STUDIES ON LEWIS ACID CATALYSED / MEDIATED SYNTHESES

by

Mesut Kacan

A thesis submitted to the University of East Anglia for the Degree of Doctor of Philosophy

March 1993

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The research described in this thesis is, to the best of my knowledge, original except where due references have been made.

Mesut Kaçan

Dedicated to my wife Nazan, my daughter Irem and my new born son Sencer.

ACKNOWLEDGEMENTS

I would like to thank all of Professor Sandy McKillop's group in lab 1.10, past and present, for their assistance during the preparation of this thesis and for generating an environment in which it has been a pleasure to work.

I would like to thank Prof.Dr.Ahmet Akar (İTÜ) for encouraging me to pursue my studies in Britain, and for his continued interest.

I am indebted to Trakya Üniversity, Edirne for providing the funds which were necessary for completing this research.

Finally, and most importantly, I wish to thank Sandy McKillop for his guidance, constructive advice and for his efficient proof-reading of this thesis.

ABSTRACT

The work described in this thesis is divided into four parts. In the first part, benzyl chlorides or benzyl methyl ethers were reacted with hydrated ferric chloride in acetonitrile in a smooth Ritter type reaction and N-benzylacetamides were obtained in excellent yields.

In the second part, a novel synthesis was attempted of flosequinan, which has valuable therapeutic activity in the treatment of heart failure and hypertension. Unfortunately, the crucial final step, a 1,4-dipolar cycloaddition reaction, failed.

In part three, Diels-Alder reactions of itaconic anhydride with substituted 1,3-butadienes were re-examined in a 5.0 M lithium perchlorate-diethyl ether solution (LPDE) at ambient temperature and pressure. Rate enhancement was observed for methyl-substituted butadienes, but other butadienes gave only polymeric materials.

In the last part of this study, reactions of 1-(4-hydroxyaryl)-2-ketoximes, 4-$HOArCH_2C(=NOH)R$,with phenyliodine(III) bis(trifluoroacetate) (PIFA) in acetonitrile or ethanol were studied. This resulted in smooth intramolecular oxidative cyclisation and gave 1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-8-ones in good to excellent yields .

ABBREVIATION

aq.	Aquous
arom.	Aromatic
bp	Boiling point
d	Doublet
DMSO	Dimethyl sulphoxide
DMAD	Dimethyl acetylenedicarboxylate
EAN	Ethylammonium nitrate
FMO	Frontier moleculer orbitals
HOMO	Highest occupied moleculer orbitals
h.	Hours
I.R	Infrared
lit.	Literature
LPDE	Lithium perchloride-diethyl ether
LDA	Lithium diisopropyl amine
LUMO	Lowest unoccupied moleculer orbitals
MTA	Manganes(III) tris(acetylacetonate)
m.p	Melting point
mCPBA	Meta chloro perbenzoic acid
min.	Minutes
m	Multiplet
nmr	Nuclear magnetic resonance
PIFA	Phenyliodine(III) bis(trifluoroacetate
PIDA	Phenyliodine(III) diacetate
s	Singlet
TMOF	Trimethyl orthoformate
TTN	Thallium(III) nitrate
t.l.c	Tin layer chromatography
TFA	Trifluoroacetic acid
THF	Tetrahydro furan
t	Triplet

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Diels-Alder Reactions Using 5.0M LPDE Solution

CHAPTER 4

Oxidative Cyclisation Reaction of p-Phenolic Oximes Using PIFA

CHAPTER 1

Methoxyacetyl Chloride in Amide Synthesis

1.1 INTRODUCTION

The work reported in this chapter is a continuation of earlier studies in these laboratories into the synthetic utility of methoxyacetyl chloride as a chloromethylating agent. Some work has also carried out to investigate the formation of aromatic esters using methoxyacetyl chloride. In the present study, methoxyacetyl chloride has been used as an amido alkylation reagent of aromatic substrates.

Over the years there has been a great deal of interest in the synthesis of amides and as a consequence many techniques for their preparations have been reported. The most common methods for the formation of amides are as follows.

Amides from Acid Halides

Ammonia and most primary and secondary amines are readily acylated by treatment with acyl halides (equation 1).

$$R^1CO\ Hal + R^2R^3NH \longrightarrow R^1CONR^2R^3 + H.Hal \qquad (1)$$

With regard to this reaction acetyl chloride is more reactive than its higher homologues. The reactivity of acyl halides is enhanced by electron-withdrawing substituents, while conjugative stabilisation of the carbonyl group decreases the reactivity. A typical reactivity series is:

$$CH_3COCl \rangle CH_3CH_2COCl \rangle CH_3CH_2CH_2COCl \rangle (CH_3)_2CHCOCl$$
$$(CH_3)_3CCOCl \rangle PhCH_2COCl$$

The order of ease of displacement of the various halogens is I > Br > Cl > F. Apparently, as in nucleophilic displacement of halogen from saturated carbon, the effect of the C-Hal bond strength outweighs that of electronegativity.[1] The mechanism is assumed to take place via direct attack of the amine on RCOHal.

For preparative purposes acyl chlorides and bromides are usually employed rather than the less readily available fluorides and iodides, but formyl fluorides are used for formylation,[2,3] and in other special cases (e.g., preparation of acetoacetamides)[4] acyl fluorides offer advantages. Acyl tetrafluoroborates, hexa-fluoroantimonates and similar oxocarbonium salts are highly efficient N-acylating agents.[3,5] Methods recently developed for the preparation of acyl chlorides and bromides under very mild conditions will undoubtedly extend the application of these reagents in amide synthesis.[6,7]

Acyl halides react with ammonia and with amines under a wide range of experimental conditions and the choice of the best procedure depends on the nature and availability of the starting materials.[8] Acylation of ammonia and the lower alkylamines is often controlled by adding the halide to a cold, stirred aqueous solution of the base,[9,10] a method which has the advantages of technical simplicity and efficiency, although yields usually diminish as the homologous series is ascended.

Aqueous ammonia is not a suitable reagent for the preparation of those primary carboxamides which, because of low molecular weight or the presence of hydrophilic functions, have high water solubility. In such cases it is usual to pass gaseous ammonia into, or over a solution of acyl halide in a suitable organic solvent. In 1954 Philbrook claimed that the reaction in benzene gives consistently higher yields of fatty acid amides than other methods.[11]

The reactions of lower acyl halides with ammonia are frequently inconveniently vigorous. A milder method consists of treating the acyl chloride with ammonium acetate in acetone.[12] The reaction, which is believed to involve free ammonia formed by dissociation of the ammonium salt, proceeds in good yield and has been applied to a wide range of representative compounds. Ammonium carbonate in water has similarly been used for mild ammonolysis of highly reactive halides.[13]

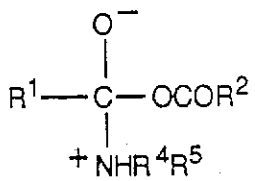
The ease of reaction of amines with the -COHal function is illustrated by the successful application of the reaction to acyl halides containing other groups sensitive to aminolysis, e.g., alkyl halide, benzyl halide and ester. Similarly, the highly nucleophilic power of the amino function allows selective N-acylation of amino alcohols and amino phenols.

Amides from Anhydrides

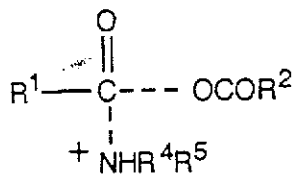
Carboxylic acid anhydrides also give amides by the reaction with amines although they tend to be less reactive than acyl halides (Equation 2).

$$R^1COOCOR^2 + R^3R^4NH \longrightarrow R^1CONR^3R^4 + R^2COOH \quad (2)$$

The mechanism of the reaction involves nucleophilic addition to a carbonyl group affording a tetrahedral intermediate (1), although Satchell[14] has obtained evidence for a synchronous displacement proceeding through the transition state (2). Both hypotheses lead



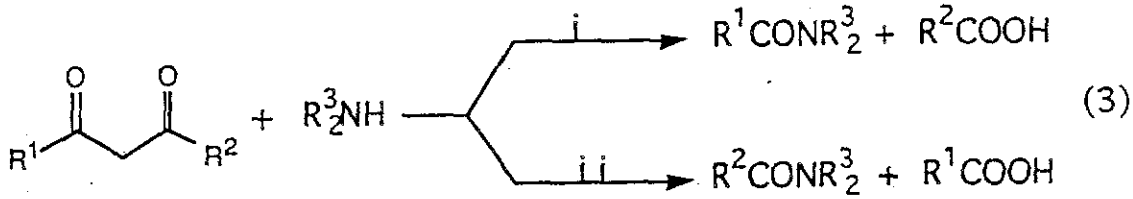
(1)



(2)

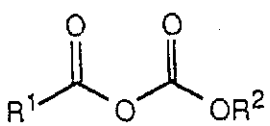
to the same generalisations concerning the effect of the structure of the reactants on the rate of the reaction. Increasing electron-withdrawing power of R in the anhydride $(RCO)_2O$ increases the reaction rate by enhancing the electrophilic character of the carbonyl carbon atom and by stabilising the leaving group, $RCOO^-$. Hence anhydrides containing strongly electronegative substituents, e.g., trifluoroacetic anhydride, are highly effective acylating agents. Conversely, increasing the electron-withdrawing power of the groups R^3 and R^4 in the amine, by lowering its nucleophilicity, decreases the rate of acylation.

Unsymmetrical carboxylic anhydrides offer two possible sites for attack by amines, leading to formation of two different acylated products (equation 3). This kind of reaction is controlled by the



(3)

steric and electronic effects of R^1 and R^2. Thus, an amine will attack the less bulky substituents at the carbonyl group, such as if R^1 is the less bulky group we should expect (i) rather than (ii). In many cases the interplay of electronic and steric effects leads to the formation of both possible products. However, attack of amines on carbonic carboxylic (3) and carbamic carboxylic (4) anhydrides usually proceeds selectively at the acyl carbonyl



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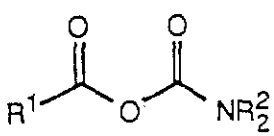
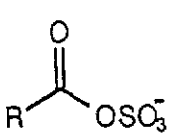


(4)

groups, R^1CO-, because the electrophilicity of the alternative positions is lowered by mesomeric release from the adjacent O or N atoms. Finally, in discussing mechanism we can say that mixed anhydrides of carboxylic acids with such other acids as sulphuric, sulphonic and phosphoric acids (i.e., 5, 6 and 7) in accord with the concepts adumbrated above undergo selective attack at the carbonyl group and are effective reagents for N-acylation.



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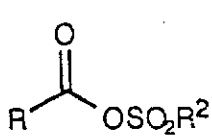

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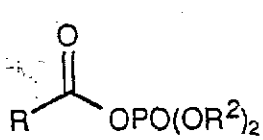
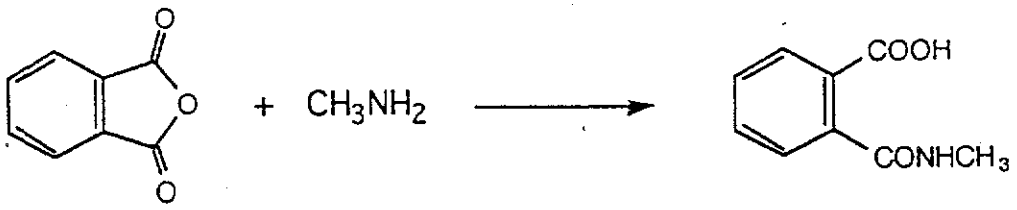


(7)

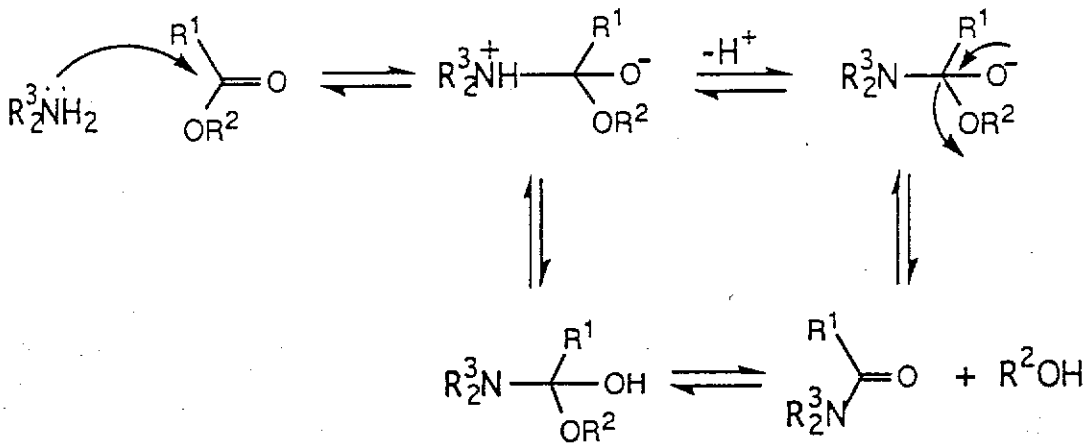
Cyclic carboxylic anhydrides can also react with ammonia or amines to give half-acid amides. In 1945, Spring obtained *N*-methylphthalamic acid in 80% yield by the reaction of phthalic anhydride with methylamine (Scheme 1).[15]

Scheme 1



Amides from Esters

Aminolysis of esters is a less frequently used method for the preparation of amides. Here again, the reaction mechanism involves nucleophilic substitution at a carbonyl carbon atom (equation 4). Reaction conditions employed for the acylation of ammonia or amines with esters vary widely according to the nature of the substrates. Ammonia is quite an effective nucleophile and reacts with many esters, particularly those containing electron-attracting substituents, in aqueous media.[16] In earlier work in 1966, Bruice *et al.*, described studies of the aminolysis of substituted aryl acetates in aqueous solution.[17,18]



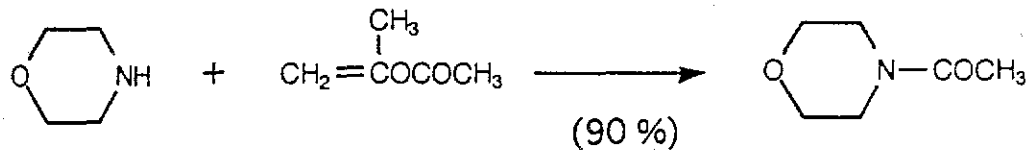
(4)

The use of concentrated ammonia solution for amide formation with esters is quite common. Examples of the preparation of primary carboxamides by treatment of an ester with concentrated ammonia solution include: cyanoacetamide prepared from ethyl cyanoacetate,[19] fumaramide from diethyl fumarate,[20] nicotinamide from ethyl nicotinate,[21] malondiamide from diethyl malonate,[22] and the monoamide of malonic acid from the monomethyl ester.[23]

Ammonia in alcoholic solution is a useful reagent for ammonolysis of esters which are too insoluble or insufficiently reactive to undergo attack in water.[24] Liquid ammonia has also been employed. Another procedure for the preparation of primary carboxamides from esters is the reaction with ammonium salts.

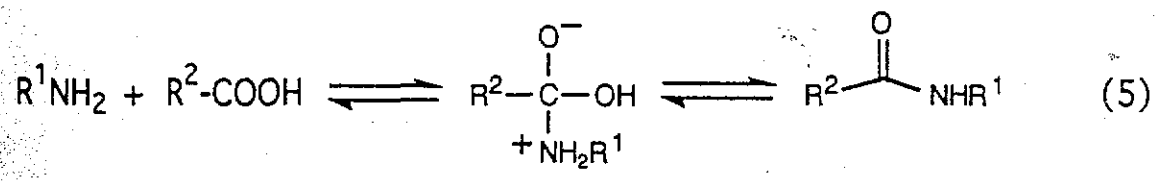
In 1905 Bodroux[25] prepared amides by reaction of an ester with the magnesium amide obtained by interaction of an amine with a Grignard reagent. The yields of amides from simple esters are often poor, but the reaction proceeds with much greater efficiency when the substrate contains an ester group adjacent to some function which is able to coordinate with magnesium. Thus esters having the general formula, RCOOA=B, in which nucleophilic attack on the carbonyl group is aided by conjugation, readily undergo aminolysis and are very useful for the preparation of amides and particularly for peptide synthesis (Scheme 2).

Scheme 2



Amides from Carboxylic Acids

At this time the mechanism of amide synthesis from carboxylic acids has not been completely clarified, but it is almost certain that the free amine and acid are in equilibrium with the salt. The reaction is formally the reverse of amide hydrolysis (Equation 5). Here again, a tetrahedral intermediate is formed in the reaction.

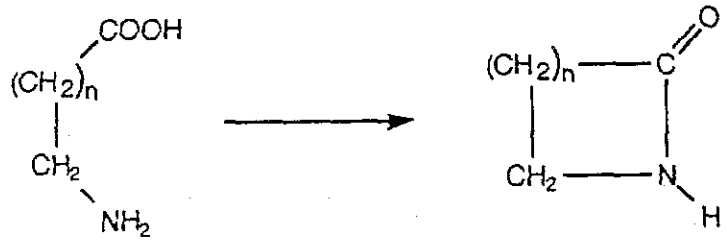


(5)

In 1963, this mechanism was supported by Morawetz[26] in his amide synthesis by reaction of monocarboxylic acids in aqueous solution, while with dicarboxylic acids, formation of the anhydride in the initial step of the reaction

has been demonstrated. A general procedure for all these reactions involves heating a mixture of acid and amine at about 200°C.[27]

In the preparation of piperidines and pyrrolidines, intramolecular amide formation can take place in amino acid compounds (equation 6). Amines, when treated with g- and d-keto acids give unsaturated lactams, presumably via cyclisation of an intermediate imino acid. The reaction has found considerable application in the preparation of aza steroids.[28]

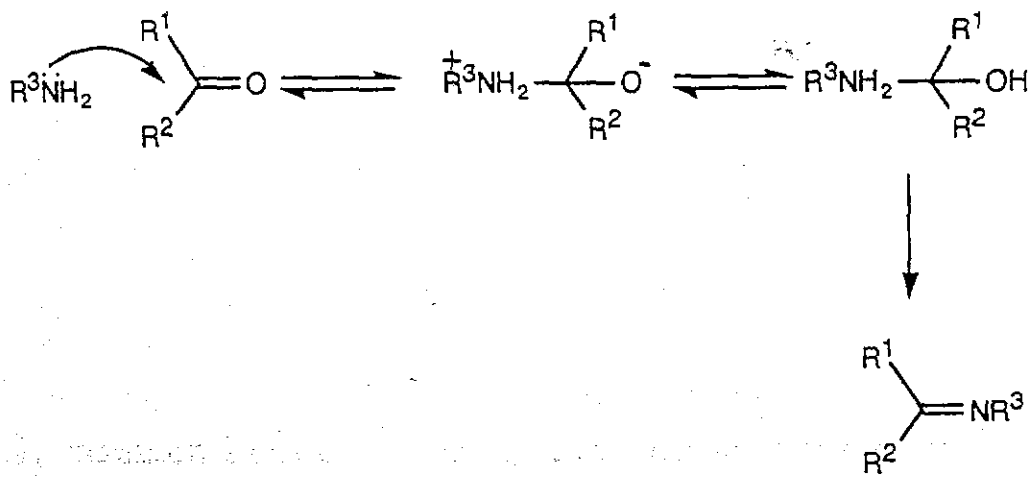


(6)

In 1965, Nelson and co-workers established another method for the preparation of amides using carboxylic acids.[29] This method involved converting acids directly to amides in good yield by treatment with tris-dialkylaminoboranes ($B(NR_2)_3$) in a reaction which is exothermic and rapid.

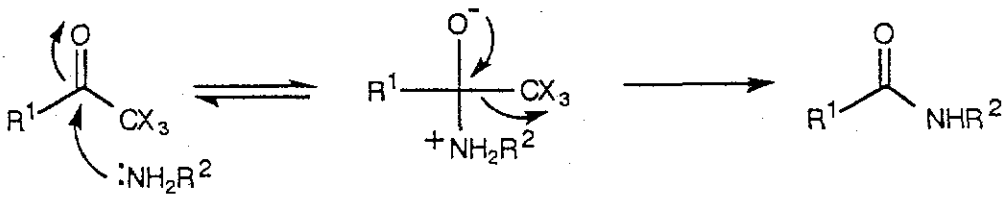
Amides From Aldehydes and Ketones

Aldehydes and ketones readily undergo addition to the carbonyl group with such nucleophiles as ammonia and amines in a similar manner to the reaction between amines and carboxylic acid derivatives. The mechanism is almost the same as that shown for the carboxylic acid mechanism (see equations 5 and 7).



(7)

The formation of amides by acylation of amines with aldehydes or ketones becomes practicable when one of the alkyl groups attached to the carbonyl carbon contains substituents which, by stabilising the related carbonium ion, allow it to function as a leaving group. Trihalomethyl ketones and aldehydes, when treated with amines, undergo addition-elimination according to the general mechanism previously discussed, with formation of amides and haloform (Equation 8).



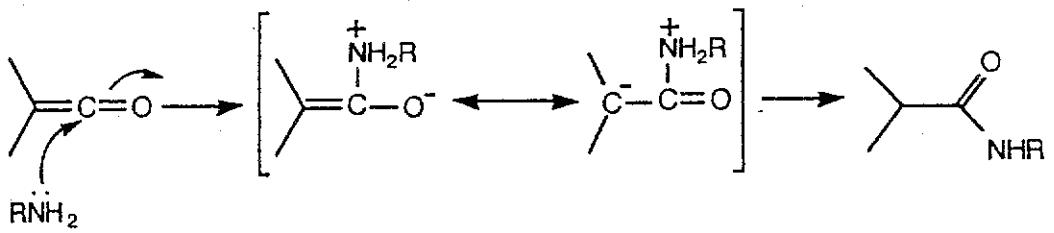
(8)

This reaction, which is mechanistically closely related to the final step in the haloform reaction, is of considerable value for the preparation of formamides under mild conditions. The method involves slow addition of one molecular equivalent of chloral to a cold solution of the amine in chloroform; it is applicable to both primary and secondary amines and the yields are usually excellent.[30]

Another method generally applied to the formation of amides from ketones is the Haller-Bauer reaction,[31] which involves heating a non-enolisable ketone with sodium amide in benzene, toluene or similar aprotic solvent. The mechanism of the reaction probably involves addition of amide ion (NH_2^-) to the carbonyl centre, followed by elimination of a carbanion. The reaction is applicable to a wide range of alkyl aryl ketones. The Haller-Bauer procedure can also be used for the preparation of amides from non-enolisable aliphatic and alicyclic ketones, but the synthetic potential of the reaction appears to be rather limited.

Amides from Ketenes

N-acyl derivatives are often obtained from ketenes and substituted ketenes.[32] The addition process is mechanistically related to other N-acylation reactions in that it involves initial nucleophilic attack of the amine on the carbonyl group (Equation 9). Acylation is quantitatively related to the basicity of the amine.



(9)

An important method for the preparation of amides which probably involves the intermediacy of ketenes is the Arndt-Eistert reaction in which an acid is converted via its chloride to a diazo ketone, which on treatment with silver ion catalyst and ammonia or an amine, affords the homologous amide (Equation 10).

$$R^1COCl \xrightarrow{CH_2N_2} R^1COCHNH_2 \xrightarrow{Ag^+} R^1CH{=}C{=}O \xrightarrow{R^2NH_2} R^1CHCONHR^2 \qquad (10)$$

Exchange methods, in which an amine reacts with a primary amide to form another amide, is also a commonly used method for amide preparation.[33] Thioacids, thioesters and thiocarboxylic anhydrides are also used in amide synthesis, yielding acyl derivatives. Such acylations occur more readily than those with the oxygen analogues. In addition to these reagents, carbon monoxide has been used as a formylating agent in amide syntheses. In 1962, Falbe and Korte treated carbon monoxide with primary and secondary amines in the presence of sodium methoxide to obtain formamides (Equation 11).[34,35]

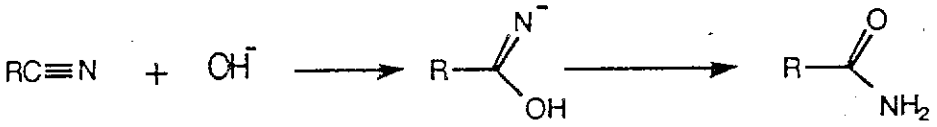
$$R^1R^2NH + CO \longrightarrow R^1R^2NCHO \qquad (11)$$

Preparation of Amides from Nitriles

A. Hydration

Hydrolysis of nitriles to obtain amides has been a commonly used method of amide preparation since 1885.[36] The hydration reaction is subject both to acid and base catalysis. The mechanism for the base-catalysed reaction involves

initial addition of hydroxide ion to the -C≡N group (Equation 12) whilst the acid-catalysed reaction proceeds through the protonated nitrile (Equation 13).



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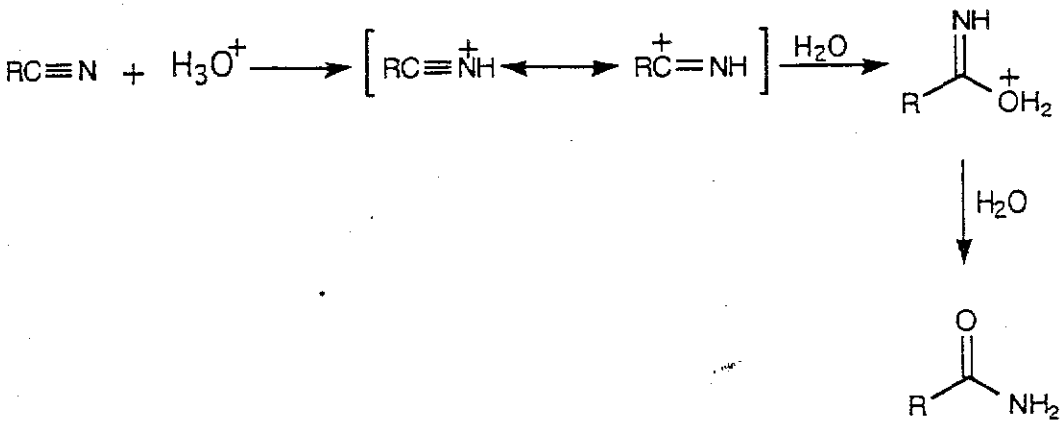
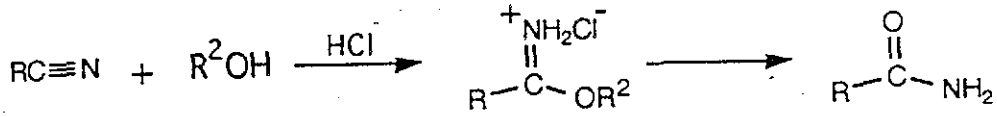


(13)

The most widely used procedure for the hydration of nitriles involves treating the substrate with mineral acid. Strong sulphuric acid is a particularly useful reagent for the preparation of aromatic amides and amides of highly sterically hindered aliphatic acids.[37,38] Also, a-keto nitriles can be hydrated in strong acid to yield a-keto amides.

Hydrochloric acid is a suitable reagent for hydration of nitriles. A lot of substituted arylacetonitriles have been converted to arylacetamides in excellent yield by using concentrated hydrochloric acid.[39] Polyphosphoric acid,[40] boron trifluoride containing a small amount of water,[41] and alkaline hydrogen peroxide,[42] have been widely used as hydrolysing reagents in the preparation of amides.

The Pinner reaction is an indirect procedure for the hydration of nitriles. In this procedure a nitrile is treated with an alcoholic solution of hydrogen chloride and heated to give a residual imido ester salt (Equation 14).[43] This method is convenient for the synthesis of a-hydroxy[44] and a-amino amides.[45]

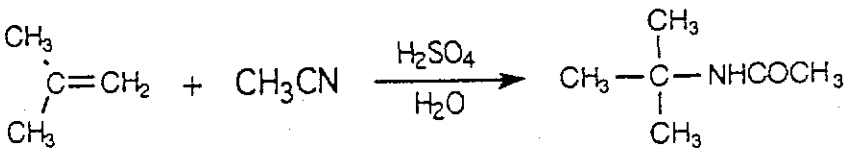


(14)

Base-catalysed hydration of nitriles is a less often used method for the preparation of amides; in many compounds the reaction proceeds to the acid by further hydrolysis of the amide.

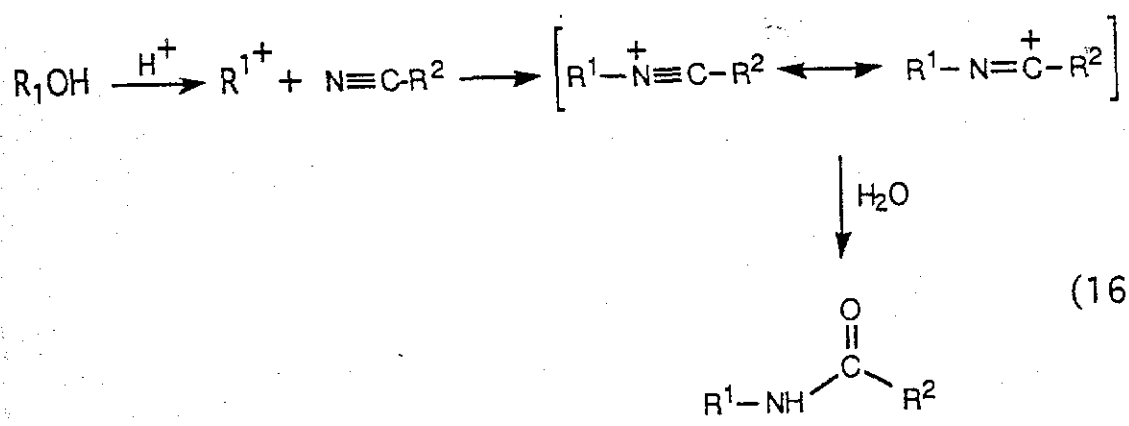
B. Alkylative Hydration

Reaction of olefins with hydrogen cyanide in the presence of a strong acid ($HCl\text{-}AlCl_3$) to yield formamides was first described in 1930.[46] In 1948, Ritter popularised the reaction of alkenes with nitriles in the presence of concentrated sulphuric acid for synthesis of *N*-substituted amides in good yield (Equation 15).[47]



(15)

Ritter also showed in his early work that tertiary alcohols could be used in place of olefins.[48] Mechanistically, the reaction is closely related to acid-catalysed hydration of nitriles, in that it is initiated by attack of an electrophilic species - in this case a carbonium ion formed by protonation of an olefin or dehydration of an alcohol - on the weakly basic cyanide nitrogen atom yielding a nitrilium salt which readily undergoes hydration on addition of water (Equation 16).



(16)

The Ritter reaction is applicable to a very wide range of substrates. Alcohols and olefins which afford tertiary carbonium ions on treatment with strong acid react particularly readily giving high yields of amides, and other compounds capable of giving stabilised carbonium ions (e.g., benzyl alcohol)[49] are also suitable substrates. The reaction is applicable to unsaturated nitriles,[50] to halohydrins and haloalkenes,[51] to long-chain nitriles,[47] to nitrilo esters,[47] to cyclo alkanals[52] and to compounds containing other reactive functions.

Alcohols and olefins which afford secondary carbonium ions on treatment with acid, undergo the Ritter reaction less readily than those that give tertiary carbonium ions. The Ritter reaction can also be applied to primary alcohols but only under very severe conditions. Thus, *N*-methylacetamide is formed by heating hydrogen chloride, methanol and acetonitrile in an autoclave at 280-315^{0}C.

Alkyl halides have also been used for the preparation of amides by the Ritter reaction. Diphenylmethyl bromide in benzene reacts with nitriles in the presence of silver sulphate to give amides (Equation 17).[53]

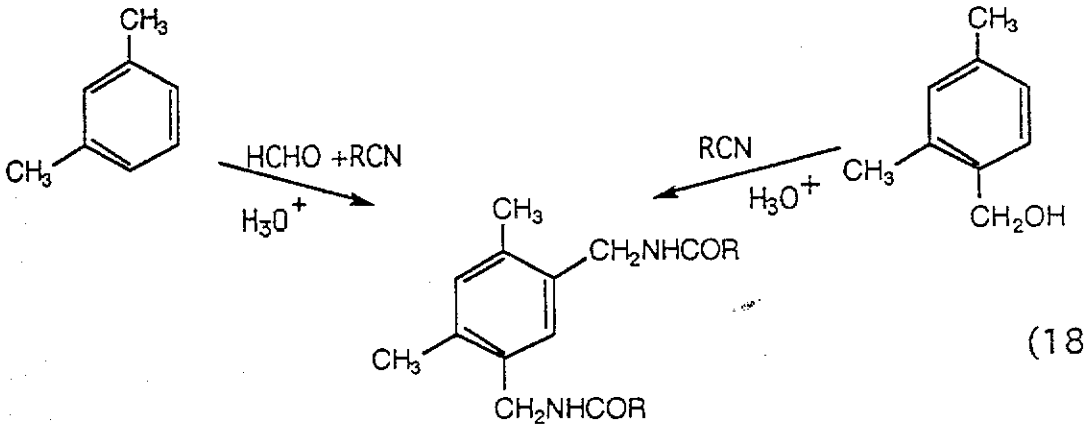
$$Ph_2CHBr + Ag^+ \longrightarrow Ph_2\overset{+}{C}H + AgBr$$

$$Ph_2\overset{+}{C}H \xrightarrow[H_2O]{RCN} Ph_2CHNHCOR \qquad (17)$$

Amides by The Amidomethylation of Aromatic Compounds

Parris and Christenson produced acetamide by reaction of benzene derivatives with formaldehyde and acetonitrile in the presence of acid (phosphoric, acetic and sulphuric) by heating at 70-90^{0}C.[54] Thus when *m*-xylene was reacted with an excess of para-formaldehyde and acetonitrile in phosphoric acid (or in a mixture of acetic and sulphuric acids) *N,N'*-diacetyl-4,6-dimethyl-1,3-di(aminomethyl)benzene (8) was obtained in yields of 50-

60% (Equation 18). When the reaction was carried out with an excess of *m*-xylene the product was *N*-(2,4-dimethylbenzyl)acetamide.[55] This reaction of aromatic compounds with formaldehyde polymers and nitriles is a general one and has been found useful for the preparation of a large number of *N*-aralkylamides and *N,N'*-bisaralkylamides in moderate yield.



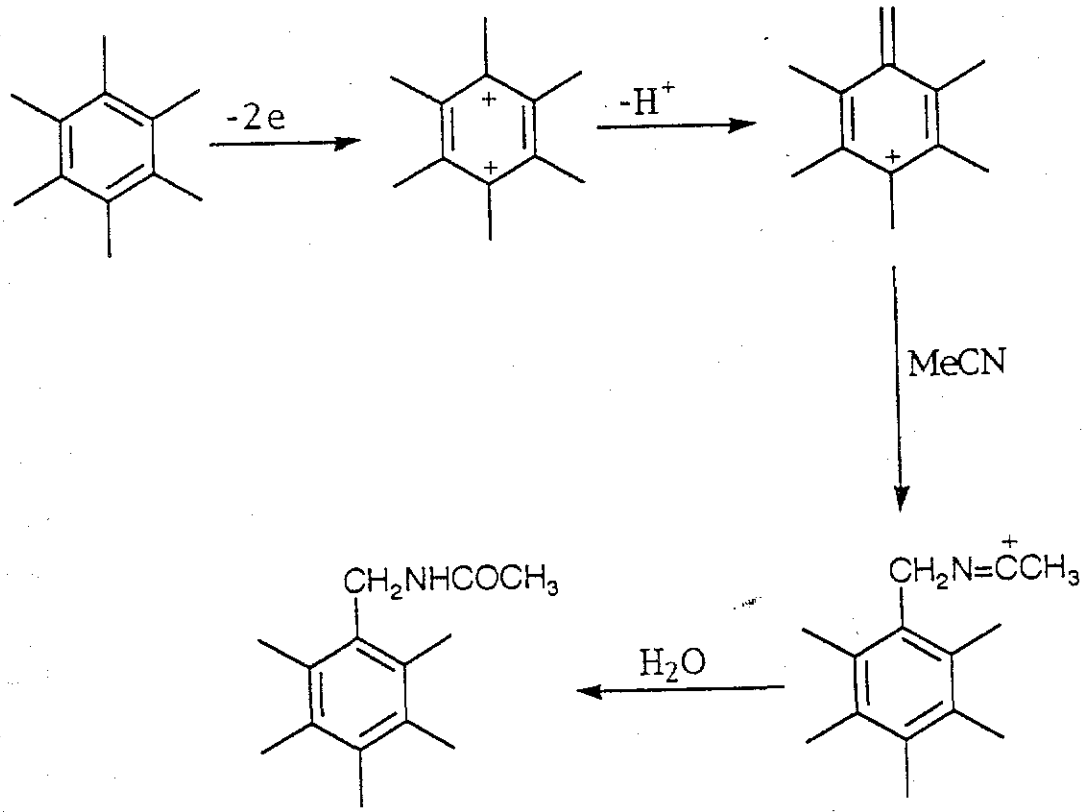
(18)

Parris and Christenson also described the formation of *N*-aralkylamides from aromatic alcohols in their earlier work[55] whereby the aralkyl type alcohols and glycols were condensed smoothly with nitriles under mild acidic (sulphuric acid) conditions to give *N*-aralkylamides in yields of 50-60% (Equation 19).

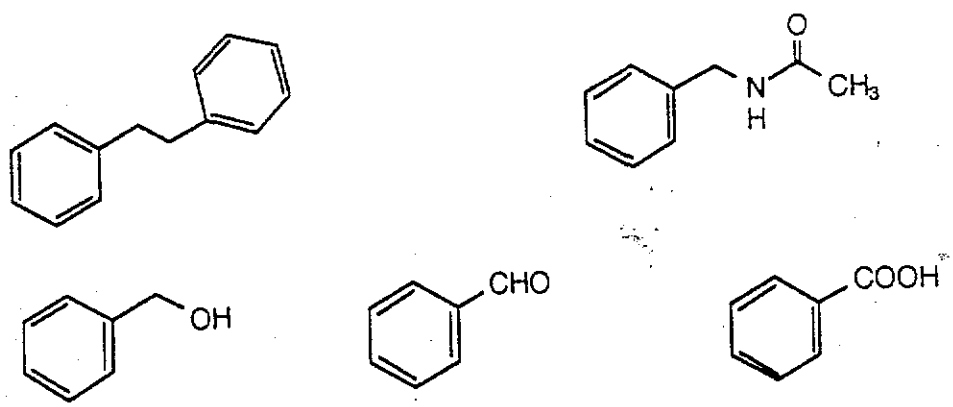
(19)

An interesting reaction for formation of amides was described by Eberson and Nyberg.[56] These authors found that the electrolysis of hexamethylbenzene or durene in acetonitrile in the presence of sodium perchlorate produces *N*-benzylacetamides and they proposed the following mechanism to account for their results (Scheme 3). Two years later Parker and Burget electrolysed

Scheme 3



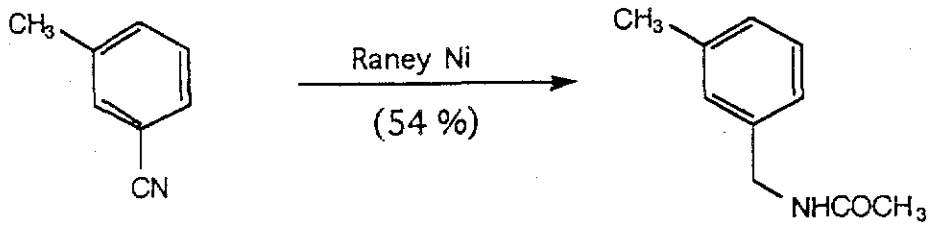
toluene in wet acetonitrile in the presence of perchlorate and they found five different compounds including benzyl acetamide.[57]



In 1975, Heidelberg prepared the 3-methylbenzylacetamide as starting material for the synthesis of antibiotics.[58] In this procedure, *m*-tolunitrile was

reacted with acetic anhydride in a hydrogenation bottle with Raney nickel catalyst and a yield of 54% was obtained (Scheme 4).

Scheme 4



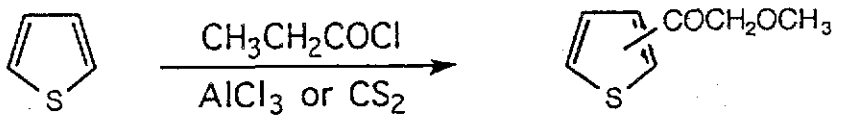
Amides can also be synthesised by solvomercuration-demercuration of olefins in the presence of acetonitrile.[59]

Amides from Methoxyacetyl Chloride

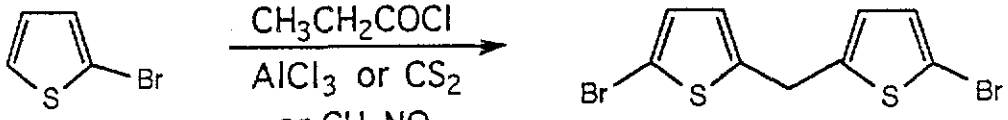
An intensive search of the literature for the preparation of amides reveals many different methods, one of which involves amide formation using methoxyacetyl chloride. This is discussed in the first part of this chapter. The second part of this chapter considers the formation of amides by the reaction of arylmethyl halide with acetonitrile as solvent using different kinds of Lewis acid catalysts.

Methoxyacetyl chloride has been extensively used to acylate amines and alcohols in Schotten-Baumann reactions.[60] However, there are no reports of it being used in Friedel-Crafts reactions. In 1982 Madjdabadi[61] investigated the possibility of incorporation of the methoxyacetyl group on to heteroaromatic rings using a Friedel-Crafts acylation reaction between heteroaromatic substrates and methoxyacetyl chloride. He obtained biaryl methane and chloromethylated products besides acylation products in many reactions (Scheme 5).

Scheme 5

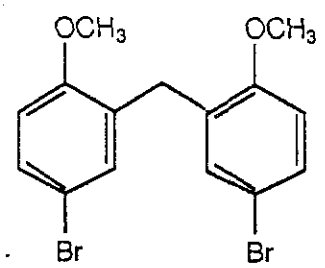


(9)

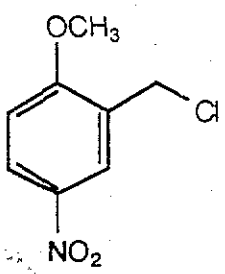


(10)

Madjdabadi performed his Friedel-Crafts methoxyacetylation reaction on a variety of heteroaromatic substrates and found that only with relatively activated aromatic systems was the acylation product (9) observed and then only in low yield. With most substrates only biarylmethane (10) was observed. At the same time, when he used the less activated benzenoid aromatic systems such as *p*-bromoanisole, biarylmethane (11) was formed in 74% yield, but with *p*-nitroanisole, the product was the corresponding chloromethyl derivative (12) in 75% yield.



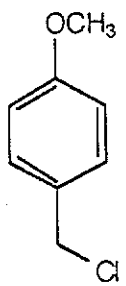
(11)



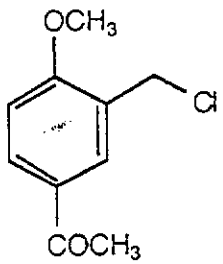
(12)

Madjdabadi however, became severely sensitised to the chloromethylated products, and he therefore concentrated on the formation of biarylmethanes.

The work with methoxyacetyl chloride as a "chloromethylating reagent" was continued by Long,[62] who chloromethylated a series of ortho and para substituted anisoles. All together, seven aromatic substrates were converted into the corresponding biarylmethanes in yields ranging from 45% for bis(3-bromo-2-thienyl)methane to 90% for bis(1,3,5-trimethylphenyl)methane and the chloromethyl group was successfully introduced into 15 aromatic substrates in yields ranging from 31% for 3-cyano-4-methoxybenzyl chloride (13) to 99% for 5-acetyl-2-methoxybenzyl chloride (14). This work was published by McKillop *et al.*, [63] in 1983.



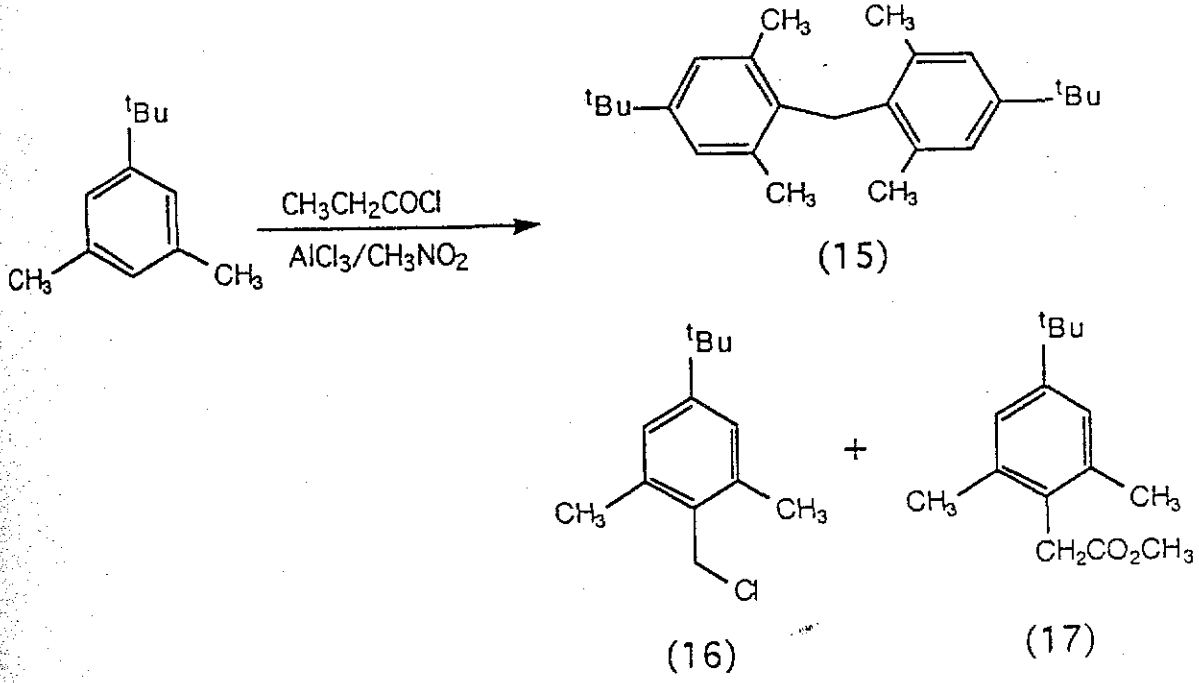
(13)



(14)

One year later, Mills was attempting to scale up the chloromethylation reaction, reported by Madjdabadi, of 5-*t*-butyl-*m*-xylene with methoxyacetyl chloride.[64] He isolated not only the expected 2,6-dimethylbenzyl chloride (16) but two other products: one he readily identified as bis(2,6-dimethyl-4-*t*-butylphenyl)methane (15), and the second he identified by spectral methods as the ester methyl 2,6-dimethyl-4-*t*-butylphenylacetate (17) (Scheme 6). He could not isolate the ester (17). He concluded that the ester was formed as a direct result of the reaction being scaled up to 100 mmol. McMurdo[65] has continued to work with methoxyacetyl chloride for the synthesis of arylacetic ester (17). Besides the ester he obtained biarylmethane (15) and chloromethylated compounds (16) by a Lewis acid catalysis system using nitromethane as solvent. When he used different solvents for the arylacetic ester synthesis, unexpectedly arylacetamide was obtained instead of esters, although he did not optimise the reaction conditions.

Scheme 6



Here, we will discuss our work concerning arylacetamide synthesis using methoxyacetyl chloride in acetonitrile as solvent. In this study, mainly 5-*t*-butyl-*m*-xylene was used as substrate in the presence of Lewis acid catalysts for the synthesis of amides. In the second part of this work we will be concerned with amide synthesis employing different catalysts with various benzyl chloride substrates and also benzyl methyl ethers.

Methoxyacetyl chloride is, at present, relatively expensive (£35.20 per 10 g from Aldrich Fine Chemicals Ltd (1991)), but it is simple to synthesise in good yield (ca. 85%) from methoxyacetic acid (£10.60 per 250 g from Aldrich) and thionyl chloride. Methoxy-acetyl chloride once prepared is stable and can be kept in well-stoppered bottles for several months without any sign of hydrolysis. If allowed in contact with water, hydrolysis leads to the parent acid and hydrogen chloride.

1.2. RESULTS AND DISCUSSION

1.2.1 Results of Experiments with Methoxyacetyl Chloride

At the beginning of this investigation, reactions were carried out with methoxyacetyl chloride with nitromethane as solvent using various Lewis acid catalysts after the methods of Long,[62] Mills[64] and McMurdo.[65] The conversion of 5-*t*-butyl-*m*-xylene into 2,6-dimethyl-4-*t*-butylbenzyl chloride, bis(2,6-dimethyl-4-t-butyl-phenyl)methane and methyl 2,6-dimethyl-4-*t*-butylphenylacetate was observed under a variety of conditions. The data from one such series of six reactions is reproduced in table 1.

