METALLATION APPROACHES TO HETEROCYCLIC ANALOGUES OF ORTHOXYLYLENE

by

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To my mother, and Nell and Tom.

ACKNOWLEDGEMENTS

I would like to extend my warmest thanks to Dr. Derek Chadwick for his supervision, encouragement and friendship throughout the duration of this work.

I would also like to thank Drs. Dick Storr and Tom Gilchrist for their help and advice on chemical and professional matters.

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Finally, I would like to thank Mrs. A. Simpson and Mrs. J. Denholm for their expeditious and expert typing of this manuscript.

ABSTRACT

The aims of the project were two-fold:

i) To develop metallation routes to precursors to heterocyclic analogues of ortho-xylylene (in particular thiophene, furan and pyrrole).

ii) To generate these o-xylylene species in the presence of trapping agents as a route to annelated heterocyclic compounds.

Carboxylate, amidate anion and oxazoline directing groups have been used in the ortho-lithiation of thiophene derivatives.

The ortho-lithiation of thiophene-2-carboxylic acid is used as the key step in a high yielding synthesis of 2,3-bis-(bromomethyl)-thiophene. Iodide ion-induced debromination results in the generation of the thiophene analogue of o-xylylene (2,3-dimethylene-2,3-dihydrothiophene) as evinced by entrapment with dienophiles.

Ortho-lithiations of N-t-butyl-3-methylthiophene-2-carboxamide and N-1-adamantyl-3-methylthiophene-2-carboxamide are used as key steps in the syntheses of 2-(N-dialkylaminomethyl)-3-trimethylsilylmethylthiophene iodides. A subsequent mild and efficient fluoride ion-induced 1,4-elimination process generates the thiophene analogue of o-xylylene. In the presence of electron-deficient dienophiles a range of annelated thiophene derivatives are obtained in high yield. In the presence of electron-rich or "unactivated" dienophiles, or in the absence of trapping agent, [4+2] spiro-dimers are produced as the sole products.

A directed-lithiation approach to 2-(3-trimethylsilylmethyl-5-methyl-2-thienyl)-3,4,4-trimethyloxazolinium iodide has been accomplished. Fluoride ion-induced desilylation generates an α-substituted o-xylylene species. High yielding, regioselective adduct formation is observed with electron-deficient dienophiles.

Preliminary studies aimed at extending this work to the furan ring system and also to encompass intramolecular trapping of the thiophene analogue of o-xylylene have been made.

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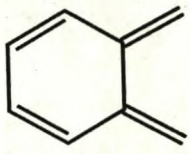
ABBREVIATIONS

Ac	Acetyl
Ad	1-Adamantyl
Bu	^{n}Butyl
^{t}Bu	tertiary-Butyl
DMAD	Dimethylacetylene Dicarboxylate
DME	Dimethoxyethane
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
E^{+}, EX	Electrophile
Et_2O	Diethyl Ether
$Eu(fod)_3$	tris(6,6,7,7,8,8,8-Heptafluoro-2,2-dimethyl-3,5-octanedionato)europium
F.V.P.	Flash Vacuum Pyrolysis
HMPA	Hexamethylphosphoramide ("Hexametapol")
LDA	Lithium Diisopropylamide
LTMP	Lithium Tetramethylpiperidide
Me	Methyl
MVK	Methyl Vinyl Ketone
Ph	Phenyl
r.t.	Room Temperature
TBAF	tetra-^{n}Butyl Ammonium Fluoride
TBDMS	tertiary-Butyldimethylsilyl
^{t}Boc	tertiary-Butyloxycarbonyl
thf	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethylene Diamine
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
uv	Ultra Violet

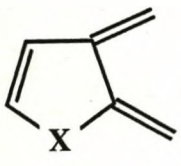
CHAPTER 1

PROJECT AIMS AND JUSTIFICATION

The generation and synthetic utility of o-xylylene (1) is well documented in the literature. However, at the commencement of this work there were relatively few reports of heterocyclic analogues of this system,[1-5] in particular corresponding to the five-membered heterocycles (2).



(1)



(2) X = S, O, NR

Indeed, prior to 1985, only the furan analogue (2), X = O, had been reported, its generation being accomplished using flash pyrolytic techniques.[6,7]

Our aims were to apply directed-metallation methodology (see Section 1.3) to the construction of appropriate precursor molecules to (2) and substituted derivatives. Generation of (2) in the presence of dienophilic trapping agents would then allow the preparation of polycyclic molecules incorporating a thiophene, furan, or pyrrole ring. The potential for synthesising more complicated systems such as heterocyclic analogues of steroids and alkaloids was also apparent.

1.1 ORTHOXYLYLENES

1.1.1 INTRODUCTION

There are many reports in the literature concerned with o-xylylene (1) (also known as o-quinodimethane and o-quinodimethide) and its derivatives. The present work concentrates on heterocyclic analogues of (1) and therefore a detailed account of the chemistry of (1) is not appropriate. However, the following aspects will be covered briefly since they are relevant to the heterocyclic work:

1. Discovery and characterisation.
2. Methods of generation.
3. o-Xylylene as a diene in the Diels-Alder reaction.
4. Asymmetric induction in the reactions of o-xylylenes.
5. o-Xylylenes in organic synthesis.

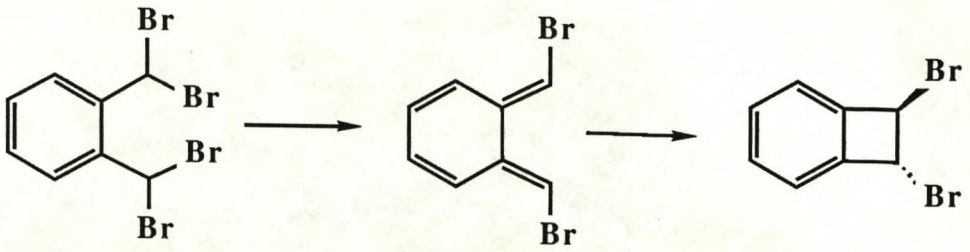
For further information concerning (1) reference should be made to the wealth of review articles.[8-21]

1.1.2 DISCOVERY AND CHARACTERISATION OF o-XYLYLENES

o-Xylylenes were first postulated as reaction intermediates in the formation of substituted benzocyclobutenes. In 1957 Cava et al., proposed the intermediacy of o-xylylene (4) in the formation of trans-α,α'-dibromobenzocyclobutene (5) from α,α,α',α'-tetrabromo-o-xylene (3),[22] a reaction earlier reported by Finkelstein[23] (Scheme 1.1).

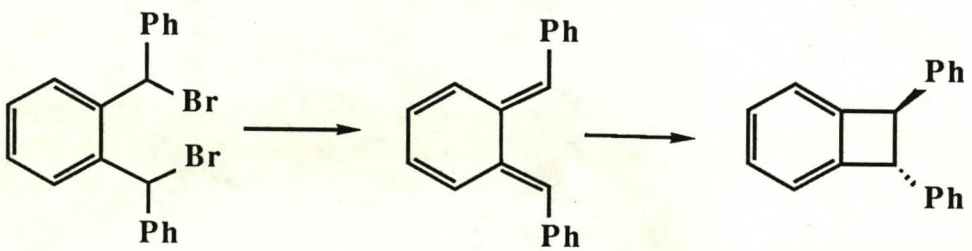
In 1958 Jensen and Coleman also reported the generation of the bis-phenyl o-xylylene (6) as an intermediate in the preparation of 1,2-diphenylbenzocyclobutene (7)[24] (Scheme 1.2).

The unsubstituted o-xylylene (1) was later generated from the thermal decomposition of sulphone (8) by Cava and co-workers, the transient species being trapped with typical dienophiles in Diels-Alder cycloaddition reactions.[25]



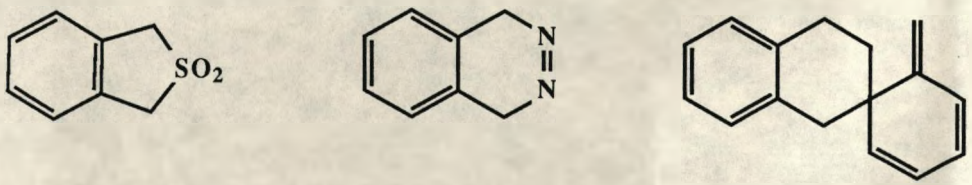
(3) (4) (5)

SCHEME 1.1



(6) (7)

SCHEME 1.2



(8) (9) (10)

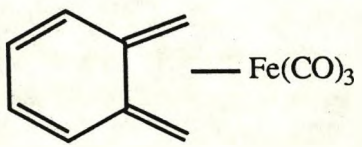
In 1973, Flynn and Michl were the first to observe (1) directly by irradiating the dihydrodiazanaphthalene (9) in a glassy matrix at -196°C.[26] They recorded the U.V. fluorescence and excitation spectra and, in a later study, recorded the i.r. and Raman spectra.[27] Other spectroscopic measurements include the U.V. photoelectron spectrum of (1) in the gas phase[28] and the estimation of the molar extinction coefficient ε (3015 at $\lambda_{max.}$) for (1) produced in acetonitrile solution.[29] In the same paper it was also noted that (1) rapidly decayed in acetonitrile solution by dimerisation with a rate constant of 9.9×10^{-3} L mol^{-1} s^{-1} (25°C).

Hehre et al., have used cyclotron double resonance spectroscopy to determine the relative heats of formation of p-, m-, and o-xylylene and found a value of 53 Kcal mol^{-1} for the ortho isomer.[30] References to other direct observations of substituted o-xylylenes can be found in papers by Michl[26] and McCullough.[12] The isolation of the dimerisation product (10) and the formation of Diels-Alder adducts with dienophiles are also considered diagnostic of the intermediacy of (1).[25,26,29,31]

Although o-xylylene is a highly reactive transient species, Roth and Meier have prepared the stable o-xylylene-iron tricarbonyl complex (11) and recorded its nmr spectrum.[32] This complex was found to be resistant to a variety of transition metal reducing agents, and only on heating to 500°C was benzocyclobutene formation observed.

o-Xylylene has also received much attention from theoreticians, whose calculations may be summarised as follows:

1. The ground state of (1) is singlet.
2. That S_0 and S_1, the ground and first excited state are planar.
3. That S_1 is very nearly degenerate with S_2.
4. The double bonds in (1) are ca. 1.36 Å in length.[12,26,33-37]



(11)

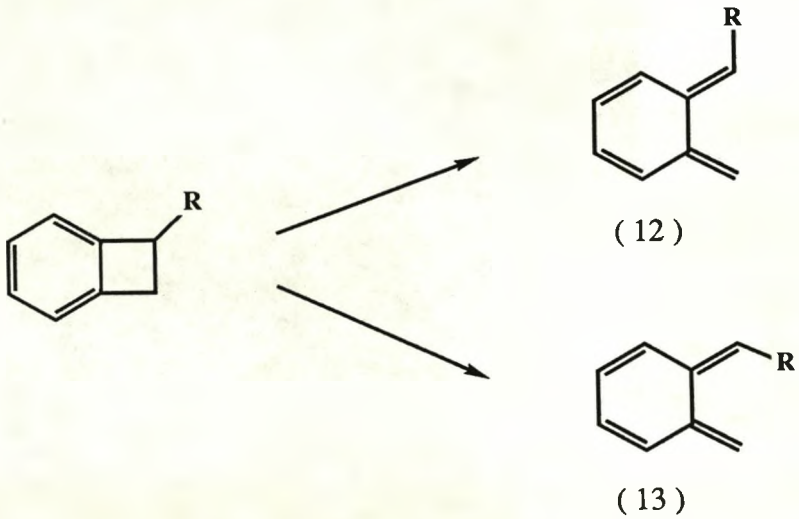
1.1.3 METHODS OF GENERATION OF o-XYLYLENES

Since the realisation that o-xylylenes could have great potential in organic synthesis when employed as Diels-Alder dienes, a host of generative procedures have been developed. These are briefly summarised below.

(a) THERMOLYSIS OF BENZOCYCLOBUTENES

The thermolysis of benzocyclobutenes is probably the most frequently used method for generation of o-xylylenes. The transformation proceeds *via* a thermally allowed conrotatory electrocyclic ring opening,[14,38] with a substituent on the four-membered ring opening outwards to produce the less sterically hindered (E)-o-xylylene (12) in preference to the (Z) form (13) (Scheme 1.3). Substitution of the four-membered ring also serves to reduce the temperature required for ring opening (e.g., benzocyclobutene 200°C,

alkyl substituted 140°C, alkoxy substituted 110°C, primary amino substituted 25°C). The synthesis and chemistry of benzocyclobutenes is well covered in the literature in a number of review articles.[17,19,22,38-41]



(12)

(13)

SCHEME 1.3

(b) 1,4-ELIMINATION PROCESS

The 1,4-elimination process to generate o-xylylenes may involve thermal elimination,[42-44] acid or base catalysed eliminations,[45] reductive eliminations[46-51] and fluoride ion induced elimination.[5,52,53] One example of each of these methods is shown in Figure 1.1.

(c) THERMAL ELIMINATION OF SULPHUR DIOXIDE FROM SULPHONES AND SULTINES

The historical importance of the generation of o-xylylene (1) from sulphone (8) has already been noted.[25]

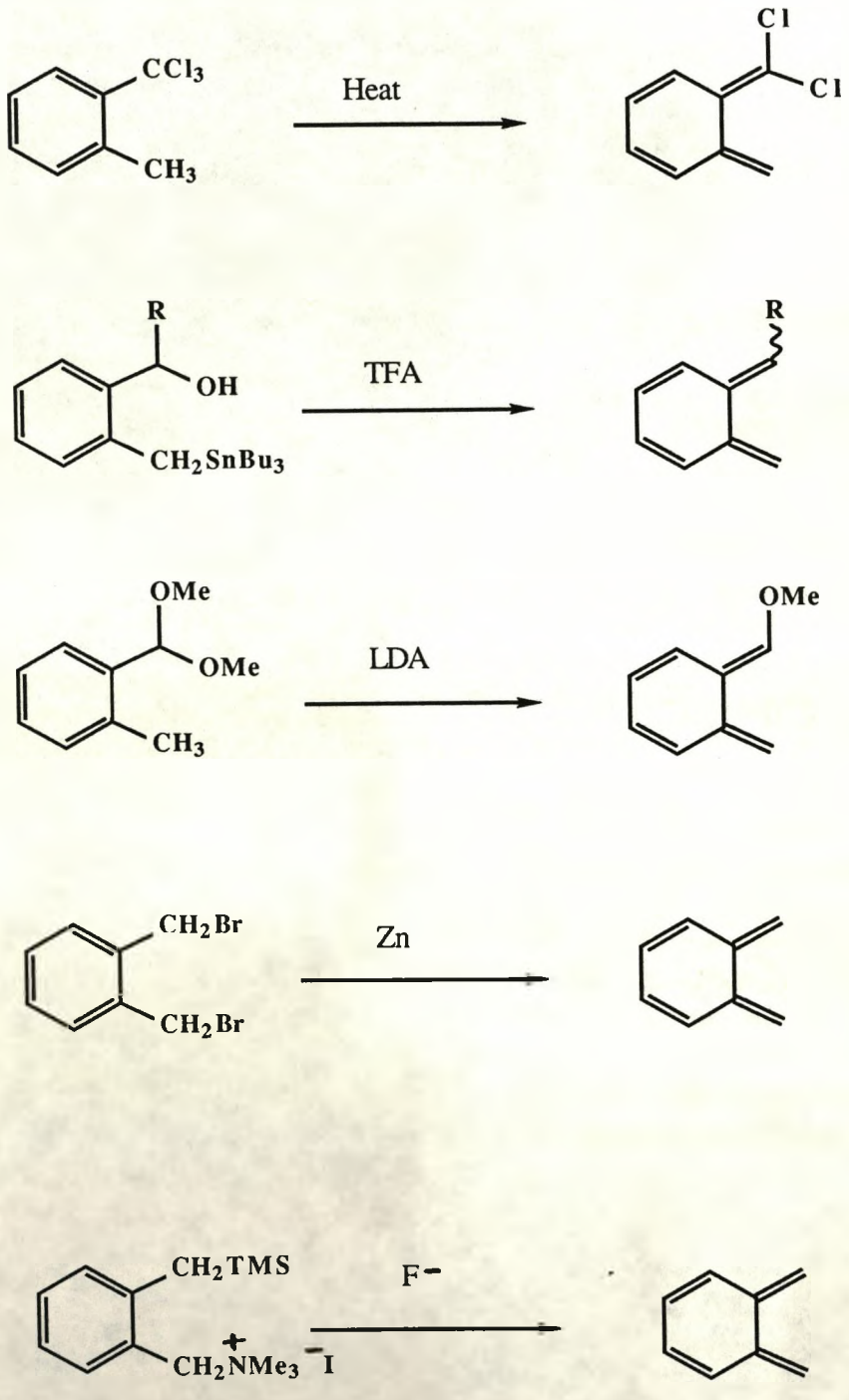
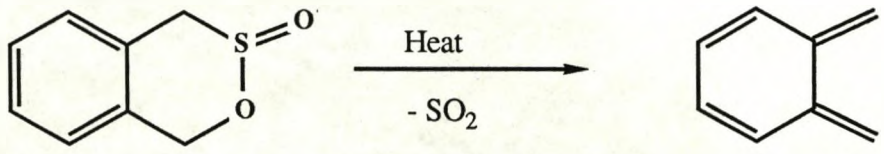

CCl3
CH3
Heat
Cl
Cl
R
OH
CH2SnBu3
TFA
R
OMe
OMe
CH3
LDA
OMe
CH2Br
CH2Br
Zn
CH2TMS
CH2NMe3 I
F-

FIGURE 1.1



(14) (1)

SCHEME 1.4

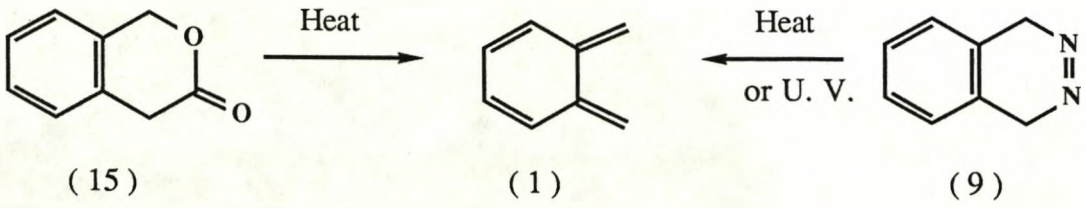
This type of reaction has been reviewed,[13] and the number of subsequent publications is testimony to the utility of this type of precursor.[54-59] Expulsion of sulphur dioxide from sultines, for example (14), has also been used to generate o-xylylenes.[13,60-64] (Scheme 1.4)

(d) DIELS-ALDER CYCLOREVERSION

Two examples of this process are the loss of carbon dioxide from isochromanone (15)[13,65,66] and the loss of nitrogen from 3,4-dihydrodiazanaphthalene (9)[27,61,67] (Scheme 1.5).

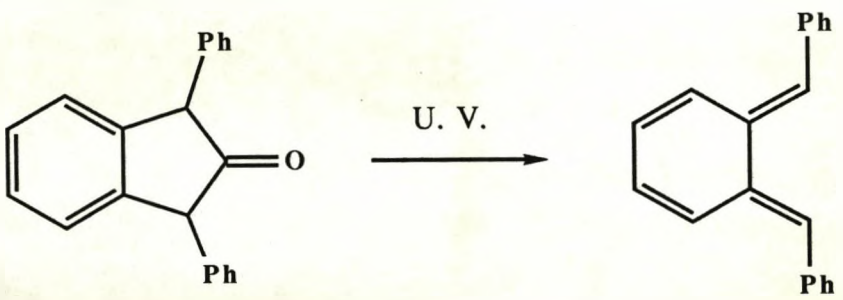
(e) PHOTOCHEMICAL EXPULSION OF CARBON MONOXIDE

α,α-Disubstituted o-xylylenes can be generated photochemically from 2-indanones by the loss of carbon monoxide[9,12] (Scheme 1.6).



(15) (1) (9)

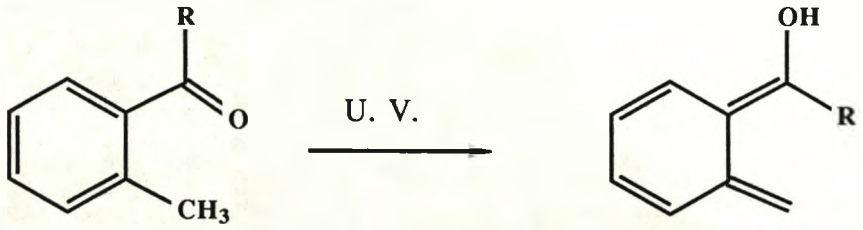
SCHEME 1.5



SCHEME 1.6

(f) PHOTOENOLISATION AND PHOTOREARRANGEMENT

o-Alkylbenzaldehydes and o-alkylbenzophenones can be useful substrates for the generation of α-hydroxy-o-xylylenes (16)[9,14,15,57,68,.69] (Scheme 1.7). Initial excitation to an $n\pi^*$ triplet state followed by intramolecular hydrogen abstraction to give a triplet diradical

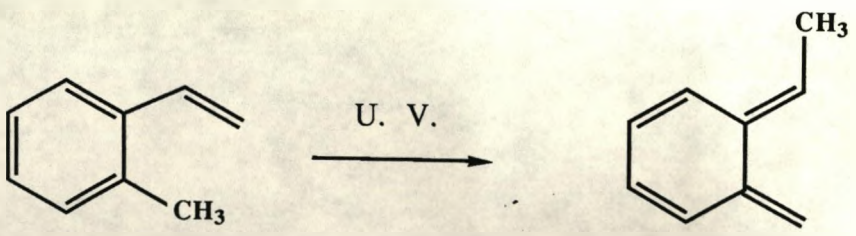


(16)

SCHEME 1.7

is the first stage in the process. This then decays to E and Z hydroxy-o-xylylenes. It is thought that the Z isomer returns rapidly to the starting carbonyl compound by a [1,5] sigmatropic shift, while the E isomer is relatively longer lived.

The photolysis of o-alkylstyrenes has also been reported to produce o-xylylenes via a [1,5] sigmatropic shift[70] (Scheme 1.8).



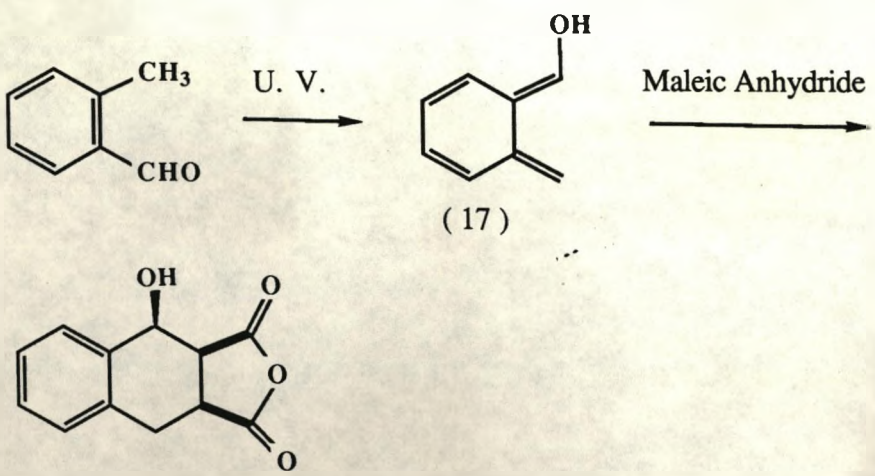
SCHEME 1.8

From the wealth of methodology available for the generation of o-xylylenes, a balance must be struck between

the availability of starting materials, the overall yield of the process, and the ease with which the method can be carried out. Each of the above methodologies has its advantages but a consideration of the aforementioned criteria is important in making the correct choice for a particular system.

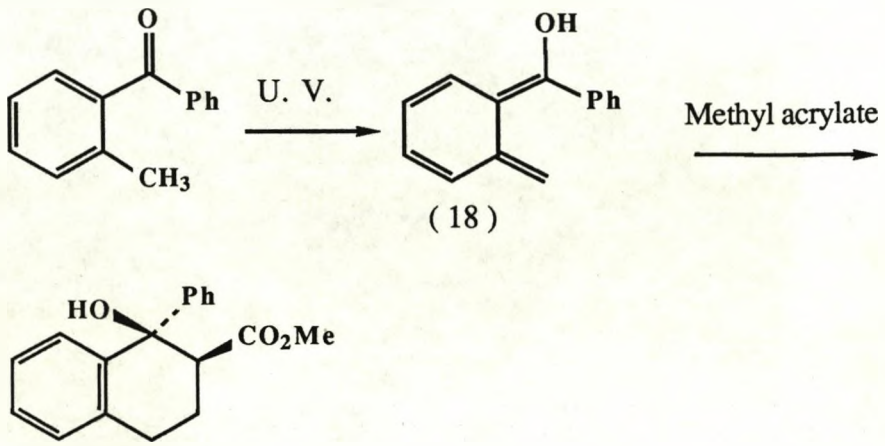
1.1.4 o-XYLYLENE AS A DIENE IN THE DIELS-ALDER REACTION

Results from cycloaddition reactions of α-oxy and/or α-phenyl substituted o-xylylenes to dienophiles[11,33,54-58] indicate that the regio- and stereochemical course of the addition follow those expected for a Diels-Alder reaction of substituted dienes with dienophiles (detailed accounts of the Diels-Alder reaction and of Frontier Molecular Orbital Theory {F.M.O.} are beyond the scope of this introduction: useful reviews are available in references 71 and 72). Thus, the E-dienol (17) formed on irradiation of 2-methylbenzaldehyde, has been shown to give the all cis adduct by endo addition[73] (Scheme 1.9).



SCHEME 1.9

Reaction of o-xylylene (18) with unsymmetrical dienophiles such as methyl acrylate shows both regio- and stereoselective addition [69,74,75] (Scheme 1.10).



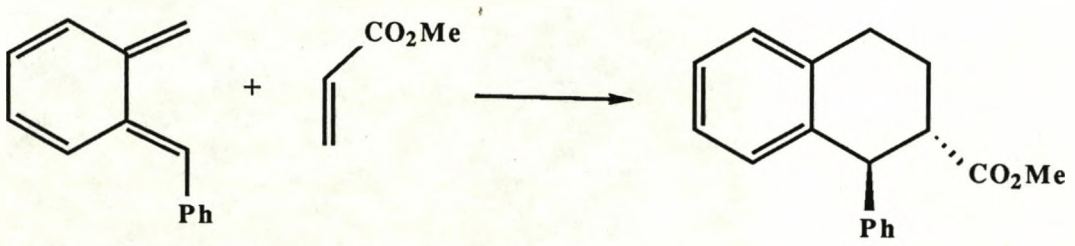
(18)

SCHEME 1.10

α-Alkoxy and α-acetoxy-o-xylylenes also add dienophiles by endo addition[57] and give 1,2-disubstituted adducts with unsymmetrical dienophiles.[53,76]

α-Alkyl-o-xylylenes react with unsymmetrical dienophiles with less regio- and stereoselectivity but the endo-1,2-adduct still appears to be the major product, as would be expected from F.M.O. theory. Some anomalies do occur however; α-aryl-o-xylylenes have been found to add to dienophiles in the exo mode. For example, reaction of o-xylylene (19) with methyl acrylate gave predominantly the trans product (20) (Scheme 1.11). The regioselectivity is predicted by F.M.O. theory but the stereoselectivity is surprising.[55]

At first this observation was rationalised in terms of equilibration of the endo and exo adducts via a reversible Diels-Alder reaction to give eventually the thermodynamically more stable product.[55] This theory was later contested by workers who had obtained the same

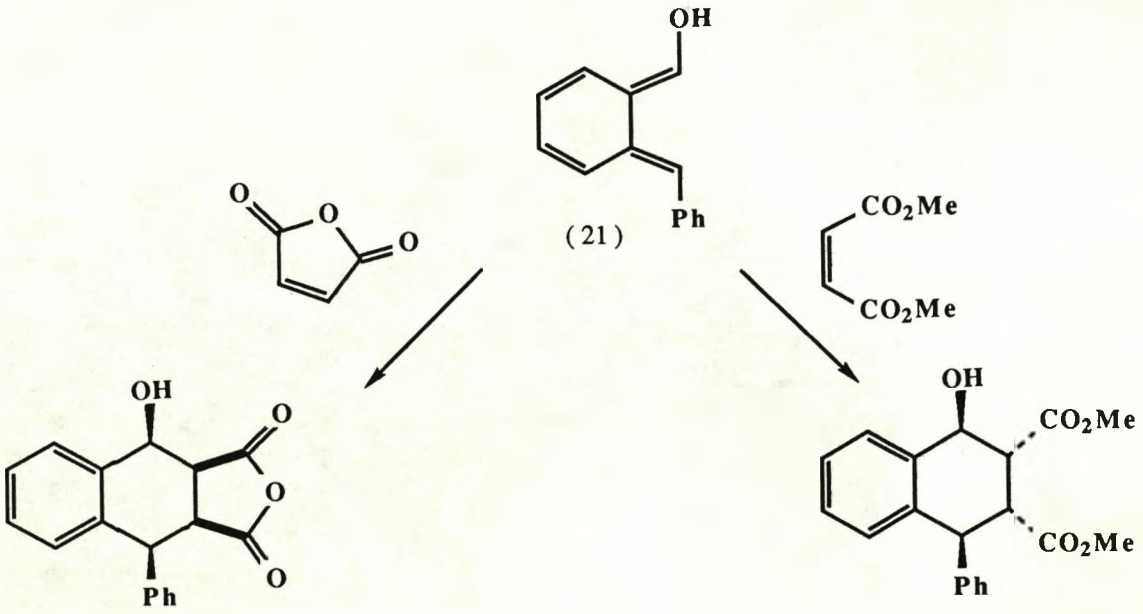


(19) (20)

SCHEME 1.11

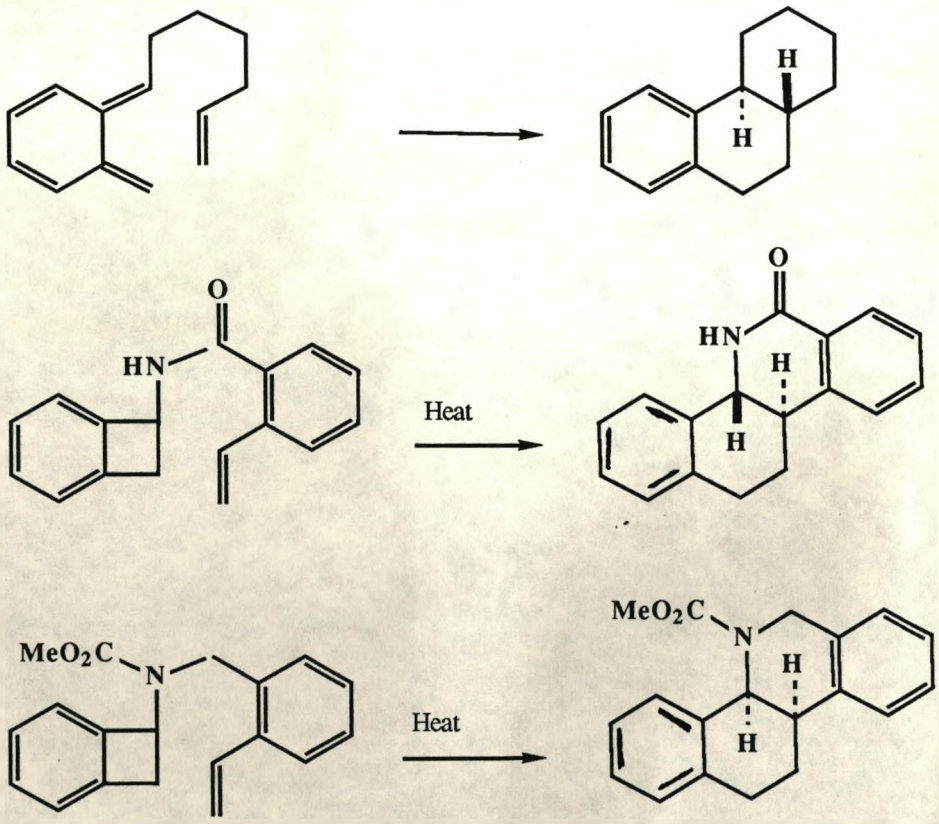
results under conditions where the possibility of a reversible Diels-Alder reaction was excluded.[57] Thus it would appear that in some cases exo addition to aryl-substituted o-xylylenes does occur. Charlton et al., have suggested that some dienophiles, such as maleic anhydride undergo endo addition to α-hydroxy-α'-phenyl-o-xylylenes (21) due to secondary orbital effects and kinetic control. Fumarate and maleate appear to add exo, guided by product development control, possibly via steric repulsion between the phenyl and carbomethoxy group[58] (Scheme 1.12). This may account for the formation of exo product (20) described above.

The intramolecular cycloadditions of o-xylylenes are of greater importance in synthesis than their intermolecular counterparts. There are many review articles concerning this area,[8,9,11,13,14,16-20] with particularly useful contributions from Fallis[8] and Quinkert[9] on the stereoselectivity of these reactions. Suffice to say, the selectivity of the addition is variable[14] and is often different from that



SCHEME 1.12

expected for an intermolecular addition due to the steric influence of the linking bridge. The following examples illustrate this point (Scheme 1.13).



SCHEME 1.13

1.1.5 ASYMMETRIC INDUCTION IN REACTIONS OF o-XYLYLENES

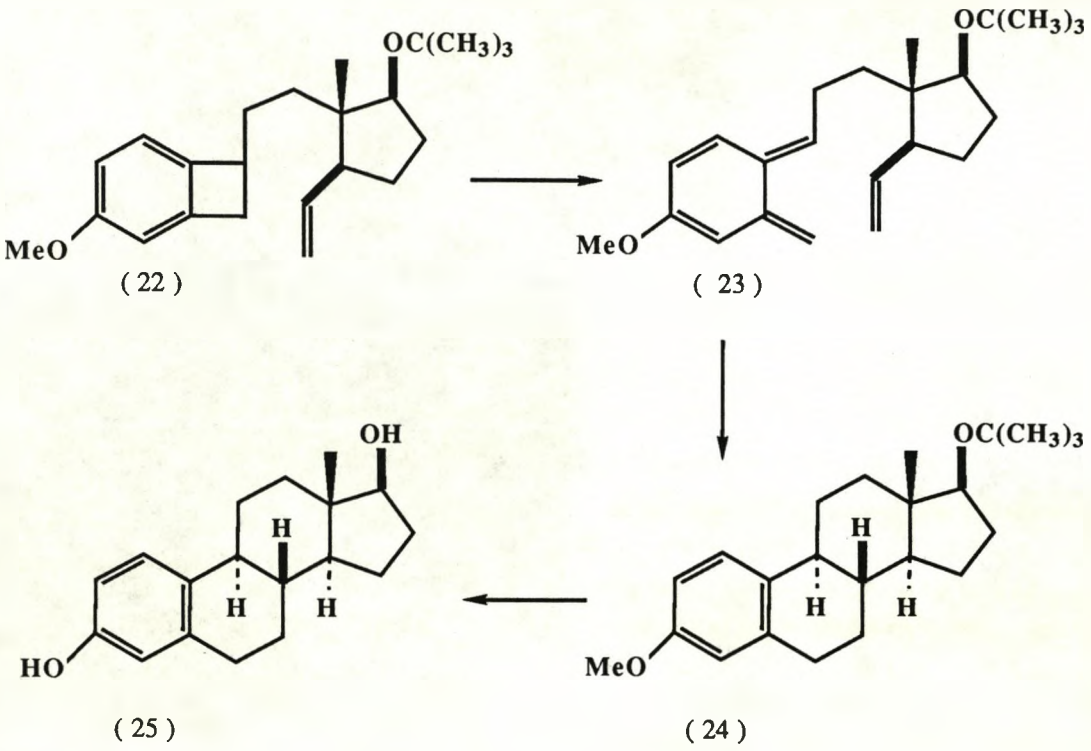
The often differing biological activity of optical antipodes presents a considerable challenge to the synthetic chemist in the search for methodology that will produce compounds in an enantiomerically pure form. The definition of an asymmetric reaction is any reaction in which an achiral substrate, or achiral unit within a molecule, is converted to a chiral substrate or unit with the resulting two chiral forms being produced in unequal amounts.

With respect to the Diels-Alder reaction, asymmetric induction can occur if the reaction can be induced to take place preferentially on one face of the diene or dienophile.

While there has been extensive work carried out on asymmetric induction in the Diels-Alder reactions of butadienes,[77-82] relatively fewer studies have been made in this area with respect to o-xylylenes.[9,16,20,53,76,83] As might be expected, the greater success has been achieved in the intramolecular cycloadditions of o-xylylenes, particularly in the field of stereoid synthesis. A representative example can be taken from the work of Kametani et al., who achieved stereoselectivity in the synthesis of estradiol (25). Thermolysis of benzocyclobutene (22) generates chiral o-xylylene (23) which ring closes to give the product (24) with the required ring junction stereochemistry[16] (Scheme 1.14).

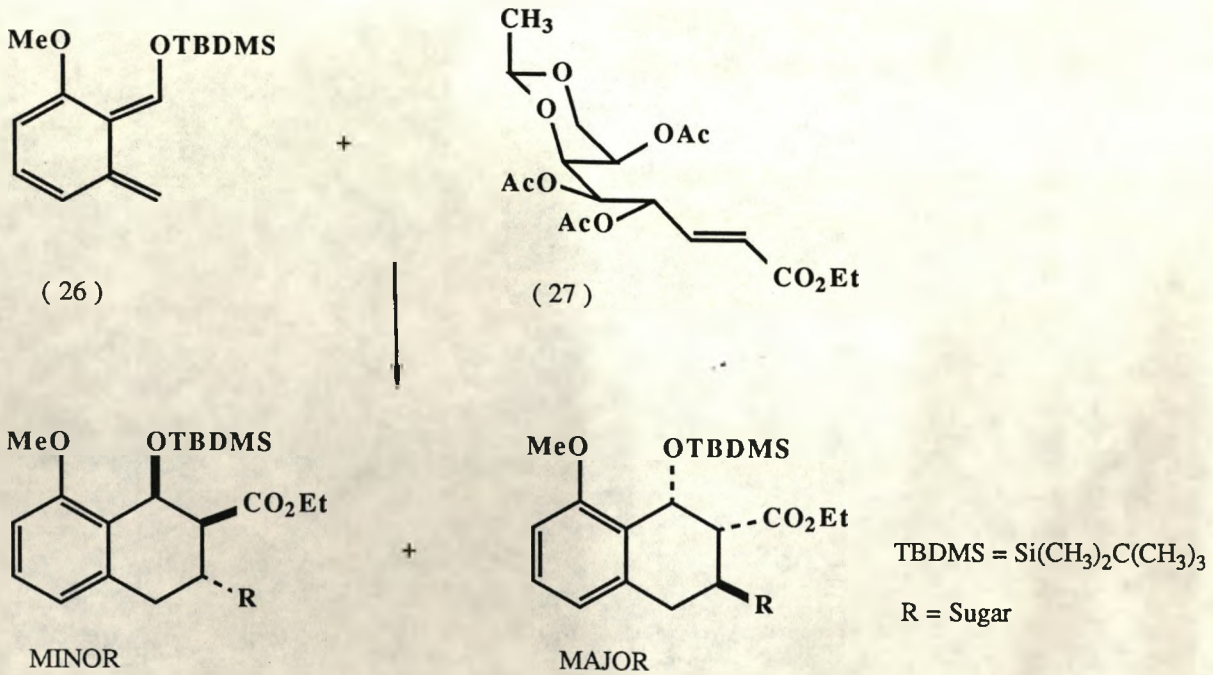
The stereochemical outcome of the reaction is controlled by the chiral auxiliary, which itself becomes part of the product. Other examples are given in Section 1.1.6. There are far fewer reports pertaining to the intermolecular cycloadditions of o-xylylenes with dienophiles in which chiral induction occurs.

Franck et al., have studied the intermolecular reaction of an achiral o-xylylene (26) with a chiral dienophile (27) to determine the



SCHEME 1.14

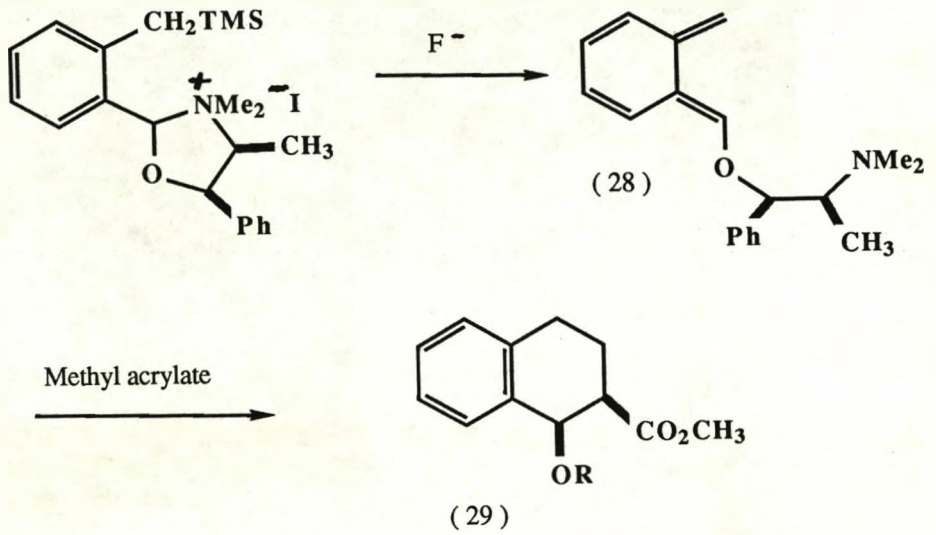
relative roles of steric and secondary orbital interactions on the asymmetric induction.[83] Two adducts were formed in the ratio of 4:1 (Scheme 1.15). Both of the adducts were the result of endo addition



SCHEME 1.15

of the ester. The authors concluded that orbital interactions predominated over steric interactions in guiding the asymmetric induction.

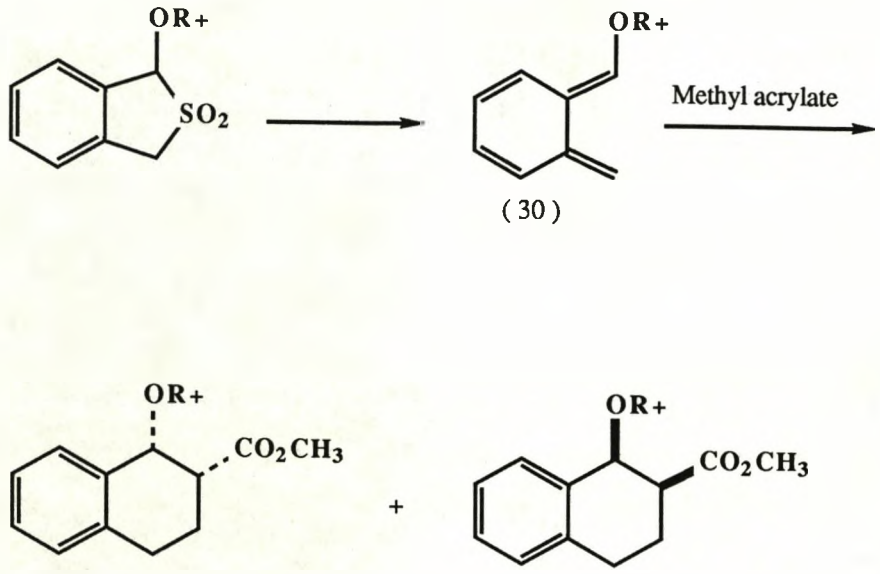
Ito et al., have obtained modest chiral induction in the reaction of chiral o-xylylene (28) with methyl acrylate, adduct (29) being formed with 33% diastereomeric excess[53] (Scheme 1.16).



SCHEME 1.16

Ito attributed the asymmetric induction to π-stacking interactions which have previously been postulated as a controlling factor in the approach of dienophiles to dienes.[80,81] Later, Charlton showed that Ito's model was incorrect and presented a different explanation for the asymmetric induction in the Diels-Alder reaction of o-xylylenes.[76] He generated a range of chiral alkoxy-substituted o-xylylenes (30), and in reaction with typical dienophiles observed diastereomeric excesses of up to 50% (Scheme 1.17).

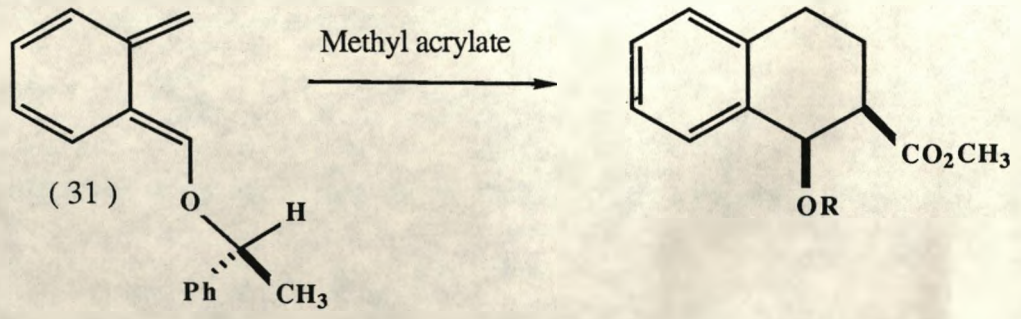
Charlton's explanation of chiral induction hinges on the reported preferred (most stable) conformation of alkyl phenyl ethers, in which the alkyl group lies in the plane of the aromatic ring to allow p-π overlap.[84] By analogy, he suggested the preferred conformation of



R^+ = Chiral Group

SCHEME 1.17

o-xylylenes would be as in (31). Thus the relative bulk of the phenyl and methyl groups serves to block the lower face of the o-xylylene and therefore dienophiles add to the upper face (Scheme 1.18).



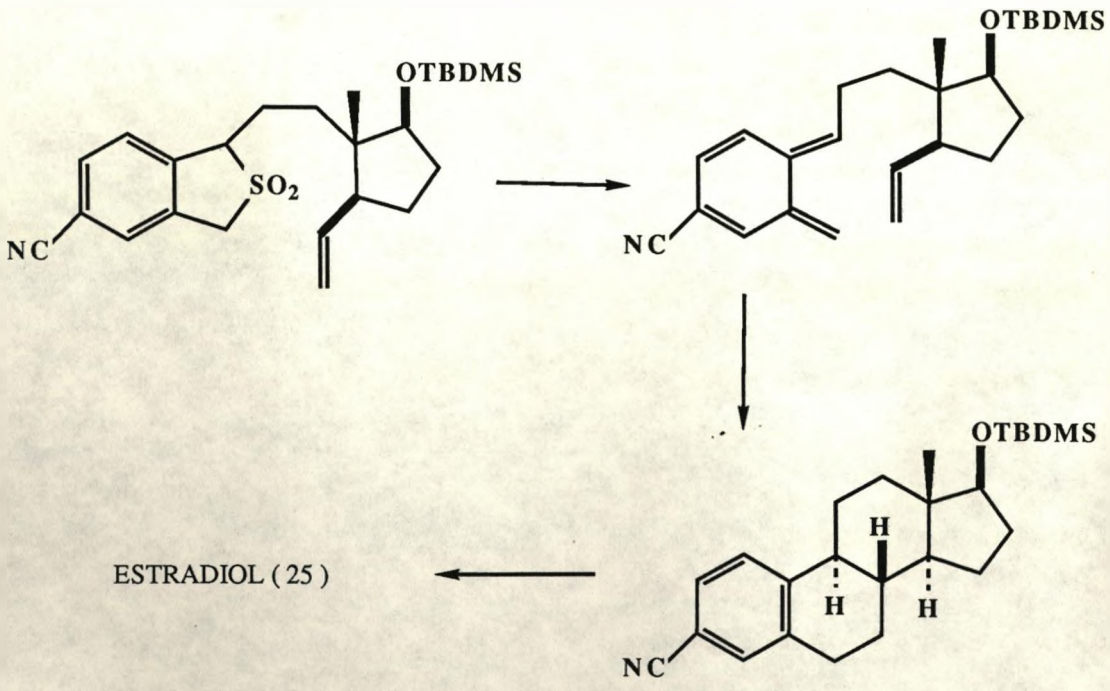
SCHEME 1.18

The scope for further research in this area is considerable and would further serve to enhance the synthetic utility of o-xylylenes in organic synthesis.

1.1.6 o-XYLYLENES IN ORGANIC SYNTHESIS

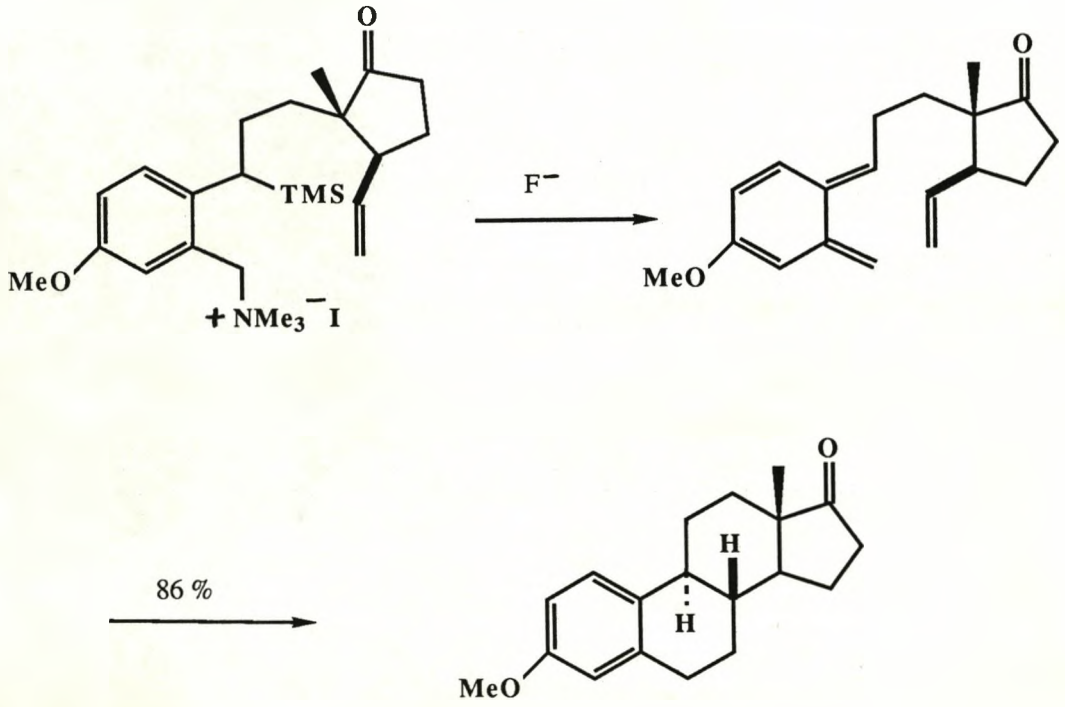
Due to the high degree of regio- and stereochemical control that can be achieved in the Diels-Alder reactions of o-xylylenes, they are much used in synthesis, notably in natural product chemistry. The literature is so extensive that an exhaustive survey would be impractical and so only a few representative examples will be given.

Intramolecular cycloaddition reactions of o-xylylenes are extensively used in the synthesis of steroids. Oppolzer *et al.*, achieved an enantioselective synthesis of (+)-estradiol (25) by the intramolecular cycloaddition of an o-xylylene generated by thermal extrusion of SO_2[85,86] (Scheme 1.19).



SCHEME 1.19

Using the fluoride ion-induced 1,4-elimination process, Ito et al., have also achieved the stereoselective synthesis of the steroid estrone methyl ether (32)[52] (Scheme 1.20).

