SYNTHETIC AND MECHANISTIC STUDIES

OF THE

THIA-FRIES REARRANGEMENT

BY

PATRICK MAUGHAN, B.Sc., A.M.R.S.C.

SUPERVISORS: Dr. DECLAN P. SHELLY
Dr. G. A. BENSON (Deceased)

INSTITUTE OF TECHNOLOGY SLIGO

EXTERNAL MENTOR: PROFESSOR WILLIAM J. SPILLANE

N.U.I.G.

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DECLARATION

I confirm that this thesis has not been submitted to any other institution and that with acknowledged exceptions, this is entirely my own work.

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DEDICATION

To Maureen, Frank, Brian and Elizabeth

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ABSTRACT

A study has been undertaken of the published literature on the Fries rearrangement, thermal, photo and microwave, since its discovery in 1908. A resume of these publications and especially of those pertaining to the thia-Fries rearrangement of sulfamate esters, has been compiled.

Phenyl sulfamate, phenyl *N,N*-dimethylsulfamate, phenyl *N,N*-diethylsulfamate and phenyl *N,N*-di-n-propylsulfamate and many of their substituted compounds have been synthesised and purified, a total of thirty nine esters. The sulfamates have been characterised by mp / bp, infrared, C, H and N microanalysis and mass spectrum.

Many of these sulfamates, twenty six in total, have been rearranged to sulfonamides in the thia-Fries rearrangement, and subsequently purified. The products were characterised by mp / bp, infrared, C, H and N microanalysis and mass spectrum.

Mechanistic studies of the sulfamates have been investigated, particularly phenyl *N,N*-dimethylsulfamate. The rearrangement with various catalysts and catalytic ratios, the effect of solvents on the rearrangement and many crossover experiments have been carried out to determine the molecularity i.e. whether it is an inter-, intra- or bimolecular reaction.

The microwave induced thia-Fries rearrangement has been examined to determine what effect this irradiation has on the rearrangement. Photo thia-Fries rearrangement has also been investigated

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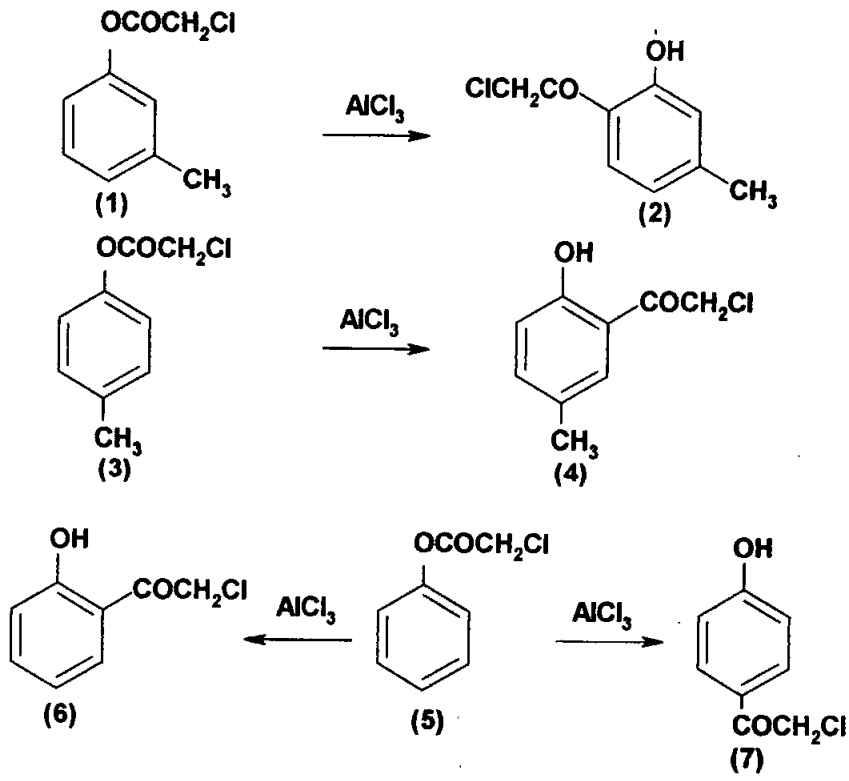
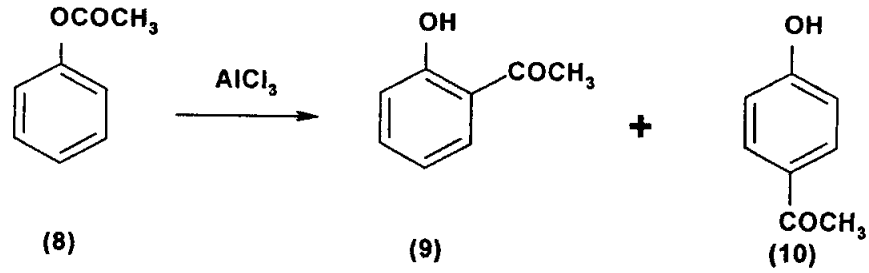
INTRODUCTION

In 1908, Karl Theofile Fries (1875-1962) published a method for preparing *ortho*-chloroacetylphenols [1a], (scheme 1) which he wished to use in the synthesis of coumaranones. He discovered this reaction while trying to avoid the difficulties encountered in preparing certain phenolic ketones by the Friedel-Crafts reaction. The reaction between phenols, chloroacetyl chloride and aluminium chloride was not satisfactory since, often, two chloroacetyl groups were introduced into the phenols. Good results were obtained when phenolic esters of chloroacetic acid were heated with aluminium chloride giving a mixture of *ortho*-, and *para*-chloroacetylphenols (6) and (7) 1(a & b)



Scheme 1

Fries also rearranged the phenolic esters of acetic acid [1b], (scheme 2)



Scheme 2

The original Fries rearrangement can thus be described by the general formulae

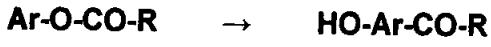


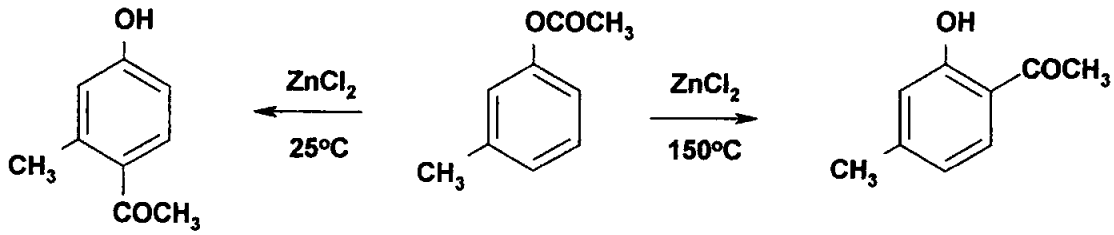
Fig. 1

Prior to discussing the Fries rearrangement it is proper to distinguish between it and the Friedel-Crafts reaction, of which it is essentially, a minor variant. The basis for this distinction is that in the Friedel-Crafts reaction for the preparation of phenolic ketones, a phenol is treated with an acid chloride and a Lewis acid, while in the Fries rearrangement a phenolic ester is reacted using a Lewis or Brønsted acid. This distinction may seem very academic for, almost without exception, the same products can be prepared using both reactions. However the Fries rearrangement has a very practical basis as it usually gives much better results [2(a & b)]. Phenolic ketones, or more correctly hydroxyaryl ketones, can also be synthesised by a number of other methods, such as the Hoesch or the Houben-Hoesche reaction (fig. 2), a Friedel-Crafts acylation with nitriles and HCl.[3]

Fig. 2

Another example would be the Nencki reaction [4], the ring acylation of phenols with acids in the presence of zinc chloride, or the modification of the Friedel-Crafts reaction by substitution of ferric chloride for aluminium chloride.

Many years before Fries ever realised the general applicability of the reaction which subsequently carried his name, there are a number of publications which report the rearrangement of phenolic esters under the influence of Lewis acids [5(a)]. In 1904, Eykmann [5(c)] had shown that *meta*-cresol and acetyl chloride, when treated with zinc chloride had furnished, at room temperature, 2-methyl-4-hydroxyacetophenone, and, at higher temperatures, 2-hydroxy-4-methylacetophenone (scheme 3). This was the first indication of the importance of the reaction temperature on the positions of the migrating group.



Scheme 3

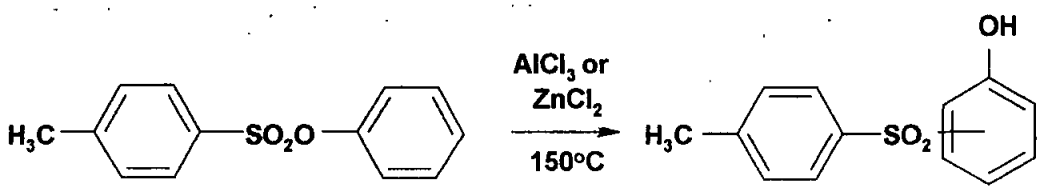
Earlier, in 1897, Behn [5(d)] patented a procedure for preparing phenolic ketones by treating phenols and acid chlorides in a nitrobenzene solution with aluminium chloride, thus demonstrating the importance of nitrobenzene as a solvent in this type of reaction. Going back earlier still, Döbner [5(b)] in 1881, prepared phenyl benzoate and, without purifying

the crude ester, heated it with benzoyl chloride and aluminium chloride to obtain the benzoate of *para*-hydroxybenzophenone.

One method of carrying out the Fries rearrangement is to heat a mixture of the phenolic ester with a catalyst at between 80°C and 180°C. The reaction may take varying lengths of time, from a few minutes to many hours, depending on temperature, catalyst used and the particular esters. All of these parameters affect reaction velocities. Another is to allow the reaction to proceed in a solvent, as already mentioned, which allows the investigation of the reaction at lower temperatures. However when using a solvent the reaction may take several hours to complete. The solvents most frequently used are, benzene, nitrobenzene, chlorobenzene, carbon disulfide and DCM. Although aluminium chloride was used initially, the catalytic activity of a large number of other compounds have been investigated. These include $AlBr_3$, AlI_3, $HgCl_2$, $SnCl_2$, $SnCl_4$, $FeCl_2$, $FeCl_3$, $TiCl_4$ and many more.

The original rearrangement carried out by Fries in 1908 in collaboration with Finch involved the migration of the acyl group from the oxygen on the side chain to carbon of the aromatic nucleus. An analogous reaction would be the movement of the sulfamoyl group from the phenolic oxygen to the aromatic carbon. In 1931 Rittler [6(a)] rearranged *para*-toluenesulfonate using both, aluminium chloride and zinc chloride at 150°C, separately, in the presence and absence of an inert solvent like nitrobenzene, and obtained a mixture *ortho* and *para* hydroxydiarylsulfones (scheme 4). Rittler later

modified this procedure [b] when he reacted phenol with *para*-toluenesulfonyl chloride in the presence of aluminium chloride at 130°C, without solvent.

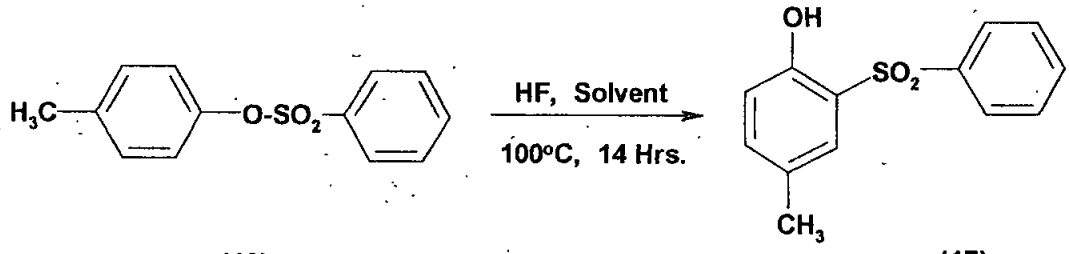


(14) with and without $C_6H_5NO_2$ (15)

Scheme 4

These conditions, which probably involve *in situ* formation of the toluenesulfonate, resulted in only *ortho*-hydroxyphenyl *para*-tolylsulfone. He observed that in the presence of nitrobenzene as solvent, the rearrangement was predominantly to the *para*- position and conversely, without solvent, the rearrangement was principally to the *ortho*- position.

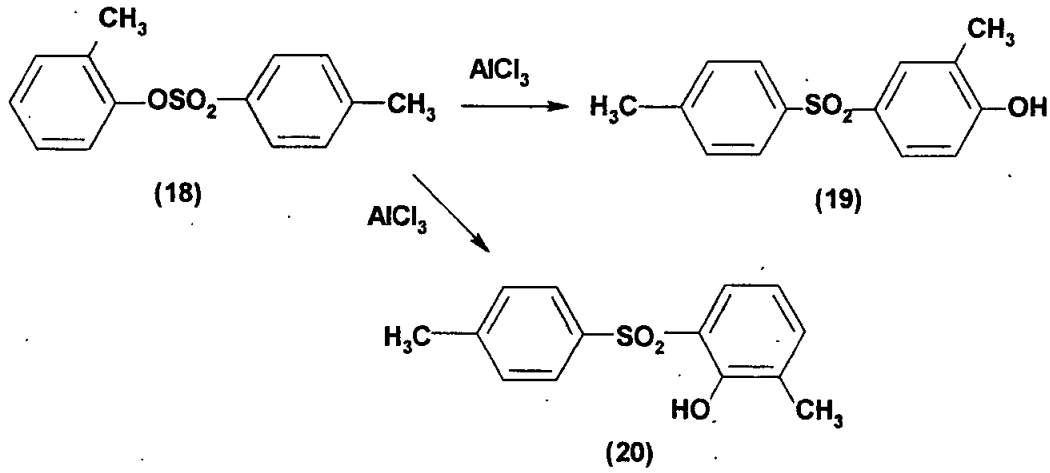
Some years later it was reported [7] that *para*-tolylbenzenesulfonate rearranged to 2-hydroxy-5-methyldiphenyl sulfone in a 10% yield by heating the sulfonate in a closed copper bomb with hydrogen fluoride at 100°C for 14 hours using ligroin, a high bp petroleum spirit, as a solvent (scheme 5).



(16) (17)

Scheme 5

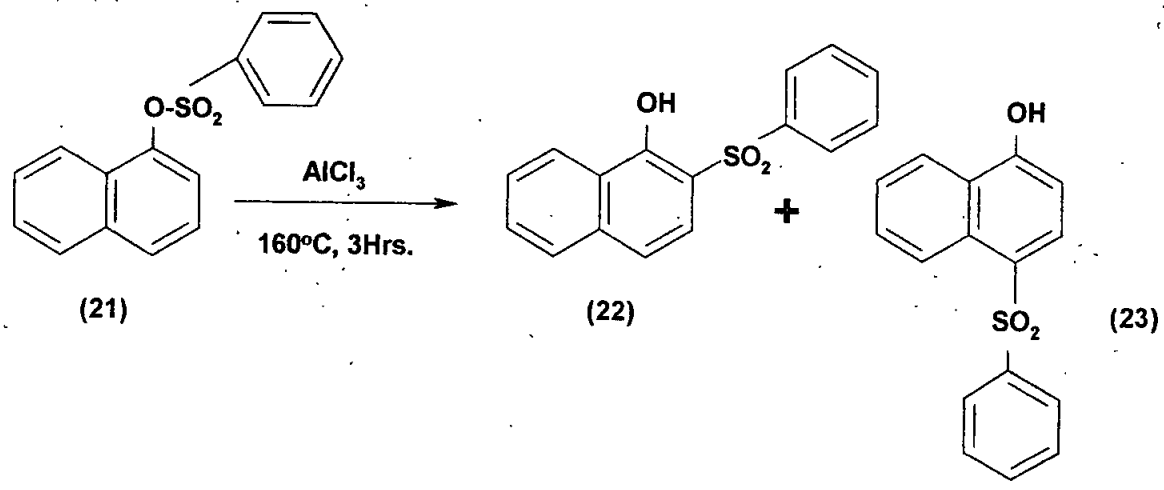
Two other groups carried out studies on the orientation of the rearrangement of arylsulfonates. Amin and co-workers[8] reported that the rearrangement gives predominantly *para*- product while subsequent reports by Baliah and his group [9 (a-d), 10 (a & b)] claim that rearrangement is usually to the *ortho*- positions. In the initial work Amin reacted a series of arylsulfonates with aluminium chloride for one hour at 140°C, an example being *ortho*-tolyl *para*-toluenesulfonate (18) which he reportedly rearranged to 4-hydroxy-3-methylphenyl-*para*-tolylsulfone (19) as in scheme 6.



Scheme 6

Baliah and Uma [10(d)] however, claimed that Amin was mistaken, because when they repeated the experiment using the same reaction conditions, 2-hydroxy-3-methylphenyl-*para*-tolylsulfone (20) was the product. This compound was synthesised by an alternative method to prove their case. Baliah and Uma [10(c)] also studied the rearrangement of the benzene sulfonates of various xylenols and observed predominately *ortho*- migration whenever that position was available. Similarly, with β-naphthyl benzenesulfonate [10(e)],

the benzenesulfonyl group migrates to the adjacent positions as is the case with the α-naphthyl unsubstituted and substituted benzenesulfonates [10(b)] (scheme 7).



Scheme 7

Joshi and Giri [11], in their series on organic pesticides, made a number of sulfonates and rearranged them to sulfones.

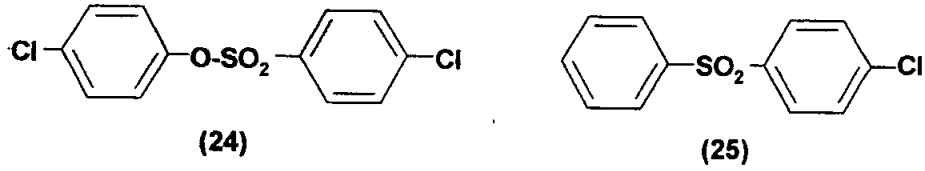
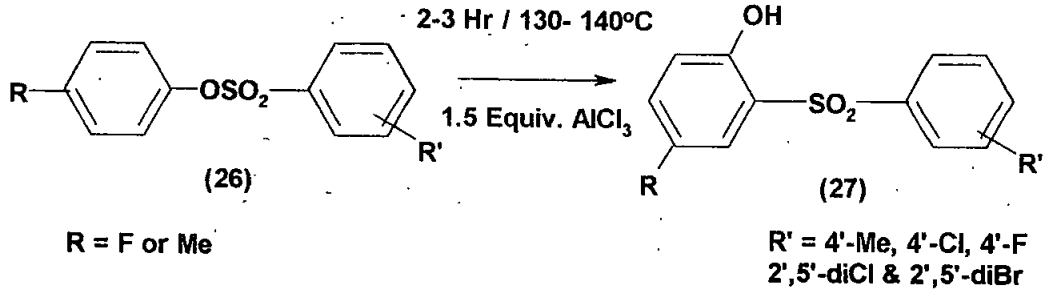


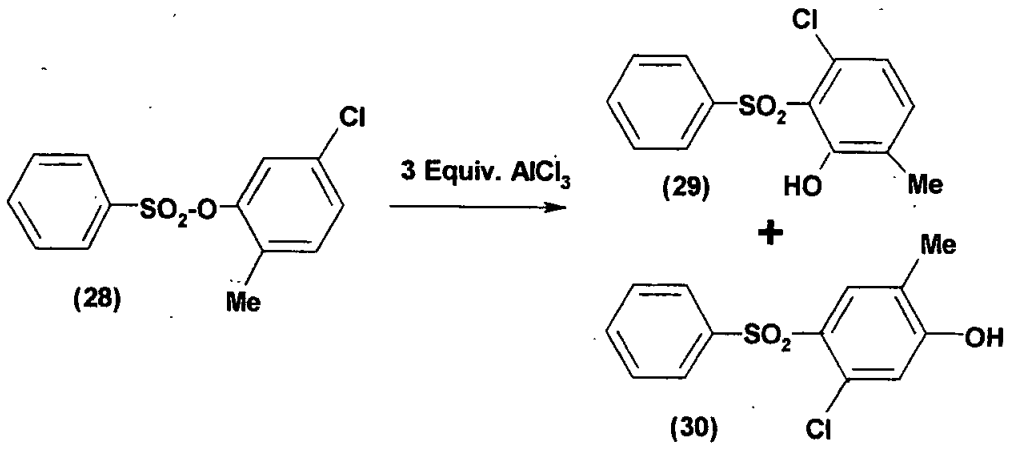
Fig 3



Scheme 8

It was because of the insecticidal and fungicidal properties of "Ovotran" (24) and "Sulphenone" (25) in fig. 3 that they synthesised several fluoro methyl analogues and converted them to the corresponding hydroxy diarylsulfones of the type (27) (scheme 8). All rearrangements have occurred to the *ortho-* positions as the *para*-positions were blocked.

At about the same time Le Van-Thoi and Co Tan Long [12], in an analogous manner, synthesised and rearranged a series of sulfonates using 3 equiv. of $AlCl_3$. The aryl sulfones which were produced included: 2-hydroxy-3-methyl-5-chlorophenyl, 3-nitro-4-

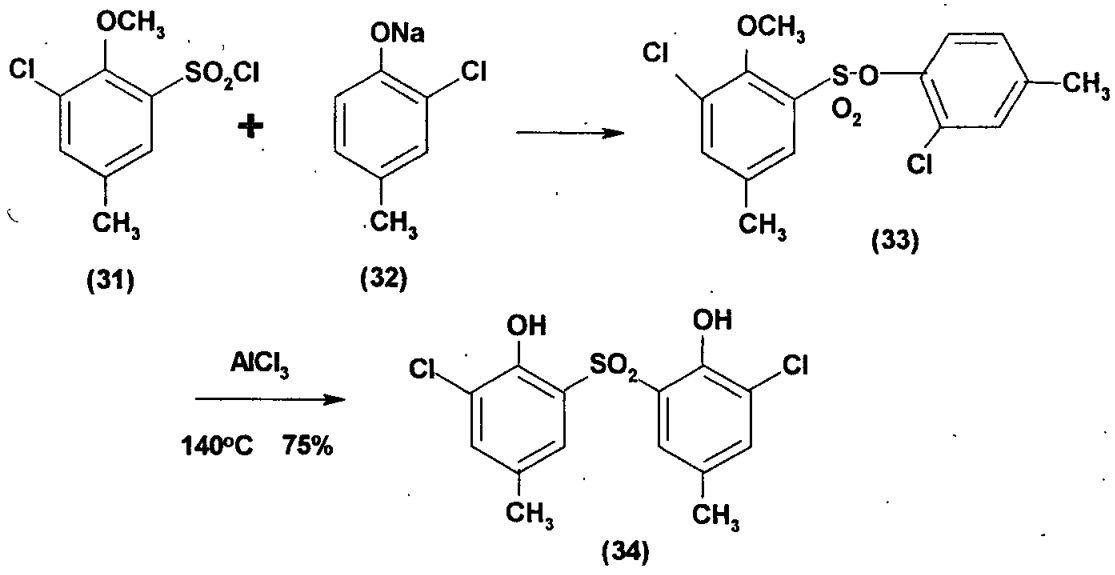


Scheme 9

hydroxyphenyl, 2,5-dimethyl-4-hydrpoxyphenyl, 2-hydroxy-4,6-dichlorophenyl, 2-hydroxy-3,5-dimethylphenyl and 3,5-dichloro-5-hydroxyphenyl among many more (scheme 9).

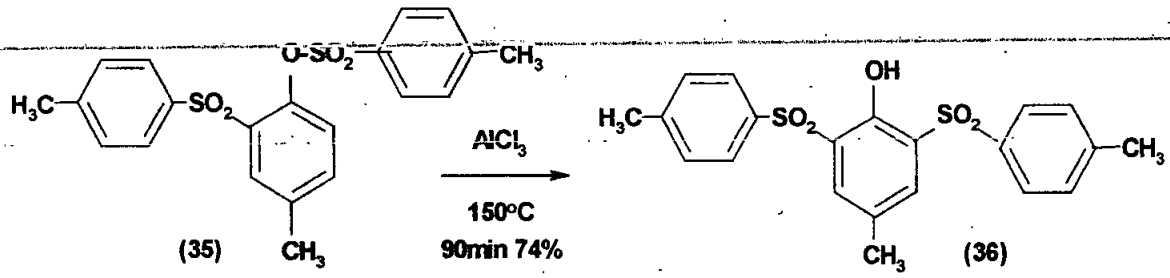
Kämmerer and Harris [13(a)] state that, "phenols can be condensed with thionyl chloride using aluminium chloride as catalyst, in good yields, to molecularly defined sulfoxides,

which can be preparatively reduced to sulfides or oxidised to sulfones. The sulfones were also obtained in good yields by condensation of sulfochlorides of the aryl esters with phenolic ethers and aluminium chloride or by the Fries rearrangement of the corresponding sulfonic esters" (scheme 10).



Scheme 10

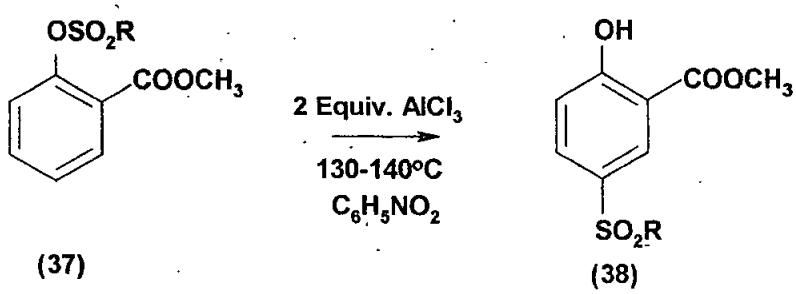
In a further publication [13(b)] continuing the above work, they indicate that two methods are generally suitable for the formation of structurally uniform phenolic polynuclear compounds with sulfonyl bridges, namely, the Fries rearrangement and the Friedel-Crafts reaction (scheme 11). This reaction shows an example of the preparation of a trinuclear compound with two sulfonyl bridges, through thia-Fries rearrangement.



Scheme 11

Robert Martin published a major review[14] (281 references, most multiple) of the Fries rearrangement titled, "Uses of the Fries Rearrangement for the Preparation of Hydroxyarylketones". This review gives a very comprehensive coverage of the subject, and refers to the earlier reviews which were published [15(a-d)]. There is a chapter on the formation of hydroxyarylsulfones from arylsulfonates, which has 17 references.

Parikh and his group have made many studies, over a number of years, of the rearrangement of various arylsulfonates, with their first publication [16(a)], being titled, "the rearrangement of some arylsulfonates of methyl salicylate" (scheme 12). The reaction products were subjected to methylation, hydrolysis and esterification.

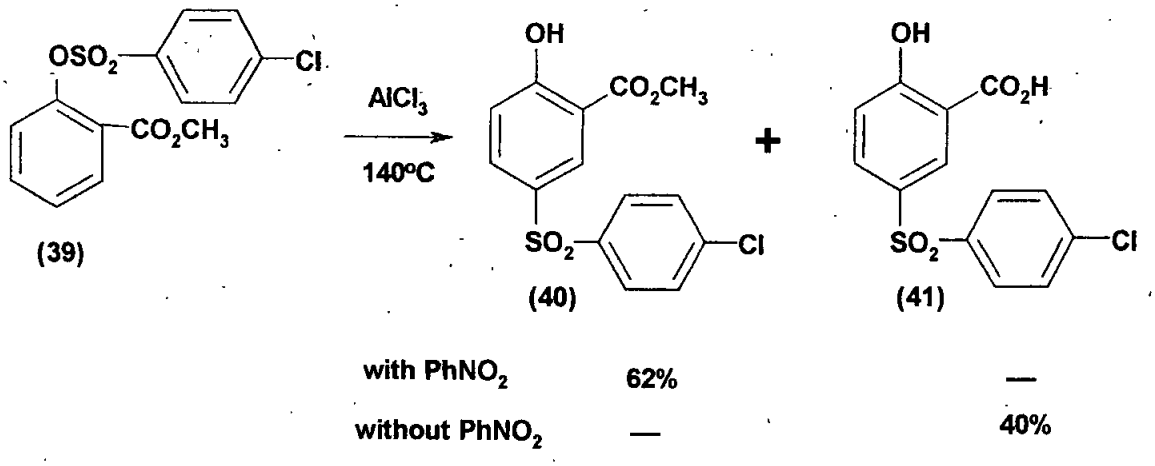


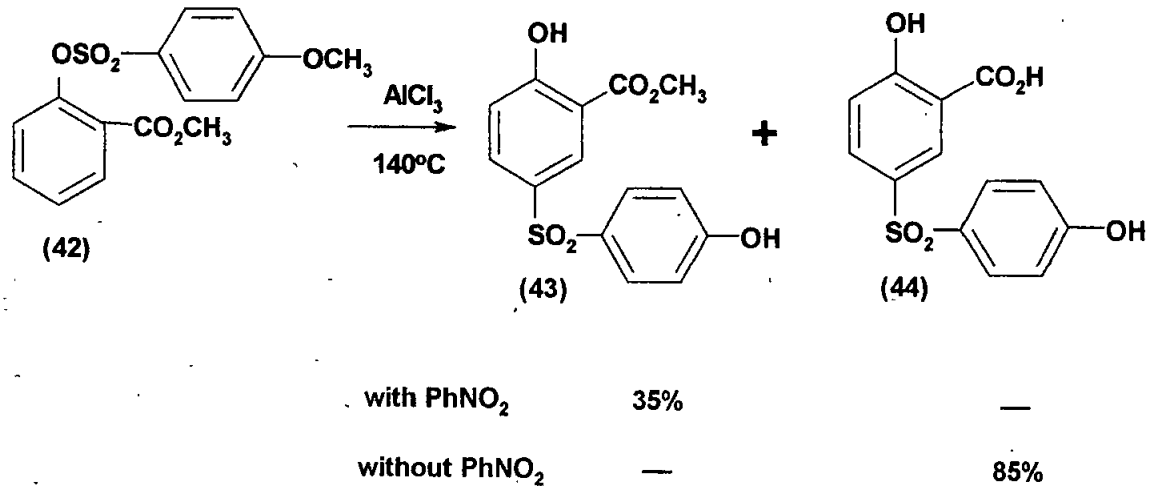
(37) (38)

R = *p*-Chlorophenyl, *p*-Bromophenyl, *p*-Hydroxyphenyl, *α*-Naphthyl and *β*-Naphthyl.

Scheme 12

Fries rearrangements of arylsulfonate were carried out with 2 equiv. $AlCl_3$ in nitrobenzene at 130-140°C for 2 hrs. and the ester was also rearranged without a solvent at 140°C for 2 hrs. The action of $AlCl_3$ on arylsulfonates involving methoxy and carbomethoxy groups, usually induces partial cleavage of methyl groups as in scheme 13.



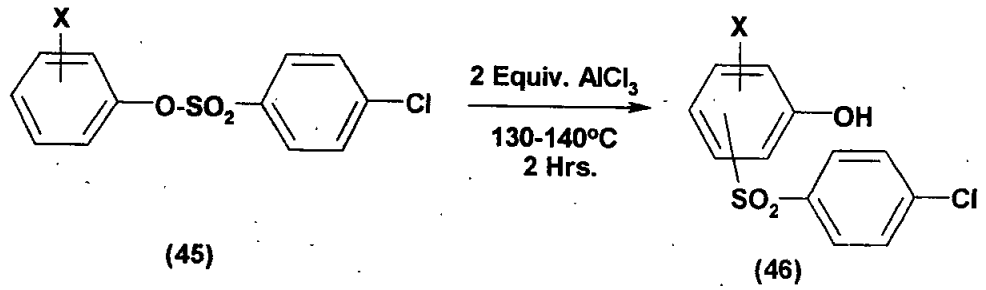


Scheme 13

Parikh's groups 1972 publication [16(b)] investigated the rearrangements of aryl-*p*-bromobenzene sulfonates of phenol, *p*-cresol, *p*-chlorophenol, *p*-chloro-*m*-cresol, *o*-

nitrophenol, α-naphthol, resorcinol, hydroquinone, and *p*-nitrophenol. The following year [16(c)] they studied the rearrangements of *p*-toluenesulfonate of, 2,4-dichlorophenol, *p*-chloro-o-cresol, 4,6-dichloro-*m*-cresol, *o*-nitrophenol, methyl-*p*-hydroxybenzoate, methyl salicylate, methyl-5-nitrosalicylate and *p*-chloro-*m*-cresol. In a separate paper [16(d)] on the same subject they report the rearrangement of α-, and β-naphthalenesulfonates of phenol and substituted phenols.

Parikh and Patwa continued the studies of the rearrangement of various sulfonates. They published two reports[17(a & b)] on the Fries rearrangement of the arylsulfonates of type R-O-SO_2-*p*-chlorophenyl, where X is a substituted phenyl. In conjunction with Goghari, Parikh [17(c)] carried out very similar work on the substituted arylsulfonates of *p*-iodophenol. The reaction conditions and substrates were similar to thoes in scheme 14.

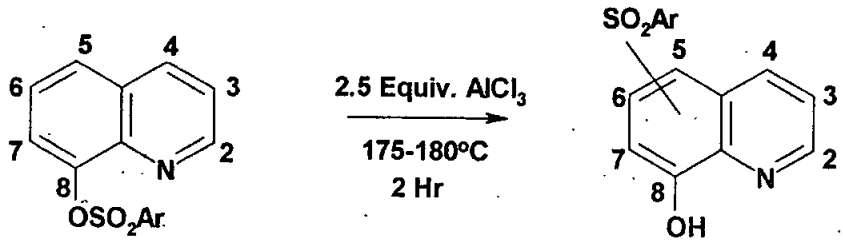


(45) (46)

Scheme 14

Parikh and Patwa carried out an interesting Fries rearrangement on a series of 8-quinolinylarylsulfonates in 1976 [18]. The aryl group was, phenyl, *p*-tolyl., *p*-chlorophenyl, *p*-bromophenyl, *p*-iodophenyl, *p*-anisyl, and α -, plus β-naphthyl. Phenyl, *p*-tolyl, *p*-bromophenyl, *p*-iodophenyl and anisyl gave predominantly the 5-

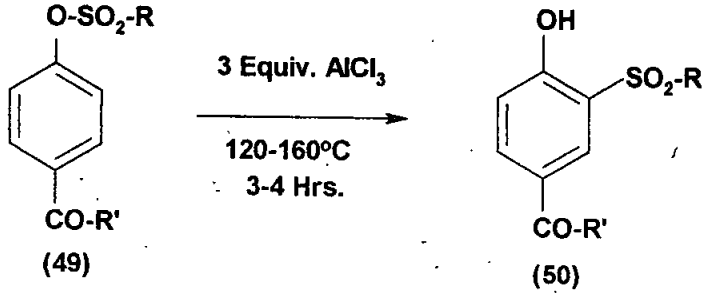
arylsulfonyl derivative, while the remainder gave the 6-arylsulfonyl derivatives (scheme 15).



(47) (48)

Scheme 15

The Fries rearrangement of 4-acylphenyl arylsulfonates leads to 2-hydroxy-5-ketoarylsulfones. However the nature of the acyl group influences the course of the reaction according to Thaker *et al.*[19 (a & b)] as in scheme 16.



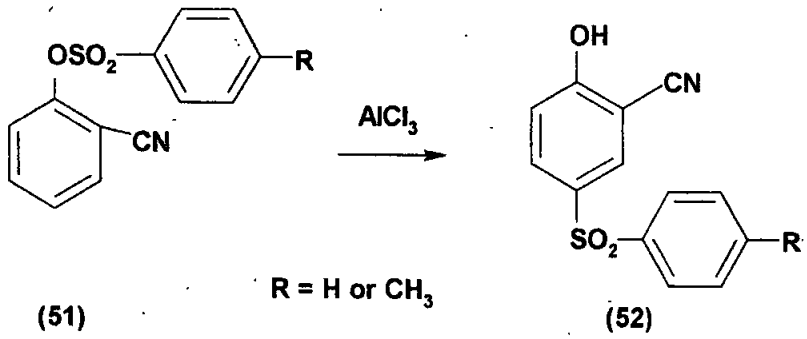
(49) (50)

R'	%
CH_3	20 - 60
C_2H_5	85 - 100

R = Ph, *p*-MeC_6H_4, *p*-Hal.C_6H_4, *α*- and *β*-$C_{10}H_7$

Scheme 16

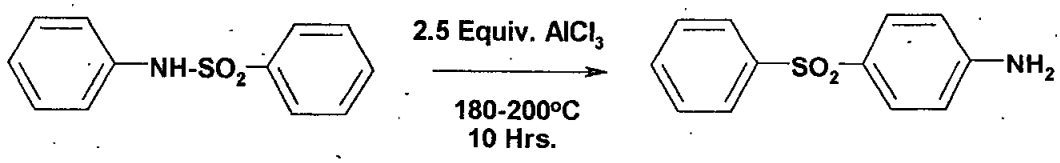
Erndt and Zubek [20] were researching diphenyl sulfones for expected acaricidal activity and they investigated the rearrangement of arylsulfonates of salicylonitrile. The reaction of these esters carried out in the presence of $AlCl_3$, without solvent, gave 3-cyano-4-hydroxydiphenyl sulfone (m.p.197-198°C) and 3-cyano-4-hydroxy-4'-methyl-diphenyl sulfone as in scheme 17.



(51) (52)

Scheme 17

The rearrangement of N-benzenesulfonylaniline to aminodiphenyl sulfone (yield 15%) was described by Srinivasan [21].

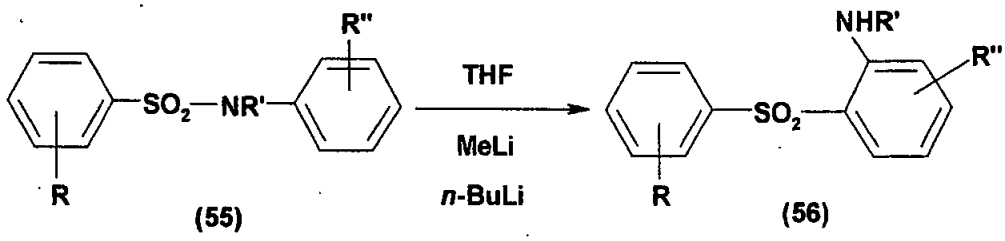


(53) (54)

Scheme 18

The interesting element in this publication is the breaking of the N – S bond (scheme 18) in the rearrangement, as there is no phenolic oxygen in the aniline moiety. The report also included the rearrangement of *o*-chloro-*N*-benzenesulfonylaniline to 3-chloro-4-aminodiphenylsulfone.

Another cleavage of the S-N bond was discussed by Shafer and Closson [22] in a base promoted rearrangement of arylsulfonamides of *N*-substituted anilines to *N*-substituted 2-aminodiarylsulfones.



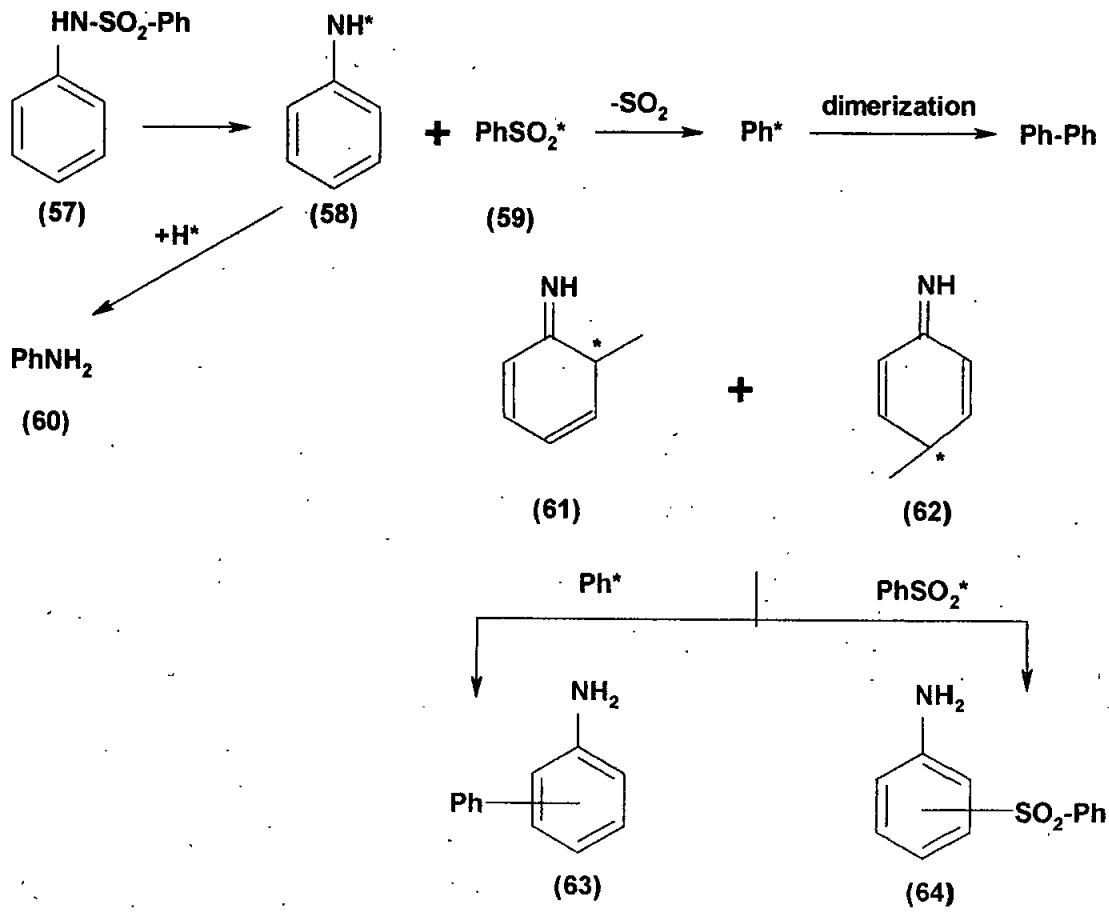
Scheme 19

The arylsulfonamides of N-substituted aromatic amines reacted readily with lithium bases and THF (tetrahydrofuran) in ether solvents to give *N*-substituted 2-aminodiaryl sulfones in quite good yield (45-89%) as in scheme 19. While the reaction is probable intramolecular according to the authors, it involves the formation of a dianion from the sulfonamide before the rearrangement occurs. This reaction would seem to be the method of choice for synthesising such aminosulfones.

Hellwinkel and Supp, [23(a-c)] during attempts to synthesise triarylamines utilizing organolithium compounds, treated *N,N*-diphenylbenzenesulfonamide and the

corresponding *p*-toluenesulfonamide with phenyl-, butyl- and methyl-lithium, they obtained not the desired products of a nucleophilic substitution of the benzenesulfinate groups, but instead, the anilinodiphenyl sulfones almost as in scheme 19.

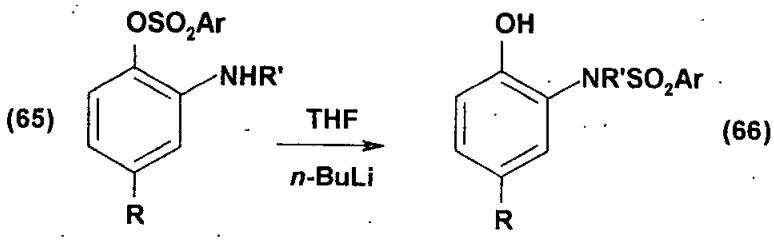
Badr *et al.*[24] while doing research on molecular rearrangements, studied the different effects of thermolysis and photolysis of *N*-arylbenzenesulfonamides. The photo-Fries rearrangement which is analogous to the Lewis acid catalysed thermal rearrangement, is one of the most studied reactions in photochemistry and will be discussed later.



Scheme 20

Heating of *N*-phenylbenzenesulfonamide in a nitrogen atmosphere at ca. 300°C for 15 hrs gave sulfur dioxide, aniline, biphenyl, carbazole and a mixture of isomeric *o*- and *p*-aminobiphenyl together with trace amounts of *o*- and *p*-aminobiphenyl sulfone. Technically, what is happening in this reaction (scheme 20), is a "Fries-type rearrangement", but the fact that sulfonamides are being rearranged to sulfones, albeit in minute quantities, it is felt that it should be included here. As shown, the anilino radicals abstract hydrogen to form aniline or are subjected to attack by phenylsulfonyl radicals in *ortho* and *para* positions forming *o*- and *p*-aminophenylsulfones. These phenylsulfonyl radicals can also extrude sulfur dioxide, forming phenyl radicals that couple with the anilino radical in the *ortho* and *para* position to form the isomeric amino-biphenyls, whereas, dimerisation of phenyl radicals leads to the formation of biphenyl.

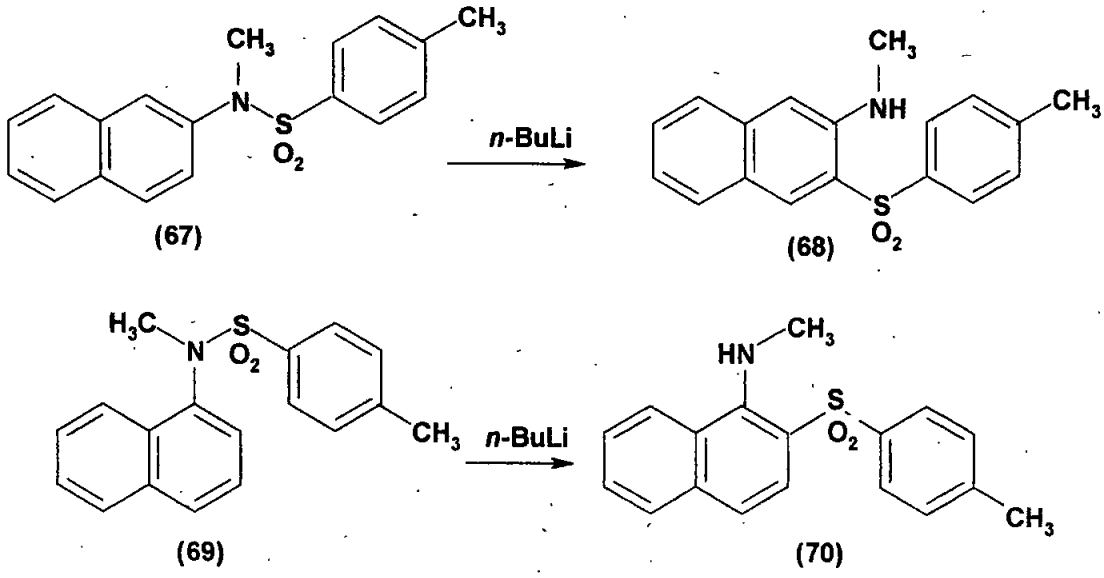
A series of 2-aminoaryl arenesulfonates which were treated by strong bases, rearranged intramolecularly into their corresponding *N*-(2-hydroxyaryl)arenesulfonamides as did the related tosylates derived from 2-amino-8-naphthol according to Anderson *et al.*[25] Treatment of the sulfonates with *n*-butyllithium in tetrahydrofuran or diethyl ether yielded the sulfonamides (scheme 21).



Scheme 21

Although a Fries rearrangement is not referred to in the paper at any stage, this reaction is in fact a base catalysed thia-Fries rearrangement and is in itself very unusual.

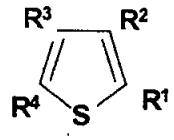
Another base catalysed rearrangement, involving a further cleavage of a N—S bond is reported by Hellwinkel and Lenz [26] (scheme 22) as a carbanionically induced sulfonamide-aminosulfone rearrangement. In the case of 2- and 1-naphthyltoluenesulfonamide the [1,3] shift of the arylsulfonyl group proceeds into the 3- and 2-positions to give the respective products. Maybe these reactions should not be included in a review of Fries rearrangement but we believe them to be relevant.



Scheme 22

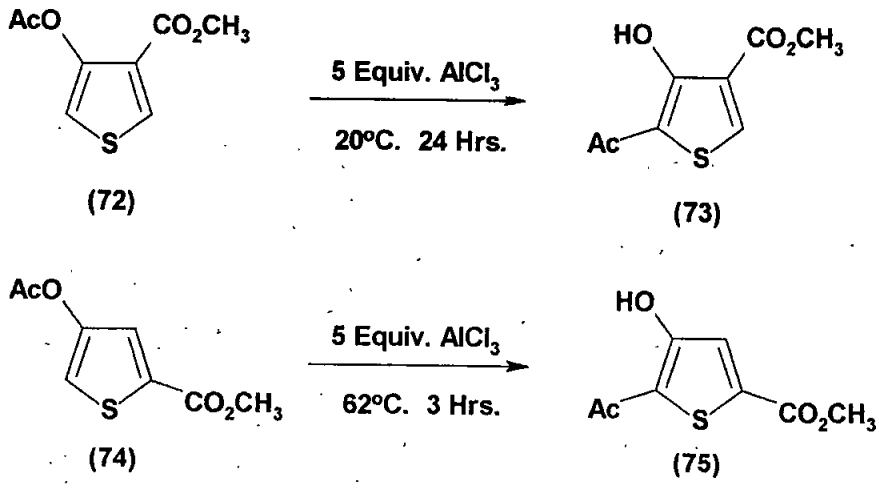
The Fries rearrangement of 3-alkanoyloxythiophenes has been studied, by Banks,[27] using $AlCl_3$ as catalyst and dichloromethane as solvent. An intermolecular component of the mechanism was demonstrated in a crossover experiment. The rearrangement proceeded

generally at ambient temperature to give 3-hydroxy-2-alkanoylthiophenes in good yields. The structures of both the acyl and the 3-thiophenoxy moieties were found to exert an influence on the rearrangement. Acetyl esters rearranged at a faster rate than propionyl esters. An acetyl group in the 4 position prevented the rearrangement, as did 2 esters in the thiophene ring. An ester or a cyano group in the 4 position had no influence (fig. 4 and scheme 23).