Table 1 - Catalysts used in conjunction with methoxyacetyl chloride and 5-*t*-butyl-*m*-xylene in nitromethane

Reaction Number	Catalyst (mmol)	Yield Distribution %		
		Ar_2CH_2	$ArCH_2Cl$	$ArCH_2COOCH_3$
1/1	$SnCl_4$ (10)	25	75	-
1/2	$AlCl_3$ (20)	20	10	30
1/3	$ZnCl_2$ (20)	-	85	-
1/4	$FeCl_3$ (30)	-	20	53
1/5	$TiCl_4$ (60)	-	89	-
1/6	$FeCl_3 + AlCl_3$ (30 + 30)	-	29	62

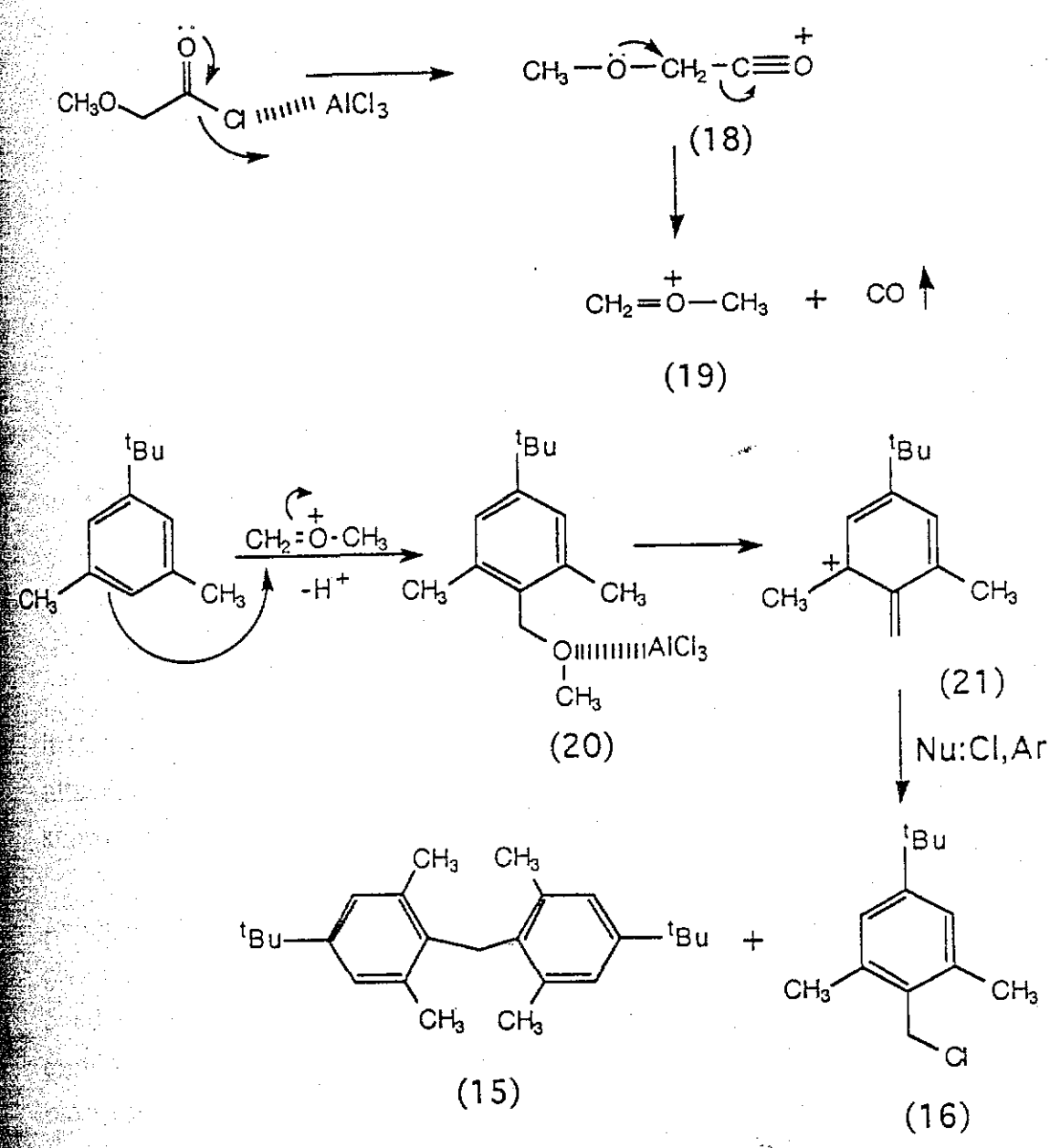
Method: see experimental section.

According to the classic reaction procedure, the catalyst in nitromethane (25 ml) was slowly added dropwise to a stirred solution of 5-*t*-butyl-*m*-xylene (10 mmol) and methoxyacetyl chloride (10 mmol) in nitromethane (25 ml) and the mixture was stirred for 30 minutes at room temperature.

The mechanism proposed by McKillop *et al.*,[63] explains the formation of both the biarylmethane and the chloromethylated product, but not the ester. These

authors proposed the active electrophile to be an oxygen Mannich type of intermediate (Scheme 7).

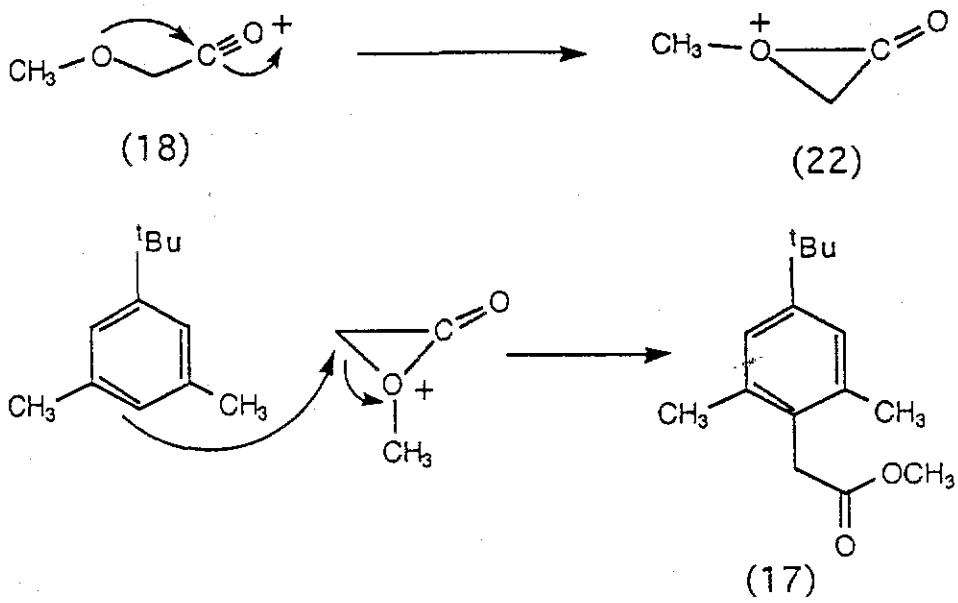
Scheme 7



Reaction of this methoxymethylene cation (19) with the aromatic substrate, via the widely accepted electrophilic aromatic substitution mechanism, would give benzyl methyl ether (20). The next step, loss of methoxide, can be envisaged as being facilitated by the catalyst, to give the carbocation (21). Reaction of (21) with chloride ion would give the chloromethylated product (16). Alternatively, the carbocation (21) could react with the aromatic substrate to give the biarylmethane (15) (Scheme 7).

In order to explain the formation of the arylacetic ester, Mills proposed generation of the transient a-lactone oxonium species (22) from the acylium ion (18). Attack by the aromatic substrate at the methylene carbon (Scheme 8) could, in principle, lead to formation of the arylacetic ester (17) directly.

Scheme 8



It is reasonable to assume that the intermediate a-lactone (22) would be attacked by a nucleophile at the methylene position, as this behaviour is known for a-lactones.

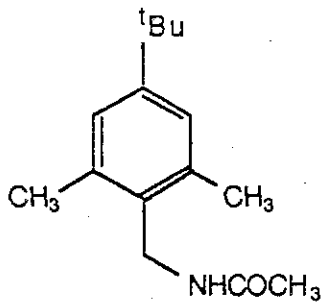
As shown in Table 1, various Lewis acid catalysts at different concentrations give rise to a variety of products in various yields. The data shows that higher catalyst concentration favours the formation of the arylacetic ester. Lower concentration favours the formation of chloromethylated product and biarylmethane. The aforementioned workers tried the same reactions at different temperatures and different concentrations of methoxyacetyl chloride. Changing the reaction temperature (-10°C - 40°C) did not affect the yield of product. But changing the concentration of acid chloride markedly affects the yields of the desired product. Higher concentrations (30 mmol for each 10 mmol of aromatic substrate) of acid chloride favoured the formation of the required ester, but more than 40 mmol of acid chloride gave polymeric material.[65]

Choosing the correct Lewis acid catalyst ($AlCl_3$, $FeCl_3$, $ZnCl_2$, $SnCl_4$, $TiCl_4$, etc.) for the desired product is very important for this series of reactions with methoxyacetyl chloride. It was also observed that higher concentrations of aluminium chloride favoured the formation of the ester. However, reactions with these higher concentrations, greater than six times the amount of aromatic substrate, proved difficult and at times impossible to work-up due to the formation of emulsions.

1.2.2 Change of Solvent

If different products of the reaction between 5-*t*-butyl-*m*-xylene and methoxyacetyl chloride are formed from different mechanistic pathways, and if ion pairs or a degree of solvation is involved in these pathways, then a change of solvent could vary the ratio of the products. Thus acetonitrile, which has almost the same polarity as nitromethane, was tried.

Thus, when 5-*t*-butyl-*m*-xylene was treated with methoxyacetyl chloride and various Lewis acid catalysts (Table 2) in acetonitrile, a colourless solid crystallised from the reaction mixture during the work-up. This was isolated and subsequently identified as the *N*-arylalkylacetamide, *N*-(2,6-dimethyl-4-*tert*-butylphenylmethyl)-acetamide (23).



(23)

Also a small amount of biarylmethane (15) and the chloromethylated product (16) were isolated from this same reaction mixture (reactions 2/1 and 2/5, Table 2).

Table 2 - Catalysts used in conjunction with methoxyacetyl (10 mmol) chloride and 5-*t*-butyl-*m*-xylene (10 mmol) in acetonitrile.

Reaction Number	Catalyst (30 mmol)	Yield Distribution %		
		Ar_2CH_2	$ArCH_2Cl$	$ArCH_2NHCOCH_3$
2/1	$AlCl_3$	5	3	10
2/2	$FeCl_3$	-	-	56
2/3	$ZnCl_2$	-	-	10
2/4	$TiCl_4$	-	-	35
2/5	$SnCl_4$	5	-	25

During these reactions a gas was evolved. That the gas was carbon monoxide was demonstrated by Long using Raman spectroscopy.[62] The volume of gas evolved during these reactions was not measured.

From the data in Table 2, it can be seen that when iron trichloride was used as catalyst, the amount of acetamide produced was higher than with the other Lewis acid catalysts. As a result of this finding, our work concentrated on iron trichloride as catalyst and a series of reactions was carried out. An attempt was then made to increase the yield of the acetamide by varying the amount of iron trichloride used as outlined in Table 3. However, the best yield of acetamide remained the same (56%).

Table 3: Results obtained by varying the amount of iron trichloride used as catalyst in the reaction of 5-*t*-butyl-*m*-xylene with methoxyacetyl chloride.

Reaction No.	$FeCl_3$ (mmol) [A]	Amide Yield % [B]
3/1	10	32.5
3/2	20	40.0
3/3	30	56.0
3/4	40	37.5
3/5	50	43.0
3/6	60	36.0

[A] In each case the amount of methoxyacetyl chloride was 30 mmol and the amount of substrate (5-*t*-butyl-*m*-xylene) was 10 mmol

[B] The remainder was intractable tar.

Several further attempts were made to improve the yield of the *N*-arylacetamide obtained in reactions 2/2 and 3/3. The temperature was varied (-20°C - 60°C). The concentrations of $FeCl_3$ and methoxyacetyl chloride were varied and small amounts of nitromethane were added to the reaction mixture. None of these variations raised the yield above the 56% initially isolated. Full details of these reactions will be found in the experimental section at the end of this chapter.

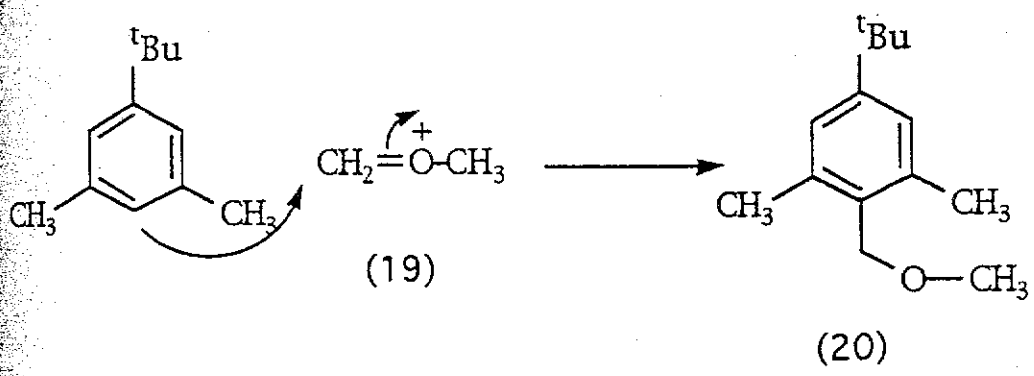
Changing the substrate to *p*-xylene gave a polymeric material, while *t*-butylbenzene gave the corresponding *N*-arylalkyl acetamide in 19% yield. When benzonitrile was used as solvent in place of acetonitrile with 5-*t*-butyl-*m*-xylene the *N*-arylbenzamide, *N*-(2,6-dimethyl-4-*t*-butylphenylmethyl)benzamide was obtained in 54% yield. Full details of this reaction will also be found in the experimental section. However, we did not concentrate our work on the synthesis of N-arylbenzamides.

1.2.3 Mechanism for Amidoalkylation using Methoxyacetyl Chloride

At the present time the mechanism of the amidoalkylation reaction, using methoxyacetyl chloride, investigated during the course of this study is not known. There is little evidence available concerning the mechanistic pathway by which N-arylalkylamides are formed. If these *N*-alkylamides are formed in a similar manner to those formed when using formaldehyde then evidence from work by Parris and Christenson indicates the possibility of more than one mechanistic pathway.[54,55]

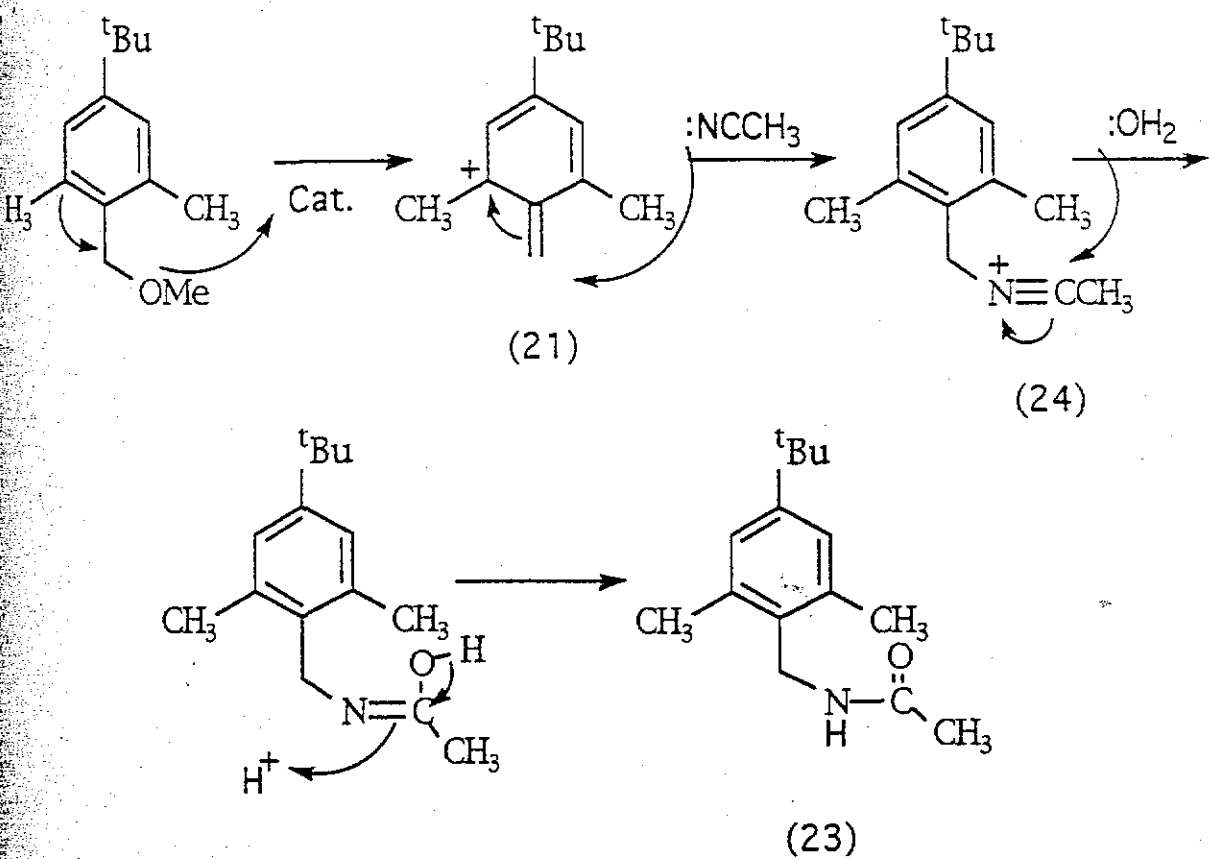
By the first mechanistic pathway, the most likely initial electrophile is that proposed by McKillop *et al.*,[53] namely the oxygen Mannich type intermediate (19) (Scheme 7). Reaction of this methoxymethylene cation (19) with the aromatic substrate, via the widely accepted aromatic electrophilic substitution mechanism, gives the benzyl methyl ether (2,6-dimethyl-4-*t*-butylbenzylmethyl ether) (20) (Scheme 9).

Scheme 9



The next step, loss of methoxide, can be envisaged as being facilitated by the catalyst, to give the carbocation (21). Reaction of this species with the nitrile would give salt (24) which is hydrolysed on aqueous work-up to the amide (23) (Scheme 10).

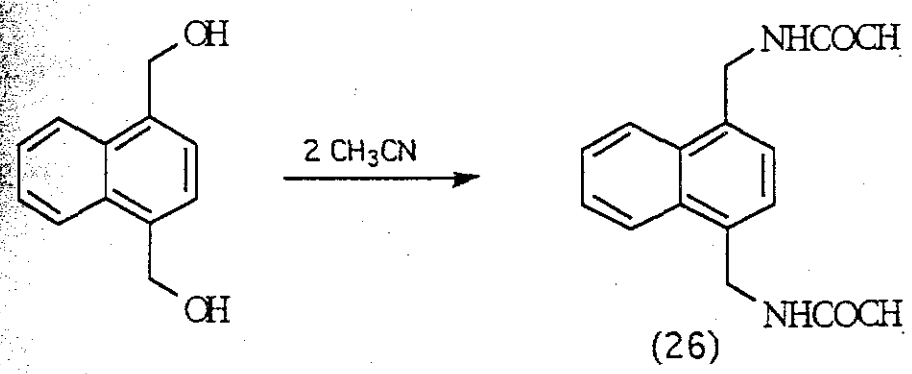
Scheme 10



That the nitrile can displace hydroxyl ion from benzyl alcohols has been demonstrated by Parris and Christenson,[54] who reacted

1,4dihydroxymethylnaphthalene (25) with acetonitrile to obtain the diamide (26) (Scheme 11).

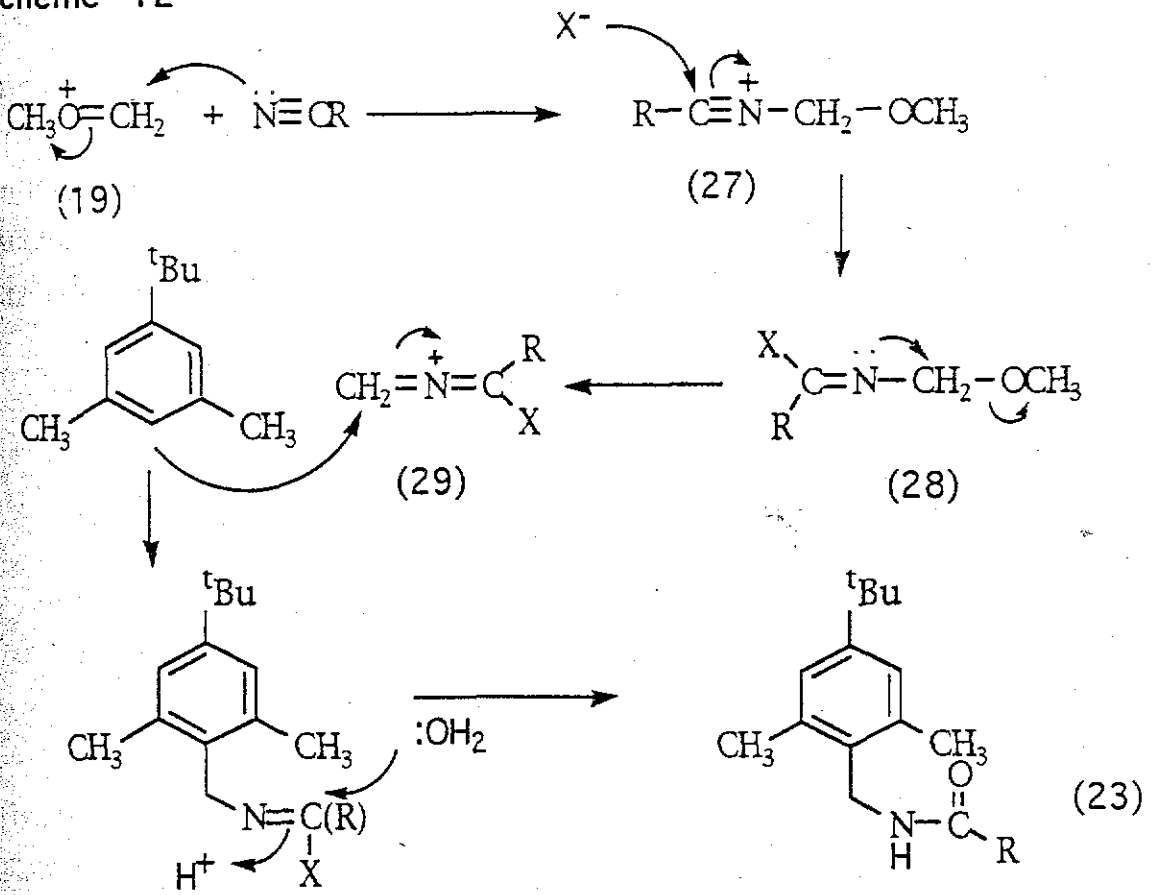
Scheme 11



(26)

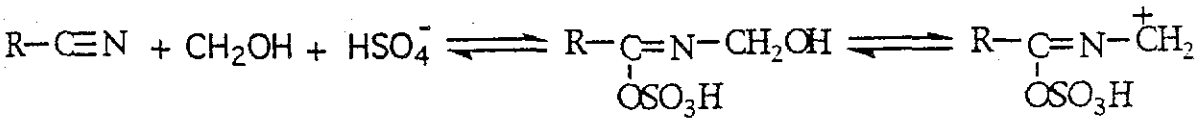
The second mechanistic pathway is via reaction of the proposed initial electrophile, the methoxymethylene cation (19), with the nitrile to give (27), followed by attack by chloride or methoxide to give (28), then loss of methoxide to give amidomethyl cation (29). Reaction of this with the aromatic substrate followed by hydrolysis would, in principle, give the amide, *N*-2,6-dimethyl-4-*t*-butylphenylmethyl)acetamide (23) (Scheme 12).

Scheme 12



Amidomethyl cation (30) similar in nature to (29) has been isolated by Maget *et al.*,[66] who treated nitriles with formaldehyde in concentrated sulphuric acid (Scheme 13).

Scheme 13

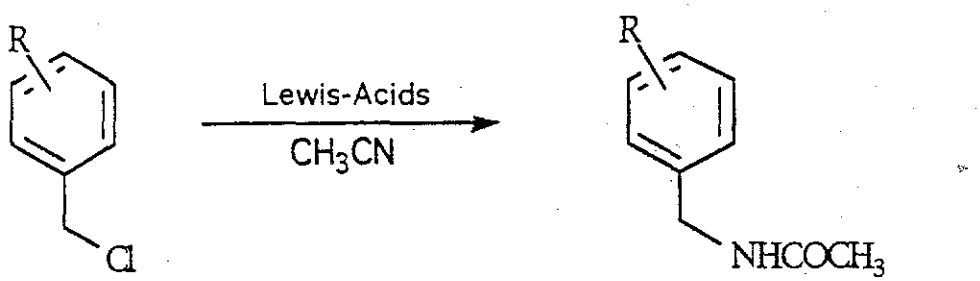


(30)

The first mechanism invokes the intermediate carbocation (21), which in principle can react in one of three ways; with acetonitrile to give the acetamide; with chloride ion to give the chloromethylated product; and with a further molecule of aromatic substrate to give the biarylmethane. In this work, neither benzyl chloride nor biarylmethane could be detected (even although their formation is implied by the mechanism postulated). In order to test this hypothesis a range of benzylic chlorides was reacted with acetonitrile in the presence of the Lewis acids, such as ferric chloride, aluminium chloride, etc.

1.2.4 The Formation of Arylalkylacetamides

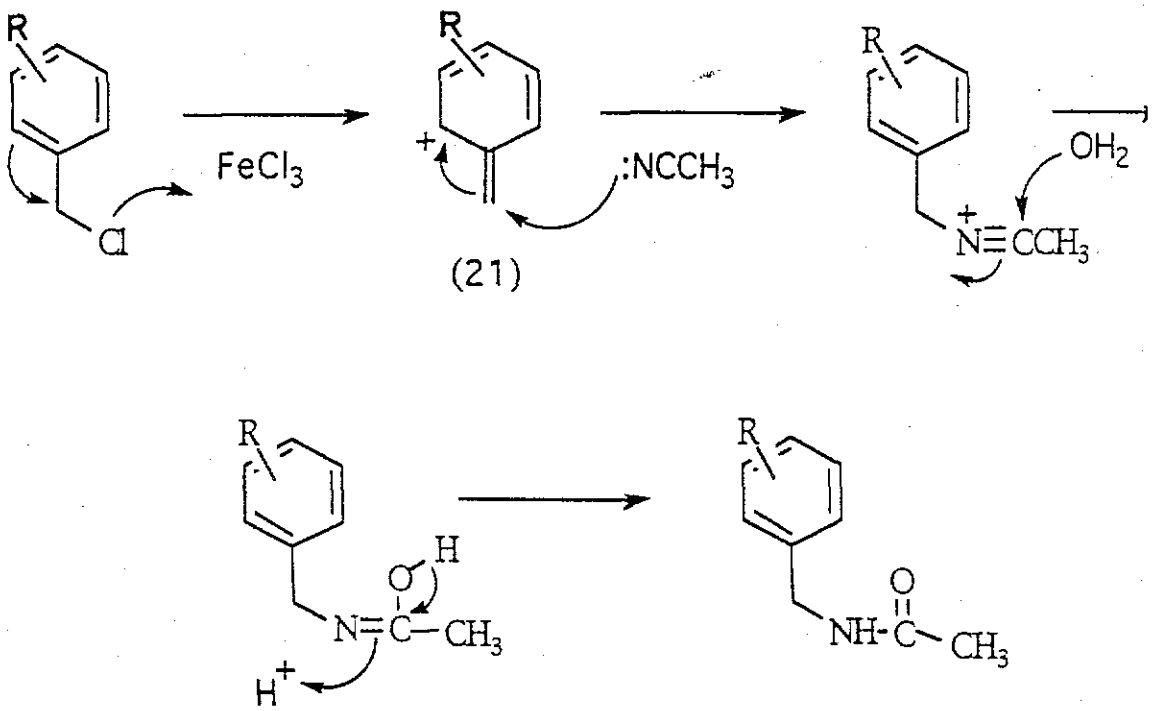
In this series of reactions substituted benzylic chlorides were reacted with acetonitrile in the presence of Lewis acids such as ferric chloride, aluminium chloride, etc., to obtain benzylic acetamides.



This kind of reaction is very closely related to the Ritter reaction. Ritter reacted alkenes and alcohols with nitriles in the presence of concentrated sulphuric acid and obtained *N*-substituted amides.[47,48] Mechanistically, the reaction is

closely related to acid-catalysed hydration of nitriles, in that it is initiated by attack of an electrophilic species - in this case a carbonium ion formed by protonation of an olefin or dehydration of an alcohol - on the weakly basic cyanide nitrogen atom yielding a nitrilium salt which readily undergoes hydration on addition of water. In our case benzyl halides were used in place of olefins and alcohols. The carbocation thus formed (21) should in principle react with the nitrile to form *N*-substituted amides after hydrolysis with water during the work-up (Scheme 14).

Scheme 14



In this part of the study, 2,6-dimethyl-4-*t*-butylbenzyl chloride and *o*-, *m*- and *p*-methyl substituted benzyl chlorides were reacted with $AlCl_3$, $FeCl_3$ and $SnCl_4$ as catalyst in acetonitrile. As seen from Table 4, ferric chloride gave a better yield than the other catalysts both at room temperature and under reflux in acetonitrile. All reactions were performed using 40 mmol of Lewis acid catalyst for each 10 mmol of benzylic chloride.

Table 4: Results of amide formation experiments using various catalysts with various benzyl chlorides and acetonitrile.

Reaction No.	$ArCH_2Cl$ Substituent	Catalyst	Reaction Time	Yield %
4/1	Unsubstituted	$AlCl_3$	12 h	70 *
4/2	4-^{t}Bu-2,6-dimethyl	$FeCl_3$	30 min	80
	"	$AlCl_3$	10 h	84 *
4/3	2-methyl	$FeCl_3$	30 min	54
	"	$FeCl_3$	4 h	78 *
4/4	4-methyl	$FeCl_3$	30 min	70
4/5	3-methyl	$FeCl_3$	30 min	46
4/6	2,4,6-trimethyl	$FeCl_3$	30 min	71
4/7	2,5-dimethyl	$FeCl_3$	30 min	78
	"	$SnCl_4$	1 h	62 *
4/8	3,4-dimethyl	$FeCl_3$	30 min	69
4/9	4-^{t}Bu	$FeCl_3$	30 min	71

* Reflux in acetonitrile
Method: see experimental section for full details.

Further investigations to elucidate the mechanistic pathway were carried out using benzyl methyl ethers with Lewis acid catalyst, the intermediate in the first mechanistic pathway (Scheme 7). Also, the possibility of amide formation from the ether (20) may give some explanation about formation of the amide using methoxyacetyl chloride in acetonitrile. Thus reactions were carried out using benzylic ether with tin(IV) chloride catalyst, and the results of this study are shown in Table 5. Other Lewis acid catalysts such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, and $TiCl_4$ were also tried besides $SnCl_4$ in the amide synthesis. But most of the catalysts gave starting material at room temperature. Extension of the reaction time did not improve the results. Ferric chloride gave slightly better results than the other catalysts but not as much as tin(IV) chloride at reflux temperature (in acetonitrile). All reaction details are given in the experimental section.

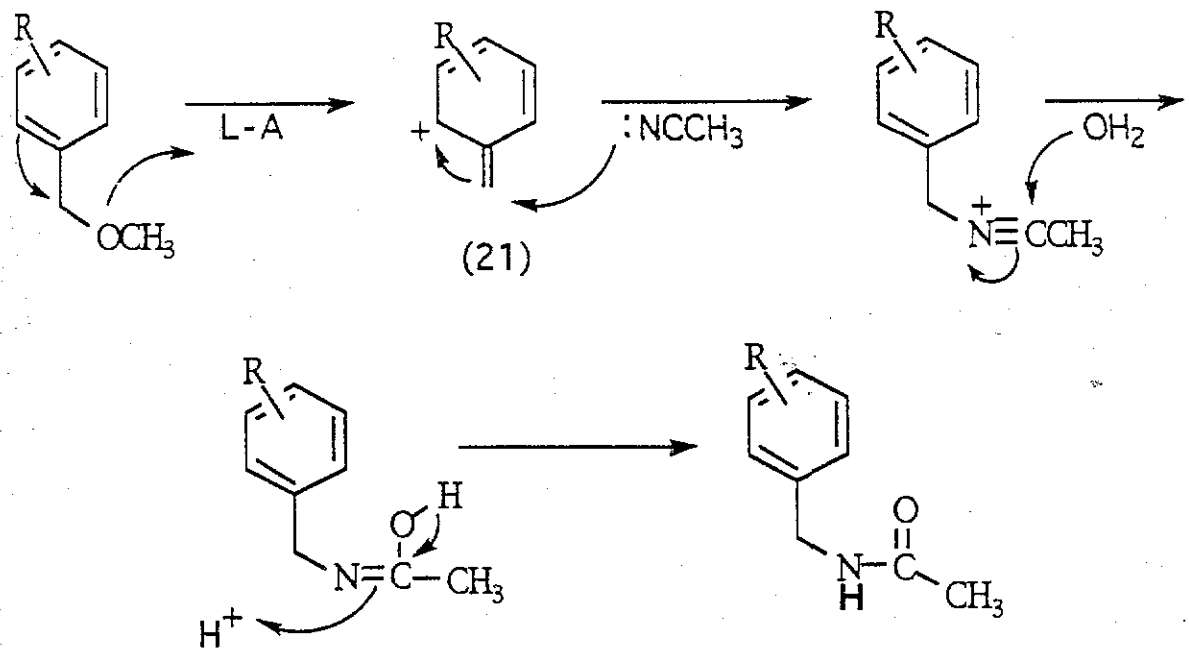
Table 5: Results of amide formation experiments using tin(IV) chloride with various benzyl ethers and acetonitrile.

Reaction No.	Substrate	Yield %
5/1	Benzyl methyl ether	48
5/2	4-Methylbenzyl methyl ether	51
5/3	2,5-Dimethylbenzyl methyl ether	62
5/4	2,4,6-Trimethylbenzyl methyl ether	65

See experimental section for full details.

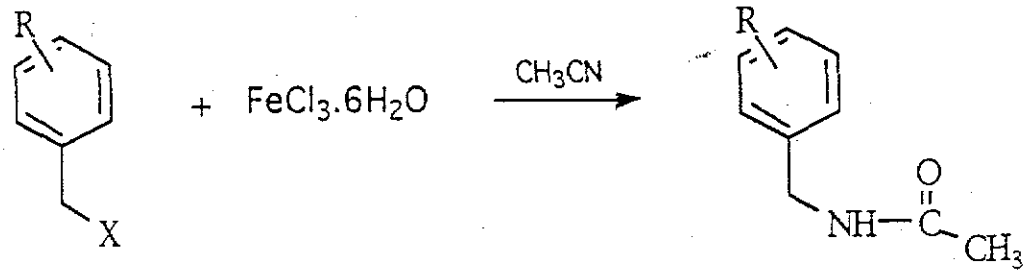
There is a similarity between the reaction mechanisms for amide formation from benzyl chlorides and from benzyl ethers. In both cases the first step involves the formation of the benzylic carbocation (21) in the presence of catalyst and secondly nitrile attacks the cation and *N*-substituted amide forms after hydrolysis with water during the work-up (Scheme 15).

Scheme 15



1.2.5 Arylalkylacetamide from $FeCl_3.6H_2O$

All the previous reactions had been carried out using anhydrous Lewis acid catalysts, and it was tacitly assumed that the hydrolysis of the nitrile occurred during aqueous work-up. It was therefore decided to attempt the reaction using hydrated catalysts. Initial work was concentrated on $FeCl_3.6H_2O$ as catalyst and the results are reproduced in Tables 5 and 6. Almost quantitative yields of the amides were obtained using this hydrated catalyst in an excess of acetonitrile.



X: Cl, OCH_3 (23)

In a preliminary study, 2,6-dimethyl-4-*t*-butylbenzyl chloride and hexahydrated ferric chloride were refluxed in acetonitrile for 5 hours. After consumption of starting material (as confirmed by TLC) the reaction mixture was worked-up in the usual way and a 98% yield of amide, *N*-2,6-dimethyl-4-*t*-butylphenylmethyl)-acetamide (23), was obtained as colourless crystals. Using the same method, various substituted benzyl chlorides were reacted with acetonitrile in the presence of hydrated catalyst and close to quantitative yields were obtained in all cases except one, as shown in Table 6.

Table 6: Results of amide formation experiments using $FeCl_3.6H_2O$ with various benzyl chlorides and acetonitrile.

Reaction No.	$ArCH_2Cl$ Substituent	Reaction Time (h)	Amide %
6/1	Unsubstituted	16	74
6/2	4-^{t}Bu-2,6-dimethyl	5	98
6/3	2-Methyl	6	98
6/4	4-Methyl	6	96
6/5	3-Methyl	12	92
6/6	2,4,6-Trimethyl	5	96
6/7	2,5-Dimethyl	6	94
6/8	3,4-Dimethyl	6	97
6/9	4-*t*-Butyl	5	98

Method: see experimental section for full details.

In the second part of this study with hexahydrated ferric chloride, various benzyl methyl ethers were refluxed in acetonitrile in the presence of hydrated catalyst. All benzylic ethers were prepared from corresponding benzylic chlorides by known methods using sodium methoxide. For each 10 mmol of benzylic ether 40 mmol of catalyst were used in 50 ml of acetonitrile. The results obtained are shown in Table 7.

Table 7: Results of amide formation experiments using $FeCl_3.6H_2O$ with various benzyl methyl ethers and acetonitrile.

Reaction No.	$ArCH_2OMe$ Substituent	Reaction Time	Amide %
7/1	Unsubstituted	6 d	22
7/2	4-^{t}Bu-2,6-dimethyl	14 h	96
7/3	2-Methyl	48 h	70
7/4	4-Methyl	18 h	96
7/5	3-Methyl	3 d	22
7/6	2,4,6-Trimethyl	16 h	96
7/7	2,5-Dimethyl	36 h	98
7/8	3,4-Dimethyl	36 h	97
7/9	4-*t*-Butyl	16 h	97

Method: see experimental section for full details.

As seen from the results in Table 7 above, the lowest yield of the amide was formed using benzyl methyl ether. When electron donating groups (methyl, *t*-butyl) were in ortho and para positions high yields were obtained and these must have stabilised the benzylic cation formed by the catalyst. However, hexahydrated ferric chloride gave excellent results compared with the other Lewis acid catalysts, and appears to be the catalyst of choice.

1.3. EXPERIMENTAL

INTRODUCTION

Melting points were determined on a Kofler hot-stage microscope melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 297 Grating Infrared Spectrophotometer. Solid samples were recorded as mulls in Nujol, while liquids were recorded neat as thin films, both between sodium chloride plates. Routine proton nuclear magnetic resonance spectra (nmr) were recorded on a Jeol FX60 MHz spectrometer. Tetramethylsilane was used as an internal standard in all nmr spectra, and all nmr data are reported on the d scale. Microanalytical and mass spectral data were determined by Mr A. W. R. Saunders of the University of East Anglia.

All organic extracts were dried with anhydrous magnesium sulphate. Thin layer chromatographic (tlc) analysis was performed on silica plates (Merck tlc aluminium sheets, silica gel 60 F_{254}, Art. No. 5554). Nitromethane was used as supplied by Fisons Scientific Apparatus Ltd., and stored in the dark over freshly conditioned molecular sieves. Acetonitrile was used after distillation and stored over molecular sieves.

The experimental procedures are, where possible, described in the sequence of the main text.

General Method I for reactions in Table 1.

A solution of the appropriate catalyst (see Table 1) in nitromethane (25 ml) was added slowly dropwise over 10 min to a stirred solution of 5-*t*-butyl-*m*-xylene (1.62 g, 10 mmol) at 25°C and methoxyacetyl chloride (1.09 g, 10 mmol) in nitromethane (25 ml). This addition caused the evolution of various amounts of gas. When addition was complete the crude reaction mixture was poured on to 2N hydrochloric acid (25 ml). Diethyl ether (25 ml) was added, and the organic layer was separated and washed with 2N hydrochloric acid (25 ml), water (25 ml), saturated brine (25 ml), then dried, filtered and the solvents removed under reduced pressure to give the products (see Table 1). Product distribution and yields were calculated from integration of the ^{1}H nmr spectra.

Reaction 1/1

As general method 1 above. The catalyst was stannic chloride (2.6 g, 10 mmol) with nitromethane (25 ml) as solvent and bis (2,6-dimethyl-4-*t*-butylphenyl)methane (**15**) was obtained as colourless plates, 0.44 g (25%), m.p. 136-137°C (lit. m.p.[67] 134-135°C) together with 2,6-dimethyl-4-*t*-butylbenzyl chloride (**16**) 1.5 g (75%) as colourless crystals, m.p. 22-24°C (lit.,[68] m.p. 24°C) as indicated by ^{1}H nmr and microanalysis.

Reaction 1/2

As general method 1 above. The catalyst was aluminium chloride (2.7 g, 20 mmol) and 5-*t*-butyl-*m*-xylene (1.62 g, 10 mmol) was used with methoxyacetyl chloride (1.08 g, 10 mmol). A brown oil was obtained which was a mixture of bis (2,6-dimethyl-4-*t*-butylphenyl)methane (**15**) (20%), 2,6-dimethyl-4-*t*-butylbenzyl chloride (**16**) (10%) and methyl 2,6-dimethyl-4-*t*-butylphenyl acetate (**17**) (30%) as indicated by ^{1}H nmr and microanalysis.

Reaction 1/3

As general method 1 above: catalyst, zinc chloride (2.7 g, 20 mmol) and nitromethane (50 ml) to give 2,6-dimethyl-4-*t*-butylbenzyl chloride (**16**) 1.6 g (85%) as colourless crystals, m.p. 22-24°C (lit.,[68] m.p. 24°C) as indicated by ^{1}H nmr analysis.

Reaction 1/4

As general method 1 above: catalyst, ferric chloride (4.86 g, 30 mmol) and nitromethane (50 ml), to give a brown oil which was a mixture of 2,6-dimethyl-4-*t*-butylbenzyl chloride (**16**) (20%) and methyl 2,6-dimethyl-4-*t*-butylphenyl acetate (**17**) (53%) as indicated by tlc and ^{1}H nmr analysis.

Reaction 1/5

As general method 1 above: catalyst, titanium(IV) chloride (11.3 g, 60 mmol) and nitromethane (50 ml) to give 2,6-dimethyl-4-*t*-butylbenzyl chloride (89%) as indicated by ^{1}H nmr analysis.

Reaction 1/6

As general method 1 above: catalysts, ferric chloride (4.86 g, 30 mmol) and aluminium chloride (4.0 g, 30 mmol) to give a mixture of the benzyl chloride (**16**) (29%) and the methyl phenylacetate (17) (62%) as indicated by ^{1}H nmr analysis.

General Method II for Reactions in Table 2/1-5.

A solution of 5-*t*-butyl-*m*-xylene (1.62 g, 10 mmol) and methoxyacetyl chloride (3.26 g, 30 mmol) in acetonitrile (20 ml) was added slowly dropwise over 15 min to a stirred solution, at 20°C, of catalyst (see Table 2) (30 mmol) in acetonitrile (20 ml). This addition caused the evolution of gas. The mixture was stirred for 30 min until gas evolution had ceased and then it was poured onto a mixture of crushed ice (15 g) and 2N hydrochloric acid (15 ml). Diethyl ether (15 ml) was added to aid separation. The organic layer was separated then washed with 2N hydrochloric acid (15 ml), water (15 ml), saturated brine

(15 ml), dried, filtered and the solvent was removed under reduced pressure to give the crude products. Column chromatography (silica gel: eluted with petroleum ether (b.p. 40-60°C)/diethyl ether (1:3)) gave a colourless solid which was recrystallised from acetone to afford as colourless needles, *N*-(2,6-dimethyl-4-*t*-butylphenylmethyl)-acetamide (**23**), m.p. 199-201°C (lit.[65] 199-201°C).

^{1}H nmr ($CDCl_3$): 1.28 (9H, s, ^{t}Bu), 1.88 (3H, s, CH_3CO), 2.33 (6H, s, CH_3Ar), 4.36 (2H, d, $ArCH_2NH$), 7.04 (2H, s, arom).

IR (cm^{-1}): 3250 (NH), 3060 (NH), 1640 n(CO).

Anal. calcd. for $C_{15}H_{23}NO$: C, 77.21; H, 9.94; N, 6.00. Found: C, 77.12; H, 10.13; N, 5.88.

MS calcd. m/z for $C_{15}H_{23}NO$: 233. Found: m/z 233.

Reaction 2/1

As general method II above, catalyst, aluminium chloride (4.0 g, 30 mmol) and acetonitrile (40 ml), to give a brown oil which was a mixture of the biarylmethane (**15**) (5%), the arylmethyl chloride (**16**) (3%) and the arylmethylacetamide (**23**) (10%).

Reaction 2/2

As general method II above: catalyst, ferric chloride (4.8 g, 30 mmol) and acetonitrile (40 ml) to give the arylmethylacetamide (**23**) in 56% yield as indicated by ^{1}H nmr analysis.

Reaction 2/3

As general method II above: catalyst, zinc chloride (4.1 g, 30 mmol) and acetonitrile (40 ml) to give the arylmethylacetamide (**23**) (10%) and intractable tar.

Reaction 2/4

As general method II above: catalyst, titanium(IV) chloride (5.7 g, 30 mmol) and acetonitrile (40 ml) to give the arylmethyl-acetamide (**23**) in 35% yield.

Reaction 2/5

As general method II above: catalyst, tin(IV) chloride and nitromethane (40 ml) to give a black oil which was a mixture of the biarylmethane (**15**) (5%) and the arylmethylacetamide (**23**) (25%).

N-(2,6-Dimethyl-4-*t*-butylphenylmethyl)benzamide

A solution of 5-*t*-butyl-*m*-xylene (1.62 g, 10 mmol) and methoxyacetyl chloride (3.26 g, 30 mmol) in benzonitrile (20 ml) was added slowly dropwise over 15 min to a stirred solution, at 20°C, of ferric chloride (4.8 g, 30 mmol) in benzonitrile (20 ml). After 30 min the work-up as in method II was followed to give as colourless needles, 1.6 g (54%) of *N*-(2,6-dimethyl-4-*t*-butylphenylmethyl)benzamide, m.p. 143.5-145°C, (lit.,[70] 144-146°C).
^{1}H nmr ($CDCl_3$): 1.30 (9H, s, ^{t}Bu), 2.40 (6H, s, CH_3 x 2), 4.62 (2H, d, CH_2), 7.06 - 7.8 (7H, m, arom).
IR (cm^{-1}): 1650 (C=O), 1590 (arom C=C) and 3250 (NH).

Reactions in Table 3

A solution of 5-*t*-butyl-*m*-xylene (1.62 g, 10 mmol) and methoxyacetyl chloride (3.26 g, 30 mmol) in acetonitrile (20 ml) was added slowly dropwise over 10 min to a stirred solution, at 20°C, of ferric chloride (in variable amounts as shown in Table 3) in acetonitrile (20 ml). The mixture was stirred for 30 min and then water (10 ml) was added and the solvent removed under reduced pressure to give a deep red oil. This residue was dissolved in diethyl ether (20 ml) and the solution washed with 2N hydrochloric acid (3 x 15 ml), water (10 ml) and saturated brine (15 ml), dried, filtered and evaporated under reduced pressure to give crude product: *N*-(2,6-dimethyl-4-*t*-butylphenylmethyl)acetamide. The crude product (**23**) was recrystallised from acetone and the various yields obtained are shown in Table 3.

General Method III for Reactions in Table 4.

A solution of the substituted benzyl chloride (see Table 4) (10 mmol) in acetonitrile (30 ml) was added slowly dropwise over 15 min to a stirred solution, at 20°C, of catalyst (40 mmol) in acetonitrile (30 ml). After the

addition was complete the mixture was stirred for 30 min or refluxed as shown in Table 4. A mixture of crushed ice (15 g) and 2N hydrochloric acid (15 ml) was added carefully to the reaction mixture and then diethyl ether (20 ml) to aid separation. The organic layer was separated and washed with 2N hydrochloric acid (15 ml), water (15 ml), saturated brine (15 ml), dried, filtered and evaporated under reduced pressure to give the crude products, which were then recrystallised to give pure compounds; see relevant section below.

Reaction 4/1

Benzyl chloride (1.49 g, 10 mmol) and aluminium chloride (5.34 g, 40 mmol) were refluxed in acetonitrile (60 ml) for 12 h according to general method III. Recrystallisation of the crude product from hexane gave as colourless crystals, 1.0 g (70%) *N*-benzylacetamide. M.p. 55-57°C (lit.,[69] 57°C).
^{1}H nmr ($CDCl_3$): 2.0 (3H, s, CH_3), 4.4 (2H, d, CH_2), 7.22 (5H, s, arom).
IR (cm^{-1}): 1680 (C=O), 3450 (NH).
Anal. calcd. for $C_9H_{11}NO$: C, 72.48; H, 7.38; N, 9.39. Found: C, 72.62; H, 7.48; N, 9.24.

Reaction 4/2

2,6-Dimethyl-4-*t*-butylbenzyl chloride (2.33 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) was reacted in acetonitrile (60 ml) at room temperature according to general method III. Recrystallisation of the crude product from acetone gave as colourless crystals, 1.8 g (80%) *N*-(2,6-dimethyl-4-*t*-butylphenylmethyl)acetamide.
M.p. 199-201°C (lit.,[65] 199-201°C).
^{1}H nmr ($CDCl_3$): 1.4 (9H, s, ^{t}Bu), 1.92 (3H, s, -CH_3), 2.4 (6H, s, 2 x CH_3), 4.44 (2H, d, CH_2), 7.04 (2H, s, arom).
IR (cm^{-1}): 3300 (NH), 1680 (C=O).
Anal. calcd. for $C_{15}H_{23}NO$: C, 77.05; H, 9.87; N, 6.00. Found: C, 76.86; H, 9.95; N, 5.87.

The same reaction was completed using aluminium chloride in place of ferric chloride, refluxing for 10 h. The acetamide was obtained in 84% yield.