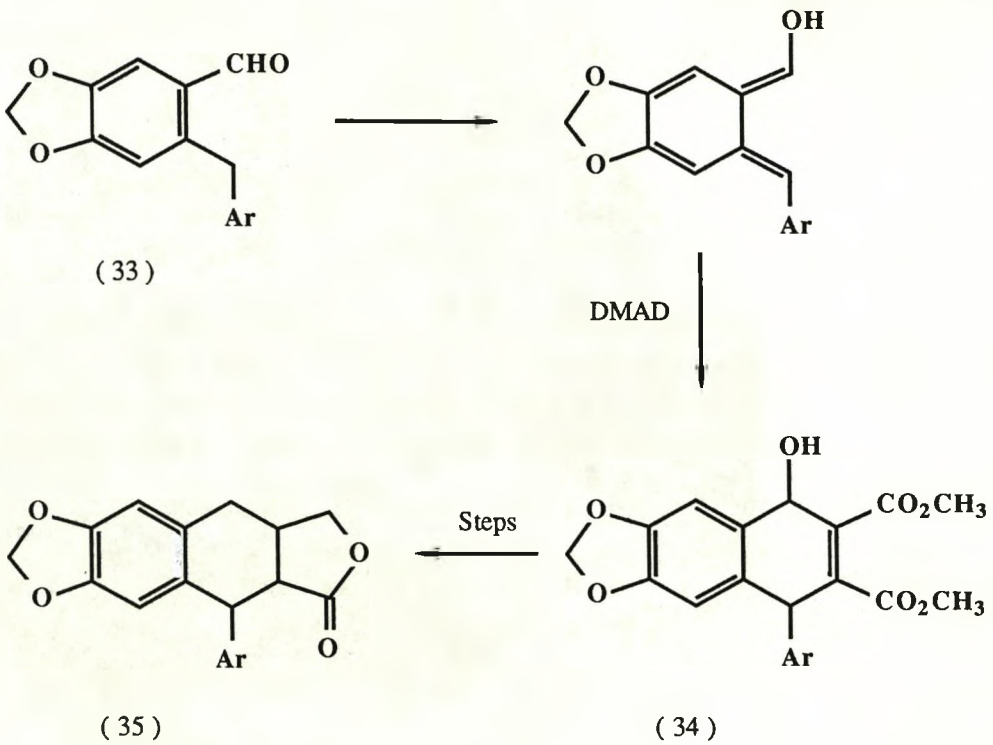


(32)

SCHEME 1.20

Intermolecular cycloadditions of o-xylylenes with dienophiles are also used in synthesis. Sammes et al., have used photoenolisation to produce o-xylylenes for the synthesis of aryltetralin lignans. For example, irradiation of aldehyde (33) in the presence of dimethyl-acetylene dicarboxylate gives adduct (34) which can be readily converted to several natural products including tetrahydropodophyllo-toxin (35)[87] (Scheme 1.21).

Another example in this category is the synthesis of (±)-4-demethoxydaunomycinone (38) by Cava et al.[88] Generation of o-xylylene (37) is accomplished by the reductive debromination of (36) with either zinc or iodide ion, which in the presence of methyl vinyl ketone gives the anthracyclinone (38) (Scheme 1.22).

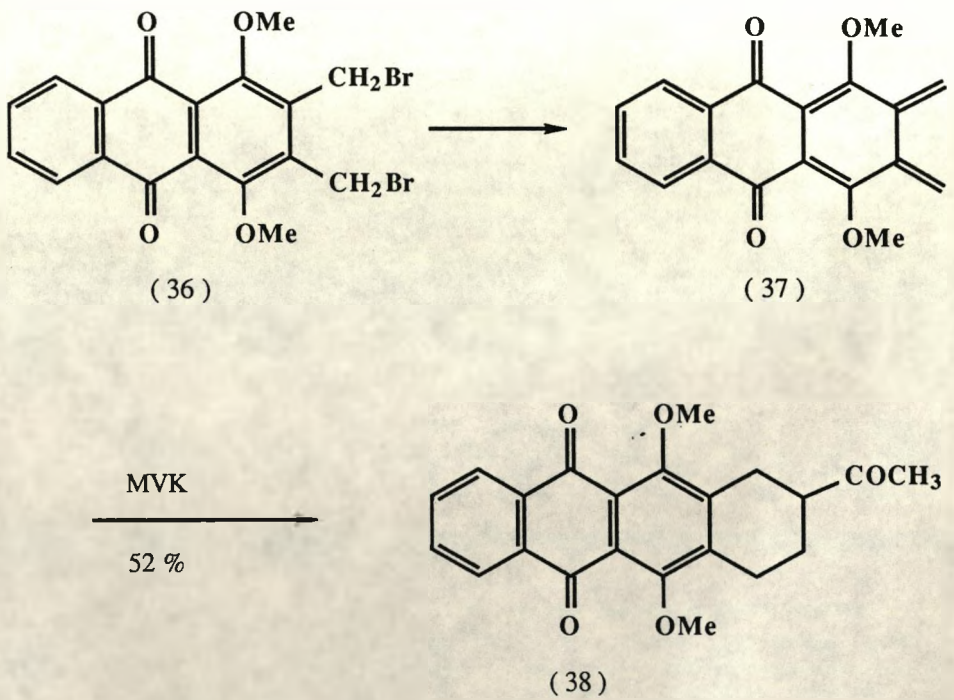


(33)

(35)

(34)

SCHEME 1.21



(36)

(37)

(38)

SCHEME 1.22

Further examples of o-xylylenes in synthesis can be found in the previously cited review articles.[8-21]

1.2 HETEROCYCLIC ANALOGUES OF o-XYLYLENES

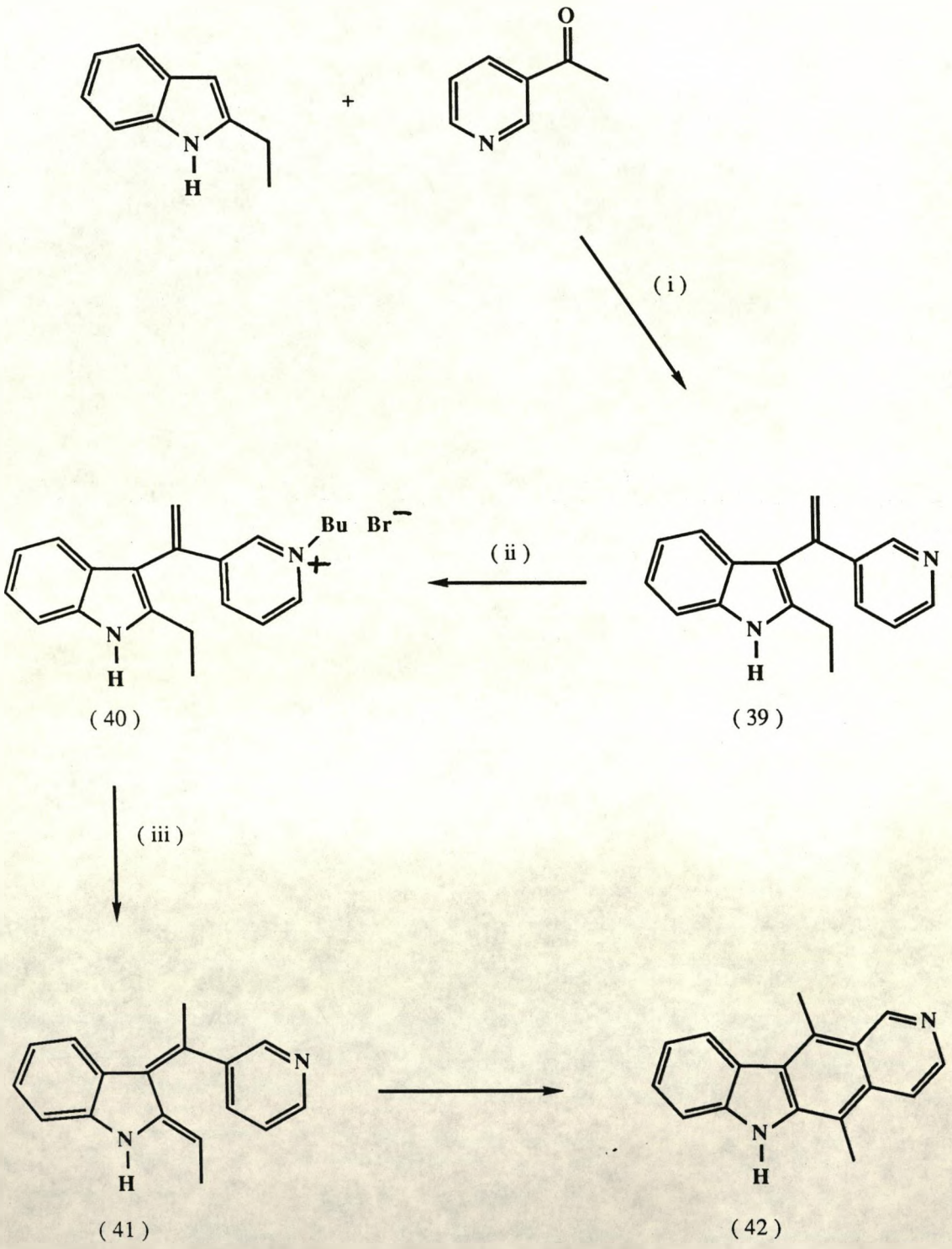
In this review, the known heterocyclic analogues of o-xylylene are described, including methods for their generation, their reactivity and synthetic applications. Individual ring systems will be dealt with separately.

1.2.1 INDOLE

The realisation that an o-xylylene strategy could be applied to the synthesis of biologically interesting indole alkaloids has resulted in several reports utilising such an approach. The first in 1977 by Bergmann and Carlsson is directed at the synthesis of the antitumour alkaloid ellipticine (42)[89] (Scheme 1.23).

Acid catalysed condensation of 2-ethylindole with 3-acetylpyridine gives a 90% yield of intermediate (39), which on quarternisation with butyl bromide gives salt (40) in quantitative yield. Heating (40) at 350°C for five minutes gives a 72% yield of ellipticine, which is presumably formed *via* o-xylylene (41). The same authors later adopted a similar approach to the anti-cancer active alkaloid olivacine (43).[90]

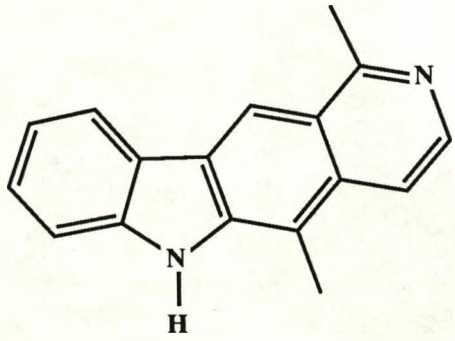
Kano and co-workers have also synthesised ellipticine (42) in a similar fashion.[91] In this case the N-protected 3-alkyl-2-lithio indole (44) is condensed with nicotinic anhydride to afford the acylated derivative (45) in 75% yield. This is then sequentially methylenylated and hydrolysed to give (46) in 67% overall yield. Heating (46) at 500°C for seven minutes produces ellipticine (42) in 50% yield. A [1,5] sigmatropic hydrogen shift from the 3-alkyl-2-



Reagents: (i) HBr, MeOH, reflux, 3 hr; (ii) BuBr;

(iii) 350°C, 5 min.

SCHEME 1.23

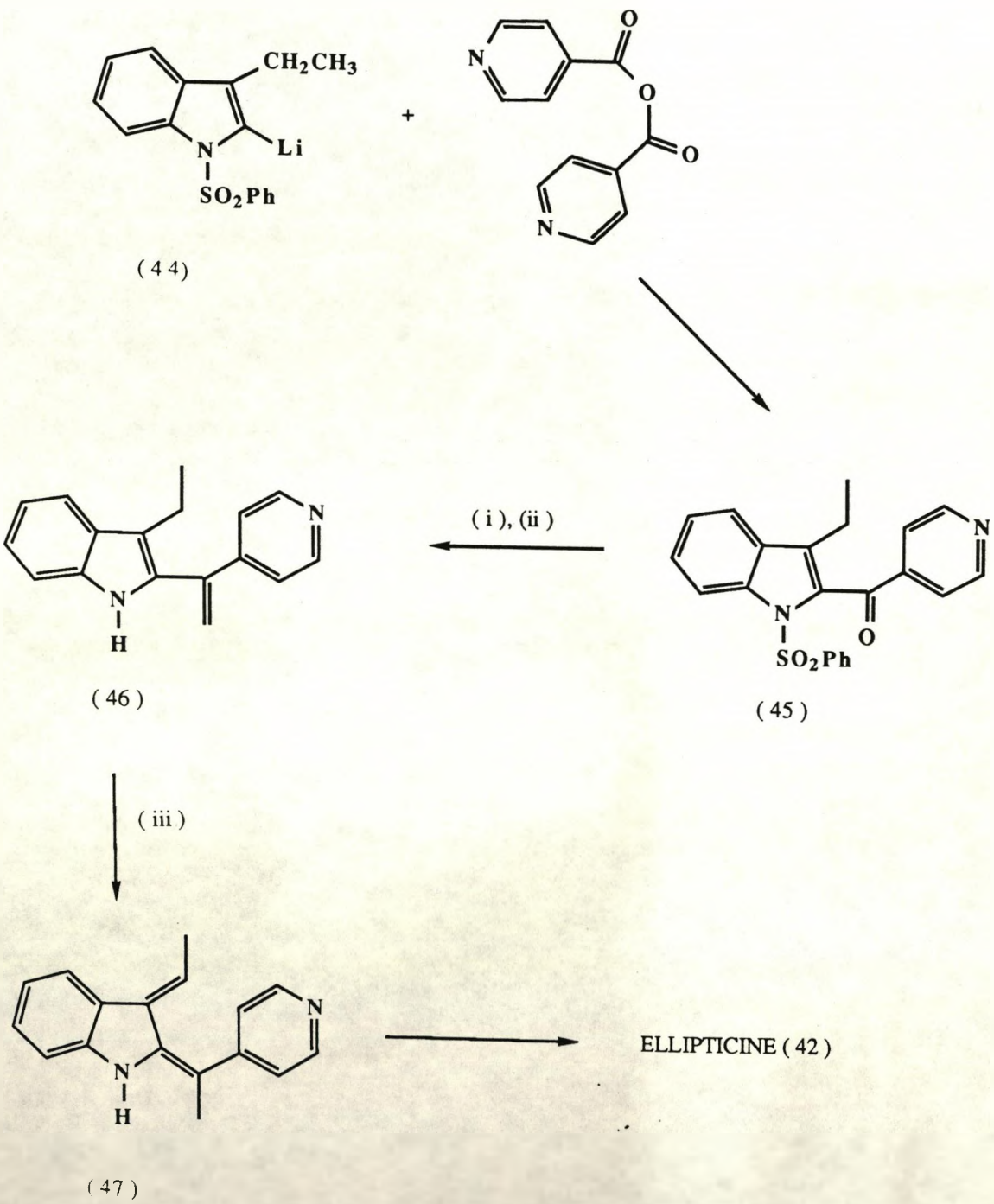


(43)

vinylindole (46) gives o-xylylene (47) which on intramolecular cyclisation and dehydrogenation furnishes the observed product (Scheme 1.24).

The propensity for 2,3-dialkylindoles to form o-xylylene species owes much to the acidity (and thus lability) of the protons of the 2-alkyl group. This feature of indole chemistry has been superbly exploited in the synthesis of alkaloids and carbazoles by Magnus and co-workers.[1] In the first[92] of a series of publications he outlines an approach to the aspidosperma alkaloids (Scheme 1.25).

The tri-substituted indole (48) is prepared in two steps from 2-methylindole.(48) Is then condensed with 4-pentenylamine to give the imine (49). Treatment of (49) with methylchloroformate in chlorobenzene at 130°C for three hours in the presence of diisopropylethylamine affords the tetracyclic carbamate (50) in 88% yield. A most significant point concerning the formation of (50) is that it is produced as a single diastereomer. X-ray crystallographic structure determination of the adduct reveals it to have a cis fusion at the newly formed ring junction, indicating a preference for the exo-E transition state (51).

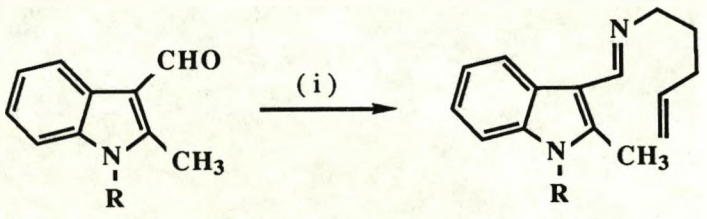


Reagents: (i) $Ph_3P=CH_2$; (ii) NaOH, EtOH, reflux;

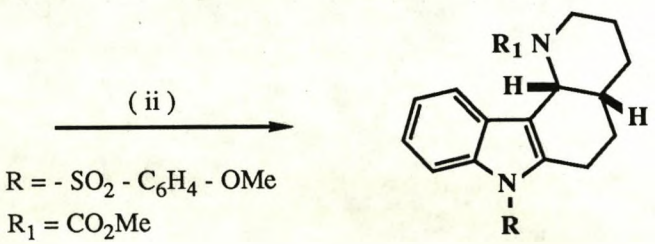
(iii) 500°C, 7 min.

SCHEME 1.24

Although literature precedent would predict the trans-fused product[14] (54) arising from transition state (53), it is probable that the steric repulsion between the substituent at the 3-position and the benzenoid ring makes this configuration less likely. This is indeed a fortuitous stereochemical outcome as tetracycle (52) has the same relative configuration as in the natural aspidosperma alkaloids.



(48) (49)

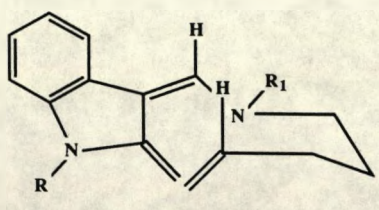


(50)

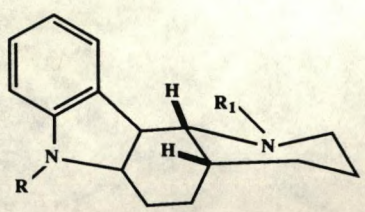
Reagents: (i) 4-pentenylamine;

(ii) MeO_2CCl, PhCl, $^{i}Pr_2NEt$, 130°C, 3.5 h.

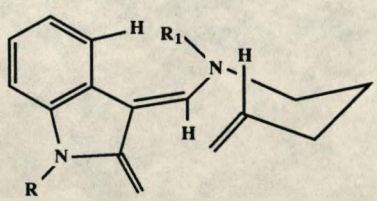
SCHEME 1.25



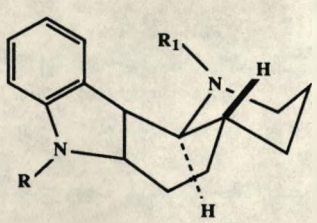
(51) EXO - E



(52) = (50)

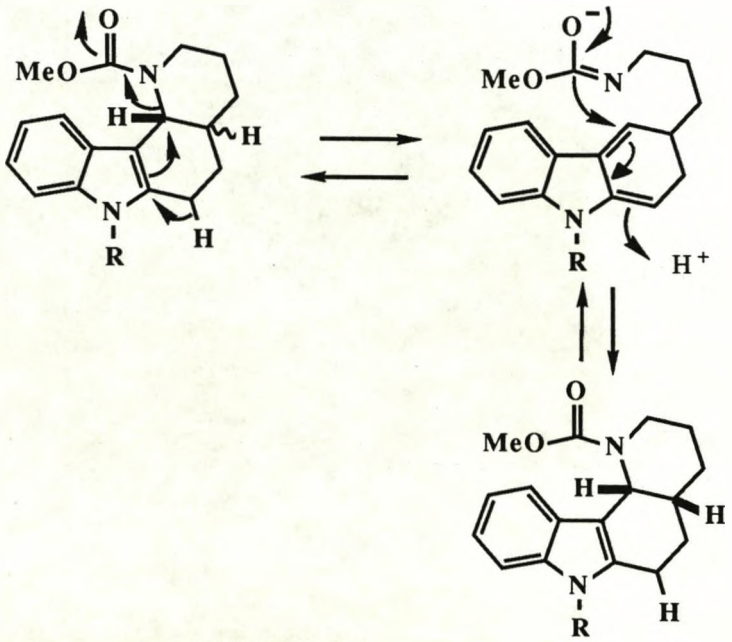


(53) EXO - Z



(54)

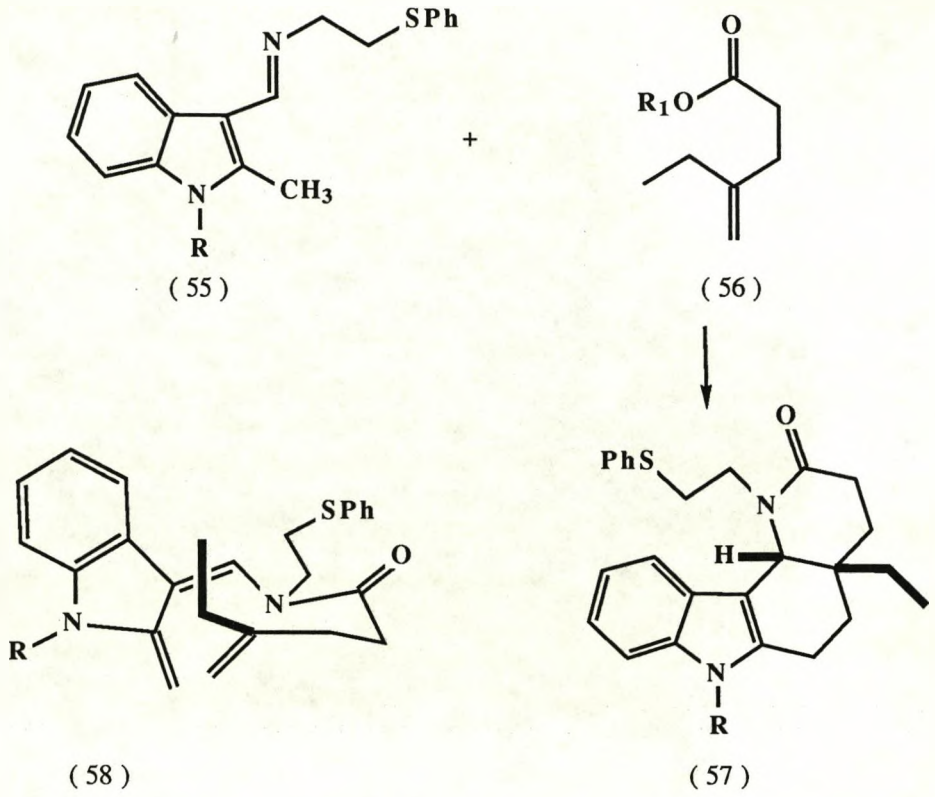
However, Magnus notes that the initial product(s), whether cis or trans can undergo reversible fragmentation, leading to the cis fused product (52), through simple stereoelectronic control (Scheme 1.26).



SCHEME 1.26

Regardless of the mechanism of steric control, Magnus has developed a novel, high-yielding method for the construction of tetracyclic pyridocarbazoles, closely related to a whole family of biologically interesting indole alkaloids.

In a subsequent paper[93] he expands this strategy to include the two carbon bridge (C10-C11) and C5 ethyl group present in the naturally occurring aspidosperma alkaloids, and exemplifies this in the total synthesis of dl-aspidospermidine (61). Treatment of imine (55) with mixed anhydride (56) in chlorobenzene gives the tetracyclic system (57) in a disappointing 33% yield. Only one diastereomer can be detected and single-crystal X-ray crystallography demonstrates the newly formed ring junction to be cis fused. The stereochemical outcome of the reaction is explained in terms of transition state (58) (Scheme 1.27).



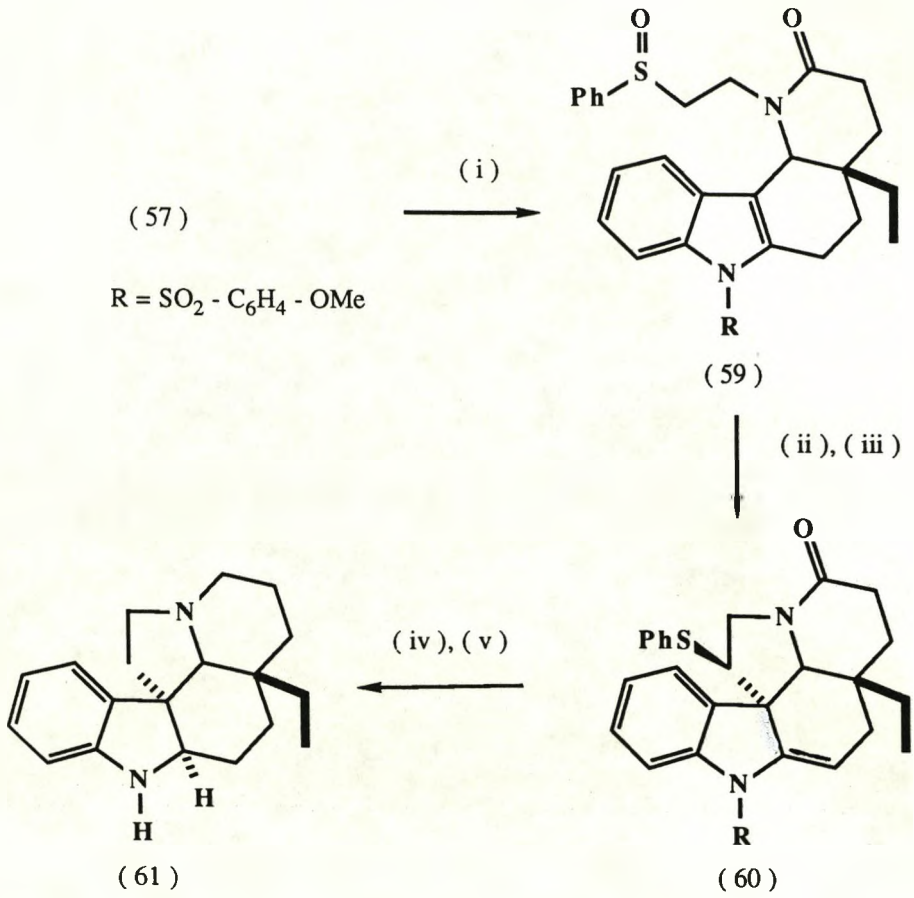
(55) (56) (58) (57)

SCHEME 1.27

The tetracycle (57) is converted into aspidospermidine (61) in a further four steps. Oxidation of (57) gives a diastereomeric mixture of sulphoxides (59), which on heating with trifluoroacetic anhydride to effect an intramolecular Pummerer-type reaction, gives the pentacyclic amide (60). Desulphurisation of (60) followed by reduction gives (±)-aspidosperimidine (61) in an overall yield of 11.7% (six steps) Scheme 1.28).

Elaboration of the aspidosperma skeleton has also permitted the synthesis of another class of indole alkaloids, the kopsanes. For example, 10,22-dioxokopsanone (62) is synthesised in fourteen steps from indole (48) in an overall 5.8% yield.[94]

Magnus further extended his strategy by reporting the enantiospecific synthesis of desethylaspidosperma-type alkaloids.[95] Imine (63) is reacted with the enantiomerically pure acid chloride (64) to give the desired cis-adduct in 67% yield (Scheme 1.29). The

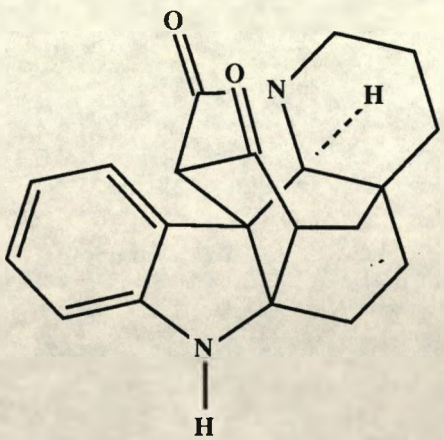


Reagents: (i) MCPBA, CH_2Cl_2, $NaHCO_3$, 0°C;

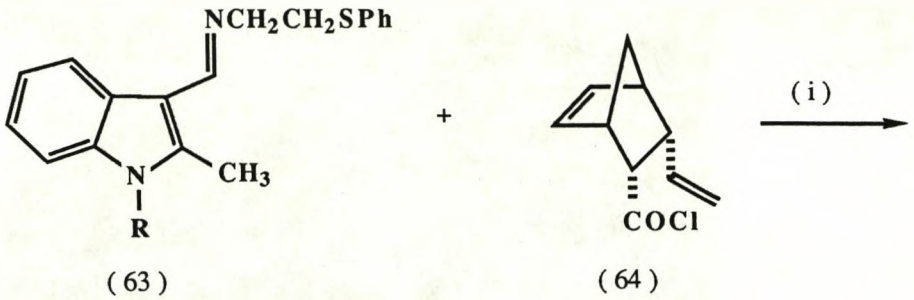
(ii) $(CF_3CO)_2O$, CH_2Cl_2, 0°C; (iii) PhCl, 130°C;

(iv) Raney Ni, EtOH, 20°C; (v) $LiAlH_4$, thf, 20°C.

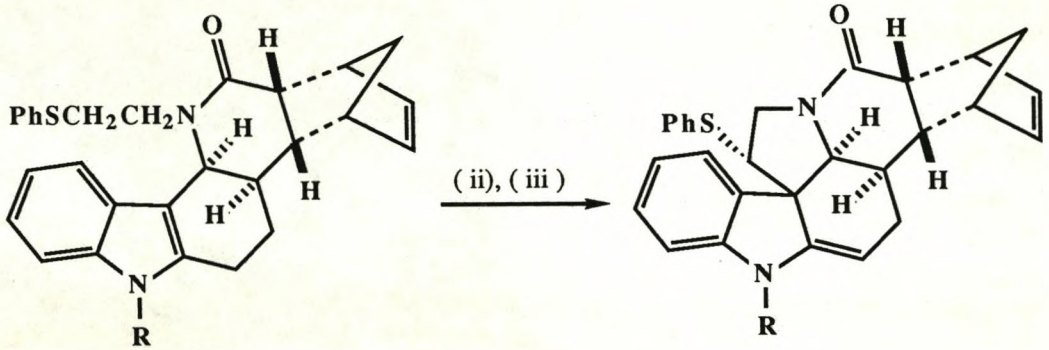
SCHEME 1.28



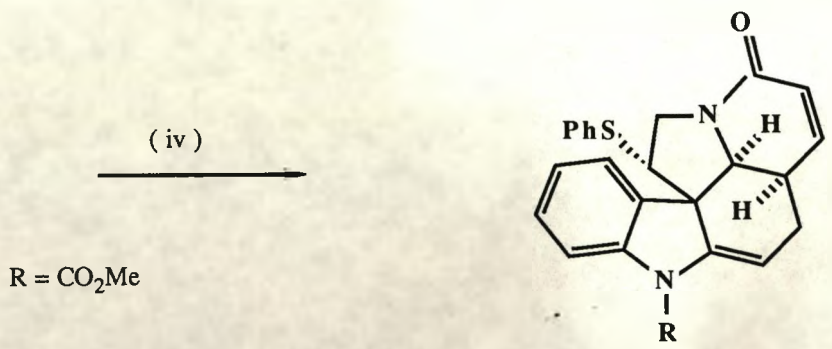
(62)



(63) (64)



(65) (66)



(67)

Reagents: (i) $PhCH_3$, $^{i}Pr_2NEt$, 110°C; (ii) MCPBA;

(iii) $(CF_3CO)_2O$, CH_2Cl_2, 0°C, then $PhCH_3$, 110°C, 1 h.;

(iv) 190 - 200°C, 24 h.

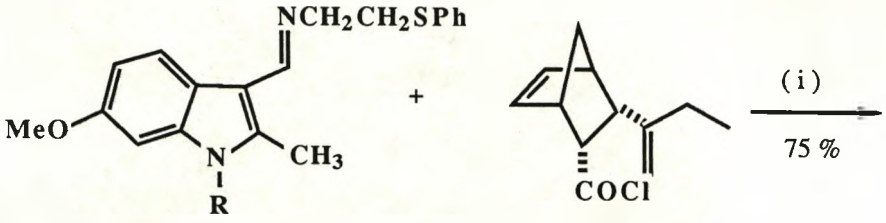
SCHEME 1.29

relatively high yield reflects the conformational rigidity of the appended alkene in the cyclisation process. Adduct (65) is then subjected to the "standard" Pummerer reaction conditions to give (66) in 80% yield. Heating at 190 - 200°C facilitates the retro-Diels-Alder extrusion of cyclopentadiene to give pentacycle (67) in greater than 95% yield. The relatively low temperature required for this particular reaction (typically 350°C) reflects the inherent ring strain present in (66) and provides an elegant method for the introduction of the 6,7-double bond present in this type of alkaloid. The sequence from imine (63), *via* (65), (66) and (67) proceeds in four steps in an overall yield of 50.9%.

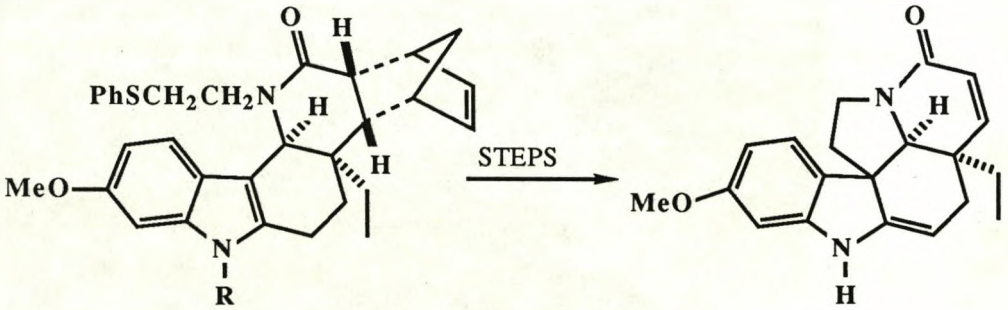
Extrapolation of this work to the 16-methoxy series has been reported very recently.[96] The synthesis of either antipode of 16-methoxytabersonine (71) hinges on the reaction between imine (68) and enantiomerically pure acid chloride (69) to produce adduct (70) (Scheme 1.30). This single transformation embodies all of the required virtues of the indole *o*-xylylene strategy: it is stereospecific, enantiospecific, and compatible with the 16-methoxy substituent, the yields are good, and it scales up to several grams without any problem.

A recent report by Herslöf and Martin utilises the cylisation of an indole *o*-xylylene as the key step in the synthesis of a serotonin homologue[97] (Scheme 1.31). The benzoate ester (72) is synthesised in five steps from 2-methylindole. Treatment as shown furnishes the *trans*-fused adduct (73) as the major product, presumably *via* *o*-xylylene (74).

So far in this section all examples of indole *o*-xylylenes quoted have been intercepted in intramolecular cycloaddition reactions. However, the "free" *o*-xylylene species has been generated and trapped



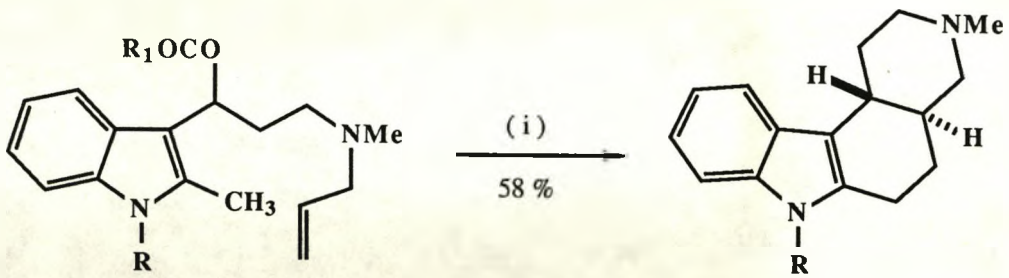
(68) (69)



(70) R = CO_2Me (71)

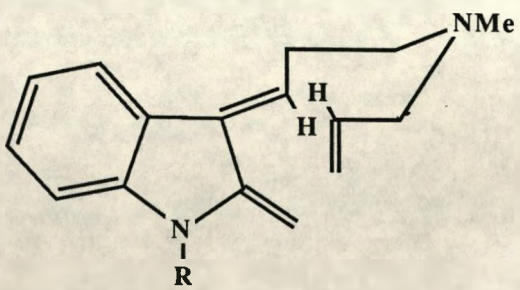
Reagents (i) $PhCH_3$, reflux, 2.5 h.

SCHEME 1.30



(72) (73)

R = MeO - C_6H_4 - SO_2
R_1 = 2, 6 - $Cl_2C_6H_3$

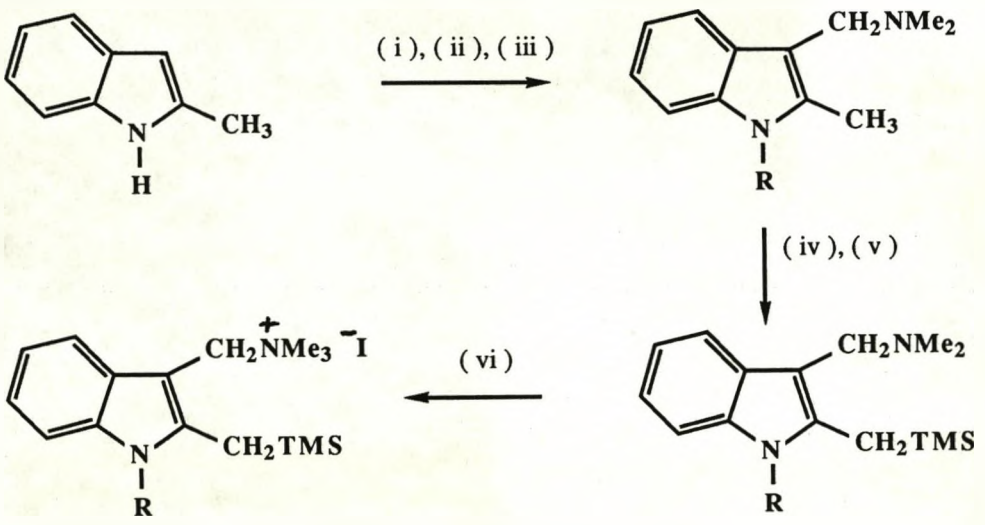


(74) TRANS - EXO

Reagents: (i) Et_3N, PhCl, 135°C.

SCHEME 1.31

in intermolecular Diels-Alder reactions. This was first accomplished by Marinelli in 1980.[2] N-protected indole o-xylylene (76) is generated by fluoride-ion-induced 1,4-elimination from quaternary ammonium salt (75) (Scheme 1.33). Salt (75) is prepared in four steps from 2-methylindole (Scheme 1.32).

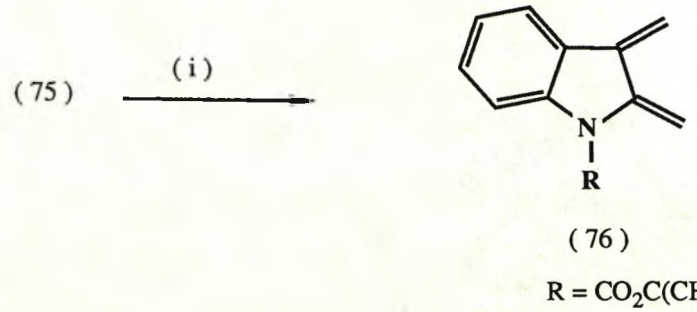


(75) $R = CO_2C(CH_3)_3$

Reagents: (i) AcOH, $HN(CH_3)_2$, CH_2O (75%); (ii) $NaCH_2SOCH_3$, DMSO; (iii) $^tBocN_3$ (71%; (v) LTMP, thf, -78°C; (v) TMSCl (75%); (vi) MeI, EtOH, 0°C (82%).

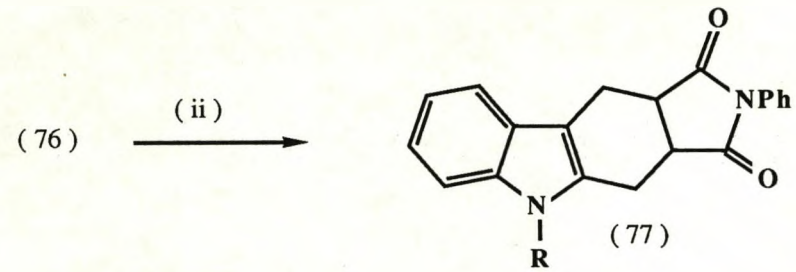
SCHEME 1.32

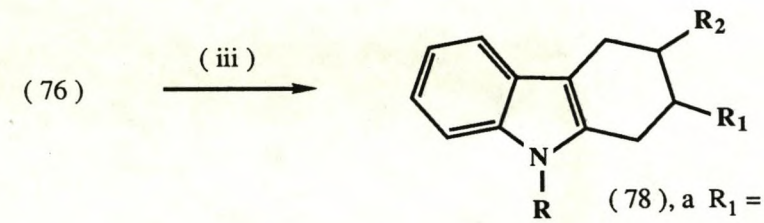
Treatment of an acetonitrile solution of (75) with tetrabutylammonium fluoride (TBAF) at room temperature, in the presence of N-phenylmaleimide gives tetrahydrocarbazole (77) in 57% yield. When a large excess of methylacrylate is used as dienophile, a 3:1 mixture of the regioisomeric adducts (78 a,b) is produced in 63% overall yield. In the absence of trapping agent the dimeric compound (79) is isolated in 80% yield. Deprotection gives indolenine (80) as structural confirmation of (79) (Scheme 1.33).



(76)

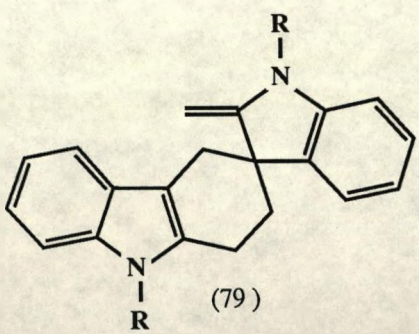
$R = CO_2C(CH_3)_3$

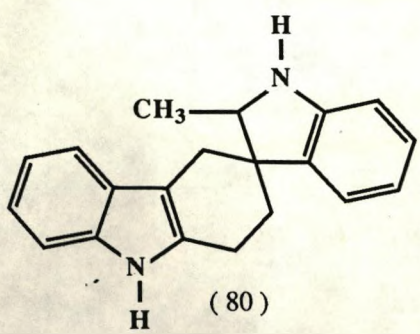




(78), a $R_1 = CO_2Me$, $R_2 = H$

b $R_1 = H$, $R_2 = CO_2Me$



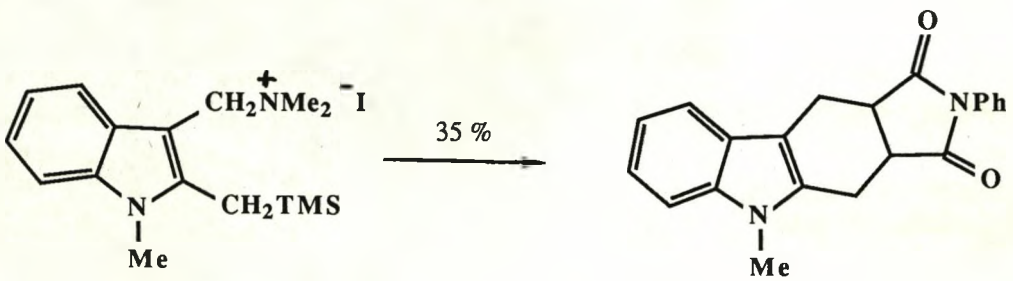


Reagents: (i) TBAF, CH_3CN, 25°C; (ii) N-phenylmaleimide;

(iii) methylacrylate

SCHEME 1.33

The selection of protecting group on nitrogen is of considerable importance as evidenced when the ^{t}Boc group is replaced by methyl. Treatment of salt (81) in an analogous fashion to (75) results in reduced yield of adduct (82) (Scheme 1.34). This reflects the



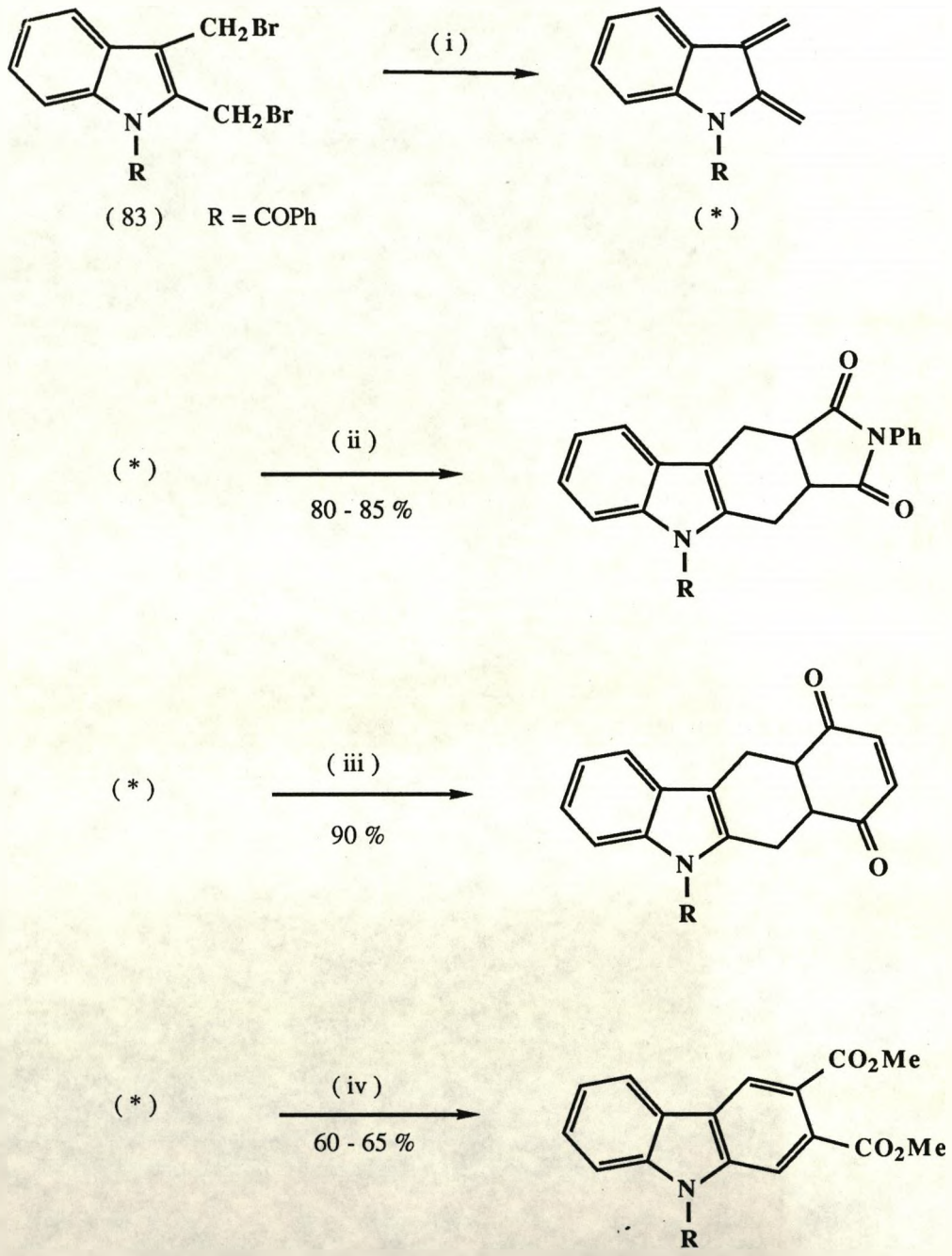
(81) (82)

SCHEME 1.34

inductive stabilising effect the ^{t}Boc group has on both the salt and o-xylylene species. It is also a readily removable group which is important if the syntheses of naturally occurring indole alkaloids is to be pursued.

A complimentary approach to the generation and intermolecular trapping of an indole o-xylylene species has been reported. Treatment of bis-bromomethyl indole (83) with sodium iodide in DMF in the presence of electron deficient dienophiles gives excellent yields of the corresponding Diels-Alder adducts[3] (Scheme 1.35).

There are also several reports of stable synthetic analogues of indole o-xylylenes, particularly of the form (84).[98,99] X is typically O, S, or Se and the indolic nitrogen has to be protected. The anionic o-xylylene equivalent (85) has also been generated by treatment of the corresponding anhydride with base.[100]

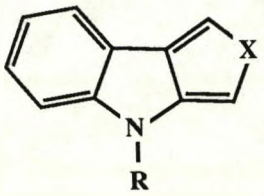


Reagents: (i) NaI, DMF, 50°C; (ii) N-phenylmaleimide;

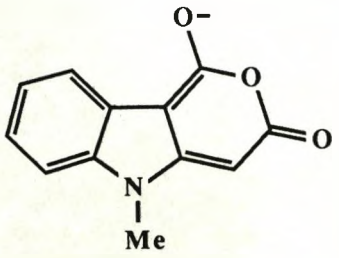
(iii) benzoquinone; (iv) dimethylacetylenedicarboxylate

SCHEME 1.35

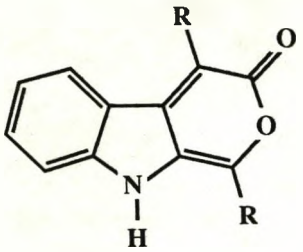
Moody has extended the original work of Plieninger[101] and has made use of pyrano-[3,4-b]-indol-3-ones (86) as stable synthetic



(84)



(85)

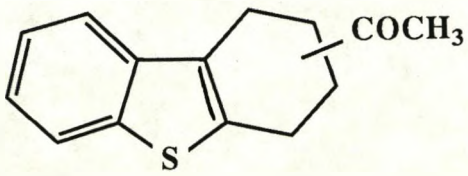


(86)

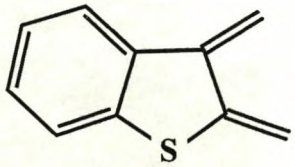
equivalents (NH free) of indole o-xylylenes. These compounds add to electron deficient olefins and acetylenes, to give (after spontaneous decarboxylation) good yields of carbazoles.[102,103] Moody has applied this methodology to the synthesis of ellipticine (42)[104] and has extrapolated the procedure to encompass intramolecular trapping with alkynes.[105]

1.2.2 BENZOTHIOPHENE

The benzothiophene analogue of o-xylylene has recently been generated by Storr et al., using the technique of flash vacuum pyrolysis (FVP).[106] FVP of 2-chloromethyl-3-methylbenzothiophene gives the isomeric Diels-Alder adducts (87), (45%), on co-condensation of the pyrolysate with methyl vinyl ketone. o-Xylylene (88) is also trapped with thiophenol to give a pair of isomeric adducts; in the absence of trap it gives a low molecular weight polymer and a [4+2] dimer.

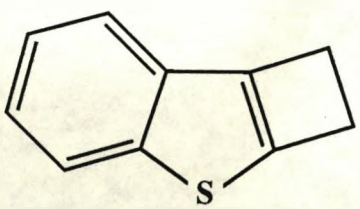


(87)



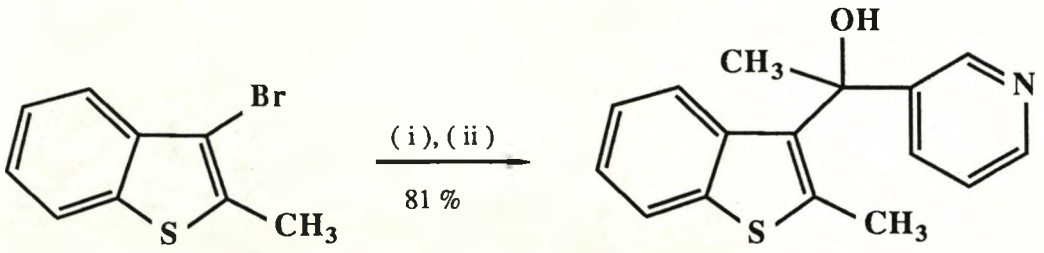
(88)

The ring closed tautomer (89) of o-xylylene (88) has also been reported.[107,108]



(89)

Shibuya and co-workers have utilised substituted benzothiophene o-xylylenes to prepare 6-thiaellipticine and related compounds.[109] A range of tertiary alcohols are simply prepared by treating lithio-benzothiophenes (formed by metal-halogen exchange procedures) with appropriate acetyl pyridines. A representative example is shown below (Scheme 1.36).