(71)

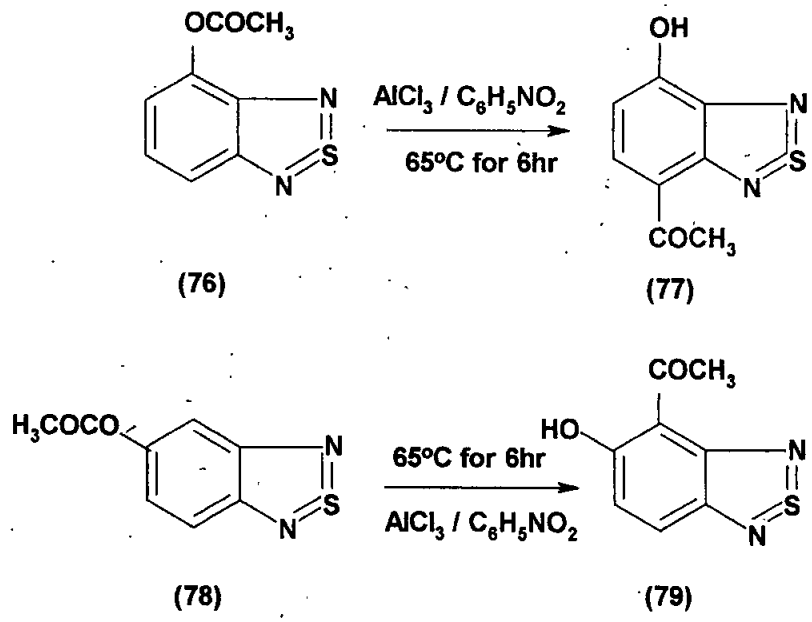
Fig. 4



Scheme 23

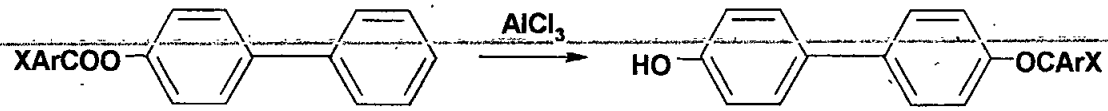
The Fries rearrangement of 4- and 5-acetoxybenzo-2,1,3-thiadiazoles which gave 4-hydroxy-7-acetyl- and 5-hydroxy-4-acetylbenzo-2.1.3-thiadiazoles was carried out as part

which were required because they were known to possess high antiviral activity in *ova.* [28]



Scheme 24

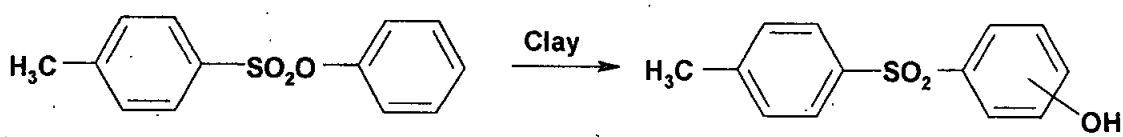
Colquhoun *et al* [29] state, in a patent registered by Imperial Chemical Industries, that they prepared arylhydroxybiphenyls by Fries rearrangements as in scheme 25. Ar is a divalent mono- or poly-aromatic group which may or may not be substituted. X is a hydrogen, halogen, nitro-, alkylsulfonyl-, arylsulfonyl-, alkylcarbonyl- or hydrocarbon group. For example, 4-ClC_6H_4COCl and 4-HOC_6H_4Ph were stirred for ≈ 9 hr at 120°C in 1,2-$Cl_2C_6H_4$ containing H_2SO_4 at which point $AlCl_3$ was added and the mixture stirred for a further 7-8 hr at 120°-130°C to give 74% 4-(4-$ClC_6H_4CO)C_6H_4C_6H_4OH$-4.



(80) (81)

Scheme 25

Cation-exchanged montmorillonite clays catalysed the Fries rearrangement of phenyl toluene-*p*-sulfonate to give, selectively, *o*- and *p*-hydroxyphenyl-*p*-tolylsulfone as major and minor products respectively, according to Pitchumani [30(a)]. The use of clays as catalysts for the rearrangement of sulfonates was new at this stage in time, because until then metal halides were the prominent catalysts. Acidic cation-exchange montmorillonites are efficient catalysts in a number of proton-assisted reactions and function as effective Lewis acid catalysts in place of conventional species such as $AlCl_3$. In the case, with a bulkier sulfonate migrating group, a steric effect exerts its presence more effectively and *ortho*-isomer formation is the major course of the reaction (scheme 26).

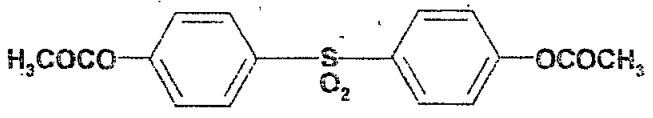


(82) (83)

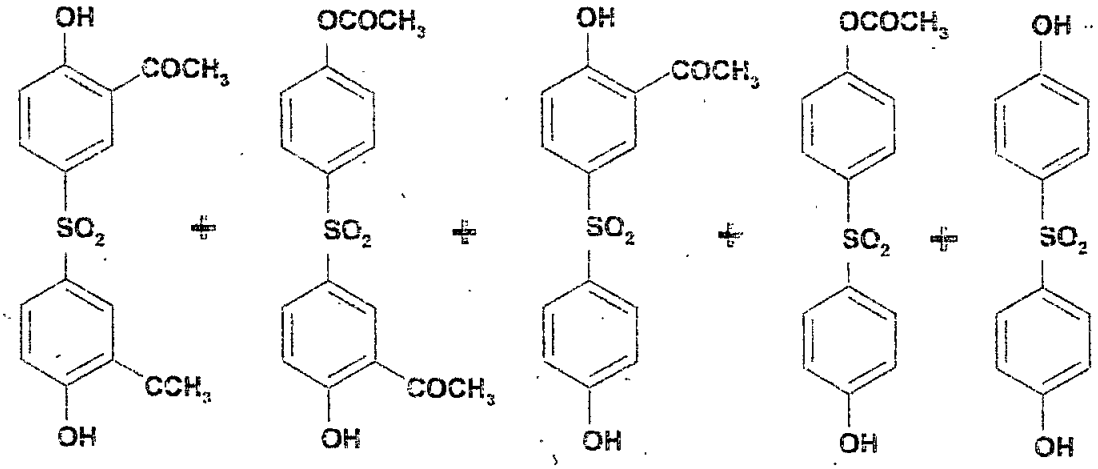
Scheme 26

The steric influence on the products distribution is also affected by the nature of the substrate. With the bulkier naphthyl *para*-toluenesulfonate the rearrangement is regiospecific and the *ortho*-isomer is the exclusive product [30(b)].

Like Babr [24] above, Sridar and Sundara Rao [31] carried out comparative studies between thermal and photo Fries rearrangements on, in this case, the bisacetete of 4,4'-dihydroxydiphenylsulfone (bisphenyl-S). They state that the photolysis procedure yields only a mono rearranged product, whereas under thermal conditions a 23% yield of the bis rearrangement product is obtained.



(84)

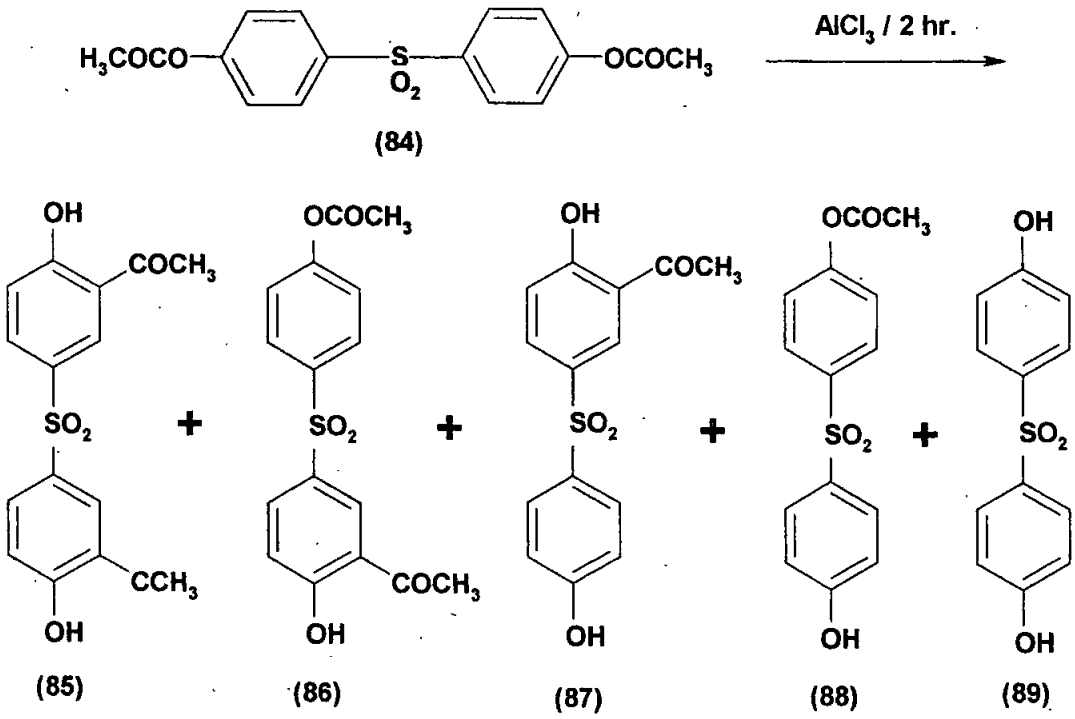


(85) (86) (87) (88) (89)

REACTION CONDITIONS	84	85	86	87	88	89
3 Equiv. $AlCl_3$ 2 Hrs.	11.7	15.2	16.8	17	20	15.2
10 Equiv. $AlCl_3$ 2 Hrs.	N/A	23	7	23	9.5	31.5

Scheme 27

Like Babr [24] above, Sridar and Sundara Rao [31] carried out comparative studies between thermal and photo Fries rearrangements on, in this case, the bisacetate of 4,4'-dihydroxydiphenylsulfone (bisphenyl-S). They state that the photolysis procedure yields only a mono rearranged product, whereas under thermal conditions a 23% yield of the bis rearrangement product is obtained.



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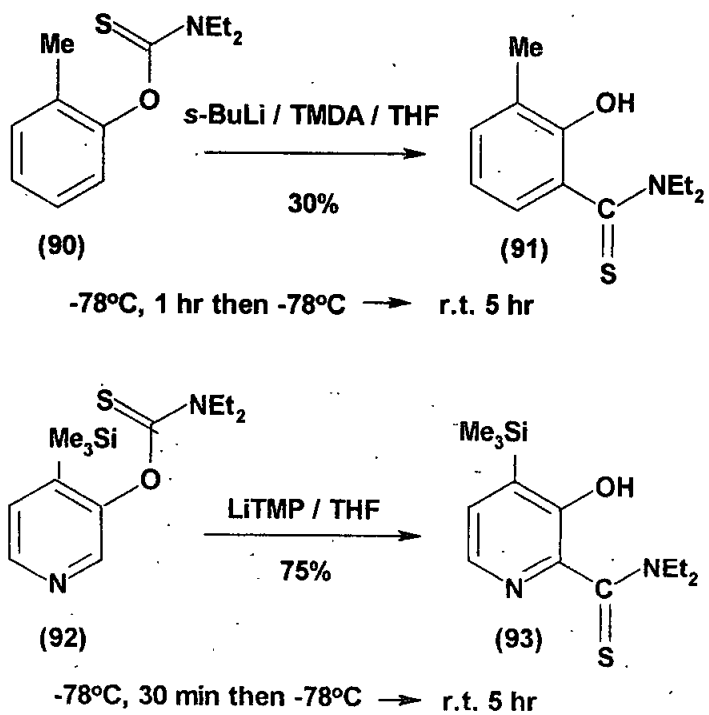
Scheme 27

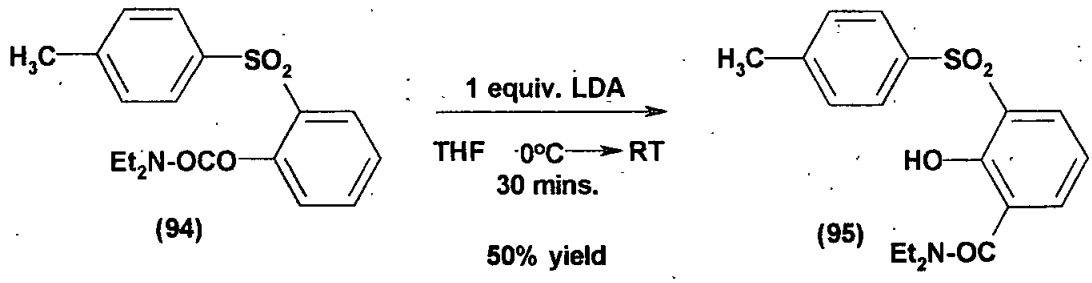
The sulfone group retards rearrangement in this particular case, under thermal conditions. This was also found to happen when the Fries rearrangement of 4-toluene arylsulfone acetate was carried out.

The anionic *ortho*-Fries rearrangement of *O*-(2-methylpheny)-*N,N*-diethylthiocarbamate (**90**) to *N,N*-diethyl-2-hydroxy-3-methylbenzenecarbothioamide (**91**) and of *O*-[4-(trimethylsilyl)pyridyl-3yl] *N,N*-diethylthiocarbamate (**92**) to *N,N*-diethyl-3-htdroxy-4-(trimethylsilyl)pyridine-3-carbothioamide (**93**) *via* the directed *ortho*-metalation protocol are described by Beaulieu and Snieckus [32(a & b)] (scheme 28)



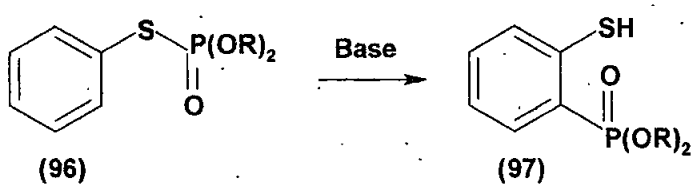
Scheme 28

As part of a generalised procedure for the construction of condensed heterocycles from heteroatom-bridged diaryl systems, Beaulieu and Snieckus [32(c)] rearranged the unprotected 2-*O*-carbamate diarylsulfone in a rapid anionic *ortho*-Fries reaction.



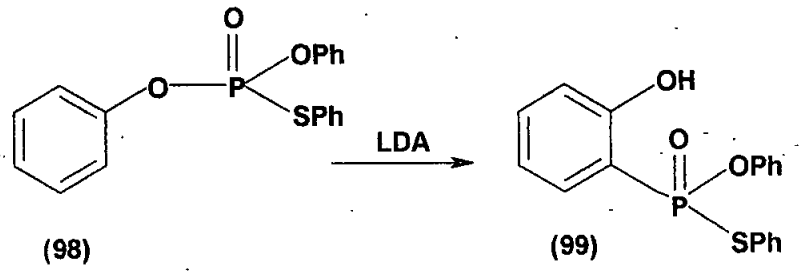
Scheme 29

The chemistry of mixed phosphorus-sulfur compounds and especially that of phosphorus-arylthiol ligands had to this time, (mid 1990's) received very little study, according to Masson *et al* [33]. In this publication they describe the synthetic potential of the phosphorothioate-mercaptophosphonate rearrangement of S-phenyl phosphorothionate (schemes 30 and 31). They also discuss the scope and limitations of this method which allows the preparation of various derivatives of mercaptoaryl and of mercaptoheteroaryl phosphonates.



Scheme 30

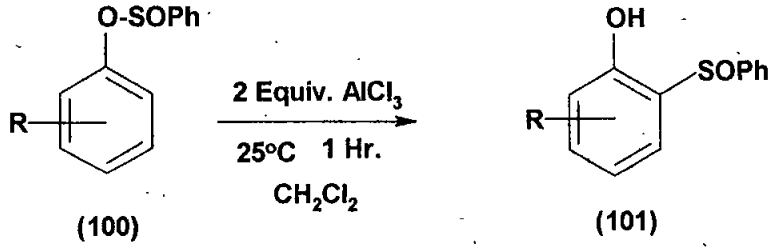
The O,O,S-triphenyl phosphorothioate (**98**) has also been rearranged (scheme 31)



Scheme 31

In these reactions we have the breaking of the S—P bond in what might be classed a phospho-Fries rearrangement.

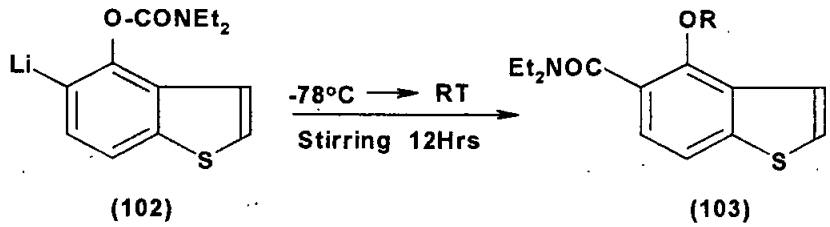
The treatment of aryl phenylsulfinates with $AlCl_3$ at 25°C furnished good yields of phenylsulfonyl phenols via a 'thia-Fries rearrangement according to Jung and Lazarova [34] as in scheme 32.



Scheme 32

In his series, "Studies in sulfur heterocycles", De *et al*[35(a)] state that an anionic *ortho*-Fries rearrangement has been carried out on *p*-carbamoyloxybenzol[*b*]-thiophene and the

product used as a starting material in the synthesis of a novel linearly fused thioenoisocromene (scheme 33).



(102) (103)

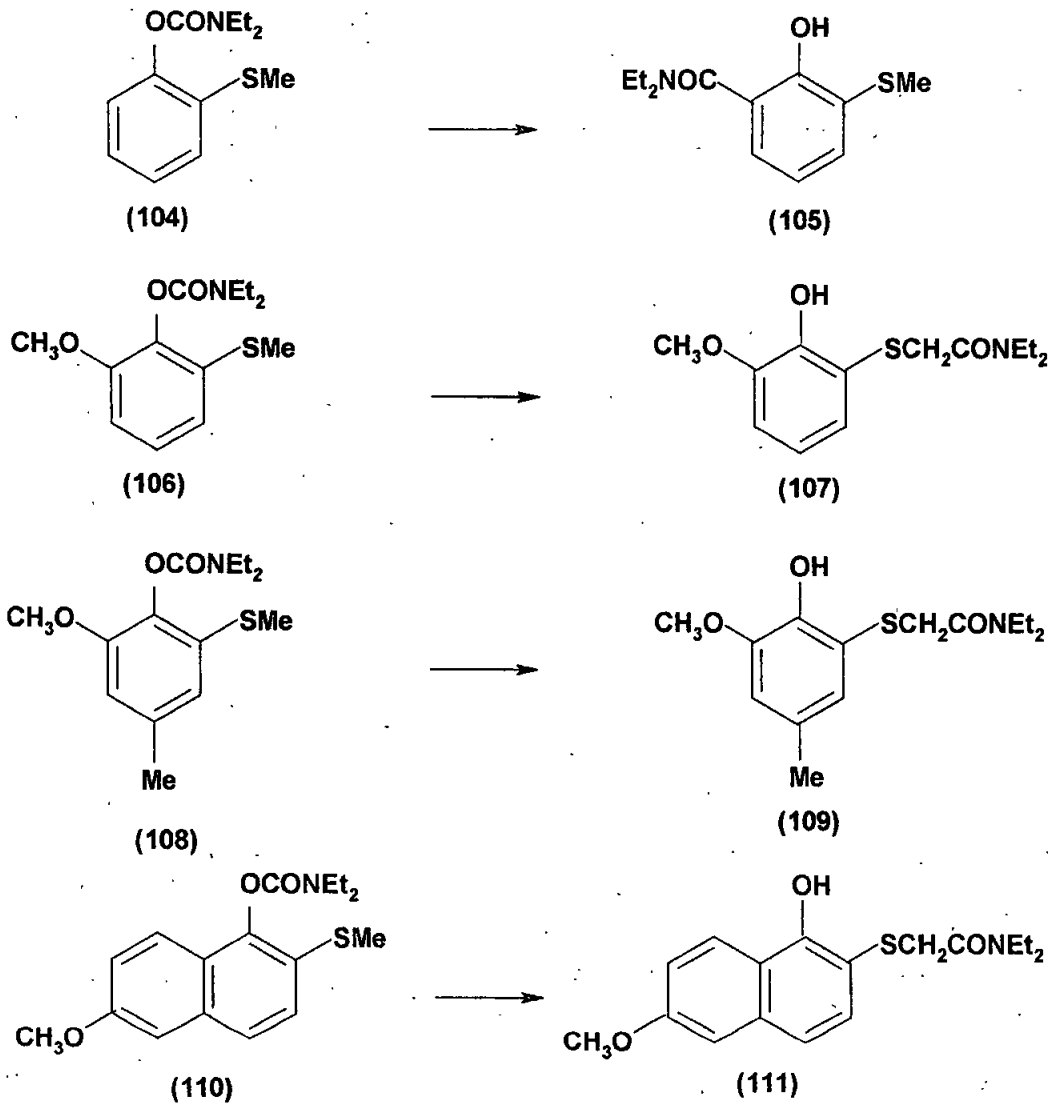
Scheme 33

This group [35(b)] also studied the "synthesis of several analogues of (±) simivioxanthin, including five thiophene analogues, using directed metalation and this strategy consisted of the synthesis of functionalised naphthalene or benzo[*b*]thiophene as building blocks followed by annulation of the pyrone." This synthetic work required Fries rearrangement for certain steps, which were as in scheme 34.

In a further publication [35(c)] they state that, "the introduction of the methyl sulfanyl function in the *ortho*-position to the *O*-carbamate functionality under standard directed metalation condition was followed by side-chain deprotonation with *sec*-butyl lithium at –78°C. Upon warming to room temperature the deprotonated species underwent intramolecular anionic-Fries rearrangement to afford *N,N*-diethyl-2-hydroxyarylthioacetamides. The rearranged products were cyclised with hot glacial acetic acid to afford condensed oxathiin-2-ones in excellent yield" (scheme 34).

In 2004 they reported [35(d)] on an anionic rearrangement under directed metalation conditions, which involves the side chain deprotonation of *ortho*-methylsulfanyl

substituents by an *O*-carbamate DMG followed by rearrangement. They specifically state that this reaction is distinct from an anionic homologous Fries rearrangement but is very much like the previous scheme.

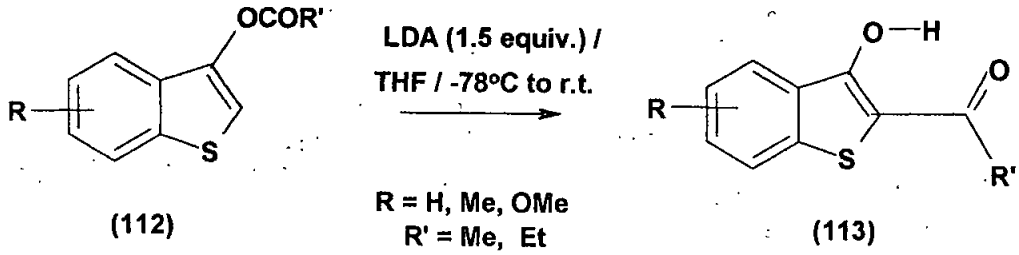


Scheme 34

And finally, in a very recent publication [e] they state that "a one pot synthesis of (3-hydroxybenzo[*b*]thiophen-2-yl) aryl methanones was achieved from *ortho*-

methylsulfanaryl *N,N*-diethylamides, 1-(3-hydroxybenzo[*b*]thiophen-2yl)ethanone and 1-(3-hydroxybenzo [*b*]thiophen-2yl)propan-1-one via an anionic *ortho*-Fries rearrangement and that the hydroxy ketones were used as key intermediates in the synthesis of benzothienopyranones."

Thus, benzo[*b*]thiophen-3-yl acetate and benzo[*b*]thiophen-3-yl propionate which were prepared by treating the thioindoxyl with acetyl chloride and propionyl chloride respectively, in the presence of sodium hydride or LDA in tetrahydrofuran, were lithiated at the 2-position with LDA. The deprotonated species upon stirring at room temperature for 8-10 hr. underwent intramolecular rearrangement to give 1-(3-hydroxybenzo[*b*]thiophen-2yl)ethanone and 1-(3-hydroxybenzo[*b*]thiophen-2yl)propan-1-one respectively (scheme 35).

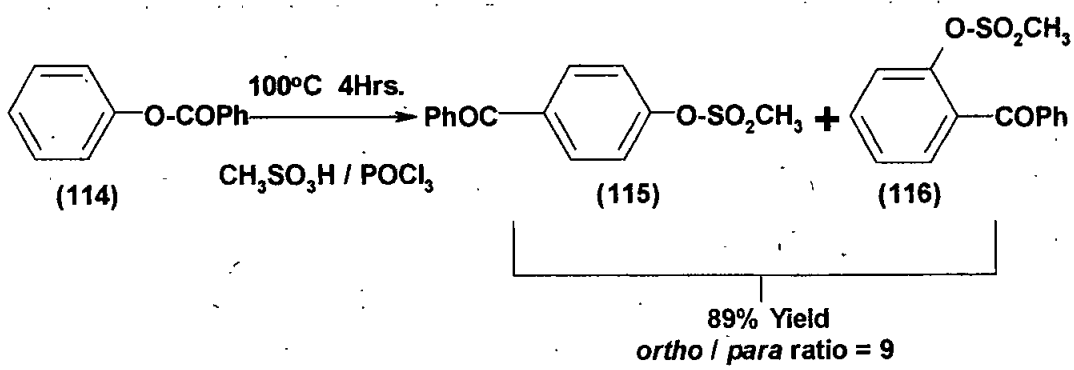


(112) (113)

Scheme 35

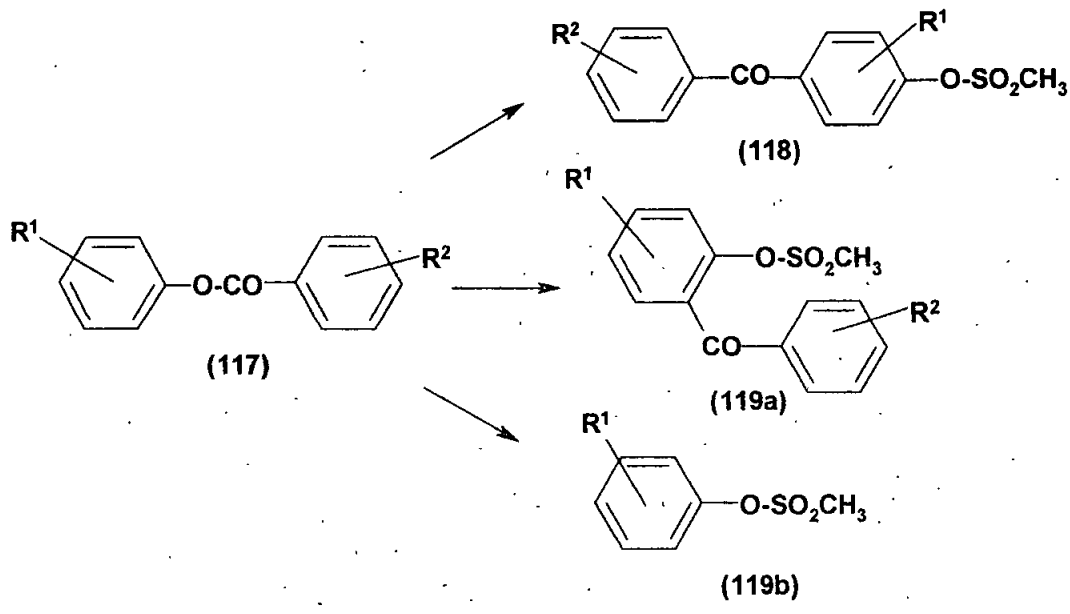
Kaboudin [36(a)] reported the Fries rearrangement of acyloxybenzene derivatives in the presence of methanesulfonic acid / phosphorus oxychloride (MAPO), as a new efficient

reagent for the one-pot synthesis of acylaryl methane sulfonates of phenolic esters as in scheme 36.



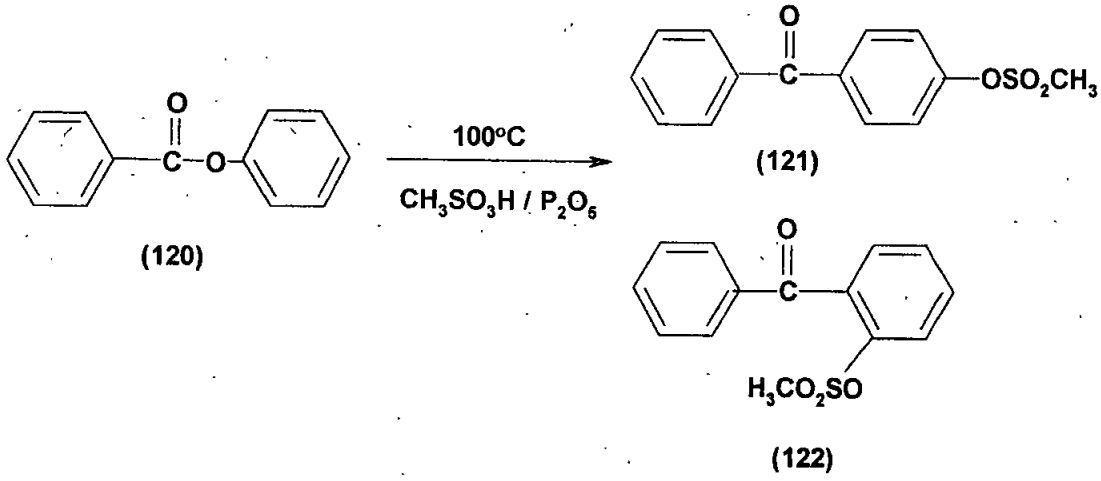
Scheme 36

The same process was successfully extended to other acyloxyarene derivatives as shown (scheme 37). The results clearly indicate that the reaction seems to be faster when the aryloxy part of the ester carries electron-donating groups; *p*-acylaryl methanesulfonates were formed selectively.



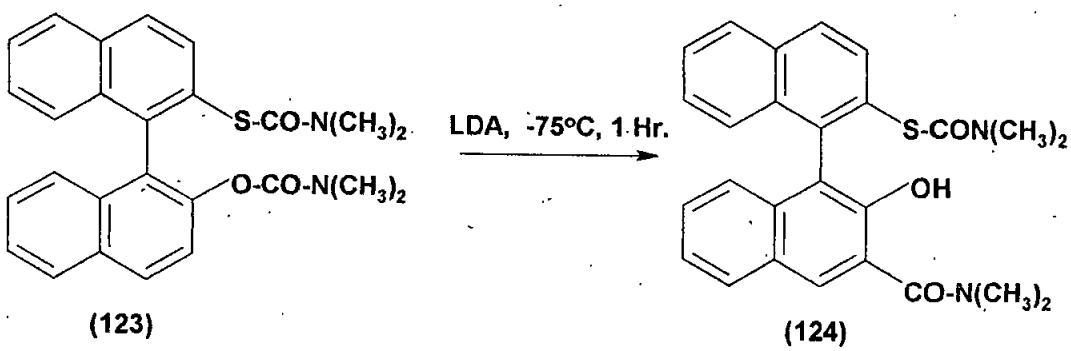
Scheme 37

In a further paper Kaboudin [36(b)] found methanesulfonic acid / diphosphorus pentoxide (4 : 1) to be an efficient reagent for the one-pot synthesis of acylaryl methanesulfonates of phenolic esters *via* the Fries rearrangement (scheme 38).



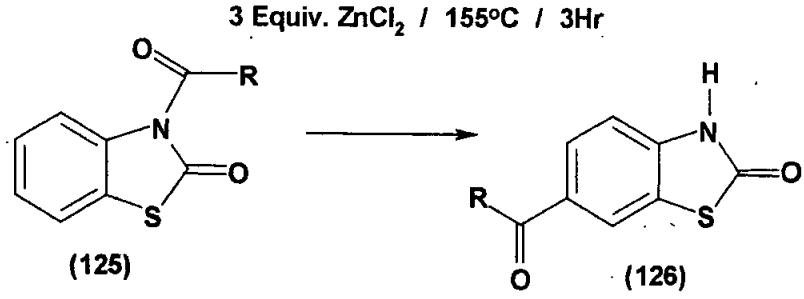
Scheme 38

2-(*N,N*-Dimethylcarbamoyloxy)-2'-(*N,N*-dimethylcarbamoylthio)-1,1'-binaphthyl undergoes anionic Fries rearrangement (scheme 39) of the *O*-aryl carbamate to afford a crystallographically characterised amido species 2'-(*N,N*-dimethylaminocarbonylthio)-2-hydroxy-3-(*N,N*-dimethylaminocarbonyl)-1,1'-binaphthyl.[37]



Scheme 39

Guenadil *et al* [38] report on "another method of acylation on the 6-position of the 2(3H)-benzothiazolone ring with Fries-like rearrangement catalysed by zinc chloride instead of aluminium chloride and 3-acyl-2(3H)-benzothiazolones derivatives as starting materials. This method is advantageous in regard to other acylation methods as it requires only three equivalents of $ZnCl_2$ to produce 6-acyl-derivatives with yields of 82-94%."

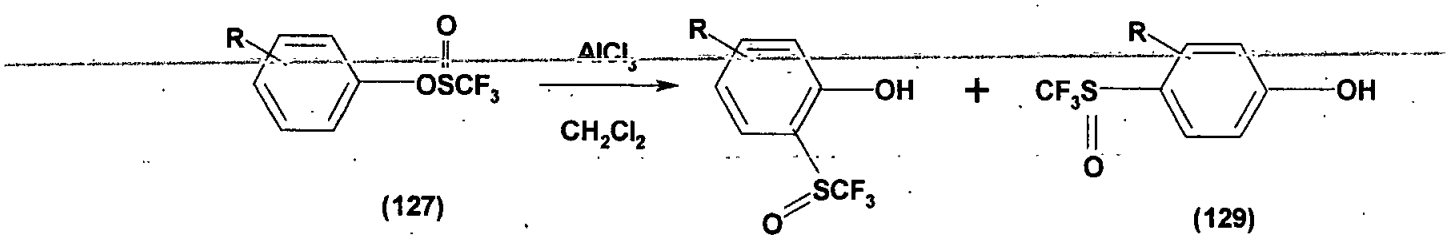


R = CH_3; CH_2CH_3; Ph; *p*-Cl-Ph; *p*-NO_2-Ph; *p*-F-Ph

Scheme 40

The product 6-acyl-2-(3H)-benzothiazolones (scheme 40), which was obtained by the Fries-like rearrangement is reported to have particularly interesting anti-inflammatory, antiepileptic, antiviral, analgesic and anti-convulsant properties. As a result of all the interest in these compounds the optimisation of their synthesis was studied.

Wakselman *et al*[39] claim that "aryl triflates are transformed to trifluoromethanesulfinyl phenols in the presence of aluminium chloride in dichloromethane at room temperature according to the thia-Fries rearrangement process. Oxygen free conditions are necessary in order to avoid the formation of 2,2'-dihydroxybiaryls as secondary products."



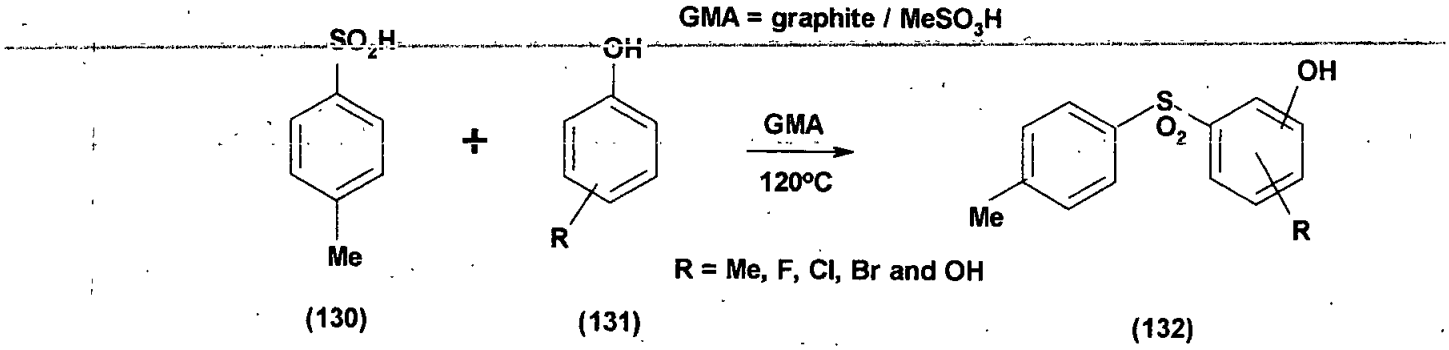
(127) (128) (129)

R = H, 4-F, 4-Cl, 4-Br, 3 & 4-Me, 4-OMe and 3 & 4 Ph

Scheme 41

Consequently the reaction was carried under argon with a very meticulous exclusion of oxygen (scheme 41). The analogous thia-Fries rearrangement of aryl sulfinates into sulfonyl phenols has been reported only in the case of aryl benzenesulfinates. This reaction allows the insertion of a sulfonyl substituent directly into the aromatic nucleus.

In a very recent paper [40] entitled "Graphite / Methanesulfonic acid (GMA) as a new reagent for sulfonylation of phenols and the thia-Fries rearrangement of aryl sulfonates to sulfonylphenols" Sharghi and Shahsavari-Fard discuss this new facile method for direct sulfonylation of phenols. The following mechanism of the sulfonylation reaction is suggested; the phenol is first converted to the arylsulfonate by reaction with *p*-toluenesulfonic acid. The arylsulfonate subsequently undergoes rapid intermolecular decomposition in the presence of GMA (0.3g graphite / 1ml $MeSO_3H$), the 'thia-Fries rearrangement, to produce the sulfonylium cation $MeC_6H_4SO_2^+$ and the phenol, which combine to form the sulfonylphenols as in scheme 42.

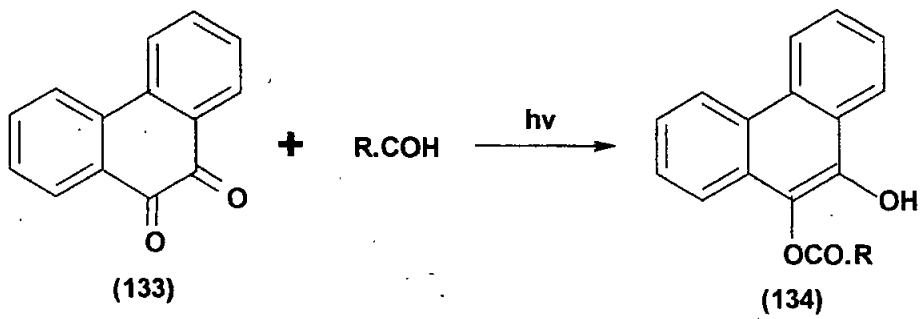

GMA = graphite / MeSO3H
SO2H
Me
OH
R
GMA
120°C
S
O2
OH
Me
R
R = Me, F, Cl, Br and OH
(130)
(131)
(132)

Scheme 42

]

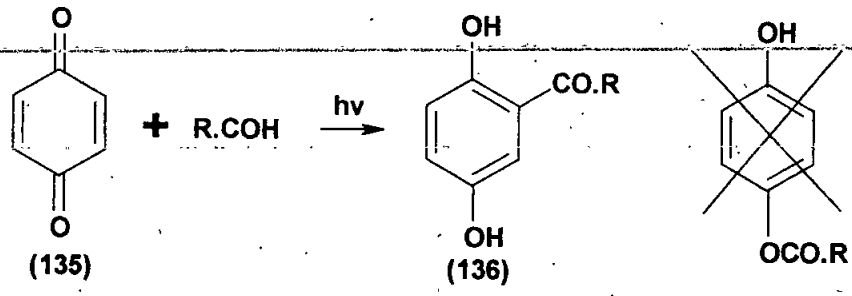
The designation photo-Fries reaction or rearrangement is simple and quite descriptive while acknowledging an ancestral relationship to its acid catalysed thermal cousin. The terms photo-induced or light-induced are equally explanatory although more cumbersome.

Two research groups,[41] working independently, came upon the reaction almost simultaneously although one study was reported later[42]. Anderson and Reese [41] state in their paper that although no rearrangement such as theirs had been previously reported, however it was possible implied in some observations made by Klinger in the 1880's who found that exposure of 9,10-phenanthraquinone to sunlight in the presence of an aldehyde (R-CHO) gave the corresponding 9-acyloxy-10-dihydroxyphenanthrene[43] (scheme 43).



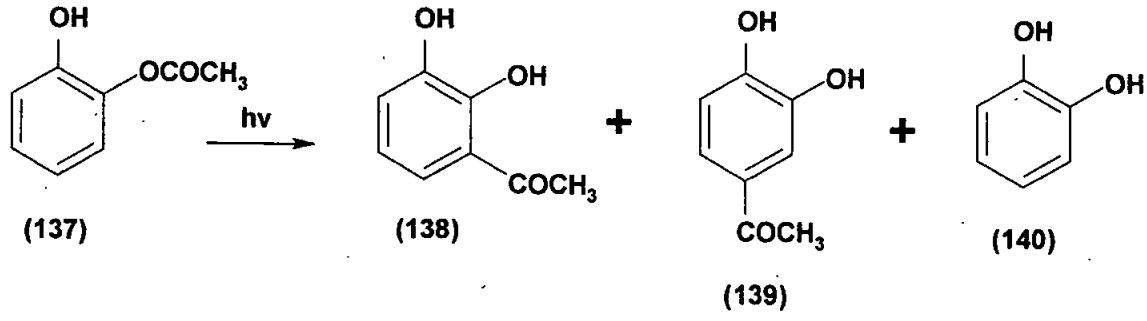
Scheme 43

A few years later Klinger also reported that *p*-benzenequinone treated in the same way, i.e. exposure to sunlight in the presence of an aldehyde, did not give the *p*-hydroxyphenyl ester but instead the ketone [44] (scheme 44).



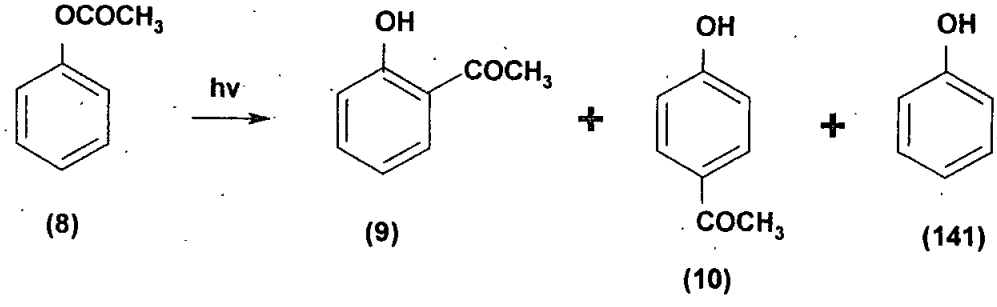
Scheme 44

Anderson and Reese [41] found that an ethanol solution of catechol monoacetate gave a 40% mixed yield of two isomeric dihydroxyacetophenones and 46% catechol when subjected to ultraviolet irradiation (scheme 45).



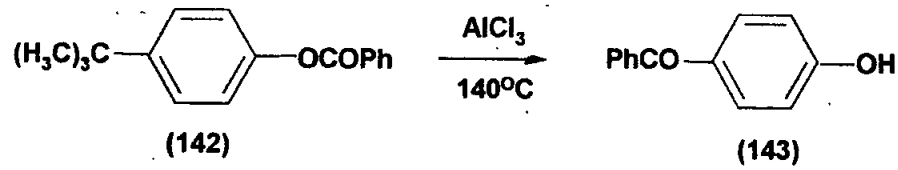
Scheme 45

And the irradiation of an ethanol solution of phenyl acetate gave *ortho-* (19%), *para-* hydroxyacetophenone (15%) and phenol (28%) (scheme 46).



Scheme 46

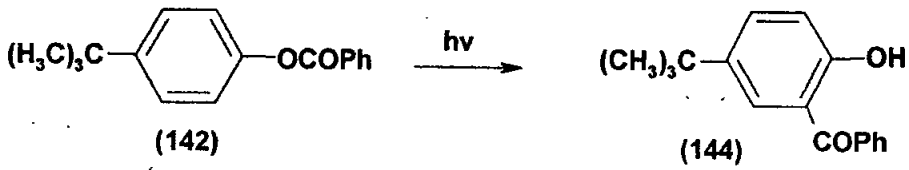
Kobsa [42] had discovered the photo-Fries rearrangement coming from a somewhat novel approach. In attempting to prepare various 2-hydroxy-5-*t*-butyl substituted benzophenone derivatives by the classical thermal Fries rearrangement of the corresponding esters he was largely unsuccessful, (with the 4-hydroxybenzophenone moiety, obtained by the elimination of the *t*-butyl group, predominating as in scheme 47).



(142) (143)

Scheme 47

In the light-catalysed rearrangement in benzene or ethanol, however, no loss of the *t*-butyl groups occurred and the only benzophenone derivatives formed were those resulting from the migration of the acyl group into the *ortho* position (scheme 48).

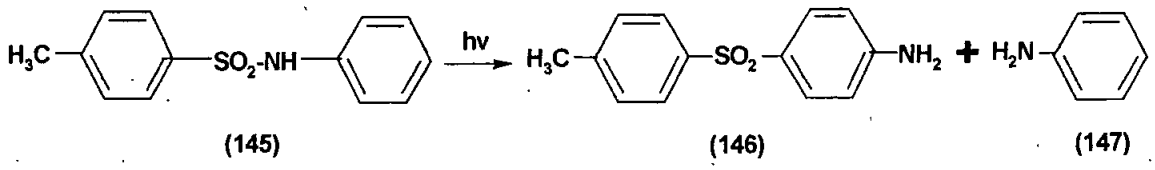


(142) (144)

Scheme 48

As regards the photo-Fries rearrangements of compounds with a sulfur moiety, it was a Japanese group led by Nozaki[45] that published the first report, "The photochemical rearrangement of arenesulfonanilides to *p*-aminodiarylsulfones". Here they discuss the irradiation of an ethanolic solution of *p*-toluensulfonanilide (and other anilides) with a

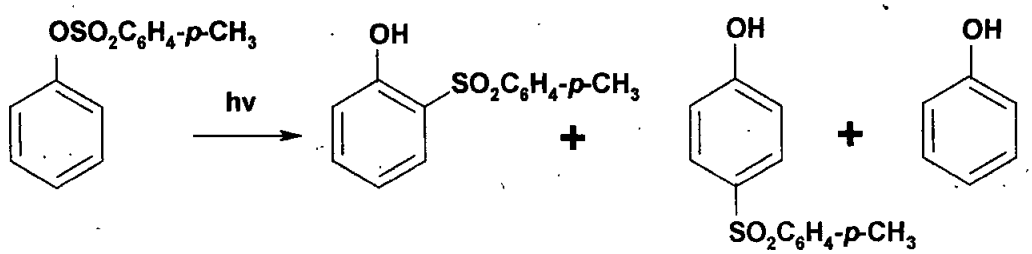
high-pressure 200-watt mercury lamp which gave, after chromatographic separation, 4-amino-4'-methyldiphenylsulfone and aniline (scheme 49).



(145) (146) (147)

Scheme 49

Havinga and Stratenus [46] carried out the rearrangement of phenyl and α-naphthyl *p*-toluenesulfonates as well as phenylmethanesulfonate. They describe a category of photo-Fries rearrangement in which an oxygen-sulfur bond is broken and hydroxysulfones are formed (scheme 50).

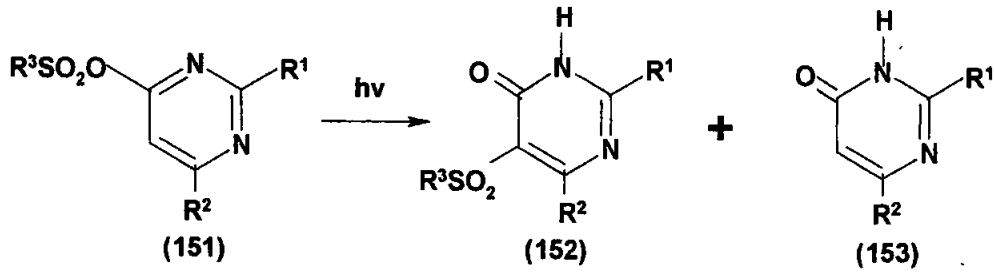


(148) (149) (150)

Scheme 50

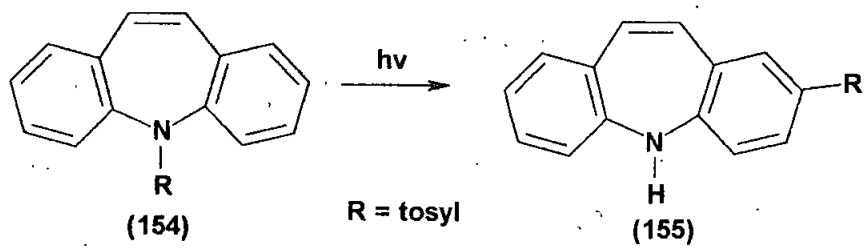
They carried out the reaction in an apparatus designed by themselves. 10g. of ester in 2 l. of absolute ethanol were pumped around a high-pressure mercury arc lamp under a nitrogen atmosphere.

The photo-Fries rearrangement of 2-dialkylamino-4-pyrimidinyl esters of alkyl and arylsulfonic acids was carried out by Snell [47] in I.C.I. The reaction in which the pyrimidine 5-position is unsubstituted, affords the corresponding 5-alkylsulfonyl and 5-arylsulfonyl-2-dialkylamino-4-hydroxypyrimidines respectively in yields of up to 60% together with smaller amounts of the parent 2-dialkylamino-4-hydroxypyrimidine (scheme 51). Irradiation of the 4-pyrimidinyl esters of alkyl or arylsulfonic acids was carried out in ethanol or isopropyl alcohol with a low-pressure mercury arc for periods of 6 to 20 hours.