Reaction 4/3

2-Methylbenzyl chloride (1.63 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III. Recrystallisation of the product from ethyl acetate/*n*-hexane/ 7:3, gave as colourless crystals 0.8 g (54%) of *N*-(2-methylbenzyl)acetamide.
M.p. 67-68^{0}C (lit.,[67] 68^{0}C).
^{1}H nmr ($CDCl_3$): 1.98 (3H, s, CH_3), 2.26 (3H, s, CH_3 arom), 4.4 (2H, d, CH_2), 7.2 (4H, s, arom).
IR (cm^{-1}): 1650 (C=O), 3300 (NH).
Anal. calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.66; H, 8.14; N, 8.45.

The yield was increased to 78% when the reaction was heated under reflux for 4 hours.

Reaction 4/4

4-Methylbenzyl chloride (1.63 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III. Recrystallisation of the product from cyclohexane gave as colourless crystals, 1.1 g (70%) of *N*-(4-methyl-benzyl)acetamide. M.p. 109-110.5^{0}C (lit.,[67] 110^{0}C).
^{1}H nmr ($CDCl_3$): 1.98 (3H, s, CH_3), 2.26 (3H, s, CH_3 arom), 4.26 (2H, d, CH_2), 7.1 (4H, s, arom).
IR (cm^{-1}): 1645 (C=O), 3400 (NH).
Anal. calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.82; H, 8.10; N, 8.34.

Reaction 4/5

3-Methylbenzyl chloride (1.63 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III to give as a colourless oil (after distillation), 0.75 g (46%) *N*-(3-methylbenzyl)acetamide.
B.p. 160-165^{0}C, 1 mm Hg (lit.,[71] 160-162^{0}C, 1 mm Hg).
^{1}H nmr ($CDCl_3$): 1.96 (3H, s, CH_3), 2.26 (3H, s, CH_3 arom), 4.2 (2H, d, CH_2), 7.0 (4H, m, arom).
IR (cm^{-1}): 1650 (C=O), 3300 (NH).

Anal. calcd. for $C_{10}H_{13}NO$: C, 73.61; H, 7.97; N, 8.58. Found: C, 73.58; H, 8.05; N, 8.47.

Reaction 4/6

2,4,6-Trimethylbenzyl chloride (1.91 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III. Recrystallisation of the product from xylene gave as colourless crystals, 1.3 g (71%) *N*-(2,4,6-trimethylbenzyl)acetamide.
M.p. 180-182°C (lit.,[72] 182°C).
^{1}H nmr ($CDCl_3$): 1.98 (3H, s, CH_3), 2.3 (9H, d, CH_3 arom x3), 4.4 (2H, d, CH_2), 6.9 (2H, s, arom).
IR (cm^{-1}): 1645 (C=O), 3350 (NH).
Anal. calcd. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 7.32. Found: C, 75.48; H, 8.98; N, 7.25.

Reaction 4/7

2,5-Dimethylbenzyl chloride (1.77 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III. Recrystallisation of the product from cyclohexane gave as colourless crystals, 1.3 g (78%) *N*-(2,5-dimethylbenzyl)-acetamide.
M.p. 81-82°C (lit.,[73] 82-83°C).
^{1}H nmr ($CDCl_3$): 1.98 (3H, s, CH_3), 2.2 (6H, s, CH_3 arom x2), 4.2 (2H, d, CH_2), 7.0 (3H, s, arom).
IR (cm^{-1}): 1640 (C=O), 3300 (NH).
Anal. calcd. for $C_{11}H_{15}NO$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.39; H, 8.66; N, 7.87.

The same substrate was treated under reflux for 1 h using tin(IV) chloride to give a 62% yield of the required amide.

Reaction 4/8

3,4-Dimethylbenzyl chloride (1.77 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III. Recrystallisation of the product from cyclohexane gave as yellow crystals, 1.2 g (69%) *N*-(3,4-dimethyl-benzyl)acetamide.

M.p. 71-73°C (lit.,[73] 73°C).
^{1}H nmr ($CDCl_3$): 1.88 (3H, s, CH_3), 2.2 (6H, s, CH_3 arom x2), 4.3 (2H, d, CH_2), 7.0 (3H, s, arom).
IR (cm^{-1}): 1650 (C=O), 3300 (NH).
Anal. calcd. for $C_{11}H_{15}NO$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.58; H, 8.53; N, 7.85.

Reaction 4/9

4-*t*-Butylbenzyl chloride (2.0 g, 10 mmol) and ferric chloride (6.4 g, 40 mmol) were reacted at room temperature according to method III. Recrystallisation of the product from cyclohexane gave as colourless crystals, 1.45 g (71%) *N*-(4-*t*-butylbenzyl)-acetamide.
M.p. 96-97°C.
^{1}H nmr ($CDCl_3$): 1.22 (9H, s, ^{t}Bu), 1.9 (3H, s, CH_3), 4.2 (2H, d, CH_2), 7.1-7.3 (4H, AA'BB', J~3.6 Hz, arom.).
IR (cm^{-1}): 1645 (C=O), 3350 (NH).
Anal. calcd. for $C_{13}H_{19}NO$: C, 76.09; H, 9.26; N, 6.82. Found: C, 76.06; H, 9.41; N, 6.82.

Reactions in Table 5

A solution of the substituted benzyl methyl ether (10 mmol) in acetonitrile (30 ml) was added slowly dropwise over 15 min to a stirred solution of catalyst, tin(IV) chloride (8.2 g, 40 mmol), in acetonitrile (30 ml). When the addition was complete, the mixture was heated under reflux for 6 h and then general method III was followed.

Reactions in Table 6

A solution of benzyl chloride (10 mmol) in acetonitrile (25 ml) was added slowly dropwise over 15 min to a stirred solution, at room temperature, of ferric chloride hexahydrate ($FeCl_3.6H_2O$) (10.8 g, 40 mmol) in acetonitrile (25 ml). When the addition was complete, the mixture was heated under reflux for the time indicated in Table 6. The mixture was then poured onto crushed ice (15 g) and 2N HCl (15 ml); diethyl ether (20 ml) was added to aid separation. The organic extracts were washed with 2N HCl (15 ml), water (15 ml), saturated

brine (15 ml), dried, filtered and the solvent removed under reduced pressure to give the acetamide products.

Reaction 6/1

Benzyl chloride (1.49 g, 10 mmol) and $FeCl_3.6H_2O$ (10.8 g, 40 mmol) were refluxed in acetonitrile for 16 h. Subsequent work-up followed by recrystallisation from hexane afforded as colourless crystals, 1.1 g (74%) of *N*-benzylacetamide, m.p. 55-57°C.

Reaction 6/2

2,6-Dimethyl-4-*t*-butylbenzyl chloride (2.33 g, 10 mmol) and $FeCl_3.6H_2O$ (10.8 g, 40 mmol) were refluxed in acetonitrile for 5 h. Subsequent work-up followed by recrystallisation from acetone afforded as colourless crystals, 2.2 g (98%) *N*-(2,6-dimethyl-4-*t*-butylphenylmethyl)acetamide, m.p. 199-201°C.

Reaction 6/3

2-Methylbenzyl chloride (1.63 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile for 6 h. Subsequent work-up followed by recrystallisation from ethyl acetate afforded as colourless crystals, 1.6 g (98%) of *N*-(2-methylbenzyl)acetamide, m.p. 66-68°C.

Reaction 6/4

4-Methylbenzyl chloride (1.63 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile (50 ml) for 6 h. Subsequent work-up followed by recrystallisation from cyclohexane afforded as colourless crystals, 1.56 g (96%) of *N*-(4-methylbenzyl)-acetamide, m.p. 109-110°C.

Reaction 6/5

3-Methylbenzyl chloride (1.63 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile (50 ml) for 12 h. Subsequent work-up followed by distillation afforded as a colourless oil, 1.5 g (92%) of *N*-(3-methylbenzyl)acetamide, b.p. 160-165°C, 1 mm Hg.

Reaction 6/6

2,4,6-Trimethylbenzyl chloride (1.91 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile (50 ml) for 5 h. Subsequent work-up followed by recrystallisation from xylene afforded as colourless crystals, 1.83 g (96%) of *N*-(2,4,6-trimethyl benzyl)acetamide, m.p. 180-182^{0}C.

Reaction 6/7

2,5-Dimethylbenzyl chloride (1.77 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile (50 ml) for 6 h. Subsequent work-up followed by recrystallisation from cyclohexane afforded as colourless crystals, 1.66 g (94%) of *N*-(2,5-dimethylbenzyl) acetamide, m.p. 81-82^{0}C.

Reaction 6/8

3,4-Dimethylbenzyl chloride (1.77 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile (50 ml) for 6 h. Subsequent work-up followed by recrystallisation from cyclohexane afforded as yellow crystals, 1.71 g (97%) of *N*-(3,4-dimethyl benzyl)acetamide, m.p. 71-73^{0}C.

Reaction 6/9

4-*t*-Butylbenzyl chloride (2.0 g, 10 mmol) and $FeCl_3.6H_2O$ (40 mmol) were refluxed in acetonitrile (50 ml) for 5 h. Subsequent work-up followed by recrystallisation from cyclohexane afforded as yellow crystals, 2.0 g (98%) of *N*-(4-*t*-butylbenzyl)acetamide, m.p. 96-97^{0}C.

Reactions in Table 7

A solution of benzyl methyl ether (10 mmol) in acetonitrile (25 ml) was added slowly dropwise over 15 min to a stirred solution, at room temperature, of ferric chloride hexahydrate ($FeCl_3.6H_2O$) (10.8 g, 40 mmol) in acetonitrile (25 ml). When the addition was complete, the mixture was heated under reflux for the times shown in Table 7. Work-up was as described for reactions in Table 6 and the corresponding amides were obtained in the yields as given in Table 7. All reaction products were identified by melting point and spectroscopic and analytical data.

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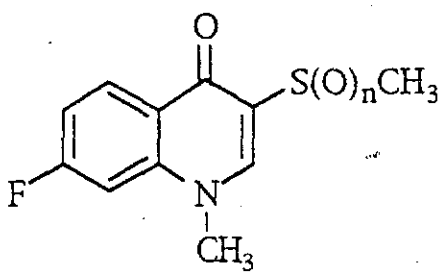
CHAPTER 2

Attempted New Synthetic Approaches to Flosequinan

2.1. INTRODUCTION

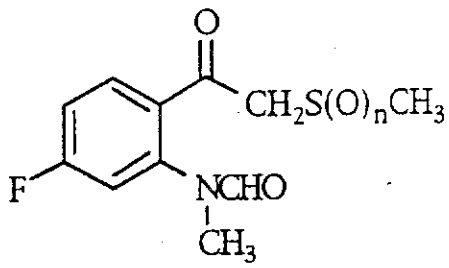
United Kingdom patent 20476911 contains a description of certain quinoline compounds having therapeutic activity as antihypertensive agents and also describes various processes for their manufacture. The same patent also claims that some of these quinoline compounds have therapeutic activity in the treatment of heart failure.

Quinolone compounds (1) in which n is 0, 1 or 2 are described in a PCT patent dated 1989.[2]



(1)

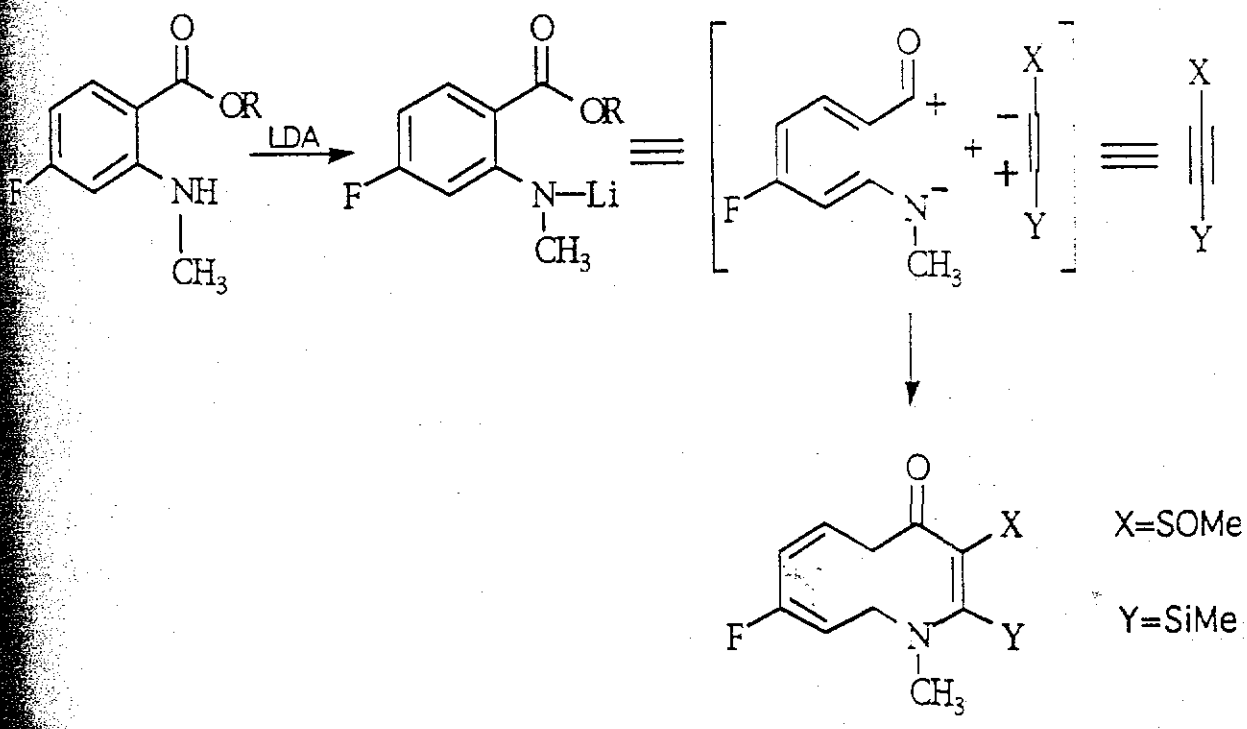
Compounds of formula (1) have valuable therapeutic activity in the treatment of cardiovascular diseases, especially in the treatment of hypertension and heart failure. A specific compound of formula (1) (n = 0) provided by a process according to the above-mentioned patents is 7-fluoro-1-methyl-3-methylthio-4-quinolone. This compound may be oxidised by known methods to give 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone (flosequinan) (1) (n = 1). Flosequinan has especially valuable therapeutic activity in the treatment of heart failure and hypertension. The PCT patent, describes a process for the preparation (1) (n = 0, 1 or 2) comprising the cyclisation of compounds of formula (2).



(2)

The synthesis of flosequinan via the cyclisation of compound (2) involves more than six steps from the starting material which is a relatively long route to the target molecule. A theoretical, alternative, method could comprise an intramolecular 1,4-dipolar cycloaddition reaction which would reduce the amount of steps required to synthesise flosequinan. This strategy for the synthesis of flosequinan is illustrated in Scheme 1.

Scheme 1

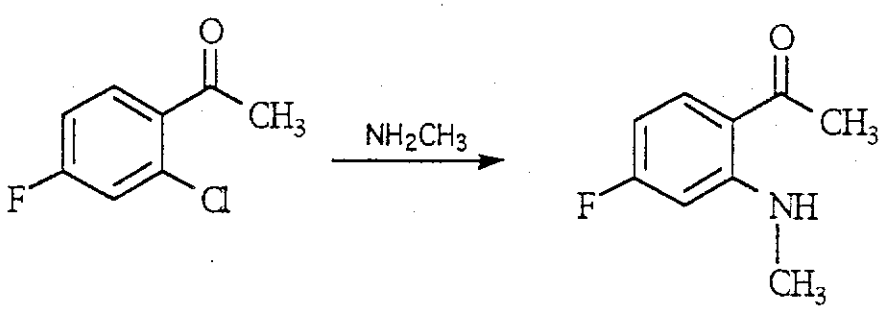


Thus the synthesis of flosequinan was attempted using this new method, namely a 1,4-dipolar cycloaddition reaction.

2.2. Literature Approaches to Flosequinan

We could not find any details about flosequinan in the literature, apart from the two patents mentioned above. Both of these studies show the same method for the synthesis of flosequinan. First, 2-chloro-4-fluoroacetophenone (3) was chosen as the starting material for the target molecule (1). Starting material (3) was reacted by heating with methylamine in a sealed vessel in the presence of copper powder catalyst to give 4-fluoro-2-(methylamino)acetophenone (4) in the first step of this synthesis (*Scheme 2*).

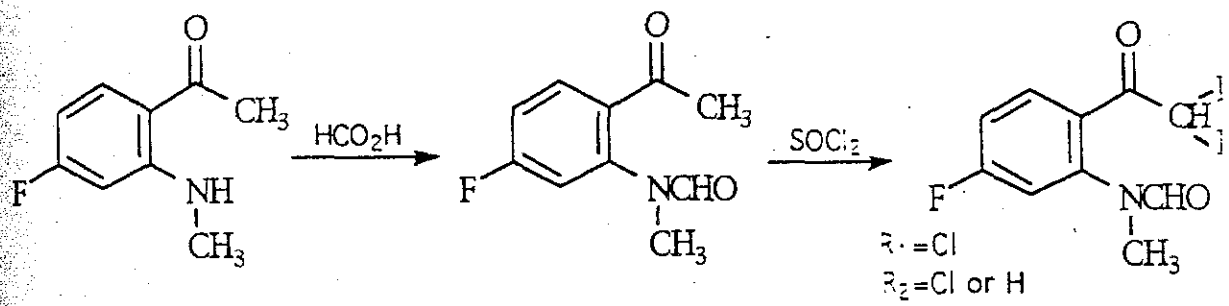
Scheme 2



(3) (4)

The compound of formula (4) (4'-fluoro-2'-(methylamino)-acetophenone) was formylated by reaction with formic acid and acetic anhydride under a nitrogen atmosphere for two hours. Then, formylated compound (5) was reacted with the halogenating reagent, thionyl chloride, followed by sodium hydroxide to give chlorinated compounds 2-chloroacetyl-5-fluoro-*N*-methyl-formanilide and 2-dichloroacetyl-5-fluoro-*N*-methyl-formanilide (6) in the form of a red/brown oil (Scheme 3).

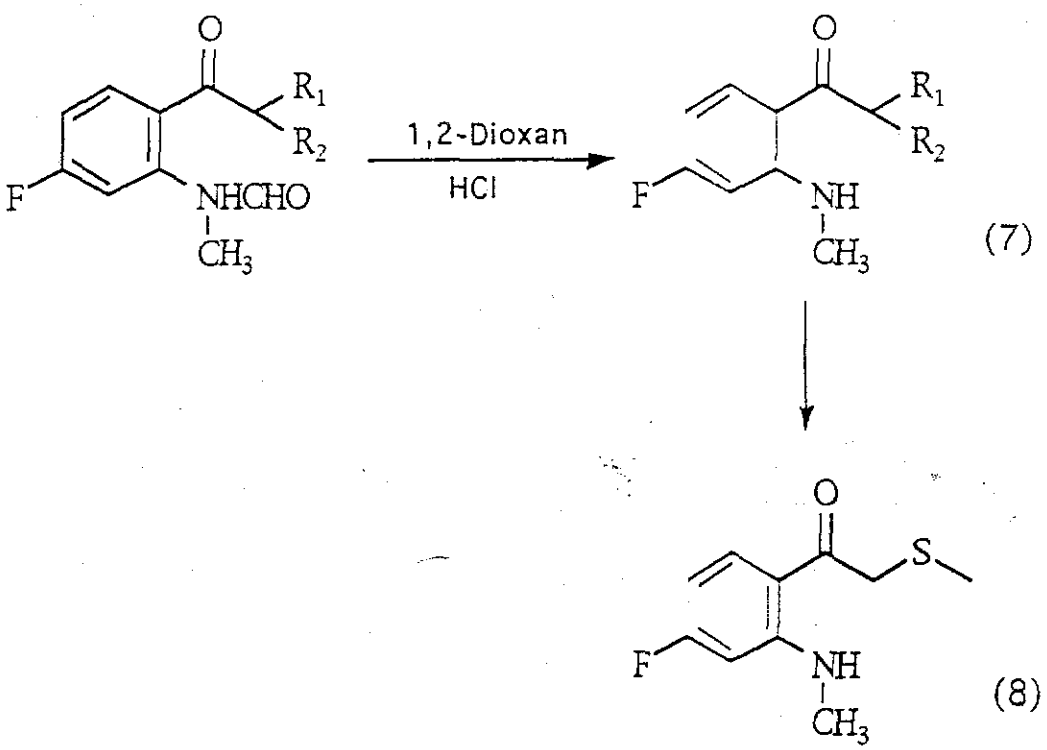
Scheme 3



(4) (5) (6)

The halogenated mixture of compounds (6) was deformylated to *N*-methylamine compound (7) and the crucial reaction of methylthiolation was carried out in methanolic sodium methanethiolate solution at 0°C to give 1-(4-fluoro-2-methylaminophenyl)-2-(methylthio)ethanone (8), m.p. 63.5-64.5°C (Scheme 4).[2]

Scheme 4

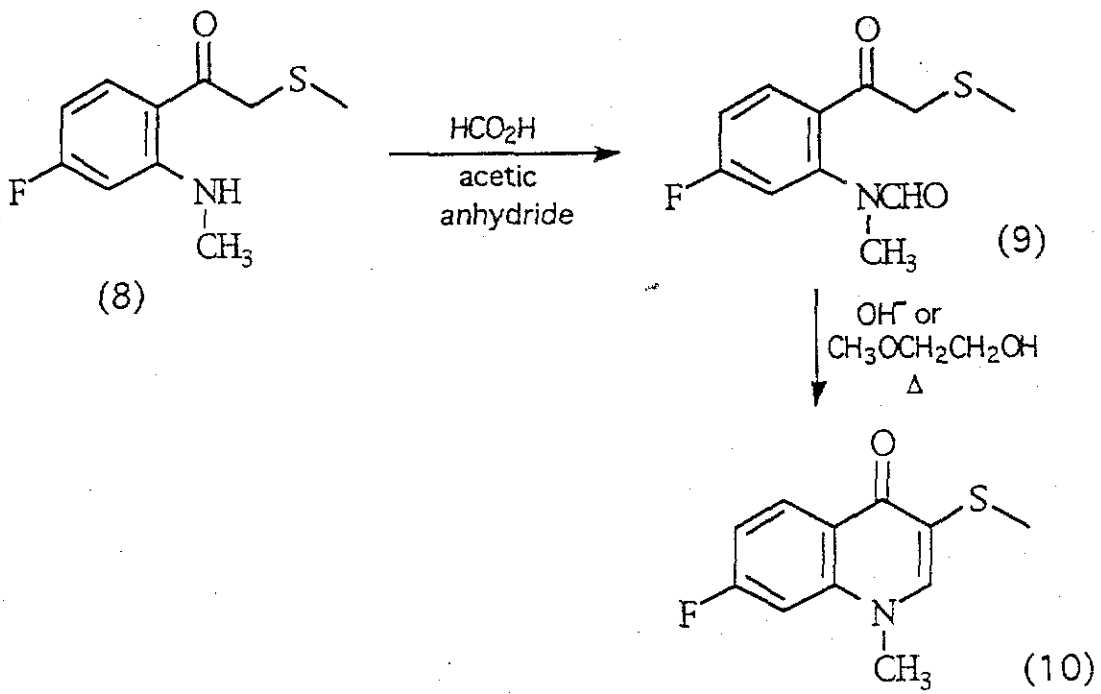


(7)

(8)

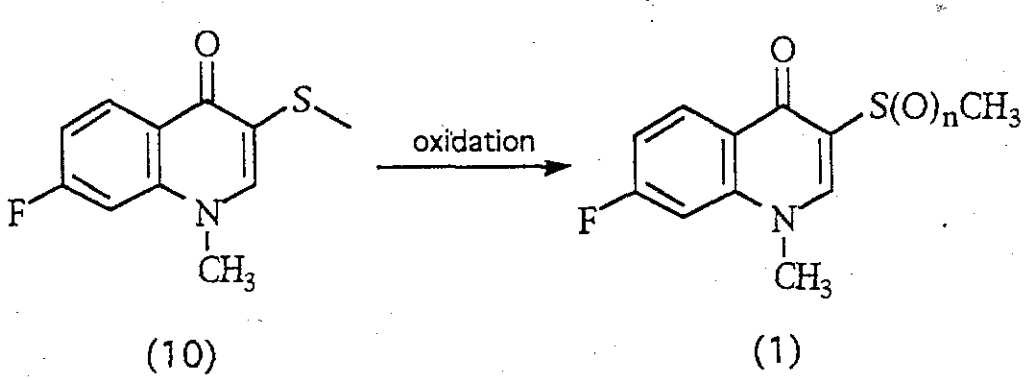
The compound (8) was reformylated to 5'-fluoro-*N*-methyl-2'-(methylthio)acetylformanilide (9) with formic acid in acetic anhydride and then another crucial reaction, that of cyclisation was carried out in refluxing 2-methoxyethanol for 6 days to give 7-fluoro-1-methyl-3-methylthio-4-quinolone (10) (Scheme 5).[2] This cyclisation reaction was also done by the same scientists using aqueous sodium hydroxide solution.

Scheme 5



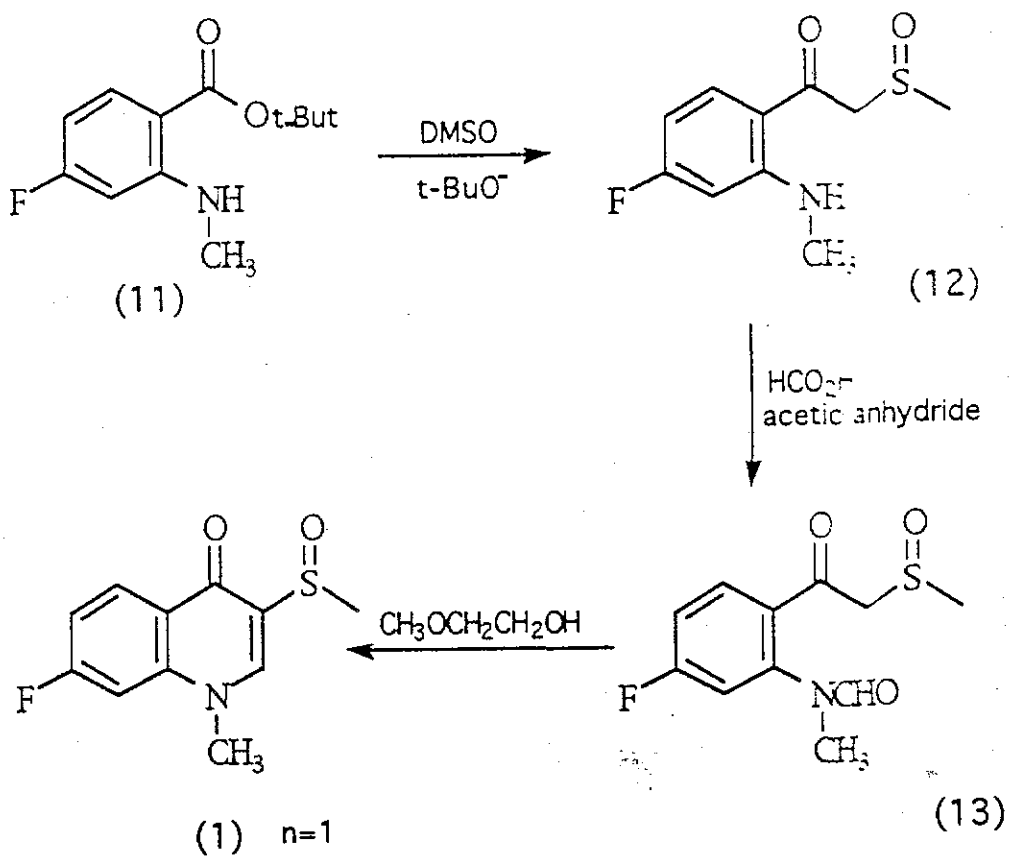
In the last step, quinolone was oxidised with 3-chloroperoxybenzoic acid to give the corresponding sulphur-oxidised quinolone compound; n=1, 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone (flosequinan) m.p. 234-236^{0}C (1) (Scheme 6).[2]

Scheme 6



The same publication also describes some different methods for the synthesis of quinolone compounds.[2] In these reactions, derivatives of *N*-methyl anthranilate are used as starting materials. For example, *t*-butyl 4-fluoro-2-(methylamino)-benzoate (11) in dimethyl sulphoxide was treated with a solution of potassium *t*-butoxide in dimethyl sulphoxide at ambient temperature to give 1-(4-fluoro-2-methylaminophenyl)-2-methylsulphinylethanone (12). Then, this *N*-methyl compound (12) was formylated with formic acid in acetic anhydride to give 5-fluoro-*N*-methyl-2-methylsulphinylacetylformanilide (13). At the cyclisation step, compound (13) was refluxed in 2-methoxyethanol for 45 minutes to obtain 7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone, (n=1) (flosequinan) (Scheme 7).[2]

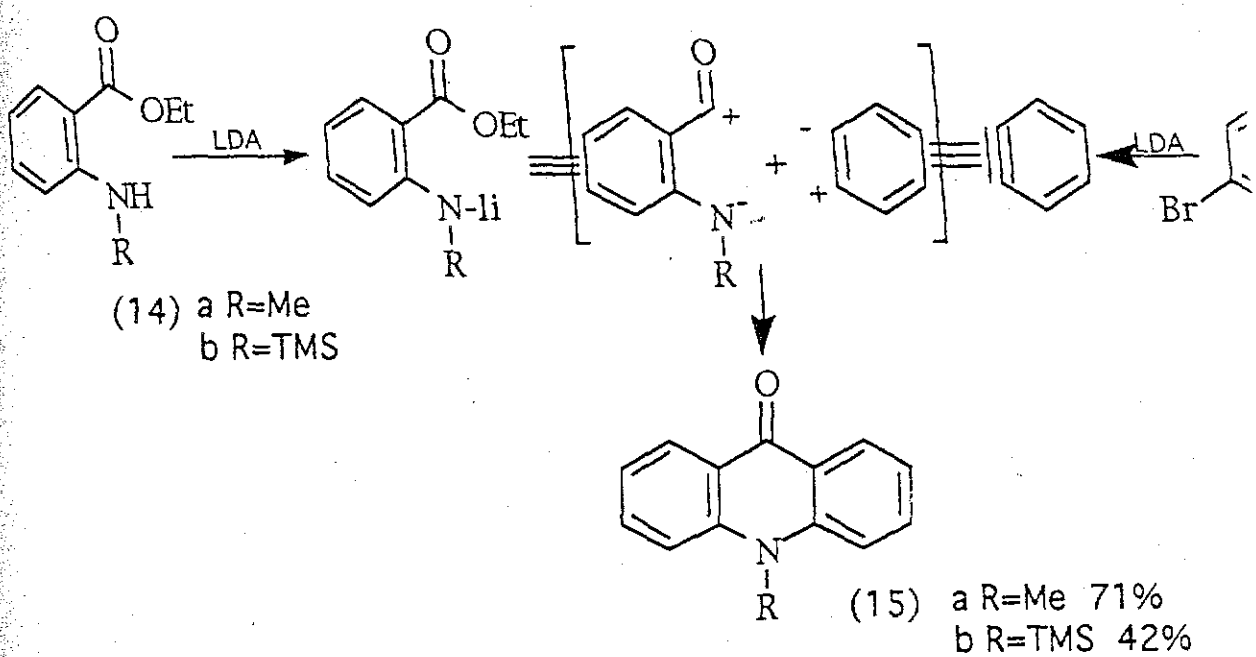
Scheme 7



The cyclisation reaction of compound (13) was also studied under different conditions, such as in an organic or inorganic base (triethylamine, sodium ethoxide or sodium hydroxide). Simply heating compound (13) in a suitable solvent such as isopropyl alcohol or 1-octanol apparently gave the "same" yield in all reactions, but the yield was not mentioned in this study.[2]

On the other hand, a 1990 literature study reveals a novel approach to the synthesis of acridones (15) which is very closely related to quinolone synthesis.[3] In this study, *N*-lithiated anthranilates (14) were used as 1,4-dipole equivalents in 1,4-dipole-aryne cycloaddition reactions under mild conditions to yield acridones (15) (Scheme 8). The key feature of this strategy,

Scheme 8



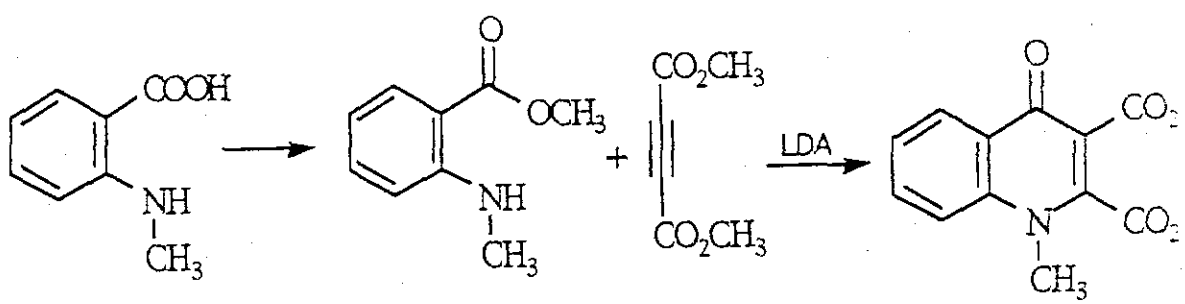
which is outlined in Scheme 8, involves the simultaneous formation of nitrogen-carbon and carbon-carbon bonds.

It was considered of interest to investigate whether the above general strategy could be adapted to a new synthetic approach to flosequinan (1). In this study we attempted to apply a 1,4-dipolar-alkyne cycloaddition reaction instead of 1,4-dipolar-aryne cycloaddition. A fluoro-substituted methyl *N*-

2.3. Results and Discussion

In a preliminary study, the 1,4-dipolar cycloaddition reaction was examined using methyl *N*-methylanthranilate (17) with dimethyl acetylenedicarboxylate (18) (DMAD). In the first step, *N*-methylanthranilic acid (16) was esterified using boron trifluoride dimethyl etherate solution ($BF_3.Me_2O$) in methanol to give methyl *N*-methylanthranilate (17) in 78% yield.[4] At the cyclisation step, anthranilate (17) was reacted with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C and the solution was warmed to -20°C over 1 hour to yield an orange solution of the anion. The solution was then cooled to -40°C and DMAD was added rapidly. After being kept at -40°C for 10 minutes the resulting solution was warmed to room temperature and quenched with aqueous saturated ammonium chloride solution. After extraction with diethyl ether, the dried solution was purified by column chromatography to give 1-methyl-2,3-dimethoxycarbonyl-4-quinolone (19) in 36% yield (Scheme 10).

Scheme 10



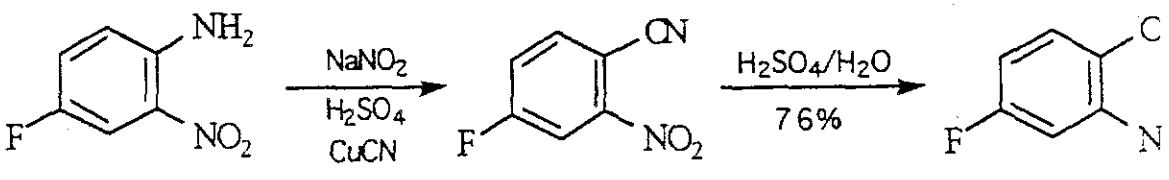
(16) (17) (18) (19)

2.3.1. The Preparation of Methyl 4-Fluoro-*N*-Methylanthranilate (26)

For the cyclisation reaction, methyl 4-fluoro-*N*-methylanthranilate (26) is the appropriate intermediate for the 1,4-dipole synthon in the projected flosequinan synthesis. Hence, 4-fluoro-2-nitroaniline (20), which is readily prepared from florobenzene[5] or 4-chloronitrobenzene,[6] was chosen as our starting material. In the first step, diazotisation of compound (20) with sulphuric acid/sodium nitrite and decomposition of the diazonium salt by the addition of a solution of cuprous cyanide at 80-90°C, resulted in a mixture

which was separated by distillation to obtain the desired nitrile, in 72% yield. Hydrolysis of nitrile (21) to the desired product, 4-fluoro-2-nitrobenzoic acid (22), was carried out with dilute sulphuric acid and after recrystallisation, colourless crystals of 4-fluoro-2-nitrobenzonitrile (21) were obtained in high yield (76%) (Scheme 11).[7]

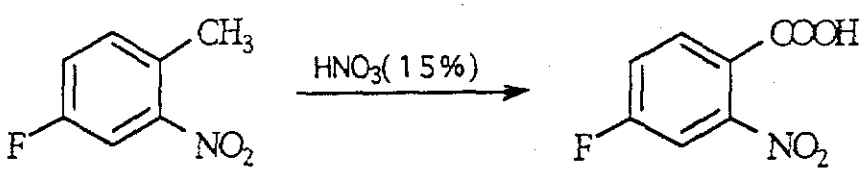
Scheme 11



(20) (21) (22)

4-Fluoro-2-nitrobenzoic acid (22) was also obtained by oxidation of a toluene. In this study, 4-fluoro-2-nitrotoluene (23) and nitric acid (15%) were heated in an autoclave over 1.5 hours at 180-190°C. After continuation of heating at 210°C for 4 hours the crude product was crystallised from methanol-water to give 4-fluoro-2-nitrobenzoic acid (22) in 22% yield (Scheme12).[8]

Scheme 12

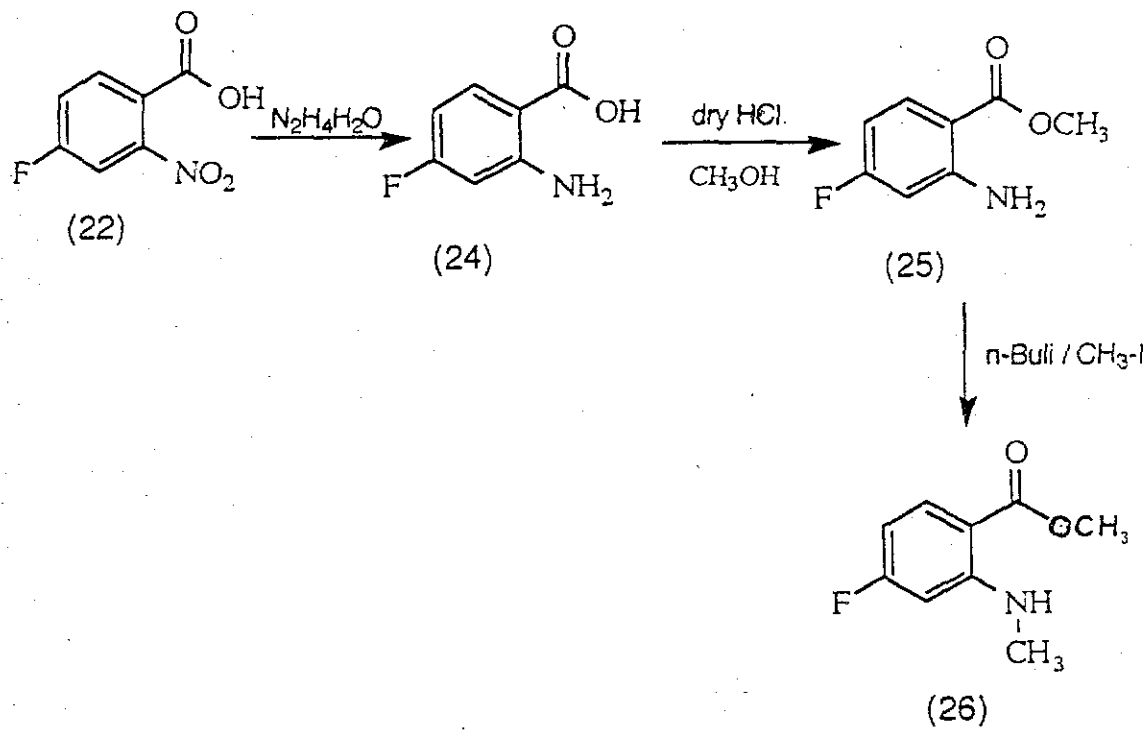


(23) (22)

The next step was the transformation of acid (22) to 4-fluoroanthanilic acid (24) by reduction (which can be carried out by various methods, e.g., catalytic hydrogenation over palladium or reduction with ferrous sulphate in aqueous ammonia). In our case the nitro group of (22) was reduced with hydrazine hydrate in boiling ethanol in the presence of ferric chloride and active carbon to furnish the amine (24) in good yield (88%) (Scheme 13).[9]

The anthranilic acid (24) was then esterified to anthranilate (25) in 88% yield using dry hydrochloric acid in excess methanol.[10] This esterification reaction was also carried out using boron trifluoride-dimethyl etherate solution in methanol, but the yield (72%) was slightly lower than that obtained by the above-mentioned procedure. Compound (26) was prepared via metallation of methyl anthranilate (25) using 1.1 equivalents of *n*-butyllithium in THF at -78°C. After the solution was warmed to 0°C, it was quenched with methyl iodide and the THF was removed under vacuum. Pure methyl 4-fluoro-*N*-methyl anthranilate (26) was obtained by column chromatography(dichloromethane)in78%yield(Scheme13).[11]

Scheme 13



(22) (24) (25) (26)

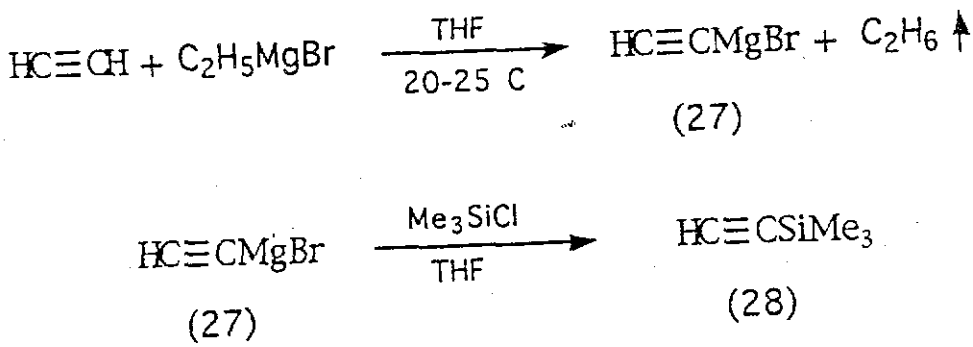
2.3.2 The Preparation of Acetylenic Sulphoxides/Sulphones (30)/(31)and (34) and Attempts at1,4-Dipolar Cycloaddition Reaction

One of the most versatile methods for the synthesis of derivatives of acetylenic compounds consists in deprotonation of the starting acetylene and consequent reaction of the anionic or organometallic intermediate with an electrophilic reagent.

Brandsma *et al.*, carried out the synthesis of trimethylsilyl-acetylene (28) with a Grignard reagent (C_2H_5MgBr),[12] and his procedure was followed in the

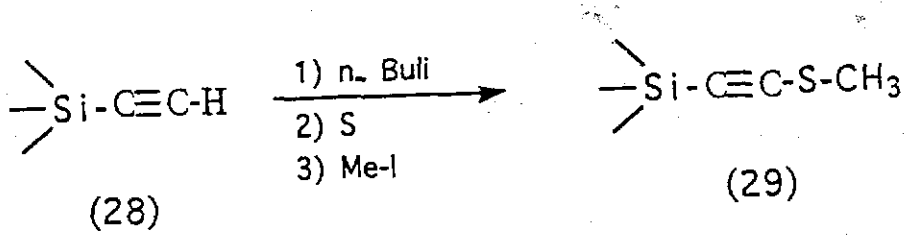
present study. In this reaction, the prepared solution of ethylmagnesium bromide in THF was treated with acetylene gas at 25°C to obtain ethynylmagnesium bromide (27).[13] The cooled solution was then treated with trimethylchlorosilane in THF at -5°C for 6 hours and after the work-up the resulting crude product was distilled through a 40 cm Vigreux column to give trimethylsilyacetylene (28) in 78% yield (Scheme 14). The IR spectrum of the trimethylsilylacetylene showed a strong band at 2180 cm^{-1} for the acetylenic C≡C stretching frequency and another at 3300 cm^{-1} for acetylenic C-H stretching.

Scheme 14



The ethynyl sulphide (29) was then prepared in one step from compound (28). Firstly, trimethylsilylacetylene was reacted with *n*-butyllithium at -78°C. After stirring for 30 minutes at this temperature sulphur was added portionwise and the reaction was allowed to warm to room temperature over 1 hour. Again, the mixture was cooled and reacted with iodomethane to give the alkyne (29) in 59% overall yield after two vacuum distillations (Scheme 15).[14]

Scheme 15

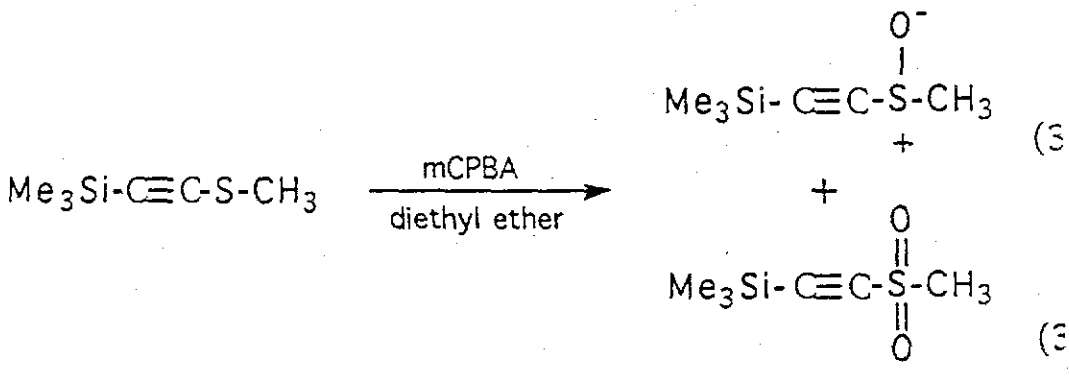


The IR spectrum of compound (29) showed a strong characteristic band at 2070 cm^{-1} for acetylenic C≡C stretching. Microanalysis of the sulphur compound was unsuccessful as it did not burn completely in the oxygen

flask. Full details of spectroscopic and analytical data are given in the experimental section.

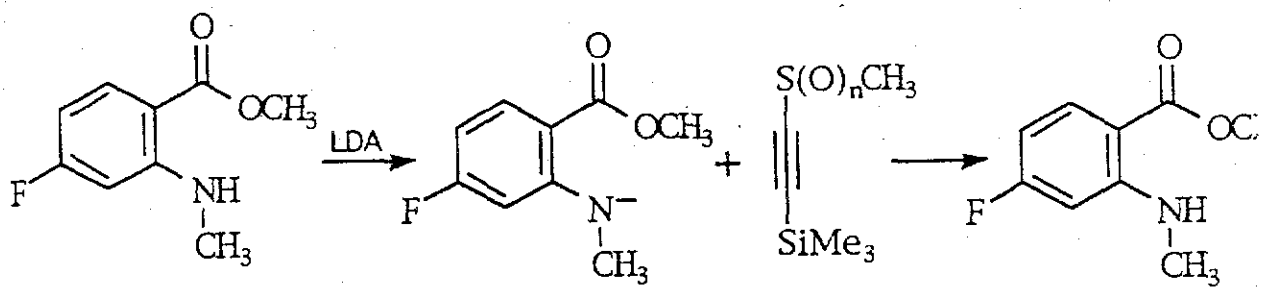
The oxidation reaction of the sulphide (29) was carried out with 3-chloroperbenzoic acid. In this reaction, 1.1 equivalents of oxidising agent (MCPBA) were used for each mole of sulphide compound. After 1 hour of stirring in petroleum ether, a colourless oil was obtained which was unstable above 20°C. This was identified as a mixture of methyl trimethylsilylethynyl sulphoxide (30) and methyl trimethylsilylethynyl sulphone (31) (Scheme 16). The mixture of novel compounds (30) and (31) could not be separated by either column chromatography or by distillation. The IR spectrum showed two bands at 2040 cm^{-1} and 2140 cm^{-1} which are characteristic of the acetylenic C≡C stretching frequency. Also found were the sulphoxide and sulphone bands at 1330 cm^{-1}, 1150 cm^{-1} ($-SO_2-$) and 1060 cm^{-1} (-SO-).

Scheme 16



In the last step - the 1,4-dipolar cycloaddition reaction - methyl anthranilate (26) was reacted with LDA and the anion thus produced was treated with the mixture of sulphoxide (30) and sulphone (31) solution in THF as described in the experimental section.[3] After work-up, methyl 4-fluoro-*N*-methylanthranilate was recovered (80%) (Scheme 17). At the second attempt, the reaction time was extended from 10 minutes to 1 hour, but again the starting material (26) was recovered in high yield.

