Intramolecular Radical Aromatic Substitution Reactions

A Thesis Presented by

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In Partial Fulfilment of the Requirements
for the Award of the Degree of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

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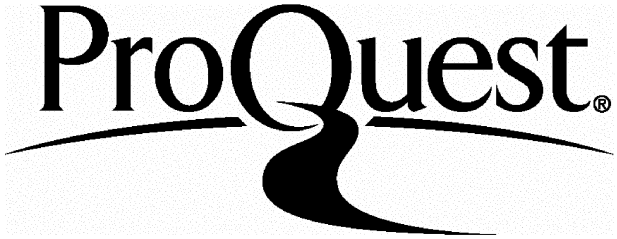
November 1994



Abstract

This thesis is divided into three chapters.

Chapter One presents a review on *ipso* substitution in aromatic and heteroaromatic rings, and is divided in two parts. The first is concerned with intermolecular *ipso* substitution reactions and the second describes the work that has been done on the intramolecular reactions.

Chapter Two describes the advances of an intramolecular free radical *ipso* substitution strategy which uses a sulfonyl moiety as an *ipso* nucleofuge. The reaction of an aryl radical with a sulfonyl substituted acceptor ring, with differing substituents on the acceptor ring and tethering chains of different nature and size, is discussed.

A strong effect on the promotion of *ipso* substitution was found with compounds where an *ortho* substituent to the sulfonyl substituted position was present. In the absence of an *ortho* substituent, preferential attack occurs in order to give the more stable radical.

The nature of the bridge between the two aromatic rings is also an important factor, and a slight change in the strain or conformation can change the course of the reaction. With simple chains was observed that in 1,5-*ipso* substitution reactions, a nitrogen atom is a more efficient *ipso* director than an oxygen atom, which in turn is better than a methylene unit.

1,6-*Ipso* substitution reactions were shown to be less efficient processes. Several linking chains, resulting from the combination of nitrogen, oxygen, methylene and carbonyl units were analysed, and in general *ipso* substitution products could be obtained, although, in some cases, only by the strategical introduction of *ortho* substituents.

A preliminary study on 1,5-*ipso* substitution reactions of α-carbonyl radicals was undertaken, in order to optimise the reaction conditions. Reactions involving tin compounds, transition metals and xanthates were studied. When tin hydride was used, the formation of indolone derivatives, by a sequential 1,5-*ipso* substitution / 1,5-addition of the intermediate amidyl radical to the aromatic ring was observed.

The temperature of the reaction was shown to be an important factor, as other competitive processes, such as reduction or β-scission can also occur.

Chapter Three provides a formal account of the experimental results and procedures.

Contents

Acknowledgements

I would like to thank my supervisor, Prof. W. B. Motherwell, for his constant flow of ideas, encouragement, guidance and friendship over the past three years.

I would like also to thank all the past and present members of the WBM group, who made these years so much enjoyable, in particular Herve, Fez and Lisa and my contemporaries Sheena, Donogh, Man-Tat and Lewis .

A very special acknowledgement to all the "eskimos" who proof read this thesis, Mark, Richard, Caroline, Tim, Alvin, Adrian, Donogh, Frederic, Mila, Peter, Phil, Sheena and Tania, Simon, Martin, Jean-Marc and Nadine, and also Eric for taking care of my bench.

This work would not have been possible without the support of the technical staff at Imperial College and University College London; especially Dick Sheppard, Paul Hammerton (IC) and Jill Maxwell (UCL) for high field nmr experiments, Geoff Tucker and John Barton (IC), Dr. J.A. Ballantine (SERC Mass Spectroscopy Centre, Swansea), Dr. M. Mruzek and John Hill (UCL) for the mass spectra. Also thanks to Dr. D. A. Tocher for the X-ray crystal structure, Alan Stones (UCL) for microanalyses Steven Corker for the HPLC and P. Leighton for help solving all the problems.

Outside the Chemistry Department, I would like to thank Ana and Barry for being good friends, Lena and Manel for the innumerous weekends they had to put up with me. A special acknowledgement to Luisa and Carlos for their friendship, and useful comments about my work. Also, to all my friends in Portugal, who did not forget me while I was away, and to all those who visited me in London, a big thank you.

For funding I am grateful to JNICT, Programa Ciência for very generous sponsorship.

Most importantly, I would like to thank my parents for their constant love and encouragement, and to my sisters, brothers, nephews and nieces, in particular to Paulina, who beat all the records in travelling to London.

Finally, I would like to thank Ian, for his love and support over the last two years.

I dedicate this thesis to my family.

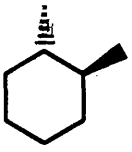
Abbreviations

Ac	Acetyl
Ad	Adamantane
AIBN	α,α'-Azoisobutyronitrile
Aq	Aqueous
Ar	Aryl
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling point
br	Broad
Bu	Butyl
Bz	Benzoyl
CI	Chemical ionization
conc.	Concentrated
conv.	Conversion
d	Doublet
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DPDC	Di-isopropyl peroxydicarbonate
DTBP	Di-t-butyl peroxide
EI	Electron impact
eq.	Equivalent(s)
Et	Ethyl
FAB	Fast Atom Bombardment
hr	Hour(s)
hν	Light
m	Multiplet
m	*meta*
m-CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
min	Minute(s)
m.p.	Melting point
^{1}H nmr	Proton nuclear magnetic resonance
o	*ortho*
p	*para*
Ph	Phenyl
ppm	Parts per million
p	Primary (^{13}C n.m.r.)

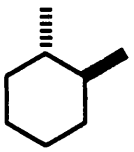
py	Pyridine
q	Quartet (^{1}H nmr) or Quaternary (^{13}C nmr)
R	Unspecified carbon substituent
r.t.	Room temperature
s	Singlet (^{1}H nmr) or Secondary (^{13}C nmr)
sat.	Saturated
SET	Single electron transfer
t	Triplet (^{1}H nmr) or Tertiary (^{13}C nmr)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	N,N,N',N',-Tetramethylethylenediamine
Tol	*p*-Tolyl
tr.	Traces
Ts	Tosyl
UV	Ultraviolet
vs	*versus*
X, Y	Unspecified groups

Stereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr.* Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.



single enantiomer



racemic

* H. Maehr, *J. Chem. Ed.*, 1985, **62**, 114.

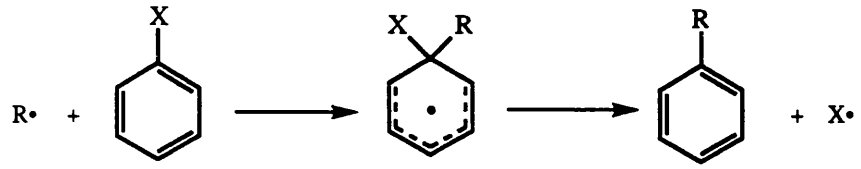
Chapter One:

Introduction

Radical *Ipso* Attack on Aromatic Compounds

The displacement of groups other than hydrogen on an aromatic ring has been generally described as *ipso* substitution. The importance of this process is that it takes advantage of an existing group on the molecule to introduce a different one in its place.

Many examples of radical *ipso* substitution reactions have been described, and it is believed that they occur *via* an addition-elimination mechanism (Scheme 1.1). The radical R• attacks the aromatic ring at the same position as the leaving group X, leading to the formation of a σ-complex intermediate. The intermediate eliminates to afford the substituted aromatic ring and the radical X•.



Scheme 1.1

Ipso attack is not the only process which can occur, since the addition to an unsubstituted position can of course be a competitive process.

There are several factors which control the selectivity of attack, either at the *ipso* carbon atom or another unsubstituted position. Thus, the nature of the attacking radical, the aromatic substrate, and the leaving groups may all be involved.

Such processes can occur either in the inter- or in the intramolecular mode.

The purpouse of the present introduction, which is divided into two sections, is to provide some background information on radical *ipso* substitution reactions on aromatic rings. The first section is concerned with intermolecular reactions, while the second part will describe intramolecular *ipso* substitution reactions.

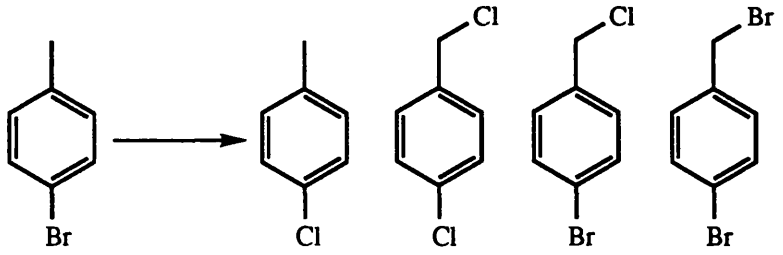
1.1. Intermolecular Aromatic *Ipso* Substitution Reactions

1.1.1. Aromatic Halogen Displacement

As the displacement of a halogen atom by another group through *ipso* substitution has been previously reviewed,[1] this introduction will highlight only the more important aspects of each type of substitution.

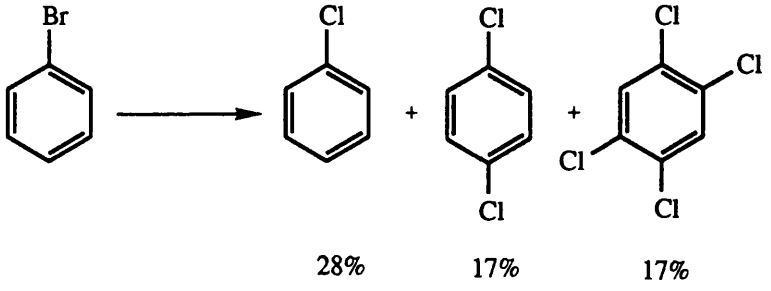
1.1.1.1. Displacement by a Halogen

The first work involving radical *ipso* substitution reactions dates from 1890, when Srpek[1] reported that chlorination of *p*-bromotoluene at room temperature gave an inseparable mixture of products with chlorine and bromine substituents in both the ring and the side chain (Scheme 1.2). Since then, several workers have described the displacement of a halogen atom by another one, but, in general, even with simple monosubstitution (Scheme 1.3) the reaction has been found to be unselective.



Reagents: SO_2Cl_2, benzoyl peroxide.[2]

Scheme 1.2

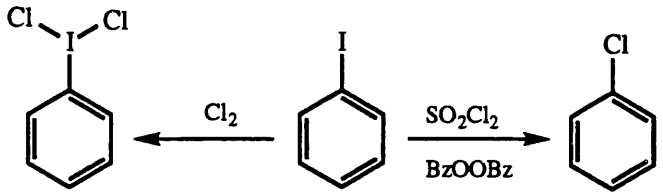


Reagents: Cl_2, light.[1]

Scheme 1.3

The presence of additional electron withdrawing substituents decreases reactivity, and in the case of *p*-bromonitrobenzene the reaction fails.[3] The same result is observed in the gas phase chlorination of a number of substituted benzenes.[4]

The displacement of an iodine atom was reported some time later.[5] Since chlorine itself reacts with iodobenzene to form iodobenzene dichloride, the reaction was performed using sulfuryl chloride and a peroxide initiator (Scheme 1.4).

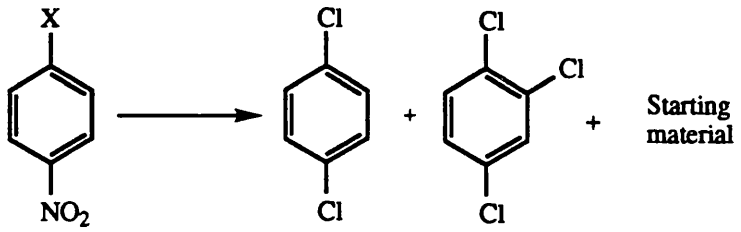


Scheme 1.4

A lack of selectivity was again observed, with formation of a mixture of chlorobenzene, *p*-dichlorobenzene (traces), and diiodobenzene. Competitive displacement of iodine and bromine by chlorine atoms showed that iodine is displaced 2.3 times as rapidly as bromine.

The substitution of a halogen by another of higher atomic number is a process that is contrary to expectations, based on bond energy data. Nevertheless bromination of chlorobenzene proceeds in the gas phase, to give low yields of dichlorobenzenes, dibromobenzenes and bromochlorobenzenes.[4]

Photo-initiated chlorination of *p*-chloronitrobenzene at room temperature gives mainly *p*-dichlorobenzene, with traces of 1,2,4-trichlorobenzene.[6] However, when the substrate is *p*-bromonitrobenzene, chlorodebromination and chlorodenitration are competitive processes. The increasing concentration of chloronitrobenzene before its conversion to dichlorobenzene, shows a preference for initial attack at the halogen substituent (Scheme 1.5).



X= Cl	Major	2	43
X= Br	49	4	42

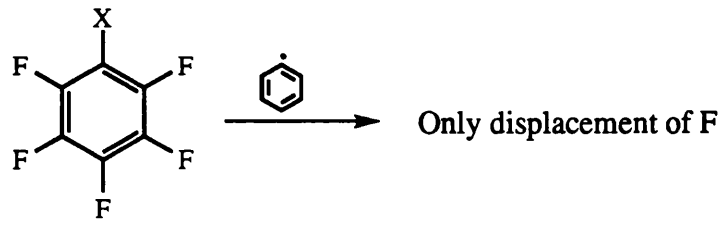
Reagents: Cl_2, CCl_4, light.

Scheme 1.5

1.1.1.2. Displacement by a Phenyl Radical

The displacement of a halogen atom by a phenyl radical is not a highly effective process, since the phenyl radical prefers to add to an unsubstituted position. However, an appreciable amount of biphenyl may be formed if iodobenzene is selected as substrate. In this case, iodine atom is lost 10 times more frequently than a hydrogen.[7] A comparative study between the reactivity of fluoro and hydrogen substituents towards the attack of a phenyl radical has been made. When phenyl radicals react with a mixture of hexafluorobenzene and benzene, comparable reactivities were detected.[1]

In a study of the relative reactivity of halogens towards displacement by the phenyl radical, a greater susceptibility of fluorine to be replaced was noted. Thus, chloropentafluorobenzene and bromopentafluorobenzene on reaction with phenyl radicals[8] gave only displacement of fluorine (Scheme 1.6). The overall nature of the pentafluoroaromatic substrate may however play an important role in this instance.

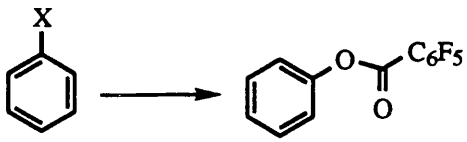


X=Cl, Br

Scheme 1.6

The presence of electron withdrawing substituents on the aryl radical leads to a decrease in the yield of the reaction, as demonstrated by the reaction of hexafluorobenzene with substituted benzoylperoxides (*m*-Me (55%), *m*-Cl (28%), *m*-Br (28%) and *p*-NO_2 (traces; reaction performed in a sealed tube)).[9]

Further studies on the homolytic reactions of pentafluorobenzoyl peroxide show that the reaction with chlorobenzene and bromobenzene occurs before decarboxylation has occurred,[10] and the phenyl ester is formed by displacement of the halogen. However, nitrobenzene exhibits different behaviour affording a mixture of biaryls and only traces of the phenolic ester are detected.



+ $C_6F_5CO_2H$ + Biaryls

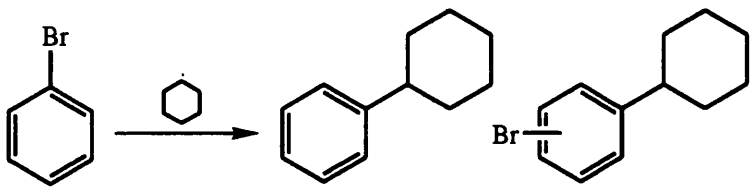
X= Br	51%	38%	0%
Cl	41	28	0
NO_2	tr.	41	28

Reagents: $(C_6F_5CO_2)_2$, 80°C. Yields based on peroxide consumed.

Scheme 1.7

1.1.1.3. Displacement by an Alkyl Radical

The reaction of an alkyl radical with a halobenzene occurs to a limited extent *via ipso* substitution. Reaction of bromobenzene with the cyclohexyl radical, produced from cyclohexane and di-*t*-butyl peroxide, gave the *ipso* substitution compound (17%) and a mixture of compounds resulting from attack at the *ortho* (48%), *meta* (26%) and *para* (8%) positions[11] (Scheme 1.8).



1 : 5

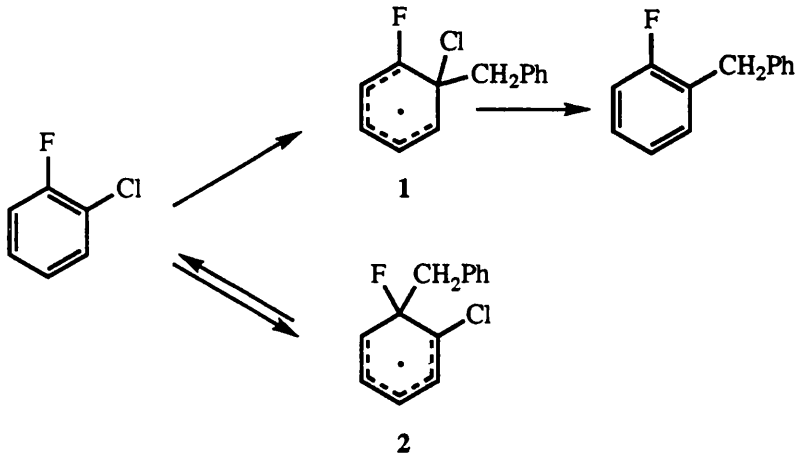
Reagents: Cyclohexane, DTBP, 115-120°C, 48h.

Scheme 1.8

A better selectivity for the substituted positions is observed on selection of *ortho* dihalobenzenes as substrates. The presence of the second electron attracting substituent on an adjacent position, the relief of steric and electronic repulsion when the radical adds to one of the carbons bearing the halogen and the ability of the halogen *ortho* to stabilise the cyclohexadienyl radical are all different factors which can influence this selectivity.[12]

The relative capacity for replacement of the halogens followed the unusual sequence of F>I>Br>Cl.[12] The electronegativity and size of the fluorine atom may well explain such a preference for initial attack at the *ipso* site by the nucleophilic cyclohexyl radical.

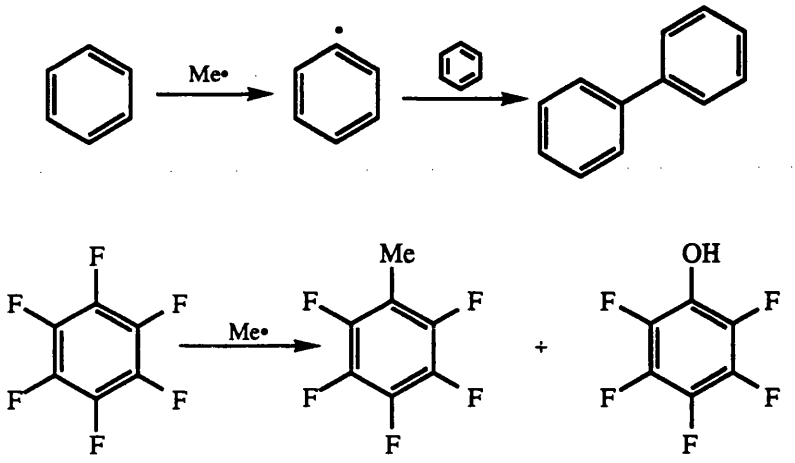
However, a different reactivity is observed when bromofluorobenzene and chlorofluorobenzene react with benzyl radicals. On the basis of the foregoing argument it would be expected that the displacement of the more electronegative halogen is the favoured reaction, but the loss of a fluorine atom was not observed. On the assumption that the addition of the benzyl radical is a reversible process, and that the carbon-fluorine bond is stronger than the carbon-chlorine bond, then intermediate **1** is more likely to proceed to product while intermediate **2** reverts to starting materials[13] (Scheme 1.9).



Scheme 1.9

Reaction of the methyl radical, formed by pyrolysis of nitromethane, with benzene does not produce toluene but only biphenyl. The methyl radical therefore

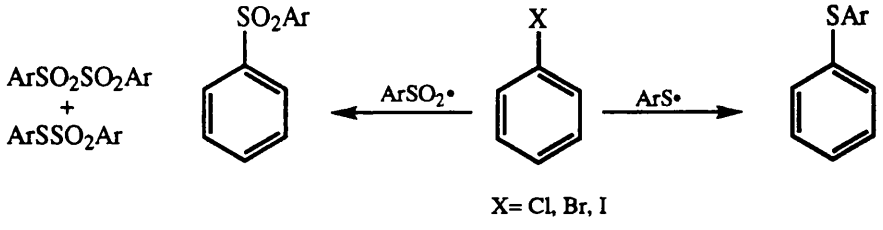
prefers to abstract a hydrogen atom and form the phenyl radical, which can then react with another molecule of benzene.[7] On the other hand, the reaction with hexafluorobenzene gives both methylpentafluorobenzene and pentafluorophenol, the latter product presumably derived by *ipso* attack of the nitro radical[7] (Scheme 1.10).



Scheme 1.10

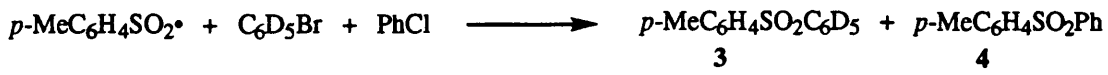
1.1.1.4. Displacement by Sulfur and Silicon Radicals

Only a few reports refer to the displacement of halogens by sulfur and silyl radicals. Benzenesulfenyl and benzenesulfonyl radicals react with chloro, bromo and iodobenzene to form products of dimerization and/or disproportionation as well as *ipso* substitution.[14] A strong dependence on temperature was observed, with the *ipso* substitution products only being formed above 150 °C. At this temperature, the sulfur based dimerization products were unstable, and regenerated the free radicals (Scheme 1.11).



Scheme 1.11

A reactivity order for the tosyl radical was determined by a series of competition reactions with mixtures of labelled and unlabelled halobenzenes (Scheme 1.12). The results, obtained by determining the relative amounts of labelled (**3**) and unlabelled sulfone (**4**), were iodobenzene > bromobenzene > chlorobenzene in a ratio 18.6 : 6 : 1.



Scheme 1.12

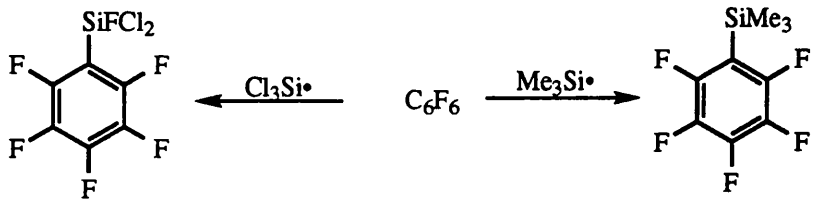
The reaction of bromobenzene, either with benzenesulfonyl or benzenesulfenyl radicals, is facilitated by electron releasing substituents, as shown in Table 1.1.

Table 1.1[14]

Reactivities of substituted bromobenzenes towards phenylsulphonyl and phenylthio radicals (relative reactivities to bromobenzene = 1)

X	$PhSO_2$	PhS
p-OMe	8.78	60
p-Me	3.59	1.84
p-CO_2Me	0.27	---
p-NO_2	---	3.00

Trimethylsilyl and trichlorosilyl radicals undergo *ipso* substitution on reaction with hexafluorobenzene (Scheme 1.13). Irradiation of trimethylsilane or trichlorosilane and hexafluorobenzene with UV light produces silyl radicals, which then attack the hexafluorobenzene nucleus. Although the reaction with trimethylsilyl radicals proceeds as expected, the reaction with trichlorosilyl radicals is further complicated by halogen exchange.[15]



Scheme 1.13

1.1.2. Aromatic Displacement with Cleavage of a Carbon-Nitrogen Bond

1.1.2.1. The Nitro Group

The displacement of a nitro group from an aromatic ring by *ipso* substitution has been extensively investigated.[13,16,17]

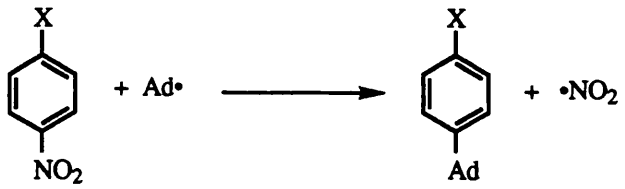
As we have noted earlier (Scheme 1.5), a nitro group may be replaced by a halogen atom. This was also observed[4] in the gas phase at 375 °C on reaction of nitrobenzene with chlorine, to give chlorobenzene as the major product, together with chloronitrobenzene in a 45 : 2 ratio.

The pentafluorobenzoyl radical, generated by decomposition of di-pentafluorobenzoyl peroxide, reacts with nitropentafluorobenzene, by displacement of the nitro group, to give mainly biaryls. In this instance, unlike the non fluorinated precursor (Scheme 1.7), the formation of esters was not observed.[10]

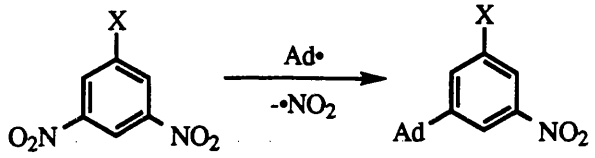
Some evidence for the replacement of nitro groups and sulfonyl groups during electrolytic oxidation has been reported, but the products were not isolated.[1]

Tiecco[18] has published an extensive study on the *ipso* substitution reaction of nitrobenzenes with alkyl radicals. This alkyl denitration was examined using primary, secondary and tertiary alkyl radicals. However, the best conversions were obtained with the adamantyl radical, produced from adamantane-1-carboxylic acid by persulfate oxidation. It was also noted that strongly electron deficient aromatic rings also favoured this process. Reaction of nitrobenzene, *p*-nitrotoluene, *p*-nitroanisole, *o* and *m*-dinitrobenzene and *o* and *m*-nitrotoluene did not produce *ipso* substitution products[16] (Scheme 1.14).

The presence of additional electron withdrawing groups is obviously necessary in order to increase the yields of *ipso* substitution products. Thus, when more than one nitro group is present, only one is replaced and reactions do not proceed further.[17]

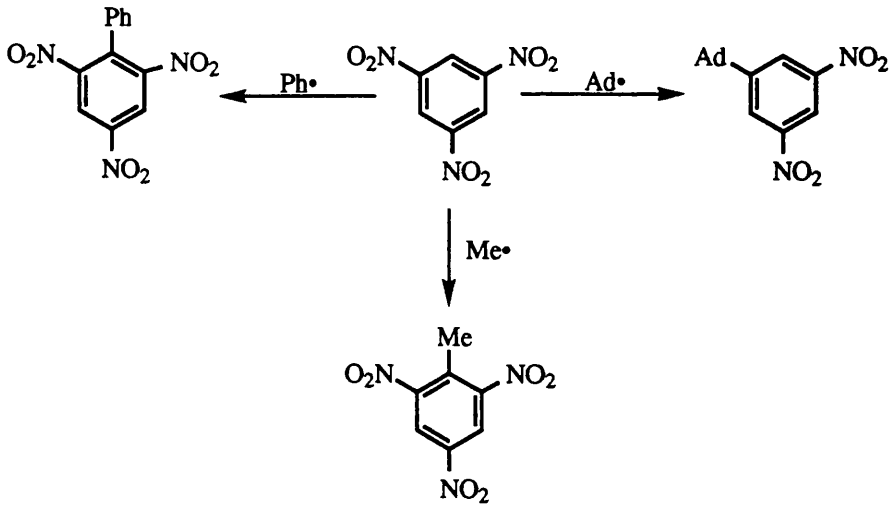


X= NO_2 (60%), SO_2R (60%), CO_2Me (60%), COMe (60%), CHO (45%), CN (45%)



Scheme 1.14

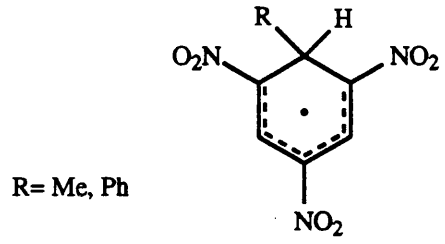
It is of interest to note that the course of this reaction changes considerably when methyl or phenyl radicals are used, inasmuch as addition is favoured over *ipso* substitution[17](Scheme 1.15).



Scheme 1.15

The difference of selectivity has been attributed to the different polarities of the radicals.[13] The adamantyl radical, as a strong nucleophilic radical, adds at the most positive carbon atom, giving the *ipso* product. In this case, polar effects operate and the addition is governed by the local charge density at the ring positions.

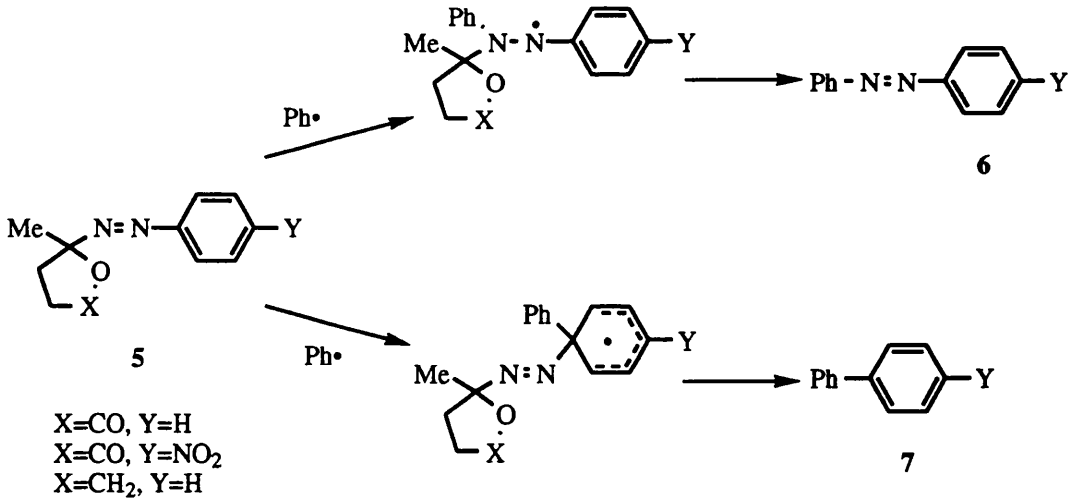
On the other hand, with methyl and phenyl radicals, which can be considered electroneutral radicals, the polar effects are expected to be negligible and the regioselectivity is governed by the stability of the σ-complex (Scheme 1.16).



Scheme 1.16

1.1.2.2. The Azo Group

In an interesting study, the reaction of a phenyl radical with an arylazo compound (**5**) has been shown to generate two different types of product; one from the process of addition / elimination at the nitrogen atom of the azo group, **6**, and the other from *ipso* substitution on the aromatic ring (**7**)[19] (Scheme 1.17).



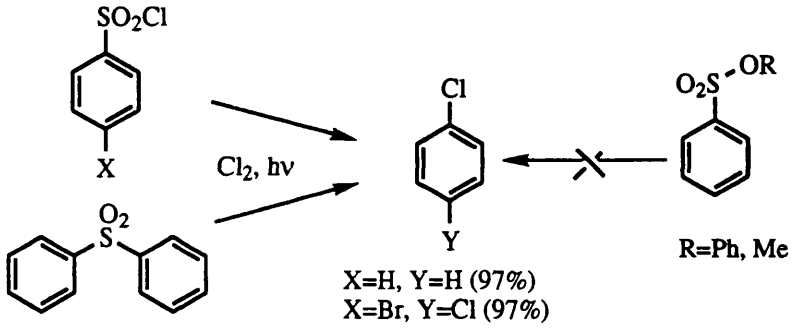
Scheme 1.17

These two competitive pathways may be channelled however, and there is an increase of *ipso* substitution product (**7**) when an electron withdrawing substituent is present on the aromatic ring (Y= NO_2, 48%).

1.1.3. Aromatic Displacement with Cleavage of a Carbon-Sulfur Bond

Although there has been little published on the displacement of sulfonyl groups from an aromatic ring by intermolecular *ipso* attack, it seems to be an efficient process.

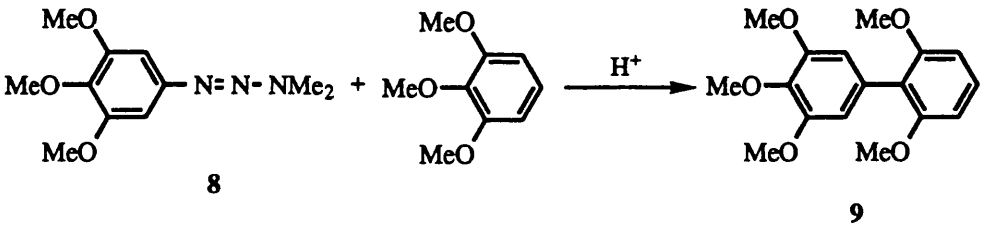
The only example[3] reports that photoinitiated chlorination of benzenesulfonyl chloride, *p*-bromobenzenesulfonyl chloride and diphenylsulfone produce nearly quantitative yields of chlorobenzene (97%), *p*-dichlorobenzene (97%) and chlorobenzene, respectively. However, phenyl and methyl benzenesulfonates showed no displacement (Scheme 1.18).



Scheme 1.18

1.1.4. Aromatic Displacement with Cleavage of a Carbon-Oxygen Bond

The possible replacement of a methoxy group by an aryl radical was observed as the only product from the reaction of the triazine **8** with 1,2,3-trimethoxybenzene producing the biaryl **9**, where the most sterically inaccessible group was remarkably replaced (Scheme 1.19). Other attempts to find further examples of methoxy replacement were unsuccessful; the reaction with dibenzoyl peroxide for example, resulting in the introduction of the benzoyloxy group on an unsubstituted position of the molecule as the major product.[20]

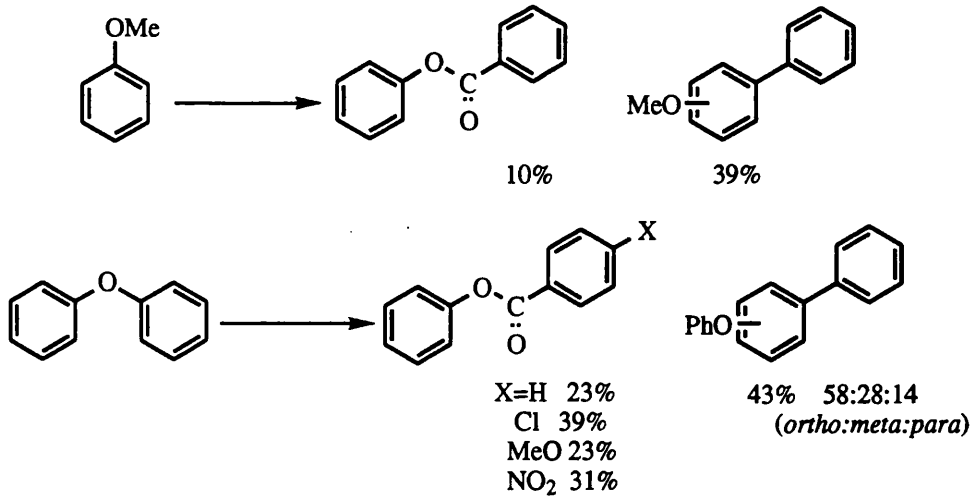


8 9

Reagents: Glacial AcOH, 100°C.

Scheme 1.19

On the other hand, reaction of dibenzoyl peroxide with anisole gave phenyl benzoate, formed by *ipso* attack, together with methoxybiphenyls in a 1 : 4 ratio. The same reaction with diphenyl ether gave similar results, but when *para* substituted aromatic peroxides (4-Cl, 4-MeO or 4-NO_2) were used only benzoates were observed[21] (Scheme 1.20).



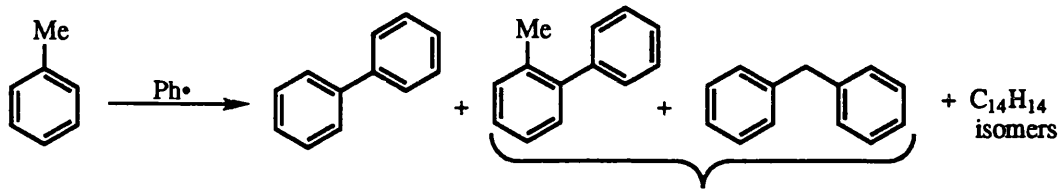
Reagents: $(ArCO_2)_2$, 80°C, N_2. Yields based on peroxide used.

Scheme 1.20

1.1.5. Aromatic Displacement with Cleavage of a Carbon-Carbon Bond

1.1.5.1. Displacement of an Alkyl Group

The displacement of an alkyl group by *ipso* substitution was only observed to a minor extent when a phenyl radical, produced from pyrolysis of nitrobenzene, reacted with toluene. The major products were derived by hydrogen atom replacement either on the aromatic ring or the side chain[7] (Scheme 1.21).

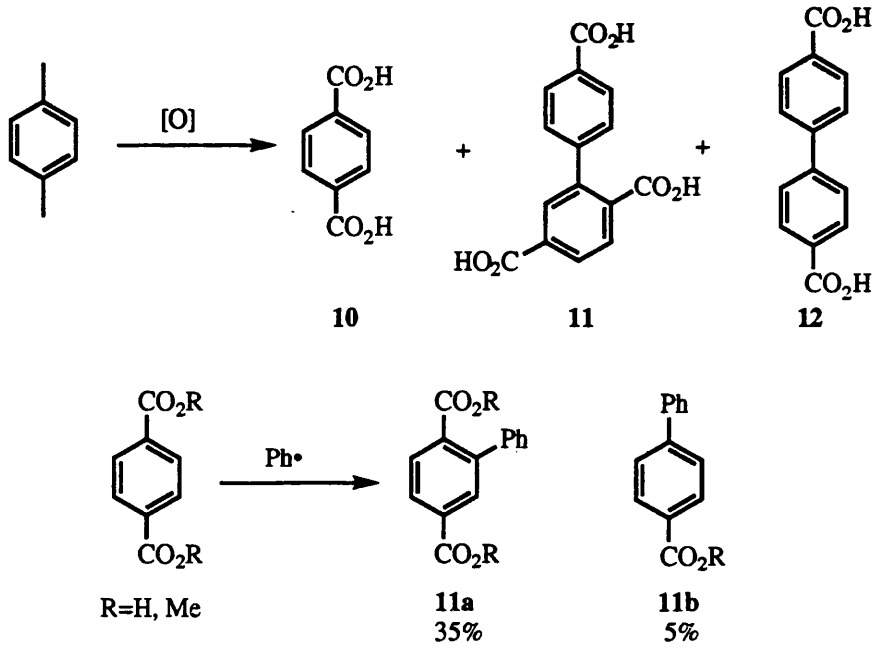


Reaction Conditions: nitrobenzene:toluene 0.05:0.25; 9.5 sec. contact time.
Relative concentrations obtained from relative intensities in low voltage mass spectra.

Scheme 1.21

1.1.5.2. Displacement of a Carboxy Group

The autoxidation of *p*-xylene to the correspondent terephthalic acid (**10**) or methyl terephthalate gives rise to two by-products, **11** and **12**. The formation of **12** through an *ipso* intermediate was suggested, and a further experiment demonstrated that phenyl radicals, produced by decomposition of dibenzoyl peroxide, reacted with methyl terephthalate to give the same ratio of products[22] (Scheme 1.22).



Scheme 1.22

1.1.6. Displacement Reactions on Heteroaromatic Rings

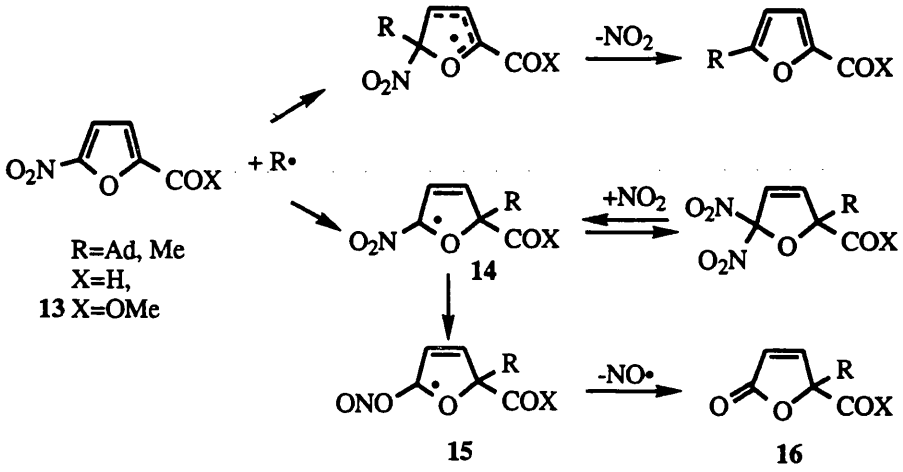
Radical *ipso* substitution reactions have been performed on several heteroaromatic rings with great success. Extensive studies on the type of attacking radical and leaving group have led to some useful conclusive results. In general, high yields were obtained with the strongly nucleophilic adamantyl radical and with strongly electron deficient substrates. When polar effects do not interfere with the course of the reaction, *ipso* substitution occurs to form the most stable σ complex.

1.1.6.1. Furan and Thiophene Derivatives

As it is known that, for furan and thiophene derivatives, radical addition occurs almost exclusively at the α-position, it is expected that 2,5-disubstituted substrates should give products derived from *ipso* attack.

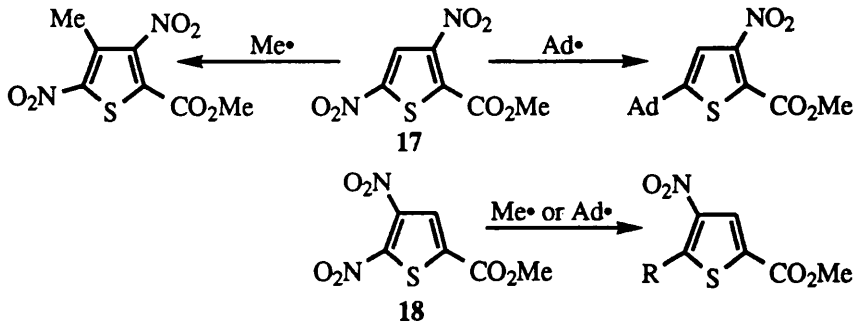
On reaction of 5-nitro-2-furancarboxylic acid with hydroxyl radicals, *ipso* substitution of the nitro rather then carboxy group was observed.[23] The same tendency has been observed to a lesser extent with the corresponding 5-bromo derivatives. 5-Nitro-2-carbomethoxyfuran (**13**) reacted in a similar way with methyl and adamantyl

radicals, to give a mixture of three products: two resulting from direct *ipso* substitution on both α-positions, and the third (**16**) derived from a rearrangement[24] (Scheme 1.23). It is claimed that the isomerisation of the nitro group in intermediate **14** occurs to give nitrite **15**, which subsequently fragments into nitric oxide and the lactone **16**.



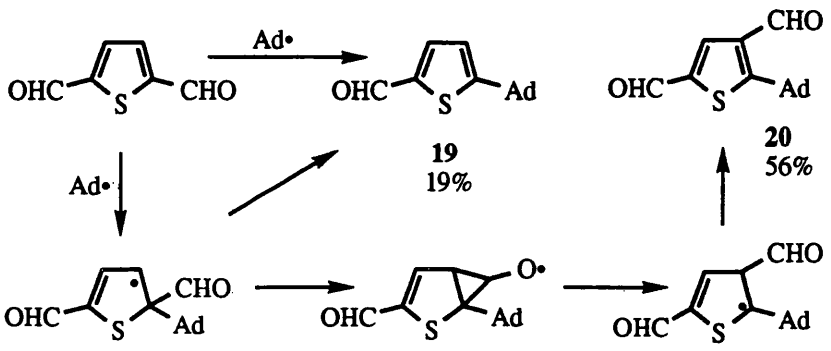
Scheme 1.23

The influence of the regiochemistry of the substituents on the molecule is well exemplified by the reaction of the two isomers **17** and **18** with methyl and adamantyl radicals (Scheme 1.24). While 3,5-dinitro-2-carbomethoxythiophene (**17**) gives the expected difference in reactivity with the methyl and adamantyl radicals, the 4,5-dinitro isomer (**18**) shows a similar reactivity towards both radicals, since *ipso* attack at the 5 position gives the more stable intermediate.[13]



Scheme 1.24

An unusual product was observed in the reaction of 2,5-thiophenedicarbaldehyde with the adamantyl radical[13] (Scheme 1.25).



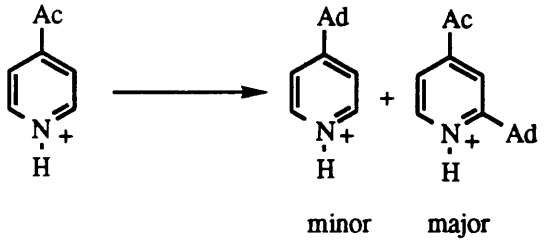
Scheme 1.25

The major products formed were the *ipso* substitution product (**19**, 19%) and compound **20** (56%). The latter is thought to be formed from the common *ipso* intermediate as **19**, followed by intramolecular migration of the aldehydic carbonyl.

1.1.6.2. Pyridine and Quinoline Derivatives

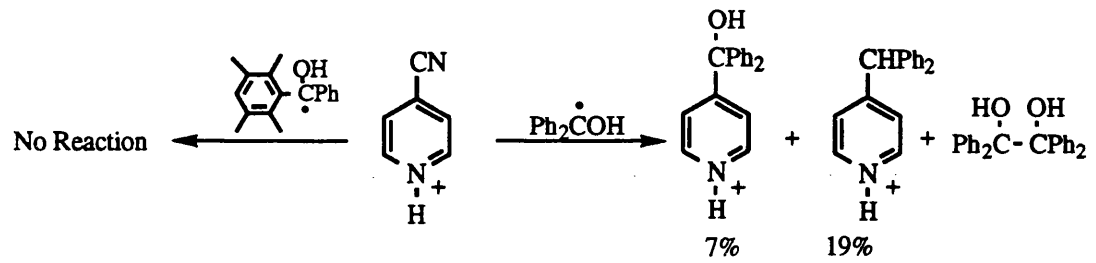
Nitrogen-containing heterocycles have been reported to undergo *ipso* substitution reactions, especially when the leaving group is an acyl or cyano group.

Monosubstituted protonated pyridines do not tend to undergo *ipso* substitution on reaction with alkyl radicals. 4-Cyano, 4-methoxycarbonyl, 4-chloro, 4-methyl and 4-methoxypyridines do not give any *ipso* substitution products. However, 2- (or 4-) acylpyridine undergo *ipso* substitution to a small extent, although the major product is formed by reaction at the unsubstituted position 4 (or 2)[25] (Scheme 1.26).



Scheme 1.26

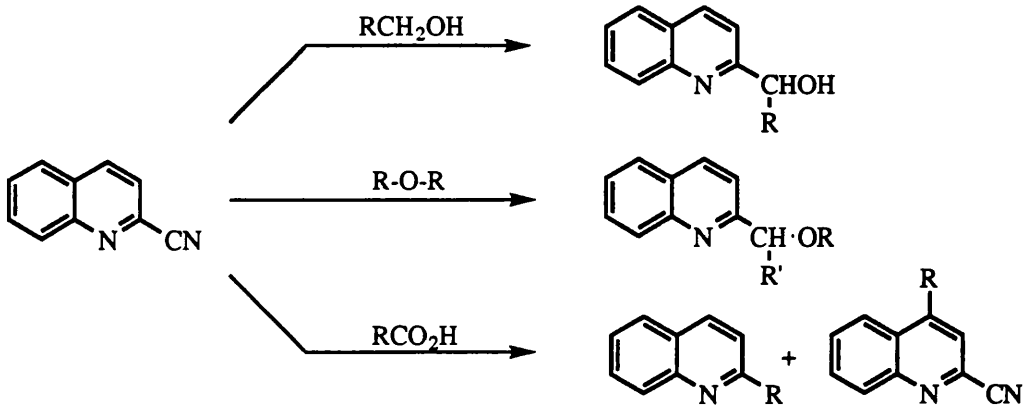
In the case of 4-cyanopyridine, *ipso* substitution has been observed with hydroxyalkyl radicals, such as the hydroxy(diphenyl)methyl radical. With the hydroxy(phenyl)-(2,3,5,6-tetramethylphenyl)methyl radical however, substitution is not observed, probably as a result of steric hindrance[26] (Scheme 1.27).



Reagents: Irradiation at 350 nm in propan-2-ol/H_2O (3:1) containing 1M H_2SO_4.

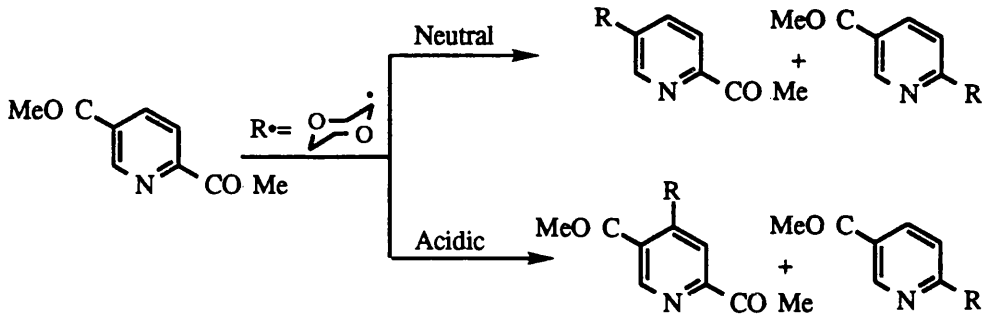
Scheme 1.27

With quinolines, depending on the nature of the attacking radical, a different reaction course is observed (Scheme 1.28). Thus, photolysis of 2-substituted quinolines in the presence of an alcohol (ethanol, 1-propanol, 2-propanol or *tert*-butyl alcohol) gave exclusively the *ipso* substitution product. Better yields were obtained with an acidified solution (20-54%). A similar result was observed from irradiation in the presence of an ether which also gave good yields of the *ipso* substitution product (59% in the presence of acid). However, when the reaction was performed in the presence of a carboxylic acid, competition between *ipso* substitution and attack at an unsubstituted position was observed, yielding the two compounds in equivalent amounts.[27]



Scheme 1.28

A comparative study of the reaction of disubstituted pyridines, either protonated or unprotonated, has been published.[28] In neutral pyridines, polar effects do not operate and substitution occurs on the position *para* to the electron withdrawing substituents. However, on protonation, polar effects intervene and substitution occurs at the most electropositive sites in the molecule (Scheme 1.29).



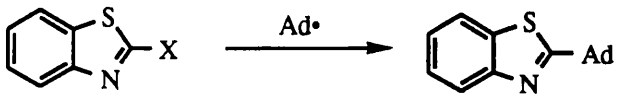
Scheme 1.29

1.1.6.3. Benzothiazole Derivatives

The reaction of benzothiazoles with alkyl radicals has been extensively studied. Again, better yields were obtained with the strongly nucleophilic adamantyl radical, and efficiency progressively decreased with isopropyl, *n*-propyl and methyl radicals.[18]

An extensive study of the influence of the leaving groups on *ipso* substitution reactions, using the adamantyl radical, revealed the necessity for the presence of strong electron withdrawing substituents.[29] A decrease in efficiency was observed when halogens or electron donating substituents were used (Table 1.2).

Table 1.2

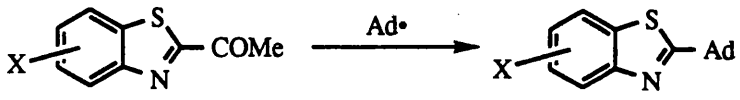


X	NO_2	$PhSO_2$	PhSO	MeCO	F	Cl	Br	I	SMe	OMe
%Conv.	100	100	100	100	50	40	40	50	50	10
%Yield	95	80	80	70	50	50	60	60	60	40

The effect of other substituents on *ipso* substitution was also considered (Table 1.3). The relative rates, obtained from the reaction with adamantyl radical, show that electron withdrawing substituents increase the rate of the reaction whereas electron donating substituents decrease it.

Table 1.3

Relative rates of the reaction of substituted benzothiazoles with adamantyl radical.

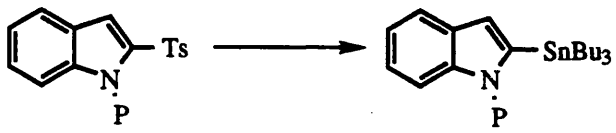


X	6-CN	6-Cl	5-Cl	5-OMe	H	5-Me	6-Me	6-OMe
Rel. rate	10.9	2.3	2.2	1.25	1	0.86	0.6	0.46

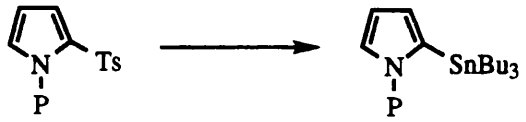
These results indicate once again, that the electron density at the ring position where attack occurs is very important in determining the reactivity of the substrate.

1.1.6.4. Indole and Pyrrole Derivatives

The ability of a heteroaromatic arenesulfonyl group to be transformed into the corresponding heteroaromatic stannane under free radical conditions has recently been demonstrated. Indole and pyrrole derivatives undergo a regiospecific and high yielding substitution reaction with nucleophilic organostannyl radicals[30] (Scheme 1.29).



P=$CO_2{}^tBu$, 96%
P=SO_2Ph, 92%



P=SO_2Ph, 69%

Reagents: Bu_3SnH, AIBN, benzene, reflux, 30 min.

Scheme 1.29

This strategy is a useful procedure for the introduction of trialkylstannyl groups into complex systems.

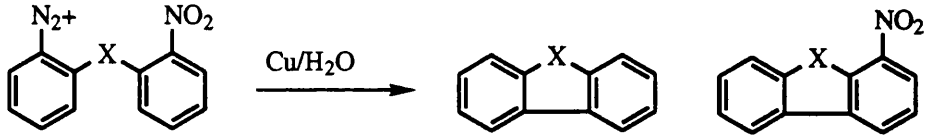
1.2. Intramolecular Aromatic *Ipso* Substitution Reactions

As we have shown in the previous section, there is a variety of groups which can act as leaving groups in an intermolecular aromatic *ipso* substitution reaction. In the present section we will describe the behaviour of different attacking radicals and leaving groups which have been used in intramolecular *ipso* substitution reactions.

1.2.1. Aromatic Displacement with Cleavage of a Carbon-Nitrogen Bond

1.2.1.1. The Nitro Group

The nitro group is a very effective leaving group towards the attack of a nucleophilic radical in intermolecular reactions. However, this potential ability has been explored to a much lesser extent in intramolecular processes. One of the few examples is the formation of **22** by the attack of an aryl radical, with extrusion of nitrogen dioxide, in the Pschorr reaction of **21** with copper in water[31] (Scheme 1.30). Substitution of the carbonyl on the linking chain by a nitrogen (X=NMe) improved considerably the yield.



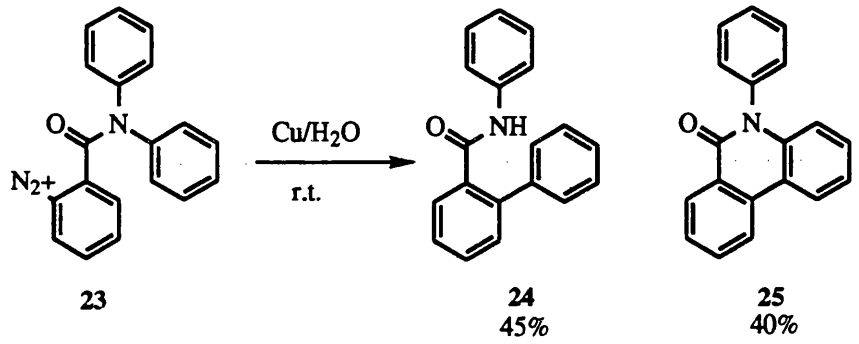
21	22	
X=CO	14%	7%
X-NMe	56%	9%

Scheme 1.30

1.2.1.2. The Amidyl Group

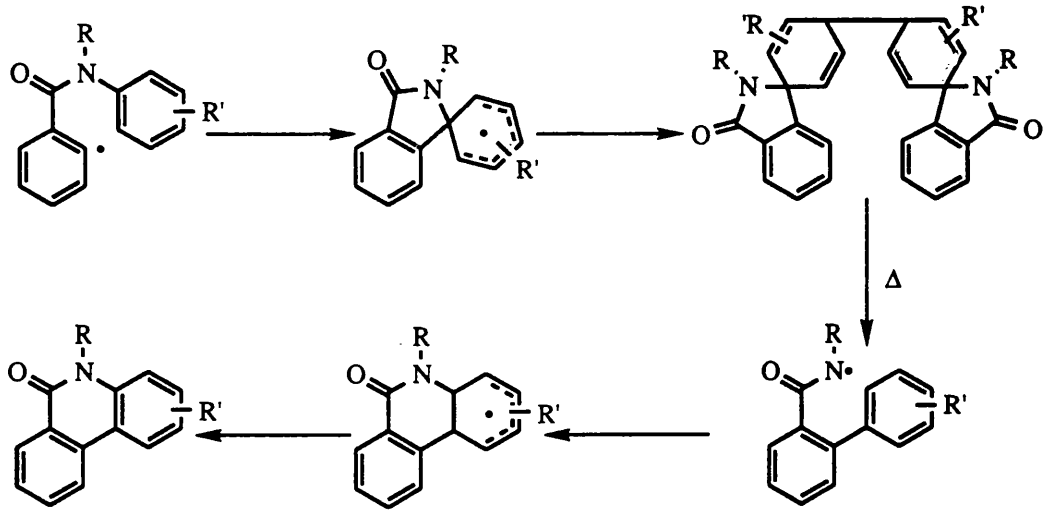
One of the most studied substituents in intramolecular *ipso* substitution reactions has been the amidyl group. Most of the work focuses on the displacement of the amidyl group by an aryl radical, with consequent formation of a biaryl.

The aryl radical, formed by the copper initiated electron transfer reaction of **23**, can react *via* two different ways. Addition to an unsubstituted position of the phenyl ring affords **25**, while attack at the substituted position, followed by cleavage of the carbon-nitrogen bond gives the *ipso* product (**24**)[32] (Scheme 1.31).



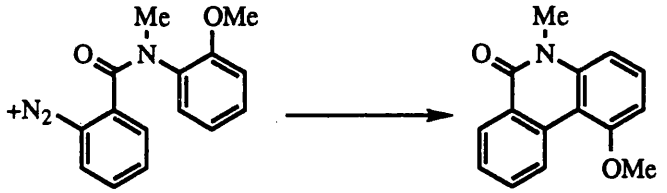
Scheme 1.31

Curiously, when one of the substituents on the nitrogen atom is changed from a phenyl to a methyl group, the spiro intermediate is generally trapped as a dimer.[33] However, on further heating, the dimer dissociates and cleavage of the relatively weak carbon-nitrogen bond can then occur to permit subsequent recyclisation of the amidyl radical[34] (Scheme 1.32).



Scheme 1.32

Evidence for the "migration" of the nitrogen atom was found in a study of substituted aromatic rings, where the substituents on the product were not on the positions expected for a simple addition reaction[35] (Scheme 1.33).

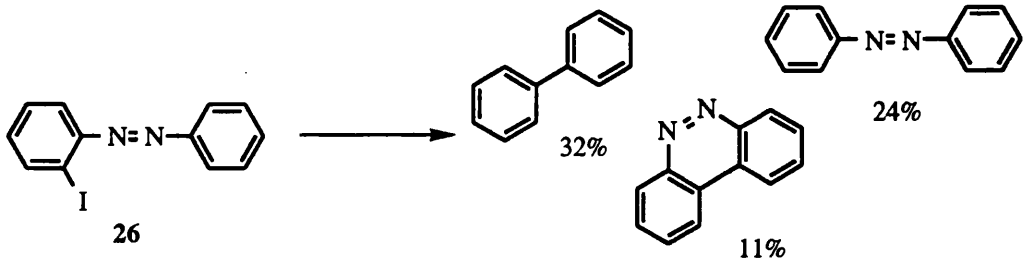


Scheme 1.33

Identical results were observed when the same reaction was performed under electrochemical conditions. The reaction proceeds by two consecutive single electron transfers to afford a mixture of products resulting from *ipso* substitution, addition and direct reduction in a ratio of 33:13:54.[36]

1.2.1.3. The Diazo Group

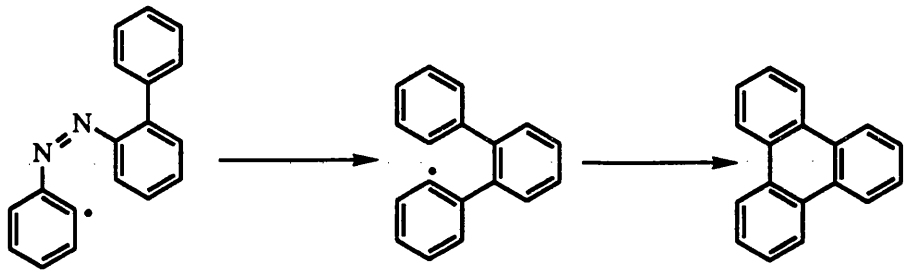
Photolysis of compound **26** showed that the diazo group is also a good leaving group in *ipso* substitution reactions, which occur with extrusion of nitrogen[37] (Scheme 1.34).



Reagents: Cyclohexane, hv (100W high-pressure mercury lamp), 48 hr.

Scheme 1.34

When the reaction was carried out on a substrate with a phenyl group at the ortho position of the acceptor ring (**27**), the extra stabilisation of the intermediate radical favoured *ipso* attack. Subsequent cyclisation gave compound **28** as the major product in 46% yield (Scheme 1.35).

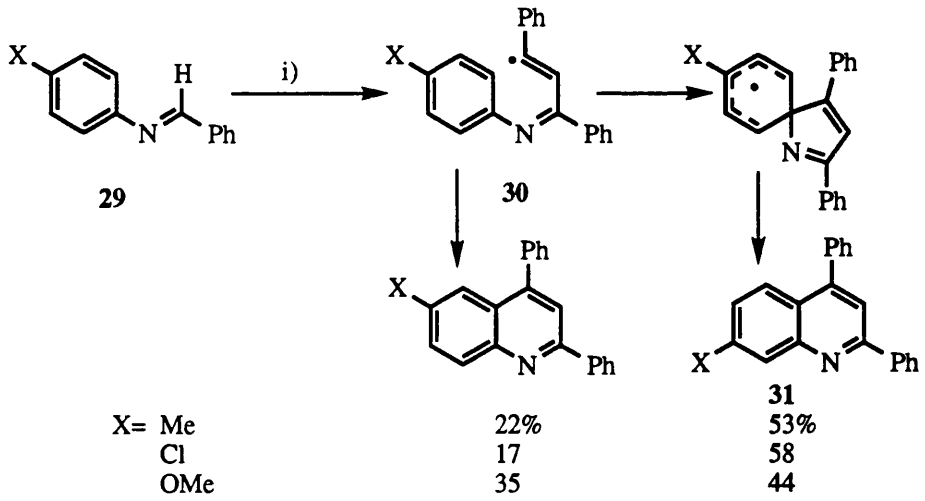


27 **28** 46%

Scheme 1.35

1.2.1.4. The Iminyl Group

N-Arylideneanilines (**29**) react with monosubstituted acetylenes in the presence of di-isopropylperoxydicarbonate (DPDC) to afford quinolines.[38] The imidoyl radical initially formed reacts with the alkyne to give the intermediate vinyl radical **30** which, by an intramolecular process, forms quinolines in good yields (Scheme 1.36).



29 **30** **31**

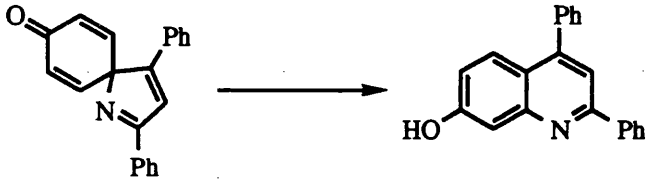
X=	**30**	**31**
Me	22%	53%
Cl	17	58
OMe	35	44

Reagents: i) DPDC, PhC≡CH, benzene, 60°C, N_2.

Scheme 1.36

The "unexpected" position of the substituent in the major product **31** is indicative of an *ipso* cyclisation followed by cleavage of the carbon-nitrogen bond.

Reaction of the spirodienone **32** (Scheme 1.37), which was obtained from the imine **29** (X=Ph_3CO), with tri-n-butyltin hydride suggests that the rearrangement of the spiro radical might be a synchronous process or, if the iminyl radical is involved, ring closure is much faster than hydrogen atom abstraction from tri-n-butyltin hydride.



32

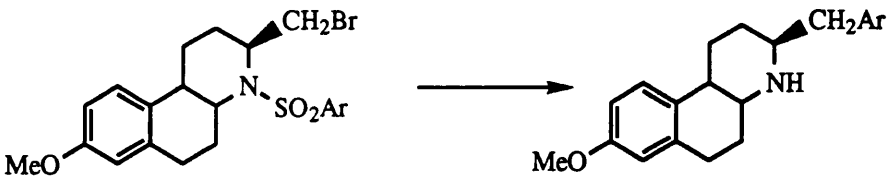
Reagents: Bu_3SnH / AIBN, benzene, 4 hr, reflux (78%).

Scheme 1.37

1.2.2. Aromatic Displacement with Cleavage of a Carbon-Sulfur Bond

In contrast to the intermolecular case, intramolecular *ipso* substitution reactions with radical displacement of a sulfonyl group have received much attention, particularly in their reaction with alkyl radicals.

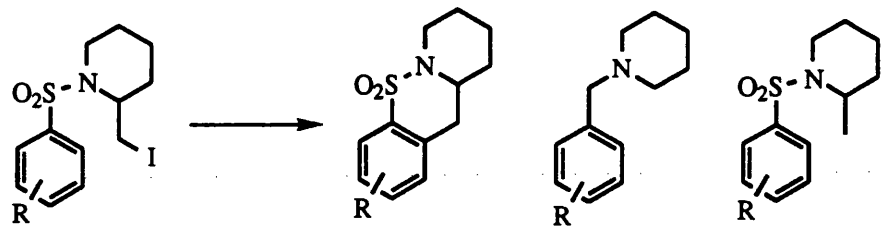
Initial work was carried out by Speckamp who noticed, in the course of a synthetic study, that an unexpected 1,4-aryl shift had occurred.[39] This product was formed by *ipso* substitution attack on the sulfonyl position of the aromatic ring (Scheme 1.38).



Reagents: Bu_3SnH, AIBN, benzene, reflux (88%).

Scheme 1.38

The reaction occurs with a wide variety of substituted aromatic[40,41] and heteroaromatic[42] derivatives, to give the addition products **33**, the *ipso* substitution products **34** and the reduction products **35**.

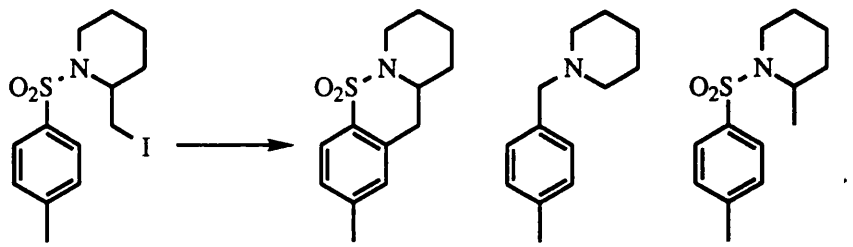


		33	**34**	**35**
a)	R= Me	45%	32%	23%
b)	OMe	40	37	23
c)	CO_2Et	27	53	20
d)	CN	20	65	15

Reagents: Bu_3SnH, AIBN, benzene, reflux.

Scheme 1.39

Further studies showed a temperature dependence on the ratio of products.[40] Thus, increasing the temperature leads to an increase in the 1,5-*ipso* substitution product, and consequently a decrease in 1,6-addition and reduced products (Scheme 1.40).

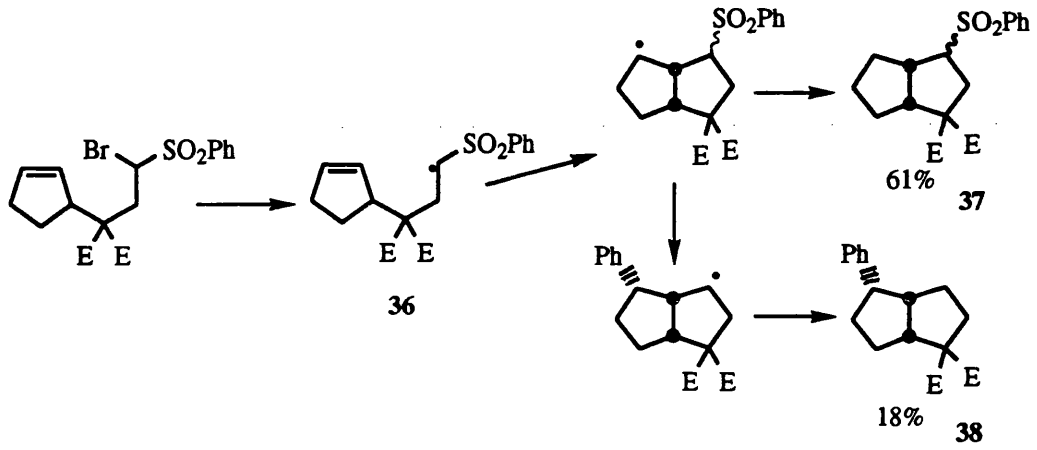


Temp.	**33a**	**34a**	**35a**
22°C	68%	-	30%
86°C	46	30	23
152°C	30	56	13
190°C	26	64	9

Reagents: Bu_3SnH, AIBN, anisole.