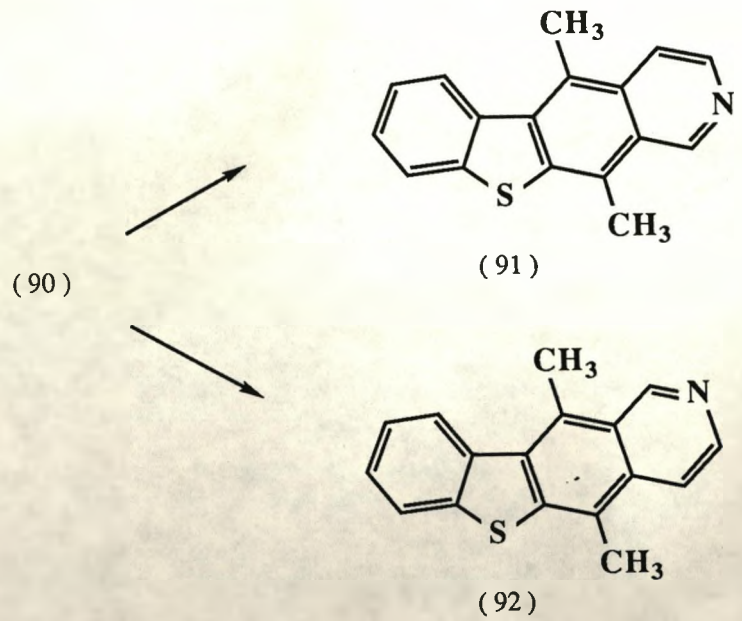


(90)

Reagents: (i) ^{n}BuLi, thf, -78°C; (ii) 3-acetylpyridine

SCHEME 1.36

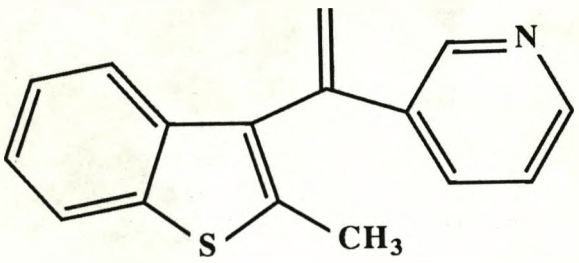
The alcohols are then pyrolysed (typically 400°C for seven minutes) and products isolated after chromatography. Alcohol (90) gives rise to isomeric adducts (91) and (92) in 33% overall yield (Scheme 1.37). Yields are similar for the pyrolysis of tertiary



SCHEME 1.37

alcohols derived from other benzothiophene derivatives and acetylpyridines.

The authors demonstrate that the transformation of alcohol (90) into adducts (91) and (92) proceeds through (93), [1,5] sigmatropic hydrogen shift followed by intramolecular cyclisation providing the mechanistic pathway.

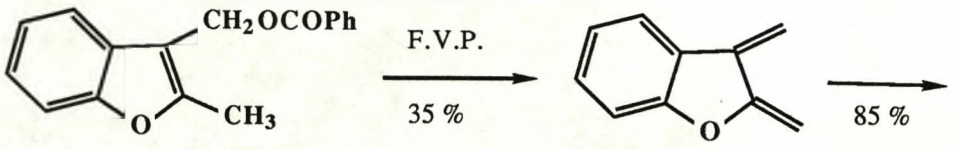


(93)

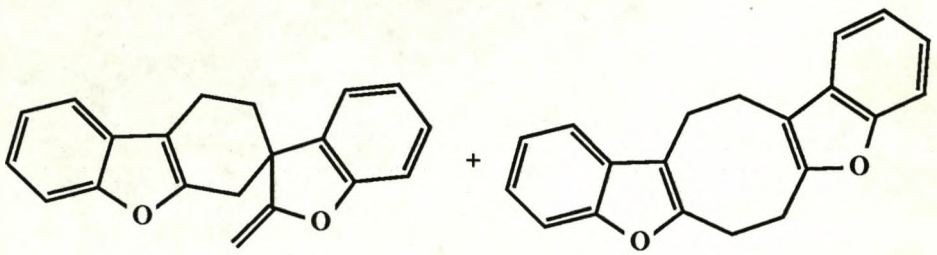
1.2.3 BENZOFURAN

The benzofuran analogue of o-xylylene (95) has been generated in the gas phase using F.V.P.[110] Elimination of benzoic acid from ester (94) (prepared in four steps from benzofuran-2,3-dicarboxylic acid) gives rise to o-xylylene (95) (Scheme 1.38). The nmr spectrum of (95) has been recorded at -60°C, quantitative analysis indicating a 35% yield from ester (94). o-Xylyene (95) is stable in solution at -60°C and reacts slowly at room temperature to give a mixture of [4+2] and [4+4] dimers, (96) and (97) in a 4:1 ratio.

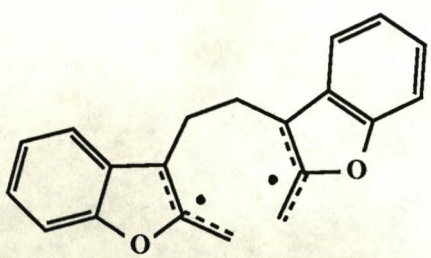
By analogy with earlier studies on the furan analogue of o-xylylene[7,111] (see Section 1.2.5, page 52), a stepwise dimerisation, proceeding via the most stable diradical (98) is favoured over a concerted process. The reasons for the predominance of the [4+2] dimer (96) are as yet unclear. When the pyrolysate is co-condensed



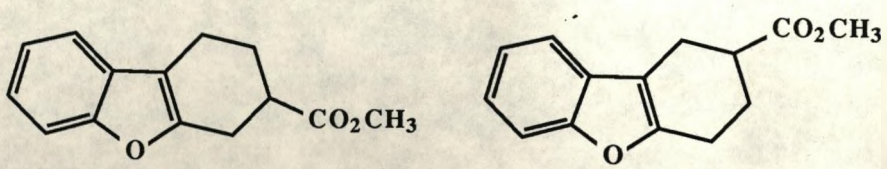
(94) (95)



(96) (97)



(98)



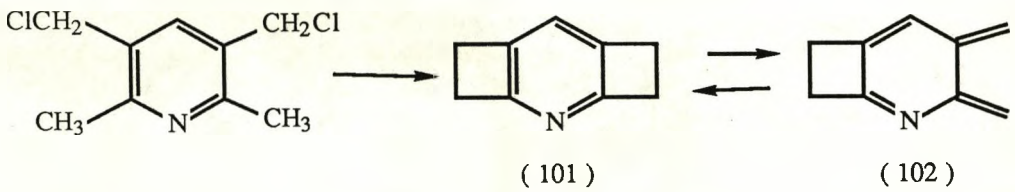
(99) (100)

SCHEME 1.38

with methyl acrylate the isomeric Diels-Alder adducts (99) and (100) are formed in a ratio of 3:1 in 30 - 40% overall yield.

1.2.4 PYRIDINE AND OTHER SIX-MEMBERED NITROGEN HETEROCYCLES

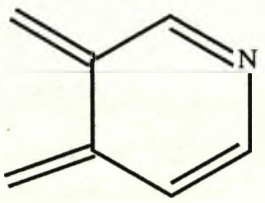
Pyridine analogues of o-xylylene have been generated by a variety of procedures, both in the gas phase and in solution. Early reports concentrate on the preparation of cyclobutapyridines,[112-114] one example being the flash vacuum pyrolytic generation of a dicyclobutapyridine (101).[115] In solution this was found to exist in tautomeric equilibrium with the ring open form (102) (Scheme 1.39).



(101) (102)

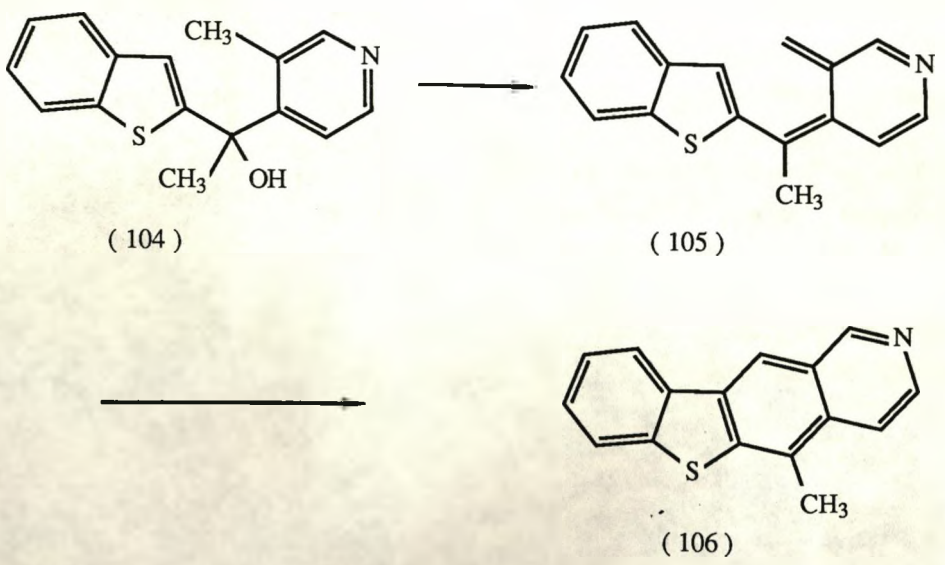
SCHEME 1.39

Although this review concentrates on ortho-xylylenes in which one of the methylene groups is adjacent to the heteroatom of the heterocycle in question, brief mention of ortho-xylylenes not falling into this category is appropriate. Thus, pyridine-3,4-quinodimethanes (o-xylylenes) have been generated and utilised in organic synthesis. Kametani has prepared the carbazole alkaloid olivacine by intermolecular cyclisation of the pyridine-3,4-quinodimethane intermediate (103) with indole.[116]



(103)

Shibuya has used an intramolecular version of this reaction to prepare 6-thiaellipticine and related compounds[109] (Scheme 1.40).



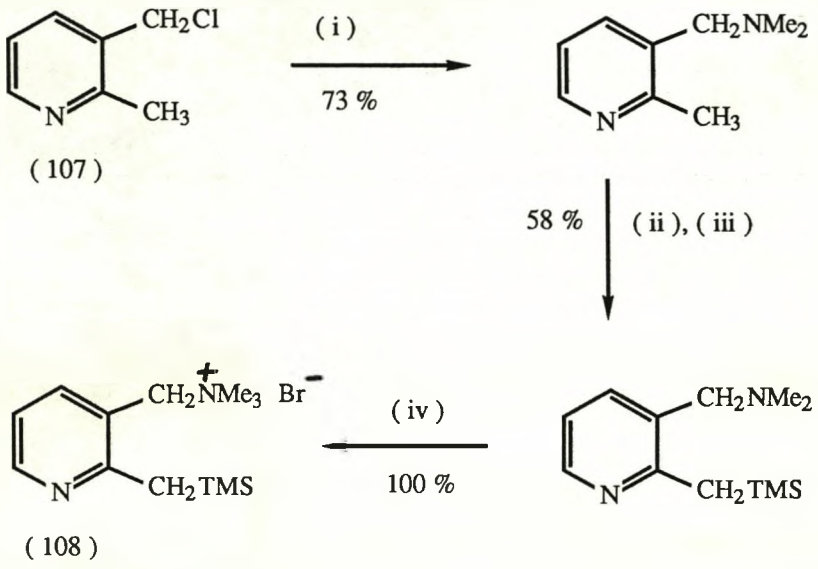
(104) (105) (106)

SCHEME 1.40

The tertiary alcohol (104) is prepared from 2-lithio-benzothiophene and 4-acetyl-3-methylpyridine in 92% yield. Pyrolysis of (104)

at 450°C for seven minutes gives (106) in 38% yield, presumably via o-xylylene (105).

Ito, Saegusa, and co-workers, who have made many valuable contributions to the wealth of literature in the field of o-xylylene chemistry have also applied their mild and elegant methodology[46] for o-xylylene generation to the pyridine ring system[5] (Scheme 1.41).



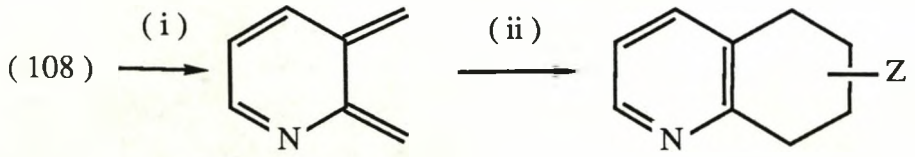
Reagents: (i) Me_2NH; (ii) $^{n}BuLi$; (iii) TMSCl; (iv) MeBr

SCHEME 1.41

The o-xylylene precursor (108) is synthesised in three steps from β-picolyl chloride (107).

Dimethylamination, lithiation at the 2-methyl group with subsequent silylation, and finally quaternisation with bromomethane gives the salt (108). This is added to a suspension of caesium fluoride in acetonitrile containing an excess of dienophile at 55°C (Scheme 1.42).

Regioisomeric Diels-Alder adducts (110 a,b) are produced in good yield from o-xylylene (109). It is interesting to note that an



(109)

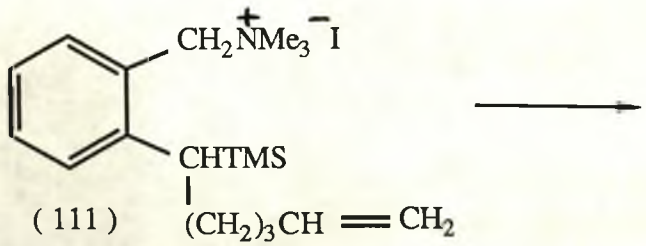
(110) a, Z = CO_2Me, 75 %
b, Z = CN, 76 %

Reagents: (i) CsF, CH_3CN, 55°C; (ii) CH_2 = CH-Z

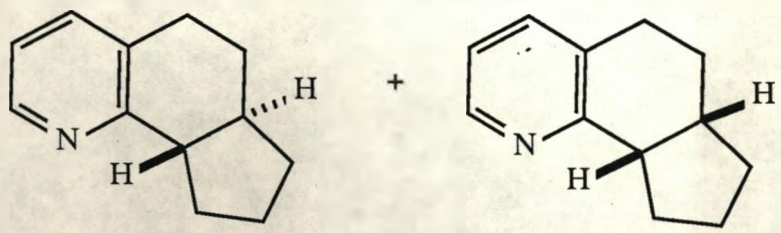
SCHEME 1.42

elevated temperature is required for good yields compared to the "all-carbon" o-xylylene which reacts perfectly well at room temperature.[46]

On extrapolation to the intramolecular version of this reaction a 1:1 ratio of the cis and trans tricycles (112) and (113) are produced in excellent yield from salt (111) (Scheme 1.43). The lack of



(111)



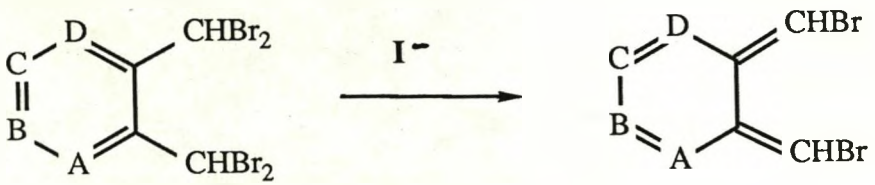
(112) (113)

Reagents: CsF, CH_3CN, reflux

SCHEME 1.43

stereoselectivity may be taken to imply that there is no significant energy difference between the respective exo and endo transition states in the intramolecular Diels-Alder reaction.

Shepherd has carried out the iodide ion-induced reductive debromination of a series of o-bis-(dibromomethyl)-nitrogen containing heteroaromatics (114) - (117) to generate the corresponding o-xylylenes (118) - (121)[117] (Scheme 1.44).

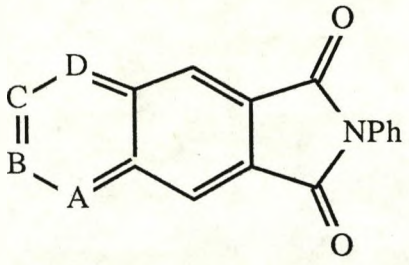


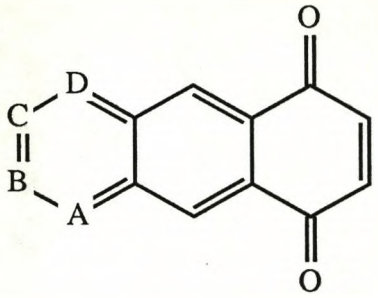
(114)	A = N;	B,C,D = CH	(118)
(115)	A,D = N;	B,C = CH	(119)
(116)	A,C = N;	B,D = CH	(120)
(117)	A,B,D = N;	C = CH	(121)

SCHEME 1.44

In the presence of N-phenylmaleimide or cyclohexa-2,5-diene-1,4-dione, the polycyclic derivatives (122) .- (129) are formed in variable yield.

The tetrabromides (114) to (117) are easily prepared by photobromination of the appropriate dimethyl compounds with NBS in CCl_4. When o-xylylene (118) is generated in the absence of dienophile a 10:1 mixture of trans and cis 1,2-dibromo-1,2-dihydrocyclobuta[b]pyridines (130 a,b) is produced in ca. 55% overall yield.





(122) 75% A = N; B,C,D = CH

(123) 78% A,D = N; B,C = CH

(124) 51% A,C = N; B,D = CH

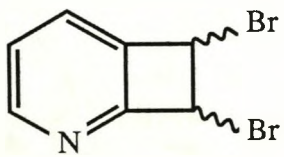
(125) 46% A,B,D = N; C = CH

(126) 69%

(127) 48%

(128) 25%

(129) 11%



(130) a <u>trans</u>

b <u>cis</u>

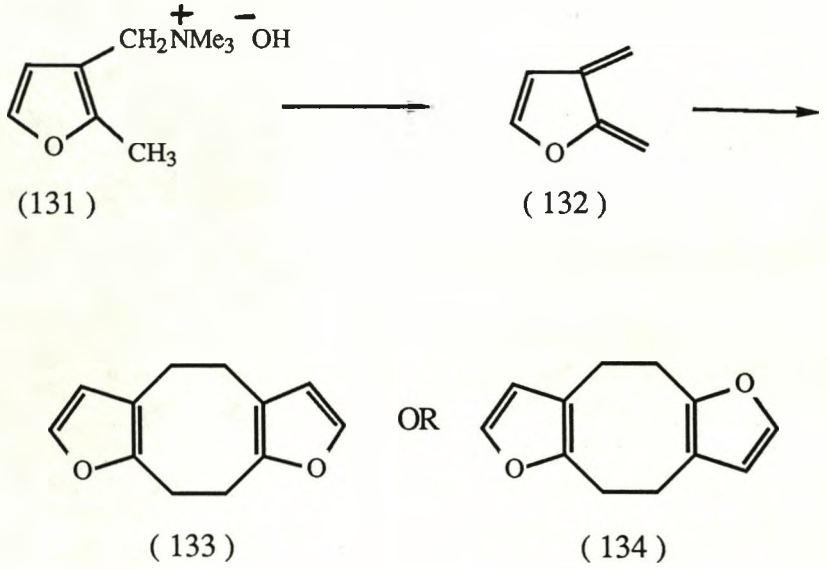
The methodology used by Shepherd has the advantage of simple precursor molecules and has allowed the generation of previously unreported heterocyclic analogues of <u>o</u>-xylylene i.e., pyrazine, pyrimidine and 1,2,4-triazine.

However, in terms of versatility, potential for functionalising the precursor molecules and finally mildness of reaction conditions, the approach adopted by Ito (previously described) seems preferable.

1.2.5 <u>FURAN</u>

The furan analogue of <u>o</u>-xylylene (132) was first postulated as an intermediate in the liquid phase pyrolysis of quaternary ammonium

hydroxide (131).[118] This reaction is reported to give a single dimer of (132), possessing either structure (133) or (134) (Scheme 1.45).



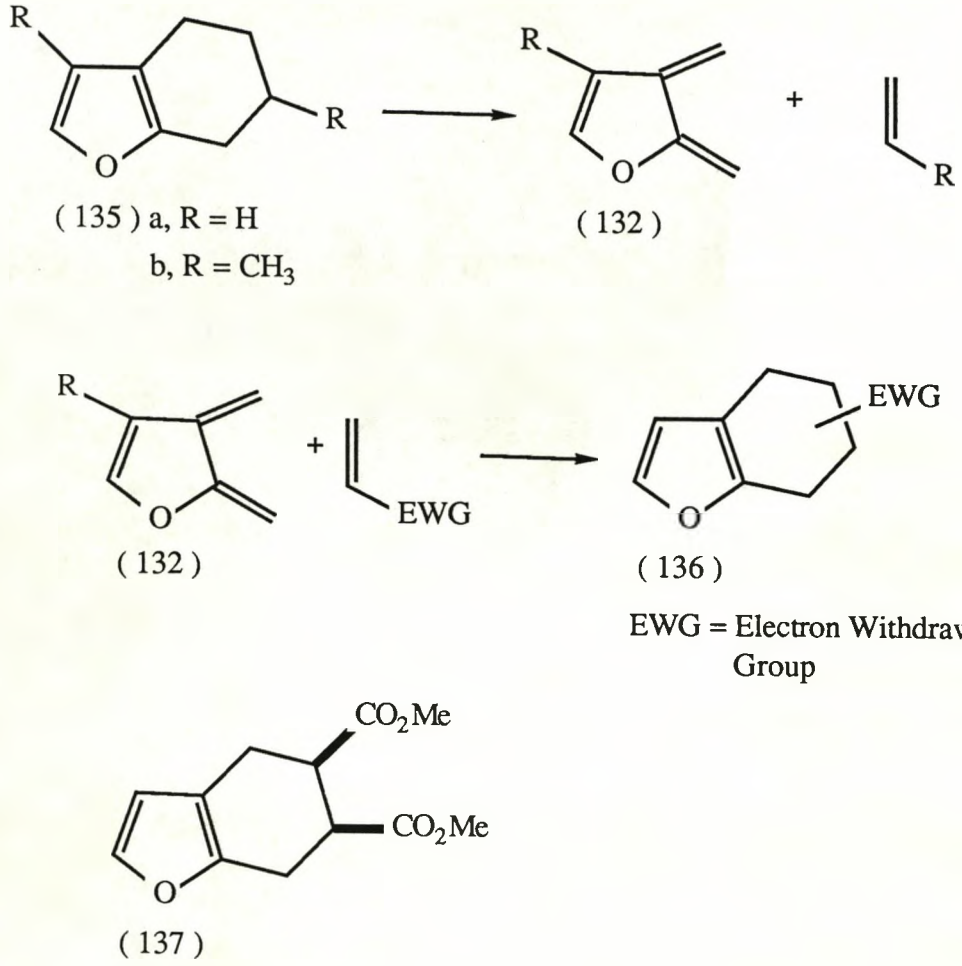
(131) (132) (133) (134)

SCHEME 1.45

F.V.P. is widely used in the generation of o-xylylenes, not least due to the often uncomplicated nature of the precursor molecules required. An early report of the furan analogue of o-xylylene again comes from application of the FVP technique.[6] The gas phase retro-Diels-Alder reaction of simple tetrahydro-benzofurans (135 a,b) is brought about at high temperature and o-xylylene (132 a) was initially identified by its mass spectrum (the flash vacuum thermolyser was coupled to a mass spectrometer)

Characterisation of o-xylylenes (132 a,b) is achieved by trapping these molecules with various dienophiles (Scheme 1.46).

Yields of adducts (136) range between 20 and 50%. Unsymmetrical dienophiles give mixtures of regioisomers whilst dimethylmaleate retains its stereochemistry in the adduct (137) in accordance with the "cis principle" of the Diels-Alder addition.[119]

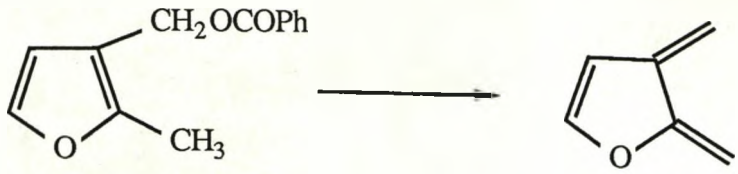


SCHEME 1.46

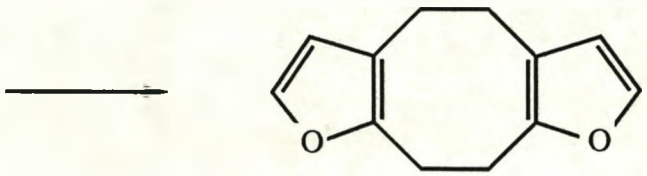
The work of Trahanovsky *et al.*, on the furan analogue of *o*-xylylene deserves special mention, particularly from a mechanistic point of view. It also illustrates the advantages of the FVP protocol when physical measurements (such as low temperature nmr spectra) are of interest.

Pyrolysis of furylmethyl ester (138) gives a 51% yield of dimer (133), presumably *via* *o*-xylylene (132)[7] (Scheme 1.47).

Structure (132) may be formed either directly from (138) by a δ-elimination of benzoic acid, or by a two-step mechanism involving a [3,3] sigmatropic shift followed by β-elimination of benzoic acid.



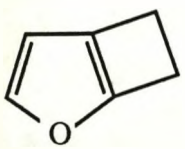
(138) (132)



(133)

SCHEME 1.47

The ^{1}H and ^{13}C nmr spectra of (132) can be recorded at -60°C and it is noted that dimerisation occurs rapidly above -30°C.[111] At no time is the furanocyclobutene (139) detected.

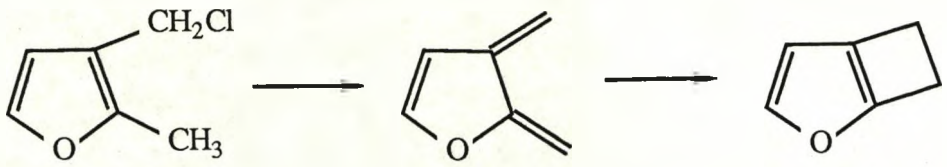


(139)

It is reasoned that the resonance energy of the furan ring in (139) is insufficient to compensate for the strain energy of the four-membered ring.

Other workers have brought about the photochemical formation of (139) and have recorded its ir uv/visible and photoelectron spectra[120] (Scheme 1.48).

Generation of o-xylylene (132) by pyrolytic means with immediate freezing in an argon matrix, permits spectroscopic analysis of (139) following irradiation.



(140) (132) (139)

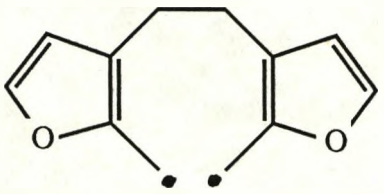
SCHEME 1.48

Comparison of empirical measurements with MNDO calculated values (for such parameters as standard reaction enthalpy and standard reaction entropy) leads the authors to conclude "... dihydrocyclobutafuran - other than dihydrocyclobutabenzene - can very probably not be generated thermally".

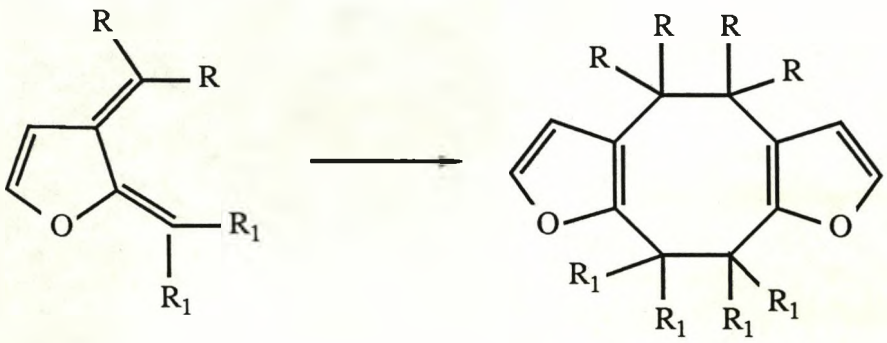
Trahanovsky postulates the formation of dimer (133) as proceeding via the diradical (141).[7] He supplied evidence for his postulate by carrying out a secondary deuterium kinetic isotope study on the dimerisation of o-xylylenes (132 a-d)[111] (Scheme 1.49).

It is observed that $K_a \approx K_c$ and $K_b/K_a \approx K_d/K_a \approx 1.8$. This indicates that in the rate determining step there is bonding at the 3-methylene position but not at the 2-methylene position, a result which firmly supports the stepwise mechanism involving diradical (141). It is also found that the rate of dimerisation is virtually unaffected by change in solvent polarity, which is unsupportive of a mechanism involving zwitterionic intermediates.

The synthetic potential of furan o-xylylenes was briefly touched upon when (132b) was treated with methyl acrylate to give a 3:1 ratio of Diels-Alder adducts, (142) and (143) in good yield (64 - 75%)[7] (Scheme 1.50).



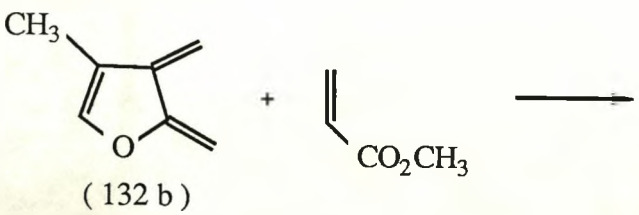
(141)



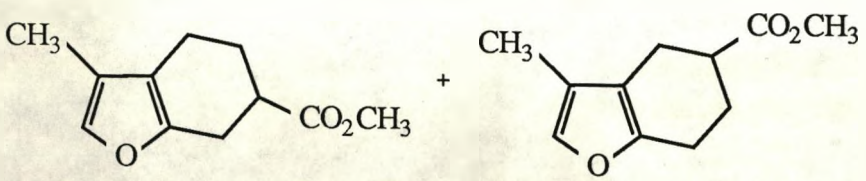
(132) (133)

a, R = R^1 = H; b, R = D, R^1 = H; c, R = H, R^1 = D; d, R = R^1 = D

SCHEME 1.49



(132 b)



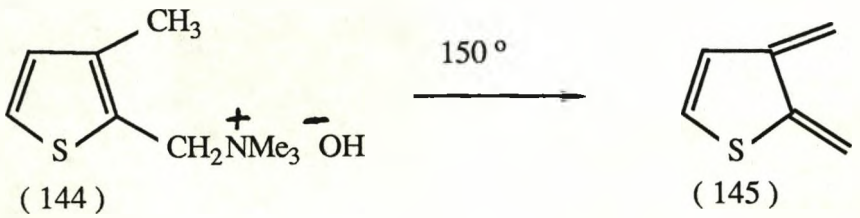
(142) (143)

SCHEME 1.50

1.2.6 THIOPHENE

As for the furan analogue of o-xylylene, the first inference of the thiophene analogue is to be found in a report by Winberg and co-workers.[118] Pyrolysis of quaternary ammonium hydroxide (144) gives

rise to low yields of an intralinear polymer attached through the 2,3-positions of the thiophene ring. 2,3-Dimethylene-2,3-dihydrothiophene (145) is postulated as the transitory intermediate, although no further evidence for its existence is advanced (Scheme 1.51).



(144) (145)

POLYMER

SCHEME 1.51

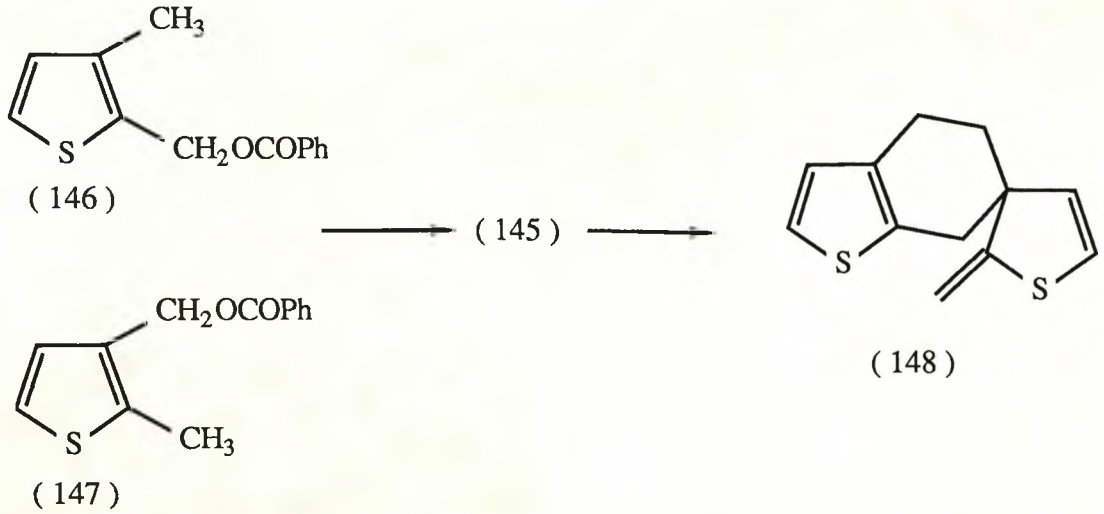
Twenty-five years later o-xylylene (145) was generated by the FVP of thiophenemethyl benzoates (146) and (147)[121] (Scheme 1.52).

Low yields of [4+2] dimer of the form (148) (~ 20%) was isolated and attempts to trap (145) with dienophiles proved unsuccessful. However in the pyrolysis of 3-methyl-α-phenyl benzoate (149), the o-xylylene moiety (150) is intercepted by the phenyl substituent to afford naphtho-[2,3-b]-thiophene (151) as the major product (Scheme 1.53).

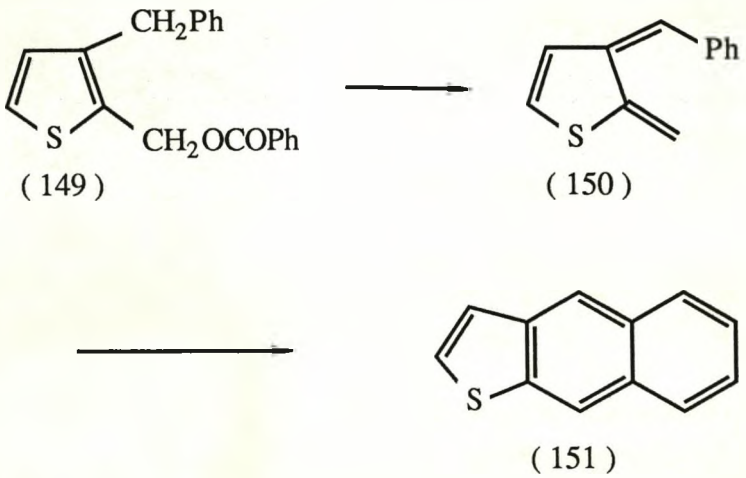
In the same year Ito et al., reported the generation of α-sulphur atom substituted o-xylylene (153) in solution[122] (Scheme 1.54).

Fluoride-induced 1,4-elimination[5] of triflate salt (152) affords the cyclooctadiene derivative (154) as a single isomer in 51% yield.

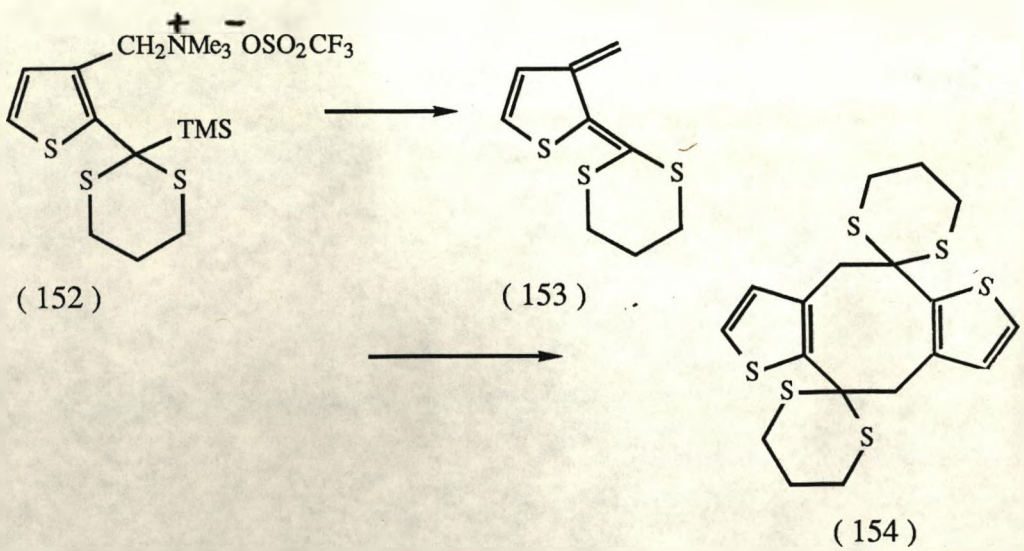
Very recently several groups have published papers on the thiophene analogue of o-xylylene. Chadwick and Plant have used



SCHEME 1.52



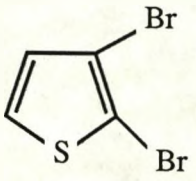
SCHEME 1.53



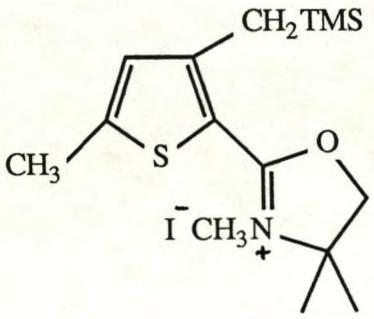
Reagents: CsF, CH_3CN, 55 - 60°C

SCHEME 1.54

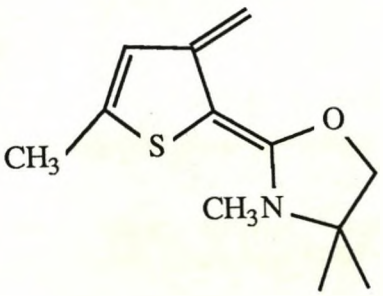
iodide-induced debromination of (155) and fluoride ion-induced desilylation of (156) to generate o-xylylenes (145) and (157) respectively.[123]



(155)



(156)



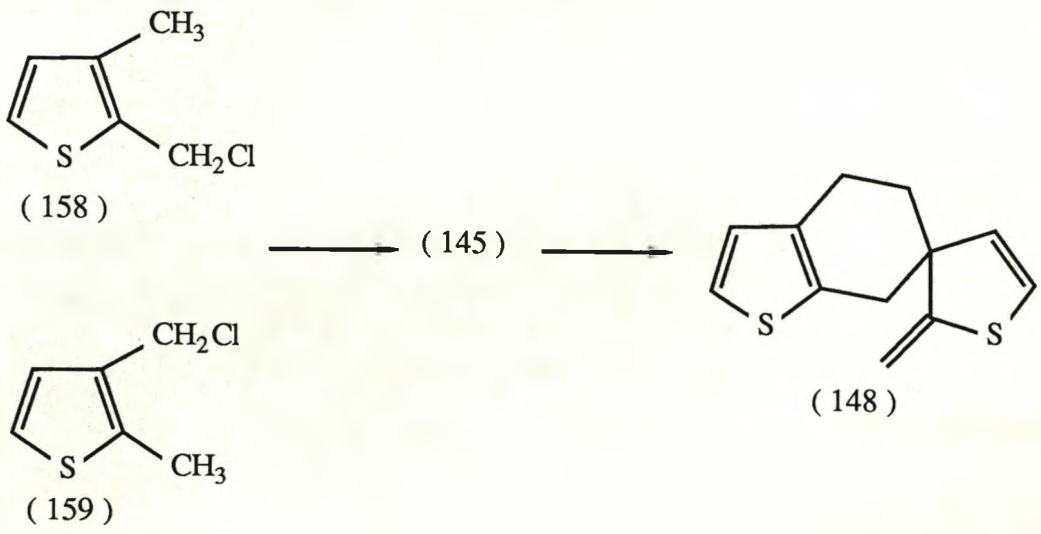
(157)

Storr et al., have generated o-xylylene (145) by the FVP of the isomeric chlorides (158) and (159),[106] and obtained qualitatively similar results to those previously reported by Huang.[121] The bulk of the pyrolysate consists of polymeric material but a [4+2] spiro dimer of the form (148) is also isolated (Scheme 1.55).

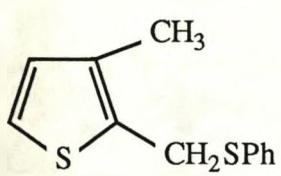
When dienophiles are co-condensed with the pyrolysate only the dimer (148) is detected in the product. However, intermolecular trapping of (145) is accomplished with thiophenol to give a 3:2 ratio of thioethers (160) and (161). (HCl is also found to re-add to (145) in the same ratio as thiophenol.)

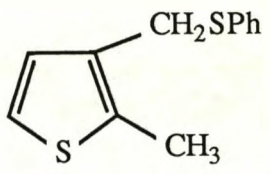
Failure to trap the flash pyrolytically generated thiophene o-xylylene (145) in Diels-Alder reactions is deemed to be due to its extremely high propensity towards polymerisation when produced in relatively high concentration.

On a more positive note the FVP approach again proved amenable to the intramolecular trapping of (145). Thus, pyrolysis of chloride



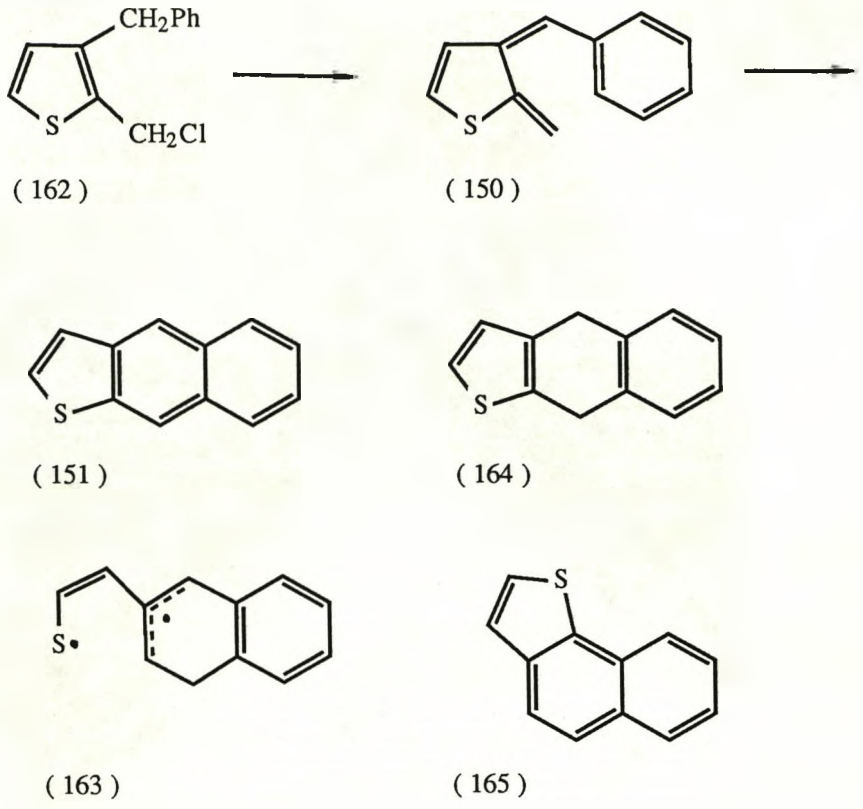
SCHEME 1.55





(160) (161)

(162) at 650°C/10^{-2} torr gives the expected naphtho-[2,3-b]-thiophene (151), (8%) and its 4,9-dihydro derivative (164), (32%), together with the unexpected naphtho-[1,2-b]-thiophene (165), (30%). At the higher temperature of 750°C naphtho-(1,2-b]-thiophene (165), (48%), is found together with the [2,3-b]-isomer (151), (6%) (Scheme 1.56). Tricycles



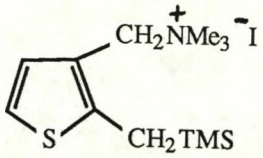
SCHEME 1.56

(151) and (164) are easily accounted for but (165) must be produced by a rearrangement involving carbon-sulphur homolytic cleavage (163) and recyclisation.

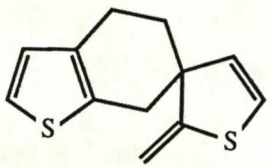
van Leusen and van den Berg have adopted the methodology developed by Ito et al., for o-xylylene generation.[5] Treatment of salt (166) with TBAF in acetonitrile at room temperature results in the formation of spiro compounds to which structures (148) and (148a) are tentatively assigned.[124]

As supportive evidence for the thiophene analogue of o-xylylene (145), the Dutch workers are also able to trap this transient species with electron-deficient dienophiles in excellent yields (Scheme 1.57).

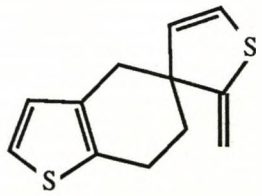
Unsymmetrical dienophiles (acrylonitrile, methyl acrylate) give mixtures of regioisomeric adducts (167) and (168), with the isomer bearing the electron-withdrawing group closest to sulphur predominating (~ 2:1 ratio). Reaction of (145) with dimethyl maleate gives a



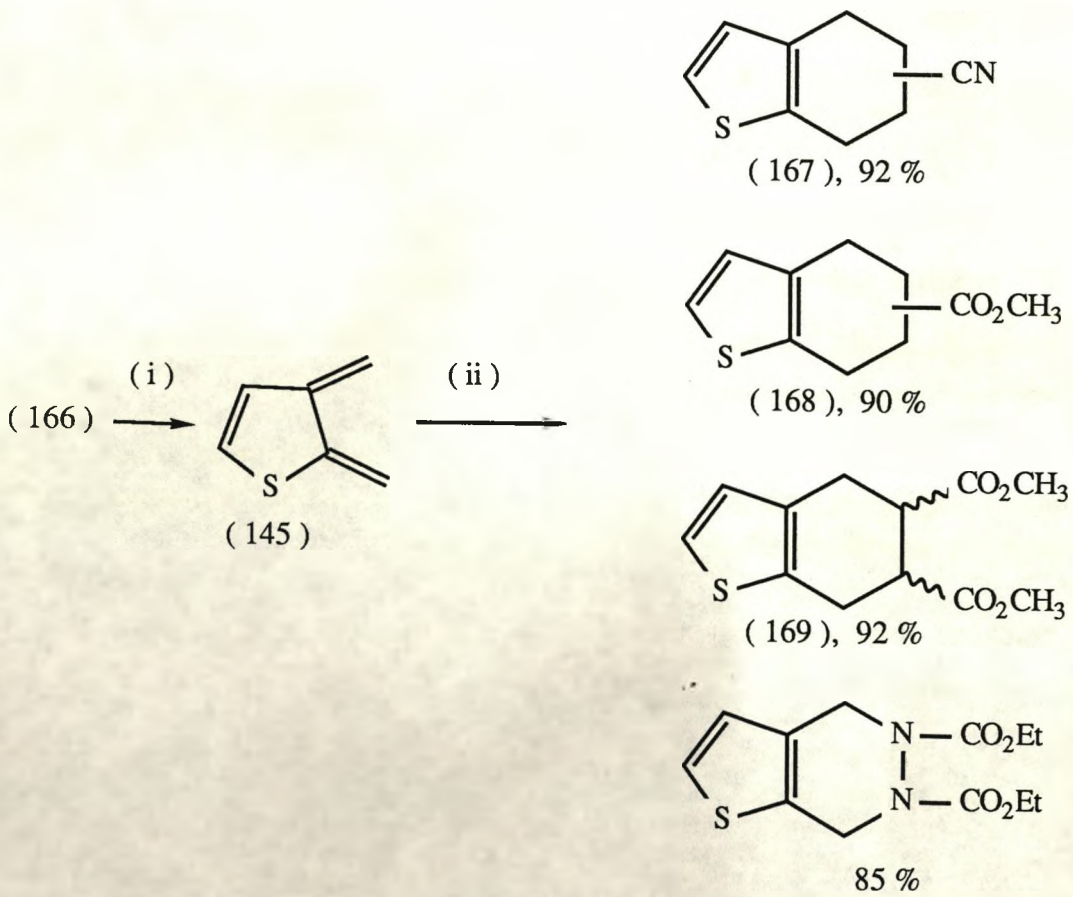
(166)



(148a)



(148)

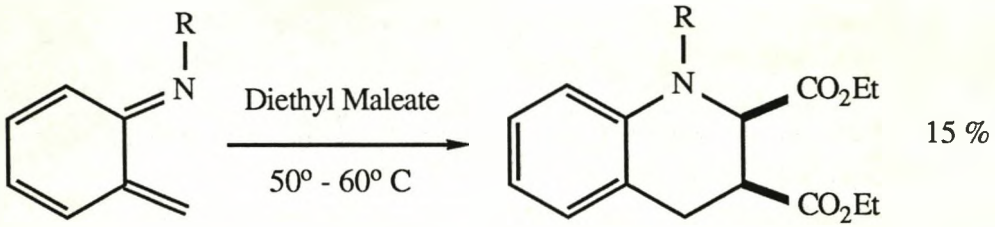


Reagents: (i) $^{n}Bu_4NF$, CH_3CN, room temperature;

(ii) dienophile

SCHEME 1.57

mixture of diastereoisomers (169) which could call into question the mechanism of the cycloaddition, in as much as it may not be a concerted process (Storr has suggested that (145) has appreciable diradical character[106]). However it is worth noting that in an analogous case, the cis adduct formed from azaxylylene (170) and diethyl maleate partially isomerises to the trans isomer under the relatively mild reaction conditions employed[125] (Scheme 1.58).



(170)

R = CH_2Ph

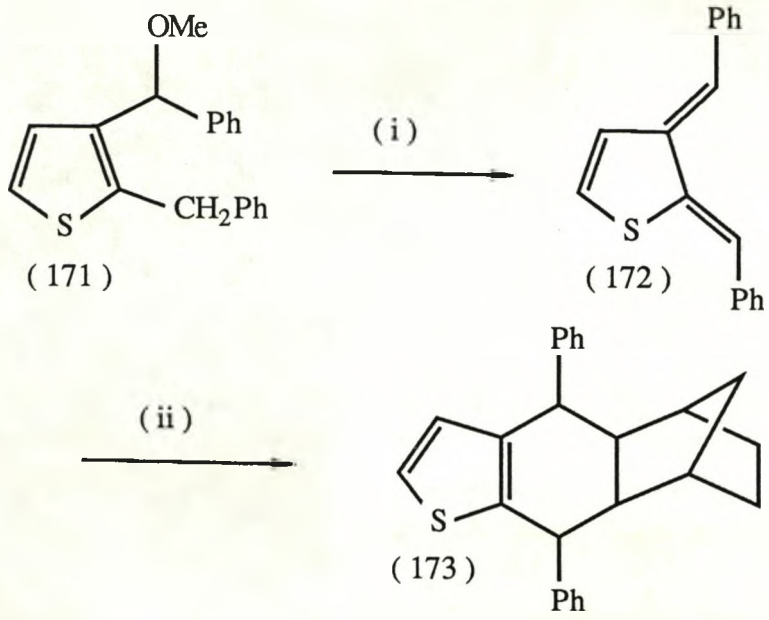
+ TRANS ISOMER, 35 %

SCHEME 1.58

Regardless of the mechanism of cycloaddition, this mild and efficient generation and entrapment of o-xylylene (145) has excellent potential for the synthesis of polycyclic molecules with varying degrees of functionalisation. (For a discussion of a closely related system see Chapter 3.)

