the areas in which these compounds are found includes those given below.

(1) The field of pesticides has many examples of organic halides and though these are mainly chlorides, bromides too have been used for this purpose[1].

(2) The flame retardant properties of halogen compounds, especially brominated compounds, has found application in the textile, plastics, elastomer and wood industries[2].

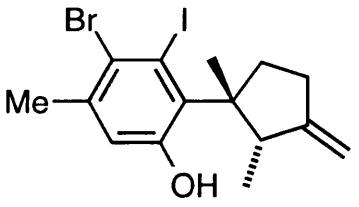
(3) Many organic halides have pharmacological importance, although their action is usually related to the presence of other groups in the molecule[1].

(4) Of particular interest, however, is the rapidly expanding field of organohalogen natural products. Until quite recently the occurance of organic compounds, containing covalently bound bromine atoms, was thought to be relatively rare. This view has now changed quite drastically with more than 1500 different halogenated chemicals known to be produced and discharged into our biosphere by plants, marine organisms, insects, bacteria, fungi, and other natural processes[3]. In addition, previously unknown naturally occurring organohalogen compound are continually being isolated and characterised.

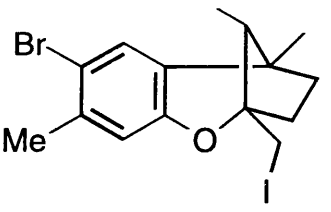
A complete review of natural products, containing bromine atoms, is obviously therefore well beyond the scope of this thesis. A few representative examples are however given below.

(i) TERPENOIDS - Monoterpenoids, sesquiterpenoids, diterpenoids and triterpenoids are ubiquitous in terrestrial organisms and play an essential role in life. A large number of halogenated terpenoids, from sources both on land and in the sea, have been isolated and identified. Red algae, for example has provided a particularly rich and diverse

range of brominated terpenes that includes compounds (**1**) and (**2**) which were isolated from *Laurenia nana*[4].

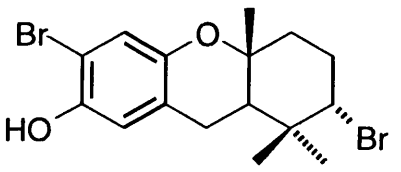



(**1**)



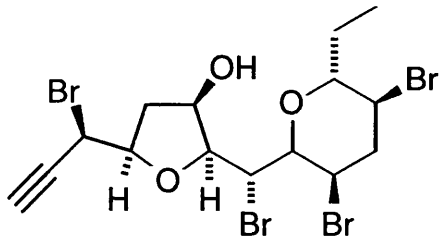

(**2**)

Green algae also contains brominated terpenes. For example, the highly antimutagenic cymobarbatol (**3**) was isolated from the green alga *Cymopolia barbata* [5].

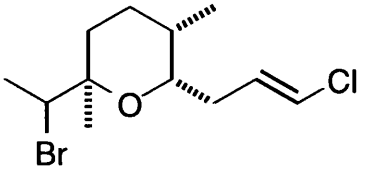



(**3**)

(ii) NONTERPENOIDS - Another very large group of halogenated organic compounds are the "nonterpenoids", compounds which may or may not arise from a terpenoid pathway but which are not obviously terpene derived. Marine organisms, in particular, biosynthesize a multitude of fascinating halogenated nonterpenes. For example, the sponge *Mycale rotalis* produces the novel metabolite (**4**)[6], while the Guam "bubble shell" (*Haminea cymbalum*) contains kumepaloxane (**5**), a feeding deterrent to carnivorous fishes which is discharged when the mollusk is disturbed[7].



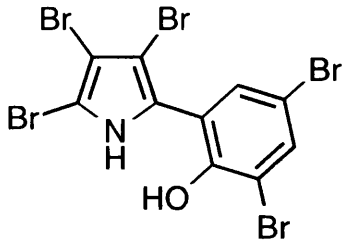

(**4**)



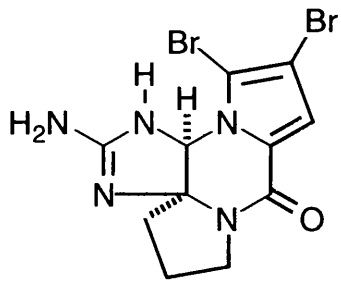

(**5**)

(iii) PYRROLES - The enormous reactivity of pyrroles in electrophilic aromatic substitution reactions makes it not surprising that halogenated pyrroles are found widely in nature. The marine bacterium *Chromobacterium* sp., for example, produces

polybrominated pyrroles[8], including (**6**), while the sponge *Phakellia flabellata,* from the Great Barrier reef, contains dibromophakellin (**7**)[9].

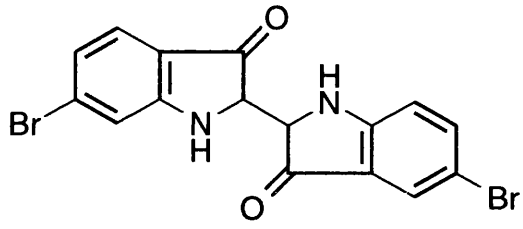


(**6**)



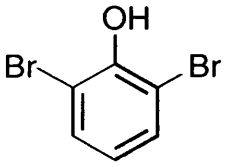
(**7**)

Brominated indole ring system are also common. A particularly interesting example is the indigo derivative Tyrian Purple (**8**), an ancient Egyptian dye extracted from mollusk shells[10].

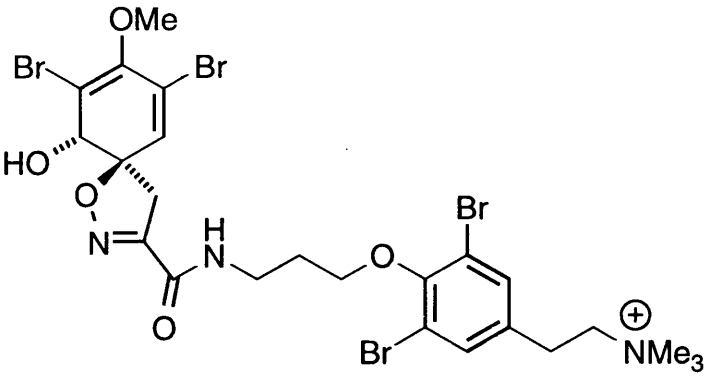


(**8**)

(iv) AROMATIC COMPOUNDS - Most of natures brominated aromatic rings are activated towards electrophilic aromatic substitution with phenols being particularly common. Perhaps the simplest example is 2,6-dibromophenol (**9**) which is present to the extent of 10-15 mg per acorn worm *Balanoglossus biminiensis,* and is believed to function as a chemical defense against predators[11]. Other, far more complicated examples are known such as purealiden B (**10**) which has been isolated from the Okinawan sponge *Psammaplysilla purea*[12].




(9)




(10)

Brominated compunds have been found in many other classes of natural products including carbolines and quinolines, with simple halogenated alkanes being particularly abundant[13]. Brominated fatty acids have also been discovered and brominated lipids found in salmon, halibut, sole, crab, dolpins, walrus and other large marine creatures[14]. Even brominated nucleic acid bases have been found to exist naturally[15].

In other natural product areas, such as furans and carbazoles, halogenated compounds are surprisingly rare[3]. Furthermore, although terrestrial plant alkaloids are ubiquitous and have been the object of attention of natural product chemists for more than 100 years, very few of these compounds contain halogen atoms. The same is also true of steroids, amino acids and peptides.

Organohalogen metabolites have been shown to exhibit a range of potentially useful biological activities (including antimicrobial, antibiotic, antitumour, antifungal, herbicidal and insecticidal), often of very high potency[16]. It therefore seems certain that the near future will see the development of medicinally important organohalogen compounds.

### 1.1.3 Conclusion

The preceeding section has illustrated the importance of benzyl and aryl bromides. Of equal importance to the synthetic chemist is the ability to understand and be able to manipulate the selectivity of reactions which give rise to these products. The following two chapters, dealing in turn with aryl and benzylic bromination, give an explanation of the mechanism and selectivity of the reactions as well as a brief description of some of the more common reagents that have been used to carry them out.

# 2

# Introduction to Aryl Bromination

## 2.1 Mechanism of Electrophilic Aromatic Substitution

Almost all electrophilic aromatic substitutions proceed by the same mechanism with respect to the substrate though the electrophile may be produced in a number of ways[17]. This mechanism is known as the arenium ion mechanism.

In the first step of this mechanism the electrophilic entity, be it a positive ion or a dipolar species, attacks the ring and removes a pair of electrons from the sextet to give a carbocation, which is a resonance hybrid, as shown in figure 3.

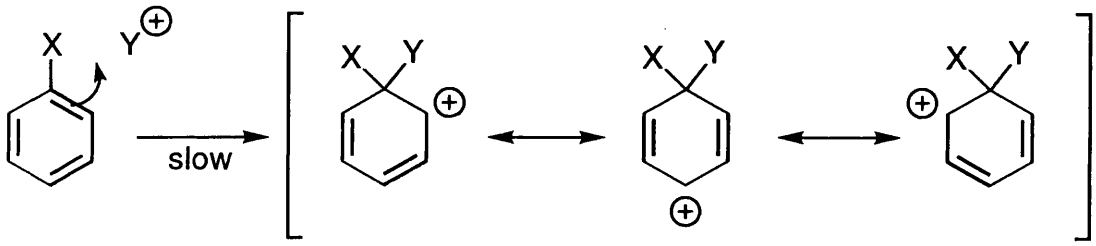



**Figure 3:** Step one of the mechanism of electrophilic aromatic substitution

These ions were previously known as Wheland intermediates[18] or σ-complexes when less was known about the structure of the carbocation. Now, following the suggestion of Olah[19], they are more commonly known as arenium ions. The great stability associated with an aromatic sextet is nolonger present in these ions and, despite being stabilised by resonance of their own, arenium ions are generally highly reactive intermediates which must stabilise themselves by further reaction. Some arenium ions have, however, been isolated[20,21].

The most common way in which these ions stabilise themselves is through loss of either $X^+$ or $Y^+$ to regenerate the aromatic sextet. This is the second step of the mechanism as shown in figure 4.

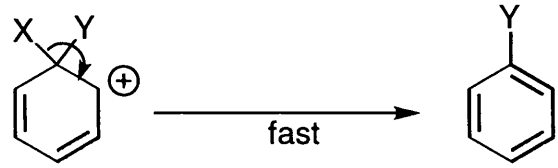



**Figure 4:** Step two of the mechanism of electrophilic aromatic substitution

If $Y^+$, the initial electrophile, is lost then there is no net reaction but if $X^+$ is lost then the result is aromatic substitution. $X^+$ is most commonly, though not exclusively, a proton and a base is necessary to remove it.

This second step is almost invariably faster than the first step which is therefore rate-determining. The rate of formation of the electrophile is however sometimes slower still and this then becomes the rate-determining step in the reaction.

## 2.2 Evidence for the Arenium Ion Mechanism

The evidence for the arenium ion mechanism comes from two main sources:

### 2.2.1 Isotope Effects[22]

If the proton left before or at the same time as the attack by the electrophile then a substantial isotope effect would be expected. That is, deuterated aromatics would be expected to undergo electrophilic substitution more slowly due to the greater strength of the C-D bond in comparison with the C-H bond. However, as the C-H bond is broken in the second step in the arenium ion mechanism rather than in the rate-determining first step, it follows that no isotope effect should be found.

In practice studies have, in the majority of cases, shown no isotope effect and this obviously supports the arenium ion mechanism. Of particular relevance is the lack of any kinetic isotope effect in many halogenations, such as the iodine-catalysed bromination of toluene[23].

It should however be noted that small isotope effects ($K_H/K_D < 3$) have been found in some cases, an example being the iodination of phenol[24]. This is most probably a result of the reversibility of the first step in the mechanism.

Step 1 $\quad ArH + Y^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHY^+$

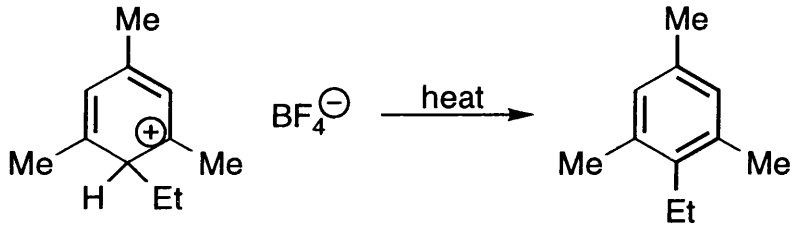
Step 2 $\quad ArHY^+ \xrightarrow[k_2]{} ArY + H^+$

If $k_{-1}$ is comparable in magnitude to $k_2$ then reversion from the arenium ion to starting materials is important. This is because $k_2$ for $ArDY^+$ will be smaller than $k_2$ for $ArHY^+$ (due to the relative C-H and C-D bond strengths) but $k_{-1}$ will be the same for both. The result of this being that the $ArDY^+$ ions are more likely to revert to starting

material, slowing the reaction and producing the isotope effect observed in the electrophilic substitution of deuterated aromatics[25].

### 2.2.2 Isolation of Arenium Ion Intermediates

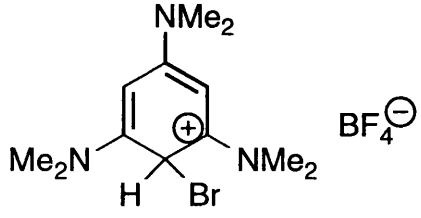
Even stronger evidence for the arenium ion mechanism has been provided by the isolation of some relatively stable arenium ions. An example is compound (**11**) shown below.




(**11**) (**12**)

This compound was isolated from the reaction of mesitylene with ethyl fluoride and $BF_3$ at 80 °C. It was obtained as a solid with a melting point of -15 °C. Further evidence to support the mechanism is provided by the fact that on heating this arenium ion lost a proton to give the normal substitution product (**12**)[20].

It is particularly noteworthy that the existence of arenium ion intermediates in bromination has been provided by the isolation of (**13**) and related compounds[21].




(**13**)

## 2.3 Regioselectivity and Reactivity of Electrophilic Attack at Substituted Benzene Rings

When a monosubstituted benzene ring undergoes electrophilic substitution the new group may be introduced into an *ortho*, *meta* or *para* position relative to the initial ring substituent. Furthermore, the substitution may be slower or faster relative to the analogous reaction with benzene. Both the position and relative rate of the electrophilic

attack are determined by the nature of the initial substituent. Some groups are predominantly *meta*-directing and all of these slow the reaction and are referred to as being deactivating. Others are predominantly *ortho-para*-directing and the vast majority of these increase the rate of the reaction and are referred to as activating. A notable exception to this rule, in regards to this thesis, are the halogens, which are *ortho-para*-directing but are at the same time deactivating. It should also be noted that groups direct predominantly but usually not exclusively.

The reactivity and directing effects of each group can be explained in terms of resonance and field effects on the stability of the intermediate arenium ion. This approach is valid because these reactions are *usually* kinetically and not thermodynamically controlled. Therefore which of the *ortho*, *meta* or *para* substituted products is formed is dependent not on the relative thermodynamic stabilities of these products but on the activation energies necessary to form each of the 3 intermediates leading to them. The free-energy profile of the electrophilic substitution reaction resembles that shown in figure 5.

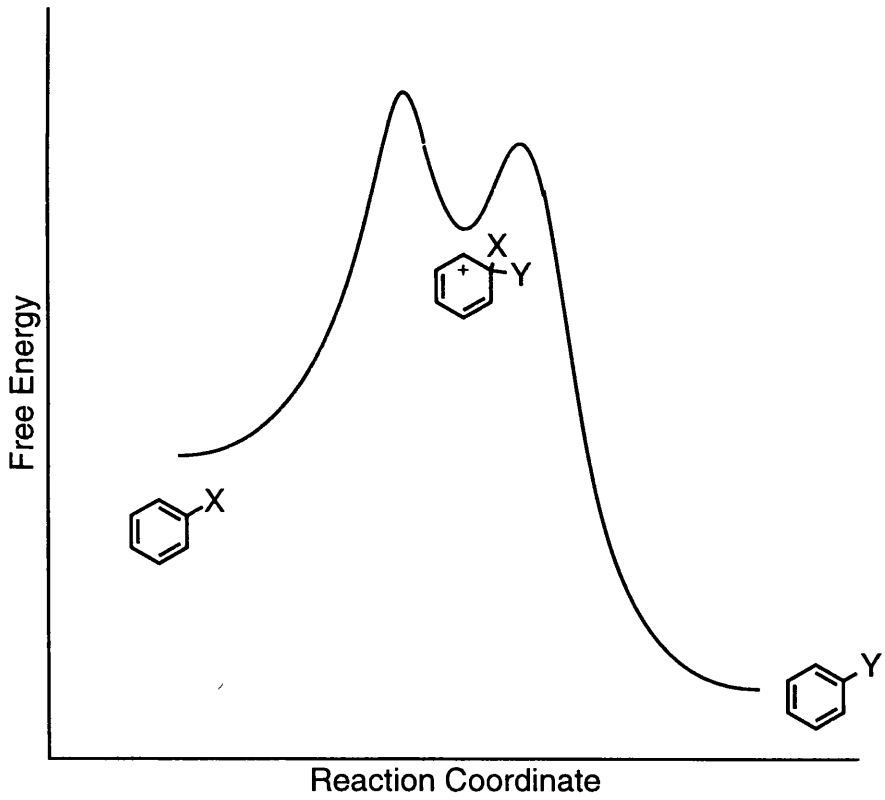



**Figure 5:** Free-energy profile of the electrophilic substitution reaction[26]

It can be seen that the transition state is closer in energy to the arenium ion than either the starting compound or product. Now, the Hammond postulate[27] states that the geometry of the transition state most closely resembles that of the stable species which

is closest in terms of free energy. Therefore it can be assumed that the geometry of the transition state resembles that of the arenium ion intermediate and that anything that increases the stability of this intermediate will also lower the activation energy necessary to reach it. As the intermediate, once formed, is known to be rapidly converted to product it is reasonable to use the relative stabilities of the 3 arenium ions to predict which product will predominantly form.

### 2.3.1 Directing Influence of Inductive and Field Effects

The inductive effect depends on the substituent electronegativity and operates through the σ-bond system whereas the field effect depends on the substituent dipole and operates directly through space. However, they produce similar effects on molecular properties and are difficult to distinguish from each other[28]. For this reason any subsequent reference to field effects can be taken to mean the combined effect of both the inductive and field effects.

The 3 possible arenium ions are shown in figure 6.

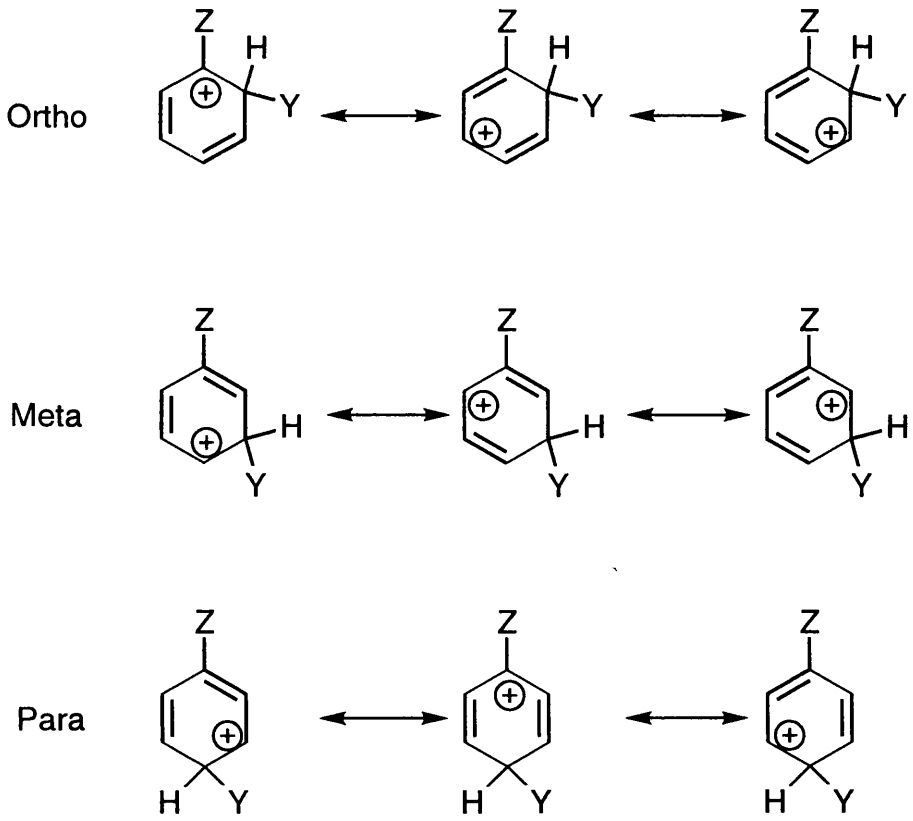



**Figure 6:** Resonance forms of the three possible arenium ions[29]

For each ion, the ring has a positive charge, delocalised over 3 positions. If the ring substituent, Z, has an electron donating field effect then it should stabilise all 3

ions. The field effect however diminishes with distance and therefore stabilises the *ortho* and *para* substituted intermediates, where there is a partial positive charge on the carbon connected to Z, to a greater extent than the *meta* substituted intermediate where all the positive charge is located further from Z. The result is therefore that substituents that have an electron donating field effect activate all three positions but activate the *ortho* and *para* positions to a greater extent. Similarly, if the substituent, Z, has an electron withdrawing field effect then by removing electron density all three intermediates are destabilised. Again the fact that the resonance hybrids for *ortho* and *para* substitution have a partial positive charge on the carbon bonded to Z results in a greater degree of destabilisation in these intermediates. Therefore substituents that have an electron withdrawing field effect deactivate all 3 positions but deactivate the *ortho* and *para* positions more with the result being *meta*-direction of the substitution.

### 2.3.2 Directing Influence of Resonance Effects

The conclusions reached by considering field effects are not sufficient to explain all the observed reactivities. In some cases there is resonance between the substituent Z and the ring and this also has an effect on the relative stabilities of the arenium ions. In some cases this effects the relative reactivity of the 3 positions in the same direction as the field effect but in other cases, notably that of the halogens, the effect is in the opposite direction.

Considering substituent Z as having a pair of electrons that may be contributed towards the ring the resonance forms of the 3 intermediates would now be those shown in figure 7.

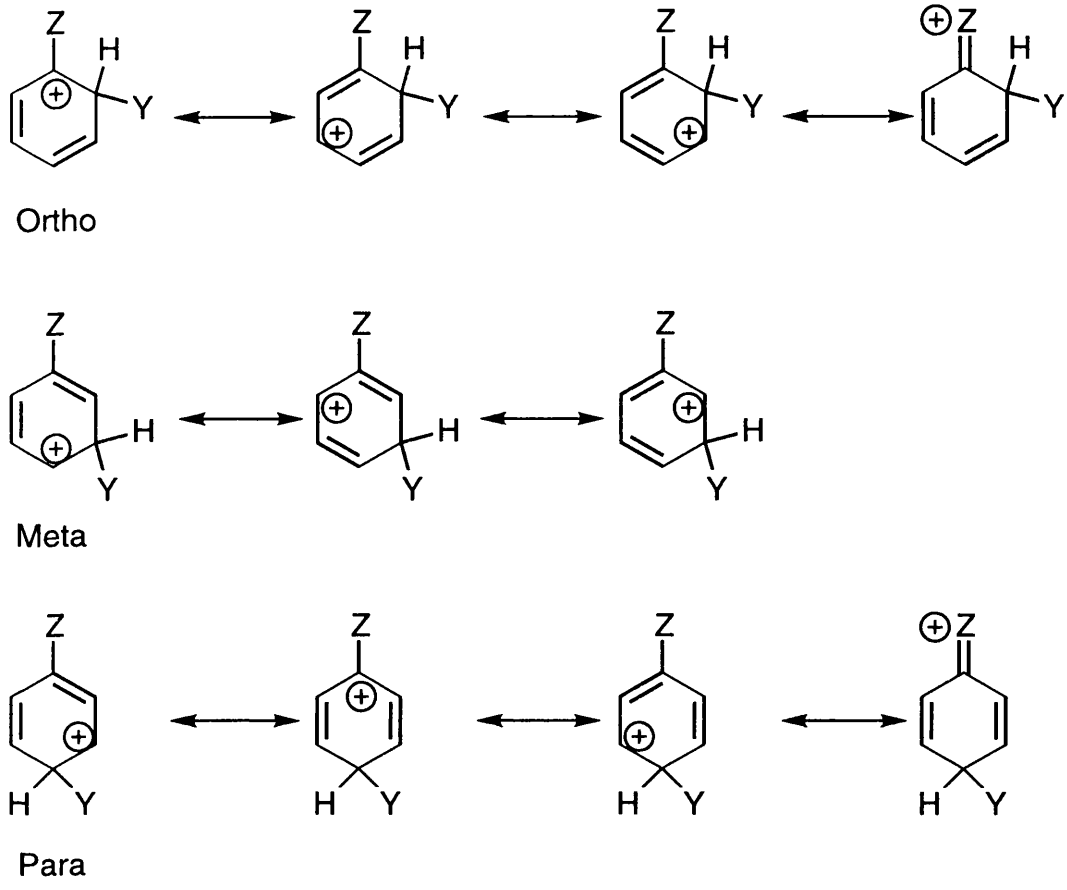



**Figure 7:** Resonance forms of the three possible arenium ions for a benzene ring with a substituent that has a lone pair of electrons[30]

Each intermediate has the same 3 resonance forms as before but those intermediates leading to *ortho* and *para* substitution have an additional resonance form where the positive charge is located at substituent Z. The stability of these 2 intermediates is therefore increased, not only because there is another resonance form which leads to greater delocalisation of charge but also because these additional resonance forms are more stable and make a greater contribution to the hybrid than the others as in these forms each atom (except hydrogen) has a complete octet of electrons. Substituent groups with a pair of electrons to contribute would therefore, if field effects are ignored, be expected to direct *ortho* and *para* and to activate these positions towards electrophilic attack.

By considering the resonance and field effects together 3 distinct classes of substituent group can be identified.

### 2.3.3 Classes of Substituent Groups

(1) Groups that contain an unshared electron pair on the atom bonded to the ring. Examples from this group are $-NR_2$, -OH, -OR, -NHCOR, -OCOR and the four halogens. By consideration of the resonance effect, as explained above, all these groups would be predicted to be *ortho-para*-directing. However all the groups listed also have an electron withdrawing field effect which should work in the opposite direction. In practice they are all found to be *ortho-para*-directing and the resonance effect would therefore appear to be more important than the field effect. All the groups are also activating, except the halogens, with $-NR_2$, -OH and -OR being more strongly activating than -NHCOR and -OCOR due to the competing donation of the lone pair towards the carbonyl in these 2 groups reducing the degree of electron pair contribution towards the ring. In the case of the halogens, they are found to be deactivating even though they direct *ortho-para.* To explain this it is assumed that the resonance forms, shown in figure 7 where the charge is located on Z, make such great contributions to the respective hybrids that they make the arenium ions which lead to *ortho* and *para* substitution more stable than that which leads to *meta* substitution even though the field effect of the halogen draws sufficient electron density from the ring to deactivate it.

(2) Groups that have an electron-withdrawing field effect and do not have an unshared pair of electrons on the atom bonded to the ring. Examples from this group include $-NR_3^+$, $-NO_2$, -CN, -CHO, -COR, -COOH, -COOR, $-CONR_2$ and $-NH_3^+$. By consideration of the field effect, as described above, then all these groups should be both deactivating and *meta*-directing. This is found to be the case for all the groups shown (except $-NH_3^+$) with them being listed in order of decreasing deactivating ability.(The behaviour of the $-NH_3^+$ is somewhat anamolous since it is found to direct *para* to the same, if not a slightly greater, extent than it directs *meta*). It should be noted that the field effect is not sufficient to explain all of the electron withdrawal from the ring and in cases where there the atom connected to the ring is double bonded to another atom resonance may also result in electron withdrawal from the ring. For example, whereas a *meta* $-NMe_3^+$ group decreases the $pK_a$ of benzoic acid to a greater degree than a *para* $-NMe_3^+$ group as expected for a group that can only act inductively, *para*-nitrobenzoic acid is stronger than its *meta* isomer[31]. This indicates that resonance forms like those shown in figure 8 must contribute to the overall resonance hybrid. This effectively lowers the electron density at the *ortho* and *para* positions and leads to *meta*-direction of the attack by an electrophile.

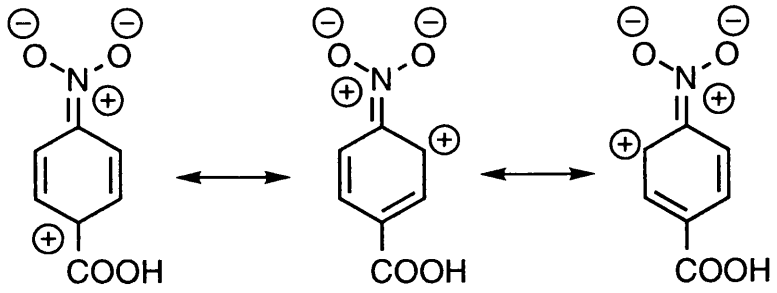



**Figure 8:** Resonance forms of *para*-nitrobenzoic acid

(3) Groups that exert an *ortho-para*-directing influence on the ring but do not have an unshared pair of electrons on the atom bonded to the ring. Examples from this group are alkyl groups, aryl groups and the $-COO^-$ group. In explaining these cases they must be treated separately. The *ortho-para*-directing influence of the $-COO^-$ is due to the field effect of the group which, due to the negative charge, is electron donating. The aryl groups however, have an electron withdrawing field effect and the *ortho-para*-directing influence is, in this case, attributed to donation of a pair of electrons from the aromatic sextet resulting in delocalisation of the charge on the arenium ion to the substituent ring as shown in figure 9.

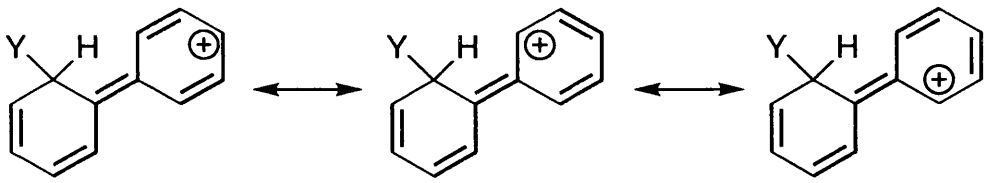



**Figure 9:** Resonance forms for an arenium ion where the charge is delocalised to a substituent ring

The effect of alkyl groups can be explained in a number of ways. Firstly, they have an electron-donating field effect and therefore, by the explanation given before, would be thought to be *ortho-para*-directing. Though the alkyl groups obviously lack an unshared pair a resonance effect can also be used to explain the *ortho-para*-directing influence if hyperconjugation forms, such as that shown in figure 10, are considered to contribute to the resonance hybrid.

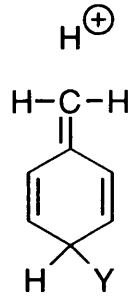


**Figure 10:** A hyperconjugation form of a *para*-substituted toluene

When alkyl groups are attached to unsaturated systems about 80% of their electron release is provided by hyperconjugation[32].

A final approach is to simply note that one of the resonance forms for the arenium ions, leading to *ortho* and *para* substitution, is a tertiary carbocation (see figure 6) which should be more stable than any of the secondary carbocations that make up the resonance forms of the arenium ion leading to *meta* substitution.

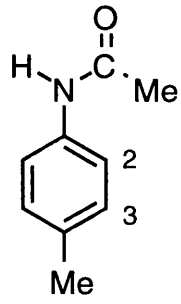
### 2.3.4 Regioselectivity of Electrophilic Attack at Benzene Rings with More than One Substituent

In order to discuss, in a quantative manner, the effect of more than one substituent the term *partial rate factor* must be defined. For a given group and a given reaction the *partial rate factor* is defined as the rate of substitution at a single position, such as *para*, relative to a single position in benzene. A partial rate factor greater than 1 for a given position therefore indicates that the group in question activates that position for a given reaction.

If the partial rate factors for the individual substituents in a given reaction are known it is possible to predict the proportion of isomers that will be obtained when 2 or more of these groups are present on the ring if the assumption is made that the effect of the substituents is additive. That is, if the introduction of each of the 2 substituents was to alter the free energy of activation at a particular position by amounts $x$ and $y$, the presence of both substituents would alter the free energy of activation by an amount $x+y$. This would lead to the partial rate factor for substitution in the disubstituted compound being equal to the product of the partial rate factors for the 2 monosubstituted compounds.

To a first approximation the additive principle is quite successful in predicting substitution patterns, particularly where steric effects are less important. There are however some discrepancies and the additive principle tends to underestimate the

substitution rates for aromatics containing 2 or more strongly deactivating groups and overestimate the reactivity of rings with 2 or more strongly activating substituents (the reason for this is explained later). The principle is of particular value when used in a semi-quantative way. For example, consider the bromination of 4-methylacetanilide (**14**).




(**14**)

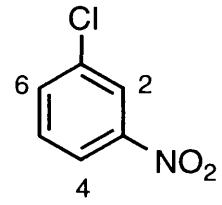
Position 2 is *ortho* to the strongly activating -NHCOMe group and *meta* to the less strongly activating methyl group. Position 3 is *meta* to the -NHCOMe group and *ortho* to the methyl. As the partial rate factor for bromination *ortho* to a -NHCOMe group is greater than the partial rate factor for bromination *ortho* to a methyl, position 2 is more reactive and bromination occurs primarily at this site.

When groups on a ring have directing effects that are in opposition there are some general observations that can be made.

(1) If a strongly activating group is in competition with one which is weaker or even deactivating the strongly activating group exerts the controlling influence (e.g the bromination of **14** as described above).

(2) Where other effects are equal, a third group is least likely to enter the position between 2 existing groups in a *meta* relationship. This is the result of steric hindrance and its importance increases with the increasing steric bulk of the groups on the ring or the electrophile. It is therefore of considerable importance in bromination due to the size of the bromine atom.

(3) Where the is a meta-directing group in a *meta* position relative to an *ortho-para*-directing group then electrophilic substitution occurs primarily *ortho* to the *meta*-directing group. For example, consider the chlorination of 1-chloro-3-nitrobenzene (**15**).




**(15)**

Chlorination occurs primarily at position 4 and to a lesser extent (see rule No.2) at position 2, both of which are *ortho* to the nitro group. Chlorination at position 6 is not observed at all. This is known as the *ortho effect* and its origin is not fully understood.

### 2.3.5 The Effect of Electrophile Reactivity on Regioselectivity and Aromatic Reactivity

The discussion of regioselectivity and reactivity to this point has centred on the role of the ring substituents. However whilst the substituent is responsible for determining whether substitution is predominantly *ortho/para* or *meta* and whether each of these positions is more or less reactive than a carbon in benzene, the quantative relationships between the reactivities of these positions also depends upon the nature of the electrophile. This is illustrated by the data in table 1[33].

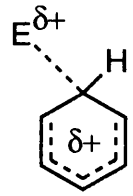
| **Reaction** | **% *meta* isomer** | **% *para* isomer** | **Relative reactivities** |
|---|---|---|---|
| Isopropylation | 25.9 | 46.2 | 1.8 |
| Mercuriation | 9.5 | 69.5 | 7.9 |
| Nitration | 3.0 | 38.0 | >23 |
| Benzoylation | 1.5 | 89.3 | 110 |
| Chlorination | 0.5 | 39.7 | 350 |
| Bromination | 0.3 | 66.8 | 605 |

**Table 1:** Isomer distributions and relative reactivities of toluene and benzene

Before the effect of electrophile can be explained it is necessary to point out that the use of the arenium ion as a model for the transition state, in this respect, has an important deficiency. If the transition state was identical with the arenium ion intermediate then the activation energies for a given group of compounds would differ

from the localisation energies by a constant amount, which would depend on the reagent, but the relative reactivities of members of the group towards differing electrophilic reagents would be the same.

In order to explain the variation in the relative reactivities with the nature the nature of the electrophilic reagent it is necessary to make the assumption that the transition state varies from the arenium ion in one important respect, *viz.* that the new σ-bond between the ring carbon and the reagent has not been completely formed and that the reorganisation of the ring's -electron system is not complete[34]. The transition state may therefore be represented as shown below.




The incomplete electronic reorganisation in the transition state results in a reduction in the differential effects of substituents in determining the free energies of the transition states in comparison with the arenium ion intermediates. The precise structure of the transition state will vary with the nature of the attacking electrophilic reagent, resulting in changes in the differential effects of substituents with a change of reagent and hence in the observed alteration of relative reactivities.

Returning to table 1 it can be seen that going down the series of reactions the *meta:para* ratio decreases and the relative reactivity of toluene relative to benzene increases. These variations can be rationalised as follows. Imagine an electrophilic reagent that was of such high reactivity that it reacted during every collision with an aromatic molecule. It would then fail to discriminate between toluene or benzene or between the *meta* or *para* positions of toluene. The relative reactivity of toluene in comparison with benzene would then be 5/6, purely by consideration of the number of possible sites of attack in the respective molecules. Similarly the *meta:para* ratio in toluene would be 2:1 simply because there are 2 *meta* positions for every *para* position. This hypothetical situation is most nearly approached, amongst the reactions shown in table, by isopropylation and as the electrophile in this case is a carbocation it is understandable why it is so reactive. As the reactivity of the reagent decreases there is an increasing need for a pair of electrons to be supplied to the electrophile in order that the activation energy barrier can be surmounted. As the ease with which a pair of electrons can be supplied at a particular position is determined by the nature and position of the ring substituents it follows that as the demand on the part of the reagent for the electron pair increases so to does the differential effects of the substituents.

Therefore the greatest differences in reactivity occur for the least reactive electrophiles, such as molecular bromine, and in general as the reactivity of the reagent decreases, its demand for an electron pair for bond formation at the transition state increases, resulting in an increase in the selectivity between different aromatic compounds and between the *meta* and *para* positions of a given compound. This is an example of the *Reactivity-Selectivity Principle.*

### 2.3.6 Effect of Substrate Reactivity on Selectivity

The foregoing discussion has suggested that the structure of the transition state depends on the reactivity of the electrophile but not on that of the aromatic. This assumption is obviously incorrect. According to the Hammond postulate in the reaction of two aromatic sites with the same electrophile the transition state formed by the less reactive aromatic site should more closely resemble the arenium ion than that formed by the more reactive, just as the arguments presented above showed that as the reactivity of the electrophile decreased the transition state more closely resembled the arenium ion.

Therefore just as a pair of aromatics show differing substrate and positional selectivities towards differing electrophiles, so a given electrophile will discriminate less between a pair of more reactive aromatic sites than between a pair of aromatic sites of lower reactivity with comparable structure. This result is again the consequence of the *Reactivity-Selectivity Principle.* It is probable that as the aromatic becomes more reactive, the transition state is formed earlier in the passage along the reaction coordinate with the consequence that the selectivity of the reagent towards different aromatic sites is reduced and that the introduction of a further activating substituent has a smaller effect than would be expected since less charge develops on the ring in the transition state. For this reason, the additive principle tends to overestimate the reactivity of aromatics with more than 1 activating group.

### 2.3.7 Factors which Determine the *ortho:para* Ratio

The factors which determine the relative reactivity of the *meta* and *para* positions in a monosubstituted aromatic compound are essentially confined to electronic effects. The *ortho:para* ratio however, is governed in addition by steric effects and elucidation of the relative importance of the 2 effects is often difficult.

The factors which are thought to contribute to the determination of the *ortho:para* ratio are steric hindrance, steric acceleration, interaction between the

substituent and the reagent, electronic effects and solvent and temperature effects. The origin of these effects are explained below.

### 2.3.7.1 Steric Hindrance

Since any substituent is larger than hydrogen, it might be expected that, in comparison with reaction at the *para* position, substitution *ortho* to an existing substituent would always be partially impeded by non-bonding repulsive forces. This is not always the case and in some reactions there is evidence to suggest that the reagent and the substituent interact by covalent or coordinate bonding so that the reagent is held in a geometrically suitable position for substitution at the *ortho* position to occur. Further even when repulsion between the substituent and the reagent does exist the effect may be outweighed by a different steric phenomenon called steric acceleration.

In some cases however, the occurance of *ortho:para* ratios lower than 2:1 is attributed to steric hindrance. For example, consider the data for the bromination, using molecular bromine in aqueous acetic acid, of the alkyl benzenes shown in Table 2.

| R | $f_o$ | $f_m$ | $f_p$ | $f_o : f_p$ |
|---|---|---|---|---|
| Me | 600 | 5.5 | 2420 | 0.25 |
| Et | 465 | - | 1800 | 0.26 |
| *i*-Pr | 180 | - | 1200 | 0.15 |
| *t*-Bu | 5.2 | 7.3 | 805 | 0.0065 |

**Table 2** Partial rate factors for the bromination of alkylbenzenes, PhR[35]

It can be seen from table 2 that the ratio of the *ortho* partial rate factor to the *para* partial rate factor, for the bromination of*tert*-butylbenzene is far smaller than the ratio observed for the other alkylbenzenes. Indeed the partial rate factor for *meta* substitution is greater than that for *ortho*. This suggests that steric hindrance impedes the introduction of the bromine atom *ortho* to the bulky *tert*-butyl group.

### 2.3.7.2 Steric Acceleration

If, during an aromatic substitution reaction, a bulky substituent is replaced, then the steric compression present between it and the *ortho* substituent in the initial eclipsed state will be relieved in the passage to the staggered transition state. This gives rise to steric acceleration. The effect is obviously opposed by steric hindrance between the

*ortho* substituent and the attacking reagent, but if the reagent is relatively small, steric acceleration may be of greater importance than steric hindrance and high *ortho:para* ratios then result. Steric acceleration is most commonly observed in reactions such as protiodebromination and other protonolyses because steric hindrance in such reactions is small. For example, whereas 2,4,6-tri-*tert*-butylbromobenzene undergoes protiodebromination with strong acid, 2,4,6-trimethylbromobenzene is unreactive under the same conditions[36].

### 2.3.7.3 Interaction between Substituent and Reagent

In certain reactions there is evidence to suggest that the reagent and the substituent interact by covalent or coordinate bonding so that the reagent is held in a geometrically suitable position for substitution at the *ortho* position to occur. This obviously leads to high *ortho:para* ratios.

A good example is the chlorination of phenol by 2,3,4,4,5,6-hexachlorohexa-2,5-dienone. Whereas, anisole is chlorinated almost exclusively at the *para* position (presumably due to steric hindrance) with this reagent, phenol gives high *ortho* selectivity, especially in non-polar solvents and this has been attributed to hydrogen bonding between the carbonyl group and the phenolic hydrogen facilitating chlorine transfer from the $CCl_2$ group to the *ortho* position[37] (see figure 11).

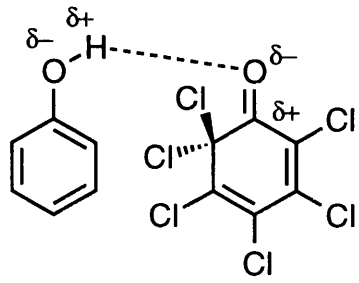



**Figure 11:** Hydrogen bonding facilitating *ortho* chlorination of phenol

### 2.3.7.4 Electronic Effects

It is often difficult to evaluate the importance of electronic effects in the determination of the *ortho:para* ratio as little is known about the magnitude of steric hindrance to *ortho* substitution. However in cases when the *ortho:para* ratio is greater than the statistical value of 2, and there is no facilitating *ortho* interaction, then electronic effects must be powerful enough to outweigh the effect of steric hindrance. The theory of the role of electronic effects in determining the *ortho:para* ratio stemmed

initially from studies of aromatic substitutions which gave rise to ratios greater than 2, and was then extended to other reactions which give lower ratios.

Consider the arenium ion formed by the attack of $H^+$ on a benzene ring. Analysis by nmr spectroscopy suggests the charge on the ring is not evenly distributed between the *para* and the 2 *ortho* positions and that it is instead more heavily concentrated at the *para* position as shown in figure 12 [38].

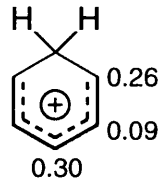



**Figure 12:** Charge distribution in the benzenonium ion

If we accept this as a model for the arenium ion in aromatic substitution then certain points can be made.

(1) An electron withdrawing group in a *para* position relative to the site of electrophilic attack will have a greater destabilising effect than if it were in an *ortho* position. Therefore in the electrophilic substitution of aromatic compounds with an electron-withdrawing substituent, the *ortho:para* ratio is greater than 2 : 1, though *meta* substitution obviously still dominates. For example, in the chlorination of nitrobenzene by hypochlorous acid, the observed *ortho:para* ratio is 11.8 : 1 [39].

(2) An electron-releasing substituent in a *para* position relative to the site of electrophilic attack should have a greater stabilising effect than if it were in an *ortho* position. Therefore in reactions of high selectivity, where the arenium ion provides a satisfactory model for the transition state, electron releasing substituents should result in *ortho:para* ratios lower than 2 : 1. For example, in the bromination of toluene with molecular bromine, a reagent of relatively low reactivity, the observed *ortho:para* ratio is 1 : 2 (see Table 2)

(3) When both the electrophile and aromatic are of high reactivity the transition state occurs earlier on the reaction coordinate and there is less extensive deformation of the aromatic system than in the arenium ion. The relative rates of substitution at the *ortho* and *para* positions should be governed approximately by the relative electron densities at these positions in the unperturbed molecule. For substituents such as methyl it is thought that the *ortho* position should be more negatively polarised than the *para* (due to

field effects diminishing with distance) and it is therefore understandable that toluene gives *ortho:para* ratios greater than 2 : 1 with unselective reagents.

When the *ortho-para*-directing group has an unshared pair then there is another effect that increases the amount of *para* product at the expense of *ortho.* Returning to figure 7, it can be seen that the resonance form, of the arenium ion leading to *ortho* substitution, with the charge delocalised to Z has an *ortho*-quinonoid structure whereas the analogous resonance form, of the arenium ion leading to *para* substitution, has a *para*-quinonoid structure. As *para*-quinones are known to be more stable than their *ortho* isomers it is reasonable to assume the latter resonance form is more stable than the former and that it makes a greater contribution to the resonance hybrid leading to the arenium ion for *para* substitution being more stable than that for *ortho* substitution.

#### 2.3.7.5 The Effects of Solvent and Temperature

There are few generalisations that can be made about solvent and temperature effects on the *ortho:para* ratio. Raising the temperature of a reaction should however reduce the selectivity and result in the *ortho:para* ratio moving towards the statistical value of 2 : 1. The solvent can also effect the reactivity and hence the selectivity of the electrophile and this in turn can effect the *ortho:para* ratio by altering the electronic structure of the transition state as described previously. Brominations in particular appear to be very solvent sensitive.

## 2.4 Reagents for Aromatic Electrophilic Bromination

There are a great number of reagents that have been used to effect the bromination of aromatic rings. Some of the more common examples are molecular bromine (with or without catalysis), *N*-bromoamides (especially NBS), quaternary ammonium polyhalides, hypobromous acid and interhalogen compounds.

### 2.4.1 Bromination by Molecular Bromine

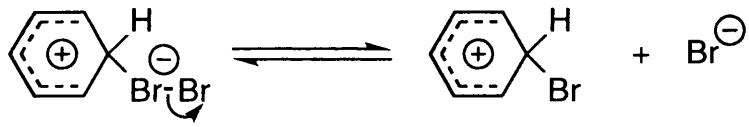
Molecular bromine has been very extensively used as a brominating reagent, probably due to its relatively high selectivity, ease of handling and wide scope of application. These brominations have been carried out in a large range of solvents, e.g.

acetic acid, trifluoroacetic acid, superacids, nitromethane, chloroform, carbon tetrachloride, dimethylformamide, sulphur dioxide, water and sulphuric acid.

The reaction is always first order with respect to the aromatic, and at least first order with respect to $Br_2$ though higher orders are commonly observed. For example, the full expression for bromination in acetic acid is given by the equation below[40].

$$\text{Rate} = k_1[\text{ArH}][\text{Br}_2] + k_2[\text{ArH}][\text{Br}_2]^2 + k_3[\text{ArH}][\text{Br}_2]^3$$

The second-order term represents the unassisted heterolysis shown




Higher order terms may represent the assistance by another molecule in breaking the Br-Br bond in the intermediate shown or they may represent polarisation of one molecule of $Br_2$ by another to give, for example, $Br^{\delta+}\cdots Br_3^{\delta-}$ prior to attack on the aromatic.

The reaction order is reduced by the addition of water, salts or acids which increase the polarity of the medium and permit unassisted heterolysis. The higher order terms are also found to be less significant for more reactive aromatics, since for these substitution is more readily achieved by the weaker electrophiles.

Hydrogen bromide is the byproduct of bromination with molecular bromine and it can interfere with the kinetics by removing $Br_2$ as $Br_3^-$, which is a much less reactive electrophile. The hydrogen bromide may also protonate the aromatic thereby reducing its reactivity.

The solvent used for the reaction can have a marked effect on the selectivity. For example, the bromination of *p*-cresol in superacid results in extensive bromination *meta* to the hydroxyl group[41]. This is thought to occur by the mechanism shown in figure 13.

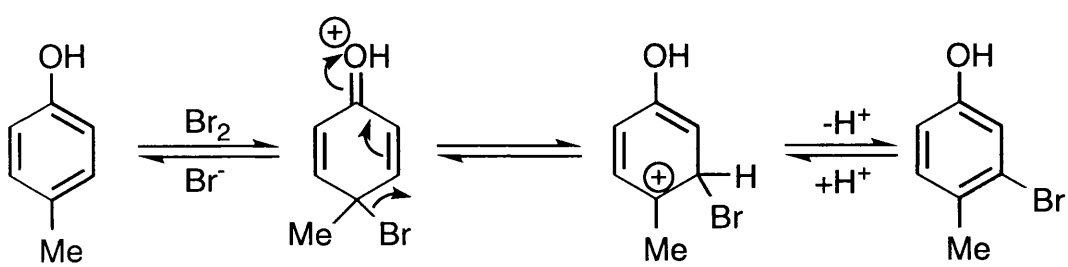



**Figure 13:** Mechanism of bromination *meta* to the hydroxyl group in *p*-cresol

The *para*-directing properties or the hydroxyl group result in bromination *ipso* with respect to the methyl group to give the conjugate acid of 4-bromo-4-methylcyclohexa-2,5-dienone. Under the strongly acidic conditions the hydrogen bromide is only slightly dissociated and is not therefore so readily available to debrominate the bromodienone conjugate acid. Bromine atom migration is therefore able to compete with debromination to give the arenium ion that would arise from direct attack by the bromine *meta* to the hydroxyl group. The main evidence to support the initial *ipso* attack is that phenol itself cannot be *meta*-brominated, under these conditions, and therefore a *para* substituent must be present to facilitate *ipso* attack.

The use of other solvents also produces a marked effect on the selectivity of the reaction with bromination in liquid $SO_2$[42] and trifluoroacetic acid[43] being reported to be particularly selective.

### 2.4.2 Bromine in the Presence of a Catalyst

A large number of catalysts have been used in conjunction with molecular bromine to effect aromatic bromination.

One of the most common catalysts is iodine which is generally more effective than either $AlCl_3$ or $PCl_3$ in catalysing bromination by molecular bromine. When iodine is added it results in the formation of iodine bromide as shown below

$$I_2 + Br_2 \rightleftharpoons 2IBr$$

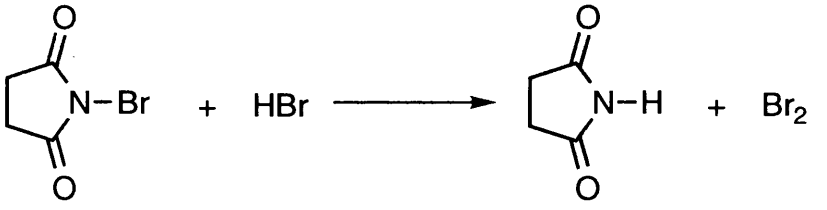
The iodine bromide formed is more efficient than molecular bromine in the aromatic substitution reaction.

Another commonly used catalyst is iron. The real catalyst is not however the iron itself, but the ferric bromide formed in small amounts from the reaction between the iron and the bromine. With this or any other Lewis acid catalyst, such as $AlCl_3$,the attacking entity may be $Br^+$, formed by $FeBr_3 + Br_2 \rightarrow FeBr_4^- + Br^+$ or it may just be a form of $Br_2$ polarised by the catalyst.

Other catalysts include $TiCl_4$ which results in bromination *ortho* to a hydroxyl group[44], presumably due to some sort of complex formation, and thallium triacetate which results mainly in *para* bromination[45].

### 2.4.3 *N*-Bromoamides

Another class of compounds that have been extensively used as reagents for aromatic bromination are *N*-bromoamides with by far the most widely utilised reagent from this class being NBS. This reagent is thought to function by providing a low steady state concentration of $Br_2$ by the reacting with HBr, produced as the side product of bromination, as shown below in scheme 1.




**Scheme 1**

Again a range of solvents have been used in conjunction with NBS. For example, the use of NBS in DMF is reported to be a selective method for the monobromination of activated aromatic compounds[46].

Other more recent developments include the use of ultrasonication[47] or a zeolite catalyst[48] to increase the efficiency of NBS as a reagent for aromatic bromination.

A common problem with the use of NBS and other *N*-bromoamides, such as 1,3-dibromo-5,5-dimethylhydantoin, as reagents for aromatic bromination is that they also have the potential to carry out benzylic bromination if the aromatic substrate has an alkyl side chain. This can however, be overcome by carrying out the reactions in the absence of light, which prevents the initiation of the benzylic bromination reaction.

Another *N*-bromoamide which is a useful reagent is dibromoisocyanuric acid (DBI). In $H_2SO_4$ this is a very powerful reagent, useful for the bromination of aromatics with strongly deactivating substituents[49].

### 2.4.4 Quaternary ammonium polyhalides

The use of quaternary ammonium polyhalides in aromatic bromination has been extensively researched by Kajigaeshi *et al.* Reagents such as benzyltrimethylammonium tribromide ($BTMA^+Br_3^-$), tetrabutylammonium tribromide ($TBA^+Br_3^-$) and benzyltrimethylammonium chlorobromate ($BTMA^+Br_2Cl^-$) have been shown to be selective reagents for the bromination of activated aromatic compounds such as substituted anilines[50], acetanilides[51], phenols[52] and aromatic ethers[53]. Three representative examples are shown below in figure 14.