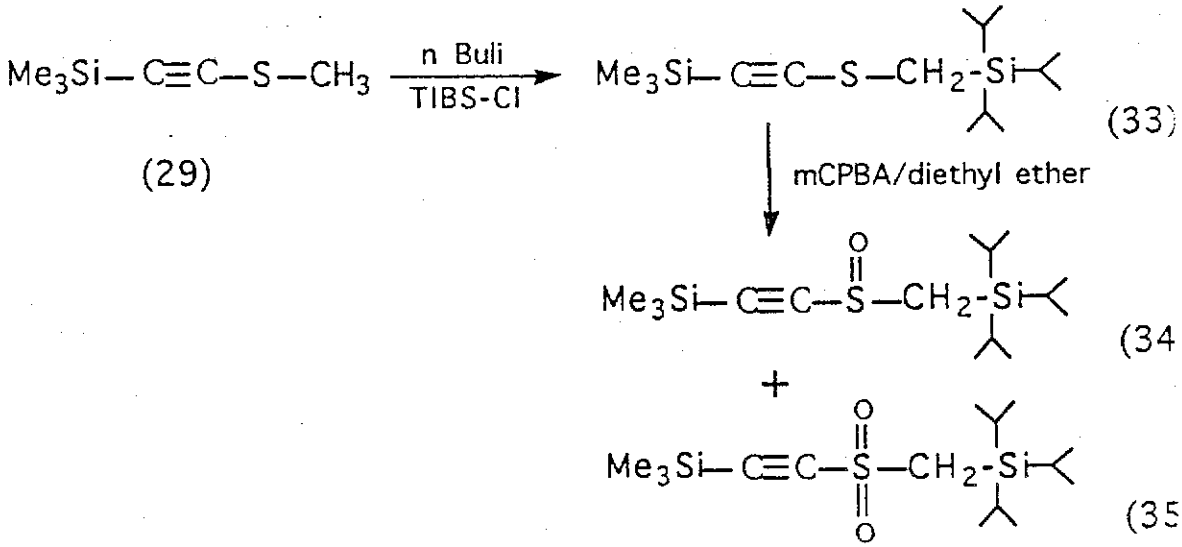
Scheme 17



The key step of this reaction is the production of the anion by LDA. This step was carried out at -78°C followed by warming to -20°C over 1 hour. During this procedure an orange colour developed in the solution, indicative of the presence of the required anion. Theoretically, in the next step this anion might attack the acetylenic carbon atom in Michael fashion to furnish the cyclised product but possibly the anion (32) attacks the methyl group attached to the sulphoxide or sulphonic group (30 + 31) instead and hence the starting material (26) is recovered. On this point we can say that the methyl sulphonic hydrogen atom is more acidic than the acetylenic hydrogen atom. From this idea, we attempted to protect the methyl group on the sulphide compound (29) using triisobutylsilyl chloride.

For further investigation, methyl trimethylsilylethynylsulphide (29) was reacted with triisobutylsilyl chloride using butyllithium in THF. The colourless oil obtained was purified by distillation and triisobutylsilylmethyltrimethylsilylethynylsulphide (33) was obtained in 68% yield (Scheme 18).[15]

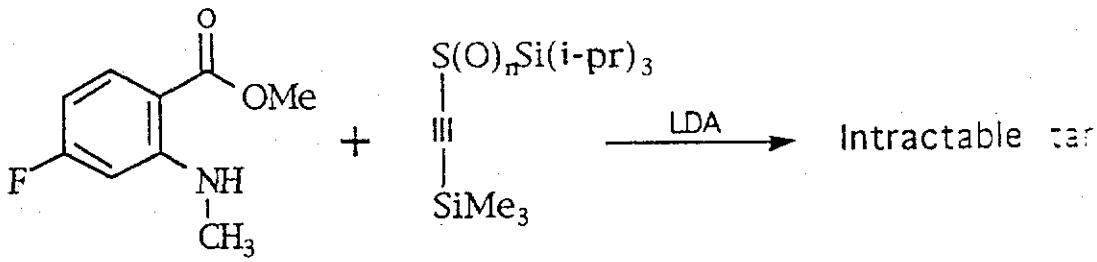
Scheme 18



Oxidation of sulphide (33) was carried out with 3-chloroperbenzoic acid according to the previously described procedure.[16] Again, after the reaction two oxidised products, triisobutylsilylmethyl-trimethylsilylethynylsulphoxide (34) and triisobutylsilylmethyl-trimethylsilylethynylsulphone (35) were obtained in good yield (85%). Separation of these two products was achieved by microdistillation (Cuburol) which showed the ratio of sulphoxide (34) to sulphone (35) to be 65:35. The spectroscopic results and microanalysis data are shown in the experimental section.

Compound (34) was reacted with anthranilate (26) using LDA in THF according to the procedure described by Biehl for the synthesis of acridones.[3] However, during the reaction, black tar was formed after addition of the acetylenic compound (Scheme 19). In another attempt, the acetylenic sulphone (35) was reacted with anthranilate (26) under the same reaction conditions. But again an intractable black tar was obtained which could not be identified (Scheme 19).

Scheme 19



In the original literature procedure,[3] the formation of the anion was carried out at -78°C using LDA, and then the reaction mixture was warmed to -20°C. The 1,4-cycloaddition step was done at -40°C and after 30 minutes the reaction mixture was allowed to warm to room temperature. We also tried the addition step at -78°C in the specific reaction with anthranilate (28) and acetylenic sulphoxide (34). But all attempts failed, and intractable black tar was obtained which could not be identified. IR spectroscopy showed two bands at 2040 cm^{-1} and 2140 cm^{-1} which is characteristic of acetylenic C≡C bond stretching, and certain sulphoxide and sulphone bands at 1330, 1150 ($-SO_2-$), and 1060 cm^{-1} (-SO-).

Methyl *N*-methylanthranilate (17)

N-Methylanthranilic acid (16) (1.2 g, 7.9 mmol) was heated under reflux for 8 h with boron trifluoride dimethyl etherate (2.2 g, 16 mmol) reagent in excess of dry methanol (12 ml). After cooling, the mixture was poured into saturated sodium hydrogen carbonate solution and the resulting solution extracted with diethyl ether (3 x 20 ml). The ether extracts were dried (magnesium sulphate) and the solvent was evaporated under vacuum. The crude product was purified by column chromatography (dichloromethane) to give 1.0 g (78%) of methyl *N*-methylanthranilate (17) as yellow crystals, m.p 19-21°C (lit.,[20] 19°C).

n_{max}(nujol mull) 1685 (C=O) and 3365 cm^{-1} (-NHMe);

d^1H ($CDCl_3$) 2.8 (3H, d, J = 4.8 Hz, NCH_3), 3.8 (3H, s, OMe), 6.6 (2H, m, arom.,), 7.3 (1H, m, arom.,), 7.6 (1H, br, NH), 7.9 (1H, m, arom.,);

Anal. calcd for $C_9H_{11}NO_2$: C, 65.45, H,6.66, N, 8.48. Found: C, 65.42, H, 6.76, N, 8.71.

1-Methyl-2,3-dimethoxycarbonyl-4-quinolone (19)

Preparation of LDA (lithium diisopropylamide): n-butyllithium in hexane (1.6 M) (7.14 ml, 11 mmol) was added with stirring to diisopropylamine (1.01 g, 10 mmol) under nitrogen at -10°C. After 20 min dry THF (20 ml) was added to this mixture and the solution was warmed to 0°C. After 10 min the LDA solution was ready.

The prepared LDA (10 mmol in 30 ml THF) solution was added dropwise over 10 min to a solution of methyl *N*-methylanthranilate (17) (10 mmol) in THF (30 ml) under nitrogen at -78°C. The solution was warmed to -20°C over 1 h to yield an orange solution of the anion. The anionic solution was then cooled to -40°C and DMAD (18) (2.13 g, 15 mmol) in THF (30 ml) was added rapidly. The resulting solution was kept at -40°C for 10 min, and then allowed to warm to room temperature. It was quenched with aqueous saturated ammonium chloride solution. The resulting mixture was extracted with diethyl ether (3 x 20 ml) and the organic phase was dried (magnesium sulphate), filtered and evaporated under reduced pressure to give a brown coloured residue which was purified by column chromatography (silica gel:

dichloromethane) to give 1.0 g (36%) of 1-methyl-2,3-dimethoxycarbonyl-4-quinolone (19) as yellow crystals, m.p. 127-129°C;
n_{max}(nujol mull) 1700, 1720, 1730 cm^{-1} (C=O);
d^{1}H (d_6-DMSO) 3.6 (3H, s, NCH_3), 3.8 (3H, s, OMe), 3.9 (3H, s, OMe), 7.4 (3H, m, arom.,), 8.2 (1H, m, arom.,);
Anal. calcd for $C_{14}H_{13}NO_5$: C, 61.09, H, 4.72, N, 5.09. Found: C, 60.76, H, 4.70, N, 4.92.

4-Fluoro-2-nitrobenzonitrile (21)

Stirred sulphuric acid (19 g) was treated over 1 h at 5-10°C with sodium nitrite (1.6 g, 18 mmol),then the mixture was slowly heated to 70°C and the nitrosylsulphuric acid solution thus obtained was finally cooled to 10°C. It was then treated whilst stirring over 1 h with a solution of 4-fluoro-2-nitroaniline (3.0 g, 21 mmol) in acetic acid (18.6 g) at 15-20°C. The mixture was stirred at this temperature for 3 h then added over 30 min under stirring to a solution of copper(I)cyanide (2.24 g, 25 mmol) in water (40 ml) at 60°C. With the copious evolution of nitrogen gas the temperature rose spontaneously to 75°C. After the cessation of the exothermic reaction the mixture was heated to 85-90°C and maintained at that temperature for 30 min. After cooling to 20°C the solid product was collected by filtration and washed with water. It was then dissolved at 70°C in benzene (25 ml) and any undissolved material was removed by filtration. The filtrate was dried with magnesium sulphate and evaporated to give crude product, which after crystallisation from a mixture of benzene and petroleum ether (b.p. 40-60°C), gave 2.5 g (72%) of 4-fluoro-2-nitrobenzonitrile (21) as yellow needles, m.p. 67-69°C (lit.,[7] 69-70°C);
n_{max}(nujol mull) (cm^{-1}): 1350, 1545 ($ArNO_2$), 1490, 3060 (Ar) and 2220 (ArCN);
d^{1}H ($CDCl_3$) 7.4-8.2 (3H, m, arom.,);
Anal. calcd for $C_7H_3FN_2O_2$: C, 50.61, H, 1.82, N, 16.87; F, 11.44. Found: C, 50.67, H, 1.72, N, 16.86; F, 11.58.

4-Fluoro-2-nitrobenzoic acid (22)

4-Fluoro-2-nitrobenzonitrile (21) (2.5 g, 15 mmol) was added to a mixture of water (13 ml) and sulphuric acid (28 g) and the mixture was stirred and heated to 95-100°C for 6 h. The brownish solution which formed was

allowed to stand overnight at room temperature. The precipitated impurities were removed by filtration and then washed with 70% sulphuric acid (2 ml). The combined filtrates were stirred and treated over 60 min at 25°C with a solution of sodium nitrite (2.3 g) in 3.3 ml of water. The mixture was stirred for 30 min at this temperature and then heated for 4 h in a boiling water bath. Nitrogen was formed and the product precipitated. After standing overnight at 4°C the mixture was filtered and the solid thus collected was washed with ice-cold water. It was then dissolved in a solution of ammonium hydroxide (3 ml) in water (8 ml) and the solution was heated with active carbon to 50°C and filtered. Acidification of the filtrate with hydrochloric acid (4 ml) and crystallisation for 12 h at 4°C gave 2.1 g (76%)of 4-fluoro-2-nitrobenzoic acid (22) as colourless crystals, m.p. 144-145°C (lit.,[16] 140-142°C);
n_{max}(nujol mull) (cm^{-1}): 1340, 1535 ($ArNO_2$), 1720 (C=O) and 3340 (OH);
d^{1}H ($CDCl_3$) 7.2-7.4 (2H, m, arom.,), 7.8-7.9 (1H, m, arom.,);
Anal. calcd for $C_7H_4FNO_4$: C, 45.40, H, 2.16, N, 7.56; F, 10.27. Found: C, 45.32, H, 2.24, N, 7.33; F, 10.49.

4-Fluoro-2-nitrobenzoic acid (22) by oxidation of toluene

4-Fluoro-2-nitrotoluene (23) (5 g, 32 mmol) and 15% nitric acid (27.5 ml) were heated in a glass vessel in an autoclave during 1.5 h to 180-190°C. Heating was continued at that temperature for a further 4 h. On cooling the acid separated. It was collected by filtration and washed with cold water until the washings were colourless and then dried. Recrystallisation from 1:1 water-methanol gave 1.3 g (22%) of 4-fluoro-2-nitrobenzoic acid (22)[8] as yellow crystals, m.p. 140-141°C. The spectroscopic and analytical results are the same as for the above acid (22).

4-Fluoroanthranilic acid (24)

A suspension of 4-fluoro-2-nitrobenzoic acid (22) (3.3 g, 18 mmol) in ethanol (17 ml) was stirred and treated with 80% hydrazine hydrate (2.3 g), active carbon (0.3 g) and a solution of ferric chloride hexahydrate (0.08 g) in 0.75 ml of ethanol and the mixture was refluxed for 10 h. After cooling the ethanol was evaporated under reduced pressure and the cooled residue was treated with 20% sodium hydroxide (13 ml), water (34 ml) and active carbon (0.3 g). This mixture was stirred and heated to 70-75°C, filtered at 50°C ; and the filtrate was cooled to 20°C. Under external cooling and stirring it

was then treated over 10 min with acetic acid (5.8 g). The suspension of the product formed was stirred for 2 h under cooling (0°C),then the product was collected by filtration , washed with ice-cold water and dried. After crystallisation from water 2.51 g (88%) of 4-fluoroanthranilic acid (24) was obtained as colourless crystals, m.p. 194-196°C (lit.,[17] 192.5-193°C);
n_{max}(nujol mull) (cm^{-1}): 1720 (C=O) and 3300 (OH, NH_2);
d^{1}H ($CDCl_3$) 6.4-6.8 (2H, m, arom.), 7.8 (1H, t, J=7.8 Hz, arom.), 8.4 (2H, br, NH_2);
Anal. calcd for $C_7H_6FNO_2$: C, 54.19, H, 3.87, N, 9.03. Found: C, 54.30, H, 3.76, N, 9.00.

Methyl 4-fluoro-2-aminobenzoate (25)

A solution of 4-fluoroanthranilic acid (24) (2.2 g, 14 mmol) in absolute methanol (50 ml, excess) was saturated with dry hydrogen chloride and refluxed overnight. Excess methanol was evaporated under reduced pressure and the mixture made alkaline with dilute (20%) sodium hydroxide and extracted with diethyl ether(3C20 ml). The organic layer was dried over potassium carbonate and subsequently removed under vacuum. The crude product was purified by column chromatography (silica gel: dichloromethane) to give 2.1 g (88%) of methyl 4-fluoroanthranilate (25) as yellow crystals, m.p. 60-62°C (lit.,[13] 60-61°C);
n_{max}(nujol mull) (cm^{-1}): 1720 (C=O) and 3400 (NH_2);
d^{1}H ($CDCl_3$) 3.8 (3H, s, OMe), 5.8 (2H, br, NH_2), 6.2-6.4 (2H. m, arom.,), 7.8 (1H, m, arom.,), ;
Anal. calcd for $C_8H_8FNO_2$: C, 56.80, H, 4.73, N, 8.28, F. 11.25. Found: C, 57.03, H, 4.63, N, 8.09, F, 11.62.

Methyl 4-fluoro-2-methylaminobenzoate (26)

A solution of the methyl anthranilate (25) (1.9 g, 11.2 mmol) in THF (34 ml) was cooled to -78°C and 1.1 equivalents of n-butyllithium (7.7 ml, 12.3 mmol) were added slowly. After standing at that temperature(1 h) the solution was warmed to 0°C over 1 hour. Almost 2 h later the solution was cooled to -78°C and then a solution of iodomethane (1.5 g, 11.2 mmol) in THF (30 ml) was added. After 30 minu the mixture was allowed to warm to room temperature and the solvent was removed by distillation under reduced pressure. The sticky product thus obtained was washed with water

and extracted with diethyl ether(3*ml). The extract was dried over magnesium sulphate, evaporated and the crude product purified by column chromatography (silica gel: dichloromethane).This gave 1.6 g (78%) 4-fluoro-2-methylamino methylbenzoate (26) as colourless crystals, m.p. 140-141^{0}C (lit.,[19] 140-142^{0}C);

ν_{max}(nujol mull) (cm^{-1}): 1750 (C=O) and 3350 (NH);

d^{1}H ($CDCl_3$) 2.8 (3H, d, J=4.8 Hz , NMe), 3.8 (3H, s, OMe), 6.3 (2H, m, arom.,), 7.6 (1H, br, NH), 7.8 (1H, m, arom.,);

Anal. calcd for $C_9H_{10}FNO_2$: C, 59.01, H, 5.46, N, 7.65, F, 10.38. Found: C, 59.23, H, 5.44, N, 7.39, F, 10.61.

Trimethylsilylacetylene (28)

A solution of ethylmagnesium bromide (2.0M) in THF (16.5 ml, 33 mmol) was added dropwise at 25^{0}C to THF (12 ml) through which acetylene was bubbled. After standing for 30 min at room temperature the anionic solution was cooled to -50^{0}C and trimethylchlorosilane (3.1 g, 20 mmol) was added with stirring in 15 min at 0^{0}C. After the addition, stirring at 0^{0}C was continued for 2 h and the mixture was allowed to stand at room temperature overnight. It was then poured into 1N HCl (20 ml). High-boiling petroleum (b.p. 100-120^{0}C) (8 ml) was added and the mixture was shaken vigorously. The organic layer was separated, washed with 1N HCl (5 x 15 ml), dried over magnesium sulphate and then distilled through a 40-cm Vigreux column to give 2.5 g (78%) of trimethylsilylacetylene (28) as a colourless oil. b.p. 52^{0}C (lit.,[12] 52^{0}C).

Methyl trimethylsilylethynyl sulphide (29)

To a solution of trimethylsilylacetylene (28) (1.96 g, 20 mmol) in THF (40 ml), 1.6M butyllithium in hexane (13.7 ml, 22 mmol) was added at -78^{0}C. The mixture was stirred at that temperature for 30 min and sulphur (0.64 g, 20 mmol) was added, maintaining the temperature at -78^{0}C. The mixture was then allowed to warm slowly to room temperature. After 4 h standing at room temperature the mixture was cooled again to -78^{0}C and iodomethane (2.8 g, 19.6 mmol) was added dropwise over 15 min. The reaction mixture was allowed to warm to room temperature and then poured into water (25 ml). The organic layer was separated, washed with saturated brine (2 x 20 ml), and dried over sodium sulphate. After evaporation of the

solvent the mixture was distilled *in vacuo* to give 1.67 g (59%) of methyl trimethylsilethynyl sulphide as a colourless oil, b.p. 58°C 40mm Hg (lit.,[14] 58°C 40mm Hg);
n_{max}(nujol mull) (cm^{-1}): 2200 (C≡C str.,);
d^{1}H ($CDCl_3$) 0.2 (9H, s, $Si(Me)_3$), 2.4 (3H, s, SMe);
Anal. calcd for $C_6H_{12}SiS$: C, 50.00, H, 8.33, S, 22.22. Found: C, 50.07, H, 8.54.

Oxidation of methyl trimethylsilylethynyl sulphide (29) with MCPBA (30 + 31).

A solution of the ethynyl sulphide (29) (2.4 g, 16.6 mmol) in petroleum ether (b.p. 40-60°C) (150 ml) was treated with 50-55% 3-chloroperbenzoic acid (5.72 g, 16.6 mmol) at 20°C. After stirring for 1 h at that temperature, solid particles were removed by filtration and the solvent was evaporated under reduced pressure to give a colourless oil (2.0 g) consisting of sulphoxide (30) and sulphone (31). A few attempts at separation (column chromatography, distillation) of these two compounds failed. Calculation of the ^{1}H nmr results indicated that 0.77 g (38.6%) of methyl trimethylsilylethynyl sulphone (31) and 1.23 g (61.4%) of methyl trimethylsilylethynyl sulphoxide (30) were present;
n_{max}(nujol mull of mixture) (cm^{-1}): 1060 (S=O), 1150, 1330 (SO_2), 2080, 2120 (C≡C str.,);
d^{1}H ($CDCl_3$ of mixture) 0.24 (9H, s, $Si(Me)_3$), 2.96 (2H, s, Me) 3.2 (1H, s, Me).

Attempted 1,4-cycloaddition reaction of (26) with (30 + 31)

Freshly prepared LDA solution (10 mmol in 30 ml THF) was added dropwise over 10 min to a solution of methyl 4-fluoro-2-methylaminobenzoate (26) (1.9 g, 10 mmol) in THF (30 ml) under a nitrogen atmosphere at -78°C. The reaction mixture was warmed to -20°C over 1 h to yield an orange solution of the anion. Then the anionic solution was cooled to -40°C and the mixture of acetylenic sulphoxide (30) and sulphone (31) (1.76 g, 10 mmol) in THF (30 ml) was added rapidly . The resulting solution was kept at -40°C for 10 min then allowed to warm to room temperature. It was then quenched with aqueous saturated ammonium chloride solution(20 ml). The solution was extracted with diethyl ether(3x20ml) and the organic

phase was dried over magnesium sulphate and evaporated under reduced pressure to yield a brown crude product. Purification by column chromatography (dichloromethane) resulted in recovery of starting material (26) (0.16 g, 80%).

A second attempted cyclisation reaction of (26) with the mixture (30 + 31) was carried out at -78°C and the addition time of the acetylenic compounds was extended to 30 min. But, after work-up starting material was again recovered.

Triisopropylsilylmethyl trimethyl silylethynyl sulphide (33)

A solution of methyl trimethylsilylethynyl sulphide (29) (1.44 g, 10 mmol) in THF (30 ml) was cooled to -78°C and a butyllithium solution in hexane (6.9 ml, 11 mmol) added slowly. After 30 min triisopropylsilyl chloride (1.9 g, 10 mmol) was added dropwise over 30 minutes and the reaction mixture was warmed to room temperature over 1 h. After evaporation of the solvent (THF), the crude product was distilled to give 2.04 g (68%) of triisopropylsilylmethyltrimethylsilylethynylsulphide as colourless oil, b.p. 140-145°C 0.5mm Hg;

n_{max}(neat) (cm^{-1}): 2220 (C≡C str.,);

d^1H ($CDCl_3$) 0.2 (9H, s, $Si(Me)_3$), 1.2 (21H, s, isopropyl), 2.1 (2H, s, CH_2);

Anal. calcd for $C_{15}H_{22}Si_2S$: C, 60.00, H, 10.66. Found: C, 60.27, H, 10.68.

Triisopropylsilylmethyl trimethylsilylethynyl sulphoxide (34)

The sulphide (33) (1.7 g, 5.7 mmol) in diethyl ether (56 ml) was reacted with 3-chloroperbenzoic acid (1.96 g, 5.7 mmol) at room temperature. After 2 h stirring, the liquid layer was separated from the solid particles by filtration and evaporated under reduced pressure to give 1.9 g of crude product. Distillation of the crude product gave 1.1 g (65%) of (34), b.p. 175-178°C 0.5mm Hg;

n_{max}(nujol mull) (cm^{-1}): 1050 (S=O), 2180 (C≡C str.,);

d^1H ($CDCl_3$) 0.3 (9H, s, $Si(Me)_3$), 1.4 (21H, d, isopropyl), 2.8 (2H, s, CH_2);

Anal. calcd for $C_{15}H_{32}SiSO$: C, 56.96, H, 10.12. Found: C, 57.14, H, 10.28.

Attempted 1,4-cycloaddition reaction of (26) with (34)

The same cycloaddition reaction procedure for(19) was repeated using the compounds (26) (1.9 g, 10 mmol) in THF (25 ml) and (34) (2.16 g, 10 mmol) using LDA solution (11 mmol) in THF (30 ml) at -78°C. After the same work-up a black tar was obtained which could not be identified.

A second attempt at the cyclisation reaction with (26) and (34) was carried out at -78°C and the addition time of acetylenic compound (34) was extended to 45 min. But again, intractable tar was obtained after the same work-up.

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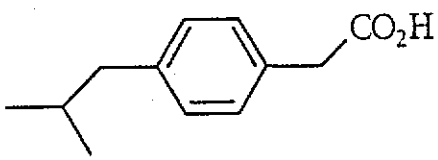
CHAPTER 3

Diels-Alder Reactions Using 5M $LiClO_4$-Diethyl Ether Catalyst

3.1. INTRODUCTION

Many drugs currently in use produce serious side-effects. For example, aspirin causes gastric ulcer formation, and cortisone adversely affects the endocrine system. Arylacetic and arylpropionic acids have become increasingly important drugs, since these compounds are highly effective anti-inflammatory agents and have less serious side-effects. Thus, a new series of compounds have come into clinical use. These drugs may have simple structures such as ibufenac[1] (1) and alclofenac[2] (2), or be more complex, such as pirprofen[3] (3), but it is evident that the arylacetic and arylpropanoic acid moiety plays an integral part in the activity of the compounds.



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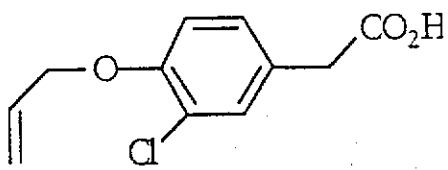

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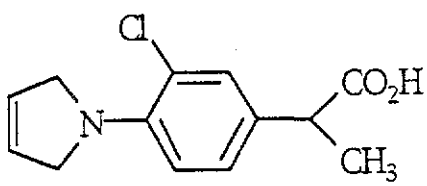


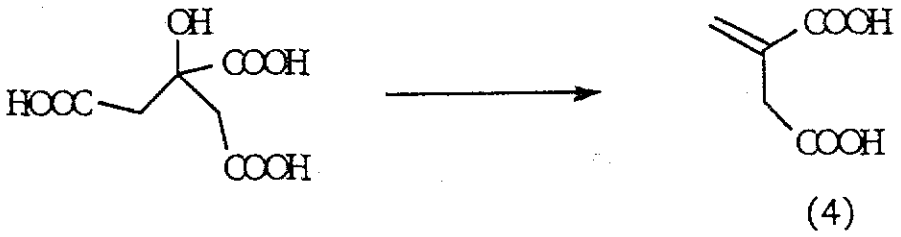
(3)

In 1980, in a projected new approach to arylacetic acid synthesis, Fletcher attempted to obtain phenylacetic acid and its derivatives by Diels-Alder reactions[4] using mainly itaconic acid and itaconic anhydride as the dienophile. Unfortunately, a low yield was obtained in most of these reactions. In this chapter Fletcher's work was re-examined using a 5.0M solution of lithium perchlorate in diethyl ether (LPDE) in Diels-Alder reactions. Itaconic acid was used as the dienophile, which was obtained from itaconic anhydride, with various dienes at ambient temperature and pressure in the presence of 5.0M LPDE solution.

Itaconic acid (4) is commercially very inexpensive, arising as a fermentation product of citric acid[5] (Scheme 1).

and it was realised that Diels-Alder type cyclisation with a variety of dienes would lead to a group of compounds(5) which, if they could be decarboxylated

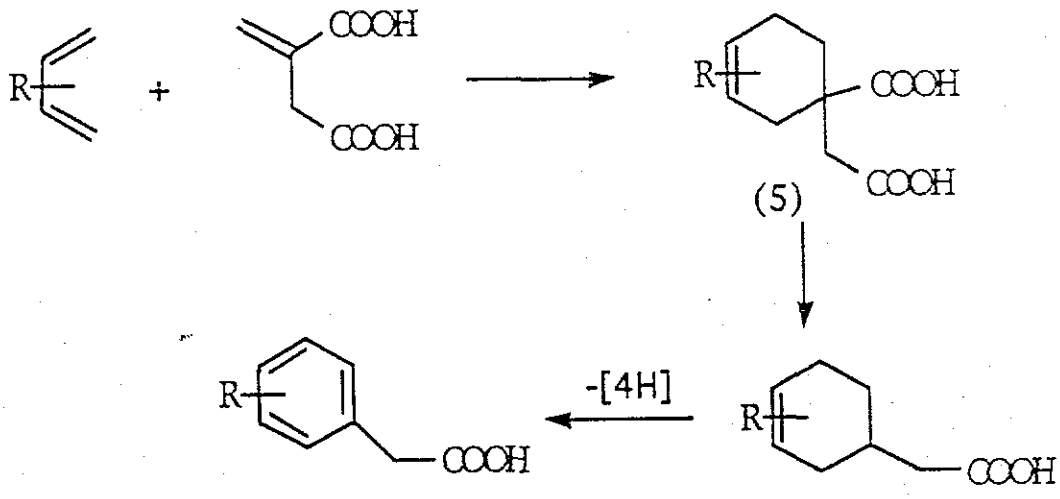
Scheme 1



(4)

at the quaternary carbon, should undergo facile dehydrogenation to yield arylacetic acids (Scheme 2). Furthermore, it was envisaged that this apparently difficult process of decarboxylation could be simplified by the correct choice of diene. For example, if compounds (6) to (9) (Scheme3),

Scheme 2

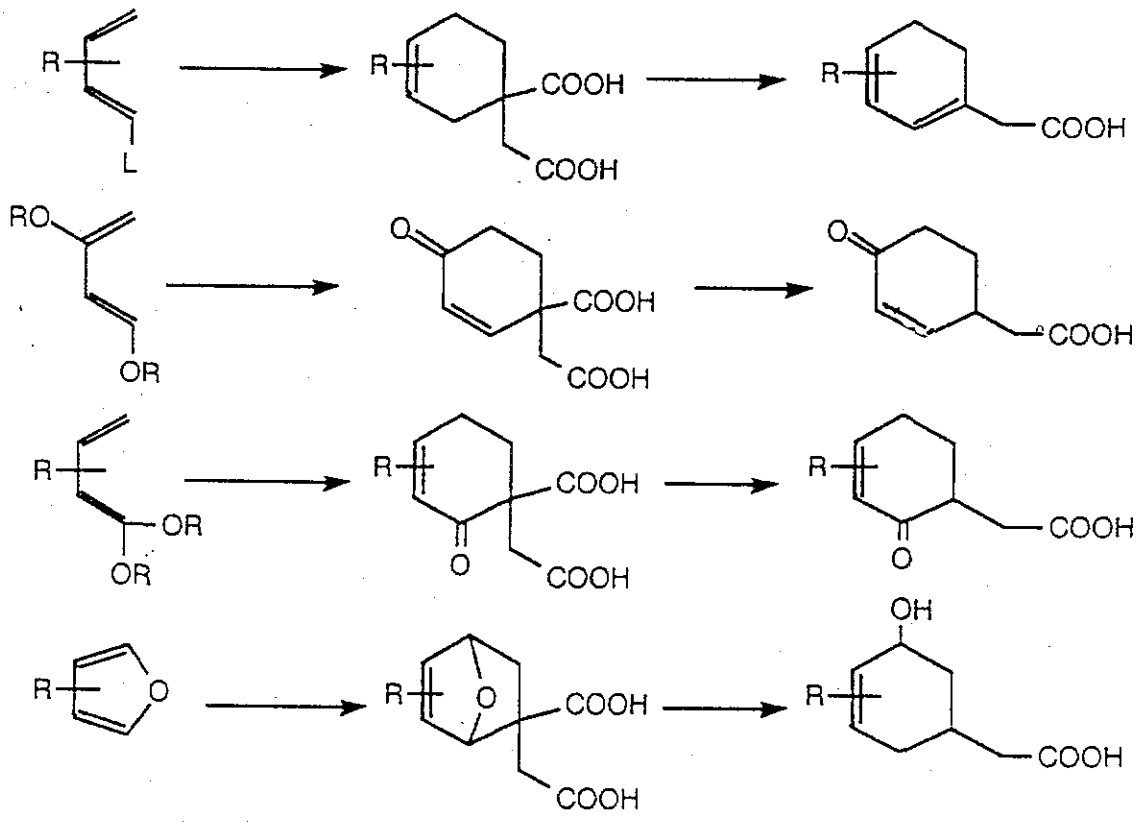


potentially available by Diels-Alder reactions, could be prepared, decarboxylation would be expected to occur readily (Scheme 3). It was also realised that the Diels-Alder adducts could be active by virtue of being protected forms of arylacetic acids (prodrugs) or, indeed, they could have pharmacological activity in their own right.

The aim of the project was thus to determine the scope of the Diels-Alder reactions of itaconic anhydride using 5.0M lithium perchloride in diethyl

ether with a view to converting the cycloadducts into the corresponding arylacetic acids.

Scheme 3

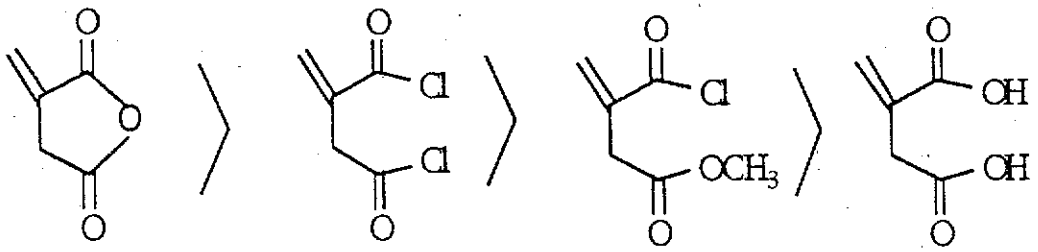


3.2 Theoretical Aspects

The reaction of interest is a (4 + 2)p cycloaddition reaction. Much work has been carried out on this type of reaction, both theoretical and experimental, and several predictions can be made.[6,7] The reaction is thermally allowed according to the Woodward-Hoffman rules and except for a few extreme cases is favoured when the 4p system, the diene, is electron rich and the 2p system, the dienophile is electron poor. This can be explained in the terms of Frontier Molecular Orbital (FMO) theory on the basis that reaction is dominated by the overlap of the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile, and the closer these two orbitals are in energy the more favourable is reaction.[8] Therefore, as electron-withdrawing substituents lower the LUMO of the dienophile and electron donating groups raise the HOMO of

the diene, when these substituents are present, the overlapping orbitals become closer together in energy and reaction takes place readily.

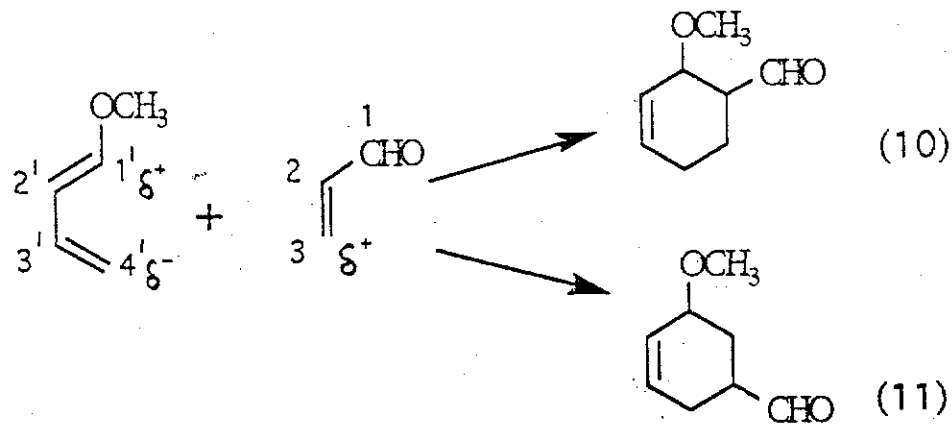
Thus, of the itaconic acid derivatives available, the order of reactivity in Diels-Alder reactions would be predicted to be:



On the other hand, it follows that the more electron rich is the diene the more rapid will be reaction.

It is also possible in most cases to predict the regioselectivity of the reaction between an unsymmetrical diene and a dienophile by consideration of the polarisation of the two molecules. Thus, reaction of acrolein with 1-methoxybutadiene leads only to the formation of (10), a predictable result as acrolein is electron deficient at C-3 whilst 1-methoxybutadiene is electron rich at C-4,[1] and the interaction of these partial charges would be expected to favour the formation of (10) (Scheme 4).

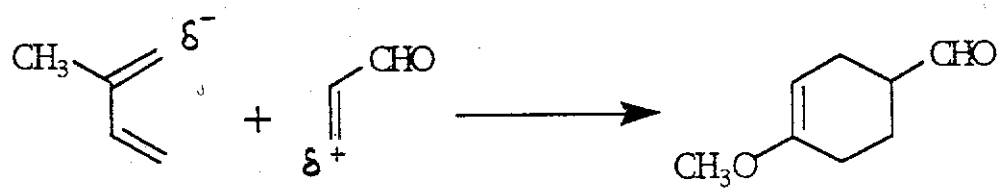
Scheme 4



In a similar manner, it can be understood why the reaction of 2-methoxybutadiene and acrolein gives (12) as the sole product (Scheme 5). Although a more sophisticated theory has been developed to explain regiospecificity,[8] this simplistic rationale favoured by Woodward and Katz[9] is

sufficient to predict the outcome of the reactions carried out in the presen study and it has not been considered necessary to invoke the use of FMC theory. In considering the possible outcome of the cycloaddition reaction tried, the itaconic acid derivatives were considered to react in a similar way tc acrolein.

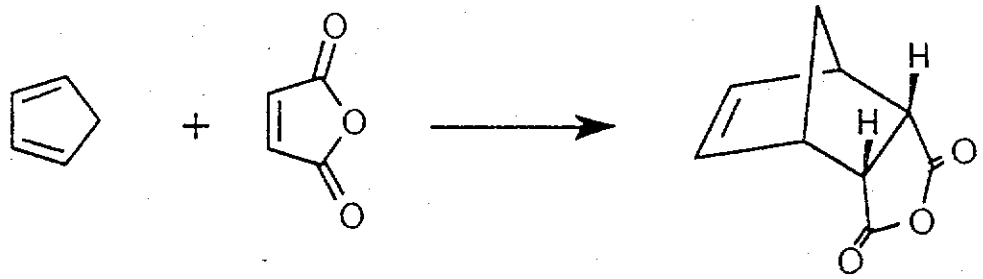
Scheme 5



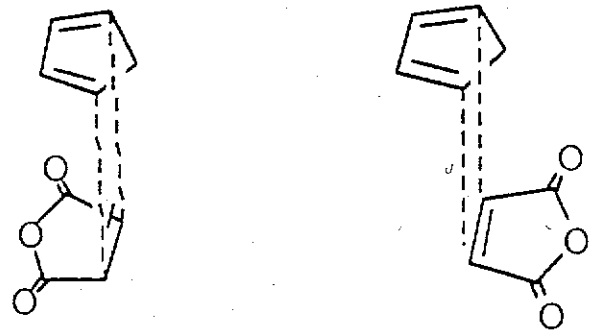
(12)

In the formation of a regioisomer two adducts are possible and a empirical rule has been introduced in an attempt to clarify the situation. Th Alder[10] rule states that if two isomeric adducts are possible, that which ha the largest p-electron cloud overlap in the transition state will be formed faste This rule was initially introduced because the addition of dienophiles t cyclopentadiene and related compounds is usually stereoselective and lead to the *endo*-adduct rather than the more thermodynamically stable *exo*-adduc and is illustrated by the addition of maleic anhydride to cyclopentadiene which results only in the formation of (13) (Scheme 6). However, the rule i not widely applicable and there are exceptions. Addition of methacrylic acid t cyclopentadiene, for instance, yields a mixture of isomeric products in whic the diastereoisomer (14) containing the *exo*-carbonyl group predominates[11] (Scheme 7). Thus it is not always possible to predict with certainty whic adduct will be formed in Diels-Alder reactions.

Scheme 6

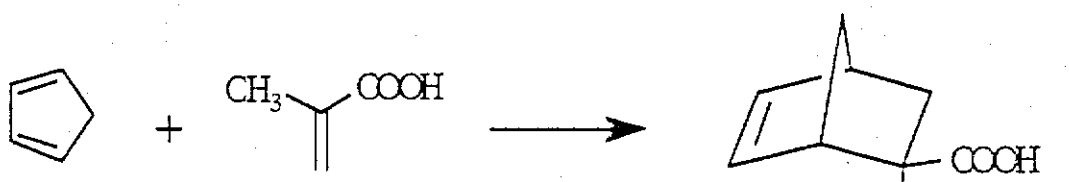


(13)

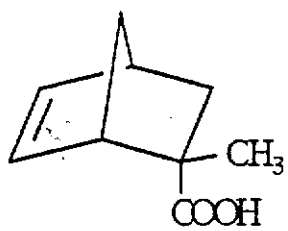


endo exo

Scheme 7



(14)

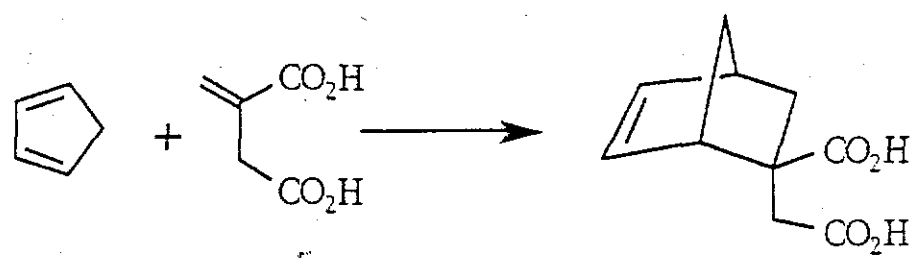


(15)

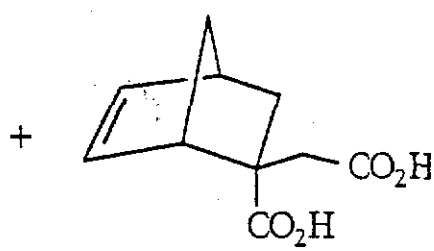
3.3. Literature Survey

A search of the literature for reactions akin to those proposed in Scheme 3-2 revealed that a few Diels-Alder reactions of itaconic acid and its derivatives have been described, but subsequently decarboxylation and aromatisation of the adducts has not been reported. Appropriately, although perhaps not unexpectedly in view of the vast amount of pioneering work they carried out, the first cycloaddition reaction of an itaconic acid derivative was recorded by Diels and Alder in 1928, when the adduct obtained from cyclopentadiene and itaconic anhydride was described.[12] Diels and Alder did not report a yield for the reaction but later workers[13] obtained the adduct in 85% yield by heating the reagents in a solvent mixture of water and isopropanol for 5 h; they also showed that the exo-isomer (16) predominated in a ratio of 3:1 over the endo-isomer (17) (Scheme 8), a violation of Alder's rule.

Scheme 8



(16)



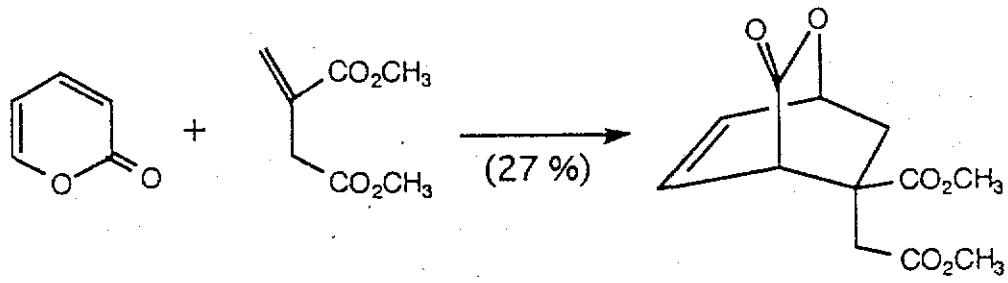
(17)

Surprisingly, the corresponding reaction with furans has not been reported.

In general, acyclic dienes react readily with itaconic anhydride or itaconic esters, but polymers are formed with butadiene.[14] Reaction of 2,3-

itaconate has been successfully combined with *a*-pyrone (22)[17] to give the corresponding adduct (Scheme 11).

Scheme 11



Russian workers in the early 1970's carried out cycloaddition reactions with itaconate esters and claimed to have reacted chloroprene with 2-chloro-3-phenyl-1,3-butadiene, though few details were given. One piece of information to come out of their work, however, is that Lewis acid and protic acids effectively catalyse these Diels-Alder reactions[18] and the authors suggested that the activity decreases in the order:

$$H_2SO_4 < ZnCl_2 < AlCl_3 < HCl$$

In 1980 Fletcher also investigated the Diels-Alder reactions of itaconic acid derivatives in the first step of projected phenylacetic acid synthesis. During his work 2,3-dimethoxy-1,3-butadiene (23), 2-methyl-3-methoxy-1,3-butadiene (24), 1,4-diphenyl-1,3-butadiene (25), anthracene (26), 2,3-bis(trimethylsilyloxy)-1,3-butadiene (27), 1-acetoxy-1,3-butadiene (28), 2-trimethylsilyloxy-1,3-butadiene (29), 2-acetoxy-1,3-butadiene (30), 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (31), furan, and furan derivatives were reacted with itaconic anhydride to obtain the corresponding adducts and his results are shown in Table 1. In all these reactions toluene and benzene were used as solvent at reflux temperature. Unexpectedly, in most cases the Diels-Alder adducts were not obtained. Also, the use of dimethyl itaconate, itaconyl chloride or itaconic acid as a dienophile in refluxing benzene gave very poor results.[4]

Table 1 : Reaction of itaconic anhydride with dienes

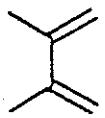
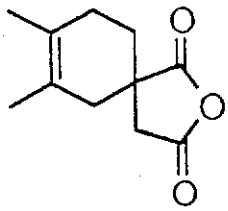
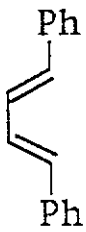
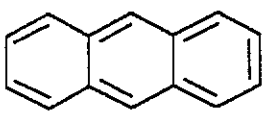
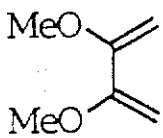
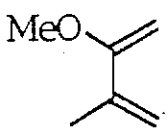
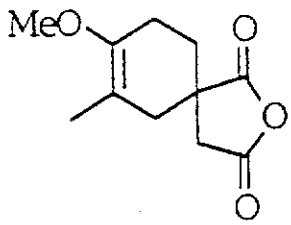
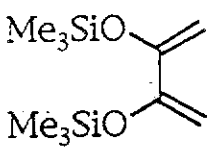
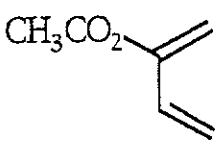
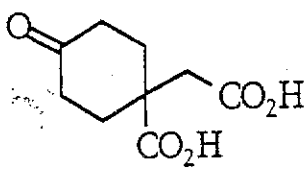
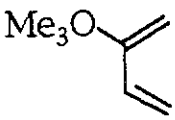
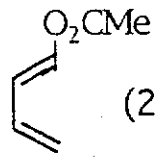
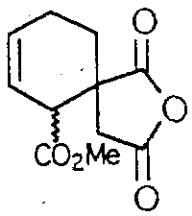
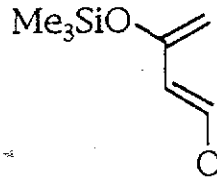
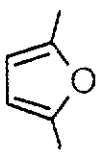
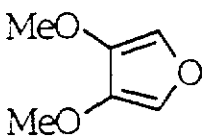
Diene	Reaction condition	Product	Yield%
 (18)	toluene, Δ 3h		70
 (25)	toluene,Δ 2h	—	0
 (26)	toluene, Δ 16h	—	0
 (23)	toluene, Δ 2h	—	0
 (24)	toluene, Δ 12h		76
 (27)	toluene, Δ 1h	—	0
 (30)	toluene, Δ 8h		53
 (29)	toluene, Δ 1h	—	0

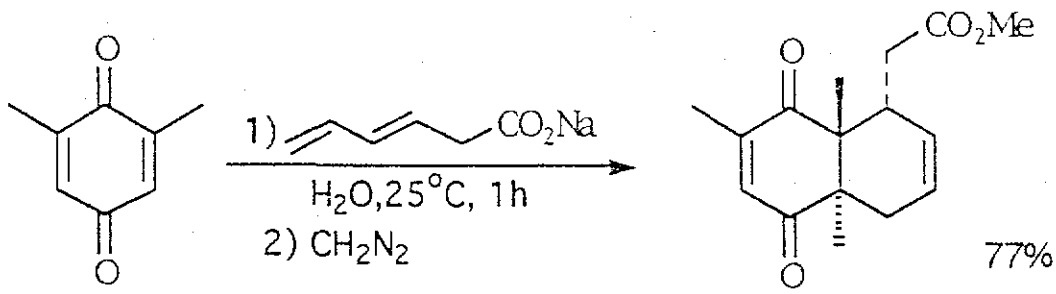
Table 1 Cont'd

Diene	Reaction condition	Product	Yield%
 (28)	toluene,Δ 8h		38
 (31)	toluene,Δ 8h	—	0
 (32)	toluene,sealed tube Δ 64h	—	0
 (33)	toluene,Δ 12h	—	0
 (34)	toluene,Δ 4h	—	0

Many examples of Diels-Alder reactions are to be found in the literature, most conducted at high temperature and pressure using a range of Lewis acid catalysts and solvents. On the other hand, many scientists have been researching the Diels-Alder reaction in an attempt to improve yields, selectivity of isomers, etc., by using mild conditions.

In 1983 Grieco and co-workers[19] were investigating intramolecular Diels-Alder reactions under mild conditions in aqueous medium. In this reaction 2,6-dimethyl benzoquinone was reacted with 5 equivalents of sodium (E)-3,5-hexadienoate in a 2M aqueous solution at ambient temperature and pressure. After 1 h reaction time, the corresponding Diels-Alder adduct was obtained in 77% yield with excellent regiochemical control. In contrast, the same reaction in hydrocarbon solvents (e.g., toluene or benzene) at room temperature employing methyl (E)-3,5-hexadienoate gave a very low yield even after several days (Scheme 12).