Scheme 1.40

Much more recently, and contemporaneous with our own studies in the biaryl area (vide infra), a similar rearrangement was observed during a radical cyclisation, where the by-product was formed by *ipso* substitution[43] (Scheme 1.41).

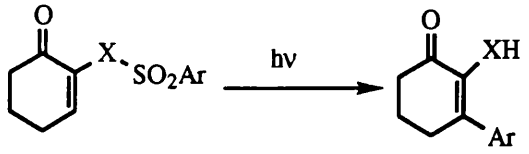


Reagents: Ph_3SnH / AIBN (slow addition), benzene, 80°C, 10 hr.

Scheme 1.41

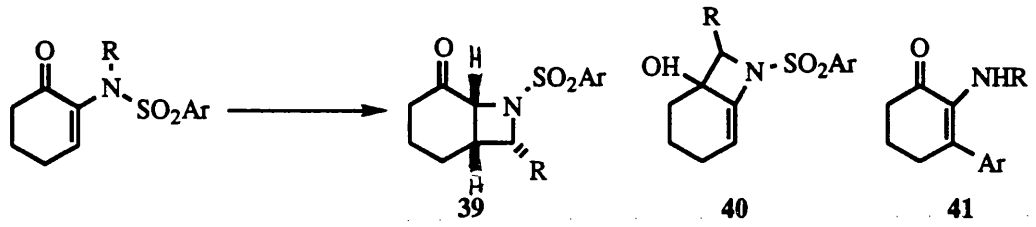
Thus, the initially generated radical **36** adds to the double bond and the resultant secondary alkyl radical is either reduced by the tri-phenyltin hydride to give **37** (61%), or undergoes *ipso* substitution, with extrusion of sulfur dioxide, to give **38** (18%). (Scheme 1.41).

Photolysis of conjugated enones substituted at the α-position by a group bearing an arylsulfonyl substituent can lead to *ipso* substitution on the aryl ring (Scheme 1.42).



Scheme 1.42

When X=NR formation of the *ipso* substitution product **41** is in competition with hydrogen abstraction from the R group (R=Et, CH_2Ph, allyl) and subsequent addition to the ring (Scheme 1.43).



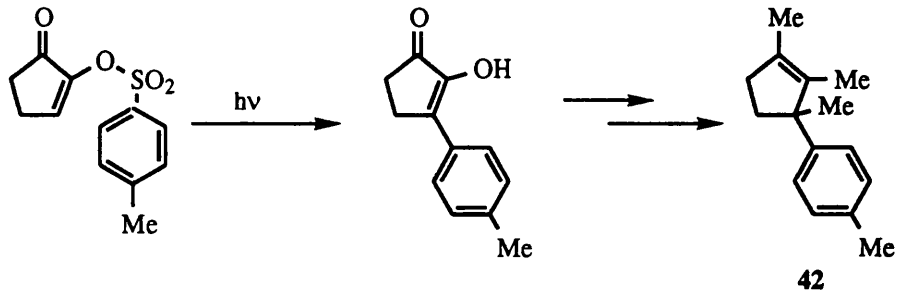
39 **40** **41**

Reagents: EtOH or Et_2O, hν.

Scheme 1.43

Compound **41** is the only product when R=$CH(CH_3)_2$ presumably since cyclisation to **39** or **40** is precluded for steric reasons.[44]

When X=O the same desulfonation and migration of the aryl group is observed in good yields (45-63%).[45] Several aryl groups were tested, showing that the *ipso* product is favoured with electron rich aryl groups (3,4-dimethoxy; 90%).[46] This methodology was then successfully applied to the synthesis of isolaurene **42** (Scheme 1.44), where the key step involving *ipso* substitution occurred in 45%.[47]

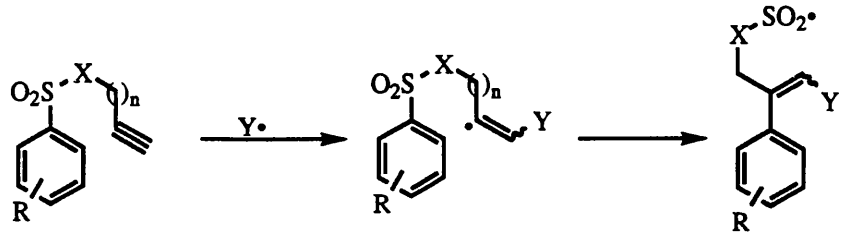


42

Scheme 1.44

The displacement of a sulfonyl group by an aryl radical has also been observed[48] but will be discussed later, in the Results and Discussion chapter (Chapter 2), where it will be more appropriate

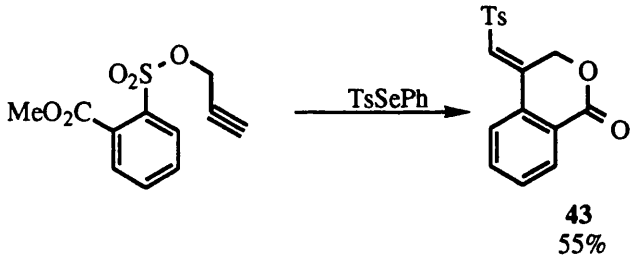
Work in our own group also demonstrated that a vinyl radical can undergo efficient *ipso* attack with displacement of sulfur dioxide[49] (Scheme 1.45).



Scheme 1.45

Although with sulfonamides (X=NMe, n=1, 2) the *ipso* attack was not observed, and with sulphones (X=CH_2, n=1) only to a small extent (6%), more interesting results were obtained with the sulfonate group (X=O, n=1, 2) on the linking chain.

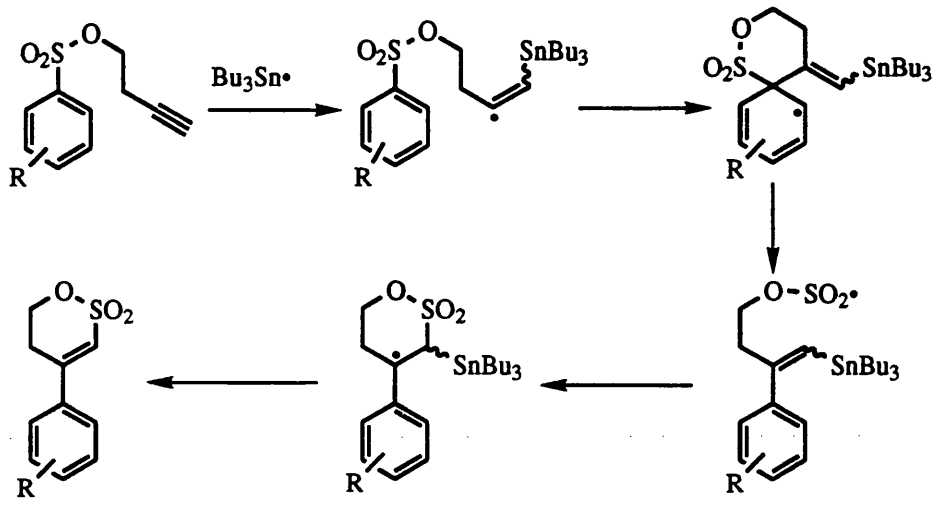
Sulfonate esters of propargyl alcohol showed good results when TsSePh was used as a radical source, with formation of the *ipso* product, which then underwent lactonization to give **43**, in 55% (Scheme 1.46).



43
55%

Scheme 1.46

An investigation of sulfonate esters of homopropargyl alcohol however, using tri-n-butyltin hydride as the radical source, led to the discovery of an unusual rearrangement reaction (Scheme 1.47).

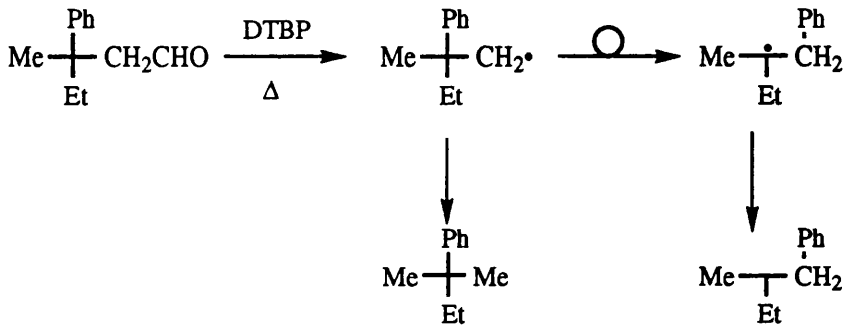


Scheme 1.47

As implied in the mechanism, the loss of sulfur dioxide is sufficiently slow to permit a further 6-endo addition-elimination sequence with expulsion of the tri-n-butylstannyl radical.[50] The reaction occurs with a wide variety of aromatic substituents, where particularly good results are obtained with the carbomethoxy derivative (R=CO_2Me, 61%), and heterocyclic systems (14-74%).

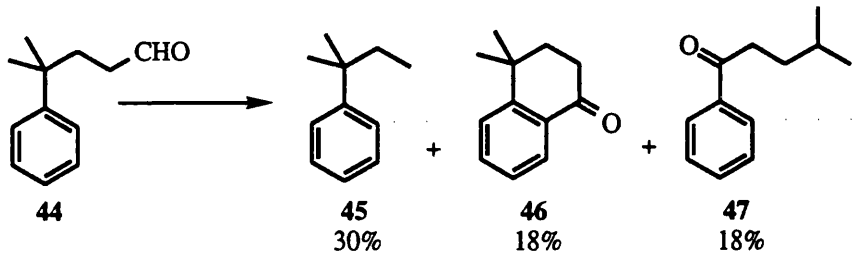
1.2.3. Aromatic Displacement with Cleavage of a Carbon-Carbon Bond

A process that involves *ipso* substitution with cleavage of a carbon-carbon bond is the neophyl rearrangement. This is a 1,2 shift of a phenyl group, and is probably one of the best known radical rearrangements[51] (Scheme 1.48).



Scheme 1.48

When there is an extra carbon atom in the chain, as in compound **44**, the acyl radical can undergo both *ipso* substitution (**47**) and addition (**46**) prior to decarbonylation, or to loose carbon monoxide to give **45**[52] (Scheme 1.49).

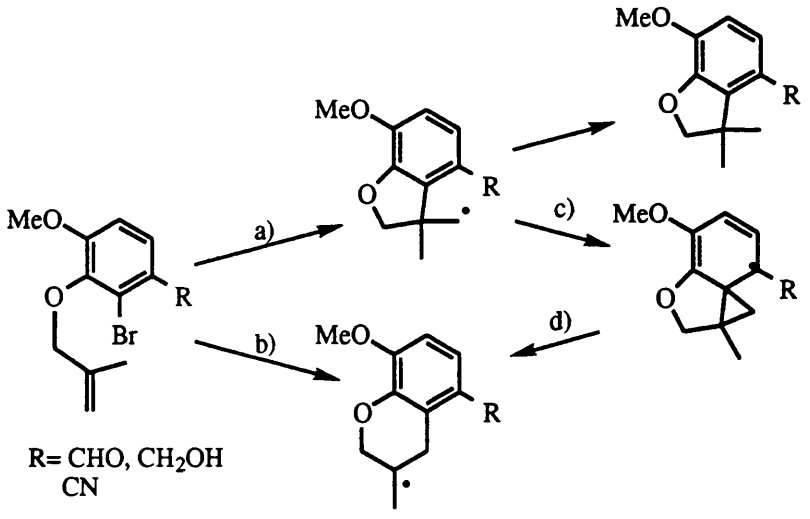


44 **45** 30% **46** 18% **47** 18%

Reagents: t-Amyl peroxide, 100°C, 24h.

Scheme 1.49

A neophyl rearrangement was recently observed in the addition of an aryl radical to a double bond[53] (Scheme 1.50).



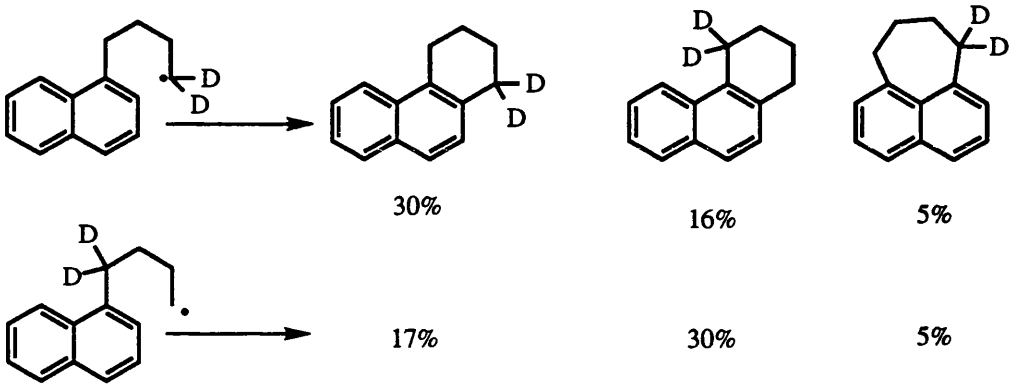
48

Reagents: Bu_3SnH

Scheme 1.50

Kinetic studies[54] of this reaction showed that the formation of compound **48** occurred both by 1,6 endo addition (path b) and also by sequential 1,5 exo addition followed by neophyl rearrangement (path a, c and d). The neophyl rearrangement is faster for radicals containing a naphthalene nucleus than for benzenoid radicals and is also facilitated by appropriately located electron withdrawing substituents.[55]

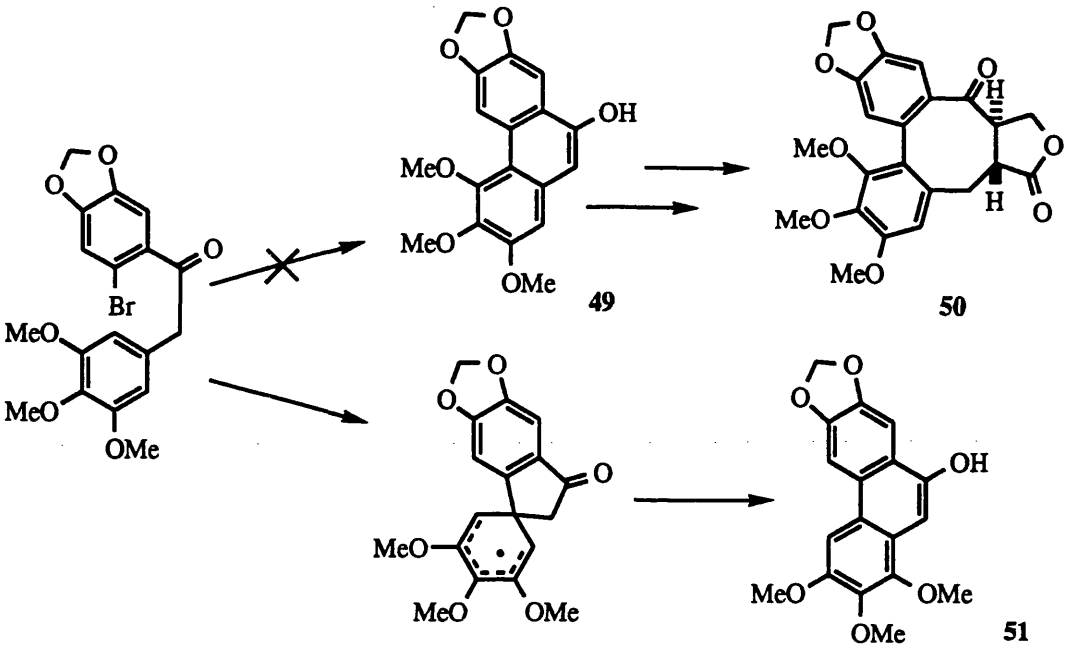
The intramolecular *ipso* substitution of an alkyl radical was confirmed by the use of deuterium labelled compounds[55] (Scheme 1.51).



Radicals formed by decarboxylation of the parent acid with Pb(OAc)4 in benzene, 50-60°C, 30 min and 24 hr reflux.

Scheme 1.51

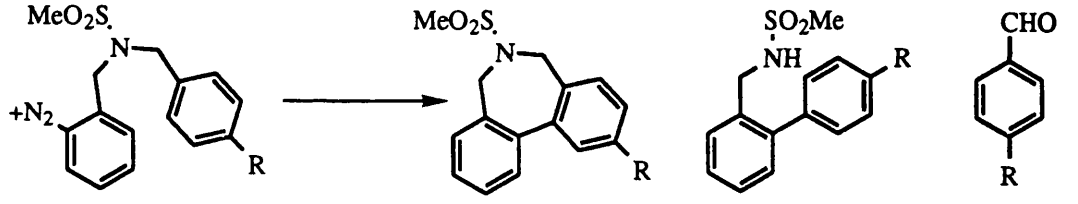
An attempted preparation of intermediate **49** for the synthesis of (±)Steganone **50**, *via* an intramolecular biaryl coupling with tri-n-butyltin hydride gave compound **51**[56] (Scheme 1.52).



Scheme 1.52

The formation of compound **51** was explained *via* the spirocyclic intermediate formed by *ipso* attack, which then rearranged to the final product.

Another example of carbon-carbon bond cleavage can be found in a minor extension of the Pschorr cyclisation of **52**[57] (Scheme 1.53).



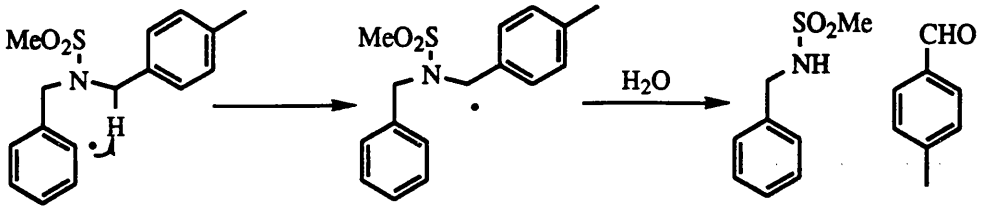
	52		**53**	**54**
R=	H	55%	--	11%
	Me	40	8	19
	Cl	41	9	18

Reagents: Cu, H_2SO_4/AcOH.

Scheme 1.53

Compound **53** may be derived from 1,6 *ipso* substitution with displacement and elimination of the methylene group adjacent to the sulfonamide nitrogen.

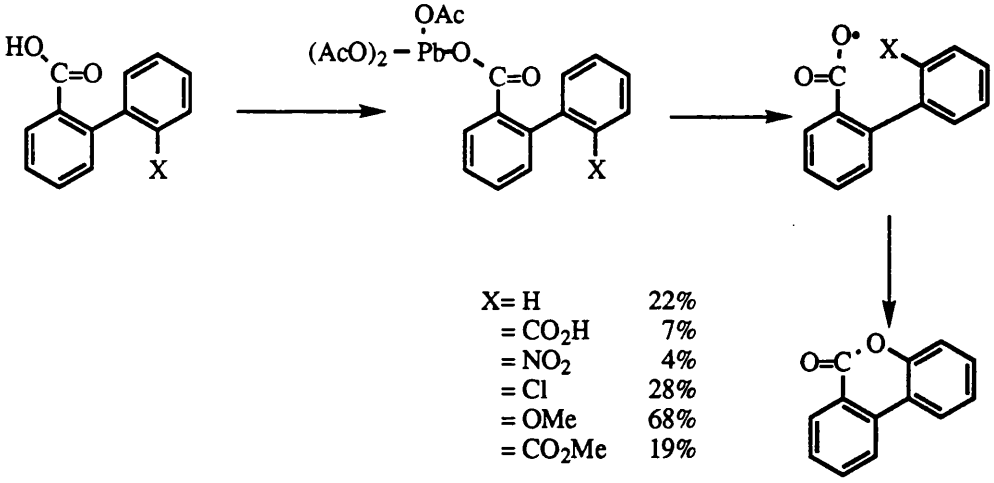
The formation of the benzaldehydes **54** suggests that a 1,5-hydrogen atom transfer is involved, followed by hydrolysis (Scheme 1.54).



Scheme 1.54

1.2.4. Aromatic Displacement with Cleavage of a Carbon-Oxygen Bond

The oxidation of 2'-substituted biphenyl-2-carboxylic acids with lead tetracetate[58] or persulphate,[59] occurs via the intermediate carboxy radical, which can displace substituents on the 2' position. In lead tetracetate oxidation, the best results were obtained in the displacement of a methoxy group, which ocurred in 68%. Other groups also underwent the displacement reaction but in lower yields (Scheme 1.55).

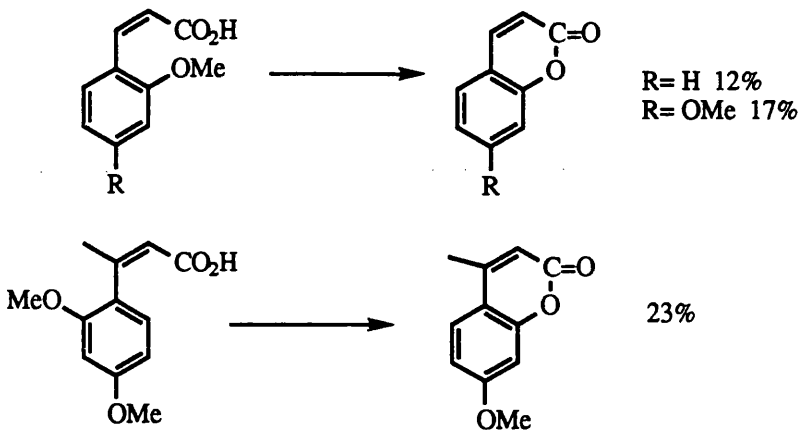


X= H	22%
= CO_2H	7%
= NO_2	4%
= Cl	28%
= OMe	68%
= CO_2Me	19%

Reagents: $Pb(OAc)_4$, benzene, 80°C, N_2.

Scheme 1.55

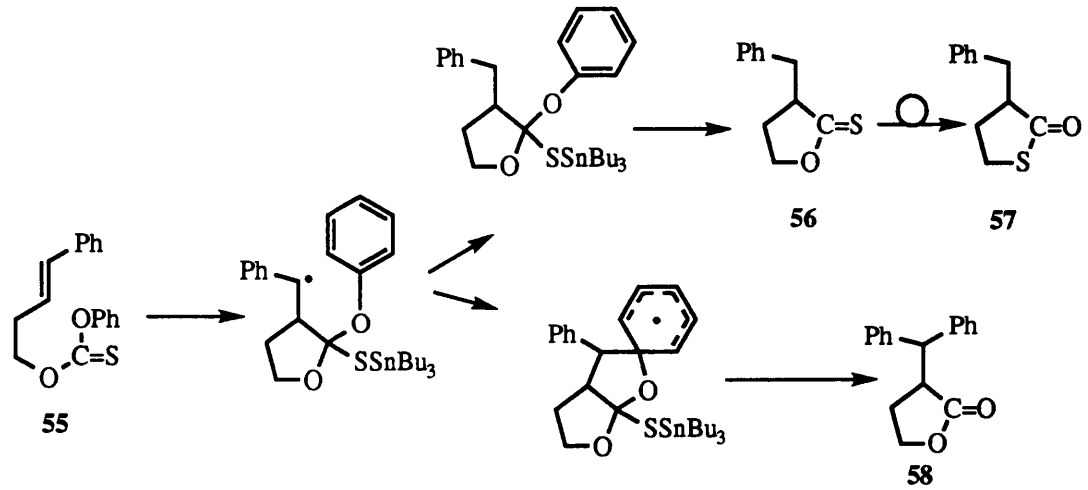
The persulphate oxidation was extended to substrates such as *o*-methoxycinnamic acid where the reaction proceeded with displacement of the methoxy group to give coumarin derivatives[60] (Scheme 1.56).



Reagents: potassium persulfate, NaOH, H_2O, reflux, 3 hr.

Scheme 1.56

The displacement of a group involving the cleavage of a carbon-oxygen bond was reported in the reaction of compound **55** with tri-n-butyltin hydride[61] (Scheme 1.57).



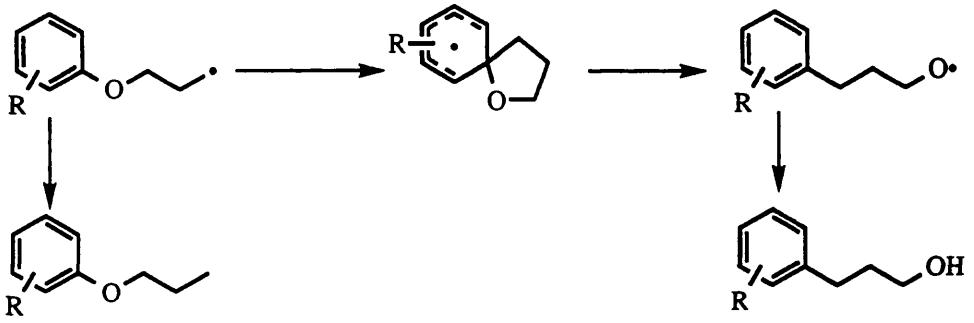
Reagents: Bu_3SnH / AIBN, benzene, reflux.

Scheme 1.57

Thus, in addition to the desired product **56** (9%), the lactone **58** (47%) was obtained as the major product.

The initial radical, formed by addition of the tri-n-butylstannyl radical to the thiocarbonyl sulfur atom is trapped in an intramolecular way by the double bond, to generate the benzylic radical. Two competitive processes can then occur: *viz.* the direct reduction or intramolecular *ipso* addition to the phenolic ring, followed by rearomatisation with loss of the tri-n-butylstannylthiyl radical and formation of lactone **58** (Scheme 1.57).

The isomerization of aryl ethers can also occur via an *ipso* process.[62] 3-Aryloxypropyl bromides in the presence of tri-n-butyltin hydride form the alkyl radical, which can either abstract a hydrogen atom from the stannane to form aryl propyl ethers, or add intramolecularly either to the *ortho* or *ipso* position of the aromatic ring (Scheme 1.58).



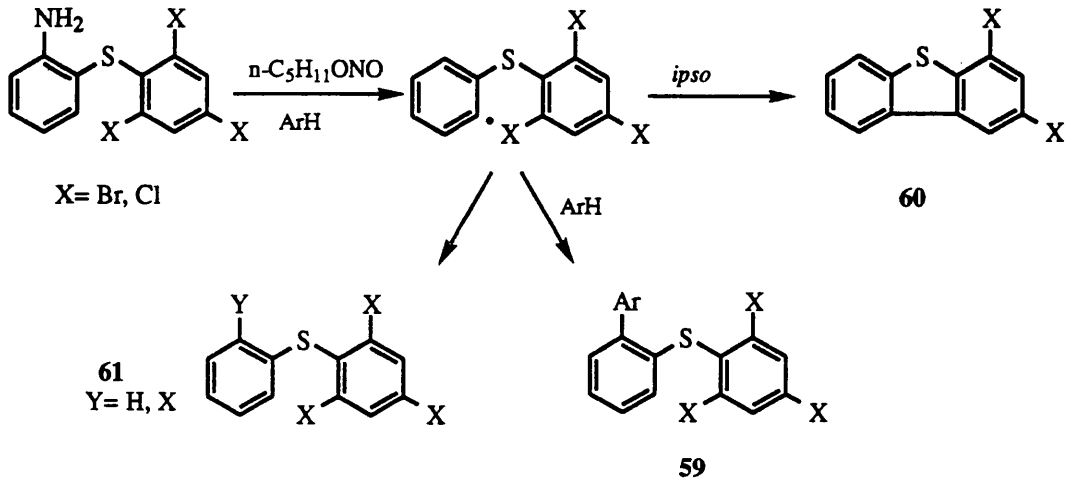
Reagents: Bu_3SnH / AIBN.

Scheme 1.58

The preferred process is the *ipso* attack, and either electron withdrawing or electron donating substituents on the aryl ring promote the reaction. Curiously the best results were obtained when both electron withdrawing and electron donating substituents were present on the aromatic ring. The most important factor seems to be the stability of the intermediate spiro radical.

1.2.5. Aromatic Displacement with Cleavage of a Carbon-Halogen Bond

o-(2,4,6-Trihalogenophenyl)thiophenyl radicals were chosen to investigate the displacement of a halogen by intramolecular *ipso* attack of an aryl radical[63] (Scheme 1.59)



Scheme 1.59

Products derived from addition of solvent (**59**), *ipso* substitution (**60**) and direct reduction (**61**; Y=H) were formed in diferent ratios according to the solvent and temperature used. In the above system when X=Br, the use of a high boiling point solvent like *o*-dichlorobenzene, gave a mixture in which the *ipso* product (**60**) was present in 25% together with **59** (66%).

1.3. CONCLUSIONS

From the foregoing overview, it can be concluded that there are several factors which determine the selectivity towards *ipso* substitution or addition to an unsubstituted position both in intermolecular and intramolecular radical reactions.

It was observed that the polar character of the attacking radical and leaving group play an important role in selectivity for the intermolecular case.

When polar effects intervene, the attack of a nucleophilic radical species occurs on the most electron deficient position, favouring the displacement of electron withdrawing leaving groups.

If polar effects do not intervene the attack occurs on the position which will give the more stable intermediate.

Most of the work presented involved attack of nucleophilic intermediates on electron deficient aromatic rings. Under these conditions the nitro and sulfonyl groups were shown to be excellent leaving groups.

There is no rule which determines the direction of the reaction in the intramolecular case, since the nature of the linking chain is an extra factor which must be taken into consideration.

The best leaving groups are those whose displacement involves the cleavage of a carbon-nitrogen or carbon-sulfur bond. Curiously, in the carbon-nitrogen case, the intermediate nitrogen centred radical (amidyl or iminyl radicals) tends to cyclise again onto the aromatic ring.

The polar effect of the attacking group has not been thoroughly investigated, since most of the work presented deals with aryl, vinyl and alkyl radicals, which are mainly neutral or slightly nucleophilic.

The preferred length of the linking chain is that which allows the formation of 5 membered spirocyclic intermediates. We are tempted to suggest that introduction of an sp^2 centre encourages *ipso* substitution.

References

1 J. G. Traynham, *Chem. Rev.*, 1979, **79**, 323.

2 G. L. Goerner and R. C. Nametz, *J. Am. Chem. Soc.*, 1951, **73**, 2940.

3 B. Miller and C. Walling, *J. Am. Chem. Soc.*, 1957, **79**, 4187.

4 J. W. Engelsma and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, 1961, **80**, 537.

5 B. Milligan, R. L. Bradow, J. E. Rose, H. E. Hubbert and A. Roe, *J. Am. Chem. Soc.*, 1962, **84**, 158.

6 C. R. Everly and J. G. Traynham, *J. Am. Chem. Soc.*, 1978, **100**, 4316.

7 E. K. Fields and S. Meyerson, *Adv. Free-Radical Chem.*, 1975, **5**, 101.

8 P. H. Oldham, G. H. Williams and B. A. Wilson, *J. Chem. Soc. (B)*, 1970, 1346.

9 P. A. Claret, G. H. Williams and J. Coulson, *J. Chem. Soc. (C)*, 1968, 341.

10 P. H. Oldham and G. H. Williams, *J. Chem. Soc. (C)*, 1970, 1260.

11 J. R. Shelton and C. W. Uzelmeier, *J. Am. Chem. Soc.*, 1966, **88**, 5222.

12 J. R. Shelton and C. W. Uzelmeier, *Recl. Trav. Chim. Pays-Bas*, 1968, **87**, 1211.

13 M. Tiecco, *Acc. Chem. Res.*, 1980, **13**, 51.

14 L. Benati, C. M. Camaggi and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2817.

15 R. Bolton and G. H. Williams, *Adv. Free-Radical Chem.*, 1975, **5**, 1.

16 L. Testaferri, M. Tiecco, M. Tingoli, M. Fiorentino and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 1978, 93.

17 L. Testaferri, M. Tiecco and M. Tingoli, *J. Chem Soc., Perkin Trans. 2*, 1979, 469.

18 M. Tiecco, *Pure Appl. Chem.*, 1981, **53**, 239.

19 H. Lui and J. Warkentin, *Can. J. Chem.*, 1973, **51**, 1148.

20 P. L. Pauson and C. Smith, *J. Org. Chem.*, 1953, **18**, 1403.

21 K. Nowada, H. Sakurgi, K. Tokumaru and M. Yoshida, *Chem. Lett.*, 1976, 1243.

22 G. H. Jones, *J. Chem. Res. (S)*, 1982, 288.

23 C. L. Greenstock, I. Dunlop and P. Neta, *J. Phys. Chem.*, 1973, **77**, 1187.

24 P. Cogolli, L. Testaferri, M. Tiecco and M. Tingoli, *J. Chem Soc., Chem Commun.*, 1979, 800.

25 M. Fiorentino, L. Testaferri, M. Tiecco and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 1976, 329.

26 B. M. Vittimberga, F. Minisci and S. Morrochi, *J. Am. Chem. Soc.*, 1975, **97**, 4397.

27 N. Hata, I. Ono, S. Matono and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 942.

28 F. Maiolo, L. Testaferri, M. Tiecco and M. Tingoli, *Tetrahedron Lett.*, 1981, **22**, 2023.

29 M. Fiorentino, L. Testaferri, M. Tiecco and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 1977, 316.

30 S. Caddick and S. Joshi, *Synlett*, 1992, 805.

31 D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, 1952, 2276.

32 D. H. Hey and T. M. Moyneham, *J. Chem. Soc.*, 1959, 1563.

33 D. H. Hey, C. W. Rees and A. R. Todd, *J. Chem. Soc. (C)*, 1967, 1518.

34 D. H. Hey , G. H. Jones and M. J. Perkins, *J. Chem. Soc., Perkin Trans. 1*, 1972, 105.

35 D. H. Hey , G. H. Jones and M. J. Perkins, *J. Chem. Soc., Chem. Commun.*, 1970, 1438.

36 J. Grimshaw, R. Hamilton and J. Trocha-Grimshaw, *J. Chem. Soc., Perkin Trans. 1*, 1982, 229.

37 L. Benati, P. Spagnolo, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 1979, 141.

38 R. Leardini, D. Nanni, G. F. Pedulli, A. Tundo and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1591.

39 R. Loven and W. N. Speckamp, *Tetrahedron Lett.*, 1972, **13**, 1567.

40 J. J. Köhler and W. N. Speckamp, *Tetrahedron Lett.*, 1977, **18**, 631.

41 W. N. Speckamp and J. J. Köhler, *J. Chem. Soc., Chem. Commun.*, 1978, 167.

42 J. J. Köhler and W. N. Speckamp, *Tetrahedron Lett.*, 1977, **18**, 635.

43 D. L. J. Clive and T. L. B. Boivin, *J. Org. Chem.*, 1989, **54**, 1997.

44 J. C. Arnould, J. Cossy and J.-P. Pete,*Tetrahedron*, 1980, **36**, 1585. J. Cossy and J.-P. Pete,*Tetrahedron*, 1981, **37**, 2287.

45 A. Feigenbaum, J-P. Pete and D. Scholler, *J. Org. Chem.* 1984, **49**, 2355.

46 A-L. Poquet, A. Feigenbaum and J.-P. Pete, *Tetrahedron Lett.*, 1986, **27**, 2975.

47 K. Tomari, K. Machiya, I. Ichimoto and H. Ueda, *Agric. Biol. Chem.*, 1980, **44**, 2135.

48 J. L. Huppatz, *Aust. J. Chem.*, 1963, **16**, 417.

49 W. B. Motherwell, A. M. K. Pennell and F. Ujjainwalla, *J. Chem. Soc., Chem. Commun.*, 1992, 1067.

50 A. Pennell, PhD thesis, University of London, 1990.

51 J. K. Kochi, "Free Radicals", Vol 1, Wiley-Interscience, New York, 1973, p 346-347.

52 W. H. Urry, D. J. Trecker and H. D. Hartzler, *J. Org. Chem.*, 1964, **29**, 1663.

53 K. A. Parker, D. M. Spero and K. C. Inman, *Tetrahedron Lett.*, 1986, **27**, 2833.

54 A. N. Abeywickrema, A. L. J. Beckwith and S. Gerba, *J. Org. Chem.*, 1987, **52**, 4072.

55 J. C. Chottard and M. Julia, *Tetrahedron Lett.*, 1971, **12**, 2561.

56 N. S. Narasimhan and I. S. Aidhen, *Tetrahedron Lett.*, 1988, **29**, 2987.

57 J. L. Huppatz, *Aust. J. Chem.*, 1973, **26**, 1307.

58 D. I. Davies and C. Waring, *J. Chem. Soc.*, 1967, 1639.

59 P. M. Brown, J. Russell, R. H. Thomson and A. G. Wylie, *J. Chem. Soc.*, 1968, 842.

60 J. Russell, R. H. Thomson and A. G. Wylie, *Chem. Ind. (London)*, 1964, 34.

61 M. D. Bachi and E. Bosch, *J. Org. Chem.*, 1989, **54**, 1234.

62 E. Lee, C. Lee, J. S. Tae, H. S. Whang and K. S. Li, *Tetrahedron Lett.*, 1993, **34**, 2343.

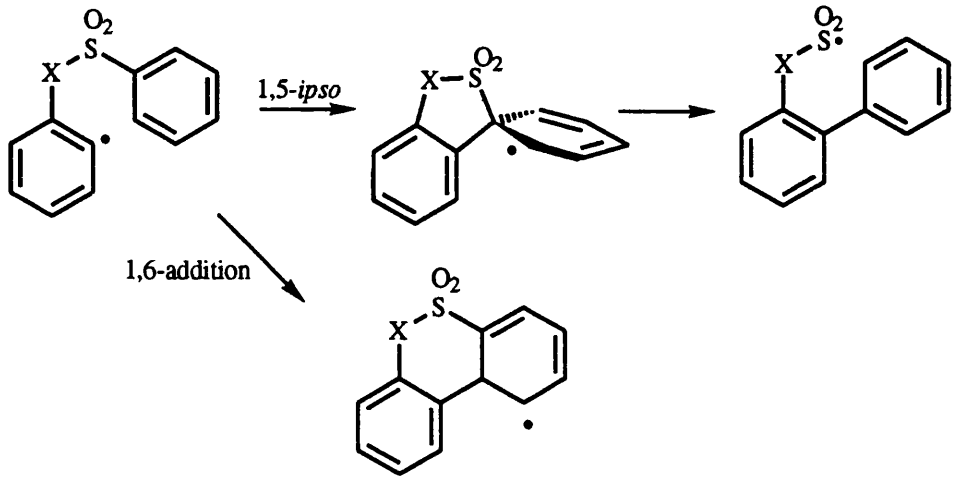
63 L. Benati, P. C. Montevecchi and A. Tundo, *J. Chem. Soc., Chem. Commun.*, 1978, 530.

Chapter Two:

Results and Discussion

2.1. Introduction and Previous Work in These Laboratories

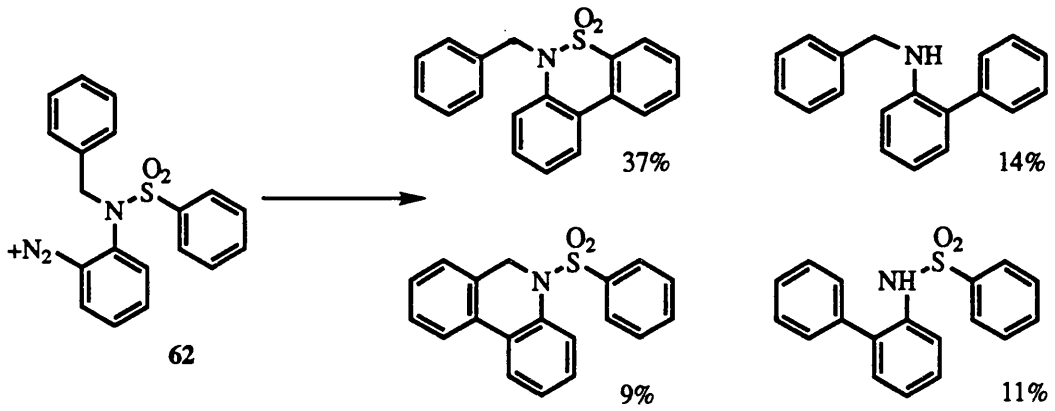
From the preceding chapter it is evident that *ipso* substitution is a powerful tool for the introduction of new groups to aromatic rings. This reaction is particularly attractive in the intramolecular mode, when it occurs between an aryl radical and an aryl acceptor ring which possesses a good radical leaving group, since a biaryl is formed (Scheme 2.1).



Scheme 2.1

The importance of the biaryl framework, present in a vast number of natural products, led us to further explore the use of radical chemistry for the construction of this unit. Thus, a project involving radical *ipso* substitution reactions for the formation of biaryls, using the sulfonyl group as the leaving group, has been developed in these laboratories.

Although the use of alkyl radicals in *ipso* substitution reactions involving the displacement of an SO_2 moiety has received much attention (Chapter 1, Section 1.2.2), the same reaction with aryl radicals has not been the subject of such interest. Nevertheless, *ipso* substitution has been reported to occur,[1] although only to a small extent, in the reaction shown in Scheme 2.2.



Reagents: Cu, 40-50°C.

Scheme 2.2

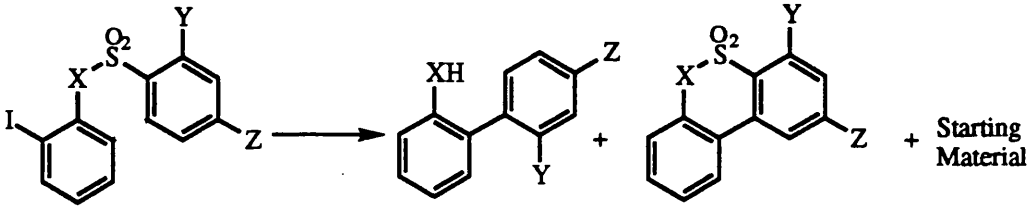
Compound **62** has two aromatic rings which can be attacked by the intermediate aryl radical. Thus, a mixture of products derived from addition and *ipso* substitution on both aromatic rings was obtained. Interestingly, *ipso* attack occurred with an almost equal facility for cleavage of either the carbon-carbon or the carbon-sulfur bonds and both biaryls isolated were formed in equivalent amounts.

Work previously carried out on this project[2] had shown that the formation of a new carbon-carbon bond between two aromatic residues by such a radical *ipso* substitution reaction, involving displacement of a sulfonyl group, was a feasible process (Scheme 2.3). In the course of the preliminary study however, it was observed that both the nature of the tethering chain and the substituents around the aromatic acceptor ring exerted an influence on the nature and ratio of products formed. These influences were not clearly understood.

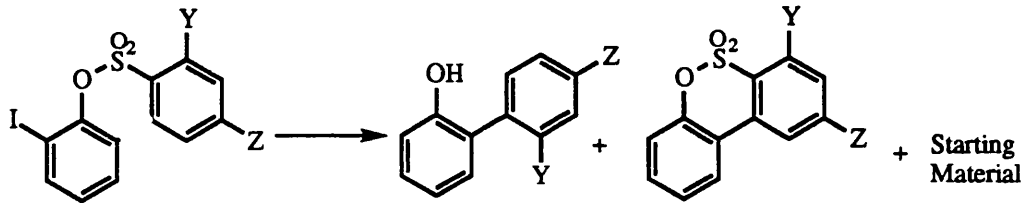
Thus for example, in the case of simple *para* toluenesulfonyl derivatives, the sulfonamide was clearly superior to the phenolic tosylate in terms of directing an *ipso* substitution pathway. Such an apparently inherent preference could however be moderated by "judicious" introduction of substituents around the sulfonyl acceptor ring. Nevertheless, in terms of developing a predictive rationale, the overall picture at this stage was extremely confusing, and highlighted the necessity for a systematic study of both:

a) the steric and electronic effect of substitution around the sulfonyl substituted acceptor ring and

b) the nature and number of atoms in the linking chain.



X=NMe	Y=H, Z=Me	44	36	18
	Y=H, Z=OMe	33	10	34
	Y=H, Z=F	29	44	26
	Y=CO_2Me, Z=H	65 a)	19	11



Y=H, Z=Me	0	63	37
Y=H, Z=OMe	18	24	31
Y=H, Z=F	0	50	0
Y=CO_2Me, Z=H	42 b)	21	37

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.
a) Isolated as the corresponding lactam. b) Isolated as the corresponding lactone.

Scheme 2.3

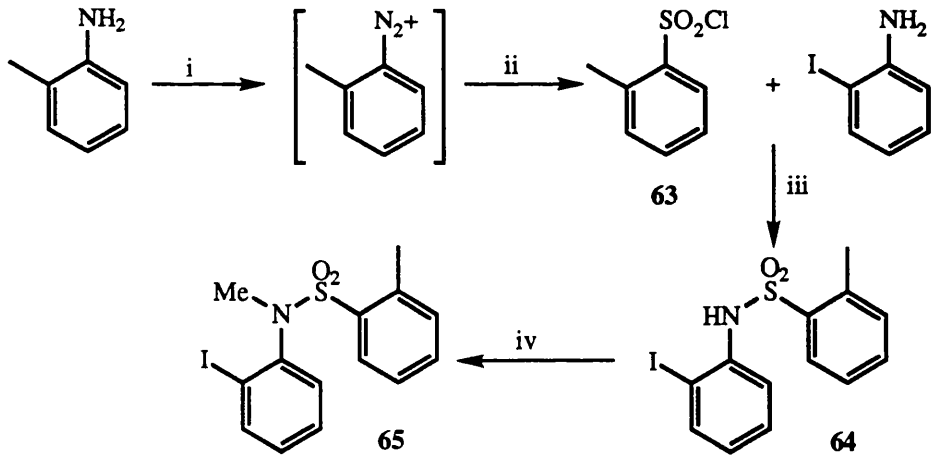
It should be appreciated however that, throughout the course of the work described in this thesis both of these areas were under active study at the same time, and that additional work by my colleague Feroze Ujjainwalla on the arylation of heterocyclic systems was also contributing to the overall picture. Hence, the following section is not necessarily chronological.

2.2. Steric and Electronic Effects on the Sulfonyl Substituted Acceptor Ring

2.2.1. The Effect of an *ortho* Substituent

In the first instance, most of the work previously carried out on the influence of additional substituents on the acceptor aromatic ring had concentrated on their polarity. In this section the influence of a specifically located *ortho* substituent on the sulfonyl substituted aromatic ring on controlling the ratio of direct addition versus *ipso* substitution, and hence the nature of the products, was examined.

Thus, compound **65** was selected, and was prepared as outlined in Scheme 2.4. The required sulfonyl chloride (**63**) was prepared by standard procedures from *o*-toluidine. Coupling with *o*-iodo aniline followed by methylation gave the sulfonamide **65**. It should be noted that additional protection of the nitrogen atom by further alkylation has been shown to be essential for success in these reactions,[3] presumably because of the acidity of the parent sulfonamide.

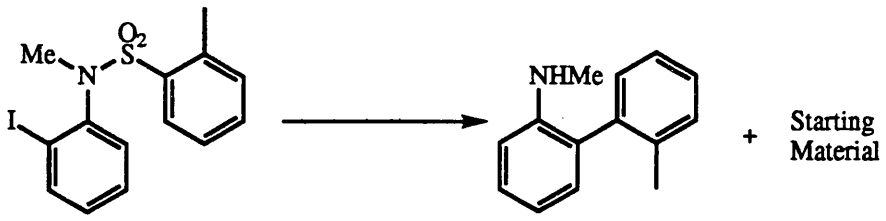


Reagents: i) HCl/AcOH, $NaNO_2$, -10°C, 30 min; ii) SO_2, CuCl, 10°C, 2 hr (62% over 2 steps); iii) Py, DMAP, r.t. (37%); iv) NaH, THF, MeI, r.t, (67%).

Scheme 2.4

The standard conditions adopted for the radical reactions consist of a slow addition of a solution of tri-n-butyltin hydride (1.3 eq.) and AIBN (0.7 eq.) in benzene to a refluxing solution of the sulfonamide in benzene. These conditions had earlier been

optimised,[3] in order to minimise the concentration of tri-n-butyltin hydride, and thus avoid the formation of the simple reduction product. The large amount of AIBN used shows that the chain processes involved are extremely inefficient. When sulfonamide **65** was submitted to these conditions, a single product derived from a 1,5-*ipso* substitution process (**66**) was obtained (Scheme 2.5).

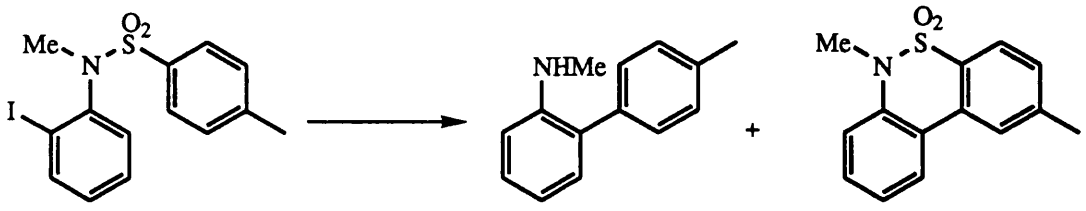


65 **66** 57% **65** 10%

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.5

This is an intriguing result, since the equivalent *para* derivative had given[2] a mixture of both 1,5-*ipso* substitution (**67**) and 1,6-addition products (**68**) (Scheme 2.6).

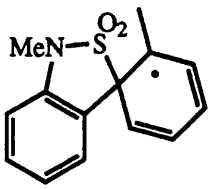


67 46% **68** 25%

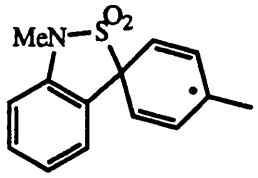
Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.6

In terms of the electronic factor, both spiro intermediates **69** and **70** are "identically" stabilised by the alkyl substituent. Thus, the difference of selectivity observed for these two substrates suggests that the influence of the methyl group in the *ortho* position is to retard the 1,6-addition process, and thereby, by default, to favour *ipso* substitution.

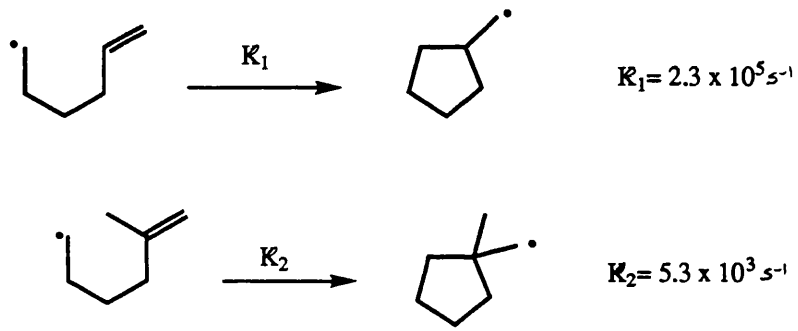


69



70

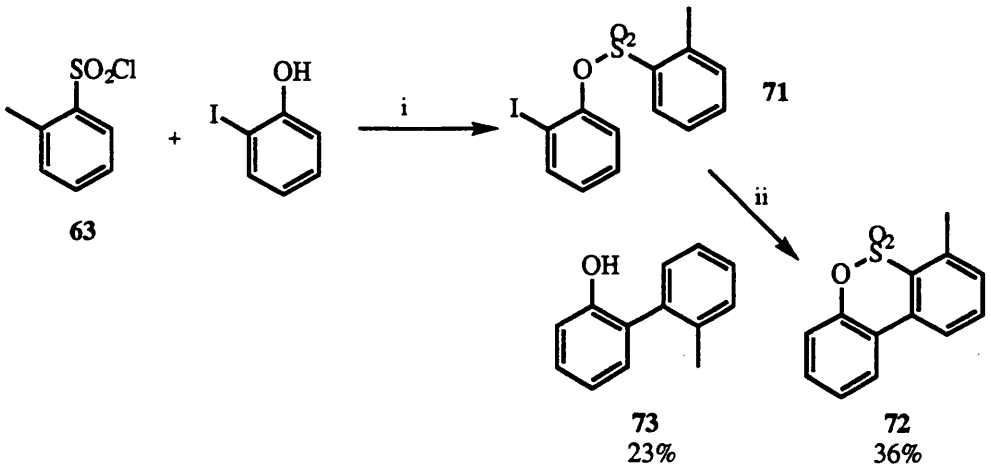
Some support for the "buttressing effect" of the *ortho* methyl group in directing 1,5-*ipso* attack may be adduced from the fact that the introduction of an additional methyl group in the classical 5-hexenyl radical ring closure has been shown to lead to a dramatic drop in the rate of the cyclisation reaction[4] (Scheme 2.7).



Scheme 2.7

Although this can explain why the addition does not occur at the substituted position of the aromatic acceptor ring, it is still not clear why it does not occur on the other possible site of reaction.

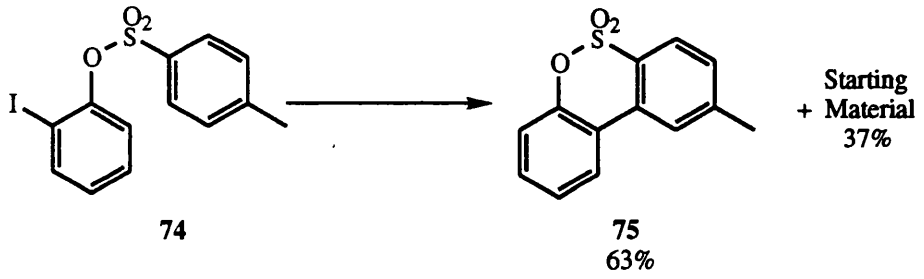
It had been noted in the initial study[2] that a sulfonate ester in the linking chain favoured the 1,6-addition process over 1,5-*ipso* substitution. It was therefore of particular interest to examine the possibility that the presence of a simple *ortho* substituent would override this tendency and favour 1,5-*ipso* substitution. The combination of both of these effects was analysed using sulfonate **71** which was prepared by reaction of sulfonyl chloride **63** and *o*-iodophenol in pyridine. Reaction of **71** under the standard radical conditions afforded a mixture of products derived from both 1,5-*ipso* substitution (**73**, 23%) and 1,6 -addition (**72**, 36%) pathways (Scheme 2.8).



Reagents: i) py, DMAP; ii) Bu_3SnH / AIBN (slow addition), benzene, reflux .

Scheme 2.8

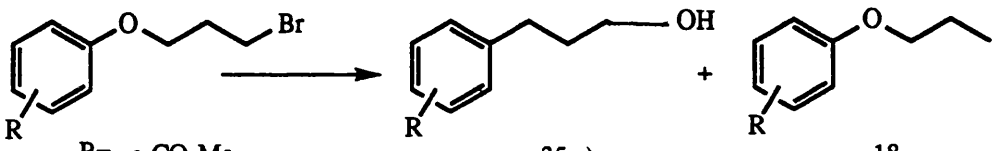
Since the corresponding *para* derivative **74** gave the cyclic sultone **75** derived by 1,6-addition as the only product (Scheme 2.9), the effect of the substituent on the *ortho* position in the reaction of **71** is clearly revealed as an important contributor to the formation of 1,5-*ipso* substitution product **73** (Scheme 2.8).



Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.9

While this work was in progress the preference for *ortho* substituted aryl ethers to undergo *ipso* substitution was also reported[5] (Scheme 2.10).

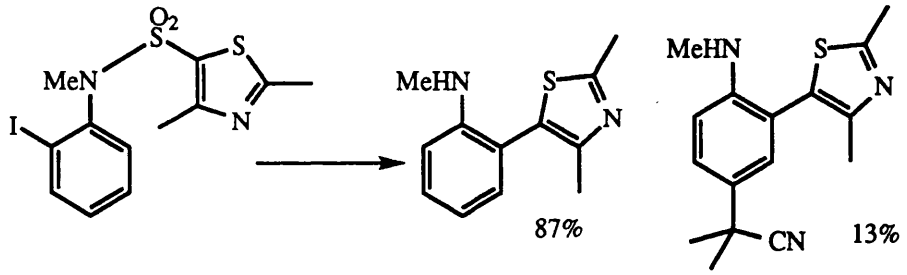


R=		35 a)	18
	o-CO_2Me		
	p-CO_2Me	25	65
	o-MeO	53	21
	p-MeO	24	61

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.
a) Isolated as the corresponding lactone.

Scheme 2.10

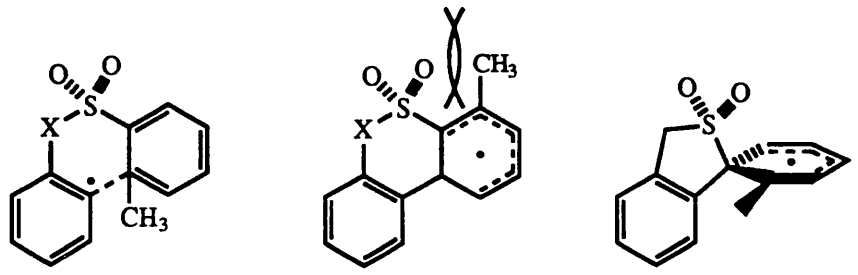
The same tendency was noted during parallel work in the heterocyclic series in our own group, where it was suggested that the excellent level of selectivity was not entirely electronic, but that retardation of the 1,6-addition process, as a consequence of the buttressing effect of the methyl group, was important[6] (Scheme 2.11).



Reagents: Bu_3SnH/AIBN (slow addition), benzene, reflux.

Scheme 2.11

Thus, the dominant effect of an *ortho* substituent is probably due to steric hindrance, both in terms of disfavouring addition of the aryl radical to the *ortho* substituted carbon and also since unfavourable interactions can develop between the *ortho* substituent and the sulfonyl group in the alternative 1,6-addition intermediate (Figure 2.1). The *ipso* substitution process is accordingly favoured.



disfavoured disfavoured favoured

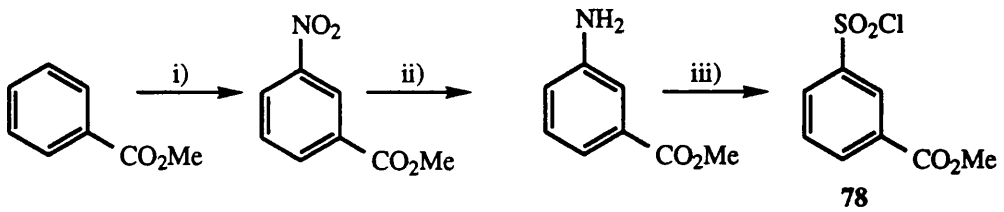
Figure 2.1

2.2.2. The Effect of a *meta* Substituent

Intramolecular reactions leading to the formation of aryl-aryl bonds are generally believed to be governed less by polar effects of the substituents than by ring strain.[7] However, even in the early stages of this project polar effects have been found to have a marked influence on the outcome of the reactions, as for example in the comparison between the *para* toluene and the methoxyphenyl sulfonate esters of *o*-iodophenol (Scheme 2.3).

The presence of a carbomethoxy group on the *ortho* position of the aryl acceptor ring favours the formation of the *ipso* substitution product, probably both by an electronic stabilisation effect and by its location in the *ortho* position (c.f. Section 2.2.1).

It was therefore of interest to examine the influence of a *meta* carbomethoxy group, using compounds **79** and **84**. (Scheme 2.13 and 2.14). Since the synthesis of these compounds required sulfonyl chloride **78**, which was not commercially available, it was prepared by standard procedures from methyl benzoate, as shown in Scheme 2.12.

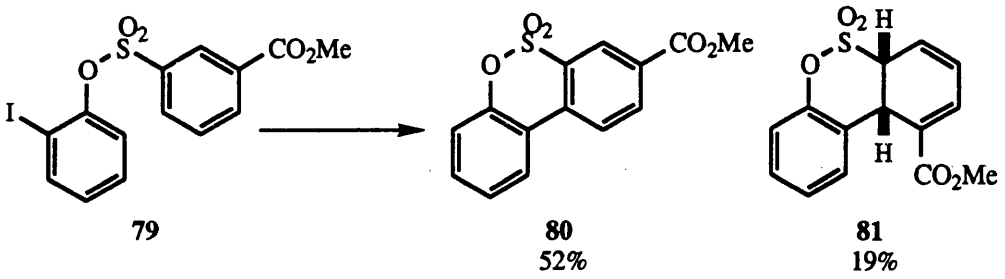


78

Reagents: i) H_2SO_4, HNO_3, 0-10°C, 1 hr (94%); ii) H_2, Pd/C, EtOH;
iii) a) HCl/AcOH, $NaNO_2$, -10 °C, b) SO_2/AcOH, CuCl, 10 °C, 1 hr (67% overall).

Scheme 2.12

Sulfonate **79** was then prepared by the standard reaction of the sulfonyl chloride **78** with *o*-iodophenol in pyridine. Reaction of the product under the usual standard radical conditions afforded only the 1,6-addition products in good yield. The addition occurred on the two possible positions, to give compounds **80** and **81** (Scheme 2.13).



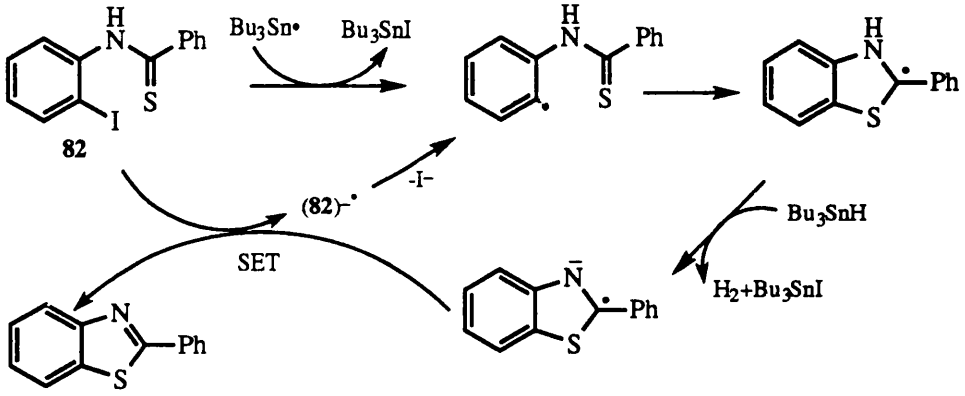
79 **80** 52% **81** 19%

Reagents: Bu_3SnH/AIBN (slow addition), benzene, reflux.

Scheme 2.13

The structure of **81** was only determined after a single crystal X-ray difffraction analysis had been carried out (Appendix 2).

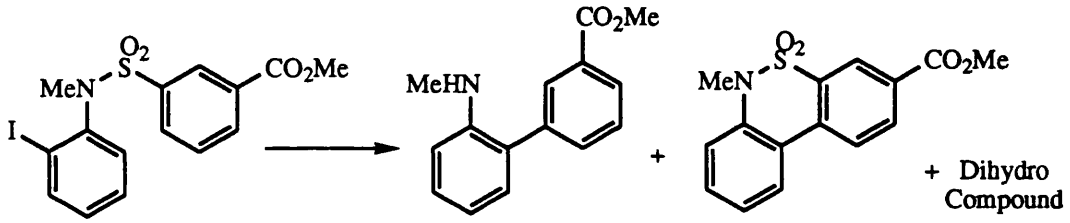
Although this reaction, as expected, did not lead to *ipso* substitution, it is worthy of comment. The isolation of the "oxidised" fully aromatic **80** is a common phenomenon in the direct addition process even although the dihydroaromatic derivatives should be the anticipated products under reducing conditions. This aspect has been fully discussed by Bowman[8] for other radical reactions. It is proposed that the oxidation of the radical formed upon 1,6-addition, occurs *via* a pseudo $S_{RN}1$ mechanism (Scheme 2.14).



Scheme 2.14

In compound **81**, it is clear that the oxidative process is more difficult. The observed regiochemistry of the carbomethoxy unit and the *cis* fused stereochemistry of the ring junction imply that although hydrogen atom capture from the stannane has occured from the least hindered face, it is nevertheless apparently delivered adjacent to the bulky sulfonyl group. Although the favoured extended conjugation of the carbomethoxy unit is thus formed, it is nevertheless surprising.

The corresponding sulfonamide **84** was prepared in a similar fashion from the sulfonyl chloride **78** and *o*-iodoaniline followed by N-methylation with sodium hydride followed by methyl iodide. By way of contrast, reaction of this substrate under the standard tin hydride conditions, was less selective and both the formation of 1,5-*ipso* substitution product **85** and the 1,6-addition product **86**, was observed (Scheme 2.15).

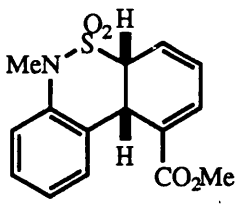


84 **85** 28% **86** 37% **87** 11%

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

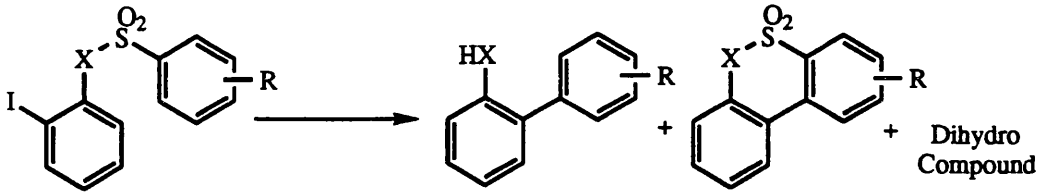
Scheme 2.15

A dihydro compound was also isolated in minor amount, but complete structural elucidation was not possible, although the similarity of its ^1H nmr spectrum with that of compound **81** is indicative of compound **87a**. The ^1H nmr spectra of compounds **81** and **87** are presented in Appendix 1.



87a

These results may now be compared with those from the corresponding *ortho* derivative (Scheme 2.16).



X=NMe	R=*o*-CO_2Me	65% a)	19%	0%
	R=*m*-CO_2Me	28	37	11
X=O	R=*o*-CO_2Me	42 b)	21	0
	R=*m*-CO_2Me	0	52	19

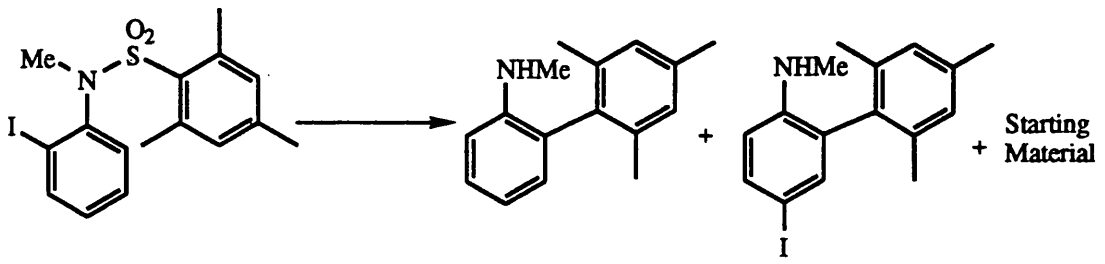
a) Isolated as the corresponding lactam.
b) Isolated as the corresponding lactone.

Scheme 2.16

From the results presented on Scheme 2.16, it can be seen that the presence of an oxygen atom in the linking chain favours the 1,6-addition mode. This effect is particularly noticeable when combined with the stabilisation of a *meta* carbomethoxy group, where formation of the *ipso* product is completly suppressed. It is nevertheless remarkable in the sulfonamide **84** that once again the nitrogen atom has allowed *ipso* attack to occur, even in the presence of an electronically "unfavoured" carbomethoxy substituent on the sulfonyl acceptor ring.

2.2.3. The Effect of Multiple Substituents

Until now, all of the work presented concerning *ipso* substitution has been carried out using compounds with a single substituent. The only reported example[2] with more than one substituent on the aromatic acceptor ring is the mesitylene derivative **89** (Scheme 2.17). In this case, both *ortho* positions are substituted, and thus only *ipso* substitution is observed. Curiously, under incomplete reaction conditions the product retained, to some degree, an iodine atom (**91**) (Scheme 2.17).