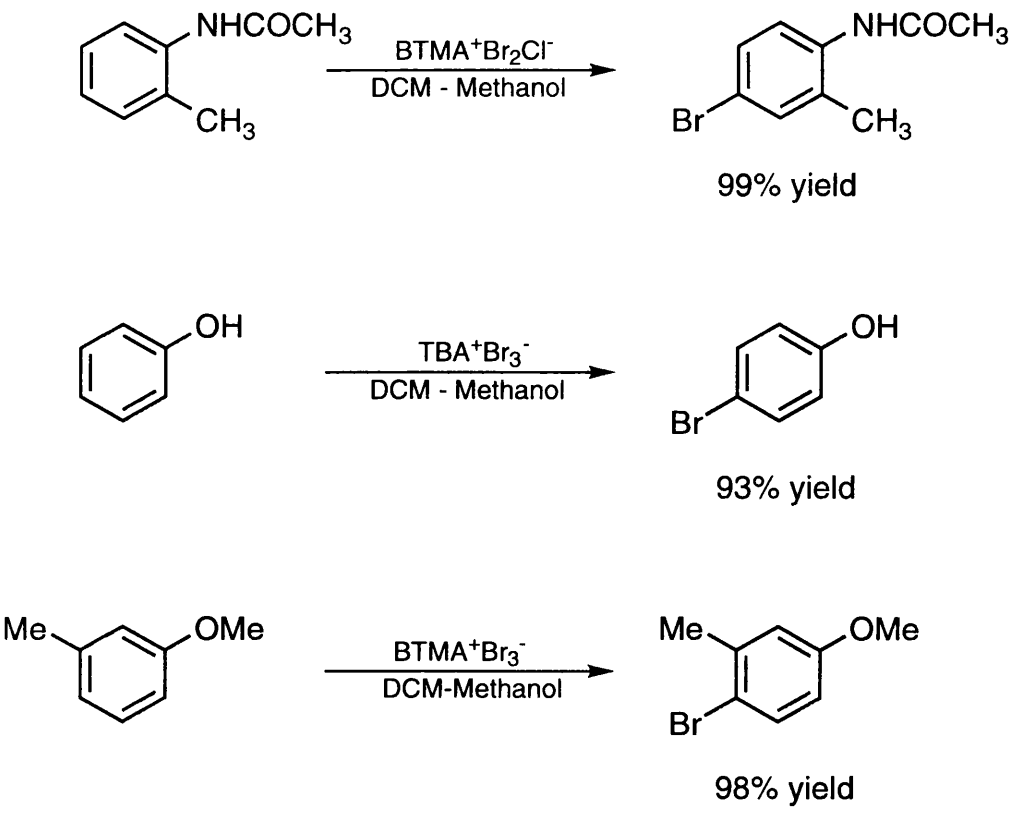



**Figure 14:** Examples of results obtained in brominations by quaternary ammonium polyhalides

In conjunction with an equimolar amount of the Lewis acid $ZnCl_2$, $BTMA^+Br_3^-$ can also effectively brominate less reactive aromatic compounds, such as alkyl benzenes[54].

As well as displaying good selectivity these compounds also have the useful property of being crystalline which can make them easier to handle than liquid bromine.

### 2.4.5 Hypobromous acid

Hypobromous acid in the presence of mineral acid is a very effective brominating reagent which is more reactive than molecular bromine. Acidic conditions are essential for the reactivity as a solution of HOBr, buffered in the range pH 7-8, has been shown to be 2000 times less effective than molecular bromine[55]. The actual effective electrophile is proposed to be $[H_2OBr]^+$ with the reaction following two possible paths (see figure 15).

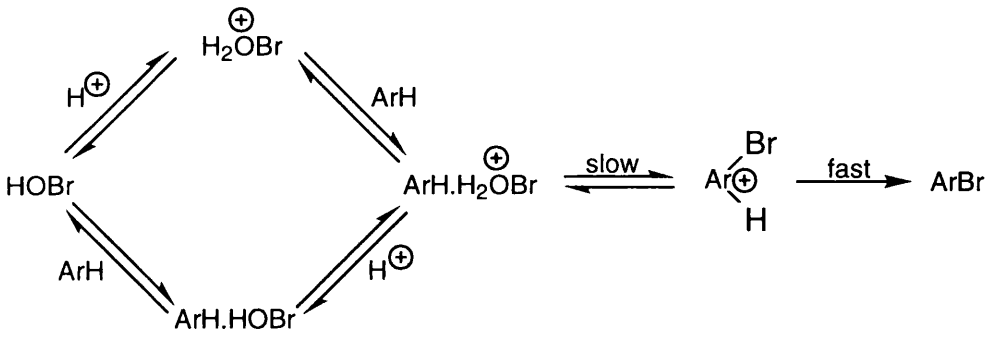



**Figure 15:** Mechanistic pathways of bromination using hypobromous acid[56]

Whether the HOBr itself or a complex of the aromatic compound with HOBr is protonated depends upon the acidity of the medium and the reactivity of the aromatic. The upper path is followed for less reactive aromatics and in more acidic media.

Bromination with potassium bromate ($KBrO_3$) in $H_2SO_4$ is a particularly useful method for the bromination of unreactive aromatics in high yield[57]. Hypobromous acid is again believed to be involved and is formed via the loss of oxygen as water, following protonation, giving $[H_2OBr]^+$ the electrophile.

### 2.4.6 Interhalogen Compounds

Bromine chloride , BrCl, and bromine fluoride, BrF, are both more polar than molecular bromine, due to the greater electronegativity of chlorine and fluorine in comparison with bromine, and consequently both of these interhalogen compounds are more reactive brominating reagents than molecular bromine itself.

Bromine fluoride can be formed by passing 10% $F_2$ in $N_2$ into a solution of $Br_2$ in chloroform at -75°C. This reagent is effective at low temperatures and is sufficiently reactive to brominate 1,3-dinitrobenzene in a 95% yield[58].

Bromine chloride may be formed in the bromination by $Br_2$ and $SbCl_5$ in $CCl_4$. This reagent gives high *para* selectivities and is also useful for the bromination of unreactive aromatics[59].

# 3

# Introduction to Benzylic Bromination

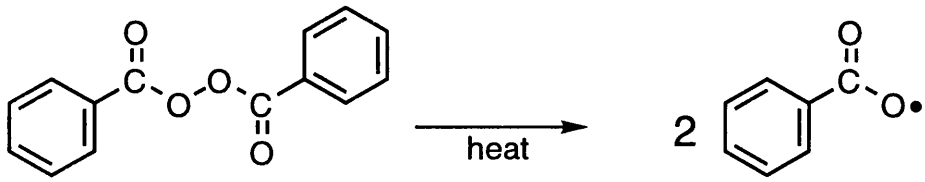
## 3.1 General Features of Free Radical Reactions

Benzylic bromination occurs through a free radical chain reaction. Like all other free radical chain processes it involves 3 main steps; initiation, propagation and termination.

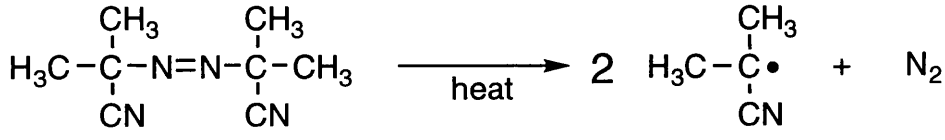
### Initiation

This is the process whereby the formation of free radicals occurs. This almost always involves the homolytic cleavage of a bond.


The bond cleavage may be induced by heat or light, depending on the type of bond involved. Thermal cleavage is common for acyl peroxides, such as benzoyl peroxide, and azo compounds, such as azo-bis-isobutyronitrile (AIBN), see figure 16.



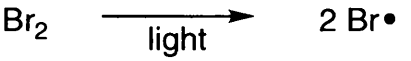

Benzoyl peroxide




AIBN

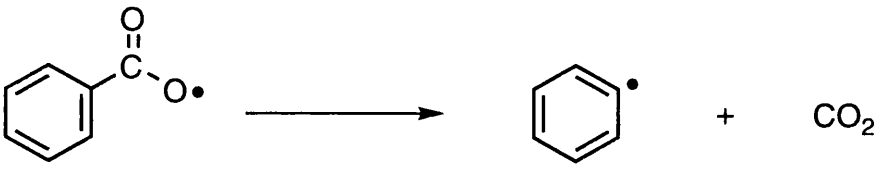
**Figure 16:** Thermal cleavage of benzoyl peroxide and AIBN

The energy of light, with wavelength in the range 600-300 nm, is the same order of magnitude as covalent bonds energies. Light can therefore be used to cleave bonds. A good example is the photochemical cleavage of $Br_2$ (see scheme 2).




**Scheme 2**

Initiator radicals may also be formed by the cleavage of other radicals. For example, see scheme 3.




**Scheme 3**

**Propagation**

When a radical (which has an odd number of electrons) reacts with a molecule (which has an even number), the total number of electrons in the products must be odd. The product of the step may be one particle, in which case it must be another free radical. For example, see scheme 4.

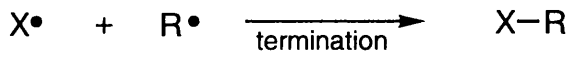

**Scheme 4**

The product may also consist of 2 particles, in which case one must be another free radical. For example,


This type of step is called a propagation step since the newly formed radical can now react with another molecule to produce another radical and so on until termination of the chain occurs.

### Termination

This step involves the destruction of free radicals. This most commonly happens when 2 radicals, which may be the same or different, combine by forming a new bond.




The destruction of the each free radical prevents further propagation reactions and terminates the chain reaction.

## 3.2 Mechanism of Benzylic Bromination with Bromine

The mechanism of benzylic bromination with molecular bromine when light is used to initiate the reaction is given below (see figure 17)[60].

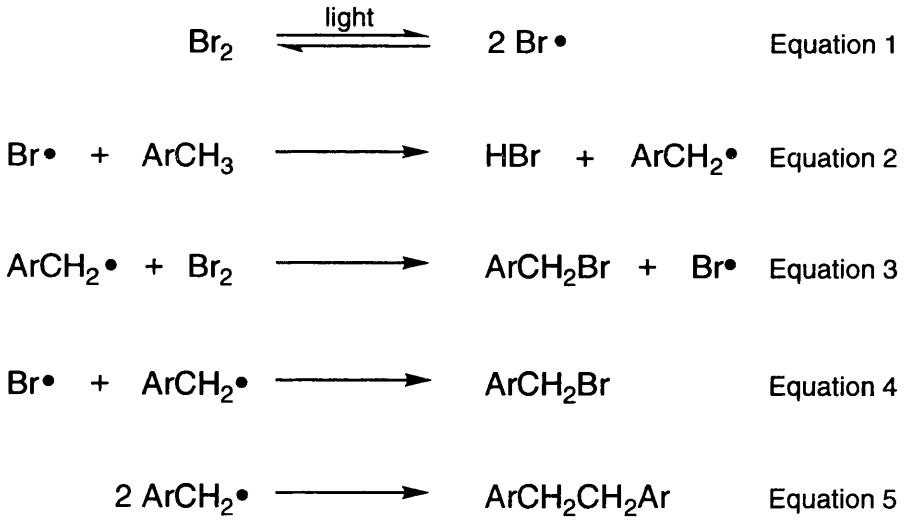



**Figure 17:** Mechanism of benzylic bromination with $Br_2$

Equation 1 shows the initiation of the reaction by photochemical homolysis of the Br-Br bond. Equations 2 and 3 represent the propagation steps. The three possible termination steps are shown by the reverse of equation 1 and equations 4 and 5. Which termination step is most important depends on the relative steady state concentrations of the chain-carrying free radicals. These steady state concentrations are determined both by the reactivities of the free radicals in their respective chain-propagating reactions as well as the relative concentrations of the reactants ArH and $Br_2$.

### 3.3 Selectivity of Hydrogen Atom Abstraction

The important step with regards to the selectivity of the bromination is the abstraction of a hydrogen atom from the aromatic compound by the bromine atom (equation 2). This step controls the selectivity as the carbon, from which the hydrogen atom is abstracted, is the site that is ultimately brominated.

Which hydrogen atom is abstracted is determined by the relative stability of the radical formed. The more stable the resultant radical, the greater the ease with which the hydrogen atom will be abstracted.

Dissociation energies (*D* values) of R-H bonds provide a measure of the relative stabilities of the free radicals R. The higher the *D* value, the less stable the radical. Some representative values are shown in table 3[61].

| R | *D*, kcal/mol | R | *D*, kcal/mol |
|---|---|---|---|
| Ph• | 110 | $Me_2CH$• | 95 |
| $CH_2$=CH• | 108 | $Me_3C$• | 92 |
| Me• | 104 | $CH_2$=$CHCH_2$• | 89 |
| Et• | 98 | HCO• | 87 |
| Pr• | 98 | $PhCH_2$• | 85 |

**Table 3:** $D_{296}$ values for some R-H bonds

For aromatic compounds with alkyl side chains (the class of compound with which this thesis is concerned) the preferential position of abstraction is on the side chain, α to the ring, as this generates the most stable radical. The stability of the benzyl radical has been attributed to resonance stabilisation (see figure 18).

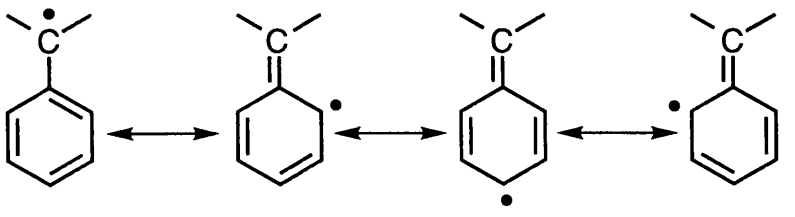


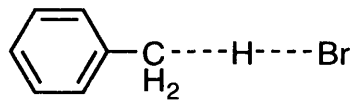
**Figure 18:** Resonance stabilisation of the benzyl radical

Aromatic hydrogens are seldom, if ever, abstracted if there are aliphatic ones to compete because the *D* value for a Ph-H bond is always higher than that for an alkyl-H bond.

### 3.4 Polar Effects on Selectivity of Hydrogen Atom Abstraction

If an aromatic compound contains more than one benzylic group then there is another selectivity question, from which of these groups will the bromine atom preferentially abstract a hydrogen atom. This is controlled by the nature of the other ring substituents and their position relative to the benzyl groups.

Consider the transition state formed during abstraction of a hydrogen atom from the methyl group of a substituted toluene by a bromine atom. It may be represented, assuming it is linear, as shown below.




Since bromine is more electronegative than carbon there is a separation of charge in the transition state. A partial negative charge develops on the bromine and a partial positive charge develops on the carbon. The transition state may be represented by the resonance forms shown in figure 19.

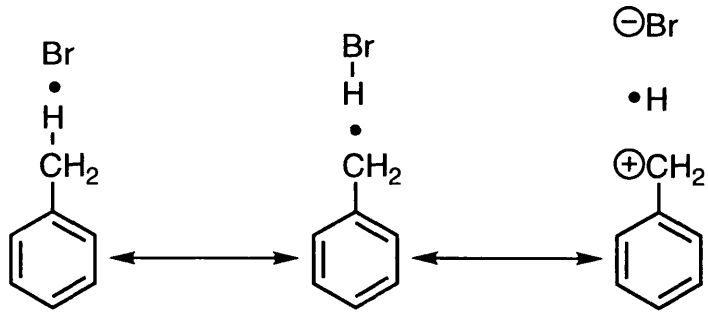



**Figure 19:** Resonance forms of the transition state for hydrogen atom abstraction by a bromine atom[62]

#### 3.4.1 Substituent Effects on Benzyl Cation Stability and Transition State Polarity

Electron donating substituents on the ring are able to stabilise positive charge formation on the benzylic carbon. Consider toluene, substituted in the *meta* and *para*

positions with a substituent, Z, that has a lone pair. The resonances forms for the benzyl cation in both cases is shown in figure 20.

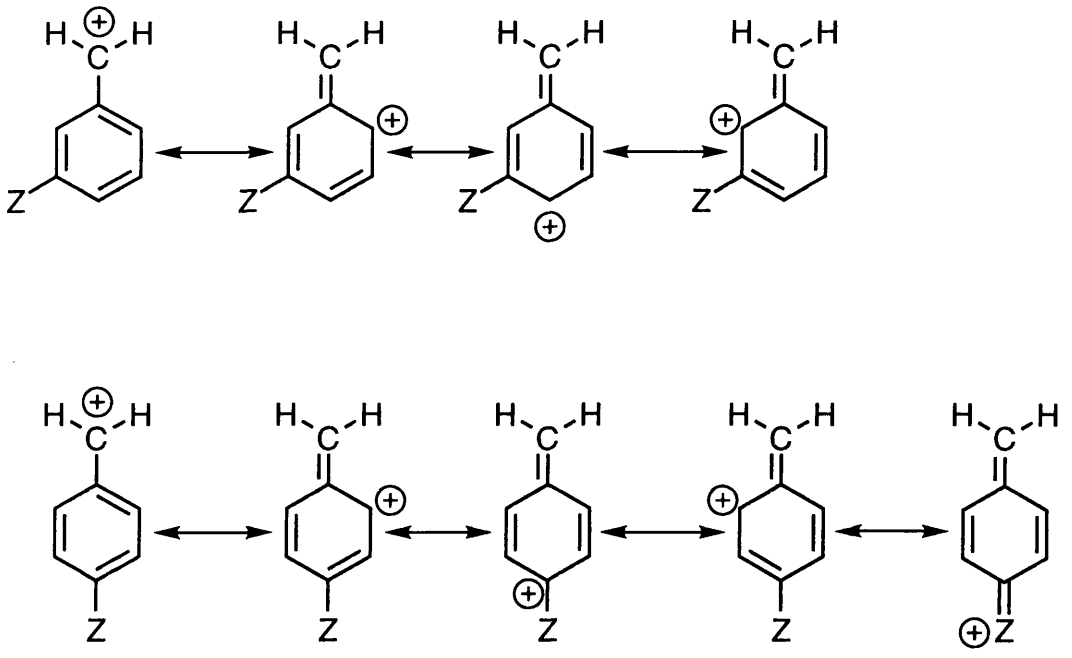


**Figure 20:** The resonances forms for the benzyl cations of toluene substituted at the *meta* or *para* position with a substituent that has a lone pair of electrons

There is an extra resonance form for the *para* substituted cation, where the charge is delocalised to Z, and this increases the stability, not only because there is an extra resonance form but because it is more stable and makes a greater contribution to the hybrid than the others. Therefore an electron-donating substituent is better able to stabilise positive charge formation at the benzylic carbon if the two groups are *para*, rather than *meta*, to each other.

Electron-withdrawing groups, such as $NO_2$, destabilise positive charge formation at the benzylic carbon. Consider toluene, substituted in the *meta* and *para* positions with an electron withdrawing group, Y. The resonances forms for the benzyl cation in both cases is shown in figure 21.

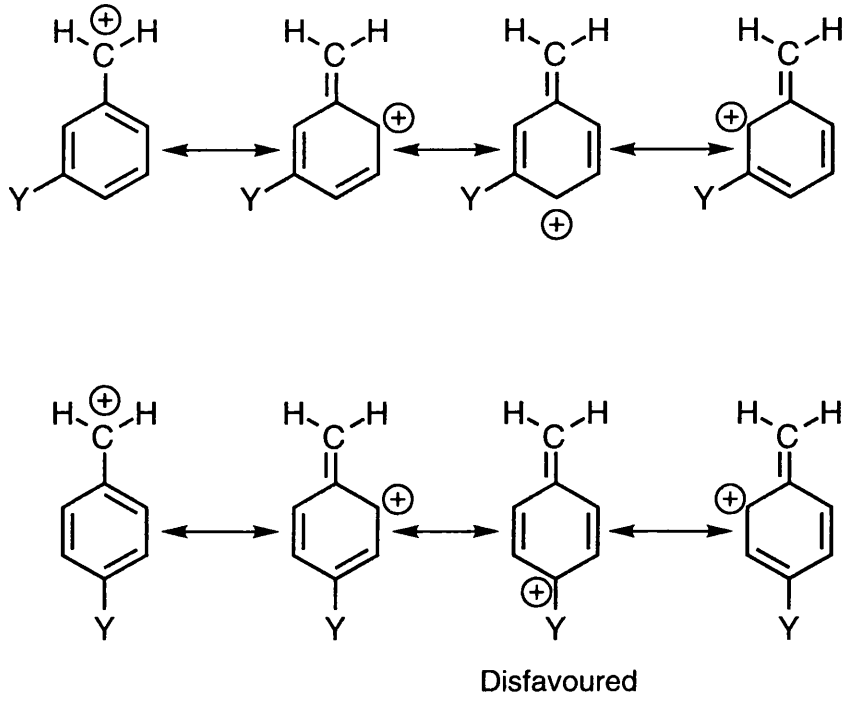



**Figure 21:** The resonances forms for the benzyl cations of toluene substituted at the *meta* or *para* position with a substituent that is electron-withdrawing

Though an electron-withdrawing group destabilises all the resonance forms shown, it particularly destabilises the resonance form for the *para* substituted compound where the charge is on the carbon adjacent to the electron withdrawing group. Therefore, though both the cations are destabilised by the electron withdrawing group, the *para* substituted cation is destabilised to a greater extent than the *meta* substituted cation.

The more stable the benzylic cation the greater the contribution of the charge seperated resonance form to the transition state for hydrogen atom abstraction from the methyl group of a substituted toluene by a bromine atom. The transition state accordingly assumes more polar character involving greater C-H bond breakage with less H-Br bond formation. This effects both the enthalpy and entropy of activation.

### 3.4.2 The Effect of Transition State Polarity on the Enthalpy and Entropy of Activation

Consider the two reactions shown in figure 22.

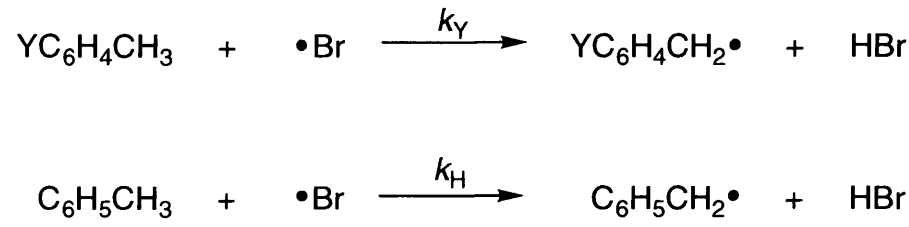



**Figure 22:** Illustration of the meaning of the terms, $k_Y$ and $k_H$, used in table 4

Some sample values of the relative rates of the two reactions ($k_Y/k_H$) are shown in the table 4 below[63].

| Reaction temperature | $k_Y/k_H$ | | | | |
|---|---|---|---|---|---|
| | *p*-$OCH_3$ | *p*-$CH_3$ | *m*-$CH_3$ | H | *m*-Cl |
| 10 °C | 9.00 | 1.82 | 0.93 | 1.00 | 0.33 |
| 60 °C | 10.6 | 2.31 | 1.07 | 1.00 | 0.26 |

**Table 4:** Relative reactivities of substituted toluenes toward bromine in $CCl_4$

As the site of hydrogen atom abstraction is controlled by kinetics it follows that the relative rates of the two reactions shown depends upon the difference between the free energies of activation for the two reactions, $\Delta\Delta G^*_{Y\text{-}H}$, which in turn depends on the difference between the enthalpies of activation, $\Delta\Delta H^*_{Y\text{-}H}$, and the differences between the entropies of activation, $\Delta\Delta S^*_{Y\text{-}H}$. The values for these latter two differential activation parameters, for the substituted toluenes shown in Table 4, are shown in Table 5.

| Parameter | *p*-$OCH_3$ | *p*-$CH_3$ | *m*-$CH_3$ | H | *m*-Cl |
|---|---|---|---|---|---|
| $\Delta\Delta H^*_{Y\text{-}H}$ | 0.73±0.04 | 0.96±0.06 | 0.54±0.02 | 0 | -1.09±0.08 |
| $\Delta\Delta S^*_{Y\text{-}H}$ | 6.90±0.35 | 4.57±0.27 | 1.74±0.07 | 0 | -6.04±0.42 |

**Table 5:** Differential activation parameters (kcal/mol) for the bromination of substituted toluenes in $CCl_4$[63]

The enthalpy of activation is governed by the degree of C-H bond breakage the toluene undergoes and is partly modified by the stability of the developing carbocation. The electron donating substituents result in a more polar transition state where there is greater C-H bond cleavage than for toluene and therefore $\Delta\Delta H^*_{Y\text{-}H}$ is positive. Conversely electron-withdrawing substituents result in a less polar transition state

where there is less C-H bond cleavage than for toluene and therefore $\Delta\Delta H^*_{Y\text{-}H}$ is negative. Note that although *p*-methoxytoluene would suffer greater bond cleavage than *p*-xylene, the resulting carbocation is better stabilised by the methoxy group and so the former compound requires a smaller enthalpy of activation. It should also be noted that all the values of $\Delta\Delta H^*_{Y\text{-}H}$ are relatively small (less than 1 kcal/mol) which is probably a result of the two opposing effects being comparable in magnitude.

The entropy of activation is primarily related to the differences in number and character of the degrees of freedom between the transition state and reactants[64].

Firstly, as mentioned previously the more polar the transition state the greater the C-H bond breakage with less accompanying H-Br bond formation. This results in the three components in the transition state ($ArCH_2$, H and Br) behaving more like three isolated bodies which should have greater translational degrees of freedom. This effect increases the entropy of the transition state.

However, as the polarity of the transition state increases, the vibrational degrees of freedom for the benzylic C-H bond are reduced and conjugation in the benzylic cation increases the Ph-$CH_2$ bond order thus removing the rotational degree of freedom between the ring and the $CH_2$ group. There should also be attraction between the ion pair, though this effect is reduced where there is delocalisation of the charge on the benzylic carbon to electron-donating substituents on the other side of the ring as this increases the distance between the charges. These effects all reduce the entropy of the transition state.

Since the order of contribution to entropy is translation >>> rotation >> vibration, the increase in the translational degrees of freedom must compensate for the negative entropy effects and be the controlling factor in determining the entropy of activation in benzylic bromination.

In conclusion, electron donating substituents increase the rate of hydrogen atom abstraction by making the transition state more polar. The increased polarity results in an increase in the entropy of the transition state (due to increased translational degrees of freedom) and consequently a reduction in the free energy of activation. Electron-withdrawing substituents decrease the rate of hydrogen atom abstraction by lowering the polarity and the entropy of the transition state thus increasing the free energy of activation[63].

The substituent effects described above are obviously very similar to those described for aromatic electrophilic bromination. However the effect of the substituents is much smaller for benzylic bromination than for aryl bromination where an intermediate with a full positive charge is involved.

## 3.5 Proposed Mechanisms of Benzylic Bromination by NBS

The first reported method for the direct introduction of a bromine atom into the allylic position of an alkene was published by Wohl in 1919[65]. Wohl's paper, although unusual, did not attract much attention at the time, partly because the reagent used, *N*-bromoacetamide was not readily available, but primarily because his work concentrated on the theoretical rather than the practical aspects of the reaction[66]. It was not until 1942 that Ziegler and his co-workers published their extensive research on the allylic bromination of alkenes[67], in which they introduced the unique brominating agent *N*-bromosuccinimide (NBS). Their work concentrated on the preparative side of the reaction and their findings were immediately utilised by chemists all round the world. The reaction has since become known as the Wohl-Ziegler reaction.

Following the discovery and development of the Wohl-Ziegler reaction there was considerable controversy surrounding the mechanism of the reaction. The first radical chain mechanism, proposed in 1944 by Bloomfield[68], involved succinimidyl radicals in the hydrogen atom abstraction propagation step (see figure 23).

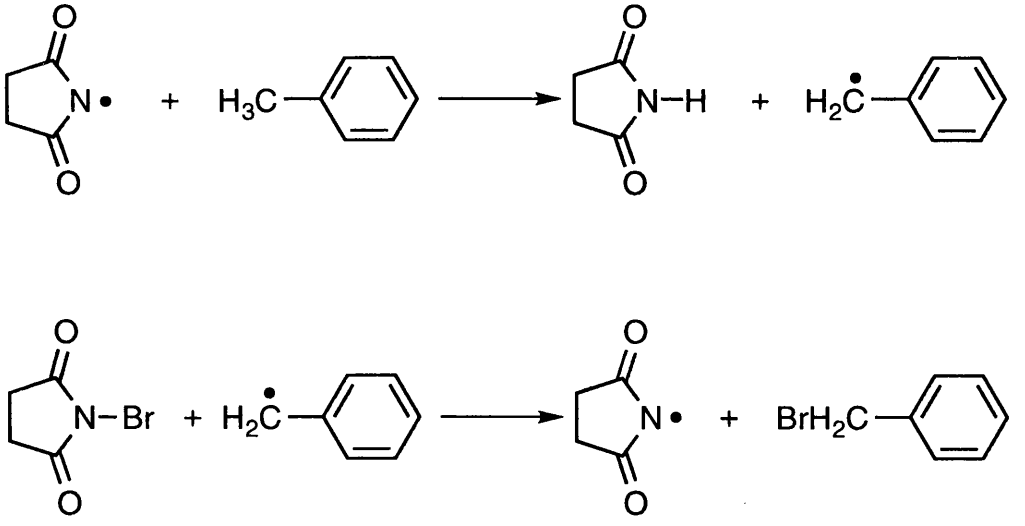



**Figure 23:** The Bloomfield mechanism of benzylic bromination with NBS

This scheme initially provided an appealingly direct route to the observed products of the reaction, benzyl bromides and succinimide, and was at the time widely accepted.

In 1953 however, an alternative scheme was proposed by Goldfinger, in connection with studies on the analogous chlorination with *N*-chlorosuccinimide, which involved a bromine atom as the hydrogen atom abstracting radical in the

propagation step[69]. In this mechanism, NBS provides and maintains a low molecular bromine concentration via its rapid ionic reaction with HBr (see figure 24).

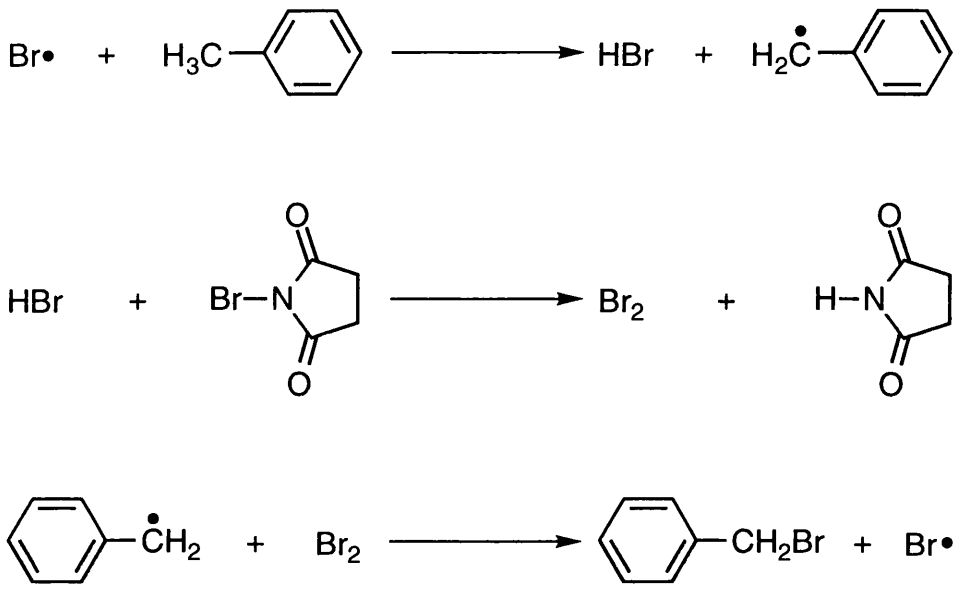



**Figure 24:** The Goldfinger mechanism of benzylic bromination with NBS

Most of the evidence published subsequently has supported the Goldfinger mechanism and the smaller amount of evidence that was initially taken to support the Bloomfield mechanism has now been reconciled with the Goldfinger mechanism. This evidence has came from a variety of investigations.

## 3.6 Evidence to Support the Goldfinger Mechanism

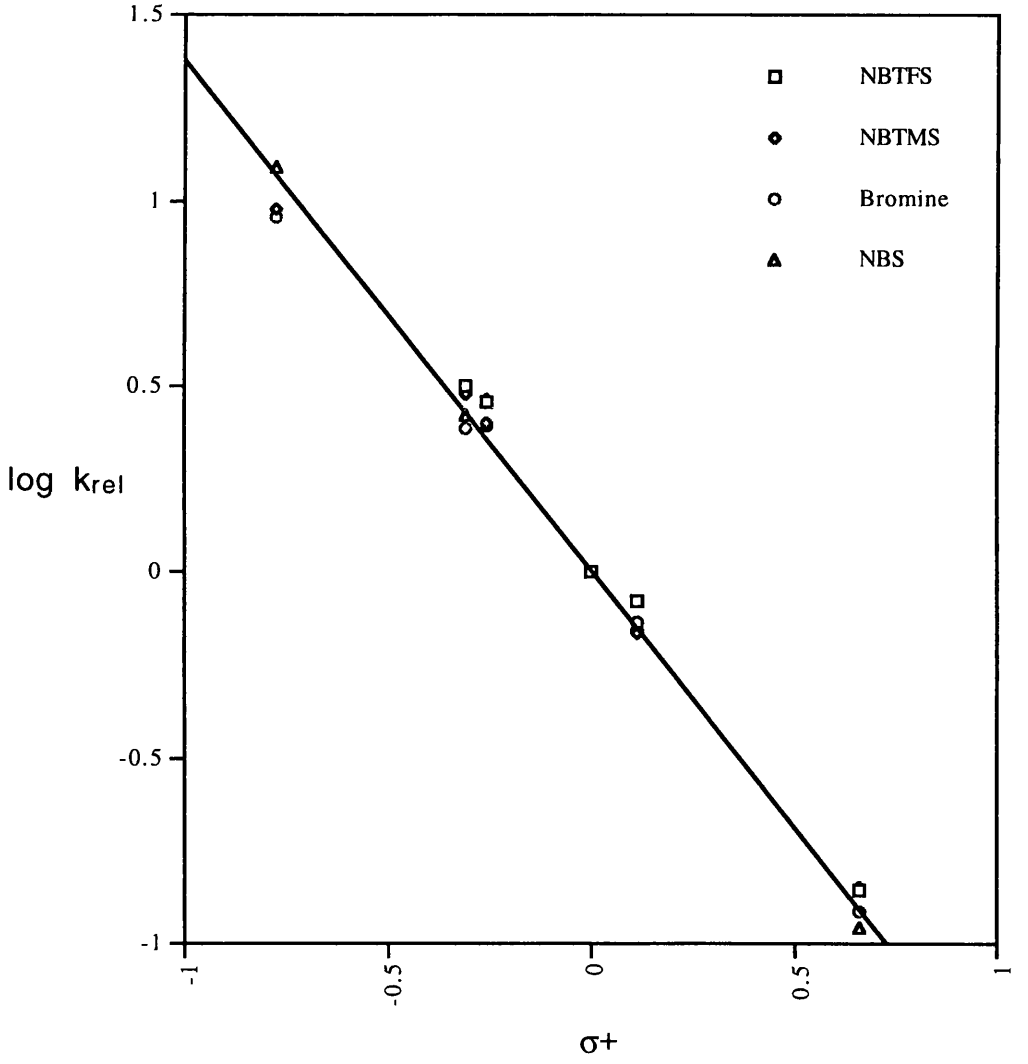
### 3.6.1 Relative Rates of Bromination

Perhaps the most compelling evidence supporting the Goldfinger Mechanism is the similarity observed in relative rates of bromination of alkyl aromatics and substituted toluenes with bromine and with NBS. For example, Pearson and Martin[70] measured the rates, relative to toluene, for hydrogen atom abstraction from a range of substituted toluenes by $Br_2$, NBS, *N*-bromotetrafluorosuccinimide (NBTFS) and *N*-bromotetramethylsuccinimide (NBTMS). A selection of the logarithms of the rates of bromination of *para*-substituted toluenes relative to toluene are shown in table 6.

| Reagent | $OCH_3$ | $CH_3$ | $C(CH_3)_3$ | H | Cl | CN |
|---|---|---|---|---|---|---|
| NBS | 1.093 | 0.418 | 0.464 | 0 | -0.145 | -0.953 |
| NBTFS | not given | 0.500 | 0.457 | 0 | -0.081 | -0.857 |
| NBTMS | 0.980 | 0.480 | 0.402 | 0 | -0.168 | -0.845 |
| $Br_2$ | 0.956 | 0.383 | 0.393 | 0 | -0.138 | -0.914 |

**Table 6**

When the logarithms of the the relative rates (shown in table 6), for all four brominating reagents, are plotted against the $\sigma^+$ values for the substituents, a graph is obtained where the standard deviation of the slope, $\rho$, is less than that for any individual series within the set (see graph 1).




**Graph 1**

This suggests that, under identical reaction conditions, the $\rho$-values for all four brominating reagents are the same. There are two possible explanations for this.

Firstly, that structural changes in the attacking radicals do not affect their sensitivity to electron availability in the substrate, which in terms of the Bloomfield mechanism would mean that the bromine atom and all three succinimidyl radicals showed identical selectivities. Though the range of ρ-values encountered in radical reactions at the side chain is relatively small, it is still somewhat improbable that the bromine atom and the three succinimidyl radicals would show the necessary identical selectivities for this explanation to be vaild. In particular the failure of the four fluorine substituents on the tetrafluorosuccinimidyl radical to alter the selectivity in comparison with the succinimidyl radical would not be in accord with expectations based on similar situations in another systems. For example, perbenzoate and *p*-chloroperbenzoate are known to exhibit sustantially different rates of hydrogen atom abstraction from substituted benzaldehydes[71].

The second, and far more plausible, explanation is that the hydrogen atom abstracting species is the same for all four reagents. As the abstracting radical for molecular bromine is undoubtedly a bromine atom it follows that this must also be the abstracting radical for NBS. This obviously supports the Goldfinger mechanism.

### 3.6.2 The Hydrogen-Abstraction Selectivity of the Succinimidyl Radical

The above evidence suggested that if the Bloomfield mechanism were to be correct then the succinimidyl radical and the bromine atom would have to show nearly identical selectivity in regards to the abstraction of hydrogen atoms from benzylic positions. This was obviously unlikely but until the behaviour of a succinimidyl radical in this regard was determined this possibility could not be completely discounted. However, it has now been demonstrated, by Day, Lindstrom and Skell, that the succinimidyl radical is a radical of low discrimination in hydrogen abstraction reactions, quite different from bromine atoms[72].

In order to investigate the behaviour of the succinimidyl radical, brominations were carried out in the presence of ethylene, which was found to be effective in scavenging both $Br_2$ and bromine atoms by addition to the double bond. DCM, rather than $CCl_4$, was used as the reaction solvent as NBS is more soluble in the former solvent and thus the concentration of NBS relative to $Br_2$ is greater. Under these conditions the role of bromine atoms in the chain reaction is minimised and NBS is the dominant chain carrier.

When 1-bromobutane was brominated under the above conditions the resultant product distribution was found to differ markedly from that obtained in the presence of $Br_2$ (see table 7).

| Abstracting Radical | % abstraction of H• from C4 | % abstraction of H• from C3 | % abstraction of H• from C2 | % abstraction of H• from C1 |
|---|---|---|---|---|
| Br• | 0 | 14 | 85 | 1 |
| succinimidyl | 18 | 44 | 31 | 7 |
| Cl• | 23 | 50 | 22 | 5 |

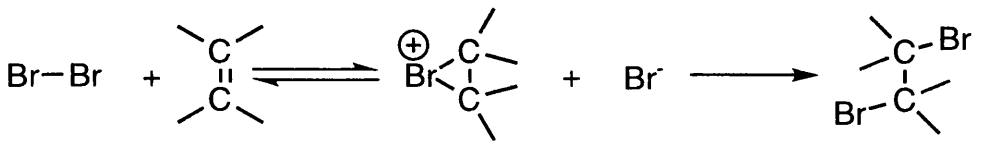
**Table 7:** Observed selectivities of hydrogen atom abstraction from 1-bromobutane.

It can be seen from table that the succinimidyl radical shows a hydrogen-abstraction selectivity that is similar to that of a chlorine atom but different to that of the more selective bromine atom.

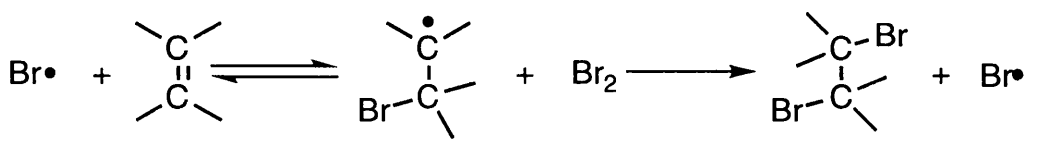
In conclusion, this evidence along with that given above, suggests that the succinimidyl radical is not an intermediate in the Wohl-Ziegler reaction and that the Bloomfield mechanism does not operate under the usual reaction conditions.

### 3.6.3 Allylic Bromination of Alkenes using $Br_2$ in Low Concentration

An objection to the Goldfinger mechanism has been why, if $Br_2$ is the reacting species, does it not add to the double bond of the alkene, by either an ionic or radical route, during allylic bromination with NBS? The apparent reason for this is that the bromine concentration is too low. During the bromination of a double bond, only one atom of an attacking bromine molecule initially becomes attached to the substrate, regardless of whether the addition is electrophilic or free-radical (see figure 25).




Electrophilic Attack




Free-Radical Attack

**Figure 25:** The reversible addition of bromine to a double bond[73]

The other bromine atom comes from another bromine molecule or from another bromide ion. If the concentration is relatively low then the probability of there being an appropriate species in the correct position, relative to the intermediate, for the second step of the reaction to occur, is relatively small. The vast majority of the intermediate in both cases reverts to the alkene, allowing the allylic bromination reaction to be completed successfully.

Evidence for this reversible addition of the bromine atom to double bonds is provided by the observation that, following the bromination of *cis*-hex-3-ene with 0.2 mole equivalents of NBS, under normal benzylic bromination conditions, 85% of the recovered hex-3-ene is converted to the *trans*-isomer[74]. This suggests that during allylic bromination the bromine atom chain carriers can add to, and dissociate from, the olefinic carbon atoms (with resultant *cis* → *trans* isomerization) several times before abstracting a hydrogen atom from the allylic position (see figure 26).

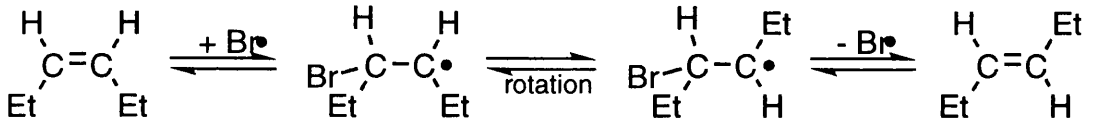



**Figure 26:** *cis* → *trans* isomerization of *cis*-hex-3-ene resulting from the reversible addition of a bromine atom to the double bond

If the bromine atom is the hydrogen abstracting species, in the allylic brominations of alkenes with NBS, then it should be possible to brominate an alkene in the allylic position, without competition from addition, using $Br_2$ in a very low concentration, if the HBr is removed as it is formed so that it is not available to complete the addition step. That allylic bromination under these conditions is possible has been demonstrated by McGrath and Tedder[74] who were able to brominate cyclohexene in the allylic position by the slow even addition of $Br_2$ in a stream of nitrogen (which served to remove the majority of evolved HBr) over a period of several hours.

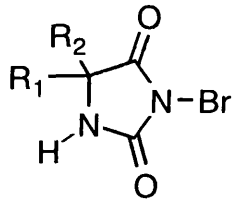
## 3.7 Conclusions about the NBS Mechanism

The evidence given above suggests that, for benzylic bromination with NBS, the chain-carrying radical is the bromine atom and not the succinimidyl radical. This does not however mean that the succinimidyl radical is not formed at all. It is possible that succinimidyl radicals are formed reversibly during the reaction, by radical abstraction of a bromine atom from NBS, followed by the reaction of the resultant succinimidyl radical with $Br_2$[75].

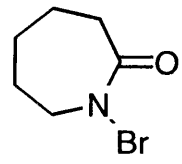
As the Wohl-Ziegler reaction involves abstraction of hydrogen atoms by bromine atoms, the earlier discussions, on the selectivity of hydrogen atom abstraction with molecular bromine as the brominating reagent, are also equally valid for NBS reactions.

### 3.8 Other Reagents for Benzylic Bromination

The lack of specificity of the chlorine atom as a hydrogen atom abstracting radical has made the search for chlorinating agents with more selective abstracting radicals of interest. The bromine atom, on the other hand, is selective in the role of a hydrogen atom abstractor and the use of brominating agents other than the element itself is generally dictated by other factors. Some of these brominating agents, in particular NBS and to a lesser extent other *N*-bromoamides, including various *N*-bromohydantoins and *N*-bromocaprolactam[76], have been used extensively because of their specificity in brominating the allylic position of compounds with double bonds.




an *N*-bromohydantoin




*N*-bromocaprolactam

The mechanism of action and the selectivity of *N*-bromoamide reagents has already been explained. The crystalline nature of these reagents also confers certain handling advantages in comparison with $Br_2$ and this has been another reason for their use.

Most of the other brominating reagents do not have any outstanding advantages over $Br_2$ and NBS and they have been investigated mainly from the standpoint of determining the mechanistic and kinetic characteristics of the free radical chain reactions in which they are involved. Some of the more common of these reagents are listed below.

#### 3.8.1 Polyhaloalkanes

Bromotrichloromethane reacts with alkylaromatics in a free radical process yielding the benzylically brominated substrate and chloroform[77,78]. Hydrogen atom abstraction in this case is performed by the trichloromethyl radical (see figure 27).

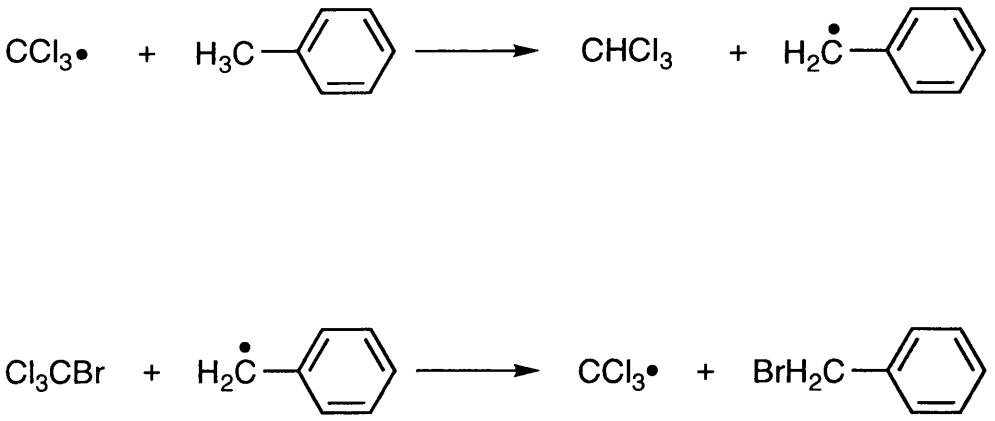
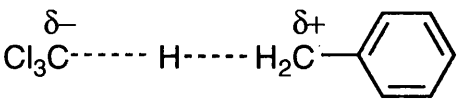


**Figure 27:** Propagation steps for benzylic bromination with bromotrichloromethane

The trichloromethyl radical has hydrogen atom abstracting characteristics that are similar to those of bromine. For example, while benzylic hydrogen atoms are readily abstracted by both bromine atoms and trichloromethyl radicals, only tertiary hydrogens in alkanes are sufficiently reactive to readily participate in chain reactions with either bromine or bromotrichloromethane. Similarities are also observed in the reactivities of the benzylic hydrogens of substituted toluenes towards attack by bromine atoms and by trichloromethyl radicals. A far better linear correlation is found when the logarithms, of the relative reactivities of substituted toluenes towards attack by the trichloromethyl radical, are plotted against the Brown and Okamoto $\sigma^+$-values of the substituents than when plotted against the $\sigma$-values[77]. The $\rho$-value, of -1.46 (at 50 °C), thus obtained is very similar to values obtained for both $Br_2$ and NBS[70]. Therefore benzylic hydrogen atom abstractions by trichloromethyl radicals and by bromine atoms are similar in that a significant degree of cationic character develops at the site of hydrogen atom abstraction in the transition state.



Bromotrichloromethane is not however a particularly good reagent for allylic bromination as the trichloromethyl radical adds readily in a non-reversible process to double bonds and the resulting adduct radical on reaction with bromotrichloromethane yields the addition product (see figure 28).

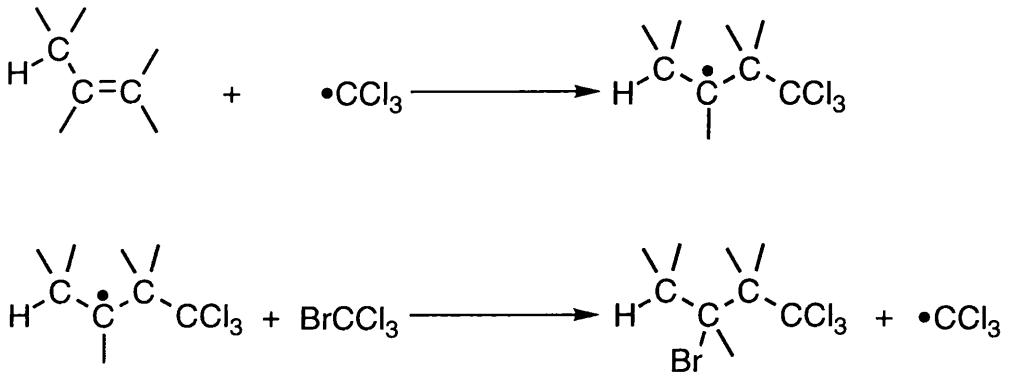


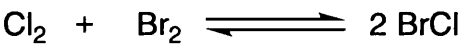
**Figure 28:** Mechanism of addition of $BrCCl_3$ to a double bond

Whilst trichloromethyl radicals do show a propensity for abstracting allylic hydrogens from alkenes, allylic bromination seldom accounts for more than 40% of the reaction[79].

Other polyhaloalkanes have been observed to be more effective in allylic bromination. An example is 1,2-dibromo-1,1,2,2-tetrachloroethane[80], where the hydrogen abstracting radicals are thought to be bromine atoms.

### 3.8.2 Bromochloride

Mixtures of molecular chlorine and bromine contain the mixed halogen bromochloride[81].



This mixed halogen can be used to brominate compounds that are normally resistant to bromination and shows selectivity similar to that of chlorine. The mechanism is therefore believed to involve hydrogen atom abstraction by the reactive chlorine atom (see figure 29).

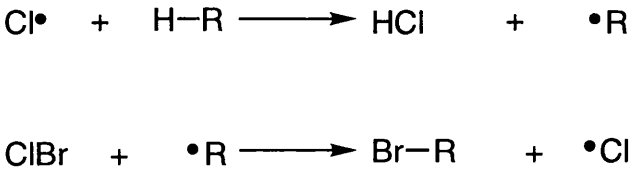


**Figure 29:** Propagation steps for bromination with bromochloride

The attack on the bromochloride by the substrate radical occurs at the bromine end of the molecule. The larger size of the bromine in comparison with the chlorine

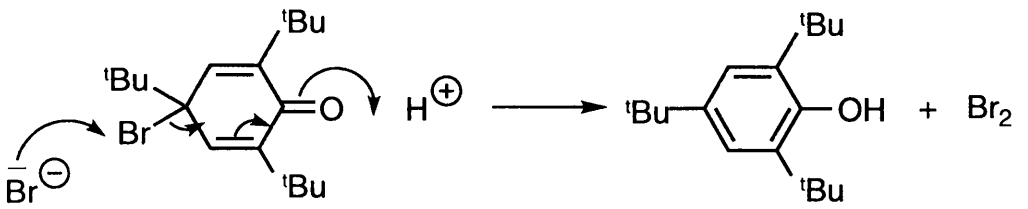
may be partly responsible for this selectivity. Another, perhaps more important factor, is that the greater electronegativity of chlorine, in comparison with bromine, may result in a greater degree of charge separation in the transition state. This is thought to be energetically favourable for the reasons given earlier.

### 3.8.3 Trichloromethanesulphonyl bromide

Trichloromethanesulphonyl bromide can be used to brominate both alkanes and alkyl aromatics. Unlike the analogous reaction with trichloromethanesulphonyl chloride, little if any of the hydrogen atom abstraction is accomplished by the trichloromethanesulphonyl radical[82]. Instead competition reactions indicate that the abstracting species is the trichloromethyl radical. Under the influence of light or peroxides, trichloromethanesulphonyl bromide has been observed to decompose to sulphur dioxide and bromotrichloromethane, which is almost certainly the actual brominating reagent in these reactions.

### 3.8.4 4-Bromo-2,4,6-tri-*tert*-butyl-2,5-cyclohexadienone (BTBC)

This reagent is reported to be a benzylic bromination reagent with similar selectivity but better solubility than NBS[83]. The abstracting radical in this case is again the bromine atom. The mechanism is the same as the Goldfinger mechanism for NBS with the reagent, BTBC, providing and maintaining a concentration of $Br_2$, through reaction with HBr (see scheme 5).




BTBC

**Scheme 5**

The brominating ability of BTBC and other cyclohexadiene reagents[84] derives from the fact that aromaticity is gained by loss of bromine.

# 4

# The Aryl Bromination of Methyl 3,5-dimethoxybenzoate

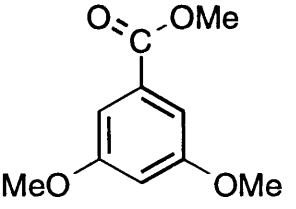
## 4.1 Objectives of Research Project

This project was in collaboration with Zeneca Pharmaceuticals at Macclesfield who have an interest in developing methodology for improving the selectivity of aryl and benzylic bromination in a range of aromatic compounds. In particular, there is an interest in improving the selectivity of those low yielding bromination steps involved in the synthesis of ZD9331, which is a potential drug substance currently under development.

The aim of the project was therefore to investigate the selectivity (or lack thereof) displayed in the bromination of a range of aromatic substrates in order to develop an understanding of the factors that contribute to the determination of this selectivity.