Base-induced 1,4-elimination[45a] has also been used to generate thiophene o-xylylenes. Expulsion of methanol from (171) furnishes bis-phenyl substituted o-xylylene (172) which is intercepted by norbornene to give a modest yield (39%) of adduct (173).[126]

This report suggests the effect of the two phenyl groups is to stabilise the o-xylylene sufficiently enough to facilitate significant reaction with the unactivated olefin (Scheme 1.59).



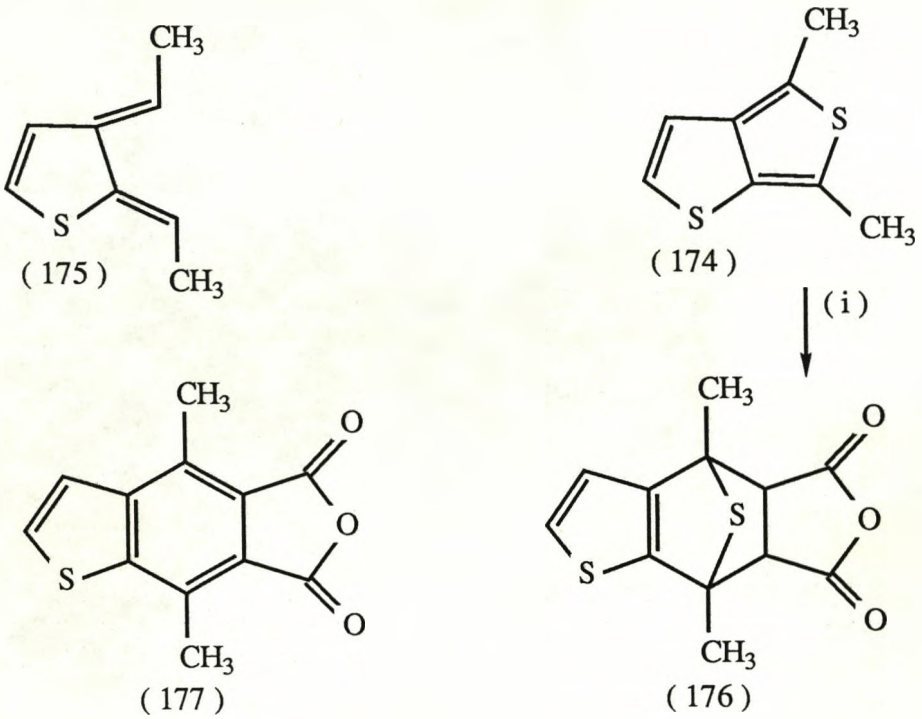
Reagents: (i) LDA; (ii) norbornene

SCHEME 1.59

Stable analogues of thiophene o-xylylenes have also been prepared. Thus, sulphide (174) has been used as a bis-methyl substituted o-xylylene equivalent.[127]

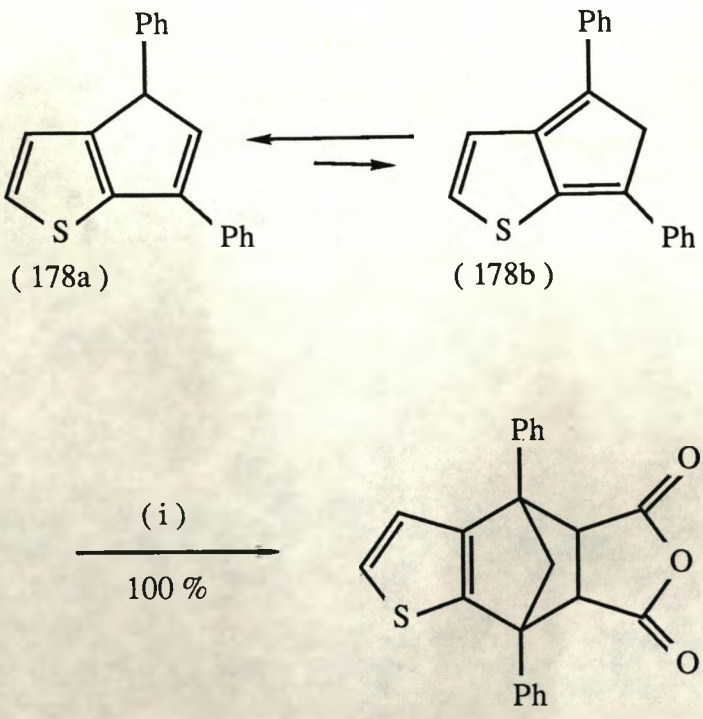
(174) is found to react with maleic anhydride to give a 47% yield of sulphur-bridged adduct (176). If the reaction is carried out at 140°C then the desulphurised compound (177) is the only product isolated (Scheme 1.60).

The cyclopentathiophene (178) also behaves as a thiophene o-xylylene equivalent.[128] The fluorescent o-quinonoid form (178b) can be trapped out of the tautomeric equilibrium mixture by dienophiles to give high yields of adducts (Scheme 1.61).



Reagents: Maleic anhydride, acetone, reflux, 6 hr.

SCHEME 1.60



Reagents; (i) Maleic anhydride, benzene, reflux, 4 hr.

SCHEME 1.61

1.3 ORGANOLITHIUM CHEMISTRY

1.3.1 HETEROATOM FACILITATED METALLATION

This extensive topic will be described only briefly here as an aid to the understanding of the results and discussion presented in this thesis. The reader is referred to the review article by Gschwend and Rodriguez for a detailed account.[129]

1.3.2 DEFINITION OF DIRECTED LITHIATION

Directed lithiation may be defined as a process whereby a hydrogen atom in a substrate molecule is regiospecifically replaced by lithium, under the control of one or more atoms or groups already forming part of the substrate.

1.3.3 MECHANISTIC CONSIDERATIONS

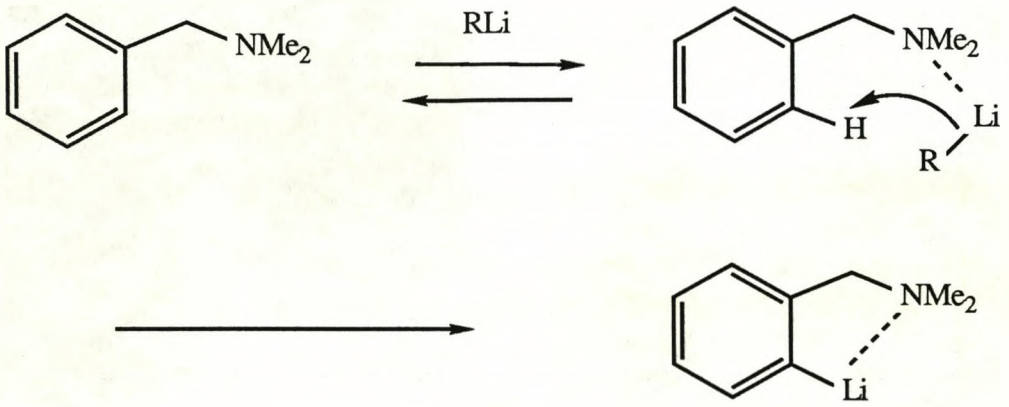
The regioselectivity of lithiation of a substrate molecule can be controlled by the electronic and coordinating abilities of its substituents. The categorisation of lithiating agents into two basic classes leads to the recognition of two limiting mechanisms.

The first type of organolithium reagents are electron deficient, Lewis-acidic aggregates such as ^{n}BuLi in a hydrocarbon solvent, which are present in solution as hexamers or tetramers (for information concerning the constitution of organolithium reagents in solution, the reader is referred to the excellent books by Wakefield, and the references cited therein[130]).

The second type of organolithium reagent differs from the first in that it has negligible Lewis acid character due to coordination by solvent or by a complexing agent such as TMEDA (this also includes the lithium amide bases such as LDA).

The "coordination only" mechanism operates when an electron-deficient organolithium reagent is used. An example is the ortho-lithiation of N,N-dimethylbenzylamine (Scheme 1.62).

Lithiation occurs at the ortho-position, more rapidly than with benzene, although the inductive effect of the substituent would be expected to decrease the rate of reaction relative to benzene. The

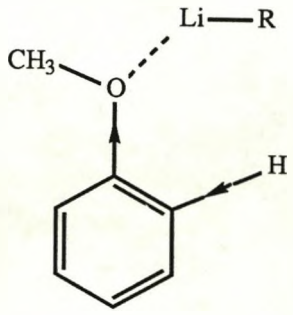


SCHEME 1.62

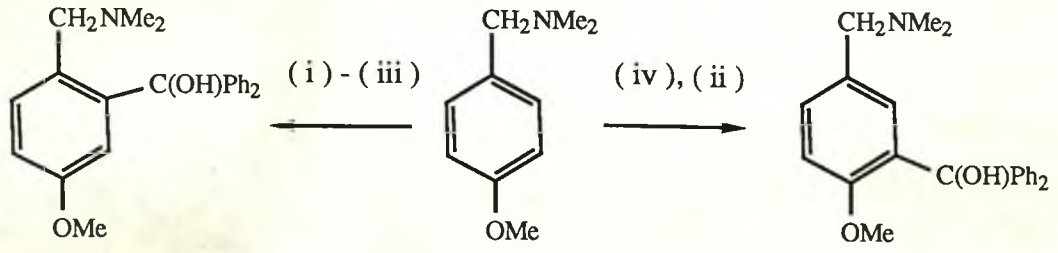
mechanism is envisaged as involving coordination of the lithiating agent with the lone pair of electrons on the nitrogen atom (with concomitant depolymerisation of the oligomer). Protophilic attack on the nearest hydrogen atom leads to an internally chelated and isolable organolithium species. In other words, the presence of the dimethylamino group brings about a very high effective molarity of activated organolithium reagent in close proximity to the ring.

The "acid-base" mechanism usually operates in conjunction with the "coordination only" mechanism. In the lithiation of anisole (179) for instance there is a rapid coordination of the lithiating agent with the ether group leading to a polarisation of the C-Li and C-H bonds, leaving the ortho-hydrogen atoms more acidic by induction.

An example of where each type of mechanism can act exclusively has been demonstrated by Slocum.[131] The lithiation of p-methoxy-N,N-dimethylbenzylamine can occur ortho to either substituent



(179)



Reagents: (i) ^{n}BuLi, Et_2O; (ii) Ph_2CO; (iii) H_2O;
(iv) ^{n}BuLi, Et_2O, TMEDA

SCHEME 1.63

depending solely upon the state of coordination of the ^{n}BuLi (Scheme 1.63).

In the first case the ^{n}BuLi is in a high aggregation state and the "coordination only" mechanism applies: lithiation thus occurs adjacent to the strongly Lewis basic dimethylamino group. On addition of TMEDA the ^{n}BuLi is transformed into a "coordinatively

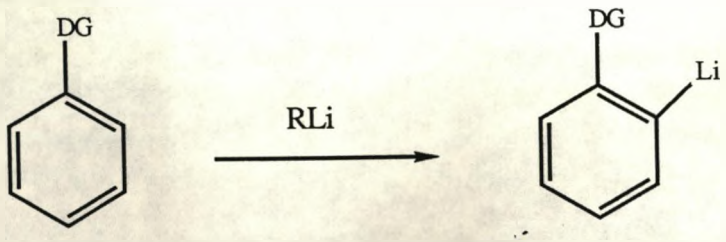
saturated" monomeric state and lithiation then occurs adjacent to the methoxy group due to its enhancement of the acidity of the adjacent ortho-hydrogen atoms by the inductive effect of the oxygen atom.

1.3.4 RECENT DEVELOPMENTS IN DIRECTED LITHIATION

The directed lithiation of benzenes, the lithiation of thiophenes, furans, pyrroles, and imidazoles, excluding the use of halogen-metal exchange, has recently been reviewed from within these laboratories.[132] Consequently, only the broad conclusions will be given here, followed by selected developments in the directed lithiation of aromatic and heteroaromatic compounds since 1986 (or works not covered in the cited thesis).

1.3.4.1 DIRECTED LITHIATIONS OF BENZENE DERIVATIVES

Several attempts to provide a "ranking" order for the directing abilities of functional groups have been made for the reaction shown in Scheme 1.64.



DG = Directing Group

SCHEME 1.64

The order given by Gschwend and Rodriguez[129] based upon data available from competition experiments using coordinatively

unsaturated lithiating agents is:

$SO_2NR_1R_2$, SO_2-Aryl, $CONR_2$ > 2-oxazolines > CONHR, COSHR > $CH_2N(CH_3)_2$ > $CR(O^-)CH_2N(CH_3)_2$ > OCH_3 > O-aryl > NH-aryl > S-aryl > NR-aryl > $N(CH_3)_2$ > $CR_1R_2O^-$.

Some generalisations based upon the published work can be made.

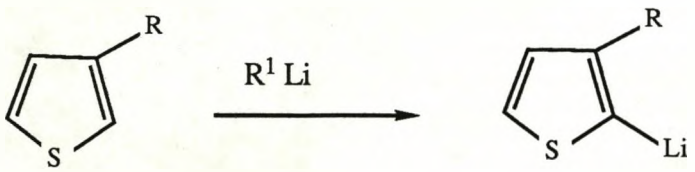
1. The strongest directors of lithiation to an ortho ring position have both an electron-withdrawing effect and the ability to coordinate with the lithiating agent.
2. Where the directing group is separated from the ring by a saturated carbon atom, a basic nitrogen is the most powerful director.
3. In the presence of coordinatively saturated lithiating agents, the ranking is determined largely by the acidifying effects of the group.

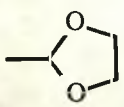
1.3.4.2 DIRECTED LITHIATIONS OF THIOPHENES, FURANS, PYRROLES AND IMIDAZOLES

1.3.4.3 LITHIATION OF 3-MONOSUBSTITUTED DERIVATIVES

Generally, lithiation of 3-monosubstituted derivatives of thiophene occur at the 2-position (Table 1.1). When situated in the C-3 position even weak directors of lithiation such as -OMe, SMe, and acetal, lead to good yields of the 2-lithio intermediates. The bulky $-O^tBu$ substituent at C-3, even though it is sterically hindering, directs lithiation into the C-2 position, since the direction is reinforced by the ring heteroatom. 3-Alkyl groups are an exception to this general trend.[129] A 3-methyl group leads to an 11:39 mixture of the 2,3- to 2,4-disubstituted products after work-up with an electrophile. However, the far bulkier 3-^{t}Butyl group yields exclusive C-5 lithiation with ^{n}BuLi.

TABLE 1.1



R	R^1Li	Reference
CO_2Li	LDA	133, 134
NO_2	LDA	133
SMe	^nBuLi	129
CH_2OMe	^nBuLi	135
CH_2NMe_2	^nBuLi	135
$CONMe_2$	^nBuLi	135
CONHMe	2-^nBuLi	138
O^tBu	^nBuLi	136
OMe	^nBuLi	129
Br	PhLi	129
	^nBuLi	137

3-Monosubstituted furans exhibit similar behaviour to their thiophene analogues. There is little information available on the lithiation of N-protected-3-substituted pyrroles, but similar behaviour to that described above would be expected.

1.3.4.4 ORTHOLITHIATION OF 2-MONOSUBSTITUTED DERIVATIVES

2-Monosubstituted thiophenes and furans have been successfully ortho-lithiated using a limited number of directing groups. Those

directing groups giving virtually regiospecific ortho-lithiation are tabulated below (Table 1.2).

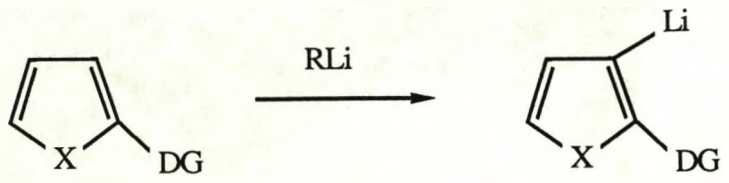


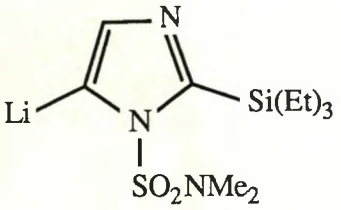
TABLE 1.2

Directing Group	X	Reference
2-oxazolines	S, O, NMe	132, 139
-CONHR	S, O	132
$-CO_2Li$	S	132
$-OP(O)(NMe_2)_2$	O	140

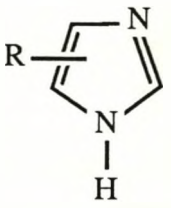
Ortho-lithiation (C3) of 1,2-disubstituted pyrroles is less successful. Lithiation of the N-methylpyrrole-2-oxazolinyl derivative gives a 15:1 ratio of the C3 and C5 lithio species, with considerably reduced levels of lithiation compared to the analogous thiophene and furan derivatives.[139]

1.3.4.5 LITHIATION OF IMIDAZOLES

As with pyrroles, effective metallation at carbon by hydrogen-metal exchange requires masking of the ring N-H either by means of a removable protecting group or by a substituent such as an alkyl group. The former is usually more desirable, the N,N-dimethyl-sulphamoyl moiety ($-SO_2NMe_2$) being one of the better groups for protection and activation towards lithiation,[141] which occurs readily at the 2-position. Lithiation at (4/5) can be achieved if C2 is blocked. Lithiation of imidazole (180) results in the formation of C4(5)



(180)



(181)

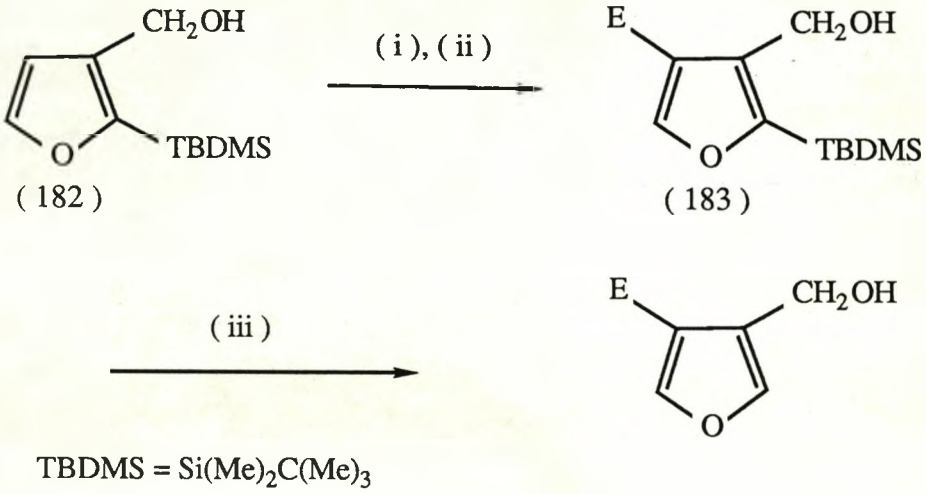
substituted products (181) on reaction with electrophiles, work-up, and deprotection.[132]

1.3.4.6 A DIRECTED LITHIATION APPROACH TO 3,4-DISUBSTITUTED FURANS

Bures and Keay have developed a high yielding synthesis of 3,4-disubstituted furans using a C3 hydroxymethyl group to direct lithiation into the adjacent C4 position.[142] The C2 position of the furan ring is blocked with a trialkylsilyl group. Compound (182) is

prepared by a base induced 1,4 O → C silyl migration from a 3-(trialkylsilyl)-oxymethyl furan.[143]

Optimum yields (typically 90%) of products (183) are obtained when 2,3-disubstituted furan (182) is treated with ^{n}BuLi in DME at 0°C, the resulting dianion being quenched with electrophiles in the presence of lithium chloride. Desilylation is accomplished under mild conditions in essentially quantitative yield (Scheme 1.65).



(182) (183)

TBDMS = $Si(Me)_2C(Me)_3$

Reagents: (i) 2.2 ^{n}BuLi, DME, 0°C, ¼ h.;
(ii) 12 LiCl, then E^{+}; (iii) TBAF, thf, r.t.

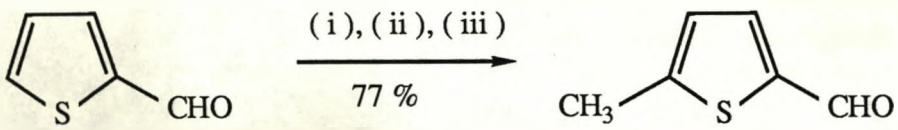
SCHEME 1.65

The authors have initially rationalised the regioselectivity of lithiation as a combination of chelation of the organolithium base with the lithium alkoxide (formed on addition of the first equivalent of ^{n}BuLi) and the inability of the organolithium reagent to coordinate to the furan ring oxygen atom because of steric hindrance caused by the bulky trialkylsilyl group (tertiary butyldimethylsilyl). However they also observe regiospecific deprotonation at C4 even with a trimethylsilyl group at C2 (and a C4:C5 anion ratio of 2:1 when C2 is substituted with a methyl group). Other factors such as solvent

coordination to the base are acknowledged as contributing factors in the regioselectivity of lithiation although no convincing argument has been put forward.

1.3.4.7 HETEROATOM FACILITATED LITHIATION OF HETEROAROMATIC ALDEHYDES

Comins and Killpack have recently reported the directed lithiation reactions of the α-amino alkoxides of a number of heterocyclic ring systems.[144] The addition of heteroaromatic aldehydes to appropriate lithium dialkylamides gives the title compounds. These are then ring-metallated using alkyllithium reagents and quenched with electrophiles, to give on work-up, substituted heteroaromatic aldehydes. This "one-pot" protocol allows the preparation of 5-methylthiophene-2-carboxaldehyde in good yield without the isolation of a protected intermediate (Scheme 1.66).



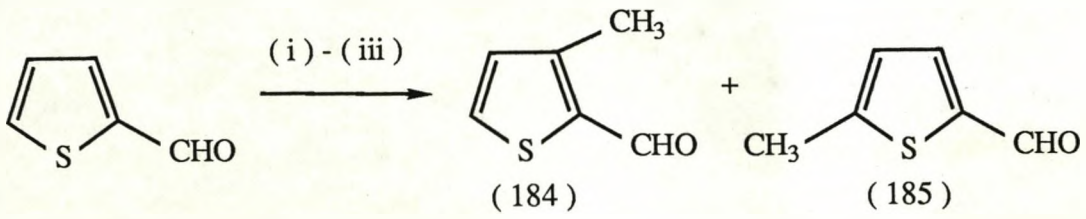
Reagents: (i) Lithium N-methylpiperazide (LNMP);

(ii) 3-^{n}BuLi, TMEDA ; (iii) CH_3I, H_2O

SCHEME 1.66

However, attempts to achieve ortho-lithiation have proved less successful. The best result is obtained from the alkoxide derived

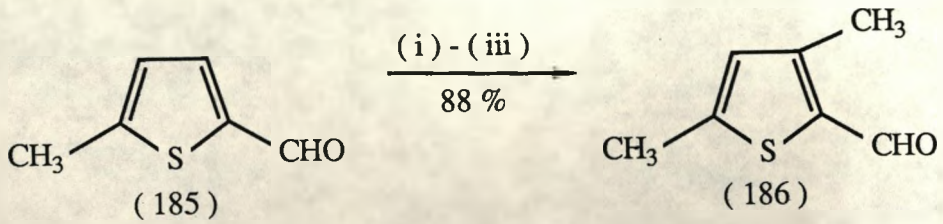
from lithium N,N,N'-trimethylethylenediamine (LTMDA). This gives a 69% yield of the isomeric aldehydes (184) and (185) in a 2:1 ratio (Scheme 1.67).



Reagents: (i) LTMDA; (ii) 3-^{n}BuLi; (iii) CH_3I; H_2O

SCHEME 1.67

Employing similar methodology the authors note that aldehyde (185) undergoes regiospecific ortho-lithiation to give the tri-substituted thiophene (186) in high yield (Scheme 1.68). As might be



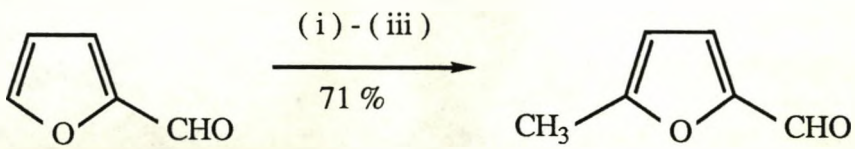
Reagents: (i) LTMDA; (ii) 2-^{n}BuLi; (iii) CH_3I; H_2O

SCHEME 1.68

expected thiophene-3-carboxaldehyde may be successfully transformed to the 2-substituted product.

Thus, as an ortho-director of lithiation in thiophenes the α-amino alkoxide is poor compared to oxazoline, carboxylate, and secondary amide.[132] However, this methodology does allow the synthesis of substituted thiophene carboxaldehydes without recourse to the prior preparation and isolation of a carboxaldehyde protected precursor.

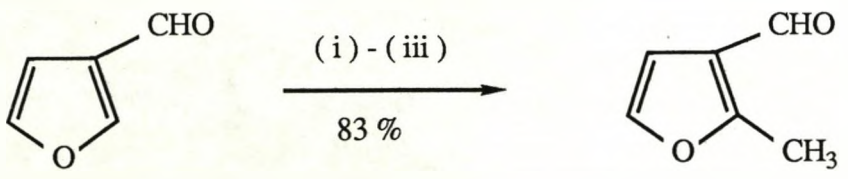
With furfural all attempts to achieve ortho lithiation have proved unsuccessful. As with thiophene, the 5-substituted and 2-substituted furan derivatives may be obtained in good yield from the appropriate carboxaldehydes (Schemes 1.69 and 1.70).



Reagents: (i) LNMP; (ii) 1.2 ^{n}BuLi; (iii) CH_3I; H_2O

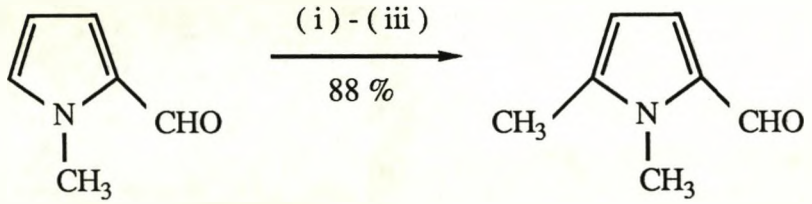
SCHEME 1.69

The nitrogen containing pyrrole and indole ring systems have also been examined. A high level of α-lithiation is obtained with 1-methyl-2-pyrrolecarboxaldehyde when the α-amino alkoxide is formed from LNMP (Scheme 1.71). Attempted β-(ortho)-lithiation using LTMDA



Reagents: (i) LTMDA; (ii) 2-^{n}BuLi; (iii) CH_3I; H_2O

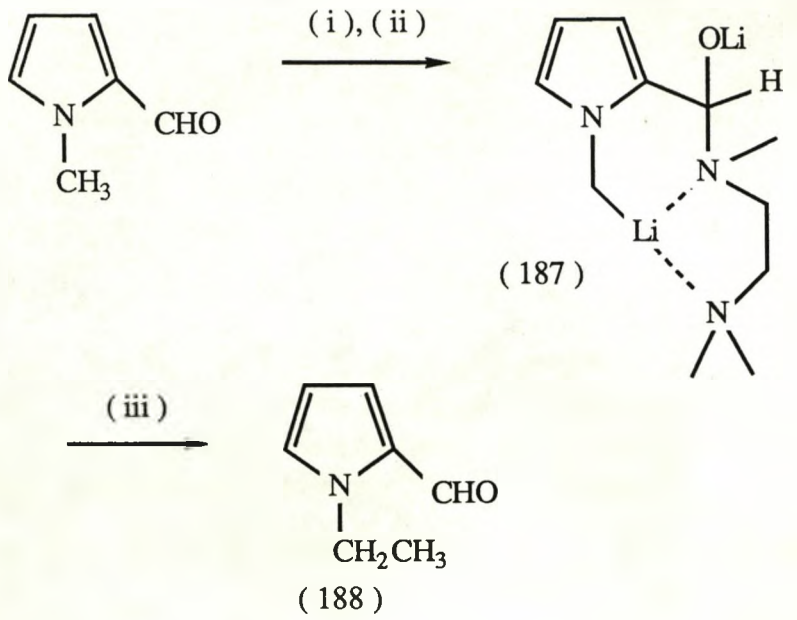
SCHEME 1.70



Reagents: (i) LNMP; (ii) 3-^{n}BuLi, TMEDA; (iii) CH_3I; H_2O

SCHEME 1.71

to form the alkoxide results in the surprising formation of the N-ethyl compound (188) in 74% yield (Scheme 1.72). This is claimed as the first example of a directed lithiation on the N-methyl group of an N-methyl pyrrole. The formation of (188) can be rationalised in terms of a complex-induced proximity effect (C.I.P.E.) process[145] and illustrated by the chelated structure (187).

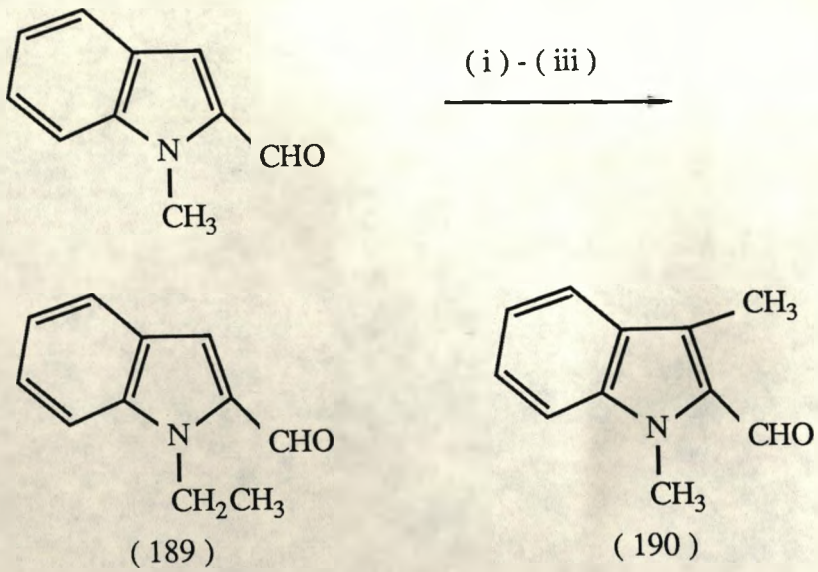


(188)

Reagents: (i) LTMDA; (ii) 3-^{n}BuLi; (iii) CH_3I; H_2O

SCHEME 1.72

A similar observation is reported in the attempted ortho-lithiation of 1-methyl-indole-2-carboxaldehyde. Using the same reagents as for the pyrrole case the di- and trisubstituted indoles (189) and (190) are produced in a 42:58 ratio. Again this is claimed to be the first example of directed metallation into the methyl group of a 1-methyl-indole derivative (Scheme 1.73).



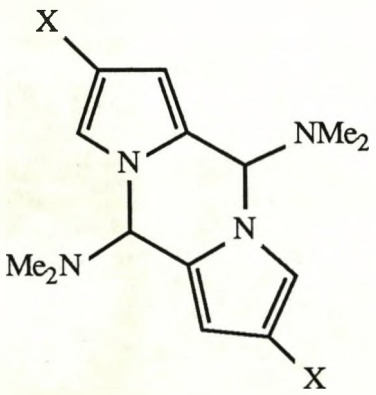
(189) (190)

Reagents: (i) LTMDA; (ii) 2-^{n}BuLi; (iii) CH_3I; H_2O

SCHEME 1.73

If LNMP is used instead of LTMDA then the trisubstituted indole (190) is produced without formation of the N-ethyl compound (189). After separation from a small amount of starting material, (190) may be isolated in 72% yield. The absence of the N-ethyl compound (189) can be explained by the poorer chelative properties of the alkoxide derived from LNMP.[146]

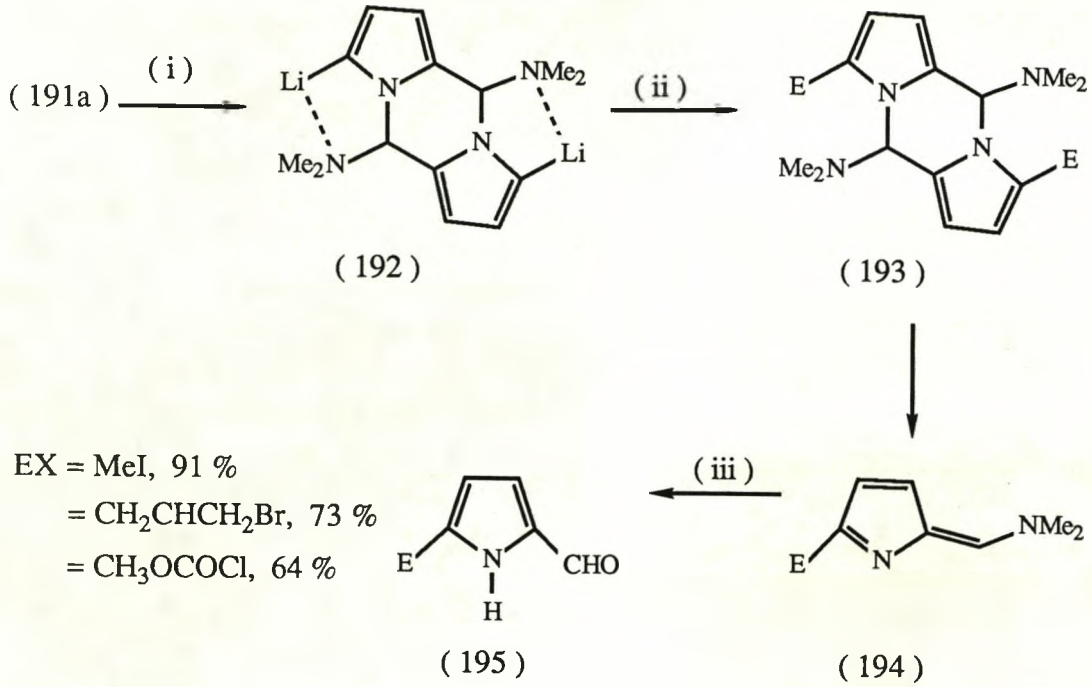
Muchowski and Hess have very recently published new routes to 4- and 5-mono- and 4,5-disubstituted pyrrole-2-carboxaldehydes. Their approach is based on heteroatom facilitated lithiation of the 6-dimethylamino-1-azafulvene dimers (191 a,b).[147]



(191) (a) X = Li

(b) X = Br

The dimers (191 a,b) are prepared by reaction of the appropriate pyrrole-2-carboxaldehydes with aqueous dimethylamine at room temperature. When (191a) is treated with two equivalents of ^{t}BuLi the dilithio species (192) is formed, which on reaction with an excess of electrophile gives the substituted dimer (193). Hydrolysis of the crude reaction mixture leads to modest to good yields of the 5-substituted pyrrole-2-carboxaldehydes (195), presumably via the azafulvene (194) (Scheme 1.74).



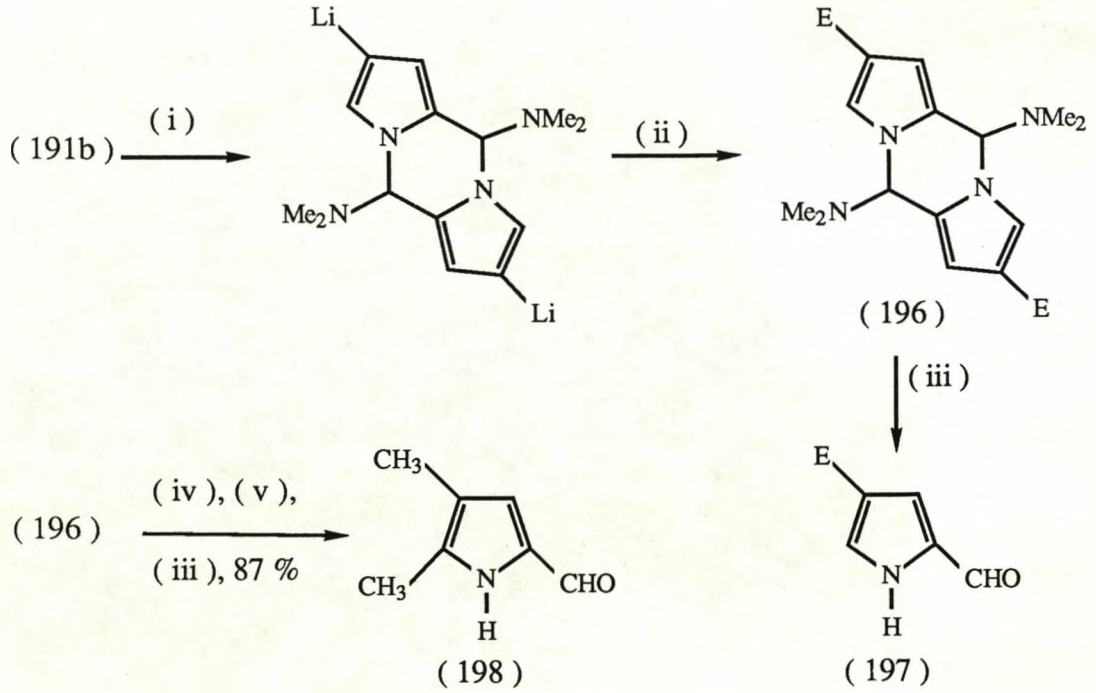
Reagents: (i) ^{t}BuLi, thf, -15°C; (ii) EX, -105°C or -78°C;

(iii) Hot $NaHCO_3$ (aq.) or CH_3CO_2Na;

SCHEME 1.74

Use of the bromo dimer (191b) allows preparation of 4-mono- or 4,5-disubstituted pyrrole-2-carboxaldehydes. Halogen-metal exchange of (191b) with two equivalents of ^{n}BuLi, followed by electrophilic quench and hydrolysis gives good yields of 4-substituted-pyrrole-2-carboxaldehydes (197). Alternatively if the substituted dimer (196, E = CH_3) is treated with three equivalents of ^{t}BuLi with subsequent methyl iodide quench, followed by in situ hydrolysis, a high yield of 4,5-dimethylpyrrole-2-carboxaldehyde (198) is obtained (Scheme 1.75).

Thus, dimer (191a) serves as a formal equivalent of 5-lithiopyrrole-2-carboxaldehyde and dimer (191b) as a 4-lithio- or 4,5-dilithiopyrrole-2-carboxaldehyde equivalent. A variety of substituted pyrrole-2-carboxaldehydes can be prepared in the above manner with efficiency and economy of steps.

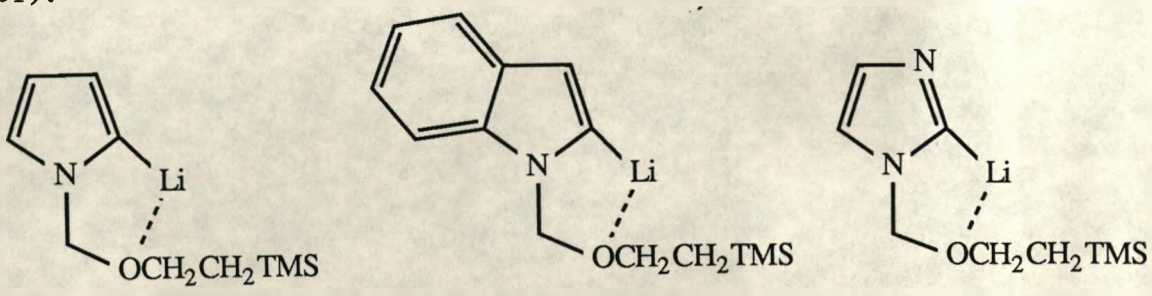


Reagents: (i) 2-^{n}-BuLi, thf, -78°C; (ii) EX; (iii) $NaHCO_3$ aq., Δ; (iv) 3-^{t}BuLi, thf, -15°C; (v) CH_3I;

SCHEME 1.75

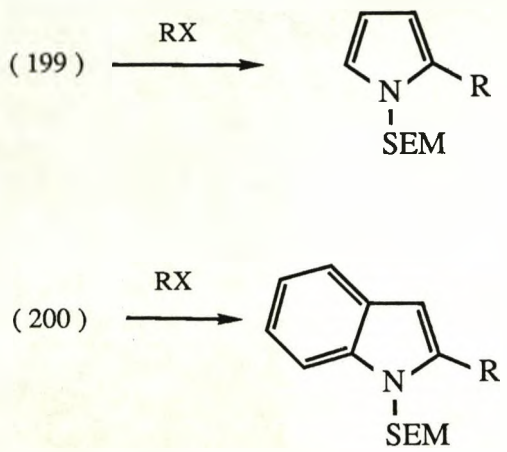
1.3.4.8 TRIMETHYLSILYLETHOXYMETHYL (SEM) PROTECTION AND ACTIVATION IN NITROGEN HETEROCYCLES

The SEM group has been utilised by a number of groups for N-protection and C2-activation of the pyrrole, indole, and imidazole ring systems. It is usually introduced by treatment of the heterocycle with a metal hydride base with subsequent addition of trimethylsilylethoxymethyl chloride. The SEM group facilitates C2-lithiation presumably via the chelated species (199), (200) and (201).



(199) (200) (201)

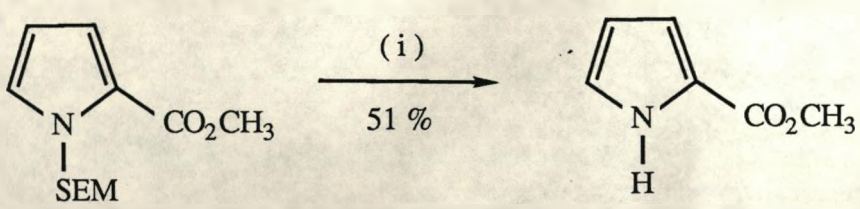
Ley and co-workers were the first to apply this group to the pyrrole ring system, with a view to natural product synthesis.[148,149] In a later publication C2-lithiated-N-SEM protected pyrroles and indoles were further examined.[150] It was noted that for respectable levels of C2-lithiation ^{n}BuLi in DME is required (Scheme 1.76).



RX	R	Yield %
PhCOCl	COPh	40
CH_3OOCCl	CO_2CH_3	42
TMSCl	TMS	40
CH_2=CHCHO	CH(OH)CH=CH_2	40
TMSCl	TMS	57
CH_2=CHCHO	CH(OH)CH=CH_2	63

SCHEME 1.76

Deprotection is achieved under mild conditions by treatment with freshly prepared anhydrous tetra-n-butylammonium fluoride (TBAF) (Scheme 1.77).



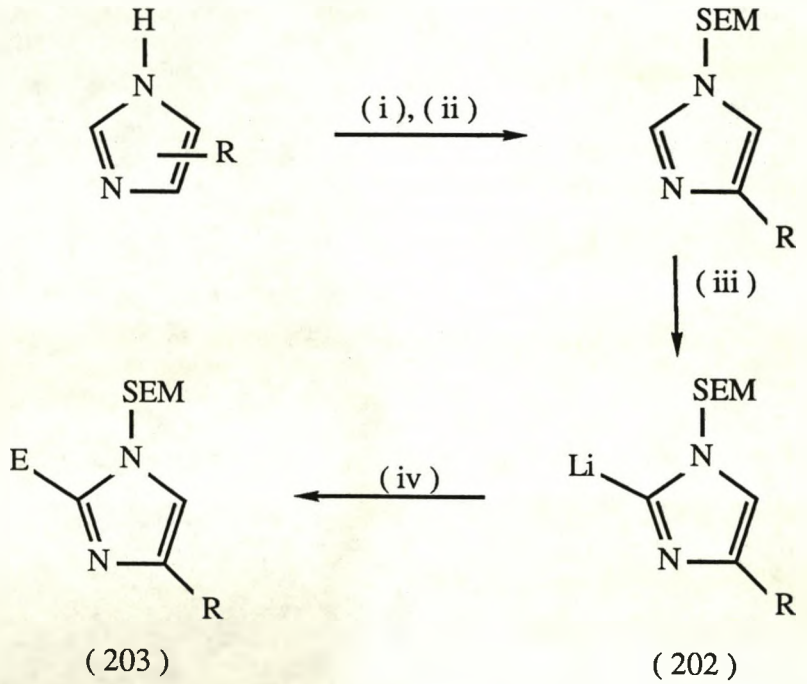
Reagents: (i) TBAF, thf, 0°C

SCHEME 1.77

Muchowski has also prepared the pyrrole and indole SEM-derivatives but deprotonation studies using ^{t}BuLi in hexane gave poor results.[151]

In separate reports Lipshutz[152] and Whitten[153] describe SEM derivatives of imidazoles. Protection is accomplished by using a metal hydride and SEM-Cl as for the pyrrole and indole cases.

Lipshutz has studied the reactions of the C2-lithiated species (202) with various electrophiles (Scheme 1.78).



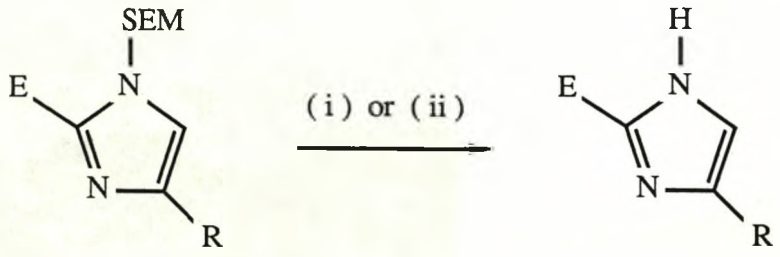
(203) (202)

Reagents: (i) KH/thf; (ii) SEM-Cl; (iii) ^{n}BuLi, thf, -78°C; (iv) E^{+}

SCHEME 1.78

Reactions with aldehydes (aryl, heteroaromatic, aliphatic) proceed smoothly (70 - 90%), reactions with ketones also giving reasonable yields of products (203). Apart from methyl iodide (R = H, 94%), alkylating and acylating agents give very low yields of products, even in the presence of additive such as HMPA, TMEDA, DMPU, 12-crown-4, $CuBr \cdot Me_2S$ or CuCN.

Deprotection of compounds (203) may be effected with either TBAF in thf or dilute acid (Scheme 1.79).



(203)

Reagents: (i) TBAF, thf, 45°C - reflux; (ii) 3N HCl, EtOH, 60 - 90°C

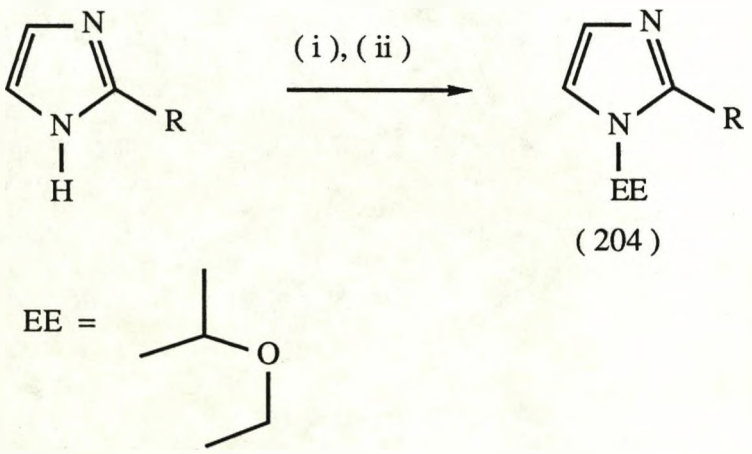
SCHEME 1.79

The SEM group is an easily introducible nitrogen protecting group. It facilitates C2-lithiation in the pyrrole, indole, and imidazole ring systems, tolerating the "usual" metallating conditions and electrophilic reagents. It is smoothly removed under mild conditions. These features make it an attractive protection-activation group in the aforementioned ring systems.

1.3.4.9 1-(1-ETHOXYETHYL) (EE) : AN EFFECTIVE PROTECTING GROUP FOR IMIDAZOLE NITROGEN

Very recently Brown has reported the synthesis and lithiation of a range of EE-imidazole derivatives.[154] This protecting group is superior to previously used alkoxymethyl and bis-(alkoxymethyl) groups in as much as it is cheap, easily introduced and removed, and reaction of lithio-derivatives with electrophiles lead to C2 or C5 substituted products in high yield. Introduction of the EE group is accomplished

by reaction of the imidazole-N-lithio species with 1-chloro-1-ethoxy-ethane (Scheme 1.80). The reaction is reported for a range of alkyl



Reagents: (i) 1-^{n}BuLi, -10°C to 0°C; (ii) $CH_3CH(Cl)OEt$, -20°C to r.t.

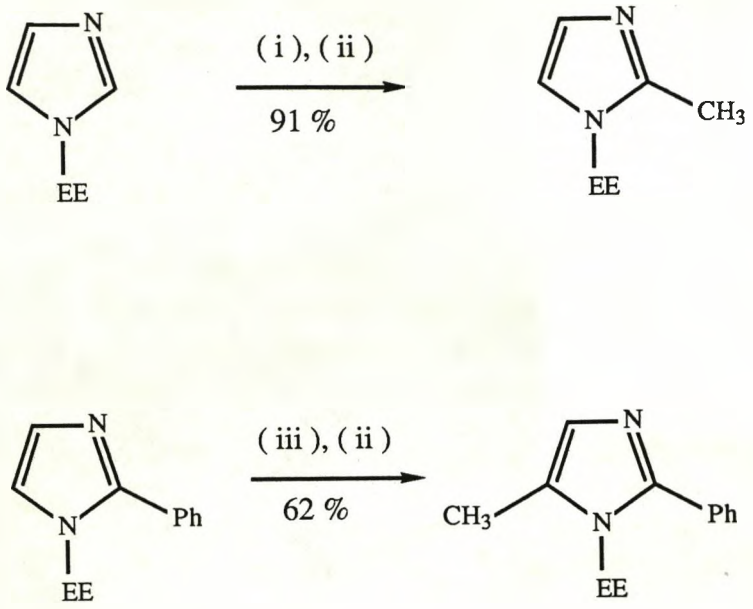
SCHEME 1.80

and alkoxy substituted imidazoles in 70 - 80% yield.

C2-lithiation of imidazole (204, R = H) is accomplished with ^{n}BuLi in thf whilst C5-lithiation of imidazole (204, R = Ph) requires ^{s}BuLi. Reaction of the lithiated intermediates with typical electrophiles proceeds in good yield (Scheme 1.81).

The EE group is sufficiently robust to allow synthetic manipulation of substituted imidazoles under acidic conditions. For example, alcohol (205) may be treated with thionyl chloride to produce the hydrochloride salt of the corresponding chloride in quantitative yield (Scheme 1.82).

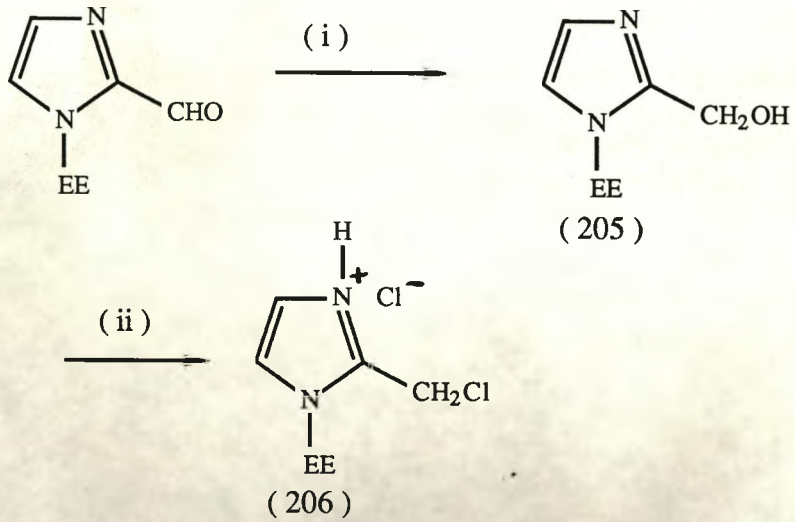
Deprotection can be accomplished by heating (50 - 100°C) a mildly acidic solution of the imidazole-EE derivative for a few hours. It has been shown that the C2-phenyl derivative (204, R = Ph) has a half-life of 7.2 minutes at 72°C in 0.1 N HCl. The corresponding



Reagents: (i) ^{n}BuLi, thf, -40°C; (ii) CH_3I;

(iii) ^{s}BuLi, thf, -10°C;

SCHEME 1.81

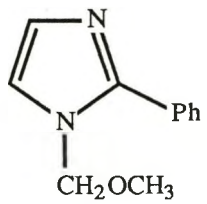


Reagents: (i) $NaBH_4$, CH_3OH, r.t.; (ii) $SOCl_2$, CH_2Cl_2, 0°C to r.t.