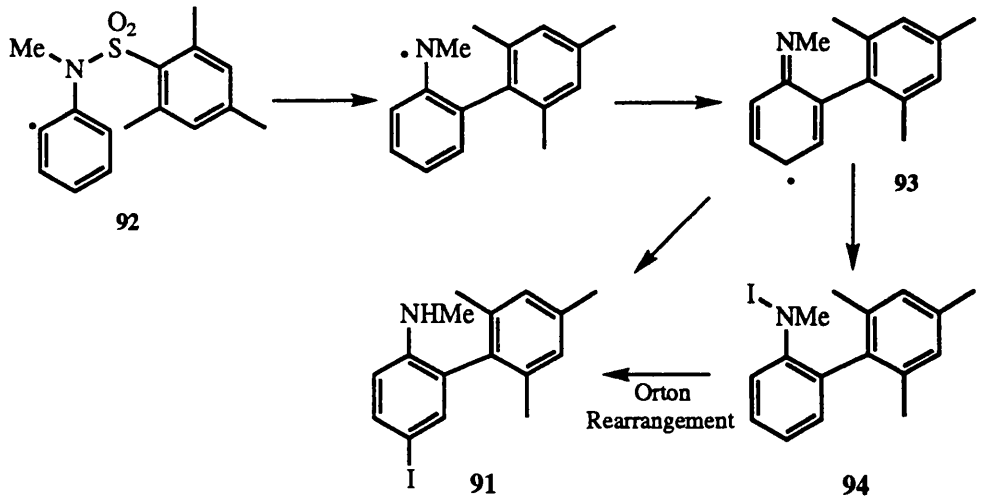
89 90 27% 91 15% 89 44%

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.17

In our hands it was of course possible to eliminate the iodo derivative **91** by using a greater amount of tri-n-butylstannane, and hence to obtain the non halogenated *ipso* product **90** in 64% yield. Nevertheless, from the mechanistic viewpoint the formation of iodide **91** is interesting, as it formally appears to involve an iodine atom transfer reaction.[9]

Thus, in principal, formation of the aryl radical, *ipso* substitution and loss of sulfur dioxide could occur in the standard fashion to give **93** (Scheme 2.18).



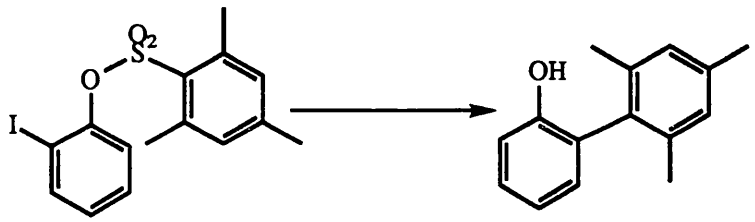
92 93 91 94

Scheme 2.18

From the thermodynamic standpoint, it seems most unlikely that **93** is capable of iodine atom abstraction from the starting sulfonamide **89** to give the chain carrying aryl radical **92**, in respect of whether iodination is finally achieved directly or *via* the

Orton rearrangement of an intermediate N-iodo derivative **94**. This reaction is certainly worth of further investigation in its own right.

The corresponding sulfonate **95** was also prepared from *o*-iodophenol and 2,4,6-trimethylbenzenesulfonyl chloride in pyridine. Reaction using the usual radical conditions afforded the *ipso* product **96** in 50% yield (Scheme 2.19), thereby contrasting with the simple *p*-toluenesulfonate **74** (Scheme 2.9) and reinforcing the idea of the importance of sterically buttressing substituents.



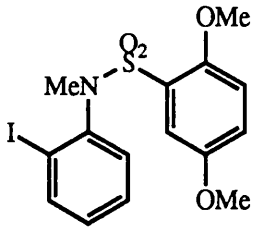
95 **96** 50%

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

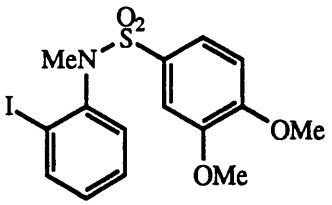
Scheme 2.19

In order to examine the effect of two substituents on the acceptor ring, compounds **98** and **100** were prepared by the usual method, of coupling the correspondent sulfonyl chloride with *o*-iodoaniline in pyridine.

In both of these compounds, the presence of the *meta* methoxy group might be envisaged to encourage the direct 1,6-addition process, while, in electronic terms the *ortho* (**98**) and *para* (**100**) methoxy group should exert a favourable influence in *ipso* substitution.

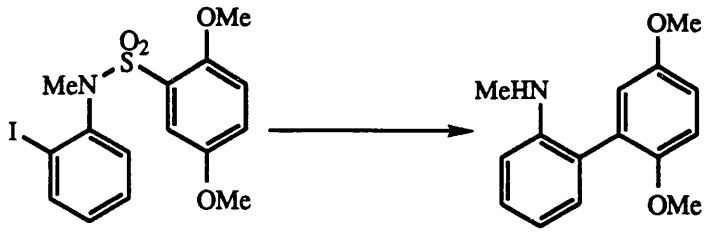


98



100

When compound **98** was submitted to the radical reaction conditions, only one product (**101**), resulting from *ipso* substitution, was detected (Scheme 2.20).

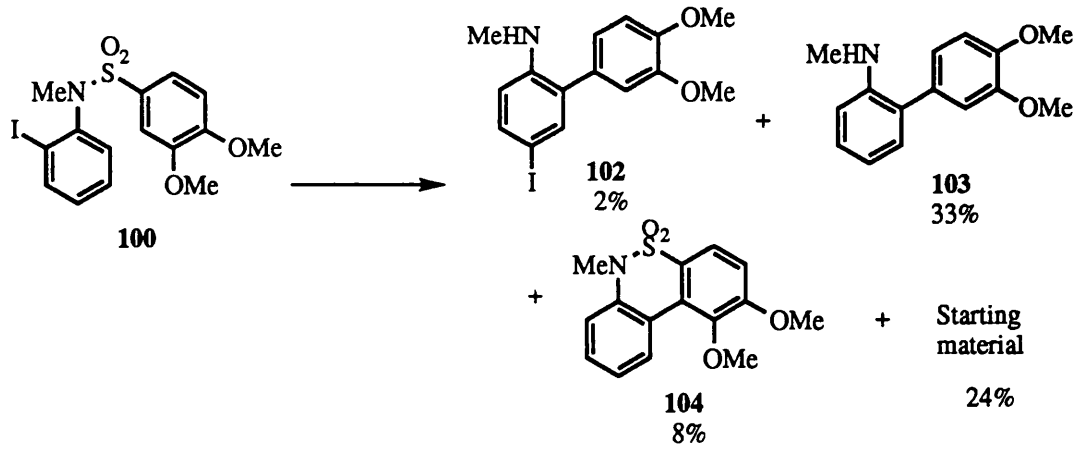


98 **101** 63%

Reagents: Bu3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.20

However, when compound **100** was submitted to the same conditions, it afforded a mixture of two compounds (4:1), inseparable by chromatogarphy on silica gel, which could be resolved by HPLC to give the *ipso* substitution (**103**) and addition products (**104**) (Scheme 2.21).



100

102 2%

103 33%

104 8%

24%

Reagents: Bu3SnH / AIBN (slow addition), benzene, reflux.

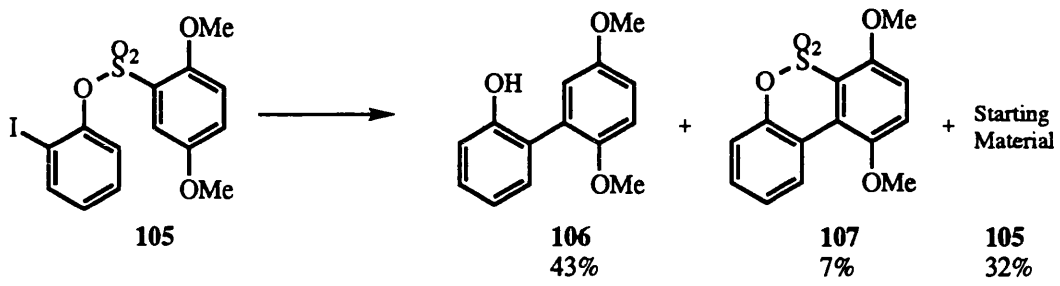
Scheme 2.21

The formation of a minor compound, **102**, retaining an iodine atom, was also noticed (as reported before in Scheme 2.17).

Comparison of these two substrates (Scheme 2.20 and 2.21) clearly reveals that the location of an *ortho* methoxy group is, yet again, the dominant factor in directing the reaction pathway towards *ipso* substitution .

Following our studies, sulfonates **105** and **108** were also prepared.

Thus, reaction of compound **105** under standard tin hydride conditions afforded the product from 1,5-*ipso* substitution, **106**, and a minor product from direct 1,6-addition, **107**. (Scheme 2.22).



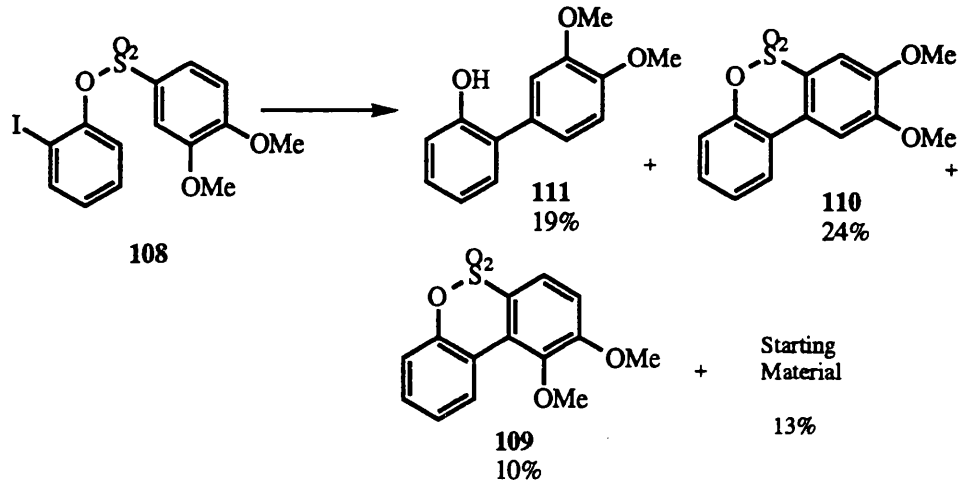
105 **106** 43% **107** 7% **105** 32%

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.22

Formation of the 1,6-addition product **107** to such a small extent can possibly be explained by a retardation of the addition process due to the presence of the methoxy group on position 2, since an *ortho* substituent favours *ipso* substitution.

In similar fashion to the case of the sulfonamide, compound **108** gives a mixture of both addition and *ipso* substitution products. Curiously, in contrast to the sulfonamide case (Scheme 2.21), addition products resulting from attack at both possible sites could be isolated (Scheme 2.23).



Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.23

Thus, it can be observed that on sulfonate (**108**), addition to the less hindered position 6 (**110**, 24%) is favoured over position 2 (**109**, 10%). It is not at all clear however, why the corresponding sulfonamide **100** (Scheme 2.21) gave only the product of addition at the apparently more congested position 2.

In summary, at this stage, the most dominant substituent effect in terms of favouring a 1,5-*ipso* attack over a 1,6-addition process is the presence of at least one functional group located at the *ortho* position of the sulfonyl acceptor. Such a group may be either electron releasing or electron withdrawing. Electron donating substituents on the *para* position also favours 1,5-*ipso* substitution, this effect being stronger for better donating groups (p.e. R= OMe).

Finally, the presence of stabilising groups on the *meta* position favours 1,6-addition, in order to give the more stable radical intermediate.

2.3. The Nature of the Linking Chain in 1,5-*Ipso* Substitution *vs* 1,6-Addition

Throughout this work on 1,5-*ipso* substitution, we have noticed the importance of the nature of the linking chain X on the distribution of products resulting from 1,5-*ipso* substitution and 1,6-addition (Figure 2.2).

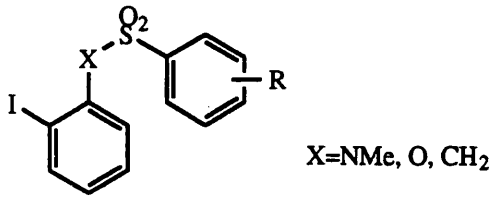
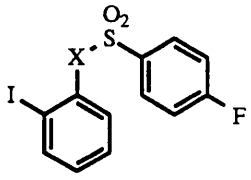
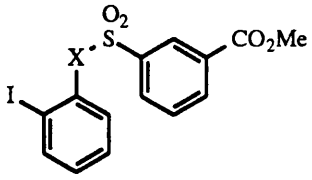


Figure 2.2

While our studies on the effect of substituents R on the sulfonyl substituted acceptor ring provided valuable information in their own right, they also served, at the same time, to reinforce the inescapable conclusion that, for the simple series 1,5-*ipso* substitution *vs* 1,6-addition reactions, an empirical rule could be clearly established *viz.*, nitrogen is more efficient than oxygen in the linking chain in the promotion of 1,5-*ipso* substitution.

With electron withdrawing groups at the *meta* or *para* positions of the acceptor aromatic ring, this rule was clearly observed as, with the oxygen linking chain, the *ipso* substitution product was completely nonexistent (Table 2.1). Although for the *meta* substituted compound, the addition product would be stabilised to a greater extent by the substituent, the nitrogen chain still shows some product from 1,5-*ipso* substitution.

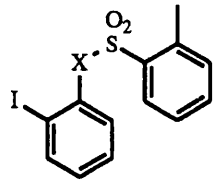
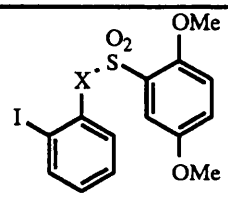
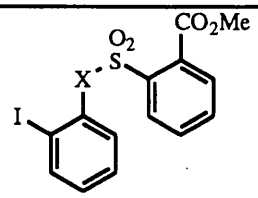
Table 2.1

	X=	1,5-*ipso*	1,6-add.	Start. Mat.	Ref.
	NMe	31%	44%	26%	3
	O	---	50		3
	NMe	28%	48%*		Sec. 2.2.2.
	O	--	71*		

* combination of addition and dihydro products.

Even when an *ortho* group was introduced in the acceptor aromatic ring, and its effect analysed (Section 2.2.1), the same tendency was always observed (Table 2.2). Thus, although the *ortho* substituent itself tended to favour 1,5-*ipso* substitution, the oxygen atom in the linking chain, lead to a relative increase in the proportion of the 1,6-addition product, when compared with the nitrogen congener.

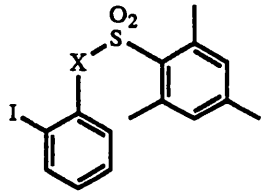
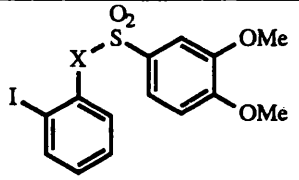
Table 2.2

	X=	1,5-*ipso*	1,6-add.	Start. Mat.	Ref.
	NMe	57%	--	9%	Sec.
	O	23	36	14	2.2.1.
	NMe	63%	--	23%	Sec.
	O	43	7%	32	2.2.3.
	NMe	65%*	19%	11%	3
	O	42@	21	37	3

* Isolated as the corresponding lactam.
@ Isolated as the corresponding lactone.

The presence of multiple substituents on the acceptor aromatic ring does, of course, present an extreme case, particularly when both addition sites are blocked, and thus, in this case, the addition product is not observed (Table 2.3). However, if these positions are not occupied, the same general trend is observed, with the addition products being formed in much higher yield when the oxygen link is used.

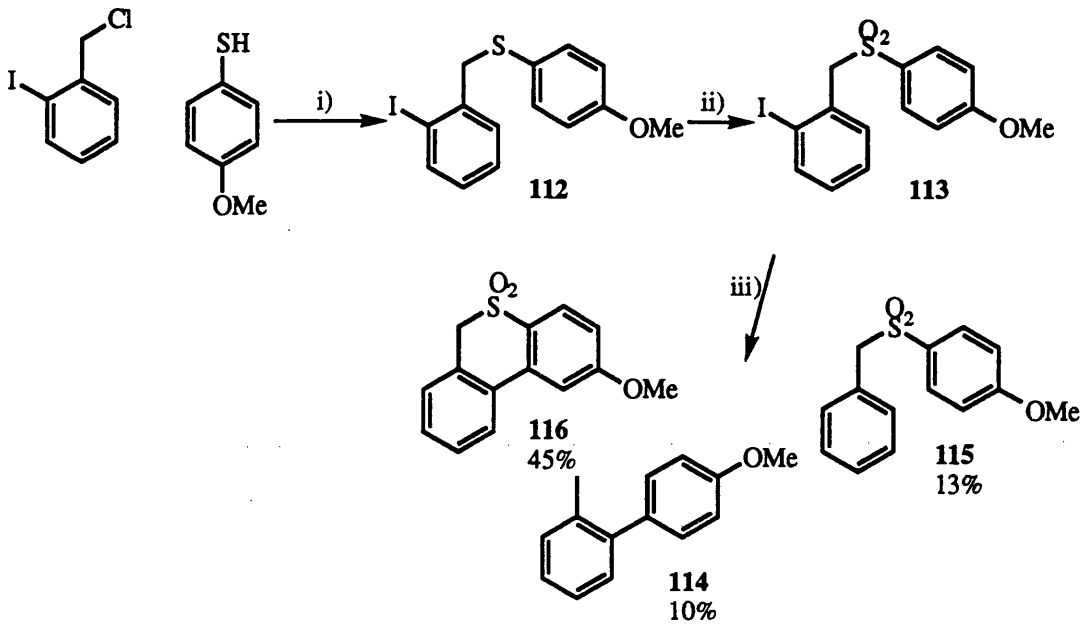
Table 2.3

	X=	1,5-*ipso*	1,6-add.	Start. Mat.	Ref.
	NMe	64%	--	--	Sec.
	O	50	--	--	2.2.3.
	NMe	33%	8%	24%	Sec.
	O	19	34*	13	2.2.3.

* Combination of the two isomers formed.

Thus, all our results confirm that a nitrogen atom in the linking chain is a better promoter for 1,5-*ipso* substitution than an oxygen. For comparison with the sulfone case ($X=CH_2$) the preparation of compound **113** was deemed necessary (Scheme 2.21). This was accomplished by nucleophilic displacement of *o*-iodobenzyl chloride with thiophenoxide anion, which occurred in excellent yield, followed by oxidation with *m*-CPBA which, although proceeding in poor yield, gave enough material to proceed with a reaction.

Reaction of **113** under standard radical conditions afforded the 1,6-addition adduct **116** as the major product, together with the 1,5-*ipso* substitution product **114** and compound **115**, as a result of direct reduction of the starting material. (Scheme 2.24).



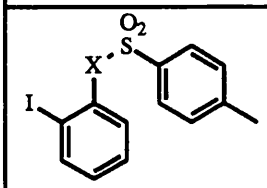
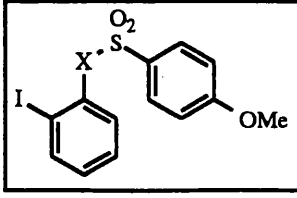
Reagents: i) NaH, THF (91%); ii) m-CPBA, DCM, 0 °C, r.t. (17%);
iii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.24

This is the first example in our 1,5-*ipso* substitution study where we observe the formation of the simple reduced product. Nevertheless, it is clear that the methylene chain favours the 1,6-addition step.

For simple *para* substituted compounds with electron donating groups the empirical rule for nitrogen and oxygen is also observed (Table 2.4), and it is possible to envisage an extension to the methylene substituted linking chain. Although on the *p*-toluenesulfonyl derivative both oxygen and methylene chains give exclusively 1,6-addition, when the *para* substituent is a methoxy group, the methylene group is even more efficient in promoting the 1,6-addition pathway.

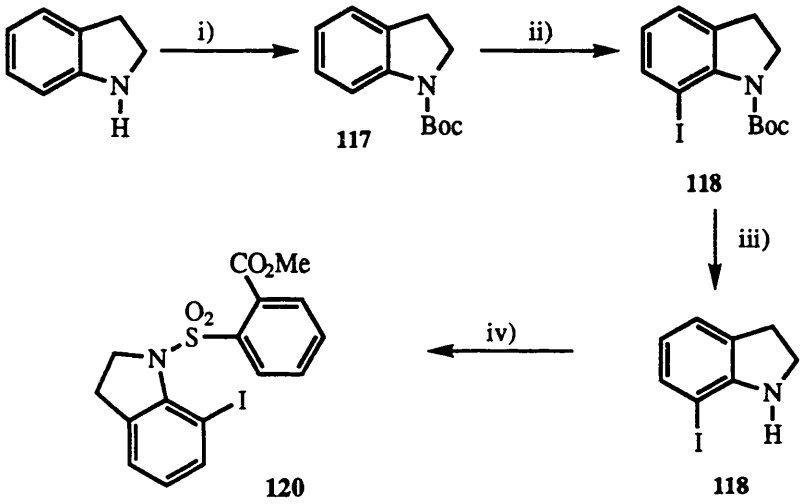
Table 2.4

	X=	1,5-*ipso*	1,6-add.	Start. Mat.	Ref.
	NMe	46%	25	17	3
	O	--	63	37	3
	CH_2	--	40	40	3
	NMe	29	10	34	3
	O	18	24	31	3
	CH_2	10	45	--	

In summary, it has been demonstrated that another important factor in the direction of attack in a 1,5-*ipso* substitution *vs* 1,6-addition reaction is the nature of the linking chain. An empirical rule is postulated where the efficiency on the promotion of the *ipso* attack decreases from a nitrogen to oxygen, and then to a methylene group of the linking chain.

2.4. Strain and Ring Effects

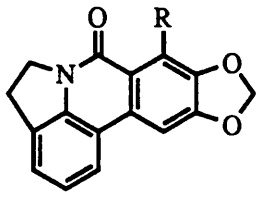
All of the examples which we have discussed this far in the sulfonamide series have had the nitrogen atom on the linking chain substituted by a methyl group. To extend the range of this reaction we therefore decided to incorporate the nitrogen atom into a ring. Hence, compound **120** was prepared by a known sequence of protection, halogenation and deprotection[10] followed by coupling with the sulfonyl chloride (Scheme 2.25).



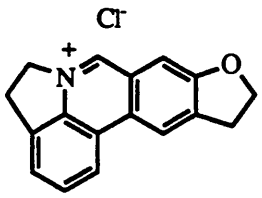
Reagents: i) (^{t}BuOCO)$_2$O, THF, r.t.; ii) a) TMEDA, ^{s}BuLi, THF, -78 °C, 1 hr, b). I_2, ether, 45 min; iii) DCM, TFA, 5 hr; iv) Py, DMAP, methyl 2-(chlorosulfonyl) benzoate, r.t., 20 hr.

Scheme 2.25

For this experiment, the selection of *o*-carbomethoxy sulfonyl chloride was made, since it had been shown to be a particularly good *ipso* director (Scheme 2.16), and also to undergo subsequent lactamization. Most of all however, we were inextricably lured by the appeal of total synthesis, since such a process would lead to the skeletal framework of the pyrrolophenthridone alkaloids.[11] These compounds have significant biological activity and some examples of this family of alkaloids are Hippadine (**121**), which was shown to reversibly inhibit fertility in male rats, Kalbretorine (**122**) which exhibits antitumor activity and Ungeremine (**123**) which has been known to be active against some type of carcinoma.

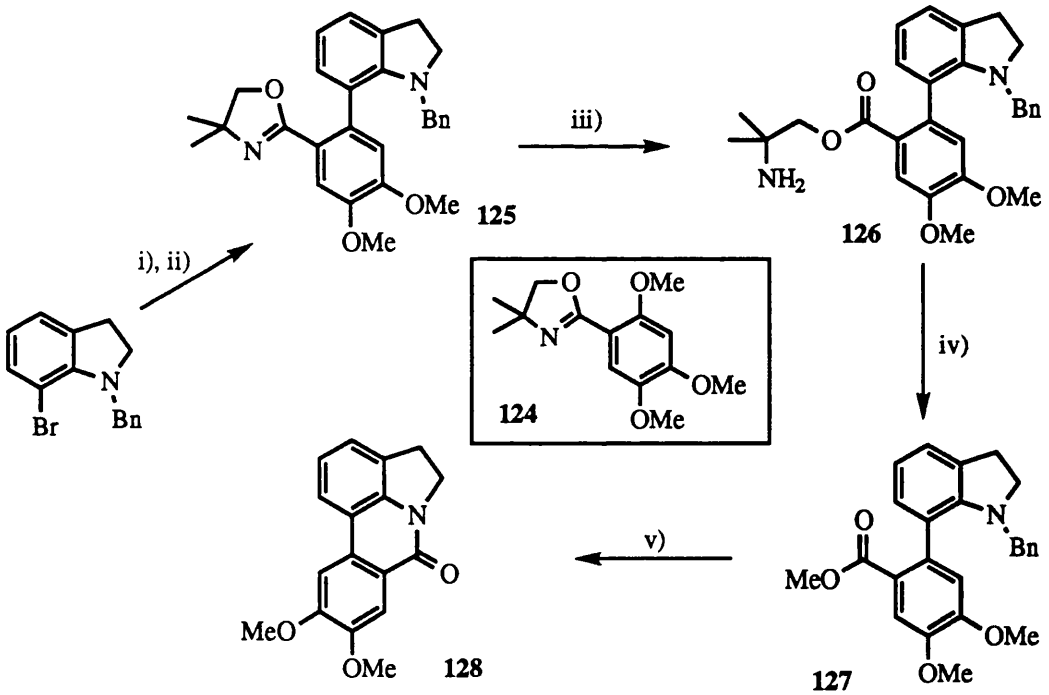


121 R= H
122 R= OH



123

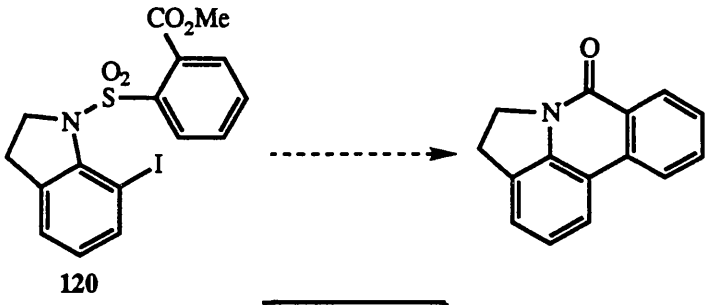
The synthetic strategy used by Meyers[11] for the construction of these alkaloids and which inspired us to undertake the study is shown in Scheme 2.26. It involves the coupling of oxazoline **124** with the aryl Grignard, to give the corresponding biaryl **125**. Hydrolysis of the oxazoline **125** to the aminoester **126** followed by trans-esterification to the methyl ester **127** and hydrogenation, affords Oxassoanine **128**, *via* spontaneous lactamization of the free amine.



i) Mg, THF, BrF_2CCF_2Br, r.t., 1 hr; ii) **124**, Δ, 12-15 hr (71%); iii) 10% H_2SO_4/EtOH, Δ, 24 hr; iv) NaOMe/MeOH, Δ, 3 hr; v) Pd/C, AcOH, MeOH, H_2 (1atm).

Scheme 2.26

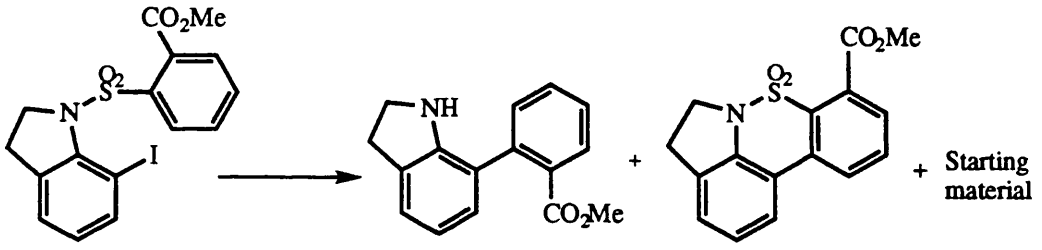
Comparison of this synthesis with the hypothetical *ipso* substitution and trans-lactamization process outlined in Scheme 2.27 reveals that such a sequence would provide a remarkably short and efficient entry to this alkaloid skeletal type.



120

Scheme 2.27

In the event however, the *ipso* substitution product **129**, although present in the reaction mixture, was formed in only 13%, and the major product of this reaction was as a result of the 1,6-addition process (**130**, 39%) (Scheme 2.28).



120 | **129** 13% | **130** 39% | **120** 10%

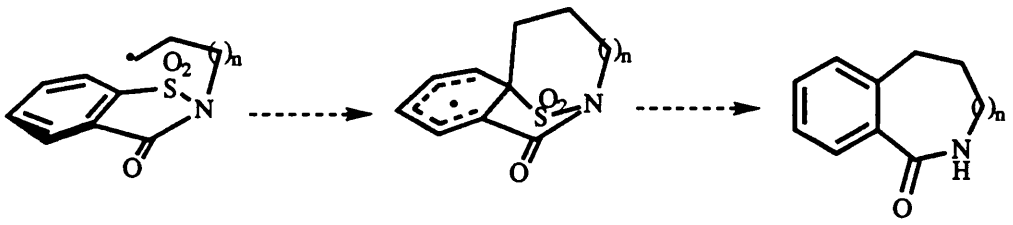
Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.28

Moreover, the lactamization step, which had presumably occurred during the basic fluoride anion work up, was not observed, presumably since it would lead to an even more strained compound.

Although the desired compound **129** was formed in minor amount, this was nevertheless an interesting example, since it reveals that the additional conformational restrictions and the strain created by incorporation of the nitrogen atom in a ring, can effectively block the progress of the reaction, even when the starting material **120** contains not only the favoured sulfonamide linkage, but also an *ortho* substituent, to facilitate *ipso* substitution.

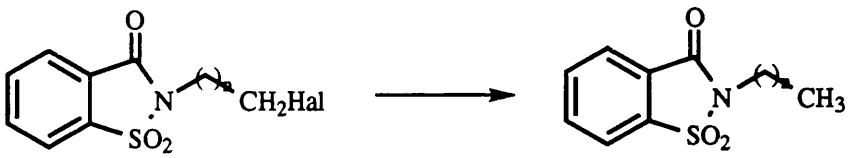
At the same time, another system for *ipso* substitution reactions, derived from saccharine, was analysed (Scheme 2.29).



Scheme 2.29

We envisaged, that in this system suitable adjustment of the chain length should lead to intramolecular displacement of the sulfonyl group by *ipso* substitution, and hence to the creation of macrocyclic molecules.

In order to find the size of chain necessary to "curl" over the molecule and reach the sulfonyl substituted position of the aromatic ring, a series of compounds of increasing chain length, as represented in scheme 2.30, was prepared. Although all experiments were performed under the standard radical conditions, at extremely low concentrations of tri-n-butylstannane, only reduced product was formed in every case. Although by analysis of the crude ^1H nmr spectrum a small signal at 2.6 ppm could be seen, which was indicative of the presence of benzylic protons, no product arising from *ipso* was ever present in sufficient quantity to be isolated.

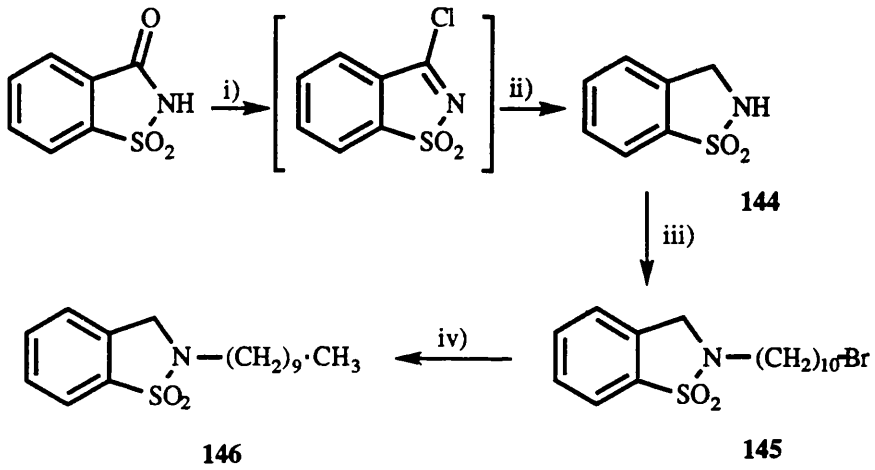


n= 2, 3, 4, 5, 9

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.30

It should be noted that the saccharine molecule is essentially planar[12] and that the narrow C-S-N angle (92.2°) in the five membered ring could be responsible for strain and angular distortions. In order to relieve this strain, the carbonyl group on the ring was therefore reduced, and the benzisothiazole derivative **145** was prepared. The 10 membered chain was then selected, since it should lead to a 14 membered macrocycle (Scheme 2.31).

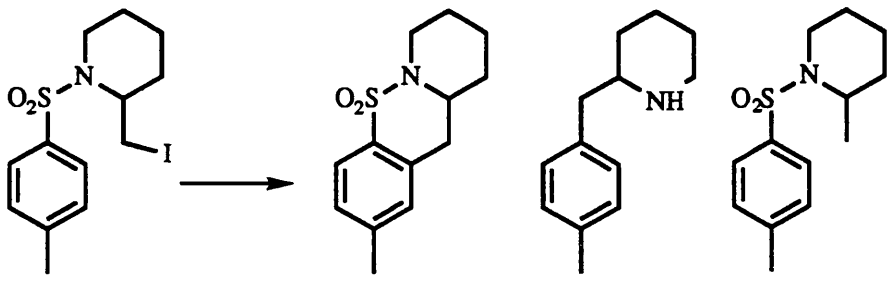


Reagents: i) PCl_5, 175-180°C, 90 min; ii) $NaBH_4$, THF, 0°C; iii) NaH, DMF, $Br(CH_2)_{10}Br$, r.t.; iv) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.31

However, reaction of compound **145** again afforded only the reduced product **146**. From the analysis of these results it is clear that the probability of the radical to adopt the required conformation is very small, and that hydrogen abstraction is the preferential pathway.

Another interesting case to be compared is that of Speckamp,[13] who had shown that the reaction of a primary radical with a sulfonyl substituted aromatic ring afforded 1,6-addition (**147**), 1,5-*ipso* substitution (**148**) and direct reduction products (**149**) (Scheme 2.32).

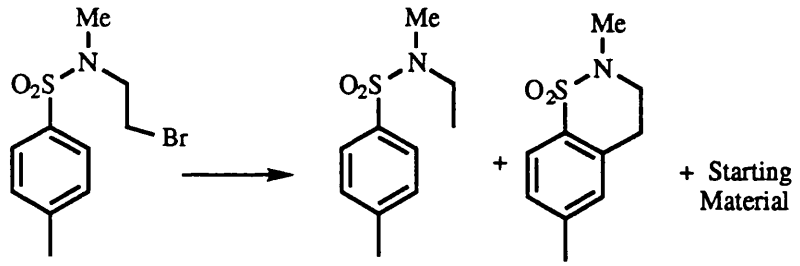


147 45% **148** 32% **149** 23%

Reagents: Bu_3SnH / AIBN, anisole, 96°C.

Scheme 2.32

However, in contrary to these results, when we examined the less rigid system **151**, the *ipso* substitution product was not formed, and only 1,6-addition (**153**) and direct reduction (**152**) products were observed (Scheme 2.33).



151 **152** 15% **153** 27% **151** 5%

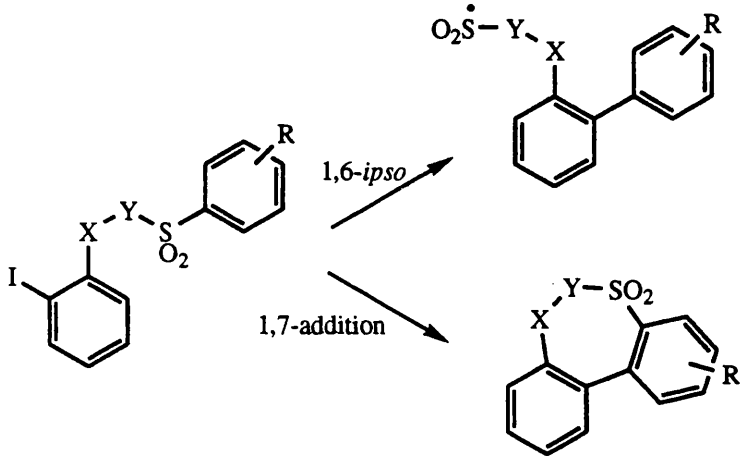
Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.33

Once again in this section, despite the fact that the selection of sulfonamide derivatives with a supposed predisposition for 1,5-*ipso* substitution was made, the overall subtlety of conformational, strain and entropic effects engendered in the linking chain, combined to frustrate us. Nevertheless they did reveal that the optimal geometry for *ipso* substitution is indeed a delicate balance.

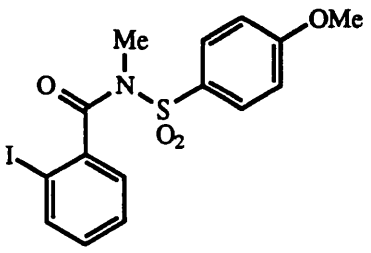
2.5. The Nature of the Linking Chain in 1,6-*ipso* Substitution vs 1,7-Addition

By increasing the size of the connecting chain between the aryl radical and the acceptor ring, so that the reaction can occur either by a 1,6-*ipso* substitution or by a 1,7-addition process, the *ipso* substitution would be generally predicted to be the favoured process, since a 6-membered ring transition state is favoured over the 7-membered ring. However, as we have seen in the case of 1,5-*ipso* substitution *vs* 1,6-addition, the nature of the linking chain can have an important role in directing the reaction pathway. Therefore, it seemed necessary a similar study with different combinations of X and Y groups (Scheme 2.34), as well as continuing and reinforcing our studies on the effect of substituents on the acceptor ring.

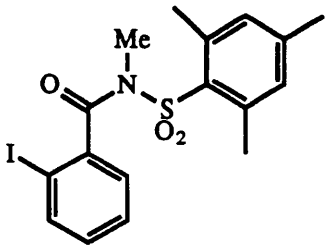


Scheme 2.34

Preliminary work in this area[3] showed that the insertion of an additional carbonyl group into the sulfonamide chain, as in compounds **154** and **155**, led under standard radical conditions, to complex reaction mixtures.

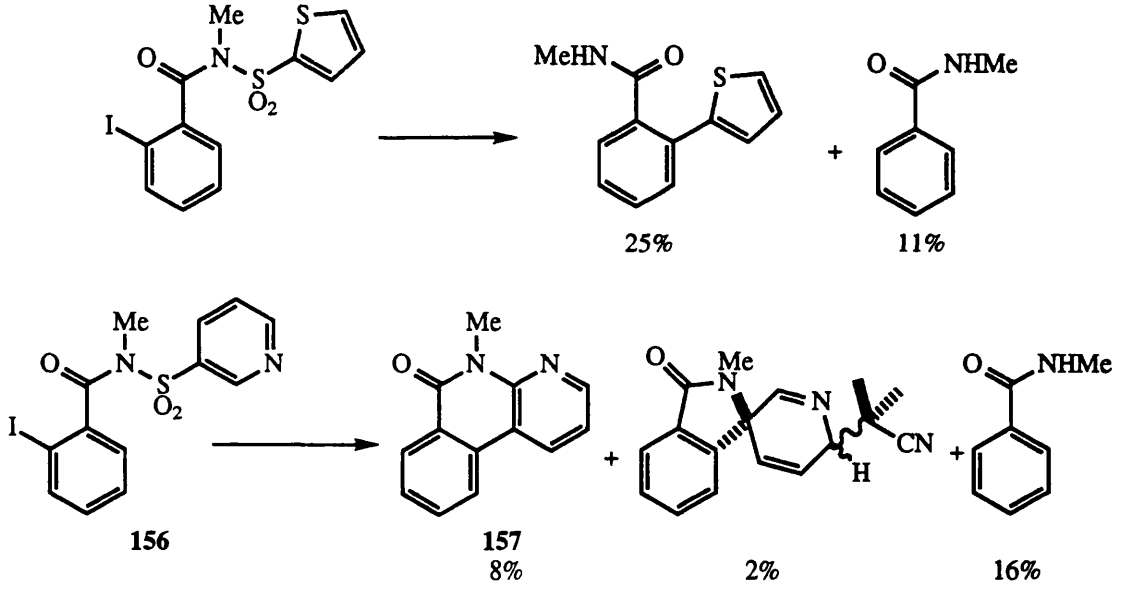


154



155

Nevertheless, contemporaneous work on the heterobiaryl series[6] showed that the same linking chain could lead to *ipso* substitution products albeit in relatively low yields. Interestingly, in the case of the pyridine derivative **156** a tandem 1,6-*ipso* substitution / cyclisation occurred, with formation of **157** (Scheme 2.35).

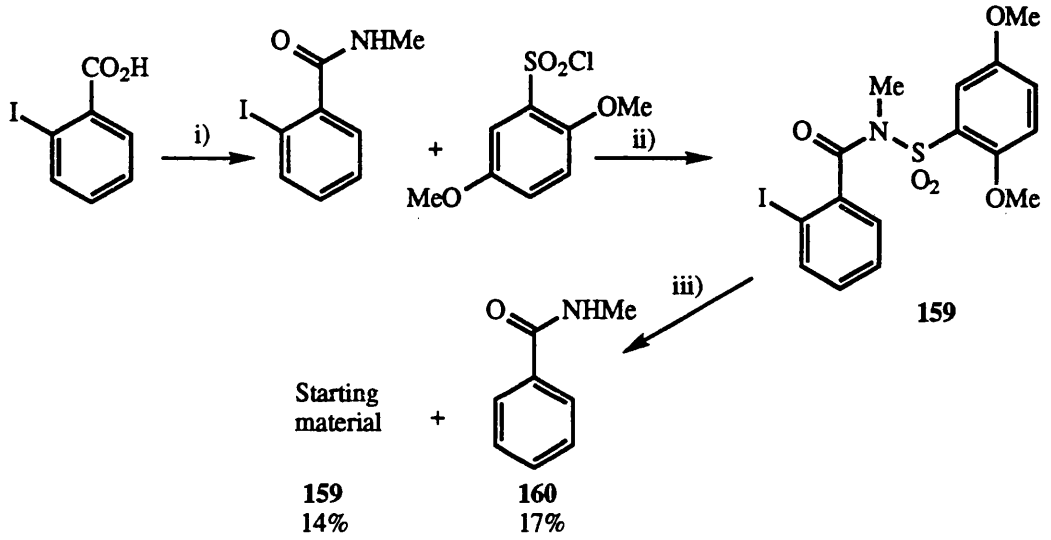


Reagents: Bu_3SnH / AIBN (slow addition), benzene, 80°C, 18 hr.

Scheme 2.35

In order to encourage *ipso* substitution in the biaryl series compound **159** was selected. In this substrate, the high electron density on the acceptor ring, and even more particularly, the presence of the *ortho* substituent, was predicted to favour the formation of the desired product. Preparation of this compound was achieved by an established method,[3] affording **159** in good yield. Although it is not clear whether sulfonylation occurs on the oxygen atom

or the nitrogen atom, and by spectroscopic mean it is not easy to clarify this doubt, we accepted that the conditions used would favour reaction through the nitrogen atom, and structure **159** was tentatively adopted (Scheme 2.36).

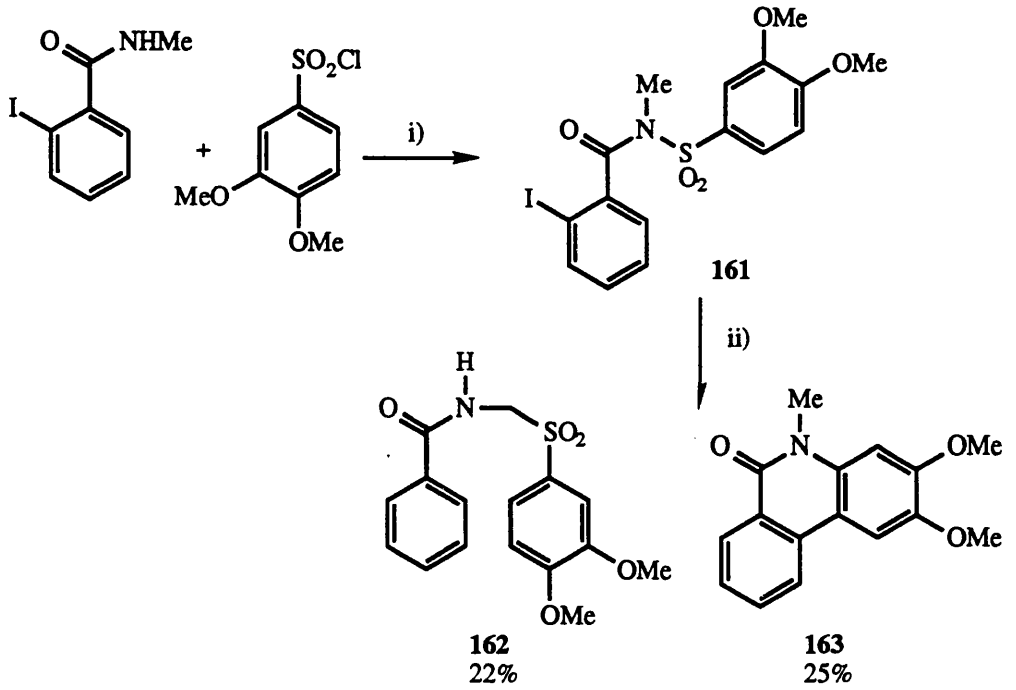


Reagents: i) $MeNH_2$, NaOH (aq) (82%); ii) NaH, THF, r.t., 25 hr (96%); iii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.36

However, treatment of compound **159** under the usual tin hydride conditions did not give any product from *ipso* substitution or addition, and the only identifiable compounds in the reaction mixture were benzamide **160** and starting material (Scheme 2.36). The formation of the benzamide **160** had also been noted in the heterobiaryl series.[6] An intermolecular *ipso* attack of the tri-n-butylstannyl radical at the sulfonyl substituted carbon atom has previously been reported to occur.[14] However, it seems strange that this intramolecular displacement is observed on this particular substrate, since compound **159** has one of the most electron rich aromatic rings used, and the stannyl radical has a nucleophilic character.

Compound **161**, prepared in a similar way, but differing in the methoxy substitution pattern, was also studied, and when exposed to standard radical conditions, afforded compounds **162** and **163** (Scheme 2.37).



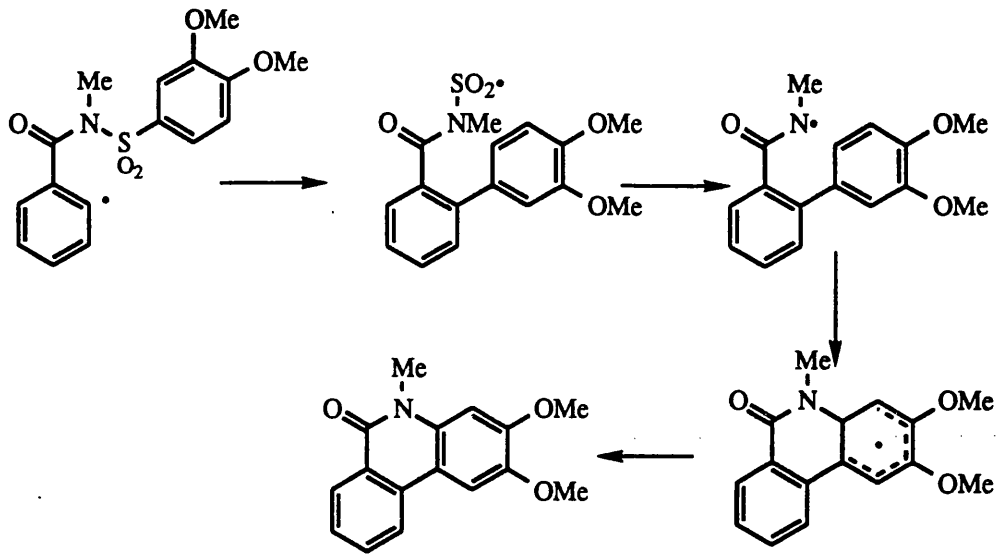
162 22%

163 25%

Reagents: i) NaH, THF, r.t., 25 hr (95%); ii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.37

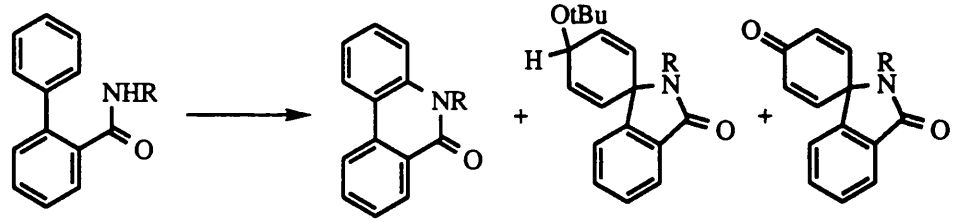
The mechanism for the formation of **163** involves a 1,6-*ipso* attack with extrusion of sulfur dioxide affording the amidyl radical, which then adds *via* a 1,6-addition process to the aromatic ring (Scheme 2.38). This second cyclisation is probably favoured, since amidyl radicals are electrophilic species, and the aromatic ring has an electron donating group on the position *para* to the site of attack.



163

Scheme 2.38

The formation of an amidyl radical *via ipso* substitution had already been seen, either in our own work in the heteroaromatic series[6] (Scheme 2.35) and also in the intramolecular attack of an aryl radical on to an aromatic residue with cleavage of a carbon-nitrogen bond[15] (cf. Section 1.2.1.2). Amidyl radical additions to aromatic rings has been the subject of a study,[16] but the formation of mixtures of phenanthridones and spiro compounds has always been observed (Scheme 2.39).

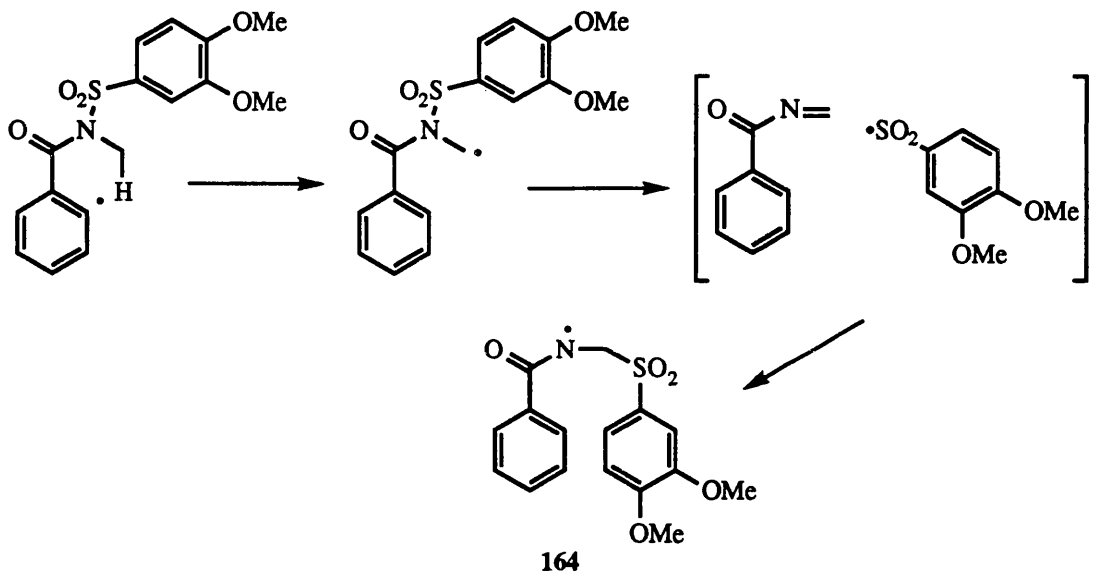


R= Me	33%	16%	28%
H	26	25	33
Ph	13	14	33

Reagents: ^{t}BuOCl, I_2, tBuOH, tBuOK, hν (1000W tungsten lamp), r.t., 5 hr.[17]

Scheme 2.39

The second product formed in the reaction, **162**, has an unusual feature, inasmuch as the sulfonyl group is separated from the nitrogen atom by a methylene group. A possible mechanism for the formation of this compound is represented in Scheme 2.40.

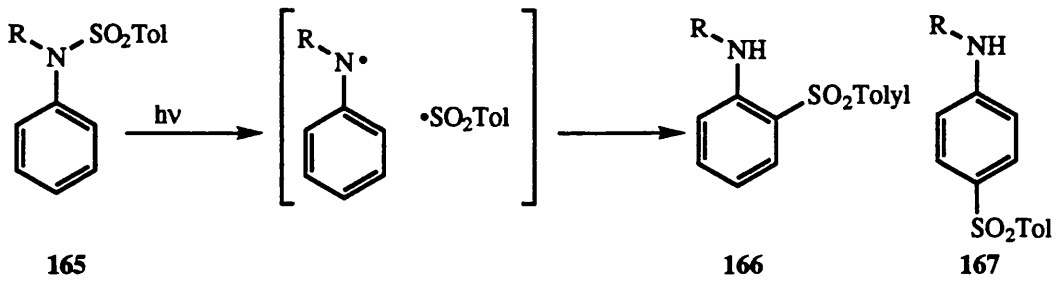


164

Scheme 2.40

The proposed mechanism involves a 1,5-hydrogen atom abstraction from the methyl group on the nitrogen atom, with formation of the primary radical, followed by elimination of the sulfonyl group which is a good radical leaving group.[18] Recombination of the two species in a cage can than occur to give **164**.

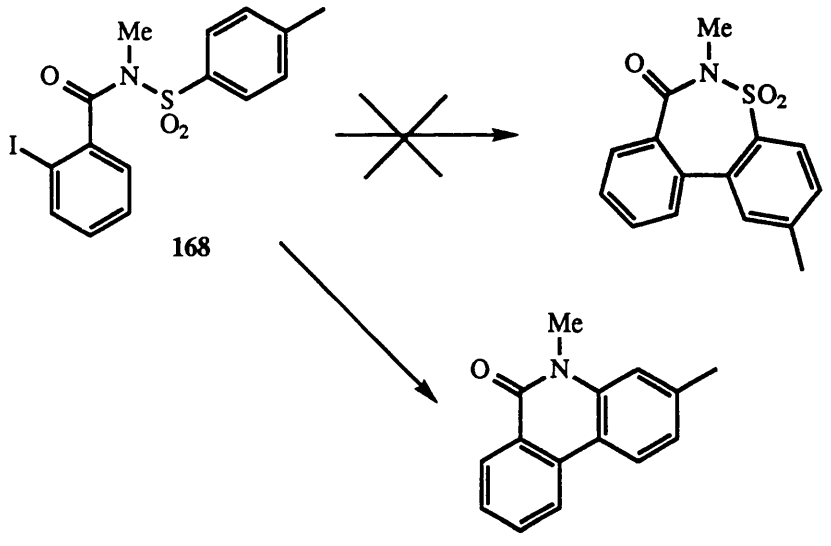
A recombination of two radical species is observed in the photo-Fries rearrangement of sulfonamides and sulfonates.[19] The accepted mechanism for this rearrangement is represented on Scheme 2.41, where irradiation of compound **165** affords a radical pair which, by recombination within a solvent cage, gives the migration products **166** and **167**.



165 166 167

Scheme 2.41

From the results presented above, and those in the heterobiaryl series[6] (Scheme 2.31), we were convinced that this type of linking chain favoured *ipso* substitution. This had also been observed in our first reaction of the *p*-toluenesulfonyl derivative **168** which had been reported[3] to give the 1,6-*ipso* substitution product (37%) and the 1,7-addition product (8%). However, when we reinvestigated this reaction, the latter compound was obtained as the sole product. This discrepancy led us to re-examine and carefully analyse the spectroscopic data and it is now clear that the original assignment as a 1,7-addition product was incorrect. The product which is in fact isolated in this reaction is compound **169** (Scheme 2.42) formed by the tandem 1,6-*ipso* substitution / 1,6-addition process, as described before (Scheme 2.38).



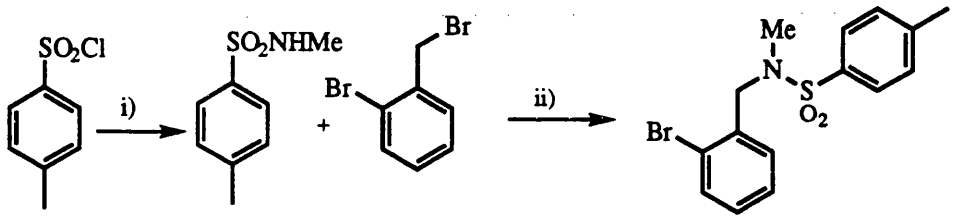
168

169
25%

Reagents: Bu3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.42

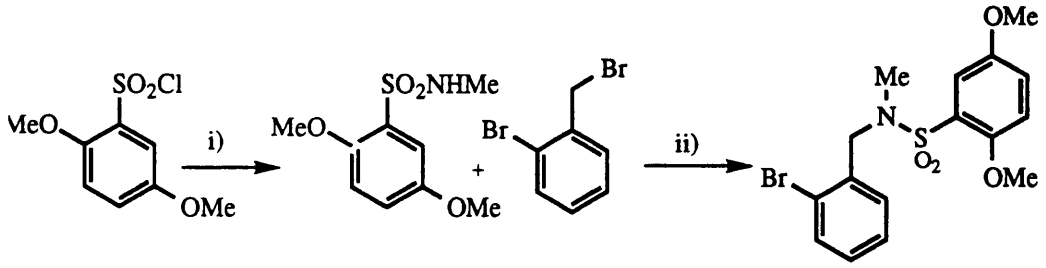
In continuation of our study of the nature of the linking chain, we then decided to add a methylene to the sulfonamide chain. Thus, compounds **170** and **172** were prepared from the corresponding sulfonyl chloride, *via* the methyl sulfonamide, followed by deprotonation with sodium hydride in THF and addition of *o*-bromobenzyl bromide (Scheme 2.43 and 2.44).



150 **170**

Reagents: i) $MeNH_2$, NaOH, 23 hr, r.t. (83%); ii) NaH, THF, 20 hr, r.t. (93%).

Scheme 2.43

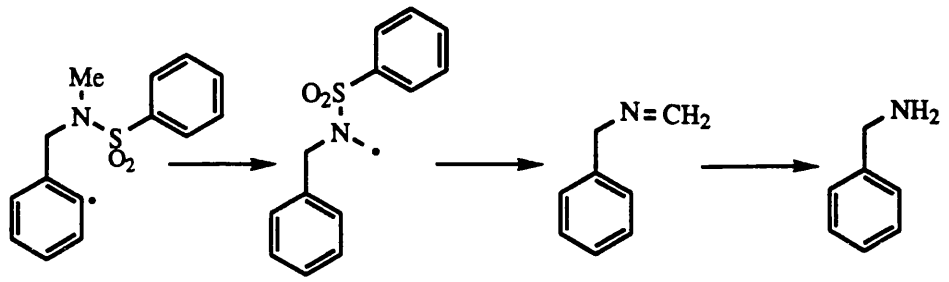


171 **172**

Reagents: i) $MeNH_2$, NaOH, 23 hr, r.t. (82%); ii) NaH, THF, 20 hr, r.t. (91%).

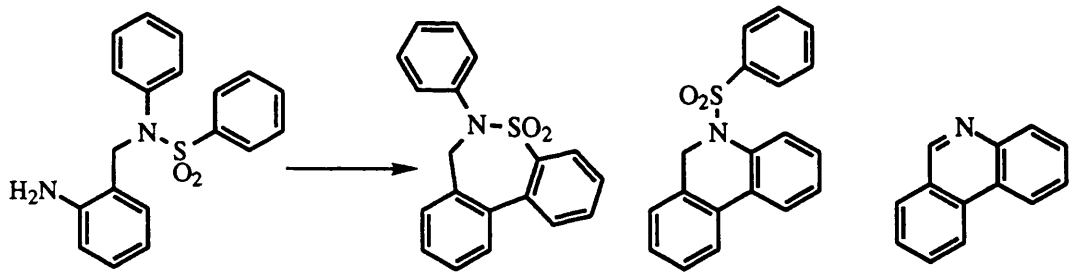
Scheme 2.44

However, both compound **170** and **172**, under standard radical conditions, afforded extremely complex mixtures. This suggests that the substrate underwent decomposition, perhaps by a process again involving a 1,5 hydrogen atom abstraction from the methyl group on the nitrogen atom, and subsequent elimination of the sulfonyl group (Scheme 2.45).



Scheme 2.45

Substitution of the methyl group on the nitrogen by an alternative functionality could provide a solution to this problem, since the Pschorr cyclisation of compound **173**, bearing a phenyl group on the nitrogen atom, has been reported to give the product from direct 1,7-addition **174**[20] (Scheme 2.46).

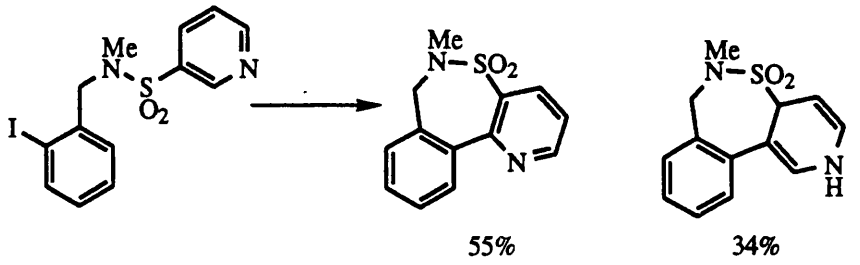


173 **174** 33% 18% 13%

Reagents: $NaNO_2$ (1.3 eq.), H_2SO_4/AcOH, Cu.

Scheme 2.46

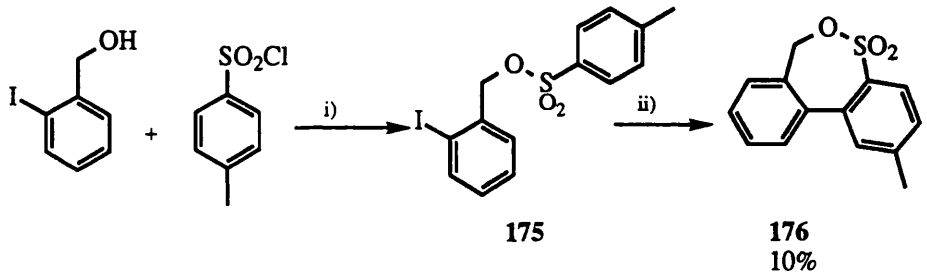
This result is in a way unexpected, since in the heterobiaryl series this type of chain reaction had given addition products in good yields (Scheme 2.47).



55% 34%

Scheme 2.47

More interesting results were obtained when the benzylic sulfonate was used instead of the sulfonamide. Thus, compound **175** was prepared as shown (Scheme 2.48).

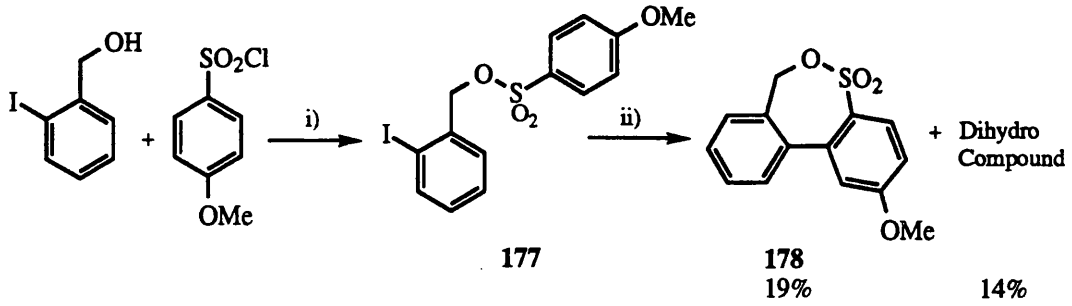


175 **176**
10%

Reagents: i) NaH, THF, r.t. , 24 hr (87%); ii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.48

When sulfonate **175** was submitted to the standard tin hydride conditions, the only isolable product was that derived from 1,7 addition, **176**. Although this reaction proceeded with a very poor mass balance, it was performed with other substituents on the acceptor aromatic ring. Thus, compound **177** was prepared (Scheme 2.49).

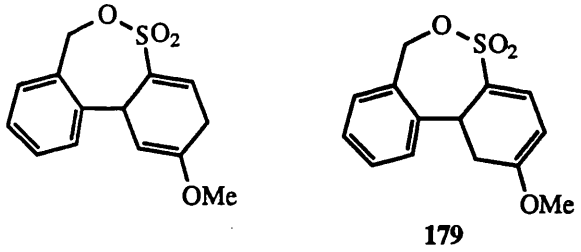


177 178 19% 14%

Reagents: i) NaH, THF, r.t., 24 hr (76%); ii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.49

Reaction under standard tin hydride conditions afforded, as in the previous case, the addition product **178**, and once again a dihydro product was isolated. Although its structure could not be fully determined, the presence in the ^{13}C nmr spectra of a secondary carbon at δ=72.3 ppm allowed us to propose the two possible structures shown in Scheme 2.50.



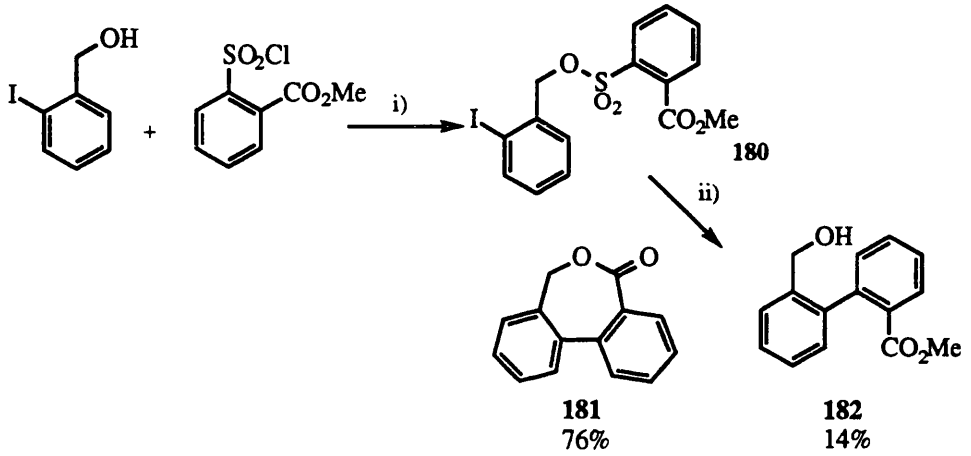
179

Scheme 2.50

The differentiation of these two compounds by simple ^1H nmr is not a trivial exercise. Nevertheless we consider that compound **179** is the more probable structure, since one of the protons of the methylene group in the ring (δ 3.23 ppm) is coupled with the proton at δ 4.15 ppm, which can be attributed to the benzylic proton.

The results presented above suggest that aryl sulfonation of benzylic alcohols leads to a chain which favours 1,7-addition over 1,6-*ipso* substitution, and this is in agreement with prior studies in this group on the heterobiaryl series.[6] However, when other factors intervene in the reaction, such as the presence of *ortho* substituents, this selectivity can be completely changed, as was shown by the following reactions.

The preparation of compound **180** caused some problems, probably as a result of the capacity of the sulfonate to act as a leaving group under the reaction conditions. Although we had to repeat the reaction, it was possible to get enough material to proceed with the radical reaction. Gratifyingly, submitting sulfonate **180** to the standard radical conditions afforded two products, both formed *via* 1,6-*ipso* substitution, in excellent overall yield, with the major product (**181**) being formed by subsequent lactonization (Scheme 2.51).



181 76%

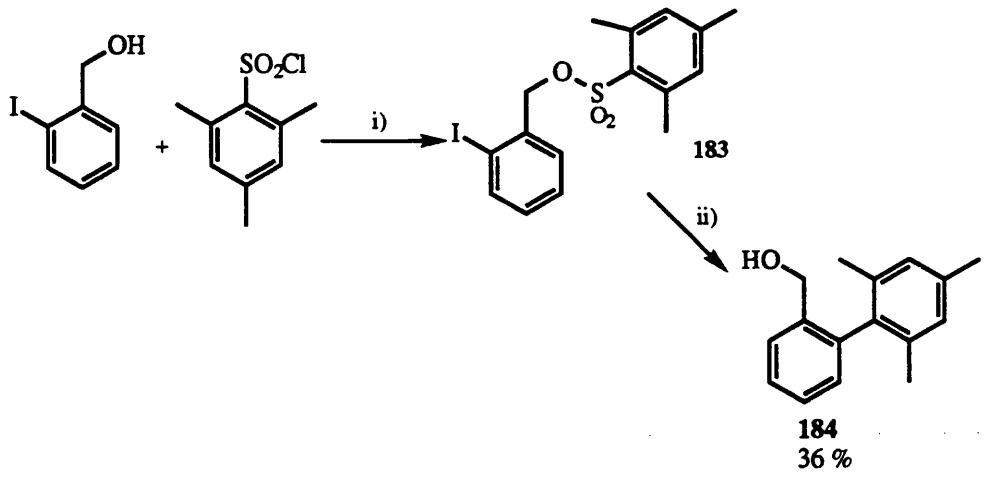
182 14%

Reagents: i) NaH, THF, 24 hr, r.t. (21%); ii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.51

The lactonization of related compounds with an *ortho* carbomethoxy substituent had been seen before,[3] and it was suggested that this process could occur during the basic fluoride anion work up. However, examination of the ^1H nmr spectrum of the crude reaction mixture, even before work up, showed that compound **182** was already present. The lactonization step must therefore occur under the reaction conditions, and transesterification processes may possibly involve organotin reagents.

The related mesitylene derivative, prepared the usual way, and with both *ortho* positions blocked, also gave the *ipso* substitution product obtained in moderate yield (Scheme 2.52).