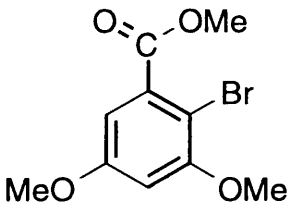
## 4.2 The Use of Molecular Bromine in the Aryl Bromination of Methyl 3,5-dimethoxybenzoate (16).

The initial work that was carried out was an investigation into the potential synthetic utility of molecular bromine, with regards to the regioselective aryl bromination of methyl 3,5-dimethoxybenzoate (**16**).

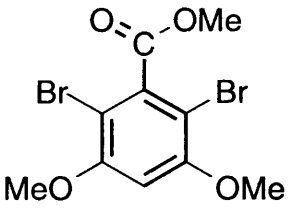



**(16)**

In the first experiments on the bromination of the benzoate **16** using molecular bromine, the standard conditions chosen (6ml dichloromethane, 1 mmol substrate, room temperature, 1 hour reaction time and rapid addition of 1 ml of a 1 M solution of bromine in dichloromethane to the stirring solution) were shown to result in a mixture of three compounds - starting material (**16**), methyl 2-bromo-3,5-dimethoxybenzoate (**17**) and methyl 2,6-dibromo-3,5-dimethoxybenzoate (**18**) in the ratio 1 : 1.06 : 1.




(17)




(18)

## 4.3 Effect of Varying Reaction Parameters on the Selectivity of Bromination

The effect of varying reaction parameters on the product distribution, that resulted from the standard conditions, provided the next area of research.

### 4.3.1 Varying the Number of Mole Equivalents of Bromine used

The first experiments involved varying the number of mole equivalents of bromine used in the reaction. The standard experiment was repeated several times, each time using a different number of mole equivalents of bromine. The resultant product distributions (determined by 200 MHz $^1$H NMR spectroscopy) are shown in figure 30.

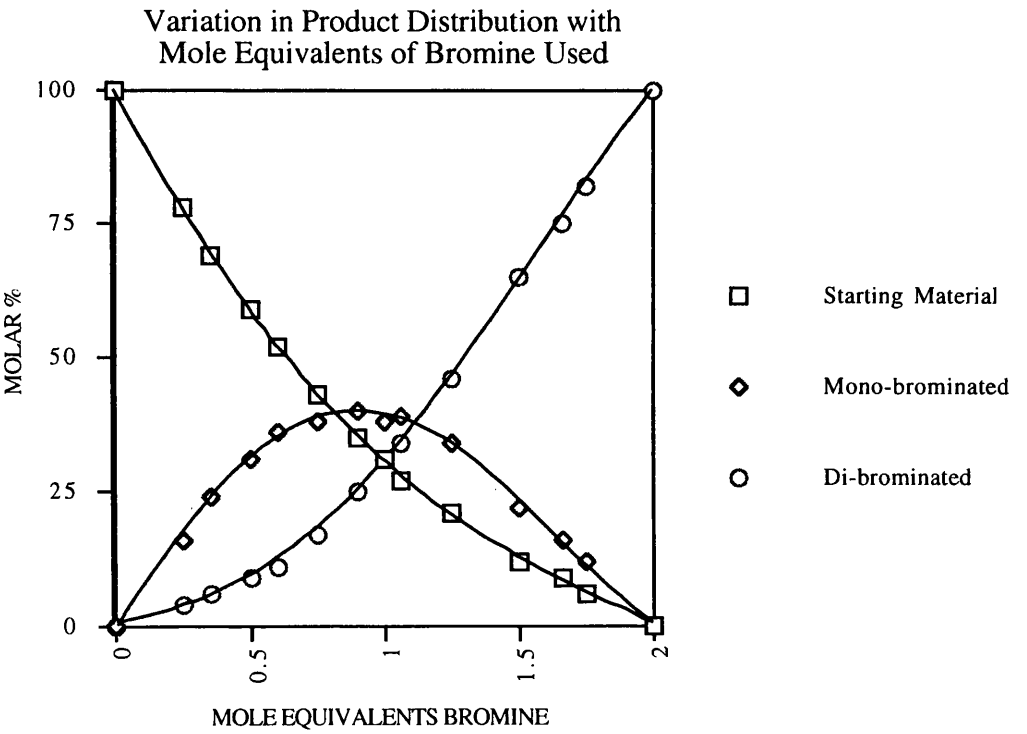



**Figure 30**

Within experimental error this graph is symmetrical about 1 mole equivalent and is very similar to the graph that would have been obtained had the activation energy for the bromination of the benzoate **16**, $E_{a1}$, been equal to the activation energy for the bromination of the 2-bromo compound **17**, $E_{a2}$. This suggests that $E_{a1}$ is only slightly smaller than $E_{a2}$. When more than 2 mole equivalents of bromine were used the excess bromine was not consumed and the product obtained consisted solely of the 2,6-dibromo compound **18**. Interestingly, no C-4 bromination was observed.

Whether these product distributions were the result of thermodynamic or kinetic control was investigated by stirring the 2,6-dibromo compound **18**, formed *in situ* along with hydrogen bromide, in the presence of an equimolar amount of the initial benzoate **16** for one hour. The lack of evidence from $^1$H NMR spectroscopy and TLC, to suggest that any of the 2-bromo compound **17** had been formed, suggests that the equilibration shown below (see figure 31) does not occur to an appreciable extent, within the timescale of the experiment, and that the product distributions obtained are the result of kinetic control.

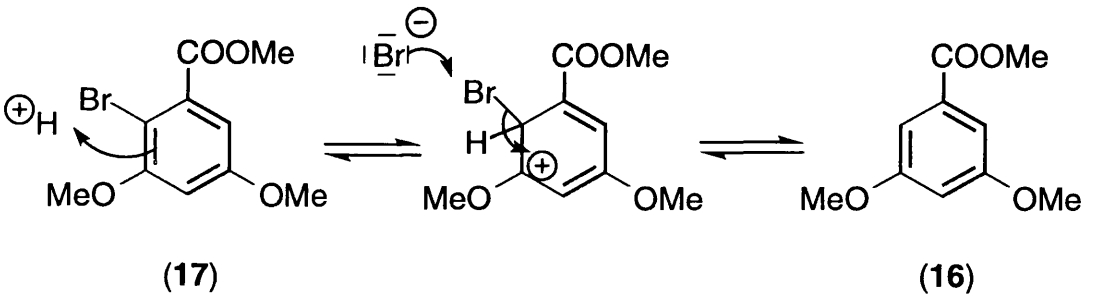
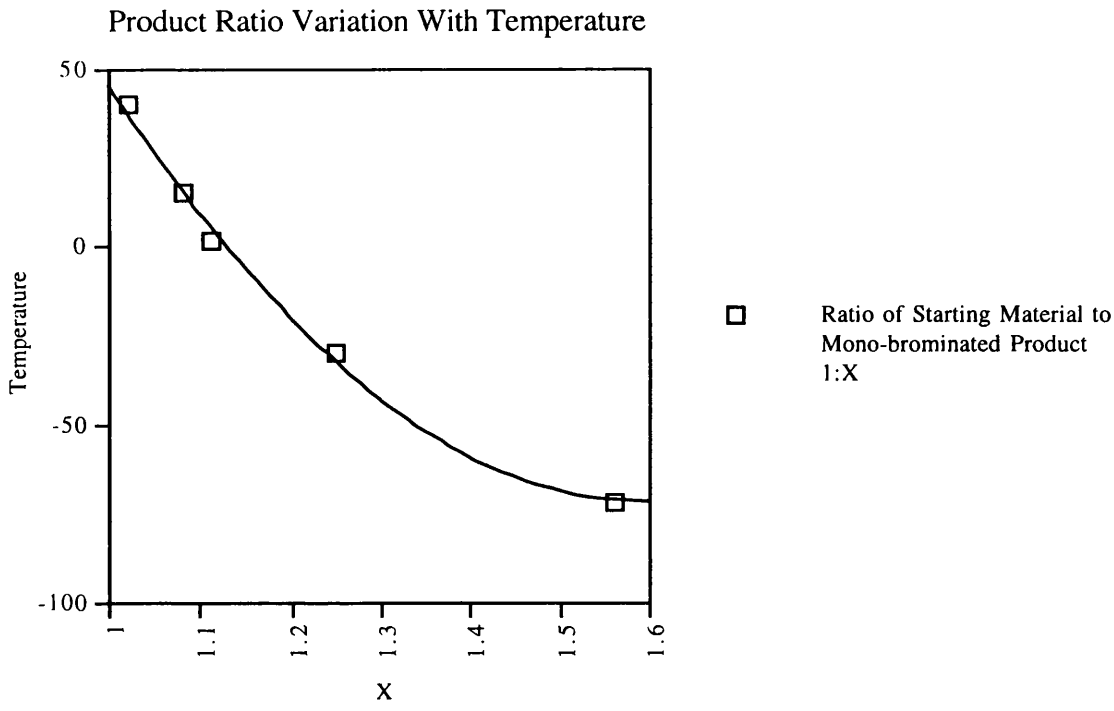



**Figure 31:** Acid catalysed bromine atom equilibration

### 4.3.2 Varying the Reaction Temperature

The next reaction parameter to be varied was reaction temperature (see graph 2).




**Graph 3**

As expected the amount of monobromination increased at low temperatures. As $E_{a1}<E_{a2}$ it follows that the term in the rate constant for the first bromination, **16**→**17**, $e^{-E_{a1}/RT}$ decreases more slowly than the term $e^{-E_{a2}/RT}$ in the rate constant for the second bromination, **17**→**18**, as the temperature, T, drops. However, as the difference between the activation energies is relatively small the observed increase in the extent of monobromination is also small.

Furthermore, this increase in selectivity towards monobromination may also be partly due to both reactions being slower. Even at low temperatures the reaction is very fast with almost instantaneous decolourisation of the bromine being observed and consequently the reaction is subject to *microscopic diffusion control* (otherwise known as *encounter control*)[85]. This occurs because the high reactivity of the substrate results in there being only a limited number of collisions between the substrate and $Br_2$ molecules before reaction occurs. This means that a disproportionately large extent of the reaction occurs at the solution surface, at the point of contact, which results in a greater degree of dibromination being observed than would be expected if the $Br_2$ were to be completely dispersed prior to reaction. Therefore at lower temperatures, where both the reactions are slower, the $Br_2$ has a greater amount of time to disperse before reacting and this reduces the amount of dibromination.

As this reaction is subject to *microscopic diffusion control,* physical factors which effect the extent of bromine dispersion prior to the bulk of the reaction will have a considerable effect on the product distribution. The effect of varying the other factors, which determine how well the bromine is dispersed, was therefore also investigated.

### 4.3.3. Bromination Without Stirring of the Reaction Mixture

The first of these experiments involved simply adding the bromine as before to a solution which was not being stirred. This gave rise to a product distribution which was composed of starting benzoate **16**, the 2-bromo compound **17** and the 2,6 dibromo compound **18**, in the ratio 1 : 0.5 : 1. Thus the removal of a dispersion facilitating factor leads, as expected, to a substantial increase in the amount of dibromination.

It therefore appeared that the best way to improve the selectivity of the reaction, with regards to monobromination, was to alter the reaction procedure in such a way that the dispersion of the bromine was improved.

### 4.3.4. Varying the Concentration of the Substrate Solution

The effect on product distribution produced by varying the concentration of the substrate solution used was therefore investigated. When the reaction was carried out in 100 ml of dichloromethane (rather than 6 ml) there was a large increase in the amount of monobromination to give a product distribution ratio of 1 : 2.15 : 1. This observed increase in selectivity with regards to monobromination is a result of increased dilution slowing down the rate of both reactions proportionately, allowing essentially complete dispersion of the bromine prior to reaction. Further increases in dilution produced no change in product distribution.

## 4.4 Conditions for Optimising Monobromonation Selectivity Using $Br_2$

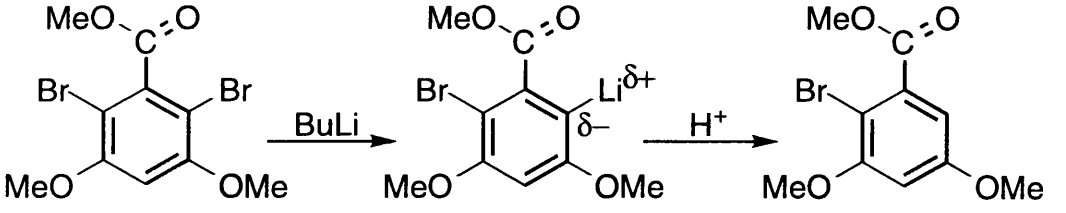
The conditions for optimising monobromination selectivity are therefore, the use of a solution of the substrate in low concentration and low reaction temperatures. For the model compound considered these conditions translate as a 0.01 M solution of benzoate **16** and as low a temperature as is practical.

However even under these conditions (temperature -70 $^{o}$C) the yield of the 2-bromo compound **17** is only 60% with the resultant product distribution being 1 : 3 : 1.

All the results obtained are however rather poor and it can be concluded that molecular bromine is too reactive to have anything other than limited synthetic utility with regards to the selective monobromination of such an activated aromatic substrate under practical working conditions.

## 4.5 Monodebromination *via* Metal-Halogen Exchange

Though the reaction of benzoate **16** with $Br_2$ displays relatively low selectivity with regards to monobromination, the reaction of benzoate **16** with two mole equivalents of bromine gives the 2,6-dibromo compound **18** in essentially quantative yield. It was thought that it may be possible to debrominate **18**→**17** thus obtaining a good yield indirectly (see scheme 6).




**(18)** **(17)**

**Scheme 6**

It was thought that since two δ- charges on one ring may be unfavourable that mono metal-halogen exchange may occur in good yield. However the yield of this reaction was only 48% with extensive di-debromination being observed.

The occurance of multiple metal-halogen exchange, on treating poly-brominated anisoles with organolithium reagents, is a reported problem which has been attributed to the strong basicity and nucleophilicity of these reagents[86]. Grignard formation is reported to be more effective in this respect but this was not attempted as it was thought that the carbonyl group would inhibit the formation of this type of organometallic compound.

## 4.6 Bromination using NBS

The electrophilic substitution of an aromatic ring by NBS in nonpolar solvents, such as $CCl_4$, is well documented. However the results are highly variable in terms of both products and yields and so these conditions were initially not examined. Instead, the use of NBS in a polar solvent, DMF, was studied as Mitchell *et al.* report that NBS/DMF is a reliable mild selective monobromination reagent for reactive aromatic compounds[46] (although compounds with the appropriate substitution pattern were not examined).

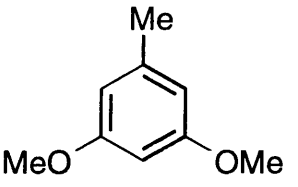
The standard conditions (stirring 1 mmol of substrate and 1 mmol NBS in 5 ml DMF for 24 hours) resulted in a mixture of the benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 7.5 : 0.1 (88% yield of **17**). Whilst this represents considerable selectivity, contrary to the reported result[46] some dibromination was observed. Reaction with 2 mole equivalents gives almost exclusively the dibromide.

This yield of 88% was not improved by either longer reaction times or the use of elevated temperatures as both of these changes result in an increase in the amount of dibromination. Therefore if higher yields are required then it would appear that the use of longer reaction times at lower temperatures may be necessary.

# 5

# The Aryl Bromination of 3,5-Dimethoxytoluene

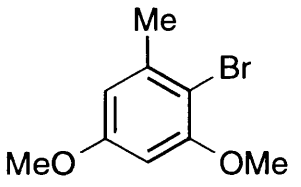
Using the results obtained for benzoate **16** the bromination of the second model compound 3,5-dimethoxytoluene (**19**), prepared from 3,5-dihydroxytoluene by a standard Williamson ether synthesis, was studied. This provided an opportunity to test whether or not any of the conditions used in the bromination of benzoate **16** would result in benzylic bromination when applied to toluene **19**.



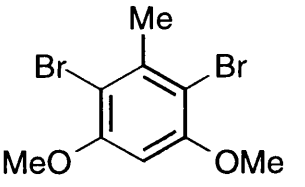

**(19)**

## 5.1 The Aryl Bromination of 3,5-Dimethoxytoluene (19) using $Br_2$

The standard conditions employed previously again gave rise to an extremely fast reaction. Immediate work-up of the reaction following the almost instantaneous decolourisation of the bromine gave rise to starting toluene **19**, 2-bromo-3,5-dimethoxytoluene (**20**) and 2,6-dibromo-3,5-dimethoxytoluene (**21**) being generated in the ratio 1 : 4 : 1. This was an unexpectedly high extent of monobromination. As toluene **19** is more activated towards electrophilic substitution than benzoate **16** less selectivity towards monobromination, than was observed for **16**, was the expected result. Even more surprisingly when a 0.01 M substrate solution and reaction temperature of -70 °C were used, the extent of monobromination decreased rather than increased, with the observed product ratio being 1 : 2.4 : 1. These seemingly anomalous results were initially attributed to the extremely fast reaction rate making the product ratio very sensitive to any slight inconsistencies in the mode of addition. The real explanation was not discovered until later (see page ). No benzylic bromination was ever observed in these reactions.




(20)




(21)

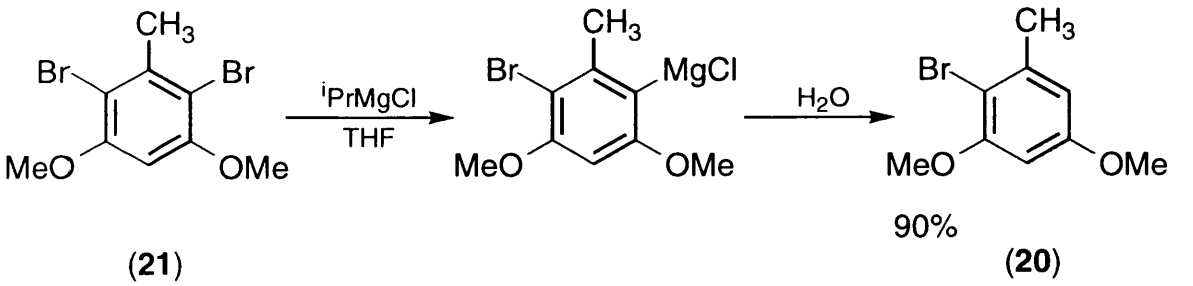
## 5.2 The Aryl Bromination of 3,5-Dimethoxytoluene (19) using NBS

However, whilst bromine proved to have almost no selectivity with such a reactive substrate, the NBS/DMF brominating system[46] gave excellent results. Under standard conditions no dibromides were observed and a 95% yield of the 2-bromo compound **20** was obtained. This improvement was proven not to be purely due to the change of solvent. The use of bromine in DMF did *not* result in extensive monobromination and resulted in a product mixture that was composed of starting toluene **19**, 2-bromo compound **20** and 2,6-dibromo compound **21** in the ratio 1 : 3.2 : 1. The solvent used for the NBS bromination was however found to be very important. The use of carbon tetrachloride as the solvent resulted in relatively low selectivity with a product ratio of 1 : 4 : 1 being obtained whilst the use of dichloromethane resulted in excellent selectivity, with a 99% yield of the 2-bromo compound **20** being obtained. Again no benzylic bromination was observed in any of these reactions.

In conclusion, it would appear that NBS in either DMF or dichloromethane is, as reported, a reliable reagent for the selective nuclear monobromination of reactive aromatic compounds whilst molecular bromine is only effective, under practical working conditions, in this respect when applied to less activated aromatic substrates.

## 5.3 Monodebromination *via* Grignard Formation

Whilst attempts to monodebrominate the 2,6-dibromo benzoate **18** by metal-halogen exchange had proved unsuccessful, it was thought that the lack of a carbonyl group in the 2,6-dibromo toluene **21** would the allow grignard formation that was not attempted for **18**. Nishiyama *et al.*[86] report that monodebromination can be achieved by reaction of 1,3-dibromoanisoles with an excess of an alkyl Grignard reagent in tetrahydrofuran. Under these type of conditions (see scheme 7) the 2,6-dibromo compound **21** was found to be monodebrominated to afford 2-bromo compound **20** in a 90% yield.

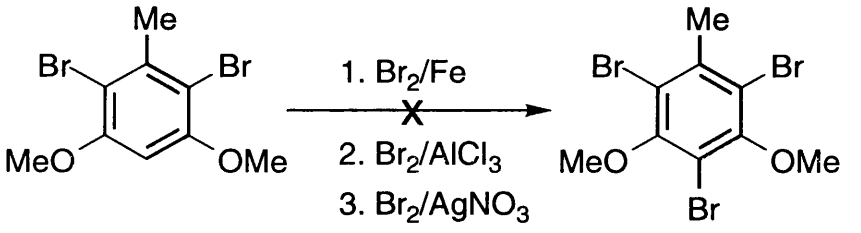



(21) (20)

**Scheme 7**

## 5.4 The Aryl Tribromination of 3,5-Dimethoxytoluene

Another result of this research is that in substrates such as benzoate **16** and toluene **19**, the 4 position on the aromatic ring is difficult to brominate, indeed bromination at this position was never observed, even when toluene **19** was refluxed with 4 mole equivalents of bromine in the presence of an iron catalyst. This is contrary to a previously reported result[87]. Other catalysts, $AlCl_3$ and $AgNO_3$[88] (see scheme 8) also failed to produce any C-4 bromination of the 2,6-dibromo compound **21**.

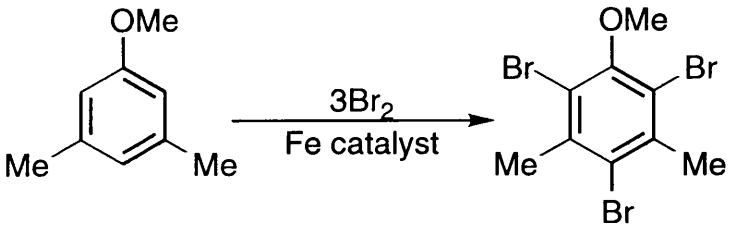



(21) (25)

**Scheme 8**

### 5.4.1 Explanation of the Low Reactivity of the C-4 Position Towards Bromination

This position is *ortho* to both methoxy groups which are strongly activating and *para* to the mildly activating methyl group. Though the principle of additivity does overestimate the reactivity of aromatics with more than one activating group, for reasons explained in chapter 2, it would still seem unlikely that electronic factors are responsible for this marked lack of reactivity. Proof of this is provided by the fact that it was found that 3,5-dimethylanisole (**22**), which is less activated towards electrophilic substitution than toluene **19**, can be tribrominated to give 2,4,6-tribromo-3,5-dimethylanisole (**23**) in 60.8% yield (see scheme 9).

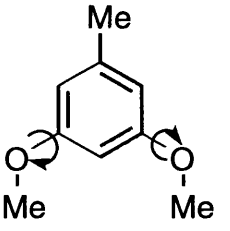



(22) (23)

**Scheme 9**

The reason for this lack of reactivity must therefore be due to steric factors. Analysis of the 200 MHz $^1$H NMR spectra of toluene **19**, 2-bromo derivative **20** and 2,6-dibromo derivative **21** shows evidence for the effect the Br substituents have upon the conformation of the neighbouring methoxy groups.

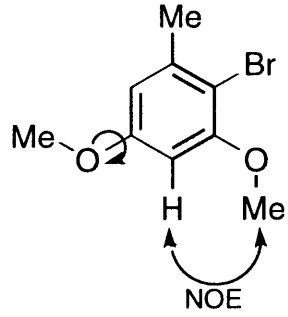
In the case of toluene **19**, irradiation at the resonance frequency of the -OMe protons does not result in a detectable NOE enhancement of the H-4 signal. This is probably due to the fact that at room temperature, rotation around the C-O bonds can occur as shown below in figure 32 and the average distance between the H-4 and the -OMe protons is therefore relatively large.




(19)

**Figure 32**

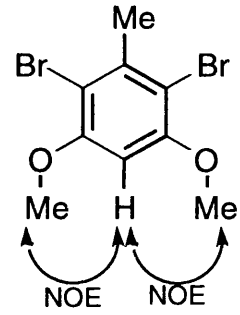
In the spectrum of 2-bromo compound **20** however, irradiation at the resonance frequency of the 3-OMe protons results in a nuclear Overhauser enhancement of the H-4 signal. This is probably due to the steric bulk of the Br substituent constraining the Me group to remain close to 4-H (see figure 33).




**(20)**

**Figure 33**

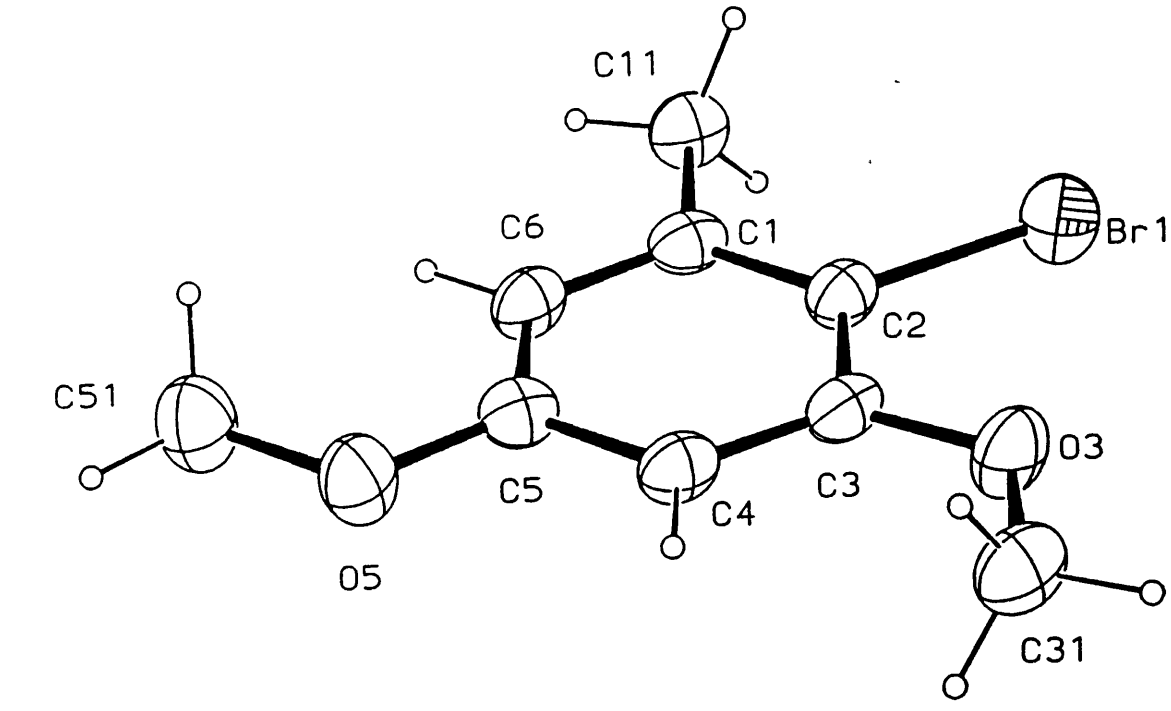
Similarly in the spectrum of the 2,6-dibromo compound **21**, irradiation at the -OMe proton resonance frequency results in a nuclear Overhauser enhancement of the H-4 signal (see figure 34).

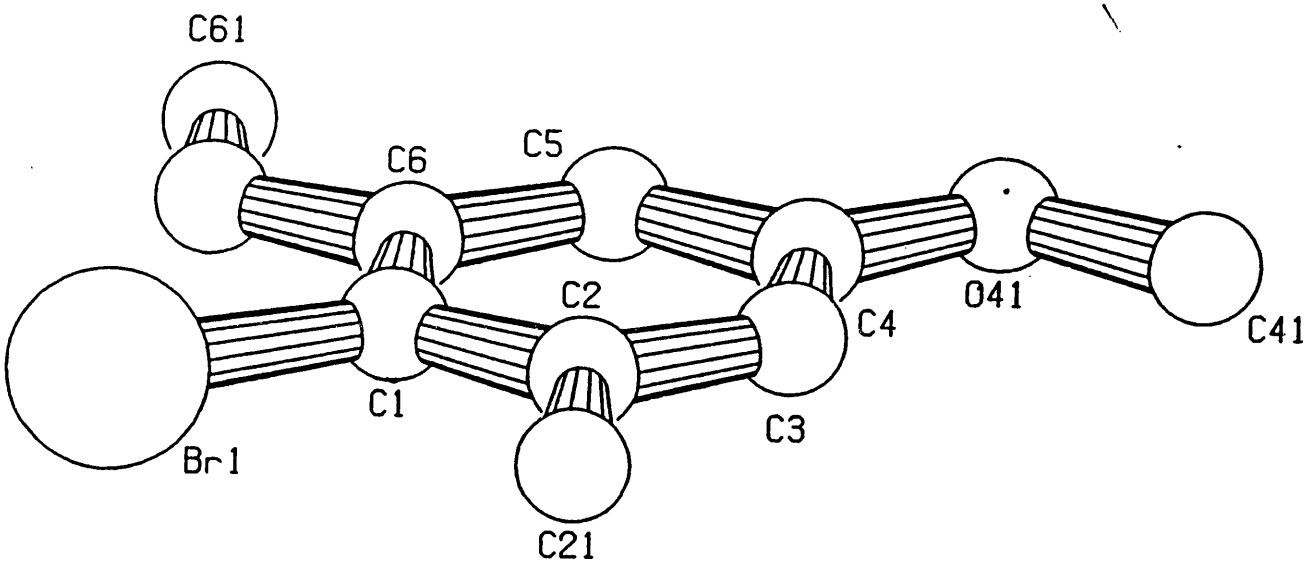



**(21)**

**Figure 34**

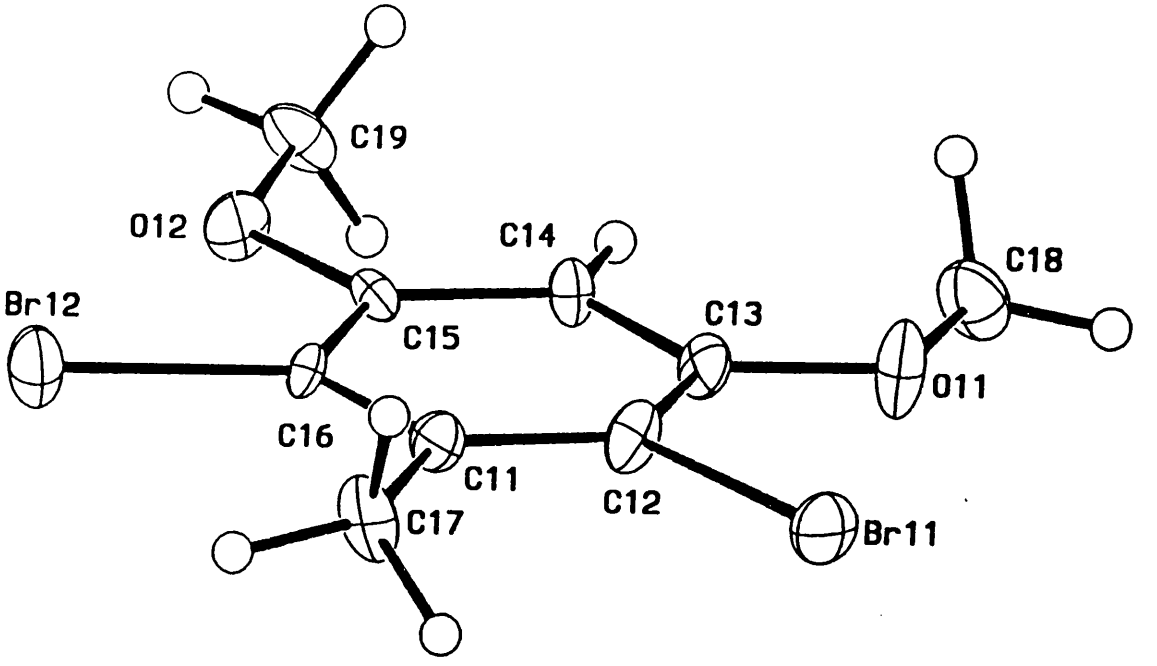
The crystal structures of the 2-bromo compound **20** (obtained by Dr. L. Farrugia of Glasgow University) and the 2,6-dibromo compound **21** (obtained by Dr. K. Muir of Glasgow University) show that, for these compounds, the -OMe groups lie within the plane of the ring in the solid state (see figures 35 and 36).




| Crystal data | | | |
|---|---|---|---|
| Empirical formula | $C_9H_{11}BrO_2$ | $\alpha$ | 92.734(7) deg. |
| Formula weight | 231.09 | $\beta$ | 101.597(7) deg. |
| Temperature | 291(2) K | $\gamma$ | 104.518(7) deg. |
| Crystal system | Triclinic | $Z$ | 2 |
| Space group | P-1 | $D_{calc}$ | 1.612 $Mgm^{-3}$ |
| $a$ | 7.3692(6) Å | $\mu$ | 4.275 $mm^{-1}$ |
| $b$ | 8.2424(7) Å | Final R indices | R1 = 0.0539 |
| $c$ | 8.3092(6) Å | | wR2 = 0.1403 |

**Figure 35:** Crystal structure of 2-bromo-3,5-dimethoxytoluene (**20**)




| Crystal data | | | |
|---|---|---|---|
| Empirical formula | $C_9H_{10}Br_2O_2$ | $\alpha$ | 90 deg. |
| Formula weight | 309.99 | $\beta$ | 91.73(2) deg. |
| Temperature | 120(0.2) K | $\gamma$ | 90 deg. |
| Crystal system | Monoclinic | $Z$ | 8 |
| Space group | P21/c | $D_{calc}$ | 2.051 $Mgm^{-3}$ |
| $a$ | 8.7681(12) Å | $\mu$ | 8.039 $mm^{-1}$ |
| $b$ | 16.463(3) Å | Final R indices | R1 = 0.0598 |
| $c$ | 13.914(5) Å | | wR2 = 0.1190 |

**Figure 36:** Crystal structure of 2,6-dibromo-3,5-dimethoxytoluene (**21**)

The space-fill representation of the crystal structure of 2,6-dibromo compound **21** (see figure 37) shows why C4 bromination of **21** is difficult. It can be seen that, if the methoxy groups stay within the plane of the ring during further bromination then this would result in the bromine substituent being subject to severe steric compression unless there was considerable deformation of the C-O-C bond angles and lengths. Either of these effects would result in the arenium ion intermediate for the C-4 bromination of 2,6-dibromo compound **21** being high in energy. If however, the methoxy groups are forced out of the plane then the overlap between the *p*-orbitals of the oxygen atoms and the π-system of the ring would be lost. This would result in the loss of resonance stabilisation in the arenium ion intermediate and again the transition state energy would be high.

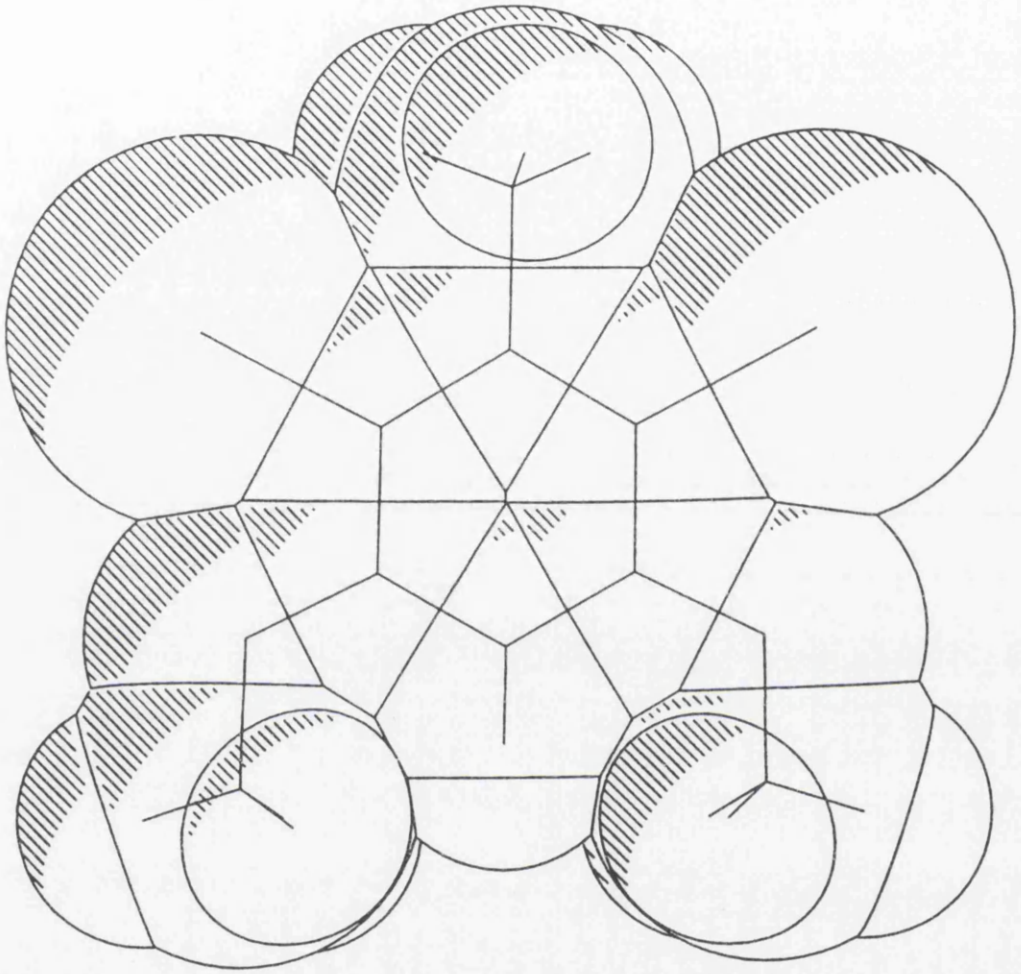
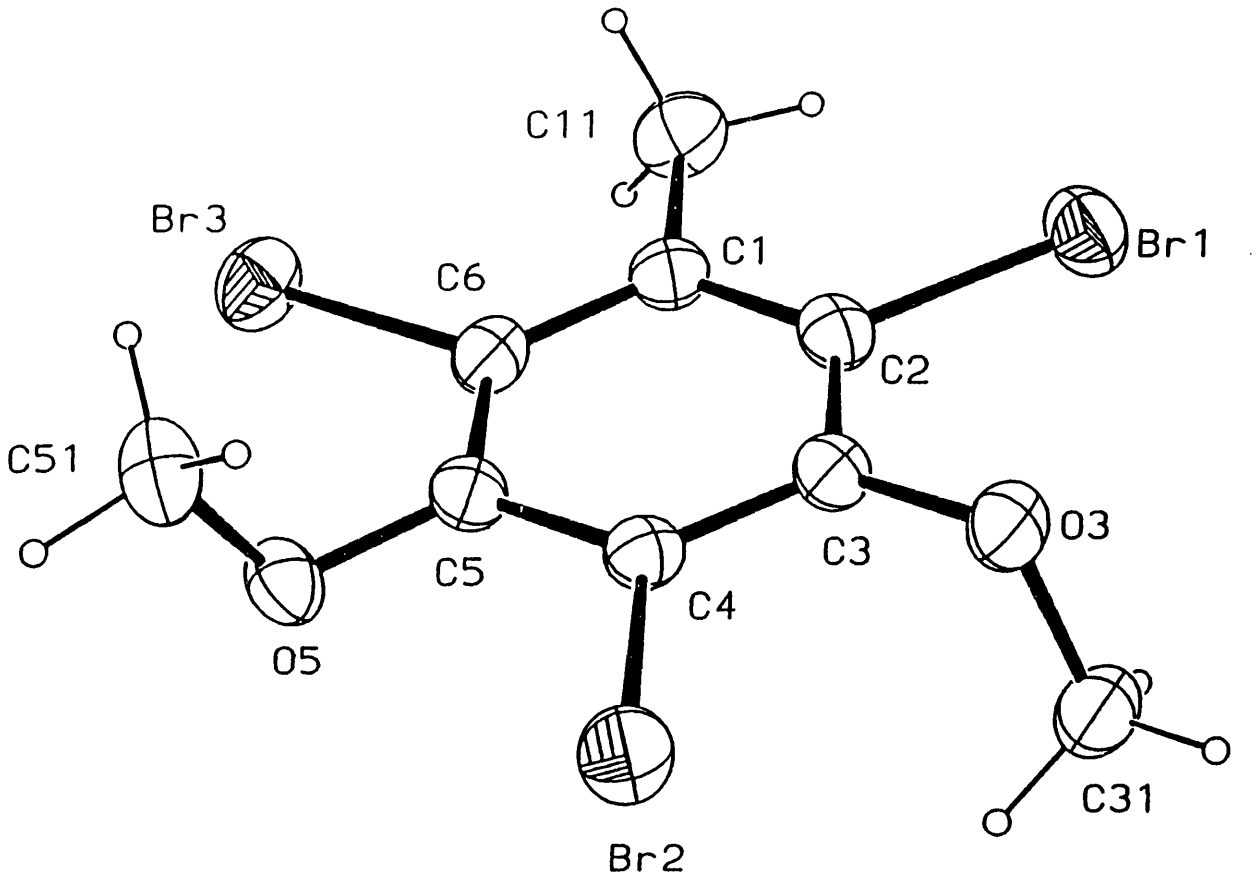


**Figure 37**

The crystal structure of 2,4,6-tribromo-3,5-dimethoxytoluene (**25**) (obtained by Dr. L. Farrugia), prepared by the route shown in scheme 9, shows that, in the solid state, the methoxy groups are indeed out of the plane of the ring (see figure 38).

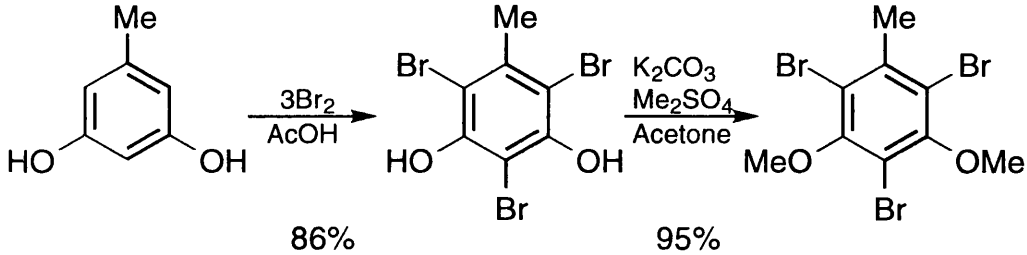



| Crystal data | | | |
|---|---|---|---|
| Empirical formula | $C_9H_9Br_3O_2$ | $\alpha$ | 90 deg. |
| Formula weight | 388.99 | $\beta$ | 118.25(2) deg. |
| Temperature | 291(2) K | $\gamma$ | 90 deg. |
| Crystal system | Monoclinic | $Z$ | 8 |
| Space group | C 2/c | $D_{calc}$ | 2.267 $Mgm^{-3}$ |
| $a$ | 36.175(4) Å | $\mu$ | 10.595 $mm^{-1}$ |
| $b$ | 4.1100(10) Å | Final R indices | R1 = 0.0275 |
| $c$ | 17.396(2) Å | | wR2 = 0.0706 |

**Figure 38:** The crystal structure of 2,4,6-tribromo-3,5-dimethoxytoluene (**25**)

### 5.4.2 Preparations of 2,4,6-Tribromo-3,5-dimethoxytoluene (25)

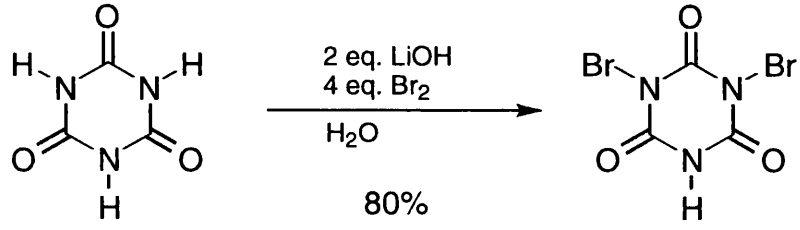
As it would appear therefore that the methyl parts of the methoxy groups are responsible for the steric inhibition of resonance in the transition state, it should therefore be possible to produce the tribrominated product (**25**) by brominating 3,5-dihydroxytoluene to give 2,4,6-tribromo-3,5-dihydroxytoluene (**24**) then methylating (see scheme 9). This was found to be correct.




**(24)** **(25)**

**Scheme 9**

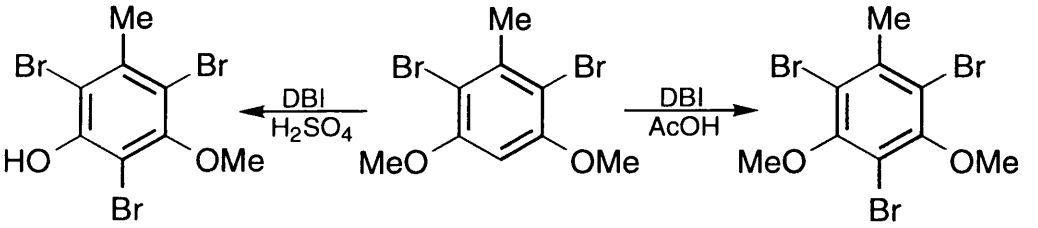
It was thought that it may be possible to tribrominate toluene **19** directly by using a more powerful brominating reagent. A possible reagent for this is dibromoisocyanuric acid, DBI, in concentrated sulfuric acid[49]. This reagent was prepared as shown in scheme 10




DBI

**Scheme 10**

It was found however, that the use of this reagent in concentrated sulfuric acid gave rise not to 2,4,6-tribromo compound **25**, but instead to 2,4,6-tribromo-5-hydroxy-2-methoxytoluene (**26**) where mono-demethylation had taken place (see scheme 11). The demethylation was thought to be almost certainly the result of extensive protonation of the oxygens of the methoxy groups (the $pK_a$ value of $H_2SO_4$ is -9 whereas the $pK_a$ value of $ArOHMe^+$ is -6)[89]. It was decided, therefore to investigate the use of this reagent in less harsh conditions, namely by using acetic acid ($pK_a$ value 5) as the solvent. This proved successful with a 90% yield of the 2,4,6-tribromo compound **25** being obtained (see scheme 11)




48% 88%

(26) (21) (25)

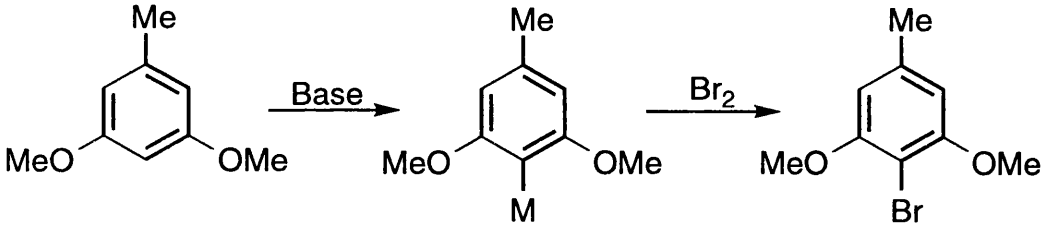
**Scheme 11**

## 5.5 Attempted Preparations of 4-Bromo-3,5-dimethoxytoluene (27)

It is clear from the results in the previous sections that it is not possible to access 4-bromo-3,5-dimethoxytoluene (**27**) by direct bromination of toluene **19**. This is in agreement with a previously reported result[87].

### 5.5.1 *via* C-4 Lithiation

The potential route to the 4-bromo toluene **27**, shown in scheme 12, was investigated under a range of conditions.




(19) (27)

**Scheme 12**

Several experiments were carried out whereby the conditions and reagents employed in the above reaction were varied. Eventually it was found that stirring toluene **19** with 1.1 mole equivalents of PhLi and tetramethylethylenediamine (which is known to increase both the rate and extent of metallation of anisoles)[90,91] for 16 hours in the dark results in essentially quantative C-4 anion formation. This result was obtained by quenching a control experiment with $D_2O$.

The origin of this regioselective lithiation of 1,3-disubstituted heteroatom aromatics has been explained by Saá *et al* [92]. The reaction was studied by means of the semiempirical MNDO method. Calculations showed clear-cut evidence for the intermediate formation of the chelated species shown in figure 39 which formally derives from the bidentate coordination of a reactive alkyl lithium dimer by the educt working as a "pair of tweezers".

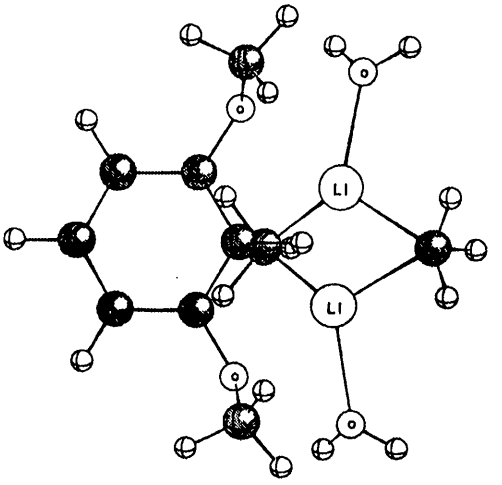



**Figure 39**

The geometry of this complex is ideal for regioselective abstraction of the hydrogen positioned between the heteroatoms[93] (see figure 40).

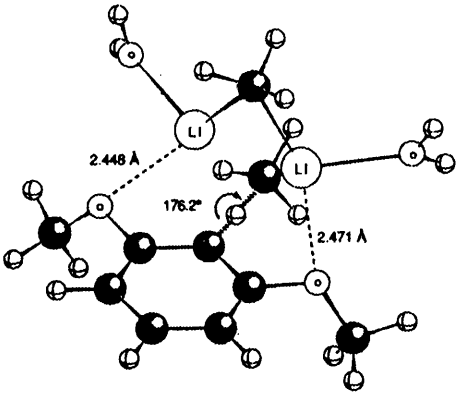


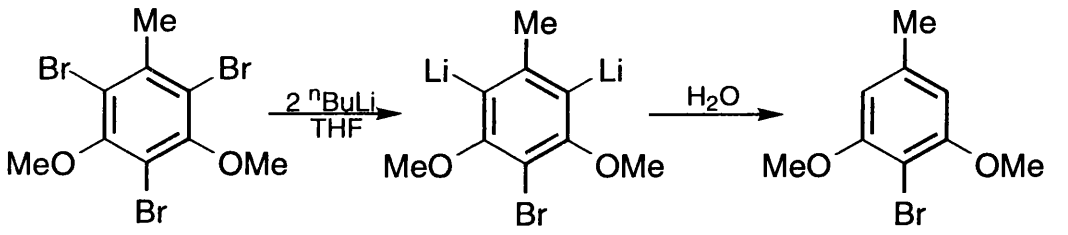

**Figure 40**

The subsequent bromination of the anion however proved difficult. 1,2-Dibromoethane has been used for this purpose[87] but when this reagent was used the only compound isolated was starting toluene **19**. A possible explanation for this is that the presence of the TMEDA results in the formation of a harder anion, and HBr instead of $Br_2$ is eliminated from the 1,2-dibromoethane. When alternative brominating reagents, NBS and $BrCCl_3$, were used the yield

of the 4-bromo compound **27** obtained was only around 50%, so there is still room for improvement in this respect.

### 5.5.2 Other Potential Routes Towards the Synthesis of 4-Bromo-3,5-dimethoxytoluene (27)

Prior to the successful completion of the above route to the 4-bromo toluene **27** several other possible routes were also investigated. The first of these is shown in scheme 13. It was thought that the bulk of the C-4 bromine atom substituent may prevent the sort of bidentate coordination shown in figure 39. If this were the case then calculations suggest that monodentate coordination would lead to predominately C-2/C-6 lithiation.

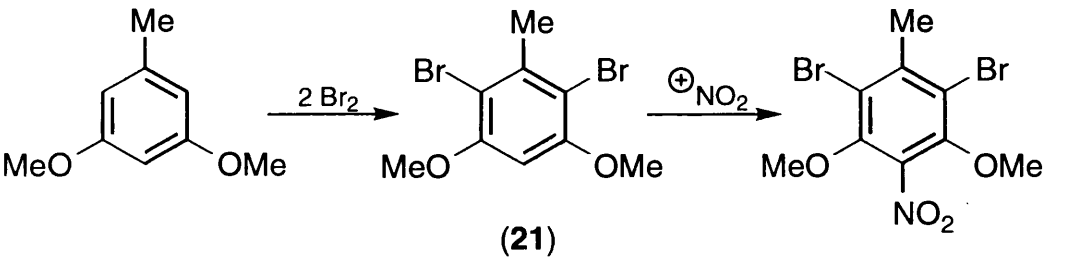



**(25)** **(27)**

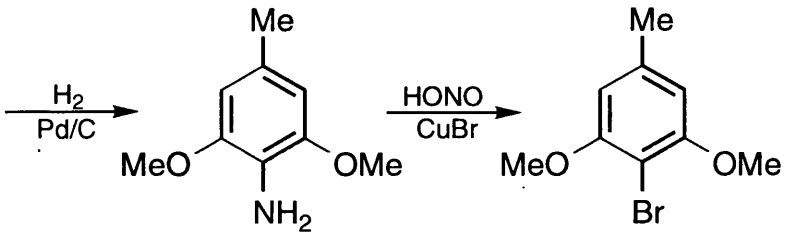
**Scheme 13**

This reaction however displayed almost no selectivity with a large number of metal-halogen exchange products and other biaryl compounds (that arise through Wurtz-type coupling) being observed.

Another possible route is *via* the Sandmeyer reaction (see scheme 14). This scheme uses the exclusive 2,6-dibromination selectivity to block the more reactive sites and direct nitration to the C4 position. The concommitant hydrogenolysis of bromo substituents and nitro group reduction is well known[94].



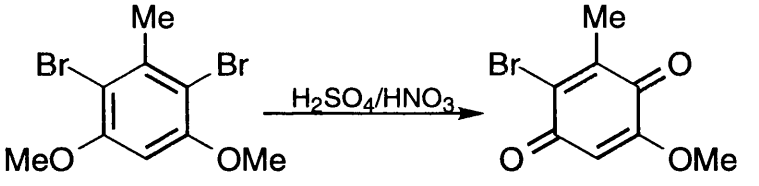

(21)




(27)

**Scheme 14**

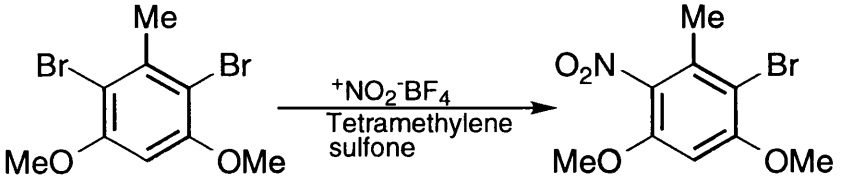
Attempts at carrying out the nitration step in this synthesis proved however to be unsuccessful. When $H_2SO_4/HNO_3$ was used as the nitrating agent, the 2,6-dibromo compound **21** was oxidised to the quinone **28** as shown in scheme 15.