SCHEME 1.82

N-methoxymethyl compound (207) remains intact after eighty hours at 80°C in 1 N DCl/H_2O. Thus the facile removal of the EE group is

clearly demonstrated and should be possible in the presence of acid sensitive functionality.

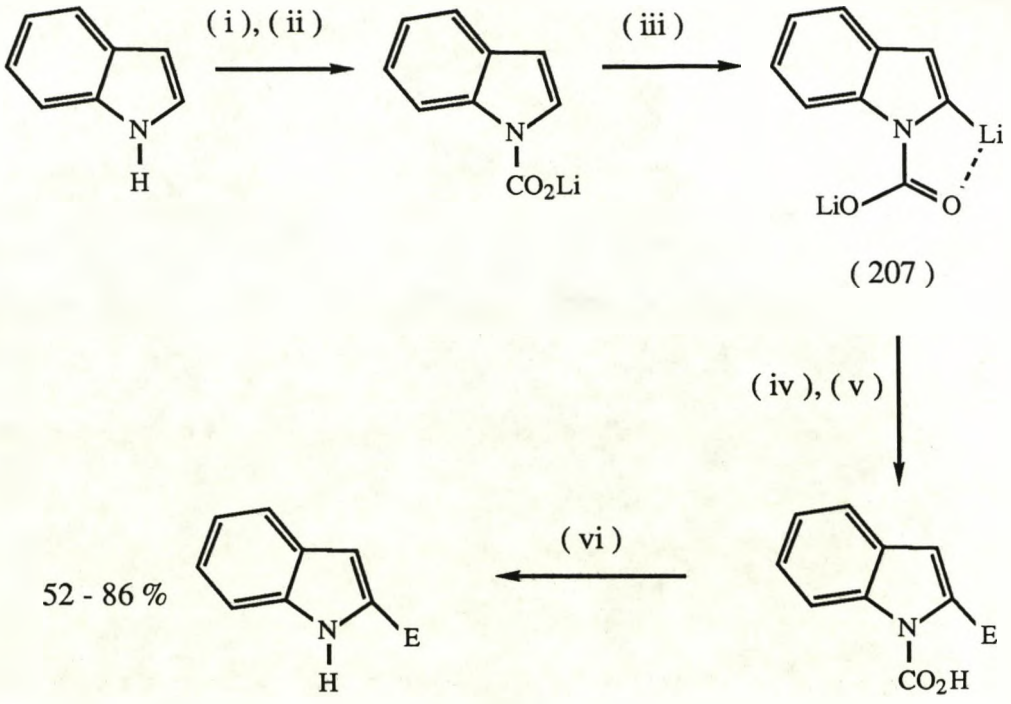


(207)

1.3.4.10 CARBON DIOXIDE PROTECTION AND ACTIVATION OF NITROGEN HETEROCYCLES

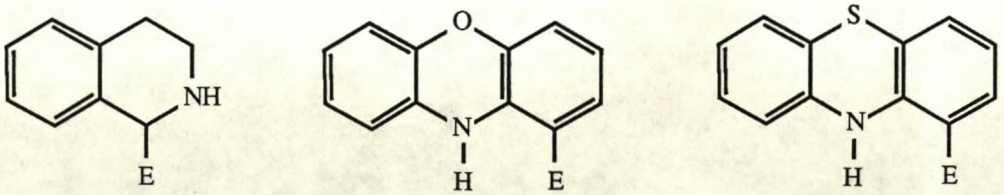
Katritzky has introduced carbon dioxide as a protecting group for nitrogen (NH functionality). This group is also effective in directing lithiation to C2 of the indole ring and stabilises the resulting carbanion.[155] Reaction of the dilithio species (207) with electrophile followed by thermal decarboxylation constitutes a new synthetic method for the 2-substitution of 1-unsubstituted indoles (Scheme 1.83).

In subsequent publications Katritzky has applied this methodology to the syntheses of 1-substituted tetrahydroisoquinolines (208),[156] 1-substituted phenoxazines (209),[157] and 1-substituted phenothiazines (210).[158] As well as providing effective protection for nitrogen and facilitating lithiation at an adjacent carbon centre carbon dioxide is a cheap, commercially available substance that is easily introduced and removed. This methodology will doubtless find further application in organic synthesis.



Reagents: (i) ^{n}BuLi, thf, -70°C; (ii) CO_2, -70°C to 20°C; (iii) ^{t}BuLi, -70°C, thf; (iv) E^{+}, thf, -70°C; (v) H_2O; (vi) heat

SCHEME 1.83



(208) (209) (210)

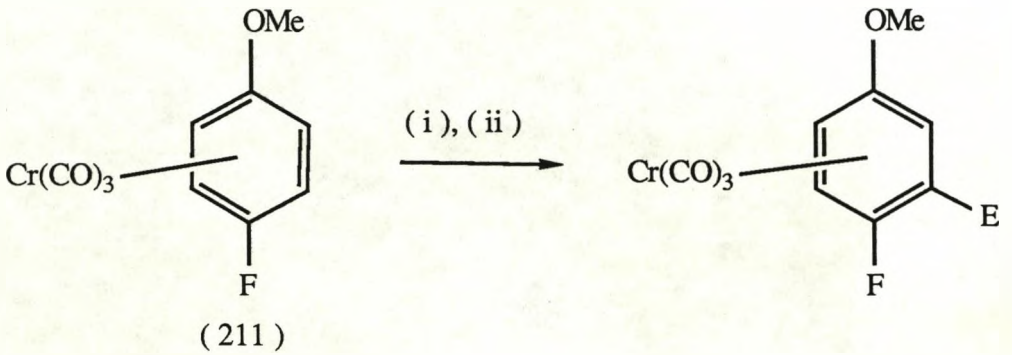
1.3.4.11 REVERSAL OF NORMAL REGIOSELECTIVITY IN DIRECTED LITHIATIONS : TRICARBONYLARENECHROMIUM (0) COMPLEXES

The withdrawal of electron density from an arene ring consequent on complexation with a tricarbonylchromium unit has long been known to enhance the acidities of the arene protons.[159] Gilday and Widdowson have established that in complexes bearing directing groups coordin-

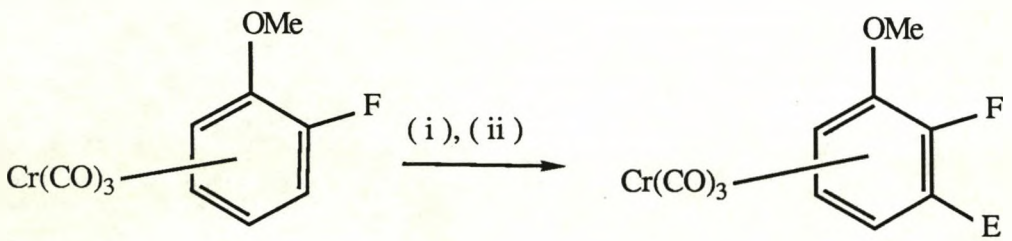
ation effects are less important than inductive effects.[160] Thus on treatment of tricarbonyl-(4-fluoroanisole)-chomium (0) (211) with ^{n}BuLi, lithiation occurs regiospecifically adjacent to fluorine (Scheme 1.84). At room temperature the uncomplexed 4-fluoroanisole is lithiated next to the methoxy group.[131] (Kirk et al., have recently shown that lithiation of 4-fluoroanisole with ^{s}BuLi at -78°C occurs predominantly next to the methoxy group, although products arising from lithiation (25%) next to fluorine may also be detected.[161])

Tricarbonyl-(2-fluoroanisole)-chromium (0) (212) also undergoes regiospecific lithiation adjacent to fluorine. As would be expected the meta-substituted isomer (213) undergoes lithiation between the two activating groups, as is the case in the uncomplexed arene.

The directed lithiation of arene complexes provides a complementary route to polyfunctionalised aromatics with substitution patterns and regiochemistry that would be difficult to achieve by other methods.



(211)



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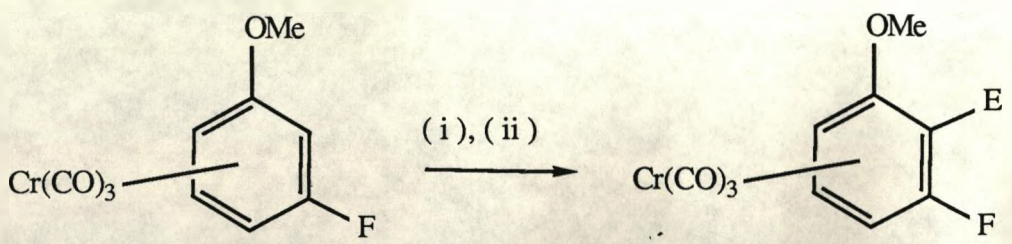


(213)

Reagents: (i) ^{n}BuLi, thf-, -78°C; (ii) E^{+}

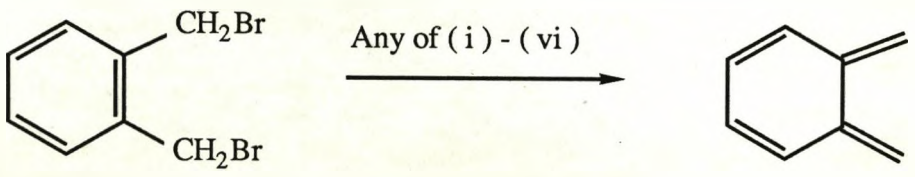
SCHEME 1.84

CHAPTER 2

2.0 CARBOXYLIC ACID MEDIATED SYNTHESIS OF AN o-XYLYLENE PRECURSOR: IODIDE ION-INDUCED GENERATION OF THE THIOPHENE ANALOGUE OF o-XYLYLENE

2.1 INTRODUCTION

bis-Bromide (214) has been used on numerous occasions for the generation of o-xylylene (1),[27,32,49,51,162-166] the reductive debromination usually being accomplished with the aid of metal atoms, ions or complexes (Scheme 2.1).



(214) (1)

Reagents: (i) Na; (ii) Zn; (iii) Fe; (iv) Ni; (v) $CrCl_2$;
(vi) Cu(^tBuCN).

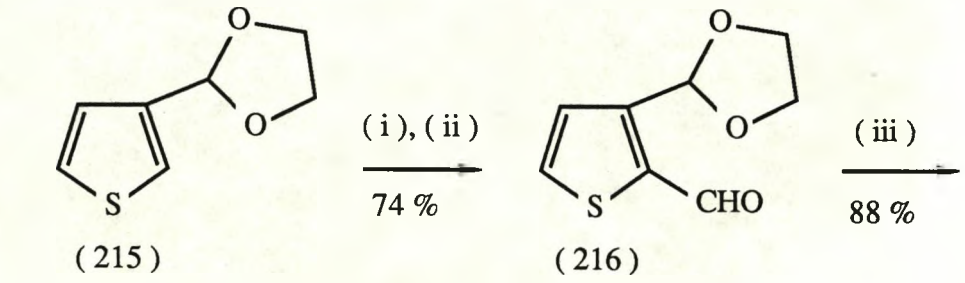
SCHEME 2.1

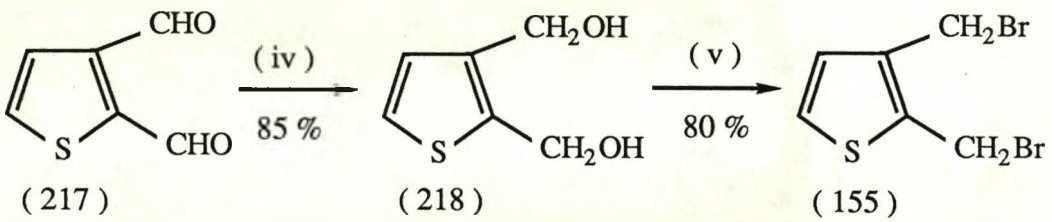
Extrapolation of this approach to the indole[3] (1.2.1) and pyridine[117] (1.2.4) ring systems has also been achieved. In the heterocyclic systems o-xylylene generation is brought about using iodide ion.

Although 2,3-bis-(bromomethyl)thiophene is a known compound, no reports of attempted o-xylylene generation have appeared in the literature prior to our work.[123]

2.2 SYNTHESIS OF 2,3-bis-(BROMOMETHYL)THIOPHENE

McDowell and Patrick have synthesised 2,3-bis-(bromomethyl) thiophene(155) in four steps from 3-thiophenealdehyde ethylene acetal (215) in 44% overall yield[167] (Scheme 2.2).





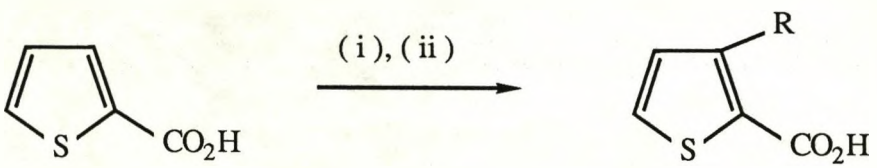
Reagents: (i) ^{n}BuLi, Et_2O; (ii) DMF; (iii) 3N HCl;
(iv) $LiAlH_4$, Et_2O; (v) PBr_3, Et_2O

SCHEME 2.2

Lithiation of acetal (215) gives regiospecific formation of the 2-lithio derivative (see Section 1.3.4.3) which on reaction with DMF gives the 2-formyl compound (216). Hydrolysis gives bis-aldehyde (217), which on hydride reduction forms diol (218). Bromination with phosphorous tribromide furnishes bis-bromide (155). All four steps are high yielding but the acetal (215) must itself be prepared[168] prior to initiating the sequence outlined in Scheme 2.2.

Carpenter and Chadwick have shown that the lithium carboxylate of thiophene-2-carboxylic acid directs lithiation into the ortho position of the ring under appropriate conditions.[169] This allows the synthesis of a range of 3-substituted thiophene-2-carboxylic acids in high yield (Table 2.1).

TABLE 2.1

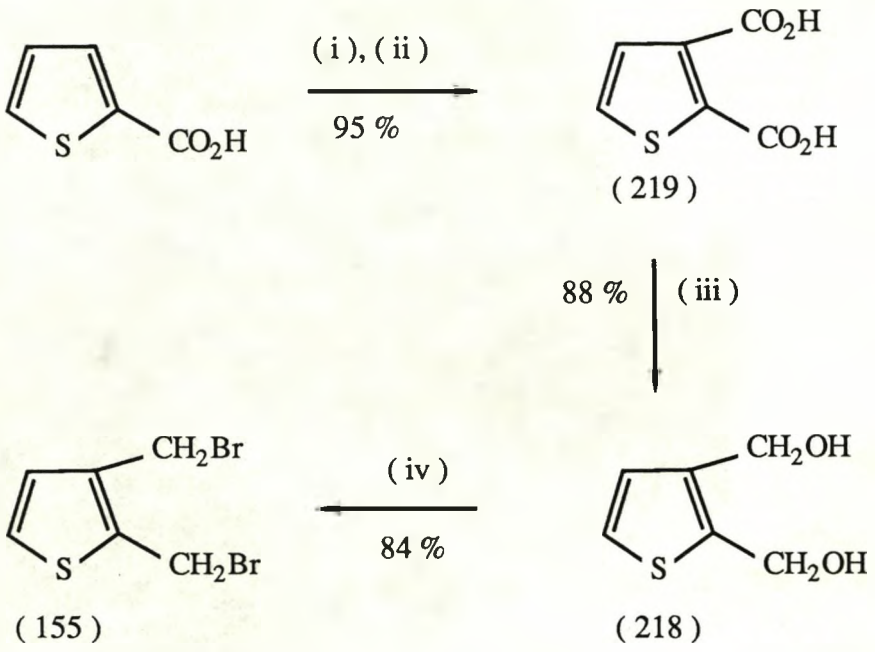


Reagents (i) ^{n}BuLi, THF, -78°C, ½ hr; (ii) electrophile; (iii) H_3O^+

Electrophile	$(CH_3)_3SiCl$	$(CH_3)_2S_2$	CH_3I	I_2	$C_6H_5CH_2Br$
R	$(CH_3)_3Si$	CH_3S	CH_3	I	$C_6H_5CH_2$
Yield (%)	85	94	83	94	70

Application of this methodology to the synthesis of 2,3-bis-(bromomethyl)thiophene (155) allows for a shorter and more convenient approach to the compound (Scheme 2.3).

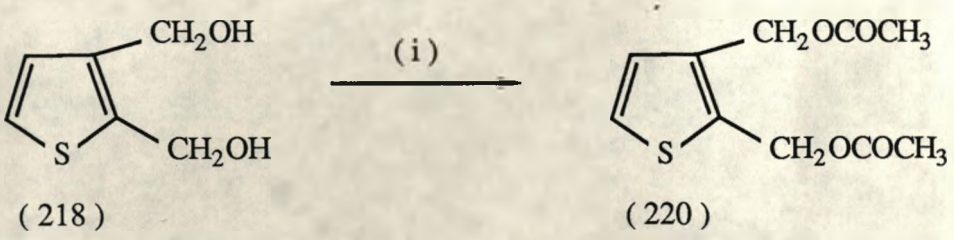
Treatment of thiophene-2-carboxylic acid with two equivalents of ^{n}BuLi and subsequent quenching of the dianion with carbon dioxide gives thiophene-2,3-dicarboxylic acid (219) in excellent yield.



Reagents (i) ^{n}BuLi, THF, -78°C, ½ hr; (ii) CO_2, then HCl (aq.); (iii) $LiAlH_4$, THF, reflux 24 h.; (iv) PBr_3, Et_2O, r.t., 22 hrs.

SCHEME 2.3

Lithium aluminium hydride reduction gives the crude diol (218) as a viscous, colourless, opaque liquid. This is a high yielding (88%) and very clean reaction. Attempted distillation of (218) results in decomposition and so bromination is best carried out on the crude material. A small sample of (218) has been converted into di-acetate (220) for analytical purposes (Scheme 2.4).



Reagents: (i) $(CH_3CO)_2O$, pyridine, r.t., 24 hrs.

SCHEME 2.4

Initially the bromination step was carried out in dry benzene[123] giving a maximum 68% yield. When carried out in dry ether (and with longer reaction times compared with earlier experiments) significantly higher yields (up to 84%) are obtained.

When purified, bis-bromide (155) is an unstable, lachrymatory tan solid, which rapidly decomposes at room temperature (ca. 24 hrs) liberating hydrogen bromide. (It is noteworthy that the relatively low acid content of commercial $CDCl_3$ is sufficient to accelerate this decomposition.) Consequently (155) was freshly prepared and used immediately as required, with storage being avoided.

2.3 IODIDE ION-INDUCED GENERATION OF 2,3-DIMETHYLENE-2,3-DIHYDROTHIOPHENE : THE THIOPHENE ANALOGUE OF o-XYLYLENE

As noted in Section 2.1 a variety of reagents are used to generate o-xylylenes from aromatic bis-bromomethyl compounds.

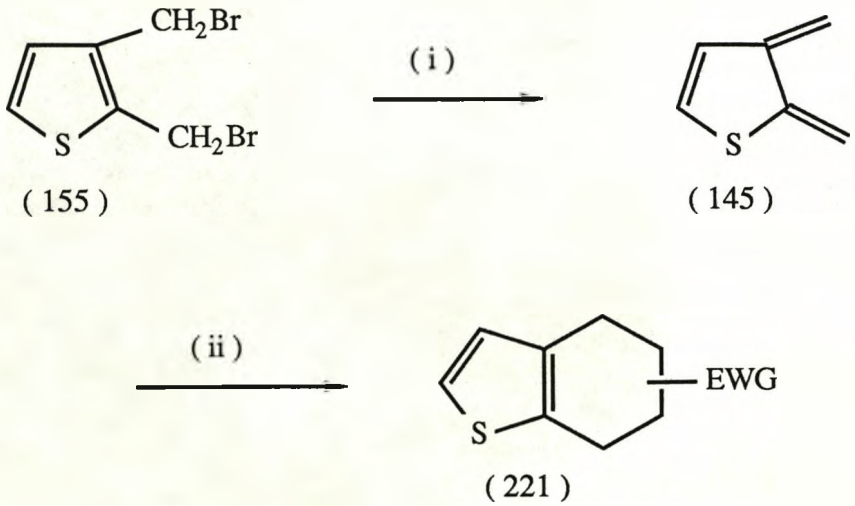
In the present work, sodium iodide (with DMF as solvent) has been chosen on the basis of previously reported results in other heterocyclic systems.[3,117]

Thus, bis-bromide (155) is added to sodium iodide in DMF at 80°C in the presence of a selection of electron-deficient dienophiles. The results are summarised in Table 2.2.

Although good yields of cycloadducts (221) are obtained with N-phenylmaleimide, MVK, and acrylonitrile, only polymer-like material of indeterminate composition is produced in all other cases. Significant amounts of polymer-like material one also produced along with adducts (222), (223), and (167).

When debromination of (155) is carried out in the absence of dienophile this polymer-like material is the sole product. There is no trace of any dimeric compound. This material is produced as a

TABLE 2.2

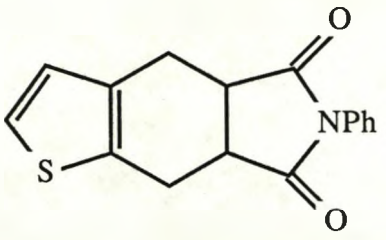


(155) (145) (221)

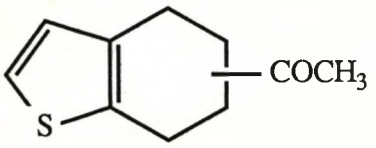
Reagents: (i) NaI, DMF, 80°C; (ii) CH_2 = CH-EWG

EWG = Electron Withdrawing Group

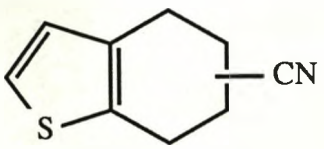
Dienophile (number of equivalents)	Reaction time (hrs)	Yield of adduct (%)
N-Phenylmaleimide (1.1)	5	60
Methyl vinyl ketone (10)	14	50
Acrylonitrile (10)	14	60
Maleic anhydride (1.1)	15	-
Diethylmaleate (1.1)	15	-
Dimethylacetylenedi-carboxylate (1.1)	15	-



(222)



(223)



(167)

black film, coating the inside of the reaction vessel. It is soluble in dichloromethane and chloroform and gives only two signals (multiplets) in the nmr spectrum at δ 1.25 and 0.85 ratio (2:1). Its identity remains unsolved.

There appears to be no logical reason why Diels-Alder adducts should be formed with some electron-deficient dienophiles and not with others, particularly in the light of the results discussed in Chapter 3. The instability of bis-bromide (155) and the generation of IBr during the reaction may in some way account for, or contribute to, the observed results. The temperature of reaction does not significantly alter its course; with maleic anhydride as dienophile the same result is obtained at room temperature i.e., no adduct formation.

Adducts (167) and (223) are formed as a mixture of regioisomers as expected from literature precedent.[2,7,124] Adducts (167) appear as a single spot on thin layer chromatography (tlc) and as a single regioisomer by 220 MHz nmr. Only at 250 MHz does it become apparent that two regioisomers are present. This is confirmed by ^{13}C nmr.

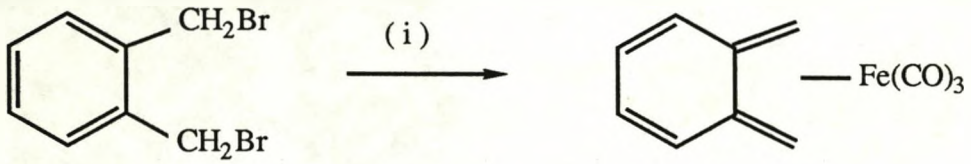
Similarly, adducts (223) are inseparable by tlc. However, absorptions at 1725 and 1712 cm^{-1} are observable in the infra red (i.r.) spectrum, corresponding to the carbonyl groups of the two regioisomers. Capillary gas chromatography (g.c.) analysis displays adducts (167) and (223) as single peaks on the g.c. trace.

Although the identity of the major isomers in adducts (167) and (223) (or indeed the ratio of isomers) has not been established unambiguously, by analogy with the results communicated by van Leusen[124] (Section 1.2.6), the major isomer may be assigned as bearing the electron-withdrawing group closest to sulphur, with some degree of certainty.

Adduct (222) is produced as a stable crystalline solid but adducts (223) and (167) are colourless mobile liquids which decompose quite rapidly following flash chromatography. Adduct (223) also decomposes on attempted distillation.

2.4 ATTEMPTED ISOLATION OF THE THIOPHENE ANALOGUE OF o-XYLYLENE AS A TRANSITION METAL COMPLEX

Roth and Meier have isolated an iron-tricarbonyl complex of o-xylylene (11) by heating an ethereal solution of bis-bromide (214) with diiron nonacarbonyl (Scheme 2.5).



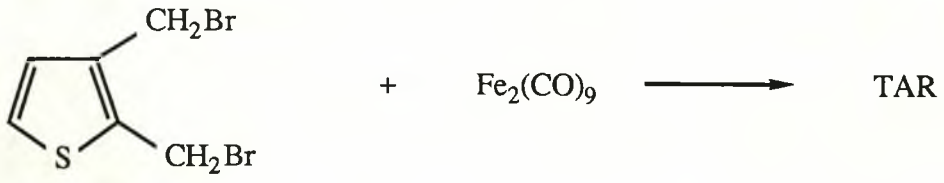
(214) (11)

Reagents : (i) $Fe_2(CO)_9$, Et_2O, reflux

SCHEME 2.5

In the hope of isolating an analogous thiophene o-xylylene complex, bis-bromide (155) has been treated with iodide ion in the presence of diiron nonacarbonyl (Scheme 2.6). Disappointingly (although not altogether unexpectedly), this reaction produces an intractable tar with no trace of transition metal complex.

The instability and unpredictability of bis-bromide (155) limits its utility as a precursor for o-xylylene generation and encourages the search for alternative synthetic routes (Chapter 3).



Reagents : (i) NaI, DMF, 80°C

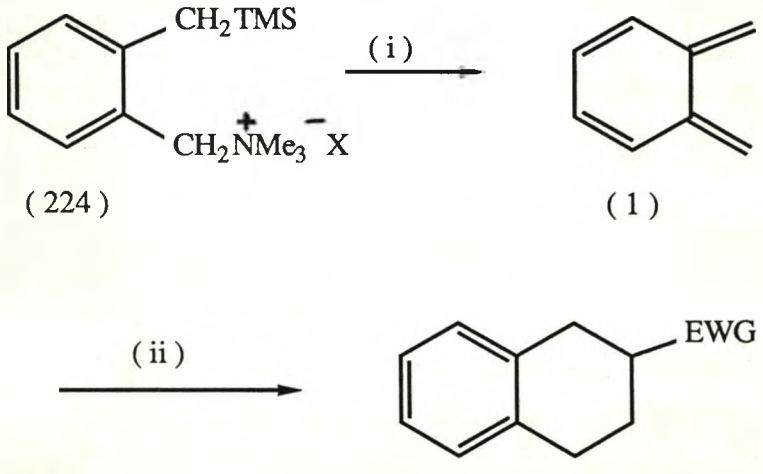
SCHEME 2.6

CHAPTER 3

3.0 AMIDE MEDIATED SYNTHESES OF o-XYLYLENE PRECURSORS : FLUORIDE ION-INDUCED GENERATION OF THE THIOPHENE ANALOGUE OF o-XYLYLENE

3.1 INTRODUCTION

The efficient and versatile method for the generation of o-xylylene intermediates by fluoride ion-induced 1,4-elimination of o-(α-trimethylsilylalkyl)-benzyltrimethylammonium halides (224) has been pioneered and developed by Ito and co-workers,[46,52] (Scheme 3.1).



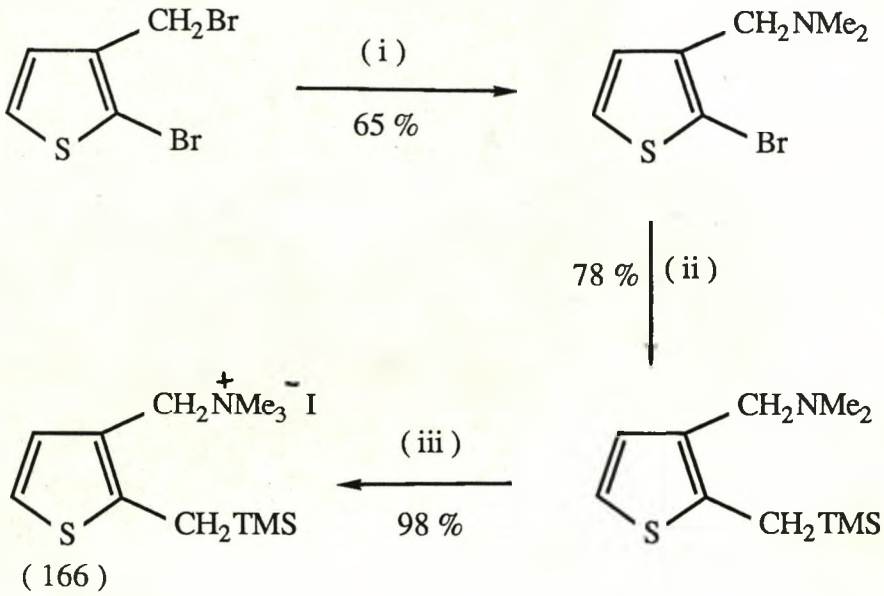
Reagents: (i) TBAF, CH_2Cl_2, r.t.; (ii) CH_2=CH - EWG

EWG = Electron Withdrawing Group

SCHEME 3.1

o-Xylylene intermediates are intercepted in both inter- and intramolecular Diels-Alder reactions, providing a flexible synthetic route to a range of polycyclic molecules.

van Leusen has recently applied this approach to the thiophene ring system with excellent results.[124] Salt (166) is prepared in three steps from 2-bromo-3-(bromomethyl)thiophene in 50% overall yield (Scheme 3.2).



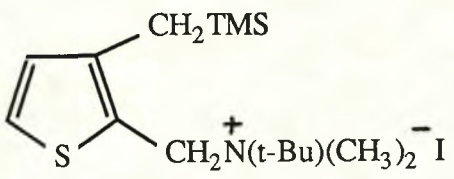
(166)

Reagents: (i) Me_2NH, ¼ h, 20°C; (ii) $TMSCH_2MgCl$, $Ni(PPh_3)_2Cl_2$, Et_2O, reflux, 20 h; (iii) MeI, CH_3CN, reflux, 1 h

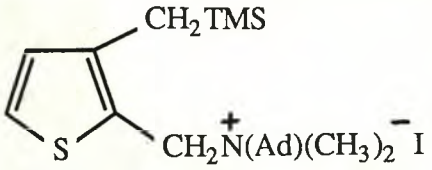
SCHEME 3.2

Treatment of salt (166) with a source of fluoride ion provides a mild and efficient generation of the thiophene analogue of o-xylylene (see Section 1.2.6 for details).

We have developed a novel synthetic route to quaternary ammonium salts (225) and (226). These compounds are very similar to the compound used by the Dutch workers in o-xylylene generation. However, the method of preparation is quite different, beginning with simpler starting materials and offering greater potential for funtionalisation of the thiophene ring prior to o-xylylene generation.



(225)

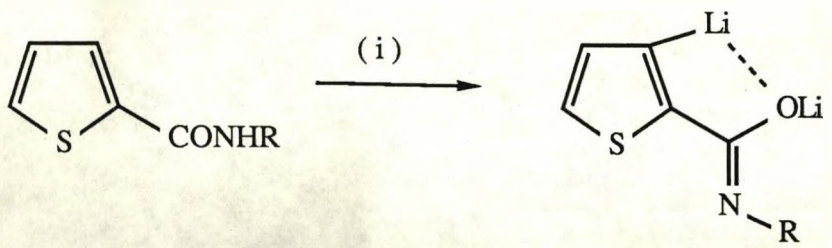


(226)

Ad = 1 - Adamantyl

3.2 SYNTHESES OF 2-(N-DIALKYLAMINOMETHYL)-3- TRIMETHYLSILYL-METHYL -THIOPHENE IODIDES

Carpenter and Chadwick have shown that the secondary amide moiety (or more precisely the amidate anion) is a very potent directing group in the thiophene ring system, facilitating regiospecific β-(ortho)-lithiation with judicious choice of metallating agent and reaction conditions[170] (Scheme 3.3).



R = t - Bu, CH_3 (227)

Reagents: (i) ^{n}BuLi, thf, -78°C, ½ h

SCHEME 3.3

The dilithio species (227) can be induced to react with a range of electrophiles to give a variety of 2,3-disubstituted thiophene

derivatives in good-to-excellent yields. Many of these compounds are inaccessible, or at least difficult to prepare by classical methodology.

Application of this chemistry to the construction of precursors to thiophene analogues of o-xylylene has been investigated. The approach is outlined in Figure 3.1.

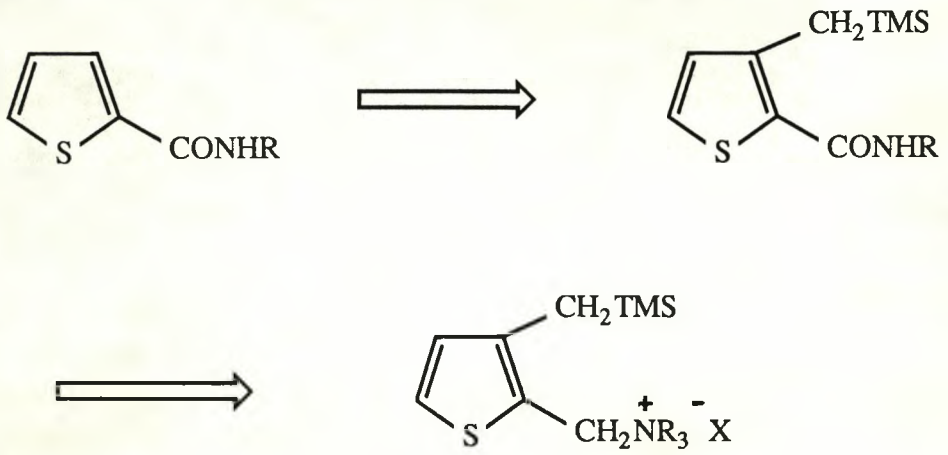
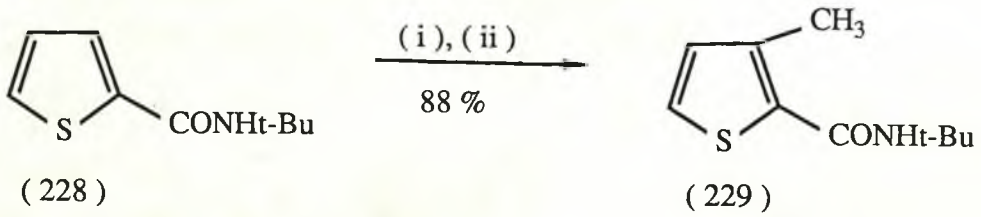


FIGURE 3.1

Introduction of the trimethylsilylmethyl group is accomplished by two successive ortho-lithiation reactions. The secondary amide functionality is then transformed into the quaternary ammonium salt (vide infra), which serves as the leaving group in the projected fluoride ion-induced 1,4-elimination reaction required for o-xylylene generation.

3.2.1 SYNTHESIS OF 2-(N-^{t}BUTYL-N-DIMETHYLAMINOMETHYL)-3-TRIMETHYLSILYLMETHYLTHIOPHENE IODIDE

3-Methylthiophene-2-N-t-butylcarboxamide (229), a key intermediate in the synthesis of the title compound, can be prepared according to the method of Carpenter and Chadwick[170] (Scheme 3.4).



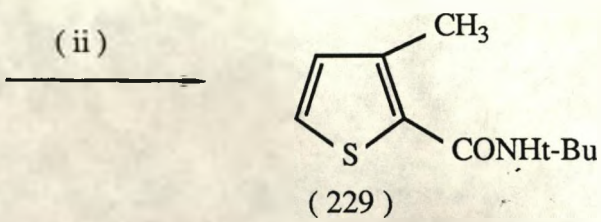
(228) (229)

Reagents: (i) ^{n}BuLi, DME, -78°C, 2 h; (ii) MeI

SCHEME 3.4

Alternatively, amide (229) can be prepared on multigram scale from 3-methylthiophene-2-carboxylic acid† via acid chloride (230) (Scheme 3.5). This two-step procedure is routinely carried out on 20

(230)



(229)

Reagents: (i) $SOCl_2$; (ii) $^{t}BuNH_2$

SCHEME 3.5

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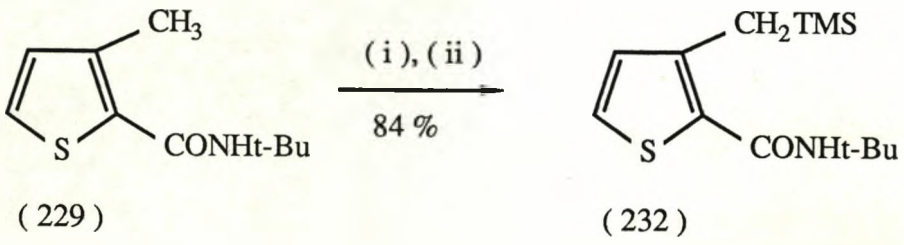
† We thank Synthetic Chemicals for a generous gift of this compound.

g of acid giving amide (229) in typically 90% overall yield.

Conditions have been established for regioselective ortho-lithiation and silylation into the C3 methyl group (Scheme 3.6).



(229) (232)

Reagents: (i) ^{s}BuLi, thf, -78°C, ½ h; (ii) TMSCl, -78°C, ¼ h, then r.t.

SCHEME 3.6

Results of a lithiation deuteriation/study (Table 3.1) shows that ^{n}BuLi in thf at 0°C may be used to obtain 100% deuteriation into the C3 methyl group. (If more than two equivalents of organolithium reagent are used then C5 deuteriation also occurs.) Alternatively, the same result is achievable with the more basic ^{s}BuLi at -78°C.

TABLE 3.1

RLi	Solvent	Temp (°C)	Deuteriation at C3 methyl group (%)
^{n}BuLi	thf	-78	0
^{n}BuLi	thf	0	100
^{s}BuLi	thf	-78	100

A plausible mechanism accounting for the high degree of regio-selectivity in the directed lithiation reaction is given in Figure 3.2.

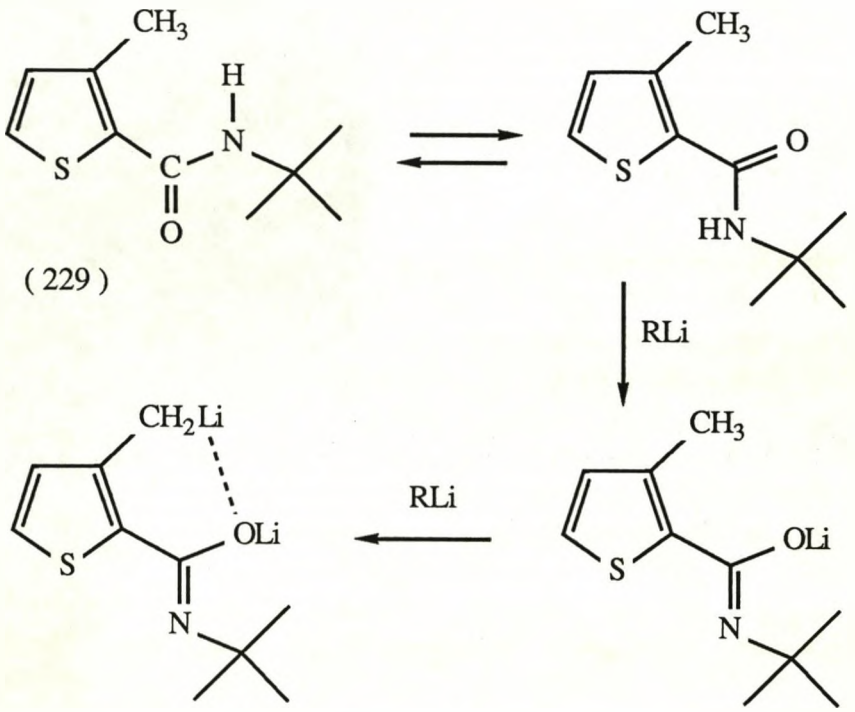


FIGURE 3.2

Firstly, the choice of the ^{t}butyl group serves to minimise the possibility of nucleophilic attack at the carbonyl group by the organolithium reagent and also to increase the solubility of any derived anions. It was further hoped (as proposed in the work of Carpenter and Chadwick) that the ^{t}butyl group would help to predispose the amidate anion to a conformation allowing maximum stabilisation of the dilithiated intermediate. Such a conformation may also, perhaps, permit efficient delivery of the second equivalent of organolithium reagent to the methyl group by the intermediate amidate anion (Figure 3.3).

The reaction outlined in Scheme 3.6 has been attempted using 3-methylthiophene-2-N-methyl-carboxamide (231), instead of the t-butyl

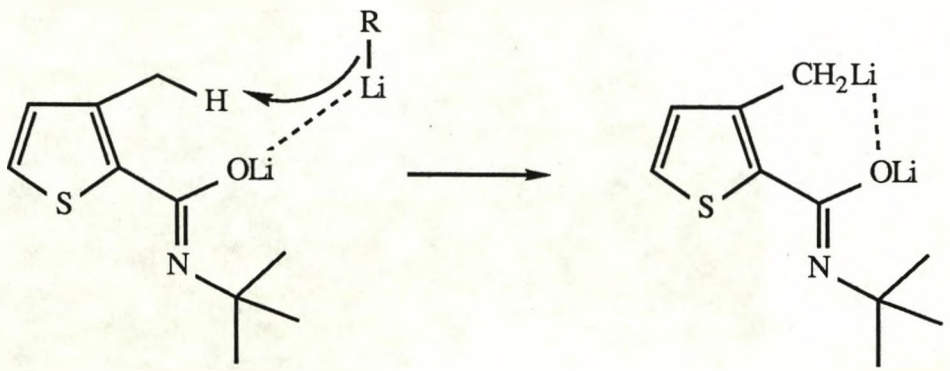
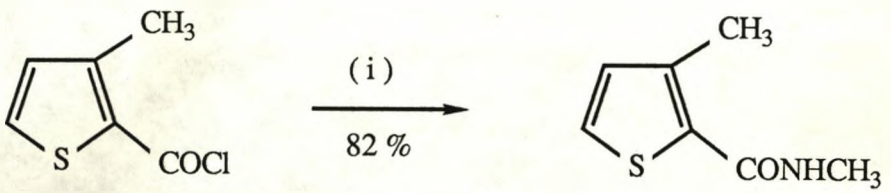


FIGURE 3.3

analogue. Amide (231) is prepared in high yield by Schotten-Baumann reaction of acid chloride (230) and aqueous methylamine (Scheme 3.7).



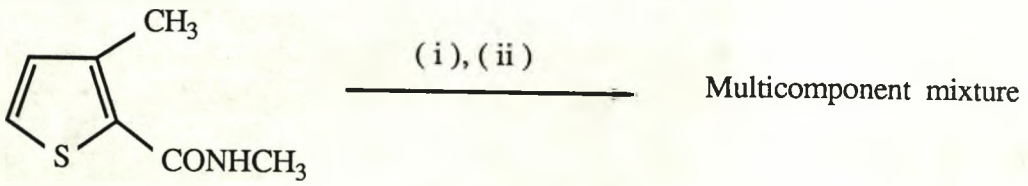
(230) (231)

Reagents: (i) CH_3NH_2 (aq.), NaOH aq. (10% w/w)

SCHEME 3.7

The reaction (Scheme 3.8) produces a number of products by ^1H nmr and tlc analysis. As well as substantial quantities of starting material, the ^1H nmr spectrum reveals both C3-methyl and C5-silylated

products. The importance of the t-butyl group is therefore well established. In consequence, no further lithiation studies were attempted on amide (231).

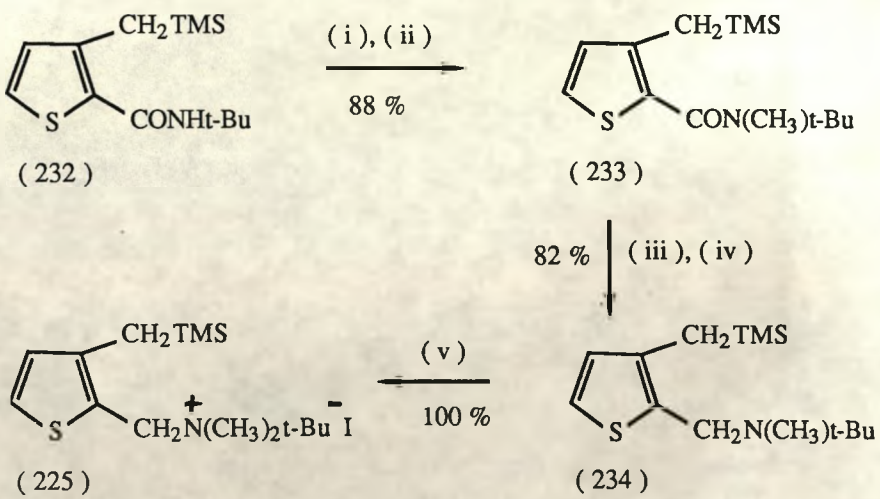


(231)

Reagents: (i) ^{s}BuLi, thf, -78°C, ½ h; (ii) TMSCl, -78°C, ¼ h, then r.t.

SCHEME 3.8

When pure, silylated secondary amide (232) is a stable, low-melting waxy white solid. Conversion into the potential o-xylylene precursor (225) is accomplished in three simple steps (Scheme 3.9).



(232) (233) (225) (234)

Reagents: (i) ^{n}BuLi, thf, -78°C, ½ h; (ii) MeI; (iii) $LiAlH_4$, Et_2O, reflux, 24 h; (iv) H_2O; (v) MeI, r.t., 12 h

SCHEME 3.9

The secondary amide is converted into the tertiary amide (233) on treatment with one equivalent of ^{n}BuLi with subsequent low temperature alkylation with methyl iodide. Reduction to amine (234) is accomplished using lithium aluminium hydride (LAH). A non-acidic work-up is employed to safeguard the potentially acid sensitive silicon functionality. Finally, quaternary ammonium salt (225) is formed on quaternisation of amine (234) with neat methyl iodide. The synthesis of salt (225) from amide (229) proceeds in a very good 61% overall yield (4 steps).

During initial quaternisation studies of tertiary amine (234), using methyl iodide in refluxing acetonitrile, (conditions that allow efficient quaternisation of a related system - see Chapter 4), significant degradation of the starting material was observed, most notably by a diminished ^{t}butyl signal in the nmr spectrum. This decomposition is postulated as being a result of attack of iodide ion on the ^{t}butyl group of salt (225) (Figure 3.4).

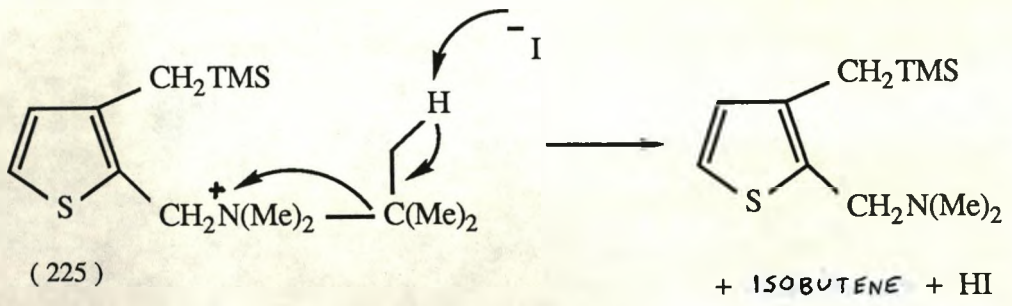


FIGURE 3.4

The reaction is not clean and attempts to verify this postulate have not been made (no such decomposition is observed at room temperature).

However, initial failure to obtain salt (225) cleanly and in satisfactory yield, prompted a search for a group that would not decompose under the quaternisation conditions (CH_3I, acetonitrile, reflux) and would also act as an ortho-director of lithiation.

With the characteristics of the ^{t}butyl group in mind (i.e., those factors that made the ^{t}butylcarboxamide such a good directing group) the adamantyl group was selected as a candidate. It is a bulky alkyl group, and it was expected that the adamantylcarboxamide would make a good directing group. Just as importantly, if the mechanism of decomposition of salt (225) (Figure 3.4) is correct, then such a pathway should be denied the corresponding adamantyl salt (226) since it would be in violation of Bredt's rule[171] (Figure 3.5).

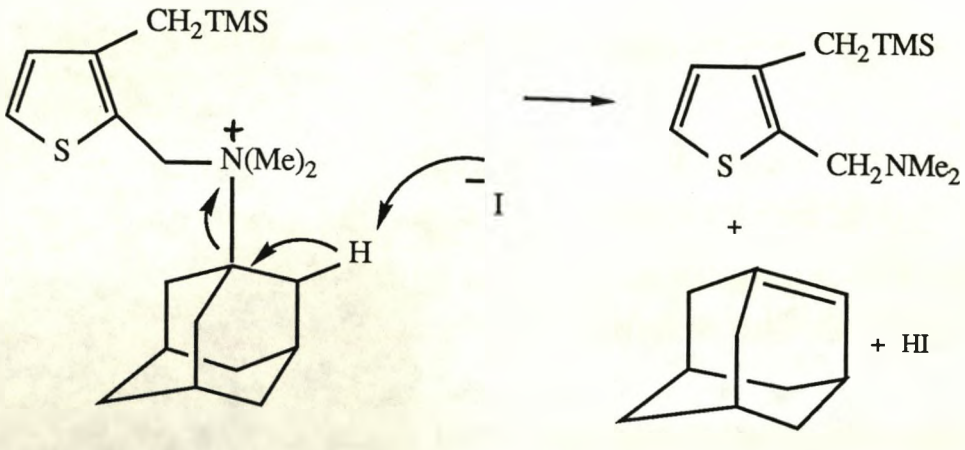
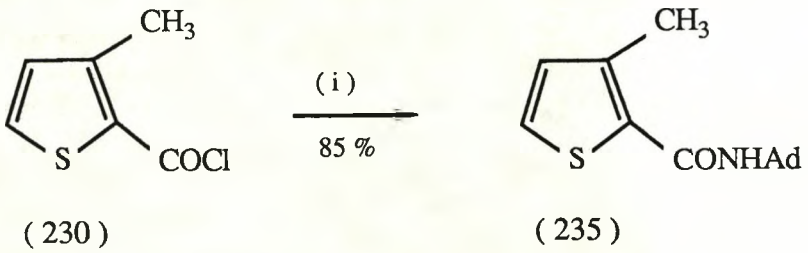


FIGURE 3.5

3.2.2 SYNTHESIS OF 2-(N-1-ADAMANTYL-N-DIMETHYLAMINOMETHYL)-3-TRIMETHYLSILYLMETHYLTHIOPHENE IODIDE

Salt (226) is synthesised in a similar fashion to salt (225) (Section 3.2.1). 3-Methylthiophene-2-carbonylchloride (230) is converted into the adamantylcarboxamide (235) in high yield (Scheme 3.10).

