SOME ASPECTS OF THE CHEMISTRY OF MODIFIED MEERWEIN REAGENTS AND OF ANALOGOUS REACTIVE INTERMEDIATES

by

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To my parents

SUMMARY

Recent developments in the chemistry of onium salts are described, with particular emphasis on the utility of oxygen, sulphur, and halogen cations in nucleophilic substitution.

Evidence is accumulated to support a cationic ring closure of 2-alkoxybiphenyl-2'-yldiazonium ions, and the study of O-methyldibenzofuranium tetrafluoroborate has been extended. It is a stronger agent than the dimethylphenyloxonium salt, and is capable of alkylating sterically hindered anions such as the mesitoate anion. Reaction with tetrahydrofuran gives a polymeric product, and no O-methyltetrahydrofuranium species was detected. A route to O-acyldibenzofuranium salts was impeded by the rearrangement of 2-acyloxy-2'-nitrobiphenyls to 2-acylamino-2'-hydroxybiphenyls during catalytic hydrogenation.

S-Methyldibenzothiophenium tetrafluoroborate has been prepared by a general synthetic sequence involving biaryls. Attempts to isolate S-benzyl and S-neopentyl derivatives were unsuccessful, and thereby question the stability and alkylating ability of the oxonium analogues. Several methods have been tried in order to improve the yield of 2-alkylthio-2'-nitrobiphenyls. The most promising involves demethylation of 2-methylthio-2'-nitrobiphenyl by a two step chlorination/acid-catalysed methanolysis procedure. Thioethoxide ion dealkylates thioanisole to give thiophenol, but it also reduces nitrobenzene to aniline, and it preferentially undergoes the latter reaction in the presence of both sulphide and nitro functions.

Diphenyliodonium hexafluorophosphate is a good arylating agent and precursor to other onium compounds such as the triphenylsulphonium salt. Diphenylene-bromonium and -iodonium tetrafluoroborates were obtained by a controlled cyclisation technique.

The stability and reactivity of various onium salts, including

N,N-dimethylcarbazolium tetrafluoroborate, has been correlated with both ^{1}H and ^{13}C NMR chemical shifts. Generally, greater reactivity to nucleophiles is associated with greater deshielding and an inability to accommodate positive charge.

Included is an extensive literature review on the synthesis of biaryls, with particular attention paid to the Ullmann reaction. The present state of the art advocates on ionic mechanism which proceeds via arylcopper intermediates. Also presented are reviews on all alkylating agents, and a chapter is devoted to the discussion of hydroxyl and sulphydryl protecting groups and cleavage reagents.

ACKNOWLEDGEMENTS

I would first like to thank my supervisor, Dr. H. Heaney, for his invaluable help and attention and his constant encouragement throughout the course of this work.

I express my thanks to Professor K.W. Bentley for the privilege of working in his laboratories, and am indebted to the Science Research Council for the provision of a maintenance grant.

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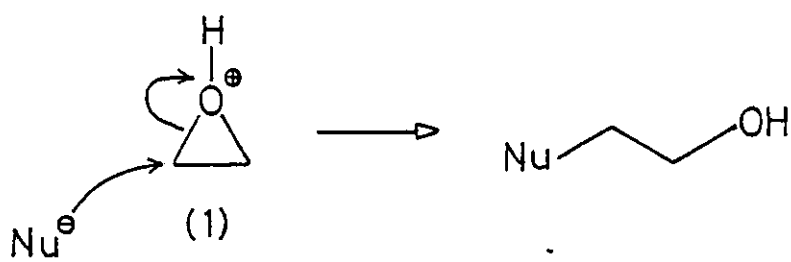
CHAPTER 1

INTRODUCTION

1.1 ALKYLATING AGENTS

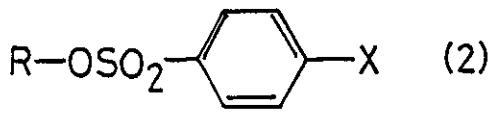
The process of alkylation involves formation of a new bond between a nucleophile and a reactive centre attached to a suitable leaving group. The more stable is the leaving group as a free entity, the more easily will it depart. As a rule, high stability may be correlated with low basicity. Therefore, the best leaving groups are the weakest bases, e.g. iodine is the best leaving halogen, and nucleophilic substitution will occur more readily at $RXH^{\oplus}$ than at RX, since the neutral species XH is a weaker base than the anion $X^{\ominus}$. Leaving group power is also enhanced by ring strain. Thus, ordinary ethers do not cleave under mild conditions, but epoxides, and especially protonated epoxides (1), cleave easily.



(1)

Conventional reagents such as alkyl iodides, dialkyl sulphates, and diazomethane are well-established in organic synthesis, but are not effective for the alkylation of weakly nucleophilic functional groups. The most common leaving groups are the halides, but sometimes it is more convenient to convert an alcohol to a reactive ester, and thereby to a better leaving group. Synthetic and especially physical organic chemistry has been well served by the sulphonic esters (2) (3) depicted below (see overleaf).

Probably the best leaving group is the nitrogen molecule, hence the versatility of diazomethane as a methylating agent of reasonably acidic substrates. However, diazonium ions generated from aliphatic



(2)

X = Me p-Toluenesulphonates, ROTs (Tosylates)

Br p-Bromobenzenesulphonates, ROBs (Brosylates)

NO_2 p-Nitrobenzenesulphonates, RONs (Nosylates)

$R-OSO_2Me$ Methanesulphonates, ROMs (Mesylates)

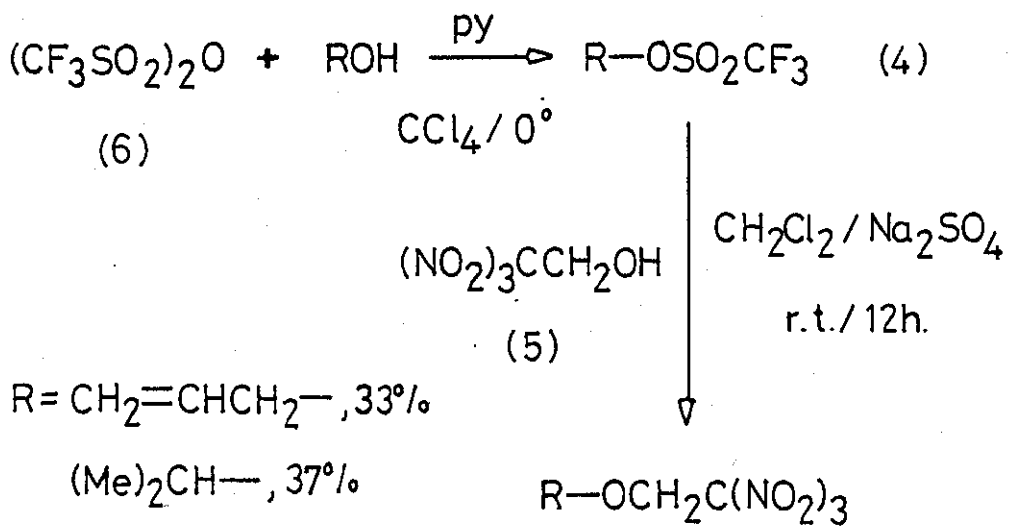
(3)

primary amines are unsuitable for synthesis since they give a mixture of products. Better leaving groups have recently been found, and compounds containing such groups make powerful alkylating agents. Among them are oxonium ions, alkyl perchlorates, alkyl fluorosulphonates, and the fluorinated compounds triflates and nonaflates.

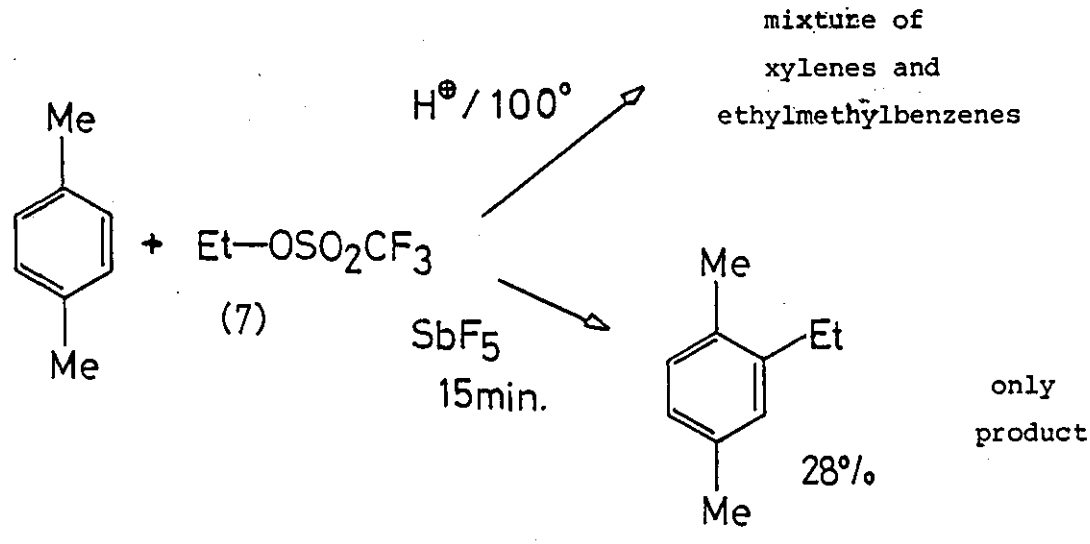
The introduction of trifluoromethanesulphonates[1] (triflates, ROTf) has increased the solvolytic reactivity spread between various sulphonate esters to ca. 80,000. However, this spread is not gradual; the commonly used leaving groups (-OMs, -OTs, -OBs) differ in reactivity by a factor of 10, whilst triflate is ca. 8,000 times more reactive than brosylate, the most reactive of these groups. The synthesis of 2,2,2-trifluoroethanesulphonates[2] (tresylates, ROTr) has provided a leaving group of intermediate solvolytic reactivity. Thus, solvolysis rates of tresylate esters appear typically to be ca. 100 times larger than those of corresponding tosylates, and 400 times smaller than those of corresponding triflates.

Baum et. al.[3] have extended the study of triflates in preparing esters more reactive than the ethyl derivative. In this way, the range of reagents that can be alkylated has been extended, illustrated by

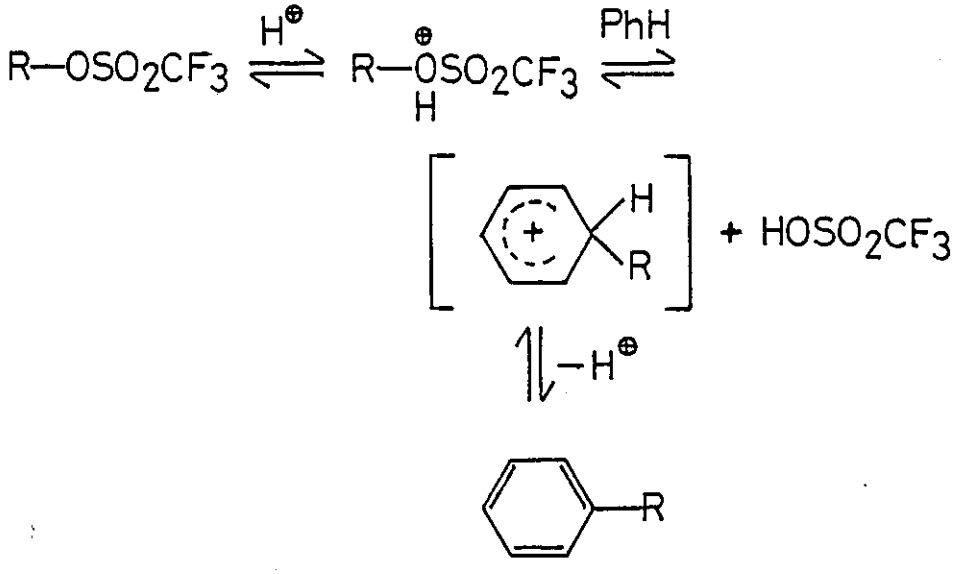
reactions with nitro alcohols of low nucleophilicity. Both allyl and isopropyl triflates are unstable, but reaction of freshly prepared solutions (4) with 2,2,2-trinitroethanol (5) at ambient temperature gave the corresponding allyl and isopropyl ethers. By analogy, methyl triflate produced no ether after 45 hours. The new reagents are useful also for alkylating normally reactive hydroxyl groups in the presence of other substituents that cannot tolerate acid or base, or are thermally unstable.



The use of organic and inorganic esters for alkylation of aromatic compounds has received comparatively little attention. Much of the work on Friedel-Crafts reactions has been based on the alkyl halide-Lewis acid system. However, a recent report[4] shows that methyl and ethyl triflates, prepared from triflic anhydride (6), contain traces of triflic acid which catalyse their reactions with aromatic compounds. Lewis-acids such as antimony pentafluoride (SbF_5) are particularly effective catalysts in increasing yields and reducing the amount of isomerisation and disproportionation products. This is exemplified by the reaction of ethyl triflate (7) with p-xylene (see overleaf).



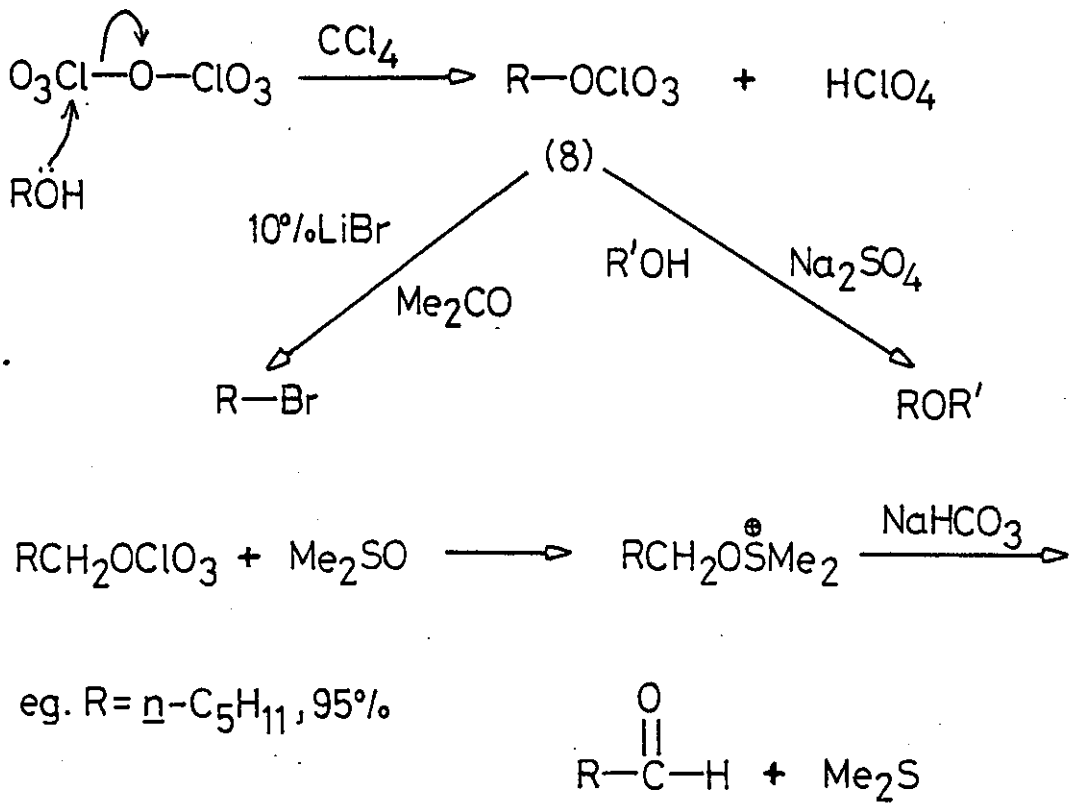
The observed trend of reactivities, benzyl > isopropyl > ethyl > methyl reflects a degree of partial ionisation of the carbon-leaving group bond.



The nonafluorobutanesulphonates[5, 6] (nonaflates, RONf) solvolyse 1.5-2 times faster than triflates. The nonaflate anion represents the best leaving group in solvolytic reactions hitherto reported, and has been used in the study of vinyl cations.

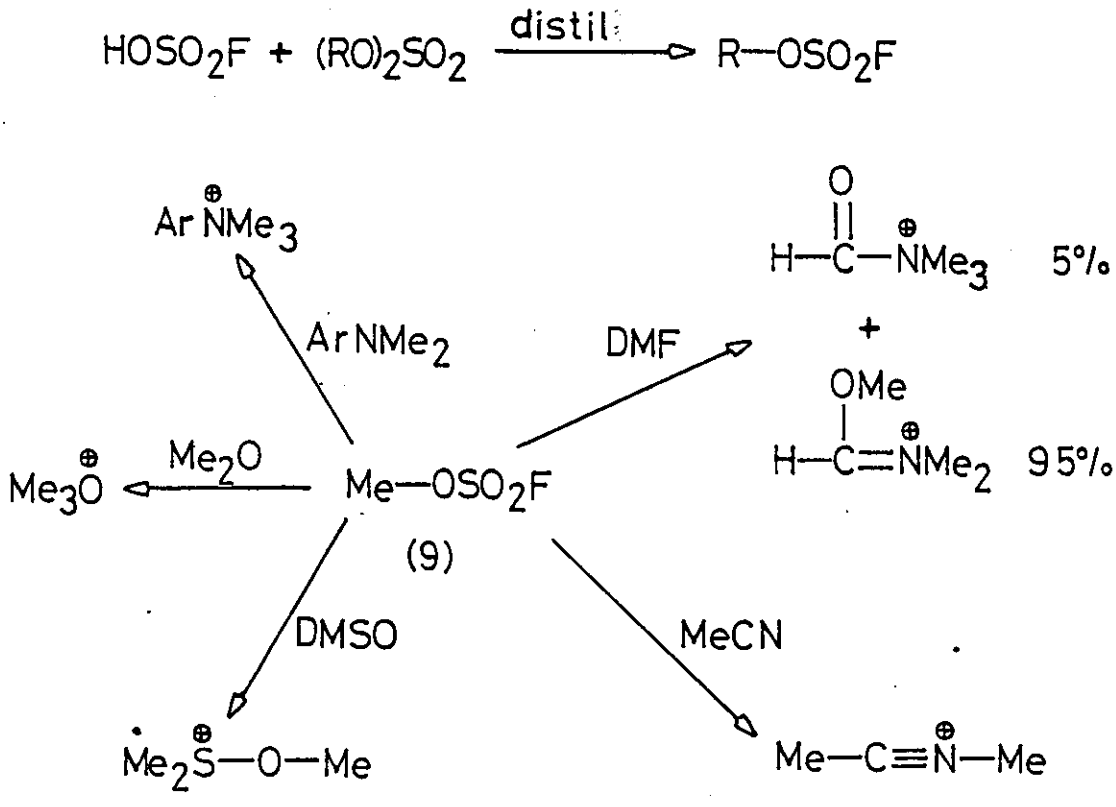
A general route to primary, secondary and tertiary alkyl perchlorates[7] has been developed which avoids the possibility of alkyl rearrangement through the intermediacy of carbenium ions. Preparation

involves nucleophilic attack by an alcohol on chlorine in dichlorine heptoxide, and the resulting alkyl perchlorate solutions (8) can be used directly. Some examples of synthetic utility are outlined below, with the formation of alkyl bromides, dialkyl ethers and aldehydes in high yields.



Scheme 1. Reactions of Alkyl Perchlorates

Fluorosulphonic acid is one of the strongest acids known, with the result that methyl and ethyl fluorosulphonates[8] have been found to be excellent alkylating agents. They are comparable in reactivity to alkyl perchlorates, triflates, trialkyloxonium ions, and alkyl halide-Lewis acid and alkyl halide-silver salt combinations, but offer advantages of easy preparation and safe handling. They are capable of alkylating a variety of n-donor bases, as illustrated in Scheme 2 by reactions of methyl fluorosulphonate (9) (see overleaf).



Scheme 2. Reactions of Methyl Fluorosulphonate

The relative leaving group ability of the systems thus far described may now be summarised as follows:

$-OSO_2F$		$-OBs$	
$-OClO_3$	> $-OSO_2CH_2CF_3$	> $-OTs$	> -X
$-OSO_2C_4F_9$ (-ONf)	(-OTr)	$-OMs$	
$-OSO_2CF_3$ (-OTf)			

X = halogen

A yet more powerful alkylating system is represented by that of the alkyl carbenium hexafluoroantimonates, which have received extensive study by Olah and colleagues.[9, 10, 11] Much work has been devoted to clarifying the exact nature of complexes formed in Friedel-Crafts alkylation reactions. In the presence of Lewis acid catalysts, alkyl halides can undergo either limiting formation of a donor-acceptor

complex, or carbenium ion formation through heterolytic cleavage of the carbon-halogen bond (10).

$$R{-}F \longrightarrow SbF_5 \rightleftharpoons R^{\oplus}\ SbF_6^{\ominus} \qquad (10)$$

For these possibilities, Friedel-Crafts alkylation can occur either via a displacement reaction of the donor-acceptor complex, or a direct alkylation by the carbenium ion.

It has been shown[9] that secondary and tertiary alkyl halides in SbF_5 solution generally form stable carbenium ion hexafluoroantimonates. Thus, all isomeric propyl, butyl, and pentyl fluorides give the isopropyl-, t-butyl, and t-amylcarbenium salts (11-13) respectively, i.e. complete isomerisation to the thermodynamically most stable carbenium ion occurs.

$$C_3H_7F + SbF_5 \rightleftharpoons CH_3{-}\overset{\oplus}{C}H{-}CH_3\ SbF_6^{\ominus} \qquad (11)$$

$$C_4H_9F + SbF_5 \rightleftharpoons \begin{array}{l} CH_3 \\ | \\ CH_3{-}C^{\oplus} \\ | \\ CH_3 \end{array}\ SbF_6^{\ominus} \qquad (12)$$

$$C_5H_{11}F + SbF_5 \rightleftharpoons \begin{array}{l} CH_3 \\ | \\ CH_3{-}CH_2{-}C^{\oplus} \\ | \\ CH_3 \end{array}\ SbF_6^{\ominus} \qquad (13)$$

Cleavage of the carbon-fluorine bond is promoted by the high Lewis acidity and coordinating ability of SbF_5, such that the ion complexes are sufficiently stable for nuclear magnetic resonance (NMR) studies at 37°C. Spectroscopic observations support the formation of a planar sp^2 hybridised carbon atom possessing substantial positive charge.

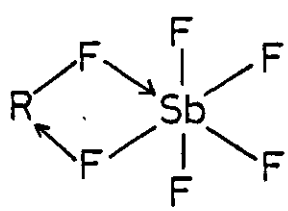
However, no direct observation of the primary methyl and ethyl cations has been made, and when methyl fluoride is dissolved in neat

SbF_5 at room temperature self-condensation occurs with formation of the t-butyl cation (12). The structure of the methyl and ethyl fluoride complexes (14) have been investigated in sulphur dioxide solution at dry-ice temperature.[10, 11]

$$RF + SbF_5 \xrightarrow[-78^\circ]{SO_2} RF \rightarrow SbF_5 \qquad (14)$$

R = Me, Et

Spectral information suggests that both fluorides form similar tightly bound 1:1 donor-acceptor complexes (15) which undergo rapid intramolecular fluorine exchange.



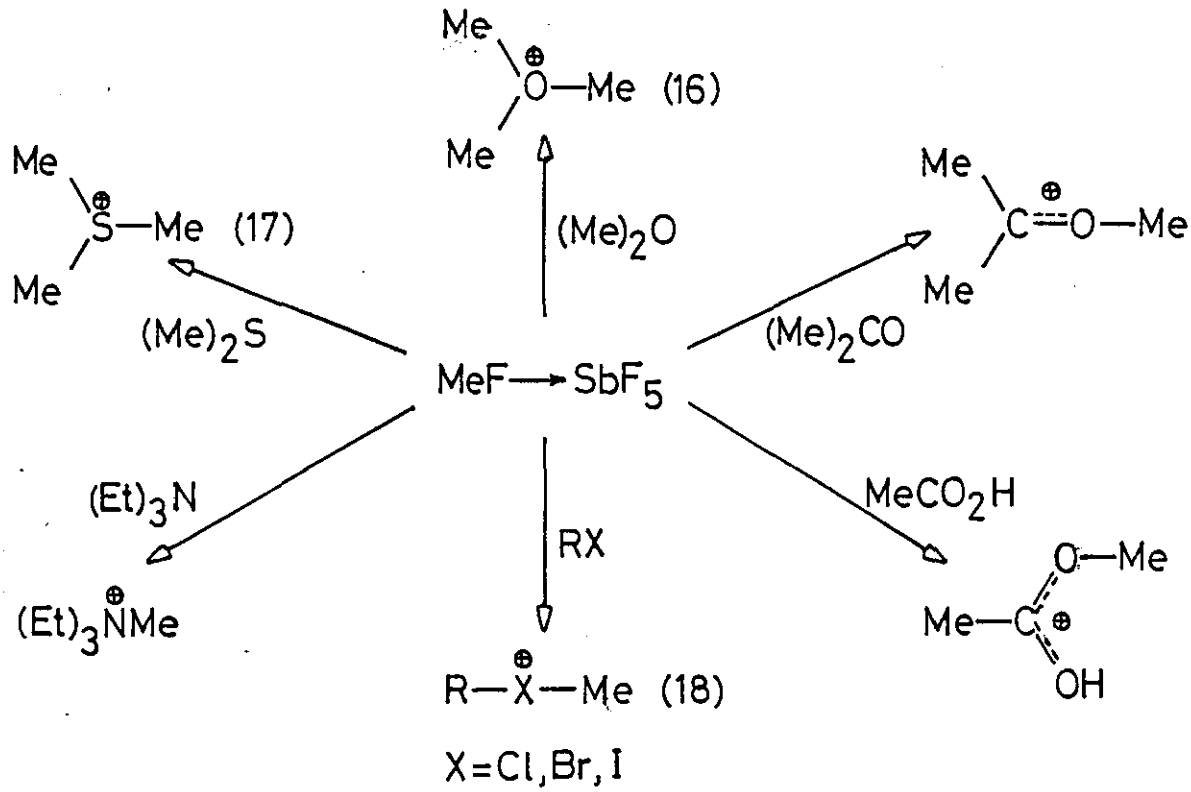
(15)

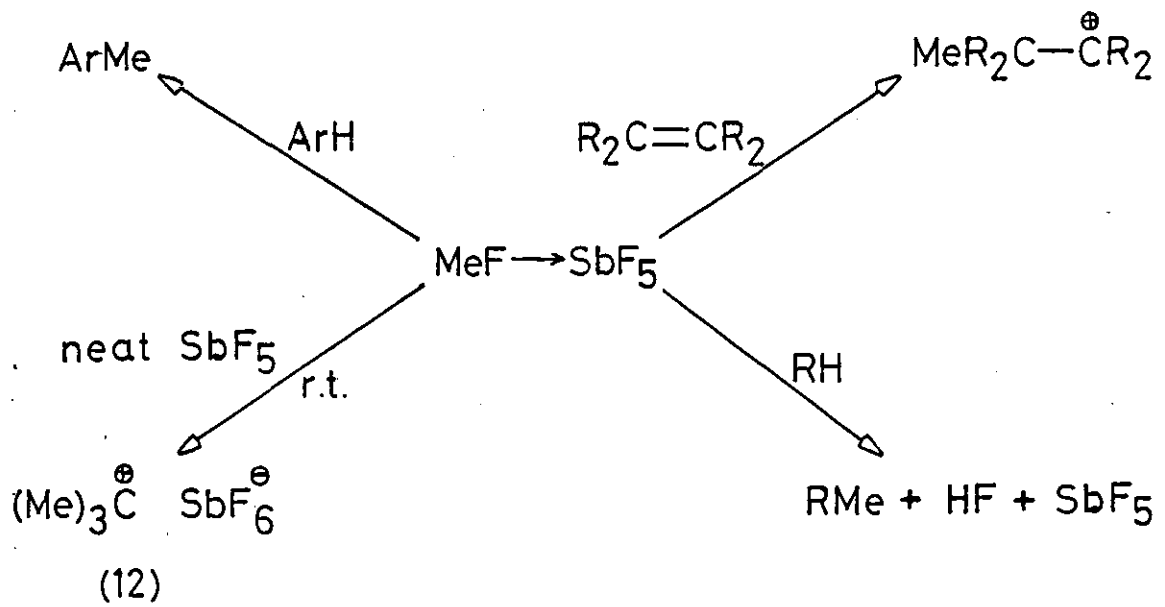
Additional isotopic labelling experiments do give evidence for the intermediacy of an ethyl cation, in that intramolecular scrambling of ^{2}H and ^{13}C is possible only through formation of an intimate ion-pair (10) in low concentration.

The alkylcarbenium hexafluoroantimonates are extremely reactive alkylating agents in carbon, oxygen, sulphur, nitrogen and halogen alkylations, as well as catalysts in olefin polymerisations. Indeed, the $MeF \rightarrow SbF_5$ and $EtF \rightarrow SbF_5$ complexes in SO_2 solution are the most reactive methylating and ethylating agents known. Their reactivity surpasses more conventional Friedel-Crafts systems, trialkyloxonium ions, dialkylhalonium ions, and alkyl fluorosulphonates. They are capable of alkylating n-, π-, and σ- donor bases, and as such have been used to prepare some of these other alkylating agents. Examples are given in

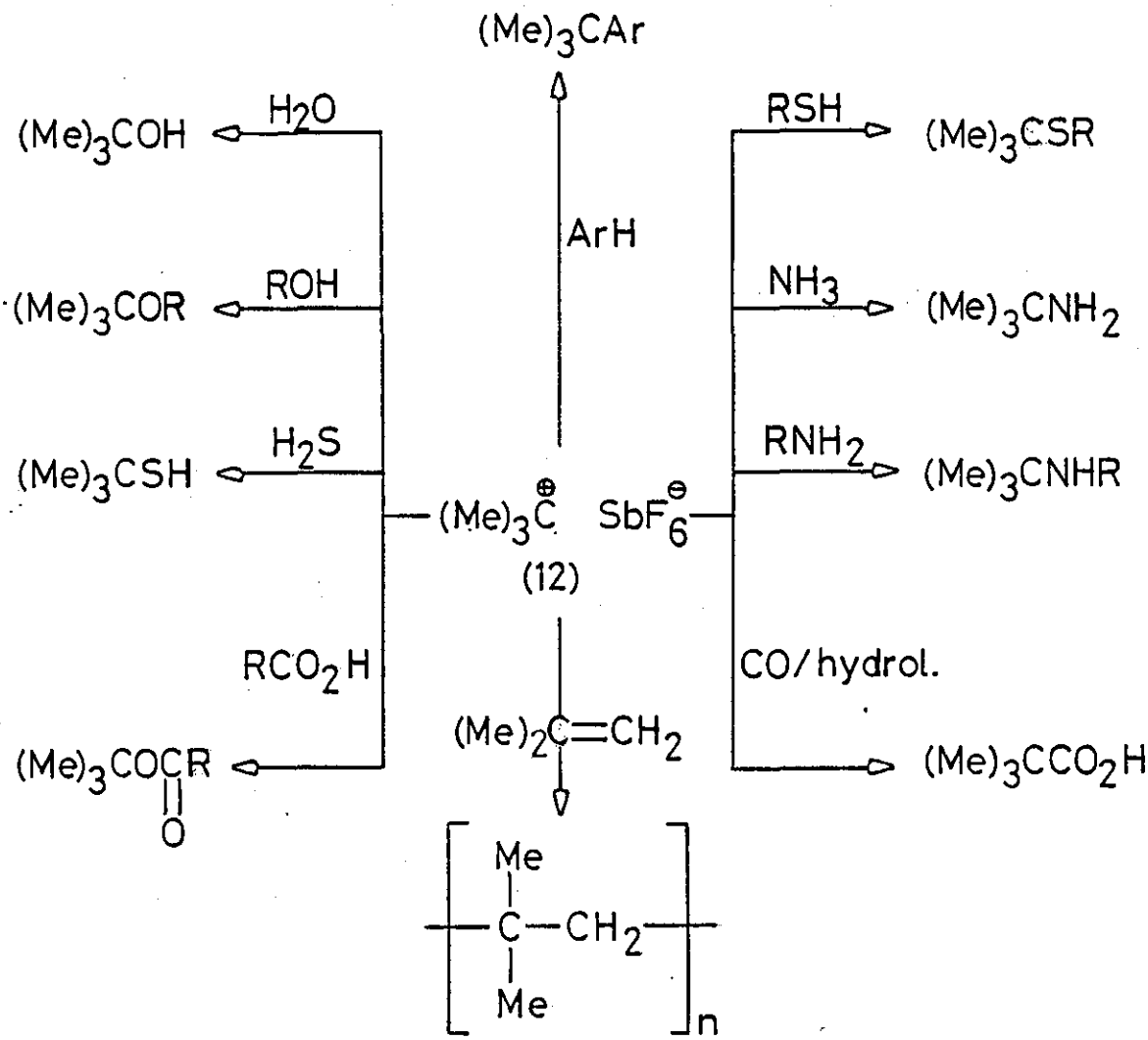
Schemes 3 and 4 for the methyl fluoride complex and t-butylcarbenium ion salts (12) respectively. Reactions are conducted in SO_2 solution at -78° to -60°C, unless otherwise stated. Neutral products are isolated by aqueous work-up at room temperature.

The study of oxonium, sulphonium and halonium salts (16-18) as reactive intermediates in nucleophilic substitution have formed the basis of the work described in this thesis.





Scheme 3. Reactions of the Methyl Fluoride-Antimony Pentafluoride Complex



Scheme 4. Reactions of t-Butylcarbenium Hexafluoroantimonate

1.2 THE SYNTHESIS OF BIARYLS

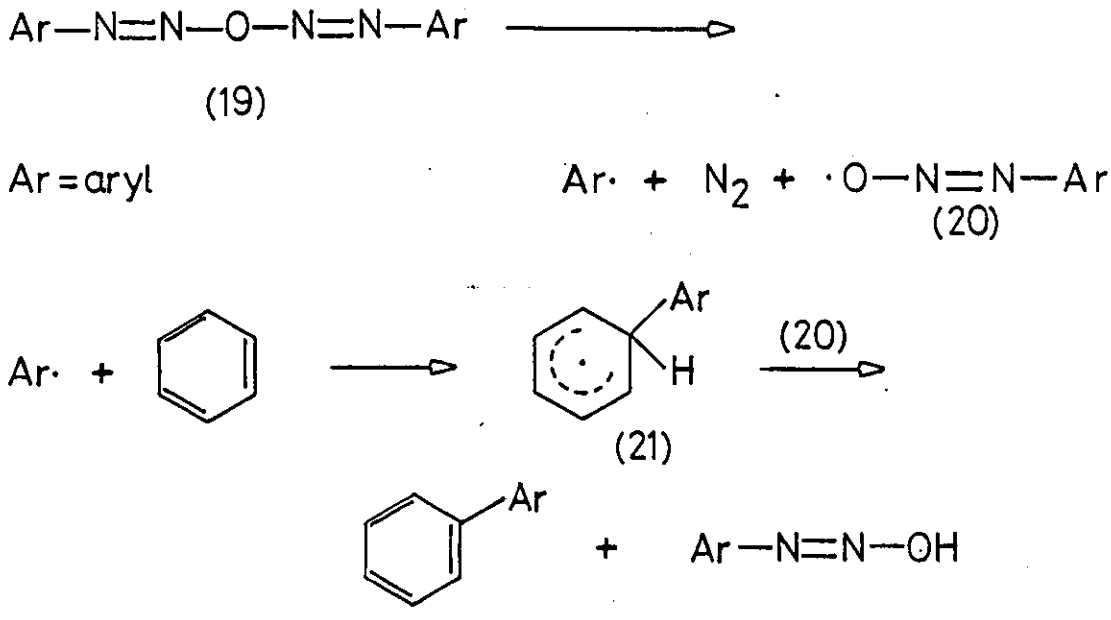
A REVIEW OF CLASSICAL AND NEW TECHNIQUES

An early step in the synthetic routes herein used for the synthesis of onium salts involves the formation of a new C-C single bond between two aromatic centres. Classical methods available for the preparation of such biaryls will be treated first. Included in this category is the Ullmann reaction, which was widely utilised in this study, and which therefore receives an extensive survey. The mechanism of the Ullmann reaction is discussed, particularly with regard to recent developments involving related copper-promoted arylations. A subsequent section outlines further the progress made with aryl organometallics of other metals, and the review ends with some miscellaneous examples of biaryl synthesis from the recent literature. Attention is drawn both to improvements in the efficiency and simplicity offered by new techniques, and to the possibility of forming unsymmetrical as well as symmetrical biaryls.

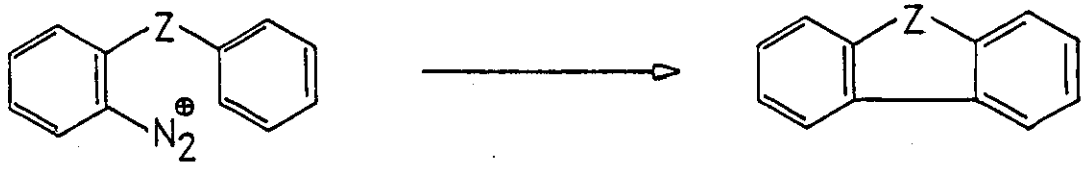
1.2.1 CLASSICAL METHODS

The arylation of aromatic compounds has in many instances proceeded by a free radical substitution mechanism. Thus, in alkaline solution, diazonium ions are converted into covalent azo compounds which cleave to free radicals. Under normal conditions, the species which cleaves in this Gomberg-Bachmann-Hey reaction is the anhydride (19). Biaryl formation is depicted in Scheme 5 (see overleaf).

The stable aryldiazotate radical (20) is capable of abstrating hydrogen, and thereby oxidises efficiently the arylcyclohexadienyl radical (21) to biaryl before side products can form. However, yields can be low due to the heterogeneity of the reaction and the instability of the diazonium solution. The intramolecular Pschorr reaction has been used to effect ring closures.

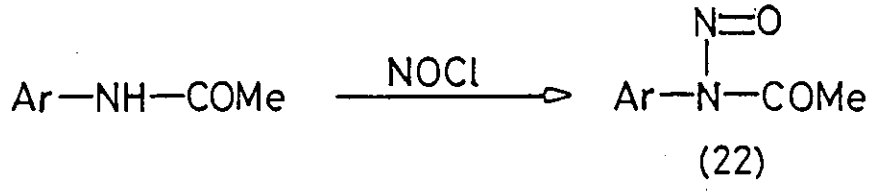


Scheme 5. Gomberg-Bachmann-Hey Arylation



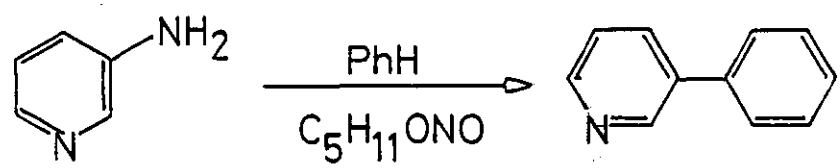
Z = o-C_6H_4, CH=CH, CH_2, CH_2CH_2, NH, C=O

Other compounds containing nitrogen-nitrogen bonds have found use as precursors of aryl radicals, e.g. nitrosation of anilides produces acylarylnitrosamines (22) which undergo initial heterolytic decomposition to the free-radical source (19).[12]



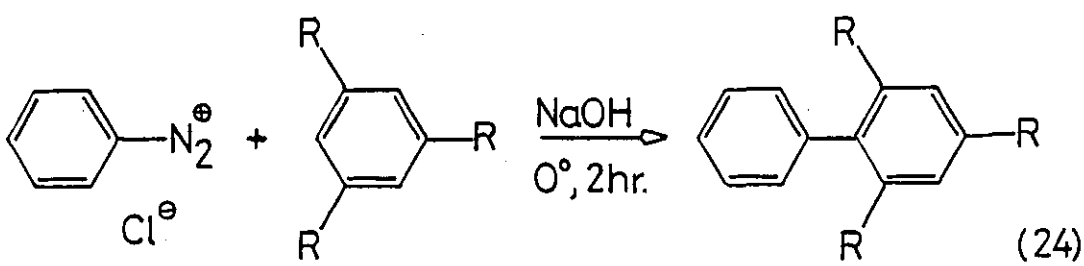
Cadogan[13] has devised an alternative method for the preparation of biaryls from primary aromatic amines. The use of alkyl nitrites in

aprotic diazotisation from protonated amines is well known. However, in the absence of acid, good yields of biaryl are afforded from the reaction of primary aromatic amines with pentyl nitrite in excess benzene. The method is particularly satisfactory for those amines, e.g. 3-aminopyridine (23), which give poor yields of corresponding biaryl in the Gomberg-Bachmann-Hey reaction.



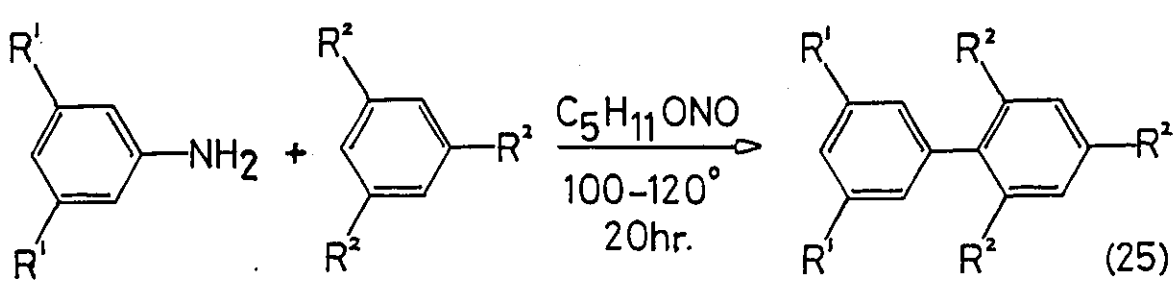
(23) 52%

Both the Gomberg-Bachmann-Hey and the Cadogan techniques have been used very recently in a study of sterically hindered polyalkylated biaryls and the effect of bulky substituents on biaryl conformation.[14] The reactions outlined below result, not surprisingly, in very low yields of the desired unsymmetrical compounds (24, 25).



(24)

R = Me(15%), Et(2%), i-Pr(0·3%)

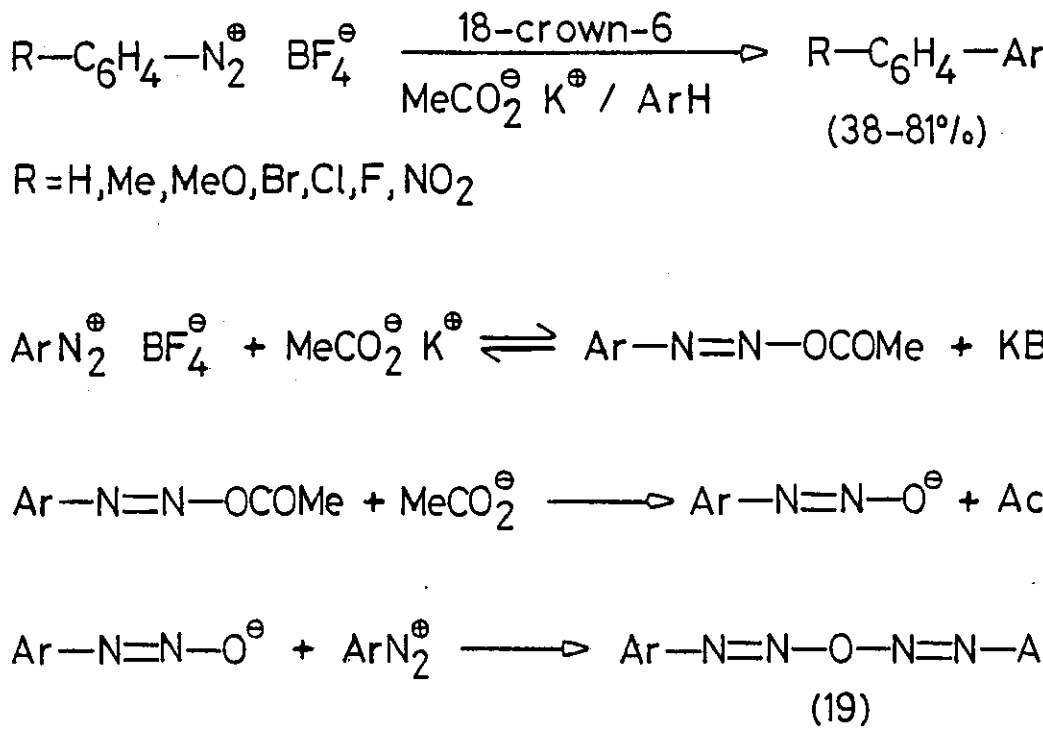


(25)

a. R' = H, R² = $(Me)_3CCH_2$ (2%)

b. R' = t-Bu, R² = i-Pr (1·4%)

A variation of the Gomberg-Bachmann-Hey reaction involving phase-transfer catalysis[15] has lately given much improved yields of mixed biaryls according to Scheme 6. The technique has the advantage that stable aryldiazonium tetrafluoroborates or hexafluorophosphates bearing either electron-releasing or electron-attracting substituents can be used as solid reagents.

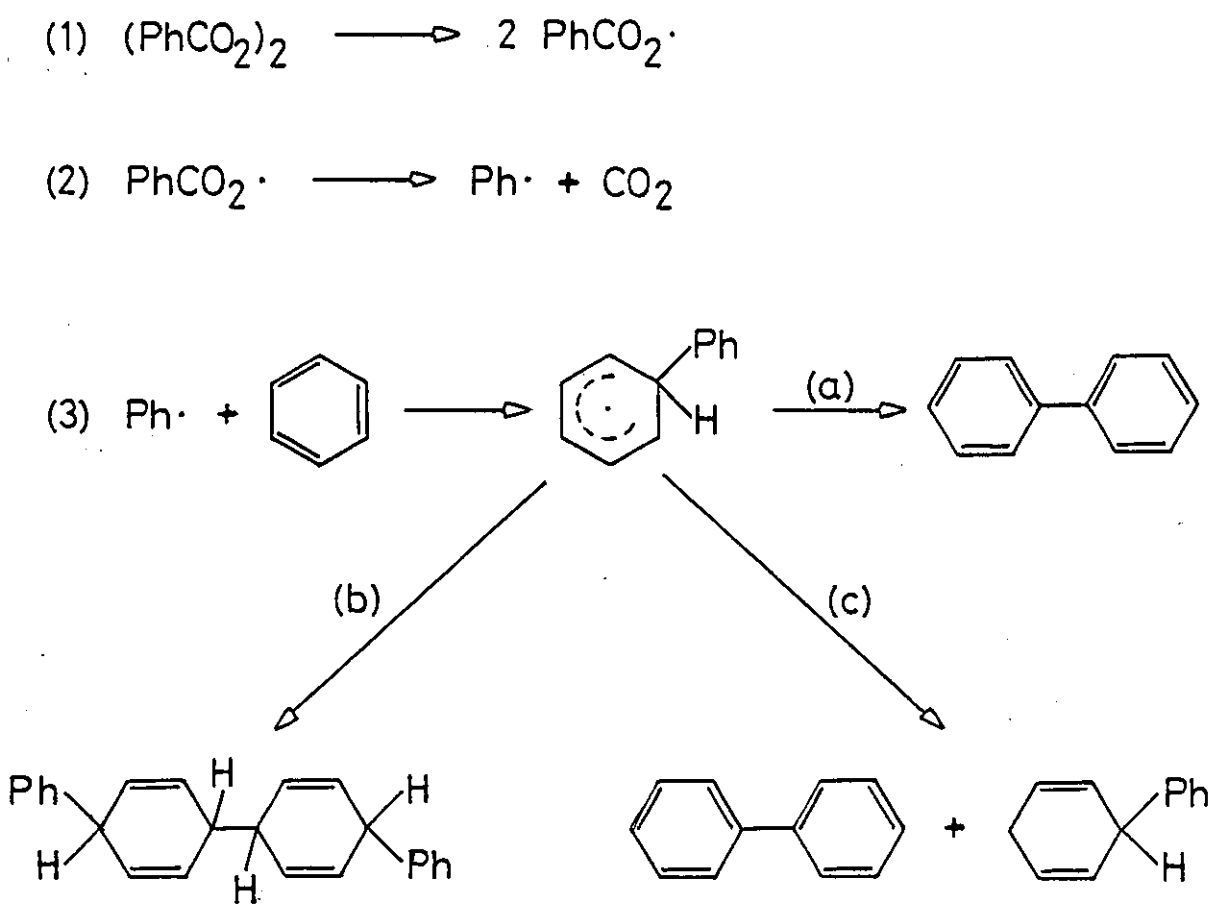


Scheme 6. Phase-Transfer Catalysed Gomberg-Bachmann-Hey Arylation

Potassium acetate is phase-transfered into the non-polar solution by the presence of 18-crown-6 and reacts with the aryldiazonium ion to produce the diazoanhydride (19). Subsequent decomposition (Scheme 5) at or below room temperature leads to coupled products between aryl radicals and the solvent, e.g. benzene, mesitylene, thiophen, in 1-2 hours.

The generation of phenyl radicals by thermal decomposition of benzoyl peroxides, and their reactions in aromatic solvents, have been well-characterised. The method is limited by the fact that some precursor carboxylic acids are unavailable. In addition products of dimerisation (path b) and disproportionation (path c) of the intermediate phenylcyclo-

hexadienyl radical (21, Ar = Ph) can arise in favour of hydrogen abstraction (path a) to the required biaryl. See Scheme 7.



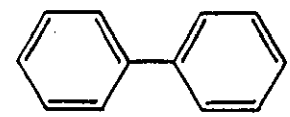
Scheme 7. Thermal Decomposition of Benzoyl Peroxide in Benzene

It has been found[16] that enhanced yields of biaryl can be obtained in the presence of small quantities of nitrobenzene. This 'nitro-group effect' can be explained by formation of a stable diphenyl nitroxide radical (26) which acts similarly to the aryldiazotate radical (20). The nitroxide is regenerated by oxidation of diphenylhydroxylamine by benzoyl peroxide as illustrated in Scheme 8. Steps (6) and (7) propagate a radical chain with steps (2) and (3) above (see overleaf).

Another free-radical arylation method consists of the photolysis of iodoaromatic compounds in dilute benzene solutions.[17] Yields are generally higher than corresponding radical reactions involving diazonium ions and peroxides. A phenyl group occupies the position vacated by

(4) $PhNO_2 \longrightarrow PhNO$

(5) $PhNO \longrightarrow Ph_2NO\cdot$
(26)

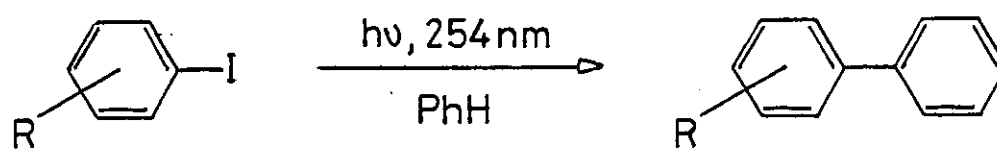
(6) $Ph_2NO\cdot$ +   + Ph_2NOH

(7) $Ph_2NOH + (PhCO_2)_2 \longrightarrow$

$Ph_2NO\cdot + PhCO_2\cdot + PhCO_2H$

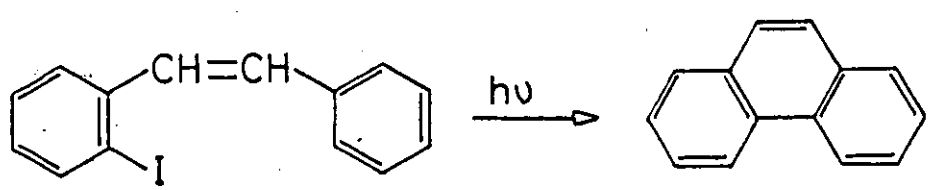
Scheme 8. The Nitro-Group Effect

iodine, and no other rearranged products have been detected.

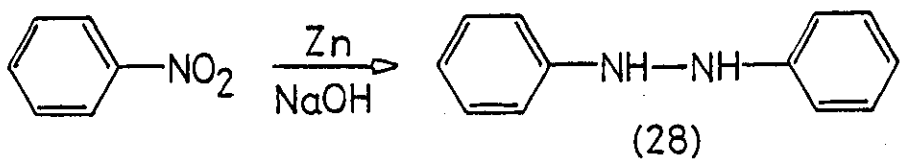


$R = H, Me, Ph, CO_2H, OH, NH_2$

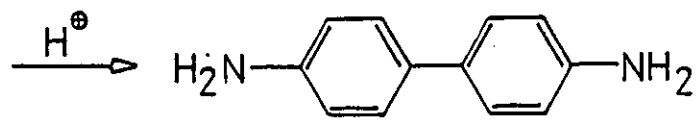
The procedure has been used analogously to the Pschorr reaction to synthesise pharmaceutically interesting phenanthrene derivatives (27) by photolysis of appropriately substituted 2-iodostilbenes.[18]

 (27)

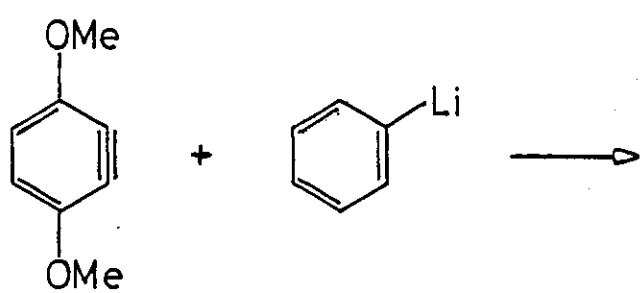
Examples by which an aryl-aryl bond may be formed by an ionic mechanism are represented by the benzidine rearrangement and the addition of an organometallic reagent to an aryne. The former reaction is general for N,N'-diarylhydrazines (28), and provides a route to symmetrical 4,4'-diaminobiphenyls from the corresponding nitrobenzenes.



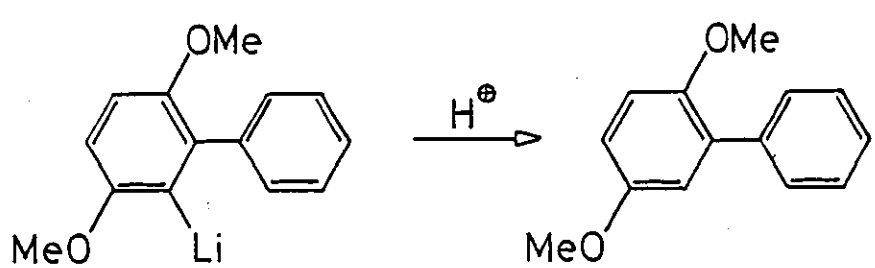
(28)



The second reaction type[19] is characterised by nucleophilic addition to the aryne e.g. (29), followed by quenching of the intermediate with an electrophile.

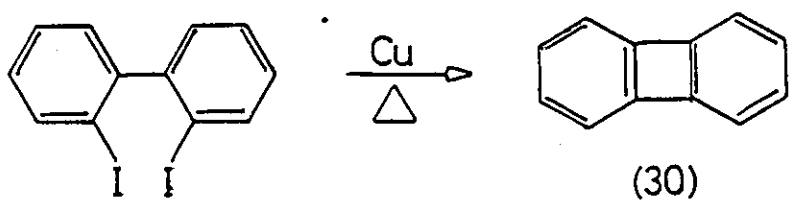


(29)

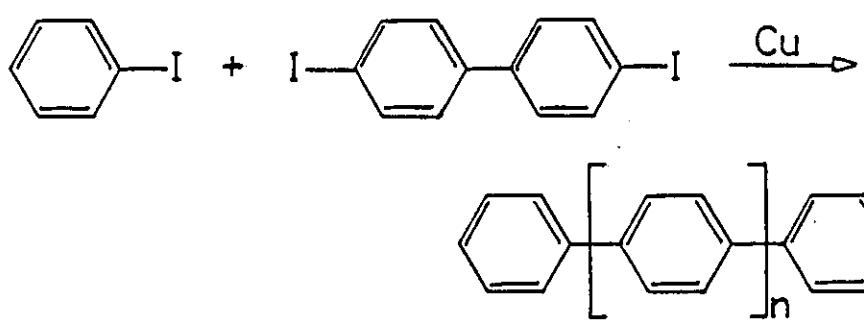


1.2.2 THE ULLMANN REACTION AND RELATED COPPER-PROMOTED ARYLATIONS

The Ullmann reaction involves the condensation of two molecules of aryl halide in the presence of finely divided copper at elevated temperature. It was first reported in 1901.[20] A new aryl-aryl bond is formed, with elimination of copper halide. Extensive reviews have been given by Fanta[21] and by Goshaev, Otroshchenko and Sadykov.[22] In addition to the synthesis of symmetrical and unsymmetrical biaryls, the reaction has been used to effect ring closures at an aryl-aryl bond, e.g. the synthesis of biphenylene (30), and to prepare linear polyphenylenes (31).



(30)

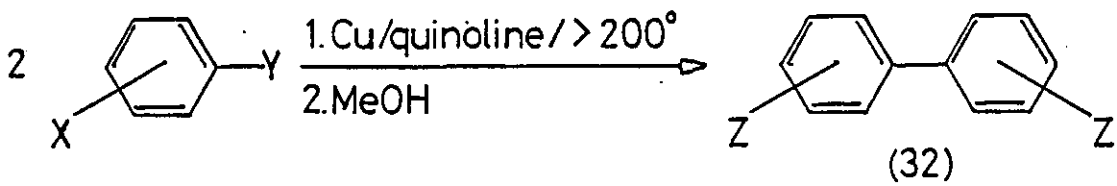


(31)

Reactivity of the aryl halides is in the order Cl < Br < I. Aromatic fluoro-compounds do not react. The halogen is markedly activated by the presence of ortho electron-withdrawing groups, e.g. NO_2, COMe. A para phenyl group has a highly activating effect, whilst in pyridine the nitrogen atom activates the halogen in the 2-position, as evidenced by the formation of 2,2'-bipyridyl in 87% yield. Bulky substituents such as nitro, halogen, alkoxy, and alkyl do not hinder the coupling reaction, but steric hindrance does become appreciable when phenyl and naphthyl groups are introduced into the 2,6-positions.

When the aromatic ring contains groups which provide alternative pathways for reaction, e.g. NH_2, OH, CO_2H, the desired coupling is inhibited. However, the influence of amino, hydroxyl, and carboxyl groups can be weakened by conversion to their acyl, ether and ester protected forms respectively. More recently, King and Walton[23] have introduced the trimethylsilyl group to protect acidic hydroxyl and amino groups in the synthesis of symmetrical biaryls (32).

Products are obtained by <u>in situ</u> desilylation, and yields are moderate to good (20-70%).



(32)

X = Br, I

Y = $OSi(Me)_3$, $CH_2OSi(Me)_3$, $CO_2Si(Me)_3$, $N[Si(Me)_3]_2$

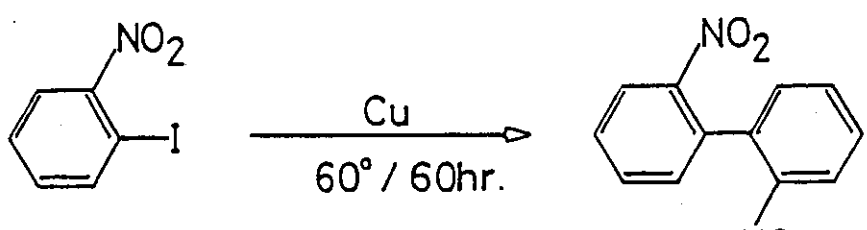
Z = OH, CH_2OH, CO_2H, NH_2

Forrest[24] has shown that the formation of unsymmetrical biaryls is dependent on the greater reactivity towards copper of an activated aryl halide (A), which generally must contain at least one electronegative group, e.g. NO_2, COMe, ortho to halogen, and is commonly used in small excess. Successful syntheses rely on the choice of halogen for the reactive (A) and relatively unreactive (B) components. Bromo-compounds, and to a smaller extent chloro-compounds, have been most useful as A components. Aryl iodides are of little use owing to predominant self-condensation. Instead, they have found general application as B components, and should lack ortho electronegative groups for the attainment of highest yields.

A decisive factor in governing the success of the mixed, or cross

Ullmann reaction is temperature. Preferential attack by copper on A is essential, so optimum conditions call for a temperature immediately below that at which B is independently attacked. Reaction of the least reactive component with copper can rarely be suppressed entirely, and operation at the lowest practicable temperature for reaction of A with copper furnishes best results. Most reactions are performed within the range 150-280°C, but temperatures in excess of 200°C can lead to reduction of nitro groups,[25] and raising of the temperature to complete a reaction can lead to unwanted self-condensation of A.

Copper powder is usually added gradually in three-fold excess to the neat aryl halide(s) at a specified temperature. It has been questioned whether the quality of the copper can have any effect. Frequently, a commercial copper bronze is used, but a large excess (x 9) of the metal, activated according to the method of Kleiderer and Adams,[26] gives 2,2'-dinitrobiphenyl (33) from o-iodonitrobenzene in almost quantitative yield[27] under very mild conditions.



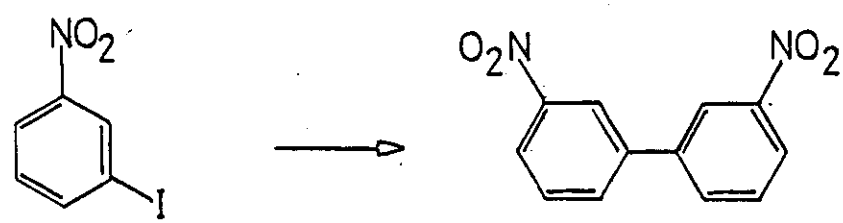
(33)

The fine demand on temperature control, particularly for unsymmetrical couplings, the elevated temperature range itself, and the inconsistencies associated with the copper powder, all contribute to making reproducibility difficult. Reactions are usually performed in air, although an inert nitrogen atmosphere has been claimed to promote acceptable yields by preventing oxidation of the copper.

The Ullmann reaction may be carried out in solution, where side reactions of labile aryl halides are to some extent suppressed.

Most suitable solvents are the high boiling hydrocarbons, e.g. biphenyl, p-cymene, and naphthalene. Alternatively, sand[25] may be employed as an inert diluent and heat exchanger. Nitrobenzene has often been used, but now cannot be regarded as inert.[24] Most extensive developments have been made in reluxing dimethylformamide (DMF), and some applications are now discussed.

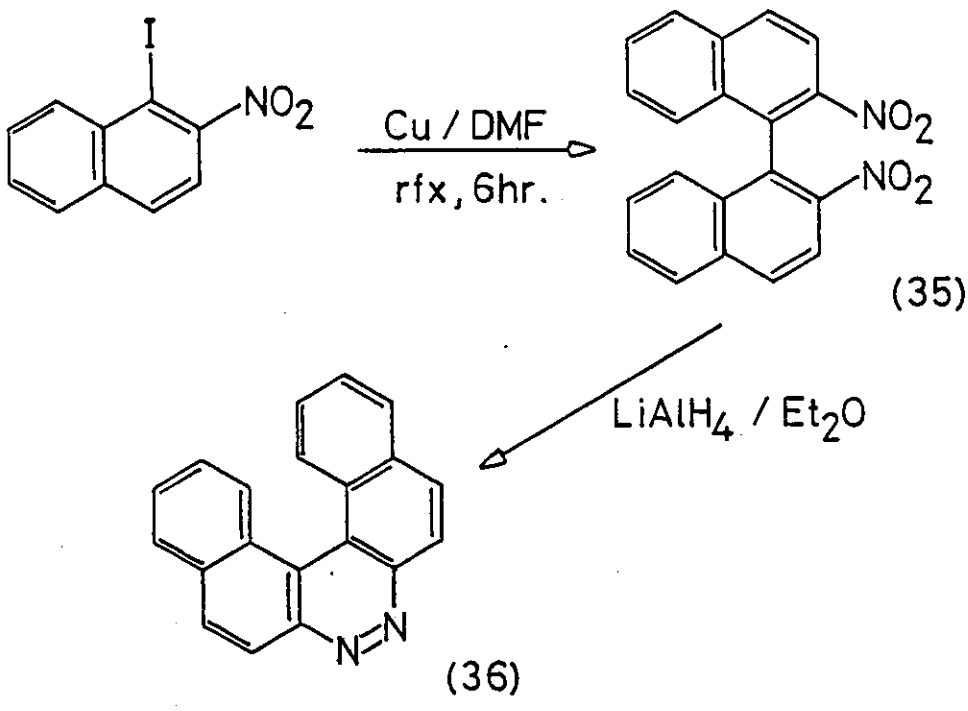
Kornblum and Kendall[28] have shown that DMF is a good solvent for the Ullmann reaction, in spite of its low boiling point (153°C). It has the advantage of being water soluble, and hence easily removed from the reaction product, and yields are significantly higher than those obtained from undiluted reactions at higher temperatures. For example, o-chloronitrobenzene gives an 80% yield of 2,2'-dinitrobiphenyl (30), cf. 52-61%.[25] Moreover, relatively unreactive aryl halides such as m-iodonitrobenzene (34) give high yields of biaryls in DMF.[29]



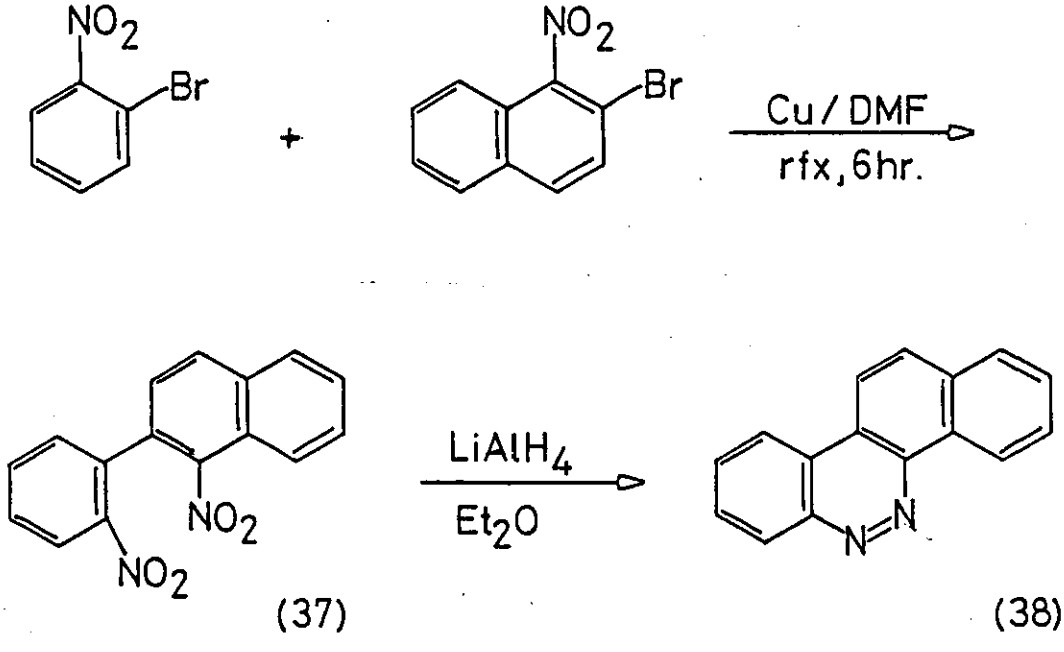
(34) 82%

The use of DMF has been extended to the preparation of complex dinitrobiaryls in studies of symmetrical (36)[30] and unsymmetrical (38)[31, 32] polycyclic cinnolines. Braithwaite and Holt[30] have raised the yields of dinitrobinaphthyls (35) to 80%, apparently owing to the solvent action of DMF, in which the copper halide, reactant, and product dissolve, leaving the copper surface uncoated (see overleaf).

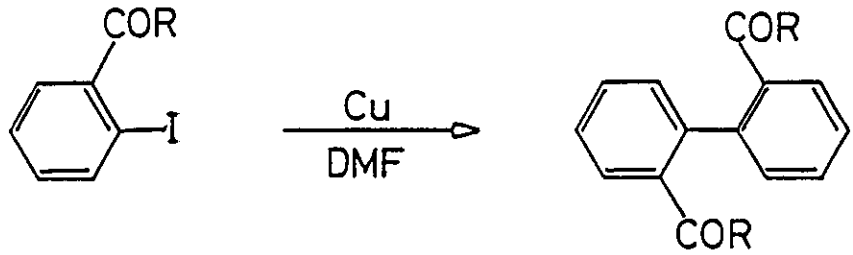
The capacity of DMF to promote dehalogenation and halogen exchange reactions has limited its application to mixed Ullmann reactions. Yields are generally less than 30%, and the three possible products are often difficult to separate.[32] However, Corbett and Holt[31]



have doubled the yield of 1-nitro-2-(o-nitrophenyl)naphthalene (37) to 30%, and subsequent reduction affords naphtho[1,2-c]cinnoline (38).



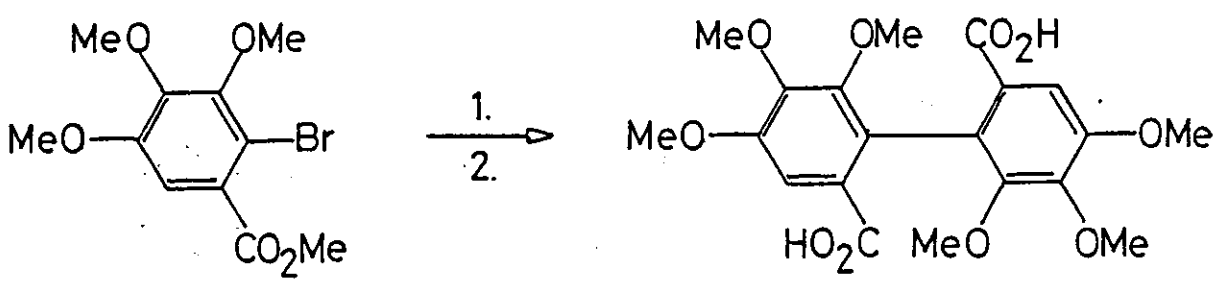
DMF appears to be particularly effective for the preparation of biaryls (39) containing free aldehyde or ketone groups.[33]



R = H, Me, Et, Ph (39)

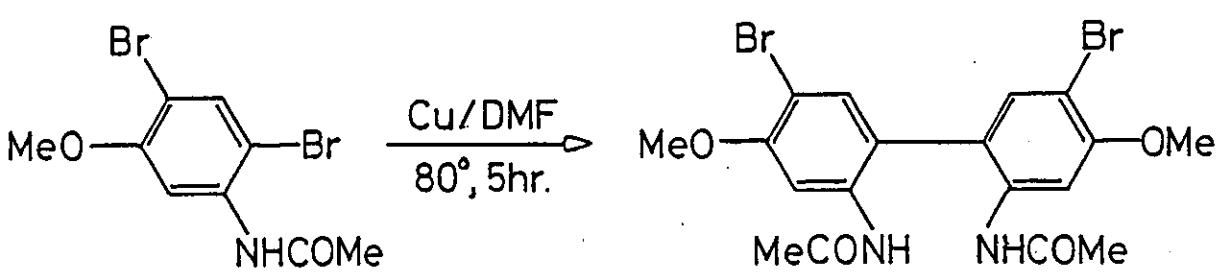
59-75%

Two further syntheses illustrate the use to which DMF can be put in isolating highly substituted biaryls which possess protected functional groups. 4,4',5,5',6,6'-Hexamethoxybiphenic acid (40) has been prepared in 40% yield by hydrolysis of the corresponding dimethyl ester,[34] and the 2,2'-diacetamidobiphenyl (41) has been obtained in excellent yield under mild conditions.[35]



(40)

1. Cu / DMF / rfx, 8hr. 2. KOH / MeOH / rfx, 3hr.

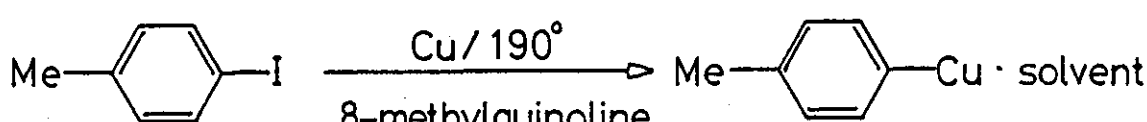


(41) 95%

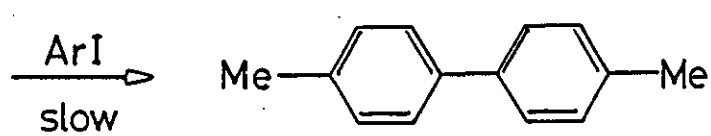
REACTION MECHANISM

The satisfactory preparation of unsymmetrical biaryls free from impurities derived from the less reactive (B) component suggests that reaction occurs without initial attack of copper on B. Forrest[24] argues that this is irreconcilable with a free-radical mechanism. Fanta[21] supports this view by suggesting initial nucleophilic attack by copper on the carbon-halogen bond to form an arylcopper complex on the surface of the metal. This is followed by reaction of the complex with a second molecule of aryl halide to form the biaryl and cuprous halide.

Substantial evidence now exists for an ionic mechanism involving organocopper intermediates. Thus, the reaction of p-iodotoluene with copper in 8-methylquinoline has been interpreted by Lewin and Cohen[36] as involving a solvent-stabilised tolylcopper complex (42). This undergoes a relatively slow displacement of halogen from additional p-iodotoluene to give 4,4'-dimethylbiphenyl (43).



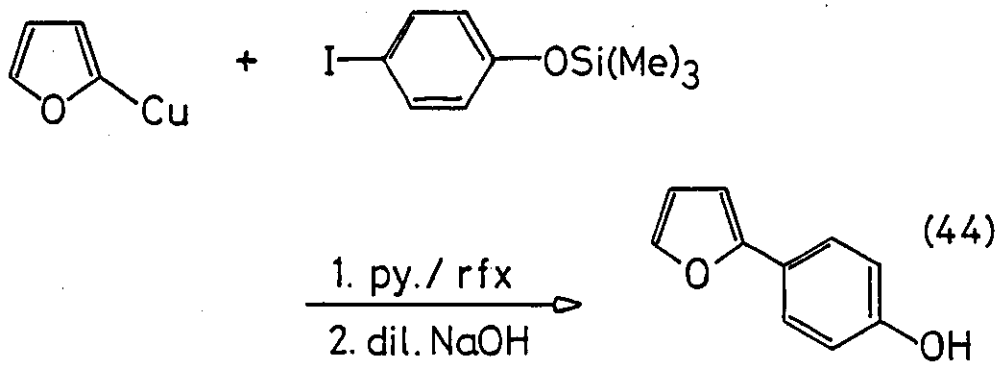
(42)



(43)

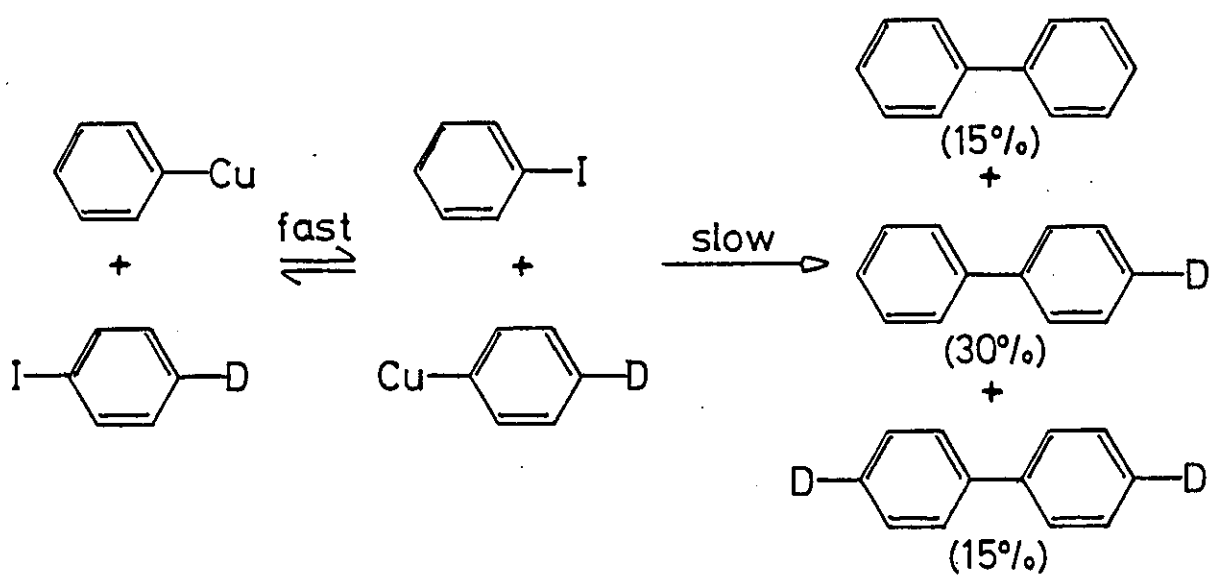
This observation suggested that formation of an arylcopper compound prior to Ullmann reaction would provide an effective route to unsymmetrical biaryls. Treatment of the arylcopper compound with a different aryl halide then avoids the formation of undesired symmetrical products. Since proton capture by authentic organocopper

reagents can impair yields, acidic functional groups in the aryl halide are suitably protected,[33] as in the synthesis of p-(2-furyl)phenol (44).



(44)

However, rapid copper-halogen exchange has been shown to disrupt the nature of some coupled products. As a result, the reaction of phenylcopper and p-deuteroiodobenzene in pyridine at 50° gives a statistical yield of products due to a copper-iodine interconversion which is fast compared to the coupling reaction.

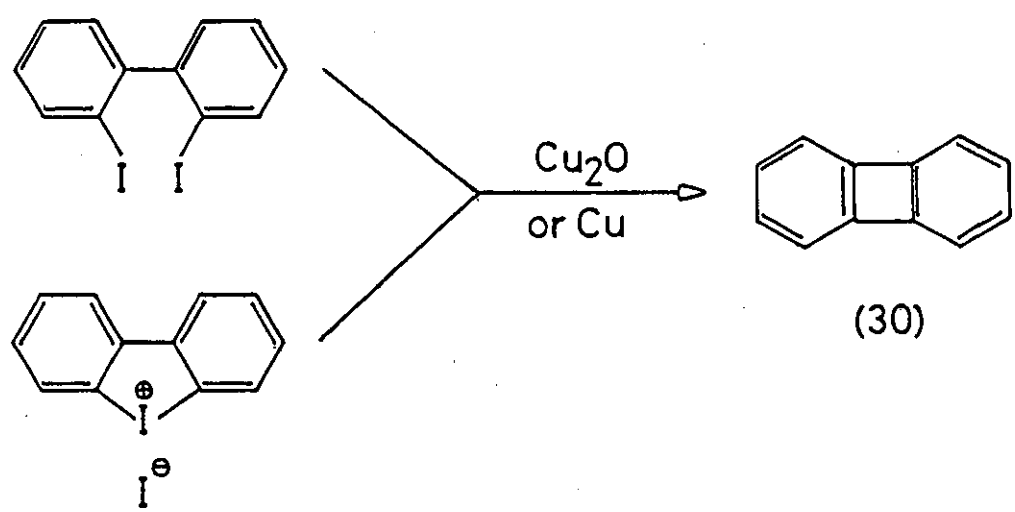


Further doubt on the viability of a radical mechanism has been cast by the fact that nitrobiphenyls are not isolated from reactions of iodobenzene with copper in nitrobenzene. Also, 2,6-dinitrobiphenyls are the major products formed by the condensation of aryl iodides with meta di- and tri-nitro compounds. Known free radical sources give different product distribution, so that the phenylation of 1,3-dinitrobenzene

by phenyl radicals derived from benzoyl peroxide affords a 9:1 mixture of 2,4- and 2,6-dinitrobiphenyl.[24] These results are consistent with formation of arylcopper intermediates, the preparation and reactions of which have been reviewed by Normant.[38]

Although copper metal is generally specificed in the Ullmann synthesis, some reactions of aryl halides with copper(I) species have been studied. Thus, 2,2'-dinitrobiphenyl (33) has been obtained in 70% yield from o-bromonitrobenzene using copper(I) oxide in boiling pyridine,[39] but the method offers no practical advantage over the conventional procedure.

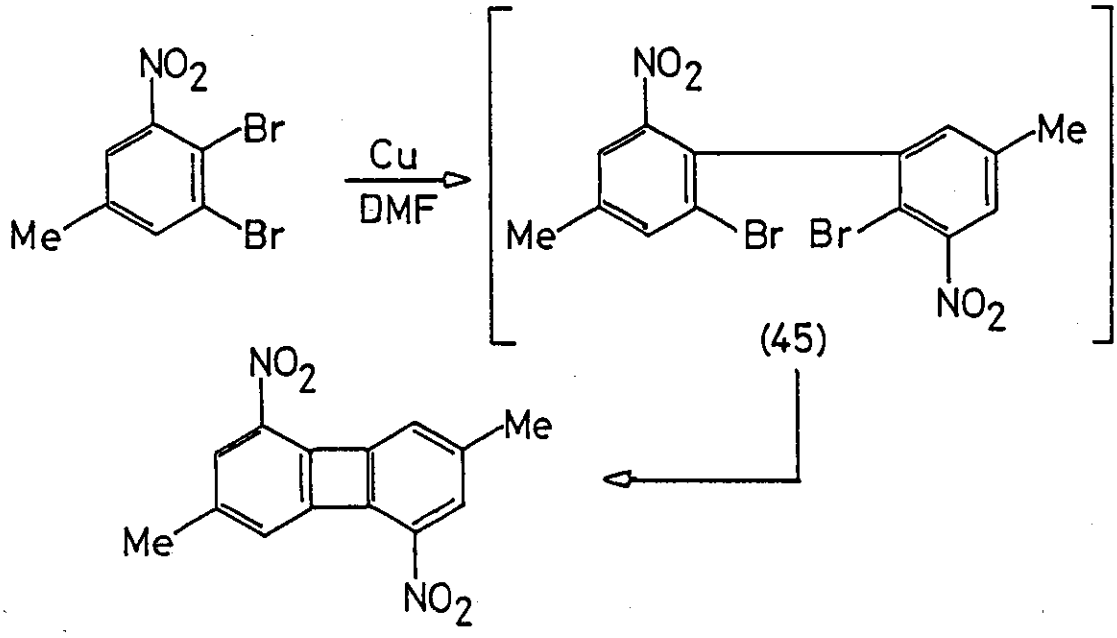
When Lothrop succeeded in synthesising biphenylene (30) from 2,2'-diiodobiphenyl or 2,2'-biphenyleneiodonium iodide,[40] it was suggested that copper(I) oxide and not metallic copper was required, and that the procedure differed distinctly in scope and mechanism from the Ullmann reaction. However, Salfeld and Baume[41] established that copper can indeed be used.



(30)

Biphenylenes may alternatively be prepared by reaction of 2,3-dihalonitrobenzenes and copper bronze in DMF. Arynes have been proposed[42] as intermediates, but the observed "head-to-tail" product may also be envisaged as arising from an activated 2,2'-dihalobiphenyl (45)[22]. This latter view is supported by the fact that no "head-to-head"

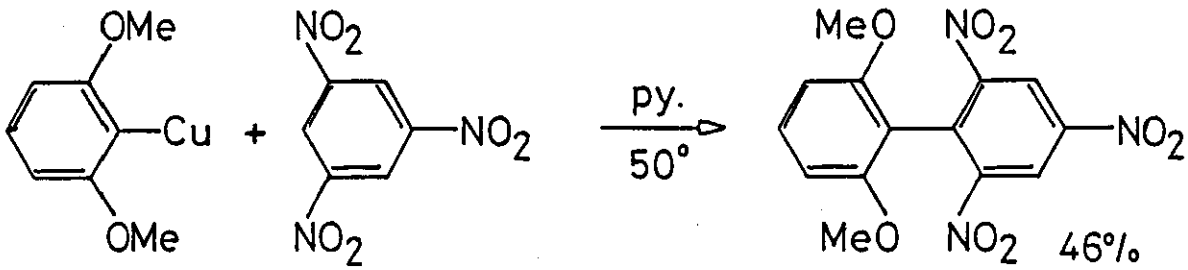
isomers were detected, and neither were they obtained from 2,2'-dihalo-6,6'-dinitrobiphenyls, owing to the presence of both nitro groups in a meta position relative to halogen.

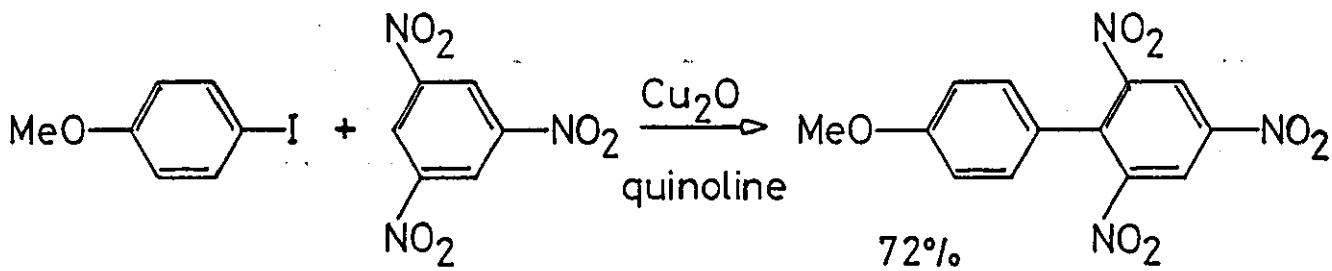


In other instances, the inclusion of copper (I) species in reaction mixtures containing copper metal has proven beneficial. For example, addition of copper(I) iodide to a mixture of o-bromonitrobenzene and copper in pyridine at 80° raises the yield of 2,2'-dinitrobiphenyl (33) from 3% to 12%. This has been explained in terms of an exchange of iodine for bromine in the substrate prior to condensation.[43] Such halogen-halogen exchange may generally permit bromoarenes to be used at temperatures where the reaction rate is otherwise too slow.

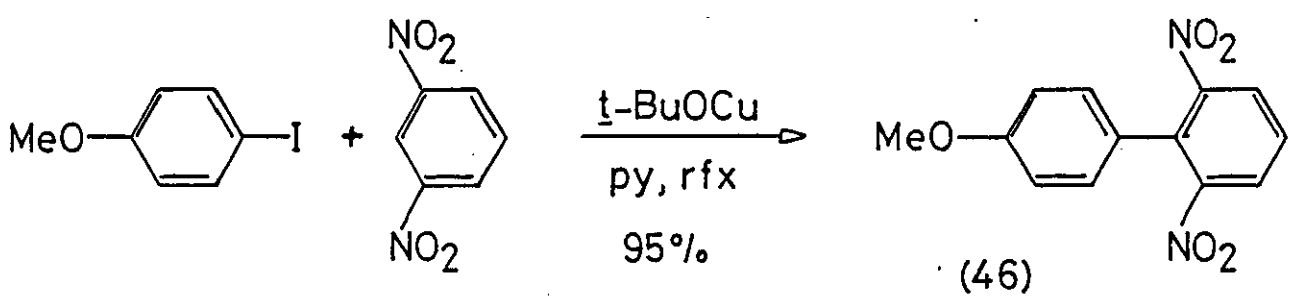
The reaction of aryl halides with polynitrobenzenes is representative of a further group of copper(I)- promoted arylation reactions closely related to the Ullmann synthesis. Investigations by Björklund, Nilsson and Wennerström[44] reveal that these reactions may have synthetic utility for the preparation of unsymmetrical biaryls less readily produced by conventional techniques. The use of coordinating solvents in the following examples aids in stabilising

the arylcopper intermediate.

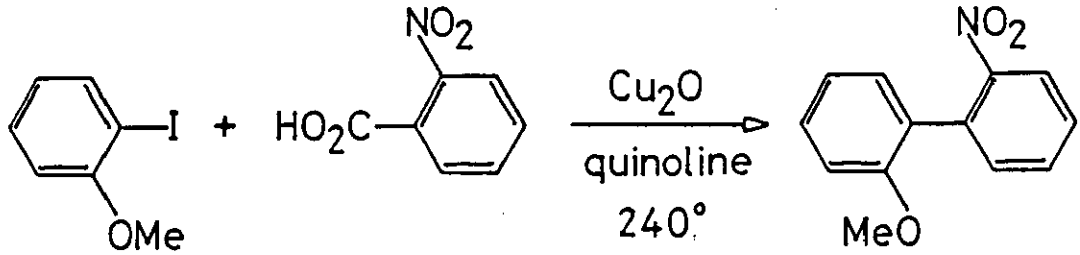




It has been shown more recently that copper(I) butoxide with pyridine mediates the reaction of aryl iodides with 1,3-dinitrobenzene to give 2,6-dinitrobiphenyls (45) in mild conditions and in excellent yields.[45] The method is more convenient than that using copper(I) oxide in quinoline, and is advantageous over conventional Ullmann coupling of aryl iodides with 2,6-dinitrochlorobenzenes.

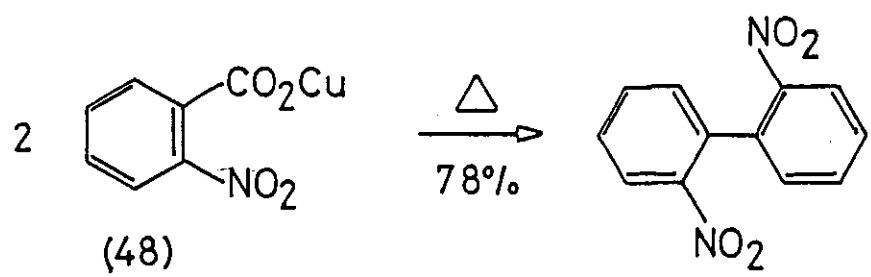


The utility of arylation by decarboxylative coupling is illustrated by the reaction of o-nitrobenzoic acid and o-iodoanisole with copper(I) oxide to give a 50% yield of 2-methoxy-2'-nitrobiphenyl (47).[41]

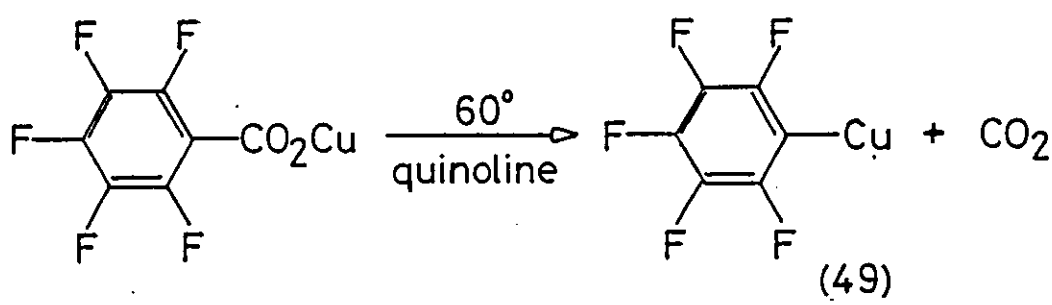


(47)

In certain instances, copper(I) benzoates (48) undergo coupling,[47] and a stable intermediate (49) has been isolated and identified.[48]



(48) (33)



(49)

Generally, the intermediate is trapped by an aryl halide,[45] since temperatures necessary for decarboxylation would otherwise rapidly destroy the arylcopper compound with formation of by-products.

The more commonly encountered organometallic derivatives of the main group metals are not suitable for effecting formation of carbon-carbon σ bonds by nucleophilic displacement at a carbon-halogen bond. Although organolithium reagents are strongly basic, they appear to be

only weakly nucleophilic toward carbon, and give mixtures in reaction with alkyl and aryl halides. Organomagnesium compounds are relatively unreactive, but reaction with activated halides again leads to complex mixtures. In contrast, it has been recognised that organocopper species play an important role in aryl-aryl bond formation. Examples of couplings of thermally stable arylcopper(I) reagents with aryl halides have been discussed above. However, the usefulness of such reactions for the preparation of unsymmetrical biaryls is limited, since less stable and uncomplexed reagents usually decompose more rapidly than they react with aryl halides. An improvement has been achieved by formation of 1:1 "ate" complexes (50) of copper(I) halides with organolithium and organomagnesium compounds.[49] This enhances the thermal stability of the carbon-copper(I) bond, and increases the nucleophilicity of the organic moiety bonded to copper.

