SYNTHETIC STUDIES:

(I) STABILISED DIAZOCARBANIONS.

(II) SOLID-PHASE IMIDAZOLIDES.

A THESIS

presented to the University of Glasgow
for the degree of Doctor of Philosophy

by

Brendan James Hamill.

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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I would also like to acknowledge the moral support afforded by my fellow research students over the period of this work; in particular I would like to thank Dr. H. Mackie, Dr. D. MacDougall, Mr. J. Bremner and Mr. J.O'Donnell for lifting my spirits during periods of depression.

Technical services were freely and competently rendered by the staff of Glasgow University Chemistry Department and to them I express my thanks.

The work described in this thesis was carried out during the tenure of a demonstratorship and a studentship from the University of Glasgow, for which I should like to express my gratitude.

Brendan Hamill.

To my wife and my parents.

SUMMARY.

The base-induced reactions of trimethylsilyldiazomethane and dimethylphosphonodiazomethane with carbonyl compounds to form the homologous acetylenes are described; the reactions are generally applicable to the preparation of di-aryl acetylenes and of certain aryl alkyl acetylenes.

The reaction of 1,1'-carbonyl-di-imidazole with hydroxy-carboxylic acids is discussed; imidazolide formation occurs only with substrates in which the hydroxyl function is secondary.

The preparation and properties of polymer-supported imidazolides are described; such compounds show lower reactivity than free imidazolides.

CONTENTS:

PART ONE:

PART TWO:

INTRODUCTION.

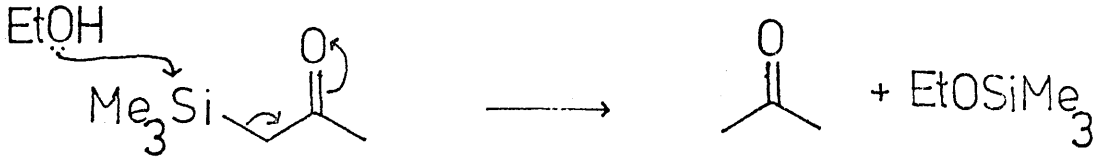
SILICON - ALMOST ORGANIC.

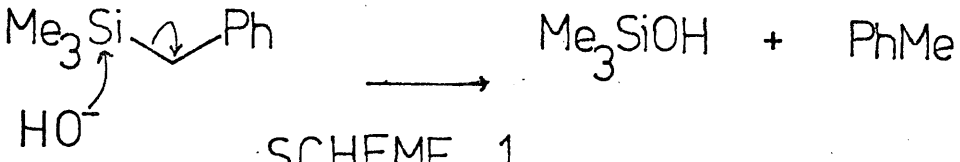
Over the past decade, the element Silicon has experienced a remarkable change in its fortunes. It has been wrenched from the hands of electronics manufacturers and purveyors of "non-stick" frying-pans, and planted firmly in the armoury of the synthetic organic chemist.

The basis of the synthetic utility of organosilicon compounds lies in the nature of the element Silicon itself: As the most electropositive of the "non-metallic" elements in the second row of the periodic table, its bonds to the more electronegative first-row elements, Oxygen and Fluorine, are stronger than the bonds of Carbon to these elements, while its bonds to Carbon and Nitrogen are weaker than the bonds of Carbon to these elements. This characteristic gives rise to a wide range of thermodynamically-favourable processes which make organosilicon compounds useful in synthetic transformations.

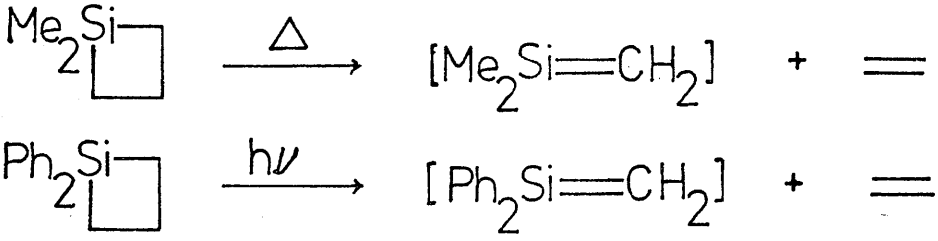
The second property of Silicon is that it possesses a set of vacant d-orbitals of suitable energy for back-bonding with a filled 2p orbital on an adjacent atom of a first-row element. This enables Silicon to stabilise an adjacent carbanion, and opens up a further series of potentially useful synthetic routes.

One very important consequence of these properties is the comparative ease with which a silyl substituent on a Carbon framework can be removed. As an electropositive element, Silicon is susceptible to attack by a nucleophile; moreover, bonding by the nucleophile through the vacant d-orbitals of Silicon can commence before the Silicon-





SCHEME 1



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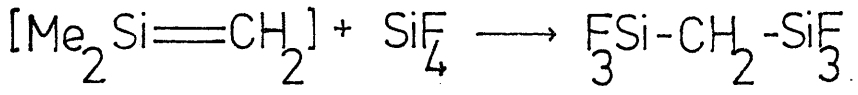

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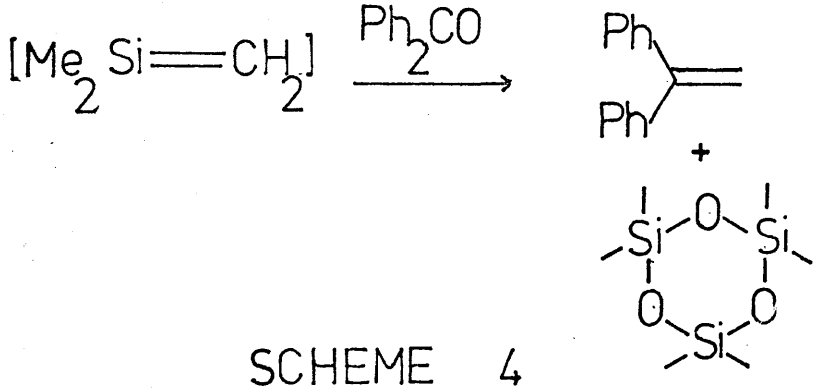
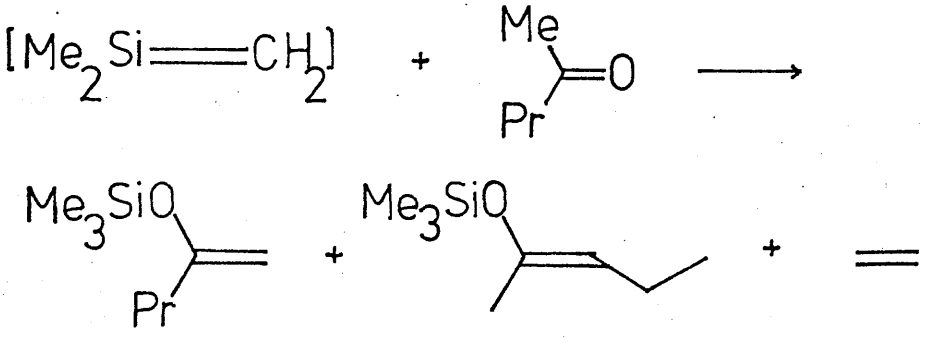


SCHEME 4



SCHEME 5

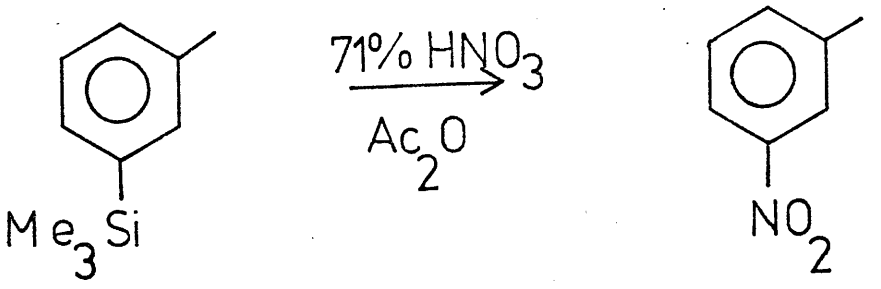
Carbon bond is broken. In general, removal of a silyl substituent can be effected by nucleophilic displacement under fairly mild conditions, provided that the Carbon fragment expelled is a good leaving group (SCHEME 1).

π-character of the Silicon-Carbon bond.

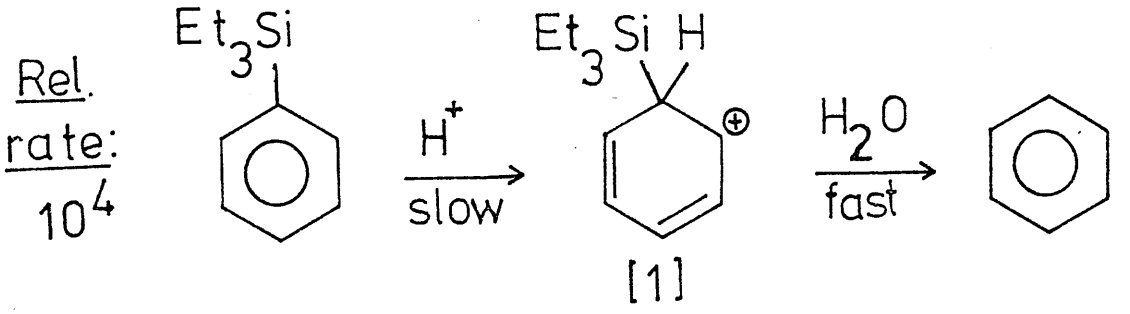
The π-character of the Silicon-Carbon bond has been a matter of controversy for many years, but it is now generally accepted that such character does exist. Numerous studies of bond-lengths[2], dipole moments[3], n.m.r. spectra[4], uv. spectra[5], i.r. spectra[6], Raman spectra[6], molecular orbital studies[7] and chemical behaviour[2,8] of organosilicon compounds have supported this conclusion.

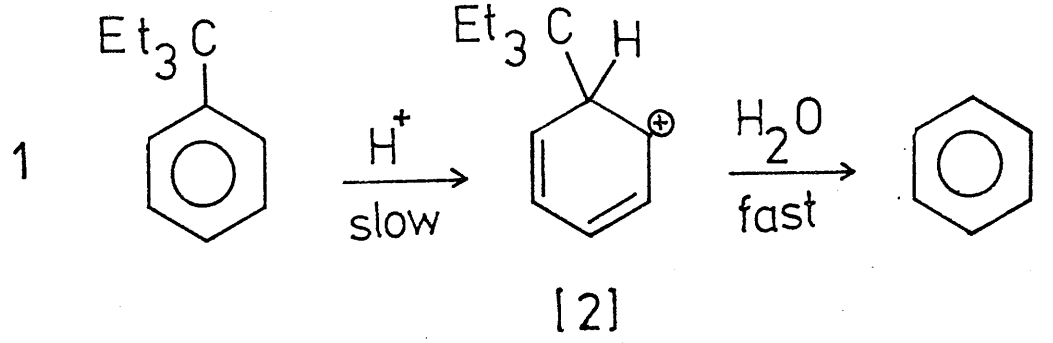
Ab-initio SCF-MO calculations have been carried out[9] for ethylene, vinyl silane and allyl silane, both with and without the inclusion of Silicon d-orbitals in the basis set. Inclusion of d-orbitals was found to give a better interpretation of the photo-electron spectra of the silanes, particularly in the case of vinyl silane.

Silicon analogues of unsaturated compounds have been prepared by thermolytic[10] or photolytic[11] cleavage of sila-cyclobutanes (SCHEME 2). The Silicon-Carbon bonds in these compounds have a high degree of dipolar character, as demonstrated by their ability[12] to cleave the very strong Silicon-Fluorine bond, a property restricted to strongly nucleophilic reagents (SCHEME 3). Such compounds also react with aldehydes and ketones[10]. Non-enolisable ketones are transformed into 1,1 disubstituted alkenes, in a process analogous to the Wittig reaction (SCHEME 4), while enolisable ketones are converted to their trialkylsilyl-enol ethers (SCHEME 5).



SCHEME 6





SCHEME 7

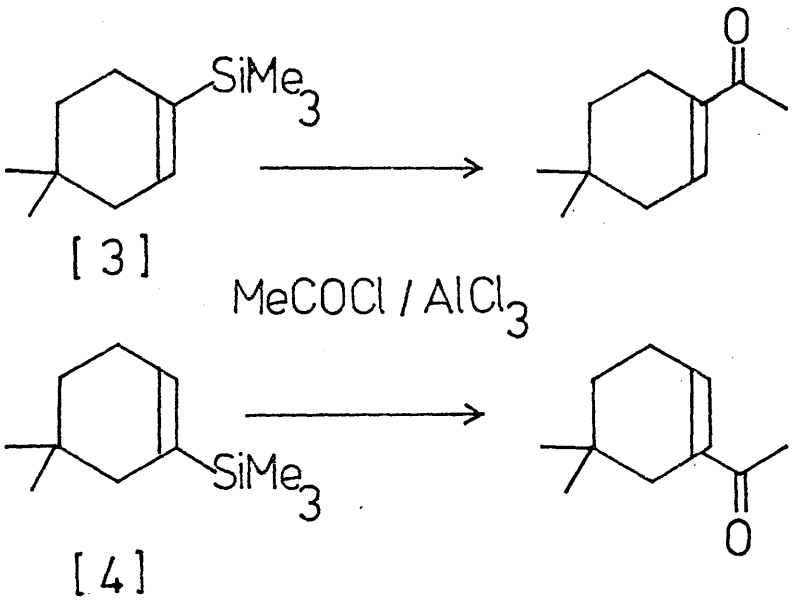
Carbonium-ion stabilisation by a β-silyl substituent.

(a): in electrophilic substitution of aryl-, vinyl- and allyl-silanes.

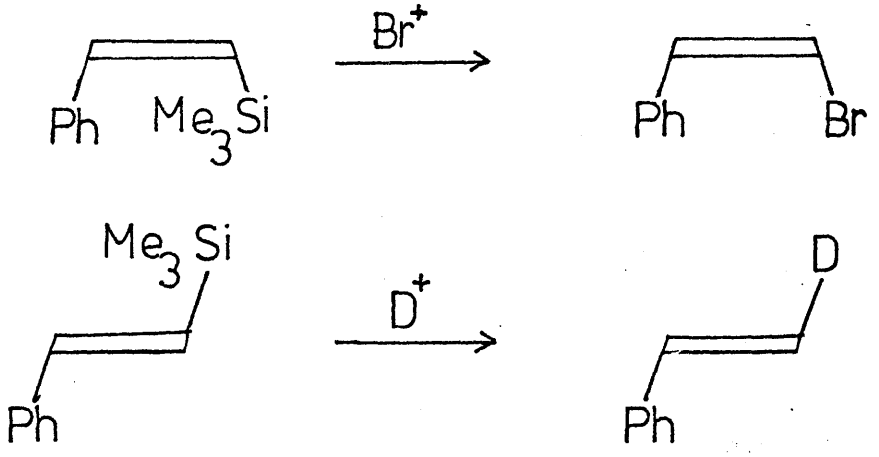
Early studies of organosilicon compounds were concerned primarily with the inductive effect of a silyl substituent, particularly in the aromatic series. It was soon discovered that a silyl substituent on an aromatic ring exerted a powerful activating effect in electrophilic substitution. Moreover, substitution took place at the site of the silyl group, which was displaced in the course of the reaction. Thus, for example, trimethylsilyl-benzene was converted to nitrobenzene under mild nitrating conditions, under which benzene itself could not be nitrated. Similarly, 3-methyl trimethylsilyl benzene was converted to 3-methyl nitro-benzene, meta-substitution occurring despite the presence of the ortho/para-directing methyl substituent (SCHEME 6)[13].

Following these investigations, it was discovered that triethylsilyl- benzene was hydrolysed to benzene by dilute aqueous acid at a rate 10^4 times faster than the corresponding hydrolysis of t-heptyl-benzene[14]. The explanation proposed was that the intermediate carbonium ion 1 formed in the rate-determining step is stabilised by the β-silyl substituent, and thus is formed much more rapidly than the corresponding β-(t-heptyl)-carbonium ion 2 (SCHEME 7).

This ability of a Carbon-Silicon bond to stabilise a carbonium ion β to it is now well understood. The same effect is seen in the electrophilic substitution of benzyl-trimethylsilane, which takes place much more



SCHEME 8



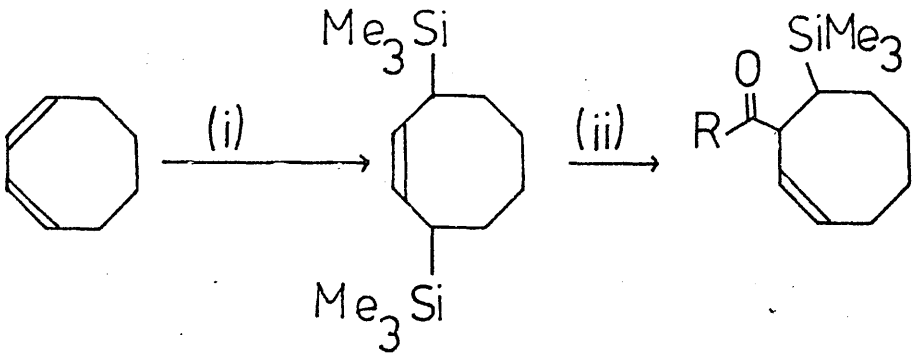
SCHEME 9

rapidly than the substitution of toluene under the same conditions, and in which ortho/para-direction is observed.[15] ^{13}C and ^{29}Si NMR studies have been performed of a variety of phenyl- and benzyl-silanes PhX and $PhCH_2X$ (X = SiRR'R'' where R, R', R'' are alkyl-, alkoxyl- or halide).[16] The results show approximately constant differences in the chemical shift of the ring-Carbon atom para- to the substituent between the two series of compounds, with greater charge-density in the ring in the benzyl series than in the phenyl series. Similarly, a linear correlation is observed between ^{29}Si chemical shifts in PhX and $PhCH_2X$ where the silyl group X is the same in both cases. These results agree well with the electron-accepting properties of an α-silyl substituent, compared with the electron-releasing ability of a β-silyl substituent.

Effects similar to those described above are also observed in the substitution of trimethylsilyl-substituted benzoic acids[17] and benzcyclobutenes[18], and in Friedel-Crafts acylation of trimethylsilyl-substituted benzenes.[19]

The aliphatic Friedel-Crafts acylation of alkenes can also be controlled by introduction of a silyl substituent. Thus, acetylation of the silylated cyclohexenes 3 and 4 occurs exclusively at the site of the trimethylsilyl group (SCHEME 8).[20]

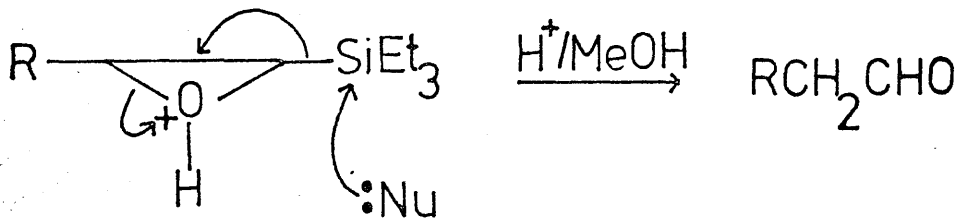
Vinyl-silanes readily undergo electrophilic substitution. Thus, β-trimethylsilyl-styrene can be brominated[21] or deuterated[22] in a stereospecific manner (SCHEME 9). In these reactions, the silyl group stabilises the developing carbonium-ion in a "bridging" manner, and therefore the stereochemistry of the original vinyl silane is preserved in the product.



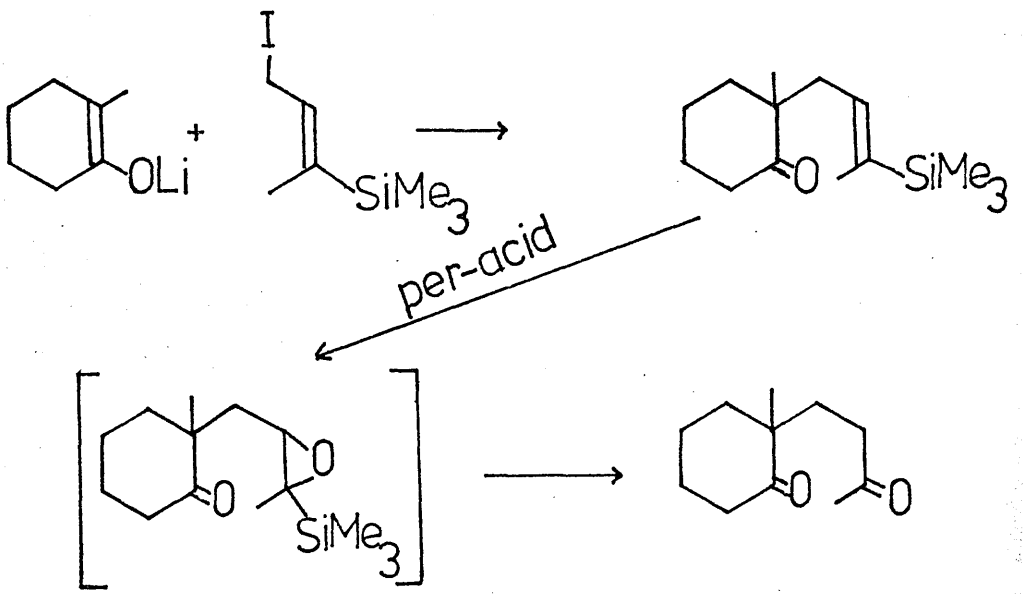
(i) = Me_3SiCl /Mg/HMPT

(ii) = $RCOCl, AlCl_3$

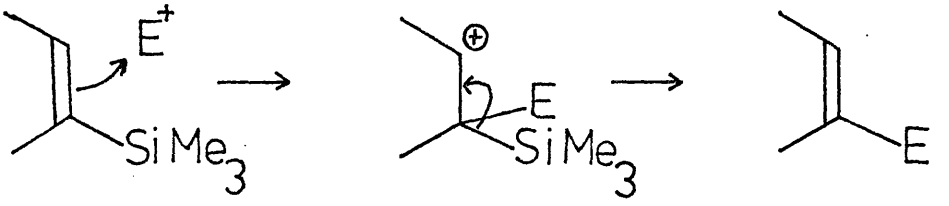
SCHEME 14



SCHEME 15

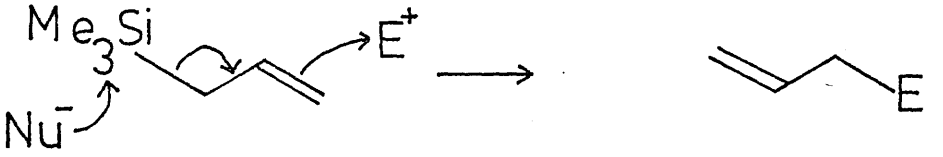


SCHEME 16



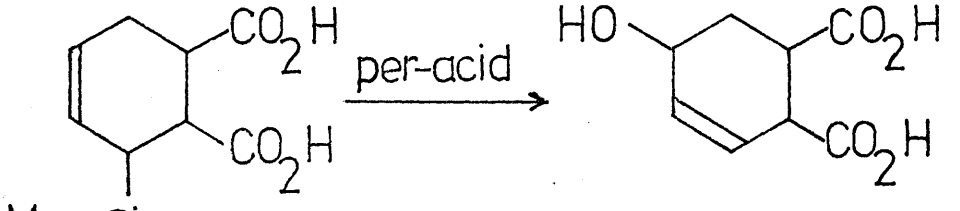
(E^+ = Electrophile)

SCHEME 10



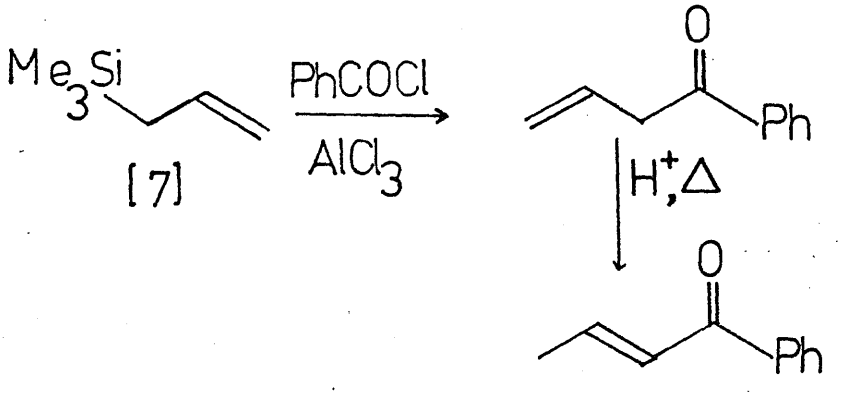
(Nu^- = Nucleophile)

SCHEME 11



[5] [6]

SCHEME 12



[7]

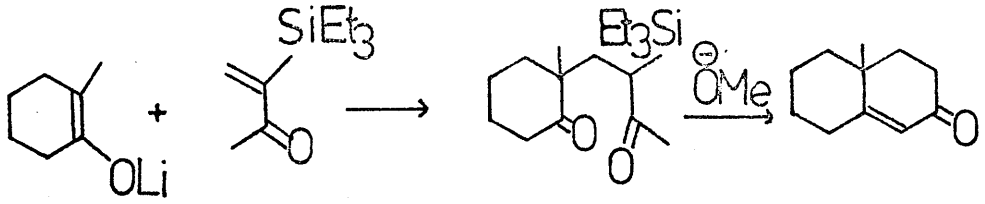
SCHEME 13

These reactions of vinyl-silanes can be summarised by the process shown in SCHEME 10.

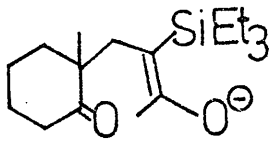
The electrophilic substitution of allyl-silanes, on the other hand, must involve attack by the electrophile at the carbon atom $\underline{\alpha}$ to the silyl-substituent, resulting in a shift in position of the double bond (SCHEME 11). Reactions of this type are also known. For example, the di-acid 5 reacts with per-acetic acid to give the allylic alcohol 6 (SCHEME 12)[19]. Similarly, allyl-trimethyl-silane 7 can be acylated under Friedel-Crafts conditions to give a variety of useful compounds[23] (SCHEME 13). The starting allyl-silanes are readily available from the reaction of chloro-trimethylsilane and Zinc with allyl chloride in polar solvents. Conjugated dienes can be doubly silylated in the 1,4- positions by a similar silylating system, and the product allyl silanes acylated (SCHEME 14).

(b): <u>in nucleophilic displacement of a silyl substituent.</u>

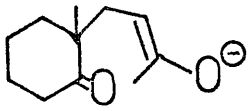
Vinyl-silanes are readily converted to epoxy-silanes, which, on nucleophilic displacement of the silyl group, are converted to carbonyl compounds[24] (SCHEME 15). This process allows vinyl-silanes to be used as masked carbonyl compounds, for example to overcome the practical difficulties encountered in the Robinson annelation procedure[25], which occur because the base strengths of the anions of the original ketone and the product diketone are very similar, and several side-reactions are therefore observed[26]. This can be avoided by rapid alkylation of the enolate with an allylic halide such as 2-(iodomethyl)-vinyl-silane, which, on epoxidation and silyl-group displacement, gives the required diketone[27] (SCHEME 16).



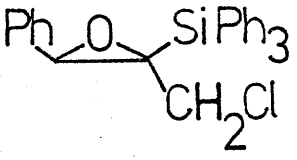
SCHEME 17



[8]

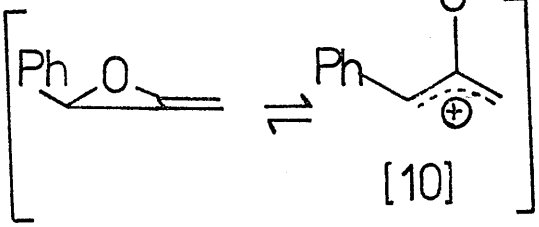


[9]

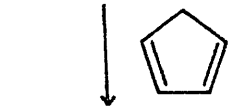


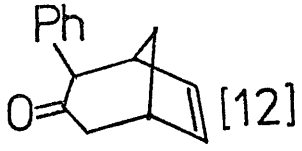
[11]

KF
MeCN



[10]





[12]

SCHEME 18

$$Me_4Si \xrightarrow[Me_2NCH_2CH_2NMe_2]{{}^{n}BuLi} Me_3SiCH_2Li$$

$$(Me_3Si)_3CH \xrightarrow{MeLi} (Me_3Si)_3CLi$$

SCHEME 19

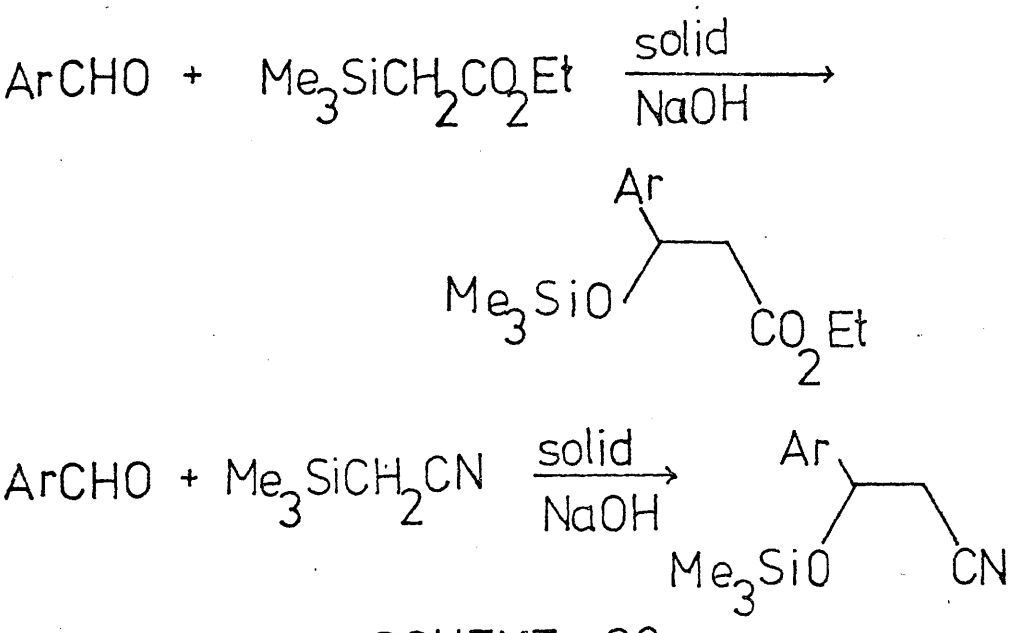
It is interesting to note that displacement of the silyl group in this case is much more rapid than with simple epoxy-silanes, presumably because of participation by the neighbouring carbonyl group. Various methods are available for the synthesis of iodomethyl-vinyl silanes[28].

An alternative approach[29] involves the use of a silylated analogue of methyl vinyl ketone (SCHEME 17). The silylated enolate ion 8 is much less basic than 9 because of the stabilisation provided by ($\pi \rightarrow d$) overlap, and side-reactions are thus avoided. With such compounds, it is possible to carry out annelation even under aprotic conditions, whereas methyl vinyl ketone itself undergoes extensive polymerisation under such conditions. The silyl group is easily displaced when all synthetic operations are complete, since it is α to a carbonyl group.

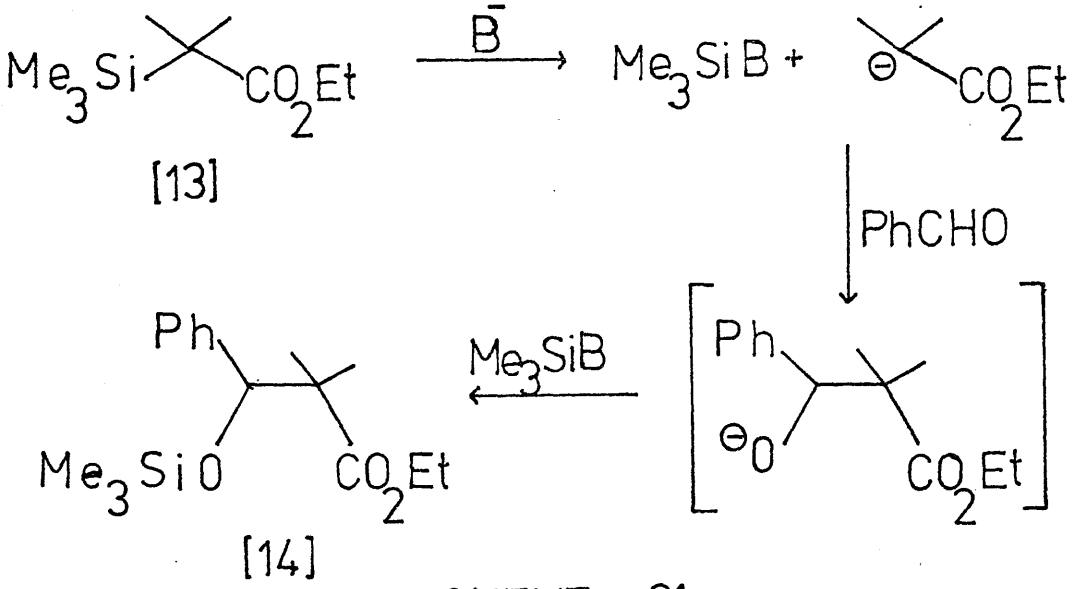
1-Chloromethyl-vinyl silanes can be epoxidised, and the resulting epoxy-silanes, on treatment with fluoride ion, undergo elimination to produce allene oxides, which are tautomeric with oxyallyl zwitterions 10. Thus, treatment of epoxy-silane 11 with fluoride ion in the presence of cyclopentadiene gave the adduct 12 (SCHEME 18)[30].

Carbanion stabilisation by an α-silyl substituent.

($p \rightarrow d)_\pi$-Backbonding between Silicon and Carbon, and consequent electron-withdrawal from Carbon is sufficiently strong in many cases to allow the removal of protons α to the silyl substituent. Many examples of reactions involving, as a first step, the formation of an α-silyl carbanion have been studied in recent years. By the use of strong bases, a proton can be removed even from alkylsilanes[31] (SCHEME 19). In most examples studied,

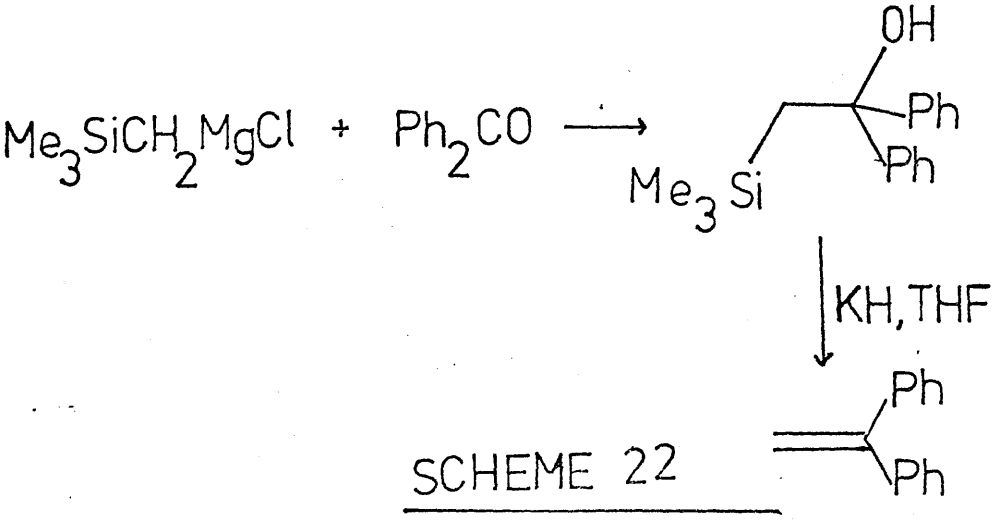


SCHEME 20



[14]

SCHEME 21

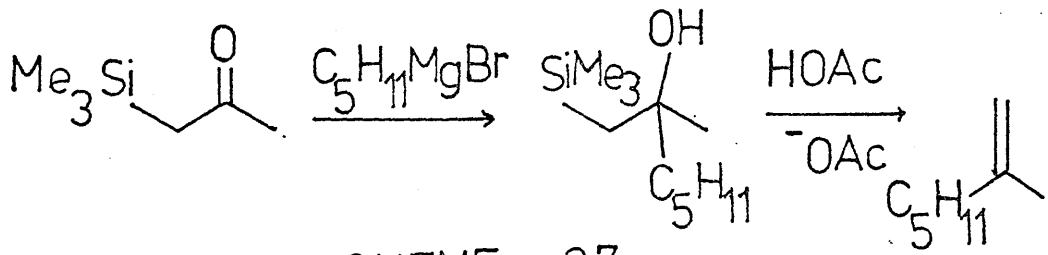


SCHEME 22

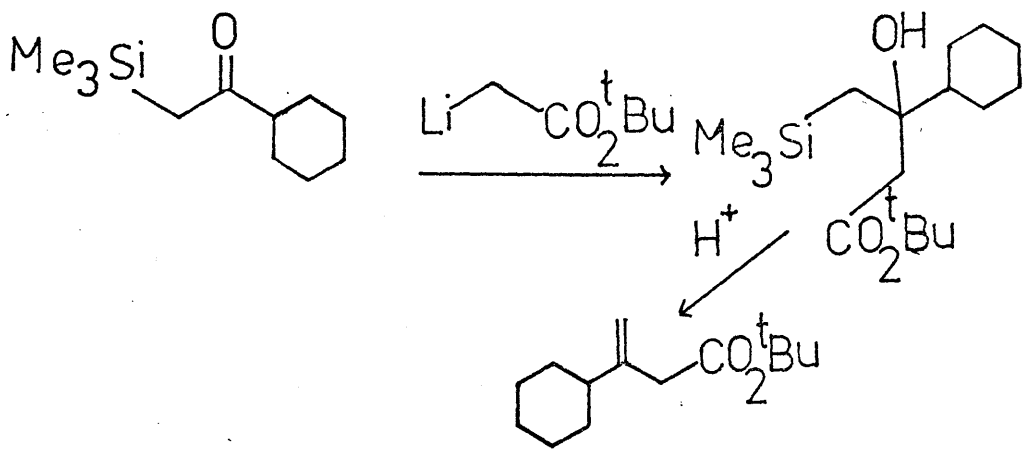
however, the carbon from which a proton is removed is flanked by another stabilising group besides the silyl group.

In one of the earlier examples of this type of process[32], an α-trimethylsilyl ester was condensed with an aldehyde in an analogue of the Reformatsky reaction. The reaction has the advantage that the β-trimethylsiloxy-ester thus produced is automatically protected from subsequent dehydration. The reaction is therefore useful in cases in which the Reformatsky product is liable to dehydrate to give an α,β-unsaturated ester. Cyanomethyl-trimethylsilane reacts similarly (SCHEME 20). It should be noted, however, that this reaction probably does not proceed through an α-silyl carbanion, since ethyl α-trimethylsilyl-isobutyrate 13 , which has no methylene protons α to the silyl group, nevertheless reacts with benzaldehyde to form the β-trimethylsiloxy-ester 14. The mechanism proposed is outlined in SCHEME 21.

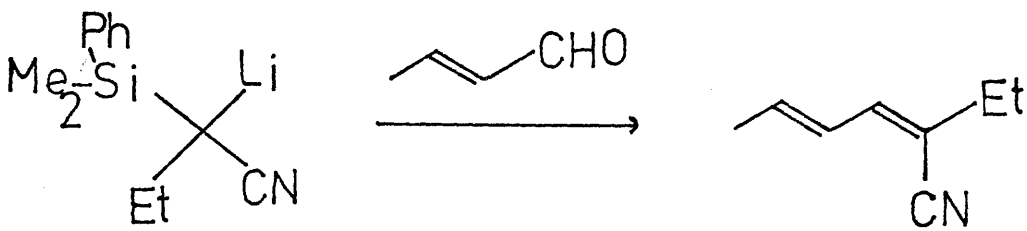
In most examples of processes involving α-silyl carbanionoids, the reaction partner is a carbonyl compound, and the β-hydroxy-silane thus formed can be converted to an alkene by elimination of trimethylsilanol or one of its salts. The classic example of this process, which is analogous to the Wittig reaction, and often superior to it, is known as the Peterson reaction[33], in which trimethylsilylmethyl-magnesium chloride is condensed with a ketone to give, after elimination, a 1,1-disubstituted alkene (SCHEME 22). It is interesting to note that the chloromagnesium salt of the intermediate β-hydroxy-silane does not undergo elimination, whereas the potassium salt



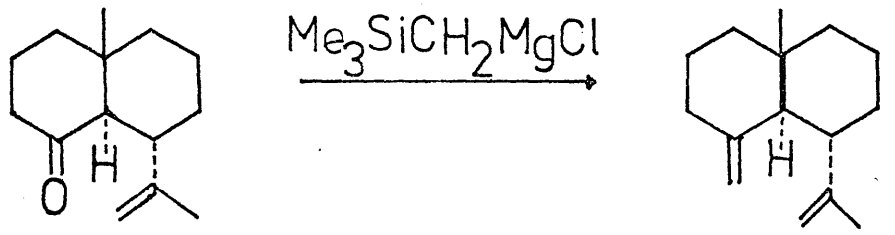
SCHEME 27



SCHEME 28

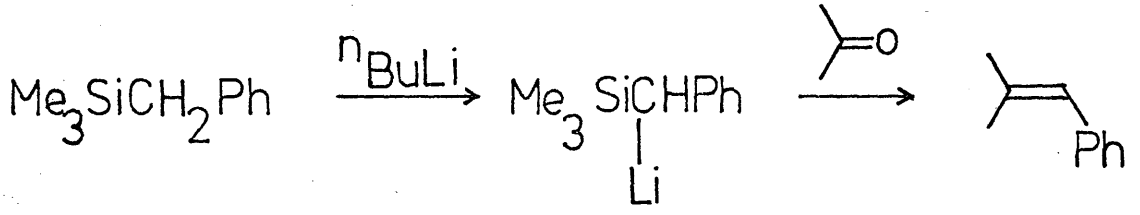


SCHEME 29

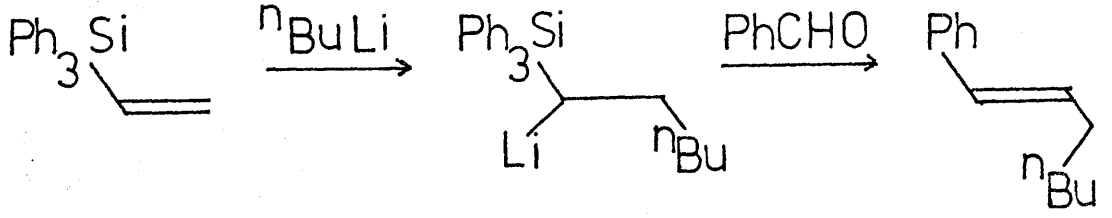


[15] [16]

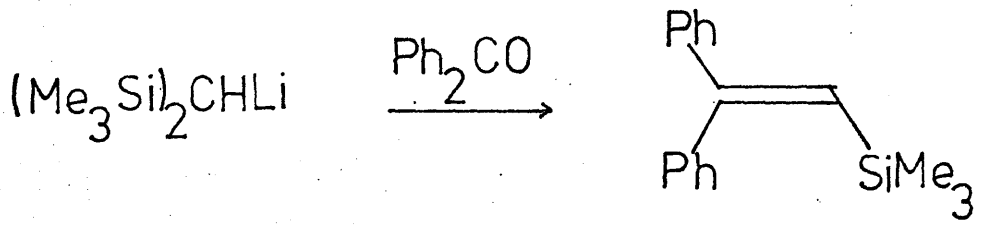
SCHEME 23



SCHEME 24



SCHEME 25



SCHEME 26

readily eliminates potassium trimethylsilanoxide to give the alkene. This cation-dependence is a common feature of such elimination processes.

The Peterson reaction was used in a successful synthesis of β-Gorgonene 16 . The intermediate ketone 15 failed to react with methylene triphenylphosphorane, but trimethylsilylmethyl-magnesium chloride effected the conversion[34] (SCHEME 23).

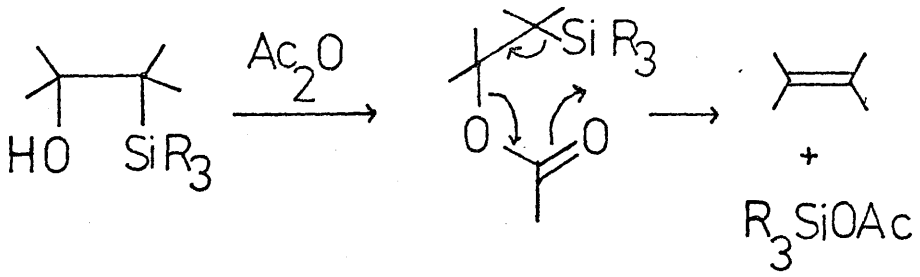
The same process can be used to produce tri-substituted alkenes or, by reaction with an aldehyde, 1,2-disubstituted alkenes[35]. The α-silyl carbanions are generated either by direct lithiation of a suitably substituted silane (SCHEME 24) or by addition of a suitable alkyl lithium to a vinyl-silane (SCHEME 25).

Vinylsilanes can be prepared in this way, by reaction of bis-(trimethylsilyl)-methyl lithium with ketones.[36] (SCHEME 26).

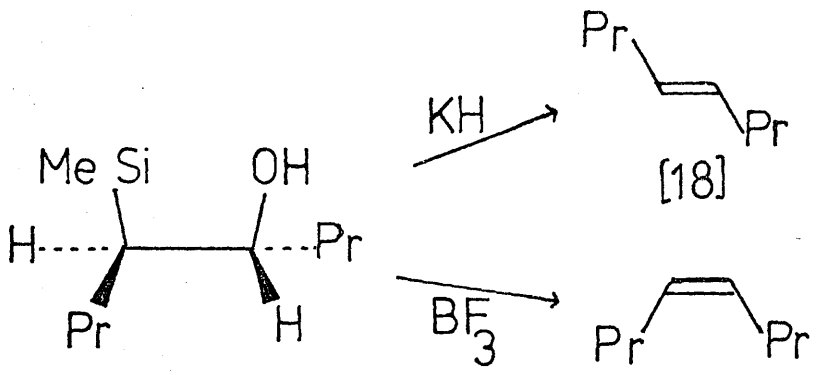
Reaction of α-trimethylsilyl-ketones with organolithium or organomagnesium compounds leads to β-hydroxy-silanes which undergo elimination to give alkenes[37] (SCHEME 27). Similarly, reaction of α-trimethyl-silyl-ketones with α-lithio-esters gives β,γ-unsaturated esters[38] (SCHEME 28).

In contrast to the examples described earlier (SCHEME 20), a recent report describing the reaction of an α-lithio-α-cyano-silane with an aldehyde indicates that the product readily eliminates lithium trimethylsilanoxide to give an α,β-unsaturated nitrile[39] (SCHEME 29).

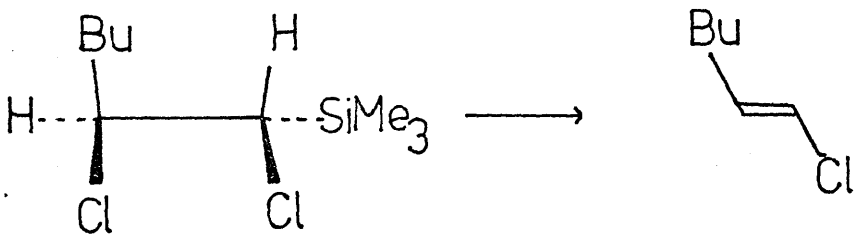
The factors influencing the ease of elimination of



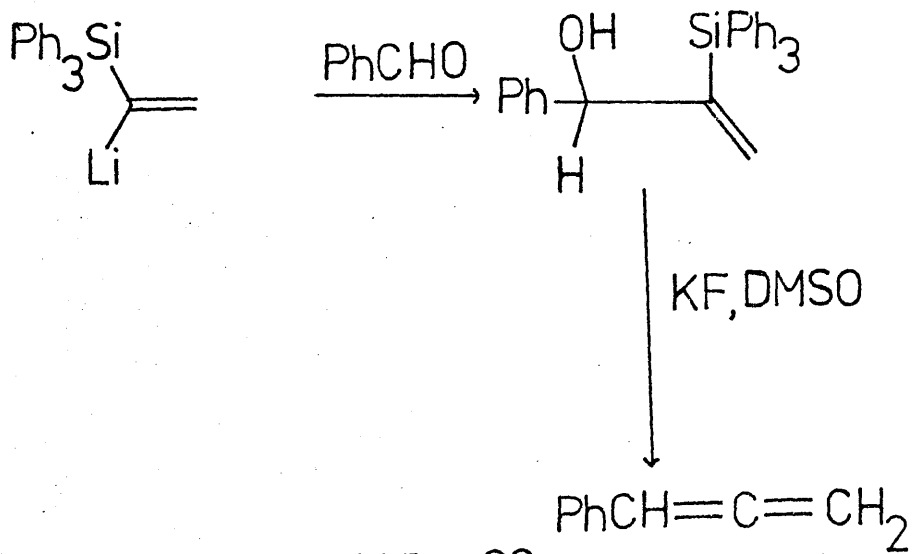
SCHEME 30



SCHEME 31



SCHEME 32

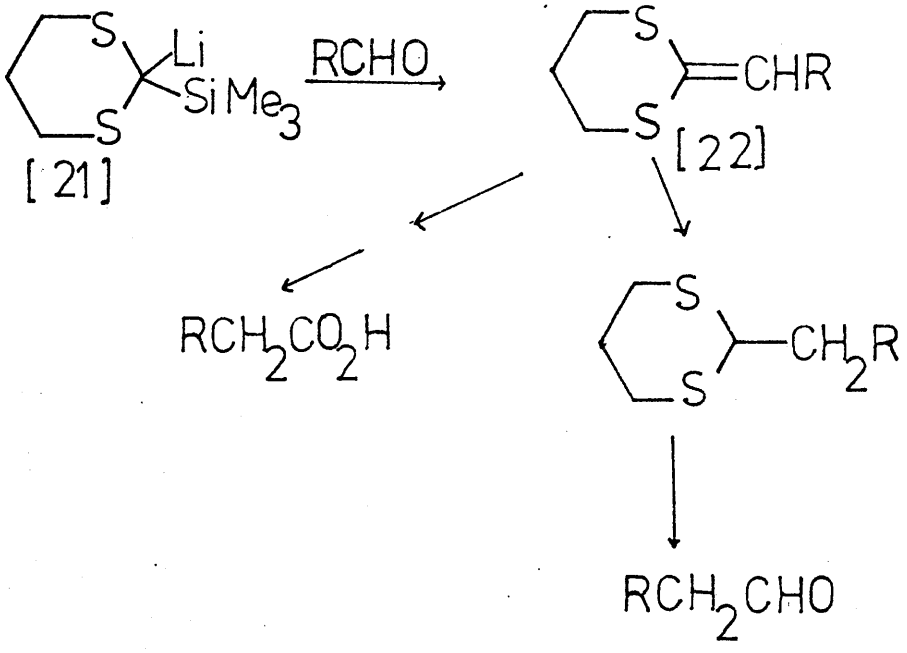


SCHEME 33

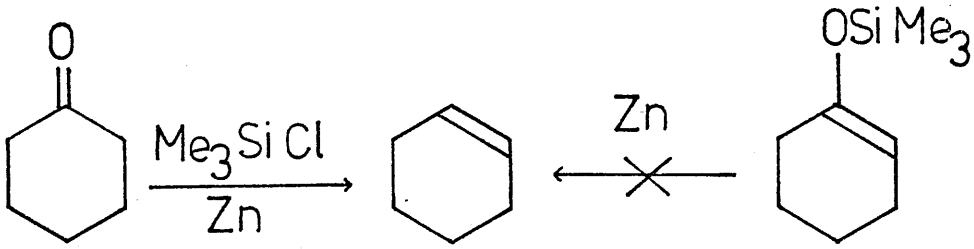
trimethylsilanol from β-hydroxy-silanes have been studied by several groups of workers. It has been observed that lithium or magnesium salts of β-hydroxy-silanes undergo elimination more readily when the resulting alkene is non-terminal than when it is terminal[40]. Treatment of β-hydroxy-silanes with acetic anhydride or thionyl chloride has been found to be effective in promoting elimination[41] (SCHEME 30). Fluoride ion is particularly effective in promoting elimination, because of the strength of the Silicon-Fluorine bond[42].

In a study[43] of the stereochemistry of silanol elimination, a β-hydroxy-silane of known configuration 17 gave almost exclusively trans-alkene 18 , the product of syn-elimination, when treated with potassium hydride. Boron trifluoride, on the other hand, effected anti-elimination to give almost exclusively cis-alkene 19 (SCHEME 31). The different elimination pathways are presumably due to the requirement, in the former case, for syn-elimination to occur in order that a Silicon-Oxygen bond can be formed, while, in the latter case, a Silicon-Fluorine bond is formed, and the usual stereo-electronic factors determine the geometry of the elimination. Similarly, 1,2-dichloro- 1-trimethyl-silyl-alkanes undergo trans-elimination of the elements of chlorotrimethylsilane to give chloro-alkenes[44] (SCHEME 32).