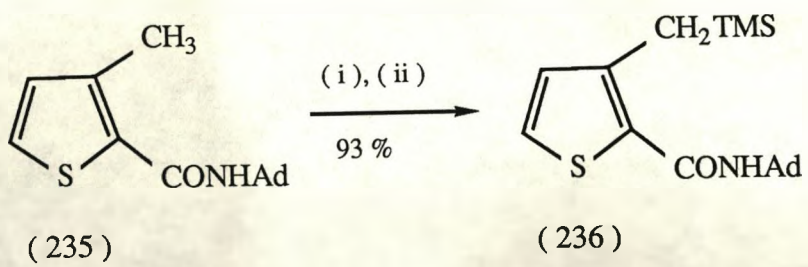


(230) (235)

Reagents: (i) 1-adamantamine, Et_3N, CH_2Cl_2, r.t., 12 h

SCHEME 3.10

In the crucial directed-lithiation step, amide (235) is smoothly converted to silylated secondary amide (236) in excellent yield (Scheme 3.11).



(235) (236)

Reagents: (i) $^{S}BuLi$, thf, -78°C, ½ h; (ii) TMSCl

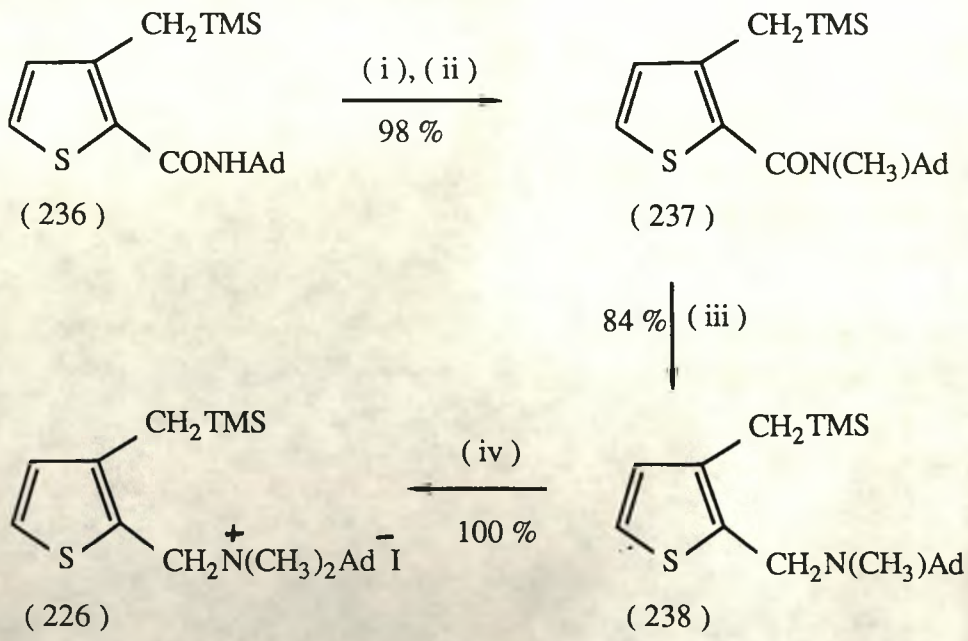
SCHEME 3.11

Thus, the proposed rationale for the use of the adamantylcarboxamide as a directing group seems justified. One can conclude that

the solubilising characteristics of the ^{t}butyl and adamantyl groups have a profound effect on the reactivity of the dilithio species and the complete regiospecificity of the reaction (Schemes 3.6 and 3.11) lends some credence to the mechanism postulated in Figure 3.2.

Silylated secondary amide (236) is converted into salt (226) using the same sequence of reactions as for the ^{t}butyl analogue (Scheme 3.12).

Quarternisation of amine (238) can be accomplished without significant decomposition with methyl iodide in refluxing acetonitrile. However, as with ^{t}butyl compound (234), stirring at room temperature in neat methyl iodide for a minimum of twelve hours results in quantitative salt formation. Salt (226) is obtained in four steps from amide (235) in an excellent overall yield of 77%.



Reagents: (i) ^{s}BuLi, thf, -78°C, ½ h; (ii) MeI;

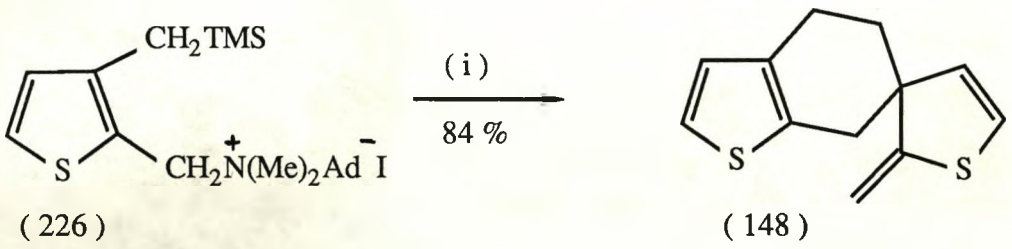
(iii) $LiAlH_4$, Et_2O, reflux, 24 h; (iv) MeI, r.t., 24 h

SCHEME 3.12

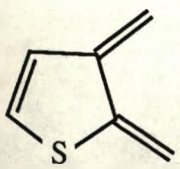
3.3 FLUORIDE ION-INDUCED GENERATION OF THE THIOPHENE ANALOGUE OF o-XYLYLENE. REACTIONS WITH DIENOPHILES

The two most common sources of fluoride ion used in o-xylylene generation are caesium fluoride and tetra-n-butylammonium fluoride (TBAF). The former is commercially available as an extremely hygroscopic white solid which is most effective if dried prior to use. TBAF is most commonly sold as a thf solution containing some 5% water (it is also available as a crystalline hydrate).

o-Xylylene generation from salts (225) and (226) is effected with caesium fluoride under mild conditions. When an acetonitrile solution of salt (226) is added to a suspension of caesium fluoride in acetonitrile at room temperature, [4+2]spiro dimers of the form (148) are produced in high yield (Scheme 3.13).



(226) (148)

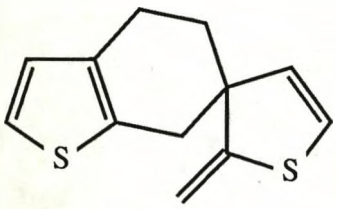


(145)

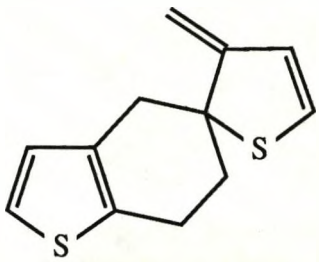
Reagents: CsF, CH_3CN, r.t., 18 h

SCHEME 3.13

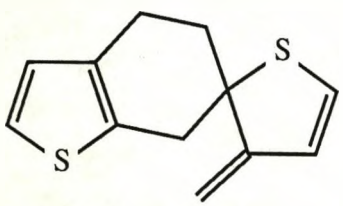
The products of this reaction infer the intermediacy of the thiophene analogue of o-xylylene (145). There are four possible [4+2] dimers (Figure 3.6).



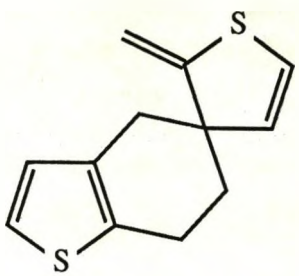
(148a)



(148b)



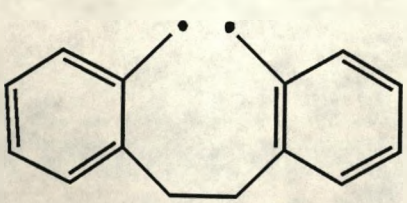
(148c)



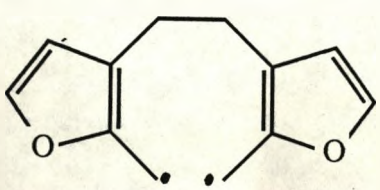
(148d)

FIGURE 3.6

Gc/ms of the crude product indicates that two dimers are actually produced. All four dimers are indistinguishable by ^{1}H nmr spectroscopy. Dimerisation of o-xylylene (1) is postulated as proceeding via diradical (239)[31] (Figure 3.7).



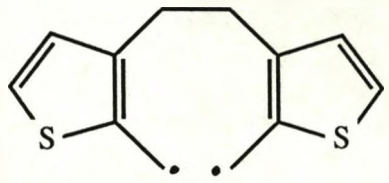
(239)



(141)

FIGURE 3.7

The furan analogue of o-xylylene is also postulated as dimerising via the most stable diradical (141)[7] (see Section 1.2.5). On this basis, the thiophene analogue of o-xylylene (145), would also be expected to dimerise via diradical (240) (Figure 3.8). If this is



(240)

FIGURE 3.8

the case then only [4+2] dimers (148a) and (148d) can be produced. This tentative explanation fits in with the gc/ms data but is without further foundation. A concerted dimerisation process cannot be discounted.

Dimers (148) are unstable compounds, decomposing in the neat state and on silica gel. Errede has proposed a free radical mechanism to account for the decomposition of spiro-dimer (10)[31] (Figure 3.9). The explanation is based upon the tendency of spiro-dimer (10) to re-aromatise. The terminal methylene group is the most accessible point of attack and on aromatisation with concomitant ring opening, radical (241) is produced which undergoes polymerisation.

N-phenylmaleimide was used as dienophile in the first attempt to intercept o-xylylene (145) by a cycloaddition reaction (Scheme 3.14). A solution of salt (226) is added dropwise onto the other reagents.

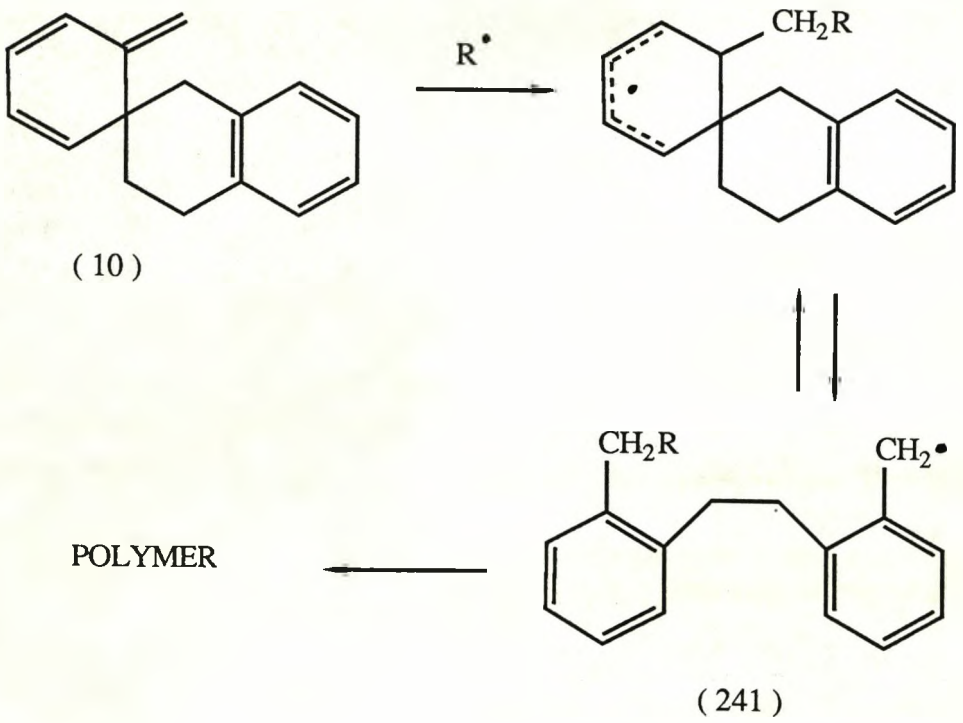
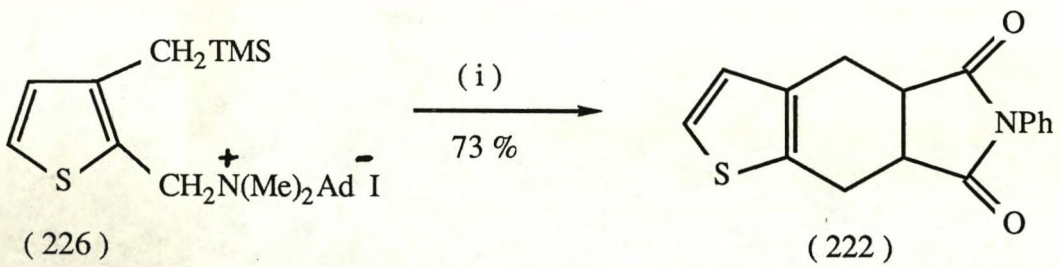


FIGURE 3.9



Reagents: (i) CsF, CH_3CN, N-phenylmaleimide, 0°C

SCHEME 3.14

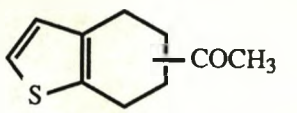
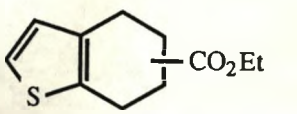
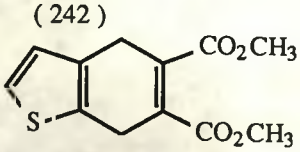
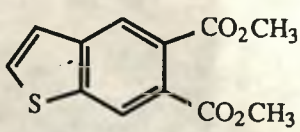
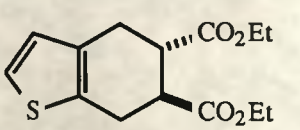
This ensures that a relatively low concentration of o-xylylene is generated in the presence of a high concentration of dienophile.

Using only one equivalent of N-phenylmaleimide, a very good yield of cycloadduct (222) is produced. Only one compound can be detected

by tlc and nmr. The newly formed ring junction is presumed cis on the basis of the observed coupling constant, which is of the order of 5 Hz. This observation supports the idea of a concerted reaction i.e., a Diels-Alder reaction.

Further cycloaddition studies were carried out using salt (225). Generation of o-xylylene (145) is efficiently brought about at either 0°C or room temperature, and Diels-Alder adducts are produced in high yield with a selection of electron deficient dienophiles (Table 3.2).

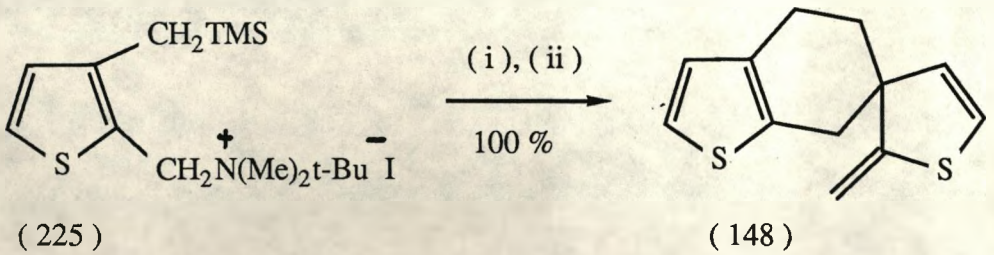
TABLE 3.2

Dienophile (number of equivalents)	Temperature (°C)	Adduct (% yield)	
MVK (10)	25	 (223)	(80)
Ethyl acrylate (10)	0	 (242)	(78)
DMAD (1.1)	25	 (243)	(79)
		 (244)	
Diethyl fumarate (1.1)	25	 (245)	(73)

Excellent yields of regioisomeric Diels-Alder adducts (223) and (242) are produced when o-xylylene (145) reacts with MVK (78%) and ethyl acrylate (80%). The difference in temperature at which these reactions take place appears to have little effect on chemical yield. o-Xylylene (145) reacts with one equivalent of dimethylacetylene dicarboxylate (DMAD) to give two compounds in 79% overall yield. These are identified as adduct (243) and the aromatised compound (244) by nmr and gc/ms analysis (3:1 ratio).

Reaction of (145) with one equivalent of diethyl fumarate gives a good yield of a single Diels-Alder adduct (245). Nmr, tlc and gc analysis all indicate a single diastereomer and it is therefore assumed that the stereochemistry of the dienophile is retained in the adduct (this is obviously the case if the reaction is truly Diels-Alder in nature). Adducts (242) to (245) are all obtained as colourless, mobile liquids after chromatographic purification, which begin to darken after only a few hours.

o-Xylylene (145) has also been generated in the presence of electron-rich and "unactivated" olefins. However, in the presence of either ethyl vinyl ether (10 equiv.) or norbornene (10 equiv.) only dimeric compounds (148) are produced (Scheme 3.15).

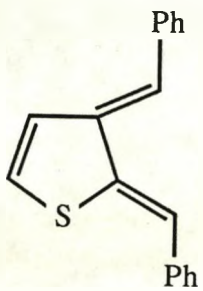


(225) (148)

Reagents: (i) CsF, CH_3CN, 0°C; (ii) ethyl vinyl ether or norbornene

SCHEME 3.15

The thiophene analogue of o-xylylene can be categorised as "electron-rich" in nature, refusing to react with electron-rich and "unactivated" olefins under conditions where high yields of adduct are obtained with electron-deficient dienophiles. It is interesting to note that bis-phenyl-o-xylylene (172) reacts with norbornene, albeit in modest yield (see Section 1.2.6). The stabilisation afforded by

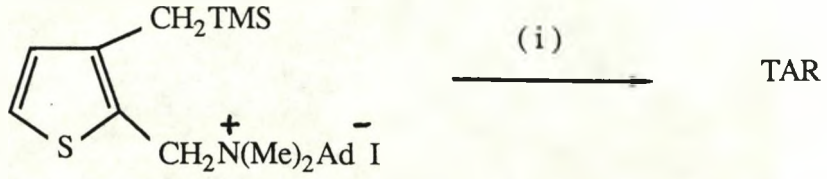


(172)

the phenyl rings and possible steric hindrance to dimerisation are probable causes for the outcome of this reaction.

3.4 ATTEMPTED ISOLATION OF THE THIOPHENE ANALOGUE OF o-XYLYLENE AS A TRANSITION METAL COMPLEX

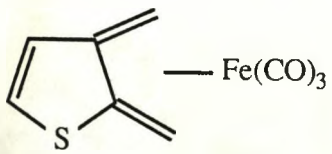
Addition of salt (226) to a suspension of caesium fluoride and diiron nonocarbonyl in acetonitrile results only in tar formation (Scheme 3.16). Under thermal conditions known to encourage dissociation of diiron nonocarbonyl to its tricarbonyl,[32] no evidence of complex (246) is found, neither does dimerisation of the o-xylylene species occur.



(226)

Reagents: (i) CsF, $Fe_2(CO)_9$, CH_3CN, 50°C

SCHEME 3.16



(246)

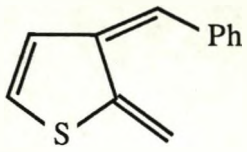
No further attempts at complex formation have been made.

3.5 AN APPROACH TO INTRAMOLECULAR TRAPPING OF THE THIOPHENE ANALOGUE OF o-XYLYLENE : SYNTHESIS OF A POTENTIAL PRECURSOR TO α-VINYL-2,3-DIMETHYLENE-2,3-DIHYDROTHIOPHENE

For the methodology described in this Chapter to become a versatile synthetic tool for synthesising annelated thiophenes, then

the intramolecular interception of o-xylylenes must be achievable.

Storr and Huang have independently achieved this goal in the gas phase by generating o-xylylene (150) (see Section 1.2.6).



(150)

Quaternary ammonium salt (247) was selected as a potential precursor to α-vinyl-2,3-dimethylene-2,3-dihydrothiophene (248). Cyclisation of o-xylylene (248) should produce adduct (249) (Figure 3.10). The synthesis of salt (247) is outlined in Figure 3.11.

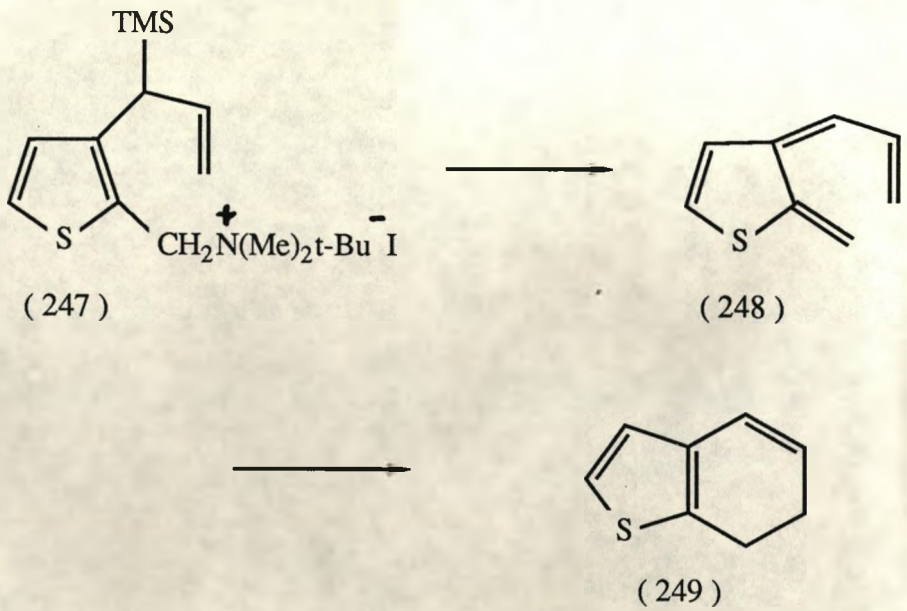


FIGURE 3.10

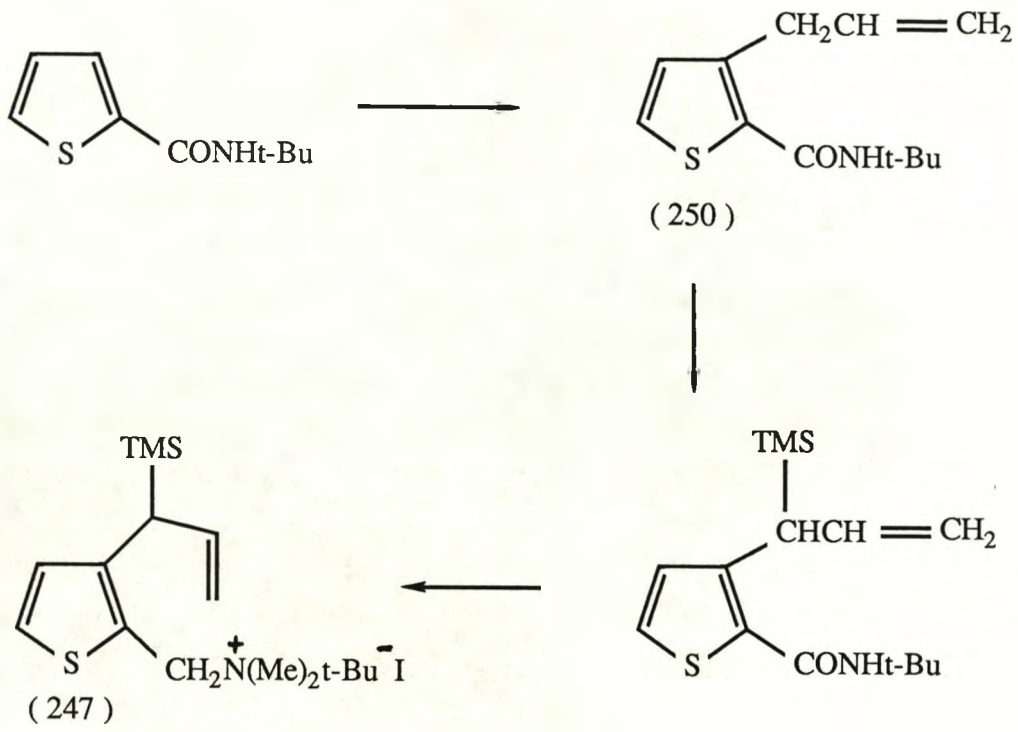
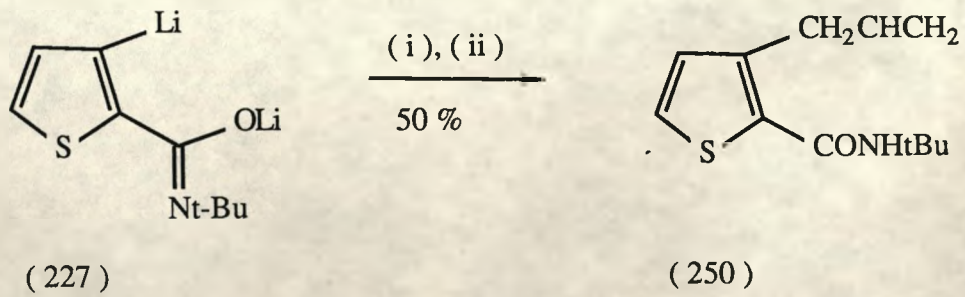


FIGURE 3.11

The first attempt to prepare allylated amide (250) used the conditions reported by Chadwick and Carpenter for efficient alkylation of dianion (227).[170] However, after several attempts the optimum yield (crude) of amide (250), as evinced by capillary gc is 50%, the remaining product being starting material (Scheme 3.17). (It is to



(227) (250)

Reagents: (i) ^{n}BuLi, DME, -78°C, 2 h; (ii) allyl iodide, -10°C, 2 h

SCHEME 3.17

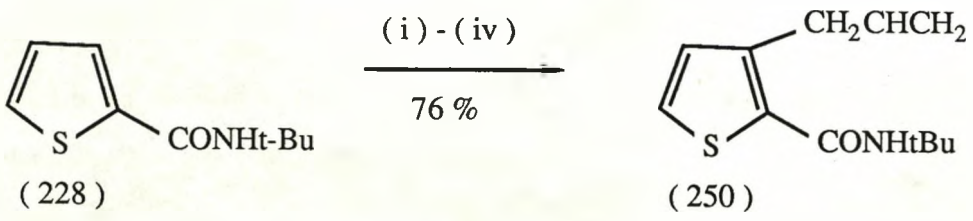
be noted that these authors do not report the actual preparation of this particular alkylated derivative).

Reaction of dianion (227) with allyl iodide in thf results in a multicomponent mixture of products, including starting material and some tertiary amide. Snieckus has reported that magnesium transmetallation of ortho-lithiated tertiary benzamides allows effective reaction with allylation agents.[172]

Generation of dianion (227) in thf at -78°C with subsequent addition of 3.0 ≡ of magnesium bromide etherate ($MgBr_2$.OEt) gives a white precipitate. This is warmed to room temperature, re-cooled to -78°C and reacted with allyl iodide (3.5 ≡) to give a 3:1 ratio of allylated amide (250) to starting material by gc. Surprisingly it is found that if the amount of $MgBr_2$·OEt is increased (10 ≡) or the amount of allyl iodide is increased (10 ≡) the ratio of allylated product to starting material falls to 1:1. Addition of allyl iodide at 40°C only raises the ratio to 2:1. Using allyl bromide as electrophile gives a 2:3 ratio of products in favour of starting material.

A 6:1 ratio of allylated product (250) to starting material is produced if the bromomagnesium species is allowed to attain room temperature gradually (1 h), prior to electrophilic quench. The reaction is completely fine-tuned when the amount of $MgBr_2$·OEt is reduced to 1.5 ≡ and complete conversion to the allylated compound is observed, giving a 76% yield of analytically pure material following flash chromatography (Scheme 3.18).

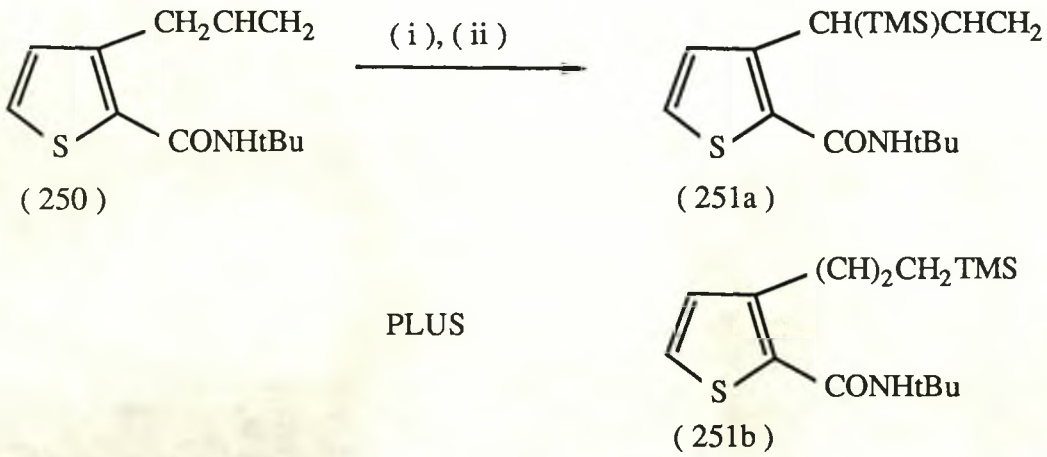
Lithiation-silylation studies performed on allylated amide (250) always give a mixture of silylated compounds (Scheme 3.19). However, as it was envisaged that each of these silylated compounds (251a) and (251b) would eventually give rise to the same o-xylylene (248), separation was not attempted.



(228) (250)

Reagents: (i) ^{n}BuLi, thf, -78°C, ½ h; (ii) $MgBr_2 \cdot OEt$;
(iii) Allyl iodide; (iv) flash chromatography.

SCHEME 3.18



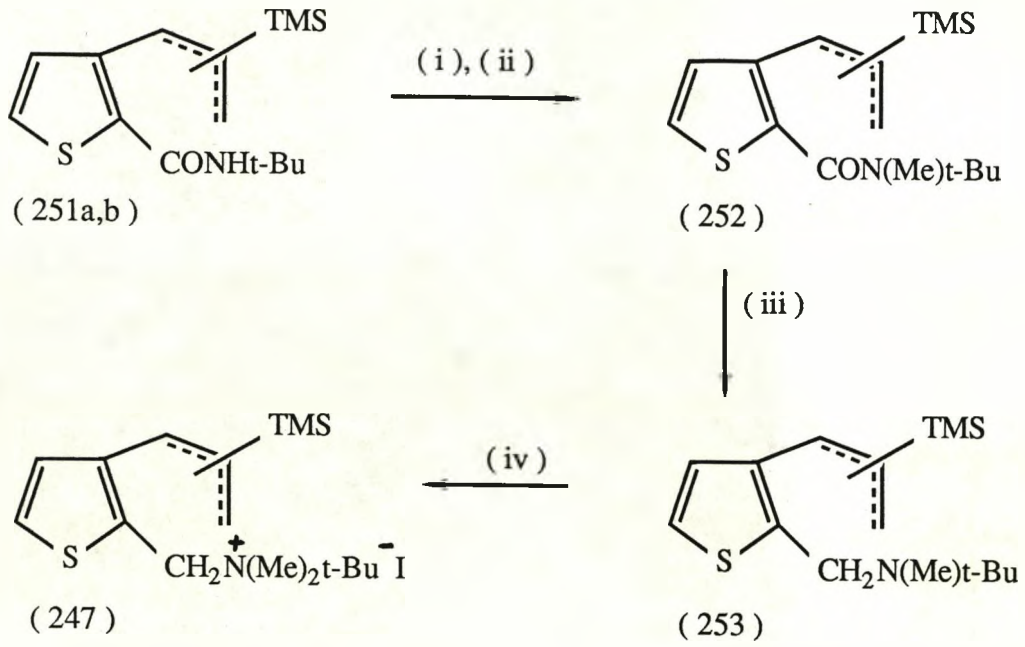
(250) (251a) (251b)

Reagents: (i) ^{n}BuLi or ^{s}BuLi, thf, -78°C or 0°C or r.t.; (ii) TMSCl

SCHEME 3.19

Conversion to salts (247) is carried out as before (Scheme 3.20). ^{1}H nmr spectra are complicated due to the presence of two isomeric compounds throughout (allyl signals also overlap with aromatic signals in most cases) but important signals are observable (e.g., TMS, NCH_3, $\underline{CH}_2$-N etc.).

A small quantity of crude salts (247) have been obtained, but lack of time (and material) has precluded further studies.



(251a,b) (252) (247) (253)

Reagents: (i) ^{n}BuLi, thf, -78°C; (ii) MeI; (iii) $LiAlH_4$, Et_2O, reflux; (iv) MeI

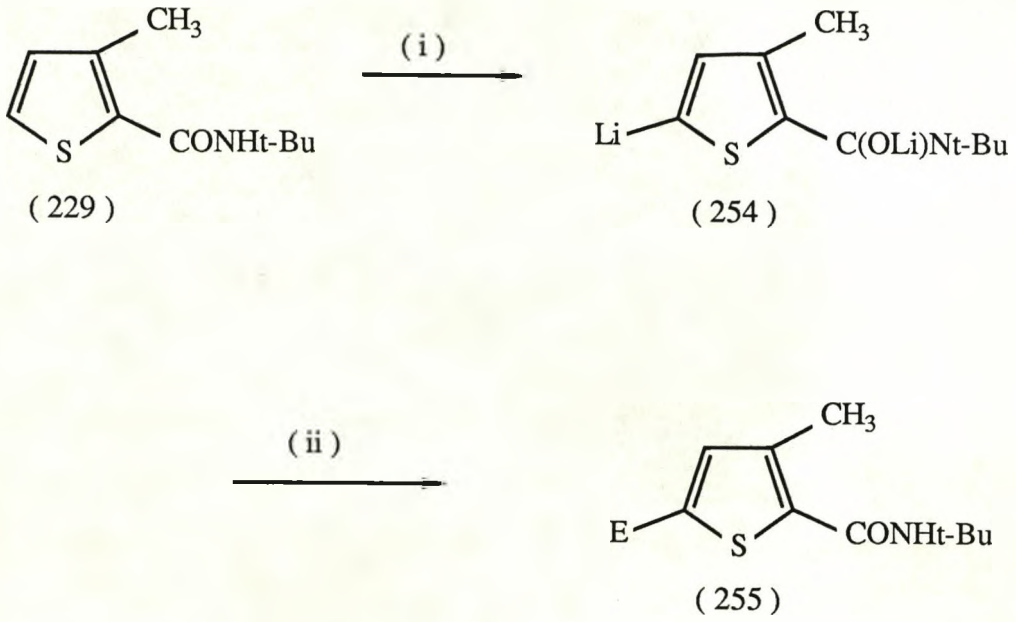
SCHEME 3.20

3.6 POTENTIAL OF SECONDARY AMIDE MEDIATED SYNTHESIS OF o-XYLYLENE PRECURSORS

The mild and efficient generation of the thiophene analogue of o-xylylene has been demonstrated using this approach.

It has the facility to functionalise the thiophene ring at the C5 position. Generation of the C5-lithio-intermediate is accomplished using LDA. Reaction of dianion (254) with electrophiles gives high yields of the C5-substituted products (255)[173] (Scheme 3.21).

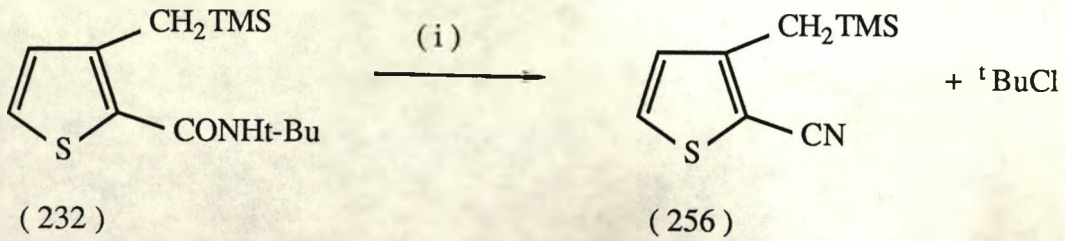
The t-butylcarboxamide (229) resists mild hydrolytic procedures, but amide (232) is converted to the potentially useful nitrile compound (256) without loss of silicon[173] (Scheme 3.22). Fluoride ion-induced desilylation of (256) and compounds derived from (256) have great potential in generating a wider range of thiophene o-xylylene intermediates.



(229) (254) (255)

Reagents: (i) LDA, thf, -78°C, ½ h; (ii) electrophile

SCHEME 3.21



(232) (256)

Reagents: (i) $SOCl_2$, reflux, 2 h

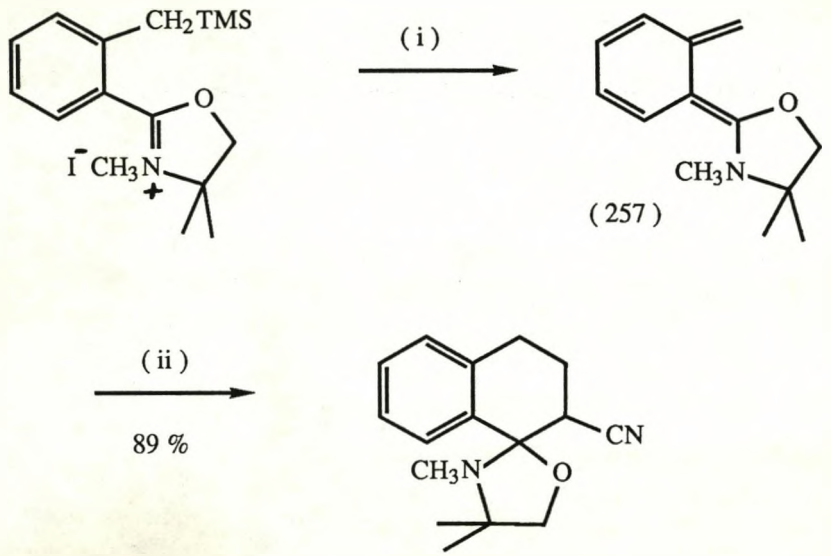
SCHEME 3.22

CHAPTER 4

4.0 OXAZOLINE MEDIATED SYNTHESES OF PRECURSORS TO THIOPHENE AND FURAN ANALOGUES OF o-XYLYLENE. FLUORIDE ION-INDUCED GENERATION OF α-SUBSTITUTED o-XYLYLENES

4.1 INTRODUCTION

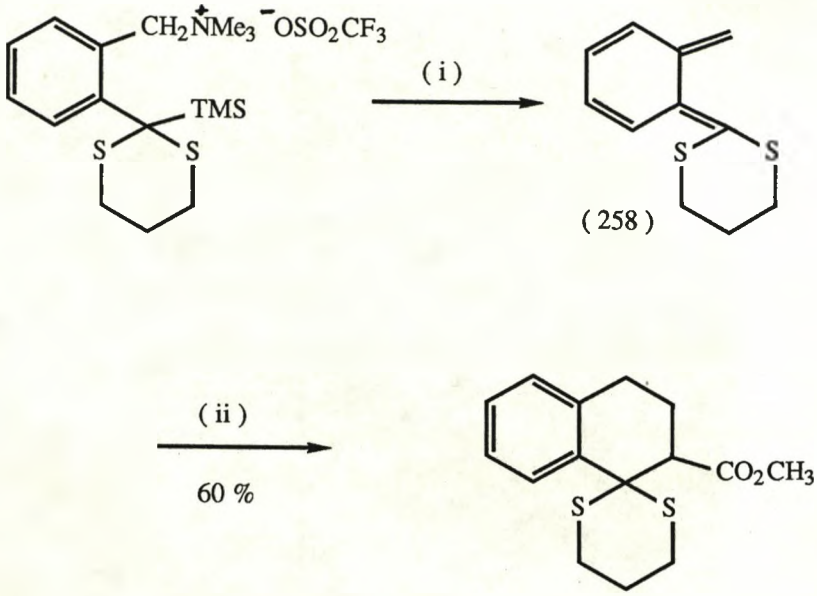
Ito et al., have generated o-xylylene intermediates bearing electron-donating substituents at an α-position.[53,122] o-Xylylenes (257) and (258) react with electron-deficient olefins to give good yields of Diels-Alder adducts with complete regioselectivity (Schemes 4.1 and 4.2).



Reagents: (i) CsF, CH_3CN, 0°C; (ii) CH_2=CHCN

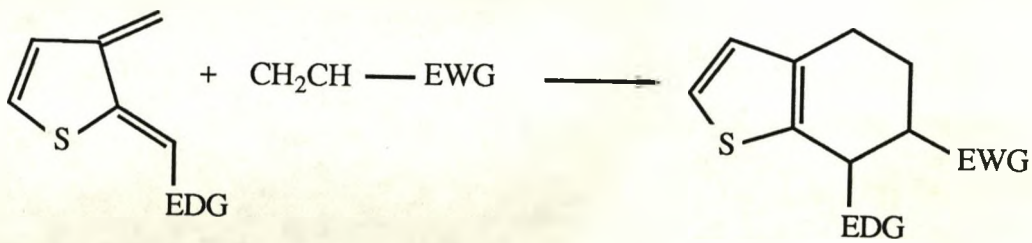
SCHEME 4.1

In view of the regiochemical outcome of cycloaddition reactions of the thiophene analogue of o-xylylene (145) with dienophiles (Chapter 3), it would be of synthetical value if the regiochemistry of such reactions could be controlled, so that a single regioisomer could be obtained exclusively. Generation of a thiophene o-xylylene derivative bearing an electron-donating group at an α-position should bias the Diels-Alder reaction with electron-deficient dienophiles in favour of the "ortho" isomer, as predicted by F.M.O. theory[72] (Figure 4.1).



Reagents: (i) CsF, CH_3CN, 55 - 60°C; (ii) $CH_2{=}CHCO_2CH_3$

SCHEME 4.2



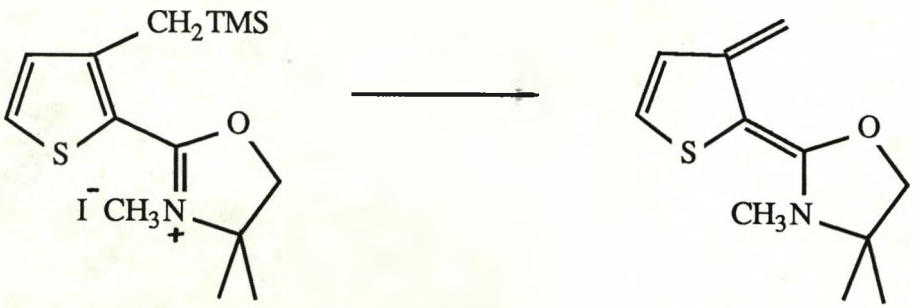
EDG ≡ Electron-donating group

EWG ≡ Electron-withdrawing group

FIGURE 4.1

4.2 SYNTHESIS OF 2-(3-TRIMETHYLSILYLMETHYL-2-THIENYL)-3,4,4-TRIMETHYLOXAZOLINIUM IODIDE AND RELATED COMPOUNDS

Initially, oxazolinium salt (259) was chosen as a potential o-xylylene precursor. It was envisaged that fluoride ion-induced

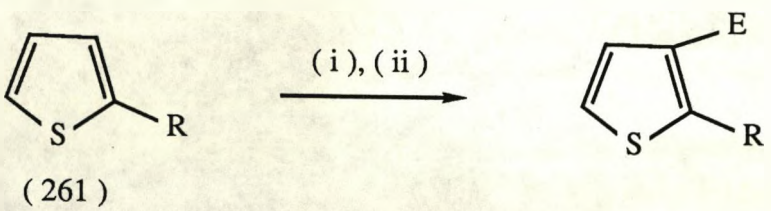


(259) (260)

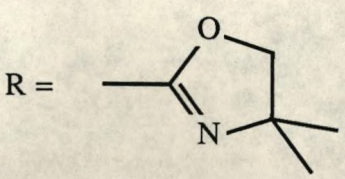
FIGURE 4.2

desilylation would generate o-xylylene (260) (Figure 4.2).

The projected synthesis of salt (259) was based on the reported ortho-directed lithiation chemistry of thienyl-oxazoline (261)[174] (Scheme 4.3).



(261)



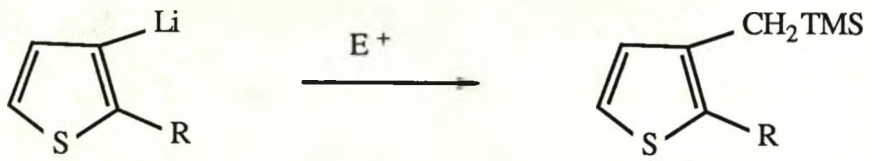
E = Electrophile

Reagents: (i) ^{n}BuLi, Et_2O; (ii) electrophile

FIGURE 4.3

Introduction of the trimethylsilylmethyl group at the β-position of the thiophene ring, followed by alkylation at nitrogen would give salt (259). Attempts to introduce the $-CH_2TMS$ group into the thiophene ring using a single step procedure met with limited success (Table 4.1). When the lithio species (262) is treated with either

TABLE 4.1



(262) (264)

	Electrophile	Yield (%)
1	$Cl-CH_2-TMS$	0
2	$I-CH_2-TMS$	0
3	$CF_3SO_3-CH_2-TMS$	40
4	$CF_3SO_3(Me_2N)_3PO-CH_2TMS$	50

chloro- or iodomethyltrimethylsilane, only protonated material is recovered. When the corresponding triflate (entry 3) is added as electrophile, a modest percentage of silylated material is detected in the ^1H nmr spectrum. If HMPA is added to the triflate, then a white

salt (entry 4) is precipitated. This is reported to be a very convenient source of electrophilic $-CH_2TMS$.[92] Addition of lithio-species (262) to this salt results in a 50% yield of the β-substituted thiophene (264) by ^1H nmr. Although encouraging, this route was left in abeyance and a stepwise procedure to compound (264) was investigated. This alternative approach is outlined in Figure 4.3.

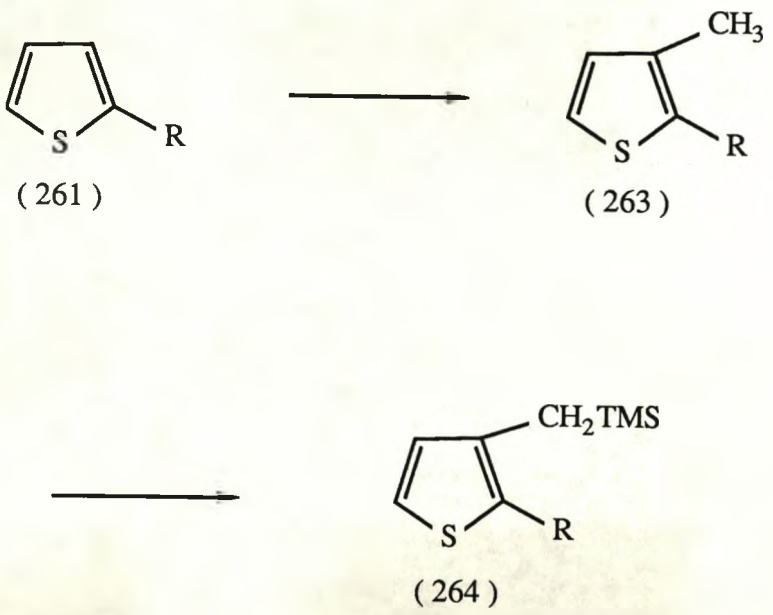
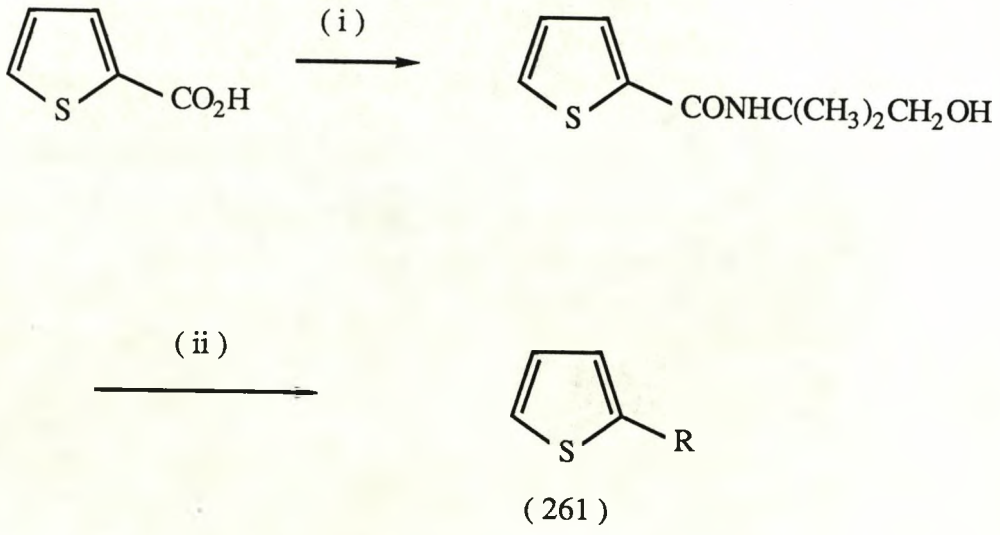


FIGURE 4.3

4,4-Dimethyl-2-(2-thienyl)oxazoline (261) is synthesised in good yield (81%) using the general method of Meyers, from thiophene-2-carboxylic acid *via* conversion to the acid chloride, formation of the intermediate amide and ring closure with thionyl chloride[175] (Scheme 4.4).

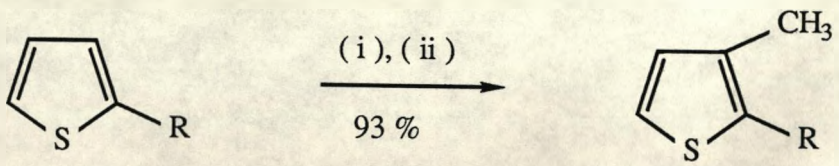
Formation of the 3-methyl derivative (263) is accomplished according to the published procedure[174] and can be carried out on multigram scale (5 - 10 g) with excellent yields (Scheme 4.5).



(261)

Reagents: (i) $SOCl_2$, $NH_2C(CH_3)_2CH_2OH$, CH_2Cl_2; (ii) $SOCl_2$, $PhCH_3$

SCHEME 4.4



(261) (263)

Reagents: (i) ^nBuLi, Et_2O, -78°C, ¼ h, then 0°C, ½ h; (ii) MeI

SCHEME 4.5

At this point conditions needed to be established for regiospecific lithiation into the C3 methyl group with subsequent silylation of the lithio-species.

The results of a range of experiments designed to elucidate the factors affecting regioselectivity of lithiation of 4,4-dimethyl-2-(3-methyl-2-thienyl)oxazoline (263) are given in Table 4.2.

Complete α-regioselectivity (i.e., lithiation adjacent to sulphur) is achieved with ^{n}BuLi as base and either thf (entry 4) or DME (entry 6) as solvent. Under these conditions lithiation is probably facilitated by an acid-base mechanism (see Section 1.3.3). The level of lithiation into the methyl group is low in all cases when ^{n}BuLi is the base, with mixtures of products arising from reactions carried out in hexane or ether. The addition of TMEDA (entry 7) favours α-lithiation, but the overall level of lithiation is poor. ^{s}BuLi gives greater selectivity for lithiation into the methyl group. This probably occurs via the coordination-only mechanism (Figure 4.4).

It is found that 1.5 equivalents of the organolithium reagent are required to give a satisfactory level of lithiation (entry 9). However, the reaction product is nearly always contaminated with C5-silylated or disilylated material. The best result (entry 14) gives a 9:1 ratio of the desired 3-trimethylsilylmethyl oxazoline (264) to the disilylated compound (266). The "tolerance" of trimethylsilyl chloride towards organolithium reagents may account for the appearance of disilylated material in the reaction products. Trimethylsilyl chloride can co-exist with organolithium reagents at low temperatures for an appreciable period of time without corruption, and consequently products may be observed arising from a sequential lithiation and silylation process. Such a process occurs when amide (229) is treated with four equivalents of ^{s}BuLi followed by four equivalents of tri-

TABLE 4.2

Entry	Solvent[c]	Temp/°C	RLi[d]	Time/h	Product Composition[e] % (263)	(264)	(265)	(266)
1	D	-78	X (1:1)	½	69	17	13	1
2	A	-78	X (1.1)	½	55	33	8	4
3	D	-78, 0	X (1.1)	¼, ½	14	49	36	1
4	C	-78	X (1.1)	½	0	0	100	0
5[f]	A	-78, 0	X (1.1)	½, ½	13	61	19	7
6	B	-78	X (1.1)	1½	0	0	100	0
7[g]	A	-78	X (1.1)	½	44	0	56	0
8	A	-78	Y (1.1)	½	31	65	4	0
9	A	-78	Y (1.5)	½	0	36	5	9
10	A	-78, 0	Y (1.1)	½, ½	37	53	10	0
11[h]	A	-78	Y (1.5)	½	13	40	3	44
12[i]	A	-78	Y (1.5)	½	1	64	5	30
13[j]	A	-78	Y (1.5)	½	15	81	4	0
14	A	-78	Y (1.5)	5	0	90	0	10
15[k]	A	-78, rt	Y (1.1)	½	36	57	7	0
16	A	-78,rt	Y(1.5)	½, 1	0	48	17	35
17[ℓ]	D	-78	Z (1.1)	1	92	0	4	4
18[m]	D	-78	Z (1.1)	½	100	0	0	0
19	D	-78	Z (1.1)	½	0	0	76	24
20	D	-78, 0	Z (1.1)	½, ½	50	10	40	0

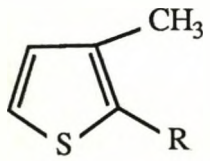
a 0.50 g of substrate was dissolved in 60 ml of solvent and all lithio-intermediates were quenched with 1.1 equivalents of TMSCl, unless otherwise stated.

b The material balance was essentially quantitative in all cases.