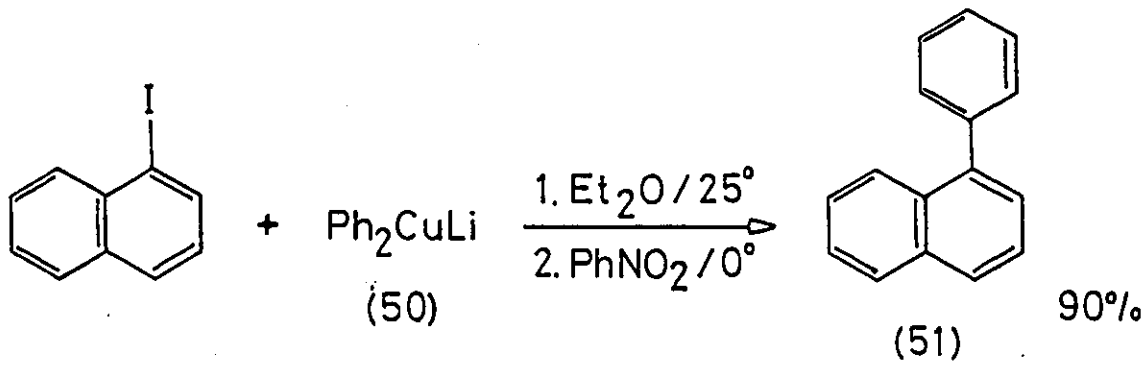
$$PhI + \underline{n}\text{-}BuLi \xrightarrow{PhH/C_6H_{14}} PhLi$$

$$2\ PhLi + CuBr \xrightarrow[0^\circ]{Et_2O} Ph_2CuLi + LiBr$$

(50)

Reaction of lithium diphenylcuprate (50) with aryl halides can produce excellent yields of unsymmetrical biaryl, e.g. 1-phenylnaphthalene (51). An initial metal-halogen exchange precedes the slower coupling reaction. Oxidation of the resulting mixture of organometallic species with nitrobenzene prior to hydrolysis gives enhanced yields of coupled product (see overleaf).

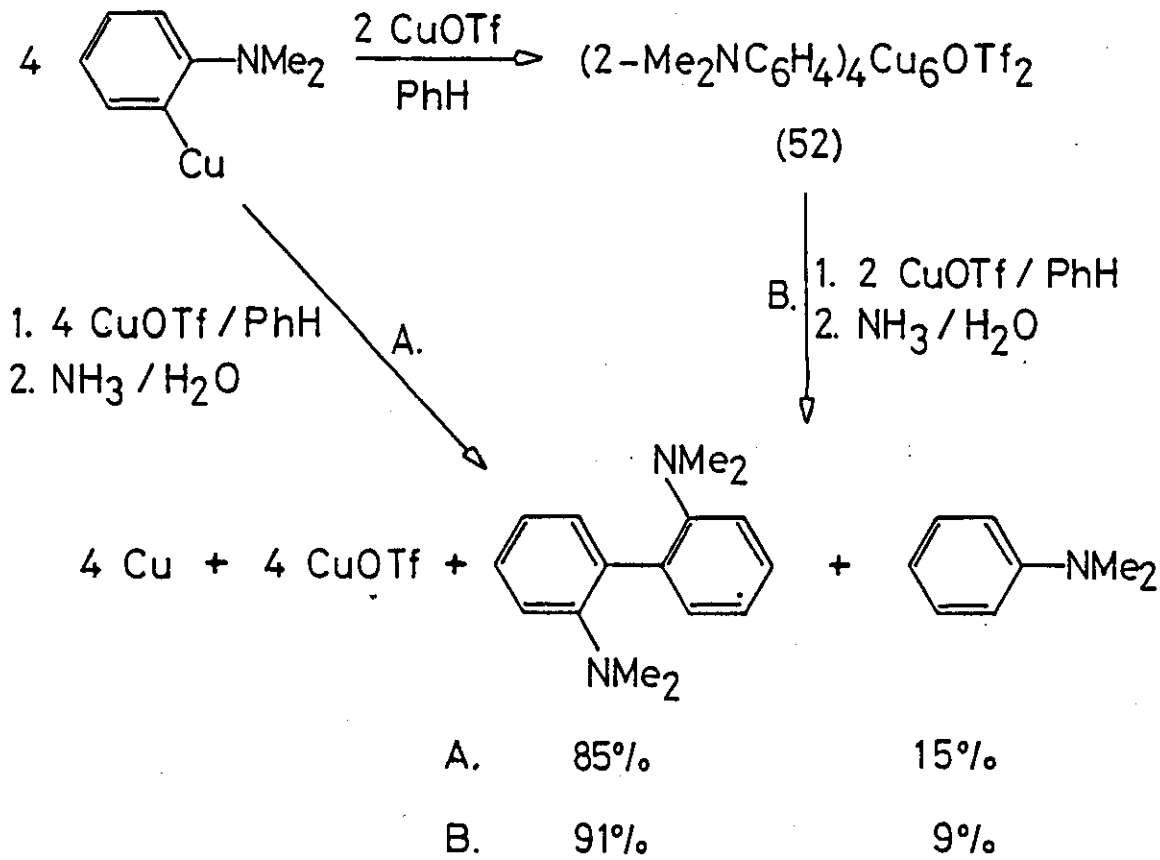
Further study of the organometallic chemistry of copper has provided a new route to symmetrical biaryls.[50] Certain arylcopper compounds have been observed to exist as well-defined clusters of the form Ar_4Cu_4. These can interact with copper(I) salts to form



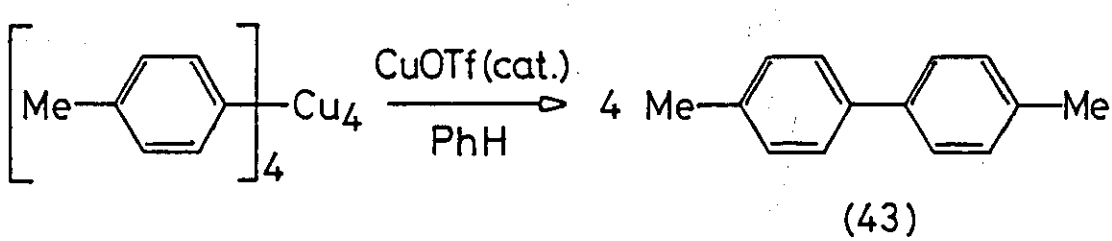
hexanuclear complexes $Ar_4Cu_6X_2$ whose stability depends on the nature of the anion X. Halides give comparatively stable complexes, but anions possessing good leaving group properties, such as trifluoromethanesulphonate(triflate, OTf) and trifluoroacetate, have induced selective formation of biaryls. Conversions are almost quantitative, examples of which are depicted in Scheme 9 (see overleaf).

Complex formation of the arylcopper cluster with copper(I) triflate is assumed prior to aryl-aryl coupling. Such a precursor (52) complex derived from 2-(dimethylamino)phenylcopper has been isolated. Subsequent reaction is explained in terms of charge transfer to the strongly electron-accepting triflate group. This weakens the carbon-copper bond and results in coupling of neighbouring aryl groups within the complex.

In the presence of coordinating ligands, e.g. NMe_2, equimolar quantities of copper(I) triflate are required. However, overall regeneration of copper(I) triflate means that catalytic amounts only are needed in the absence of such ligands. This is demonstrated by the quantitative formation of 4,4'-dimethylbiphenyl (43) from p-tolylcopper (see overleaf).



Scheme 9. Interaction of Polynuclear Arylcopper Compounds with Copper(I) Trifluoromethanesulphonate



(43)

Very significant contributions to the understanding of the Ullmann reaction have been made by Cohen and co-workers.[36, 51-54] Whilst the central mechanistic feature appears to be the formation of an organocopper compound, the exact nature and oxidation state of the intermediate which decomposes to yield biaryls is less well-documented. The processes which occur upon interaction of an arylcopper(I)

compound with an aryl halide have remained obscure. Either the products could be immediately formed, or another intermediate produced which is rapidly converted to product.

In the copper(I) induced decomposition of aromatic diazonium salts using tetrakis(acetonitrile)copper(I) perchlorate (53), it was observed that yields of dinuclear products derived from free radicals could be mediated by copper(I) ion.[51] In addition, the ratio of biaryl to azoarene could be raised by increasing the concentrations of diazonium and copper(II) ions.

$$ArN_2^{\oplus}\ BF_4^{\ominus} + (MeCN)_4Cu^{\oplus}\ ClO_4^{\ominus} \longrightarrow Ar{-}Ar + Ar{-}N{=}N{-}Ar$$

(53)

These results were interpreted as indicating that biaryl is not formed by direct radical coupling, but that a diarylcopper(III) species (54) undergoes reductive elimination to produce the biaryl and copper(I).

$$ArN_2^{\oplus} + e \longrightarrow ArN_2\cdot \longrightarrow Ar\cdot + N_2$$

$$Ar\cdot + Cu^{I} \longrightarrow ArCu^{II}$$

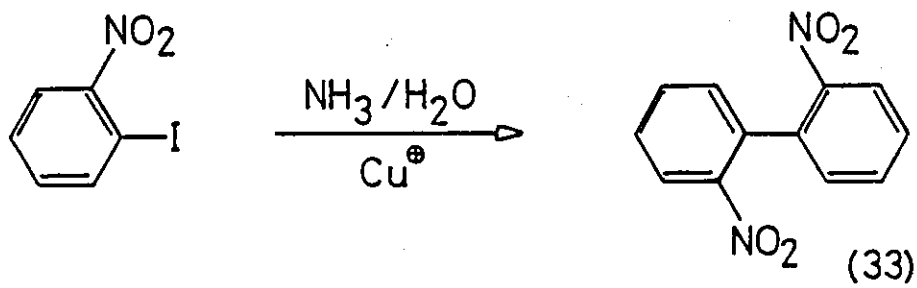
$$Ar\cdot + ArCu^{II} \longrightarrow Ar_2Cu^{III} \longrightarrow Ar{-}Ar + Cu^{I}$$

(54)

Just as the Ullmann reaction proceeds via arylcopper intermediates,[36] so also does the displacement of aromatic halogens by anions of copper(I) salts.[52] These are believed to involve arylcopper(III) species formed by oxidative addition of the aryl halides to copper(I). By analogy, it has been suggested that the first steps in the Ullmann coupling is also such an oxidative addition to any copper(I) species on the surface of the metal. Indeed,

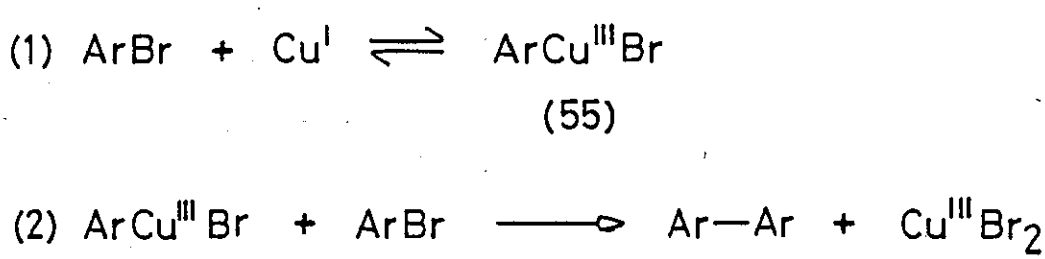
pretreatment of the copper[26] and the use of solid copper(I) species[39-48] have been successful.

To support these considerations, it has been shown[53] that symmetrical Ullmann couplings may be possible in organic solvents containing copper(I) ions, and due to the homogeneous nature of the reaction mixture a detailed kinetic and mechanistic study[54] has been performed. Thus, reaction of o-iodonitrobenzene and copper(I) triflate in acetone and 5% aqueous ammonia at room temperature gives a 92% yield of 2,2'-dinitrobiphenyl (33) in 5 minutes.[53]



(33)

These conditions are by far the mildest, and the reaction time the shortest, for any other reported Ullmann coupling. The reactivity order of aryl halides parallels that of conventional couplings, but the formation of unsymmetrical biaryls has not been established. A kinetic survey[54] rules out the possibility of reaction proceeding via free o-nitrophenyl radicals and postulates instead the existence of an arylcopper(III) (55) intermediate.



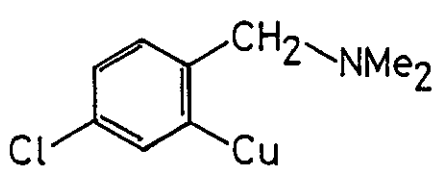
Certain similarities between this homogeneous process and the heterogeneous Ullmann coupling induced by copper metal have now become

apparent. These are summarised below. Note that the conventional synthesis of unsymmetrical biaryls may follow a route analogous to equation (2) above.

1. The homogeneous reaction is initiated by copper(I), and some indication exists that copper(I) on the surface of the metal plays a role.
2. Both processes proceed by intermediates, thought to be organocopper, which can give protonated by-products.
3. Free radicals do not appear as intermediates in either reaction.
4. In both reactions, the reactivity sequence is I > Br, and ortho nitro groups cause significant acceleration.

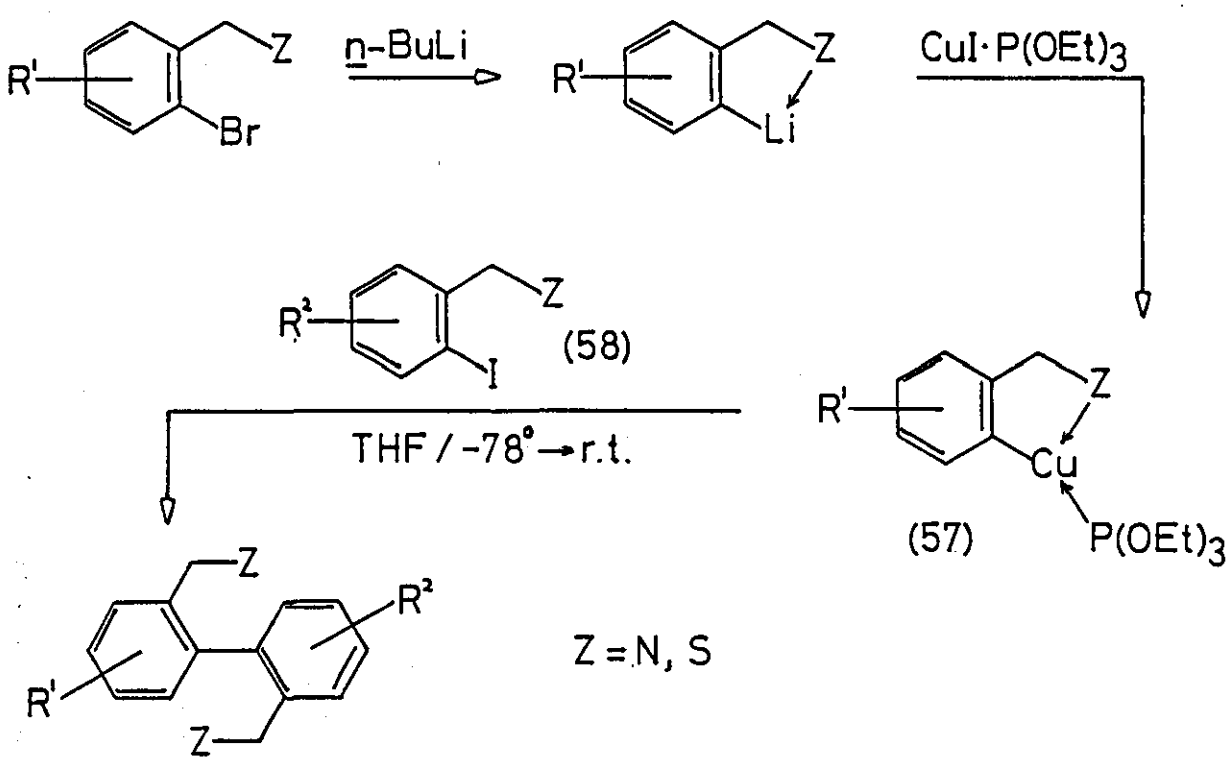
Whilst the conditions of the two processes differ considerably, these mutual characteristics offer valuable insights into the mechanism of the Ullmann reaction.

The work of Ziegler and coworkers[55] illustrates well the way in which recent understandings of the Ullmann reaction can be used to advantage in synthesis. Earlier, it was known that lone-pair donor atoms in arylcopper compounds confer resistance to high temperatures, oxidation, and hydrolysis, e.g. 5-chloro-2-(dimethylaminomethyl)phenyl copper (56) remains unchanged after 24 hours in air.[56]



(56)

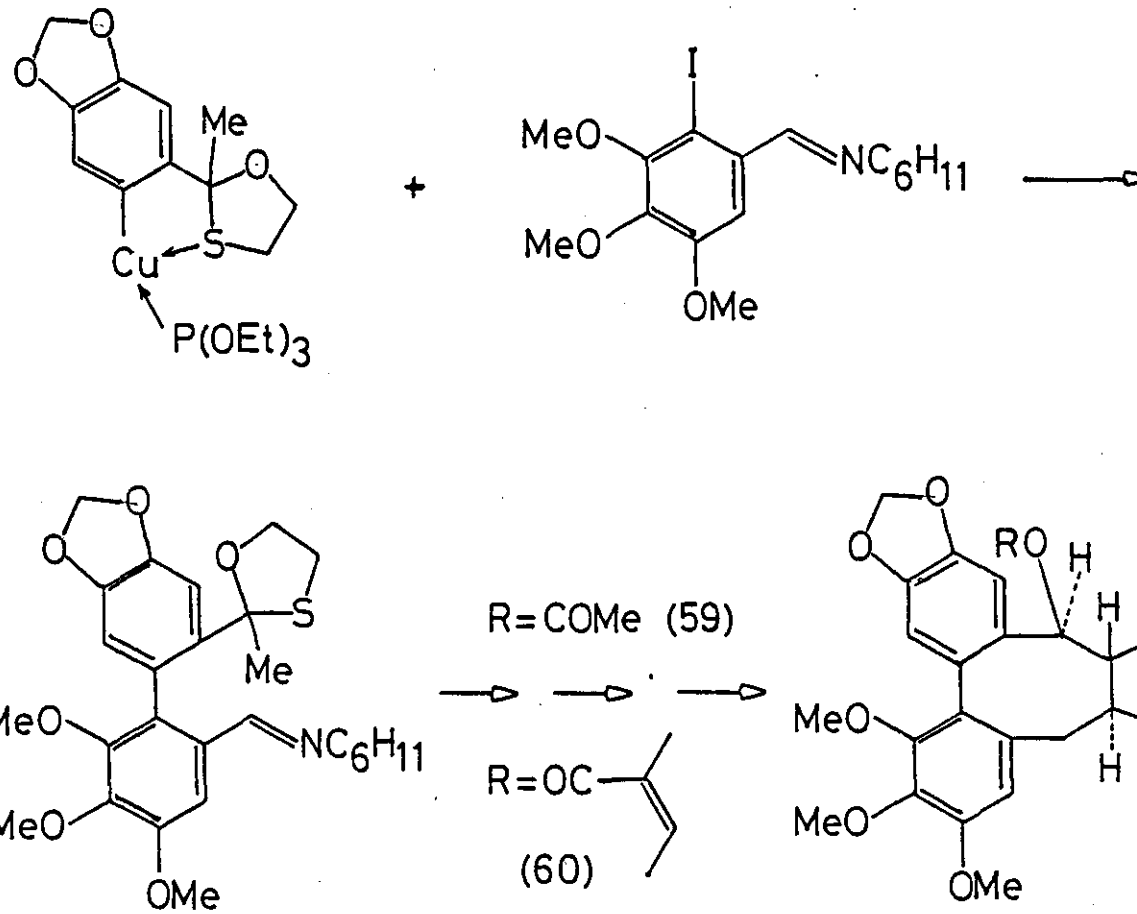
Ziegler has overcome the shortcomings of the conventional reaction by generating a similar intramolecular, heteroatom-stabilised arylcopper(I) species (57), which reacts with an aryl iodide (58) also bearing a heteroatom ligand to produce a biaryl at ambient temperature in a few hours. The general sequence is shown in Scheme 10 (see overleaf).



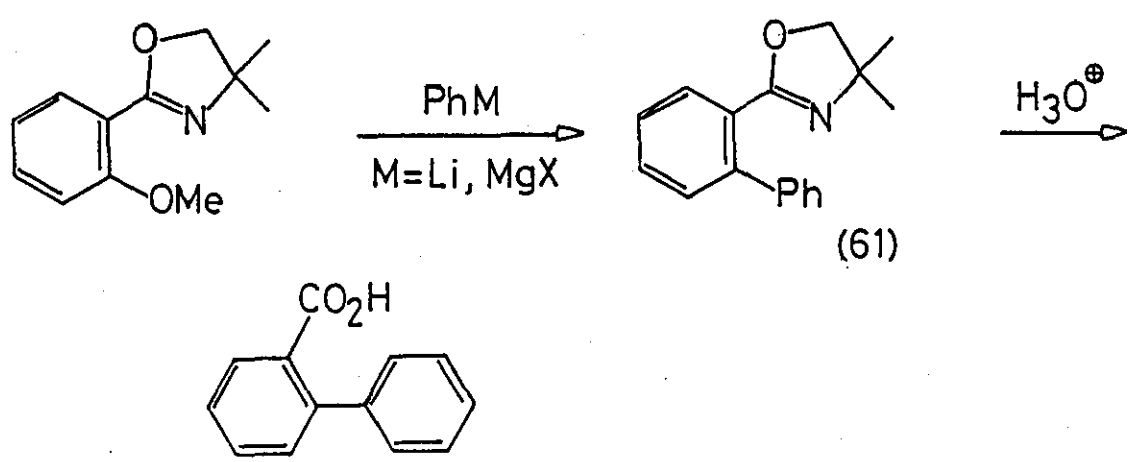
Scheme 10. Ambient Temperature Ullmann Reaction

The mechanism is viewed as an oxidative addition of the aryl iodide to the copper(I) reagent to form a ligand-stabilised diarylcopper(III) iodide. Subsequent decomposition yields the biaryl and cuprous iodide.

The method is applicable to the synthesis of both symmetrical and unsymmetrical biaryls, whose intramolecular ligands can be selectively removed to allow independent elaboration of the 2- and 2'-carbon atoms. Nitrogen ligands in the form of oxazolines and cyclohexylimines act as protecting groups for carboxylate and aldehyde functions respectively, and sulphur ligands are best suited to the masking of acetophenones in the form of thioketals. An important application has been to the total synthesis of the antileukemic biaryl lactones steganacin (59) and steganangin (60) (see overleaf).



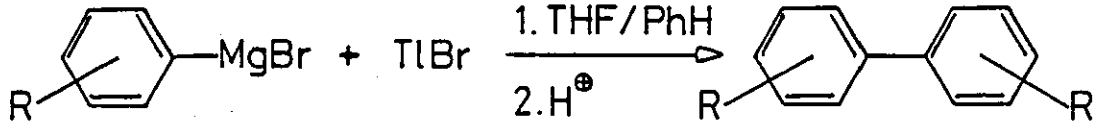
The oxazoline group finds further use as a metal chelating agent in an alternative mild approach to unsymmetrical biaryls.[57] In this, nucleophilic aromatic substitution is accomplished by displacement of an ortho methoxy group by aryllithium or Grignard reagents. The resulting 2-substituted phenyl oxazoline (e.g. 61) is hydrolysed to the corresponding biphenic acid.



1.2.3 OTHER METAL-INDUCED BIARYL SYNTHESES

The problems associated with the classical Ullmann reaction, such as the need of an activating substituent or the relatively expensive aryl iodide, has led to the development not only of other copper-promoted modifications, but also to the investigation of related couplings in the presence of reagents containing different metals.

Kharasch-type reactions,[58] in which catalytic amounts of transition metal salts induce the coupling of Grignard reagents with organic halides, have been known for many years, but seldom employed since they are difficult to control and give mixtures of products. However, during their extensive studies on the organic chemistry of thallium, McKillop and Taylor have found that aryl-, and secondary alkyl-, magnesium bromides may be coupled by a simple procedure using thallium(I) bromide.[59] Reaction results in rapid reduction of the inorganic halide (1.5 equiv.) to metallic thallium, and simultaneous formation of symmetrical biaryls in yields of 65-100%.



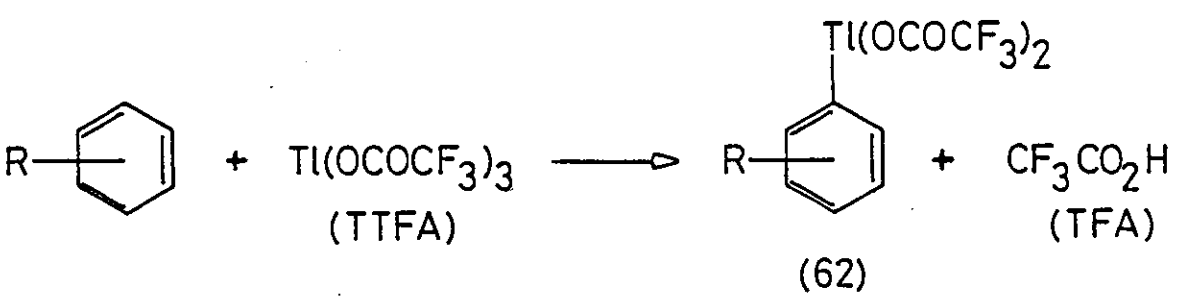
The overall coupling process is explained by a sequence of redox reactions among the three thallium valence states. Due to some regeneration of thallium(I) bromide in the product-forming steps, yields can be raised by addition of further Grignard reagent at the end of the first reaction cycle. Nonetheless, the method does suffer from the following limitations.

1. Stoichiometric amounts of thallium reagent are needed.
2. Ortho-substituted aryl Grignard reagents do not react.
3. Mixtures of two different Grignard reagents give all three

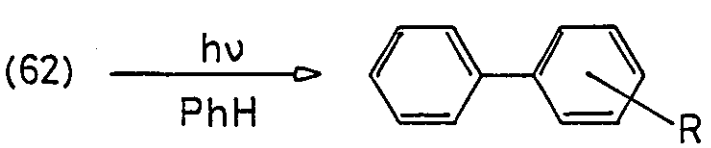
possible biaryls, and efforts to improve the yield of unsymmetrical biaryl have been unsuccessful.

4. The range of possible aromatic substituents is confined to those groups which are compatible with formation of a Grignard reagent.

Further work by McKillop and Taylor into aromatic electrophilic thallation reactions has produced new syntheses based on reagents containing a carbon-thallium bond.[60, 61] Direct thallation of a wide variety of aromatic substrates is readily accomplished by addition of the aromatic compound to a solution of thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA). Reaction with activated substrates is generally complete within minutes at room temperature, with direct formation of the stable crystalline arylthallium ditrifluoroacetate (62).

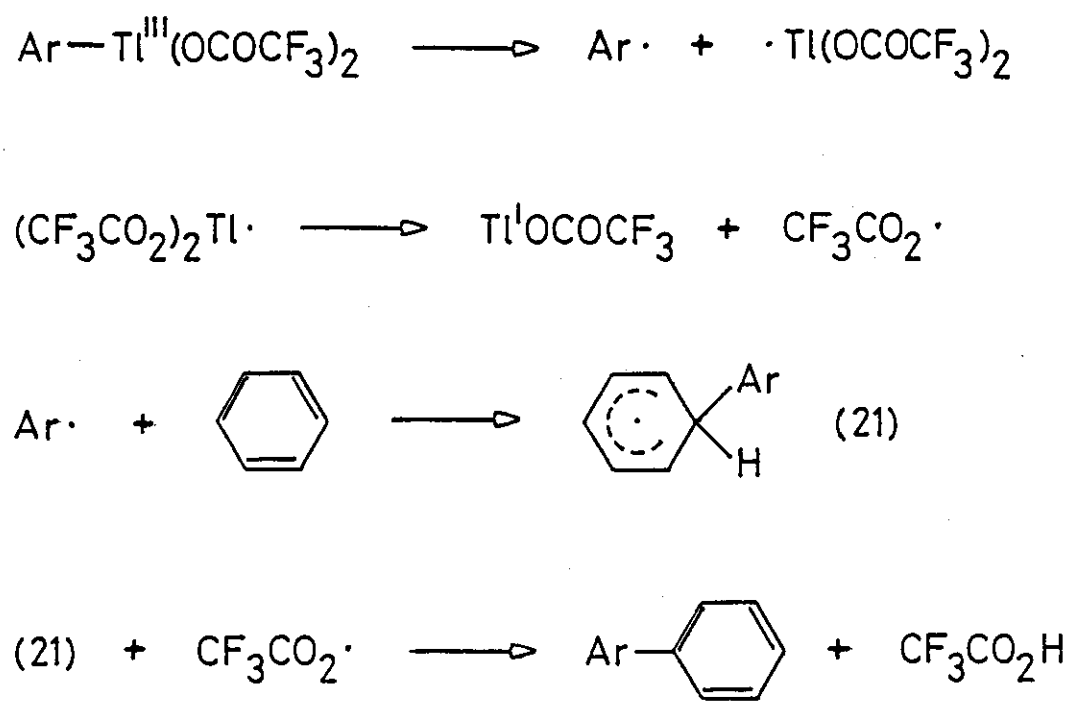


Photolysis of arylthallium ditrifluoroacetates in benzene[60] provides an alternative to similar arylation reactions using aromatic iodides.[17] Products are formed in high yield and in a high state of purity.



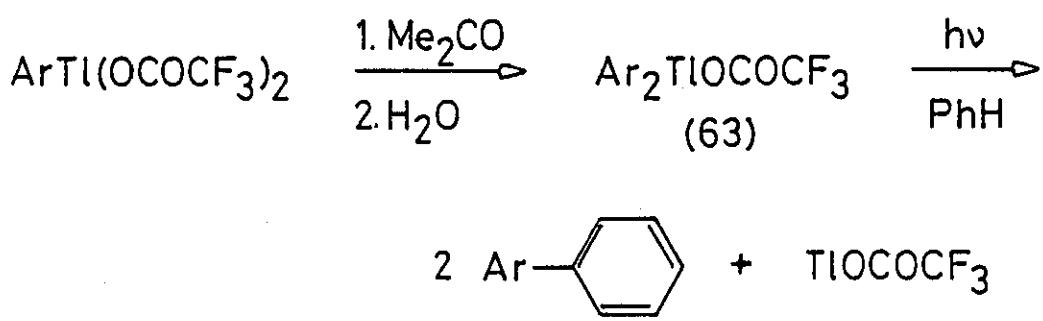
R = H, Me, Et, Cl, Br

Replacement of thallium by the phenyl group is regiospecific, and no positional isomers are obtained. Results. are consistent with a free radical mechanism, initiated by homolysis of the carbon-thallium bond, and illustrated in Scheme 11.

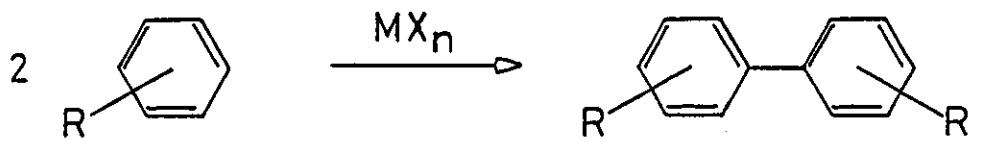


Scheme 11. Photolysis of Arylthallium Ditrifluoroacetates in Benzene

Diarylthallium trifluoroacetates (63), formed by the disproportionation of arylthallium ditrifluoroacetates in hot acetone, undergo similar photochemical reactions.[61]



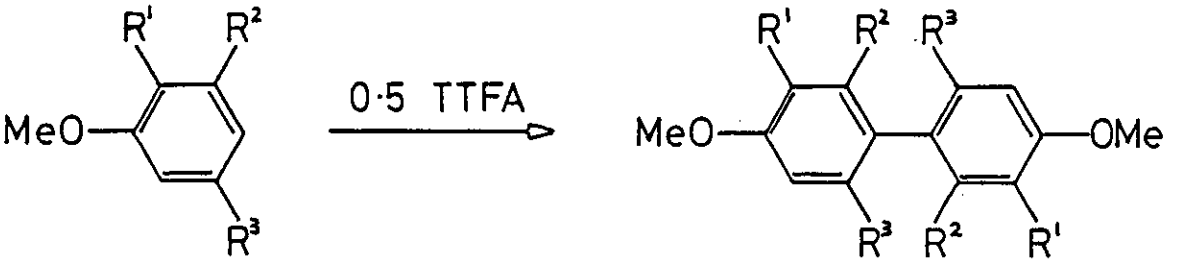
The metal salt-induced oxidative dehydrodimerisation of aromatic compounds has long been known and referred to as the Scholl reaction. It proceeds most readily (a) with relatively electron-rich aromatic substrates, and (b) when the metal salt (MX_n) can function as a one-electron oxidant.



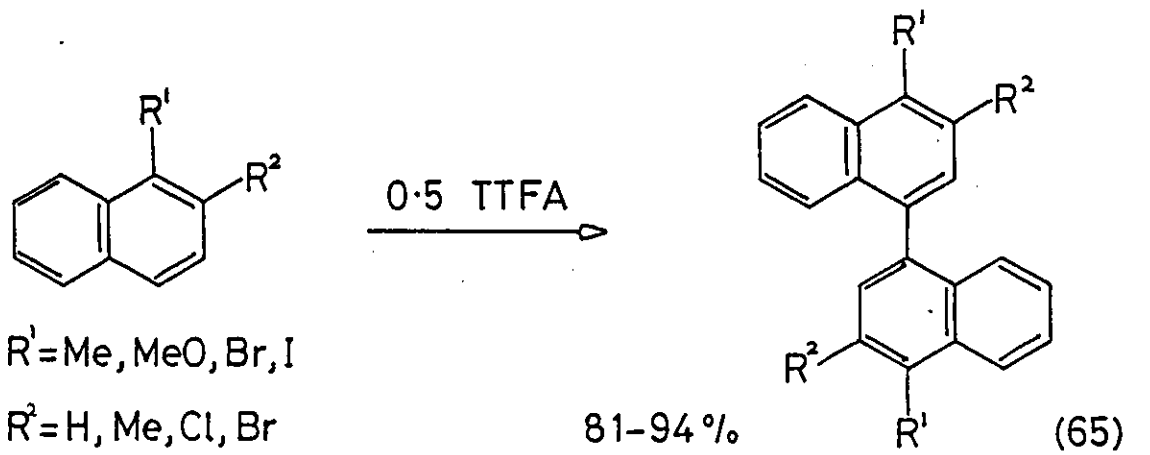
Scholl Reaction

Yields have been impaired by formation of complex mixtures, until Elson and Kochi[62] revealed that TTFA can also serve as an efficient one-electron oxidant. Subsequent treatment of electron-rich aromatic compounds with TTFA in TFA, or in carbon tetrachloride or acetonitrile containing boron trifluoride-etherate, has resulted in rapid (few mins.) formation of symmetrical biaryls (64) and binaphthyls (65) in excellent yields.[63] Intramolecular non-phenolic oxidative coupling has been applied to the synthesis of alkaloids.[64] (see overleaf).

The technique constitutes a simple, effective route to highly substituted biaryls in which ring substituents are either electron-donating or mildly electron-withdrawing. Aromatic substrates containing powerful electron-withdrawing groups, e.g. CO_2R, CN, NO_2, fail to react, and thereby the reaction is complementary to the Ullmann synthesis. A noteable advantage stems from the fact that, unlike most other biaryl syntheses, the starting material does not require a group which is eventually lost during the coupling process. The mechanism involves



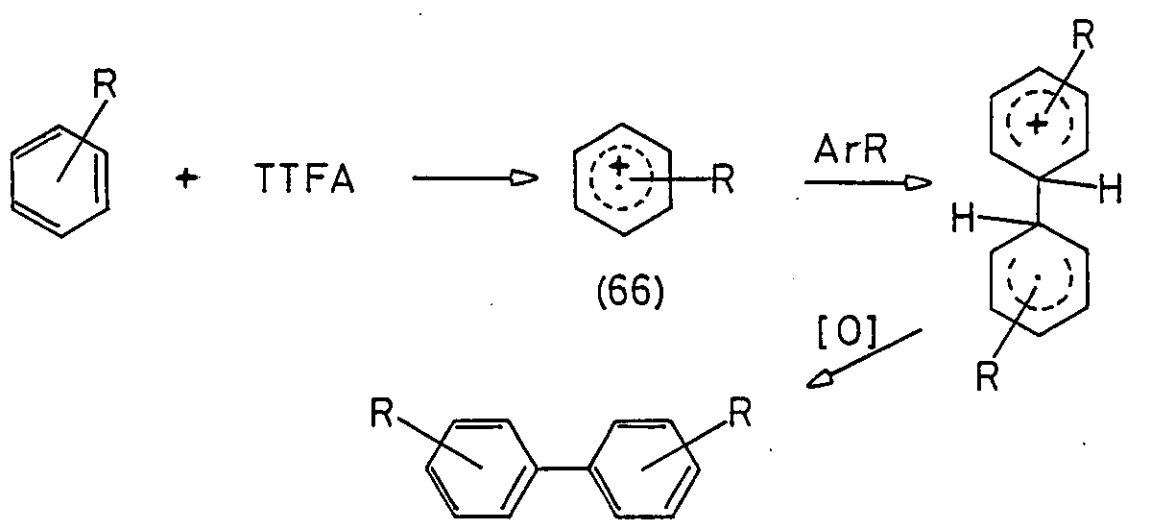
R^1=Me, MeO; R^2=H, Me; R^3=Me, Br, I (64) 60-99%



R^1=Me, MeO, Br, I

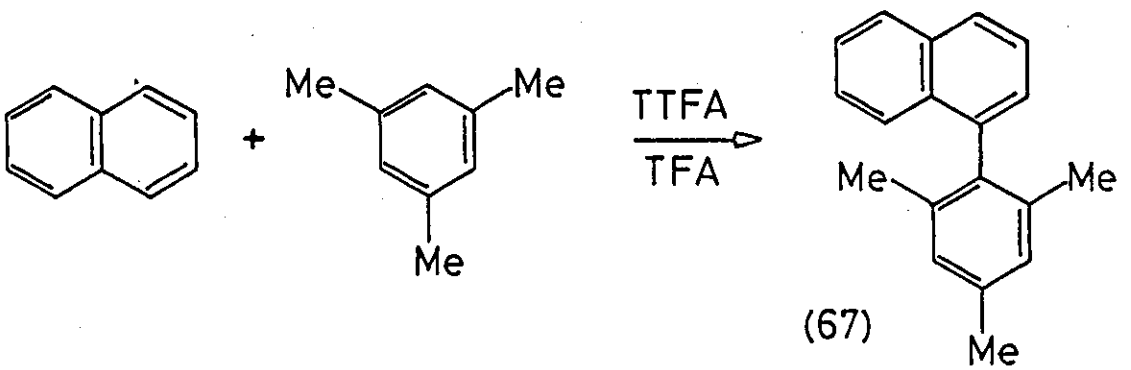
R^2=H, Me, Cl, Br 81-94% (65)

generation of a radical cation (66) by one-electron transfer to TTFA, followed by electrophilic substitution of a second molecule of substrate and oxidative aromatisation of the resulting intermediate by TTFA.



A consequence of this mechanism is that the oxidation potential of the aromatic substrate will govern the course of reaction with TTFA,

i.e. either the above oxidative coupling or electrophilic aromatic thallation.[60] That biaryl formation does not involve arylthallium intermediates can be demonstrated by the isolation of 1-mesitylnaphthalene (67) as the major coupling product in the reaction of naphthalene and mesitylene.[65]



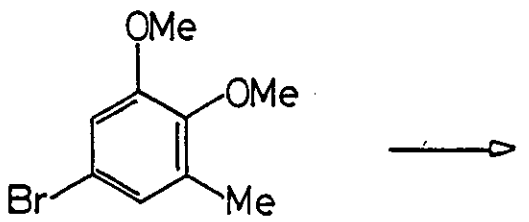
(67)

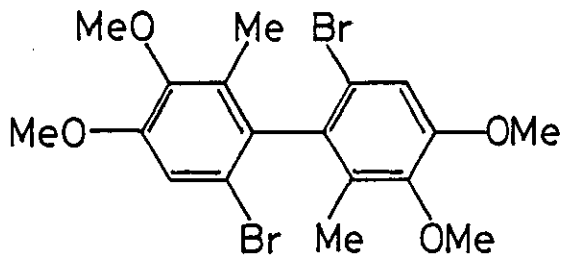
Thus, naphthalene is preferentially oxidised (E_{ox} = 1.64V vs. 1.85V), and the resulting radical cation reacts with the most basic species, i.e. mesitylene (pk_B 0.4 vs. 4.0). Future application to the synthesis of unsymmetrical biaryls may be possible with information on relative redox potentials and basicities of proposed reactants.

A second consequence of the mechanism is that other reagents besides TTFA can be effective, providing that the redox potential between the two valence states is sufficient to oxidise the substrate. Reagent systems using mercury(II) trifluoroacetate, lead(IV) acetate, iron(III) chloride, and cobalt(III) fluoride have been successful.[65] Comparison yields for the preparation of a symmetrical biaryl (68) are given below (see overleaf).

Cobalt(III) fluoride especially reacts smoothly and cleanly to give exceptionally pure products in high yields. The more powerful oxidants, e.g. lead(IV) acetate, can reduce yields by overoxidation, whilst other reagents may not be sufficiently strong oxidising agents.

The improved formation of new carbon-carbon bonds from active





(68)

Reagent	$Hg(OCOCF_3)_2$	$Tl(OCOCF_3)_3$	$Pb(OCOMe)_4$	$FeCl_3$	CoF_3
Yield %	42	99	42	28	92

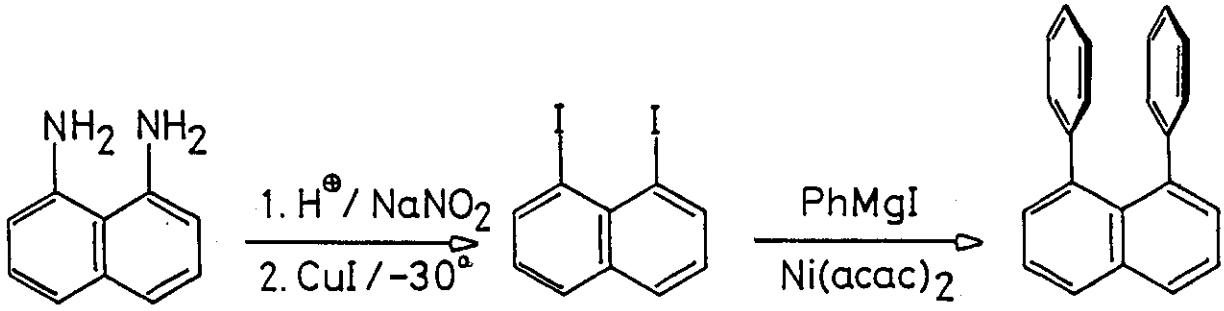
organometallic reagents[59] has the disadvantage that equivalent amounts of transition metal are needed. In addition, such procedures are ineffective for the preparation of unsymmetrical biaryls. These drawbacks have now been overcome by the introduction of various nickel and palladium complexes, which exhibit high catalytic activity in the selective cross coupling of aryl Grignard reagents with aryl halides.[66, 67] Examples include dichloro[1,3-bis(diphenylphosphino)propane]nickel(II), $Ni(dppp)Cl_2$, (69) for simple aryl-, and bis(triphenylphosphine)nickel(II) chloride (70) for sterically hindered aryl Grignard reagents.[66] The scope of the reaction can be extended with other dihalodiphosphine nickel(II) complexes to the coupling of alkyl and alkenyl residues. Extended alkanes and conjugated dienes are obtained, respectively.

$$RMgBr + R'X \xrightarrow[Et_2O]{L_2NiCl_2} R{-}R' + MgBrX$$

$L_2NiCl_2 = Ni[Ph_2P(CH_2)_3PPh_2]Cl_2$ (69)

$Ni(PPh_3)_2Cl_2$ (70)

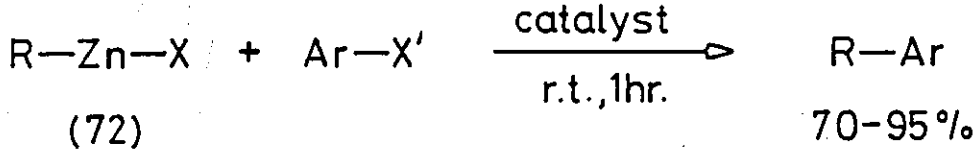
The use of soluble nickel(II) acetylacetonate, $Ni(acac)_2$, has been applied to a synthesis of the sterically interesting 1,8-diarylnaphthalenes. Thus, 1,8-diphenylnaphthalene (71) can be prepared from the commercial 1,8-diamino compound in two steps with an overall yield of 35%.[67]



(71)

This method compares favourably with that of House,[49] which uses a lithium diarylcuprate instead of the Grignard reagent.

Whilst the reactions of highly reactive organolithium and organomagnesium compounds have received much attention, the generally low nucleophilicity of organozinc compounds has restricted their synthetic utility. Such reagents (72) are easily prepared, and have now been shown to provide a mild route to symmetrical and unsymmetrical biaryls, as well as to diarylmethanes.[68]



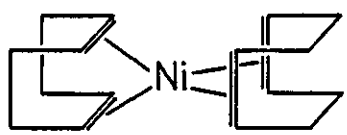
(72)

R = Ar, $ArCH_2$ X = Br, Cl, or Ar X' = Br, I

Aryl-aryl coupling proceeds smoothly at room temperature with aryl halides containing both electron-donating and electron-withdrawing groups. Suitable catalysts include the zerovalent nickel tetrakis(triphenylphosphine) complex, $Ni(PPh_3)_4$, and that derived

from bis(triphenylphosphine)palladium(II) chloride, $Pd(PPh_3)_2Cl_2$, with diisobutylaluminium hydride. The palladium catalyst has the advantage of being compatible with nitro groups. The zinc reagents themselves can be preferable to other organometallics in reducing the amounts of homocoupled products, cf. [67], and are especially superior to magnesium reagents in their ability to tolerate electrophilic functional groups, such as nitrile and ester.

Another zerovalent nickel complex, bis(1,5-cyclooctadiene)nickel(0), $Ni(COD)_2$, (73) reacts directly with aryl halides at moderate temperatures in DMF to produce symmetrical biaryls.[69] Yields are usually high (54-93%).



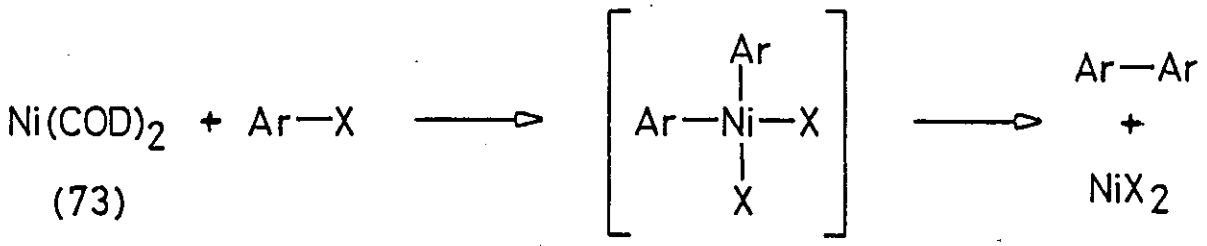
(73)

$$+ \; 2\,Ar{-}X \xrightarrow[25\text{-}50^{\circ},\,11\text{-}90hr.]{DMF} Ar{-}Ar + NiX_2 + COD$$

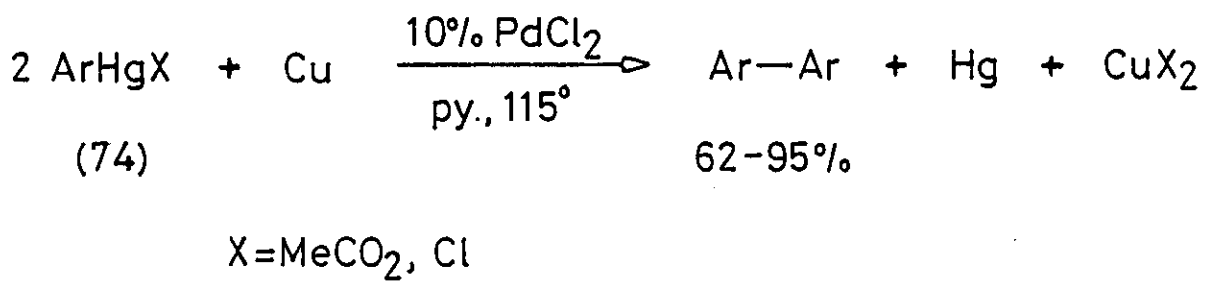
Reactivity of the aryl halides is in the order I > Br > Cl. Both electron-withdrawing groups, e.g. COMe, CN, CHO, and electron-donating groups, e.g. Me, NH_2, allow efficient coupling, but the reaction is inhibited by nitro groups, and acidic functions cause preferential reduction of the carbon-halogen bond. The procedure is complementary to that of Ziegler's[55] in failing completely in the presence of ortho substituents.

Semmelhack[69] considers the reagent (73) to be essentially solvated nickel metal, a very reactive form which is selective for reactions at the carbon-halogen bond. In accord with theories developed for the copper-promoted couplings, [36, 51-54] oxidative addition to the low-valent nickel, to form an arylnickel intermediate, is implicated. (see overleaf).

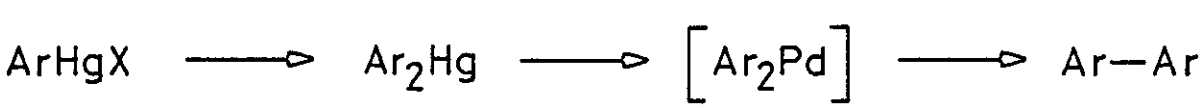
Organomercury compounds are attractive synthetic intermediates



since the pure materials are readily obtained. A palladium(II) chloride catalysed conversion of arylmercuric salts (74) to symmetrical biaryls has been described by Kretchmer and Glowinski.[70] An excess of copper metal is essential.



The reaction proceeds well with most functional groups, but is inhibited by acidic groups and fails with two substituents ortho to mercury. No selectivity is observed in the attempted synthesis of unsymmetrical biaryls from two different arylmercuric acetates. A suggested mechanism involves symmetrisation of the arylmercuric salt, followed by rapid reaction with catalyst to form an unstable arylpalladium derivative which decomposes to the biaryl.



Alternatively, a variety of symmetrically coupled products, which include conjugated diynes, conjugated dienes, and alkanes, can be obtained when a rhodium(I) catalyst is used. Some reactions of diorganomercury compounds with tris(triphenylphosphine)chlororhodium,

$RhCl(PPH_3)_3$,[71] are summarised below.

$$R_2Hg \xrightarrow[HMPT\ /\ N_2\ /\ 50\text{-}130^\circ]{RhCl(PPh_3)_3} R\text{—}R + Hg$$

R	PhC≡C	PhCH=CH	$PhCH_2$	Ph
Yield %	95	99	44	100

The first step (1) probably involves oxidative addition of a carbon-mercury bond to the catalyst to produce a rhodium(III) species. Evidence indicates that the second reductive step (2) is bimolecular. The rhodium(I) catalyst is regenerated and metallic mercury is deposited.

$$(1)\ R_2Hg + Rh^{I}Cl \longrightarrow (R)(RHg)Rh^{III}Cl$$

$$(2)\ 2\ (R)(RHg)Rh^{III}Cl \longrightarrow R\text{—}R + 2\ Rh^{I}Cl + R_2Hg + Hg$$

A second rhodium(I) complex, bis[chlororhodium(dicarbonyl)], $[ClRh(CO)_2]_2$, has been used by Larock[72] to produce isomerically pure symmetrical biaryls from the corresponding arylmercuric chlorides. The addition of lithium chloride substantially improves the yield. Contrary to methods using palladium,[70] this reaction proceeds only poorly with amines but successfully with phenols. The mechanism may be interpreted in a manner similar to that above, with an initial transfer of organic moiety from mercury to rhodium prior to oxidative addition.

$$2\ ArHgCl \xrightarrow[HMPT\ /\ N_2\ /\ 80°\ /\ 24hr.]{0{\cdot}5\%\ [ClRh(CO)_2]_2\ /\ 4\ LiCl} 40\text{-}96\%\ Ar{-}Ar + HgCl_2 + Hg$$

$$(1)\ ArHgCl + Rh^{I}Cl \longrightarrow ArRh^{I} + HgCl_2$$

$$(2)\ ArRh^{I} + ArHgCl \longrightarrow Ar_2Rh^{III}HgCl$$

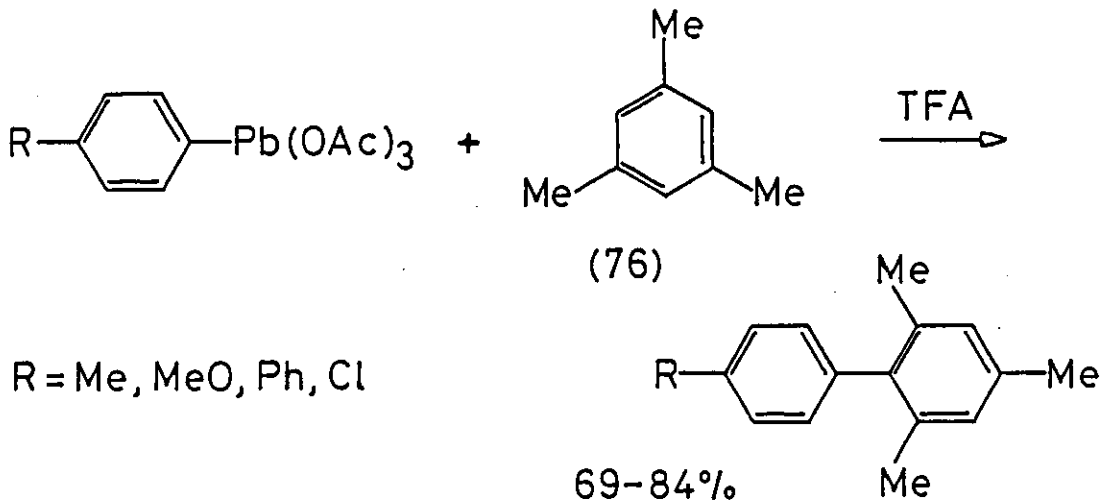
$$(3)\ Ar_2Rh^{III}HgCl \longrightarrow Ar{-}Ar + Rh^{I}Cl + Hg$$

In relation to the oxidative couplings using thallium(III) salts,[65] there have arisen two additional techniques[73, 74] by which no group is required to leave the starting material. Both incorporate the isolation of stable organometallic species, and neither requires the assistance of any catalyst, as described above for organometallic compounds of magnesium, zinc, and mercury.

Pinhey and co-workers[73] have thus modified the reaction of aryllead(IV) tricarboxylates (75) with TFA. At ambient temperature, high yields of aryl trifluoroacetates are given, and an aryl cation intermediate is proposed.

$$\underset{(75)}{ArPb(OCOMe)_3} \xrightarrow{TFA} ArOCOCF_3$$

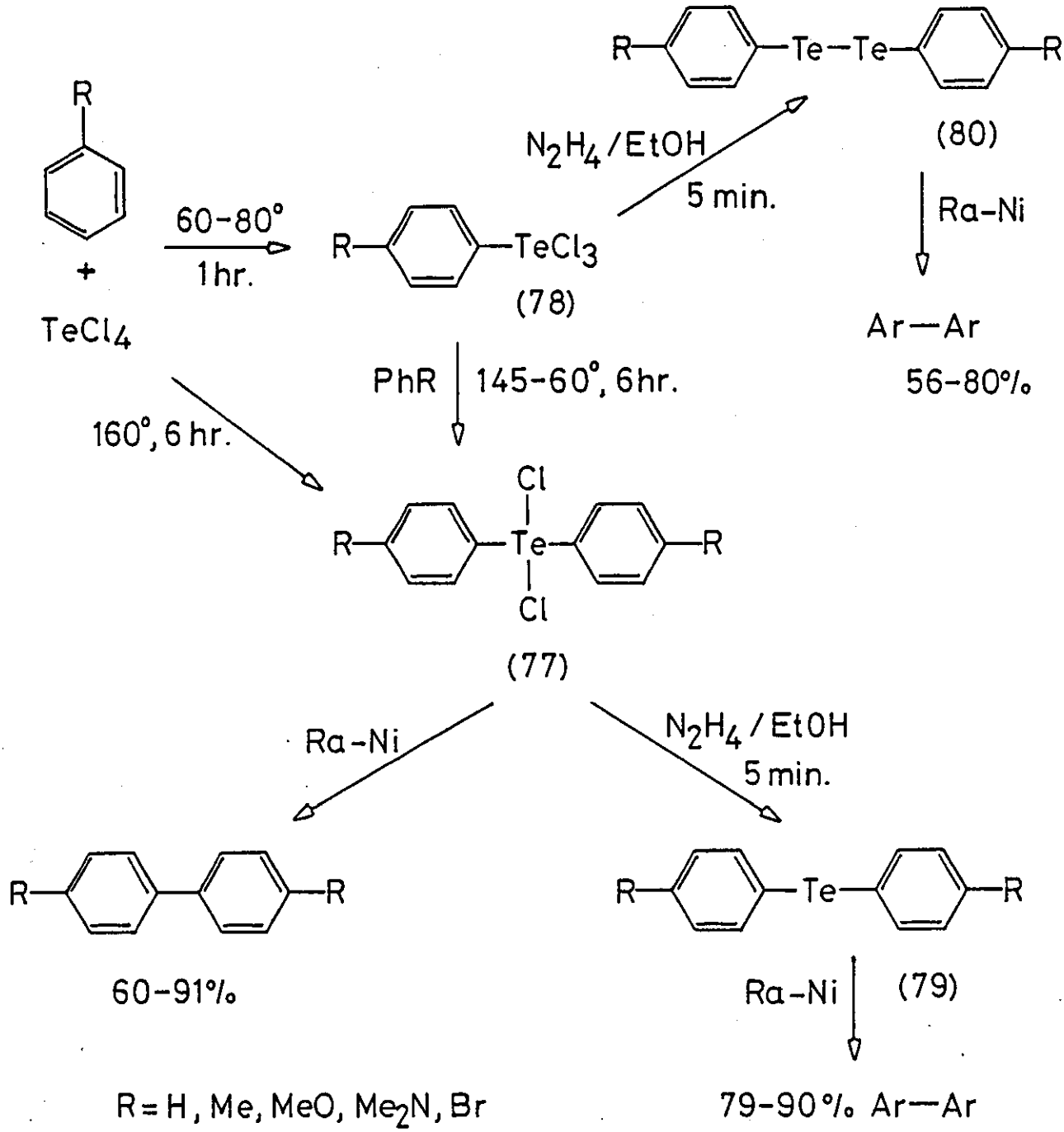
However, in the presence of aromatic compounds possessing high electron density, it has been possible to trap the intermediate with formation of unsymmetrical biaryls. Moreover, with polymethyl benzenes such as durene, mesitylene (76), and p-xylene, only one isomer is possible.



The biaryls are envisaged as arising via a preliminary π-complex between the aromatic substrate and a species which still possesses an intact aryl-lead bond, i.e. not a free aryl cation. It is the formation of this intermediate complex which lowers the activation energy needed for heterolysis of the aryl-lead bond, and thereby allows for competition for the aryl residue with TFA.

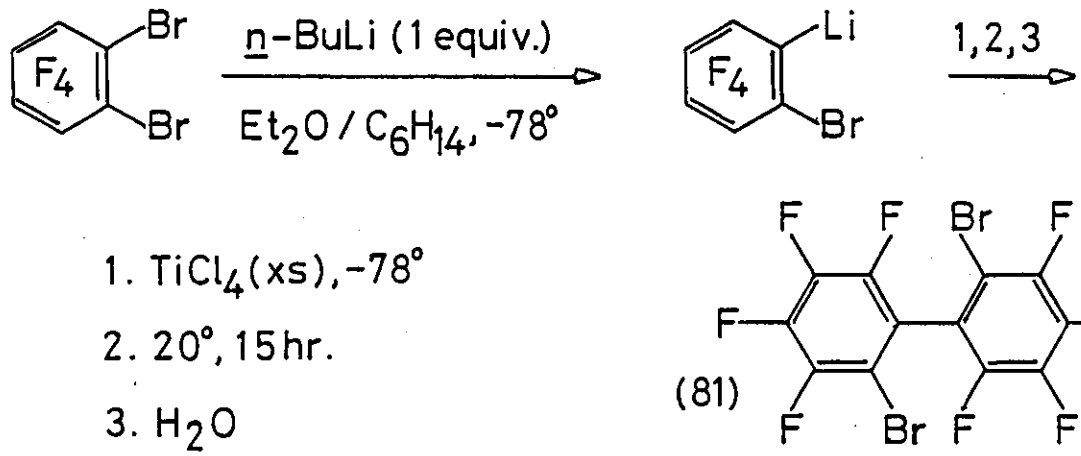
Secondly, Bergman[74] has employed organotellurium compounds in a novel synthesis of symmetrical biaryls. The intermediate bis(aryl)tellurium dichlorides (77) are prepared by electrophilic substitution of aromatic compounds with tellurium tetrachloride. The intermediate aryltellurium trichloride (78) may be isolated, and in the absence of activating substituents, e.g. RO, R_2N, RS, a Lewis acid catalyst is employed. Subsequent treatment with degassed Raney nickel readily affords the corresponding biaryl.

Diaryl tellurides (79) are likely intermediates. They are conveniently prepared by addition of hydrazine to the dichloride in ethanol, and give biaryls in similar yields when treated with Raney nickel. This is in direct analogy to the previously reported reaction[75] of diaryl selenides, Ar_2Se. Furthermore, the diaryl ditellurides (80) derived from aryltellurium trichlorides also serve as a source of symmetrical biaryls. These results are summarised in Scheme 12.



Scheme 12. Aryltellurium Compounds in Biaryl Synthesis

The ether-solubility of titanium tetrachloride, and the instability of titanium-carbon bonds, have been exploited in the synthesis of symmetrical octafluorobiphenyls (81).[76] The reaction makes use of a readily formed aryllithium reagent, and supposes the intermediacy of an aryltitanium species which slowly decomposes at room temperature.



(81)

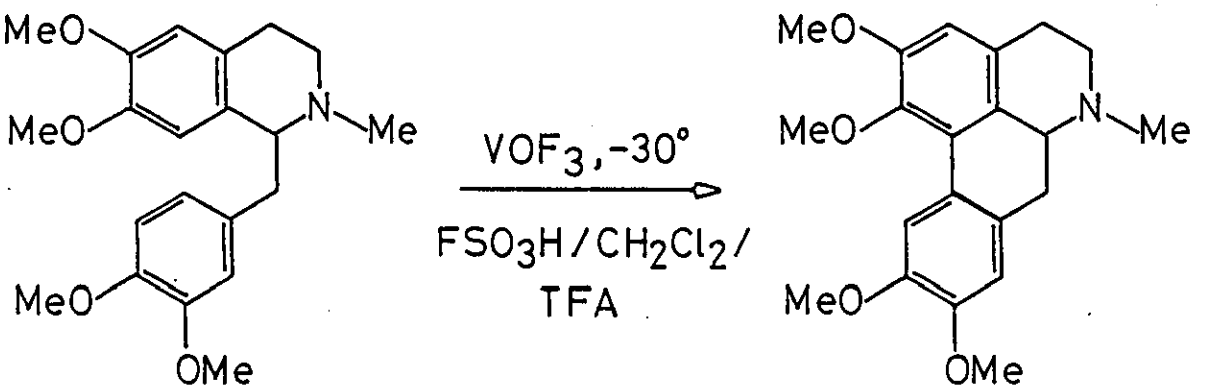
This coupling reaction is superior to the Ullmann reaction for the preparation of polyhalogenobiphenyls because no polymeric materials or product mixtures are obtained.

1.2.4 SOME RECENT DEVELOPMENTS

The literature in recent years has contained a considerable number of innovations in biaryl synthesis. Some have enhanced the more established procedures by the introduction of new and more effective reagents, whilst others may be specific to one particular application and are unique in their own right. A few examples are now quoted to illustrate the range and diversity of the methods employed.

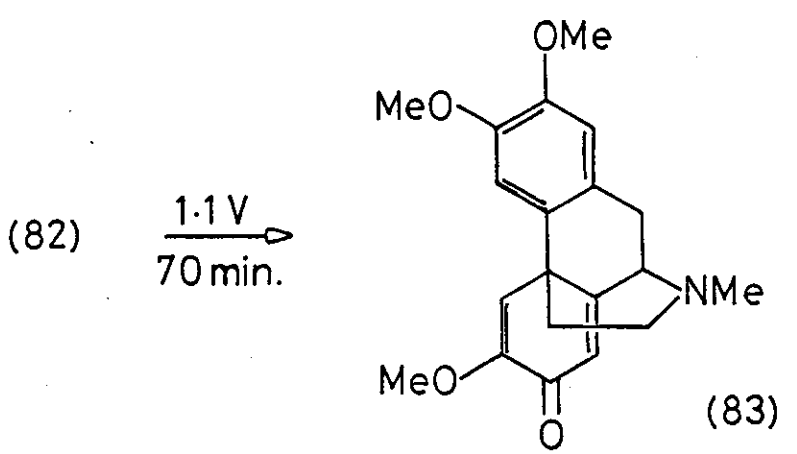
A prominent mode of carbon-carbon bond formation in the biosynthesis and synthesis of alkaloids is represented by the oxidative coupling of phenols. It is now possible to effect smooth inter- and intramolecular coupling of nonphenolic benzylisoquinolines upon treatment with vanadium oxytrifluoride, VOF_3, as exemplified by the conversion of (±)-laudanosine (82) to (±)-glaucine.[77] (see overleaf).

The need for easily oxidised phenols has further been eliminated by the introduction of a novel electrochemical technique,[78] which uses the powerful but selective anode as the oxidant. For example, oxidation of (±)-laudanosine (82) at a platinum electrode in acetonitrile at 0°,



(82)

with lithium perchlorate as electrolyte, gave O-methylflavinantine (83) in 52% yield. The reaction was performed at a potential of 1.1V in the presence of sodium carbonate.

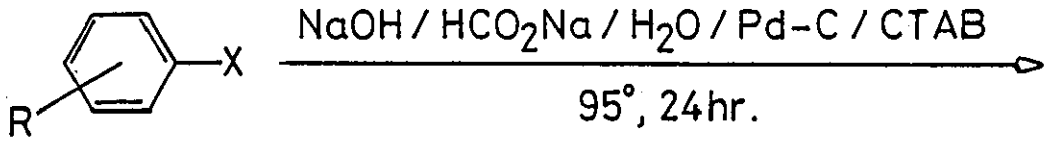


(83)

The method possesses several advantages over Pschorr-type ring closures, not least of which is a five- to six-fold improvement in yield. When repeated with an equivalent amount of bis(acetonitrile)palladium(II) chloride the yield rises to 63%.

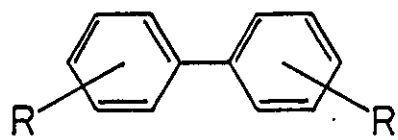
The reaction conditions used by Bamfield and Quan to reduce nitro- and halo-arenes have been modified to afford a general route to symmetrical biaryls.[79] An aryl halide is treated with an alkaline solution of sodium formate, in the presence of palladium-on-charcoal

and surfactant, to give the biaryl as the major product.



R = H, Me, Ph, MeO, Ac, F

X = Cl, Br

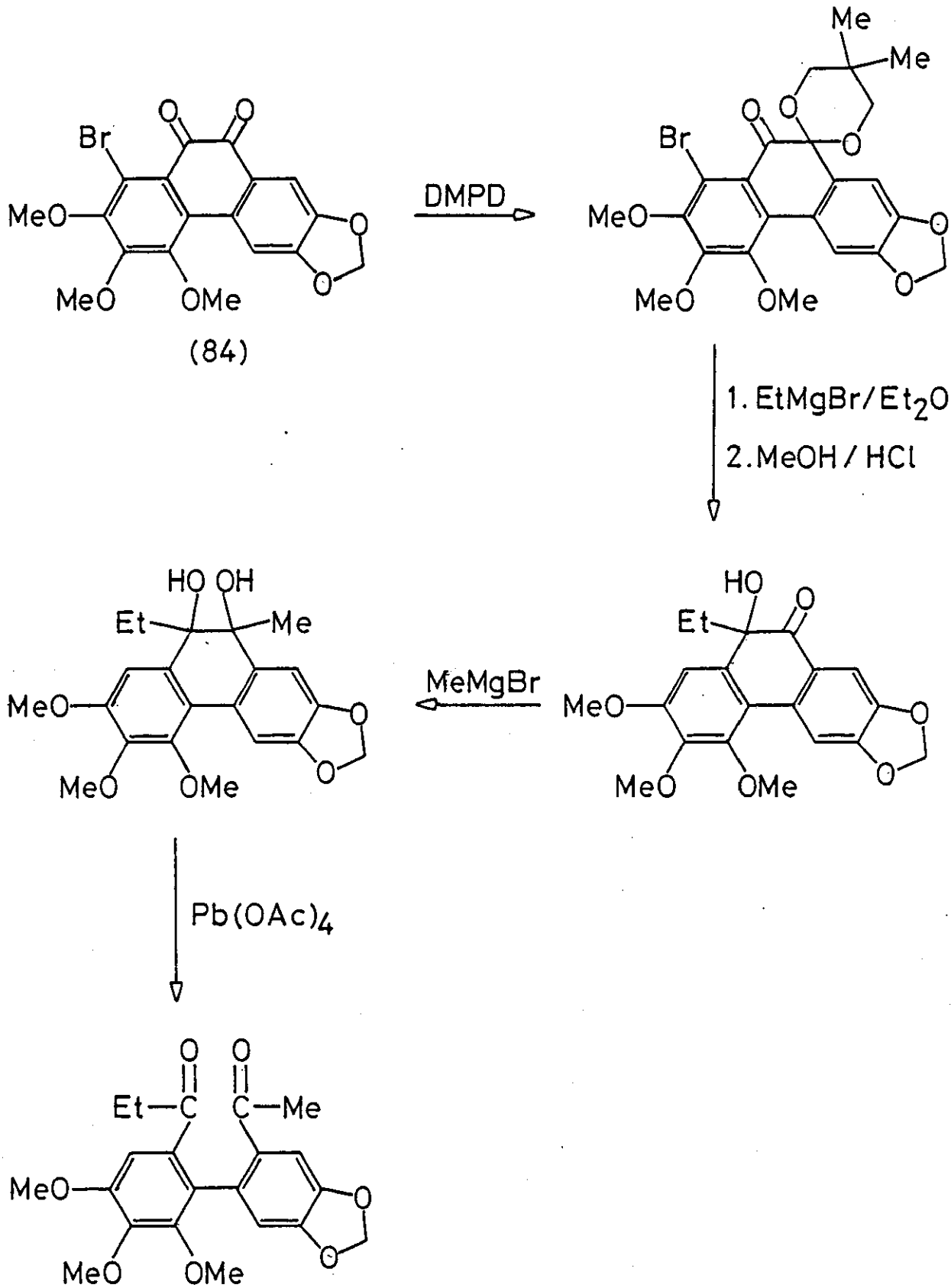


36-65%

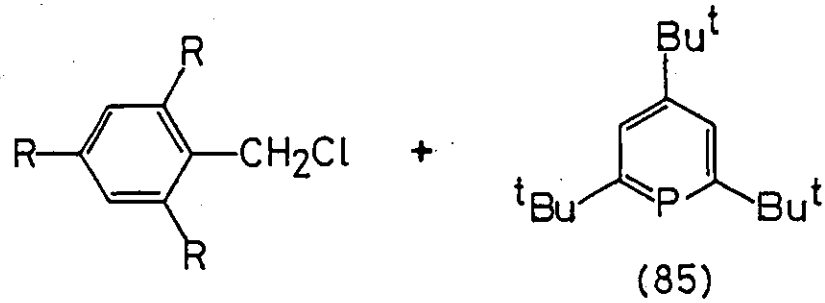
Yields are only moderate, but dehalogenated starting material may be recovered and re-cycled. Cetyltrimethylammonium bromide (CTAB), $C_{16}H_{33}\overset{\oplus}{N}Me_3\ \overset{\ominus}{Br}$, is the most generally applicable surfactant. An interesting facet of the reaction is the possibility for one-step synthesis of aminobiaryls from the corresponding nitroaryl halides.

The synthesis of biaryls containing carbonyl functions in the 2,2'-positions has already been mentioned.[33, 55] However, an alternative route has been approached via a regiocontrolled substitution of the 9,10-bond of phenanthrenes.[80] This has been achieved by selective ketalisation, using the bulky 2,2-dimethyl-1,3-propanediol (DMPD), when a bromine substituent is adjacent to one of the carbonyl functions of the corresponding phenanthrenequinone, e.g. (84). The method is novel in that the aryl-aryl bond is present during the functionalisation steps, and that the biaryl itself is not generated until a final oxidative cleavage step. Relevant stages in the formation of an unsymmetrical biaryl are illustrated below (see overleaf).

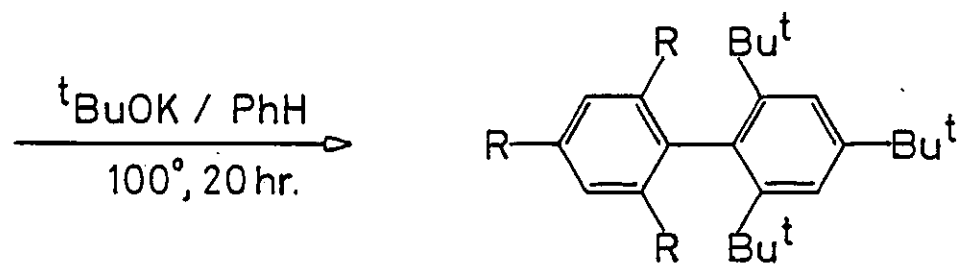
Conventional routes to highly substituted biaryls have been noted to result in very low yields, but in their work, Häfelinger and Beyer[14] developed an improved route to the 2,4,6-tri-t-butyl biphenyls. In the presence of a large excess of potassium t-butoxide, benzyl chlorides are allowed to react with tri-t-butylphosphorin (85) (see overleaf).


Br
MeO
MeO
OMe
DMPD
Me
Me
1. EtMgBr/Et2O
2. MeOH / HCl
HO OH
Et
Me
MeMgBr
HO
Pb(OAc)4
Et—C
C—Me

(84)

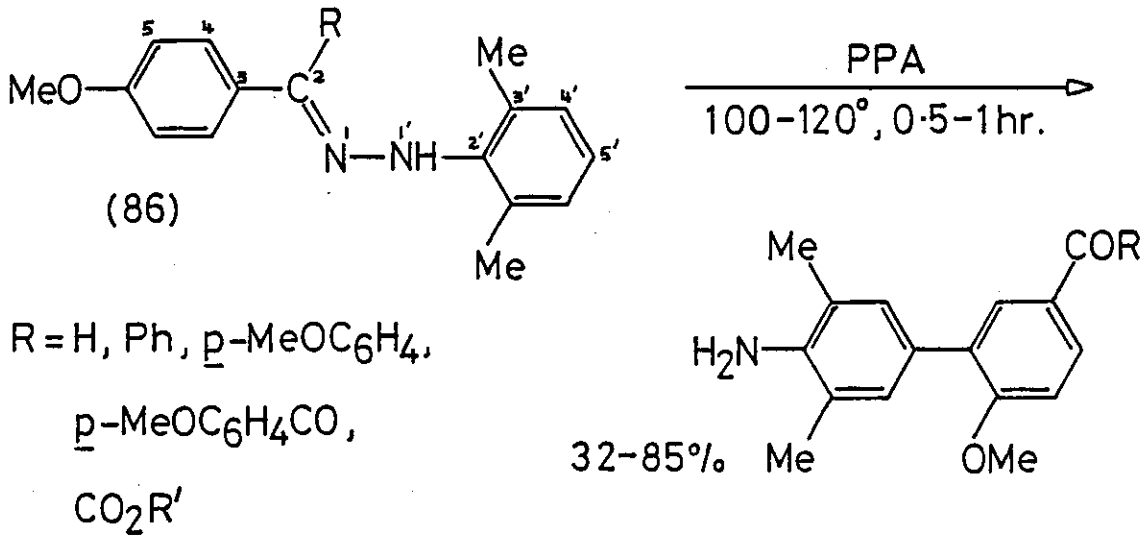


(85)



R = H (31%), Me (22%)

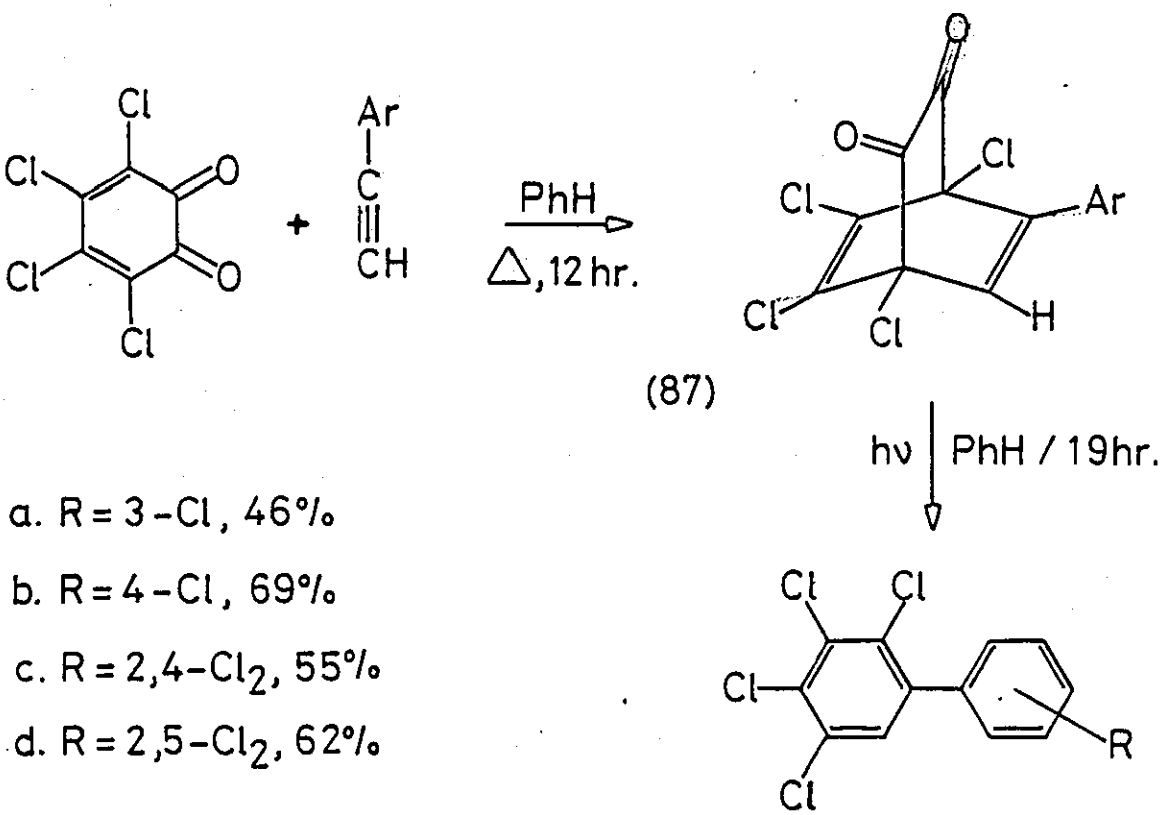
The phenanthrene route of Mervič and Ghera[80] represents a class of techniques which seek to apply a broader range of fundamental chemistry to the synthesis of biaryls. The rearrangement of 2,6-dimethylphenylhydrazones of p-carbonylanisoles (86) in a ten-fold excess of hot polyphosphoric acid (PPA)[81] serves as another example.



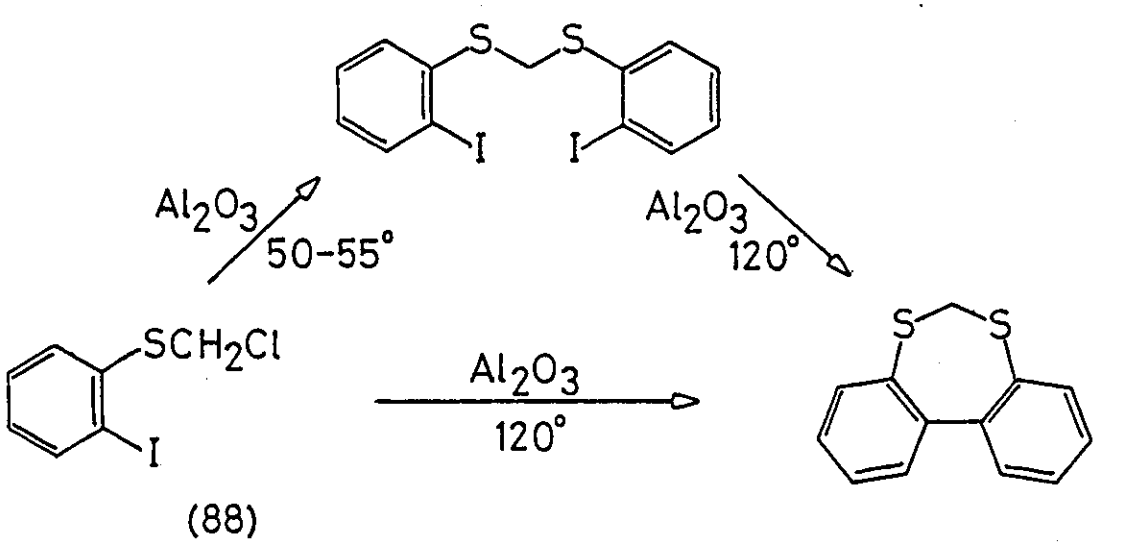
Reaction proceeds through a [5,5] sigmatropic rearrangement, involving nitrogen-nitrogen bond fission and simultaneous bond formation between carbon atoms 5 and 5'. The 2- and 6-methyl groups in the hydrazine moiety are necessary to prevent competing Fischer indole synthesis, which can occur if the appropriate structural features are available in the carbonyl moiety, i.e. $ArCOCH_2R$.

Also included in the above category is a new approach to specific unsymmetrically substituted chlorobiphenyls,[82] designed in order to study the toxicological properties associated with such materials. The method involves photodecomposition of a bridged dione Diels-Alder adduct (87) formed from a (chlorophenyl)acetylene and o-chloranil (see overleaf).

Finally, a unique alumina-catalysed equivalent of the Ullmann synthesis has been observed.[83] By analogy with the observed transformation of ω-chloroalkyl aryl sulphides to α, ω-bisaryl thioalkanes, it has been observed that o-iodophenyl chloromethyl sulphide (88) is converted on gentle warming with alumina into the appropriate dithioacetal. Both,



on heating with alumina to 120°, eliminate iodine to give the cyclised product in near quantitative yield.



(88)

To complete the review, mention is made of a mechanical technique which may find application in the conventional Ullmann procedure. It entails the use of ultrasonic irradiation, which produces strong agitation of reaction mixtures and thereby maintains the surface of any metal in a highly activated form. The effect can be significant, as revealed in the

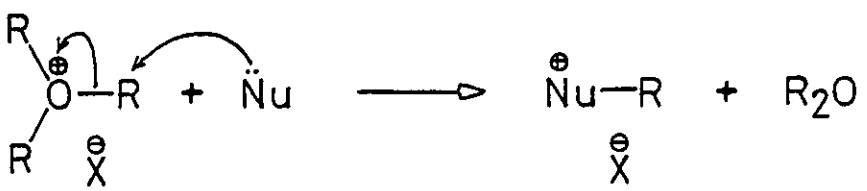
Barbier one-step coupling of organic halides with carbonyl compounds.[84] This reaction is customarily performed with magnesium, but the ultrasonic method allows the use of lithium in wet technical grade tetrahydrofuran.

CHAPTER 2

OXONIUM SALTS

2.1 REVIEW[85]

Until 1937 the unsaturated pyrylium salts remained the only compounds known in which trivalent oxygen is bonded only to carbon. However, the discovery of trialkyloxonium salts (89) by Meerwein[86, 87] provided examples of the first pure oxonium ions, with positive charge localised on oxygen, and has led to the development of a variety of powerful alkylating agents. As a result, the study of alkylation reactions in organic chemistry has spread to incorporate those weakly nucleophilic functional groups which do not react with more conventional alkylating agents, e.g. alkyl halides, dialkyl sulphates and diazomethane.



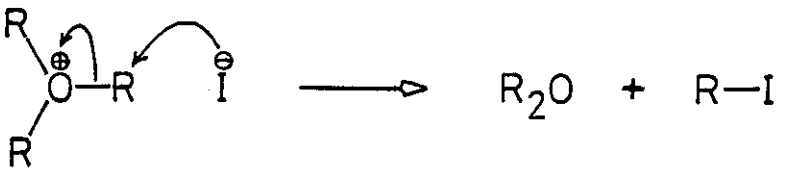
(89)

R = Me, Et, n-Pr, n-Bu

X = BF_4, $SbCl_6$, PF_6, SbF_6, $(NO_2)_3C_6H_2SO_3$

Nu = O, S, N, P

Meerwein's synthesis was based on the reaction between epichlorohydrin and boron trifluoride-etherate in excess of the appropriate ether, and the resulting trialkyloxonium ions were shown to exist only with complex anions (X) of low polarisability, e.g. tetrafluoroborate (X = BF_4). Thus, being strong alkylating agents, trialkyloxonium ions give alkyl halides in reaction with halide anions. Such a reaction represents the converse of all previous attempts at synthesis, although ethers may be alkylated by alkyl halides in the presence of a suitable silver salt. Removal of the solid silver halide can afford a number of unsymmetrical trialkyloxonium ions (90) (see overleaf).

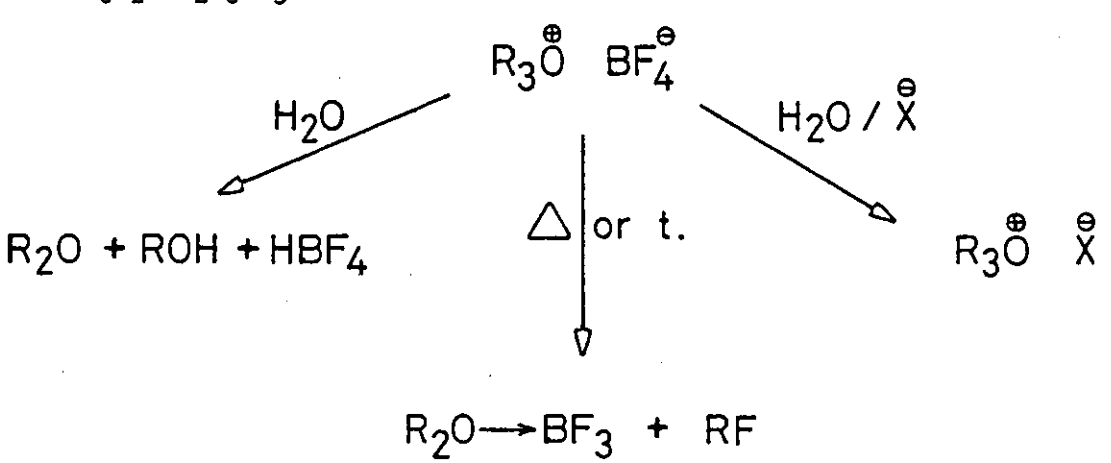


$$R'\text{—Hal} + R_2O \xrightarrow{AgBF_4} R_2\overset{\oplus}{O}R'\ \overset{\ominus}{BF_4} + AgHal\downarrow$$

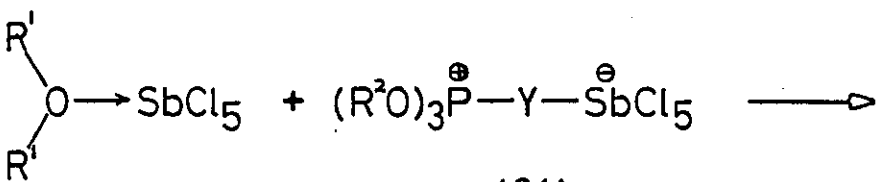
(90)

Since Meerwein's original studies, considerable attention has been focussed on developing new syntheses of trialkyloxonium salts and on broadening the scope of their utility as synthetic intermediates. Meerwein himself discusses such progress,[88] and an excellent review has been given by Granik, Pyatin and Glushkov.[89] More recent coverage has been provided by Kemp[90] and by Baggett.[91] The reader is referred to these sources and to Perst[85] for extensive detail, whilst only extracts and other relevant material will be treated herein.

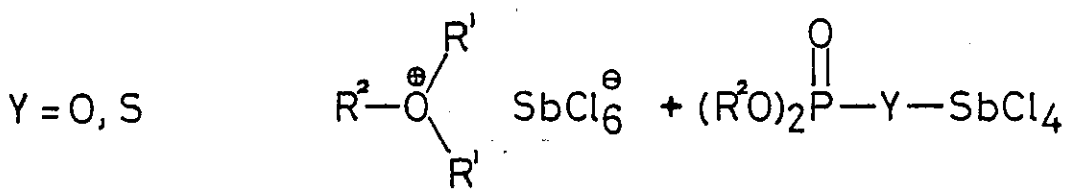
The early $\overset{\ominus}{BF_4}$ salts are highly hygroscopic, and decompose on warming or on standing, but hydrolysis is sufficiently slow to enable the isolation of more stable salts containing less nucleophilic anions, e.g. hexachloroantimonate (X = $SbCl_6$), and 2,4,6,-trinitrobenzenesulphonate (X = $C_6H_2(NO_2)_3SO_3$).[87]



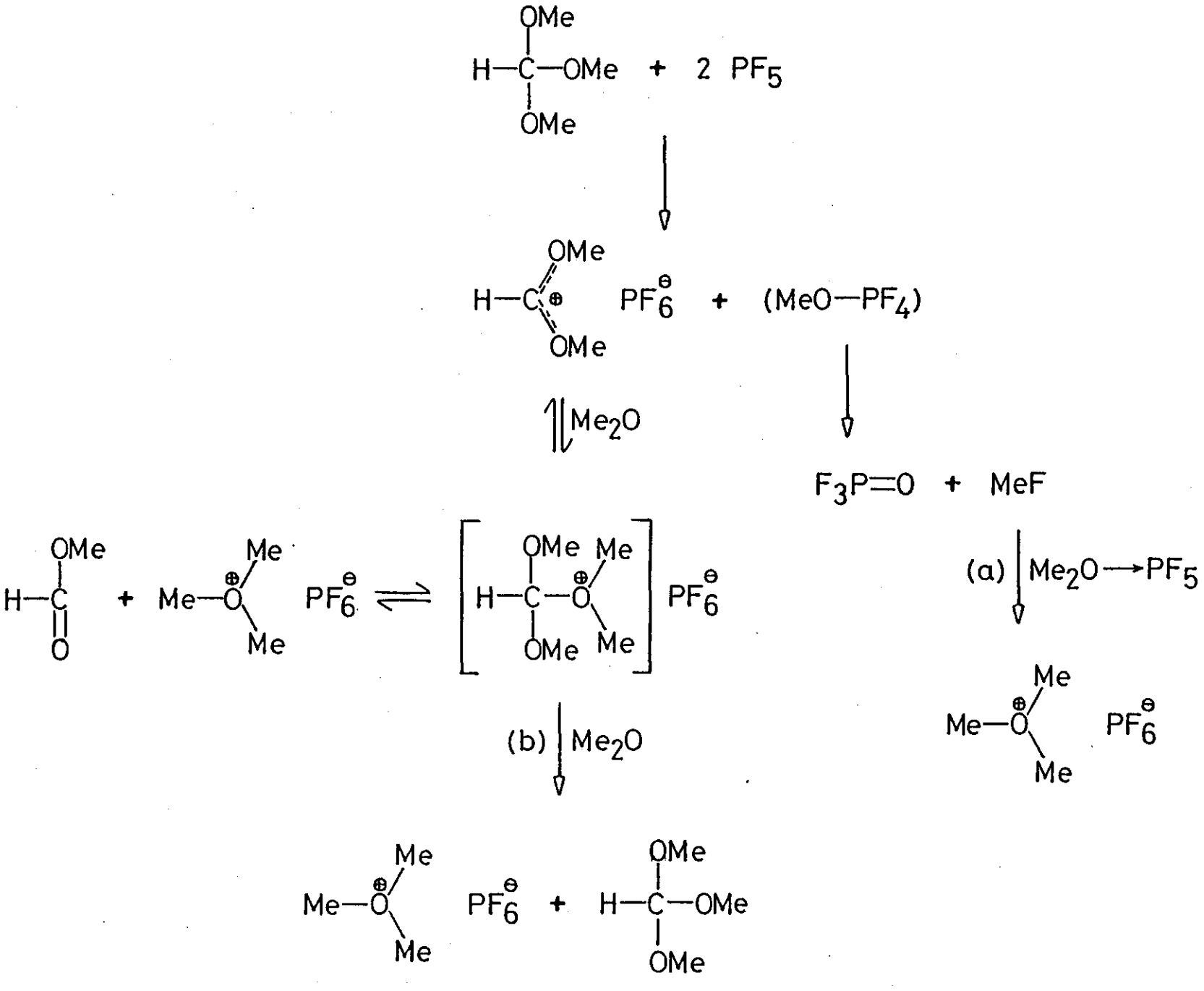
The yields obtained by Meerwein[86, 87] diminished with increasing size of the alkyl group, falling to 30% for the tri-n-propyloxonium salt, and no oxonium salts containing alkyl groups higher than n-butyl have been prepared due to steric hindrance. More recently, however, trialkylesters of phosphoric and monothiophosphoric acids (91) have exhibited a pronounced alkylating ability in the presence of antimony pentachloride.[92] Consequently, ethers have been alkylated in good to high yield, and the success of the reaction is reflected in an appreciable 47% yield of the bulky tri-n-butyloxonium hexachloroantimonate.