(21) (28)

**Scheme 15**

Even when non-acidic conditions involving the use of nitrating agent $^{+}NO_2^{-}BF_4$ in tetramethylene sulphone[95] were used the reaction did not proceed as intended and spectroscopic data suggests the isolated product is 2-bromo-3,5-dimethoxy-6-nitrotoluene **29** (see scheme 16).




(21) (29)

**Scheme 16**

The replacement of halogens with nitro groups during the nitration of halo anisoles is not uncommon and is known as a Reverdin reaction[96]. The reaction proceeds by the electrophilic attack of the $^{+}NO_2$ ion at the *ipso* position, relative to the bromine, to form the arenium ion with subsequent loss of the bromine to give the product of substitution. In this particular reaction the bromine is probably removed as hypobromous acid during aqueous work-up. That the attack of the $^{+}NO_2$ ion occurred *ipso* relative to the bromine substituent is not surprising. Perrin and Skinner[96] have obtained a value of 0.08 for the *ipso* partial rate factor of a bromine substituent, in the nitration of anisoles. This means that, though the bromine substituent does deactivate the ring towards *ipso* attack by the $^{+}NO_2$ ion, the degree of deactivation is not great and is comparable in magnitude to the degree of deactivation towards *meta* attack (this is partially due to the fact that $^{+}NO_2$ is a relatively unselective electrophile). Therefore, as the C-4 position in the 2,6-dibromo toluene **21**, is particularly unreactive, relative to the C-2 position in toluene **19**, it follows that the deactivation of the C-2 position in 2,6-dibromo toluene **21**, by the *ipso* bromine substituent, is not sufficiently great to prevent electrophilic attack at C-2 still being favoured over attack at C-4. The quinone **28** is also probably formed *via* the initial attack of the $^{+}NO_2$ ion *ipso* to a bromine substituent in the 2,6-dibromo toluene **21**. A possible mechanism for the reaction is shown in figure 41.

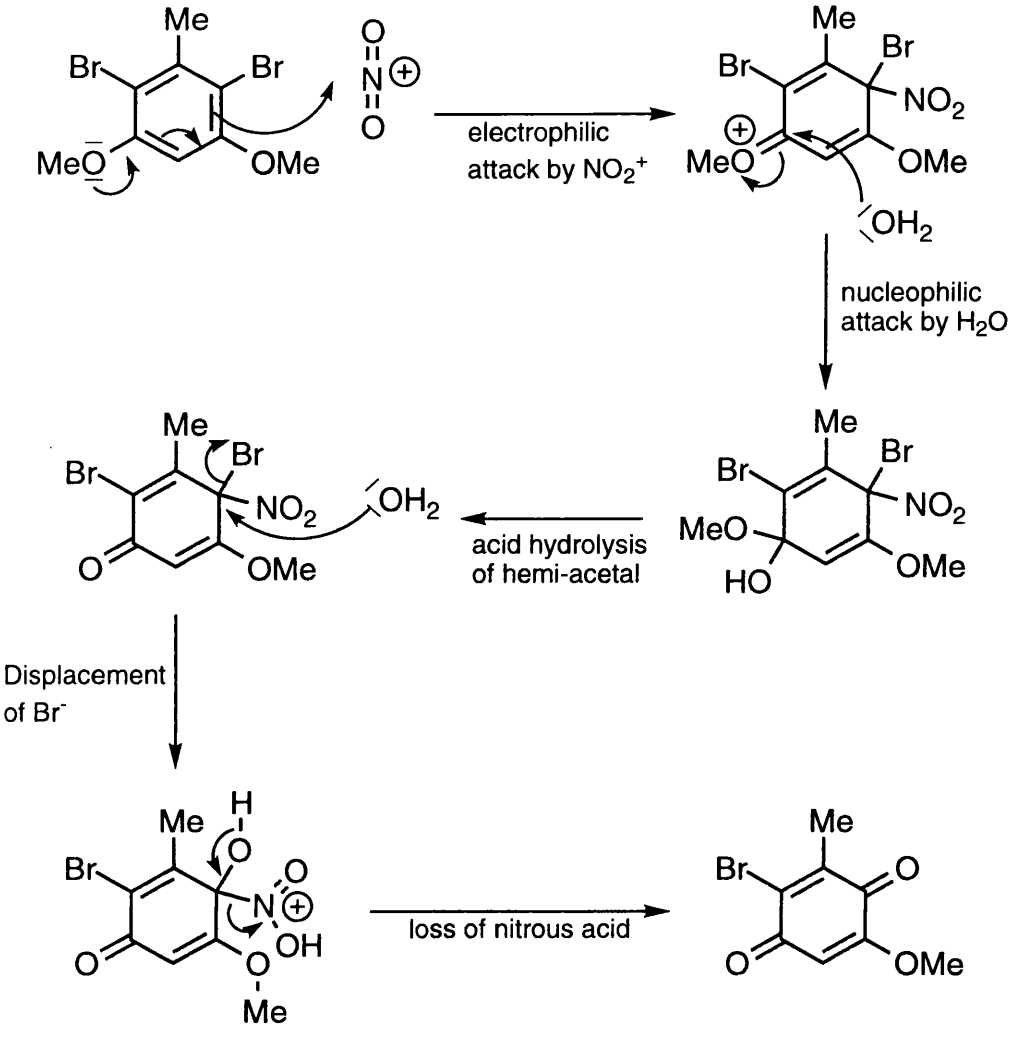
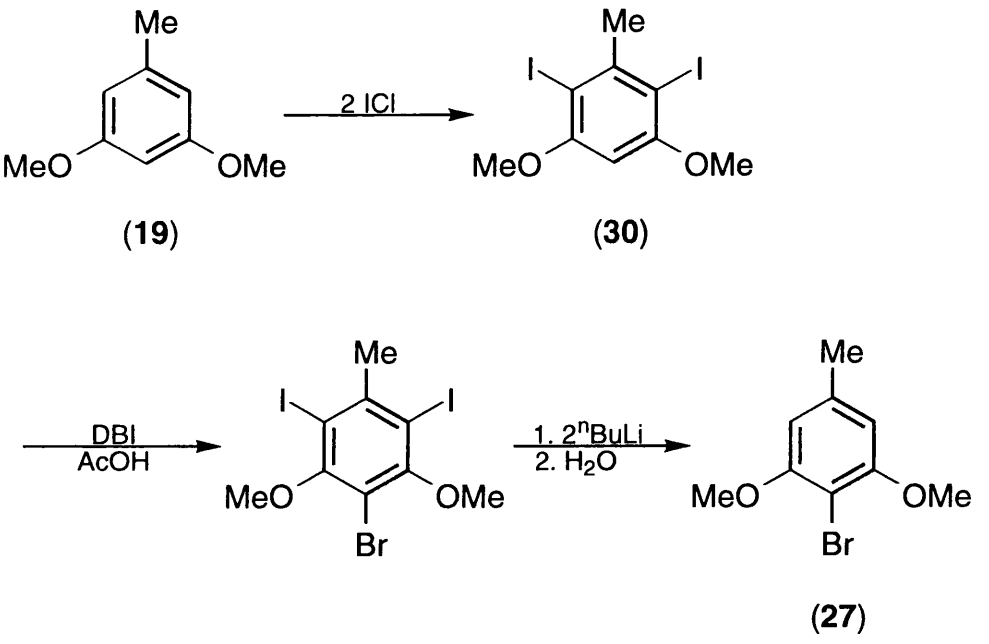



**Figure 41:** Possible mechanism for the oxidation of the 2,6-dibromo toluene **21**

As all direct nitrating reagents involve $^{+}NO_2$ in some form it seems unlikely that conditions could be found such that this step would proceed in the desired manner and so this potential route to the 4-bromo toluene **27** was abandoned.

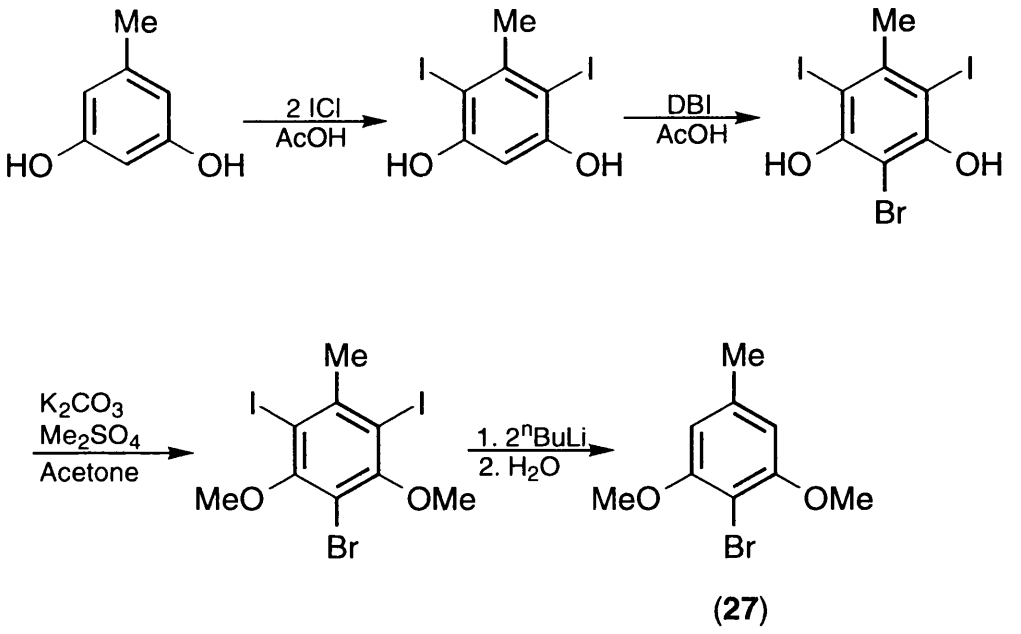
Having discovered that the 2,6-dibromo toluene **21** could be brominated further to give the 2,4,6-tribromo toluene **25**, using DBI in acetic acid, it was thought that the route, shown in scheme 17, where iodine is used to block the more reactive sites on the ring may be viable.




**Scheme 17**

The first step in this synthesis was, as expected, straightforward with only 2,6-diiodo-3,5-dimethoxytoluene (**30**) being formed. The second step however did not proceed as intended as DBI in acetic acid was not sufficiently reactive to brominate the C-4 position of the 2,6-diiodo compound **30**. The use of harsher conditions, with $H_2SO_4$, as the solvent resulted in strong iodine colouration being formed in the reaction suggesting that in some way iodine was being lost from the starting material. The reluctance of the C-4 position to brominate is probably the result of the added bulk of the iodine substituents, in comparison with the bromine substituents in the 2,6-dibromo compound **21**, forcing the methoxy groups further round, resulting in the C-4 position in the 2,6-diiodo compound **30** being even more sterically congested than in 2,6-dibromo analogue **21**.

In order to try to overcome this problem the reaction route was altered to that shown in scheme 18.

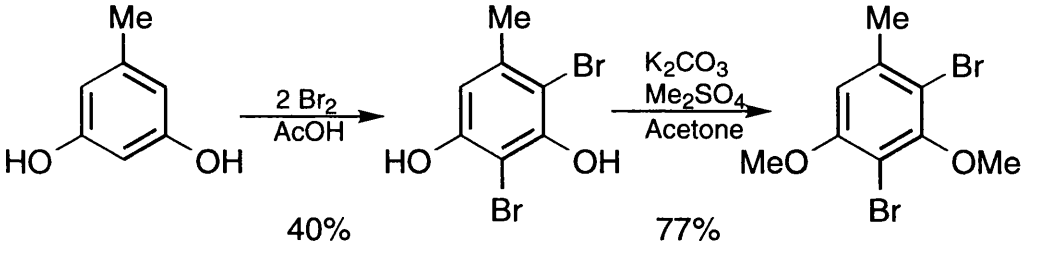



**(27)**

**Scheme 18**

This first step in this scheme was successfully completed but the yield was very low, approximately 28%, and the scheme was abandoned. This yield was low due to a marked lack of selectivity shown by the diiodination which produced a mixture of iodinated products. This should perhaps have been anticipated since the exclusive 2,6-dihalogenation selectivity exhibited by toluene **19** has been attributed to the methyl parts of the two methoxy groups sterically blocking the C-4 position.

(N.B. The lack of selectivity shown by the above reaction suggests that it should be possible to access 2,4-dibromo-3,5-dimethoxytoluene (**32**), in reasonable yield, *via* scheme 19 shown below.

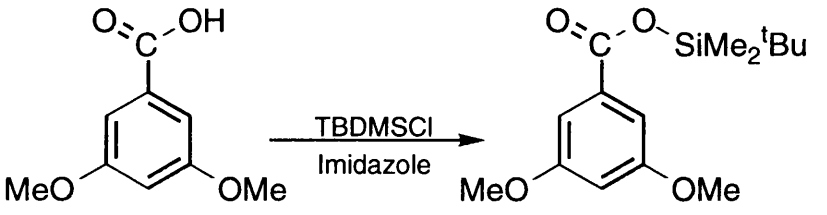



**(31)** **(32)**

**Scheme 19**

Without the presence of the two methoxy groups the exclusive 2,6-selectivity is absent and 2,4-dibromo-3,5-dihydroxytoluene (**31**) is the major dibromo product, because there are two possible reaction pathways to this isomer, compared with only one to the 2,6 dibromide. This pathway allows the 2,4-dibromo compound **32** to be obtained without going through the 4-bromo compound **27** which was thought may be of considerable advantage).

As the lack of reactivity at C-4 in benzoate **16** and toluene **19** is attributed to steric factors it was thought that it may be possible to direct bromination to some extent to this position by sterically hindering the 2/6 position. The first attempt at this involved preparing a bulky ester derivative of 3,5-dimethoxybenzoic acid, namely the $^{t}$butyldimethylsilylester (**33**) as shown in scheme 20.



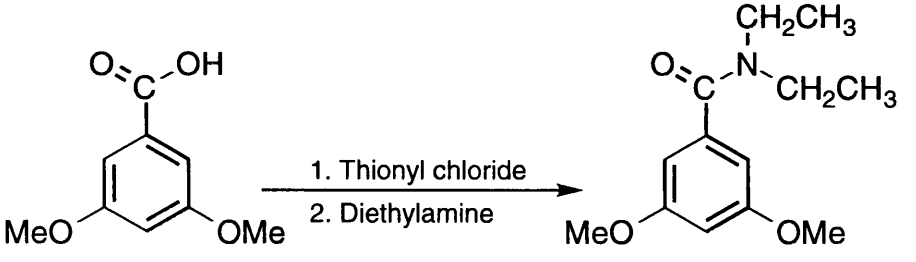

**(33)**

**Scheme 20**

Bromination of this ester (**33**), using either molecular bromine or NBS, however just yielded 2-bromo- and 2,6-dibromo-3,5-dimethoxybenzoic acid as the products, the ester group having been hydrolysed.

As the rotation about the C-O ester bond probably allows the ester group to fold out of the way, preventing steric hindrance to bromination of the 2/6 position, it was thought that amides might be better for this purpose.

It was thought that an amide might be better at blocking the site since *p*-orbital overlap between the flat amide group and the ring would be maximised if the whole molecule was planar. The diethyl amide (**34**) was therefore prepared as shown below (see scheme 21).



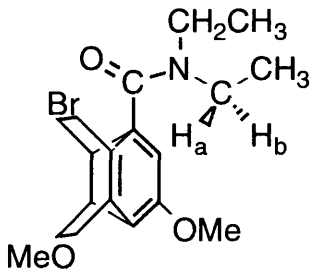

68.4%

**(34)**

**Scheme 21**

Unfortunately, bromination of this amide using 1 mole equivalent of bromine leads to a mixture of the 2-bromo (**35**) and 2,6-dibromo (**36**) derivatives along with starting material with no C-4 bromination being observed. When NBS is employed as the brominating agent the product is composed almost exclusively of the 2-bromo derivative **35** and the use of 2 mole equivalents of bromine or NBS leads exclusively to the 2,6-dibromo derivative **36**.

Analysis of the $^1H$ nmr spectra of the amide **34** and the 2-bromo derivative **35** provides evidence to explain why no C-4 bromination is observed.




**(35)**

**Figure 42**

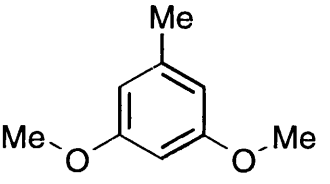
In the $^1H$ nmr spectrum of the 2-bromo compound **35**, $H_a$ and $H_b$ are non-equivalent (see figure 42) and give rise to separate signals that are both double quartets with a geminal coupling constant of 14 Hz. It follows that simple rotation about the Ar-C bond must be restricted (at the probe temperature) otherwise $H_a$ and $H_b$ would be equivalent. Similarly as the ethyl groups give completely different sets of resonances it follows that rotation about the OC-N bond must also be restricted. In the $^1H$ nmr spectrum of the starting amide both $-CH_2-$ groups give broad resonances which are close together (and at 60 °C are completely equivalent). This can be attributed to *p*-orbital overlap between the amide group and the aromatic ring as the two groups approach coplanarity reducing the C-N bond order sufficiently to allow rotation about this bond. As the Br substituent restricts rotation about the C-N bond it follows that it must be preventing the amide group and the aromatic ring from approaching coplanarity. This may simply be due to steric interaction between the Br substituent and the carbonyl group.

In conclusion, as the protons attached to C-2 and C-6 are equivalent in amide **34** it follows that the amide group and the aromatic ring do not stay coplanar all of the time. This means that whilst the planes of the 2 groups are at right angles C-2 bromination is not blocked. After C-2 bromination has occured the 2 groups are prevented from becoming coplanar again and hence C-6 bromination is not blocked. A direct analogy between the amide group of **34** and the methoxy groups of the 2,6-dibromo toluene **21** being forced out of the plane is not appropriate anyway as the *p*- orbital overlap in the case of the amide would destabilise, rather than stabilise (as in the case of **21**) the arenium ion intermediate leading to bromination. Therefore the loss of orbital overlap, between the ring and the amide group, in amide **34** could not possibly raise transition state energy for C-2 bromination.

Overall it appears that the route shown to the 4-bromo compound **27** in scheme 12 has the most potential and further work should concentrate on how to brominate the C-4 anion in better yield.

## 5.6 The Acid-catalysed Migration of Bromine Atoms from C-4 to C-6 (Part 1)

One question which remained to be answered was why no C-4 bromination was observed when toluene **19** was brominated. The explanation must be slightly different to that given for why 2,6-dibromo derivative **21** was so difficult to brominate, because it seems possible that the toluene **19** could in part adopt the conformation, shown below in figure 43, where C-4 bromination seems possible




**(19)**

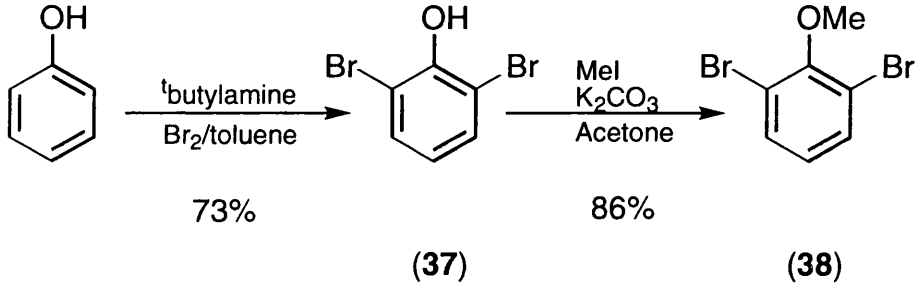
**Figure 43**

The apparent answer was found by stirring the 4-bromo compound **27** in the presence of hydrogen bromide for an hour. A rearrangement was found to occur whereby the 4-bromo compound **27** was converted to a mixture of the toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21**, in the ratio 1 : 7 : 1, by an intermolecular reaction involving the migration of a bromonium ion or its equivalent (e.g. HOBr or $Br_2$). Similarly the 2,4-dibromo compound **32** was found to be converted to its 2,6-dibromo isomer **21** under these conditions (though a longer reaction time was necessary for complete conversion). Therefore it was thought that when the toluene **19** is brominated, even if any of the 2,4-dibromo derivative **32** or the 4-bromo derivative **27** were formed then the HBr produced would result in the migration of the Br atoms in these compounds from C-4 to C-2/C-6.

## 5.7 Does a Methoxy Group in an *ortho* Position, Relative to Two Bromine Substituents, Still Exert an Activating Influence on the Ring?

Having attributed the lack of C-4 reactivity in the 2,6-dibromo compound **21** to the loss of resonance stabilisation in the arenium ion intermediate, that results from the methoxy groups being twisted out of the plane of the ring on further bromination, a question remained. Do methoxy groups forced out of the plane by steric congestion still exert a degree of activating influence on the ring? It was thought that since resonance was lost and the inductive effect of

the oxygen atom is electron-withdrawing that a methoxy group in this position may now exert a deactivating effect on the ring. To investigate this a competitive bromination between 2,6-dibromoanisole (**38**) and 1,3-dibromobenzene was set up. Anisole **38** was prepared by the selective di-*ortho* bromination of phenol using the method of Pearson *et al*[97] to give 2,6-dibromophenol (**37**) followed by a standard Williamson ether synthesis (see scheme 22).




**Scheme 22**

The selective *ortho*-bromination is thought to occur by the mechanism shown in figure 44.

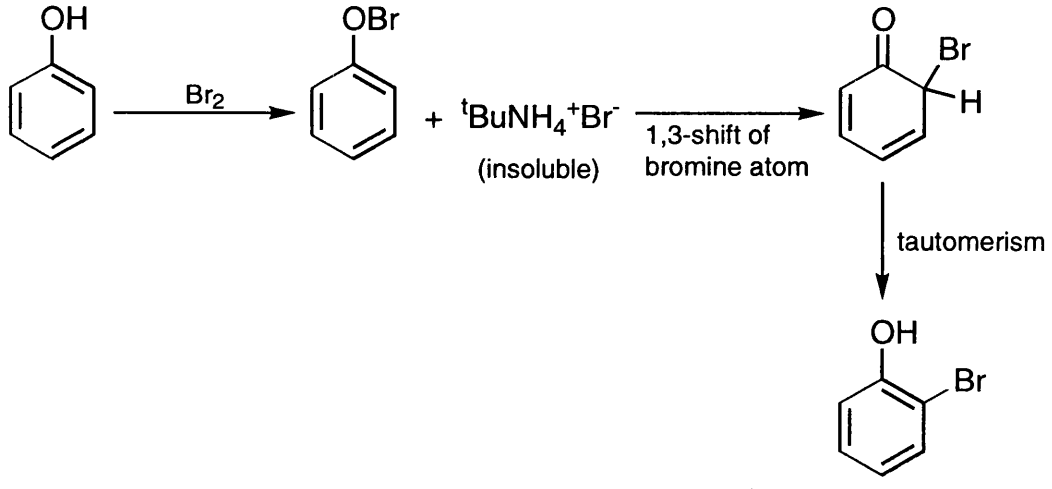



**Figure 44:** Mechanism of *ortho*-bromination of phenol

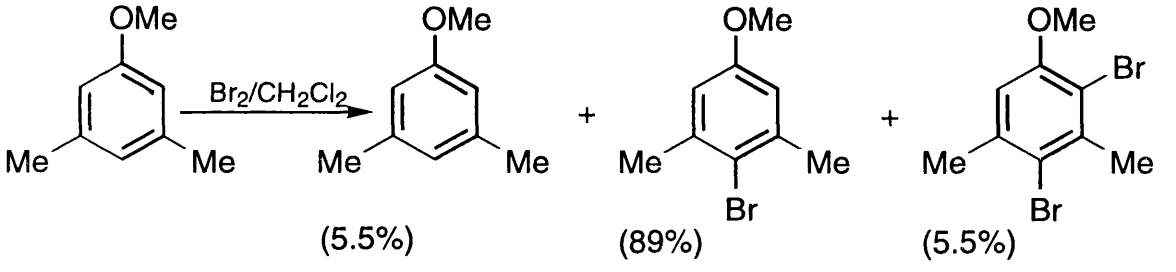
Here there is initial formation of the hypobromite (with the HBr being removed from solution through formation of the insoluble ammonium salt) followed by a 1,3 shift of the bromine atom and subsequent keto-enol tautomerism.

Using the 2,6-dibromoanisole **38** prepared in this way, the aforementioned competitive bromination between **38** and 1,3-dibromobenzene was set up, using DBI in acetic acid as the brominating reagent. After stirring for 24 hours only the anisole **38** was observed to have

undergone further bromination to give 2,4,6-tribromoanisole (**39**) in 60% yield. This indicates that the methoxy group still exerts a degree of activating influence on the ring, which in turn suggests that, though there is undoubtedly steric inhibition of resonance by the bromine atoms they are not sufficiently bulky to remove it completely.

## 5.8 Bromination of 3,5-Dimethylanisole (22)

Further work was carried out on the bromination of the dimethylanisole **22** to investigate the *ortho/para* directing effects of a single -OMe group in a 1,3,5-trisubstituted ring. The use of one mole equivalent of bromine was investigated at this point to determine to what extent the directing influence of a methoxy group favours *para* bromination over *ortho* bromination in 1,3,5-trisubstituted systems. The result of brominating the dimethylanisole **22** with one mole equivalent of bromine is that an 89% yield of 4-bromo-3,5-dimethylanisole (**40**) is obtained with the other compounds isolated being unreacted starting anisole (**22**) and the 2,4-dibromo derivative (**41**) (see scheme 23). This indicates that *para* bromination predominates over *ortho* bromination by at least a factor of 18.




**(22)** **(40)** **(41)**

**Scheme 23**

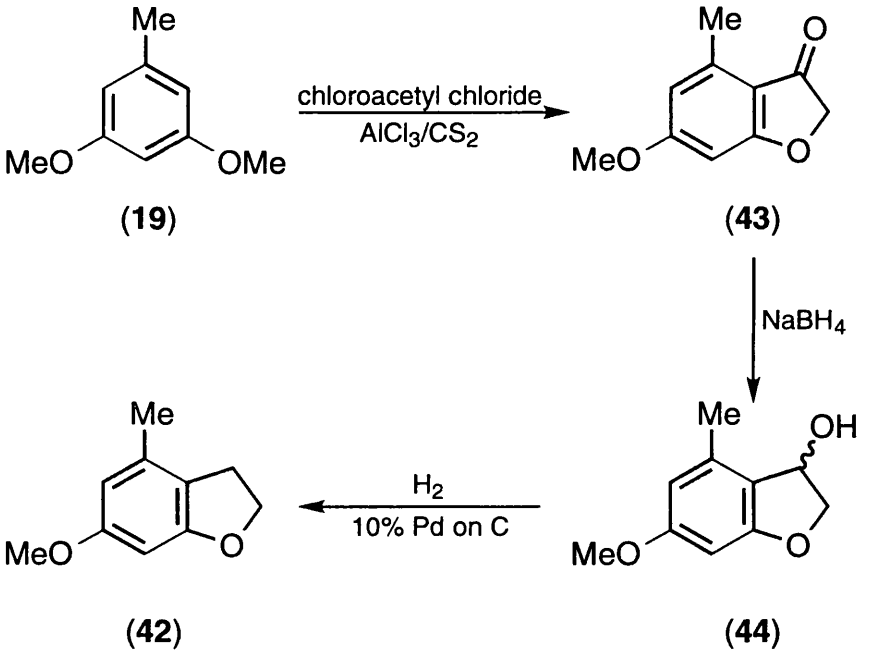
Interestingly bromination of the dimethyl anisole **22** with two mole equivalents of bromine results in an essentially quantative yield of the 2,4-dibromo compound **41**. The formation of the tribromide **23** and 2,6-dibromo-3,5-dimethylanisole does not occur under these conditions, presumably for the same reason that the 2,6-dibromo toluene **21** is reluctant to undergo further bromination. That is, the arenium ion intermediates leading to these two products would have the methoxy group twisted out of the plane of the ring and so resonance stabilisation of these intermediates would be lost or at least greatly reduced. This obviously results in a higher energy transition state.

## 5.9 Studies on the Bromination of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42)

The compound 6-methoxy-4-methyl-2,3-dihydrobenzofuran (**42**) was identified as a synthetic target. It was thought that benzofuran **42** would serve as a useful model for toluene **19**, where one of the methoxy groups was constrained to remain in the plane of the ring thus keeping the oxygen *p*-orbital in conjugation with the -system of the ring.

### 5.9.1 Synthesis of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42)

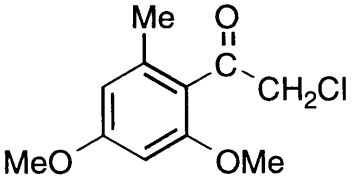
A simple 3 step synthesis of benzofuran **42** has been published by Murai *et al* [98](see scheme 24).




(**19**) (**43**) (**44**) (**42**)

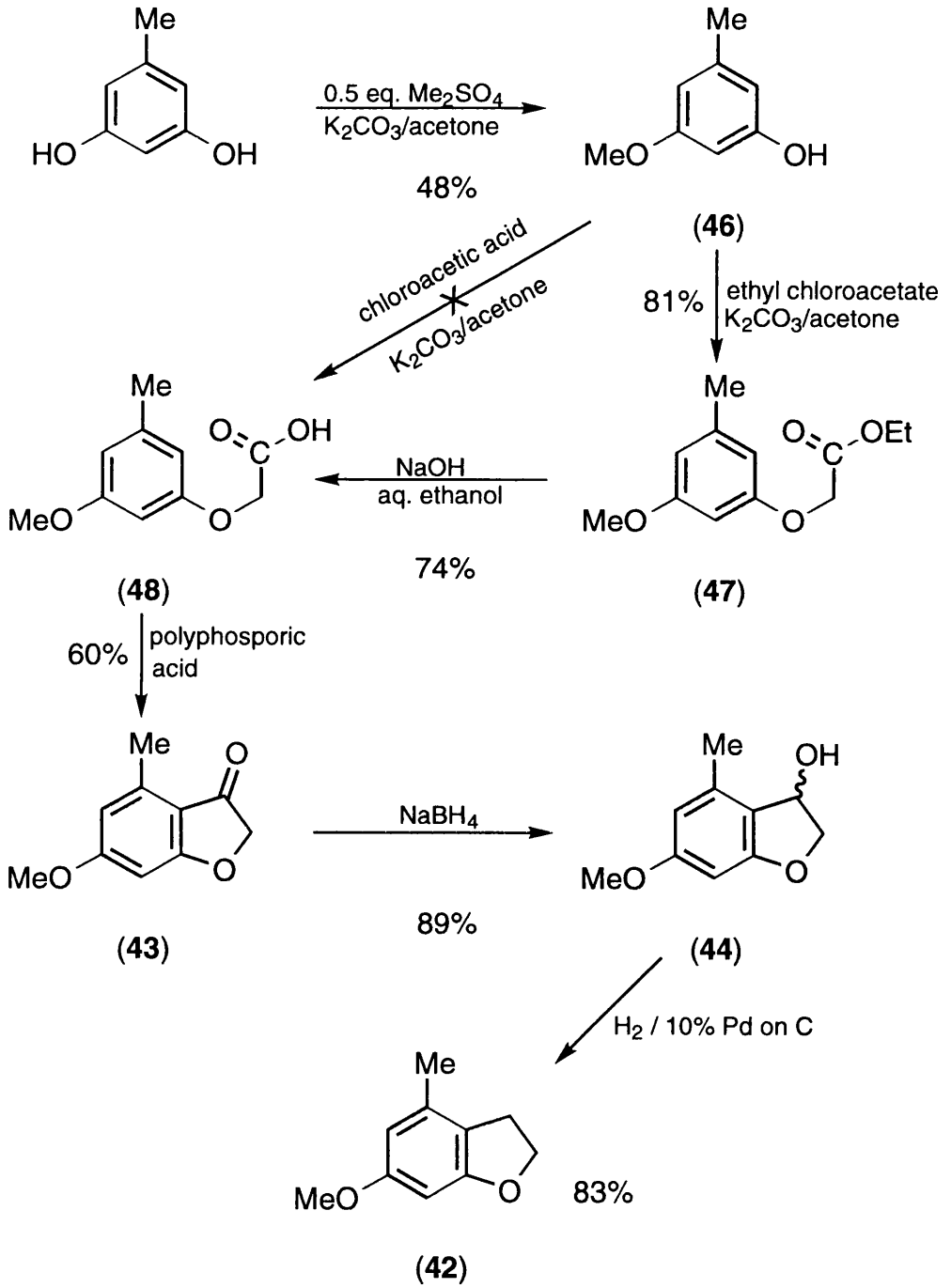
**Scheme 24**

The first step in this synthesis (which involves a Friedel-Crafts acylation, demethylation of the neighbouring methoxy group and finally a substitution reaction to close the furan-3-one ring) proved difficult to replicate. Despite several attempts the desired product, 6-methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (**43**) was never obtained with the only product ever isolated being 2-chloroacetyl-3,5-dimethoxytoluene (**45**).




(**45**)

It was therefore decided to approach benzofuran **42** from the alternative route shown in scheme 25. This scheme was successfully completed as shown (all the yields are unoptimised).




**Scheme 25**

The key step in the synthesis is the formation of the furanone ring. This was achieved through dehydration of 3-methoxy-5-methylphenoxyacetic acid (**48**) to give 6-methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (**43**) using PPA[99]. The acylation involved, occurs at C-6, rather than at C-2, as a result of the methoxy group directing *para* to a greater extent than *ortho*.

### 5.9.2 The Bromination of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42)

Before experiments were carried out whereby benzofuran **42** was brominated it was predicted that bromination with 1 mole equivalent of bromine would lead exclusively to the formation of 5-bromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**49**). This prediction was based upon the fact that *para* bromination is expected to predominate and by analogy with the 2,4-dibromo toluene **32** and the 4-bromo toluene **27** any 5,7-dibromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**50**) and 7-bromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**51**) formed are expected to undergo an intermolecular C-7 to C-5 bromine atom shift to give the 5-bromo benzofuran **49**. It was also predicted that the use of 2 mole equivalents of bromine would give rise, without the need of catalysis, to a quantative yield of the 5,7-dibromo benzofuran **50**. This prediction was based upon the fact that the furan oxygen *p*-orbital is kept in conjugation with the ring -system and thus the energy of the arenium ion intermediate (and thus the transition state), leading to the 5,7-dibromo benzofuran **50**, should be lowered by resonance stabilisation of the positive charge.

However, whilst the latter of these predictions turned out to be correct, bromination of benzofuran **42** with one mole equivalent of bromine did not give rise to exclusive formation of the 5-bromo derivative **49** (see figure 45).

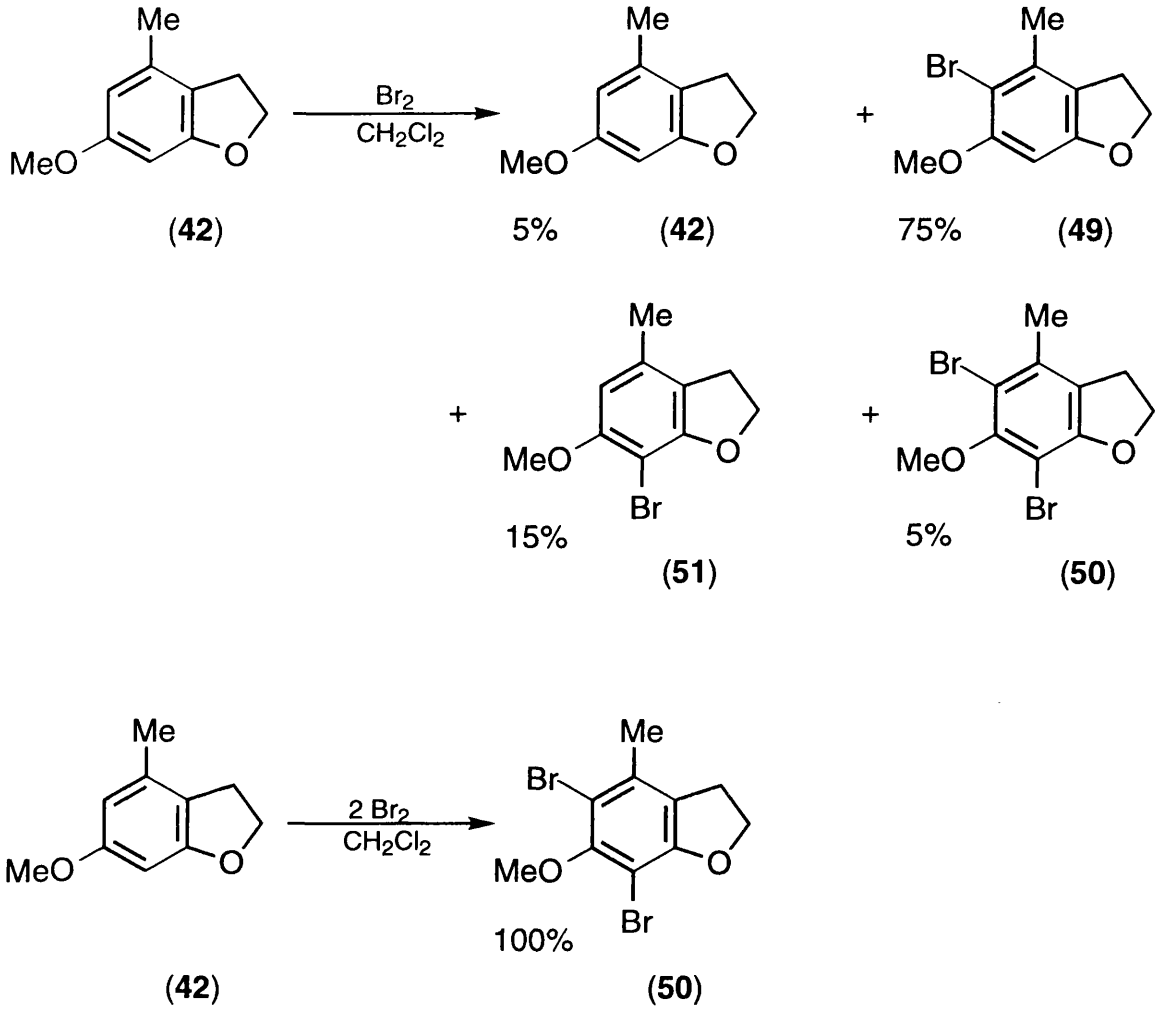
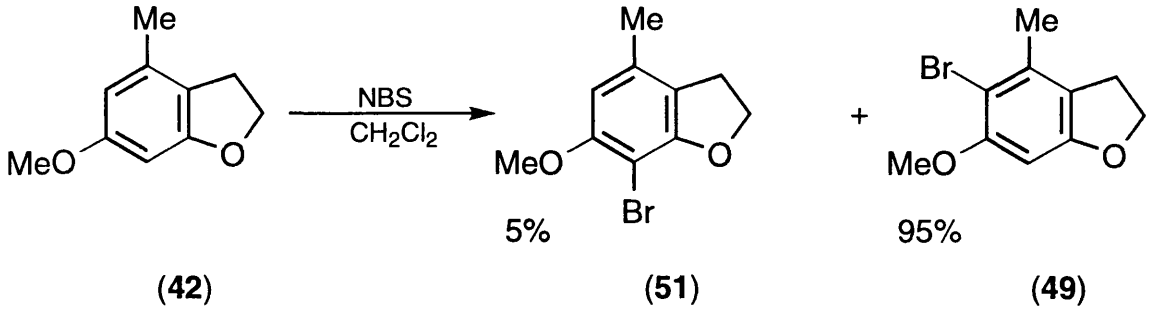



**Figure 45**

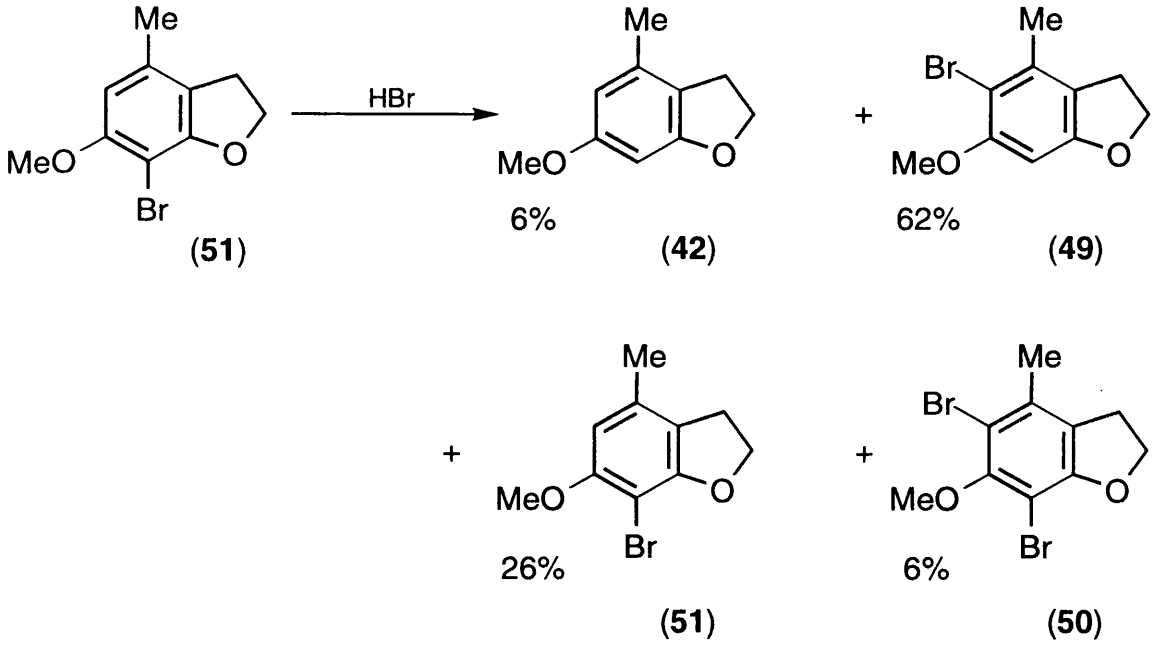
Even the use of NBS as the brominating reagent did not give exclusively the 5-bromo benzofuran **49**, though a 95% yield was obtained (see scheme 26).




**Scheme 26**

### 5.9.3 Acid-catalysed Bromine Atom Migration in the Brominated Derivatives of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42)

It was thought that perhaps that the reason for lack of selectivity was that the 7-bromo benzofuran **51** and the 5,7-dibromo benzofuran **50** did not undergo the intermolecular bromine atom migration observed for the 4-bromo toluene **27** and the 2,4-dibromo toluene **32**. In order to test whether this was the case, the 7-bromo benzofuran **51** was stirred in the presence of hydrogen bromide for 4 hours. This resulted in a mixture of compounds **42**, **49**, **51** and **50** being formed as shown in scheme 27.

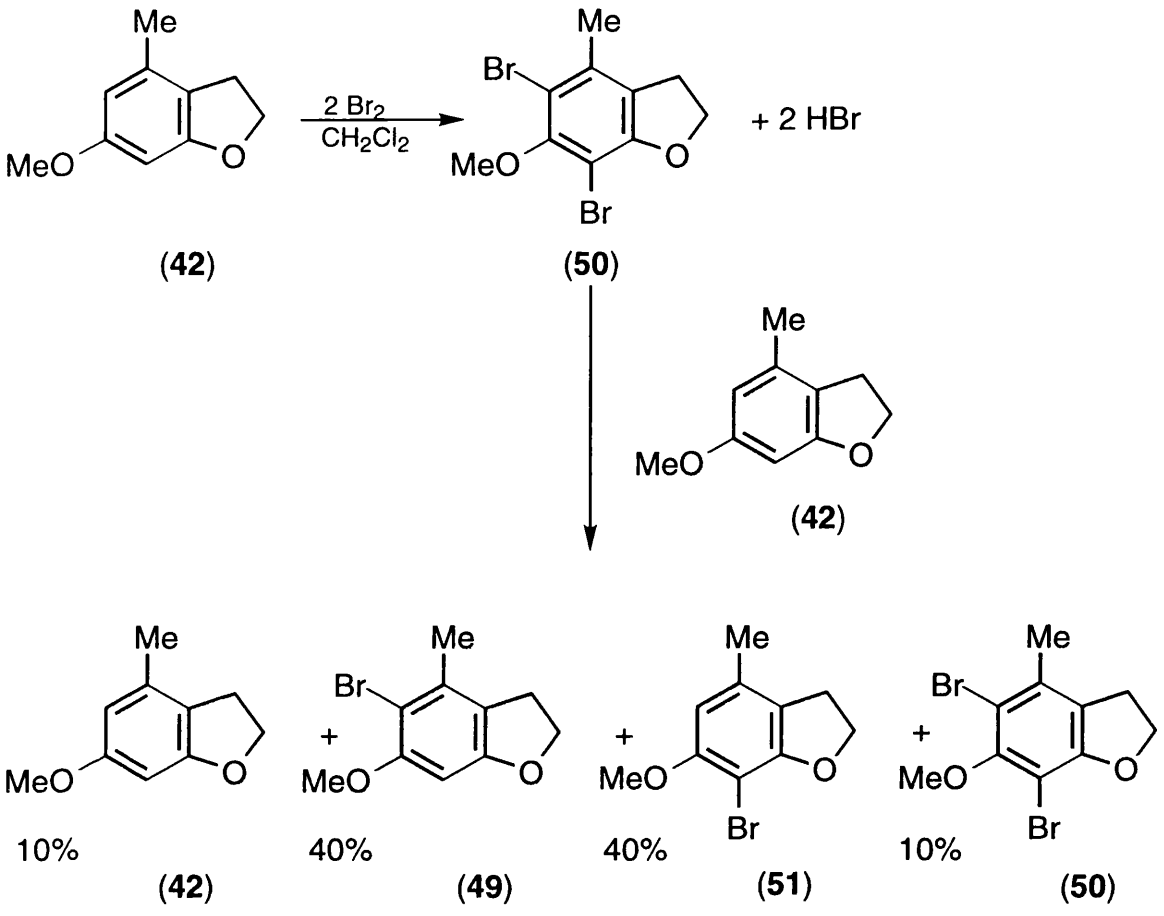



(51) (42) (49) (51) (50)

**Scheme 27**

This result was initially interpreted as showing that the aforementioned acid-catalysed bromine atom migration did occur in the 7-bromo benzofuran **51** and that 4 hours was simply not a long enough period of time to allow this migration reaction to go to completion.

However, a very surprising result was obtained when an attempt was made to see whether the C-7 bromine atom of the 5,7-dibromo benzofuran **50** would migrate to the C-5 position of benzofuran **42** in the presence of hydrogen bromide. The 5,7-dibromo benzofuran **50**, formed *in situ* along with an equivalent amount of hydrogen bromide, was treated with an equimolar amount of the starting benzofuran **42** and stirring continued for one hour. This resulted in the formation of compounds **42**, **49**, **51** and **50** in the ratio 1 : 4 : 4 : 1 as shown in scheme 28.




**Scheme 28**

The explanation of this result is, that it is the bromine atom on the C-5 position in the 5,7-dibromo benzofuran **50** that most readily undergoes intermolecular migration and that migration of the bromine atom from the C-7 position takes considerably longer. This is actually very easily understood as the loss of the bromine atom is thought to occur simply by the same process as bromination only in reverse. This means that there is electrophilic attack on the ring by a proton to form the same arenium ion intermediate involved in bromination. Obviously therefore the proton will most readily attack that site which is most activated towards electrophilic substitution (in this case C-5) and the bromine atom from this site will be lost.

This result has several implications. Firstly, it is possible to obtain the 7-bromo benzofuran **51** in reasonable yield without the use of a strong base. This is done by an iterative process whereby benzofuran **42** dibrominated then an equivalent amount of **42** added and stirred. The 40% of the 7-bromo derivative **51** that results can be separated and the remainder of product recycled by fully brominating then adding more of the starting benzofuran **42** etc.

Secondly, in view of the fact that the product distributions, obtained in the bromination of benzofuran **42**, appeared to be thermodynamic, and not kinetic, in nature, was this also true for toluene **19** ? Experiments had been carried out to show that benzoate **16** gave kinetic

product distributions (see pages ) but the analogous experiments for toluene **19** had never been tried.

## 5.10 Acid-Catalysed Bromine Atom Equilibration in the Brominated Derivatives of 3,5-Dimethoxytoluene (19)

The two experiments shown in figure 46 indicate that the product distributions obtained in the bromination of toluene **19** with molecular bromine are indeed the result of thermodynamic control.

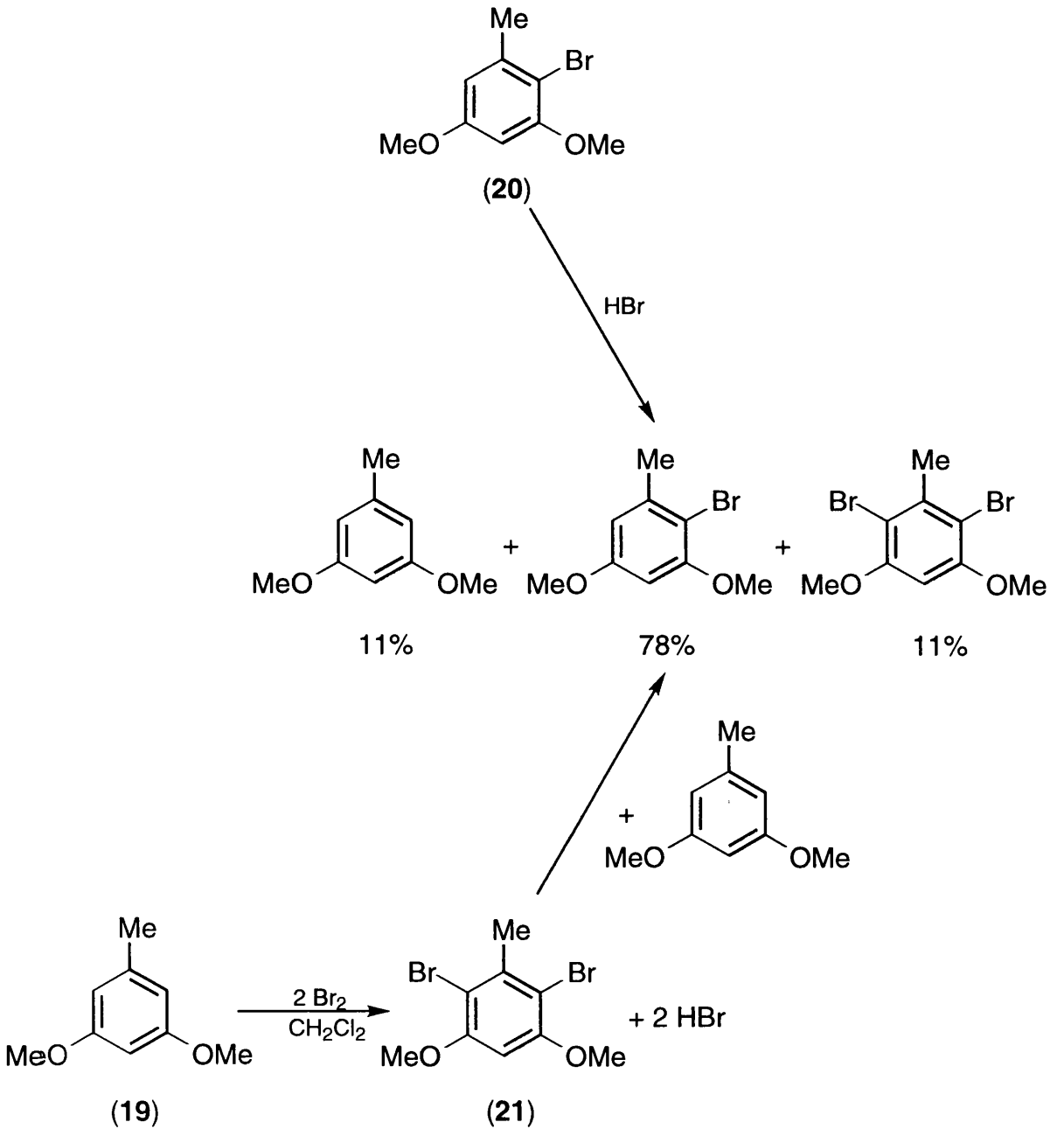
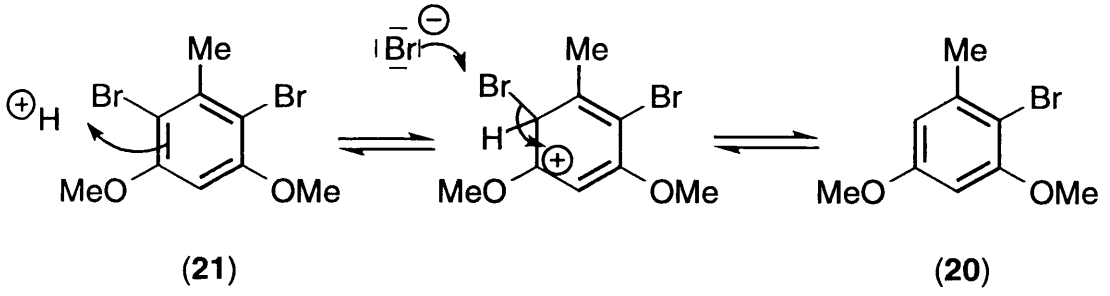



**Figure 46**

It can be seen that treatment of the 2-bromo toluene **20** with hydrogen bromide for 30 minutes results in a product distribution indistinguishable from that obtained from treating the 2,6-dibromo toluene **21** with an equimolar amount of starting toluene **19** in the presence of hydrogen bromide for 30 minutes.

These results provide an explanation for the apparently anomalous earlier results obtained for the bromination of toluene **19** (see page ). The reason why toluene **19** showed a greater degree of monobromination selectivity than benzoate **16** is that whilst **16** gives rise to a kinetic distribution, **19** gives a thermodynamic distribution and is therefore not subject to microscopic diffusion control to the same extent. Therefore, though toluene **19** and the 2,6-dibromo derivative **21** were presumably initially formed in relatively large amounts the equilibration of the bromine atoms shown in figure 47 would greatly reduce their concentrations before the reaction was actually worked up.