Scheme 51

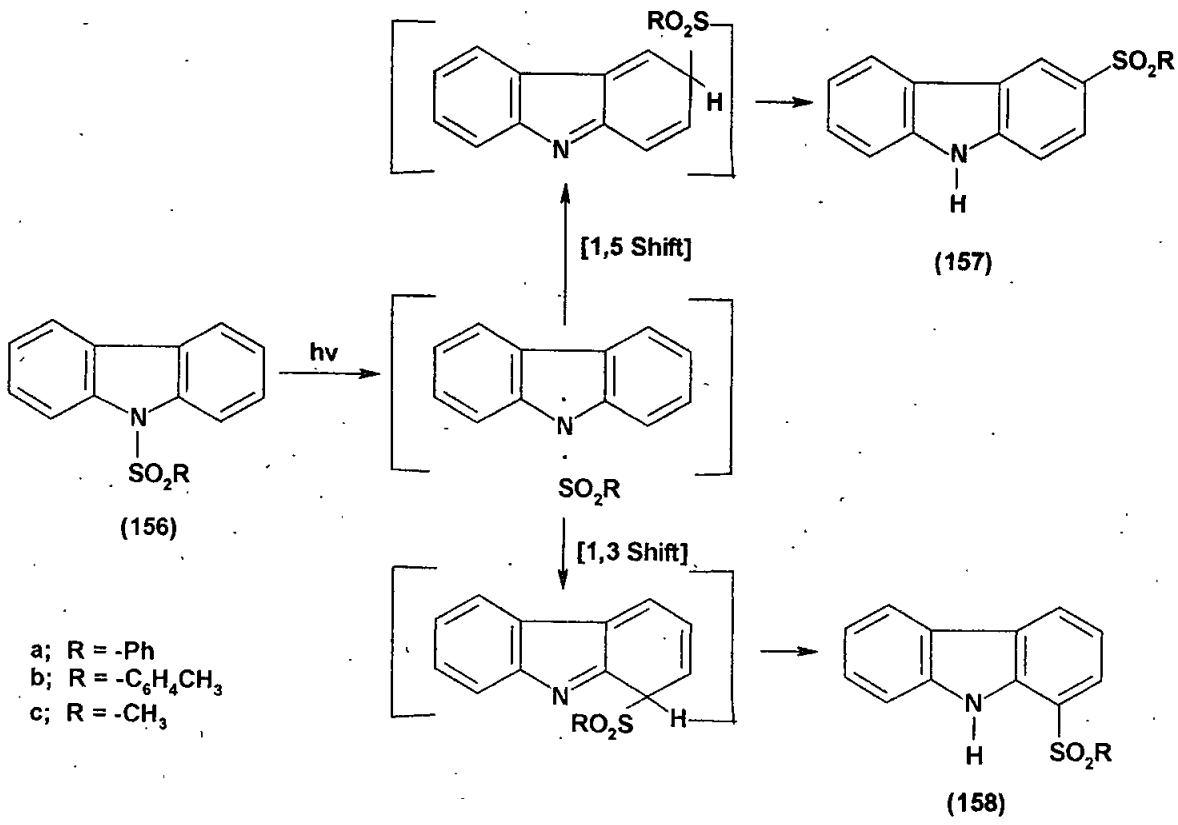
While carrying out photochemical cyclodimerisation and rearrangement studies of 5*H*-dibenzyl[*b*,*f*]azepine derivatives, Ledwith *et al* [48] discovered that the *N*-tosyl- compound only, underwent photo-Fries rearrangement (scheme 52).



Scheme 52

They noted that of the 9 derivatives they investigated, 5-tosyliminostilbene rearranged to 2-tosyliminostilbene both when unsensitised and benzophenone-sensitised. Irradiation was with a Hanovia reactor, yields were quite low (27%) and the product was isolated by column chromatography.

Chakrabarti [49] was interested in studying the photo-Fries rearrangement of *N*-sulfonylcarbazoles. Irradiation of these compounds (**156** a-c) in both solvents, benzene and methanol and at two wavelengths, 254 nm and 365 nm, in a nitrogen atmosphere, at room temperature, clearly afforded the migrated photoproducts (**157** a-c) and (**158** a-c) (scheme 53).

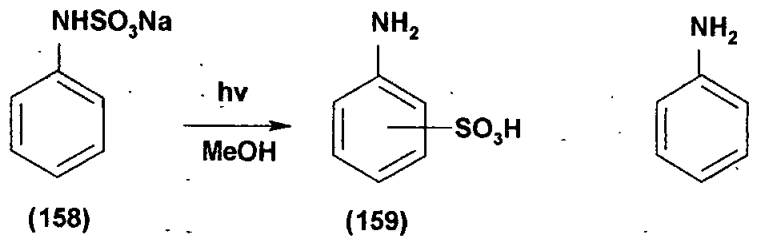


Scheme 53

In all cases formation of photo rearranged 1- and 3-sulfonylcarbazoles from the respective *N*-sulfonylcarbazoles was accompanied by the formation of small amounts of carbazole and some unreacted starting material. The reactant was photo-chemically excited and underwent a fast homolytic cleavage of the nitrogen-sulfur covalent bond thereby creating a solvent-caged intermediate.

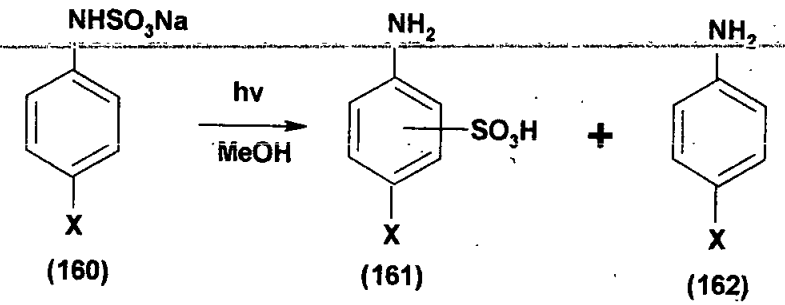
The formation of the products could be rationalised by the intramolecular 1,3 and 1,5 migration of the sulfonyl radical $RSO_2\cdot$. Leakage of the carbazole radical from the solvent cage at this stage, with extraction of hydrogen (H ·) from neighbouring molecules, thereby producing carbazole.

Spillane and Lally published a communication[50 (a)] on the details of the photo-Fries type rearrangement of the sodium salt of phenylsulfamic acid which yielded the isomeric *ortho*- and *para*-anilinesulfonic acids and aniline (scheme 54).



Scheme 54

They further reported [50(b)] the photolysis of a series of *para*-substituted phenylsulfamates in degassed methanolic solutions (scheme 55).

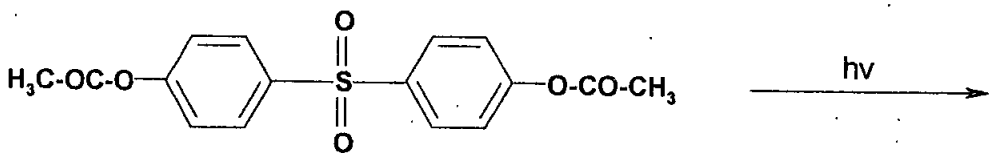


X = (a, CH_3) (b, F) (c, Cl) (d, Br) (e, NO_2)

Scheme 55

For (**160**) a and b photo-Fries type rearrangement to sulfonic acids and photo degradation to anilines were observed. The halosulfamates (**160**) c and d do not rearrange but degrade to anilines and are photo-solvolysed to *p*-methoxyphenylsulfamic acids.

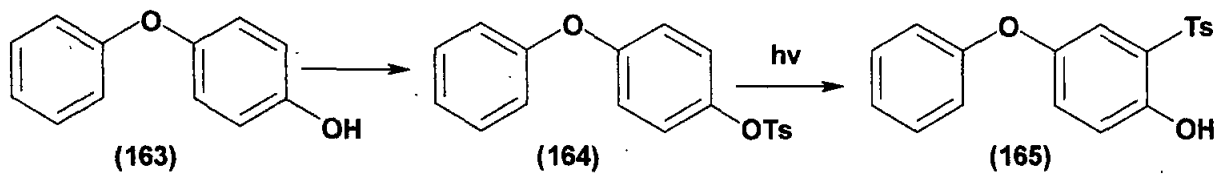
According to Sridar and Rao [31] the photo-Fries rearrangement of the biacetate of 4,4'-dihydroxydiphenyl sulfone (bisphenol-S) yields only a mono-rearranged product with no bisrearranged product (scheme 56), whereas under thermal conditions a 23% yield of the bisrearranged product is obtained (scheme 27). They also state that a 40% yield of the photo-rearranged product is obtained when 4-(*p*-tolylsulfonyl)phenyl-acetate is irradiated under identical conditions.



(84)

Scheme 56

As part of a large study on the design, synthesis and biological evaluation of aryloxyethyl thiocyanate derivatives for pharmacological use Rodriguez *et al*[51] used a Fries photochemical reaction in a critical synthetic step. Starting with 4-phenoxyphenol (**163**) which was easily tosylated to give (**164**) in excellent yield the critical synthetic step for the preparation of the required product was the photo-Fries rearrangement of the tosyl group of (**164**) to form the corresponding sulfone at C-2' on (**165**) as in scheme 57.



Scheme 57

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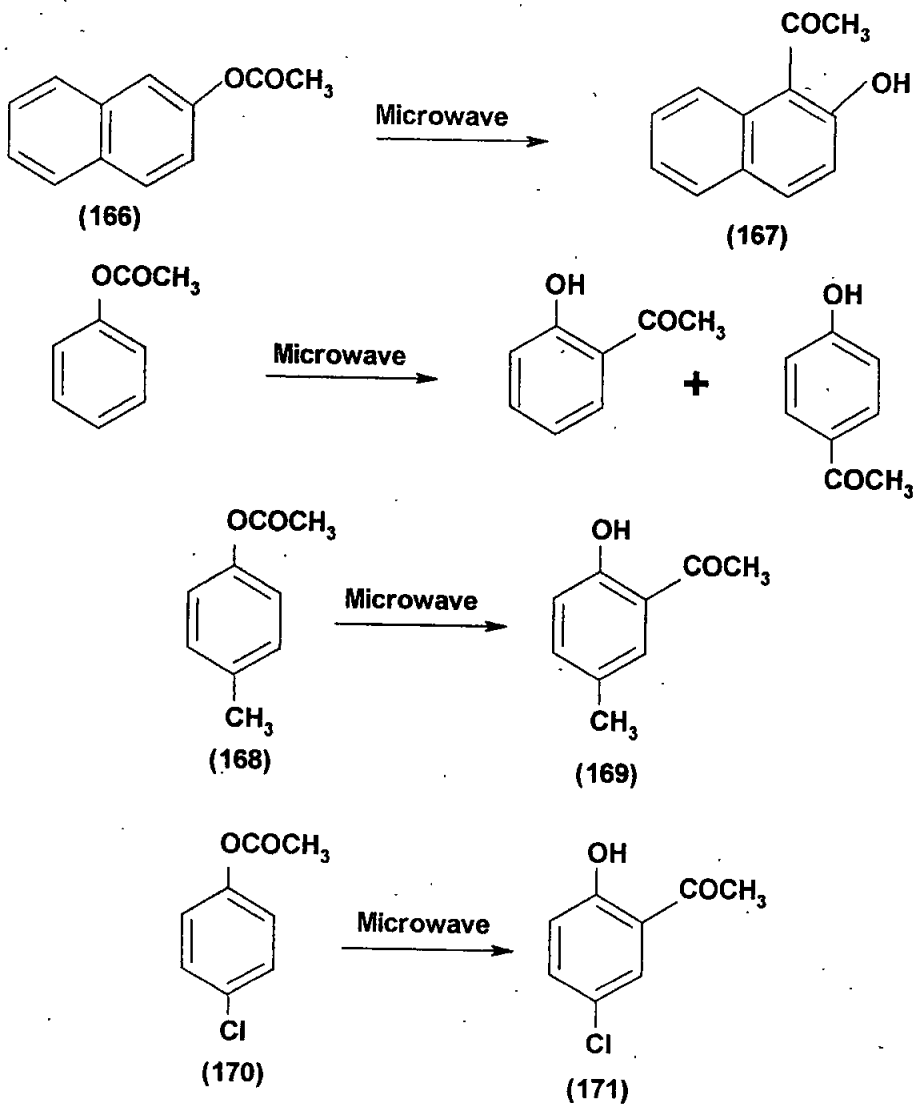
In 1986, Gedye *et al.*[52] and Giguere *et al.*[53] demonstrated for the first time, that many organic reactions can be conducted very rapidly under microwave irradiation and in 1994 Sridar and Sundara Rao[54] published the first report on "Microwave-induced rate enhancement of Fries rearrangement".

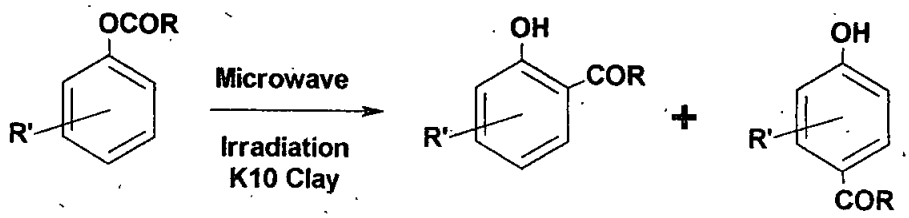


Scheme 58

Using distilled chlorobenzene as a pure solvent with a high dielectric constant and a ratio of 1:1.5 equivalents of substrate to $AlCl_3$ (Lewis acid catalyst), the rearrangements were

carried out in sealed tubes for two minutes. A domestic, multi-mode, 2.45 GHz oven was used without modification and at 100% power. The Fries rearrangements of 2-naphthyl, phenyl, *p*-cresyl and *p*-chlorophenyl acetates were studied (scheme 58).

"An expeditious solvent free Fries rearrangement occurs under mild conditions on K10 montmorillonite using microwave radiation" according to Kad *et al.*[55] when they used a selection of acylated and benzoylated phenols as substrate (scheme 59). In a typical procedure, 1g. of K10 montmorillonite was added to 5 ml of dry CH_2Cl_2 which contained 0.5g. (3.68 mmol) phenylacetate and this mixture were stirred for 5 min before the solvent was removed under reduced pressure. The resulting free flowing solid, in a 50 ml Pyrex beaker was placed in a domestic 2.45 GHz domestic multimode microwave oven, alongside a beaker containing 150 ml water, which acted as a heat sink. The reactant was irradiated at 640 W for 4 min.

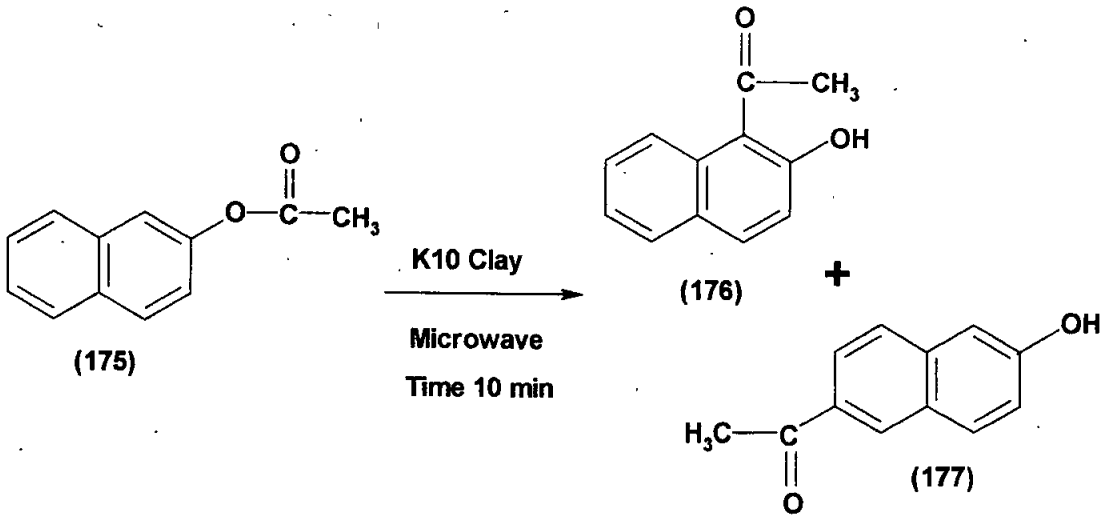


(172) (173) (174)

Scheme 59

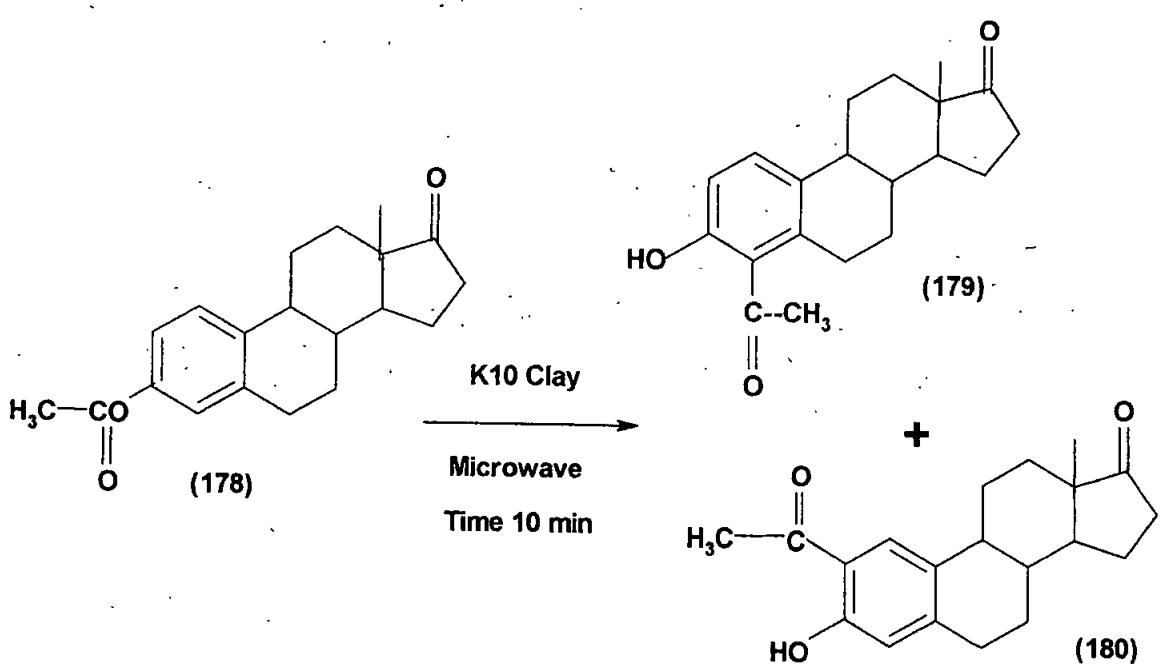
In a publication entitled "Fries rearrangement accelerated by microwave radiation in the undergraduate organic laboratory" a group [56] from Punjab University write about the opportunity of undergraduates to use microwave in chemical reactions. The Fries rearrangement of arylesters to *ortho*- and *para*-hydroxy acetophenones can be carried out

in dry open media in ordinary glassware using a commercial microwave oven (scheme 60). This reaction normally requires a Lewis acid and long reflux times or photochemical conditions.



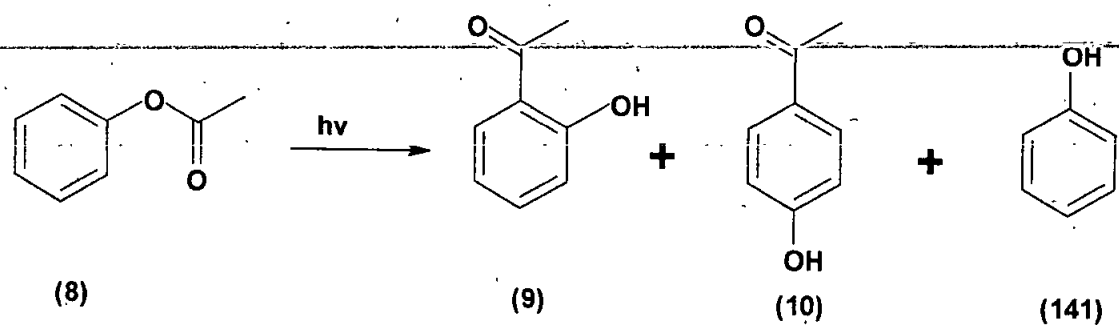
Scheme 60

They discuss two schemes of the Fries rearrangement on K-10 montmorillonite in dry open media as reactions to illustrate the suitability of microwave acceleration as distinct from conventional techniques. The acetate of β-naphthol was irradiated for 10 min (level 9) in an ordinary household instrument and gave 70% conversion into *ortho* and *para* products in 9:1 ratio scheme. The second example used the steroid estrone under the same conditions and gave the two *ortho* products in 65% yield (scheme 61).



Scheme 61

There are two publications by Klán *et al* [57(a)] where they discuss the use of an electrodeless discharge lamp i.e. a microwave lamp (MWL) which, when placed in the reactor cavity of a microwave oven, the microwave field generates ultraviolet irradiation in the lamp at the same time that it interacts with the sample under study. The sample is therefore subjected to a simultaneous UV/Vis and MW irradiation. Five different photo reactions were investigated, one of them being the photo-Fries rearrangement and their study confirmed that MW-UV conditions could be beneficial in synthetic organic photochemistry (scheme 62).

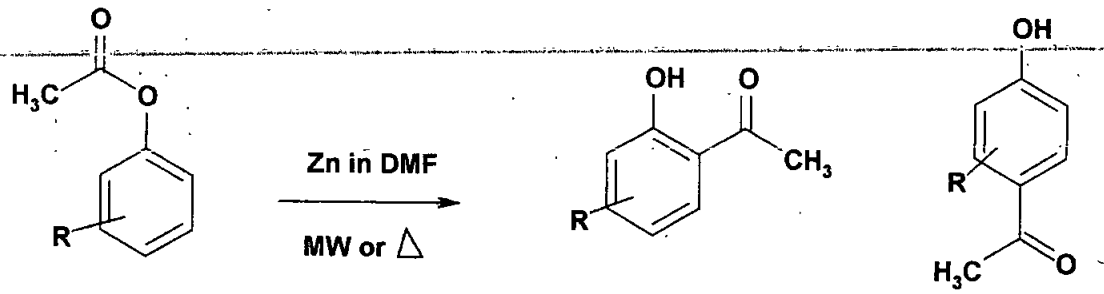


(8) (9) (10) (141)

Scheme 62

In the second paper [57(b)] they examine what they claim is the first study of temperature dependant photochemical reactions in the microwave field on the solvent effect in the Norrish type II reaction and the photo-Fries reaction under various thermal conditions including microwave heating. These MW-UV/Vis rearrangements probable involve interesting synergistic effects and it would be interesting to make a comparative study if MW and UV/Vis were tried separately.

"Zinc powder in the presence of *N,N*-dimethylformamide efficiently catalyses the selective Fries rearrangement of acylated phenols under microwave heating or with conventional heating using an oil bath and different products were obtained. Selective migration of the acyl group has been noted with good yields," according to Paul and Gupa[58]. Fifteen acylated phenol were tested both by thermal and microwave irradiation. For microwave, 5 mmol of substrate and the equivalent of zinc powder in 2.5 mmol of DMF were mixed thoroughly and irradiated in an oven at 480 watts for various times (scheme 63).



(172) (173) (174)

Scheme 63

In this introduction to the thesis a selection of publications have been chosen, out of maybe two thousand papers which have been published on all aspects of the Fries rearrangement in the last century. The selection is arbitrary but there is a leaning towards compounds with a sulfur moiety because the body of this work is on the rearrangement of sulfamates to sulfonamides.

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SULFAMATE ESTER SYNTHESIS AND THERMAL

THIA-FRIES REARRANGEMENT

INTRODUCTION

As various aspects of the Fries rearrangement have already been discussed, a comment about sulfamic acid esters, sulfamates and sulfonamides may be appropriate because all of the presented studies are based on the attempted synthesis of *N,N*-dialkylsulfonamides utilising the thia-Fries rearrangement of *O*-sulfamates to hydroxysulfonamides.

The first step in this process is the sulfamoylation of the hydroxyl group of phenol and substituted phenols. As March[59] states, "sulfonic asters are most frequently prepared by treating the corresponding halides with alcohols in the presence of a base (Fig. 5). The method is much used for the conversion of alcohols to tosylates, brosylates and similar sulfonic esters.

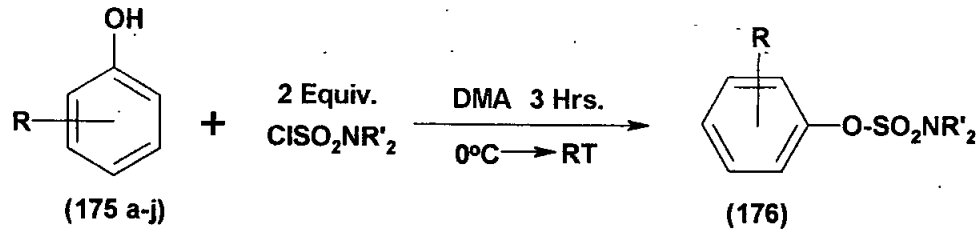
$$RSO_2Cl + R'OH \rightarrow RSO_2OR' + HCl$$

$$RSO_2NR''_2 + R'OH \rightarrow RSO_2OR' = NHR''_2$$

Fig. 5

In these reactions R and R' may be alkyl or aryl and the base is often pyridine, which functions as a nucleophilic catalyst. Primary alcohols react most rapidly and it is often possible to sulfonate selectively a primary OH group in a molecule that also contains secondary or tertiary hydroxyl groups."

There are a number of general methods for the synthesis of arylsulfamates, one is the reaction of phenols with sulfamoyl chloride or *N,N*-dialkylsulfamoyl chloride, a method first proposed by Schwarz and Weber [60] and carried out for all of the following compounds which are used in this study (scheme 64).



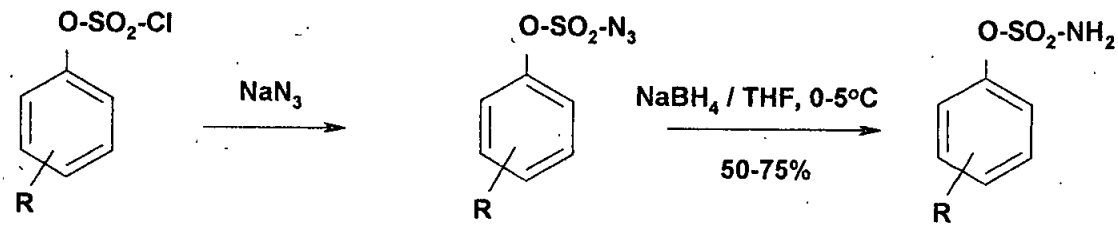
(175 a-j) (176)

R = (a)H, (b)CH_3, (c)C_2H_5, (d)$^-$, (e)Cl, (f)Br, (g)I, (h)2,6-DiF, (i)2,6-DiCl & (j)2,6-DiBr

R' = H, CH_3, C_2H_5 & C_3H_7

Scheme 64

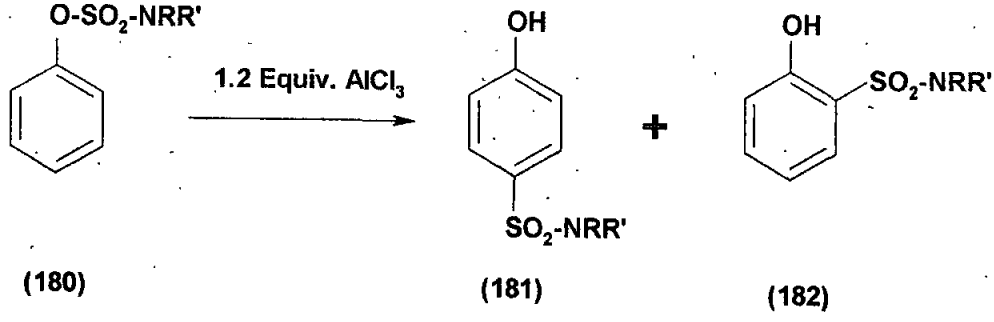
The reaction of phenols with chlorosulfonyl isocyanate is another method [61 & 62 (a)] of preparation, but like the first method both reagents are very toxic and their manipulation is difficult. Hedayatullah and Guy developed a further method [62(b)], which involves the reduction of aryloxysulfonyl azides with sodium borohydride under mild conditions (scheme 65).



(177) (178) (179)

Scheme 65

It is important to emphasise that to date, no Fries rearrangement of sulfamates to sulfonamides has been claimed. In a recent publication [63] a new synthetic route to aryl hydroxysulfonamides *via* a novel Fries-type rearrangement of aryl *N,N*-dialkylsulfamates has been developed (scheme 66).



(180) (181) (182)

Scheme 66

The Fries rearrangement of the first series of esters, the phenylsulfamates, where R and R' = H, was not very successful under the conditions in the above scheme. Farbenfabriken Bayer Aktiengesellschaft, the German drug company were the first to synthesise and patent [64] some of the aryl sulfamates produced for this study, mostly of the form phenyl(substituted) *N,N*-dimethylsulfamate.

The esters of sulfamic acid (H_2NSO_3H), a rather simple molecule, are used extensively by medicinal chemists for the design of a host of derivatives with pharmacological applications. The acid gives rise to four types of derivatives: *O*-substituted, *N*-substituted and the di- and tri-substituted sulfamates, which all show specific biological activities. Sulfamate inhibitors of aminoacyl-*t*RNA synthetases were reported to constitute a new class of antibiotic, useful in the fight of drug-resistant infections. Antiviral agents

incorporating sulfamate moieties have also been synthesised with the nucleoside / nucleotide HIV reverse transcriptase inhibitors and the HIV protease inhibitors. In the increasing armamentarium of anticancer drugs the sulfamates occupy a special position. A large number of anticonvulsant sulfamates have been described, with topiramate (Fig. 6), whose chemical formula is 2,3:4,5-di-*O*-(l-isopropylidene)-ß-D-fructopyranose sulphamate is a derivative of the naturally-occurring monosaccharide D-fructose. It is generally used clinically as an anti-epileptic drug and this medicine, along with other sulfamates have recently been recommended for the treatment of obesity.

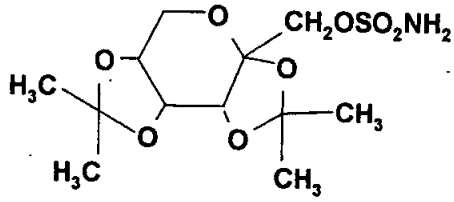


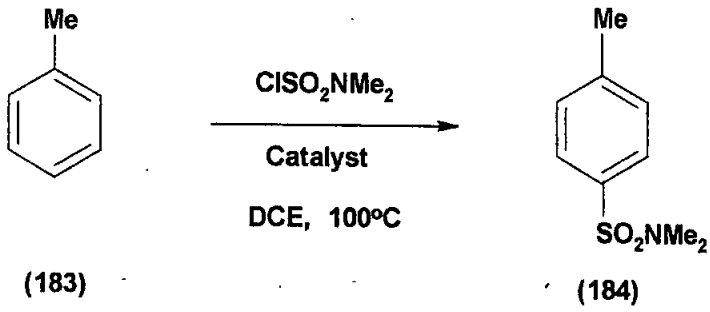
Fig. 6

While the large number of sulfamate esters in this study were subjected to the thia-Fries rearrangement in order to synthesis a range of hydroxysulfonamides, there are many other methods in the literature for synthesising these esters. March[59] in his section on nucleophilic substitution at a sulfonyl sulfur atom, discusses the attack by a nitrogen lone pair *i.e.* the formation of sulfonamides in an *S*-amino-de-chlorination reaction (Fig. 7).

$$RSO_2Cl + NH_3 \rightarrow RSO_2NH_2$$

Fig. 7

The treatment of sulfonyl chlorides with ammonia or amines is one way of preparing sulfonamides (Fig. 7). Primary amines give N-alkylsulfonamides and secondary amines give N,N-dialkylsulfonamides. Another method, recently published by Frost *et al* [65], is the catalytic arylation of sulfamoyl chloride (scheme 67). This reaction is a practical synthesis of sulfonamides and it involves commercially available indium(III) triflate.



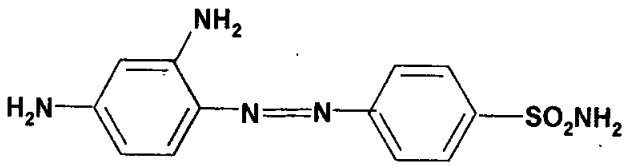
(183) (184)

Scheme 67

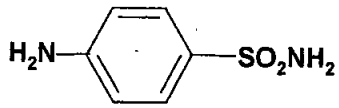
Five equivalents of toluene are stirred with one equivalent of *N,N*-dimethylsulfamoyl chloride and 20 mol% catalyst at 100°C for 24 hours in dichloroethane, to give 86% of the sulfonamide.

Sulfonamides, the chemical name for Sulfa drugs, were the first chemical compounds to provide safe and effective treatment for most common bacterial infections. This was before the arrival of penicillin in the mid 1940's. Sulfa drugs played a major role in antibacterial treatment, which resulted in a sharp decrease in deaths due to those bacterial infections. The first of these chemotherapeutic drugs being Prontosil which breaks down in the body to produce sulphanilamide (Fig. 8).

Instead of killing bacteria, sulfonamides prevent them from multiplying, making it easier for the bodies natural defences to overcome and destroy them.



Prontosil



Sulfanilamide

Fig. 8

Bacteria require *para*-aminobenzoic acids to multiply and sulfonamides resemble the chemical structure of the acids which are adsorbed by the bacteria. The sulfa drugs combine with the outer shells of the organism preventing the real acids from penetrating. In modern therapeutics,[66] sulfonamides constitute an important class of drugs with several types of pharmacological agents possessing antibacterial, anti-carbonic anhydrase, diuretic, hypoglycaemic and antithyroid activity among others. A large number of structurally novel sulfonamide derivatives have ultimately been reported to show substantial antitumor activity in *vitro* and in *vivo*. Although they have a common chemical motif of aromatic, heterocyclic or amino acid sulfonamide, there are a variety of mechanisms by which they act against tumors. Some of these compounds selected via elaborate preclinical screenings or obtained through computer-based drug design, are currently being evaluated in clinical trials.

I.R. spectra were recorded on a Nicolet 210 FTIR spectrophotometer. Mass spectra were acquired using a Shimadzu QP-5000 at 70 eV, where samples were introduced through coupling to a Shimadzu GC-17A gas chromatograph. This instrument was also used for the monitoring of the reactions in conjunction with TLC on Merck silica gel 6 F_{254} plates. All melting points were obtained using a Fisher, Model 355 digital m.p. analyser, and are uncorrected. Boiling points under reduced pressure were carried out using a Büchi GKR 50 distillation unit. Microanalyses were obtained by a Perkin Elmer 2400 Series II Analyser. All compounds were dried in a Büchi TO–50 under reduced pressure before mp and bp were determined. Chemicals and solvents were obtained from various commercial sources, and unless otherwise stated in the text, were used without further purification.

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Synthesis of phenylsulfamates (185-194):

The synthesis of the sulfamoyl chloride $ClSO_2NH_2$ from which the sulfamates were derived is the initial important step. Methanoic acid and sulfur free toluene must be freshly distilled and stored with the drying agent, $MgSO_4$, under nitrogen. To a 150 ml ice cold toluene solution of 25g chlorosulfonyl isocyanate from Aldrich, was added, in a drop wise manner, 6 ml of methanoic acid while maintaining a temperature < 5°C. The resultant emulsion was stirred overnight, filtered and the toluene removed under reduced

pressure while maintaining a temperature of < 30 °C. This synthesis was carried out in an inert, nitrogen atmosphere and the resultant product can be stored in a fridge for up to two months.

Phenylsulfamates were synthesised by the method of Okada *et al* [67] whereby the sulfamoyl chloride (2 equiv.) was added to a stirred mixture of the particular phenol (1 equiv.) in dimethylacetamide, (DMA, at 1.5 cm^3 per mmol) on ice cooling. Stirring was continued at room temp. for 3 hrs., after which the mixture was poured into 100 ml of cold brine and the resultant solution was extracted with 3 x 50 ml aliquots of ethyl acetate. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. This method gave near quantitative yields for sulfamates (**185-194**) made with unsubstituted and *p*-substituted phenols. The crude product was purified by column chromatography, Merck Kiselgel 60 eluting with *n*-hexane / diethyl ether in a stepwise manner, from 100/0 in 5% increments. While compounds **185**, **187** and **190** were synthesised previously, **186**, **188**, **189**,**191**, **192**, **193** and **194** are novel.

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Phenylsulfamate $C_6H_5OSO_2NH_2$ [68(a-b)] **(185)**

0.16 Mol sulfamoyl chloride were added to a stirring mixture of 0.08 mol phenol in 120 ml dimethylacetamide on ice cooling.

White crystals; mp 80.8°C - 81.2 °C; 92% yield from (*n*-hexane / diethyl ether);

Found: C, 41.53; H, 3.92; N, 7.73. $C_6H_6NO_3S$ requires C, 41.61; H, 4.07; N, 8.09.

$\upsilon_{max/}$ cm^{-1} (KBr disc) 1370, 1181 (sym & antisym S=O *str*), 3416 (sym & antisym N-H *str*), 1590 (C-H Ar.).

m/z (EI) 173 (M^+, 12.2), 94 (Ph, 100 base peak), 65 (37.1), and 66 (15.9).

4-Fluorophenylsulfamate *p*-$FC_6H_4OSO_2NH_2$ **(186)**

0.11 Mol sulfamoyl chloride were added to a stirring mixture of 0.055 mol of 4-fluoro phenol in 85 ml dimethylacetamide on ice cooling.

White crystals; mp 83.0°C - 84.0 °C; 87% yield from (*n*-hexane / diethyl ether);

Found: C, 38.07; H, 3.27; N, 7.54. $C_6H_6NO_3SF$ requires C, 37.70; H, 3.16; N, 7.33.

$\upsilon_{max/}$ cm^{-1} (KBr disc) 1152, 1386 (sym & antisym S=O *str.*), 3287, 3379 (N-H *str.* sym & antisym)

m/z (EI) 191 (M^+, 10.1), 112 (100 base peak), 83 (33.7) and 57 (28.3).

4-Chlorophenylsulfamate *p*-$ClC_6H_4OSO_2NH_2$ [61 & 68 (a)] **(187)**

0.145 Mol sulfamoyl chloride were added to a stirring mixture of 0.0725 mol of 4-chloro phenol in 110 ml dimethylacetamide on ice cooling.

White crystals; mp101.5°C - 102 °C; 92% yield from (*n*-haxane / diethyl ether);

υ_{max}/ cm^{-1} (KBr disc) 1180, 1363 (S=O *str.* sym & antisym), 3270, 3396 (N-H *str.* sym & antisym)

m/z (EI) 207 (M^+, 11.8), 128 (Ph, 100 base peak), 130 (32.2) and 99 (26.9).

4-Bromophenylsulfamate *p*-$BrC_6H_4OSO_2NH_2$ **(188)**

0.12Mol sulfamoyl chloride were added to a stirring mixture of 0.06 mol of 4-bromo phenol in 90 ml dimethylacetamide on ice cooling.

White crystals; mp114.5°C – 116.5 °C; 84% yield from (*n*-haxane / diethyl ether);

υ_{max}/cm^{-1} (KBr disc) 1185, 1360 (S=O *str.* sym & antisym), 3280, 3385 (N-H *str.* sym & antisym)

m/z (EI) 252 (M^+, 14.7), 172 (100 base peak), 174 (97.2), 63 (62.7) and 65 (42.9).

0.11 Mol sulfamoyl chloride were added to a stirring mixture of 0.055 mol of 4-iodo phenol in 85 ml dimethylacetamide on ice cooling.

Yield: ≤ 0.1%, as estimated from GC.

m/z (EI) 298 (M^+, 35.3), 220 (100 base peak), 93 (20.6) and 64 (44.5).

4-Methylphenylsulfamate *p*-$MeC_6H_4OSO_2NH_2$ [61 & 69 (a)] **(190)**

0.16 Mol sulfamoyl chloride were added to a stirring mixture of 0.08 mol of 4-methyl phenol in 120 ml dimethylacetamide on ice cooling. White crystals; mp 79 °C – 79.5 °C; 88% yield from (*n*-haxane / diethyl ether). υ_{max} (KBr disc) 1180, 1354 (S=O *str.* sym & antisym), 3276, 3408 (N-H *str.* sym & antisym)

m/z (EI) 187 (M^+, 32.7), 108 (100 base peak), 107 (58.1) and 77 (46.5).

0.16 Mol sulfamoyl chloride were added to a stirring mixture of 0.08 mol of 4-ethylphenol in 120 ml dimethylacetamide on ice cooling.

Brown crystals; mp 65°C – 66°C; 77% yield from (n-hexane / diethyl ether).

υ_{max} (KBr disc) 1178, 1328 (S=O *str.* sym & antisym), 3279, 3418 (N-H *str.* sym & antisym).

m/z (EI) 201 (M^+, 29.7), 107 (100 base peak), 121 (57.5) and 77 (32.7).

2,6-Difluorophenylsulfamate 2,6-di$FC_6H_3OSO_2NH_2$ **(192)**

0.17 Mol sulfamoyl chloride were added to a stirring mixture of 0.085 mol of 2,6-difluoro phenol in 130 ml dimethylacetamide on ice cooling.

White crystals; m.p. 104.3°C - 104.7°C. 88% yield from (*n*-hexane / diethyl ether).

Found: C, 34.73; H, 2.21; N, 6.22. $C_6H_5NO_3SF_2$ requires C, 34.45; H, 2.41; N, 6.70.

υ_{max} (KBr disc) 1174, 1306 (S=O *str.* sym & antisym), 3289, 3421 (N-H *str.* sym & antisym).

m/z (EI) 209 (M^+, 2.8), 130 (100 base peak), 101 (26.1) and 82 (25.3).

2,6-Dichlorophenylsulfamate 2,6-di$ClC_6H_3OSO_2NH_2$ **(193)**

0.15 Mol sulfamoyl chloride were added to a stirring mixture of 0.075 mol of 2,6-dichloro phenol in 120 ml dimethylacetamide on ice cooling.

Yield < 1% as estimated from GC.

m/z (EI) 241 (M^+, 3.3), 161 (100 base peak), 164 (62.4) and 63 (49.2).

2,6-Dibromophenylsulfamate 2,6-di$BrC_6H_3OSO_2NH_2$ **(194)**

0.19 Mol sulfamoyl chloride were added to a stirring mixture of 0.095 mol of 2,6-dibromo phenol in 150 ml dimethylacetamide on ice cooling.

Yield < 1% as estimated from GC.

m/z (EI) 331 (M^+, 2.1) 43 (100 base peak), 251 (33.2) and 253 (14.9).

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N,N-Dimethylsulfamoyl chloride (Aldrich) was used as purchased while *N,N*-diethyl-, *N,N*-di-*n*-propyl- and *N,N*-di-*n*-butylsulfamoyl chlorides were synthesised by the method of Gupta [69]. To a solution of 500 mmol of SO_2Cl_2 (Merck) in 500 ml dried CH_2Cl_2 (Lab Scan) stirring over ice, was added, drop wise, a mixture of 500 mmol of *N,N*-diethylamine, *N.N*-di-*n*-propylamine or *N,N*-di-*n*-butylamine(Aldrich) and 500 mmol of triethylamine (Ridel-de-Haen). The temperature was maintained < 5°C and usually required 3 hrs. The reaction was allowed to continue stirring for a further 3 hrs at room temperature after which it was washed with 0.5 M HCl (500 ml) and twice with water (500 ml), dried ($MgSO_4$, Lancaster) and the solvent evaporated. Further purification was carried out by reduced pressure distillation with yields of 88 - 92% obtained.

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Synthesis of phenyl *N,N*-dialkylarylsulfamates (195-223).

The appropriate *N,N*-dialkylsulfamoyl chloride was added slowly, to a stirring mixture of 200 mmol of the required phenol in triethylamine with dried dichloromethane (100 ml) as solvent. A molar ratio of 0.9 : 1 : 1.2 (sulfamoyl chloride / phenol / triethylamine) was used to prevent the formation of side product. The reaction progress was monitored by TLC and GC-MS and required from 24 hrs to 25 days at room temperature. On completion, the mixture was filtered using a further 100 ml of CH_2Cl_2, washed with 0.5

M NaOH (3 x 100 ml aliquots) to extract any remaining phenol, washed with water, dried and evaporated to product. The crude product was purified by column chromatography, Merck Kiselgel 60 eluting with *n*-hexane / diethyl ether in a stepwise manner, from 100/0 in 5% increments or by partial distillation under reduced pressure. Compounds **195, 197, 200, 203, 209, 210, 211** and **213** have been synthesised previously, while **196, 198, 199, 201, 202, 204, 205, 206, 207, 208, 212, 214, 215, 216, 217, 218, 219, 220, 221, 222,** and **223** are novel compounds.

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Phenyl *N,N*-dimethylsulfamate $C_6H_5OSO_2NMe_2$ [70 (a) & (b).] **(195)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol phenol in 0.24 mol of triethylamine. Stirring continued for 48 hours.

Pale yellow liquid; bp 129°C – 130°C @ $7x10^{-1}$ mm Hg.; yield 82% from reduced pressure distillation. Found: C, 47.73; H, 5.49; N, 6.97. $C_8H_{11}NO_3S$ requires C, 47.76; H, 5.47; N, 6.96

υ_{max}/cm^{-1} (Neat) 1153, 1374 (S=O *str.* sym & antisym), 1589 (C-H Ar.).

m/z (EI) 201 (M^+ 10.5), 108 (100 base peak), 65 (99) and 94 (25.6).

4-Fluorophenyl *N,N*-dimethylsulfamate *p*-$FC_6H_4OSO_2NMe_2$ **(196)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-fluorophenol in 0.24 mol of triethylamine. Stirring continued for 24 hours.

White crystals; mp 51°C – 52°C; 84% yield from (*n*-hexane / diethyl ether).

Found: C, 44.16; H, 5.06; N, 7.59. $C_8H_{10}O_3SNF$ requires C,43.84; H, 4.57; N, 8.68.

υ_{max}/ cm^{-1} (KBr disc) 1160 and 1189 (sym S=O *str.*) 3087 (S-N *w*).

m/z (EI) 219 (M^+ 7.1), 108 (100 base peak), 83 (52.5) and 57 (37.9).

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-chlorophenol in 0.24 mol of triethylamine. Stirring continued for 120 hours.

Clear liquid; bp 130°C – 132°C @ 5 x 10^{-1} mm Hg.; yield 80% from reduced pressure distillation. Found: C, 40.62; H, 4.02; N, 5.69. $C_8H_{10}NClO_3S$ requires C, 40.76; H, 4.25 N, 5.94.

υ_{max}/cm^{-1} (Neat) 1161 and 1375 (sym & antisym S=O *str*), 1586 (C-H Ar) and 3097 (S-N *w*).

m/z (EI) 235 (M^+ 3.8), 108 (100 base peak), 99 (33.5) and 73 (26.4).

It was synthesised by an alternative route, *N,N*-dimethylsulfamoyl chloride was added drop wise at 100°C with good stirring, to the sodium salt of 4-chlorophenol in xylene. The reaction is initially exothermic and is continued by refluxing for one hour. After filtering off the salt the solvent was removed by reduced pressure distillation and the compound was purified by bulb to bulb distillation.

0.225 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 4-bromophenol in 0.30 mol of triethylamine. Stirring continued for 14 days.

Clear liquid; bp 108°C – 111°C @ 14 x 10^{-1} mm Hg.; yield 84% from reduced pressure distillation. Found: C, 34.46; H, 3.66; N, 5.37. $C_8H_{10}NBrO_3S$ requires C, 34.29; H 3.57; N, 5.00.

υ_{max}/cm^{-1} (Neat) 1197 and 1382 (sym & antisym S=O *str*), 1581 (C-H Ar) and 3097 (S-N *w*).

m/z (EI) 281 (M^+ 8.7), 108 (100 base peak), 63 (54) and 143 (22.2).

4-Iodophenyl *N,N*-dimethylsulfamate *p*-$IC_6H_4OSO_2NMe_2$ **(199)**

0.225 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 4-iodophenol in 0.3 mol of triethylamine. Stirring continued for 25 days.

Brown crystals; mp 68.5°C – 71.5°C; yield 23.5% from reduced pressure distillation. Found: C, 29.79; H, 3.14; N, 4.54. $C_8H_{10}NIO_3S$ requires C, 29.36; H, 3.06; N, 4.28.

υ_{max}/cm^{-1} (KBr disc) 1195 and 1367 (sym & antisym S=O *str*), 1580 (C-H Ar) and 3084 (S-N *w*).

m/z (EI) 327 (M^+ 6.1), 108 (100 base peak), 64 (76.6) and 92 (28.3).

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4-Methylphenyl *N,N*-dimethylsulfamate *p*-$MeC_6H_4OSO_2NMe_2$ [72 (a) & (b)] **(200)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-methylphenol in 0.24 mol of triethylamine. Stirring continued for 72 hours.

Clear liquid; bp 126°C – 129°C @ 4 x 10^{-1} mm Hg.; yield 40% from reduced pressure distillation. Found: C, 50.43; H, 6.01; N, 6.66. $C_9H_{13}NO_3S$ requires C, 50.23; H, 6.05; N, 6.51.

υ_{max}/cm^{-1} (Neat) 1104 and 1375 (sym & antisym S=O *str*), 1597 (C-H Ar) and 3031 (S-N *w*).

m/z (EI) 215 (M^+ 19.4), 108 (100 base peak), 77 (95) and 135 (18.8).