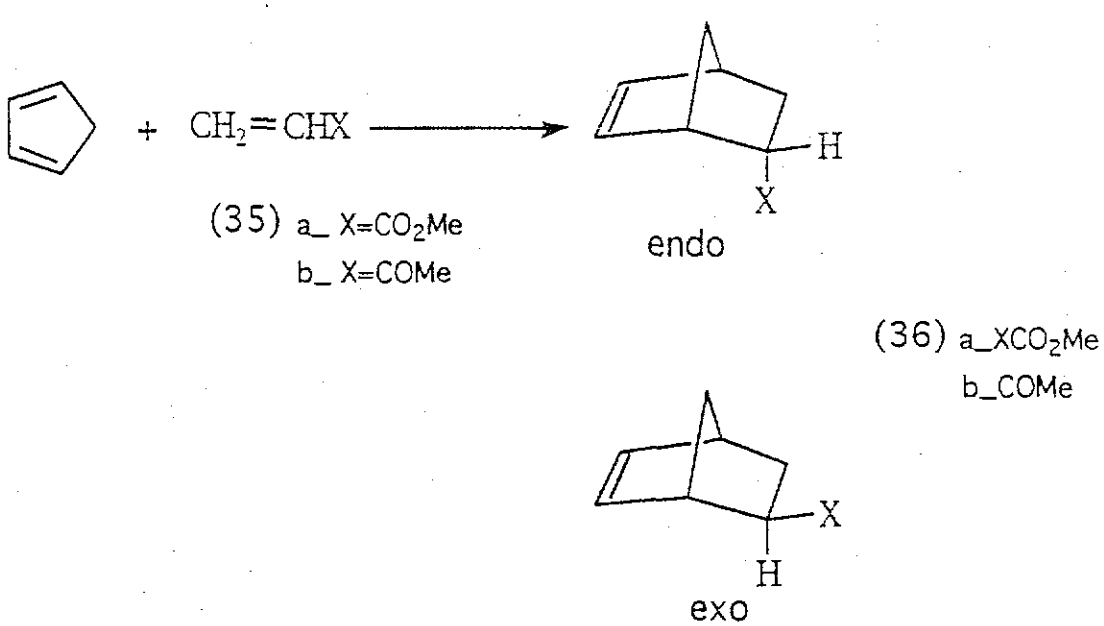
Scheme 12



Aqueous medium Diels-Alder reactions were continued by Grieco and 51-94% yields were obtained using sodium (E)-4,6-heptadienoate with different dienophiles.[19] Also, the derivatives of sodium 4,5-heptadienoate were examined with a series of dienophiles in water at ambient temperatures and pressure and high yields were obtained.[20]

Water has been used to considerable effect as a solvent for Diels-Alder reactions as mentioned. Ethylammonium nitrate (EAN) is low-melting (m.p. 12°C) fused salt that shares some, but not all, of the characteristic features of water and has also been used as a solvent in Diels-Alder reactions in 1989.[21] In this work, cyclopentadiene was reacted with methyl acrylate (35a) and methyl vinyl ketone (35b) to give *endo* (36a) and *exo* (36b) cycloaddition products in EAN (Scheme 13). In this reaction, a solution

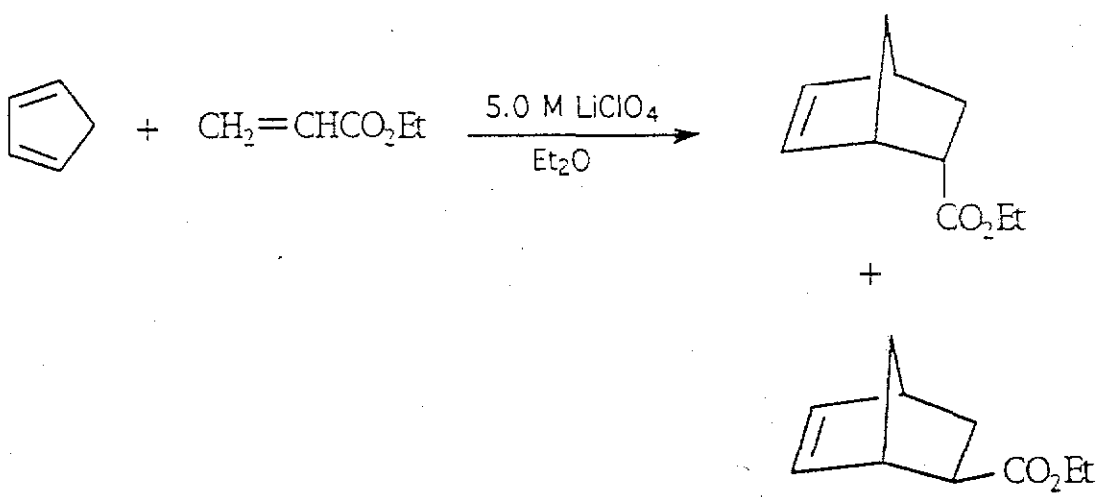
Scheme 13



of 0.20M cyclopentadiene and 0.20M (35a) in EAN was stirred at 25^{0}C for 72 h to give the adducts (36) in 98% yield and *endo:exo* ratio of 6:7. EAN gave *endo* selectivity for the reactions of cyclopentadiene with 35a and 35b. Although the rate and *endo* selectivity enhancement results were obtained using water as solvent for the same reactions.[21]

A large number of Lewis acid catalysed Diels-Alder reactions have been reported. In addition to the classic Lewis acids such as $BF_3.OEt_2$, $TiCl_4$, $SnCl_4$ and $AlCl_3$, several alkyl- and alkoxyaluminium chlorides[22], WCl_4[22], $NbCl_5$[22], CF_3CO_2H[23], H_2SO_4[24], HF[25], $HSbCl_6$[26], CF_3SO_3H[26] and *p*-TsOH[26] have been used with varying degrees of success. Besides these catalysts lithium perchlorate ($LiClO_4$) has also been used for Diels-Alder reactions by Grieco[27] in 1990. In this report, 5.0M lithium perchlorate in diethyl ether was mentioned as a powerful medium for facilitating [4+2] cycloaddition reactions. In the preliminary study, ethyl acrylate dissolved in a 5.0M solution of lithium perchlorate in diethyl ether was treated with 1.0 eq of cyclopentadiene (Scheme 14). After 5 h at ambient temperature and pressure, a 93% yield of cycloadducts with *endo:exo* ratio 8:1 was obtained.

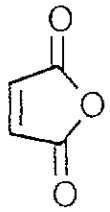
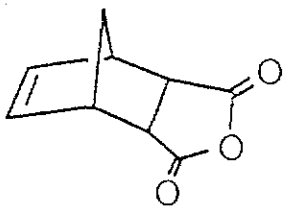
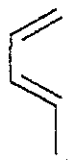
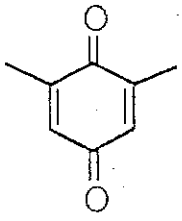
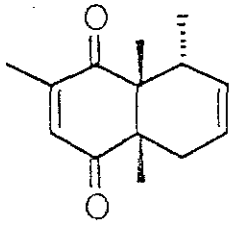
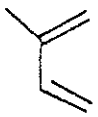
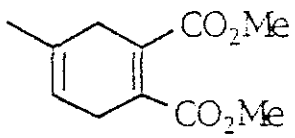
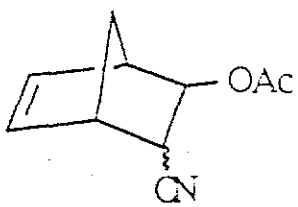
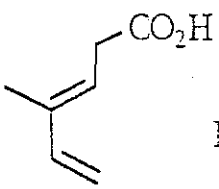
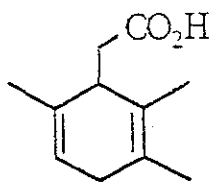
Scheme 14



For comparison purposes, the reaction between cyclopentadiene and ethyl acrylate was conducted in water. After 5 h a 73% yield of cycloadducts with *endo:exo* ratio of 4:1 was obtained. Grieco has continued Diels-Alder reactions using 5.0M $LiClO_4$ in diethyl ether (LPDE) using different dienes and

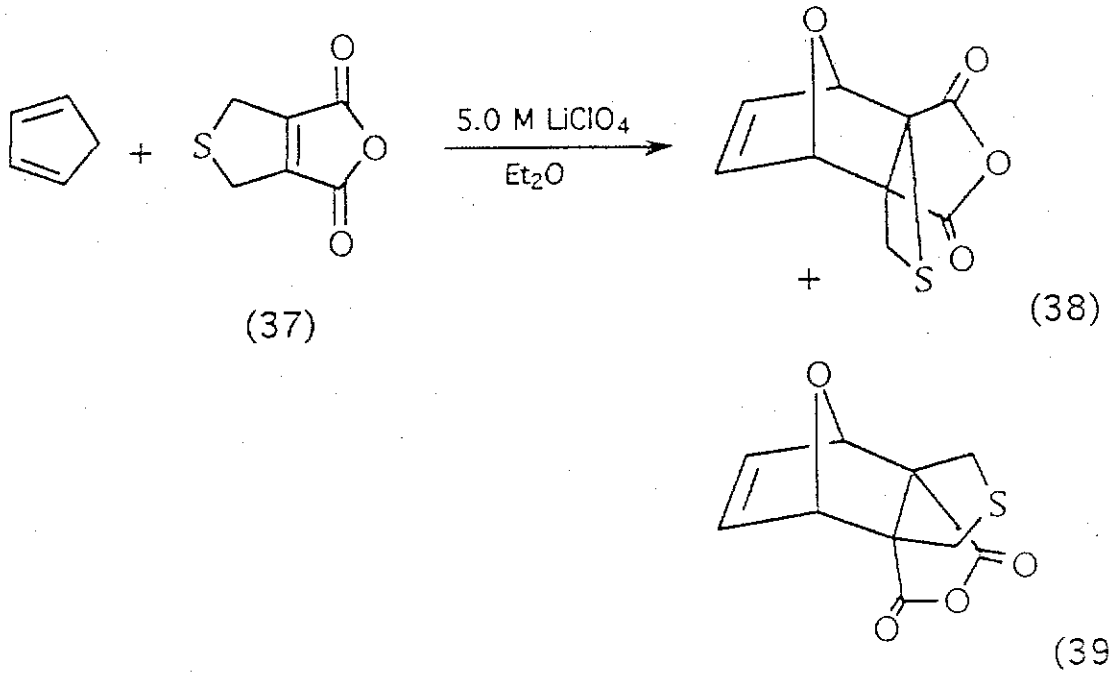
dienophiles and reproducible high yields were obtained (Table 2). All reactions were performed 1.0M in diene and 0.2M in dienophile.

Table 2: [4+1] Cycloadditions Employing 5M Lithium Perchlorate in Diethyl Ether

Diene	Dienophile	Product	time	yield%
			3 h	90
			15 min	80
	$MeO_2CC{\equiv}CCO_2Me$		12 h	94
	$CH_2{=}C(OAc)CN$		4 h	79
	$MeO_2CC{\equiv}CCO_2Me$		24 h	68

Furan is a poor Diels-Alder diene due to its aromaticity and generally requires pressure in the range of 10-20 kbar to effect cycloaddition.[28] High temperatures are not compatible with furan Diels-Alder chemistry since the derived cycloaddition products undergo cycloreversion at high temperatures. In the classic synthesis of cantharidin,[29] the reaction of furan with 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (37) in methylene choride required 6 h under 15 kbar of pressure in order to realise an 85:15 mixture of cycloadducts (38) and (39) (Scheme 15).

Scheme 15



In sharp contrast, the Diels-Alder reaction between furan and dienophile (37) in 5.0M LPDE proceeded at ambient temperature and pressure, giving rise (70% yield) after 9.5 h to cycloadducts (38) and (39) in 70% yield and 85:15 ratio.[27] A systematic examination of this reaction by Grieco confirmed a direct correlation between reaction rate and molarity, with the rate increasing on going from 1.0 to 5.0M lithium perchlorate in diethyl ether (Table 3).

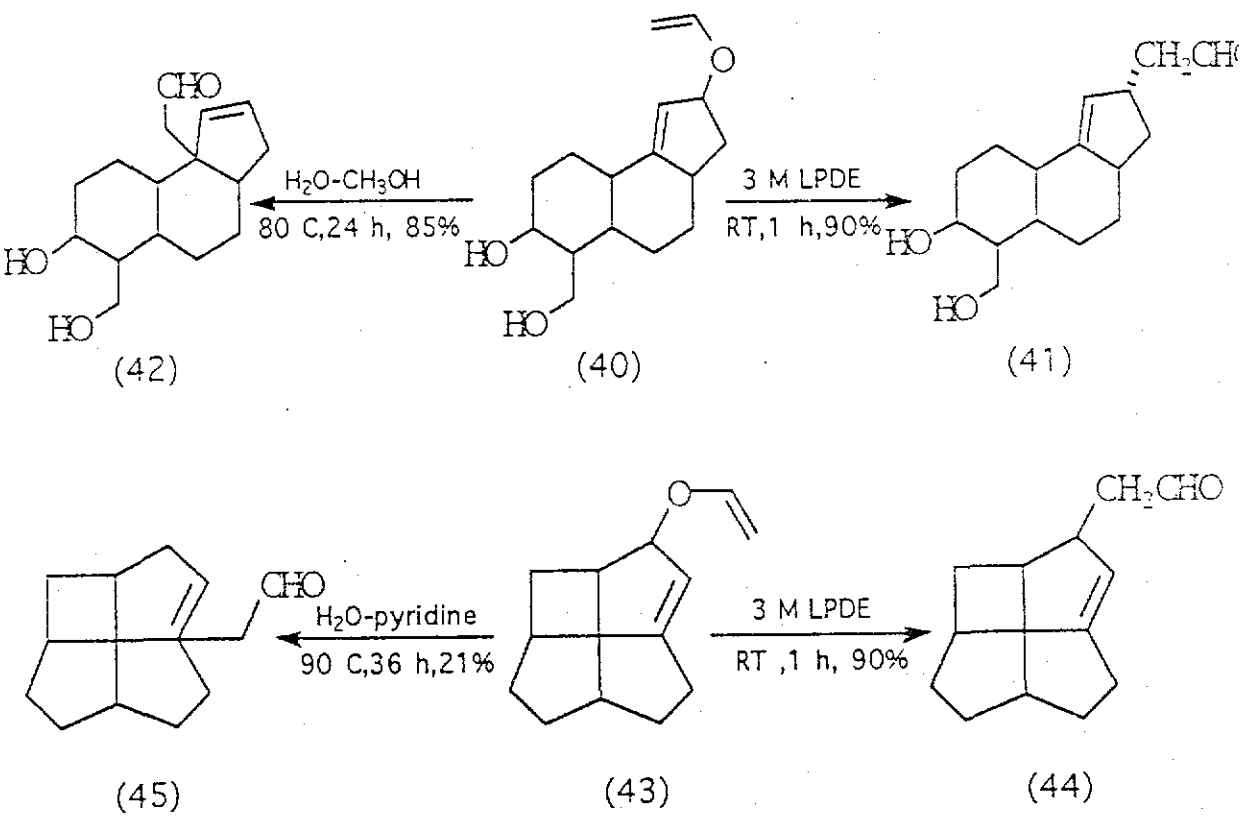
Table 3: Reaction of Dienophile (37) with Furan at Ambient Temperature and Pressure in Varying Concentrations of $LiClO_4$-Et_2O.

Molarity	Yield %	Ratio (38:39)
1.0	15	85:15
2.0	22	87:13
3.0	36	86:14
4.0	62	83:17
5.0	70	85:15

All reactions were run 0.5M in dienophile for 9.5 h in the presence of 10 equivalents of furan.

The suprising observation was made by Grieco *et al.*,[30] using the system $LiClO_4$/diethyl ether - that allyl vinyl ethers, contrary to expectation, do not undergo [3,3]-sigmatropic rearrangements in 3M LPDE solutions, but give aldehydes by a [1,3]-sigmatropic rearrangment (Scheme 16). Thus, (40) reacts under these conditions to give (41) in 90% yield within 1 h at room temperature (in 5M salt solution the reaction is already completed after 10 minutes), and also fenestrane (43) is transformed into the aldehyde (44) in high yield. These observations, particularly the steric course of the rearrangements, are in sharp contrast to the findings that (40) undergoes the expected Claisen rearrangements to (42) in water-methanol (2.5:1) at 80^0C and also that fenestrane (43) rearranges to (45) in water-pyridine at 90^0C.

Scheme 16



(42) (40) (41)

(45) (43) (44)

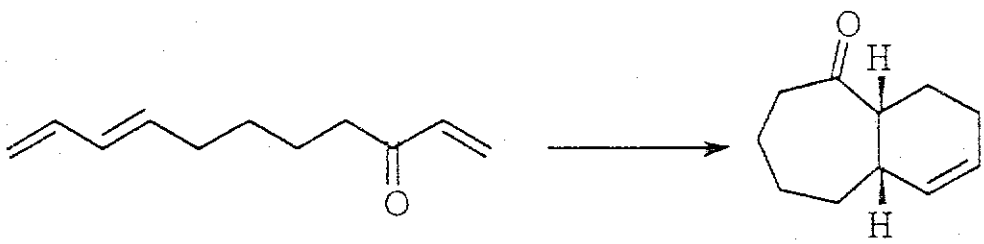
The writer explained the good results he obtained as being due to the ability of 5.0M $LiClO_4$-Et_2O, a unique ionic medium, to confine solvent

movement and hence retain solvent ordering and this may well be responsible for the observed rate accelerations by compressing the reactants in much the same manner as the "macroscopic" applicatiojn of external pressure.He thus asserted that 5.0M LPDE was creating very high "internal solvent pressure".

After Grieco, Dailey and co-workers were interested in Diels-Alder reactions using 5.0M LPDE solution.[31] In this work, 1,3-diphenyliso benzofuran was reacted with styrene in the presence of lithium perchlorate-diethyl ether solutions but they have discovered that the rate of the Diels-Alder reaction between this diene and dienophile is unaffected by the medium.

The lithium salts, $LiClO_4$ and $LiBF_4$, also were studied as catalysts for the intramolecular Diels-Alder reaction of trienone (46).[32] Surprisingly, no cycloaddition of the trienone was observed when $LiClO_4$ was used, but $LiBF_4$ provides the cis-fused cycloadduct (47) (bicyclo[5.4.0]undecenone) in quantitative yield in 72 h at room temperature (Scheme 17).

Scheme 17



(46) (47)

The cycloaddition reactions were run in dry benzene at room temperature, and 1.1 equivalents of lithium salt as a 1M solution in acetonitrile were added to the trienone and stirred for 48-72 hours. The use of $LiClO_4$ gave only quantitative recovery of starting material. The thermal and the lithium salt reaction results are given in Table 4.[31]

Table 4: Intramolecular Diels-Alder Reaction of Trienone (40)

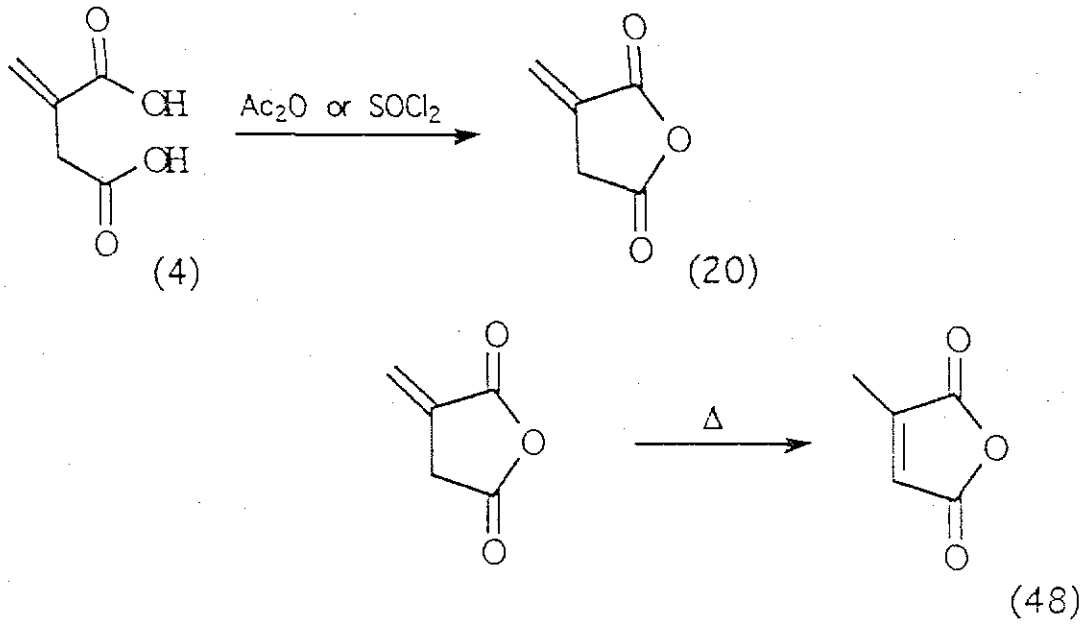
Conditions	Time	Temperature °C	Yield %	cis:trans ratio
Thermal 0.016M (40)	5 h	155	90	62:38
1.0M $LiBF_4$ 0.016M (40)	72 h	25	100	100:0
1.0M $LiClO_4$)	72 h	25	Recovery of starting material	

Discussions are still continuing concerning the rate acceleration effect of LPDE solution on Diels-Alder reactions. Irrespective of the final outcome of these, it was felt that real effects could be possible, and that use of the LPDE medium might prove advantageous in Diels-Alder reactions with itaconic anhydride. If so, then it might be possible to develop a general and useful new approach to arylacetic acids. Investigation of these possibilities is the subject of the following discussion.

3.4. Results and Discussion

Initially, itaconic acid (4) was converted to the anhydride (20) in high yield by reaction with acetic anhydride using a known procedure[33] and purified carefully from the isomeric impurity viz., citraconic anhydride (48). Citraconic anhydride is often obtained as a side product in thermal Diels-Alder reactions of itaconic anhydride. The formation of (48) is easily understood, however, as it is generally prepared by distillation of itaconic anhydride at atmospheric pressure[34] (Scheme 18).

Scheme 18

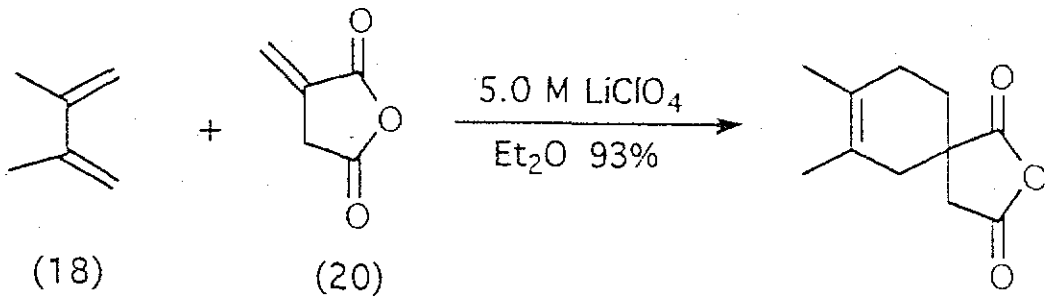


(4) (20) (48)

On the other hand, lithium perchlorate was prepared according to the literature procedure[35]. Commercially available anhydrous $LiClO_4$ was found unsuitable for our use. Consequently, it was recrystallised twice from distilled water in the form $LiClO_4.H_2O$ and finally dried at 160°C (0.5mm Hg) for at least 48 h.

In the first attempted Diels-Alder reaction, itaconic anhydride was reacted with the non-functionalised diene 2,3-dimethyl-1,3-butadiene (18) in 5.0M lithium perchlorate diethyl ether solution. In this reaction itaconic anhydride and diene (18) were added to a prepared solution of 5.0M LPDE at atmospheric pressure and the reaction mixture was stirred for 4 h at room temperature (Scheme 19).

Scheme 19

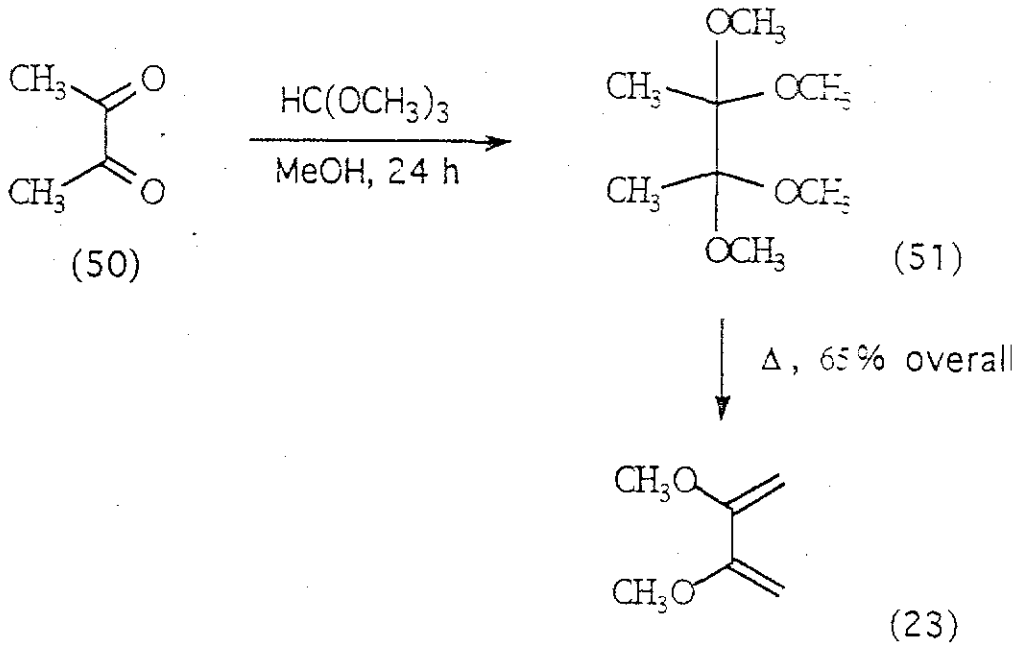


(18) (20) (49)

After work-up a 93% yield of the anhydride of 4-carboxy-4-carboxymethyl-1,2-dimethylcyclohexene (49) was obtained as colourless needles, the details of which are given in the experimental section. The same Diels-Alder reaction was also run without catalyst (LPDE) at reflux temperature between diene (18) and dienophile (20) in toluene and after 3 hours reflux, the cycloaddition product (49) was obtained in 70% yield. As seen from these two results employing LPDE and reflux in toluene, a significantly higher yield was obtained using LPDE at room temperature.

Following a literature procedure,[36] 2,3-dimethoxy-1,3-butadiene (23) was prepared by thermolysis of 2,2,3,3-tetramethoxybutane (51), which in turn was prepared by the

Scheme 20

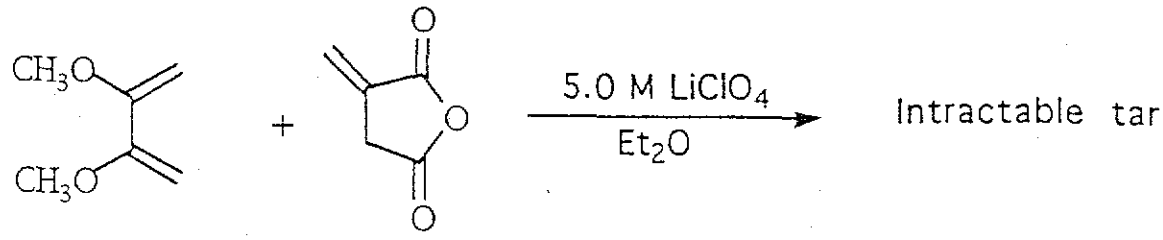


(50) (51) (23)

action of trimethyl orthoformate (TMOF) on butane-2,3-dione (50); the diene was isolated in 63% overall yield from (50) (Scheme 20).

Attempts were then made to induce reaction between (23) and itaconic anhydride (20) in the presence of LPDE solvent. After 12 h stirring at room temperature and atmospheric pressure only a small amount of itaconic anhydride was recovered together with an intractable black tar. Changing the concentration of components also gave intractable tar under the same reaction conditions (Scheme 21).

Scheme 21

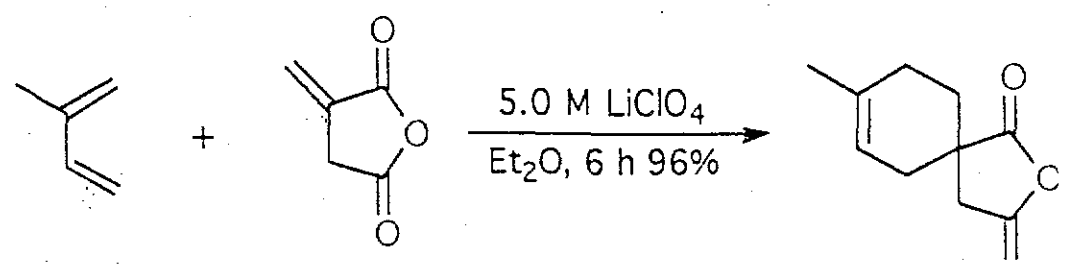


(23) (20)

The thermal reaction between 2,3-dimethoxy-1,3-butadiene and itaconic anhydride also resulted in re-isolation of itaconic anhydride after 2 hours reflux in benzene, this thermal reaction being a part of Fletcher's work.[4] The reaction period was extended to 12 h but this simply resulted in isomerisation of itaconic to citraconic anhydride. No cycloadduct was formed.

The LPDE approach was then examined with the non-functionalised diene, 2-methyl-1,3-butadiene (52), using dienophile (20). This reaction was performed 1.0M in diene and 0.2M in dienophile employing 5.0M lithium perchlorite in diethyl ether. After 6 h reaction time and usual work-up a 96% yield of cycloadduct (53) was obtained as colourless crystals (Scheme 22).

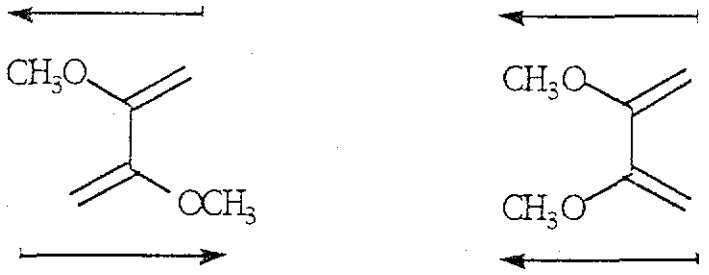
Scheme 22



(52) (20) (53)

Under the 5.0M LPDE condition, a high yield was obtained using non-functionalised dienes (18) and (52) with (20). However, (23) gave intractable tar under the same conditions. It is of interest to consider why (23) is less reactive than (18) and (52) on electronic grounds. The more electron rich diene, would be expected to be the more reactive. It is the cis form of the diene which undergoes the reaction and it is likely that the formation of this species for (23) is unfavourable. This can be explained on the basis of dipolar interactions. The C-O bonds in (23) are strongly polarised and in the cis form these dipoles have an unfavourable interaction which is not present in the trans form (Scheme 23).

Scheme 23



(23)

1-Acetoxy-1,3-butadiene, which was expected to be highly reactive for Diels-Alder reactions, was reacted with (20) in 5.0M LPDE solution under Grieco's conditions.[27] After 1 h reaction time polymeric material was obtained. Changing the concentration of components, diene and dienophile, again gave polymeric material. 1,4-Diphenyl-1,3-butadiene was also reacted with itaconic anhydride in the 5.0M LPDE solution system. After 4 days stirring at ambient temperature and pressure in 5.0M LPDE solution only starting material (25) was recovered.

Several attempts were also made to condense furan and substituted furans with itaconic anhydride in the presence of 5.0M LPDE solution. Thus, 2,5-dimethylfuran and 3,4-dimethoxyfuran were prepared. These furan derivatives were reacted with itaconic anhydride for different lengths of time (1 to 6 days) in the 5.0M LPDE solution. After the usual work-up only the

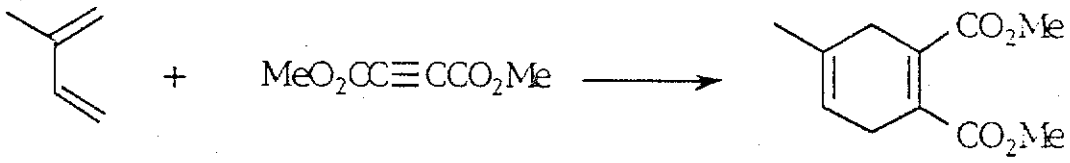
corresponding starting materials recovered. The furan derivatives were also reacted with itaconic anhydride just by heating in toluene, but partial isomerisation of itaconic to citraconic anhydride occurred in each case, as reported by Fletcher in the PhD thesis.[4] Despite the fact that furan and its derivatives are poor Diels-Alder dienes because of their aromatic nature, a surprisingly high yield was obtained in the reaction with furan with 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (37) in the presence of 5.0M LPDE solution using Grieco's procedure[27] (Scheme 15).

Besides the above dienes, cyclopentadiene and 2-trimethylsilyloxy-1,3-butadiene (29) also were used in an attempted reaction with itaconic anhydride in the presence of LPDE solution. Unfortunately, the reaction did not proceed. Cyclopentadiene gave a polymer within 1 minute at ambient temperature and pressure. All attempts to achieve condensation of (29) with itaconic anhydride failed because of cleavage of the silyl enol ether, and itaconic anhydride was partially recovered after 1 h reaction in 5.0M LPDE solution.

Most of the Diels-Alder reactions involving itaconic anhydride using $LiClO_4$-Et_2O as catalyst were carried out at ambient temperature and pressure. Only, the non-functionalised dienes (18) and (52) gave high yields of cycloadduct with itaconic anhydride under these conditions. At the moment the very limited efficiency of 5.0M LPDE solution as a catalyst in the Diels-Alder reactions using itaconic anhydride is not understandable. Using 5.0M LPDE as a rate accelerator for Diels-Alder reactions, we had expected to obtain moderate to high yields of cycloadducts with itaconic anhydride.

The largely negative results obtained in the present limited study contrast with the apparently straightforward and general rate accelerations and yield improvements recorded by Grieco for a variety of Diels-Alder reactions. In view of this unexpected discrepancy it was decided to re-examine part of Grieco's work. Thus, 2-methyl-1,3-butadiene (52) was reacted with dimethyl acetylenedicarboxylate (DMAD) (54) in 5.0M lithium perchlorate-diethyl ether. This reaction was performed 1M in diene (52) and 0.2M in dienophile (54) employing 5.0M LPDE solution and after 8 h stirring at ambient temperature and pressure a 92% yield of cycloadduct (55) was obtained (Scheme 24). At the same reaction 94% yield was obtained by Grieco (Table 2). This was a good

Scheme 24

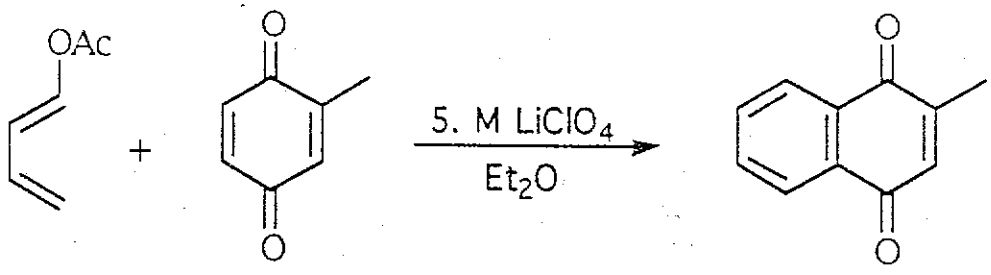


(52) (54) (55)

result for the Diels-Alder reaction. But, it is clear that both diene (52) and dienophile (DMAD) are highly reactive in the [4+2] cycloaddition reaction. Sc the high yield is partially due to the reactivity of these reactants and not only to the effect of the 5M LPDE solution.

After examination of Grieco's study, 5M LPDE solution were tried on the different dienes and dienophiles. In this section the study was continued by using 1-acetoxy-1,3-butadiene (28) and methyl-1,4-benzoquinone (56) in the 5M LPDE solution. In this reaction (28) and (56) were stirred in 5M LPDE solution for 5 h at ambient temperature and pressure. The reaction mixture was then extracted with diethyl ether and the solvent was evaporated under reduced pressure to give a 96% yield of crude product, 2-methyl-1,4-naphthoquinone (57), as white crystals. The crude product was purified by column chromatography (dichloromethane:diethyl ether/ 3:1) to give pure product 2-methyl-1,4-naphthoquinone (57) in good yield 90% (Scheme 25).

Scheme 25

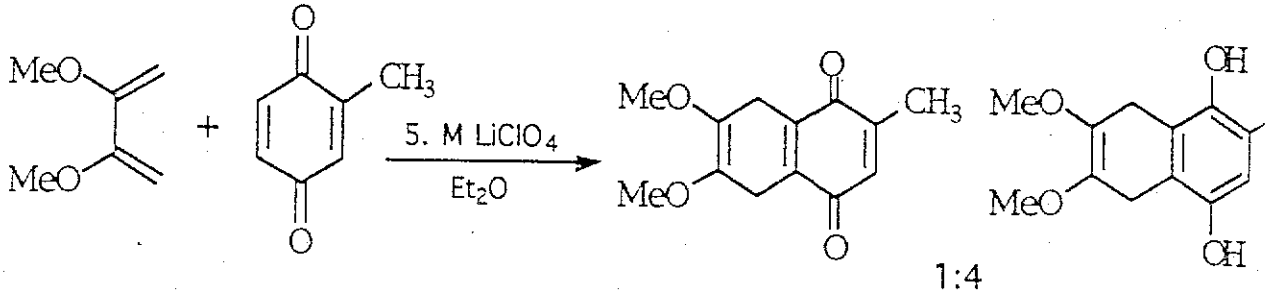


(28) (56) (57)

Another successful result was obtained in the reaction of 2,3-dimethoxy-1,3-butadiene (23) with methyl-1,4-benzoquinone (56). Using the same procedure a mixture of (23) and (56) was stirred with the catalyst solution for 6 h at room temperature and atmospheric pressure. After the

usual work-up, 3 spots were seen on the TLC of which one was baseline and the other two were the Diels-Alder cycloadducts (58) and the tautomeric diphenol (59) (Scheme 26).

Scheme 26



(23) (56) (58) (59)

^{1}H nmr and IR results indicated that these two products were 4a,5,8,8a-tetrahydro-6,7-dimethoxy-1,4-naphthalenedione (58) and 5,8-dihydro-6,7-dimethoxy-1,4-naphthalenediol (59) in a ratio of 1:4. Full details of this reaction are given in the experimental section.

The study with 5M LPDE solution in the Diels-Alder reaction was also carried out using 2,5-dimethylfuran. At ambient temperature and pressure an attempt was made to react the diene with citraconic anhydride (48). After 4 days, during which the reaction was monitored by TLC, no reaction occurred. In the second attempt, 2,5-dimethylfuran and methyl-1,4-benzoquinone was stirred in the presence of 5.0M LPDE solution for 4 days, but again starting materials were recovered.

1-Acetoxy-1,3-butadiene (25) was also reacted with maleic anhydride in 5M LPDE solution. In this reaction polymeric material was obtained after 3 h stirring at room temperature and atmospheric pressure and this has not been identified. Thus three attempts to obtain Diels-Alder adducts failed using 5M LPDE solution.

In this study 5M LPDE solution was examined in the Diels-Alder reaction using itaconic anhydride with different dienes.. Rate acceleration has been observed with non-functionalised dienes, but functionalised dienes gave

starting material or polymeric products. However, a few novel compounds have been obtained by using 5.0M LPDE solution. If rate enhancement is due to a "pressure" effect caused by the lithium perchlorate-diethyl ether solution as postulated by Grieco,[27] then the rates of all Diels-Alder reactions should by increased in this medium. But, for most reactions studied here, rate enhancements have not been observed. An alternative explanation is that rate acceleration of the Diels-Alder reaction in lithium perchlorate-diethyl ether is due to Lewis acid catalysis, with lithium ion functioning as the Lewis acid.

3.5. EXPERIMENTAL

Preparation of Itaconic Anhydride (20)

Employing the method of D'Alelio *et al.*,[33] acetic anhydride (330 g, 3.2 mol) and itaconic acid (105 g, 0.8 mol) were heated to 60-70°C with stirring in a 1 litre flask equipped with a 0.5m x 3 cm Vigreux column for distillation. When the mixture had become homogeneous, the pressure was lowered and 120 ml of distillate was collected, b.p. 54°C/30 mm Hg. Care had to be taken at this stage to avoid overheating since when this did occur isomerisation to give citraconic anhydride resulted. The mother liquor was subsequently cooled to 0°C for several hours and the resulting product was collected by filtration to give a combined yield of 70 g of product which was recrystallised from dichloromethane/ether at -30°C to give 65 g (71%) of pure material, m.p. 68°C (lit.,[33] 67-68°C).

Preparation of 5.0 M Lithium Perchlorate-Diethyl Ether (LPDE).

Reagent grade anhydrous $LiClO_4$ was found unsuitable for our use and it was therefore recrystallised twice from distilled water in the form $LiClO_4.H_2O$ and finally dried at 160°C (0.5 mm Hg) for at least 48 h.

In a 100 ml volummetric flask, the solvent-salt solution was prepared by first weighing in the necessary amount of lithium perchlorate (53.2 g, 0.5 mol). The flask was filled with the required solvent (anhydrous diethyl ether distilled over $LiAlH_4$), and the contents were stirred for 2 hours at 20°C.[37] The 5.0M LPDE solution was kept in a closed flask and used with a syringe for the reactions.

Preparation of 2,3-dimethoxy-1,3-butadiene (23)

This diene was prepared by the method of McDonald *et al.*,[36] in 62% yield and showed identical properties (IR, NMR) to those reported, b.p. 132-133°C (lit.,[36] b.p. 134-136°C).

Preparation of 1-acetoxy-1,3-butadiene (28).

This compound was prepared by the method of Hagermeyer *et al.*,[38] in 56% yield, b.p. 67-79°C/80 mm Hg (lit.,[38] b.p. 58°C/40 mm Hg).

The Cyclisation Reaction of 2,3-Dimethyl-1,3-butadiene (18) with Itaconic Anhydride.

A mixture of 2,3-dimethyl-1,3-butadiene (18) (1.8 g, 25 mmol), itaconic anhydride (20) (0.56 g, 5 mmol) and 5.0 M LPDE solution (5 ml) was stirred at ambient temperature and pressure for 4 h. Water (20 ml) was added to the reaction mixture and extracted with diethyl ether (3 x 25 ml), the solvent was evaporated under reduced pressure to give the crude colourless solid product. After column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/diethyl ether (3:1)), 0.9 g (93%) of pure 4-carboxy-4-carboxymethyl-1,2-dimethylcyclohexene (49) was obtained as colourless crystals, m.p. 102-103°C (lit.,[15] 102.5-105°C); ν_{max} (nujol mull) 1710, 1780 cm^{-1} (C=O); δ ^1H 1.64 (6H, s, 2 x CH_3), 1.7-2.3 (6H, m, ring protons), 2.75 (2H, s, CH_2CO); Anal. calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 68.21; H, 7.24.

Cycloaddition Reaction of 2-Methyl-1,3-butadiene (52) with Itaconic Anhydride.

To a solution of 5.0M LPDE (5 ml), 2-methyl-1,3-butadiene (52) (1.7 g, 25 mmol) and itaconic anhydride (0.56 g, 5 mmol) were added and the mixture was stirred at ambient temperature and pressure for 6 h. When the reaction was completed water (20 ml) was added to the reaction mixture which was then extracted with diethyl ether (3 x 20 ml). The organic phase was dried over magnesium sulphate and evaporated under reduced pressure. The solid crude product was purified by column chromatography to give 0.81 g (96%) of 4-carboxy-4-carboxymethyl-1-methyl-cyclohexene (53) as colourless crystals, m.p. 126-128°C (lit.,[15] 127-128°C); ν_{max} (nujol mull) 1720, 1780 cm^{-1} (C=O); δ ^1H 1.72 (3H, s, CH_3), 1.94-2.22 (6H, m, ring protons), 2.8 (2H, s, CH_2CO) 5.4 (1H, t, vinyl H); Anal. calcd. for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found: C, 66.72; H, 6.62.

Attempted Cycloaddition of 2,3-Dimethoxy-1,3-butadiene (23) with Itaconic Anhydride.

To a solution of 5.0M LPDE (5 ml), 2,3-dimethoxy-1,3-butadiene (0.34 g, 3 mmol) and itaconic anhydride (0.33 g, 3 mmol) were added and the mixture was stirred for 4 h at ambient temperature and pressure. The work-up was carried out as described for (43). An attempt was made to purify the dark brown coloured crude product by column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/ethyl acetate (3:1)). However, only itaconic anhydride was recovered. The black tar on the baseline remained unidentified.

The amount of diene (23) was increased to three fold that of itaconic anhydride but the same intractable black tar was obtained together with recovery of itaconic anhydride. Increasing the concentration of itaconic anhydride to five fold also gave intractable tar when the above reaction was repeated.

Attempted Cycloaddition of 1-Acetoxy-1,3-butadiene (25) with Itaconic Anhydride.

The above procedure was repeated using 1-acetoxy-1,3-butadiene and itaconic anhydride in the presence of 5.0M LPDE solution. After 1 h reaction time, again intractable, gummy material was obtained.

Attempted Cycloaddition of 1,4-Diphenyl-1,3-butadiene with Itaconic Anhydride.

The above procedure was repeated using 1,4-diphenyl-1,3-butadiene (1.2 g, 6 mmol) with itaconic anhydride in 5.0M LPDE solution (20 ml). The reaction mixture was stirred in a flask for 4 d at ambient temperature and pressure. After the usual work-up the starting materials were recovered in high yield.

Attempted Cycloaddition of Furan Derivatives with Itaconic Anhydride.

All furan reactions were performed at 1.0M concentration in diene and 0.2M in dienophile (itaconic anhydride) employing 5.0M LPDE solution. Reaction times were varied from 1 to 6 d but starting materials were always obtained in high yield.

The amount of diene (furan derivative) was varied from 1 equivalent to a 15-fold excess relative to itaconic anhydride, but again starting materials were obtained after 6 d reaction in 5.0M LPDE solution.

Cycloaddition of 2-Methyl-1,3-butadiene (52) with DMAD (54).

DMAD (0.43 g, 3 mmol) and 2-methyl-1,3-butadiene (1.07 g, 15 mmol) were added to a 5.0M solution of LPDE (15 ml). The reaction mixture was stirred at ambient temperature and pressure for 6 hours at which point TLC of the mixture indicated consumption of the starting material (52). The solution was quenched with water and extracted with diethyl ether (3 x 25 ml). The organic phase was dried over magnesium sulphate and evaporated under reduced pressure. The pale-yellow oily product was purified by column chromatography (silica gel: dichloromethane) to give 0.58 g (92%) of the cycloadduct dimethyl 4-methyl-1,4-cyclohexadiene-1,2-dicarboxylate (55) as a colourless liquid, b.p. 129-132°C (0.1 mm Hg) (lit.,[39] 133-136°C); ν_{max} (nujol mull) 1680, 1705 cm^{-1} (2 x C=O) 1640 cm^{-1}(C=C); δ ^1H 1.65 (3H, s, CH_3), 2.9 (4H, br, ring protons), 3.76 (6H, s, 2 x OCH_3) 5.4 (1H, m, vinyl H); Anal. calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.66. Found: C, 63.10; H, 6.72.

Cycloaddition of 1-Acetoxy-1,3-butadiene (28) with Methyl-1,4-benzoquinone (56).

1-Acetoxy-1,3-butadiene (1.68 g, 15 mmol) and methyl-1,4-benzoquinone (0.36 g, 0.3 mmol) were reacted in the presence of 5.0M LPDE solution (15 ml) according to the usual procedure. After 4 hours stirring at room temperature the reaction mixture was quenched with water and extracted with diethyl ether (3 x 30 ml). The organic phase was dried over magnesium sulphate and evaporated under reduced pressure. The crude residue was recrystallised

from ethanol to give 0.48 g (90%) of 2-methyl-1,4-naphthoquinone (57) as bright yellow crystals, m.p. 104-106°C (lit.,[40] 104-105°C); ν_{max} (nujol mull) 1680 cm^{-1} (C=O); δ ^1H 2.2 (3H, s, $-CH_3$), 6.8 (1H, m, vinyl H), 7.6-8.2 (4H, m, arom.,). Anal. calcd. for $C_{11}H_8O_2$: C, 76.74; H, 4.65. Found: C, 76.81; H, 4.58.

Cycloaddition of 2,3-Dimethoxy-1,3-butadiene (23) with Methyl-1,4-benzoquinone (56).

To a 5.0M solution of LPDE (15 ml) the diene (23) (1.68 g, 15 mmol) and the dienophile (56) were added and the reaction mixture was stirred for 6 h at ambient temperature and pressure. The reaction mixture was worked-up and TLC showed consumption of the starting material (56); two spots were present in addition to some baseline material. The crude product was purified by column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/diethyl ether (2:3)) to give 0.62 g (88%) of (58) and (59). These two products were then separated (silica gel: dichloromethane) using a chromatotron and 4a,5,8,8a-tetrahydro-6,7-dimethoxy-1,4-naphthalenedione (58) (0.10 g, 18%) and 5,8-dihydro-6,7-dimethoxy-1,4-naphthalenediol (59) (0.4 g, 72%) were obtained as colourless products.

Spectral Data for (58)

M.p. 172-174°C ;

IR (nujol mull) cm^{-1}: ν_{max} 1680, 1705 (C=O), and 1640 (C=C);

NMR: δ ^1H 2.2 (3H, s, $-CH_3$), 3.4 (4H, s, ring), 3.64 (6H, s $-OCH_3$), 6.42 (1H, s, vinyl H).

Anal. calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 5.98. Found: C, 66.91; H, 6.04.

Spectral Data for (59)

M.p. 143-145°C ;

IR (nujol mull) cm^{-1}: ν_{max} 2450-3500 (br., -OH);

NMR (d_6-acetone) : δ ^1H 2.12 (3H, s, $-CH_3$), 3.36 (4H, s, ring), 3.6 (6H, s $-OCH_3$), 6.40 (2H, br., -OH) 7.42 (1H, s, arom.,).

Anal. calcd. for $C_{13}H_{16}O_4$: C, 66.10; H, 6.77. Found: C, 66.23; H, 6.76.