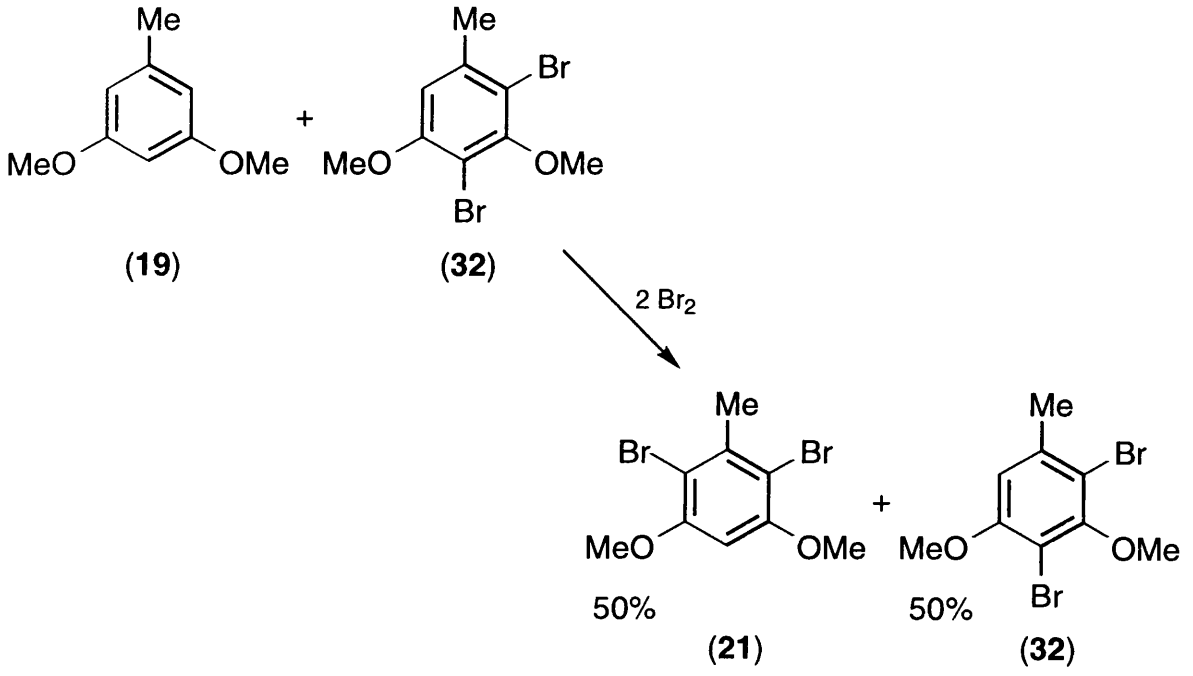

**(21)** **(20)**

**Figure 47**

Similarly the reason that dilution of the substrate solution reduced monobromination selectivity is that the initially formed product would presumably have greater concentrations of toluene **19** and the 2,6-dibromo derivative **21** (than the final isolated product) due to *microscopic diffusion control* and the extra dilution would slow down the bromine atom equilibration. It would appear that when the reaction was worked up insufficient reaction time had been allowed for the (slowed) bromine atom migration to reach equilibrium.

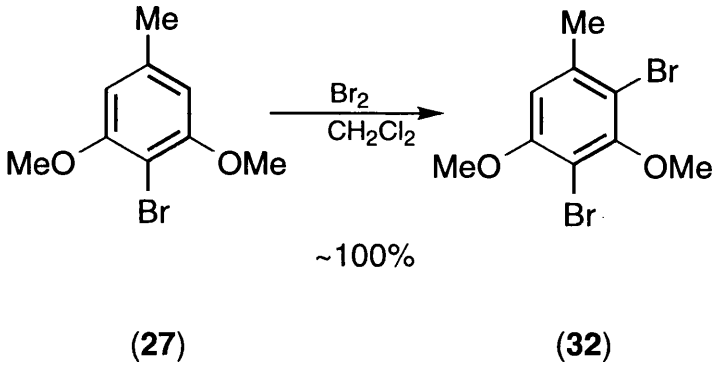
In view of the relatively slow migration of the C-7 bromine atoms in the 7-bromo benzofuran **51** and the 5,7-dibromo benzofuran **50** it was decided to re-examine the migration of the C-4 bromine atoms in the 2,4-dibromo toluene **32** and the 4-bromo toluene **27**. The first point noted was that it took approximately 4 hours for the bromine atoms in the 2,4-dibromo toluene **32** to reach equilibrium (this is presumably because the C-3 methoxy group is twisted out of conjugation with the ring which is therefore not so activated towards electrophilic attack by a proton at C-4). This would seem to suggest that under standard reaction conditions (which only involved stirring for 1 hour) there would be insufficient time for any of the 2,4-dibromo compound **32** which may form to be fully converted to its 2,6-dibromo isomer **21**. Therefore

the fact that no 2,4-dibromide **32** was ever observed in the direct bromination of toluene **19** indicates that **32** was simply *never* formed in detectable quantaties in these reactions. This was proven by dibrominating toluene **19** in the presence of an equimolar amount of the 2,4-dibromo derivative **32**. When the reaction was worked up the vast majority of the 2,4-dibromo toluene **32** remained unconverted (see scheme 29).




**Scheme 29**

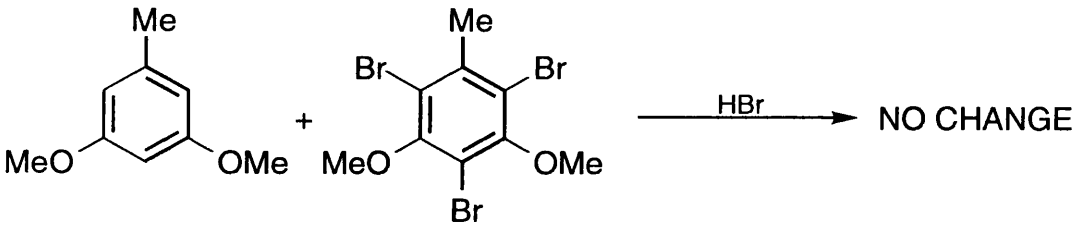
Furthermore, in view of its rate of its relatively slow rate of bromine atom equilibration, could the 4-bromo toluene **27** be brominated directly to give the 2,4-dibromo derivative **32** ? The answer to this question again turned out to be yes. Immediate work-up of the reaction following the decolourisation of the bromine gave an essentially quantative yield of the 2,4-dibromo toluene **32** (see scheme 30).




**Scheme 30**

It therefore follows that the 4-bromo toluene **27** undergoes bromination at a faster rate than bromine atom equilibration. This in turn implies that, since the 2,4-dibromo toluene **32** was never observed in the dibromination reaction under standard conditions, then the 4-bromo toluene **27** could also simply never have been formed in observable quantities either because if any **27** formed had an inadequate amount of time to undergo further bromination then it would also have had an inadequate time to undergo bromine atom equilibration. Therefore, as the 4-bromo toluene **27** was never observed, then it must simply not be formed at all.

Unsurprisingly when the tribromide **25** is stirred with 2 mole equivalents of the toluene **19** in the presence of hydrogen bromide for 4 hours then no intermolecular bromine atom migration is observed. This is to be expected because the loss of a bromine atom from the tribromo compound **25** would involve the same high energy arenium ion intermediate that is observed to be unattainable during the attempted bromination of the 2,6-dibromo toluene **21** with bromine (see scheme 31).




**(19)** **(25)**

**Scheme 31**

The conclusion that observable quantaties of the 4-bromo compound **27** are never formed leaves the question posed earlier (see page ) as to why this is the case unanswered. It is worthy of note however that *para* bromination in the dimethyl anisole **22** is observed to predominate over *ortho* bromination by at least a factor of 18. In this example there are 2 *ortho* positions and 1 *para* position (with respect to the methoxy group). Drawing an analogy with the case of toluene **19** where there are effectively 2 *para* positions and only one purely *ortho* position (with respect to the methoxy groups) then *para* bromination may be expected to predominate by a factor of 72 and it is therefore possible that the directing influence exerted on the ring (by the 2 methoxy groups) is entirely responsible for the apparent lack of formation of the 4-bromo compound **27.**

# 6

# The Benzylic Bromination of 3,5-Diacetoxytoluene

## 6.1 Attempted Benzylic Bromination of 3,5-Dimethoxytoluene

As mentioned previously no benzylic bromination had been encountered in any of the experiments on the bromination of toluene **19**. Both bromine and NBS have the potential to carry out this reaction. However, due to the greater reactivity of bromine towards aryl bromination, NBS is the reagent of choice with regards to developing selective benzylic bromination methodology.

The use of this reagent in this respect (Wohl Ziegler Reaction) is well documented[66]. Toluene **19** however, proved to be too activated towards aromatic electrophilic substitution to undergo benzylic bromination selectively. This problem is also reported in the literature[100]. Experiments using NBS in $CCl_4$ with either AIBN, light or both as the initiator all gave rise to product mixtures composed solely of unreacted toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21**. Under the same conditions toluene underwent benzylic bromination to give a mixture of toluene, benzyl bromide and benzal bromide.

The reason for this lack of reactivity towards benzylic bromination in toluene **19** is that the radical chain mechanism involved in the Wohl Ziegler reaction (see figure 24) involves $Br_2$. The electrophilic substitution reaction between toluene **19** and molecular bromine is extremely rapid and so any bromine formed is likely to be consumed by aryl rather than benzylic bromination.

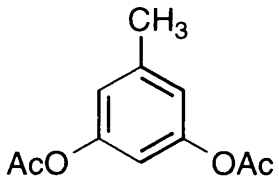
## 6.2 The Benzylic Bromination of 3,5-Diacetoxytoluene (52)

It was however, found that 3,5-diacetoxytoluene (**52**), which is much less activated towards aromatic electrophilic substitution than toluene **19**, undergoes exclusive benzylic bromination under the previously mentioned benzylic bromination conditions. The difference in reactivity between dimethoxy compound **19** and diacetoxy compound **52** can be explained as follows. By replacing the methoxy groups of **19** with acetoxy groups which are much less effective at stabilising positive charge formation, both on the ring and at the benzylic carbon, the rate of both the aryl and benzylic bromination reactions are reduced. However, aryl bromination involves an intermediate with a full positive charge whereas the transition state for benzylic bromination has only a partial positive charge, therefore the rate of aryl bromination is much more sensitive to changes in the electronic properties of the ring substituents. This results in the rate of aryl bromination being reduced to a greater extent than that of benzylic

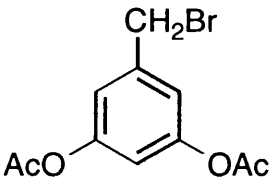
bromination. This differential rate reduction is sufficient to make the diacetoxytoluene **52** more reactive towards benzylic bromination than towards aryl bromination.

Initial experiments used both AIBN and light to initiate the reaction but it was later found that light alone leads to a slower more selective reaction. The benzylic bromination of the diacetoxytoluene **52** was carried out using 1, 2 and 3 mole equivalents of NBS.

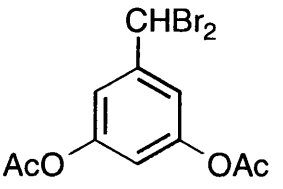
With 1 mole equivalent of NBS was used the product mixture was found to be composed of the unreacted diacetoxytoluene **52**, the benzyl bromide derivative **53** and the benzal bromide derivative **54** in the ratio 1 : 3.6 : 1, which represents a 64% yield of monobromide **53**.




**(52)**

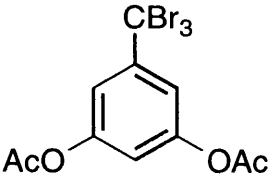



**(53)**




**(54)**

With 2 mole equivalents of NBS, the product mixture was found to be composed of unreacted diacetoxytoluene **52** (trace amount), monobromide **53**, dibromide **54** and the tribromide **55** in the ratio trace : 1 : 7.9 : 1, which represents a 79% yield of the dibromide **54**. There was also evidence for very small amounts of a radical combination product.




**(55)**

With 3 mole equivalents of NBS the major products are the dibromide **54** and tribromide **55** in the ratio 1 : 2.6. There are also several other biradical combination products present in smaller amounts.

These reactions were all carried out at reflux, due to the proximity of the light source. It was found that with external cooling to keep the reaction temperature at around 20°C the selectivity of the reaction (with 1 mole equivalent of NBS) increased with regards to mono-benzylic bromination to 66%. This represents however only a small increase in selectivity and further reductions in reaction temperature proved impractical.

It was later found (see page ) that the use of a solvent with a lower refractive index leads to greater benzylic bromination selectivity in brominations with NBS[101]. The benzylic

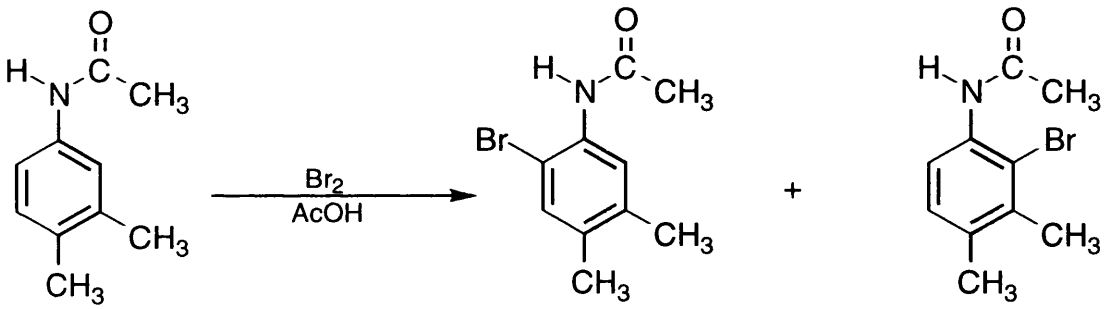
bromination of the diacetoxytoluene **52** with 1 and 2 mole equivalents of NBS was therefore reinvestigated using dichloromethane as the solvent instead of carbon tetrachloride. With 1 mole equivalent of NBS there was a large increase in selectivity with the ratio, unreacted diacetoxytoluene **52**: monobromo derivative **53** : dibromo derivative **54**, obtained being 1 : 6.9 : 1. This represents a 78% yield of the monobromide **53** and a 14% improvement in comparison with the yield obtained using carbon tetrachloride as the solvent. The same considerable improvement in yield was not however observed when 2 mole equivalents of NBS were used. This gave rise to monobromide **53**, dibromide **54** and tribromide **55** in the ratio 1 : 7 : 0.6 which represents an 81% yield of the dibromide **55** and only a 2% improvement on the yield obtained using carbon tetrachloride as the solvent.

# 7

# Zeneca Pharmaceuticals Bromination Projects

## 7.1 The C-6 Bromination of 3,4-Dimethylacetanilide (56)

An early bromination step involved in the synthetic pathway to the potential drug substance ZD9331, currently being developed by Zeneca Pharmaceuticals, is shown in scheme 32.




**(56)** **(57)** **(58)**

**Scheme 32**

The aim of this section of work is to optimise the selectivity of the reaction towards the desired isomer, 2-bromo-4,5-dimethylacetanilide (**57**). This isomer is the main product of the reaction as the C-6 position of 3,4-dimethylacetanilide (**56**) is more reactive than the C-2 position as bromination at the latter position is subject to a greater degree of steric hindrance.

Two main possibilities exist for improving the selectivity of the reaction towards 2-bromo-4,5-dimethylacetanilide (**57**) rather than the unwanted isomer 2-bromo-3,4-dimethylacetanilide (**58**).

1. Increase of the steric bulk of the amide group.

2. The use of more selective brominating reagents and/or conditions.

The latter possibility is the more viable approach as the former would require two extra steps to be added to the synthetic pathway since the acetyl group is not simply a protecting

group (to prevent the problem of extensive dibromination that would occur if the corresponding aniline was brominated) and becomes part of a ring in later synthetic steps.

The first experiment to be carried out involved the use of the standard conditions of 1 mole equivalent of bromine in dichloromethane. This lead to a product composed of **57** and **58** in the ratio 12 : 1. In order to try and improve upon this and test the potential of this brominating system the reaction was carried out at -70 °C. This produced an improvement in the product ratio to 16 : 1. Doubtless further temperature reductions would improve the selectivity of the reaction further but this was not considered to be practical.

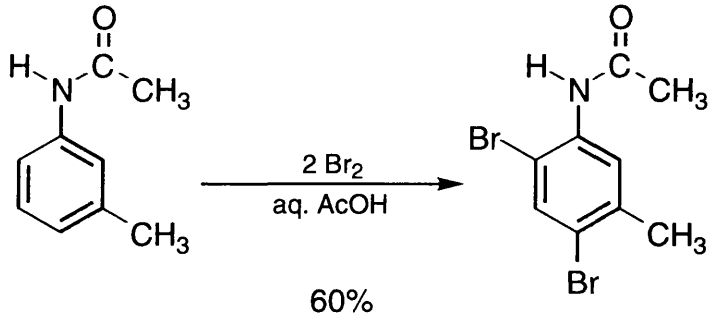
A system which had previously exhibited excellent selectivity in the bromination of benzoate **16**, toluene **19** and benzofuran **42** was NBS in DMF. The use of this reagent however, resulted in a surprisingly poor **57** : **58** ratio of just 8 : 1.

Another *N*-bromoamide, DBI, was also tried. Though this had previously been shown to be a very powerful brominating reagent it was thought that the extra bulk of DBI may help improve the selectivity of the bromination towards the less hindered position. Perhaps unsurprisingly, however, this was found not to be the case and a poor **57** : **58** ratio of just 7 : 1 resulted. The use of DBI also lead to the production of some dibromide and the recovery of some starting acetanilide **56**.

Analysis of the literature revealed that quaternary ammonium polyhalides[51] had been found to be very selective reagents for the regioselective bromination of acetanilides. In particular it was reported that **57** could be obtained from **56** in 92% yield using benzyltrimethylammonium chlorobromate in a 5:2 mix of $CH_2Cl_2$ and MeOH. This reagent was therefore prepared (from $Br_2$ and benzyltrimethylammonium chloride) and the experiment repeated. As reported this system showed excellent selectivity with a 19 : 1 product ratio being obtained. This improved selectivity may be the result of the bulkier brominating reagent having a greater preference for reaction at less hindered positions.

## 7.2 The C-4/C-6 Dibromination of 3-Methylacetanilide (59)

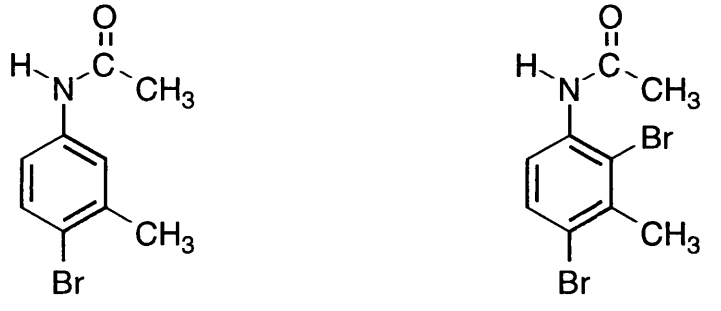
An alternative route to the same target drug substance is also currently under investigation at Zeneca Pharmaceuticals. This involves a different bromination step (see scheme 33).




**(59)** **(60)**

**Scheme 33**

Though this step would appear to have the added complication of requiring 2 regioselective brominations this should actually pose no additional problems as the product of C-4 reported is reported to be obtained in 98.5% yield during mono bromination of this system[102]. This is again due to steric inhibition of resonance resulting in the arenium ion intermediates, leading to bromination *ortho* to the -$NHCOCH_3$ group, being high in energy in comparison with the arenium ion for bromination *para* to the -$NHCOCH_3$ group. Therefore, as bromination *para* to the -$NHCOCH_3$ group is preferred over bromination *ortho*, along with the desired product 2,4-dibromo-5-methylacetanilide (**60**) the expected main impurity is 2,4-dibromo-3-methylacetanilide (**62**).



**(61)** **(62)**

The first experiment to be carried out again involved the use the adopted standard conditions of 2 mole equivalents of bromine in dichloromethane. This reaction turned out to be rather slow and even after stirring at room temperature for 16 hours the characteristic colour of

the bromine had not completely disappeared. Despite this the reaction was worked up and the product mixture analysed. The products obtained were **60**, **62** and 4-bromo-3-methylacetanilide (**61**) in the ratio 3 : 1 : 0.1. When the reaction was allowed to go to completion by stirring for 72 hours the only products obtained were **60** and **62** in the ratio 3.1 : 1. This suggests that the C-4 position of 3-methylacetanilide (**59**) is the most reactive and that the initially formed monobromide is probably almost exclusively the 4-bromo acetanilide **61** as reported.

Again the use of NBS was investigated, but even on refluxing 4 mole equivalents of NBS in DMF for 72 hours the reaction did not go to completion with only a small amount of dibromination being observed. It therefore appears that NBS in DMF is too mild a reagent to dibrominate such a substrate that is only moderately activated towards electrophilic substitution.

The next experiment to be carried out again involved bromine as the brominating reagent but used 100% acetic acid as the solvent instead of the previously used dichloromethane. After stirring a 0.2667 M solution of acetanilide **59** with 2 mole equivalents of bromine for 1 hour, TLC analysis of the reaction mixture suggested that no dibromination had taken place. However, despite this, it was decided to work up the reaction to investigate the nature of the initially formed products. On pouring the solution into water, however, decolourisation of the remaining bromine was observed to take place and a white solid precipitated out of solution. The composition of this solid was found to vary with the amount of water used (see table 8).

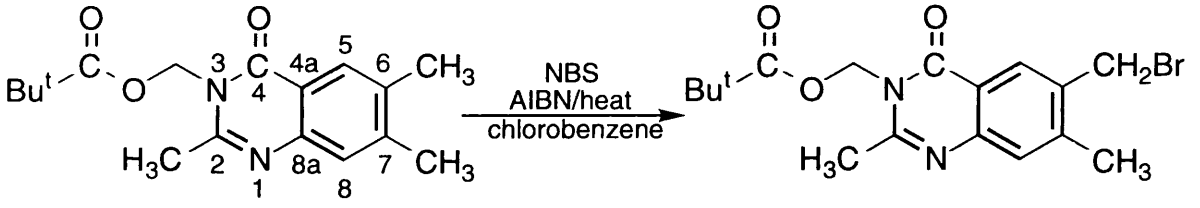
| No. of Volumes of Water Used | % of Compound 60 in Precipitate | % of Compound 62 in Precipitate | Mixed Yield (%) |
|---|---|---|---|
| 6.67 | 71 | 29 | 90 |
| 4.00 | 91 | 9 | 80 |
| 3.33 | 94 | 6 | 76 |
| 2.00 | ~100 | 0 | 70 |

**Table 8**

It can be seen that whilst reducing the amount of water used reduces the amount of crude material that precipitates out of solution it also improves the percentage of the desired dibromide (**60**) in the precipitate until essentially pure **60** can be obtained. This is of considerable advantage since the separation of the isomeric compounds **60** and **62** is somewhat difficult. Indeed the 70% yield obtained (10% improvement) without the need of further purification means that this could be a useful method that is also viable on an industrial scale.

## 7.3 The Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethyl quinazolinone (63)

A key step that occurs later in the synthetic pathway to the same potential drug substance is the benzylic bromination of 2,6,7-trimethyl-*N*(3)-pivaloyloxymethyl quinazolinone (**63**) shown in scheme 34.




**(63)** **(66)**

**Scheme 34**

### 7.3.1 Explanation of the Observed Selectivity of Bromination

The observed selectivity of this reaction can be explained as follows. During the process of benzylic bromination those hydrogen atoms, bonded to sites at which a developing positive charge can be delocalised most extensively (thus stabilising the partially charged intermediate), are most readily abstracted (see page ). A positive charge on the C-6 methyl group carbon can be delocalised to the amide nitrogen as shown in figure 48. This is not possible for the C-7 methyl group carbon.

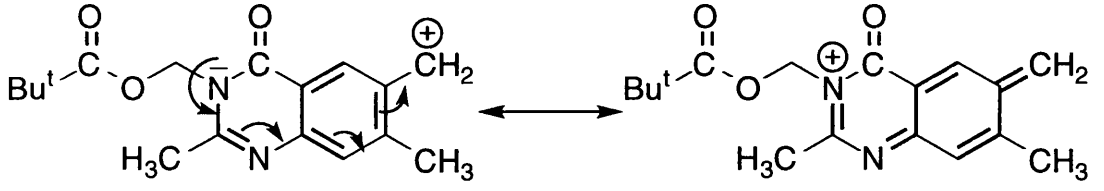


**Figure 48**

Furthermore, delocalisation of positive charge from the C-7 methyl group carbon to two of the ring carbons is also disfavoured. Delocalisation of charge to C-4a is disfavoured by the electronic withdrawing properties of the adjoining carbonyl group and similarly delocalisation of the charge to C-8 is disfavoured as this carbon can be considered as having an adjoining imine group, which is also electron withdrawing (see figure 49).

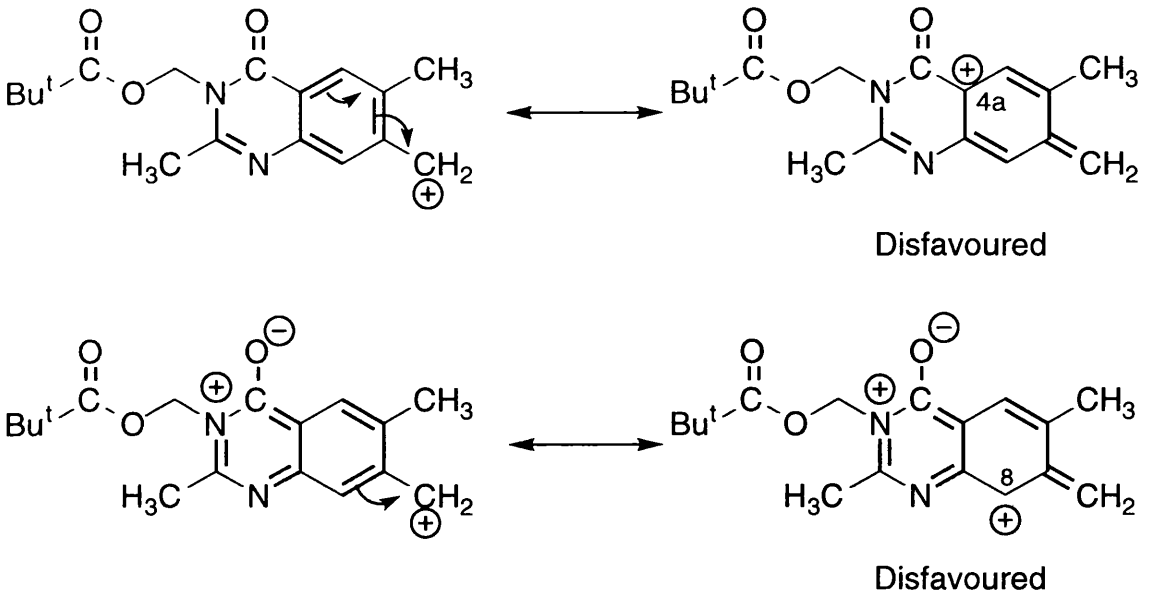



**Figure 49**

Delocalisation of a positive charge from the C-6 methyl carbon to the corresponding ring carbons, C-5 and C-8a, is however not disfavoured in this way and therefore benzylic bromination occurs more readily at the C-6 methyl group than the C-7 methyl group. Furthermore benzylic bromination of both the C-6 and C-7 methyl groups is favoured over benzylic bromination of the C-2 methyl group as the pyrimidinone ring does not have as great a degree of aromatic character as the adjoining benzene ring.

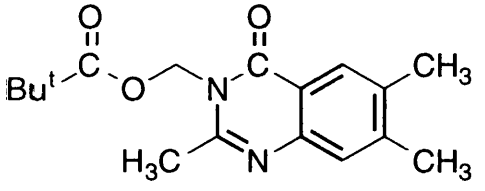
### 7.3.2 Importance of the Bromination Step in the Synthesis of ZD9331

This step is of key importance in the synthesis as the benzyl bromide produced is coupled, in the convergent step of the synthesis, with a functionalised amine which takes several steps to prepare. Therefore, it is not only important to improve the yield of this reaction but also to improve the purity of the product obtained to avoid the formation, in the next step, of unwanted side products where coupling has occured at the wrong site(s). These side products have proven difficult to separate and their formation results in a proportion of the amine being effectively wasted.

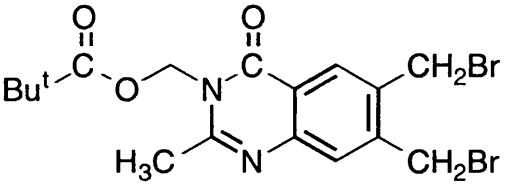
### 7.3.3 Initial Experiments on the Benzylic Bromination of Quinazolinone (63)

When the first experiments were carried out, the details of the process that was currently in use at Zeneca Pharmaceuticals were unavailable. The initial choice of conditions was therefore based on results obtained for the benzylic bromination of the diacetoxytoluene **52**. These results suggested that a photo-initiated reaction of NBS in carbon tetrachloride would result in a reasonably clean reaction. It was decided however to change the solvent to

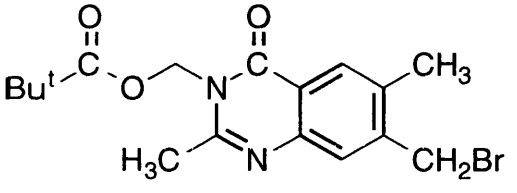
1,1,1-trichloroethane as this is considerably less toxic than carbon tetrachloride. The use of these conditions gave rise to a product mixture which TLC analysis suggested was composed of at least 5 constituents. A chromatographic separation afforded compounds identified as 6,7-di(bromomethyl)-2-methyl-*N*(3)-pivaloyloxymethylquinazolinone (**64**), 6-bromomethyl-2,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**66**), 7-bromomethyl-2,6-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**65**) and starting quinazolinone **63** with the other components not being isolated. These latter 2 compounds were not completely separated as they had identical $R_f$ values but the spectroscopic identification of the 7-bromomethyl compound **65** was still possible from the mixed sample by subtraction of the known signals for quinazolinone **63**.



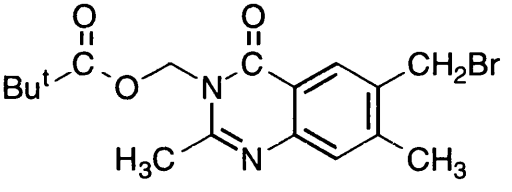
**(63)**



**(64)**



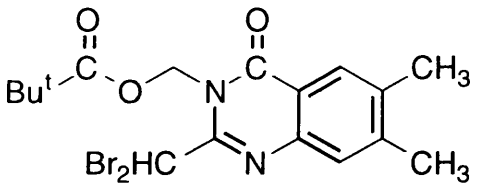
**(65)**



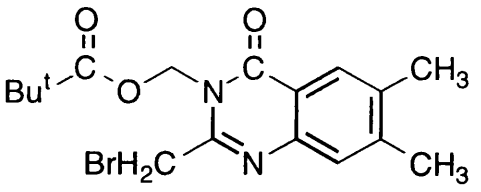
**(66)**

Analysis of the $^1H$ nmr spectrum of the initial crude product suggested that these 4 compounds **63**, **64**, **65** and **66** were present in the ratio 2.5 : 1 : 1 : 13.7 and that at least 2 other unidentified components were present.

Though the nature of all the products had not been determined it was decided to investigate the effect of adding 1 mole equivalent of hydrogen bromide to the reaction to determine the effect this would have on the product distribution. It was thought that protonation of N-1 would occur and that this would effect the relative reactivities of the C-6 and C-7 methyl groups. However, it was found that this change resulted in an entirely different product distribution with 2-dibromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**67**), 2-bromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**68**) and starting quinazolinone **63** being obtained in the ratio 1 : 2 : 1.

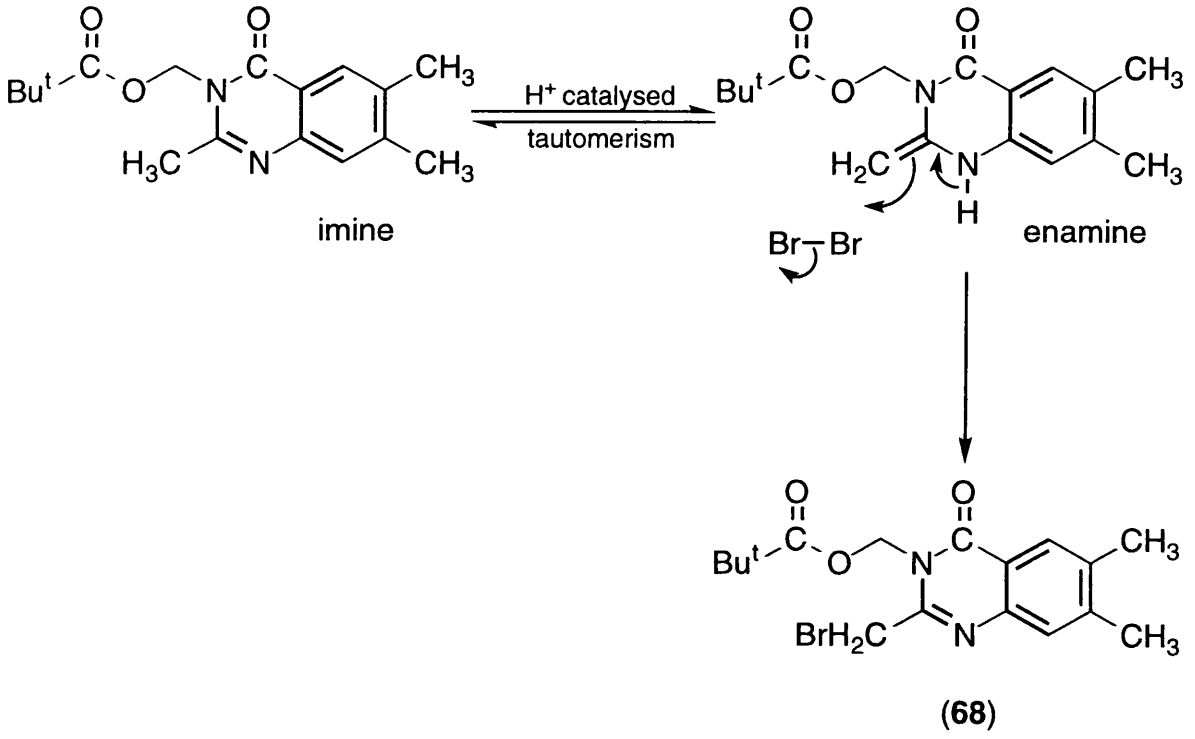


(67)



(68)

The reason for this change in the product distribution is that the acid catalyses ionic bromination of the C-2 methyl group *via* imine-enamine tautomerism (see figure 50).




(68)

**Figure 50**

The 2-bromomethyl quinazolinone **68** was also demonstrated to be one of the unidentified products in the previous reaction present at a level of around 2%.

### 7.3.4 Determination of the Product Distribution Arising from Conditions Based on a Zeneca Pharmaceuticals Method

The method concerned involved the use of NBS as the brominating reagent, chlorobenzene as the solvent and thermal decomposition of AIBN as the mode of initiation. After filtration of the succinimide, the product was isolated by a reduction in the volume of chlorobenzene then precipitation with cyclohexane. The bromination of quinazolinone **63** under these conditions, using 1 equivalent of NBS, produced a crude product which was shown to be composed of at least 6 constituents; unreacted quinazolinone **63** (23.6%), 6,7-

di(bromomethyl) quinazolinone **64** (5.8%), 7-bromomethyl quinazolinone **65** (5.8%), 6-bromomethyl quinazolinone **66** (47.2%), 2-bromomethyl quinazolinone **68** (5.8%) and another compound, **69**, (11.8%) which had not, at this time, been identified. Following purification the product is still composed of at least 5 constituents; **63** (12%), **64** (4.5%), **65** (12%), **66** (67%) and compound **69** (4.5%).

### 7.3.5 Experiments to Investigate the Effect on Product Distribution of Varying the Solvent and Mode of Initiation

In order to try to improve the level of selectivity, a series of experiments were carried out whereby the mode of initiation and reaction solvent were varied. The *crude* product compositions that resulted from these experiments are shown in table 9.

| Solvent | Initiator | % (63) | % (64) | % (65) | % (66) | % (68) | % (69) |
|---|---|---|---|---|---|---|---|
| chlorobenzene | AIBN | 23.6 | 5.8 | 5.8 | 47.2 | 5.8 | 11.8 |
| chlorobenzene | light | 15.7 | 5.2 | 8.4 | 63.2 | 2.6 | 5.2 |
| $CCl_3CH_3$ | light | 12.8 | 5.2 | 5.2 | 71 | 2 | 3.8 |
| DCM | AIBN | 27.5 | 2.8 | 5.6 | 50 | 5.6 | 8.4 |
| DCM | light | 10 | 5 | 5 | 80 | - | trace |
| $HCO_2CH_3$ | light | 22 | 5 | 5 | 67 | trace | trace |
| 1 : 1 DCM $HCO_2CH_3$ | light | 17.6 | 5 | 5 | 70.6 | trace | trace |

**Table 9**

It can be seen from table 9 that the use of light, rather than the thermal decomposition of AIBN, as the means of initiation resulted in an improvement in selectivity towards the desired 6-bromomethyl product **66** of approximately 16%. This improvement being mainly at the expense of starting quinazolinone **63** and compound **69**.

Changing the reaction solvent to dichloromethane whilst retaining the use of the thermal decomposition of AIBN as the means of initiation resulted in a very slow reaction as dichloromethane has a very low boiling point, 40 °C, and the rate of decomposition of AIBN at this temperature is very slow (the 10 hour half-life temperature of AIBN is 65 °C). The product mixture obtained from this reaction is very similar to that obtained on using chlorobenzene as the solvent with thermal AIBN initiation.

The best results were obtained by using dichloromethane and/or methyl formate as the solvent and light as the means of initiation. These solvents combine the two properties that are reported by Offermann and Vögtle[101] to promote selectivity in benzylic bromination, low boiling point (hence low reaction temperature) and low refractive index (see table 10). In this

particular case the use of dichloromethane appears to be the more applicable as considerable solubility problems arise with the use of methyl formate.

| Solvent | Boiling Point | $\eta_D^{20}$ |
|---|---|---|
| chlorobenzene | 132 °C | 1.5248 |
| $CCl_3CH_3$ | 75 °C | 1.4366 |
| DCM | 40 °C | 1.4242 |
| methyl formate | 32.1 °C | 1.3433 |

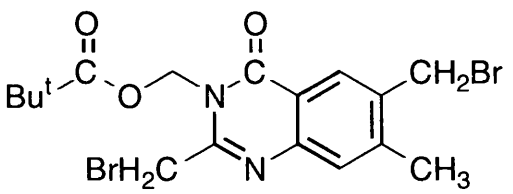
**Table 10**

The use of dichloromethane as the solvent can be seen from table 9 to result in a substantial increase in selectivity, towards the desired 6-bromomethyl compound **66**, of approximately 30% in comparison with the reaction in chlorobenzene using thermal AIBN initiation.

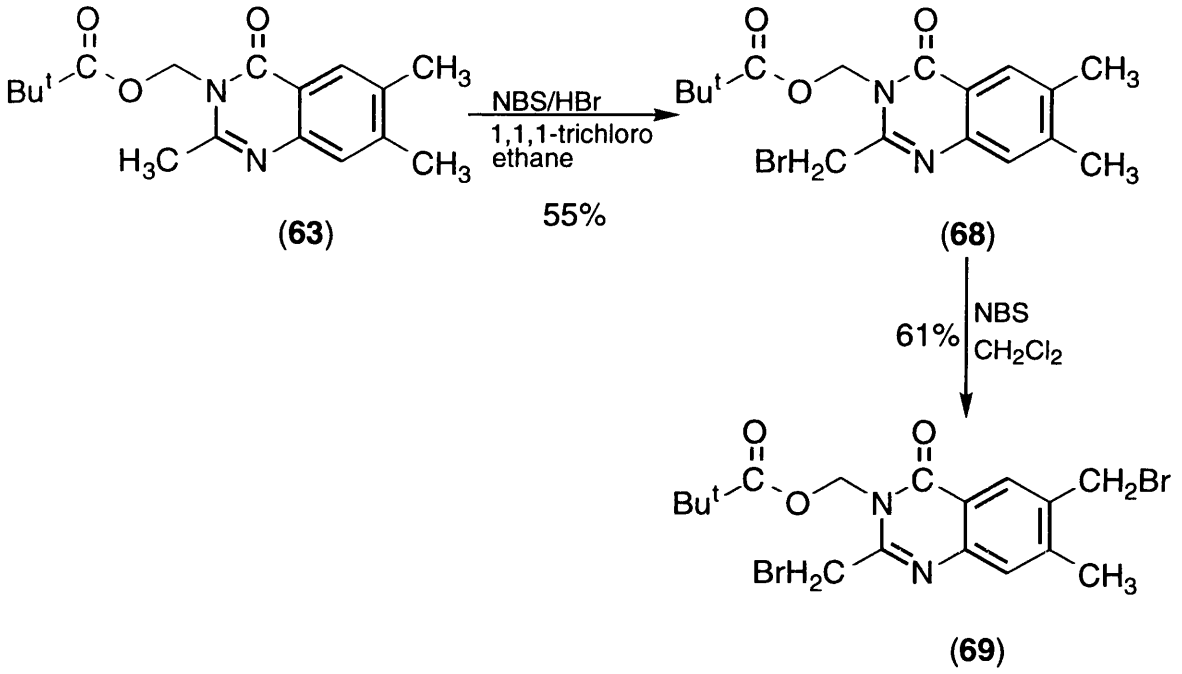
It can also be seen from table 9 that the use of solvents with a lower boiling point and hence lower reaction temperature usually resulted in the essentially complete disappearance of the 2-bromomethyl quinazolinone **68** and compound **69** from the product mixtures. As mentioned previously it is possible that bromination of the C-2 methyl group in quinazolinone **63** may occur purely through an ionic rather than radical route. It was found that it was possible to brominate the C-2 methyl group, in the absence of any form of initiator, by merely heating a mixture of quinazolinone **63** and NBS in chlorobenzene in the dark. This result indicates that the 2-bromomethyl quinazolinone **68** is indeed almost certainly brominated through an ionic mechanism and this explains why it is not observed when dichloromethane is used as the solvent as the lower reaction temperature would greatly slow its rate of formation (ionic reactions being more temperature dependent than radical reactions).

### 7.3.6 Identification of Quinazolinone 69

It would also appear from table 9 that compound **69** is only formed when the 2-bromomethyl quinazolinone **68** is also formed and this suggests that the structure of **69** also probably contains a C-2 bromomethyl group. This unknown constituent **69** was therefore thought to be 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone (see below).



As bromination of the C-6 methyl group is unlikely to have a significant effect on the reactivity of the C-2 methyl group, and *vice versa*, it follows that if both the 2-bromomethyl quinazolinone **68** and the 6-bromomethyl quinazolinone **66** are formed then the formation of 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone should also be observed. In order to verify that this was the structure of **69**, a sample of 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone was prepared by the 2 step synthesis shown below (see scheme 35).




(63) (68) (69)

**Scheme 35**

As expected the 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone prepared had an identical $R_f$ value to **69** and gave rise to Ar-H signals in the $^1H$ nmr spectrum with identical chemical shifts to those of **69**. This suggests that compound **69** is, as expected, 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone.

### 7.3.7 Effect of Other Changes on the Product Distribution

Having identified all the main products of this reaction it was decided to investigate the effect of some other changes on the product distribution in an attempt to further improve the selectivity. Firstly the use of a nitrogen atmosphere was investigated. This is reported by Baldwin and O'Neill to be effective in improving the yield and selectivity of benzylic brominations with bromotrichloromethane[78]. However, when the photo-initiated benzylic bromination of quinazolinone **63** in dichloromethane was carried out under a nitrogen

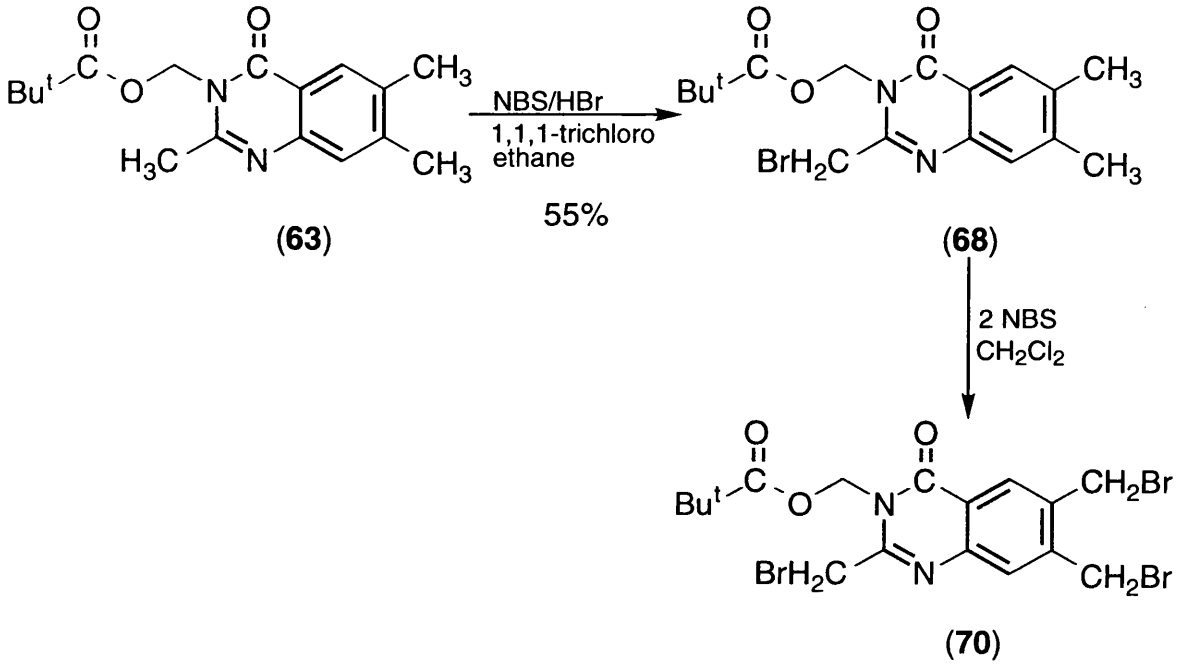
atmosphere there was no noticeable change in selectivity with regards to that observed in the analogous reaction that was open to the air.

A second area of investigation was into the effect that the addition of a Lewis acid to the system would have. It was thought that chelation of the amide group oxygen to the Lewis acid may occur and that this would make the carbonyl group more electron withdrawing. Exactly what effect this would have on the observed benzylic bromination selectivity was hard to predict as the C-6 methyl group would presumably be less reactive as electron pair donation through the -system from the amide nitrogen would be reduced. The C-7 methyl group would also however be less reactive towards hydrogen atom abstraction as delocalisation of positive charge to C-4a would be less favourable due to the increased greater degree of electron withdrawal from the adjoining carbonyl group. In the end however it was found that the addition of each of the Lewis acids tried, boron trifluoride diethyl etherate and titanium(IV) isopropoxide, resulted in the reaction being completely inhibited with no benzylic bromination taking place. This is thought to be due to reaction of the nucleophilic $Br^-$ and the Lewis acid effectively removing the $Br^-$ thus preventing the chain reaction.

### 7.3.8 The Synthesis of 2,6,7-Tri(bromomethyl)-*N*(3)-pivaloyloxymethyl quinazolinone (70)

Another objective of this work, other than improving the selectivity of the bromination towards the 6-bromomethyl compound **66**, was to prepare pure samples of those impurities that were either known to be, or predicted to be, produced in the reaction. These samples are required in order that HPLC methods can be developed to quantify the levels of these impurities in the product mixtures produced by the reaction on the plant. As described previously, pure samples of almost all impurities known to be formed in the reaction had already been isolated. These were starting quinazolinone **63**, the 6,7-di(bromomethyl) quinazolinone **64**, the 6-bromomethyl quinazolinone **66**, the 2-bromomethyl quinazolinone **68** and the 2,6-di(bromomethyl) quinazolinone **69**. The notable exception is the 7-bromomethyl quinazolinone **65** which, as explained earlier, is difficult to separate from starting quinazolinone **63**. Two other compounds were also predicted to be formed in small amounts. These were 2,7-di(bromomethyl)-6-methyl-*N*(3)-pivaloyloxymethylquinazolinone and 2,6,7-tri(bromomethyl)-*N*(3)-pivaloyloxymethylquinazolinone (**70**). These were predicted to be formed as it was thought that bromination of the C-2 methyl group was unlikely to have a significant effect on the reactivity of the C-6 & C-7 methyl groups (and *vice versa*) and therefore as the 6,7-di(bromomethyl) quinazolinone **64**, the 7-bromomethyl quinazolinone **65** and the 2-bromomethyl quinazolinone **68** are all observed both these compounds should also be present, though in smaller amounts. The former of these represented a difficult synthetic target as it required selective C-7 methyl group bromination methodology which was not known. For this reason it was decided that this compound, along with 7-bromomethyl

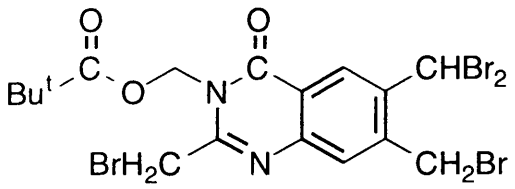
quinazolinone **65**, would be best approached by a strategy whereby requisite functionality to produce a C-7 bromomethyl group was introduced at an earlier point in the synthesis. This work was not, however, carried out as it was regarded as being beyond the scope of the project. The synthesis of the 2,6,7-tribromomethyl quinazolinone **70** however, appeared to pose no real problems and it was thought that it would be possible to prepare this compound *via* the two step synthesis shown in scheme 36.



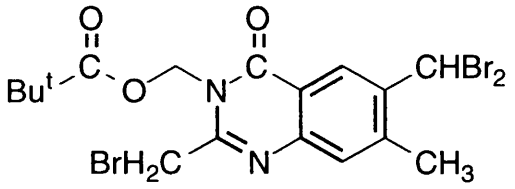

(**63**) (**68**) (**70**)

**Scheme 36**

The second step in this synthesis, the radical dibromination of 2-bromomethyl quinazolinone **68**, did not however proceed as cleanly as expected. With the apparent absence of any geminal dibromides in any of the earlier reaction mixtures it was predicted that this dibromination would proceed relatively cleanly but this was not the observed result. Instead a mixture of 4 compounds, tentatively assigned as the 2,6-dibromomethyl quinazolinone **69**, the 2,6,7-tribromomethyl quinazolinone **70**, 2,7-di(bromomethyl)-6-dibromomethyl-*N*(3)-pivaloyloxymethylquinazolinone (**71**) and 2-bromomethyl-6-dibromomethyl-7-methyl quinazolinone (**72**), was formed. Unfortunately no combination of solvents could be found that would form a suitable eluent such that a chromatographic separation of these compounds could be obtained.

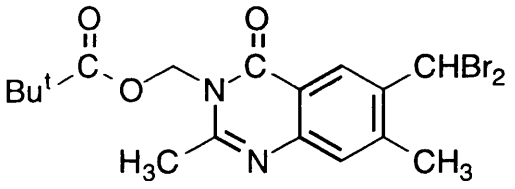


(71)

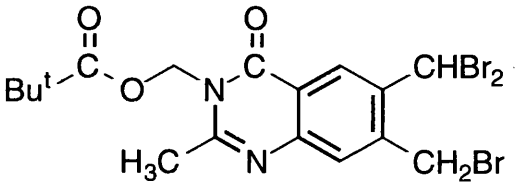


(72)

It was decided to try to approach the synthesis of the 2,6,7-tribromomethyl quinazolinone **70** by reversing the order of the steps shown in scheme 36. Again the radical dibromination proceeded with a relatively low level of selectivity and a mixture of 4 compounds, assigned as the desired 6,7-di(bromomethyl) quinazolinone **64**, the 6-bromomethyl quinazolinone **66**, 6-dibromomethyl-2,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**73**) and 7-bromomethyl-6-dibromomethyl-2-methyl-*N*(3)-pivaloyloxymethylquinazolinone (**74**), was obtained in the ratio 8 : 1.4 : 1.7 : 1.

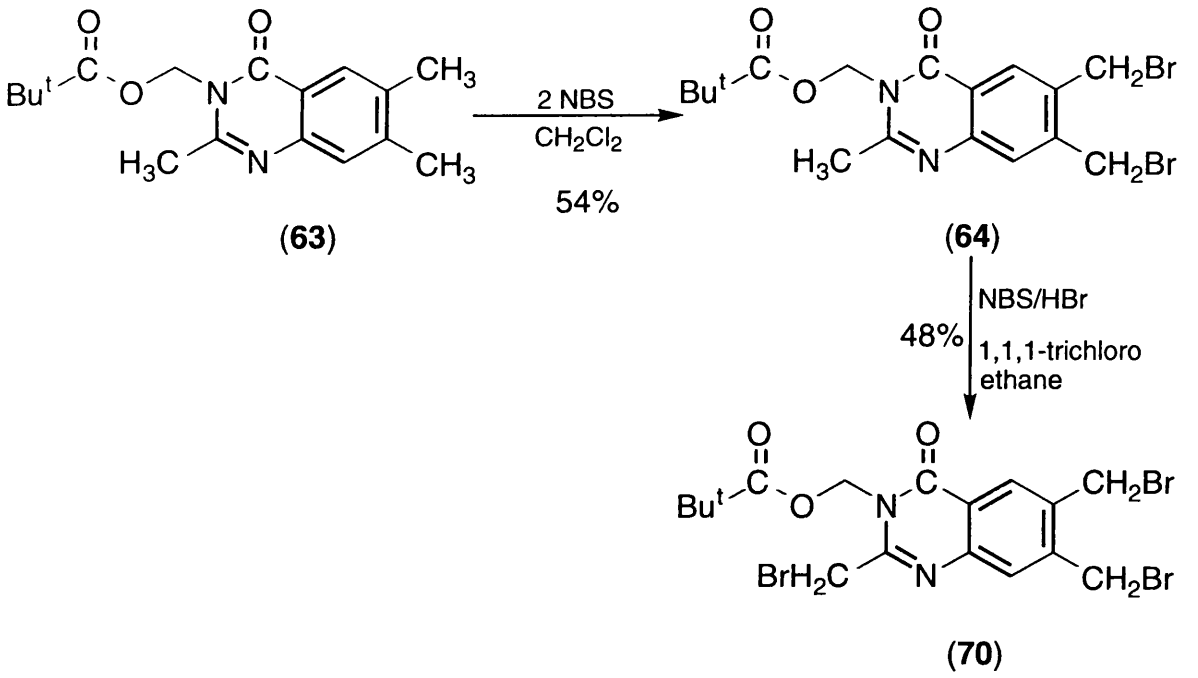


(73)



(74)

The desired 6,7-di(bromomethyl) quinazolinone **64** was separated from the rest of the product mixture by column chromatography but the isolated yield was only 54%. The ionic bromination of the C-2 methyl group of **64** proceeded as expected with the desired product the 2,6,7-tribromomethyl quinazolinone **70** being obtained in a 48% yield (see scheme 37).