(91)

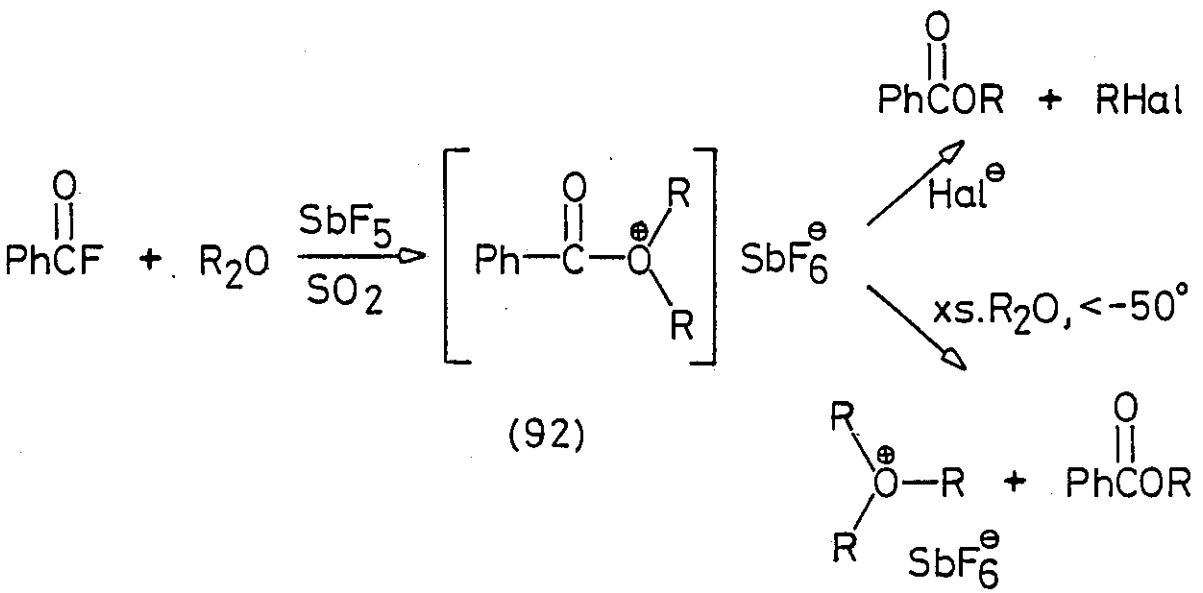


The $SbCl_6^{\ominus}$ salts are more stable, but their utility as alkylating agents is impaired by limited solubility and the need for cold storage. This problem has been alleviated by Olah,[93] who prepared the trimethyl- and triethyloxonium hexafluorophosphates (X = PF_6) by reaction of a trialkyl orthoformate with the corresponding dialkyl ether-phosphorus pentafluoride complex. The very high yield (> 200%) of trimethyl-oxonium salt, based on trimethyl orthoformate used, is shown in Scheme 13 to arise from (a) participation of the dimethyl ether-phosphorous pentafluoride complex in oxonium salt formation, and (b) regeneration of trimethyl orthoformate in the presence of excess ether. These $PF_6^{\ominus}$ salts are stable at room temperature and are soluble in dichloromethane and in liquid sulphur dioxide.



Scheme 13. Preparation of Trimethyloxonium Hexafluorophosphate

The hexafluoroantimonate salts (X = SbF_6) exhibit similar characteristics, and a new synthetic route has been devised.[94] The reaction is based on the cleavage of ethers with acyl halides, which normally gives carboxylic esters and alkyl halides. However, at low temperature with excess ether, competing nucleophilic attack by halide anion is suppressed. Instead, the ether is alkylated by an acyldialkyloxonium intermediate (92) to afford a trialkyloxonium hexafluoroantimonate.



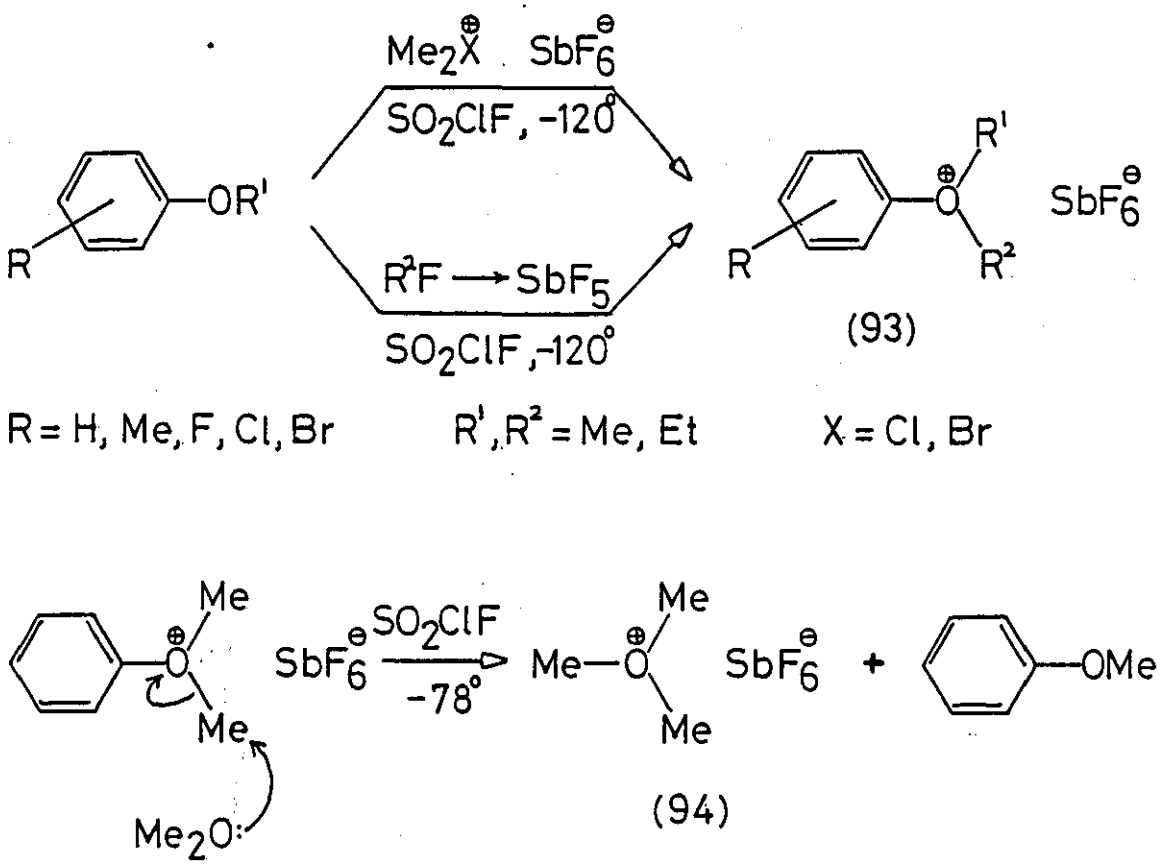
At present, therefore, the $PF_6^{\ominus}$ and $SbF_6^{\ominus}$ salts are considered most convenient for preparative work. They give excellent yields in alkylation reactions, and maintain their integrity without decomposition, and as such are favourable over the less stable $BF_4^{\ominus}$ salts.

Order of stability: $SbF_6^{\ominus} \geqslant PF_6^{\ominus} > SbCl_6^{\ominus} > BF_4^{\ominus}$

Other syntheses of trialkyloxonium salts include the reaction of dialkyloxonium salts with diazoalkanes[95] or with ethyl diazoacetate,[96] alkyl exchange in preformed-trialkyloxonium salts,[97] and the alkylation of ethers with more powerful alkylating agents. e.g. methyl fluorosulphonate,[8] dimethoxycarbenium hexafluorophosphate,[93] dialkylhalonium ions,[98] and alkylcarbenium reagents.[10, 11]

Treatment of various anisoles in sulphuryl chloro-fluoride (SO_2ClF) at -120° with either dialkylhalonium or, preferably,

alkylcarbenium hexafluoroantimonates has given rise to a second class of saturated oxonium salts.[99] These dialkylaryloxonium salts (93) are stable only at low temperatures (-70°), and are transformed into ring-alkylated alkoxybenzenes when warmed to 0° or when a small excess of anisole is present. However, they are strong alkylating agents in reactions with both π- and n-donor bases and thereby provide another route to trialkyloxonium salts. Alkylation is visualised to proceed via intermolecular nucleophilic displacement on the oxonium ion, as exhibited in Scheme 14 for the preparation of the trimethyloxonium salt (94).

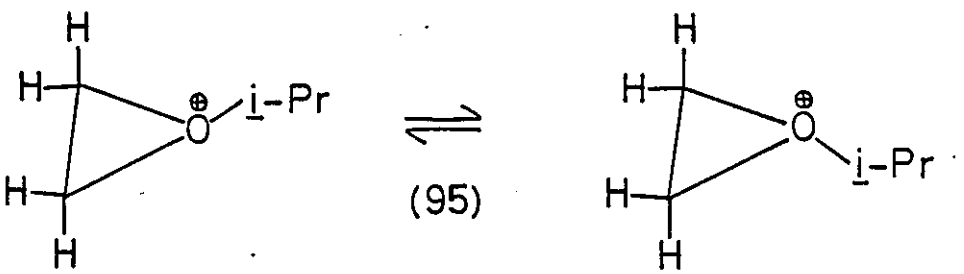


Scheme 14. Dialkylaryloxonium Ions

That the reverse reaction is not observed shows that these dialkylaryloxonium ions are stronger alkylating agents than Meerwein's salts (89), which do not ring-alkylate aromatic substrates.

The structure of trialkyloxonium ions has been studied by low

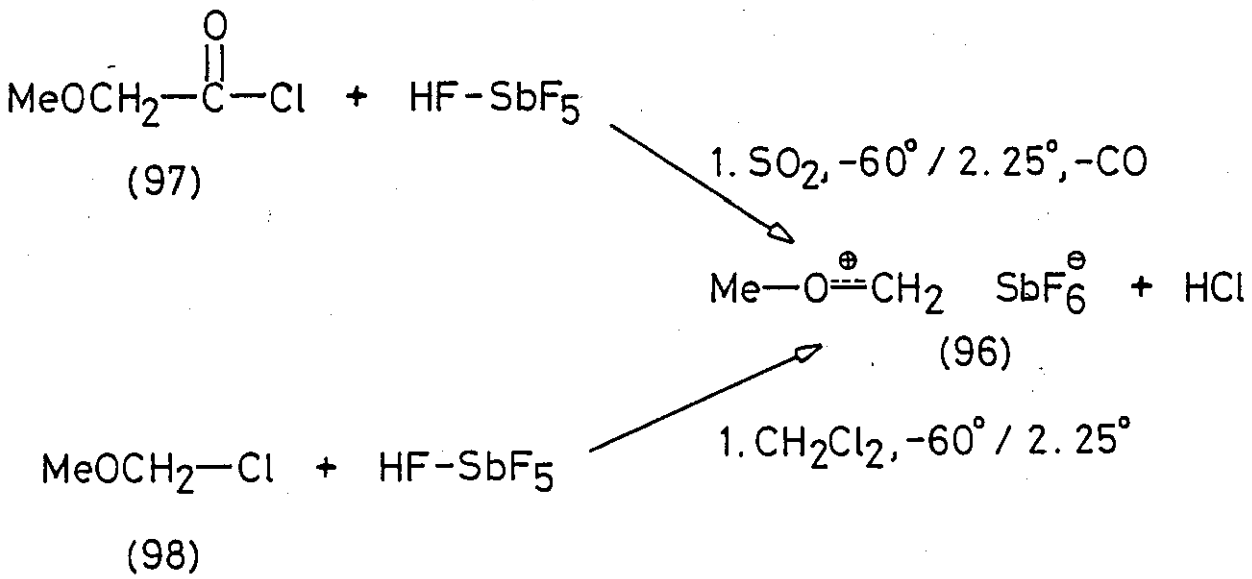
temperature ^{1}H NMR spectroscopy. Lambert and Johnson[100] confirm a tetrahedral stereochemistry. Such configurational stability is lost at ambient temperatures due to rapid thermal inversion of oxygen, as illustrated for the O-isopropyloxiranium ion (95). Calculations indicate an activation energy (E_a) of 10 ± 2 Kcal mol^{-1}.

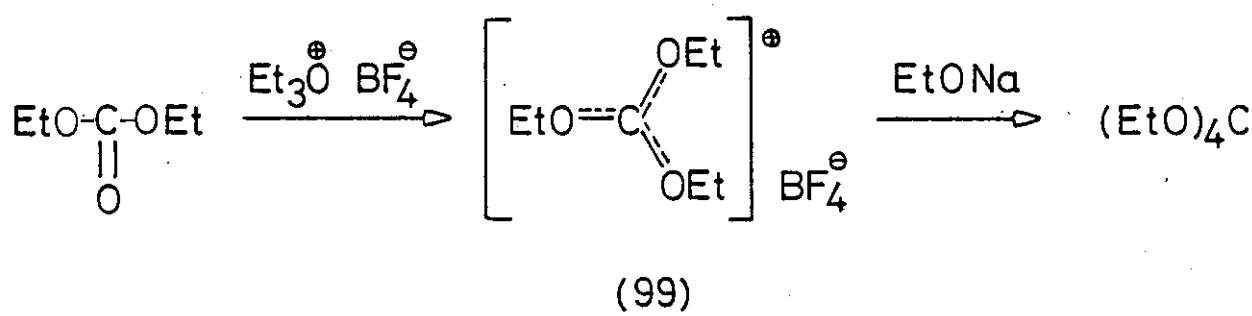


The reactions of trialkyloxonium salts (89) with lone-pair bases have been fully reported,[85, 88, 89] with alkylation of oxygen-, nitrogen-, phosphorus-, and sulphur-containing substrates being effected. A group of unsaturated alkoxylcarbenium ions has been recognised, either directly or indirectly, as a result of these investigations.[101] They are formally derived from the parent carbonyl compound, and further studies have shown some to be powerful alkylating agents.

Thus, although saturated aldehydes and ketones do not readily undergo O-alkylation, the formal O-methyl derivative of formaldehyde has been isolated and characterised as a new methylating agent.[102] Thus, methoxycarbenium hexafluoroantimonate (96) is stable at room temperature, and is sufficiently reactive to methylate benzene in high yield. It is prepared by reaction of anhydrous hexafluoroantimonic acid and either methoxyacetyl chloride (97) or methoxymethyl chloride (98) (see overleaf).

The only success with esters has involved the trialkoxycarbenium salts (99) derived from dialkylcarbonates, in which the cation is highly stabilised by conjugation (see overleaf).[89]

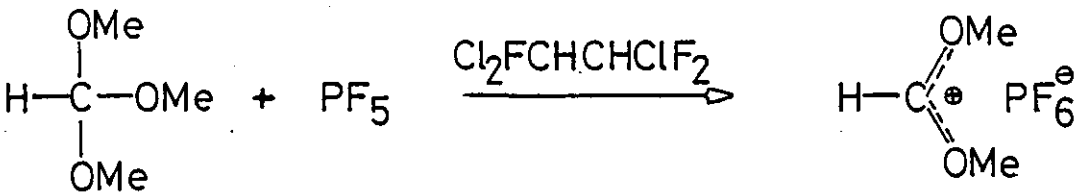




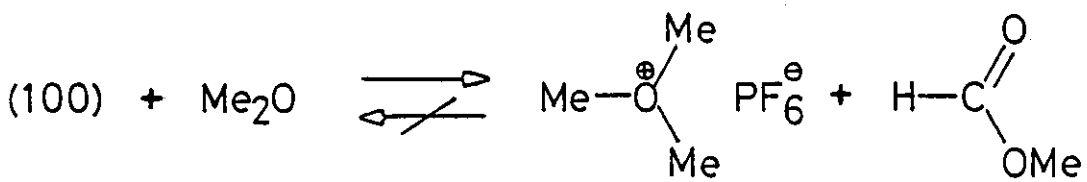
(99)

That carboxylic esters are not alkylated by trialkyloxonium ions seems unexpected for the same stability reasons. Nonetheless, dimethoxycarbenium hexafluorophosphate (100) can be isolated as a stable salt by reaction of trimethylorthoformate and phosphorus pentafluoride.[93] It is a strong methylating agent, witnessed by its reaction with dimethyl ether. The reverse reaction, methylation of methyl formate with trimethyloxonium ion, has not been observed (see overleaf).

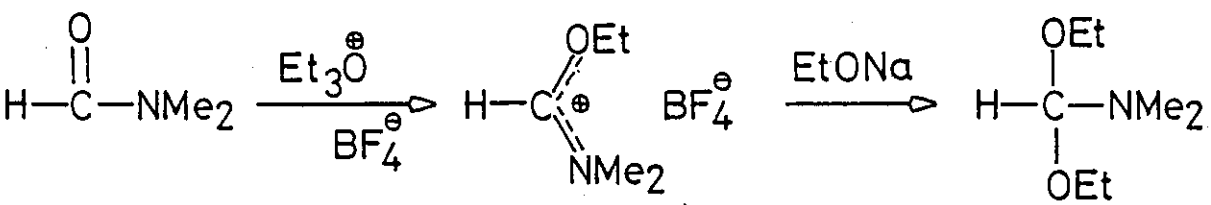
The reactivity of carbonyl compounds with trialkyloxonium ions follows the order, aldehyde < ketone < carboxylic ester < lactone < amide < lactam. Compounds containing the amide function have been most useful synthetically, with preferential alkylation of the carbonyl oxygen being observed. The resulting imidic ester salts (101) undergo



(100)

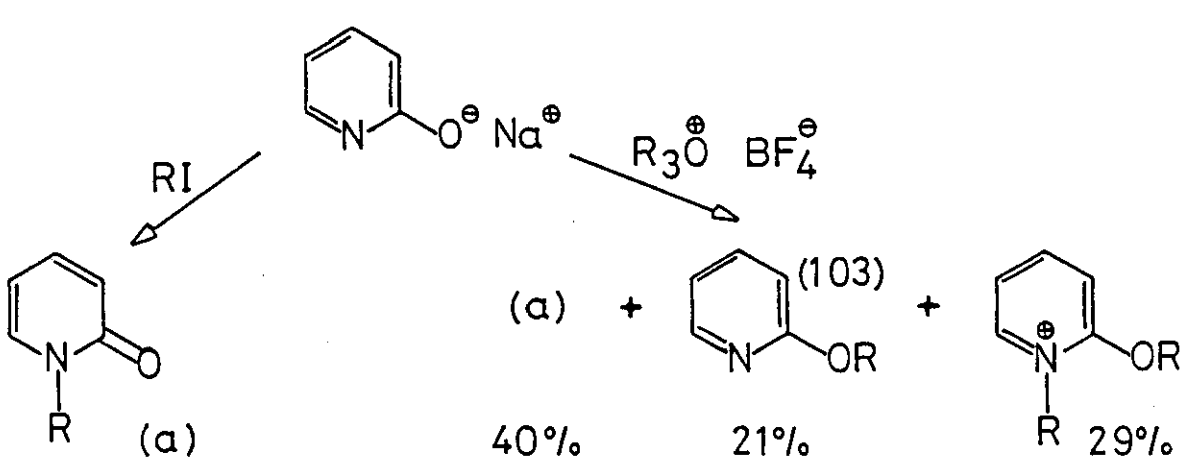


a number of transformations,[89] including formation of the previously unknown amide acetals (102).

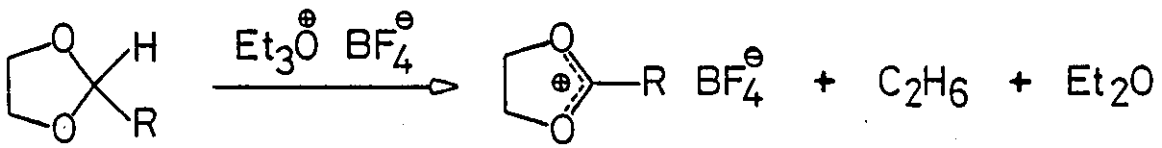


(101) (102)

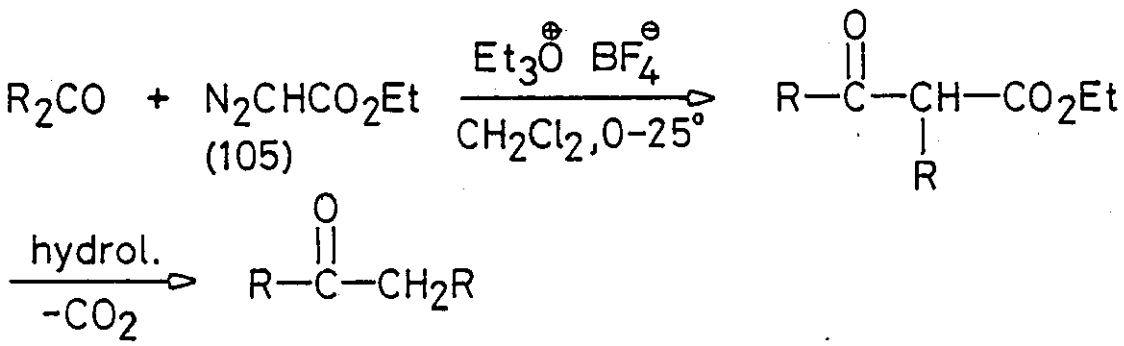
In general, trialkyloxonium salts display an affinity for oxygen-containing groups, i.e. the site of highest electron density, in reaction with ambifunctional compounds. As a result, appreciably greater proportions of O-alkylated products, e.g. (103), are obtained than with less strongly electrophilic reagents such as alkyl halides.[89]



The alkylating ability of oxonium ions has been appropriately stressed, but alternative uses in synthesis have been found. Thus, triethyloxonium tetrafluoroborate can function as a hydride ion acceptor in the formation of 1,3-dioxolenium salts (104),[103] but as a Lewis acid catalyst in the homologation of ketones by one carbon atom using ethyl diazoacetate (105).[104]



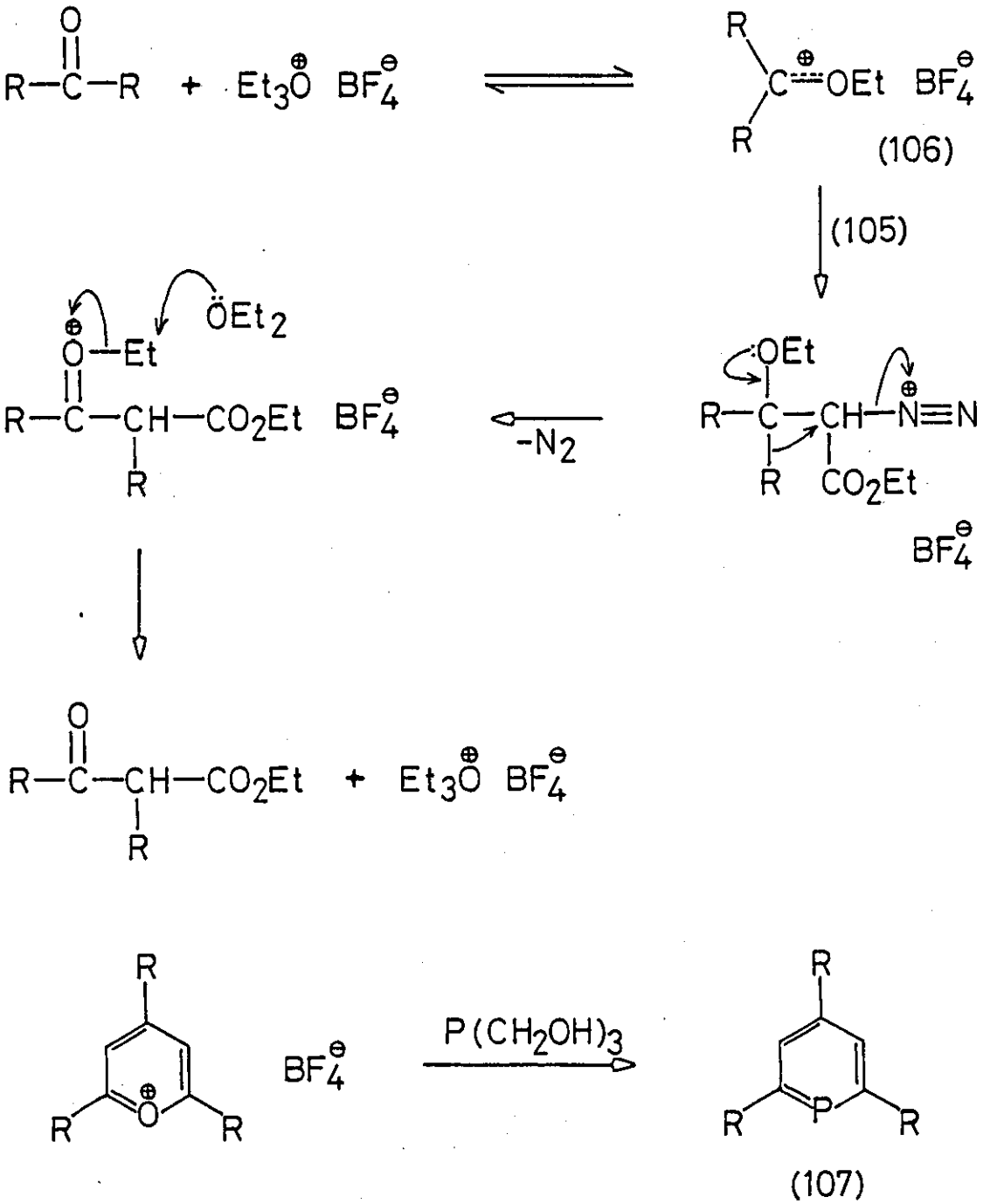
(104)



In the latter example, the rate-determining step is O-alkylation of the carbonyl group by the triethyloxonium ion to yield a monoalkoxycarbenium ion (106). However, it was stated earlier that ketones do not readily undergo such reactions, and a large excess of catalyst (1.5-3 equiv.) is needed, presumably to provide a reasonable concentration of the dialkylethoxycarbenium ion (see overleaf).

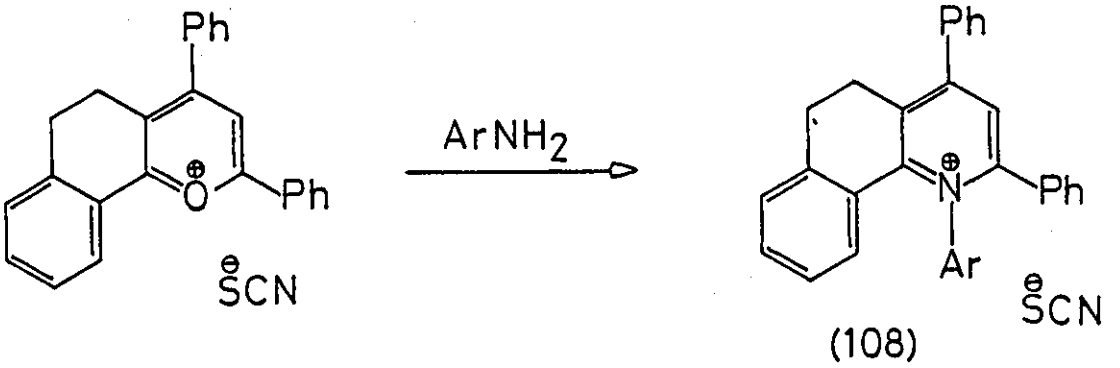
Finally, mention is made of the increasing utility of pyrylium salts in providing new and improved synthetic routes to a range of products. Their choice is based to a considerable extent on the ease with which they are converted into other heterocycles. For example, phosphorins of type (107)[105] have been used in the preparation of highly substituted biaryls[14] (see overleaf).

Katritzky[106, 107] has modified certain well-established procedures by the use of pyridinium salts. Thus, the standard conversion of aryl

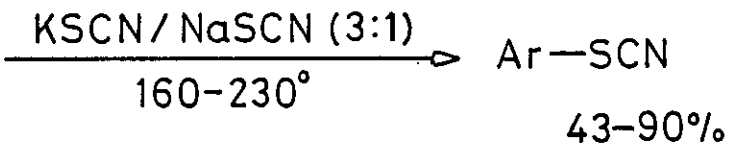


amines into aryl thiocyanates via diazonium salts suffers from many side-reactions, but N-aryl-dihydrobenzoquinolinium salts (108) thermolyse smoothly to give the desired thiocyanates[106] (see overleaf).

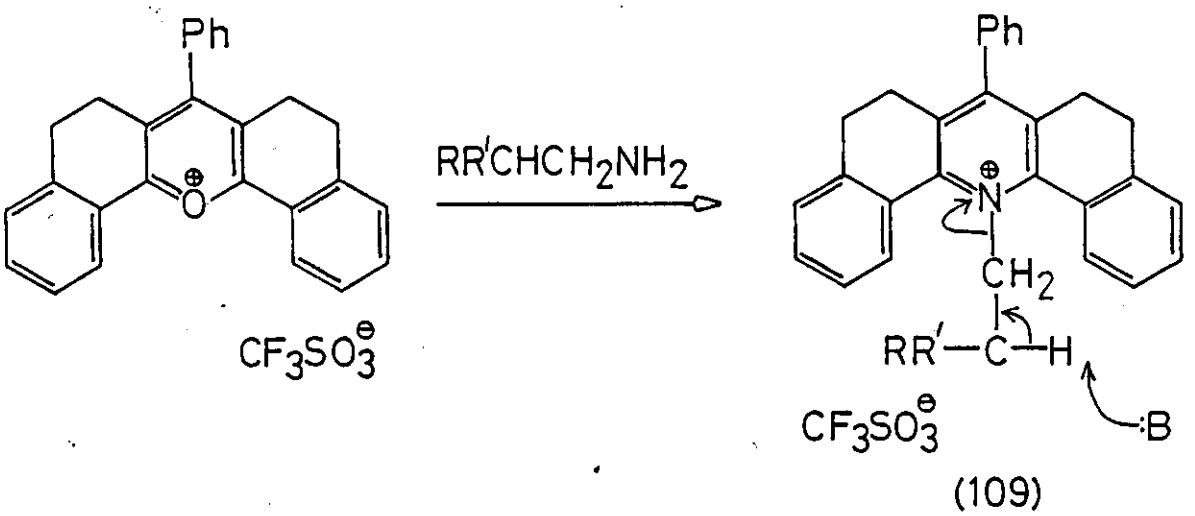
Similarly, the traditional conversion of primary amines into terminal olefins by Hofmann exhaustive methylation requires several stages and vigorous conditions. The reaction has been mediated by the transformation of these amines into acridinium salts (109),



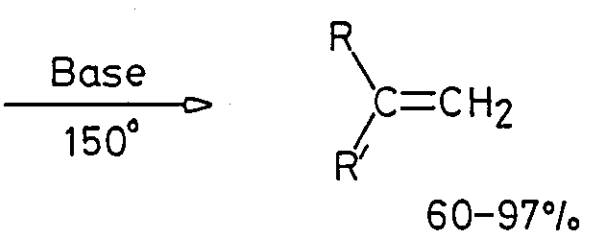
(108)



followed by elimination at 150° in the presence of a non-nucleophilic base, e.g. triphenylpyridine.[107]



(109)



2.2 ALKYLATING AGENTS

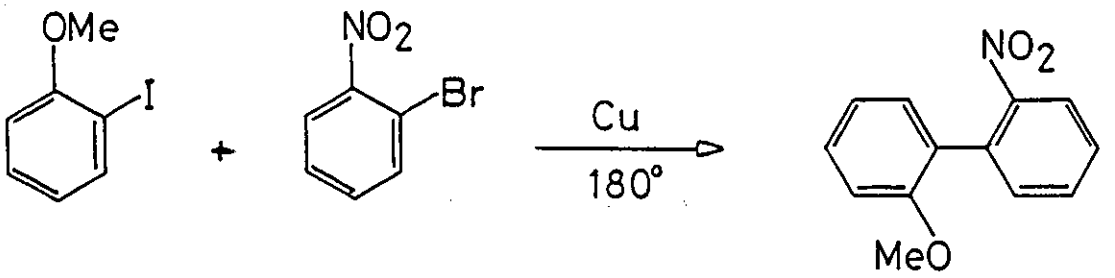
O-ALKYLDIBENZOFURANIUM SALTS

The synthetic utility of reagents such as the alkylcarbenium salts[9, 10, 11] suffers from the unconventional nature of the solvents required, and is restricted by practical difficulties associated with preparation and handling. In addition, whilst triethyloxonium tetrafluoroborate has found widespread use, the trimethyloxonium salt is less conveniently prepared, hydrolyses more rapidly, and is almost insoluble in common solvents such as dichloromethane.

Attempts to prepare the diphenylmethyloxonium ion by treatment of diphenyl ether with the methyl fluoride-antimony pentafluoride complex resulted only in methylation of the aromatic rings.[99] However, Heaney[108] and Kemp[90] have reported the synthesis and electrophilic properties of O-methyldibenzofuranium tetrafluoroborate (110). This modified diaryloxonium salt is potentially a more powerful methylating agent than trimethyloxonium ion due to the stability of the leaving group, dibenzofuran, and comparisons can be drawn with methyl fluorosulphonate.[8] Good yields of methylated derivatives of weak nucleophiles have been obtained when the reagent is generated *in situ* in dichloromethane. Some examples of reactions with lone-pair bases are collected in Scheme 15 (see overleaf).

In order to study further the chemistry of this new reagent, the established[108] synthetic sequence was adopted. The significant step involves the formation of 2-methoxy-2'-nitrobiphenyl (47) by a mixed Ullmann reaction between *o*-iodoanisole and *o*-bromonitrobenzene in the presence of a large excess of copper powder. Whilst temperatures in excess of 200° have been considered suitable,[90] the possibility of nitro group reduction has been noted,[25] and best results were reproduced at a temperature of about 180°[109] (see overleaf).

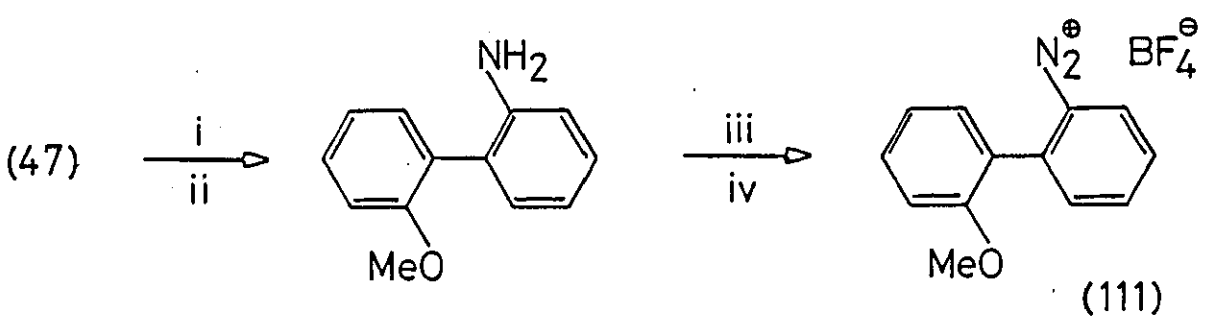
Scheme 15. Reactions of O-Methyldibenzofuranium Tetrafluoroborate



(47)

Activation of the copper metal, according to the method of Kleiderer and Adams,[26] produced no improvement in yield, and the symmetrical adduct, 2,2'-dinitrobiphenyl (33), was always obtained as the major by-product.

The nitro-compound was reduced with hydrazine hydrate in the presence of palladium-on-charcoal to give 2-amino-2'-methoxybiphenyl. Subsequent treatments with sodium nitrite in the presence of aqueous fluoroboric acid gave the bright yellow 2'-methoxybiphenyl-2-yldiazonium tetrafluoroborate (111) in a near quantitative yield. Although the oxonium salt (110) has not been isolated, it is thought to arise by intramolecular cyclisation of this diazonium salt prior to any methylation or decomposition.



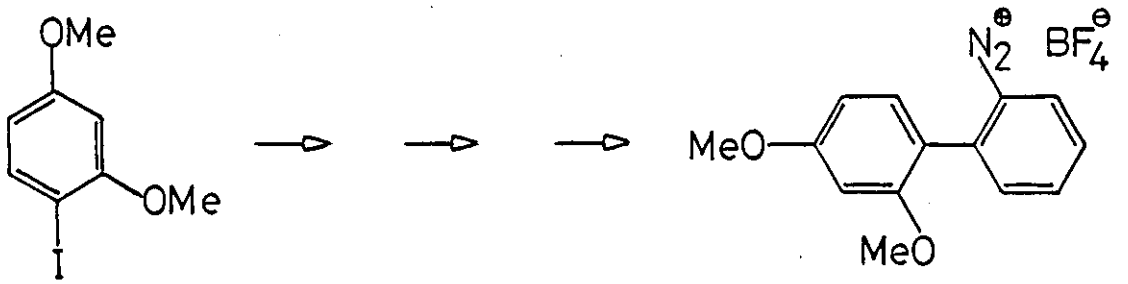
(111)

i $N_2H_4.H_2O$; ii 10% Pd-C / EtOH ; iii HBF_4 / THF

iv $NaNO_2$ / H_2O , 0°

The diazonium salt may be stored <u>in vacuo</u> over phosphorus

pentoxide for a safe maximum of 2-3 days at room temperature. In an attempt to improve the stability, an electron-releasing substituent was introduced into the biphenyl moiety. Thus, 4-iodoresorcinoldimethylether was prepared by dimethylation of resorcinoland subsequent iodination, and incorporation into the above synthetic sequence produced the desired 2',4'-dimethoxybiphenyl-2-yldiazonium tetrafluoroborate (112).

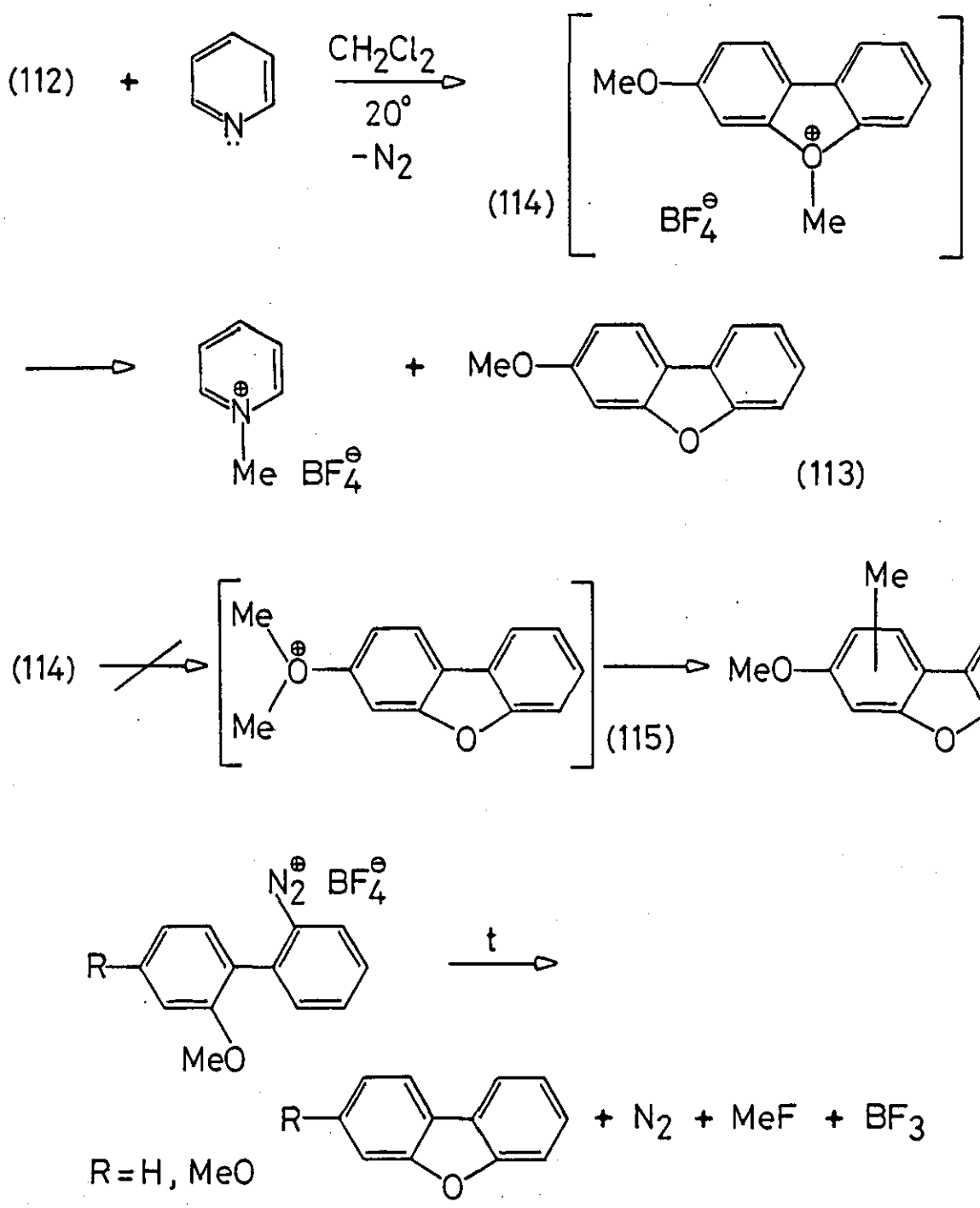


(112)

That this salt could function as a precursor to a methylating agent was shown by its reaction with pyridine in dichloromethane. The formation of N-methylpyridinium tetrafluoroborate was confirmed by isolation of the characteristic double picrate salt. In addition, 3-methoxydibenzofuran (113) was recovered quantitatively, indicating that no rearrangement of the intermediate oxonium ion (114) had occurred; any presence of a dialkylaryloxonium species (115) would be inferred from the formation of ring-alkylated alkoxybenzenes[99] (see overleaf).

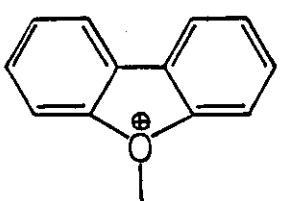
In the absence of nucleophiles, the diazonium salts decompose to the dibenzofuran, with liberation of nitrogen and the volatile products methyl fluoride and boron trifluoride. (see overleaf).

To compare the relative stabilities, control experiments were performed in both light and dark conditions, with each sample stored in vacuo over phosphorus pentoxide. With reference to the typical N ≡ Nstr. vibrations at about 2270 cm^{-1}, and to other changes in the



infrared (IR) spectra with time, it was possible to conclude that the presence of an electron-donating substituent does confer a small improvement in storage life. However, the effect was more enhanced at low temperatures, the dimethoxy salt retaining its integrity for a minimum of 20 days at -20° in the dark. The general photosensitivity of aryldiazonium salts[110] was reflected in a faster rate of decomposition for those samples subjected to the light.

For safety reasons, tetrafluoroborates are made when it becomes necessary to isolate a diazonium salt, but more weakly nucleophilic counter ions can be used, and thereby provide a second route to improving stability. Best results have been achieved with the 2,4,6-trinitrobenzenesulphonate derivative, which could be stored *in vacuo* over phosphorus pentoxide for 10-12 days.[90] Kemp was also able to isolate a solid decomposition product which proved to be a potent methylating agent, but the existence of a stabilised oxonium salt (116) could not be substantiated due to complete insolubility in the common ^1H NMR solvents.



Me $C_6H_2(NO_2)_3SO_3^{\ominus}$ (116)

Hexafluoroantimonates ($SbF_6^{\ominus}$) have been reported to exhibit good solubility characteristics,[94] but a sample (25 mg) of the corresponding diazonium salt was incompletely dissolved in dichloromethane (5 ml). However, both stability and solubility were appreciably enhanced by use of the orange tetraphenylborate ($BPh_4^{\ominus}$) salt. Some comparison data are tabulated overleaf.

The tetraphenylborate salt is therefore considered most appropriate for ^1H NMR studies, although strong aromatic absorptions present a disadvantage. Under perfectly anhydrous conditions, the oxonium salt (117) should be highly stable due to the virtually non-nucleophilic properties of the anion (see overleaf).

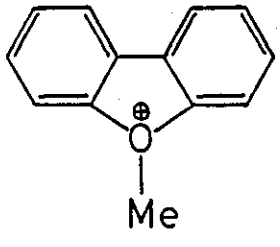
Table 1. Stability and Solubility of 2'-Methoxybiphenyl-2-yldiazonium Salts

Anion	Stability[a]/days	Solubility[b]/mg ml^{-1}
$BF_4^{\ominus}$	2-3	10
$SbF_6^{\ominus}$	2-3	<5
$C_6H_2(NO_2)_3SO_3^{\ominus}$	10-12	-
$BPh_4^{\ominus}$	15-20[c]	>50

[a] In vacuo over P_2O_5 at room temperature.

[b] In dichloromethane (CH_2Cl_2).

[c] Several weeks at -20°.

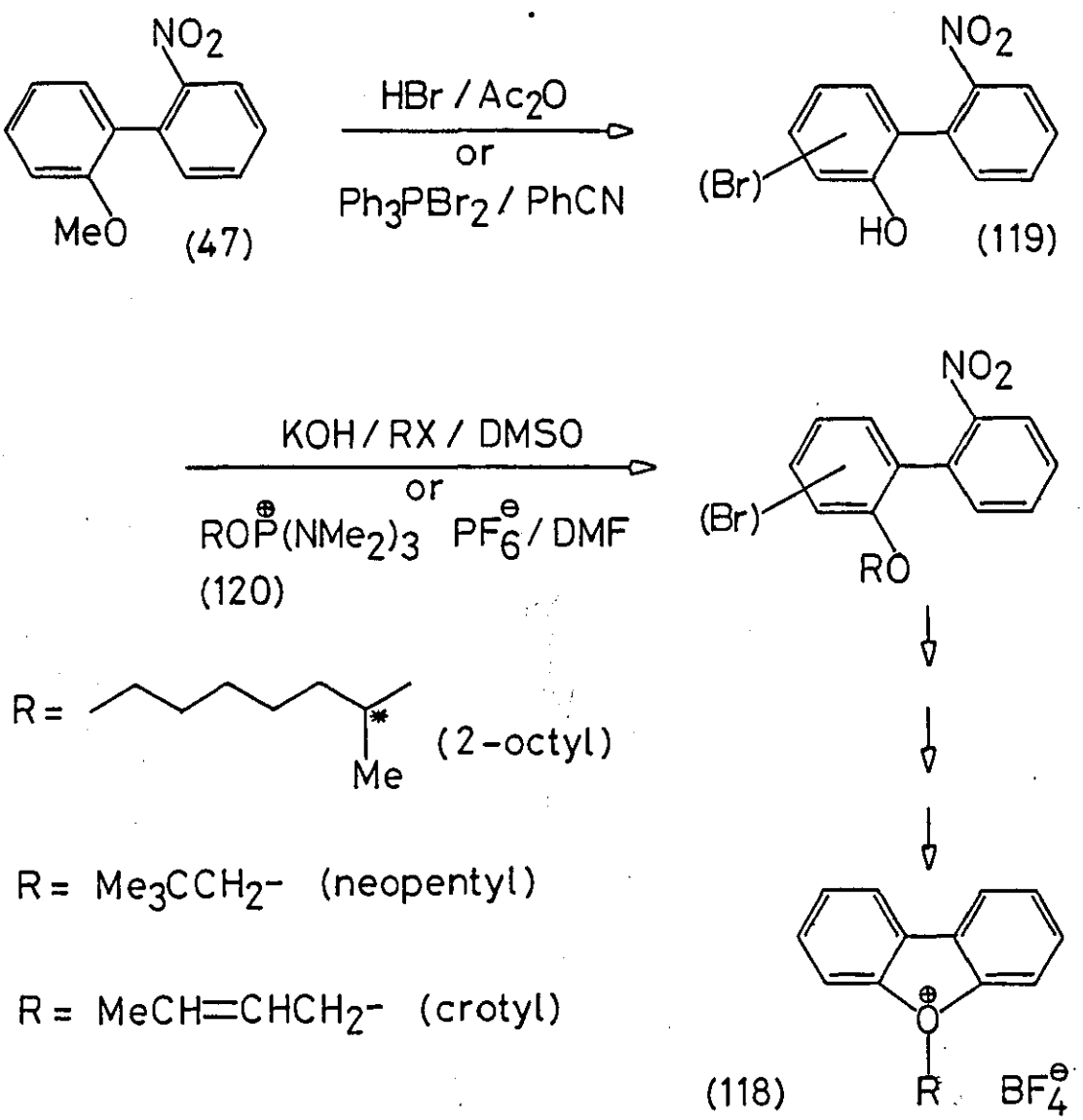


Me $BPh_4^{\ominus}$ (117)

In dichloromethane the diazonium salt decomposed with evolution of a gas, and a dark solid was recovered which showed a strong singlet at δ3.73. This chemical shift would seem to be insufficiently low field for the expected oxonium ion, and further examination is warranted.

So far the wide diversity of alkylating agents discussed (see Chapter 2.1) have been successful only for the transfer of methyl and ethyl groups. However, the introduction of higher alkyl groups can now be envisaged using a series of 2-alkoxy-2'-nitrobiphenyls as precursors to the corresponding O-alkyldibenzofuranium salts (118). Thus, 2-methoxy-2'-nitrobiphenyl (47) can be demethylated either by reaction with hydrogen bromide in refluxing acetic acid,[111] or with

the exclusion of ring brominated impurities by reaction with triphenyldibromophosphorane in hot benzonitrile.[112] The resulting 2-hydroxy-2'-nitrobiphenyl (119) can be alkylated[90] either by a Williamson-type ether synthesis using powdered potassium hydroxide and an alkyl halide in dimethyl sulphoxide (DMSO), or by use of an alkoxy-tris (dimethylamino) phosphonium hexafluorophosphate (120) in DMF[113] for the transfer of alkyl groups susceptible to racemisation, e.g. 2-octyl, or to rearrangement, e.g. neopentyl and crotyl. Any arylbromides are dehalogenated during subsequent reduction in the presence of hydrazine hydrate.[114] See Scheme 16.

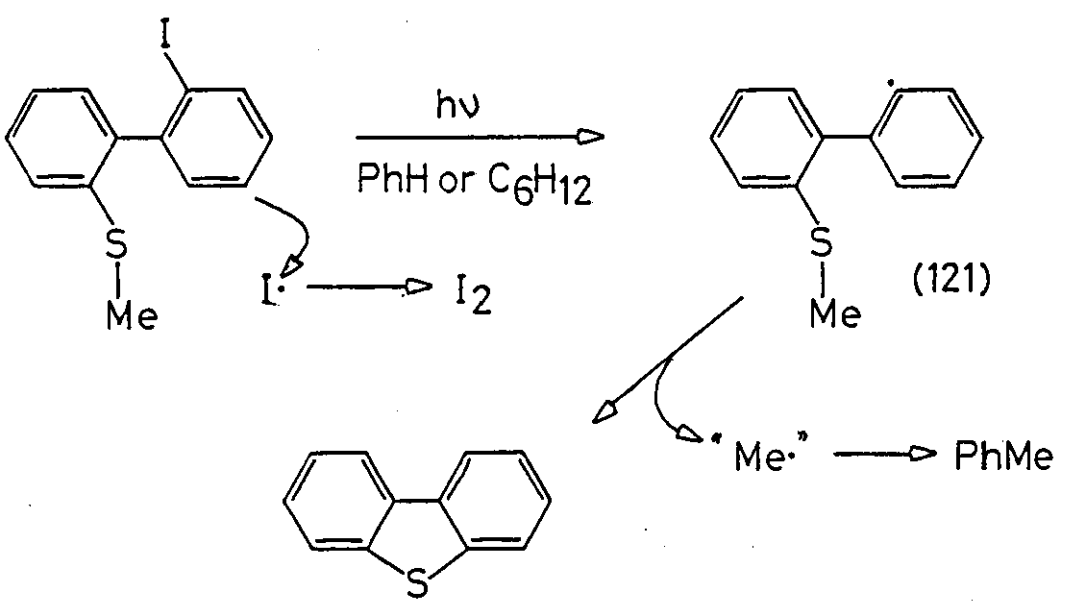


Scheme 16. Proposed Route to O-Alkyldibenzofuranium Salts

The ethoxy diazonium salt has proved successful in reactions with pyridine and α-pyridone, but preliminary tests with the isopropyl derivative have not yielded any alkylated substrates.[90]

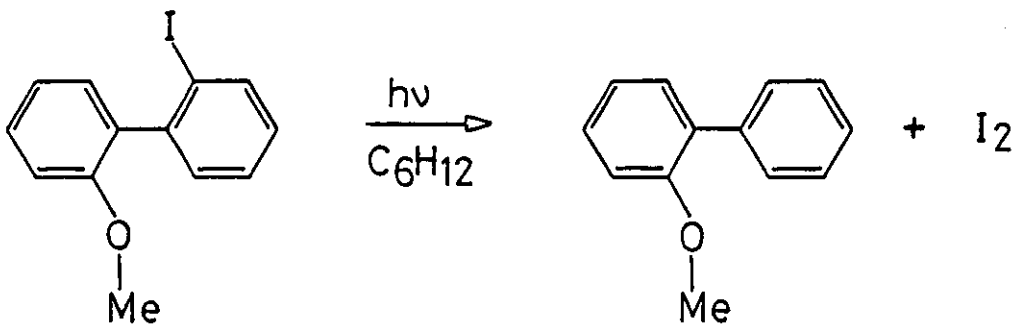
MECHANISMS OF RING CLOSURE AND ALKYLATION (PART 1)

A study of the radical reactions of organic sulphides, and a comparison with oxygen analogues, has provided evidence that 2-alkoxybiphenyl-2'-yldiazonium salts undergo ring closure by a cationic mechanism. Thus, Kampmeier and Evans[115] have reported chemical evidence for the involvement of neighbouring sulphur in reactions of the 2-(2'-methylthio)biphenylyl radical (121).

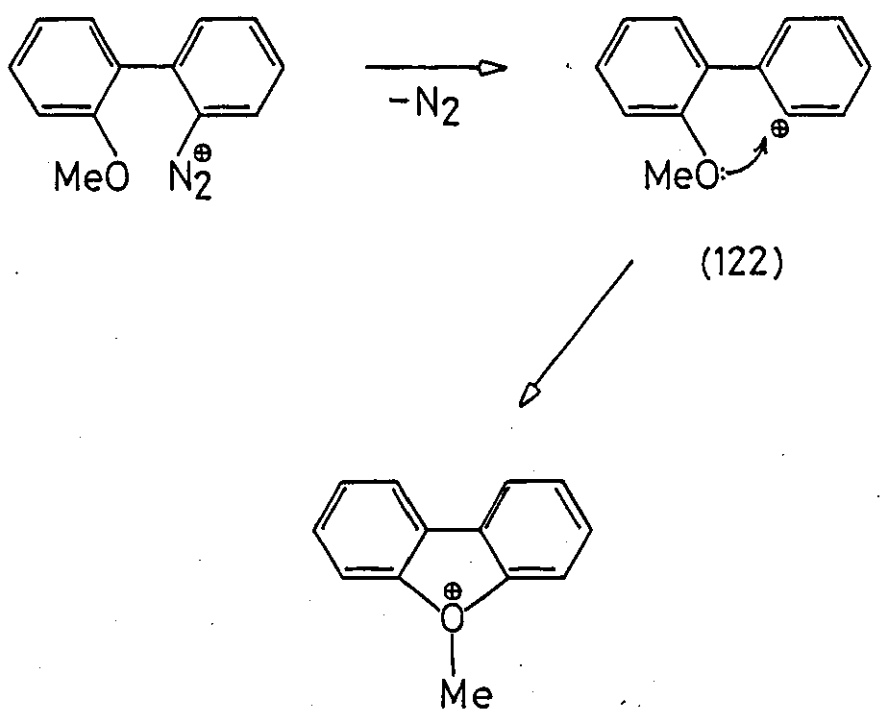


However, photolysis of 2-iodo-2'-methoxybiphenyl under identical conditions follows straightforward radical chemistry, i.e. iodine and the hydrogen transfer product, 2-methoxybiphenyl, are obtained (see overleaf).

That no similar product derived from hydrogen abstraction is observed in reactions of the diazonium salt indicates that radical chemistry is not involved. Instead, identification of the by-product



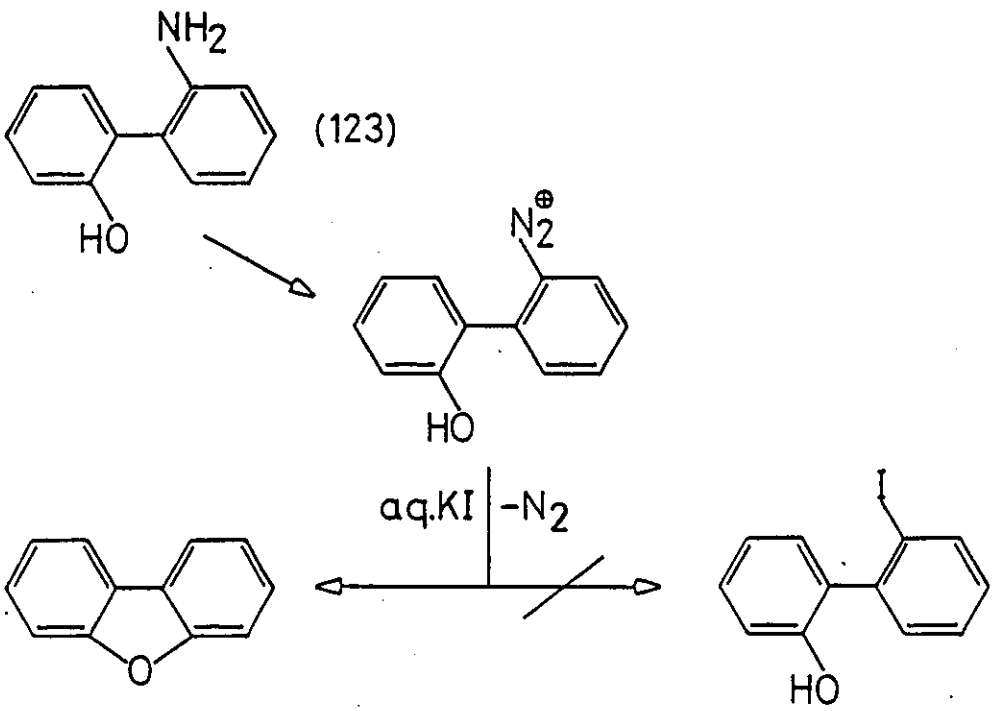
as dibenzofuransuggests that the diazonium salt collapses by an intramolecular cyclisation via the oxonium salt.



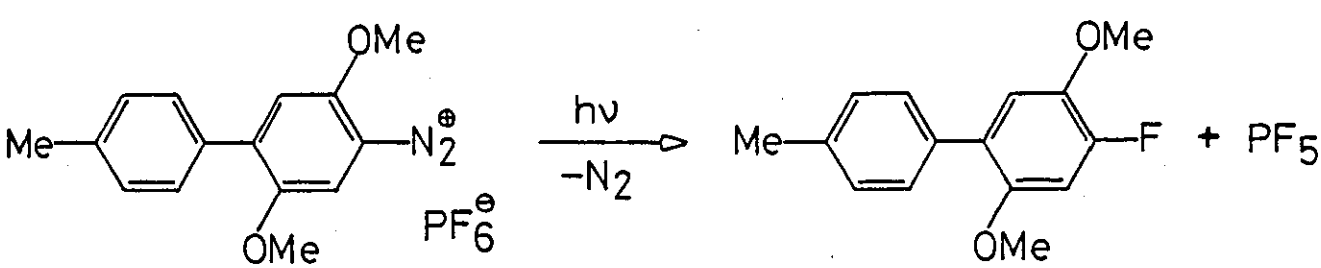
Such heterolytic dediazoniations are generally considered the only instances of an S_N1 mechanism in nucleophilic aromatic substitution, and two pieces of evidence indicate that oxygen performs an appreciable neighbouring group role in the intermediate

aryl cation (122).

1. Treatment of the water soluble diazonium salt derived from 2-amino-2'-hydroxybiphenyl (123) with potassium iodide gives dibenzofuran, i.e. ring closure occurs in preference to iodination.[116]



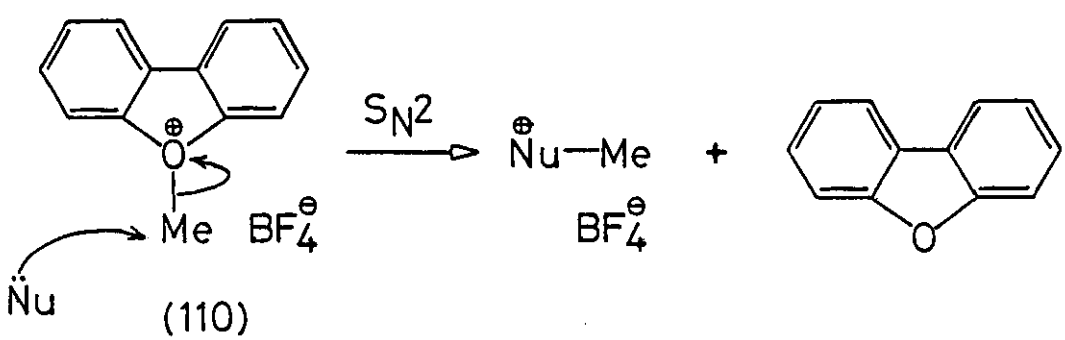
2. Thermolysis or photolysis of usually stable diazonium tetrafluoroborates represents the best method of introducing fluorine into an aromatic ring. This Schiemann reaction is successful also with other complex metal fluoride anions, as illustrated by the photolysis of 2,5-dimethoxy-4-(p-tolyl)benzene diazonium hexafluorophosphate (124).[117]



(124)

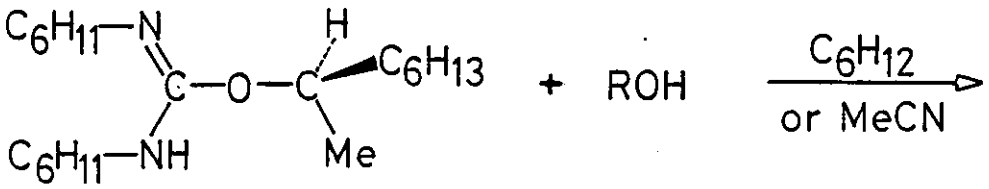
The Lewis acid produced, e.g. BF_3, PF_5, is capable of initiating the ring opening of epoxides, so that arenediazonium salts have been developed as photoinitiators for the cationic polymerisation of epoxy resins.[118] However, decomposition of the 2-alkoxybiphenyl-2'-yldiazonium salts occurs readily at room temperature, and no aryl fluorides have been detected.

As methyl and ethyl cations are unlikely to exist in any free state, the transfer of simple primary alkyl groups probably proceeds through an S_N2 displacement on the O-alkyldibenzofuranium ion, e.g. (110). However, the possibility that the active alkylating species is the aryl cation (122), with nucleophilic attack and cyclisation being concerted, cannot be excluded.

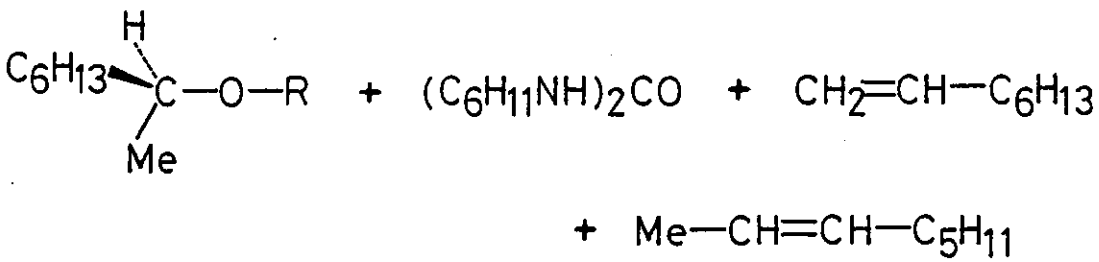


With more stable secondary and tertiary alkyl systems, alternative mechanisms can be expected. Thus, Vowinkel and Jaeger[119] have shown that the alkylation of both phenol and acetic acid using optically active O-(2-octyl)-N,N'-dicyclohexylisourea (125) proceeds with 100% inversion (see overleaf).

Bond cleavage precedes formation of the new bond, so that the intermediate 2-octyl cation can eliminate a proton to form 1- and 2-octene. Formation of the ether and ester by a conventional S_N1 reaction would be expected to result in racemisation of the 2-octyl group, so the observed total inversion has been explained on the basis of ion-pair participation. Similar behaviour may be anticipated for an



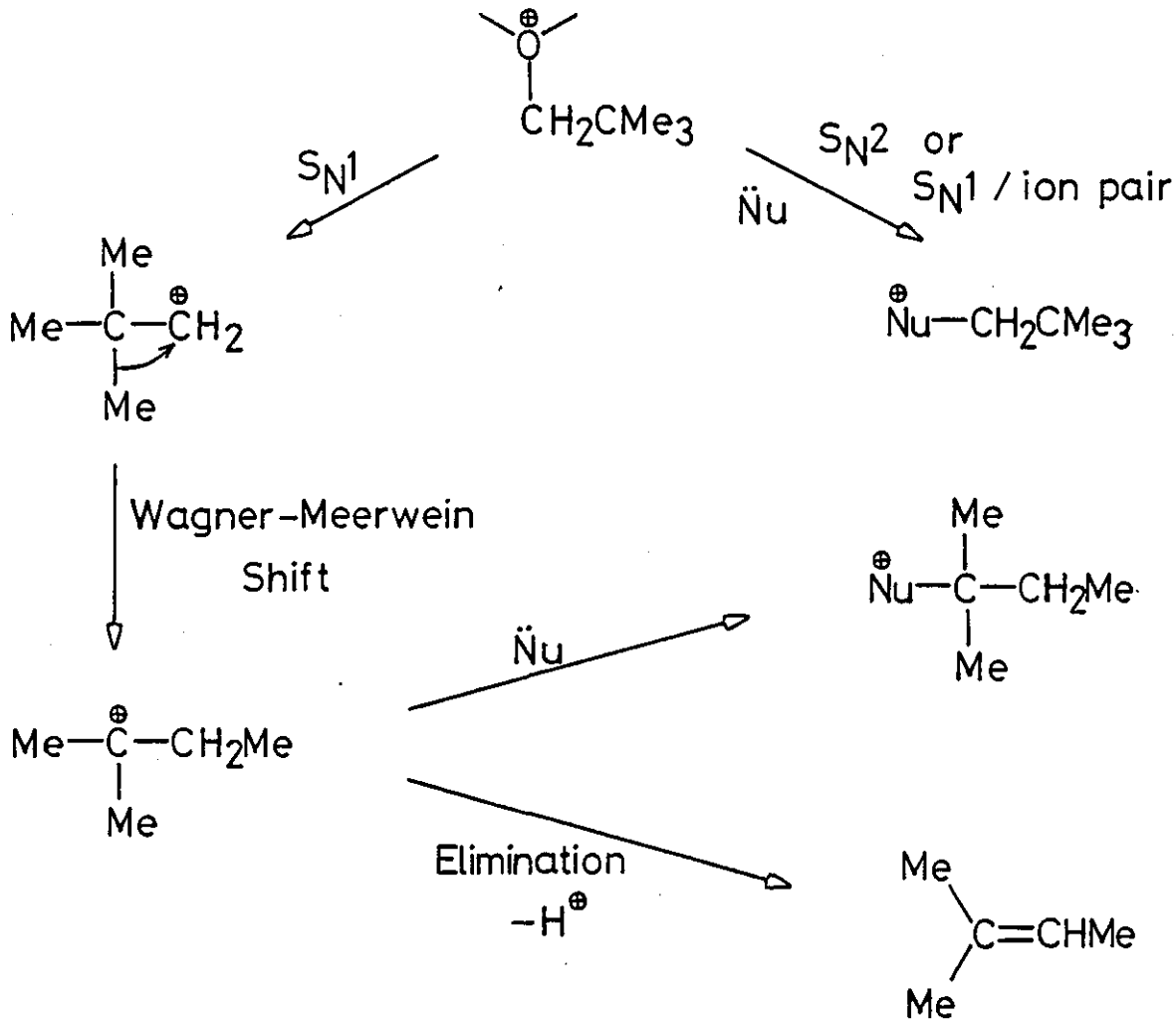
(125) R = Ph, Ac



O-(2-octyl)-dibenzofuranium species, whilst for alkyl groups such as isopropyl[90] and neopentyl the desired alkylations may also be complicated by rearrangements and/or eliminations. Possible reaction pathways for a neopentyloxonium ion are depicted in Scheme 17 (see overleaf).

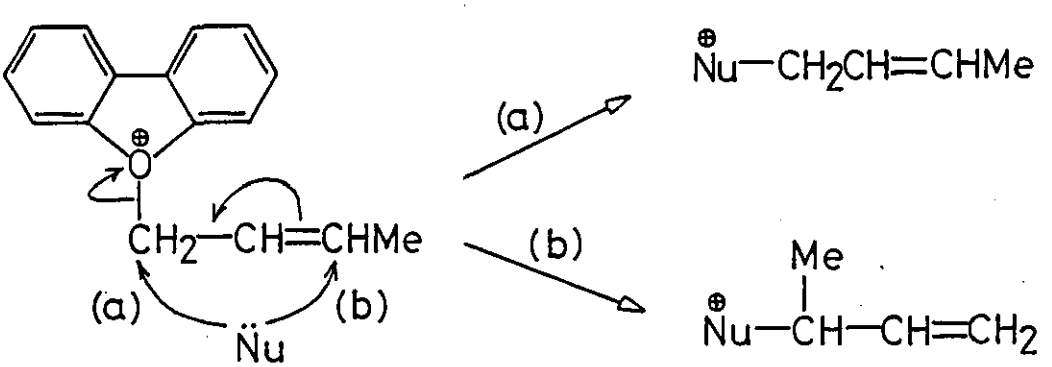
Combination of the good leaving group ability of dibenzofuran and the resonance stability of the benzyl cation suggests that the O-benzyldibenzofuranium ion would react via an S_N1 mechanism. No rearrangement is possible, but reaction may not be viable with the more weakly nucleophilic substrates. So far, 2-benzyloxy-2'-nitrobiphenyl has been reduced without concomitant cleavage of the benzyl group, but diazotisation of the amine has met with some difficulty. Possibly aprotic conditions are needed to avoid acid-catalysed hydrolysis of the ether (cf. Chapter 3.2).

Additional information regarding reaction mechanisms is expected to arise from studies involving the crotyl (2-butene) group, which possesses two possible sites for reaction with nucleophiles. The particular reaction pathway should be deducible from the nature of the



Scheme 17. Reaction Pathways of a Neopentyloxonium Salt.

alkylated products, as illustrated below for an S_N2 mechanism.



Crotyl bromide, prepared according to Downie[120] via the alkoxy-tris(dimethylamino)phosphonium bromide, alkylated 2-hydroxy-

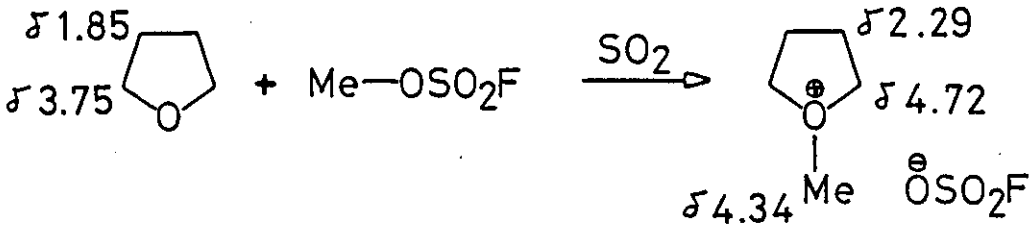
2'-nitrobiphenyl (119) without rearrangement (cf. path a.). However, subsequent treatment with hydrazine hydrate resulted in simultaneous reduction of the double bond and isolation of 2-amino-2'-n-butoxybiphenyl. Use of acid stannous chloride in acetic acid gave inconclusive results. Since there is usually a significant difference between the rate of catalytic hydrogenation of an aromatic nitro group and that of a nonaromatic double bond in the same molecule,[121] this may prove the method of choice. Interruption of the reaction after uptake of the theoretical amount of hydrogen would give the amine with the double bond intact.

It now appears evident that whilst the proposed O-alkyldibenzofuranium salts are potentially powerful alkylating agents, for higher alkyl groups modifications to the established synthetic sequence are necessary, and unwanted side-reactions are likely during the ultimate interactions with nucleophiles. Clearly, further investigations are required.

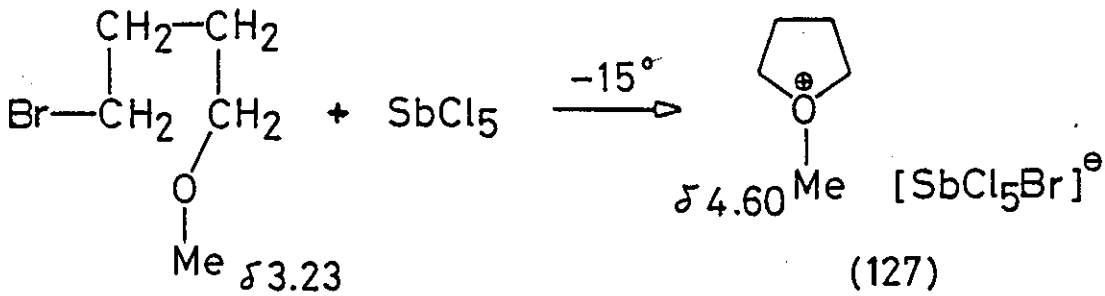
SOME REACTIONS OF O-METHYLDIBENZOFURANIUM SALTS

At present some conflict exists with regard to the chemistry of O-methyltetrahydrofuranium salts. Published syntheses include the reactions of tetrahydrofuran (THF) with methyl iodide and silver tetrafluoroborate[100] or with methyl fluorosulphonate,[8] and the intramolecular cyclisation of 1-bromo-4-methoxybutane in the presence of antimony pentachloride.[122] ^{1}H NMR chemical shifts for the fluorosulphonate (126) and bromopentachloroantimonate (127) salts are significantly deshielded relative to THF (see overleaf).

Kemp[90] has reported the conversion of THF into the O-methyl tetrafluoroborate derivative by reaction with the 2'-methoxybiphenyl-2-yldiazonium salt (110) in the presence of excess THF, and suggests that subsequent reaction with nucleophiles, e.g. pyridine, proceeds by demethylation.



(126)



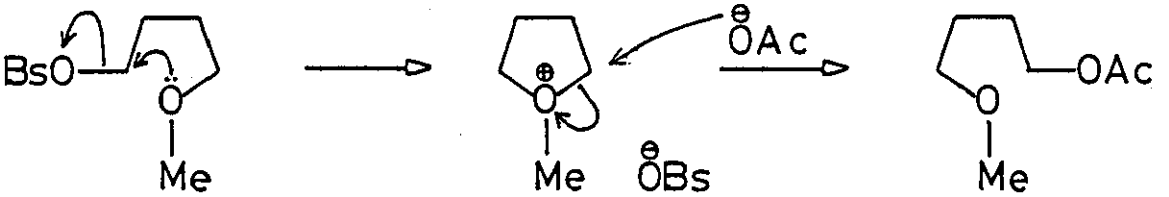
(127)

However, it has been demonstrated[123] that nucleophilic attack on 5-membered cyclic onium salts leads mainly to ring opening, and that it is the analogous reactions with 6-membered rings which lead largely to displacement of an exocyclic methyl group. The role of 5- and 6-membered cyclic methyl oxonium ions as intermediates in ethanolysis, acetolysis and reduction reactions has been evaulated by Allred and Winstein.[124] The possibility for neighbouring group participation in the solvolysis of alkoxyalkyl sulphonates affords an enhanced rate of reaction, as depicted in Scheme 18 (see overleaf).

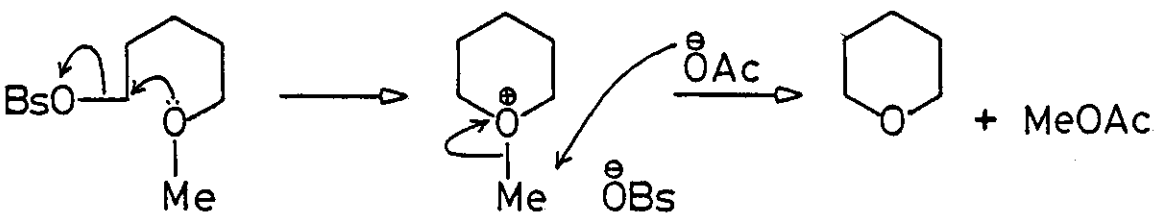
Any isolation of an O-methyltetrahydrofuranium species in the presence of excess THF seems doubtful in the light of extensive reviews on the cationic polymerisation of THF.[125, 126] The propagating species is a tertiary oxonium ion (128) which undergoes ring cleavage, as described above, by nucleophilic attack of monomer (see overleaf).

The reaction with 2'-methoxybiphenyl-2-yldiazonium tetrafluoroborate (111) was repeated using one equivalent of THF in dichloromethane. After discharge of colour (about 30 h at room temperature) a solid was isolated

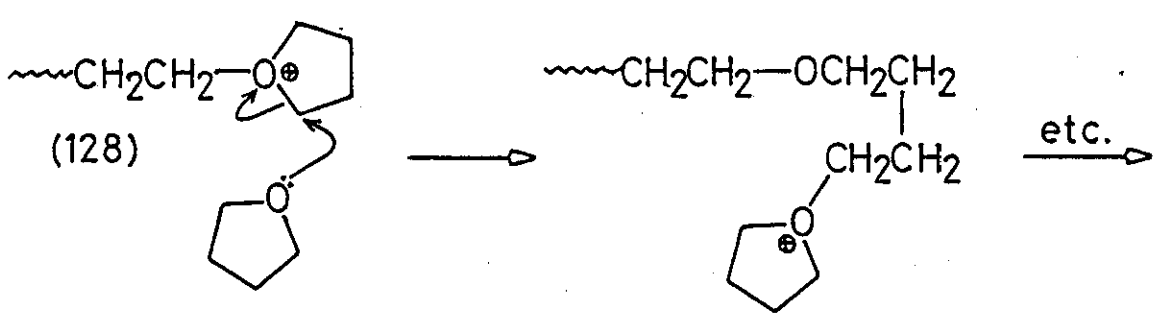
Ring Opening



Demethylation

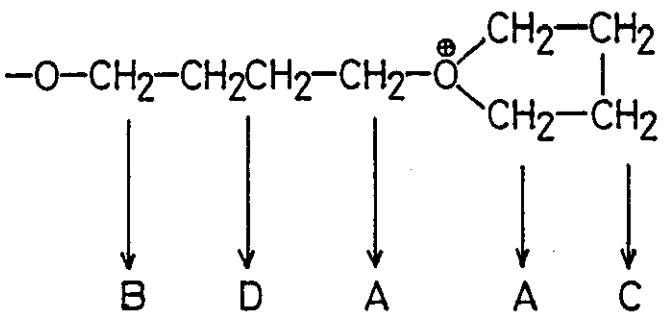


Scheme 18. Acetolysis of Alkoxyalkyl p-Bromobenzenesulphonates.



which was unable to methylate pyridine. Instead, ^{1}H NMR analysis revealed the presence of dibenzofuran together with a group of signals in the ranges δ2.3-1.5 and δ4.3-3.3. No THF was detected. This analysis compares very favourably with that of Pruckmayr and Wu[127] in their investigation of the solution polymerisation of cyclic ethers,

wherein spectral assignments for isolated methylene ($-CH_2-$) and for methylene next to oxygen ($-CH_2-O-$) fall respectively within the ranges quoted above.

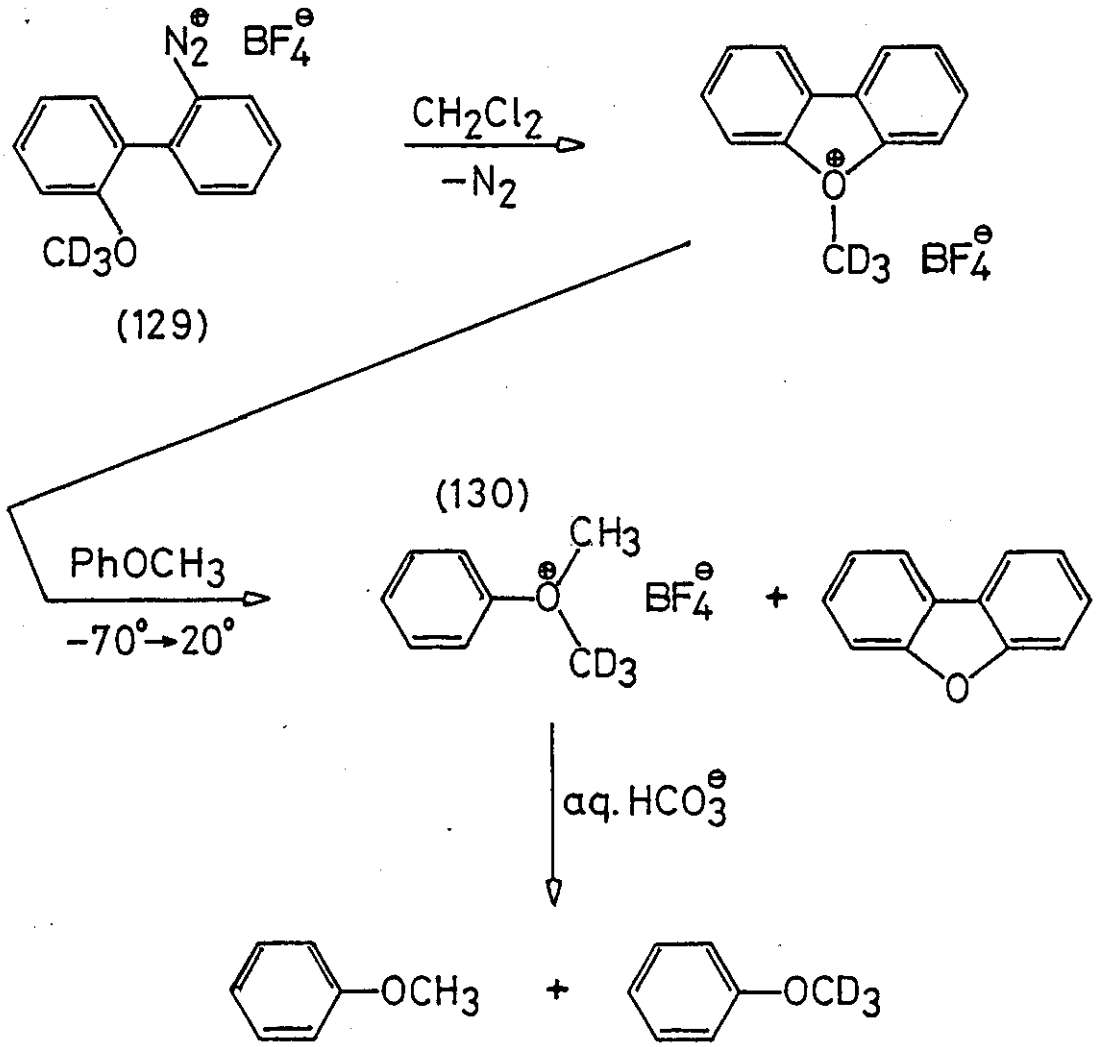


Signal	Chemical Shift/δ
A	4.25(t)
B	3.41(m)
C	2.19(m)
D	1.65(m)

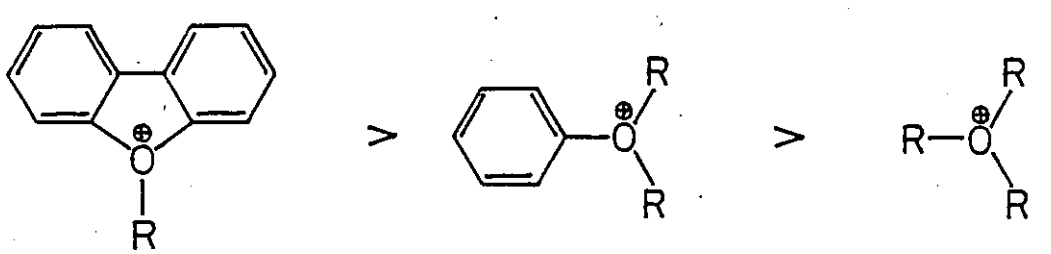
The effectiveness of O-methyltetrahydrofuranium salts as methylating agents is therefore questionable.

The relative alkylating ability of O-alkyldibenzofuranium salts was examined. 2-Hydroxy-2'-nitrobiphenyl (119) was alkylated by trideuteriomethyl iodide, and the resulting ether was reduced then treated with acid sodium nitrite to procure 2'-trideuteriomethoxybiphenyl-2-yldiazonium tetrafluoroborate (129). Subsequent reaction with anisole gave, after quenching, a sample of the alkylaryl ether which incorporated a proportion of deuterium in its methyl group. This was concluded from the observation both of a C-D str. absorption at 2070 cm^{-1} in the IR spectrum, and of the appropriate molecular ions in the mass spectrum. The recovery also of dibenzofuran reaffirms its good leaving group capabilities. This indicates, according to Scheme 19, that O-alkyldibenzofuranium salts are more powerful alkylating agents than the dialkylaryloxonium[99] counterparts, e.g. (130) (see overleaf).

The properties of O-alkyldibenzofuranium salts have so far been assessed in terms of their reactions with weak nucleophiles. However, trialkyloxonium tetrafluoroborates have proved highly effective for the



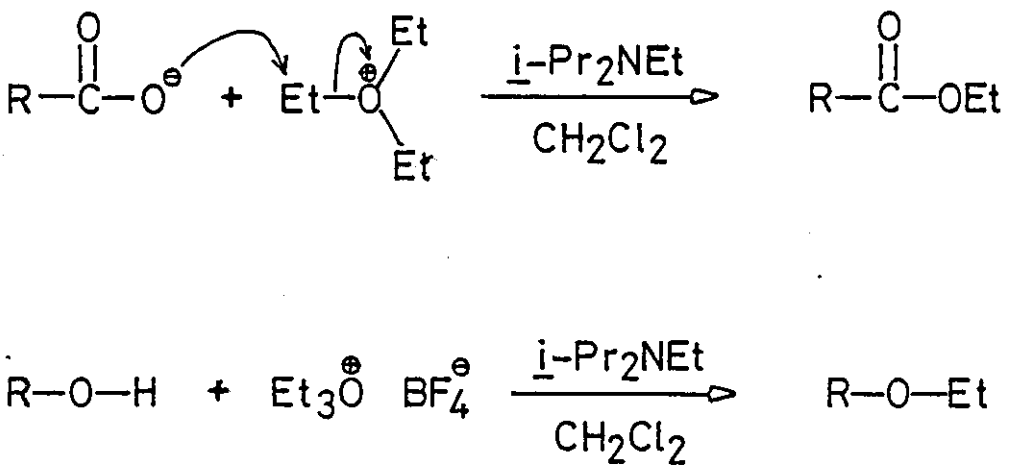
Order of alkylating ability:



Scheme 19. Alkylating Ability of O-Alkyldibenzofuranium Salts.

esterification of hindered (and unhindered) carboxylic acids,[128] and for the synthesis of optically active ethers from labile alcohols.[129] Each reaction is performed in the presence of the bulky organic base, diisopropylethylamine, i-Pr_2NEt, which serves to generate the more reactive anion and neutralise fluoroboric acid as it is formed. See

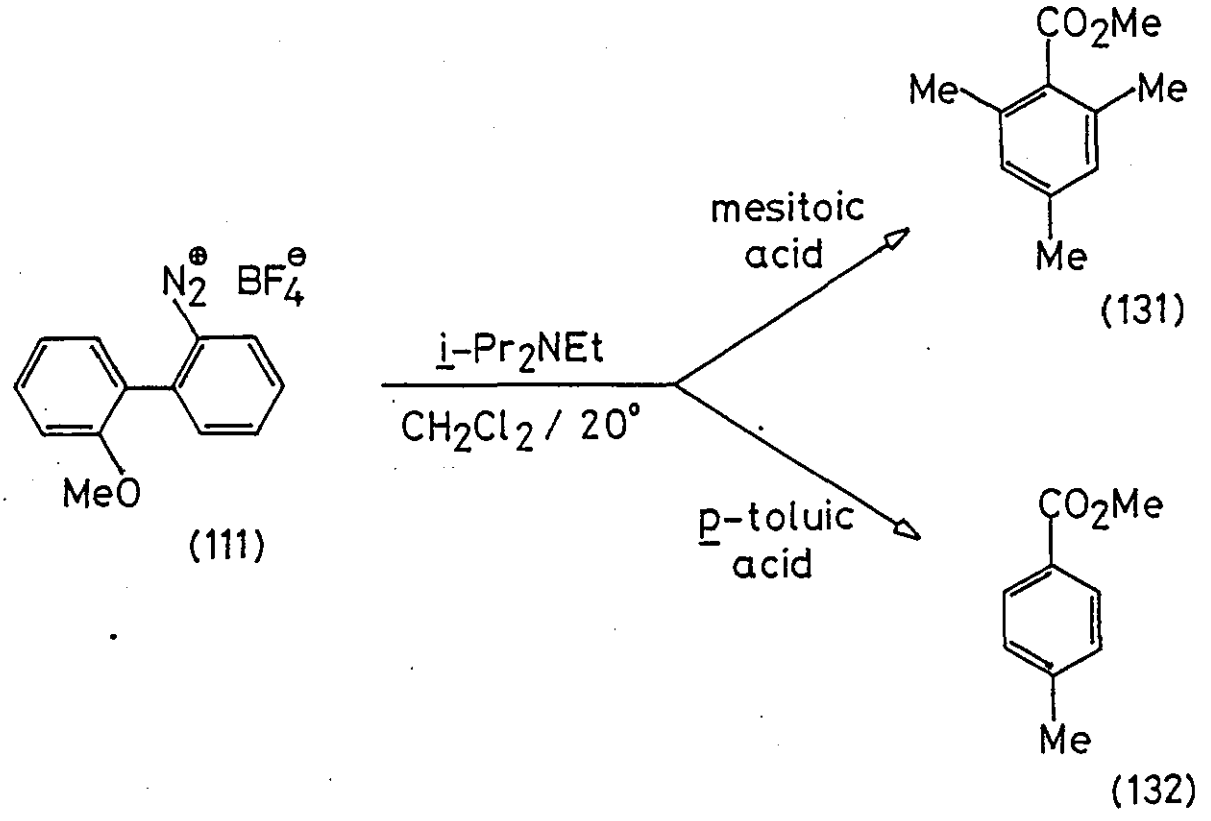
Scheme 20.



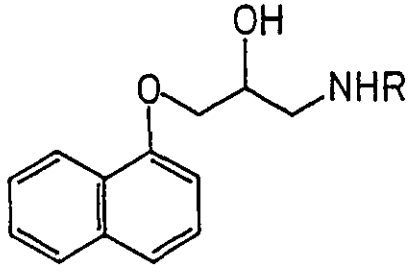
Scheme 20. Oxonium Salt Alkylation of Carboxylic Acids and Alcohols.

2'-Methoxybiphenyl-2-yldiazonium tetrafluoroborate (111) was shown to possess similar qualities and is more soluble than the trimethyloxonium salt. Thus, methylation of the sterically hindered mesitoic acid (2,4,6-trimethylbenzoic acid) was carried out using an equivalent of diisopropylethylamine in dichloromethane at room temperature. The resulting methyl mesitoate (131) was characterised by a shift in the IR carbonyl absorption to higher wavenumbers, and by correlation with available ^{1}H NMR data.[130] Successful preparation of p-methyl toluate (132) was also achieved, but in neither case were yields optimised (see overleaf).