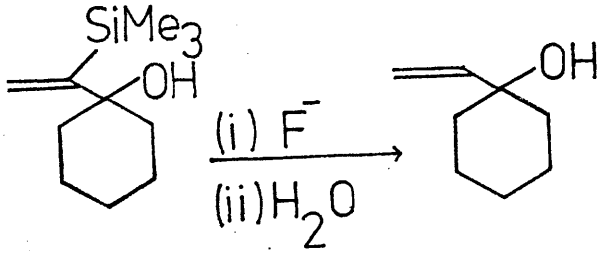
The reaction of 1-triphenylsilyl-vinyl lithium with aldehydes leads to allenes[45] (SCHEME 33). In this case, silanoxide elimination does not occur readily, and fluoride ion is used to displace the silyl moiety. It seems, however, that this reaction cannot be extended to ketones



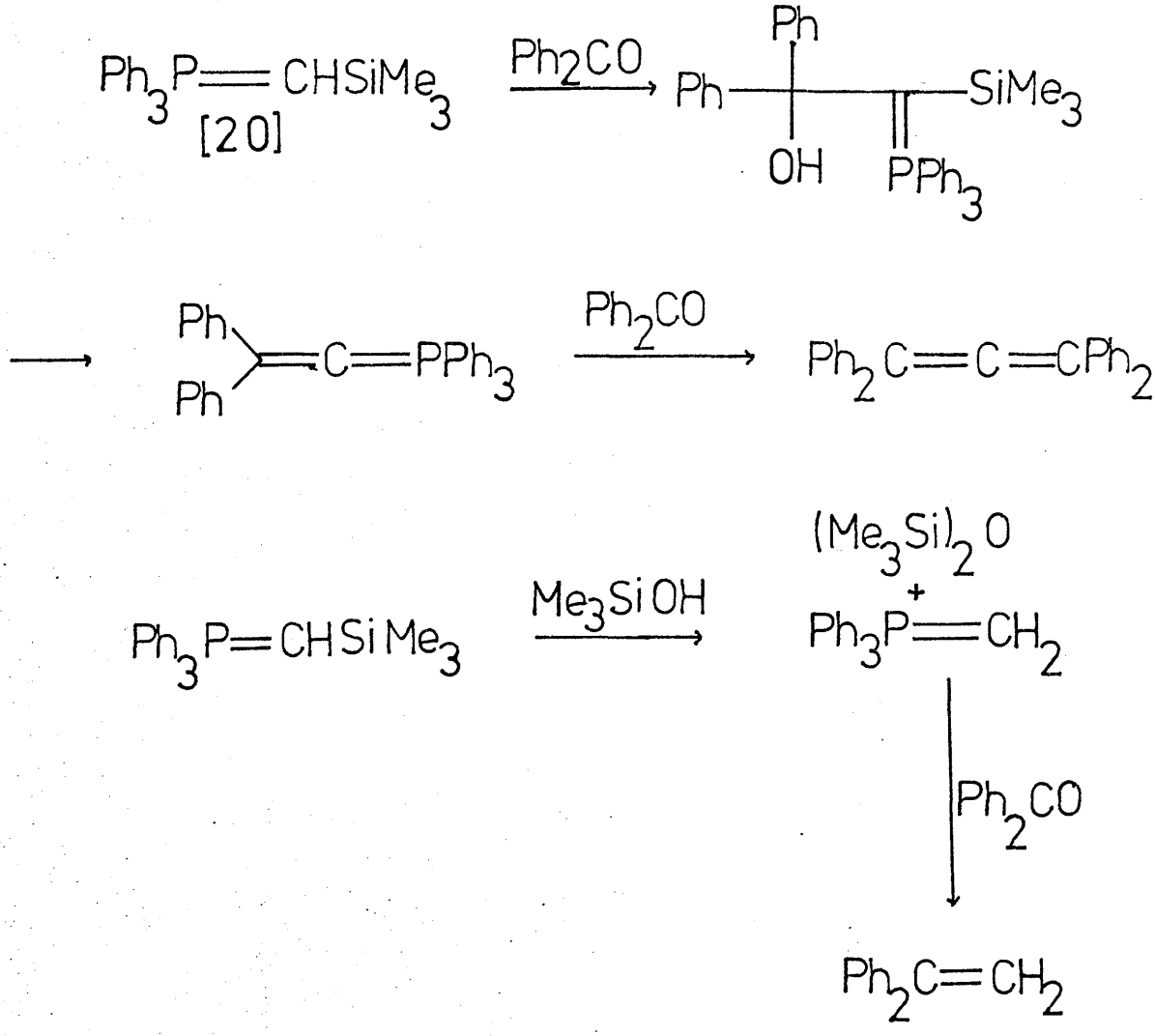
SCHEME 36



SCHEME 37



SCHEME 34



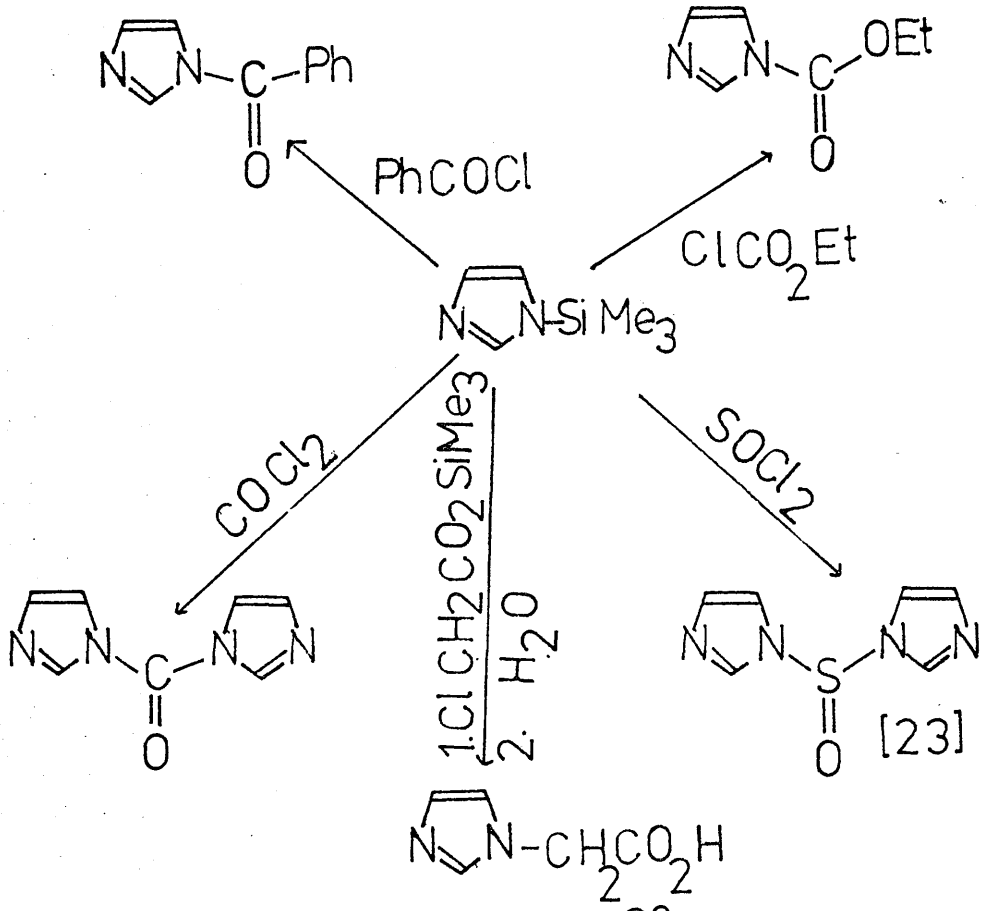
SCHEME 35

to produce 1,1-disubstituted allenes, for in this case the β-hydroxy-silane does not undergo elimination on treatment with fluoride ion, although the silyl group is removed[46] (SCHEME 34).

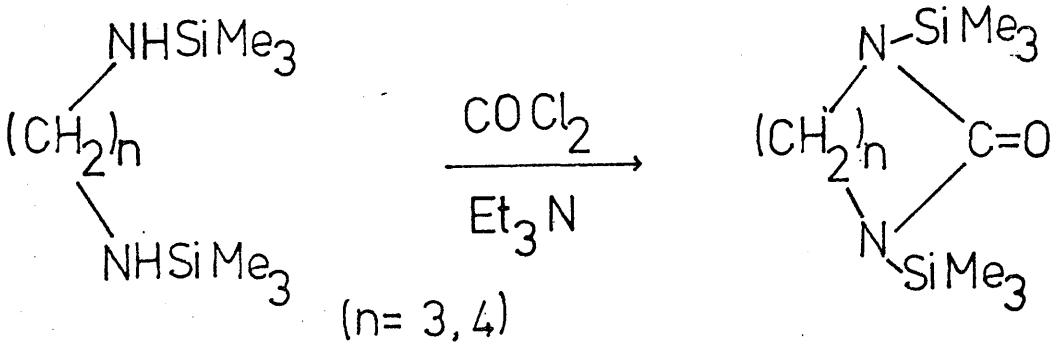
Symmetrical allenes are formed by reaction of trimethylsilylmethylene triphenylphosphorane 20 with ketones. Alkenes are always formed simultaneously, as a result of trimethylsilyl group displacement from the phosphorane, followed by normal Wittig reaction with the ketone. Quantitative yields of both allene and alkene can be obtained by using a suitable excess of ketone[47] (SCHEME 35). Silyl ylids are useful intermediates for the preparation of ylids substituted with other second- or third-row elements, by trans-silylation. They are also very useful in the preparation of pure, salt-free ylids, often difficult or impossible to prepare otherwise. Purification of the silyl ylid, followed by desilylation, avoids these problems[48].

2-Lithio- 2-trimethylsilyl-(1,3)-dithianes 21 react with aldehydes to give ketene-thioacetals 22 , which can be hydrolysed to the homologous carboxylic acids[49], or, after reduction, to the homologous aldehydes[50] (SCHEME 36).

Treatment of cyclohexanone with chloro-trimethylsilane and Zinc produced cyclohexene[51]. This process may be related to the Peterson reaction, but the available evidence favours a carbenoid mechanism. The trimethylsilyl ether of cyclohexanone, on treatment with Zinc, did not give cyclohexene (SCHEME 37).

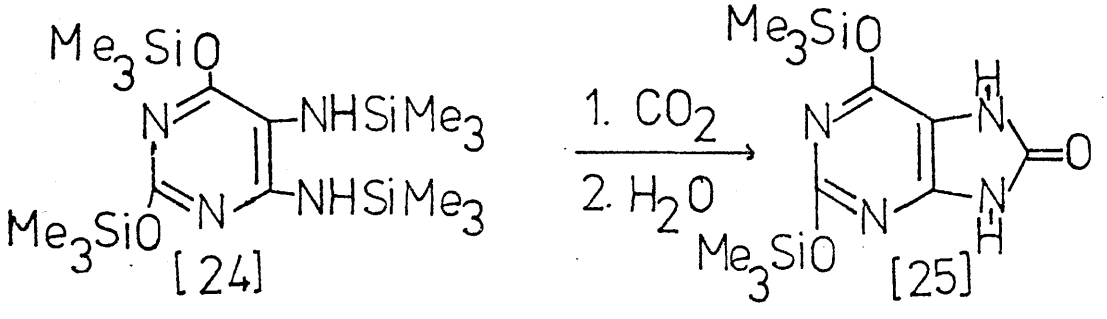


SCHEME 38



(n= 3, 4)

SCHEME 39



SCHEME 40

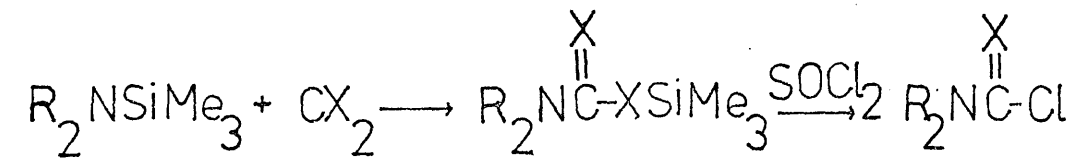
Reactivity of the Silicon-Nitrogen bond.

Aminosilanes have been extensively used in preparations of amides, ureas and glycosides. The advantages of using aminosilanes rather than the corresp--onding amines in reactions with alkyl or acyl halides are twofold: firstly, the silylated amine is often more reactive than the parent amine, and, secondly, the halo-silane by-product is usually removed easily by distillation. For example, N-trimethylsilyl-imidazole reacts more readily than the parent heterocycle with acyl chlorides[52] to give, after removal of chloro-trimethylsilane by distillation, essentially pure products. Thionyl chloride reacts similarly to give 1,1'-thionyl di-imidazole[53] 23 ; this is the only method by which this compound can be prepared pure. N-Trimethylsilyl-imidazole also reacts with α-halo-carboxylic esters, unlike imidazole itself[54] (SCHEME 38). Silylated triazoles react in an analogous manner.[54,55]

α,ω -Diamines cannot be converted to the corr--esponding cyclic ureas by treatment with phosgene, but the N,N'-bis-(trimethylsilyl)-diamines are cyclised readily[56] (SCHEME 39). In these cases, it is the N-H bond that is cleaved, and the silyl substituents are retained in the products.

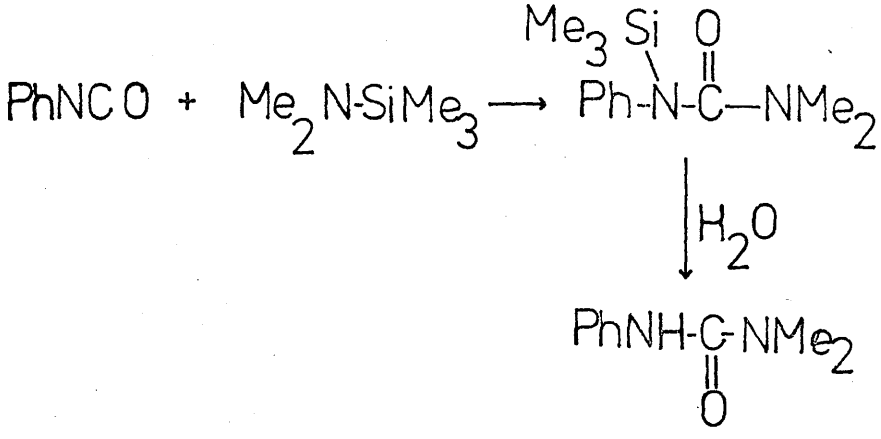
The activating effect of the N-silyl substituents in the uracil 24 is such that conversion to the cyclic urea can be effected even by carbon dioxide, yielding, on hydrolysis, the uric acid derivative 25 (SCHEME 40).

Trialkylsilylated carboxamides can exist either in the O-silyl or the N-silyl form, and examples of both

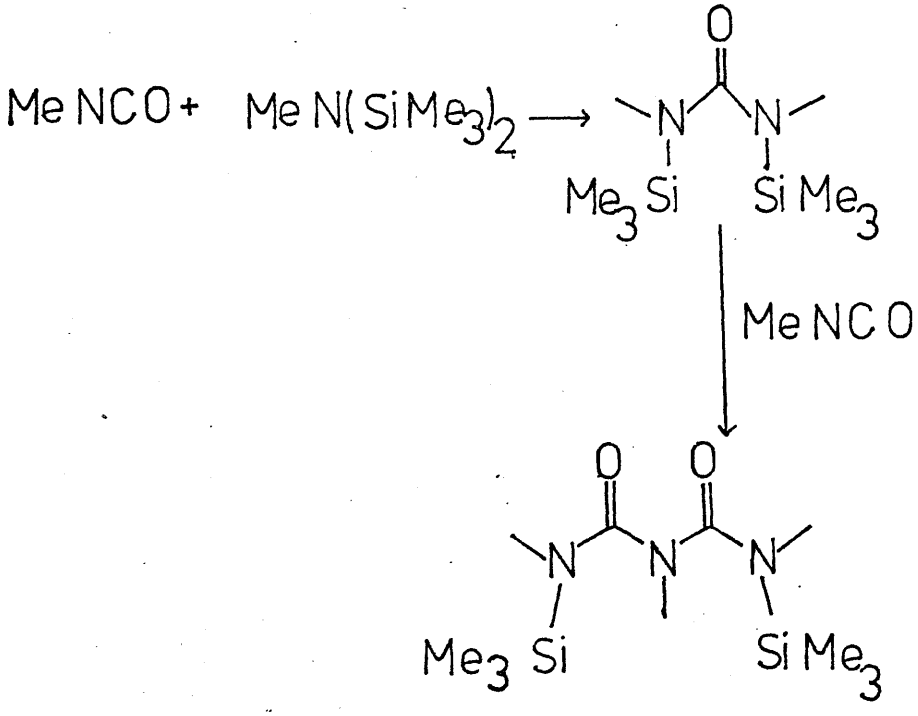


(X= O, S)

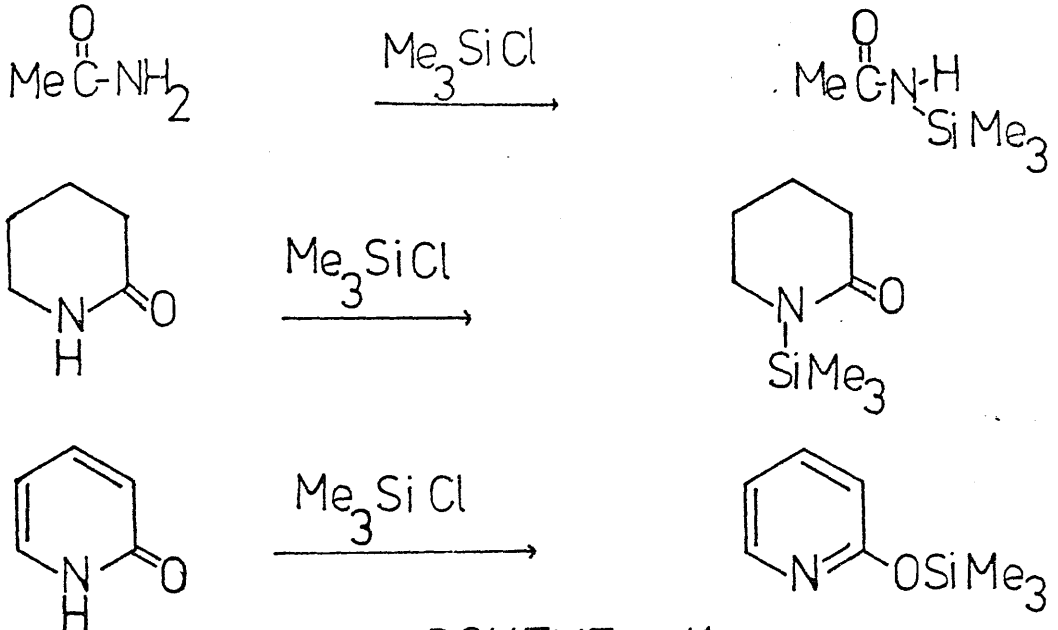
SCHEME 45



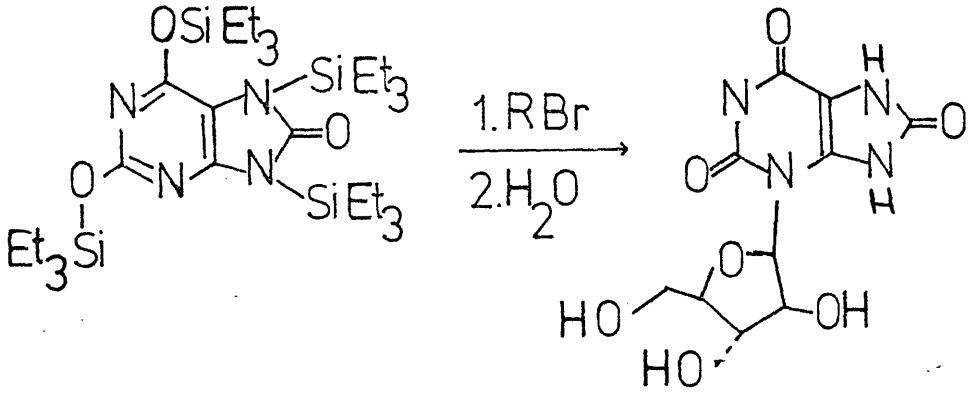
SCHEME 46



SCHEME 47

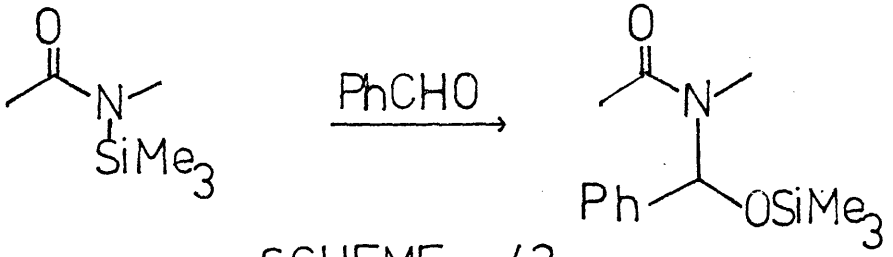


SCHEME 41

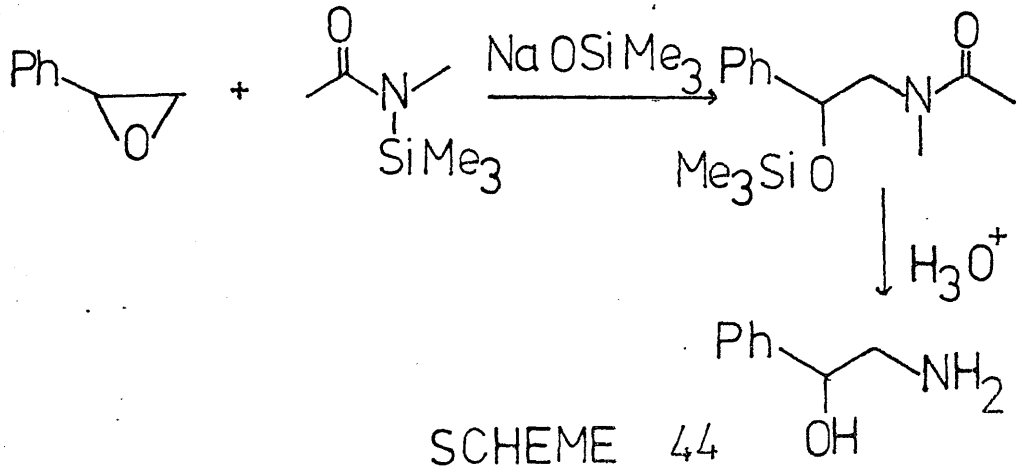


(RBr=1-bromo, 2,3,5-tri-O-benzoyl-ribofuranose)

SCHEME 42



SCHEME 43



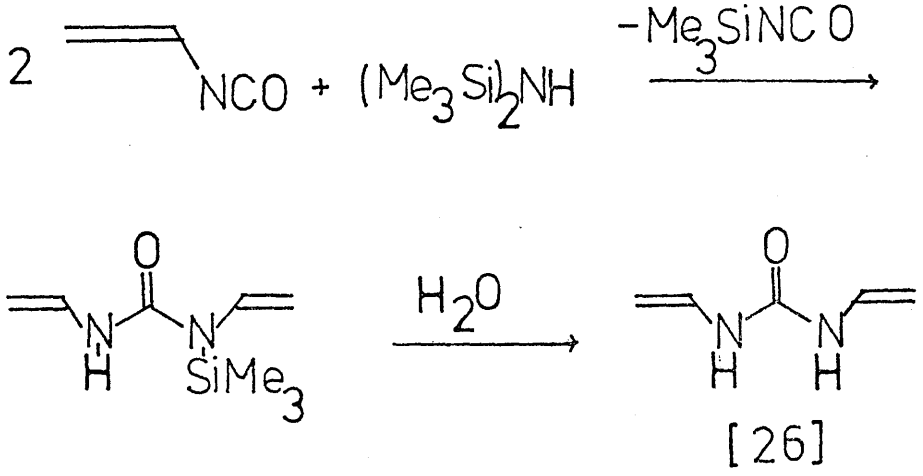
SCHEME 44

types of compound are known.[57,58] In general, open-chain amides and non-aromatic lactams give the N-silyl derivatives, which, unlike the O-silyl derivatives, are still capable of resonance stabilisation.[59] These compounds undergo acylation by acyl chlorides. Lactams in which hetero-aromatisation is possible generally exist in the O-silyl (imidate) form (SCHEME 41). Compounds of the latter type can be alkylated on Nitrogen with alkyl halides. This process has been used extensively in the preparation of N-glycosides[58,60] (SCHEME 42). It has the advantage that the halo-silane produced as the reaction proceeds does not react further with the hetero-aromatic compound involved, whereas, in the classical procedure, the alkyl halide produced leads to mixtures of products.[61]

N-Silylated secondary amides react with aldehydes[62] to give O-trimethylsilyl derivatives of N- (α-hydroxyalkyl) amides (SCHEME 43), while reaction with epoxides[63], catalysed by sodium trimethylsilanoxide, leads, after acid hydrolysis, to β-amino-alcohols (SCHEME 44).

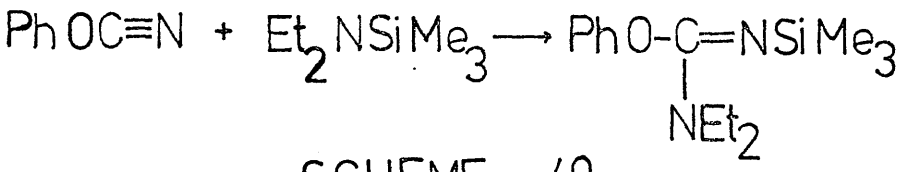
Carbamoyl and thio-carbamoyl chlorides are prepared by reaction of trimethylsilylated secondary amines with carbon dioxide or carbon disulphide, followed by treatment with thionyl chloride or phosphorus pentachloride[64] (SCHEME 45). Isocyanates and iso-thio-cyanates react similarly to give, after hydrolysis, ureas and thio-ureas (SCHEME 46).[65-68]

Silazanes react with isocyanates to form biuret derivatives[68] (SCHEME 47). If the silazane bears a proton rather than an alkyl group on Nitrogen, the initially-formed product reacts with a second molecule of iso-

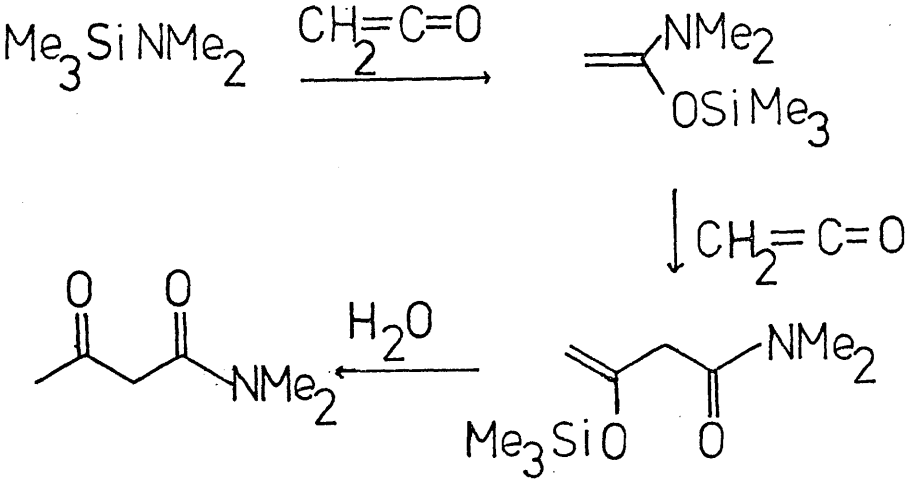


[26]

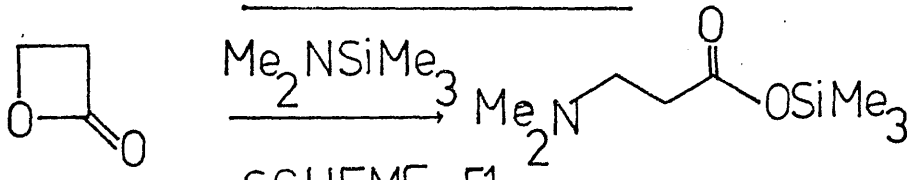
SCHEME 48



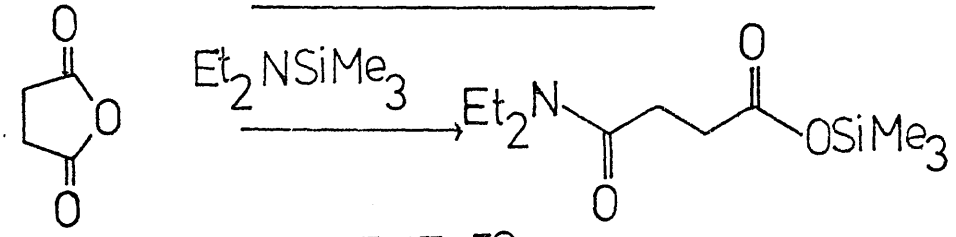
SCHEME 49



SCHEME 50



SCHEME 51



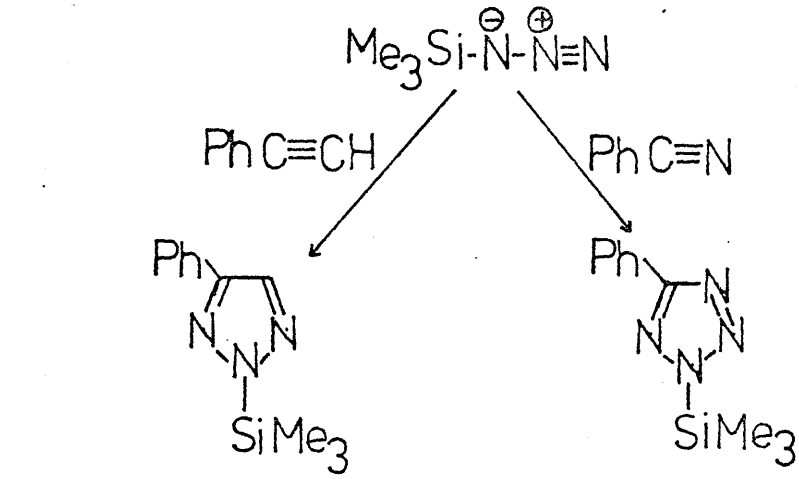
SCHEME 52

cyanate, and trimethylsilyl isocyanate is eliminated to give a symmetrical urea[69]. Di-vinyl-urea 26 was prepared in this way[70] (SCHEME 48).

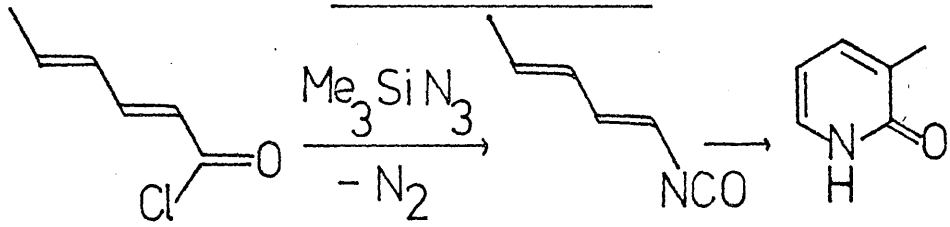
Silyl-amines react with cyanates to give derivatives of iso-ureas[71] (SCHEME 49), with ketenes to give β-keto-amides[72] (SCHEME 50), and with anhydrides to give mixtures of amides and trialkylsilyl esters[73] (SCHEME 51). Lactones react with silyl-amines to give ω-amino-esters[73] (SCHEME 52). The other possible product, an ω-siloxy- amide, is not observed; presumably, a four-centre mechanism operates, with reaction being initiated by nucleophilic attack of the ether Oxygen on Silicon.

Trimethylsilyl Azide.

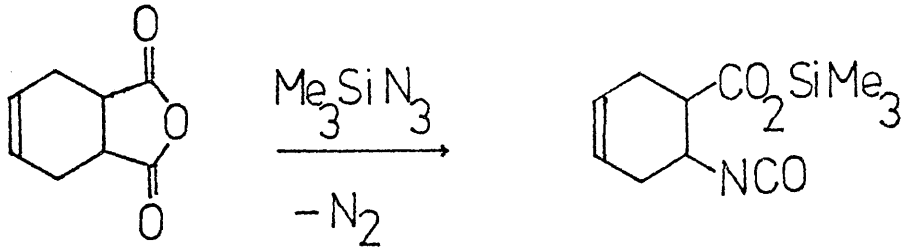
Trimethylsilyl azide is a useful reagent for a number of synthetic transformations[74]. It is more stable than most organic azides, probably because of $(p\rightarrow d)\pi$ - backbonding between Nitrogen and Silicon. The geometry of the molecule, as indicated by the Raman spectrum[75], seems to confirm the existence of this back-bonding. Because of its stability, trimethylsilyl azide is to be preferred to highly explosive hydrazoic acid in heterocyclic syntheses involving the azide grouping, the silyl group being easily removed hydrolytically after addition is complete. Many syntheses of 1,2,3-triazoles have been carried out using this reagent[76]. In the course of the addition, the silyl group migrates to the 2-position[77]. Trimethylsilyl azide is complementary to sodium azide in these syntheses, as it works poorly with alkynes containing electron-withdrawing substituents, and well with others, whereas sodium azide shows the opposite characteristics. Addition to nitriles



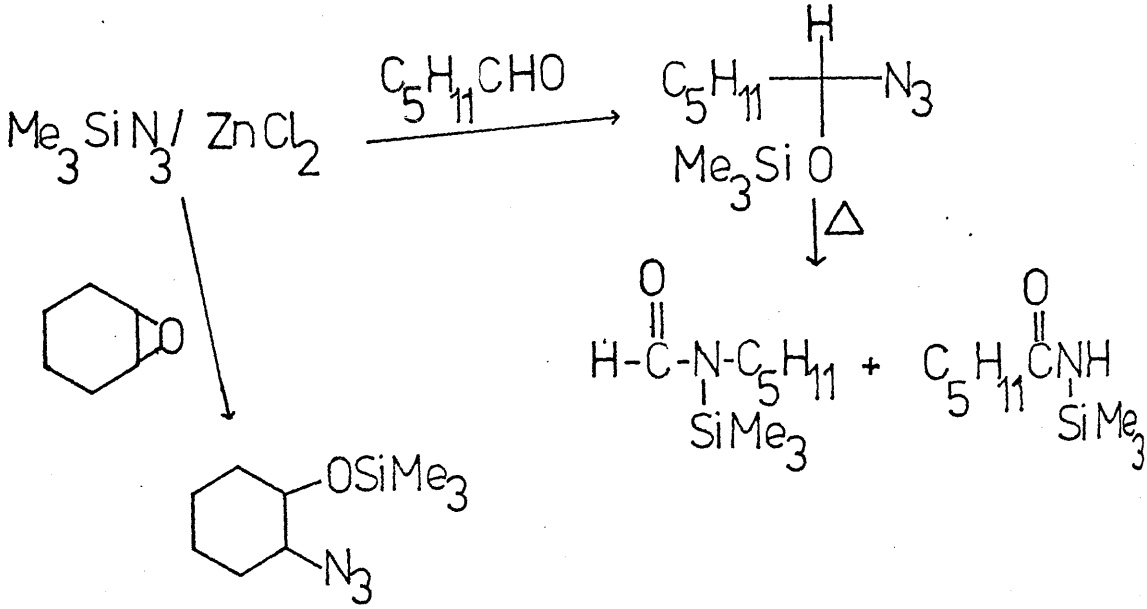
SCHEME 53



SCHEME 54



SCHEME 55



SCHEME 56

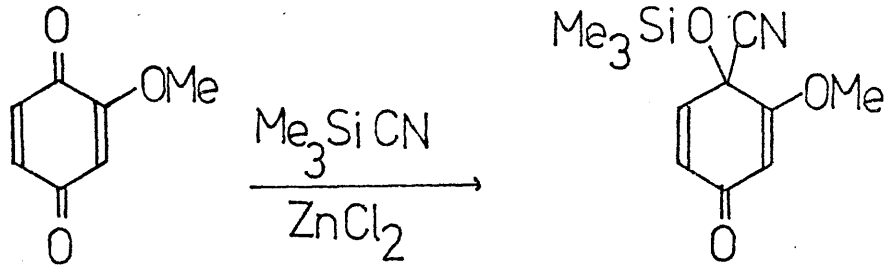
gives tetrazoles, once again with accompanying migration of the silyl group[78] (SCHEME 53). Addition of trimethylsilyl azide to alkenes proceeds slowly.[78]

Trimethylsilyl azide is a useful reagent for the preparation of acid azides, intermediates in the synthesis of isocyanates by the Curtius rearrangement. This method has been used to prepare perfluoroalkyl isocyanates[79], long-chain aliphatic isocyanates[80], and cyclopropyl isocyanates[81]. An interesting synthesis of 2-pyridones *via* a conjugated isocyanate has been described[82] (SCHEME 54). Anhydrides also react with trimethylsilyl azide[83] (SCHEME 55).

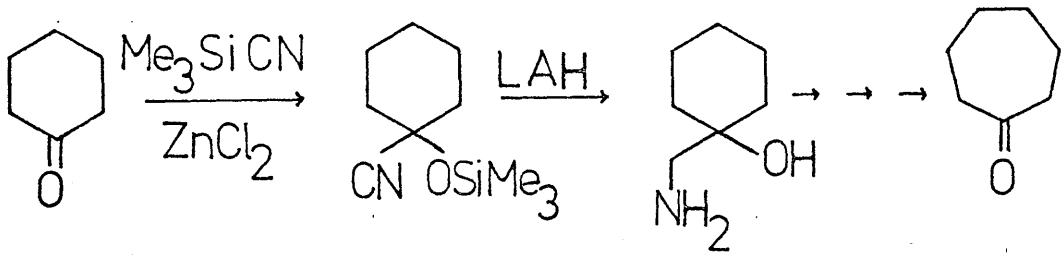
Trimethylsilyl azide reacts with aldehydes in the presence of zinc chloride to form α-trimethylsiloxyalkyl azides, which lose Nitrogen on heating to form amides[84]. However, straight-chain aldehydes give adducts which, on heating, give a mixture of isomeric amides. Epoxides react with trimethylsilyl azide in a similar manner.[85] (SCHEME 56)

Trimethylsilyl cyanide.

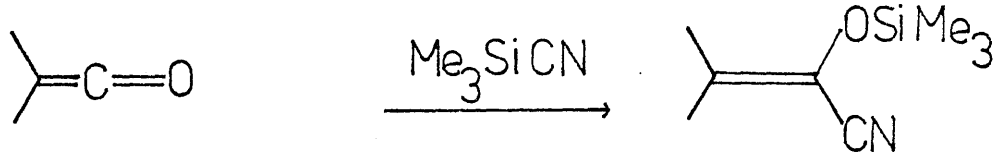
Trimethylsilyl cyanide has been the subject of study by several groups of workers in recent years. The reagent can be used to protect carbonyl functions, with which it reacts under the influence of Lewis acid catalysts.[86-88] The reaction proceeds even with carbonyl compounds which do not form a cyanohydrin derivative. The carbonyl group is regenerated on hydrolysis. Of particular interest is the selective protection of one carbonyl function of *para*-quinones[89]. With unsymmetrical quinones, the site of attack is determined by the relative electrophilicity of the two carbonyl groups (SCHEME 57).



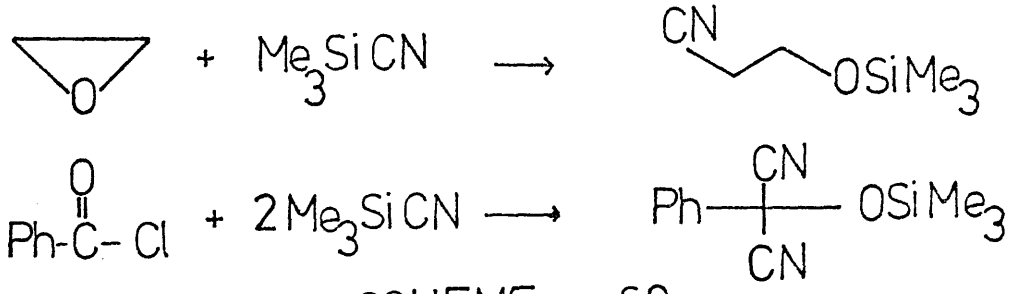
SCHEME 57



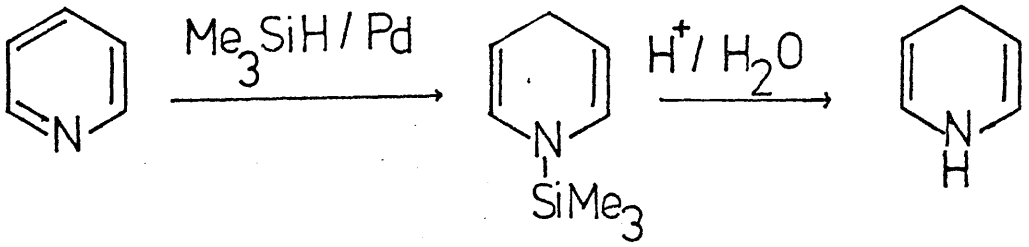
SCHEME 58



SCHEME 59



SCHEME 60



SCHEME 61

The trimethylsilyl cyanohydrins of aldehydes and ketones can be used for further transformations as well as for simple protection of the carbonyl function. For example, reduction with lithium aluminium hydride leads to the β-amino alcohols (SCHEME 58). This is a useful route to these compounds, which can be converted to the ring-expanded ketones[90]. The sequence is equally applicable to α,β-unsaturated ketones, which are difficult to convert to β-amino-alcohols by other routes, because of conjugate addition. Addition of trimethylsilyl cyanide to α,β-unsaturated aldehydes and ketones gives 1,2 adducts only.

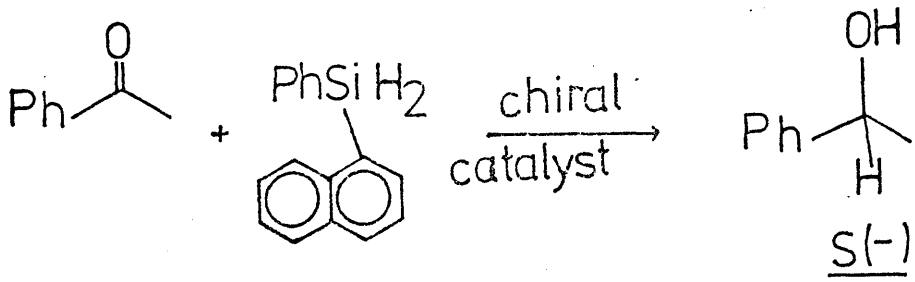
Trimethylsilyl cyanide also adds in 1,2 fashion to ketenes, which normally undergo 2,3-addition only[91]. (SCHEME 59). No synthetic applications of the product ketene cyanohydrins have yet been reported.

Trimethylsilyl cyanide reacts with epoxides to give β-trimethylsiloxy nitriles, and with acyl halides to give 1-trimethylsiloxy-1,1-dicyano-alkanes[92] (SCHEME 60).

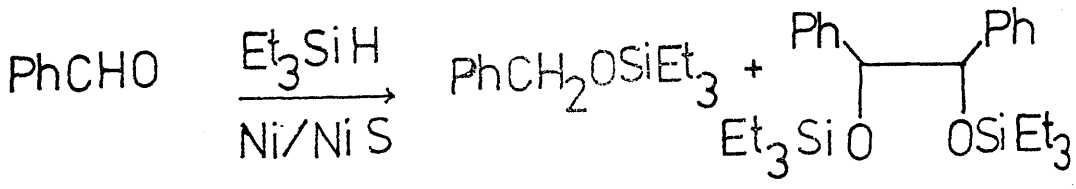
Reactivity of the Silicon-Hydrogen bond.

Processes involving cleavage of the Silicon-Hydrogen bond have been studied extensively. Transition-metal catalysed addition of silanes to unsaturated systems is used to prepare vinyl-silanes and allyl-silanes[93]. Pyridines are reduced by trialkylsilanes to give 1-trialkylsilyl-1,4-dihydro-pyridine derivatives, which can be converted to the parent 1,4- dihydro-pyridines by controlled hydrolysis[94] (SCHEME 61).

Carbonyl compounds are reduced by trialkylsilanes in the presence of transition-metal catalysts. Acyl halides



SCHEME 65



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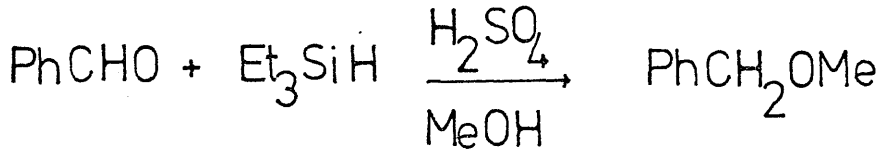
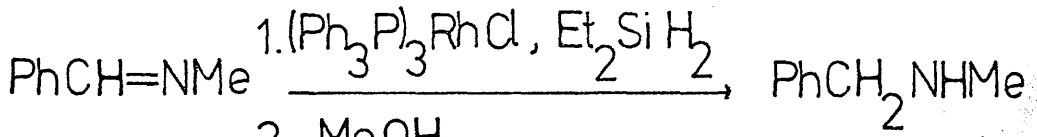


SCHEME 67



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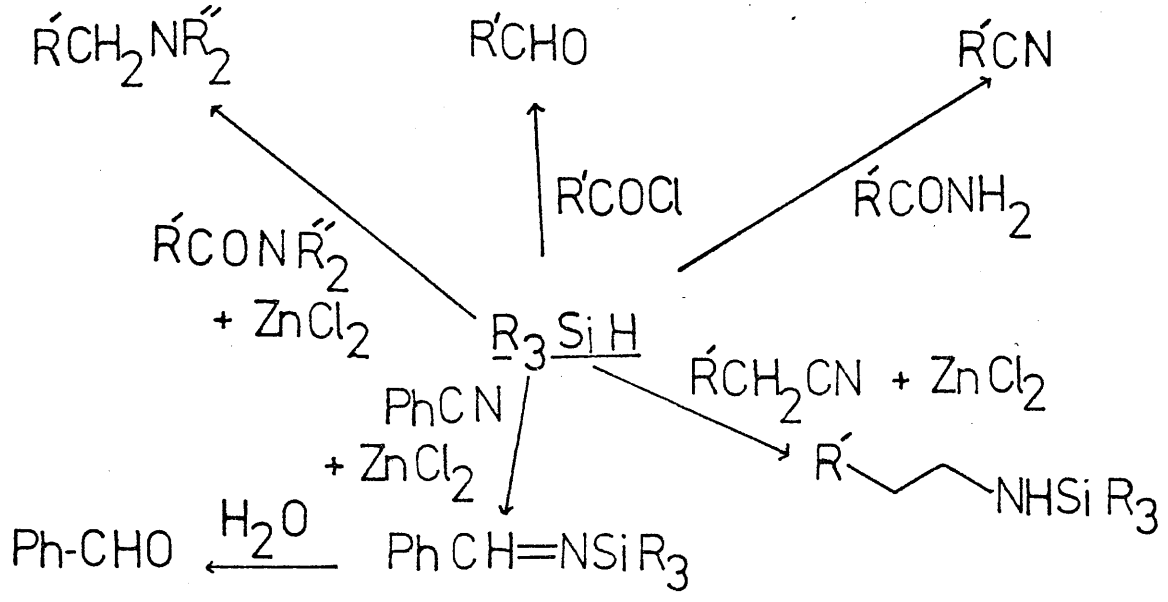
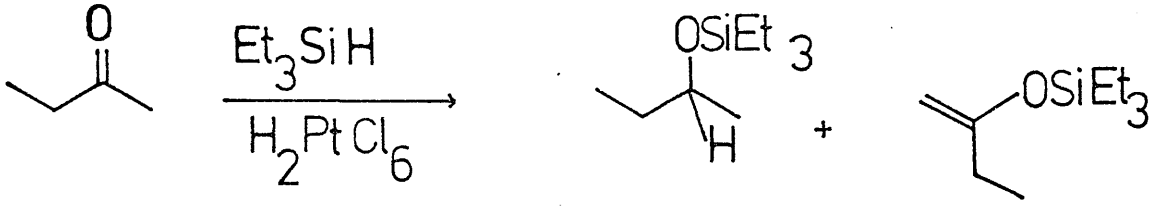
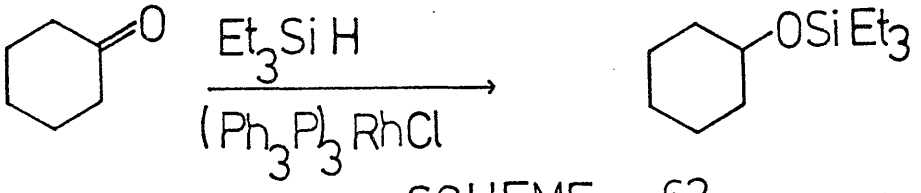
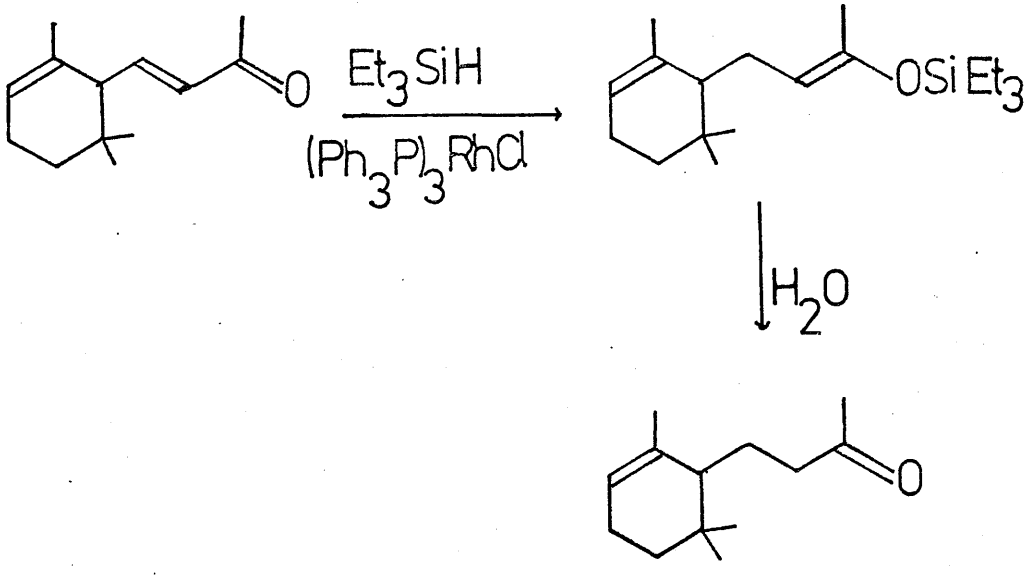


SCHEME 62





SCHEME 63



SCHEME 64

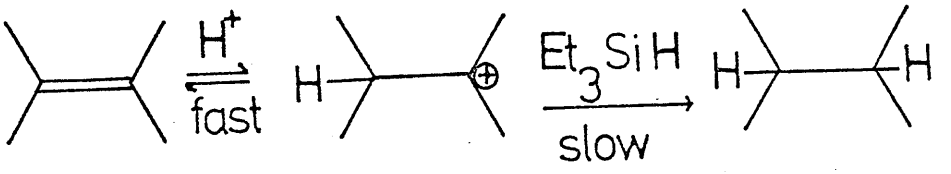
are reduced to aldehydes[95], secondary and tertiary amides are reduced to amines[96], while primary amides are dehydrated to nitriles[97]. Under suitable conditions, nitriles are also reduced[98]: aliphatic nitriles are converted to N-silyl amines, while aromatic nitriles are converted to N-silyl imines, which give aldehydes on hydrolysis (SCHEME 62).

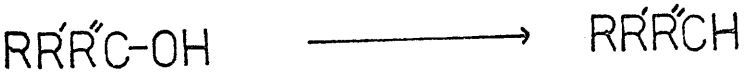
Ketones are reduced by trialkylsilanes in the presence of transition-metal catalysts. Saturated ketones give the trialkylsilyl ether of the corresponding alcohol[99], although, under certain conditions, the trialkylsilyl enol ether of the starting ketone is formed[100] (SCHEME 63); α,β-unsaturated ketones are selectively reduced to saturated ketones[101] (SCHEME 64). More highly-conjugated ketones, however, give mixtures of products.

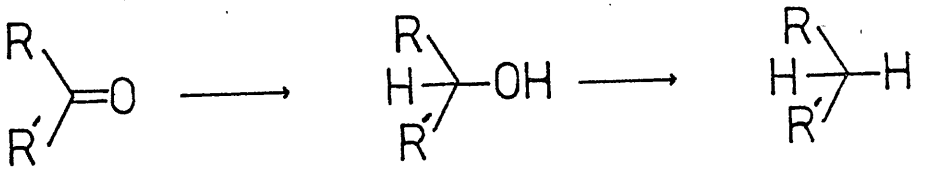
The best catalysts for these reductions seem to be Rhodium chloride-Phosphine complexes[99]. Polymer-supported chiral phosphines have been used to prepare insoluble chiral catalysts[102]. In conjunction with silanes containing bulky substituents, such catalysts effect chiral reduction of ketones. For example, acetophenone can be converted to S(-) 1-phenyl-ethanol in 58% optical yield and quantitative chemical yield (SCHEME 65).