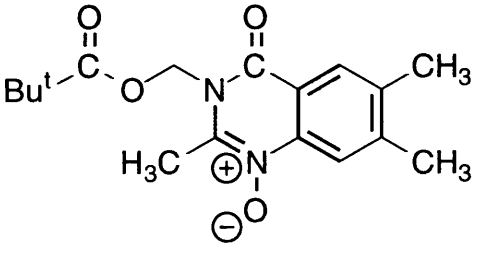

(63) (64) (70)

**Scheme 37**

An important result that was observed in the dibromination is that the 7-bromomethyl-6-dibromomethyl quinazolinone **74** and particularly the 6-dibromomethyl quinazolinone **73** are likely to be present in the earlier obtained reaction mixtures in small amounts. In fact, once the chemical shifts of the Ar-H signals for **73** were identified, traces of this compound were observable in many of the earlier reaction mixtures. Pure samples of these compounds were however never isolated due the difficulty of their chromatographic separation.

### 7.3.9 The Attempted Preparation of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethyl quinazolinone *N*-oxide (75)

As mentioned previously, the preparation of significant quantities of the 7-bromomethyl quinazolinone **65** required the reversal of the observed selectivity. It was thought this may be possible by preparing the *N*-oxide of quinazolinone **63**, 2,6,7-trimethyl-*N*(3)-pivaloyloxymethylquinazolinone *N*-oxide (**75**).



(75)

The oxidation of N-1 would result in this group changing from being electron withdrawing to electron donating. Donation of an electron pair from the *N*-oxide oxygen atom would help stabilise the formation of a positive charge on the C-7 methyl group carbon (see figure 51) and this would result in the hydrogen atoms of this group being more readily abstracted.

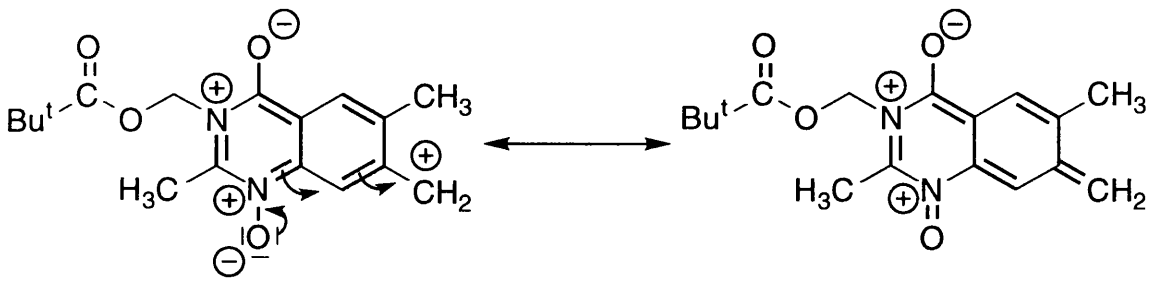


**Figure 51**

The preparation of the *N*-oxide **75** proved however to be surprisingly difficult. When the conditions of Ochiai[103] (which involve acetic acid and hydrogen peroxide) were used to form the oxidant peracetic acid *in situ*, then no oxidation of quinazolinone **63** was observed to take place (see figure 52). The conditions of Kobiyashi *et al.* [104], in which trifluoroacetic acid (which forms the more powerful oxidising agent trifluoroperacetic acid) is used, also failed to produce the desired *N*-oxide and instead resulted in extensive deprotection of the amide nitrogen of quinazolinone **63** to give, as the main product, 2,6,7-trimethyl quinazolinone (**76**) (see figure 52). Even the use of *Oxone*® (potassium peroxymonosulfate) in acetone, which is reported to be a reliable reagent for this transformation under neutral conditions[105], failed to result in the formation of the *N*-oxide **75** to an appreciable extent (see figure 52).

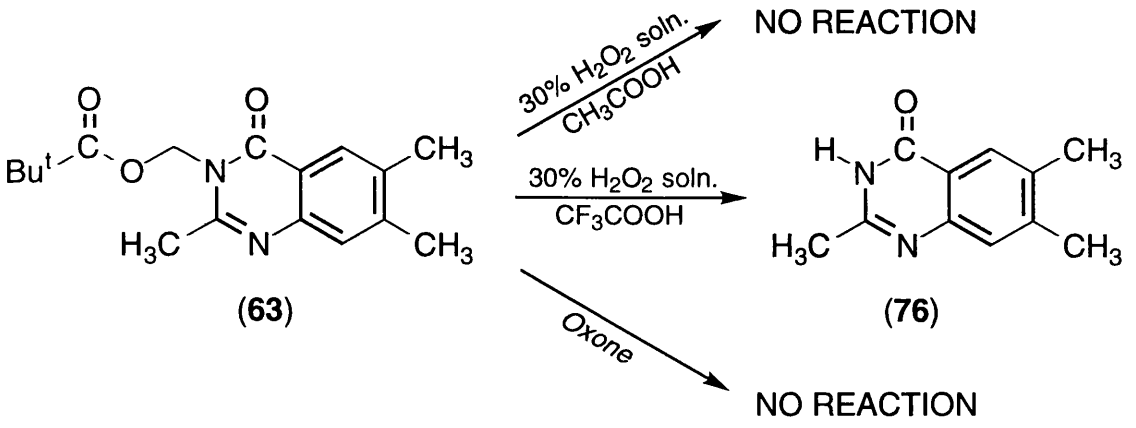



**Figure 52**

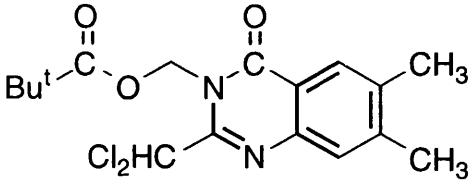
Further time was not spent of the synthesis of the *N*-oxide **75** as it was felt that the selectivity in the bromination of this compound would be such that the brominatiuon of the C-2 methyl group by an ionic route would be favoured over the radical bromination of the C-6 and C-7 methyl groups.

### 7.3.10 Attempted Benzylic Iodination and Chlorination of Quinazolinone (63)

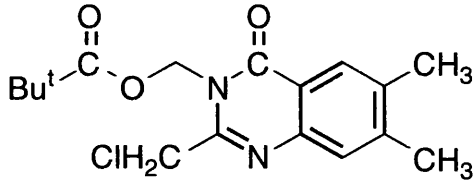
A final area of investigation was to determine whether or not either benzylic iodination or benzylic chlorination of quinazolinone **63** would be a viable means of improving the selectivity or allowing the preparation of the C-7 methyl group halogenated derivative.

Attempts at benzylic iodination with the use of either the thermal decomposition of AIBN or light to initiate the reaction failed to result in the formation of the desired product. The only product observed was the C-2 iodomethyl derivative which is almost certainly the product of an ionic rather than radical reaction.

Surprisingly attempts at benzylic chlorination also failed to result in the chlorination of either the C-6 or C-7 methyl groups. The crude product of this reaction was just composed of unreacted starting quinazolinone **63**, 2-chloromethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethyl quinazolinone (**77**) and 2-dichloromethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**78**) in the ratio 1 : 2 : 1.



**(78)**



**(77)**

Again the formation of the 2-dichloromethyl quinazolinone **78** and the 2-chloromethyl quinazolinone **77** is almost certain to have occured through an ionic, rather than radical, route. This result was somewhat disappointing as it was thought that the chlorination of quinazolinone **63** would be less selective than the bromination, due to chlorine atoms being more reactive and less selective in hydrogen atom abstraction, and that this would result in the formation of greater quantities of the C-7 chloromethyl compound which it was hoped would be separable chromatographically from quinazolinone **63**. This would have been extremely useful as the C-7 chloromethyl compound could have been converted to the C-7 bromomethyl compound (**65**), a pure sample of which had still not been obtained.

# 8

# Experimental to Chapters 4-7

## 8.1 General Experimental Section

All chemicals were purchased either from the Aldrich Chemical Co. (Gillingham, Dorset, UK) or from Lancaster Synthesis Ltd. (Eastgate, White Lund, Morecambe, UK) except for ZD9331 POM quinazolinone which was supplied by the Process Development Department of Zeneca Pharmaceuticals (Hurdsfield Industrial Estate, Macclesfield).

All melting points (m.p.) were measured with a Gallenkamp apparatus and are all uncorrected.

All nmr spectra, except those given in Section 8.5, were obtained either on a Bruker WP200-SY spectrometer or on a Bruker AM200-SY spectrometer with both instruments operating at 200 MHz for $^{1}H$ nmr spectra and 50 MHz for $^{13}C$ nmr spectra. The nmr spectra given in Section 8.5 were obtained on a JEOL GX-270 spectrometer operating at 269.6 MHz for $^{1}H$ nmr spectra and 67.7 MHz for $^{13}C$ nmr spectra.

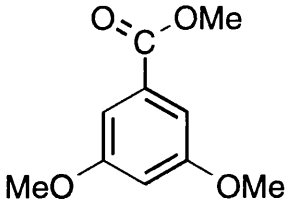
Mass spectra were recorded on AEI MS12 or MS902 spectrometers except for those in Section 8.5 which were recorded on a VG Auto Spec EQ spectrometer.

Thin layer chromatography (TLC) was carried out on silica gel G plates of 0.25 mm thickness. Compounds were visualised by UV and with iodine.

Column chromatography was carried out on silica gel, 70-230 mesh, 60 Å except for experiments in Section 8.5,where silica gel, 70-230 mesh, 40 Å was used.

# 8.2 Experimental Details for Chapter 4

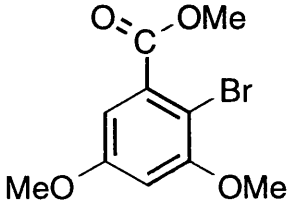
**Methyl 3,5-dimethoxybenzoate (16)**



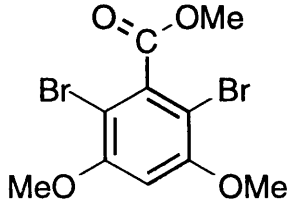

**(16)**

To a solution of 3,5-dihydroxybenzoic acid (5 g , 0.0325 mol) in dry acetone (50 ml) was added anhydrous potassium carbonate (16 g , 0.116 mol) and dimethyl sulphate (10 ml , 0.10 mol). The resultant mixture was heated at reflux for 7 hours with vigorous stirring. After cooling the solution was filtered and the residue washed with acetone (2 x 25 ml). The acetone solutions were combined and evaporated to leave a brown viscous residue. This residue was dissolved in diethyl ether and the resultant solution washed with 10% sodium hydroxide solution (2 x 25 ml) and water (2 x 25 ml) before being dried and evaporated to leave a pale yellow solid. Recrystallisation from ethanol afforded methyl 3,5-dimethoxybenzoate (**16**), (4.8 g , 73.4%) as needles, m.p. 39.5 - 40 °C (lit.,[106] 40.2-40.6 °C). (Found : C, 60.97 ; H, 6.16. $C_{10}H_{12}O_4$ requires C, 61.22 ; H, 6.16%) ; $\delta_H$ (200 MHz , $CDCl_3$) 7.18 (2H, d, *J* 2.8, 2-H), 6.64 (1H, t, *J* 2.8, 4-H), 3.90 (3H, s, $CO_2Me$) and 3.82 (6H, s, OMe) ; $\delta_C$ 166.8 ($CO_2Me$), 160.5 (3-C), 131.9 (1-C), 107.0 (2-CH), 105.7 (4-CH), 55.5 (OMe) and 52.2 ($CO_2Me$) ; m/z 196 ($M^+$).

**Bromination of Methyl 3,5-dimethoxybenzoate (16) with $Br_2$**




**(17)**




**(18)**

To a stirring solution of benzoate **16** (0.196 g, 0.001 mol) in dichloromethane (5 ml) was added, dropwise, a 1 M solution of bromine in dichloromethane (1 ml, 0.001 mol). Stirring was allowed to continue for 30 minutes. The solution was then washed

with 5% sodium hydroxide solution (2 x 5 ml) and water (2 x 5 ml) dried and evaporated to leave an oily crystalline solid which TLC indicated was composed of three constituents. The crude product was chromatographed over a column of silica gel with petroleum ether - ethylacetate (10:1) as the eluant. Early fractions afforded starting compound **16** (0.060 g, 0.30 mmol), followed by methyl 2-bromo-3,5-dimethoxybenzoate (**17**) (0.087 g, 0.32 mmol) and then methyl 2,6-dibromo-3,5-dimethoxybenzoate (**18**) (0.106 g, 0.30 mmol).

Compound **17** was recrystallised from ethanol to give prisms, m.p. 57-58 °C (lit.,[87] 58-59 °C); $\delta_H$ 6.81 (1H, d, *J* 2.8, 6-H), 6.59 (1H, d, *J* 2.8, 4-H), 3.94 (3H, s, $CO_2Me$), 3.89 (3H, s, OMe) and 3.83 (3H, s, OMe) ; $\delta_C$ 166.6 (*C*$O_2$Me), 159.1 (3-C), 157.1 (5-C), 131.4 (1-C), 107.2 (6-CH), 101.5 (4-CH), 99.4 (2-CH), 56.5 (OMe), 56.0 (OMe) and 52.8 ($CO_2$*Me*) ; m/z 274, 276 ($M^+$).

Compound **18** was recrystallised from petroleum ether to give needles, m.p. 149-150 °C (lit.,[87] 149-150 °C); $\delta_H$ 6.51 (1H, s, 4-H), 3.98 (3H, s, $CO_2Me$) and 3.92 (6H, s, OMe) ; $\delta_C$ 166.5 (*C*$O_2$Me), 156.3 (3-C), 131.6 (1-C), 99.5 (2-C), 97.3 (4-CH), 56.7 (OMe) and 53.1 ($CO_2$*Me*) ; m/z 352, 354, 356 ($M^+$).

## Bromination of Methyl 3,5-dimethoxybenzoate (16)-Varying Mole Equivalents of Bromine

To a stirring solution of benzoate **16** (0.196 g, 0.001 mol) in dichloromethane (5 ml) was added, dropwise, a 1 M solution of bromine in dichloromethane (N ml, N mmol). Stirring was allowed to continue, at room temperature for 1 hour. The solution was then washed with 5% sodium hydroxide solution (2 x 10 ml), 5% sodium thiosulphate solution (sufficient to remove unreacted bromine) and water (2 x 10 ml) before being dried and evaporated to leave crude product.

The above procedure was repeated for the following values of N - 0.25, 0.33, 0.50, 0.66, 0.75, 0.90, 1.00, 1.10, 1.25, 1.5, 1.66, 1.75, 2.00, 2.50, 3.00.

The resultant yields and product distributions are shown in the table below.

| Mole Equivalents of $Br_2$ | Mixed yield (g) | Product Ratio **16**:**17**:**18** |
|---|---|---|
| 0.25 | 0.210 | 1 : 0.20 : 0.04 |
| 0.33 | 0.215 | 1 : 0.33 : 0.07 |
| 0.50 | 0.226 | 1 : 0.53 : 0.16 |
| 0.66 | 0.230 | 1 : 0.69 : 0.22 |
| 0.75 | 0.243 | 1 : 0.88 : 0.41 |
| 0.90 | 0.256 | 1 : 1.13 : 0.65 |
| 1.00 | 0.270 | 1 : 1.06 : 1.00 |
| 1.10 | 0.272 | 1 : 1.44 : 1.26 |
| 1.25 | 0.280 | 1 : 1.62 : 2.19 |
| 1.50 | 0.310 | 1 : 1.79 : 5.26 |
| 1.66 | 0.314 | 1 : 2.10 : 9.37 |
| 1.75 | 0.315 | 1 : 2.00 : 13.67 |
| 2.00 | 0.342 | 0.00 : 1 : 0.00 |
| 2.50 | 0.327 | 0.00 : 1 : 0.00 |
| 3.00 | 0.337 | 0.00 : 1 : 0.00 |

**Bromination of Methyl 3,5-dimethoxybenzoate (16) - Varying the Temperature**

To a stirring solution of benzoate **16** (0.196 g, 0.001 mol) in dichloromethane (5 ml), held at X °C, was added, dropwise, a 1 M solution of bromine in dichloromethane (1 ml, 0.001 mol). Stirring was allowed to continue whilst the temperature was held constant (within 2 °C of X) for 1 hour. The reaction mixtures were then worked up as described previously.

The above experiment was repeated for the following values of X; 40, 15, 0, -30, -72.

The resultant yields and product distributions are shown in the table below.

| Reaction Temperature (°C) | Mixed Yield | Product Ratio **16**:**17**:**18** |
|---|---|---|
| 40 | 0.260 | 1 : 1.02 : 1 |
| 15 | 0.262 | 1 : 1.08 : 1 |
| 0 | 0.254 | 1 : 1.10 : 1 |
| -30 | 0.257 | 1 : 1.24 : 1 |
| -72 | 0.251 | 1 : 1.56 : 1 |

**Proof that Product Distribution in the Bromination of Methyl 3,5-dimethoxybenzoate (16) with $Br_2$ is Controlled by Kinetics**

To a stirring solution of benzoate **16** (0.196 g, 0.001 mol) in dichloromethane (5 ml) was added dropwise a 1 M solution of bromine in dichloromethane (2 ml, 0.002mol). Following the, almost immediate, decolourisation of the bromine a further 0.196 g (0.001 mol) of benzoate **16** was added and stirring allowed to continue for 1 hour. An aliquot of the reaction mixture (2 ml) was then removed and worked up as described previously. The remainder of the solution was heated at reflux for 8 hours before being worked up in an identical manner. Analysis of both crude products by $^1H$ nmr spectroscopy suggested that both were composed solely of equimolar amounts of benzoate **16** and the 2,6-dibromo derivative **18**.

**Bromination of Methyl 3,5-dimethoxybenzoate (16)- Without Stirring**

To a solution of benzoate **16** (0.196 g, 0.001 mol) in dichloromethane (5 ml), which was **not** being stirred, was added, dropwise, a 1 M solution of bromine in dichloromethane (1 ml, 0.001 mol). The solution was then allowed to stand for 1 hour before being worked up as described previously to give an oily white solid (0.254 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was composed of benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 0.5 : 1.

**Bromination of Methyl 3,5-dimethoxybenzoate (16)- Varying the Concentration of the Substrate Solution**

To a stirring solution of benzoate **16** (0.196 g, 0.001 mol) in dichloromethane (50 ml) was added, dropwise, a 5% by volume solution of bromine in dichloromethane (1 ml, 0.001 mol). Stirring was then allowed to continue for 1 hour. The volume of the solution was then reduced to 6 ml by evaporation of the solvent under reduced pressure and the remaining solution worked up as described previously to give a solid (0.249 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was composed of benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 1.74 : 1.

The above experiment was repeated using 100 ml and 200 ml volumes of dichloromethane in the intial solution. Work up of these reactions again afforded solids

(0.251 g and 0.246 g). The crude products were analysed as before and both were composed of benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 2.15 : 1.

**Formation of Methyl 2-bromo-3,5-dimethoxybenzoate (17) *via* Debromination of Methyl 2,6-dibromo-3,5-dimethoxybenzoate (18) with Butyllithium**

To a stirring solution of the 2,6-dibromo benzoate **18** (0.354 g, 0.001 mol) in dry tetrahydrofuran (10 ml) at -70°C, under a nitrogen atmosphere, was added dropwise butyllithium (0.625 ml of 1.6 M in hexane, 0.001 mol). After the addition was complete stirring was continued at -70 °C for 2 hours and the solution then allowed to warm to room temperature. To the resulting cloudy solution was added water (10 ml) and the solution extracted with diethyl ether (2 x 20 ml). The combined extracts were then washed with water (2 x 10 ml) dried and evaporated to give a light brown oil (0.170 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was primarily composed of benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 3 : 2.5.

**Bromination of Methyl 3,5-dimethoxybenzoate (16)- Using *N*-Bromosuccinimide (NBS)**

To a solution of benzoate **16** (0.196 g, 0.001 mol) in dimethylformamide (5 ml) was added a solution of NBS (0.178 g, 0.001 mol) in dimethylformamide (5 ml). The resulting mixture was stirred at room temperature for 24 hours before being poured into water (20 ml) and extracted with dichloromethane (2 x 15 ml). The extracts were combined and washed thoroughly with saturated salt solution (4 x 20 ml) and water (2 x 20ml) before being dried and evaporated under reduced pressure to give an oil (0.230 g) which subsequently crystallised upon standing for 4 hours. Analysis of the crude product by $^1$H nmr spectroscopy indicated that exclusive monobromination had occured, with only a trace amount of the 2,6-dibromo product being formed, and that benzoate **16** and the 2-bromo derivative **17** were present in the ratio 1 : 7.5.

**Bromination of Methyl 3,5-dimethoxybenzoate (16)- Using 2 Mole Equivalents of NBS**

The previous experiment was repeated using twice the amount of NBS (0.356 g, 0.002 mol). Work up of the reaction as described previously afforded a white solid (0.300 g).Analysis of the crude product by $^1H$ nmr spectroscopy indicated that it was composed solely of the 2-bromo benzoate **17** and the 2,6-dibromo benzoate **18** in the ratio 1 : 6.14.

**Bromination of Methyl 3,5-dimethoxybenzoate (16)- Using NBS at a Higher Temperature**

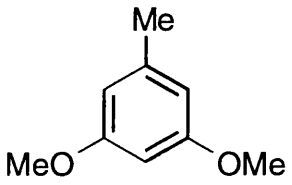
The experiment was carried out as described previously using 1 mole equivalent of NBS except that the reaction mixture was kept at 60 °C for the duration of the reaction. Work up of the reaction as before afforded an oil (0.240 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was composed of benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 8 : 0.5.

**Bromination of Methyl 3,5-dimethoxybenzoate (16)- Using NBS and a Longer Reaction Time**

The experiment was carried out as described previously using 1 mole equivalent of NBS except that the reaction mixture was stirred at room temperature for 48 hours. Work up of the reaction again afforded an oil (0.236 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was composed of benzoate **16**, the 2-bromo derivative **17** and the 2,6-dibromo derivative **18** in the ratio 1 : 8.5 : 0.5.

# 8.3 Experimental Details for Chapter 5

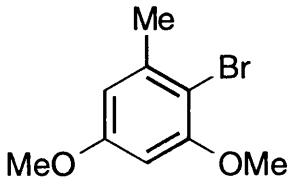
**Preparation of 3,5-Dimethoxytoluene (19)**[87]



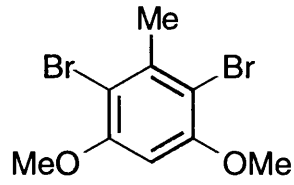

**(19)**

To a solution of 3,5-dihydroxytoluene monohydrate (4.26 g, 0.03 mol) in acetone (50 ml) was added anhydrous potassium carbonate (12 g, 0.087 mol) and dimethyl sulphate (3.8 ml, 0.04 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 25 ml). The combined acetone solutions were evaporated and the brown viscous residue stirred whilst 35% ammonia solution (10 ml) was added. After 1 hour the mixture was extracted with diethyl ether (2 x 25 ml) and the combined extracts washed with 5% hydrochloric acid solution (25 ml), 5% sodium hydroxide solution (25 ml) and water (2 x 25 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded 3,5-dimethoxytoluene (**19**) as a pale yellow oil (4.0 g, 87.7%) ; $\delta_H$ 6.32 (2H, d, *J* 2, 2-H), 6.28 (1H, t, *J* 2, 4-H), 3.75 (6H, s, OMe) and 2.29 (3H, s, 1-$CH_3$); $\delta_C$ 160.7 (3-C), 140.2 (1-C), 107.0 (2-CH), 97.5 (4-CH), 55.1 (OMe) and 21.8 (Ar*C*$H_3$); m/z 152 ($M^+$, 100%).

**Bromination of 3,5-Dimethoxytoluene (19) with Molecular Bromine**




**(20)**




**(21)**

To a stirring solution of toluene **19** (0.304 g, 0.002 mol) in dichloromethane (10 ml) was added a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol). Stirring was allowed to continue for 1 hour. The solution was then washed with 10% sodium hydroxide solution (10 ml) and water (2 x 10 ml), dried over anhydrous magnesium

sulphate and evaporated under reduced pressure to give oily white crystals (0.431 g). Analysis of this crude product by TLC (with 4/1 hexane/ethyl acetate as the eluent) suggested that it was composed of 3 constituents with $R_f$ values of 0.61, 0.51, 0.36. These constituents were separated by chromatographing the crude product over a column of silica gel using 20 : 1 hexane/ethyl acetate as the eluent. Early fractions afforded starting toluene **19** (0.042 g, 0.28 mmol), followed by 2-bromo-3,5-dimethoxytoluene (**20**) (0.304 g, 1.32 mmol) and then 2,6-dibromo-3,5-dimethoxytoluene (**21**) (0.086 g, 0.27 mmol).

Compound **20** was recrystallised from methanol to give plates, m.p. 55-58 °C (lit.,[87] 56-58 °C); $\delta_H$ 6.33 (1H, d, *J* 2.6, 6-H), 6.24 (1H, d, *J* 2.7, 4-H), 3.76 (3H, s, OMe), 3.67 (3H, s, OMe) and 2.29 (3H, s, $ArCH_3$); $\delta_C$ 159.3 (3-C), 156.6 (5-C), 139.7 (1-C), 107.2 (6-CH), 105.0 (2-C), 97.1 (4-CH), 56.2 (OMe), 55.4 (OMe) and 23.5 ($ArCH_3$); m/z 230 ($M^+$, 57%), 232 (58).

Compound **21** was recrystallised from petroleum ether to give needles, m.p. 170-172 °C (lit.,[87] 171-172 °C); $\delta_H$ 6.32 (1H, s, 4-H), 3.82 (6H, s, OMe) and 2.53 (3H, s, $ArCH_3$); $\delta_C$ 155.6 (3-C), 139.1 (1-C), 105.5 (2-C), 94.6 (4-CH), 56.5 (OMe) and 24.1 ($ArCH_3$); m/z 308 ($M^+$, 52%), 310 (100), 312 (50).

## Bromination of 3,5-Dimethoxytoluene (19)- Using More Dilute Substrate Solutions

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) dissolved in dichloromethane (100 ml), was added a 1 M solution of bromine in dichloromethane (1 ml, 0.001 mol). Stirring was allowed to continue for 1 hour before the volume of the solution was reduced to approximately 10 ml by evaporation of the excess solvent under reduced pressure. The solution was then worked up as before to give an oily solid (0.209 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 2.40 : 1.

The above experiment was repeated using 200 ml of dichloromethane in the initial substrate solution. Work up of the reaction as described previously afforded another oily solid. Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 2 : 1.

**Bromination of 3,5-Dimethoxytoluene (19)- Using NBS in Dimethylformamide**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) in dimethylformamide (5 ml) was added a solution of NBS (0.178 g, 0.001 mol) in dimethylformamide (5 ml). Stirring was then allowed to continue, at room temperature, for 24 hours. The mixture was then poured into water (20 ml) and extracted with dichloromethane (2 x 20 ml). The extracts were combined andwashed thoroughly with saturated salt solution (4 x 20 ml) and water (2 x 20ml) before being dried and evaporated under reduced pressure to give a white crystalline solid (0.197 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC suggested that it was composed almost entirely of the 2-bromo toluene **20** with the starting toluene **19** being the only other constituent. The ratio of **19** : **20** was determined to be 1 : 30.

**Bromination of 3,5-Dimethoxytoluene (19)- Using Molecular Bromine in Dimethylformamide**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) in dimethylformamide (9 ml) was added a 1 M solution of bromine in dimethylformamide (1 ml, 0.001 mol). Stirring was allowed to continue for 1 hour until the bromine was observed to be decolourised. The solution was then poured into water (50 ml) and extracted with dichloromethane (2 x 25 ml). The combined extracts were thoroughly washed with saturated sodium chloride solution (4 x 20 ml) and water (20 ml) before being dried and evaporated under reduced pressure to give a light brown solid (0.190 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 3.2 : 1.

**Bromination of 3,5-Dimethoxytoluene (19)- Using NBS in Carbon Tetrachloride**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.178 g, 0.001 mol). Stirring was then allowed to continue for 24 hours. The solution was then filtered and the solvent removed from the filtrate under reduced pressure to give a white solid (0.224 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 4 : 1.

**Bromination of 3,5-Dimethoxytoluene (19)- Using NBS in Dichloromethane**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) in dichloromethane (10 ml) was added NBS (0.178 g, 0.001 mol). Stirring was then allowed to continue for 24 hours. The solution was then washed with water (2 x 10 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give a pale yellow crystalline solid (0.219 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed almost exclusively of the 2-bromo toluene **20** with about 1% of the 2,6-dibromo toluene **21** being the only other observable product.

**Bromination of 3,5-Dimethoxytoluene (19)- Using 2 Mole Equivalents of Bromine**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) in dichloromethane (10 ml) was added a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol). Work up of the reaction as described previously afforded fine cream crystals (0.290 g).Analysis of the product by $^1$H nmr spectroscopy and TLC suggested that it was composed entirely of the 2,6-dibromo toluene **21**. Recrystallisation from petroleum ether gave needles identical to those obtained earlier.

**Formation of 2-Bromo-3,5-Dimethoxytoluene (20) *via* Debromination of 2,6-Dibromo-3,5-dimethoxytoluene (21) with Isopropylmagnesium Chloride**[86]

To a 2.0 M solution of isopropylmagnesium chloride in THF (2.5 ml, 0.005 mol) at 40 °C was added slowly a solution of the 2,6-dibromo toluene **21** (0.620 g, 0.002 mol) in THF (5 ml). After stirring for 5 hours the mixture was cooled to 0 °C and treated with water (1 ml). The mixture was then extracted with diethyl ether (2 x 5 ml) and the combined extracts washed with water (5 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a very light brown solid (0.53 g) which $^1$H nmr spectroscopic analysis suggested was primarily composed of the 2-bromo toluene **20** and the starting 2,6-dibromo toluene **21** in the ratio 9 : 1.

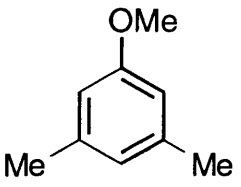
**Attempted Bromination of 2,6-Dibromo-3,5-dimethoxytoluene (21) Using Bromine and an Iron Catalyst**

To a solution of the 2,6-dibromo toluene **21** (0.310 g, 0.001 mol) in glacial acetic acid (5 ml) was added a solution of bromine (0.052 ml, 0.001 mol) in glacial acetic acid (5 ml). Iron filings (0.05 g) were then added and the mixture refluxed for 16 hours. After cooling the solution was filtered and the filtrate poured into 5% sodium thiosulphate solution (30 ml) and extracted with diethyl ether (2 x 20 ml). The combined extracts were then washed with saturated sodium bicarbonate solution (until effervescence was observed to have ceased) and water (20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave a light brown solid (0.240 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC failed to provide any evidence to suggest that the 2,6-dibromo toluene **21** had been brominated to an appreciable extent.

**Attempted Bromination of 2,6-Dibromo-3,5-dimethoxytoluene (21) Using Bromine and a Silver Nitrate Catalyst[88]**

To a solution of the 2,6-dibromo toluene **21** (0.310 g, 0.001 mol) in a mixture of glacial acetic acid (4 ml), concentrated nitric acid (1 ml) and water (1 ml) was added bromine (0.052 ml, 0.001 mol). The mixture was then treated dropwise, with vigorous stirring, with a solution of silver nitrate (0.170 g, 0.001 mol) in water (2 ml). After stirring for 4 hours the mixture was poured into water (30 ml) and extracted with dichloromethane (2 x 20 ml). The combined extracts were washed with 5% sodium hydroxide solution (2 x 30 ml), 5% sodium thiosulphate solution (sufficient to remove unreacted bromine) and water (2 x 20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a light brown solid (0.214 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC again failed to provide any evidence to suggest that the 2,6-dibromo toluene **21** had been brominated to an appreciable extent.

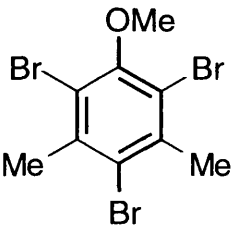
**Preparation of 3,5-Dimethylanisole (22)**




**(22)**

To a solution of 3,5-dimethylphenol (1.22 g, 0.01 mol) in acetone (40 ml) was added anhydrous potassium carbonate (4 g, 0.029 mol) and methyl iodide (1.6 ml, 0.026 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 25 ml). The combined acetone solutions were evaporated under reduced pressure to give a colourless oil which was redissolved in dichloromethane (25 ml). The solution was then washed with 5% sodium hydroxide solution (20 ml) and water (20 ml) before being dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure afforded a dark yellow oil which was distilled at 61 °C at 4.5 mmHg (lit.,[107] 60.5 °C) to afford 3,5-dimethylanisole **22** (1.02 g, 75%) as a pale yellow oil ; $\delta_H$ 6.58 (1H, t, *J* unresolved, 4-H), 6.52 (2H, d, *J* unresolved, 2-H), 3.74 (3H, s, OMe) and 2.28 (6H, s, $ArCH_3$); $\delta_C$ 159.6 (1-C), 139.2 (3-C), 122.4 (4-CH), 111.7 (2-CH), 55.0 (OMe) and 21.4 ($ArCH_3$); m/z 136 ($M^+$, 75%).

**Tribromination of 3,5-Dimethylanisole (22)**

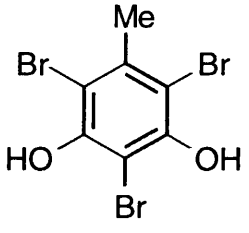



**(23)**

To a stirring solution of anisole **22** (0.136 g, 0.001 mol) in dichloromethane (10 ml) was added a 1 M solution of bromine in dichloromethane (3 ml, 0.003 mol). After stirring for 2 hours the solution had not completely decolourised so iron filings (20 mg) were added and the solution heated at reflux for 16 hours. After cooling the solution was filtered and the filtrate diluted with dichloromethane (10 ml). The solution was then

washed with 5% sodium hydroxide solution (20 ml) and water (2 x 10 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave a black oil which was diluted with dichloromethane and pre-adsorbed onto silica. Flash column chromatography with 10 : 1 petroleum ether/ethyl acetate eluted the desired tribromide. Removal of the solvent under reduced pressure and recrystallisation from ethanol afforded 2,4,6-tribromo-3,5-dimethyl anisole (**23**) (0.227 g, 60.8%) as needles, m.p. 115-117 °C (lit.,[108] 116.5 °C); $\delta_H$ 3.85 (3H, s, OMe) and 2.60 (6H, s, $ArCH_3$); $\delta_C$ 153.2 (1-C), 138.0 (3-C), 122.8 (4-C), 118.2 (2-C), 60.1 (OMe) and 25.3 ($ArCH_3$); m/z 376 ($M^+$, 31.1%), 374 (86.1), 372 (100), 370 (49.3).

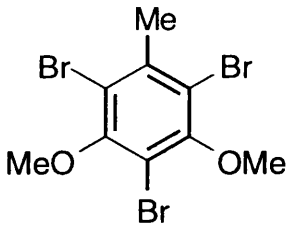
**Tribromination of 3,5-Dihydroxytoluene**




**(24)**

To a stirring solution of 3,5-dihydroxytoluene monohydrate (0.142 g, 0.001 mol) in glacial acetic acid (5 ml) was added a 5% by volume solution of bromine in glacial acetic acid (3 ml, 0.003 mol). Stirring was allowed to continue until decolourisation was observed to be complete (about 30 minutes) and the solution then poured into water (40 ml). The resultant white precipitate was filtered, washed with water (3 x 20 ml) and dried over phosphorous pentoxide. Recrystallisation from chloroform afforded 2,4,6-tribromo-3,5-dihydroxytoluene (**24**) (0.311 g, 86%) as long fine needles, m.p. 104-105 °C (lit.,[109] 105 °C); $\delta_H$ 2.47 (3H, s, $ArCH_3$) and 5.99 (2H, br s, OH); $\delta_C$ 149.1 (3-C), 136.9 (1-C), 103.2 (2-C), 94.6 (4-C) and 24.7 ($ArCH_3$); m/z 363 ($M^+$, 32.0%), 361 (96.5), 359 (100), 357 (34.5).

## 2,4,6-Tribromo-3,5-dimethoxytoluene (25) By Methylation of 2,4,6-Tribromo-3,5-dihydroxytoluene (24)




**(25)**

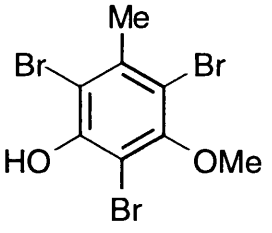
To a solution of 2,4,6-tribromo-3,5-dihydroxytoluene (**24**) (0.722 g, 0.002 mol) in acetone (40 ml) was added anhydrous potassium carbonate (2 g, 0.014 mol) and dimethyl sulphate (0.6 ml, 0.006 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 15 ml). The combined acetone solutions were evaporated and the brown viscous residue stirred whilst 35% ammonia solution (10 ml) was added. After 1 hour the mixture was extracted with diethyl ether (2 x 25 ml) and the combined extracts washed with 5% hydrochloric acid solution (25 ml), 5% sodium hydroxide solution (25 ml) and water (2 x 25 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure and recrystallisation from petroleum ether afforded 2,4,6-tribromo-3,5-dimethoxytoluene (**25**) (0.739 g, 95%) as needles m.p 101-102 °C (lit.,[87] 103-103.5 °C); $\delta_H$ 3.79 (6H, s, OMe) and 2.53 (3H, s, $ArCH_3$); $\delta_C$ 154.2 (3-C), 138.6 (1-C), 116.4 (2-C), 111.3 (4-C), 60.4 (OMe) and 24.5 ($ArCH_3$); m/z 391 ($M^+$, 31.6%), 389 (95.3), 387 (100), 385 (34.0) (Found: $M^+$, 387.8105; $C_9H_9{}^{79}Br_2{}^{81}BrO_2$ requires $M$, 387.8098).

## Preparation of Dibromoisocyanuric Acid (DBI)[49]

To a solution of cyanuric acid (6.45 g, 0.05 mol) and lithium hydroxide (2.39 g, 0.1 mol) in water (600 ml) at 20 °C was added bromine (10 ml, 0.2 mol) in one portion. By vigorous shaking all the bromine was brought into solution and the mixture placed in a freezer. After 48 hours standing in the freezer with occasional shaking the mixture was filtered and washed with water (4 x 50 ml). The crystalline product was pressed dry and then dried thoroughly, first over sodium hydroxide then phosphorous pentoxide. This afforded DBI (11.5 g, 80%) as a white solid, m.p. 302-304 °C, which

was used without further purification : $\delta_H$ ($D_6$-acetone) 3.47 (1H, br s, N-H); $\delta_C$ 207.8 (C=O); m/z 288, 286.

## Attempted Bromination of 2,6-Dibromo-3,5-dimethoxytoluene (21) Using DBI in Concentrated Sulphuric Acid




**(26)**

To a stirring solution of the 2,6-dibromo toluene **21** (0.930 g, 0.003 mol) in concentrated sulphuric acid (10 ml) was added a solution of DBI (0.574 g, 0.002 mol) in concentrated sulphuric acid (10 ml). Once the initially formed dark brown colour had faded (10 minutes) the mixture was poured on ice (100 ml) and the resulting precipitate filtered and washed with water (4 x 10 ml). The residue was washed through with ethanol (50 ml) and the solution evaporated to give a light brown oil (1.052 g). Analysis of the crude product by TLC, using 10: 1 petroleum ether/ethyl acetate as the eluant, indicated that it was composed of three constituents, with $R_f$ values 0.8, 0.5 and 0.46. On standing overnight the product with $R_f$ 0.46 crystallised out as long needles. This was demonstrated to be the starting 2,6-dibromo toluene **21** (0.106 g, 23%) by $^1H$ and $^{13}C$ nmr spectroscopic analysis. The remaining oil was chromatographed over a column of silica gel with petroleum ether - ethyl acetate (12:1) as the eluant. Early fractions afforded the 2,4,6-tribromo toluene **25** (0.156 g, 13.4%) as light feathery needles, identical to those obtained by methylation of 2,4,6-tribromo-3,5-dihydroxytoluene (**24**). Removal of the solvent under reduced pressure from later fractions and recrystallisation from petroleum ether afforded 2,4,6-tribromo-3-hydroxy-5-methoxytoluene (**26**) (0.540 g, 48.1%) as needles m.p. 90-91.5 °C (lit.,[87] 91-91.5 °C); $\delta_H$ 6.05 (1H, s, OH), 3.85 (3H, s, OMe) and 2.57 (3H, s, $ArCH_3$); $\delta_C$ 153.8 (5-C), 149.4 (3-C), 137.9 (1-C), 111.3 (2-C), 107.9 (6-C), 103.1 (4-C), 60.4 (OMe) and 24.4 ($ArCH_3$); m/z 377 ($M^+$, 26.6%), 375 (100), 373 (93.4), 371 (31.3) (Found: $M^+$, 373.7978 ; $C_8H_7{}^{79}Br_2{}^{81}BrO_2$ requires $M$, 373.7978).

## Bromination of 2,6-Dibromo-3,5-dimethoxytoluene (21) Using DBI in Glacial Acetic Acid

To a solution of the 2,6-dibromo toluene **21** (0.155 g, 0.5mmol) in glacial acetic acid (20 ml) was added DBI (0.086 g, 0.3 mmol). The solution was then stirred vigorously until all of the DBI had went into solution. Stirring was allowed to continue for a further 2 hours, when TLC analysis, using 10: 1 petroleum ether/ethyl acetate as the eluant, suggested the reaction was complete. The mixture was then poured into water and the resulting precipitate filtered and washed with water (4 x 10 ml). The solid was then dried over phosphorous pentoxide and recrystallised from petroleum ether to give the 2,4,6-tribromo toluene **25** (0.174 g, 88%) as feathery crystals.

## Tribromination of 3,5-Dimethoxytoluene (19) Using DBI in Glacial Acetic Acid

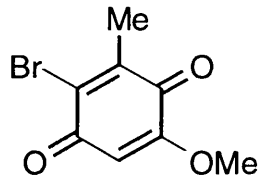
To a solution of toluene **19** (0.152 g, 0.001 mol) in glacial acetic acid (20 ml) was added DBI (0.431 g, 0.0015 mol). The solution was stirred vigorously for 30 minutes then a further portion of glacial acetic acid (20 ml) added to dissolve the remainder of the DBI which had not gone into solution. Stirring was allowed to continue for a further 90 minutes before the mixture was poured into water (120 ml). The resulting precipitate was filtered before being washed through with dichloromethane (50 ml). The solution was then washed with saturated sodium bicarbonate solution (until effervescence was observed to have ceased) and water (20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a white solid (0.330 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed of the desired 2,4,6-tribromo toluene **25** (90%) along with the 2,6-dibromo toluene **21** (10%).

## Debromination of 2,4,6-Tribromo-3,5-dimethoxytoluene (25) *via* Metal-Halogen Exchange

To a stirring solution of the 2,4,6-tribromo toluene **25** (0.389 g, 0.001 mol) in dry tetrahydrofuran (10 ml), under a nitrogen atmosphere at -78 °C, was added, dropwise, butyllithium (1.25 ml of 1.6 M in hexane, 0.002 mol). The temperature of the solution was then allowed to increase slowly up to 15 °C. Water (20 ml) was then added and the solution extracted with diethyl ether (2 x 25 ml). The combined extracts were washed with water (2 x 10 ml), dried over anhydrous magnesium sulphate and evaporated to give a brown oil (0.241 g). $^1$H nmr spectroscopic analysis of the crude product indicated that at least 9 constituents were present. TLC analysis suggested that a

chromatographic separation would be extremely difficult and consequently no attempt was made to purify the crude product further.

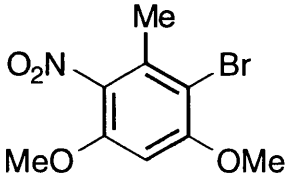
**Attempted C-4 Nitration of 2,6-Dibromo-3,5-dimethoxytoluene (21)**




**(28)**

To a stirring solution of the 2,6-dibromo toluene **21** (0.155 g, 0.5 mmol) in glacial acetic acid (10 ml) was added dropwise a 1 : 1 mixture of concentrated sulfuric and nitric acid. The solution was then poured into water (30 ml) and extracted with dichloromethane (3 x 20 ml). The combined extracts were washed with 5% sodium hydroxide solution (2 x 20 ml) and water (2 x 20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave a waxy yellow solid which was crystallised from hexane to give fine yellow needles, m.p.142-145 °C (lit.,[110] 148 °C), of a compound identified as 5-bromo-2-methoxy-6-methyl-cyclohex-2,5-dien-dione (**28**) (0.071 g, 61%); $\delta_H$ 6.07 (1H, s, 3-H), 3.83 (3H, s, OMe) and 2.23 (3H, s, C=C-$CH_3$); $\delta_C$ 179.1 and 178.8 (1-C=O and 4-C=O), 158.6 (2-C), 143.7 (6-C), 137.3 (5-C), 106.5 (4-CH), 56.6 (OMe) and 16.7 (C=C-$CH_3$); m/z 232 ($M^+$, 13.4%), 230 (12.4), 151 (12.8).

**Attempted C-4 Nitration of 2,6-Dibromo-3,5-dimethoxytoluene (21) using Nitronium Tetrafluoroborate**

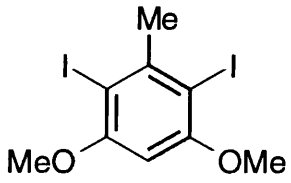



**(29)**

To an externally cooled solution of the 2,6-dibromo toluene **21** (0.310 g, 0.001 mol) in tetramethylene sulfone (5 ml) was added a solution of nitronium tetrafluoroborate (0.133 g, 0.001 mol) in tetramethylene sulfone (10 ml) at such a rate as to allow the

temperature to remain in the range 15-25 °C. After the addition was complete the reaction mixture was stirred for a further 3 hours at room temperature before being diluted with water (30 ml) and extracted with diethyl ether (2 x 30 ml). The combined extracts were washed thoroughly with water (8 x 20 ml), dried over anhydrous magnesium sulphate and evaporated to give a yellow solid. Recrystallisation from ethanol afforded long yellow needles, m.p. 162-163 °C, of a compound identified as 2-bromo-3,5-dimethoxy-6-nitrotoluene (**29**) (0.172 g, 62%); $\delta_H$ 6.44 (4-CH), 3.94 (OMe), 3.90 (OMe) and 2.36 ($ArCH_3$); $\delta_C$ 157.5 (3-C), 151.0 (5-C), 136.5 (6-C), 132.2 (1-C) 105.2 (2-C), 94.2 (4-CH), 56.6 (OMe), 56.5 (OMe) and 18.4 ($ArCH_3$); m/z 277 ($M^+$, 62.9%), 275 (62.5)

**Preparation of 2,6-Diiodo-3,5-dimethoxytoluene (30)**




**(30)**

To a stirring solution of toluene **19** (0.912 g, 0.006 mol) in acetic acid (20 ml) was added a solution of iodine monochloride (1.948 g, 0.012 mol) in acetic acid (20 ml) dropwise over a period of 15 minues. Stirring was continued for a further 2 hours until TLC analysis, with 4 : 1 hexane/ethyl acetate as the eluent, indicated the reaction was complete. The solution was then poured into iced water (100 ml) and allowed to stand for 1 hour. The resulting precipitate was filltered, washed with water (3 x 20 ml) and dried to give a light brown solid (0.921 g). The initial filtrate was then extracted with diethyl ether (2 x 50 ml) and the combined extracts washed with 5% sodium hydroxide solution (2 x 50 ml), 5% sodium thiosulphate solution (50 ml) and water (50 ml). Drying of the solution, over anhydrous magnesium sulphate, and removal of the solvent under reduced pressure afforded a further 0.813 g of crude product. The combined crude products were recrystallised from chloroform to give 2,6-diiodo-3,5-dimethoxytoluene (**30**) (1.60 g, 66%) as colourless square plates, m.p. 193.5-194.5 °C (lit.,[111] 196.5 °C); $\delta_H$ (temp. 60 °C) 6.26 (1H, s, 4-H), 3.88 (6H, s, OMe) and 2.84 (3H, s, $ArCH_3$); $\delta_C$ 159.2 (3-C), 144.8 (1-C), 93.0 (2-C), 81.8 (4-CH), 56.7 (OMe) and 35.5 ($ArCH_3$); m/z 404 ($M^+$, 100%), 262 (34.5).

**Attempted Preparation of 4-Bromo-2,6-diiodo-3,5-dimethoxytoluene**

To a solution of DBI (0.144 g, 0.5 mmol) in glacial acetic acid (15 ml) was added 2,6-diiodo toluene **30** (0.404 g, 0.001 mol) in a single portion. Immediately after the addition the solution developed a very dark colouration. This was attributed to a loss of iodine from **30** and the experiment was not worked up.

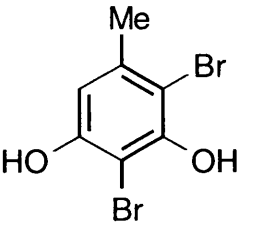
**Attempted Preparation of 4-Bromo-2,6-diiodo-3,5-dimethoxytoluene using Dichloromethane as the Solvent**

To a stirring solution of the 2,6-diiodo toluene **30** (0.404 g, 0.001 mol) in dichloromethane (10 ml) was added DBI (0.144 g, 0.5 mmol). After stirring for 3 hours TLC analysis, using 6 : 1 petroleum ether/ethyl acetate as the eluent, failed to show any evidence of reaction. A catalytic amount of concentrated sulphuric acid was then added. After stirring for a further 3 hours the solution had began to develop a purple colouration and TLC still suggested that the desired bromination had not occured. The reaction was abandoned at this point.

**Attempted Preparation of 2,6-Diiodo-3,5-dihydroxytoluene**

To a stirring solution of 3,5-dihydroxytoluene monohydrate (1.42 g, 0.01 mol) in glacial acetic acid (30 ml) was added a solution of iodine monochloride (3.247 g, 0.02 mol) in glacial acetic acid (10 ml) dropwise over a period of 20 minutes. Stirring was allowed to continue for a further 2 hours. The solution was then poured onto ice (50 ml) and extracted with diethyl ether (2 x 50 ml). The combined extracts were washed with 5% sodium hydroxide solution (2 x 50 ml), 5% sodium thiosulphate solution (50 ml) and water (50 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a brown oil (3.1 g). Analysis of the crude product by $^{1}H$ nmr spectroscopy suggested that it was composed of at least 4 constituents and that the level of desired compound in the isolated oil was less than 40%. The crude product was not purified further.

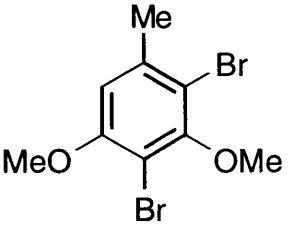
**Preparation of 2,4-Dibromo-3,5-dihydroxytoluene (31)**




**(31)**

To a stirring solution of 3,5-dihydroxytoluene monohydrate (1.42 g, 0.01 mol) in glacial acetic acid (20 ml) was added a 10% by volume solution of bromine in acetic acid (10 ml, 0.02 mol) in 2 portions. After stirring for 10 minutes the solution was poured onto ice (100 ml) and extracted with diethyl ether (2 x 40 ml). The combined extracts were then washed with saturated sodium bicarbonate solution, until effervescence was observed to have ceased, and water (40 ml). The solution was then dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give a brown oil (2.42 g). TLC analysis of the crude product, with 5 : 1 petroleum ether/ethyl acetate as the eluent, suggested it was composed of 3 constituents with $R_f$ values 0.42, 0.33 and 0.17. The components were separating by chromatographing the oil over a column of silica gel with petroleum ether - ethylacetate (20:1) as the eluant. Early fractions afforded 2,4,6-tribromo-3,5-dihydroxytoluene (**24**) (0.50 g, 14%) followed by 2,4-dibromo-3,5-dihydroxytoluene (**31**), which was obtained as an oil that crystallised on standing to give a solid (1.13 g, 40%); $\delta_H$ 6.54 (1H, s, 6-H), 5.81 (2H, br s, OH) and 2.32 (3H, s, $ArCH_3$). This was used without further purification. Further elution gave an oil (0.95 g) which $^1H$ nmr spectroscopic analysis indicated was composed of 2,6-dibromo-3,5-dihydroxytoluene and 2-bromo-3,5-dihydroxytoluene in the ratio 2 : 1.

## Preparation of 2,4-Dibromo-3,5-dimethoxytoluene (32)

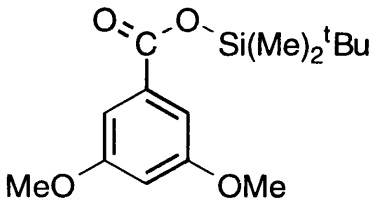



**(32)**

To a stirring solution of 2,4-dibromo-3,5-dihydroxytoluene (**31**) (0.8 g, 0.0028 mol) in acetone (20 ml) was added anhydrous potassium carbonate (1 g, 0.0072 mol) and

dimethyl sulphate (0.4 ml, 0.0042 mol). Stirring was continued and the solution heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 10 ml). The combined extracts were evaporated under reduced pressure to give a brown oily residue. 35% ammonia solution (10 ml) was then added and the mixture stirred for 1 hour before being extracted with diethyl ether (2 x 30 ml). The combined extracts were washed with 5% hydrochloric acid solution (20 ml) and water (2 x 30 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded 2,4-dibromo-3,5-dimethoxytoluene (**32**) (0.673 g, 77%) as a yellow oil which was crystallised from methanol to give prisms, m.p. 59-60 °C (lit.,[87] 59-60 °C); $\delta_H$ 6.52 (1H, s, 6-H), 3.77 (6H, s, OMe) and 2.29 (3H, s, $ArCH_3$); $\delta_C$ 155.6 (3-C), 154.8 (5-C), 138.4 (1-C), 111.5 (2-C), 109.6 (6-CH), 104.8 (4-C), 60.3 (OMe), 56.5 (OMe) and 23.6 ($ArCH_3$); m/z 312 ($M^+$, 50%), 310 (100), 308 (51).