4-Ethylphenyl *N,N*-dimethylsulfamate *p*-$EtC_6H_4OSO_2NMe_2$ **(201)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-ethylphenol in 0.24 mol of triethylamine. Stirring continued for 120 hours.

Clear liquid; bp 92°C - 94°C @ 3 x 10^{-1} mm Hg.; yield 13.5% from reduced pressure distillation. Found: C, 52.32; H, 6.66; N, 6.03. $C_{10}H_{15}NO_3S$ requires C, 52.38; H, 6.59; N, 6.11.

υ_{max}/cm^{-1} (Neat) 1112 and 1372 (sym & antisym S=O *str*), 1601 (C-H Ar) and 3033 (S-N *w*).

m/z (EI) 229 (M^+ 15.3), 108 (100 base peak), 121 (60.1) and 91 (59.9)

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4-Methoxyphenyl *N,N*-Dimethylsulfamate *p*-$MeOC_6H_4OSO_2NMe_2$ **(202)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-methoxyphenol in 0.24 mol of triethylamine. Stirring continued for 120 hours.

White crystals; yield and other properties not acquired.

m/z (EI) 231 (M^+ 34.0), 123 (100 base peak), 95 (42.1) and 152 (26.8).

4-Nitrophenyl *N,N*-Dimethylsulfamate *p*-$NO_2C_6H_4OSO_2NMe_2$ [72 (a)] **(203)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-nitrophenol in 0.24 mol of triethylamine. Stirring continued for 8 days.

White crystals; mp 119.5°C – 121°C; 52% yield from (*n*-hexane / diethyl ether)

m/z (EI) 246(M^+ 21.2), 108 (100 base peak), 63 (25.8) and 64 (20.3).

2,6-Dichlorophenyl *N,N*-dimethylsulfamate 2,6-di$ClC_6H_3OSO_2NMe_2$ **(204)**

0.225 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 2,6-dichlorophenol in 0.3 mol of triethylamine. Stirring continued for 12 days.

Off-white crystals; mp 79°C – 80.5°C; 76% yield from (*n*-hexane / diethyl ether).

Found: C, 35.78; H, 3.12; N, 6.42. $C_8H_9NCl_2O_3S$ requires C, 35.56; H, 3.33; N, 5.18.

υ_{max}/cm^{-1} (KBr disc) 1180 and 1374 (sym & antisym S=O *str*), 1569 (C-H Ar) and 2985 (S-N *w*).

m/z (EI) 269 (M^+ 2.2), 108 (100 base peak), 63 (26.2) and 73 (18.5).

2,5-Dichlorophenyl *N,N*-Dimethylsulfamate 2,5-di$ClC_6H_3OSO_2NMe_2$ **(205)**

0.225 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 2,5-dichlorophenol in 0.3 mol of triethylamine. Stirring continued for 12 days.

White crystals; yield and other properties not acquired

m/z (EI) 269 (M^+ 23.7), 108 (100 base peak), 133 (11.7) and 271 (16.5).

2,6-Dimethylphenyl *N,N*-dimethylsulfamate 2,6-di$MeC_6H_3OSO_2NMe_2$ **(206)**

0.225 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 2,6-dimethylphenol in 0.3 mol of triethylamine. Stirring continued for 12 days

White crystals; yield and other properties not acquired.

m/z (EI) 229 (M^+ 30.7), 121 (100 base peak), 108 (57.70) and 91 (53.7).

0.45 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol 2-hydroxyphenol in 0.3 mol of triethylamine. Stirring continued for 20 days

Off-white crystals; yield and other properties not acquired

m/z (EI) 324 (M^+ 1.7), 108 (100 base peak), 217 (30.6) and 52 (33.0).

Phenyl 1,3-Di-(*N,N*-Dimethylsulfamate) C_6H_4 1,3-di(OSO_2NMe_2)$_2$ (208)

0.45 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 3-hydroxyphenol in 0.3 mol of triethylamine. Stirring continued for 20 days.

Off-white crystals; yield and other properties not acquired.

m/z (EI) 324 (M+ 22.4), 108 (100 base peak), 244 (11.2) and 92 (12.4).

1-Naphthyl *N,N*-Dimethylsulfamate $C_{10}H_7OSO_2NMe_2$ [72 (a)] **(209)**

0.18 Mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 1-naphthol in 0.24 mol of triethylamine. Stirring continued for 120 hours.

White crystals; MP 65°C – 66.5°C; 48% yield from (n-hexane / diethyl ether).

m/z (EI) 251 (M^+ 43.1), 115 (100 base peak) 143 (90.9) and 144 (28.4).

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0.225 mol of *N,N*-dimethylsulfamoyl chloride in 100 ml dries CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 2,4,6-trichlorophenol in 0.3 mol of triethylamine. Stirring continued for 120 hours.

White crystals: mp 115.5°C – 116.5°C; 67% yield from (*n*-hexane/diethyl ether).

υ_{max}/cm^{-1} (KBr disc) 1136 and 1294 (sym & antisym S=O str), 1562 (C-H Ar) and 2980 (S-N w).

m/z (EI) 305 (M^+ 1.8), 108 (100 base peak),167 (4.8) and 197 (4.3).

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0.18 Mol of *N,N*-diethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of phenol in 0.24 mol of triethylamine. Stirring continued for 48 hours.

Clear liquid: bp 106°C – 109°C @ 7 x 10^{-1} mm Hg.; yield 70% from reduced pressure distillation.

Found: C, 52.61; H, 6.52; N, 6.40. $C_{10}H_{15}NO_3S$ requires C, 52.40; H, 6.55; N, 6.11.

υ_{max}/cm^{-1} (Neat) 1150 and 1372 (sym & antisym S=O *str*), 1587 (C-H Ar) and 2985 (S-N *w*).

m/z (EI) 229 (M^+ 29.9), 136 (100 base peak), 108 (66.8) and 214 (25.2).

4-Fluorophenyl *N,N*-diethylsulfamate *p*-$FC_6H_4OSO_2NEt_2$ **(212)**

0.18 Mol of *N,N*-diethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-fluorophenol in 0.24 mol of triethylamine. Stirring continued for 24 hours.

Clear liquid: bp 127°C – 129°C @ 8 x 10^{-1} mm Hg.; yield 77% from reduced pressure distillation.

Found: C, 48.57; H, 6.06; N, 5.69. $C_{10}H_{14}O_3SNF$ requires c, 48.57; H, 5.71; N, 5.66.

υ_{max}/cm^{-1} (Neat) 1156 and 1371 (sym & antisym S=O *str*), 1599 (C-H Ar) and 2980 (S-N *w*).

m/z (EI) 247 (M^+, 8.3); 136 (100, base peak); 83 (63.1); and 111 (34.9).

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0.18 Mol of *N,N*-diethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-chlorophenol in 0.24 mol of triethylamine. Stirring continued for 72 hours.

Clear liqud; bp 123°C – 125°C @ 4 x 10^{-1} mm Hg.; yield 81% from reduced pressure distillation.

Found: C, 45.62; H, 5.24; N, 5.00. $C_{10}H_{14}NClO_3S$ requires C, 45.54; H, 5.31; N, 5.31.

υ_{max}/cm^{-1} (Neat) 1167 and 1371 (sym & antisym *str*), 1583 (C-H Ar) and 2981 (S-N *w*).

m/z (EI) 263 (M^+, 5.6); 136 (100 base peak); 94 (34.6); and 108, (20.4).

It was synthesised by an alternative route As per method in [72 (a)] *N,N*-diethyl sulfonyl chloride was added dropwise at 100°C with good stirring, to the sodium salt of 4-chlorophenol in xylene. The reaction is initially exothermic and is continued by refluxing for one hour. After filtering off the salt the solvent is removed by reduced pressure distillation and the compound is purified by bulb to bulb distillation.

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0.225 Mol of *N,N*-diethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 4-bromophenol in 0.3 mol of triethylamine. Stirring continued for 14 days.

Clear pale yellow liquid: bp 156°C – 159°C @ 4 mm Hg.; yield 72% from reduced pressure distillation.

Found: C, 39.52; H, 4.95; N, 4.92. $C_{10}H_{14}NBrO_3S$ requires C, 38.99; H, 4.55; N, 4.55.

υ_{max}/cm^{-1} (Neat) 1152 and 1366 (sym & antisym S=O *str*), 1582 (C-H Ar) and 2980 (S-N *w*).

m/z (EI) 309 (M^+ 4.8), 136 (100 base peak), 108 (18.3) and 143 (10.7).

4-Iodophenyl *N,N*-diethylsulfamate *p*-$IC_6H_4OSO_2NEt_2$ **(215)**

0.225 Mol of *N,N*-diethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 4-iodophenol in 0.3 mol of triethylamine. Stirring continued for 24days.

Yield ≤ 0.1%, as estimated from GC.

m/z (EI) 355 (M^+ 15.1), 136 (100 base peak), 92 (26.6) and 219 (14.0).

0.225 Mol of *N,N*-diethylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 2,6-dichlorophenol in 0.3 mol of triethylamine. Stirring continued for 12 days.

White crystals: mp 46.5°C – 47.5°C; 43% yield from (*n*-hexane/diethyl ether).

Found: C, 40.06; H, 4.19; N, 4.19. $C_{10}H_{13}NCl_2O_3S$ requires C, 40.27; H, 4.36; N, 4.69.

υ_{max}/cm^{-1} (KBr disc) 1182 and 1372 (sym & antisym S=O *str*), 1572 (C-H Ar) and 2978 (S-N *w*).

m/z (EI) 297 (M^+ 3.1), 136 (100 base peak), 108 (17.0) and 73 (12.5)

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0.18 mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dries CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of phenol in 0.24 mol of triethylamine. Stirring continued for 72 hours.

Pale yellow liquid: bp 112°C- 113°C @ 4 x 10^{-1} mm Hg; yield 83% from reduced pressure distillation. Found: C, 56.04; H, 7.32; N, 5.77. $C_{12}H_{19}NO_3S$ requires C, 56.03; H, 7.39; N, 5.45.

υ_{max}/cm^{-1} (Neat) 1149 and 1376 (sym & antisym S=O *str*), 1589 (C-H Ar) and 3069 (S-N *w*).

m/z (EI) 257 (M^+ 2.6), 65 (100 base peak), 107 (53.2) and 186 (19.7).

4-Fluorophenyl *N,N*-di-*n*-propylsulfamate *p*-$FC_6H_5OSO_2N(n\text{-}Pr)_2$ (218)

0.18 Mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-fluorophenol in 0.24 mol of triethylamine. Stirring continued for 48 hours.

Clear pale yellow liquid: bp 116°C – 118°C @ 3 x 10^{-1} mm Hg.; yield 72% from reduced pressure distillation. Found: C, 52.12; H, 6.44; N, 4.26. $C_{12}H_{18}O_3SNF$ requires C, 52.35; H, 6.59; N, 5.09.

υ_{max}/cm^{-1} (Neat) 1156 and 1377 (sym & antisym S=O *str*), 1591 (C-H Ar) and 2970 (S-N *w*).

m/z (EI) 275 (M^+ 10.9), 43 (100 base peak), 164 (34.2) and 246 (23.6).

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0.18 Mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-chlorophenol in 0.24 mol of triethylamine. Stirring continued for 120 hours.

Clear liquid: bp 126°C – 129°C @ 4 x 10^{-1} mm Hg.; yield 87% from reduced pressure distillation. Found: C, 49.51; H, 6.06; N, 5.05. $C_{12}H_{18}NClO_3S$ requires C, 49.40; H, 6.17; N, 4.80.

υ_{max}/cm^{-1} (Neat) 1162 and 1376 (sym & antisym S=O *str*), 1585 (C-H Ar) and 3100 (S-N *w*).

m/z (EI) 291 (M^+ 6.0), 58 (100 base peak), 164 (65.0) and 127 (61.6).

4-Bromophenyl *N,N*-di-*n*-propylsulfamate *p*-$BrC_6H_5OSO_2N(n\text{-}Pr)$ (220)

0.225 Mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 4-bromophenol in 0.3 mol of triethylamine. Stirring continued for 14days.

Clear yellow liquid: bp 135°C – 138°C @ 1.5 mm Hg.; yield 83% from reduced pressure distillation. Found: C, 43.50; H, 5.71; N, 3.95. $C_{12}H_{18}O_3SNBr$ requires C, 42.87; H, 5.40; N, 4.17.

υ_{max}/cm^{-1} (Neat) 1154 & 1165 (sym & antisym S=O *str*) 1580 (C-H Ar) and 2969 (S-N *w*).

m/z (EI) 337 (M^+ 5.7), 58 (100 base peak), 164 (68.7) and 173 (21.2).

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0.18 Mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-methylphenol in 0.24 mol of triethylamine. Stirring continued for 120 hours.

Pale yellow liquid: bp 122°C – 124°C @ 3 x 10^{-1} mm Hg.; yield 74% from reduced pressure distillation.

m/z (EI) 271 (M^+ 4.8), 58 (100 base peak), 121 (53.2) and 200 (19.7).

4-Ethylphenyl *N,N*-di-*n*-propylsulfamate *p*-$EtC_6H_5OSO_2N(n\text{-}Pr)_2$ **(222)**

0.18 Mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.2 mol of 4-ethylphenol in 0.24 mol of triethylamine. Stirring continued for 7 days.

Pale yellow viscous liquid: 128°C – 130°C @ 2 x 10^{-1} mm Hg.; yield 67% from reduced pressure distillation.

m/z (EI) 285 (M^+ 11.7), 58 (100 base peak), 135 (44.2) and 214 (23.2).

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0.225 Mol of *N,N*-di-*n*-propylsulfamoyl chloride in 100 ml dried CH_2Cl_2 was added slowly to a stirring mixture of 0.25 mol of 2,5-dichlorophenol in 0.3 mol of triethylamine. Stirring continued for 14 days.

White crystals: mp 46.5°C – 47.5°C; 52% yield from (n-hexane/diethyl ether). Found: C, 43.94; H, 5.18; N, 5.55. $C_{12}H_{17}O_3SNCl_2$ requires C, 44.18; H, 5.25; N, 4.29.

υ_{max}/cm^{-1} (KBr disc) 1176 and 1377 (sym & antisym S=O *str*), 1570 (C-H Ar) and 2976 (S-N *w*).

m/z (EI) 327 (M+ -), 58 (100 base peak), 164 (57.6) and 122 (49.4).

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The general procedure for this novel thia-Fries rearrangement involves the reaction of ≈500 mg of sulfamate in a 1:1.2 molar ratio with the catalyst $AlCl_3$ at a temperature of 140 ± 3°C for 30 mins. The reaction was carried out in a 25 ml round-bottomed flask using an oil bath as a heat source and quenched with 10 ml of 1 molar HCl. After extraction with 3 aliquots of CH_2Cl_2 the product(s) were washed (H_2O), dried and the solvent evaporated off. Purification and separation was carried out by column chromatography, (Merck Kiselgel 60 eluting with *n*-hexane / diethyl ether in a stepwise manner, from 100/0 in 5% moieties) or by reduced pressure distillation.

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2-Hydroxyphenylsulfonamide[73 (a-c)]. (224)

2.5 Mmol of phenylsulfamate was rearranged using 3.75 mmol $AlCl_3$ at 150°C for 60 min.

White crystals; m.p. 137°C - 139°C. 18% yield from (*n*-hexane/diethyl ether).

m/z (EI) 173 (M^+ 51.0), 64 (100 base peak), 156 (75.1) and 80 (45.3).

3-Fluoro-6-hydroxyphenylsulfonamide: (225)

2.4 Mmol of 4-fluorophenylsulfamate was rearranged using 2.9 mmol $AlCl_3$ at 140°C for 30 mins.

Yield ≤ 0.1% as estimated from GC.

m/z (EI) 191 (M^+ 42.7), 82 (100 base peak), 174 (49.0) and 126 (24.6).

3-Chloro-6-hydroxyphenylsulfonamide: (226)

2.4 Mmol of 4-chlorophenylsulfamate was rearranged using 2.9 mmol $AlCl_3$ at 140°C for 30 mins.

Yield ≤ 0.1% as estimated from GC.

m/z (EI) 207 (M^+ 30.9), 63 (100 base peak), 126 (51.2) and 190 (51.1).

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3-Bromo-6-hydroxyphenylsulfonamide: **(227)**

2.4 Mmol of 4-bromophenylsulfamate was rearranged using 2.9 mmol $AlCl_3$ at 140°C for 30 mins.

Yield ≤ 0.1% as estimated from GC.

m/z (EI) 251 (M+ 19.7), 63 (100 base peak), 253 (20.2) and 236 (32.3).

2-Hydroxy-5-methylphenylsulfonamide: **(228)**

2.4 mmol of 4-methylphenylsulfamate was rearranged using 2.9 mmol of $AlCl_3$ at 140°C for 30 mins.

Yield ≤ 0.1% as estimated from GC.

m/z (EI) 187 (M+ 69.9), 78 (100 base peak) and 170 (75.4).

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The rearrangement of the phenyl *N,N*-dialkylsulfamates to the phenyl *N,N*-dialkylsulfonamides (229-250)

2-Hydroxyphenyl *N,N*-dimethylsulfonamide [74]: **(229)**

3 Mmol phenyl *N,N*-dimethylsulfamate was rearranged by heating, using 3.6 mmol $AlCl_3$ at 140°C for 30 mins to give the two isomers (**229** and **230**) in 88% total yield.

White crystals: 91°C – 92°C from (*n*-hexane / diethyl ether); yield 42%

Found C, 47.70; H, 5.37; N, 6.92. $C_8H_{11}NO_3S$ requires C, 47.76; H, 5.47; N, 6.96.

υ_{max}/cm^{-1} (KBr disc) 1131 and 1331 (sym & antisym S=O *str*), 1585 (C-H Ar), 3094 (S-N *w*) and 3383 (Ar-OH *str*).

m/z (EI): 201 (M^+ 19.7), 65 (100 base peak), 64 (46) and 92 (22.2).

This compound was synthesised by an alternative route. To 55 mmol of 2-nitrobenzenesulfonyl chloride (Aldrich) was added two equivalents of 40% aqueous dimethylamine in 35 ml of CH_2Cl_2, stirred for two hours, washed with water, 1M HCl and water again dried and the solvent evaporated. 2-Nitrophenyl *N,N*-dimethylsulfonamide, the product, was recovered in 91% yield. The reduction of the nitro group to an amine was carried out by catalytic hydrogenation with acid and tin. 20 Mmol of 2-nitrophenyl *N,N*-dimethylsulfonamide was stirred with 50 ml 10M HCl and 5g tin for two hours which gave 78% yield (estimated from GC) of 2-aminophemyl *N,N*-dimethylsulfonamide after work up. This product was not purified but was subjected to

the Sandmeyer type reaction where the diazonium group was replaced by the hydroxyl group to give compound **229**. 9 Mmol of 2-aminophenyl *N,N*-dimethylsulfonamide was warmed in 15 ml of 6M H_2SO_4 to dissolve and cooled to ≤ 5°C where 1 equivelent of $NaNO_2$, dissolved in 15 ml water, was added slowly while maintaining the temperature. This reaction gave a yield of 42% of 2-hydroxyphenyl *N,N*-dimethylsulfonamide after purification by column chromatography (*n*-hexane / diethyl ether).

4-Hydroxyphenyl *N,N*-dimethylsulfonamide [75(a-c)]: **(230)**

3 Mmol phenyl *N,N*-dimethylsulfamate was rearranged by heating, using 3.6 mmol $AlCl_3$ at 140°C for 30 mins to give the two isomers (**229** and **230**) in 88% total yield.

White crystals: 97°C – 98°C from (*n*-hexane / diethyl ether); 46% yield.

Found: C, 47.68; H, 5.26; N, 6.91. $C_8H_{11}NO_3S$ requires C, 47.76; H, 5.47; N, 6.96.

υ_{max}/cm^{-1} (KBr disc) 1162 and 1338 (sym & antisym S=O str), 1590 (C-H Ar), 3069 (S-N *w*) and 3377 (Ar-OH *str*) .

m/z (EI) 201 (M^+ 15.0), 93 (100 base peak), 65 (90.7) and 94 (25.3).

3-Fluoro-6-hydroxyphenyl *N,N*-dimethylsulfonamide: **(231)**

3 Mmol of 4-fluorophenyl *N,N*-dimethylsulfamate was rearranged with 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

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White crystals: mp 74.4°C – 74.9°C; 59% yield from (n-hexane / diethyl-ether).

Found: C, 43.86; H, 4.72; N, 6.70. $C_8H_{10}NO_3SF$ requires: C, 43.93; H, 4.60 N, 6.39.

υ_{max}/cm^{-1} (Kbr disc) 1141 and 1320 (sym & antisym S=O *str*), 1581 (C-H Ar), 3082 (S-N *w*) 3417 (Ar-OH *str*).

m/z (EI) 219 (M^+ 14.9), 44 (100 base peak), 45 (91.1) and 83 (17.9).

3-Chloro-6-hydroxyphenyl *N,N*-dimethylsulfonamide: **(232)**

3 Mmol of 4-chlorophenyl *N,N*-dimethylsulfamate was rearranged with 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: mp 62°C – 63°C; 69% yield from reduced pressure distillation.

Found: C, 40.65; H, 4.13; N, 5.72. $C_8H_{10}NClO_3S$ requires C, 40.76; H, 4.25 N, 5.94.

υ_{max}/cm^{-1} (KBr disc) 1136 and 1331 (sym & antisym S=O *str*), 1577 (C-H Ar), 3074 (S-N *w*) and 3323 (Ar-OH *str*).

m/z (EI) 235 (M^+ 34.1), 63 (100 base peak), 99 (45.0) and 73 (44.7).

3-Bromo-6-hydroxyphenyl *N,N*-dimethylsulfonamide: **(233)**

3 Mmol of 4-bromophenyl *N,N*-dimethylsulfamate was rearranged with 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Pale brown crystals: mp 71.5°C – 72.5°C; 72% yield from reduced pressure distillation.

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Found: C, 34.28; H, 3.48; N, 4.90. $C_8H_{10}NBrO_3S$ requires C, 34.29; H 3.57; N, 5.00.

υ_{max}/cm^{-1} (KBr disc) 1136 and 1338 (sym & antisym S=O str), 1564 (C-H Ar), 3100 (S-N w) and 3358 (Ar-OH *str*).

m/z (EI) 279 (M^+ 7.5), 281 (M^+ 7.5), 63 (100 base peak) and 53 (42.6).

2-Hydroxy-5-iodophenyl *N,N*-dimethylsulfonamide: **(234)**

3 Mmol of 4-iodophenyl *N,N*-dimethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Yield ≤ 0.1% as estimated by GC.

m/z (EI) 327 (M^+ 34.8), 63 (100 base peak), 53 (69.9) and 92 (37.0).

2-Hydroxy-5-methylphenyl *N,N*-dimethylsulfonamide: **(235)**

3 Mmol of 4-methylphenyl *N,N*-dimethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: mp 57°C – 58°C; 49% yield from reduced pressure distillation.

Found: C, 50.30; H, 6.06; N, 6.47. $C_9H_{13}NO_3S$ requires C, 50.23; H, 6.09; N, 6.51.

υ_{max}/cm^{-1} (KBr disc) 1124 and 1324 (sym & antisym S=O *str*), 1585 (C-H Ar), 2973 (S-N *w*) and 3335 (Ar-OH *str*).

m/z (EI) 215 (M^+ 28.6), 77 (100 base peak), 107 (28.6) and 108 (17.7).

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3-Ethyl-6-hydroxyphenyl *N,N*-dimethylsulfonamide: **(236)**

3 Mmol of 4-ethylphenyl *N,N*-dimethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Pale yellow liquid: bp 110°C – 112°C @ 9 x 10^{-1} mm Hg.; yield 48% from reduced pressure distillation.

Found: C, 52.56; H, 6.66; N, 5.92. $C_{10}H_{15}NO_3S$ requires C, 52.38; H, 6.59; N, 6.11.

υ_{max}/cm^{-1} (Neat) 1136 and 1335 (sym & antisym S=O *str*), 1582 (C-H Ar), 3031 (S-N *w*) and 3347 (Ar-OH *str*).

m/z (EI) 229 (M^+ 29.5), 77 (100 base peak), 107 (30.3) and 214 (7.7).

2,4-Dichloro-3-hydroxyphenyl *N,N*-dimethylsulfonamide [76(a & b)]: **(237)**

3 Mmol of 2,6-dichlorophenyl *N,N*-dimethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: 158°C – 159.5°C; 76% yield from (*n*-hexane/diethyl ether).

Found: C, 35.94; H, 2.72; N, 4.86. $C_8H_9NCl_2O_3S$ requires C, 35.55; H, 3.33; N, 5.18.

υ_{max}/cm^{-1} (KBr dsc) 1132 and 1393 (sym & antisym S=O *str*), 1568 (C-H Ar), 3077 (S-N *w*) and 3348 (Ar-OH *str*).

m/z (EI) 269 (M^+ 46.7) 62 (100 base peak), 161 (55.2) and 177 (36.6).

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2-Hydroxyphenyl *N,N*-diethylsulfonamide: (238)

3 Mmol of phenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Clear liquid: bp 137°C - 139°C @ 1 mm Hg,; 85% joint yield with o/p ratio = 1 from (*n*-hexane/diethyl ether).

Found: C, 52.04; H, 6.06; N, 5.78. $C_{10}H_{15}NO_3S$ requires C, 52.40; H, 6.55; N, 6.11.

υ_{max}/cm^{-1} (Neat) 1128 and 1323 (sym & anti sym S=O *str*), 1581 C-N Ar), 2979 (S-N *w*) and 3315 (Ar-OH *str*).

m/z (EI) 229 (M^+ 1.5), 58 (100 base peak), 93 (19.9) and 157 (16.3).

4-Hydroxyphenyl *N,N*-diethylsulfonamide [75(a) &77]: (239)

3 Mmol of phenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: mp 94.5°C – 95.5°C; 85% joint yield with o/p ratio = 1 from (*n*-hexane/diethyl ether).

Found: C, 52.34; H, 6.37; N, 6.01. $C_{10}H_{15}NO_3S$ requires C, 52.40; H, 6.55; N, 6.11.

υ_{max}/cm^{-1} (KBr disc) 1155 and 1325 (sym & antisym S=O *str*), 1590 (C-H Ar), 2980 (S-N *w*) and 3358 (Ar-H *str*).

m/z (EI) 229 (M^+ 1.6), 58 (100 base peak), 65 (22.6) and 157 (19.6).

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This compound was synthesised by an alternative method. To 70 mmol of 4-nitrobenzenesulfonyl chloride (Aldrich) was added two equivalents of diethylamine in 50 ml of dichloromethane. After stirring for two hours the reaction mixture was washed with water, 1M HCl and water again before drying and evaporating the solvent. 4-Nitrophenyl *N,N*-diethylsulfomamide, the product, was recovered in quantitative yield. The reduction of the nitro group to an amine was carried out by catalytic hydrogenation with acid and tin. 20 Mmol of 4-nitrophenyl *N,N*-diethylsulfonamide was stirred with 50 ml 10M HCL and 5g tin for two hours which gave 66% yield (estimated from GC) of 4-aminophemyl *N,N*-diethylsulfonamide after work up. This product was not purified but was subjected to the Sandmeyer type reaction where the diazonium group was replaced by the hydroxyl group to give compound **239**. 6 Mmol of 4-aminophenyl *N,N*-diethylsulfonamide was warmed in 13 ml of 6M H_2SO_4 to dissolve and then cooled to $\leq$ 5°C. One equivalent of $NaNO_2$ dissolved in 10 ml water, was added slowly while temperature was maintained. The mixture was stirred at room temperature for 15 minutes, then at 50°C for a further 15 minutes and then extracted with 3 aliquots of CH_2Cl_2 which gave a yield of 33% of 4-hydroxyphenyl *N,N*-diethylsulfonamide after purification by column chromatography (*n*-hexane / diethyl ether).

3-Fluoro-6-hydroxyphenyl *N,N*-diethylsulfonamide: **(240)**

3 Mmol of 4-fluorophenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Clear pale yellow liquid: bp 99°C-101°C @ 1mm Hg.; 69% yield from reduced pressure distillation.

Found: C, 48.38; H, 5.76; N, 5.77. $C_{10}H_{14}NO_3SF$ requires C, 48.57; H, 5.71; N, 5.66 υ_{max}/cm^{-1} (Neat) 1124 and 1326 (sym & antisym S=O str), 1597 (C-H Ar), 2980 (S-N w) and 3337 (Ar-OH str)

m/z (EI) 247 (M^+ 13.9), 83 (100 base peak), 127 (60.3) and 232 (28.2).

3-Chloro-6-hydroxyphenyl *N,N*-diethylsulfonamide: **(241)**

3 Mmol of 4-chlorophenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White solid (at low temp.): mp 29°C – 31°C; yield 67% from reduced pressure distillation.

Found: C, 45.57; H, 5.30; N, 5.33. $C_{10}H_{14}NClO_3S$ requires C, 45.54; H, 5.31; N, 5.31. υ_{max}/cm^{-1} (Neat) 1136 and 1325 (sym & antisym S=O *str*), 1577 (C-H Ar), 3081 (S-N *w*) and 33.20 (Ar-H *str*).

m/z (EI) 263 (M^+ 14.3), 72 (100 base peak), 64 (38.3) and 248 (23.2).

3-Bromo-6-hydroxyphenyl *N,N*-diethylsulfonamide: **(242)**

3 Mmol of 4-bromophenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Pale yellow liquid: bp 139°C –142°C @ 8 x 10^{-1} mm Hg.; yield 86% from reduced pressure distillation.

Found: C, 39.36; H, 4.60; N, 4.56. $C_{10}H_{14}NBrO_3S$ requires C, 38.96; H, 4.55; N, 4.55.

υ_{max}/cm^{-1} (Neat) 1131 and 1319 (sym & antisym S=O str), 1588 (C-H Ar), 2979 (S-N *w*) and 3328 (Ar-OH *str*).

m/z (EI) 309 (M^+ 10.1), 72 (*100* base peak), 294 (21.0) and 292 (20.8).

2-Hydroxy-5-iodophenyl *N*,N-diethylsulfonamide: **(243)**

3 Mmol of 4-iodophenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Yield ≤ 0.1% as estimated by GC.

m/z (EI) 355 (M^+ 26.4), 63 (100 base peak), 92 (41.4) and 340 (33.9).

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2,4-Dichloro-3-hydroxyphenyl *N,N*-diethylsulfonamide: (244)

3 Mmol of 2,6-dichlorophenyl *N,N*-diethylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: mp 200°C – 203°C; 69% yield from (*n*-hexane/diethyl ether).

Found: C, 40.13; H, 4.03, N, 4.68. $C_{10}H_{13}NCl_2O_3S$ requires C, 40.27; H, 4.36; N, 4.70.

υ_{max}/cm^{-1} (KBr disc) 1149 and 1325 (sym & antisym S=O *str*), 1564 (C-H Ar), 3069 (S-N *w*) and 3345 (Ar-OH *str*).

m/z (EI) 297 (M^+ 8.7), 225 (100 base peak), 227 (64.6) and 299 (5.7).

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2-Hydroxyphenyl *N,N*-di-*n*-propylsulfonamide: (245)

3 Mmol of phenyl *N,N*-di-*n*-propylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Pale yellow liquid: 122°C – 124°C @ 1 mm Hg.; 77% joint yield with o/p ratio = 1.65 from (*n*-hexane/diethyl ether).

Found: C, 55.91; H, 7.14; N, 5.22. $C_{12}H_{19}NO_3S$ requires C, 56.03; H, 7.39; N, 5.45.

υ_{max}/cm^{-1} (KBr disc) 1125 and 1382 (sym & antisym S=O *str*), 1580 (C-H Ar), 2967 (S-N *w*) and 3310 Ar-OH *str*). *m/z* (EI) 257 (M^+ 3.7), 72 (100 base peak), 228 (28.7) and 157 (22.4).

4-Hydroxyphenyl *N,N*-di-n-propylsulfonamide [75(a)]. **(246)**

3 Mmol of phenyl *N,N*-di-*n*-propylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: mp 100°C – 102°C; 77%; joint yield with o/p ratio = 1.65 from (n-hexane/diethyl ether).

Found: C, 55.18; H, 7.20; N, 5.33. $C_{12}H_{19}NO_3S$ requires C, 56.03; H, 7.39; N, 5.45.

υ_{max}/cm^{-1} (KBr disc) 1152 and 1317 (sym & antisym S=O *str*), 1596 C-H Ar), 2962 (S-N *w*) and 3355 (Ar-OH *str*).

m/z (EI) 257 (M^+ 0.5), 72 (100 base peak), 93 (20.0) and 157 (19.8).

3-Fluoro-6-hydroxyphenyl *N,N*-di-n-propylsulfonamide: **(247)**

3 Mmol of 4-fluorophenyl *N,N*-di-*n*-propylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Clear yellow liquid: bp 127°C – 129°C @ 6 x 10^{-1} mm Hg.; yield 52% from reduced pressure distillation.

υ_{max}/cm^{-1} (Neat) 1125 and 1328 (sym & antisym S=O *str*), 1588 (C-H Ar), 2971 (S-N *w*) and 3333 (Ar-OH *str*).

m/z (EI) 275 (M^+ 8.8), 72 (100 base peak), 246 (38.8) and 127 (28.3).

3-Chloro-6-hydroxyphenyl *N,N*-di-n-propylsulfonamide: **(248)**

3 Mmol of 4-chlorophenyl *N,N*-di-*n*-propylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Pale yellow liquid: bp 138°C – 140°C @ 7 x 10^{-1} mm Hg.; yield 36% from reduced pressure distillation.

Found: C, 49.55; H, 5.92; N, 4.37. $C_{12}H_{18}NClO_3S$ requires C, 49.40; H, 6.17; N, 4.80.

υ_{max}/cm^{-1} (Neat) 1132 and 1324 (sym & antisym S=O *str*), 1570 (C-H Ar), 2968 (S-N *w*) and 3324 (Ar-OH *str*).

m/z (EI) 291 (M^+ 0.9), 72 (100 base peak), 262 (4.5) and 143 (4.7).

3-Bromo-6-hydroxyphenyl *N,N*-di-*n*-propylsulfonamide: **(249)**

3 Mmol of 4-bromophenyl *N,N*-di-*n*-propylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

Pale yellow liquid: bp 155°C – 158°C @ 1.2 mm Hg.; yield 44% from reduced pressure distillation.

Found: C, 42.43; H, 5.26; N, 4.09. $C_{12}H_{18}NBrO_3S$ requires C, 42.85; H, 5.36; N, 4.17.

υ_{max}/cm^{-1} (Neat) 1132 and 1320 (sym & antisym S=O *str*), 1588 (C-H Ar), 2967 (S-N *w*) and 3332 (Ar-OH *str*).

m/z (EI) 335 (M^+ 0.6), 337 (M^+ 0.6), 72 (100 base peak) and 308 (3.3).

2,4-Dichloro-3-hydroxyphenyl *N,N*-di-n-propylsulfonamide: **(250)**

3 Mmol of 2,6-dichlorophenyl *N,N*-di-*n*-propylsulfamate was rearranged using 3.6 mmol $AlCl_3$ at 140°C for 30 mins.

White crystals: mp 131.5°C – 135°C; 44% yeld from (n-hexane/diethyl ether).

Found: C, 44.34; H, 5.18; N, 4.11. $C_{12}H_{17}NCl_2O_3S$ requires C, 44.17; H, 5.21; N, 4.29.

υ_{max}/cm^{-1} (KBr disc) 1149 and 1388 (sym & antisym S=O *str*), 1564 C-H Ar), 2965 (S-N *w*) and 3345 (Ar-OH *str*).

m/z (EI) 72 (100 base peak), 225 (9.7), 296 (7.2) and 298 (5.0).

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The sulfamates and sulfonamides above which have a reference beside them have been synthesised previously, **185, 187, 190, 195, 197, 200, 203, 209, 210, 213, 224, 229, 230, 237, 239** and **246**. The other fifty compound which have been synthesised, from **185-250,** are novel products. Unless stated otherwise the b.p. / m.p. agree with the published values in the literature and where they differ other methods of synthesis have been carried out as detailed. For all of the compounds a boiling point / melting point, a %yield, a C, H and N microanalysis, an infrared spectrum and an electron impact induced mass spectra was acquired. For a few of the compounds their yield was so minute that only with separation by gas chromatography coupled to mass spectrometry could the product of interest be identified.

The phenylsulfamates, compounds **185-194**, gave very good yields except for **189**, **193** and **194** (Table 1). The method used was that of Okada [67] and described previously.

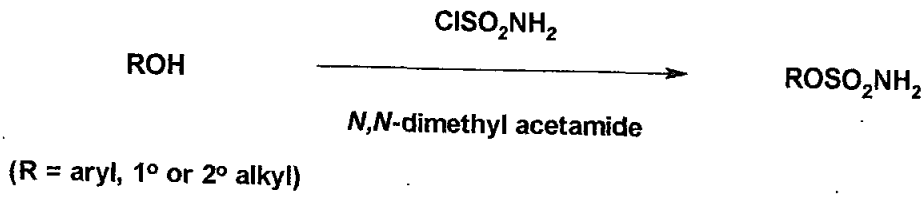

Fig. 9

The parent compound, phenylsulfamate (**185**), when synthesised was found to have a m.p. of 80.8 – 81.2°C. (lit [68(a)] 86°C, lit [68(b)] 85°C) and because the rearrangement to the

Properties of phenyl sulfamates (1)

Table 1

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
Phenylsulfamate	White Crystals	80.8°C-81.2°C	92%	$C_6H_6NO_3S$	C,41.61; H,4.07; N,8.09	C,41.53; H,3.92; N,7.73	173 (M^+,12.2), 94 (100 base peak)
4-Fluorophenylsulfamate	White Crystals	83.0°C-84.0°C	87%	$C_6H_6NO_3SF$	C,37.7; H3.16; N,7.33	C,38.07; H,3.27; N7.54	191 (M^+, 10.1), 112 (100 base peak)
4-Chlorophenylsulfamate	White Crystals	101.5°C-102.0°C	92%	$C_6H_6NO_3SCl$			207 (M^+, 11.8), 128 (100 base peak)
4-Bromophenylsulfamate	White Crystals	114.5°C-116.5°C	84%	$C_6H_6NO_3SBr$			252 (M^+, 14.7), 172 (100 base peak)
4-Iodophenylsulfamate			≤ 1%	$C_6H_6NO_3SI$			298 (M^+, 35.3), 220 (100 base peak)

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Properties of phenyl sulfamates (2)

Table 2

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
4-Methylphenylsulfamate	White Crystals	79.0°C-79.5°C	88%	$C_7H_9NO_3S$			187 (M^+, 32.7), 108 (100 base peak)
4-Ethylphenylsulfamate	Brown Crystals	65.0°C-66.0°C	77%	$C_8H_{11}NO_3S$			201 (M^+, 29.7), 107 (100 base peak)
2,6-Difluoropentlsulfamate	White Crystals	104.3°C-104.7°C	88%	$C_6H_5NO_3SF_2$	C,34.45; H2.41; N,6.70	C,34.73; H,2.21; N,6.22	209 (M^+, 2.8), 130 (100 base peak)
2,6-Dichlorophenylsulfamate			≤ 1%	$C_6H_5NO_3SCl_2$			241 (M^+, 3.3), 161 (100 base peak)
2,6-Dibromophenylsulfamate			≤ 1%	$C_6H_5NO_3SBr_2$			331 (M^+, 2.1), 43 (100 base peak)

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sulfonamide was not very successful no further or alternative synthesis was carried out.

Likewise, 4-chlorophenyl sulfamate (**187**) was found to have a m.p. of 101.5°C -102°C (lit. 105°C [61] and 104°C [68 (a)]) but because its rearrangement was not successful no further action was undertaken. 4-iodophenylsulfamate, 2,6-dichlorophenylsulfamate and 2,6-dibromophenylsulfamate, 189, 193 and 194, gave very poor yields due assumingly to steric effects of the large iodine, chlorine and bromine atoms compared to the fluorine compound. These compounds were not purified by chromatographic separations as their yields were so small. Rearrangement of these phenylsulfamates was not successful so analysis and characterisation of these compounds was not carried out.

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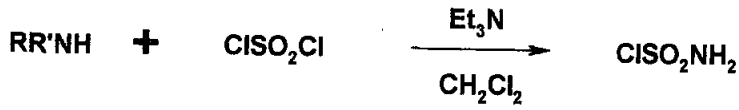
N,N-Dimethylsulfamoyl chloride (Aldrich) was used as purchased while *N,N*-diethyl-*N,N*-di-*n*-propyl- and *N,N*-di-*n*-butylsulfamoyl chlorides were synthesised by the method of Gupta [69] as mentioned above. The synthesis of the phenyl *N,N*-di-*n*-butylsulfamates was attempted but the yields were very low, ≤ 5% so this line of experimentation was not followed.



$R = R' = CH_2CH_3$ or $(CH_2)_2CH_3$

Fig. 10

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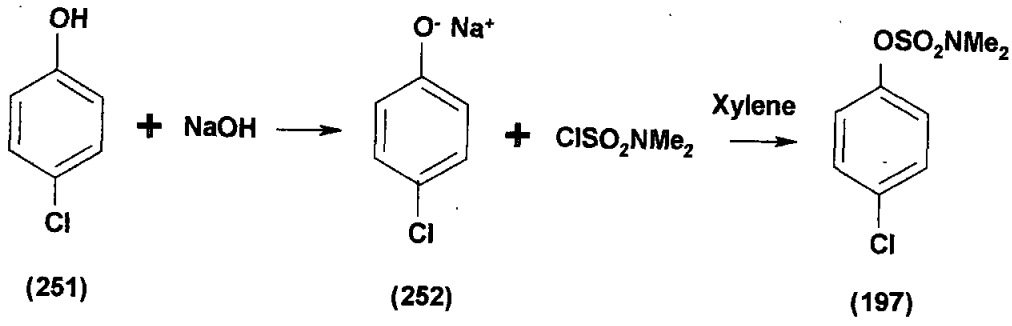
In the synthesis of phenyl *N,N*-dimethylsulfamate (**195**) the formation of *N,N,N',N'*-tetramethylsulfamide was a major problem which required multiple bulb to bulb distillations for purification and as a consequence the yield rarely topped 50%. By changing the ratio of phenol to sulfamoyl chloride to 1 : 0.9 the problem was overcome.

4-Chloropheny *N,N*-dimethyllsulfamate (**197**) was required to be synthesised by an alternative method as in scheme 68, because the boiling point did not correspond to published values. The synthesis was as stated in the experimental section.



Scheme 68

Compounds **(202)**, **(203)**, **(205)**, **(206)**, **(207)**, **(208)** and **(209)** were synthesised at various times during the project but were not planned for rearrangement. For this reason they were not characterised apart from their mass spectra.

The rearrangement of 2,4,6-trichlorophenyl *N,N*-dimethylsulfamate **(210)** was attempted but with the para and both ortho positions blocked no *meta*- compound was formed

Properties of N,N-dimethylsulfamates (1)

Table 3

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
Phenyl *N,N*-dimethylsulfamate	Pale Yellow Liquid	129°C-130°C @ $7x10^{-1}$ mm Hg	82%	$C_8H_{11}NO_3S$	C 47.76; H 5.47; N 6.96	C 47.73; H 5.49; N 6.97	201 (M^+,10.5), 108 (100 base peak)
4-Fluorophenyl *N,N*-dimethylsulfamate	White Crystals	51.0°C-52.0°C	84%	$C_8H_{10}NO_3SF$	C 43.84; H 4.57; N 8.68	C 44.16; H 5.06; N 7.59	219 (M^+, 7.1), 108 (100 base peak)
4-Chlorophenyl *N,N*-dimethylsulfamate	Clear Liquid	130°C-132.0°C @ $5x10^{-1}$mm Hg	80%	$C_8H_{10}NO_3SCl$	C 40.76; H 4.25; N 5.94	C 40.62; H 4.02; N 5.69	235 (M^+, 3.8), 108 (100 base peak)
4-Bromophenyl *N,N*-dimethylsulfamate	Clear Liquid	108°C-111°C @ $14x10^{-1}$ mm Hg	84%	$C_8H_{10}NO_3SBr$	C 34.29; H 3.57; N 5.00	C 34.46; H 3.66; N 5.37	281 (M^+, 8.7), 108 (100 base peak)
4-Iodophenyl *N,N*-dimethylsulfamate	Brown Crystals	68.5°C 71.5°C	23.5%	$C_8H_{10}NO_3SI$	C 29.36; H 3.06; N 4.28	C 29.79; H 3.14; N 4.54	327 (M^+ 6.1), 108 (100 base peak)

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Properties of phenyl *N,N*-dimethylsulfamates (2)

Table 4

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
4-Methylphenyl *N,N*-dimethylsulfamate	Clear Liquid	126°C-129°C @ $4x10^{-1}$ mm Hg	40%	$C_9H_{13}NO_3S$	C 50.23; H 6.05; N 6.51	C 50.43; H 6.01; N 6.66	215 (M^+, 19.4), 108 (100 base peak)
4-Ethylphenyl *N,N*-dimethylsulfamate	Clear Liquid	92°C-94°C @ 3X10-1 mm Hg	14%	$C_{10}H_{15}NO_3S$	C 52.38; H 6.59; N 6.11	C 52.32; H 6.66; N 6.03	229 (M^+, 15.3), 108 (100 base peak)
2,6-Dichlorophenyl *N.N*-dimethylsulfamate	Off-White Crystals	79°C-80.5°C	76%	$C_8H_9NO_3SCl_2$	C 35.56; H 3.33; N 5.18	C 35.78; H 3.12; N 6.42	269 (M^+, 2.2), 108 (100 base peak)
2, 4, 6-Trichlorophenyl N,N-dimethylsulfamate	White Crystals	115.5°C-116.5°C	67%	$C_8H_9NO_3SCl_3$	Not Acquired	Not Acquired	305 (M^+, 1.8), 108 (100 base peak)

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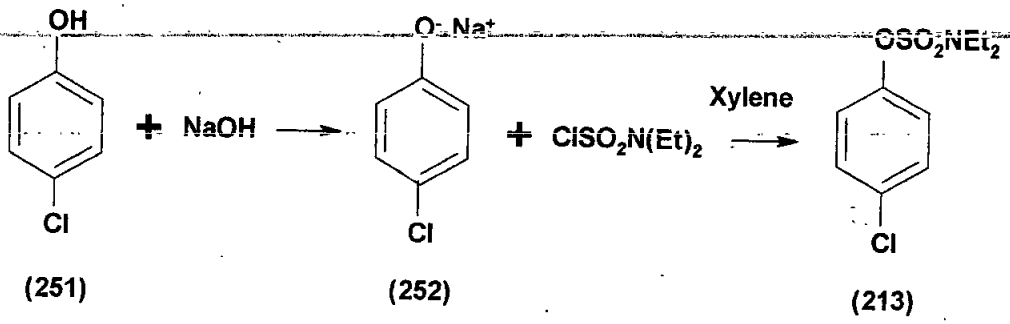

Scheme 69

Compound (**213**), 4-chlorophenyl *N,N*-diethylsulfamate required alternative synthesis as with the case of (**197**) the b.p. did not agree with the published figures so the reaction in scheme 69, was carried out.

Compound (**215**), 4-iodophenyl *N,N*-diethylsulfamate was found to be very difficult to synthesise and the reason for that is assumed to be steric hindrance on account of the large iodine atoms. The low yield of 2,6-dichlorophenyl *N,N*-diethylsulfamate (**216**) is also believed to be caused by steric hindrance.The only comment on the dipropyl series is that 4-methyl—and 4-ethylphenyl *N,N*-dipropylsulfamate (**221**) and (**222**) were not rearranged so consequently were not fully characterised.