Attempted Cycloaddition of 1-Acetoxy-1,3-butadiene (25) with Maleic Anhydride.

Diene (25) (1.68 g, 15 mmol) and dienophile (0.3 , 3 mmol) were added to 5.0M LPDE solution (25 ml), and the reaction mixture was stirred for 2 h at room temperature. Viscous material was formed during the reaction which could not be identified. Changing the concentration of reactants gave the same results.

Attempted Cycloaddition of 2,5-Dimethylfuran with Citraconic Anhydride (48).

Dimethylfuran (1.44 g, 15 mmol) and anhydride (48) (0.34 g, 3 mmol) were added to 5.0M LPDE solution (15 ml) and the mixture was stirred for 3 d at ambient temperature and pressure. After work-up starting material was recovered in good yield.

Attempted Cycloaddition of 2,5-Dimethylfuran with Methyl-1,4-benzoquinone (56).

Dimethylfuran (1.44 g, 15 mmol) and benzoquinone (56) (0.36 g, 3 mmol) were stirred at room temperature and pressure for 3 days in the presence of 5.0M LPDE solution (25 ml) but again starting materials were recovered in good yield.

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CHAPTER 4

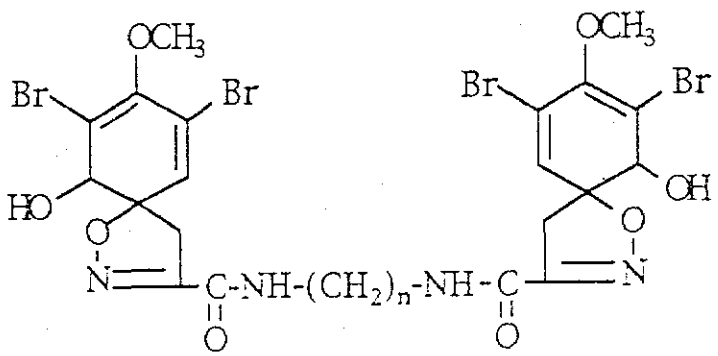
Oxidative Cyclisation Reaction of p-Phenolic Oximes Using PIFA

4.1 INTRODUCTION

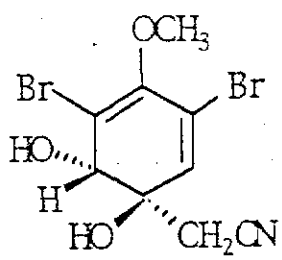
4.1.1 Oxidative Cyclisation Reactions

The sponge metabolites aerothionin (1) and homoaerothionin (2) have been isolated from *Verongia thiona* and *Verongia aero-phoba*,[1] and shown to have antimicrobial properties. Many organobromo compounds are of marine origin and are found widely in algae[2] and sponges.[3] Other examples include simple dibromo compounds such as (3) and (4), which have also been isolated from *Verongia* sponge (Scheme 1). [4,5]

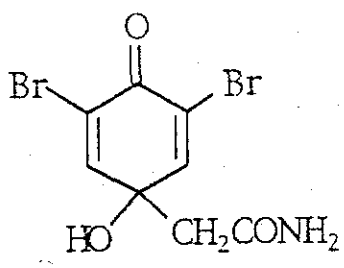
Scheme 1



1, n=4
2, n=5



(3)

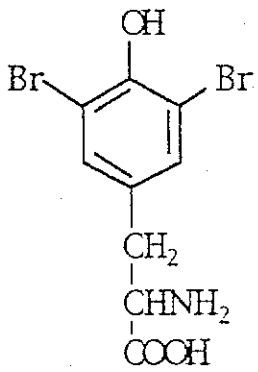


(4)

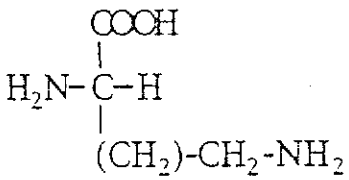
It is probable that the *Verongia* metabolites which are shown above have 3,5-dibromotyrosine (5) as a precursor[5] and presumably the central C_4N_2 and

C_5N_2 chains of aerothionin and homoaerothionin are derived from ornithine (6) and lysine (7) respectively (Scheme 2). Consistent with this postulate, dibromotyrosine and lysine both exist in sponge proteins.[6]

Scheme 2



(5)

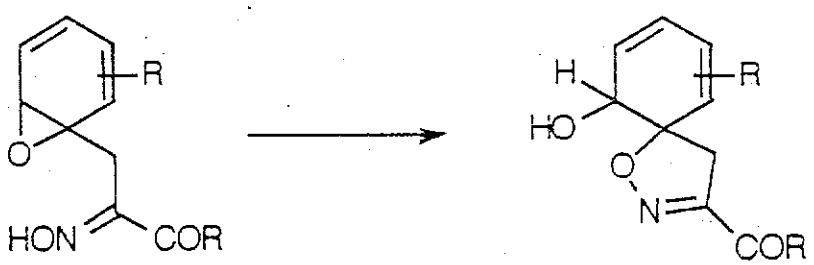


(6),n=2

(7),n=3

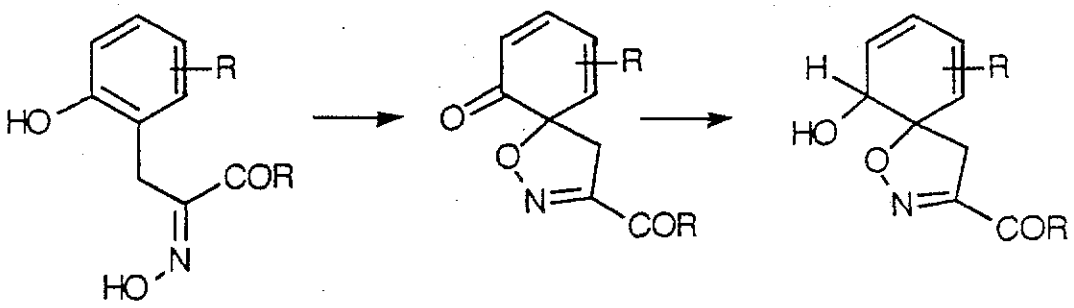
At this point we will discuss the spirocyclohexadienylisoxazoline system common to aerothionin and homoaerothionin and exemplified by (9). The isoxazoline system may arise in various ways, including nucleophilic attack by an oxime function in a modified tyrosinyl unit on an arene oxide (8) (Scheme 3),[7] or by conversion of the latter into a phenol (10) followed by intramolecular phenol-oxime coupling to form the dienone (11), which would be reduced to give (9) (Scheme 4).

Scheme 3



(8) (9)

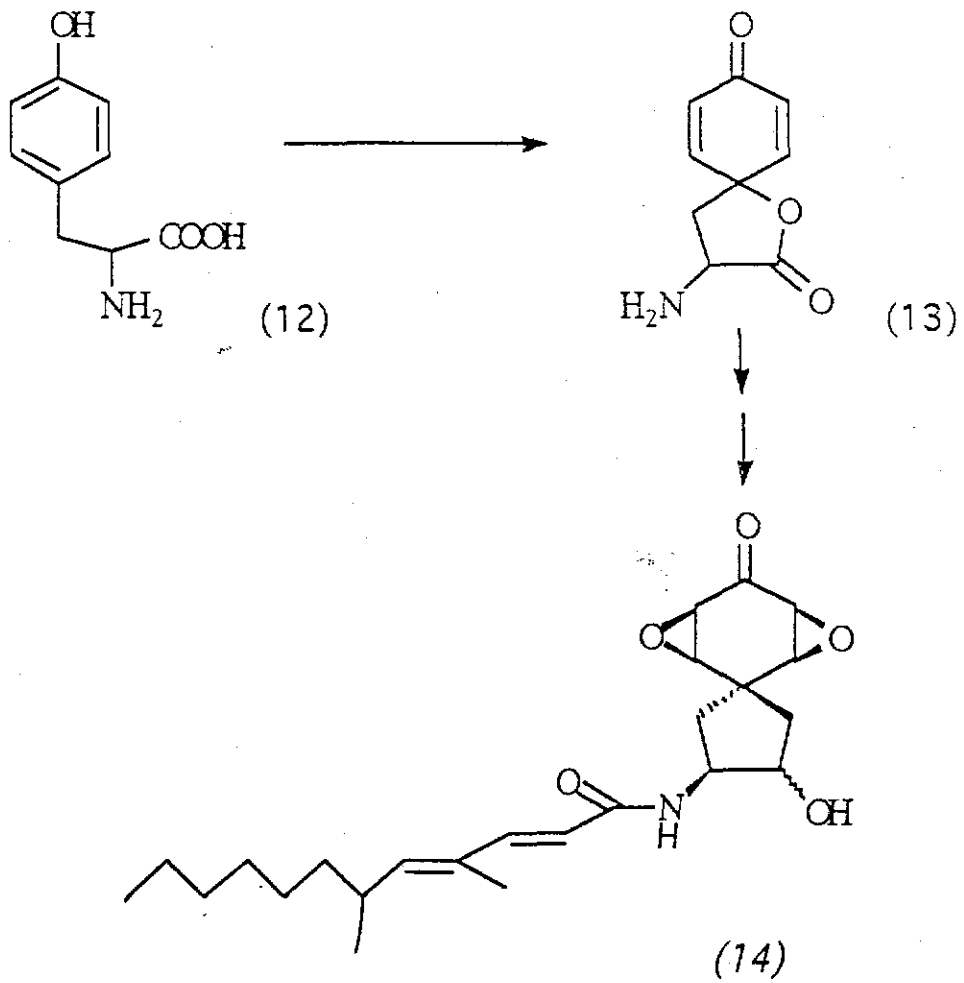
Scheme 4



(10) (11) (9)

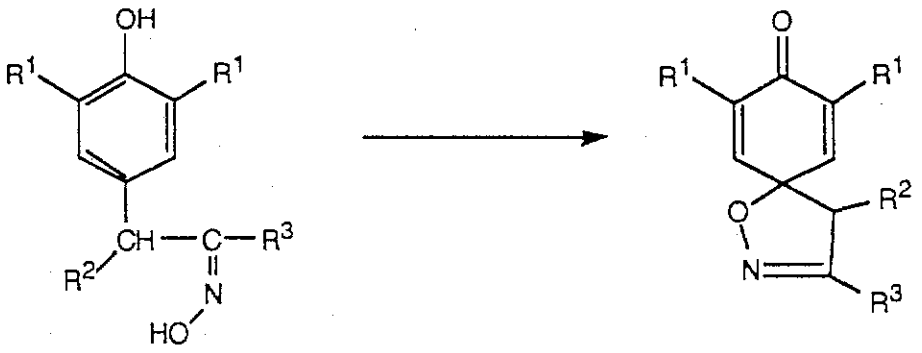
Phenolic cyclisation reactions have been proposed previously in the literature as biosynthetic steps in the formation of many other natural products. For example, aranorosin (14) is a naturally occurring molecule isolated from the fungal strain *Pseudoarachniotus roseus*,[8] which may be derived from

Scheme 5

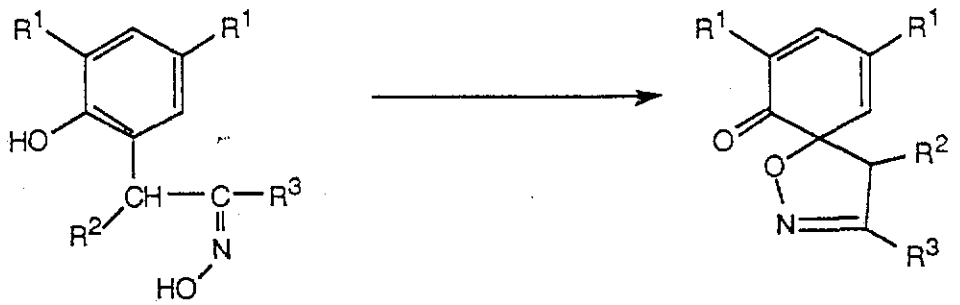


tyrosine (12) by an initial cyclisation reaction to form the spirolactone derivative (13) (Scheme 5).

Scheme 6



(15) **a** R^1=H, R^2=H, R^3=H (16)
b R^1=H, R^2=H, R^3=CH_3
c R^1=^{t}Bu, R^2=H, R^3=CH_3
d R^1=^{t}Bu, R^2=CH_3, R^3=CH_3
e R^1=H, R^2=H, R^3=CO_2CH_3
f R^1=Br, R^2=H, R^3=CO_2CH_3
g R^1=^{t}Bu, R^2=H, R^3=CO_2CH_3



(17) **a** R^1=H, R^2=H, R^3=CO_2CH_3 (18)
b R^1=H, R^2=H, R^3=CH_3
c R^1=^{t}Bu, R^2=H, R^3=CH_3

In model studies,[9,10] the cyclisation of the *p*-phenolic oximes (15a-g) and *o*-phenolic oximes (17a-c) into the corresponding spiro-isoxazolines (16a-g), and (18a-c) have been studied as a potential basis for the synthesis of aerothionin (1) and homoaerothionin (2) (Scheme 6).

A number of oxidising agents have been examined for the cyclisation of the phenolic oximes. Lead tetraacetate, potassium ferricyanide, silver oxide, sodium periodate, Fremy's salt and manganese(III) tris(acetylacetonate) (MTA) have been employed for the preparation of 1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (16a-g). Among these oxidising agents, MTA has been found to be the most effective reagent. Sodium periodate, silver oxide and Fremy's salt failed to achieve cyclisation of 1-(4-hydroxy-3,5-di-*t*-butylphenyl)propan-2-one oxime (15c) and 3-(4-hydroxy-3,5-di-*t*-butylphenyl)butan-2-one oxime (15d), and gave mainly the parent ketones. Alkaline ferricyanide yielded a symmetrical dimer when it was reacted with *p*-phenolic oxime (15d). But oxidation of the same oxime with lead tetraacetate afforded the corresponding spiro-isoxazoline (16d) in 19% yield.

The results of oxidations of the *p*-phenolic oximes with MTA are summarised in Table 1.

Table 1 Oxidative Cyclisation of p-Phenolic Oximes (15) with MTA.[10]

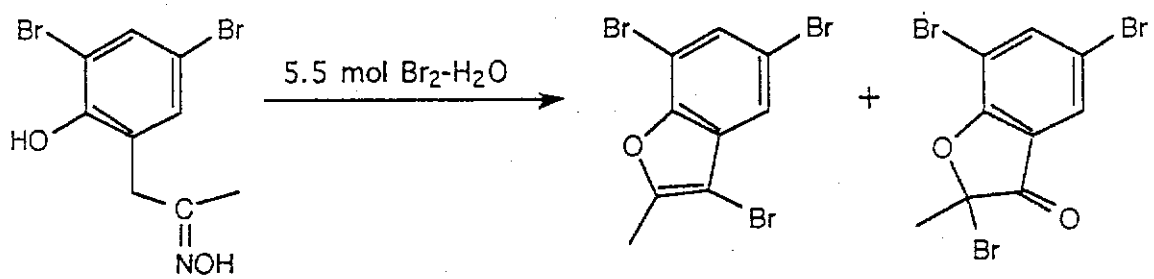
Oximes	Solvent	Conditions	Yield of (16) %
15a	CH_3CN	Δ[1]	19
15b	CH_3CN	Δ	50
15c	CH_3CN	Δ	40
	CH_3CN	R.T.[2]	40
	CH_3OH	Δ	60
	C_2H_5OH	Δ	62
15d	CH_3CN	Δ	31
	CH_3CN	R.T.	31
	CH_3OH	Δ	25
15e	CH_3CN	Δ	42

[1] Δ=Reflux for 5 h.

[2] R.T.=Stirring in acetonitrile at room temperature for 25 h

MTA has also been examined for the cyclisation of the *o*-phenolic oxime 17c, but unfortunately failed to give the spiro-isoxazoline 18c. MTA was not in fact an effective reagent for the conversion of *o*-phenolic oximes into the corresponding spiro-isoxazolines and hence could not be used in a possible biogenetic route to aerothionin or homoaerothionin. Besides MTA, molecular bromine, N-bromosuccinimide and 2,4,4,6-tetrabromocyclohexa-2,5-dienone have also been examined for the cyclisation of para and, especially, ortho phenolic oximes. The cyclisation of methyl 4-hydroxyphenylpyruvate oxime (15f) with bromine-water was successful, and gave 7,9-dibromo-8-oxo-1-oxa-2-azaspiro-[4,5]deca-2,6,9-triene-3-carboxylate (16f) in 65% yield. However, use of molecular bromine with the o-phenolic oxime (19) gave the tribromobenzofuran(20),together with the tribromobenzofuranone (21) (Scheme 7); no spirocyclic products were obtained.

Scheme 7



(19) (20) (21)

N-Bromosuccinimide reacted smoothly with the *p*-phenolic oxime (15c) and a 72% yield of corresponding spiroisoxazoline product was obtained. Attempted cyclisation of *o*-phenolic oximes with N-bromosuccinimide was, however, unsuccessful.[9] For the cyclisation of o-phenolic oximes, 2,4,4,6-tetrabromocyclohexa-2,5-dienone was used and 20% was the highest yield obtained when (17c) was the cyclisation substrate.[10]

Hypervalent iodine compounds, especially (diacyloxyiodo)arenes have been found to be useful reagents for the oxidative cyclisation of certain phenol derivatives, and have been used in some natural product syntheses. The most frequently used (diacyloxyiodo)-arene reagents are phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis-trifluoroacetate (PIFA).

4.1.2. PIFA and Related Reactions

The general reactivity of PIDA and PIFA are very similar. PIFA, whose preparation and molecular structure will be mentioned in the results section, has been used in a variety of synthetic transformations and moderate to good yields are generally obtained.

In 1990 PIFA and its derivatives were examined at the University of East Anglia as reagents for the cyclisation of 3-(4-hydroxyphenyl)propionic acid (22) to 1-oxaspiro[4,5]deca-6,9-dien-2,8-dione (23) (Scheme 8).[11] It was hoped that the efficiency of the cyclisation reaction might be improved by introducing different substituents into the benzene ring of the hypervalent iodine reagent and that these substituents would have an effect by altering the electron density on the iodine atom. The yields obtained in this study are given in Table 2 and show that substituents on the aromatic ring can indeed affect the yield of the cyclisation reaction.

Scheme 8

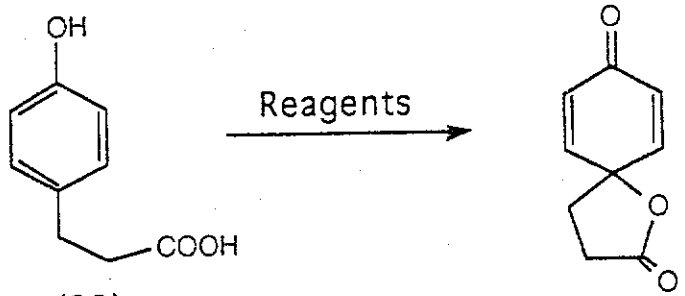


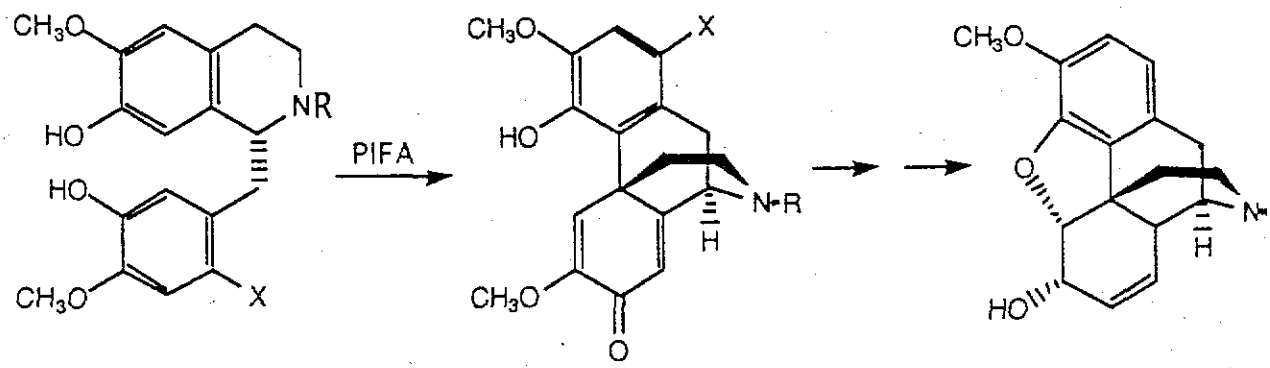
Table 2 Cyclisation of 22 to 23 in Acetonitrile

Reagent*	Yield of 23 %
$PhI(OCOCF_3)_2$	83
$4\text{-}CH_3C_6H_4I(OCOCF_3)_2$	69
$4\text{-}ClC_6H_4I(OCOCF_3)_2$	52
$4\text{-}NO_2C_6H_4I(OCOCF_3)_2$	67
$4\text{-}(F_3CCO_2)IC_6H_4I(OCOCF_3)_2$	65

* The yield of (23) using PIDA was only 27 %

Phenolic oxidative cyclisation with PIFA and related iodonium salts has also been examined in the case of (R)-N-trifluoroacetyl-6-bromonorreticuline (24), and this cyclisation step provides a very important first step for the synthesis of (-)-codeine (26) (Scheme 9).[12] PIFA was shown to be the most efficient reagent of all those examined, and gave the highest yield of 21% in the cyclisation of (24) to (25).

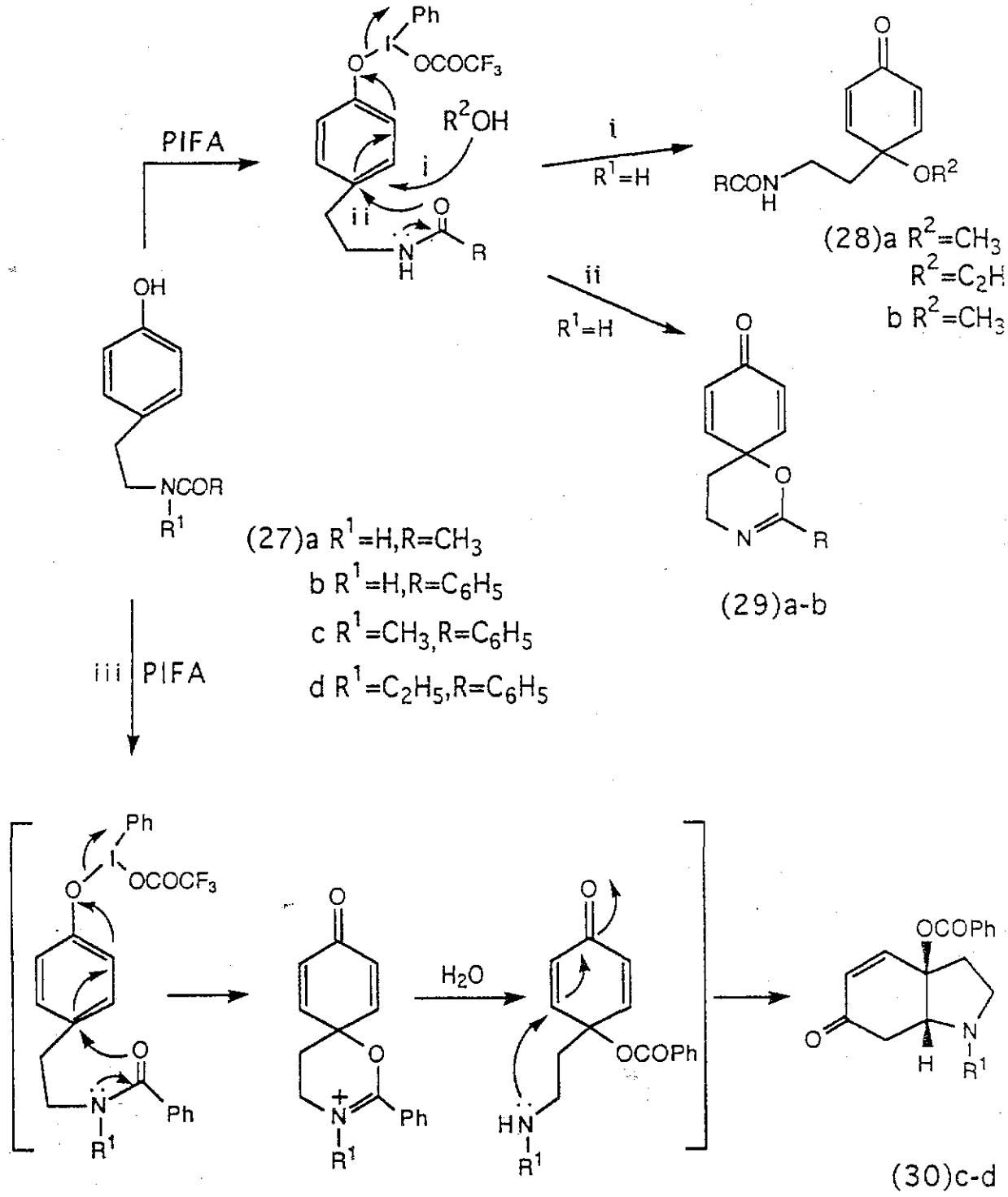
Scheme 9



(24) R=$COCF_3$, X=Br (25) (26)

PIFA has been used in a number of oxidative cyclisation reactions of phenols and related compounds which lead to different types of products. For example, oxidation of *N*-acyltyramines (27a-d) with PIFA gives quinol ethers, spirohexadienones and hexahydroindol-6-ones, depending on the reaction conditions and the starting material (Scheme 10).[6] Oxidation of *N*-acyltyramines with PIFA leads to two modes of reaction, depending mainly on the solvent used.[13] In a nucleophilic solvent such as alcohol or acetic acid, the solvent attacks the para position of the *N*-acyltyramines to give the corresponding quinol ether (28a-b) (Scheme 10-i). In a poorly nucleophilic polar solvent such as 2,2,2-trifluoroethanol, however, cyclisation occurs by the attack of the amido oxygen atom to give spirocyclohexadienone derivatives (29a-b) (Scheme 10-ii). The nature of the final product may also depend on the degree of substitution at the nitrogen atom. Thus, treatment of N-methyl and N-ethyl-N-benzoyltyramines (27c-d) with PIFA in 2,2,2-trifluoroethanol followed by aqueous work-up gave the corresponding hexahydroindol-6-ones in fair yields (30c, 54% and 30d, 48%). The mechanism of the reaction was assumed to proceed as illustrated in Scheme 10, iii.

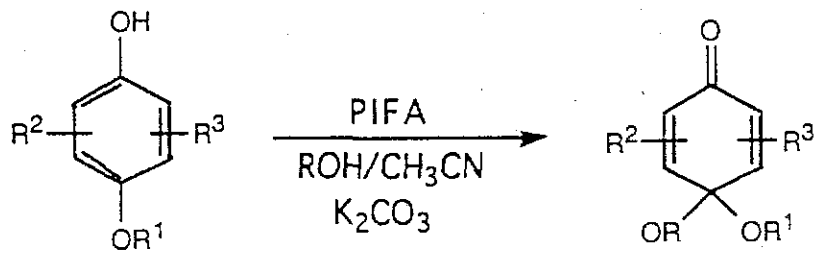
Scheme 10



Various types of *p*-alkoxyphenols (31a-d) react with PIFA to give *p*-benzoquinone monoacetals (32a-d) in excellent yields under mild conditions

(Scheme 11).[14] These are useful precursors to various types of natural products, such as tropolones[15] and rynodols.[16] In the oxidation reactions different alcohols such as methyl alcohol or isopropyl alcohol are normally used with acetonitrile as a mixed solvent system, and yields of 85-95% are obtained.

Scheme 11



(31) (32)

a R^1=CH_3 , R^2=2-allyl , R^3=3-OCH_3

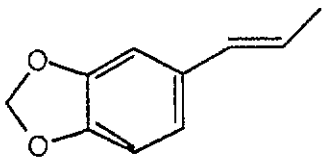
b R^1=CH_3 , R^2=3-OCH_3 , R^3=6-OCH_3

c R^1=CH_3 , R^2=3-OCH_3 , R^3=5-OCH_3

d R^1=CH_3 , R^2=3-OCH_3 , R^3=5-OCH_3

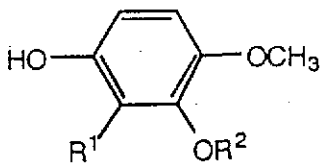
One class of neolignans, which are biologically active plant metabolites, possesses the dihydrobenzofuran skeleton (35) with trans stereochemistry, and one approach to the synthesis of the dihydrobenzofuran structure involves 1,3-cycloaddition of electron rich olefins to oxidised phenols (Scheme 12).[17] PIFA has been used for oxidative cycloaddition of styrenes, such as 1,2-methylenedioxy-4-(1-propenyl)benzene (33) to *p*-methoxy substituted phenols, such as (34a) and (34b) to form trans-dihydrobenzofurans (35a) and (35b) in 69 and 71% yields respectively. Although the scope and mechanism of this cycloaddition reaction is not completely understood, this oxidative carbon-carbon bond-forming reaction has been employed as a novel, convergent approach to neolignans containing the dihydrobenzofuran unit.

Scheme 12



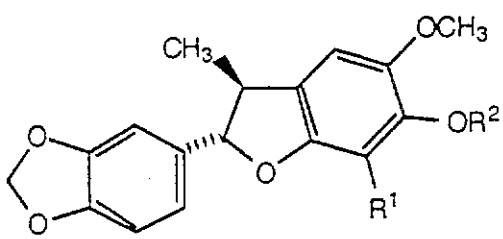
(33)

+



(34) a: R^1=H ,R^2=allyl
b: R^1=allyl,R^2=H

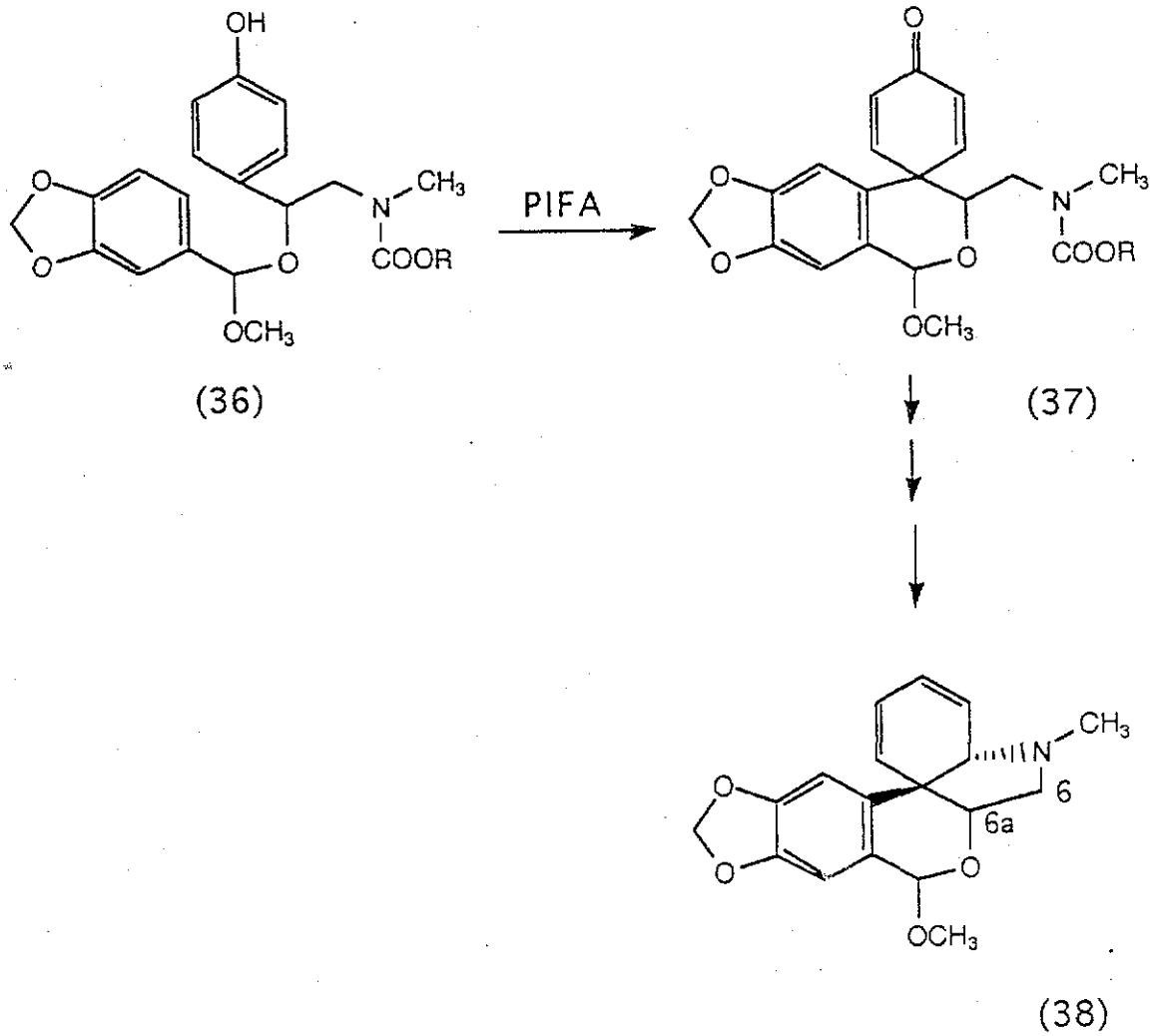
PIFA



(35) a: 69%
b: 71%

PIFA also has been employed as reagent for a key intramolecular oxidative cyclisation reaction in the synthesis of codeine and 6a-epipretazettine. In the synthesis of epipretazettine (38), it was found that the labile acetal (36) could be converted in low (13%) yield to the oxidatively coupled product (37) by treatment with PIFA in the presence of propylene oxide and dichloromethane at -10°C (Scheme 13).[18]

Scheme 13

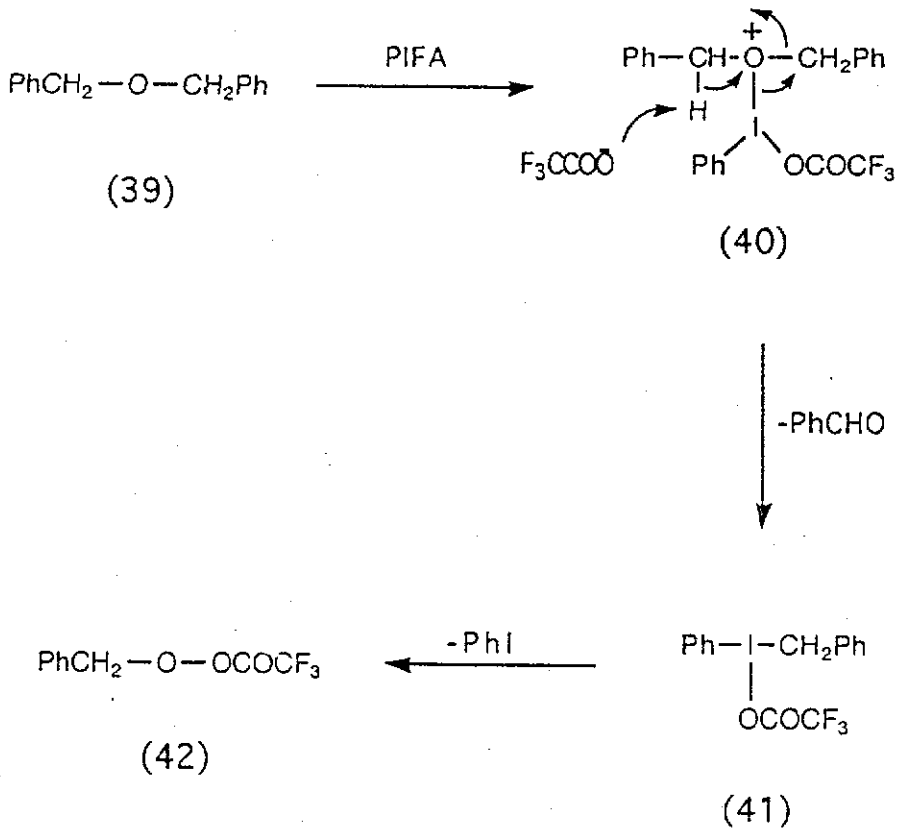


(36) (37) (38)

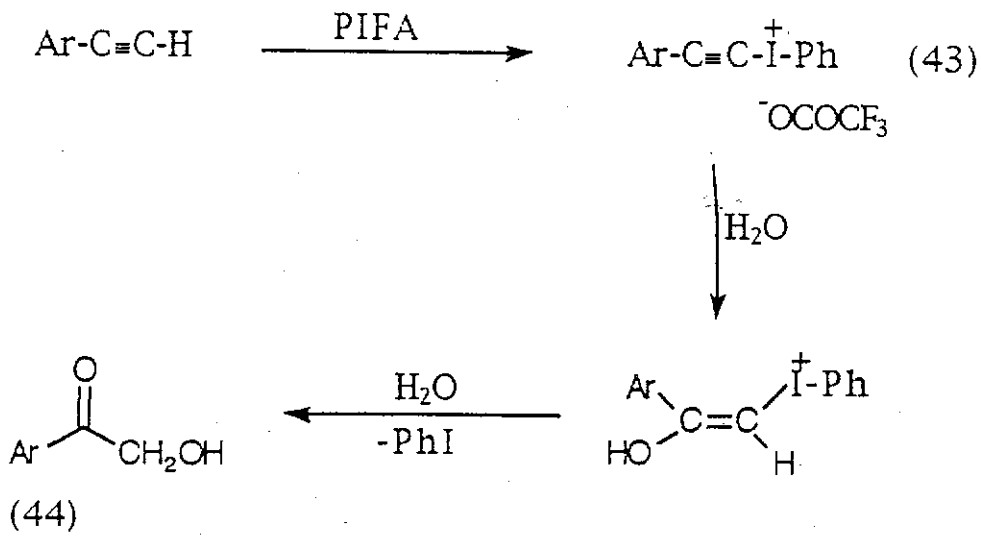
PIFA reacts readily with alkenes to give a mixture of cis- and trans-1,2-bis(trifluoroacetoxy) derivatives, but alkenes substituted with aryl groups may also form other products due to rearrangement or cleavage of the double bond.[20] The reaction of PIFA with internal alkynes gives tetrakis(trifluoroacetoxy) derivatives which form alpha-diketones on hydrolysis. With terminal alkynes, an arylalkynyliodonium salt (43) is initially formed, which is then hydrolysed to an a-hydroxy ketone (44) (Scheme 15).

In addition to its value for oxidative cyclisation, PIFA has found application for other types of oxidation, some of which are more useful than others. Dibenzyl ether (39), for example, undergoes oxidative cleavage on treatment with the reagent to give benzaldehyde and benzyl trifluoroacetate (42). The mechanism is probably as outlined in Scheme 14.[19]

Scheme 14

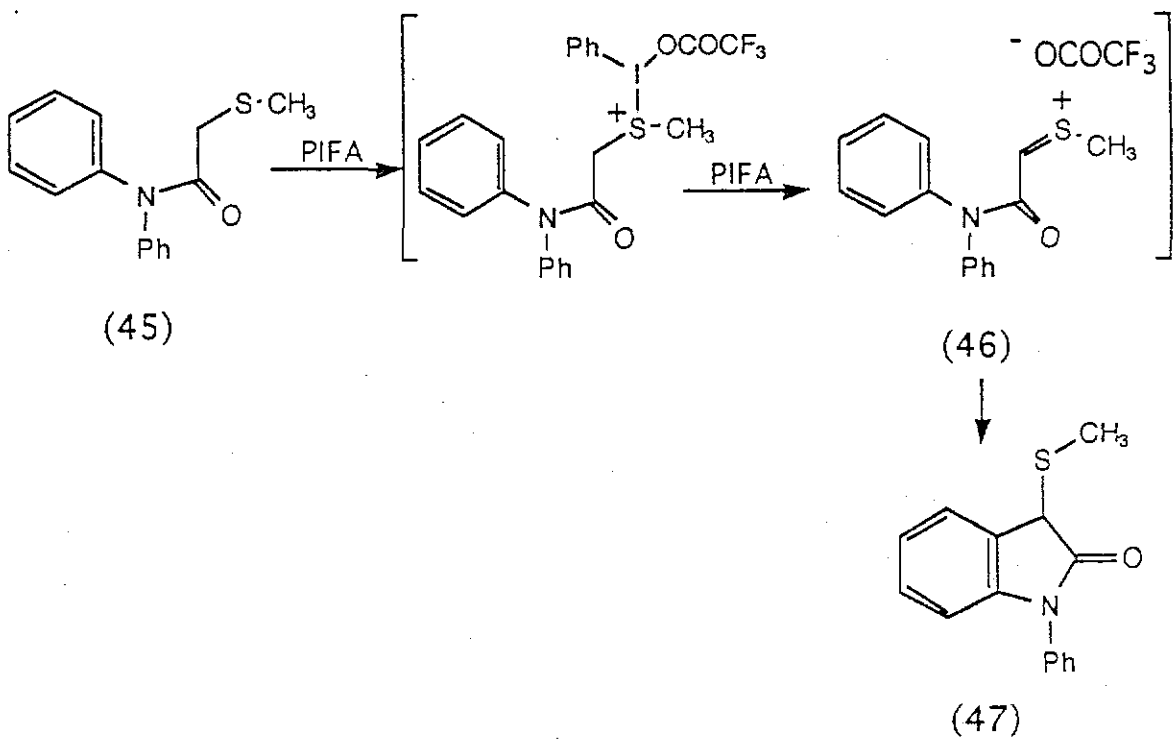


Scheme 15



In 1986 an interesting result was observed when PIFA was reacted with a-acylsulphides (45). As shown in Scheme 16, the cyclisation of *N*-phenyl-a-(methylthio)acetamide (45) to *N*-phenyl-3-(methylthio)oxindole (47) was assumed to proceed through the Pummerer reaction intermediate (46) which would be formed by attack of PIFA on the sulphur atom of (45) followed by elimination.[21]

Scheme 16



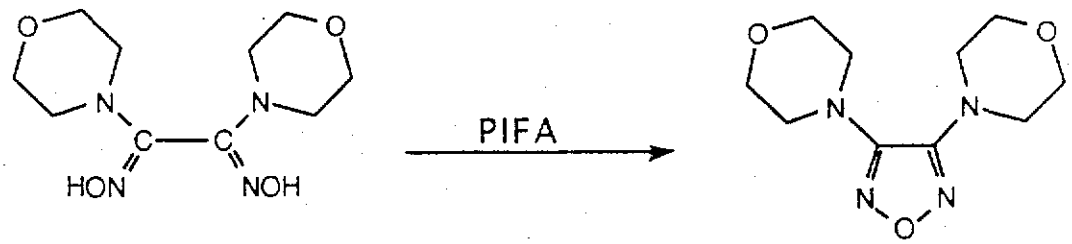
(45)

(46)

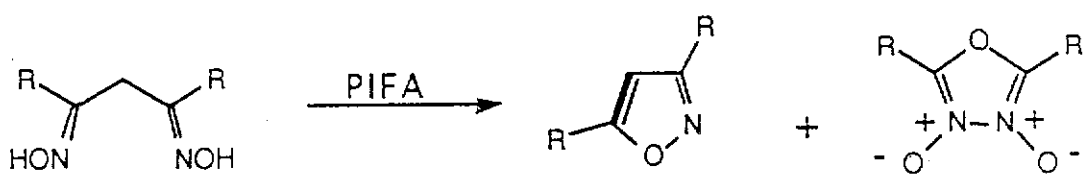
(47)

PIFA is an efficient reagent for the conversion of a number of a-dioxime derivatives such as (48) to the corresponding furoxans (49) in high yield. b-Dioximes (50), however, react to give mixtures of isoxazoles (51) and 1,3,4-oxadiazole di-*N*-oxides (52) (Scheme 17).[20]

Scheme 17



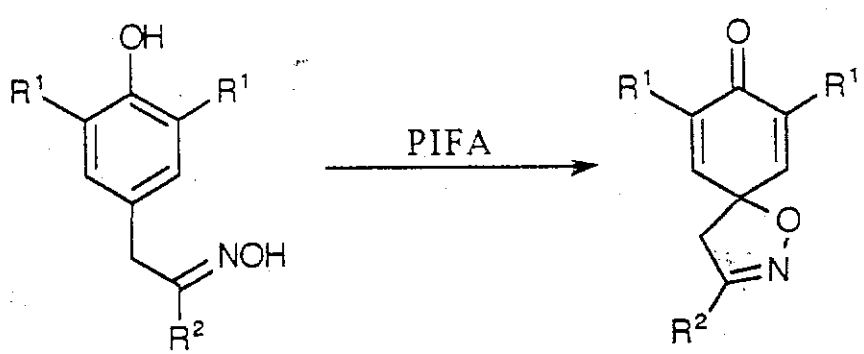
(48) (49)



(50) (51) (52)

In McKillop's group, Koyuncu attempted to cyclise various *o*- and *p*-phenolic oximes to the corresponding spiroisoxazoline compounds[22] (Scheme 18). Different solvents (acetonitrile, methanol and ethanol) and different reaction conditions were examined and moderate to excellent yields of spirocyclic

Scheme 18



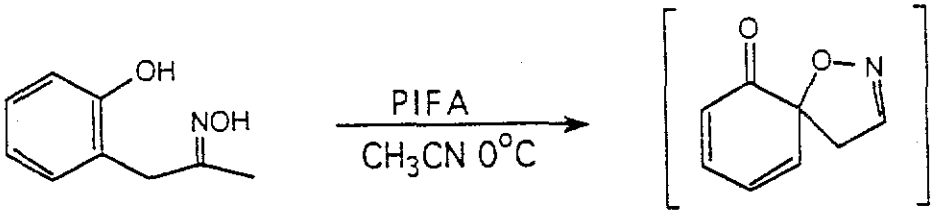
products were obtained from the *p*-phenolic oximes in a rather limited study (see Table 3).

Table 3 Oxidative cyclisation of some ketoximes in Scheme 18 with PIFA to the corresponding isoxalines.

R^1	R^2	Solvent	Spiroisoxazoline %
H	H	CH_3CN	20
H	CH_3	CH_3CN	63
Br	CH_3	C_2H_5OH	57
H	^tBu	CH_3CN	93
Br	^tBu	CH_3CN	87

Attempts to extend these results to oxidative cyclisation of the *o*-phenolic oxime (53) gave only the dimer of the initially formed oxidation product (54). The structure of the dimer was established both by spectroscopic methods and by X-ray crystallography.[22]

Scheme 19



(53) (54)

4.2. RESULTS AND DISCUSSION

In the synthetic approach to aerothionin (1), oxidative cyclisation of *p*-phenolic oximes seems to be a very promising reaction. Furthermore, spiro-isoxazoline compounds, obtained by oxidative cyclisation of phenols (ortho and para), could be very useful starting materials in various other natural product syntheses.

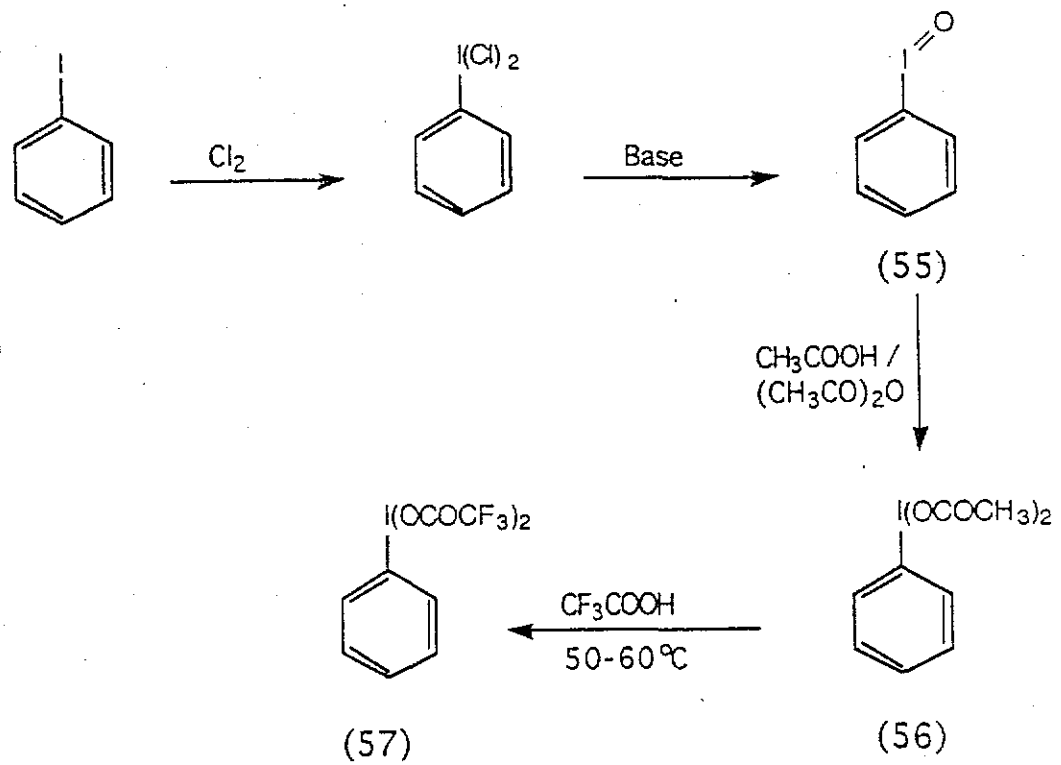
So far, a number of oxidising agents have been used for the cyclisation of para and ortho phenolic oximes as mentioned previously. Among these oxidising agents, lead tetraacetate, alkaline ferricyanide, silver oxide and Fremy's salt failed to cyclise *p*-phenolic oximes to the corresponding spirodienones. Although use of manganese (III) tris(acetylacetonate) (MTA) was successful with *p*-phenolic oximes, this reagent failed to bring about the cyclisation of *o*-phenolic oximes to the corresponding spirodienones. Cyclisation of *p*-phenolic oximes with brominating agents such as bromine and *N*-bromosuccinimide resulted in the formation of brominated spirodienones. Both bromine and *N*-bromosuccinimide also failed to cyclise *o*-phenolic oximes. The only reagent which seemed quite promising for the cyclisation of *o*-phenolic oximes was 2,4,4,6-tetrabromocyclohexa-2,5-dienone.