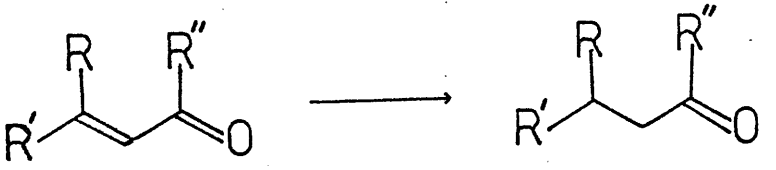
Aldehydes are reduced by silanes to alkoxy-silanes, although aromatic aldehydes can give dimeric products as well[103] (SCHEME 66). If the reduction is carried out in alcohol solution in the presence of an acid catalyst, the corresponding alkyl ether is formed directly[104] (SCHEME 67).

Schiff-bases are reduced to amines by silanes. this is reported to be the best method of reduction of such compounds[105] (SCHEME 68).









SCHEME 69

The use of polymeric siloxanes containing Si-H bonds in silane reductions has been described.[106]

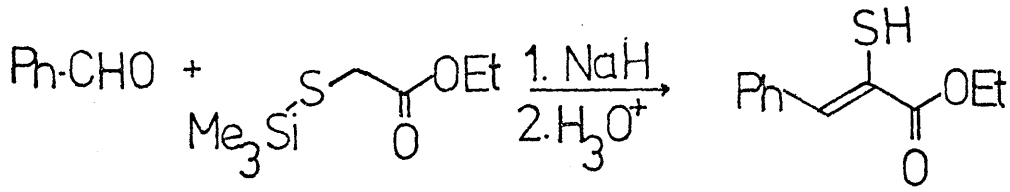
The recently-developed technique of ionic hydrogenation, using a mixture of a silane and a strong acid, provides a method of performing many selective reductions of functional groups which are often difficult to perform by conventional methods (SCHEME 69). The system commonly used is a mixture of triethylsilane and trifluoro-acetic acid. This field has recently been reviewed.[107]

The trialkylsilyl group as a protecting group.

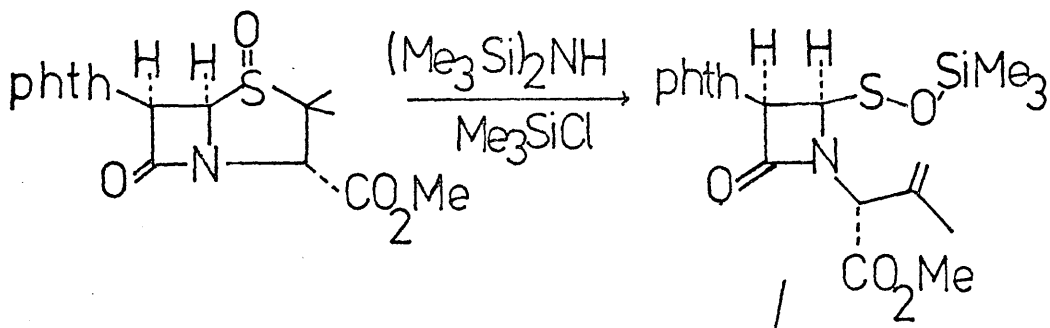
(a): Hydroxyl protection.

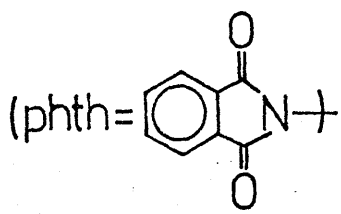
Trialkylsilyl substituents have been used as protecting groups for a number of functions, chiefly the hydroxyl function. Protection of hydroxyl groups as their trimethylsilyl ethers has been used in several natural product syntheses.[108-111] The susceptibility of this group to solvolysis limits its usefulness.

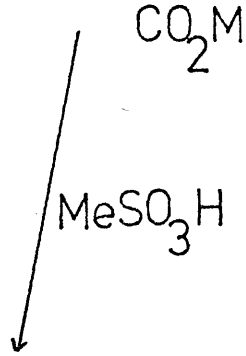
The t-butyl-dimethylsilyl ethers are approximately 10^4 times more stable than their trimethylsilyl analogues, and this group has been used in several synthetic schemes.[112-114] It is stable to aqueous or alcoholic base under the conditions normally used for ester saponification, it is stable to hydrogenolysis over palladium catalysts, and it resists mild reducing agents.[112] It is unaffected by hydrazine hydrate under the conditions used to remove β-benzoyl-propionyl or N-acyl groups,[114] and it can be removed efficiently by treatment with a quaternary ammonium fluoride without affecting acyl or trityl groups. The t-butyl-dimethylsilyl ethers have the advantage over

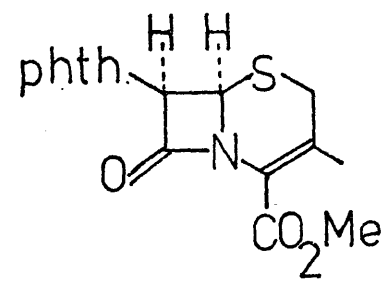


SCHEME 76

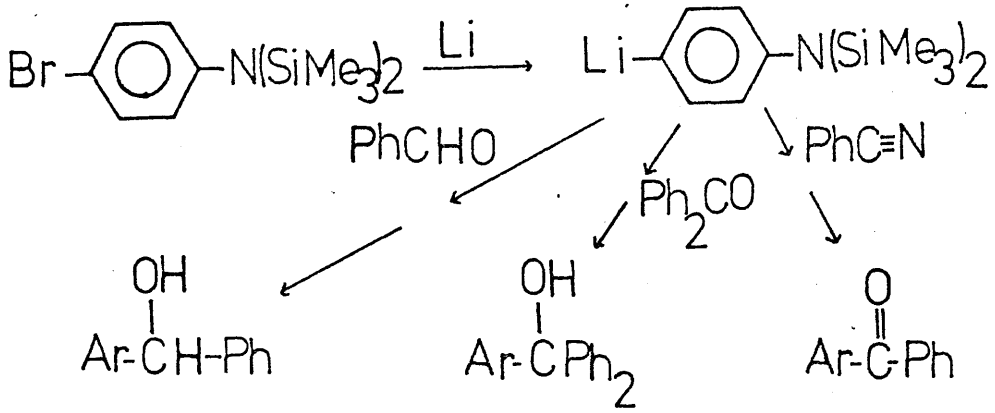


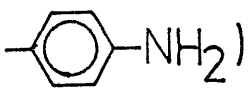






SCHEME 77



(Ar = 

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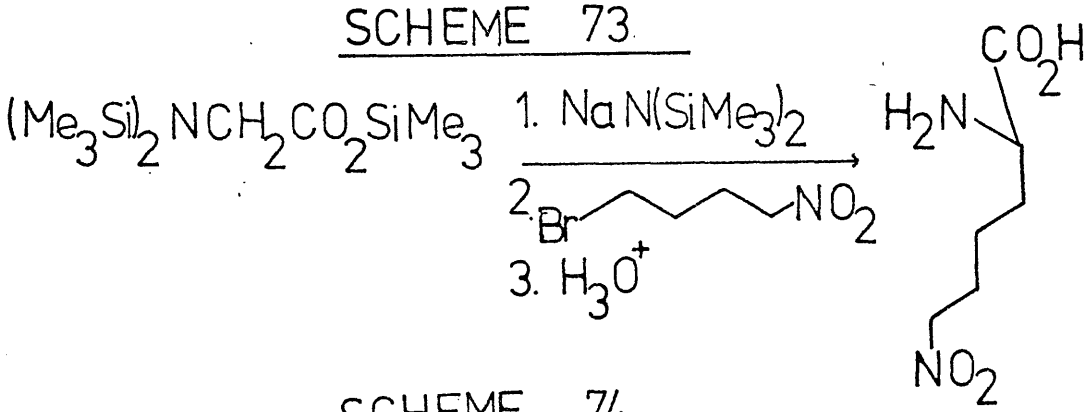
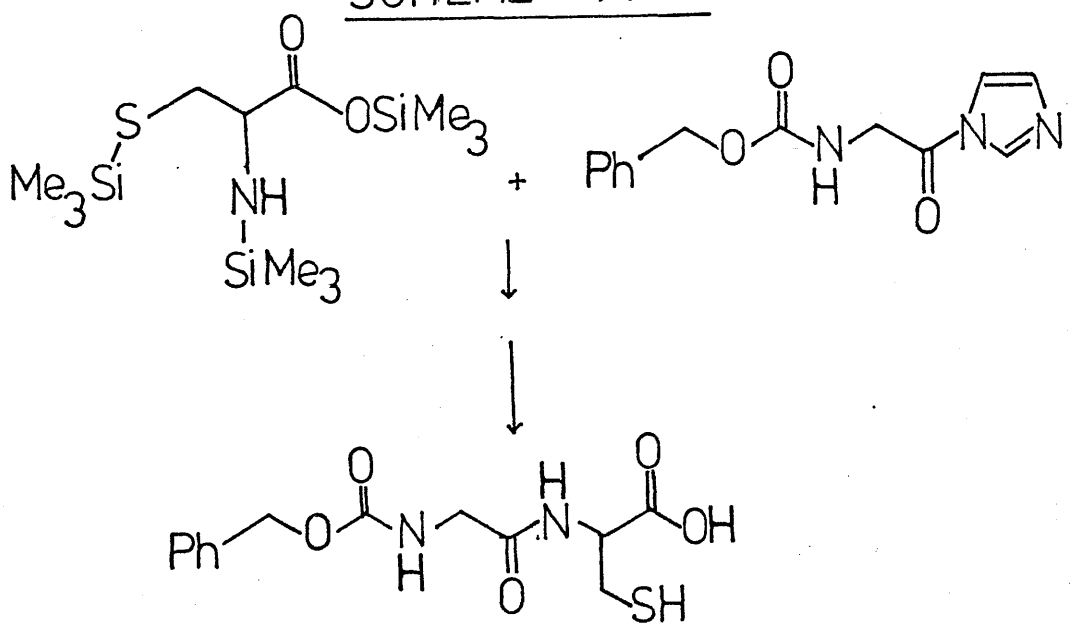
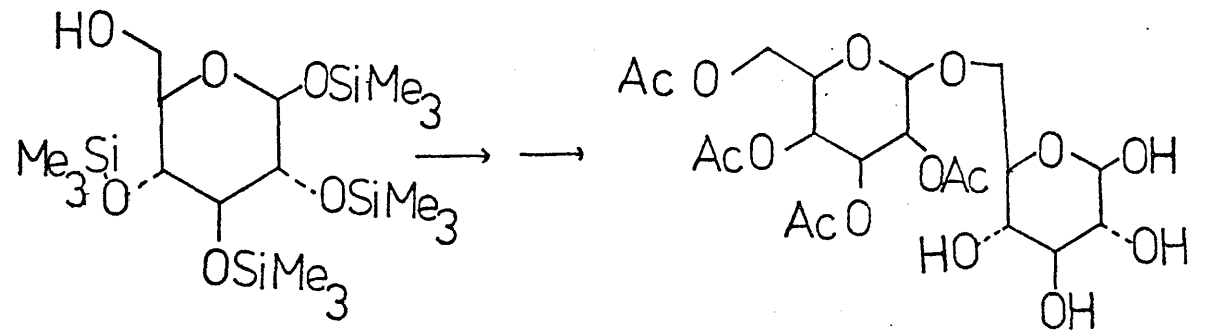
SCHEME 73



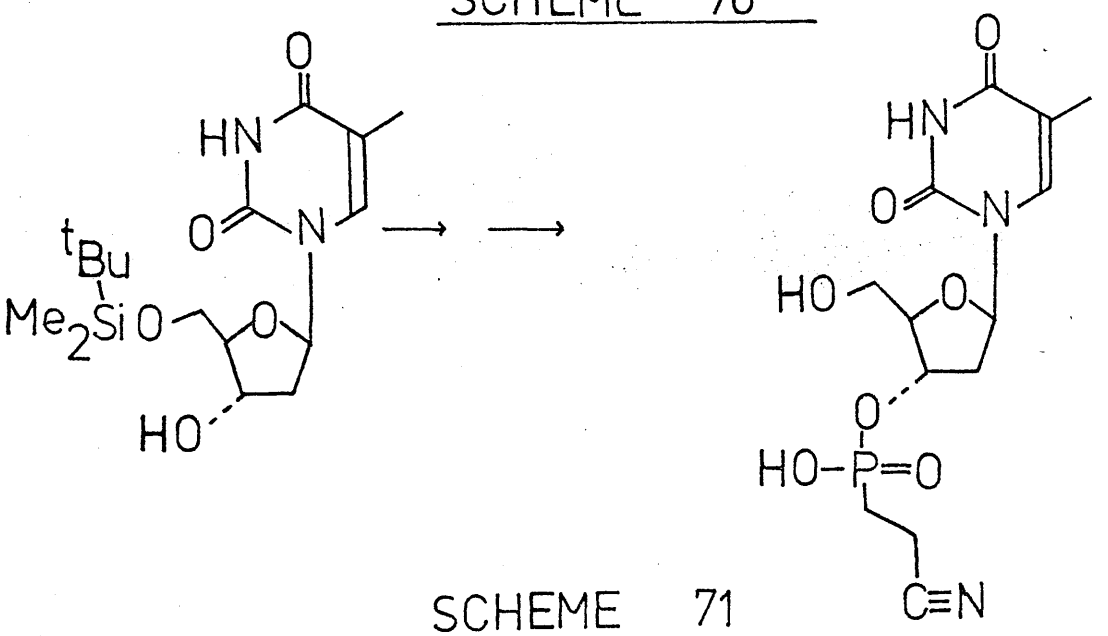
SCHEME 74



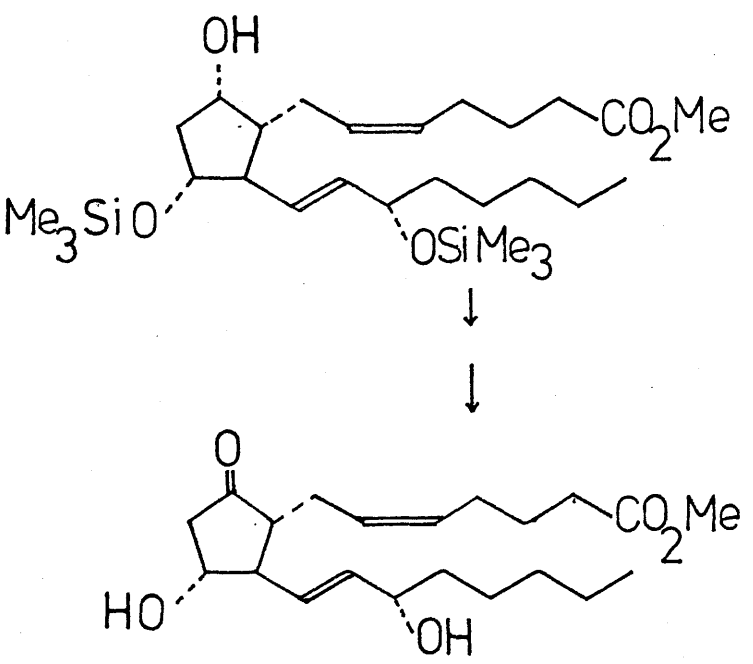
SCHEME 75



SCHEME 70



SCHEME 71



SCHEME 72

tetrahydropyranyl ethers that they do not possess a chiral centre, and therefore do not lead to mixtures of diastereomeric ethers. They are frequently crystalline derivatives. The group is easily introduced by treatment of the hydroxyl-containing compound with t-butyl-chloro-dimethylsilane in dimethyl-formamide solution in the presence of imidazole as catalyst.[112]

It is frequently possible to effect selective protection of one or more hydroxyl functions in poly-hydroxy- compounds. Applications of this technique include synthesis of disaccharides[115] (SCHEME 70), phosphorylation of nucleosides[114] (SCHEME 71), and interconversion of prostaglandin F and prostaglandin E derivatives[116] (SCHEME 72).

(b): Amine protection.

Protection of amine functions by silylation has been used in syntheses of amino-aryl compounds[117] (SCHEME 73) and alkylation of α-amino-acids[118] (SCHEME 74).

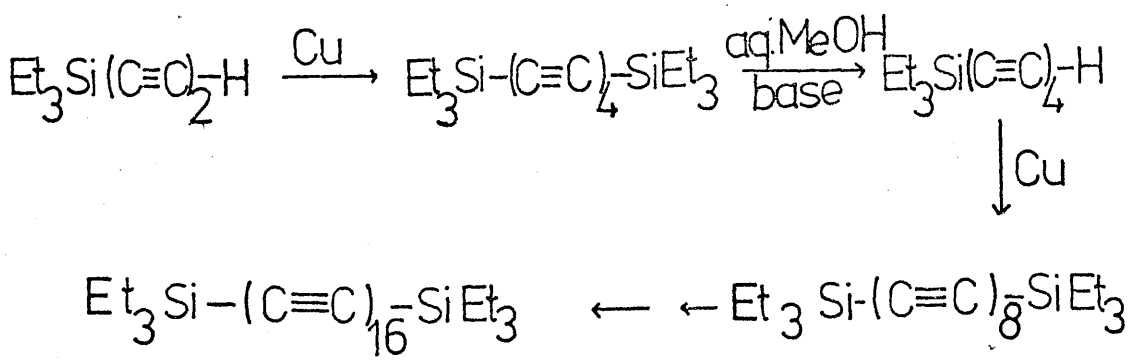
(c): Thiol protection.

Protection of the thiol function as the trialkyl-silyl thio-ether has been reported. This procedure was used in the synthesis of cysteine -containing peptides.[119] (SCHEME 75) and in the preparation of the hitherto-unknown α-thionic esters[120] (SCHEME 76).

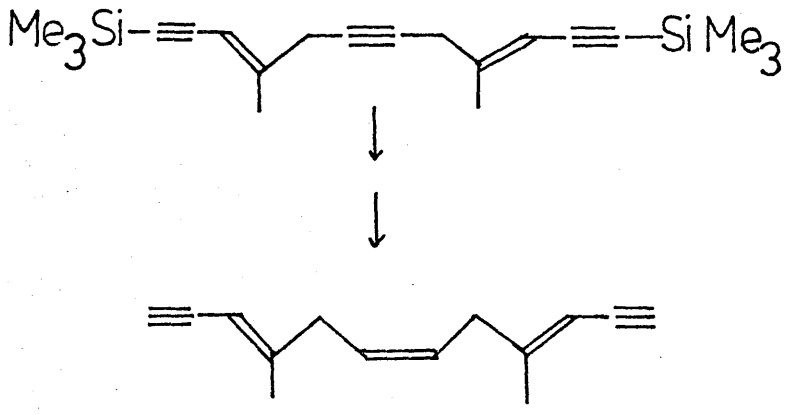
Trapping of the labile sulphenic acid function in the interconversion of penicillin and cephalosporin derivatives was effected by trimethylsilylation[121] (SCHEME 77).

(d): Carboxyl protection.

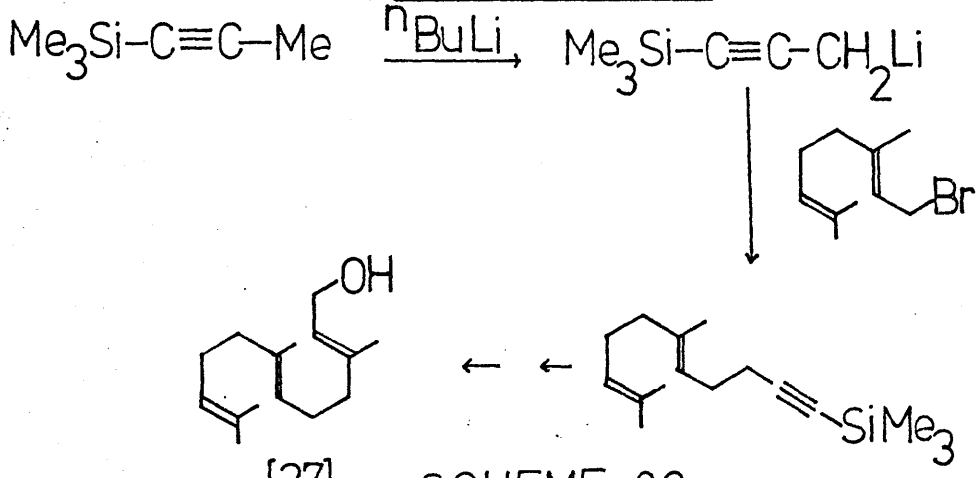
The use of trialkylsilyl esters as protected carboxylic acid functions has so far been limited by the extreme sensitivity of this group to solvolysis.[122]



SCHEME 78

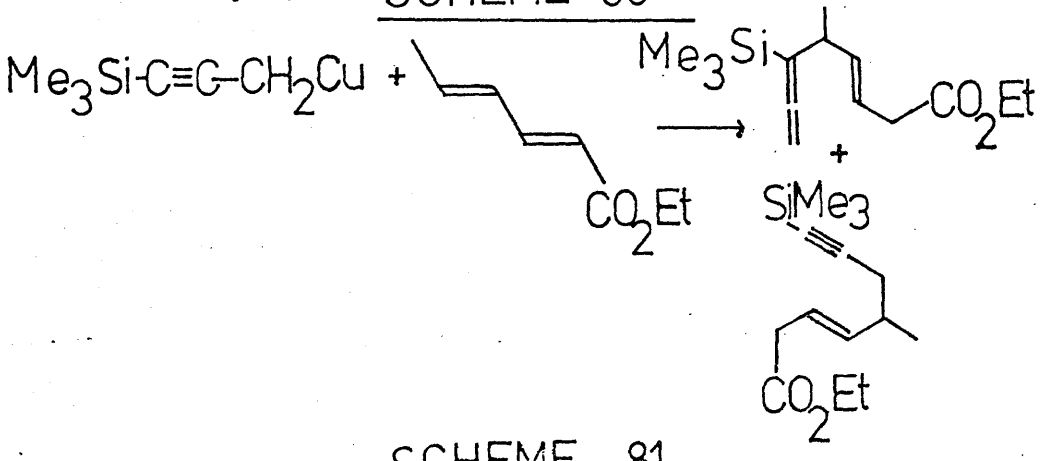


SCHEME 79



[27]

SCHEME 80



SCHEME 81

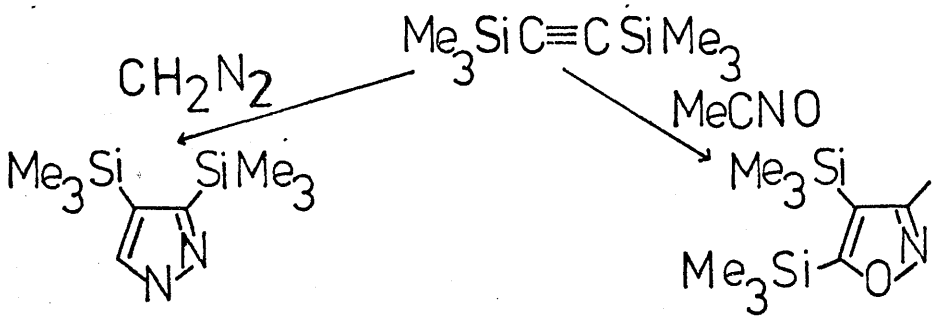
(e): Protection of terminal acetylenes.

Protection of terminal acetylenes by conversion to trialkylsilyl derivatives allows the controlled synthesis of poly-acetylenes by oxidative coupling. The trialkylsilyl group is removed by treatment with dilute methanolic alkali or with an ionic fluoride. This technique is now the standard method of poly-acetylene synthesis.[123] Selective removal of one trialkylsilyl group is possible, allowing repetition of the synthetic cycle (SCHEME 78).

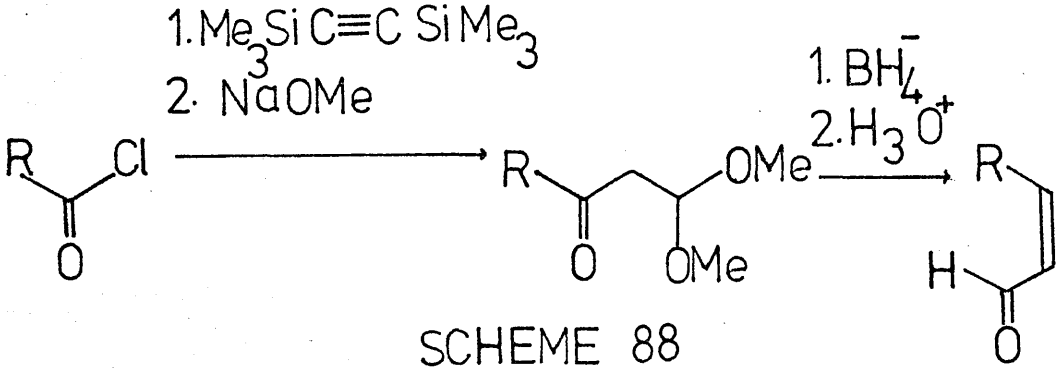
The trialkylsilyl group is introduced by reaction of alkynyl lithium or alkynyl magnesium bromide with chloro-trialkylsilane. Selective reduction of non-terminal triple bonds in poly-acetylenes is possible if the terminal acetylenes are first protected by silylation[124] (SCHEME 79).

1-Trialkylsilyl acetylenes can be metalated and alkylated by alkyl halides in the 3-position,[125] the trialkylsilyl substituent preventing alkylation in the 1-position, which would result in the formation of an allene. This process was used in a synthesis of trans, trans-farnesol[126] 27 (SCHEME 80). The α-lithiated acetylenes can be converted to the corresponding organo-copper reagents and coupled with $\alpha,\beta;\gamma,\delta$-unsaturated esters, to give mixtures of allenic and acetylenic products. The ratio of these components in the product mixture can be dramatically altered by using a bulky silyl substituent[127] (SCHEME 81).

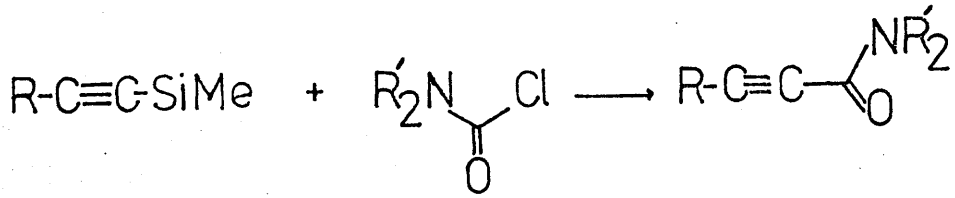
Synthesis of conjugated enynes can be accomplished[128] by Wittig reaction of an acetylenic ylid with aldehydes or ketones. The terminal acetylene is protected as the



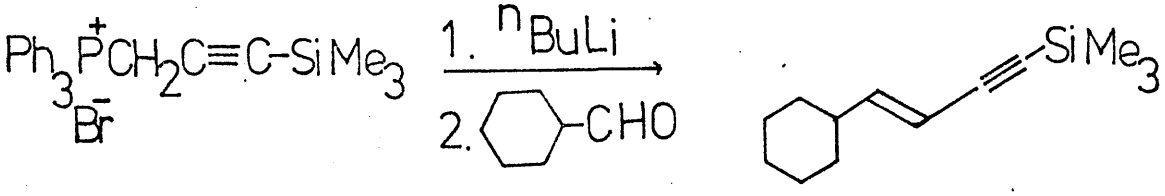
SCHEME 87



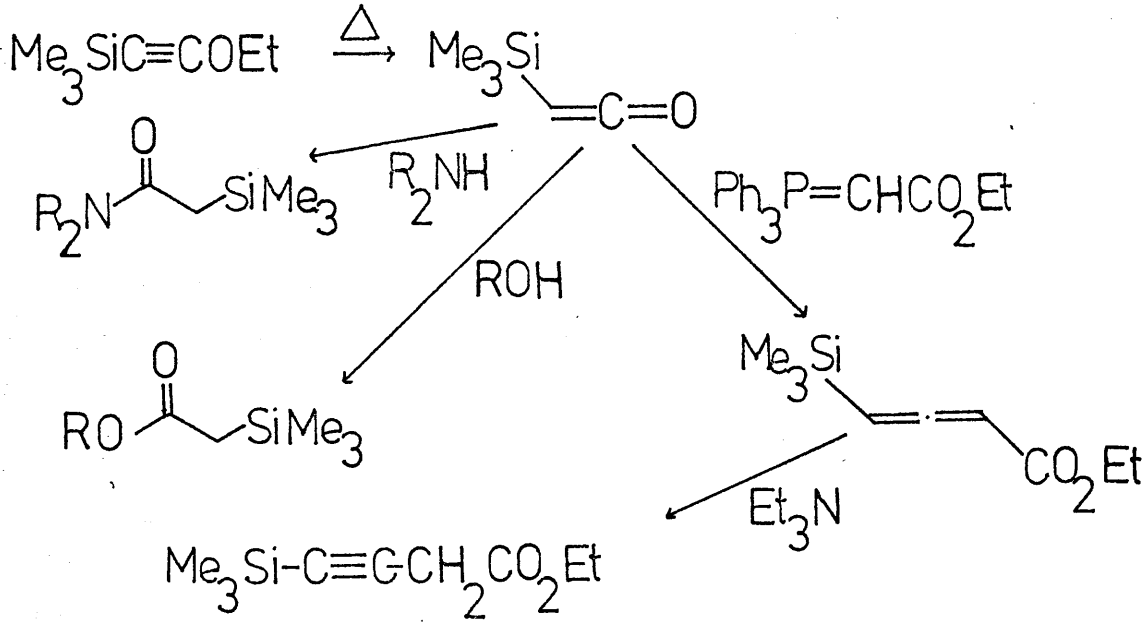
SCHEME 88



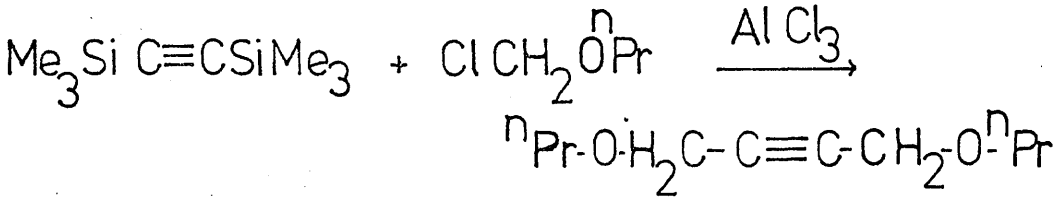
SCHEME 89



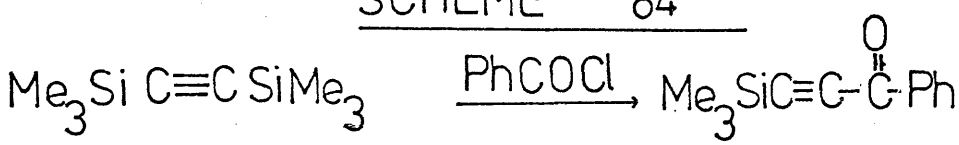
SCHEME 82



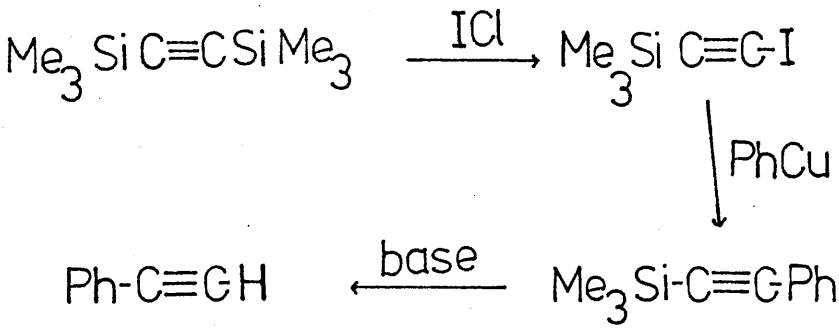
SCHEME 83



SCHEME 84



SCHEME 85



SCHEME 86

trimethylsilyl derivative (SCHEME 82).

1-Trimethylsilyl-2-ethoxy acetylene is converted on heating to trimethylsilyl-ketene. This compound serves as the starting point for the preparation of α-trimethylsilyl amides and esters, and α-acetylenic esters[129]. (SCHEME 83)

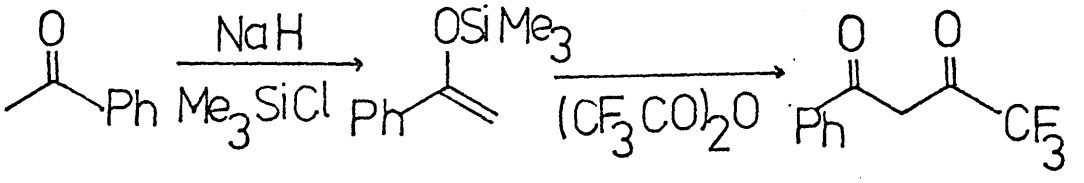
Bis-(trimethylsilyl)-acetylene is the starting point of many syntheses. Treatment with α-chloro-alkyl ethers in the presence of Lewis acids leads to di-alkoxy-acetylenes[130] (SCHEME 84). With acyl halides, only one silyl group is displaced, the introduction of the first acyl group deactivating the molecule towards further acylation[130] (SCHEME 85). Reaction with halogens proceeds similarly, with the introduction of only one halogen atom. This reaction is used in a general synthesis of terminal acetylenes[131] (SCHEME 86).

Bis-(trimethylsilyl)- acetylene undergoes 1,3-dipolar addition reactions to give silylated heterocycles. The trimethylsilyl groups can be removed by hydrolysis or displaced by electrophiles (SCHEME 87)[132,133].

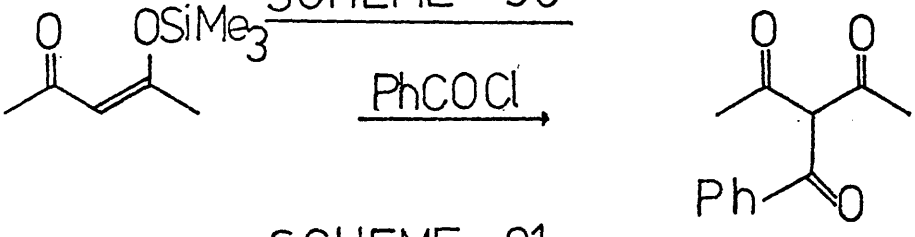
Bis-(trimethylsilyl)-acetylene is used in a conversion of acyl halides to α,β-unsaturated aldehydes[134] (SCHEME 88), while 1-trimethylsilyl-acetylenes react with carbamoyl halides to give acetylenic amides[135] (SCHEME 89).

(f): Trialkylsilyl-enol ethers.

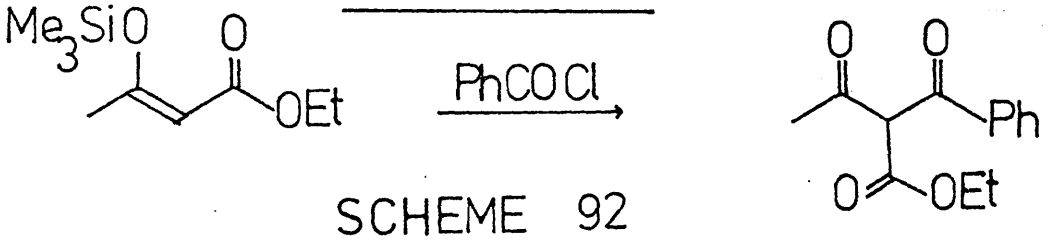
Reaction of enolisable ketones with sodium bis-(trimethylsilyl)-amide[136], or with strong bases followed by addition of chlorotrimethylsilane[63], or even, in some cases, with bis-(trimethylsilyl)-acetamide[137-138], leads to the trimethylsilyl ethers of the corresponding enols. These compounds are useful in a number of synthetic



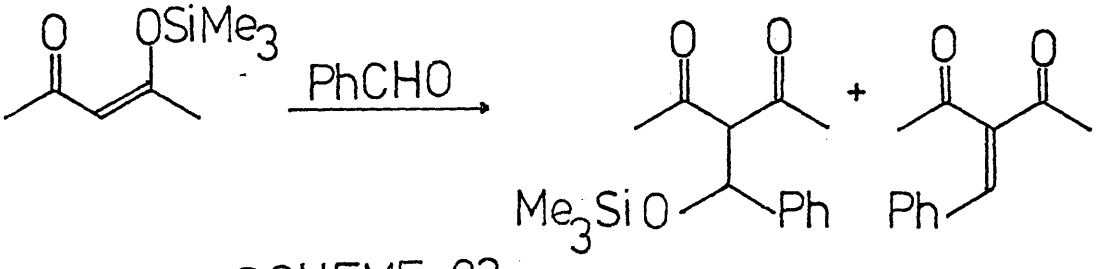
SCHEME 90



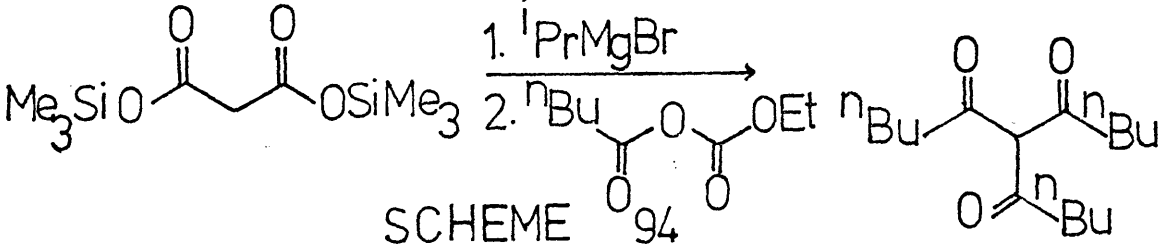
SCHEME 91



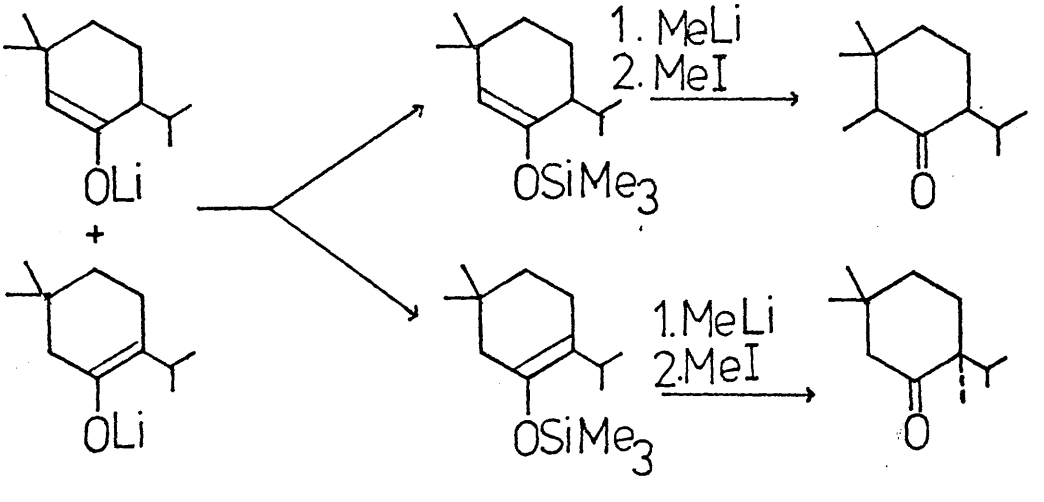
SCHEME 92



SCHEME 93



SCHEME 94

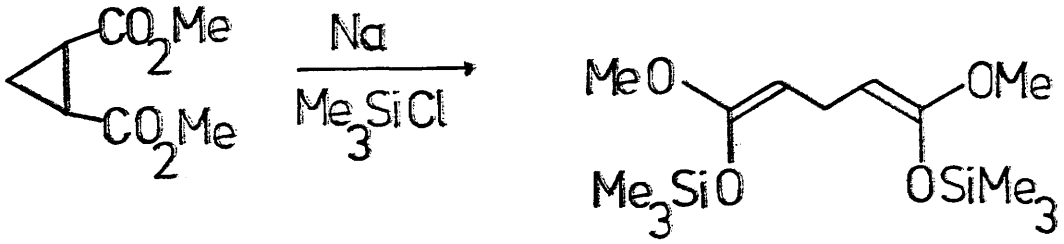


SCHEME 95

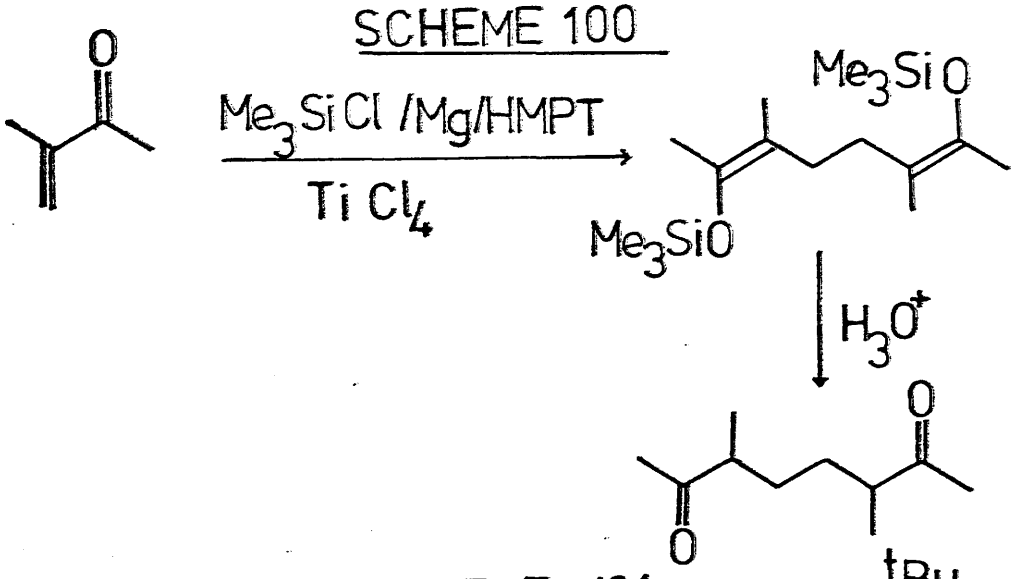
transformations. For example, they can be acylated to give β-diketones[139] (SCHEME 90). This scheme is applicable to a number of cases in which the alternative Claisen condensation is unsatisfactory. β-Diketones can be converted, via their trimethylsilyl enol ethers, to tri-ketones (SCHEME 91), and β-keto-esters can be similarly transformed to diketo-esters (SCHEME 92). Silyl enol ethers of β-diketones also react with aldehydes. In this case, however, the product retains the siloxy-grouping, and silanol elimination leads to mixtures of products (SCHEME 93).[140]

Trimethylsilyl esters of malonic acid exhibit markedly different behaviour from alkyl malonates in condensation reactions. A second condensation takes place, in the course of which decarboxylation and trimethylsilyl group cleavage occurs. This allows the preparation of diketo-esters, diketones and triketones from such compounds (SCHEME 94). Such processes have been used in the synthesis of poly-carbonyl compounds.[141-142]

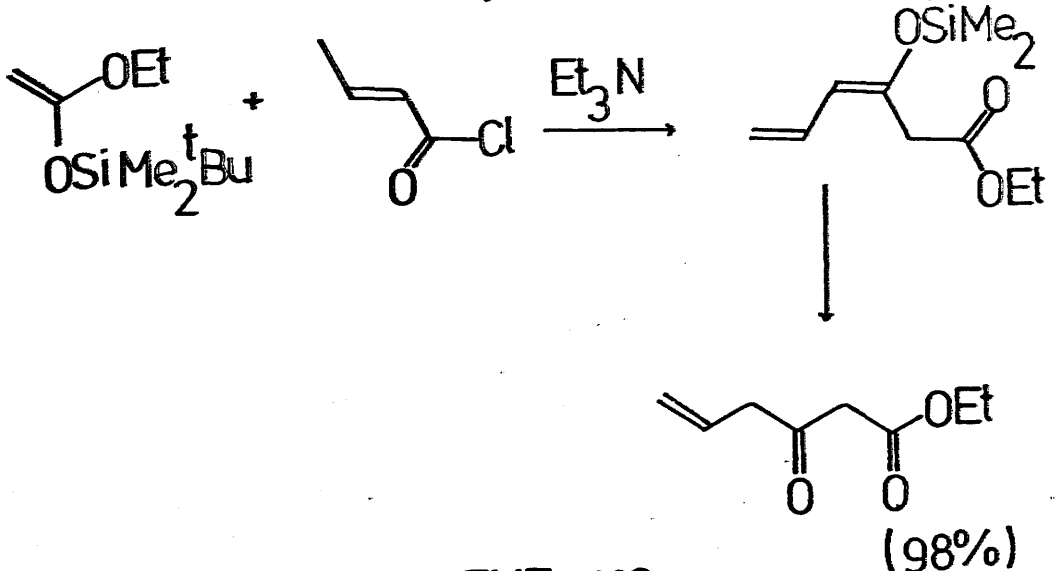
A special feature of silyl enol ethers is their regio-stability. Where a ketone can form two possible enolates, addition of a silylating agent to the mixture produces a mixture of the corresponding silyl enol ethers in the same ratio. These enol ethers show no tendency to interconvert and can usually be separated and purified.[143] Addition of an alkyl lithium regenerates the original enolates which are also regio-stable under aprotic conditions. This procedure thus allows the generation of a specific lithium enolate, and, in consequence, alkylation of ketones at a specific site[144] (SCHEME 95).



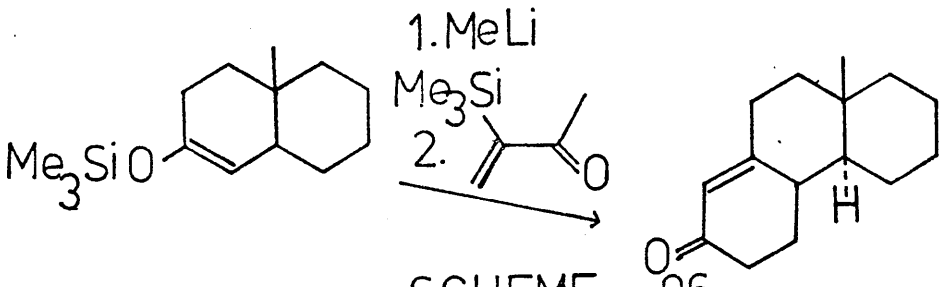
SCHEME 100



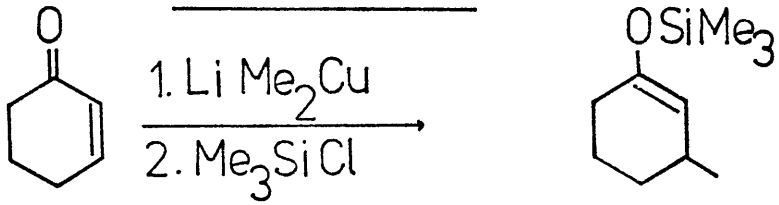
SCHEME 101



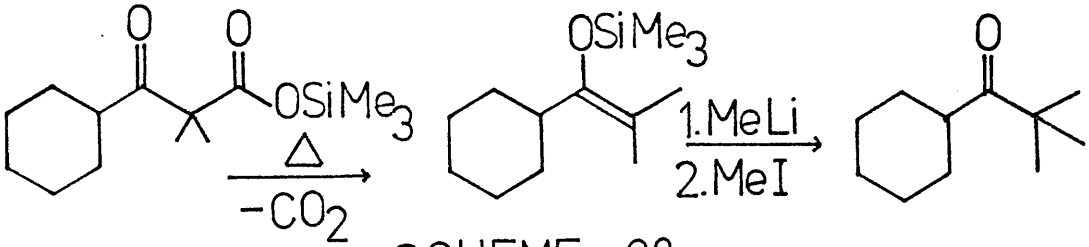
SCHEME 102



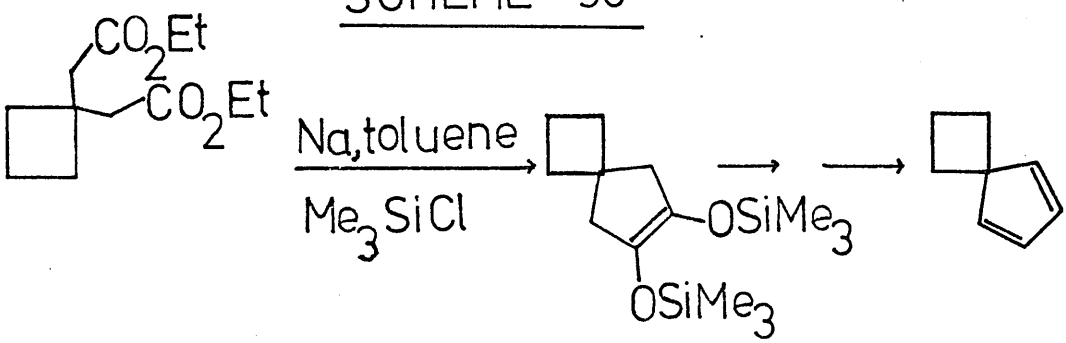
SCHEME 96

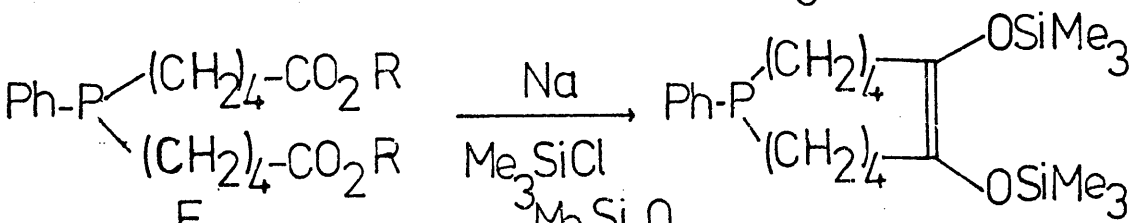


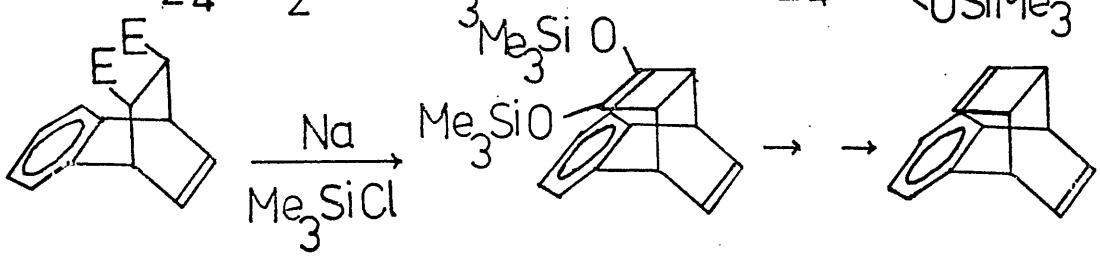
SCHEME 97



SCHEME 98







(E= $-CO_2Me$)

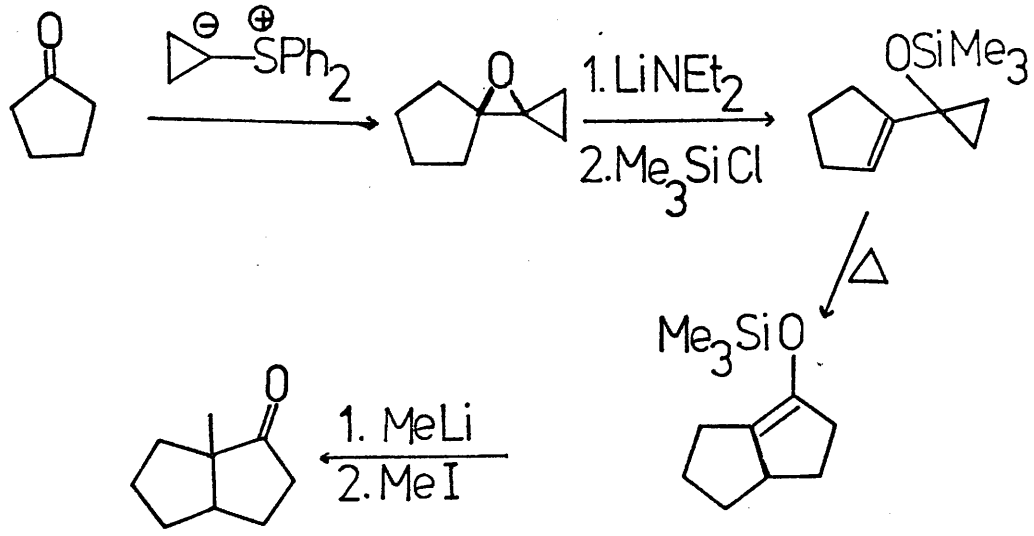
SCHEME 99

The trapping of the enolate(s) by chlorotrimethylsilane allows purification and spectral identification of the enolate before proceeding with the synthetic scheme. This was used to advantage in a modification of the Robinson annelation procedure[145] (SCHEME 96). In the case of alkylation of enones, the enolate resulting from 1,4-addition of organo-copper reagents can be trapped directly with chlorotrimethylsilane (SCHEME 97)[146].