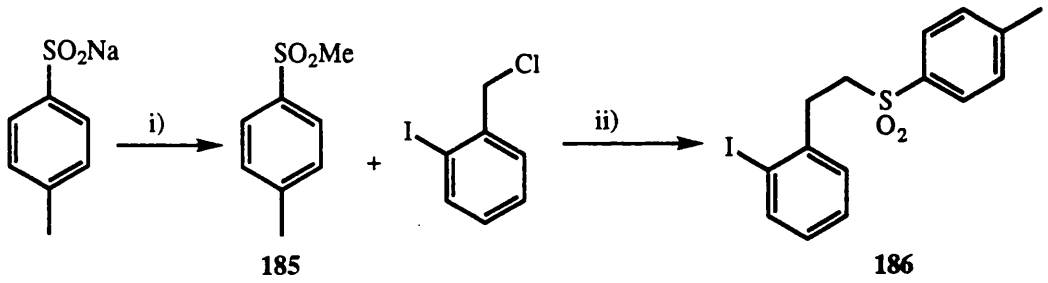


Reagents: i) NaH, THF, 24 hr, r.t. (76%); ii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.52

Thus, the course of the reaction could be completely reversed from 1,7-addition to 1,6-*ipso* substitution, when *ortho* substituents were present in the acceptor aromatic ring, and these examples were also therefore contributing valuable knowledge to the overall picture summerised earlier in section 2.2.

The effect of two methylene groups on the linking chain was then examined using compound **186**, which was prepared in several steps, as shown in Scheme 2.53.

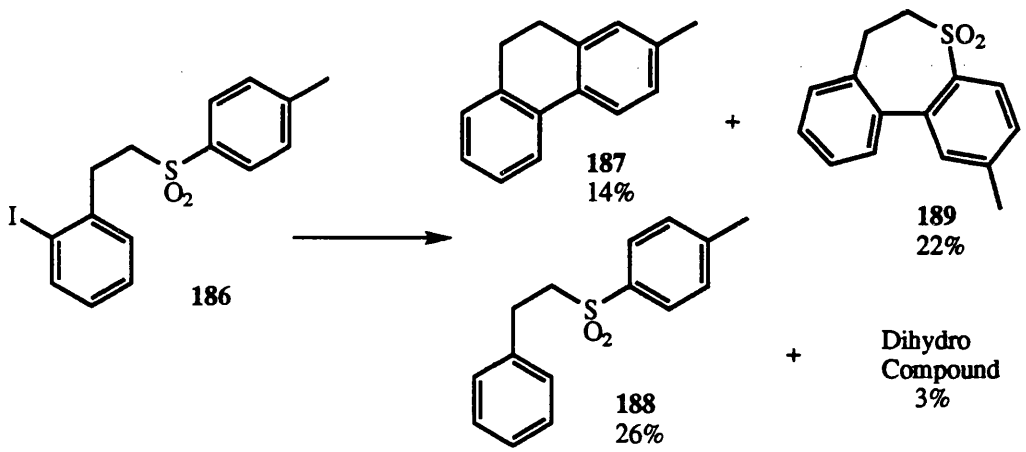


Reagents: i) $NaHCO_3$, Me_2SO_4, H_2O (81%); ii) nBuLi, THF, -70°C (46%).

Scheme 2.53

Thus, methylation of sodium *p*-toluenesulfinate with dimethyl sulfate, followed by deprotonation with butyl lithium and reaction with *o*-iodobenzyl chloride afforded sulfone **186**.

In this case, reaction of **186** under the usual tin hydride conditions afforded a mixture of products from 1,6-*ipso* substitution (**187**), 1,7-addition (**189**) and direct reduction (**188**), as shown in Scheme 2.54.

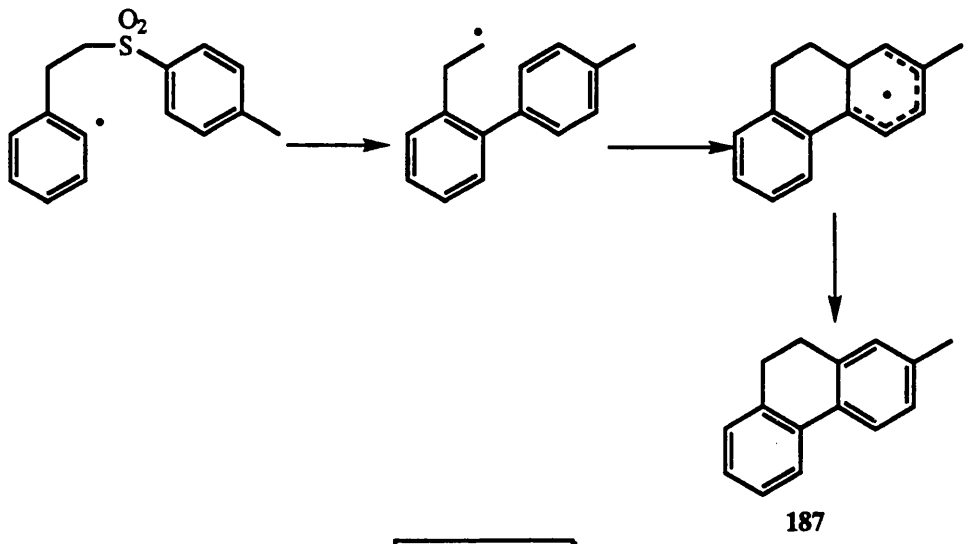


Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.54

This is the first example of an attempted 1,6-*ipso* substitution reaction in which the direct reduction product (**188**) can be isolated, indicating that for this type of chain the cyclization step of the aryl radical competes with hydrogen atom abstraction.

As in the heterobiaryl series,[6] although with less selectivity, this type of chain has favoured the 1,7-addition process. The formation of **187** involves an *ipso* attack followed by 1,6-addition of the alkyl radical to the aromatic ring (Scheme 2.55).

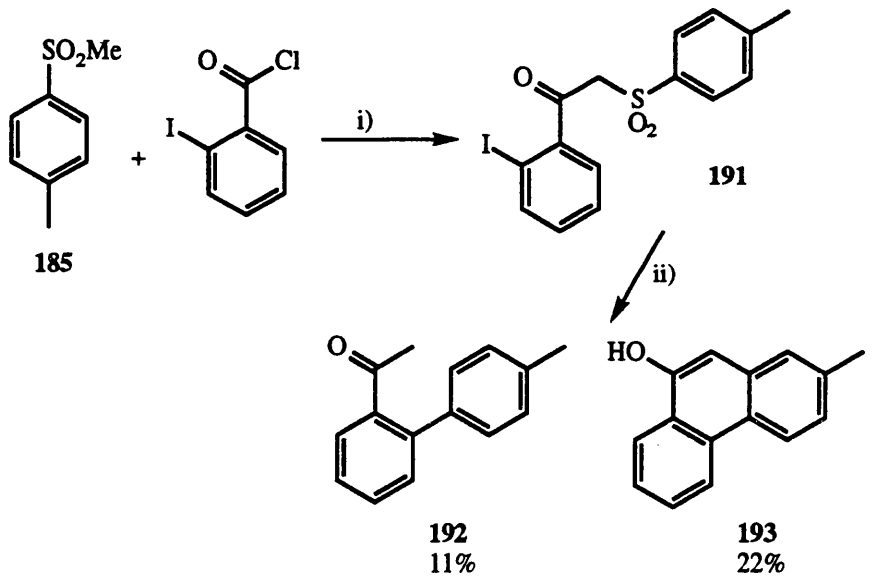


187

Scheme 2.55

Although there is not much work in the literature concerning the addition of alkyl radicals to aromatic rings, particularly when another aromatic ring is incorporated on the linking chain, this result is nevertheless consistent with the observations of Julia[21] who studied the reactivity of naphthylbutyl radicals, and observed both addition and *ipso* substitution (Chapter 1, Scheme 1.50).

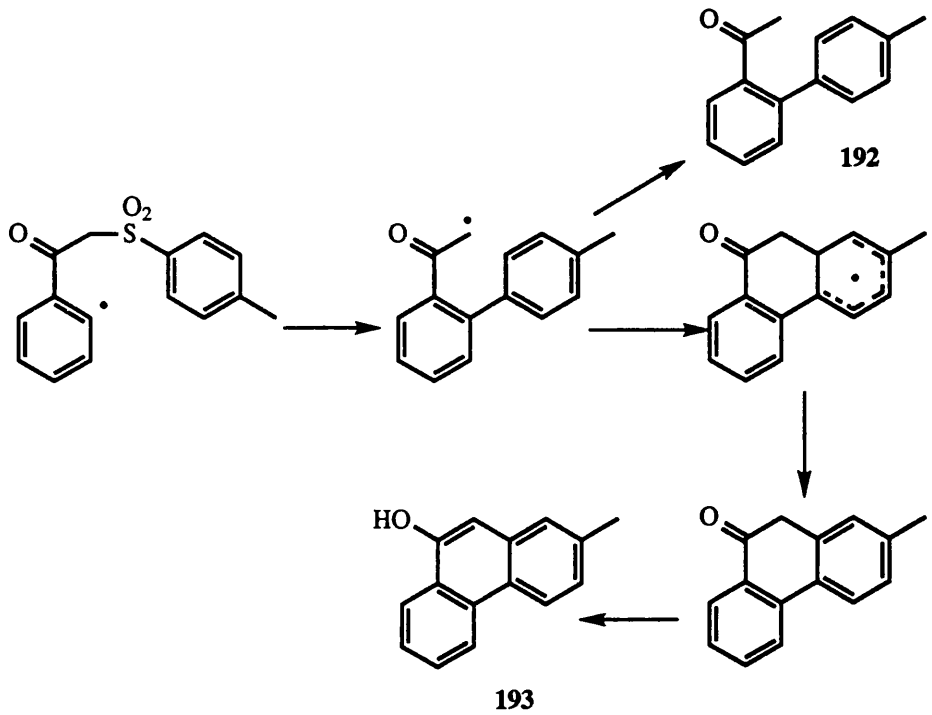
Finally, we decided to investigate the effect of having both a carbonyl group and a methylene spacer in the linking chain. Accordingly, the β-ketosulfone **191** was prepared, and we found that both compounds isolated (**192** and **193**) were formed *via ipso* substitution (Scheme 2.56).



Reagents: i) ^{n}BuLi, THF, -78°C (73%); ii) Bu_3SnH / AIBN (slow addition), benzene, reflux.

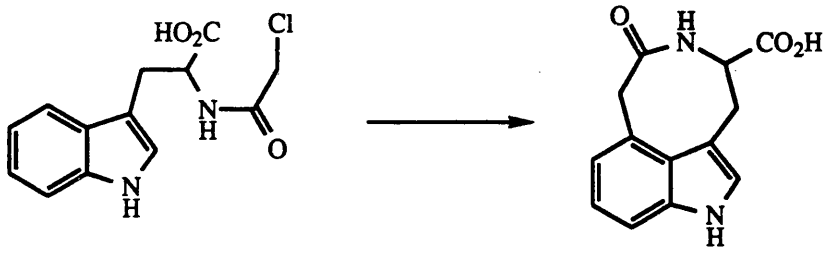
Scheme 2.56

The intermediate α-carbonyl radical, formed as a result of *ipso* substitution followed by the loss of sulfur dioxide, undergoes either hydrogen abstraction to give **192**, or further cyclization leading to the phenanthrene derivative **193** (Scheme 2.57).



Scheme 2.57

Again, there is not much work concerning the intramolecular addition of α-carbonyl radicals to aromatic nuclei particularly when they are connected by an all carbon linking chain. However, macrocyclization of compound **194** has been observed[22] under photolytic conditions (Scheme 2.58).



194 40%

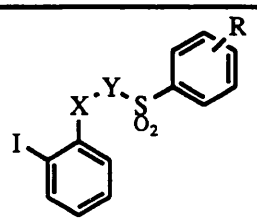
Reagents: hν (Hg)/H_2O (pH=7).

Scheme 2.58

By way of summary, in this section we can see that once again, although the nature of the linking chain by itself can control the products formed, the effect of the substituents can never be forgotten, especially when they are on the *ortho* position.

Moreover, as shown in Table 2.5, the following general trends can be discerned, for the different chains which were studied:

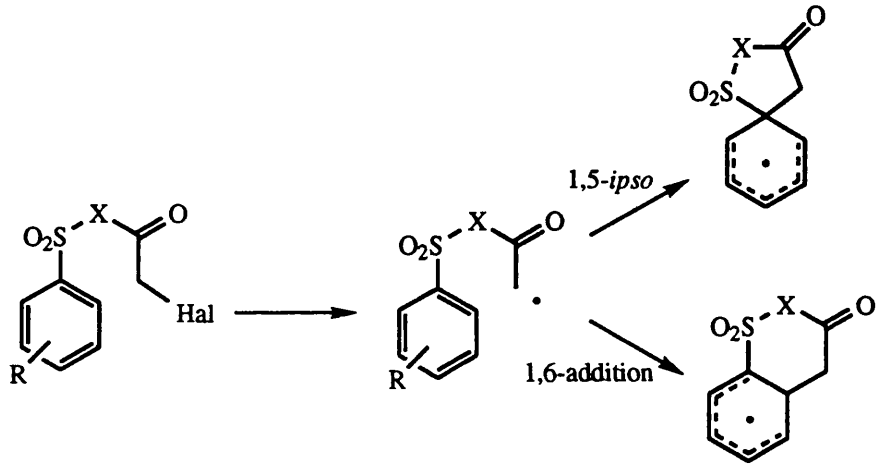
Table 2.5

 X-Y in	**Observation**
CH_2NMe	Decomposition. Probably a 1,5 hydrogen abstraction is a competitive process
CH_2O	When there is a *para*-substituent it is formed exclusively 1,7-addition; Although, when the substituent is in the *ortho* position exclusive 1,6-*ipso* substitution takes place.
CH_2CH_2	A mixture of reduced, 1,6-*ipso* substitution and 1,7-addition products is observed, although 1,7-addition is preferred to 1,6-*ipso* substitution.
$COCH_2$	Exclusive 1,6-*ipso* substitution.
CON	Exclusive 1,6-*ipso* substitution.

2.6. α-Carbonyl Radicals in *ipso* Substitution Reactions

2.6.1. Reaction Under Atom Transfer Conditions

Proceeding with our studies on *ipso* substitution we turned our attention to a different radical species, the α-carbonyl radical, which could be formed from compounds like **194**, by halogen abstraction (Scheme 2.59). The radicals formed in this way, can undergo *ipso* substitution or addition, and it was our aim to examine these possibilities.

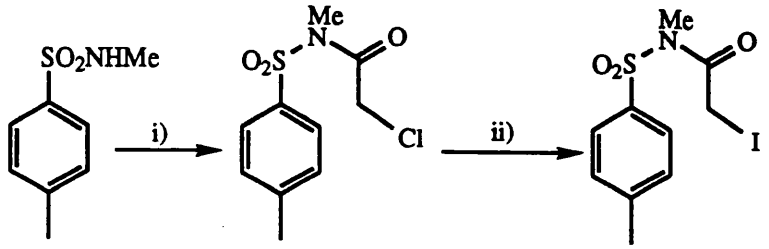


194

Scheme 2.59

α-Carbonyl radicals are very stable species, which in general prefer to abstract a hydrogen atom, rather than undergo a cyclisation step. We thought that this problem could be overcome by using our standard radical conditions, where the concentration of tin hydride is minimised by slow addition and large amounts of AIBN are present.

Thus, compound **196** was selected for this preliminary study, and it was prepared from the corresponding methyl sulfonamide **150** by deprotonation with NaH in THF, followed by addition of chloroacetyl chloride and finally halogen exchange with NaI in acetone (Scheme 2.60).

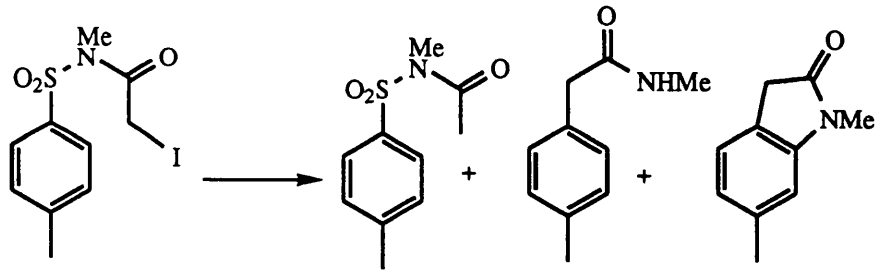


150 195 196

Reagents: i) NaH, THF, $ClCH_2COCl$, r.t., 2 days (79%); ii) NaI, acetone, reflux (58%).

Scheme 2.60

When compound **196** was submitted to the standard tin hydride conditions the formation of reduced product **197** (29%), *ipso* substitution product **199** (17%) and indol-2-one **198** (14%) was observed (Scheme 2.61). However, the addition product was not formed, which was indicative of the fact that the amidyl chain was a good promoter for *ipso* substitution.

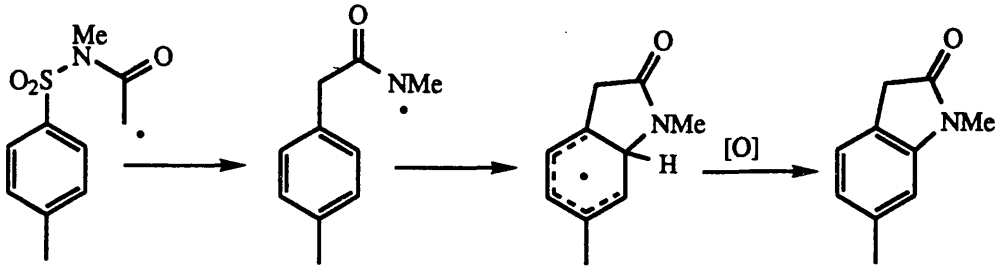


196 **197** 29% **199** 17% **198** 14%

Reagents: Bu_3SnH / AIBN (slow addition), benzene, reflux.

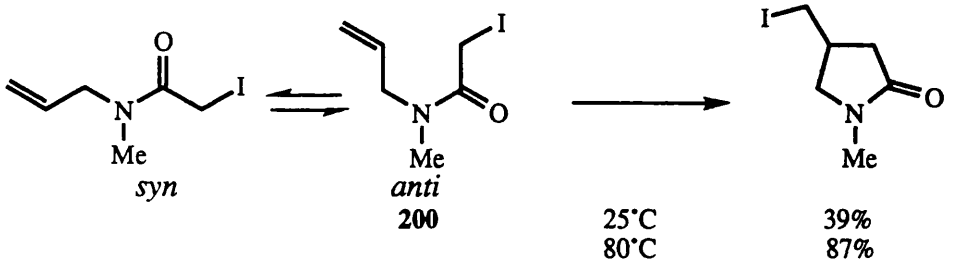
Scheme 2.61

The large amount of reduced product **197** shows that, although the amount of tin hydride in solution was minimised by slow addition, it is still enough to interfere with the reaction. The formation of indol-2-one **198** seems particularly interesting, since it occurs *via* a sequential 1,5-*ipso* substitution with loss of sulfur dioxide, followed by a 1,5-addition of the resultant amidyl radical on to the aromatic ring (Scheme 2.62). In this way, from a very simple precursor, annulation of the aromatic ring involving both a carbon-carbon and carbon-nitrogen bond formation can be achieved.



Scheme 2.62

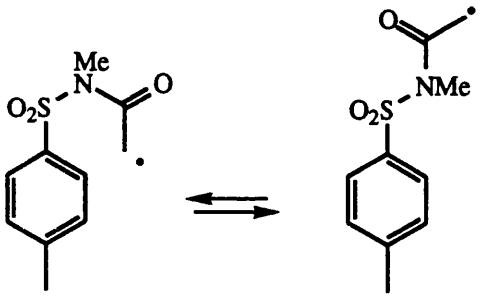
Curran,[9] in his study on the effect of temperature on cyclization reactions, has observed that for simple amides the population of the *syn* and *anti* conformations at room temperature for amide **200** was 52:48. Based on this observation he explained why the yield of the radical cyclization of compound **200** increases from 39% at 25°C, to 87% at 80°C. Thus, by increasing the temperature the equilibrium between the two rotamers is faster, leading to an increase in the rate of conversion (Scheme 2.63).



Reagents: 10% $Bu_3SnSnBu_3$, benzene, hν.

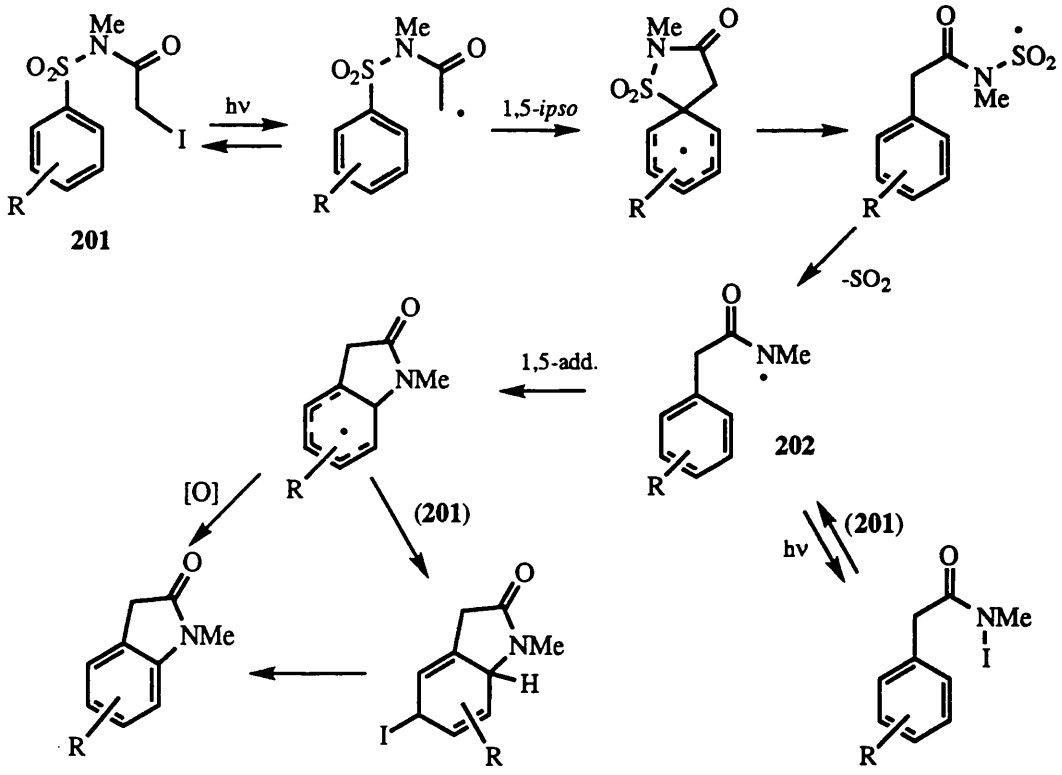
Scheme 2.63

The same principle can be applied to the reaction of **196**, where both the carbonyl and the sulfonyl groups around the nitrogen atom can interfere with the conformation adopted (Scheme 2.64). Hence, an increase in temperature would increase the ratio of conversion, and consequently, *ipso* substitution. Gratifyingly, when the reaction was performed in toluene at reflux (110°C), the ratio between *ipso* substitution / reduced product was increased from 31:29 to 64:7. Unexpectedly, however, the formation of compound **198** was not observed under this set of conditions.



Scheme 2.64

Alternative methods for effecting radical annulations, which involve atom transfer propagation steps and avoid the formation of reduced product, have been developed by Curran.[23] The use of photolytic conditions could be ideal, to avoid the formation of reduced product as well as inducing the second cyclization step to form indolones, since in general these are the conditions used for the cyclization of amidyl radicals. Under these conditions, once the α-carbonyl radical is formed it can only undergo *ipso* substitution with extrusion of sulfur dioxide and formation of the amidyl radical, or revert to starting material (**201**) (Scheme 2.65).

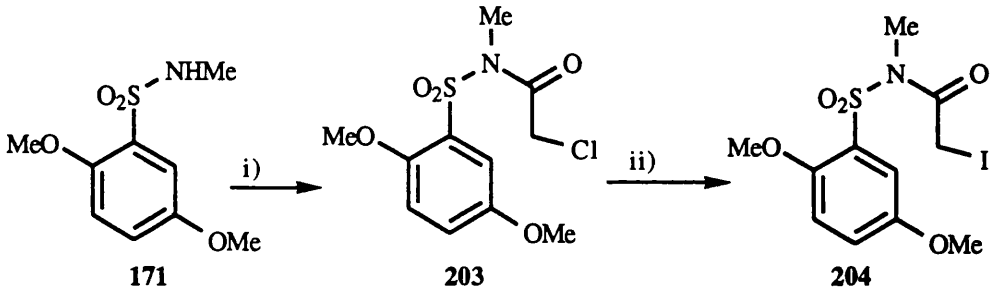


Scheme 2.65

The amidyl radical **202** formed in this way was expected to cyclize *via* a 1,5-addition process, or capture an iodine atom from another molecule of starting material to form the N-iodo-amide which, under the reaction conditions, would revert to the amidyl radical **202**.

When **196** was irradiated with UV light, in the presence of *bis*(tri-n-butyltin) and ethyl iodide[24] in benzene, the *ipso* substitution product **199** was the only compound detected in the ^1H nmr spectrum of the mixture. Under these conditions, the hydrogen abstraction by the amidyl radical appears to be faster than 1,5-addition to the aromatic ring. Ethyl iodide is used in these reactions as a source of iodine atoms, either towards the amidyl radical **202**, or for the α-carbonyl radical, when the latter is not in the correct conformation for cyclisation.

As amidyl radicals are electrophilic species, the presence of electron donating groups on the aromatic acceptor ring could promote the second addition step. Thus, the dimethoxy substituted derivatives **204** and **209**, which had given good results on promoting 1,5-*ipso* substitution in the biaryl series (section 2.2.3), were prepared. Deprotonation of sulfonamide **171** with sodium hydride followed by addition of chloroacetyl chloride afforded **203**, which on further halogen exchange with sodium iodide in acetone, gave the desired product **204**(Scheme 2.66).

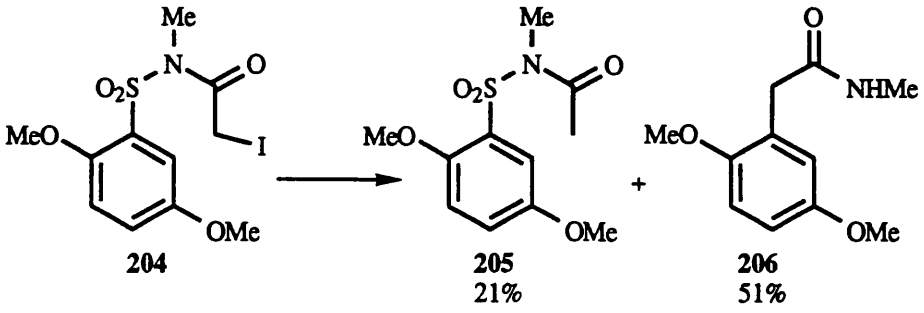


171 **203** **204**

Reagents: i) NaH, THF, $ClCH_2COCl$, 2 days (63%); ii) NaI, acetone, reflux (64%).

Scheme 2.66

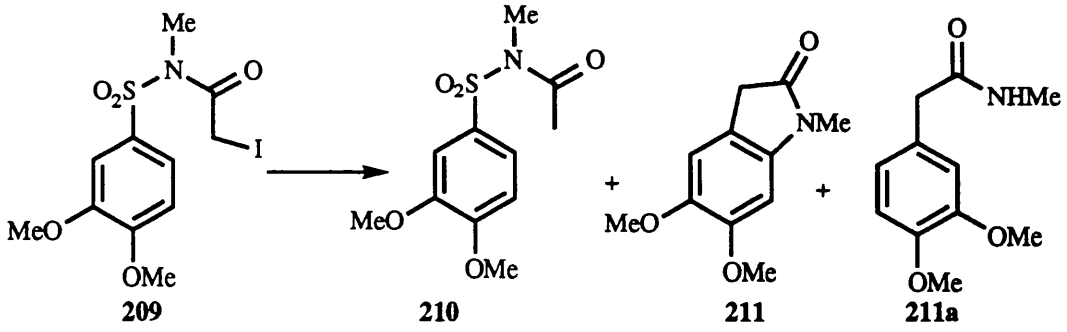
Reaction of **204** under standard tin hydride conditions (Scheme 2.67) afforded the *ipso* substitution product **206** in good yield (51%), together with some reduced product **205** (21%).



Reagents: Bu3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.67

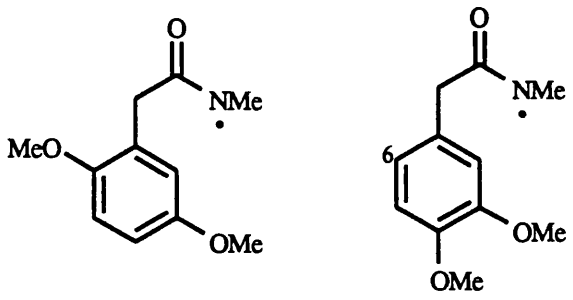
Acetamide **209** was also prepared, in a similar way to that described above for **204** (Scheme 2.66) and, when exposed to the usual radical conditions, the formation of three products in the same ratio, deriving from direct reduction, **210** (26%), and *ipso* substitution (**211** and **211a**), was observed (Scheme 2.68).



Reagents: Bu3SnH / AIBN (slow addition), benzene, reflux.

Scheme 2.68

Our attention turned again to the formation of the indolone derivative **211** (21%), which had not been formed in the reaction of **204** (Scheme 2.67). Both substrates undergo *ipso* substitution, but only intermediate **213** (Scheme 2.69) favours the second cyclization to form the indolone derivative.



212 213

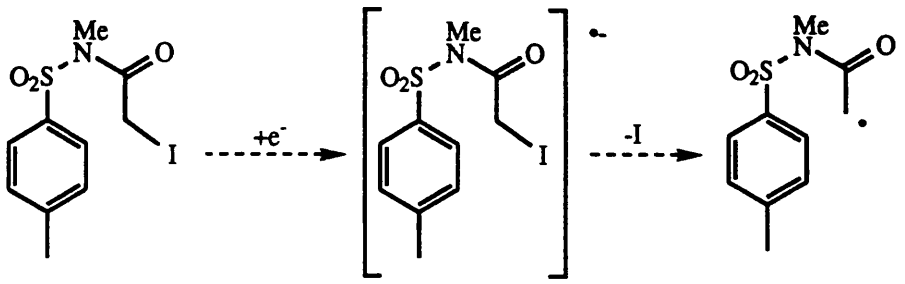
Scheme 2.69

Both intermediates **212** and **213** have a methoxy group on the *ortho* or *para* positions, which can stabilise the radical formed by 1,5 addition of the electrophilic amidyl radical to the aromatic ring. However, while intermediate **212** has only one position available for the attack of the amidyl radical, intermediate **213** has both positions available and position 6, in particular, is less hindered than the other . It may well be that, although both situations are electronically favourable, the resultant outcome in this case is dictated by steric effects.

Most of synthetic radical reactions are based on tin hydride chemistry. The limitations of this method are obvious in this section, where an irreversible hydrogen atom transfer occurs, giving the reduced product. In the next sections, alternative ways of generating an α-carbonyl radical with the potential to retain or incorporate further funcionality were investigated.

2.6.2. Reaction Using Copper (I)

Another approach to the *ipso* substitution reactions was the use of transition metals, which react *via* single electron transfer. Subsequent loss of iodide anion can then occur, to form the α-carbonyl radical (Scheme 2.70).

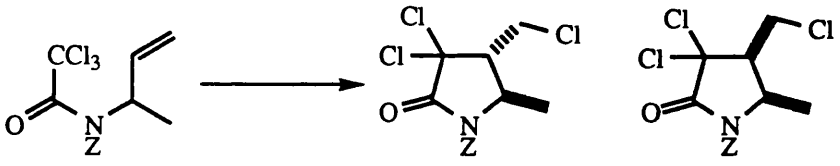


196

Scheme 2.70

Preliminary experiments on **196** in the presence of catalytic copper (I) iodide in acetonitrile at reflux, yielded only starting material. Clearly, copper (I) iodide on its own, is not sufficiently powerful to deliver an electron to the starting iodide **196**.

During the course of this work, the transition metal catalysed radical cyclization of N-substituted-N-allyltrichloroacetamides to give N-substituted trichlorinated γ-lactams at low temperatures in high yields was reported[25] (Scheme 2.71).

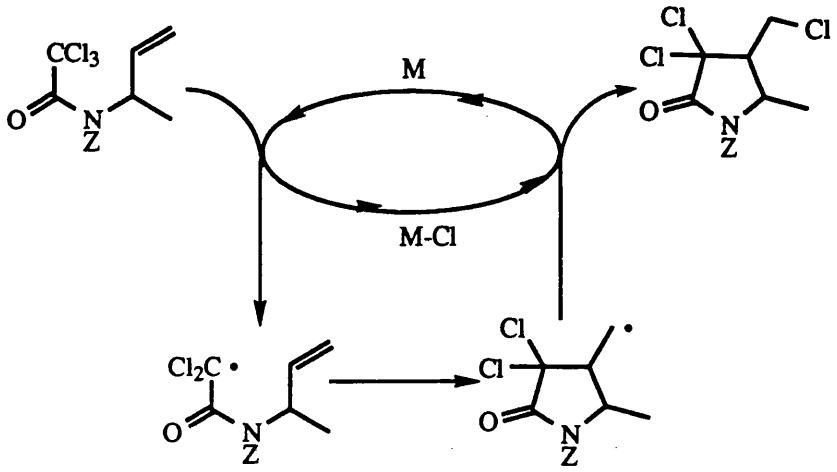


Z=Me	90	: 10	98%
Z=Ts	15	: 85	90

Reagents: CuCl, bipyridine, -15°C.

Scheme 2.71

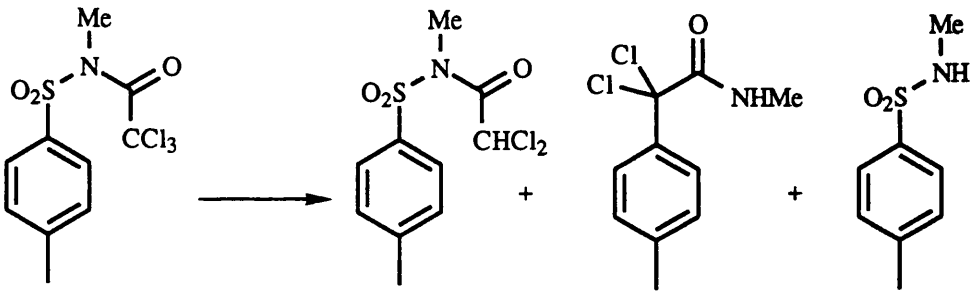
The mechanism (Scheme 2.72) involves the coordination of electron donating amine ligands (bipyridine or TMEDA) to form complexes such as CuCl(bipyridine) or $[Cu(bipyridine)_2]^+Cl^-$. This coordination facilitates abstraction of a chlorine atom from the N-allyltrichloroacetamide to form the N-allyldichloroacetamide radical.



Scheme 2.72

This low temperature copper mediated reaction seemed a good method for *ipso* substitution and we hoped that by using it, the formation of the reduced product could be minimised.

Compound **214**, prepared from the corresponding sulfonamide (**150**) and trichloroacetyl chloride, was submitted to the copper (I) conditions described above. When TMEDA was added to a solution of the substrate in dry DCM at r.t. in the presence of copper (I) chloride, there was a colour change to dark green, indicating the presence of copper (II) species in solution. Analysis of the reaction mixture showed that the major product formed was the sulfonamide **150** (39%), together with the *ipso* substitution product **216** (36%) and traces of **215** resulting from a reductive process (Scheme 2.73). Under these conditions however, further cyclisation to indolones was not observed.



214 | **215** traces | **216** 36% | **150** 39%

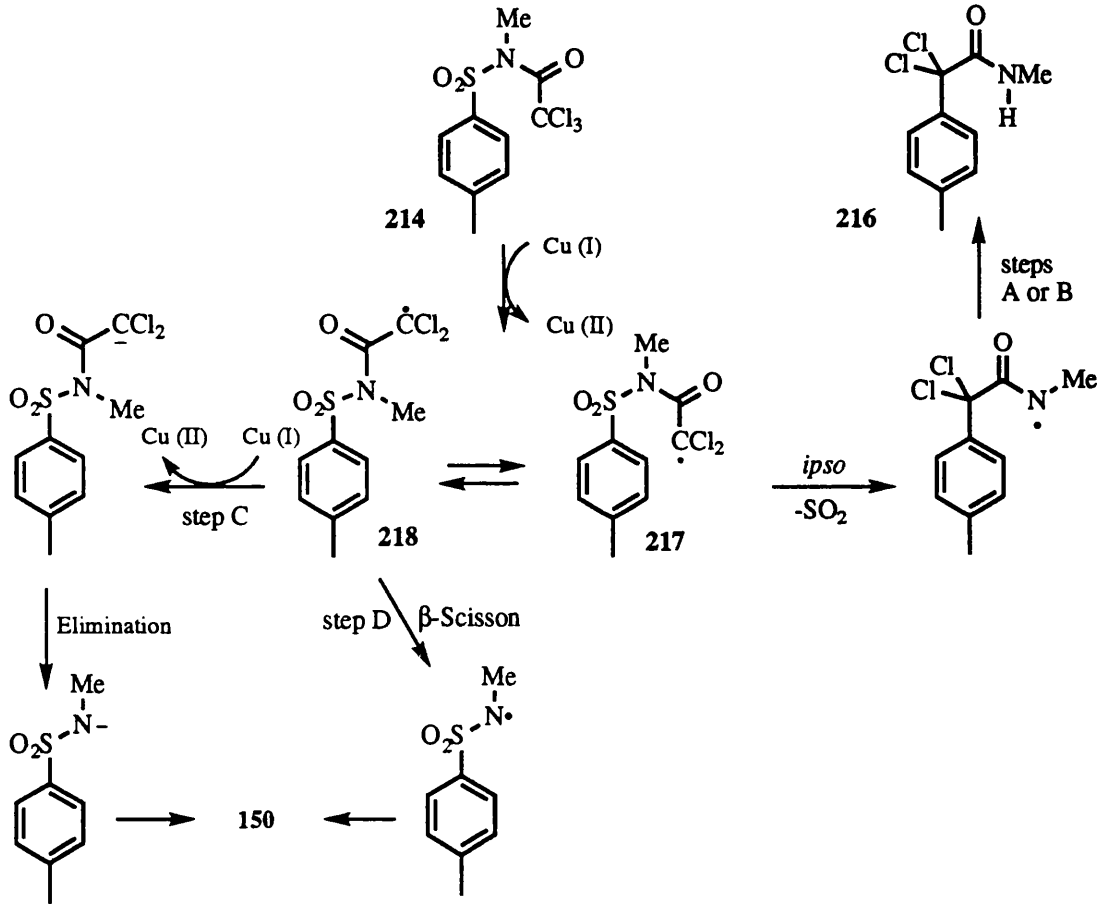
Reagents: Cu(I)Cl, DCM, TMEDA, r.t.

Scheme 2.73

It is interesting that *ipso* substitution can occur even at room temperature, although the major drawback of this method is the large amount of the sulfonamide **150** which was formed.

Although there are aspects of the mechanism of this reaction which are not clear, some different alternatives are presented in Scheme 2.74.

Abstraction of a chlorine atom or single electron transfer (SET) from **214** by the copper (I) complex occurs with the formation of the electrophilic dichloro radical. If the molecule adopts the conformation **217**, the reaction can then proceed *via ipso* substitution and extrusion of sulfur dioxide, with formation of the amidyl radical. At this stage the pathway for further reaction is not very clear however, and two alternative routes can be considered:



Scheme 2.74

A) a single electron transfer (SET) occurs with formation of the amidyl anion. Hence, consuming another molecule of Cu (I).

B) chlorine atom transfer occurs with formation of the N-chloro amide derivative. This would involve a reduction of Cu (II), and thus, the completion of the catalytic cycle. The main disadvantage of this step is that it involves the combination of two electrophilic radical species.

Due to the low temperature of the reaction there must be a significant population of molecules which are in the **218** conformation. These cannot cyclise and, again two alternative pathways can be postulated:

C) a second electron is transferred to the electrophilic dichloro radical, with formation of the dichloroanion, which eliminates dichloroketene with formation of the sulfonamide anion. Hence, copper (I) is oxidised to copper (II), which breaks the catalytic cycle. The alternative chlorine atom transfer to the dichloro radical would revert to starting material.

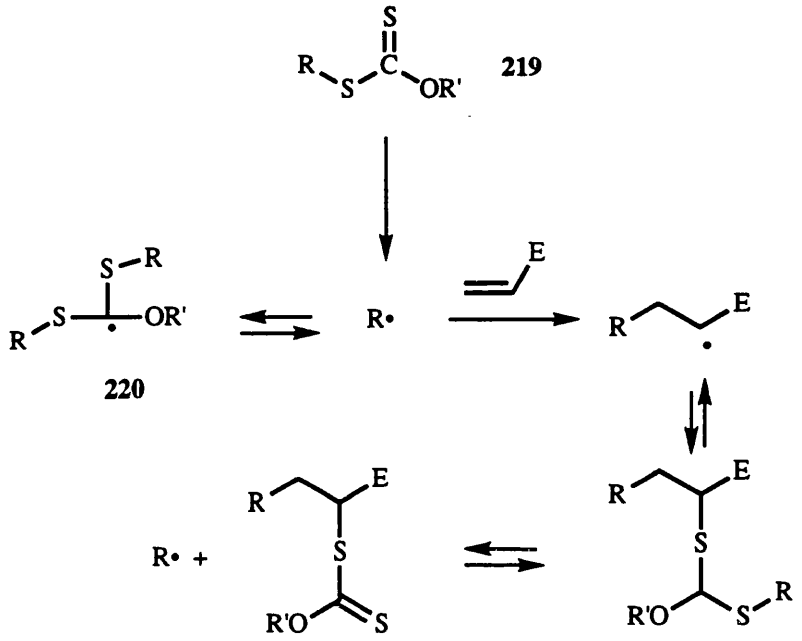
D) as the dichloro radical can not cyclise, β-scission occurs, with formation of the sulfonamidyl radical, which is than oxidised by the copper species. However, to the best of our knowledge β-scission with formation of a sulfonamidyl radical has not been observed, although the amidyl group can act as a leaving group in *ipso* substitution reactions.

The mechanism discussed presumes that the copper-TMEDA complex can react either by single electron transfer or by chlorine atom transfer. However, those steps involving SET would break the cycle in a very early stage, which clearly does not occur, since 75% of the starting material is transformed.

An important factor in this reaction is the effect of the temperature. Thus, changing the solvent and increasing the temperature of the reaction would probably increase the conversion to the products of *ipso* substitution.

2.6.3. Reaction Involving Xanthates

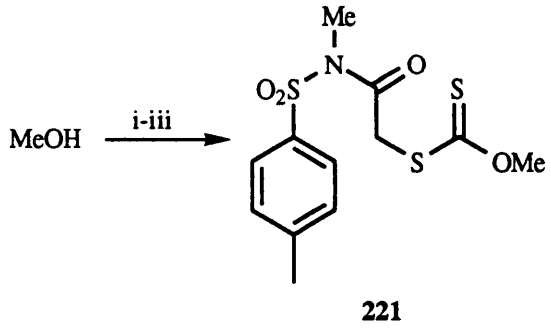
An alternative way of forming a radical is the use of xanthates. This approach involves the generation of a radical R• from a xanthate **219** by either photochemical or chemical means[26] (Scheme 2.75)



Scheme 2.75

In the presence of olefinic compounds, R• can either add to the alkene or to the thiocarbonyl group of the starting xanthate (**219**) to give **220**. If R' is primary or aromatic, radical **220** can only fragment to give back R• and **219**.

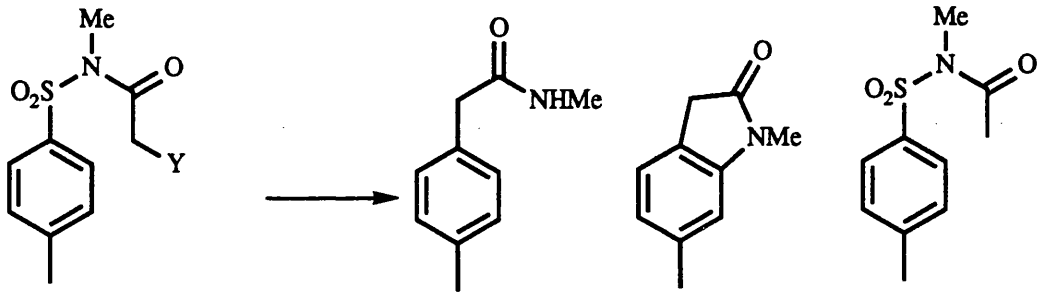
The extension of this approach to an *ipso* substitution process was envisaged and hence compound **221** was prepared from the iodide **196** by halogen substitution (Scheme 2.76).



Reagents: i) NaH, THF; ii) CS_2; iii) **196**

Scheme 2.76

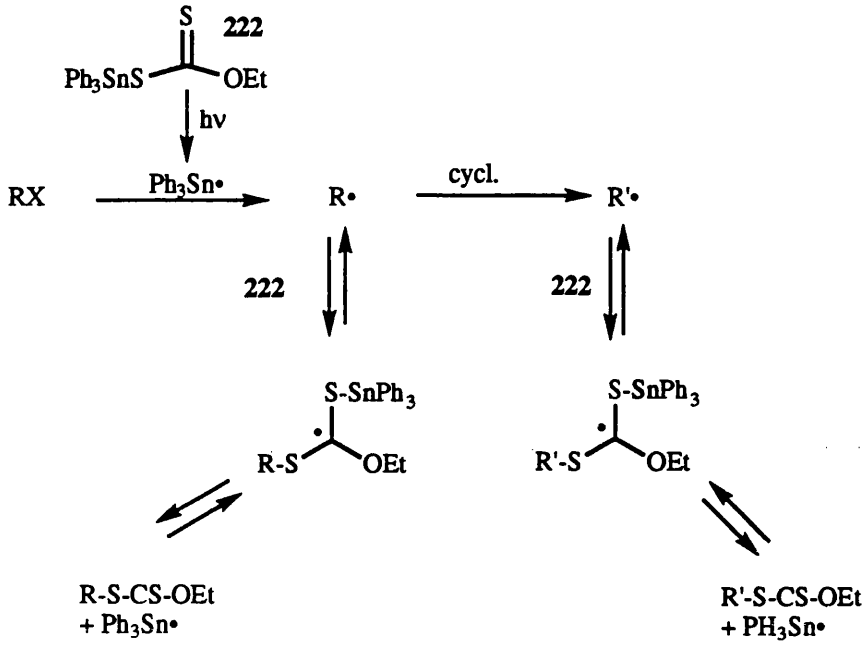
Irradiation of **221** using a medium pressure mercury vapour lamp (125W) in benzene or toluene afforded indolone **198** and the amide **199** as shown in Scheme 2.77. Comparing these results with those obtained in the reaction of **196** with tin hydride, it can be seen that although the reduced product is not formed when photolytic conditions are used, the ratio between **198** and **199** is similar under both conditions.



	199	**198**	**197**
221, Benzene, hv	1.1	1	-
221, Toluene, hv	2.7 (27%)	1 (10%)	-
196, Bu_3SnH, Benzene	1.2 (17%)	1 (14%)	2 (29%)
196, Bu_3SnH, Toluene	(64%)	--	(11%)

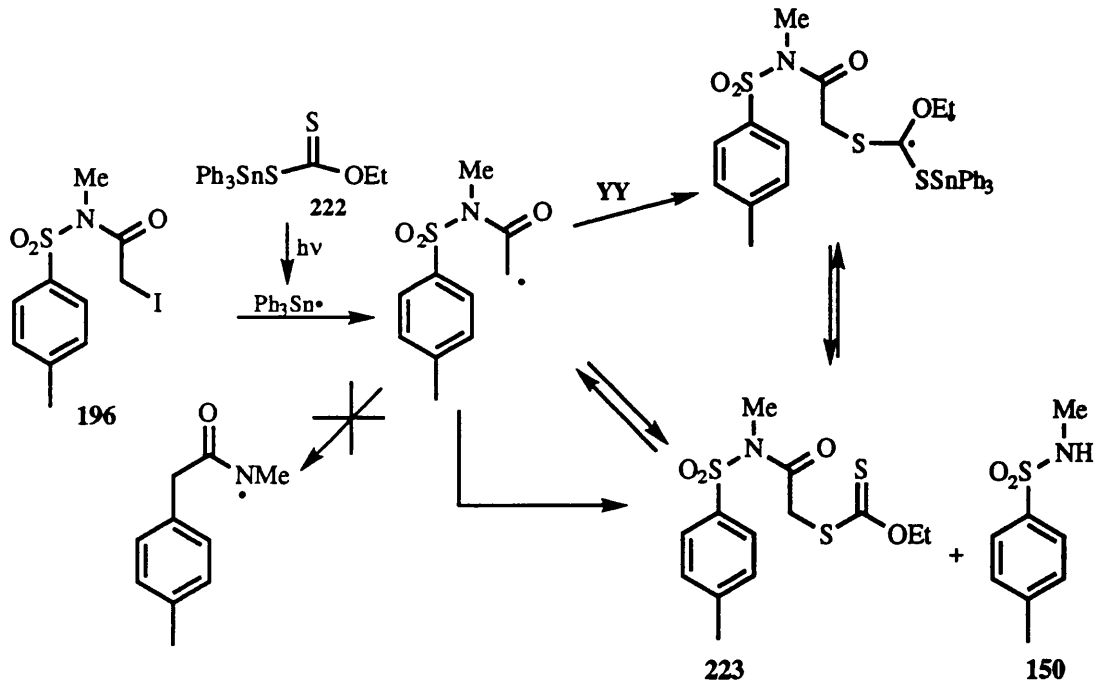
Scheme 2.77

Recently, a different approach using tin xanthates as a source of stannyl radicals was reported.[27] Once again, this methodology avoids the use of tin hydride and consequently the reduced product is not formed, even though, stannyl radicals are involved as the radical source. Thus, by irradiation with visible light, the reaction between the substrate (RX) and *O*-ethyl triphenyltin xanthate (**222**), proceeds through a chain as shown on Scheme 2.78. All the steps involving the xanthate group are reversible, hence there should not be any competitive process to the cyclization step.



Scheme 2.78

When iodide **196** was submitted to these conditions, a different result was obtained. The major product formed was the xanthate **223** (77%) and the sulfonamide **150** (17%) (Scheme 2.79). This shows that the α-carbonyl radical is trapped by another molecule of the tin xanthate **222** before it is able to cyclise.



Scheme 2.79

Slow addition of tin xanthate was used to minimise its concentration in solution, but this lead only to the formation of the sulfonamide **150**. Here again, formation of this compound is unexpected. Considering the discussion in the last section (Section 2.6.2), and since single electron transfer does not occur in the reaction conditions, the mechanism for this elimination must proceed *via* a free radical mechanism. As a result of the different character of the dichloro radical and the simple methylene radical, *ipso* substitution does not occur at all, and the only product obtained is that formed by β-scission.

In conclusion, we have seen that α-carbonyl radicals can undergo *ipso* substitution, and a second cyclization of the amidyl radical can also occur. Preliminary studies on the use of tin compounds, transition metals and xanthates have been made, but competitive reactions, like reduction or elimination, could not be suppressed. However, the importance of temperature in maximising theproducts of *ipso* substitution is now clear.

2.7. Conclusions and Perspectives

This work has demonstrated that the outcome of *ipso* substitution reactions is based on a delicate balance of substituents, linking chain, conformation and strain. All these factors have their own influence on the selectivity of a 1,5-*ipso* substitution *vs* 1,6-addition in the reaction between an aryl radical and a sulfonyl substituted acceptor ring.

It was found that the presence of a substituent *ortho* to the sulfonyl group in the acceptor ring, which can be either electron releasing or electron donating, has a significant effect of possible steric origin in promoting *ipso* substitution. It is still not immediatly apparent however, why the presence of a single *ortho* substituent does not simply encourage 1,6-addition to the alternative ortho carbon atom adjacent to the sulfonyl group. At the same time, the *ortho* substituent increases the stabilisation of the radical formed, and even in the presence of other stabilising groups in other positions, this *ortho* effect is dominant and *ipso* substitution is favoured. Nevertheless, polar effects are also an important factor overall in *ipso* substitution reactions, with the position of the substituent playing an important role, since the attack occurs in order to form the most stabilised radical.

Throughout this work in 1,5-*ipso* substitution, it was noted that the nature of the linking chain also has a relevant role on the distribution of products. Thus, although the reasons are not very clear, it may be postulated that a nitrogen atom in the linking chain is more efficient in promoting *ipso* substitution than an oxygen atom, which in turn is more efficient than a methylene group. On the latter, much more work needs to be done, in order to confirm our predictions, that a methylene group is a more efficient promoter of 1,6-addition than an oxygen atom. It remains to be understood whether this factor is related to the geometry of the molecule, and thus, the angle of the chain and the distance between the position where the radical is formed and the site of attack.

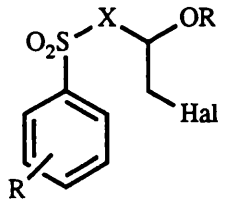
Biaryl synthesis *via* 1,6-*ipso* substitution is however a less effective process. The analysis of several linking chains allows us to have a better knowledge of this subject, and to suggest a general pattern for these reactions. Thus, the presence of a carbonyl group in the sulfonamide or sulfone chains gives only *ipso* substitution products. However, the addition of a methylene spacer to the methyl sulfonamide chain leads to decomposition, the same spacer in a sulfone chain gives a mixture of products, while the selectivity of the related sulfonate chain is dependent of the position of the substituents. Hence, the presence of an *ortho* substituent shows again, a preponderant

influence on *ipso* substitution, as well as an increase in the efficiency of the reaction, while the *para* substituted rings give exclusively 1,7-addition product.

Another area for further investigation, is the effect of substituents other than a methyl on the nitrogen of the linking chain. Thus, selection of a bulky group on the nitrogen atom or methylene chain, which can dominate the conformation of the molecule in a more favourable position, will most probably enhance the likelyhood of *ipso* substitution. Also, the effect of substituent groups on the ring where the aryl radical is formed could be an interesting area for further analysis.

We have also shown that α-carbonyl radicals can undergo *ipso* substitution, with displacement of a sulfonyl group. The influence of the temperature of the reaction on the ratio and nature of products was observed, however, further work is required, in order to optimise the conditions for the subsequent cyclisation with formation of indolone derivatives. The use of stannane compounds, transition metals and xanthates was analysed, but competitive reactions, such as reduction or elimination were also observed. The influence of the substituents on the aromatic ring was also investigated. Thus, both the *ipso* substitution as well as the formation of the indolone are more efficient when electron rich aromatic rings are used, .

The introduction of other groups in the chain (p.e. CH_2), or use of analogues that show more reactivity than an α-carbonyl radical can be an area of further study. For example, the substitution of the carbonyl in the linking chain by an acetal, may avoid the reduction step.



References

1 J. L. Huppatz and W. H. F. Sasse, *Aust. J. Chem.*, 1963, **16**, 417.

2 W. B. Motherwell and A. M. Pennell, *J. Chem. Soc., Chem. Commun.*, 1991, 877.

3 A. Pennel, PhD Thesis, University of London, 1991.

4 A. L. J. Beckwith and C. H. Schisser, *Tetrahedron*, 1985, **41**, 3925.

5 E. Lee, C. Lee, J. S. Tae, H. S. Whang and K. S. Li, *Tetrahedron Lett.*, 1993, **34**, 2343.

6 F. Ujjainwalla, PhD Thesis, University of London, 1993.

7 B. Giese, "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds", Pergamon Press, 1986, p. 218.

8 W. R. Bowman, H. Heaney and B. M. Jordan, *Tetrahedron*, 1991, **47**, 10119.

9 D. P. Curran and J. Tamine, *J. Org. Chem.*, 1991, **56**, 2746.

10 M. Iwao and T Kuraishi, *Heterocycles*, 1992, 1031.

11 A. I. Meyers and R. H. Hutchings, *Tetrahedron Lett*, 1993, **34**, 6185.

12 H. Hettler, *Adv. Heterocycl. Chem.*, 1973, **15**, 233.

13 J.J. Köhler and W. N. Speckamp, *Tetrahedron Lett.*, 1977, **18**, 631.

14 S. Caddick and S. Joshi, *Synlett*, 1992, 805.

15 D.H. Hey, G. H. Jones and M. J. Perkins, *J. Chem. Soc., Chem. Commun.*, 1970, 1438.

16 a) Forrester b) S. A. Glover, A. Goosen and H. A. H. Laue, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1647; b) S. A. Glover and A. Goosen, *J. Chem. Soc., Perkin Trans 1*, 1977, 1349.

17 S. A. Glover and A. Goosen, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2353.

18 N. Ono, H. Miyake, R. Tamura, I. Hamamoto and A. Kaji, *Chem Lett*, 1981, 1139.

19 W. Horspool and D. Armesto, "Organic Photochemistry: A Comprehensive Treatment", Ellis Horwood Limited, 1992, p. 299.

20 J. L. Huppatz, *Aust. J. Chem.*, 1965, **18**, 206.

21 J. C. Chottard and M. Julia, *Tetrahedron Lett.*, 1971, **12**, 2561.

22 O. Yonemitsu, T. Tokuyama, *J. Am. Chem. Soc.*, 1968, **90**, 776.

23 D. P. Curran, M.-H. Chen and D. Kim, *J. Am. Chem. Soc.*, 1989, **111**, 6265.

24 R. S. Jolly and T. Livinghouse, *J. Am. Chem. Soc.*, 1988, **110**, 7536.

25 H. Nagashima, N. Ozaki, M. Ishii, K. Seki, M. Washiyama and K. Itoh, *J. Org. Chem.*, 1993, **58**, 464.

26 P. Deluc, C. Tailhan and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1988, 308.

27 J. Boivin, J. Camara and S. Z. Zard, *J. Am. Chem. Soc.*, 1992, **114**, 7909.

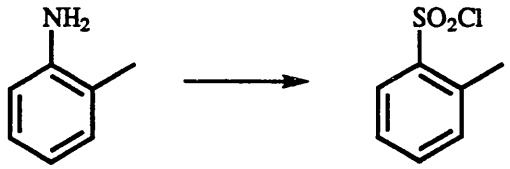
Chapter Three:

Experimental

General Procedure:

^1H nmr spectra were recorded in $CDCl_3$ at 200 MHz on a Varian XL-200, 270 MHz on a Joel GSX 270 and 400 MHz on a Varian VXR-400.^{13}C nmr spectra were recorded 68 and 100 MHz on a Joel GSX 270 and Varian VXR-400. Residual protic solvent, i.e. $CHCl_3$ (δ_H=7.26 ppm; δ_C=77.0 ppm) was used as internal reference. Coupling constants were measured in hertz. Infrared spectra were recorded on a Perkin Elmer 983G and FT-IR 1600 spectrometers. Mass spectra and accurate mass measurements were recorded by EI on a VG 7070B instrument at Imperial College, on a VG 12 253 and VG ZAB-e instruments by the SERC mass spectrometry service and by EI and CI with NH_3 carrier gas, and FAB, on a VG 7070 instrument at UCL. Melting points were determined on a Reichert hot-stage instrument. Microanalysis were performed at Imperial College Chemistry Department microanalytical laboratory and at UCL Chemistry Department microanalytical laboratory. HPLC separation was performed on a Partisil 5 silica gel column (250mm x 10mm), using a UV detector (254 nm) and a solvent mixture of 2% isopropanol in hexane, at a flow rate of 5.0 cm^3/min. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) at low positive pressure. Preparative thin layer chromatography was performed on pre-coated glass plates (Merck Kieselgel 60 F_{254}, 2mm) and visualised using ultraviolet light (245 nm). Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}, 0.2 mm) and visualised using ultraviolet light (245 nm), potassium permanganate, acidic ammonium molybdate and iodine, as appropriate. "Petrol" refers to petroleum ether (b.p. 40-60 °C) which was distilled prior to use. Diethyl ether (referred as ether), tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl; dichloromethane from phosphorous pentoxide and toluene from sodium. All free radical reactions were carried out in glassware oven dried, teflon sealed and degassed with dry argon or nitrogen for approximately 20 min, which was maintained for the entire period of the reaction.

Preparation of *2-methyl-benzenesulfonyl chloride* (**63**)



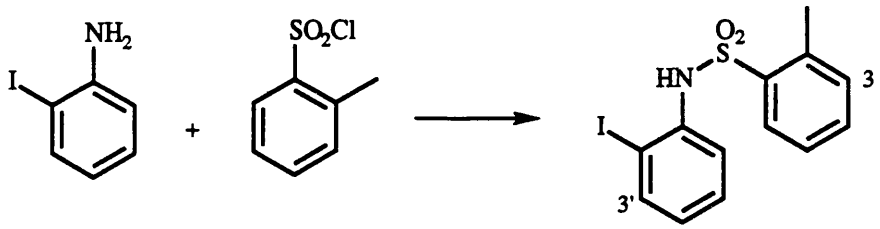
63

To a mixture of conc. HCl (16 ml) and glacial acetic acid (5 ml) was added *o*-toluidine (5.3 ml, 50 mmol) dropwise, and the hydrochloric salt precipitated. The flask was cooled in a dry ice-ethanol bath to -10°C, and a solution of sodium nitrite (3.8 g, 55 mmol) in water (5.5 ml) was added dropwise at such a rate that the temperature did not exceed -5 °C. The mixture was left under stirring at -10 to -5 °C for 30 min.

Meanwhile sulfur dioxide (SO_2) was introduced to acetic acid (50 ml) by a tube immersed below the surface, over a period of 20 min CuCl (1.24 g) was added and the sulfur dioxide (SO_2) bubbled through for a further 30 min. The mixture was cooled with ice to 10 °C and the diazonium salt added dropwise so as to maintain the temperature at 10 °C. After a further 2 hr at this temperature the mixture was warmed to r.t. and stirred overnight. Water was added (150 ml) and the mixture extracted with ether (3x75 ml), washed with aq. $NaHCO_3$, water (50 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude *sulfonyl chloride* **63** (5.9 g, 62%) as an oil; ν_{max}(film)/cm^{-1} 1494, 1371 (S=O), 1182 (S=O); δ_H(200 MHz; $CDCl_3$) 8.06 (1H, d, *J* 8.3, H-6), 7.61 (1H, t, *J* 7.5, H-4), 7.44-7.37 (2H, m, H-3 and H-5), (3H, s, $ArCH_3$); which was used without further purification.

2.78

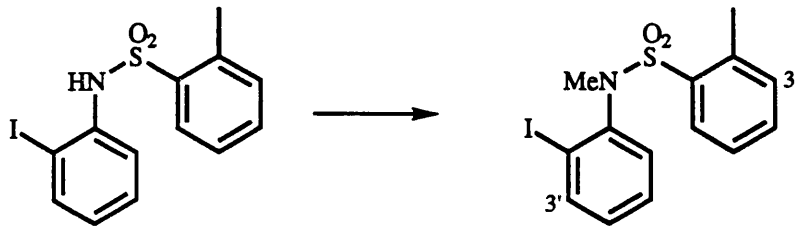
Preparation of *N-(2-iodophenyl)-2-methylbenzenesulfonamide* (**64**)



63 **64**

To 2-iodoaniline (1.1 g, 5.0 mmol) and DMAP (30 mg, 0.24 mmol) was added a solution of the crude sulfonyl chloride **63** (1.1 g, 6.0 mmol) in pyridine (10 ml), and the reaction mixture was stirred at room temperature for 2 days. The pyridine was removed *in vacuo,* the residue dissolved in DCM (25 ml) washed with sat. aq. $CuSO_4$ (2x20 ml) and water (20 ml), dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (DCM/petrol 25-33 %) to give the *sulfonamide* **64** (682 mg; 37%) as white prisms, m.p. 58-59 °C (from ether-petrol); ν_{max}(film)/cm^{-1} 3324, 1474, 1393, 1334 (S=O), 1161 (S=O); δ_H(400 MHz; $CDCl_3$) 7.96 (1H, dd, *J* 1.2 and 8.2, H-3' or H-6), 7.67 (1H, dd, *J* 1.3 and 7.9, H-3' or H-6), 7.47 (1H, dd, *J* 1.5 and 8.3, H-6'), 7.45 (1H, dt, *J* 1.3 and 7.5, H-5' or H-4), 7.30-7.26 (2H, m, H-3 and H-4 or H-5'), 7.21 (1H, dt, *J* 1.4 and 8.4, H-4'), 6.99 (1H, bs, NH), 6.77 (1H, ddd, *J* 1.5, 7.4 and 7.9, H-5), 2.68 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 139.2 (1C, t), 137.5 (1C, q), 137.4 (1C, q), 136.9 (1C, q), 133.4 (1C, t), 132.8 (1C, t), 130.1 (1C, t), 129.4 (1C, t), 126.2 (1C, t), 126.0 (1C, t), 120.2 (1C, t), 90.3 (1C, q, C-I), 20.8 (1C, p, CH_3); *m/z* 373 (M^+), 218, 91 (100%); (Found: C, 41.5; H, 3.2; N, 3.6. $C_{13}H_{12}INO_2S$ requires C, 41.8; H, 3.2; N, 3.75%).

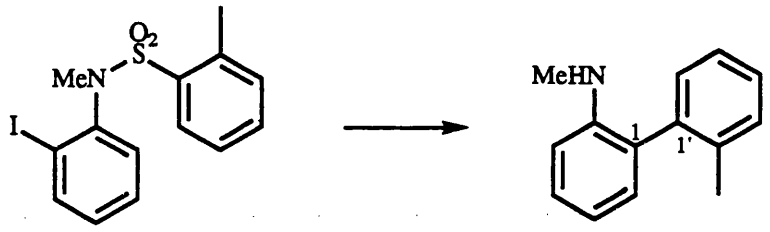
Preparation of *N,2-dimethyl-N-(2-iodophenyl)-benzenesulfonamide* (**65**)



64 **65**

To a stirred suspension of NaH (60% dispersion in mineral oil; 125 mg, 3.1 mmol) in THF (3 ml) at room temperature was added a solution of the sulfonamide **64** (538 mg, 1.4 mmol) in THF (4 ml). Vigorous effervescence occurred. After 30 minutes methyl iodide (0.8 ml, 13 mmol) was added and the reaction mixture stirred for 24 hr. Water (25 ml) was added and the solution extracted with DCM (3x20 ml), dried ($MgSO_4$), the solvent removed *in vacuo* and the residue chromatographed (DCM/petrol 40%) to give the *methyl sulfonamide* **65** (375 mg, 67%) as white prisms, m.p. 102.5-104 °C (from DCM/petrol); ν_{max}(film)/cm^{-1} 2924, 1468, 1347 (S=O), 1156 (S=O), 716; δ_H(400 MHz; $CDCl_3$) 7.84 (1H, dd, *J* 1.5 and 8.0, H-6), 7.80 (1H, dd, *J* 1.4 and 7.9, H-3'), 7.43 (1H, dt, *J* 1.4 and 7.9, H-5'), 7.29-7.22 (4H, m, H-4', H-6', H-3 and H-4), 6.99 (1H, ddd, *J* 1.8, 7.2 and 8.0, H-5), 3.23 (3H, s, NCH_3), 2.50 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 143.3 (1C, q), 140.3 (1C, t), 138.3 (2C, q), 137.3 (1C, t), 132.9 (1C, t), 130.4 (1C, t), 130.3 (1C, t), 129.8 (1C, t), 129.1 (1C, t), 126.1 (1C, t), 100.5 (1C, q, C-I), 39.3 (1C, p), 21.7 (1C, p); *m/z* 387 (M^+), 323 (M^+-SO_2), 260 (M^+-I), 232, 105 (100%); (Found: C, 43.3; H, 3.8; N, 3.3. $C_{14}H_{14}INO_2S$ requires C, 43.4; H, 3.6; N, 3.6%).

Reaction of *N,2-dimethyl-N-(2-iodophenyl)-benzenesulfonamide* (**65**) with tri-n-butyltin hydride

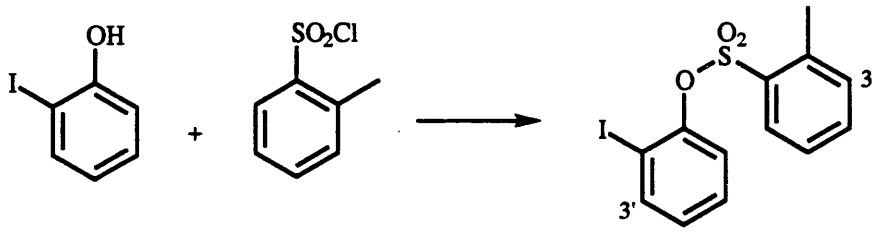


65 **66**

To a stirred solution of the sulfonamide **65** (332 mg, 0.86 mmol) in benzene (17 ml) at reflux, was added a solution of tri-n-butyltin hydride (290 µl, 1.06 mmol) and AIBN (101 mg; 0.61 mmol) in benzene (4.5 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction mixture was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (DCM/petrol 50%) to give in order of elution *N,2'-dimethyl-1,1'-biphenyl-2-amine* (**66**) (97 mg, 57%) and the *sulfonamide* **65** (31 mg, 9.5%).