In this chapter a series of oxidative cyclisation reactions using PIFA is described. The efficiency of PIFA is compared with the other oxidative cyclisation reagents mentioned earlier.

4.2.1 Preparation of PIFA

A number of methods are available for the synthesis of PIFA (57). One commonly used preparative method for PIFA and its substituted derivatives is that of White *et al.*,[12] whereby PIDA (56) is easily converted to PIFA by reaction with trifluoroacetic acid at 50-60°C. PIDA can also readily be prepared from (dichloroiodo)benzene. The method involves the conversion of (dichloroiodo)arenes, which are in turn easily available from iodoarenes and chlorine, to the iodosylarenes (55) by treatment with base. These can then be converted to diacetates by dissolution in acetic acid containing a few drops of acetic anhydride (Scheme 20).

Scheme 20



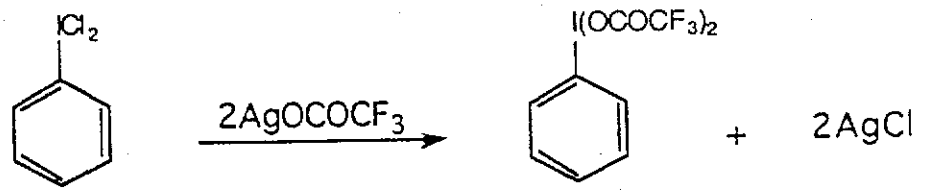
One other method for the preparation of PIDA involves the direct conversion of an iodoarene to its diacetate. This can be accomplished by various oxidising agents, such as 40% peracetic acid,[23] 30% hydrogen peroxide in acetic anhydride,[24] or sodium perborate tetrahydrate in glacial acetic acid.[25]

An alternative reagent for the preparation of PIFA and substituted derivatives of PIFA is fuming nitric acid in the presence of trifluoroacetic anhydride, which oxidises iodoarenes directly to the corresponding substituted PIFA derivatives.[26] Oxidation of iodoarenes by fuming nitric acid forms initially iodosylarenes, which are in turn known to react with carboxylic acid anhydrides to form (diacyloxyiodo)arenes. Hence the mechanism of the reaction involves a combination of these two reactions.

PIFA can also be prepared by reaction of (dichloroiodo)arenes with silver(I) trifluoroacetate in acetonitrile by a simple reaction (Scheme 21).[27] Apart from the cost of the reagent, this approach may also suffer from the

disadvantage that the product may be contaminated by silver salts, and separation and purification may be difficult.

Scheme 21

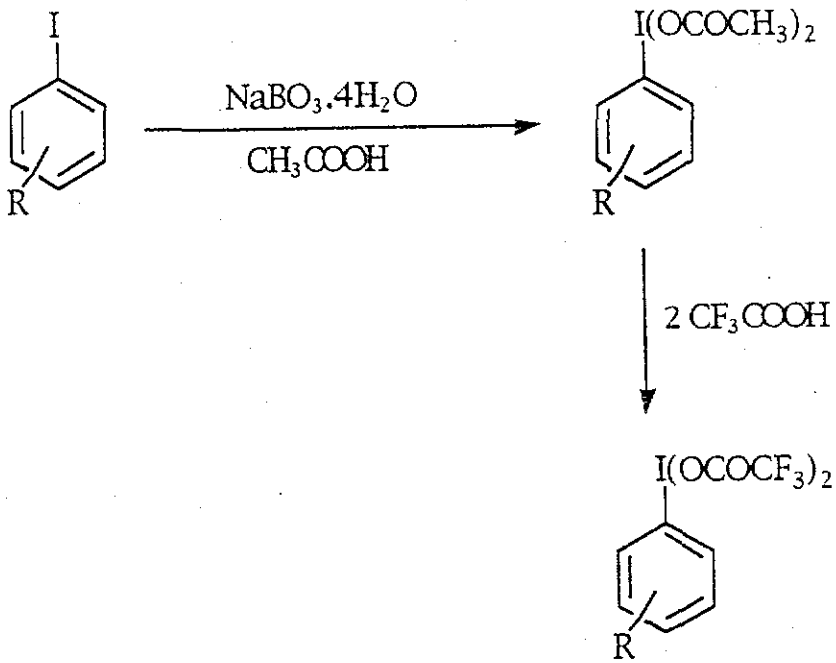


(57)

As seen above, there are many synthetic methods to obtain PIFA and its derivatives. Actually PIFA is commercially available, although it is rather expensive (Aldrich Chemical Company Limited, £10.50/10 g). The choice of the best procedure for the preparation of PIFA depends on the cost of the chemicals used, the suitability of the reactions under normal laboratory conditions and most importantly, the yield. With these factors in mind, McKillop's method[25] seems very suitable. This method has also been useful for the preparation of a number of substituted derivatives of PIFA (Scheme 22).

The procedure followed for the preparation of PIFA was via PIDA, from iodobenzene and sodium perborate tetrahydrate in acetic acid solution, as follows. A solution of the iodobenzene in glacial acetic acid was treated with a ten molar excess of sodium perborate tetrahydrate to form PIDA. The reaction mixture was stirred for about six to twelve hours, until TLC showed complete consumption of starting material. The reaction temperature was controlled with a thermostat at 40-45^{0}C. The low reaction temperature resulted in a thickening of the reaction mixture, while higher temperatures resulted in decomposition of the sodium perborate.

Scheme 22



After the consumption of all of the starting material, excess acetic acid was removed under reduced pressure and the residue was washed with water. PIDA was extracted into dichloromethane and the solvent was removed to give PIDA in 72% yield as a colourless solid. Characterisation of the colourless product was based on comparison of the physical (m.p.) and spectroscopic (^{1}H nmr) data with the literature data.[25]

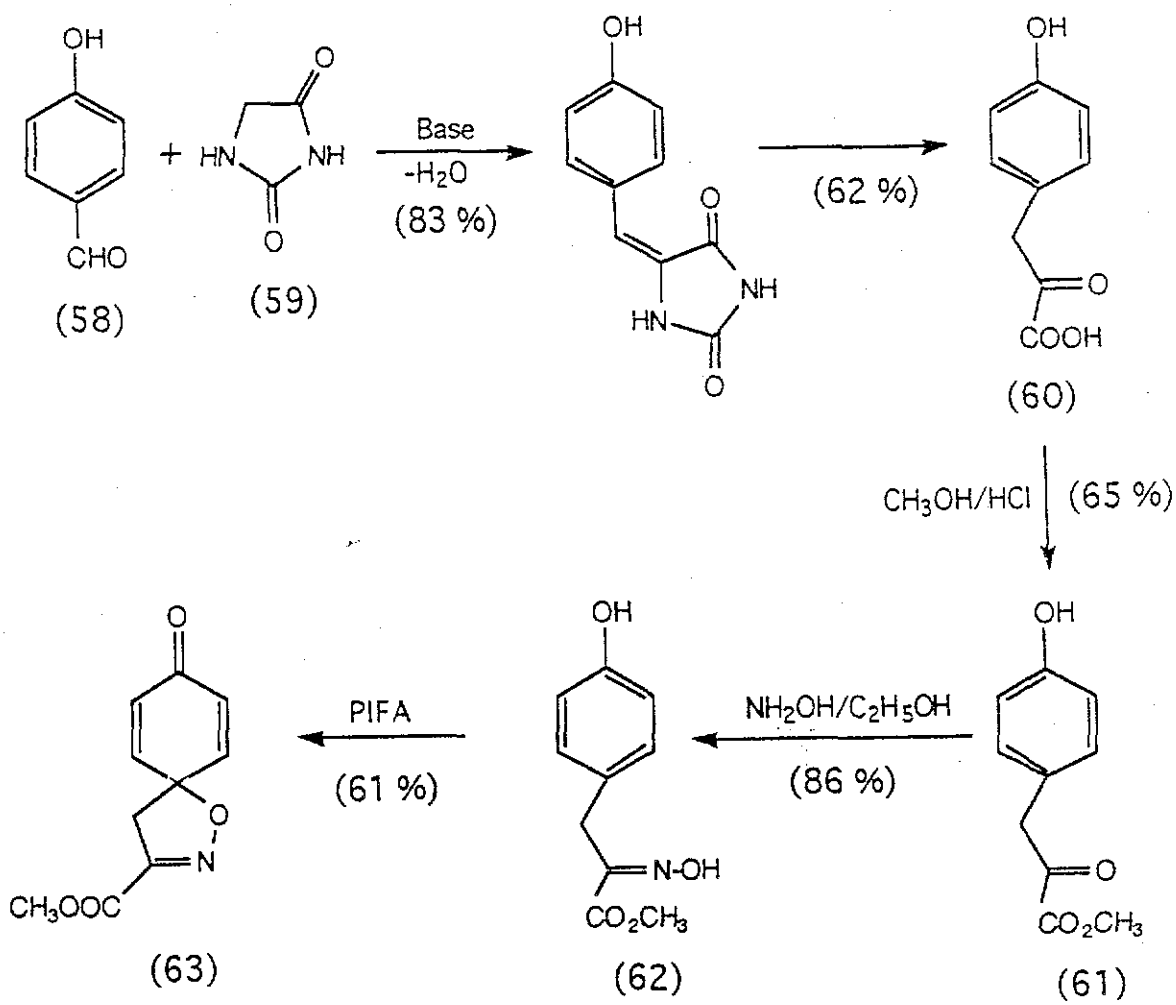
PIDA was dissolved in trifluoroacetic acid and the solution warmed up to 55-60^{0}C for a few minutes. PIFA was deposited as colourless crystals on cooling. The crystals were washed with petroleum ether and dried. An 80% yield was obtained. Physical (m.p.) and spectroscopic (^{1}H nmr) values were comparable with the literature values.[12]

4.2.2. Reaction of PIFA with *p*-Phenolic Oximes

In the cyclisation of methyl *p*-hydroxyphenylpyruvate oxime and methyl (3,5-dibromo-4-hydroxyphenyl)pyruvate oxime to the corresponding spiroisoxazoline low yields (42%, 21%) were obtained by using MTA.[10] Attempts to improve the yield of oxidative cyclisation of these oximes (62), (65) by using PIFA gave moderate yields (65%, 58%).Methyl *p*-hydroxyphenylpyruvate oxime (62) was prepared in four steps as shown inScheme 23. In the first step *p*-hydroxybenzaldehyde (58) was reacted with

hydantoin (59) in the presence of dry piperidine to give 5-(*p*-hydroxybenzal)hydantoin. At the second stage, hydantoin was reacted with sodium hydroxide solution under a nitrogen atmosphere to give *p*-hydroxyphenylpyruvic acid (60) as a pale yellow crystalline solid in good yield.[28] This acid was treated with methanol-HCl to obtain methyl *p*-hydroxyphenylpyruvate (61), and the resulting ketoester was reacted with hydroxylamine in aqueous methanol to yield 86% of ketoxime. Oximes often show characteristic C=N stretching absorptions in the IR at 1600-1690 cm^{-1}, and N-O stretching at 940-985 cm^{-1}. However, C=N absorptions cannot always be identified since they often give very weak bands. However in the IR spectrum of the ketoxime (62), the C=N stretching absorption appeared as a strong band at 1690-1720 cm^{-1} due to the presence of the ester C=O bond.

Scheme 23



Oxidative cyclisation of the ketoxime (62) by PIFA was carried out according to the procedure described for the cyclisation of phenolic oximes by MTA.[10] The dissolved solution of ketoxime and PIFA in acetonitrile was heated to reflux for almost an hour under a nitrogen atmosphere. The reaction was followed by TLC, which showed complete consumption of the starting material in 40 minutes. After separation by column chromatography, the desired product, methyl 8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (63) was obtained as a pure solid product in 65% yield. The spiro-isoxazoline (63) was identified by its characteristic dienone and carbonyl absorptions which were observed at 1715, 1680 and 1635 cm^{-1} in the IR for the carbonyl and C=C bond stretching. Full details are shown in the experimental section.

The oxidative cyclisation reaction with PIFA was repeated under different conditions. The most frequently used method is the refluxing of oximes in acetonitrile. Alternatively, ethanol can be used as solvent in place of acetonitrile. The cyclisation reaction was also carried out at 0^0C in acetonitrile but there was no significant difference in yield. However, if the amount of PIFA is changed from one to two moles, a better yield can be obtained. It was found that a 1.1:1 ratio of PIFA to ketoxime was enough for complete consumption of the starting material. Thus all these reactions were carried out using a 0.1 molar excess of PIFA and some reactions were repeated under different conditions. The reaction time for all reactions was kept to 30 to 45 minutes.

In the cyclisation of methyl *p*-hydroxyphenylpyruvate oxime to the corresponding spirodienones slightly different yields were obtained as the conditions were varied. All data are shown in Table 4.

Table 4 : Cyclisation of Methyl p-Hydroxyphenylpyruvate Oxime (62) to Methyl 8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9 -triene-3-carboxylate (63).

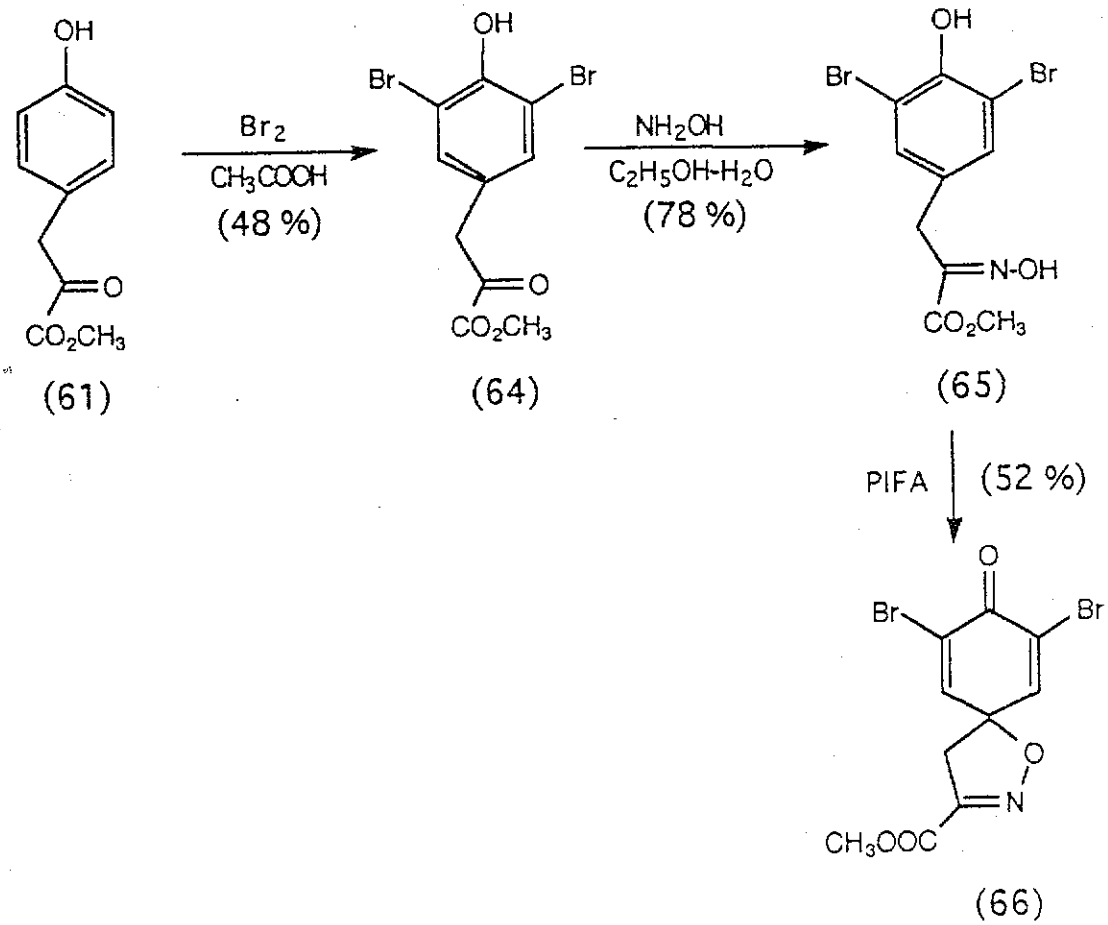
Conditions	Reaction time (min)	Yield of (63) %
CH_3CN , Δ	30	61
CH_3CN , 0^oC	45	65
C_2H_5OH , Δ	30	60

Method: see experimental section for full details.

The oxidative cyclisation of a number of different phenolic oximes was studied under the conditions established for the synthesis of the spiro-isoxazoline (63). Methyl (3,5-dibromo-4-hydroxy-phenyl) pyruvate oxime (65) was prepared from the corresponding ketone (64), which was obtained via bromination of methyl (p-hydroxyphenyl)pyruvate (61) (Scheme 24). The ketone (61) was treated with bromine in acetic acid-potassium acetate solution at 0^oC. After purification of the crude product, which had five spots on the TLC, by column chromatography, the brominated ketone (64) was obtained in 48% yield. The relatively low yield of the ketone obtained from bromination of the phenol (61) was probably due to competitive bromination a to the carbonyl group. Pure brominated ketone was treated with hydroxylamine in aqueous ethanol solution to give the keto oxime (65) in 78% yield. The oxime (65) was characterised by spectroscopic methods and elemental analysis.

The oxidative cyclisation of ketoxime (65) by PIFA was carried out under two different reaction conditions. Firstly, refluxing in ethanol, which gave 58% yield, and secondly by stirring in acetonitrile at 0^oC for the same reaction time (40 minutes), which gave a yield of 52%. The product, methyl 7,9-dibromo-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-triene-3-carboxylate (66) was obtained as colourless crystals in both cases. A slightly better yield was obtained in ethanol than in acetonitrile.

Scheme 24

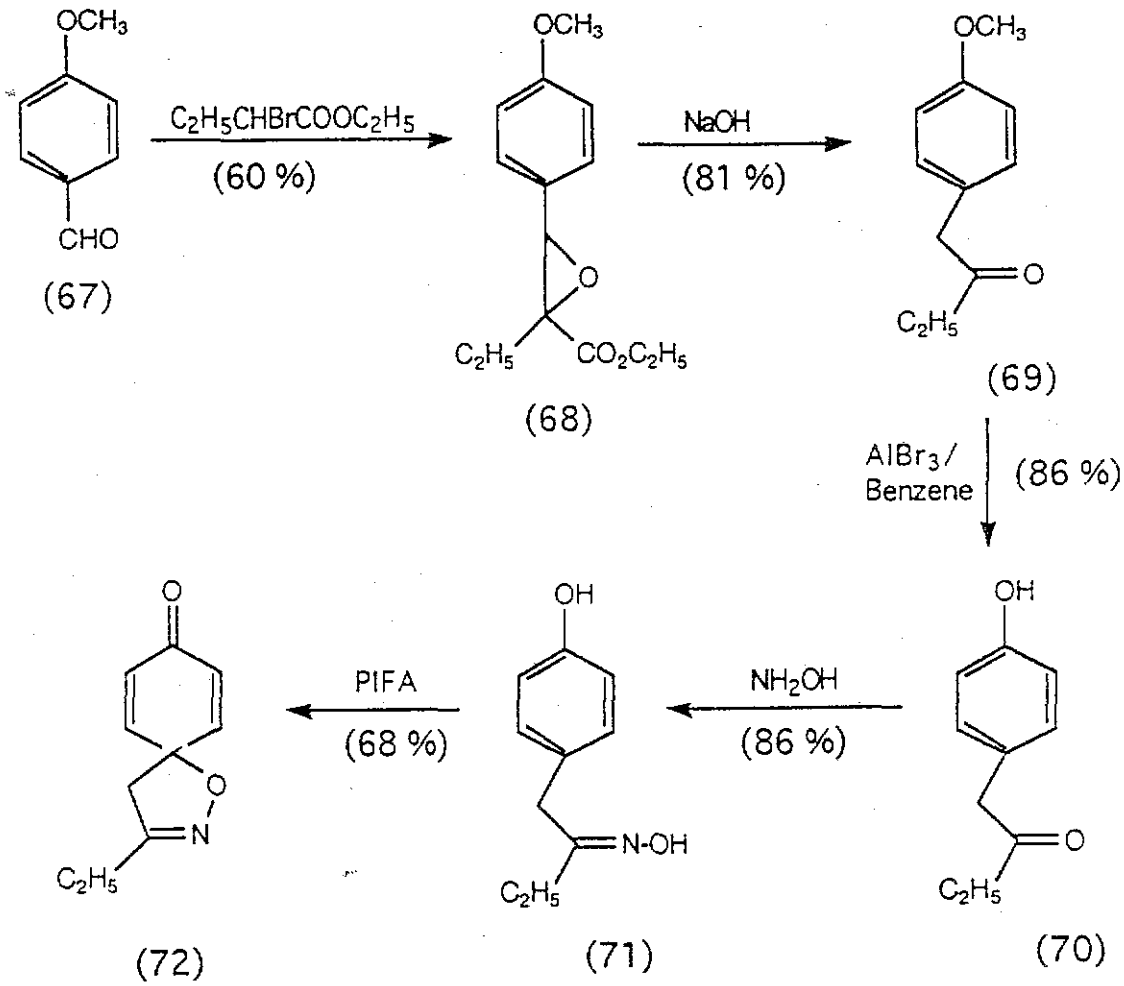


In the cyclisation reaction of methyl *p*-hydroxypyruvate oxime (62), reaction in acetonitrile gave a better yield than in ethanol. But, in the cyclisation of the dibromo substituted pyruvate oxime (65), a better yield was obtained in ethanol.

Preparation of starting material was very important in the oxidative cyclisation work. In the case of 1-(4-hydroxy-phenyl)butan-2-one oxime (71), 1-(*p*-anisyl)butan-2-one (69) was chosen as starting material. *p*-Anisaldehyde was reacted with ethyl a-bromobutyrate in the presence of strong base (NaOH) to give the glycidic ester (68) (ethyl a-ethyl-a,b-epoxy-(b-4-anisyl)propionate). The glycidic ester was refluxed in sodium hydroxide and then acidified with hydrochloric acid whereupon carbon dioxide was evolved and 1-(*p*-anisyl)butan-2-one (78%)[29] was obtained (Scheme 25). Demethylation of 1-(*p*-anisyl)butan-2-one using aluminium bromide gave 1-(4-hydroxyphenyl)butan-2-one (70) in good yield (86%). Ketone (70) was treated with hydroxylamine to give 1-(*p*-anisyl)butan-2-one oxime (71) in 86%

yield. Oxidative cyclisation of ketoxime (71) by PIFA was carried out by the previously described procedure in acetonitrile at 0°C. On TLC three spots were shown and the desired compound was separated by column chromatography to give 3-ethyl-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (72) in 68% yield.

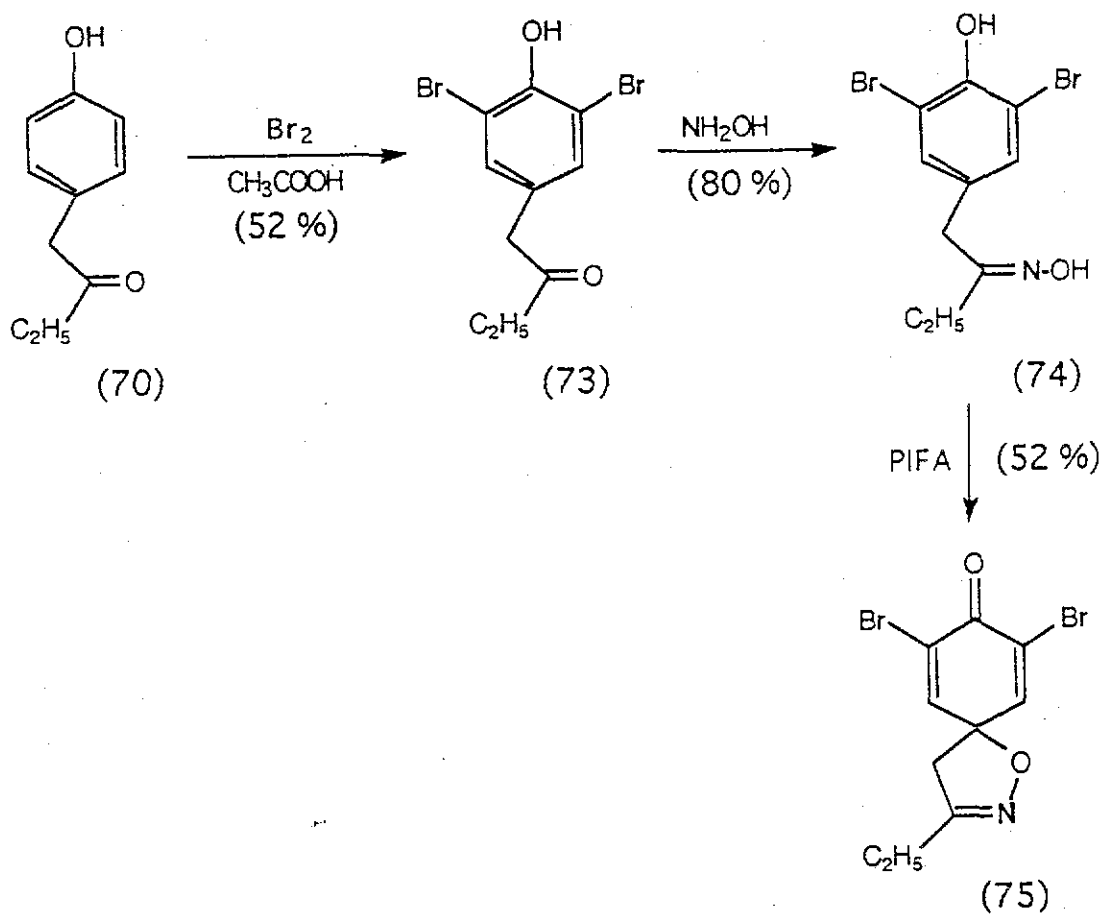
Scheme 25



Bromination of 1-(4-hydroxyphenyl)butan-2-one (70) was carried out with bromine in acetic acid and 53% yield was obtained. The yield was relatively low and TLC of the crude product showed five spots. After column chromatography the desired product, 1-(4-hydroxy-3,5-dibromophenyl)butan-2-one (73) was obtained as a pure compound. Then the brominated ketone (73) was reacted with hydroxylamine to give 1-(4-hydroxy-3,5-dibromophenyl)butan-2-one oxime (74), as a colourless crystalline solid. The ketoxime (74) was reacted with PIFA to give 3-ethyl-7,9-dibromo-1-oxa-2-

azaspiro[4,5]deca-2,6,9-trien-8-one (75) in 52% yield (Scheme 26). Oxidative cyclisation of the brominated ketoxime was carried out in ethanol at reflux temperature. In the cyclisation reactions of the brominated ketone a slightly better yield was obtained with ethanol rather than acetonitrile. Spectroscopic results and elemental analyses of these compounds are given in the experimental section.

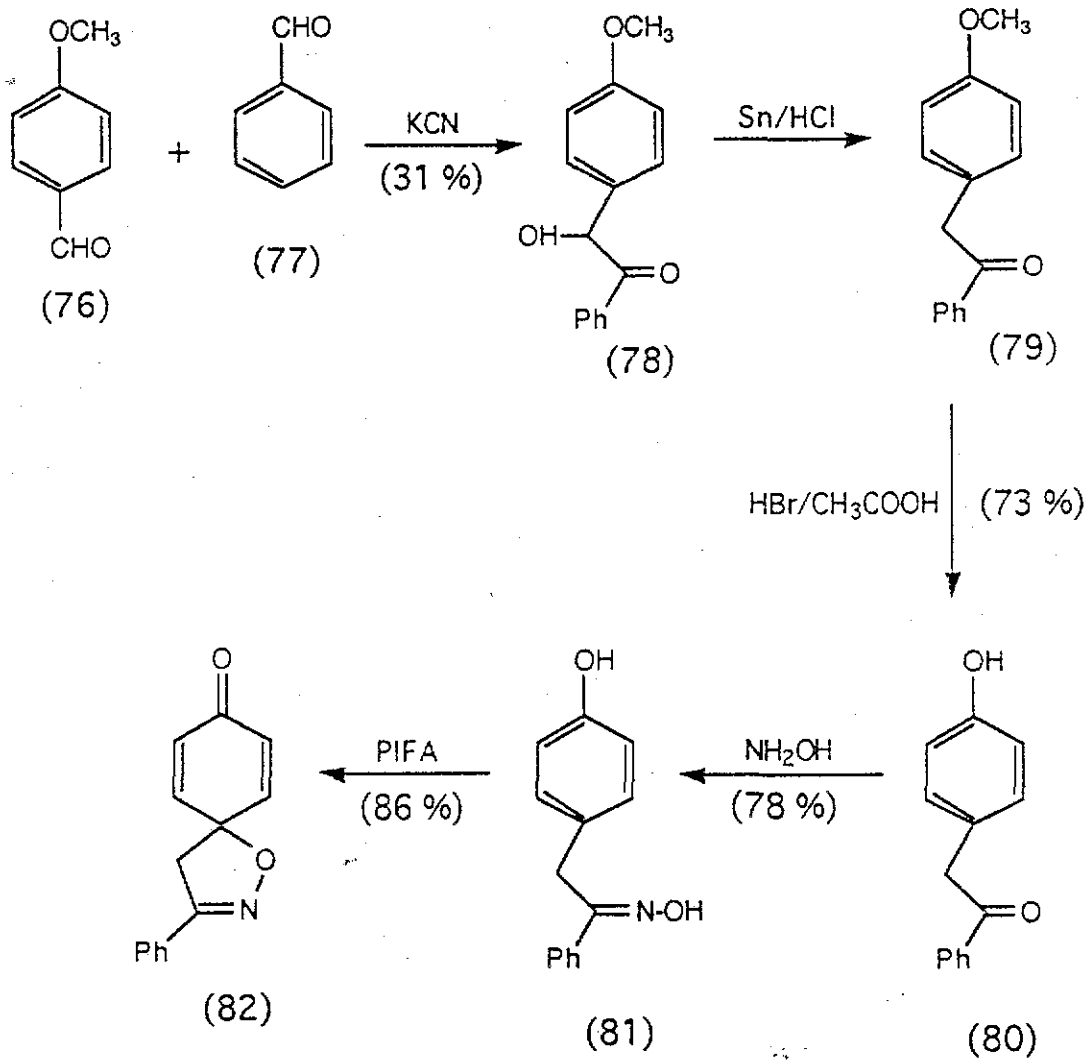
Scheme 26



p-Hydroxybenzyl phenyl *ketoxime* (80) was prepared in four steps (Scheme 27). Initially, by means of the benzoin condensation reaction, anisaldehyde (76) and benzaldehyde (77) were reacted with potassium cyanide in ethanol-water solution to form the unsymmetrical benzoin (78). Secondly, the deoxybenzoin reaction was carried out by using "mossy" tin, hydrated copper sulphate and concentrated hydrochloric acid to form *p*-methoxybenzyl phenyl *ketone* (79) in 45% yield.[30,31] Demethylation of ketone (79) was carried out using hydrobromic acid in acetic acid to form *p*-hydroxybenzyl phenyl ketone (80), and then this ketone was treated with hydroxylamine to form ketoxime

(81) (*p*-hydroxybenzyl phenyl ketoxime). Cyclisation of the ketoxime using the usual procedure with PIFA gave, after the separation of crude product by column chromatography, 3-phenyl-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (82) as colourless crystals in 86% yield (Scheme 27).

Scheme 27



Preparation of p-methoxybenzyl phenyl ketone was also studied under Friedel-Crafts conditions by using *p*-methoxyphenylacetyl chloride in benzene but all attempts failed.[32] In this reaction, *p*-methoxyphenylacetyl chloride was treated with aluminium chloride in benzene, but polymeric material was

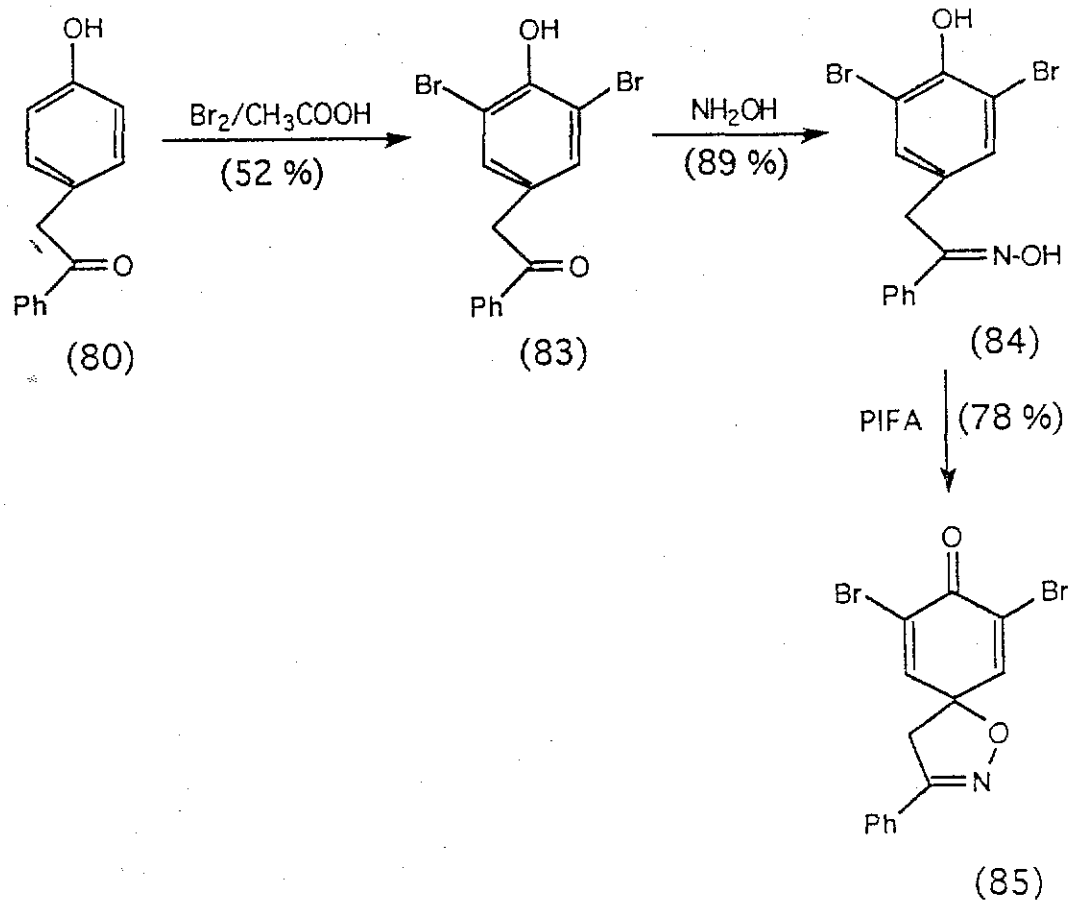
obtained after only one minute of reaction time. In another attempt carbon disulphide was used as solvent,[33] but this also failed.

The studies to obtain ketone (79) were continued using 4-methoxyphenylacetonitrile in dry ether. In this reaction, the nitrile was reacted with the Grignard reagent, phenylmagnesium bromide, in attempts to obtain the ketone, [34] but intractable tar was always obtained as product.

The oxidative cyclisation reaction of ketoxime (81) was carried out in acetonitrile at 0°C. The reaction time of cyclisation was controlled by TLC which showed complete consumption of starting material in forty minutes. Three spots were observed on the TLC plate: one due to the product, one to the formation of *iodobenzene* and finally a dark baseline spot. After column chromatography 3-phenyl-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (82) was obtained in good yield. ^{1}H nmr, ^{13}C nmr and elemental analysis are shown in the experimental section.

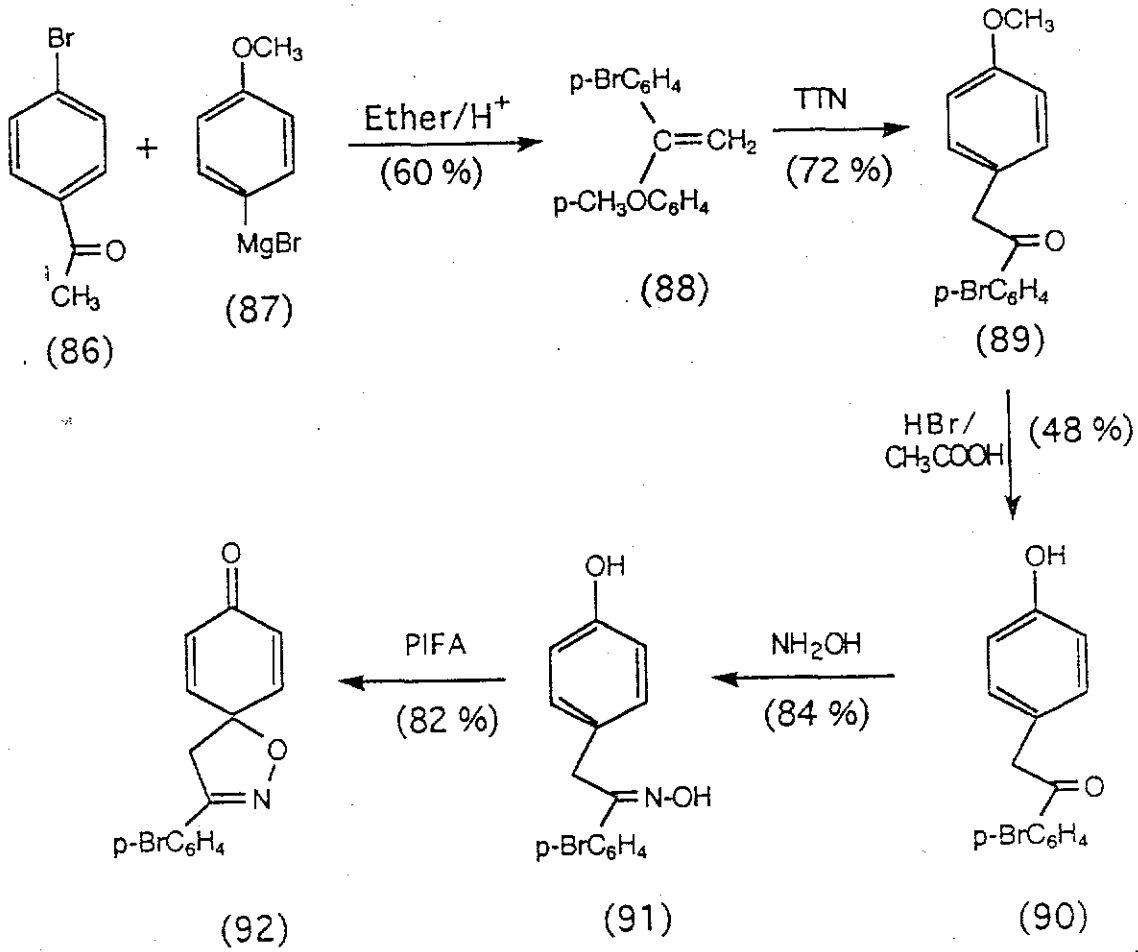
Oxidative cyclisation of the dibromo derivative of *p*-hydroxybenzyl phenyl ketoxime (81) to the corresponding isoxazoline was also attempted by using PIFA. Thus, ketone (80) was brominated with bromine in acetic acid to get 3,5-dibromo-4-hydroxybenzyl phenyl ketone (83). Ketone (83) was then reacted with hydroxylamine hydrochloride in ethanol-water to furnish the oxime, 3,5-dibromo-4-hydroxybenzyl phenyl ketoxime (84) in good yield (89%) (Scheme 28). Here, again, the main reaction of oxidative cyclisation was studied by using PIFA on the oxime (84). The ketoxime (84) was dissolved in acetonitrile at 0°C and stirred for forty minutes at this temperature. When the reaction was completed (as seen from tlc), the product was purified by column chromatography and this gave the isoxazoline, 3-phenyl-7,9-dibromo-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (85) in 72% yield. When ethanol was used in place of acetonitrile, a 78% yield was obtained when the reaction was carried out at reflux temperature for 30 minutes. This isoxazoline was characterised by IR, ^{1}H nmr and ^{13}C nmr spectra and by elemental analysis. Full details are shown in the experimental section.

Scheme 28



Study of the oxidative cyclisation reaction was continued by using *p*-hydroxybenzyl *p*-bromophenyl ketoxime (91) with PIFA. This ketoxime was prepared by demethylation of *p*-methoxybenzyl *p*-bromophenyl ketone (89). McKillop and co-workers have described the preparation of ketone (89) by the rearrangement of an olefin.[35] This reaction was repeated as follows: *p*-bromo-acetophenone (86) was reacted with *p*-methoxyphenylmagnesium bromide (87) to give 1-*p*-bromophenyl-1-*p*-methoxy-phenylethylene (88). Then the olefin was reacted with TTN in methanol and after the rearrangement reaction *p*-methoxybenzyl *p*-bromophenyl ketone (89) was obtained in high yield (92%). The demethylation reaction was carried out with 48% hydrogen bromide in acetic acid and *p*-hydroxybenzyl *p*-bromophenyl ketone (90) was obtained in 45% yield. The hydroxy ketone was treated with hydroxylamine in ethanol-water and with the usual work-up *p*-hydroxybenzyl *p*-bromophenyl ketoxime (91) was obtained as colourless crystals. Cyclisation of the ketoxime with PIFA was examined in acetonitrile and gave 3-*p*-bromophenyl-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (92) in 82% yield (Scheme 29).

Scheme 29



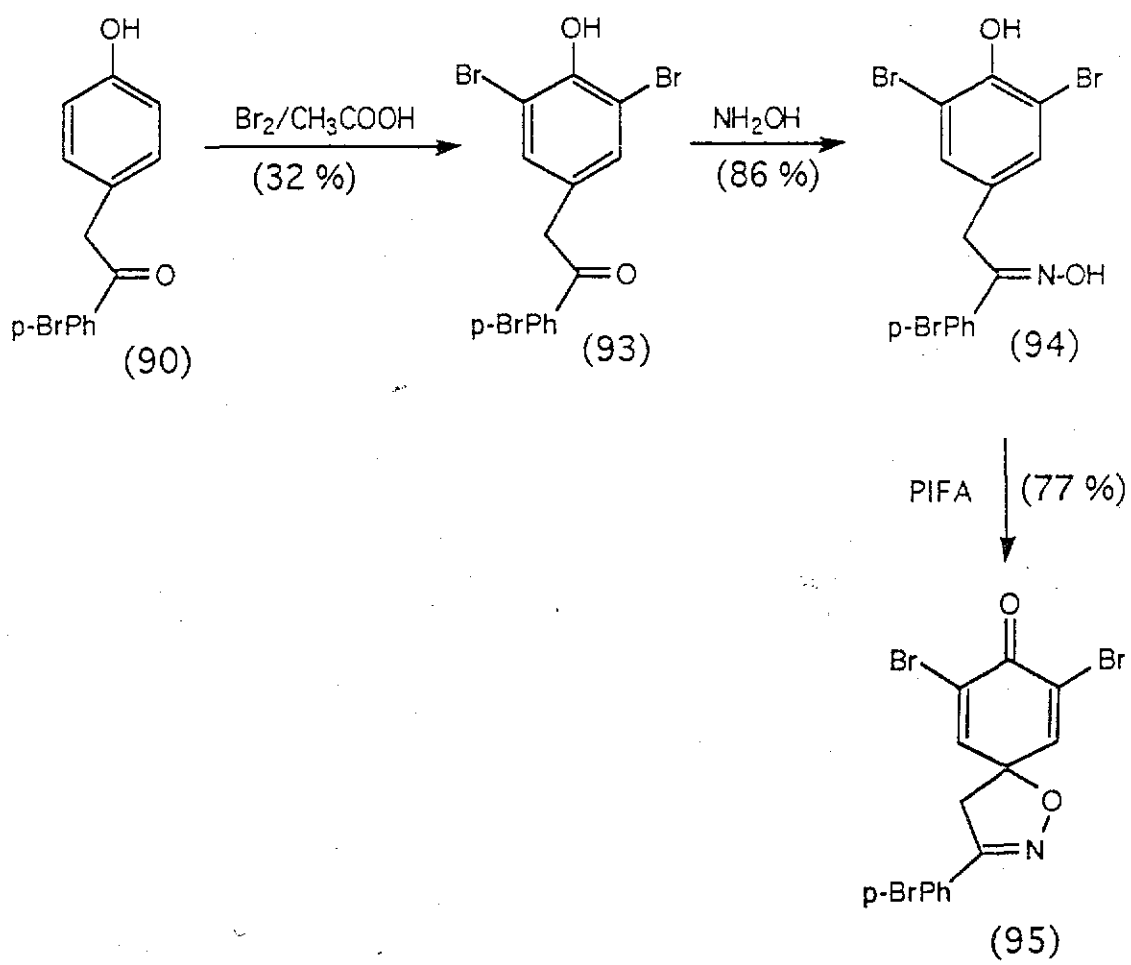
The oxidative cyclisation reaction of ketoxime (91) by PIFA was followed by TLC, which showed that the starting material was completely consumed after 40 minutes. Two distinct spots were observed by TLC: one due to iodobenzene, the other due to the desired product isoxazoline (92). One fainter spot also appeared on the baseline of the plate, apparently tar. The IR spectrum of (92) showed two characteristic absorption bands at 1670 and 1615 cm^{-1} for C=O and C=C bonds respectively. In the ^1H nmr spectrum of (92), one singlet was observed at 3.35 ppm for methylene protons. Two doublets were observed at 6.3 and 6.95 ppm for the dienone ring protons. Aromatic protons were observed in the aromatic region. The full spectral data are shown in the experimental section.

PIFA was also examined in the oxidative cyclisation of the dibromo derivative of (91), 4-hydroxy-3,5-dibromobenzyl 4-bromophenyl ketone oxime (94). The ketoxime was obtained in two steps, starting from the compound (90). Initially,the hydroxy ketone was brominated to give 4-hydroxy-3,5-

dibromobenzyl 4-bromophenyl ketone (93). This ketone was treated with hydroxylamine to form the ketoxime (94) (Scheme 30). The bromination reaction was carried out using bromine in acetic acid containing potassium acetate at 0°C, the reaction being completed in 30 minutes. The ketone (93) was obtained in 42% yield after column chromatography. The ketoxime (94) was obtained in 84% yield by treatment of the ketone with hydroxylamine. In the IR spectrum of the ketoxime, the characteristic C=N bond was too weak to be unambiguously assigned. However, ^{1}H nmr and elemental analysis of the compound were consistent with the assigned structure.

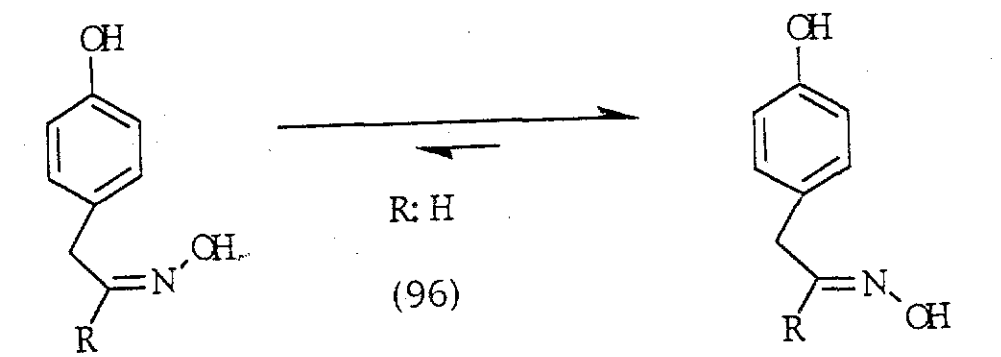
The ketoxime (94) was dissolved in ethanol and reacted with PIFA at reflux temperature (Scheme 30). After 35 minutes reaction, TLC showed two main spots and baseline material. After column chromatography the desired compound, 3-*p*-bromophenyl-7,9-dibromo-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (95) was obtained in 77% yield as a pure product.

Scheme 30



The oxidative cyclisation studies of oximes with PIFA gave very good results compared with other oxidative cyclisation reagents such as MTA, lead tetraacetate, potassium ferricyanide, silver oxide, and sodium periodate. Eight oximes were cyclised to the corresponding isoxazolines as shown above.

The other oxidative cyclisation reaction on the *p*-phenolic oximes with PIFA was studied in our laboratory by Dr Koyuncu as mentioned earlier. In this reaction different *p*-phenolic oximes were reacted with PIFA. The results obtained are summarised in Table 3.[22] The cyclisation of aldoxime (96) gave the lowest yield (20%) (Scheme 31). During the studies of the aldoxime reaction two different products were usually obtained: one the anti-oxime, and the other the syn-oxime. The attempted cyclisation of both isomers with PIFA in a reaction vessel at 0°C in acetonitrile failed. Iodobenzene and intractable tar were the main products obtained after 15 minutes reaction. It is possible that the failure of this reaction was a result of the aldoxime existing primarily in an isomeric form (syn) which was not favourable for this cyclisation. It was clear that the isomer which undergoes ring closure has the oxime hydroxyl group on the same side as the aromatic ring, and is therefore the anti-isomer of the oxime (96).