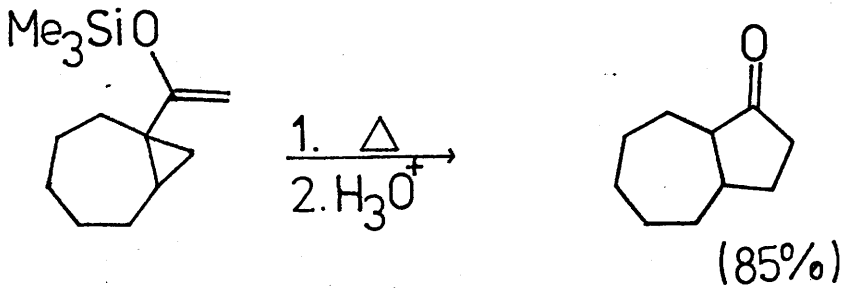
A useful synthesis of α-quaternary ketones makes use of a trimethylsilyl enol ether generated regiospecifically by silatropic rearrangement of a β-keto-trimethylsilyl ester (SCHEME 98)[147].

The enolate intermediates formed in the acyloin condensation can be trapped by chlorotrimethylsilane, thus preventing the alternative condensation and polymerisation reactions which often complicate the synthesis of α-hydroxy-ketones by this method. The resulting bis-(trimethylsiloxy)-cycloalkenes are easily hydrolysed to the parent acyloins. This modification has been used in many syntheses of cyclic compounds[148-153] (SCHEME 99), although some cyclic 1,2-di-esters give ring-cleavage products[154] (SCHEME 100). A related process has been used to prepare ε-diketones (SCHEME 101)[155].

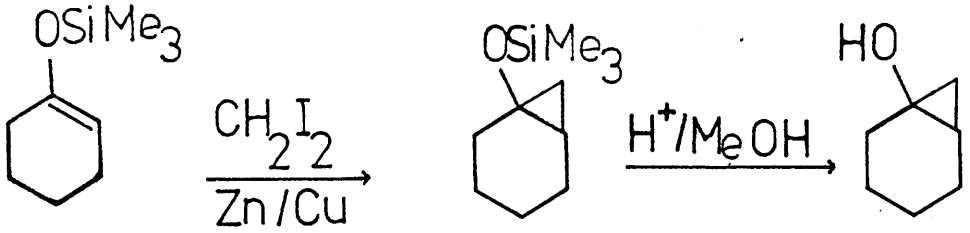
The t-butyl-dimethylsilyl enol ethers of esters (ketene acetals) have been prepared by reaction of the lithium ester enolates with t-butyl-chloro-dimethylsilane. These compounds can be acylated to give, on hydrolysis, β-keto-esters. The mechanism involves the formation of a ketene, since the reaction proceeds sluggishly in the absence of triethylamine (SCHEME 102)[156].



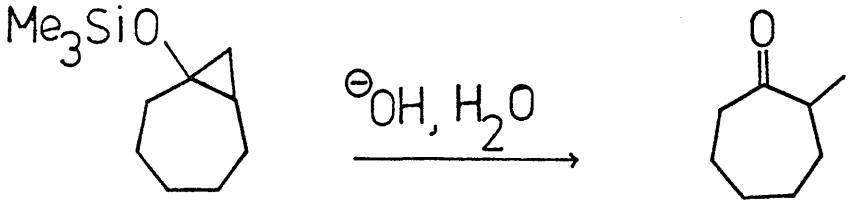
SCHEME 107



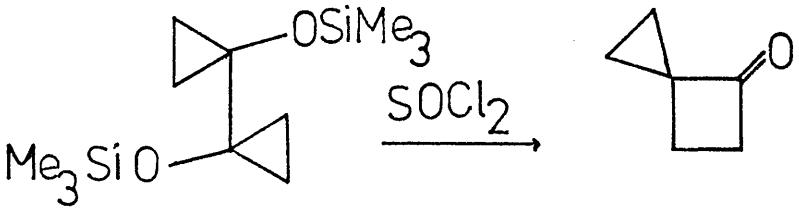
SCHEME 108



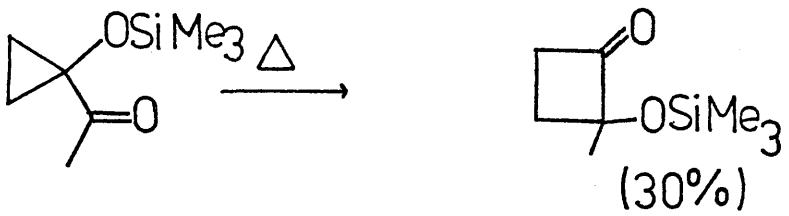
SCHEME 103

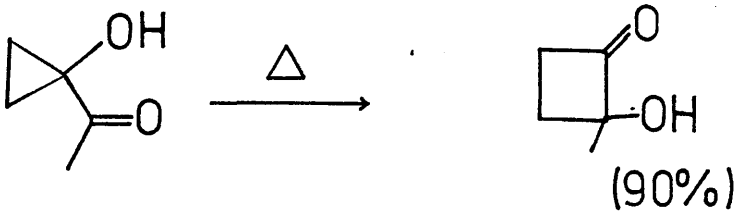


SCHEME 104



SCHEME 105





SCHEME 106

Trimethylsilyl enol ethers react readily with the Simmons-Smith reagent to give α-trimethylsiloxy-cyclopropanes, which are easily hydrolysed to cyclopropanols.[157-159] (SCHEME 103). The intermediate α-trimethylsiloxy-cyclopropanes can also be converted to α-methyl ketones[160, 161] (SCHEME 104). The overall process thus provides a method for the α-monomethylation of ketones and aldehydes. The α-trimethylsiloxy-cyclopropanes undergo a series of rearrangements to give cyclobutanones (SCHEME 105).[162] It has been demonstrated that this rearrangement is not confined to α-trimethylsiloxy-cyclopropanes, but is a general property of cyclopropanes bearing an electron-donor atom on a cyclopropyl carbon, and an electron-accepting substituent on the same carbon atom (SCHEME 106).[163] An alternative rearrangement can occur if the siloxy-cyclopropane bears a vinyl-substituent in the 1-position.[164,165] The product in this case is a cyclopentanone, and this rearrangement has been used in a cyclopentane annelation procedure. The procedure also allows specific alkylation of the product enol ether if desired (SCHEME 107). The trimethylsilyl enol ethers of cyclopropyl ketones also rearrange to cyclopentanones (SCHEME 108).[166]

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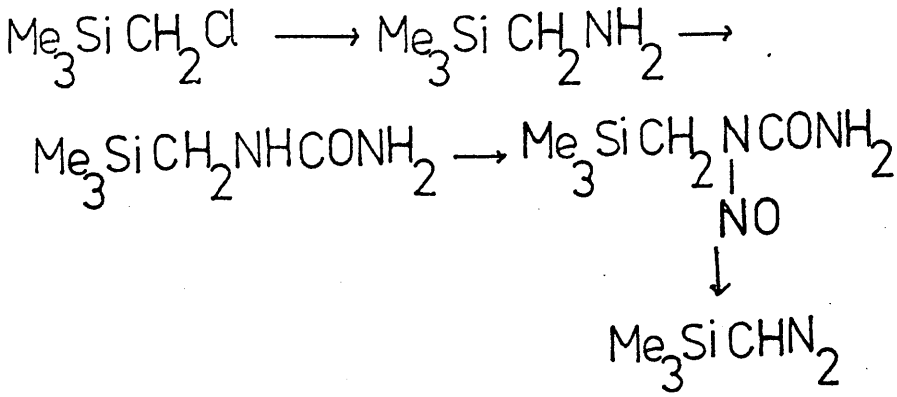
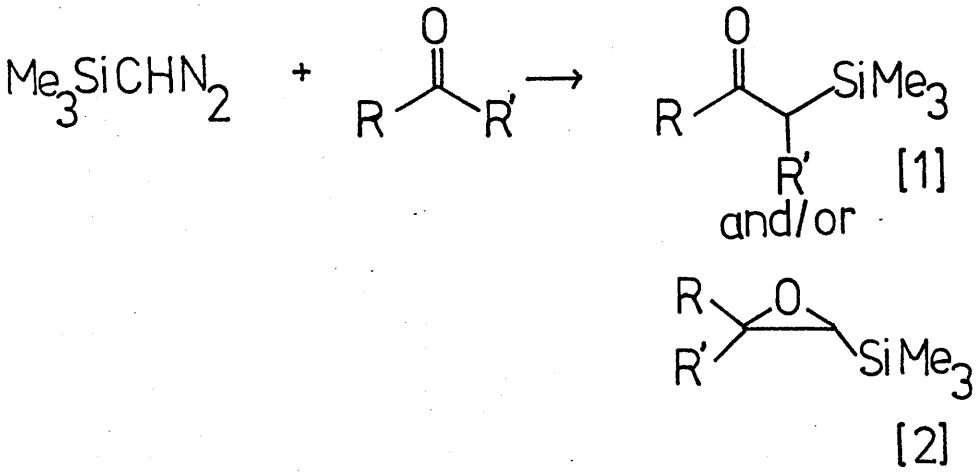
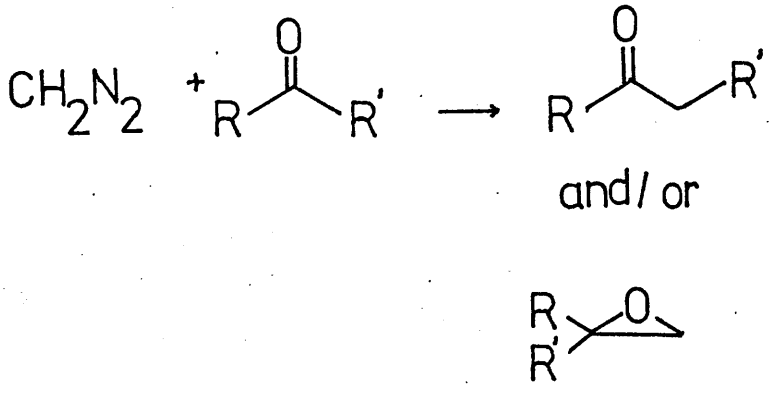
DISCUSSION.



SCHEME 1



SCHEME 2



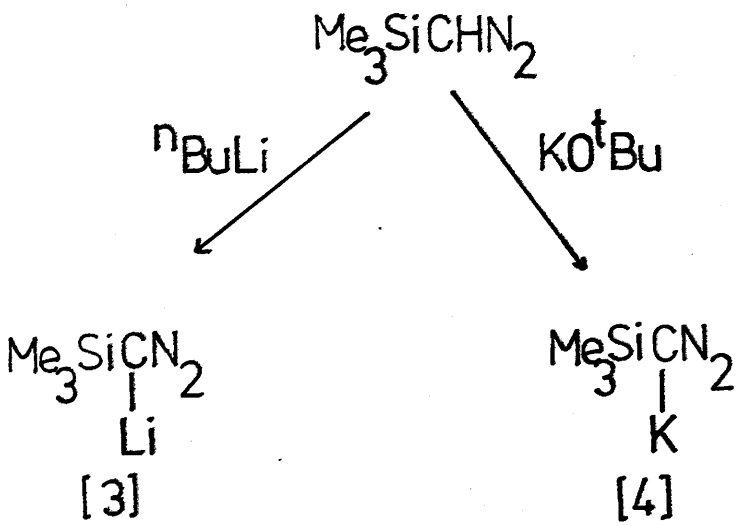
SCHEME 3

The preparation of trimethylsilyldiazomethane, reported by Seyferth[1], (SCHEME 1) coupled with increasing interest in the synthetic utility of organosilicon compunds, prompted an investigation of the properties of this reagent. It was thought possible that reaction of this diazoalkane with ketones might provide a route to β-keto-silanes 1 or α-silyl-oxiranes 2, useful intermediates for the synthesis of trisubstituted alkenes[2] and aldehydes[3] respectively (SCHEME 2), by analogy with the well-known reaction of diazomethane itself with carbonyl compounds[4] (SCHEME 3).

However, reaction of trimethylsilyldiazomethane with cyclohexanone, under a variety of conditions, yielded no β-keto-silane or α-silyl-oxirane, starting material being recovered unchanged. Addition of Lewis acid catalysts, which has been shown to be effective in promoting reaction of diazoalkanes[5] and diazo-esters[6] with carbonyl compounds, had no effect in this case.

Attempts were therefore made to promote reaction of trimethylsilyldiazomethane with cyclohexanone by the use of basic condensing agents. The presence of the silyl substituent should facilitate the removal of a proton from the methine carbon by allowing stabilisation of the resultant carbanion by (p→d) π-backbonding between carbon and silicon[7].

No reaction, other than decomposition of the diazoalkane, was observed when a mixture of trimethylsilyldiazomethane and cyclohexanone in benzene was stirred vigorously with aqueous potassium hydroxide solution.

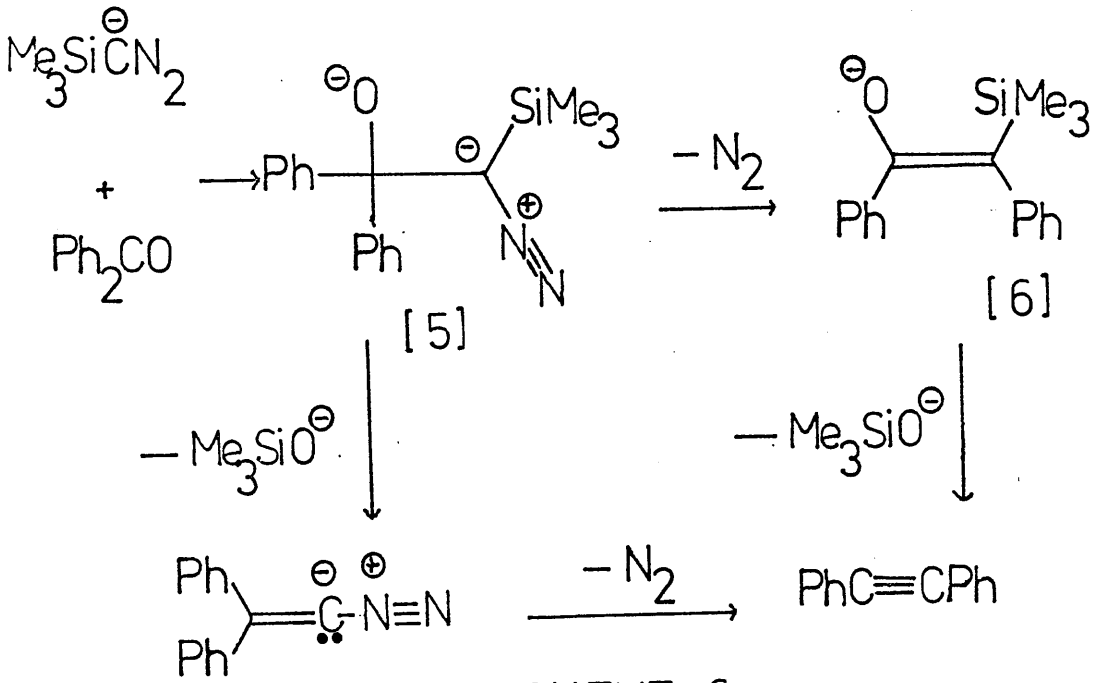


SCHEME 4

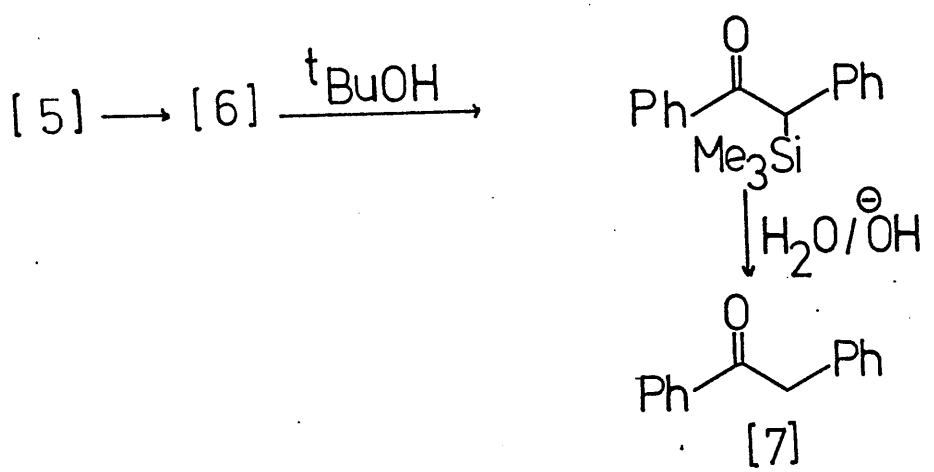
SCHEME 5

Treatment of trimethylsilyldiazomethane with n-butyl lithium, carried out at 0° in benzene solution, resulted in the formation of a white solid, presumably the lithium salt 3 . Similarly, trimethylsilyldiazomethane could be converted to its potassium salt 4 by treatment with potassium t-butoxide (SCHEME 4). Neither of these salts, however, reacted with cyclohexanone, possibly because the methine proton in trimethylsilyldiazomethane is less acidic than the methylene protons α to the carbonyl group in cyclohexanone, in which case the preferred process might be simple proton-exchange between reagent and substrate. To overcome this difficulty, a non-enolisable ketone, benzophenone, was selected for further experiments.

Benzophenone did not react with trimethylsilyldiazomethane alone, and Lewis acids were ineffective in promoting condensation. No reaction was observed when aqueous potassium hydroxide solution or triethylamine were used as bases. The lithium salt, however, did react with benzophenone in benzene/ether solution to give, in addition to residual benzophenone, a less polar component whose i.r. spectrum showed no absorptions characteristic of diazoalkane, silane, carbonyl or oxirane functions, and whose p.m.r. spectrum showed the presence of aromatic protons only. The product was tentatively identified as diphenyl acetylene, and comparison with an authentic sample confirmed this identification. The yield of diphenyl acetylene, based on the benzophenone initially added, was 34%. This yield was raised to 80% when a 2:1 molar excess of lithium trimethylsilyldiazomethide was reacted with benzophenone in ether solution (SCHEME 5).



SCHEME 6



SCHEME 7

Mechanistically, the conversion of benzophenone to diphenyl acetylene must involve two distinct stages after the initial condensation of trimethylsilyldiazomethide anion with the ketone, namely Wolff[8] rearrangement with expulsion of nitrogen, and elimination of trimethylsilanoxide anion (SCHEME 6). The order in which these steps occur could not be deduced at this stage.

The potassium salt of trimethylsilyldiazomethane also reacted with benzophenone in benzene solution to give diphenyl acetylene in 52% yield, together with residual benzophenone, and a third compound, a crystalline solid whose i.r. spectrum showed an absorption characteristic of an alkyl aryl ketone. The p.m.r. spectrum showed the presence of two non-identical phenyl rings, and a deshielded methylene group. The compound was thus identified as phenyl benzyl ketone, and this identification was confirmed by comparison with an authentic sample. This compound was isolated in 6% yield.

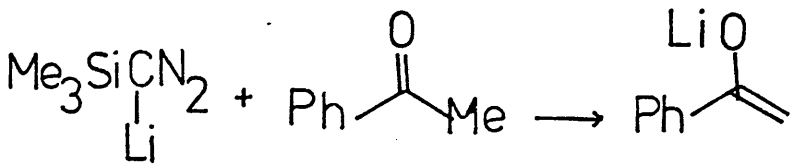
The formation of phenyl benzyl ketone in addition to diphenyl acetylene can be explained if Wolff rearrangement of the adduct 5 to give the enolate ion 6 precedes elimination of trimethylsilanoxide anion in the conversion of benzophenone to diphenyl acetylene (SCHEME 7). Since the solution also contains one equivalent of t-butanol, formed in the reaction of potassium t-butoxide with trimethylsilyldiazomethane, it is conceivable that this alcohol can act as a proton source, converting the enolate ion 6 to the corresponding β-keto-silane, and thus preventing elimination of trimethylsilanoxide. The β-keto-silane would undergo rapid hydrolysis to phenyl benzyl ketone 7

under the conditions used for isolation of the products.

This type of process is, of course, impossible when n-butyl lithium is used as base, since there is then no proton-source present in the reaction mixture, and, under all conditions studied, benzophenone reacted with lithium trimethylsilyldiazomethide to give only diphenyl acetylene, and no phenyl benzyl ketone. It is interesting to note also that the amount of phenyl benzyl ketone formed in the reaction described above is very dependent on the solvent-system used. In general, significant amounts of phenyl benzyl ketone were obtained only when the reaction was performed in benzene solution. Use of ether or THF as solvent gave only diphenyl acetylene. This solvent dependence is presumably due to the effect of solvent ionising-power on the propensity towards elimination of the silyl enolate ion 6. In solvents of high ionising-power, the enolate 6 will exist as a solvent-separated ion-pair; in these circumstances, the high electron-density on the oxygen atom will lead to rapid elimination of trimethylsilanoxide anion. In solvents of low ionising-power, on the other hand, the enolate 6 will exist as an intimate ion-pair; elimination of trimethylsilanoxide will therefore be slow, thus allowing proton-capture from t-butanol to compete with elimination, and leading to the formation of phenyl benzyl ketone.

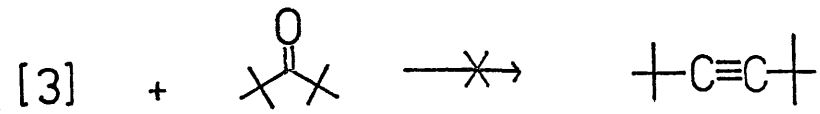
After experimentation to optimise yields, attention turned to the study of other substrates.

Acetophenone reacted with lithium trimethylsilyldiazomethide to give a mixture whose major component

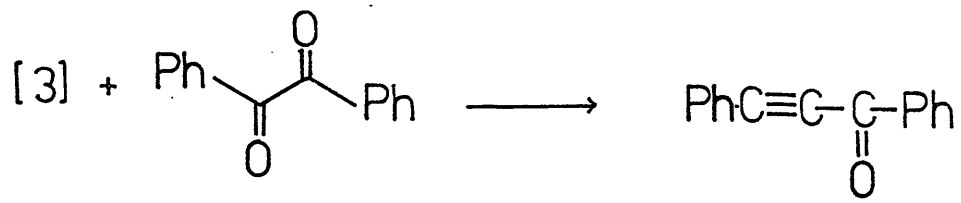


[3] [8]

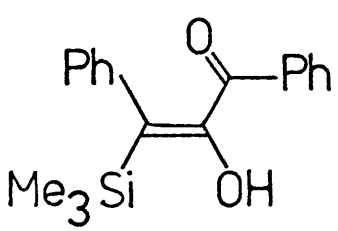
SCHEME 8



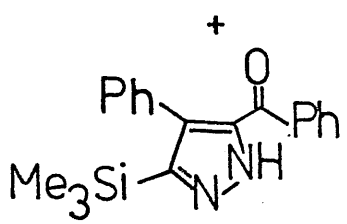
SCHEME 9



[9] [10]



[11]



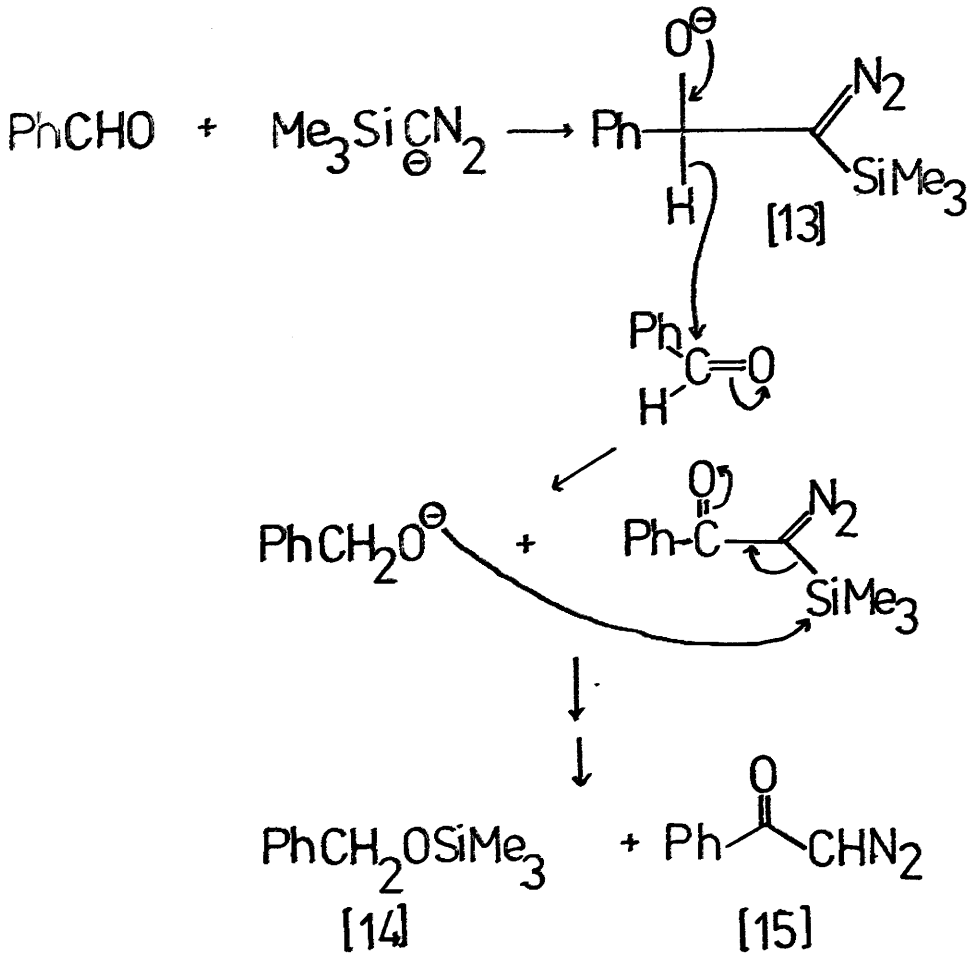
[12]

SCHEME 10

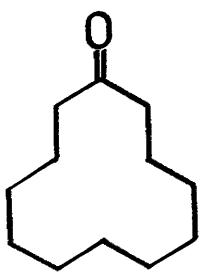
was unreacted acetophenone, together with a small amount of 1-phenyl-propyne 8, identified by its i.r. spectral characteristics. Presumably, in this case, the main process occurring is proton-exchange between acetophenone and lithium trimethylsilyldiazomethide to form the lithium enolate and the neutral diazoalkane respectively (SCHEME 8).

The highly-hindered ketone, di-t-butyl ketone, did not react with lithium trimethylsilyldiazomethide, even when hexamethylphosphoric-triamide (HMPT) was added to the solvent (SCHEME 9).

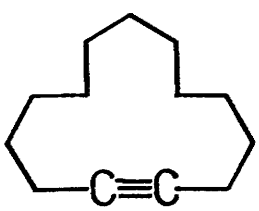
Benzil 9 , however, did react with lithium trimethylsilyldiazomethide to give 1,3- diphenyl-prop-3-yn-1-one 10 , identified by its spectral characteristics and by comparison with an authentic sample (SCHEME 10). In addition to this compound, which was obtained in 59% yield, another product was isolated. This compound was quite polar, and showed a carbonyl absorption at 1665 cm^{-1}, a silane absorption at 1245 cm^{-1}, and an absorption at 3460 cm^{-1} in its i.r. spectrum, and was at first thought to be the intermediate silyl enol 11 . However, all attempts to convert this compound to 10 by elimination of trimethylsilanol proved unsuccessful. The mass spectrum showed the molecular weight to be 320. The compound was thus identified as 5-benzoyl- 4-phenyl- 3-trimethylsilyl- (1H)-pyrazole 12 , and microanalysis confirmed this identification; this product arises by 1,3-dipolar addition of lithium trimethylsilyldiazomethide and 10. The formation of this compound is consistent with the well-known reactivity of conjugated alkynes such as 10 in dipolar addition reactions[9].



SCHEME 11



[16]

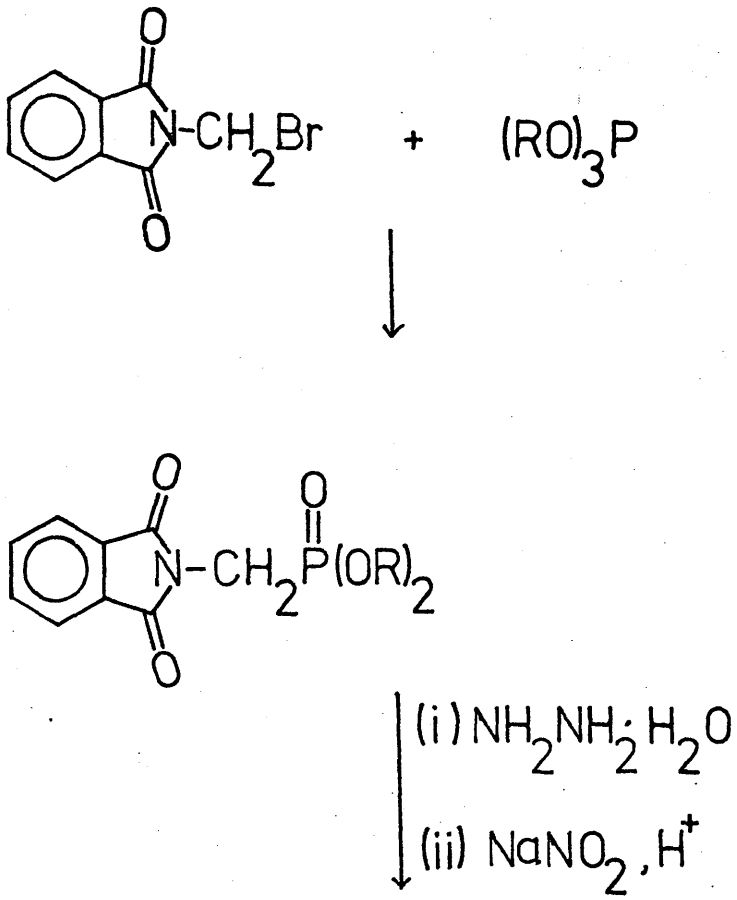


[17]

Reaction of 10 with lithium trimethylsilyldiazomethide led only to the formation of the pyrazole 12 ; no di-alkyne formation was observed.

Benzaldehyde was expected to react with lithium trimethylsilyl-diazomethide to give phenyl acetylene. It was found, however, that the products of this reaction were benzyloxy-trimethylsilane 14 and α-diazo-acetophenone 15, both of which were identified by comparison with authentic samples. The formation of these compounds indicates that the initially-formed adduct 13 does not undergo Wolff rearrangement, but transfers a hydride ion to a second molecule of benzaldehyde in a process analogous to the Cannizarro reaction[10] (SCHEME 11).

Having established that lithium trimethyl-silyldiazomethide reacts with ketones to form the homologous acetylenes, the failure of cyclohexanone to react in this way, or to form any intermediate compound, was reconsidered. In this case, the product cyclo-heptyne would be very highly strained, and this might have explained the failure of these reactions. A large-ring cyclic ketone, cyclo-dodecanone 16, was therefore reacted with lithium trimethylsilyldiazomethide. The expected product of this reaction, cyclo-tridecyne 17 , has been prepared previously and is quite stable[11]. However, none of this compound was obtained, presumably due to proton-exchange between reagent and substrate. It thus appears that the methine proton in trimethylsilyldiazomethane is considerably less acidic than methylene protons α to a carbonyl group, and this obviously limits the applicability of lithium trimethylsilyldiazomethide



$(RO)_2\overset{O}{\overset{\|}{P}}CHN_2$

[18]: R = Me

[19]: R = Et

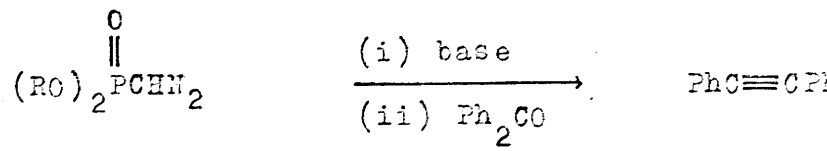
SCHEME 12

to the preparation of aliphatic alkynes.

A search of the literature was therefore instituted, to identify other diazo-alkanes which might react in an analogous manner to trimethylsilyldiazomethane, while having weaker conjugate bases. Such compounds would bear a substituent with greater carbanion-stabilising ability than the silyl moiety, while retaining its propensity towards elimination when in the β-position to a hydroxyl function. An obvious contender was the phosphonate group, by analogy with the well-known Wadsworth-Emmons reagents[12]. N.m.r. studies of diazoalkane phosphonates have shown a considerable degree of double-bond character in the carbon-phosphorus bond[13]; the ability of the phosphonate group to take part in (p⟶d)π-backbonding, and hence to stabilise an adjacent carbanion, is thus unimpaired by the presence of the diazoalkane system.

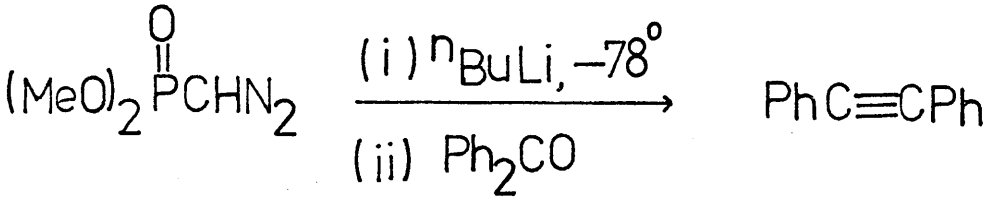
Two suitable diazoalkanes were found: dimethylphosphono-diazomethane 18[14] and diethylphosphono-diazomethane 19[15]; both compounds are easily prepared from readily-available starting materials (SCHEME 12).

Reaction of dimethylphosphono-diazomethane with n-butyl lithium at 0° resulted in the decomposition of the diazoalkane; in this respect, dimethylphosphono-diazomethane, unlike trimethylsilyldiazomethane, is similar to most diazo-alkanes, which undergo decomposition on treatment with strong bases[16]. It was found possible to generate the anion of dimethylphosphono-diazomethane by reaction in THF with n-butyl lithium at -78°, and the

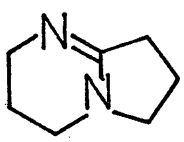


R:	base:	solvent:	temperature:	Moles reagent : substrate	YIELD(%)
		CONDITIONS:			
Me	^{n}BuLi	THF	0	1.4:1	0
Me	^{n}BuLi	THF	-78	1.4:1	80
Me	^{n}BuLi	THF	-78	2.2:1	94
Et	^{n}BuLi	THF	-78	2.5:1	94
Me	KO^{t}Bu	THF	-78	1.7:1	77
Me	NaOEt	EtOH	70	1:1	5
Me	MeMgCl	THF	-78	1.2:1	35
Me	DBN	THF	20	1.9:1	0
Me	DBN	THF/HMPT	20	1.8:1	0
Me	DBN	THF/HMPT/$LiClO_4$	20	1.1:1	0
Me	piperidinium acetate	THF	20	1.3:1	0
Me	Et_2NH	MeCN	20	1.2:1	0
Me	Et_2NH	MeCN/$LiClO_4$	20	1.2:1	0
Me	Et_2NH	Dioxan/ Ag(I)	100	1.2:1	0
Et	$LiN^{i}Pr_2$	THF	-78	2.7:1	66

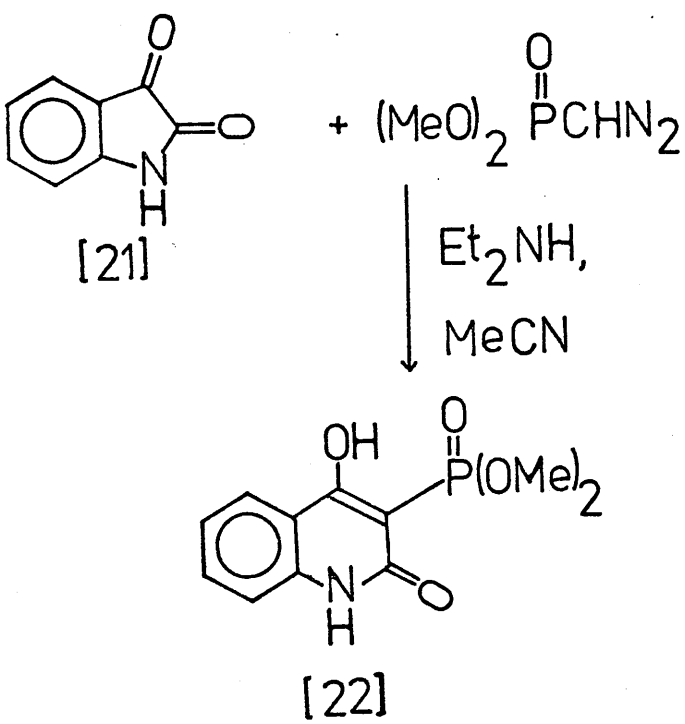
TABLE 1.



SCHEME 13



[20]



SCHEME 14

solution thus obtained converted benzophenone to diphenyl acetylene in 94% yield (SCHEME 13). Diethylphosphono-diazomethane reacted in a similar manner, although the lithium salt appeared to be more prone to decomposition than that of the dimethyl analogue.

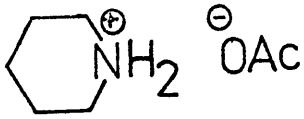
An investigation was then conducted to discover the range of conditions under which the conversion of benzophenone to diphenyl acetylene could be performed (TABLE 1); n-butyl lithium and potassium t-butoxide were equally effective in promoting reaction in THF solution, while other organometallic bases were less effective. When the reaction was performed in ethanol solution using sodium ethoxide as base, vigorous conditions were required, and diphenyl acetylene was obtained in only 5% yield. Methyl-magnesium chloride promoted reaction under the same conditions used with n-butyl lithium, but the reaction did not go to completion.

Strong amine bases were completely ineffective in promoting reaction of dimethyl-phosphono-diazomethane with benzophenone. For example, 1,5- diaza-bicyclo-[3,4,0] non-5-ene (DBN) 20, a very strong base[17], did not induce the reaction either in THF or HMPT/THF solution. The possibility that the presence of alkali-metal ions might be required in order to enhance the electrophilicity of the carbonyl group[18] was considered, but addition of lithium salts to the reaction medium had no effect.

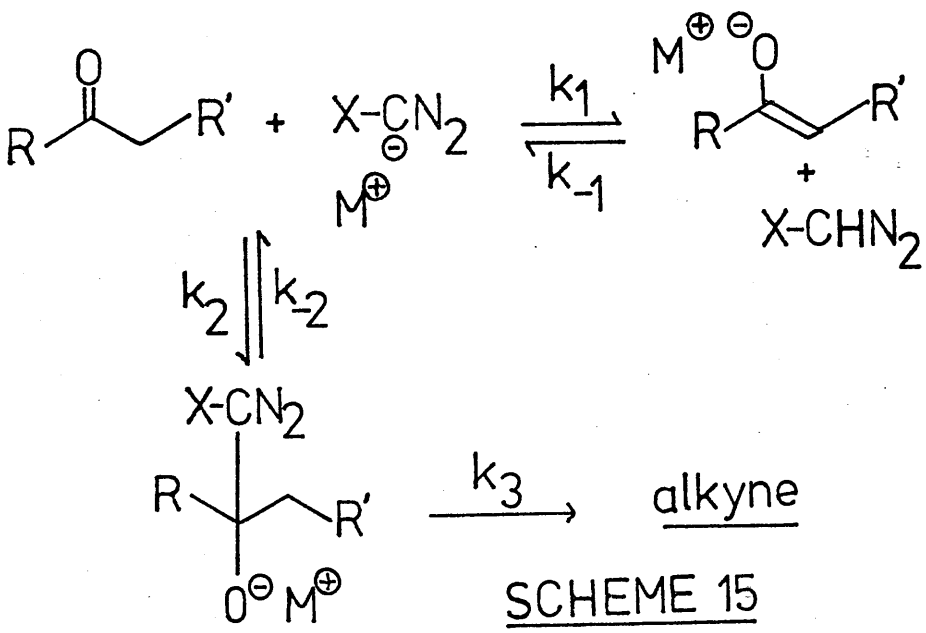
In the course of this investigation, a report appeared in the literature[19] of the reaction of isatin 21 in acetonitrile solution with dimethylphosphono-diazomethane, catalysed by diethylamine, to give 22 , the product of Wolff

rearrangement (SCHEME 14). Under these conditions, neither benzophenone nor benzil reacts with dimethylphosphono-diazomethane. There are two possible explanations for this: firstly, the product 22 obtained from reaction with isatin is insoluble in the reaction medium and precipitates out as the reaction proceeds. Assuming the initial addition of dimethylphosphonodiazomethane to isatin is reversible, this would drive the equilibrium to the right, thus ensuring complete reaction. It may be that the products obtained by the addition of dimethylphosphonodiazomethane to either benzophenone or benzil are soluble in the reaction medium, and that the equilibrium of the first step lies well to the side of reactants rather than products. Experiments in other, less polar, solvent systems were, however, also unsuccessful. Possibly the important factor is the electrophilicity of the carbonyl group involved; the 3-carbonyl group of isatin is much more electrophilic than the carbonyl functions of either benzil or benzophenone. Attempts to increase the electrophilicity of these compounds by adding lithium perchlorate to the reaction medium were unsuccessful, and the use of more vigorous reaction conditions merely resulted in the decomposition of the diazoalkane. Addition of a silver salt, silver heptafluorobutyrate, in an attempt to increase the electrophilicity of the carbonyl group by complex-formation[20] had no effect.

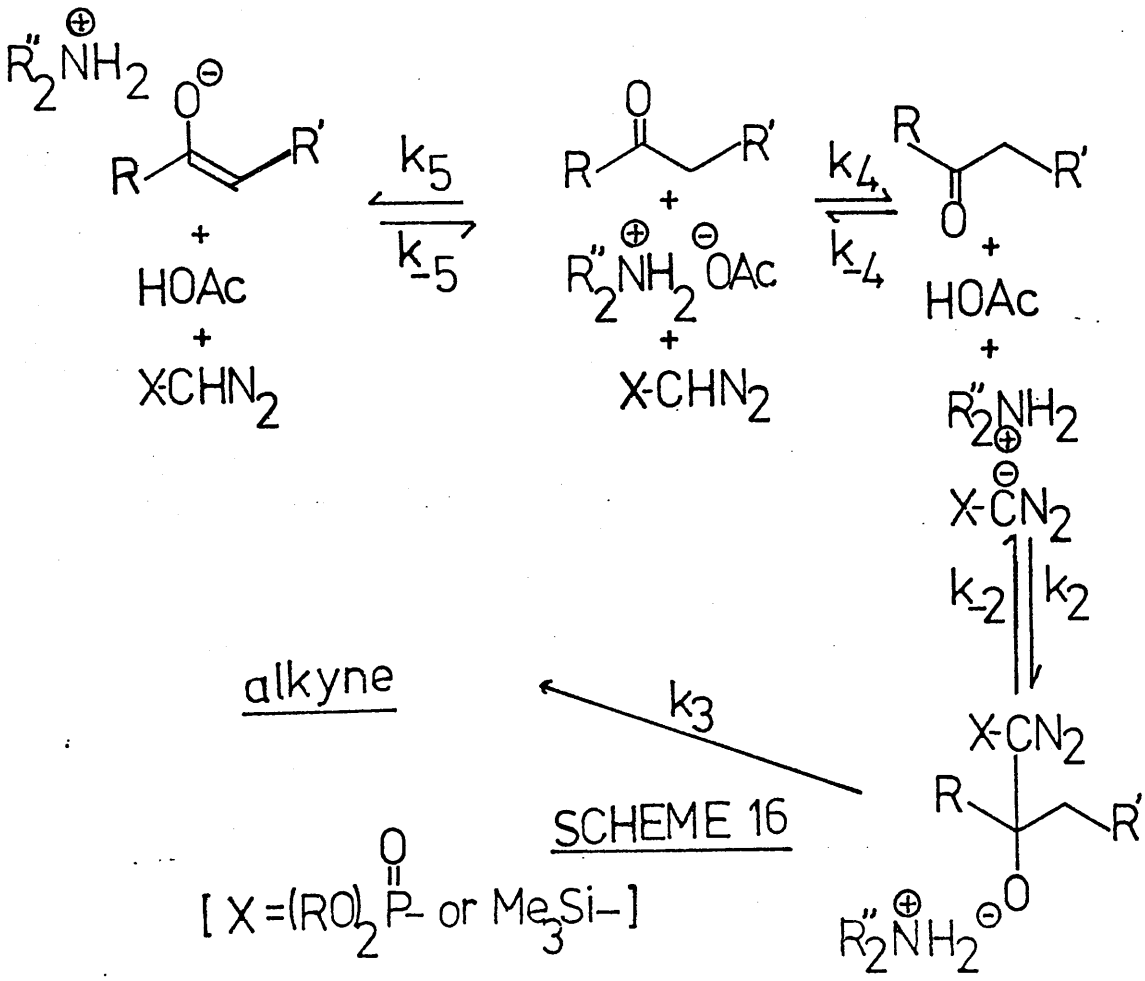
Use of the amine salt, piperidinium acetate[21], was suggested by consideration of the factors involved in the reaction of lithium or potassium salts of the diazoalkanes with enolisable ketones; in these processes, the initial



[23]



SCHEME 15



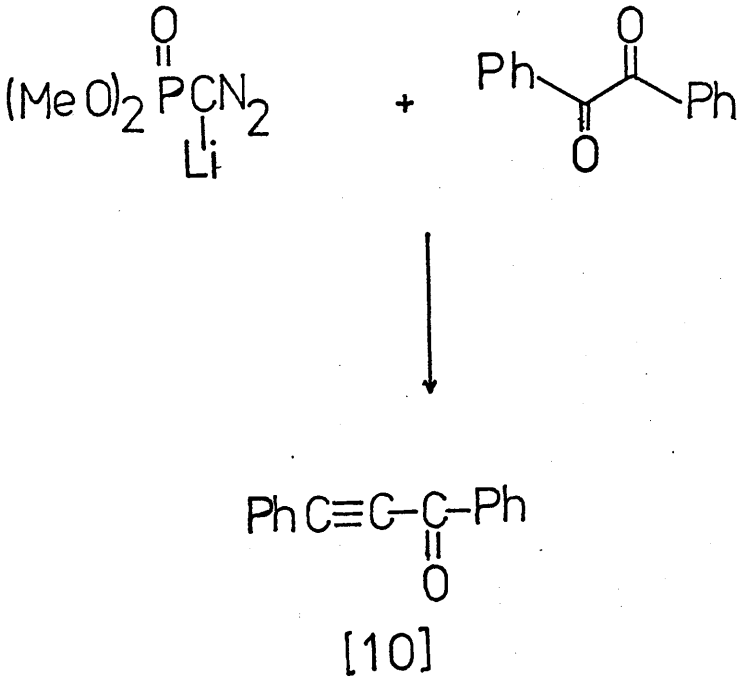
SCHEME 16

[X = $(RO)_2\overset{O}{\overset{\|}{P}}-$ or Me_3Si-]

removal of a proton from the diazoalkane is essentially irreversible, and the ratio of products obtained is dependent on the equilibria outlined in SCHEME 15.

In order for unreacted ketone to predominate in the product mixture, the kinetic requirements are that $k_1 > k_2$; $k_1 \gg k_{-1}$ and $k_2 < k_{-2}$. It is assumed that the Wolff rearrangement and elimination steps are irreversible. It was anticipated that the use of an amine salt, a "thermodynamic" rather than "kinetic" base[22], might avoid this difficulty (SCHEME 16). In this system, it is reasonable to predict that, because of the presence of a proton source, $k_5 \approx k_{-5}$ and $k_4 \approx k_{-4}$; thus, all the ketone should be available for eventual reaction.

However, piperidinium acetate failed to catalyse the reaction of dimethylphosphono-diazomethane with benzophenone to give diphenyl acetylene, even under vigorous reaction conditions. Clearly, the problem is that $k_3 \ll k_{-2}$; thus, reaction with enolisable ketones will never go to completion, and, even with non-enolisable ketones, reaction will proceed only if conditions are such that $k_2 \approx k_{-2}$ and k_3 is finite. Thus, the main factors influencing the outcome of the reaction are the electrophilicity of the carbonyl compound and the extent of steric hindrance to adduct formation, which together determine the ratio $k_2 : k_{-2}$, and, depending on the order in which subsequent steps occur, either the nature of the migrating groups in the Wolff rearrangement, or the propensity of the β-silyl or β-phosphono- alkoxide towards elimination, which determines k_3 . The nature of the base is probably less important than



[10]

SCHEME 17

any of these factors, except insofar as the cation involved influences the electrophilicity of the carbonyl group and the tendency of silanoxide or phosphonate to eliminate.

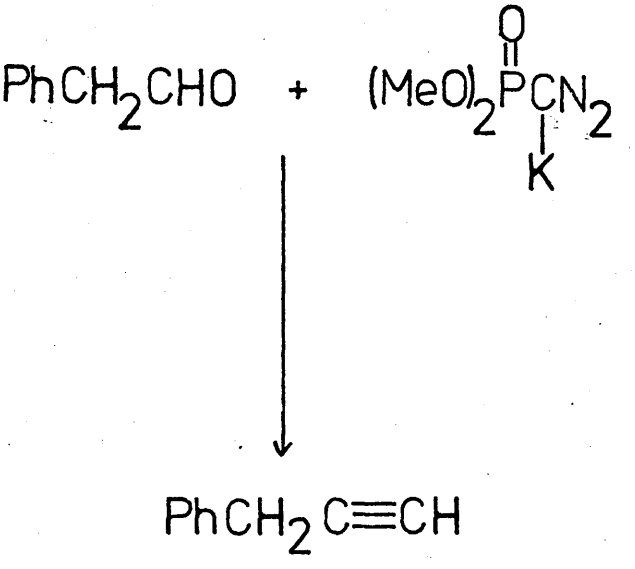
Studies were made of the ability of Lewis acids to catalyse reaction of dimethylphosphono-diazomethane with benzophenone. Mock and Hartman[23] found that triethyloxonium fluoroborate was an effective catalyst for the reaction of diazoketones with ketones; however, neither this reagent nor boron trifluoride etherate were effective catalysts for the transformation of benzophenone to diphenyl acetylene by dimethylphosphonodiazomethane.[21]

Benzil reacted with lithium dimethylphosphono-diazomethide to give 1,3- diphenyl-prop-2-yn-1-one (SCHEME 17). The yield was only modest, however; this was probably due to further reaction of the product with excess reagent to give a pyrazole, as was the case in the analogous reaction with trimethylsilyldiazomethane (SCHEME 10). In this case, however, no pyrazole was present in the ether-soluble fraction of the product mixture.

Acetophenone reacted with both the lithium and potassium salts of dimethylphosphonodiazomethane to give 1-phenyl propyne, together with residual acetophenone. Clearly, the methine proton in dimethylphosphonodiazomethane is less acidic than the protons α to the carbonyl group in acetophenone. The potassium salt seemed to be a more effective reagent than the lithium salt of the diazoalkane in performing the conversion to alkyne; when n-butyl lithium was used as base, the yield of 1-phenyl propyne was 9%, and 50% of the initial acetophenone was recovered unchanged, while,

when potassium t-butoxide was used as base, the yield of 1-phenyl propyne was 22%, again with 50% recovery of starting material. This can be attributed to the greater covalent character of the oxygen-lithium "bond" compared with the oxygen-potassium "bond"; elimination of phosphate from the initially-formed adduct should take place less rapidly when lithium is the counter-ion than when potassium is the counter-ion, since electron density on oxygen is lower in the former case than in the latter. Thus, when the potassium salt of dimethylphosphonodiazomethane is reacted with acetophenone, k_3 is increased relative to k_{-2} (SCHEME 15) as compared with the corresponding reaction of the lithium salt. It was expected, in view of this effect, that the use of a solvent of greater ionising-power might further enhance the ratio of alkyne produced to ketone recovered in this reaction[24]. When the reaction of potassium dimethylphosphonodiazomethide with acetophenone was carried out in 25% dimethylsulphoxide in THF, however, little change in yield was observed. This perhaps indicates that, even in THF solution, the initially-formed adduct exists as a solvent-separated ion pair rather than an intimate ion-pair.

The use of "thermodynamic" rather than "kinetic" bases did not result in formation of 1-phenyl propyne from acetophenone. Sodium ethoxide in ethanol caused some self-condensation of the ketone, but produced no alkyne. Similar results were obtained when acetophenone and dimethylphosphono-diazomethane were reacted in acetonitrile solution in the presence of diethylamine.



[24]

SCHEME 18

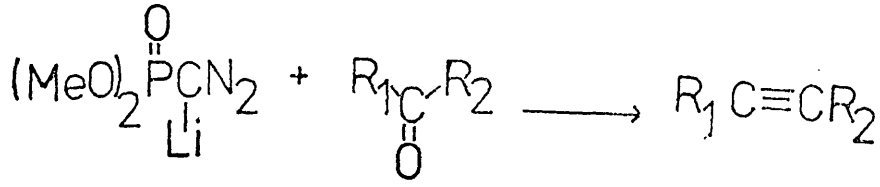
1,3- Diphenyl-prop-2-yn-1-one 10 reacted with lithium dimethylphosphonodiazomethide to give a complex mixture of products. T.l.c. comparison with an authentic sample of the expected product, 1,4-diphenyl-buta-1,3-diyne[25], showed that this compound was not present in the product mixture. The processes occurring here are probably dipolar addition reactions, in view of the high reactivity of conjugated yn-ones in such processes. As was found earlier, in the reaction of benzil with lithium dimethylphosphono-diazomethide, no pyrazole was isolated from the ether-soluble fraction of the product mixture; in contrast to the analogous trimethylsilyl-pyrazole (SCHEME 10), the dimethylphosphono-pyrazole which is presumably formed in this reaction appears to be water-soluble.