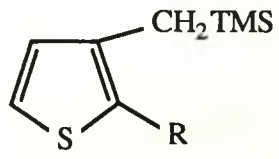
c A = hexane, B = dimethoxyethane (DME), C = tetrahydrofuran (thf), D = diethylether (Et_2O).

d X = ^{n}BuLi, Y = ^{s}BuLi, Z = LDA (lithium diisopropylamide). The figures in parentheses refer to the number of equivalents of organolithium reagent with respect to substrate.

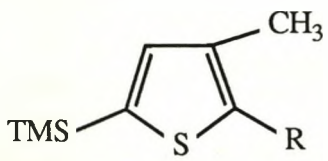
e



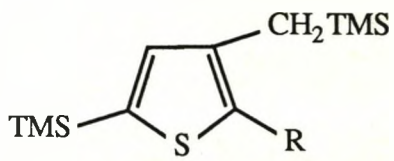
(263)



(264)



(265)



(266)

Estimated by nmr analysis

f Following the addition of the electrophile the reaction mixture was stirred at 0°C for one hour, before allowing it to attain room temperature.

g TMEDA equimolar with RLi present.

h 2.0 g of substrate dissolved in 60 ml of solvent.

i 0.50g of substrate dissolved in 15 ml of solvent.

j 0.50g of substrate dissolved in 120 ml of solvent.

k The reaction mixture was warmed quickly to room temperature and quenched immediately.

ℓ Inverse addition.

m Inverse addition. 1 ml CH_3OH added after half an hour at -78°C.

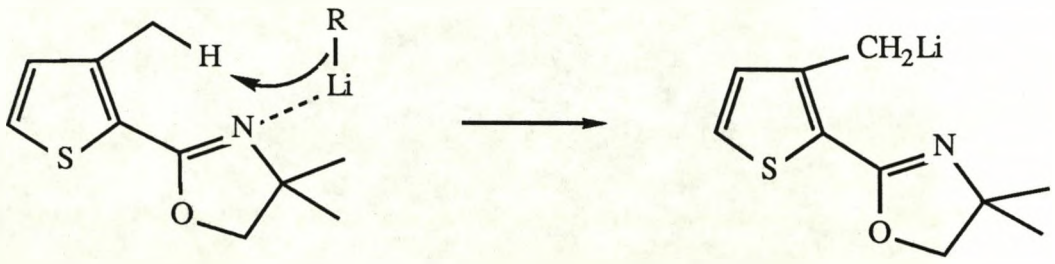
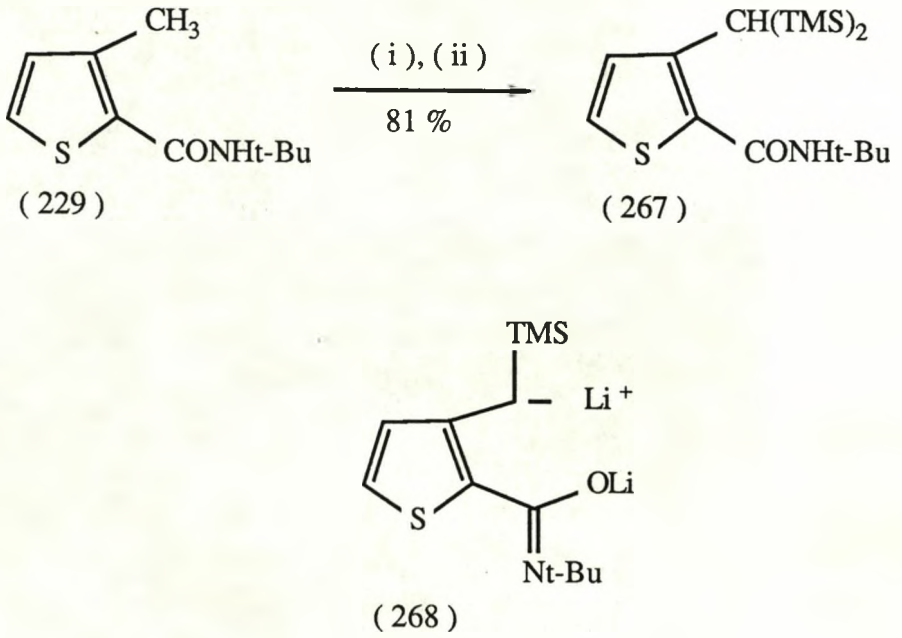


FIGURE 4.4

methylsilyl chloride. The disilylated compound (267) is formed in high yield, presumably via dianion (268) (Scheme 4.6).

The proportion of disilylated material (266) would appear to be sensitive to substrate (263) concentration (entries 11, 12 and 13). An increase in substrate concentration gives rise to increased amounts of disilylated material. Decrease in the substrate concentration (entry 13) has the effect of removing all traces of disilylated material but at the expense of a reduced level of lithiation (probably associated with the difficulties in avoiding traces of moisture in such a large volume of solvent). Such a high dilution procedure would be impractical on a multigram scale. In general, LDA gives low levels of lithiation (entries 17 - 20) but shows some degree of α-selectivity (entry 19). Although untried, higher levels of lithiation (with α-selectivity) are anticipated for reactions performed in thf or DME.

Additional information is gleaned from the deuteriation study carried out on the same compound (263) (Table 4.3). For quantitative, regioselective deuteriation at the methyl group, two



(229) (267) (268)

Reagents: (i) ^{s}BuLi, thf, -78°C, ½ h; (ii) TMSCl

SCHEME 4.6

equivalents of ^{s}BuLi are required with hexane as solvent (entry 2). Reduction of the quantity of ^{s}BuLi and the addition of TMEDA has a deleterious effect on the selectivity for lithiation into the methyl group (entry 3). The same seems to be the case when diethyl ether is substituted for hexane (entry 4).

In both cases, competition between the oxazoline moiety and the solvent or additive for coordination/complexation with the organolithium reagent will be in operation and, as a result, a shift away from a coordination-only mechanism occurs. Consequently C5-deuteriated material appears in the product. It is interesting to note the result of the experiment carried out in the mixed solvent system (entry 5). Only α-deuteriated material is recovered, suggesting that extensive deoligomerisation of the organolithium reagent by DME occurs, once again resulting in a shift away from a coordination-only mechanism.

TABLE 4.3

Entry	Solvent[a]	RLi[a]	Add-itives	Electro-phile	Product composition derived from Methyl Lithia-tion	from C5 Lith-iation	Yield %
1	A	Y (1.5)	-	CH_3OD	88	0	92
2	A	Y (2.0)	-	CH_3OD	100	0	92
3	A	Y (1.1)	TMEDA (1.1)	CH_3OD	93	17	100
4	D	Y (1.1)	-	CH_3OD	93	17	100
5[b]	A-B	Y (1.1)	-	D_2O	0	75	92

a The conventions of Table 4.2 apply.

b 75% Hexane, 25% DME (v/v).

The following conclusions may be drawn from the silylation and deuteriation studies:

1 Conditions for regioselective α-lithiation have been established i.e., ^{n}BuLi, thf, or DME, -78°C, 1½ h.

2 Hexane is the solvent of choice for regioselective lithiation into the methyl group.

3 ^{s}BuLi in the organolithium reagent of choice for ortho-lithiation into the methyl group.

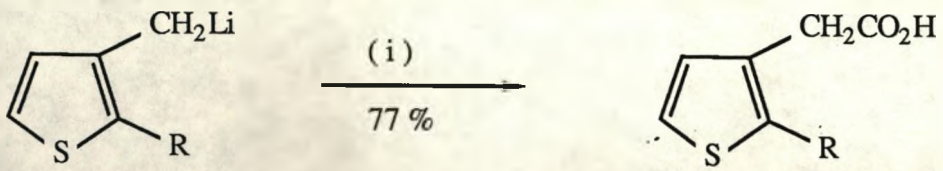
4 The effect of additives capable of complexation with the organolithium reagent or the use of coordinating solvents such as thf, lead to an increase in the proportion of α-lithiated material.

5 The tolerance of TMSCl to organolithium reagents at low temperatures accounts for the formation of disilylated material in several cases.

6 The factors controlling the regioselectivity of lithiation are finely balanced.

Reaction of the lithio-intermediate (269) generated under the conditions of entry 9, Table 4.2, with a range of electrophiles (e.g., MeI, Me_2S_2, I_2, $PhCH_2Br$) does not deliver synthetically useful yields of the corresponding products. In all cases a significant amount of starting material (ca. 20 - 50%) is detected in ^1H nmr spectrum of the crude product mixture. This suggests that the anion exists in an aggregated state and consequently reacts inefficiently with all but the most reactive of electrophiles (e.g., MeOD, TMSCl). This observation is in line with that made by Carpenter on the reaction of lithio-intermediate (262), generated in hexane, with a wide range of electrophiles.[132]

Atypically, a good yield of carboxylic acid (270) is obtained on reaction of lithio-intermediate (269) with carbon dioxide (Scheme 4.7).



(269) (270)

R = Oxazoline

Reagents: (i) CO_2, Et_2O

SCHEME 4.7

The problems of aggregation and solubility which are responsible for the poor reactivity of lithio-intermediate (269) are difficult to overcome.

With a view to preparing compounds of the form (271), the approach outlined in Figure 4.5 was investigated.

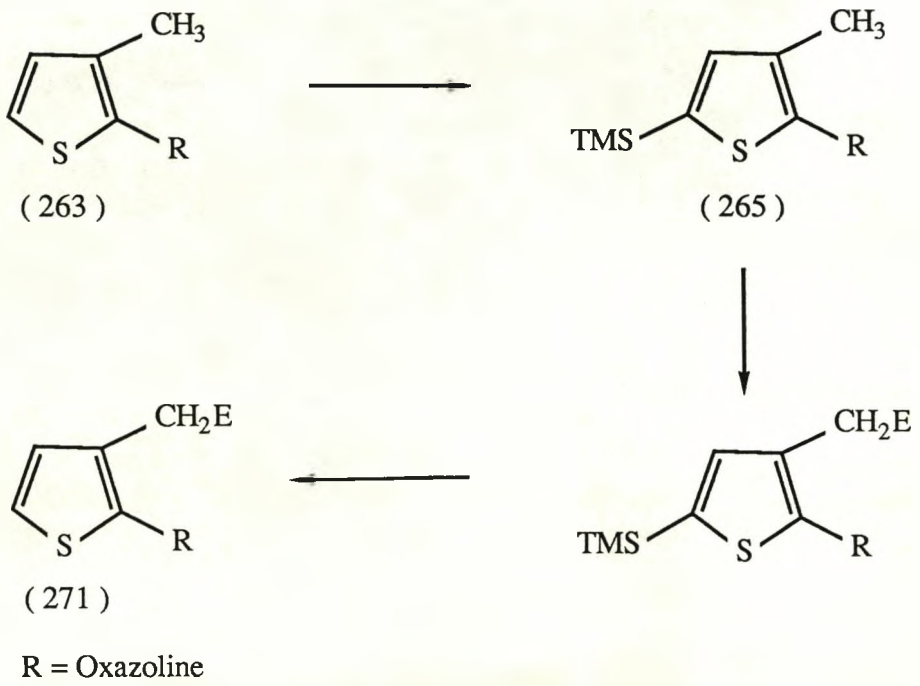
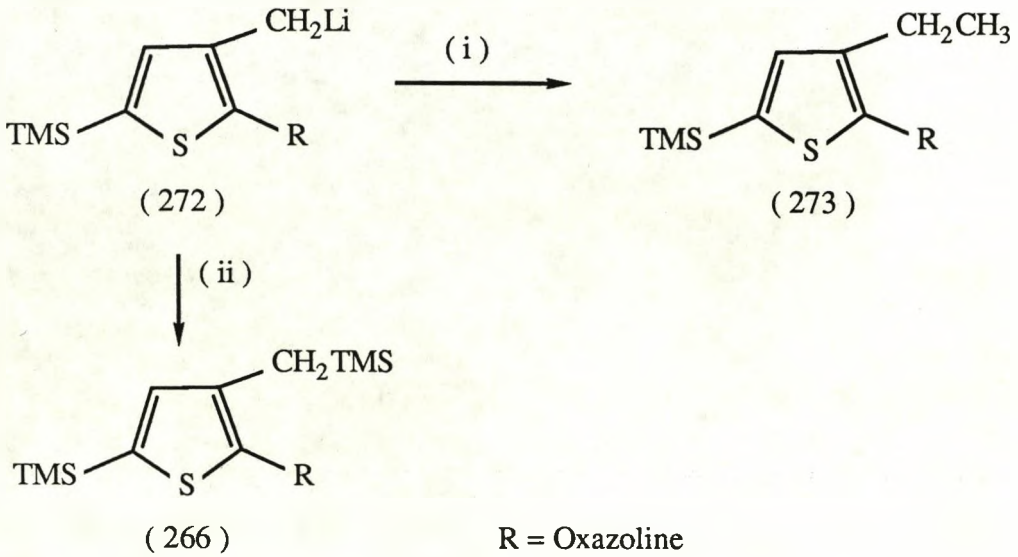


FIGURE 4.5

Protection of the C5 proton using a silicon blocking group allows the use of a coordinating solvent such as diethyl ether. Generation of the lithio-intermediate and reaction with electrophiles, followed by deprotection of the C5-position could, in theory, provide a route to compounds of the form (271). Generation of the C5-lithio-intermediate of thiophene (263) (entry 6, Table 4.2) and reactions with TMSCl gives a 95% yield of silylated thiophene (265). This is quantitatively ortho-lithiated using ^{s}BuLi in diethyl ether as evinced by MeOD quench and ^{1}H nmr analysis.

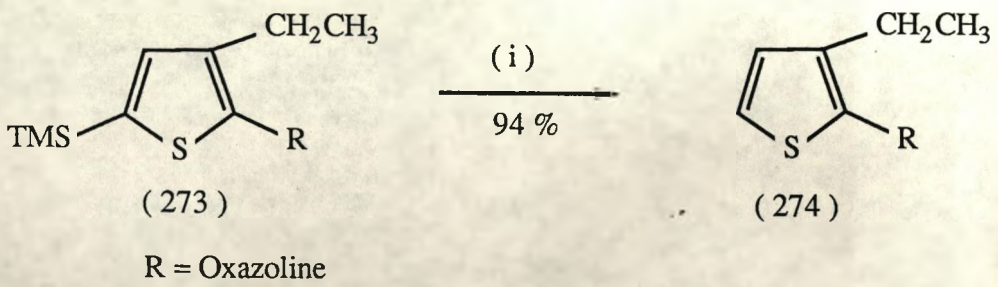
Reaction of lithio-intermediate (272) with methyl iodide and trimethylsilyl chloride gives trisubstituted thiophenes (273) and (266) in 67% and 91% yields respectively (Scheme 4.8).



Reagents: (i) MeI; (ii) TMSCl

SCHEME 4.8

Compound (273) is readily desilylated under mild conditions (Scheme 4.9).

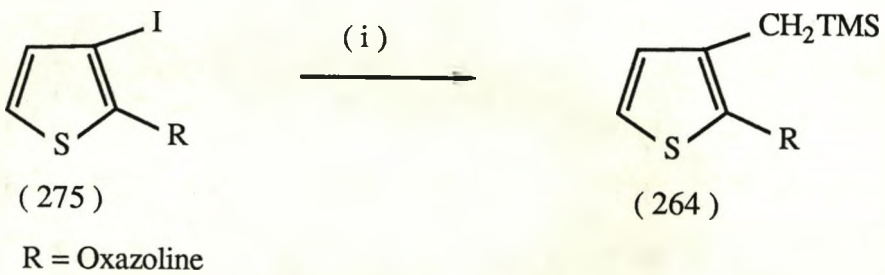


Reagents: (i) CsF, CH_3CN, 25°C, 14 h

SCHEME 4.9

The original objective of preparing 2,3-disubstituted thiophene (264) exclusively, by a directed lithiation route has proved unobtainable.

In the light of recently reported results, and with time permitting, the approach outlined in Scheme 4.10 could have been examined. The iodo-substituted thiophene (275) can be prepared in good yield according to the previously cited methodology of Chadwick and Carpenter. Literature precedent suggests that a nickel-catalysed cross-coupling reaction with trimethylsilylmethyl magnesium chloride would yield the desired compound (264).[124]



(275)

R = Oxazoline

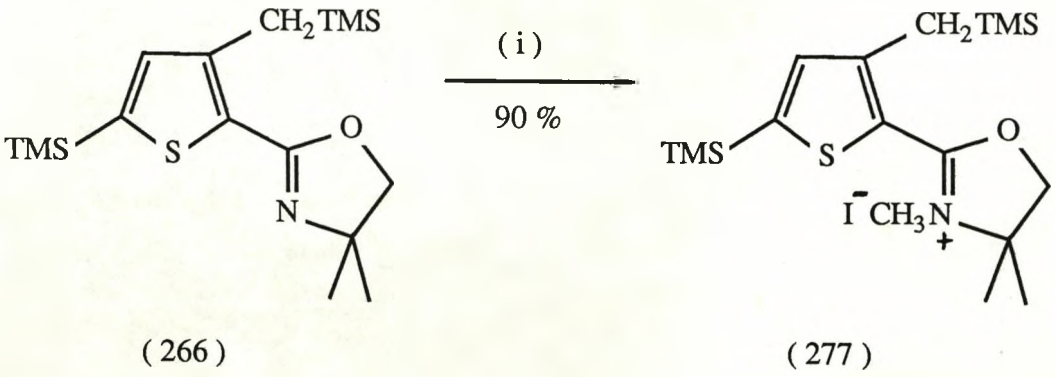
(264)

Reagents: (i) $TMSCH_2MgCl$, $Ni(PPh_3)_2Cl_2$, Et_2O

SCHEME 4.10

However, it was appreciated that quaternisation of disilylated thiophene (266) would furnish a potential o-xylylene precursor. Alkylation of (266) with methyl iodide gives an excellent yield of oxazolinium salt (276) (Scheme 4.11). Trisubstituted thiophene (266) can also be formed in a single step process on silylation of dianion (277) (Scheme 4.12).

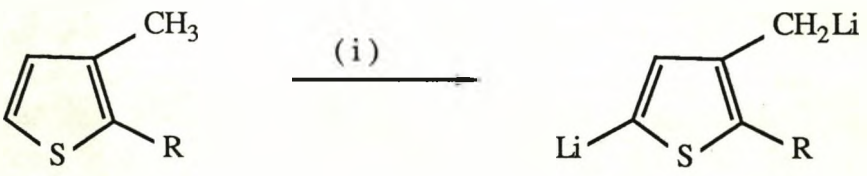
A second o-xylylene precursor has been prepared from disubstituted thiophene (263) (Scheme 4.13). Generation of the C5-lithio



(266) (277)

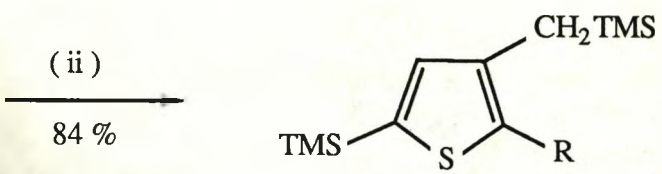
Reagents: (i) MeI, CH_3CN, reflux, 24 h

SCHEME 4.11



(263) (277)

R = Oxazoline

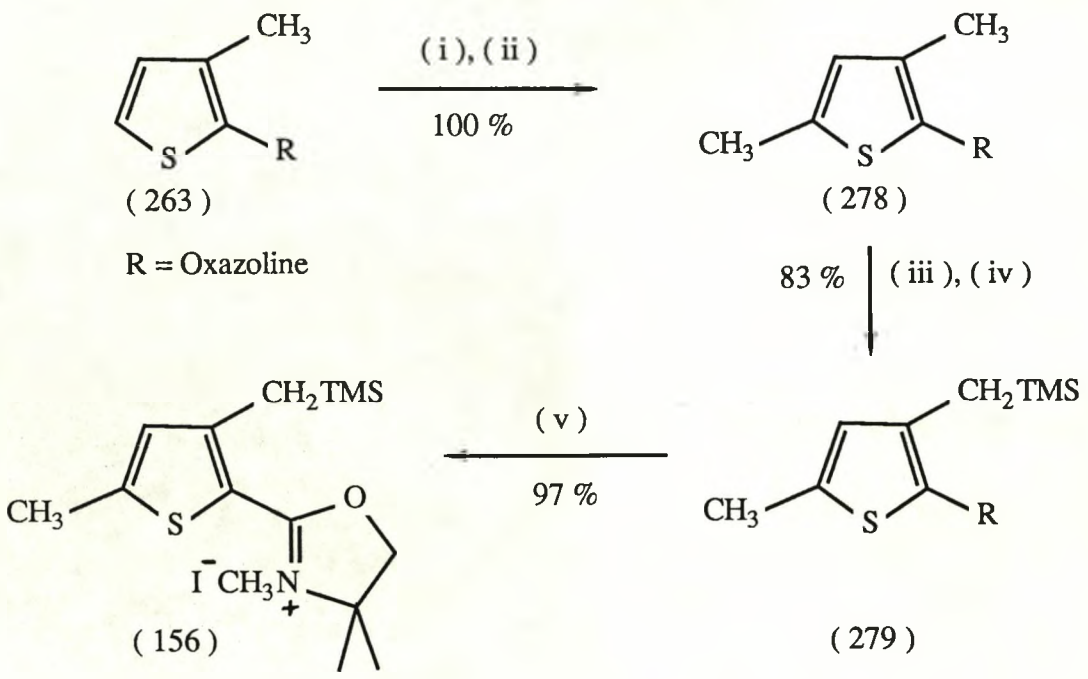


(266)

Reagents: (i) ^{s}BuLi, thf, -20°C, ½ h; (ii) TMSCl

SCHEME 4.12

intermediate of compound (263) and addition of methyl iodide gives a quantitative yield of dimethylated thiophene (278). Generation of the 3-lithiomethyl derivative of (278) and reaction with trimethylsilylchloride gives a high yield of the silylated compound (279). Quaternisation with methyl iodide gives the yellow oxazolinium salt in



Reagents: (i) ^{n}BuLi, DME, -78°C, 1 h; (ii) MeI; (iii) ^{s}BuLi, Et_2O or thf, -78°C, ½ h, then warm quickly to r.t.; (iv) TMSCl; (v) MeI, CH_3CN, reflux 24 h

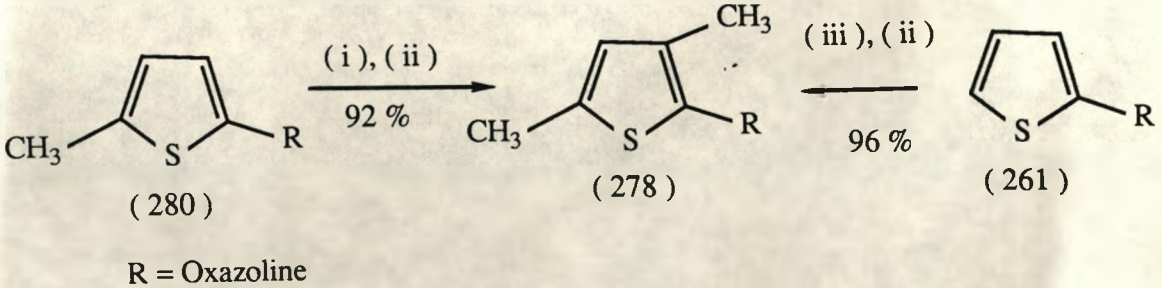
SCHEME 4.13

almost quantitative yield. Salt (156) is prepared in four steps from monosubstituted thiophene (261) in an overall 75% yield.

An interesting point concerns the dimethylated compound (278). In $CDCl_3$ the thiophene methyl resonances are virtually coincident in the ^{1}H nmr spectrum. In D_6 benzene they are 0.5 ppm apart. It was important to establish that the 3-lithiomethyl species is formed during metallation and not the 5-lithiomethyl species. It is assumed that the 3-methyl substitutent is to lower field with respect to the 5-methyl substituent, as are the ring proton signals for the mono-substituted thiophene (261). Addition of the lanthanide shift reagent $Eu(fod)_3$ to a $CDCl_3$ solution of compound (278) results in a

downfield shift of all signals, with a difference of 0.20 ppm between the two methyl groups. Lithiation and deuteriation under conditions subsequently used for silylation, result in the lower field signal becoming a triplet (integral 2H) in the ^{1}H nmr spectrum. Assuming coordination of the lanthanide reagent to the oxazoline oxygen or nitrogen atom, it is to be expected that the greater downfield shift will be observed for the 3-methyl group as this is in closer proximity to the oxazoline ring. Therefore, on the basis of the deuteriation experiments, the 3-lithiomethyl derivative is formed on metallation using the conditions given in Scheme 4.13. This is also consonant with the known properties of the oxazoline ring as a metallation directing group.

Dimethylated thiophene (278) can also be prepared from thienyl-oxazolines (261) and (280) (Scheme 4.14). Dilithiation of thiophene (261) is achieved using three equivalents of ^{s}BuLi in thf at -20°C, and ortho-lithiation of 2,5-disubstituted thiophene (280) is accomplished with ^{n}BuLi in diethyl ether at -78°C. Anions are quenched with excess methyl iodide to give tri-substituted thiophene (278) in excellent yields. Inclusion of the dilithio-approach to compound (278) shortens the synthesis of salt (156) to three steps and the overall yield is increased slightly to 77%.



(280)

(278)

(261)

R = Oxazoline

Reagents: (i) ^{n}BuLi, Et_2O, -78°C, ¼ h, then 0°C, ½ h;

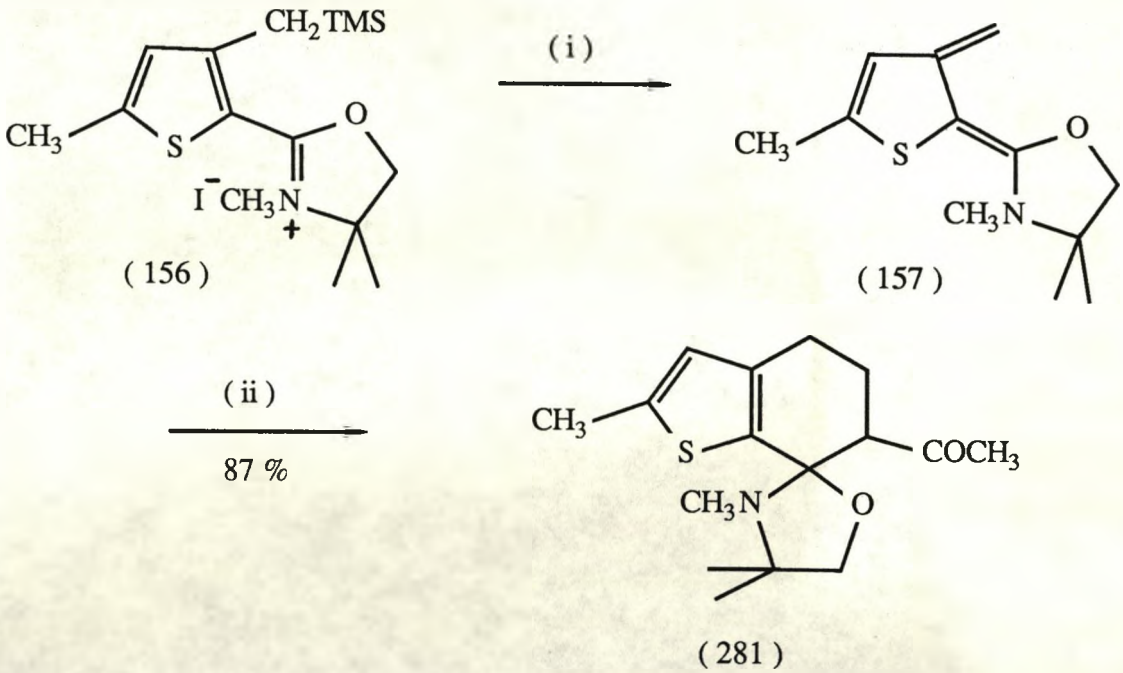
(ii) MeI; (iii) ^{s}BuLi, thf, -20°C, ½ h

SCHEME 4.14

4.3 FLUORIDE ION-INDUCED GENERATION OF AN α-SUBSTITUTED o-XYLYLENE

Using the procedure reported by Ito[53] (Scheme 4.1), α-substituted o-xylylene (157) is generated under mild conditions, as evinced by interception with electron-deficient dienophiles.

When o-xylylene (157) is generated in the presence of MVK, an excellent yield of cycloadduct (281) is obtained (Scheme 4.15). The



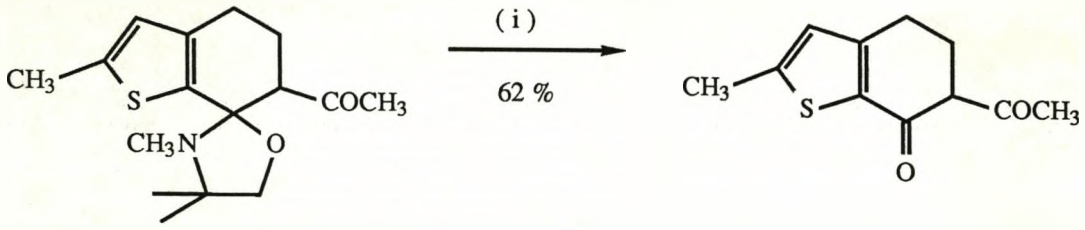
Reagents: (i) CsF, CH_3CN, 0°C; (ii) MVK

SCHEME 4.15

^1H nmr, ir, and mass spectra are clearly supportive of adduct (281), which capillary gc shows as a 1:1 mixture of diastereomers (assuming a

single regioisomer). However, adduct (281) is isolated as a viscous gum following work-up and is not amenable to chromatography or distillation.

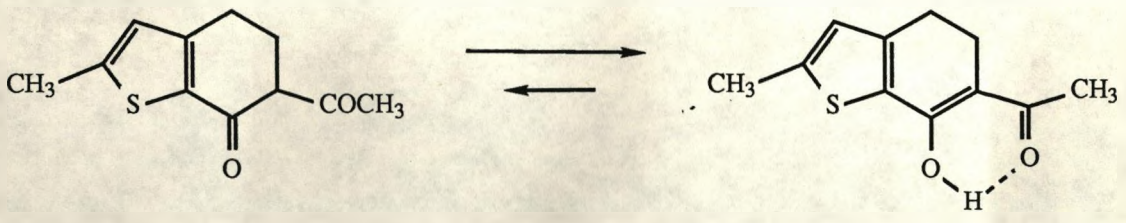
To prove a single regioisomer had been produced, hydrolysis of the oxazolidine ring was carried out to give β-diketone (282) (Scheme 4.16). ^{1}H Nmr and ir spectra indicate that β-diketone (282) is heavily enolised, the hydroxyl proton resonating at δ 15.68 (Figure 4.6).



(281) (282)

Reagents: (i) HCl aq. (5% v/v), 25°C, 24 h

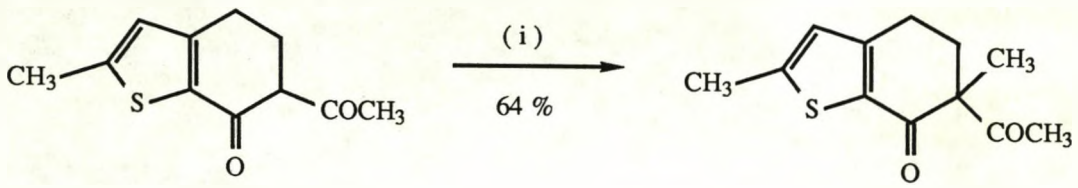
SCHEME 4.16



(282)

FIGURE 4.6

Due to keto-enol tautomerism, the ^{1}H nmr spectrum of (282) is somewhat complicated. To simplify matters, and as further structural proof, the β-diketone was alkylated at the enolisable position to give compound (283) (Scheme 4.17). Compound (283) has been characterised by ^{1}H nmr, ^{13}C nmr, ir., and ms analyses.



(282) (283)

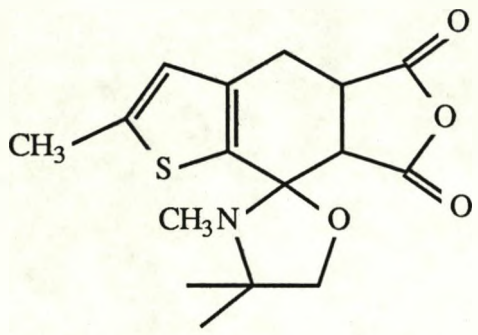
Reagents: (i) K_2CO_3, MeI, acetone, reflux, 20 h

SCHEME 4.17

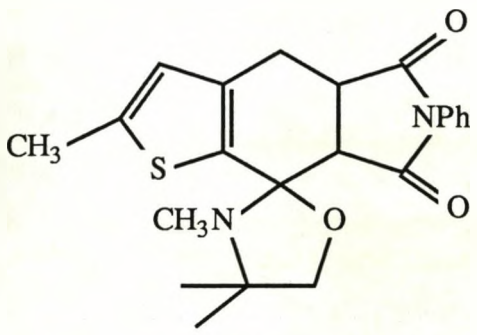
No products other than those described above have been detected from the cycloaddition, hydrolytic, and alkylation reactions. Thus, it is concluded that the reaction between o-xylylene (157) and MVK is completely regioselective. (α-Alkoxy-o-xylylenes are known to add dienophiles by endo addition and give 1,2-disubstituted adducts with unsymmetrical dienophiles.[53,76])

Cycloadducts have also been formed on reaction of o-xylylene (157) with several other electron-deficient dienophiles (in each case the reaction conditions are as for Scheme 4.15). Reaction of o-xylylene (157) with maleic anhydride and N-phenylmaleimide gives adducts (284) and (285) in 77% and 74% yields respectively. The stereochemical outcome of these reactions is predicted by the

"cis-endo" rule of the Diels-Alder reaction[72] and spectroscopic data does not suggest otherwise in these cases. Both adducts are isolated as fine powdery solids and satisfactory crystals for X-ray diffraction studies could not be obtained.



(284)



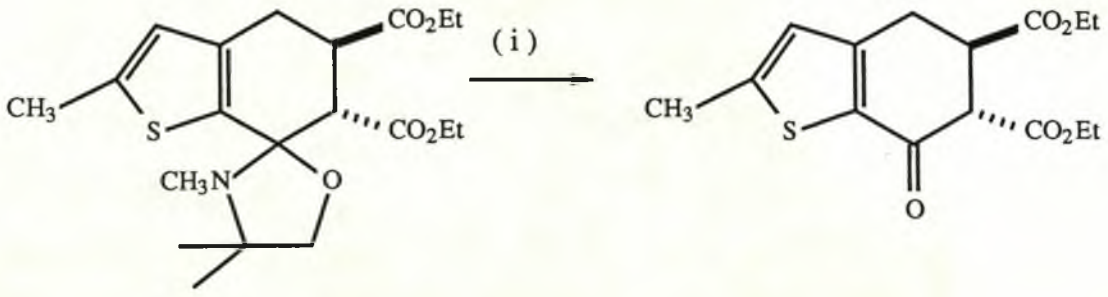
(285)

Initial spectroscopic examination of the presumed product (286) (85%) formed on reaction of o-xylylene (157) with diethylfumarate supports adduct formation. Interestingly though, three singlets, ratio 1:1:2, are present in the aromatic region of the ^{1}H nmr spectrum, possibly indicative of a number of diastereomers.

Other regions of the spectrum are also unexpectedly complicated. Capillary gc shows only two products, one of which is residual diethyl fumarate.

Hydrolytic cleavage of the oxazolidine ring gives β-ketoester (287) (Scheme 4.18). Two singlets (ratio 1:2) are now observable in the aromatic region of the ^{1}H nmr spectrum and the ir spectrum shows considerable keto-enol tautomerism.

We are unable to state unambiguously that the stereochemistry of the dienophile is retained in the adduct (286). It is possible that

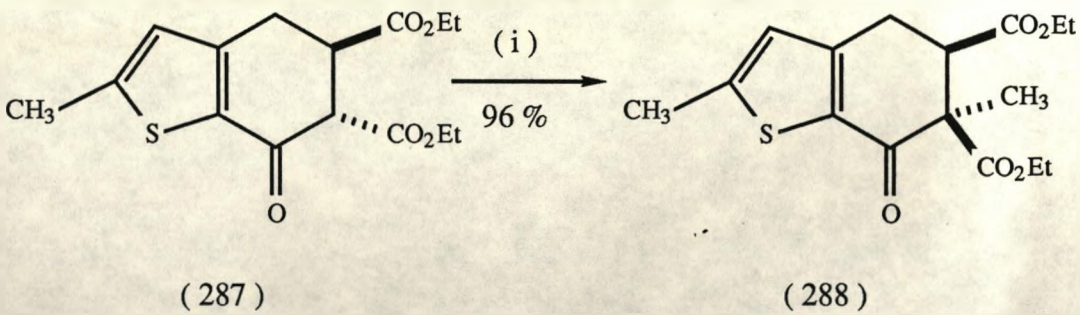


(286) (287)

Reagents: (i) HCl aq. (5%, v/v), 25°C, 24 h

SCHEME 4.18

a mixture of cis and trans products (with respect to the ester groups) is produced. This gives rise to speculation concerning the mechanism of the cycloaddition (vide infra). To provide unambiguous proof of adduct formation, β-ketoester (287) was alkylated at the enolisable (most acidic) position to give compound (288) (Scheme 4.19).

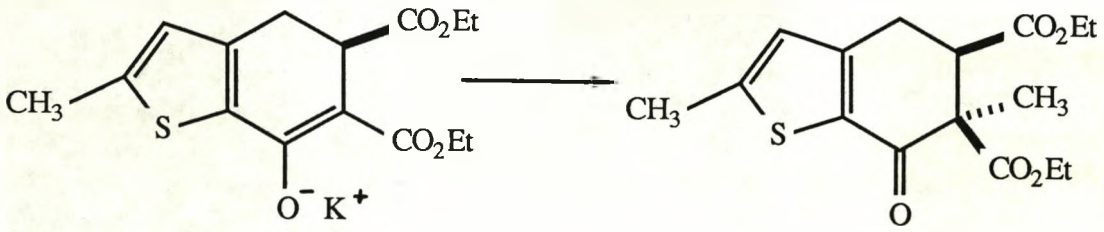


(287) (288)

Reagents: (i) K_2CO_3, MeI, acetone, reflux, 20 h

SCHEME 4.19

Regardless of the original stereochemistry of the ester groups in adduct (286), they would be expected to have a cis relationship in compound (287) on the basis of steric approach control in the alkylation of enolate (289) (Figure 4.7).



(289) (288)

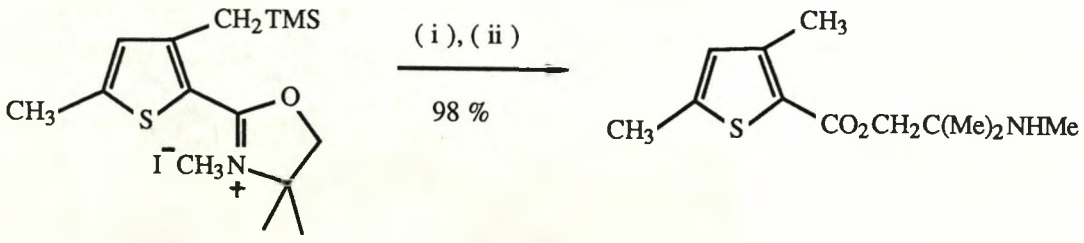
FIGURE 4.7

Reaction of o-xylylene (157) with diethyl maleate and ethyl acrylate gives products in which initial spectroscopic examination is supportive of adduct formation.

However, attempts to follow the hydrolytic and alkylation procedures described earlier for similar compounds result in multi-component mixtures. Alternative manipulative procedures (e.g., reductions) have not been attempted.

o-Xylylene (157) has also been generated in the presence of ethyl vinyl ether (an electron-rich olefin) and cyclohexene (an "unactivated" alkene). In neither case is adduct formation observed, only the ester (290) is isolated following aqueous work-up (Scheme 4.20).

As noted in Chapter 3 o-xylylene (145) fails to react with similar traps, dimerisation being the preferred reaction pathway. It



(156) (290)

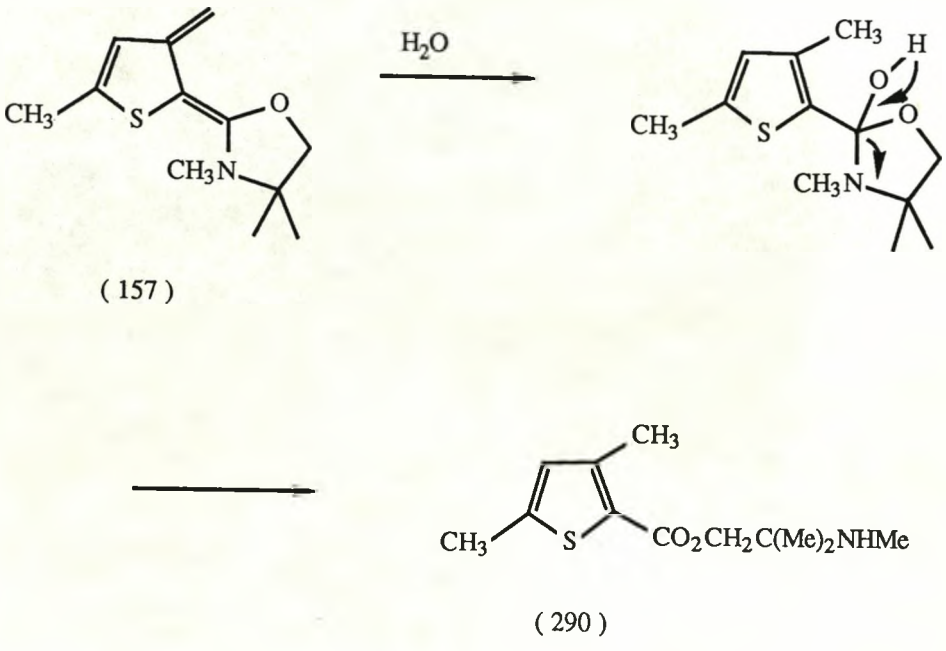
Reagents: (i) CsF, CH_3CN, 0°C;

(ii) ethyl vinyl ether or cyclohexene, Na_2CO_3 (aq.) or H_2O

SCHEME 4.20

is not surprising then that electron-rich o-xylylene (157) does not react with either of the aforementioned alkenes. This observation can be rationalised by Generalised Perturbation Molecular Orbital Theory[72] and is not unusual when considering reactivity between electron-rich dienes and electron-rich dienophiles. The formation of ester (290) can be explained by the addition of water to o-xylylene (157) on work-up although this remains unsubstantiated (Figure 4.8). Dimerisation could be disfavoured on steric grounds.

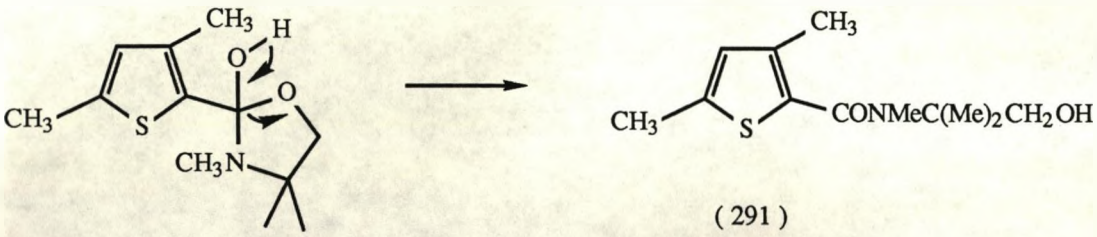
It is interesting to note that the ester (290) is formed rather than the amide (291) on opening of the oxazolidine ring (Figure 4.9). This judgement is based primarily upon ir spectroscopy, as the ^1H nmr spectra of ester (290) and amide (291) are expected to be very similar. The carbonyl stretching frequency appears at 1705 cm^{-1} which compares well with the value of 1710 cm^{-1} for methyl ester (292).



(157)

(290)

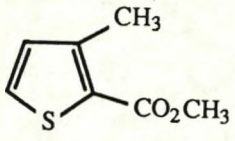
FIGURE 4.8



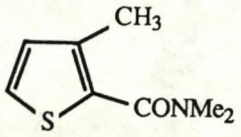
(291)

FIGURE 4.9

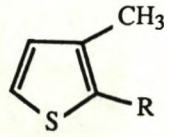
Amides (293) and (294) have absorbtions at 1620 cm^{-1} and 1615 cm^{-1} respectively. There is no O-H stretch in the ir spectrum of (290) which is strong in amide (294).



(292)

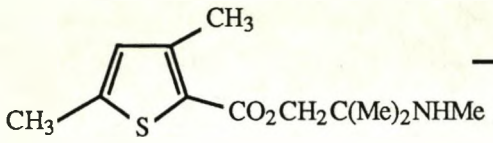


(293)



R = $CONHC(Me)_2CH_2OH$

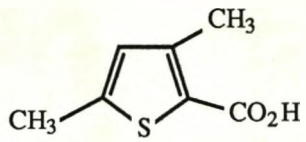
(294)



(290)

(i), (ii)

89 %



(295)

Reagents: (i) KOH aq. (10% w/w), EtOH, reflux, 24 h

SCHEME 4.21

Ester (290) is readily hydrolysed to 3,5-dimethylthiophene-2-carboxylic acid (295) (Scheme 4.21). Acid (295) is spectroscopically identical to a sample prepared by an independent route (Scheme 4.22).†

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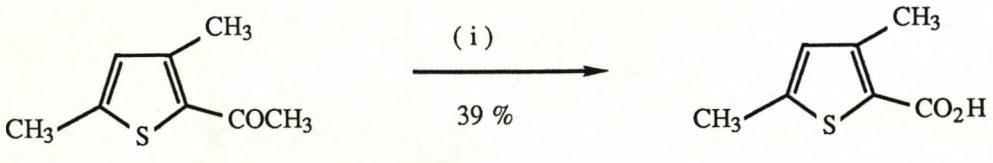
† Synthetic Chemicals are thanked for a gift of 2-acetyl-3,5-dimethylthiophene.



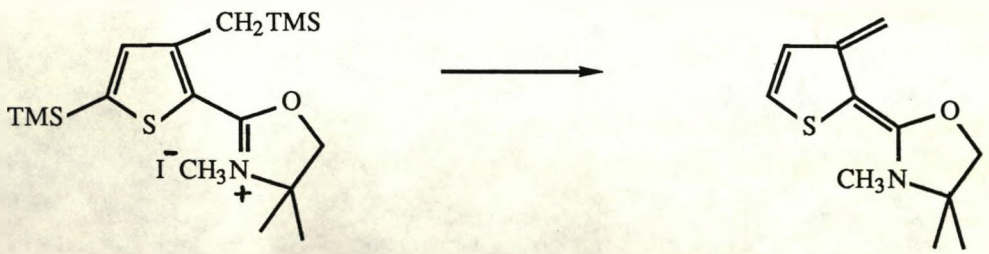
(295)

Reagents: (i) NaOCl, dioxan, reflux, 24 h

SCHEME 4.22

When o-xylylene (157) is generated in the absence of trapping agent, ester (291) is the only isolable product.

Oxazolinium salt (276) has also been treated with fluoride ion in anticipation of generating o-xylylene (260) (Figure 4.10). Prelim-



(276) (260)

FIGURE 4.10

inary studies have proved encouraging but further work is required before detailed discussion can be made.

4.4 MECHANISTIC CONSIDERATIONS

Although it has been established that o-xylylene (157) reacts with electron-deficient dienophiles in a regioselective manner to give adducts such as (281), the cycloaddition is not necessarily concerted in nature.

A stepwise process invoking zwitterionic intermediates (296) and (297) is a possibility (Figure 4.11). Although mechanistic studies

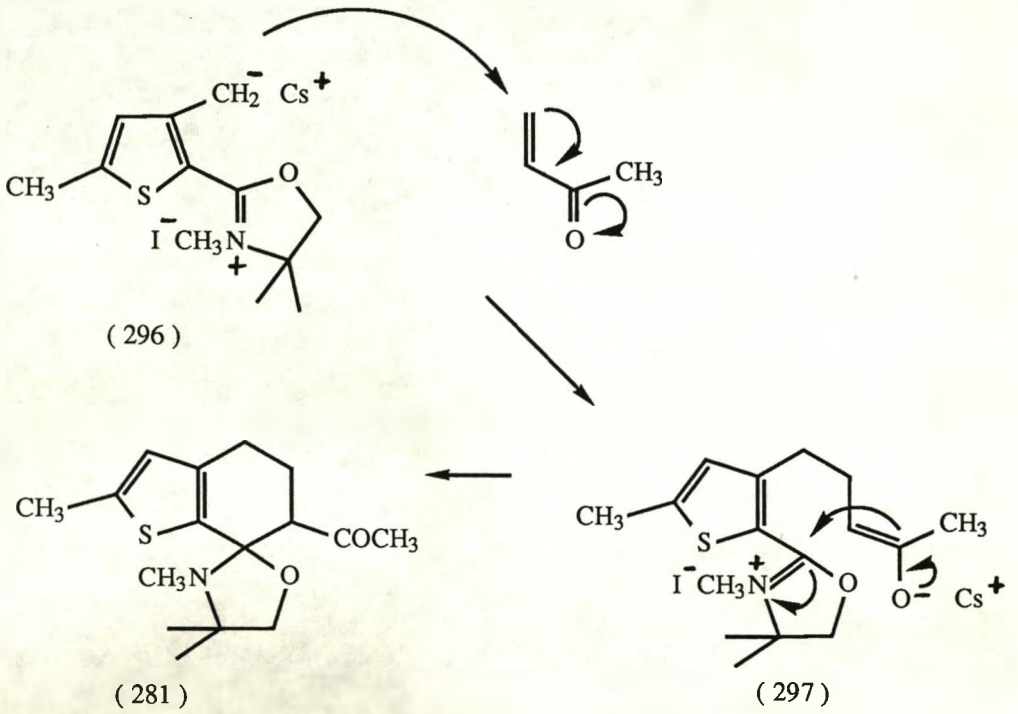


FIGURE 4.11

have not been performed to support or discount the zwitterionic pathway, the sequence of events outlined in Figure 4.11 seems unlikely. Zwitterion (296) is unlikely to undergo conjugate-1,4-addition to MVK. Rather, as in the case of lithio species (262), it is more likely to be protonated or undergo 1,2-addition to the carbonyl group.[132] Reaction pathways involving free-radical intermediates cannot be discounted either, but seem less likely than the proposed zwitterionic pathway in this particular case.

4.5 CONCLUSIONS

Regardless of the mechanistic pathway, the ability to engineer the regioselective cycloaddition of thiophene o-xylylene intermediates to dienophiles has been demonstrated. The methodology described in this Chapter can be viewed as a high yielding route to annelated thiophenes possessing a high degree of functionalisation. Provision for further synthetic manipulations on derived cycloadducts has also been demonstrated.