Finally, some preliminary tests were performed on two aryloxypropanolamines, which have shown potential for adrenergic blocking activity for the treatment of coronary disease.[131] The drugs 1-amino- and 1-t-butylamino-3-(1-naphth- yloxy)-2-propanol (133 and 134) were isolated from their hydrochloride salts and treated with 2'-methoxybiphenyl-2-yldiazonium tetraphenylborate. The known preference of oxonium salts to react with oxygen-containing



functional groups[89] was supported by ^{1}H NMR analysis. However, that the major fraction exhibited a strong aromatic methoxyl singlet at δ3.75, with no evidence of the aminopropanol unit, leaves the structure of the product in doubt.

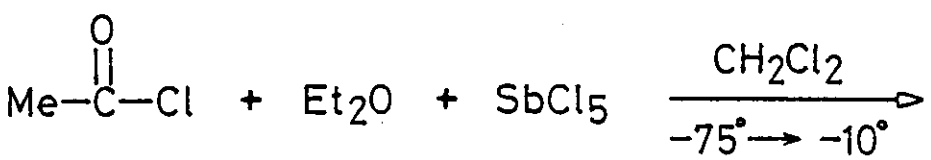


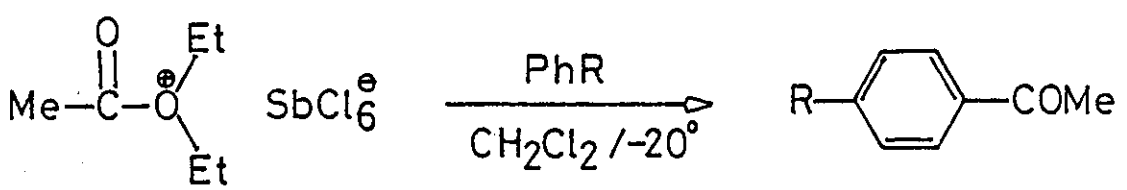
R = H (133)

R = t-Bu (134)

2.3 ACYLATING AGENTS

The synthetic utility of acyloxonium salts as acylating agents is limited by their instability, though their participation as reactive intermediates has often been inferred, as in the synthesis of trialkyloxonium salts.[94] In this reaction, the acyldialkyloxonium ion (92) functions as an alkylating agent. However, the intermediate can be isolated *in vacuo* at low temperature, and acetyldiethyloxonium hexachloroantimonate (135) prepared by Klages[132] is stable up to 0°. Subsequent reactions show this salt to be a powerful acylating agent, and highly effective for the Friedel-Crafts acetylation of benzene and activated aromatics.

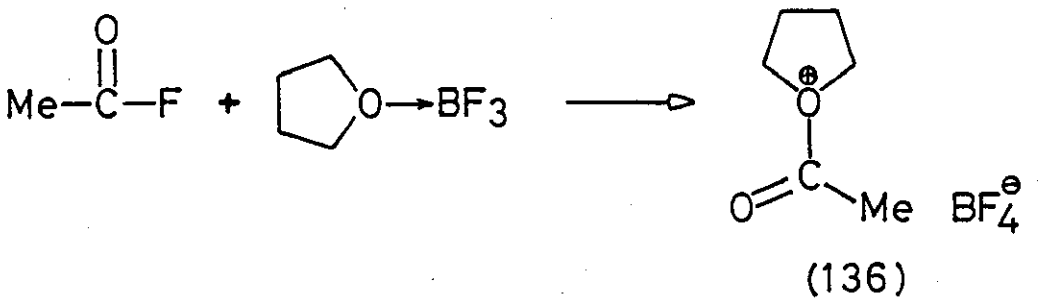




(135) R = H (19%), MeO (50%)

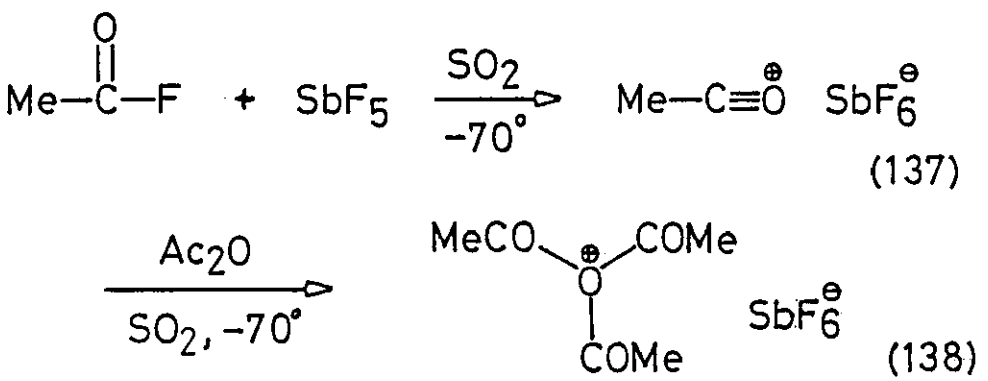
Similar combinations of active halide and Lewis acid can act as catalysts for the polymerisation of THF,[126] but O-acetyltetrahydrofuranium tetrafluoroborate (136) has been synthesised by Meerwein[125] (see overleaf).

Acylium ions, e.g. (137), are proposed as intermediates, and studies in the presence of acetic anhydride have suggested that triacyloxonium ions may be the active initiators in reactions performed at temperatures below -30°. As a result, triacetyloxonium



(136)

hexafluoroantimonate (138) has been characterised by Boekhoff and Heitz.[133] The yellow salt decomposes irreversibly at -26° to -24°, but can be stored at -70° for several months.



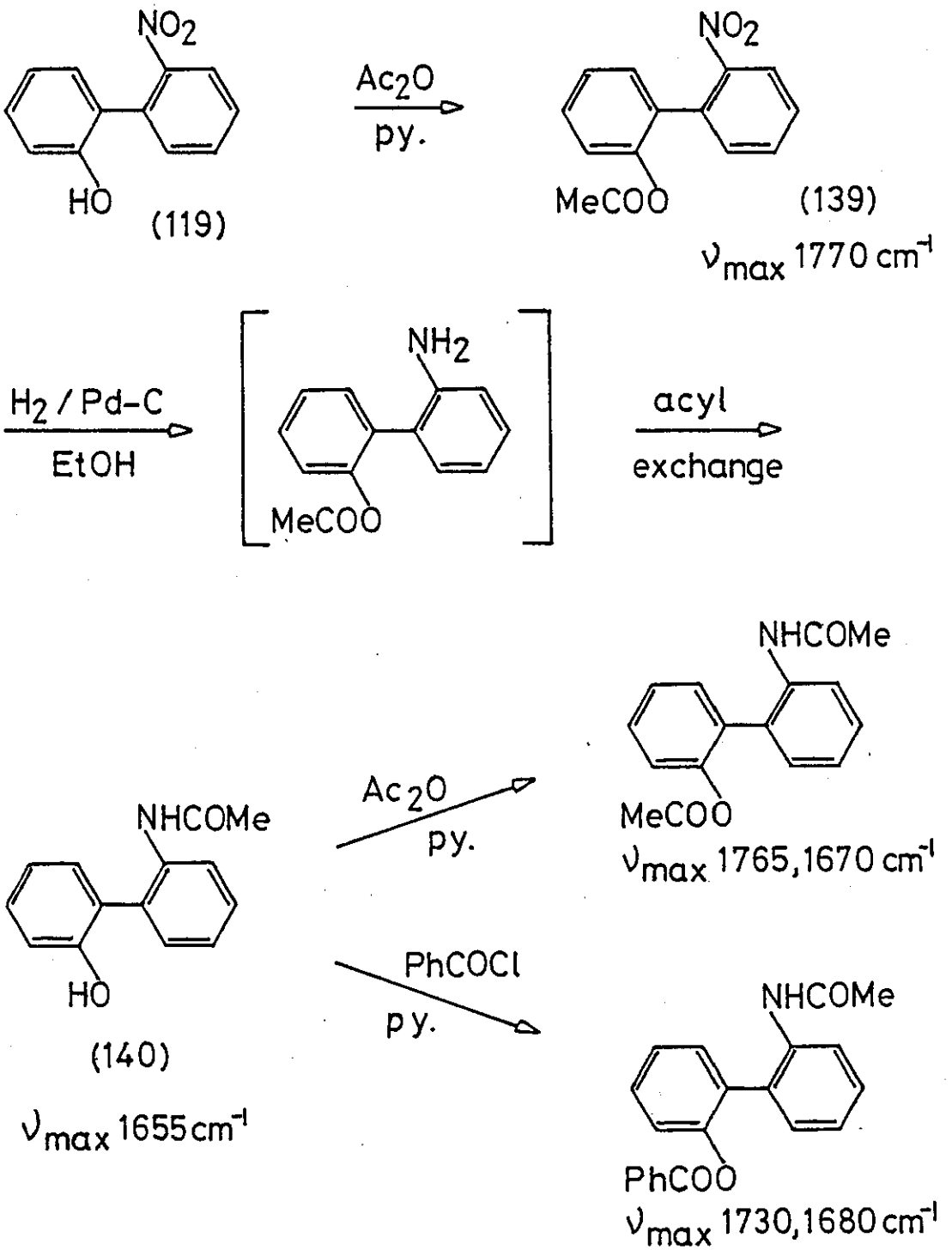
(137)

(138)

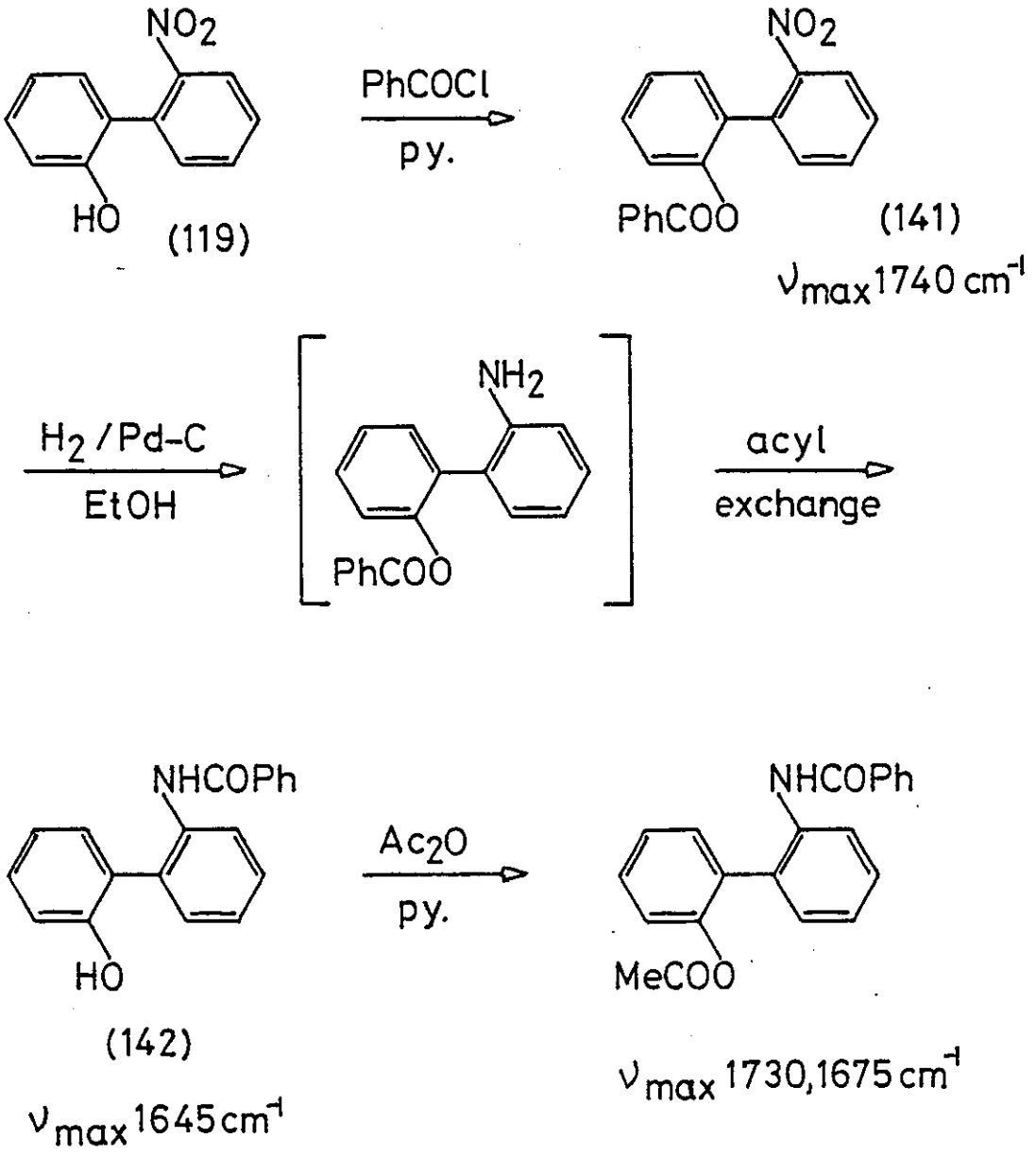
By analogy with the alkylating agents described previously, it was proposed to examine a route to O-acyldibenzofuranium salts and to evaluate their potential in electrophilic aromatic substitution. It was reasoned that the precursor diazonium salts would make for a relatively stable acylating system. However, unforeseen difficulties encountered in the reduction step of the synthetic sequence have halted further progress.

Thus, 2-acetoxy-2'-nitrobiphenyl (139) was readily prepared from the phenol (119), but none of the required amine was obtained upon catalytic hydrogenation. Instead, the product possessed an IR carbonyl absorption at ca. 1650 cm^{-1} which was far removed from that at 1770 cm^{-1} given by the starting ester. This unexpected result was attributed to

rearrangement of the amine as it was formed, to afford an amide by acyl shift from oxygen to nitrogen. The product was characterised as 2-acetylamino-2'-hydroxybiphenyl (140) by further acetylation and benzoylation of its phenolic group.



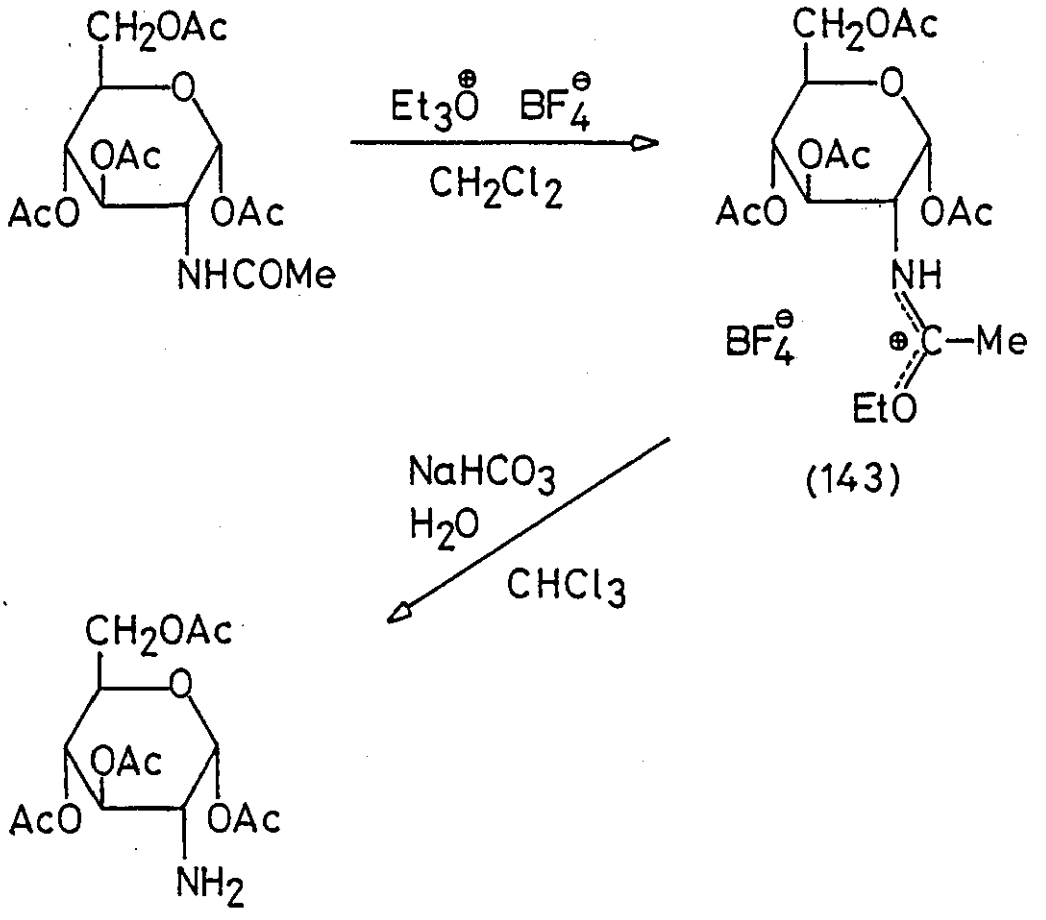
Similar results were given by 2-benzoyloxy-2'-nitrobiphenyl (141), the product of reduction being identified as 2-benzamido-2'-hydroxybiphenyl (142) (see overleaf).



Attempts to isolate an amine hydrochloride during reduction failed to preclude acyl exchange, whilst at ice temperature starting nitro compound only was recovered. Furthermore, acetylation of 2-amino-2'-hydroxybiphenyl (123) produced the N-acylated phenol (140).

Alternative routes to 2-acyloxybiphenyl-2'-yldiazonium salts, including heterolytic decomposition of N-nitrosoacylarylamines,[12] do not appear viable, but attention is drawn to a selective detachment of N-acyl groups in sugars bearing acetoxy groups.[134] The reaction uses triethyloxonium tetrafluoroborate to form the salt of an imidic ester

(143), in accord with the observed reactivity of carbonyl compounds.[101] Subsequent hydrolysis affords the amine.



CHAPTER 3

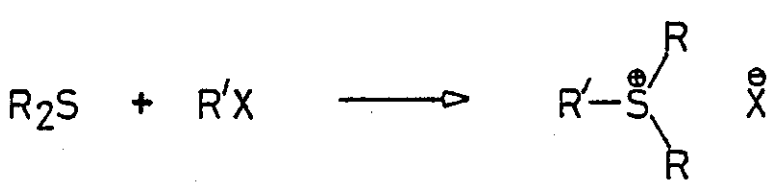
SULPHONIUM SALTS

3.1 REVIEW[135]

Much of the significant work on sulphonium salts and their derivatives is of very recent origin, and reviews by Stirling[136] and Barrett[137] are available. The versatility of the sulphonium group as a carbanion stabiliser and a leaving group in displacement reactions has rendered sulphonium salts as useful tools in organic synthesis. Their greater stability over oxygen analogues is demonstrated by their preparation from an oxonium salt and a sulphide. Indeed, sulphonium salts are naturally occurring substances and function as important biological methyl transfer agents.

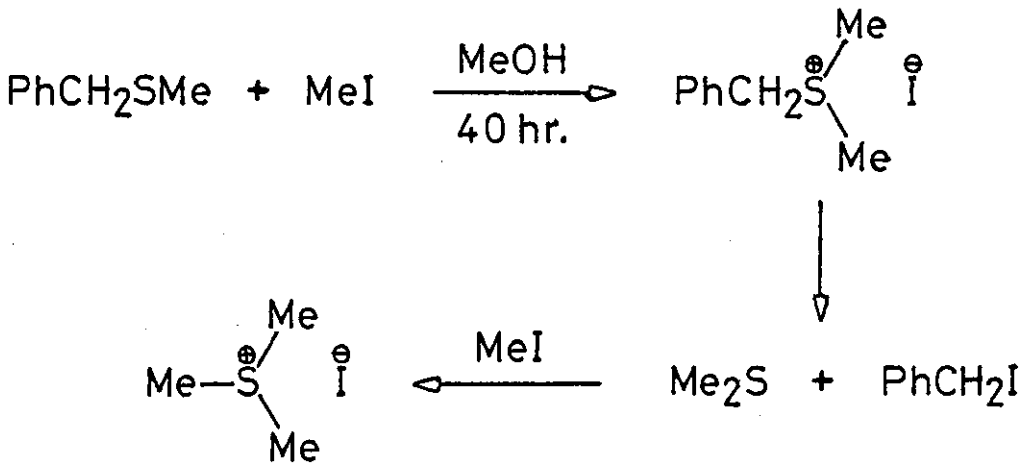
The common definition of sulphonium salts covers alkyl- or aryl-substituted species, but aza-, alkoxy-, acetoxy-, halogeno-, and hydroxy-sulphonium salts feature as intermediates in reactions of sulphides and sulphoxides with electrophiles.

The sulphur atom in dialkyl sulphides is weakly nucleophilic and, unlike the oxygen atom in dialkyl ethers, is alkylated by alkyl halides, dialkyl sulphates or sulphonate esters under simple reaction conditions. The corresponding trialkylsulphonium salts (144) are stable, easy to handle, and crystallise well.



$X = I, R'OSO_3^{\ominus}, ArSO_3^{\ominus}$ (144)

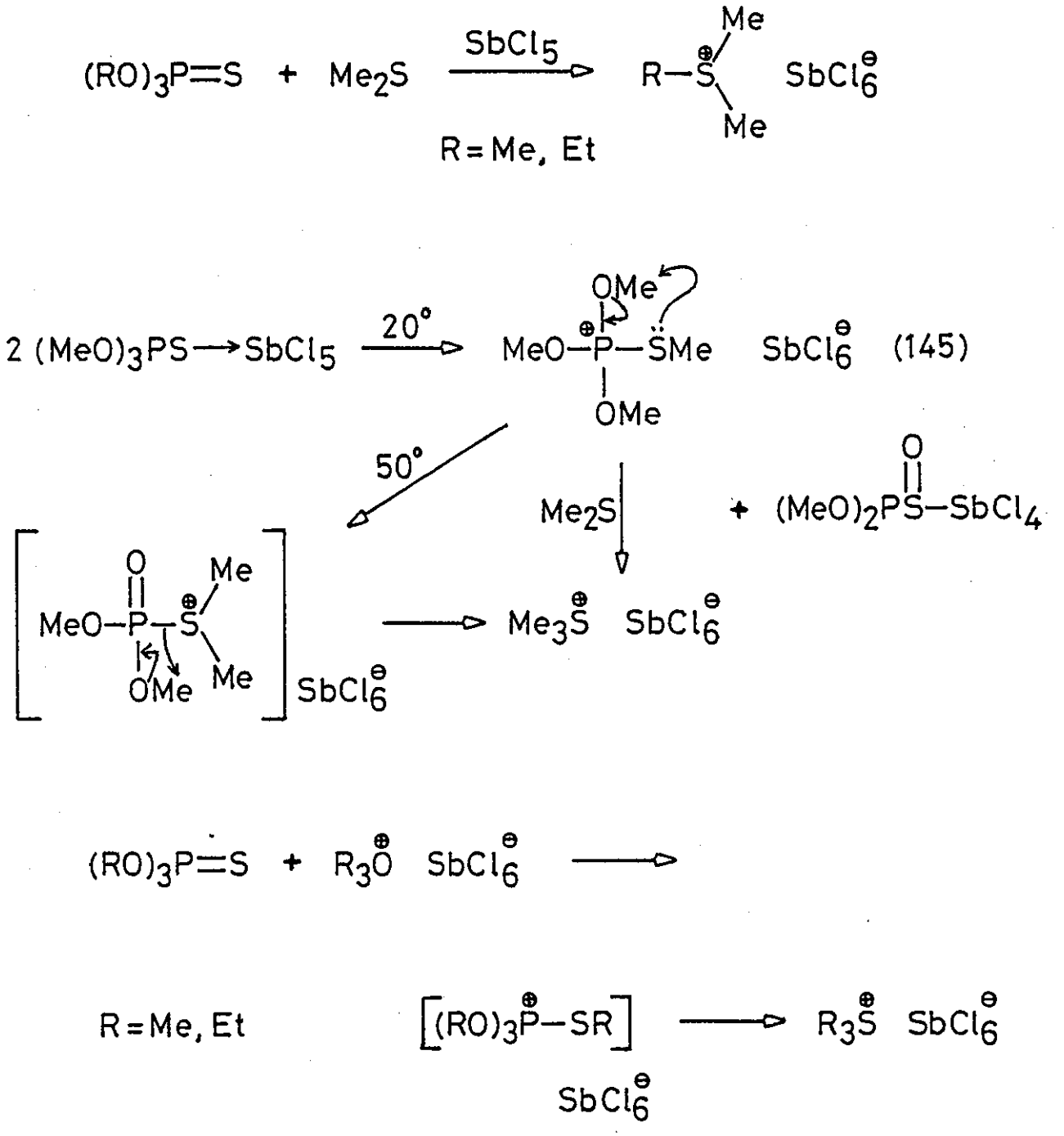
A characteristic of simple trialkylsulphonium halides is that they may reversibly dissociate, a process which frequently leads to unexpected products. For example, alkylation of benzylmethyl sulphide with an excess of methyl iodide gives trimethylsulphonium iodide in 50% yield by a sequence of alkylation and reversion[138] (see overleaf).



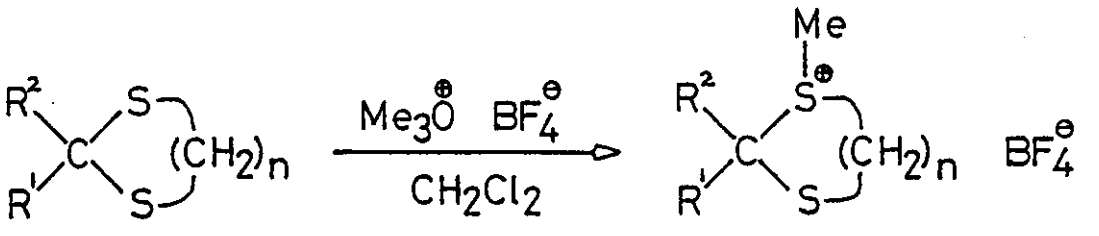
Hexachloroantimonate salts have been isolated by the reaction of trimethyl- and triethyl-thionophosphates with dimethyl sulphide in the presence of antimony pentachloride.[92] Further study[139] has led to the isolation of an intermediate (145) which alone is capable of forming the sulphonium salt by a series of intramolecular alkylations. An interesting transformation of an oxonium salt to a sulphonium salt can be effected, as depicted in Scheme 21 (see overleaf).

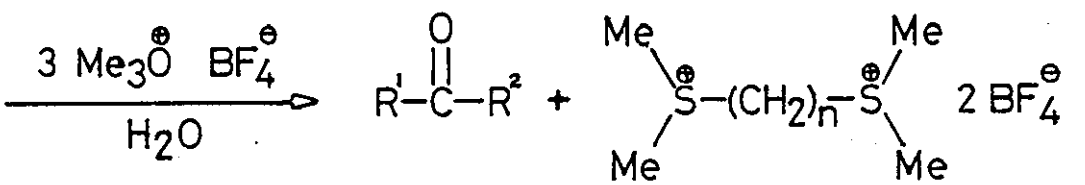
The formation of bis-sulphonium salts by double alkylation of bis-sulphides has been achieved, but a more recent synthesis is based on a new technique for the regeneration of carbonyl compounds from dithioacetals. The fact that sulphides are less basic than ethers and amines means that thioacetals are stable to acids and normally require heavy metal catalysis, e.g. $Hg^{2\oplus}$, for cleavage. However, hydrolysis can be facilitated by heterolysis of the C-S bond in a sulphonium salt, as in dethioacetalisation with excess trimethyloxonium tetrafluoroborate.[140] Both the de-protected carbonyl compound and the bis-sulphonium salt (146) are isolated in high yield (see overleaf).

The alkylation of sulphides by an alkyl halide constitutes a readily accessible route to simple sulphonium salts, but is less effective for higher members. Aryl sulphides in particular are less



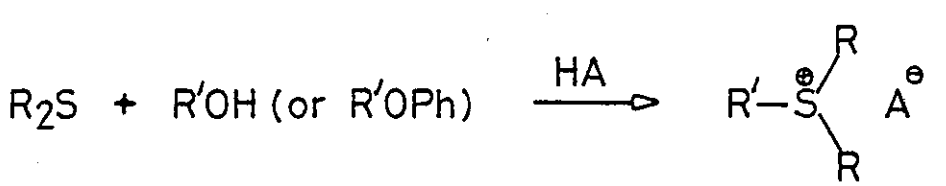
Scheme 21. Trialkylsulphonium Salts from Trialkylthionophosphates





(146)

nucleophilic and require the use of stronger agents such as trialkyloxonium salts or alkyl halides in the presence of silver salts. Nonetheless, Badet and Julia[141] have now shown that several acids can bring about thealkylation of aliphatic, allylic, and aromatic sulphides using a range of alcohols and alkylphenyl ethers. Furthermore, no isomerism is detected in those alkyl groups that are usually susceptible to rearrangement, e.g. prenyl.



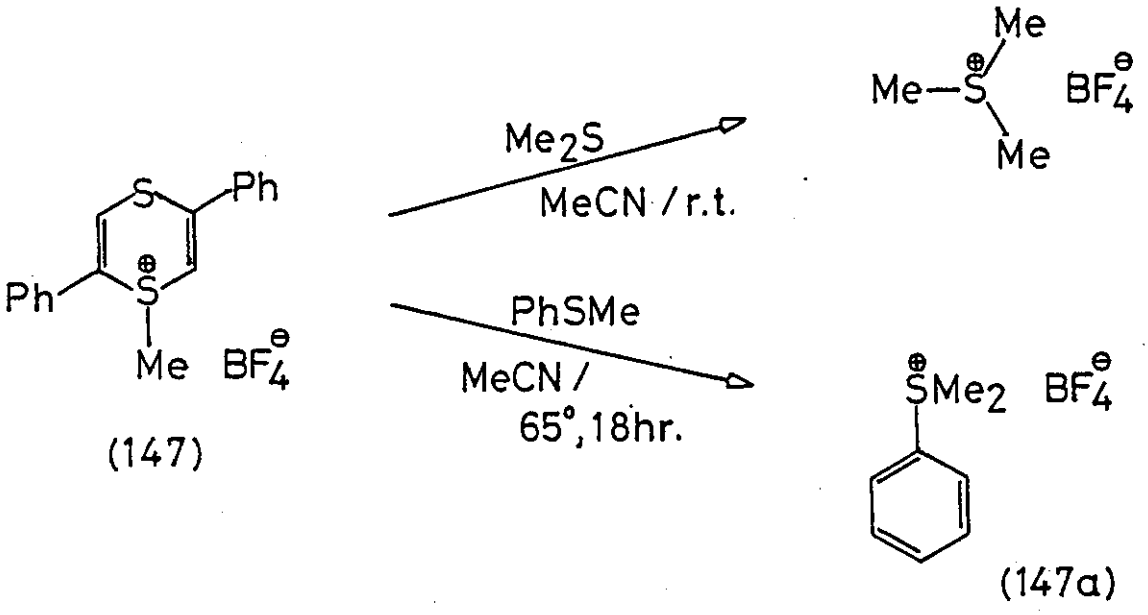
R = alkyl, aryl

R′ = alkyl

HA = CF_3CO_2H, HBF_4–Et_2O, $MeSO_3H$, CF_3SO_3H

1-Methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate (147) has proved a methylating agent compatible both with simple dialkyl

sulphides and with less reactive aryl sulphides. Thus, methylation of dimethyl sulphide[142] and of thioanisole[143] gives the corresponding salts in 79% and 82% yields respectively.

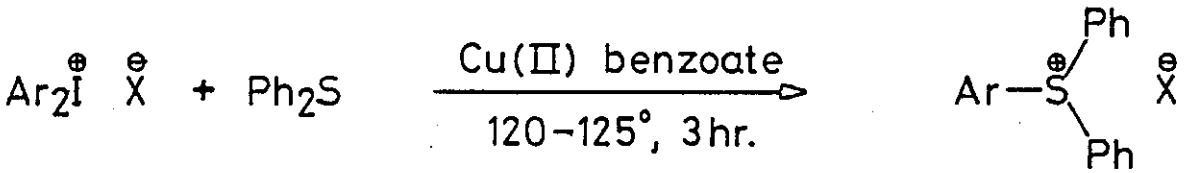


(147) (147a)

Triarylsulphonium salts are relatively inaccessible, but have been obtained from aromatic hydrocarbons and sulphoxides in the presence of Lewis acids,[144] and by the reactions of arylmagnesium halides with diarylsulphoxides[145] and with diarylethoxysulphonium salts.[146] Many of these procedures suffer from low yields, a high degree of complexity, and long reaction times. However, with regard to their development of photoinitiators for the cationic ring opening polymerisation of cyclic ethers, Crivello and Lam[147] have developed a route to high yields of pure triarylsulphonium salts. The method involves an arylation of diarylsulphides with diaryliodonium salts (148), which proceeds smoothly in the presence of copper(II) catalysts (see overleaf).

The photochemistry of triarylsulphonium and diaryliodonium salts will be discussed collectively (see Chapter 5.2).

The formation of cyclic sulphonium salts by intramolecular alkylation has been extensively studied because of their frequent occurrence as reaction intermediates, in particular the three-

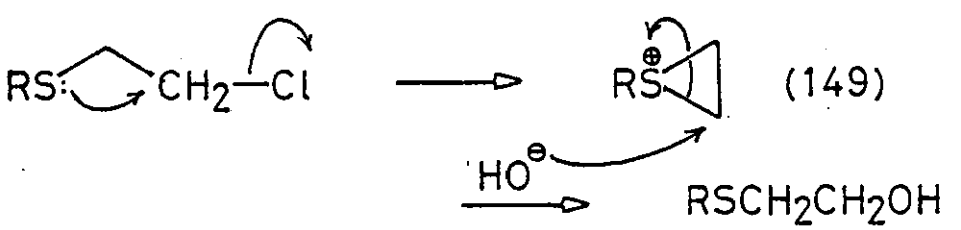


(148)

65-100%

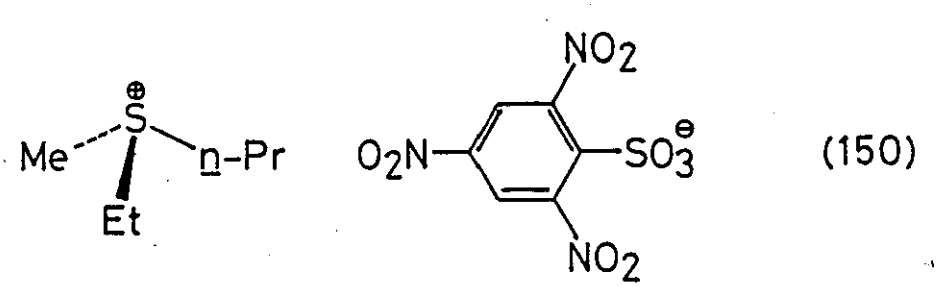
$X = BF_4, PF_6, AsF_6, SbF_6$

membered ring thiiranium (epi-sulphonium) salts, e.g. (149).[148] Thus, sulphur is more nucleophilic and a much more effective neighbouring group than oxygen, and this is illustrated by the rapid solvolysis of β-chloroalkyl sulphides. The intermediate is susceptible to nucleophilic substitution due to relief of ring strain.



(149)

The geometry of sulphonium salts, like their oxonium counterparts, has been shown to be pyramidal by resolution into enantiomeric forms, e.g. the (S)-configuration of (+)-methylethyl-n-propylsulphonium 2,4,6-trinitrobenzenesulphonate (150) has been confirmed by X-ray crystallography.[149]



(150)

Direct synthesis of optically active sulphonium salts may be achieved by reaction of chiral sulphoxides with triethyloxonium

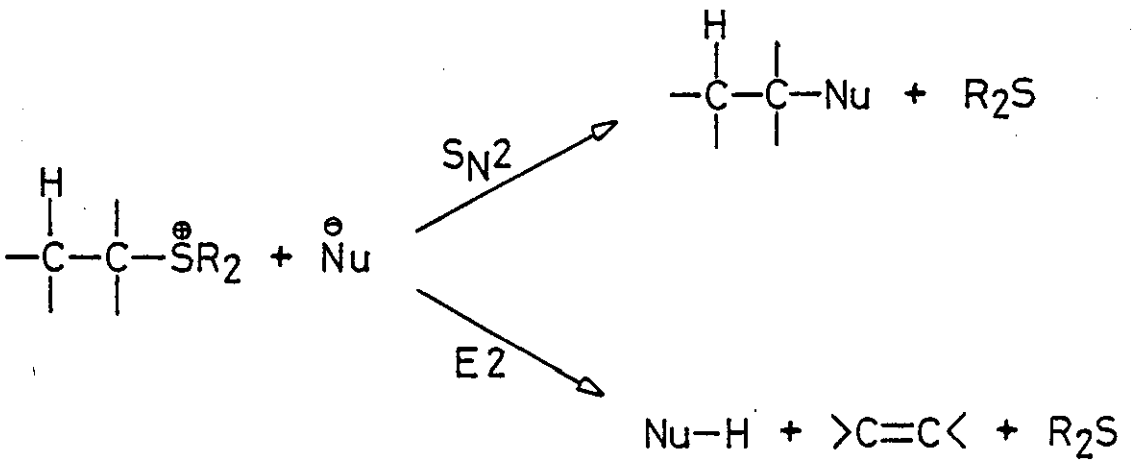
tetrafluoroborate, followed by treatment of the chiral ethoxysulphonium salt with a dialkylcadmium reagent.[150]

Many of the properties exhibited by sulphonium salts stem from the fact that in solution it is easier to generate a carbanion adjacent to sulphur than to oxygen. This is because of the greater polarisability of the sulphur atom, but has also been attributed to d-orbital resonance ($p_\pi - d_\pi$ bonding). Stabilisation of an adjacent carbanion is comparable with that shown by other second row elements, e.g. phosphorus, and is best exemplified by the formation of sulphonium ylides. These are given more thorough treatment in section 3.3.

On the other hand, carbocations adjacent to bivalent sulphur are less stable than those next to oxygen. In this instance, stabilisation is by $p_\pi - p_\pi$ conjugation, and its magnitude is proportional to the nuclear separation. Consequently, alkylthiocarbenium ions ($\rangle\overset{\oplus}{C}R-S- \leftrightarrow \rangle CR=\overset{\oplus}{S}-$) find less significance than the alkoxycarbenium ions ($\rangle\overset{\oplus}{C}R-O- \leftrightarrow \rangle CR=\overset{\oplus}{O}-$) reviewed in Chapter 2.

Polarisation of the C-S bond in sulphonium salts, and the ability of the positively charged sulphur atom to accept the electron-pair of this bond, confer leaving group ability on the sulphonium group in S_N2 displacement reactions. In this respect, the sulphonium group is a better leaving group from sp^3 carbon than an ammonium group. In addition, however, it is well to point out that these onium centres can act as leaving groups in conventional E2 elimination reactions owing to an acidifying effect on β protons. The exact mode of reaction is then governed by the relative proton and carbon nucleophilicities of the nucleophile in question (see overleaf).

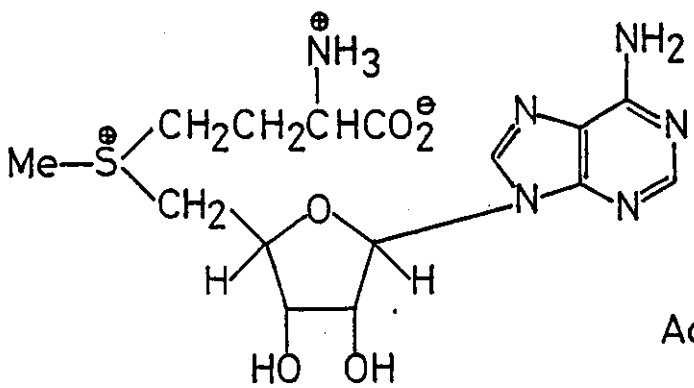
The abstraction of a methyl group from a sulphonium ion has been demonstrated to follow second order kinetics.[151] However, in spite of the formal positive charge, the leaving group ability of R_2S in S_N2 reactions is lower than that of, say, p-toluenesulphonate (-OTs) or



halide ions. Hence the stability of these salts. Displacement of a methyl group is greatly favoured over that of ethyl and higher alkyl groups, and a study[152] has shown the relative reactivities in alkylation reactions to be of the order, Me(1.0)>Et(0.2)>n-Pr(0.16)>i-Pr(0.05).

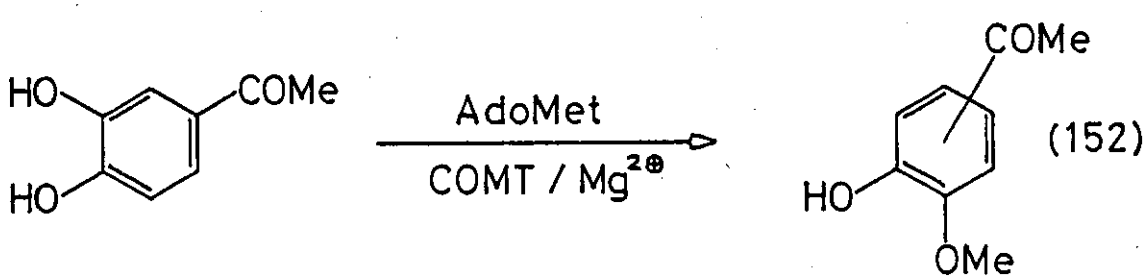
Reactions of sulphonium salts with nucleophiles have contributed significantly towards an understanding of displacement processes in aliphatic systems. Alkylation of carboxylate ions has been observed,[138] wherein trimethylsulphonium iodide with silver mesitoate gives the sterically crowded methyl ester (131) in 38% yield. Reactions of triarylsulphonium salts with methoxide ion give the aryl methyl ether and diaryl sulphide as major products. Whilst a radical mechanism has been proposed[153] and substantiated[154] to account, at least, for hydrocarbon by-products, the possibility of concomitant aromatic bimolecular nucleophilic substitution is not excluded. With the ready availability of higher alkylsulphonium salts,[141] it has subsequently been shown[155] that these can act as powerful alkylating and arylating agents under phase-transfer conditions. Thus, alkyldiphenylsulphonium salts are particularly efficient in the alkylation of aromatic and aliphatic carboxylic acids, arylsulphonic acids, phenols, alcohols, aromatic amines, and heterocyclic NH groups.

The transfer of an intact methyl group from a donor to a suitable acceptor, with enzyme catalysis, is a reaction of profound biological significance. The methyl donor is in general S-adenosylmethionine (AdoMet, 151), which is an important cofactor for enzymes which methylate a diverse array of nucleophilic accepters within the cell.



AdoMet (151)

Extensive studies regarding the mode of action of the enzyme catechol O-methyltransferase (COMT) have been performed[156-159] by Coward, Schowen, and associates. In these, the construction of model systems and the observance of kinetic isotope effects have produced an understanding of the sulphur-to-oxygen methyl transfer reaction (152).



(152)

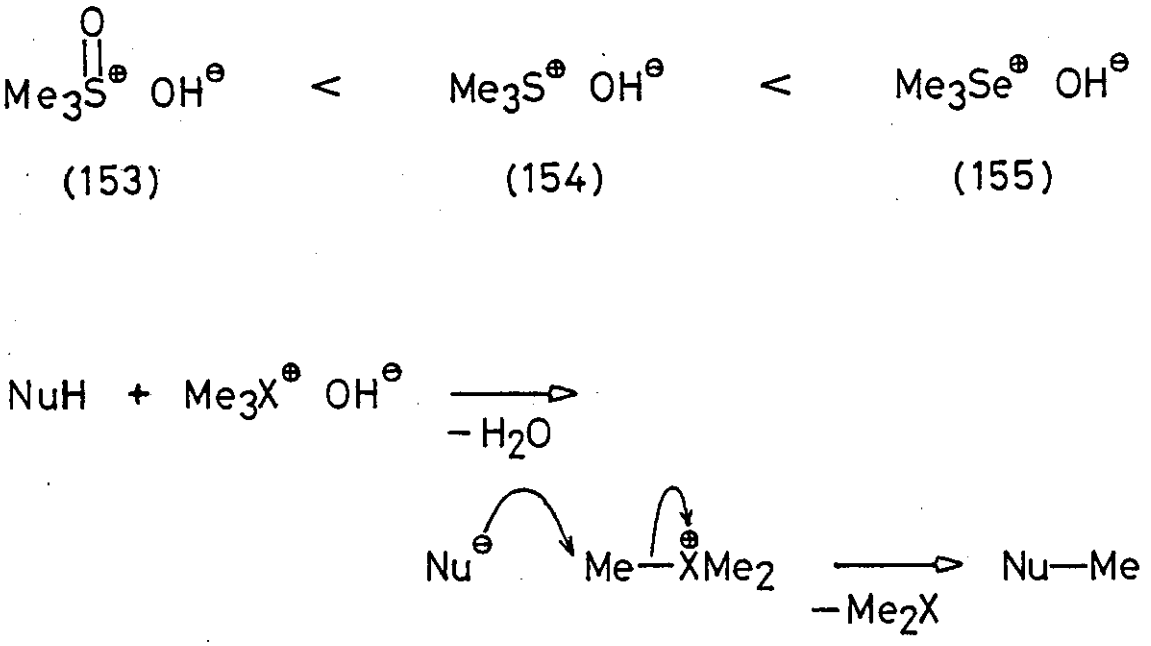
Results indicate that the enzyme derives much of its catalytic power from processes which influence the structure of the transition state. The conclusion[159] is that transfer of the methyl group is rate-limiting, with an S_N2-like transition state in which the methyl is located "symmetrically" and "tightly" between leaving group and

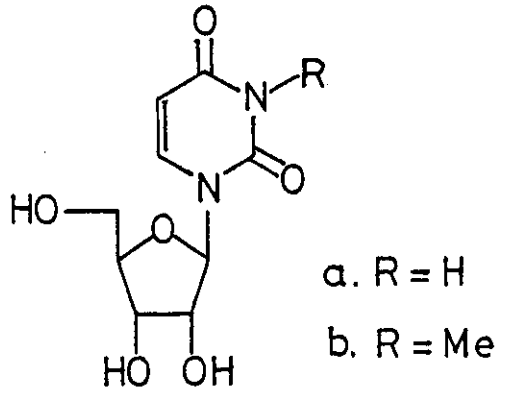
nucleophile.

The alkylation of nucleic acids has received considerable attention due to the discovery of various methylated ribonucleosides from ribonucleic acid (RNA), and from studies of mutagenic and carcinogenic effects observed in living systems upon administration of alkylating agents. In the course of their own work, Yamauchi and Kinoshita[160-164] have developed several new methylating agents which may be considered analogues of S-adenosylmethionine and which are capable of methylating nucleosides.

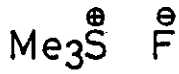
Trimethyloxosulphonium hydroxide (MOSH, 153),[160] trimethylsulphonium hydroxide (154),[161, 162] and the related trimethylselenonium hydroxide (155)[163] are conveniently prepared in aqueous methanolic solution by treatment of the respective onium iodides with silver oxide. As well as affording predominantly N-methylated nucleosides, e.g. 3-methyluridine (156b), these reagents are generally useful in synthesis for the rapid, nearly quantitative methylation of CO_2H, SH, and aromatic OH functions, i.e. $pK_a<12$. However, they are not effective for the methylation of aromatic and aliphatic NH_2 or aliphatic OH (cf.[155]). Their order of reactivity and mechanism of alkylation is shown in Scheme 22 (see overleaf).

Trimethylsulphonium fluoride (157) and n-butyldimethylsulphonium fluoride (158) have found similar application.[164] In every case results are comparable with or superior to methylations by more common agents such as methyl iodide, dimethyl sulphate, and diazomethane. Easy isolation and purification of products is an added advantage. Both the onium hydroxides and fluorides exhibit reactivities markedly different to those of the corresponding iodides. Thus, uridine (156a) gives no reaction with trimethylsulphonium iodide. The difference can be attributed to enhanced activation of nucleophilic sites by the counterion.

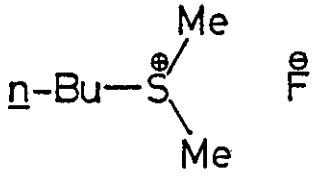




(156)



(157)



(158)

Scheme 22. New Methylating Agents. Onium Hydroxides and Fluorides

3.2 ALKYLATING AGENTS

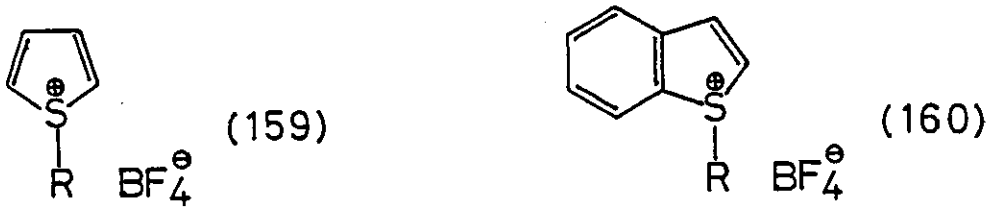
S- ALKYLDIBENZOTHIOPHENIUM SALTS

A detailed study of the sulphur compounds analogous to the O-alkyldibenzofuranium salts was initiated with reference to reports by Acheson and co-workers.[165, 166] They have shown that S-alkylthiophenium, -benzo[b]thiophenium, and -dibenzo[b,d]thiophenium salts (159, 160, 161) can be obtained by treatment of the corresponding weakly nucleophilic thiophens with alkyl halides in the presence of silver salts and, in some instances, with trialkyloxonium salts (see also[167]).

Dibenzothiophen is alkylated most easily and also produces the most stable salt. This is reflected in the fact that 1-alkylthiophenium salts are prepared in low yield and decompose slowly at room temperature *in vacuo* and more rapidly upon solvolysis. Consequently, a more thorough examination was devoted to the 1-alkylbenzothiophenium salts of intermediate reactivity. These are powerful alkylating agents, and are toxic, probably for this reason. Thus, 1-methylbenzothiophenium tetrafluoroborate at room temperature has been used to methylate pyridine, acridine, 2-methylbenzotriazole, and DMSO on the oxygen atom. Some syntheses and reactions are summarised in Scheme 23 (see overleaf).

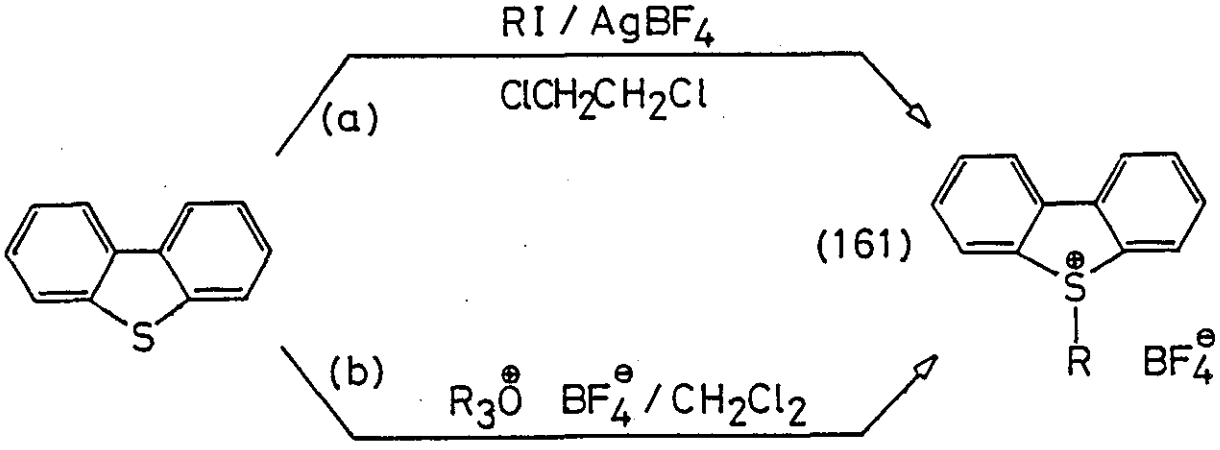
Evidence for pyramidal, and not planar, bonding about sulphur was forthcoming from ^{1}H NMR measurements of the 1-ethylbenzothiophenium cation.[165] The observed magnetic nonequivalence of the methylene protons was attributed to sulphur adopting the role of an asymmetric centre. Now, very recently, Acheson[168] has published X-ray crystallographic data of 1,2,3,5-tetramethylbenzothiophenium tetrafluoroborate (162) to confirm this prediction (see overleaf).

The relative lack of aromaticity in the fused thiophenium ring is revealed by an easy addition of molecular bromine to the 2,3-bond in (160). Therefore, benzothiophenium salts may best be considered as cyclic derivatives of styrene rather than as highly stabilised 10π

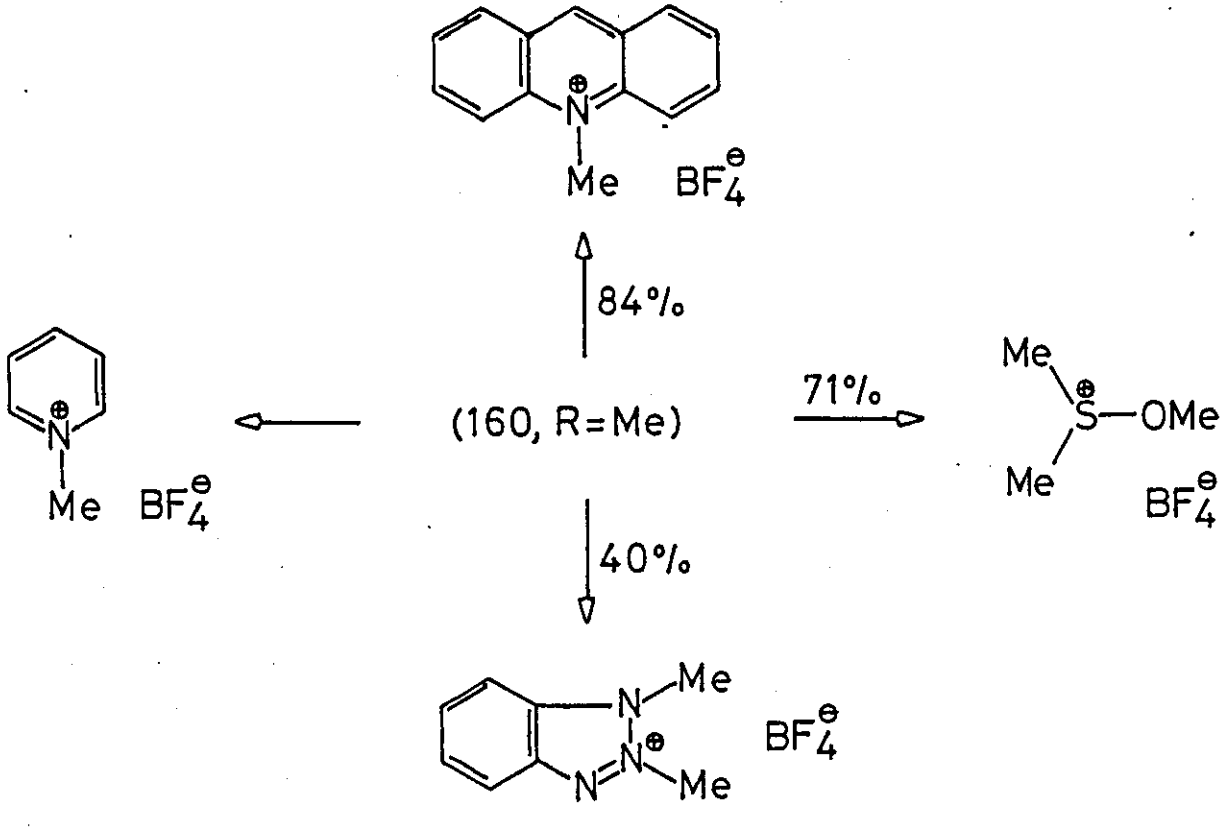


(159)

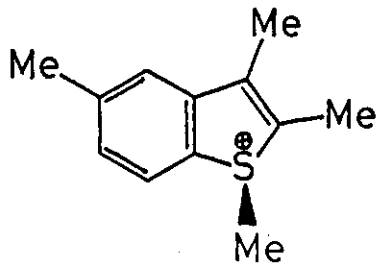
(160)



Yield (a/b)/%: R = Me (93/12), Et (98/40), i-Pr (14/0)



Scheme 23. Syntheses and Reactions of S-Alkylthiophenium Tetrafluoroborates



$BF_4^{\ominus}$ (162)

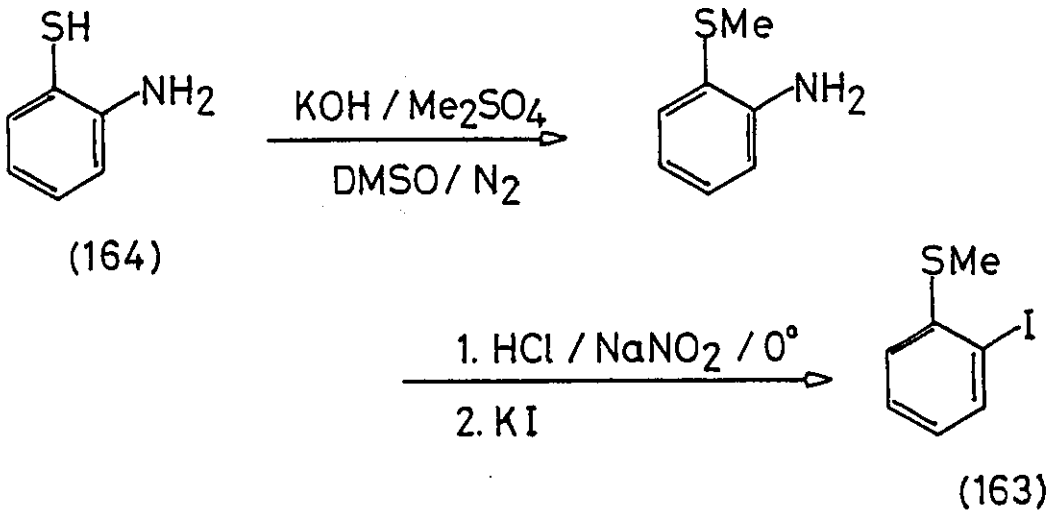
aromatic systems. The conclusion is that the sulphur atoms in all thiophenium salts are sp^3 hybridised to give tetrahedral stereochemistry.

As shown in Scheme 23, only the methyl-, ethyl-, and isopropyl-dibenzothiophenium salts have been described. It was then of interest to investigate an alternative, though longer, route to such materials in an attempt to incorporate higher alkyl groups. With this view in mind, the synthesis of Acheson's S-methyldibenzothiophenium tetrafluoroborate (161, R = Me) via an Ullmann biaryl was tested.

o-Iodothioanisole (163) was required as co-reactant in the coupling step, and initially a preparative route was devised from orthanilic acid. The acid was successfully diazotised and iodinated,[169] and the resulting o-iodobenzenesulphonic acid was converted to the acid chloride by reaction with phosphorus pentachloride at 170-180°.[170] However, in our hands, subsequent reduction using zinc and sulphuric acid[171] proceeded with simultaneous hydrogenolysis of the carbon-iodine bond, so that only thiophenol was isolated, and that in low yield. A more convenient and straightforward synthesis was achieved by S-methylation of o-aminobenzenethiol (164), followed by consecutive diazotisation and iodination of o-thioanisidine, with an overall yield of 55% (see overleaf).

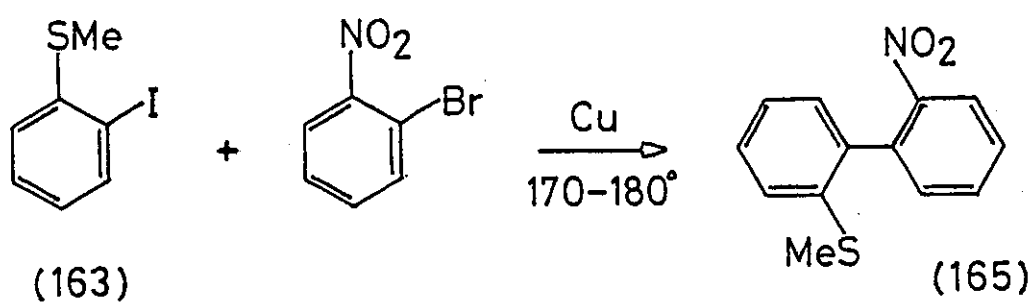
Hazard Note

Addition of aqueous potassium iodide to the cold diazonium



salt solution generally proceeded without incident, but on one occasion resulted in several loud explosions. Consequently, the addition should always be carried out gradually and with efficient stirring.

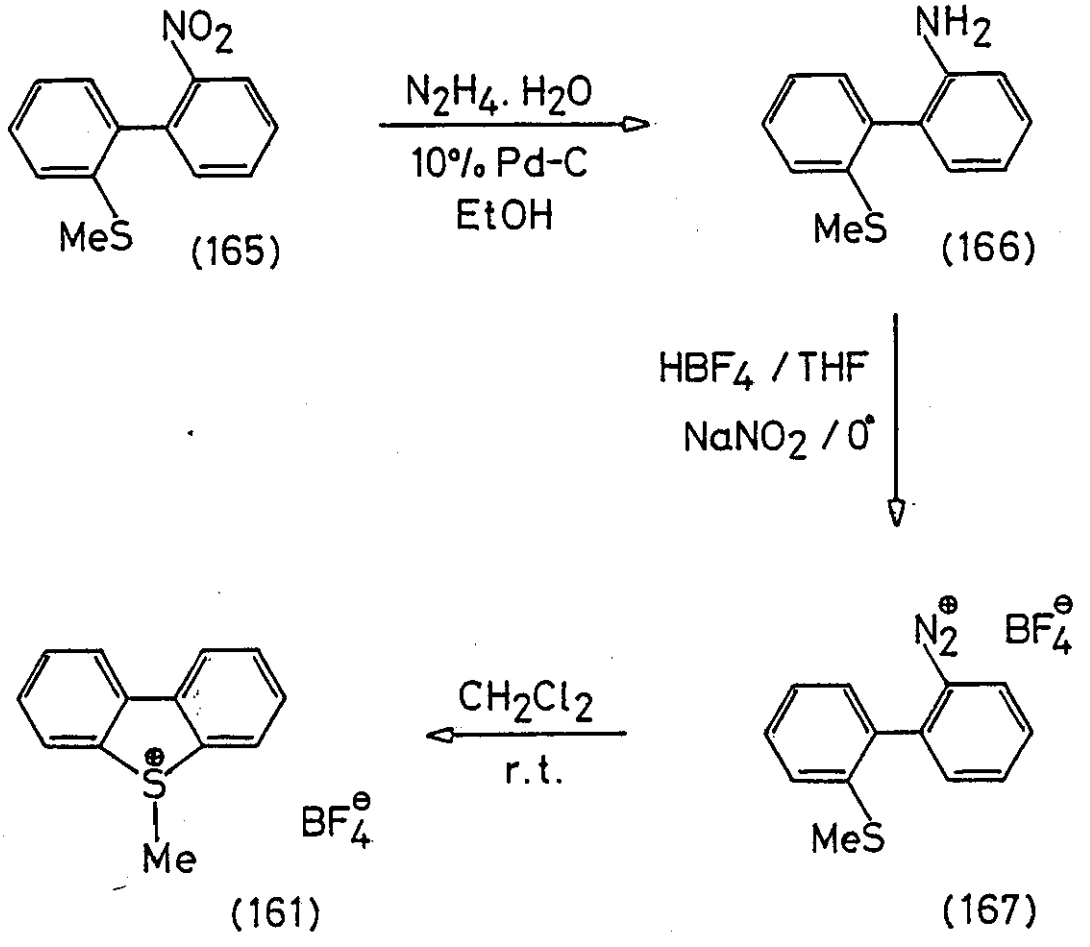
2-Methylthio-2'-nitrobiphenyl (165) was obtained as a bright yellow crystalline solid, after chromatography, from the mixed Ullmann reaction between o-iodothioanisole (163) and o-bromonitrobenzene.



Considerable inconsistencies in yield, which never exceeded 26% for the pure biaryl, serve to illustrate the difficulty in acquiring optimum conditions for the Ullmann reaction. At all times the symmetrical 2,2'-dinitrobiphenyl (33) was obtained in appreciable amount, and the use of activated copper[26] gave no improvement.

Reduction of the nitro compound gave a near quantitative yield of the corresponding amine (166), which afforded the orange, 2'-methylthiobiphenyl-2-yldiazonium tetrafluoroborate (167). This

diazonium salt is appreciably more stable than its oxygen counterpart (111), and no decomposition was detected after 50 days when stored in vacuo over phosphorus pentoxide at -20°. However, when stirred at room temperature in dichloromethane the colour was discharged within 1-2 days, and a white crystalline solid was isolated in 86% yield. Comparison of IR, ^{1}H NMR, and ultraviolet (UV) spectra with those of an authentic sample[165] confirmed the formation of the desired S-methyldibenzothiophenium salt (161). Some dibenzothiophen was also recovered from the reaction mixture.



The thiophenium salt is extremely stable, and can be stored almost indefinitely at -20°. This is in marked contrast to the dibenzofuranium analogue (110), whose identity has only been inferred, and reflects the more pronounced nucleophilicity of sulphur. Indeed, the S-methyldibenzothiophenium salt exhibits a ^{1}H NMR methyl resonance

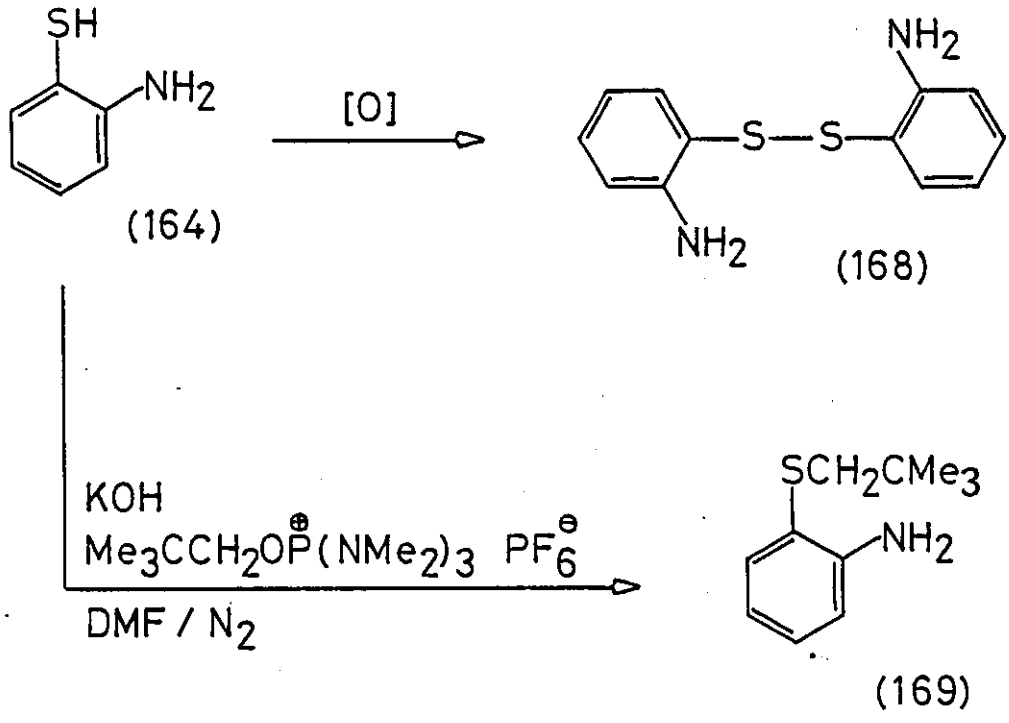
at δ3.35 in acetonitrile, whereas the highly reactive oxonium species has been shown to methylate the nitrile group.[90] As previously suggested (Chapter 2.2), appreciable anchimeric assistance by the heteroatom is presumed in order to explain the decomposition and cyclisation of normally stable aryldiazonium tetrafluoroborates. Further discussion is given in Chapter 6.

SULPHIDE FORMATION BEFORE ULLMANN REACTION

Having verified the success of the general synthetic sequence, the study was extended to those salts containing higher alkyl groups, which may be more accessible and more stable than similar salts in which the alkyl group is bonded to oxygen. Neopentyl and benzyl groups were introduced by alkylation of o-aminobenzenethiol (164), and in both series experimental difficulties were encountered.

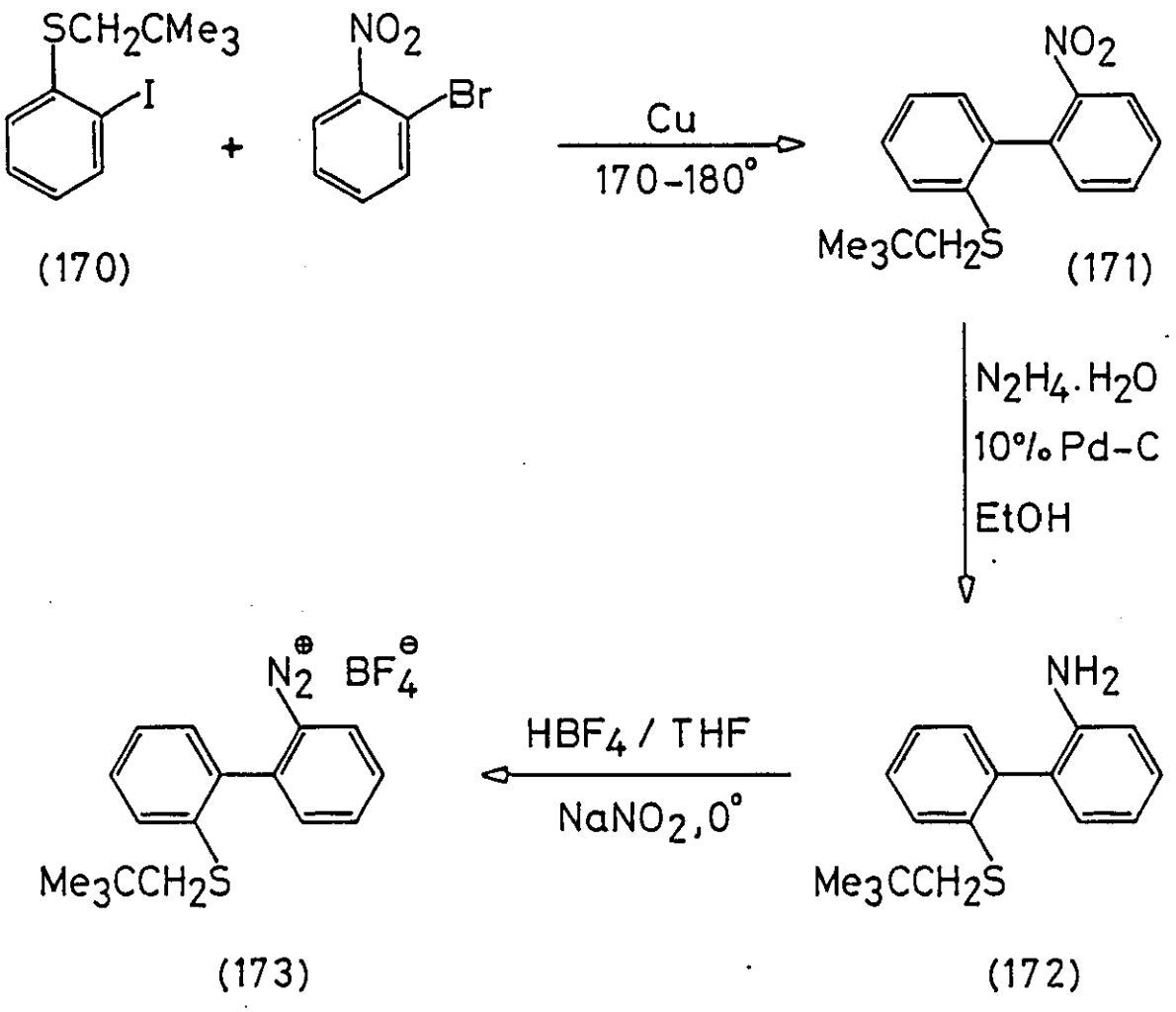
To avoid rearrangement, the neopentyl group was attached to sulphur by way of its alkoxy-tris(dimethylamino)phosphonium hexafluorophosphate (120). However, preliminary reactions gave none of the desired material, and instead a crystalline solid was obtained which analysed for 2,2'-diaminodiphenyl disulphide (168). This illustrates a general characteristic of thiols, in that the sulphur-hydrogen bond can be cleaved by mild oxidising agents, eg atmospheric oxygen, to give dimers via thiyl radicals, RS$^{\cdot}$. As a result, all sulphur alkylations were performed under nitrogen, using solvents previously purged with nitrogen, and best results were achieved with freshly vacuum distilled o-aminobenzenethiol. Nonetheless, alkylations using higher alkyl groups were usually more difficult to perform, and gave more complex mixtures, than the methylation process. Thus, o-aminophenyl neopentyl sulphide (169) was obtained as a slightly impure oil (see overleaf).

Diazotisation and iodination of the amine produced o-iodophenyl



neopentyl sulphide (170), also as an oil, which was used immediately with o-bromonitrobenzene to prepare the mixed Ullmann adduct, 2-neopentylthio-2'-nitrobiphenyl (171). The biaryl was isolated from the reaction mixture as an oil of reasonable purity in 45% yield, and when treated with hydrazine hydrate provided 2-amino-2'-neopentylthiobiphenyl (172) which very slowly crystallised on standing. The amine was characterised by acetylation and was readily converted to the bright yellow diazonium tetrafluoroborate (173) (see overleaf).

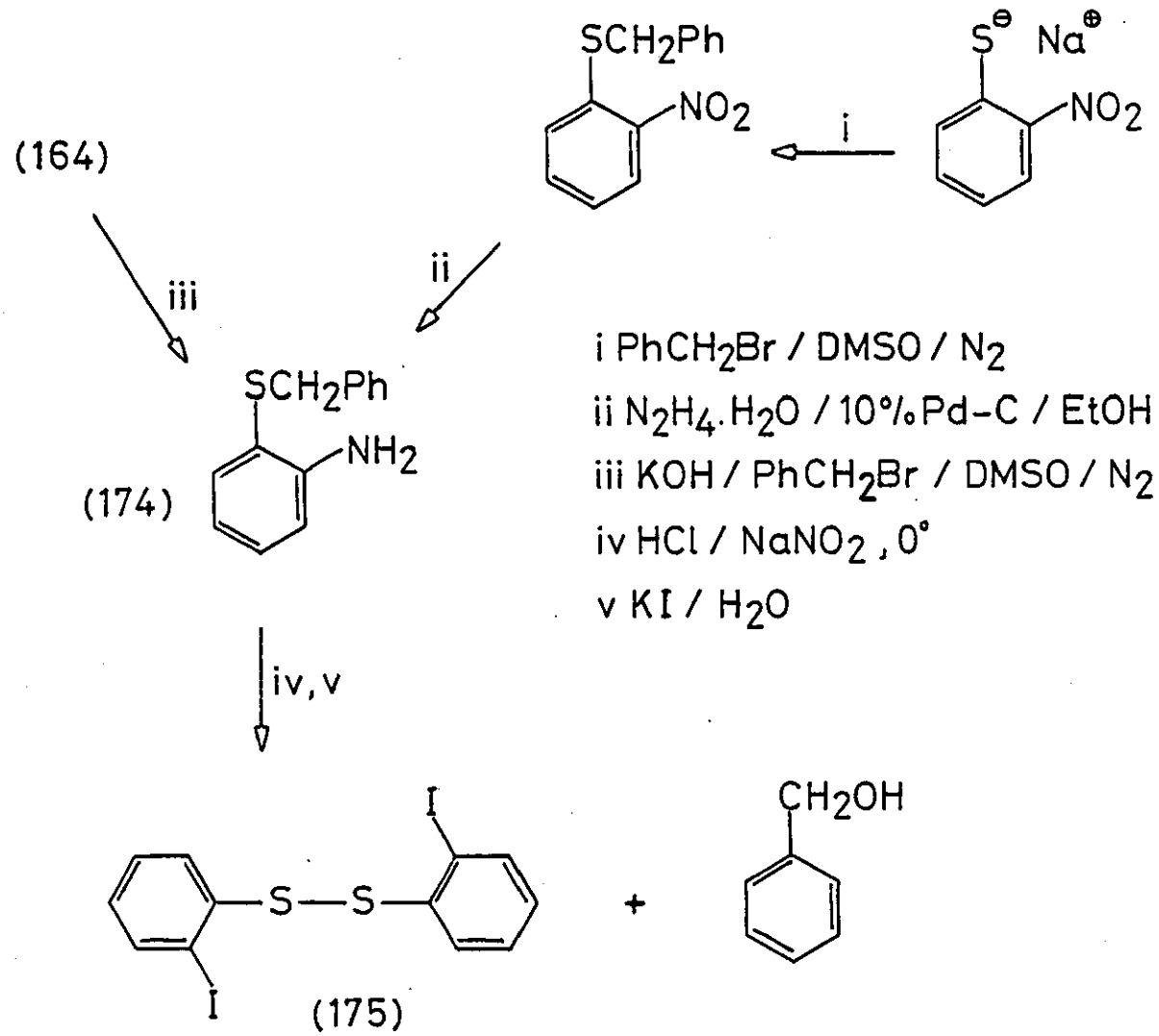
Formation of the benzyl sulphide (174) was carried out successfully under non-oxidative conditions, but could equally well be obtained by benzylation of sodium o-nitrobenzenethiolate followed by chemical reduction. However, a problem was encountered when attempts were made to synthesise the iodo compound via diazotisation in an aqueous medium. The major products were identified as 2,2'-diiododiphenyl disulphide (175) and benzyl alcohol, and can be rationalised by an acid-catalysed hydrolysis which is assisted by the stability of the benzyl cation as



a leaving group (see overleaf).

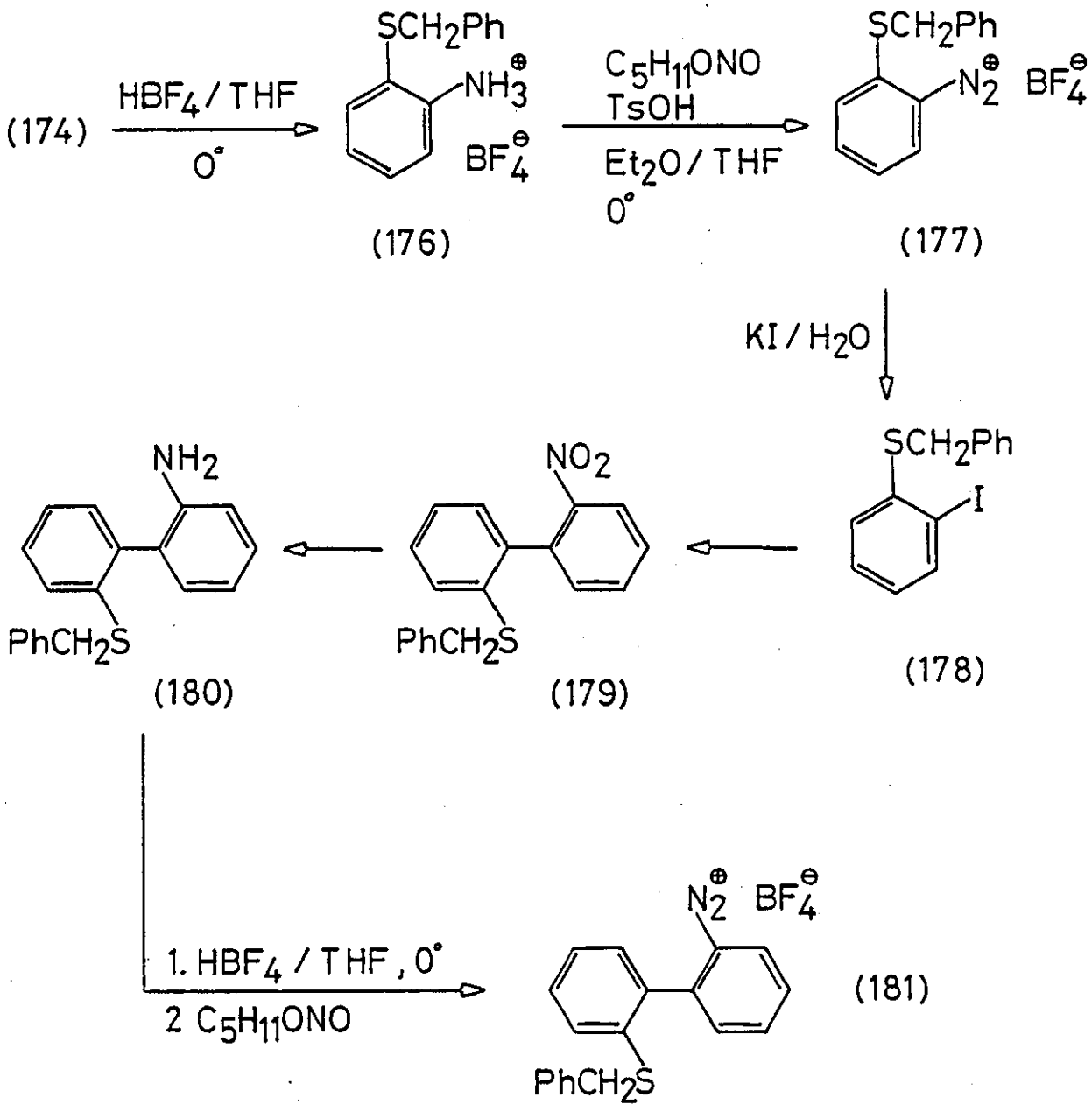
A modified approach involved three separate stages. At first, the crystalline amine tetrafluoroborate (176) was isolated, then the dry salt was diazotised under aprotic conditions in the presence of pentyl nitrite. At this point the benzyl group remained intact, and the diazonium salt (177) was added to a stirred solution of potassium iodide in water. A small amount (6%) of crystalline benzyl o-iodophenyl sulphide (178) was recovered, but the principle products were those derived from debenzylation and dimerisation.

The Ullmann material, 2-benzylthio-2'-nitrobiphenyl (179), was obtained as an oil, and the reduction product was identified as 2-amino-2'-benzylthiobiphenyl (180) by spectral data. Interestingly,



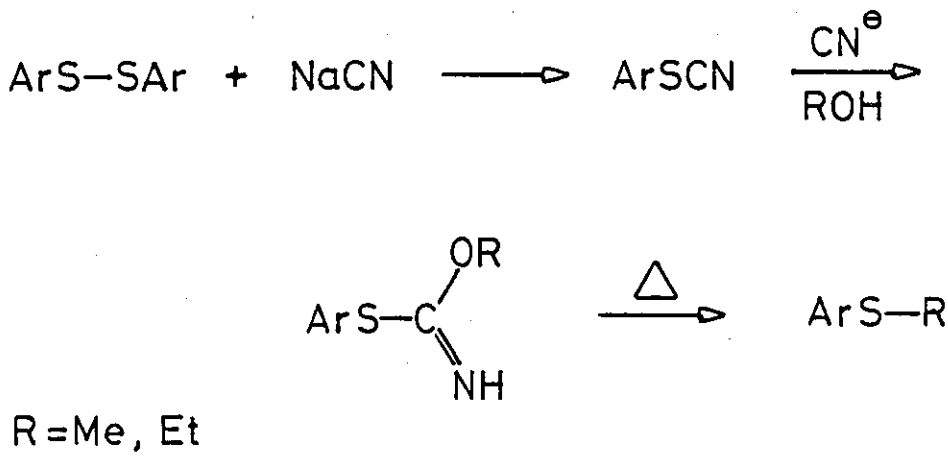
no cleavage of the benzyl sulphide was detected. In the light of previous observations, 2-benzylthiobiphenyl-2'-yldiazonium tetrafluoroborate (181) was prepared under anhydrous conditions (see overleaf).

It is worth considering that formation of the sulphide (178) might better be achieved by benzylation of o-iodothiophenol, although so far reduction of o-iodobenzenesulphonyl chloride has been unsuccessful, and diazotisation/iodination of o-aminobenzenethiol (164) resulted in isolation of the dimer (175). Nevertheless, the reduction of disulphides is an established method for the generation of thiols.[172] Reagents include triphenylphosphine in aqueous dioxane[173] and zinc in acetic acid, but simultaneous removal of halogen may also occur.[174]



Tanaka, Hayami and Kaji[175] have shown that an alternative approach, involving direct formation of an alkyl aryl sulphide, may be possible by reacting a diaryl disulphide and an alcohol in the presence of sodium cyanide (see overleaf).

Suspension of both diazonium salts (173, 181) in warm benzene was accompanied by evolution of nitrogen and loss of colour. That the product in each was identified as dibenzothiophen, with no trace of the desired S-alkyldibenzothiophenium salts, gives indication of their instability. Furthermore, an attempted alkylation of dibenzothiophen



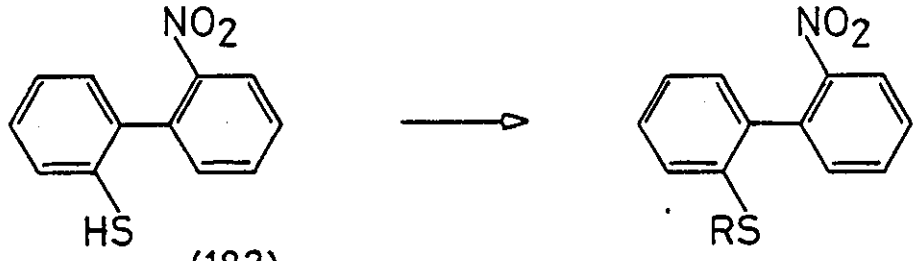
using a combination of benzyl bromide and silver hexachloroantimonate met without success.

These results conform with those presented by Acheson.[165] Thus, the S-isopropyl salt was prepared in low yield only (see Scheme 23), and was found to be too unstable for a reliable analysis, decomposition occurring in two days to regenerate dibenzothiophen. This also agrees with the failure of Kemp[90] to isolate an O-isopropyldibenzofuranium salt, or to observe any isopropylated nucleophiles, since any sulphonium species is expected to be more stable than the oxonium analogue.

Present evidence does suggest, therefore, that any furanium or thiophenium salts bearing groups other than simple alkyl will be insufficiently stable for effective preparative work. It is possible that some of the experimental difficulties mentioned above may be overcome by S-alkylation subsequent to the Ullmann biaryl synthesis.

SULPHIDE FORMATION AFTER ULLMANN REACTION

Demethylation of 2-methoxy-2'-nitrobiphenyl (47) has proven to be an effective step towards a range of alkyl aryl ethers via the phenol (119). At present, no reproducible or efficient S-demethylation technique is generally available, and previous attempts[176] to prepare 2-mercapto-2'-nitrobiphenyl (182) have met with no success. Nonetheless, a route to this compound, and hence to a selection of alkyl aryl sulphides, was sought.



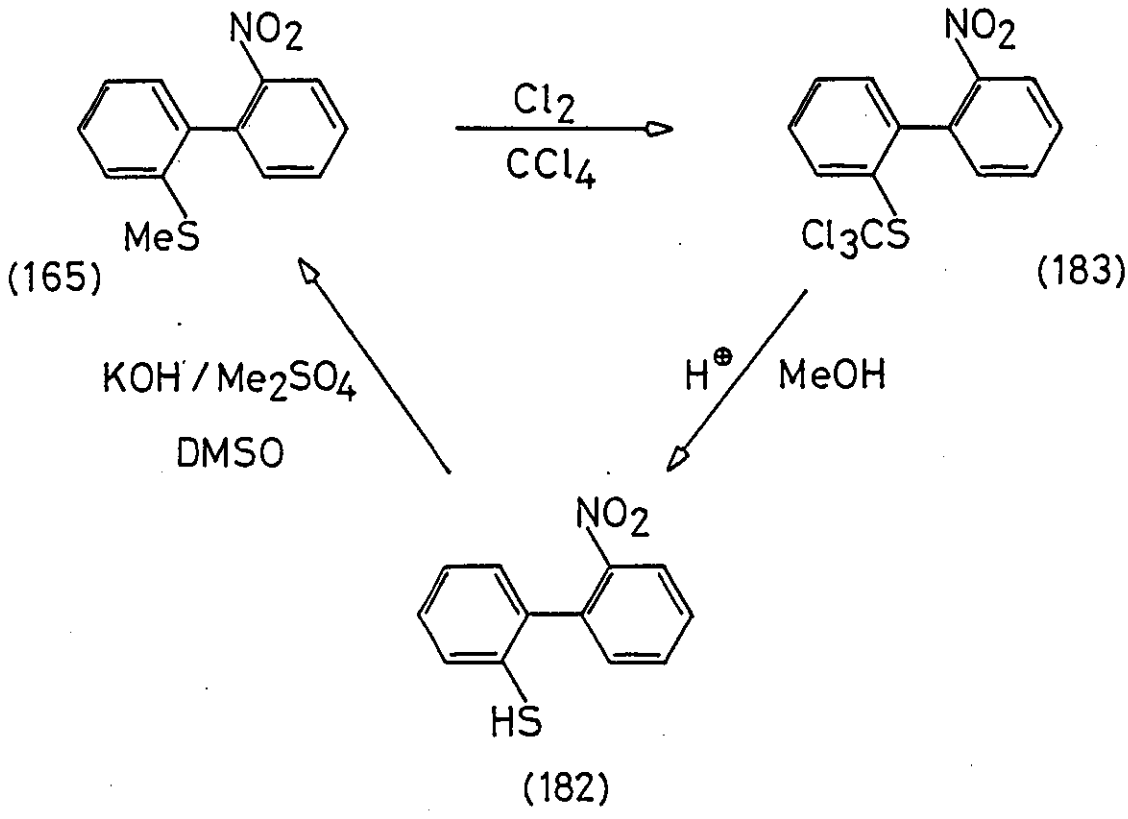
(182)

a. Demethylation of 2-Methylthio-2'-nitrobiphenyl

Sulphides are in general cleaved very much less readily than ethers, and mention has already been made to the effect that secondary sulphonium salts, $R_2S^{\oplus}H$, are less readily formed than the corresponding oxonium salts, $R_2O^{\oplus}H$. Consequently, it was not surprising that 2-methylthio-2'-nitrobiphenyl (165) was not demethylated by hydrogen bromide in refluxing acetic acid. Several alternative methods have been reported. They are reviewed in the next chapter, but some which received more thorough examination are described below.

The most successful technique in our hands was that introduced by Lavanish.[177] Thus, treatment of the aryl methyl sulphide with chlorine at room temperature gave selective and quantitative chlorination of the methyl group. The slightly impure 2-nitro-2'-trichloromethylthiobiphenyl (183) was characterised by its mass spectrum. Subsequent acid-catalysed methanolysis produced a mixture which was shown to contain at least 50% of the desired thiophenol (182) by methylation.

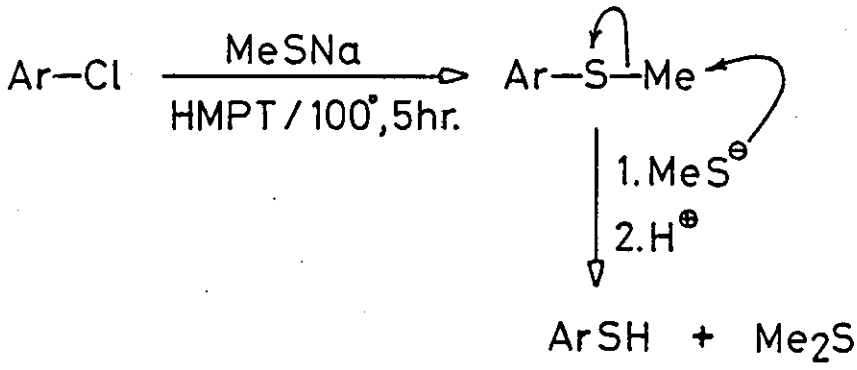
The product isolated gave spectral data consistent with an authentic sample of starting material (165).



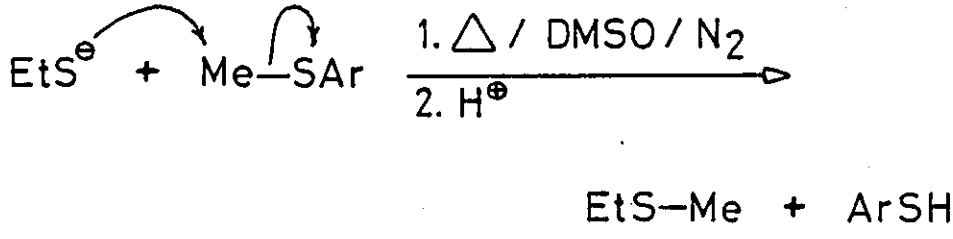
One important criterion in establishing an effective demethylation procedure is to choose a reagent which is more nucleophilic than the leaving group. Thus, Feutrill and Mirrington[178] have developed a method for demethylating aryl methyl ethers using thioethoxide ion, $EtS^{\ominus}$, in hot DMF. In view also of Crampton's order of carbon nucleophilicity,[179]

$$EtS^{\ominus} > MeO^{\ominus} > PhS^{\ominus} > EtO^{\ominus} > PhO^{\ominus}$$

it was reasoned that aryl methyl sulphides should undergo a displacement reaction with the anion of an alkanethiol. Indeed, aromatic thiols have recently been prepared by treatment of unactivated aryl halides with sodium methanethiolate, MeSNa.[180] The reaction involves initial nucleophilic aromatic substitution to produce the aryl methyl sulphide, which can be isolated, followed by nucleophilic displacement (see overleaf).