Attempted conversion of cinnamaldehyde to a conjugated en-yne was similarly unsuccessful; it would appear that α,β-unsaturated carbonyl compounds cannot be converted to alkynes using this reagent.

Phenyl-acetaldehyde reacted with potassium dimethylphosphonodiazomethide to give, in addition to residual aldehyde, 3-phenyl-propyne 24 , identified by its characteristic i.r. and p.m.r. spectra. The yield of 3-phenyl-propyne was 30% (SCHEME 18).

Di-t-butyl ketone did not react with either the lithium or potassium salts of dimethylphosphonodiazomethane, presumably because of steric hindrance.

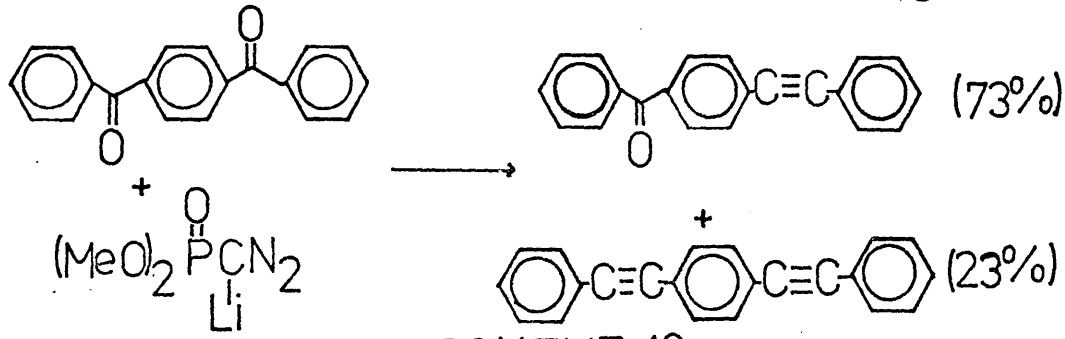
Attempts to convert di-aliphatic ketones to alkynes were, in fact, uniformly unsuccessful. Reaction of the lithium or potassium salts of diethylphosphono-diazomethane with phenyl benzyl ketone, dibenzyl ketone



R_1	R_2	molar ratio reagent : substrate	% yield* of alkyne
Ph-	-Ph	2.2:1	94[b]
Ph-	-COPh	5:1	25[a]
Me-C$_6$H$_4$-	-C$_6$H$_4$-Me	2:1	97[b]
Ph-	-C$_6$H$_4$-Cl	2:1	100[b]
Ph-	-C$_6$H$_4$-NO$_2$	2.4:1	32[a]
Ph-	-C$_6$H$_4$-OMe	2.4:1	66[b]
C$_{10}$H$_7$-	-C$_{10}$H$_7$	10:1	75[b]
Ph-	-C$_6$H$_4$-COPh	3.6:1	73[b]
Ph-	-C$_4$H$_3$S	2.7:1	44[b]
Ph-	-C$_5$H$_4$N	4.2:1	38[a]
Ph-	-C$_4$H$_3$O	— polymerises —	0
Ph-	-C$_6$H$_{11}$	3.8:1	43[b]

*a = isolated
b = g.l.c.

TABLE 2



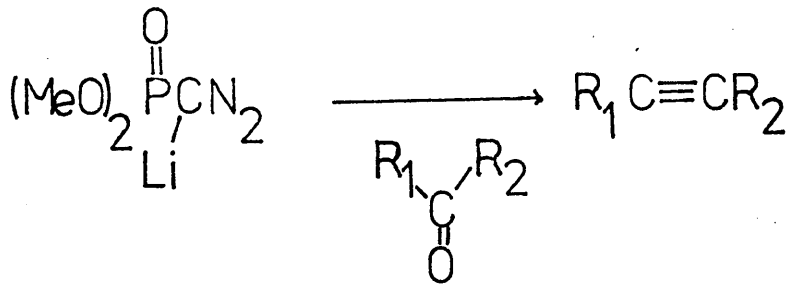
SCHEME 19

and di-cyclohexyl-ketone resulted, in every case, in the recovery of unchanged starting material.

At this point in the investigation, it was felt prudent to study the reaction of lithium dimethyl-phosphonodiazomethide with a variety of aryl ketones, in case the conversion of benzophenone to diphenyl acetylene should be due to some anomalous and undefined property of benzophenone itself. Mercifully, the reaction proved to be general for such aromatic substrates, and the results of these investigations are summarised in TABLE 2.

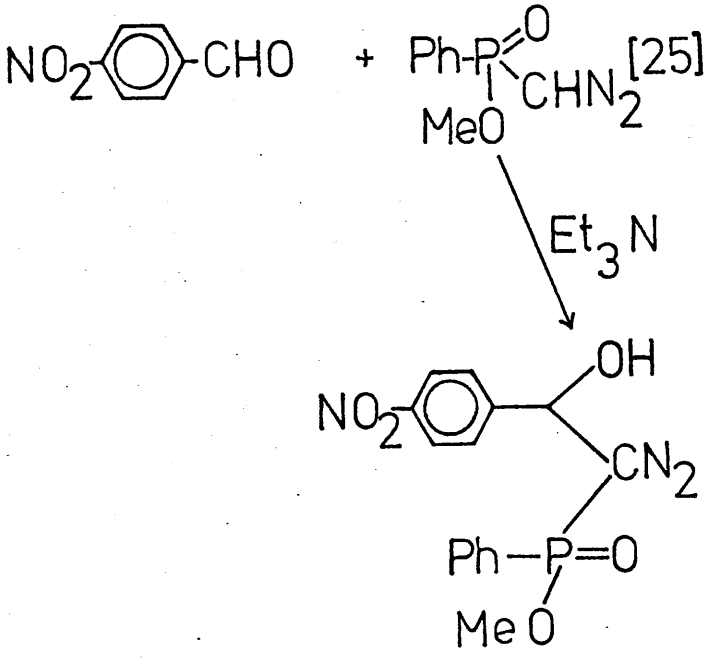
Substitution of the aromatic ring appears to have little effect on the reaction, provided of course that no active-hydrogen-containing substituents are present. As has already been described, conjugated carbonyl compounds are not converted to alkynes, and α-dicarbonyl compounds give low yields of alkyne due to subsequent dipolar addition reactions. However, dicarbonyl compounds in which the carbonyl groups are mutually isolated react normally, to give a mixture of mono-alkyne and di-alkyne (SCHEME 19). Hetero-aromatic ketones reacted normally, although all attempts to convert 2-benzoyl-furan to the alkyne resulted in substrate polymerisation.

The relatively high yield of phenyl cyclohexyl acetylene obtained by reaction of phenyl cyclohexyl ketone with the reagent is noteworthy: one would expect the methine proton in this ketone to be less acidic than the methylene protons of acetophenone; competing proton-exchange should therefore be less evident

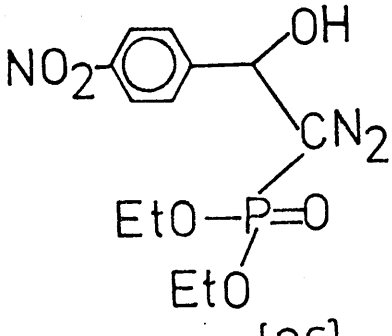


R_1:	R_2:	yield of alkyne:
Ph-		43%
Ph-	-Me	9%
Ph-	$-CH_2Ph$	0

TABLE 3



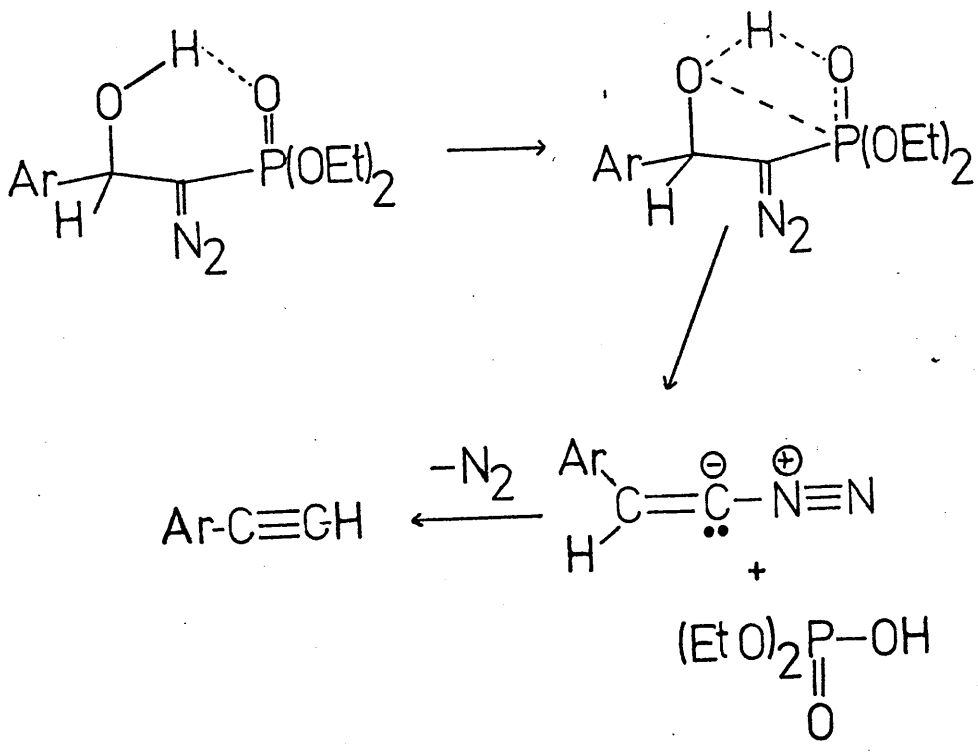
SCHEME 20



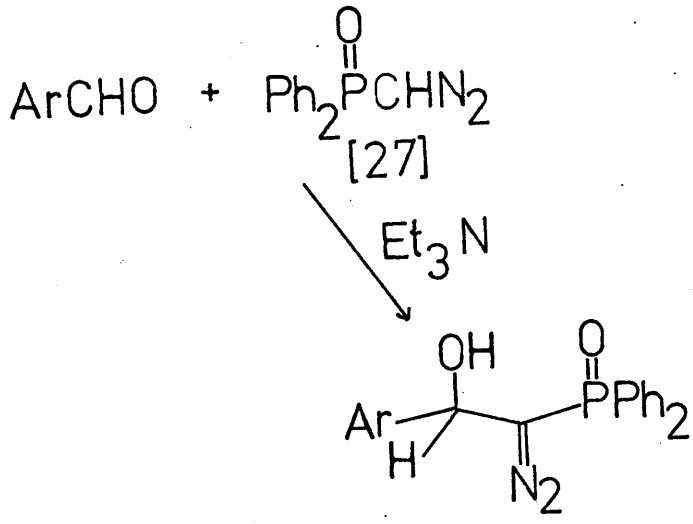
[26]

for this ketone than for acetophenone in their reactions with lithium dimethylphosphonodiazomethide, and the yield of alkyne is thus increased. Taking this argument a step further, the failure of phenyl benzyl ketone to react at all with the reagent can be attributed to the increased acidity of its methylene protons compared with those of acetophenone; proton exchange is therefore the only process occurring here (TABLE 3).

A recent report by Regitz[26] describes the formation and isolation of adducts of electrophilic carbonyl compounds with methyl-diazomethyl-phenylphosphinate 25 under the influence of a catalytic amount of triethylamine (SCHEME 20). As described earlier in this discussion, all attempts to condense dimethylphosphono-diazomethane with carbonyl compounds under similar conditions were unsuccessful. In view of Regitz's findings, however, some further investigation was undertaken. Initially, attempts to prepare the adduct of p-nitro-benzaldehyde and diethylphosphonodiazomethane were unsuccessful. These reactions were performed in the solvent system (1:1 dimethoxyethane/ether) used by Regitz for the corresponding reaction of methyl- diazomethyl-phenylphosphinate with p-nitro-benzaldehyde. After experimentation with various solvent systems, it was found that the adduct 26 could be obtained by performing the reaction in ether solution in the presence of 0.2 equivalents of triethylamine. The reaction did not go to completion, and the adduct 26 was obtained pure, as a crystalline solid, only after repeated trituration and careful recrystallisation. The i.r. spectrum of this compound showed absorptions characteristic



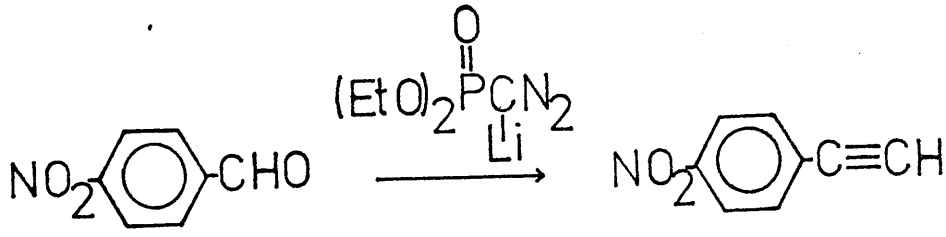
SCHEME 21



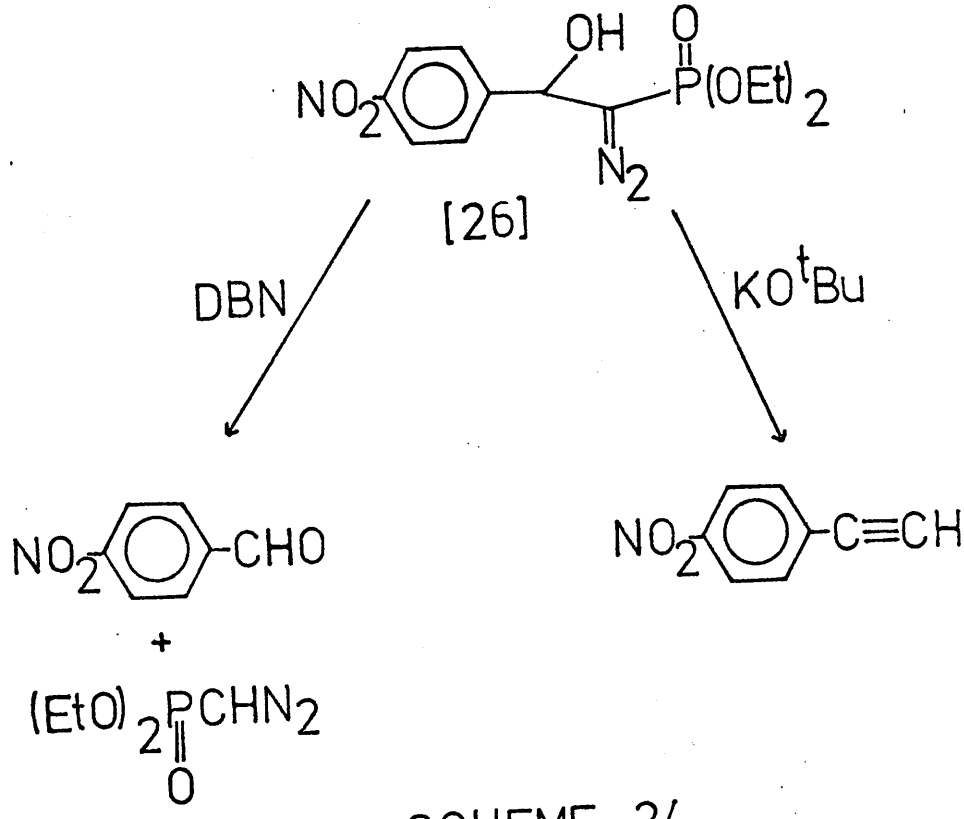
SCHEME 22

of hydroxyl, diazoalkane and phosphonate functions. The wavelength of the hydroxyl absorption did not vary with concentration, thus demonstrating the existence of intramolecular hydrogen bonding between the phosphonate and hydroxyl groups. If spontaneous elimination of phosphoric acid diethyl ester were possible, then this intramolecular hydrogen bond would be expected to facilitate the elimination process (SCHEME 21). The fact that no such process occurs partially explains the failure, described earlier, to induce reaction of dimethylphosphonodiazomethane with ketones to give alkynes by the use of strong amine bases.

Another factor to be considered is the position of equilibrium in processes of the type shown in SCHEME 20; Regitz[26] reported that the adducts formed in these processes crystallise out as the reaction proceeds, and, in a subsequent paper[27], has described the reaction of diphenylphosphinyl-diazomethane 27 with a range of aldehydes to form crystalline adducts (SCHEME 22). In every case, the adducts precipitate from solution, and a variety of solvent systems were used to ensure that this occurred. Clearly, it is this precipitation of the product which allows the reaction to proceed to completion, by displacement of the equilibrium towards the side of products. It is significant that Regitz[27] reports only one example of an adduct formed from dimethylphosphono-diazomethane and an aldehyde, in this case p-nitro-benzaldehyde; by use of diphenylphosphinyl-diazomethane, the solubility of the adducts is reduced sufficiently to



SCHEME 23



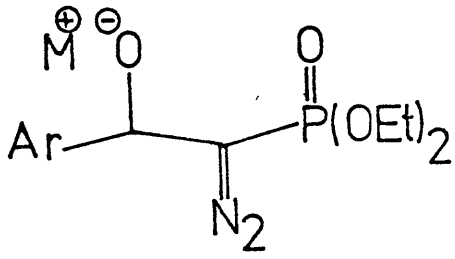
SCHEME 24

allow conditions to be found under which crystallisation from the reaction mixture will occur. In addition, the anion of diphenylphosphinyl-diazomethane is probably more stable than the dimethylphosphonodiazomethide anion, since, in the latter, the negative charge on carbon has to compete with the lone-pair electrons on the two alkoxyl oxygen atoms in $(p \rightarrow d)\pi$-backbonding with phosphorus.

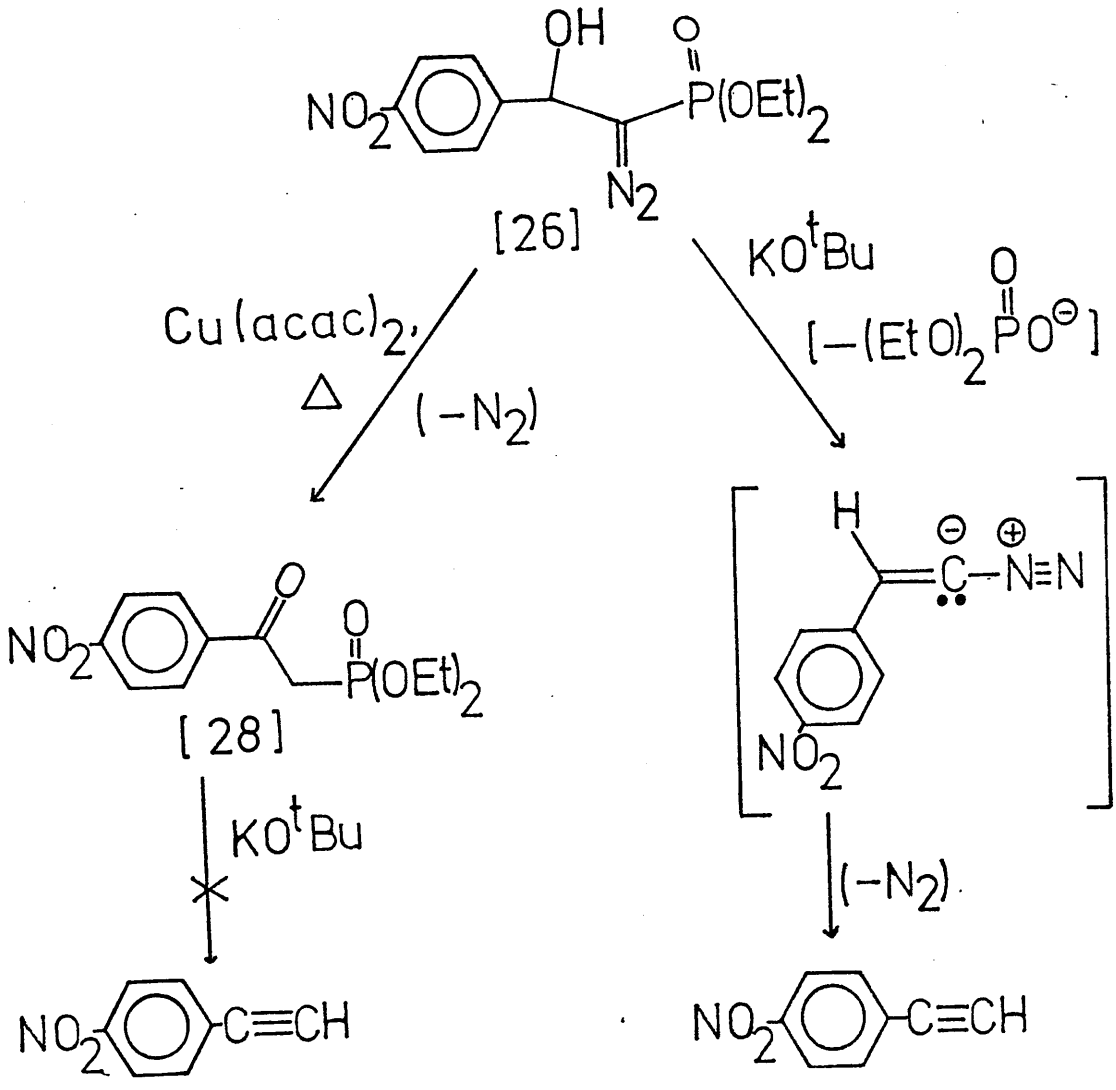
Two conclusions can therefore be drawn: firstly, amine bases will only catalyse adduct formation if the resulting adduct can be induced to precipitate from solution; and, secondly, amine bases will not catalyse the subsequent rearrangement and elimination reactions of the adduct leading to alkyne.

In contrast, reaction of the lithium salt of diethylphosphonodiazomethane with p-nitrobenzaldehyde leads to p-nitrophenyl acetylene in 86% yield (SCHEME 23). Since this reaction presumably proceeds through the lithium salt of the adduct 26, an attempt was made to convert 26 to p-nitrophenyl acetylene by treatment with an alkali-metal base. Reaction of the adduct 26 in THF solution with potassium t-butoxide gave p-nitrophenyl acetylene in 68% yield. In contrast, on reaction with DBN in THF solution, the adduct 26 reverted to diethylphosphonodiazomethane and p-nitrobenzaldehyde (SCHEME 24).

Thus, it can be deduced that the conversion of carbonyl compounds to homologous alkynes is a property shown only by metal salts of dialkylphosphono - diazomethanes, and not simply by their conjugate bases.



[27]



SCHEME 25

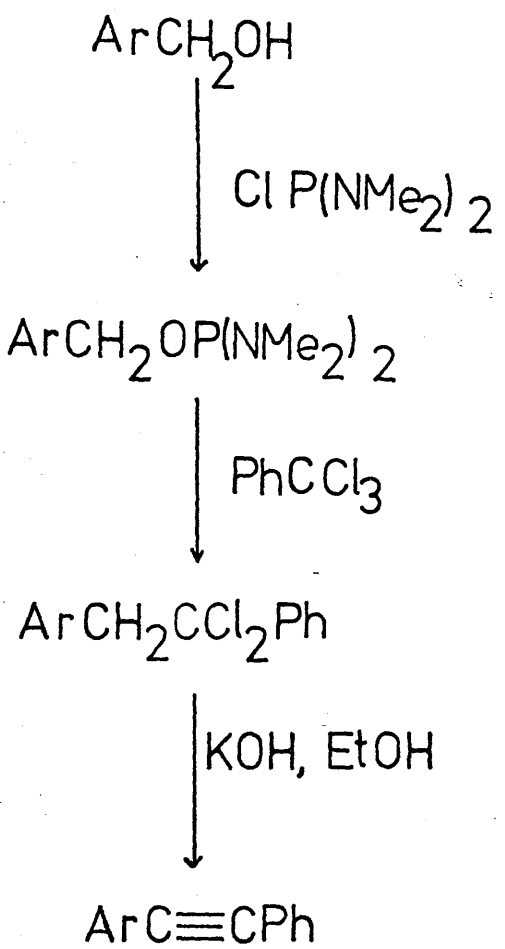
The implication of this finding is that the decisive stage of this conversion of carbonyl compound to alkyne is the elimination of the alkali-metal phosphate from the initially-formed adduct 27 , that if this process does not occur then the reaction will not proceed, and that this step must therefore precede Wolff rearrangement. In order to test this hypothesis, the adduct 26 was heated in refluxing benzene in the presence of a trace of bis-(acetylacetonato-) Copper(II), in order to bring about Wolff rearrangement.[8,28] The product was a yellow oil whose i.r. spectrum showed absorptions characteristic of aryl alkyl ketone and phosphonate functions, and was thus identified as α-diethylphosphono-, p-nitro-acetophenone 28. The yield of this compound was 98%.

No change occurred when 28 was treated with potassium t-butoxide in THF solution. This confirms that phosphate elimination precedes Wolff rearrangement, as shown in SCHEME 25.

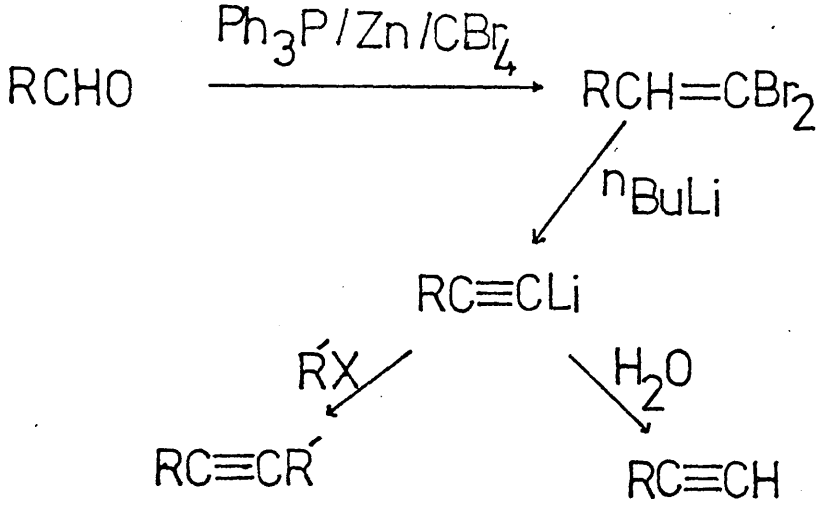
This account would be incomplete without an assessment (hopefully, an objective one) of the synthetic utility of the reagents described herein.

With a few exceptions, these reagents cannot be applied to the preparation of aryl alkyl acetylenes, unless the alkyl group is secondary. In no case studied was it possible to prepare di-alkyl acetylenes by this route; this possibly reflects the poor migratory aptitude of alkyl groups as compared with aryl or hydride groups.

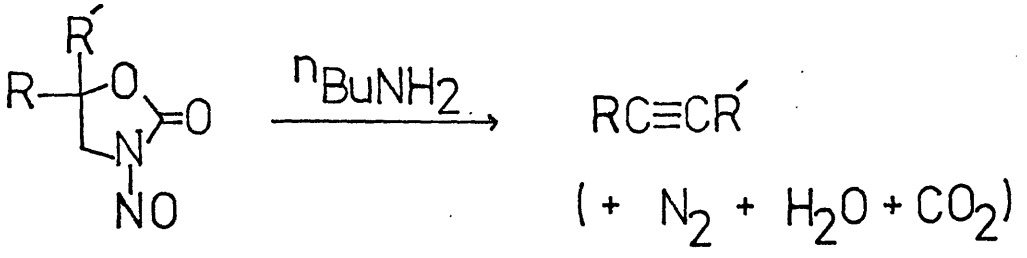
This method is very useful, however, in the preparation of di-aryl acetylenes. The reaction seems to be relatively insensitive to substitution of the aromatic


ArCH2OH
Cl P(NMe2) 2
ArCH2OP(NMe2) 2
PhCCl3
ArCH2CCl2Ph
KOH, EtOH
ArC≡CPh

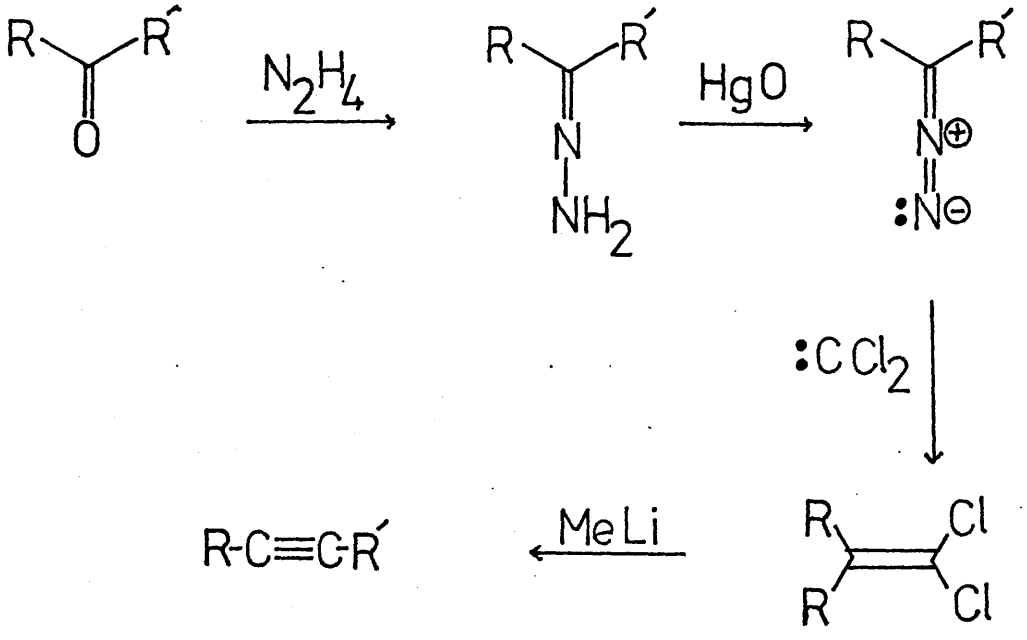
SCHEME 29



SCHEME 26



SCHEME 27



SCHEME 28

nuclei, provided that no active hydrogen atom is present. The preparations summarised in TABLE 2 were all carried out under a set of standard conditions, and some optimisation of yields should be possible.

Some alternative methods for the preparation of acetylenes are shown in SCHEME 26[29], SCHEME 27[30], SCHEME 28[31] and SCHEME 29.[32]

For the preparation of di-aryl acetylenes, the method[56] described above is superior to all these methods. The diazoalkanes used are easily prepared from readily available starting materials, and can be stored under refrigeration for long periods without deterioration. In addition, the method is a simple one-step process, purification is facilitated by the water-solubility of all the unwanted products of the reaction, and a wide range of suitable ketones are available both commercially and from Friedel-Crafts reactions.

EXPERIMENTAL.

EXPERIMENTAL : CONTENTS.

6. Preparation of acetylenes:

7. Diethyl [1-diazo- 2-hydroxy- 2-(4-nitrophenyl)] -ethyl phosphonate:

EXPERIMENTAL

Melting points were recorded on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Pye Unicam SP1000 or on a Perkin-Elmer 225 double-beam spectrophotometer and are for liquid films, unless otherwise stated. U.v. spectra were recorded on a Pye Unicam SP600 spectrophotometer. ^{1}H n.m.r. spectra were measured on a Varian T-60 60 MHz. or on a Varian HA 100 100 MHz. spectrometer, with tetramethylsilane as internal reference, unless otherwise stated. ^{13}C n.m.r. spectra were measured on a Varian XL-100-12 FT spectrometer, at natural abundance. Raman spectra were recorded on a Spex Ramalog 4 laser spectrometer. Mass spectra were determined on an A.E.I.-G.E.C. MS12 spectrometer. Analytical g.l.c. was performed on Perkin-Elmer F11 and Pye Argon gas chromatographs; g.l.c. yields were normally calculated relative to diphenyl acetylene as internal standard, assuming identical detector response; in other cases, a standard solution of the compound under analysis was used as external standard.

Kieselgel G (Merck) was used for analytical t.l.c., while Kieselgel HF_{254} (Merck) was used for preparative t.l.c. Light petroleum refers to that fraction which boils between 60 and 80°. Organic solutions were concentrated on a Büchi rotary evaporator; all organic solutions were dried over anhydrous magnesium sulphate, unless otherwise stated.

Solvents were purified before use as follows: ether, benzene, toluene and xylene (AnalaR grade) were dried over sodium wire; methylene chloride was percolated

through alumina (Woelm basic, grade I) immediately before use; tetrahydrofuran and 1,4-dioxan were distilled from lithium aluminium hydride in an atmosphere of nitrogen, and stored under nitrogen over molecular sieves (Linde type 5A); acetonitrile was distilled from calcium hydride and stored over molecular sieves (Linde type 4A); dimethyl sulphoxide and hexamethylphosphoric triamide were dried over molecular sieves (Linde type 5A).

1. Preparation of trimethylsilyldiazomethane.

Trimethylsilyldiazomethane was prepared by a published procedure[1], and was obtained as a yellow oil, b.p. 94-5°/755mm., ν_{max} 2060, 1250, 1030, 840 cm^{-1}., $\tau(CDCl_3)$ 10.0 (9H, s , Me_3Si), 7.8 (1H, s , $C\underline{H}N_2$) (no tetramethylsilane added)

2. Reactions of trimethylsilyldiazomethane:

(a) with cyclohexanone:

(i) and potassium t-butoxide. A solution of trimethylsilyldiazomethane (230mg., 2mmol.) in dry benzene (5 ml.) was stirred with potassium t-butoxide (229mg., 2 mmol.) for 5 min., and a solution of freshly-distilled cyclohexanone (208 mg., 2 mmol.) in ether (3 ml.) was added. After 18h., the solution was poured into water, the organic layer separated, the aqueous layer extracted with ether (2 x 5 ml.), the combined organic solutions washed with brine, dried and concentrated *in vacuo* to give an oil, shown by t.l.c. (5% ethyl acetate/light petroleum) to consist largely of unreacted cyclohexanone.

(ii) and potassium hydroxide solution. A solution of trimethylsilyldiazomethane (230 mg., 2 mmol.) in benzene (5 ml.) was stirred vigorously with aqueous potassium hydroxide solution (2M; 1.5 ml., 3 mmol.) and a solution of cyclohexanone (206 mg., 2 mmol.) in ether (3 ml.) was added.

After 22h., work-up (as in section 2(a), (i)) gave an oil, shown by t.l.c. (5% ethyl acetate/light petroleum) to consist only of cyclohexanone.

2(a) ctd.

(iii) and n-butyl lithium. A solution of trimethylsilyldiazomethane (230 mg., 2 mmol.) in benzene (5 ml.) was stirred at room temperature under nitrogen, and treated with a solution of n-butyl lithium in hexane (2.1M; 0.95 ml., 2 mmol.); the yellow colour of the solution faded, and a fine white precipitate was formed. On addition of a solution of cyclohexanone (204mg., 2 mmol.) in ether (3 ml.), the precipitate disappeared and the solution regained its original colour.

After 21 h., work-up (as in 2(a), (i)) gave an oil, shown by preparative t.l.c. (5% ethyl acetate/light petroleum) to consist almost entirely of cyclohexanone.

(iv) and triethyloxonium fluoroborate. A solution of cyclohexanone (104 mg., 1.06 mmol.) in methylene chloride (5 ml.) was stirred at 0° under nitrogen and treated with triethyloxonium fluoroborate[33] (approx. 2 mmol.). A solution of trimethylsilyldiazomethane (180 mg., 1.6 mmol.) in methylene chloride (2 ml.) was added, and the solution was stirred for 16h. Anhydrous sodium carbonate (approx. 4 mmol.) was added, and stirring was continued for 1.5h., after which the solution was filtered and concentrated in vacuo to give a brown oil (98 mg.); preparative t.l.c. (10% ethyl acetate/ light petroleum) showed cyclohexanone to be the only significant component.

2 (ctd.)

(b) with benzophenone:

(i) without added base. A solution of trimethylsilyldiazomethane (230 mg., 2 mmol.) in benzene (5 ml.) was treated with a solution of benzophenone (365 mg., 2 mmol.) in ether (4 ml.) and stirred for 18h.

The solution was poured into water(10 ml.), the organic layer separated, the aqueous layer extracted with ether (2 x 5 ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo to give an oil, shown by g.l.c. (1% OV-17, 150°) to consist only of benzophenone.

(ii) and potassium hydroxide solution. A solution of trimethylsilyldiazomethane (230 mg., 2 mmol.) in benzene (5 ml.) was stirred vigorously with aqueous potassium hydroxide solution (2M; 1 ml., 2 mmol.) and a solution of benzophenone (365 mg., 2 mmol.) in ether (4 ml.) was added. After 18h., work-up (as in 2(b), (i)) gave an oil, shown by t.l.c. (20% ethyl acetate/light petroleum) to consist only of benzophenone.

(iii) and triethylamine. A solution of trimethylsilyldiazomethane (230 mg., 2 mmol.) in benzene (5 ml.) was treated with triethylamine (202 mg., 2 mmol.) and a solution of benzophenone (365 mg., 2 mmol.) in ether (4 ml.) was added.

After 21h., work-up (as in 2(b), (i)) gave unchanged benzophenone.

2(b) ctd.

(iv) and n-butyl lithium. A solution of trimethylsilyldiazomethane (114 mg., 1 mmol.) in benzene (5 ml.) was cooled to 0°, stirred under nitrogen, and treated with a solution of n-butyl lithium in hexane (2.1M; 0.48 ml., 1 mmol.). A solution of benzophenone (182 mg., 1 mmol.) in ether (5 ml.) was added, and the solution was allowed to warm up to room temperature.

After 2h., work-up (as in 2(b), (i)) gave a yellow oil (202 mg.). Preparative t.l.c. (20% ethyl acetate/light petroleum) gave pure diphenyl acetylene (60 mg., 34%), m.p. 60-61° (aqueous ethanol) (lit[34]: 62.5°); $\nu_{max.}$ 3060 , 1600 , 1500 $cm.^{-1}$, Raman spectrum (solid sample): 2240 , 1608 , 1165 , 1017 $cm.^{-1}$, $\tau(CCl_4)$: 2.7 (s, $C_6\underline{H}_5$).

A solution of trimethylsilyldiazomethane (170 mg., 1.5 mmol.) in ether (6 ml.) was cooled to 0°, stirred under nitrogen, and treated with a solution of n-butyl lithium in hexane (2.1M; 0.76 ml., 1.5 mmol.). A solution of benzophenone (182 mg., 1 mmol.) in ether (6 ml.) was added, and the solution was allowed to warm up to room temperature.

After 16h., work-up (as in 2(b), (i)) gave a yellow oil (260 mg.). Preparative t.l.c. (20% ethyl acetate/light petroleum) gave pure diphenyl acetylene (143 mg., 80%), identified by comparison (g.l.c., 1% OV-17, 150°) with an authentic sample.

2(b) ctd.

(v) and potassium t-butoxide. A solution of trimethylsilyldiazomethane (230 mg., 2 mmol.) in benzene (5 ml.) was treated with potassium t-butoxide (227 mg., 2 mmol.). After stirring for 5 min., a solution of benzophenone (365 mg., 2 mmol.) in benzene (4 ml.) was added. After 18h., work-up (as in 2(b), (i)) gave an oil (404 mg.,) which showed three components on g.l.c. analysis (1% OV-17, 150°). The major component was diphenyl acetylene (187 mg., 52%), and unreacted benzophenone was also recovered (61 mg., 17%). The third component (21mg.) was purified by preparative t.l.c. (20% ethyl acetate/light petroleum) to give a white crystalline solid, m.p. 53-4°, $\nu_{max.}$ 1685 $cm.^{-1}$, τ($CDCl_3$): 5.8 (2H, s , $PhC\underline{H}_2CO$), 2.8 (5H, s , $C_6\underline{H}_5CH_2$) , 2.6 (3H, m , 2,4,6- $C_6\underline{H}_5CO$) and 2.1 (2H, m , 3,5-$C_6\underline{H}_5CO$), which gave a 2,4-dinitrophenyl-hydrazone m.p. 203-4°, and was identified as phenyl benzyl ketone (lit[35]: m.p. of DNP derivative: 204°) by comparison (g.l.c., mixed m.p.) with an authentic sample. The yield of this component was thus 6%.

(vi) and triethyloxonium fluoroborate A solution of benzophenone (150mg., 0.85 mmol.) in methylene chloride (5 ml.) was stirred at 0° under nitrogen and treated with freshly-prepared triethyloxonium fluoroborate[33] (300mg., 1.6 mmol.). Trimethylsilyldiazomethane (180mg., 1.55 mmol.) was added, and the mixture was stirred 16h. at room temperature. Anhydrous sodium carbonate (approx. 2 mmol.) was added, and the mixture was stirred for 2.5h., filtered, and concentrated in

vacuo to give a brown oil, shown by t.l.c. (20% ethyl acetate/light petroleum) to consist of unchanged benzophenone.

(vii) and boron trifluoride etherate. A solution of benzophenone (150 mg., 0.85 mmol.) and boron trifluoride etherate (120 mg., 0.85 mmol.) in ether (1.5ml.) was stirred under nitrogen at -78°, and treated with trimethylsilyldiazomethane (95 mg., 0.85 mmol.). The mixture was stirred at -78° for 10 min., then at room temperature for 1.5h., and then treated with saturated sodium bicarbonate solution and stirred 16h. at room temperature. The organic layer was separated, the aqueous layer extracted with ether (2 x 5ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo to give a yellow oil (137 mg.) shown by t.l.c. (20% ethyl acetate/light petroleum) to consist of unchanged benzophenone.

(c) with acetophenone: A solution of trimethylsilyldiazomethane (132 mg., 1.15 mmol.) in ether (5 ml.) was cooled to 0°, stirred under nitrogen, and treated with a solution of n-butyl lithium in hexane (2.1M, 0.5 ml., 1.05 mmol.). A solution of freshly-distilled acetophenone (100 mg., 0.85 mmol.) in ether (3 ml.) was added, and the cooling bath removed. After 30 min., the solution was treated with water (5 ml.), the organic layer separated, the aqueous layer extracted with ether (2 x 5ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo to give an oil (163 mg.). Preparative t.l.c. (20% ethyl acetate/light

petroleum) gave acetophenone (70mg., 70%), identified by comparison with an authentic sample, and a small amount of a substance presumed to be 1-phenyl propyne, from its i.r. spectrum: $\nu_{max.}$ 3080 , 2970 , 2265 , 2230 , 1600 , 1500 $cm.^{-1}$

(d) with di-t-butyl ketone:

A solution of trimethylsilyldiazomethane (360 mg., 3,1 mmol.) in 30% hexamethylphosphoric triamide (HMPT) in THF (5ml.) was treated , at 0° with stirring in an atmosphere of nitrogen, with a solution of n-butyl lithium in hexane (2.1M; 1.4ml., 2.94 mmol.). A solution of di-t-butyl ketone (130mg., 0.9 mmol.) in 30% HMPT/THF (5 ml.) was added, the cooling bath was removed, and stirring was continued for 16 h. Work-up (as in 2(c)) gave an oil, shown by t.l.c. (10% ethyl acetate/light petroleum) to consist of unchanged di-t-butyl ketone.

(e) with benzil:

A solution of trimethylsilyldiazomethane (137 mg., 1.2 mmol.) in ether (5 ml.) was cooled to 0°, stirred in an atmosphere of nitrogen, and treated with a solution of n-butyl lithium in hexane (2.3M; 0.6ml., 1.38 mmol.). A solution of benzil (164mg., 0.75 mmol.) in ether (5 ml.) was added; the colour of the solution changed to red, brown and eventually black. After 10 min., work-up (as in 2(c)) gave a brown oil (220 mg.) Preparative t.l.c. (20% ethyl acetate/light petroleum)

gave 1,3-diphenyl-prop-2-yn-1-one[36] 10 (90 mg., 59%) as an oil, ν_{max} 2215 , 1645 cm.$^{-1}$, τ ($CDCl_3$) 2.75 (s); and a more polar compound, an impure yellow solid; successive trituration with pentane, 1:1 ether/pentane and ether removed the yellow impurity, and recrystallisation from ether/pentane gave a white solid (20mg.), m.p. 162-4°, ν_{max} (CCl_4) 3460 , 3260b , 3060 , 2960 , 1665 , 1245 , 1165 , 910 cm.$^{-1}$, λ_{max}^{EtOH} 253(ε = 7450) and 212(ε = 13360)nm., τ($CDCl_3$): 9.7 (9H, s , Me_3Si) , 2.7 (6H, bs , $C_6\underline{H}_5$ and N$\underline{H}$, one H exchanges with D_2O) , 2.5 (3H, m , 2,4,6-$C_6\underline{H}_5CO$) and 1.9 (2H, m , 3,5-$C_6\underline{H}_5CO$); $\underline{M}^+$: 320; this compound was therefore identified as 5-benzoyl, 4-phenyl, 3-trimethylsilyl-(1H)-pyrazole 12. (Found: C, 70.8; H, 6.66; N, 8.35. $C_{19}H_{20}N_2OSi$ requires C, 71.2; H, 6.29; N, 8.74.) The yield of this compound was thus 8%.

(f) with benzaldehyde:

A solution of trimethylsilyldiazomethane (228 mg., 2 mmol.) in benzene (5 ml.) was stirred under nitrogen, cooled to 0° and treated with a solution of n-butyl lithium in hexane (2.1M; 0.96 ml., 2 mmol.). A solution of freshly-distilled benzaldehyde (106 mg., 1 mmol.) in ether (5 ml.) was added, and the cooling bath was removed. After 18 h., work-up (as in 2(c)) gave an oil which showed two components on t.l.c. (10% ethyl acetate/light petroleum); the less polar component was an oil ν_{max} 1260, 1080 and 860 cm.$^{-1}$, τ($CDCl_3$) 9.9 (9H, s , Me_3Si), 4.3 (2H, s , $PhC\underline{H}_2O$), 2.6 (5H, m , Ph) and was identified as benzyloxy-trimethylsilane 14 by

g.l.c. comparison (1% OV-1, 85°) with an authentic sample; the more polar component was a yellow oil, ν_{max} 2140, 1630, 1380 $cm.^{-1}$, $\tau(CDCl_3)$ 5.7 (1H, s, $C\underline{H}N_2$) and 2.6 (5H, m, PhCO-), and was identified as α-diazo-acetophenone 15 by comparison with an authentic sample. The ^1H n.m.r. spectrum of the product mixture showed that these compounds were present in approximately equimolar amounts.

(g) with cyclododecanone.

A solution of trimethylsilyldiazomethane (115 mg., 1 mmol.) in benzene (2.5 ml.) was stirred under nitrogen, cooled to 0° and treated with a solution of n-butyl lithium in hexane (2.1M; 0.48 ml., 1 mmol.). A solution of cyclododecanone (182 mg., 1 mmol.) in ether (2 ml.) was added, and the cooling bath was removed.

After 18 h., work-up (as in 2(c)) gave an oil, shown by t.l.c. (10% ethyl acetate/light petroleum) to consist mainly of cyclododecanone.

3. Preparation of dimethylphosphonodiazomethane[14] and diethylphosphonodiazomethane.

A solution of N-(bromomethyl-) phthalimide[37] (120g., 500 mmol.) in dry xylene (380ml.) was stirred in an atmosphere of nitrogen, and heated to 120°. Trimethyl phosphite (59 ml., 62g., 500 mmol.) was added dropwise, and the solution was heated at reflux for 3h., and allowed to cool overnight. Light petroleum (490 ml.) was added slowly, with stirring, and the solution was allowed to stand for 2h. The precipitated solid was filtered off and dried in an evacuated desiccator to give N-(dimethylphosphono-methyl-)phthalimide as white crystals (116g., 86%) m.p. 112-4° (lit.[14] 114-5°). This compound was dissolved in methanol (435 ml.) and the solution treated successively with hydrazine hydrate (21.5g., 430 mmol.) and acetic acid (50 ml.), and heated 1h. at reflux. The solution was cooled to -5°, filtered and concentrated *in vacuo* at 30°; the residue was taken up in a solution of acetic acid (50 ml.) in water (430 ml.) and extracted with methylene chloride (4 x 50 ml.); the aqueous layer was then filtered and stirred vigorously at -5° with methylene chloride (280 ml.). A solution of sodium nitrite (30g., 434 mmol.) in water (75 ml.) was added, and stirring and cooling was continued for 1h. The methylene chloride layer was separated, and the aqueous layer extracted with methylene chloride (4 x 80ml.); the combined organic extracts were washed with saturated sodium bicarbonate solution (3 x 50 ml.), dried over sodium sulphate and concentrated *in vacuo* at 30° to give crude dimethyl-

phosphono-diazomethane as an orange oil (23.7g., 158 mmol., 37%). The crude product was dissolved in ether (50 ml.), filtered through a short column of alumina (Woelm neutral, grade III), and the solution concentrated *in vacuo* at 30°. Distillation gave pure dimethylphosphono-diazomethane, b.p. 59° (0.1mm. Hg.) as a yellow oil (10.5g., 70 mmol., 16%) ν_{max} 2110 and 1250 $cm.^{-1}$; τ ($CDCl_3$) 6.3 (6H, d , J = 11.5 Hz., $C\underline{H}_3O$-P(O)-) and 5.5 (1H, d , J = 11 Hz., -$C\underline{H}N_2$).

Diethylphosphonodiazomethane was prepared by a published procedure[38] from N-(bromomethyl)-phthalimide[37] (70g., 291 mmol.) and triethyl phosphite (52 ml., 49.7g., 299 mmol.), and was obtained as a yellow oil, b.p. 52° (0.1 mm. Hg.) (15.8g., 89 mmol., 31%), ν_{max} 2113 and 1253 $cm.^{-1}$; ^{13}C n.m.r.: δ (C_6D_6) 16.29 (d, $^3J_{P-C}$ = 6.6 Hz., $\underline{C}H_3$) , 29.64 (d, $^1J_{P-C}$ = 225.9 Hz., $\underline{C}HN_2$) and 62.44 (d, $^2J_{P-C}$ = 5.1 Hz., $\underline{C}H_2O$).

4. Reactions of dimethylphosphonodiazomethane:

(a) with benzophenone:

(i) and n-butyl lithium. A solution of dimethylphosphonodiazomethane (165 mg., 1.1 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen, and treated with a solution of n-butyl lithium in hexane (2M; 0.6ml., 1.2 mmol.); the colour of the solution changed from yellow to red. A solution of benzophenone (140 mg., 0.77 mmol.) in THF (5 ml.) was added, and the cooling bath was removed.

After 16h., the solution was poured into water (5 ml.), the organic layer separated, the aqueous layer extracted with ether (2 x 5ml.) and the combined organic solutions washed with brine, dried and concentrated *in vacuo* to give a yellow solid. Preparative t.l.c. (20% ethyl acetate/light petroleum) gave pure diphenyl acetylene as a white crystalline solid (106 mg., 79%) m.p. 60-61° (lit. 62.5°), identified by comparison with an authentic sample.

The above experiment was repeated, using 95 mg. dimethylphosphonodiazomethane (0.63 mmol.), the equivalent amount of n-butyl lithium in hexane, and 52 mg. benzophenone (0.29 mmol.); the product was analysed by g.l.c. (1% OV-1, 125°). The yield of diphenyl acetylene was 48 mg. (94%).

(ii) and potassium t-butoxide. A solution of dimethylphosphonodiazomethane (153 mg., 1.02 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen and treated with a suspension of potassium t-butoxide (119 mg., 1.06

mmol.) in THF (5 ml.). A solution of benzophenone (107 mg., 0.59 mmol.) in THF (5 ml.) was added, and the cooling bath was removed.

After 16h., work-up (as in section 4(a), (i)) gave a yellow solid (104 mg.). Preparative t.l.c. (20% ethyl acetate/light petroleum) gave pure diphenyl acetylene, m.p.60-61° (lit.[34] 62.5°) , identified by comparison with an authentic sample.

(iii) and sodium ethoxide. A solution of dimethylphosphonodiazomethane (132mg., 0.88 mmol.) and benzophenone (150 mg., 0.82 mmol.) in dry ethanol (7 ml.) was treated with a solution of sodium ethoxide (0.82 mmol.) in ethanol (3 ml.) and heated at reflux for 2h. The solution was cooled, poured into water (25 ml.) and extracted with ether (3 x 10 ml.). The combined ethereal extracts were washed with brine, dried and concentrated in vacuo to give a colourless oil (117 mg.). Preparative t.l.c. (20% ethyl acetate/light petroleum) gave diphenyl acetylene (8mg., 5%) and unchanged benzophenone (98 mg., 65%), both of which were identified by comparison with authentic samples.

(iv) and methylmagnesium chloride. A solution of dimethylphosphonodiazomethane (250 mg., 1.66 mmol.) in THF (6 ml.) was stirred at -78° under nitrogen and treated with a solution of methylmagnesium chloride (3M; 0.55 ml., 1.65 mmol.) . After 10min., a solution of benzophenone (265 mg., 1.45 mmol.) in THF (5 ml.) was added, and the cooling bath was removed.

After 16h., work-up (as in 4(a),(i)) gave a yellow oil (248 mg.). Preparative t.l.c. (20% ethyl

acetate/light petroleum) gave unchanged benzophenone (135 mg., 50%) and diphenyl acetylene (90 mg., 35%), both of which were identified by comparison with authentic samples.