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Properties of *N,N*-diethylsulfamates

Table 5

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
Phenyl *N,N*-diethylsulfamate	Clear Liquid	106°C-1090°C @ $7x10^{-1}$ mm Hg	70%	$C_{10}H_{15}NO_3S$	C 52.4; H 6.55; N 6.11	C 52.61; H 6.52; N 6.40	229 (M^+, 29.9), 136 (100 base peak)
4-Fluorophenyl *N,N*-diethylsulfamate	Clear Liquid	127°C-129°C @ 8x10-1 mm Hg	84%	$C_{10}H_{14}NO_3SF$	C 48.57; H 5.71; N 5.66	C 48.57; H 6.06; N 5.69	247 (M^+, 78.3), 136 (100 base peak)
4-Chlorophenyl *N,N*-diethylsulfamate (**213**)	Clear Liquid	123°C-125.0°C @ $4x10^{-1}$mm Hg	81%	$C_{10}H_{14}NO_3SCl$	C 45.54; H 5.31; N 5.31	C 45.62; H 5.24; N 5.00	263 (M^+, 5.6), 136 (100 base peak)
4-Bromophenyl *N,N*-diethylsulfamate (**214**)	Clear Pale Yellow Liquid	156°C-159°C @ 4 mm Hg	72%	$C10H_{14}NO_3SBr$	C 38.99; H 4.55; N 4.55	C 39.52; H 4.95; N 4.92	309 (M^+, 4.8), 135 (100 base peak)
4-Iodophenyl *N,N*-diethylsulfamate			≤ 1%				355 (M^+ 15.1), 136 (100 base peak)
2,6-Dichlorophenyl *N.N*-diethylsulfamate	White Crystals	46.5°C-47.5°C	43%	$C10H13NO_3SCl_2$	C 40.27; H 4.36; N 4.69	C 40.06; H 4.19; N 4.19	297 (M^+, 3.1), 136 (100 base peak)

Properties of phenyl *N,N*-di-*n*-propylsulfamates (1)

Table 6

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
Phenyl *N,N*-di-*n*-propylsulfamate	Pale Yellow Liquid	112°C-113°C @ $4x10^{-1}$ mm Hg	83%	$C_{12}H_{19}NO_3S$	C 56.03; H 7.39; N 5.45	C 56.04; H 7.32; N 5.77	257 (M^+, 2.6), 65 (100 base peak)
4-Fluorophenyl *N,N*-di-*n*-propylsulfamate (218)	Pale Yellow Liquid	116°C-118°C @ 3x10-1 mm Hg	72%	$C_{12}H_{18}NO_3SF$	C 52.35; H 6.59; N 5.09	C 52.12; H 6.44; N 4.26	275 (M^+, 10.9), 43 (100 base peak)
4-Chlorophenyl *N,N*-di-*n*-propylsulfamate (219)	Clear Liquid	126°C-129.0°C @ $4x10^{-1}$mm Hg	81%	$C_{12}H_{18}NO_3SCl$	C 49.40; H 6.17; N 4.80	C 49.51; H 6.06; N 5.05	291 (M^+, 6.0), 58 (100 base peak)

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Properties of phenyl *N,N*-di-*n*-propylsulfamates (2)

Table 7

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectra (EI)
4-Bromophenyl *N,N*-di-*n*-propylsulfamate (220)	Yellow Liquid	135°C-138°C @ 1.5 mm Hg	83%	$C_{12}H_{18}NO_3SBr$	C 42.87; H 5.4; N 4.17	C 43.5; H 5.71; N 3.95	337 (M^+, 5.7), 58 (100 base peak)
4-Methylphenyl *N,N*-di-*n*-propylsulfamate	Yellow Liquid	122°C-124°C @ $3x10^{-1}$ mm Hg	74%				271 (M^+ 4.8), 58 (100 base peak)
4-Ethylphenyl N,N-di-*n*-propylsulfamate (222)	Yellow Viscous Liquid	128°C-130°C @ $2x10^{-1}$ mm Hg	67%				285 (M^+ 11.7), 58 (100 base peak)
2,6-Dichlorophenyl *N,N*-di-*n*-propylsulfamate (223)	White Crystals	46.5°C-47.5°C	52%	$C_{12}H_{17}NO_3SCl_2$	C 44.18; H 5.25; N 4.29	C 43.94; H 5.18; N 5.55	327 (M^+0.6), 58 (100 base peak)

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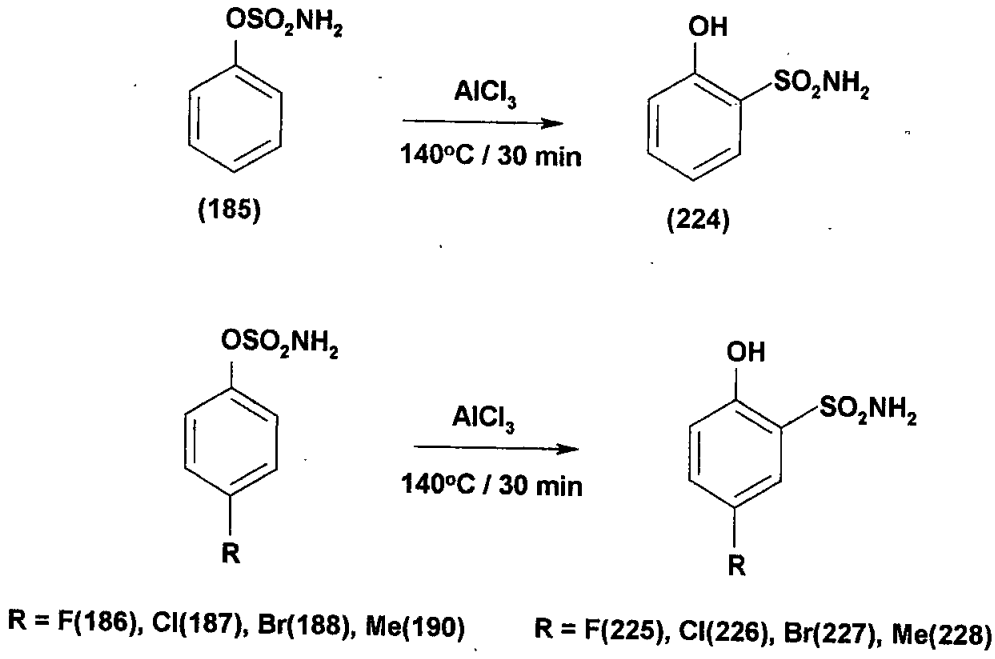

Scheme 70

Phenylsulfamate (**185**), the parent compound in this series (**185-194** scheme 70) was the only one to rearrange. The *ortho*- product 2-hydroxyphenylsulfonamide only was identified and then just from comparison to the mass spectra of the corresponding compounds in the other series i.e. phenyl *N,N*-dimethylsulfamate, phenyl *N,N*-diethylsulfamate and phenyl *N,N*-di-*n*-propylsulfamate. The mp temperature of this compound was reported as [74 (a-c)] 139-141°C. Found 137°C – 139°C. No alternative synthesis was attempted.

Fries rearrangement of phenyl sulfamate using no catalyst and also using $AlCl_3$ and at varying temperatures and differing catalytic ratios

Table 8

Catalyst	Ratio	Temp.°C	Time Hr.	%Rearranged	O / P Ratio
None		80	6	0	0
"		"	48	0	0
$AlCl_3$	1 : 1.2	"	6	0	0
"	"	"	14	0	0
"	"	"	24	0	0
"	1 : 1.5	"	3	0	0
"	1 : 1	140	0.33	0	0
"	"	"	2.5	0	0
"	1 : 1.2	150	1	≈20	All Ortho
"	1 : 1.5	"	3	≈35	"
"	1 : 2	"	3	≈30	"
"	"	"	5	≈25	"

Fries rearrangement of phenyl sulfamate using various catalysts and differing catalytic ratios and using a range of temperatures

Table 9

Catalyst	Ratio	Temp. °C	Time Hr.	%Rearranged	O / P Ratio
$ZnCl_2$	1 : 1.2	80	24	0	0
"	1 : 1.5	"	3	0	0
"	1 : 1.2	140	1	0	0
"	"	150	3	≈10	All Ortho
$CuCl_2$	1 : 1.2	140	2	0	0
"		150	3	0	0
$TiCl_4$	1 : 1.2	80	6	0	0
"	1 : 1.5	"	3	0	0
"	"	150	"	≈20	All Ortho
$FeCl_2$	"	"	"	≈5	"
$SnCl_2$	"	"	"	≈10	"
$NiCl_3$	"	"	"	≈ 0.1	"

Table 10

Catalyst 1M $AlCl_3$	Ratio	Temp. °C	Time Hr.	% Rearranged	O / P Ratio
Nitrobenzene	1 : 1.2	80	14	0	0
"	1 : 5	"	"	0	0
"	1 : 1.5	140	1	0	0
"	1 : 5	150	2	0	0

The yields for the above reactions in Tables 8, 9 and 10 are estimated from GC and are accurate to ± 5%. 200 mg of ester was rearranged in each of the above reactions and the catalysts and temperature are as stated. An oil bath was used for the heat source and temperature was maintained ± 5°C.

The other four compounds in this group (**225-228**) were the products of attempted rearrangement of the corresponding sulfamates and only minute amounts, ≤ 0.1%, identifiable by GC-MS, were formed. Of course this one physical property is not sufficient to characterise these compounds beyond doubt. Gas chromatography coupled to mass spectrometry was by far the premier qualitative technique.

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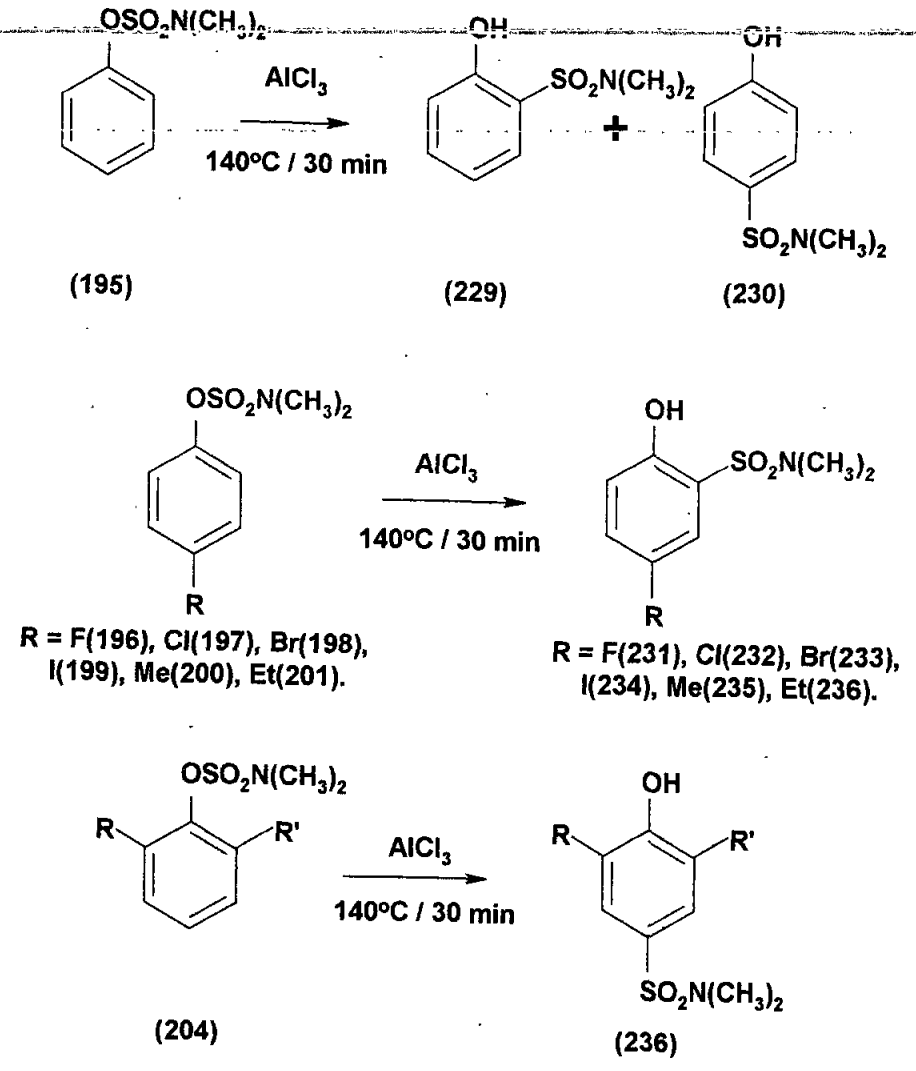


Scheme 71

The rearrangement of the phenyl *N,N*-dimethylsulfamates to the phenyl *N,N*-dimethylsulfonamides (scheme 71) is the first series to have been studied and they are also the compounds most used in the mechanistic studies which were carried out. The parent compound in this series (**195**) phenyl *N,N*-dimethylsulfamate was taken as the model and rearranges to the *ortho*- and *para*- products (**229** and **230**) in various ratios and quantities according to the temperature and time of the reaction.

Using 0.5 g of ester and a 1 : 1.2 molar ratio of ester to $AlCl_3$, the rearrangements were carried out at the various temperatures, which were maintained in an oil bath (± 5°C) to give the results in tables 11 and 12. Quantitative analysis of these results was carried out by HPLC.

Ortho / para ratio obtained in the rearrangement of phenyl _N,N_-dimethylsulfamate (195)

Table 11

Temp.(°C)	_ortho / para_ Time (min)				
	5	**10**	**15**	**30**	**60**
90	2.7	1.3	1.1	1.3	0.7
100	1.2	1.2	0.8	0.9	0.7
110	1.2	1:1	0.6	0.7	0.6
120	0.6	0.6	0.5	0.4	0.5
130	0.5	0.5	0.5	0.5	0.5
140	0.5	1	0.9	0.5	0.5

The quantity of the *ortho*- and *para*- rearranged products of phenyl *N,N*-dimethylsulfamate is also temperature and time dependant. The reaction conditions are as above and the results are in table 12.

Total yield of 2- and 4-hydroxy-*N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

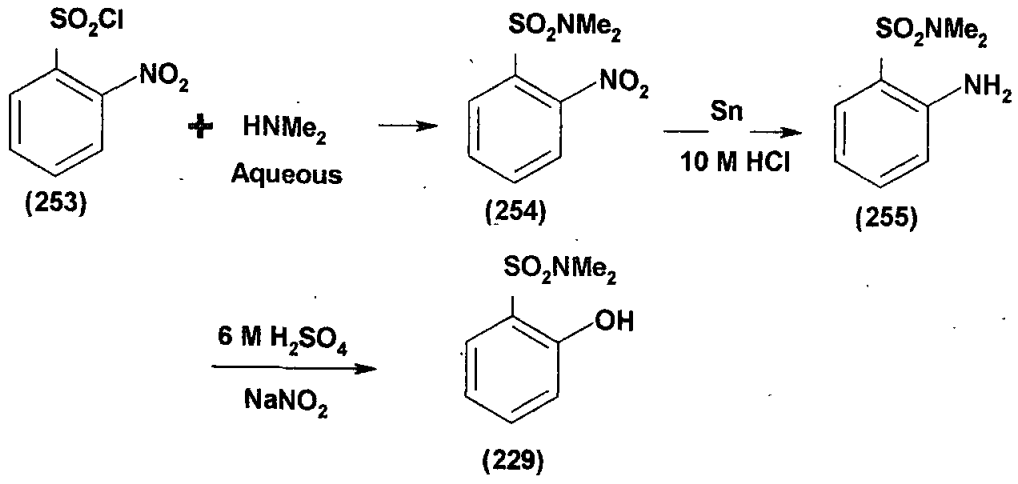
Table 12

Temp (°C)	Time (min) 5	10	15	30	60	120
60				1.9	3.1	3.8
70			2.5	3.1	10.9	21.5
80		3.6	5.2	11.8	25.9	33.3
90	2.7	9.0	17.6	13.2	35.7	63.6
100	19.9	36.7	35.0	48.2	57.9	93.4
110	28.0	50.5	61.3	64.1	67.6	
120	53.8	61.7	66.7	68.4	66.3	
130	63.6	76.1	67.4	74.5		
140	67.5	81.9	88.4	67.3		
150	79.0	80.4	99.2			

These experiments on yield and product ratio were quantified by HPLC using an internal standard method, the internal standard used was ethyl 4-aminobenzoate. At this stage both the sulfamate and the two sulfonamides had been purified and characterised so together with phenol and the internal standard a method of quantitation was possible. A C18 column was used with 49.5% H_2O / 49.5% MeOH / 1% Acetic Acid (buffer)as mobile phase. These conditions gave good separations and reproducible results (RSD = 7.2% - 9.1%). Standards and samples were run three times each.

The reported mp temperature of 2-hydroxyphenyl *N,N*-dimethylsulfonamide (**229**) was 67-70°C [75(a)] so this sulfonamide was synthesised by an alternative route (scheme 72)

which gave an identical m.p. (91°C – 92°C) and mass spectrum to the compound from the original rearrangement. The method is that described in the experimental section.



Scheme 72

The properties of the other rearranged products in this series (**230-237**) matched, where applicable, published values so no alternative synthesis was required. 2-Hydroxy-5-iodophenyl *N,N*-dimethylsulfonamide (**234**) gave a very small yield and again it must be assumed this is on account of steric hindrance.

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Properties of phenyl *N,N*-dimethylsulfonamides (1)

Table 13

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectrum (EI)
2-Hydroxyphenyl *N,N*-dimethylsulfonamide	White crystals	91°C-92°C	88% 2 Isomers	$C_8H_{11}NO_3S$	C,47.76; H,5.47; N,6.96	C,47.70; H,5.37; N,6.92	201 (M^+,19.7), 65 (100 base peak)
4-Hydroxypheny *N,N*-dimethylsulfonamide	White Crystals	97°C – 98°C	88% 2 Isomers	$C_8H_{11}NO_3S$	C,47.76; H,5.47; N,6.96	C,47.68; H,5.26; N,6.91	201 (M^+,15.0), 93 (100 base peak)
3-Fluoro-6-hydroxyphenyl *N,N*-dimethylsulfonamide	White Crystals	74.4°C-74.9°C	59%	$C_8H_{10}NO_3SF$	C,43.93; H,4.60; N,6.39	C,43.86; H,4.72; N6.7	219 (M^+, 14.9), 44 (100 base peak)
3-Chloro-6-hydroxyphenyl *N,N*-dimethy sulfonamide	White Crystals	62°C-63°C	69%	$C_8H_{10}NO_3SCl$	C,40.76; H,4.25; N,5.94	C,40.65; H,4.13; N,5.72	235 (M^+, 34.1), 63 (100 base peak)
3-Bromo-6-hydroxyphenyl *N,N*-dimethy sulfonamide	Pale Brown Crystals	71.5°C-72.5°C	72%	$C_8H_{10}NO_3SBr$	C,34.29; H,3.57; N,5.00	C,34.28; H,3.48; N,4.90	281 (M^+, 7.5), 63 (100 base peak)

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Properties of phenyl N,N-dimethylsulfonamides (2)

Table 14

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectrum (EI)
2-Hydroxy-5-iodophenyl *N,N*-dimethylsulfonamide							327 (M^+, 34.8), 63 (100 base peak)
2-Hydroxy-5-methylphenyl *N,.N*-dimethylsulfonamide	White Crystals	57°C – 58°C	49%	$C_9H_{13}NO_3S$	C,50.23; H,6.09; N,6.51	C,50.30; H,6.06; N,6.47	215 (M^+,28.6), 77 (100 base peak)
3-Ethyl-6-hydroxyphenyl *N,N*-dimethylsulfonamide	Pale Yellow Liquid	110°C-112°C @ $9X10^{-1}$ mm Hg.	48%	$C_{10}H_{15}NO_3S$	C,52.38; H,6.59; N,6.11	C,52.56; H,6.66; N,5.92	229 (M^+, 29.5), 77 (100 base peak)
2,4-Dichloro-3-hydroxyphenyl *N,N*-dimethylsulfonamide	White Crystals	158°C-159°C	76%	$C_8H_{10}NO_3SCl_2$	C,35.55; H,3.33; N,5.18	C,35.94; H,2.72; N,4.86	269 (M^+, 46.7), 62 (100 base peak)

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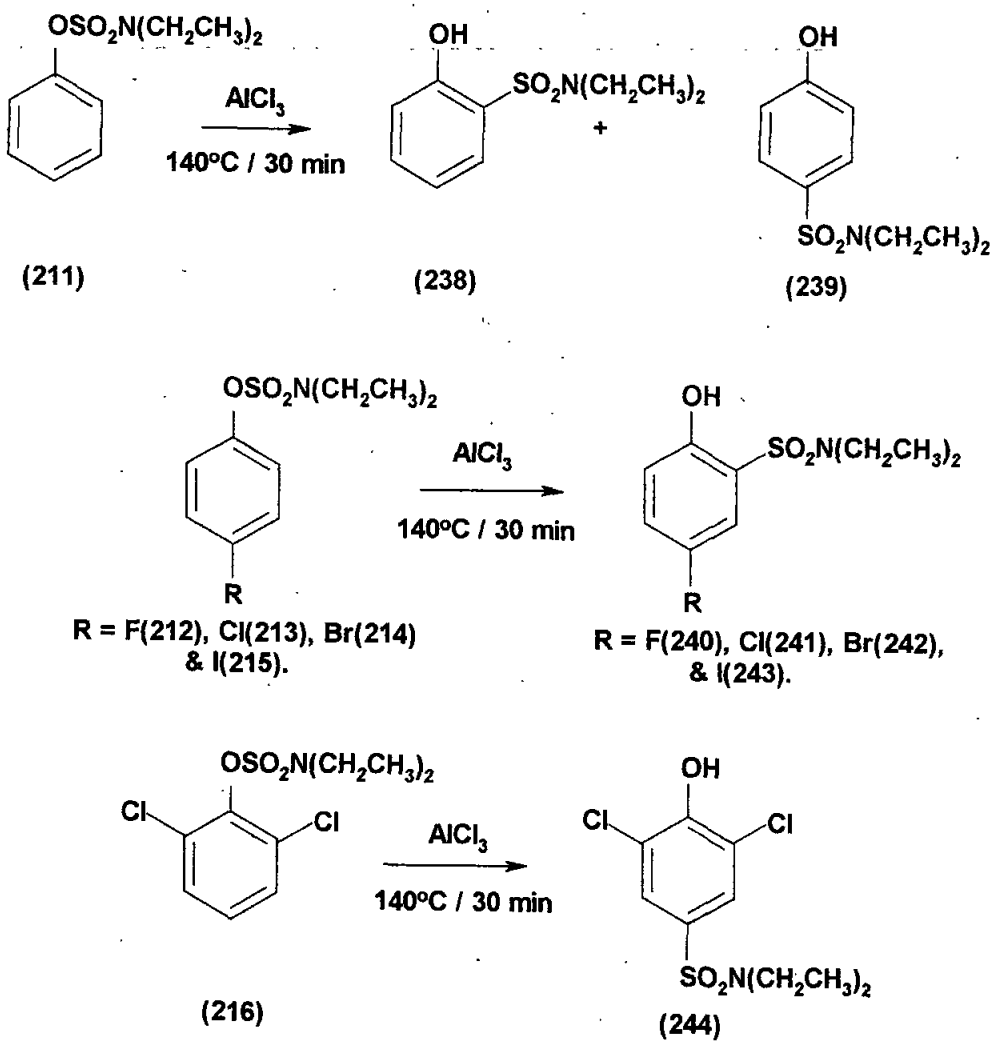
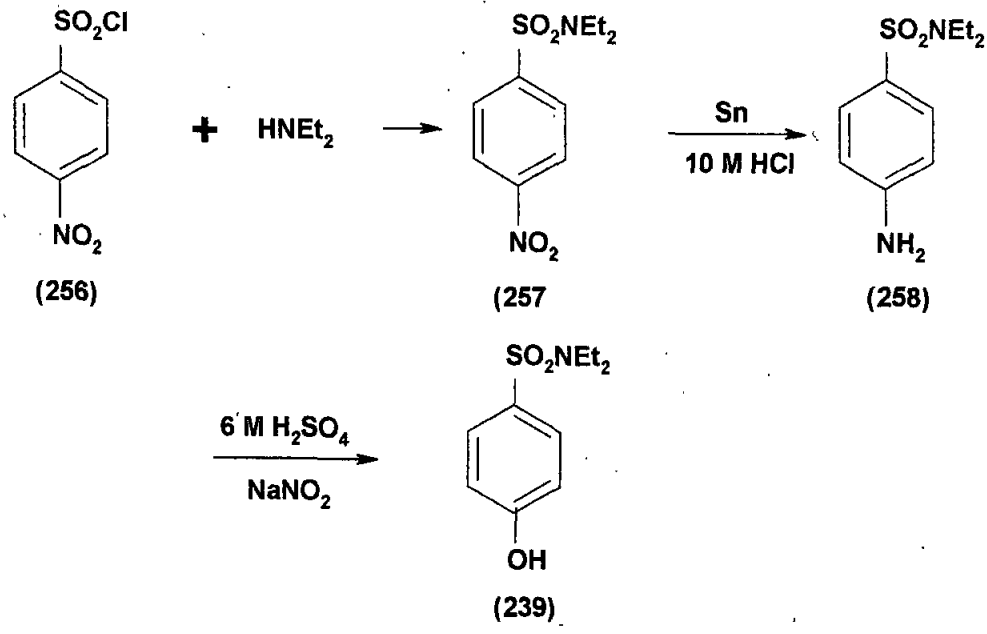


Scheme 73

In this series, the *N,N*-diethylsulfonamides there are seven rearranged products from six esters (scheme 73) in which only one is recorded as having been synthesised previously 4-hydroxyphenyl *N,N*-diethylsulfonamide.

This *para*-hydroxy compound (**239**), m.p. 94.5-95.5°C (lit.[72(c)] m.p. 68-70°C; lit.[74(a)] m.p. 49-50°C) was synthesised by an alternative method which gave m.p. (94.5°C – 95.5°C) and mass spectrum exactly as reported for the original rearranged product above. The method was that described in the experimental section and shown in scheme 74.



Scheme 74

Some of these sulfonamides were also used in the mechanistic crossover studies which will be described later. Again, the iodo compound (**243**) had very small yields. No large scale studies on ortho- / para- ratios and combined yields were carried out on products (**238** and **239**) as was done in the above section.

Properties of phenyl *N,N*-diethylsulfonamides (1)

Table 15

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectrum (EI)
2-Hydroxyphenyl *N,N*-diethylsulfonamide	Clear Liquid	136°C-139°C @ 1mm Hg.	86% 2 Isomers	$C_{10}H_{15}NO_3S$	C,52.40; H,6.55; N,6.11	C,52.04; H,6.06; N,5.78	229 (M^+,1.5), 58 (100 base peak)
4-Hydroxypheny *N,N*-diethylsulfonamide	White Crystals	94.5°C – 95.5°C	86% 2 Isomers	$C_{10}H_{15}NO_3S$	C,47.76; H,5.47; N,6.96	C,52.34; H,6.37; N,6.01	229 (M^+,1.6), 58 (100 base peak)
3-Fluoro-6-hydroxyphenyl *N,N*-diethylsulfonamide	Pale Yellow Liquid	99°C-101°C @ 1mm Hg.	69%	$C_{10}H_{14}NO_3SF$	C,48.57; H,5.71; N,5.66	C,48.38; H,5.76; N,5.77	247 (M^+, 13.9), 83 (100 base peak)
3-Chloro-6-hydroxyphenyl *N,N*-diethylsulfonamide	White Solid	29°C-31°C	67%	$C_{10}H_{14}NO_3SCl$	C,45.54; H,5.31; N,5.31	C,45.57; H,5.30; N,5.33	263 (M^+, 14.3), 72 (100 base peak)

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Properties of phenyl *N,N*-diethylsulfonamides (2)

Table 16

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectrum (EI)
3-Bromo-6-hydroxyphenyl *N,N*-diethylsulfonamide	Pale Yellow Liquid	139°C-142°C @ $8X10^{-1}$ mm Hg.	86%	$C_{10}H_{14}NO_3SBr$	C,38.96; H,4.55; N,4.55	C,39.36; H,4.60; N,4.56	309 (M^+, 10.1), 72 (100 base peak)
2-Hydroxy-5-iodophenyl *N,N*-diethylsulfonamide			≤ 0.1%				355 (M^+, 26.4), 63 (100 base peak)
2,4-Dichloro-3-hydroxyphenyl *N,N*-dimethylsulfonamide	White Crystals	200°C-203°C	69%	$C_{10}H_{13}NO_3SCl_2$	C,40.27; H,4.36; N,4.70	C,40.13; H,4.03; N,4.68	297 (M^+, 8.7), 225 (100 base peak)

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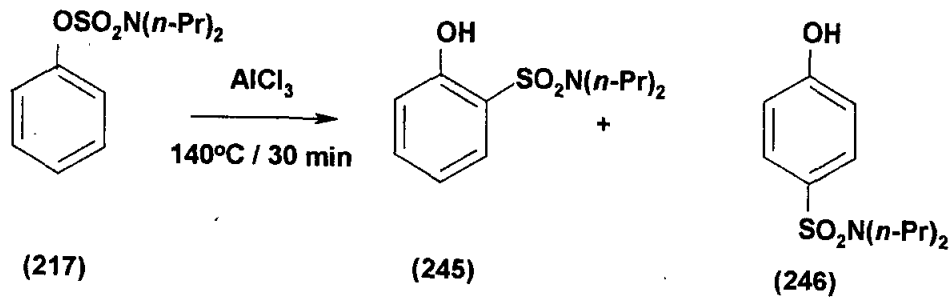
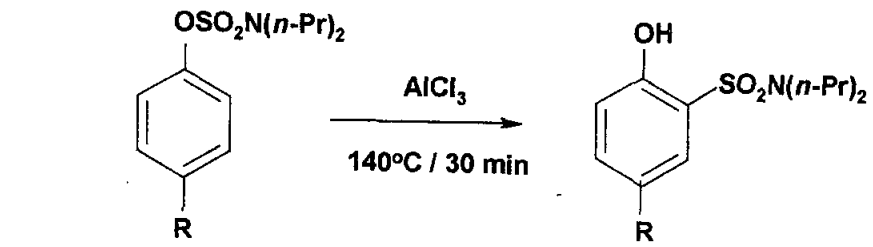
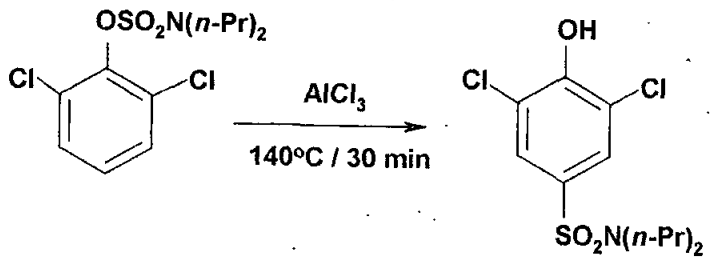
The final group of sulfamates (scheme 75) which were rearranged are the di-*n*-propyls (**217-220** and **223**), for some reason (**221** and **222**) did not rearrange very well and no extra time was spent trying to find out why. Only one of these compounds had been synthesised previously, the *ortho*-hydroxyphenyl *N,N*-di-*n*-propylsulfomamide but as the m.p. matched the published value alternative synthesis was not required. Yields were lower in this series compared to the previous two series, dimethyl and diethyl, which may be because of the bulkier group of atoms rearranging.



(217) (245) (246)



R = F(218), Cl(219) & Br(220) R = F(247), Cl(248) & Br(249),



(223) (250)

Scheme 75

Properties of phenyl *N,N*-di-*n*-propylsulfonamides (1)

Table 17

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectrum (EI)
2-Hydroxyphenyl *N,N*-di-*n*-propylsulfonamide	Pale Yellow Liquid	122°C-124°C @ 1 mm Hg.	77% 2 Isomers	$C_{12}H_{19}NO_3S$	C,56.03; H,7.39; N,5.45	C,55.19; H,7.14; N,5.22	257 (M^+,3.7), 72 (100 base peak)
4-Hydroxypheny *N,N*-di-*n*-propylsulfonamide	White Crystals	97°C – 98°C	77% 2 Isomers	$C_{12}H_{19}NO_3S$	C,56.03; H,7.39; N,5.45	C,55.18; H,7.20; N,5.33	257 (M+, 0.5), 72 (100 base peak)
3-Fluoro-6-hydroxyphenyl *N,N*-di-*n*-propylsulfonamide	Clear Yellow Liquid	127°C-129°C @ $6X10^{-1}$ mm Hg.	52%	$C_8H_{10}NO_3SF$			275 (M^+, 8.8), 72 (100 base peak)

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Properties of phenyl *N,N*-di-*n*-propylsulfonamides (2)

Table 18

Compound	Appearance	MP / BP	Yield	Formulae	Requires	Found	Mass Spectrum (EI)
3-Chloro-6-hydroxyphenyl *N,N*-di-*n*-propylsulfonamide	Pale Yellow Liquid	128°C-140°C @ $7X10^{-1}$ mm Hg.	36%	$C_{12}H_{18}NO_3SCl$	C,49.40; H,6.17; N,4.8	C,49.55; H,5.92; N,4.37	291 (M^+, 0.9), 72 (100 base peak)
3-Bromo-6-hydroxyphenyl *N,N*-di-*n*-propylsulfonamide	Pale Yellow Liquid	155°C-158°C @ 1.2 mm Hg.	44%	$C_{12}H_{18}NO_3SBr$	C,42.85; H,5.36; N,4.17	C,42.43; H,5.26; N,4.09	335 (M^+, 0.6), 72 (100 base peak)
2,4-Dichloro-3-hydroxyphenyl *N,N*-di-*n*-propylsulfonamide	White Crystals	131.5°C-135°C	44%	$C_{12}H_{17}NO_3SCl_2$	C,44.17; H,5.21; N,4.29	C,44.34; H,25.18; N,4.11	327 (M^+, N/A), 72 (100 base peak)

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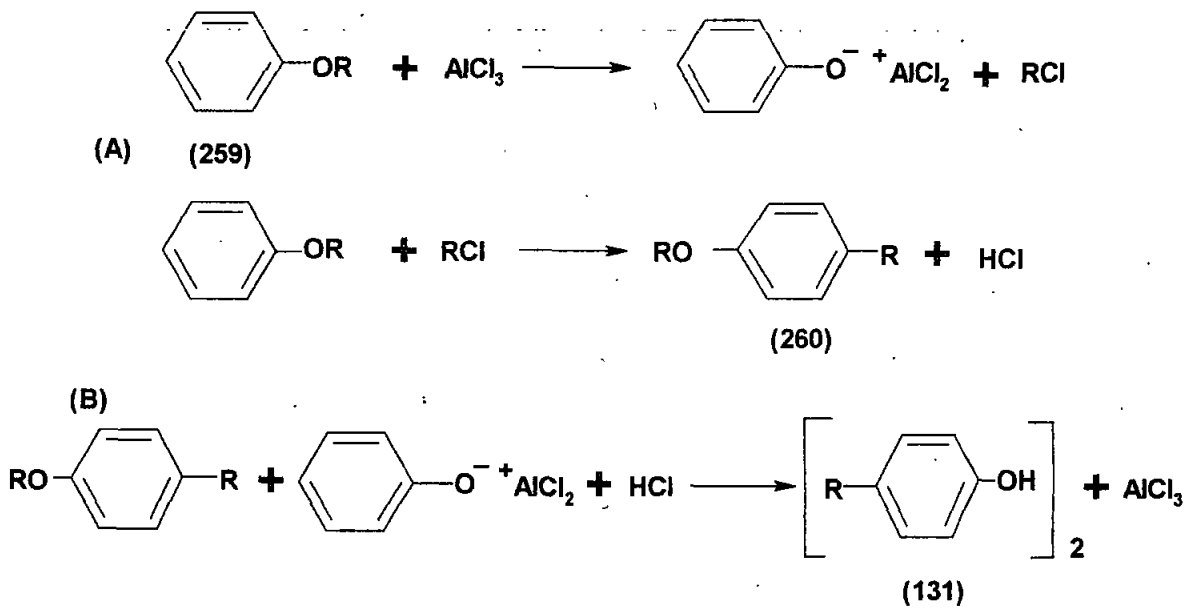
INTRODUCTION

Early Conceptions

The outcome of the Fries rearrangement is the formation of *o*-hydroxy and *p*-hydroxy ketones, in most cases both been formed simultaneously. In very exceptional instances *m*-hydroxy ketones can result when the influence exerted by the substituent of the phenolic part directs the reaction along this path [15 (d)].

From the earliest publication the reaction mechanism was always questionable, whether the Fries rearrangement is a inter- or a intramolecular process. Skraup and Poller[78], and later Cox [79], assumed the reaction to involve an intermolecular pathway in the course of which an acyl chloride is formed from the ester as an intermediate (pathway A scheme 76).

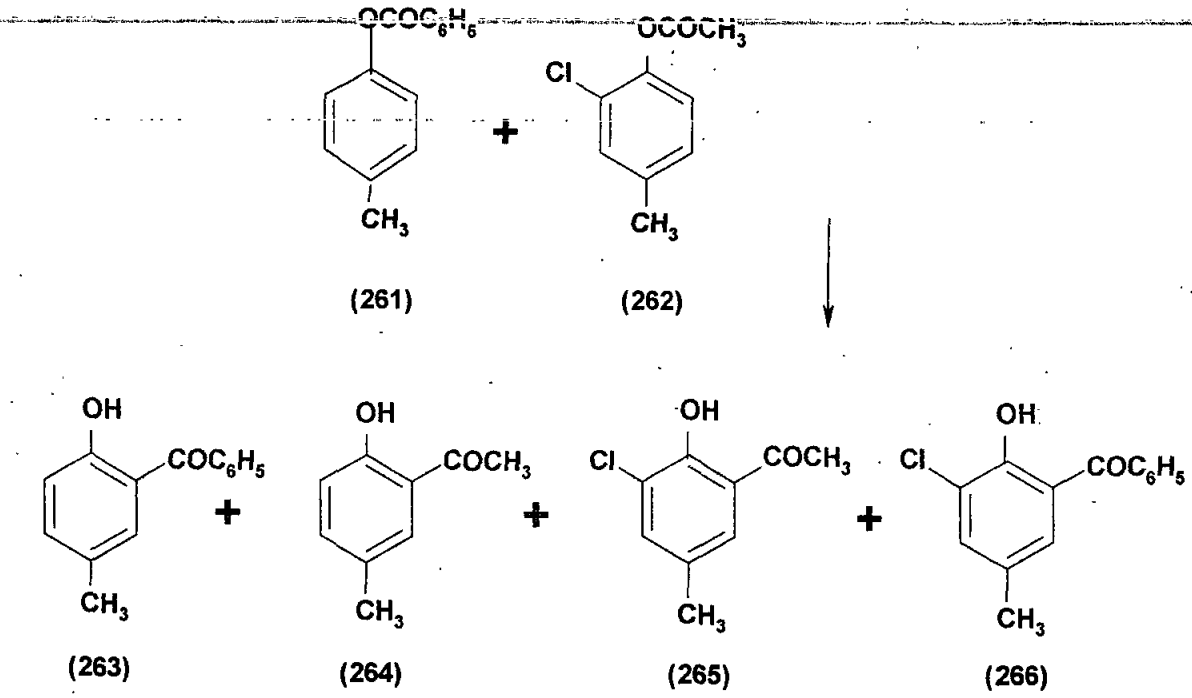
Rosenmund and Schnurr[80] were also of the opinion that an intermolecular rearrangement occurs, insofar as one molecule of the ester is acylated by a second one (pathway B scheme 76). They were the first to report the effect of temperature on the Fries rearrangement stating that at 25°C only the *p*-hydroxyketone (60%) was formed and at 175°C the *ortho*- isomer (95%) was the sole product.



Scheme 76

In order to verify this supposition a number of experiments were carried out wherein mixtures of two different phenolic esters were made to react with $AlCl_3$. The compounds resulting from such a reaction would constitute a proof for the intermolecularity of the process, were it not for the fact that transesterification or acyl interchange may also take place, as shown by experimental evidence published by von Auwers and Mauss [81 (a)] (scheme 77). However, crossover experiments such as these support multiple mechanistic pathways.

Other early exponents of the intermolecular pathway were Fries [1 (b)] himself, Schronberg and Mustafa [82 (a)] and Ogata *et al* [(b)].

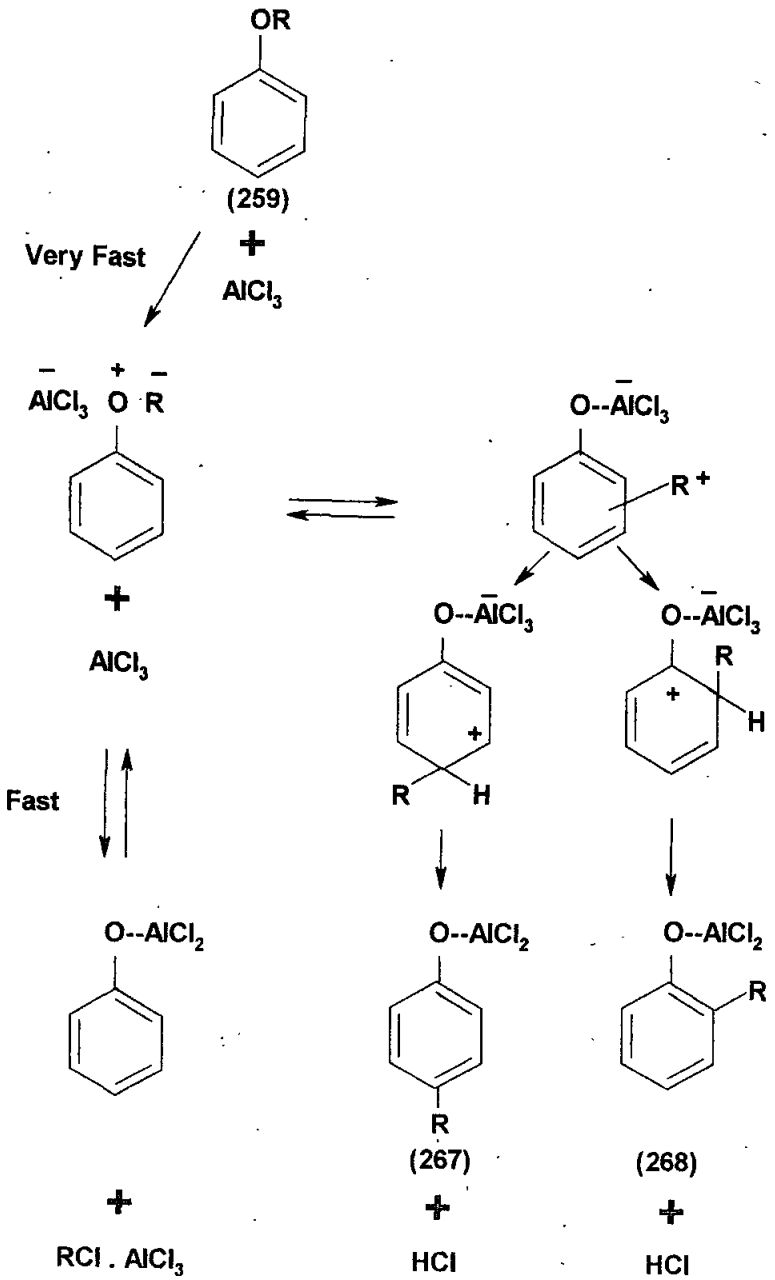


Scheme 77

von Auwers considered the intramolecular rearrangement to be proved by the fact that a Fries reaction does not lead to the same products as those formed in a Friedel-Crafts reaction carried out under the same conditions [97 (b)] These experiments, however, cannot be accepted as decisive since all the initial substances were not the same in the two reactions. Lal *et al* [83 (a)], Sen and Tiwari [(b)] and Baltzly *et al* [(c)] were early proponants of the intramolecular pathway (scheme 78).

It can be stated that these early researchers knew the course of the rearrangement to be influenced by a number of factors, the roles of which are difficult to evaluate in terms of reaction mechanisms and the substantial number of compounds or coordination

complexes and ions which are formed either simultaneously or consecutively in the course of the reaction.



Scheme 78

Cullinane[84 (a & b)] stated emphatically that the mechanism of the rearrangement was both inter- and an intramolecular *i.e.* a bimolecular reaction. In this he was supported by Klamann [(c)] among others. Even still to the present time there is indecision as to the exact mechanism of the Fries rearrangement, many aspects of the reaction may have an effect on the result e.g. the substrate ester or the reaction conditions of solvent or catalyst.

Sharghi and Eshghi [85] claim that an acylation reaction of *m*-cresol with 2-chlorobenzoic acid in polyphosphoric acid (PPA) occurred through a prior esterification followed by a Fries rearrangement to give benzophenones. As it is seen in scheme 79 they suggest the following possibilities:

1; The compound (**272**) can be obtained from the intramolecular rearrangement of ester (**271**) and also by the rearrangement of compound (**273**) (Gores's reversibility concept [86 (a & b)]).

2; The compound (**273**) can be obtained can be obtained from the intermolecular rearrangement of ester (**271**) and also by the transesterification of compound (**274**).

3; The compound (**274**) can be obtained from the esterification of compound (**273**) and also by the bimolecular rearrangement of ester (**271**).

4; The compound (**275**) can be obtained from the electrophilic aromatic substitution of compounds (**272**) and (**273**) and also from the rearrangement of compound (**274**).

In a separate experiment, when compound (**273**) was added to PPA and stirred for 24 hours at 70°C, the compounds (**272**) and (**274**) were formed in the ratio of 4 : 1 respectively. These results show that the conversion of compound (**273**) to compound (**272**) occurred with decomposition of compound (**273**) to m-cresol (**270**) and

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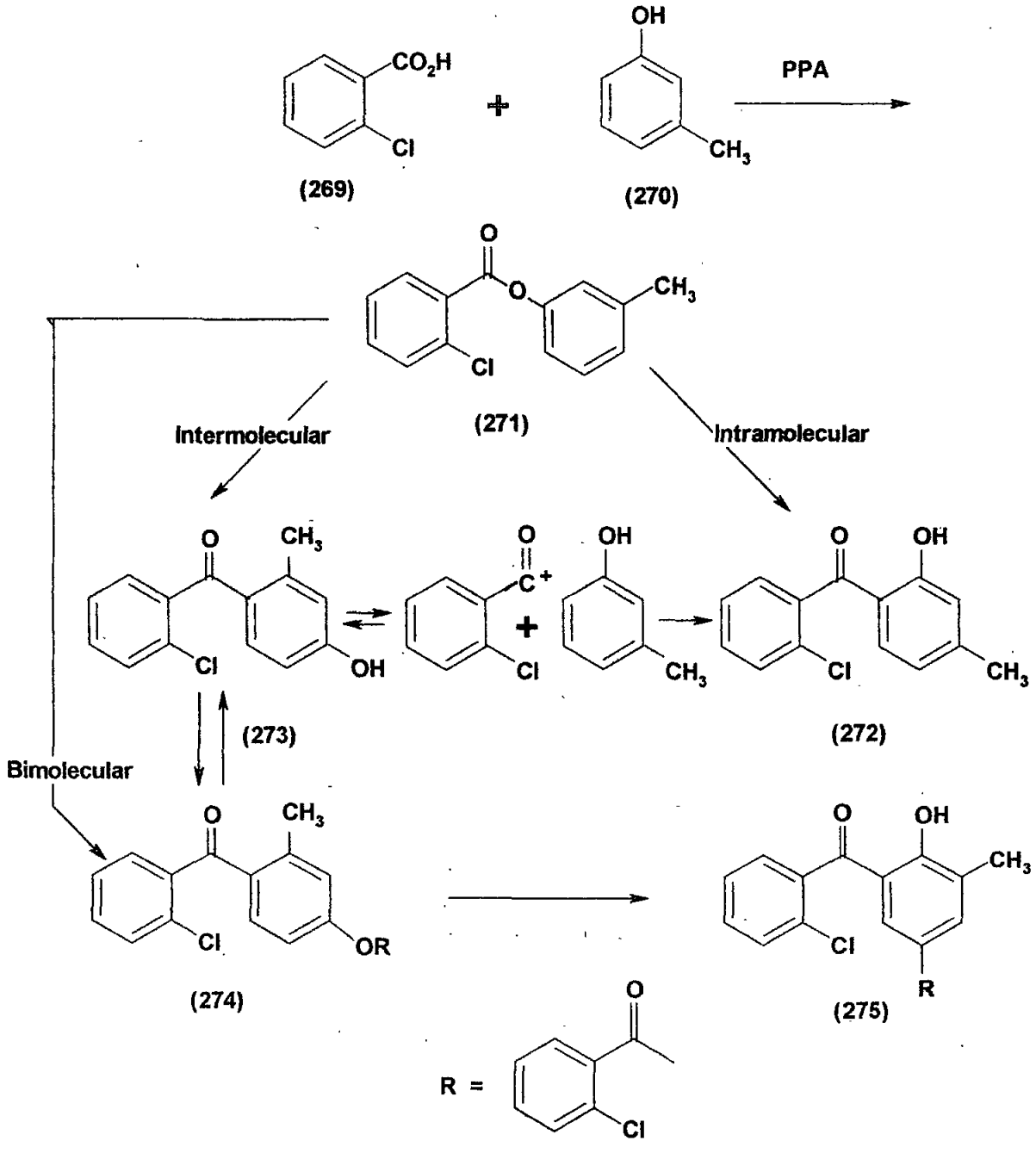
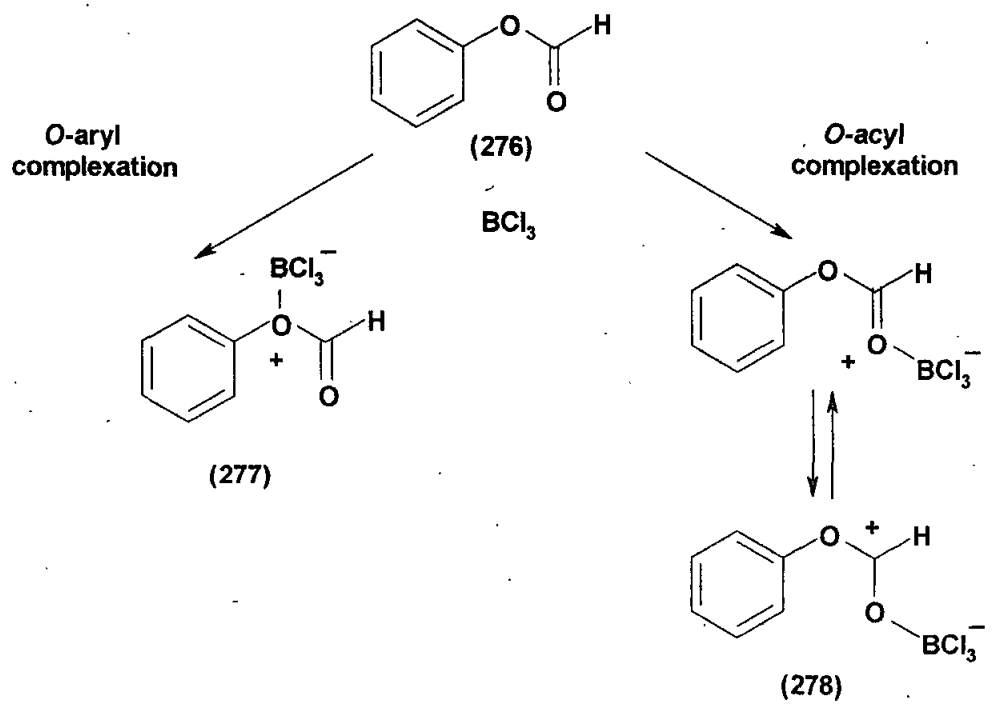
oxycarbonium ion followed by re-formation to compound (272) (Gore's reversibility concept). When compound (272) was treated with PPA at 130°C for 6 hours, the compound (275) was formed in 14% yield.