**Preparation of Butyldimethylsilyl 3,5-dimethoxybenzoate (33)**




**(33)**

To a solution of 3,5-dimethoxybenzoic acid (0.910 g, 0.005 mol) in dry dimethylformamide (5 ml) under a nitrogen atmosphere was added 'butyldimethylsilyl chloride (0.906 g, 0.006 mol) and imidazole (0.510 g, 0.0075 mol). Stirring was allowed to continue for 90 minutes. The solution was then diluted with dichloromethane (25 ml) and washed with 2% sodium hydroxide solution (2 x 20 ml), 2% hydrochloric acid solution (2 x 20 ml), saturated sodium chloride solution (4 x 20 ml) and water (20 ml). Drying of the solution over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded an oil which crystallised on standing to give 'butyldimethylsilyl 3,5-dimethoxybenzoate (**33**) (0.817 g, 55.2%) as glistening rectangular prisms m.p. 58-60 °C : $\delta_H$ 7.11 (2H, d, *J* 2.4, 2-H), 6.55 (1H, t, 4-H), 3.73 (6H, s, OMe), 0.93 (9H, s, $CMe_3$) and 0.28 (6H, s, $SiMe_2$); $\delta_C$ 166.4 (C=O), 160.5 (3-C), 133.4 (1-C), 107.6 (2-CH), 105.4 (4-CH), 55.4 (OMe), 25.6 ($CMe_3$), 17.8 ($CMe_3$) and -4.9 ($SiMe_2$); m/z 296 ($M^+$, 1%), 239 (100, M-$^t$Bu).

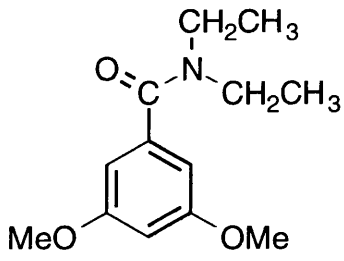
## Bromination of Butyldimethylsilyl 3,5-dimethoxybenzoate (33) with Molecular Bromine

To a solution of $^t$butyldimethylsilyl 3,5-dimethoxybenzoate (**33**) (0.296 g, 0.001 mol) in dry dichloromethane (5 ml), under a nitrogen atmosphere, was added a 1 M solution of bromine in dry dichloromethane (1 ml, 0.001 mol). The solution was then stirred for 8 hours. The solution was then diluted with dichloromethane (15 ml) and washed with water (2 x 10 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a crystalline solid (0.160 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed solely of C-2 and C-6 brominated derivatives of 3,5-dimethoxybenzoic acid. No further purification of the crude product was attempted.

## Bromination of Butyldimethylsilyl 3,5-dimethoxybenzoate (33) with NBS

To a stirring solution of $^t$butyldimethylsilyl 3,5-dimethoxybenzoate (**33**) (0.296 g, 0.001 mol) in dry dimethylformamide (10 ml), under a nitrogen atmosphere was added NBS (0.178 g, 0.001 mol) in a single portion. Stirring was allowed to continue for 24 hours. The solution was then poured into water (30 ml) and extracted with dichloromethane (2 x 25 ml). The combined extracts were washed with saturated sodium chloride solution (4 x 20 ml) and water (20 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a white solid (0.165 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed solely of C-2 and C-6 brominated derivatives of 3,5-dimethoxybenzoic acid. No further purification of the crude product was attempted.

**Attempted Preparation of *N,N*-Diethyl-3,5-dimethoxybenzamide (34)**




**(34)**

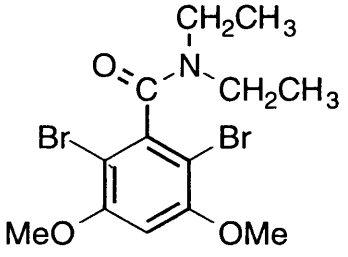
To a stirring solution of 3,5-dimethoxybenzoic acid (1.822 g, 0.01 mol) in dry tetrahydrofuran (40 ml) was added diethylamine (0.8 g, 0.011 mol) and diisopropylcarbodiimide (1.56 ml, 0.01 mol). Stirring was continued and the solution heated at reflux for 8 hours. After cooling the solvent was evaporated under reduced pressure and the resulting yellow oil dissolved in dichloromethane (40 ml). This solution was then washed with 5% sodium hydroxide solution (40 ml), 1 M hydrochloric acid solution (40 ml) and water (2 x 40 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a yellow crystalline solid (0.456 g). Analysis of the crude product by $^1$H nmr spectroscopy showed no evidence to suggest that amide formation had occured to any appreciable extent.

**Preparation of *N,N*-Diethyl-3,5-dimethoxybenzamide (34)[112]**

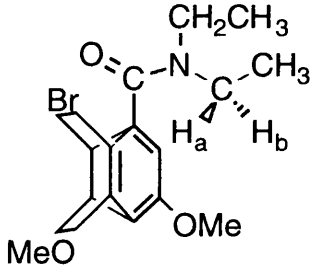
To a flask containing iron filings (2 g) was added thionyl chloride (30 ml). This mixture was heated at reflux for 2 hours and then distilled into a dry flask under a nitrogen atmosphere. To the thionyl chloride was added 3,5-dimethoxybenzoic acid (1.822 g, 0.01 mol) and the resulting mixture stirred for 16 hours. Removal of the excess thionyl chloride under reduced pressure gave a yellow solid which was dissolved in dry tetrahydrofuran (30 ml). Diethylamine (3 ml, 0.030 mol) was then added and the solution stirred until TLC, using 10 : 1 petroleum ether/ethyl acetate as the eluent, suggested the reaction was complete (3 hours). Removal of the solvent under reduced pressure gave an oil which was dissolved in dichloromethane (25 ml) and washed with 5% sodium hydroxide solution (20 ml) and water (2 x 20 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded **34** (1.62 g, 68.4%) as a viscous yellow oil ; $\delta_H$ (60 °C) 6.39 (3H, m, 2-CH & 4-CH), 3.69 (6H, s, OMe), 3.30 (4H, br q, *J* 6.8, -C*H*$_2$CH$_3$) and 1.08 (6H, t, *J*

7.1, $-CH_2CH_3$); $\delta_C$ 170.7 (C=O), 160.7 (3-C), 139.0 (1-C), 104.0 (2-CH), 101.1 (4-CH), 55.3 (OMe), 43.1 ($-CH_2CH_3$), 39.0 ($-CH_2CH_3$), 14.2 ($-CH_2CH_3$) and 12.8 ($-CH_2CH_3$); m/z 237 ($M^+$, 31.1%), 165 (100, M-$NEt_2$) and 138 (57.5, M-$CONEt_2$).

## Bromination of *N,N*-Diethyl-3,5-dimethoxybenzamide (34) with Molecular Bromine




**(36)**




**(35)**

To a stirring solution of benzamide **34** (0.237 g, 0.001 mol) in dichloromethane (20 ml) was added a 1 M solution of bromine in dichloromethane (1 ml, 0.001 mol). Stirring was allowed to continue for 1 hour. The solution was then washed with 5% sodium hydroxide solution (20 ml) and water (2 x 20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded an oily crystalline solid (0.286 g). TLC analysis of the crude product, with 1 : 1 petroleum ether/ethyl acetate as the eluent, suggested it was composed of 3 constituents, starting benzamide **34** and products with $R_f$ values 0.62 and 0.54. The components were separating by chromatographing the crude product over a column of silica gel with petroleum ether - ethylacetate (10 : 1) as the eluant. Fractions containing the product with $R_f$ value 0.62 were combined and evaporated to give *N,N*-diethyl-2,6-dibromo-3,5-dimethoxybenzamide (**36**) as needles (0.075 g, 0.2 mmol), m.p. 180-181 °C; $\delta_H$ 6.22 (1H, s, 4-CH), 3.64 (6H, s, OMe), 3.32 (2H, q, *J* 7.1, $-CH_2CH_3$), 2.88 (2H, q, *J* 7.2, $-CH_2CH_3$), 1.01 (3H, t, *J* 7.1, $-CH_2CH_3$) and 0.87 (3H, t, *J* 7.2, $-CH_2CH_3$); $\delta_C$ 166.2 (C=O), 156.4 (3-C), 140.7 (1-C), 99.7 (2-C), 96.6 (4-CH), 56.7 (OMe), 42.5 ($-CH_2CH_3$), 38.6 ($-CH_2CH_3$), 13.4 ($-CH_2CH_3$) and 12.1 ($-CH_2CH_3$); m/z 397 ($M^+$, 16.9%), 395 (34.2), 393 (17.2) (Found: $M^+$, 396.9549; $C_{13}H_{17}NO_3{}^{81}Br_2$ requires *M*, 396.9561). Removal of the solvent from fractions containing the product with $R_f$ value 0.54 afforded *N,N*-diethyl-2-bromo-3,5-dimethoxybenzamide (**35**) (0.136 g, 0.43 mmol) as a solid, m.p. 54-56 °C; $\delta_H$ 6.25 (1H, d, *J* 2.67, 6-CH), 6.19 (1H, d, *J* 2.68, 4-CH), 3.66 (3H, s, OMe), 3.60 (1H, dq, $J_d$ 14, $J_q$ 6.8, $-CH_aH_bCH_3$), 3.58 (3H, s, OMe), 3.11 (1H, dq, $J_d$ 14, $J_q$ 7.1, $-CH_aH_bCH_3$), 3.08 (2H, q, *J* 7.2, $-CH_2CH_3$), 1.06 (3H, t, *J* 7.1, $-CH_2CH_3$) and

0.87 (3H, t, *J* 7.1, $-CH_2CH_3$) ; $\delta_C$ 166.2 (C=O), 160.2 &156.7 (3-C and 5-C), 140.2 (1-C), 103.3 (6-CH), 99.6 (4-CH), 99.5 (2-C), 56.3 (OMe), 55.6 (OMe), 42.6 ($-CH_2CH_3$), 38.8 ($-CH_2CH_3$), 13.8 ($-CH_2CH_3$) and 12.4 ($-CH_2CH_3$); m/z 317 ($M^+$, 55.6%), 315 (60.9), 245 (97.2, M-$NEt_2$), 243 (100, M-$NEt_2$) (Found: $M^+$, 317.0418; $C_{13}H_{18}NO_3{}^{81}Br$ requires *M*, 317.0449).

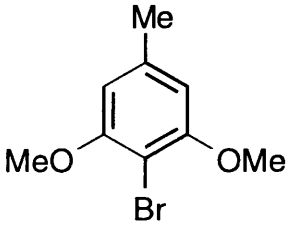
## Bromination of *N,N*-Diethyl-3,5-dimethoxybenzamide (34) with 2 Mole Equivalents of Molecular Bromine

To a stirring solution of benzamide **34** (0.237 g, 0.001 mol) in dichloromethane (20 ml) was added a 5% by volume solution of bromine in dichloromethane (2 ml, 0.002 mol). Stirring was allowed to continue for 24 hours. The solution was then washed with 5% sodium hydroxide solution (20 ml) and water (2 x 20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a white crystalline solid (0.343 g) which analysis by $^1H$ nmr spectroscopy suggested was composed solely of *N,N*-diethyl-2,6-dibromo-3,5-dimethoxybenzamide (**36**).

## Bromination of *N,N*-Diethyl-3,5-dimethoxybenzamide (34) with NBS

To a stirring solution of benzamide **34** (0.237 g, 0.001 mol) in dry dimethylformamide (10 ml) was added a solution of NBS (0.178 g, 0.001 mol) in dry dimethylformamide (10 ml). Stirring was allowed to continue for 24 hours. The solution was then poured into water (50 ml) and extracted with dichloromethane (2 x 30 ml). The combined extracts were washed with saturated sodium chloride solution (4 x 40 ml) and water (40 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded oily white crystals (0.252 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested it was composed of starting benzamide **34** and the 2-bromo derivative **35** in the ratio 1 : 60.

**Attempted Preparation of 4-Bromo-3,5-dimethoxytoluene (27) *via* C-4 Lithiation (Part 1)**




**(27)**

To a solution of toluene **19** (0.152 g, 0.001 mol) in anhydrous tetrahydrofuran (6 ml), under a nitrogen atmosphere at -78 °C, was added a 1.6M solution of $^{n}$butyllithium in hexane (0.625 ml, 0.001 mol). The solution was allowed to warm slowly to room temperature and was then heated at reflux for 3 hours. After cooling bromine (0.05 ml, 0.001 mol) was added and stirring continued for three hours. Removal of the solvent gave a dark oil which was dissolved in dichloromethane (20 ml) and washed with water (2 x 20 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a brown oil (0.208 g). Analysis of the crude product by TLC, using 10 : 1 petroleum ether/ethyl acetate as the eluent, and $^{1}$H nmr spectroscopy suggested that it was composed solely of starting toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21**. As no C-4 bromination had been observed the crude product was not purified further.

**Attempted Preparation of 4-Bromo-3,5-dimethoxytoluene (27) *via* C-4 Lithiation (Part 2)**

To 2 flame dried flasks under nitrogen atmospheres were each added toluene **19** (1.52 g, 0.01 mol), a 1.8M solution of phenyllithium in 70 : 30 cyclohexane/ether (6.5 ml, 0.012 mol) and freshly distilled *N,N,N',N'*--tetramethylethylenediamine (1.76 ml, 0.012 mol). Light was then excluded and the mixtures allowed to stir for 20 hours when the solutions were observed to have turned from transparent and dark in colour to opaque and white. To one of the flasks was then added deuterium oxide (5 ml) and stirring continued for a further hour. The solution was then poured into water (20 ml) and extracted with diethyl ether (2 x 20 ml). The combined extracts were washed with 1M hydrochloric acid solution (20 ml) and water (20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a pale yellow oil (1.47 g). Analysis of the crude product by $^{1}$H nmr

spectroscopy suggested was composed exclusively of 4-deutero-3,5-dimethoxytoluene ; $\delta_H$ 6.32 (2H, s, 2-H), 3.75 (6H, s, OMe) and 2.29 (3H, s, $ArCH_3$). Having proved that C-4 lithiation had occured essentially quantitatively, bromine (0.5 ml, 0.01 mol) was added to the remaining flask and stirring continued for 1 hour. The solution was then poured into water (20 ml) and extracted with diethyl ether (2 x 20 ml). The combined extracts were washed with 1M hydrochloric acid solution (20 ml) and water (20 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded an oily brown solid. Analysis of the crude product by TLC, using 10 : 1 petroleum ether/ethyl acetate as the eluent, and $^1H$ nmr spectroscopy suggested that it was composed solely of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21**.

## Attempted Preparation of 4-Bromo-3,5-dimethoxytoluene (27) *via* C-4 Lithiation (Part 3)

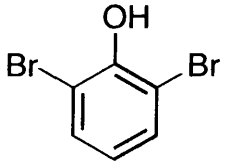
Toluene **19** (1.52 g, 0.01 mol) was lithiated at C-4 as described above. The resulting opaque white solution was cooled to 0 °C and 1,2-dibromoethane (0.95 ml, 0.011 mol) added. The solution was then allowed to warm to room temperature and stirring continued for a further 12 hours. The solution was then poured into water (20 ml) and extracted with diethyl ether (2 x 20 ml). The combined extracts were washed with 1 M hydrochloric acid solution (20 ml) and water (20 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded an oil which analysis by $^1H$ nmr spectroscopy suggested was composed solely of starting toluene **19**.

## Preparation of 4-Bromo-3,5-dimethoxytoluene (27) *via* C-4 Lithiation

Toluene **19** (1.52 g, 0.01 mol) was lithiated at C-4 as described above. To the resulting opaque white solution was added NBS (1.958 g, 0.011 mol) in a single portion whilst maintaining the nitrogen atmosphere. Stirring was allowed to continue for 5 hours. The solution was then poured into water (20 ml) and extracted with diethyl ether (2 x 20 ml). The combined extracts were washed with 1 M hydrochloric acid solution (20 ml) and water (20 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a dark blue oil (1.84 g). Analysis of this oil by TLC, using 10 : 1 petroleum ether/ethyl acetate as the eluent, suggested it was composed of at least 3 constituents. These components were separating by chromatographing the oil over a column of silica gel with petroleum ether - ethylacetate

(50 : 1) as the eluant. Early fractions afforded oily white crystals identified as biphenyl (0.214 g). Further elution gave starting toluene **19** (0.248 g, 0.0016 mol) and finally 4-bromo-3,5-dimethoxytoluene (**27**). Removal of the solvent under reduced pressure and recrystallisation from petroleum ether afforded **27** (0.926 g, 40%) as plates, m.p. 75-77 °C (lit.,[87] 75-76 °C); $\delta_H$ 6.31 (2H, s, 2-H), 3.78 (6H, s, OMe) and 2.45 (3H, s, $ArCH_3$); $\delta_C$ 156.7 (3-C), 138.6 (1-C), 105.5 (2-CH), 98.5 (4-C), 56.2 (OMe) and 21.9 ($ArCH_3$); m/z 230 ($M^+$, 98%), 232 (100).

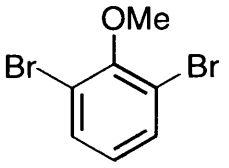
**Preparation of 2,6-Dibromophenol (37)**




**(37)**

To a solution of $^t$butylamine (4.2 ml, 0.04 mol) in toluene (50 ml), cooled to -30 °C, was added a solution of bromine (1 ml, 0.02 mol) in toluene (5 ml), dropwise over a 10 minute period. The solution was then cooled to -78 °C and a solution of phenol (0.941 g, 0.01 mol) in dichloromethane (5 ml) added. The solution was then allowed to warm slowly to room temperature, over a 5 hour period, and extracted with 10% sodium hydroxide solution (2 x 20 ml). The combined extracts were acidified with concentrated hydrochloric acid and extracted with dichloromethane (2 x 40 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a brown oil. This crude product was purified by flash chromatography over a column of silica and recrystallised from hexane to give 2,6-dibromophenol (**37**) (1.84 g, 73%) as a white crystalline solid, m.p. 54-56 °C (lit.,[113] 56 °C); $\delta_H$ 7.42 (2H, d, *J* 8, 3-H), 6.68 (1H, t, *J* 8, 4-H) and 5.92 (1H, br s, OH); $\delta_C$ 149.4 (1-C), 132.0 (3-CH), 122.4 (4-CH) and 110.0 (2-C) ; m/z 254 ($M^+$, 50%), 252 (100), 250 (51).

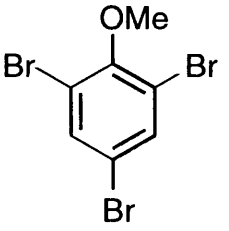
**Preparation of 2,6-Dibromoanisole (38)**




**(38)**

To a solution of 2,6-dibromophenol (**37**) (1.26 g, 0.005 mol) in acetone (40 ml) was added anhydrous potassium carbonate (4 g, 0.029 mol) and methyl iodide (0.8 ml, 0.013 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 25 ml). The combined acetone solutions were evaporated under reduced pressure to give an oily white solid which was redissolved in dichloromethane (25 ml). The solution was then washed with 5% sodium hydroxide solution (20 ml) and water (20 ml) before being dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure afforded 2,6-dibromoanisole (**38**) (1.14 g, 86%) as an oil which crystallised on standing at 0 °C to give a solid, m.p. 12-14 °C (lit.,[114] 14.5 °C); $\delta_H$ 7.40 (2H, d, *J* 8, 3-H), 6.76 (1h, t, *J* 8, 4-H) and 3.79 (3H, s, OMe); $\delta_C$ 154.2 (1-C), 132.7 (3-CH), 126.3 (4-CH), 118.3 (2-C) and 60.5 (OMe) ; m/z 268 ($M^+$, 50%), 266 (100), 264 (50).

**Bromination of 2,6-Dibromoanisole (38)**




**(39)**

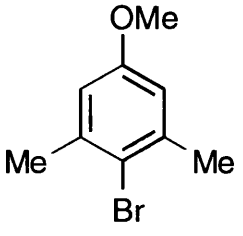
To a stirring solution of 2,6-dibromophenol (**38**) (0.266 g, 0.001 mol) in glacial acetic acid (5 ml) was added a solution of DBI (144 g, 0.5 mmol) in glacial acid acid (10 ml). Stirring was allowed to continue for 24 hours. The solution was then poured into water (50 ml) and extracted with dichloromethane (2 x 25 ml). The combined extracts were washed with 5% sodium hydroxide solution (2 x 20 ml) and water (20 ml) before being

dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a crystalline solid (0.303 g). Analysis of the crude product by $^1H$ nmr spectroscopy and TLC suggested that it was composed of 2 components, starting compound **38** and 2,4,6-tribromoanisole (**39**). The crude product was then chromatographed over a column of silica gel using 20 : 1 petroleum ether/ethyl acetate as the eluent. Those fractions containing 2,4,6-tribromoanisole **39** were combined and evaporated under reduced pressure to afford **39** (0.187 g, 54%) as white crystals, m.p. 87-89 °C (lit.,[115] 87 °C); $\delta_H$ 7.64 (2H, s, 3-H) and 3.86 (3H, s, OMe); $\delta_C$ 153.6 (1-C), 135.0 (3-CH), 118.8 (2-C), 117.4 (4-C) and 60.7 (OMe); m/z 348 ($M^+$, 7%), 346 (20), 344 (21), 342 (8), 334 (23, M-$CH_2$), 332 (68), 330 (68), 328 (25).

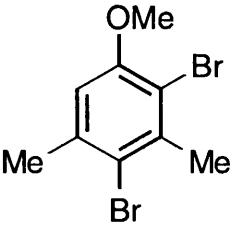
## Competitive Bromination of 1,3-Dibromobenzene and 2,6-Dibromoanisole (38)

To a stirring solution of 2,6-dibromoanisole (**38**) (0.266 g, 0.001 mol) and 1,3-dibromobenzene (0.236 g, 0.001 mol) in glacial acetic acid (10 ml) was added a solution of DBI (144 g, 0.5 mmol) in glacial acid acid (10 ml). Stirring was allowed to continue for 24 hours. The solution was then poured into water (50 ml) and extracted with dichloromethane (2 x 25 ml). The combined extracts were washed with 5% sodium hydroxide solution (2 x 20 ml) and water (20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded an oil (0.500 g). Analysis of this crude product by $^1H$ nmr spectroscopy suggested that only anisole **38** had undergone bromination (to an extent of 60%).

## Bromination of 3,5-Dimethylanisole (22) using 1 Mole Equivalent of Bromine




**(40)**




**(41)**

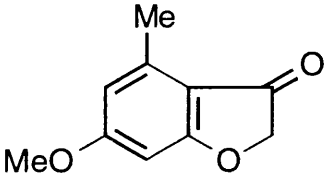
To a stirring solution of anisole **22** (0.545 g, 0.004 mol) in dichloromethane (20 ml) was added a 5% by volume solution of bromine in dichloromethane (4 ml, 0.004 mol).

Stirring was allowed to continue for 1 hour. The solution was then washed with 5% sodium hydroxide solution (20 ml) and water (20 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give an oily white solid (0.8 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC suggested that it was composed of 3 constituents. These constituents were separated by chromatographing the crude product over a column of silica, using 20 : 1 petroleum ether/ethyl acetate as the eluent. Early fractions afforded unreacted starting anisole **22** (0.025 g, 0.18 mmol) followed by 4-bromo-3,5-dimethylanisole (**40**) (0.69 g, 0.0029 mol) which was obtained as an oil that crystallised on standing to give a solid, m.p. 24-25 °C (lit.,[116] 24 °C); $\delta_H$ 6.63 (2H, s, 2-H), 3.74 (3H, s, OMe) and 2.37 (6H, s, $ArCH_3$); $\delta_C$ 158.0 (1-C), 139.0 (3-C), 118.2 (4-C), 113.8 (2-CH), 55.3 (OMe) and 24.0 ($ArCH_3$); m/z 216 ($M^+$, 100%), 214 (99). Further elution gave fractions containing 2,4-dibromo-3,5-dimethylanisole (**41**) (0.056 g, 0.19 mmol) which was obtained as fine needles, m.p. 111-112 °C (lit.,[108] 107-110 °C); $\delta_H$ 6.65 (1H, s, 6-H), 3.85 (3H, s, OMe), 2.60 (3H, s, $ArCH_3$) and 2.38 (3H, s, $ArCH_3$); $\delta_C$ 154.5 (1-C), 138.4 (3-C), 137.8 (5-C), 118.5 (4-C), 111.7 (2-C), 111.2 (6-CH), 56.3 (OMe), 24.6 ($ArCH_3$) and 24.5 ($ArCH_3$); m/z 296 ($M^+$, 40%), 294 (80), 292 (42). The intial $^1$H nmr spectrum of the crude product suggested that **22**, **40** and **41** were formed in the ratio 1 : 16 : 1.

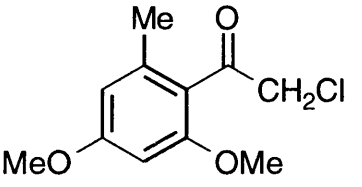
## Bromination of 3,5-Dimethylanisole (22) using 2 Mole Equivalents of Bromine

To a stirring solution of anisole **22** (0.136 g, 0.001 mol) in dichloromethane (10 ml) was added a 5% by volume solution of bromine in dichloromethane (2 ml, 0.002 mol). Stirring was allowed to continue for 1 hour. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a crystalline white solid (0.280 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC suggested that it was composed solely of 2,4-dibromo-3,5-dimethylanisole **41** (95% yield).

**Attempted One Step Preparation of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (43)[98]**



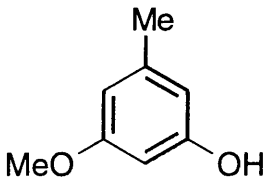

(43)




(45)

To a solution of toluene **19** (1.52 g, 0.01 mol) in carbon disulphide (10 ml), held at 0 °C, was added carefully powdered aluminium chloride (1.34 g, 0.01 mol) with vigorous stirring and then at room temperature a solution of chloroacetyl chloride (0.8 ml, 0.01 mol) in carbon disulphide (5 ml) over a 1 hour period. The mixture was then stirred under reflux for 16 hours when it was observed to have turned deep red in colour. The solvent was then removed by distillation and the residue cooled to 0 °C. Chloroform (20 ml), ice-water (10 ml) and 2 M hydrochloric acid solution (10 ml) were then added successively and the mixture stirred for 40 minutes at 0 °C. The aqueous layer was then separated and the chloroform extract washed with 2 M hydrochloric acid solution (10 ml) and water (2 x 10 ml) and dried. Removal of the solvent under reduced pressure afforded a viscous red oil (1.50 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 5 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed a large number of constituents. The oil was then chromatographed over a column of silica gel using 20 : 1 petroleum ether/ethyl acetate as the eluent. The only compound separated was 2-chloroacetyl-3,5-dimethoxytoluene (**45**) (0.46 g, 0.002 mol),obtained as a yellow solid, m.p. 67-70 °C (lit.,[98] 69-70.5 °C); $\delta_H$ 6.28 (1H, d, *J* 2, 6-H), 6.23 (1H, d, *J* 2, 4-H), 4.44 (2H, s, -$CH_2$-), 3.73 (6H, s, OMe) and 2.20 (3H, s, Ar$CH_3$); $\delta_C$ 162.1 (5-C), 159.1 (3-C), 140.3 (1-C), 119.6 (2-C), 107.9 (6-CH), 95.8 (4-CH), 55.6 and 55.3 (3-O$CH_3$ and 5-$CH_3$), 50.2 ($CH_2$Cl) and 20.4 (1-$CH_3$); m/z 230 ($M^+$, 2.1%), 228 (6.0) and 179 (100, M-$CH_2$Cl). The remainder of the crude product was seemingly intractable and was not purified further.

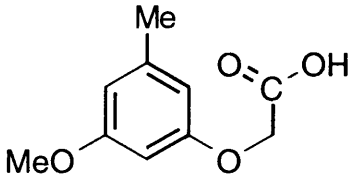
**Preparation of 5-Hydroxy-3-methoxytoluene (46)**




**(46)**

To a solution of 3,5-dihydroxytoluene monohydrate (12.78 g, 0.09 mol) in acetone (100 ml) was added anhydrous potassium carbonate (13.8 g, 0.1 mol) and dimethyl sulphate (4.26 ml, 0.045 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 40 ml). The combined acetone solutions were evaporated and the brown viscous residue dissolved in diethyl ether (60 ml) and extracted with 10% sodium hydroxide solution (40 ml).The aqueous extract was acidified using hydrochloric acid solution and extracted with diethyl ether (2 x 40 ml). The combined extracts were washed with water (2 x 40 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a viscous brown oil (8.95 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested it was composed of 5-hydroxy-3-methoxytoluene (**46**) and 3,5-dihydroxytoluene in the ratio 2 : 1. These 2 constituents were separated by flash chromatography over a column of silica using 4 : 1 petroleum ether/ethyl acetate as the eluent. Fractions containing the first compound to elute were combined and evaporated under reduced pressure to give 5-hydroxy-3-methoxytoluene (**46**) (5.84 g, 48%) as a solid, which was recrystallised from petroleum ether to give needles, m.p. 60-62 °C (lit.,[87] 61-62 °C); $\delta_H$ 6.64 (1H, br s, OH), 6.30 (3H, m, 2-H 4-H and 6-H), 3.74 (OMe) and 2.25 ($ArCH_3$); $\delta_C$ 160.5 (5-C), 156.7 (3-C), 140.6 (1-C), 108.9 (2-CH), 107.2 (6-CH), 98.7 (4-CH), 55.2 (OMe) and 21.5 ($ArCH_3$); m/z 138 ($M^+$, 100%).

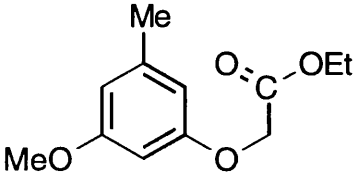
**Attempted Preparation of 3-Methoxy-5-methylphenoxyacetic acid (48)**




**(48)**

To a solution of 5-hydroxy-3-methoxytoluene (**46**) (5.52 g, 0.04 mol) in acetone (100 ml) was added anhydrous potassium carbonate (11.06 g, 0.08 mol) and chloroacetic acid (3.78 g, 0.04 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 40 ml). The combined acetone solutions were evaporated to leave a light brown solid (5.20 g). Analysis of the crude product by $^1H$ nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested it was composed solely of starting phenol **46**. The filtered residue was added to water (100 ml) and acidified using hydrochloric acid. This solution was then extracted with dichloromethane (2 x 30 ml). Analysis of the combined extracts by TLC failed to show any evidence of product formation and the solutions were not worked up any further.

**Preparation of Ethyl 3-Methoxy-5-methylphenoxyacetate (47)**




**(47)**

To a solution of 5-hydroxy-3-methoxytoluene (**46**) (5.52 g, 0.04 mol) in acetone (100 ml) was added anhydrous potassium carbonate (11.06 g, 0.08 mol) and ethyl chloroacetate (4.90 g, 0.04 mol). The mixture was then stirred vigorously and heated at reflux for 8 hours. After cooling the solution was filtered and the residue washed with acetone (2 x 40 ml). The combined acetone solutions were evaporated to leave an oil which was dissolved in dichloromethane (50 ml) and washed with 5% sodium hydroxide solution (30 ml) and water (30 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded ethyl 3-methoxy-

5-methylphenoxyacetate (**47**) (7.26 g, 81%) as an oil which was used without further purification ; $\delta_H$ 6.36 (1H, br s, Ar-H), 6.30 (2H, br s, 2 x Ar-H), 4.56 (2H, s, $-OCH_2CO-$), 4.25 (2H, q, *J* 7.1, $-OCH_2CH_3$), 3.74 (3H, s, OMe), 2.27 (3H, s, $ArCH_3$) and 1.28 (3H, t, *J* 7.1, $-CH_2CH_3$); $\delta_C$ 168.8 (C=O), 160.6 (3-C), 158.8 (1-C), 140.2 (5-C), 108.1 and 107.4 (4-CH & 6-CH), 98.3 (2-CH), 65.3 ($-OCH_2CO-$), 61.2 ($-OCH_2CH_3$), 55.1 (OMe), 21.7 ($ArCH_3$) and 14.1 ($-CH_2CH_3$); m/z 224 ($M^+$, 100%).

## Preparation of 3-Methoxy-5-methylphenoxyacetic Acid (48)

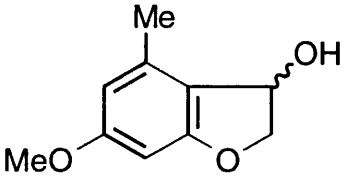
To a solution of ethyl 3-methoxy-5-methylphenoxyacetate (**47**) (6.94 g, 0.031 mol) in ethanol (40 ml) was added 4 M sodium hydroxide solution (8 ml, 0.032 mol). The solution was then refluxed for 4 hours. After cooling, water (100 ml) was added and the solution extracted with diethyl ether (2 x 30 ml). The aqueous layer was then acidified with 35% hydrochloric acid solution and extracted with ethyl acetate (2 x 50 ml). The combined extracts were dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give 3-methoxy-5-methylphenoxyacetic acid (**48**) (4.48 g, 74%) as a solid that was used without further purification, m.p. 123-125 °C; $\delta_H$ (DMSO-$d_6$) 9.12 (1H, br s, COOH), 6.39 (3H, m, 2-H, 4-H & 6-H), 4.69 (2H, s, $-CH_2-$), 3.77 (3H, s, OMe) and 2.30 (3H, s, $ArCH_3$); $\delta_C$ 170.3 (C=O), 160 4 (3-C), 158.9 (1-C), 139.9 (5-C), 107.5 (4-CH & 6-CH), 98.2 (2-CH), 64.6 ($-OCH_2CO-$), 55.1 (OMe) and 21.5 ($ArCH_3$); m/z 196 ($M^+$, 100%), 151 (20, M-COOH), 121 (50, M-$OCH_2COOH$).

## Preparation of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (43)

Polyphosphoric acid (20 g), prepared by dissolving phosphorus pentoxide (12.8 g, 0.09 mol) in 85 weight % solution of phosphoric acid (7.2 g), was heated to 80 °C and 3-methoxy-5-methylphenoxyacetic acid (**48**) (3.92 g, 0.02 mol) added with manual stirring. The mixture was then removed from the heat and stirred for a further 10 minutes when it was observed to have turned black in colour. Crushed ice (40 ml) was then added and the solution stirred for 20 minutes. The resultant yellow precipitate was extracted into diethyl ether (3 x 30 ml) and the combined extracts washed with 5% sodium hydroxide solution (40 ml) and water until the washings were neutral. Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a yellow crystalline residue. Purification by flash chromatography over a column of silica, using 10 : 1 petroleum ether/ethyl acetate as the eluent, afforded 6-

methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (**43**) (2.1 g, 59%) as yellow solid which was recrystallised from diethyl ether to give needles, m.p. 123-124 °C (lit.,[98] 123-124 °C); $\delta_H$ 6.29 (2H, br s, 5-H & 7-H), 4.50 (2H, s, -$CH_2$-), 3.77 (3H, s, OMe) and 2.46 (3H, s, Ar$CH_3$); $\delta_C$ 176.8 (C=O), 167.5 (6-C & 7a-C), 140.6 (4-C), 112.8 (3a-C), 112.0 (5-CH), 93.8 (7-CH), 75.4 (-O*C*$H_2$CO-), 55.7 (OMe) and 17.9 (Ar$CH_3$); m/z 178 ($M^+$, 100%).

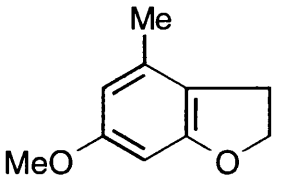
**Preparation of 3-Hydroxy-6-methoxy-4-methyl-2,3-dihydrobenzofuran (44)[98]**




(**44**)

To a solution of 6-methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (**43**) (2.0 g, 0.0112 mol) in tetrahydrofuran (40 ml) and methanol (25 ml) was added sodium borohydride (1.30 g, 0.034 mol) in 4 portions at 0 °C and the mixture stirred for an additional 1.5 hours. To the reaction mixture was added acetone (20 ml) and the mixture concentrated under reduced pressure. The residue was poured into a mixture of saturated brine (30 ml) and 5% sodium bicarbonate solution (15 ml), and extracted with ethyl acetate (3 x 40 ml). The combined extracts were washed with water (2 x 50 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give 3-hydroxy-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**44**) as a crystalline residue (1.8 g, 89%). Recrystallisation from methanol afforded an analytical sample; m.p. 67-68 °C (lit.,[98] 67-68 °C); $\delta_H$ 6.15 (1H, d, *J* 1.8, 5-H), 6.09 (1H, d, *J* 1.8, 7-H), 5.02 (1H, dd, *J* 1.9, *J* 5.7, -C*H*OH-), 4.31 (1H, dd, *J* 5.8, *J* 10.6, -C$H_a$$H_b$-), 4.23 (1H, dd, *J* 2.0, *J* 10.6, -$CH_a$$H_b$-), 3.62 (3H, s, OMe), 2.93 (1H, br s, OH) and 2.21 (3H, s, Ar$CH_3$); $\delta_C$ 162.0 and 161.4 (7a-C & 6-C), 136.9 (4-C), 119.3 (3a-C), 108.4 (5-CH), 93.4 (7-CH), 80.1 (-O*C*$H_2$CO-), 70.7 (-*C*HOH-), 55.3 (OMe) and 18.1 (Ar$CH_3$); m/z 180 ($M^+$, 100%). The crude residue was used for the next reaction without further purification.

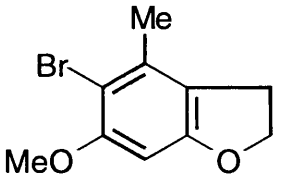
**Preparation of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42)[98]**



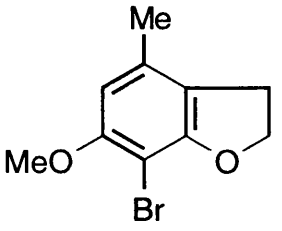

**(42)**

A solution of crude 3-hydroxy-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**44**) (1.5 g, 0.0083 mol) in tetrahydrofuran (20 ml) and ethanol (20 ml), under a hydrogen atmosphere, was stirred over 10% palladium on charcoal (1 g) until TLC analysis, using 5 : 1 petroleum ether/ethyl acetate as the eluent, suggested that the reaction was complete. The solution was then filtered through Celite and the filtrate evaporated under reduced pressure. The residue was recrystallised from methanol to give 6-methoxy-4-methyl-2,3-dihydrobenzofuran (**42**) (1.13 g, 83%) as glistening prisms, m.p. 53.5-56 °C (lit.,[98] 54.5-56.5); $\delta_H$ 6.16 (2H, s, 5-H & 7-H), 4.49 (2H, t, *J* 8.6, -$OCH_2$-), 3.67 (3H, s, OMe), 2.97 (2H, t, *J* 8.6, $ArCH_2$-) and 2.13 (3H, s, $ArCH_3$); $\delta_C$ 160.8 and 160.2 (7a-C & 6-C), 134.9 (4-C), 117.9 (3a-C), 106.8 (5-CH), 93.5 (7-CH), 71.7 (-$OCH_2$-), 55.4 (OMe), 28.0 ($ArCH_2$-) and 19.2 ($ArCH_3$); m/z 164 ($M^+$, 100).

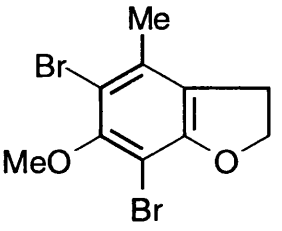
**Bromination of (42) with 1 Mole Equivalent of Bromine**




**(49)**




**(51)**




**(50)**

To a stirring solution of 6-methoxy-4-methyl-2,3-dihydrobenzofuran (**42**) (0.328 g, 0.002 mol) in dichloromethane (20 ml) was added, dropwise, a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol). Stirring was allowed to continue for 30 minutes. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to leave an oily crystalline solid (0.461 g). Analysis of this crude product by $^1H$ nmr spectroscopy and TLC, using 5 : 1 petroleum ether/ethyl acetate as the eluent, indicated it was composed of four primary constituents, with $R_f$ values

0.54, 0.43, 0.40 and 0.36. In order to separate these components the crude product was chromatographed over a column of silica gel with 30 : 1 petroleum ether/ethyl acetate as the eluent. Early fractions afforded starting benzofuran **42** (0.015 g, 0.095 mmol) followed by 5-bromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**49**) (0.330 g, 0.0014 mol), obtained as a crystalline solid, m.p. 76-77 °C; $\delta_H$ 6.29 (1H, s, 7-H), 4.57 (2H, t, *J* 8.7, $-OCH_2-$), 3.82 (3H, s, OMe), 3.10 (2H, t, *J* 8.7, $ArCH_2-$) and 2.24 (3H, s, $ArCH_3$); $\delta_C$ 159.4 (7a-C), 156.0 (6-C), 134.8 (4-C), 118.8 (3a-C), 104.0 (5-C), 92.4 (7-CH), 71.7 ($-OCH_2-$), 56.3 (OMe), 29.2 ($ArCH_2-$) and 20.0 ($ArCH_3$); m/z 244 ($M^+$, 98%), 242 (100). Further elution afforded 5,7-dibromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**50**) (0.028 g, 0.09 mmol) as fine violet coloured needles, m.p. 83-84 °C; $\delta_H$ 4.68 (2H, t, *J* 8.7, $-OCH_2-$), 3.84 (3H, s, OMe), 3.24 (2H, t, *J* 8.7, $ArCH_2-$), 2.26 (3H, s, $ArCH_3$); $\delta_C$ 156.9 (7a-C), 153.6 (6-C), 133.7 (4-C), 123.4 (3a-C), 110.7 (5-C), 96.0 (7-C), 72.0 ($-OCH_2-$), 60.4 (OMe), 30.4 ($ArCH_2-$) and 19.9 ($ArCH_3$); m/z 324 ($M^+$, 40%), 322 (80), 320 (41). The final product to elute from the column was 7-bromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (**51**) (0.064 g, 0.26 mmol); $\delta_H$ 6.22 (1H, s, 5-H), 4.68 (2H, t, *J* 8.6, $-OCH_2-$), 3.85 (3H, s, OMe), 3.17 (2H, t, *J* 8.6, $ArCH_2-$), 2.21 (3H, s, $ArCH_3$); $\delta_C$ 158.5 (7a-C), 156.3 (6-C), 133.3 (4-C), 119.5 (3a-C), 104.9 (5-CH), 90.0 (7-C), 72.2 ($-OCH_2-$), 56.6 ($OCH_3$), 29.1 ($ArCH_2-$) and 19.2 ($ArCH_3$); m/z 244 ($M^+$, 98%), 242 (100).

The $^1H$ nmr spectrum of the initial crude product suggested that the 4 constituents **42**, **49**, **51** and **50** were present in the ratio 1 : 15 : 3 : 1.

## Bromination of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42) with 2 Mole Equivalent of Bromine

To a stirring solution of benzofuran **42** (0.164 g, 0.001 mol) in dichloromethane (20 ml) was added, dropwise, a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol). Stirring was allowed to continue for 30 minutes. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to leave a violet crystalline solid (0.296 g). Analysis of this crude product by $^1H$ nmr spectroscopy and TLC indicated was composed almost solely of the 5,7-dibromo benzofuran **50**.

**Bromination of 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42) with 1 Mole Equivalent of *N*-Bromosuccinimide**

To a stirring solution of benzofuran **42** (0.164 g, 0.001 mol) in dichloromethane (10 ml) was added a solution of *N*-bromosuccinimide (0.178 g, 0.001 mol) in dichloromethane (10 ml). Stirring was allowed to continue for 4 hours. The solution was then washed with water (2 x 10 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure to give a white crystalline solid (0.221 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed almost exclusively of the 5-bromo benzofuran **49** with about 5% of 7-bromo isomer **51** being the only other observable product.

**Equilibration of the Bromine Atom in 7-Bromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (51)**

To a solution of the 7-bromo benzofuran **51** (0.121 g, 0.5 mmol) in dichloromethane (10 ml) was added a 30 weight % solution of hydrogen bromide in acetic acid (0.2 ml, 0.001 mol). The solution was allowed to stir for 6 hours before being washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a crystalline residue (0.110 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it was composed of 4 constituents, benzofuran **42**, the 5-bromo benzofuran **49**, the 7-bromo benzofuran **51** and the 5,7-dibromo benzofuran **50**, present in the ratio 1 : 10 : 4 : 1.

**Equilibration of the Bromine Atoms from 5,7-Dibromo-6-methoxy-4-methyl-2,3-dihydrobenzofuran (50) to 6-Methoxy-4-methyl-2,3-dihydrobenzofuran (42)**

To a stirring solution of benzofuran **42** (0.164 g, 0.001 mol) in dichloromethane (10 ml) was added, dropwise, a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol). Stirring was allowed to continue for 30 minutes when the bromine was observed to be completely decolourised. To this solution was then added a further portion of benzofuran **42** (0.164 g, 0.001 mol) and the solution stirred for a further 1 hour. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml), dried over anhydrous magnesium sulphate and evaporated under reduced

pressure to afford an oily crystalline residue. Analysis of this crude product by $^1H$ nmr spectroscopy of suggested that it was composed of the 4 constituents, benzofuran **42**, the 5-bromo benzofuran **49**, the 7-bromo benzofuran **51** and the 5,7-dibromo benzofuran **50**, present in the ratio 1 : 3 : 3 : 1.

## Equilibration of the Bromine Atoms in 2,4-Dibromo-3,5-dimethoxytoluene (32)

To a stirring solution of 2,4-dibromo-3,5-dimethoxytoluene (**32**) (0.155 g, 0.5 mmol) in dichloromethane (10 ml) was added a 30 weight % solution of hydrogen bromide in acetic acid (0.2 ml, 0.001 mol). Stirring was allowed to continue for 4 hours. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a white crystalline residue (0.147 g). Analysis of this crude product by $^1H$ nmr spectroscopy of suggested that it was composed almost exclusively of 2,6-dibromo-3,5-dimethoxytoluene (**21**) with a trace amount of the starting 2,4-dibromo toluene **32** being the only other observable component.

## Equilibration of the Bromine Atom in 4-Bromo-3,5-dimethoxytoluene (27)

To a stirring solution of 4-bromo-3,5-dimethoxytoluene (**27**) (0.116 g, 0.5 mmol) in dichloromethane (10 ml) was added a 30 weight % solution of hydrogen bromide in acetic acid (0.1 ml, 0.5 mmol). Stirring was allowed to continue for 4 hours. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a white crystalline residue (0.107 g). Analysis of this crude product by $^1H$ nmr spectroscopy of suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 7 : 1.

## Equilibration of the Bromine Atoms in 2,4-Dibromo-3,5-dimethoxytoluene (32) in the Presence of an Equimolar Amount of 3,5-Dimethoxytoluene (19)

To a stirring solution of 2,4-dibromo-3,5-dimethoxytoluene (**32**) (0.155 g, 0.5 mmol) and 3,5-dimethoxytoluene (**19**) (0.076 g, 0.5 mmol) in dichloromethane (10 ml) was

added a 30 weight % solution of hydrogen bromide in acetic acid (0.2 ml, 0.001 mol). Stirring was allowed to continue for 4 hours. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a light brown crystalline residue (0.213 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 7 : 1.

**Equilibration of the Bromine Atom in 2-Bromo-3,5-dimethoxytoluene (20)**

To a stirring solution of 2-bromo-3,5-dimethoxytoluene (**20**) (0.116 g, 0.5 mmol) in dichloromethane (10 ml) was added a 30 weight % solution of hydrogen bromide in acetic acid (0.1 ml, 0.5 mmol). Stirring was allowed to continue for 30 minutes. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a white crystalline residue (0.102 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 7 : 1.

**Equilibration of the Bromine Atoms in 2,6-Dibromo-3,5-dimethoxytoluene (21) in the Presence of an Equimolar Amount of 3,5-Dimethoxytoluene (19)**

To a stirring solution of the 2,6-dibromo toluene **21** (0.155 g, 0.5 mmol) and toluene **19** (0.076 g, 0.5 mmol) in dichloromethane (10 ml) was added a 30 weight % solution of hydrogen bromide in acetic acid (0.2 ml, 0.001 mol). Stirring was allowed to continue for 30 minutes. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a light brown crystalline residue (0.210 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it was composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 7 : 1.

**Dibromination of 3,5-Dimethoxytoluene (19) using Bromine in the Presence of an Equimolar Amount of 2,4-Dibromo-3,5-dimethoxytoluene (32)**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) and the 2,4-dibromo toluene **32** (0.310 g, 0.001 mol) was added dropwise a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol). The solution was then stirred for 10 minutes, when it was observed to have been completely decolourised, and washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a white crystalline residue (0.210 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it was composed of the 2,6-dibromo toluene **21** and 2,4-dibromo isomer **32** in equimolar amounts.

**Bromination of 4-Bromo-3,5-dimethoxytoluene (27) using Bromine**

To a stirring solution of 4-bromo-3,5-dimethoxytoluene **27** (0.231 g, 0.001 mol) in dichloromethane (10 ml) was added a 1 M solution bromine in dichloromethane (1 ml, 0.001 mol). Stirring was allowed to continue until the solution was observed to have been completely decolourised. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a crystalline residue (0.294 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it was composed solely of the 2,4-dibromo toluene **32**, with no other products being present in detectable amounts.

**Attempted Equilibration of the Bromine Atoms in 2,4,6-Tribromo-3,5-dimethoxytoluene (25) in the Presence of an Equimolar Amount of 3,5-Dimethoxytoluene (19)**

To a stirring solution of 2,4,6-tribromo toluene (**25**) (0.389 g, 0.001 mol) and toluene **19** (0.152 g, 0.001 mol) in dichloromethane (10 ml) was added a 30 weight % solution of hydrogen bromide in acetic acid (0.2 ml, 0.001 mol). Stirring was allowed to continue for 4 hours. The solution was then washed with 5% sodium hydroxide solution (10 ml) and water (2 x 10 ml) and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded an oily light brown solid (0.510 g). Analysis of this crude product by $^1$H nmr spectroscopy of suggested that it

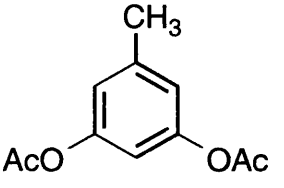
was composed of equimolar amounts of 2,4,6-tribromo toluene **25** and toluene **19** and that no equilibration of the bromine atoms had been observed to occur.

# 8.4 Experimental Details For Chapter 6

**Attempted Benzylic Bromination of 3,5-Dimethoxytoluene (19)- Using NBS in Carbon Tetrachloride**

To a stirring solution of toluene **19** (0.152 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.178 g, 0.001 mol) and azoisobutyronitrile (5 mg). The mixture was then stirred for 3 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling, the solution was filtered and the solvent removed from the filtrate under reduced pressure to give a white solid (0.224 g). Analysis of the crude product by $^1H$ nmr spectroscopy suggested that it was only composed of toluene **19**, the 2-bromo derivative **20** and the 2,6-dibromo derivative **21** in the ratio 1 : 4.5 : 1 and that benzylic bromination had not occured to an appreciable extent.

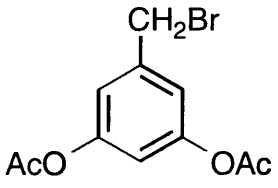
**Preparation of 3,5-Diacetoxytoluene (52)**[117]



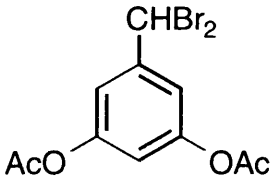

**(52)**

To a stirring solution of 3,5-dihydroxytoluene monohydrate (1.42 g, 0.01 mol) in acetic anhydride (6 ml) was added pyridine (0.05 g, 0.6 mmol) and the mixture heated at reflux for 3 hours. After cooling the excess solvent was evaporated under reduced pressure and the resultant residue dissolved in dichloromethane (20 ml). The solution was then washed with 5% sodium hydroxide solution (20 ml), 5% hydrochloric acid solution (10 ml) and water (2 x 20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded 3,5-diacetoxytoluene (**52**) (1.90 g, 91%) as a pale yellow oil; $\delta_H$ 6.70 (2H, d, *J* 2.0, 2-H), 6.63 (1H, t, *J* 1.9, 4-H), 2.25 (3H, s, $ArCH_3$) and 2.16 (6H, s, $-COCH_3$); $\delta_C$ 169.1 ($-COCH_3$), 150.8 (3-C), 140.3 (1-C), 119.7 (2-CH), 112.5 (4-CH), 21.3 ($ArCH_3$) and 21.0 ($-COCH_3$); m/z 208 ($M^+$, 11%), 166 (18, M-$COCH_3$), 124 (100, M-2x$COCH_3$).

**Benzylic Bromination of 3,5-Diacetoxytoluene (52)**[117]



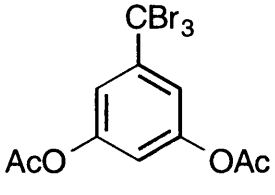

(53)




(54)

To a stirring solution of 3,5-diacetoxytoluene (**52**) (0.208 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.178 g, 0.001 mol) and azoisobutyronitrile (5 mg). The mixture was then stirred at reflux for 3 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling the solution was filtered and the solvent removed from the filtrate under reduced pressure to give a yellow oil (0.280 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed of three constituents. No eluting system could, however, be found that would resolve these components by TLC. The $^1$H nmr spectrum of the crude product showed three distinct sets of signals; those due to unreacted 3,5-diacetoxytoluene (**52**), a set attributed to 3,5-diacetoxybenzyl bromide (**53**) [$\delta_H$ 6.94 (2H, d, *J* 2.0, 2-H), 6.79 (1H, t, *J* 2, 4-H), 4.33 (2H, s, $ArCH_2Br$) and 2.17 (6H, s, $-COCH_3$)] and a set attributed to 3,5-diacetoxybenzal bromide (**54**) [$\delta_H$ 7.13 (2H, d, *J* 2.0, 2-H), 6.64 (1H, t, *J* 2, 4-H), 6.51 (1H, s, $ArCHBr_2$) and 2.16 (6H, s, $-COCH_3$)]. These three constituents were present in the ratio 1 : 3.6 : 1.