(v) and DBN. A solution of dimethylphosphono-diazomethane (290 mg., 1.94 mmol.) and benzophenone (195 mg., 1.05 mmol.) in THF (10 ml.) was treated with DBN (240 mg., 1.92 mmol.) and stirred for 16h. Water (5 ml.) was added, the mixture was stirred for 5 min., treated with saturated ammonium chloride solution (10 ml.) and extracted with pentane (4 x 5 ml.); the combined organic extracts were washed with brine, dried and concentrated in vacuo to give an oil (156 mg.), shown by t.l.c. (20% ethyl acetate/light petroleum) to consist only of benzophenone.

The above experiment was repeated, using 20% HMPT in THF as solvent; the same result was observed.

The above experiment was repeated, using 20% HMPT in THF as solvent, in the presence of lithium perchlorate (212 mg., 1.93 mmol.); the same result was observed.

(vi) and piperidinium acetate. To a solution of piperidine (94 mg., 1.1 mmol.) and acetic acid (66 mg., 1.1 mmol.) in THF (10 ml.) were added dimethylphosphono-diazomethane (145 mg., 0.97 mmol.) and benzophenone (150 mg., 0.83 mmol.). After stirring for 16h., t.l.c. (20% ethyl acetate/light petroleum) showed that no change had taken place. The solution was then heated under reflux for 8 days, cooled, and treated with brine (10 ml.); the organic phase was separated, the aqueous phase extracted with ether (3 x 5ml.), the combined organic solutions

washed with brine, dried and concentrated *in vacuo* to give an oil, shown by t.l.c. to consist of benzophenone.

(*vii*) *and diethylamine.* To a solution of dimethylphosphonodiazomethane (167 mg., 1.1 mmol.) and benzophenone (175 mg., 0.96 mmol.) in acetonitrile (5 ml.) was added diethylamine (25mg.), and the solution was stirred overnight, poured into water (5 ml.), extracted with pentane (3 x 5 ml.), the combined organic extracts washed with brine, dried and concentrated *in vacuo* to give a colourless oil (168 mg.), shown by t.l.c. (20% ethyl acetate/light petroleum) to consist of benzophenone.

The above experiment was repeated in the presence of lithium perchlorate (120 mg., 1.12 mmol.); the same result was observed.

A solution of benzophenone (60 mg., 0.33 mmol.) in 1,4-dioxan (12 ml.) was stirred under nitrogen and treated with silver heptafluorobutyrate (5 mg.); dimethylphosphonodiazomethane (60 mg., 0.40 mmol.) and diethylamine (10 mg.) were added, and the solution was heated 16h. at reflux, cooled, and the supernatant liquid removed and concentrated *in vacuo*. The gummy residue was extracted with toluene (5 ml.) and the extract concentrated *in vacuo* to give an oil, shown by t.l.c. to consist only of benzophenone.

(*viii*) *and triethyloxonium fluoroborate.* A solution of benzophenone (175 mg., 0.96 mmol.) in methylene chloride (5 ml.) was stirred at 0° under nitrogen and treated successively with triethyloxonium fluoroborate[33] (300 mg., 1.6 mmol.) and dimethylphosphonodiazomethane

(250 mg., 1.67 mmol.). After 16h., ether (20 ml.) was added, and the supernatant liquid decanted; the residue was washed with ether (10 ml.), and the combined solutions were centrifuged, decanted, dried and concentrated *in vacuo* to give a colourless oil, shown by t.l.c. (20% ethyl acetate/light petroleum) to consist of benzophenone.

(b) with benzil:

(i) and n-butyl lithium. A solution of dimethylphosphonodiazomethane (550 mg., 3.7 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen and treated with a solution of n-butyl lithium in hexane (2.3M; 1.2 ml., 2.76 mmol.) to give a cloudy yellow-orange solution; after 5 min., a solution of benzil (150 mg., 0.72 mmol.) in THF (5 ml.) was added, and the cooling bath was removed; the colour of the solution changed to purple.

After 4h., water (5 ml.) was added, the organic layer was separated, the aqueous layer extracted with ether (2 x 5ml.), the combined organic solutions washed with brine, dried and concentrated *in vacuo* to give an orange oil (175 mg.). Preparative t.l.c. (20% ethyl acetate/light petroleum) gave 1,3-diphenyl-prop-2-yn-1-one **10** as an oil (35mg., 25%) ν_{max} 3090, 2215, 1645 $cm.^{-1}$, $\tau(CCl_4)$ 2.75 (s), identified by comparison with an authentic sample.[36]

(ii) and diethylamine. A solution of dimethylphosphonodiazomethane (280 mg., 1.87 mmol.) in acetonitrile (3 ml.) was treated successively with a solution of benzil (380 mg., 1.8 mmol.) in acetonitrile (4 ml.), and diethylamine (70 mg., 1 mmol.).

The mixture was stirred at room temperature for 22h., poured into water (10 ml.), extracted with light petroleum (3 x 10 ml.), the combined organic solutions washed with brine, dried and concentrated *in vacuo* to give a yellow solid (167 mg.), which was shown to be unchanged benzil.

(c) with acetophenone:

(i) and n-butyl lithium. A solution of dimethylphosphonodiazomethane (165 mg., 1.1 mmol.) in THF (5 ml.) was stirred under nitrogen at -78° and treated with a solution of n-butyl lithium in hexane (2M; 0.6 ml., 1.2 mmol.); a solution of redistilled acetophenone (120 mg., 1 mmol.) in THF (5 ml.) was added, and the cooling bath was removed.

After 17 h., work-up (as in section 4(a),(i)) gave a yellow oil (134 mg.); preparative t.l.c. (20% ethyl acetate/light petroleum) gave acetophenone (60mg., 50%) and 1-phenyl-propyne (10 mg., 9%) as an oil, ν_{max} 3080 , 2970 , 2265 , 2230 , 1600 $cm.^{-1}$, $\tau(CDCl_3)$ 8.0 (3H, s , $C\underline{H}_3$) , 2.7 (5H, m , $C_6\underline{H}_5$).

(ii) and potassium t-butoxide. A solution of dimethylphosphonodiazomethane (270 mg., 1.8 mmol.) in THF (6 ml.) was stirred under nitrogen at -78°, and a suspension of potassium t-butoxide (205 mg., 1.8 mmol.) in THF (7 ml.) was added; a solution of redistilled acetophenone (116 mg., 0.97 mmol.) in THF (5 ml.) was added, and the cooling bath was removed.

After 15h., work-up (as in 4(a), (i)) gave a pale yellow oil (116 mg.); preparative t.l.c.

(20% ethyl acetate/light petroleum) gave acetophenone (60 mg., 50%) and 1-phenyl-propyne (25 mg., 22%), both of which were identified by comparison with authentic samples.

(iii) and sodium ethoxide. A solution of dimethylphosphonodiazomethane (245 mg., 1.63 mmol.) in dry ethanol (6 ml.) was stirred at -78° and treated with a solution of sodium ethoxide prepared by adding sodium (38 mg.) to dry ethanol (10 ml.); a solution of redistilled acetophenone (119 mg., 1 mmol.) in ethanol (5 ml.) was added, and the mixture was allowed to warm up to room temperature.

After 41 h., work-up (as in 4(a), (iii)) gave an oil (65 mg.), shown to be unchanged acetophenone by comparison with an authentic sample.

(iv) and lithium di-iso-propylamide. A solution of redistilled acetophenone (120 mg., 1 mmol.) and dimethylphosphonodiazomethane (165 mg., 1.1 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen, and treated with a solution of lithium di-iso-propylamide (prepared by adding a solution of n-butyl lithium in hexane (2M; 0.6ml., 1.2 mmol.) to di-iso-propylamine (110mg., 1.1 mmol.) in THF (5 ml.) at room temperature, under nitrogen). Stirring was continued for 20 min. at -78°, and then for 16 h. at room temperature; brine (5 ml.) was added, the organic layer separated, the aqueous layer extracted with ether (3 x 5 ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo to give an oil, shown to be acetophenone by comparison with an authentic sample.

(v) and diethylamine. A solution of dimethylphosphonodiazomethane (405 mg., 2.7 mmol.), redistilled acetophenone (310 mg., 2.58 mmol.) and diethylamine (50 mg., 0.7 mmol.) in acetonitrile (10 ml.) was stirred at room temperature for 72 h., poured into water, extracted with pentane (4 x 5 ml.), the combined organic extracts washed with brine, dried and concentrated *in vacuo* to give a colourless oil (140 mg.), shown to consist only of acetophenone by comparison with an authentic sample.

(d) with 1,3-diphenyl-prop-2-yn-1-one (10):

A solution of dimethylphosphonodiazomethane (190 mg., 1.26 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen and treated with a solution of n-butyl lithium in hexane (2M; 0.6 ml., 1.2 mmol.); after 5 min., a solution of 1,3-diphenyl-prop-2-yn-1-one (70mg., 0.3 mmol.) in THF (5 ml.) was added, and the cooling bath was removed; after 16 h., saturated ammonium chloride solution (10 ml.) was added, the organic phase was separated, the aqueous phase extracted with ether (3 x 5ml.), the combined organic extracts washed with brine, dried and concentrated *in vacuo* to give a brown oil (117 mg.); t.l.c. comparison with an authentic sample of 1,4-diphenyl-buta-1,3-di-yne[25] showed that none of this compound was present in the product mixture.

(e) with di-t-butyl ketone:

A solution of dimethylphosphonodiazomethane (270 mg., 1.8 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen, and treated with a solution of n-butyl lithium in hexane (2M; 0.9 ml., 1.8 mmol.); a solution

of di-t-butyl ketone (140 mg., 1 mmol.) in THF(5 ml.) was added, and the cooling bath was removed; after 16 h., work-up (as in 4 (a),(i)) gave an oil, shown to consist of unchanged di-t-butyl ketone by comparison with an authentic sample.

(f) with phenyl-acetaldehyde:

A solution of dimethylphosphonodiazomethane (114 mg., 0.76 mmol.) in dimethyl sulphoxide (2 ml.) was stirred at -78°, and a suspension of potassium t-butoxide (75 mg., 0.67 mmol.) in THF (5 ml.) was added; after 5 min., a solution of phenyl-acetaldehyde (85 mg., 0.7 mmol.) in THF (2 ml.) was added, and the cooling bath was removed.

After 16h., work-up (as in 4(a),(i)) gave an oil (78 mg.); preparative t.l.c. (10% ethyl acetate/light petroleum) gave 3-phenyl propyne as an oil (24 mg., 30%) ν_{max} 3300 , 2145 , 1600 $cm.^{-1}$, τ ($CDCl_3$) 8.0 (1H, t , J = 2Hz., $C\underline{H}$) , 6.45 (2H, d , J = 2Hz., $C\underline{H}_2$) , 2.75 (5H, s , $C_6\underline{H}_5$).

(g) with cinnamaldehyde:

A solution of dimethylphosphonodiazomethane (310 mg., 2.06 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen, and treated with a solution of n-butyl lithium in hexane (2M, 1 ml., 2 mmol.); after 5 min., a solution of cinnamaldehyde (freshly distilled; 130 mg., 1 mmol.) in THF (5 ml.) was added, and the cooling bath was removed.

After 16 h., work-up (as in 4(d)) gave an oil (144 mg.), shown by t.l.c. to consist largely of unchanged cinnamaldehyde.

5. Reactions of diethylphosphonodiazomethane:

(a) with benzophenone:

(i) and n-butyl lithium. A solution of diethylphosphonodiazomethane (187 mg., 1.05 mmol.) in THF (10 ml.) was stirred at -78° under nitrogen and treated with a solution of n-butyl lithium in hexane (2.2M; 0.47 ml., 1.03 mmol.); a solution of benzophenone (76 mg., 0.42 mmol.) in THF (2 ml.) was added, and the cooling bath was removed. After 1 h., the solution was concentrated in vacuo, water(5 ml.) and ether (5 ml.) were added, the organic layer was separated, and the aqueous layer extracted with ether (2 x 5 ml.); the combined organic solutions were washed with brine, dried and concentrated in vacuo to give an oil (85 mg.), shown by g.l.c. (1% OV-1, 125°) to contain diphenyl acetylene (70 mg., 94%) and benzophenone (2 mg., 2.6%).

(ii) and lithium di-iso-propylamide. A solution of diethylphosphonodiazomethane (218 mg., 1.22 mmol.) in THF (10 ml.) was stirred at -78° under nitrogen and treated with a freshly-prepared solution of lithium di-iso-propylamide (1.14 mmol.) in THF (1 ml.), followed by a solution of benzophenone (81 mg., 0.45 mmol.) in THF (2 ml.); the cooling bath was removed, and stirring continued for 2 h. Work-up (as in 5(a),(i)) gave an oil (70 mg.), shown by g.l.c. (1% OV-1, 125°) to contain diphenyl acetylene (52 mg., 66%) and benzophenone (15 mg., 19%).

(iii) and sodium hydroxide solution. A solution of diethylphosphonodiazomethane (210 mg., 1.18 mmol.) and benzophenone (75 mg., 0.41 mmol.) in ethanol (15 ml.)

was treated with aqueous sodium hydroxide solution (1M; 25 ml., 25 mmol.) and heated at reflux for 72 h. The cooled solution was neutralised with dilute hydrochloric acid (5M) and extracted with ether (3 x 10 ml.); the combined organic solutions were washed with brine, dried and concentrated *in vacuo* to give an oil, shown by t.l.c. to consist only of unreacted benzophenone.

(b) with phenyl benzyl ketone: A solution of diethylphosphonodiazomethane (174 mg., 0.98 mmol.) in THF (10 ml.) was stirred at -78° under nitrogen and treated with a suspension of potassium t-butoxide (109 mg., 0.97 mmol.) in THF (10 ml.); a solution of phenyl benzyl ketone (63 mg., 0.32 mmol.) in THF (2 ml.) was added, and the cooling bath was removed.

After 16 h., work-up (as in 5(a), (i)) gave an oil (48 mg.) which was analysed by g.l.c. (1% OV-1, 125°) and found to contain phenyl benzyl ketone as the only volatile component.

(c) with di-benzyl ketone.:

A solution of diethylphosphonodiazomethane (174 mg., 0.98 mmol) in THF (10 ml.) was stirred at -78° under nitrogen, and treated with a suspension of potassium t-butoxide (107 mg., 0.95 mmol.) in THF (10 ml.); a solution of di-benzyl ketone (87 mg,, 0.41 mmol.) in THF (2 ml.) was added, and the cooling bath was removed.

After 16 h., work-up (as in 5(a),(i)) gave an oil (41 mg.), shown by g.l.c. (1% OV-1, 110°) to contain di-benzyl ketone as the only volatile component.

(d) with di-cyclohexyl ketone:

A solution of diethylphosphonodiazomethane (175 mg., 0.98 mmol.) in THF (10 ml.) was stirred at -78° under nitrogen and treated with a suspension of potassium t-butoxide (109 mg., 0.97 mmol.) in THF (10 ml.); a solution of di-cyclohexyl ketone[39] (80 mg., 0.41 mmol.) in THF (2 ml.) was added, and the cooling bath was removed. After 16 h., work-up (as in 5(a), (i)) gave an oil (95 mg.) which was analysed by g.l.c. (1% OV-1, 110°) and found to contain di-cyclohexyl ketone as the only volatile component.

6: General method for preparation of acetylenes:

A solution of dimethylphosphonodiazomethane in THF (15 ml./mmol.) was stirred at -78° under nitrogen, and treated with a solution of n-butyl lithium in hexane; a solution of the carbonyl compound in THF (10 ml./mmol.) was added, and the cooling bath was removed.

After stirring for 16 h. at room temperature, the reaction mixture was diluted with water (5 ml. per mmol. of diazoalkane used), the organic layer separated, the aqueous layer extracted with ether (3 x 5 ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo.

6(a) Di-p-tolyl acetylene:

Reaction of dimethylphosphonodiazomethane (102 mg., 0.68 mmol.) with n-butyl lithium (1.8M; 0.38 ml., 0.68 mmol.) and 4,4' - dimethyl-benzophenone (70 mg., 0.33 mmol.) gave 88 mg crystals, m.p. 121-3°; g.l.c. analysis (1% OV-17, 140°) showed the presence of di-p-tolyl acetylene, R.I. 2130, (66mg., 97%).

Recrystallisation from light petroleum gave di-p-tolyl acetylene as white crystals, m.p. 134-5° (lit.[40] 135-6°), ν_{max} (CCl_4) 3060 , 2940 , 1600 $cm.^{-1}$, τ (CCl_4) 7.72 (6H, s , $C\underline{H}_3$) , 3.03 (4H, d , J = 7Hz., 3,5- $C_6\underline{H}_4$) , 2.72 (4H, d , J = 7Hz., 2,6- $C_6\underline{H}_4$) , Raman spectrum (solid sample, excitation at 5145 Å): 2233 , 1622 , 1145 $cm.^{-1}$, $\underline{M}^+$ 206 ($C_{16}H_{14}$ requires 206).

6(b) p-Chlorophenyl phenyl acetylene:

Reaction of dimethylphosphonodiazomethane (43 mg., 0.29 mmol.) with n-butyl lithium (1.8M; 0.16 ml., 0.29 mmol.) and p-chloro-benzophenone (31 mg., 0.14 mmol.) gave a crystalline solid (45 mg.), g.l.c. analysis of which (1% QF-1, 155°) showed the presence of p-chlorophenyl phenyl acetylene, R.I. 2105, (30mg., 100%).

Preparative t.l.c. (20% ethyl acetate/ light petroleum) gave p-chlorophenyl phenyl acetylene (25 mg., 82%) as white crystals, m.p. 82-3° (lit.[41] 83-4°), ν_{max} (CCl_4) 3060, 3020 , 2220 $cm.^{-1}$, τ (CCl_4) 2.7 (m), $\underline{M}^+$ 212, 214. ($C_{14}H_9Cl$ requires 212, 214).

6(c) m-Nitrophenyl phenyl acetylene:

Reaction of dimethylphosphonodiazomethane (160 mg., 1.07 mmol.) with n-butyl lithium (1.8M; 0.6 ml., 1.07 mmol.) and m-nitro-benzophenone[42] (100 mg., 0.44 mmol.) gave an oil (80 mg.); purification by preparative t.l.c. (20% ethyl acetate/light petroleum) gave m-nitrophenyl phenyl acetylene as yellow crystals, (38 mg., 32%) m.p. 56-7° (light petroleum) (lit.[43]), ν_{max} 3080 , 2220 , 2200 , 1595 , 1520 , 1350 $cm.^{-1}$, τ (CCl_4) 2.5 (5H, m , $C_6\underline{H}_5$), 2.2 (2H, m , 3,5-$C_6\underline{H}_4$), 1.7 (2H, m , 2,6-$C_6\underline{H}_4$),

$\underline{M}^+$ 223 ($C_{14}H_9NO_2$ requires 223).

6(d) p-Phenylethynyl anisole:

Reaction of dimethylphosphonodiazomethane (150 mg., 1 mmol.) with n-butyl lithium (1.8M; 0.6 ml, 1.08 mmol.) and p-methoxy-benzophenone[44] (95 mg., 0.45 mmol.) gave an oil (70 mg.), g.l.c. analysis of which (1% OV-17, 140°) showed the presence of p-phenylethynyl-anisole, R.T. 21.2min., (61 mg., 66%).

Purification by preparative t.l.c. (20% ethyl acetate/light petroleum) gave p-phenylethynyl-anisole as white crystals, m.p. 58-9° (aq. ethanol) (lit.[45] 59-60°), ν_{max} 3060, 2960 , 2220 , 1610 , 1600 $cm.^{-1}$, τ (CCl_4) 6.2 (3H, s , $OC\underline{H}_3$), 3.2 (2H, d , J= 8Hz., 3,5-$C_6\underline{H}_4$), 2.6 (5H, m , C_6H_5), 2.5 (2H, d, J = 8Hz., 2,6-$C_6\underline{H}_4$),

$\underline{M}^+$ 208 ($C_{15}H_{12}O$ requires 208).

6(e) Di-2-naphthyl acetylene:

Reaction of dimethylphosphonodiazomethane (75 mg., 0.5 mmol.) with n-butyl lithium (1.8M; 0.3ml., 0.54 mmol.) and di-2-naphthyl ketone[45] (15 mg., 0.05 mmol.) gave a crystalline solid (14 mg.), g.l.c. analysis of which (1% QF-1, 225°) showed the presence of di-2-naphthyl acetylene, R.T. 5.5 min., (11mg., 75%).

Purification by preparative t.l.c. (20% ethyl acetate/light petroleum) gave di-2-naphthyl acetylene as white crystals, m.p. 225-6° (light petroleum) (lit.[46] 228-9°); ν_{max} (CCl_4) 3040, 1600, 1500 $cm.^{-1}$, λ_{max} (EtOH): 332, 315 and 265 nm., (lit.[46] 336, 317 and 267 nm.) M^+ 278 ($C_{22}H_{14}$ requires 278).

6(f) p-Phenylethynyl-benzophenone and p-bis-(phenylethynyl)-benzene:

Reaction of dimethylphosphonodiazomethane (43 mg., 0.29 mmol.) with n-butyl lithium (1.8M; 0.16 ml., 0.29 mmol.) and 1,4-dibenzoyl-benzene[47] (23 mg., 0.08 mmol.) gave a crystalline solid (32 mg.), g.l.c. analysis of which (1% QF-1, 225°) showed the presence of p-bis-(phenylethynyl)-benzene, R.T. 2.9 min., (5.0 mg., 23%) and p-phenylethynyl-benzophenone, R.T. 3.6 min., (16.7 mg., 73%).

Purification by preparative t.l.c. (20% ethyl acetate/light petroleum) gave p-bis-(phenylethynyl)-benzene as pink crystals, (3 mg., 13%) m.p. 178-9° (light petroleum) (lit.[48] 181-2°),

ν_{max} (CCl_4) 3080, 3060, 3030, 2210 $cm.^{-1}$, λ_{max} (hexane): 335, 315, 223 nm. (lit.[48] 337, 318, 222 nm.);
M^+ 278 ($C_{22}H_{14}$ requires 278);

and p-phenylethynyl-benzophenone as yellow crystals, (15 mg., 66%) m.p. 121-2° (light petroleum), ν_{max} (CCl_4) 3080, 3060, 3040, 2230, 1665, 1600 $cm.^{-1}$, Mass spectrum: 282 (M^+), 205 (M^+-PhCHO), 105 ($Ph\overset{+}{C}O$), 77 (Ph^+); ($C_{21}H_{14}O$ requires 282).
Elemental analysis: C, 89.26; H, 5.12.
($C_{21}H_{14}O$ requires C, 89.33; H, 5.00.).

6(g) 2-Phenylethynyl-thiophene:

Reaction of dimethylphosphonodiazomethane (107 mg., 0.71 mmol.) with n-butyl lithium (1.8M; 0.4 ml., 0.72 mmol.) and 2-benzoyl-thiophene[49] (50 mg., 0.27 mmol.) gave an oil (43 mg.), g.l.c. analysis of which (1½% QF-1, 145°) showed the presence of 2-phenylethynyl-thiophene, R.I. 1950, (21 mg., 44%) and 2-benzoyl-thiophene, R.I. 2090, (7 mg., 14%).

Purification by preparative t.l.c. (20% ethyl acetate/light petroleum) gave 2-phenylethynyl-thiophene[50] as white crystals (20 mg., 41%), m.p. 48-9° (aq. ethanol), ν_{max} 3100, 3070, 2190, 1590, 1210 $cm.^{-1}$, τ (CCl_4) 2.6 (7H, m, $C_6\underline{H}_5$ and 3,4-$C_4\underline{H}_3S$), 3.0 (1H, m, 5-C_4H_3S);
M^+ 184 ($C_{12}H_8S$ requires 184).

6(h) 3-Phenylethynyl-pyridine:

Reaction of dimethylphosphonodiazomethane (350 mg., 2.33 mmol.) with n-butyl lithium (1.8M; 1.3 ml., 2.34 mmol.) and 3-benzoyl pyridine[51] (100 mg., 0.55 mmol.) gave an oil (107 mg.).

Purification by preparative t.l.c. (ethyl acetate) gave 3-phenylethynyl-pyridine as white crystals (37 mg., 38%), m.p. 46-7° (ethyl acetate/light petroleum) (lit.[52] 47-48.5°),

ν_{max} 3080, 3060, 3030, 2220, 1600, 1560 $cm.^{-1}$,

$\tau(CCl_4)$ 2.7 (m);

M^+ 179 ($C_{13}H_9N$ requires 179).

6(i) Cyclohexyl phenyl acetylene:

Reaction of dimethylphosphonodiazomethane (86 mg., 0.57 mmol.) with n-butyl lithium (1.8M; 0.32 ml., 0.58 mmol.) and cyclohexyl phenyl ketone[53] (29 mg., 0.15 mmol.) gave an oil (44 mg.), g.l.c. analysis of which (1% QF-1, 125°) showed the presence of cyclohexyl phenyl acetylene, R.I. 1725, (12 mg., 43%) and cyclohexyl phenyl ketone, R.I. 1940, (13 mg., 45%).

Purification by preparative t.l.c. (light petroleum) gave cyclohexyl phenyl ketone (10 mg., 35%) and cyclohexyl phenyl acetylene as an oil (7 mg., 25%),

ν_{max} 3060, 2930, 2860, 2235, 1600 $cm.^{-1}$,

$\tau(CCl_4)$ 8.25 (11H, bm , $C_6\underline{H}_{11}$) and 2.7 (5H, m, $C_6\underline{H}_5$)

M^+ 184 ($C_{14}H_{16}$ requires 184).

7. Diethyl [1-diazo- 2-hydroxy- 2-(4-nitrophenyl)-ethyl phosphonate (26).

(a) Preparation:

A solution of diethylphosphonodiazomethane (487 mg., 2.74 mmol.) and p-nitro-benzaldehyde (370 mg., 2.45 mmol.) in dry ether (5 ml.) was treated with triethylamine (50 mg., 0.5 mmol.) and allowed to stand for 1 week at room temperature in the dark. The solution was concentrated in vacuo at room temperature to give a mixture of a red oil and yellow crystals. Two recrystallisations from ethyl acetate/ether gave 26 as pale yellow crystals, m.p. 87-8° (rapid heating), ν_{max} (CCl_4) 3600w, 3300b, 2980, 2070s, 1330b, 1150 $cm.^{-1}$, τ (CCl_4) 8.9 (6H, d(J = 2Hz.) of t (J = 6Hz.), $C\underline{H}_3CH_2OP(O)$), 6.7 (1H, d , J = 9Hz., $CH\underline{O}H$), 6.0 (4H, d(J = 15Hz.) of q(J = 6Hz.), $CH_3C\underline{H}_2OP(O)$), 2.3 (1H, bs, exchanges with D_2O, $O\underline{H}$) 2.4 (2H, d, J = 7Hz., 2,6-$C_6\underline{H}_4$) and 1.8 (2H, d, J = 7Hz., 3,5-$C_6\underline{H}_4$).

(b) Reaction with potassium t-butoxide:

A solution of 26 (16 mg., 0.05 mmol.) in THF (2 ml.) was treated with a suspension of potassium t-butoxide (8 mg., 0.07 mmol.) in THF (1 ml.); the pale yellow colour of the solution rapidly changed to deep red. After 30 min., water (5 ml.) was added, and the mixture was extracted with ether (2 x 5 ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo to give p-nitrophenyl acetylene as a pale brown solid (5 mg., 68%), ν_{max} ($CHCl_3$) 3300, 2180, 2100,

1590, 1340 $cm.^{-1}$, identified by comparison with an authentic sample.[54]

(c) Reaction with sodium hydroxide solution:

A solution of 26 (18 mg., 0.055 mmol.) in THF (1 ml.) was treated with aqueous sodium hydroxide solution (5M; 2 drops); the solution rapidly changed colour to deep red, but no ether-soluble products were obtained.

(d) Reaction with DBN:

A solution of 26 (59 mg., 0.147 mmol.) in THF (3 ml.) was treated with DBN (31 mg., 0.25 mmol.), stirred for 16 h., and concentrated *in vacuo*; the residue was taken up in dilute hydrochloric acid (0.2M; 5 ml.) and ether (5 ml.), the organic layer separated, the aqueous layer extracted with ether(2 x 5 ml.), the combined organic solutions washed successively with dilute hydrochloric acid (0.2M) and brine, dried and concentrated *in vacuo* to give p-nitro-benzaldehyde as ochre crystals (27 mg.), identified by comparison with an authentic sample.

(e) Reaction with bis-(acetylacetonato)-Copper (II):

A solution of 26 (157 mg., 0.48 mmol.) in dry benzene (25 ml.) was treated with bis-(acetylacetonato)-Copper(II)[55] (5 mg.) and heated at reflux for 90h. The solution was concentrated *in vacuo*, the residue taken up in ether (5 ml.), filtered through Celite and concentrated *in vacuo* to give α-diethylphosphono-p-nitro-acetophenone 28 as a yellow oil (143 mg., 98%), ν_{max} 3070, 2980, 1690, 1600, 1520, 1340, 1250 $cm.^{-1}$

(f) Reaction of α-diethylphosphono- p-nitro-acetophenone with potassium t-butoxide:

A solution of 28 (24 mg., 0.08 mmol.) in THF (1 ml.) was treated with a suspension of potassium t-butoxide (10 mg., 0.09 mmol.) in THF (1 ml.) and stirred for 16 h. The solution was concentrated in vacuo, and water (5 ml.) was added; the mixture was extracted with ether (3 x 5 ml.), the combined organic solutions washed with brine, dried and concentrated in vacuo to give unaltered 28, identified by comparison with an authentic sample.

(g) Preparation of p-nitrophenyl acetylene:

A solution of diethylphosphonodiazomethane (185 mg., 1.04 mmol.) in THF (5 ml.) was stirred at -78° under nitrogen, and treated with a solution of n-butyl lithium in hexane (2.1M; 0.5 ml., 1.05 mmol.); a solution of p-nitrobenzaldehyde (100mg., 0.66 mmol.) in THF (3 ml.) was added, and the cooling bath was removed. After 2h., work-up (as in section 5(a),(i)) gave a light brown solid; purification by preparative t.l.c. (20% ethyl acetate/light petroleum) gave p-nitrophenyl acetylene as ochre crystals, m.p. 150-2° (water) (lit.[54] 152°), $\nu_{max}(CHCl_3)$ 3300, 2180, 2100, 1590, 1340 $cm.^{-1}$, $\tau(CCl_4)$ 6.8 (1H, s, C$\underline{H}$), 2.45 (2H, d, J= 8Hz., 2,6-$C_6\underline{H}_4$) and 1.87(2H,d, J= 8Hz., 3,5-$C_6\underline{H}_4$).

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PART TWO : CONTENTS.

INTRODUCTION.

Polymer-supported Reagents in Organic Synthesis.

Reagents attached to insoluble polymer supports have found widespread application in recent years, and several reviews[1,2] and monographs[3,4] have described these developments. While much of the early work in this field was directed to the synthesis of polypeptides[5], polysaccharides[6], and polynucleotides[7], the application of polymeric reagents in general synthetic procedures now attracts increasing attention.

There are several properties of polymeric reagents which make them superior to analogous non-polymeric reagents in certain types of process. The first, and most widely exploited of these properties is the ease of handling and purification of intermediates and products. Thus, several polymer-supported reagents have been prepared in order to facilitate the removal of spent reagents; such by-products are readily removed by filtration if they are attached to an insoluble polymeric carrier. Examples of reagents of this type include polymer-supported per-acids[8], acylating agents[9], ylides[10,11,12], carbodiimides[13], metal hydrides[14], photosensitisers[15], and phosphine dichlorides[16].

A second useful property of polymer-supported reagents is that, by varying the concentration of active sites on the polymer, it is possible to obtain reaction conditions corresponding to the extremes of infinite dilution or extremely high concentration, and

thus influence the course of the reaction. By using low concentrations of reactive sites on the polymer, a "high dilution" effect can be obtained, and this property has been exploited in the synthesis of cyclic peptides[17], in the Dieckmann condensation of diesters[18], and in the mono-acylation[19] and mono-alkylation[20] of active methylene esters. Conversely, by close spacing of reactive sites on the polymer backbone, intermolecular reactions of the desired type can be promoted, for example in mixed-ester condensations[21].

The extent of cross-linking in a polymer support, and thus the accessibility of the reactive sites to substrate molecules, can have a pronounced effect on the selectivity of reactions. Thus, for example, the rate of hydrogenation of cyclic alkenes over a polymer-supported Rhodium(I) catalyst is dependent on the ring-size of the substrate[22].

Most polymeric reagents prepared to date have been based on a commercially-available cross-linked resin prepared by co-polymerisation of styrene (98%) and di-vinyl benzene (2%). Some use has also been made of phenol-formaldehyde resins[23].

Another class of polymeric reagents is based on homopolymers and copolymers of 4-(5-) vinyl-imidazole. Here, the emphasis has been on the pseudo-enzymic properties of such polymers rather than the development of synthetically useful reagents. Studies on these polymers have almost invariably been performed in solution, and have centred on their ability to catalyse ester hydrolysis. Poly-4-(5-) vinyl-imidazole is a more effective catalyst for ester hydrolysis than imidazole itself, particularly

with esters of long-chain fatty acids. This effect is attributed to the increasingly non-polar nature of the intermediate poly-1-acyl 4-(5-) vinyl-imidazole as the chain-length of the acyl group is increased. The resulting apolar environment of the polymer enhances the rate of hydrolysis by promoting association of catalyst and substrate[24]. The discovery of the role played by imidazole and hydroxyl functions in α-Chymotrypsin-catalysed ester hydrolysis[25] has prompted investigations of the catalytic activity of copolymers containing imidazole and hydroxyl functions[26]. Considerable rate-enhancements were observed when the catalytic activity in ester hydrolysis of such polymers was compared with that of low molecular-weight analogues, and this was attributed to bifunctional catalysis involving imidazole and anionic phenol or alcohol groups.

The activity of the above-described dissolved polymers was found to be highly dependent on solvent composition, illustrating the importance of the polymer conformation in these processes.

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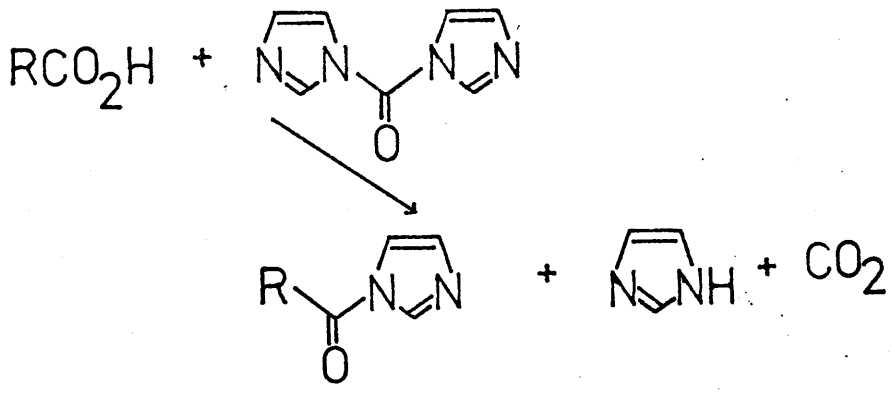
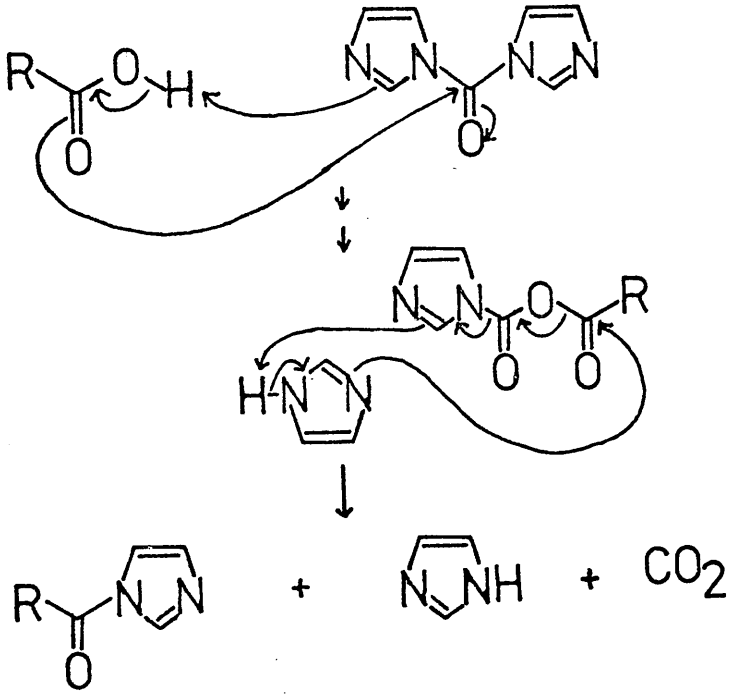
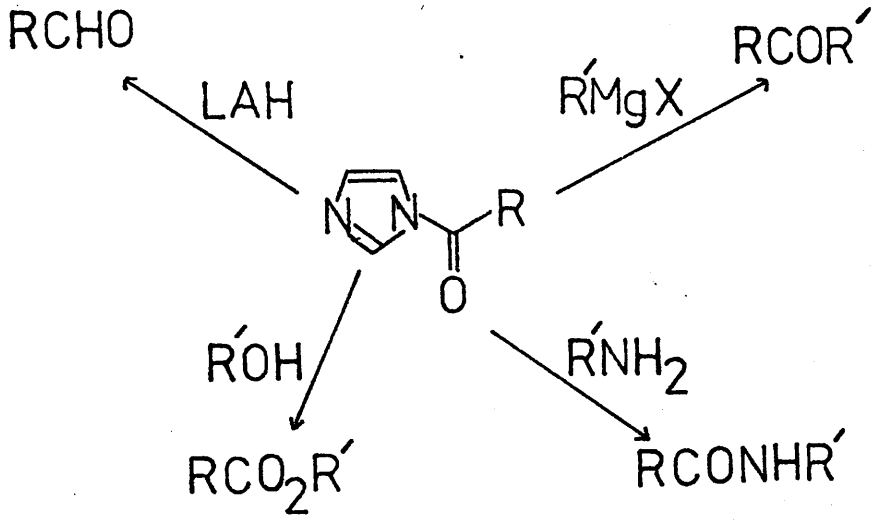


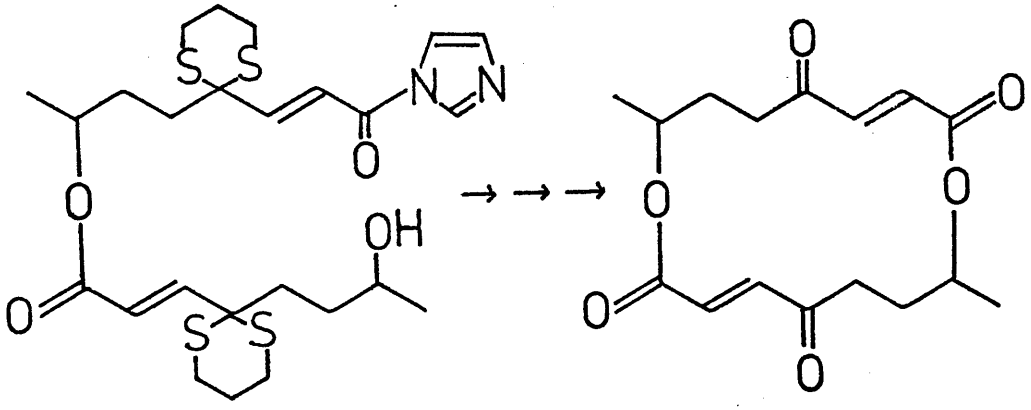
SCHEME 3



SCHEME 4



SCHEME 1

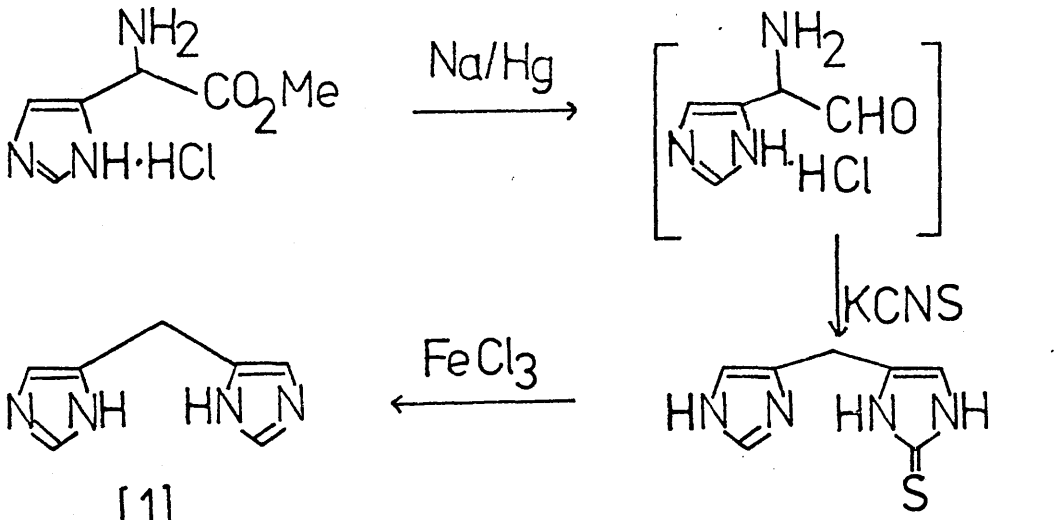


SCHEME 2

The development of reagents for organic synthesis based on the imidazole ring system, in particular the acid imidazolides[1] (SCHEME 1), prompted attempts to prepare polymer-supported reagents of this type, in order to facilitate the handling and use of such reagents. Imidazole is always present in the products of reactions when these compounds are used, and is often difficult to remove, particularly in cases in which the sensitivity of the substrate precludes aqueous washing as a means of purification.

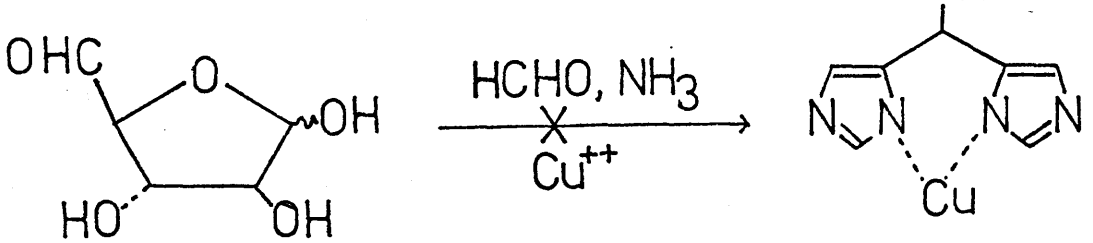
A further application of polymer-supported imidazole reagents was suggested by the discovery[2] that long-chain (ω-1)-hydroxy-carboxylic acids could be converted into macrolides via the imidazolides (SCHEME 2). In order to maximise intramolecular reaction, "high-dilution" techniques are required in such processes; the relatively slow rate of cyclisation of hydroxy-acids to form medium ring-size lactones[3] further increases the experimental difficulties encountered in this type of reaction. By use of a polymer-supported activating group with a suitably large spacing between reactive sites on the polymer backbone, these problems might be circumvented[4].

The mildest and most convenient method for the preparation of imidazolides involves the reaction of 1,1' carbonyl-di-imidazole[1] (CDI) with carboxylic acids (SCHEME 3). A study of the mechanism[1] of this reaction (SCHEME 4) shows that, in order for a polymer-supported reagent of this type to react with carboxylic

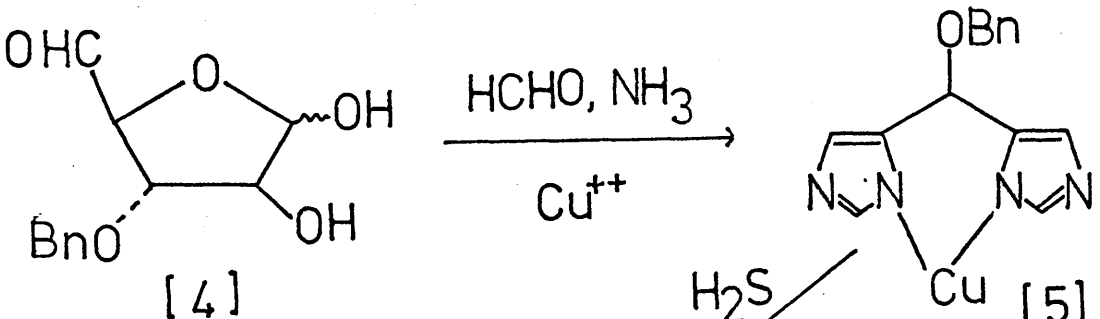


[1]

SCHEME 8



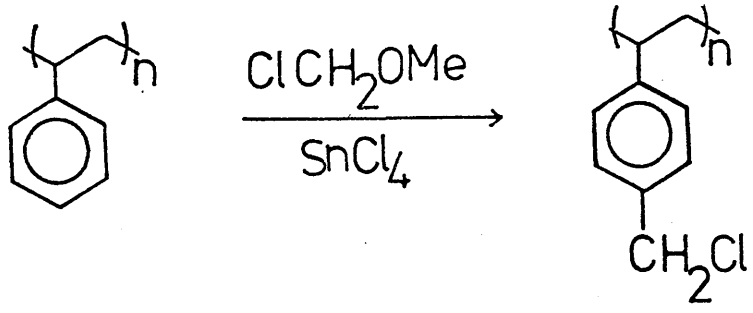
[2] [3]



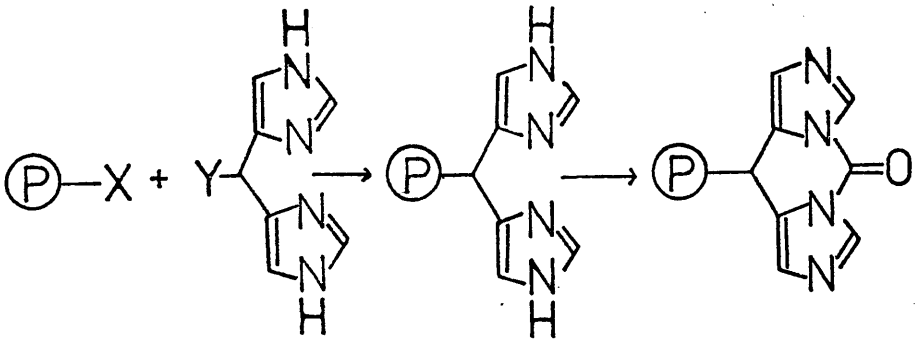
[4] [5] [6]

(Bn- = $PhCH_2$-)

SCHEME 9

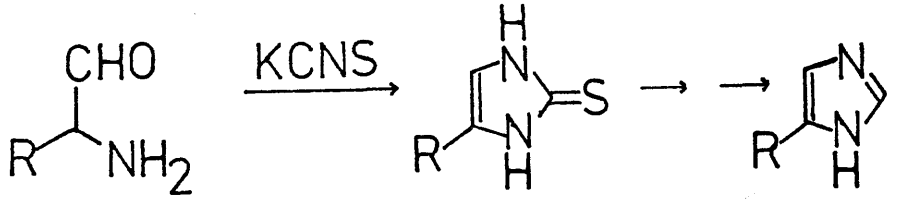


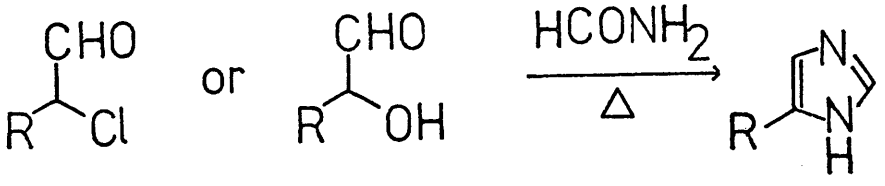
SCHEME 5

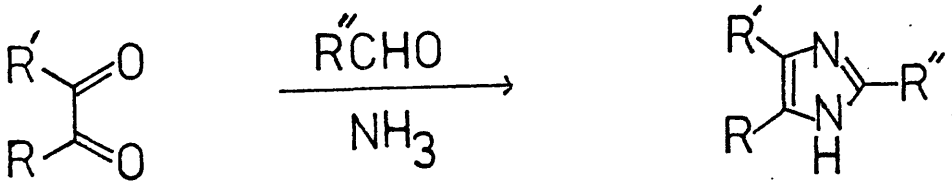


(Ⓟ = polymer support)

SCHEME 6







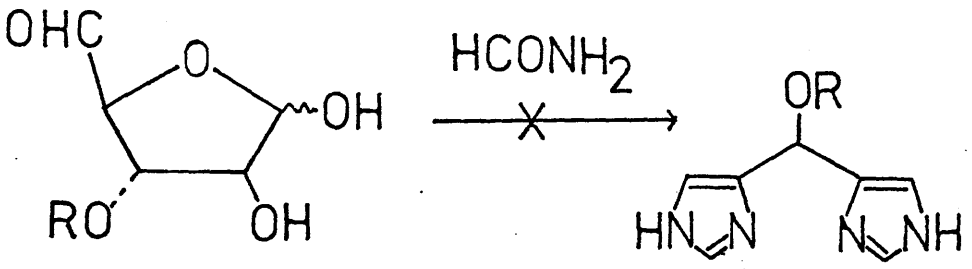
SCHEME 7

acids to form polymer-supported imidazolides, both imidazole rings must be attached to the polymer support. The most widely-used polymer support is a cross-linked porous resin prepared by copolymerisation of styrene (98%) with divinyl benzene (2%), and chloromethylated under Friedel-Crafts conditions with chloromethyl methyl ether ("Merrifield resin")[5] (SCHEME 5). Attention was therefore directed to the preparation of a suitably functionalised di-imidazole which, by reaction with such a resin or one of its derivatives, would yield a polymer-supported di-imidazole which could then be converted to a polymer-supported 1,1' carbonyl-di-imidazole reagent (SCHEME 6).

Methods of imidazole preparation[6] generally involve reaction of α-amino-, α-hydroxy-, or α-halo-carbonyl compounds or α-dicarbonyl compounds with thiocyanate ion, formamide or an ammoniacal solution of an aldehyde respectively (SCHEME 7).

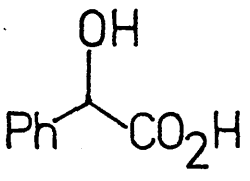
All attempts to repeat a published[7] method for the preparation of bis-4(5)-imidazolyl methane 1 were unsuccesful (SCHEME 8).

The possibility of preparing a suitably functionalised di-imidazole from a carbohydrate precursor by the classical Weidenhagen[8] synthesis was investigated (SCHEME 9); xylo-pentodialdose 2 was condensed with formaldehyde and ammonia in the presence of cupric ion, but none of the expected imidazole-copper complex 3 was obtained. The 3-O-benzyl ether of xylo-pentodialdose 4 , however, gave, in low yield, an insoluble brown copper-containing complex, presumed



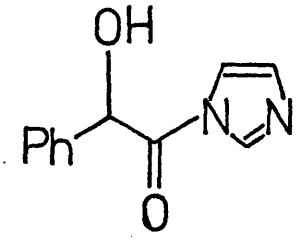
(R = H, Bn)

SCHEME 10

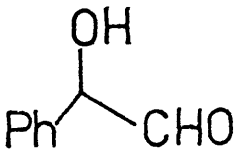


[7]

CDI



LAH



[8]

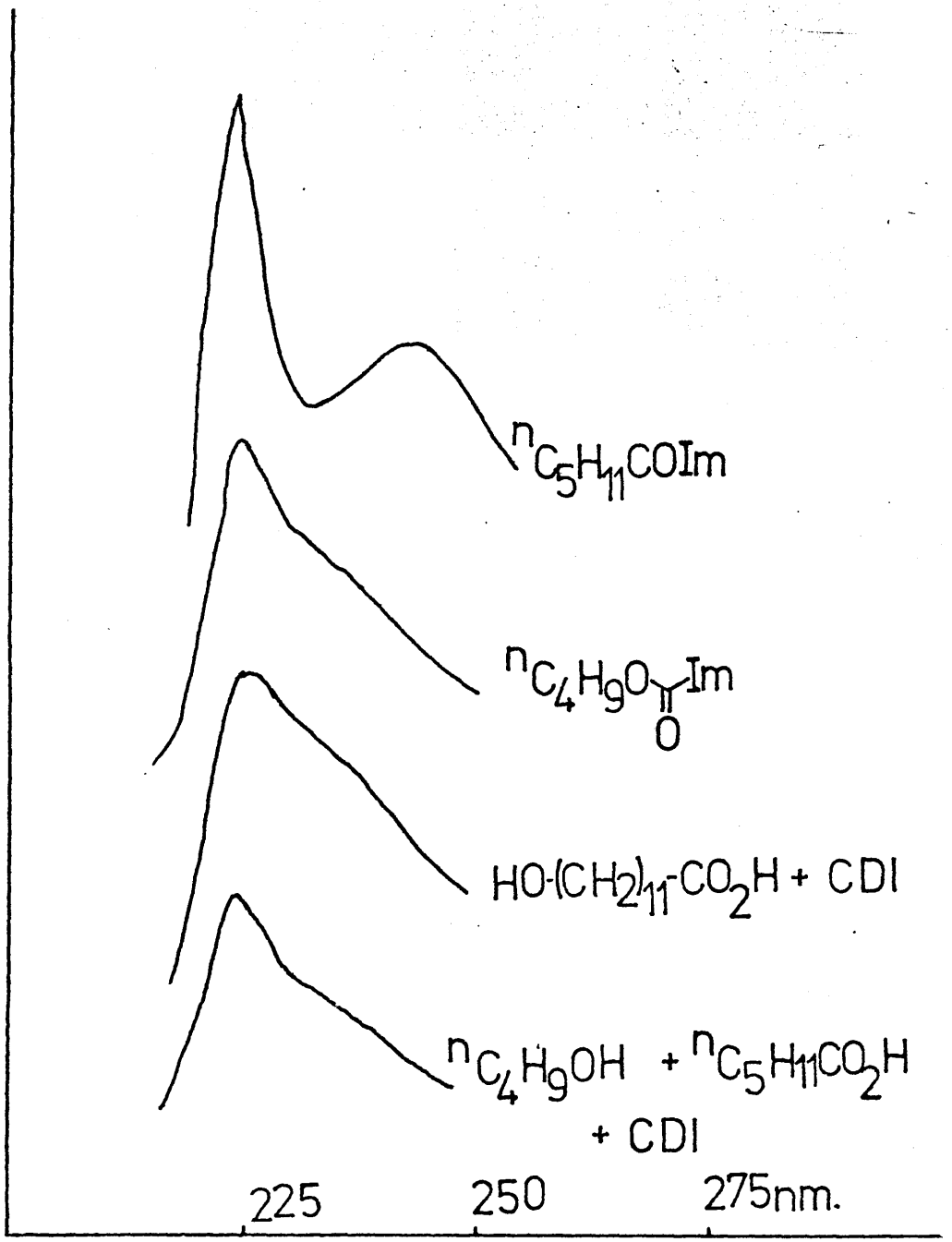
SCHEME 11

to be 5 . Treatment of this complex with hydrogen sulphide, however, failed to liberate the free imidazole, presumably because of the strongly chelating character of the di-imidazole 6 . The stability constants of complexes of imidazole with various transition-metal ions have been determined[10], and it has been demonstrated that cupric ions form very stable polynuclear complexes with this heterocycle. Attempts to liberate the di-imidazole from this copper complex by treatment with 8-hydroxy quinoline or ethylenediamine tetraäcetic acid were unsuccessful, while nitric acid treatment resulted in degradation of the ligand.