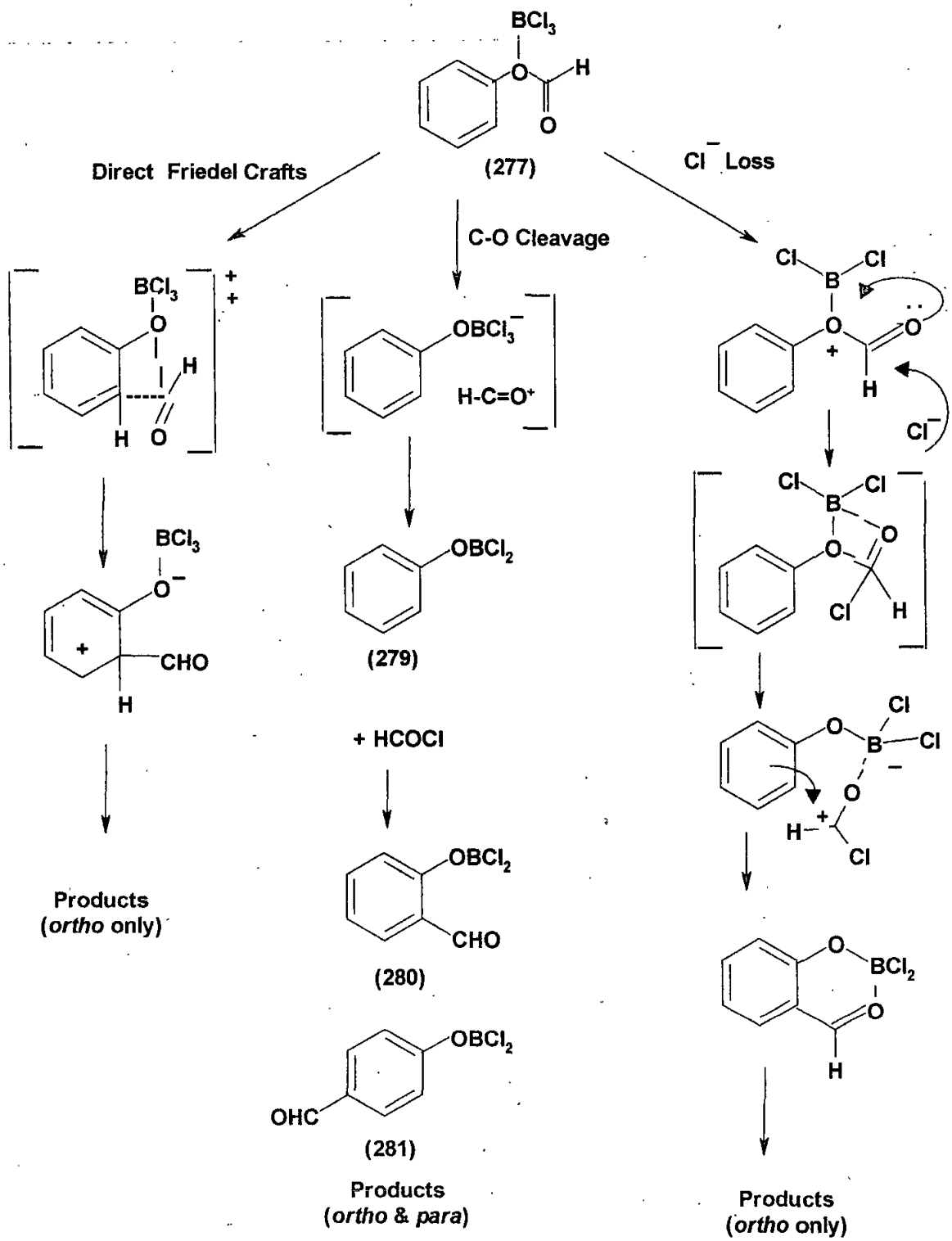
Scheme 79

Bagno *et al.*[87] in a recent publication have employed a very novel method to study the mechanistic pathways of the Fries rearrangement of aryl formats promoted by boron trichloride. They obtained ^{11}B NMR spectra during the course of the reaction and attempted to understand the ^{11}B spectra of reaction intermediates through the comparison with chemical shifts calculated by density functional theory (DFT).

Esters [RC(O)OR'] possess two sites capable of acting as a Lewis base, *i.e.* the oxygen of the alcolol residue (-**O**R') and the acyl oxygen, RC(**O**). Therefore, in principle BCl_3 may bind to the formate ester in each of the following ways, *O*-aryl or *O*-acyl complexation. These are the possible complexation modes of phenyl formate with BCl_3 (Scheme 80).



Scheme 80


BCl3
O
H
O
(277)
Direct Friedel Crafts
C-O Cleavage
Cl⁻ Loss
BCl3
O
H
H
O
+
+
OBCl3⁻
H-C=O+
Cl
B
Cl
O
O
H
Cl⁻
BCl3
O⁻
+
CHO
H
OBCl2
(279)
Cl
B
Cl
O
O
Cl
H
+ HCOCl
OBCl2
CHO
(280)
Cl
O
B
Cl
O
H
+
Cl
OBCl2
OHC
(281)
O
BCl2
O
H
Products
(ortho & para)
Products
(ortho only)
Products
(ortho only)

Scheme 81

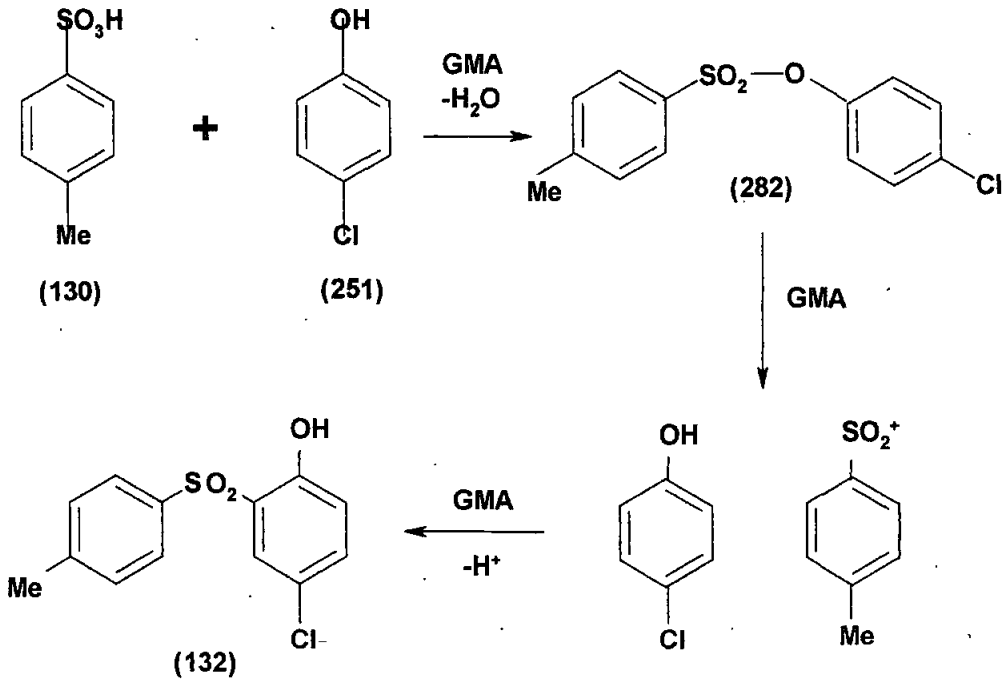
A straightforward way to represent the initial stage *i.e.* addition of the Lewis acid, is *O*-aryl complexation, which, although at times less favourable energy wise than the O-acyl protonation, leads essentially to C—O fission and to a loose complex between solvent and the acelium cation (scheme 81).

Sharghi and Shahsavari-Fard [40] whose publication was mentioned earlier, have demonstrated that the readily available and inexpensive reagent graphite / methanesulfonic acid (GMA) is very effective for the direct sulfonylation of phenol and naphthol derivatives with *p*-toluenesulfonic acid and for the thia-Fries rearrangement of aryl sulfonates. They also state that the formation of sulfonylphenols by the thia-Fries rearrangement of the aryl sulfonate occurs *via* an intermolecular mechanism.

The relative reactivity of the aromatic substrates in the GMA sulfonylation is consistent with a mechanism involving attack at the aromatic ring by a weak electrophilic reagent that requires an electron-rich ring. Appearently, the sulfonylium cation $MeC_6H_4SO_2^+$ is involved, which is very similar to the occurrence of the acyl cation $ArCO^+$ in the mechanism proposed for the formation of aromatic ketones in PPA [101].

The sulfonylation of 4-chlorophenol with *p*-toluenesulfonic acid in the presence of GMA was monitored by ^{1}H-NMR srectroscory under different reaction conditions. The results clearly established that, in all cases, first the aryl sulfonate was formed, which then decomposed to give the final product, sulfonylphrnol. The rate of formation increased with increased temperature.

The following mechanism of the sulfonylation reaction is suggested: the phenol is first converted to the arylsulfonate by reaction with p-toluenesulfonic acid. The arylsulfonate subsequently undergoes rapid intermolecular decomposition in the presence of GMA (thia-Fries rearrangement) to produce the sulfonylium cation $MeC_6H_4SO_2^+$ and the phenol, which combine to form the sulfonylphenol (scheme 82).



Scheme 82

Studies in catalysis and catalytic ratios were carried out on the target ester, phenyl *N,N*-dimethylsulfamate (**195**) using a number of catalysts. As this sulfamate is a liquid, this means the mixture with $AlCl_3$ gives a homogeneous reaction. Some data on $AlCl_3$ at a catalytic ratio of 1 : 1.2 is shown in a previous section tables 11 and 12. Here these experiments will be continued.

Using 200-250 mg of ester and an initial molar ratio of ester to $AlCl_3$ of 1 : 0.5 the rearrangements were carried out at various temperatures which were maintained in an oil bath (± 5°C) to give the results which are tabulated later. Also 1 : 1, 1 : 1.5, 1 : 2 and 1 : 2.5 molar ratios were studied.

These experiments on yield and product ratio were quantified by GC-FID using the method of internal standard, the internal standards used were *n*-tetradecane (0.21 mmolar) and *n*-octadecane (0.87 mmolar). Phenol (1.14 mmolar), phenyl *N,N*-dimethylsulfamate (1.08 mmolar), 2-hydroxyphenyl *N,N*-dimethylsulfonamide (0.55 mmolar) and 4-hydroxyphenyl *N,N*-dimethylsulfonamide (1.81 mmolar) These were pure samples of the sulfamate and the two sulfonamides which had previously been purified and characterised. Standards and samples were run three times and standards were re-analysed after every five sets of samples. Phenol and un-rearranged ester were not recorded for these rearrangements.

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Twenty four rearrangements of the sulfamate ester phenyl *N,N*-dimethylsulfamate (**195**) in a 1 : 0.5 molar ratio with the catalyst $AlCl_3$ were carried out. Four experiments at 15, 30, 60 and 120 min for each of the temperatures 100°C, 110°C, 120°C, 130°C, 140°C and 150°C were carried out in the oil bath which was maintained at the stated temperature ± 5°C. All of these twenty four samples were in the range of 200 to 250 mg of ester, 1 to 1.25 mmol, which was mixed thoroughly with the 0.5 to 0.625 mmol of the catalyst. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of twenty four rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 19 and 20).

Seventeen rearrangements of the sulfamate ester phenyl *N,N*-dimethylsulfamate (**195**) in a 1 : 1 molar ratio with the catalyst $AlCl_3$ were carried out. Four experiments at 15, 30, 60 and 120 min for the temperatures 100°C. Three experiments each at 15, 30 and 60 min for the temperatures 110°C, 120°C, 130°C and 140°C. One rearrangement at 150°C for 30 min with them all being carried out in the oil bath which was maintained at the stated temperature ± 5°C. All of these seventeen samples were in the range of 200 to 250 mg of ester, 1 to 1.25 mmol, which was mixed thoroughly with the 1 to 1.25 mmol of the catalyst. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of seventeen rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 21 and 22).

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Eighteen rearrangements of the sulfamate ester phenyl *N,N*-dimethylsulfamate (**195**) in a 1 : 1.5 molar ratio with the catalyst $AlCl_3$ were carried out. Three experiments each at 15, 30 and 60 min for the temperatures 100°C, 110°C, 120°C, 130°C, 140°C and 150°C All the experiments were carried out in the oil bath which was maintained at the stated temperature ± 5°C. All of these eighteen samples were in the range of 200 to 250 mg of ester, 1 to 1.25 mmol, which was mixed thoroughly with the 1.5 to 1.875 mmol of the catalyst. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of eighteen rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 23 and 24).

Fourteen rearrangements of the sulfamate ester phenyl *N,N*-dimethylsulfamate (**195**) in a 1 : 2 molar ratio with the catalyst $AlCl_3$ were carried out. Three experiments each at 15, 30 and 60 min for the temperatures 100°C, 110°C, 120°C and 130°C and at 15 min for 140°C and 150°C. All the experiments were carried out in the oil bath which was maintained at the stated temperature ± 5°C. All of these fourteen samples were in the range of 200 to 250 mg of ester, 1 to 1.25 mmol, which was mixed thoroughly with the 2 to 2.5 mmol of the catalyst. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of fourteen rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 25 and 26).

Eleven rearrangements of the sulfamate ester phenyl *N,N*-dimethylsulfamate (**195**) in a 1 : 2.5 molar ratio with the catalyst $AlCl_3$ were carried out. Two experiments each at 30 and 60 min for the temperatures 80°C and 100°C, at 15 and 30 min for 120°C, at 60 min for 130°C and at 15, 30 and 60 min for 140°C. Finally there was one at 15 min for 150°C. All the experiments were carried out in the oil bath which was maintained at the stated temperature ± 5°C. All of these eleven samples were in the range of 200 to 250 mg of ester, 1 to 1.25 mmol, which was mixed thoroughly with the 2.5 to 3.125 mmol of the catalyst. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of eleven rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 27 and 28).

A number of investigations, twenty six in total, with different catalysts were carried out. Phenyl *N,N*-dimethylsulfamate was heated with a 1 : 1 molar ratio of various catalysts to 140°C ± 5°C for 30 mins in an oil bath. Some reactions were also carried out using nitrobenzene and chlorobenzene as solvents. There were four rearrangements with $TiCl_4$, four with $FeCl_3$, two with $ZnCl_2$, two with $CuCl_2$, two with $SnCl_2$ and one with $NiCl_2$. Titanium tetrachloride and ferric chloride were the only catalysts to have any success. There were three reactions with 1molar $AlCl_3$ in nitrobenzene, two with 1 molar $FeCl_3$ in nitrobenzene, two with 1 molar $AlCl_3$ in chlorobenzene and two with 1 molar $FeCl_3$ in chlorobenzene, all of which gave very little rearrangement. Finally there were two attempts to rearrange the ester on it's own without any catalyst at 140°C for 30 min

without success. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of twenty six rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 29 and 30).

There were a further number of experiments carried out using $FeCl_3$ as the Lewis acid catalyst. This catalyst was used because it gave quite good results for thia-Fries rearrangements in the previous set of experiments. Five reactions of the sulfamate ester phenyl *N,N*-dimethylsulfamate (**195**) in a 1 : 2.5 molar ratio with the catalyst were carried out. Two experiments each at 30 and 60 min for the temperatures 80°C and 100°C, and at 15 min for 140°C. All the experiments were carried out in the oil bath which was maintained at the stated temperature ± 5°C. All of these eleven samples were in the range of 200 to 250 mg of ester, 1 to 1.25 mmol, which was mixed thoroughly with the 2.5 to 3.125 mmol of the catalyst. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results of this set of eleven rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (tables 31 and 32).

Some further rearrangements were carried out later to check on reproducibility of the reaction. These again involved the ester, phenyl *N,N*-dimethylsulfamate with $AlCl_3$ and $FeCl_3$ as catalysts in a 1 : 1 molar ratio at 140°C. All the experiments were carried out in

the oil bath which was maintained at the stated temperature ± 5°C. Two reactions for each of the catalysts were carried out at 30 min and at 60 min, a total of eight rearrangements. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. All of the reactions showed small quantities of phenol ≤ 1% and there was very little of the ester which was not rearranged. The results of this set of eight rearrangements were analysed and tabulated to give the *ortho / para* ratios and the total of the ester rearranged (table 33).

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To determine the molecularity of the thia-Fries rearrangement a number of crossover experiments were carried out. According to the literature this is the method of choice to ascertain whether the reaction is inter-, intra-, or bimolecular.

For the first set of crossover experiments, phenyl *N,N*-dimethylsulfamate (**195**) with 4-chlorophenol (**251**) and 4-chlorophenyl *N,N*-dimethylsulfamate (**197**) with phenol (**141**), a single set of standards covered the analysis of both reactions. The standards were phenol, 4-chlorophenol, phenyl *N,N*-dimethylsulfamate, 2-hydroxyphenyl *N,N*-dimethylsulfonamide (**229**), 4-hydroxyphenyl *N,N*-dimethylsulfonamide (**230**), 4-chlorophenyl *N,N*-dimethylsulfamate and 3-chloro-6-hydroxyphenyl *N,N*-dimethylsulfonamide (**232**). No internal standard was included with these standards so consequently the results are shown as molar ratios to each other. Stability tests were carried out on the three sulfonamides involved. They were heated in a 1 : 1.1 molar ratio with $AlCl_3$ at 140°C for 90 min. In analysis by GC-MS nor further rearrangement, reversal to sulfamate or breakdown was observed.

200 mg of phenyl *N,N*-dimethylsulfamate was heated with an equivalent of 4-chlorophenol and 2.2 equivalents of the catalyst $AlCl_3$ to 140°C for 90 min. The sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above and the results as a ratio to each other. (**141**) 1 : (**251**) 4 : (**232**) 1 : (**230**) 4.5 : (**237**) 1. They are tabulated later.

200 mg of 4-chlorophenyl *N,N*-dimethylsulfamate was heated with an equivalent of phenol and 2.2 equivalents of the catalyst $AlCl_3$ to 140°C for 90 min. The sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above and the results as a ratio to each other. (**141**) 12 : (**251**) 12 : (**195**) 1 (**229**) 3 : (**230**) 46 : (**197**) 1.5 : (**237**) 2. They are tabulated later.

The second set of crossover experiments has 4-methylphenyl *N,N*-dimethylsulfamate (**200**) with 4-chlorophenol (**251**) and 4-chlorophenyl *N,N*-dimethylsulfamate (**197**) with 4-methylphenol (**283**), a single set of standards covered the analysis of both reactions. The standards were 4-methylphenol, 4-chlorophenol, 4-methylphenyl *N,N*-dimethylsulfamate, 2-hydroxy-5-methylphenyl N,N-dimethylsulfonamide (**235**) 4-chlorophenyl *N,N*-dimethylsulfamate and 3-chloro-6-hydroxyphenyl *N,N*-dimethylsulfonamide (**232**). No internal standard was included with these standards so consequently the results are shown as molar ratios to each other. Stability tests were carried out on the two sulfonamides involved. They were heated in a 1 : 1.1 molar ratio with $AlCl_3$ at 140°C for 90 min. In analysis by GC-MS nor further rearrangement, reversal to sulfamate or breakdown was observed.

200 mg of 4-methylphenyl *N,N*-dimethylsulfamate was heated with an equivalent of 4-chlorophenol and 2.2 equivalents of the catalyst $AlCl_3$ to 140°C for 90 min. The sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described

above and the results as a ratio to each other. (**283**) 4 : (**251**) 14 : (**200**) 0.25 : (**235**) 12 : (**197**) 0.5 : (**232**) 5.5. They are tabulated later.

200 mg of 4-chlorophenyl *N,N*-dimethylsulfamate was heated with an equivalent of 4-methylphenol and 2.2 equivalents of the catalyst $AlCl_3$ to 140°C for 90 min. The sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above and the results as a ratio to each other. (**141**) 11 : (**251**) 17 : (**200**) 1 : (**235**) 14 : (**197**) 2 : (**232**) 6. They are tabulated later.

Two compounds were used in a number of crossover experiments, 4-bromophenyl *N,N*-dimethylsulfamate (**198**) and 4-chlorophenyl *N,N*-diethylsulfamate (**213**). These experiments were carried out over a range of temperatures and for various times. Tests were carried out on the two above esters and also on 4-bromophenyl *N,N*-diethylsulfamate (**214**) and 4-chlorophenyl *N,N*-di-*n*-propylsulfamate (**219**) to estimate their reaction speeds *i.e.* the rate of rearrangement from ester to sulfonamide, over set times and at certain temperatures. These reactions were homogeneous because all of the above esters are liquid at room temperature. The initial two compounds above were found to have rates of rearrangement quite close to each other at 140°C.

Twelve samples of 100 mg each of 4-bromophenyl *N,N*-dimethylsulfamate (**198**) and 4-chlorophenyl *N,N*-diethylsulfamate (**213**) were heated seperately with $AlCl_3$ in a 1 : 1.1 molar ratio at 140°C for varying lengths of time from 0.25 min to 30 min. These twenty

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four reactions were quenched with 5 ml 1 molar HCl and the mixture was made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID against the set of standards below. Analysis of the results confirmed these two sulfamates to be the most suitable for the crossover investigations.

A set of standards which includes the following, along with *n*-tetradecane, *n*-heptadecane and *n*-octadecane were made up. The alkanes were included as internal standards and all the concentrations were in the 0.2 mmolar region. 4-Chlorophenol (**251**), 4-bromophenol (**284**), 4-chlorophenyl *N,N*-dimethylsulfamate (**195**), 3-chloro-6-hydroxyphenyl *N,N*-dimethylsulfamate (**232**), 4-bromophenyl *N,N*-dimethylsulfamate (**198**), 3-bromophenyl *N,N*-dimethylsulfonamide (**233**), 4-chlorophenyl *N,N*-diethylsulfamate (**213**), 3-chloro-6-hydroxyphenyl *N,N*-diethylsulfonamide (**241**), 4-bromophenyl *N,N*-diethylsulfamate (**214**) and 3-bromophenyl-6-hydroxyphenyl *N,N*-diethylsulfonamide (**242**) made up the remainder of the standards.

Six samples of 1 mmol each of 4-bromophenyl *N,N*-dimethylsulfamate (**198**) and 4-chlorophenyl *N,N*-diethylsulfamate (**213**) were heated with $AlCl_3$ in a 1 : 1 : 2.2 molar ratio at 140°C for 5, 10, 15, 20, 25 and 30 min. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results show transesterification as there were the two non starting esters (**197**) and (**214**) and some of their rearranged products. All of the results are tabulated later.

Further crossover experiments were carried out with the same two starting esters (**198**) and (**213**) with $AlCl_3$ and at the same molar ratios of 1 : 1 : 2.2. There were eight different reactions in this set, 1, 2, 5, 10, 15, 20, 25, and 30 minuets in duration and all at 80°C. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results show transesterification as there were the two non starting esters (**197**) and (**214**) and some of their rearranged products. All of the results are tabulated later.

A third set of experiments were carried out using the same esters (**198**) and (**213**), the same catalyst, $AlCl_3$ the same molar ratio 1 : 1 : 2.2 and no solvent. These experiments were carried out at 100°C for periods of time 30, 40, 60 and 120, min as well as 10 and 20 hr. Each sample was quenched with 5 ml of 1 molar HCl at the set time and then when it had cooled, made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID using the standards described in the above paragraph. The results show transesterification as there were the two non starting esters (**197**) and (**214**) and some of their rearranged products. All of the results are tabulated later.

The rearrangement of the individual esters (**198**) and (**213**) was also carried out at the same temperature of 100°C and at a 1 : 1.1 molar ratio to the catalyst $AlCl_3$ for the same periods of time. Analysis was again by GC-FID using the same standards and the results are compared and tabulated.

A number of other crossover experiments were examined, not so much to study the actual mechanism but more to observe what transesterification or transsulfamoylation was occuring. Phenyl *N,N*-dimethylsulfamate was heated with aniline and $AlCl_3$ as catalyst in a 1 : 1 : 2.2 molar ratio at 140°C for 90 min. The products of this reaction as separated and identified by GC-MS were phenol ≈ 5% , the starting ester (**195**) ≈ 50%, both of the rearranged sulfonamides (**229**) ≈ 25% and (**230**) ≈ 3% and a compound anilino *N,N*-dimethylsulfonamide ≈ 4% as deduced from it's mass spectra. Quantitation is purely an estimation from the peak areas of the chromatograph.

This reaction was also carried out using 2 molar $AlCl_3$ in nitrobenzene for 90 min at 140°C. The result was ≈ 90% of the ester remained and ≈ 5% of the *ortho*- sulfonamide with none of the *para*- product showing. ≈ 2% each of phenol and aniline *N,N*-dimethylsulfonamide compound were also detected.

200 mg of phenyl *N,N*-dimethylsulfamate was heated with an equivalent of pyrrole and 2.2 equivalents of $AlCl_3$ to 120°C for 4 hr. No transsulfamoylation could be detected by GC-MS with only the starting ester, phenol and the two rearrangement sulfonamides being found on the chromatograph.

100 mg of phenol and an equivalent of *N,N*-dimethylsulfamoylchloride were heated to 140°C for 60 min with 50 ml acetonitrile. The reaction mixture was analysed by GC-MS and apart from the two starting materials, *N,N*-dimethylsulfamoylchloride (≈ 25%) and phenol (≈ 20%) , phenyl *N,N*-dimethylsulfamate (≈ 3%), 4-hydroxyphenyl *N,N*-

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dimethylsulfonamide (≈ 30%) and an unknown compound with an M^+ of 243 (≈ 20%) were found. This reaction could be studied further as a one pot synthesis of the *para*-isomer.

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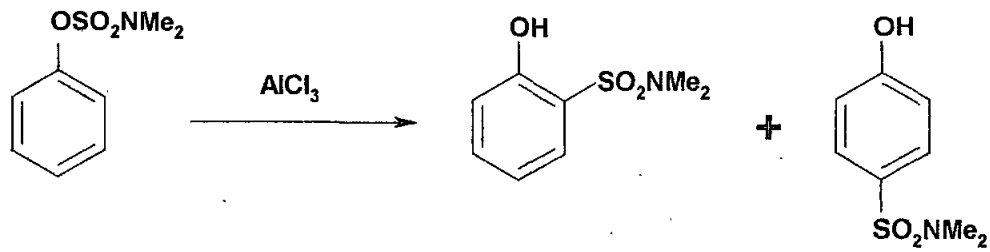
Since the early days [1 (b), 2 (a)] of the Fries reaction, the rearrangement of phenolic esters to 2- and 4-hydroxy ketones has been accepted that at low temperature the reaction gives the *para-* compound while at higher temperatures the reactions ($\geq 120^{\circ}C$) favour the *ortho-* compound. This theorem has been widely expounded across most of the literature over the last 100 years so it is quite a surprise that the above data does not agree. Tables 36, 38, 40, 42, 44 and 46 all show that an increase in time of reaction and an increase in temperature of reaction give a decrease in the *ortho / para* isomeric ratio, *i.e.* the higher temperature increases the *para-* product.

For the present studies phenyl *N,N*-dimethylsulfamate was reacted with $AlCl_3$ in the following ratios 1 : 0.5, 1 : 1, 1 : 1.5, 1 : 2 and 1 : 2.5. These investigations were carried out at varying temperatures using an oil bath (± 5_oC), and for different lengths of time. The quantity of the *ortho-* and *para-* rearranged products of phenyl *N,N*-dimethylsulfamate together with the ortho / para ratio is temperature and time dependant. The reaction conditions are as stated in the experimental above.



(195) (229) (230)

Scheme 83

The *ortho* / *para* ratio obtained in the homogeneous rearrangement of phenyl *N,N*-dimethylsulfamate (195) with $AlCl_3$ at 1 : 0.5 to give 2- and 4- hydroxyphenyl *N,N*-dimethylsulfonamide.

Table 19

	Time (min)			
Temp (°C)	**15**	**30**	**60**	**120**
100	2.6	1.8	1.9	2.1
110	1.9	1.8	1.7	1.6
120	2.1	1.4	2.1	1.6
130	2.4	1.3	1.6	1.4
140	2.5	1.1	1.6	1.2
150	1.6	1.0	1.1	0.9

The total yield of 2- and 4-hydroxy *N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

Table 20

	Time (min)			
Temp (°C)	**15**	**30**	**60**	**120**
100	22	23	27	39
110	33	35	26	41
120	41	37	39	40
130	39	43	49	47
140	40	49	54	59
150	52	61	58	67

The *ortho* / *para* ratio obtained in the homogeneous rearrangement of phenyl *N,N* dimethylsulfamate (195) with $AlCl_3$ at 1 : 1 to give 2- and 4- hydroxyphenyl *N,N*-dimethylsulfonamide

Table 21

	Time (min)			
Temp (°C)	**15**	**30**	**60**	**120**
100	0.8	0.9	0.7	1.0
110	0.6	0.7	0.6	
120	0.5	0.4	0.5	
130	0.9	0.5	0.4	
140	1.0	0.5	0.4	
150	1.6			

Total yield of 2- and 4-hydroxy *N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

Table 22

	Time (min)			
Temp (°C)	**15**	**30**	**60**	**120**
100	36	52	58	93
110	61	64	67	
120	67	68	69	
130	78	74	76	
140	88	87	88	
150	98			

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The *ortho* / *para* ratio obtained in the homogeneous rearrangement of phenyl *N,N* dimethylsulfamate (195) with $AlCl_3$ at 1 : 1.5 to give 2- and 4- hydroxyphenyl *N,N*-dimethylsulfonamide

Table 23

	Time (min)		
Temp (°C)	15	30	60
100	0.7	0.8	0.7
110	0.9	0.5	0.6
120	0.7	0.7	0.5
130	0.7	0.6	0.6
140	0.5	0.6	0.4
150	0.5	0.5	0.4

Total yield of 2- and 4-hydroxy *N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

Table 24

	Time (min)		
Temp (°C)	15	30	60
100	60	65	73
110	73	69	77
120	79	78	86
130	89	92	79
140	88	90	92
150	92	91	87

The *ortho* / *para* ratio obtained in the homogeneous rearrangement of phenyl *N,N* dimethylsulfamate (195) with $AlCl_3$ at 1 : 2 to give 2- and 4- hydroxyphenyl *N,N*-dimethylsulfonamide

Table 25

	Time (min)		
Temp (°C)	**15**	**30**	**60**
100	0.8	0.5	0.4
110	0.6	0.5	0.5
120	0.6	0.4	0.4
130	0.7	0.5	0.4
140	0.5		
150	0.4		

Total yield of 2- and 4-hydroxy *N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

Table 26

	Time (min)		
Temp (°C)	**15**	**30**	**60**
100	75	79	83
110	78	85	90
120	80	91	89
130	92	94	93
140	91		
150	94		

The *ortho* / *para* ratio obtained in the homogeneous rearrangement of phenyl *N,N* dimethylsulfamate (195) with $AlCl_3$ at 1 : 2.5 to give 2- and 4- hydroxyphenyl *N,N*-dimethylsulfonamide

Table 27

	Time (min)		
Temp (°C)	**15**	**30**	**60**
80		0.9	1.0
100		0.9	1.1
120	0.8	0.7	1.3
130			
140	1.5	0.4	1.3
150	0.9		

Total yield of 2- and 4-hydroxy *N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

Table 28

	Time (min)		
Temp (°C)	**15**	**30**	**60**
80		25	49
100		80	94
120	76	90	
130			30
140	39	60	26
150	90		

As already stated, these experiments on yield and product ratio were quantified by GC-FID using the method of internal standard, the internal standards used were *n*-tetradecane and *n*-octadecane. The method is the same as has already been described above using pure samples of the sulfamate and both sulfonamides. These conditions gave good reproducible results for both standards and samples (n = 3, RSD = 8.2% - 12.3%).. Phenol and remaining ester were not recorded but the total of both can be deduced.

There are no publications found on the thia-Fries rearrangement of sulfamate esters in the literature apart from the one paper by the present group. With no precedent on these particular esters it can only be assumed that all ester do not rearrange in the same manner and that with phenyl *N,N*,-dialkylsulfamates the higher reaction temperature favours the *para*-isomer.

Over many years a number of groups working at the Fries rearrangement and in particular a group led by Robert Martin[88 (a and b)], claim that why higher temperatures and longer reaction times favour the *ortho*-isomer is because "the *p*-hydroxyarylketones rearrange further to the *o*-hydroxyarylketones with $AlCl_3$". This can not be the case for the above sulfamates because as already stated, 2- and 4-hydroxyphenyl *N,N*-dimethylsulfonamide were heated with $AlCl_3$ to 140°C for 30 min and were found to be stable with no rearrangement.

The same group[89] claim that *ortho / para* ratio also depends on the on the catalysts used, boron trifluoride favours the *para*- while titanium and tin tetrachloride favours the *ortho*-

product. The above experiments do not agree with that statement as far as $TiCl_4$ is concerned, the four experiments all favour the *para*-sulfonamide. Of the Lewis acid catalysts investigated, $AlCl_3$, $FeCl_3$ and $TiCl_4$ were the only ones which resulted in any appreciable amounts of rearranged sulfonamides. A number of other experiments with different catalysts were carried out, phenyl *N,N*-dimethylsulfamate was heated with a 1 : 1 molar ratio of the various catalysts to 140°C ± 5°C for 30 min in an oil bath.

Catalyst / Sulfamate Ratio = 1, 140°C, 30 Min

Table 29

Catalyst	2-Hydroxyphenyl *N,N*-dimethylsulfonamide	4-Hydroxyphenyl *N,N*-dimethylsulfonamide	*Ortho/Para* Ratio	% Ester Rearranged
$TiCl_4$	38%	42%	0.9	80
"	17%	59%	0.3	76
"	19%	60%	0.3	79
"	26%	41%	0.6	67
$FeCl_3$	35%	28%	1.3	99
"	22%	55%	0.4	77
"	26%	54%	0.5	95
"	24%	62%	0.4	86
$ZnCl_2$	1%	6%	0.1	7
"	0	1	N/A	1
$CuCl_2$	1%	4%	0.2	5
"	0	1%	N/A	1
$NiCl_2$	2%	2%	1.0	4

As can be seen from the data, only $AlCl_3$ (the original Lewis acid used 100 years ago), $FeCl_3$ and $TiCl_4$ are effective at rearranging this particular phenyl *N,N*-dimethylsulfamate. FeCl3 has been used in a number of other investigations.

Catalyst / Sulfamate Ratio = 1, 140°C, 30 Min

Table 30

Catalyst	2-Hydroxyphenyl *N,N*-dimethylsulfonamide	4-Hydroxyphenyl *N,N*-dimethylsulfonamide	*Ortho/Para* Ratio	% Ester Rearranged
$SnCl_2$	1%	1%	1.0	2
"	0	1%	N/A	1
1 Molar $AlCl_3$ Nitrobenzene	0	1%	N/A	1
"	0	1%	N/A	1
"	0	1%	N/A	1
1Molar $AlCl_3$ Chlorobenzene	0	1%	N/A	1
"	0	1%	N/A	1
1 Molar $FeCl_3$ Nitrobenzene	7%	10%	0.7	17
"	8%	12%	0.7	20
1 Molar $FeCl_3$ Chlorobenzene	1%	1.5%	0.7	2.5
"	1%	1%	1.0	2
No Catalyst	0	1%	N/A	1
	0	0	N/A	0

Inert solvents such as nitrobenzene, chlorobenzene and dichloroethane have been used extensively in the Fries rearrangement to create homogeneous reaction conditions, according to the literature. As the starting sulfamate esters used in these reactions are liquids, even though sometimes quite viscous, the reaction mixtures are all homogeneous without solvent. $AlCl_3$ was dissolved in nitrobenzene and chlorobenzene to a 1 molar concentration and this was used as catalyst in a number of thia-Fries rearrangements. These reactions were unsuccessful and this is possible because the ester and catalyst molecules are not in close enough proximity within the solvent cage at a concentration of 1 molar.

A number of experiments were also carried out using $FeCl_3$ as the Lewis acid catalyst.

The *ortho* / *para* ratio obtained in the homogeneous rearrangement of phenyl *N,N* dimethylsulfamate (195) with $FeCl_3$ at 1 : 2.5 to give 2- and 4- hydroxyphenyl *N,N*-dimethylsulfonamide

Table 31

	Time (min)		
Temp (°C)	15	30	60
80		0.9	0.9
100		0.9	1.1
120			
130			
140	1.4		
150			

Total yield of 2- and 4-hydroxy *N,N*-dimethylsulfonamides (229 and 230) at various temperatures and times.

Table 32

Temp (°C)	Time (min) 15	30	60
80		57	53
100		41	56
120			
130			
140	18		
150			

Some further rearrangements were carried out later with to check on reproducibility of the reaction. These again involved the ester, phenyl *N,N*-dimethylsulfamate with $AlCl_3$ and $FeCl_3$ as catalysts in a 1 : 1 molar ratio at 140°C. All the experiments were carried out in the oil bath which was maintained at the stated temperature ± 5°C. Two reactions for each of the catalysts were carried out at 30 min and at 60 min, a total of eight rearrangements. This quantitative analysis was carried out by GC-FID using the same conditions and standards as stated previously. All of the reactions showed small quantities of phenol ≤ 1% and, as is shown by the amount of the ester which rearranged, a small % of starting material.

Catalyst / Sulfamate Ratio = 1, 140°C, 60min and 30 Min

Table 33

Catalyst	2-Hydroxyphenyl *N,N*-dimethylsulfonamide	4-Hydroxyphenyl *N,N*-dimethylsulfonamide	*Ortho/Para* Ratio	% Ester Rearranged
		60 min		
$AlCl_3$	33%	55%	0.6	88
"	34%	48%	0.7	82
$FeCl_3$	30%	69%	0.4	99
"	31%	64%	0.5	95
		30 min		
$AlCl_3$	25%	55%	0.5	80
"	24%	59%	0.4	83
$FeCl_3$	26%	57%	0.5	83
"	24%	50%	0.5	74

These results are very reproducible but compared to table 32 much more of the sulfamate ester has been rearranged.

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As stated earlier, to determine the molecularity of the thia-Fries rearrangement a number of crossover experiments were carried out. According to the literature this is the method of choice to ascertain whether the reaction is inter-, intra- or bimolecular.

All of the rearranged compounds, the sulfonamides, which are the product, or potential product of the following crossover experiments were subjected to stability tests. Each sulfonamide, singly, was heated to 140°C in the oil bath for 30 min to determine if a further rearrangement, or reversal to sulfamate, might happen. Under the conditions all of the sulfonamides tested showed no reaction or breakdown.

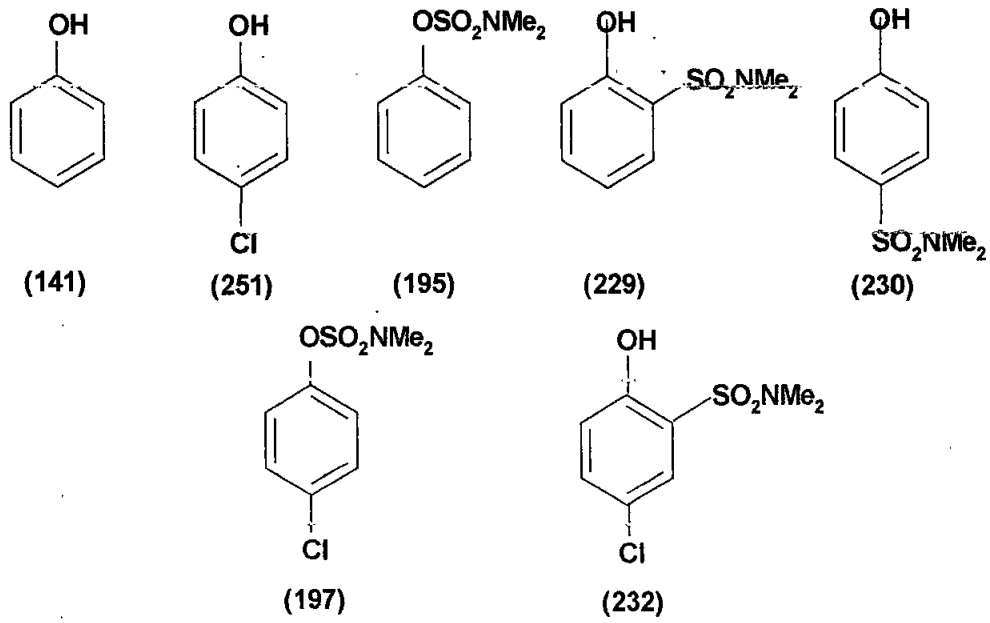
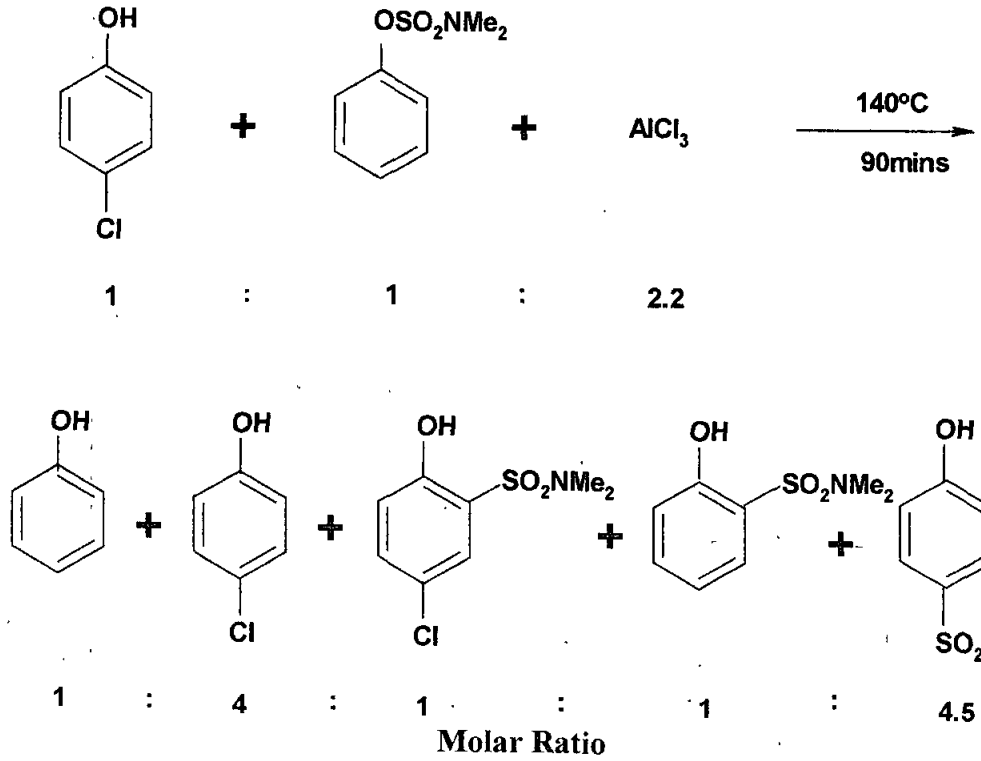
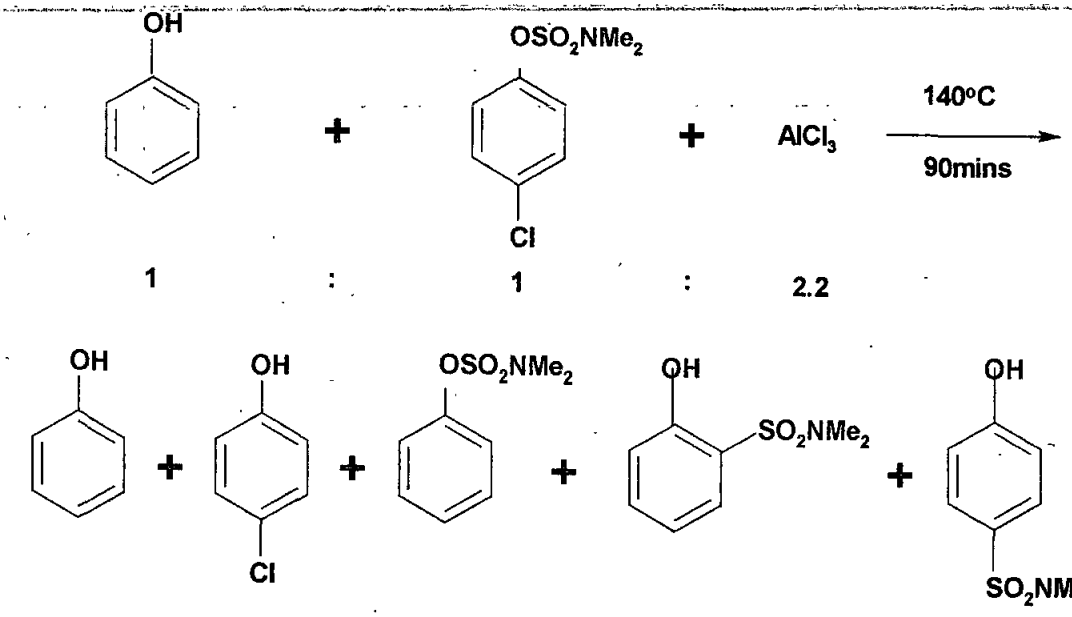


Fig. 11

The same set of standards (fig. 11) were used for both of the crossover experiments, schemes 84 and 85. In the first case neither of the esters, phenyl *N,N*-dimethylsulfamate nor 4-chlorophenyl *N,N*-dimethylsulfamate were detected but in the second experiment a small amount of both were found. As no internal standard was used in the analysis of these crossover experiments the products are shown as molar ratios to each other.



Scheme 84



Scheme 85

A further set of crossover experiments similar to the first two, were carried out. Stability tests were initiated on the two sulfonamides in the set, 4-chloro 6 hydroxyphenyl *N,N*-dimethylsulfonamide and 2-hydroxy-5-methyl *N,N*-dimethylsulfonamide and they were deemed to be stable in a 1 : 1 ratio with $AlCl_3$ to 140°C for 30 min.

A set of standards suitable for the set of experiments were made up and used to quantify the products of both reactions as molar ratios to each other (fig. 12).

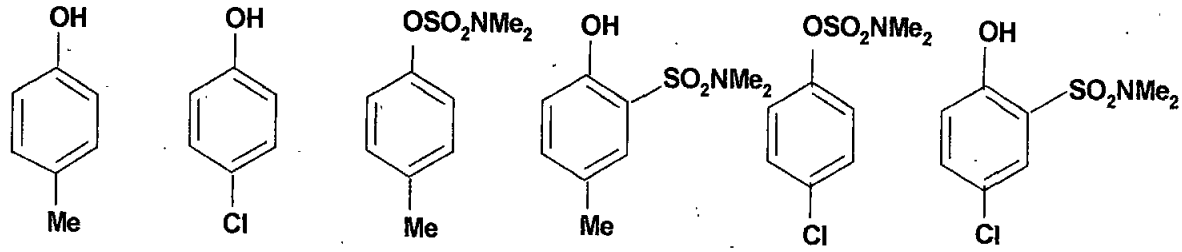
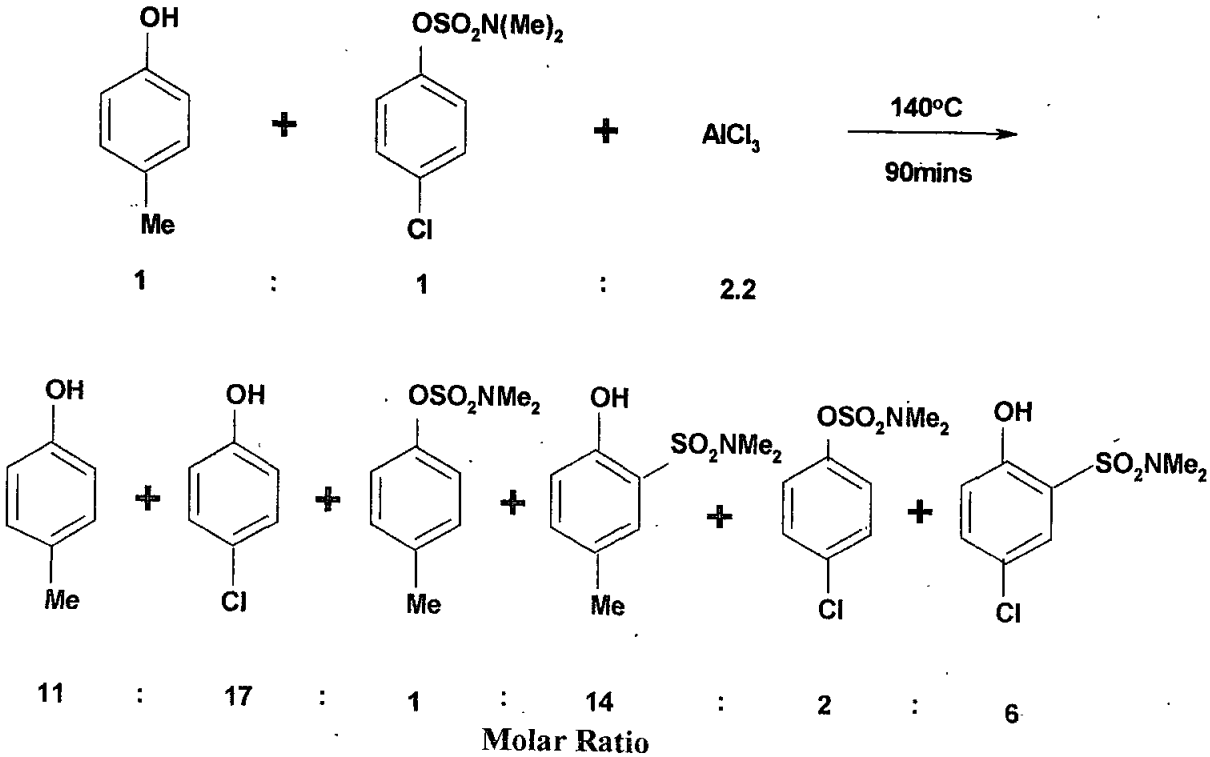
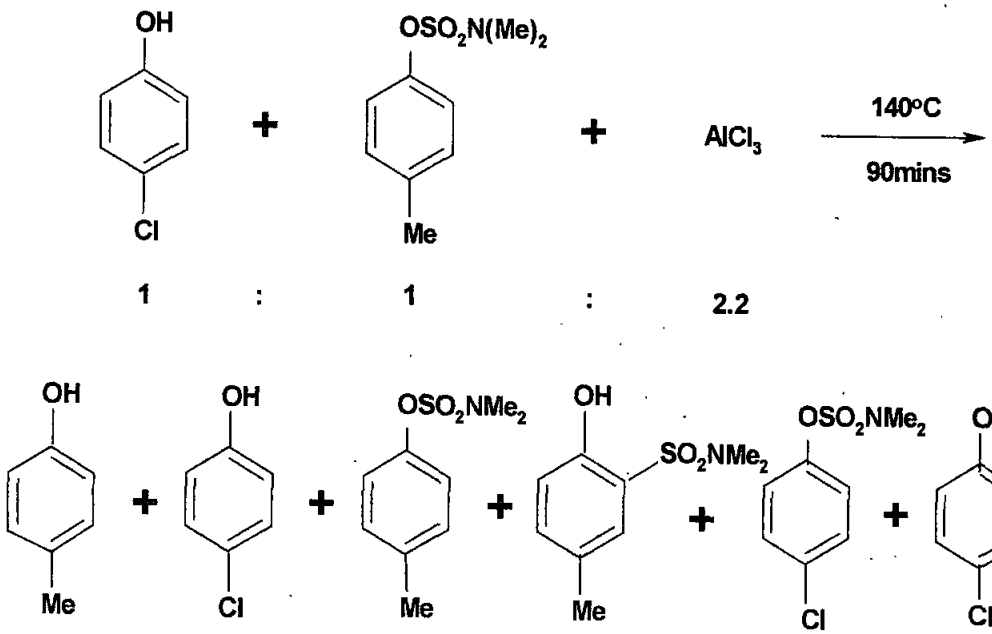


Fig 12.