N,2'-dimethyl-1,1'-biphenyl-2-amine (**66**) as an oil; ν_{max}(film)/cm^{-1} 3426 (NH), 2919, 1512, 742; δ_H(400 MHz; $CDCl_3$) 7.29-7.21 (4H, m, ArH), 7.18-7.16 (1H, m, ArH), 6.97 (1H, dd, *J* 1.5 and 7.3, H-6), 6.74 (1H, dt, *J* 1.1 and 7.4, H-5), 6.67 (1H, d, *J* 8.2, H-3), 3.40 (1H, bs, NH), 2.76 (3H, s, NCH_3), 2.11 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 146.2 (1C, q), 138.5 (1C, q), 137.2 (1C, q), 130.3 (1C, t), 130.2 (1C, t), 129.5 (1C, t), 128.5 (1C, t), 127.6 (1C, t), 127.1 (1C, q), 126.2 (1C, t), 116.4 (1C, t), 109.4 (1C, t), 30.6 (1C, p, NCH_3), 19.6 (1C, p, $ArCH_3$); *m/z* 197 (M^+, 100%), 182, 167; (Found: M^+, 197.1204. $C_{14}H_{15}N$ requires *M*, 197.1204).

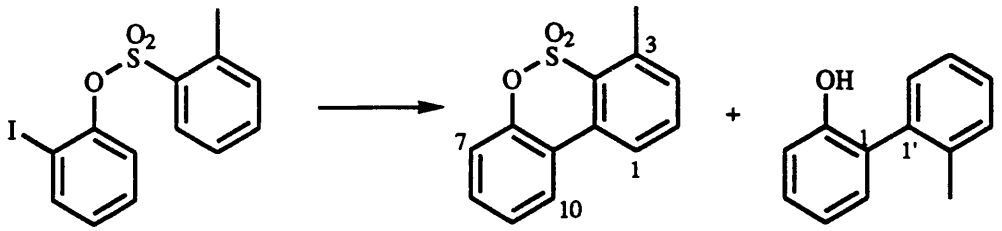
Preparation of *(2-iodophenyl) 2-methylbenzenesulfonate* (**71**)



63 **71**

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (30 mg, 0.24 mmol) was added a solution of the crude sulfonyl chloride **63** (1.3 g, 6.0 mmol) in pyridine (10 ml). The mixture was left stirring overnight at r.t. The pyridine was removed *in vacuo*, the residue dissolved in DCM (25 ml), washed with sat. aq. $CuSO_4$ (2x20 ml) and water (20 ml) dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (DCM/petrol 25%) to give an inseparable mixture of 2-iodophenol and the *sulfonate* **71**. The mixture was dissolved in ether (5 ml), added to a suspension of sodium hydride (excess) in ether (5 ml) and filtered by cannula to give the *sulfonate* **71** (458 mg, 25%) as white prisms, m.p. 53-55 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 1462, 1372 (S=O), 1199, 1174 (S=O); δ_H(400 MHz; $CDCl_3$) 7.89 (1H, d, *J* 8.1, H-3'), 7.80 (1H, dd, *J* 1.6 and 7.9, H-6), 7.58 (1H, dt, *J* 1.3 and 7.6, H-5'), 7.41 (1H, d, *J* 7.6, H-6'), 7.32 (1H, t, *J* 8.0, H-4'), 7.27 (1H, dt, *J* 1.5 and 7.4, H-4), 7.05 (1H, dd, *J* 1.4 and 8.2, H-3), 6.97 (1H, dt, *J* 1.4 and 7.4, H-5), 2.79 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 150.2 (1C, q), 140.2 (1C, t), 139.1 (1C, q), 135.1 (1C, q), 134.3 (1C, t), 132.8 (1C, t), 130.2 (1C, t), 129.4 (1C, t), 128.3 (1C, t), 126.3 (1C, t), 122.7 (1C, t), 90.1 (1C, q, C-I), 21.0 (1C, p, Ar CH_3); *m/z* 374 (M^+), 155, 91 (100%); (Found: M^+, 373.9474. $C_{13}H_{11}IO_3S$ requires *M*, 373.9474).

Reaction of *(2-iodophenyl) 2-methylbenzenesulfonate* (**71**) with tri-n-butyltin hydride



71 **72** **73**

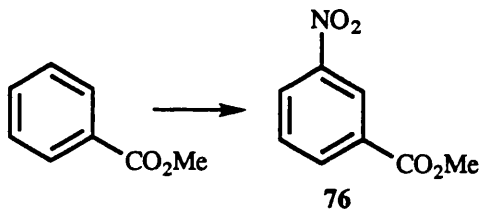
To a stirred solution of the sulfonate **71** (336 mg, 0.90 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (106 mg; 0.65 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed in vacuo, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in DCM (30 ml), washed with aq. NaOH (10%, 3x 20ml), the aq. layer acidified with conc. HCl to pH 1 and extracted with DCM (3x30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to give *2'-methyl-1,1'-biphenyl-2-ol* (**73**) (38 mg, 23%).

The organic layer was dried ($MgSO_4$), the solvent removed under reduced pressure and the residue chromatographed (DCM/petrol 30%) to give in order of elution the *sulfonate* **71** (28 mg, 8%) and *4-methyl-dibenz[c,e]oxathiine-S,S-dioxide* (**72**) (80 mg, 36%).

2'-methyl-1,1'-biphenyl-2-ol (**73**) as an oil; ν_{max}(film)/cm^{-1} 3501, 3434 (OH), 3060, 2922, 1472, 1185, 754; δ_H(400 MHz; $CDCl_3$) 7.60-7.49 (5H, m, ArH), 7.37 (1H, dd, *J* 1.4 and 7.3, H-3), 7.26-7.22 (2H, m, ArH), 5.06 (1H, bs, OH), 2.43 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 152.4 (1C, q), 137.4 (1C, q), 135.6 (1C, q), 130.6 (1C, t), 130.4 (1C, t), 130.1 (1C, t), 129.1 (1C, t), 128.5 (1C, t), 127.6 (1C, q), 126.4 (1C, t), 120.4 (1C, t), 115.2 (1C, t), 19.7 (1C, p, Ar CH_3); *m/z* 184 (M^+, 100%), 169 (M^+-Me); (Found: M^+, 184.0900. $C_{13}H_{12}O$ requires *M*, 184.0888).

4-methyl-dibenz[c,e]oxathiine-S,S-dioxide (**72**) as white needles, m.p. 119-121 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 1367 (S=O), 1177 (S=O), 790, 757; δ_H(400 MHz; $CDCl_3$) 7.86 (1H, dd, *J* 1.5 and 7.9, H-10), 7.76 (1H, d, *J* 8.1, H-1), 7.59 (1H, t, *J* 7.8, H-2), 7.44 (1H, dt, *J* 1.6 and 7.7, H-3), 7.38-7.34 (2H, m, H-3 and H-9), 7.30 (1H, dd, *J* 1.3 and 8.0, H-7), 2.75 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 149.1 (1C, q), 136.5 (1C, q), 133.1 (1C, t), 132.2 (1C, t), 130.9 (1C, t), 129.1 (1C, q), 128.1 (1C, q), 126.6 (1C, t), 125.7 (1C, t), 122.8 (1C, t), 122.0 (1C, q), 119.7 (1C, t), 21.0 (1C, p, $ArCH_3$); *m/z* (EI) 246 (M^+, 100%), 181 (100%); (CI) 263 (MNH_4^+, 100%); (Found: M^+, 246.0351. $C_{13}H_{10}O_3S$ requires *M*, 246.0351).

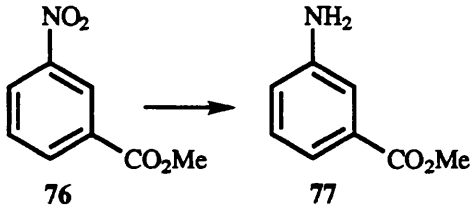
Preparation of *methyl 3-nitrobenzoate* (**76**)[1]



76

To the methyl benzoate (7.2 ml, 58 mmol) at 0 °C was added conc. H_2SO_4 (16 ml). Meanwhile, in another flask, HNO_3 (6 ml) was mixed with H_2SO_4 (6 ml), and the mixture cooled in an ice bath. This solution was added to the methyl benzoate solution, maintaining the temperature between 0-10°C, over 1 hr. After stirring for a further 10 min at r.t., the mixture was poured into ice and stirred until a granular precipitate was seen. The product was filtered and washed with water to give the *benzoate* **76** (9.8 g, 94%) as white prisms, m.p. 79-80 °C (Lit.[1] 78 °C); ν_{max}(film)/cm^{-1} 2958, 1713 (C=O), 1530 (NO_2), 1350 (NO_2); δ_H(200 MHz; $CDCl_3$) 8.87 (1H, s, H-2), 8.39-8.34 (2H, m, H-4 and H-6), 7.65 (1H, dd, *J* 7.9 and 8.2, H-5), 3.98 (3H, s, OCH_3).

Preparation of *methyl 3-aminobenzoate* (**77**)

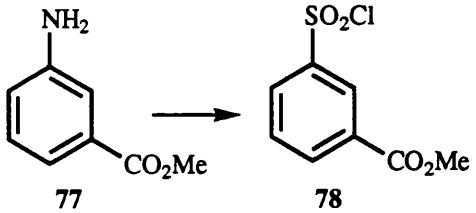


76 **77**

To a suspension of the benzoate **76** (8.8 g, 48.5 mmol) in ethanol (32 ml) was added Pd/C (230 mg) and the flask flushed with argon and than with hydrogen. After stirring vigorously for 2 days the mixture was filtered through a pad of celite, and the solvent removed *in vacuo* to give the *aminobenzoate* **77** which was used without futher purification.

methyl 3-aminobenzoate (**77**) as an oil, (Lit.[2] m.p. 54 °C) ν_{max}(film)/cm^{-1} 3374, (NH) 2951 (CH), 1709 (C=O), 1320 (C-N), 1242 (C-O), 1102 (C-O), 754; δ_H(270 MHz; $CDCl_3$) 7.42 (1H, td, *J* 1.0 and 7.3, H-6), 7.34 (1H, t, *J* 2.0, H-2), 7.21 (1H, t, *J* 7.8, H-5), 6.85 (1H, ddd, *J* 1.0, 2.4 and 7.8, H-4), 3.88 (3H, s, OCH_3), 3.76 (2H, bs, NH_2); *m/z* 151 (M^+), 120 (M^+-OMe, 100%), 92 (M^+-CO_2Me).

Preparation of *methyl 3-(chlorosulfonyl) benzoate* (**78**)



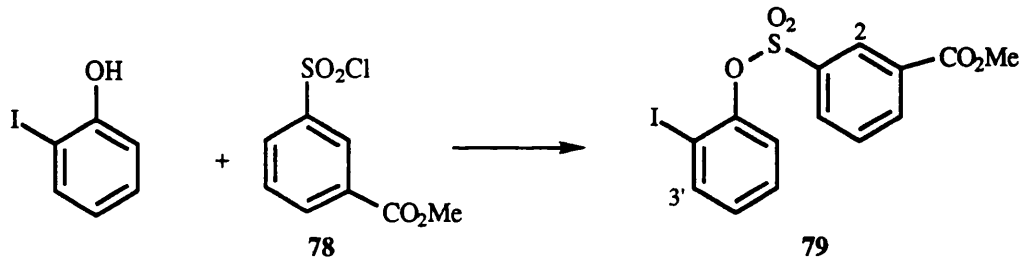
77 **78**

To a mixture of conc. HCl (16 ml) and glacial acetic acid (5 ml), was added the crude benzoate **77** (49 mmol). The flask was placed in a dry ice-ethanol bath and the temperature of the mixture lowered to -10°C. A solution of sodium nitrite (3.7 g, 53 mmol) in water (5.4 ml) was added dropwise, at such a rate so that the temperature did not exceed -5 °C. The mixture was left stirring at -10 to -5 °C, while the other solution was prepared.

Sulfur dioxide (SO_2) was introduced into acetic acid (49 ml) by a tube immersed below the surface, over a period of 30 min. CuCl (1.35 g, 13.6 mmol) was added and SO_2 was kept bubbling for a further hour. The mixture was cooled with ice to 5 °C and the diazonium salt was added dropwise so as to maintain the temperature.

After the addition the mixture was allowed to warm to 10 to 15 °C and stirred for 1 hr. Ice was added and the mixture stirred until it melted, extracted with ether (3x120 ml) washed with $NaHCO_3$ (100 ml) dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *benzoate* **78** (7.7 g, 67%) as orange plates m.p. 64-66 °C (Lit.[3] 68 °C); ν_{max}(film)/cm^{-1} 3104, 2956, 1736 (C=O), 1435, 1368 (S=O), 1179 (S=O), 1124, 855, 750, 672, 657; δ_H(400 MHz; $CDCl_3$) 8.67 (1H, dd, *J* 1.4 and 1.7, H-2), 8.39 (1H, ddd, *J* 1.2, 1.6 and 7.8, H-4 or H-6), 8.20 (1H, ddd, *J* 1.2, 2.0 and 7.9, H-4 or H-6), 7.72 (1H, t, *J* 7.8, H-5), 3.97 (3H, s, CO_2Me); δ_C($CDCl_3$) 164.4 (1C, q, C=O), 144.7 (1C, q), 135.9 (1C, t), 132.0 (1C, q), 130.7 (1C, t), 130.0 (1C, t), 128.1 (1C, t), 52.9 (1C, p, CH_3); *m/z* 236, 234 (M^++2 and M^+), 205, 203, (M^+-OMe), 199, (M^+-Cl), 135 (M^+-SO_2Cl, 100%);

Preparation of *methyl 3-[(2-iodophenyl)oxysulfonyl]benzoate* (**79**)

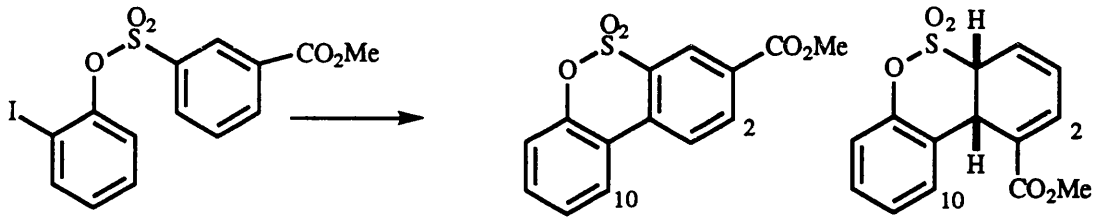


78 **79**

To 2-iodophenol (1.0 g, 4.7 mmol) and DMAP (40 mg) was added a solution of the benzoate **78** (1.5 g, 6.4 mmol) in pyridine (10 ml). The mixture stirred overnight at r.t. The pyridine was removed *in vacuo*, the residue dissolved in DCM (25 ml), washed with sat. aq. $CuSO_4$ (2x25 ml) and water (20 ml) dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (DCM/petrol 75%) to give the *benzoate* **79** (1.8 g, 91%) as an oil; ν_{max}(film)/cm^{-1} 3072, 2955, 1730 (C=O), 1383 (S=O), 1202, 1173 (S=O); δ_H(270 MHz; $CDCl_3$) 8.60 (1H, t, *J* 1.7, H-2), 8.34 (1H, td, *J* 1.5 and 7.8, H-4 or H-6), 8.08 (1H, td, *J* 1.5 and 8.1, H-4 or H-6), 7.72 (1H, d, *J* 7.3, H-3'), 7.63 (1H, dd, *J* 7.8 and 8.1, H-5), 7.35 (2H, d, *J* 3.9, H-5' and H-6'), 7.01-6.95 (1H, m, H-4'), 3.94 (3H, s,

CO_2CH_3); δ_C($CDCl_3$) 164.9 (1C, q, C=O), 149.7 (1C, q), 140.1 (1C, t), 136.4 (1C, q), 135.2 (1C, t), 132.6 (1C, t), 131.4 (1C, q), 129.9 (1C, t), 129.6 (1C, t), 129.4 (1C, t), 128.6 (1C, t), 123.0 (1C, t), 89.8 (1C, q, C-I), 52.7 (1C, p, OCH_3); *m/z* 418 (M^+), 387, 291, 219, 199, 135 (100%); (Found: M^+, 417.9372. $C_{14}H_{11}IO_5S$ requires *M*, 417.9372).

Reaction of *methyl 3-[(2-iodophenyl)oxysulfonyl]benzoate* (**79**) with tri-n-butyltin hydride



79 **80** **81**

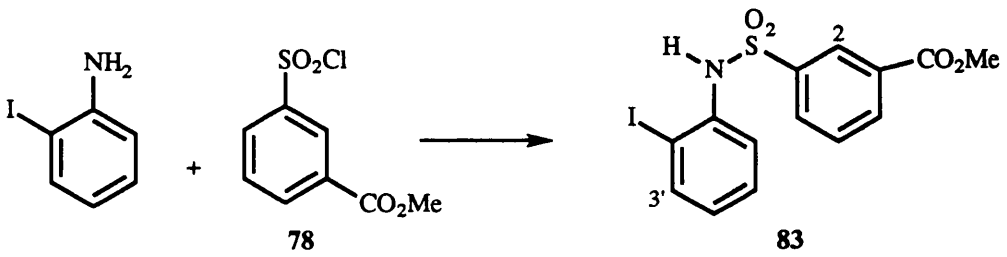
To a stirred solution of the benzoate **79** (371 mg, 0.89mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (121 mg; 0.74 mmol) in benzene (4.6 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in DCM (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give, in order of elution, *methyl dibenz[c,e]oxathiine-S,S-dioxide-3-carboxylate* (**80**) (135 mg, 52%) and *methyl (4aR,10bR)-4a,10b-dihydrodibenz[c,e]oxathiine-S,S-dioxide-1-carboxylate* (**81**) (50 mg, 19%);

methyl dibenz[c,e]oxathiine-S,S-dioxide-3-carboxylate (**80**) as white prisms, m.p. 183-185 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2956 (CH), 1728 (C=O), 1377 (S=O), 1202, 1176 (S=O), 758; δ_H(400 MHz; $CDCl_3$) 8.65 (1H, d, *J* 1.7, H-4), 8.40 (1H, dd, *J* 1.7 and 8.3, H-2), 8.03 (1H, d, *J* 8.3, H-1), 7.98 (1H, dd, *J* 1.7 and 7.8, H-10 or H-7), 7.53 (1H, dt, *J* 1.7 and 8.1, H-10 or H-7), 7.44 (1H, dt, *J* 1.5 and 7.6, H-8 or H-9), 7.37 (1H, dd, *J* 1.2 and 8.1, H-8 or H-9), 3.99 (3H, s, CO_2CH_3); δ_C($CDCl_3$) 164.7 (1C, q, C=O),

150.1 (1C, q), 135.4 (1C, q), 134.4 (1C, t), 132.3 (1C, t), 130.7 (1C, q), 126.9 (1C, t), 125.7 (2C, t), 125.1 (1C, t), 120.9 (2C, q), 120.2 (1C, t), 52.8 (1C, p, OCH_3); *m/z* 290 (M^+, 100%), 259, 195, 139; (Found: M^+, 290.0238. $C_{14}H_{10}O_5S$ requires *M*, 290.0249).

(4aR,10bR)-4a,10b-dihydrodibenz[c,e]oxathiine-S,S-dioxide-1-carboxylate (**81**) as white prisms, m.p. 125-126 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 1710 (C=O), 1375 (S=O), 1227, 1156 (S=O); δ_H(270 MHz; $CDCl_3$) 7.28-7.24 (2H, m, H-8 or H-9 and H-2), 7.13 (1H, dt, *J* 1.2 and 7.3, H-8 or H-9), 7.06 (1H, d, *J* 7.8, H-7 or H-10), 6.99 (1H, dd, *J* 1.2 and 8.3, H-7 or H-10), 6.31 (2H, d, *J* 2.9, H-3 and H-4), 4.83 (1H, d, *J* 7.3, H-10b), 4.37 (1H, d, *J* 7.8, H-4a), 3.93 (3H, s, CO_2CH_3); δ_C($CDCl_3$) 166.6 (1C, q, C=O), 150.9 (1C, q), 134.4 (1C, t), 129.1(1C, t), 128.5 (1C, q), 128.4 (1C, t), 128.1 (1C, t), 125.9 (1C, t), 125.2 (1C, t), 121.7 (1C, q), 118.6 (1C, t), 55.9 (1C, p), 52.6 (1C, t), 33.9 (1C, p, NCH_3); *m/z* 292 (M^+), 290, 196 (100%), 168; the X-ray of this compound is on Apendix 2.

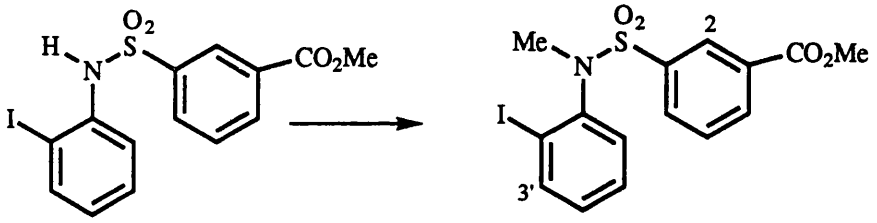
Preparation of *methyl 3[(2-iodophenyl)aminosulfonyl] benzoate* (**83**)



To 2-iodoaniline (628 mg, 2.9 mmol) and DMAP (20 mg, 0.2 mmol) was added a solution of the benzoate **78** (1.1 g, 4.5 mmol) in pyridine (6 ml), and the reaction mixture was stirred at room temperature for 3 days. The pyridine was removed *in vacuo*, the residue dissolved in DCM (25 ml) washed with sat. aq. $CuSO_4$ (2x20 ml) and water (20 ml), dried ($MgSO_4$), concentrated *in vacuo* and chromatographed (DCM/petrol 50-75%) to give the *benzoate* **83** (820 mg, 69%) as an oil; ν_{max}(film)/cm^{-1} 3267 (NH), 1762 (C=O), 1471, 1342 (S=O), 1271, 1166 (S=O), 1125, 754; δ_H(270 MHz; $CDCl_3$) 8.43 (1H, t, *J* 1.5, H-2), 8.21 (1H, ddd, *J* 1.2, 1.7 and 7.8, H-4 or H-6), 7.87 (1H, ddd, *J* 1.2, 2.0 and 7.8, H-4 or H-6), 7.65 (2H, m, H-3' and H-6'), 7.50 (1H, t, *J* 7.8, H-5), 7.33 (1H, dt, *J* 1.2 and 7.6, H-4' or H-5'), 6.85 (1H, m, H-4' or H-5'), 6.82

(1H, bs, NH), 3.92 (3H, s, CH_3); δ_C($CDCl_3$) 165.2 (1C, q, C=O), 139.5 (1C, q), 139.2 (1C, t), 136.9 (1C, q), 134.1 (1C, t), 131.4 (1C, t), 131.3 (1C, q), 129.7 (1C, t), 129.3 (1C, t), 128.7 (1C, t), 127.4 (1C, t), 123.3 (1C, t), 92.8 (1C, q, C-I), 52.6 (1C, p, CH_3); *m/z* 417 (M^+), 386, 218 (100%), 135; (Found: M^+, 416.9532. $C_{14}H_{12}INO_4S$ requires *M*, 416.9532).

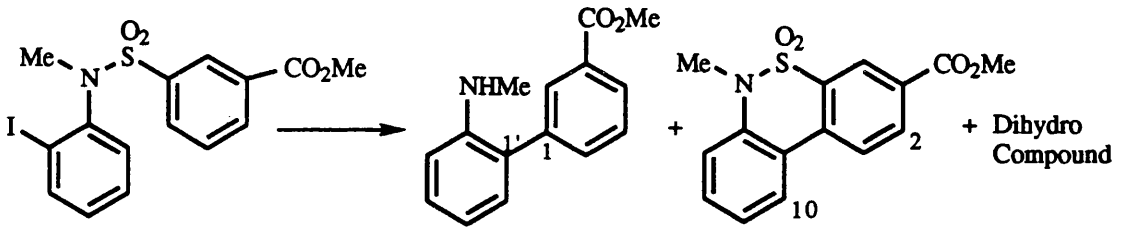
Preparation of *methyl 3[(2-iodophenyl)methylaminosulfonyl] benzoate* (**84**)



83 **84**

To a stirred suspension of NaH (60% dispersion in mineral oil; 160 mg, 3.9 mmol) in THF (3 ml) at room temperature was added a solution of the benzoate **83** (820 mg, 2.0 mmol) in THF (5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (1.0 ml, 16 mmol) was added and the reaction mixture stirred for 24 hr. Water (25 ml) was added and the solution extracted with DCM (3x15 ml), dried ($MgSO_4$), the solvent removed *in vacuo* and the residue chromatographed (DCM/petrol 75%) to give the *benzoate* **84** (337 mg, 40%) as white needles, m.p. 112-114 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2952 (CH), 1728 (C=O), 1356 (S=O), 1271, 1157 (S=O), 705; δ_H(270 MHz; $CDCl_3$) 8.50 (1H, t, *J* 1.5, H-2), 8.28 (1H, ddd, *J* 1.2, 1.5 and 7.8, H-4 or H-6), 7.97 (1H, ddd, *J* 1.2, 1.5 and 7.8, H-4 or H-6), 7.90 (1H, dd, *J* 1.5 and 8.3, H-3'), 7.61 (1H, dt, *J* 0.5 and 7.8, H-5), 7.30 (1H, ddd, *J* 1.5, 7.6 and 8.6, H-5'), 7.07-7.01 (2H, m, H-4' and H-6'), 3.95 (3H, s, CO_2CH_3), 3.19 (3H, s, NCH_3); δ_C($CDCl_3$) 165.5 (1C, q, C=O), 143.3 (1C, q), 140.5 (1C, t), 139.6 (1C, q), 133.8 (1C, t), 132.1 (1C, t), 131.3 (1C, q), 130.1 (1C, t), 129.4 (1C, t), 129.2 (2C, t), 129.1 (1C, t), 101.0 (1C, q, C-I), 52.6 (1C, p, OCH_3), 38.9 (1C, p, NCH_3); *m/z* 431 (M^+), 400 (M^+-OMe), 304 (M^+-I), 232 (100%), 183, 105; (Found: M^+, 430.9688. $C_{15}H_{14}INO_4S$ requires *M*, 430.9688).

Reaction of *methyl 3[(2-iodophenyl)methylaminosulfonyl] benzoate* (**84**) with tri n-butyltin hydride



84 **85** **86** **87**

To a stirred solution of the benzoate **84** (322 mg, 0.74 mmol) in benzene (15 ml) at reflux, was added a solution of tri-n-butyltin hydride (260 µl, 0.95 mmol) and AIBN (101 mg; 0.62 mmol) in benzene (3.8 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added, and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in DCM (20 ml), washed with sat. KF (2x15 ml) and water (15 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%, ethyl acetate/petrol 20%) to give in order of elution *methyl (N-methyl-1,1'-biphenyl-2'-amine)-3-carboxylate* (**86**) (50 mg, 28%), *methyl 6-methyl-6H-dibenzo[c,e]thiazine-S,S-dioxide-3-carboxylate* (**85**) (84 mg, 37%) and a *dihydro compound* **87** (28 mg, 11%).

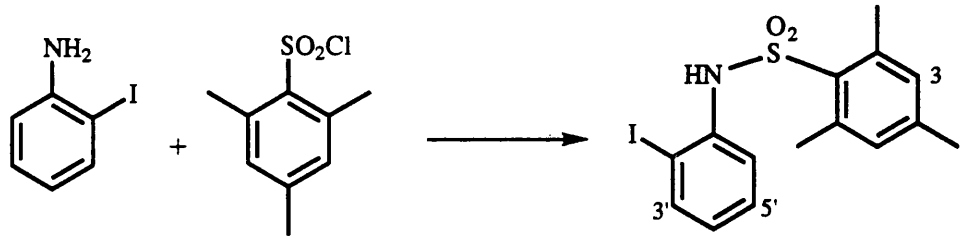
methyl (N-methyl-1,1'-biphenyl-2'-amine)-3-carboxylate (**85**) as white prisms m.p. 93-95°C (DCM/petrol); ν_{max}(film)/cm^{-1} 3423 (NH), 2950 (CH), 1722 (C=O), 1511, 1462, 1305, 1260, 1231; δ_H (270 MHz; $CDCl_3$) 8.10 (1H, t, *J* 1.7, H-2), 8.02 (1H, td, *J* 1.7 and 7.8, H-4), 7.62 (1H, td, *J* 1.5 and 7.6, H-6), 7.51 (1H, t, *J* 7.6, H-5), 7.29 (1H, ddd, *J* 1.7, 7.8 and 8.5, H-4'), 7.08 (1H, dd, *J* 1.5 and 7.3, H-6'), 6.79 (1H, t, *J* 7.3, H-5'), 6.71 (1H, d, *J* 8.5, H-3'), 3.92 (3H, s, CO_2CH_3), 2.80 (3H, s, NCH_3); δ_C ($CDCl_3$) 166.8 (1C, q, C=O), 145.9 (1C, q), 139.7 (1C, q), 133.9 (1C, t), 130.7 (1C, q), 130.5 (1C, t), 129.9 (1C, t), 129.1 (1C, t), 128.9 (1C, t), 128.3 (1C, t), 126.4 (1C, q), 116.8 (1C, t), 109.9 (1C, t), 52.0 (1C, p, OCH_3), 30.7 (1C, p, NCH_3); *m/z* 367 (M^+), 266, 241 (100%); (Found: M^+, 241.1103. $C_{15}H_{15}NO_2$ requires *M*, 241.1103).

methyl 6-methyl-6H-dibenzo[c,e]thiazine-S,S-dioxide-3-carboxylate (**86**) as white prisms, m.p. 178-180 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 1720 (C=O), 1292, 1166;

δ_H(270 MHz; $CDCl_3$) 8.65 (1H, d, *J* 2.0, H-4), 8.33 (1H, dd, *J* 2.0 and 8.3, H-2), 8.04-8.00 (2H, m, H-1 and H-7), 7.54 (1H, dt, *J* 1.7 and 7.3, H-8 or H-9), 7.30-7.37 (2H, m, H-8 or H-9 and H-10), 3.97 (3H, s, CO_2CH_3), 3.46 (3H, s, NCH_3); δ_C($CDCl_3$) 169.4 (1C, q, C=O), 139.9 (1C, q), 136.2 (1C, q), 134.2 (1C, q), 132.9 (1C, t), 131.4 (1C, t), 129.8 (1C, q), 126.0 (1C, t), 125.6 (1C, t), 124.8 (1C, t), 124.0 (1C, t), 123.2 (1C, q), 119.4 (1C, t), 52.5 (1C, p, OCH_3), 32.7(1C, p, NCH_3); *m/z* 303 (M^+, 100%), 272, 238, 208, 180; (Found: M^+, 303.0576. $C_{15}H_{13}NO_4S$ requires *M*, 303.0565).

Dihydro compound **87** as a clear oil; ν_{max}(film)/cm^{-1} 2948 (CH), 1707 (C=O), 1335 (S=O), 1138 (S=O); δ_H(270 MHz; $CDCl_3$) 7.30-7.22 (2H, m, ArH and H-2), 7.02-7.00 (2H, m, ArH), 6.98 (1H, d, *J* 8.1, ArH), 6.27-6.21 (1H, ddd, *J* 2.7, 5.1 and 9.5, H-3), 6.14-6.19 (1H, ddd, *J* 1.0, 2.0 and 9.5, H-4), 4.81 (1H, d, *J* 7.8, H-10b), 4.32-4.27 (1H, td, *J* 2.0 and 8.0, H-44), 3.91 (3H, s, CO_2CH_3), 3.38 (3H, s, NCH_3); δ_C($CDCl_3$) 166.9 (1C, q, C=O), 140.6 (1C, q), 134.3 (1C, t), 129.1 (1C, q), 128.3 (1C, t), 128.1 (1C, t), 127.5 (1C, t), 125.9 (1C, t), 124.9 (1C, q), 123.7 (1C, t), 117.1 (1C, t), 57.3 (1C, p, OCH_3), 52.5 (1C, t), 34.3 (1C, p, NCH_3), 32.2 (1C, t); *m/z* (EI) 303 (M^+-2), 241, 182 (100%), 167; (CI) 323 $(MNH_4)^+$, 242 (100%); (Found: MNH_4^+, 323.1066. $C_{15}H_{19}N_2O_4S$ requires *MNH_4*, 323.1066).

Preparation of *N-(2-iodophenyl)-2,4,6-trimethylbenzenesulfonamide* (**88**)[4]



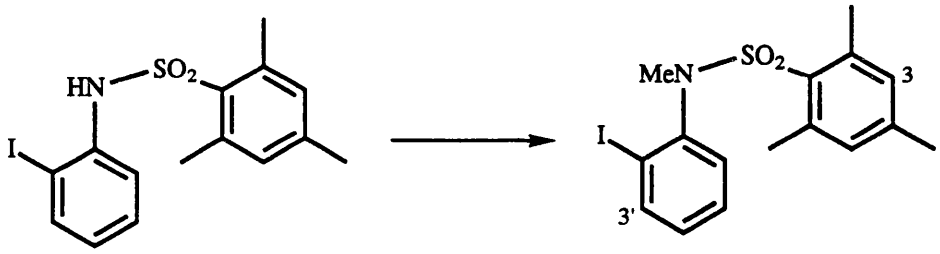
88

To 2-iodoaniline (1.1 g, 4.9 mmol) and DMAP (33 mg, 0.3 mmol) was added a solution of 2,4,6-trimethylbenzenesulfonyl chloride (1.6 g, 7.3 mmol) in pyridine (12 ml), and the reaction mixture stirred at room temperature for 24 hr.

Pyridine was removed *in vacuo*, the residue washed with sat. aq. $CuSO_4$ (20 ml), extracted with DCM (2x15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed (DCM/petrol 50-100%) to give the *sulfonamide* **88**

(1.9 g, 95%) as white needles, m.p. 107-108 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3328, 1602, 1583, 1469, 1334 (S=O), 1157 (S=O); δ_H(270 MHz; $CDCl_3$) 7.69 (1H, dd, *J* 1.5 and 8.0, H-3`), 7.29 (1H, dd, *J* 1.7 and 8.0, H-6`), 7.23 (1H, ddd, *J* 1.5, 7.6 and 8.0, H-5`), 6.96 (1H, bs, NH), 6.93 (2H, s, H-3 and H-5), 6.78 (1H, dt, *J* 1.7 and 8.0, H-4`), 2.64 (6H, s, C2-CH_3, C6-CH_3), 2.29 (3H, s, C4-CH_3).

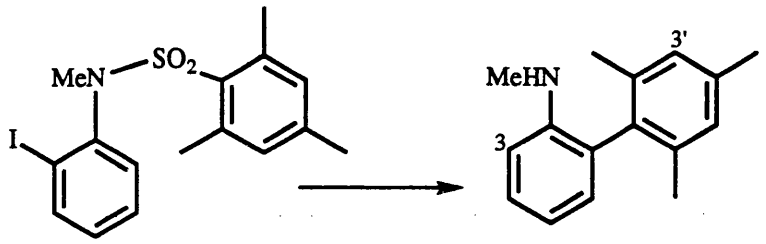
Preparation of *N- (2-iodophenyl)- N,2,4,6- tetramethylbenzenesulfonamide* (**89**)[4]



88 **89**

To a stirred suspension of NaH (60% dispersion in mineral oil; 0.25 g, 6.4 mmol) in THF (7.5 ml) at room temperature was added a solution of the sulfonamide **88** (1.3 g, 3.2 mmol) in THF (7.5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (1.9 ml; 31 mmol) was added and the reaction mixture stirred for 43 hr at r.t.. Water was added (25 ml) and the solution extracted with DCM (2x20 ml), dried ($MgSO_4$), the solvent removed *in vacuo* and the residue purified by column chromatography (DCM/petrol 60-100%) to give the *sulfonamide* **89** (1.2 g, 87%) as white needles, m.p. 77-80 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2938, 1603, 1469, 1329, 1152; δ_H(270 MHz; $CDCl_3$) 7.79 (1H, dd, *J* 1.5 and 8.0, H-3`), 7.53 (1H, dd, *J* 1.6 and 7.9, H-6`), 7.33 (1H, dt, *J* 1.5 and 7.3, H-5`), 6.98 (1H, ddd, *J* 1.6, 7.3 and 7.9, H-4`), 6.88 (2H, bs, H-3 and H-5), 3.28 (3H, s, NCH_3), 2.42 (6H, s, C2-CH_3 and C6-CH_3), 2.27 (3H, s, C4-CH_3).

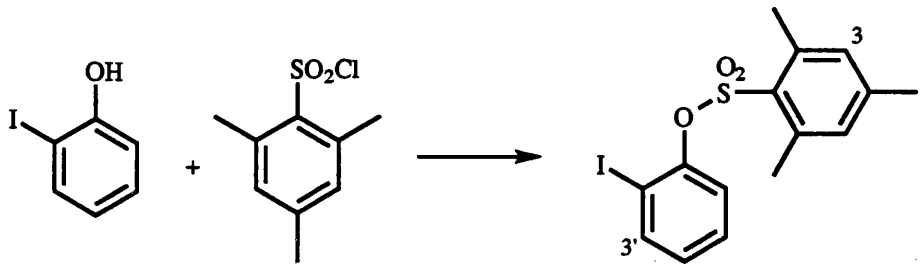
Reaction of *N- (2-iodophenyl)- N,2,4,6- tetramethylbenzenesulfonamide* (**89**) with tri-n-butyltin hydride



89 **90**

To a stirred solution of the sulfonamide **89** (233 mg, 0.56 mmol) in benzene (12 ml) at reflux, was added a solution of tri-n-butyltin hydride (190 µl; 0.69 mmol) and AIBN (64 mg, 0.39 mmol) in benzene (3.9 ml) dropwise over 17 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue washed with sat. aq. KF (15 ml), extracted with ether (3x10 ml), dried (MgSO4) and the solvent removed under reduced pressure. The residue chromatographed (DCM/ petrol 20-50%) to give *N,2',4',6'-tetramethyl-1,1'-biphenyl-2-amine* (**90**)[4] (82 mg; 65%) as white needles m.p. 46-48°C (Lit.[4] oil) ν_{max}(film)/cm^{-1} 3400 (bs), 2921, 1602, 1513, 1479, 1315 (S=O), 1166 (S=O); δ_H (270 MHz; $CDCl_3$) 7.28 (1H, ddd, *J* 1.7 and 7.3, 8.0, H-4), 6.98 (2H, s, H-3`and H-5`), 6.89 (1H, dd, *J* 1.7 and 7.3, H-6), 6.78 (1H, dt, *J* 1.0 and 7.3, H-5), 6.71 (1H, dd, *J* 1.0 and 8.0, H-3), 3.32 (1H, bs, NH), 2.78 (3H, s, N-CH_3), 2.35 (3H, s, C4`-$CH_3$), 1.99 (6H, s, C2`-CH_3 and C6`-CH_3).

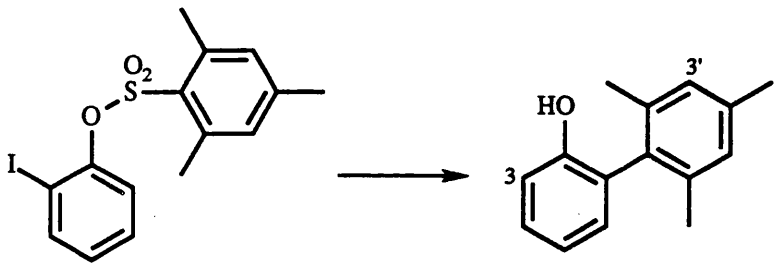
Preparation of *(2-iodophenyl) 2,4,6-trimethylbenzenesulfonate* (**95**)[4]



95

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (31 mg) was added a solution of 2,4,6-trimethylbenzenesulfonyl chloride (1.3 g, 6.0 mmol) in pyridine (10 ml). The mixture was left stirring overnight at r.t. Pyridine was removed *in vacuo*, the residue dissolved in DCM (25 ml), washed with sat. aq. $CuSO_4$ (2x20 ml) and water (20 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 20%) to give the *sulfonate* **95** (1.7 g, 85%) as white prisms, m.p. 82-83 °C (DCM/petrol) (Lit.[4] 81-82.5 °C); δ_H(270 MHz; $CDCl_3$) 7.82 (1H, dd, *J* 1.5 and 8.1, H-3'), 7.26 (1H, dt, *J* 1.7 and 7.8, H-5'), 7.01 (2H, s, H-3 and H-5), 7.00-6.93 (2H, m, H-4' and H-6'), 2.61 (6H, s, C-2 CH_3 and C-6 CH_3), 2.35 (3H, s, C-4 CH_3); *m/z* 402 (M^+), 196, 183, 119 (100%).

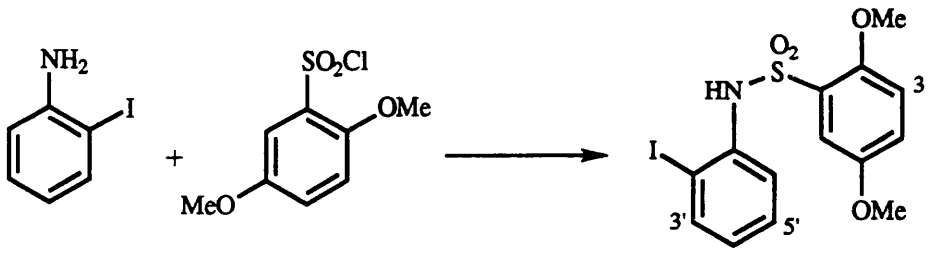
Reaction of *(2-iodophenyl) 2,4,6-trimethylbenzenesulfonate* (**95**) with tri-n-butyltin hydride



95 **96**

To a stirred solution of the sulfonate **95** (357 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (104 mg; 0.63 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 ml), sat. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the ethyl acetate layer washed with sat. KF (15 ml) and water (15 ml) dried ($MgSO_4$), and concentrated under reduced pressure. Preparative thin layer chromatography (DCM/petrol 75%) gave in order of elution the *sulfonate* **95** (118 mg, 33%) and *2',4',6'-trimethyl-1,1'-biphenyl-2-ol* (**96**) (94 mg, 50%) as an oil; ν_{max}(film)/cm^{-1} 3493 (OH), 2920; δ_H(270 MHz; $CDCl_3$) 7.27 (1H, m, H-3), 7.03-6.94 (5H, m, H-3', H-5', H-4, H-5 and H-6), 4.62 (1H, s, OH), 2.34 (3H, s, $ArCH_3$), 2.01 (6H, s, 2x$ArCH_3$); δ_C($CDCl_3$) 152.5 (1C, q), 138.1 (1C, q), 137.8 (1C, q), 131.6 (1C, q), 130.0 (1C, t), 128.9 (1C, t), 128.7 (1C, t), 126.4 (1C, q), 120.7 (1C, t), 115.1 (1C, t), 21.1 (1C, p), 20.2 (2C, p); *m/z* 215 (M^+), 197 (100%), 182, 119; (Found: M^+, 212.1209. $C_{15}H_{16}O$ requires *M*, 212.1201).

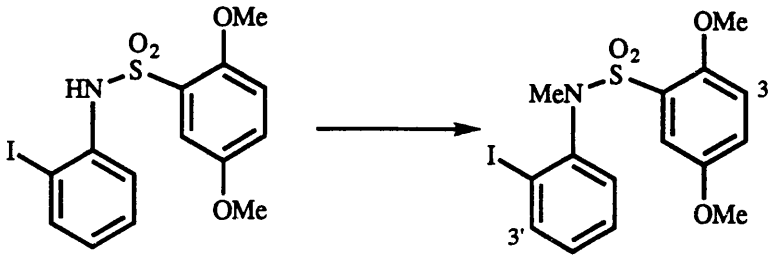
Preparation of *2,5-dimethoxy-N-(2-iodophenyl)-benzenesulfonamide* (**97**)



97

To 2-iodoaniline (0.7 g, 3.11 mmol) and DMAP (20 mg, 0.2 mmol) was added a solution of the 2,5-dimethoxybenzenesulfonyl chloride (1.1 g, 4.4 mmol) in pyridine (7 ml), and the reaction mixture was stirred at r.t. for 3 days. Pyridine was removed *in vacuo*, the residue washed with sat. aq. $CuSO_4$, extracted with DCM, dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give the *sulfonamide* **97** (1.0 g, 77%) as white needles, m.p.117-117.5 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3300 (NH), 2493, 1582, 1495, 1398, 1337 (S=O), 1159 (S=O), 1042, 912, 812, 745; δ_H(270 MHz; $CDCl_3$) 7.68 (1H, dd, *J* 1.5 and 7.8, H-3`), 7.57 (1H, dd, *J* 1.5 and 8.3, H-6`), 7.46 (1H, d, *J* 3.2, H-6), 7.36 (1H, bs, NH), 7.21 (1H, ddd, *J* 1.5, 7.8 and 8.3, H-5`), 7.04 (1H, dd, *J* 3.2 and 9.0, H-4), 6.88 (1H, d, *J* 9.0, H-3), 6.74 (1H, ddd, *J* 1.5, 7.8 and 8.3, H-4`), 3.92 (3H, s, $OC\underline{H}_3$), 3.77 (3H, s, $OC\underline{H}_3$); δ_C ($CDCl_3$) 152.9 (1C, q), 150.5 (1C, q), 139.3 (1C, t), 138.1 (1C, q), 129.4 (1C, t), 126.7 (1C, q), 125.7 (1C, t), 121.1 (1C, t), 119.6 (1C, t), 115.5 (1C, t), 113.3 (1C, t), 89.3 (1C, q, C-I), 56.7 (1C, p, OCH_3), 56.1 (1C, p, OCH_3); *m/z* 419 (M^+, 100%), 218, 201, 137; (Found: M^+, 418.9691. $C_{14}H_{14}INO_4S$ requires *M*, 418.9688).

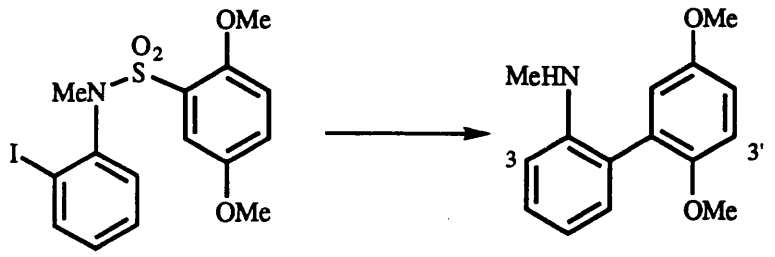
Preparation of *2,5-dimethoxy-N-(2-iodophenyl)-N-methyl-benzenesulfonamide* (**98**)



97 **98**

To a stirred suspension of NaH (60% dispersion in mineral oil; 177 mg, 4.4 mmol) in THF (4.5 ml) at room temperature was added a solution of the sulfonamide **97** (0.93 g, 2.2 mmol) in THF (4.5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (1.2 ml, 19 mmol) was added and the reaction mixture stirred for 4 days. Water (20 ml) was added and the solution extracted with DCM (3x15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed (DCM/petrol 70-100%) to give the *sulfonamide* **98** (818 mg; 86%) as white needles, m.p. 122-123 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2358, 1495, 1340 (S=O), 1274, 1223, 1149 (S=O), 1036; δ_H(270 MHz; $CDCl_3$) 7.88 (1H, dd, *J* 1.7 and 7.8, H-3'), 7.28 (1H, d, *J* 2.9, H-6), 7.23 (1H, dt, *J* 1.2 and 7.8, H-5'), 7.07 (1H, dd, *J* 3.1 and 9.0, H-4), 7.02-6.96 (3H, m, H-3, H-4' and H-6'), 3.91 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.39 (3H, s, NCH_3); δ_C($CDCl_3$) 152.8 (1C, q), 151.0 (1C, q), 143.5 (1C, q), 140.2 (1C, t), 130.1 (1C, t), 129.7 (1C, t), 129.2 (1C, q), 129.0 (1C, t), 120.5 (1C, t), 115.5 (1C, t), 113.6 (1C, t), 101.0 (1C, q, C-I), 56.5 (1C, p, OCH_3), 55.9 (1C, p, OCH_3), 39.9 (1C, p, NCH_3); *m/z* 433 (M^+), 306 (M^+-I), 232, 201, 137, 105 (100%); (Found: M^+, 432.9854. $C_{15}H_{16}INO_4S$ requires *M*, 432.9845).

Reaction of *2,5-dimethoxy-N-(2-iodophenyl)-N-methyl-benzenesulfonamide* (**98**) with tri-n-butyltin hydride

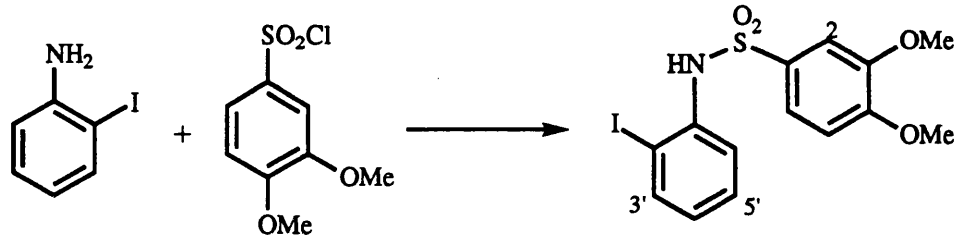


98 **101**

To a stirred solution of the sulfonamide **98** (293 mg, 0.68 mmol) in benzene (13.5 ml) at reflux, was added a solution of tri-n-butyltin hydride (242 μl, 0.88 mmol) and AIBN (82 mg; 0.5 mmol) in benzene (3.5 ml) dropwise over 18 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue washed with sat. aq. KF (15 ml), extracted with ether (3x20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM) to give in order of elution *2',5'-dimethoxy-N-methyl-1,1'-biphenyl-2-amine* (**101**) (112 mg, 63%), and the *sulfonamide* **98** (77 mg; 26%).

*2`,5`-dimethoxy-N-methyl-1,1`-biphenyl-2-amine* (**101**) as an oil; $\nu_{max}$(film)/$cm^{-1}$ 3428 (NH), 2935, 1603, 1579, 1494, 1460, 1313, 1267, 1224, 1047, 807, 749; $\delta_H$(270 MHz; $CDCl_3$) 7.28 (1H, dt, *J* 1.7 and 7.6, H-3), 7.08 (1H, dd, *J* 1.7 and 7.6, H-5), 6.94 (1H, d, *J* 9.0, H-3`), 6.88 (1H, dd, *J* 2.7 and 9.0, H-4`), 6.82 (1H, d, *J* 2.7, H-6`), 6.80-6.71 (2H, m, H-4 and H-6), 3.78 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 2.81 (3H, s, NCH_3); δ_C($CDCl_3$) 153.8 (1C, q), 151.0 (1C, q), 146.7 (1C, q), 130.3 (1C, t), 129.0 (1C, q), 128.6 (1C, t), 124.4 (1C, q), 117.1 (1C, t), 116.5 (1C, t), 113.7 (1C, t), 112.8 (1C, t), 109.8 (1C, t), 56.4 (1C, p, OCH_3), 55.5 (1C, p, OCH_3), 30.7 (1C, p, NCH_3); *m/z* 243 (M^+), 212 (M^+-OMe, 100%), 197, 168. (Found: M^+, 243.1261. $C_{15}H_{17}NO_2$ requires *M*, 243.1259).

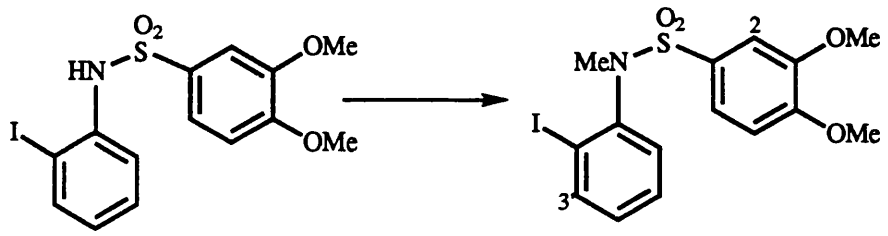
Preparation of *3,4-dimethoxy-N-(2-iodophenyl)-benzenesulfonamide* (**99**)



99

To 2-iodoaniline (0.68 g, 3.1 mmol) and DMAP (20 mg, 0.2 mmol) was added a solution of 3,4-dimethoxybenzenesulfonyl chloride (1.1 g, 4.5 mmol) in pyridine (7 ml), and the reaction mixture stirred at r.t. for 24 hr. Pyridine was removed *in vacuo*, the residue dissolved in DCM (20 ml), washed with sat. aq. $CuSO_4$ (2x 15 ml), water (15 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 60-100%) to give the *sulfonamide* **99** (878 mg; 67%) as white plates, m.p. 125-126°C (DCM/petrol); ν_{max}(film)/cm^{-1} 3300 (bs, NH), 2965 (CH), 1586, 1511, 1469, 1407, 1333 (S=O), 1262, 1156 (S=O); δ_H(400 MHz; $CDCl_3$) 7.66 (1H, dd, *J* 1.5 and 8.1, H-3'), 7.62 (1H, dd, *J* 1.4 and 8.0, H-6'), 7.35 (1H, dd, *J* 2.2 and 8.5, H-6), 7.29 (1H, m, H-5'), 7.07 (1H, d, *J* 2.2, H-2), 6.84-6.80 (1H, m, H-4'), 6.81 (1H, d, *J* 8.5, H-5), 6.74 (1H, bs, NH), 3.88 (3H, s, OCH_3), 3.76 (3H, s, OCH_3); δ_C($CDCl_3$) 153.1 (1C, q), 149.0 (1C, q), 139.1 (1C, t), 137.7 (1C, q), 130.3 (1C, q), 129.5 (1C, t), 127.0 (1C, t), 122.9 (1C, t), 121.6 (1C, t), 110.4 (1C, t), 109.8 (1C, t), 92.9 (1C, q, C-I), 56.2 (2C, p, 2xOCH_3); *m/z* 419 (M^+), 355 (M^+-SO_2), 314 (M^+-$NHSO_2$), 218, 201, 137; (Found: C, 39.9; H, 3.5; N, 3.2. $C_{14}H_{14}INO_4S$ requires C, 40.1; H, 3.4; N, 3.3%).

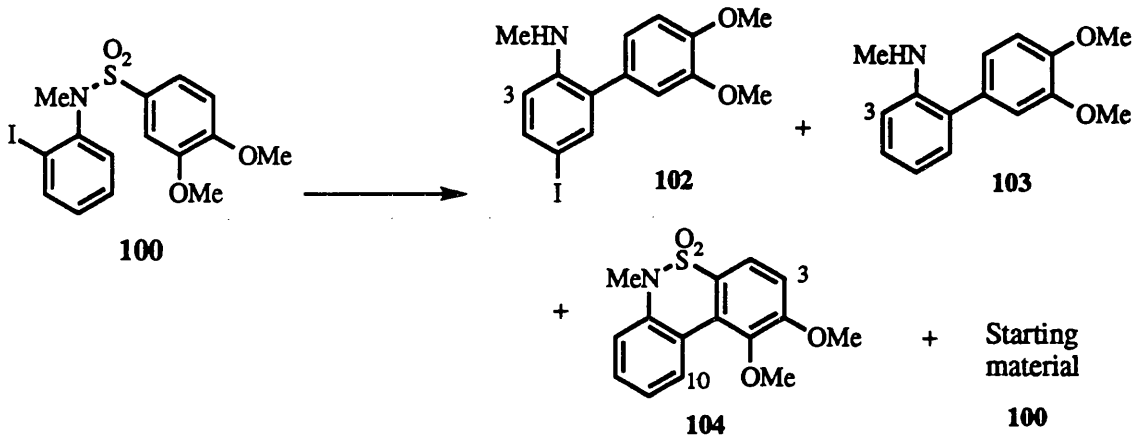
Preparation of *3,4-dimethoxy-N-(2-iodophenyl)-N-methylbenzenesulfonamide* (**100**)



99 **100**

To a stirred suspension of NaH (60% dispersion in mineral oil; 130 mg, 3.2 mmol) in THF (3.5 ml) at r.t. was added a solution of the sulfonamide **99** (0.68 g, 1.6 mmol) in THF (3.5 ml). Vigorous effervescence occurred. After 30 min methyl iodide (0.9 ml, 14 mmol) was added and the reaction mixture stirred for 24 hr. Water (25 ml) was added and the solution extracted with DCM (3x20 ml), dried ($MgSO_4$), the solvent removed under reduced pressure. The residue was chromatographed (DCM) to give the *sulfonamide* **100** (703 mg, 99%) as white prisms; m.p. 170-171 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2926, 1587, 1510, 1462, 1349 (S=O), 1262, 1138 (S=O), 1021; δ_H(270 MHz; $CDCl_3$) 7.91 (1H, dd, *J* 1.5 and 7.8, H-3'), 7.47 (1H, dd, *J* 2.2 and 8.3, H-6), 7.32-7.26 (2H, m, H-5' and H-2), 7.09-6.99 (2H, m, H-6' and H-4'), 6.95 (1H, d, *J* 8.3, H-5), 3.96 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.13 (3H, s, NCH_3); δ_C($CDCl_3$) 152.7 (1C, q), 148.8 (1C, q), 143.7 (1C, q), 140.2 (1C, t), 130.0 (1C, q), 129.8 (1C, t), 128.9 (2C, t), 122.1 (1C, t), 110.8 (1C, t), 110.3 (1C, t), 101.6 (1C, q, C-I), 56.2 (1C, p, OCH_3), 56.1 (1C, p, OCH_3), 38.6 (1C, NCH_3); *m/z* 433 (M^+), 306 (M^+-I), 232, 201, 185 (100%), 137; (Found: M^+, 432.9845. $C_{15}H_{16}INO_4S$ requires *M*, 432.9845).

Reaction of *3,4-dimethoxy-N-(2-iodophenyl)-N-methylbenzenesulfonamide* (**100**) with tri-n-butyltin hydride



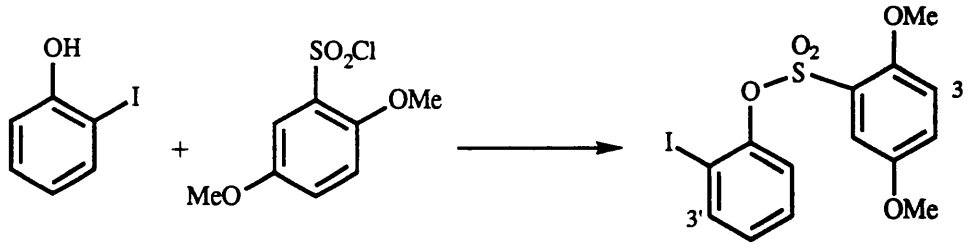
To a stirred solution of the sulfonamide **100** (284 mg, 0.65 mmol) in benzene (13 ml) at reflux, was added a solution of tri-n-butyltin hydride (233 µl, 0.85 mmol) and AIBN (76 mg; 0.46 mmol) in benzene (3.4 ml) dropwise over 18 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue washed with sat. aq. KF (10 ml), extracted with ether (3x20 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue chromatographed (DCM/petrol 75-100%, methanol/DCM 1%) to give in order of elution *N-Methyl-3`,4`-dimethoxy-5-iodo-1,1`-biphenyl-2-amine* (**102**) (5 mg; 2.0%), an inseparable mixture (4:1; 68 mg) of *3`,4`-dimethoxy-N-methyl-1,1`-biphenyl-2-amine* (**103**, 33%) and *dimethoxy-6-methyl-6H-dibenzo[c,e][1,2]thiazine-S,S-dioxide* (**104**, 8%), which was resolved by HPLC, and the *sulfonamide* (**100**) (68 mg; 24%).

*N-methyl-3`,4`-dimethoxy-5-iodo-1,1`-biphenyl-2-amine* (**102**) as yellow prisms, m.p. 110-112 °C; $\nu_{max}$(film)/$cm^{-1}$ 3450 (bs, NH), 2932, 1587, 1503, 1469, 1324, 1208, 1169, 1027; $\delta_H$(270 MHz; $CDCl_3$) 7.49 (1H, dd, *J* 2.2 and 8.5, H-4), 7.35 (1H, dd, *J* 2.2 and 8.5, H-6), 6.95-6.86 (3H, m, H-2`, H-5` and H-6`), 6.44 (1H, d, *J* 8.5, H-3), 3.92 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 2.76 (3H, s, NCH_3); *m/z* 369 (M^+, 100%), 241 (M^+-HI), 226, 183.; FAB 368 (M^+-H); (Found: M^+-H, 368.0143. $C_{15}H_{15}INO_2$ requires *M*, 368.0148).

*3`,4`-dimethoxy-N-methyl-1,1`-biphenyl-2-amine* (**103**) as white prisms, m.p. 95-96 °C; $\nu_{max}$(film)/cm$^{-1}$ 3415 (NH), 2933 (CH), 1504, 1249, 1169; $\delta_H$(400 MHz; $CDCl_3$) 7.25 (1H, dt, *J* 1.6 and 8.1, H-4), 7.08 (1H, dd, *J* 1.5 and 7.6, H-6), 6.94-6.91 (3H, m, H2`, H5` and H6`), 6.75 (1H, dt, *J* 1.1 and 7.5, H-5), 6.67 (1H, d, *J* 8.2, H-3), 4.00 (1H, bs, NH), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 2.79 (3H, s, NCH_3); δ_C($CDCl_3$) 149.1 (1C, q), 148.1 (1C, q), 146.2 (1C, q), 131.9 (1C, q), 129.9 (1C, t), 128.6 (1C, t), 127.4 (1C, q), 121.4 (1C, t), 116.7 (1C, t), 112.6 (1C, t), 111.4 (1C, t), 109.8 (1C, t), 55.9 (2C, p, OCH_3), 30.8 (1C, p, NCH_3); *m/z* 243 (M^+), 84 (100%), 86 (100%); (Found: M^+, 243.1253. $C_{15}H_{17}NO_2$ requires *M*, 243.1259).

1,2-dimethoxy-6-methyl-6H-dibenzo[c,e][1,2]thiazine-S,S-dioxide (**104**) as a clear oil; ν_{max}(film)/cm^{-1} 2941 (CH), 1456, 1325 (S=O), 1264, 1147 (S=O); δ_H(400 MHz; $CDCl_3$) 8.61 (1H, dd, *J* 1.5 and 7.9, H-10), 7.75 (1H, d, *J* 8.6, H-4), 7.46 (1H, dt, *J* 1.5 and 7.5, H-8 or H-9), 7.32-7.27 (2H, m, H-7 and H-8 or H-9), 7.08 (1H, d, *J* 8.7, H-3), 3.97 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.35 (3H, s, NCH_3); δ_C($CDCl_3$) 156.6 (1C, q), 146.3 (1C, q), 139.5 (1C, q), 130.1 (1C, t), 129.9 (1C, t), 128.3 (1C, q), 126.0 (1C, q), 124.6 (1C, t), 122.6 (1C, q), 119.5 (1C, t), 119.4 (1C, t), 111.6 (1C, t), 60.4 (1C, p, OCH_3), 56.3 (1C, p, OCH_3), 32.8 (1C, p, NCH_3); *m/z* 305 (M^+), 290 (M^+-Me), 49 (100%); (Found: MH^+, 306.0803. $C_{15}H_{16}NO_4S$ requires *MH*, 306.0800).

Preparation of *(2-iodophenyl) 2,5-dimethoxybenzenesulfonate* (**105**)

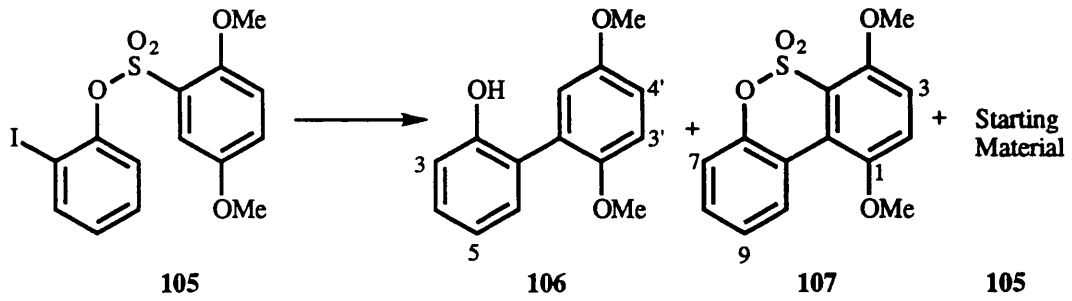


105

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (30 mg) was added a solution of 2,5-dimethoxybenzenesulfonyl chloride (1.3 g, 5.5 mmol) in pyridine (12 ml). The mixture was left under stirring for 2 days at r.t.. Pyridine was removed under reduced pressure the residue dissolved in DCM (25 ml), washed with sat. aq. $CuSO_4$ (2x25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure.

The residue was chromatographed (DCM/petrol 50-75%) to give the *sulfonate* **105** (1.9 g, 88%) as a white prisms, m.p. 74.5-75.5 °C; ν_{max}(film)/cm^{-1} 2945 (CH), 1499, 1373 (S=O), 1170 (S=O), 886, 858, 705; δ_H(270 MHz; $CDCl_3$) 7.76 (1H, dd, *J* 8.1 and 1.7, H-3'), 7.39 (1H, d, *J* 3.2, H-6), 7.27 (1H, ddd, *J* 1.5, 7.3 and 8.3, H-5'), 7.19-7.13 (2H, m, H-6' and H-4), 6.98 (1H, d, *J* 8.8, H-3), 6.94 (1H, dt, *J* 1.5 and 7.8, H-4'), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3); δ_C($CDCl_3$) 152.6 (1C, q), 151.9 (1C, q), 150.6 (1C, q), 139.8 (1C, t), 129.2 (1C, t), 127.9 (1C, t), 124.5 (1C, q), 122.6 (1C, t), 122.4 (1C, t), 115.5 (1C, t), 114.0 (1C, t), 89.5 (1C, q, C-I), 56.5 (1C, p, OCH_3), 55.9 (1C, p, OCH_3); *m/z* 420 (M^+), 201, 137, 122, 107 (100%); (Found: C, 39.7; H, 2.9. $C_{14}H_{13}IO_5S$ requires C, 40.0; H, 3.1%).

Reaction of *(2-iodophenyl) 2,5-dimethoxybenzenesulfonate* (**105**) with tri-n-butyltin hydride



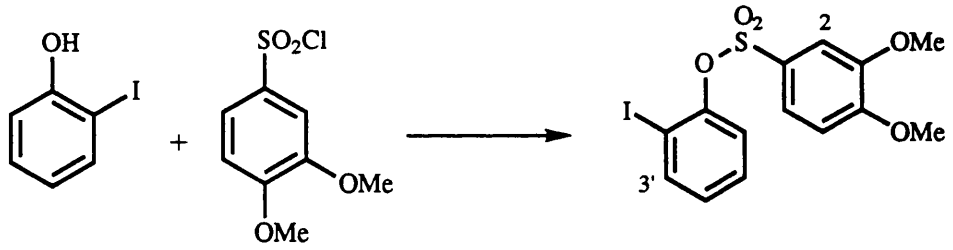
105 **106** **107** **105**

To a stirred solution of the sulfonate **105** (380 mg, 0.90 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to r.t., carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in DCM (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml), dried ($MgSO_4$), concentrated *in vacuo* and the residue chromatographed (ether/petrol 30-100%) to give in order of elution *2',5'-dimethoxy-1,1'-biphenyl-2-ol* (**106**) (90 mg, 43%), the *sulfonate* **105** (121 mg, 32%) and *1,4-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide* (**107**) (17 mg, 7%).

2',5'-dimethoxy-1,1'-biphenyl-2-ol (**106**) as an oil; ν_{max}(film)/cm^{-1} 3393 (OH), 2941 (CH), 1271, 1219; δ_H(400 MHz; $CDCl_3$) 7.33-7.28 (2H, m, H-4 and H-6), 7.06-7.01 (2H, m, H-3 and H-5), 7.00 (1H, d, *J* 8.7, H-3), 6.95-6.90 (2H, m, H-4' and H-6'), 6.54 (1H, bs, OH), 3.84 (3H, s, OCH_3), 3.81 (3H, s, OCH_3); δ_C($CDCl_3$) 154.7 (1C, q), 153.7 (1C, q), 149.6 (1C, q), 131.1 (1C, t), 129.3 (1C, t), 128.3 (1C, q), 126.2 (1C, q), 121.0 (1C, t), 117.7 (1C, t), 117.6 (1C, t), 114.3 (1C, t), 113.4 (1C, t), 57.1 (1C, p, OCH_3), 55.7 (1C, p, OCH_3); *m/z* 230 (M^+, 100%), 215, 200, 184; (Found: M^+, 230.0943. $C_{14}H_{14}O_3$ requires *M*, 230.0943).

1,4-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (**107**) as white prisms, m.p. 155-156 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2944 (CH), 1374 (S=O), 1257, 1175 (S=O); δ_H(270 MHz; $CDCl_3$) 8.48 (1H, dd, *J* 1.7 and 8.1, H-10), 7.44-7.27 (3H, m, H-7, H-8 and H-9), 7.24, (1H, d, *J* 9.3, H-2 or H-3), 7.05 (1H, d, *J* 9.3, H-2 or H-3), 3.97 (3H, s, OCH_3), 3.91 (3H, s, OCH_3); δ_C($CDCl_3$) 150.6 (1C, q), 150.3 (1C, q), 148.2 (1C, q), 130.3 (1C, t), 129.9 (1C, t), 125.8 (1C, t), 123.1 (1C, q), 121.8 (1C, q), 120.4 (1C, q), 119.4 (1C, t), 117.9 (1C, t), 113.6 (1C, t), 57.2 (1C, p, OCH_3), 56.7 (1C, p, OCH_3); *m/z* 292 (M^+, 100%), 277; (Found: M^+, 292.0420 $C_{14}H_{12}O_5S$ requires *M*, 292.0405).