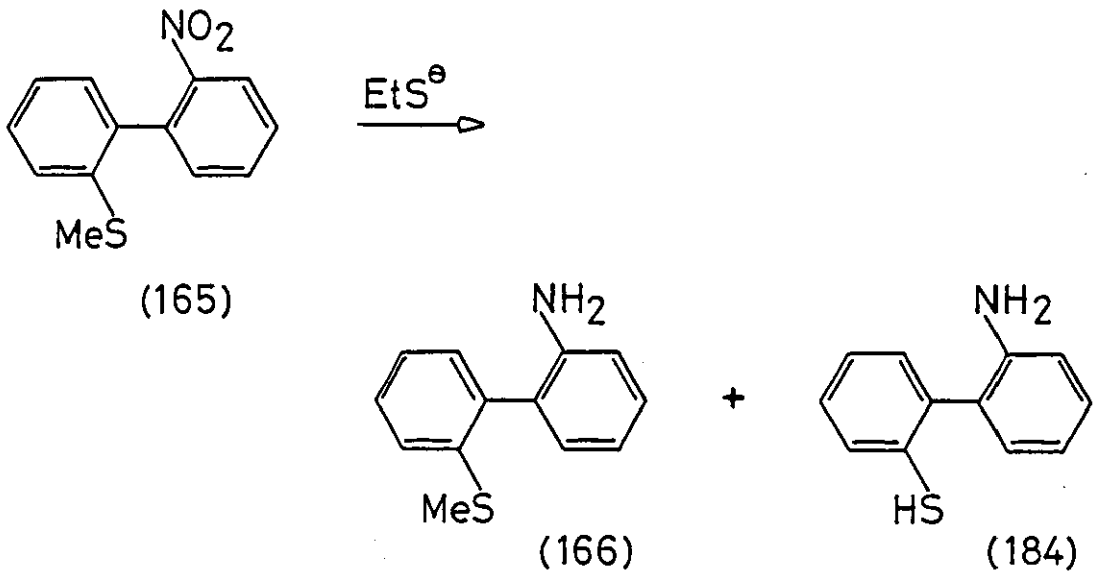


The use of a dipolar aprotic solvent is expected to enhance S_N2 attack on the methyl group, as depicted below.



Model studies revealed that thioanisole, when heated with a 2.5 fold excess of thioethoxide ion under nitrogen for three days, gives a 45% yield of thiophenol. The remainder of the product was unreacted starting material, which emphasises the reluctance of sulphides to cleave in contrast to ethers. When 2-methylthio-2'-nitrobiphenyl was subjected to identical conditions, no nitroaromatic products could be isolated. Instead, 2-amino-2'-methylthiobiphenyl (166) was identified, and a small amount of demethylated substance, which gave evidence for 2-amino-2'-mercaptobiphenyl (184), was detected. (see overleaf).

To substantiate this observation, nitrobenzene was reduced to aniline in 65% yield, and p-nitrothioanisole gave p-thioanisidine. It therefore seems apparent that the thioethoxide ion has a greater tendency to reduce an aromatic nitro function than it has to displace a methyl group bonded to sulphur. The reduction may bear some semblance



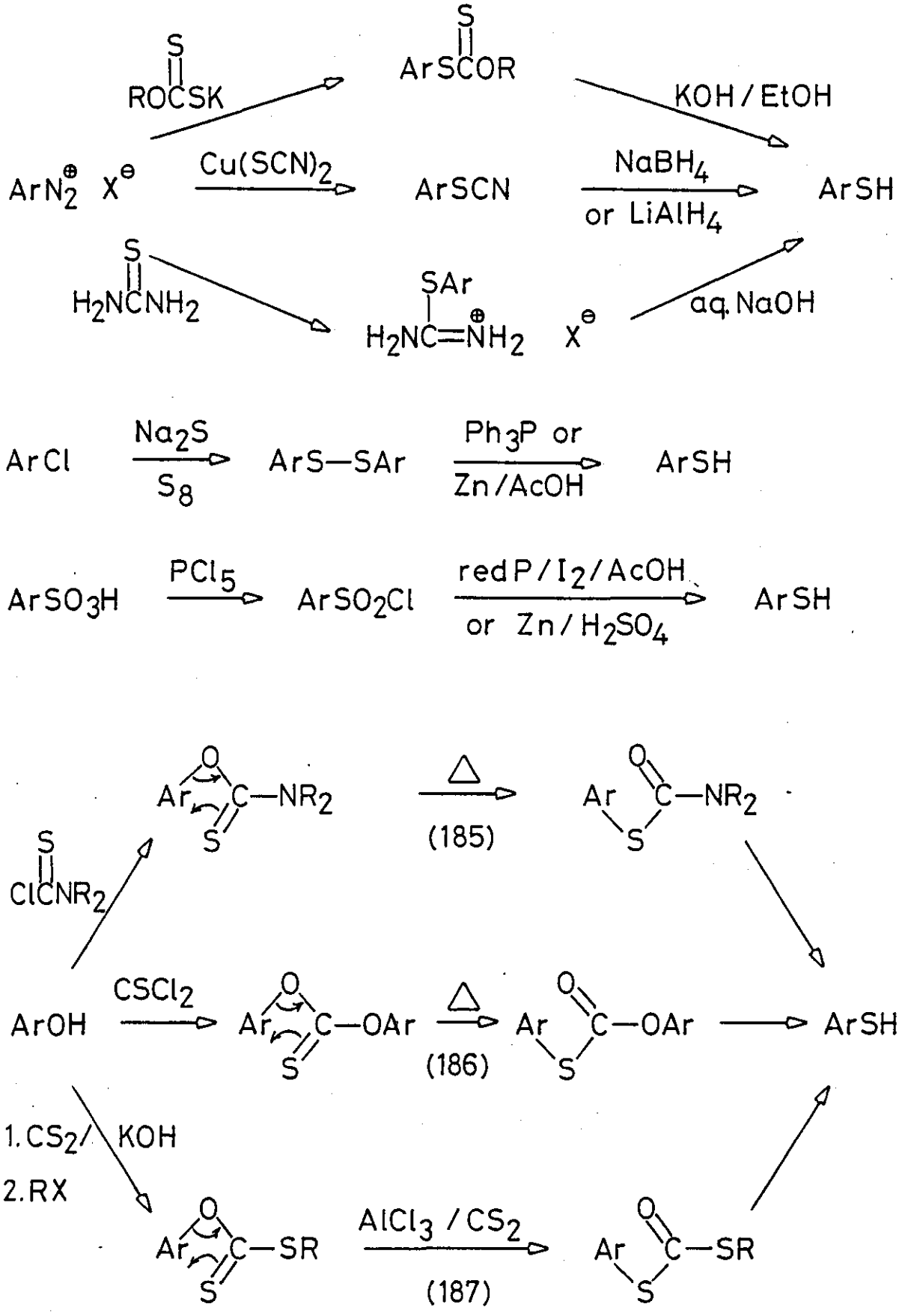
to a similar transformation effected by sulphides and polysulphides (Zinin reduction: see Chapter 5.3).

b. Other Thiophenol Syntheses

The preparation of aromatic thiols has been reviewed extensively by Wardell,[172] and methods include the use of arenediazonium salts (overall, $ArNH_2 \rightarrow ArSH$), disulphides,[173] and phenols.[181, 182] Some examples are illustrated in Scheme 24 (see overleaf).

A well-established method for converting a phenol into a thiophenol is that developed by Newman and Karnes (185).[181] It uses the route, phenol to O-aryl dialkylthiocarbamate, then pyrolysis to S-aryl dialkylthiocarbamate and alkaline hydrolysis to thiophenol. Methods for accomplishing each step in high yield are described. In addition, since the thiol compounds formed are readily desulphurised by heating with Raney nickel, the overall transformation of a phenol to the corresponding hydrocarbon may be accomplished.

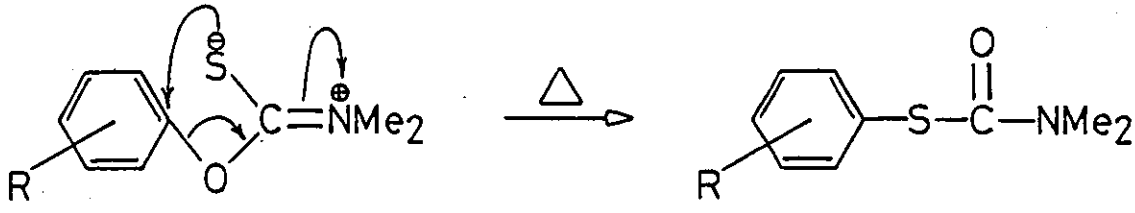
Independent of Newman, and at about the same time, Kwart and Evans[182] reported the vapour phase rearrangement at 400° of two O-aryl diethylthiocarbamates (R = Et) to the corresponding S-aryl compound. They also studied the Schönberg rearrangement[183] of di-O-aryl thiocarbonates (186), but this procedure is limited to a



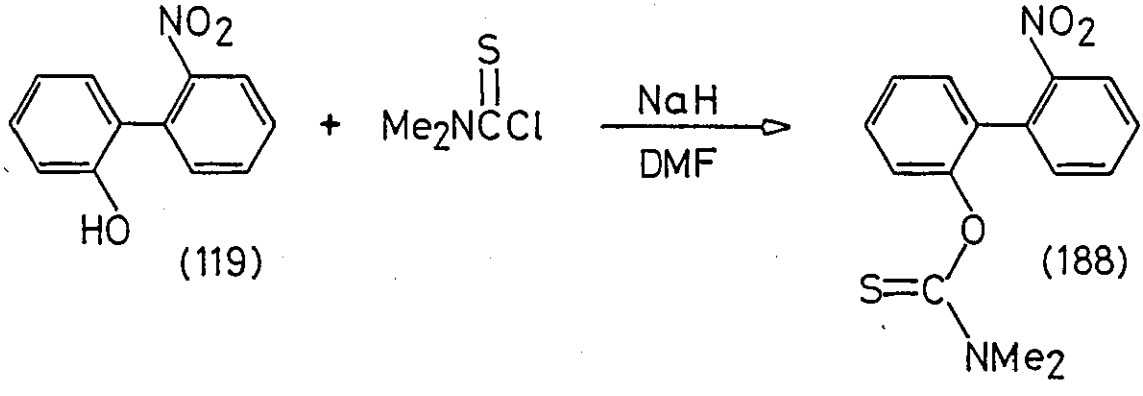
Scheme 24. Synthesis of Aromatic Thiols

maximum possible yield of 50% with respect to thiophenol formation. More recently, the related Kawata-Harano-Taguchi rearrangement (187) has been introduced.[184]

The driving force for each of the above rearrangements appears to originate from the nucleophilic character of sulphur in displacements on carbon, and the leaving group tendency of oxygen that correlates with its high electronegativity. Reaction is intramolecular and in keeping with a four-membered cyclic transition state, and the desired polarisation is assisted especially by a dialkylamino group (185).



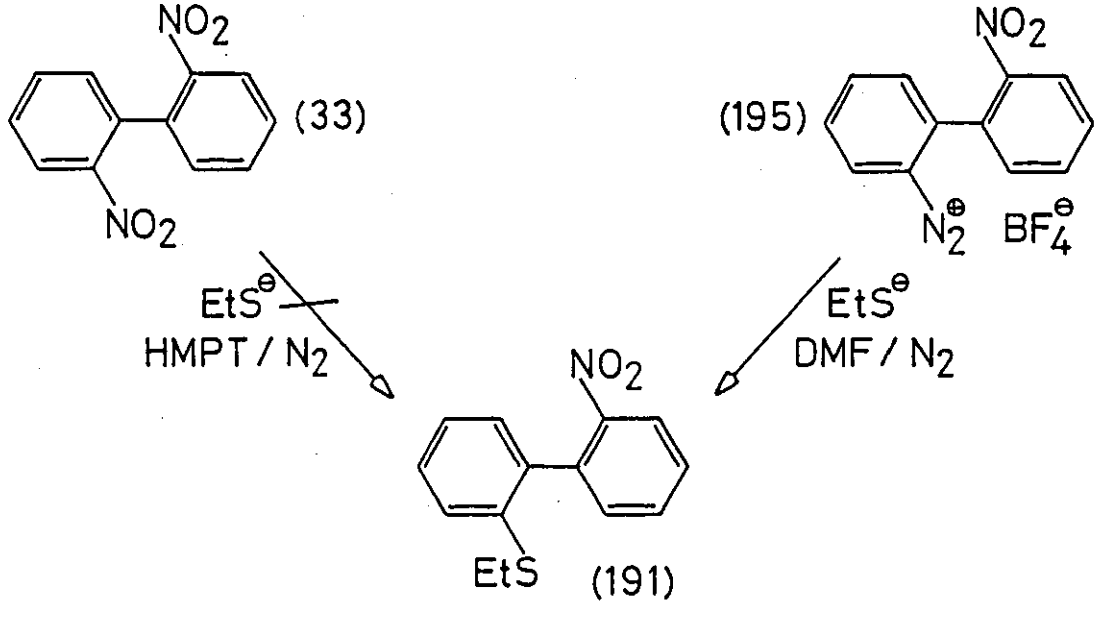
As a result, the Newman-Kwart procedure was adopted in an attempt to transform the readily available phenol (119) into the desired sulphur analogue (182). Treatment of the sodium salt of 2-hydroxy-2'-nitrobiphenyl with N,N-dimethylthiocarbamoyl chloride afforded O-2-(o-nitrophenyl)phenyl N,N-dimethylthiocarbamate (188) in 22% yield. However, prolonged heating of the neat reagent at 200° produced no rearranged material.

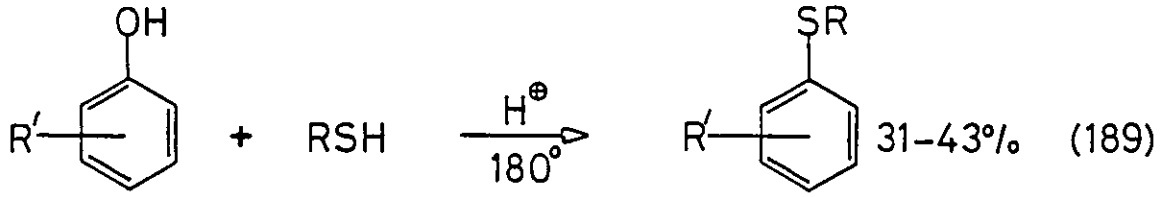


c. Direct Synthesis of Alkyl Aryl Sulphides

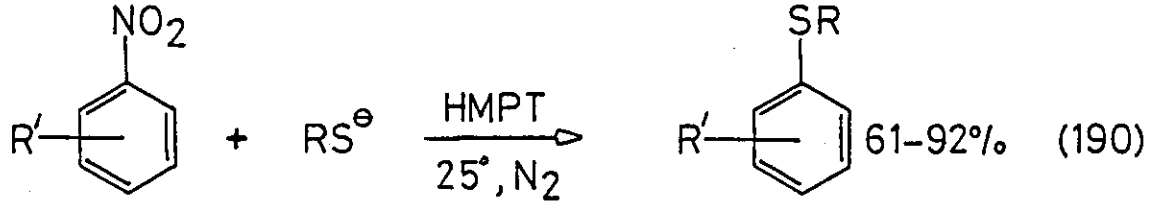
Many sulphide preparations depend on the transformation of another sulphur-containing functional group, eg, reduction of disulphides.[175] Several methods in particular are available for the reduction of sulphoxides (eg, [137], p 33), and often involve the intermediacy of a sulphonium species.[185, 186] Nonetheless, methods do exist by which sulphur nucleophiles undergo aromatic substitution reactions, and which appeared more relevant to our aims. These are summarised in Scheme 25 (see overleaf).

Oae and Kiritani[187] have shown that addition of an alkanethiol to a mixture of a phenol and concentrated hydrochloric acid gives the corresponding alkyl aryl sulphide (189). However, the method requires heating at 180° for a few days in a sealed tube, and yields are moderate (20-40%). Kornblum's procedure[188] seemed more promising. His team showed that nitrobenzenes substituted by a variety of electron-withdrawing groups undergo displacement of the nitro group by nucleophiles at 25° if reaction (190) is conducted in a dipolar aprotic solvent. Accordingly, 2,2'-dinitrobiphenyl (33) was treated with sodium thioethoxide in hexamethylphosphoric triamide (HMPT), but no 2-ethylthio-2'-nitrobiphenyl (191) was obtained.

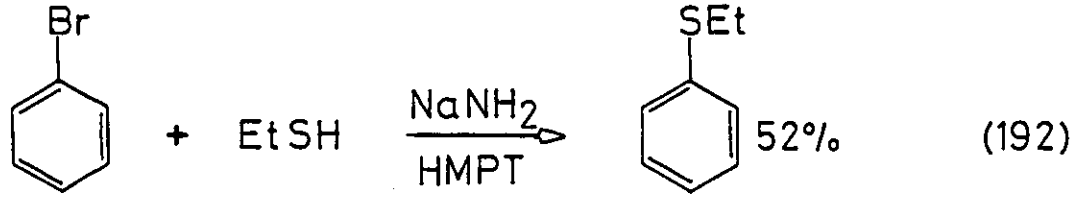


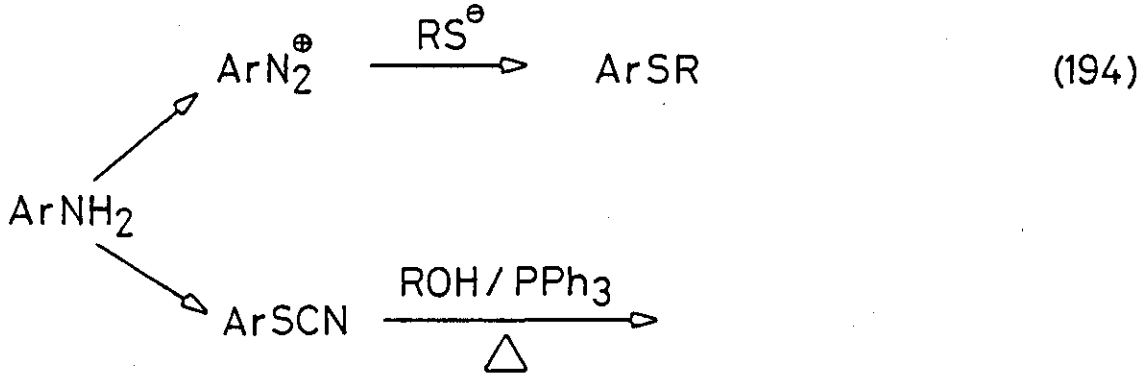


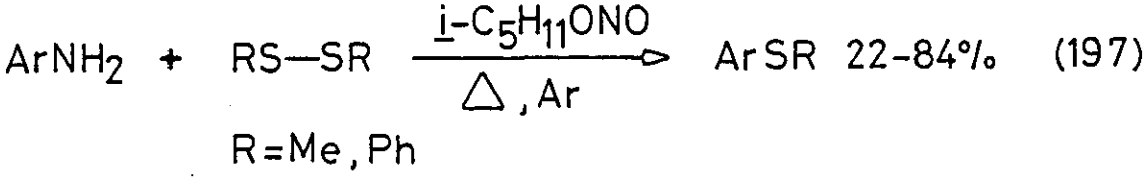
R = H, Me R = n-Bu, $PhCH_2$, Ph



R = Me, $PhCH_2$, Ph



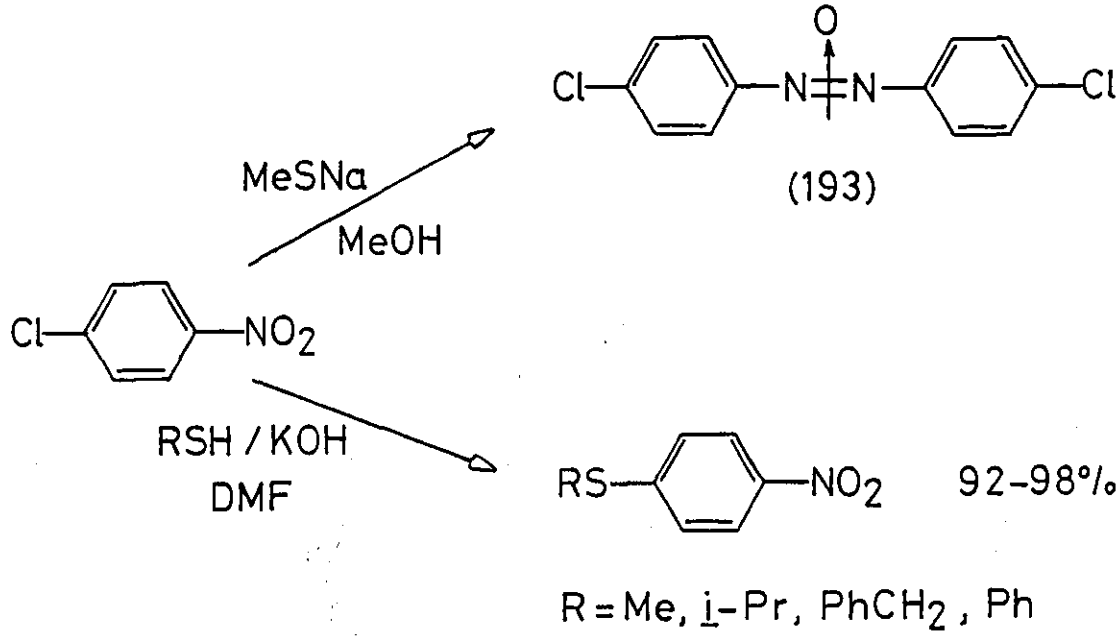




R = Me, Ph

Scheme 25. Synthesis of Alkyl Aryl Sulphides

Instead, reduction of the nitro group was predominant, as observed in earlier attempted demethylation studies (a), and this agrees with similar findings in the literature. Thus, the use of direct thioalkylation of arylhalides, eg,(192), is often a convenient route to sulphides,[189] but with halonitrobenzenes the desired reaction can be almost completely precluded by reduction of the nitro group, as illustrated by almost total formation of the azoxybenzene (193).[190] More recently, however, the versatility of this unpredictable reaction has been improved by generating the thiolate anion in the presence of both excess thiol and aromatic substrate, and by performing the reaction in DMF.[191]



(193)

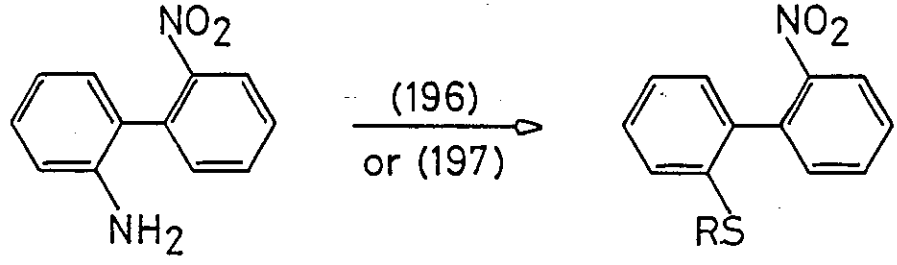
A frequently cited sulphide synthesis is the reaction (194) of arenediazonium salts with thiolate ions.[187, 192] Therefore, 2'-nitrobiphenyl-2-yldiazonium tetrafluoroborate (195) was added to a solution of sodium thioethoxide in DMF. After two days a product was isolated which contained the S-ethyl group, but both the corresponding nitro (191) and amino biaryls were evident. It is possible that modification of the reaction conditions might provide a one-step

route to the amino sulphide.

Finally, two alternative routes from primary aromatic amines may be considered. These can be converted to aryl thiocyanates either via diazonium salts (see Scheme 24) or via pyrylium and pyridinium salts.[106] Subsequent reaction (196) with primary alcohols in the presence of triphenylphosphine gives alkyl aryl sulphides in high yield,[193] but competitive eliminations occur with secondary, and especially tertiary, alcohols.

The diazotisation of some amines is only moderately successful, so that overall yields of sulphides are low. However, with regard to Cadogan's generation of aryl radicals,[13] a simple preparation (197) of alkylthio aromatic compounds has been effected using isopentyl nitrite and the appropriate disulphide.[194] The technique is equally successful with amines containing both electron-withdrawing and electron-donating substituents, and thereby possesses a further advantage over the use of diazonium salts.

Application of these methods to 2-amino-2'-nitrobiphenyl (198) would now seem the next appropriate area of investigation.



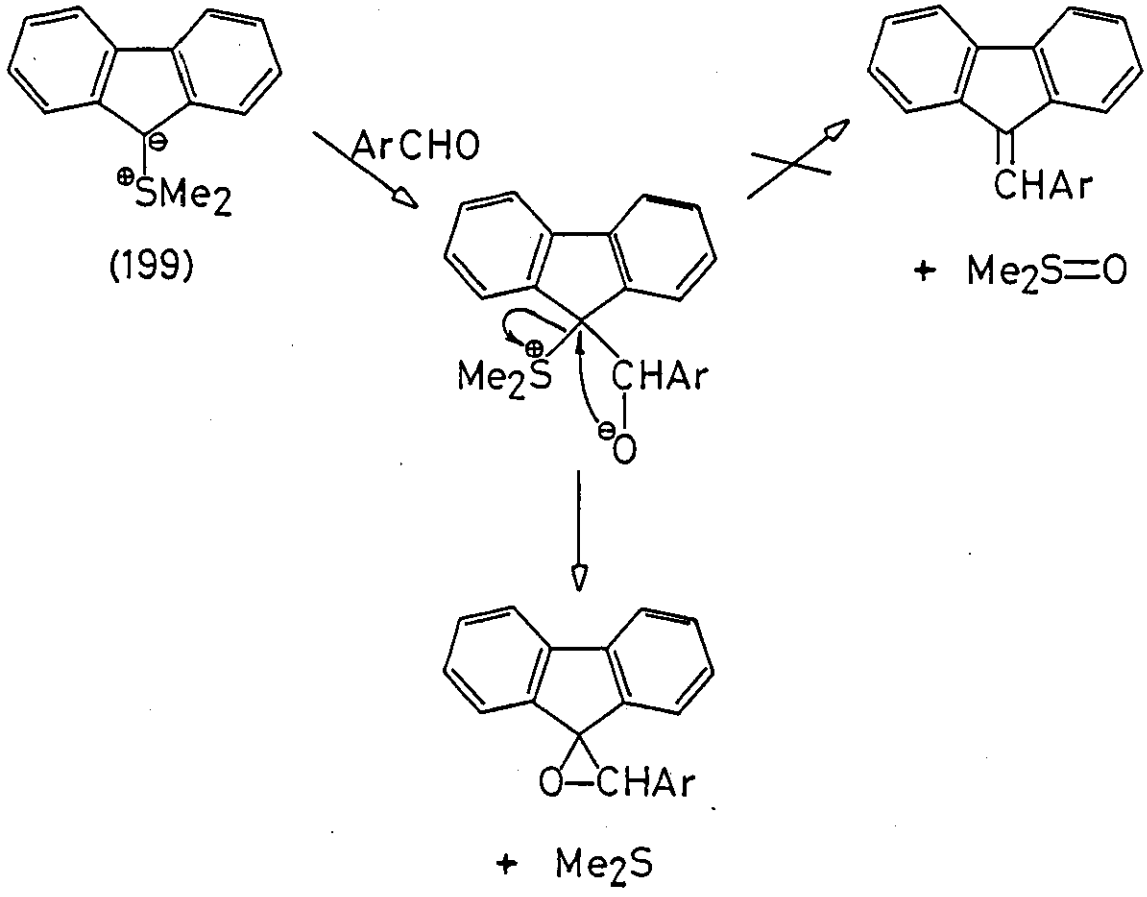
(198)

3.3 SULPHONIUM YLIDES[195]

There has been a great deal of recent interest in this aspect of the chemistry of sulphonium salts because of the importance of sulphonium ylides in a number of novel synthetic procedues, and because of their postulated role in biogenetic sequences. Reactions of sulphonium salts under basic conditions, such as the Stevens and Sommelet rearrangements, almost certainly involve ylide intermediates. Reviews by Durst,[196] Lowe,[197] and Johnson[198] are available.

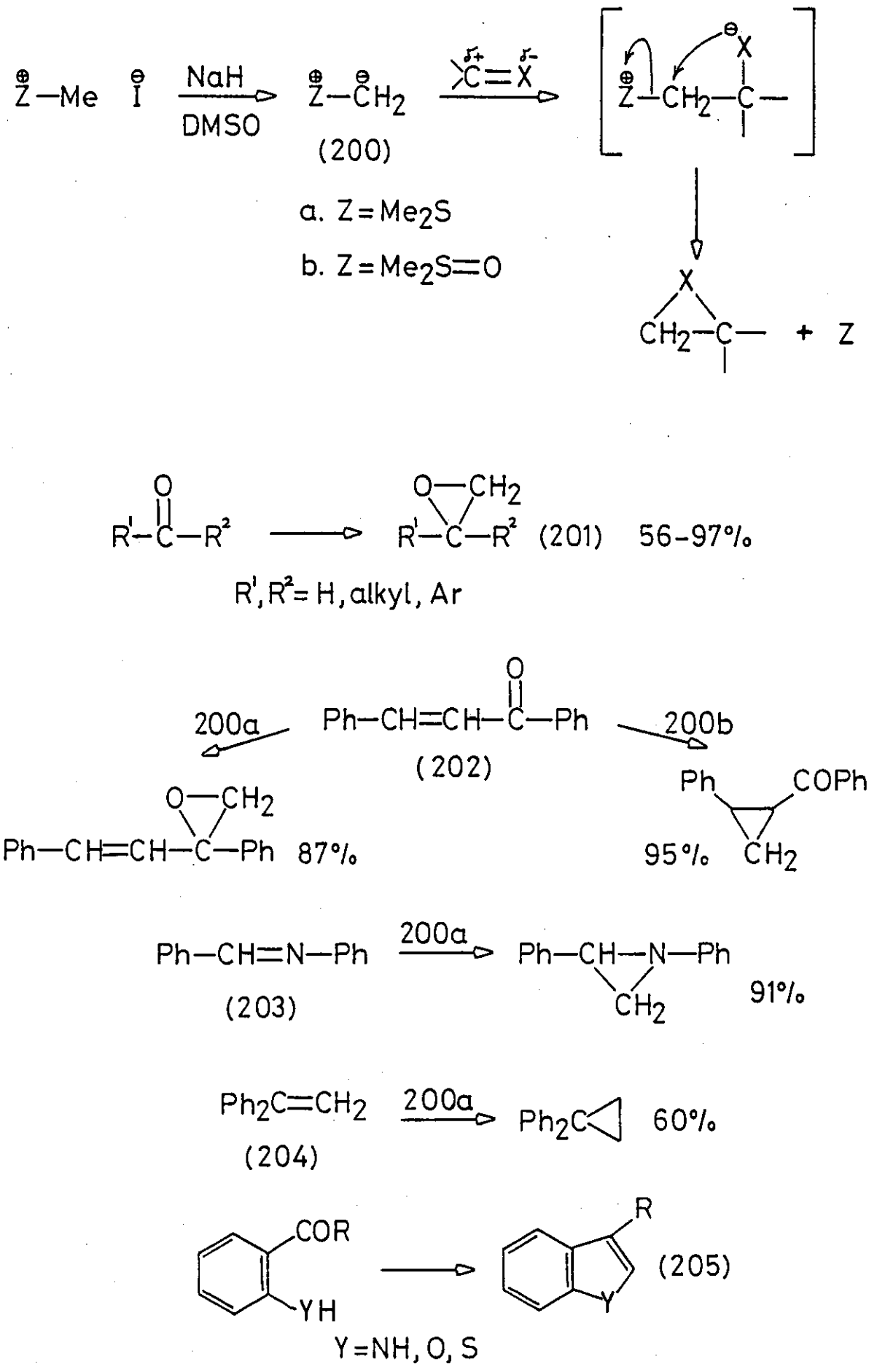
Sulphonium ylides represent a class of compound in which a carbanion is stabilised by an adjacent positively charged sulphur, and proton transfer from sulphonium salts is the most common method of preparation. The first to be isolated was the resonance-stabilised dimethylsulphonium fluorenylide (199), which Ingold[199] obtained in 1930 by reaction of the corresponding sulphonium bromide with aqueous sodium hydroxide. However, further activity was not forthcoming until Johnson and LaCount[200] attempted to parallel the successful Wittig reaction of phosphonium ylides. They observed that the ylide (199), with substituted benzaldehydes, gave epoxides instead of the anticipated olefins, and the difference in reaction pathway was attributed to the superior leaving ability of the sulphonium group (see overleaf).

Since then the preparation and reactions of many other sulphonium ylides have been examined. Particular reference is made to the excellent work of Corey and Chaykovsky,[201] who reported findings on the chemistry of two reactive methylides. Dimethyl-sulphonium methylide (200a) is generated and utilised at low temperature (0-10°), but the more stable dimethyloxosulphonium methylide (200b) can be used at room temperature. Both require a strong base such as sodium hydride in DMSO for their formation, and each exhibits a reactivity typical of carbanions towards



carbonyl groups and other electrophilic double bonds. The high yields of three-membered ring compounds which result benefit from the fact that both the reagent and the leaving group are neutral molecules. The general sequence is shown in Scheme 26, together with some applications to organic synthesis (see overleaf).

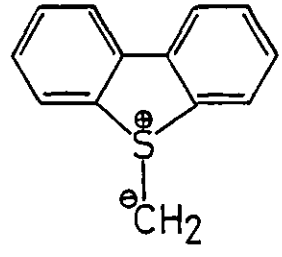
Each ylide reacts with nonconjugated aldehydes and ketones to produce an epoxide (201). However, the sulphonium ylide (200a) is a far more powerful methylene transfer agent, and this difference is reflected in the modes of addition to α, β-unsaturated substrates. Thus, α, β-unsaturated ketones, such as benzalacetophenone (202), react with dimethylsulphonium methylide to give the kinetically controlled unsaturated epoxide, but the oxosulphonium ylide (200b) undergoes conjugate addition to produce a thermodynamically stable cyclopropyl ketone. The more nucleophilic reagent also gives cleaner



Scheme 26. Reactions of Sulphonium Ylides (200a, b)

aziridine syntheses with imines such as benzalaniline (203), and activated olefins, eg (204), in general yield cyclopropanes. Unactivated olefins do not react. When aromatic carbonyl compounds possess suitable substituents on adjacent atoms, various heterocyclic systems can be produced (205) via epoxide intermediates.[202]

This utility in synthesis prompted investigations into the possibility of effecting analogous transfer reactions involving alkyl-substituted methylene (alkylidene) groups. Although the corresponding mono- and dialkylated ylides are unstable, they can be generated at low temperature (-78°) using strong soluble bases, and conditions are now defined for efficient alkylidene transfer from ylides of the type $Ph_2\overset{\oplus}{S}-\overset{\ominus}{C}HR$,[203] and $Ph_2\overset{\oplus}{S}-\overset{\ominus}{C}RR'$.[204] In view of the above results, an attempt was made to generate the methylide (206) and to study its reactions with carbonyl compounds.

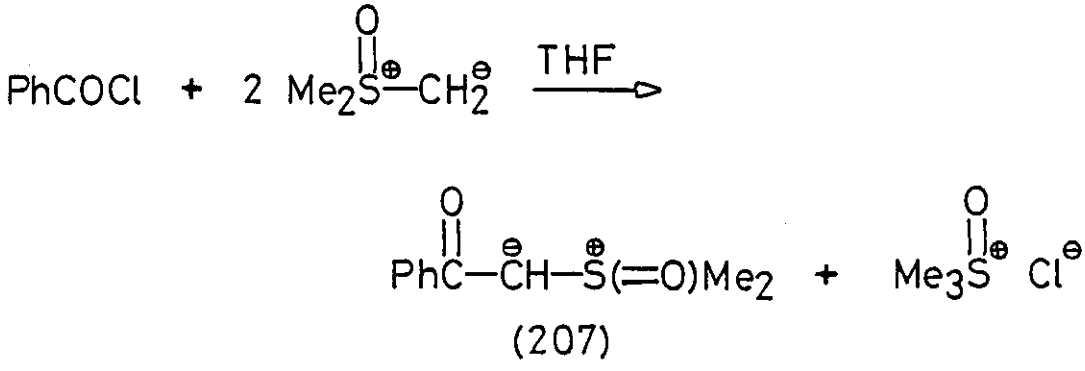


(206)

S-Methyldibenzothiophenium tetrafluoroborate (161, R = Me) was treated both with the methylsulphinyl carbanion, $MeSOCH_2^{\ominus}$, at 0°[201] and with n-butyl lithium at -70°.[203] However, addition of benzaldehyde afforded no styrene oxide, and dibenzothiophen was obtained quantitatively in each case.

The presence of electron-withdrawing groups adjacent to the carbanionic centre in ylides confers considerable stability. Thus, dimethyloxosulphonium methylide (200b) can be acylated with reactive carboxylic acid derivatives such as acid chlorides and phenyl esters

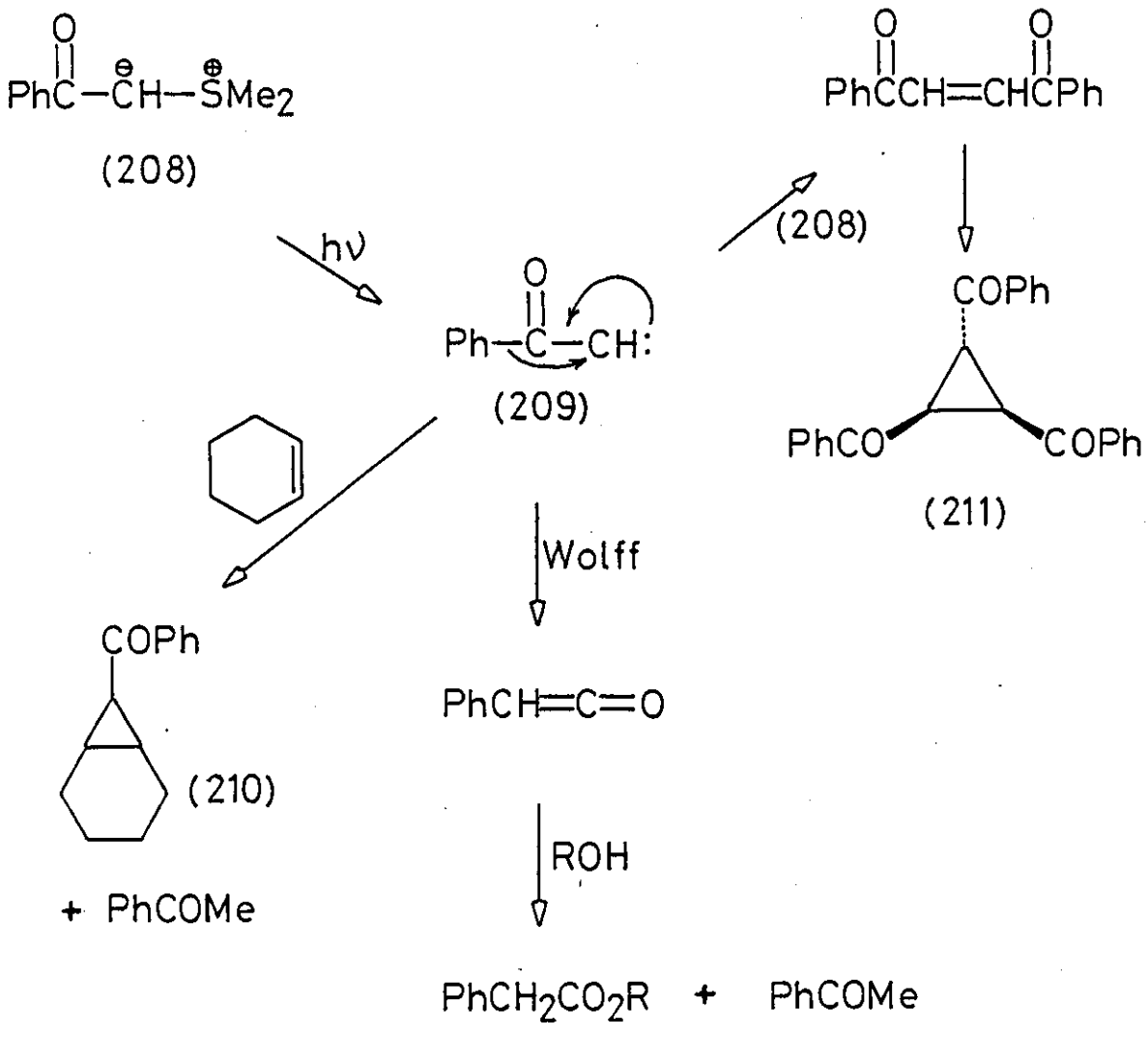
to give β-keto-oxosulphonium ylides, eg (207), which can be isolated and stored.[205] Such stabilised ylides are necessarily less reactive, so that the related dimethylsulphonium phenacylide (208), has been shown to react only with suitable Michael acceptors to produce cyclopropanes.[206]



(207)

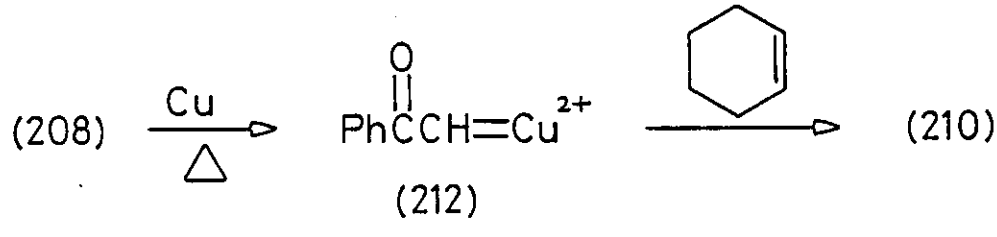
However, the most interesting property of these ylides is their susceptibility to photochemical decomposition,[205] and it was Trost[206] who recognised the similarity between sulphur ylides and aliphatic diazo compounds. The latter can be considered to be nitrogen ylides, $R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} \leftrightarrow R_2\overset{\ominus}{C}{-}\overset{\oplus}{N}{\equiv}N$, and both classes of intermediates form epoxides from aldehydes and ketones, form cyclopropanes from olefinic compounds, and undergo Wolff rearrangement upon photolysis. That the photochemical behaviour of (208) was similar to that of diazoacetophenone, $PhCOCHN_2$, represents compelling evidence for a benzoylcarbene intermediate (209), and enables analogies with the Arndt-Eistert reaction to be made. See Scheme 27 (see overleaf).

The transfer of an alkylidene group to a carbonyl derivative has applications in natural product synthesis, where epoxides and cyclopropanes occur quite often. Furthermore, the biosynthesis of the cyclopropane ring in a number of natural products is now known to occur by the transfer of a methylene group from the methyl group of S-adenosylmethionine (151) to an unactivated olefin.[207] Involvement of the corresponding methylide was proposed. It had previously been shown[205] that thermally stable ylides decompose



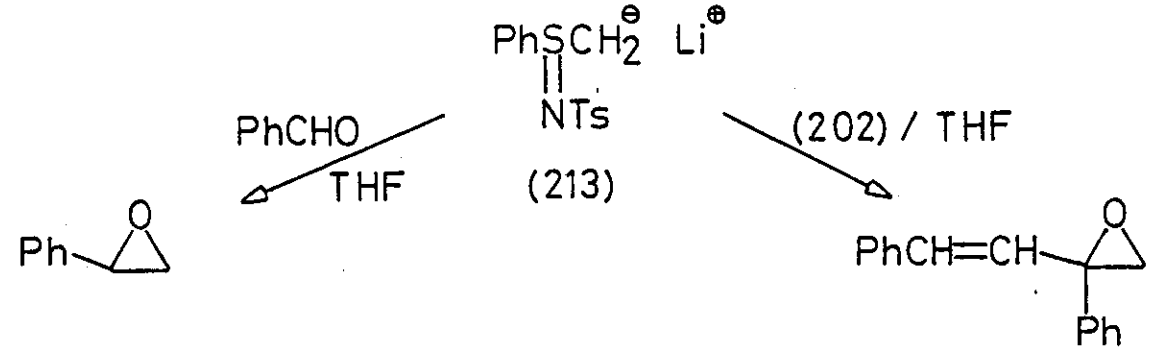
Scheme 27. Photochemical Decomposition of Sulphonium Ylides

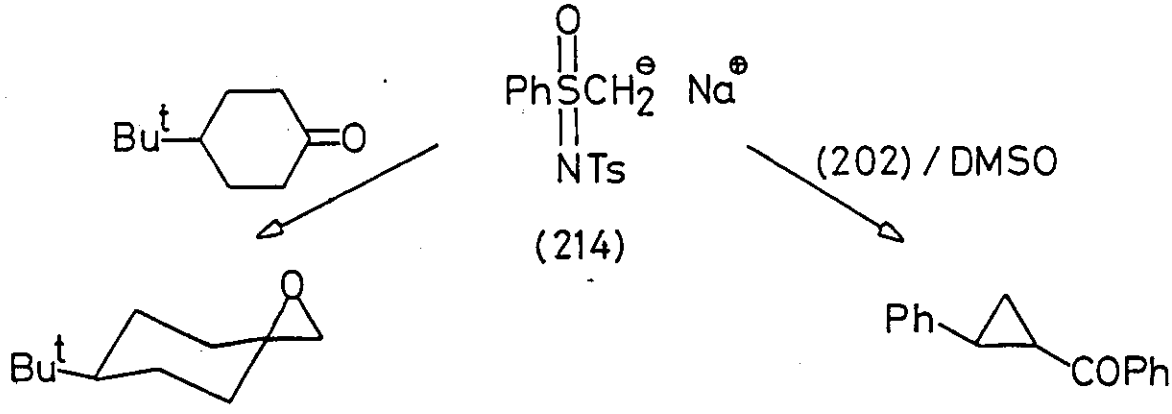
when heated in the presence of copper(II) sulphate in a like manner to diazoalkanes. The formation of benzoylnorcarane (210) in addition to trans-1,2,3-tribenzoylcyclopropane (211), using cyclohexene as solvent, was attributed to the presence of a copper-carbene complex (212).



Accordingly, the biosynthetic reaction has been interpreted in terms of copper-catalysed methylene transfer via a complex such as $^{\oplus}Cu{=}CH_2$,[208] and the credibility of the scheme was demonstrated by the cyclopropanation of olefins with diphenylsulphonium methylide at room temperature. No reaction occurred in the absence of copper(II) acetylacetonate.

Alkylidene transfer reactions are not limited to sulphonium ylides and diazoalkanes. Effective alternatives include the anions of N-p-tolylsulphonyl-sulphimides (213)[209] and -sulphoximides (214).[210] The former appear to react like sulphonium ylides, and the latter like oxosulphonium ylides. Simplicity of preparation and manipulation, and high yields, make these reagents attractive synthetic intermediates.



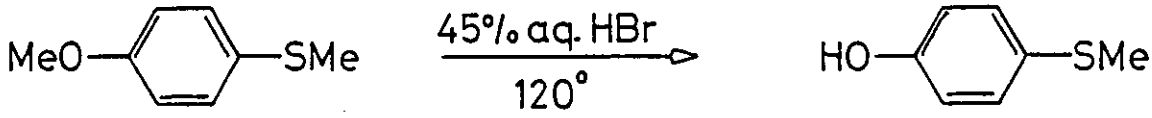


CHAPTER 4

HYDROXYL AND SULPHYDRYL PROTECTIVE GROUPS AND CLEAVAGE REAGENTS

INTRODUCTION

During the course of work described within the previous two chapters it was found that an aryl methyl sulphide (165) is considerably more resistant to demethylation than the corresponding ether (47). This is extremely well illustrated by the cleavage of (p-methylthio)anisole (215) under Zeisel-type conditions.[211]



(215)

The cleavage of ethers has been reviewed by Burwell,[212] who classified the various methods into the following groups. Sulphides generally are subjected to similar processes, but react very much less readily with both acidic and basic reagents.

1. Cleavage by acidic reagents, involving an oxonium intermediate.
2. Cleavage by nucleophilic reagents in the absence of acids.
3. Cleavage by alkali metals.
4. Cleavage by reactions involving heterogeneous catalysts.

It seemed that if an efficient technique for S-demethylation was available, then the use of the methyl function as a protecting group for thiols could become more widespread. At present, alkyl aryl sulphides are only occasionally used if the alkyl group can be removed by hydrogenolysis with sodium in liquid ammonia.

There exists an ever-increasing need of protective groups for the synthesis or transformation of large and complex molecules such as carbohydrates, nucleotides, peptides, and steroids. This is usually accomplished by forming a derivative which is stable under the conditions to be used on another part of the molecule, but from

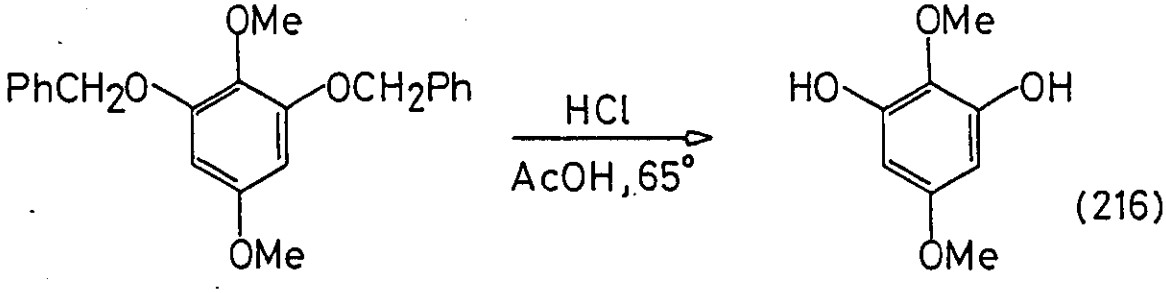
which the protected group can be regenerated. Use may also be made of indirect methods involving chelation or steric hindrance. The protection of O-H and S-H bonds in both aliphatic and aromatic systems has received extensive coverage in reviews by McOmie[213, 214] and very recently by Greene.[215] It is effected in most cases by acylation (eg acetates, benzoates, sulphonates, and carbomethoxy derivatives) or alkylation, but a method unique to thiols is oxidation to the disulphide.

This chapter sets out to discuss ways in which both ethers and sulphides can be prepared and cleaved, with particular reference being made to improvements over conventional procedures by recent developments. With regard to our own interests, special attention is given throughout to the protection of thiophenols and the demethylation of corresponding methyl sulphides. Recent evidence,[180] whereby an intermediate aryl methyl ether was cleaved by nucleophilic displacement, indicates that the methyl group may indeed be viable as a sulphur protecting agent. The section ends with a summary of results obtained when the methoxy- and methylthio-biaryls (47, 165) were treated with a variety of cleavage reagents.

4.1 HYDROXYL AND SULPHYDRYL PROTECTING GROUPS

Many alkyl ethers have found extensive use in organic chemistry as protecting groups for alcohols. Foremost among these are benzyl, triphenylmethyl (trityl), and t-butyl ethers, all of which can be removed under relatively mild conditions, ie hydrogenation, mild aqueous acid, and non-aqueous acid, respectively. Methyl ethers of primary and secondary alcohols are stable under both acidic and basic conditions, but as a result are difficult to cleave and therefore little used.

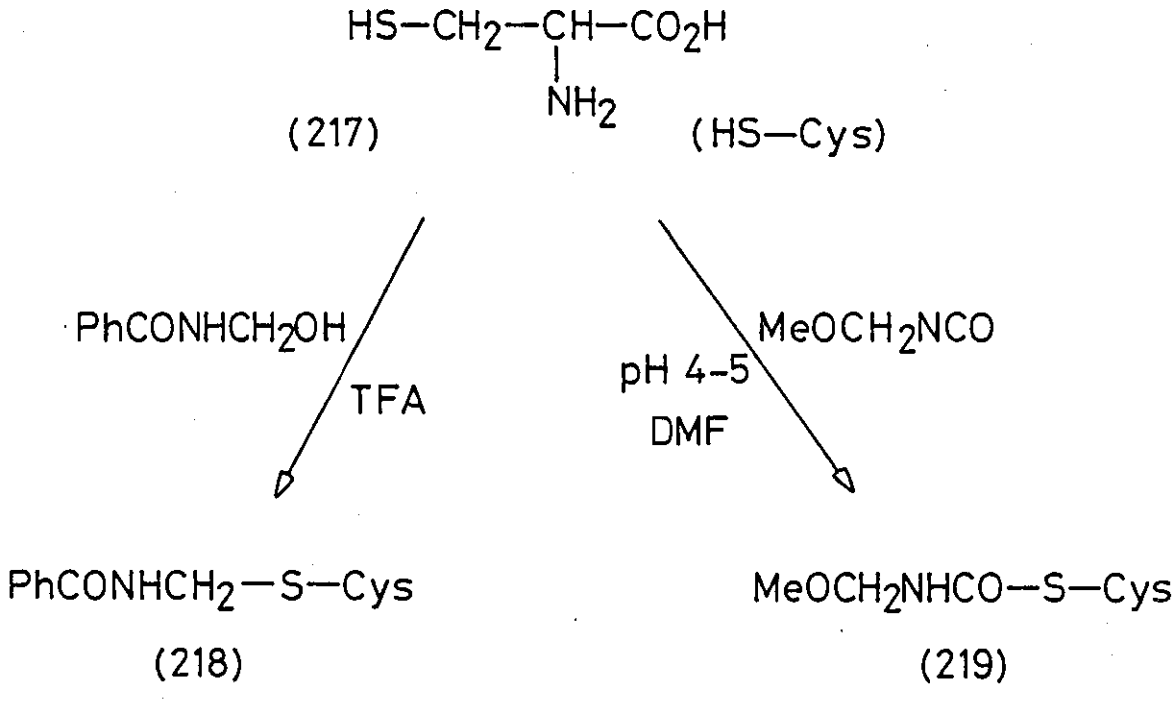
On the other hand, methyl ethers are the most commonly used protective groups for phenols.[212] They are easily prepared, are stable to a wide variety of reagents, and then are easily cleaved. In fact, the synthesis of compounds containing a mixture of free and methylated phenolic groups is sometimes best achieved by partial demethylation of the fully methylated product. Benzylic ethers of phenols are also widely used, and allow for selective removal in the presence of methoxy groups by acid hydrolysis or catalytic hydrogenation. This is exemplified in a synthesis of 2,5-dimethoxyresorcinol (216).[216]



(216)

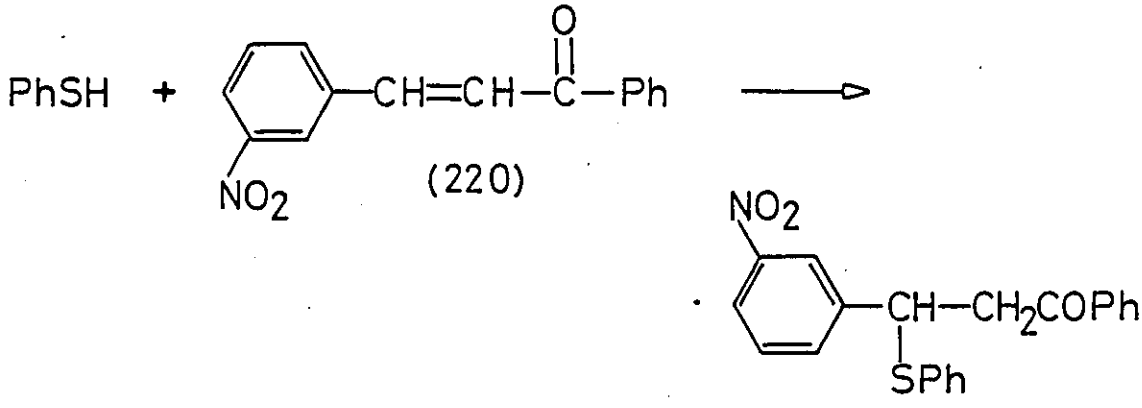
Benzylation has been the most common method of protecting aliphatic thiols, and occupies significant importance in syntheses of peptides containing cysteine (217) or cystine. Trifluoroacetic acid has proven an effective solvent and catalyst for the preparation of S-trityl derivatives[217] but new thiol protecting groups are of current interest. Thus, the S-benzyl group is now little used, and has been replaced by

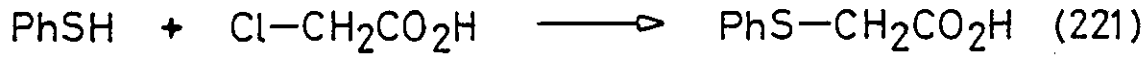
the S-acetamidomethyl (Acm) group[218] in complex peptide syntheses. The related benzamidomethyl (Bam) group of (218) is stable to a wide variety of conditions and is cleaved at pH4 in the presence of mercuric acetate.[219] Complementary to this is the carbamoyl derivative (219), which is prepared by reaction with methoxymethyl isocyanate at pH4-5 and which is cleaved in aqueous alkali.[220] Very recently, the utility of an S-t-butyl group has been demonstrated.[221] Other thiol protecting groups such as benzyl and acetamidomethyl can be removed selectively, and the t-butyl sulphide is cleaved by treatment with (2-nitrophenyl)sulphenyl chloride (NpsCl), followed by reduction.



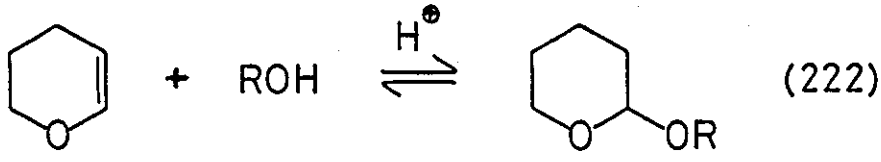
Special mention is accorded to thiophenols, the sulphur atom of which must be protected prior to carrying out electrophilic substitution reactions in the benzene ring. Removal of an alkyl protecting group, or the introduction of substituents prior to the thiol group, are not attractive possibilities. However, an improved method[222] utilises the ability of thiols to add to activated double bonds, such as that in 3-nitrobenzalacetophenone (220). The resulting substituted benzyl

sulphide is amenable to acetylation, bromination, and nitration in the thiophenyl ring, and subsequent removal of the blocking group with basic lead acetate occurs smoothly. Phenylmercaptoacetic acids (221) may be used to the same effect, the carboxymethyl group being readily removed by acid hydrogen peroxide.[223]



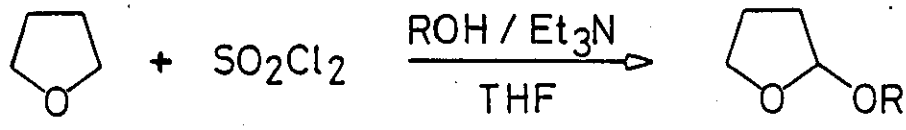


Tetrahydropyranylation of hydroxyl groups is a widely recognised method for the protection of alcohols. The so formed 2-tetrahydropyranyl (THP) ethers (222) are stable to alkali and nucleophilic reagents, but hydrolyse easily in aqueous mineral acids. Although p-toluenesulphonic acid is the usual catalyst employed, a more efficient preparation of THP ethers from acid-sensitive alcohols uses pyridinium p-toluenesulphonate (PPTS).[224]



At about the same time, it was shown[225] that tetrahydrofuranyl (THF) ethers (223) can be hydrolysed under still milder acidic

conditions, whilst retaining stability to the conditions of organometallic, Wittig, and metal hydride reactions. Interestingly, the procedure is applicable also to phenols and to aliphatic and aromatic thiols, as verified for the semithioacetal (224). Catechols, by virtue of their ortho disposed hydroxyl groups, can be protected in ketal form (225).



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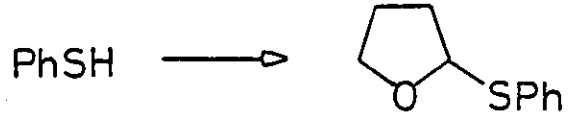

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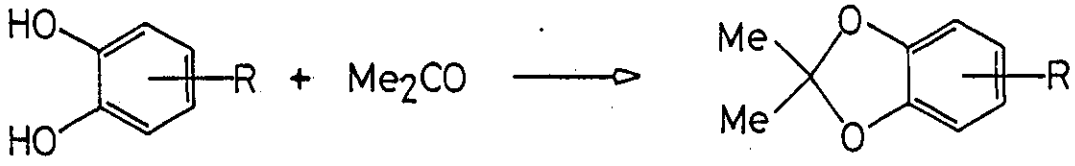
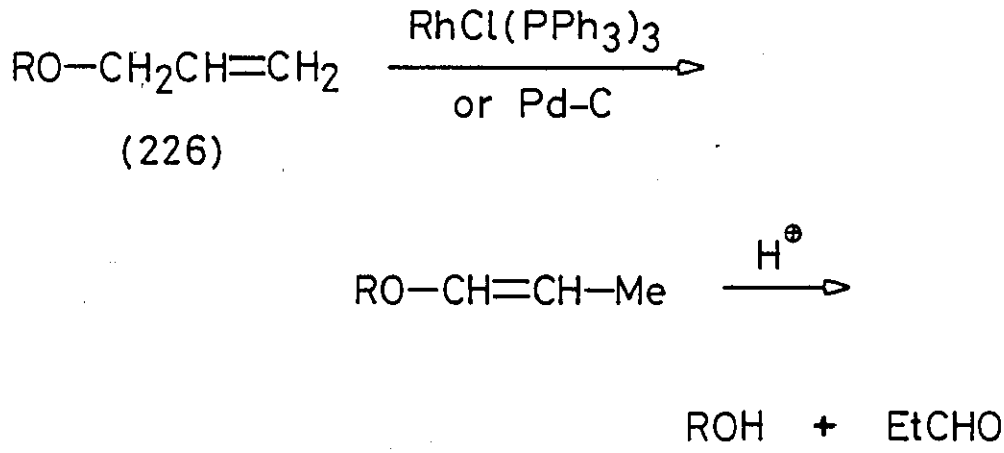


(225)

Allyl ethers (226) are to a large extent stable to acid and base, and have found application as protecting groups in carbohydrate chemistry.[226] Cleavage can be carried out selectively by catalysed isomerisation to the corresponding enol ether, followed by hydrolysis. Suitable reagents for the isomerisation step include rhodium (I) complexes[227] and palladium on activated charcoal,[228] the latter also being compatible with phenolic derivatives (see overleaf).

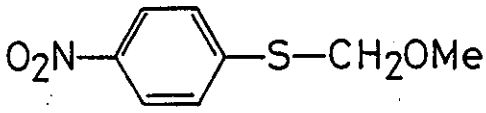
In many instances, the use of common protecting groups such as methyl, benzyl, acetyl, and benzoyl is precluded. Removal would require conditions which may induce molecular rearrangements or cause



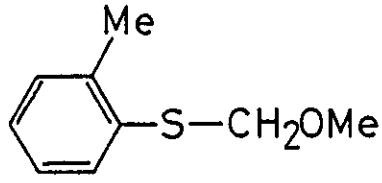
the destruction of other sensitive functional groups, as in the synthesis of flavanoid partial methyl ethers. However, a useful method for the partial protection of hydroxyl groups in polyphenolics by methoxymethylation has been developed.[229] Deblocking is carried out under mild acid conditions.

Whilst this protecting group has conventionally been introduced using the readily available methoxymethyl chloride, the reagent is carcinogenic. An effective alternative[230] uses dimethoxymethane as source of the methoxymethyl cation. It is suitable for thiophenols, eg (227a, b), but requires conversion of the substrate into an organozinc derivative. Similar protection of alcohols is common in natural product synthesis, and a new facile preparation[231] of methoxymethyl ethers (228) involves reaction with dimethoxymethane in the presence of a solid superacidic catalyst (Nafion-H) (see overleaf).

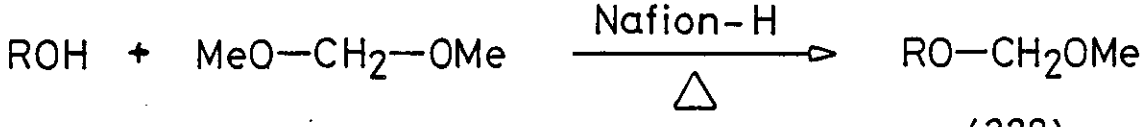
The 1-oxido-2-pyridylmethyl (OP) group has found use in the protection of nucleosides and nucleotides.[232] It is quite stable both to alkaline or acid conditions, but is readily removed by treatment with acetic anhydride, followed by hydrolysis. Applications include the synthesis of biologically important thiol derivatives, but



(227a)

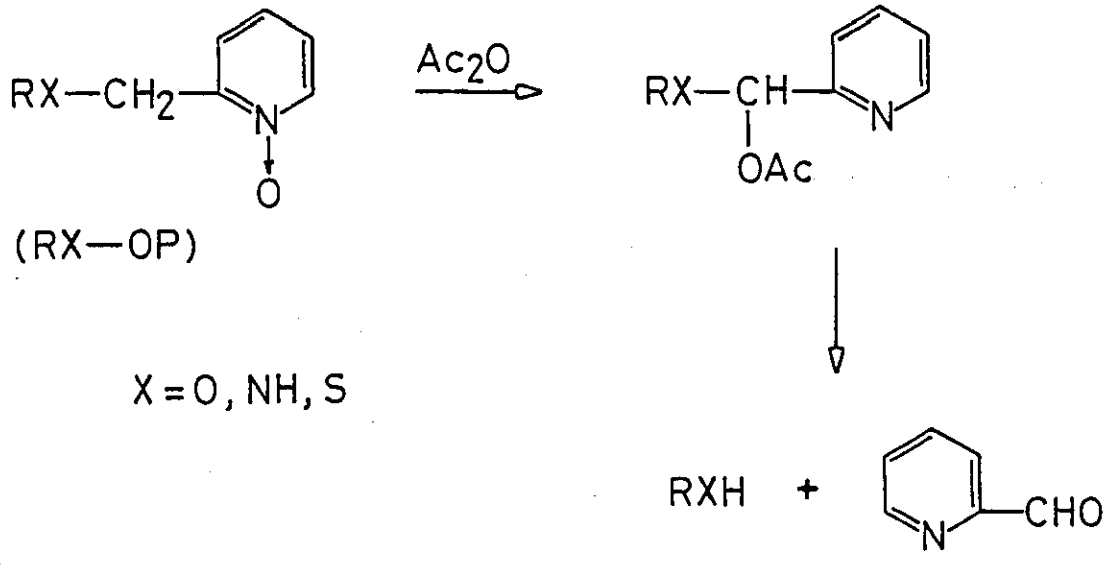


(227b)



(228)

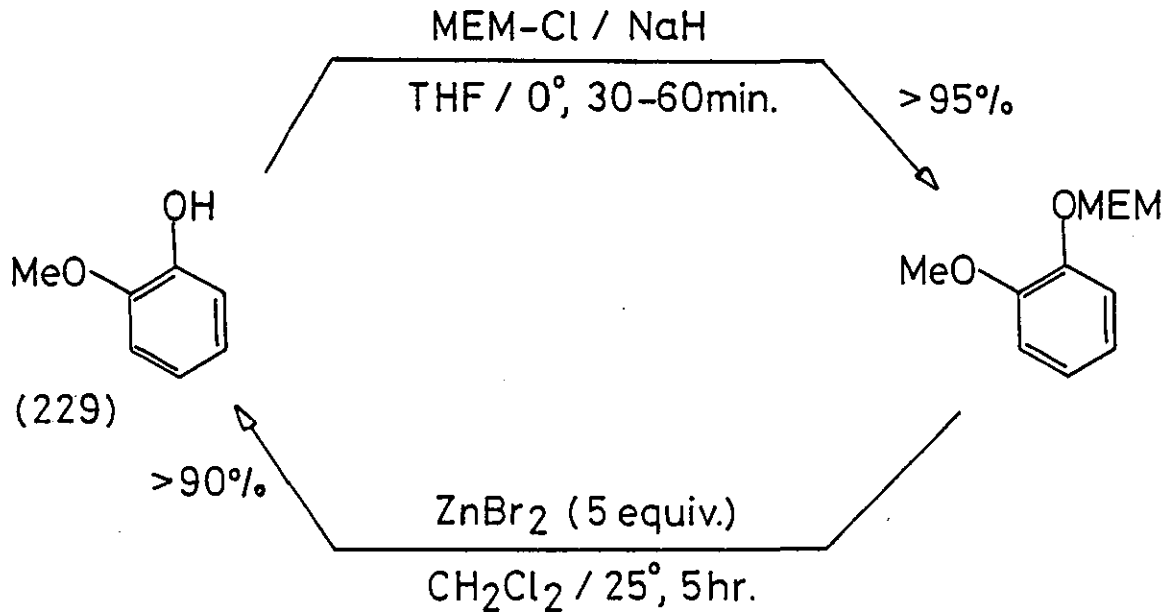
simpler aromatic thiols such as p-thiocresol[233] can be protected.



Recent studies have resulted in several new methods for the protection of hydroxyl groups. These methods are complementary to one another and also to more established techniques based on acetate, benzoate, benzyl ether, THP ether, and other groups. As a result, several ways of effecting selective protection/deprotection in the

synthesis of polyfunctional molecules are available.

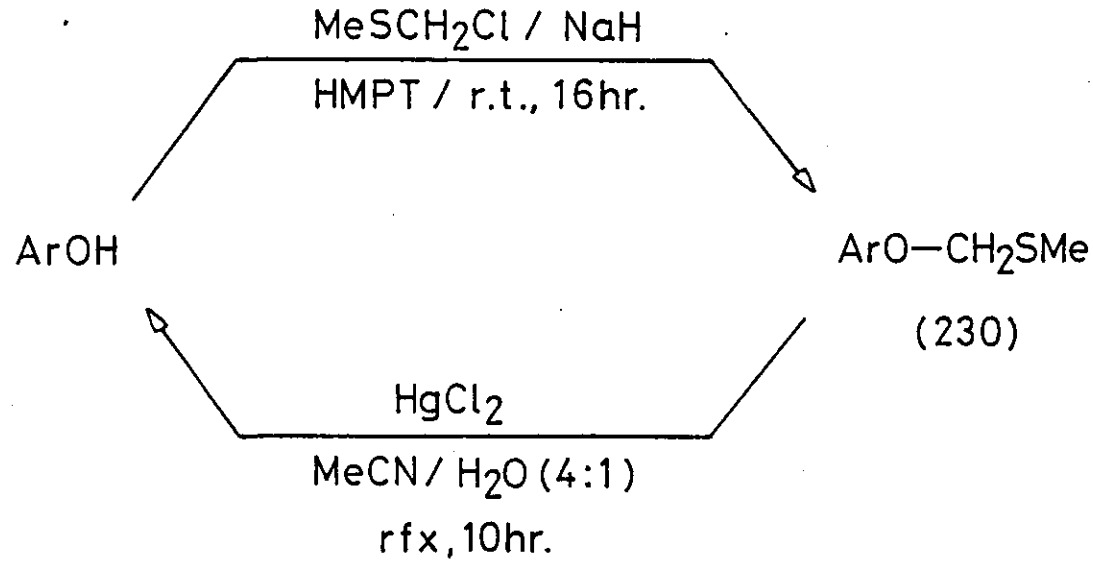
The β-methoxyethoxymethyl (MEM) group[234] is one of several developed by Corey and his co-workers. It can be introduced under aprotic-basic or aprotic-neutral conditions, and is stable to strong bases and nucleophiles, many oxidising agents, and mild acids. Removal is accomplished under the influence of a mild Lewis acid at a rate markedly faster than that shown by methoxymethyl ethers.[229] The MEM group is a general protecting group for alcohols and for some phenols, as illustrated for catechol monomethyl ether (229).



MEM = $MeOCH_2CH_2OCH_2$—

Methylthiomethyl (MTM) ethers, prepared by reaction of a sodium alkoxide with <u>in situ</u>-generated iodomethyl methyl sulphide, serve as protecting groups for primary alcohols.[235] By a modified procedure,[236] aryl MTM ethers (230) are formed, and are found to be resistant to the hydrolysis conditions (Hg^{2+}, room temperature) used to cleave the alkyl derivatives (see overleaf).

A number of hindered triorganosilyl groups have been employed



for the purpose of masking hydroxyl functions. Use of the thermally stable trimethylsilyl group in the synthesis of symmetrical biaryls[23] has already been mentioned. However, other silyl ethers have exhibited greater stability over a wide range of conditions and are susceptible to removal by specific reagents. Thus, the t-butyldimethylsilyl (TBDMS) group has been used to considerable advantage in prostaglandin synthesis, and can be cleaved by tetra-n-butylammonium fluoride in THF.[237] The dimethylisopropylsilyl (DMIS) group[238] has found application in the same field, and yet more recently the triisopropylsilyl (TIPS) group[239] has shown potential as a hydroxyl-protecting moiety. An order of stability to mild acid-catalysed hydrolysis is depicted below.

$$i\text{-}Pr_3Si > t\text{-}BuMe_2Si > i\text{-}PrMe_2Si > Me_3Si$$

To give an example, the systematic removal of protecting groups from a pentahydric alcohol may therefore have the following sequence.

1. β-Methoxyethoxymethyl ether, $RO\text{-}CH_2OCH_2CH_2OCH_3$ ($ZnBr_2$).
2. Methylthiomethyl ether, $RO\text{-}CH_2SCH_3$ ($Ag^{\oplus}$).

3. Benzyl ether, RO-CH_2Ph (H_2-Pd).

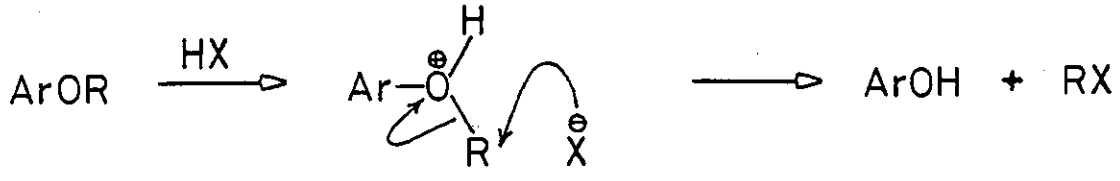
4. t-Butyldimethylsilyl ether, RO-$SiMe_2$-t-Bu ($F^{\ominus}$).

5. Tetrahydropyranyl ether, RO-THP (PPTS/EtOH).

4.2 ETHER AND SULPHIDE CLEAVAGE REAGENTS

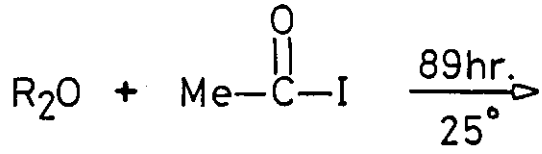
The majority of established and newly developed cleavage reagents can be categorised as either acidic or nucleophilic according to Burwell's classification.[212]

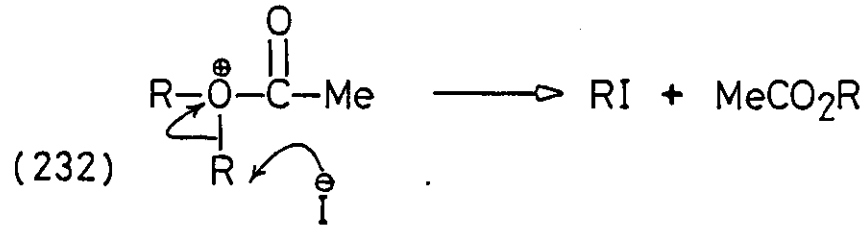
The classical acid reaction involves saturation of an ether with anhydrous hydrogen iodide or bromide. This leads to one mole of alcohol and one of halide, but refluxing with excess aqueous acid affords an overall conversion of dialkyl ether to two moles of halide. With alkyl aryl ethers, concentrated hydriodic and hydrobromic acids at reflux effect exclusive cleavage to phenol and alkyl iodide via an oxonium intermediate of type (231). If the solubility in refluxing acids is low, the use of a co-solvent such as phenol or acetic anhydride is helpful.



(231)

The exceptional stability of methyl ethers has warranted their use as protecting groups, and in particular for phenols, where addition of methionine as a methyl group acceptor facilitates cleavage by methanesulphonic acid at room temperature.[240] It has long been known that aliphatic ethers can be cleaved by acid iodides at ordinary temperatures.[241] An acyldialkyloxonium intermediate (232), analogous to that (92) proposed in a synthesis of trialkyloxonium salts,[94] is involved. However, selective demethylation is difficult, the reaction takes several days, and the rate of cleavage of sulphides is much slower (see overleaf).



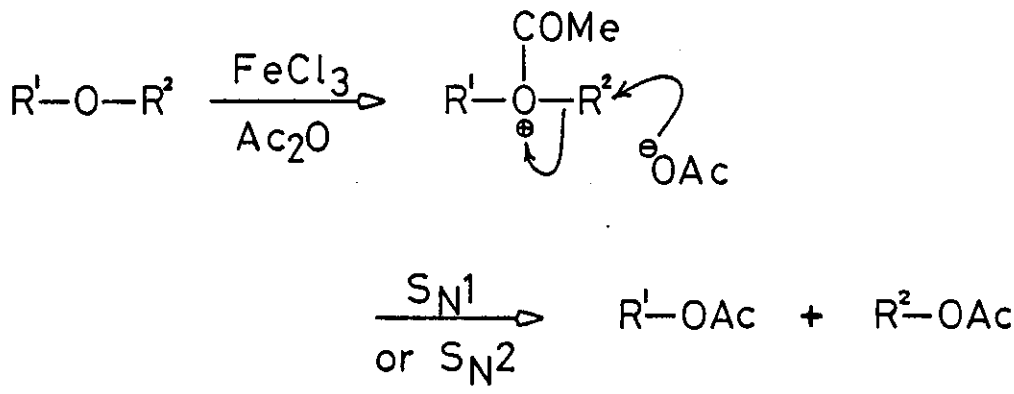


(232)

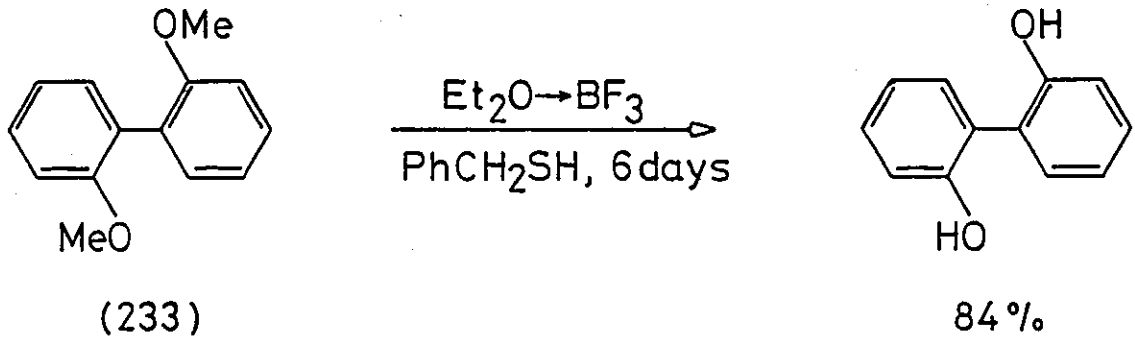
Sulphides are virtually unaffected by proton acids. Thus, under conditions which give complete cleavage of anisole, no demethylation of thioanisole is observed.

Until recently, demethylation from aliphatic ethers has received little attention, but several new modifications of long-standing procedures have been published which increase somewhat the usefulness of such ethers as protecting groups. These include the generation of hydrogen iodide *in situ*[242] and the use of acetic anhydride-Lewis acid media.[243] Thus, with diiodomethyl methyl ether catalysis in acetonitrile,[242] the classic acid cleavage reaction has been transformed into the gentle and effective class for methyl ethers of primary and secondary alcohols. In addition, whilst cleavage occurs within 30 minutes at room temperature, weaker Lewis bases such as anisole do not react. Ferric chloride in acetic anhydride[243] has effected the mild conversion of a variety of ethers to the corresponding acetates, including removal of the TBDMS and benzyl moieties. Results again support a mechanism involving O-acylation (see overleaf).

Some of the more important demethylations are the reactions of methyl ethers with boron trihalides. One method[244] uses the combination of boron trifluoride-etherate and an aliphatic thiol to cleave methyl ethers of primary and secondary alcohols in good yields. Under

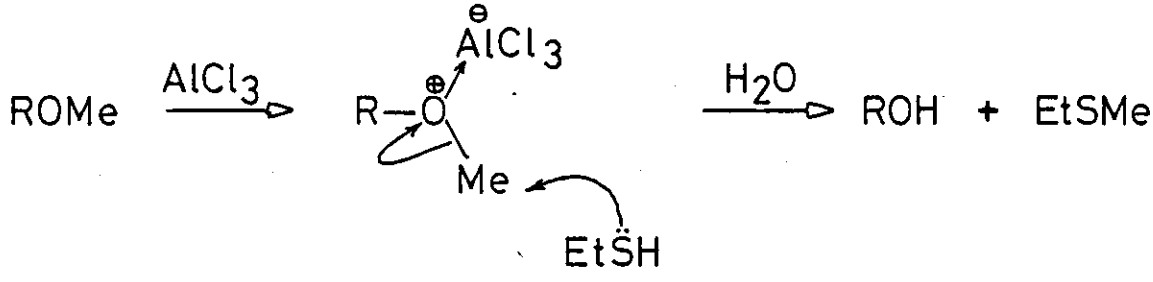


conditions of high reagent concentrations and prolonged reaction times, aromatic ethers such as 2,2'-dimethoxybiphenyl (233) react similarly.



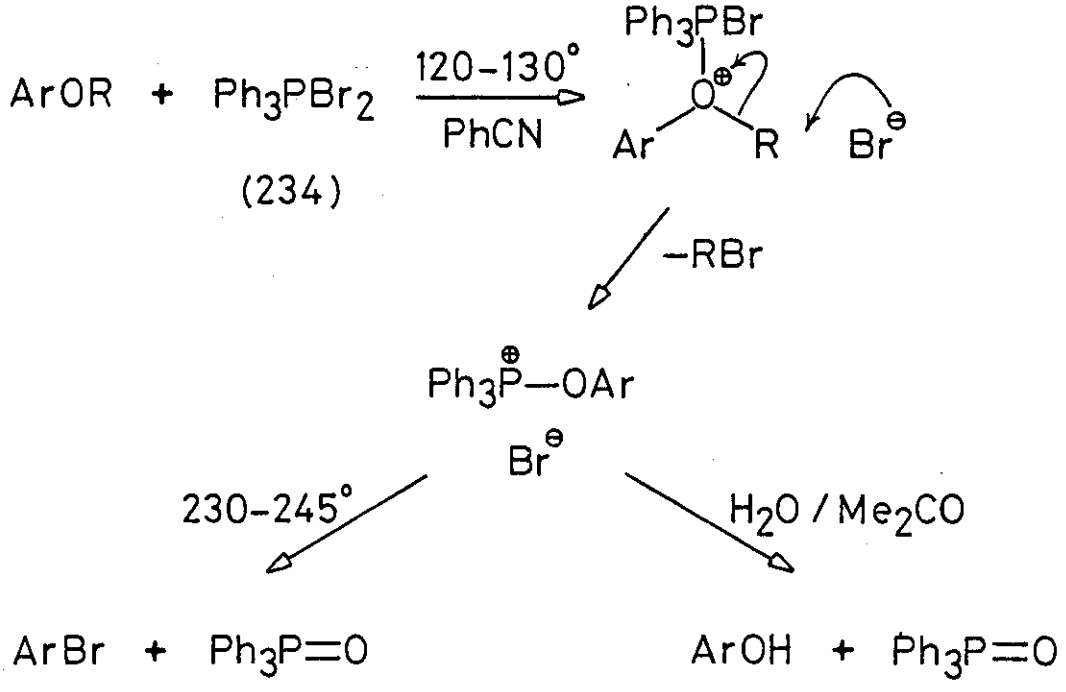
(233) 84%

A more reactive system incorporates a metal halide as the Lewis acid component. Thus, aluminium chloride in ethanethiol demethylates methyl ethers of alcohols and phenols, and also cleaves aromatic methylenedioxy compounds to catechols.[245] No preferential demethylation of aliphatic ethers is observed, and the biaryl (233) gives a quantitative yield of phenol in 30 minutes. The overall reaction, below, can be explained by the principle of hard and soft acids and bases.

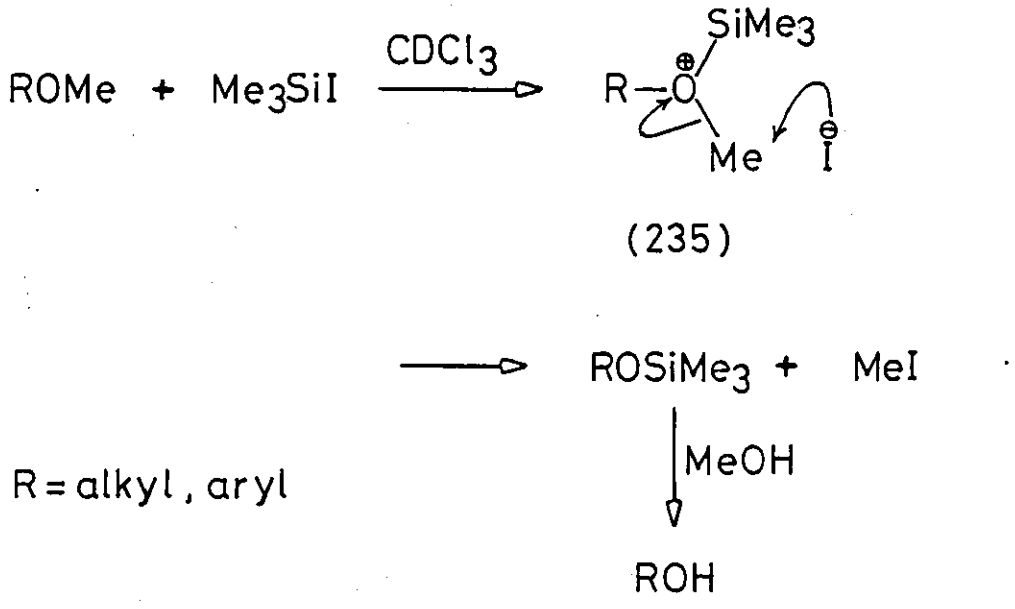


Lewis acid halides alone have been used occasionally to cleave aliphatic methyl ethers, but generally give higher yields with aromatic counterparts. Examples include the cleavage of aryl methyl ethers at or below room temperature by means of boron tribromide,[246] and the use of boron tri-iodide[247] as a selective reagent for ether cleavage in aromatic aldehydes. Aluminium bromide in chlorobenzene has been employed to study the ease of cleavage of the carbon-sulphur bond in a series of alkyl- and aralkyl-phenyl sulphides.[248] As expected, rates are considerably inferior to those of corresponding ethers, and whilst trityl-, benzhydryl-, and benzyl-groups do undergo efficient removal, no reaction was detected with thioanisole.

The conversion of alcohols to alkyl halides by tertiary phosphine dihalides has been extended by Anderson and Freenor[112] to the cleavage of both carbon-oxygen bonds in primary and secondary alkyl ethers. As a result, however, the method is not amenable to the regeneration of parent alcohols. When applied to phenetole, the reaction with triphenyldibromophosphorane (234) was modified to give phenol under essentially neutral conditions, a procedure which was put to good use by Kemp.[90]



Most of the methods discussed so far do not solve the problem of clean and efficient demethylation of alkyl methyl ethers, since they often result in mixtures of dealkylated products. The use of trimethylsilyl iodide (TMSI) now provides an effective alternative. Jung and Lyster[249] showed that methyl, and other alkyl ethers, in both aliphatic and aromatic systems, can be dealkylated simply and efficiently. The mechanism is presumed to involve initial formation of a trimethylsilyl oxonium ion (235) which is converted to the silyl ether by nucleophilic attack of iodide. The alcohol is liberated by methanolysis.



All yields reported are quantitative, dialkyl ethers can be cleaved in preference to alkyl aryl ethers, and many functional groups are stable to the reaction conditions. More recently, the removal of urethane and benzyl ether blocking groups from peptides has been accomplished.[250]

TMSI is commercially unavailable, and combinations of phenyltrimethylsilane/iodine[251] and chlorotrimethylsilane/sodium iodide[252] have proven very effective for <u>in situ</u> generation of the reagent. Of special interest is the observation that Olah's method[251]

offers a substantial reduction in the time needed to cleave alkyl aryl ethers. In addition, Olah et al[253] have very recently reported the use of trichloromethylsilane/sodium iodide for the selective cleavage of methyl, benzyl, trityl and tetrahydropyranyl ethers to alcohols. This reagent is easy to handle and free of some of the difficulties associated with TMSI reagents, and thereby should find substantial synthetic use.

TMSI is now utilised successfully in achieving a multitude of chemical transformations in high yield and under mild and neutral conditions. In addition to ethers, it is used to cleave acetals, carboxylic esters, and carbamates, and alcohols may be converted to alkyl iodides. A review[254] is available. Yet more new innovations include the dealkylation of phosphate esters,[255] a deoxygenation of alcohols and ethers to alkanes,[256] and the transesterification of esters.[257] At present, though, no mention of sulphide cleavage has been made.

The methods so far discussed have as their common factor a positively charged oxonium ion intermediate which readily undergoes nucleophilic displacement. However, in the absence of acidic reagents, the cleaving species can be so chosen to have much greater nucleophilic character, and this has become the basis of a second major group of dealkylation techniques. Nonetheless, an increase in nucleophilicity does not compensate for loss of positive charge. Consequently, no useful cleavage reactions of dialkyl ethers by basic reagents alone have been reported. On the other hand, alkyl aryl ethers are more reactive, and several ways have been used to generate the parent phenol. Of particular interest are those methods which have been successful in cleaving the corresponding sulphides. The general equation is illustrated overleaf.

Carbanions are strongly basic, yet solutions of Grignard

$$Ar-Y-R + Nu^{\ominus} \longrightarrow$$

$$Nu-R + Ar-Y^{\ominus} \xrightarrow{H^{\oplus}}$$

$$Y = O, S$$

$$Ar-Y-H$$

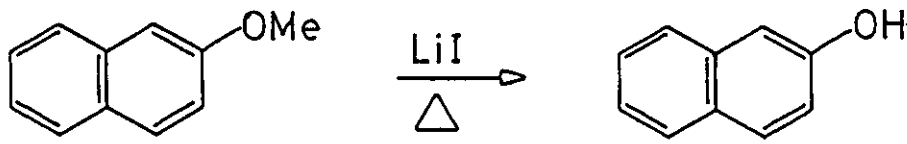
reagents and alkali metal alkyls are prepared in simple aliphatic ethers. However, methylmagnesium iodide (236) has been used occasionally to cleave aryl methyl ethers at elevated temperatures, as in a synthesis of hexahydro meso-hexestrol.[258] Hydrolysis of the reaction mixture yields the required phenol.

$$ArOMe + \underset{(236)}{MeMgI} \xrightarrow{180\text{-}190^{\circ}} Ar-O-MgI + Me-Me$$

$$Ar-O-MgI \xrightarrow{H_2O} ArOH$$

The iodide ion has already been shown to be effective in acid media.[212] With certain aromatic substrates, eg methyl β-naphthyl ether (237), lithium iodide in dry 2,4,6-collidine is suitable.[259] Frequently, conventional cationic systems are replaced by more successful anionic methods. In one such instance, potassium hydroxide in ethylene glycol proved the reagent of choice in a synthesis of the acid-sensitive 5-hydroxypyrimidine (238)[260] (see overleaf).