Scheme 86

The reaction of 4-chlorophenyl *N,N*-dimethylsulfonamide with an equivalent of 4-methylphenol and 2.2 equivalents of $AlCl_3$ (scheme 86) and the reaction of 4-methylphenyl *N,N*-dimethylsulfonamide with an equivalent of 4-chlorophenol and 2.2 equivalents of $AlCl_3$ (scheme 87) were the two crossover investigations in this setAnalysis as usual was by GC-FID using the same conditions and column as stated previously.



Scheme 87

Two compounds were used in a number of crossover experiments, 4-bromophenyl *N,N*-dimethylsulfamate (**198**) and 4-chlorophenyl *N,N*-diethylsulfamate (**213**). These experiments were carried out at a number of temperatures and for various times. Tests were carried out on the two above esters and also on 4-bromophenyl *N,N*-diethylsulfamate (**214**) and 4-chlorophenyl *N,N*-di-*n*-propylsulfamate (**219**) to estimate their reaction speeds *i.e.* the rate of rearrangement from ester to sulfonamide, over set times and at certain temperatures. These reactions were homogeneous because all of the above esters are liquid at room temperature. The initial two compounds above were found to have rates of rearrangement quite close to each other at 140°C (fig. 13 table 51).

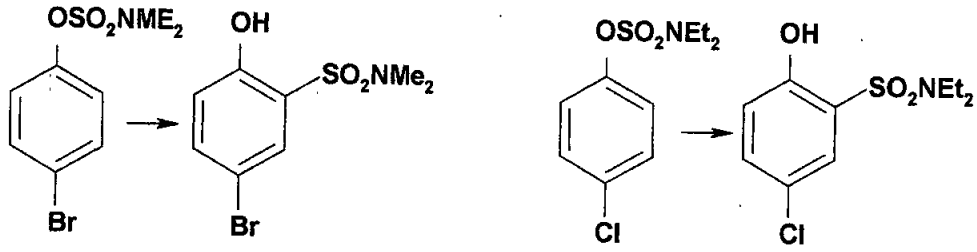


Fig. 13

Table 34

Time (min)	% Ester Rearranged	Time (min)	% Ester Rearranged
0.25	2.5	0.25	
0.5	4.5	0.5	1.5
1	6	1	9
2	12.5	2	11
4	28	4	14
6	36	6	20
8	38	8	22
10	40	10	23
15	45	15	24
20	48	20	28
25	40	25	29
30	41	30	31

A set of standards which includes all of the following, along with *n*-tetradecane, *n*-heptadecane and *n*-octadecane were made up. The alkanes were included as internal standards and all the concentrations were in the 0.2 mmolar region.

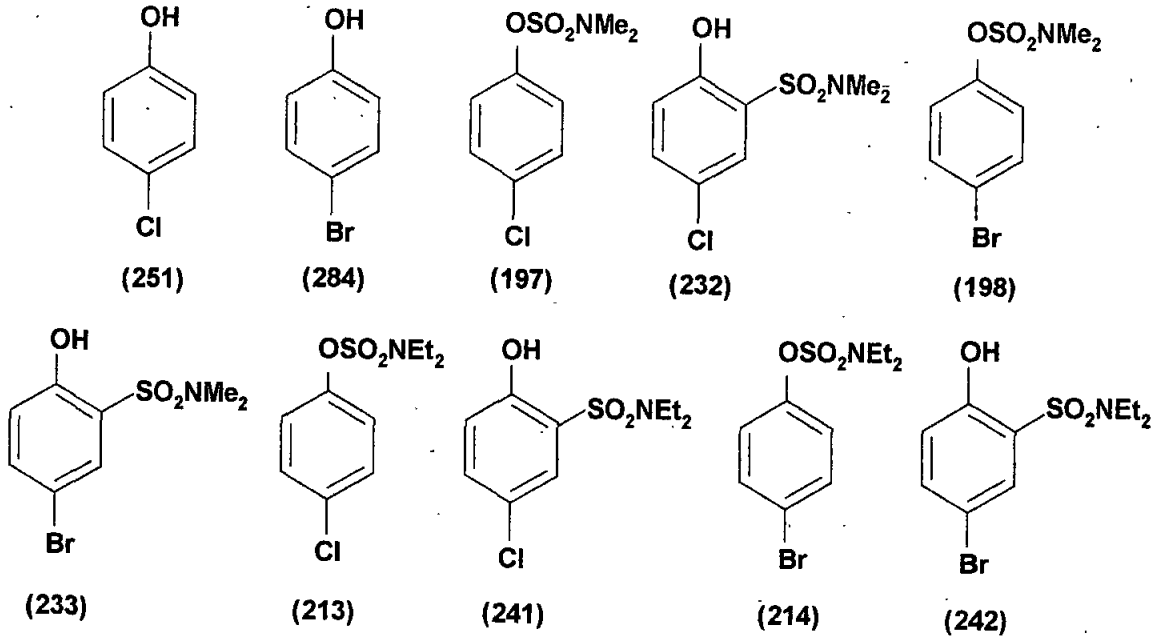
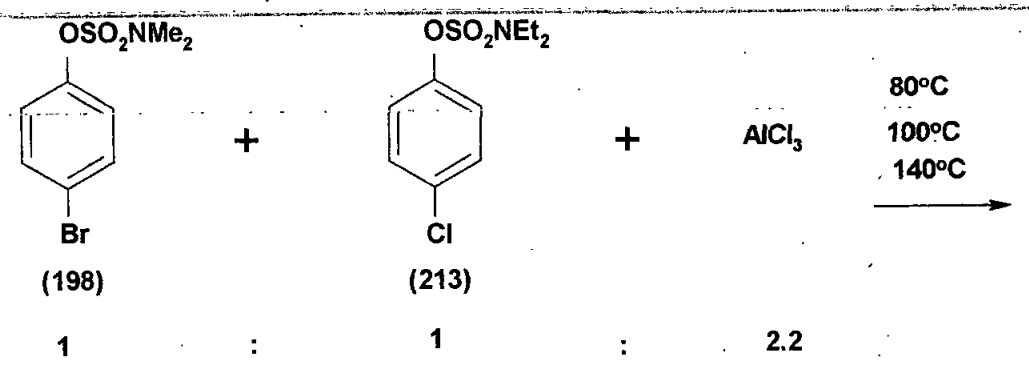


Fig. 14

Six samples of 200 mg each of 4-bromophenyl *N,N*-dimethylsulfamate (**198**) and 4-chlorophenyl *N,N*-diethylsulfamate (**213**) were heated with $AlCl_3$ in a 1 : 1 : 2.2 molar ratio at 140°C for varying lengths of time. The reactions were quenched with 5 ml 1 molar HCl and the mixture was made up to 100 ml with CH_2Cl_2. Analysis was by GC-FID against the above set of standards and the results are as in table 35.



Scheme 88

A further set of crossover experiments were carried out with the same two starting esters (**198**) and (**213**) with $AlCl_3$ and at the same molar ratios of 1 : 1 : 2.2. There were 8 different reactions in this set, 1, 2, 5, 10, 15, 20, 25, and 30 min in duration and all at 80°C (table 36).

A third set of experiments were carried out using the esters (**198**) and (**213**), the same catalyst, $AlCl_3$ the same molar ratio 1 : 1 : 2.2 and no solvent. These experiments were carried out at 100°C for periods of time from 30 min to 20 hr (table 37). The rearrangement of the individual esters was also carried out at the same temperature of 100°C and at a 1 : 1.1 molar ratio to the catalyst (table 38 and 39). The double sulfamate reactions as well as the individual sulfamate rearrangements were all analysed by the same method as above with the GC-FID and using the same set of standards.

Results of crossover experiment of 4-bromophenyl *N,N*-dimethylsulfamate and 4-chlorophenyl *N,N*-diethylsulfamate

140°C

Table 35

Time		4-Chlorophenol	4-Bromophenol	(197)	(232)	(198)	(233)	(213)	(241)	(214)	(242)
5 Min	%	3.8	1.2	1.0		47.8		43.2	0.8	2.1	
10 Min	%	5.3	3.0	2.3		42.9	0.7	40.2	1.1	4.2	0.4
15 Min	%	4.6	3.2	2.0		46.5	1.0	37.6	1.4	3.7	
20 Min	%	3.2	2.7	1.5		45.1	12.4	31.1	1.1	3.0	
25 Min	%	5.1	3.0	3.4		42.9		37.4	2.0	6.2	
30 Min	%	5.1	4.0	7.3	0.9	36.4	2.5	29.1	2.8	10.9	1.0

Crossover experiment of 4-Chlorophenyl *N,N*-diethylsulfamate and 4-Bromophenyl *N,N*-dimethylsulfamate

80°C

Table 36

Time	4-Chlorophenol %	4-Bromophenol %	(197) %	(232) %	(198) %	(233) %	(213) %	(241) %	(214) %	(242) %
1Min	2.7	4.2	0.8	0.3	43.2	0.6	50.3	0.2	0.1	0.1
2Min	3.1	3.6	0.8	0.2	41.5	0.6	47.3	0.2	0.5	
5 Min	1.7	3.0	0.7	0.2	29.7	0.7	47.9	0.3	0.1	0.1
10 Min	6.1	5.2	2.7	0.3	37.7	1.3	44.9		1.9	0.1
15 Min	4.6	4.7	1.7	0.3	37.1	1.2	41.8	0.4	1.0	0.1
20 Min	4.1	4.3	1.1	0.2	39.7	1.0	43.8	0.3	0.	0.1
25Min	6.3	5.6	3.2	0.2	37.7	1.0	37.8	0.5	2.4	
30 Min	4.8	4.6	1.4	0.2	38.0	1.3	39.9	0.4	0.7	0.1

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Results of crossover experiment of 4-bromophenyl *N,N*-dimethylsulfamate and 4-chlorophenyl *N,N*-diethylsulfamate

100°C

Table 37

Time		4-Chlorophenol	4-Bromophenol	(197)	(232)	(198)	(233)	(213)	(241)	(214)	(242)
30 Min	%	4.9	2.9	2.6	0.8	28.4	2.0	33.8	1.5	1.9	0.4
40 Min	%	5.5	3.8	3.7	1.1	27.2	2.4	29.7	1.7	2.4	0.7
60 Min	%	10.5	8.3	10.2	1.5	25.1	2.9	28.4	4.6	7.1	1.4
120 Min	%	8.3	6.5	7.3	1.4	29.2	2.9	31.3	3.4	5.1	1.2
10 Hr	%	8.3	8.3	9.4	1.4	25.2	3.9	26.2	4.6	6.5	1.4
20 Hr	%	12.5	12.3	6.5	4.5	5.3	5.3	7.0	9.6	3.0	5.6

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The individual homogeneous thia-Fries rearrangement of 4-bromophenyl *N,N*-dimethylsulfamate and 4-chlorophenyl *N,N*-diethylsulfamate at 100°C with $AlCl_3$.

Table 38

Time	4-Bromophenol	4-Bromophenyl *N,N*-dimethylsulfamate (198)	3-Bromo-6-hydroxyphenyl *N,N*-dimethylsulfonamide (233)
30 Min	12.0	66.2	13.7
40 Min	11.3	69.5	11.7
60 Min	6.5	76.8	7.4
120 Min	9.4	16.0	67.6
10 Hr	18.0	47.3	30.5
20 Hr	13.8	19.6	22.1

Table 39

Time	4-Chlorophenol	4-Chlorophenyl *N,N*-diethylsulfamate (213)	3-Chloro-6-hydroxyphenyl *N,N*-diethylsulfonamide (241)
30 Min	22.3	61.6	8.7
40 Min	9.1	81.4	1.4
60 Min	26.5	45.7	21.3
120 Min	12.5	39.6	41.1
10 Hr	14.0	77.6	4.5
20 Hr	4.5	66.1	2.1

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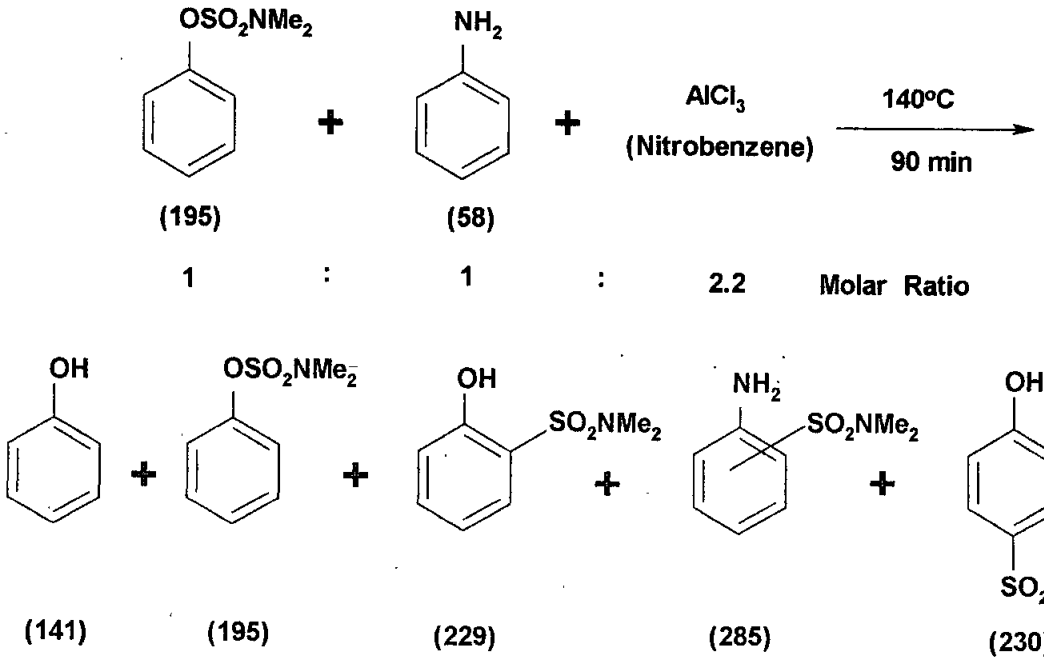
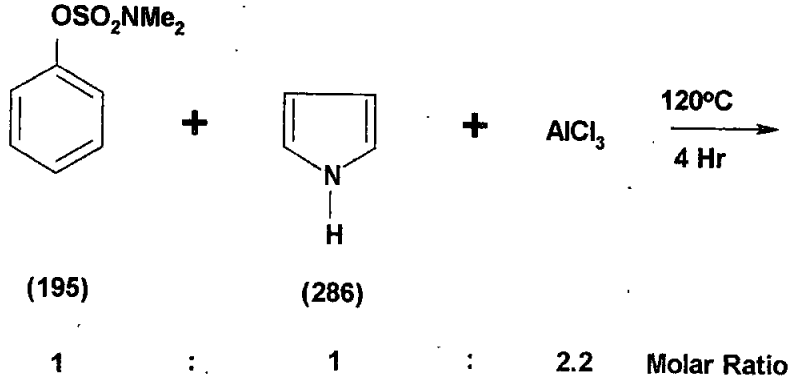
A number of other crossover experiments were examined, not so much to study the actual mechanism but more to observe what transesterification or transsulfamoylation was happening. One of these reactions as seen in scheme 89, involved the heating of phenyl *N,N*-dimethylsulfamate with aniline and $AlCl_3$ as catalyst in a 1 : 1 : 2.2 molar ratio at 140°C for 90 min. The products of this reaction as separated and identified by GC-MS were phenol ≈ 5% , the starting ester (**195**) ≈ 50%, both of the rearranged sulfonamides (**229**) ≈ 25% and (**230**) ≈ 3% and a compound anilino *N,N*-dimethylsulfonamide (**285**) ≈ 4% as deduced from it's mass spectra. Quantitation is purely by estimation from the peak areas of the chromatograph.



Scheme 89

This reaction was also carried out using 2 molar $AlCl_3$ in nitrobenzene. ≈ 90% of the ester remained and ≈ 5% of the *ortho*- sulfonamide with none of the *para*- product showing. ≈ 2% each of phenol and the anilino *N,N*-dimethylsulfamate compound were also detected.

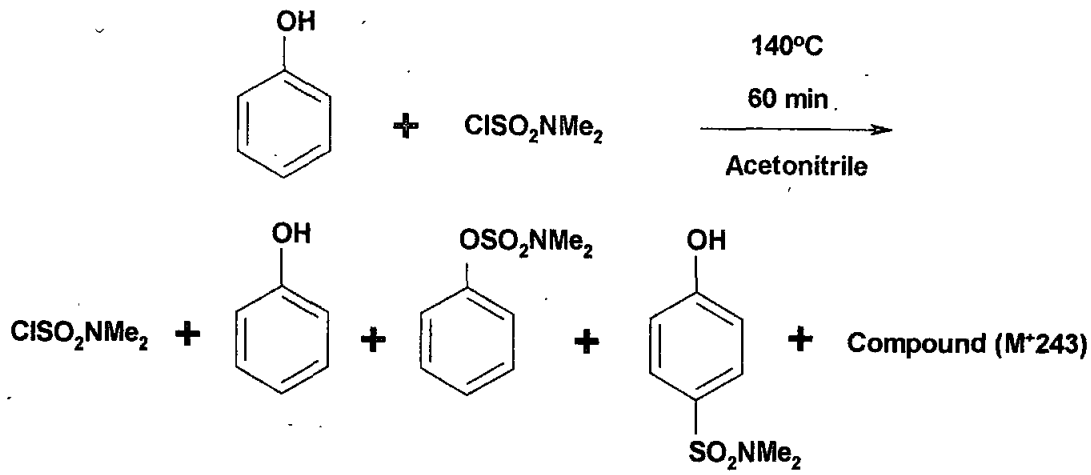
Phenyl *N,N*-dimethylsulfamate was heated with an equivalent of pyrrole and 2.2 equinelents of $AlCl_3$ to 120°C for 4 hr. No transsulfamoylation could be detected by GC-MS with only the starting ester, phenol and the two rearrangement sulfonamides being found on the chromatograph.



Scheme 90

Phenol and an equivalent of *N,N*-dimethylsulfamoylchloride were heated to 140°C for 60 min with 50 ml acetonitrile. The reaction mixture was analysed by GC-MS and apart from the two starting materials, *N,N*-dimethylsulfamoylchloride ≈ 25% and phenol ≈ 20% , phenyl *N,N*-dimethylsulfamate ≈ 3%, 4-hydroxyphenyl *N,N*-dimethylsulfonamide

≈ 30% and an unknown compound with an M^+ of 243 ≈ 20% were found (scheme 91). This reaction worked as a one pot synthesis of the *para*-isomer.



Scheme 91

Transesterification, or ester transfer, is a reaction which can be catalysed by either acids or bases, it is an equilibrium reaction which may be shifted in either direction [90]. In many cases low-boiling esters can be converted to higher-boiling ones by the distillation of the lower-boiling alcohol as soon as it is formed.

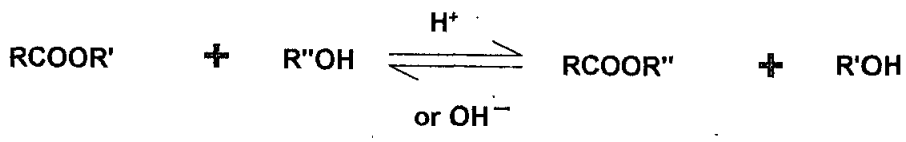
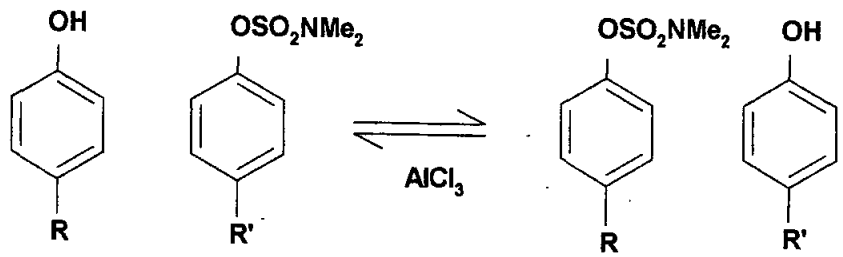


Fig. 15

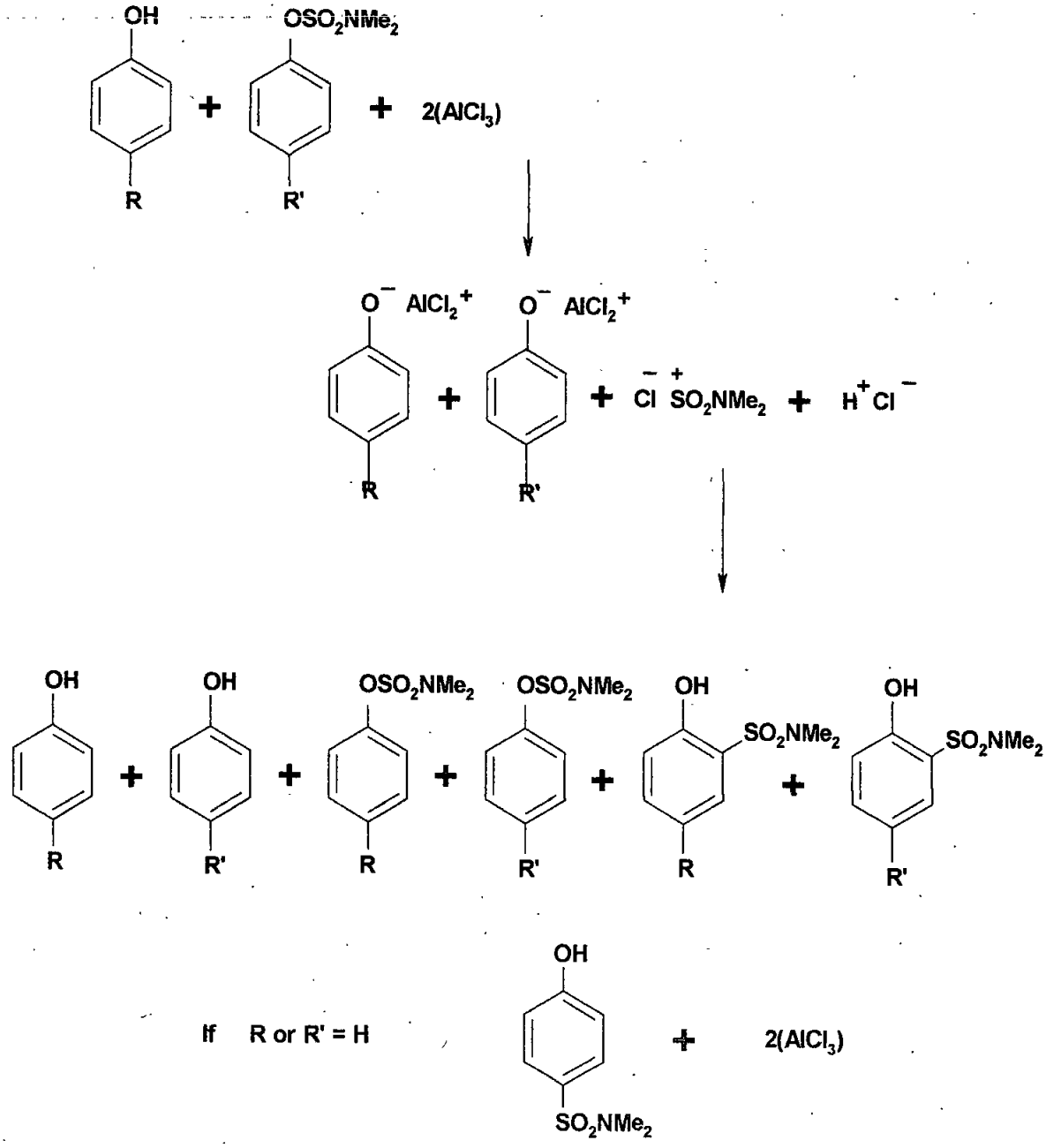
This reaction has been used for the acylation of a primary alcohol in the presence of a secondary alcohol where the diol is treated with ethyl acetate in the presence of Woelm neutral alumina. Transesterification can also be carried out with phase transfer catalysts without added solvent[91].

Transsulfamoylation, or sulfamate ester transfer, is an analogous reaction to the above and is part of the mechanism that is taking place in the series of reactions depicted in schemes 84 to 88.



Scheme 92

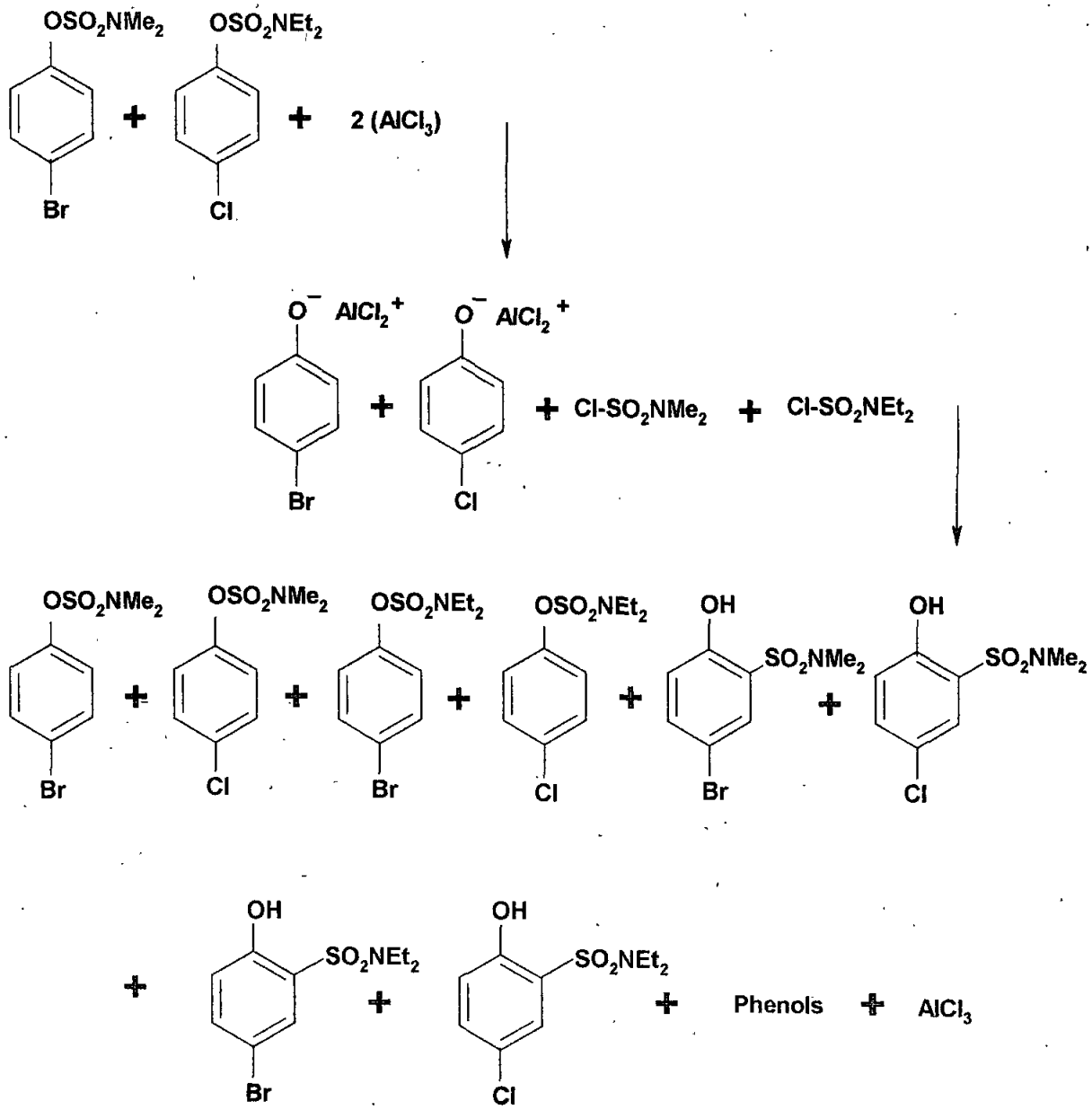
Whether the transsulfamoylation occurs before or simultaneously with the rearrangement can not be determined from these mechanistic experiments but the balance of probability would indicate the latter. According to scheme 93 this would be the mechanism best indicated, where there is a transsulfamoylation and an intermolecular thia-Fries rearrangement occurring simultaneously. $AlCl_3$ acts as a phase transfer catalyst and there is no solvent involved. What can be said definitely is that there is an intermolecular element in the rearrangement.



Scheme 93

In the other set of crossover experiments (tables 35 to 39) involving 4-bromophenyl *N,N*-dimethylsulfamate and 4-chlorophenyl *N,N*-diethylsulfamate there is as before, formation

of sulfamoyl chloride by, and including, the $AlCl_3$ and this may be the rate determining step. The sulfamoyl chloride then acts in a one-pot synthesis of the other phenyl sulfamate and at the same time, or just subsequently, the rearrangement of the sulfamate esters (scheme 94).



Scheme 94

The formation of the *N,N*-dimethylsulfamoyl chloride is itself an intermolecular mechanism and its sulfamoylation of the aryl entities either to sulfamates or sulfonamides would unequivocally be an intermolecular element in the rearrangement.

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THIA-FRIES MICROWAVE REARRANGEMENT

INTRODUCTION

In the electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Considerable knowledge of microwave radiation was obtained from the development of radar before and during the Second World War. Microwaves have wavelengths of 1mm – 1m, corresponding to frequencies between 0.3 and 300 GHz. Telecommunication and microwave radar equipment occupies many of the band frequencies in this region. The frequencies allotted to microwave dielectric heating (also referred to as microwave heating or dielectric heating) are 918 MHz and 2.45 GHz with the latter predominating, and used totally in domestic appliances. These frequencies correspond to respective wavelengths of 33.3 and 12.2cm.

Microwaves are electromagnetic waves, which by their nature contain electric and magnetic field components. The electric field applies a force on charged particles as a result of which the charged particles start to migrate or rotate. Due to the movement of charged particles further polarisation of polar particles takes place. The concerted forces applied by the electric and magnetic components of microwaves are rapidly changing in direction (2.4×10^9 per sec.) thus causing warming, because the assembly of molecules,

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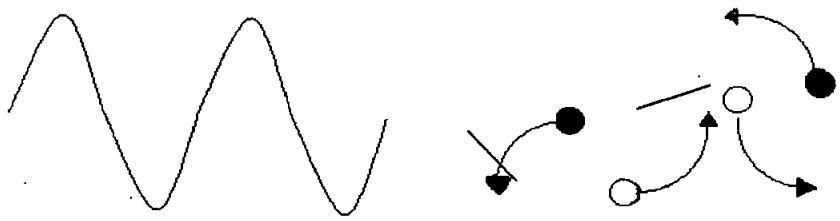
e.g. a liquid or a semi-solid cannot respond instantaneously to the changing direction of the field, which manifests itself as heat.[92]

To further explain the dipolar polarisation mechanism, as with all electromagnetic radiation, microwave radiation can be divided into an electric field component and a magnetic field component. The former component is responsible for the dielectric heating, which is effected via two major mechanisms. One of the interactions of the electric field component with the matrix is called the dipolar polarisation mechanism. For a substance to generate heat when irradiated with microwaves it must possess a dipole moment, which a water molecule has.



Dipolar molecules which try to align with an oscillating electric field.

Fig. 16

A dipole is sensitive to external electric fields and will attempt to align itself with the field, by rotation. The applied field provides the energy for this rotation (fig. 16).

In gasses, molecules are spaced far apart and their alignment with the applied field is, therefore, rapid, while in liquids instantaneous alignment is prohibited by the presence of other molecules. The ability of molecules in a liquid to align with the applied electric

field will vary with different frequencies and with the viscosity of the liquid. Under low frequency irradiation, the molecule will rotate in phase with the oscillating electric field. The molecule gains some energy by this behaviour, but the overall heating effect by this full alignment is small. Alternatively, under the frequency of a high frequency electric field the dipoles do not have sufficient time to respond to the oscillating field and do not rotate. Since no motion is induced in the molecules, no energy transfer takes place and therefore no heating occurs. If the applied field is in the microwave radiation region, however, a phenomenon occurs between these two extremes. At this frequency the applied radiation is low enough so that the dipoles have time to respond to the alternating electric field and therefore rotate. The frequency is not high enough for the rotation to precisely follow the field; therefore, as the dipole re-orientates to align it with the electric field, the field is already changing and generates a phase difference between the orientation of the field and that of the dipole. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating.

In a solution containing ions, or even a single isolated ion with a hydrogen bonded cluster, the ions will move through the solution under the influence of an electric field. This will result in expenditure of energy due to an increased collision rate, converting the kinetic energy to heat This conductivity mechanism is a much stronger interaction than the dipolar mechanism with regards the heat-generating capacity. In the above example, the heat generated by the conduction mechanism due to the presence of ions adds to the heat produced through the dipolar mechanism, resulting in a higher final temperature.

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The heart of every microwave oven is the high voltage system, the magnetron [93]. Its purpose is to generate microwave energy. The high-voltage components accomplish this by stepping up AC line voltage to high voltage, which is then changed to an even higher DC voltage. This DC power is then converted to RF energy. The nucleus of the high-voltage system is the magnetron tube. The magnetron is a diode-type electron tube, which is used to produce the required 2450 MHz of microwave energy. It is classed as a diode because it has no grid, as does an ordinary electron tube.

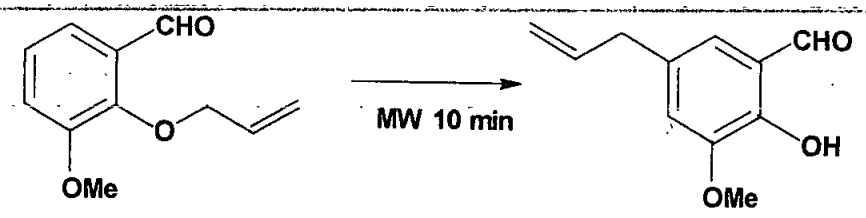
In the 1970's the construction of the microwave generator, the magnetron, was both improved and simplified. Consequently the prices of microwave ovens fell considerable, leading to them becoming mass-produced. The design of the oven chamber or cavity, however, which is crucial for the heating characteristics, was not significantly improved until the end of the 1980's. [94] Microwave ovens can range from simple multimode ovens to continuous multimode ovens to large-scale batch ovens. In some cases glassware has been redesigned in order to carry out reactions in multimode microwave ovens. Microwave dielectric heating is a well-established procedure not only for the domestic preparation of meals, but also it is widely used industrially for the processing of food and industrial materials.

The classic work of von Hippel and his co-workers [95] in the early 1950's provided a sound theoretical basis for these technological developments, and his group provided an important database of dielectric properties on common substances, foodstuffs and materials. This database has been expanded upon as the technological need arose and

more recently a considerable effort has been directed toward the measurement of the dielectric properties of biological materials. [96,97] This was prompted in part by the need to provide fundamental data which would underpin the public and scientific discussion concerning the health hazards, which may arise from the interactions of electromagnetic radiation in the microwave and radio frequencies ranges with biological tissues.

As stated above, in 1986, Gedye et al. [52] and Giguere et al. [53] demonstrated for the first time, that many organic reactions can be conducted very rapidly under microwave irradiation and in 1994 Sridar and Sundara Rao [54] published the first report on 'Microwave-induced rate enhancement of Fries rearrangement'.

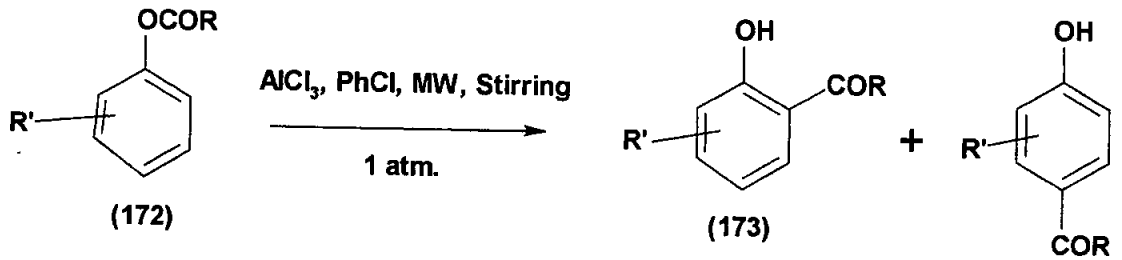
A convenient and general procedure is described by Mali and Massey [98] for the synthesis of 5-allyl-2-aryl-7-methoxybenzofurans from 2-allyloxy-3-methoxybenzaldehyde as part of a scheme to provide the naturally occurring benzofurans which have medicinal properties. When a solution of the aldehyde in *N,N*-dimethylanaline was irradiated in a microwave oven for 10 min (power not reported), 5-allyl-2-hydroxy-3-methoxybenzaldehyde was obtained in 65% yield along with a minor (15%) amount of 2-allyl-6-methoxyphenol. This is the principle step of interest in the study i.e. the Fries rearrangement under microwave conditions of compound (**287**) to product (**288**) as in scheme 95.



(287) (288)

Scheme 95

Kadilkar and Madyar [99] describe "a very safe, fast and practical Fries rearrangement with conventional $AlCl_3$ catalyst, carried out in a modified microwave oven at atmospheric pressure".



(172) (173) (174)

R = CH_3, CH_2CH_3 and Ph
R' = H, CH_3 & NO_2

Scheme 96

The instrument was fitted with a stirring motor below the floor of the cavity and a condenser through the roof of the cavity. To 10 mmol of ester in 5 ml chlorobenzene was added 15 mmol of $AlCl_3$ and the mixture was stirred for a predetermined time while the temperature was recorded (scheme 96 and table40).

Table 40

Substrate	Time (mins.)	Temp °C	(%) Yield with MW	(%) Yield with Thermal
Phenyl acetate	3	106	2-Hydroxy (73); 4-Hydroxy (23)	2-Hydroxy (70); 4-Hydroxy --
Phenyl propionate	3	106	2-Hydroxy (28); 4-hydroxy (62)	2-Hydroxy (32); 4-Hydroxy (45)
Phenyl benzoate	4	108	4-Hydroxy (70)	4-Hydroxy (quantitative)
2-Naphthyl benzoate	5	110	1-Benzoyl (72)	1-Benzoyl (66)
3-Methylphenyl benzoate	12	112	4- Benzoyl (25)	4-Benzoyl (32); 6-Benzoyl (50)
4-Nitrophenyl benzoate	12	112	2-Benzoyl (38)	

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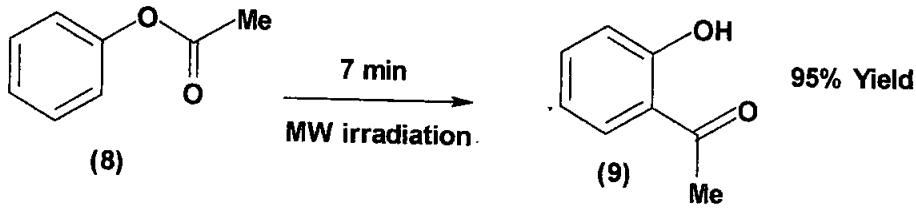
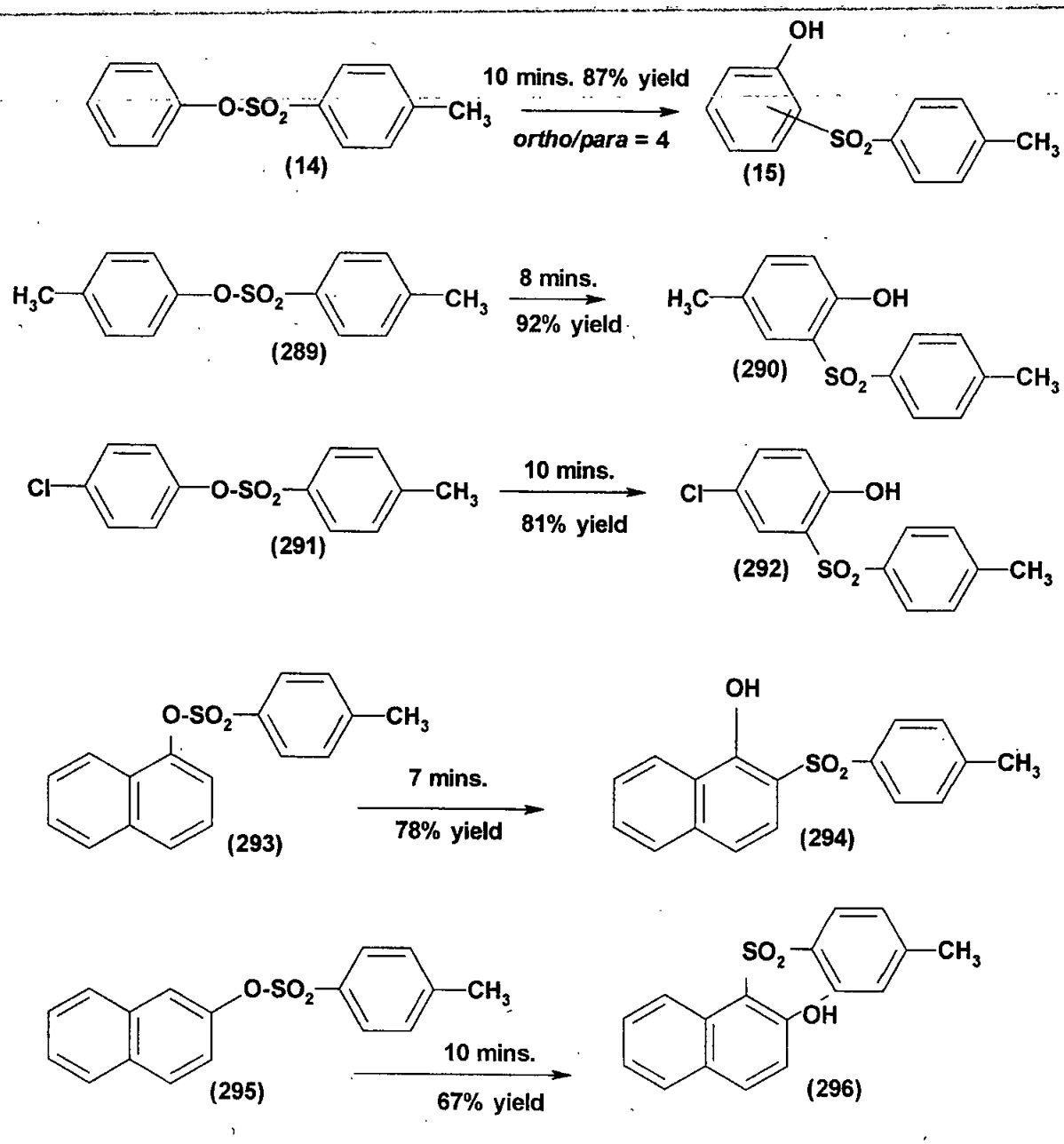
Moghaddam *et al* [100(a)] state that, although the thermal Fries rearrangement of acyloxybenzenes provides useful routes to acylphenols, a long reflux time with more than a stoichiometric amount of a Lewis acid such as $AlCl_3$, is required. These thermal reactions give rise to a mixture of *ortho*- and *para*-substituted products, the proportion of each being strongly influenced by the temperature (high temperature favours *ortho*-shifts) and the reaction media. It was therefore necessary to develop a new catalyst that would promote the Fries rearrangement cleanly and regioselectivity. It was discovered that an $AlCl_3$-$ZnCl_2$ mixture supported on silica gel is an efficient medium for the Fries rearrangement without solvent under microwave dielectric heating. Neither of the Lewis acids alone, on silica gel, promoted the reaction (scheme 97).



Scheme 97

A new activation method for the Fries rearrangement of arylsulfonates is described by the same group [86(b)]. The coupling of microwave irradiation with the use of catalysts or mineral supported reagents, under solvent-free conditions, provides chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and improved ease of manipulation, according to the authors (scheme 98).

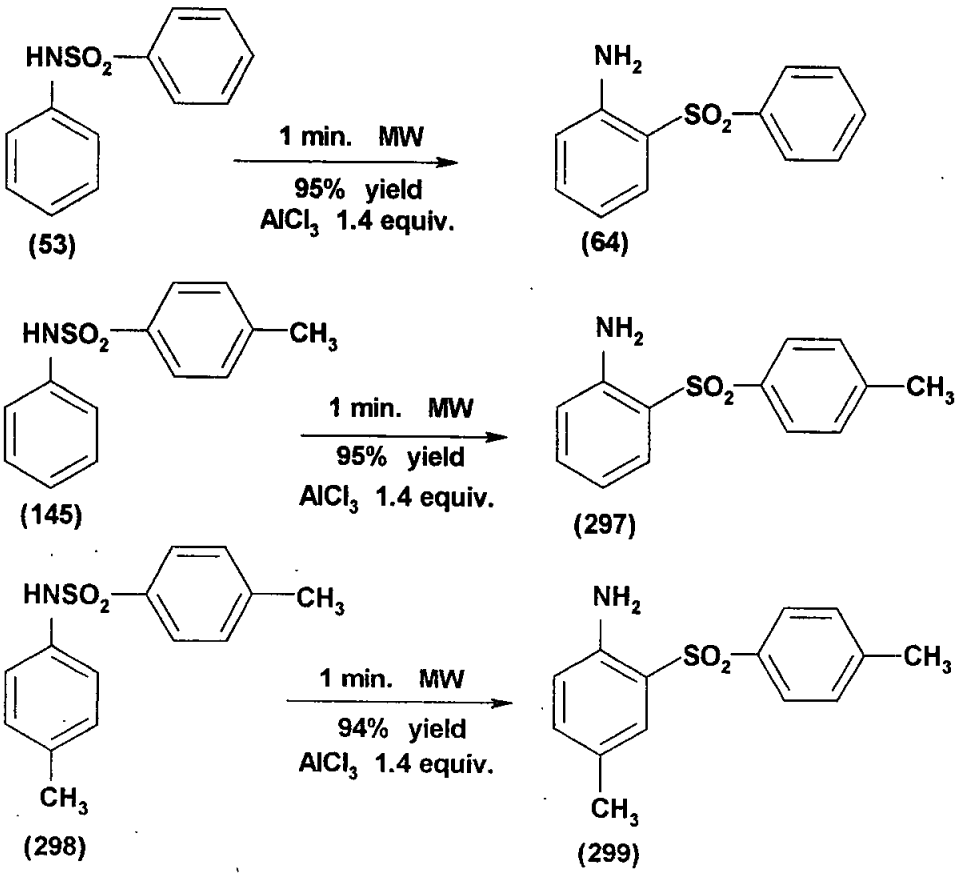


Scheme 98

This report states that an $AlCl_3 - ZnCl_2$ mixture supported on silica gel is an efficient medium for the promotion of the Fries rearrangement of arylsulfonates under environmentally benign conditions through microwave irradiation. The synergies promoted by these conditions leads to excellent yields.

As an example, when neat *p*-methylphenyl-*p*-toluenesulfonate was mixed with the support (1:3 w/w) and subjected to microwave irradiation, 650 watts at 2450 MHz for 8 mins. A 92% yield of *ortho*-directed product, 2-hydroxy-5-methyl *p*-tolylsulfone, was obtained (scheme 98).