An alternative approach involved the condensation of xylo-pentodialdose or its 3-O-benzyl ether with formamide[11] (SCHEME 10); in both cases, intractable tars were produced.

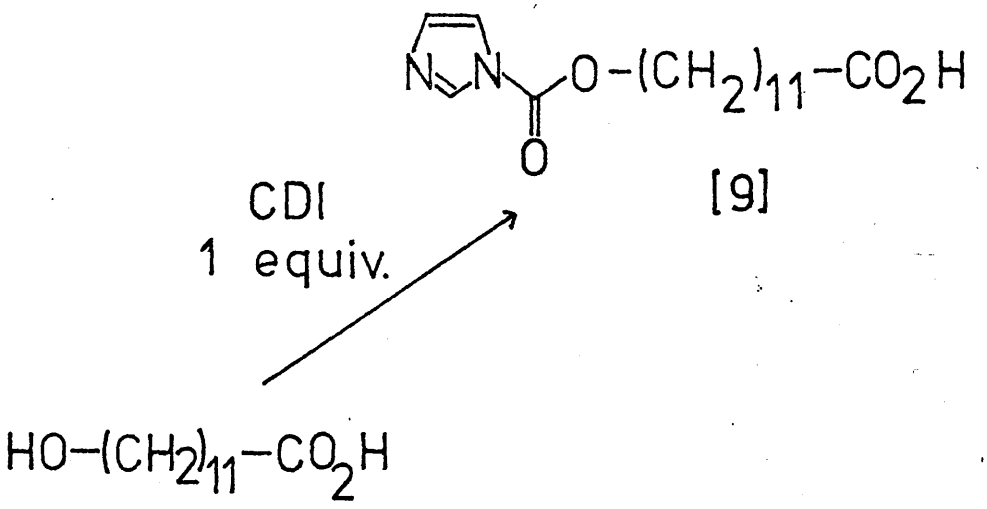
Concurrent with the studies described above, further investigation of the reaction of CDI with carboxylic acids, in particular hydroxy-carboxylic acids, was undertaken.

Staab[1] reported that mandelic acid 7 could be converted to mandelaldehyde 8 via the imidazolide, formed by reaction with CDI, followed by reduction with lithium aluminium hydride (SCHEME 11). On the basis of this finding, he concluded that the reaction of CDI with hydroxy-carboxylic acids proceeds preferentially at the carboxylic acid group. Further investigation has shown that this is not true in all cases; thus, when 12-hydroxy-dodecanoic acid was reacted with CDI

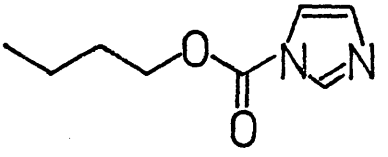

$^{n}C_5H_{11}COIm$
$^{n}C_4H_9O$ O Im
HO-$(CH_2)_{11}$-CO_2H + CDI
$^{n}C_4H_9OH$ + $^{n}C_5H_{11}CO_2H$
+ CDI
225
250
275nm.

(Im.= )

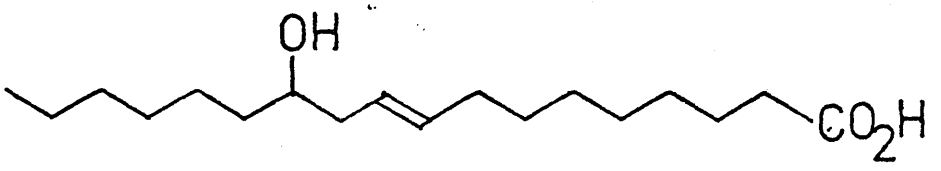
Figure 1



SCHEME 12



[11]

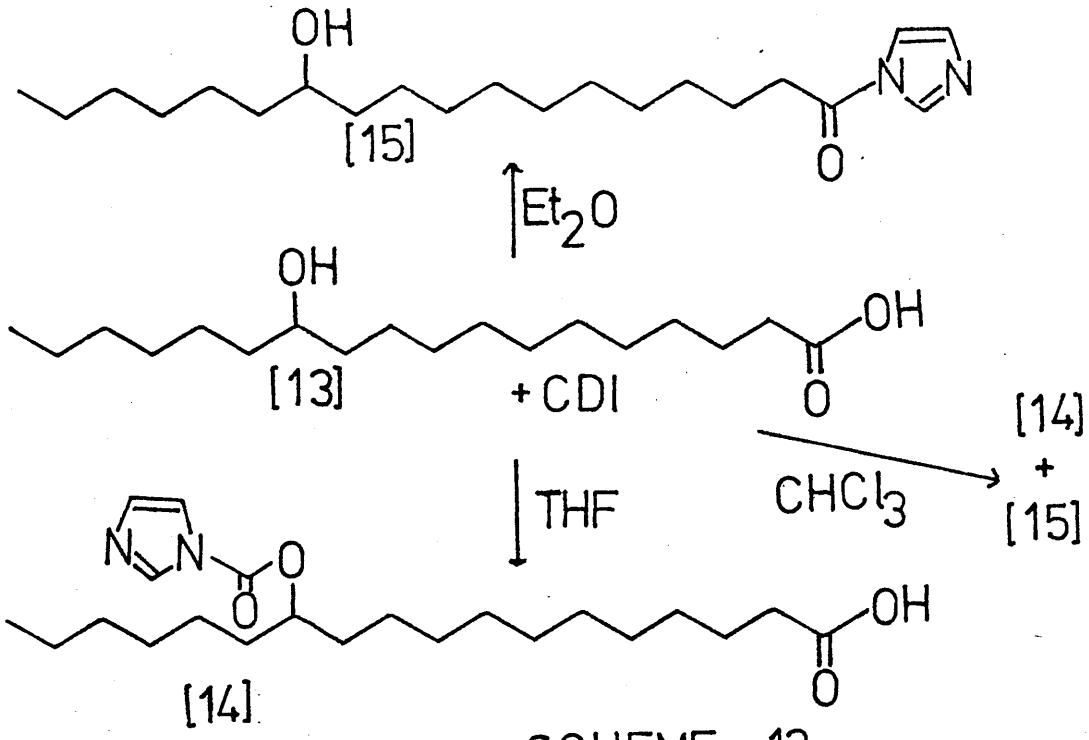


[12]

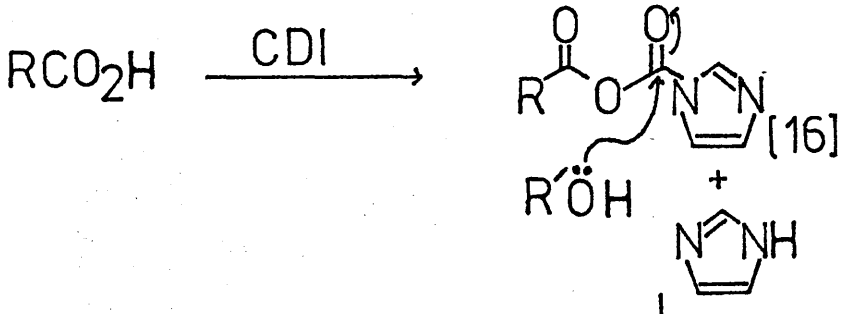
in THF solution, the only product formed was the carbamate 9, while reaction with two equivalents of CDI led to the formation of 10, the product of reaction with both the hydroxyl and the carboxylic acid functions (SCHEME 12). Earlier investigations[2], however, had shown that hydroxy-carboxylic acids in which the hydroxyl group is secondary could be converted to the acid imidazolides by reaction with CDI (SCHEME 2).

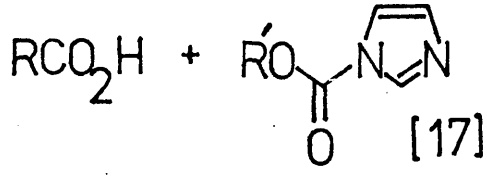
It was found possible to monitor the progress of reaction of CDI with carboxylic acids and with alcohols by u.v. spectroscopy; thus, while hexanoic imidazolide shows a broad absorption centred at 240-245nm., and a sharp peak at 227 nm., N-(n-butyl-oxycarbonyl)-imidazole 11 shows a sharp absorption at 224 nm., with a shoulder at 232 nm. Monitoring the reaction of 12-hydroxy-dodecanoic acid with CDI by u.v. spectroscopy, and comparison of the spectra thus obtained with the spectra of hexanoic imidazolide and N-(n-butyl-oxycarbonyl)-imidazole showed that, in this reaction, CDI reacts preferentially with the hydroxyl group (Figure 1). Reaction of an equimolar mixture of hexanoic acid and n-butanol with CDI (1 equivalent) showed that, in this case too, reaction occurs predominantly with the alcohol.

The reaction of an equimolar mixture of hexanoic acid and isopropanol with CDI (1 equivalent) was also studied spectrophotometrically; in this case, the electronic spectrum which developed was similar to that of hexanoic imidazolide, indicating that reaction occurs preferentially at the carboxylic acid group. Ricinoleic acid 12 reacted similarly with CDI to form the

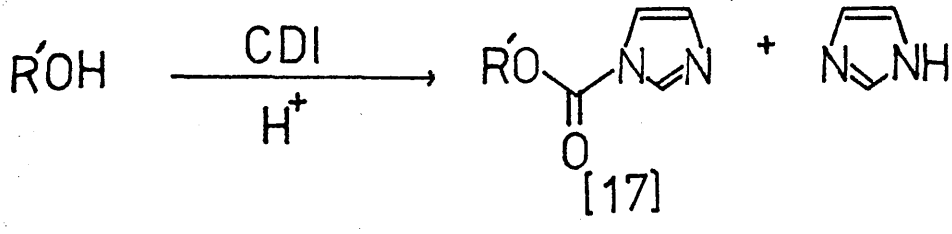


SCHEME 13





SCHEME 14



SCHEME 15

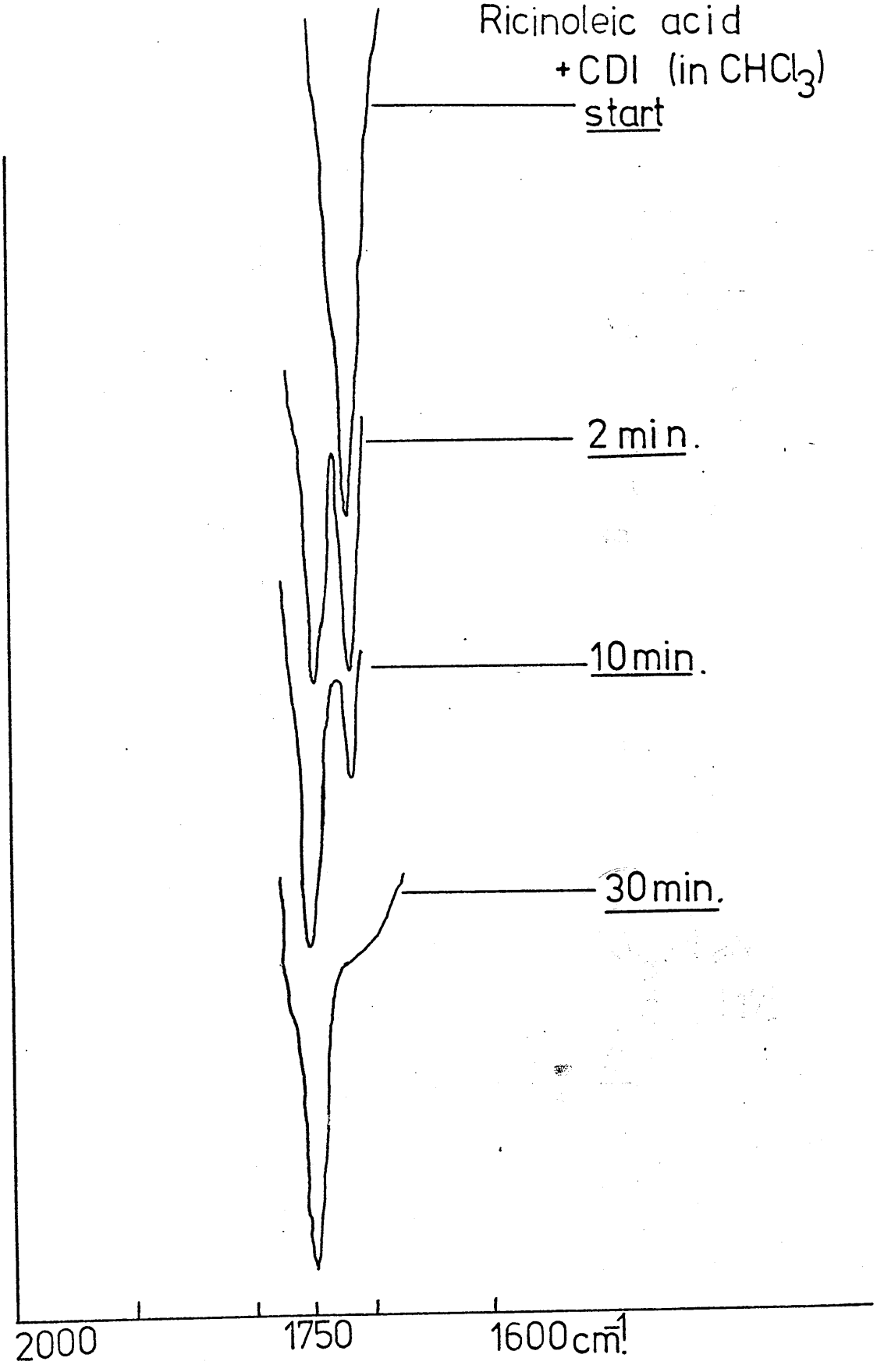

Ricinoleic acid
+CDI (in $CHCl_3$)
start
2 min.
10 min.
30 min.
2000
1750
1600 cm^{-1}

Figure 3

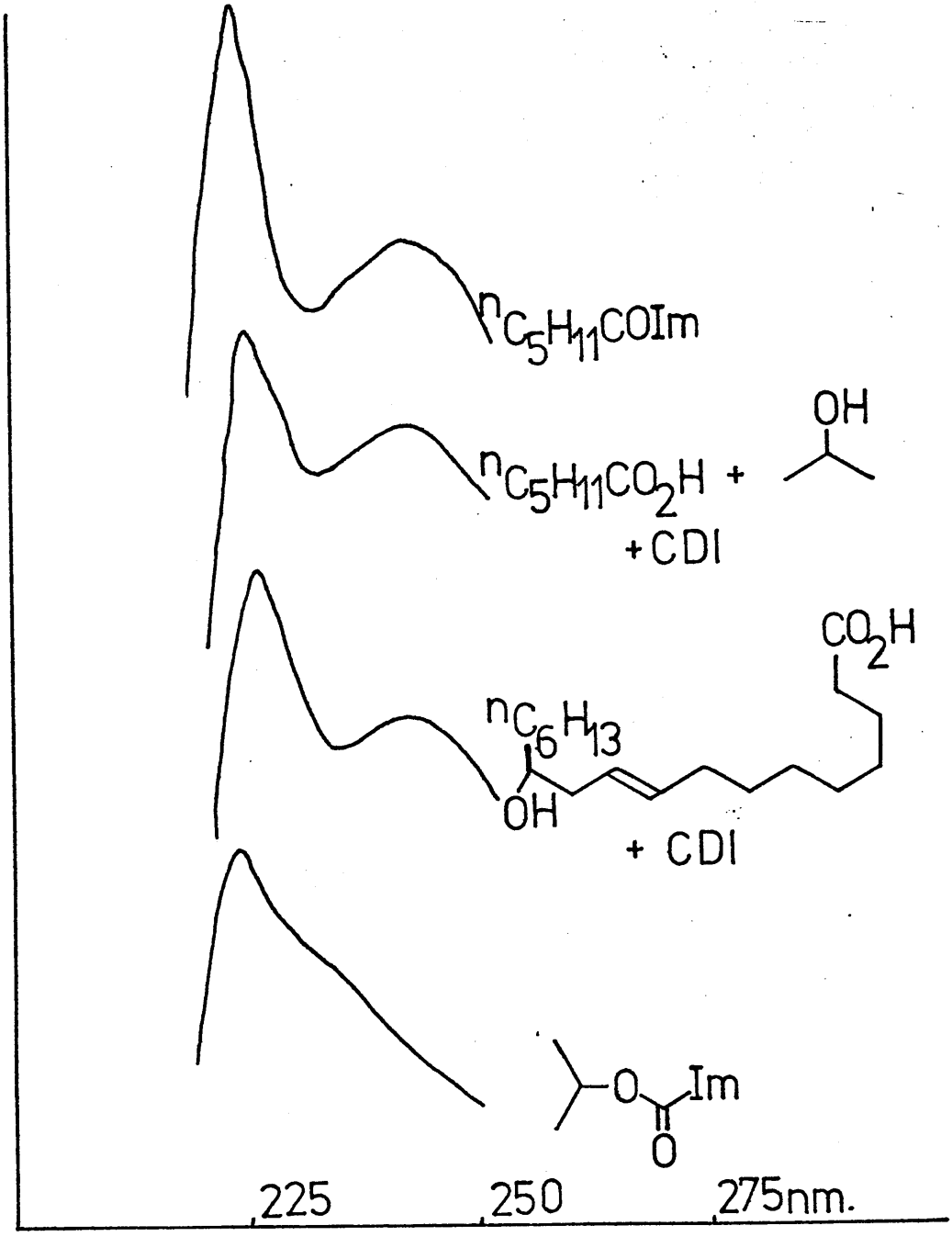

$^{n}C_5H_{11}COIm$
$^{n}C_5H_{11}CO_2H$ +
OH
+CDI
CO_2H
$^{n}C_6H_{13}$
OH
+ CDI
O
Im
O
225
250
275nm.

Figure 2

acid imidazolide (Figure 2).

I.r. spectroscopy was also used to monitor the reaction of CDI with hydroxy-acids. In the solid state, acid imidazolides show a carbonyl absorption at 1747 $cm.^{-1}$, while N-alkoxycarbonyl-imidazoles show absorption at 1770-1780 $cm.^{-1}$ The reaction of ricinoleic acid with CDI was monitored by i.r. spectroscopy (Figure 3); a rapid development of absorptions characteristic of the acid imidazolide group was observed.

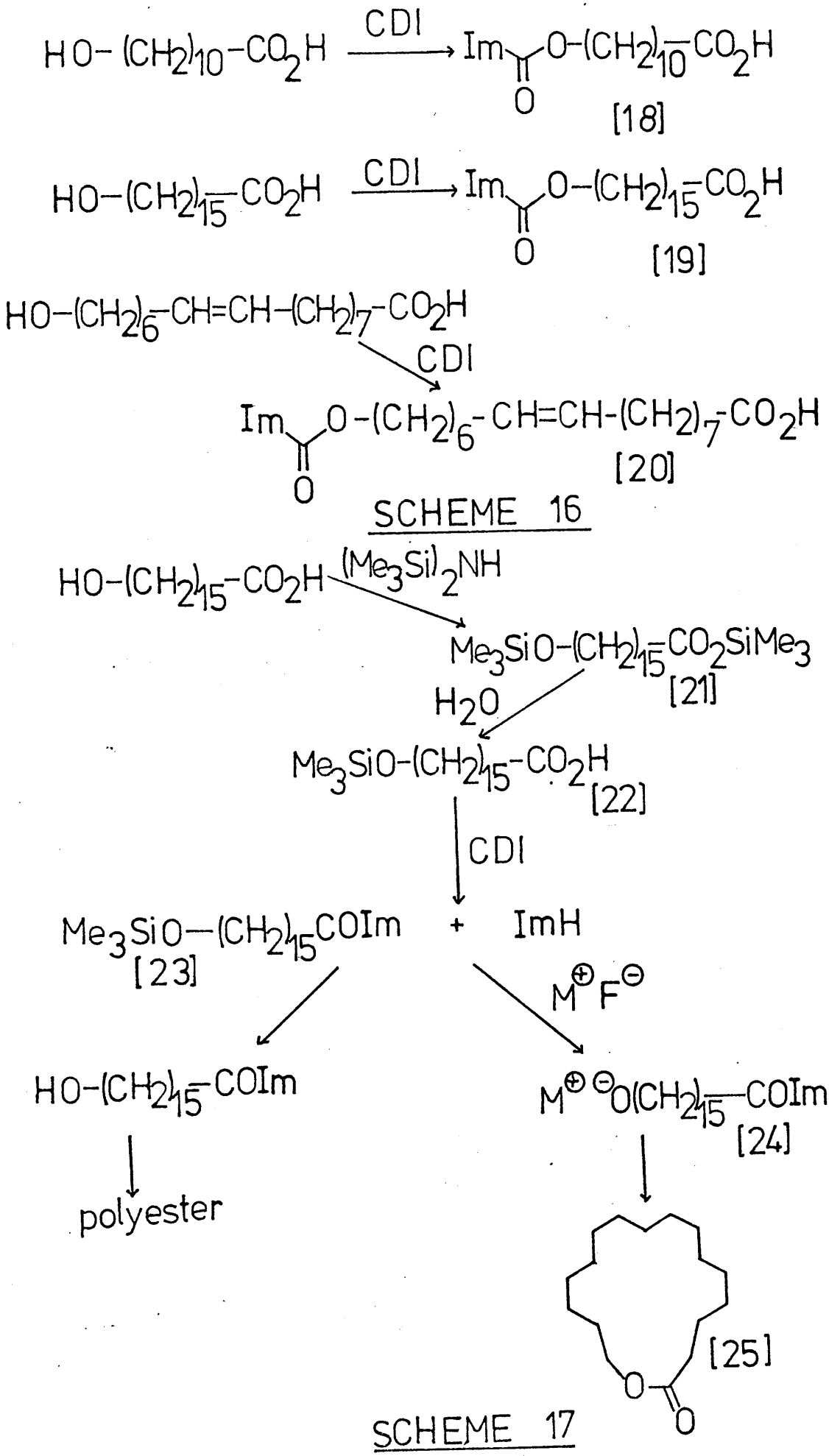
A marked solvent-dependence was observed in the reaction of 12-hydroxy-stearic acid 13 with CDI. In THF solution, the sole product was the N-alkoxy-carbonyl-imidazole 14 , while in ether solution, the sole product was the acid imidazolide 15 ; in chloroform solution, both compounds were formed in approximately equimolar amounts (SCHEME 13); this indicates that, in this case, the factors influencing the course of the reaction are finely balanced, and attempts were therefore made to change the course of the reaction by modification of the reaction conditions.

The preferential formation of carbamate 17 in the reaction of hydroxy-acids with CDI might arise in two ways: firstly, attack on the intermediate anhydride 16 by the hydroxyl function, leading to carbamate formation, may be more favourable than attack of imidazole on 16, which would lead to imidazolide formation (SCHEME 14); alternatively, the presence of a carboxylic acid function may catalyse the normally slow reaction of the hydroxyl function with CDI,

leading directly to carbamate formation (SCHEME 15). In order to test the first of these hypotheses, 12-hydroxy-stearic acid was reacted with CDI in chloroform solution in the presence of one equivalent of imidazole; since, in the reaction of this acid with CDI in the absence of added imidazole, the concentration of imidazole is initially very low, it was thought possible that this might have encouraged formation of carbamate rather than imidazolide, at least in the initial stages of reaction, thus leading to a mixture of products.

However, addition of one equivalent of imidazole to the reaction mixture had no effect; again, imidazolide and carbamate were formed in equimolar amounts. However, when an equimolar mixture of imidazole and 12-hydroxy-stearic acid in chloroform solution was stirred for 30 min. before addition of one equivalent of CDI, the imidazolide was formed exclusively; this indicates that the carboxylate anion of this acid reacts more rapidly with CDI than either the hydroxyl function or the carboxylic acid function. When this reaction was repeated using a primary hydroxy-acid, 16-hydroxy-hexadecanoic acid, carbamate formation was the only process observed.

It can therefore be concluded that carbamate formation follows the path shown in SCHEME 15, i.e., that reaction of the hydroxy-acid with CDI is the rate-determining step, and that, in this step, carboxylate ions react more rapidly than secondary hydroxyl functions or carboxylic acid functions, but

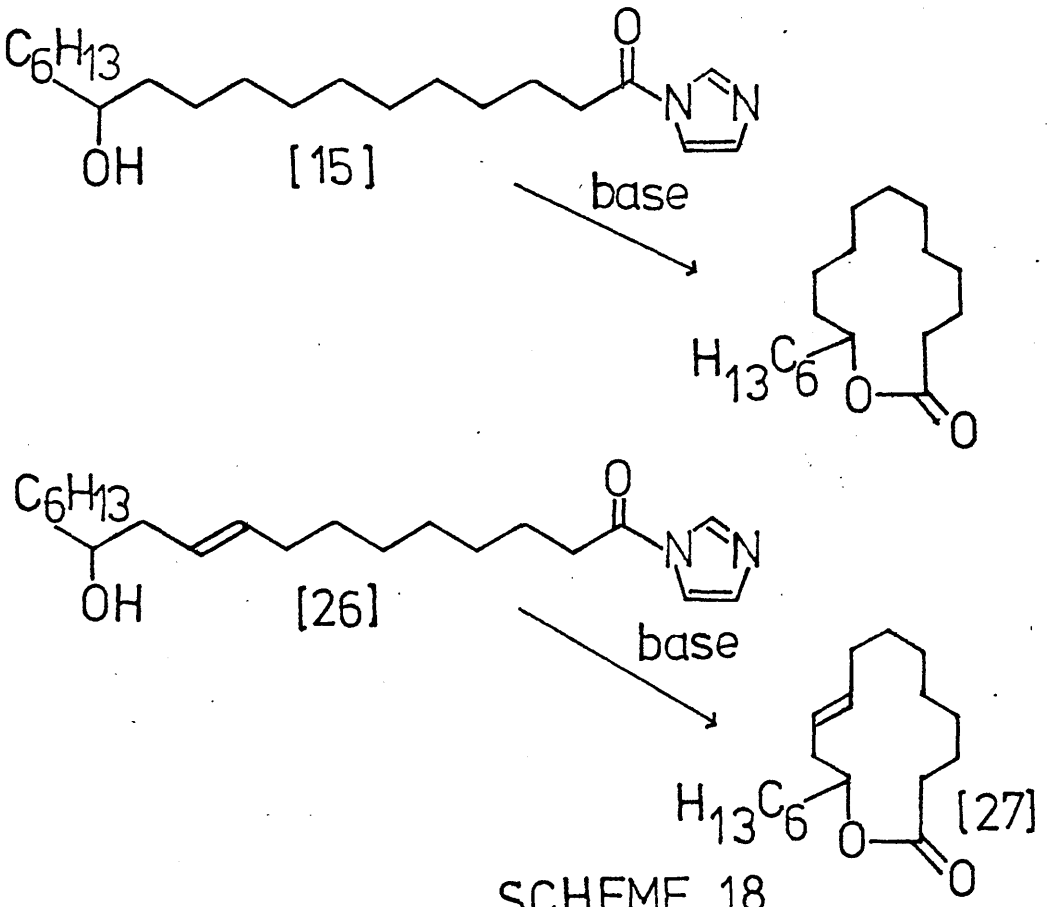


SCHEME 16

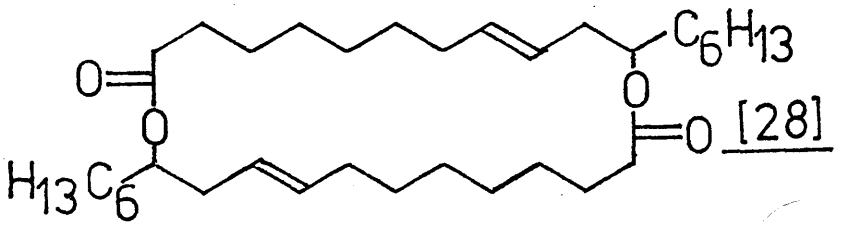
SCHEME 17

less rapidly than primary hydroxyl functions, when an acid catalyst is present. The solvent-dependence observed in the reaction of CDI with 12-hydroxy-stearic acid is probably due either to the effect of solvent ionising-power on the dissociation of the carboxylic acid function, and thus on the extent to which it catalyses reaction of the hydroxyl group with CDI, or to the effect of conformational changes on the relative nucleophilicities of the hydroxyl and carboxylic acid functions; indeed, both factors may be operative.

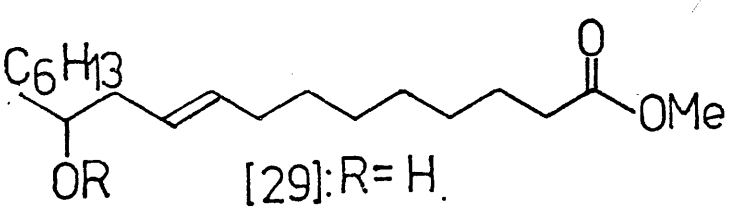
While it was possible to prepare the imidazolides of hydroxy-acids in which the hydroxyl group is secondary, under all conditions studied, primary hydroxy-acids gave only the N-alkoxycarbonyl-imidazoles (SCHEME 16). Selective protection of the primary hydroxyl group was possible: conversion of 16-hydroxy-hexadecanoic acid to the bis-trimethylsilyl derivative 21 , selective hydrolysis to the free acid 22, and reaction with CDI gave the imidazolide 23 (SCHEME 17); it was anticipated that treatment of this compound with an ionic fluoride under conditions of high dilution, or with a suitable polymer-supported quaternary ammonium fluoride would generate the alkoxide 24 which would cyclise to the macrolide 25 . However, the imidazolide 23 was unstable, undergoing cleavage of the trimethylsilyl ether followed by polymerisation; this was presumably due to catalysis of the ether cleavage by the imidazole formed in the reaction of 22 with CDI. A more stable silyl ether, possibly the t-butyl-dimethylsilyl ether[12], might allow this difficulty to be circumvented.



SCHEME 18

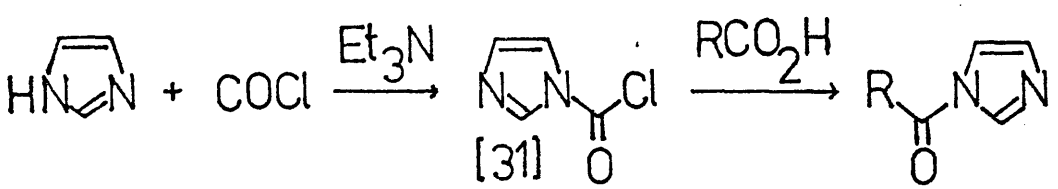


[28]



[29]: R= H.

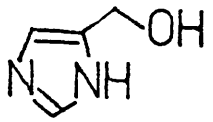
[30]: R= Ac.



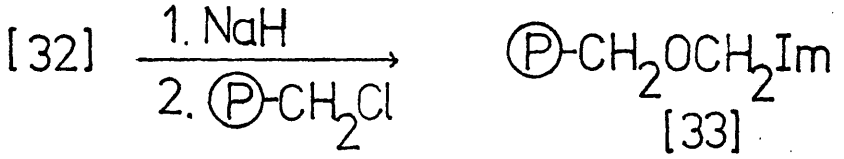
SCHEME 19

Attempts were made to cyclise the imidazolides of 12-hydroxy-stearic acid 15 and ricinoleic acid 26 (SCHEME 18) under conditions of high dilution. 12-Hydroxy-stearic imidazolide gave only polyester products under all conditions studied. Ricinoleic imidazolide gave, in addition to polymeric products, some lower molecular weight material whose spectral characteristics were consistent with the presence of a lactone structure. Preparative t.l.c. of the product mixture gave two compounds which were less polar than ricinoleic acid; neither compound showed a hydroxyl absorption in the i.r. : the more polar compound showed absorptions at 1737 and 1180 $cm.^{-1}$, while the less polar compound showed absorptions at 1732, 1230, 1180, 1120 and 1050 $cm.^{-1}$; their p.m.r. spectra were almost identical. These compounds may have been the macrolide 27 and the dilide 28 , both of which are known to be present in commercial ricinoleic acid[13]. Ricinoleic imidazolide reacted with methanol to give methyl ricinoleate 29 , which shows a carbonyl absorption at 1750 $cm.^{-1}$; methyl acetyl ricinoleate 30 has a carbonyl absorption at 1745 $cm.^{-1}$, while commercial ricinoleic acid shows two carbonyl absorptions at 1715 and 1735 $cm.^{-1}$, the latter presumably due to lactone impurities 27 and 28 ; attempts to isolate pure samples of these compounds from commercial ricinoleic acid were unsuccessful.

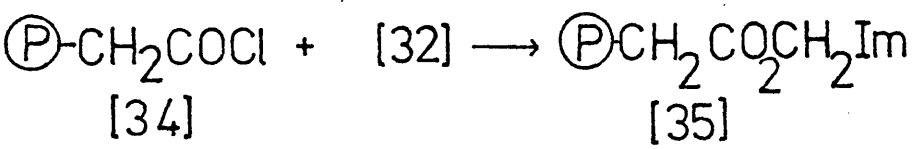
Other possible methods of preparing imidazolides were investigated; attempts were made to prepare N-chlorocarbonyl-imidazole 31 (SCHEME 19)



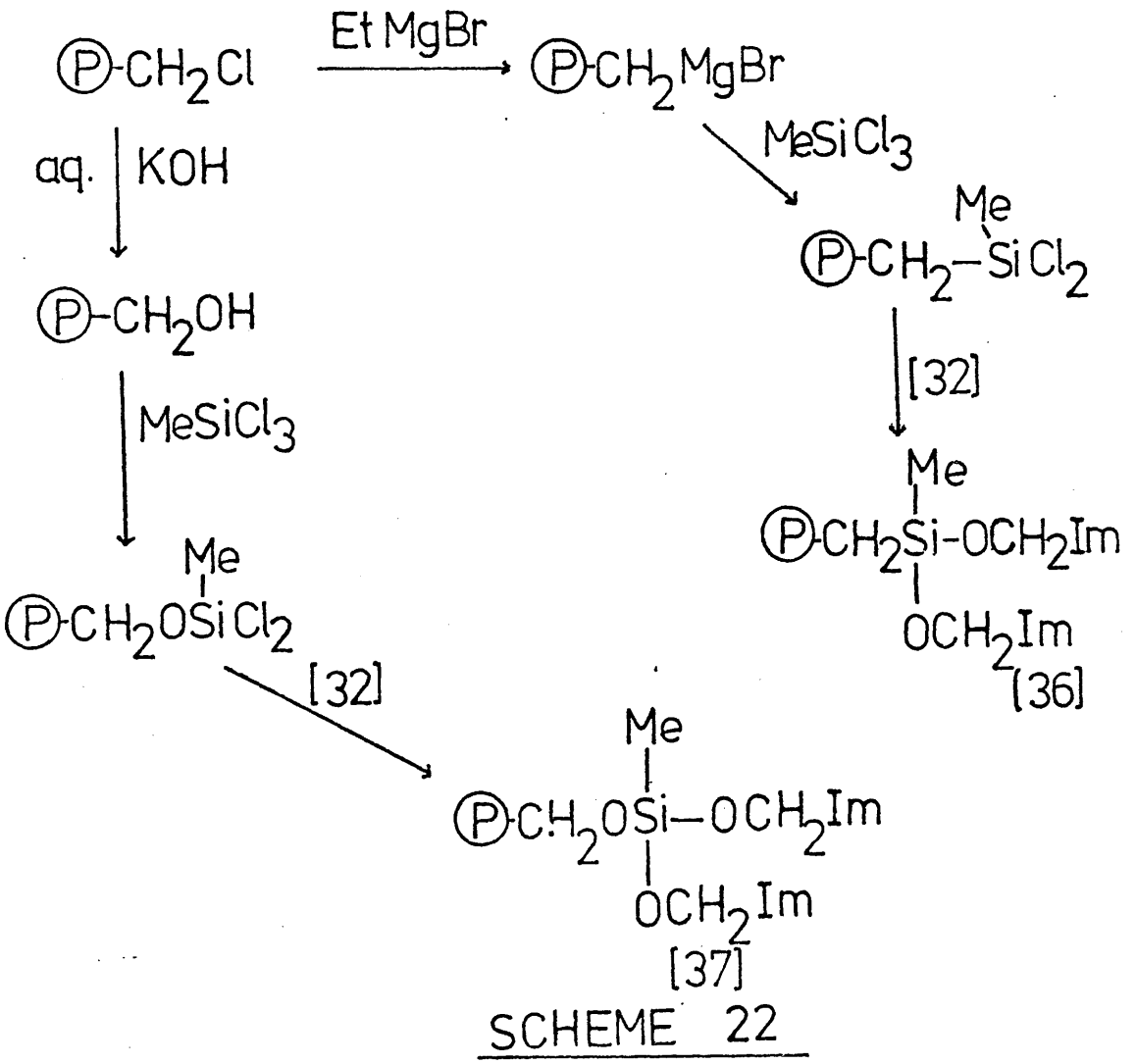
[32] (= $ImCH_2OH$) Ⓟ = polymer support



SCHEME 20



SCHEME 21



SCHEME 22

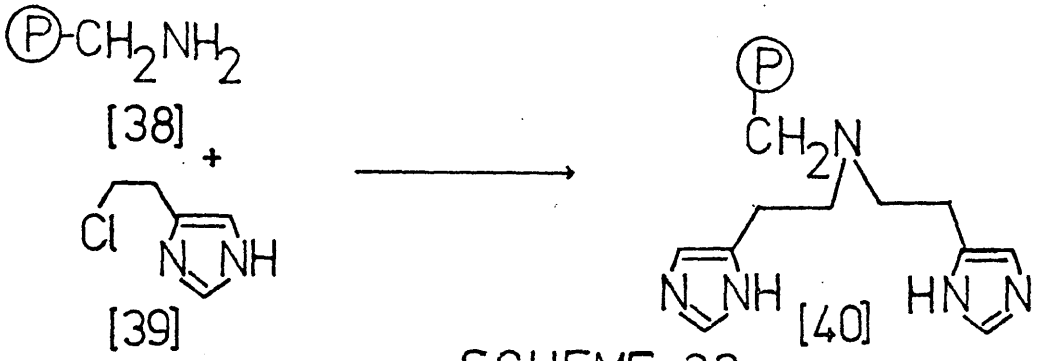
and investigate its reaction with carboxylic acids.

Reaction of equimolar quantities of imidazole, phosgene and triethylamine, followed by addition of hexanoic acid produced, in fair yield, hexanoic imidazolide. Attempts were then made to repeat this process using a polymer-supported imidazole.

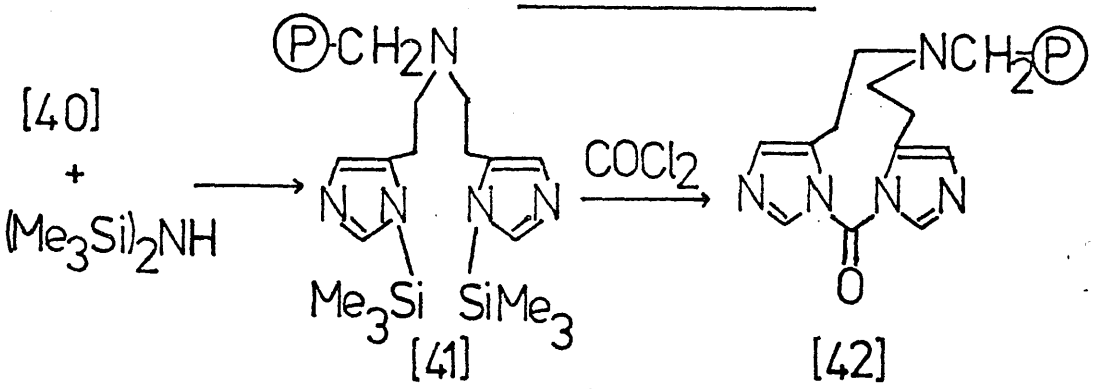
Reaction of partially chloromethylated poystyrene beads with the sodium salt of 4(5)-hydroxymethyl-imidazole[9] 32 (SCHEME 20) gave a polymer which was shown by combustion analysis to contain nitrogen. The i.r. spectrum of the polymer was consistent with the presence of free imidazole groupings. Similarly, reaction of the polymer-supported acid chloride 34 with 4(5)-hydroxymethyl-imidazole 32 gave a polymer 35 which was shown by combustion analysis to contain nitrogen and oxygen in the correct ratio and whose i.r. spectrum showed the presence of ester and imidazole groups.

Both polymers were separately reacted sequentially with phosgene and triethylamine, followed by excess hexanoic acid; hexanoic acid was recovered quantitatively, and in neither case did the polymer show any appreciable gain in weight during the reaction.

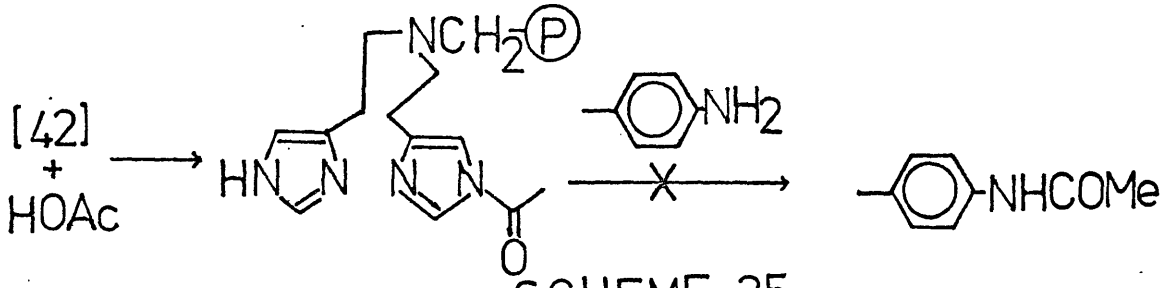
Attempts were made to attach two imidazole groups to a polymer support through a siloxane linkage (SCHEME 22); both polymers 36 & 37 so produced were shown by microanalysis to contain nitrogen but no silicon, and no further investigation of these materials was undertaken.



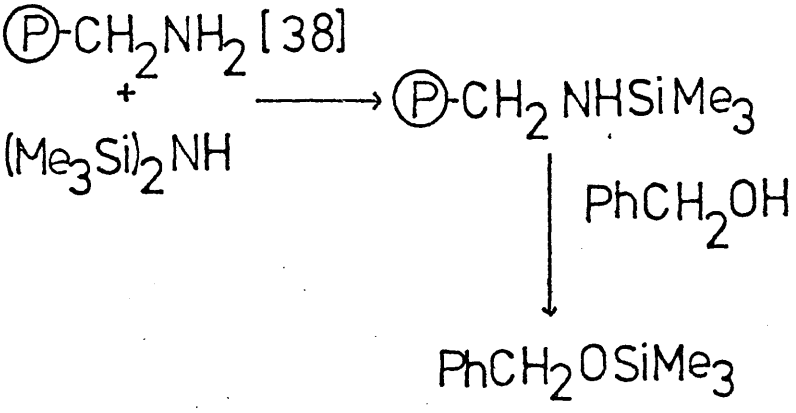
SCHEME 23



SCHEME 24



SCHEME 25



SCHEME 26

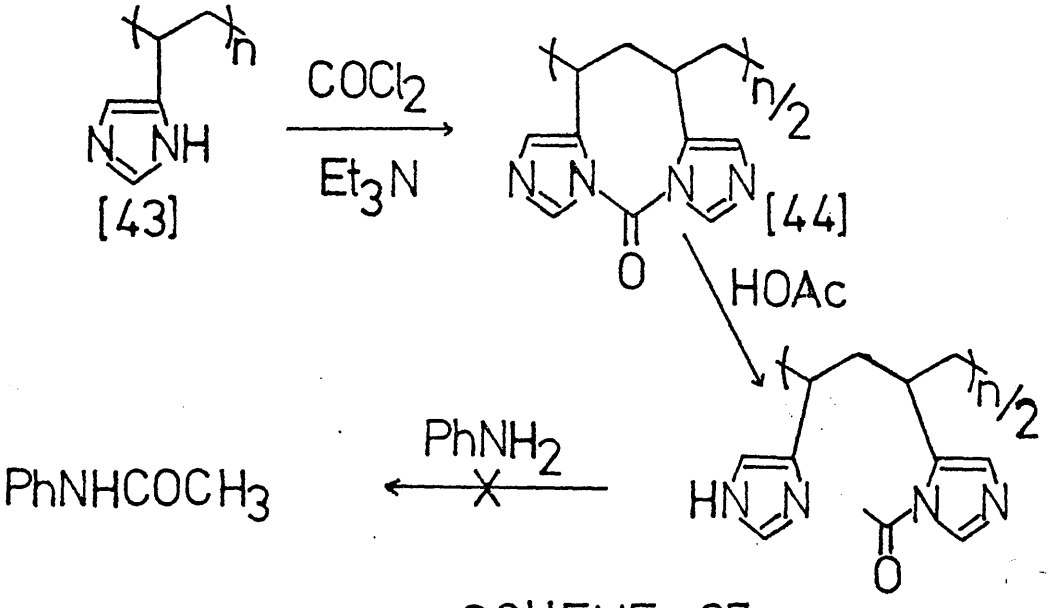
Reaction of partially aminomethylated polystyrene beads 38 with an excess of 4-(2-chloroethyl)-imidazole 39 (SCHEME 23) gave a polymer whose spectral characteristics were consistent with the part-structure 40 . Titration with mineral acid showed the presence of three amine groups for every one present in the original aminomethyl polymer. This polymer was reacted with an excess of hexamethyldisilazane and the product so obtained, after thorough washing, was reacted with phosgene (SCHEME 24); addition of acetic acid, followed, after thorough washing, by addition of p-toluidine resulted in the recovery of unchanged p-toluidine (SCHEME 25). The presumed intermediate polymer-supported silyl imidazole 41 did however transform benzyl alcohol to its trimethylsilyl ether. Since this property was also shown by the polymer obtained by treatment of aminomethyl-polymer 38 with hexamethyldisilazane, this could not be taken as conclusive evidence of the presence of imidazole groups on the polymer (SCHEME 26).

The reason for the failure of the above-described polymers to react in the expected manner is not clear. It is possible that the polymer-supported imidazoles or imidazolides are less reactive than their non-polymeric counterparts; alternatively, the well-known tendency[14] for imidazoles to exhibit intermolecular aggregation may restrict access to the pores of the polymer beads. This tendency is particularly marked in non-polar solvents: for example, 4(5)-methyl-

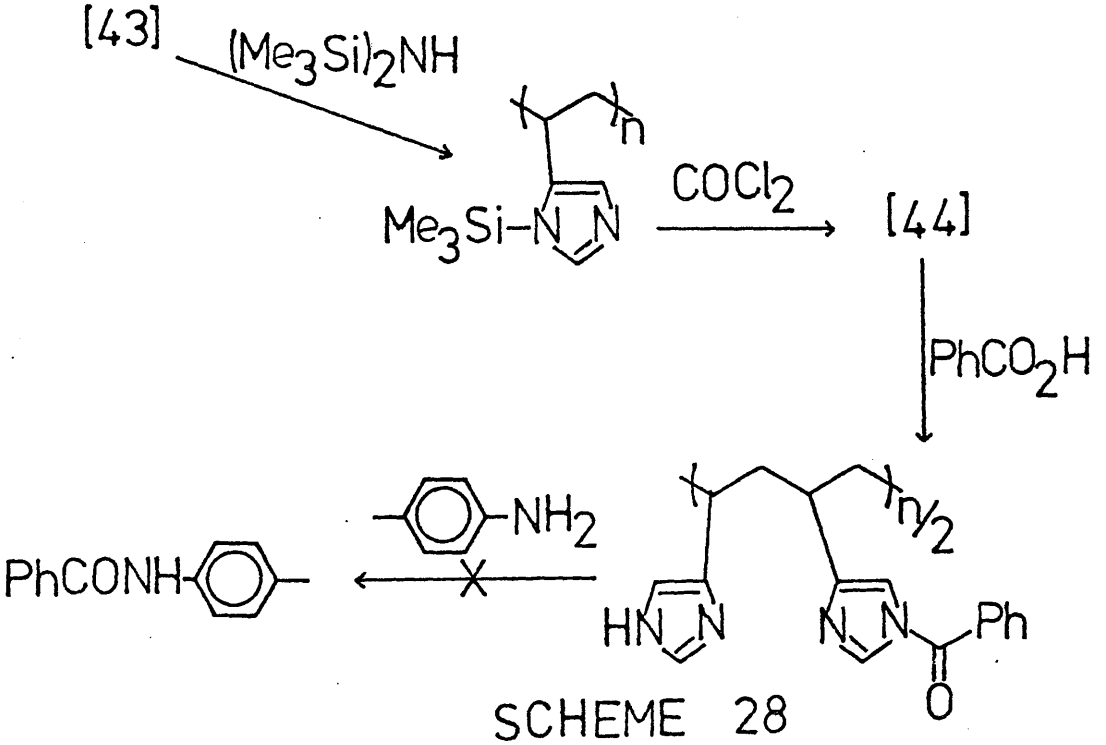
imidazole exhibits an apparent molecular weight of 1500 when cryoscopic molecular weight determination is performed at a concentration of 6M in benzene solution, while imidazole itself has an apparent molecular weight, determined ebulliometrically, of 250 at a concentration of 4M in boiling benzene[14]; aqueous solutions of imidazoles behave normally in such determinations.

Since all the studies of polymer-supported reagents described above were carried out in non-polar solvents, it is possible that association of pendant imidazole groups may create a highly cross-linked polymer which is consequently impervious to substrate imidazoles. This possibility encouraged investigation of a different polymer system, namely that of poly-4(5)-vinyl-imidazole (pVIm) 43 , which has been shown in several studies[15] to be more reactive than free imidazole in catalysing ester-solvolyses.

pVIm was prepared by the method of Overberger and Vorchheimer[16] . Analysis of this polymer showed the presence of 0.66 equivalent of water per equivalent of pendant imidazole, and attempts to remove this water by prolonged drying over phosphorus pentoxide were unsuccessful[16] . The presence of water in the polymer creates problems in attempts to prepare polymeric 1,1' carbonyl-di-imidazole, which would be hydrolysed rapidly. The polymer was therefore dissolved completely in methanol, and, after drying the solution over molecular sieves, reprecipitated by dilution with ethyl acetate, and thoroughly dried over phosphorus pentoxide.



SCHEME 27



SCHEME 28

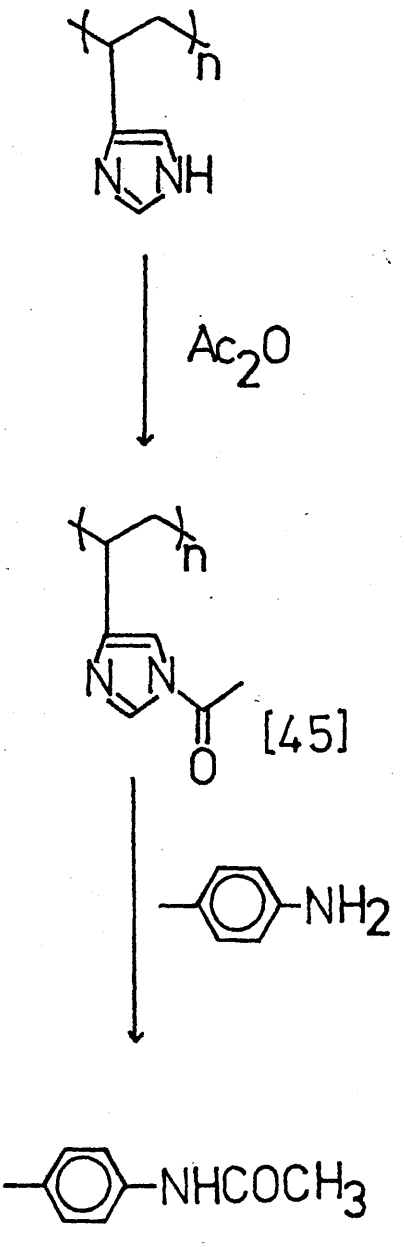
SCHEME 29

All reactions thereafter were performed in an atmosphere of dry nitrogen. Treatment of this polymer with phosgene and triethylamine (both in excess) followed, after thorough washing, by addition of acetic acid, followed, after further washing, by treatment with aniline produced no acetanilide (SCHEME 27).