Oxygen nucleophiles such as hydroxide and alkoxide are not, however, widely used. High temperatures, long reaction times, and even sealed tube conditions are needed. Lithium iodide also appears to react very slowly. Instead, much improved results have been



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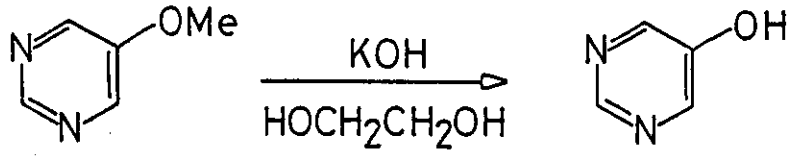
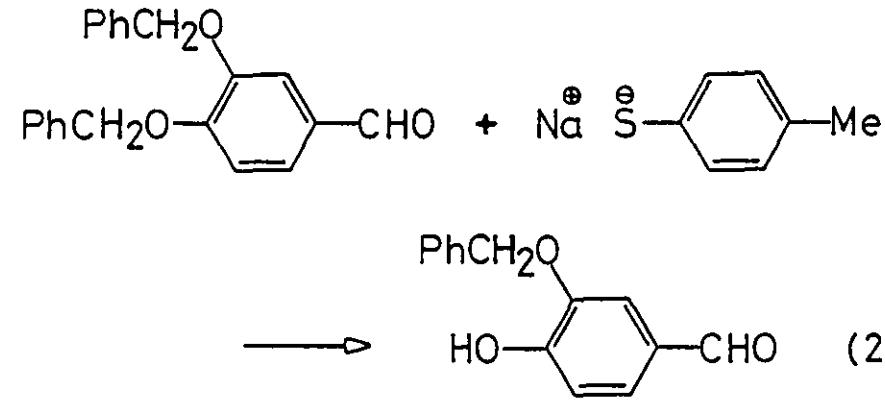


(238)

obtained using sulphur derivatives, and the use of thioethoxide ion has been discussed in the previous chapter.[178] Demethylations in general are rapid and clean, give excellent yields, and provide useful alternatives to the more common acidic methods.

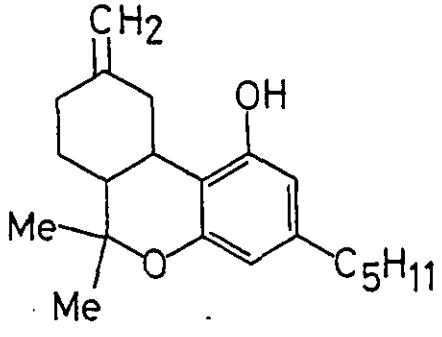
Aliphatic sodium thiolate reagents have not been used extensively for selective ether cleavage in aromatics containing electron-attracting groups. This is probably due to the possibility of competing nucleophilic aromatic substitution of electronegative functions, such as halogen atoms.[189] However, sodium p-thiocresolate in toluene, with a limited amount of HMPT, has been reported[261] to be effective for the selective dealkylation of unsymmetrical alkyl aryl ethers containing a formyl group. This reagent can be used for both demethylations and debenzylations under mild conditions, and no substitution has been observed. The directing power of the formyl substituent in ether cleavage is in the order, ortho > para > meta, which is used to advantage in the preparation of 3-benzyloxy-4-hydroxybenzaldehyde (239) (see overleaf).

Potassium thiophenolate in ethylene glycol has been employed as



(239)

a demethylating agent in the synthesis of $\Delta^{9(11)}$-trans-tetrahydrocannabinol (240).[262] Its success may be attributed to its high nucleophilicity and to the absence of competing double bond migrations observed with pyridine hydrochloride, methylmagnesium iodide, lithium iodide, and potassium hydroxide.



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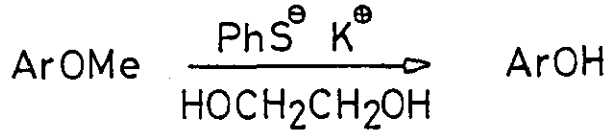
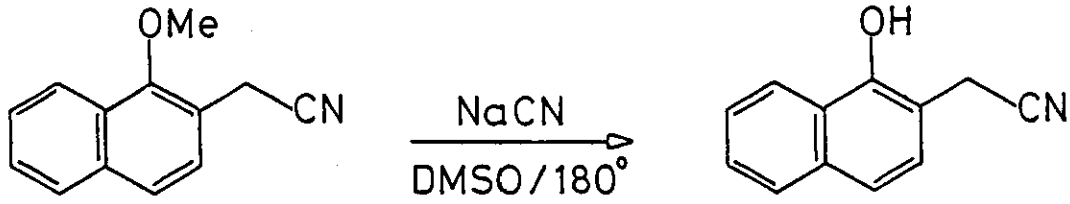


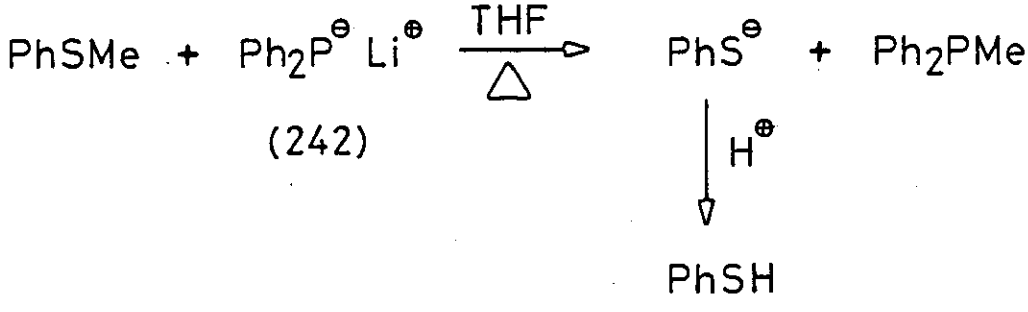
A convenient new method for converting aromatic methyl ethers to phenols uses sodium cyanide in DMSO at 160-180°.[263] The reaction is compatible with substrates containing acyl, amido, and carboxyl substituents, but fails to proceed cleanly with aromatic nitro compounds owing to the von Richter reaction. It is especially advantageous for deblocking aromatic methoxy nitriles, eg. 2-cyanomethyl-1-methoxynaphthalene (241) (see overleaf).

Just as sulphides are resistant to cleavage by acidic reagents,



(241)

so too are they relatively inert to nucleophiles. It has been known for some time[264] that sodium amide in piperidine is capable of cleaving diaryl and alkyl aryl ethers and sulphides, but thioanisole gives products both of alkyl-sulphur fission (thiophenol, 21%) and of aryl-sulphur fission (N-phenylpiperidine, 32%). Probably the most promising system so far disclosed is that of Mann and Pragnell.[265] They showed that the diphenylphosphide ion (242) in refluxing THF rapidly dealkylates methyl-, benzyl-, and allyl-phenyl ethers, and that the corresponding sulphides undergo similar but slower fission. Thus, after four hours, thioanisole and benzyl phenyl sulphide afforded thiophenol in 41% and 79% yields respectively. The diphenylarsenide ion, $Ph_2As^{\ominus}$, is almost as effective.



(242)

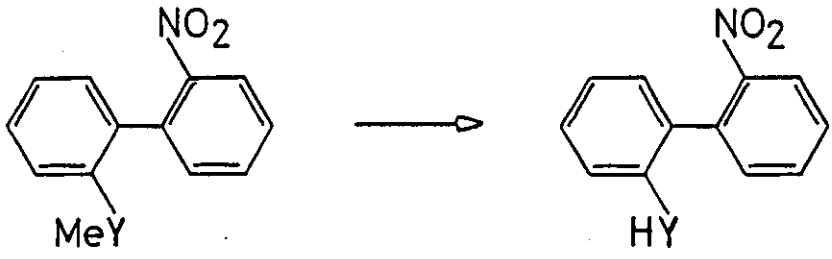
One type of reaction does remain by which alkyl aryl- and diaryl-sulphides are cleaved at least as easily as the ether analogues. This is cleavage by alkali metals.[212] Furthermore, while dialkyl ethers are very resistant to alkali metals and in particular to sodium in liquid

ammonia, dialkyl sulphides are readily split. Controlled addition of lithium in methylamine is likewise effective,[266] but although several alkyl aryl sulphides have been cleaved to the desired aromatic thiols in good yields, more extensive use is often negated by a need for milder conditions.

$$Ar{-}S{-}R \xrightarrow[\text{or } Li/MeNH_2]{Na/NH_3} ArSH + RH$$

4.3 REACTIONS OF AN ARYL METHYL ETHER AND SULPHIDE WITH CLEAVAGE REAGENTS

The reactions of 2-methoxy-2'-nitrobiphenyl (47) and 2-methylthio-2'-nitrobiphenyl (165) with a variety of cleavage reagents are summarised in Table 2. Where appropriate, the major products are listed.



Y = O (47) Y = O (119)

Y = S (165) Y = S (182)

Results clearly indicate that concentrated aqueous hydrogen halides are the reagents of choice for ether cleavage, provided that no other acid-sensitive functions are present. However, the iodide ion is insufficiently nucleophilic when an oxonium intermediate is not available, so that refluxing with lithium iodide[259] in pyridine for 68 hours gave only recovered starting material. Amine salts such as pyridine hydrochloride cleave many phenolic ethers,[212] but prolonged reflux with N-methylmorpholine hydrochloride (Reagent 3) in N-methylmorpholine (40 hours, 116°) failed to demethylate the sulphide.

The aryl methyl sulphide was unaffected by all acidic reagents. Trimethylsilyl iodide[249] seemed promising, but reactions with both the ether and the sulphide resulted in formation of hexamethyldisiloxane, $Me_3SiOSiMe_3$, as evidenced by a sharp ^{1}H NMR absorption at δ 0.1. Difficulties in storage and handling of the extremely water-sensitive silyl iodide (δ 0.75) are probably responsible, so success may depend on the use of freshly prepared material.

Table 2

	Reagent	Ether, ArOMe	Sulphide, ArSMe
1.	HBr/AcOH	ArOH	X[a]
2.	HI/PhOH	ArOH[c]	-[b]
3.		-	X
4.	$Me_3SiI/CDCl_3$	X	X
5.	LiI/pyridine	X	X
6.	$EtS^{\ominus}$/DMF	-	$ArNH_2$ (+ ArSH)
7.	$Ph_2P^{\ominus}$/THF	X	X
8.	NaCN/HMPT	-	X
9.	(i) Cl_2/CCl_4 (ii) $H^{\oplus}$/MeOH	-	ArSH

[a]Designates no demethylation observed.

[b]Designates reaction not studied.

[c]Performed with 2-amino-2'-methoxybiphenyl to give the corresponding phenol (123).

The sulphide was treated with several nucleophilic reagents, but again with limited success. Thus, the diphenylphosphide ion has shown considerable potential,[265] and sodium cyanide in HMPT has been used to cleave methyl esters,[267] but neither were effective. The one reagent to show some signs of the desired cleavage was the thioethoxide ion in refluxing DMF, but products of nitro group reduction were prevalent over any thiophenol (see Chapter 3).

It therefore remains to be concluded that, in our hands, the two-stage chlorination/solvolysis technique of Lavanish[177] has given the best results with regard to dealkylation of an aryl methyl sulphide. Further discussion has been given in the previous chapter.

CHAPTER 5

HALONIUM SALTS

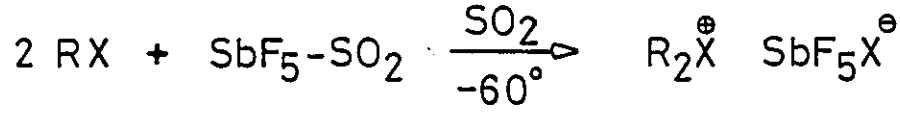
5.1 REVIEW

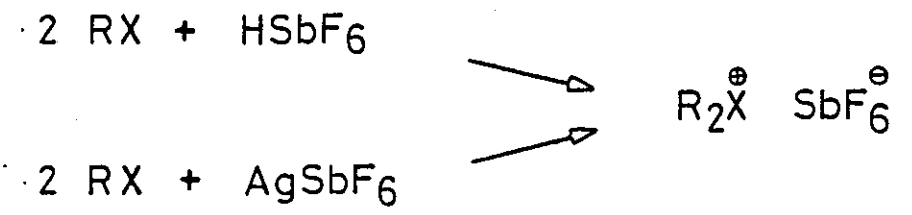
The development of high acidity, low nucleophilicity solvent systems, eg SbF_5-SO_2, SbF_5-SO_2ClF, has enabled the preparation, direct observation by both ^1H and ^{13}C NMR spectroscopy, and even isolation, of stable halonium ions. There is abundant evidence for the intermediacy of halonium ions in a number of reactions and their chemistry has been rapidly explored in recent years, particularly by Olah and his associates. They are now recognised as an important class of onium compounds, and may be classified according to acyclic and cyclic types. Both have received extensive ^{13}C NMR structural studies.[268]

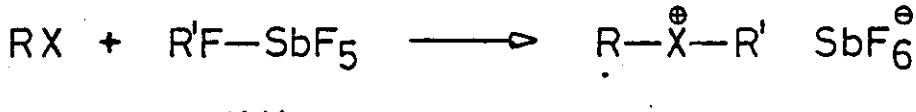
5.1.1 ACYCLIC HALONIUM IONS

The physical properties and behaviour of diaryliodonium salts have been known for some time, and further discussion is reserved for section 5.2. However, it was not until much later that dialkylhalonium ions,[269] $R_2\overset{\oplus}{X}$, were prepared in super acid solutions at -60°, characterised by NMR techniques, and eventually isolated as hexafluoroantimonate salts.[98,270] The methods of preparation, summarised in Scheme 28, include the alkylation of alkyl halides with previously described MeF → SbF_5 and EtF → SbF_5 complexes (14)[10, 11] as a route to unsymmetrical ions. Note that fluorine, as the most electronegative element, is unable to acquire positive charge (see overleaf).

The dimethylhalonium salts (243) are fluffy white crystalline solids, which are very hygroscopic and stable only in a dry nitrogen atmosphere at room temperature. Chemical shifts (ppm from TMS) are deshielded with respect to the starting alkyl halides (244), and

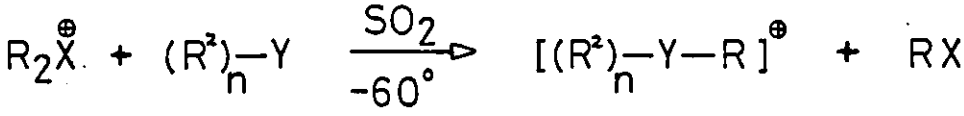






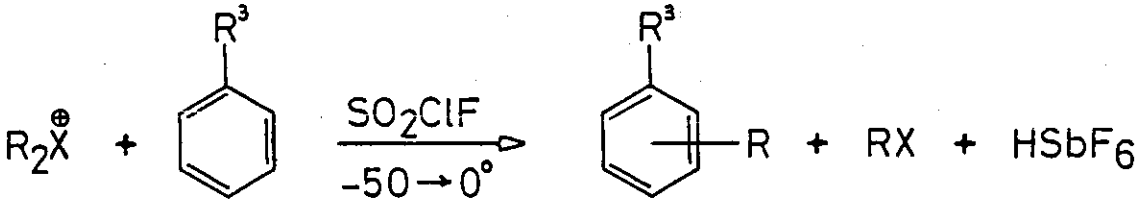
(14)

R=Me, Et, i-Pr R'=Me, Et X=Cl, Br, I



(245)

R=Me, Et Y=N, O, S X=Cl, Br n=1, 2, 3



(246)

R=Me, Et R^3=H, Me, Et X=Cl, Br, I

Scheme 28. Dialkylhalonium Salts: Synthesis and Reactions

reflect the trend in stability, I > Br > Cl, ie the larger halogen is more capable of localising positive charge. Laser Raman and IR measurements[269] indicate that dialkylhalonium ions possess an sp^3-hybridised halogen atom, resulting in approximately tetrahedral geometry.

$Me-\overset{\oplus}{X}-Me$

(243)

Me-X

(244)

X	δ^1H	$\delta^{13}C$
I	3.60	9.40
Br	4.13	37.50
Cl	4.20	48.80

X	δ^1H	$\delta^{13}C$
I	2.20	-19.60
Br	2.60	11.70
Cl	3.00	26.20

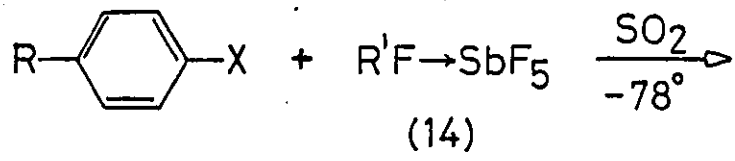
Dialkylhalonium ions represent a powerful new class of alkylating agent, and even the weakest nucleophiles are capable of displacing alkyl halide from these compounds, eg O-methylation of anisole.[99] The order of reactivity suggested by the methyl group chemical shifts above is Cl > Br > I. Thus, dialkylchloronium and dialkylbromonium ions react with a variety of n-donor bases (245),[271] but dialkyliodonium ions do not react in SO_2 or SO_2ClF solution at temperatures varied from -78° to 0°.

Alkylation of ethers, alcohols, water, ketones, aldehydes, carboxylic acids, sulphides, thiols, amines, and nitro compounds has made available a wide range of onium salts of both synthetic and theoretical interest. Many can be isolated. The advantage of these halonium salts over Meerwein's oxonium salts[86, 87] lies in their ease of preparation, greater alkylating ability, and wide range in selectivity arising from the possibility of changing the nature of the halogen onium centre.

In the absence of heteroatom substituents, C-alkylation of aromatics (246) takes place with ease, and prompted the idea that dialkylhalonium ions may participate in Friedel-Crafts reactions.[270] Indeed, it was shown[269] that isomer distributions in methylation reactions were similar to those obtained with methyl halide-Lewis acid halide combinations, but a significant lowering of the ortho/para ratio was observed with the diethylhalonium salts. Furthermore, whilst the MeBr-$AlBr_3$ complex readily alkylates olefins and aromatics, reaction with an n-donor base simply gives rise to the stronger substrate-$AlBr_3$ complex. That reactions with $Et_2X^{\oplus}$ are affected by increased steric hindrance at an ortho position implies therefore that dialkylhalonium ions are not the active alkylating agents in conventional Friedel-Crafts systems.

When the MeF → SbF_5 and EtF → SbF_5 complexes (14) react with aryl bromides and iodides in SO_2 at -78°, alkylation of halogen results in the formation of alkylarylhalonium ions (247).[272] These are depicted in Scheme 29. Aryl fluorides and chlorides are not methylated on halogen, but instead undergo para sulphinyl methylation. Presumably the aromatic nucleus is more reactive towards a methylated solvent species, $MeSO_2^{\oplus}$ $SbF_6^{\ominus}$, than are the lone electron pairs on fluorine and chlorine (see overleaf).

All of the alkylarylhalonium ions are stable only in solution at low temperatures, and decompose to ring-alkylated products on warming or in the presence of excess aryl halide. These properties, and others, resemble those of the dialkylaryloxonium ions.[99] Thus, at -78° the methylphenylbromonium ion (248) can methylate π-bases such as benzene by an intermolecular reaction, and results[272] do not support the involvement of alkylarylhalonium ions in Friedel-Crafts alkylations of aryl halides. Under normal Friedel-Crafts conditions such ions would not be stable, and direct attack of the aromatic ring

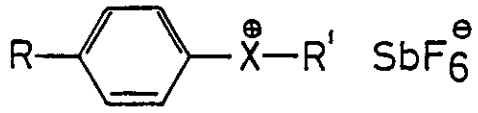


(14)

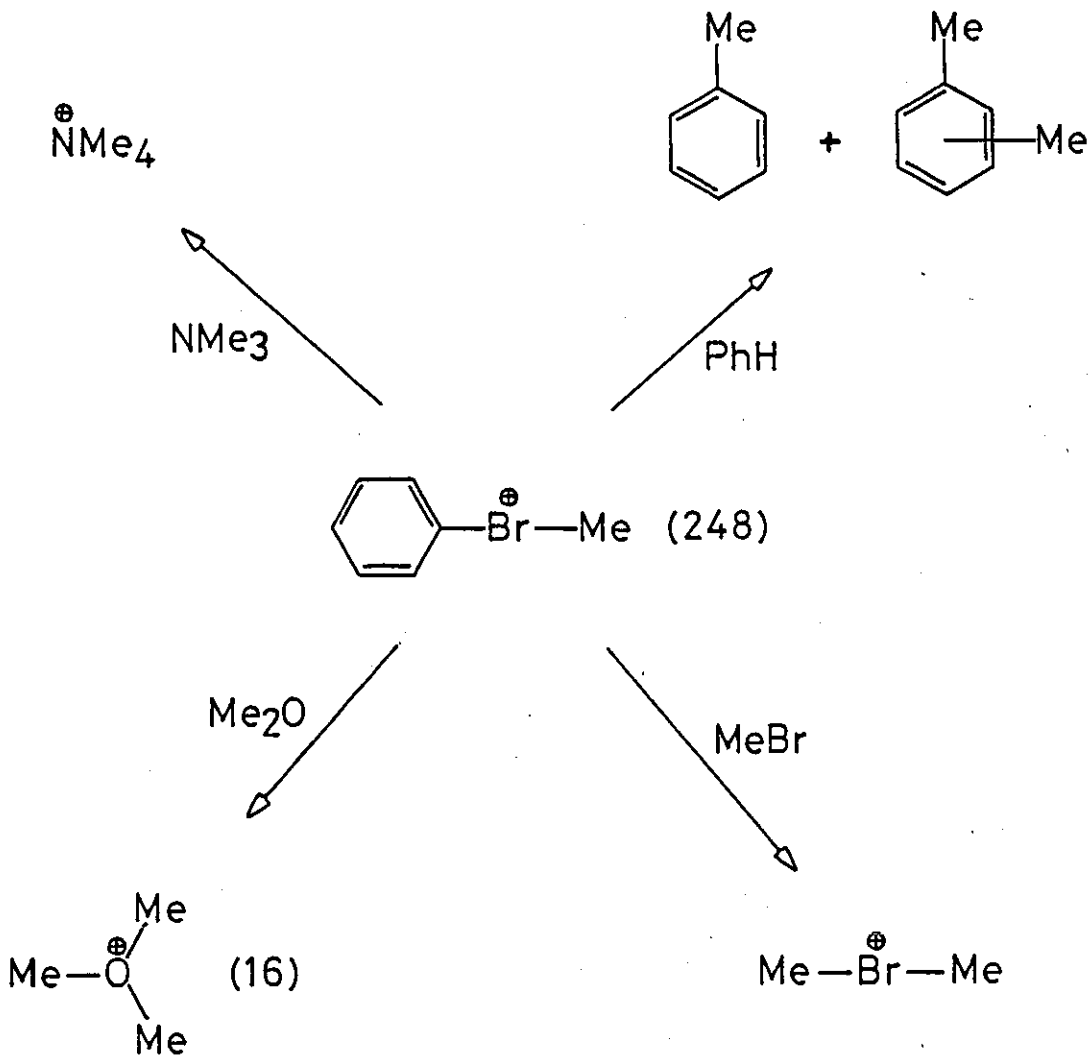
R = H, Me, F

R' = Me, Et

X = Br, I



(247)

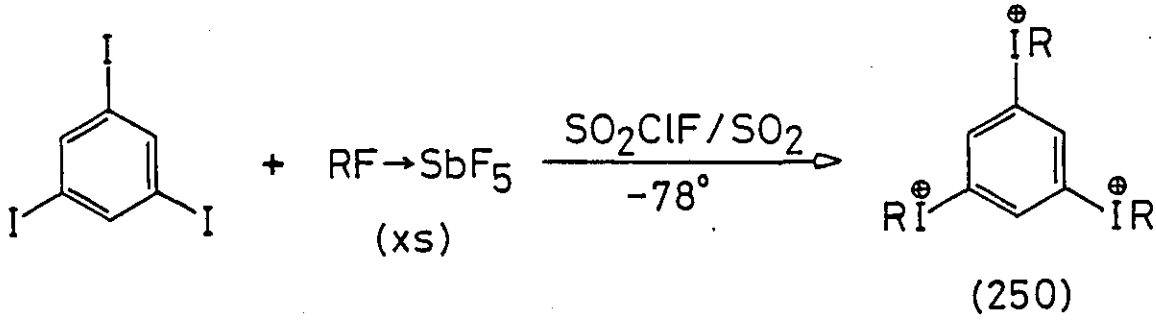


Scheme 29. Alkylarylhalonium Ions: Synthesis and Reactions

is more likely. A variety of n-bases can also be alkylated, and irreversible reaction with methyl bromide shows clearly that alkylaryl halonium ions are stronger alkylating agents than dialkylhalonium ions. ^{13}C NMR studies[268] reveal no significant delocalisation of positive charge into the aromatic nucleus.

The unusual donor ability of iodine toward electrophiles has been emphasised by the observation at low temperature of di- and tri-iodonium ions (249, 250), in which most of the positive charge resides on iodine.[273] Dibromo substrates are less susceptible to dialkylation, and dichloronium ions have not been detected.

$$I(CH_2)_nI + \underset{(xs)}{RF{\rightarrow}SbF_5} \xrightarrow[-78^\circ]{SO_2} \underset{(249)}{R\overset{\oplus}{I}(CH_2)_n\overset{\oplus}{I}R}$$

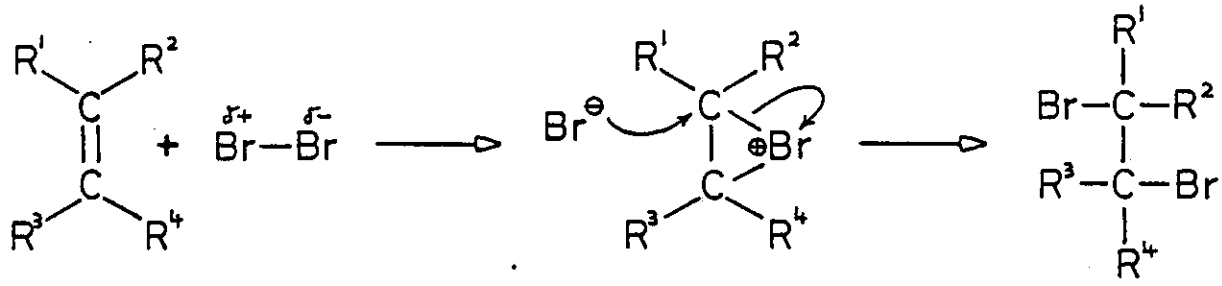


(250)

R = Me, Et

5.1.2 CYCLIC HALONIUM IONS

The observed stereospecificity in electrophilic additions of bromine to olefins has generally been assumed to arise via formation of a bromonium ion (251). Similarly, from results of rate measurements and stereochemistry, bromine has been suggested as a good neighbouring group, participating through the same type of bridged ion.

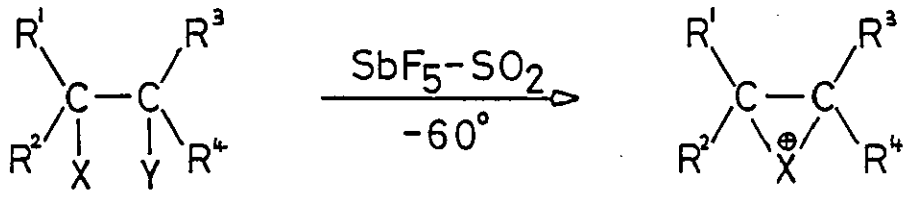


(251)

Cyclic iodonium ions have also been postulated. However, less evidence is available to suggest that chlorine can give appreciable anchimeric assistance, so that polar chlorination is more inclined to proceed via classical chlorocarbenium ions. There is no indication that bridged fluoronium ions can occur, and for electronegativity reasons would not be expected.

Ionisation of 2,3-dihalo-2,3-dimethylbutanes enabled the first direct experimental observation of halonium ions in solution.[274] Tetramethylethylenehalonium ions (252, $R^1=R^2=R^3=R^4=Me$) were obtained with chlorine, bromine, and iodine acting as n-donor neighbouring groups, but fluorine gave rapidly equilibrating α-fluorocarbenium ions. More recently, ^{13}C NMR studies[268] have been extended to the structural elucidation of a wide variety of symmetrically and unsymmetrically substituted ethylenehalonium ions (252) (see overleaf).

For the dimethylbutane derivatives described above, ionisation produces a tertiary cation. As the size of halogen increases, this



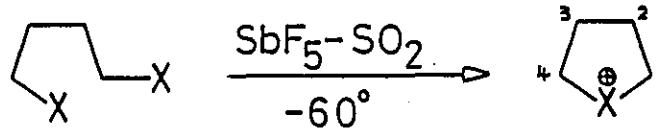
(252)

X:	Cl	Br	I
Y:	F, Cl	F, Br	F

R^1, R^2, R^3, R^4 = H, Me

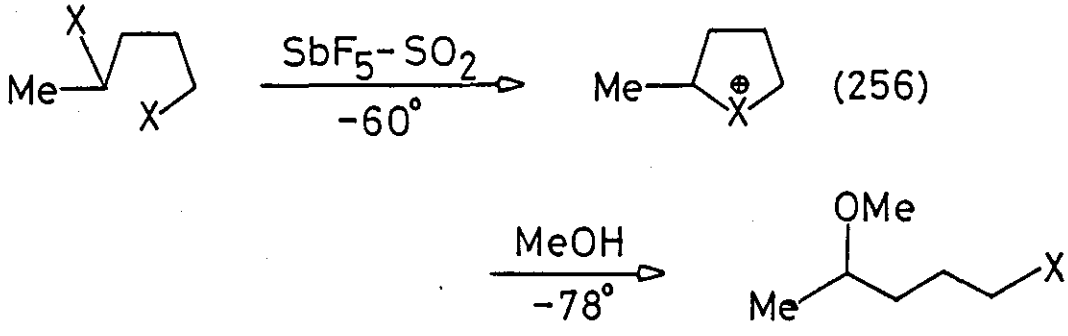
cationic site becomes more tetrahedral, with increased dispersal of charge to the bridged halogen atom. Such behaviour is reflected in ^{13}C chemical shifts for C_1 and C_2 (below), which reveal the poor neighbouring group qualities of chlorine. Thus, increasing carbenium ion character at $C_{1,\ 2}$ suggests that the chloronium ion exists in equilibrium with a pair of open chain β-chlorocarbenium ions. The extent of such an equilibrium (253) is reduced in the case of iodine, since it is more capable of accommodating positive charge. Considerably more shielding occurs at $C_{1,\ 2}$ in the parent ethylenehalonium ions (254), and static symmetrically bridged structures result. Similar analysis is extended to other ions containing various degrees of methyl substitution[268] (see overleaf).

Analogous five-membered ring ions have been proposed to account for rate-accelerating 1,4-halogen participation effects in solvolysis reactions.[275] A number of tetramethylenehalonium ions have since been prepared by the ionisation of 1,4-dihaloalkanes and the protonation of 5-halo-1-alkenes (257),[276, 277] as depicted in Scheme 30. Thermal studies show them to be more stable than the three-membered counterparts. Quenching of the 1-methyl and 1,1-dimethyl derivatives (256, 258) with

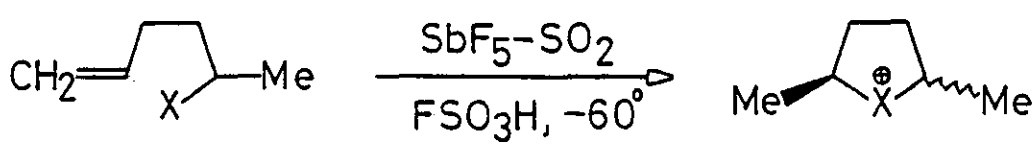


(255)

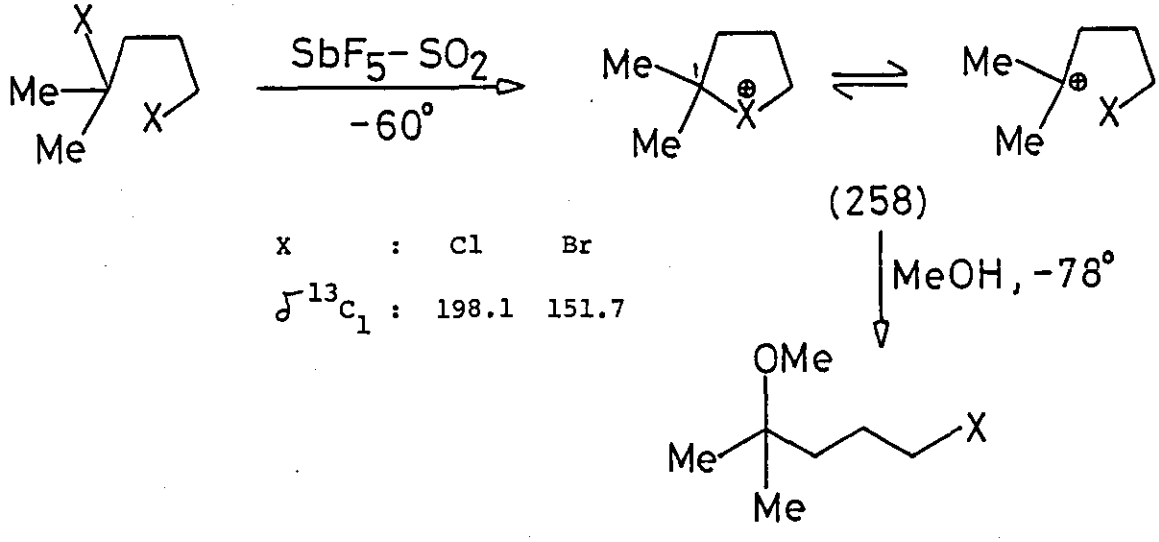
X	:	Cl	Br	I
$\delta^{13}C_{1,4}$	:	75.8	70.7	51.0



(256)



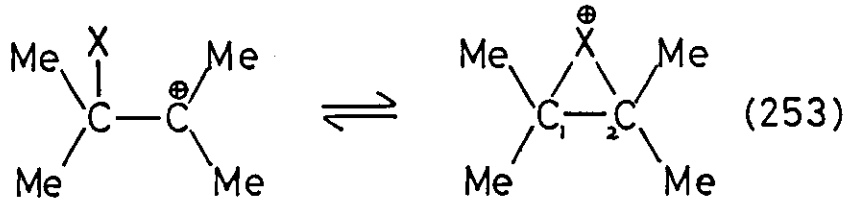
(257)



(258)

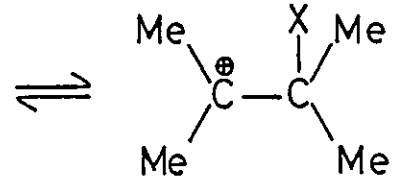
X	:	Cl	Br
$\delta^{13}C_1$	:	198.1	151.7

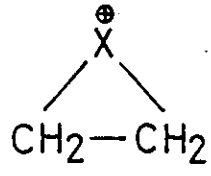
Scheme 30. Tetramethylenehalonium Ions



(253)

X	:	Cl	Br	I
$\delta^{13}C_{1,2}$	:	151.6	139.6	124.7





(254)

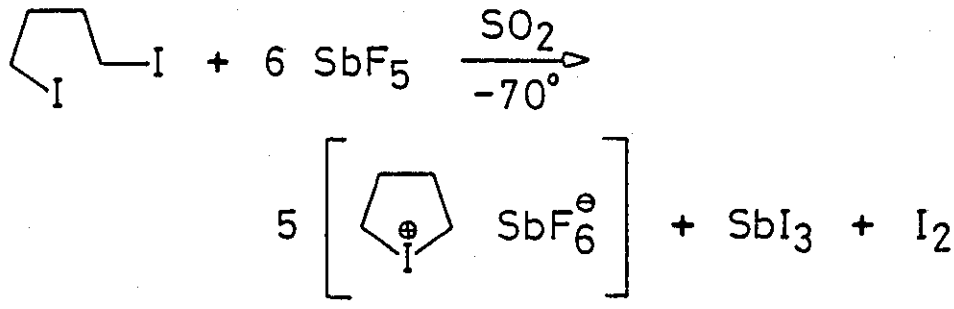
X	:	Cl	Br	I
$\delta^{13}C$	:	74.0	72.9	67.8

methanol shows a preference for S_N1-type ring opening. The chloronium ion substrates possess possibly the most reactive leaving group, RCl, of any compound yet obtained as a stable species, and the influence of (a) substituent inductive and steric effects, and (b) reactant nucleophilicity, in chloronium ion reactions has been evaluated.[278]

From ^{13}C NMR spectra[268] it follows that the parent tetramethylenehalonium ions (255) exist as static bridged species, but increasing methyl substitution at $C_{1,4}$ produces downfield shifts which indicate increasing carbenium ion character. Consequently, the 1,1-dimethyl derivatives (258) are in equilibrium with small amounts of the open chain ion, the more so as the size of halogen diminishes.

Reinvestigation of the direct reaction of diiodides with SbF_5 in SO_2 has given rise to tetramethyleneiodonium hexafluoroantimonate

(259) as the first crystalline cyclic salt of its kind.[279]

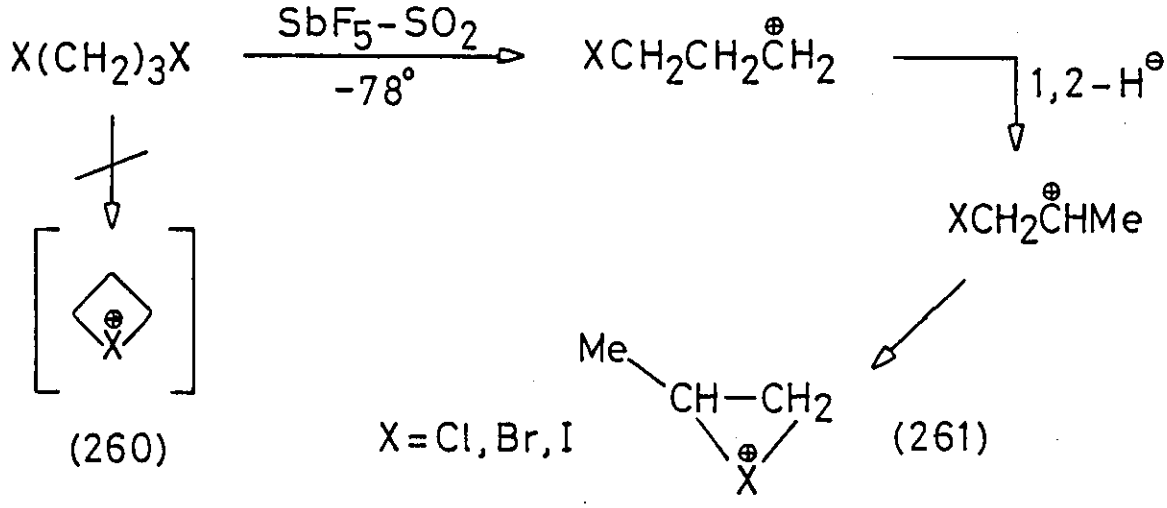


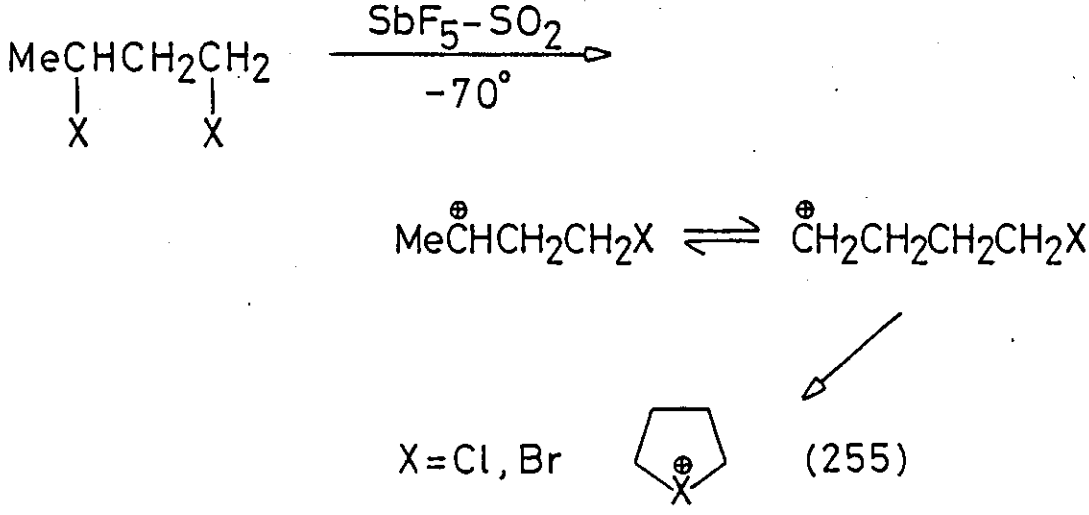
(259)

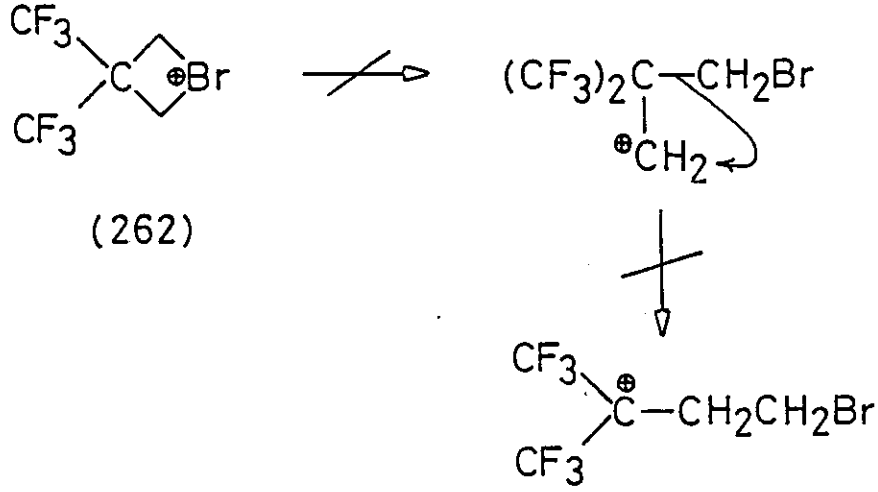
Calorimetric measurements of heats of formation from dihalides reveal that both three- and five-membered rings are subject to pronounced thermodynamic stabilisation by methyl substituents.[280] The interaction of a methyl group with a three-membered ring seems to be unusually favourable.

Attempts to prepare strained four-membered ring trimethylenehalonium ions (260) have generally been unsuccessful. Ionisation of 1,3-dihaloalkanes has consistently yielded product ions containing three- or five-membered rings,[281] and rapid 1,2-hydride shifts are invoked to account for the observed rearrangements to these thermodynamically more stable systems. Thus, 1,3-dihalopropanes afford methylethylenehalonium ions (261), with chlorine exerting the weakest anchimeric assistance, but 1,3-dibromo- and 1,3-dichlorobutanes form tetramethylenehalonium ions (255) in preference to any three-membered product. The attainment of a more stable five-membered ring is considered the driving force for the latter reaction, which involves a rare rearrangement of branched to non-branched cation (see overleaf).

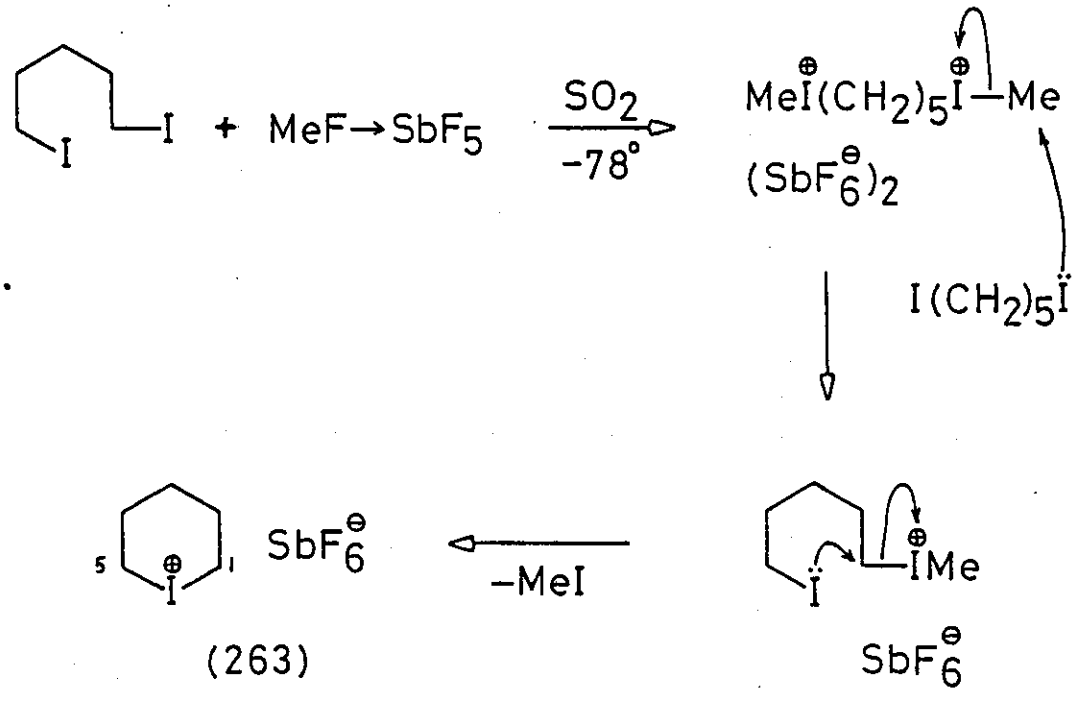
The preparation of a fluorinated derivative of a four-membered ring (262) has been reported.[282] Its stability is probably due to the destabilising effects of the trifluoromethyl groups on a potential tertiary carbenium centre (see overleaf).


X(CH2)3X
SbF5-SO2
-78°
XCH2CH2CH2
1,2-H⊖
XCH2CHMe
(260)
X=Cl, Br, I
Me
CH—CH2
(261)


MeCHCH2CH2
X
X
SbF5-SO2
-70°
MeCHCH2CH2X
CH2CH2CH2CH2X
X=Cl, Br
(255)


CF3
C
Br
CF3
(262)
(CF3)2C—CH2Br
CH2
CF3
C—CH2CH2Br
CF3

Potential precursors to six-membered ring pentamethylenehalonium ions, eg 1,5-dihalopentanes, rearrange to five-membered rings,[276] which are substantially lower in free energy. However, a modified procedure, involving monomethylation of the 1,5-dihalide with MeF → SbF_5 followed by cyclisation, gives the desired six-membered rings.[279] Thus, pentamethyleneiodonium hexafluoroantimonate (263) has been obtained as a white crystalline solid which can be stored indefinitely at -70°. The analogous bromonium ion is less stable and contaminated with rearranged 1-methyltetramethylenebromonium ion (256, X = Br). Evidence suggests that the immediate precursor to the cyclic product, the monoalkylated dihalide, does not arise in a simple fashion. In particular, most alkyl iodides have a low solubility in SO_2. Accordingly, rapid methylation at both ends of the slowly dissolving molecules is expected.[273] The resulting dihalonium ion (249, R = Me, n = 5) may then react with further diiodide to generate the mono-methylated ions, which subsequently react by an internal nucleophilic attack to give the product.



(263)

$\delta^{13}C_{1,5}$ = 36.3 (I), 63.8 (Br)

The larger downfield shifts of the $^{13}C_1$ NMR resonances in three- and five-membered rings, cf (254, 255, 263), and the high susceptibility of these chemical shifts to further deshielding upon methyl substitution (253, 258), has led to the suggestion[279] that stabilising effects[280] are associated with an electron deficiency of the ring carbon atoms, giving them carbenium ion character. Indeed, chemical shifts for ^{13}C attached to vacant d orbital atoms such as $I^{\oplus}$, $Br^{\oplus}$, and S are upfield in six-membered rings compared to five-membered rings. However, effects other than charge transfer are probably involved. That increased deshielding is also correlated with increased reactivity to nucleophiles may also be rationalised in terms of electron deficiency.

Biphenylenehalonium salts represent a group of five-membered ring compounds which possess particularly high levels of stabilisation, and they are treated separately in section 5.3.

5.2 ARYLATING AGENTS

DIARYLHALONIUM SALTS

Diaryliodonium salts have been known for many years, and several synthetic pathways to this class of compound have been developed. Banks[283] has reviewed the literature to 1965. In contrast, routes to the less stable and more reactive bromonium and chloronium ions are less numerous and considerably more inefficient. It is therefore not surprising that the majority of studies have been performed on readily accessible iodonium materials.

Diaryliodonium salts have exhibited greater promise as general arylating agents than any other reagent. Thus, aryl halides are inert and react only at elevated temperatures; diazonium salts do have applications, but their generality is limited; tetraarylammonium ions are rare (see Chapter 6); phosphonium salts can react alternatively with nucleophiles to form pentavalent phosphorus compounds; and triarylsulphonium salts are relatively stable and unreactive.

Diaryliodonium salts are substantially more stable than dialkyl[98, 269-271] and alkylaryl[272] counterparts, and may be isolated and purified by conventional techniques. The specific method of synthesis is often governed by the substitution pattern in the required ion. Extensive work has been carried out by Beringer and his co-workers, some examples of which are illustrated in Scheme 31.

For salts having symmetrically placed substituents, two methods involving the coupling of two molecules of an aromatic substrate through electrophilic substitution are available. Aromatic substrates bearing deactivating substituents such as NO_2, halogen, or CO_2H are best coupled by the procedure of Masson (264)[284] employing iodyl sulphate. Salts containing electron-donating groups, eg alkyl, are prepared (265) by the direct coupling of their aromatic precursors using potassium iodate.[285]

$$ArH + (IO)_2SO_4 \xrightarrow[Ac_2O]{H_2SO_4} Ar\overset{\oplus}{I}OH \xrightarrow{ArH} Ar_2\overset{\oplus}{I}\ \overset{\ominus}{HSO_4}$$

(264)

$$ArH + KIO_3 \xrightarrow[Ac_2O\ /\ AcOH]{H_2SO_4} Ar_2\overset{\oplus}{I}\ \overset{\ominus}{HSO_4}$$

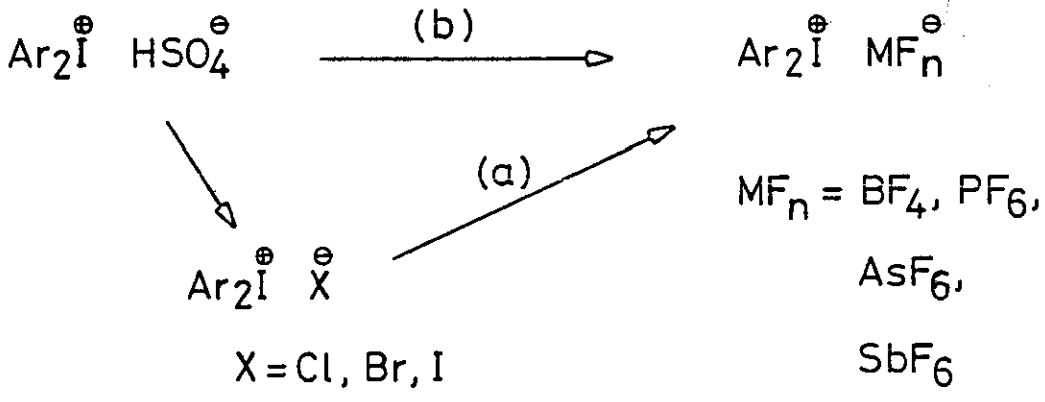
(265)

$$ArIO + Ar'H \xrightarrow[Ac_2O\ /\ AcOH]{H_2SO_4} Ar\overset{\oplus}{I}Ar'\ \overset{\ominus}{HSO_4}$$

(266)

$$ArIO + Ar'IO_2 \xrightarrow{NaOH} Ar\overset{\oplus}{I}Ar'\ \overset{\ominus}{IO_3}$$

(267)



Scheme 31. Synthesis of Diaryliodonium Salts

Unsymmetrical products can be obtained from iodoso compounds either by an acid-catalysed condensation (266) with an aromatic hydrocarbon or by a base-catalysed condensation (267) with an iodoxy compound. In the former,[286] it is likely that the iodoso compound is converted into its conjugate acid, $ArI^{\oplus}OH$, which then undergoes electrophilic attack on the aromatic ring. The latter reaction[287] led to the first reported observation of iodonium salts, but it is now less favoured due to time-consuming preparations of starting materials.

These last two reactions indicate that syntheses (264, 265) also proceed with iodoso intermediates. More recently, however,[288] it has been recognised that such materials can react further in the presence of carboxylic acids and/or corresponding anhydrides to afford aryliodine(III)dicarboxylates, eg (268). Subsequent reaction with an aromatic substrate requires sulphuric acid for the isolation of iodonium salts. The present view, therefore,[288] is that the protonated dicarboxylate is the active electrophilic species, which gives with the arene first a π-complex and then a σ-complex. The latter is transformed irreversibly into the iodonium salt, and this is the rate-determining step of the reaction.

$$ArIO \xrightarrow[\text{or } Ac_2O]{AcOH} ArI(OAc)_2 \quad (268) \xrightarrow{H^{\oplus}}$$

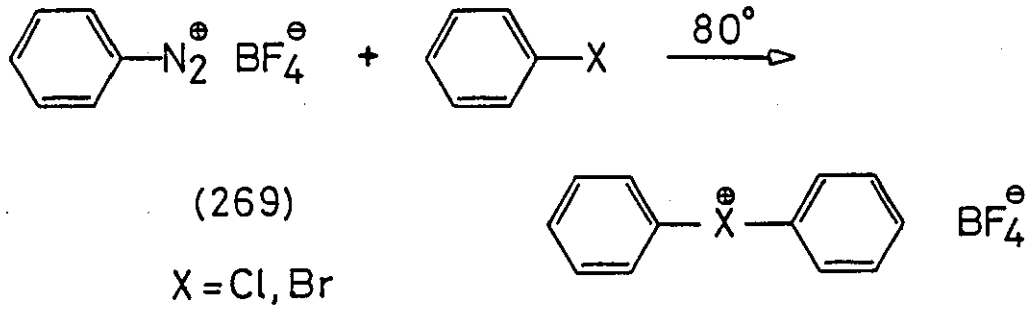
$$[ArI(OAc)_2H]^{\oplus} \xrightarrow{Ar'H} [ArI(OAc)Ar'H]^{\oplus} + AcOH$$

$$\downarrow$$

$$Ar\overset{\oplus}{I}Ar' + AcOH$$

Iodonium salts prepared by three of the methods described above have as their counterion the bisulphate anion. Since these salts are often rather hygroscopic and somewhat unstable, the corresponding halides are usually isolated by addition of ammonium chloride, sodium bromide, or potassium iodide. Complex metal halide anions may be introduced by direct metathesis of (a) the halides with silver tetrafluoroborate, and (b) the bisulphates with alkali metal hexafluoro-phosphates, -arsenates, or -antimonates (see Scheme 31).

Diarylchloronium and -bromonium salts are prepared in very low yields (6%) by the reaction (269) of arenediazonium tetrafluoroborates with the appropriate halobenzene as solvent.[289] Reaction involves heterolytic transfer of an aryl group to the halogen, but is impaired by competing Schiemann fluorination. It represents one of only a few cases thought to involve an S_N1-type mechanism in aromatic substitution, although the existence of free aryl cations in solution has been questioned.[192] Interestingly, the same diazonium reagents were used to obtain very stable triaryloxonium salts, $Ar_3O^{\oplus}\ BF_4^{\ominus}$, by arylation of diaryl ethers. The chloronium and bromonium species exhibit similar properties to those of iodonium salts described below, but their enhanced reactivities generally mean that milder conditions can be used in their reactions.



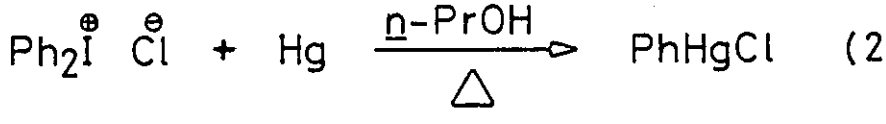
(269)

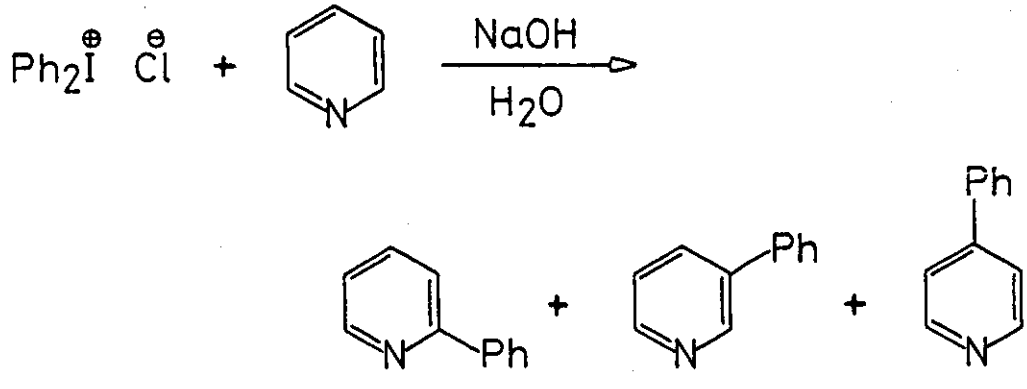
X = Cl, Br

The mechanism by which nucleophiles are arylated by iodonium salts appears to be related, at least in part, to the nature of the

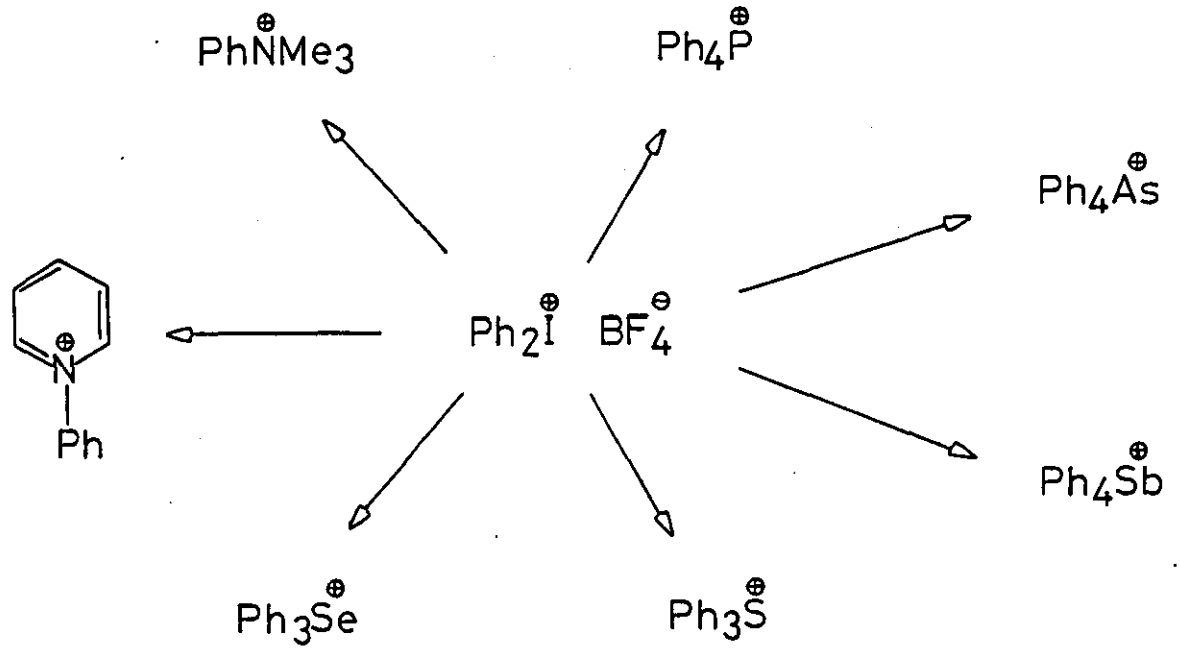
counterion. Thus, like diazonium ions in the presence of stable complex anions, corresponding iodonium salts undergo heterolytic cleavage of aryl groups. Nesmeyanov[289] has used this type of reaction to extend synthetic procedures and thereby obtain new onium salts in excellent yields. Under such conditions halide salts, eg $Ph_2I^{\oplus}\ Cl^{\ominus}$, do not react or are less effective. Diphenyliodonium tetrafluoroborate can also phenylate the oxygen of phenols and carboxylic acids, and the nitrogen of amides and amines. Syntheses are summarised in Scheme 32.

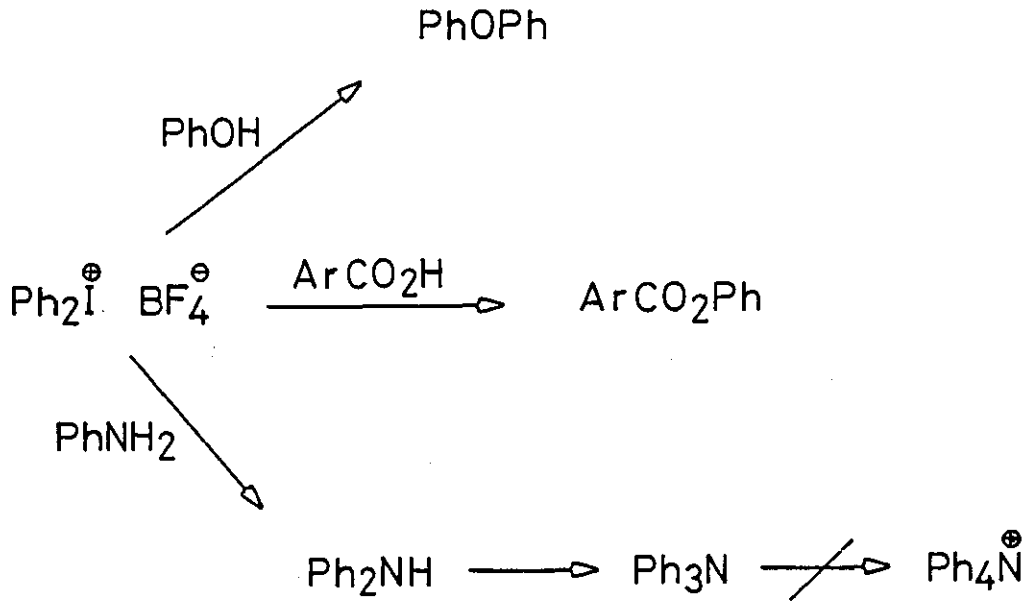
By analogy with diazonium salts, it has been suggested that the decomposition of iodonium halides might to some extent proceed through intermediate formation of free radicals. Experimental evidence includes the formation of organometallic products, such as phenylmercuric chloride (270), in reactions with metals,[290] and the reaction with pyridine in aqueous sodium hydroxide solution,[291] which affords a mixture of all three phenylpyridines (271). This indicates that the normal directive influence of the pyridine nucleus is not operative, and favours a radical mechanism.





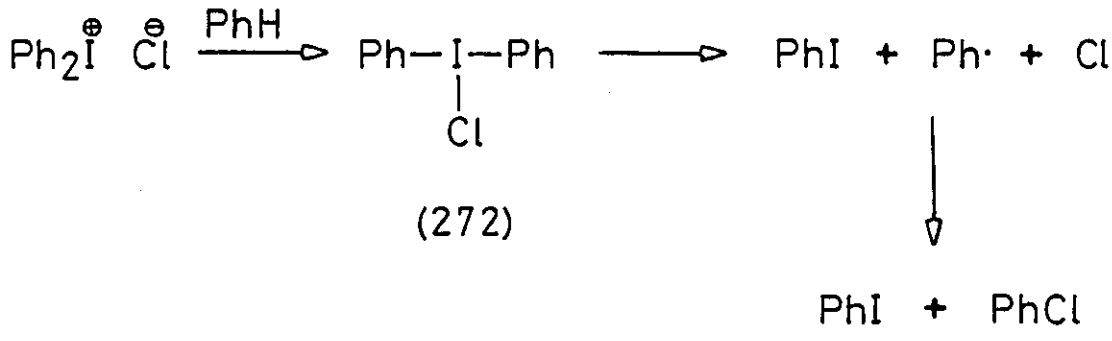
(271)





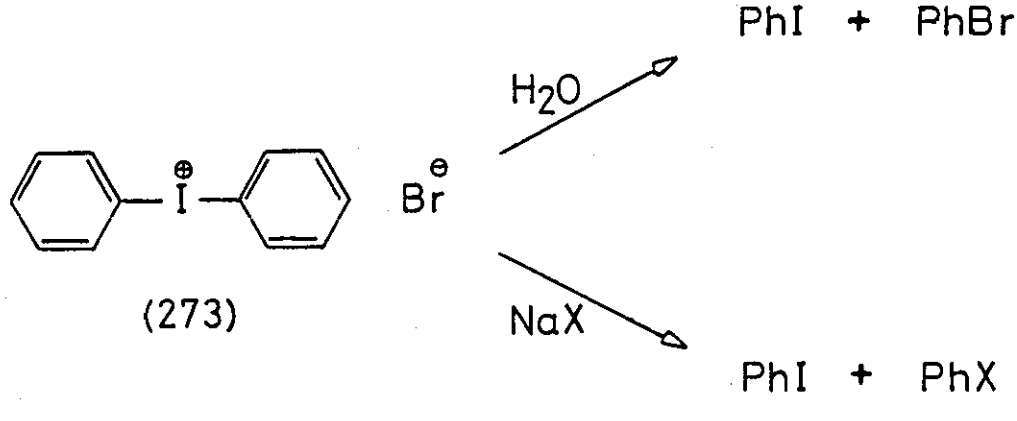
Scheme 32. Reactions of Diphenyliodonium Tetrafluoroborate

The formation of covalent iodonium compounds is implicated. Certain triaryliodine compounds are known, but they are unstable and decompose immediately to free radicals.[283] The same type of intermediate (272) can be used to interpret the rapid first order decomposition of diaryliodonium halides in apolar solvents.



(272)

It is not until the reaction medium becomes more polar that this decomposition becomes slower and second order. It was proposed that this is due to sterically hindered nucleophilic displacement by the counterion.[283] Thus, diphenyliodonium bromide (273) requires three weeks in boiling water, but rates are enhanced in the presence of electron-withdrawing substituents and more powerful nucleophiles.[292] Products are iodobenzene and the phenyl derivative of an organic or inorganic base, isolated in low to high yield (23-95%).

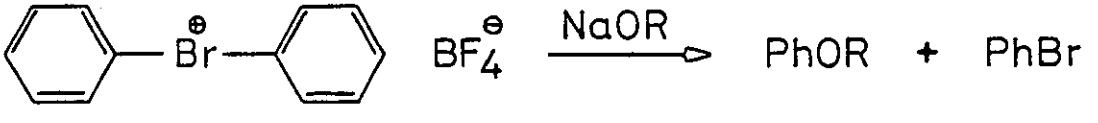


(273)

X = MeO, PhO, $PhCO_2$, CN, NO_2, HSO_3

Strong evidence for nucleophilic attack[292] contrasts with the behaviour of synthetically useful arenediazonium salts, which undergo homolytic cleavage with transfer of an aryl radical, eg the Gomberg-Bachmann-Hey synthesis of biaryls (Scheme 5). Nonetheless, slow competing homolysis in aqueous solution cannot be totally discounted, as it has been shown with iodonium salts possessing non-nucleophilic anions that hydrolysis occurs by homolytic fission of the carbon-iodine bond.[293] A covalent iodonium hydroxide, Ar_2IOH, was suggested as an intermediate. The reported phenylation of thiols by diphenyliodonium chloride[294] seems to support a heterolytic mechanism, since these materials are known to be efficient terminators of radical chain reactions.

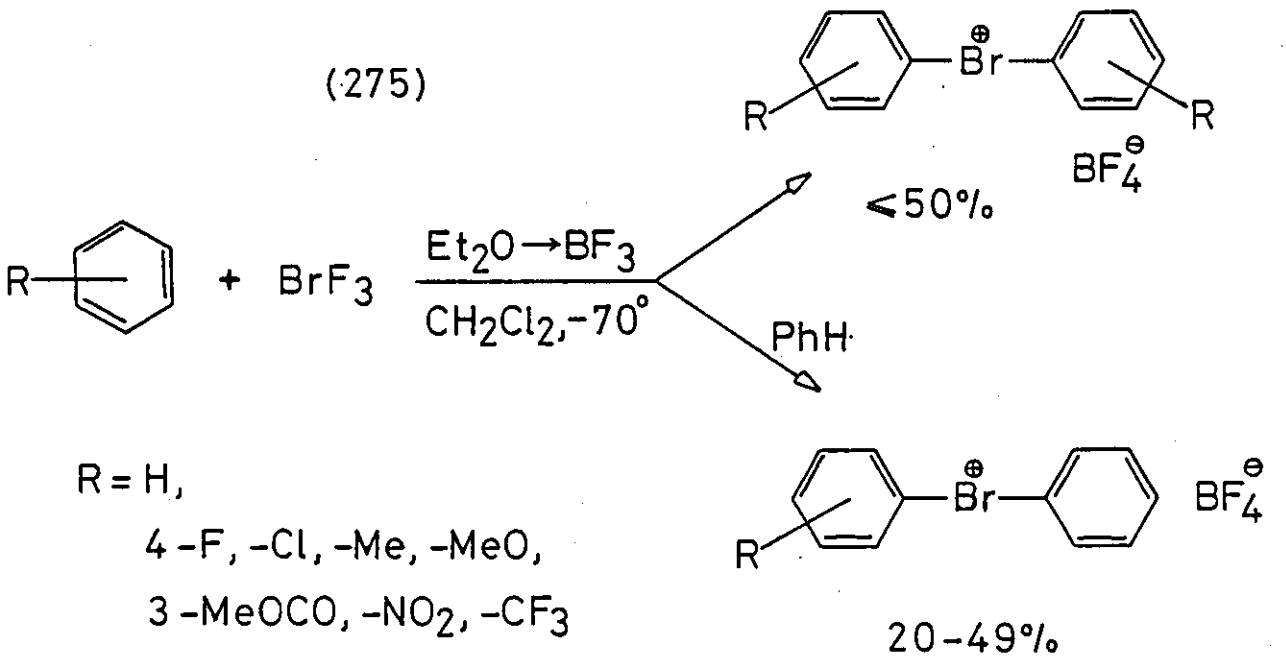
Despite Beringer's claims,[292] more recent studies[295] of the reactions of sodium alkoxides with diaryliodonium salts have recovered hydrocarbon by-products derived from radical abstraction processes. Triarylsulphonium salts exhibit similar characteristics,[153, 154] and the proposed sulphurane precursor to free radicals, $Ar_3S\text{-}OR$, compares with a covalent iodonium species such as (272). However, Lubinkowski and McEwen[296] have raised the yields of alkyl aryl ethers to quantitative levels by employing analogous bromonium tetrafluoroborates (274). This superiority is attributed to the greater ease of iodine over bromine in forming the tricovalent halogen intermediate which initiates the undesirable radical chain reaction. In addition, the more electronegative bromine enhances the desired nucleophilic attack at the 1-carbon.



(274)

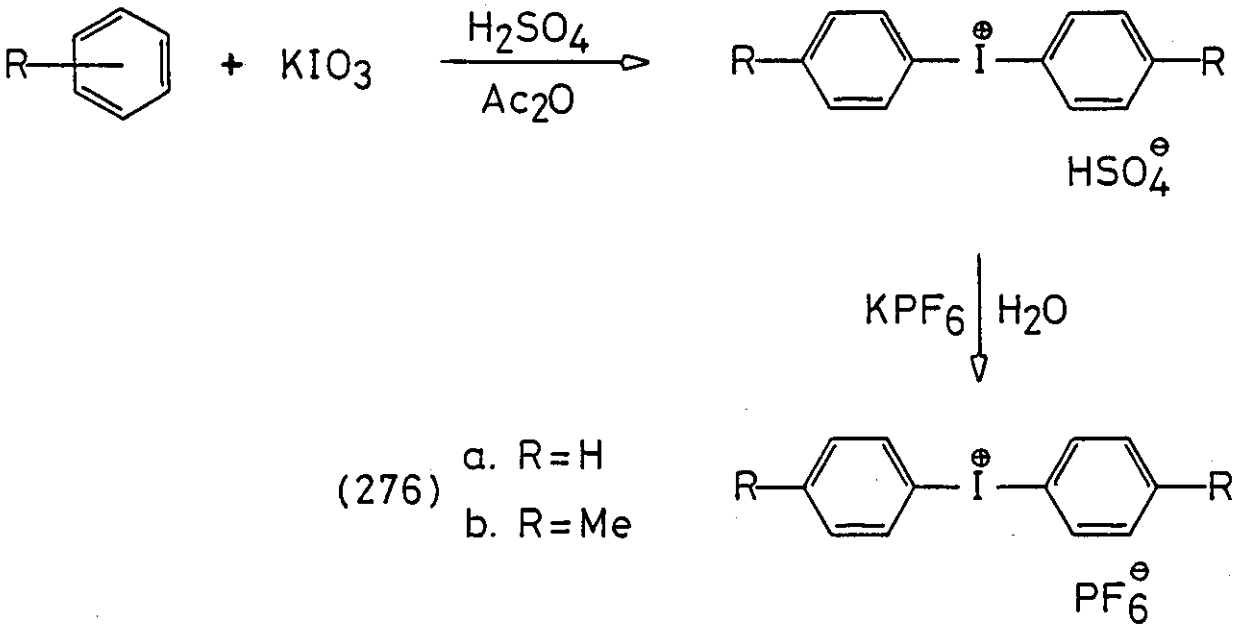
So far, the use of diarylbromonium salts has been restricted by their inefficient preparation,[289] but a new synthesis (275) described by Nesmeyanov and co-workers[297] has yielded both symmetrical and unsymmetrical tetrafluoroborates in yields of 20-50%. The reaction utilises a condensation of arenes with bromine trifluoride in dichloromethane, containing boron trifluoride-etherate, at -70°.

(275)



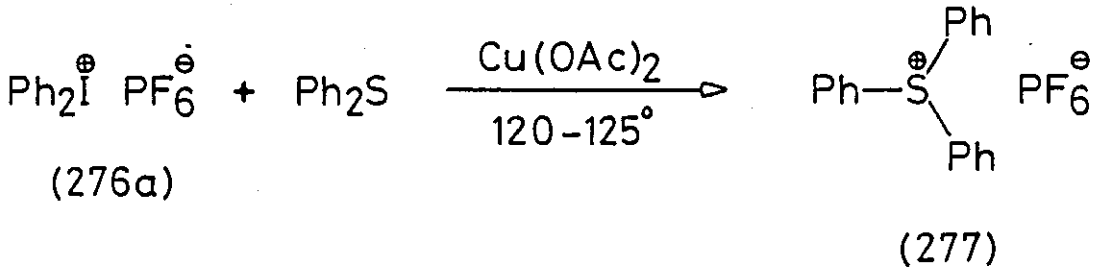
In order to illustrate the arylating abilities of diaryliodonium salts, and to investigate their NMR characteristics (see Chapter 7), we undertook the synthesis of two symmetrical hexafluorophosphates. Diphenyliodonium and di-p-tolyliodonium salts (276a, b) were obtained by the procedure of reaction (265). They were precipitated as white crystalline solids in moderate yields by the addition of potassium hexafluorophosphate to an aqueous solution of the bisulphate (see overleaf).

The synthesis of onium compounds depicted in Scheme 32 relies on the presence of a stable counterion to avoid competition with the weakly nucleophilic substrates. Elevated temperatures (200°) are



(276) a. R=H
b. R=Me

generally required,[289] but by a previously reported modification,[147] we used a copper(II) acetate catalyst at 120-125° to prepare triphenylsulphonium hexafluorophosphate (277) in 88% yield.



(276a)

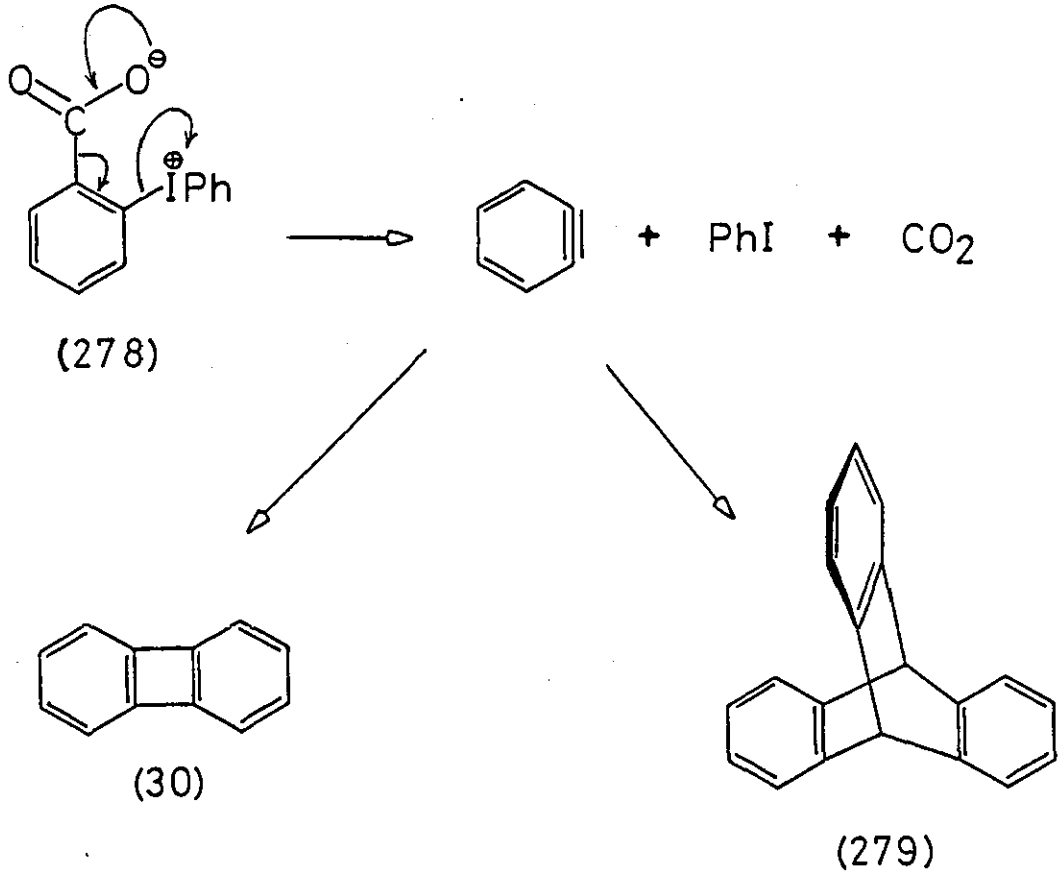
(277)

Diaryliodonium salts possessing non-nucleophilic anions are of commercial interest because of their high photosensitivity. Thus, when subjected to UV irradiation, they induce the cationic polymerisation of a wide variety of monomers, including olefins and epoxides. Considerable research has been performed by Crivello,[118] who reports also the utility of triarylsulphonium salts and triarylselenonium salts, $Ar_3Se^{\oplus}X^{\ominus}$. During the photolysis, the anions remain unchanged and appear in the products as corresponding Brönsted acids, HX, which are the ultimate initiators of polymerisation. All three types of

reagent undergo photolysis by an identical radical mechanism, which is illustrated in Scheme 33 for the iodonium salts.

Overall, a much improved result is achieved over the longer established arenediazonium salts,[118] which are often coloured, of limited stability, and present difficulties in eliminating nitrogen from thick films.

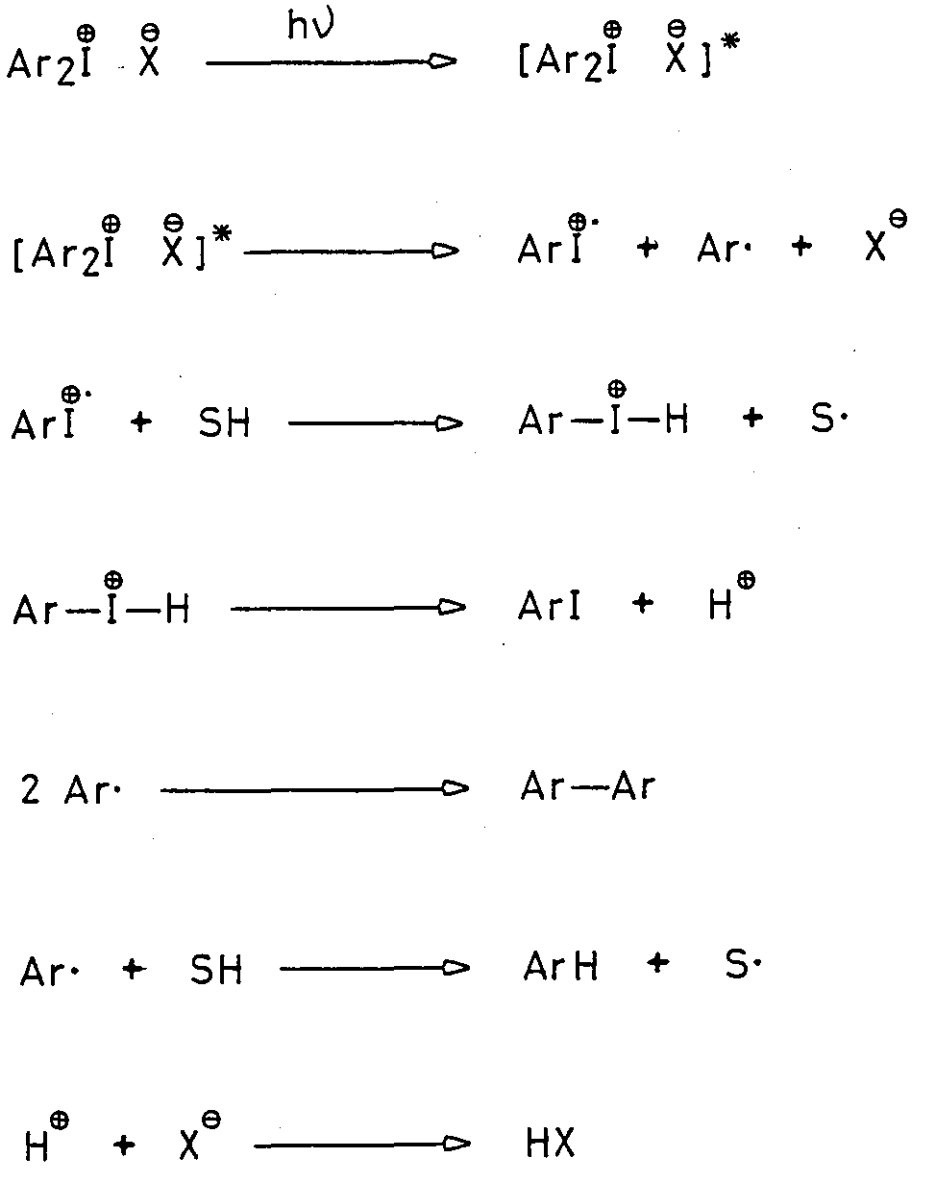
Although much attention has been given to arylations of various nucleophiles, two examples can be quoted in which diaryliodonium salts effect the formation of carbon-carbon bonds. The first[298, 299] uses diphenyliodonium-2-carboxylate (278) as a source of the highly reactive intermediate benzyne. In the absence of trapping agents, flash pyrolysis at 325° gives biphenylene (30) as the major product, but thermal cleavage affords triptycene (279) in the presence of anthracene.[299]



(278)

(30)

(279)

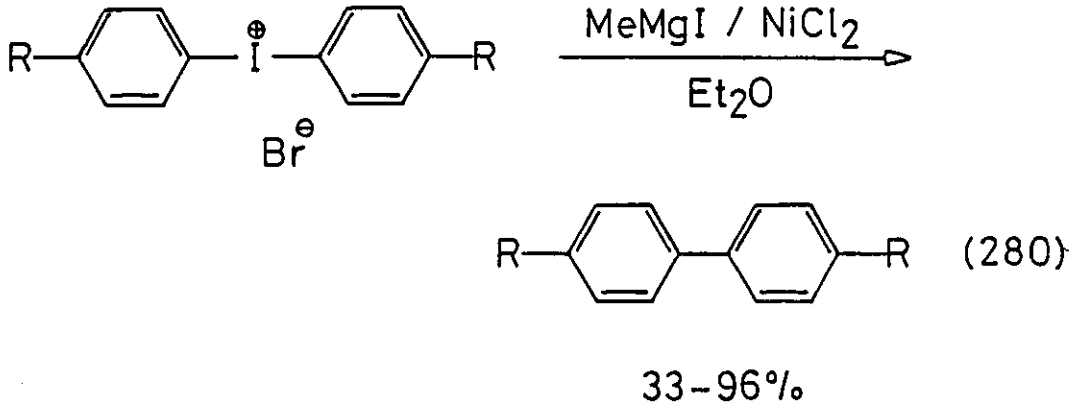


$X = BF_4, PF_6, AsF_6, SbF_6$

SH = solvent

Scheme 33. Photodecomposition of Diaryliodonium Salts

The second reaction,[300] with Grignard reagents and a catalytic amount of nickel(II) chloride, represents a novel synthesis of biaryls (280), and adds to the methods described in Chapter 1. It is best suited to the synthesis of symmetrical biaryls with electron-donating substituents, but unsymmetrical iodonium bromides do give the corresponding unsymmetrical compounds as major products. As previously observed with nickel species,[69] salts bearing nitro substituents fail to react.



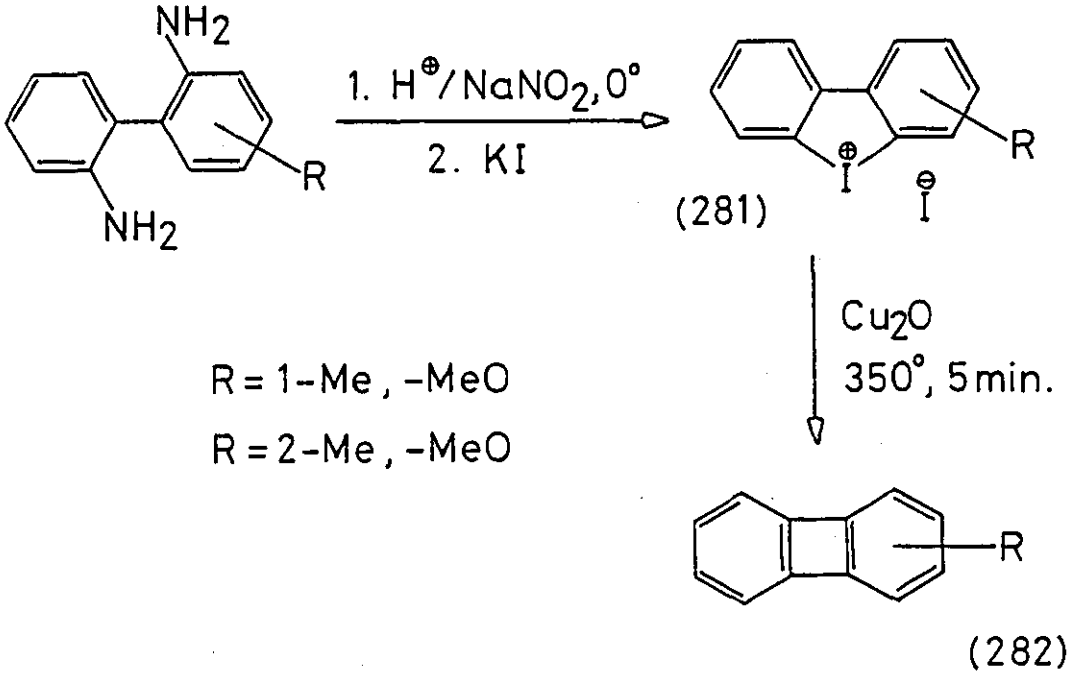
(280)

33-96%

R = H, Me, Et, i-Pr, MeO, F, Cl, Br

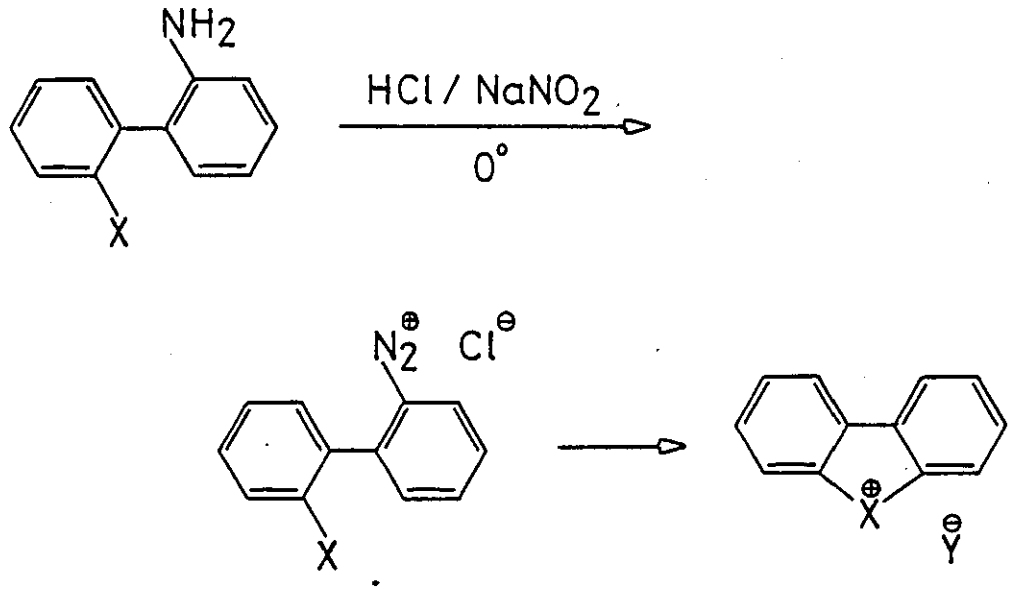
5.3 BIPHENYLENEHALONIUM SALTS

The first report of a stable cyclic iodonium salt dates back to 1908, when Mascarelli and Benati[301] prepared biphenylene-2,2'-iodonium iodide by the addition of potassium iodide to tetrazotised 2,2'-diaminobiphenyl. Baker, Barton, and McOmie[302] subsequently employed the same reaction to obtain corresponding substituted salts (281), which upon rapid heating with a large excess of copper(I) oxide afforded the Lothrop[40] biphenylenes (282) via 2,2'-diiodobiphenyls.



The first isolation of stable crystalline chloronium and bromonium compounds of any description is credited to Sandin and Hay.[303] They prepared biphenylene-2,2'-halonium halides (283) in 30-40% overall yields by a sequence of diazotisation and cylisation, a procedure which was later adopted in a synthesis of related oxonium salts[108] (see overleaf).

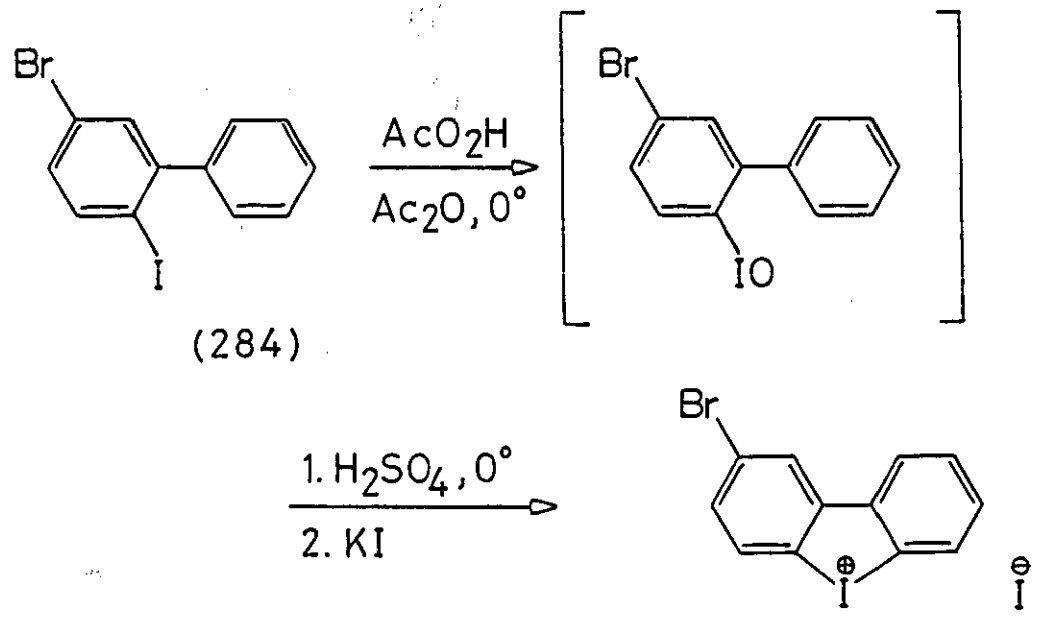
Alternative ring closures, analogous to reactions used in preparing unsymmetrical diaryliodonium salts,[283] may be used to produce the biphenyleneiodonium counterparts. An example[302] uses



(283)

X = Cl, Br, I Y = Cl, I, NO_3

the method of reaction (266) in a conversion of 5-bromo-2-iodobiphenyl (284) to the cyclic iodide. It is likely that the iodoso intermediate proposed is transformed first into the aryliodine(III) diacetate derivative (268). The cyclic iodonium salt therefore results from <u>in situ</u> I-acetoxylation of the aryl iodide, followed by intramolecular cyclisation with sulphuric acid.[288]

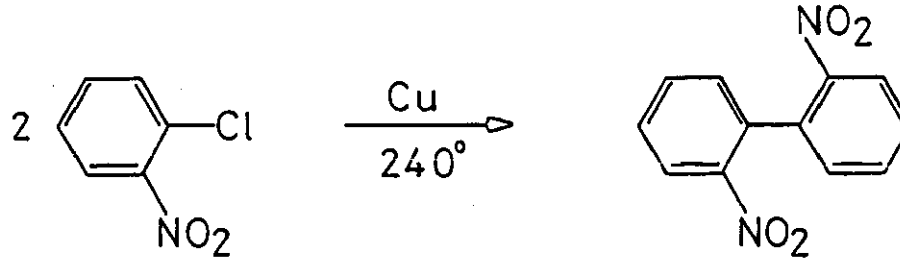


(284)

During their work towards 2,2'-dihalogenobiphenyls, Heaney and Lees[304] devised probably the best route now available to biphenylenehalonium salts. Their attempts to incorporate fluorine as a second halogen, by Schiemann thermolysis of 2'-halobiphenyl-2-yldiazonium tetrafluoroborates and hexafluorophosphates, led instead to cyclic products in high yield (70-90%). As with oxonium and sulphonium salts previously discussed (Chapters 2.2, 3.2), cyclisation can be rationalised in terms of intramolecular nucleophilic attack by the participating heteroatom. The ability to control the cyclisation of an isolable diazonium salt intermediate gives a much cleaner product, and thereby makes this method superior to others[303] using water soluble diazonium salts.