Preparation of *(2-iodophenyl) 3,4-dimethoxybenzenesulfonate* (**108**)

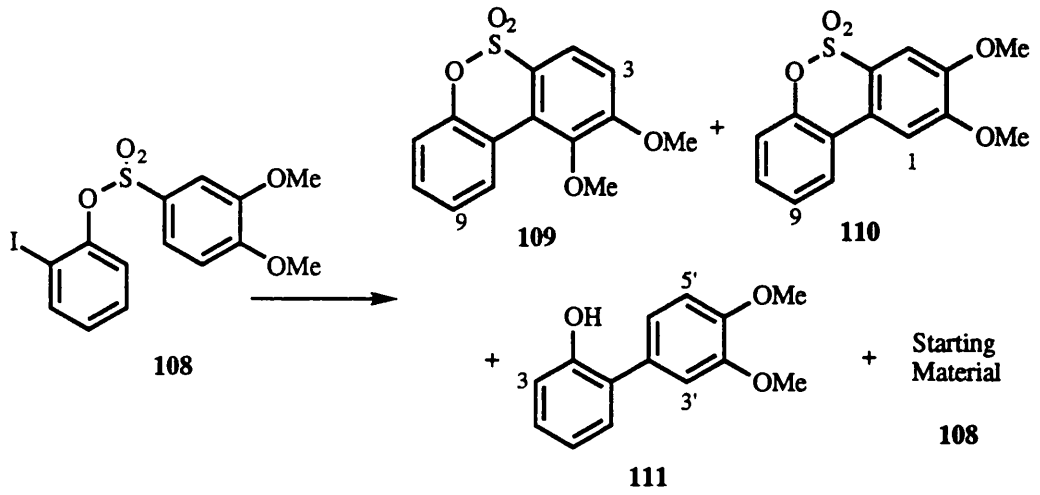


108

To 2-iodophenol (1.1 g, 5.0 mmol) and DMAP (30 mg) was added a solution of 3,4-dimethoxybenzenesulfonyl chloride (1.5 g, 6.5 mmol) in pyridine (10 ml). The mixture was stirred overnight at r.t.. Pyridine was removed *in vacuo*, the residue dissolved in DCM (25 ml), washed with sat. aq. $CuSO_4$ (2x25 ml) and water (20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-75%) to give the *sulfonate* **108** (2.0 g, 96%) as white plates, m.p. 91-92 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2935 (CH), 1508, 1375 (S=O),

1266, 1168 (S=O); δ_H(270 MHz; $CDCl_3$) 7.75 (1H, dd, *J* 1.0 and 7.6, H-3'), 7.51 (1H, dd, *J* 2.0 and 8.5, H-6), 7.35-7.32 (3H, m, H-2, H-5' and H-6'), 6.95-7.00 (1H, m, H-4'), 6.92 (1H, d, *J* 8.5, H-5), 3.95 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); δ_C($CDCl_3$) 154.1 (1C, q), 150.1 (1C, q), 149.1 (1C, q), 140.0 (1C, t), 129.4 (1C, t), 128.3 (1C, t), 126.9 (1C, q), 123.3 (1C, t), 123.0 (1C, t), 111.0 (1C, t), 110.4 (1C, t), 90.2 (1C, q, C-I), 56.3 (2C, p, 2xOCH_3); *m/z* 420 (M^+), 201, 137 (100%); (Found: C, 39.7; H, 3.0. $C_{14}H_{13}IO_5S$ requires C, 40.0; H, 3.1).

Reaction of *(2-iodophenyl) 3,4-dimethoxybenzenesulfonate* (**108**) with tri-n-butyltin hydride



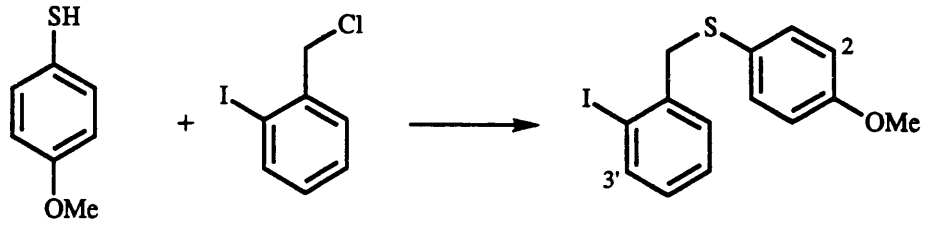
To a stirred solution of the sulfonate **108** (381 mg, 0.90 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (110 mg; 0.67 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to r.t., carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was evaporated under reduced pressure, the residue dissolved in DCM (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (DCM/petrol 60-100%) to give in order of elution *1,2-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide* (**109**) (27 mg, 10%), *2,3-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide* (**110**) (64 mg, 24%) and *3',4'-dimethoxy-1,1'-biphenyl-2-ol* (**111**) (38 mg, 19%)

1,2-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (**109**) as white prisms, m.p. 144.5-145.5 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2945 (CH), 1493, 1414, 1370 (S=O), 1183 (S=O); δ_H(270 MHz; $CDCl_3$) 8.62 (1H, dd, *J* 1.5 and 7.8, H-10), 7.75 (1H, d, *J* 8.5, H-4), 7.49-7.30 (3H, m, H-7, H-8 and H-9), 7.09 (1H, d, *J* 8.5, H-3), 3.99 (3H, s, OCH_3), 3.79 (3H, s, OCH_3); δ_C($CDCl_3$) 157.5 (1C, q), 149.3 (1C, q), 146.6 (1C, q), 130.8 (1C, t), 129.5 (1C, t), 126.4 (1C, t), 125.6 (1C, q), 125.1 (1C, q), 121.0 (1C, t), 120.5 (1C, q), 119.8 (1C, t), 112.0 (1C, t), 60.4 (1C, p, OCH_3), 56.3 (1C, p, OCH_3); *m/z* 292 (M^+, 100%), 277; (Found: M^+, 292.0414. $C_{14}H_{12}O_5S$ requires *M*, 292.0405).

2,3-dimethoxy-dibenz[c,e]oxathiine-S,S-dioxide (**110**) as white needles, m.p. 218 °C (DCM/petrol); ν_{max}($CHCl_3$)/cm^{-1} 2939 (CH), 2850, 1603, 1515, 1368 (S=O), 1170 (S=O), 1030, 861; δ_H(270 MHz; $CDCl_3$) 7.81 (1H, dd, *J* 1.7 and 7.6, H-10), 7.41-7.28 (5H, m, ArH), 4.03 (3H, s, OCH_3), 3.98 (3H, s, OCH_3); δ_C($CDCl_3$) 153.3 (1C, q), 149.7 (1C, q), 149.4 (1C, q), 130.3 (1C, t), 126.4 (1C, t), 125.3 (1C, q), 124.5 (1C, t), 121.5 (1C, q), 119.9 (1C, t), 106.7 (1C, t), 106.0 (1C, t), 56.5 (1C, p, OCH_3), 56.4 (1C, p, OCH_3); *m/z* 292 (M^+, 100%), 277, 228 (M^+-SO_2); (Found: M^+, 292.0420. $C_{14}H_{12}O_5S$ requires *M*, 292.0405).

3',4'-dimethoxy-1,1'-biphenyl-2-ol (**111**) as orange prisms, m.p. 121-122 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3439 (OH), 2935 (CH), 1268, 1220; δ_H(270 MHz; $CDCl_3$) 7.25-7.21 (2H, m, H-4 and H-6), 7.03-6.95 (5H, m, H-3, H-5, H-2', H-5' and H-6'), 5.4 (1H, bs, OH), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3); δ_C($CDCl_3$) 152.5 (1C, q), 149.5 (1C, q), 148.7 (1C, q), 130.0 (1C, t), 129.5 (1C, q), 128.8 (1C, t), 127.9 (1C, q), 121.1 (1C, t), 120.6 (1C, t), 115.6 (1C, t), 112.3 (1C, t), 111.7 (1C, t), 55.9 (2C, p, 2xOCH_3); *m/z* 230 (M^+, 100%), 215; (Found: M^+, 230.0943. $C_{14}H_{14}O_3$ requires *M*, 230.0943).

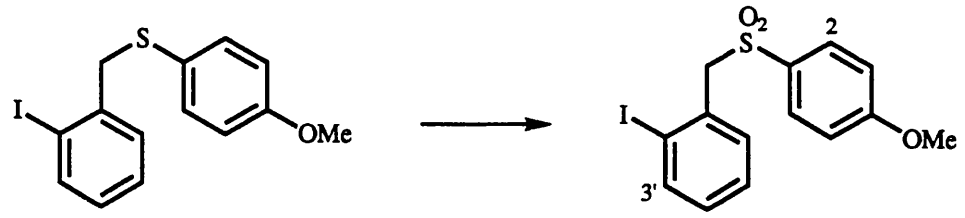
Preparation of *(2-iodophenyl)methyl 4-methoxyphenyl sulfide* **(112)**



112

To a stirred suspension of NaH (60% dispersion in mineral oil; 395 mg, 10 mmol) in THF (19 ml) at 0°C was added 4-methoxythiophenol (1.0 ml, 8.1 mmol). Vigorous effervescence occurred. After 30 min the mixture was allowed to warm to r.t., a solution of 2-iodobenzyl chloride (3.1 g, 12 mmol) in THF (10 ml) was added and the reaction mixture stirred for 24 hr. Water (20 ml) was added and the solution extracted with DCM (3x20 ml), dried ($MgSO_4$), the solvent removed *in vacuo* and the residue chromatographed (DCM/petrol 5-50%) to give the *sulfide* **112** (2.7 g, 91%) as an oil; ν_{max}(film)/cm^{-1} 3056, 3001, 2936 (CH), 1590, 1492, 1285, 1172, 1012, 827; δ_H(270 MHz; $CDCl_3$) 7.38 (1H, dd, *J* 1.2 and 7.8, H-3'), 7.28 (2H, d, *J* 8.9, H-3 and H-5), 7.18 (1H, dt, *J* 1.2 and 7.6, H-5'), 7.05 (1H, dd, *J* 1.7 and 7.6, H-6'), 6.90 (1H, dt, *J* 1.7 and 7.8, H-4'), 6.80 (2H, d, *J* 8.9, H-2 and H-6), 4.08 (2H, s, CH_2), 3.79 (3H, s, OCH_3); δ_C($CDCl_3$) 159.4 (1C, q), 140.4 (1C, q), 139.6(1C, t), 134.8 (2C, t, C-3 and C-5), 130.1 (1C, t), 128.6 (1C, t), 128.0 (1C, t), 125.3 (1C, q), 114.4 (2C, t, C-2 and C-6), 100.6 (1C, q, C-I), 55.2 (1C, p, OCH_3), 46.5 (1C, s, CH_2); *m/z* 356 (M^+), 217 (100%), 139, 90; (Found: C, 47.2; H, 3.5. $C_{14}H_{13}IOS$ requires C, 47.2; H, 3.7%)

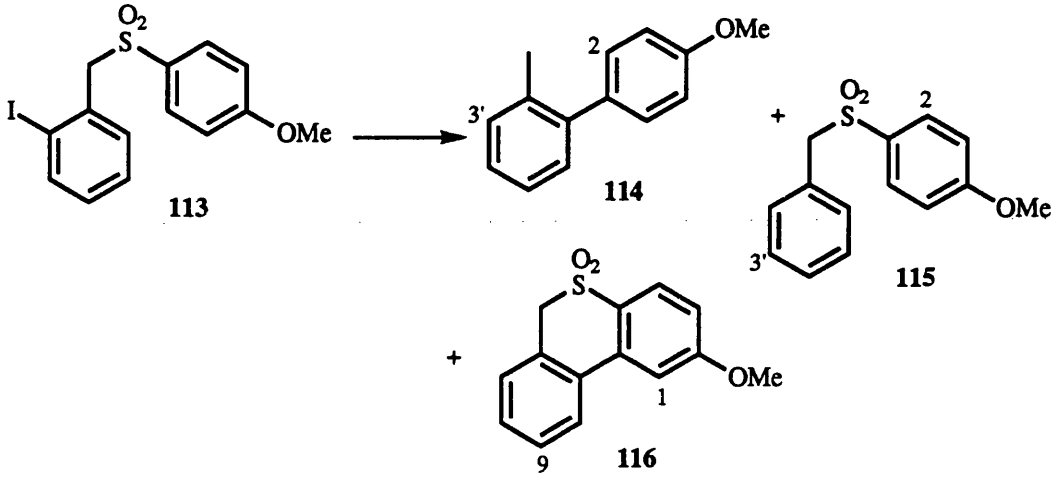
Preparation of *(2-iodophenylmethyl)-(4-methoxyphenyl)sulfone* (**113**)



112 **113**

To *m*-chloroperbenzoic acid (4.6 g, 27 mmol) was added a solution of the sulfide **112** (2.1 g, 6.0 mmol) in DCM (60 ml) at 0 °C. The mixture was allowed to warm to r.t. and left overnight. The mixture was washed with $NaHCO_3$ (50 ml) water (50 ml), dried ($MgSO_4$), the solvent removed *in vacuo* and the residue chromatographed (DCM) to give the *sulfone* **113** (383 mg, 17%) as white prisms, m.p. 134-136 °C (DCM/petrol), ν_{max}(film)/cm^{-1} 2927, 1595, 1495, 1321 (S=O), 1263, 1135 (S=O), 1015, 777; δ_H(270 MHz; $CDCl_3$) 7.73 (1H, dd, *J* 1.2 and 7.8, H-3'), 7.53 (2H, d, *J* 9.0, H-2 and H-6), 7.49 (1H, dd, *J* 1.7 and 7.6, H-6'), 7.35 (1H, dt, *J* 1.2 and 7.3, H-5'), 7.00 (1H, dt, *J* 1.7 and 7.8, H-4'), 6.90 (2H, d, *J* 9.0, H-3 and H-5), 4.56 (2H, s, CH_2), 3.85 (3H, s, OCH_3); δ_C($CDCl_3$) 164.1 (1C, q), 139.8 (1C, t), 132.2 (2C, t and q), 131.2 (2C, t), 130.3 (1C, t), 129.8 (1C, q), 128.5 (1C, t), 114.2 (2C, t), 102.3 (1C, q, C-I), 66.3 (1C, s, CH_2), 55.7 (1C, p, OCH_3); *m/z* 388 (M^+), 324 (M^+-SO_2), 261, 217 (100%), 90; (Found: M^+, 387.9621. $C_{14}H_{13}IO_3S$ requires *M*, 387.9630).

Reaction of *(2-iodophenylmethyl)-(4-methoxyphenyl)sulfone* (**113**) with tri-n-butyltin hydride



To a stirred solution of the sulfone **113** (348 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to r.t., carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed under reduced pressure, the residue dissolved in ethyl acetate (20 ml), washed with sat. aq. KF (2x15 ml) and water (15 ml) dried ($MgSO_4$), concentrated *in vacuo* and the residue chromatographed (ethyl acetate/petrol 15-100%,) to give in order of elution *4-methoxy-2'-methyl-1,1'-biphenyl* (**114**) (18 mg, 10 %), *4-methoxyphenyl phenylmethylsulfone* (**115**) (31 mg, 13%) and *2-methoxy-6H-dibenzo[b,d]thiine-S,S-dioxide* (**116**) (105 mg, 45%).

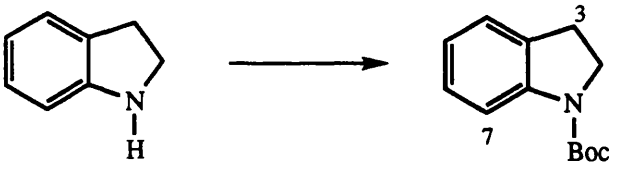
4-methoxy-2'-methyl-1,1'-biphenyl (**114**)[5] as an oil; ν_{max}(film)/cm^{-1} 2930 (CH), 1613, 1515, 1484, 1268, 1244, 1176, 1039, 834, 761; δ_H(270 MHz; $CDCl_3$) 7.19-7.28 (6H, m, H-2', H-3', H-4', H-5', H-2 and H-6), 6.97 (2H, d, *J* 8.8, H-3 and H-5), 3.86 (3H, s, OCH_3), 2.29 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 158.5 (1C, q), 141.5 (1C, q), 135.5 (1C, q), 134.4 (1C, q), 130.3 (1C, t), 130.2 (2C, t), 129.9 (1C, t), 126.9 (1C, t), 125.7 (1C, t), 113.5 (2C, t), 55.3 (1C, p, OCH_3), 20.5 (1C, p, CH_3); *m/z* 198 (M^+, 100%), 183, 167.

4-methoxyphenyl phenylmethylsulfone (**115**) as white prisms m.p. 103-104 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2943 (CH), 1317 (S=O), 1296, 1149 (S=O), 1090, 837,

696; δ_H(270 MHz; $CDCl_3$) 7.52 (2H, d, *J* 9.0, H-2 and H-6), 7.31-7.22 (3H, m, H-3', H-4' and H-5'), 7.08 (2H, dd, *J* 1.7 and 7.8, H-2' and H-6'), 6.88 (2H, d, *J* 9.0, H-3 and H-5), 4.27 (2H, s, CH_2), 3.85 (3H, s, OCH_3); δ_C($CDCl_3$) 163.7 (1C, q), 130.8 (t), 129.4 (1C, q), 128.6 (t), 128.5 (2C, t), 114.1 (1C, q), 114.0 (t), 63.1 (1C, s, CH_2), 55.6 (1C, p, OCH_3); *m/z* 262 (M^+), 198, 91 (100%); (Found: M^+, 262.0664. $C_{14}H_{14}O_3S$ requires *M*, 262.0664).

2-methoxy-6H-dibenzo[b,d]thiine-S,S-dioxide (**116**) as white plates, m.p. 168-169 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2969 (CH), 1595, 1562, 1306 (S=O), 1236, 1192, 1164 (S=O); δ_H(270 MHz; $CDCl_3$) 7.98 (1H, d, *J* 8.8, H-4), 7.80 (1H, d, *J* 7.6, H-10), 7.47 (1H, dt, *J* 1.5 and 7.6 H-8 ou H-9), 7.38 (1H, dt, *J* 1.5 and 7.6, H-8 ou H-9), 7.30 (2H, m, H-1 and H-7), 7.00 (1H, dd, *J* 2.4 and 8.8, H-3), 4.37 (2H, s, CH_2), 3.90 (3H, s, OCH_3); δ_C($CDCl_3$) 163.5 (1C, q), 137.1 (1C, q), 131.0 (1C, q), 130.4 (1C, t), 129.5 (1C, t), 129.4 (1C, t), 128.4 (1C, q), 127.5 (1C, q), 126.2 (1C, t), 126.0 (1C, t), 113.4 (1C, t), 111.9 (1C, t), 22.9 (1C, s, CH_2), 21.6 (1C, p, CH_3); *m/z* 260 (M^+, 100%), 196, 195, 181; (Found: M^+, 260.0493. $C_{14}H_{14}O$ requires *M*, 260.0507).

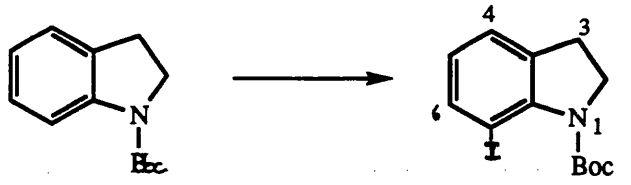
Preparation of *N-(t-butoxycarbonyl)indoline* (**117**)[6]



117

To a solution of di-*tert*-butyl dicarbonate (18 g, 83 mmol) in THF (60 ml) was added a solution of indoline (8.1 g, 68 mmol) in THF (25 ml) and the mixture was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the residue distilled twice by Kugelrohl to give the *indoline* **117** (14 g, 92%) as white prisms, m.p. 47-48 °C (Lit.[6] liquid); ν_{max}(film)/cm^{-1} 2981(CH), 1704 (C=O); δ_H(400 MHz; $CDCl_3$) 7.80 (1H, bs, H-7), 7.13-7.09 (2H, m, H-4 and H-6), 6.88 (1H, dt, *J* 0.9 and 8.3, H-5), 3.95-3.91 (2H, bs, H-2), 3.05 (2H, t, *J* 8.5, H-3), 1.50 (9H, s, $C(CH_3)_3$; *m/z* 219 (M^+), 163, 146, 119.

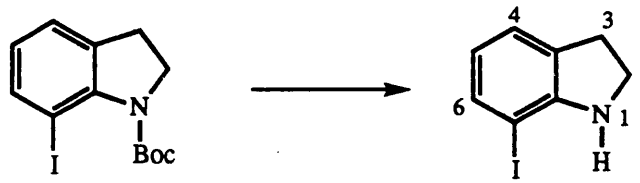
Preparation of *N-(t-butoxycarbonyl)-7-iodoindoline* (**118**)[6]



117 **118**

To a solution of indoline **117** (14 g, 63 mmol) and TMEDA (12.5 ml, 83 mmol) in ether (300 ml), under nitrogen, at -78°C was added *sec*-BuLi in cyclohexane (1.3 M, 75.6 ml), dropwise. After stirring the mixture for 1 hr, a solution of iodine (16 g, 63 mmol) in ether (120 ml) was added and stirring continued for a further 45 min. The cooling bath was removed and after 1.5 hr at room temperature the mixture was quenched with aq. NH_4Cl (10%, 150 ml), extracted with ether (3x100 ml), washed with water (200 ml), brine (200 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 40%) to give the *iodoindoline* **118** (16 g, 76%) as an oil; ν_{max}(film)/cm^{-1} 2976, 1704 (C=O), 1366, 1333, 1245, 1157; δ_H(400 MHz; $CDCl_3$) 7.59 (1H, d, *J* 7.9, H-6), 7.13 (1H, d, *J* 7.3, H-4), 6.71 (1H, t, *J* 7.5, H-5), 4.07 (2H, t, *J* 7.6, H-2), 2.99 (2H, t, *J* 7.6, H-3), 1.54 (9H, s, $C(CH_3)_3$); δ_C($CDCl_3$) 153.0 (1C, q, C=O), 146.3 (1C, q, CN), 138.1 (1C, t), 136.6 (1C, q), 125.7 (1C, t), 124.1 (1C, t), 85.4 (1C, q, C-I), 81.5 (1C, q, $\underline{C}(CH_3)_3$), 51.4 (1C, s, NCH_2), 30.4 (1C, s, $ArCH_2$), 28.3 (3C, p, CH_3); *m/z* 345 (M^+), 290, 272 (M^+-^tBuO), 245 (100%);

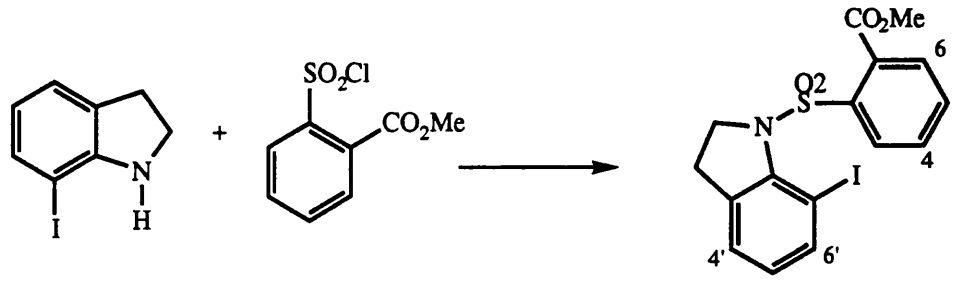
Preparation of *7-iodoindoline* (**119**)



118 **119**

To a stirred solution of the iodoindoline **118**(13 g, 38 mmol) in DCM (30 ml) was added trifluoracetic acid (20 ml) and effervescence occurred. After 5.5 hr the mixture was neutralized with aq $NaHCO_3$ (10%), the organic layer washed with water (2x20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (ether/petrol 10%) to give *7-iodoindoline* (**119**) (7.7 g, 83%) as a clear oil; ν_{max}(film)/cm^{-1} 3374 (NH), 2947, 1602, 1458, 1251, 753; δ_H(400 MHz; $CDCl_3$) 7.35 (1H, dd, *J* 0.9 and 8.0, H-6), 7.04 (1H, dd, *J* 1.1 and 7.2, H-4), 6.44 (1H, dd, *J* 7.3 and 7.9, H-5), 3.89 (1H, bs, NH), 3.62 (2H, t, *J* 8.5, NCH_2), 3.21 (2H, t, *J* 8.5, $ArCH_2$); δ_C($CDCl_3$) 153.4 (1C, q), 135.5 (1C, t), 129.2 (1C, q), 124.2 (1C, t), 120.1 (1C, t), 75.1 (1C, q, C-I), 46.0 (1C, s, NCH_2), 31.3 (1C, s, $ArCH_2$); *m/z* 245 (M^+, 100%), 117 (M^+-HI), 91; (Found: M^+, 244.9709. C_8H_8IN requires *M*, 244.9702).

Preparation of *methyl 2-(7-iodoindoline-N-sulfonyl)benzoate* (**120**)

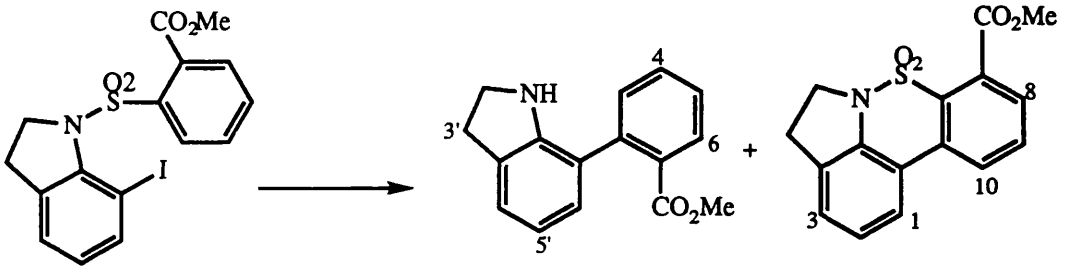


119 **120**

To 7-iodoindoline (**119**) (1.2 g, 5.1 mmol) and DMAP (59 mg) was added a solution of methyl 2-(chlorosulfonyl)benzoate (1.5 g, 6.2 mmol) in pyridine (10 ml)

and the mixture stirred at r.t. for 20 hr. The pyridine was removed under reduced pressure, the residue dissolved in DCM (50 ml), washed with a sat. solution of $CuSO_4$ (2x25 ml), water (30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was cromathographed (DCM/petrol 80%) to give the *sulfonamide* **120** (1.2 g, 52%) as white prisms, m.p. 194-195 °C; ν_{max}(film)/cm^{-1} 2960 (CH), 1734 (C=O), 1361 (S=O), 1297, 1259, 1169 (S=O); δ_H(400 MHz; $CDCl_3$) 7.70 (1H, dd, *J* 0.9 and 7.9, H-6), 7.57 (1H, dt, *J* 1.2 and 7.5, H-4), 7.52 (1H, dd, *J* 0.9 and 8.1, H-3), 7.48 (1H, dd, *J* 1.2 and 7.5, H-6'), 7.40 (1H, dt, *J* 1.4 and 8.1, H-5), 7.09 (1H, dd, *J* 1.0 and 7.4, H-4'), 6.85 (1H, t, *J* 7.8, H-5'), 4.12 (2H, t, *J* 7.1, NCH_2), 3.93 (3H, s, CO_2CH_3), 2.52 (2H, t, *J* 7.1, $ArCH_2$); δ_C($CDCl_3$) 168.4 (1C, q, C=O), 145.6 (1C, q), 139.4 (1C, q), 139.1 (1C, t), 135.9 (1C, q), 133.3 (1C, q), 133.0 (1C, t), 129.9 (1C, t), 129.5 (1C, t), 128.3 (2C, t), 124.6 (1C, t), 87.9 (1C, q, C-I), 53.3 (1C, p, OCH_3), 52.4 (1C, s), 30.6 (1C, s); *m/z* 443 (M^+), 412 (M^+-OMe), 199 (100%), 117 (100%); (Found: C, 43.2; H, 3.1; N, 3.0. $C_{16}H_{14}INO_4S$ requires C, 43.35; H, 3.2; N, 3.2%).

Reaction of *methyl 2-(7-iodoindoline-N-sulfonyl)benzoate* (**120**) with tri-n-butyltin hydride



120 **129** **130**

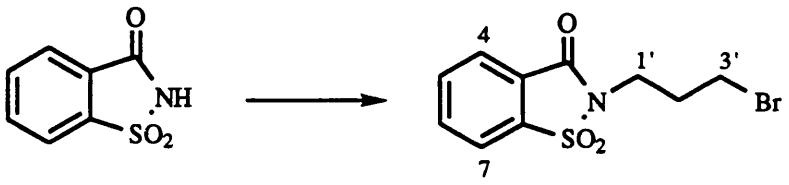
To a stirred solution of **120** (399 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butultin hydride (320 µl, 1.17 mmol) and AIBN (106 mg; 0.64 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After a further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and vigorous stirring continued for 2 hr. The suspension was filtered, the ethyl acetate layer washed with sat. aq. KF (15 ml) and water (15 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 6-20%,) to give in order of elution

methyl 2-[indolin-7-yl]benzoate (**129**) (29 mg, 13%), the *sulfonamide* **120** (39 mg, 10%) and *methyl 4,5-dihydro-dibenzo[c,e]pyrro[1,2-b]thiazine-S,S-dioxide-7-carboxylate* (**130**) (110 mg, 39%).

methyl 2-[indolin-7-yl]benzoate (**129**) as brown prisms, m.p. 78-79 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3368 (NH), 2949, 1722 (C=O), 1454, 1305, 1251, 1114, 753; δ_H (400 MHz; $CDCl_3$) 8.21 (1H, s, H-6), 7.95 (1H, d, *J* 7.9, H-4), 7.73 (1H, d, *J* 7.7, H-3), 7.47 (1H, t, *J* 7.7, H-5), 7.11 (1H, d, *J* 7.2, ArH), 7.08 (1H, d, *J* 7.6, ArH), 6.78 (1H, t, *J* 7.4, ArH), 3.91 (3H, s, CO_2CH_3), 3.53 (2H, t, *J* 8.3, H-2'), 3.08 (2H, t, *J* 8.3, H-3'); δ_C ($CDCl_3$) 167.0 (1C, q, C=O), 148.9 (1C, q), 139.8 (1C, q), 132.4 (1C, t), 130.6 (1C, q), 129.9 (1C, q), 128.9 (1C, t), 128.8 (1C, t), 127.9 (1C, t), 127.3 (1C, t), 124.1 (1C, t), 121.8 (1C, q), 119.1 (1C, t), 52.2 (1C, p, OCH_3), 47.2 (1C, s, NCH_2), 29.9 (1C, s, $ArCH_2$); *m/z* 253 (M^+, 100%), 220, 193; (Found: M^+, 253.1103. $C_{16}H_{15}NO_2$ requires *M*, 253.1103).

methyl 4,5-dihydro-dibenzo[c,e]pyrro[1,2-b]thiazine-S,S-dioxide-7-carboxylate (**130**) as white prisms, m.p. 194-196 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2953, 1736 (C=O), 1324 (S=O), 1165 (S=O); δ_H (400 MHz; $CDCl_3$) 8.02 (1H, dd, *J* 1.2 and 8.0, H-8), 7.70 (1H, t, *J* 7.9, H-9), 7.69 (1H, d, *J* 7.7, H-1), 7.60 (1H, dd, *J* 1.2 and 7.6, H-10), 7.28 (1H, d, *J* 7.4, H-3), 7.15 (1H, t, *J* 7.7, H-2), 4.25 (2H, t, *J* 8.5, NCH_2), 3.99 (3H, s, CO_2CH_3), 3.32 (2H, t, *J* 8.5, $ArCH_2$); δ_C ($CDCl_3$) 167.5 (1C, q, C=O), 141.7 (1C, q), 133.6 (2C, q), 132.2 (1C, t), 131.1 (2C, q), 128.1 (1C, t), 126.7 (1C, t), 126.3 (1C, t), 124.2 (1C, t), 122.1 (1C, t), 117.9 (1C, q), 53.4 (1C, p, OCH_3), 44.9 (1C, s, NCH_2), 28.3 (1C, s, $ArCH_2$); *m/z* 315 (M^+), 199, 118, 117, 43 (100%); (Found: M^+, 315.0565. $C_{16}H_{13}NO_4S$ requires *M*, 315.0565).

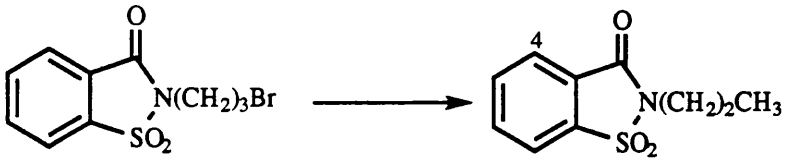
Preparation of N-*(3-bromopropyl)saccharine* (**131**)



131

To a stirred suspension of NaH (60% dispersion in mineral oil; 602 mg, 15 mmol) in DMF (15 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 30 min 1,3-dibromopropane (3.0 ml, 30 mmol) was added and the reaction mixture heated at 100 °C for 1 hr. The mixture was cooled and the solvent removed under reduced pressure. Water was added (40 ml), the solution extracted with DCM (3x20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 5-25%) to give *N-(3-bromopropyl)saccharine* (**131**) (1.8 g; 61%); as white plates, m.p. 87-90 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2937, 1731 (C=O), 1594, 1463, 1334, 1181; δ_H(270 MHz; $CDCl_3$) 7.80-8.09 (4H, m, ArH), 3.94 (2H, t, *J* 6.8, H-3`), 3.50 (2H, t, *J* 6.6, H-1`), 2.40 (2H, qt, *J* 6.6, H-2`); *m/z* 305 ($[M+2]^+$), 303 (M^+), 224 (M^+-Br), 196 (100%), 159, 104; (Found M^+, 304.9544. $C_{10}H_{10}Br^{81}NO_3S$ requires *M*, 304.9524).

Reaction of *N-(3-bromopropyl)saccharine* (**131**) with tri-n-butyltin hydride

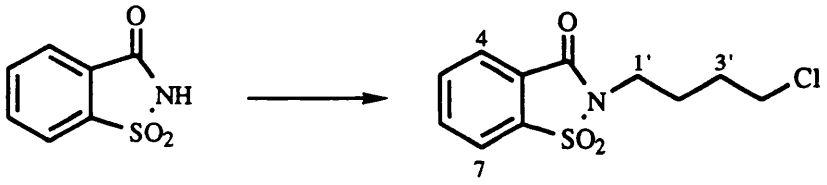


131 **132**

To a stirred solution of N-(3-bromopropyl)saccharine (**131**) (297 mg, 0.97 mmol) in benzene (20 ml) under reflux, was added a solution of tri-n-butyltin hydride (350 µl, 1.28 mmol) and AIBN (120 mg, 0.7 mmol) in benzene (5 ml), dropwise, over

11 hr, *via* a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed *in vacuo* the residue dissolved in DCM (30 ml), washed with sat. aq. KF (3x20 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 20%) to give *N-propyl saccharine* (**132**) (83 mg, 38%) as white plates, m.p. 69-72 °C; ν_{max}(film)/cm^{-1} 1731 (C=O), 1333 (S=O), 1184 (S=O); δ_H(270 MHz; $CDCl_3$) 8.06 (1H, dd, *J* 1.7 and 6.4, H-7), 7.79-7.94 (3H, m, ArH), 3.75 (2H, t, *J* 7.6, H-1'), 1.89 (2H, q, *J* 7.6, H-2'), 1.02 (3H, t, *J* 7.6, CH_3); *m/z* 225 (M^+), 210, 196 (100%); (Found M^+, 225.0460. $C_{10}H_{11}NO_3S$ requires *M*, 225.0460).

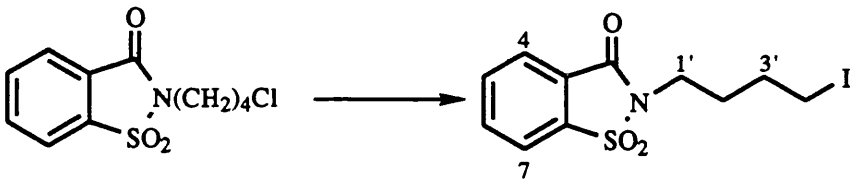
Preparation of *N-(4-chlorobutyl)saccharine* (**133**)[7]



133

To a stirred suspension of NaH (60% dispersion in mineral oil; 600 mg, 15 mmol) in DMF (15 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 30 min. 1-bromo-4-chlorobutane (2.8 ml, 24 mmol) was added and the reaction mixture heated at 110°C for 1hr. The mixture was cooled and the solvent removed *in vacuo*. The residue was dissolved in DCM (50 ml), washed with water (3x20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give *N-(4-chlorobutyl)saccharine* (**133**) (1.8 g, 66%) as white prisms, m.p. 63-64 °C; ν_{max}(film)/cm^{-1} 2944, 1730 (C=O), 1595, 1461, 1336 (S=O), 1183 (S=O); δ_H(270 MHz; $CDCl_3$) 8.05 (1H, dd, *J* 1.7 and 5.9, H-7), 7.80-7.94 (3H, m, ArH), 3.82 (2H, t, *J* 6.8, H-1'), 3.59 (1H, t, *J* 6.1, H-4'), 3.46 (1H, t, *J* 6.1, H-4'), 1.56-2.08 (4H, m, H-2' and H-3'); *m/z* 273 (M^+), 238, 196(100%);

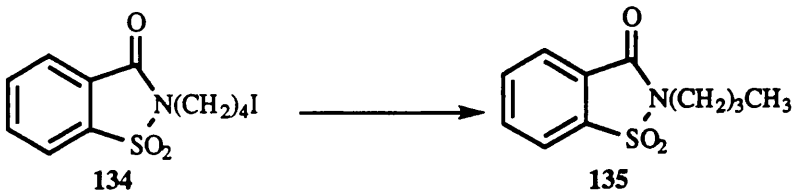
Preparation of *N-(4-iodobutyl)saccharine* (**134**)



133 **134**

To sodium iodide (1.7 g, 11 mmol) was added a solution of N-(4-chlorobutyl)saccharine (**133**) (1.5 g, 5.5 mmol) in acetone (7 ml) and the mixture refluxed overnight. The mixture was then cooled and ether (6 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (40 ml), washed with NaOH (2%; 2x25 ml), water (25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give *N-(4-iodobutyl)saccharine* (**134**) (1.8 g, 90%) as white prisms, m.p. 65-67 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2935, 1728 (C=O), 1460, 1333 (S=O), 1183 (S=O); δ_H(270 MHz; $CDCl_3$) 8.06 (1H, dd, *J* 1.7 and 6.3, H-7), 7.80-7.94 (3H, m, H-4, H-5 and H-6), 3.81 (2H, t, *J* 6.6, H-1'), 3.23 (2H, t, *J* 6.6, H-4'), 1.90-2.01 (4H, m, H-2' and H-3'); *m/z* 238 (M^+-I), 196 (100%), 184; (Found: C, 36.3; H, 3.3; N, 3.8. $C_{11}H_{12}INO_3S$ requires C, 36.2; H, 3.3; N, 3.8%).

Reaction of *N-(4-iodobutyl)saccharine* (**II-19**) with tri-n-butyltin hydride

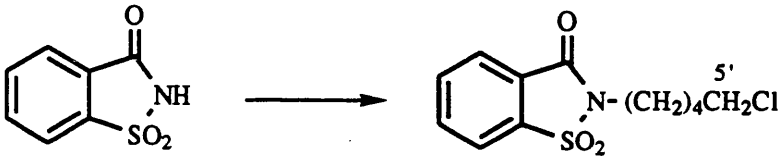


134 **135**

To a stirred solution of N-(4-iodobutyl)saccharine (**134**) (331 mg, 0.9 mmol) in benzene (18 ml) under reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (114 mg, 0.7 mmol) in benzene (4.7 ml), dropwise, over 11hr,

via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed *in vacuo* and analysis of the ^1H nmr spectrum of the crude mixture showed reduced product *N-butyl-saccharine* (**135**); δ_H(270 MHz; $CDCl_3$) 8.05 (dd, *J* 1.7 and 7.3), 7.93-7.81 (m), 3.78 (t, *J* 7.5, N-CH_2).

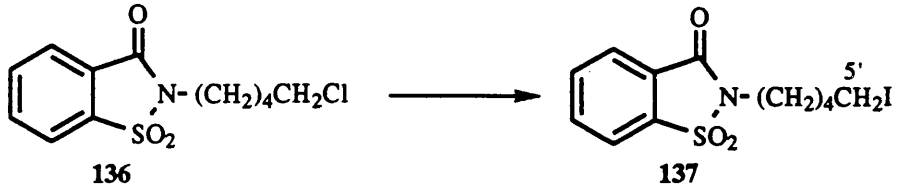
Preparation of *N-(5-chloropentyl)saccharine* (**136**)



136

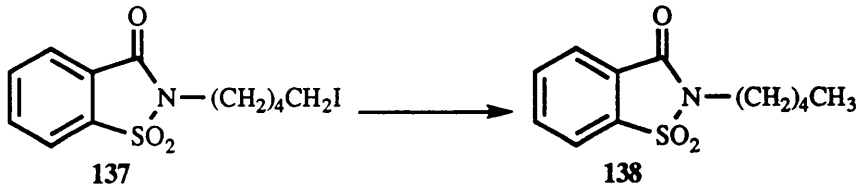
To a stirred suspension of NaH (60% dispersion in mineral oil; 600 mg, 15 mmol) in DMF (12 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 1 hr 1-bromo-5-chloropentane (3.3 ml, 25 mmol) was added and the reaction mixture heated at 100 °C for 2 hr. The mixture was cooled and the solvent removed *in vacuo*. The residue was dissolved in DCM (50 ml), washed with water (3x20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give *N-(5-chloropentyl)saccharine* (**136**) (1.7 g, 60%) as a clear oil; ν_{max}(film)/cm^{-1} 2940, 1731 (C=O), 1596, 1461, 1335 (S=O), 1183 (S=O); δ_H(270 MHz; $CDCl_3$) 8.06 (1H, dd, *J* 1.7 and 6.3, H-7), 7.82-7.94 (3H, m, ArH), 3.79 (2H, t, *J* 7.5, H-1'), 3.54 (1H, t, *J* 6.6, H-5'), 3.41 (1H, t, J 6.6, H-5'), 1.96-1.82 (4H, m, H-2' and H-4'), 1.63-1.54 (2H, m, H-3'); *m/z* 287 (M^+), 252, 196 (100%), 184; (Found: MNH_4^+, 305.0727. $C_{12}H_{18}Cl^{35}N_2O_3S$ requires *MNH4*, 305.0727).

Preparation *N-(5-iodopentyl)saccharine* (**137**)



To sodium iodide (1.5 g, 10 mmol) was added a solution of N-(5-chlorobutyl)saccharine (**136**) (1.4 g, 5 mmol) in acetone (5 ml) and the mixture refluxed overnight. The mixture was then cooled, ether (6 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (40 ml), washed with an aq. solution of NaOH (2%, 2x25 ml), water (25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give *N-(5-iodopentyl)saccharine* (**137**) (1.7 g, 87%) as white prisms, m.p. 62-63 °C (DCM/petrol), ν_{max}(film)/cm^{-1} 2937, 1636 (C=O), 1334 (S=O), 1259, 1185 (S=O); δ_H (270 MHz; $CDCl_3$) 8.05 (1H, m, H-7), 7.82-7.94 (3H, m, ArH), 3.78 (2H, m, H-1'), 3.20 (2H, m, H-5'), 1.94-1.82 (4H, m, H-2' and H-4'), 1.59-1.54 (2H, m, H-3'); *m/z* 252 (M^+-I), 196, 184, 68 (100%); (FAB) 380 (MH^+); (Found: M^+, 379.9813. $C_{12}H_{15}INO_3S$ requires *M*, 379.9817).

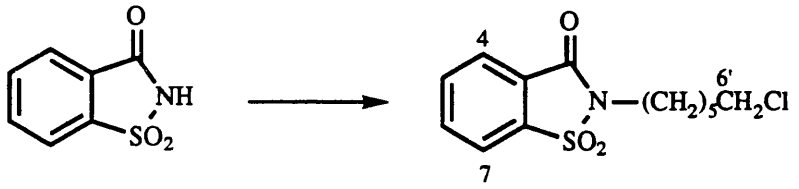
Reaction of *N-(5-iodopentyl)saccharine* (**137**) with tri-n-butyltin hydride



To a stirred solution of N-(5-iodopentyl)saccharine (**137**) (343 mg, 0.9 mmol) in benzene (18 ml) under reflux, was added a solution of tri-n-butyltin hydride (310 µl, 1.13 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After a further hour, the reaction was

cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed *in vacuo* the residue dissolved in DCM (25 ml), washed with KF (3x20 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Analysis of the ^1H nmr spectrum of the crude mixture showed reduced product *N-pentyl-saccharine* (**138**); δ_H(270 MHz; $CDCl_3$) 8.1 (dd, *J* 1.7 and 7.3), 8.0-7.8 (m), 3.8 (t, *J* 7.5, N-CH_2).

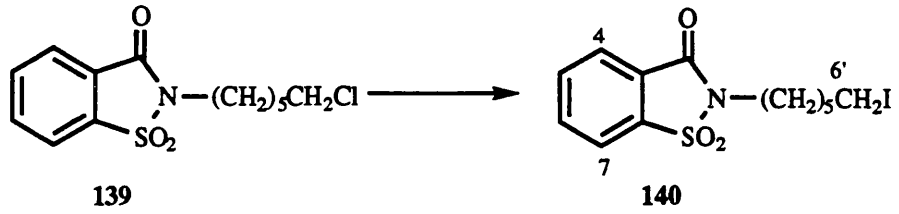
Preparation of *N-(6-chlorohexyl)saccharine* (**139**)



139

To a stirred suspension of NaH (60% dispersion in mineral oil; 600 mg, 15 mmol) in DMF (13 ml) at room temperature was added a solution of saccharine (1.8 g, 10 mmol) in DMF (17 ml). Vigorous effervescence occurred. After 1 hr 1-bromo-6-chlorohexane (3.1 ml, 20 mmol) was added and the reaction mixture heated at 100 °C for 1.5 hr. The mixture was cooled and the solvent removed under reduced pressure Water was added (50 ml) and the solution extracted with DCM (3x50 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 70-100%) to give *N-(6-chlorohexyl)saccharine* (**139**) (1.7 g, 55%) as white prisms, m.p. 61-63 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2938, 2862, 1730 (C=O), 1595, 1462, 1336 (S=O), 1184 (S=O); δ_H(270 MHz; $CDCl_3$) 8.06 (1H, dd, *J* 6.4 and 1.7, H-7), 7.80-7.94 (3H, m, ArH), 3.78 (2H, t, *J* 7.3, H-1'), 3.53 (1H, t, *J* 6.6, H-6'), 3.40 (1H, t, *J* 6.6, H-6'), 1.92-1.74 (4H, m, H-2' and H-5'), 1.57-1.41 (4H, m, H-3' and H-4'); *m/z* 301 (M^+), 266, 252, 238, 224, 210, 196 (100%), 184; (FAB) 304, 302 (MH^+); (Found: MH^+, 302.0614. $C_{13}H_{17}Cl^{35}NO_3S$ requires *MH*, 302.0618).

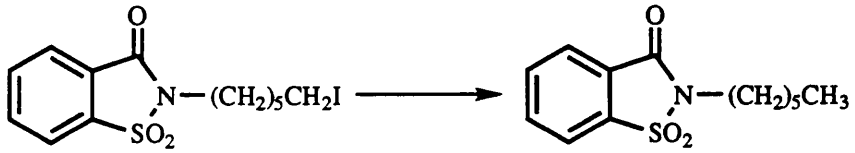
Preparation of *N-(6-iodohexyl)saccharine* (**140**)



139 **140**

To sodium iodide (1.5 g, 10 mmol) was added a solution of N-(6-chlorohexyl)saccharine (**139**) (1.5 g, 5 mmol) in acetone (5.5 ml) and the mixture refluxed overnight. The mixture was then cooled, ether (6 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in ether (40 ml), washed with an aq. solution of sodium thiosulphate (10%, 25 ml), water (25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give *N-(6-iodohexyl)saccharine* (**140**) (1.3 g, 69%) as white prisms, m.p. 70-73 °C; ν_{max}(film)/cm^{-1} 2935, 2859, 1731 (C=O), 1336 (S=O), 1184 (S=O); δ_H(270 MHz; $CDCl_3$) 8.06 (1H, dd, *J* 6.4 and 1.7, H-7), 7.79-7.94 (3H, m, ArH), 3.53 (2H, t, *J* 6.6, H-1'), 3.18 (2H, t, *J* 6.8, H-6'), 1.92-1.77 (4H, m, H-2' and H-5'), 1.57-1.40 (4H, m, H-3' and H-4'); *m/z* (EI) 266 (M^+-I), 196, 184, 82 (100%); FAB 394 (MH^+); (Found: MH^+, 393.9970. $C_{13}H_{17}INO_3S$ requires *MH*, 393.9974).

Reaction of N-(6-iodohexyl)saccharine (**140**) with tri-n-butyltin hydride

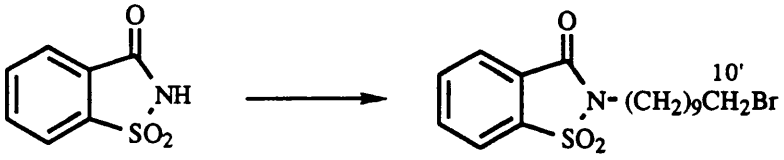


140 **141**

To a stirred solution of N-(6-iodohexyl)saccharine (**140**) (353 mg, 0.9 mmol) in benzene (18 ml) under reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (107 mg, 0.65 mmol) in benzene (4.7 ml), dropwise, over 11 hr,

via a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed *in vacuo* the residue dissolved in DCM (25 ml), washed with sat. aq. KF (3x20 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Analysis of the ^1H nmr spectrum of the crude mixture showed reduced product (**141**) δ_H(270 MHz, $CDCl_3$) 8.02 (dd, *J* 1.7 and 6.4), 7.90-7.76 (m), 3.74 (t, *J* 7.6, N-CH_2); and traces of benzylic protons δ 2.48 (t).

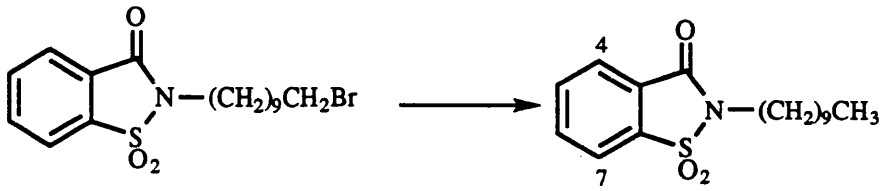
Preparation of *N-(10-bromodecyl)saccharine* (**142**)



142

To a stirred suspension of NaH (60% dispersion in mineral oil; 399 mg; 10 mmol) in DMF (14 ml) at room temperature was added a solution of saccharine (1.8 g; 10 mmol) in DMF (15 ml). Vigorous effervescence occurred. After 1.5 hr 1,10-dibromodecane (4.6 ml; 20 mmol) was added and the reaction mixture heated at 100 °C for 2 hr. The mixture was cooled and the solvent removed *in vacuo*. Water was added (50 ml) and the solution extracted with DCM (3x50 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 25-100%) to give *N-(10-bromodecyl)saccharine* (**142**) (2.7 g, 67%) as white prisms, m.p. 41-42 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3447, 2929, 2855, 1730 (C=O), 1336 (S=O), 1183 (S=O); δ_H (270 MHz; $CDCl_3$) 8.07-7.81 (4H, m, ArH), 3.76 (2H, t, *J* 7.6, H-1'), 3.40 (2H, t, *J* 7.8, H-10'), 1.89-1.79 (4H, m, H-2' and H-9'), 1.43-1.23 (12H, m, H-3',H-4',H-5',H-6',H-7', and H-8'); *m/z* 322 (M^+-Br), 258, 184 (100%); (Found: C, 50.7; H, 5.6; N, 3.3. $C_{17}H_{24}BrNO_3S$ requires C, 50.75; H, 6.0; N, 3.5).

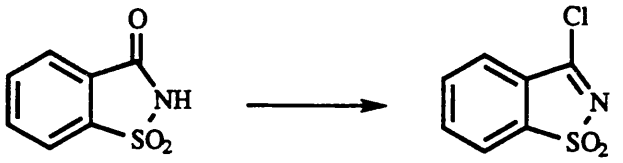
Reaction of *N-(10'-bromodecyl)saccharine* (**142**) with tri-n-butyltin hydride



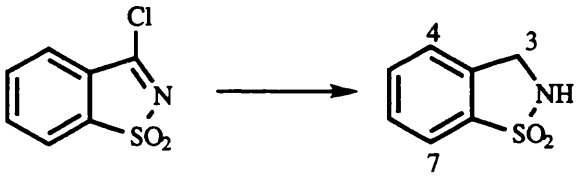
142 **143**

To a stirred solution of N-(10'-bromodecyl)saccharine (**142**) (367 mg, 0.9 mmol) in benzene (18 ml) at reflux was added a solution of tri-n-butyltin hydride and AIBN (106 mg, 0.65 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed *in vacuo* the residue dissolved in ether (30 ml), washed with sat. aq. KF (3x20 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give *N-decyl-saccharine* (**143**) (196 mg, 66%) as a clear oil; ν_{max}(film)/cm^{-1} 2925, 2855, 1737 (C=O), 1338 (S=O), 1184 (S=O); δ_H (400 MHz; $CDCl_3$) 8.03 (1H, dd, *J* 1.8 and 7.0, H-7), 7.90 (1H, dd, *J* 1.7 and 7.0, H-4), 7.86-7.78 (2H, m, H-5 and H-6), 3.74 (2H, t, *J* 7.7, H-1'), 1.85 (2H, qt, *J* 7.6, H-2'), 1.42-1.24 (14H, 7xCH_2), 0.85 (3H, t, *J* 7.0, CH_3); δ_C ($CDCl_3$) 158.9 (1C, q, C=O), 137.7 (1C, q), 134.6 (1C, t), 134.2 (1C, t), 127.4 (1C, q), 125.1 (1C, t), 120.9 (1C, t), 39.5 (1C, s), 31.8 (1C, s), 29.5 (1C, s), 29.4 (1C, s), 29.2 (1C, s), 29.0 (1C, s), 28.4 (1C, s), 26.8 (1C, s), 22.7 (1C, s), 14.1 (1C, p, CH_3); *m/z* 323 (M^+), 196 (100%), 184 (100%), 133 (100%); (Found MNH_4^+, 341.1899. $C_{17}H_{29}N_2O_3S$ requires *MNH4*, 341.1899).

Preparation of *2,3-dihydro-1,2-benzisothiazole-1,1-dioxide* (**144**)[8,9]



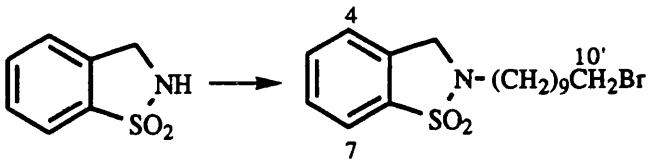
A mixture of saccharine (35 g, 0.2 mol) and phosphorous pentachloride (70 g; 0.3 mol), was heated at 175-180°C for 90 min; at the end of this period the evolution of HCl had ceased. $POCl_3$ was removed by distillation, the residue poured onto ice (100ml), extracted with DCM (3x100 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to give *pseudosaccharine chloride*, which was used without further purification.



144

Sodium borohydride (4.1 g, 108 mmol) was added in small portions to a solution of pseudosaccharine chloride (**II-11**) (5.0 g, 27 mmol) in THF (100 ml) at 0 °C. After stirring the mixture for 24 hr at r.t., water (15 ml) was added while cooling, the solvent was removed *in vacuo* and the mixture was further hydrolysed with HCl (4 N) until pH 4. The aqueous layer was extracted with DCM (3x75 ml), combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to give *2,3-dihydro-1,2-benzisothiazole-1,1-dioxide* (**II-12**) as white plates, m.p. 110-112 °C (DCM/petrol) (Lit.[9]; 110-112 °C); ν_{max}(film)/cm^{-1} 3267 (NH), 1288 (S=O), 1164 (S=O); δ_H(270 MHz; $CDCl_3$) 7.82 (1H, d, *J* 7.6, H-7), 7.63 (1H, t, *J* 7.6, H-5), 7.54 (1H, t, *J* 7.6, H-6), 7.41 (1H, t, *J* 7.6, H-4), 4.70 (1H, bs, NH), 4.55 (2H, d, *J* 4.2, CH_2); *m/z* 169 (M^+, 100%), 168, 104.

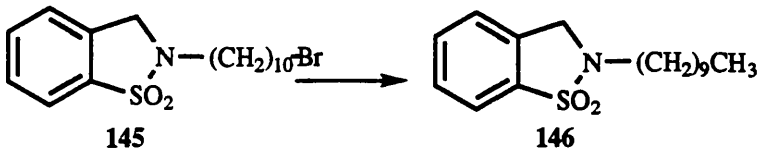
Preparation of *2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide* (**145**)



144 **145**

To a stirred suspension of NaH (60% dispersion in mineral oil; 46 mg, 2.4 mmol) in DMF (2.5 ml) at room temperature was added a solution of 2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (**144**) (336 mg, 2.0 mmol) in DMF (3 ml). Vigorous effervescence occurred. After 30 min 1,10-dibromodecane (0.7 ml, 3.1 mmol) was added and the reaction mixture heated at 100 °C for 2 hr. The mixture was then cooled and the solvent removed under reduced pressure. Water was added (15 ml) and the solution extracted with DCM (3x10 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give *2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide* (**145**) (426 mg, 55%) as a clear oil; ν_{max}(film)/cm^{-1} 2930, 2854, 1296 (S=O), 1171 (S=O); δ_H(270 MHz; $CDCl_3$) 7.81 (1H, d, *J* 7.3, H-7), 7.49-7.62 (2H, m, H-5 and H-6), 7.38 (1H, d, *J* 7.6, H-4), 4.35 (2H, s, NCH_2), 3.40 (2H, t, *J* 6.8, H-1' or H-10'), 3.28 (2H, t, *J* 7.6, H-1' or H-10'), 1.90-1.68 (4H, m, H-2' and H-9'), 1.55-1.25 (12H, m, H-3' to H-8'); *m/z* (FAB) 390, 388 (MH^+); (Found: MH^+, 388.0942. $C_{17}H_{27}Br^{79}NO_2S$ requires *MH*, 388.0946).

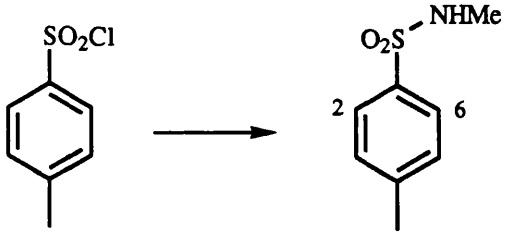
Reaction of *2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide* (**145**) with tri-n-butyltin hydride



145 **146**

To a stirred solution of 2-(10-bromodecyl)-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (**145**) (273 mg, 0.7 mmol) in benzene (14 ml) at reflux was added a solution of tri-n-butyltin hydride (250 µl, 0.9 mmol) and AIBN (84 mg, 0.5 mmol) in benzene (3.6 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After a further hour, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 1 hr. The solvent was removed *in vacuo* and analysis of the ^1H nmr spectrum showed peaks corresponding to the reduced product **146** at δ_H(270 MHz, $CDCl_3$) 7.80 (d), 7.62-7.45 (m), 7.38 (d), 4.35 (s), 3.28 (t).

Preparation of *N-methyl -p-toluenesulfonamide* (**150**)

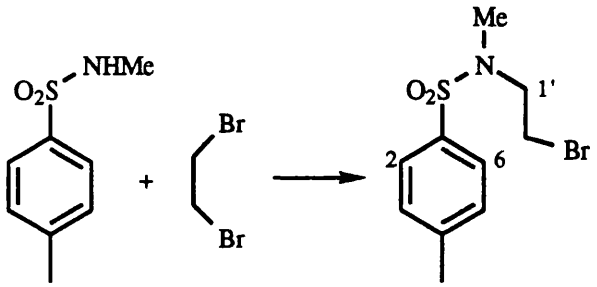


150

To a suspension of *p*-toluenesulfonyl chloride (1.9 g, 10 mmol) in aq. NaOH (10%, 14 ml) was added methylamine (25-30% in water, 2.8 ml) and the mixture stirred vigorously for 23 hr. The reaction mixture was diluted with water (20 ml), extracted with DCM (3x25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure, to give the *sulfonamide* **150** (1.5 g, 83%) as white prisms, m.p. 79-80 °C (DCM/petrol);

ν_{max} (film)/cm^{-1} 3294 (NH), 1319 (S=O), 1157 (S=O); δ_H (270 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.3, H-2 and H-6), 7.32 (2H, d, *J* 8.3, H-3 and H-5), 4.37 (1H, bs, NH), 2.64 (3H, d, *J* 5.4, NCH_3), 2.43 (3H, s, $ArCH_3$); *m/z* 185 (M^+), 155, 139, 91 (100%).

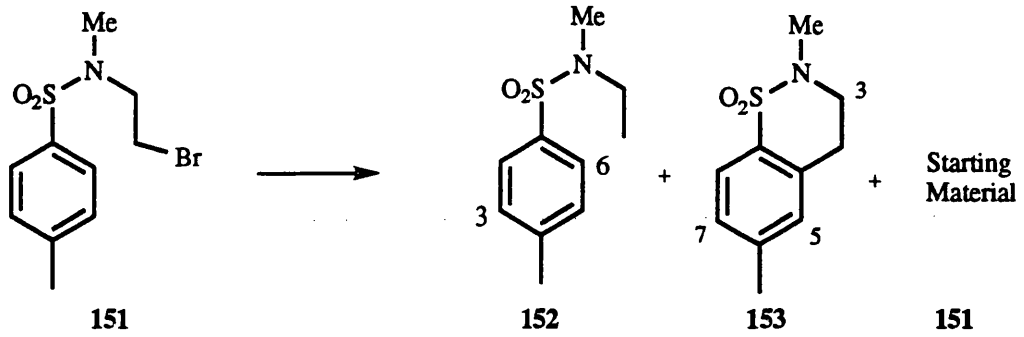
Preparation of *N-(2-bromoethyl)-N-methyl-p-toluenesulfonamide* (**151**)



150 **151**

To a suspension of NaH (60% dispersion in mineral oil; 725 mg, 18 mmol) in DMF (20 ml) was added a solution of the sulfonamide **150** (2.8 g, 15 mmol) in DMF (30 ml). The mixture was left for 1 hr and then 1,2-dibromoethane (3.9 ml, 45 mmol) was added. After 2 hr at 95 °C another portion of 1,2-dibromoethane (2 ml, 23 mmol) was added and the reaction kept at 95 °C for 20 hr. The solvent was removed under reduced pressure, the mixture dissolved in DCM (30 ml), washed with water (3x20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 60-100%) to give *sulfonamide* **151** (1.2 g, 28%) as white prisms, m.p. 75-76 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3029, 2978, 2926, 1597, 1462, 1315 (S=O), 1157 (S=O); δ_H (270 MHz; $CDCl_3$) 7.68 (2H, d, *J* 8.3, H-2 and H-6), 7.33 (2H, d, *J* 8.6, H-3 and H-5), 3.50-3.35 (2H, m, H-1' and H-2'), 2.83 (3H, s, NCH_3), 2.43 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 143.7 (1C, q), 134.6 (1C, q), 129.8 (2C, t), 127.3 (2C, t), 51.8 (1C, s, H-1'), 36.0 (1C, p, NCH_3), 28.9 (1C, s, H-2'), 21.5 (1C, p, $ArCH_3$); *m/z* 293, 291 (M^+), 212, 198, 155, 91 (100%); (Found: C, 41.2; H, 4.6; N, 4.65. $C_{10}H_{14}BrNO_2S$ requires C, 41.1; H, 4.8; N, 4.8%)

Reaction of *N-(2-bromoethyl)-N-methyl-p-toluenesulfonamide* (**151**) with tri-n-butyltin hydride



151 **152** **153** **151**

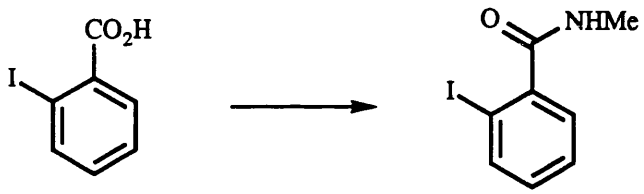
To a stirred solution of sulfonamide **151** (260 mg, 0.89 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (123 mg; 0.75 mmol) in benzene (4.7 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) was added, and left with strong stirring for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%,) to give in order of elution *sulfonamide* **151** (13 mg, 5%), *N-ethyl-N-methyl-p-toluenesulfonamide* (**152**) (28 mg, 15%) and *3,4-dihydro-2,6-dimethyl-2H-benzo[e]thiazine-S,S-dioxide* (**153**) (51 mg, 27%).

N-ethyl-N-methyl-p-toluenesulfonamide (**152**) as an oil; ν_{max}(film)/cm^{-1} 2977, 1598, 1454, 1338 (S=O), 1159 (S=O); δ_H (270 MHz; $CDCl_3$) 7.66 (2H, dd, *J* 1.7 and 8.3, H-2 and H-6), 7.30 (2H, dd, *J* 0.7 and 8.5, H-3 and H-5), 3.07 (2H, q, *J* 7.3, CH_2), 2.71 (3H, s, NCH_3), 2.41 (3H, s, $ArCH_3$), 1.12 (3H, t, *J* 7.3, $CH_2\underline{C}H_3$); δ_C ($CDCl_3$) 143.1 (1C, q), 129.8 (1C, q), 129.6 (2C, t), 127.3 (2C, t), 44.8 (1C, s), 33.9 (1C, p, NCH_3), 21.4 (1C, p, $ArCH_3$), 13.0 (1C, p, $CH_2\underline{C}H_3$); *m/z* 213 (M^+), 198, 155, 91 (100%); (Found: MNH_4^+, 231.1167. $C_{10}H_{19}N_2O_2S$ requires *MNH4*, 231.1167).

3,4-dihydro-2,6-dimethyl-2H-benzo[e]thiazine-S,S-dioxide (**153**) as white prisms, 68-71 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2928, 1326 (S=O), 1171 (S=O), 1144, 719;

δ_H (270 MHz; $CDCl_3$) 7.71 (1H, d, *J* 8.1, H-8), 7.18 (1H, dd, *J* 0.7 and 8.1, H-7), 7.03 (1H, s, H-5), 3.84 (2H, t, *J* 6.4, H-3), 2.97 (2H, t, *J* 6.4, H-4), 2.86 (3H, s, NCH_3), 2.36 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 142.5 (1C, q), 134.7 (1C, q), 133.0 (1C, q), 129.7 (1C, t), 128.4 (1C, t), 125.0 (1C, t), 48.2 (1C, s, NCH_2), 35.1 (1C, p, NCH_3), 22.9 (1C, s, $ArCH_2$), 21.4 (1C, p, $ArCH_3$); *m/z* 211 (M^+), 146, 104 (100%); (Found: MNH_4^+, 229.1010. $C_{10}H_{17}N_2O_2S$ requires *MNH4*, 229.1010).

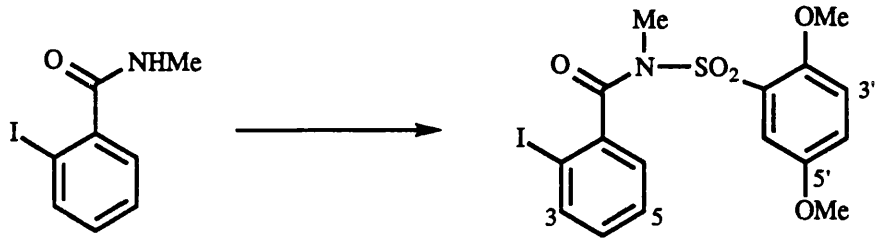
Preparation of *2-iodo-N-methyl benzamide* (**158**)[10]



158

To a stirred solution of 2-iodobenzoic acid (5.0 g, 20 mmol) in diethyl ether (20 ml) was added oxalyl chloride (4.4 ml, 50 mmol). Upon cooling to 0 °C, one drop of DMF was added which was accompanied by a vigorous effervescence. After 90 min, the solvent was removed under reduced pressure. Aqueous NaOH (10%, 25 ml) was then added, followed by a 25-30% solution of methylamine in water (5.2 ml). After stirring vigorously for 4 hr, the resulting solid was filtered off, washed with water, dissolved in DCM and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *benzamide* **158** (4.3 g, 82 %) as white prisms, m.p. 150-150.5 °C (DCM/petrol); δ_H (270 MHz; $CDCl_3$) 7.81 (1H, dd, 1.5 and 7.8, H-3), 7.34-7.30 (2H, m, H-5 and H-6), 7.06 (1H, m, H-4), 5.99 (1H, bs, NH), 2.96 (3H, d, *J* 4.9, NCH_3).