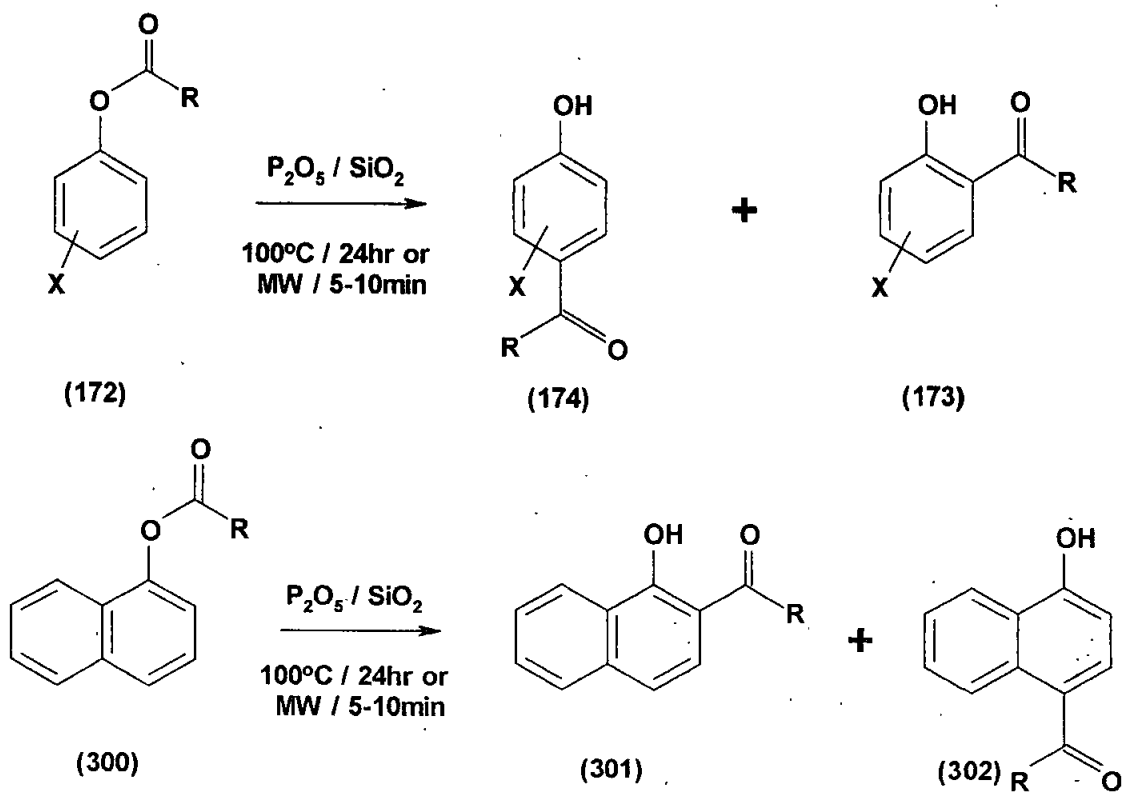
At the same time, another paper was published by Das *et al.*[101] entitled "The Fries rearrangement of arylsulfonates and sulfonanilides under microwave irradiation."



Scheme 99

These reactions were carried out in the presence of $AlCl_3$ under microwave irradiation and prepared hydroxy and aminoaryl sulfones. The rearrangements were carried out in 1 min and gave good yields (scheme 99).

Eshghi *et al* [102] stated that "P_2O_5 / SiO_2 was found to be an efficient new reagent in the Fries rearrangement of acyloxybenzene or naphthalene derivatives and in the direct acylation reactions of phenol and naphthol derivatives with carboxylic acids under microwave irradiation in solvent-free media" (scheme 100 and table 41).



Scheme 100

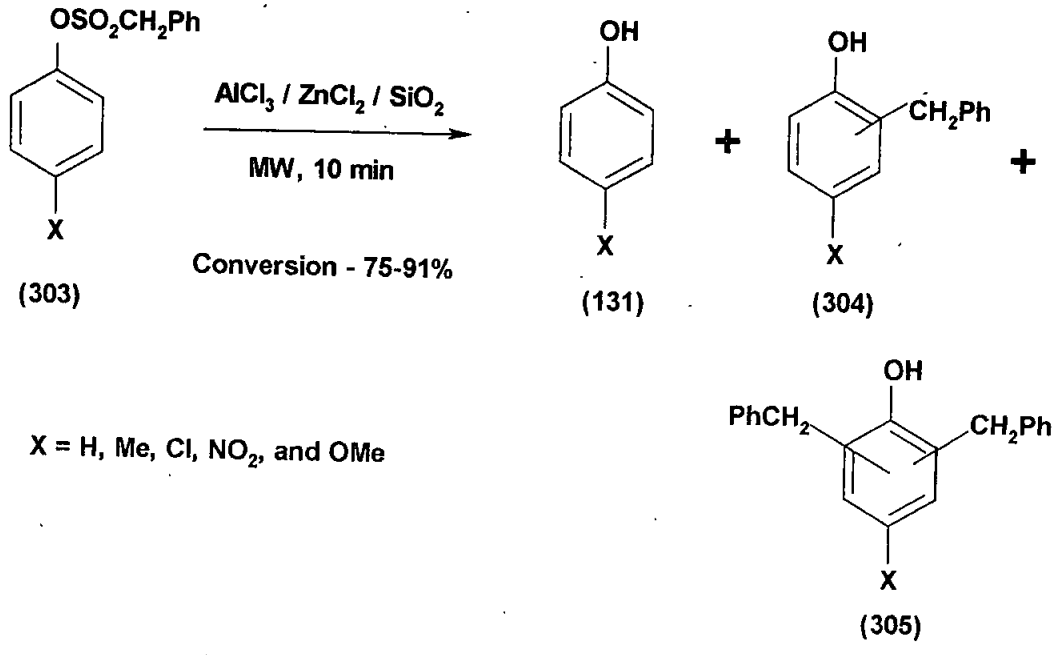
Fries rearrangement of acyloxy benzene and naphthalene derivatives by microwave irradiation

Table 41

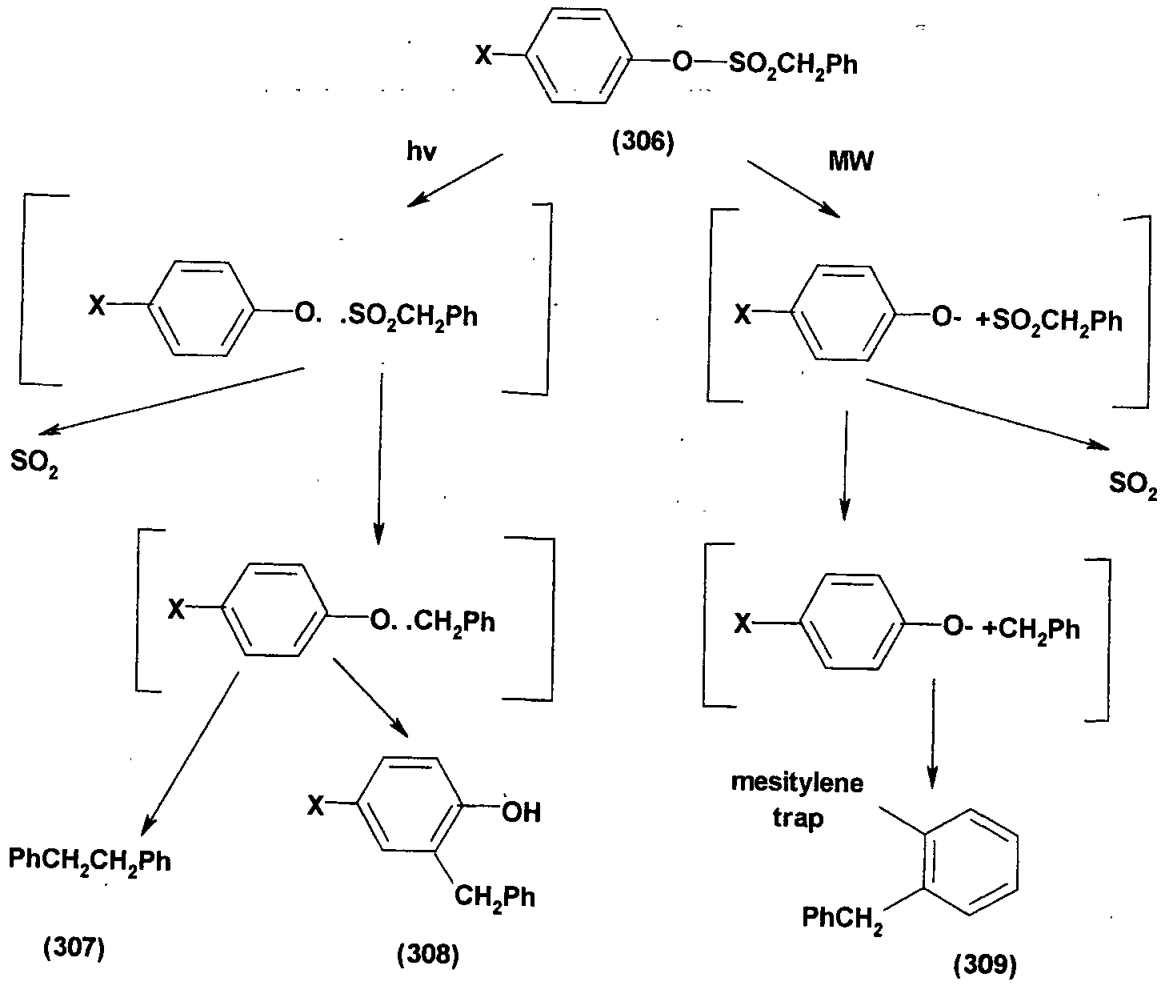
Entry	Reactants	R	X	Reaction Conditions	Yield (%) of Products		
1	172	CH_3	H	100°C / 24 hr	172a (2)	174a (38)	173a (60)
2	172	CH_3	H	MW / 5 min	172a (0)	174a (15)	173a (85)
3	172	CH_3	*m*-CH_3	100°C / 24 hr	172b (2)	174b (28)	173b (70)
4	172	CH_3	*m*-CH_3	MW / 5 min	172b (0)	174b (0)	173b (100)
5	172	CH_3	*p*-CH_3	100°C / 24 hr	172c (15)		173c (85)
6	172	Ph	*p*-CH_3	MW / 5 min	172c (0)		173c (100)
7	172	Ph	*m*-CH_3	100°C / 24 hr	172d (32)	174d (12)	173d (56)
8	172	Ph	*m*-CH_3	MW / 5 min	172d (15)	174d (15)	173d (70)
9	172	Ph	*p*-CH_3	100°C / 24 hr	172e (100)		173e (0)
10	172	Ph	*p*-CH_3	MW / 5 min	172e (95)		173e (5)
11	172	Ph	*p*-CH_3	MW / 5 min	172e (10)		173e (90)
12	282	CH_3		100°C / 24 hr	282a (0)	283a (32)	284a (68)
13	282	CH_3		MW / 5 min	282a (0)	283a (15)	284a (85)
14	282	Ph		100°C / 24 hr	282b (27)	283b (23)	284b (50)
15	282	Ph		MW / 5 min	282b (5)	283b (5)	284b (90)

Moghaddam and his group[103] continued with their "research into microwave promoted pseudo-thia-Fries rearrangement of aryl benzylsulfonates; highly reactive benzyl cation generation".

During Previous investigations [86(b)] they observed that the irradiation of aryl benzylsulfonate esters under the same reaction conditions of aryl *p*-toluenesulfonates (scheme 79) did not proceed by the same reaction pathway. Spectroscopic analysis of the reaction products indicates that aryl benzylsulfonate produce benzylated phenolic compounds with loss of SO_2 under microwave irradiation (scheme 101 and 102) in what has become called photo-acid generators, PAG's.



Scheme 101

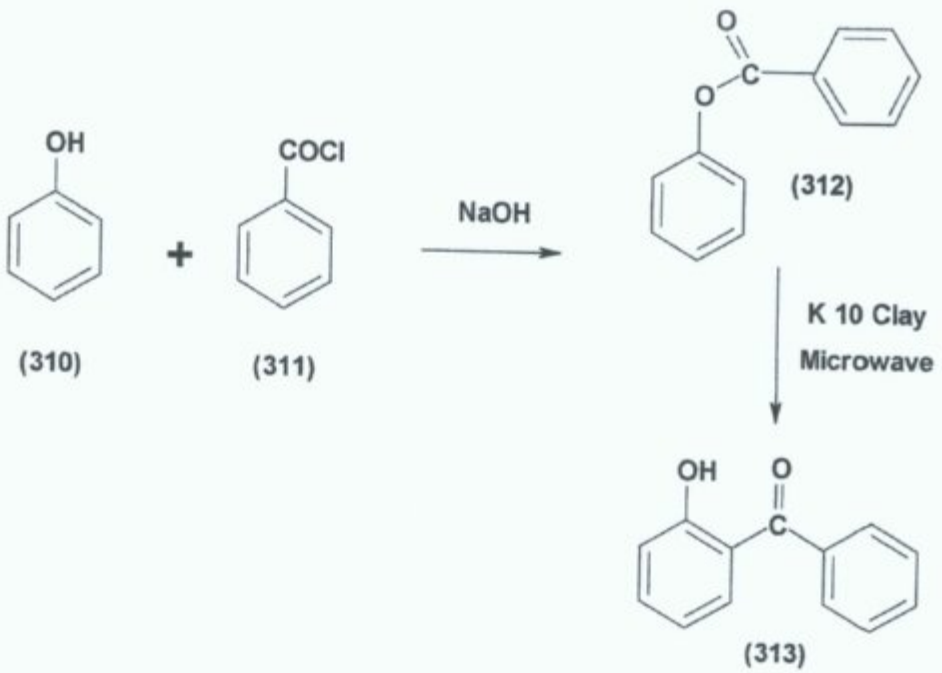


Scheme 102

A similar reaction has been observed by photolytic irradiation of these compounds, which generate SO_2 *via* a pseudo-thia-Fries type rearrangement.

Nonsteroidal anti-inflammatory drugs such as (**313**) are therapeutic agents useful in the treatment of inflammation, pain and pyresis and for this reason Shashikanth *et al* [104] carried out a facile synthesis of dibenzoyl phenols. The synthetic sequence is outlined below. Benzoylation of substituted hydroxybenzophenones with respective benzoyl

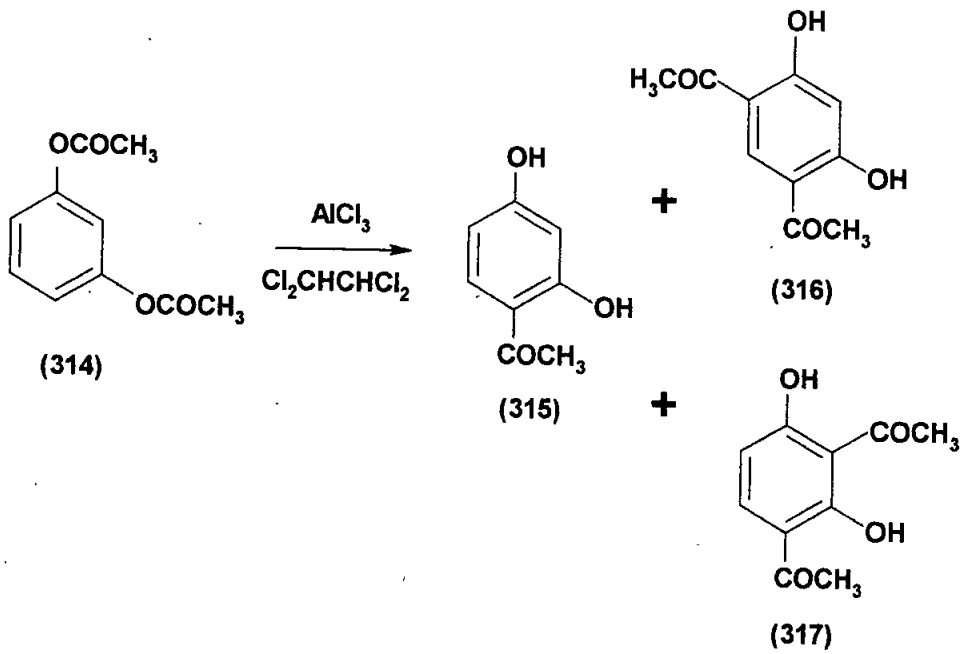
chlorides gives substituted benzoyl phenylbenzoate (scheme 103). These compounds, on thorough mixing with an equal amount of montmorillonite K 10 clay, when subjected to microwave irradiation for 10-13 min undergo a Fries rearrangement, which affords substituted dibenzoyl phenols in excellent yields.



Scheme 103

Synthesis of 2-substituted resorcinol is known to be a very difficult and unproductive process, acylation occurs at 4-position (*ortho* to one hydroxyl) rather than the 2-posisition (*ortho* to both hydroxyls). Chae *et al*, [105] required large amounts of this acylated resorcinol so they developed a convenient synthetic method of diacylation of resorcinol through the Fries rearrangement. A conventional Fries rearrangement of resorcinol diacetate (**314**) in $AlCl_3$ / 1,1,2,2-tetrachloroethane complex results in

2',4'-dihydroxyacetophenone (**315**), 4,6-diacetylresorcinol (**316**) and 2,4-diacetylresorcinol (**317**). Microwave irradiation with the same complex gave the three products in much shorter time, while irradiation at 254nm in diethyl ether just afforded small quantities of product (**315**) and (**316**) as in scheme 104.



Scheme 104

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Calibration of Microwave instrument

Before any rearrangements were carried out in the microwave instrument which was used, a Whirlpool Model 1L 10WH, a calibration of the instrument was performed. The instrument tube is classed as 2450 ± 50 MHz.

Calibration of a cavity type microwave involves the measurement of the microwave field versus percent power setting of the unit. Since the direct measurement of the microwave field would require expensive specialised equipment, modification of the microwave appliance and specialised training, an indirect technique of measuring the microwave field is employed. The strength of the microwave field is measured by determining the amount of microwave energy absorbed by a strongly absorbing substance, usually water. Water is used for power calibrations almost uniformly in commercial and laboratory microwave units.

Using the following thermodynamic relationship, the microwave field strength can be determined and the applied microwave field defined.

$$P = \frac{K \cdot C_p \cdot m \cdot dT}{t}$$

Fig. 16

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P is the apparent absorbed power in watts (joule . sec^{-1}).

K is the conversion factor for calories . $second^{-1}$ to W (4.184 J . cal^{-1}).

C_p is the heat capacity of the microwave absorbing medium, water (0.997 cal . g^{-1} . $°C^{-1}$).

m is the total mass of the microwave absorber in the cavity.

dT is the change in temperature of the microwave absorber from the irradiation of the microwave energy.

t is the time of the microwave exposure.

The calibration format required for microwave units depends on the type of electronic system used by the manufacturer to provide partial microwave power. Few instruments have an accurate and precise linear relationship between percent power setting and absorbed power, so a multiple point calibration is required. In the case of these experiments the multiple point calibration involved measurements at each of the different power setting on the instrument, namely 160, 350, 500 and 750 watts.

A fluorocarbon beaker (glass absorbs microwave energy) of reagent water, of known mass, at 20°C ± 2°C is circulated continuously through the microwave field for a pre determined time. The temperature before and after irradiation is recorded accurately and the power (P) is calculated in the above equation.

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Using six varying amounts of water from 120 g to 450 g and varying times from 45 sec to 180 sec at a nominal setting of 750 watts, the average of the calculated energy output was 582 watts (RSD = 17%). Likewise with the nominal setting of 500 watts, water from 120 g to 1400 g and time from 60 sec to 240 sec the average was 387 watts (RSD = 11%). When the setting was 350 watts and with the mass of water from 400 g to 1250 g and the time variation of 180 sec to 300 sec, an average output of 273 watts (RSD = 14%) was achieved. Finally, with 160 watt nominal setting, 350 g to 1100 g of water and 240 sec to 600 sec for the times an average of 122 watts (RSD = 13%) was recorded.

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Calibration of the microwave oven

Table 41

Nominal Power	Standard	n =	Weight of Standard (g)	Time Sec.	Calculated Power	RSD
750 Watts	H_2O	6	120 -450	45 - 180	582 Watts	17%
500 Watts	H_2O	6	120 - 1400	60 - 240	387 Watts	11%
350 Watts	H_2O	6	400 - 1250	180 - 300	273 Watts	14%
160 Watts	H_2O	6	350 - 1100	240 - 600	122 Watts	13%

The experiments were carried out using phenyl *N,N*-dimethyl sulfamate (**195**) to give 2- and 4-hydroxyphenyl *N,N*-dimethylsulfonamide (**229** and **230**). As the ester and sulfonamides had been previously purified and characterised, they, along with phenol- and the internal standards, *n*-tetradecane and *n*-octadecane were used as the set of standards for quantitation of the products of irradiation by GC-FID.

Although HPLC had previously been used for quantitation in experiments in the thermal rearrangement of this ester, it was found that the gas chromatograph with a flame ionisation detector required shorter sampling time and was equally reproducible, n = 3. The RSD for the standards varied from 6.8% - 9.2%. The molar concentration of the compounds in the standard which is made up in CH_2Cl_2 were as in table 42.

The peak areas of phenol and phenyl *N,N*-dimethylsulfamate were ratioed to the peak area of *n*-tetradecane while the peak area of both sulfonamides were quantified by ratioing to the peak area of *n*-octadecane.

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Molar concentration of standards for quantitative analysis of the microwave irradiated thia-Fries rearrangement of phenyl *N,N*-dimethylsulfamate

Table 42

Compounds	Phenol	*n*-Tetradecane	Phenyl *N,N*-Dimethylsulfamate	2-Hydroxypl *N,N*-dimethylsulfonamide	*n*-Octadecane	4-Hydroxyphenyl *N,N*-dimethylsulfonamide
Molar Concentration	0.00114	0.00021	0.00108	0.00055	0.00087	0.00181

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For each experiment 250 mg of ester (**195**), with an equivalent of $AlCl_3$, was mixed thouroughly and placed in a 25 ml quartz round bottom flask. The flask was supported in a quartz 50 ml beaker and centred on the microwave turntable. The sample was then irradiated for the required time and the reaction was immediately quenched with 3 ml of 1 molar HCl and made up to 100 ml with CH_2Cl_2. Each sample was analysed three times by the GC-FID and the RSD varied from a low of 2.8% to a high of 19.3% over the total range of samples.

For the nominal setting of 160 watts, *i.e.* calculated output of 122 watts, 12 samples were irradiated and rearranged. The times of the irradiation varied from 2 mins. to 30 mins. On analysis, the total of the product compounds varied between 82% and 109% while the total of the rearranged compounds, the 2- and 4-hydroxy *N,N*-dimethylsulfonamides, varied between 63% and 93%. There was between 16% and 25% of the starting ester phenyl *N,N*-dimethylsulfamate and every reaction showed some phenol.

For the nominal setting of 350 watts, *i.e.* calculated output of 273 watts, 12 samples were irradiated and rearranged. The times of the irradiation varied from 2 mins. to 30 mins. On analysis, the total of the product compounds varied between 86% and 108% while the total of the rearranged compounds, the 2- and 4-hydroxy *N,N*-dimethylsulfonamides, varied between 60% and 88%. There was between 14% and 25% of the starting ester phenyl *N,N*-dimethylsulfamate and every reaction showed some phenol.

For the nominal setting of 500 watts, *i.e.* calculated output of 367 watts, 9 samples were irradiated and rearranged. The times of the irradiation varied from 1 mins. to 12 mins. On analysis, the total of the product compounds varied between 81% and 102% while the total of the rearranged compounds, the 2- and 4-hydroxy *N,N*-dimethylsulfonamides, varied between 61% and 82%. There was between 7% and 29% of the starting ester phenyl *N,N*-dimethylsulfamate and every reaction showed some phenol.

For the nominal setting of 750 watts, *i.e.* calculated output of 582 watts, 9 samples were irradiated and rearranged. The times of the irradiation varied from 0.5 mins. to 10 mins. On analysis, the total of the product compounds varied between 68% and 103% while the total of the rearranged compounds, the 2- and 4-hydroxy *N,N*-dimethylsulfonamides, varied between 46% and 79%. There was between 12% and 24% of the starting ester phenyl *N,N*-dimethylsulfamate and every reaction showed some phenol.

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The instrument used to irradiate and rearrange the phenyl *N,N*-dimethylsulfamate is a Whirlpool microwave oven with a turntable, model 1L 10WH with a 2450 ± 50 MHz tube (magnetron). The calibration of the oven showed very good reproducibility both in results for each power settings and also the relationship of nominal setting to the output found, which was between a 20% and a 25% reduction. For the calibration of microwave ovens it is recommended to use 1000 g of water but in this case varying amounts of standard were used and they all gave reproducible results.

When microwaves enter a cavity, they are reflected by the walls. The reflection of the waves eventually creates a three dimensional stationary pattern of standing waves within the cavity, called modes. The cavity in a microwave oven is designed to have typically three to six different modes intended to provide a uniform heating pattern for general food items. Despite being a good solution for these purposes, the use of the multi-mode technique will provide a field pattern with areas of high and low field strength, commonly referred to as "hot and cold spots". The net result is that the heating efficiency can vary dramatically between different positions of the load. When small samples are been irradiated, as in this case, no matter how carefully they are placed in the centre of the turntable there is no guarantee that they not by affected by a "cold spot". Considering all of these drawbacks, every sample introduced into the instrument, rearranged.

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Nominal setting of 160 Watt, calculated output 122 Watt

Table 43

TIME (min)	Phenol %	Phenyl *N,N*-dimethylsulfamate %	2-Hydroxyphenyl *N,N*-dimethylsulfonamide %	4-Hydroxyphenyl *N,N*-dimethylsulfonamide %	Total %	% Rearranged	O/P Ratio
2.00	2.40	24.30	40.20	26.10	93.00	66.30	1.54
4.00	4.30	19.40	36.80	34.40	94.90	71.20	1.07
6.00	3.80	18.90	44.20	34.30	101.20	78.50	1.29
8.00	3.20	21.30	39.30	32.50	96.30	71.80	1.21
10.00	4.10	24.80	37.70	32.20	98.80	69.90	1.17
12.00	3.90	19.40	48.60	44.20	116.10	92.80	1.10
14.00	3.70	15.70	31.80	30.90	82.10	62.70	1.03
16.00	4.50	25.60	34.10	30.20	94.40	64.30	1.13
18.00	3.80	21.40	35.40	32.80	93.40	68.20	1.08
20.00	4.10	18.70	42.50	43.80	109.10	86.30	0.97
25.00	4.70	19.30	40.10	39.30	103.20	79.40	1.02
30.00	4.60	22.30	41.20	46.80	114.90	88.00	0.88

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Nominal setting 350 Watt, calculated output 273 Watt

Table 44

TIME (min)	Phenol %	Phenyl *N,N*-dimethylsulfamate %	2-Hydroxyphenyl *N,N*-dimethylsulfonamide %	4-Hydroxyphenyl *N,N*-dimethylsulfonamide %	Total %	% Rearranged	O/P Ratio
2.00	4.60	21.80	35.60	24.60	86.60	60.20	1.45
4.00	3.80	17.90	38.30	30.60	90.60	68.90	1.25
6.00	5.10	22.20	37.90	31.90	97.10	69.80	1.19
8.00	4.70	18.20	37.50	27.70	88.10	65.20	1.35
10.00	4.20	21.70	42.70	35.60	104.20	78.30	1.20
12.00	5.40	24.10	35.90	33.30	98.70	69.20	1.08
14.00	3.80	19.80	42.70	34.40	100.60	77.10	1.24
16.00	3.90	14.90	41.30	40.00	100.10	81.30	1.03
18.00	4.10	22.10	36.90	42.00	105.10	78.90	0.88
20.00	2.70	21.30	32.70	51.20	107.90	83.90	0.64
25.00	4.30	18.30	33.30	54.50	110.40	87.80	0.61
30.00	3.30	14.10	33.90	47.80	99.20	81.70	0.71

Nominal setting 500 Watt, calculated output 367 Watt

Table 45

TIME (min)	Phenol %	Phenyl *N,N*-dimethylsulfamate %	2-Hydroxyphenyl *N,N*-dimethylsulfonamide %	4-Hydroxyphenyl *N,N*-dimethylsulfonamide %	Total %	% Rearranged	O/P Ratio
1.00	3.60	28.60	34.00	29.10	95.30	63.10	1.17
2.00	4.20	19.20	32.30	29.10	84.80	61.40	1.11
3.00	2.90	9.80	37.20	31.30	81.20	68.50	1.19
4.00	4.10	6.90	39.20	42.10	92.30	81.30	0.93
5.00	4.80	12.70	36.20	38.60	92.30	74.80	0.94
6.00	3.70	15.50	38.20	43.50	100.90	81.70	0.88
8.00	5.20	16.10	35.40	44.90	101.60	80.30	0.79
10.00	4.60	14.80	20.70	51.80	91.90	72.50	0.40
12.00	4.30	22.30	24.80	46.00	95.40	70.80	0.54

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Nominal setting 750 Watt, calculated output 582 Watt

Table 46

TIME (min)	Phenol %	Phenyl *N,N*-dimethylsulfamate %	2-Hydroxyphenyl *N,N*-dimethylsulfonamide %	4-Hydroxyphenyl *N,N*-dimethylsulfonamide %	Total %	% Rearranged	O/P Ratio
0.50	5.20	23.60	13.20	59.80	101.80	73.00	0.22
1.00	4.80	11.90	37.00	31.20	84.90	68.20	1.19
2.00	3.00	14.30	49.10	30.20	99.60	79.30	1.63
3.00	4.20	18.10	47.30	33.30	102.90	80.60	1.42
4.00	3.80	21.70	38.80	30.80	95.10	69.60	1.26
5.00	5.60	16.60	44.90	31.60	98.70	76.50	1.42
6.00	6.10	12.90	41.30	35.30	91.60	76.60	1.17
8.00	5.80	17.30	32.70	35.40	91.20	68.10	0.92
10.00	4.30	17.60	18.20	27.50	67.60	45.70	0.66

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Microwave activation as a non-conventional energy source has become a varied and useful technology in organic chemistry. The number of annual publications on microwave assisted organic reactions is growing rapidly, with more than one thousands reports in print since the pioneering work by Gedye *et al* [52] in 1986. Since this time the main debate has dealt with the question of what actually alters the outcome of the reaction. Is it merely the effect of the thermal heat generated by the microwaves or is it an effect specific for microwave heating? In order to be able to make this distinction, the term "specific microwave effect" should be defined. Historically, "specific microwave effect" has been claimed, when the outcome of a synthesis or reaction, performed using microwave irradiation, differs from its thermally heated counterpart. The main advantage of using microwave assisted organic synthesis is the shorter reaction times.

Microwave effects are most likely to be observed in solvent-free reactions which can be grouped according to the three following methods: (a) reactions between the neat reagents in quasi-equivalent amounts, requiring preferable at least one liquid phase in heterogeneous media and leading to interfacial reactions;[106] (b) solid-liquid phase transfer catalyst (PTC) conditions, in the case of anionic reactions using the liquid electrophile as both reactant and organic phase, and (c) reactions using impregnated reagents on solid mineral supports (alumina's, silica's and clays) in dry media. These procedures coupled with microwave activation have proven beneficial and have led to a lot of success.

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Contrary to the above, the absence of microwave effect can result from at least three different origins: (a) a similar polarity of the transition state (TS) when compared to the ground state (GS). (b) A very early transition state along the reaction coordinates which cannot allow the development of polarity between the GS and the TS. This will occur when the reactions only require classical mild conditions. Slight differences can appear when performing the reaction in the presence of a solvent, due to a superheating effect, if no stirring is carried out, and, (c) a too high temperature level, which may produce good yields in short reaction times under conventional heating. In order to find evidence of 'specific microwave effect', it is necessary to reduce the temperature under conventional conditions in order to start from rather a poor yield ≈30-40%, to appreciate microwave activation. These cases have been revealed in some studies where a microwave effect appeared at relatively low temperatures but are masked at higher temperatures where yields of conventionally heated reactions are elevated.

It is impossible to obtain information on a specific microwave effect from the results of the current rearrangements carried out, but one would assume that it was solely thermal effects which gave the rearranged products. An attempt to find any relationship between the experiment at the various power settings are set out below (tables 47) and again it is very difficult to find anything that one could claim as a connection.

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Table 47

Nominal Setting (Watts)				
	160.00		350.00	
Calculated Output (Watts)				
	122.00		273.00	
Time (min)	*O/P* Ratio of 2- and 4-hydroxyphenyl N,N-dimethylsulfonamide	Time X Power Watts min^{-1}	*O/P* Ratio of 2- and 4-hydroxyphenyl N,N-dimethylsulfonamide	Time X Power Watts min^{-1}
0.50				
1.00				
2.00	1.54	244.00	1.45	546.00
3.00				
4.00	1.07	488.00	1.25	1092.00
5.00				
6.00	1.29	732.00	1.19	1638.00
8.00	1.21	976.00	1.35	2184.00
10.00	1.17	1220.00	1.20	2730.00
12.00	1.10	1444.00	1.08	3276.00
14.00	1.03	1708.00	1.24	3822.00
16.00	1.13	1952.00	1.03	4368.00
18.00	1.08	2196.00	0.88	4914.00
20.00	0.97	2440.00	0.64	5460.00
25.00	1.02	3050.00	0.61	6825.00
30.00	0.88	3660.00	0.71	8190.00

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INTRODUCTION

Many of the reactions carried out in the organic chemistry laboratory take place between molecules all of which are in their ground electronic states. In a photochemical reaction, however, a reacting molecule has been previously promoted by absorption of light to an electronically excited state. A molecule in an excited state must lose its extra energy in some manner, it cannot remain in the excited condition for long. A chemical reaction is one but not the only method of relinquishing this extra energy[59].

Electrons can move from the ground-state energy level of a molecule to a higher level (i.e. an unoccupied orbital of higher power) if outside excitation takes place. In a photochemical process the energy is in the form of light. Light of any wavelength has associated with it an energy value given by $E = h\nu$ where ν is the frequency of light (ν = the velocity of light divided by the wavelength λ) and h is Planck's constant. Since the energy levels of a molecule are quantised, the amount of energy require to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level, i.e. the energy will be used by the molecule for electron promotion and the light that leaves the sample will be diminished in intensity or completely absorbed.

When a molecule absorbs a quantum of light, it is promoted to an excited state and because the energy of visible and UV light is of the same order of magnitude as that of covalent bonds there is the possibility that the molecule may cleave into two parts, a process known as photolysis.

Typical energies for some covalent single bonds and the corresponding wavelengths

Table 48

E

Bond	Bond Energy (kJ/mol)	Wavelength (nm)
C-H	397	300
C-O	368	325
C-C	347	345
Cl-Cl	243	495
O-O	146	820

There are two types of excited molecules called species, a singlet and a triplet, both of which can undergo chemical reaction but it is much more common for triplets because they have a longer lifetime. Excited singlet species generally have a lifetime of less than 1^{-10} sec, and undergo a physical process such as fluorescence or even phosphorescence as they go from an excited state to a ground state, before they have a chance to react chemically. Photochemistry is therefore largely the chemistry of triplet states[107] and the possible chemical pathways that may be taken by an excited molecule include: simple cleavage into radicals, decomposition into molecules, intramolecular rearrangement, intermolecular rearrangement, photoisomerisation, hydrogen atom abstraction, photodimerisation and photosensitisation.

The reactor used for these experiments was an enclosed round PVC container 150 mm in diameter and about 220 mm high. This was capped on top with a heavy-duty blanking-cap into which four holes were bored, one in the centre for the 200 mm quartz narrow-necked test tube (the reaction vessel) and three at equidistant around this for the UV lamps. All the inside of this assembly was lined with reflective aluminium foil (fig. 17)

The lamps used were Ace Glass Inc. UV quartz 12 watt low pressure and the power supply was a UV low pressure power supply 12 watt all from the same supplier.

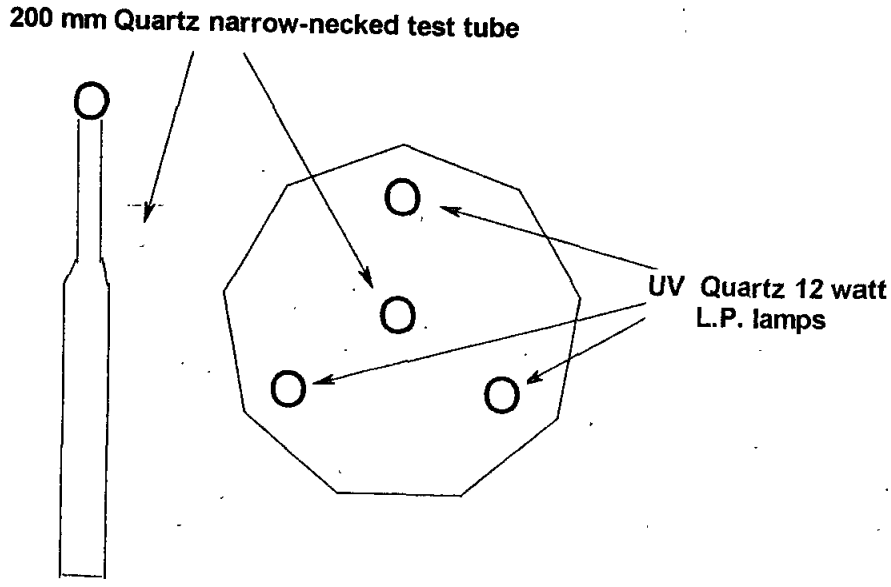

Fig. 17

Phenyl *N,N*-dimethylsulfamate (**195**), 200 mg in 50 ml hexane was exposed to the three lamps clamped on a retort stand (before the reactor was made). The lamps were placed above the solution which was in an open vessel. The whole assemble was covered for safety. No rearrangement products, 2- or 4-hydroxyphenyl *N,N*-dimethylsulfonamide could be identified after one hour of irradiation. The quantity of ester was reduced and a number of other unidentified peaks were on the chromatograph. Qualitative analysis was by GC-MS.

For the second experiment the solvent was changed to CH_2Cl_2, dichloromethane. 100 mg in 25 ml was subjected to the UV irradiation. Samples were analysed at 30, 60, 90 and 120 minutes but no rearranged compound could be identified and the quantity of the starting ester reduced with time. Other unknown compounds were detected by GC-MS.

A third attempt was made, still under the initial conditions, but this time acetonitrile was the solvent used. Sampling of the reaction mixture took place every 30 minutes, up to four hours by which time the starting ester had disappeared. Neither of the rearrangement products was identified and again, there were many unknowns as analysed on the GC-MS, which presumably were from the breakdown of the ester.

When the above reactor was commissioned, a new set of experiments was carried out. 100 mg of the ester, phenyl *N,N*-dimethylsulfamate in 10 ml of methanol, which was degassed by bubbling N_2 through the solution, was placed in a quartz test tube, the reaction vessel. This was irradiated by the three lamps for one hour and a minute amount

of 2-hydroxyphenyl *N,N*-dimethylsulfonamide was identified, ≤ 0.1%. There was no quantitative analysis carried but based on the known peak areas of the sulfamates and sulfonamides for the instrument, the GC-MS, the estimate is quite accurate.

Under the same conditions but with CH_2Cl_2 as solvent, this compound rearranged to the same degree. In both of these experiments there was considerable breakdown of the starting ester to unidentifiable compounds.

1 mmol of phenyl *N,N*-dimethylsulfamate was slurried with 1 equiv. of β cyclodextrin (1.135 g) in H_2O and the mixture was stirred for 18 hours. This mixture was then filtered, washed with 10 ml diethyl ether and dried. The reactant was irradiated by the three UV lamps in the dry form in the reaction vessel. Four samples were irradiated for varying lengths of time as in table 50.

After the irradiation the reaction mixture was extracted with three 20 ml aliquots of CH_2Cl_2 and initial analysis was by GC-MS. This identified the sulfonamides and many unknown compounds. A quantitative analysis was carried out by GC-FID using the standards discussed previously.

Table 49

Compounds	Phenol	C 14	Phenyl *N,N*-Dimethylsulfamate	2-Hydroxyphenyl *N,N*-dimethylsulfonamide	C 18	4-Hydroxyphenyl *N,N*-dimethylsulfonamide
Molar Concentration	0.00114	0.00021	0.00108	0.00055	0.00087	0.00181

Table 50

Time (mins.)	Sample Weight	2-Hydroxyphenyl *N,N*-dimethylsulfonamide	4-Hydroxyphenyl *N,N*-dimethylsulfonamide	Starting Ester
30	210 mg	≤ 0.1%	Not Detected	≈ 90%
60	214 mg	≤ 1%	Not Detected	≈ 75%
120	195 mg	≈ 2-3%	≤ 0.1%	≈ 58%
180	223 mg	≈ 5-7%	≤ 1%	≈ 32%

4-Fluorophenyl *N,N*-dimethylsulfamate (**196**) was irradiated in the reactor, first in CH_2Cl_2 and then in methanol at 100 mg in 10 ml solvent. Irradiation time in both cases was 30 mins and analysis was carried out by GC-MS. No rearranged product was identified but again a number of unknowns showed peaks on the chromatograph.

UV irradiation of 4-chlorophenyl *N,N*-dimethylsulfamate (**197**) and of 4-bromophenyl *N,N*-dimethylsulfamate (**198**) in both CH_2Cl_2 and methanol, (100 mg in 10 ml solvent) were carried out in the reactor, but without any rearrangement taking place. Again there was breakdown of the starting ester and the dichloromethane possible formed tetrachloroethane.

Phenyl sulfamate (**185**), 4-fluorophenylsulfamate (**186**), 4-chlorophenylsulfamate (**187**) and 2,6-difluorophenylsulfamete (**192**) were all irradiate in the UV reactor in methanol and with the β cyclodextrin without any success. For this series of compounds the starting ester appeared to break down very easily.

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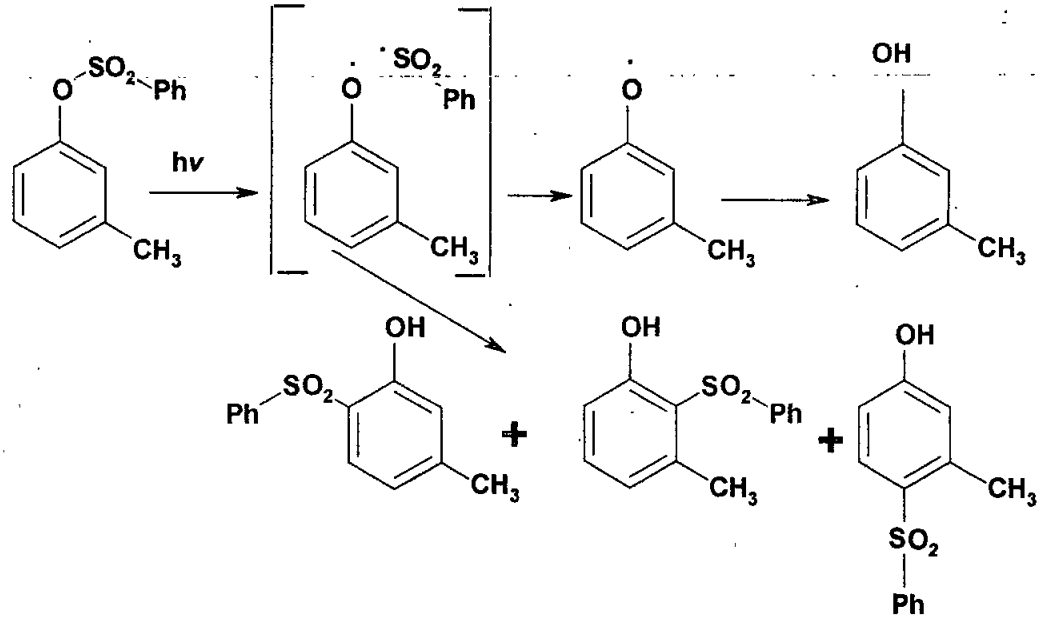
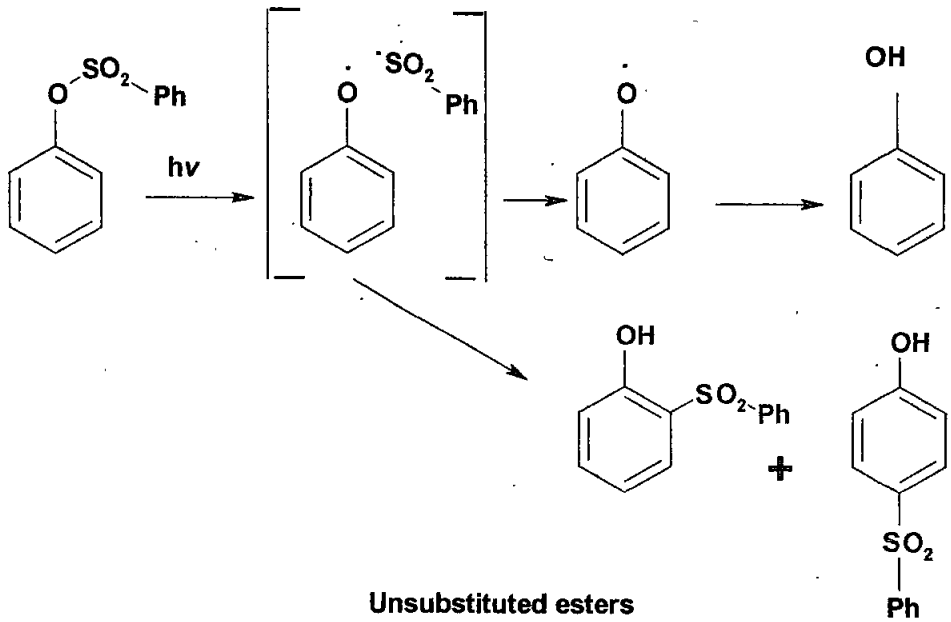
The thia-photo-Fries rearrangement reactions which were carried out yielded little informative data but scope for further investigation is obvious.

The one method that showed any promise was adapted from a publication by Pitchumani et al.[108] wherein they state that "cyclodextrin complexation shows remarkable selectivity in the photo-Fries rearrangement of sulfonate esters and sulfonanilide and that an impressive regioselectivity is observed with *meta*-substituted sulfonate esters." The results, they claim are explained on the basis of selective modes of complexation of the substrate within the cyclodextrin cavity (schemes 105 and 106).

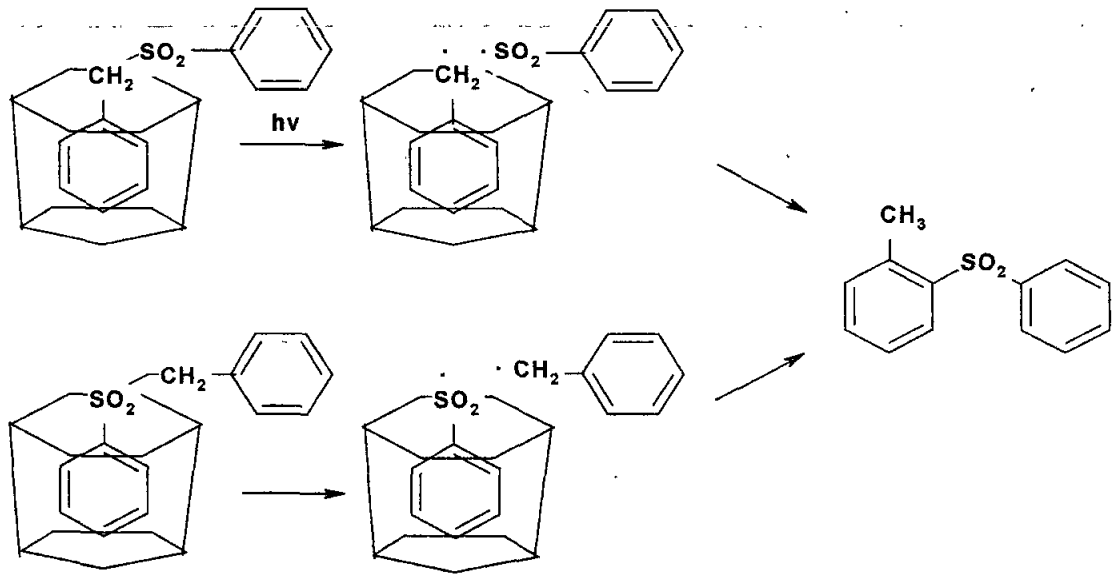
The striking feature of cyclodextrin complexation is its ability to exert geometric control over the traffic of the entrapped molecular species resulting in selectivity in a variety of thermal and photo-chemical reactions. Cyclodextrin is a naturally occurring sugar produced from starch by an enzyme. There are three forms found in nature, alpha, beta and gamma and they differ structurally by containing 6, 7 or 8 D-glucopyranosyl units. β CD has the correct size of cavity to suit the molecules which are used in these experiments (scheme 107).



Scheme 105



Scheme 106



Scheme 107

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Sonochemistry

Sonochemistry is chemistry assisted / enhanced by ultrasound This means that chemical reactions which take place under more conventional conditions are accelerated , or even yield totally different products. The reason for this can be due to either physical or chemical effects of cavitation. The physical effects can enhance the reactivity of a catalyst by enlarging the surface area, or accelerate a reaction by proper mixing of reagents. The chemical effects of ultrasound enhance reaction rates because of the formation of highly reactive radical species formed during cavitation.

Sonochemistry is being mentioned at this stage as it is envisaged that, although preliminary attempts were unsuccessful this technique may have scope for future work. There is only one instance in the literature of ultrasound being of possible assistance to the Fries rearrangement[109]. They state that the bulk electrolysis of [3-(3,4-dichlorophenyl)-1,1-dimethyl urea] was carried out at a glassy carbon anode with ultrasound used to avoid a total blockage of the electrode surface by a passivating film. This oxidation of diuron gave one major product, a dimmer, and 2 other compounds which are suggested to originate from an intramolecular Fries rearrangement of the first. They continue by saying that the rearrangement would occur at the positively charged electrode surface which would be facilitated by the ultrasound maintaining the electrode surface free of film. Although assisting, the reaction is not a sonochemical rearrangement.

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300 mg of phenyl *N,N*-dimethylsulfamate (**195**) was mixed with a 1 : 1.1 molar ratio of $AlCl_3$ in a 50 ml rb flask. This was placed in an active sonic bath for in total of about 6 hr. Sampling and analysis were carried out every 20 min as the sonic bath was re-set. No rearrangement or even breakdown of the ester could be detected by GC-MS. It is believed that this instrument is not sufficiently powerful to create the cavitation to instigate the rearrangement.

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