With regard to our interest in ^{13}C NMR interpretation (see Chapter 7), we undertook the synthesis of a bromonium and iodonium salt according to the latter technique.

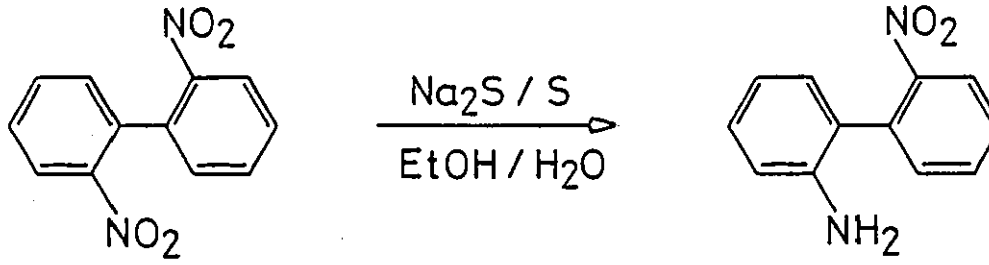
Each of the routes outlined above requires in its early stages the synthesis of a 2,2'-dinitrobiphenyl. The parent compound (33) has already been mentioned in connection with a number of procedures,[25, 27, 28, 39, 53] and for our purposes was prepared by the conventional Ullmann coupling of o-chloronitrobenzene[25] in 48% yield.



(33)

The next step demanded selective reduction of one nitro group to afford 2-amino-2'-nitrobiphenyl (198). The most established method

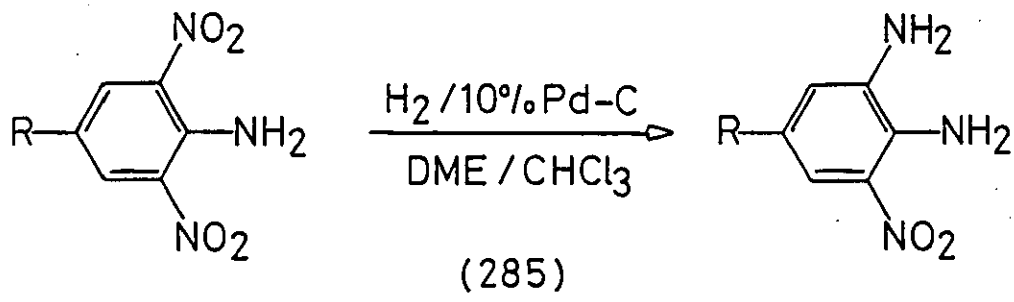
for such transformations uses a sulphide or polysulphide (Zinin reduction), and three variations were examined. Reaction with sodium hydrogen sulphide, NaHS, in methanol[305] was inconsistent due to difficulties in preparing the reagent, and the reported high yields could not be repeated. When an aqueous suspension of the dinitrobiphenyl was refluxed with a polysulphide derived from sodium sulphide nonahydrate and sulphur,[306] the major product was 3,4-benzocinnoline N-oxide.[307] Such materials are generally prepared from dinitrobiaryls with sodium sulphide.[30] However, when the same polysulphide was used in aqueous alcoholic solution,[308] the desired reduction was effected in reproducible yields of the order of 60%. Even so, product mixtures associated with the Zinin reduction are often difficult to purify, and the crystalline amine was only gradually obtained from a slowly solidifying oil.



(33) (198)

The foregoing experimental observations reinforce the view that reductions involving sulphides are frequently not straightforward. Yields are often only moderate, and some functional groups are sensitive to the conditions used. Consequently, alternative methods have recently been examined, and examples as applied to various dinitrobenzenes are shown in Scheme 34.

Lyle and LaMattina[309] describe a heterogeneous catalytic hydrogenation technique (285) for a range of 2,6-dinitroanilines. Using low pressures (3 atm) and ambient temperatures it gives yields superior in every case to those using sulphide reagents, being



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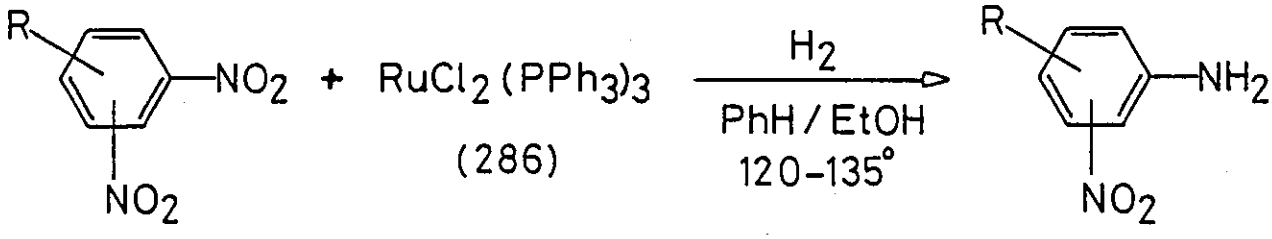
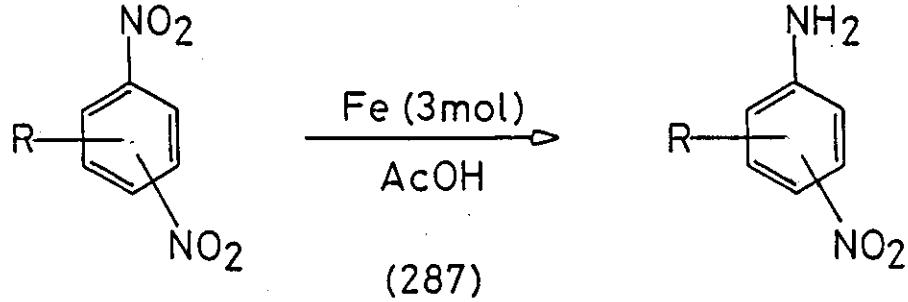




(287)

Scheme 34. Monoreduction of Dinitrobenzenes

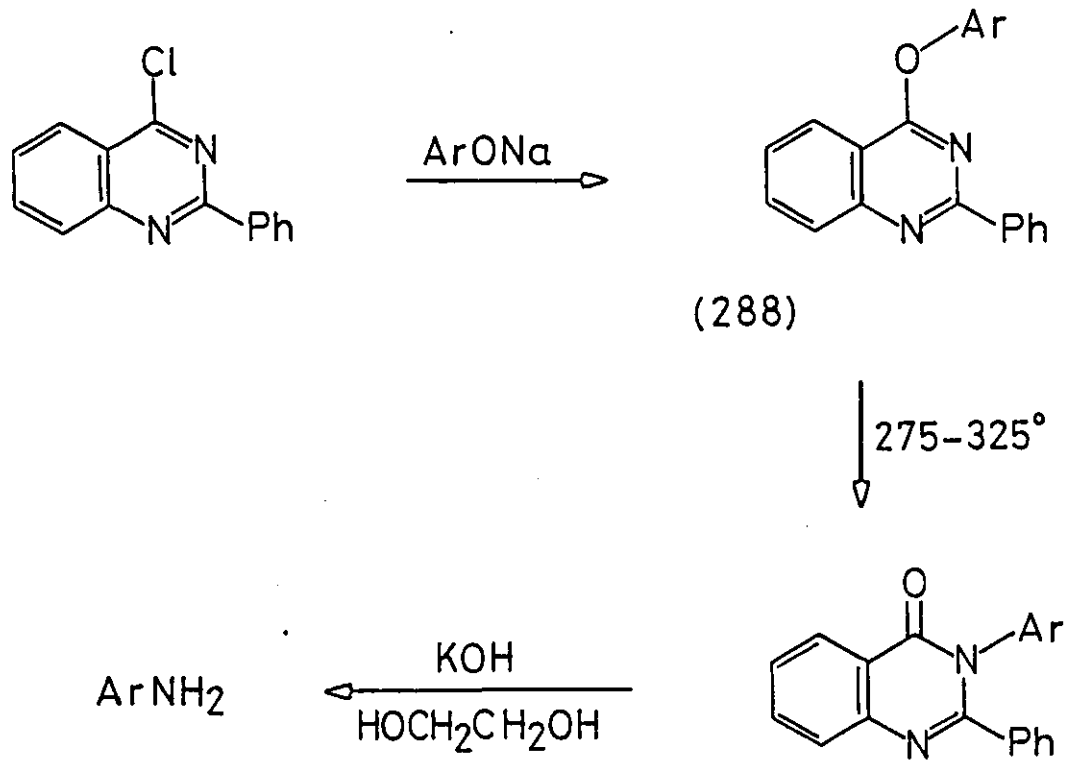
terminated after the necessary uptake of hydrogen. Owing to the apparent simplicity of the technique, a solution of 2,2'-dinitrobiphenyl in 1,2-dimethoxyethane (DME) and chloroform (10:1) was similarly hydrogenated. At atmospheric pressure the rate of reduction was, however, very slow, and starting material was recovered to the extent of 64% after 16 hours. Thus, although the 27% yield of 2-amino-2'-nitrobiphenyl was of reasonable purity, for large scale work the method of Purdie[308] was preferred.

A second hydrogenation technique[310] employs dichlorotris(triphenylphosphine)ruthenium (II) (286) as catalyst in homogeneous solution. Raised temperatures and pressures usually mean for enhanced rates of reactions, yet a high degree of selectivity is still maintained.

Possibly the most attractive monoreduction so far reported is that (287) with iron powder in glacial acetic acid,[311] wherein the product is the free amine and not an acetamide. The reaction is comparable in yields and availability of reagents to polysulphide and hydrogenation procedures, and is far more rapid, being complete within minutes instead of hours.

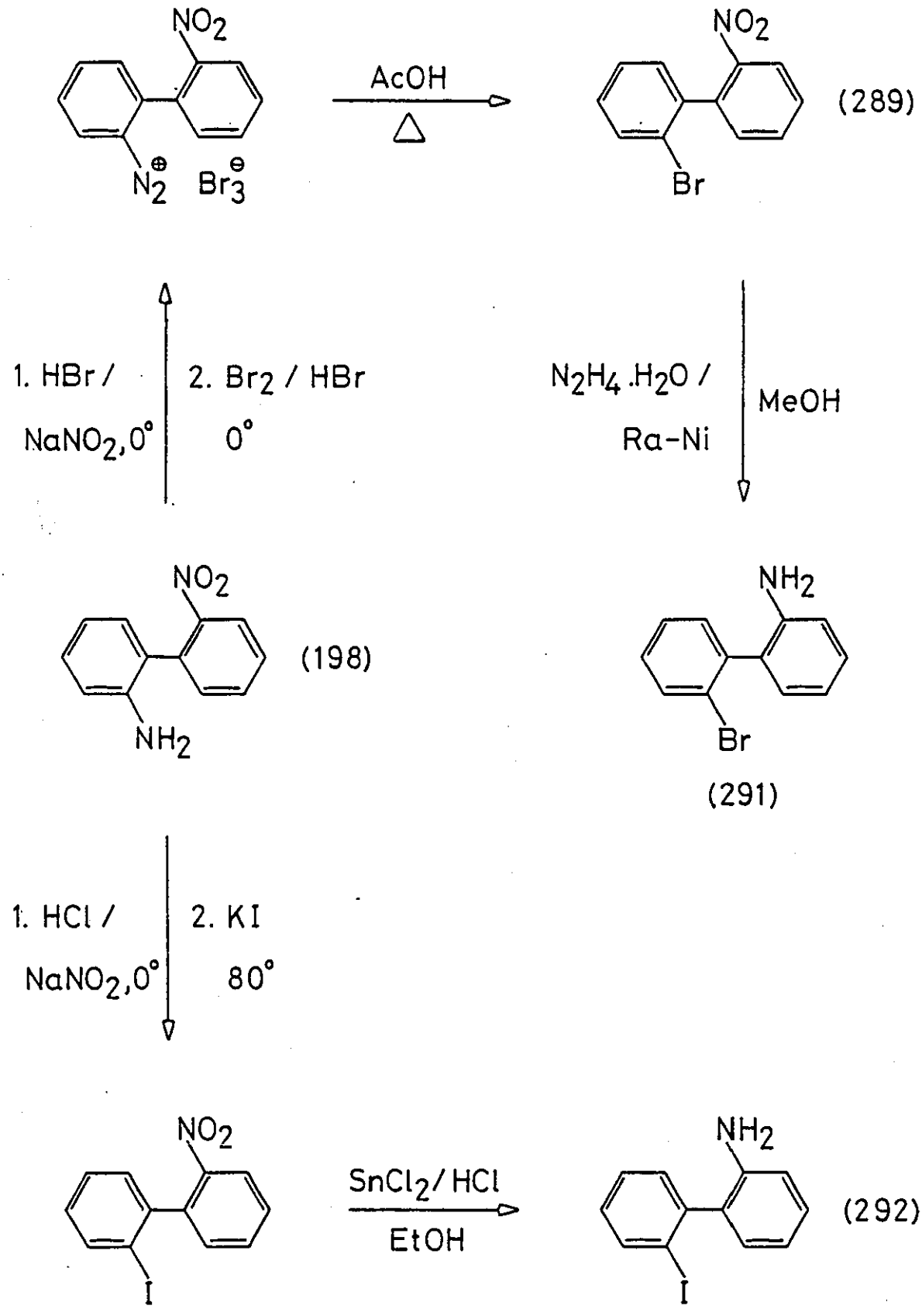
Before proceeding further, it is worth considering a reaction which makes 2-hydroxy-2'-nitrobiphenyl (119) a potential source of nitroamine (198). Whilst most anilines can be transformed to the corresponding phenol by way of a diazonium salt, the reverse path has been severely restricted. Now a new procedure, introduced by Scherrer and Beatty,[312] appears to be the first general conversion of phenols to anilines. The key step is a thermal Chichibabin rearrangement of a 4-aryloxy-2-phenylquinazoline (288), and subsequent hydrolysis with potassium hydroxide in ethylene glycol gives the final product. (see overleaf).

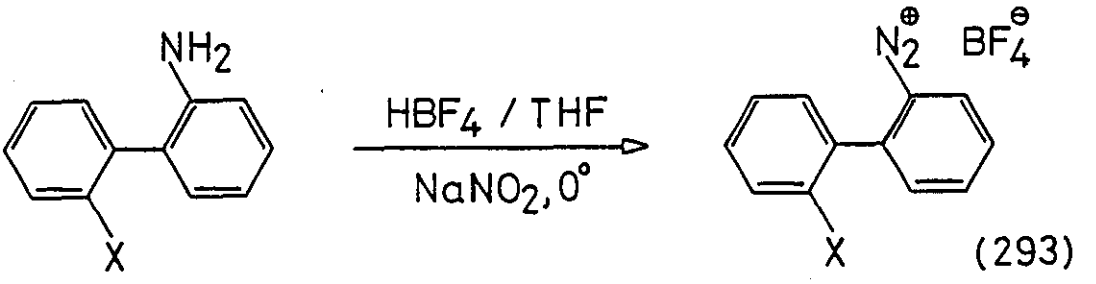
2-Amino-2'-nitrobiphenyl served as precursor to 2-bromo-2'-nitrobiphenyl (289) and to 2-iodo-2'-nitrobiphenyl (290). Each was prepared by halogenation of an intermediate diazonium salt. They were isolated respectively as pale yellow and pale green crystalline solids in yields of 9% and 27%. Subsequent reduction steps gave 2-amino-2'-bromobiphenyl (291) and 2-amino-2'-iodobiphenyl (292), as viscous oils. Corresponding yields were 62% and 70%, with high levels of purity verified by spectral analyses (see overleaf).



Treatment of each amine with sodium nitrite in fluoroboric acid produced the stable diazonium salts.[304] 2-Bromobiphenyl-2'-yldiazonium tetrafluoroborate (293a) was isolated as yellow crystals in 48% yield. 2'-Iodobiphenyl-2-yldiazonium tetrafluoroborate (293b) was obtained as a cream solid in 70% yield. Both salts were dried in vacuo over phosphorus pentoxide and stored at -20°.

Suspension of the diazonium salts in refluxing benzene resulted in evolution of nitrogen and loss of colour associated with formation of the white crystalline biphenylene-2-2'-halonium tetrafluoroborates (294). Filtration gave the bromo and iodo derivatives in yields of 76% and 70%, respectively (see overleaf).


NO2
N2⊕ Br3⊖
AcOH
Δ
Br
(289)
1. HBr / NaNO2, 0°
2. Br2 / HBr 0°
N2H4 .H2O / Ra-Ni
MeOH
NH2
(198)
(291)
1. HCl / NaNO2, 0°
2. KI 80°
I
SnCl2 / HCl
EtOH
(290)
(292)



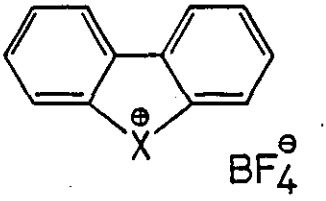
(293)

a. X = Br

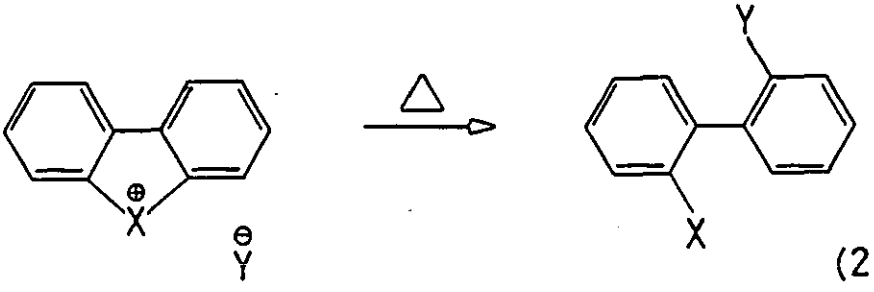
b. X = I

PhH | △

(294)



Biphenylenehalonium halides exhibit several properties characteristic of diarylhalonium salts.[283] In particular,[304] pyrolysis lends itself to a range of synthetically useful 2,2'-dihalogenobiphenyls (295).



(295)

X = Y = Cl, Br, I

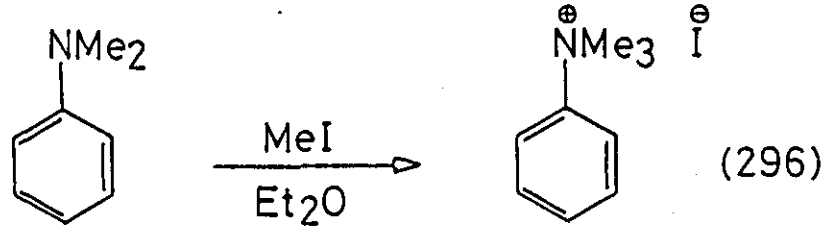
CHAPTER 6

QUATERNARY AMMONIUM SALTS

6.1 REVIEW

The chemistry of quaternary ammonium salts is well documented, and only mention relevant to the present study will be accorded herein.

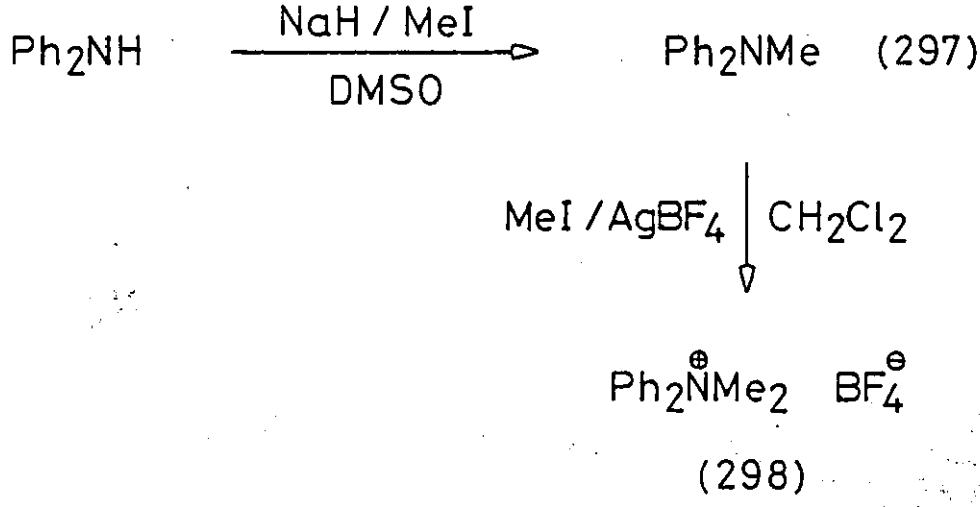
Amines, unlike ethers and most alcohols, are generally sufficiently basic themselves to react with alkyl halides, sulphates, or sulphonates. The reaction is most useful for the preparation of tertiary amines and quaternary ammonium salts. The latter conversion, known as the Menschutkin reaction, is exemplified by our formation of trimethylanilinium iodide (296).



(296)

The conversion of primary or secondary amines to quaternary salts (exhaustive alkylation) conventionally needs a strong inorganic base, eg. sodium hydroxide, to bind the generated acid. However, prolonged heating of strongly basic and heterogeneous mixtures is not ideal, and milder conditions can now be employed by using a sterically hindered non-nucleophilic strong organic base.[313] In this way, using aniline and excess methyl iodide, Sommer et. al. prepared the above salt (296) in the presence of diethylaniline at room temperature.

Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. Thus, we generated the conjugate base of diphenylamine in order to synthesise methyldiphenylamine (297), and in a subsequent step, dimethyldiphenylammonium tetrafluoroborate (298) was obtained upon treatment with methyl iodide in the presence of silver tetrafluoroborate, though in low yield (5%) (see overleaf).

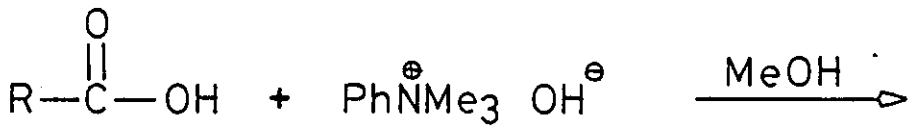


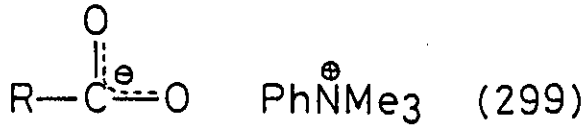
(298)

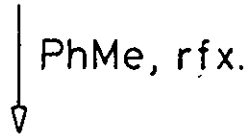
The natural abundance and ease of preparation of quaternary ammonium salts, in contrast to the markedly more unstable oxonium salts, does limit the extent to which they can be used as alkylating agents. Moreover, like sulphonium salts, they may undergo competing elimination reactions to afford olefins when a β-hydrogen is present, and Sommelet and Stevens rearrangements similarly proceed via ylide intermediates.

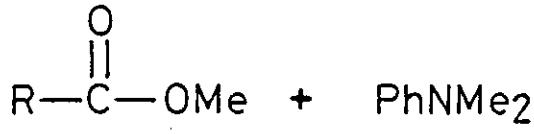
Pyrolysis of tetramethylammonium salts has long been used to prepare methyl esters of carboxylic acids, but the requirement of high temperatures (250-300°) is an obvious disadvantage. However, the procedure has been moderated by first forming carboxylic acid trimethylanilinium salts (299), then allowing these to decompose in refluxing toluene[314] (see overleaf).

Even esters of sterically hindered acids, such as methyl mesitoate (131), are produced in excellent yields (>90%). Therefore, the method offers considerable potential as a single step methylation reaction for both carboxylic acids and phenols.





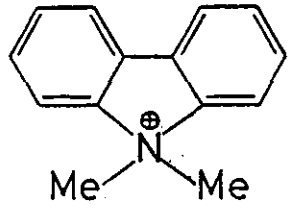




6.2 CARBAZOLIUM SALTS

In 1963, Nesmeyanov[315] prepared the first known tetraarylammonium salt containing the diphenylcarbazolium cation. The subsequent synthesis of alkylarylammonium salts based on the carbazole system is credited to Hellwinkel and Seifert,[316, 317] who utilised similar reaction principles. In all examples, the ultimate step involves ring closure of a 2-aminobiphenyl-2'-yldiazonium species.

We aimed to repeat their synthesis of the N,N-dimethylcarbazolium tetrafluoroborate (300a), with slight modification, in order to make comparisons with the physical data and chemical properties (see Chapter 7) of previously discussed O- and S-methyl analogues (110 and 161).



$\overset{\ominus}{X}$

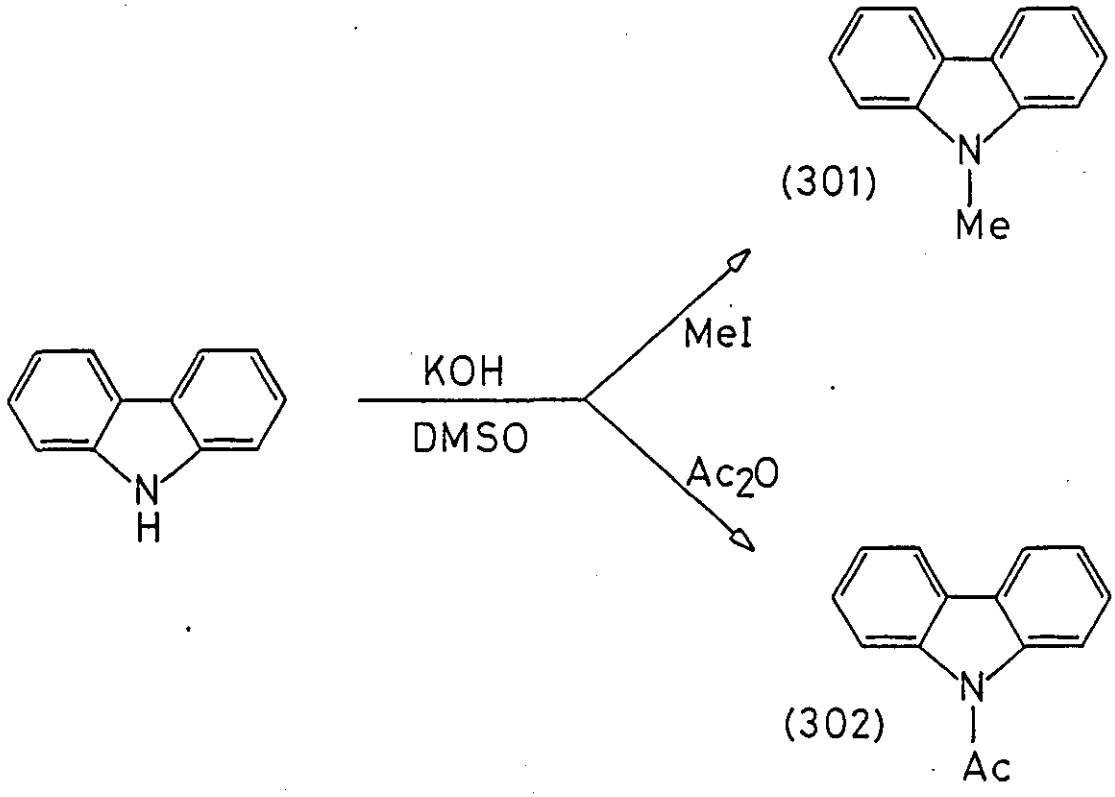
(300) a. $X = BF_4$

b. $X = PF_6$

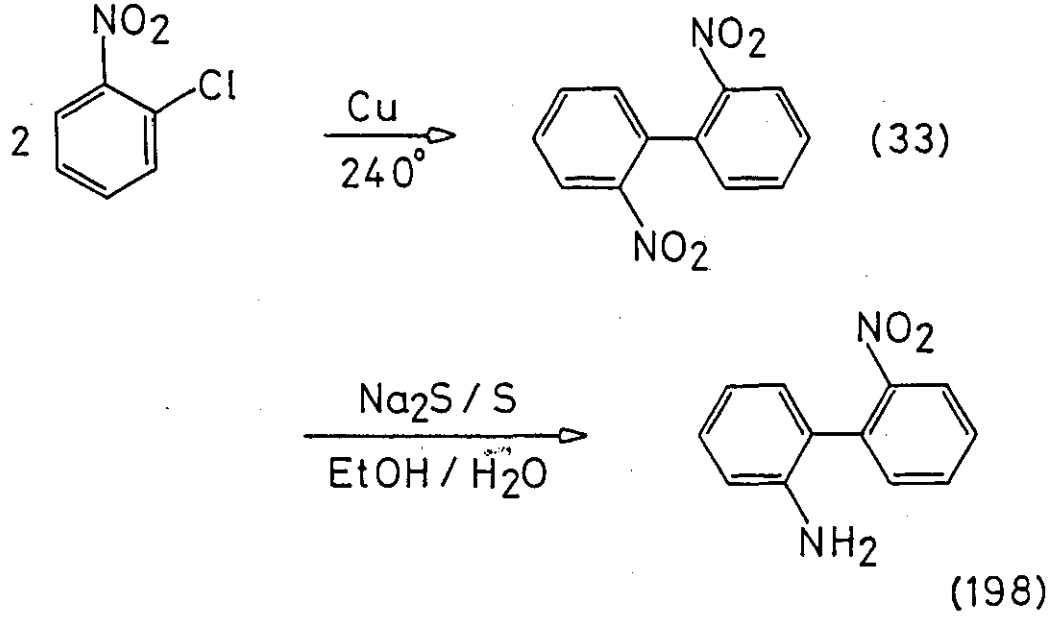
Related studies, detailed at the end of this chapter, enabled further conclusions to be drawn concerning the mechanism of diazonium salt ring closure in alkylation reactions.

Carbazole is a relatively weak acid, but does react with inorganic bases in heterogeneous media to give salts which can be alkylated or acylated. N-Methylcarbazole (301) and N-acetylcarbazole (302) are examples, respectively (see overleaf).

Carbazoles are also weak bases, and considered insufficiently nucleophilic to afford quaternary ammonium salts with the common alkylating systems. Consequently, the route to the desired salt (300a) followed a sequence originally adopted by Hellwinkel and Seifert,[316, 317] and later adapted by Heaney and co-workers to oxonium salts[90, 108] and to sulphonium salts (this thesis, Chapter 3).

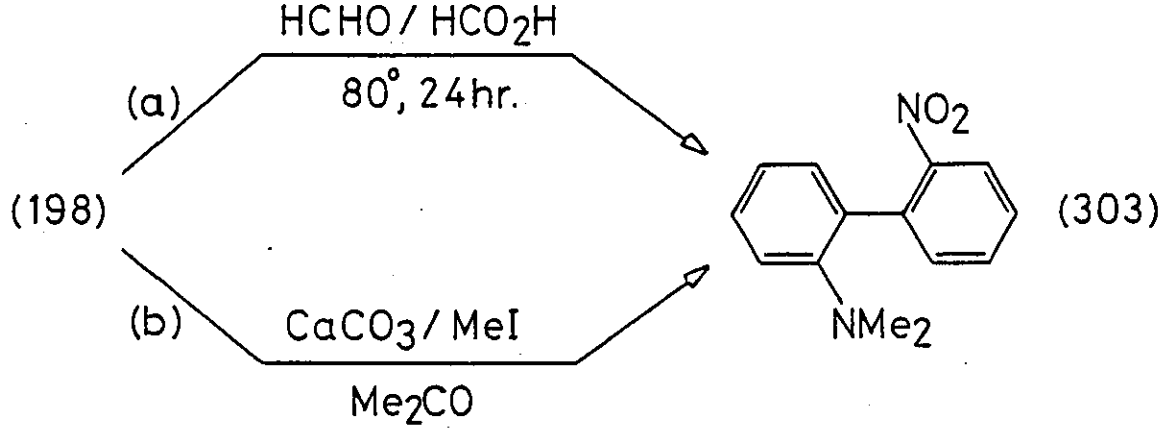


The first two steps involved Ullmann coupling of o-chloronitrobenzene, followed by polysulphide (Zinin) reduction[308] of the resulting 2,2'-dinitrobiphenyl (33) to 2-amino-2'-nitrobiphenyl (198).



The next stage required methylation to the corresponding tertiary amine. Mixtures are often obtained upon treatment of primary amines with methyl iodide, so in an attempt to improve upon past conversions,[317] a process of reductive alkylation was examined. The Eschweiler-Clarke procedure[318] uses formaldehyde as methylating agent and formic acid as reducing agent, and usually leads to good yields of N,N-dimethyl tertiary amines, at least from simple primary and secondary aliphatic amines. The reaction has been investigated further by Pine and Sanchez,[319] whose typical procedure we followed.

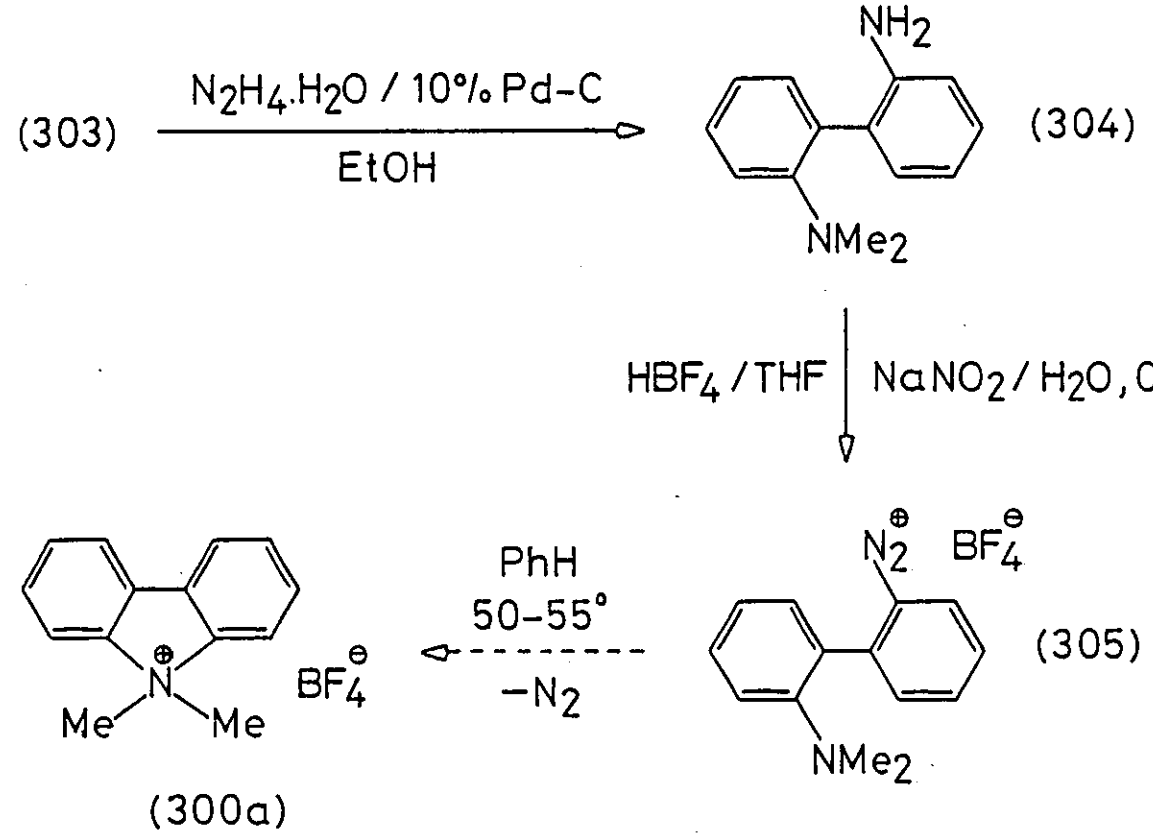
An aqueous mixture of 2-amino-2'-nitrobiphenyl, 90% formic acid (3 equiv.), and 40% formaldehyde (2-3 equiv.) was heated at 80° for 24 hours (path a), but the desired 2- (N,N-dimethylamino)-2'-nitrobiphenyl (303) could not be isolated in reasonable yield. Instead, a complex mixture containing other basic impurities was obtained.



Interestingly, two additional methods for reductive methylation of amines have been developed. They replace formic acid in the original Eschweiler-Clarke procedure by sodium cyanoborohydride[320] and by sodium borohydride.[321] The former in particular appears to be general for a wide variety of aliphatic and the less basic aromatic amines, and may prove more appropriate to our aims.

The established method of Hellwinkel and Seifert, using calcium

carbonate and methyl iodide in acetone (path b), was then reconsidered and successfully adhered to. Chromatography of the crude product gave a 42% yield of crystalline tertiary amine (303). Subsequent reduction afforded 2-amino-2'-(N,N-dimethylamino)biphenyl (304) as a viscous colourless oil after vacuum distillation.

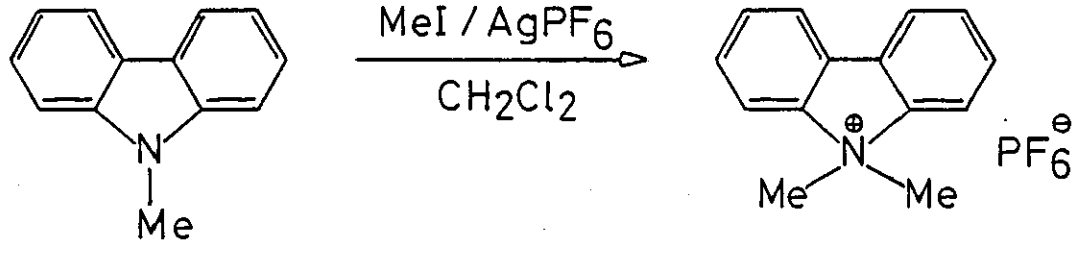


Hellwinkel and Seifert next made the diazonium acetate, which was decomposed in aqueous solution, and the carbazolium tetrafluoroborate (300a) was precipitated by addition of sodium tetrafluorcborate. We alternatively isolated 2-(N,N-dimethylamino)biphenyl-2'-yldiazonium tetrafluoroborate (305) in quantitative yield, and consequently hoped to imitate the controlled heterogeneous cyclisation exhibited by precursors to biphenylenehalonium salts.[304]

Warming of the diazonium salt in benzene at 50-55° for several hours gave rise to gas evolution and formation of an off-white solid. However, recrystallisation from ethanol-acetone (1:1) afforded a product

whose melting point (ca. 170°, lit.,[316] m.p. 220-22°) and ^{1}H NMR methyl resonance (δ3.48) were both low compared with reported figures.

We ultimately attempted the procedure used by Acheson and Harrison[165] to methylate dibenzothiophen. N-Methylcarbazole (301) was treated with one equivalent of silver hexafluorophosphate and a large excess of methyl iodide in dichloromethane. After 24 hours at room temperature, removal of silver iodide, followed by trituration of the filtrate with ether, gave the previously unreported N,N-dimethylcarbazolium hexafluorophosphate (300b) in 11% yield before recrystallisation.



(301) (300b)

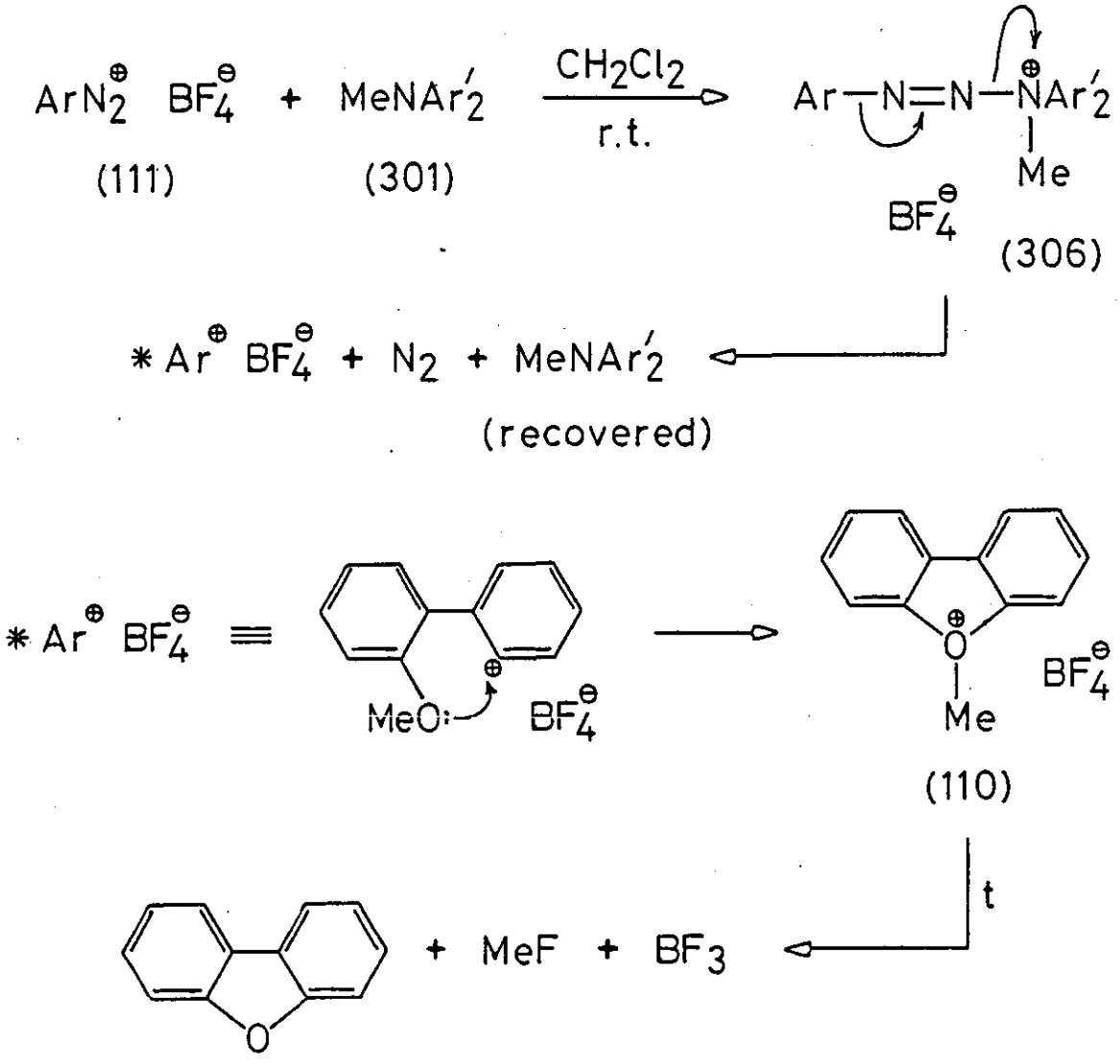
^{1}H NMR data for the carbazolium ion - δ8.55-7.70 (m, 8H); and 4.07 (s, 6H) - was in excellent agreement with that of Hellwinkel and Seifert[316] (δ8.60-7.70 and 4.08). A relatively short and simple route to the desired material had therefore been found, but time was not available to carry out any methylation studies.

MECHANISM OF RING CLOSURE (PART 2)

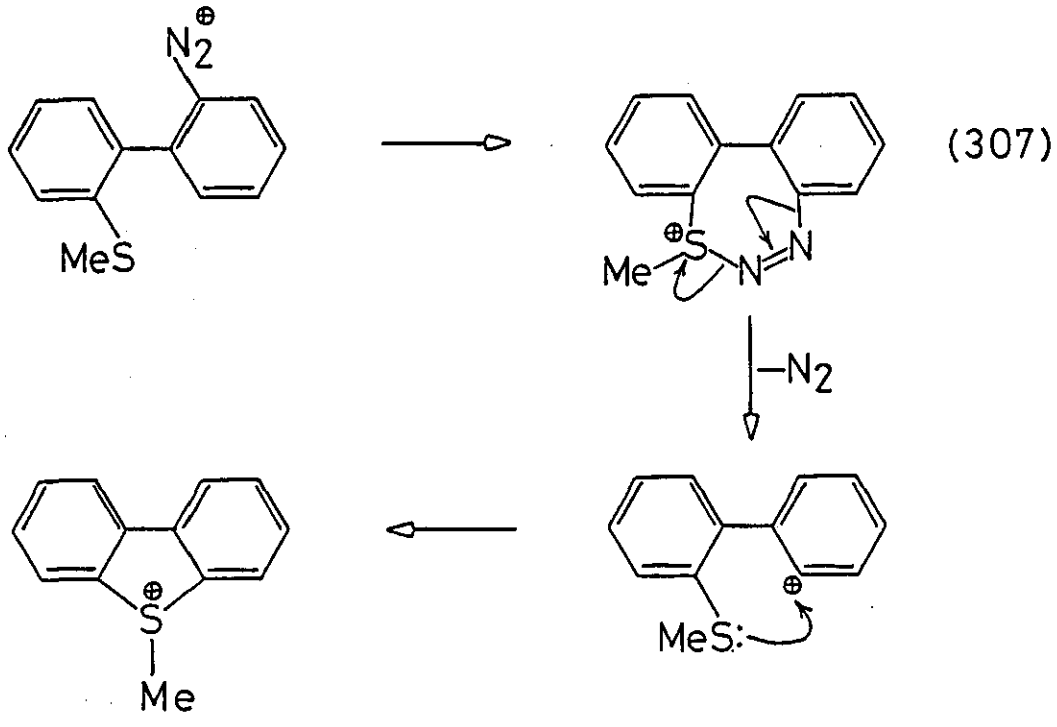
Arenediazonium tetrafluoroborates are normally stable under ambient conditions, but 2-methoxy-, 2-methylthio-, 2-halo-, and 2-dimethylamino-biphenyl-2'-yldiazonium salts (111, 167, 293, and 305) have all been shown to decompose with comparative ease. Ring closure has occurred in each case, and no aromatic fluorination has been detected. In Part 1 (Chapter 2) evidence was cited for a cationic

mechanism in which the heteroatom plays a significant neighbouring group role.

In a separate attempt to find a more direct route to the dimethylcarbazolium salt (300a), N-methylcarbazole (301) was reacted with the powerful methylating agent, 2-methoxybiphenyl-2'-yldiazonium tetrafluoroborate (111), in dichloromethane at room temperature. Only quantitative amounts of starting material and dibenzofuran were isolated. However, of note was the rapid colour discharge (ca. 4 hours) of the yellow diazonium salt solution compared with that (>24 hours) observed for a THF substrate (see Chapter 2). This observation led to the proposal that anchimeric assistance by the amine enhances decomposition of the diazonium salt via a triazene-type intermediate (306).

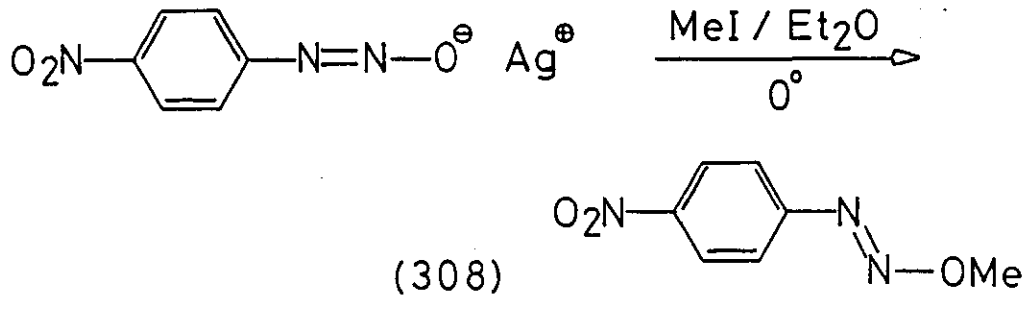


An intramolecular mechanism of similar nature may then be responsible for the ready formation of the stable carbazolium and also dibenzothiophenium ions. Thus, loss of nitrogen from the diazosulphonium intermediate (307) precedes ring closure induced by the neighbouring sulphur.



(307)

Triazenes ($Ar-N=N-NAr'_2$) and diazosulphides ($Ar-N=N-SAr'$) themselves are well known. Each results from interaction of arenediazonium ions with aromatic amines and thiophenols, respectively. Conversely, few diazoethers have been made, and most are unstable oils, although Bunnett and Takayama[322] have succeeded in synthesising the anti stereoisomer of methyl p-nitrophenylazo ether (308). This stable solid is obtained by methylation of silver p-nitrobenzeneisodiazotate.



(308)

However, phenols generally couple with arenediazonium ions to form hydroxy azo compounds, so it would seem less likely for oxonium analogues of the species (306) and (307) to occur. Hence the slower rate of decomposition of the diazonium salt (111) with THF.

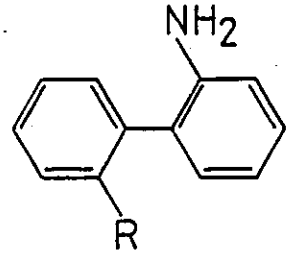
CHAPTER 7

PROTON AND CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY STUDY OF ONIUM IONS

INTRODUCTION

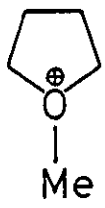
This concluding chapter aims to illustrate how an interpretation of both proton (^{1}H) and carbon-13 (^{13}C) NMR spectra can lead to valuable information concerning structure, bonding, and electron distributions. It further outlines how such information can relate to the observed behaviour and properties of molecules and ions.

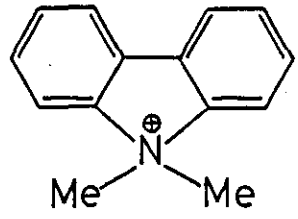
The chemical shifts (δ) and coupling constants of protons provide conclusive information about the structures of many organic compounds, and ^{1}H resonance has become an important routine method of instrumental analysis. For example, in substituted methanes MeX, as X becomes more electronegative, so the electron density around the methyl protons decreases and they resonate at lower fields. Indeed, a reasonable correlation between δ_H and the electronegativity of X does exist, as exhibited by our analogous series of 2-aminobiphenyls below. Note that all chemical shifts in this chapter refer to tetramethylsilane (TMS) as internal standard.

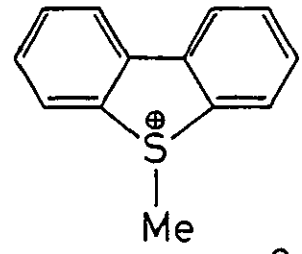


R	SMe (166)	NMe_2 (304)	OMe
δ_H/ppm	2.35	2.57	3.75

The same trend has already been noted[269] for the dimethylhalonium ions (243), wherein increasing δ_H values were associated with enhanced reactivity to nucleophiles and correspondingly lower thermal stability. Similar criteria can also be applied to the O-methyldibenzofuranium, S-methyldibenzothiophenium, and N,N-dimethylcarbazolium ions (110, 161, and 300). However, no NMR data are available for the highly reactive dibenzofuranium salts, so a δ_H (Me) value for the O-methyltetrahydrofuranium bromopentachloroantimonate (127)[122] is shown for comparison.







	$[SbCl_5Br]^{\ominus}$	$PF_6^{\ominus}$	$BF_4^{\ominus}$
	(127)	(300b)	(161)
δ_H /ppm	4.60	4.07	3.35

increasing reactivity ⟵ increasing stability ⟶

The greater stability of sulphonium ions over their oxonium counterparts derives from the inherently stronger nucleophilicity of sulphur over oxygen. As a result, the S-methyl group is less deshielded by the positive charge and resonates at higher field, but the O-methyl group is more electron-deficient and susceptible to nucleophilic attack. By virtue of its N-methyl resonance, the carbazolium species would be anticipated to be of intermediate character.

This general pattern of increasing δ_H values for more positive protons often arises, though there are many exceptions. For example, caution must be exercised in rationalising the relative deshielding of aromatic protons as a function of charge delocalisation, since shielding due to ring current effects of adjacent phenyl groups can have a profound effect. A regular or quantitative trend is not, therefore, always evident. However, in a study of the triphenylcarbenium ion system, Farnum[323] did conclude that there is definitely charge alternation in these cations, with the greatest amount of charge being delocalised to the ortho and para positions.

We were interested in studying the extent of charge dispersal

in our own onium ions, and how this might be used as a measure of their intrinsic properties. To do this, we examined the ever increasing potential of ^{13}C NMR spectroscopy, and consequently were able to elaborate on data from ^{1}H spectra which alone provide insufficient information about the basic carbon skeleton.

In recent years, Olah in particular has had considerable success in using ^{13}C spectra as evidence for the existence of stable cations in solution, and as a probe for determining the pattern of charge distributions in such ions. Of significant advantage over the complex and frequently overlapping multiplets in ^{1}H spectra is the fact that individual carbons can generally be observed, and hence arises a sound basis for structural assignment. In the sections which follow, some appropriate aspects of ^{1}H and especially ^{13}C NMR techniques are given.

7.1 ^{13}C NMR AND CHARGE DISTRIBUTION

In recent years the theoretical treatment of ^{13}C chemical shifts has been extensively discussed, especially for aromatic systems. As a result, it has been shown that a successful rationalisation of various structural and reactivity trends can be possible by focussing on molecular orbital interactions.

Approximate molecular orbital calculations, eg CNDO/2 and INDO, can provide values of the total electronic charge density, ie π plus σ electronic distributions, at each position in a number of monosubstituted benzenes. In turn, the relationship between these electronic effects and ^{13}C chemical shifts can be studied.

Particular attention has been devoted to the para carbon, which is shielded by electron-donating substituents and deshielded by electron-withdrawing groups. Nelson, Levy, and Cargioli[324] have plotted calculated electronic charge densities versus para carbon shifts (relative to δ_C benzene = 128.5 ppm), and obtained reasonable linear correlation (coefficient, r = 0.95). Therefore, the para carbon resonance of other monosubstituted benzenes can be used to estimate total charge density at this position. Correlations of ortho carbon shifts with charge densities are, however, much less satisfactory, although the same overall trend of the dependence of shielding on charge is evident. Meta carbon chemical shifts are relatively insensitive to the nature of the substituent, and show no apparent correlation with calculated charge densities. The directly substituted ipso carbons absorb over a wide range, but the observed shieldings cannot be used as a direct measure of charge densities owing to characteristic magnetic and geometric constraints of each different substituent group.

The use of ^{13}C chemical shifts as a probe in the understanding of the electronic nature of aromatic systems has been further aided by the use of Hammett σ constants. These parameters have been used considerably

in structure-reactivity predictions, including studies of rates of reactions, equilibria, and organic mechanisms, and thereby they are often more meaningful than total charge densities. Plots of para carbon shifts versus σ enable σ values for any substituent to be found,[324] but correlations for other carbons have shown less regularity.

More recently, Olah[325] has extended the study of charge distributions to a range of phenylcarbenium ions, $PhC^{\oplus}RR'$, and related phenyl substituted onium ions. The outcome was again a linear correlation of para carbon shifts with charge densities, which extended and coincided with that[324] earlier obtained for electronically neutral benzenes, showing that organic cations can be treated as isolated species with neglect of the counterion. Hence, the para carbon chemical shift can be seen as a quantitatively reliable indicator of charge density at the para position. It was found that π charge densities are as good as total charge densities in this correlation, suggesting that π-system resonance and polarisation interactions with the substituents are the dominant influences at the para carbon.

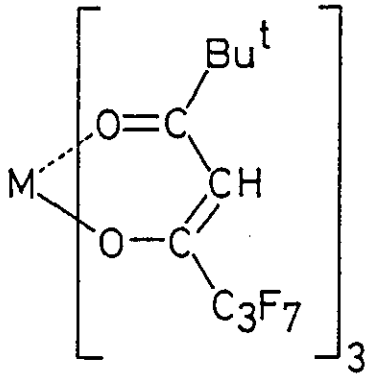
Olah[325] also provides extensive reasoning to explain the inferior correlations at other carbons in both neutral and cationic species. For example, most deviations of ortho carbon shifts can be attributed to the steric shielding effect of a δ-substituent, eg NO_2, CF_3, and carbonyl-containing groups.

7.2 STRUCTURE, STABILITY, AND REACTIVITY

One of the easiest ways of simplifying a complex NMR spectrum is to administer a paramagnetic lanthanide shift reagent (LSR). The reagents are usually β-diketone complexes of europium or praseodymium and are soluble in the common solvents. Their use stems from an ability to alter markedly the spectra of oxygen- and nitrogen-containing compounds, the europium complexes giving mainly downfield shifts and the praseodymium complexes causing shifts to higher field. The magnitude of a lanthanide-induced shift (LIS) experienced by any one nucleus becomes smaller as its distance from the site of interaction increases.

These shift reagents have been routinely applied to a wide variety of structural problems, but not so with ionic materials owing to difficulty in finding solvents compatible with both reagent and substrate. However, reports have now appeared to suggest that at least certain ammonium and sulphonium salts can act as powerful lanthanide shift donors.[326, 327]

Seeman and Bassfield[326] have shown that the proton resonances of quaternary ammonium halides are more strongly shifted by $Eu(fod)_3$ (309a) than the corresponding resonances of the related tertiary amine functionalities. This enhancement has been attributed to complexation of the counterion with the LSR, resulting in a complex, eg $Eu(fod)_3\text{-}I^{\ominus}$, which is associated strongly with the positively charged moiety.

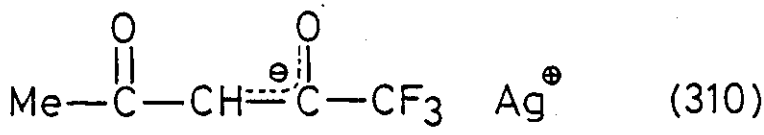


(309) a. M=Eu

b. M=Pr

In addition, Caret and Vennos[327] have detected observable shifts in the ^{1}H spectra of trialkyl- and dialkylarylsulphonium salts using $Pr(fod)_3$ (309b). In a manner analogous to that above, these salts are more strongly shifted by the LSR than are the corresponding neutral sulphides, and evidence indicates that complexation of the LSR occurs at the anion in preference to the electron pair on sulphur.

Substrates which are weak Lewis bases, eg olefins and aromatics, generally experience weak or negligible induced shifts, but silver β-diketonates such as Ag(tfa) (310) and Ag(fod) have recently been demonstrated to act as bridging compounds between such samples and the LSR.[328] The effect is to hold the substrate in an appropriate configuration to the lanthanide so that selective shifts are observed.

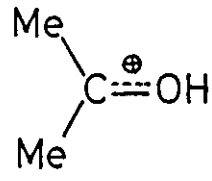


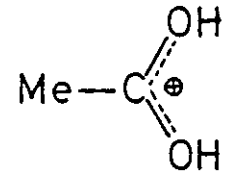
Ag(tfa) (310)

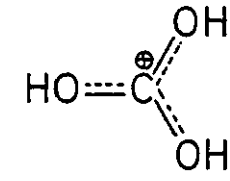
In structural investigations, shift reagents probably find greater application in the analysis of ^{1}H spectra. On the other hand, the interpretation of a ^{13}C spectrum is simplified by a broader chemical shift spread and an absence of ^{13}C-^{13}C couplings. Specific peak assignments are aided further by running completely proton (broad-band) decoupled spectra and off-resonance decoupled spectra, which allow the differentiation between carbons bearing different numbers of hydrogens. In the special case of onium ions, ^{13}C chemical shifts can now readily be transformed into knowledge relating to structure and to distribution of the unit positive charge.

Olah and White[329] have studied a wide range of carbenium ions, and shown that hydroxyl and phenyl groups are capable of delocalising the charge. This is illustrated below for protonated acetone, acetic

acid, and carbonic acid. Larger δ_C values indicate a more positively charged carbon.







$\delta_C(sp^2)$/ppm	249.4	195.3	165.7
δ_C(Me)/ppm	31.7	20.1	

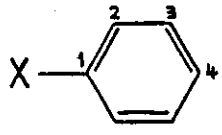
Increasing substitution by hydroxyl groups results in δ_C for the sp^2 carbon moving to successively higher field, and this in turn can be matched with an improvement in stability. A linear correlation of these shifts with calculated π-electron densities was found. The changing charge density on the electron-deficient carbon is also reflected in the δ_C values for adjacent methyl groups.

In an extension of results such as these to the elucidation of structures, it was described[329] how ^{13}C resonance can be a powerful method for differentiating between bridged and equilibrating open-chain carbenium ions. It has earlier been mentioned[268] that the technique can be applied equally as well to a range of three- and five-membered ring halonium ions.

Using similar criteria we examined our own onium ions and their neutral precursors, and a discussion follows. Appropriate ^1H data are included. However, we were more interested in the information that ^{13}C spectra can provide concerning the electronic character of aromatic substituents, particularly with regard to the extent of charge stabilisation in onium ions through resonance interaction with the

aromatic nucleus. Chemical shift values are our own, except where otherwise indicated.

Much of the NMR data forthcoming from our own studies can be analysed in the light of extensive investigations involving monosubstituted benzenes.[324, 325] In addition, Bernardi et. al.[330] have shown that, although ^{13}C results relate to total ($\pi + \sigma$) atomic electron densities, they can provide a qualitative understanding of the π-donating ability of heteroatoms. Theoretical computations predict that the order of π donation is RO > RS.



cf δ_C(PhH) = 128.5

* δ_C(PhOMe) Ref 330

\+ δ_C($PhNMe_2$) Bruker Data Bank, Vol. 1

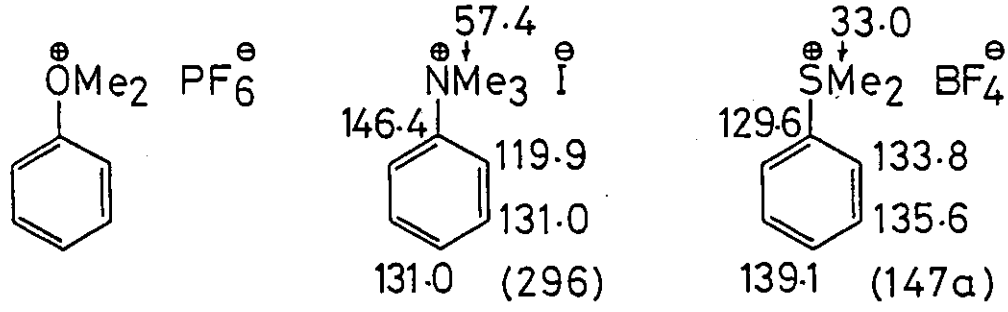
X	1	2	3	4	δ_C(Me)	δ_H(Me)
OMe	160.2	114.1	129.5	120.7	54.7*	3.70
NMe_2	150.7	112.7	129.0	116.7	40.3+	2.87
SMe	138.6	126.8	128.9	125.1	15.9	2.40

Experimental results above reveal that this order does indeed materialise in those positions, ie ortho and para, mostly affected by π donation. Conversely, positions which are influenced more by the inductive effect, ie ipso and meta, show the reverse order. Note that the trend in δ_H for the methyl groups reflects the changing electronegativity of the heteroatom.

When the substituent bears a formal positive charge its electron-donating power is reduced considerably, and ^{13}C chemical shifts can be used to monitor the changes in charge distribution. Under conditions of proton noise decoupling, the methyl and quaternary carbon peaks could be identified by their characteristically low intensities. The para position was distinguished from ortho and meta resonances by consideration of relative peak intensities and also its relative downfield shift. In several instances the ortho and meta resonances

were nearly equivalent, leaving some ambiguity in assigning δ_C values to the specific carbon.

NMR information for dimethylphenylsulphonium tetrafluoroborate (147a) and trimethylanilinium iodide (296) is detailed below. Proton resonances for the analogous dimethylphenyloxonium ion[99] are also given for comparison.

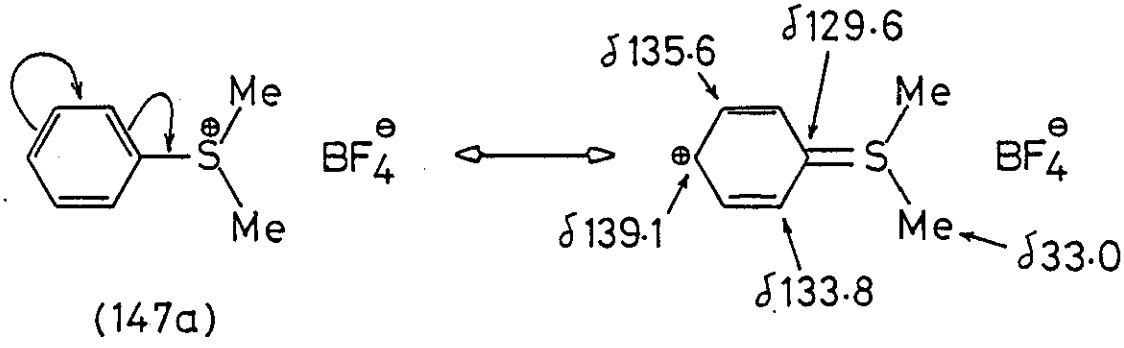


δ_H(Me)/ppm	4.95	3.63	3.25

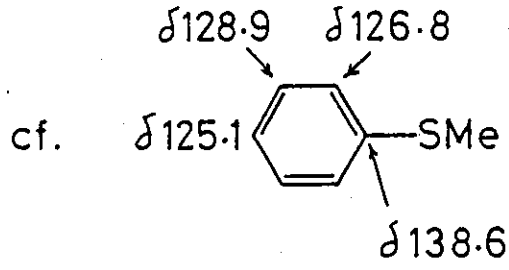
All methyl resonances are appreciably deshielded in comparison with the corresponding neutral precursors, but once again the more pronounced shielding effect is exhibited by the sulphur-containing species. Very much evident as well is a greater degree of charge delocalisation into the aromatic ring of the sulphonium ion, and such phenomena can be used as a measure of stability and reactivity trends. Accordingly, the effects of positively charged substituents on rates and isomer distributions in electrophilic aromatic substitution reactions have been studied by various investigators.

Aromatic nitrations, for example, have been found to be predominantly, or completely, meta-directing.[331, 332] All positive poles involving elements of groups V and VI exert a strong inductive electron-withdrawing effect (-I), which has least influence at the farthest removed para position. Consequently, the trimethylanilinium ion, $PhNMe_3^{\oplus}$, which can undergo no resonance interaction with the ring π electrons owing to an absence of empty d orbitals, reacts with

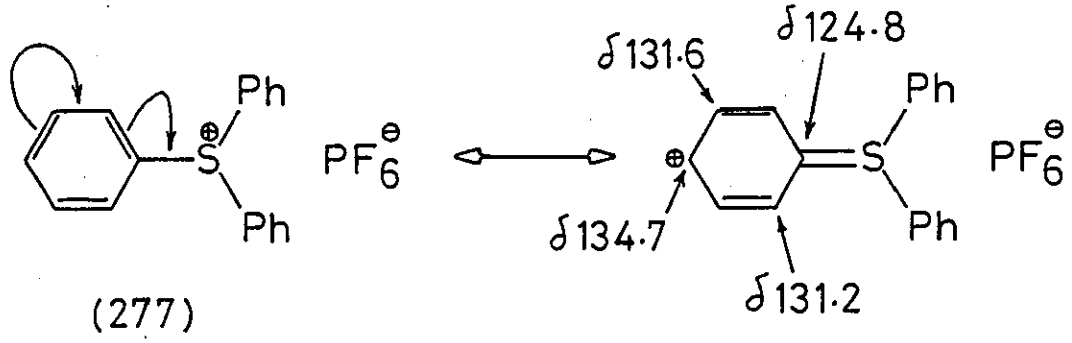
nitric acid-sulphuric acid to give the meta (89%) and para (11%) nitroarenes only.[331] The dimethylsulphonium ion, $PhS^{\oplus}Me_2$, was shown to be less reactive owing to greater aromatic deshielding and hence more pronounced deactivation to electrophiles. However, this deactivation cannot be due simply to a stronger -I effect, since Gilow and co-workers isolated a reasonable amount of ortho (3.6%) in addition to the meta (90.4%) and para (6.0%) isomers. Consequently, the occurrence of a p_π-d_π resonance interaction (-M) was proposed.



(147a)

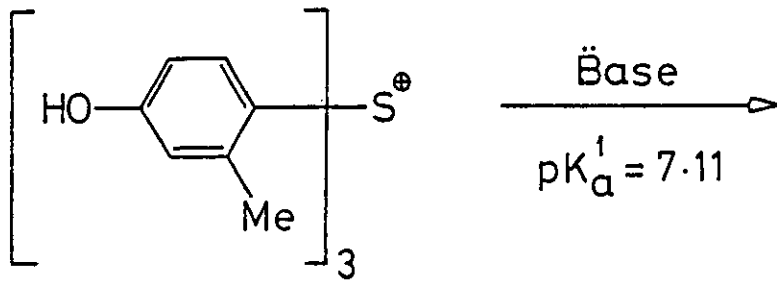


A resonance form also contributes to the structure of the triphenylsulphonium species (277).

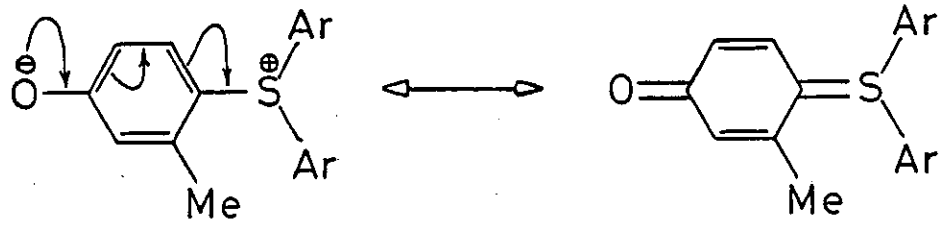


(277)

Even when free rotation of all three phenyl rings is severely hindered, such that coplanarity is sterically impossible, the conjugative effect of the sulphonium moiety is preserved. Thus, introduction of three 2-methyl groups into the tris(4-hydroxyphenyl)sulphonium ion makes the molecule (311) extremely rigid, yet Oae and Zalut[332] observed no weakening in acidity. They concluded that there is little angular requirement for π (pd) overlap between sulphur and aromatic carbon. This is reasonable when one considers the geometry and number of 3d orbitals available on sulphur, and applies to aromatic sulphoxides and sulphones as well.

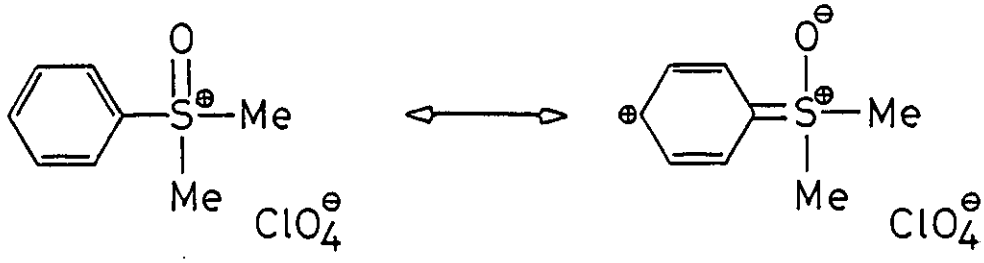


(311)



A view that it is actually unnecessary to invoke a bonding role for the 3d orbitals on sulphur has recently gained in popularity. Shorter[333] discusses the electronic effects of the sulphonium group in traditional conjugative terminology, as above, but also refers to some experimental evidence that casts doubt on d-orbital participation in bonding. It is suggested instead that the main mechanism whereby sulphur stabilises adjacent carbanionic centres in, eg. sulphonium ylides (Chapter 3.3), involves polarisation of the polarisable sulphur electrons.

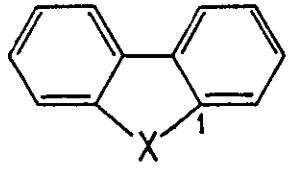
The electronic effect of an oxosulphonium group, $-\overset{\oplus}{S}(=O)Me_2$, has also been determined.[334] Thus, nitration of dimethylphenyloxosulphonium perchlorate (312) resulted in exclusive formation of the meta product. This salt was over 500 times less reactive than the sulphonium analogue, a deactivation which was ascribed in part to a yet stronger -I effect, but also to $2p_\pi$-$3p_\pi$ resonance between the phenyl ring and the S=O bond.



(312)

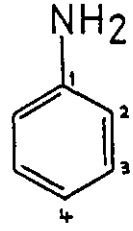
Overall, it was shown[331] that (a) reactivity, ie rate of nitration, (b) the para ^1H chemical shift, and (c) the Hammett σ values for substituents, can all be related to one another. The very small rate of nitration of (312) suggested that the Hammett σ value of an oxosulphonium group should be large. Calculations[334] gave $\sigma_m = 1.38$, a value exceeded only by that of the diazonium ion (σ_m ($-N_2\oplus$) = 1.76).

The general pattern of behaviour found in monosubstituted benzenes can be extended to other ions and their precursors. Thus, for the five-membered heterocyclic compounds dibenzofuran, N-methylcarbazole (301), and dibenzothiophen, the electronegativity of the heteroatom influences δ_C for the carbon to which it is bonded.



X	O	NMe	S
δ_{C1}/ppm	156.4	141.1	139.5

Interestingly, the S-methylated salt (161) exhibits two quaternary resonances at δ139.3 and δ130.7, which suggests that the carbon of attachment has become relatively shielded in the positively charged ion. A similar effect has previously been noted in protonated aniline (below),[324] and can further be discerned from our δ_{C1} values for thioanisole and its methylated derivative (147a). In each case, a positively charged substituent increases the total amount of positive charge in the aromatic ring, but the electronic perturbation is such that that experienced at the carbon of attachment is opposite to that experienced by the deshielded ortho, para, and to a lesser extent, meta positions.

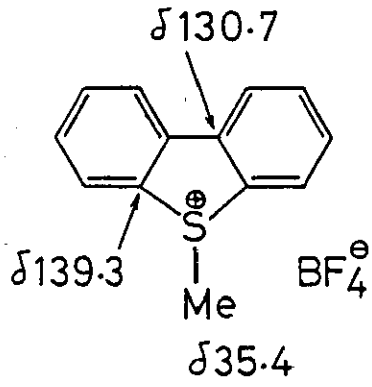


Solvent	1	2	3	4
CCl_4	146.7	115.5	129.6	119.0
$MeSO_3H$	129.1	123.6	130.6	130.4

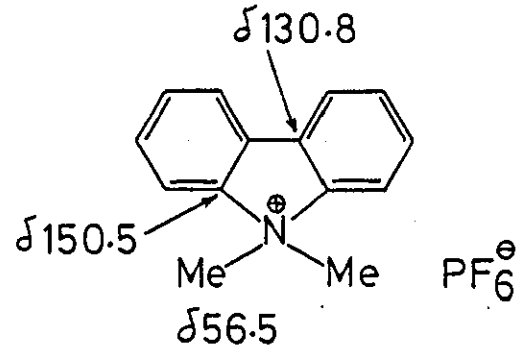
The dispersal of charge in the N,N-dimethylcarbazolium salt (300b) follows a somewhat different pattern, in that the quaternary carbon adjacent to the onium centre appears to low field of the same carbon in N-methylcarbazole by 9 ppm. The low intensity signal detected at δ150.5 is considerably broad. As above, all other aromatic positions are also deshielded.

This observation suggests that the extent of charge delocalisation into the carbazolium nucleus is less than that in the dibenzothiophenium system. A larger concentration of positive charge on nitrogen would also contribute to the lower field resonance of the methyl groups compared to the S-methyl group. The same trend has already been noted in the respective δ_H(Me) values (see Introduction), and can be interpreted again as reflecting a gradation of physical and chemical properties. However, reactivity predictions such as alkylating ability should not

be made on the basis of chemical shifts alone.



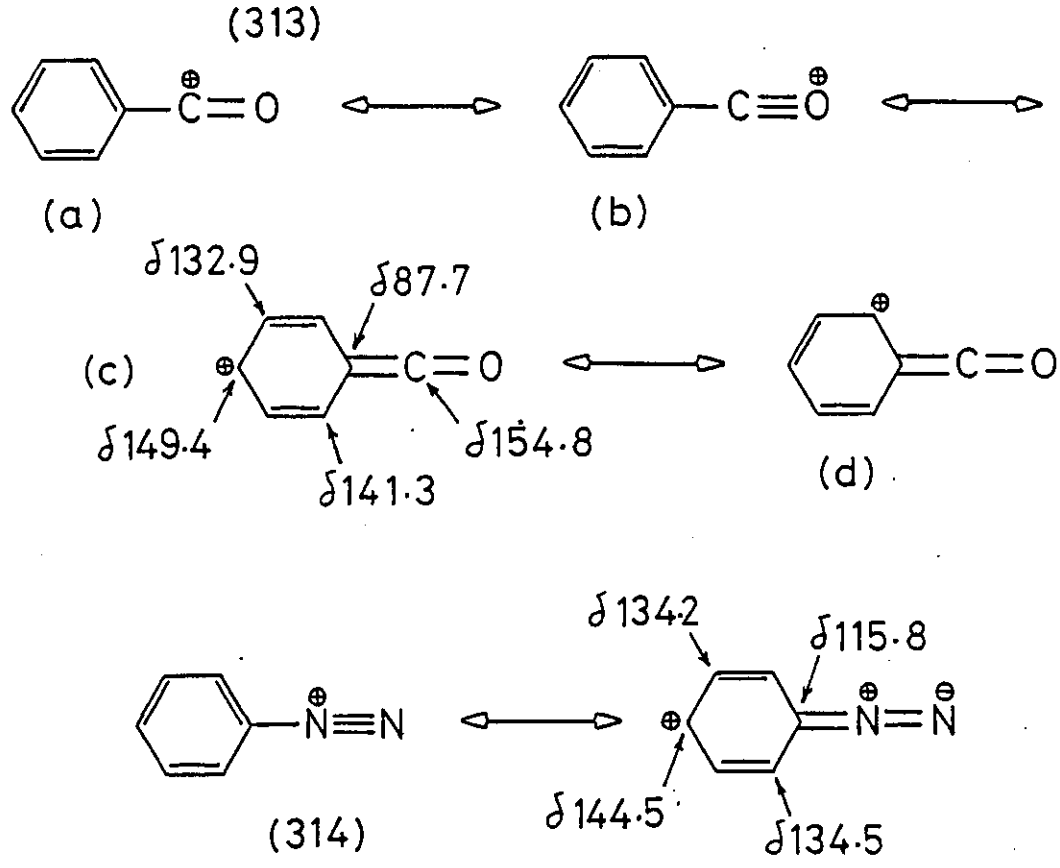
(161)



(300b)

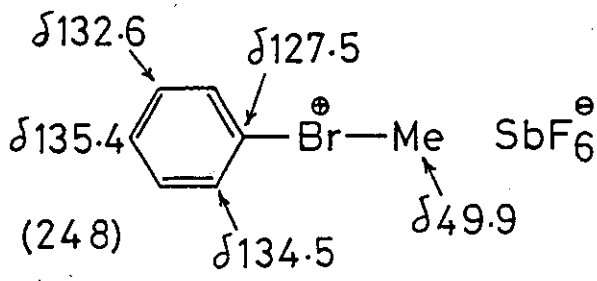
In an analysis of the benzoyl cation (313), Olah and Westerman[335] detected significant charge delocalisation into the aromatic ring, and reinforced an earlier conclusion from ^{1}H studies[336] that ketene-like resonance forms (c) and (d) are major contributors to the structure. The accumulation of substantial positive charge at the para position is supported by the ipso carbon chemical shift, which is shielded from the corresponding resonance in its precursor, benzoyl fluoride, by 49 ppm. A comparable study has also provided direct experimental proof for the ambident nature of the benzenediazonium ion (314),[337] which further enhances an understanding of nucleophilic aromatic substitutions at ring positions other than that containing the $-N_2^{\oplus}$ substituent[192] (see overleaf).

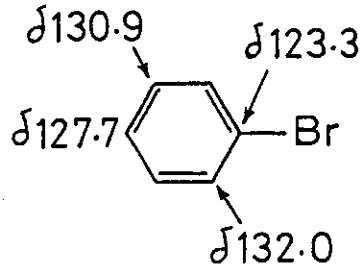
We found that our diaryliodonium hexafluorophosphates (276a, b) can be analysed along the same lines. This time, however, the largest downfield shifts occur at the ipso and para carbons, and the ortho resonance in the diphenyliodonium salt (276a) is in fact upfield compared to the same in iodobenzene. As already observed with alkylarylhalonium ions (247),[272] the chemical shift changes are small and reflect less delocalisation of positive charge into the aromatic

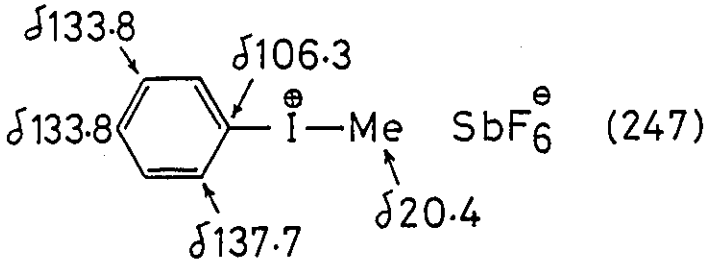


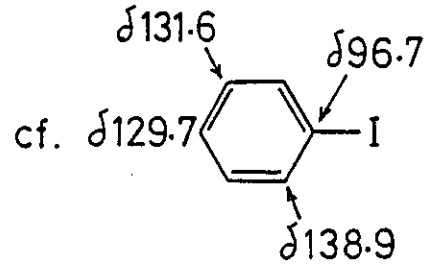
nucleus. However, para electron-donating substituents in the di-p-tolyliodonium salt (276b) serve to increase the deshielding at the para position, whilst the ipso carbon becomes more shielded, so that resonance forms of the type (276c) may make a greater contribution to the overall structure (see overleaf).

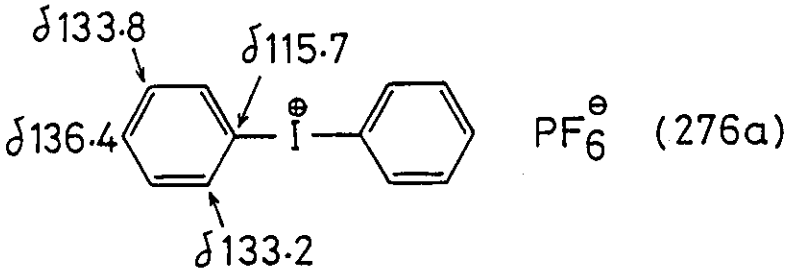
In bromonium ions this reluctance of the halogen lone pairs to interact with the π electrons of a benzene ring remains, but to a slightly lesser degree. Thus, comparison of bromobenzene with the methylphenylbromonium ion (248) reveals a marginally larger change in the para carbon shift, ($\Delta\delta$ = 7.7 ppm), cf (247) and iodobenzene gives $\Delta\delta$ = 4.1 ppm.[268]

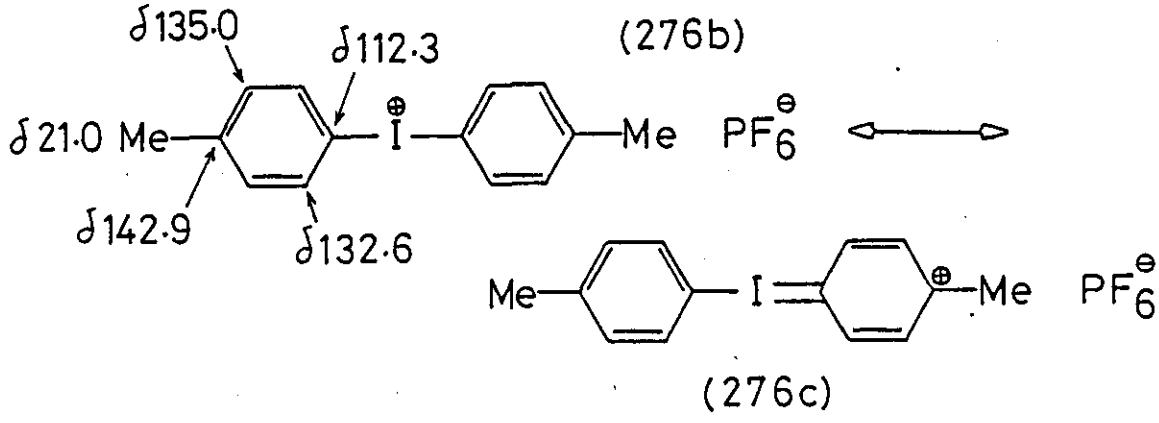








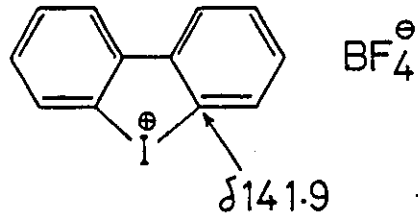




Note that δ_C values for the methyl groups in methylphenylhalonium ions are deshielded by 11-13 ppm from the corresponding signals in dimethylhalonium ions (243). This implies that $PhX^{\oplus}$ is more electronegative than $MeX^{\oplus}$, and may be regarded as evidence for perhaps some charge delocalisation into the aromatic ring.

It has, however, been mentioned (Chapter 5) that the larger the halogen the more capable it is of localising a positive charge, and this property is well illustrated by biphenylene-2,2'-iodonium tetrafluoroborate (294b). The carbon adjacent to the onium centre is considerably more deshielded than any others, and reinforces the view that little or no charge is delocalised around the aromatic system. The ion is, of course, quite stable, and reacts with halide anions

only under pyrolysis conditions.[304]



(294b)

This chapter has shown that in monosubstituted benzenes the carbon resonances of particular interest are those of the ipso and para positions. The former occupy a wide range of shifts, whilst the latter reflect the electron-withdrawing or electron-donating properties of the substituents. Correlations of chemical shift with Hammett σ values, and in turn reactivity, have proved extremely valuable, and can be extended to predict or explain variations in chemical reactivity of more intricate systems. Thus, the dimethylphenylsulphonium ion (147a) is expected to be less reactive to electrophilic substitution than the oxonium analogue, $PhO\overset{\oplus}{M}e_2$, owing to greater dispersal of positive charge into the phenyl ring. For the same reason, O-methyldibenzofuranium tetrafluoroborate (110) is found to be more potent as a methylating agent toward nucleophiles than the corresponding S-methyl derivative (161), which is more capable of accommodating positive charge and can be isolated and stored with ease.

EXPERIMENTAL

GENERAL COMMENTS

Experiments have been placed in the order in which they appear in the text, by chapter. Numbers in parentheses correspond to the chemical reference number appearing in the text.

All solvents were distilled and dried by conventional methods prior to use (consult A.I.Vogel, "A Textbook of Practical Organic Chemistry", 4th Ed, Longman, London and New York, 1978, p 264. Melting points were determined on a Kofler block, and are uncorrected.

Routine analytical thin layer chromatography was performed on silica gel (type 60 PF_{254} according to Stahl), and column chromatography carried out either with silica gel (Fisons) or 'CAMAG' alumina (Brockmann activity I).

IR spectra for solids and liquids were determined on a Perkin-Elmer 177 spectrometer as potassium bromide discs and thin films, respectively. UV spectra were recorded on a Pye-Unicam SP 8000 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM 360A 60 MHz spectrometer for approximately 10-20% w/v solutions using tetramethylsilane as internal standard. A Bruker WP 80 20.1 MHz instrument was used to record ^{13}C NMR spectra. Mass spectra were run on an AEI MS 12 spectrometer.

CHAPTER 2

1 o-Iodoanisole

o-Anisidine (186 g, 1.51 mol) was dissolved in a mixture of concentrated hydrochloric acid (360 ml) and water (360 ml). The resulting hydrochloride solution was cooled to 0°, and a solution of sodium nitrite (129 g, 1.87 mol) in water (300 ml) was added with stirring, maintaining the temperature below 5°. After a further 15 minutes, a solution of potassium iodide (375 g, 2.26 mol) in water (600 ml) was slowly added to the cold diazonium salt solution. Stirring was continued at room temperature for another 1 hour to ensure complete decomposition of the diazonium salt.

The solution was made alkaline by the addition of sodium hydroxide solution (1300 ml, 10%). A black oil which separated out was extracted into ether (6 x 250 ml), the combined extracts were successively washed with saturated aqueous solutions of sodium bicarbonate, sodium thiosulphate, and sodium metabisulphite, then dried over anhydrous magnesium sulphate.

Removal of solvent gave a black oil, which on distillation gave o-iodoanisole (292g, 82%) as a golden orange oil, b.p. 82°/1.4 mm (lit., b.p. 86°/1.5 mm,[90] 237-8°/760 mm[338]).

ν_{max} 3080, 3020, 2940, 2840, 1585, 1475, 1435, 1295, 1280, 1250, 1055, 1020, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.80-7.55 (m, 1H); 7.40-7.05 (m, 1H); 6.85-6.40 (m, 2H); and 3.82 (s, 3H).

2 o-Bromonitrobenzene

o-Nitroaniline (207 g, 1.5 mol) was dissolved in concentrated hydrochloric acid (450 ml), and crushed ice (300 g) was added. The hydrochloride solution was cooled to 0°, and a solution of sodium nitrite (114 g, 1.65 mol) in water (190 ml) was added with stirring,

maintaining the temperature below 5°. Insoluble material was removed by filtration, then a solution of bromine (300 g, 3.75 mol) in hydrobromic acid (500 ml, 48% aq) was slowly added to the orange diazonium salt solution at 0°.

The orange diazonium perbromide precipitate was filtered off and carefully added in small portions to glacial acetic acid (300 ml) at 100°. Addition of the hot solution to water (5 l) yielded a solid which was recrystallised from ethanol to give pale yellow crystals of o-bromonitrobenzene (219 g, 72%), mp 42-43° (lit.,[339] mp 42°).

ν_{max} 3100, 1590, 1530, 1470, 1350, 1040, 850, 780, 730, 700, and 640 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.95-7.20 (m, 4H).

3 2-Methoxy-2'-nitrobiphenyl (47)

Copper powder (224 g, 3.5 mol) was added in portions over a period of 1 hour to a well-stirred mixture of o-iodoanisole (203 g, 0.87 mol) and o-bromonitrobenzene (210 g, 1.04 mol) at 170-180°. Stirring and heating was continued for an additional 4 hours, during which the metal lost its shiny appearance and the viscosity of the mixture increased.

After cooling, the mixture was exhaustively extracted with ether, removal of which gave an orange oil which was adsorbed onto alumina and placed on a column of the same. Elution with 5% ether-petroleum ether (b.p. 40-60°) afforded 2-methoxy-2'-nitrobiphenyl (106 g, 53%) as a bright yellow solid, mp 82-83° from methanol (lit.,[109] mp 83°).

ν_{max} 2940, 2840, 1615, 1530, 1360, 1250, 1125, 1025, 860, 760, and 745 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.00-6.70 (m, 8H); and 3.66 (s, 3H).

^{13}C NMR $\delta(CDCl_3/DMSO\text{-}d_6)$ 156.0, 149.7, 132.9, 132.6, 129.8, 129.7,

128.3, 127.1, 123.7, 122.5, 121.2, 111.0, 55.1.

4 2-Amino-2'-methoxybiphenyl

Hydrazine hydrate (35 ml, 64% aq) was slowly added to 2-methoxy-2'-nitrobiphenyl (25.8 g, 0.11 mol) and palladium-on-charcoal (1.35 g, 5%) in ethanol (300 ml) at 50°. After complete addition (30 minutes) a further quantity of catalyst (0.45 g, 5%) was added and the mixture was heated under reflux for 6 hours. Removal of catalyst by filtration and the solvents by evaporation gave a colourless oil, which crystallised from methanol to give 2-amino-2'-methoxybiphenyl (19.8 g, 90%), mp 78-79° (lit.,[109] mp 80°).

ν_{max} 3420, 3290, 3180, 2840, 1635, 1575, 1505, 1480, 1450, 1435, 1270, 1230, and 755 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.45-6.60 (m, 8H); 3.75 (s, 3H); and 3.52 (broad s, 2H, exchangeable with D_2O).