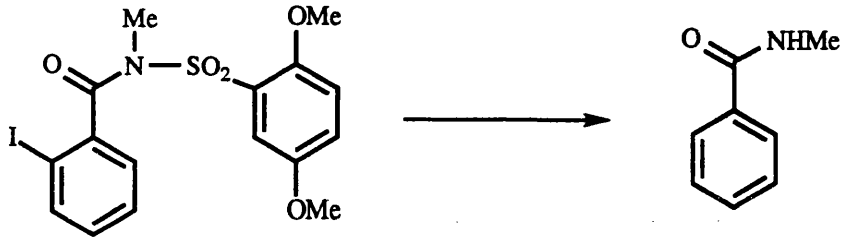
Preparation of *N-[(2,5-dimethoxyphenyl)sulfonyl]-2-iodo-N-methylbenzamide* (**159**)



158 **159**

To a suspension of NaH (60% dispersion in oil; 614 mg, 15 mmol) in THF (5 ml) was added a solution of the benzamide **158** (2.0 g, 7.7 mmol) in THF (20 ml). Slow effervescence occurred. The solution was stirred at room temperature for 3 hr. A solution of 2,5-dimethoxybenzenesulfonyl chloride (2.2 g, 9.2 mmol) in THF (10 ml) was then added and the resulting mixture was stirred for 25 hr. Water (20 ml) was added and the mixture extracted with DCM (3x20 ml), dried (MgSO4) and the solvent removed *in vacuo*. The residue was chromatographed (DCM/petrol 75-100%) to give the *benzamide* **159** (3.4 g, 96%) as white needles m.p. 136-138 °C (DCM/ether); ν_{max} (film)/cm^{-1} 2954, 1691 (C=O), 1583, 1496, 1353 (S=O), 1276, 1225, 1166 (S=O); δ_H (270 MHz; $CDCl_3$) 7.71 (1H, dd, *J* 0.7 and 7.8, H-3), 7.32 (1H, dt, *J* 1.0 and 7.5, H-4 or H-5), 7.14-7.01 (4H, m, H-4 or H-5 and H-6, H-4` and H-6`), 6.96 (1H, d, *J* 9.5, H-3`), 3.95 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.42 (3H, s, N-CH_3); δ_C ($CDCl_3$) 169.7 (1C, q, C=O), 152.7 (1C, q), 151.3 (1C, q), 140.9 (1C, q), 139.0 (1C, q), 130.7 (1C, t), 128.0 (1C, t), 127.4 (1C, t), 126.8 (1C, q), 122.5 (1C, t), 114.9 (1C, t), 113.6 (1C, t), 92.3 (1C, q, C-2), 56.7 (1C, p, OCH_3), 55.8 (1C, p, OCH_3), 34.3 (1C, p, NCH_3); *m/z* 461(M^+), 397 (M^+-SO_2), 366, 334, 244 (100%), 231, 203; (Found: M^+, 460.9805. $C_{16}H_{16}INO_5S$ requires *M*, 460.9794).

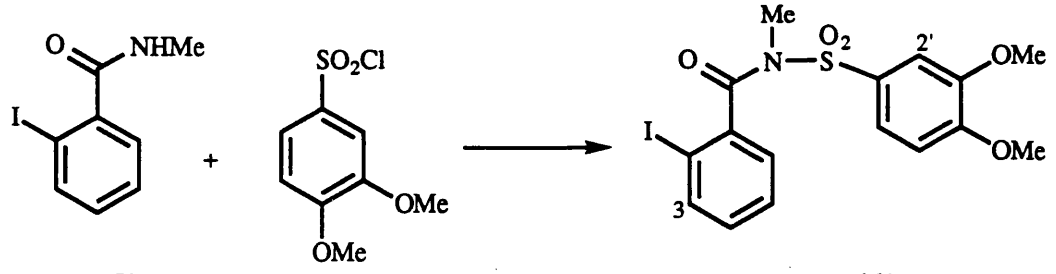
Reaction of *N-[(2,5-dimethoxyphenyl)sulfonyl]-2-iodo-N-methylbenzamide* (**159**) with tri-n-butyltin hydride



159 **160**

To a stirred solution of the benzamide **159** (410 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (310 µl, 1.13 mmol) and AIBN (104 mg, 0.6 mmol) in benzene (4.5 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo,* the residue dissolved in DCM (40 ml), washed with sat. aq. KF (3x25 ml) and water (30 ml), dried ($MgSO_4$), concentrated *in vacuo* and the residue chromatographed (ethyl acetate/petrol 10-40%) to give, in order of elution, the *benzamide* **159** (57 mg, 14%) and *N-methyl benzamide* (**160**)[11] (20 mg, 17%), as white needles, m.p. 75-76 °C (Lit.[11a] 82 °C); ν_{max} (film)/cm^{-1} 3320 (NH), 2938, 1643 (C=O), 1549, 1310, 694; δ_H (270 MHz; $CDCl_3$) 7.76 (2H, dd, *J* 1.7 and 8.1, H-2 and H-6), 7.48-7.38 (3H, m, H-3, H-4 and H-5), 6.23 (1H, bs, NH), 3.00 (3H, d, *J* 4.9, NCH_3); δ_C ($CDCl_3$) 168.2 (1C, q, C=O), 134.6 (1C, q, C-1), 131.3 (1C, t, C-4), 128.5 (2C, t, C-2 and C-6), 126.8 (2C, t, C-3 and C-5), 26.8 (1C, p, CH_3); *m/z* 135 (M^+), 105 (100%), 77.

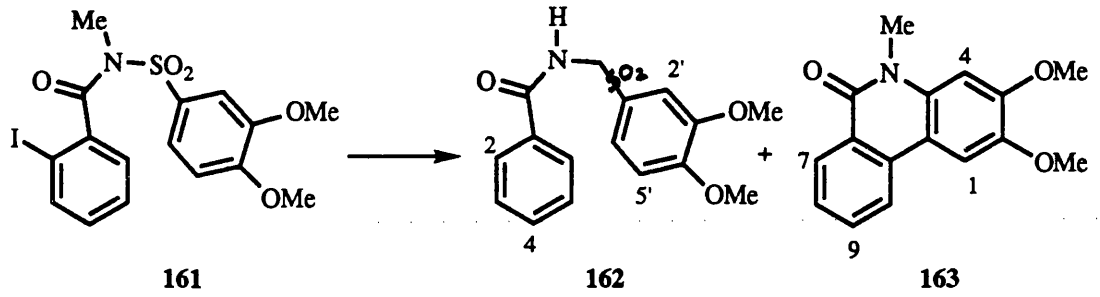
Preparation of *N-[(3,4-dimethoxyphenyl)sulfonyl]-2-iodo-N-methylbenzamide* (**161**)



158 **161**

To a suspension of NaH (60% dispersion in oil; 614 mg) in THF (5ml), was added a solution of the benzamide **158** (2.0 g; 7.7 mmol) in THF (20 ml). Slow effervescence occurred. The solution was stirred at room temperature for 3 hr. A solution of 3,4-dimethoxybenzenesulfonyl chloride (2.2 g) in THF (6 ml) was then added and the resulting mixture was stirred for 25 hr. Water was added and the mixture extracted with DCM (3x20 ml) dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was chromatographed (DCM/petrol 75-100%) to give the *benzamide* **161** (3.4 g, 95%) as white prisms, m.p. 119-120 °C (DCM/ether); ν_{max} (film)/cm^{-1} 2933, 1689 (C=O), 1508, 1363 (S=O), 1265, 1167 (S=O); δ_H (270 MHz; $CDCl_3$) 7.79 (1H, d, *J* 7.8, H-3), 7.60 (1H, dd, *J* 2.2 and 8.5, H-6`), 7.45 (1H, d, *J* 2.2, H-2`), 7.40 (1H, t, *J* 7.8, H-5), 7.24 (1H, dd, *J* 1.7 and 7.8, H-6), 7.11 (1H, dt, *J* 1.7 and 7.8, H-4), 6.95 (1H, d, *J* 8.5, H-5`), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.26 (3H, s, NCH_3); δ_C ($CDCl_3$) 168.5 (1C, q, C=O), 153.7 (1C, q), 148.8 (1C, q), 141.3 (1C, q), 139.2 (1C, t), 131.0 (1C, t), 129.5 (1C, q), 128.0 (1C, t), 127.5 (1C, t), 122.9 (1C, t), 111.3 (1C, t), 110.3 (1C, t), 91.6 (1C, q, C-2), 56.3 (1C, p, OCH_3), 56.2 (1C, p, OCH_3), 34.3(1C, p, NCH_3); *m/z* 461 (M^+), 431, 397 (M^+-SO_2), 244 (100%), 231 (100%); (Found: M^+, 460.9769. $C_{16}H_{16}INO_5S$ requires *M*, 460.9794).

Reaction of *N-[(3,4-dimethoxyphenyl)sulfonyl]-2-iodo-N-methylbenzamide* (**161**) with tri-n-butyltin hydride



161 **162** **163**

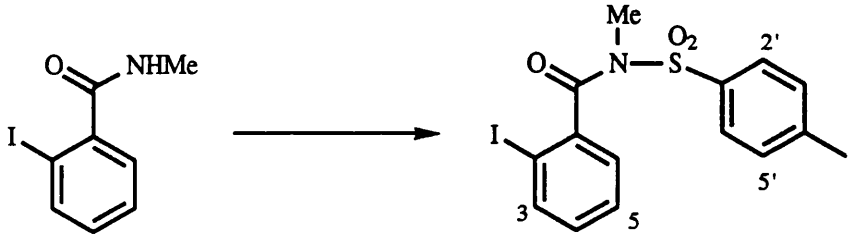
To a stirred solution of the benzamide **161** (409 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (310 µl, 1.13 mmol) and AIBN (103 mg, 0.6 mmol) in benzene (4.5 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo* the residue dissolved in DCM (40 ml), washed with sat. aq. KF (3x25 ml) and water (30 ml), dried ($MgSO_4$), concentrated *in vacuo* and the residue chromatographed (ethyl acetate/petrol 10-60%) to give, in order of elution the *benzamide* **161** (21 mg, 5%), *N-(3,4-dimethoxyphenylmethyl) benzamide* (**162** (67 mg, 22%) and *2,3-dimethoxy-5-methyl-benzo[c]quinoline-5H-6-one* (**163**) (60 mg, 25%)

N-[(3,4-dimethoxyphenylsulfonyl)methyl]benzamide (**162**) as a foam; ν_{max} (film)/cm^{-1} 3343, 3061, 2936, 1669 (C=O), 1508, 1320, 1263, 1130; δ_H (400 MHz; $CDCl_3$) 7.66 (2H, d, *J* 7.2, H-2 and H-6), 7.49-7.54 (2H, m, H-4 and H-6'), 7.42 (2H, t, *J* 7.5, H-3 and H-5), 7.26 (1H, d, *J* 2.2, H-2'), 6.91 (2H, bd, *J* 8.4, H-5' and NH), 4.86 (2H, d, *J* 6.7, CH_2), 3.90 (3H, s, OCH_3), 3.74 (3H, s, OCH_3); δ_C ($CDCl_3$) 166.4 (1C, q, C=O), 153.9 (1C, q), 149.2 (1C, q), 132.7 (1C, q), 132.4 (1C, t), 128.7 (2C, t), 128.2 (1C, q), 127.1 (2C, t), 123.0 (1C, t), 110.8 (2C, t), 61.0 (1C, s, CH_2), 56.2 (1C, p, OCH_3), 56.1 (1C, p, OCH_3); *m/z* (EI) 270 ($M-H^+$), 239, 105 (100%); (Found: MH^+, 272.1287. $C_{16}H_{18}NO_3$ requires *MH*, 272.1287).

2,3-dimethoxy-5-methyl-5H-benzo[c]quinoline-6-one (**163**) as a clear oil; ν_{max} (film)/cm^{-1} 2970, 1639 (C=O), 1528, 1493, 1256; δ_H (270 MHz; $CDCl_3$) 8.45 (1H, dd, *J* 1.0 and 8.1, H-10), 7.98 (1H, d, *J* 8.3, H-7), 7.65 (1H, dt, *J* 1.2 and 8.3, H-8), 7.50

(1H, s, H-4), 7.46 (1H, dt, *J* 1.0 and 8.1, H-5), 6.72 (1H, s, H-1), 3.96 (6H, s, 2xOCH3), 3.70 (3H, s, NCH3); δ_C ($CDCl_3$) 161.4 (1C, q, C=O), 150.6 (1C, q), 144.9 (1C, q), 133.3 (1C, q), 132.8 (1C, q), 132.1 (1C, t), 128.8 (1C, t), 126.7 (1C, t), 124.5 (1C, q), 120.8 (1C, t), 111.7 (1C, q), 105.1 (1C, t), 98.4 (1C, t), 56.2 (1C, p, OCH3), 55.9 (1C, p, OCH3), 29.9 (1C, p, NCH3); *m/z* 269 (M^+, 100%), 254, 226; (Found: M^+, 269.1052. $C_{16}H_{15}NO_3$ requires *M*, 269.1052).

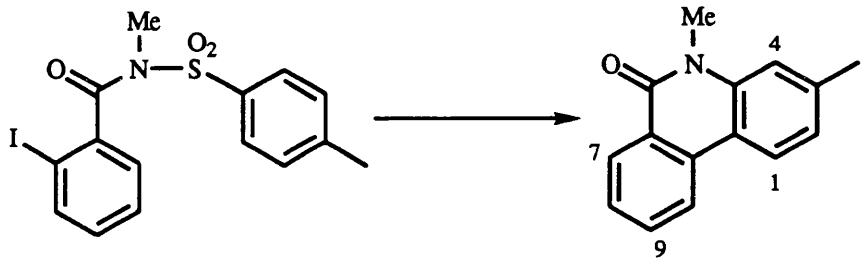
Preparation of *2-iodo-N-methyl-N-p-toluenesulfonyl benzamide* (**168**)[4]



158 **168**

To a suspension of NaH (60% dispersion in oil; 228 mg) in THF (5 ml), was added a solution of the benzamide **158** (771 mg; 2.95 mmol) in THF (10 ml). Slow effervescence occurred. The solution was stirred at room temperature for 3 hr. A solution of tosyl chloride (728 mg; 3.82 mmol) in THF (3 ml) was then added and the resulting mixture was stirred for 25 hr. Water (20 ml) was added and the mixture extracted with DCM (3x20 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was chromatographed (DCM/petrol 75-100%) to give the *benzamide* **168** (1.1 g, 92%) as white prisms, m.p. 107-109 °C (DCM/petrol); δ_H (270 MHz; $CDCl_3$) 7.84 (2H, d, *J* 8.3, H-2' and H-6'), 7.77 (1H, dd, *J* 0.8 and 8.1, H-3), 7.40 (1H, dt, *J* 1.0 and 7.6, H-5), 7.33 (2H, d, *J* 8.5, H-3' and H-5'), 7.22 (1H, dd, *J* 1.6 and 7.7, H-6), 7.11 (1H, ddd, *J* 1.7, 7.5 and 7.9, H-4), 3.27 (3H, s, NCH3), 2.45 (3H, s, ArCH3); δ_C ($CDCl_3$) 169.4 (1C, q, C=O), 145.1 (1C, q), 141.2 (1C, q), 139.1 (1C, t), 135.1 (1C, q), 131.0 (1C, t), 129.4 (2C, t), 128.6 (2C, t), 128.0 (1C, t), 127.4 (1C, t), 91.5 (1C, q, C-2), 34.2 (1C, p, NCH3), 21.6 (1C, p, ArCH3).

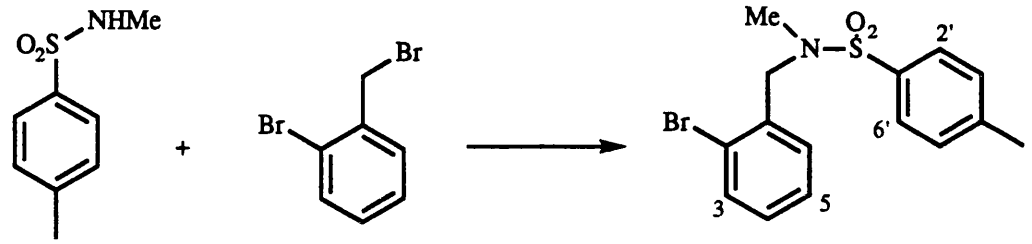
Reaction of *2-iodo-N-methyl-N-p-toluenesulfonyl benzamide* (**168**) with tri-n-butyltin hydride[4]



168 **169**

To a stirred solution of the benzamide **168** (371 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (105 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (ether/petrol 30 %) to give in order of elution the *benzamide* **168** (65 mg, 18%) and *3,5-dimethyl-5H-benzo[c]quinoline-6-one* (**169**) (50 mg, 25%) as white needles, m.p. 112-114 °C (DCM/petrol); δ_H (270 MHz; $CDCl_3$) 8.54 (1H, dd, *J* 1.4 and 8.0, H-10), 8.24 (1H, d, *J* 8.2, H-1 or H-7), 8.17 (1H, d, *J* 8.2, H-1 or H-7), 7.74 (1H, ddd, *J* 1.4, 7.1 and 8.3, H-9), 7.55 (1H, ddd, *J* 1.0, 7.0 and 8.0, H-8), 7.23 (1H, s, H-4), 7.15 (1H, dd, *J* 1.1 and 8.2, H-2), 3.81, (3H, s, NCH_3), 2.52 (3H, s, $ArCH_3$); *m/z* (CI) 224 (MH^+); (Found: C, 80.6; H, 5.95; N, 6.1. $C_{15}H_{13}NO$ requires C, 80.2; H, 5.8; N, 6.2).

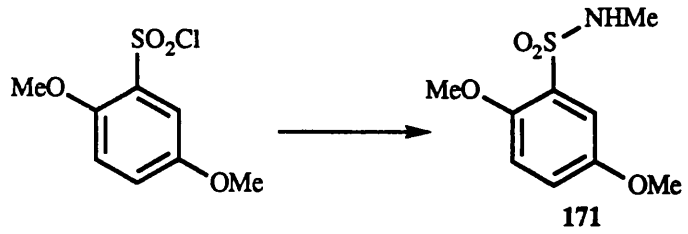
Preparation of *N-(2-bromophenylmethyl)-N,4-dimethyl-benzenesulfonamide* (**170**)



150 **170**

To a suspension of NaH (60% dispersion in oil; 242 mg) in THF (6 ml), was added a solution of the sulfonamide **150** (917 mg; 5.0 mmol) in THF (8 ml). Effervescence occurred and the mixture was stirred at room temperature for 2 hr. Then, 2-bromo benzyl bromide (2.4 g, 9.8 mmol) was added and the mixture stirred for 20 hr. Then, water (50 ml) was added and the mixture extracted with ether (3x30 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (ether/petrol 50-100%) to give the *sulfonamide* **170** (1.6 g; 93%) as white prisms m.p. 81-82 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2923, 1339 (S=O), 1163 (S=O), 748; δ_H (270 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.3, H-2' and H-6'), 7.54 (1H, t, *J* 8.3, H-5), 7.38-7.30 (4H, m, H-3', H-5', H-3 and H-6), 7.15 (1H, t, *J* 8.1, H-4), 4.29 (2H, s, CH_2), 2.67 (3H, s, NCH_3), 2.46 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 146 (1C, q), 134.9 (1C, q), 134.3 (1C, q), 132.7 (1C, t), 129.8 (3C, t), 129.2 (1C, t), 127.8 (1C, t), 127.4 (2C, t), 123.4 (1C, q), 53.5 (1C, s), 35.0 (1C, p, NCH_3), 21.5 (1C, p, $ArCH_3$); *m/z* 355 (M^+), 353, 274, 198, 91 (100%); (Found: M^+, 355.0024. $C_{15}H_{16}Br^{81}NO_2S$ requires *M*, 355.0065); (Found: C, 50.7; H, 4.9; N, 4.0. $C_{15}H_{16}BrNO_2S$ requires C, 50.9; H, 4.55; N, 3.95).

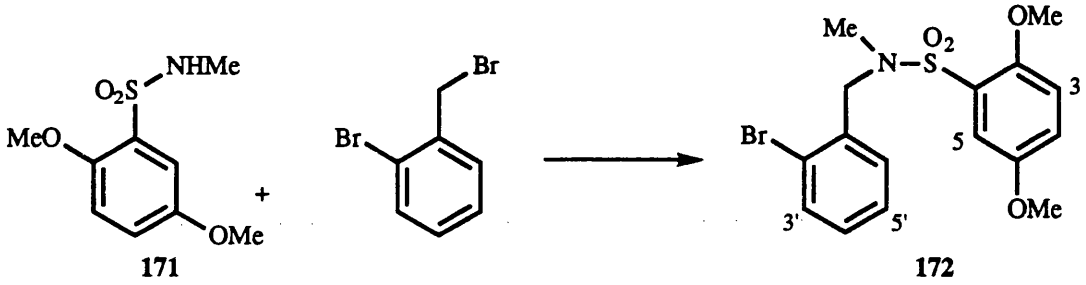
Preparation of *2,5-dimethoxy-N-methylbenzenesulfonamide* (**171**)



171

To a suspension of 2,5-dimethoxybenzenesulfonyl chloride (2.0 g, 8.4 mmol) in aq. NaOH (10%, 16 ml) was added methylamine (25-30% in water, 2 ml) and the mixture stirred vigorously for 23 hr. The reaction mixture was diluted with water (20 ml) extracted with DCM (3x50 ml), dried ($MgSO_4$) and evaporated under reduced pressure, to give the *sulfonamide* **171** (1.6 g, 82%) as white prisms, m.p. 112-113 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 3322 (NH), 2949, 1497, 1323 (S=O), 1276, 1223, 1161 (S=O); δ_H (270 MHz; $CDCl_3$) 7.45 (1H, d, *J* 2.2, H-6), 7.08 (1H, dd, *J* 2.2 and 9.0, H-4), 6.98 (1H, d, *J* 9.0, H-3), 4.82 (1H, bs, NH), 3.93 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.59 (3H, d, *J* 5.6, NCH_3); δ_C ($CDCl_3$) 153.4 (1C, q, C-5), 150.2 (1C, q, C-2), 126.7 (1C, q, C-1), 120.5 (1C, t, C-4), 115.1 (1C, t, C-3), 113.8 (1C, t, C-6), 57.1 (1C, p, OCH_3), 56.0 (1C, p, OCH_3), 29.6 (1C, p, NCH_3); *m/z* 231 (M^+, 100%), 202, 170; (Found: M^+, 231.0554. $C_9H_{13}NO_4S$ requires *M*, 231.0565).

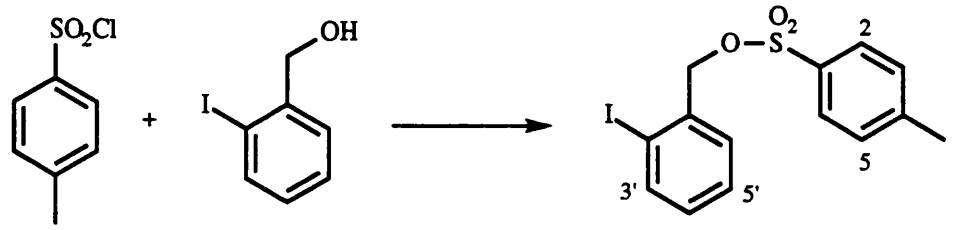
Preparation of *N-(2-bromophenylmethyl)-2,5-dimethoxy-N-methylbenzenesulfonamide* (**172**)



171 **172**

To a suspension of NaH (60% dispersion in oil; 107 mg) in THF (2.5 ml) was added a solution of the sulfonamide **171** (465 mg; 2.0 mmol) in THF (3.5 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. Then, *o*-bromobenzyl bromide (750 mg, 3.0 mmol) was added and the mixture left under stirring for 20 hr. Water was added (20 ml) and the mixture extracted with ether (3x15 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50-100%) to give the *sulfonamide* **172** (704 mg, 91%) as white needles, m.p. 95-96 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2943, 1494, 1334 (S=O), 1275, 1224, 1158 (S=O); δ_H (270 MHz; $CDCl_3$) 7.55 (1H, d, *J* 7.7, H-3'), 7.52 (1H, dd, *J* 1.1 and 7.6, H-6'), 7.50 (1H, d, *J* 3.0, H-6), 7.33 (1H, dt, *J* 1.2 and 7.6, H-5'), 7.12 (1H, dt, *J* 1.5 and 7.7, H-4'), 7.06 (1H, dd, *J* 3.2 and 9.0, H-4), 6.96 (1H, d, *J* 9.0, H-3), 4.52 (2H, s, CH_2), 3.92 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.76 (3H, s, NCH_3); δ_C ($CDCl_3$) 153.0 (1C, q), 150.8 (1C, q), 135.9 (1C, q), 132.6 (1C, t), 129.2 (1C, t), 128.9 (1C, t), 127.9 (1C, t), 127.3 (1C, q), 123.1 (1C, q), 120.4 (1C, t), 116.1 (1C, t), 113.6 (1C, t), 56.5 (1C, p, OCH_3), 56.0 (1C, p, OCH_3), 54.2 (1C, s, CH_2), 35.0 (1C, p, NCH_3); *m/z* 401, 399 (M^++2 and M^+), 320, 202 (100%), 200, 198, 171, 169; (Found: M^+, 401.0114. $C_{16}H_{18}Br^{81}NO_4S$ requires *M*, 401.0119).

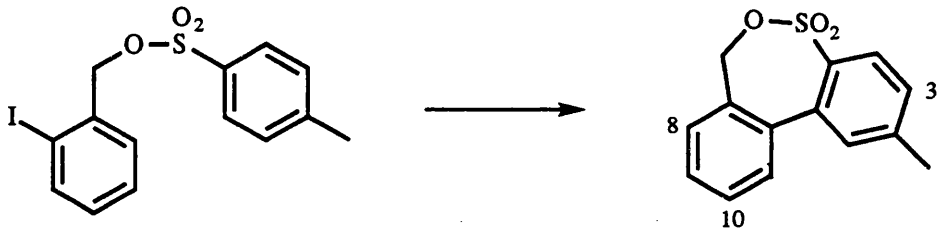
Preparation of *(2-iodophenyl)methyl 4-methylbenzenesulfonate* (**175**)



175

To a suspension of NaH (60% dispersion in oil; 297 mg) in THF (7 ml) was added a solution of *o*-iodobenzyl alcohol (1.4 g; 6.0 mmol) in THF (12 ml). Effervescence occurred and the mixture was stirred at room temperature for 20 min. A solution of p-toluenesulfonyl chloride (1.7 g, 9.0 mmol) in THF (10 ml) was added and the mixture left under stirring for 24 hr. Water (30 ml) was added and the mixture extracted with DCM (3x25 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 25-75 %) to give the *sulfonate* **175** (2.0 g, 87%) as white prisms, m.p. 56-57 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 3064, 1360 (S=O), 1190, 1177 (S=O), 937, 666; δ_H (270 MHz; $CDCl_3$) 7.84 (2H, d, *J* 8.3, H-2 and H-6), 7.79 (1H, dd, *J* 1.2 and 8.1, H-3'), 7.38-7.28 (4H, m, H-5', H-6', H-3 and H-5), 7.00 (1H, dd, *J* 2.2 and 7.8, H-4'), 5.09 (2H, s, $C\underline{H}_2$), 2.44 (3H, s, CH_3); δ_C ($CDCl_3$) 144.9 (1C, q), 139.5 (1C, t), 136.1 (1C, q), 133.0 (1C, q), 130.5 (1C, t), 130.0 (1C, t), 129.9 (2C, t), 128.5 (1C, t), 128.1 (2C, t), 98.2 (1C, q, C-2'), 75.2 (1C, s, CH_2), 21.7 (1C, p, $ArCH_3$); *m/z* 388 (M^+), 261 (M^+-I), 233, 217 (100%); (Found: M^+, 387.9620. $C_{14}H_{13}IO_3S$ requires *M*, 387.9630).

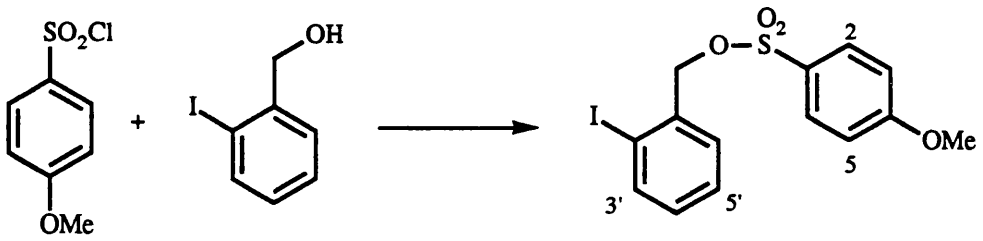
Reaction of *(2-iodophenyl)methyl 4-methylbenzenesulfonate* (**175**) with tri-n-butyltin hydride



175 **176**

To a stirred solution of the sulfonate **175** (349 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (104 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (15 ml) and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (ethyl acetate/petrol 5-100%) to give, in order of elution the *sulfonate* **175** (11 mg, 3%), and *2-methyl-7H-dibenz[c,e]oxathiepin-S,S-dioxide* (**176**) (23 mg, 10%) as white prisms, m.p. 148-150 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2925, 1351 (S=O), 1179 (S=O), 936, 770; δ_H (270 MHz; $CDCl_3$) 8.04 (1H, d, *J* 8.1, H-4), 7.60-7.56 (2H, m, ArH), 7.49-7.37 (4H, m, ArH), 5.03 (2H, s, CH_2), 2.53 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 145.2 (1C, q), 140.6 (1C, q), 138.8 (1C, q), 132.0 (1C, q), 131.8 (1C, q), 131.0 (1C, t), 130.7 (1C, t), 130.5 (1C, t), 129.3 (1C, t), 129.2 (1C, t), 128.6 (1C, t), 128.5 (1C, t), 72.8 (1C, s, CH_2), 21.6 (1C, p, $ArCH_3$); *m/z* 260 (M^+), 195 (100%), 181, 165; (Found: M^+, 260.0531. $C_{14}H_{12}O_3S$ requires *M*, 260.0507).

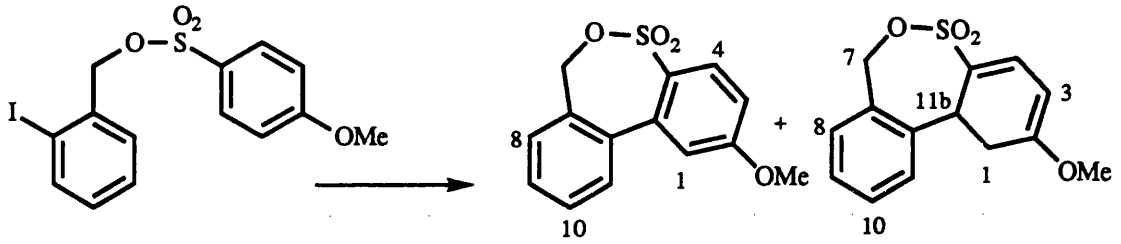
Preparation of *(2-iodophenyl)methyl 4-methoxybenzenesulfonate* (**177**)



177

To a suspension of NaH (60% dispersion in oil; 290 mg) in THF (10 ml) was added a solution of *o*-iodobenzyl alcohol (1.4 g; 6.0 mmol) in THF (10 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. A solution of 4-methoxy-benzenesulfonyl chloride (1.9 g, 9.0 mmol) in THF (10 ml) was added and the mixture left under stirring for 24 hr. Water was added (30 ml) and the mixture extracted with DCM (3x25 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 25-75 %) to give the *sulfonate* **177** (1.9 g, 76%) as white prisms, m.p. 82-83 °C; ν_{max} (film)/cm^{-1} 2948, 1598, 1360 (S=O), 1263, 1171 (S=O), 1099, 1020; δ_H (270 MHz; $CDCl_3$) 7.88 (2H, d, *J* 9.0, H-2 and H-6), 7.78 (1H, dd, *J* 1.0 and 7.8, H-3'), 7.37-7.28 (2H, m, ArH), 7.03-6.96 (1H, m, ArH), 6.99 (2H, d, *J* 9.0, H-3 and H-5), 5.07 (2H, s, CH_2), 3.88 (3H, s, OCH_3); δ_C ($CDCl_3$) 163.8 (1C, q), 139.5 (1C, t), 136.0 (1C, q), 130.5 (1C, t), 130.3 (2C, t), 130.0 (1C, t), 128.4 (1C, t), 127.3 (1C, q), 114.4 (2C, t), 98.6 (1C, q, C-2'), 75.0 (1C, s, CH_2), 55.7 (1C, p, OCH_3); *m/z* 404 (M^+), 277 (M^+-I), 233, 217 (100%), 171; (Found: M^+, 403.9602. $C_{14}H_{13}IO_4S$ requires *M*, 403.9579).

Reaction of *(2-iodophenyl)methyl 4-methoxybenzenesulfonate* (**177**) with tri-n-butyltin hydride



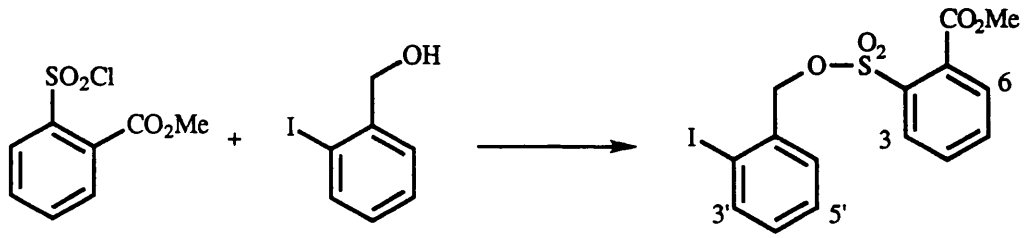
177 **178** **179**

To a stirred solution of the sulfonate **177** (362 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (106 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml) and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (ethyl acetate/petrol 8-20%) to give, in order of elution, the *dihydro compound* **179** (35 mg, 14%) and *2-methoxy-7H-dibenz[c,e]oxathiepin-S,S-dioxide* (**178**) (48 mg, 19%).

dihydro compound **179** as beige prisms, m.p. 160-162 °C (DCM/petrol); ν_{max} (film)cm^{-1} 1567, 1349 (S=O), 1171 (S=O), 1157, 1022; The interpretation of the ^1H nmr is based on the discussion on page 91. δ_H (400 MHz; $CDCl_3$) 7.43-7.37 (2H, m, H-9 and H-10), 7.32 (1H, d, *J* 7.0, H-8), 7.16 (1H, d, *J* 7.6, H-11), 6.87 (1H, d, *J* 6.7, H-4), 5.63 (1H, d, *J* 13.5, CH_2O), 5.05 (1H, dd, *J* 2.2 and 6.7, H-3), 5.03 (1H, d, *J* 13.5, CH_2O), 4.15 (1H, d, *J* 8.4, H-11b), 3.80 (3H, s, OCH_3), 3.23 (1H, ddd, *J* 2.2, 8.4 and 17.3, H-1a), 2.87 (1H, d, *J* 17.1, H-1b); δ_C ($CDCl_3$) 163.2 (1C, q), 139.1 (1C, q), 133.4 (1C, q), 132.6 (1C, t), 132.5 (1C, t), 131.2 (1C, t), 129.9 (1C, t), 127.4 (1C, t), 125.5 (1C, t), 90.4 (1C, t), 72.3 (1C, s), 55.9 (1C, t), 34.4 (1C, p, OCH_3), 30.7 (1C, s); *m/z* 278 (M^+), 214 (M^+-SO_2), 165, 152, 91 (100%); (Found: M^+, 278.0613. $C_{14}H_{14}O_4S$ requires *M*, 278.0613).

2-methoxy-7H-dibenz[c,e]oxathiepin-S,S-dioxide (**178**) as white prisms, m.p. 164-165 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2945, 1593, 1563, 1350 (S=O), 1177 (S=O), 769; δ_H (270 MHz; $CDCl_3$) 8.08 (1H, d, *J* 8.8, H-4), 7.60-7.57 (2H, m, ArH), 7.50-7.48 (2H, m, ArH), 7.11 (1H, d, *J* 2.4, H-1), 7.04 (1H, dd, *J* 2.7 and 8.8, H-3), 5.03 (2H, s, CH_2O), 3.95 (3H, s, OCH_3); δ_C ($CDCl_3$) 163.8 (1C, q), 140.9 (1C, q), 140.4 (1C, q), 131.8 (1C, q), 131.0 (1C, t), 130.8 (1C, t), 130.6 (1C, t), 129.5 (1C, t), 128.4 (1C, t), 126.6 (1C, q), 115.9 (1C, t), 113.0 (1C, t), 72.6 (1C, s, CH_2), 55.8 (1C, p, OCH_3); *m/z* 276 (M^+), 212 (M^+-SO_2), 211 (100%); (Found: M^+, 276.0467. $C_{14}H_{12}O_4S$ requires *M*, 276.0456).

Preparation of *methyl 2-(2-iodophenylmethyloxysulfonyl)benzoate* (**180**)

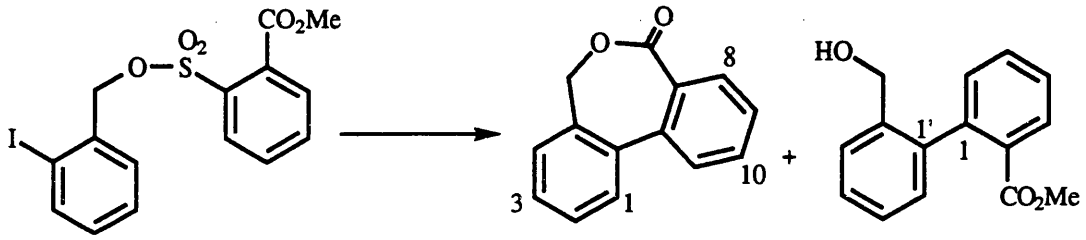


180

To a suspension of NaH (60% dispersion in oil; 115 mg) in THF (2 ml) was added a solution of *o*-iodobenzyl alcohol (937 mg; 4.0 mmol) in THF (6 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. Then, a solution of 2-carbomethoxybenzenesulfonyl chloride (1.2 g, 5.3 mmol) in THF (6 ml) was added and the mixture left under stirring for 24 hr. Water was added (30 ml) and the mixture extracted with DCM (3x25 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50%) to give the *sulfonate* **180** (354 mg, 21%) as white prisms, m.p. 95-97 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2951, 1737 (C=O), 1366 (S=O), 1298, 1184 (S=O); δ_H (270 MHz; $CDCl_3$) 8.03 (1H, td, *J* 1.0 and 7.6, H-6), 7.78 (1H, dd, *J* 1.0 and 7.8, H-3'), 7.67-7.57 (3H, m, H-3, H-4 and H-5), 7.41 (1H, dd, *J* 1.7 and 7.6, H-6'), 7.30 (1H, dt, *J* 1.2 and 7.6, H-5'), 6.99 (1H, dt, *J* 1.7 and 7.8, H-4'), 5.22 (2H, s, CH_2), 3.93 (3H, s, CO_2CH_3); δ_C ($CDCl_3$) 166.8 (1C, q), 139.3 (1C, t), 135.7 (1C, q), 133.9 (1C, q), 133.5 (1C, t), 133.0 (1C, q), 130.7 (1C, t), 130.4 (1C, t), 129.8 (1C, t), 129.6 (1C, t), 129.2 (1C, t), 128.3 (1C, t), 97.9 (1C, q, C-2'), 75.8 (1C, s, CH_2), 53.0 (1C, p, OCH_3);

m/z (EI) 433 (MH^+), 217, 199 (100%); (CI, NH_3) 450 (MNH_4^+, 100%); (Found: C, 41.45; H, 3.1. $C_{15}H_{13}IO_5S$ requires C, 41.7; H, 3.0).

Reaction of *methyl 2-(2-iodophenylmethyloxysulfonyl)benzoate* (**180**) with tri-n-butyltin hydride



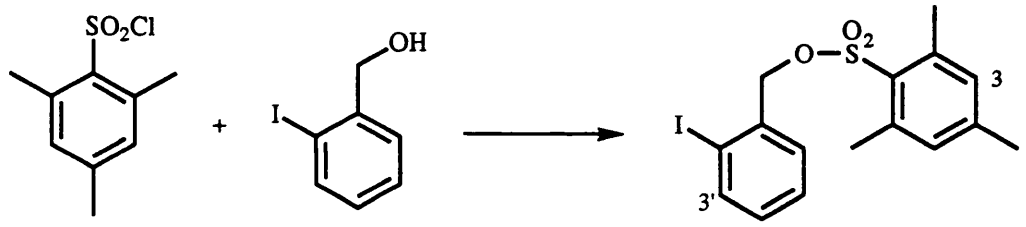
180 **181** **182**

To a stirred solution of the sulfonate **180** (386 mg, 0.89 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (110 mg, 0.67 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml) and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50-75 %) to give in order of elution *5H-dibenz[c,e]oxepin-7-one* (**181**) (143 mg, 76%) and *methyl 2-(2'-hydroxymethyl-1,1'-biphenyl)-carboxylate* (**182**) (29 mg, 14%).

5H-dibenz[c,e]oxepin-7-one (**181**) as white needles, m.p. 133-135 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 1715 (C=O), 1277, 1111, 739; δ_H (400 MHz; $CDCl_3$) 7.97 (1H, dd, *J* 1.3 and 7.9, H-8), 7.67-7.58 (3H, m, ArH), 7.54-7.48 (2H, m, ArH), 7.39-7.45 (2H, m, ArH), 5.05 (1H, d, *J* 11.3, H-5a), 5.03 (1H, d, *J* 11.3, H-5b); δ_C ($CDCl_3$) 170.2 (1C, q, C=O), 138.9 (1C, q), 137.2 (1C, q), 134.8 (1C, q), 132.5 1C, t), 131.9 (1C, t), 130.6 (1C, q), 130.1 (1C, t), 128.7 (1C, t), 128.6 (1C, t), 128.5 (1C, t), 128.5 (1C, t), 128.4 (1C, t), 69.2 (1C, s, CH_2); *m/z* 210 (M^+, 100%), 181, 165, 152; (Found: M^+, 210.0684. $C_{14}H_{10}O_2$ requires *M*, 210.0681).

methyl 2-(2'-hydroxymethyl-1,1'-biphenyl)carboxylate (**182**) as an oil; ν_{max} (film)/cm^{-1} 3411 (OH), 2951, 1722 (C=O), 1309, 1244, 749; δ_H (400 MHz; $CDCl_3$) 8.03 (2H, m, H-3), 7.56 (2H, m, ArH), 7.48 (1H, t, *J* 7.8, ArH), 7.40 (1H, dt, *J* 1.4 and 7.4, ArH), 7.35 (1H, dt, *J* 1.7 and 7.5, ArH), 7.26 (1H, dd, *J* 1.5 and 7.5, ArH), 4.58 (2H, d, *J* 3.6, CH_2O), 3.90 (3H, s, CO_2CH_3), δ_C ($CDCl_3$) 166.9 (1C, q, C=O), 140.9 (1C, q), 140.2 (1C, q), 137.9 (1C, q), 133.6 (1C, t), 130.2 (1C, t), 130.0 (1C, t), 128.5 (1C, t), 128.4 (1C, t), 128.3 (1C, t), 128.1 (1C, t), 127.8 (1C, t), 63.0 (1C, s, CH_2O), 52.2 (1C, p, OCH_3); *m/z* 242 (M^+), 224 (M^+-H_2O), 165 (100%); (Found: M^+, 2242.0941. $C_{15}H_{14}O_3$ requires *M*, 242.0943).

Preparation of *(2-iodophenyl)methyl 2,4,6-trimethylbenzenesulfonate* (**183**)

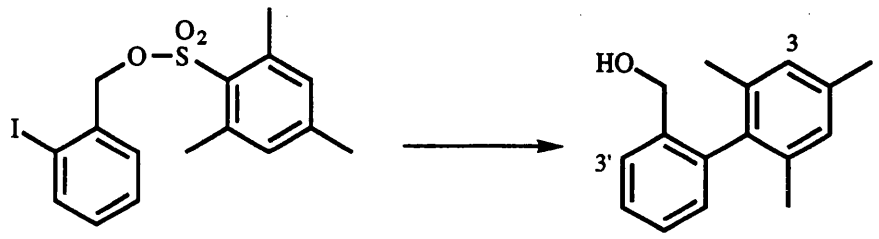


183

To a suspension of NaH (60% dispersion in oil; 289 mg) in THF (14 ml) was added a solution of *o*-iodobenzyl alcohol (1.4 g; 6.0 mmol) in THF (10 ml). Effervescence occurred and the mixture was stirred at room temperature for 30 min. A solution of mesitylenesulfonyl chloride (2.0 g, 9.0 mmol) in THF (10 ml) was added and the mixture left under stirring for 24 hr. Water was added (30 ml) and the mixture extracted with DCM (3x25 ml) dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 20-50%) to give the *sulfonate* **183** (1.9 g, 76%) as white prisms, m.p. 72-75 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2978, 1605, 1439, 1356 (S=O), 1175 (S=O); δ_H (270 MHz; $CDCl_3$) 7.80 (1H, dd, *J* 1.2 and 8.0, H-3'), 7.38-7.28 (2H, m, H-5' and H-6'), 7.01 (1H, m, H-4'), 6.97 (2H, s, H-3 and H-5), 5.05 (2H, s, CH_2), 2.66 (6H, s, 2xCH_3), 2.32 (3H, s, CH_3); δ_C ($CDCl_3$) 143.4 (1C, q), 140.0 (2C, q), 139.5 (1C, t), 136.2 (1C, q), 131.7 (2C, t), 130.6 (1C, q), 130.4 (1C, t), 129.9 (1C, t), 128.5 (1C, t), 98.3 (1C, q, C-2'), 74.4 (1C, s, CH_2),

22.7 (2C, p, ArCH3), 21.0 (1C, p, Ar CH3); *m/z* 416 (M^+), 289, 217 (100%); (Found: M^+, 415.9921. $C_{16}H_{17}IO_3S$ requires *M*, 415.9943).

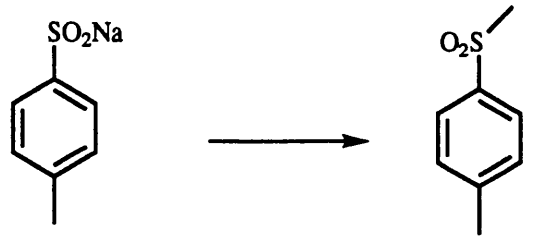
Reaction of *(2-iodophenyl)methyl 2,4,6-trimethylbenzenesulfonate* (**183**) with tri-n-butyltin hydride



183 **184**

To a stirred solution of the sulfonate **183** (375 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (104 mg, 0.6 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50-75 %) to give *2',4',6'-trimethyl-1,1'-biphenyl-4-yl-methanol* (**184**) (72 mg, 36%) as an oil; ν_{max} (film)/cm^{-1} 3340 (OH), 2918, 1613, 1451, 1377; δ_H (270 MHz; $CDCl_3$) 7.59-7.55 (1H, m, H-3), 7.36-7.42 (2H, m, H-4 and H-5), 7.08-7.05 (1H, m, H-6), 6.97 (2H, s, H-3' and H-5'), 4.33 (2H, s, CH_2), 2.36 (3H, s, $ArCH_3$), 1.95 (6H, s, 2x$ArCH_3$); δ_C ($CDCl_3$) 139.1 (1C, q), 138.3 (1C, q), 136.7 (1C, q), 136.6 (1C, q), 135.7 (2C, q), 129.3 (1C, t), 128.0 (2C, t), 127.6 (1C, t), 127.3 (1C, t), 127.2 (1C, t), 62.9 (1C, s, CH_2), 20.9 (1C, p, $ArCH_3$), 20.3 (2C, p, 2x$ArCH_3$); *m/z* 226 (M^+), 208 (M^+-H_2O), 193 (100%), 178, 165; (Found: M^+, 226.1361. $C_{16}H_{18}O$ requires *M*, 226.1358).

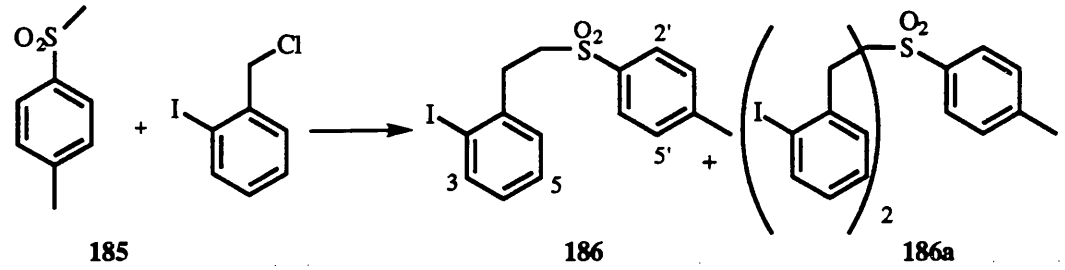
Preparation of *methyl p-tolyl sulfone* (**185**)[12]



185

To a mixture of sodium p-toluenesulfinate (11 g, 50 mmol) and sodium bicarbonate (8.4 g, 0.1 mol) was added dimethyl sulfate (7.1 ml, 75 mmol) and some water (3 ml) was added to make the mixture fluid enough for stirring. The rest of the water (15 ml) was added dropwise and the mixture heated at reflux for 22 hr. After cooling to room temperature, the mixture was diluted with water (30 ml), extracted with DCM (3x25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the *sulfone* **185** (6.9 g, 81%) as white prisms, m.p. 87.5-88 °C (Lit.[12] 83-87.5 °C), ν_{max} (film)/cm^{-1} 2926, 1300 (S=O), 1289, 1148 (S=O), 1091; δ_H (400 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.2, H-2 and H-6), 7.36 (2H, d, *J* 8.2, H-3 and H-5), 3.04 (3H, s, SO_2CH_3), 2.45 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 144.6 (1C, q, C-1), 137.6 (1C, q, C-4), 129.9 (2C, t, C-2 and C-6), 127.3 (2C, t, C-3 and C-5), 44.6 (1C, p, SO_2CH_3), 21.6 (1C, p, $ArCH_3$).

Preparation of *[2-(2-iodophenyl)ethyl] (4-methylphenyl) sulfone* (**186**)



185 **186** **186a**

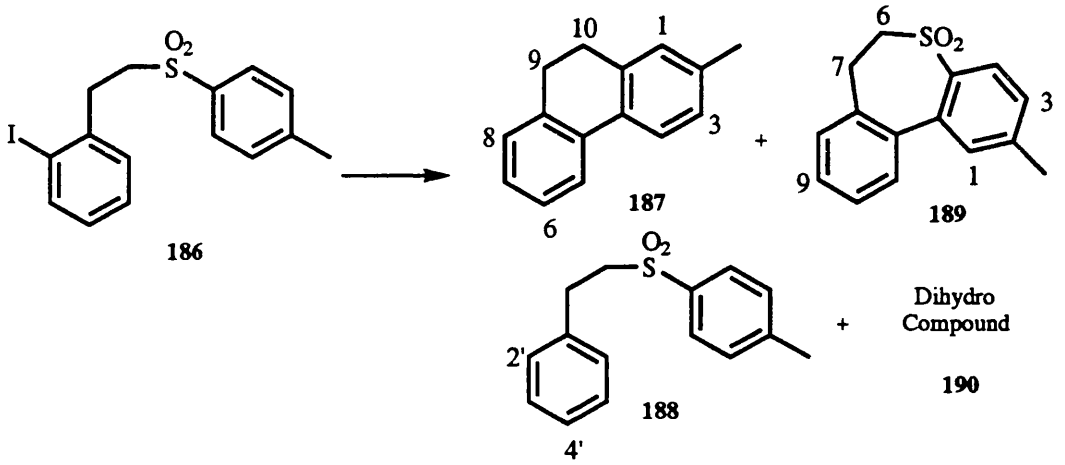
To a solution of the sulfone **185** (1.0 g, 6 mmol) in THF (30 ml) at -70 °C, under nitrogen, was added a solution of ^{n}BuLi (2.5 M in cyclohexane; 2.6 ml) and left for 1 hr. Then, a solution of 2-iodobenzyl chloride (1.8 g, 7.2 mmol) in THF (10 ml) was added and the mixture allowed to warm to 0 °C over 1.5 hr. The cooling bath was removed and the mixture allowed to warm to room temperature over 1 hr. The reaction mixture was quenched with NH_4Cl (30 ml) and extracted with DCM (3x30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 40%) to give the *bis-alkylated* compound **186a** (867 mg, 24%), the *sulfone* **186** (1.1 g, 46%) and the *sulfone* **185** (218 mg, 21%).

bis[2-(2-iodophenyl)methyl]methyl(4-methylphenyl) sulfone (**186a**) as white prisms, m. p. 100-102 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2925, 1305 (S=O), 1138 (S=O), 1079, 745; δ_H (400 MHz; $CDCl_3$) 7.68 (2H, td, *J* 1.9 and 8.5, 2xH-3'), 7.60 (2H, dd, *J* 1.2 and 7.9, H-2 and H-6), 7.21-7.12 (6H, m, ArH), 6.78 (2H, dt, *J* 1.9 and 7.8, 2xH-4'), 4.22 (1H, m, $CHSO_2$), 3.39 (2H, dd, *J* 6.5 and 14.3, 2x1H-CH_2), 2.95 (2H, dd, *J* 8.0 and 14.4, 2x1H-CH_2), 2.36 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 144.3 (1C, q), 139.5 (2C, t), 139.2 (2C, q), 135.4 (1C, q), 131.9 (2C, t), 129.5 (2C, t), 128.7 (2C, t), 128.5 (2C, t), 128.0 (2C, t), 100.5 (2C, q, 2xC-2), 61.3 (1C, t, $CHSO_2$), 39.0 (2C, s, 2xCH_2), 21.6 (1C, p, $ArCH_3$); *m/z* (EI) 602 (M^+), 475 (M^+-I), 446, 259, 230 (100%); (FAB) 303 (MH^+, 100%); (Found: MH^+, 602.9350. $C_{22}H_{21}I_2O_2S$ requires *MH*, 602.9352).

[2-(2-iodophenyl)ethyl] (4-methylphenyl) sulfone (**186**) as white prisms, m.p. 68-69 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2917, 1312 (S=O), 1152 (S=O), 1079, 745; δ_H (400 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.1, H-2' and H-6'), 7.73 (1H, d, *J* 7.9, H-3), 7.36 (2H, d, *J* 8.1, H-3' and H-5'), 7.24 (1H, t, *J* 7.5, H-5), 7.17 (1H, dd, *J* 1.4 and 7.7, H-6), 6.88 (1H, dt, *J* 1.7 and 7.7, H-4), 3.30 (2H, m, CH_2), 3.07 (2H, m, CH_2), 2.44 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 144.8 (1C, q), 140.2 (1C, q), 139.7 (1C, t), 135.6 (1C, q), 129.9

(2C, t), 129.8 (1C, t), 128.8 (1C, t), 128.3 (2C, t), 99.8 (1C, q, C-2), 55.7 (1C, s, CH_2SO_2), 34.3 (1C, s, $ArCH_2$), 21.7 (1C, p, $ArCH_3$); *m/z* 387 (MH^+), 259 (100%), 230; (Found: C, 46.3; H, 3.7. $C_{15}H_{13}IO_2S$ requires C, 46.6; H, 3.9).

Reaction of *[2-(2-iodophenyl)ethyl] (4-methylphenyl) sulfone* (**186**) with tri-n-butyltin hydride



To a stirred solution of the sulfone **186** (349 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (110 mg, 0.67 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (DCM/petrol 50-100 %) to give in order of elution *2-methyl-9,10-dihydro-phenanthrene* (**187**) (25 mg, 14%), *(phenylethyl) (4-methylphenyl) sulfone* (**188**) (62 mg, 26%), a *dihydro compound* **190** (7 mg, 3%) and *2-methyl-6,7-dihydro-dibenzo-[b,d]-thiepin-S,S-dioxide* (**189**) (51 mg, 22%)

2-methyl-9,10-dihydro-phenanthrene (**187**) as an oil; ν_{max} (film)/cm^{-1} 2933, 1484, 764; δ_H (400 MHz; $CDCl_3$) 7.74 (1H, d, *J* 7.7, H-4 or H-5), 7.66 (1H, d, *J* 8.0, H-5 or H-4),

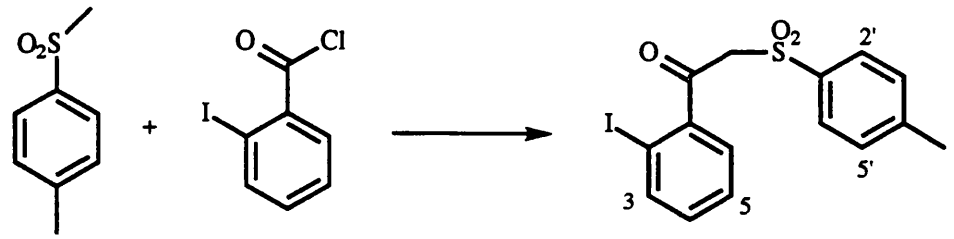
7.32-7.21 (3H, m, H-6, H-7 and H-8), 7.13 (1H, d, *J* 7.9, H-3), 7.08 (1H, bs, H-1), 2.87 (4H, m, 2xCH_2), 2.39 (3H, s, ArCH_3); δ_C ($CDCl_3$) 137.3 (1C, q), 137.1 (1C, q), 137.0 (1C, q), 134.5 (1C, q), 131.7 (1C, q), 128.8 (1C, t), 128.0 (1C, t), 127.6 (1C, t), 126.9 (1C, t), 126.8 (1C, t), 123.6 (1C, t), 123.4 (1C, t), 29.1 (1C, s), 29.0 (1C, s), 21.2 (1C, p, ArCH_3); *m/z* 194 (M^+, 100%), 179 (M^+-CH_3); (Found: M^+, 194.1104. $C_{15}H_{14}$ requires *M*, 194.1096).

(2-phenylethyl) (4-methylphenyl) sulfone (**188**) as an oil, ν_{max} (film)/cm^{-1} 1302 (S=O), 1149 (S=O), 1084; δ_H (400 MHz; $CDCl_3$) 7.79 (2H, d, *J* 8.2, H-2' and H-6'), 7.34 (2H, d, *J* 8.3, H-3' and H-5'), 7.26-7.20 (3H, m, H-3, H-4 and H-5), 7.09 (2H, d, *J* 6.7, H-2 and H-6), 3.34-3.29 (2H, m, SO_2CH_2), 3.03-2.99 (2H, m, ArCH_2), 2.44 (3H, s, ArCH_3); δ_C ($CDCl_3$) 144.8 (1C, q), 137.5 (1C, q), 135.9 (1C, q), 129.9 (2C, t), 128.7 (2C, t), 128.2 (2C, t), 128.1 (2C, t), 126.8 (1C, t), 57.6 (1C, s, CH_2SO_2), 28.8 (1C, s, ArCH_2), 21.6 (1C, p, ArCH_3); *m/z* 259 (M-H^+), 180 (100%), 91 (100%); (Found: M-H^+, 259.0790. $C_{15}H_{15}O_2S$ requires *M*, 259.0793).

dihydro compound **190** as white prisms, m.p. 180-181 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 1586, 1291 (S=O), 1124 (S=O), 726; δ_H (400 MHz; $CDCl_3$) 7.28-7.21 (3H, m, ArH), 6.99-6.97 (1H, m), 6.80 (1H, d, *J* 5.6), 5.84-5.81 (1H, m), 4.04 (1H, d, *J* 7.3), 3.50-3.41 (2H, m), 3.12-3.06 (1H, m), 3.02-2.91 (2H, m), 2.72 (1H, dd, *J* 1.7 and 18.3), 2.13 (3H, s, ArCH_3); δ_C ($CDCl_3$) 143.8 (1C, q), 139.9 (1C, q), 137.5 (1C, q), 133.2 (1C, q), 131.6 (1C, t), 130.5 (1C, t), 127.6 (2C, t), 125.8 (1C, t), 117.4 (1C, t), 56.2 (1C, s), 33.6 (1C, t), 33.1 (1C, s), 29.6 (1C, s), 23.5 (1C, p, CH_3); *m/z* 260 (M^+), 195, 181 (100%), 165; (Found: M^+, 260.0870. $C_{15}H_{16}O_2S$ requires *M*, 260.0871).

2-methyl-6,7-dihydro-dibenzo[b,d]thiepin-S,S-dioxide (**189**) as white prisms, m.p. 134-135 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 1303 (S=O), 1152, 1125 (S=O), 756, 745; δ_H (400 MHz; $CDCl_3$) 8.02 (1H, d, 7.8, H-4), 7.44-7.32 (6H, m, ArH), 3.77 (2H, m, SO_2CH_2), 2.98 (2H, bs, ArCH_2), 2.51 (3H, s, ArCH_3); δ_C ($CDCl_3$) 145.1 (1C, q), 140.3 (1C, q), 139.5 (1C, q), 135.3 (1C, q), 134.2 (1C, q), 131.5 (1C, t), 128.9 (2C, t), 128.8 (1C, t), 128.5 (1C, t), 128.4 (1C, t), 128.0 (1C, t), 63.6 (1C, s, CH_2SO_2), 29.6 (1C, s, ArCH_2), 21.6 (1C, p, ArCH_3); *m/z* 258 (M^+), 193 (100%), 178; (Found: M^+, 258.0709. $C_{15}H_{14}O_2S$ requires *M*, 258.0714).

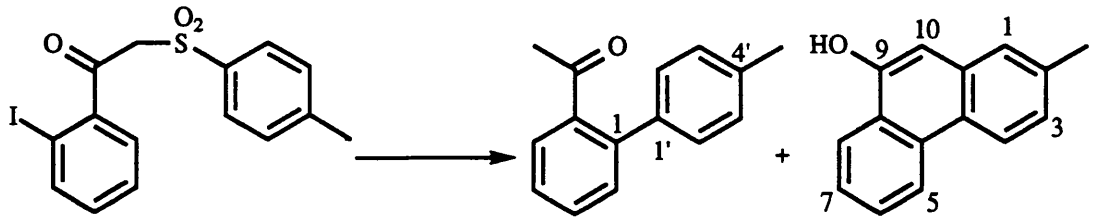
Preparation of *(2-iodophenyl) tosylmethyl ketone* (**191**)



185 **191**

To a solution of the sulfone **185** (1.5 g, 8.6 mmol) in THF (35 ml) at -78 °C, under N_2, was added a solution of *n*-BuLi (2.5 M in cyclohexane; 7 ml). After 1 hr a solution of 2-iodobenzoyl chloride (1.9 g, 7.2 mmol) in THF (10 ml) was added and left for another hour. The mixture allowed to warm to room temperature over 1 hr and quenched with NH_4Cl (30 ml), extracted with DCM (3x30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The mixture was purified by recrystalisation (DCM/ether/petrol) to give the *sulfone* **191** (2.1 g, 73%) as white plates, m.p. 98-100 °C; ν_{max} (film)/cm^{-1} 1691 (C=O), 1322 (S=O), 1153 (S=O); δ_H (400 MHz; $CDCl_3$) 7.90 (1H, dd, *J* 1.1 and 7.8, H-3), 7.75 (2H, d, *J* 8.4 H-2' and H-6'), 7.55 (1H, dd, *J* 1.6 and 7.6, H-6), 7.42 (1H, dt, *J* 1.0 and 7.6, H-5), 7.33 (2H, d, *J* 8.6, H-3' and H-5'), 7.15 (1H, dt, *J* 1.7 and 7.8, H-4), 4.73 (2H, s, CH_2), 2.43 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 191.1 (1C, q, C=O), 145.4 (1C, q), 141.9 (1C, q), 141.0 (1C, t), 135.6 (1C, t), 132.9 (1C, t), 130.1 (1C, t), 129.9 (2C, t), 128.6 (2C, t), 128.2 (1C, t), 91.8 (1C, q, C-2'), 65.4 (1C, s, CH_2), 21.7 (1C, p, $ArCH_3$); *m/z* (FAB) 401 (MH^+); (Found: M^+, 399.9627. $C_{15}H_{13}O_3IS$ requires *M*, 399.9630).

Reaction of *(2-iodophenyl) tosylmethyl ketone* (**191**) with tri-n-butyltin hydride



191 **192** **193**

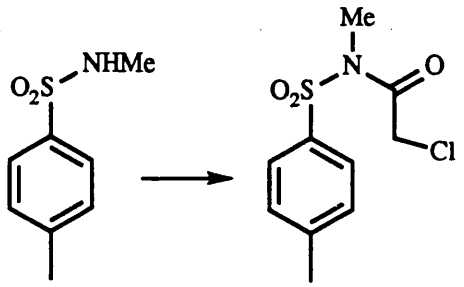
To a stirred solution of the ketone **191** (360 mg, 0.9 mmol) in benzene (18 ml) at reflux, was added a solution of tri-n-butyltin hydride (320 µl, 1.17 mmol) and AIBN (107 mg, 0.67 mmol) in benzene (4.7 ml), dropwise, over 11 hr, *via* a needle placed above the refluxing solution. After further 2 hr, the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for 3 hr. The solvent was removed *in vacuo* the residue dissolved in ethyl acetate (15 ml), and stirred with sat. aq. KF (15 ml) for 2 hr. The mixture was filtered, the organic layer washed with sat. aq. KF (25 ml) and water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was chromatographed (ethyl acetate/petrol 3-10%) to give in order of elution the *2-acetyl-4'-methyl-1,1'-biaryl* (**192**) (20 mg, 11%), *2-methyl-9-phenanthrenol* (**193**) (42 mg, 22%) and the *ketone* **191** (117 mg, 32%).

2-acetyl-4'-methyl-1,1'-biaryl (**192**) as an oil; ν_{max} (film)/cm^{-1} 2923, 1682 (C=O), 1261; δ_H (400 MHz; $CDCl_3$) 7.53 (1H, d, *J* 7.6, H-3), 7.49 (1H, t, *J* 7.5, H-5), 7.42-7.37 (2H, m, H-4 and H-6), 7.24 (4H, s, ArH), 2.41 (3H, s, $ArCH_3$), 2.02 (3H, s, $COCH_3$); δ_C ($CDCl_3$) 140.8 (1C, q), 140.5 (1C, q), 137.8 (1C, q), 137.7 (1C, q), 130.6 (1C, t), 130.2 (1C, t), 129.4 (2C, t), 128.7 (2C, t), 127.8 (1C, t), 127.2 (1C, t), 30.5 (1C, p, $CO\underline{C}H_3$), 21.2 (1C, p, $ArCH_3$); *m/z* (EI) 210 (M^+), 195 (M-Me^+, 100%), 165, 152; (FAB) 211 (MH^+); (Found: M^+, 210.1054. $C_{15}H_{14}O$ requires *M*, 210.1045).

2-methyl-9-phenanthrenol (**193**) as orange needles, m.p. 162-165 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 3206, 1626, 1602, 1220, 1067, 757; δ_H (400 MHz; $CDCl_3$) 8.64 (1H, d, *J* 8.2, H-4), 8.49 (1H, d, *J* 8.4, H-3), 8.30 (1H, dd, *J* 0.9 and 8.0, H-8), 7.67 (1H, dt, *J* 1.3 and 8.1, H-6), 7.62 (1H, dt, *J* 1.3 and 8.2, H-7), 7.49 (1H, bs, OH), 7.34 (1H, dd, *J* 1,7 and 8.4, H-5), 6.95 (1H, s, H-1), 5.31 (1H, s, H-10), 2.54 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 150.8 (1C, q), 136.2 (1C, q), 133.3 (1C, q), 131.4 (1C, q), 126.6 (1C, t), 126.1

(1C, t), 125.9 (1C, q), 125.5 (1C, t), 123.9 (1C, q), 122.6 (1C, t), 122.3 (1C, t), 122.2 (1C, t), 105.3 (2C, t), 23.2 (1C, p, $ArCH_3$) *m/z* 208 (M^+, 100%), 178, 165; (Found: M^+, 208.0896. $C_{15}H_{12}O$ requires *M*, 208.0888).