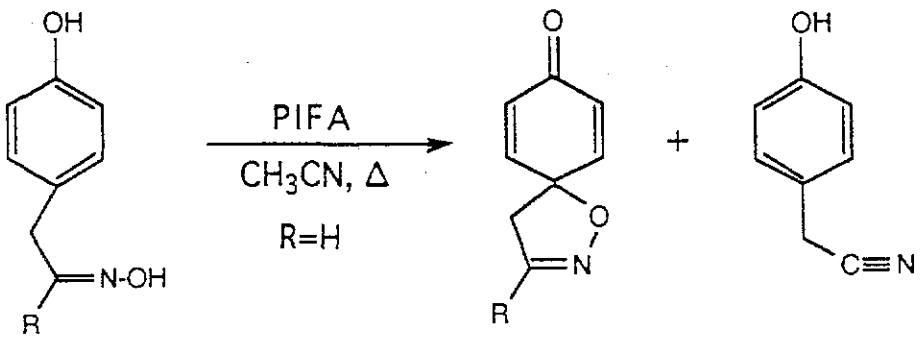


Anti-aldoxime Syn-aldoxime

Attempted isomerisation of the oxime to the desired anti-isomer by salt or complex formation was unsuccessful. However, when the reaction was carried out by refluxing the solution of the oxime (96) in acetonitrile, and then treating it with PIFA, the spiro-isoxazoline, 1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one (97) was obtained in 20% yield together with 4-hydroxybenzyl cyanide (98).[22] Hence it seems likely that refluxing the aldoxime in acetonitrile

allows isomerisation (syn- to anti-) to take place in the reaction mixture. The oxidative cyclisation reaction with PIFA may be affected by the R group on the

Scheme 31



(96) (97) (98)

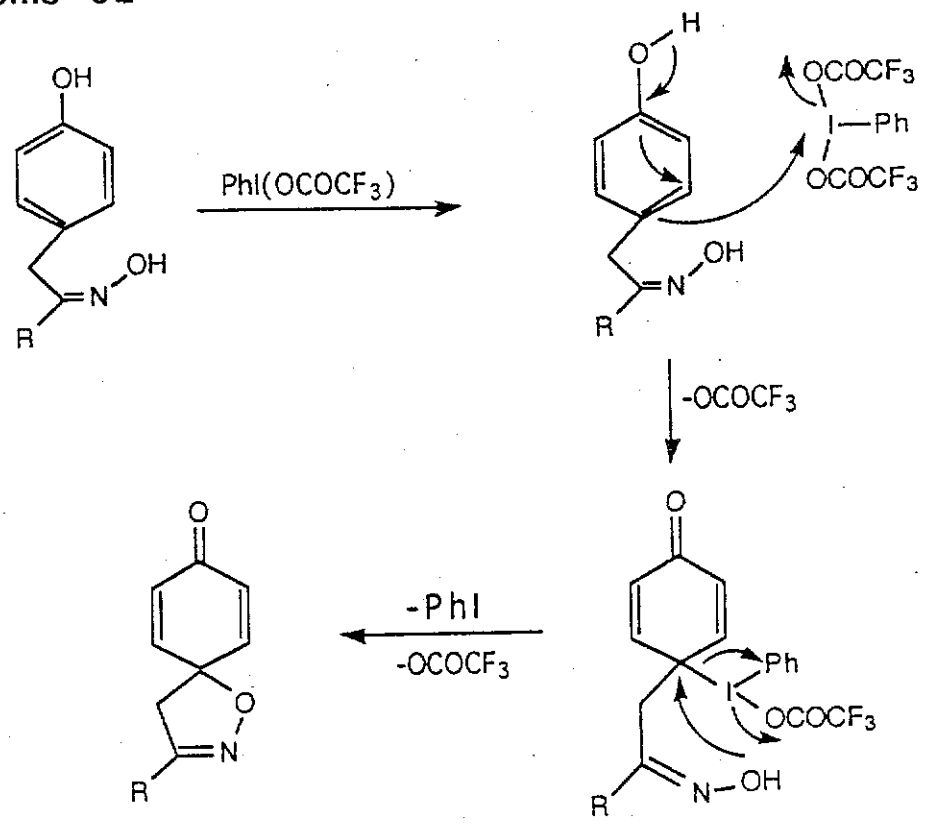
aldoxime and if a bulky group on the ketoxime were chosen, the desired syn-oxime structure might be obtained. It is assumed that the oximic hydroxyl group would preferably be located on the opposite side to the bulky group (R) due to steric hindrance.

Different R groups such as R = CO_2CH_3, C_2H_5, C_6H_5, *p*-BrC_6H_4 were investigated and different yields were obtained according to the bulkiness of the groups.

4.3. The Mechanism for the Oxidative Cyclisation of Phenolic Oximes with PIFA.

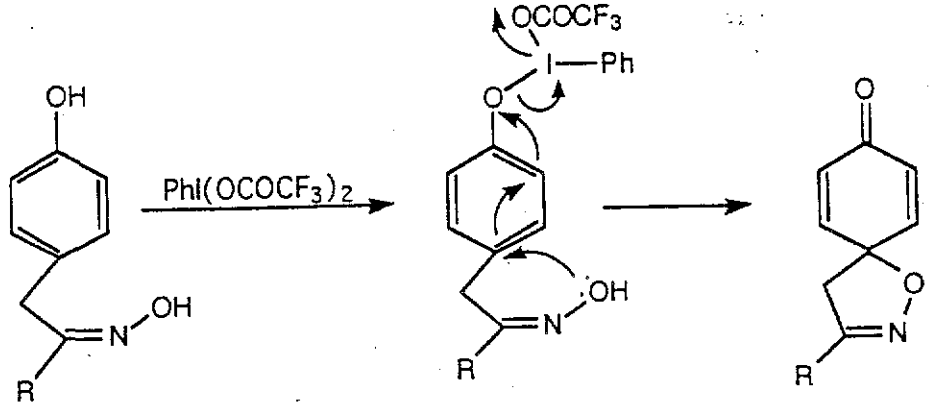
The reaction mechanism of the cyclisation of phenolic oximes with PIFA is not known, but a mechanism may be proposed by looking at the other reagents or by comparing other similar reactions. Two possible mechanisms can be proposed The first, which is illustrated in Scheme 32, involves initial *ipso* substitution at the *p*-position of the phenol ring by PIFA, followed by intramolecular displacement of the iodine substituent by the hydroxyl group of the oxime. Similar types of mechanism have been suggested by McKillop *et al.*, for the oxidation of phenols by both thallium(III) and lead(IV) salts, which show similar reactivity patterns to PIFA.[36]

Scheme 32

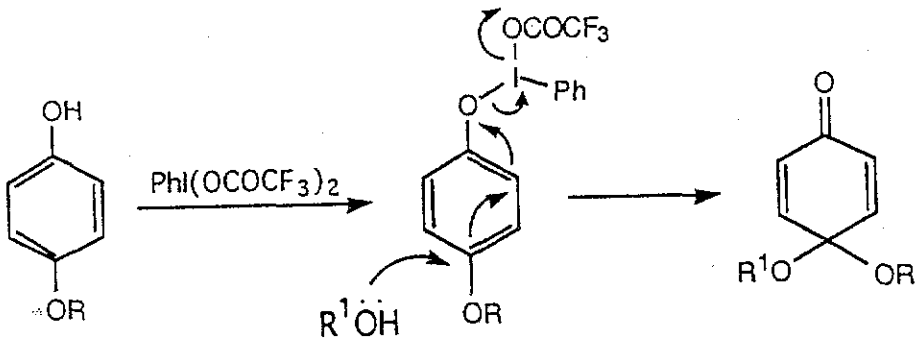


A second possible mechanism for the oxidation of phenolic oximes by PIFA involves the replacement of one of the trifluorocarboxylate ligands of PIFA by the phenol. Reductive elimination of iodobenzene with simultaneous oxidation of the phenolic oxime to the spiroisoxazoline would then complete the transformation (Scheme 33). This type of reaction mechanism has been proposed by Tamura *et al.* for the PIFA oxidation of alkoxyphenols (Scheme 34).[14]

Scheme 33



Scheme 34



4.4 EXPERIMENTAL

Phenyliodo(III) Diacetate (PIDA)

Into a solution of iodobenzene (2.0 g, 10.0 mmol) in glacial acetic acid (80 ml), sodium perborate tetrahydrate (15.38 g, 100.0 mmol) was added portionwise over 20 min. The stirred solution was held at 40-45^{0}C and the reaction was completed in 6 h. Then the solution was concentrated to half volume by evaporation of excess acetic acid under reduced pressure and water (130 ml) was added. The precipitated solid was separated by filtration, washed with water, and dried. To increase the yield, the filtrate was extracted with chloroform (3 x 30 ml) and evaporated under reduced pressure. The combined crude products were purified by recrystallisation from acetic acid/hexane to give 2.2 g (68%) of PIDA as colourless crystals, m.p. 158^{0}C (lit.,[25] 158^{0}C); ν_{max} (nujol mull) 1650 cm^{-1} (C=O); δ^1H 2.0 (6H, s, -OAc), 7.2-8.2 (5H, m, arom.).

Phenyliodo(III) Bis(trifluoroacetate) (PIFA)

PIDA (5.0 g, 0.016 mol) was dissolved in trifluoroacetic acid (8 ml) at 60^{0}C, and the solution was left at room temperature until colourless crystals appeared (90 min). The solid product was collected by filtration, washed with petroleum ether (b.p. 40-60^{0}C), and dried in the vacuum oven to give 5.38 g (81%) of PIFA as colourless crystals, m.p. 119-122^{0}C (lit.,[12] 121-126^{0}C); ν_{max} (nujol mull) 1690 cm^{-1} (C=O); δ ^{1}H 7.6-8.5 (5H, m, arom.).

p-Hydroxyphenylpyruvic Acid (60)

To a mixture of 6.11 g, (0.050 mol) of *p*-hydroxybenzaldehyde and 5.5 g (0.055 mol) of hydantoin, dry piperidine (10 ml) was added. The reaction mixture was heated to 130^{0}C and held at this temperature for 30 min. The reaction mixture was cooled and 200 ml of water at about 60^{0}C was added. The contents of the flask were stirred until a clear red solution was obtained. The solution was cooled to room temperature and acidified by dropwise addition of 20 ml of 12N hydrochloric acid. After standing at room temperature (5 h), a yellow precipitate of 5-(*p*-hydroxybenzal)hydantoin was collected by

filtration, and dried to give 8.5 g (83%) product. A 20% aqueous solution of sodium hydroxide (240 ml) was added dropwise to the crude 5-(*p*-hydroxybenzal)hydantoin (8.5 g, 0.042 mol) and refluxed at 170-180°C for 3 h under nitrogen. The deeply coloured solution was cooled and 100 ml of 12N hydrochloric acid was added. Sodium bicarbonate (5.0 g) was dissolved in the mixture. The liquid was extracted with ether (3 x 25 ml) until the supernatant layer of ether was colourless. The ethereal extract was discarded and the aqueous solution was acidified by adding 60 ml of 12N hydrochloric acid. The acidified solution was extracted with ether (3 x 25 ml) until no more *p*-hydroxyphenylpyruvic acid was obtained. The ether was evaporated and the crude acid was obtained as a pale-yellow solid. After recrystallisation from water, 5.0 g (62%) of pure *p*-hydroxyphenylpyruvic acid was obtained as colourless crystals, m.p. 215-217°C (lit.,[28] 216-218°C); ν_{max} (nujol mull) 3350 cm^{-1} (-OH) and 1638, 1720 cm^{-1} (2 x C=O); δ ^{1}H 6.55 (2H, s, $-CH_2$), 6.95 (2H, d, arom.), 7.0-7.7 (4H, AA'BB', J 12 Hz, arom.).

Methyl p-hydroxyphenylpyruvate (61)

p-Hydroxyphenylpyruvic acid (5.0 g, 0.027 mol) was dissolved in a mixture of ethylene dichloride (15 ml) and absolute methanol (5 ml). After addition of concentrated sulphuric acid (0.5 ml), the reaction mixture was refluxed overnight. The cooled mixture was extracted with ether (3 x 20 ml), washed with water, sodium bicarbonate solution (15 ml) and again with water. The organic phase was dried and evaporated under reduced pressure to give crude methyl *p*-hydroxyphenylpyruvate. After recrystallisation from ethanol 3.4 g (65%) of pure pyruvate was obtained as colourless crystals, m.p. 83-85°C; ν_{max} (nujol mull) 3350 cm^{-1} (OH), and1640, 1730 cm^{-1} (2 x C=O); δ ^{1}H 3.6 (3H, s, -OMe), 6.2 (2H, s, $-CH_2$), 7.0-7.5 (4H, AA'BB', J 9.6 Hz, arom.).

Methyl p-hydroxyphenylpyruvate Oxime (62)

To a solution of hydroxylamine hydrochloride (3.82 g, 0.053 mol) in water (15 ml) was added 10% sodium hydroxide (7 ml). The pH of the solution was kept around 4 to optimise the yield of oxime. To this solution, methyl *p*-hydroxyphenylpyruvate (2.0 g, 0.010 mol) (61) in ethanol (11 ml) was added and the mixture was refluxed until TLC analysis indicated complete

consumption of the starting material (90 min). The reaction mixture was then cooled in an ice bath to give colourless crystals which were collected by filtration, washed with water and dried. This gave 1.92 g (86%) of oxime (62), m.p. 134-135°C (lit.,[10] 135.5-137°C); ν_{max} (nujol mull) 3200-3355 cm^{-1} (OH), 1670 cm^{-1} (C=N) and 1715 cm^{-1} (C=O); δ ^1H 3.4 (3H, s, -OMe), 4.2 (2H, s, $-CH_2$), 4.6 (2H, s, -OH), 6.9 (2H, d, J 8.4 Hz, arom.), 7.6 (2H, d, J 8.4 Hz, arom.).

Cyclisation of Methyl p-hydroxyphenylpyruvate Oxime with PIFA to (63)

A solution of methyl *p*-hydroxyphenylpyruvate oxime (0.62 g, 3.0 mmol) and PIFA (1.42 g, 3.3 mmol) in dry acetonitrile (20 ml) was stirred at 0°C under nitrogen for 30 min by which time the reaction was completed. The reaction mixture was quenched with saturated sodium carbonate solution and extracted with dichloromethane (3 x 20 ml). The organic phase was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give a deep red oil which was purified by column chromatography (petroleum ether 40-60°C/ diethyl ether (3:2)) to give 0.38 g (61%) of methyl 8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-3-carboxylate (63) as colourless plates. M.p. 81-83°C (lit.,[10] 82-83°C); ν_{max} (nujol mull) 1710, 1670 and1640 cm^{-1} (2 x C=O and C=N); δ^1H 3.4 (2H, s, $-CH_2$), 3.9 (3H, s, -OMe), 6.3 (2H, d, J 10 Hz, 2 x CH=), 6.9 (2H, d, J 10 Hz, 2 x CH=). Anal. calcd. for $C_{10}H_9NO_4$: C, 58.0; H, 4.3; N, 6.8. Found: C, 58.21; H, 4.4; N, 6.9.

The same reaction procedure and work-up was carried out using ethanol as solvent at reflux temperature, instead of acetonitrile at 0° C, and the reaction was completed in 45 min. After the purification of crude product a 60% yield was obtained.

Methyl (3,5-dibromo-4-hydroxyphenyl)pyruvate (64)

To a solution of methyl *p*-hydroxyphenylpyruvate (61) (0.97 g, 5.0 mmol) and anhydrous potassium acetate (2.9 g, 29.0 mmol) in acetic acid (17.5 g, 0.29 mol), bromine (1.6 g, 10.0 mmol) was added dropwise over 30 min at 0°C. When the addition was complete the reaction mixture was stirred for a further 15 min whereupon TLC analysis indicated consumption of the starting material. The solution was quenched with water and extracted with diethyl ether (3 x 80 ml). The organic phase was dried over magnesium sulphate and

evaporated under reduced pressure. TLC of the red residue showed five spots and the desired product was separated by column chromatography (silica gel: dichloromethane) to give 0.84 g (48%) of brominated ketone (64) as colourless crystals, m.p. 110-112°C (lit.,[10] 111-112°C); ν_{max} (nujol mull) 3350 cm^{-1} (OH), 1705, 1730 cm^{-1} (2 x C=O); δ ^1H 3.67 (3H, s, -OMe), 6.65 (2H, s, $-CH_2$), 7.3 (2H, s, arom.).

Methyl (3,5-dibromo-4-hydroxyphenyl)pyruvate Oxime (65)

Methyl (3,5-dibromo-4-hydroxyphenyl)pyruvate (0.5 g, 1.42 mmol) was treated with hydroxylamine (1.1 g, 15.70 mmol) in a water-ethanol (9:6.5 ml) mixture over 60 min as described for (62). Following the same work-up procedure and recrystallisation from water the oxime (62) (0.40 g, 78%) was obtained as colourless crystals, m.p. 135-137°C (lit.,[10] 136-138°C); ν_{max} (nujol mull) 3250 cm^{-1} (broad, -OH), 1660 cm^{-1} (C=N), 1720 cm^{-1} (C=O); δ ^1H 3.30 (3H, s, -OMe), 5.2 (1H, s, OH), 6.2 (2H, s, $-CH_2$), 7.3 (2H, s, arom.). Anal. calcd. for $C_{10}H_9Br_2NO_4$: C, 32.69; H, 2.45; N, 3.81; Br, 43.59. Found: C, 32.91; H, 2.60; N, 3.76; Br, 43.62.

Cyclisation of Methyl (3,5-dibromo-4-hydroxyphenyl)-pyruvate Oxime with PIFA (66)

A solution of ketoxime (65) (0.367 g, 1.0 mmol) and PIFA (0.47 g, 1.1 mmol) in dry acetonitrile (10 ml) was reacted under nitrogen at 0°C for 60 min. The reaction mixture was quenched with saturated sodium carbonate solution and extracted with dichloromethane (3 x 15 ml). The organic phase was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give a black product which was purified by column chromatography (petroleum ether (40-60 °C)/ethyl acetate (1:1)) to give 0.19 g (52%) of methyl 7,9-dibromo-8-oxo-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-3-carboxylate (66) as colourless plates, m.p. 198-199°C (lit.,[10] 199-200°C); ν_{max} (nujol mull) 1750 and1680 cm^{-1}; δ ^1H (CD_3COCD_3) 3.65 (2H, s, $-CH_2$), 3.80 (3H, s, OMe), 7.65 (2H, s, vinyl CH). Anal. calcd. for $C_{10}H_7Br_2NO_4$: C, 32.9; H, 1.9; Br, 43.8; N, 3.8. Found: C, 32.7; H, 2.3; Br, 44.1; N, 3.9.

The same reaction procedure and work-up was carried out using ethanol as a solvent at reflux temperature instead of acetonitrile at 0°C, and the reaction was completed in 30 min; a 58% yield was obtained.

1-(*p*-Anisyl)-butan-2-one (69)

To a solution of *p*-anisaldehyde (10.9 g, 0.08 mol) and ethyl a-bromobutyrate (15.6 g, 0.08 mol), sodium methoxide (4.8 g, 0.089 mol) was added over a period of 4 h under a nitrogen atmosphere at -5°C. After stirring for six hours at 0°C and overnight at room temperature, 10 ml of water was added and the organic material was separated by extraction into ether (3 x 35 ml) and the crude product was distilled *in vacuo* to yield, after a forerun of 6.0 g, ethyl a-ethyl-a,b-epoxy-b-anisylpropionate (12.0 g, 60%) (68), b.p. 110-120°C (0.1 mm Hg). The glycidic ester (11.5 g, 0.046 mol) was refluxed with sodium hydroxide (1.8 g, 0.046 mol) in ethanol (50 ml) for 3 h under nitrogen. The concentrated solution was diluted with water (10.0 ml). The aqueous solution was washed with ether and acidified with hydrochloric acid. The product was extracted with ether (3 x 25 ml) and the ethereal solution washed with water, sodium bicarbonate solution, and with brine. After evaporation of the solvent, the reddish oil obtained was heated for 6 h at 180°C, whereupon carbon dioxide was evolved. After cooling, the reaction mixture was dissolved in ether (30 ml) and the solution washed with sodium hydroxide (5%, 30 ml), with water (25 ml) and finally with brine (25 ml). The ether was evaporated and the remaining oil distilled at reduced pressure to yield anisylbutanone (69) (6.7 g, 81%), b.p. 93-96°C (0.5 mm Hg) (lit.,[29] 93-96°C, 0.5 mm Hg); δ ^{1}H 1.20 (3H, t, $-CH_3$), 2.65 (2H, m, $-CH_2$), 3.45 (3H, s, OMe), 3.75 (2H, s, $-CH_2$), 6.9-7.4 (4H, AA'BB', J~10 Hz, arom.). Anal. calcd. for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. Found: C, 74.23; H, 7.88.

1-(4-Hydroxyphenyl)butan-2-one (70)

To a solution of aluminium bromide (12.28 g, 46 mmol) in dry benzene (80 ml) was added a solution of 1-(*p*-anisyl)butan-2-one (3.48 g, 19.6 mmol) in dry benzene (10 ml). The resulting solution was heated under reflux for 8 hours on a water bath. During this process a red oil appeared. After standing for 10 hours at room temperature the reaction mixture was quenched with concentrated hydrochloric acid. The organic phase was separated and the

aqueous phase was extracted with diethyl ether (3 x 100 ml). The combined benzene-ether layers were extracted with 2% sodium hydroxide solution (30 ml). The aqueous layer was then re-acidified with acetic acid and extracted with diethyl ether (3 x 25 ml). The organic phase was dried, filtered and evaporated under reduced pressure to give 1-(4-hydroxyphenyl)butan-2-one (70) as crude product, which was purified by column chromatography (petroleum ether (b.p. 40-60^{0}C)/diethyl ether/(1:1)) to give 2.76 g (86%) of (70) as colourless crystals, m.p. 49-51^{0}C;(Lit.,[39] 49.5-50^0 C)ν_{max} (nujol mull) 3430 cm^{-1} (-OH), 1620 cm^{-1} (aromatic C=C) and 1675 cm^{-1}(C=O); δ ^{1}H ($CDCl_3$) 1.25 (3H, t, $-CH_3$), 2.60 (2H, m, $-CH_2CH_3$), 3.70 (2H, s, $-CH_2$), 6.9-7.4 (4H, AA'BB', J 10 Hz, arom.). Anal. calcd. for $C_{10}H_{12}O_2$: C, 73.17; H, 7.31. Found: C, 73.22; H, 7.36.

1-(4-Hydroxyphenyl)butan-2-one Oxime (71)

The oxime (71) was obtained by refluxing 1-(4-hydroxy-phenyl)butan-2-one (70) (2.10 g, 12.80 mmol) with hydroxylamine (6.0 g, 83.33 mmol) in a water (24 ml) - ethanol (30 ml) mixture for 60 min as described for (62). After recrystallisation from water 1.96 g (86%) of (71), was obtained as colourless crystals, m.p. 110-111^{0}C; ν_{max} (nujol mull) 3450 cm^{-1} (OH), 1620 cm^{-1} (aromatic C=C) and 1660 cm^{-1} (C=N); δ ^{1}H ($CDCl_3$) 1.85 (3H, t, $-CH_3$), 2.70 (2H, m, $-CH_2CH_3$), 3.75 (2H, s, $-CH_2$), 4.75 (1H, s, -OH), 6.9-7.3 (4H, AA'BB', J 8.4 Hz, arom.,); δ ^{13}C (90 MHz;$CDCl_3$) 15.26, 27.68, 38.22, 115.28, 131.69, 133.66, 156.72, 163.19. Anal. calcd. for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.26; N, 7.82. Found: C, 67.35; H, 7.31; N, 7.76.

Cyclisation of 1-(4-Hydroxyphenyl)butan-2-one Oxime with PIFA to (72)

1-(4-Hydroxyphenyl)butan-2-one oxime (71) (1.35 g, 7.54 mmol) in acetonitrile (45 ml) was treated with PIFA (1.75 g, 8.29 mmol) in acetonitrile (25 ml) at 0^{0}C for 30 min. The reaction mixture was worked up according to the procedure described for (63), and the crude product was purified by column chromatography (petroleum ether (b.p. 40-60^{0}C)/diethyl ether/(1:3)) to give 0.90 g (68%) of the spiro-isoxazoline (3-ethyl-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one) (72) as colourless crystals, m.p. 78-81^{0}C; ν_{max} (nujol mull) 1610 cm^{-1} (aromatic C=C) and 1675 cm^{-1} (C=O); δ ^{1}H ($CDCl_3$) 1.45 (3H, t, $-CH_3$), 2.15 (2H, m, $-CH_2CH_3$), 3.20 (2H, s, $-CH_2$), 6.35 (2H, d, J = 8.4 Hz, 2 x CH=), 7.15 (2H, d, J = 8.4 Hz, 2 x CH=); δ ^{13}C (90 MHz;$CDCl_3$) 18.72, 33.58,

44.51, 82.81, 128.63, 144.91, 162.24, 184.66. Anal. calcd. for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.90. Found: C, 67.85; H, 6.27; N, 7.93.

1-(3,5-Dibromo-4-hydroxyphenyl)butan-2-one (73)

Bromine (1.75 g, 10.9 mmol) was added dropwise to a stirred solution of 1-(4-hydroxyphenyl)butan-2-one (70) (0.9 g, 5.5 mmol) and anhydrous potassium acetate (3.1 g, 0.032 mol) in acetic acid (19.1 g, 0.32 mol) at 0°C. The reaction mixture was stirred for 25 min and worked-up as described for (64). The resultant red crude product was purified by column chromatography (petroleum ether (b.p. 40-60°C)/ether/(1:1)) to give 0.92 g (52%) of 1-(3,5-dibromo-4-hydroxyphenyl)butan-2-one as yellow crystals, m.p. 77-79°C; ν_{max} (nujol mull) 3240 cm^{-1} (-OH) and 1685 cm^{-1} (C=O); δ ^1H ($CDCl_3$) 1.25 (3H, t, $-CH_3$), 2.45 (2H, m, CH_2CH_3), 3.80 (2H, s, $-CH_2$), 5.78 (1H, s, OH), 7.34 (2H, s, arom.,). Anal. calcd. for $C_{10}H_{10}Br_2O_2$: C, 37.26; H, 3.10; Br, 49.69. Found: C, 37.38; H, 3.18; Br, 49.83. M/z 322 (4% M^+).

1-(3,5-Dibromo-4-hydroxyphenyl)butan-2-one Oxime (74)

The oxime (74) was obtained by refluxing 1-(3,5-dibromo-4-hydroxyphenyl)-2-butanone (0.76 g, 2.36 mmol) with hydroxylamine (2.14 g, 30.0 mmol) in a water (8 ml) - ethanol (10 ml) solvent mixture following the procedure already described for (62). After recrystallisation from ethanol this gave 0.63 g (80%) of 1-(3,5-dibromo-4-hydroxyphenyl)-2-butanone oxime, as colourless crystals, m.p. 157-160°C; ν_{max} (nujol mull) 3470 cm^{-1} (OH) and 1590 cm^{-1} (aromatic C=C); δ^1H (d_6-acetone)1.15 (3H, t, $-CH_3$), 2.18 (2H, m, $-CH_2CH_3$), 3.62 (2H, s, $-CH_2$), 4.61 (OH), 7.32 (2H, s, arom.); δ ^{13}C (90 MHz;d_6-aceton) 19.22, 32.16, 41.08, 110.76, 131.38, 133.10, 149.96, 159.44. Anal. calcd. for $C_{10}H_{11}Br_2O_2$: C, 35.60; H, 3.26; N, 4.15; Br, 47.47. Found: C, 35.76; H, 3.28; N, 4.32; Br, 47.57. M/z 337 (2% M^+).

Cyclisation of 1-(3,5-Dibromo-4-hydroxyphenyl)butan-2-one Oxime with PIFA to (75)

1-(3,5-Dibromo-4-hydroxyphenyl)butan-2-one oxime (74) (0.25 g, 0.74 mmol) in acetonitrile (40 ml) was treated with PIFA (0.35 g, 0.81 mmol) in acetonitrile (5 ml) at 0°C for 45 min. The reaction mixture was worked-up as described for

(63) and the crude product was purified by column chromatography (dichloromethane/diethyl ether, 1:3) to give 0.13 g (52%) of the spiro-isoxazoline (3-ethyl-7,9-dibromo-1-oxa-2-azaspiro[4,5]-deca-2,6,9-trien-8-one (75), m.p. 199-202^{0}C; ν_{max} (nujol mull) 1592 cm^{-1} (aromatic C=C) and 1680 cm^{-1} (C=O); δ ^{1}H ($CDCl_3$)1.38 (3H, t, CH_3), 2.23 (2H, m, -CH_2CH_3), 3.52 (2H, s, -CH_2), 7.34 (2H, s, arom.); δ ^{13}C (90 MHz;$CDCl_3$) 18.04, 36.41, 44.20, 84.91, 121.68, 146.10, 158.98, 165.23. Anal. calcd. for $C_{10}H_9Br_2NO_2$: C, 35.84; H, 2.68; N, 4.18; Br, 47.78. Found: C, 36.12; H, 2.72; N, 4.31; Br, 47.88.

The same reaction procedure and work-up was carried out using ethanol as solvent at reflux temperature, instead of acetonitrile at 0^{0}C, and the reaction was completed in 45 min. After the purification of crude product a 57% yield was obtained.

p-Methoxybenzyl Phenyl Ketone (79)

To a solution of benzaldehyde (4.0 g, 0.037 mol), anisaldehyde (5.2 g, 0.038 mol) and ethanol (11.5 ml) was added on to the potassium cyanide (1.2 g) solution in water (8 ml). The mixture was refluxed for 90 min and allowed to stand in a cool place overnight. The crystalline material was collected by filtration and washed twice with water and then with a small portion of alcohol. After three crystallisations from alcohol 2.9 g (31%) of benzanisoin was obtained as pure crystals, m.p. 106^{0}C (lit.,[30] 107-108^{0}C).

A mixture of benzanisoin (2.5 g), mossy tin (2.0 g), hydrated copper sulphate (0.05 g), alcohol (10 ml) and concentrated hydrochloric acid (7 ml) was refluxed for 6 h and then filtered hot. After standing for some time in a refrigerator, the crystalline material was collected by filtration, washed twice with small portions of alcohol (2 x 5 ml) and dried *in vacuo* .Recrystallisation in ethanol gave 2.12 g (82 %) of (79) as colourless plates, m.p. 94-96^{0}C (lit.,[31] 96-97^{0}C). ν_{max} (nujol mull) 1705 cm^{-1} (C=O); δ ^{1}H 3.45 (3H, s, OCH_3), 3.6 (2H, s, -CH_2), 6.9-7.6 (9H, m, arom.).

p-Hydroxybenzyl Phenyl Ketone (80)

p-Methoxybenzyl phenyl ketone (79) (1.8 g, 8.5 mmol) in a solution of 48% aqueous hydrobromic acid (9.61 ml) and acetic acid (38 ml) was heated for 18

h. The reaction mixture was diluted with water (50 ml) and extracted with diethyl ether (3 x 50 ml). The organic phase was dried and the solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether (b.p. 40-60°C)/ether/(1:1)) to give 1.31 g (73%) of *p*-hydroxybenzyl phenyl ketone (80), as colourless crystals, m.p. 137-139°C (lit.,[37] 137-138°C); ν_{max} (nujol mull) 3390 cm^{-1} (-OH) and 1698 cm^{-1} (C=O); δ ^{1}H 3.75 (2H, s, $-CH_2$), 6.24 (1H, s, -OH), 6.7-7.4 (9H, m, arom.); Anal. calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66; Found: C, 79.42; H, 5.68.

p-Hydroxybenzyl Phenyl Ketoxime (81)

The oxime (81) was obtained by refluxing *p*-hydroxybenzyl phenyl ketone (80) (0.89 g, 4.2 mmol) with hydroxylamine (2 g, 0.028 mol) in a water (8 ml) - ethanol (10 ml) solvent mixture over 60 min as described for (62). This gave 0.74 g (78%) of *p*-hydroxybenzyl phenyl ketoxime (81) was obtained as colourless crystals, m.p. 119-120°C (lit.,[37] 121-122°C); ν_{max} (nujol mull) 3340 cm^{-1} (-OH) and 1630 cm^{-1} (C=N); δ ^{1}H (CD_3OD) 3.62 (2H, s, $-CH_2$), 6.34 (1H, s, OH), 6.7-7.5 (9H, m, arom.); Anal. calcd. for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72; N, 6.16. Found: C, 74.23; H, 5.76; N, 6.22.

Cyclisation of *p*-Hydroxybenzyl Phenyl Ketoxime with PIFA (82)

p-Hydroxybenzyl phenyl ketoxime (81) (0.33 g, 1.5 mmol) in acetonitrile (45 ml) was treated with PIFA (0.71 g, 1.65 mmol) in acetonitrile (7 ml) at 0°C for 35 min. The reaction mixture was worked-up according to the procedure described for (63), and the crude product was purified by column chromatography (petroleum ether (b.p. 40-60°C)/ether/(1:1)) to give 0.29 g (86%) of the spiro-isoxazoline (82) (3-phenyl-1-oxa-2-azaspiro[4,5]deca-2,6,9-trien-8-one) as colourless crystals, m.p. 71-73°C; ν_{max} (nujol mull) 1670 cm^{-1} (C=O) and 1620 cm^{-1} (C=C); δ ^{1}H (d_6-acetone)3.54 (2H, s, $-CH_2$), 6.3 (2H, d, J=7.2 Hz, 2xCH=), 6.9 (2H, d, J=7.2 Hz,2xCH=), 7.4-7.6 (5H, m, arom.); δ ^{13}C (90 MHz;d_6-acetone) 43.86, 78.80, 128.76, 128.93, 129.88, 132.08, 134.21, 145.21, 145.69, 166.24, 184.72. Anal. calcd. for $C_{14}H_{11}NO_2$: C, 74.66; H, 4.88; N, 6.22; Found: C, 74.82; H, 5.11; N, 6.28. M/z 225 (8% M^+).

3,5-Dibromo-4-hydroxybenzyl Phenyl Ketone (83)

Bromine (1.05 g, 6.6 mmol) was added dropwise to a stirred solution of 4-hydroxybenzyl phenyl ketone (82) (0.63 g, 3.0 mmol) and anhydrous potassium acetate (1.75 g, 18.0 mmol) in acetic acid (10.74 g, 0.18 mol) at 0°C. The reaction mixture was stirred for 20 min and worked up as described for (64). The resultant red crude product was purified by column chromatography (petroleum ether (b.p. 40-60°C)/dichloro-methane/(1:1)) to give 0.57 g, (52%) of 3,5-dibromo-4-hydroxybenzyl phenyl ketone (83), as colourless crystals, m.p. 104-105°C; ν_{max} (nujol mull) 3250 cm^{-1} (-OH) and 1685 cm^{-1} (C=O); δ ^1H 3.62 (2H, s, CH_2), 6.15 (1H, s, -OH), 6.9-7.6 (7H, m, arom.); Anal. calcd. for $C_{14}H_{10}Br_2O_2$: C, 45.42; H, 2.70; Br, 43.21. Found: C, 45.71; H, 2.83; Br, 43.38. M/z 369.8 (4% M^+).

3,5-Dibromo-4-hydroxybenzyl Phenyl Ketoxime (84)

The oxime (84) was obtained by refluxing 3,5-dibromo-4-hydroxybenzyl phenyl ketone (83) (0.52 g, 1.4 mmol) with hydroxylamine (1.2 g, 16.8 mmol) in water (5 ml) - ethanol (5 ml) solvent system following the procedure already described for (62). Recrystallisation from ethanol gave 0.48 g, (89%) of 3,5-dibromo-4-hydroxybenzyl phenyl ketoxime, as colourless crystals, m.p. 171-173°C; ν_{max} (nujol mull) 3450 cm^{-1} (-OH), 1660 cm^{-1} (C=N) and 1570 cm^{-1} (arom., C=C); δ ^1H (CD_3OD) 3.52 (2H, s, CH_2), 5.10 (2H, s, -OH), 6.9-7.5 (7H, m, arom.); δ ^{13}C (d_6-acetone) 43.89, 111.58, 128.72, 129.56, 132.38, 133.41, 133.63, 134.05, 150.26, 158.81. Anal. calcd. for $C_{14}H_{11}Br_2NO_2$: C, 43.65; H, 2.85; Br, 41.52; N, 3.63. Found: C, 43.71; H, 3.14; Br, 41.62; N, 3.68. M/z 385 (3% M^+).

Cyclisation of 3,5-Dibromo-4-hydroxybenzyl Phenyl Ketone with PIFA (85)

A solution of PIFA (0.52 g, 1.21 mmol) in ethanol (12 ml) was added slowly to a solution of 3,5-dibromo-4-hydroxybenzyl phenyl ketoxime (84) (0.42 g, 1.1 mmol) in ethanol (25 ml) under reflux. The work-up was carried out after 40 min using the procedure already described for (63). The brown crude product was purified by column chromatography (silica gel; dichloromethane/diethyl ether (1:3)) to give 0.33 g (78%) of the spiro-isoxazoline (85) (3-phenyl-7,9-

dibromo-1-oxa-2-azaspiro-[4,5]deca-2,6,9-trien-8-one), as colourless crystals, m.p. 209-211°C; ν_{max} (nujol mull) 1680 cm^{-1} (C=O) and 1600 cm^{-1} (C=C); δ ^1H (d_6-acetone) 3.42 (2H, s, $-CH_2$), 6.7-7.4 (7H, m, arom., and 2 x vinyl H); δ ^{13}C (90 MHz;d_6-acetone) 48.11, 83.72, 123.61, 128.87, 129.96, 133.41, 133.54, 146.16, 155.60, 161.24. Anal. calcd. for $C_{14}H_9Br_2NO_2$: C, 43.86; H, 2.35; Br, 41.77; N, 3.65; Found: C, 44.17; H, 2.42; Br, 41.96; N, 3.71. M/z 383 (6% M^+).

The same reaction procedure and work-up was carried out using acetonitrile as solvent at 0°C, instead of ethanol at reflux temperature, and the reaction was completed in 60 min. After the purification of crude product 52% yield of (3-phenyl-7,9-dibromo-1-oxa-2-azaspiro-[4,5]deca-2,6,9-trien-8-one (85) was obtained as colourless crystals.

p-Methoxybenzyl *p*-bromophenyl Ketone (89)

p-Bromoacetophenone (4.0 g, 0.022 mol) was added dropwise during 2 h to a stirred solution of *p*-methoxyphenyl-magnesium bromide in ether (prepared from 4.1 g (0.022 mol) of *p*-bromoanisole and 0.52 g (0.022 mol) of magnesium in 20 ml of dry ether). Sulphuric acid (10 ml, 30% aqueous) was then added and the mixture heated under reflux for 1 hour. The organic layer was separated, the aqueous layer was extracted with ether (3 x 20 ml), and the combined extracts were dried over magnesium sulphate. Evaporation of the solvent and crystallisation of the residue from 2-propanol gave 3.8 g (60%) of pure product, 1-*p*-bromophenyl-1-*p*-methoxyphenylethylene as fine colourless needles, m.p. 94-95°C (lit.,[35] 94-95°C).

Thallium(III) nitrate trihydrate (5.72 g, 0.013 mol) was dissolved in 65 ml of methanol and olefin (1-*p*-bromophenyl-1-*p*-methoxyphenyl ethylene) (3.8 g, 0.013 mol) was added. The reaction mixture was stirred at room temperature for 30 min. The mixture was then filtered, and an alcoholic solution containing 0.013 mol of 2,4-dinitrophenylhydrazine was added to the filtrate. The resulting mixture was evaporated to one third of its volume, and after addition of 10 ml of water, it was heated on a steam bath for 10 min. After cooling to 0°C, the 2,4-dinitrophenylhydrazone of the carbonyl compound was collected by filtration. The resulting mixture of carbonyl compound was heated on a steam bath for 30 min with an excess of 5% sulphuric acid and the free carbonyl compound was isolated by ether extraction (3 x 50 ml). After the

purification of crude product by column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/ethyl acetate (3:1)) 2.85 g (72%) *p*-methoxy *p*-bromophenyl ketone (89) was obtained as colourless crystals, m.p. 88-89°C (lit.,[35] 89°C); ν_{max} (nujol mull) 1680 cm^{-1} (C=O); δ ^1H ($CDCl_3$) 3.24 (3H, s, $-OCH_3$), 3.80 (2H, s, CH_2), 6.9-7.6 (8H, m, arom.); Anal. calcd. for $C_{15}H_{13}BrO_2$: C, 59.01; H, 4.26; Br, 26.22. Found: C, 59.28; H, 4.32; Br, 36.36.

4-Hydroxybenzyl 4-bromophenyl Ketone (90)

p-Methoxybenzyl *p*-bromophenyl ketone (89) (2.6 g, 8.5 mmol) in a solution of 48% aqueous hydrobromic acid (10 ml, 0.085 mol) and acetic acid (38 ml) was heated under reflux for 18 h. The reaction mixture was diluted with water (50 ml) and extracted with diethyl ether (3 x 50 ml). The organic phase was dried and the solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/ethyl acetate (3:2)) to give 1.20 g (48%) of 4-hydroxybenzyl 4-bromophenyl ketone (90), as colourless crystals, m.p. 133-135°C ; ν_{max} (nujol mull) 3450 cm^{-1} (-OH) 1686 cm^{-1} (C=O) 1615 cm^{-1} (arom., C=C); δ ^1H ($CDCl_3$) 3.72 (2H, s, $-CH_2$), 6.18 (1H, s, -OH) 6.9-7.4 (8H, m, arom.); Anal. calcd. for $C_{14}H_{11}BrO_2$: C, 57.73; H, 3.78; Br, 27.49. Found: C, 58.05; H, 3.86; Br, 27.61. M/z 291 (18% M^+).

4-Hydroxybenzyl 4-bromophenyl Ketoxime (91)

The oxime (91) was obtained by refluxing 4-hydroxybenzyl 4-bromophenyl ketone (90) (0.97 g, 3.36 mmol) with hydroxylamine (1.57 g, 0.022 mol) in water (6.5 ml) - ethanol (8 ml) solvent mixture for 60 min as described for (62). After recrystallisation in water 0.82 g (84%) of 4-hydroxybenzyl 4-bromophenyl ketoxime (91), was obtained as colourless crystals, m.p. 158-160°C ; ν_{max} (nujol mull) 3465 cm^{-1} (OH) 1650 cm^{-1} (C=N) 1610 cm^{-1} (arom., C=C); δ ^1H (CD_3OD) 3.62 (2H, s, CH_2), 4.98 (1H, s, -OH) 6.8-7.4 (8H, m, arom.); δ ^{13}C (90 MHz;CD_3OD) 43.86, 118.25, 124.11, 128.92, 131.08, 132.29, 132.83, 133.45, 156.13, 161.54. Anal. calcd. for $C_{14}H_{12}BrNO_2$: C, 54.90; H, 3.92; Br, 26.14; N, 4.57; Found: C, 55.16; H, 3.98; Br, 26.32. N,4.71 M/z 306 (8% M^+).

Cyclisation of 4-Hydroxybenzyl 4-bromophenyl Ketoxime with PIFA to (92)

4-Hydroxybenzyl 4-bromophenyl ketoxime (91) (0.65 g, 2.1 mol) in acetonitrile (60 ml) was treated with PIFA (1.0 g, 2.3 mmol) in acetonitrile (8 ml) at 0°C for 35 min. The reaction mixture was worked-up according to the procedure described for (63), and the crude product was purified by column chromatography (silica gel: dichloromethane/diethyl ether (1:1)) to give 0.52 g (82%) of the spiro-isoxazoline (3-*p*-bromophenyl-1-oxa-2-azaspiro[4,5]-deca-2,6,9-trien-8-one (92) as colourless crystals, m.p. 96-98°C ; ν_{max} (nujol mull) 1675 cm^{-1} (C=O) 1615 cm^{-1} (arom., C=C); δ ^1H ($CDCl_3$) 3.16 (2H, s, $-CH_2$), 6.2 (2H, d, J = 7.2 Hz, 2 x CH=), 6.8 (2H, d, J = 7.2 Hz, 2 x CH=) 7.4-7.7 (4H, d, AA'BB', J = 8.4 Hz, arom.); δ ^{13}C (90 MHz;$CDCl_3$) 44.21, 78.80, 125.42, 128.11, 129.33, 129.46, 133.10, 145.69, 167.81, 185.08 Anal. calcd. for $C_{14}H_{12}BrNO_2$: C, 55.42; H, 3.32; Br, 26.48; N, 4.65; Found: C, 55.26; H, 3.28; Br, 26.31; N, 4.60. M/z 304 (2% M^+).

4-Hydroxy-3,5-dibromobenzyl 4-bromophenyl Ketone (93)

Bromine (0.95 g, 6.0 mmol) was added dropwise to a stirred solution of 4-hydroxybenzyl 4-bromophenyl ketone (90) (0.87 g, 3.0 mmol) and anhydrous potassium acetate (1.75 g, 0.018 mol) in acetic acid (10.74 g, 0.18 mol) at 0°C. The reaction mixture was stirred for 25 min and worked-up as described for (64). Five spots were seen on the TLC plate and the red crude product was purified by column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/diethyl ether (3:1)) to give 0.43 g (32%) of 4-hydroxy-3,5-dibromobenzyl 4-bromophenyl ketone (93) as light brown crystals, m.p. 103-105°C ; ν_{max} nujol mull) 3350 cm^{-1} (-OH) and 1680 cm^{-1} (C=O); δ ^1H ($CDCl_3$) 3.62 (2H, s, CH_2), 5.86 (1H, s, -OH), 7.28 (2H, s, arom.,), 7.4-7.7 (4H, AA'BB', J 8.4 Hz, arom.); Anal. calcd. for $C_{14}H_9Br_3O_2$: C, 37.44; H, 2.00; Br, 53.42. Found: C, 37.69; H, 2.21; Br, 53.74. M/z 448.7 (1% M^+).

4-Hydroxy-3,5-dibromobenzyl 4-bromophenyl Ketoxime (94)

The oxime (94) was obtained by refluxing 4-hydroxy-3,5-dibromobenzyl 4-bromophenyl ketone (93) (0.4 g, 0.9 mmol) with hydroxylamine (0.6 g, 8.0 mmol) for 1.5 h in a water (3 ml) - ethanol (4 ml) solvent system following the

procedure already described for (62). This gave 0.33 g (86%) of 4-hydroxy-3,5-dibromobenzyl phenyl ketoxime as yellow crystals, m.p. 151-153°C ; ν_{max} (nujol mull) 3480 cm^{-1} (-OH) and 1660 cm^{-1} (C=N); δ ^1H (CD_3OD) 3.56 (2H, s, $-CH_2$), 5.72 (2H, broad, -OH), 7.12 (2H, s, arom.), 7.3-7.7 (4H, m, arom.); δ ^{13}C (90 MHz;CD_3OD) 41.05, 110.54, 123.66, 129.02, 129.89, 131.35, 133.22, 133.76, 151.14, 155.81. Anal. calcd. for $C_{14}H_{10}Br_3NO_2$: C, 36.23; H, 2.15; Br, 51.69; N, 3.01. Found: C, 36.42; H, 2.21; Br, 51.53; N, 2.96. M/z 463.7 (3% M^+).

Cyclisation of 4-Hydroxy-3,5-dibromobenzyl 4-bromophenyl Ketoxime with PIFA to (95).

A solution of PIFA (0.31 g, 0.71 mmol) in ethanol (8 ml) was added slowly to a solution of 4-hydroxy-3,5-dibromobenzyl 4-bromophenyl ketoxime (94) (0.3 g, 0.65 mmol) in ethanol (15 ml) under reflux. The work-up was carried out after 45 min using the procedure already described for (66). The brown crude product was purified by column chromatography (silica gel: petroleum ether (b.p. 40-60°C)/diethyl ether (1:3)) to give 0.24 g (77%) of 3-(*p*-bromophenyl)-7,9-dibromo-1-oxa-2-azaspiro[4,5]-deca-2,6,9-trien-8-one (95) as yellow crystals, m.p. 216-217°C ; ν_{max} (nujol mull) 1680 cm^{-1} (C=O) and 1600 cm^{-1} (C=C); δ ^1H ($CDCl_3$) 3.42 (2H, s, $-CH_2$), 7.2-7.8 (6H, m, arom.); δ ^{13}C (90 MHz;d_6-acetone) 46.30, 84.15, 122.68, 123.84, 126.19, 129.34, 133.96, 146.81, 165.92, 171.31. Anal. calcd. for $C_{14}H_8Br_3NO_2$: C, 36.38; H, 1.73; Br, 51.91; N, 3.03. Found: C, 36.42; H, 1.69; Br, 52.14; N, 2.86. M/z 461.7 (1% M^+).

Attempted Cyclisation of *p*-Hydroxyphenylpyruvic Acid Oxime with PIFA.

p-Hydroxyphenylpyruvic acid oxime (0.52 g, 2.7 mmol) in acetonitrile (60 ml) was treated with PIFA (1.28 g, 2.96 mmol) in acetonitrile (10 ml) at 0°C for 35 min. The reaction mixture was worked-up according to the procedure described for (63) and purification of the crude brown product, which consisted of seven compounds, was attempted by column chromatography, but isolation of the desired product was not achieved.

Attempt to Obtain *p*-Methoxybenzyl Phenyl Ketone by a Friedel-Crafts Reaction.

4-Hydroxyphenylacetyl chloride (0.68 g, 5.0 mmol) was added dropwise to a solution of aluminium chloride (1.29 g, 9.7 mmol) in dry benzene (5 ml) and the reaction mixture was refluxed 15-20 min. The cooled mixture was poured into acidified ice-water and extracted with water (20 ml), once with 5% sodium hydroxide solution (20 ml) and again with water (20 ml).[38] After drying the ethereal solution over anhydrous magnesium sulphate, it was evaporated under reduced pressure but only intractable red polymeric material was obtained.

On the second attempt carbon disulphide was used as solvent but again onlyintractable red polymeric material was obtained.

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