**Benzylic Bromination of 3,5-Diacetoxytoluene (52) using 2 Mole Equivalents of NBS**[117]




(55)

To a stirring solution of 3,5-diacetoxytoluene (**52**) (0.208 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.356 g, 0.002 mol) and azoisobutyronitrile (5 mg). The mixture was then stirred at reflux for 3 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling the

solution was filtered and the solvent removed from the filtrate under reduced pressure to give a yellow oil (0.360 g). Analysis of the crude product by $^1$H nmr spectroscopy suggested that it was composed primarily of four constituents; starting toluene **52**, the benzyl bromide **53**, the benzal bromide **54** and a compound assigned as 3,5-diacetoxytribromomethylbenzene (**55**) which gave rise to the following signals; $\delta_H$ 7.54 (2H, d, *J* 2.0, 2-H), 6.91 (1H, t, *J* 2, 4-H) and 2.15 (6H, s, -$COCH_3$). These 4 constituents were present in the ratio trace : 2.7 : 9 : 1.

## Benzylic Bromination of 3,5-Diacetoxytoluene (52) at 20 °C

To a stirring solution of toluene **52** (0.208 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.178 g, 0.001 mol) and azoisobutyronitrile (5 mg). The mixture was maintained at 20 °C by external cooling and stirred for 3 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. The solution was then filtered and the solvent removed from the filtrate under reduced pressure to give a yellow oil (0.283 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of starting toluene **52**, the benzyl bromide **53** and the benzal bromide **54** in the ratio 1 : 3.8 : 1.

## Benzylic Bromination of 3,5-Diacetoxytoluene (52) using only Photo-Initiation

To a stirring solution of toluene **52** (0.208 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.178 g, 0.001 mol). The mixture was then stirred at reflux for 3 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling, the solution was filtered and the solvent removed from the filtrate under reduced pressure to give a yellow oil (0.283 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of starting toluene **52**, the benzyl bromide **53** and the benzal bromide **54** in the ratio 1 : 3.6 : 1.

**Benzylic Bromination of 3,5-Diacetoxytoluene (52) with 2 Mole Equivalents of NBS using only Photo-Initiation**

To a stirring solution of toluene **52** (0.208 g, 0.001 mol) in carbon tetrachloride (10 ml) was added NBS (0.356 g, 0.002 mol). The mixture was then stirred at reflux for 3 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling the solution was filtered and the solvent removed from the filtrate under reduced pressure to give a yellow oil (0.359 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was primarily composed of the benzyl bromide **53**, the benzal bromide **54** and the tribromomethyl compound **55** in the ratio 1 : 7.9 : 1 with trace amounts of another unidentified product also being present.

**Benzylic Bromination of 3,5-Diacetoxytoluene (52) using Dichloromethane as the Solvent**

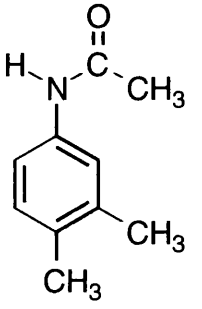
To a stirring solution of toluene **52** (0.208 g, 0.001 mol) in dichloromethane (10 ml) was added NBS (0.178 g, 0.001 mol). The mixture was then stirred at reflux for 5 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling, the solution was evaporated under reduced pressure to give an oily yellow solid (0.384 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of starting toluene **52**, the benzyl bromide **53** and the benzal bromide **54** in the ratio 1 : 6.9 : 1.

**Benzylic Bromination of 3,5-Diacetoxytoluene (52) with 2 Mole Equivalents of NBS using Dichloromethane as the Solvent**

To a stirring solution of toluene **52** (0.208 g, 0.001 mol) in dichloromethane (10 ml) was added NBS (0.356 g, 0.002 mol). The mixture was then stirred at reflux for 5 hours whilst being irradiated by a 100W lamp, situated approximately 3 cm from the reaction vessel. After cooling, the solution was evaporated under reduced pressure to give an oily yellow solid (0.559 g). Analysis of the crude product by $^1$H nmr spectroscopy and TLC, using 2 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of the benzyl bromide **53**, the benzal bromide **54** and the tribromomethyl compound **55** in the ratio 1 : 7.0 : 0.6.

# 8.5 Experimental Details for Chapter 7

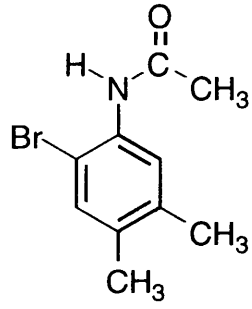
**Formation of 3,4-Dimethylacetanilide (56)**



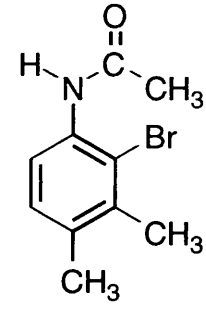
**(56)**

To a solution of 3,4-dimethylaniline (1.21 g, 0.01 mmol) in acetic anhydride (10 ml) was added pyridine (0.1 ml). The solution was then stirred at reflux for 3 hours and the excess solvent evaporated under reduced pressure. The resulting residue was dissolved in dichloromethane (20 ml) and washed with 5% sodium hydroxide solution (20 ml), 5% hydrochloric acid solution (20 ml) and water (20 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a pale yellow oil which was crystallised from THF/water to give 3,4-dimethylacetanilide (**56**) (0.675 g, 42%) as plates, m.p. 98.5-99 °C (lit.,[118] 99 °C); $\delta_H$ 8.30 (1H, br s, N-H), 7.27 (1H, d, *J* unresolved, 2-H), 7.24 (1H, dd, $^4J$ 2, $^3J$ 10, 6-H), 7.01 (1H, d, *J* 8, 5-H), 2.18 (3H, s, 3-Me), 2.17 (3H, s, 4-Me) and 2.11 (3H, s, COMe); $\delta_C$ 169.1 (C=O), 137.0 (3-C), 135.8 (1-C), 132.5 (4-C), 129.8 (5-CH), 121.6 (2-CH), 117.8 (6-CH), 24.2 ($COCH_3$), 19.8 (3-$CH_3$) and 19.1 (4-$CH_3$); m/z 163 ($M^+$, 43.5%), 121 (100, M-Ac), 106 (75, M-NHAc).

**Bromination of 3,4-Dimethylacetanilide (56) using 1 Mole Equivalent of Bromine in Dichloromethane**



(57)



(58)

To a stirring solution of acetanilide **56** (0.326 g, 0.002 mol) in dichloromethane (10 ml) was added a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol) in a single portion. Stirring was allowed to continue until complete decolourisation of the bromine was observed to have taken place. The solution was then washed with 5% sodium hydroxide solution (2 x 10 ml) and water (2 x 10 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a light brown solid (0.436 g). Recrystallisation from aqueous ethanol afforded 2-bromo-4,5-dimethylacetanilide (**57**) (0.27 g, 56%) as long needles, m.p. 162.5-163.5 °C (lit.,[51] 163-164 °C); $\delta_H$ 7.93 (1H, s, 6-H), 7.42 (1H, br s, N-H), 7.19 (1H, s, 3-H), 2.12 and 2.10 (6H and 3H, both s, 4-Me 5-Me and COMe); $\delta_C$ 168.2 (C=O), 137.0 (1-C), 134.2 (5-C), 133.1 (4-C), 132.5 (3-CH), 123.3 (6-CH), 110.2 (2-C), 24.8 ($COCH_3$), 19.7 (5-$CH_3$) and 19.1 (4-$CH_3$); m/z 243 ($M^+$, 18%), 242 (19), 201 (48, M-$COCH_3$), 199 (49), 162 (100, M-Br). Evaporation of the mother liquors afforded a light brown solid (0.16 g). Analysis of this crude product by $^1H$ nmr spectroscopy suggested that it was composed of **57** and 1 other unidentified product. Unfortunately no eluent could be found which would separate these constituents by TLC and hence the crude product was not purified further. Subtraction of the signals for **57** from the $^1H$ nmr spectrum of the crude product left the following signals; $\delta_H$ 7.88 (1H, d, *J* 8.5, 6-H), 7.60 (1H, br s, N-H), 6.99 (1H, d, *J* 8.5, 5-H), 2.28 (3H, s, 3-Me), 2.21 (3H, s, 4-Me) and 2.12 (3H, s, COMe). This suggests that the other component is 2-bromo-3,4-dimethylacetanilide (**58**). Analysis of the $^1H$ nmr spectrum of the initial crude product suggests that it was composed of **57** and **58** in the ratio 12 : 1.

**Bromination of 3,4-Dimethylacetanilide (56) using 1 Mole Equivalent of Bromine in Dichloromethane at -70 °C**

To a stirring solution of acetanilide **56** (0.326 g, 0.002 mol) in dichloromethane (10 ml), cooled to -70 °C, was added a 1 M solution of bromine in dichloromethane (2 ml, 0.002 mol) in a single portion. Stirring was allowed to continue and the temperature maintained constant at -70 °C until complete decolourisation of the bromine was observed to have taken place. After warming to room temperature the solution was washed with 5% sodium hydroxide solution (2 x 10 ml) and water (2 x 10 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a light brown solid (0.412 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of 2-bromo-4,5-dimethylacetanilide (**57**) and 2-bromo-3,4-dimethylacetanilide (**58**) in the ratio 16 : 1.

**Bromination of 3,4-Dimethylacetanilide (56) using 1 Mole Equivalent of NBS in Dimethylformamide**

To a stirring solution of acetanilide **56** (0.163 g, 0.001 mol) in dimethylformamide (5 ml) was added a solution of NBS (0.178 g, 0.001 mol) in dimethylformamide (5 ml). Stirring was then allowed to continue for 24 hours before the solution was poured into water (30 ml) and extracted with dichloromethane (2 x 15 ml). The combined extracts were then washed with saturated sodium chloride solution (3 x 20 ml) and water (20 ml). Drying over anhydrous magnesium sulphate and evaporation of the solvent under reduced pressure afforded a light brown solid (0.202 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of 2-bromo-4,5-dimethylacetanilide (**57**) and 2-bromo-3,4-dimethylacetanilide (**58**) in the ratio 8 : 1.

**Bromination of 3,4-Dimethylacetanilide (56) using 0.5 Mole Equivalents of DBI in Acetic Acid**

To a stirring solution of acetanilide **56** (0.163 g, 0.001 mol) in glacial acetic acid (5 ml) was added a solution of DBI (0.144 g, 0.5 mmol) in glacial acetic acid (5 ml). The resultant mixture was then stirred at room temperature for 5 hours before being poured into water (30 ml) and extracted with dichloromethane (2 x 20 ml). The combined extracts were washed with 5% sodium hydroxide solution (2 x 20 ml), saturated sodium bicarbonate solution (20 ml) and water (20 ml). Drying over anhydrous magnesium sulphate and evaporation of the solvent under reduced pressure afforded a

light brown solid (0.193 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of 2-bromo-4,5-dimethylacetanilide (**57**) and 2-bromo-3,4-dimethylacetanilide (**58**) in the ratio 7 : 1, and also shows evidence of small amounts of starting acetanilide **56** and some dibromide which is presumably 2,6-dibromo-3,4-dimethylacetanilide.

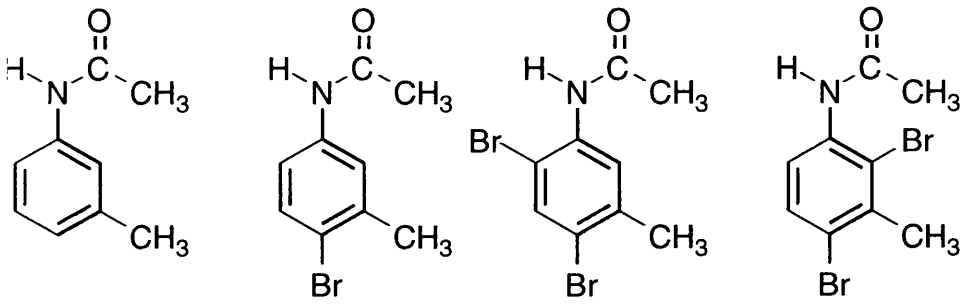
**Preparation of Benzyltrimethylammonium Chlorobromate**[51]

To a vigorously stirring solution of bromine (1.596 g, 0.01 mol) in dichloromethane (10 ml) was added dropwise a solution of benzyltrimethylammonium chloride (1.857 g, 0.01 mol) in water (100 ml). Stirring was allowed to continue for 30 minutes and the layers then separated. The dichloromethane layer was dried over anhydrous magnesium sulphate and evaporated under reduced pressure. The resultant residue was crystallised from 10 : 1 dichloromethane/diethyl ether to give benzyltrimethylammonium chlorobromate (2.23 g, 65%) as orange crystals, m.p.100-102 °C (lit.[51], 101-102 °C).

**Bromination of 3,4-Dimethylacetanilide (56) using Benzyltrimethylammonium Chlorobromate**[51]

To a stirring solution of acetanilide **56** (0.163 g, 0.001 mol) in dichloromethane (10 ml) and methanol (4 ml) was added benzyltrimethylammonium chlorobromate (0.345 g, 0.001 mol). Stirring was allowed to continue until decolourisation of the initial orange coloured solution was observed to have taken place. Then solvent was then removed under reduced pressure and to the obtained residue was added water (20 ml). The mixture was then extracted with diethyl ether (2 x 30 ml) and the combined extracts dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave a pale solid (0.220 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of 2-bromo-4,5-dimethylacetanilide (**57**) and 2-bromo-3,4-dimethylacetanilide (**58**) in the ratio 19 : 1.

**Bromination of 3-Methylacetanilide (59) using 2 Mole Equivalents of Bromine in Dichloromethane (Reaction Incomplete)**



**(59)** **(61)** **(60)** **(62)**

To a stirring solution of 3-methylacetanilide (**59**) (0.597 g, 0.004 mol) in dichooromethane (20 ml) was added a 1 M solution of bromine in dichoromethane (8 ml, 0.008 mol) in a single portion. After stirring for 10 hours, when the characteristic colouration produced by the bromine was observed *not* to have completely disappeared, the solution was washed with 5% sodium hydroxide solution (2 x 20 ml), 5% sodium thiosulphate solution (20 ml) and water (20 ml). Drying over anhydrous magnesium sulphate and evaporation of the solvent under reduced pressure afforded a light brown solid (1.14 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed primarily of 3 constituents but no TLC system could be found that would afford a complete resolution of these components. The use of 2 : 1 petroleum ether/ethyl acetate as the eluent, resulted in the resolution of 2 constituents with $R_f$ values 0.50 and 0.28. The crude product was chromatographed over a column of silica gel with petroleum ether - ethylacetate (3 : 1) as the eluant. Early fractions afforded a white solid (0.810 g) which $^1$H nmr spectroscopic analysis suggested was composed of 2 constituents. Further elution afforded 4-bromo-3-methylacetanilide (**61**) (0.25 g, 1.1 mmol) as a light brown crystalline solid, m.p. 101-103 °C (lit.,[118] 101 °C); $\delta_H$ 8.10 (1H, br s, NH), 7.32 (1H, d, $^4J$ 2.4, 2-H), 7.30 (1H, d, $^3J$ 8.4, 5-H), 7.11 1H, dd, $^4J$ 2.4 $^3J$ 8.6, 6-H), 2.22 (3H, s, Ar-$CH_3$) and 2.05 (3H, s, $COCH_3$); $\delta_C$ 169.0 (C=O), 138.4 (3-C), 137.2 (1-C), 132.4 (5-CH), 122.3 (2-CH), 119.4 (4-C), 119.1 (6-CH), 24.4 (Ar$CH_3$) and 22.9 ($COCH_3$); m/z 229 ($M^+$, 24%), 227 (25), 187 (98, M-$COCH_3$), 185 (100). The white solid obtained earlier was then recrystallised from ethanol to give 2,4-dibromo-5-methylacetanilide (**60**) (0.40 g, 1.3 mmol) as fine white needles, m.p. 170-171 °C (lit.,[119] 172 °C); $\delta_H$ 8.14 (1H, s, 3-H), 7.58(1H, s, 6-H), 7.44 (1H, br s, NH), 2.26 (3H, s, Ar-$CH_3$) and 2.14 (3H, s, $COCH_3$); $\delta_C$ 168.5 (C=O), 138.3 (1-C), 134.6 (5-C), 134.5 (3-CH), 123.4 (6-CH),

119.1 (4-C), 110.5 (2-C), 24.8 (Ar$CH_3$) and 22.8 ($COCH_3$); m/z 309 ($M^+$, 12%), 307 9 (25), 305 (13), 267 (50, M-$COCH_3$), 265 (100), 263 (51). Evaporation of the mother liquors afforded a white soild which $^1H$ nmr spectroscopic analysis suggested was still composed of 2 constituents, **60** and another unidentified product. Subtraction of the signals for **60** from the $^1H$ nmr spectrum of the crude product left the following signals; $\delta_H$ 7.96 (1H, d, *J* 8.9, 5-H), 7.44 (1H, br s, NH), 7.40 (1H, d, *J* 8.9, 6-H), 2.50 (3H, s, Ar-$CH_3$) and 2.14 (3H, s, $COCH_3$). This suggests that the other component is 2,4-bromo-3-methylacetanilide (**62**). Analysis of the $^1H$ nmr spectrum of the *initial* crude product suggested that 2,4-dibromo-5-methylacetanilide (**60**) and 2,4-bromo-3-methylacetanilide (**62**) were present in the ratio 3 : 1.

## Bromination of 3-Methylacetanilide (59) using 2 Mole Equivalents of Bromine in Dichloromethane

To a stirring solution of acetanilide **59** (0.597 g, 0.004 mol) in dicholoromethane (20 ml) was added a 1 M solution of bromine in dichoromethane (8 ml, 0.008 mol) in a single portion. After stirring for 72 hours, when the characteristic colouration produced by the bromine was observed to have completely disappeared, the solution was washed with 5% sodium hydroxide solution (2 x 20 ml) and water (20 ml). Drying over anhydrous magnesium sulphate and evaporation of the solvent under reduced pressure afforded a very light brown solid (1.15 g). Analysis of this crude product by $^1H$ nmr spectroscopy suggested that it was composed of 2,4-dibromo-5-methylacetanilide (**60**) and 2,4-bromo-3-methylacetanilide (**62**) in the ratio 3.1 : 1.

## Bromination of 3-Methylacetanilide (59) using 2 Mole Equivalents of NBS in Dimethylformamide

To a stirring solution of acetanilide **59** (0.149 g, 0.001 mol) in dimethylformamide (5 ml) was added a solution of NBS (0.356 g, 0.002 mol) in dimethylformide. After stirring for 24 hours at room temperature, analysis of the solution by TLC (using 2 : 1 petroleum ether/ethyl acetate as the eluent) suggested that dibromination had not occured to an appreciable extent. The solution was then refluxed for a further period of 72 hours. After this time TLC analysis still suggested that dibromination had only occured to a small extent and the reaction was not worked up further.

**Bromination of 3-Methylacetanilide (59) using 2 Mole Equivalents of Bromine in Acetic Acid/Water**

To a stirring solution of acetanilide **59** (0.597 g, 0.004 mol) in acetic acid (7 ml) was added a 1 M solution of bromine in acetic acid (8 ml, 0.008 mol) in a single portion. After stirring for 1 hour, analysis by TLC suggested that exclusive monobromination had occured. The solution was then poured into water (60 ml) whereupon decolourisation of the remaining bromine was observed to take place and a white solid precipitated out of solution. This solid was then filtered, dissolved in dichloromethane (20 ml) and washed with 5% sodium hydroxide solution (2 x 20 ml) and water (20 ml). Drying over anhydrous magnesium sulphate and removal of the solvent under reduced pressure afforded a pale pink crystalline solid (0.989 g, 78% crude yield). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of 2,4-dibromo-5-methylacetanilide (**60**) and 2,4-bromo-3-methylacetanilide (**62**) in the ratio 10 : 1.

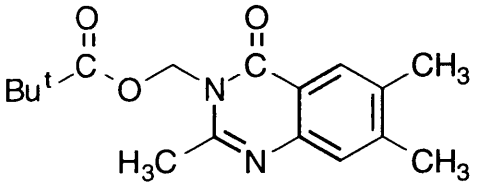
**Bromination of 3-Methylacetanilide (44) using 2 Mole Equivalents of Bromine in Acetic Acid then Varied Amounts of Water**

The previous experiment was repeated 3 further times, each time pouring the initial acetic acid solution into a different amount of water. In the first experiment 100 ml of water was used affording a 90% crude yield of a pink crystalline solid. Analysis of this crude product by $^1$H nmr spectroscopy suggested was composed of 2,4-dibromo-5-methylacetanilide (**60**) and 2,4-bromo-3-methylacetanilide (**62**) in the ratio 2.4 : 1.

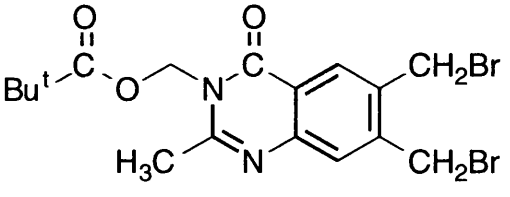
In the second experiment 50 ml of water was used resulting in a 76% crude yield of a pale pink crystalline solid. Analysis, by $^1$H nmr spectroscopy, of this crude product suggested that it was composed of 2,4-dibromo-5-methylacetanilide (**60**) and 2,4-bromo-3-methylacetanilide (**62**) in the ratio 15 : 1.

In the final experiment, when 30 ml of water was employed, a 70% crude yield of pale pink crystals was obtained. $^1$H nmr spectroscopic analysis of this product suggested that it was essentially pure 2,4-dibromo-5-methylacetanilide (**60**).

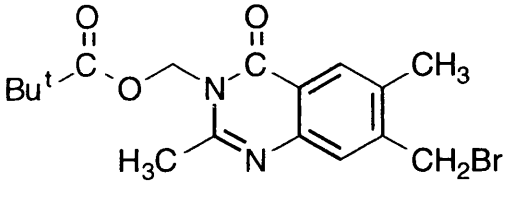
**Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using NBS in 1,1,1-Trichloroethane**



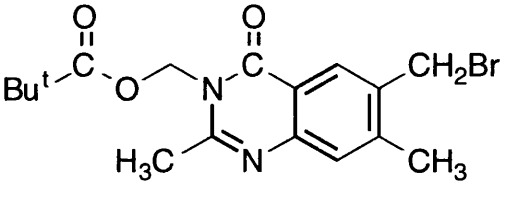
**(63)**



**(64)**



**(65)**

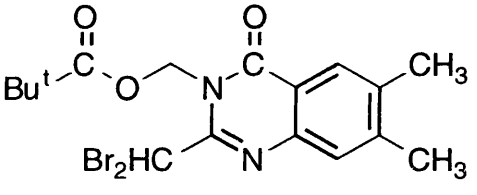


**(66)**

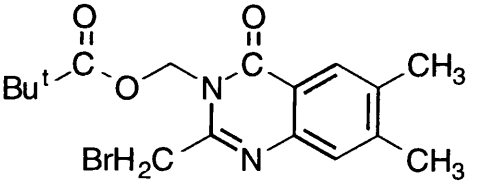
To a solution of the 2,6,7-trimethyl quinazolinone **63** (0.604 g, 0.002 mol) in 1,1,1-trichloroethane was added NBS (0.356 g, 0.002 mol) in a single portion. This solution was then stirred at reflux for 24 hours whilst being irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. After cooling, the solvent was evaporated under reduced pressure to leave a yellow solid (0.96 g). Analysis of this crude product by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of at least 5 constituents with $R_f$ values 0.85, 0.74, 0.46, 0.37, and 0.31. The crude product was then chromatographed over a column of silica gel using 8 : 1 petroleum ether/ethyl acetate as the eluent. The first two components co-eluted in early fractions and were not isolated. Later fractions afforded 6,7-di(bromomethyl)-2-methyl-*N*(3)-pivaloyloxymethylquinazolinone (**64**) (0.046 g) as flat needles, m.p. 129-130 °C; $\delta_H$ 8.17 (1H, s, 5-H), 7.56 (1H, s, 8-H), 6.02 (2H, s, O-$CH_2$-N), 4.68 (2H, s, 7-$CH_2$Br), 4.65 (2H, s, 6-$CH_2$Br), 2.54 (3H, s, 2-$CH_3$) and 1.14 (9H, s, $CMe_3$); $\delta_C$ 177.3 (-$CO_2$-), 160.5 (4-C=O), 154.8 (2-C), 147.5 (8a-C), 143.6 (4a-C), 135.1 (7-C), 129.6 (5-CH), 129.3 (8-CH), 120.8 (6-C), 67.0 (O-$CH_2$-N), 39.0 (*C*$Me_3$), 29.4 (7-*C*$H_2$Br), 28.8 (6-*C*$H_2$Br), 27.1 (-C(*C*$H_3$)$_3$) and 22.5 (2-$CH_3$); m/z 462 ($M^+$, 5%), 460 (10), 458 (5), 381 (92, M-Br), 379 (90). Further elution afforded the component with $R_f$ value 0.37 as a white solid (0.113 g). Analysis of this component of the crude product by $^1$H nmr spectroscopy suggested that it was composed of 2 constituents, one of which was starting quinazolinone **63**. Subtraction of the signals for **63** from the $^1$H nmr spectrum left the following signals; $\delta_H$ 7.95 (1H, s, 5-H),

7.48 (1H, s, 8-H), 6.00 (2H, s, O-$CH_2$-N), 4.46 (2H, s, 7-$CH_2$Br), 2.52 (3H, s, 2-$CH_3$), 2.43 (3H, s, 6-$CH_3$) and 1.13 (9H, s, $CMe_3$) which suggests that the other component is 7-bromomethyl-2,6-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**65**). Later fractions afforded 6-bromomethyl-2,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**66**) (0.48 g) as a crystalline solid, m.p. 147-148 °C; $\delta_H$ 8.09 (1H, s, 5-H), 7.34 (1H, s, 8-H), 6.01 (2H, s, O-$CH_2$-N), 4.51 (2H, s, 6-$CH_2$Br), 2.54 (3H, s, 2-$CH_3$), 2.47 (3H, s, 7-$CH_3$) and 1.13 (9H, s, $CMe_3$); $\delta_C$ 177.4 (-$CO_2$-), 161.0 (4-C=O), 154.2 (2-C), 147.3 (8a-C), 145.4 (4a-C), 135.5 (7-C), 128.7 (5-CH), 128.5 (8-CH), 118.5 (6-C), 66.9 (O-$CH_2$-N), 38.9 ($CMe_3$), 31.0 (6-$CH_2$Br), 27.1 (-C($CH_3$)$_3$), 22.5 (2-$CH_3$) and 19.4 (7-$CH_3$); m/z 382 ($M^+$, 15%), 380 (15), 301 (93, M-Br).

## Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using NBS and HBr in 1,1,1-Trichloroethane



(67)

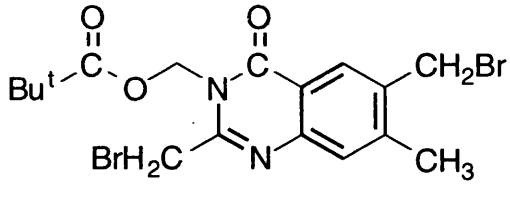


(68)

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in 1,1,1-trichloroethane (10 ml) was added NBS (0.356 g, 0.002 mol) and a 30% by weight solution of hydrobromic acid in acetic acid (0.4 ml, 0.002 mol) in a single portion. This solution was then stirred at reflux for 24 hours whilst being irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. After cooling, the precipitated succinimide was filtered and the solvent evaporated from the filtrate under reduced pressure. The resultant residue was dissolved in diethyl ether (20 ml) and washed with a 5% solution of sodium hydroxide (20 ml) and water (2 x 20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a light brown solid (0.592 g). Analysis of this crude product by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of 3 constituents with $R_f$ values 0.85, 0.74 and 0.31. The crude product was then chromatographed over a column of silica gel using 10 : 1 petroleum ether/ethyl acetate as the eluent. Early fractions afforded 2-dibromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**67**) (0.101 g) as a crystalline solid, m.p. 115-116

°C; $\delta_H$ 8.04 (1H, s, 5-H), 7.53 (1H, s, 8-H), 6.82 (1H, s, 2-$CHBr_2$), 6.32 (2H, s, O-$CH_2$-N), 2.41 (6H, s, 6-$CH_3$ and 7-$CH_3$) and 1.22 (9H, s, $CMe_3$); $\delta_C$ 177.3 (-$CO_2$-), 161.0 (4-C=O), 149.1 (2-C), 145.7 (8a-C), 144.1 (4a-C), 138.8 (7-C), 128.4 (5-CH), 127.1 (8-CH), 118.5 (6-C), 66.5 (O-$CH_2$-N), 38.9 ($CMe_3$), 34.5 (2-$CHBr_2$), 26.9 (-C($CH_3$)$_3$), 20.4 (7-$CH_3$) and 19.8 (6-$CH_3$); m/z 462 ($M^+$, 14%), 460 (24), 458 (15). Further elution gave fractions which afforded 2-bromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**68**) (0.151 g) as a crystalline solid, m.p. 138-139 °C; $\delta_H$ 8.02 (1H, s, 5-H), 7.45 (1H, s, 8-H), 6.23 (2H, s, O-$CH_2$-N), 4.58 (1H, s, 2-$CH_2$Br), 2.41 (3H, s, 7-$CH_3$), 2.39 (3H, s, 6-$CH_3$) and 1.21 (9H, s, $CMe_3$); $\delta_C$ 177.7 (-$CO_2$-), 161.2 (4-C=O), 150.5 (2-C), 145.4 (8a-C), 145.0 (4a-C), 137.9 (7-C), 128.0 (5-CH), 127.1 (8-CH), 118.5 (6-C), 66.4 (O-$CH_2$-N), 38.9 ($CMe_3$), 29.1 (2-$CH_2$Br), 27.0 (-C($CH_3$)$_3$), 20.6 (7-$CH_3$) and 19.9 (6-$CH_3$); m/z 382 ($M^+$, 21%), 380 (21), 268 (83, M-POM). Later fractions afforded unreacted starting quinazolinone **63** (0.107 g).

**Benzylic Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using NBS in Chlorobenzene with Thermal AIBN Initiation**




**(69)**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in chlorobenzene (6 ml) was added NBS (0.356 g, 0.002 mol) and AIBN (0.033 g, 0.2 mmol). The reaction mixture was then heated to 75-85 °C over 1 hour and maintained at this temperature for a further hour. After cooling to 20-25 °C, the succinimide was filtered and washed with chlorobenzene (2 ml). The combined filtrate and washings were evaporated under reduced pressure to leave a brown solid (0.760 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of at least 6 constituents; quinazolinone **63** (23.6%), the 6,7-di(bromomethyl) quinazolinone **64** (5.8%), the 7-bromomethyl quinazolinone **65** (5.8%), the 6-bromomethyl quinazolinone **66** (47.2%), the 2-bromomethyl quinazolinone **68** (5.8%) and compound **69*** (11.8%). The crude product was then redissolved in chlorobenzene (2 ml), cyclohexane (4.8 ml) added and the mixture heated to 80 °C, to ensure complete

solvation. After cooling slowly to 20-25 °C the resultant precipitate was filtered, washed with cyclohexane (1.2 ml) and pulled dry on the filter. Analysis of the precipitated product by $^1$H nmr spectroscopy suggested that it was still composed of at least 5 constituents; **63** (12%), **64** (4.5%), **65** (12%), **66** (67%) and **69*** (4.5%).

*At the time of the experiment the structure of this product was not known. It was later proven to be 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone.

**Benzylic Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using Photo-Initiated Reaction of NBS in Chlorobenzene**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in chlorobenzene (6 ml) was added NBS (0.356 g, 0.002 mol) in a single portion. Stirring was allowed to continue whilst the mixture was irradiated, for 5 hours, by a 100W lamp situated approximately 5 cm from the reaction vessel. After cooling to 20-25 °C, the succinimide was filtered and washed with chlorobenzene (2 ml). The combined filtrate and washings were evaporated under reduced pressure to leave a light brown solid (0.752 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of at least 6 constituents; quinazolinone **63** (15.8%), the 6,7-di(bromomethyl) quinazolinone **64** (5.3%), the 7-bromomethyl quinazolinone **65** (7.9%), the 6-bromomethyl quinazolinone **66** (57.9%), the 2-bromomethyl quinazolinone **68** (2.6%) and compound **69** (5.3%).

**Benzylic Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using NBS in Dichloromethane with Thermal AIBN Initiation**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) was added NBS (0.356 g, 0.002 mol) and AIBN (0.033 g, 0.2 mmol). The mixture was then refluxed for 8 hours. After cooling, the solvent was removed under reduced pressure to leave a light cream coloured solid (0.956 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of NBS, succinimide and at least 6 other constituents; quinazolinone **63** (27.5%), the 6,7-di(bromomethyl) quinazolinone **64** (2.8%), the 7-bromomethyl quinazolinone **65** (5.6%), the 6-bromomethyl quinazolinone **66** (50%), the 2-bromomethyl quinazolinone **68** (5.6%) and compound **69** (8.4%).

**Benzylic Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using Photo-Initiated Reaction of NBS in Dichloromethane**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) was added NBS (0.356 g, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. The flask was then allowed to cool to 20 °C before the solvent was evaporated under reduced pressure to leave a very light brown coloured solid (0.960 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of NBS, succinimide and 5 other constituents; quinazolinone **63** (10%), the 6,7-di(bromomethyl) quinazolinone **64** (5%), the 7-bromomethyl quinazolinone **65** (5%), the 6-bromomethyl quinazolinone **66** (80%) and compound **69** (trace).

**Benzylic Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using Photo-Initiated Reaction of NBS in Dichloromethane under a Nitrogen Atmosphere**

To a dry round bottom flask under a nitrogen atmosphere was added a solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) and NBS (0.356 g, 0.002 mol) in a single portion. The solution was then stirred for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. The flask was then allowed to cool to 20 °C before the solvent was evaporated under reduced pressure to leave a very light brown coloured solid (0.960 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of NBS, succinimide and 5 other constituents; quinazolinone **63** (10%), the 6,7-di(bromomethyl) quinazolinone **64** (5%), the 7-bromomethyl quinazolinone **65** (5%), the 6-bromomethyl quinazolinone **66** (80%) and compound **69** (trace).

**Benzylic Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using Photo-Initiated Reaction of NBS in Methyl Formate**

Quinazolinone **63** (0.604 g, 0.002 mol) and NBS (0.356 g, 0.002 mol) were added to a flask containing methyl formate (6 ml) and brought into solution by vigorous stirring

and the application of heat. This solution was then stirred for 8 hours whilst being irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. During this time the flask was occasionally shaken to prevent the build up of a precipitate around the edges of the solution. After the irradiation period was complete the solution was allowed to cool to 20 °C and the solvent removed under reduced pressure to leave a light brown coloured solid (0.960 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of NBS, succinimide and at least 6 other constituents; quinazolinone **63** (22%), the 6,7-di(bromomethyl) quinazolinone **64** (5%), the 7-bromomethyl quinazolinone **65** (5%), the 6-bromomethyl quinazolinone **66** (67%), the 2-bromomethyl quinazolinone **68** (trace) and compound **69** (trace).

**Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using Photo-Initiated Reaction of NBS in 1:1 Methyl Formate/Dichloromethane**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (3 ml) and methyl formate (3 ml) was added NBS (0.356 g, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. The flask was then allowed to cool to 20 °C before the solvent was evaporated under reduced pressure to leave light brown coloured solid (0.960 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed of succinimide and at least 6 other constituents; quinazolinone **63** (16.7%), the 6,7-di(bromomethyl) quinazolinone **64** (3.6%), the 7-bromomethyl quinazolinone **65** (5.6%), the 6-bromomethyl quinazolinone **66** (63.7%), the 2-bromomethyl quinazolinone **68** (2.8%) and compound **69** (5.6%).

**Bromination 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) using Ionic Reaction of NBS in Chlorobenzene**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in chlorobenzene (6 ml) was added NBS (0.356 g, 0.002 mol) in a single portion. Light was then excluded from the reaction vessel and the reaction mixture heated to 80 °C and maintained at this temperature for 18 hours. After cooling to 20 °C the succinimide was filtered and washed with chlorobenzene (2 ml). The combined filtrate and washings were evaporated under reduced pressure to leave a pale yellow solid (0.742 g). Analysis of

this crude product by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, and $^1$H nmr spectroscopy suggested that this solid was composed of quinazolinone **63** (38.9%), the 2-dibromomethyl quinazolinone **67** (5.5%) and the 2-bromomethyl quinazolinone **68** (55.6%).

**Preparation of 2-Bromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (68) *via* Acid Catalysed Reaction of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) with NBS**

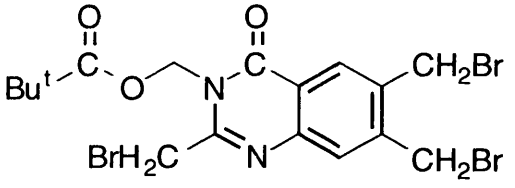
To a stirring solution of quinazolinone **63** (1.208 g, 0.004 mol) in 1,1,1-trichloroethane (12 ml) was added NBS (0.712 g, 0.004 mol) and a 30% by weight solution of hydrobromic acid in acetic acid (0.8 ml) in a single portion. The solution was then heated to 75 °C and held at this temperature for 4 hours. After cooling to 20 °C the solution was washed with 5% sodium hydroxide (20 ml) and water (20 ml) before being evaporated to dryness. Analysis of the resultant light brown solid by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of quinazolinone **63**, the 2-dibromomethyl quinazolinone **67** and the 2-bromomethyl quinazolinone **68**. The crude product was then chromatographed over a column of silica gel using 15 : 1 petroleum ether/ethyl acetate as the eluent. Early fractions afforded **67** (0.404 g, 22%) followed by **68** (0.838 g, 55%) then unreacted starting quinazolinone **63** (0.254 g).

**Preparation of 2,6-Di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone (69) *via* Benzylic Bromination of 2-Bromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (68) using Photo-Initiated Reaction of NBS in Dichloromethane**

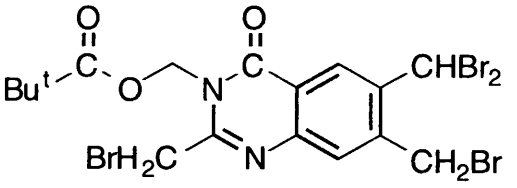
To a stirring solution of the 2-bromomethyl quinazolinone **68** (0.381 g, 0.001 mol) in dichloromethane (4 ml) was added NBS (0.178 g, 0.001 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. The flask was then allowed to cool to 20 °C before the solvent was evaporated under reduced pressure to leave a very light brown coloured solid (0.550 g). Analysis of this crude product by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of 4 constituents with $R_f$ values 0.78, 0.74 (**68**), 0.68 and 0.62 (**69**). The crude product was then chromatographed over a column of silica gel using 12 : 1 petroleum ether/ethyl acetate as the eluent. The first three comounds to elute from the

column were not separated. Later fractions afforded 2,6-di(bromomethyl)-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone (**69**) (0.280 g, 61%) as a crystalline solid, m.p. 134-135 °C; $\delta_H$ 8.22 (1H, s, 5-H), 7.51 (1H, s, 8-H), 6.21 (2H, s, O-$CH_2$-N), 4.60 & 4.58 (both 2H, both s, 2-$CHBr_2$ & 6-$CHBr_2$), 2.57 (3H, s, 7-$CH_3$) and 1.18 (9H, s, $CMe_3$); $\delta_C$ 177.6 (-$CO_2$-), 160.9 (4-C=O), 152.0 (2-C), 147.0 (8a-C), 145.6 (4a-C), 136.8 (7-C), 129.5 (5-CH), 128.8 (8-CH), 119.0 (6-C), 66.6 (O-$CH_2$-N), 38.9 ($CMe_3$), 30.8 (6-$CH_2$Br), 29.0 (2-$CH_2$Br), 27.0 (-C($CH_3$)$_3$) and 19.6 (7-$CH_3$); m/z 462 ($M^+$, 14%), 460 (24), 458 (15).

## Attempted Preparation of 2,6,7-Tri(bromomethyl)-*N*(3)-pivaloyloxymethylquinazolinone (70) via Radical Dibromination of 2-Bromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (68)



(70)



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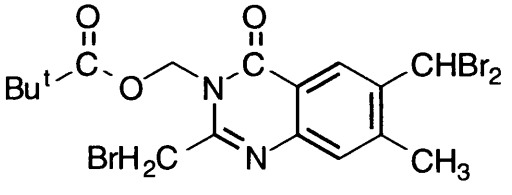
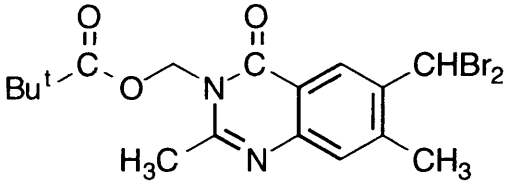


(72)

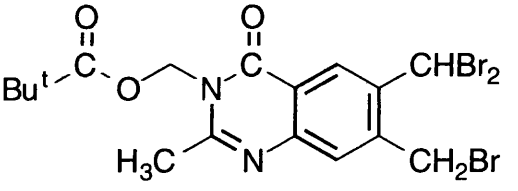
To a stirring solution of 2-bromomethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**68**) (0.381 g, 0.001 mol) in dichloromethane (6 ml) was added NBS (0.356 g, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. The flask was then allowed to cool to 20 °C before the solvent was evaporated under reduced pressure to leave a pale yellow coloured solid (0.735 g). Analysis of this crude product by $^1$H nmr spectroscopy suggested that it was composed primarily of succinimide and 4 brominated derivatives of **63**. These constituents were tentatively assigned as 2,7-di(bromomethyl)-6-dibromomethyl-*N*(3)-pivaloyloxymethylquinazolinone (**71**), 2-bromomethyl-6-dibromomethyl-7-methyl-*N*(3)-pivaloyloxymethylquinazolinone (**72**), 2,6,7-tri(bromomethyl)-*N*(3)-pivaloyloxymethylquinazolinone (**70**) and the 2,6-

di(bromomethyl) compound **69**, and were present in the ratio 1 : 1.5 : 4 : 4. Unfortunately, no eluting system could be found which would afford a complete chromatographic separation of these 4 constituents and the crude product was not purified further.

**Preparation of 6,7-Di(bromomethyl)-2-methyl-*N*(3)-pivaloyloxymethylquinazolinone (64) By Radical Dibromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63)**




(73)




(74)

To a stirring solution of quinazolinone **63** (0.906 g, 0.003 mol) in dichloromethane (12 ml) was added NBS (1.068 g, 0.006 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. The flask was then allowed to cool to 20 °C before the solvent was evaporated under reduced pressure to leave a yellow solid (1.972 g). Analysis of this crude product by $^1$H nmr spectroscopy and TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed primarily of succinimide, the 6,7-di(bromomethyl) quinazolinone **64**, the 6-bromomethyl quinazolinone **66** and 2 other brominated derivatives of quinazolinone **63**, tentatively assigned as 6-dibromomethyl-2,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**73**) and 7-bromomethyl-6-dibromomethyl-2-methyl-*N*(3)-pivaloyloxymethylquinazolinone (**74**). These 4 constituents were present in the ratio 8 : 1.4 : 1.7 : 1. The crude product was then chromatographed over a column of silica gel, using 10 : 1 petroleum ether/ethyl acetate as the eluent. The first compound to elute was the 6,7-di(bromomethyl) quinazolinone **64** (0.909 g, 54%), obtained as a crystalline solid as before. The remaining 3 constituents co-eluted and were not separated.

**Preparation of 2,6,7-Tri(bromomethyl)-*N*(3)-pivaloyloxymethylquinazolinone (70) By Ionic Bromination of 6,7-Di(bromomethyl)-2-methyl-*N*(3)-pivaloyloxymethylquinazolinone (64)**

To a stirring solution of the 6,7-di(bromomethyl) quinazolinone **64** (0.560 g, 0.001 mol) in 1,1,1-trichloroethane (4 ml) was added NBS (0.178 g, 0.001 mol) and a 30% by weight solution of hydrobromic acid in acetic acid (0.2 ml) in a single portion. The solution was then heated to 75 °C and held at this temperature for 6 hours. After cooling to 20 °C the solution was washed with 5% sodium hydroxide (20 ml) and water (20 ml) before being dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded a viscous yellow oil (0.623 g). Further purification by column chromatography, using 15 : 1 petroleum ether/ethyl acetate as the eluent, afforded the 2,6,7-tri(bromomethyl) quinazolinone **70** as an oily solid (0.307 g, 48%); $\delta_H$ 8.28 (1H, s, 5-H), 7.70 (1H, s, 8-H), 6.22 (2H, s, O-$CH_2$-N), 4.75 & 4.73 (both 2H, both s, 6-$CHBr_2$ & 7-$CHBr_2$), 4.58 (2H, s, 2-$CH_2Br$) and 1.20 (9H, s, $CMe_3$); $\delta_C$ 177.5 (-$CO_2$-), 160.4 (4-C=O), 152.6 (2-C), 146.9 (8a-C), 143.8 (4a-C), 136.5 (7-C), 130.3 (5-CH), 129.9 (8-CH), 121.0 (6-C), 66.4 (O-$CH_2$-N), 38.9 ($CMe_3$), 28.9 28.8 (6-$CH_2Br$ and 7-$CH_2Br$), 28.5 (2-$CH_2Br$) and 26.9 (-$C(CH_3)_3$); m/z 542, 540, 538, 536.

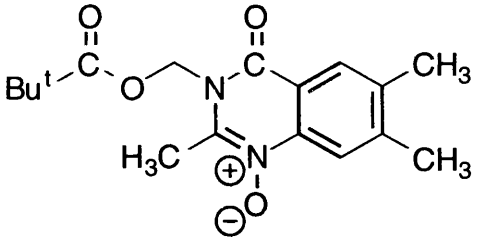
**Attempted Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) in the Presence of Boron Trifluoride Diethyl Etherate**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) was added NBS (0.356 g, 0.002 mol) and boron trifluoride diethyl etherate (0.25 ml, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. Analysis of the reaction mixture, after this period of irradiation, by TLC failed to provide any evidence to suggest that benzylic bromination had occured to an appreciable extent and the reaction was not worked up further.

## Attempted Benzylic Bromination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63) in the Presence of Titanium(IV) Isopropoxide

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) was added NBS (0.356 g, 0.002 mol) and titanium isopropoxide (0.568 g, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. Analysis of the reaction mixture, after this period of irradiation, by TLC failed to provide any evidence to suggest that benzylic bromination had occured to an appreciable extent and the reaction was not worked up further.

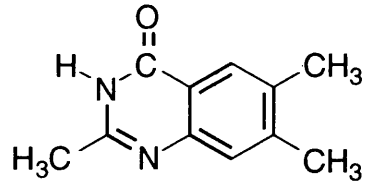
## Attempted Preparation of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone *N*-oxide (75) using Acetic Acid/Hydrogen Peroxide as the Oxidant



**(75)**

A mixture of quinazolinone **63** (0.604 g, 0.002 mol), glacial acetic acid (4 ml) and 30% hydrogen peroxide solution (1 ml) was heated at 70-75 °C for 12 hours. The excess acid was removed under reduced pressure and the remaining solution was neutralised with saturated sodium bicarbonate solution. The mixture was then extracted with dichloromethane (10 ml) and the resultant extract evaporated under reduced pressure to afford a light brown solid (0.570 g). Analysis of this crude product by $^1H$ nmr spectroscopy and TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, failed to provide any evidence to suggest that product formation had occured to an appreciable extent and the reaction was not worked up further.

**Attempted Preparation of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone *N*-oxide (75) using Trifluoroacetic Acid/Hydrogen Peroxide as the Oxidant**



**(76)**

A mixture of quinazolinone **63** (0.604 g, 0.002 mol), trifluoroacetic acid (4 ml) and 30% hydrogen peroxide solution (1 ml) was heated to 70 °C and held at this temperature for 12 hours. The excess acid was removed under reduced pressure and the remaining solution was neutralised with saturated sodium bicarbonate solution. The mixture was then extracted with dichloromethane (10 ml) and the resultant extract evaporated under reduced pressure to afford a brown solid (0.489 g). Analysis of this crude product by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that the crude product was composed of unreacted starting quinazolinone **63** and another unidentified constituent. Column chromatography using 10 : 1 petroleum ether/ethyl acetate as the eluent, afforded this compound (**76**), identified as the deprotected quinazolinone, as a white solid (0.186, 49%); $\delta_H$ ($d_6$-DMSO) 7.77 (1H, s, 5-H), 7.32 (1H, s, 8-H), 2.30 (9H, br s, 7-$CH_3$ 6-$CH_3$ and 2-$CH_3$); $\delta_C$ 161.8 (4-C=O), 153.6 (2-C), 147.6 (10-C), 144.1 (9-C), 135.0 (7-C), 126.7 (5-CH), 125.5 (8-CH), 118.5 (6-C), 21.5 (2-$CH_3$), 20.1 (7-$CH_3$) and 19.3 (6-$CH_3$); m/z 188 ($M^+$, 100%).

**Attempted Preparation of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone *N*-oxide (75) using *Oxone*® as the Oxidant[105]**

To a mixture of quinazolinone **63** (0.604 g, 0.002 mol), acetone (1 ml) and phosphate buffer (10 ml) was added dropwise a solution of *Oxone*® (3 g, 0.0048 mol) in water (20 ml). Potassium hydroxide solution was added simultaneously to maintain the pH in the region 7.5-8.0. After stirring for 4 hours the mixture was extracted with dichloromethane (2 x 20 ml) and washed with water (20 ml). The solution was then evaporated to dryness leaving leaving a pale brown solid residue (0.556 g). Analysis of this crude product by $^1$H nmr spectroscopy and TLC, using 4 : 1 petroleum ether/ethyl

acetate as the eluent, failed to provide any evidence to suggest that product formation had occured to an appreciable extent and the reaction was not worked up further.

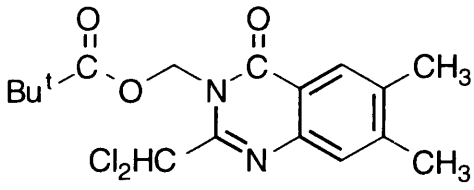
**Attempted Thermally Initiated Benzylic Iodination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63)**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in chlorobenzene (6 ml) was added *N*-iodosuccinimide (0.450 g, 0.002 mol) and AIBN (0.033 g, 0.2 mmol). The reaction mixture was then heated to 80 °C and held at this temperature for 3 hours. After cooling to 20 °C and filtering, the solvent was evaporated under reduced pressure to leave a white solid (1.05 g). Analysis of this crude product by $^1$H nmr spectroscopy suggests that it is composed primarily of unreacted starting compound (**63**) and about 5% of the C-2 Me monoiodinated derivative. The crude product was not purified further.

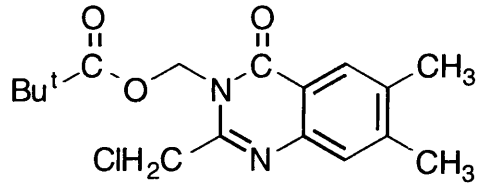
**Attempted Photo-Initiated Benzylic Iodination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63)**

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) was added *N*-iodosuccinimide (0.450 g, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. After cooling to 20 °C and filtering the solvent was evaporated under reduced pressure to afford a white solid (1.05 g). Analysis of this crude product by $^1$H nmr spectroscopy suggests that it is composed primarily of unreacted starting quinazolinone **63** with the only other product being the C-2 Me monoiodinated derivative, present at a level of about 10%. The crude product was not purified further.

**Photo-Initiated Benzylic Chlorination of 2,6,7-Trimethyl-*N*(3)-pivaloyloxymethylquinazolinone (63)**



(78)



(77)

To a stirring solution of quinazolinone **63** (0.604 g, 0.002 mol) in dichloromethane (6 ml) was added *N*-chlorosuccinimide (0.267 g, 0.002 mol) in a single portion. Stirring was allowed to continue for 8 hours whilst the mixture was irradiated by a 100W lamp situated approximately 5 cm from the reaction vessel. After cooling to 20 °C the solution was filtered and the solvent removed from the filtrate under reduced pressure to leave a white solid (0.806 g). Analysis of this crude product by TLC, using 4 : 1 petroleum ether/ethyl acetate as the eluent, suggested that it was composed of 3 constituents derived from quinazolinone **63**. The crude product was then chromatographed over a column of silica gel using 15 : 1 petroleum ether/ethyl acetate as the eluent. Early fractions afforded 2-dichloromethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**78**) (0.178 g, 24%) as a crystalline solid, m.p. 125-126 °C; $\delta_H$ 8.03 (1H, s, 5-H), 7.50 (1H, s, 8-H), 6.93 (1H, s, 2-$CHCl_2$), 6.34 (2H, s, O-$CH_2$-N), 2.41 (6H, s, 6-$CH_3$ and 7-$CH_3$) and 1.22 (9H, s, $CMe_3$); $\delta_C$ 177.3 (-$CO_2$-), 161.0 (4-C=O), 148.6 (2-C), 145.7 (8a-C), 143.8 (4a-C), 138.7 (7-C), 128.3 (5-CH), 127.1 (8-CH), 118.6 (6-C), 67.5 (2-*C*$HCl_2$), 66.4 (O-$CH_2$-N), 38.8 (*C*$Me_3$), 26.7 (-C(*C*$H_3$)$_3$), 20.3 (7-$CH_3$) and 19.8 (6-$CH_3$); m/z 372.3 ($M^+$, 6.1%), 370.3 (9.1), 258.3 (M-POM, 53.7), 256.3 (81.9). Further elution gave fractions which afforded 2-chloromethyl-6,7-dimethyl-*N*(3)-pivaloyloxymethylquinazolinone (**77**) (0.329 g, 49%) as a crystalline solid, m.p. 124-125 °C; $\delta_H$ 8.01 (1H, s, 5-H), 7.44 (1H, s, 8-H), 6.23 (2H, s, O-$CH_2$-N), 4.73 (1H, s, 2-$CH_2Cl$), 2.40 (3H, s, 7-$CH_3$), 2.39 (3H, s, 6-$CH_3$) and 1.21 (9H, s, $CMe_3$); $\delta_C$ 177.5 (-$CO_2$-), 161.1 (4-C=O), 150.1 (2-C), 145.4 (8a-C), 144.8 (4a-C), 137.9 (7-C), 127.9 (5-CH), 127.1 (8-CH), 118.5 (6-C), 66.3 (O-$CH_2$-N), 43.6 (2-*C*$H_2Cl$), 38.8 (*C*$Me_3$), 26.9 (-C(*C*$H_3$)$_3$), 20.4 (7-$CH_3$) and 19.7 (6-$CH_3$); m/z 336.3 ($M^+$, 12.3%), 222.3 (100, M-POM). Later fractions afforded unreacted starting quinazolinone **63** (0.144 g, 24%).

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