More vigorous drying conditions were used in a second approach (SCHEME 28); pVIm was heated with excess hexamethyldisilazane, then treated successively with phosgene, benzoic acid and p-toluidine, with the polymer being thoroughly washed after each operation. p-Toluidine was recovered unchanged.

A major problem in the study of pVIm and reagents derived therefrom was the change in properties of the polymer on chemical modification; for example, while pVIm itself is a fine white powder, upon silylation with hexamethyldisilazane it is transformed into a brown gum, from which residual traces of solvent are removed only with difficulty. Similar problems were encountered when the carbonylation of pVIm by excess CDI was attempted (SCHEME 29); the polymer was transformed into a hard friable resin, presumably because of cross-linking of the polymer chains. Purification of this polymer proved impossible and no further studies on it were attempted.

An extensive survey[17] of the published literature on the reactions of pVIm reveals that, in no cases, have reactions of pVIm or any of its derivatives in non-polar solvents been reported.

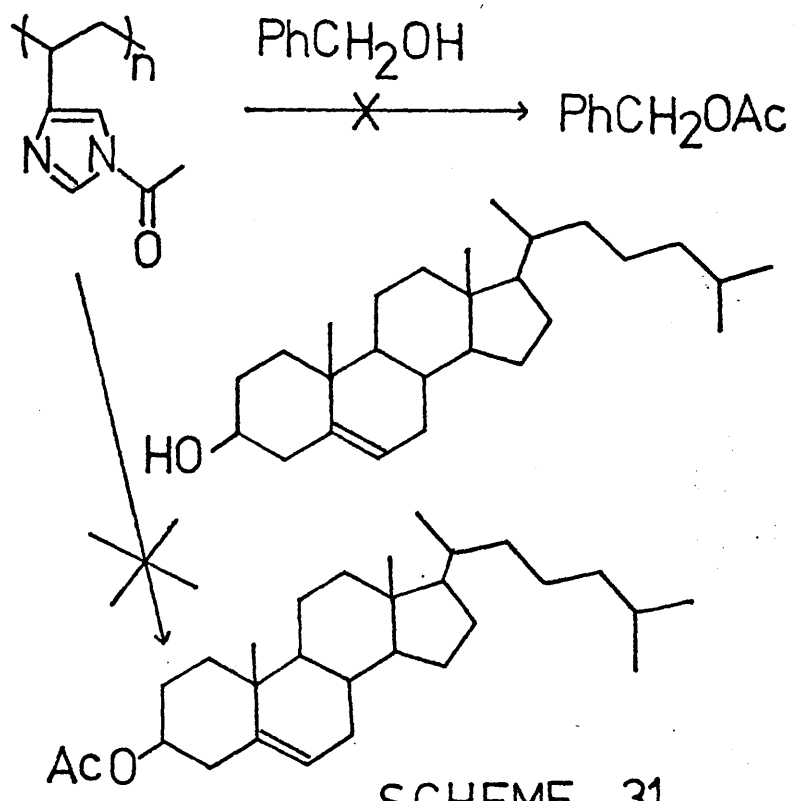


SCHEME 30

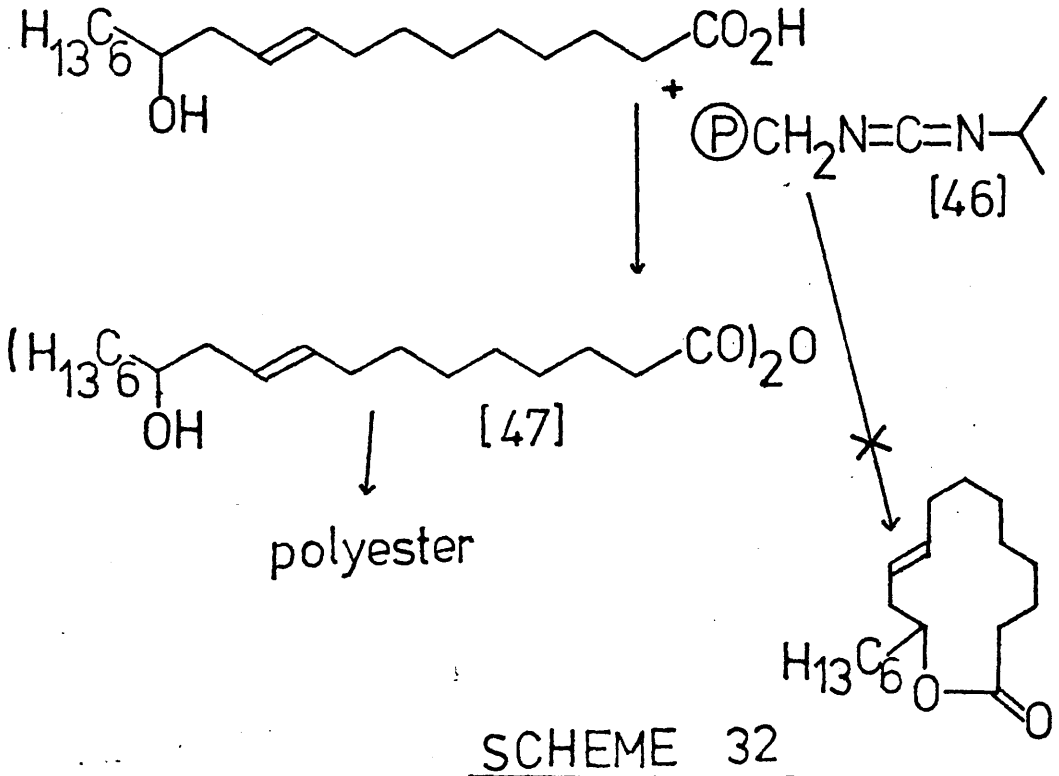
Studies with this system[17] have been confined almost exclusively to studies of its catalytic effect in ester solvolysis, and have been carried out in water or aqueous ethanol or methanol solutions; such conditions would clearly be impracticable in the present study.

It has recently been reported[18] that, contrary to the behaviour usually observed in studies of pVIm-mediated reactions in aqueous media, pVIm was 50 times less effective than imidazole itself in the formation of N-acetyl imidazole species with p-nitrophenyl acetate in dimethylformamide solution. This observation suggests that good solvents for pVIm-mediated reactions must not only be polar but also protic, and supports the explanation proposed above for the failure of attempts to carbonylate this polymer with phosgene in relatively non-polar aprotic solvents.

However, studies with pVIm were not uniformly unsuccessful; when the polymer was heated under reflux with excess acetic anhydride, followed by repeated azeotropic distillation of the solvent with toluene, followed by freeze-drying at room temperature, a brown resinous polymer was obtained, which quantitatively converted p-toluidine to p-~~acetotoluidide~~ P-METHYL ACETANILIDE. This reaction presumably proceeds through a polymeric imidazolide (SCHEME 30). The reactivity of this imidazolide, however, seems to be lower than that of N-acetyl imidazole; treatment of the polymer with either cholesterol or benzyl alcohol, in the presence of catalytic amounts of base, failed to produce any cholesteryl acetate or



SCHEME 31



SCHEME 32

benzyl acetate (SCHEME 31); both compounds are readily acetylated by N-acetyl imidazole[1] under similar conditions.

Following the discovery that pVIm could be converted to the N-acetyl derivative by acetic anhydride, all the presumed polymeric imidazoles 33 , 35 , 40 prepared previously were subjected to similar treatment; in every case, the polymer thus obtained converted p-toluidine to p-~~acetotoluidide~~ METHYL ACETANILIDE. To verify that this was not simply due to the presence of residual acetic anhydride in the resin, unfunctionalised polystyrene resin was also treated with acetic anhydride under these conditions; the polymer beads thus obtained did not convert p-toluidine to p-~~acetotoluidide~~ METHYLACETANILIDE. The conclusion to be drawn is that all these polymers did contain imidazole groups, and that the failure to convert these polymers to polymer-supported 1,1' carbonyl-di-imidazole species was not due to the absence of imidazole functions, but due to the properties of the polymeric imidazoles themselves.

The preparation of a polymer-supported carbodiimide reagent has been described[19]. This reagent was used in an attempt to prepare macrolides from long-chain hydroxy-acids. It was hoped that cyclisation might occur rapidly enough to allow a "high-dilution" effect to be achieved by suitable spacing of reactive sites on the polymer support. In the event, however, anhydride formation was the only process observed, together with consequent polymerisation (SCHEME 32).

In conclusion, this investigation has demonstrated, firstly, that the earlier report[1] that hydroxy-carboxylic acids can be converted to their imidazolides by reaction with CDI does not apply to primary hydroxy-carboxylic acids, and holds for secondary hydroxy-carboxylic acids only under certain reaction conditions; and, secondly, that, while it is possible to prepare polymer-supported imidazolides which may be of use in certain specialised applications, in general, polymer-supported imidazole species do not show the same reactivity, in non-polar solvent systems, as free imidazoles, and their synthetic utility is therefore limited.

EXPERIMENTAL.

EXPERIMENTAL : CONTENTS.

EXPERIMENTAL.

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Pye Unicam SP1000 or on a Perkin-Elmer 225 double-beam spectrophotometer, and are for liquid films, unless otherwise stated; i.r. spectra of polymer-supported reagents were recorded as KBr discs. ^{1}H n.m.r. spectra were recorded on a Varian T-60 60 MHz. or on a Varian HA 100 100 MHz. spectrometer, with tetramethylsilane as internal reference. Analytical g.l.c. was performed on a Perkin-Elmer F11 or on a Pye Argon gas chromatograph.

Kieselgel G (Merck) was used for analytical t.l.c., while Kieselgel HF_{254} (Merck) was used for preparative t.l.c. Light petroleum refers to that fraction which boils between 60 and 80°. All organic solutions were dried over anhydrous magnesium sulphate.

Solvents were purified before use as follows: ether, benzene and toluene (AnalaR grade) were dried over sodium wire; tetrahydrofuran and 1,4-dioxan were distilled from lithium aluminium hydride in a nitrogen atmosphere, and stored under nitrogen over molecular sieves (Linde type 5A); n-butanol, isopropanol and n-pentane were dried over molecular sieves (Linde type 4A); chloroform (AnalaR grade) was freed of ethanol immediately before use by standing over silica gel; pyridine (AnalaR grade) was dried over solid potassium hydroxide; triethylamine was distilled at atmospheric pressure and stored over solid potassium hydroxide;

acetonitrile was distilled from calcium hydride and stored over molecular sieves (Linde type 4A); methylene chloride was percolated through alumina (Woelm basic, grade I) immediately before use; formamide and dimethylformamide were dried over molecular sieves (Linde type 4A), distilled under reduced pressure and stored over molecular sieves (Linde type 4A).

Cross-linked polystyrene beads were purified by a published procedure[5] before use.

1. Attempted preparations of di-imidazoles:

(a) bis-(4(5)-imidazolyl)-methanol, copper complex (3)

(i) A solution of xylo-pentodialdose[20] 2 (600 mg., 4 mmol.) in formamide (30 ml.) was purged with nitrogen for 1 h., and heated in a nitrogen atmosphere at 190° for 2 h.; on cooling, the solution was poured into an aqueous solution of cupric acetate (10 gm. in 100ml.) and allowed to stand overnight. On filtration, none of the expected copper complex 3 was obtained.

(ii) Xylo-pentodialdose[20] 2 (2.15g., 14.5 mmol.) was added to a solution of cupric acetate (12 g., 66 mmol.) and formaldehyde (40% aq. solution; 5 ml, 2 g., 67 mmol.) in ammonia (25%, 100 ml.). The solution was heated at 100° for 2.5 h., cooled and filtered. No copper complex 3 was obtained.

(b) bis-(4(5)-imidazolyl)-methyl benzyl ether, copper complex (5)

(i) A solution of 3-O-benzyl-xylo-pentodialdose[21] 4 (1 g., 4.2 mmol.) in formamide (30 ml.) was purged with nitrogen for 1h., and heated in a nitrogen atmosphere at 190° for 3 h.; the solvent was removed *in vacuo*, and the residue was taken up in water (50 ml.). Picric acid (600 mg., 2.6 mmol.) and charcoal were added, the solution was boiled, filtered through a Celite pad, and allowed to cool; no crystals were deposited. The solution was concentrated until crystals were obtained; these proved to be picric acid.

(ii) To a solution of cupric acetate (13.5 g., 74 mmol.) and formaldehyde (40% aq. solution; 6 ml, 2.4 g., 80 mmol.) in ammonia (25%, 115 ml.) was added 3-O-benzyl-xylo-pentodialdose[21] 4 (3.9 g., 16 mmol.). The solution was heated at 100° for 2.5 h., cooled and refrigerated overnight, filtered and the brown copper complex 5 thus obtained was washed with water. A sample of this compound was thoroughly washed with water and oven-dried at 110° before combustion analysis (closest approximation is to $(C_{14}H_{12}N_4O)Cu_2(OH)_2$:

Calculated: C, 40.68; H, 3.41; N, 13.55%

Found: C, 39.75; H, 3.02; N, 13.62%.).

The remainder of this compound was kept in a moist condition to avoid difficulties which have been experienced by earlier workers[9] in converting the dry copper complexes to the free imidazoles; the weight of the product obtained was approximately 5 g.

(c) bis-(4(5)-imidazolyl)-methyl benzyl ether 6

The following attempts were made to liberate the free di-imidazole 6 from the copper complex 5 :

(i) The complex 5 (1 g.) was suspended in water (50 ml.) made just acid to litmus by addition of hydrochloric acid, and hydrogen sulphide was passed through the solution for 3.5 h.; the solution was filtered through a Celite pad, the collected solid washed with hot water, and the combined solutions treated with picric acid (3 g., 13 mmol.) and boiled. On cooling, crystals of picric acid were deposited.

(ii) The complex 5 (1 g.) was unchanged after heating overnight at reflux in a solution of ethylenediamine tetraäcetic acid (820 mg., 3.4 mmol.) in water (20 ml.).

(iii) The complex 5 (1 g.) was heated at reflux overnight in nitric acid (3M, 25 ml.) to give a green solution. The solution was evaporated, and the residue triturated with methylene chloride; evaporation of this extract gave benzaldehyde. The remaining solid residue was dissolved in a small volume of saturated aqueous sodium bicarbonate solution, filtered, and extracted with chloroform; no material was obtained on evaporation of this extract.

(iv) The complex 5 (850 mg.) was stirred for 24 h. in nitric acid (1M, 20 ml.) to give a green solution which was basified with sodium hydroxide solution (5M), whereupon cupric hydroxide precipitated. The solution was centrifuged and decanted, neutralised with hydrochloric acid (5M), and evaporated to dryness. The solid residue was extracted with acetone in a Soxhlet apparatus; no material was obtained on evaporation of this extract.

2. Studies with 1,1' carbonyl di-imidazole (CDI):

(a) hexanoic imidazolide

This compound was prepared by the method of Staab[1], and was obtained as an oil, ν_{max} 1745 $cm.^{-1}$, λ_{max}^{THF} 243 ($\log\varepsilon = 3.8$) and 227 ($\log\varepsilon = 3.9$) nm.

(b) N-(n-butyloxycarbonyl)-imidazole 11 .

This compound was prepared by the method of Staab[1], and was obtained as an oil, ν_{max} 1770, 1200, 1075 $cm.^{-1}$, λ_{max}^{THF} 232($\log\varepsilon$ = 3.7) and 224($\log\varepsilon$ = 3.8)nm.

(c) N-(isopropyloxycarbonyl)-imidazole.

This compound was prepared by the method of Staab[1], and was obtained as an oil, ν_{max} 1770 $cm.^{-1}$, λ_{Max}^{THF} 232($\log\varepsilon$ = 3.7) and 224($\log\varepsilon$ = 3.8)nm.

(d) reaction with n-butanol and hexanoic acid.

To a stirred solution of n-butanol (37 mg., 0.5 mmol.) and hexanoic acid (58 mg., 0.5 mmol.) in THF (5 ml.) was added a solution of CDI (81 mg., 0.5 mmol.) in THF (5 ml.); after 30 min., a sample of the solution was diluted with THF and the u.v. spectrum recorded: λ_{max}^{THF} 225 ($\log\varepsilon$ = 3.8)nm. The remainder of the solution was evaporated to give an oil, ν_{max} 1770 $cm.^{-1}$, which therefore contained 11.

(e) reaction with isopropanol and hexanoic acid.

To a stirred solution of isopropanol (30 mg., 0.5 mmol.) and hexanoic acid (58 mg., 0.5 mmol.) in THF (5 ml.) was added a solution of CDI (81 mg., 0.5 mmol.) in THF (5 ml.); after 30 min., a sample of the solution was diluted with THF and the u.v. spectrum recorded: λ_{max}^{THF} 243 ($\log\varepsilon$ = 3.8) and 227 ($\log\varepsilon$ = 3.9)nm. The remainder of the solution was evaporated to give an oil, ν_{max} 1745 $cm.^{-1}$, which therefore contained hexanoic imidazolide.

(f) reaction with 12-hydroxy-dodecanoic acid.

(i) To a solution of 12-hydroxy-dodecanoic acid[22] (100 mg., 0.46 mmol.) in THF (5 ml.) was added, with stirring, a solution of CDI (80 mg., 0.49 mmol.) in THF (3 ml.). After heating under reflux for 30 min., the solution was evaporated *in vacuo*; the residue was triturated with ice-water, centrifuged, and the supernatant liquid removed. The residue was dissolved in ether, dried and evaporated to give 9 as a waxy white solid (120 mg.),

ν_{max} ($CHCl_3$) 1765, 1712, 1100, 1005 $cm.^{-1}$,

λ_{max}^{THF} 233 ($\log\varepsilon = 3.7$) and 225 ($\log\varepsilon = 3.8$) nm.

(ii) To a solution of 12-hydroxy-dodecanoic acid (100 mg., 0.46 mmol.) in THF (5 ml.) was added, with stirring, a solution of CDI (160 mg., 0.98 mmol.) in THF (3 ml.). After heating under reflux for 30 min., work-up (as in 2(f),(i)) gave 10 as a waxy white solid, ν_{max} (CCl_4) 1770, 1747 $cm.^{-1}$

(iii) A solution of 12-hydroxy-dodecanoic acid (100 mg., 0.46 mmol.) and CDI (80 mg., 0.49 mmol.) in THF (10 ml.) was stirred at room temperature, and samples were removed after 2, 10, 20, and 30 min., evaporated, and the i.r. spectra of the resulting oils recorded immediately. The spectra thus obtained showed the following absorptions:

Time (min.)	(A) 3580 $cm.^{-1}$	(B) 1770 $cm.^{-1}$	Intensity Ratio (A)/(B):
2	✓	absent	-
10	✓	✓	0.25
20	✓	✓	0.14
30	✓	✓	0.09

Thus, reaction occurs rapidly at the hydroxyl group.

(g) reaction with ricinoleic acid (12).

Commercial ricinoleic acid was purified[23] by conversion to the methyl ester, acetylation, double distillation and saponification; the purity of the resulting acid was assessed by t.l.c. before each experiment, and a further purification, by preparative t.l.c. (10% ethyl acetate/light petroleum), performed if necessary.

To a stirred solution of ricinoleic acid (80 mg., 0.27 mmol.) in ether (1 ml.) was added a solution of CDI (50 mg., 0.31 mmol.) in ether (1 ml.). After 1 h., a portion of the solution was diluted with ether and the u.v. spectrum recorded; $\lambda_{max}^{Et_2O}$ 243 ($\log\varepsilon = 3.9$) and 227 ($\log\varepsilon = 4.0$) nm.; the remainder of the solution was evaporated to give an oil, ν_{max} (CCl_4) 3480, 1748 $cm.^{-1}$, indicating the presence of 26.

(h) methyl ricinoleate (29).

To a stirred solution of ricinoleic acid (145 mg., 0.49 mmol.) in ether (2 ml.) was added a solution of CDI (80 mg., 0.49 mmol.) in methylene chloride (5 ml.); after 90 min., a solution of sodium methoxide (5 mg.) im methanol (5 ml.) was added, and the resulting solution was stirred for 1 h. After concentration in vacuo, the residue was diluted with water, extracted with ether, the organic extracts washed with saturated aqueous sodium bicarbonate solution, dried and evaporated to give 29 as an oil (145 mg., 95%), ν_{max} 3480b, 1750, 1180 $cm.^{-1}$

(j) ricinoleide[15] (27)

A stirred solution of ricinoleic acid (380 mg., 1.28 mmol.) in benzene (15 ml.) was treated with a solution of CDI (208 mg., 1.28 mmol.) in benzene (15 ml.) and heated under reflux for 5 min.; the solution was cooled, diluted with benzene (125 ml.) and sodium hydride (25 mg, 50% suspension in benzene, 0.5 mmol.) was added. The solution was heated under reflux for 48 h., cooled and evaporated to give a resinous product; n-pentane (10 ml.) was added, and the resulting precipitate filtered off to give a brown resinous polyester (237 mg.), ν_{max} (CCl_4) 3010w, 1732, 1250 and 1180 $cm.^{-1}$ The pentane extract was evaporated *in vacuo* to give an oil (35 mg.), which gave two components on preparative t.l.c. (5% ethyl acetate/light petroleum):

the less polar component (R_f: 0.43) was an oil (13 mg.), ν_{max} (CCl_4) 3010w, 1732, 1230, 1180, 1120 and 1050 $cm.^{-1}$, τ (100 MHz., CCl_4) 9.0 (3H, t , J = 7 Hz., $C\underline{H}_3$) , 8.6 (20H, s , 10 x $C\underline{H}_2$) , 7.8 (6H, m , $C\underline{H}_2$-CH=CH-$C\underline{H}_2$ and $C\underline{H}_2$-CO-O) , 6.3 (1H, m , $C\underline{H}$-O-) and 4.6 (2H, m , $C\underline{H}$=$C\underline{H}$), consistent with the structure 28;

the more polar component (R_f: 0.22) was also an oil (6 mg.), ν_{max} (CCl_4) 3010w, 1737, 1180 $cm.^{-1}$, τ (100 MHz., CCl_4) 9.0 (3H, t , J = 7 Hz., $C\underline{H}_3$), 8.6 (20H, s , 10 x $C\underline{H}_2$), 7.8 (6H, m , $C\underline{H}_2$-CH=CH-$C\underline{H}_2$ and $C\underline{H}_2$-CO-O), 6.3 (1H, m , $C\underline{H}$-O-) and 4.6 (2H, m , $C\underline{H}$=$C\underline{H}$), consistent with the structure 27.

(k) reaction with 12-hydroxy-stearic acid (13).

Commercial 12-hydroxy-stearic acid was purified by a published procedure[24] to give white crystals, m.p.76-7° (acetone) (lit.[24] 77-77.5°), ν_{max} ($CHCl_3$) 3600, 3520, 3480, 1745w, 1710 $cm.^{-1}$

(i) To a stirred solution of 12-hydroxy-stearic acid (160 mg., 0.53 mmol.) in THF (10 ml.) was added a solution of CDI (85 mg., 0.53 mmol.) in THF (5 ml.); after 45 min., the solution was concentrated *in vacuo* to give an oil which, on dissolution in carbon tetrachloride and filtration to remove excess imidazole, showed ν_{max} (CCl_4) 1780, 1060 $cm.^{-1}$, indicating the structure 14.

(ii) To a stirred solution of 12-hydroxy-stearic acid (109 mg., 0.36 mmol.) in chloroform (10 ml.) was added a solution of CDI (58 mg., 0.36 mmol.) in chloroform (5 ml.); after 3 h., a sample of the solution was removed and the i.r. spectrum recorded: ν_{max} ($CHCl_3$) 1765, 1747, 1710 and 1055 $cm.^{-1}$ The ratio of the intensities of the carbonyl absorptions was 3:3:2 respectively, indicating that the product was an equimolar mixture of 14 and 15.

(iii) To a stirred solution of 12-hydroxy-stearic acid (155 mg., 0.52 mmol.) in ether (10 ml.) was added a solution of CDI (87 mg., 0.54 mmol.) in ether (8 ml.); after 4 h., the solution was filtered and a sample concentrated *in vacuo* to an oil, ν_{max} ($CHCl_3$) 3680w, 3600w, 1747 $cm.^{-1}$, indicating the structure 15. The remaining solution was treated with sodium hydride (10 mg., 50% suspension in cyclohexane) and stirred for

3 h., during which time a white gelatinous solid precipitated. The solution was filtered through a Celite pad and concentrated; the resulting gummy solid was purified by preparative t.l.c. (20% ethyl acetate/light petroleum) to give a polyester as a viscous oil (11 mg., R_f: 0.66) ν_{max} ($CHCl_3$) 3680w, 3600w, 1730b, 1060s $cm.^{-1}$

(iv) Experiment 2(k) (ii) was repeated as described, except that imidazole (28 mg., 0.41 mmol.) was added to the solution of CDI before the solutions of reactants were mixed. After 3 h., the i.r. spectrum of the solution was recorded as ν_{max} ($CHCl_3$) 1765, 1747, 1710 and 1055 $cm.^{-1}$ The ratio of the intensities of the carbonyl absorptions was 3:3:2 respectively, indicating that the product was an equimolar mixture of 14 and 15.

(v) Experiment 2(k) (ii) was repeated as described, except that imidazole (28 mg., 0.41 mmol.) was added to the stirred solution of 12-hydroxy-stearic acid 30min. before addition of the solution of CDI; after 3 h., the i.r. spectrum of the solution was recorded as ν_{max} ($CHCl_3$) 3680, 3600, 1747 $cm.^{-1}$, indicating that the product was the imidazolide 15.

(m) reaction with 16-hydroxy-hexadecanoic acid.

(i) To a stirred solution of 16-hydroxy-hexadecanoic acid (22 mg., 0.08 mmol.) in ether (15 ml.) was added a solution of CDI (13 mg., 0.08 mmol.) in ether (5 ml.). After 16 h., the solution was evaporated to give an oil, ν_{max} ($CHCl_3$) 3680w, 3620w, 1765, 1710 $cm.^{-1}$,

indicating the presence of the structure 19.

(ii) A solution of 16-hydroxy-hexadecanoic acid (55 mg., 0.2 mmol.) in chloroform (3 ml.) was treated with imidazole (15 mg., 0.22 mmol.), heated slightly to dissolve the reactants and stirred at room temperature for 30 min.; a solution of CDI (33 mg., 0.2 mmol.) in chloroform (1 ml.) was added, and, after 5 min., the i.r. spectrum of the solution was recorded as ν_{max} ($CHCl_3$) 1765, 1710 $cm.^{-1}$, indicating the presence of 19.

(n) reaction with iso-ambrettolic acid.

Iso-ambrettolic acid was prepared by saponification of commercial iso-ambrettolide: to a mixture of aqueous sodium hydroxide solution (5M, 2 ml.) and methanol (2 ml.) was added iso-ambrettolide (55 mg.) and the mixture was heated 16 h. at reflux. After cooling and dilution with water (6 ml.), the alkaline solution was washed with ether (3 x 10 ml.) and acidified to pH 1 with aqueous hydrochloric acid (5M); the resulting emulsion was extracted with ether (3 x 10 ml.), the combined ether extracts washed with brine, dried and evaporated to give a white solid (38 mg.) which was purified by preparative t.l.c. (60% ethyl acetate/light petroleum) to give iso-ambrettolic acid as white crystals, m.p. 67-8° (lit.[25] 70°)

To a stirred solution of iso-ambrettolic acid (20 mg., 0.074 mmol.) in THF (7 ml.) was added a solution of CDI (12 mg., 0.074 mmol.) in THF (1 ml.).

After 2 h., the solution was evaporated to give an oil (28 mg.), $\nu_{max}(CHCl_3)$ 1775 $cm.^{-1}$, indicating the presence of the structure 20.

(o) reaction with 16-trimethylsiloxy-hexadecanoic acid(22).

(i) To a stirred solution of 16-hydroxy-hexadecanoic acid (196 mg., 0.72 mmol.) in pyridine (2 ml.) were added hexamethyldisilazane (1 ml.) and chloro-trimethylsilane (0.5 ml.). After 16 h., the solution was concentrated, the residue taken up in ether (5 ml.), and the ethereal solution filtered through a Celite pad, washed with water (5 ml.), dried and evaporated to give 22 as low melting white crystals (203 mg.), ν_{max} 1710, 1246 and 1090 $cm.^{-1}$, $\tau(CCl_4)$ 9.9 (9H, s , Me_3SiO), 8.7 (26H, s , $(C\underline{H}_2)_{13}$), 7.8 (2H, t, J = 6 Hz., $C\underline{H}_2CO_2H$) and 6.4 (2H, t , J = 7 Hz., $C\underline{H}_2O$-)

(ii) To a stirred solution of 22 (175 mg., 0.51 mmol.) in THF (1 ml.) was added a solution of CDI (87 mg., 0.54 mmol.) in THF (1 ml.); effervescence was observed, and the flask became warm. After 45 min., a sample was taken from the solution and concentrated to give a polyester as a resinous white solid ν_{max} (CCl_4) 1725, 1135 $cm.^{-1}$; the remainder of the solution was diluted with light petroleum (8 ml.), whereupon a white solid precipitated and was filtered off. This compound showed similar spectral characteristics to the polymer obtained above, indicating that it was also a polyester. On evaporation of the remaining solution, no material was obtained.

3. Reaction of N-chlorocarbonyl-imidazole (31) with hexanoic acid.

To a stirred solution of phosgene in toluene (1M, 1 ml., 1 mmol.) and THF (15 ml.) was added, at -78° in a nitrogen atmosphere, a solution of imidazole (68 mg., 1 mmol.) and triethylamine (108 mg., 1.07 mmol.) in THF (6 ml.); after 5 min., the solution was treated with triethylamine (101 mg., 1 mmol.) in THF (3 ml.), followed by hexanoic acid (116 mg., 1 mmol.) in THF (3 ml.), and the cooling bath was removed. After 16 h., the solution was filtered and evaporated to give an oil (167 mg.) ν_{max} 1745 $cm.^{-1}$, indicating the presence of hexanoic imidazolide.

4. Preparation and reactions of polystyrene-supported imidazoles:

(a) poly-p-4(5)-imidazolylmethoxymethyl-styrene (33).

(i) A stirred solution of 4(5)-hydroxymethyl-imidazole 32 (490 mg., 5 mmol.) in dimethylformamide (DMF, 5 ml.) was treated with sodium hydride (50% suspension in cyclohexane, 480 mg., 10 mmol.); after 30 min., chloromethylated polystyrene beads bearing 3.6 meq. chloride per gram of polymer (1 g., 3.6 mmol.) were added. After 16 h., the polymer beads were filtered, washed successively with ethanol (50 ml.), water (500 ml.), 1,4-dioxan (100 ml.), hydrochloric acid (1M, 250 ml.), water (250 ml.), sodium hydroxide solution (1M, 250 ml.), water (100 ml.) and methanol (100 ml.), and dried at 100°, 0.1 torr. to give a cream-coloured polymer

ν_{max} 3380, 3200, 2760, 2320 cm^{-1}; combustion analysis showed C, 76.07; H, 6.90; N, 4.95%, corresponding to 1.77 mmol. imidazole per gram.

(ii) To a stirred suspension of 33 (1 g., 1.77 mmol.) in benzene (5 ml.) was added, in an atmosphere of nitrogen, a solution of triethylamine (198 mg., 1.96 mmol.) in benzene (1 ml.), followed by a solution of phosgene in toluene (1M, 0.9 ml., 0.9 mmol.); after 10 min., a solution of hexanoic acid (53 mg., 0.46 mmol.) in benzene (3 ml.) was added, and the solution was stirred for 16 h., filtered and evaporated to give unchanged hexanoic acid (50 mg.).

(b) poly-p-styryl acetic acid, 4(5)-imidazolylmethyl ester (35).

(i) A suspension of poly-p-styryl acetic acid[26] (823 mg., 2 mmol.) in toluene (5 ml.) was treated with thionyl chloride (5 ml.), heated 24 h. at reflux, cooled and filtered. The vermilion-coloured beads were washed with toluene (5 x 25 ml.) and ether (3 x 25 ml.) with minimal exposure to atmospheric moisture. The polymer was then suspended in a solution of 4(5)-hydroxymethyl-imidazolium chloride[9] (920 mg., 6.8 mmol.) in acetonitrile (20 ml.) and heated at reflux for 96 h. On cooling, the polymer beads were filtered and washed successively with acetonitrile (3 x 10 ml.), methanol (3 x 10 ml.), water (5 x 10 ml.), methanol (3 x 10 ml.) and ether (3 x 10 ml.) and dried in an evacuated desiccator to give 35 as maroon-coloured beads (779 mg.)

ν_{max} 3400b, 3140b, 1720b, 1280b, 1175 and 1100 $cm.^{-1}$

(ii) To a stirred suspension of 35 (770 mg.) in chloroform(10 ml.) were added successively triethylamine (1 ml.) and a solution of phosgene in toluene (1M, 3 ml., 3 mmol.); after 15 min., the beads were filtered and washed with chloroform (2 x 10 ml.), atmospheric moisture being excluded. The polymer was then suspended in a solution of hexanoic acid (410 mg., 3.5 mmol.) in chloroform (10 ml.) and stirred 16 h.; the solution was filtered and evaporated to give unchanged hexanoic acid (400 mg.).

(c) poly-p-styrylmethoxy-, bis-(4(5)-imidazolylmethoxy)-methylsilane (37).

Chloromethyl-polystyrene (2.5 mmol./g.) was converted to hydroxymethyl-polystyrene by heating under reflux with aqueous potassium hydroxide solution (5M) for 16 h., followed by thorough washing with water, methanol and ether, and drying at 100°, 0.1 torr. The product thus obtained showed ν_{max} 3420b and 1260 $cm.^{-1}$ This polymer (3.1 g.) was stirred for 16h. with methyltrichlorosilane (10 ml.); chloroform (25 ml.) was added, and the mixture was transferred to a stoppered centrifuge tube, centrifuged, and the supernatant liquid removed. The residue was washed with ether (3 x 25 ml.), centrifuging and removing the supernatant liquid after each washing, and dried at 100°, 0.1 torr. The product thus obtained was suspended in a solution of 4(5)-hydroxymethyl-imidazolium chloride (1.8 g., 13.4 mmol)-

and triethylamine (10 ml.) in DMF (30 ml.) and stirred for 16 h. The polymer beads were filtered and washed successively with DMF (3 x 10 ml.), methanol (6 x 20 ml.), water (3 x 20 ml.), methanol (6 x 10 ml.) and ether (3 x 20 ml.) and dried at 50°, 0.1 torr. to give a cream-coloured polymer. Combustion analysis showed:

C, 72.24; H, 8.11; N, 4.18; O, 15.65% (TOTAL: 100.24%);

The polymer therefore contained no silyl group, and was not 37.

(d) poly-p-styrylmethyl-, bis(4(5)-imidazolylmethoxy)-methylsilane (36).

Chloromethyl-polystyrene[5] (5.5 g., 13.75 mmol.) was oven-dried at 100°, stirred in an atmosphere of nitrogen, and treated with a solution of ethyl magnesium bromide (prepared from 1.2 g. Magnesium and 5 g. ethyl bromide in 25 ml. ether); after 90 min., the polymer beads were filtered, washed with ether (2 x 20 ml.) and suspended in ether (20ml.) in a nitrogen atmosphere. Methyl-trichlorosilane (7 ml.) was added, and stirring was continued for 1 h. The polymer was then filtered, washed successively with ether (2 x 20 ml.) and chloroform (2 x 20 ml.) and suspended in a stirred solution of 4(5)-hydroxymethyl-imidazolium chloride[9] (1.9 g., 14 mmol.) and triethylamine (2 ml.) in chloroform (20 ml.) in a nitrogen atmosphere. After 16h., the polymer was filtered, washed successively with chloroform (2 x 20 ml.), methanol (2 x 20 ml.), DMF (2 x 20 ml.) and ether (3 x 20 ml.) and finally dried

at 80°, 0.1 torr. over P_2O_5 to give a white polymer. Combustion analysis showed :

C, 77.8; H, 7.25; N, 1.16; O, 13.93% (TOTAL: 100.14%); the polymer therefore contained no silyl group, and was not 36.

(e) poly-p-(di-(2-(4(5)-imidazolyl)-ethyl)-aminomethyl-styrene (40).

(i) Aminomethyl-polystyrene was prepared by a reported method[19] and carefully standardised as follows: a centrifuge tube was charged with polymer (106 mg.) and standardised hydrochloric acid (3.35M, 0.20 ml.) and allowed to stand for 30 min. The supernatant liquid was carefully removed, and the polymer was washed successively with water (2 x 25 ml.) and ethanol (10 ml.), carefully centrifuging and removing supernatant liquid each time. The combined solutions thus obtained were titrated against sodium hydroxide solution (0.1M) using methyl orange as indicator; the activity of the polymer was found to be 0.38 mmol./g.

A suspension of aminomethyl-polystyrene (1.014g.) in a solution of 4(5)-(2-chloroethyl)-imidazolium chloride[16] and triethylamine (1 ml.) in n-butanol (10 ml.) was heated under reflux for 16 h.; after cooling, the solution was diluted with ethanol (25 ml.) and the polymer beads were filtered, washed with ethanol (10 x 25 ml.) and ether (4 x 25 ml.), and dried at 80°, 0.1 torr. to give an ochre-coloured polymer, which, on titration as described above, was found to

contain 1.15 mmol. amine /g. Thus, neglecting the small change in weight resulting from the substitution, the specific activity of the product, in terms of amine groups per gram, was 1.15/0.38 = 3.02 times the activity of the original polymer, corresponding to complete di-alkylation of the polymeric amine by the alkyl halide.

(ii) A stirred suspension of 40 (470 mg.) in hexamethyldisilazane (2 ml.) was heated under reflux, with exclusion of atmospheric moisture, for 21 h.; the excess reagent was distilled off in a carefully-dried rotary evaporator, and the last traces of silylating agent were removed by azeotropic distillation with toluene (2 x 2 ml.) to give a yellow-brown polymer 41.

(iii) A solution of benzyl alcohol (3 mg.) in benzene (1 ml.) was treated with polymer 41 (65 mg.) and allowed to stand for 16 h. A sample of the solution was analysed by g.l.c. (1% OV-1, 85°) and shown to contain benzyloxy-trimethylsilane, identified by comparison with an authentic sample.

(iv) To a stirred suspension of polymer 41 (375 mg., 0.14 mmol.) in toluene (2 ml.) was added a solution of phosgene in toluene (1M, 1 ml., 1 mmol.). After 42 h., the solvent was evaporated in a dry rotary evaporator (a trap containing sodium hydroxide solution (5M) was inserted in the vacuum line to destroy excess phosgene). The last traces of reactants were removed by azeotropic distillation with toluene (3 x 2 ml.). The

yellow-brown polymer thus obtained was suspended in a stirred solution of acetic acid (10 mg., 0.17 mmol.)in THF (2 ml.). After 84 h., the polymer was filtered off, washed with THF (5 ml.) and suspended in a stirred solution of p-toluidine (16 mg., 0.15 mmol.) in THF (1 ml.). After 72 h., the polymer was filtered, washed with ether (2 x 5 ml.) and the combined filtrates evaporated to give an oil (13 mg.), identified as p-toluidine by comparison with an authentic sample.

(v) Aminomethyl-polystyrene (1.07 g., 0.4 mmol.) was suspended in hexamethyldisilazane (2 ml.) and heated at reflux for 2 h.; the excess reagent was removed by vacuum distillation in a dry rotary evaporator and azeotropic distillation with toluene (2 x 2 ml.) to give a yellow polymer. A sample (90 mg.) of this polymer was suspended in a solution of benzyl alcohol (5 mg.) in ethyl acetate (1 ml.)and allowed to stand for 16 h. On g.l.c. analysis (1%OV-1, 85°), the solution was found to contain benzyloxytrimethylsilane.

(f) Reaction of 33 , 35 & 40 with acetic anhydride.

(i) Polymer 33 (60mg., 0.1 mmol.) was suspended in acetic anhydride (5 ml.) and allowed to stand for 1 week at room temperature, after which the excess reagent was evaporated at 90°, 12 torr., and the polymer freed of the last traces of acetic anhydride by azeotropic distillation with toluene (4 x 15 ml.). The polymer thus obtained was suspended in a solution of p-toluidine (9 mg., 0.084 mmol.) in THF (1 ml.); after 16 h., the

polymer was filtered, washed with THF (5 ml.), and the combined filtrates evaporated to give p-acetotoluidide as yellow crystals (12 mg., 96%), m.p. 144-5° (EtOH) (lit[27]. 145°), ν_{max} ($CHCl_3$) 3440, 1685, 1595 and 1510 cm^{-1}.

(ii) Reaction of 35 (70mg.) with acetic anhydride (5 ml.), followed by reaction with p-toluidine (9 mg., 0.084 mmol.) in THF (1 ml.) as in 4(f),(i) gave p-acetotoluidide as yellow crystals (11 mg, 88%), m.p.144-5° (EtOH).

(iii) Reaction of 40 (175 mg., 0.133 mmol.) with acetic anhydride (5 ml.), followed by reaction with p-toluidine (9 mg, 0.084 mmol.) in THF (1 ml.), as in 4(f),(i) gave p-acetotoluidide as yellow crystals (11 mg., 88%), m.p. 144-5° (EtOH).

(iv) Treatment of unfunctionalised polystyrene beads (500 mg.) with acetic anhydride (10 ml.), followed by treatment with p-toluidine (45 mg., 0.42 mmol.) in THF (5 ml.) as in 4(f),(i) gave unchanged p-toluidine.

5. Studies with poly-4(5)-vinyl-imidazole (pVIm) 43:

(a) 4(5)-vinyl-imidazole[16]

Commercially-available urocanic acid dihydrate was dried at 80° / 0.1 torr. over P_2O_5 ; very little weight-loss was observed, and it was concluded that this material was already in the anhydrous state. This was confirmed by the absence of absorptions due to water in the i.r. spectrum.

Anhydrous urocanic acid (5 g., 36.2 mmol.) was heated in a short-path vacuum-distillation apparatus until decarboxylation commenced at 220°, and then heated further at 250°; 4(5)-vinyl-imidazole (2.37 g., 25.2 mmol., 66%) was collected as white crystals b.p. 250° (0.1 torr.), m.p. 79-81° (lit.[16] 83.2-84.5°), ν_{max} ($CHCl_3$) 3460s, 3300b, 1640s, 980s cm^{-1}

(b) poly-4(5)-vinyl-imidazole.[16]

To a stirred solution of 4(5)-vinyl-imidazole (1.04 g., 11 mmol.) in benzene (100 ml.) was added, in an atmosphere of nitrogen, α,α'-azo-bis-isobutyronitrile (4 mg.). The solution was heated under reflux for 90 h., cooled, filtered and the product dried at 100°/ 0.1 torr. to give pVIm as a fine white powder (870 mg., 84%). Combustion analysis gave the following results:

C, 57.5; H, 6.3; N, 25.65; O, 11.13%.

$C_5H_6N_2 \cdot (H_2O)_{0.66}$ requires:

C, 56.59; H, 6.97; N, 26.40; O, 10.05%

$C_5H_6N_2 \cdot (H_2O)_{0.75}$ requires:

C, 55.8; H, 6.98; N, 26.04; O, 11.16%

Thus, the polymer contains approximately 2 molecules of water for every three monomer units. Prolonged drying at 100°/ 0.1 torr. over P_2O_5 failed to remove this water; the polymer was therefore dissolved in methanol (20 ml.) and the solution dried over molecular sieves (Linde type 3A) for 60h. The solution thus obtained was filtered and added dropwise to dry ethyl acetate (200 ml.) with vigorous stirring, centrifuged, and the supernatant liquid removed. The precipitated polymer was obtained

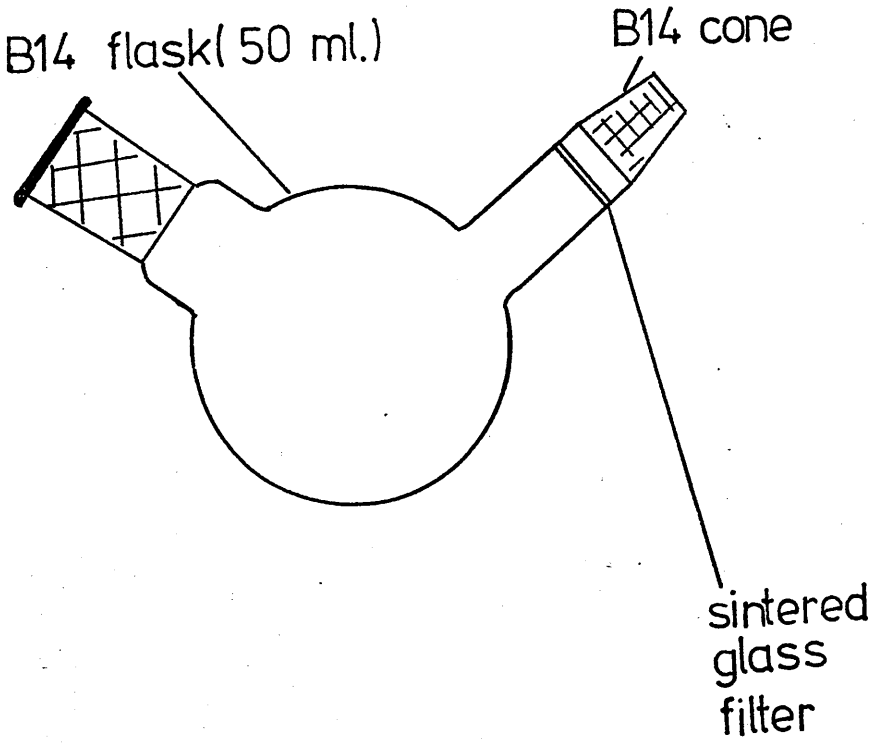


Figure 1.

as a cream-coloured powder (250 mg.) after drying at 80°/ 0.1 torr. over P_2O_5, and was stored over P_2O_5. Unless otherwise stated, subsequent experiments were carried out in a dry-box in an atmosphere of nitrogen.

(c) Reaction with phosgene.

PVIm (193 mg., 1.7 mmol.) was placed in a sintered glass filter column (porosity 3) and treated successively with a solution of triethylamine (252 mg., 2.5 mmol.) in chloroform (1 ml.) and phosgene in toluene (1M, 1 ml., 1 mmol.); the column was stoppered to prevent loss of reagents and shaken intermittently. After 5 min., the polymer was filtered, washed successively with chloroform (3 x 10 ml.) and THF (10 ml.) amd then treated with a solution of acetic acid (51 mg., 0.85 mmol.) in THF (10 ml.). After 10 min., the polymer was filtered, washed with THF (10 ml.) and treated with a solution of aniline (80 mg., 0.85 mmol.) in THF (10 ml.). The column was stoppered, shaken, and allowed to stand for 16 h.; on filtration and evaporation of the filtrate, aniline was recovered unchanged (67 mg., 84%).

(d) poly-N-trimethylsilyl-4(5)-vinyl-imidazole.

PVIm (470 mg., 5.0 mmol.) was treated with hexamethyldisilazane (5 ml.) and heated at reflux for 72 h., with stirring, in a flask equipped with a sintered-glass filter (Figure 1). The flask was then stoppered and transferred to the dry-box. After cooling, the solution was diluted with n-pentane (10 ml.) and filtered; the polymer thus collected was washed with

n-pentane (2 x 10 ml.), a solution of phosgene in toluene (1M, 2.3 ml., 2.3 mmol.) was added, and the solution was stirred for 16 h. After filtration and washing with n-pentane (3 x 10 ml.) and THF (2 x 10 ml.), a solution of benzoic acid (244 mg., 2 mmol.) in THF (5 ml.) was added and stirring continued for 16 h. The flask was removed from the dry-box, and the suspension transferred to a stoppered centrifuge tube, centrifuged, and the supernatant liquid removed; the polymer was washed successively with THF (2 x 10 ml.), n-pentane (3 x 10 ml.) and THF (10 ml.), centrifuging and removing the supernatant liquid each time. A solution of p-toluidine (214 mg., 2 mmol.) in THF (10 ml.) was added, and the suspension was stirred for 16 h.; ether (20 ml.) was added, and the suspension stirred vigorously, centrifuged and the supernatant liquid was removed; this process was repeated, and the combined extracts were evaporated to give an oil (240 mg.), which was shown by its i.r. spectrum to consist largely of unchanged p-toluidine. The product was dissolved in ethyl acetate (25 ml.), washed with hydrochloric acid (1M, 10 ml.), brine (10 ml.), dried and evaporated; no material was obtained.

(e) Reaction with CDI.

PVIm (60 mg., 0.64 mmol.) was mixed intimately with CDI (210 mg., 1.3 mmol.) and heated at 100° in a stoppered tube. Imidazole was deposited on the walls of the tube over a period of several hours.

After 6 h., the tube was cooled and the hard friable product was washed with THF (3 x 10 ml.), and stirred with THF (10 ml.) for 3 days. At the end of this period, no discernible change had occurred in the physical state of the polymer; since this polymer was obviously contaminated with CDI, no further investigation was attempted.

(f) Poly-N-acetyl-4(5)-vinyl-imidazole. (45)

(i) PVIm (170 mg., 1.8 mmol.) was suspended in acetic anhydride (10 ml.) and stirred for 60 h., after which period the excess reagent was evaporated at 90°/ 12 torr., and the polymer freed of the last traces of reagent by azeotropic distillation with toluene (4 x 15 ml.). The polymer was then freeze-dried at 20°/ 0.1 torr. (trap at -196°) to give 45 as a brown/white polymer (257 mg.).

(ii) Polymer 45 (65 mg., 0.48 mmol.) was suspended in a stirred solution of p-toluidine (39 mg., 0.36 mmol.) in THF (3 ml.); after 40 h., the solvent was evaporated, ether (10 ml.) was added, the solution was filtered through a Celite pad, and evaporated to give p-acetotoluidide as white crystals (41 mg., 76%), m.p. 143-4° (aq. EtOH) (lit.[27] 145°), ν_{max} ($CHCl_3$) 3440, 1685, 1595 and 1510 cm^{-1}

(iii) Polymer 45 (120 mg., 0.89 mmol.) was suspended in a stirred solution of cholesterol (40 mg., 0.1 mmol.) in THF (4 ml.) and sodium hydride (50% suspension in benzene; ca. 5 mg.) was added. After 96 h., the solution

was filtered and evaporated, taken up in ether (10 ml.), filtered through a Celite pad and evaporated to give unchanged cholesterol.

(iv) Polymer 45 (42 mg., 0.31 mmol.) was suspended in a stirred solution of benzyl alcohol (13 mg., 0.12 mmol.) in THF (2 ml.) and sodium hydride (50% suspension in benzene, ca. 5 mg.) was added; after 36 h., the solvent was evaporated, and the residue extracted with ether (3 x 5 ml.), the combined solutions filtered through a Celite pad and evaporated to give unchanged benzyl alcohol.

6. Polystyrene-supported carbodiimide(46).

(i) 46 was prepared by a published[19] procedure from chloromethyl-polystyrene[5] (3.64 mmol./g.); the product gave, on combustion analysis:

C, 80.17; H, 8.08; N, 6.96%, corresponding to a maximum activity of 2.5 mmoles of active carbodiimide per gram of polymer; 46 had ν_{max} 2115 $cm.^{-1}$.

As a test of the polymer activity, stearic acid (555 mg., 2.17 mmol.) was reacted with the polymer (1.08g., 2.7 mmol. max.) as a suspension in benzene/ether (2:1; 10 ml.). On filtration and evaporation of the filtrate, stearic anhydride was obtained as white crystals (400 mg., 73%) m.p. 70-1° (light petroleum) (lit.[28] 72°), ν_{max} 1818 and 1740 $cm.^{-1}$

(ii) Polymer 46 (1 g., 2.5 mmol.) was suspended in a stirred solution of ricinoleic acid (85 mg., 0.28 mmol.) in benzene (7 ml.); after 48 h., the solution was filtered and evaporated to give ricinoleic anhydride 47 as an oil (58 mg., 70%), $\nu_{max}(CCl_4)$ 3600, 3020w, 1825 and 1755 $cm.^{-1}$

(iii) Polymer 46 (1.24 g., 3.1 mmol.) was suspended in a stirred solution of 12-hydroxy-stearic acid (300 mg., 1 mmol.) in THF (10 ml.); after 72 h., the solution was filtered and evaporated to give 12-hydroxy-stearic anhydride as an oil (192 mg., 66%), ν_{max} 3300b, 1820, 1760 $cm.^{-1}$

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