5 2'-Methoxybiphenyl-2-yldiazonium Tetrafluoroborate (111)

2-Amino-2'-methoxybiphenyl (2 g, 10 mmol) was dissolved in a warm mixture of fluoroboric acid (25 ml, 40% aq) and THF (5 ml). The solution was cooled to 0°, and a solution of sodium nitrite (0.76 g, 11 mmol) in water (10 ml) was slowly added with vigorous stirring. After stirring at 0° for 30 minutes, the bright yellow diazonium salt was isolated by filtration, washed with cold 5% methanol-ether and cold ether, then dried overnight in vacuo over phosphoric anhydride at -20°. The yield of crystalline 2'-methoxybiphenyl-2-yldiazonium tetrafluoroborate was 2.86 g (96%), mp 67-72° (dec).

ν_{max} 3100, 2275, 1605, 1590, 1550, 1500, 1480, 1420, 1290, 1260, 1180, 1050 (broad), 1010, 765, and 755 cm^{-1}.

6 Resorcinoldimethylether

Resorcinol (110 g, 1 mol) was added to a stirred solution of sodium hydroxide (84 g, 2.1 mol) in water (800 ml). After cooling to 10°, dimethyl sulphate (252 g, 2 mol) was added dropwise over a period of 1 hour with vigorous stirring, then the mixture was refluxed for 4 hours.

On cooling, water (500 ml) was added, and the alkaline mixture was extracted with ether (3 x 150 ml). Combined extracts were washed repeatedly with dilute sodium hydroxide solution and then water before drying over potassium hydroxide pellets. After filtration and evaporation of solvent, distillation at atmospheric pressure afforded resorcinoldimethylether (66 g, 48%) as a pale yellow oil, bp 212-14° (lit.,[340] bp 217-18°).

ν_{max} 3000, 2960, 2830, 1595, 1495, 1465, 1440, 1295, 1270, 1215, 1155, 1050, 910, 835, 765, and 690 cm^{-1}.

7 4-Iodoresorcinoldimethylether

Finely divided iodine (130 g, 0.51 mol), followed by freshly precipitated yellow mercuric oxide (100 g, 0.46 mol), were added in small portions to resorcinoldimethylether (65 g, 0.48 mol) with vigorous stirring. Complete decolourisation was awaited before each new addition of iodine. The exothermic reaction was maintained for a further 1 hour, then the hot mixture was filtered and the inorganic material thoroughly washed with ether.

Removal of solvent gave a dark oil. Most of the iodine impurity was removed by elution with ether through a column of alumina. The orange oil so obtained solidified on standing, and this crude product when recrystallised from methanol yielded colourless needles of 4-iodoresorcinoldimethylether (70 g, 56%), mp 39-40° (lit.,[341] 40°).

ν_{max} 3000, 2960, 2935, 2830, 1580, 1485, 1460, 1435, 1410, 1305, 1280, 1210, 1160, 1055, 1030, 1010, 830, 820, and 785 cm^{-1}.

^1H NMR $\delta(CCl_4)$ 7.42 (d, 1H, J_o = 8Hz); 6.20 (d, 1H, J_m = 3Hz); 6.12 (q, 1H, J_o = 8Hz, J_m = 3Hz); 3.76 (s, 3H); and 3.68 (s, 3H).

8 2,4-Dimethoxy-2'-nitrobiphenyl

A mixture of 4-iodoresorcinoldimethylether (60 g, 0.23 mol), o-bromonitrobenzene (46 g, 0.23 mol), copper powder (150 g, 2.35 mol), and freshly distilled nitrobenzene (450 ml) was refluxed for 3 hours with vigorous stirring. The reaction mixture was filtered and the solid thoroughly washed with chloroform (ca 500 ml). Chloroform and nitrobenzene were removed from the filtrate under reduced pressure and by steam distillation respectively. The residue was taken into chloroform, and the dark extract dried over anhydrous magnesium sulphate. After filtration and evaporation, column chromatography on alumina, using a chloroform-petroleum ether (bp 40-60°) solvent (composition 1:2), gave rise to an orange oil. This yielded bright orange crystals on scratching with petroleum ether (bp 40-60°), and recrystallisation from methanol afforded 2,4-dimethoxy-2'-nitrobiphenyl (17 g, 29%), mp 100-102° (lit.,[342] 101.5-102°).

ν_{max} 300, 2955, 2930, 2830, 1620, 1590, 1350, 1210, 1170, 1135, 1055, 1025, 855, 840, 810, 790, and 760 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.00-6.30 (m, 7H); 3.80 (s, 3H); and 3.63 (s, 3H).

9 2-Amino-2',4'-dimethoxybiphenyl

Reaction as 4, using 2,4-dimethoxy-2'-nitrobiphenyl (11.65 g, 45 mmol), hydrazine hydrate (20 ml, 64% aq), and palladium-on-charcoal (0.8 g, 5%) in ethanol (200 ml), gave colourless crystalls of 2-amino-2',4'-dimethoxybiphenyl (8.86 g, 86%), mp 67.5-69.5° from methanol

(lit.,[342] mp 68.5-69°).

ν_{max} 3440, 3360, 3005, 2960, 2935, 2830, 1610, 1310, 1210, 1160, 1135, 830, 795, and 755 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.25-6.35 (m, 7H); 3.77 (s, 3H); 3.70 (s, 3H); and 3.50 (broad s, 2H, exchangeable with D_2O).

10 2',4'-Dimethoxybiphenyl-2-yldiazonium Tetrafluoroborate (112)

Reaction as 5, using 2-amino-2',4'-dimethoxybiphenyl (1.15 g, 5 mmol), fluoroboric acid (30 ml, 40% aq), THF (20 ml), and sodium nitrite (0.38 g, 5.5 mmol) in water (5 ml), gave the yellow crystalline 2',4'-dimethoxybiphenyl-2-yldiazonium tetrafluoroborate (1.59 g, 97%), mp 72-75° (dec).

ν_{max} 2275, 1620, 1585, 1505, 1285, 1225, 1150, 1050 (broad), 850, 775, 750, and 720 cm^{-1}.

11 Reaction of 2',4'-Dimethoxybiphenyl-2-yldiazonium Tetrafluoroborate with Pyridine

2',4'-Dimethoxybiphenyl-2-yldiazonium tetrafluoroborate (0.6 g, 1.8 mmol) was decomposed in a stirred solution of pyridine (dry, 0.53 g, 6.7 mmol) in dichloromethane (dry, 20 ml). The bright orange solution gradually became dark red in colour, and after 2 hours at room temperature the reaction was taken to completion by heating under reflux overnight. Solvent was removed under reduced pressure to give a viscous red oil which was washed with ether (dry, 4 x 15 ml). The combined extracts were washed with water and dried over anhydrous magnesium sulphate.

The ether-insoluble residue was a tan oil which proved readily soluble in water. It was identified as N-methylpyridinium

tetrafluoroborate (0.16 g, 48%; lit.,[343] mp 10-11.5°) by addition of an excess of a saturated aqueous solution of sodium picrate to the oil in water. This produced a yellow precipitate which was filtered off, washed with ether, and recrystallised from ethanol to afford N-methylpyridinum picrate-sodium picrate (0.2 g, 39%), mp 215-17° (lit.,[344] mp 216-19°).

ν_{max} 3070, 1635, 1565, 1520, 1370, 1340, 1280, 790, and 745 cm^{-1}.

Removal of solvent from the dried ether extract gave, after recrystallisation from petroleum ether (bp 60-80°), 3-methoxydibenzofuran (0.31 g, 87%), mp 94-96° (lit.,[342] 95-95.5°).

ν_{max} 3040, 2840, 1605, 1460, 1445, 1280, 1150, 1115, 1035, 935, 845, 830, 815, 760, 750, and 720 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.90-6.75 (m, 7H); and 3.80 (s, 3H).

12 2'-Methoxybiphenyl-2-yldiazonium Hexafluoroantimonate

2-Amino-2'-methoxybiphenyl (1.99 g, 10 mmol) in concentrated hydrochloric acid (6 ml) was cooled to 0° and diazotised by the slow addition of a solution of sodium nitrite (0.76 g, 11 mmol) in water (4 ml). The yellow diazonium chloride solution was stirred for a further 15 minutes, then sodium hexafluoroantimonate (2.59 g, 10 mmol) in water (10 ml) was added rapidly, followed by ether (10 ml). After stirring at 0° for 30 minutes, a yellow precipitate was isolated by filtration, washed with cold 5% methanol-ether and cold ether, then dried overnight in vacuo over phosphoric anhydride at -20°. The yield of 2'-methoxybiphenyl-2-yldiazonium hexafluoroantimonate was 3.67 g (82%), mp 90-95° (dec).

ν_{max} 2270, 1590, 1260, 1175, 1020, 775, and 760 cm^{-1}.

13 2'-Methoxybiphenyl-2-yldiazonium Tetraphenylborate

Reaction as 12 using 2-amino-2'-methoxybiphenyl (1.99 g, 10 mmol), sodium nitrite (0.76 g, 11 m ol) in water (4 ml), and sodium tetraphenylborate (3.42 g, 10 mmol) in water (15 ml), gave orange crystals of 2'-methoxybiphenyl-2-yldiazonium tetraphenylborate (4.77 g, 90%), mp 79-82° (dec).

ν_{max} 2260, 1585, 1255, 1170, 1125, 1020, 780, 770, 760, 750, 740, and 715 cm^{-1}.

14 2-Hydroxy-2'-nitrobiphenyl (119)

Hydrobromic acid (25 ml, 46-48 aq) was added slowly to a solution of 2-methoxy-2'-nitrobiphenyl (25.14 g, 0.11 mol) in acetic anhydride (50 ml) at 0°. The solution was heated under reflux for 60 hours, producing a dark brown viscous mixture which was diluted by the addition of water (300 ml) and extracted with ether (5 x 150 ml). The combined ether layers were washed with 10% sodium hydroxide solution, the aqueous washings were acidified with concentrated hydrochloric acid, and the dark oil so liberated was extracted with ether.

After drying over anhydrous magnesium sulphate, removal of solvent gave a brown oil which was column chromatographed on silica. Elution with 10% ether-petroleum ether (bp 40-60°) afforded 2-hydroxy-2'-nitrobiphenyl (12.4 g, 52%) as a bright yellow crystalline solid, mp 132-138° (lit.,[345] mp 140°), containing also some 3-bromo derivative.

ν_{max} 3350, 1615, 1530, 1500, 1400, 1350, 1275, 1190, 1130, 890, 860, 825, 780, 725, 700, and 670 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.10-6.55 (m, 8H); and 5.15 (broad s, 1H, exchangeable with D_2O).

Mass Spectrum: $M^{\cdot+}$ = 215 and 295/293.

15 2-Benzyloxy-2'-nitrobiphenyl

Powdered potassium hydroxide (4.5 g, 80 mmol) was added to DMSO (dry, 100 ml) and the mixture stirred for 30 minutes. 2-Hydroxy-2'-nitrobiphenyl (4.3 g, 20 mmol) was then added and the mixture stirred for another 30 minutes. Subsequent addition of benzyl bromide (10.26 g, 60 mmol) resulted in evolution of heat and formation of a clear pale yellow solution.

After stirring for an additional 2 hours, water (150 ml) was added and the mixture extracted with ether. The combined extracts were washed with water and dried over anhydrous magnesium sulphate. Removal of solvent gave a yellow oil which was placed on a column of silica. Elution with 10% ether-petroleum ether (bp 40-60°) afforded 2-benzyloxy-2'-nitrobiphenyl (5 g, 82%) as pale yellow crystals, mp 75-80° from petroleum ether (bp 60-80°) (lit.,[90] mp 84-85°).

ν_{max} 3080, 2880, 1620, 1590, 1535, 1505, 1455, 1360, 1130, 860, and 755 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.05-6.65 (m, 13H); and 4.95 (s, 2H).

Mass Spectrum: M^+ = 305 and 385/383.

16 2-Amino-2'-benzyloxybiphenyl

Reaction as 4 using 2-benzyloxy-2'-nitrobiphenyl (4.9 g, 16 mmol), hydrazine hydrate (7.5 ml, 64% aq), and palladium-on-charcoal (0.35 g, 10%) in ethanol (75 ml), gave a colourless oil. Elution with 10% ether-petroleum ether (bp 40-60°) through a column of silica afforded 2-amino-2'-benzyloxybiphenyl (3.54 g, 74%), mp 94-96° from petroleum ether (bp 60-80°) (lit.,[90] mp 96-97°).

ν_{max} 3470, 3380, 3060, 3040, 2970, 2880, 1610, 1500, 1480, 1435, 1270, 1220, 1115, and 755 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 7.40-6.40 (m, 8H); 4.86 (s, 2H); and 3.45 (broad s, 2H, exchangeable with D_2O).

Mass Spectrum: $M^+ = 275$.

17 Crotyl Bromide

Tris(dimethylamino)phosphine (12.2 g, 75 mmol) in ether (dry, 50 ml) was added dropwise to a stirred solution of crotyl alcohol (5.4 g, 75 mmol) and carbon tetrachloride (24.9 g, 75 mmol) in ether (dry, 50 ml) at -40°. After the addition was complete, the reaction mixture was allowed to come to room temperature and stirring continued for 1 hour. The ethereal solution was washed with water and dried over anhydrous magnesium sulphate. Filtration and evaporation, followed by distillation at atmospheric pressure, gave crotyl bromide (2.54 g, 25%) as a colourless oil, bp 102-10° (lit.,[346] bp 103-6°).

ν_{max} 3020, 2970, 2940, 2920, 2860, 1670, 1440, 1380, 1205, 1145, 1020, 965, 930, 735, 690, and 655 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 5.90-5.60 (m, 2H); 4.10-3.80 (m, 2H); and 1.90-1.60 (m, 3H).

18 2-Crotyloxy-2'-nitrobiphenyl

Reaction as 15 using potassium hydroxide (3.36 g, 60 mmol), 2-hydroxy-2'-nitrobiphenyl (3.23 g, 15 mmol), and crotyl bromide (2.46 g, 18 mmol) in DMSO (75 ml), gave 2-crotyloxy-2'-nitrobiphenyl (3.25 g, 80%) as a yellow crystalline solid, mp 75-80° from petroleum ether (bp 60-80°) (lit.,[90] mp 81-82°).

ν_{max} 3040, 2930, 2880, 1615, 1585, 1530, 1500, 1450, 1360, 1250, 1230, 1130, 1000, 860, 760, and 735 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.10-6.60 (m, 8H); 5.75-5.40 (m, 2H): 4.55-4.20

(m, 2H); and 1.80-1.50 (dd, 3H).

Mass Spectrum: $M^{+\cdot}$ = 269 and 349/347.

19 2-Amino-2'-n-butoxybiphenyl

Hydrazine hydrate (0.5 ml, 64% aq) was added dropwise to a warm solution of 2-crotyloxy-2'-nitrobiphenyl (26.9 mg, 0.1 mmol) in ethanol (5 ml) containing palladium-on-charcoal (2 mg, 10%). The mixture was heated under reflux for 15 hours. Removal of catalyst by filtration, and evaporation of solvents, gave 2-amino-2'-n-butoxybiphenyl as a colourless oil[90] in quantitative yield.

ν_{max} 3490, 3400, 2980, 2950, 2890, 1625, 1510, 1495, 1450, 1275, 1250, 1130, 1010, and 755 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.45-6.60 (m, 8H); 3.90 (t, 2H, J = 6Hz); 3.65 (broad s, 2H, exchangeable with D_2O); 1.75-1.10 (m, 4H); and 0.85 (t, 3H, J = 6Hz).

20 Reaction of 2'-Methoxybiphenyl-2-yldiazonium Tetrafluoroborate with Tetrahydrofuran

A solution of 2'-methoxybiphenyl-2-yldiazonium tetrafluoroborate (626 mg, 2.1 mmol) and tetrahydrofuran (152 mg, 2.1 mmol) in dichloromethane (dry, 20 ml) was stirred at room temperature until discharge of the yellow colour was complete (ca 28 hours). Evaporation of solvent produced a cream solid (620 mg, 86%) which was shown by ^1H NMR analysis to contain a polyether[127] and dibenzofuran.

^1H NMR $\delta(CDCl_3)$ 7.95-7.70 (m); 7.50-7.05 (m); 4.30-3.30 (m); and 2.30-1.50 (m).

21 2-Nitro-2'-trideuteriomethoxybiphenyl

Reaction as 15 using potassium hydroxide (7.85 g, 0.14 mol), 2-hydroxy-2'-nitrobiphenyl (7.53 g, 35 mmol), and trideuteriomethyl iodide (10 g, 70 mmol) in DMSO (100 ml), afforded a bright yellow crystalline solid directly from the ether extract. The yield of 2-nitro-2'-trideuteriomethoxybiphenyl was 8 g (99%), mp 77-82° from methanol (lit.,[90] mp 83-84°).

ν_{max} 3070, 2930, 2230, 2080, 1615, 1590, 1530, 1500, 1360, 1290, 1250, 1125, 1105, 990, 755, and 740 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.00-6.60 (m, 8H).

Mass Spectrum: $M^{+\cdot}$ = 232 and 312/310.

22 2-Amino-2'-trideuteriomethoxybiphenyl

Reaction as 4 using 2-nitro-2'-trideuteriomethoxybiphenyl (7.8 g, 33.6 mmol), hydrazine hydrate (20 ml, 64% aq), and palladium-on-charcoal (0.55 g, 10%) in ethanol (125 ml), gave 2-amino-2'-trideuteriomethoxybiphenyl (5.2 g, 77%) as a colourless oil which crystallised on cooling, mp 79-81° from methanol (lit.,[90] 71-72°).

ν_{max} 3450, 3380, 2220, 2080, 1625, 1600, 1505, 1485, 1445, 1275, 1250, 1125, 1110, and 755 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.40-6.50 (m, 8H); and 3.55 (broad s, 2H, exchangeable with D_2O).

Mass Spectrum: $M^{+\cdot}$ = 202.

23 2'-Trideuteriomethoxybiphenyl-2-yldiazonium Tetrafluoroborate (129)

Reaction as 5 using 2-amino-2'-trideuteriomethoxybiphenyl (1.01 g, 5 mmol), fluoroboric acid (10 ml, 40% aq), THF (3 ml), and sodium nitrite (0.38 g, 5.5 mmol) in water (5 ml), gave the yellow crystalline

2'-trideuteriomethoxybiphenyl-2-yldiazonium tetrafluoroborate (1.17 g, 78%) mp 65-70° (dec).

ν_{max} 2280, 1585, 1300, 1265, 1060 (broad), and 760 cm^{-1}.

24 Reaction of 2'-Trideuteriomethoxybiphenyl-2-yldiazonium Tetrafluorobroate with Anisole

Under high vacuum, anisole (200 mg, 2.08 mmol) was condensed into a reaction flask containing 2'-trideuteriomethoxybiphenyl-2-yldiazonium tetrafluoroborate (627 mg, 2.08 mmol) and dichloromethane (dry, 30 ml) cooled by liquid nitrogen. The mixture was warmed to -70° and stirred at this temperature for 1 hour. The bright yellow solution darkened in colour on stirring at room temperature overnight, and was then poured into a saturated aqueous solution of sodium bicarbonate (25 ml). The mixture was extracted with dichloromethane, the combined extracts washed with water and dried over anhydrous calcium chloride.

Removal of solvent yielded a pale yellow semi-crystalline oil which was chromatographed on a column of silica. Elution with petroleum ether (bp 40-60°) gave dibenzofuran (300 mg, 84%) as colourless crystals, mp 84-86° from petroleum ether (bp 60-80°) (lit.,[347] mp 86-87°).

ν_{max} 3050, 1590, 1470, 1240, 1200, 1150, 1100, 925, 845, 840, 750, and 720 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 7.95-7.70 (m, 2H); and 7.50-7.05 (m, 6H).

^{13}C NMR $\delta(CDCl_3)$ 156.4, 127.2, 124.3, 122.7, 120.7, and 111.7.

Gradual increase in solvent strength to ca 10% ether-petroleum ether (bp 40-60°) gave a pale yellow oil (40 mg, 20%) which was analysed as a mixture of anisole and its trideuteriomethyl analogue, ν_{C-D} = 2070 cm^{-1}, M^+ = 111.

ν_{max} 3060, 3025, 2960, 2830, 2220, 2070, 1600, 1495, 1300, 1245, 1175, 1080, 1045, 755, and 695 cm^{-1}.

Mass Spectrum: $M^{+\cdot}$ = 111 and 108.

25 Reaction of 2'-Methoxybiphenyl-2-yldiazonium Tetrafluoroborate with 2,4,6-Trimethylbenzoate (Mesitoate) Anion: Methyl Mesitoate (131)

To a stirred solution of mesitoic acid (0.47 g, 2.85 mmol) and 2'-methoxybiphenyl-2-yldiazonium tetrafluoroborate (0.94 g, 3.15 mmol) in dichloromethane (dry, 40 ml) was added diisopropylethylamine (0.5 ml, 2.85 mmol). The solution changed colour from bright yellow to deep red and was maintained at room temperature for 30 hours. The mixture was washed with 2N hydrochloric acid (3 x 25 ml), 1N sodium bicarbonate (3 x 25 ml), and a single portion of saturated aqueous sodium chloride (25 ml), then the dichloromethane layer dried over anhydrous magnesium sulphate.

Evaporation of solvent gave a red oil which was placed on a column of silica. Elution with petroleum ether (bp 40-60°) isolated dibenzofuran (130 mg, 24%). Increasing the solvent strength to 3% ether-petroleum ether (bp 40-60°) then afforded methyl mesitoate (100 mg, 25%) as a pale yellow oil, $\nu_{C=O}$ = 1725 cm^{-1}, δ_{OMe} = 3.80 (lit.,[130] $\nu_{C=O}$ = 1730 cm^{-1}, δ_{OMe} = 3.77, bp 93°/0.4 mm).

ν_{max} 1725, 1610, 1505, 1485, 1270, 1240, 1090, 1030, 855, 755, and 700 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 6.72 (s, 2H); 3.80 (s, 3H); and 2.23 (s, 9H).

26 Reaction of 2'-Methoxybiphenyl-2-yldiazonium Tetrafluoroborate with p-Methylbenzoate (p-Toluate) Anion: Methyl p-Toluate (132)

Reaction as 25 using p-toluic acid (0.39 g, 2.85 mmol), 2-methoxybiphenyl-2-yldiazonium tetrafluoroborate (0.94 g, 3.15 mmol), and diisopropylethylamine (0.5 ml, 2.85 mmol) in dichloromethane (dry, 40 ml), gave dibenzofuran (120 mg, 23%) and methyl-p-toluate (130 mg, 30%) as a pale yellow oil, $\nu_{C=O}$ = 1720 cm^{-1}, δ_{OMe} = 3.83 (lit.,[348] mp 33°).

ν_{max} 1720, 1600, 1505, 1485, 1435, 1285, 1180, 1125, 1030, 840, 800, 755, 735, and 700 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.10-7.70 (d, 2H, J = 8Hz); 7.25-6.95 (d, 2H, J = 8Hz); 3.83 (s, 3H); and 2.36 (s, 3H).

27 Reaction of 2'-Methoxybiphenyl-2-yldiazonium Tetraphenylborate with 1-Amino-3-(1-naphthalenyloxy)-2-propanol (133)

The hydrochloride salt of 1-amino-3-(1-naphthalenyloxy)-2-propanol (127 mg, 0.5 mmol) was added in portions to a solution of sodium bicarbonate (42 mg, 0.5 mmol) in water (25 ml). A clear solution was obtained on vigorous swirling and gentle warming. Evaporation of solvent from a dried ether extract subsequently gave the free amine[131] (78 mg, 71%) as a white crystalline solid, mp 106-8°.

^{1}H NMR $\delta(CDCl_3)$ 8.35-6.60 (m, 7H); 4.07 (m, 3H); 2.95 (m, 2H); and 2.15 (broad s, 3H, exchangeable with D_2O).

A solution of the aryloxypropanolamine (51 mg, 0.24 mmol) and 2'-methoxybiphenyl-2-yldiazonium tetraphenylborate (125 mg, 0.24 mmol) in dichloromethane (dry, 20 ml) was stirred at room temperature for 3 hours, then under reflux for 2 hours. An aqueous solution of sodium

bicarbonate was added and the mixture extracted with ether (4 x 10 ml). The combined extracts were washed with water, then dried over anhydrous magnesium sulphate.

Removal of solvent gave a dark oil (100 mg) which was separated on silica by preparative layer chromatography, using 30% ether-petroleum ether (bp 40-60°) as the mobile phase. Two major fractions were collected, the first of which was shown to be dibenzofuran (21 mg, 52%). A second oil (25 mg) exhibited a strong methoxy singlet at δ3.73, but its identity could not be confirmed owing to the absence of other aliphatic absorptions.

28 Reaction of 2'-Methoxybiphenyl-2-yldiazonium Tetraphenylborate with 1-t-Butylamino-3-(1-naphthalenyloxy)-2-propanol (134)

Treatment of the hydrochloride salt of 1-t-butylamino-3-(1-naphthalenyloxy)-2-propanol (155 mg, 0.5 mmol) with a solution of sodium bicarbonate (42 mg, 0.5 mmol) in water (25 ml), gave the free amine[131] (137 mg, 100%), mp 73-75°.

^{1}H NMR δ($CDCl_3$) 8.30-6.65 (m, 7H); 4.10 (m, 3H); 2.85 (m, 2H); 2.55 (broad s, 2H, exchangeable with D_2O); and 1.13 (s, 9H).

Reaction as 27 using the aryloxypropanolamine (52 mg, 0.19 mmol) and 2'-methoxybiphenyl-2-yldiazonium tetraphenylborate (101 mg, 0.19 mmol) in dichloromethane (dry, 20 ml), gave a dark oil (85 mg). Preparative layer chromatography yielded dibenzofuran (16 mg, 50%) and an oil (19 mg), which exhibited a strong methoxy singlet at δ3.73, but gave no indication of aminopropanol functions.

29 2-Acetoxy-2'-nitrobiphenyl (139)

A solution of 2-hydroxy-2'-nitrobiphenyl (5.3 g, 24 mmol) and

acetic anhydride (12.6 g, 0.12 mol) in pyridine (dry, 50 ml) was stirred at room temperature for 3 days. Addition to a large excess of ice produced an off-white solid which was recrystallised from petroleum ether (bp 60-80°) to give 2-acetoxy-2'-nitrobiphenyl (5.12 g, 83%), mp 107-12° (lit.,[349] mp 102°).

ν_{max} 3065, 2870, 1770, 1525, 1375, 1360, 1210, 1190, 1090, 1020, 1010, 910, 900, 845, 790, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.10-6.85 (m, 8H); and 1.95 (s, 3H).

Mass Spectrum: $M^{+\cdot}$ = 257 and 337/335.

30 Catalytic Hydrogenation of 2-Acetoxy-2'-nitrobiphenyl 2-Acetylamino-2'-hydroxybiphenyl (140)

2-Acetoxy-2'-nitrobiphenyl (514 mg, 2 mmol) in ethanol (70 ml), containing palladium-on-charcoal (51.4 mg, 10%), was vigorously stirred under hydrogen at atmospheric pressure until the theoretical volume of gas was consumed (ca 24 hours). Removal of catalyst by filtration and solvent by evaporation gave 2-acetylamino-2'-hydroxybiphenyl (415 mg, 79%) as colourless crystals, mp 225-230° from ethanol.

ν_{max} 3340, 1655, 1585, 1540, 1480, 1445, 1410, 1370, 1315, 1270, and 745 cm^{-1}.

^1H NMR $\delta(CDCl_3/DMSO\text{-}d_6)$ 8.25 (broad s, 2H, exchangeable with D_2O); 7.90-6.70 (m, 8H); and 1.98 (s, 3H).

Mass Spectrum: $M^{+\cdot}$ = 227 and 307/305.

31 2-Acetylamino-2'-acetoxybiphenyl

2-Acetylamino-2'-hydroxybiphenyl (43 mg, 0.19 mmol) was dissolved in pyridine (dry, 10 ml), acetic anhydride (100 mg, 1 mmol) was added, and the solution stirred overnight. A large excess of ice was added, the

mixture extracted with ether (3 x 20 ml), then the combined extracts were washed with water and dried over anhydrous magnesium sulphate. Removal of solvent afforded 2-acetylamino-2'-acetoxybiphenyl (57 mg, 85%) as a viscous oil.

ν_{max} 3280 (broad), 1765, 1670, 1585, 1520, 1450, 1370, 1300, 1210, 1190, 1110, 1020, 910, and 760 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.20-6.85 (m, 8H); 2.00 (s, 3H); and 1.96 (s, 3H).

Mass Spectrum: M^+ = 269 and 349/347.

32 2-Acetylamino-2'-benzoyloxybiphenyl

Reaction as 31 using 2-acetylamino-2'-hydroxybiphenyl (40 mg, 0.18 mmol) and benzoyl chloride (140 mg, 1 mmol) in pyridine (dry, 10 ml), gave 2-acetylamino-2'-benzoyloxybiphenyl (43 mg, 83%) as an oil.

ν_{max} 3400, 1730, 1680, 1580, 1440, 1370, 1105, and 1015 cm^{-1}.

Mass Spectrum: M^+ = 331 and 411/409.

33 2-Amino-2'-hydroxybiphenyl

2-Amino-2'-methoxybiphenyl (0.96 g, 4.8 mmol) was dissolved in warm phenol (1.5 g). Hydriodic acid (30 ml, 57% aq) was added to the ice-cold mixture, then the solution heated under reflux for 5 hours. After cooling, water (75 ml) was added, and the mixture extracted with ether (5 x 15 ml) to remove phenol. The remaining aqueous acid solution was neutralised by addition of solid sodium bicarbonate, then extracted with ether (5 x 20 ml). From the dried extracts was obtained a yellow oil which solidified on standing. Recrystallisation from petroleum ether (bp 60-80°) gave 2-amino-2'-hydroxybiphenyl (0.63 g, 70%) as colourless crystals, mp 96-98° (lit.,[116] mp 92-93°).

^{1}H NMR $\delta(CDCl_3)$ 7.40-6.60 (m, 8H); and 4.62 (broad s, 3H, exchangeable with D_2O).

34 Acetylation of 2-Amino-2'-hydroxybiphenyl

2-Acetylamino-2'-hydroxybiphenyl (140)

Powdered potassium hydroxide (123 mg, 2.2 mmol) was added to DMSO (dry, 20 ml) and the mixture stirred for 15 minutes. 2-Amino-2'-hydroxybiphenyl (0.37 g, 2 mmol) was then added and the mixture stirred for another 15 minutes. Acetic anhydride (204 mg, 2 mmol) was next added, the clear solution was stirred for a further 3 hours, then added to ice-cold water (30 ml) and extracted with ether (5 x 20 ml). The combined extracts were washed with water (2 x 25 ml) and dried over anhydrous magnesium sulphate.

Filtration, then evaporation of solvent, gave an off-white solid (0.34 g) which was placed on a column of silica. Elution with ether gave recovered starting material (0.24 g) followed by 2-acetylamino-2'-hydroxybiphenyl (0.1 g, 22%). Analysis as 30 except:

Mass Spectrum: M^+ = 227.

35 2-Benzoyloxy-2'-nitrobiphenyl (141)

A mixture of 2-hydroxy-2'-nitrobiphenyl (1.65 g, 7.7 mmol) and benzoyl chloride (5.25 g, 38 mmol) in pyridine (dry, 50 ml) was stirred vigorously at room temperature overnight. Addition to a large excess of ice produced an off-white solid which was recrystallised from ethanol to give 2-benzoyloxy-2'-nitrobiphenyl (1.16 g, 47%), mp 143-150° (lit.,[345] mp 116°).

ν_{max} 1740, 1525, 1355, 1265, 1240, 1190, 1055, 1020, 860, 785, 745, 705, and 685 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.00-6.90 (m, 13H).

Mass Spectrum: M^+ = 319 and 399/397.

36 Catalytic Hydrogenation of 2-Benzoyloxy-2'-nitrobiphenyl

2-Benzamido-2'-hydroxybiphenyl (142)

Reaction as 30 using 2-benzoyloxy-2'-nitrobiphenyl (0.32 g, 1 mmol) and palladium-on-charcoal (25 mg, 5%) in ethanol (50 ml), gave 2-benzamido-2'-hydroxybiphenyl (0.21 g, 75%, mp 190-195° from ethanol.

ν_{max} 3340, 3100 (broad), 1645, 1575, 1530, 1450, 1445, 1400, 1310, 1265, 820, 815, 750, 710, and 690 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.53 (broad s, 2H, exchangeable with D_2O); and 8.20-6.60 (m, 13H).

Mass Spectrum: M^+ = 289 and 369/367.

37 2-Acetoxy-2'-benzamidobiphenyl

Reaction as 31 using 2-benzamido-2'-hydroxybiphenyl (90 mg, 0.3 mmol) and acetic anhydride (150 mg, 1.5 mmol) in pyridine (dry, 10 ml), gave 2-acetoxy-2'-benzamidobiphenyl (94 mg, 91%) as an oil.

ν_{max} 3410, 1730, 1675, 1580, 1440, and 1110 cm^{-1}.

Mass Spectrum: M^+ = 331 and 411/309.

CHAPTER 3

38 Dimethylphenylsulphonium Tetrafluoroborate (147a)

Methyl iodide (1.14 g, 8 mmol) was added to a stirred mixture of thioanisole (0.31 g, 2.5 mmol) and silver tetrafluoroborate (0.49 g, 2.5 mmol) in dichloromethane (dry, 20 ml). A precipitate was formed

almost immediately, and stirring was continued for 2 hours. The mixture was filtered, the solid washed with dichloromethane, then the filtrate was triturated with dry ether. Cooling in the freezer afforded dimethylphenylsulphonium tetrafluoroborate (0.1 g, 18%) as shiny white crystals, mp 136-38° (lit.,[143] mp 132.5-133.5° from acetonitrile-ether).

ν_{max} 1475, 1290, 1195, 1050 (broad), 925, 760, and 685 cm^{-1}.
^1H NMR $\delta(D_2O)$ 8.05-7.60 (m, 5H); and 3.25 (s, 6H)
^{13}C NMR $\delta(D_2O)$ 139.1, 135.6, 133.8, 129.6, 33.0.

39 o-Iodobenzenesulphonic Acid

Orthanilic acid (64 g, 0.37 mol) was dissolved in 2N sulphuric acid (500 ml) and the stirred solution cooled to 0°. A solution of sodium nitrite (28.3 g, 0.41 mol) in water (50 ml) was then added in small volumes, the simultaneous addition of crushed ice maintaining the temperature below 5°. To the diazonium sulphate solution was added, slowly and with stirring, a solution of potassium iodide (84 g, 0.51 mol) in water (100 ml). Nitrogen was evolved, and after allowing the mixture to stand at room temperature for 48 hours a brown solid was obtained. Filtration and recrystallisation from ethanol-water gave o-iodobenzenesulphonic acid (83 g, 79%), mp >300° (dec).

ν_{max} 3655, 3480 (broad), 1630, 1420, 1220, 1140, 1105, 1060, 1005, 765, 735, and 650 cm^{-1}.

40 o-Iodobenzenesulphonyl Chloride

o-Iodobenzenesulphonic acid (42.5 g, 0.15 mol) and powdered phosphorus pentachloride (15.65 g, 75 mmol) were heated at 170-180° for 12 hours. Every 3 hours the reaction flask was allowed to cool for 15-20 minutes, stoppered, and shaken thoroughly until the mass

became pasty. At the end of the heating period the mixture was allowed to cool, then poured onto crushed ice (200 g). The crude product was extracted with carbon tetrachloride (3 x 150 ml), then the solvent removed under atmospheric pressure. Distillation of the residue under reduced pressure afforded o-iodobenzenesulphonyl chloride (23.5 g, 52%) as a colourless oil, bp 140-45°/2 mm, which solidified on cooling in ice, mp 46-48° (lit.,[170] mp 51°).

ν_{max} 3130, 3090, 3060, 2990, 1570, 1450, 1425, 1375, 1280, 1260, 1185, 1090, 1015, 760, 725, 695, and 635 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.30-8.10 (m, 2H); and 7.70-7.10 (m, 2H).

41 o-Thioanisidine

Reaction as 15 using powdered potassium hydroxide (3.1 g, 55 mmol), o-aminobenzenethiol (6.25 g, 50 mmol), and dimethyl sulphate (6.3 g, 50 mmol) in DMSO (dry, 100 ml), yielded a yellow oil upon concentration of the ether extract. Vacuum distillation afforded o-thioanisidine (5.6 g, 80%) as a pale yellow oil, bp 82-83°/1 mm (lit.,[350] bp 234° (part dec)).

ν_{max} 3450, 3360, 3065, 3015, 2990, 2920, 1610, 1505, 1480, 1450, 1425, 1310, 1155, 970, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.40-6.40 (m, 4H); 4.14 (broad s, 2H, exchangeable with D_2O); and 2.32 (s, 3H).

42 o-Iodothioanisole (163)

Reaction as 1 using o-thioanisidine (22 g, 0.158 mol), 2N hydrochloric acid (240 ml), sodium nitrite (12 g, 0.174 mol) in water (20 ml), and potassium iodide (28.9 g, 0.174 mol) in water (40 ml), gave o-iodothioanisole (27.3 g, 69%) as a yellow oil, bp 109-10°/1 mm

(lit.,[351] bp 173°/20 mm).

ν_{max} 3050, 2980, 2915, 1570, 1440, 1430, 1250, 1110, 1040, 1005, 740, 700, and 640 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.83-6.62 (m, 4H); and 2.42 (s, 3H).

43 2-Methylthio-2'-nitrobiphenyl (165)

Reaction as 3 using o-iodothioanisole (30 g, 0.12 mol), o-bromonitrobenzene (28.3 g, 0.14 mol), and copper powder (30 g, 0.48 mol), afforded an orange oil which, when chromatographed on alumina with 5% ether-petroleum ether (bp 40-60°), gave 2-methylthio-2'-nitrobiphenyl (7.7 g, 26%) as bright yellow crystals, mp 51-52° from methanol.

ν_{max} 3050, 2915, 2850, 1610, 1575, 1530, 1460, 1430, 1350, 1010, 850, 785, 765, 730, 700, 685, and 660 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.10-6.90 (m, 8H); and 2.30 (s, 3H).

Mass Spectrum: $M^{+\cdot}$ = 245.

44 2-Amino-2'-methylthiobiphenyl (166)

Reaction as 4 using 2-methylthio-2'-nitrobiphenyl (5.6 g, 23 mmol), hydrazine hydrate (20 ml, 64% aq), and palladium-on-charcoal (0.4 g, 5%) in refluxing ethanol (100 ml) for 24 hours, gave quantitatively 2-amino-2'-methylthiobiphenyl (4.9 g) as a colourless crystalline solid, mp 87-88° from methanol.

ν_{max} 3465, 3370, 3050, 3030, 2985, 2915, 1615, 1500, 1465, 1435, 1300, 1160, 1085, 1005, 760, 740, and 675 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.35-6.60 (m, 8H); 3.45 (broad s, 2H, exchangeable with D_2O); and 2.35 (s, 3H).

Mass Spectrum: $M^{+\cdot}$ = 215.

45 2'-Methylthiobiphenyl-2-yldiazonium Tetrafluoroborate (167)

Reaction as 5 using 2-amino-2'-methylthiobiphenyl (0.92 g, 4.3 mmol), fluoroboric acid (45 ml, 40% aq), THF (10 ml), and sodium nitrite (0.33 g, 4.8 mmol) in water (10 ml), afforded 2'-methylthiobiphenyl-2-yldiazonium tetrafluoroborate (1.11 g, 82%) as bright orange crystals, mp 65-70° (dec).

ν_{max} 3100, 2275, 1585, 1550, 1310, 1290, 1275, 1260, 1240, 1175, 1050 (broad), 765, 755, and 730 cm^{-1}.

46 S-Methyldibenzo [b, d] thiophenium Tetrafluoroborate (161)

2'-Methylthiophenyl-2-yldiazonium tetrafluorobroate (0.9 g, 2.9 mmol) was stirred in dichloromethane (dry, 25 ml) until the solution was completely discoloured (ca 48 hours). An excess of dry ether was added until a cloudiness formed, then cooling at -20° for 3 days produced a white crystalline solid which was filtered off and washed with cold ether. The yield of S-methyldibenzo [b, d] thiophenium tetrafluoroborate was 0.71 g (86%), mp 148-50° from dichloromethane-ether (lit.,[165] mp 149-51°).

ν_{max} 1485, 1470, 1450, 1420, 1380, 1320, 1300, 1285, 1165, 1050 (broad), 985, 960, 890, 780, 765, and 710 cm^{-1}.

$\lambda_{max}^{H_2O}$ ($\epsilon/10^4$) 210 (3.25); 230 (2.74); 236 (2.70); 270 (1.13); and 310 (0.30).

^1H NMR (MeCN) 8.35-7.64 (m, 8H); and 3.35 (s, 3H).

^{13}C NMR (CD_2Cl_2) 139.3, 134.5, 131.8, 130.7, 128.5, 124.4, and 35.4

Evaporation of solvent from the filtrate gave dibenzothiophen

(70 mg, 14%), mp 97-100° from ethanol (lit.,[340] mp 99-100°).

ν_{max} 3060, 1585, 1460, 1305, 1230, 1130, 1065, 1020, 930, 765, 735, 725, 710, and 700 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.30-7.20 (m, 8H).

^{13}C NMR $\delta(CDCl_3)$ 139.5, 135.6, 126.7, 124.4, 122.8, and 121.6.

Mass Spectrum: M^+ = 184.

47 Neopentyloxy-tris(dimethylamino)phosphonium Hexafluorophosphate

A solution of tris(dimethylamino)phosphine (32.6 g, 0.2 mol) in ether (dry, 100 ml) at 0° was slowly added to a stirred solution of neopentyl alcohol (18 g, 0.2 mol) and carbon tetrachloride (38.5 g, 0.25 mol) in ether (dry, 100 ml), maintaining the temperature at 0°. When the addition was complete, the cold mixture was poured into an ice-chilled saturated aqueous solution of ammonium hexafluorophosphate (34 g, 0.21 mol) with the immediate formation of a white solid. The precipitate was collected, washed with cold water (75 ml) and cold ether (75 ml), then dried over calcium chloride. Recrystallisation from ethanol gave neopentyloxy-tris(dimethylamino)phosphonium hexafluorophosphate (41.4 g, 52%) as colourless plates, mp 201-3° (lit.,[352] mp 202-4°).

ν_{max} 2960, 1460, 1310, 1170, 1065, 995, 825, 765, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 3.80 (d, 2H, J_{PH} = 4Hz); 2.80 (d, 18H, J_{PH} = 11Hz); and 1.05 (s, 9H).

48 o-Aminophenyl Neopentyl Sulphide (169)

o-Aminobenzenethiol (6.25 g, 50 mmol) was added to a stirred mixture of powdered potassium hydroxide (3.1 g, 55 mmol) in DMF (dry, 100 ml) under nitrogen. After 30 minutes, neopentyloxy-tris(dimethylamino)phosphonium hexafluorophosphate (19.8 g, 50 mmol) was added,

then the mixture was heated under reflux for 22 hours.

After cooling, water (200 ml) was added and the mixture extracted with ether (3 x 100 ml). The combined extracts were washed with 2N sodium hydroxide solution (2 x 75 ml), water (2 x 75 ml), and dried over anhydrous magnesium sulphate. Removal of solvent gave a dark residue, which upon vacuum distillation afforded o-aminophenyl neopentyl sulphide (4.2 g, 43%) as a pale yellow oil, bp 140-42°/5 mm.

ν_{max} 3450, 3350, 3060, 2950, 2905, 2865, 1605, 1480, 1450, 1365, 1310, 1250, and 745 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.50-6.40 (m, 4H); 4.17 (broad s, 2H, exchangeable with D_2O); 2.70 (s, 2H); and 1.00 (s, 9H).

Mass Spectrum: $M^{+\cdot}$ = 195.

49 o-Iodophenyl Neopentyl Sulphide (170)

Reaction as 1 using o-aminophenyl neopentyl sulphide (1.8 g, 9.2 mmol), 2N hydrochloric acid (14 ml), sodium nitrite (0.69 g, 10 mmol) in water (4 ml), and potassium iodide (1.66 g, 10 mmol) in water (4 ml), yielded a dark oil which was purified by column chromatography on silica. Elution with petroleum ether (bp 40-60°) gave o-iodophenyl neopentyl sulphide (2.32 g, 82%) as a colourless oil.

ν_{max} 3050, 2930, 1570, 1470, 1450, 1370, 1245, 1015, and 740 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.85-6.60 (m, 4H); 2.83 (s, 2H); and 1.07 (s, 9H).

Mass Spectrum: $M^{+\cdot}$ = 306.

50 2-Neopentylthio-2'-nitrobiphenyl (171)

Reaction as 3 using o-iodophenyl neopentyl sulphide (2.32 g, 7.6 mmol), o-bromonitrobenzene (1.62 g, 8 mmol), and copper powder (1.92 g, 30 mmol), followed by chromatography on silica with 5% ether

petroleum ether (bp 40-60°), gave 2-neopentylthio-2'-nitrobiphenyl (1.02 g, 45%) as a yellow oil.

ν_{max} 3065, 2965, 2875, 1615, 1580, 1530, 1470, 1435, 1355, 1250, 1010, 855, 790, 750, and 705 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.15-7.85 (m, 1H); 7.65-7.00 (m, 7H); 2.68 (s, 2H); and 0.90 (s, 9H).

Mass Spectrum: M^+ = 301.

51 2-Amino-2'-neopentylthiobiphenyl (172)

Reaction as 4 using 2-neopentylthio-2'-nitrobiphenyl (0.69 g, 2.3 mmol), hydrazine hydrate (10 ml, 64% aq), and palladium-on-charcoal (70 mg, 10%) in refluxing ethanol for 17 hours, gave an oil which slowly solidified on cold storage. The yield of 2-amino-2'-neopentylthiobiphenyl was 0.4 g (64%), mp 64-67° from methanol.

ν_{max} 3460, 3370, 3050, 2955, 2870, 1615, 1500, 1465, 1430, 1370, 1305, 1245, 1160, 1045, 1010, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.40-6.55 (m, 8H); 3.37 (broad s, 2H, exchangeable with D_2O); 2.70 (s, 2H); and 0.94 (s, 9H).

Mass Spectrum: M^+ = 271.

52 2-Acetylamino-2'-neopentylthiobiphenyl

Acetyl chloride (78.5 mg, 1 mmol) was added to a solution of 2-amino-2'-neopentylthiobiphenyl (50 mg, 0.18 mmol) in pyridine (dry, 10 ml), and the bright yellow solution was stirred at room temperature for 24 hours. The mixture was poured onto an excess of ice and extracted with ether (3 x 20 ml). Drying over anhydrous magnesium sulphate, followed by evaporation of solvent, gave 2-acetylamino-2'-neopentylthiobiphenyl (49 mg, 85%) as an oil.

ν_{max} 3400, 1670, 1570, 1500, 1450, 1430, 1360, 1290, and 1000 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.35-8.00 (m, 1H); 7.55-6.90 (m, 7H); 2.73 (s, 2H); 1.97 (s, 3H); and 0.97 (s, 9H).

Mass Spectrum: $M^{+\cdot}$ = 313.

53 2'-Neopentylthiobiphenyl-2-yldiazonium Tetrafluoroborate (173) and Subsequent Decomposition

Reaction as 5 using 2-amino-2'-neopentylthiobiphenyl (43 mg, 0.16 mmol), fluoroboric acid (1 ml, 40% aq), THF (few drops), and sodium nitrite (12.4 mg, 0.18 mmol) in water (0.5 ml), afforded a yellow precipitate of 2'-neopentylthiobiphenyl-2-yldiazonium tetrafluoroborate (30 mg, 51%), mp 49-53° (dec).

ν_{max} 2285, 1550, 1365, 1300, 1240, 1060 (broad), 775, and 760 cm^{-1}.

The diazonium salt was suspended in benzene (dry, 10 ml) at 50-55°. Nitrogen was evolved from the stirred mixture, and the yellow colour gradually disappeared. Removal of solvent produced a white crystalline solid which was characterised as dibenzothiophen (14 mg, 95%), analysis as 46.

54 Benzyl o-Nitrophenyl Sulphide

Benzyl bromide (0.9 g, 5.3 mmol) was added to a stirred solution of sodium o-nitrobenzenethiolate (0.93 g, 5.3 mmol) in DMSO (dry, 30 ml) under nitrogen. Heat was evolved and the colour changed from dark red to green, then stirring was continued for 4 hours.

Addition of water (50 ml) liberated a precipitate which was extracted with ether (3 x 50 ml). The combined extracts were washed with water, dried over anhydrous magnesium sulphate, then concentrated to give benzyl o-nitrophenyl sulphide (1.05 g, 80%) as lemon yellow

needles, mp 82-84° from methanol (lit.,[353] mp 82-83°).

ν_{max} 3080, 2930, 1595, 1565, 1515, 1500, 1455, 1440, 1335, 1305, 1255, 1105, 1060, 1045, 855, 780, 735, 720, 710, 700, and 655 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.20-8.00 (d, 1H, J = 8Hz); 7.50-6.95 (m, 8H); and 4.15 (s, 2H).

55 o-Aminophenyl Benzyl Sulphide (174)

a Reaction as 15 using potassium hydroxide (18.5 g, 0.33 mol), o-aminobenzenethiol (37.5 g, 0.3 mol), and benzyl bromide (53 g, 0.3 mol) in DMSO (dry, 600 ml) under nitrogen, gave a yellow oil which crystallised readily on standing. Recrystallisation from petroleum ether (bp 40-60°) afforded o-aminophenyl benzyl sulphide (53 g, 82%) as colourless plates, mp 43-45° (lit.,[353] mp 45°).

ν_{max} 3450, 3355, 3055, 3020, 2920, 1605, 1490, 1475, 1445, 1305, 1250, 1235, 1155, 1070, 1025, 750, and 700 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.30-6.35 (m, 9H); 4.15 (broad s, 2H, exchangeable with D_2O); and 3.80 (s, 2H).

Mass Spectrum: M^+ = 215.

b Reaction as 4 using benzyl o-nitrophenyl sulphide (0.75 mg, 3.1 mmol), hydrazine hydrate (10 ml, 64% aq), and palladium-on-charcoal (53 mg, 5%) in refluxing ethanol (50 ml) for 24 hours, gave a quantitative yield of o-aminophenyl benzyl sulphide (0.66 g). Analysis as above.

56 o-Benzylthio Anilinium Tetrafluoroborate (176)

o-Aminophenyl benzyl sulphide (45.9 g, 0.213 mol) was dissolved in a mixture of fluoroboric acid (230 ml, 40% aq) and THF (40 ml) with

gentle warming. The solution was stirred and cooled to 0°, whereupon a white precipitate was formed. The solid was dried in vacuo over phosphoric anhydride for 3 days to give the crystalline o-benylthio anilinium tetrafluoroborate (52 g, 81%), mp 145-147°.

ν_{max} 2840 (broad), 2590, 1605, 1550, 1495, 1475, 1310, 1075 (broad), 760, and 705 cm^{-1}.

57 o-Benylthio Benzenediazonium Tetrafluoroborate (177)

o-Benylthio anilinium tetrafluoroborate (52 g, 0.172 mol) was dissolved in a mixture of ether (dry, 500 ml) and THF (dry, 150 ml), then the solution was cooled to 0° with vigorous stirring. p-Toluenesulphonic acid (0.1 g) was added, followed by slow addition of pentyl nitrite (22.1 g, 0.189 mol) whilst maintaining the low temperature. A pale green crystalline solid was filtered off and washed with cold ether. The yield of o-benzylthio benzenediazonium tetrafluoroborate was 50 g (93%), mp 55-60° (dec).

ν_{max} 2280, 1550, 1290, 1260, 1245, 1075 (broad), 765, 700, and 655 cm^{-1}.

58 Benzyl o-Iodophenyl Sulphide (178)

o-Benzylthio benzenediazonium tetrafluoroborate (50 g, 0.159 mol) was carefully added in portions, with efficient stirring, to a solution of potassium iodide (29 g, 0.175 mol) in water (200 ml). After standing overnight, the mixture was made alkaline with 2N sodium hydroxide solution then extracted with ether. The combined extracts were washed with a saturated aqueous solution of sodium thiosulphate, then with water, before drying over anhydrous magnesium sulphate.

Evaporation of solvent produced a golden orange oil (36 g) which

was placed on a column of silica. Elution with petroleum ether (bp 40-60°) gave benzyl o-iodophenyl sulphide (2.91 g, 6%) as colourless crystals, mp 73-78° from petroleum ether (bp 40-60°).

ν_{max} 3060, 3025, 1590, 1495, 1450, 1295, 900, 775, 760, 745, 730, and 695 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.85-7.00 (m, 9H); and 3.80 (s, 2H).

Mass Spectrum: M^+ = 326.

59 2-Benzylthio-2'-nitrobiphenyl (179)

Reaction as 3 using benzyl o-iodophenyl sulphide (2.91 g, 9 mmol), o-bromonitrobenzene (2 g, 10 mmol), and copper powder (2.25 g, 35 mmol), followed by chromatography on silica with 10% ether-petroleum ether (bp 40-60°), gave 2-benzylthio-2'-nitrobiphenyl (0.88 g, 30%) as a yellow oil.

ν_{max} 3070, 3030, 1600, 1525, 1355, 860, 770, 740, and 705 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.30-8.10 (m, 1H); 7.70-6.70 (m, 12H); and 4.10 (s, 2H).

Mass Spectrum: M^+ = 321.

60 2-Amino-2'-benzylthiobiphenyl (180)

Reaction as 4 using 2-benzylthio-2'-nitrobiphenyl (0.35 g, 1.1 mmol), hydrazine hydrate (5 ml, 64% aq), and palladium-on-charcoal (50 mg, 10%) in refluxing ethanol for 24 hours, afforded 2-amino-2'-benzylthiobiphenyl (0.18 g, 56%) as an oil.

ν_{max} 3445, 3330, 1670, 1615, 1480, 1455, 1375, 1045, and 880 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.60-6.50 (m, 13H); 4.05 (s, 2H); and 3.70 (broad s, 2H, exchangeable with D_2O).

Mass Spectrum: M^+ = 291.

61 2-Benzylthiobiphenyl-2'-yldiazonium Tetrafluoroborate (181) and Subsequent Decomposition

Reaction as 56/57 using 2-amino-2'-benzylthiobiphenyl (0.1 g, 0.34 mmol), fluoroboric acid (2 ml, 40% aq), and THF (few drops), followed by pentyl nitrite (43 mg, 0.37 mmol) with p-toluenesulphonic acid (trace) in ether-THF, gave a yellow precipitate of 2-benzylthiobiphenyl-2'-yldiazonium tetrafluoroborate (79 mg, 60%).

ν_{max} 2290, 1560, 1360, 1255, 1060 (broad), 775, 750, 740, and 715 cm^{-1}.

The diazonium salt was suspended in benzene (dry, 10 ml) at 50-55°. Nitrogen was evolved, the yellow colour gradually disappeared, and a white solid was identified as dibenzothiophen (33 mg, 90%), analysis as for 46.

62 2-Nitro-2'-trichloromethylthiobiphenyl (183)

Chlorine was bubbled into a solution of 2-methylthio-2'-nitrobiphenyl (1.42 g, 5 mmol) in carbon tetrachloride (dry, 50 ml) at room temperature for 17 hours. Evaporation of solvent produced 2-nitro-2'-trichloromethylthiobiphenyl (1.70 g, 97%) as an orange oil.

ν_{max} 3060, 1615, 1580, 1530, 1465, 1350, 1155, 1100, 860, 790, 755, and 705 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.30-6.90 (m, 8H).

Mass Spectrum: M^+ = 353/351/349/347 (1:9:27:27).

63 2-Mercapto-2'-nitrobiphenyl (182) and Subsequent Methylation

To 2-nitro-2'-trichloromethylthiobiphenyl (1.7 g, 5 mmol) was added methanol (25 ml) and Amberlyst 15 acid cation exchange resin

(0.1 g). Solvent was partially removed by distillation through a 6" Vigreux column until the head temperature reached 64°. Removal of catalyst by filtration and remaining solvent under vacuum gave 2-mercapto-2'-nitrobiphenyl (1.1 g, 95%) as an oil.

ν_{max} 2540, 1610, 1575, 1515, 1345, 1150, 1095, 855, 785, 750, and 700 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.20-7.80 (m, 1H); 7.70-6.90 (m, 7H); and 1.70 (broad s, 1H, exchangeable with D_2O).

Mass Spectrum: $M^+ = 231$.

Under nitrogen a sample of the crude thiol (0.2 g, 0.86 mmol) was added to powdered potassium hydroxide (0.14 g, 2.5 mmol) in DMSO (dry, 10 ml). After addition of dimethyl sulphate (126 mg, 1 mmol), the mixture was stirred at room temperature for 6 hours, then added to water (15 ml). Evaporation of solvent from the dried ether extracts yielded 2-methylthio-2'-nitrobiphenyl (0.12 g, 56%), analysis as 43.

64 Reaction of Thioanisole with Sodium Thioethoxide

Ethanethiol (1.24 g, 20 mmol) was added to a stirred suspension of sodium hydride (0.48 g, 20 mmol) in DMF (dry, 40 ml) under nitrogen at room temperature. After evolution of hydrogen had ceased, thioanisole (1 g, 8.1 mmol) was added and the clear solution heated under reflux for 3 days.

The reaction was quenched by addition of 2N hydrochloric acid (50 ml). The mixture was extracted with ether (4 x 25 ml), then combined extracts were washed with 2N sodium hydroxide (4 x 25 ml) and water before drying over anhydrous magnesium sulphate. Removal of solvent gave recovered thioanisole (0.5 g, 50%).

The aqueous alkaline extracts were acidified with concentrated

hydrochloric acid, giving a suspension which was extracted into ether. The yield of thiophenol was 0.4 g (45%; 90% based on amount of starting material consumed).

ν_{max} 3070, 3050, 3010, 3000, 2560, 1580, 1475, 1440, 1115, 1090, 1070, 1020, 730, 695, and 685 cm^{-1}.

65 Reaction of 2-Methylthio-2'-nitrobiphenyl with Sodium Thioethoxide

Reaction as 64 using ethanethiol (0.31 g, 5 mmol), sodium hydride (0.12 g, 5 mmol), and 2-methylthio-2'-nitrobiphenyl (0.49 g, 2 mmol) in DMF (dry, 35 ml), followed by neutralisation of the reaction mixture with 2N hydrochloric acid before work-up, afforded 2-amino-2'-methylthiobiphenyl (0.21 g, 49%), analysis as 44, and 2-amino-2'-mercaptobiphenyl (40 mg, 10%) as an oil.

^{1}H NMR $\delta(CDCl_3)$ 7.50-6.80 (m, 8H); 5.35 (broad s, 2H, exchangeable with D_2O); and 3.83 (broad s, 1H, exchangeable with D_2O).

66 Reaction of Nitrobenzene with Sodium Thioethoxide

Reaction as 64, using ethanethiol (1.24 g, 20 mmol), sodium hydride (0.48 g, 20 mmol), and nitrobenzene (1 g, 8.1 mmol) in DMF (dry, 40 ml). The mixture was added to 2N hydrochloric acid (50 ml) and washed with ether. The aqueous acid solution was then basified with 5N sodium hydroxide and extracted with ether (4 x 20 ml). The combined extracts were washed with water, dried over anhydrous magnesium sulphate, and concentrated to give aniline (0.49 g, 65%) as a red oil.

ν_{max} 3430, 3350, 3080, 3040, 1600, 1500, 1280, 1180, 1030, 1000, 885, 760, and 695 cm^{-1}.

67 p-Nitrothioanisole

Reaction as 15 using potassium hydroxide (7.28 g, 0.13 mol), p-nitrothiophenol (5 g, 32.3 mmol), and methyl iodide (9.23 g, 65 mmol) in DMSO (dry, 110 ml) under nitrogen, gave p-nitrothioanisole (5.18 g, 95%) as a bright yellow crystalline solid, mp 71-73° from acetic acid-water (lit.,[354] mp 72°).

^{1}H NMR $\delta(CDCl_3)$ 8.25-7.90 (d, 2H, J = 9Hz); 7.40-7.10 (d, 2H, J = 9Hz); and 2.53 (s, 3H).

68 Reaction of p-Nitrothioanisole with Sodium Thioethoxide

Reaction as 64, using ethanethiol (3.66 g, 59 mmol), sodium hydride (0.36, 15 mmol), and p-nitrothioanisole (1 g, 5.9 mmol) in refluxing DMF (dry, 40 ml) for 20 hours. The mixture was added to 2N hydrochloric acid (50 ml) and washed with ether. The aqueous acid solution was basified with 5N sodium hydroxide and extracted with ether (4 x 20 ml). The combined extracts were then washed with water, dried over anhydrous magnesium sulphate, and concentrated to give p-thioanisidine (0.66 g, 80%) as a red oil, (lit.,[340] bp 140°/15 mm).

ν_{max} 3440, 3350, 3030, 2980, 2930, 2870, 1600, 1495, 1280, 1180, 970, 830, 760, and 695 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 7.30-6.95 (d, 2H, J = 9Hz); 6.70-6.35 (d, 2H, J = 9Hz); 3.55 (broad s, 2H, exchangeable with D_2O); and 2.35 (s, 3H).

69 O-2-(o-Nitrophenyl)phenyl N,N-Dimethylthiocarbamate (188)

Sodium hydride (72 mg, 3 mmol) was added slowly to a stirred solution of 2-hydroxy-2'-nitrobiphenyl (645 mg, 3 mmol) in DMF (dry, 25 ml) under nitrogen at 15°. N,N-Dimethylthiocarbamoyl chloride (494 mg, 4 mmol) was added all at once, then the mixture was slowly heated to reflux over a period of 1 hour. Reflux conditions were

maintained for a further 30 minutes.

After cooling, the mixture was poured into water (50 ml) and a pale precipitate extracted into ether (4 x 25 ml). The combined extracts were washed with water and dried over anhydrous magnesium sulphate. Removal of solvent afforded a viscous oil which was placed on a column of silica. Elution with 2% ether-petroleum ether (bp 40-60°) gave O-2-(o-nitrophenyl)phenyl N,N-dimethylthiocarbamate (0.2 g, 22%) as pale yellow crystals, mp 140-150°.

ν_{max} 2940, 2870, 1520, 1395, 1360, 1290, 1200, 860, 790, and 745 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.10-6.80 (m, 8H); 3.17 (s, 3H); and 3.00 (s, 3H).

Mass Spectrum: M^+ = 302 and 382/380.

70 2'-Nitrobiphenyl-2-yldiazonium Tetrafluoroborate (195)

Reaction as 5 using 2-amino-2'-nitrobiphenyl (1.07 g, 5 mmol), fluoroboric acid (10 ml, 40% aq), THF (3 ml), and sodium nitrite (0.38 g, 5.5 mmol) in water (3 ml), gave a quantitative yield of orange crystalline 2'-nitrobiphenyl-2-yldiazonium tetrafluoroborate (1.56 g).

ν_{max} 2280, 1525, 1345, 1300, 1050 (broad), 855, 790, 760, 745, 720, and 695 cm^{-1}.

71 Reaction of 2'-Nitrobiphenyl-2-yldiazonium Tetrafluoroborate with Sodium Thioethoxide

Reaction as 64, using ethanethiol (0.31 g, 5 mmol), sodium hydride (0.12 g, 5 mmol), and 2'-nitrobiphenyl-2-yldiazonium tetrafluoroborate (626 mg, 2 mmol) in DMF (dry, 25 ml). The deep red solution was stirred at room temperature for 2 days, heated under reflux for 1 hour, then added to water (50 ml). The mixture was extracted with ether

(4 x 25 ml), then the combined extracts washed with 2N sodium hydroxide (2 x 25 ml) and water (2 x 25 ml) before drying over anhydrous magnesium sulphate. Removal of solvent gave an oil (0.2 g) which was analysed as a mixture containing both 2-ethylthio-2'-nitrobiphenyl (191) and 2-amino-2'-ethylthiobiphenyl.

ν_{max} 3450, 3370, 3050, 2960, 2920, 2865, 1605, 1520, 1350, 855, 755, and 700 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.80-8.30 (m); 8.10-7.65 (m); 7.50-6.50 (m); 3.60 (broad s, exchangeable with D_2O); 2.80 (q, J = 7Hz); and 1.25 (t, J = 7Hz).

72 Dibenzothiophenium Methylide (206) and Subsequent Reaction with Benzaldehyde

a An 0.05M solution of methylsulphinyl carbanion was prepared from sodium hydride (22 mg, 0.9 mmol) in DMSO (dry, 18 ml) under nitrogen at 75°. After several hours with vigorous stirring, a pale yellow solution was diluted with an equal volume of THF (dry), then cooled in a salt-ice bath.

A solution of S-methyldibenzothiophenium tetrafluoroborate (0.26 g, 0.9 mmol) in DMSO (dry, 0.7 ml) was added over a period of ca 3 minutes. The mixture was stirred for 1 minute longer before addition of benzaldehyde (90 mg, 0.85 mmol) at a moderately rapid rate. The orange solution was stirred for several minutes at salt-ice temperature, then for 2 hours with the bath removed.

The reaction mixture was diluted with water (100 ml) and extracted with ether (4 x 15 ml). The combined extracts were washed with water, dried over anhydrous magnesium sulphate, then concentrated. Dibenzothiophen, analysis as 46, and recovered benzaldehyde were obtained in quantitative yield.

b A 2.3M solution of n-butyl lithium in hexane (0.5 ml, 1.15 mmol) was added to S-methyldibenzothiophenium tetrafluoroborate (315 mg, 1.1 mmol) in THF (dry, 20 ml) under nitrogen at -70°. After stirring for 15 minutes, benzaldehyde (106 mg, 1 mmol) was added, and the mixture was slowly warmed to room temperature (ca 3 hours).

The reaction mixture was diluted with water (60 ml) and extracted with ether (4 x 15 ml). Concentration of the dried extracts afforded dibenzothiophen and recovered benzaldehyde (net 84%).

CHAPTER 4

73 N-Methylmorpholine

Morpholine (84 g, 0.966 mol) was cooled in an ice bath, and formic acid (148 ml, 90% aq) was slowly added, followed by formaldehyde (145 ml, 37–40% aq). The mixture was stirred at 80° for 24 hours, then cooled and acidified with 6N hydrochloric acid (300 ml). The aqueous solution was washed with ether (3 x 100 ml), then basified with 50% aqueous sodium hydroxide and extracted exhaustively with ether. The combined extracts were dried over anhydrous magnesium sulphate. Removal of solvent, followed by distillation, gave N-methylmorpholine (18.9 g, 20%) as a pale yellow oil, bp 116-18° (lit.,[340] bp 115-16°/750 mm).

ν_{max} 2930, 2850, 2790, 1455, 1375, 1285, 1200, 1145, 1115, 1070, 1035, 1010, 905, 865, and 785 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 3.67 (t, 4H, J = 4.5Hz); 2.37 (t, 4H, J = 4.5 Hz); and 2.25 (s, 3H).

74 N-Methylmorpholine Hydrochloride

N-Methylmorpholine (1 g, 10 mmol) was dissolved in 2N hydrochloric acid (10 ml). Ethanol was added and evaporation to dryness produced an off-white solid. Recrystallisation from ethanol afforded N-methylmorpholine

hydrochloride (0.4 g, 29%) as colourless prisms, mp 201-3° (lit.,[355] mp 205°).

ν_{max} 2930, 2680, 1460, 1420, 1275, 1185, 1115, 1090, 1035, 990, 895, and 865 cm^{-1}.

75 Reactions of 2-Methoxy-2'-nitrobiphenyl (47) with Demethylating Agents

a Hydrobromic Acid See 14

b Trimethylsilyl Iodide

In a dry box under nitrogen, 2-methoxy-2'-nitrobiphenyl (115 mg, 0.5 mmol) was dissolved in $CDCl_3$ (0.4 ml) in an NMR tube. By means of an oven-dried syringe, trimethylsilyl iodide (130 mg, 0.65 mmol) was added to the sealed tube, the reaction was maintained at room temperature, and progress was monitored by ^1H NMR analysis. After 24 hours complete transformation of the iodide to hexamethyldisiloxane (δ0.1) had occurred, and no demethylation was observed.

c Lithium Iodide

A solution of 2-methoxy-2'-nitrobiphenyl (229 mg, 1 mmol) in pyridine (dry, 20 ml) containing lithium iodide (268 mg, 2 mmol) was heated to reflux under nitrogen. After 68 hours, thin layer chromatography revealed no change, and after quenching the reaction with 4N hydrochloric acid (100 ml) an ether extract yielded a quantitative recovery of starting material.

d Lithium Diphenylphosphide

A 2.3M solution of n-butyl lithium in hexane (0.5 ml, 1.15 mmol) was added to an ice-cold solution of diphenylphosphine (186 mg, 1 mmol) in THF (dry, 10 ml) under nitrogen. 2-Methoxy-2'-nitrobiphenyl (252 mg, 1.1 mmol) was added, and the orange solution heated under reflux for 18 hours. Solvent was removed, and the residue treated with ether

(30 ml) and water (15 ml). The ethereal layer was separated and the aqueous solution further extracted (3 x 15 ml). The combined extracts were dried, then concentrated, to give unreacted starting material. No phenolic material was isolated by acidification and extraction of the aqueous layer.

76 Reactions of 2-Methylthio-2'-nitrobiphenyl (165) with Demethylating Agents

a Hydrobromic Acid

Reaction as 14 using hydrobromic acid (10 ml, 48% aq) and 2-methylthio-2'-nitrobiphenyl (1 g, 4.1 mmol) in acetic anhydride (10 ml), gave only recovered sulphide from the first ether extract.

b N-Methylmorpholine Hydrochloride

N-Methylmorpholine hydrochloride (69 mg, 0.5 mmol) was added to a solution of 2-methylthio-2'-nitrobiphenyl (122 mg, 0.5 mmol) in N-methylmorpholine (10 ml), and the mixture was refluxed under nitrogen for 40 hours. Upon cooling, water (25 ml) was added, then the mixture was extracted with ether (3 x 20 ml). A quantitative amount of starting material was isolated.

c Trimethylsilyl Iodide

Reaction as 75b using 2-methylthio-2'-nitrobiphenyl (123 mg, 0.5 mmol) gave hexamethyldisiloxane only, and no detectable demethylation.

d Lithium Iodide

Reaction as 75c using 2-methylthio-2'-nitrobiphenyl (245 mg, 1 mmol) gave no change after 68 hours.

e Sodium Thioethoxide See 65.

f Lithium Diphenylphosphide

Reaction as 75d using 2-methylthio-2'-nitrobiphenyl (270 mg, 1.1 mmol) gave unreacted sulphide only, and no thiophenolic material.

g Sodium Cyanide

2-Methylthio-2'-nitrobiphenyl (0.64 g, 2.5 mmol) was added to a stirred solution of sodium cyanide (125 mg, 2.5 mmol) in HMPT (dry, 25 ml) under nitrogen at 75°, and the temperature was maintained for 5 days. Quenching of the reaction mixture in 2N hydrochloric acid (100 ml), followed by ether extraction, gave a product which exhibited no change in the characteristic S-methyl ^{1}H NMR resonance.

h Chlorination/Methanolysis See 62, 63.

CHAPTER 5

77 Diphenyliodonium Hexafluorophosphate (276a)

A stirred mixture comprising potassium iodate (25 g, 0.116 mol), dichloromethane (60 ml), acetic anhydride (50 ml), and benzene (32 g, 0.41 mol) was cooled to -10°. Concentrated sulphuric acid (25 ml) was added in drops, ensuring that the temperature did not rise above -5°. When the addition was complete, the low temperature was maintained for 3 hours, then the mixture was allowed to warm to room temperature.

After standing for 16 hours, water (100 ml) was added slowly to hydrolyse remaining acetic anhydride. Next, potassium hexafluorophosphate (21.4 g, 0.116 mol) in water (100 ml) was added, and the mixture stirred for 1 hour to complete the metathesis.

The organic layer was separated and the aqueous layer extracted further with dichloromethane (2 x 50 ml). Trituration of the combined extracts with ether gave, after standing, diphenyliodonium hexafluorophosphate (21.9 g, 44%) as colourless crystals, mp 138-40° (lit.,[147] mp 138-40°).

ν_{max} 3090, 3060, 1580, 1560, 1470, 1445, 995, 985, 830 (broad), 745, 735, 690, 680, and 650 cm^{-1}.

^{1}H NMR (Me_2CO-d_6) 8.50-8.20 (m, 4H); and 7.80-7.50 (m, 6H).

^{13}C NMR ($CDCl_3$/DMSO-d_6) 136.4, 133.8, 133.2, 115.7.

78 Di-p-tolyliodonium Hexafluorophosphate (276b)

Reaction as 77 using toluene (37.7 g, 0.41 mol) gave di-p-tolyliodonium hexafluorophosphate (24.2 g, 46%), mp 159-60° (lit.,[356] 169-73°).

ν_{max} 3090, 3050, 2920, 1475, 1390, 1295, 1205, 1180, 1115, 995, 840 (broad), 800, and 745 cm^{-1}.

^{1}H NMR δ(Me_2CO-d_6) 8.35-7.95 (m, 4H); 7.50-7.20 (m, 4H); and 2.40 (s, 6H).

^{13}C NMR δ($CDCl_3$/DMSO-d_6) 142.9, 135.0, 132.6, 112.3, 21.0.

79 Triphenylsulphonium Hexafluorophosphate (277)

Diphenyliodonium hexafluorophosphate (17 g, 40 mmol), diphenylsulphide (7.44 g, 40 mmol), and anhydrous copper(II) acetate (0.29 g, 1.6 mmol) were stirred under nitrogen at 120-125° for 3 hours. The mixture was poured whilst hot into a beaker, whereupon crystallisation occurred. The product was washed several times with ether to remove iodobenzene. Recrystallisation from ethanol-water (19:1) gave triphenylsulphonium hexafluorophosphate (14.4 g, 88%) as colourless crystalls, mp 198-9°.

ν_{max} 3090, 3070, 1580, 1475, 1445, 1060, 995, 875, 850, 830, 755, and 685 cm^{-1}.

^{1}H NMR δ(Me_2CO-d_6) 8.00-7.70 (m, 15H).

^{13}C NMR δ($CDCl_3$/DMSO-d_6) 134.7, 131.6, 131.2, 124.8.

80 2,2'-Dinitrobiphenyl (33)

A mixture of o-chloronitrobenzene (100 g, 0.63 mol) and clean dry sand (150 g) was stirred at 240°, and copper powder (100 g, 1.55 mol) was added over a period of 1 hour. Stirring and heating was continued for a further 2 hours, then the hot mixture was added to sand (200 g) and broken up on cooling.

The solid mass was extracted with hot ethanol (3 x 500 ml), then cooling of the filtrates produced a crystalline solid. Recrystallisation from ethanol (after treatment with activated charcoal) afforded 2,2'-dinitrobiphenyl (36.6 g, 48%) as pale yellow needles, mp 122-24° (lit.,[25] 124-6°).

ν_{max} 3090, 3070, 3030, 1610, 1570, 1520, 1475, 1355, 1300, 1260, 850, 785, 755, 745, and 680 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.30-7.95 (m, 2H); and 7.80-7.05 (m, 6H).

Mass Spectrum: $M^{+\cdot}$ = 244.

81 2-Amino-2'-nitrobiphenyl (198)

a 2,2'-Dinitrobiphenyl (34.2 g, 0.14 mol) in ethanol (500 ml) was heated under reflux, and a solution of sodium polysulphide (prepared by boiling sodium sulphide nonahydrate (39.4 g, 0.164 mol) and sulphur (9.8 g, 0.3 mol) in water (125 ml) until dissolved) was added over a period of 1½ hours. The solution turned green then orange, heating was continued for an additional 3 hours, then the mixture was allowed to stand overnight.

Most of the ethanol was removed under vacuum, and the dark residue poured into ice water (800 ml). The mixture was thoroughly extracted with ether, then the combined extracts were washed with water and dried over sodium hydroxide pellets. The organic solution was next filtered and washed with 2N hydrochloric acid (4 x 100 ml).

The acid solution was treated with charcoal and warmed, then filtered whilst hot. Basification with 10N sodium hydroxide, followed by extraction with ether and drying over anhydrous magnesium sulphate, produced an orange oil which slowly solidified.

The solid was dissolved in hot ethanol, and the solution treated with charcoal, filtered, and cooled. 2-Amino-2'-nitrobiphenyl (19.7 g, 66%) was obtained as bright yellow crystals, mp 61-63° from ethanol (lit.,[305] mp 64-64.5°).

ν_{max} 3465, 3380, 1625, 1525, 1360, 1305, 855, 790, and 755 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.00-6.55 (m, 8H); and 3.50 (broad s, 2H, exchangeable with D_2O).

Mass Spectrum: $M^{+\cdot}$ = 214.

b A solution of 2,2'-dinitrobiphenyl (244 mg, 1 mmol) in 1,2-dimethoxyethane (30 ml) and chloroform (3 ml), containing palladium-on-charcoal (20 mg, 10%), was vigorously stirred under hydrogen at atmospheric pressure and ambient temperature.

After 16 hours, catalyst and solvent were removed, and the residue taken up in ether (50 ml). The ethereal solution was washed with 2N hydrochloric acid (3 x 10 ml) and water (2 x 10 ml), dried over anhydrous magnesium sulphate, then concentrated to yield recovered 2,2'-dinitrobiphenyl (0.16 g, 64%), analysis as 79.

The aqueous acid washings were neutralised with 5N sodium hydroxide then extracted with ether (3 x 10 ml). The combined extracts gave, after drying and evaporation, 2-amino-2'-nitrobiphenyl (58 mg, 27%) as an oil, analysis as above.

82 2-Bromo-2'-nitrobiphenyl (289)

2-Amino-2'-nitrobiphenyl (13.1 g, 61 mmol) in hydrobromic acid

(60 ml, 48% aq) and water (200 ml) was diazotised at 0° by the slow addition of sodium nitrite (4.64 g, 67 mmol) in water (50 ml) After stirring for 15 minutes, the diazonium salt solution was filtered, then bromine (14.7 g, 0.184 mol) in hydrobromic acid (30 ml, 48% aq) was added slowly, with stirring, to the cold filtrate.

The aqueous layer was decanted from a viscous orange residue, which was washed with water (2 x 100 ml) then gradually warmed to decomposition in glacial acetic acid (100 ml). The mixture was refluxed gently overnight, then added to water (1 l). The aqueous layer was decanted, the residue taken up in ether, and the organic layer dried over sodium hydroxide pellets.

Filtration, then evaporation of solvent, gave an oil which was treated with hot petroleum ether (bp 60-80°) and charcoal. Filtration and cooling afforded 2-bromo-2'-nitrobiphenyl (1.51 g, 9%) as pale yellow crystals, mp 63-65° (lit.,[349] mp 66-67°).

ν_{max} 1610, 1520, 1355, 1315, 1150, 1005, 860, 790, 750, 705, and 680 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.20-7.00 (m, 8H).

83 2-Amino-2'-bromobiphenyl (291)

2-Bromo-2'-nitrobiphenyl (0.63 g, 2.3 mmol) in methanol (10 ml) was added dropwise to a stirred mixture of hydrazine hydrate (1 ml, 64% aq) and Raney nickel (0.2 g) in methanol (10 ml). After the initial reaction had subsided, the mixture was refluxed for 15 minutes. Removal of catalyst and solvent gave a dark residue which was extracted with ether (3 x 15 ml), then combined extracts were washed with water and dried over anhydrous magnesium sulphate. Concentration gave 2-amino-2'-bromobiphenyl (0.35 g, 62%) as a viscous oil (lit.,[349] mp 46-50° from petroleum ether (bp 60-80°)).

ν_{max} 3450, 3370, 3060, 3030, 2970, 1615, 1500, 1485, 1470, 1450, 1425, 1300, 1265, 1160, 1025, 1000, 755, 705, and 660 cm^{-1}.

^1H NMR ($CDCl_3$) 7.70-6.40 (m, 8H); and 3.83 (broad s, 2H, exchangeable with D_2O).

84 2-Bromobiphenyl-2'-yldiazonium Tetrafluoroborate (293a)

Reaction as 5 using 2-amino-2'-bromobiphenyl (0.28 g, 1.1 mmol), fluoroboric acid (3 ml, 40% aq), THF (few drops), and sodium nitrite (83 mg, 1.2 mmol) in water (1 ml), gave the yellow crystalline 2-bromobiphenyl-2'-yldiazonium tetrafluoroborate (0.19 g, 48%), mp 88-91° (dec) (lit.,[304] mp 90°).

ν_{max} 2290, 1600, 1570, 1555, 1495, 1425, 1310, 1295, 1060 (broad), 970, 780, 765, and 720 cm^{-1}.

85 Biphenylene-2,2'-bromonium Tetrafluoroborate (294a)

2-Bromobiphenyl-2'-yldiazonium tetrafluoroborate (0.17 g, 0.5 mmol) was suspended in refluxing benzene (dry, 10 ml) for 2 hours. Nitrogen was evolved, and a white solid was formed. Recrystallisation from water afforded biphenylene-2,2'-bromonium tetrafluoroborate (0.12 g, 76%), mp 201-3° (lit.,[304] mp 204-5°).

ν_{max} 1300, 1170, 1050 (broad), 965, 760, and 725 cm^{-1}.

86 2-Iodo-2'-nitrobiphenyl (290)

Reaction as 1 using 2-amino-2'-nitrobiphenyl (6.39 mg, 30 mmol), concentrated hydrochloric acid (40 ml) and water (300 ml), sodium nitrite (2.28 g, 33 mmol) in water (30 ml), and potassium iodide (16.6 g, 0.1 mol) in water (50 ml), gave an oil which was placed on a column of silica. Elution with 15% ether-petroleum ether (bp 40-60°) yielded

2-iodo-2'-nitrobiphenyl (2.6 g, 27%) as pale green crystals, mp 85-86° (lit.,[349] mp 81-82°).

ν_{max} 3070, 1615, 1525, 1350, 1000, 855, 750, and 690 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.15-6.80 (m, 8H).

87 2-Amino-2'-iodobiphenyl (292)

Stannous chloride dihydrate (8 g, 35.4 mmol) in concentrated hydrochloric acid (8 ml) was added to a solution of 2-iodo-2'-nitrobiphenyl (2.5 g, 7.7 mmol) in ethanol (20 ml), and the mixture was heated under reflux for 6 hours. Solvent was evaporated, the residue basified with 2N sodium hydroxide then extracted with ether (4 x 25 ml). The combined extracts were washed with water, dried over anhydrous magnesium sulphate, then concentrated. Vacuum distillation gave 2-amino-2'-iodobiphenyl (1.58 g, 70%) as a pale yellow oil, bp 160-65°/1 mm (lit.,[357] bp 115-125°/0.1 mm).

ν_{max} 3480, 3390, 3060, 3030, 2980, 1615, 1580, 1500, 1465, 1450, 1425, 1305, 1160, 1115, 1015, 1000, 750, 730, and 650 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.10-7.70 (m, 1H); 7.50-6.50 (m, 7H); and 3.43 (broad s, 2H, exchangeable with D_2O).

88 2'-Iodobiphenyl-2-yldiazonium Tetrafluoroborate (293b)

Reaction as 5 using 2-amino-2'-iodobiphenyl (0.75 g, 2.5 mmol), fluoroboric acid (5 ml, 40% aq), THF (few drops), and sodium nitrite (0.19 g, 2.8 mmol) in water (2 ml), gave 2'-iodobiphenyl-2-yldiazonium tetrafluoroborate (0.7 g, 70%) as a cream crystalline solid, mp 227-32° (dec) (lit.,[304] mp 230°).

ν_{max} 2280, 1590, 1555, 1310, 1060 (broad), 775, 765, and 720 cm^{-1}.

89 Biphenylene-2,2'-iodonium Tetrafluoroborate (294b)

Reaction as 85 using 2-iodobiphenyl-2'-yldiazonium tetrafluoroborate (0.4 g, 1 mmol) afforded biphenylene-2,2'-iodonium tetrafluoroborate (0.26 g, 70%) as colourless needles, mp 238-40° from water (lit.,[304] mp 239-40°).

ν_{max} 3100, 1285, 1240, 1050 (broad), and 750 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.35-7.25 (m, 8H).

^{13}C NMR $\delta(CDCl_3/DMSO\text{-}d_6)$ 141.9, 130.9, 130.8, 130.7, 126.8, 121.4.

CHAPTER 6

90 Trimethylanilinium Iodide (296)

Dimethylaniline (0.6 g, 5 mmol) and methyl iodide (1.14 g, 8 mmol) were mixed and allowed to stand. Within 5 minutes the mixture had set solid. Recrystallisation from ethanol gave trimethylanilinium iodide (0.9 g, 68%) as colourless plates, mp 220-25° (lit.,[358] mp 228-29°).

ν_{max} 1595, 1500, 1400, 1235, 1125, 1035, 950, 940, 845, 770, and 695 cm^{-1}.

^{1}H NMR $\delta(D_2O)$ 7.90-7.40 (m, 5H); and 3.63 (s, 9H).

^{13}C NMR $\delta(SO_2, -30°)$ 146.4, 131.0, 119.9, 57.4.

91 Methyldiphenylamine (297)

Sodium hydride (0.12 g, 5 mmol) was added to DMSO (dry, 20 ml) and stirred for 15 minutes. Diphenylamine (0.34 g, 2 mmol) was added next, followed by methyl iodide (0.43 g, 3 mmol) after a further 15 minutes. The solution changed colour from dark green to deep red and was stirred at 75° for 20 hours. Water (50 ml) was added, then the

mixture extracted with ether. Removal of solvent after drying over anhydrous magnesium sulphate yielded methyldiphenylamine (0.28 g, 75%) as a tan oil (lit.,[340] mp -7.5°).

ν_{max} 3060, 3040, 2950, 2880, 2810, 1495, 1345, 1275, 1255, 1130, 1030, 865, 750, and 695 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.40-6.70 (m, 10H); and 3.27 (s, 3H).

92 Dimethyldiphenylammonium Tetrafluoroborate (298)

Methyl iodide (0.68 g, 4.8 mmol) was added to a stirred mixture of methyldiphenylamine (0.26 g, 1.4 mmol) and silver tetrafluoroborate (0.28 g, 1.4 mmol) in dichloromethane (dry, 20 ml). The mixture was stirred overnight, then filtered, and dry ether added until a cloudiness formed. Cooling in the freezer produced white crystals of dimethyldiphenylammonium tetrafluoroborate (20 mg, 5%), mp 194-99° (lit.,[359] mp 201-3°).

ν_{max} 1595, 1500, 1250, 1155, 1080 (broad), 830, 755, 725, and 700 cm^{-1}.

93 N-Methylcarbazole (301)

Reaction as 15, using potassium hydroxide (16.8 g, 0.3 mol), carbazole (16.7 g, 0.1 mol), and methyl iodide (28.4 g, 0.2 mol) in DMSO (dry, 150 ml). Evaporation of solvent from the ether extract afforded a white crystalline solid which was recrystallised from ethanol. The yield of N-methylcarbazole was 14.7 g (81%), mp 90-91° (lit.,[360] mp 87°).

ν_{max} 3050, 1600, 1485, 1470, 1455, 1325, 1245, 1150, 1115, 745, and 720 cm^{-1}.

^{1}H NMR $\delta(CDCl_3)$ 8.15-7.85 (m, 2H); 7.50-6.90 (m, 6H); and 3.67 (s, 3H).
^{13}C NMR $\delta(CDCl_3)$ 141.1, 125.7, 122.8, 120.3, 118.9, 108.4, 28.8.
Mass Spectrum: M^{+} = 181.

94 N-Acetylcarbazole (302)

Reaction as 15 using potassium hydroxide (16.8 g, 0.3 mol), carbazole (16.7 g, 0.1 mol), and acetic anhydride (20.4 g, 0.2 mol) in DMSO (dry, 150 ml), gave a solid product from the ether extract. N-Acetylcarbazole was obtained as white needles (15.9 g, 76%) mp 68-70° from water (lit.,[340] mp 69°).

ν_{max} 1675, 1495, 1480, 1450, 1380, 1330, 1310, 1240, 1210, 1195, 1035, 1015, 930, 745, and 720 cm^{-1}.
^{1}H NMR $\delta(CDCl_3)$ 8.20-7.10 (m, 8H); and 2.76 (s, 3H).
^{13}C NMR $\delta(CDCl_3)$ 169.5, 141.1, 125.7, 122.8, 120.3, 118.9, 108.4, 28.7.
Mass Spectrum: M^{+} = 209.

95 2-(N,N-Dimethylamino)-2'-nitrobiphenyl (303)

To a stirred mixture of 2-amino-2'-nitrobiphenyl (9.5 g, 44 mmol) and calcium carbonate (8.9 g, 89 mmol) in acetone (85 ml) was added a solution of methyl iodide (15.4 g, 0.11 mol) in acetone (15 ml) over a period of 2 hours. Stirring at room temperature was continued for another 3 hours, then the mixture was refluxed gently for 15 hours.

After cooling, the mixture was filtered, the solid washed with acetone, then the filtrate evaporated to produce a dark red oil. This was extracted with warm ether (5 x 25 ml) and the combined extracts dried over anhydrous magnesium sulphate.

Removal of solvent gave a yellow, partially crystalline solid which was placed on a column of silica. Elution with 10% ether-petroleum ether (bp 40-60°) afforded 2-(N,N-dimethylamino)-2'-nitrobiphenyl (4.46 g, 42%) as yellow crystals, mp 132-34° from

ethyl acetate-methanol (lit.,[317] mp 133-35°).

ν_{max} 2990, 2950, 2870, 2840, 2790, 1605, 1525, 1355, 950, 855, 790, 775, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 8.00-6.90 (m, 8H); and 2.38 (s, 6H).

96 2-Amino-2'-(N,N-dimethylamino)biphenyl (304)

Reaction as 4 using 2-(N,N-dimethylamino)-2'-nitrobiphenyl (4.46 g, 18.4 mmol), hydrazine hydrate (7.5 ml, 64% aq), and palladium-on-charcoal (0.45 g, 5%) in ethanol (250 ml), gave a pale yellow oil. Purification by vacuum distillation gave 2-amino-2'-(N,N-dimethylamino)-biphenyl (1.22 g, 31%) as a viscous colourless oil.[317]

ν_{max} 3420, 3380, 3050, 3010, 2940, 2860, 2830, 2780, 1610, 1590, 1480, 1445, 1435, 1300, 1155, 1050, 1005, 940, and 750 cm^{-1}.

^1H NMR $\delta(CDCl_3)$ 7.45-6.60 (m, 8H); 3.93 (broad s, 2H, exchangeable with D_2O); and 2.57 (s, 6H).

97 2-(N,N-Dimethylamino)biphenyl-2'-yldiazonium Tetrafluoroborate (305)

Reaction as 5 using 2-amino-2'-(N,N-dimethylamino)biphenyl (1.12 g, 5.3 mmol), fluoroboric acid (10 ml, 40% aq), THF (4 ml), and sodium nitrite (0.4 g, 5.8 mmol) in water (1 ml), with final stirring at -30° for 1 hour, afforded 2-(N,N-dimethylamino)biphenyl-2'-yldiazonium tetrafluoroborate (1.65 g) as a pale green crystalline solid in quantitative yield, mp 85-90° (dec).

ν_{max} 2280, 1560, 1505, 1305, 1070 (broad), 885, 770, and 720 cm^{-1}.

98 N,N-Dimethylcarbazolium Hexafluorophosphate (300b)

Methyl iodide (6.4 g, 45 mmol) was added dropwise to a stirred solution of N-methylcarbazole (1.36 g, 7.5 mmol) and silver hexafluorophosphate (1.9 g, 7.5 mmol) in dichloromethane (dry, 20 ml), and the mixture was stirred at room temperature for 24 hours, with exclusion of moisture.

The silver iodide precipitate was filtered off and washed with dichloromethane. An excess of ether was then added to the combined filtrates, producing a cloudiness, and the flask scratched at dry ice-acetone temperature until solid formed. Further cooling in the freezer gave N,N-dimethylcarbazolium hexafluorophosphate (0.24 g, 11%) as a white crystalline solid, recrystallised from dichloromethane-ether, mp 208-12°.

^{1}H NMR $\delta(Me_2CO\text{-}d_6)$ 8.55-7.70 (m, 8H); and 4.07 (s, 6H).

^{13}C NMR $\delta(Me_2CO\text{-}d_6)$ 150.5, 133.0, 131.7, 130.8, 123.7, 119.2, 56.5.

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