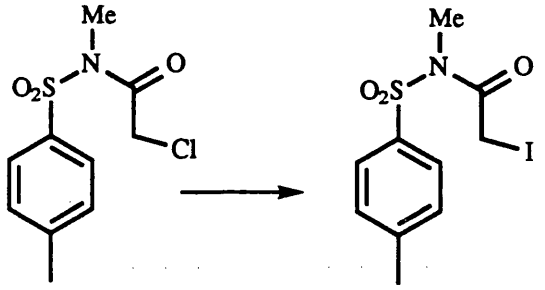
Preparation of *2-chloro-N-methyl-N-(p-toluenesulfonyl)acetamide* (**195**)



150 **195**

To a suspension of NaH (60% dispersion in oil; 728 mg) in THF (20 ml) was added a solution of N-methyl-*p*-toluenesulfonamide **150** (2.8 g, 15 mmol) in THF (30 ml). Effervescence occurred and the mixture was stirred for 30 min. Chloroacetyl chloride (1.8 ml, 23 mmol) was added and the mixture stirred for 2 days. Water (50 ml) was added and the mixture extracted with ether (3x40 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 60%) to give the *acetamide* **195** (3.1 g, 79%) as white prisms, m.p. 70-72 °C (ether/petrol); ν_{max}(film)/cm^{-1} 2924 (CH), 1712 (C=O), 1360 (S=O), 1164 (S=O), 665; δ_H(270 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.6, H-2' and H-6'), 7.38 (2H, d, *J* 8.6, H-3' and H-5'), 4.61 (2H, s, CH_2), 3.24 (3H, s, NCH_3), 2.46 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 166.4 (1C, q, C=O), 145.6 (1C, q, C-1), 135.0 (1C, q, C-4), 130.2 (2C, t, C-2), 127.4 (2C, t, C-3), 44.4 (1C, s, CH_2Cl), 33.4 (1C, p, NCH_3), 21.6 (1C, p, $ArCH_3$); *m/z* (EI) 225 (M^+-HCl), 199 and 197 (M^+-SO_2), 185, 155, 90 (100%); (CI) 281, 279 (MNH_4^+, 100%), 264, 262 (MH^+), 203; (Found: C, 45.6; H, 4.5; N, 5.5. $C_{10}H_{12}ClNO_3S$ requires C, 45.9; H, 4.6; N, 5.35 %)

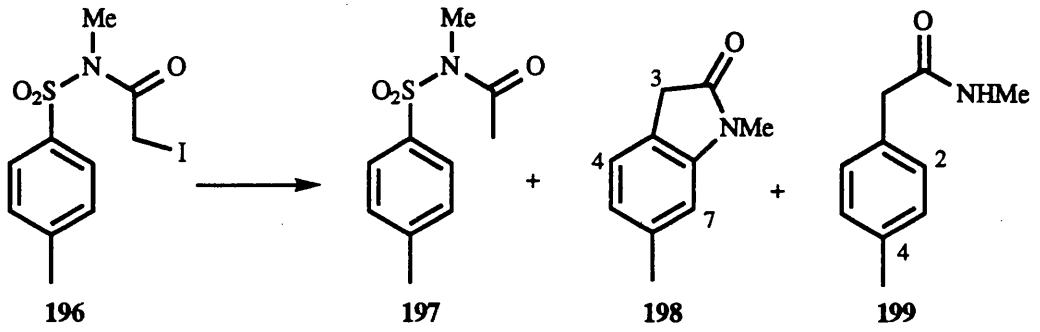
Preparation of *2-iodo-N-methyl-N-(p-toluenesulfonyl)acetamide* (**196**)



195 **196**

To sodium iodide (3.4 g, 24 mmol) in acetone (25 ml) at reflux was added the acetamide **195** (3.1 g, 12 mmol) and the mixture left overnight under reflux. Ether (25 ml) was added, the mixture filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (20 ml), washed with aq. sodium thiosulfate (10%, 2x15 ml), water (20 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give the *acetamide* **196** (2.4 g, 58%) as white prisms, m.p. 67-68 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2952, 1685, 1355 (S=O), 1166 (S=O), 705; δ_H(270 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.5, H-2' and H-6'), 7.37 (2H, d, *J* 8.5, H-3' and H-5'), 4.24 (2H, s, CH_2), 3.26 (3H, s, NCH_3), 2.45 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 167.6 (1C, q, C=O), 145.4 (1C, q, C-1), 135.0 (1C, q, C-4), 129.9 (2C, t, C-2 and C-6), 127.7 (2C, t, C-3 and C-5), 33.8 (1C, p, NCH_3), 21.6 (1C, p, $ArCH_3$), -1.5 (1C, s, CH_2I); *m/z* 289 (M^+-SO_2), 226 (M^+-I), 155, 91 (100%); (Found: C, 34.1; H, 3.5; N, 3.7. $C_{10}H_{12}INO_3S$ requires C, 34.0; H, 3.4; N, 4.0 %).

Reaction of *2-iodo-N-methyl-N-(p-toluenesulfonyl)acetamide* (**196**) with tri-n-butyltin hydride



196 **197** **198** **199**

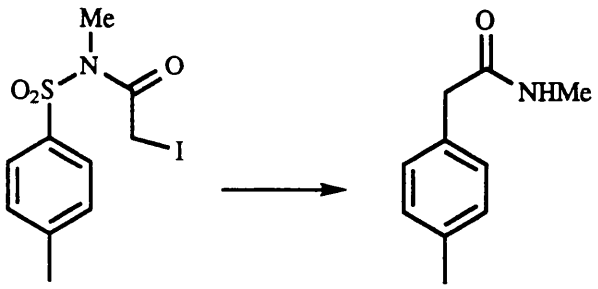
To a stirred solution of the acetamide **196** (312 mg, 0.88 mmol) in benzene (17.6 ml) at reflux, was added a solution of tri-n-butyltin hydride (313 µl, 1.15 mmol) and AIBN (115 mg; 0.7 mmol) in benzene (4.6 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 ml), added sat. aq. KF (15 ml) and left with strong stirring for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ether/petrol 25-50% and EtOAc) to give in order of elution *N-methyl-N-(p-toluenesulfonyl)acetamide* (**197**) (58 mg, 29%), *2,3-dihydro-1,6-dimethyl -indol-2-one* (**198**) (20 mg, 14%) and *N-methyl-p-tolylacetamide* (**199**) (24 mg, 17%).

N-methyl-N-(p-toluenesulfonyl)acetamide (**197**) as orange prisms, m.p. 45-50 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2955, 1702 (C=O), 1597, 1494, 1362 (S=O), 1164 (S=O); δ_H (270 MHz; $CDCl_3$) 7.50 (2H, d, *J* 8.3, H-2 and H-6), 7.34 (2H, d, *J* 8.1, H-3 and H-5), 3.24 (3H, s, NCH_3), 2.43 (3H, s, $ArCH_3$), 2.37 (3H, s, CH_3CO); δ_C ($CDCl_3$) 170.3 (1C, q, C=O), 144.9 (1C, q, C-1), 136.1 (1C, q, C-4), 129.9 (2C, t,C-2 and C-6), 127.2 (2C, t, C-3 and C-5), 32.9 (1C, p, NCH_3), 24.9 (1C, p, $COCH_3$), 21.5 (1C, p, $ArCH_3$); *m/z* (EI) 185 (M^+-CH_3CO), 163, 155, 91, 56 (100%); (CI) 472 ($[2M+NH_4]^+$), 228 (MH^+, 100%); (Found: MH^+, 228.0694. $C_{10}H_{14}NO_3S$ requires *MH*, 228.0694).

2,3-dihydro-1,6-dimethyl-indol-2-one (**198**) as beige needles, m.p. 92-93 °C (DCM/petrol); ν_{max} (film)/cm^{-1} 2939, 1701 (C=O), 1622, 1376, 949, 801; δ_H(270 MHz; $CDCl_3$) 7.11 (1H, d, *J* 7.6, H-4), 6.84 (1H, d, *J* 7.6, H-5), 6.64 (1H, s, H-7), 3.46 (2H, s, CH_2), 3.18 (3H, s, NCH_3), 2.38 (3H, s, $ArCH_3$); $\delta C(CDCl_3)$ 175.5 (1C, q, C=O), 145.3 (1C, q,), 137.9 (1C, q), 121.4 (1C, q), 124.0 (1C, t), 122.8 (1C, t), 109.0 (1C, t), 35.5 (1C, s, CH_2), 26.1 (1C, p, NCH_3), 21.7 (1C, p, $ArCH_3$); *m/z* 161 (M^+, 100%), 146, 132; (Found: M^+, 161.0841. $C_{10}H_{11}NO$ requires *M*, 161.0841).

N-methyl-p-tolylacetamide (**199**) as white needles, m.p. 116-117 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3292 (NH), 1653 (C=O), 1558, 1403; δ_H (270 MHz; $CDCl_3$) 7.15 (4H, s, ArH), 5.30 (1H, bs, NH), 3.53 (2H, s, CH_2), 2.74 (3H, d, NCH_3), 2.34 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 171.8 (1C, q, C=O), 136.9 (1C, q, C-1), 131.8 (1C, q, C-4), 129.6 (2C, t, C-2 and C-6), 129.3 (2C, t, C-3 and C-5), 43.2 (1C, s, CH_2), 26.4 (1C, p, NCH_2), 21.0 (1C, p, $ArCH_3$); *m/z* 163 (M^+), 106 (100%), 91; (Found: M^+, 163.0997. $C_{10}H_{13}NO$ requires *M*, 163.0997).

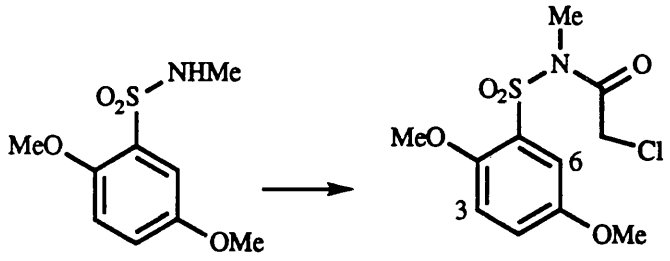
Photochemical reaction of *2-iodo-N-methyl-N-(p-toluenesulfonyl)acetamide* (**196**)



196 **199**

A solution of acetamide **196** (101 mg, 0.28 mmol) in benzene (5.6 ml), *bis*(tri-n-butyltin) (143 µl, 0.28 mmol) and ethyl iodide (91 µl, 1.12 mmol), was irradiated using a medium pressure mercury vapour lamp (125 W) for 7 hr. Analysis of the ^1H nmr spectrum of the crude mixture showed only the acetamide **199**.

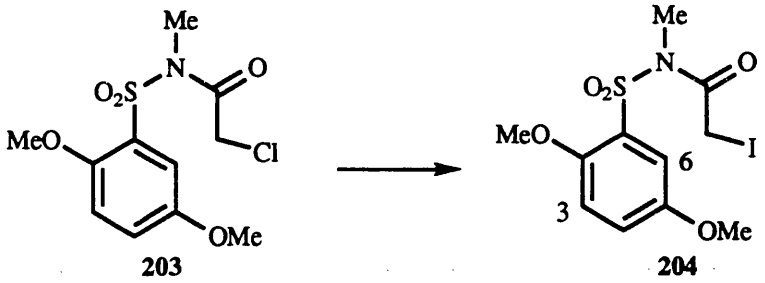
Preparation of *2-chloro-N-(2,5-dimethoxyphenylsulfonyl)N-methyl acetamide* (**203**)



171 **203**

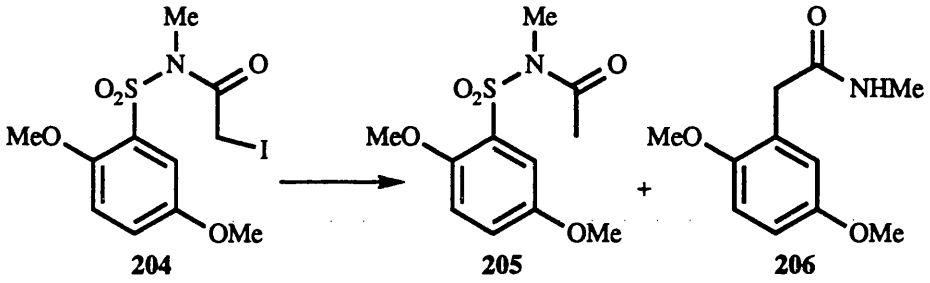
To a suspension of NaH (60% dispersion in oil; 167 mg) in THF (4 ml) was added a solution of benzenesulfonamide **171** (805 mg, 3.5 mmol) in THF (9 ml). Effervescence occurred and the mixture was stirred for 1/2hr. Chloroacetyl chloride (420 µl, 5.3 mmol) was added and the mixture stirred for 2 days. Water (20 ml) was added and the mixture extracted with ether (3x10 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give the *acetamide* **203** (673 mg, 63%) as white prisms, m.p. 117-119 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2952 (CH), 1712 (C=O), 1500, 1359 (S=O), 1159 (S=O); δ_H (270 MHz; $CDCl_3$) 7.49 (1H, d, *J* 3.2, H-6), 7.16 (1H, dd, *J* 3.2 and 9.0, H-4), 6.97 (1H, d, *J* 9.0, H-3), 4.80 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.06 (3H, s, NCH_3); δ_C ($CDCl_3$) 167.7 (1C, q, C=O), 153.2 (1C, q, C-5), 150.7 (1C, q, C-2), 124.9 (1C, q, C-1), 122.3 (1C, t, C-6), 115.5 (1C, t, C-4), 113.7 (1C, t, C-3), 56.6 (1C, p, OCH_3), 56.1 (1C, p, OCH_3), 45.5 (1C, s, CH_2), 33.2 (1C, p, NCH_3); *m/z* 309, 307 (M^+), 243, 245 (M^+-SO_2), 231, 201, 180, 137, 90 (100%); (Found: M^+, 307.0281. $C_{11}H_{14}Cl^{35}NO_5S$ requires *M*, 307.0281).

Preparation of *2-iodo-N-(2,5-dimethoxyphenylsulfonyl)N-methyl acetamide* (**204**)



To sodium iodide (602 mg, 4.3 mmol) in acetone (2 ml) at reflux was added a solution of acetamide **203** (647 mg, 2.1 mmol) in acetone (7 ml) and the mixture left overnight under reflux. DCM (10 ml) was added, the mixture filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (15 ml), washed with sodium thiosulfate (2x15 ml), water (10 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give *acetamide* **204** (536 mg, 64%) as white prisms, m.p. 109-110 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2948, 1668 (C=O), 1573, 1499, 1355 (S=O), 1164 (S=O); δ_H (270 MHz; $CDCl_3$) 7.47 (1H, d, *J* 3.2, H-6), 7.13 (1H, dd, *J* 3.2 and 9.3, H-4), 6.96 (1H, d, *J* 9.3, H-3), 4.37 (2H, s, CH_2), 3.85 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.13 (3H, s, NCH_3);*m/z* 399 (M^+), 335 (M^+-SO_2), 304, 272 (M^+-I), 231, 182 (100%); (Found: C, 33.0;H, 3.4; N, 3.6. $C_{11}H_{14}INO_5S$ requires C, 33.1; H, 3.5; N, 3.5%).

Reaction of *2-iodo-N-(2,5-dimethoxyphenylsulfonyl)N-methyl acetamide* (**204**) with tri-n-butyltin hydride



204 **205** **206**

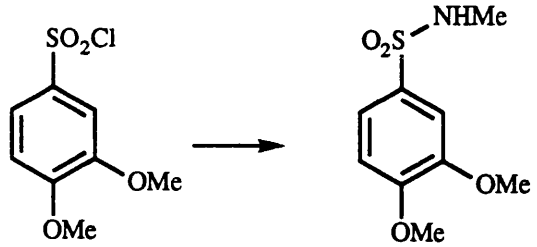
To a stirred solution of acetamide **204** (184 mg, 0.46 mmol) in benzene (9 ml) at reflux, was added a solution of tri-n-butyl tin hydride (163 µl, 0.60 mmol) and AIBN (54 mg; 0.33 mmol) in benzene (2.4 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (5 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (15 ml), sat. aq. KF (10 ml) added and stirred vigorously for 2 hr. The suspension was filtered, the organic layer washed with sat. aq. KF (10 ml) and water (10 ml) dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (ethyl acetate/petrol 40-100%,) to give in order of elution *N-(2,5-dimethoxyphenylsulfonyl)-N-methyl acetamide* (**205**) (26 mg, 21%), and *N-(2,5-dimethoxyphenyl)-N-methyl acetamide* (**206**) (49 mg, 51%).

N-(2,5-dimethoxyphenylsulfonyl)-N-methyl acetamide (**205**) as an orange oil; ν_{max}(film)/cm^{-1} 2952, 1700 (C=O), 1500, 1466, 1354 (S=O), 1161 (S=O); δ_H (270 MHz; $CDCl_3$) 7.52 (1H, d, *J* 3.2, H-6), 7.13 (1H, dd, *J* 3.2 and 9.0, H-4), 6.96 (1H, d, *J* 9.4, H-3), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.16 (3H, s, NCH_3), 2.40 (3H, s, $COCH_3$); δ_C ($CDCl_3$) 171.0 (1C, q, C=O), 153.0 (1C, q, C-5), 150.8 (1C, q, C-2), 126.5 (1C, q, C-1), 121.8 (1C, t, C-6), 115.3 (1C, t, C-4), 113.7 (1C, t, C-3), 56.5 (1C, p, OCH_3), 56.1 (1C, p, OCH_3), 32.8 (1C, p, NCH_3), 25.0 (1C, p, $COCH_3$); *m/z* 273 (M^+), 231, 209, 178, 56 (100%); (Found: MNH_4^+, 291.1015. $C_{11}H_{19}N_2O_5S$ requires *MNH4*, 291.1015).

N-(2,5-dimethoxyphenyl)-N-methyl acetamide (**206**) as white needles, m.p. 84-86 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 3302 (NH), 2940, 1652 (C=O), 1503, 1227, 1046; δ_H

(270 MHz; $CDCl_3$) 6.83-6.74 (3H, m, ArH), 5.77 (1H, bs, NH), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.51 (2H, s, CH_2), 2.71 (3H, d, *J* 4.6, NCH_3); δ_C ($CDCl_3$) 171.6 (1C, q, C=O), 153.7 (1C, q, C-5), 151.2 (1C, q, C-2), 124.7 (1C, q, C-1), 116.9 (1C, t), 113.1 (1C, t), 111.8 (1C, t), 56.0 (1C, p, OCH_3), 55.6 (1C, p, OCH_3), 38.5 (1C, s, CH_2), 26.3 (1C, p, NCH_3); *m/z* 209 (M^+), 151, 137 (100%), 121; (Found: C, 63.0;H, 7.3; N, 6.9. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%)

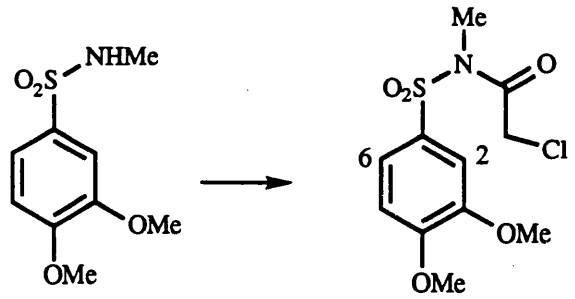
Preparation of *N-methyl-3,4-dimethoxybenzenesulfonamide* (**207**)



207

To a suspension of 3,4-dimethoxybenzenesulfonyl chloride (3.6 g, 15 mmol) in aq. NaOH (10%, 21 ml) was added methylamine (25-30% in water, 4.6 ml) and the mixture stirred vigorously for 24 hr. The reaction mixture was diluted with water (20 ml), extracted with DCM (3x30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure, to give the *sulfonamide* **207** (2.1 g, 61%) as white needles, m.p. 123-124 °C; ν_{max}(film)/cm^{-1} 3291 (NH), 2939, 1325 (S=O), 1158 (S=O); δ_H (270 MHz; $CDCl_3$) 7.47 (1H, dd, *J* 2.2 and 8.6, H-6), 7.34 (1H, d, *J* 2.0, H-2), 6.94 (1H, d, *J* 8.3, H-5), 4.59 (1H, bs, NH), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.63 (3H, d, *J* 5.6, NCH_3); δ_C ($CDCl_3$) 152.5 (1C, q, C-4), 149.1 (1C, q, C-3), 130.3 (1C, q, C-1), 121.2 (1C, t, C-6), 110.5 (1C, t, C-2), 109.6 (1C, t, C-5), 56.2 (1C, p, OCH_3), 56.1 (1C, p, OCH_3), 29.2 (1C, p, NCH_3); *m/z* 231 (M^+), 201, 137 (100%); (Found: C, 46.7;H, 5.5; N, 5.9. $C_9H_{13}NO_4S$ requires C, 46.7; H, 5.7; N, 6.1%)

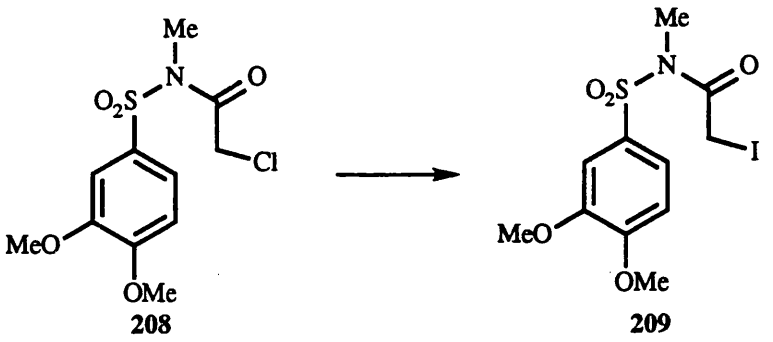
Preparation of *2-chloro-N-(3,4-dimethoxyphenylsulfonyl)-N-methyl acetamide* (**208**)



207 **208**

To a suspension of sodium hydride (60% dispersion in oil; 212 mg) in THF (5 ml) was added a solution of benzenesulfonamide **207** (1.0 g, 4.3 mmol) in THF (12 ml). Effervescence occurred and the mixture was stirred for 30 min. Chloroacetyl chloride (0.7 ml, 8.9 mmol) was added and the mixture stirred for 2 days. Water (50 ml) was added and the mixture extracted with DCM (3x50 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (EtOAc/petrol 30-100%) to give *acetamide* **208** (630 mg, 47%) as white prisms, m.p. 118-120 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2939, 1709, 1509, 1371 (S=O), 1266, 1162 (S=O); δ_H (270 MHz; $CDCl_3$) 7.51 (1H, dd, *J* 2.4 and 8.5, H-6), 7.32 (1H, d, *J* 2.4, H-2), 6.98 (1H, d, *J* 8.5, H-5), 4.61 (2H, s, CH_2Cl), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.24 (3H, s, NCH_3); δ_C ($CDCl_3$) 166.4 (1C, q, C=O), 154.0 (1C, q, C-4), 149.5 (1C, q, C-3), 129.2 (1C, q, C-1), 121.9 (1C, t, C-6), 110.8 (1C, t, C-2), 109.7 (1C, t, C-5), 56.3 (2C, p, OCH_3), 44.1 (1C, s, CH_2Cl), 33.4 (1C, p, NCH_3); *m/z* 309, 307 (M^+), 154 (100%), 137 (100%), 90 (100%); (Found: C, 42.8; H, 4.25; N, 4.4. $C_{11}H_{14}ClNO_5S$ requires C, 42.9; H, 4.6; N, 4.55%)

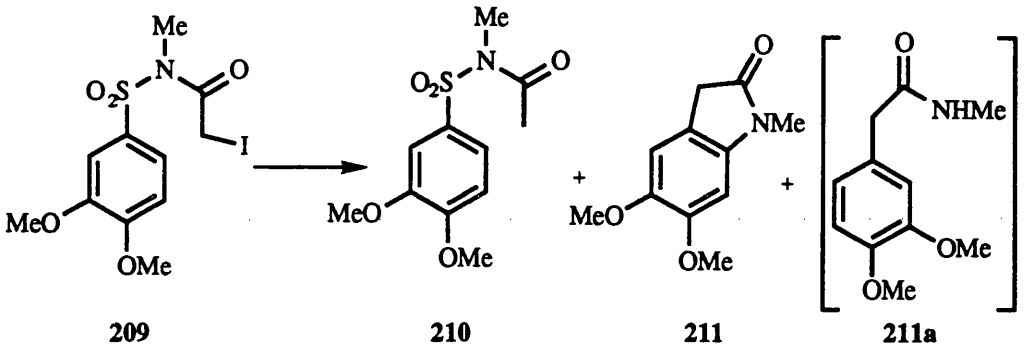
Preparation of *N-(3,4-dimethoxyphenylsulfonyl)-2-iodo-N-methyl acetamide* (**209**)



208 **209**

To sodium iodide (779 mg, 5.5 mmol) in acetone (5 ml) at reflux was added a solution of acetamide **208** (562 mg, 1.8 mmol) in acetone (6 ml) and the mixture left overnight under reflux. The mixture was cooled to room temperature, DCM (10 ml) was added, filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (15 ml), washed with sodium thiosulfate (2x15 ml), water (10 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75-100%) to give *acetamide* **209** (527 mg, 72%) as white prisms, m.p. 87-89 °C; ν_{max}(film)/cm^{-1} 2952, 1684 (C=O), 1353 (S=O), 1164 (S=O); δ_H (270 MHz; $CDCl_3$) 7.57 (1H, dd, *J* 2.4 and 8.5, H-6), 7.42 (1H, d, *J* 2.2, H-2), 6.97 (1H, d, *J* 8.5, H-5), 4.27 (2H, s, CH_2I), 3.96 (3H, s, OCH_3), 3.95 (1H, s, OCH_3), 3.24 (3H, s, NCH_3); δ_C ($CDCl_3$) 167.7 (1C, q, C=O), 153.9 (1C, q, C-4), 149.3 (1C, q, C-3), 129.2 (1C, q, C-1), 122.3 (1C, t, C-6), 110.6 (1C, t, C-2), 109.1 (1C, t, C-5), 56.4 (1C, p, OCH_3), 56.3 (1C, p, OCH_3), 33.8 (1C, p, NCH_3), -1.6 (1C, s, CH_2I); *m/z* 399 (M^+) 335, 231, 201, 182, 154 (100%); (Found: M^+, 398.9637. $C_{11}H_{14}INO_5S$ requires *M*, 398.9637).

Reaction of *N-(3,4-dimethoxyphenylsulfonyl)-2-iodo-N-methyl acetamide* (**209**) with tri-n-butyltin hydride



209 **210** **211** **211a**

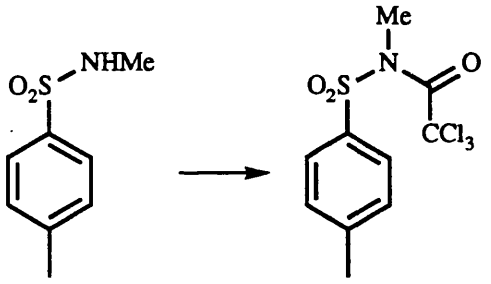
To a stirred solution of acetamide **209** (344 mg, 0.86 mmol) in benzene (167 ml) at reflux, was added a solution of tri-n-butyltin hydride (310 µl, 1.13 mmol) and AIBN (100 mg; 0.61 mmol) in benzene (4.5 ml) dropwise over 11 hr, *via* a needle placed directly above the refluxing solution. After further 2 hr the reaction was cooled to room temperature, carbon tetrachloride (10 ml) and a few crystals of iodine were added and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (20 ml), sat. aq. KF (15 ml) added and stirred vigorously for 2 hr. The suspension was filtered to a separation funnel, the organic layer washed with sat. aq. KF (15 ml) and water (15 ml) dried ($MgSO_4$), and concentrated under reduced pressure. Analysis of the ^1H nmr spectrum of the crude mixture shows a doublet at 2.75 ppm and a singulet at 3.53 ppm, which probably corresponds to the *ipso* product **211a**.in a relative ratio of the three products of 1:1:1. Due to its hight polarity it could not be removed from the silica, when the mixture was chromatographed. The residue was chromatographed (ethyl acetate/petrol 50-100%) to give in order of elution *N-(3,4-dimethoxyphenylsulfonyl)-N-methyl acetamide* (**210**) (62 mg, 26%) and *5,6-dimethoxy-2,3-dihydro-1-methyl-indol-2-one* (**211**) (37 mg, 21%).

N-(3,4-dimethoxyphenylsulfonyl)-N-methyl acetamide (**210**) as an orange oil; ν_{max}(film)/cm^{-1} 2943, 1694 (C=O), 1510, 1356 (S=O), 1261, 1154 (S=O); δ_H(270 MHz; $CDCl_3$) 7.47 (1H, dd, *J* 2.2 and 8.5, H-6), 7.30 (1H, d, *J* 2.2, H-2), 6.94 (1H, d, *J* 8.5, H-5), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.25 (3H, s, NCH_3), 2.37 (3H, s, $COCH_3$); δ_C($CDCl_3$) 170.2 (1C, q, C=O), 153.4 (1C, q), 149.2 (1C, q), 130.5 (1C, q), 121.4 (1C, t), 110.6 (1C, t), 109.7 (1C, t), 56.2 (2C, p, OCH_3), 32.9 (1C, p, NCH_3),

24.9 (1C, p, $COCH_3$); *m/z* (EI) 274 (MH^+); (CI) 291 (MNH_4^+), 274 (MH^+, 100%); (Found: MH^+, 274.0749. $C_{11}H_{16}NO_5S$ requires *MH*, 274.0749).

5,6-dimethoxy-2,3-dihydro-1-methyl-indol-2-one (**211**) as red needles, m.p. 118-119.5 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 2937, 1703 (C=O), 1378, 1070; δ_H(270 MHz; $CDCl_3$) 6.86 (1H, s, H-7), 6.44 (1H, s, H-4), 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.44 (2H, s, $ArCH_2$), 3.18 (3H, s, NCH_3); δ_C($CDCl_3$) 175.4 (1C, q, C=O), 149.4 (1C, q), 144.9 (1C, q), 138.9 (1C, q), 115.1 (1C, q), 109.9 (1C, t), 94.4 (1C, t), 56.9 (1C, p, OCH_3), 56.4 (1C, p, OCH_3), 35.8 (1C, s, $ArCH_2$), 26.2 (1C, p, NCH_3); *m/z* EI: 207 (M^+), 192 (100%), 164, 136;

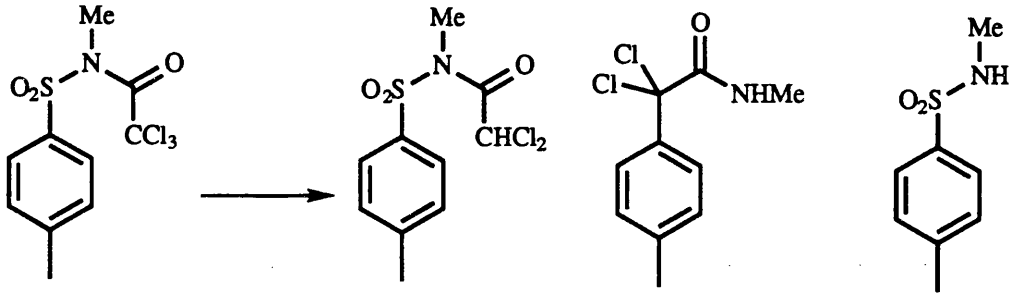
Preparation of *trichloro-N-(p-toluenesulfonyl) acetamide* (**214**)



150 **214**

To a suspension of sodium hydride (60% dispersion in oil; 569 mg) in THF (14 ml) was added a solution of benzenesulfonamide **150** (2.2 g, 12 mmol) in THF (20 ml). Effervescence occurred and the mixture was stirred for 1 hr. Trichloroacetyl chloride (2.0 ml, 18 mmol) was added and the mixture stirred for 4 days. Water (40 ml) was added and the mixture extracted with DCM (3x30 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 75%) to give *acetamide* **214** (1.9 g, 47%) as white needles, m.p. 130-132.5 °C (DCM/petrol); ν_{max}(film)/cm^{-1} 1695 (C=O), 1361 (S=O), 1169 (S=O); δ_H (270 MHz; $CDCl_3$) 7.92 (2H, d, *J* 8.3, H-2 and H-6), 7.35 (2H, d, *J* 8.3, H-3 and H-5), 3.78 (3H, s, NCH_3), 2.45 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 158.9 (1C, q, C=O), 145.7 (1C, q, C-1), 134.4 (1C, q, C-4), 129.6 (2C, t, C-2 and C-6), 128.6 (2C, t, C-3 and C-5), 92.2 (1C, q, CCl_3), 36.1 (1C, p, NCH_3), 21.7 (1C, p, $ArCH_3$); *m/z* 265, 267, 269 (M^+-SO_2), 173, 155; (Found: C, 36.4; H, 2.85; N, 4.4. $C_{10}H_{10}Cl_3NO_3S$ requires C, 36.3; H, 3.05; N, 4.2%).

Reaction of *trichloro-N-(p-toluenesulfonyl) acetamide* (**214**) with Copper (I) Chloride



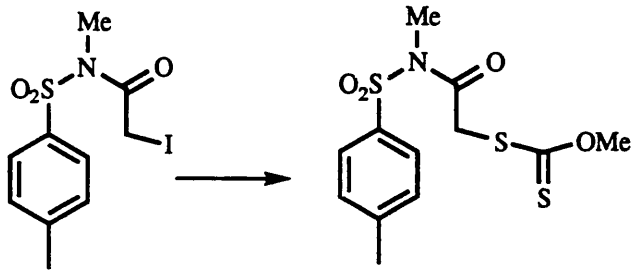
214 **215** **216** **150**

To the sulfonamide **214** (98.6 mg; 0.30 mmol) and CuCl (9 mg; 0.09 mmol) in DCM (2 ml), under argon, was added TMEDA (45 µl, 0.30 mmol) and the mixture turned immediately dark green. After 1 hr, the solvent was removed under reduced pressure, and the residue chromatographed (DCM/petrol 50-100% and EtOAc) to give in order of elution *sulfonamide* **214** (14 mg, 14%), *dichloro-N-(p-toluenesulfonyl) acetamide* (**215**) (traces), *dichloro-N-methyl-p-tolylacetamide* (**216**) (25 mg, 36%), and *sulfonamide* **150** (21 mg, 39%);

dichloro-N-(p-toluenesulfonyl) acetamide (**215**) as a clear oil; ν_{max}(film)/cm^{-1} (C=O), (S=O), (S=O); δ_H (270 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.5, H-2 and H-6), 7.39 (2H, d, *J* 8.5, H-3 and H-5), 7.11 (1H, s, $CHCl_2$), 3.26 (3H, s, NCH_3), 2.46 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 164.3 (1C, q, C=O), 146.1 (1C, q, C-S), 134.2 (1C, q, C-C), 130.2 (2C, t), 127.9 (2C, t), 64.8 (1C, t, $CHCl_2$), 33.9 (1C, p, NCH_3), 21.7 (1C, p, $ArCH_3$); *m/z* (FAB) 300, 298, 296 (MH^+), 155, 91; (Found: MH^+, 295.9912. $C_{10}H_{12}Cl_2NO_3S$ requires *MH*, 295.9915).

dichloro-N-methyl-p-tolylacetamide (**216**) as a clear oil; ν_{max}(film)/cm^{-1} 3351 (NH), 2925, 1680 (C=O), 1518; δ_H(270 MHz; $CDCl_3$) 7.59 (2H, d, *J* 8.5, H-2 and H-6), 7.20 (2H, d, *J* 8.5, H-3 and H-5), 6.80 (1H, bs, NH), 2.94 (3H, d, *J* 4.9, NCH_3), 2.36 (3H, s, $ArCH_3$); δ_C($CDCl_3$) 166.2 (1C, q, C=O), 140.0 (1C, q, C-S), 136.7 (1C, q), 129.1 (2C, t), 126.5 (2C, t), 86.7 (1C, q, CCl_2), 27.7 (1C, p, NCH_3), 21.1 (1C, p, $ArCH_3$); *m/z* 235, 233, 231 (M^+), 196, 176, 174 (100%), 58; (Found: MH^+, 232.0292. $C_{10}H_{12}Cl_2NO$ requires *MH*, 232.0296).

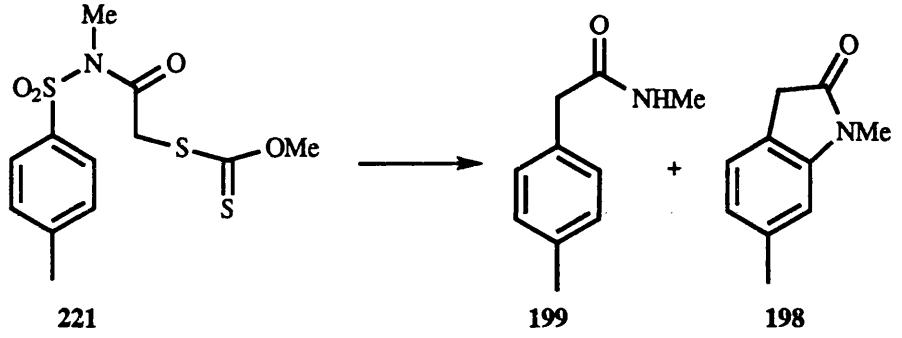
Preparation of *N-(p-toluenesulfonyl) (O-methyldithiocarbonate) acetamide* (**221**)



196 **221**

To a suspension of NaH (60% dispersion in oil; 120 mg) in THF (10 ml) was added methanol (120 µl, 3.0 mmol). After 20 min. carbon disulfide (540 µl, 9.0 mmol) was added and the mixture left at r.t. for 30 min. Than, a solution of the sulfonamide **196** (1.1 g, 3 mmol) in THF (10 ml) was added and the mixture left for another hour. Acetic acid (2 ml) was added and the mixture poured onto water, extracted with ether (3x25 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (DCM/petrol 50%) to give the *xanthate* **221** (731 mg, 73%) as yellow prisms, m.p. 66-68 °C; ν_{max}(film)/cm^{-1} 2946, 1702 (C=O), 1358 (S=O), 1234, 1162 (S=O), 1066; δ_H (400 MHz; $CDCl_3$) 7.83 (2H, d, *J* 8.4, H-2 and H-6), 7.36 (2H, d, *J* 8.6, H-3 and H-5), 4.46 (2H, s, CH_2), 4.11 (3H, s, OCH_3), 3.27 (3H, s, NCH_3), 2.44 (3H, s, $ArCH_3$); δ_C ($CDCl_3$) 166.9 (1C, q, C=O), 145.4 (1C, q, C-1), 135.3 (1C, q, C-1), 130.1 (2C, t, C-2 and C-6), 127.6 (2C, t, C-3 and C-5), 60.8 (1C, p, OCH_3), 42.3 (1C, s, SCH_2), 33.5 (1C, s, NCH_3), 21.7 (1C, p, $ArCH_3$); *m/z* (EI) 333 (M^+), 149, 91 (100%); (CI) 351 (M^++NH_4), 334 (MH^+), 149 (100%); (Found: MH^+, 334.0241. $C_{12}H_{16}NO_4S_3$ requires *MH*, 334.0241).

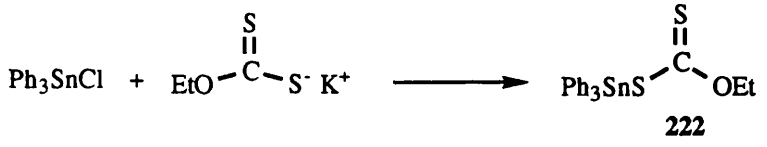
Reaction of *N-(p-toluenesulfonyl) (O-methyldithiocarbonate) acetamide* (**221**) under UV light



221 **199** **198**

A solution of the xanthate **221** (101 mg, 0.3 mmol) in toluene (6 ml) at reflux was irradiated for 16 hr using a medium pressure mercury vapour lamp (125 W). The solvent was removed under reduced pressure and the residue chromatographed on silica gel (ether/petrol 25-100% and EtOAc) to give, in order of elution, *indolone* **198** (5 mg, 10%) and *acetamide* **199** (13 mg, 27%).

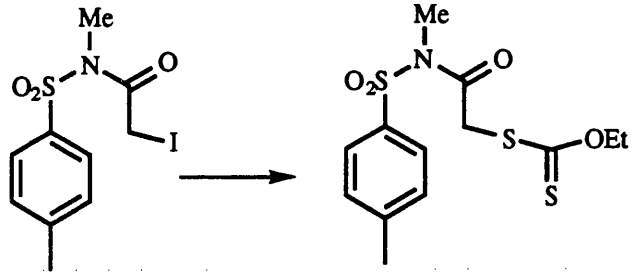
Preparation of *O-ethyl triphenyltin xanthate* (**222**)[13]



222

To a mixture of chlorotriphenyltin (3.9 g, 1.0 mmol) and potassium *O*-ethyl xanthate (1.6 g, 1.0 mmol) under argon was added dry ether (25 ml), and stirred at r.t. for 24 hr. The mixture was filtered by cannula and the solvent removed under reduced pressure to give *O-ethyl triphenyltin xanthate* (**222**) (3.3 g, 69%), which was used without further purification.

Reaction of **196** under visible light, in the presence of tri-phenyltin xanthate



196 **223**

A solution of the acetamide **196** (108 mg, 0.31 mmol), *O*-ethyl triphenyltin xanthate (**222**) (289 mg, 0.61 mmol) and hexaphenylditin (32 mg) in benzene (6 ml) was irradiated with a tungsten lamp (500W) for 5 hr. The solvent was removed under reduced pressure and the residue chromatographed (ether/petrol 10-100% and EtOAC) to give, in order of elution, *N-(p-toluenesulfonyl) (O-ethyldithiocarbonate) acetamide* (**223**) (82 mg, 77%) and *sulfonamide* **150** (10 mg, 17%).

N-(p-toluenesulfonyl) (O-ethyldithiocarbonate) acetamide (**223**) as an oil; ν_{max}(film)/cm^{-1} 1702 (C=O), 1359 (S=O), 1231, 1163 (S=O), 1049; δ_H(400 MHz; $CDCl_3$) 7.82 (2H, d, *J* 8.4, H-2 and H-6), 7.35 (2H, d, *J* 7.9, H-3 and H-5), 4.55 (2H, q, *J* 7.1, OCH_2), 4.44 (2H, s, S-CH_2), 3.27 (3H, s, NCH_3), 2.43 (3H, s, ArCH_3), 1.35 (3H, t, *J* 7.1, $CH_2\underline{C}H_3$); δ_C($CDCl_3$) 166.9 (1C, q, C=O), 145.3 (1C, q), 135.3 (1C, q), 130.2 (2C, t), 127.6 (2C, t), 70.7 (1C, s, OCH_2), 41.9 (1C, s, S-CH_2), 33.4 (1C, p, NCH_3), 21.6 (1C, p, ArCH_3), 13.7 (1C, p, $CH_2\underline{C}H_3$); *m/z* 347 (M^+), 155, 91 (100%);

References

1 O. Kamm and J. B. Segur, *Org. Synth.*, 1941, **1**, 372.

2 Dictionary of Organic Compounds (J. I. G. Cadogan, R. A. Raphael and C. W. Rees, Eds), Chapman & Hall, New York, 1982.

3 M. Budesínsky and O. Exner, *Mag. Res. Chem.*, 1989, **27**, 585.

4 A. Pennel, PhD Thesis, University of London, 1991.

5 C.-G. Huang and P. Wan, *J. Org. Chem.*, 1991, **56**, 4846.

6 M. Iwao and T. Kuraishi, *Heterocycles,* 1992, **34**, 1031.

7 G. M. A. Abou, G. A. Schiehser and S. J. Childress, **Eur. Pat. Appl. EP 220,051**. Chem. Abst. 108:112497x.

8 Vogel's Textbook of Practical Organic Chemistry (B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith and A. R. Tatchell, Eds), 4th ed., Longman Scientific & Technical, 1987, p. 649.

9 H. Teeninga and J. B. F. N. Engberts, *J. Org. Chem.*, 1983, **48**, 537.

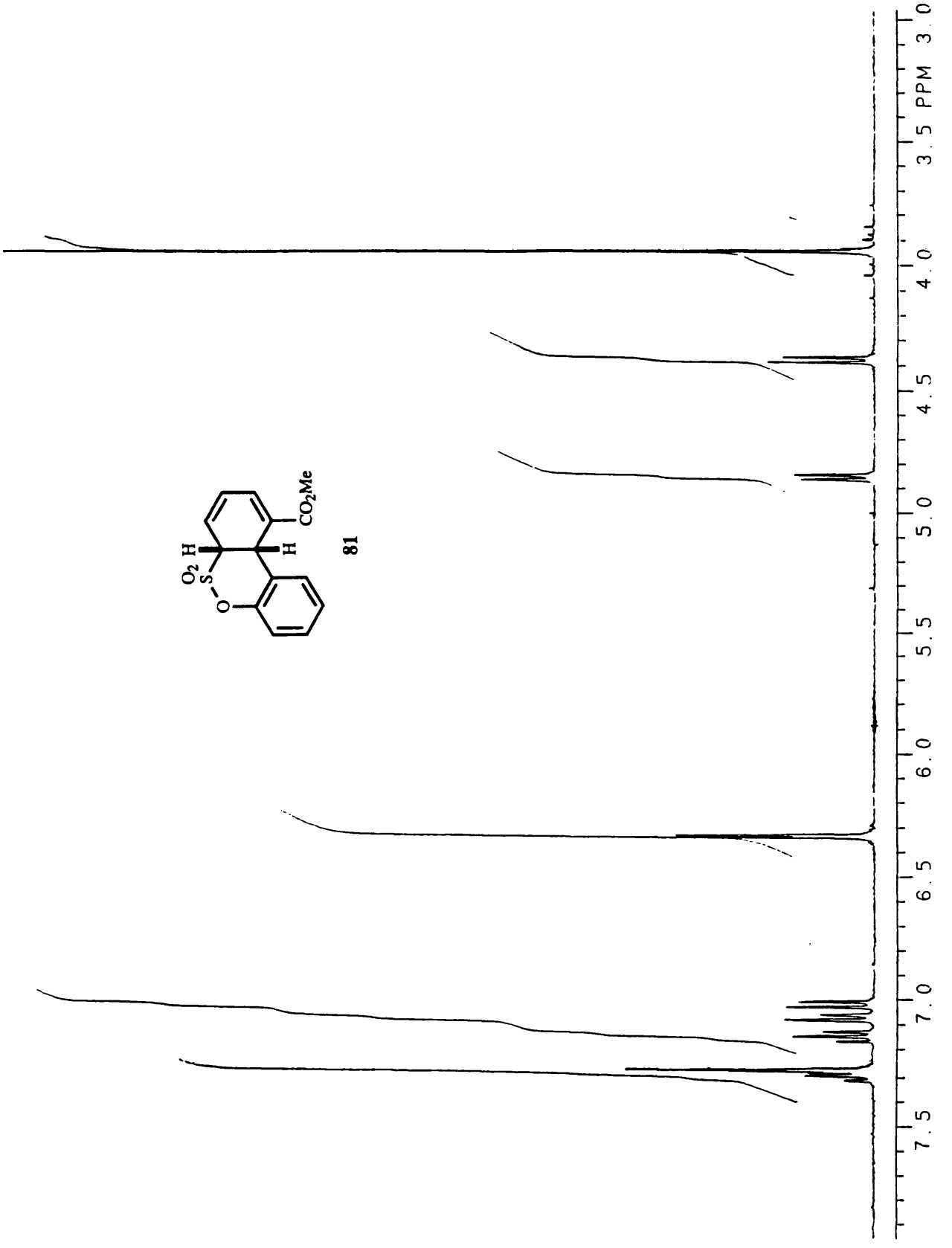
10 T. Sakamoto, M. Annaka, Y. Kondo, H. Yakamaka, *Chem. Pharm. Bull.*, 1986, **34**, 2754.; A. Pennel, PhD Thesis, University of London, 1991.

11. a) Dictionary of Organic Compounds (J. I. G. Cadogan, R. A. Raphael and C. W. Rees, Eds), Chapman & Hall, New York, 1982; b) F. Ujjainwalla, PhD Thesis, University of London, 1993.

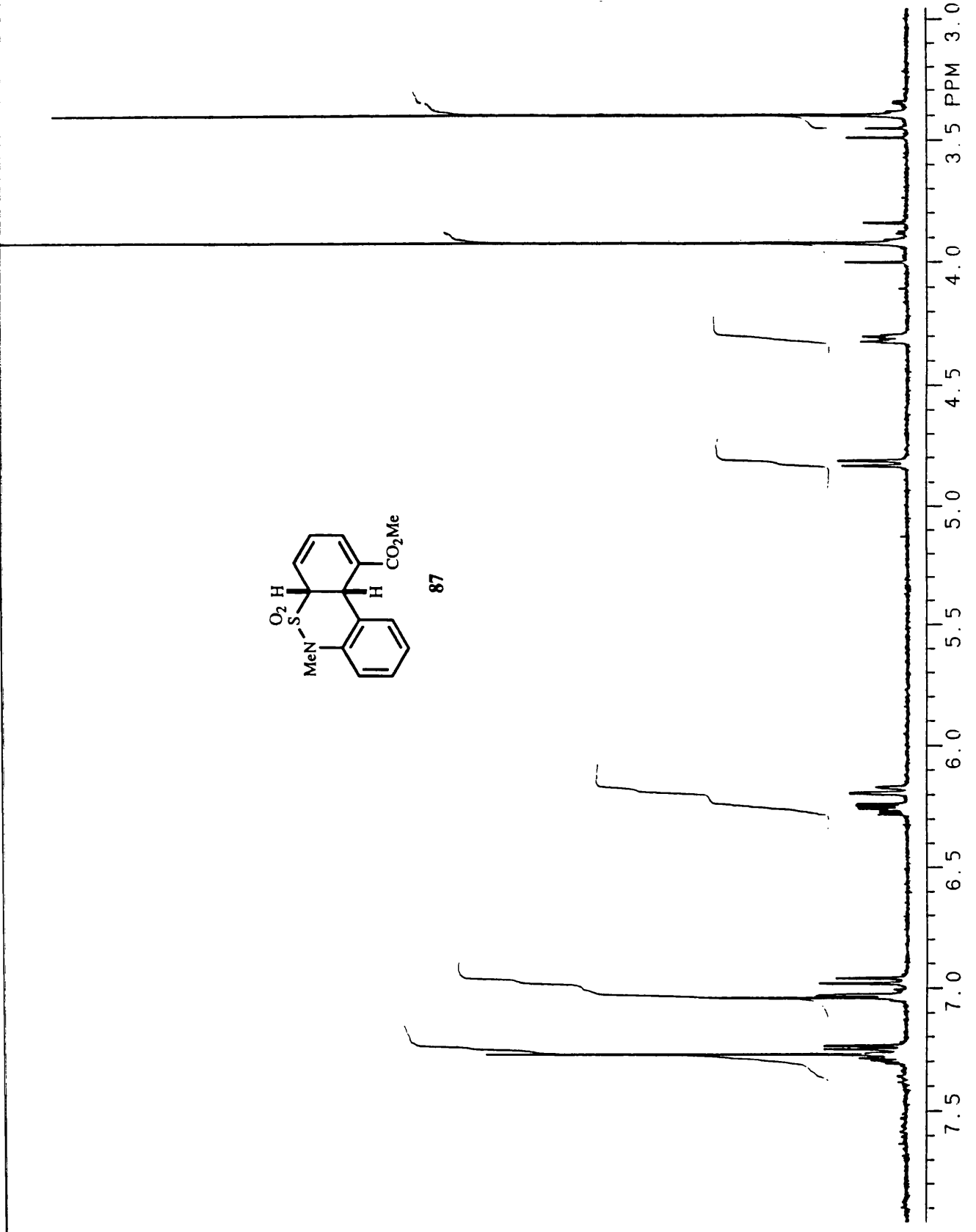
12 L. Field and R. D. Clark, *Org. Synth.*, 1963, **4**, 674.

13 M. Schmidt, H. Schumann, F. Gliniecki and F. J. Jaggard, *J. Organomet. Chem.*, 1969, **17**, 277.

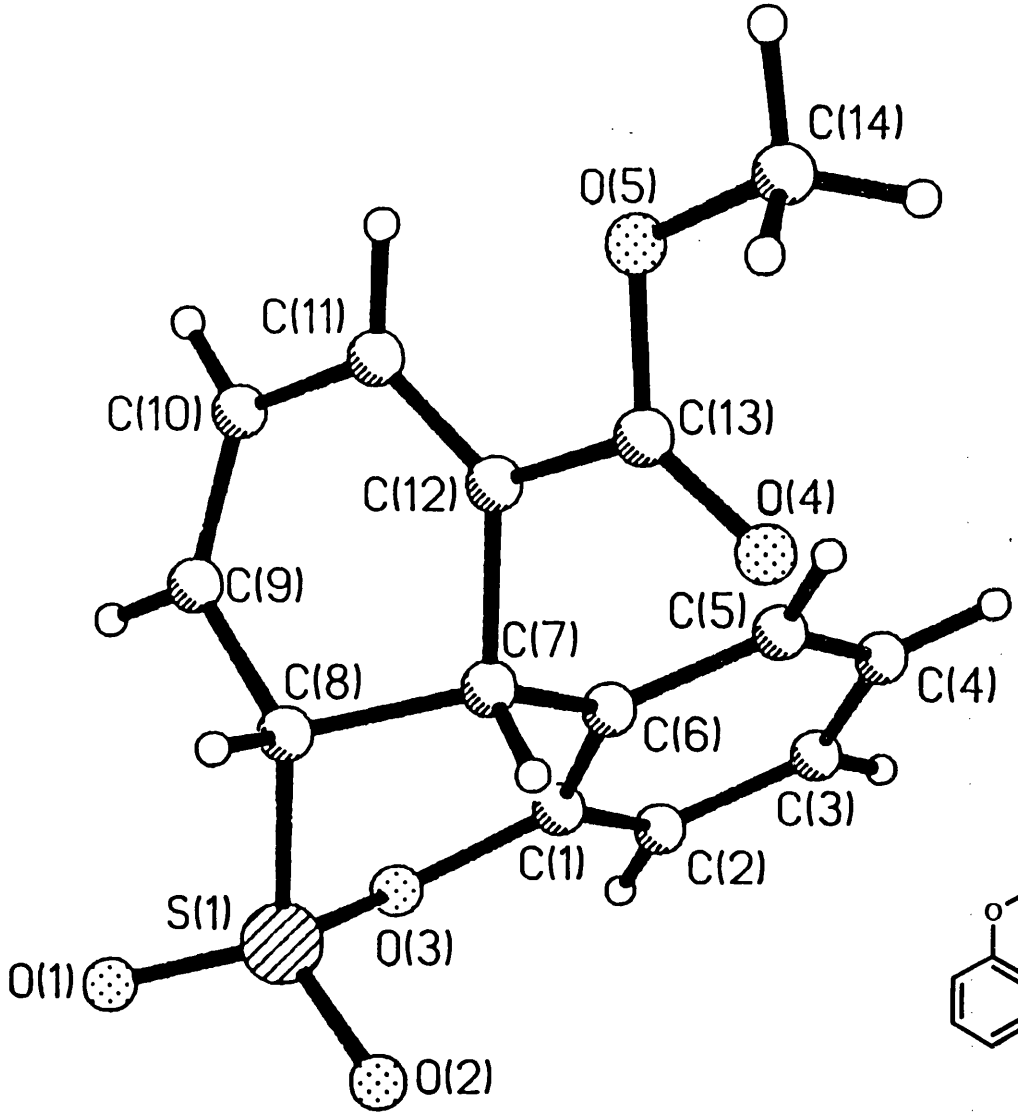
Appendix 1

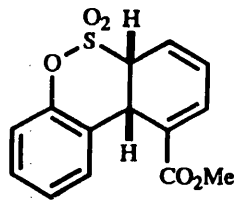


81

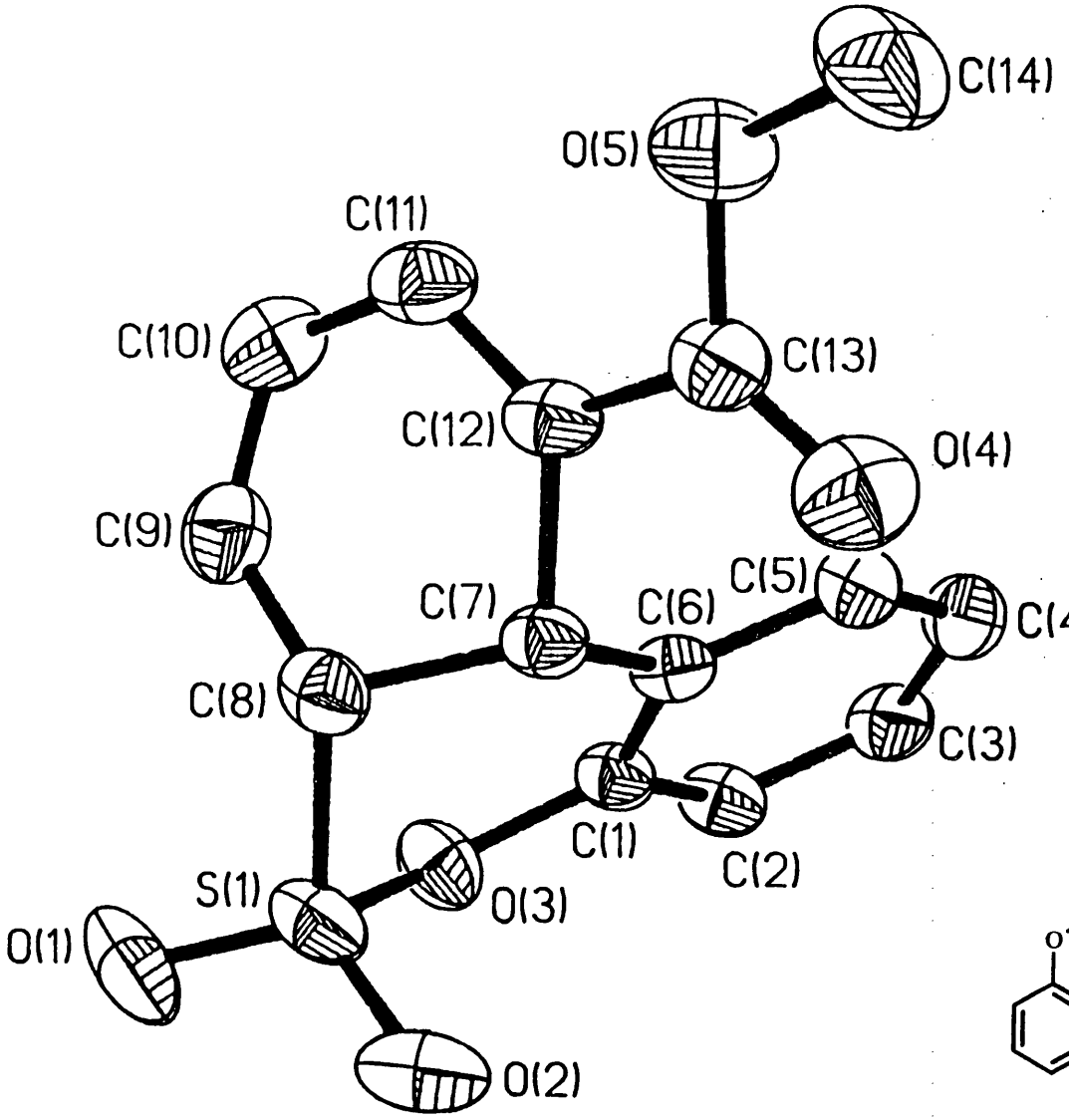

MeN
S
O2 H
H
CO2Me
87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5 PPM 3.0

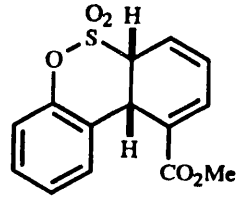
Appendix 2


C(14)
O(5)
C(11)
C(10)
C(13)
C(12)
O(4)
C(9)
C(5)
C(7)
C(4)
C(8)
C(6)
C(3)
C(1)
C(2)
S(1)
O(3)
O(1)
O(2)


O2 H
S
O
H
CO2Me

81


C(14)
O(5)
C(11)
C(10)
C(13)
C(12)
O(4)
C(9)
C(5)
C(7)
C(6)
C(4)
C(8)
C(3)
C(1)
C(2)
S(1)
O(3)
O(1)
O(2)


O2 H
S
O
H
CO2Me

81

Details of the crystal structure determination of $C_{14}H_{12}O_5S_1$.

A colourless single crystal of approximate size 0.65×0.50×0.38 mm was mounted on a glass fibre. All geometric and intensity data were taken from this sample using an automated four-circle diffractometer (Nicolet R3mV) equipped with Mo-Kα radiation (λ=0.71073 Å). Important crystallographic parameters are summarised in the table.

The lattice vectors were identified by application of the automatic indexing routine of the diffractometer to the positions of 22 reflections taken from a rotation photograph and centred by the diffractometer. The ω-2θ technique was used to measure 1370 reflections (1231 unique) in the range $5° \leq 2\theta \leq 50°$. Three standard reflections (remeasured every 97 scans) showed no significant loss in intensity during data collection. The data were corrected for Lorentz and polarisation effects. The 1061 unique data with $I \geq 2.0\sigma(I)$ were used to solve and refine the structure in the orthorhombic space group $Pn2_1a$.

The structure was solved by direct methods and developed by using alternating cycles of least-squares refinement and difference-fourier synthesis. The non-hydrogen atoms were refined anisotropically while hydrogens were placed in idealised positions (C-H 0.96 Å) and assigned a common isotropic thermal parameter ($U=0.08$ Å^2) . The final cycle of least-squares refinement included 180 parameters for 1061 variables and did not shift any parameter by more than 0.005 times its standard deviation. The final R values were 0.0388 and 0.0447, and the final difference-fourier was featureless with no peaks greater than 0.24 eÅ^{-3}.

Structure solution used the SHELXTL PLUS program package on a microVax II computer.

Table 1. Crystallographic data for $C_{14}H_{12}O_5S_1$.

Formula	$C_{14}H_{12}O_5S_1$
Space group	$Pn2_1a$
a, Å	8.526(2)
b, Å	10.190(2)
c, Å	15.297(4)
α, deg	90.0
β, deg	90.0
γ, deg	90.0
V, Å^3	1329
Z	4
F(000)	608
d_{calc}, g/cm^3	1.46
Cryst. size, mm	0.65x0.50x0.38
μ(Mo-K_α), cm^{-1}	2.47
Data collection instrument	Nicolet R3mV
Radiation	Mo-K_α (λ = 0.71073 Å)
Orientation reflections: no.;	22
range (2θ)	16≤2θ≤24°
Temp., K	293
Data measured	1370
Unique data	1231
No. of unique with I≥2.0σ(I)	1061
No. of parameters	180
R [a]	0.0388
R_w [b]	0.0447
Weighting scheme	$w^{-1} = \sigma^2(F) + 0.00158F^2$
Largest shift/esd, final cycle	0.005
Largest peak, e/Å^3	0.24

[a] $R = \Sigma[\,|F_o| - |F_c|\,]/\Sigma|F_o|$

[b] $R_w = \Sigma w^{½}.[\,|F_o| - |F_c|\,]/\Sigma w^{½}.|F_o|$

Table 1. Atomic coordinates ($x10^4$ Å) and equivalent isotropic displacement parameters ($Å^2x10^3$) for $C_{14}H_{12}O_5S_1$.

	x	y	z	U(eq)
S(1)	2384(1)	2284	9160(1)	52(1)
O(1)	1861(4)	2177(6)	8281(2)	78(1)
O(2)	1836(4)	3334(4)	9690(3)	70(1)
O(3)	1914(4)	933(3)	9594(2)	48(1)
O(4)	6797(4)	3332(5)	11553(2)	65(1)
O(5)	8992(3)	2508(5)	11001(2)	69(1)
C(1)	2551(4)	620(4)	10424(3)	37(1)
C(2)	1675(5)	-293(5)	10886(3)	44(1)
C(3)	2203(5)	-685(5)	11691(3)	48(1)
C(4)	3569(5)	-185(5)	12031(3)	50(1)
C(5)	4425(5)	729(5)	11549(3)	43(1)
C(6)	3945(4)	1149(4)	10729(2)	36(1)
C(7)	4862(4)	2194(5)	10226(2)	38(1)
C(8)	4450(5)	2233(6)	9256(2)	46(1)
C(9)	5148(6)	1126(5)	8745(3)	56(2)
C(10)	6551(6)	668(6)	8975(3)	60(2)
C(11)	7371(5)	1253(6)	9704(3)	53(2)
C(12)	6632(4)	1998(5)	10286(3)	42(1)
C(13)	7450(5)	2683(5)	11014(3)	47(1)
C(14)	9877(6)	3186(7)	11654(3)	77(2)

Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2. Bond lengths (Å) for $C_{14}H_{12}O_5S_1$.

S(1)-O(1)	1.421 (4)	S(1)-O(2)	1.422 (4)
S(1)-O(3)	1.580 (4)	S(1)-C(8)	1.768 (4)
O(3)-C(1)	1.416 (5)	O(4)-C(13)	1.195 (6)
O(5)-C(13)	1.327 (5)	O(5)-C(14)	1.430 (7)
C(1)-C(2)	1.387 (6)	C(1)-C(6)	1.386 (5)
C(2)-C(3)	1.370 (6)	C(3)-C(4)	1.374 (6)
C(4)-C(5)	1.395 (7)	C(5)-C(6)	1.387 (6)
C(6)-C(7)	1.528 (6)	C(7)-C(8)	1.526 (5)
C(7)-C(12)	1.525 (5)	C(8)-C(9)	1.496 (7)
C(9)-C(10)	1.331 (7)	C(10)-C(11)	1.445 (7)
C(11)-C(12)	1.329 (7)	C(12)-C(13)	1.487 (6)

Table 3. Bond angles (°) for $C_{14}H_{12}O_5S_1$.

O(1)-S(1)-O(2)	119.6(3)	O(1)-S(1)-O(3)	104.5(3)
O(2)-S(1)-O(3)	109.4(2)	O(1)-S(1)-C(8)	112.9(2)
O(2)-S(1)-C(8)	107.6(2)	O(3)-S(1)-C(8)	101.1(2)
S(1)-O(3)-C(1)	118.4(3)	C(13)-O(5)-C(14)	116.6(4)
O(3)-C(1)-C(2)	113.6(3)	O(3)-C(1)-C(6)	122.9(4)
C(2)-C(1)-C(6)	123.4(4)	C(1)-C(2)-C(3)	118.5(4)
C(2)-C(3)-C(4)	120.7(4)	C(3)-C(4)-C(5)	119.4(4)
C(4)-C(5)-C(6)	122.0(4)	C(1)-C(6)-C(5)	116.0(4)
C(1)-C(6)-C(7)	122.7(3)	C(5)-C(6)-C(7)	121.2(3)
C(6)-C(7)-C(8)	112.9(3)	C(6)-C(7)-C(12)	112.6(4)
C(8)-C(7)-C(12)	106.9(3)	S(1)-C(8)-C(7)	108.2(2)
S(1)-C(8)-C(9)	112.0(3)	C(7)-C(8)-C(9)	113.4(4)
C(8)-C(9)-C(10)	119.0(4)	C(9)-C(10)-C(11)	119.6(5)
C(10)-C(11)-C(12)	121.6(4)	C(7)-C(12)-C(11)	120.2(4)
C(7)-C(12)-C(13)	116.6(4)	C(11)-C(12)-C(13)	123.2(4)
O(4)-C(13)-O(5)	123.1(4)	O(4)-C(13)-C(12)	123.9(4)
O(5)-C(13)-C(12)	113.0(4)		

Table 4. Anisotropic displacement parameters ($Å^2x10^3$) for $C_{14}H_{12}O_5S_1$.

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	43(1)	49(1)	63(1)	20(1)	-9(1)	2(1)
O(1)	75(2)	95(3)	65(2)	36(3)	-26(2)	-7(3)
O(2)	48(2)	53(2)	109(3)	6(2)	-6(2)	12(2)
O(3)	44(2)	49(2)	51(2)	7(1)	-12(1)	-9(1)
O(4)	53(2)	64(2)	77(2)	-6(2)	0(2)	-10(2)
O(5)	35(2)	94(3)	80(2)	0(2)	-6(1)	-10(2)
C(1)	33(2)	34(2)	44(2)	6(2)	0(2)	1(2)
C(2)	34(2)	41(2)	56(2)	6(2)	-3(2)	-5(2)
C(3)	40(2)	50(2)	54(3)	14(2)	12(2)	-3(2)
C(4)	47(2)	55(3)	46(2)	11(2)	7(2)	0(2)
C(5)	41(2)	41(2)	46(2)	4(2)	0(2)	-3(2)
C(6)	29(2)	33(2)	46(2)	1(2)	4(1)	2(2)
C(7)	33(2)	33(2)	47(2)	7(2)	3(1)	3(2)
C(8)	40(2)	45(2)	53(2)	16(2)	0(2)	-3(2)
C(9)	57(3)	59(3)	51(2)	4(2)	7(2)	-6(2)
C(10)	55(3)	57(3)	67(3)	-9(3)	8(2)	0(3)
C(11)	36(2)	53(3)	71(3)	10(2)	6(2)	1(2)
C(12)	30(2)	38(2)	59(2)	12(2)	3(2)	-4(2)
C(13)	40(2)	48(3)	52(2)	11(2)	2(2)	-6(2)
C(14)	48(3)	102(5)	80(3)	9(4)	-20(2)	-18(3)

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for $C_{14}H_{12}O_5S_1$.

	x	y	z	U
H(2A)	720	-640	10648	80
H(3A)	1610	-1307	12027	80
H(4A)	3933	-464	12595	80
H(5A)	5380	1073	11790	80
H(7A)	4615	3034	10475	80
H(8A)	4861	3034	9018	80
H(9A)	4579	758	8263	80
H(10A)	7000	-63	8669	80
H(11A)	8480	1118	9761	80
H(14B)	10973	2994	11589	80
H(14C)	9711	4113	11593	80
H(14D)	9531	2907	12221	80