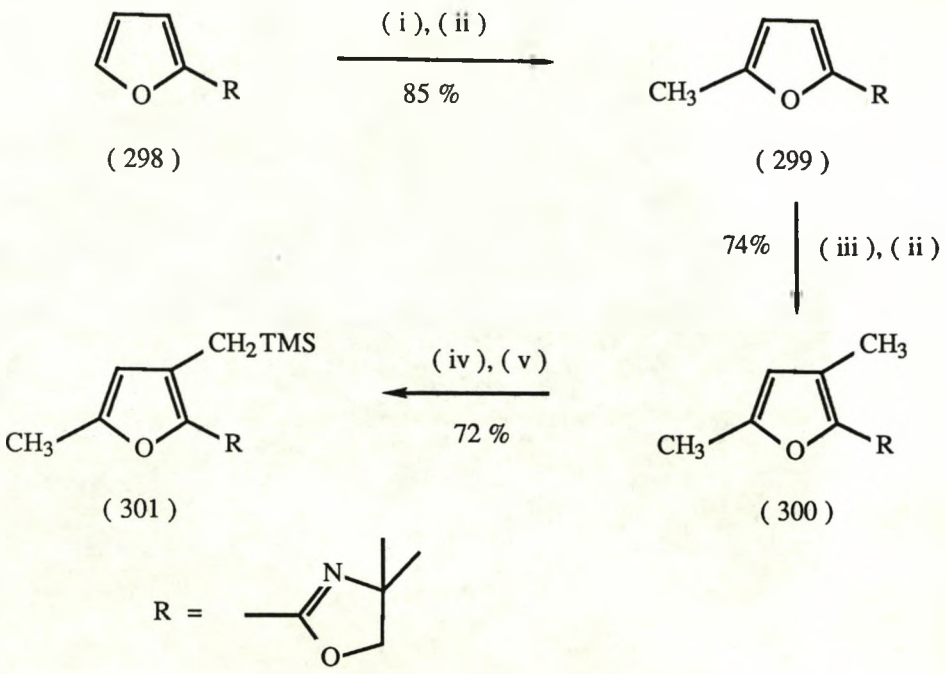
4.6 AN APPROACH TO A PRECURSOR OF A FURAN ANALOGUE OF o-XYLYLENE

The furan analogue of o-xylylene has been generated in the gas phase and trapped with dienophiles[6,7] (see Section 1.2.5). There do not appear to be any reports in the literature concerning the generation of furan o-xylylene intermediates in solution.

The oxazoline mediated approach to the synthesis of o-xylylene precursors has been applied to the furan ring system (Scheme 4.23). Furyl-oxazoline (298) is formed in 83% yield according to the method of Meyers.[175] The C5-lithiated intermediate is formed using LDA-TMEDA, this being quenched with methyl iodide to give a high yield of the 5-methyl derivative (299). The 3-lithio intermediate derived from this compound is formed with ^{n}BuLi and again quenched with methyl iodide to give the 3,5-dimethyl derivative (300) in good yield. Lithiation into the 3-methyl group is accomplished with ^{s}BuLi, subsequent silylation giving a high yield of compound (301).

Attempts to quaternise compound (301) with methyl iodide under a variety of conditions always give a gummy material, with evidence of desilylation in some cases.

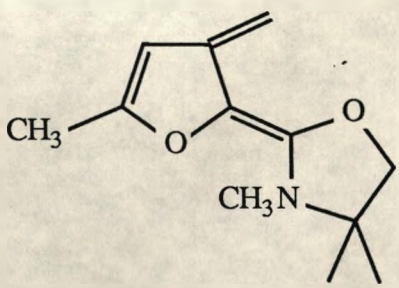
Further alkylation studies are required before a satisfactory investigation into o-xylylene generation can take place. However,



Reagents: (i) LDA, TMEDA, thf, -78°C, 1 h; (ii) MeI; (iii) ^{n}BuLi, thf, -78°C, ½ h; (iv) ^{s}BuLi, thf, -78°C, ½ h, then warm quickly to 25°C; (v) TMSCl

SCHEME 4.23

preliminary studies aimed at the generation of o-xylylene (302) conducted in these laboratories is encouraging, but will not be discussed here.[176]



(302)

CHAPTER 5

EXPERIMENTAL

Product purity was checked by thin layer chromatography (tlc) on Merck 10 x 2 cm aluminium-backed plates with an 0.2 mm layer of Kieselgel 60 F_{254}.

Flash column chromatography was carried out using Mackerey Nagel MN-Kieselgel 60, and dry flash column chromatography was carried out using Merck Kieselgel 60H.

Melting points (m.p.) were determined on a Köfler block and are uncorrected. Melting points are expressed in degrees Celcius (°C).

Microanalyses were performed in the University of Liverpool Microanalyses Laboratory.

^1H Nmr spectra were recorded, either on a Perkin Elmer R34 (220 MHz), Bruker WM250 (250 MHz), or a Jeol JMN-PMX60 (60 MHz) spectrometer. For signals other than singlets (s), doublets (d), doublet of doublets (dd), triplets (t), quartets (q) and multiplets (m), the number of lines is indicated.

Ir spectra were recorded on an A.E.I. MS902, VG Analytical 7070E, or a Mattson Alpha Centauri spectrometer.

Solvents were dried and distilled prior to use: diethyl ether (Et_2O), dimethoxy ethane (DME) and tetrahydrofuran (thf) from sodium-benzophenone; hexane, light petroleum (b.p., 60 - 80°C), acetonitrile, diisopropylamine and N,N,N',N'-tetramethylethylenediamine (TMEDA) from CaH_2, dimethylformamide (DMF) and hexamethylphosphoramide ("HEXAMETAPOL", HMPA) were distilled from CaH_2 under reduced pressure and were stored under an inert atmosphere over molecular sieves type 4 Å.

Ethyl acetate was distilled from calcium sulphate.

CsF was dried by heating (137°C) under vacuum (0.10 mmHg) for twenty-four hours.

Unless impractical, commercial Argon gas was used to provide an inert atmosphere in all reactions.

The concentrations of solutions of commercial ^{n}BuLi and ^{s}BuLi were determined by means of the double-titration method of Jones and Gilman.[177]

The temperature reported for certain reactions, e.g., -78°C, refers to the temperature of the cooling medium rather than the internal temperature of the reaction itself. We apologise for the inherent inaccuracies in the experimental details.

THIOPHENE-2,3-DICARBOXYLIC ACID (219)[132]

To thiophene-2-carboxylic acid (1.0 g, 7.80 mmol) in thf (60 ml) at -78°C was added ^{n}BuLi (17.20 mmol) and the mixture stirred at -78°C for half an hour. The solution was then poured onto a slurry of crushed CO_2 and thf and allowed to warm to room temperature. The solvent was removed *in vacuo* and the residues were suspended in water (50 ml), the solution acidified to pH 2 (conc. HCl) and extracted with ethyl acetate (3 x 50 ml). The extracts were dried ($MgSO_4$) and evaporated. Recrystallisation (ethyl acetate - light petroleum) gave the pure diacid (219) (1.28 g, 95%); m.p., 269 - 270°C (decomp.) (lit.,[132] 270 - 271°C); (Found: C, 41.83; H, 2.23. Calculated for $C_6H_4O_4S$, C, 41.87; H, 2.34%); δ (d_6-DMSO), 13.62 (2H, s, removed by D_2O shake, 2 x OH), 7.86 (1H, d, *J* 5.5 Hz, thiophene 5-H), 7.45 (1H, d, *J* 5.55 Hz, thiophene 4-H); *m/z* 171.9824 (calculated for $C_6H_4O_4S$, 171.9830).

2,3-bis(HYDROXYMETHYL)THIOPHENE (218)

Thiophene-2,3-dicarboxylic acid (0.50 g, 2.91 mmol) dissolved in thf (20 ml) was added dropwise to $LiAlH_4$ (0.33 g, 8.68 mmol) suspended

in thf (30 ml). The mixture was then heated under reflux for twenty-four hours. After cooling, ethyl acetate (ca. 20 ml) was added dropwise until no further effervescence was observed. Water (ca. 10 ml) was added, and the slurry was filtered under suction, the residues being repeatedly washed with ethyl acetate and water (ca. 50 ml of a 1:1 mixture). The filtrate was evaporated under vacuum and the residue taken up into ethyl acetate (100 ml) and water (10 ml). After separation, the organic layer was washed with water (2 x 10 ml) and brine (1 x 10 ml). The organic layer was then dried ($MgSO_4$) and evaporated to give the crude diol (218) (0.37 g, 88%) as a viscous, colourless, opaque liquid which decomposes at 170°C at 0.30 mmHg on attempted distillation; δ ($CDCl_3$), 7.09 (1H, d, J 5.0 Hz, thiophene 5-H), 6.88 (1H, d, J 5.0 Hz, thiophene 4-H), 4.78 (2H, br., 2 x O-H), 4.52 (2H, s, $-CH_2-O$), 4.38 (2H, s, $-CH_2-O$); $\nu_{max.}$ (film), 3300, 2900, 2850, 1430, 990 cm^{-1}; m/z 144.0244 (M^+, 30%, calculated for $C_6H_6O_2S$, 144.0245), 126 (100), 113 (31), 97 (78) and 85 (42).

2,3-bis(ACETOXYMETHYL)THIOPHENE (220)

To 2,3-bis(hydroxymethyl)thiophene (0.20 g, 1.39 mmol) dissolved in pyridine (2 ml) was added acetic anhydride (5.56 mmol). The solution was stirred at room temperature fot twenty-four hours, after which, methanol (ca. 10 ml) was added and the reaction was left to stir for a further sixteen hours. Solvents were removed in vacuo and then ethyl acetate (100 ml) was added to the residue. The solution was washed with dilute aqueous HCl (5% v/v, 2 x 15 ml) and water (1 x 15 ml). The organic layer was then dried ($MgSO_4$) and evaporated. Distillation gave the pure diacetate (220) (0.17 g, 54%) as a colourless liquid, b.p., 160°C at 0.50 mmHg; (Found: C, 52.81; H, 5.39.

$C_{10}H_{12}O_4S$ requires, C, 52.63; H, 5.30%); δ ($CDCl_3$), 7.26 (1H, d, J 5.12 Hz, thiophene 5-H), 7.02 (1H, d, J 5.12 Hz, thiophene 4-H), 5.29 (2H, s, $-CH_2-O-$), 5.12 (2H, s, $-CH_2-O-$), 2.04 (6H, s, 2 x CH_3); $\nu_{max.}$ (film), 3055, 2930, 1740, 1602, 1445, 1380, 1245, 1025, 965 and 700 cm^{-1}; m/z 228.0459 (M^+, 1%, $C_{10}H_{12}O_4S$ requires 228.0456), 168 (22), 126 (100) and 97 (13).

2,3-bis(BROMOMETHYL)THIOPHENE (155)[167]

To 2,3-bis(hydroxymethyl)thiophene (0.60 g, 4.17 mmol) dissolved in diethyl ether (10 ml) was added dropwise, a solution of PBr_3 (12.0 mmol) in diethyl ether (20 ml). The solution was stirred at room temperature for twenty-two hours, after which it was poured onto crushed ice (ca. 30 g). The layers were separated whilst still cold and the aqueous phase was extracted with diethyl ether (2 x 50 ml). The combined ethereal extracts were washed with brine and dried ($MgSO_4$). Solvent was removed in vacuo leaving a dark, oily residue which solidified yielding a tan solid (155) (0.95 g, 84%); δ ($CDCl_3$), 7.23 (1H, d, J 5.04 Hz, thiophene 5-H), 7.00 (1H, d, J 5.04 Hz, thiophene 4-H), 4.73 (2H, s, CH_2-Br), 4.52 (2H, s, CH_2-Br); m/z 269.8534 (M^+, 8% (calculated for $C_6H_6{}^{79}Br{}^{81}Br$ 269.8536), 191 (94), 189 (94), 169 (24) and 110 (100).

IODIDE ION-INDUCED GENERATION OF o-XYLYLENE (145) : REACTION WITH N-PHENYLMALEIMIDE; ADDUCT (222)

A solution of 2,3-bis(bromomethyl)thiophene (0.60 g, 2.12 mmol) in DMF (15 ml) was added dropwise into a 50 ml round bottomed flask containing sodium iodide (3.33 g, 21.20 mmol), N-phenylmaleimide (0.42 g, 2.43 mmol) and DMF (15 ml) at 80°C. The resulting mixture was stirred at 80°C for five hours. The bulk of the DMF was removed in

vacuo and the residue was diluted with ethyl acetate (150 ml) and washed with sodium thiosulphate (2 x 20 ml), water (1 x 20 ml) and brine (1 x 20 ml). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo to give a pale yellow solid. Recrystallisation (ethyl acetate - light petroleum) gave the pure adduct (222) (0.36 g, 60%); m.p., 164 - 165°C (decomp). (Found: C, 67.56; H, 4.60; N, 4.75. $C_{16}H_{13}NO_2S$ requires C, 67.84; H, 4.63; N, 4.95%); δ ($CDCl_3$), 7.33 (3H, m, ortho and para-phenyl hydrogens), 7.05 (1H, d, J 4.90 Hz, thiophene 5-H), 6.98 (2H, br.d., meta-phenyl hydrogens), 6.84 (1H, d, J 4.90 Hz, thiophene 4-H), 3.48 - 3.26 (4H, m, 2 x $-CH_2-$), 2.90 (1H, dd, J 4.90 Hz, 14.7 Hz, -S-C-CH_2-CH-), 2.72 (1H, dd, J 4.90 Hz, 14.7 Hz, -S-C-C-CH_2-CH-); $\nu_{max.}$ (KBr), 1706, 1398, 1206 and 584 cm^{-1}; m/z 283.0662 (M^+, 80%, $C_{16}H_{13}NO_2S$ requires 283.0667), 135 (100) and 110 (23).

5- (AND 6-)ACETYL-4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE (223)

A solution of 2,3-bis(bromomethyl)thiophene (0.90 g, 3.33 mmol) in DMF (20 ml) was added dropwise into a 100 ml round bottomed flask containing sodium iodide (5.0 g, 33.30 mmol), MVK (2.77 ml, 33.30 mmol) and DMF (30 ml) at 80°C, and stirred for fourteen hours. The reaction was worked-up as for adduct (222). Following flash chromatography (ethyl acetate - light petroleum 3:7 as eluant), a mixture of regioisomeric adducts (223) (0.30 g, 50%) were isolated as a clear mobile liquid. (Found: C, 66.06; H, 6.87. $C_{10}H_{20}OS$ requires C, 66.65; H, 6.71%); δ ($CDCl_3$), 7.12 (1H, d, J 5.14 Hz, thiophene 5-H), 6.81 (1H, d, J 5.14 Hz, thiophene 4-H), 3.05 - 2.69 (6H, m), 2.27 (3H, s, CH_3), 1.89 - 1.69 (1H, m); $\nu_{max.}$ (film), 2912, 1725, 1712, 1442, 1162 and 862 cm^{-1}; m/z 180.0611 (M^+, 70%, $C_{10}H_{22}OS$ requires 180.0608), 165 (39), 137 (100), 110 (32) and 43 (53).

5- (AND 6-)CYANO-4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE (167)

A solution of 2,3-bis(bromomethyl)thiophene (0.80 g, 2.96 mmol) in DMF (20 ml) was added dropwise into a 100 ml round bottomed flask containing sodium iodide (4.44 g, 29.60 mmol), acrylonitrile (1.95 ml, 29.60 mmol) and DMF (20 ml) at 80°C, and was then stirred for fourteen hours. The reaction was worked-up and chromatographed as for adducts (223) to give adducts (167) (0.29 g, 60%) as a clear mobile liquid; δ ($CDCl_3$), 7.09 (1H, d, J 5.05 Hz, thiophene 5-H), 6.75 (1H, d, J 5.05 Hz, thiophene 4-H), 3.17 - 2.57 (4H, m), 2.24 - 1.18 (3H, m); ^{13}C δ ($CDCl_3$), 133.78, 130.52, 127.05, 126.73, 122.99, 122.85, 121.58, 121.32, 28.77, 28.16, 28.10, 26.48, 25.92, 25.66, 25.60, 25.10, 23.19, 22.69; $\nu_{max.}$ (film), 3100, 3065, 2925, 2845, 2230, 1440 and 710 cm^{-1}; m/z 163.0458 (M^+, 35%, C_9H_9NS requires 163.0456), 110 (100).

IODIDE ION-INDUCED DEBROMINATION OF bis-BROMIDE (155) IN THE ABSENCE OF TRAPPING AGENT

A solution of bis-bromide (155) (4.19 mmol) in DMF (20 ml) was added dropwise to a suspension of NaI (6.30 g, 41.90 mmol) in DMF (20 ml) at 70°C. The mixture was stirred at 70°C for twelve hours and worked-up as for adduct (222). The product was isolated as a black film coating the inside of the reaction vessel and was found to be soluble in CH_2Cl_2 and $CHCl_3$; δ ($CDCl_3$), 1.25 (2H) and 0.85 (1H). Further analysis was not attempted.

IODIDE ION-INDUCED DEBROMINATION OF bis-BROMIDE (155) IN THE PRESENCE OF MALEIC ANHYDRIDE, DIETHYL MALEATE, OR DIMETHYLACETYLENE DICARBOXYLATE

When the previously described debromination procedure is carried out in the presence of maleic anhydride (1.1 ≡), diethyl maleate (1.1

≡), or dimethylacetylene dicarboxylate (1.1 ≡), the product is identical to that described for the experiment conducted in the absence of dienophile.

IODIDE ION-INDUCED DEBROMINATION OF bis-BROMIDE (155) IN THE PRESENCE OF $Fe_2(CO)_9$

A solution of bis-bromide (1.30 g, 4.81 mmol) in DMF (10 ml) was added dropwise to a suspension of NaI (7.22 g, 48.10 mmol) and $Fe_2(CO)_9$ (1.75 g, 4.81 mmol) in DMF (25 ml) at 80°C. The mixture was stirred at 80°C for sixteen hours and worked-up as for adduct (222) to give an intractable tar. Identification and characterisation were not attempted.

N-t-BUTYLTHIOPHENE-2-CARBOXAMIDE (228)[132]

A mixture of thiophene-2-carboxylic (19.20 g, 0.15 mol) and thionyl chloride (35.70 g, 0.30 mol) were boiled under reflux for three hours. Excess of thionyl chloride was removed by distillation under reduced pressure, the residue taken up in CH_2Cl_2 (100 ml), and a solution of t-butylamine (21.95 g, 0.30 mol in CH_2Cl_2 (100 ml) was added with stirring, keeping the reaction temperature below 10°C.

The resulting solution was stirred at 25°C for twelve hours, washed with water (3 x 30 ml), and dried ($MgSO_4$). The combined washings were basified to pH 11 (KOH aq., 40% w/w) and extracted with CH_2Cl_2 (3 x 30 ml) and the extracts dried ($MgSO_4$). The combined organic solutions were evaporated under reduced pressure to give the crude product. Recrystallisation (ethyl acetate - light petroleum) gave the pure amide (228) (23.10 g, 84%) as a white solid, m.p., 144 - 145°C (lit.,[132] 144 - 145°C); δ ($CDCl_3$), 7.41 (2H, m, thiophene 3-H and 5-H), 7.06 (1H, m, thiophene 4-H), 5.82 (1H, br., NH), 1.46 (9H,

s, ^{t}Bu); $\nu_{max.}$ (KBr), 3320, 3050, 2950, 1615, 1530, 840 cm^{-1}; m/z 183 (M^{+}, 20%), 168 (25), 153 (17), 115 (100) and 83 (26).

3-METHYLTHIOPHENE-2-CARBONYL CHLORIDE (230)

3-Methylthiophene-2-carboxylic acid (20.0 g, 0.14 mol) was heated under reflux with thionyl chloride (ca. 50 ml) for four hours. Excess of thionyl chloride was removed in vacuo and the residue distilled under reduced pressure to give the pure acid chloride (231) (21.34 g, 94%) as a colourless liquid, b.p., 110°C at 122 mmHg; δ ($CDCl_3$), 7.52 (1H, d, J 5.05 Hz, thiophene 5-H), 6.99 (1H, d, J 5.05 Hz, thiophene 4-H), 2.52 (3H, s, CH_3); $\nu_{max.}$ (film), 3100, 1745, 1390, 1370, 1200 and 805 cm^{-1}; m/z 159.9759 (M^{+}, 8%, calculated for $C_6H_5{}^{35}ClOS$ 159.9752), 125 (100), 53 (23) and 45 (17).

N-METHYL-3-METHYLTHIOPHENE-2-CARBOXAMIDE (231)

3-Methylthiophene-2-carboxylic acid (20.0 g, 0.14 mol), and thionyl chloride (20.55 ml, 0.28 mol) were heated under reflux for eight hours. The excess of thionyl chloride was removed under reduced pressure and the crude acid chloride added dropwise to a solution of commercial aqueous $MeNH_2$ (0.14 mol) in dilute aqueous sodium hydroxide (10%, w/w, 75 ml); after addition of the acid chloride the mixture was stirred for a further twelve hours during which time a dark brown oil collected on the surface. This was extracted into ethyl acetate (150 ml) and washed with dilute aqueous HCl (5% v/v, 30 ml), water (2 x 30 ml) and brine (1 x 30 ml). The organic layer was dried ($MgSO_4$) and evaporaed to give the crude product as a dark brown oil. This was purified by bulb-to-bulb distillation to give amide (231) as a clear oil (17.75 g, 82%), b.p., 141°C at 0.15 mmHg. (Found: C, 53.97; H, 5.85; N, 9.09. Calculated

for C_7H_9ONS, C, 54.19; H, 5.85; N, 9.03%); δ ($CDCl_3$, 7.20 (1H, d, J 5.86 Hz, thiophene 5-H), 6.84 (1H, d, J 5.86 Hz, thiophene 4-H), 6.32 (1H, br., NH), 2.93 (1.5 H, s, NCH_3), 2.90 (1.5 H, s, NCH_3), 2.47 (3H, s, CH_3); $\nu_{max.}$ (film), 3295, 1630, 1540, 1405, 1255 and 720 cm^{-1}; m/z 155.0411 (M^+, 46%, calculated for C_7H_9ONS 155.0405), 125 (100), 53 (18) and 45 (12).

N-t-BUTYL-3-METHYLTHIOPHENE-2-CARBOXAMIDE (229)

^{t}Butylamine (17.55 g, 0.24 mol) was added dropwise to 3-methylthiophene-2-carbonyl chloride (20.0 g, 0.12 mol) dissolved in dichloromethane (50 ml) with the reaction temperature maintained below 10°C. When the amine had been added the mixture was stirred for sixteen hours at room temperature. The solution was then washed with water (2 x 50 ml) and separated. The aqueous washings were basified to pH 11 (KOH aq., 40% w/w) and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by dry flash chromatography (ethyl acetate - light petroleum, 1:20 as eluant) to give the pure amide N-t-butyl- 3-methylthiophene-2-carboxamide (229) as a waxy solid (23.79 g, 97%); m.p., 32 - 34°C, (lit.,[132] 32 - 34°C). (Found: C, 61.01; H, 7.75; N, 6.98. Calculated for $C_{10}H_{15}NOS$, C, 60.89; H, 7.67; N, 7.10%); δ ($CDCl_3$), 7.16 (1H, d, J 5.04 Hz, thiophene 5-H), 6.82 (1H, d, J 5.04 Hz, thiophene 4-H), 5.67 (1H, br., NH), 2.47 (3H, s, CH_3), 1.44 (9H, s, ^{t}Bu); $\nu_{max.}$ (film), 3300, 2950, 1640, 1505, 1450, 1360, 1285 and 1210 cm^{-1}; m/z 197.0883 (M^+, 24%, calculated for $C_{10}H_{15}NOS$ 197.0874), 149 (38), 125 (100) and 69 (25).

N-t-BUTYL-3-TRIMETHYLSILYLMETHYLTHIOPHENE-2-CARBOXAMIDE (232)

To the amide (229) (4.0 g, 20.30 mmol) in thf (150 ml) at -78°C was added ^{s}BuLi (40.60 mmol) and the mixture stirred at -78°C for half

an hour, after which time TMSCl (9.02 ml, 71.05 mmol) was added and the mixture was stirred at -78°C for a further quarter of an hour. The mixture was then allowed to warm to room temperature. Thf was removed *in vacuo* and ethyl acetate (150 ml) and water (20 ml) were added to the residue. The organic phase was washed with water (2 x 20 ml) and brine (1 x 20 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the crude product as a dark oil. Purification by bulb-to-bulb distillation gave the pure amide N-t-butyl-3-trimethylsilyl-methylthiophene-2-carboxamide (232) as a clear liquid (4.58 g, 84%), b.p., 185°C at 0.1 mmHg. On cooling a waxy white solid was obtained, m.p., 26 - 28°C. (Found: C, 57.92; H, 8.70; N, 4.95. $C_{13}H_{23}NOSSi$ requires, C, 57.94; H, 8.60; N, 5.20%); δ ($CDCl_3$), 7.17 (1H, d, J 6.19 Hz, thiophene 5-H), 6.73 (1H, d, J 6.19 Hz, thiophene 4-H), 3.05 (2H, s, CH_2TMS), 1.89 (9H, s, ^tBu), 0.44 (9H, s, TMS); $\nu_{max.}$ (film), 3420, 3320, 2950, 1650, 1530, 1497 and 845 cm^{-1} m/z 269.1274 (M^+, 19%, $C_{13}H_{23}NOSSi$ requires 269.1270), 212 (33), 73 (100) and 57 (22).

N-t-BUTYL-N-METHYL-3-TRIMETHYLSILYLMETHYLTHIOPHENE-2-CARBOXAMIDE (233)

To the secondary amide (232) (3.50 g, 13.01 mmol) in thf (100 ml) at -78°C was added ^nBuLi (13.01 mmol) and the mixture stirred at -78°C for half an hour, after which time MeI (8.10 ml, 0.13 mol) was added and the mixture allowed to warm to room temperature. After stirring for a further fourteen hours the thf was removed *in vacuo* and ethyl acetate (150 ml) and water (20 ml) were added to the residue. The organic phase was washed with water (2 x 10 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent and subsequent bulb-to-bulb distillation gave the pure tertiary amide N-t-butyl-N-methyl-3-trimethylsilylmethyl-thiophene-2-carboxamide (233) as a clear liquid (3.24 g, 88%), b.p.,. 180°C at 0.15 mmHg. On cooling a waxy white

solid was obtained, m.p., 52 - 54°C. (Found: C, 58.99; H, 9.11; N, 4.62. $C_{14}H_{25}NOSSi$ requires C, 59.31; H, 8.89; N, 4.94%); δ ($CDCl_3$), 7.19 (1H, d, J 4.83 Hz, thiophene 5-H), 6.66 (1H, d, J 4.83 Hz, thiophene 4-H), 3.42 (3H, s, NCH_3), 2.79 (2H, s, CH_2TMS), 1.90 (9H, s, ^tBu), 0.40 (9H, s, TMS); $\nu_{max.}$ (film), 2940, 1630, 1350, 1240 and 840 cm^{-1}; m/z 283.1426 (M^+, 5%, $C_{14}H_{25}NOSSi$ requires 283.1426), 268 (6), 73 (100) and 57(21).

2-[N-^{t}BUTYL-N-METHYLAMINOMETHYL]-3-TRIMETHYLSILYLMETHYLTHIOPHENE (234)

A solution of tertiary amide (233) (2.85 g, 10.0 mmol) in diethyl ether (35 ml) was added dropwise to a suspension of $LiAlH_4$ (0.77 g, 20.0 mmol) in diethyl ether. The mixture was then heated under reflux for twenty-four hours. After cooling, ethyl acetate was added until no further effervescence was observed. Water (ca. 10 ml) was added and the slurry was filtered under suction, the residues being repeatedly washed with ethyl acetate and water (ca. 100 ml of a 4:1 mixture). The filtrate was separated and the organic layer washed with water (2 x 20 ml) and dried ($MgSO_4$). Removal of solvent in vacuo with subsequent bulb-to-bulb distillation gave the pure amine 2-[N-^{t}butyl-N-methylaminomethyl]-3-trimethylsilylmethylthiophene (234) as a clear oil (2.20 g, 82%), b.p., 150°C at 0.10 mmHg. (Found: C, 62.05; H, 10.29; N, 4.89. $C_{14}H_{27}NSSi$ requires C, 62.38; H, 10.10; N, 5.20%); δ ($CDCl_3$), 7.05 (1H, d, J 4.87 Hz, thiophene 5-H), 6.64 (1H, d, J 4.87 Hz, thiophene 4-H), 3.82 (2H, s, CH_2-N), 2.45 (3H, s, NCH_3), 2.32 (2H, s, CH_2-TMS), 1.41 (9H, s, ^tBu), 0.27 (9H, s, TMS); $\nu_{max.}$ (film), 2950, 1460, 1355, 1240, 960 and 830 cm^{-1}; m/z 269.1632 (M^+, 16%, $C_{14}H_{27}NSSi$ requires 269.1633), 255 (86), 167 (26) and 73 (100).

2-[N-^{t}BUTYL-N-DIMETHYLAMINOMETHYL]-3-TRIMETHYLSILYLMETHYLTHIOPHENE IODIDE (225)

Tertiary amine (234) (2.0 g, 7.43 mmol) was stirred with a large excess of methyl iodide (10 ml) for twelve hours, after which the excess of methyl iodide was removed in vacuo. The crude product was washed with light petroleum (3 x 30 ml) to give the spectroscopically pure salt (225) (3.05 g, 100%) as a pale yellow solid, m.p., 116 - 118°C (decomp.); δ ($CDCl_3$, 7.42 (1H, d, J 5.43 Hz, thiophene 5-H), 6.80 (1H, d, J 5.43 Hz, thiophene 4-H), 4.85 (2H, s, CH_2-$\overset{+}{N}$), 3.37 (6H, s, $\overset{+}{N}Me_2$), 2.46 (2H, s, $C\underline{H}_2$-TMS), 2.04 (9H, s, ^{t}Bu), 0.33 (9H, s, TMS); $\nu_{max.}$ (KBr), 3010, 2960, 2850, 1460, 1240 and 840 cm^{-1}; m/z 284.1861 (M^+, 4%, $C_{15}H_{30}NSSi$ requires 284.1868), 269 (11), 197 (62) and 73 (100).

N-1-ADAMANTYL-3-METHYLTHIOPHENE-2-CARBOXAMIDE (235)

3-Methylthiophene-2-carbonyl chloride (2.57 g, 16.0 mmol) was added dropwise to a 250 ml round bottomed flask containing 1-adamantamine (2.45 g, 16.0 mmol), triethylamine (3.40 ml, 24.0 mmol) and dichloromethane (150 ml). The solution was stirred for twelve hours and then washed with water (2 x 20 ml). The aqueous washings were basified to pH 11 (KOH aq., 40% w/w) and extracted with dichloromethane (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting solid was recrystallised from ethyl acetate - light petroleum to give the pure amide N-1-adamantyl-3-methylthiophene-2-carboxamide (235) as white crystals (4.13 g, 94%), m.p., 123 - 124°C. (Found: C, 69.69; H, 7.83; N, 5.00. $C_{16}H_{21}NOS$ requires C, 69.79; H, 7.69; N, 5.09%); δ ($CDCl_3$), 7.21 (1H, d, J 5.01 Hz, thiophene 5-H), 6.85 (1H, d, J 5.01 Hz, thiophene 4-H), 5.97 (1H, br., NH), 2.48 (3H, s, CH_3), 2.09 (9H, s), 1.71 (6H, s); $\nu_{max.}$ (KBr),

3299, 3098, 2972, 2908, 1620, 1525, 1342 and 732 cm^{-1}; m/z 275.1343 (M^+, 67%; $C_{16}H_{21}NOS$ requires 275.1344), 260 (10), 242 (30), 218 (69) and 125 (100).

N-1-ADAMANTYL-3-TRIMETHYLSILYLMETHYL-2-CARBOXAMIDE (236)

To the amide (235) (1.50 g, 5.45 mmol) in thf (60 ml) at -78°C was added ^{s}BuLi (10.90 mmol) and the mixture stirred at -78°C for half an hour, after which TMSCl (2.42 ml, 19.01 mmol) was added and the mixture was allowed to warm to room temperature. The solvent was removed in vacuo and ethyl acetate (150 ml) and water (20 ml) were added to the residue. The organic phase was washed with water (2 x 20 ml) and brine (1 x 20 ml) and dried ($MgSO_4$). Evaporation of the solvent and recrystallisation from light petroleum gave the pure amide N-1-adamantyl-3-trimethylsilylmethyl-2-carboxamide (236) as a white solid (1.76 g, 93%), m.p., 102 - 104°C. (Found: C, 65.79; H, 8.56; N, 3.91. $C_{19}H_{29}NOSSi$ requires C, 65.65; H, 8.41; N, 4.03%); δ ($CDCl_3$), 7.12 (1H, d, J 5.85 Hz, thiophene 5-H), 6.68 (1H, d, J 5.85 Hz, thiophene 4-H), 2.86 (2H, s, $-CH_2TMS$), 2.38 (9H, s), 2.00 (6H, s), 0.28 (9H, s, TMS); $\nu_{max.}$ (KBr), 3413, 2854, 1646, 1498, 1452, 1246 and 892 cm^{-1}; m/z 347.1739 (M^+, 21%; $C_{19}H_{29}NOSSi$ requires 347.1739), 332 (70), 314 (22), 135 (100) and 73 (36).

N-1-ADAMANTYL-N-METHYL-3-TRIMETHYLSILYLMETHYLTHIOPHENE-2-CARBOXAMIDE (237)

To the secondary amide (236) (0.37 g, 1.07 mmol) in thf (30 ml) at -78°C was added ^{s}BuLi (1.07 mmol) and the mixture stirred at -78°C for half an hour, after which MeI (0.67 ml, 10.7 mmol) was added and the mixture was allowed to warm to room temperature. After a further twelve hours the solvent was removed in vacuo and ethyl acetate (70

ml) and water (10 ml) were added to the residue. The organic phase was washed with water (2 x 10 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave an oil which solidified on cooling. Recrystallisation (light petroleum) gave the pure amide N-1-adamantyl-N-methyl-3-trimethylsilylmethylthiophene-2-carboxamide (236) as a white solid (0.38 g, 98%), m.p., 107 - 108°C. (Found: C, 66.49; H, 8.78; N, 3.71. $C_{20}H_{31}NOSSi$ requires C, 66.43; H, 8.64; N, 3.87%); δ ($CDCl_3$), 7.33 (1H, d, J 4.43 Hz, thiophene 5-H), 6.80 (1H, d, J 4.43 Hz, thiophene 4-H), 3.43 (3H, s, NCH_3), 2.75 (7H, m), 2.64 (4H, m), 2.23 (6H, m), 0.49 (9H, s, TMS); $\nu_{max.}$ (film), 2920, 1635, 1530, 1060 and 850 cm^{-1}; m/z 361.1895, (M^+, 19%, $C_{20}H_{31}NOSSi$ requires 361.1895), 346 (22), 328 (18), 226 (14), 197 (19), 135 (100) and 73 (30).

2-[N-(1-ADAMANTYL)-N-METHYLAMINOMETHYL]-3-TRIMETHYLSILYLMETHYL-THIOPHENE (238)

A solution of the tertiary amide (237) (4.23 g, 12.0 mmol) in diethyl ether (50 ml) was added dropwise to a suspension of $LiAlH_4$ (0.91 g, 24.0 mmol) in diethyl ether (50 ml). The mixture was then heated under reflux for twenty-four hours. After cooling, ethyl acetate was added until no further effervescence was observed. Water (ca. 20 ml) was added and the slurry was filtered under suction, the residues being repeatedly washed with ethyl acetate and water (ca. 100 ml of a 4:1 mixture). The filtrate was separated and the organic layer washed with water (2 x 20 ml) and dried ($MgSO_4$). Removal of the solvent in vacuo gave the spectroscopically pure amine 2-[N-(1-adamantyl)-N-methylaminomethyl]-3-trimethylsilylmethylthiophene (238) as a viscous oil (3.49 g, 84%); δ ($CDCl_3$), 7.02 (1H, d, J 4.98 Hz, thiophene 5-H), 6.62 (1H, d, J 4.98 Hz, thiophene 4-H), 3.77 (2H, s,

CH_2-N), 2.37 (3H, s, NCH_3), 2.26 (3H, m), 2.18 (2H, m), 1.92 (6H, m), 1.80 (6H, m), 0.24 (9H, s, TMS); $\nu_{max.}$ (film), 2950, 1465, 1350, 1240 and 840 cm^{-1}; m/z 347.2109, (M^+, 14%, $C_{20}H_{33}NSSi$ requires 347.2103), 255 (18), 182 (59), 135 (27), 99 (67) and 73 (100).

2-[N-(1-ADAMANTYL)-N,N-DIMETHYLAMINOMETHYL]-3-TRIMETHYLSILYLMETHYL-THIOPHENE IODIDE (226)

Tertiary amine (238) (1.0 g, 2.88 mmol) was stirred with a large excess of methyl iodide (15 ml) for twenty-four hours, after which time a deep yellow solid was precipitated. This was filtered from the solution and washed with light petroleum (3 x 30 ml). Evaporation of the filtrate yielded more solid material which was also washed with petroleum (3 x 30 ml). After drying *in vacuo* salt (226) (1.40 g, 99%) was isolated as a spectroscopically pure pale yellow solid, m.p., 120 - 122°C (decomp.); δ ($CDCl_3$), 7.43 (1H, d, J 5.04 Hz, thiophene 5-H), 6.81 (1H, d, J 5.04 Hz, thiophene 4-H), 4.92 (2H, s, CH_2-$\overset{+}{N}$), 3.42 (6H, s, $\overset{+}{N}Me_2$), 2.85 (3H, m), 2.71 (6H, m), 2.56 (2H, m), 2.18 (6H, m), 0.43 (9H, s, TMS); $\nu_{max.}$ (film), 3013, 2951, 2906, 2854, 1476, 1448, 1247, 856 and 841 cm^{-1}; m/z 362.2335 (M^+, 6%, $C_{21}H_{36}NSSi$ requires 362.2334), 347 (11), 197 (51) and 73 (100).

N-^{t}-BUTYL-3-PROP-2-ENYLTHIOPHENE-2-CARBOXAMIDE (250)

To amide (228) (3.0 g, 16.39 mmol) dissolved in thf (100 ml) at -78°C was added ^{n}BuLi (36.09 mmol) and the solution stirred at -78°C for half an hour, after which time $MgBr_2 \cdot OEt$ (6.36 g, 24.59 mmol) was added and the mixture was allowed to warm to room temperature gradually, over a period of *ca*. one hour. The white precipitate which

was formed was re-cooled to -78°C and allyl iodide (57.37 mmol) was added. The mixture was allowed to warm to room temeprature and stirred for a further five hours. The thf was removed *in vacuo* and the residue treated with saturated aqueous ammonium chloride (30 ml) and then extracted with ethyl acetate (2 x 100 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the crude product as a brown oil. Purification by flash chromatography (ethyl acetate - light petroleum, 1:9 as eluant) gave the pure amide *N-t-butyl-3-prop-2-enyl-thiophene-2-carboxamide* (250) as a white solid (2.74 g, 76%), m.p., 28 - 30°C. (Found: C, 64.50; H, 7.73; N, 6.14. $C_{12}H_{17}NOS$ requires C, 64.55; H, 7.68; N, 6.27%); δ ($CDCl_3$), 7.22 (1H, d, *J* 5.03 Hz, thiophene 5-H), 6.84 (1H, d, *J* 5.03 Hz, thiophene 4-H), 6.05 (1H, br., NH), 5.98 (1H, m), 5.05 (2H, m), 3.61 (2H, m), 1.38 (9H, s, ^tBu); $\nu_{max.}$ (film), 3420, 3340, 2995, 1655, 1520, 1300 and 1230 cm^{-1}; *m/z* 223.1037 (M^+, 17%, $C_{12}H_{17}NOS$ requires 223.1031), 208 (28), 152 (100), 123 (24) and 84 (66).

N-^{t}-BUTYL-[3-(bis-TRIMETHYLSILYL)METHYL]-THIOPHENE-2-CARBOXAMIDE (267)

To the amide (229) (0.50 g, 2.54 mmol), dissolved in thf (30 ml) at -78°C was added ^{s}BuLi (10.16 mmol) and the mixture stirred at -78°C for half an hour, after which time TMSCl (2.25 ml, 8.89 mmol) was added. The mixture was allowed to warm to room temperature and the thf was removed *in vacuo*. The residue was treated with ethyl acetate (50 ml) and water (10 ml). The organic layer was washed with water (1 x 10 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* and bulb-to-bulb distillation of the residue gave the pure amide *N-t-butyl-[3-(bis-trimethylsilyl)methyl]-thiophene-2-carboxamide* (267) as a clear oil (0.70 g, 81%), b.p., 180°C at 0.10 mmHg. (Found: C, 56.00; H, 9.35; N, 3.74. $C_{16}H_{31}NOSSi_2$ requires C,

56.24; H, 9.15; N, 4.10%); δ ($CDCl_3$), 7.16 (1H, d, J 5.07 Hz, thiophene 5-H), 6.75 (1H, d, J 5.07 Hz, thiophene 4-H), 3.66 (1H, s, -CH), 1.90 (9H, s, ^tBu), 0.48 (18H, s, 2 x TMS); $\nu_{max.}$ (film), 3410, 2950, 1650, 1515, 1245 and 850 cm^{-1}; m/z 341.1665 (M^+, 21%, $C_{16}H_{31}NOSSi$ requires 341.1665), 268 (13), 181 (19), 73 (100) and 57 (17).

[4+2] SPIRO-DIMERS (148)

A solution of salt (226) (0.50 g, 1.02 mmol) in acetonitrile (20 ml) was added dropwise to a suspension of CsF (0.46 g, 3.06 mmol) in acetonitrile (10 ml) at room temperature. The mixture was stirred for eighteen hours, after which time the acetonitrile was removed *in vacuo* and the residue taken up into ethyl acetate (100 ml) and dilute aqueous HCl (5% v/v, 10 ml). The organic layer was washed with dilute HCl (1 x 10 ml), water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent gave the spiro dimers (148) as a colourless oil (0.11 g, 98%). Attempted flash chromatography or distillation resulted in decomposition; δ ($CDCl_3$), 7.10 (1H, d, J 5.52 Hz), 6.78 (1H, d, J 5.52 Hz), 6.20 (1H, d, J 5.10 Hz), 5.65 (1H, d, J 5.10 Hz), 5.20 (1H, s), 5.10 (1H, s), 2.78 (2H, m), 2.70 (2H, m), 2.22 (2H, m); m/z 220.0389 (M^+, 33%, $C_{12}H_{12}S_2$ requires 220.0380), 110 (100).

FLUORIDE ION-INDUCED GENERATION OF o-XYLYLENE (145) : REACTION WITH N-PHENYLMALEIMIDE ; ADDUCT (222)

A solution of salt (226) (1.30 g, 2.66 mmol) in acetonitrile (30 ml) was added dropwise to a 50 ml round bottomed flask containing CsF (1.20 g, 7.98 mmol), N-phenylmaleimide (0.51 g, 2.93 mmol) and acetonitrile (10 ml), at 0°C. When the addition was complete the mixture was stirred at room temperature for fifteen hours. The reaction was

worked-up as for dimers (148) and the crude product was recrystallised (ethyl acetate - light petroleum) to give the pure adduct (222) as a pale yellow solid (0.55 g, 73%), m.p., 164 - 165°C. (Found: C, 67.77; H, 4.65; N, 4.78. $C_{16}H_{13}NO_2S$ requires C, 67.84; H, 4.63; N, 4.95%). This compound was chromatographically and spectroscopically identical to adduct (222) obtained by a similar route (see page 165).

5- (AND 6-)ACETYL 4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE (223)

The basic experimental procedure described previously for adduct (222) was used. Salt (225) (0.80 g, 1.95 mmol) dissolved in acetonitrile (20 ml) was added dropwise to CsF (0.88 g, 5.85 mmol), MVK (1.62 ml, 19.50 mmol) and acetonitrile (10 ml), at room temperature. The mixture was stirred for seventeen hours and then worked-up as for (148) and (222). Flash chromatography (ethyl acetate - light petroleum, 3:7 as eluant) gave adducts (223) (0.28 g, 80%) as a clear mobile liquid, spectroscopically identical to a sample prepared by a similar route (see page 166).

ETHYL 4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE 5- (AND 6-)CARBOXYLATE (242)

Salt (225) (0.50 g, 1.22 mmol) dissolved in acetonitrile (20 ml) was added dropwise to CsF (0.55 g, 3.66 mmol), ethyl acrylate (1.32 ml, 12.20 mmol) and acetonitrile (20 ml) at 0°C. The mixture was then stirred at room temperature for fourteen hours and worked-up as for (148). Flash chromatography (ethyl acetate - light petroleum, 1:9 as eluant) gave adducts (242) as a clear mobile liquid (0.20 g, 78%). (Found: C, 63.07; H, 6.93. $C_{11}H_{14}O_2S$ requires C, 62.83; H, 6.71%); δ ($CDCl_3$), 7.08 (1H, d, J 5.00 Hz, thiophene 5-H), 6.76 (1H, d, J 5.00 Hz, thiophene 4-H), 4.23 (2H, q, CH_2CH_3), 3.11 - 2.62 (4H, m), 2.39 - 1.81 (3H, m), 1.29 (3H, t, CH_2CH_3); $\nu_{max.}$ (film), 2920, 1730, 1180 and

840 cm^{-1}; m/z 210.0717 (M^+, 30%, $C_{11}H_{14}O_2S$ requires 210.0714), 136 (100), 110 (27) and 73 (20).

DIMETHYL 4,7-DIHYDROBENZO[b]THIOPHENE-5,6-DICARBOXYLATE (243) AND DIMETHYL BENZO[b]THIOPHENE-5,6-DICARBOXYLATE (244)

Salt (225) (0.40 g, 0.97 mmol) dissolved in acetonitrile (20 ml) was added dropwise to CsF (0.44 g, 2.91 mmol), dimethylacetylene-dicarboxylate (0.13 ml, 1.07 mmol) and acetonitrile (10 ml) at room temperature. The mixture was stirred for sixteen hours and worked-up as for (148). Flash chromatography (ethyl acetate - light petroleum, 1:3 as eluant) gave the inseparable adducts (243) and (244) as a colourless liquid (0.19 g, 78%)

COMPOUND (243); δ ($CDCl_3$), 7.34 (1H, d, J 4.82 Hz, thiophene 5-H), 6.92 (1H, d, J 4.82 Hz, thiophene 4-H), 3.93 (2H, s), 3.88 (2H, s), 3.79 (3H, s), 3.59 (3H, s); $\nu_{max.}$ (film), 1750 cm^{-1}; m/z 252.0465 (M^+, 16%, $C_8H_{12}O_4S$ requires 252.0456), 220 (18), 207 (16), 193 (89), 161 (88), 149 (68), 134 (100) and 59 (49).

COMPOUND (244); δ ($CDCl_3$), 7.65 (1H, s), 7.64 (1H, s), 7.08 (1H, d, J 5.04 Hz, thiophene 5-H), 6.94 (1H, d, J 5.04 Hz, thiophene 4-H), 3.77 (3H, s), 3.57 (3H, s); $\nu_{max.}$ (film), 1720 cm^{-1}; m/z 250.0031 (M^+, 38%, $C_{10}H_{10}O_4S$ requires 250.0029), 219 (100), 133 (14) and 89 (8).

DIETHYL 4,5,6,7-TETRAHYDROBENZO[b]THIOPHENE-5,6-DICARBOXYLATE (245)

Salt (225) (0.65 g, 1.58 mmol) dissolved in acetonitrile (30 ml) was added dropwise to CsF (0.71 g, 4.74 mmol), diethyl fumarate (0.28 ml, 1.74 mmol) and acetonitrile (10 ml) at room temperature. The mixture was stirred for fifteen hours and worked-up as for (148). Flash chromatography (ethyl acetate - light petroleum, 1:3 as eluant)

gave the chromatographically and spectroscopically pure adduct (245) (0.32 g, 73%) as a colourless liquid; δ ($CDCl_3$), 7.06 (1H, d, J 5.03 Hz, thiophene 5-H), 6.71 (1H, d, J 5.03 Hz, thiophene 4-H), 4.33 - 4.10 (4H, m, 2 overlapping quartets, CH_2CH_3), 3.24 - 2.99 (4H, m), 2.97 - 2.64 (2H, m), 1.37 - 1.21 (6H, m, 2 overlapping triplets, CH_2CH_3); $\nu_{max.}$ (film), 3000, 1745, 1045 and 720 cm^{-1}; m/z 282.0926 (M^+, 12%, $C_{14}H_{18}O_4S$ requires 282.0926), 237 (18), 208 (36), 149 (20), 135 (100) and 91 (15).

FLUORIDE ION-INDUCED GENERATION OF o-XYLYLENE (145) IN THE PRESENCE OF $Fe_2(CO)_9$

A solution of salt (226) (0.50 g, 1.22 mmol) in acetonitrile (15 ml) was added dropwise to a suspension of CsF (0.55 g, 3.66 mmol) and $Fe_2(CO)_9$ (0.88 g, 2.44 mmol) in acetonitrile (10 ml) at 50°C. The mixture was stirred at 50°C for a quarter of an hour and then at room temperature for eighteen hours. The reaction was worked-up as for compounds (148) to give an intractable tar. Characterisation was not attempted.

4.4-DIMETHYL-2-(2-THIENYL)OXAZOLINE (261)[132]

Meyers' general approach to oxazoline synthesis was followed.[175] Commercial thiophene-2-carboxylic acid (20.0 g, 0.16 mol) and freshly distilled thionyl chloride (76.16 g, 0.64 mol) were heated under reflux for six hours. The excess of thionyl chloride was removed in vacuo and the residue distilled under reduced pressure to give the acid chloride (20.16 g, 86%), b.p., 100°C at 15 mmHg (lit.,[178] 190°C at 760 mmHg); $\nu_{max.}$ (film), 1680 cm^{-1}.

A solution of 2-amino-2-methyl-propan-1-ol (24.98 g, 0.28 mol) in dichloromethane (100 ml) was added to a solution of the acid chloride

(20.16 g, 0.14 ;mol) in dichloromethane (150 ml), with the reaction temperature held below 20°C. The mixture was stirred for twelve hours, washed with water (2 x 50 ml), dried ($MgSO_4$), and evaporated to give the crude amide, N-(2-hydroxy-1,1-dimethylethyl)thiophene-2-carboxamide as a tan solid which was used without further purification.

The amide was suspended in toluene (20 ml) and thionyl chloride (55.0 g, 0.46 mol) was added dropwise keeping the reaction temperature below 30°C. Stirring was continued for twelve hours at 25°C, after which the toluene was removed in vacuo and the residue taken up into water (100 ml). The solution was basified with aqueous sodium hydroxide (40% w/w) to pH 11 and extracted with diethyl ether (4 x 50 ml). The organic extracts were combined and dried ($MgSO_4$). Evaporation gave the crude product as an oil that was distilled under reduced pressure (b.p., 120°C at 15 mmHg) (lit.,[132] 120°C at 15 mmHg), to give the pure oxazoline (261) (20.53 g, 81%) as a white solid, m.p., 29 - 31°C (lit.,[132] 29 - 30°C); δ ($CDCl_3$), 7.56 (1H, dd, J 3.80, 1.32 Hz, thiophene 3-H), 7.38 (1H, dd, J 5.41 H, 1.32 Hz, thiophene 5-H), 7.01 (1H, dd, J 5.41, 3.80 Hz, thiophene 4-H), 4.01 (2H, s, O-CH_2), 1.36 (6H, s, CH_3);; $\nu_{max.}$ (film), 3160, 2960, 1640, 1425, 1045, 1010 and 700 cm^{-1}; m/z 181 (M^+, 15%), 166 (100), 151 (14), 138 (23) and 110 (54).

4,4-DIMETHYL-2-(3-METHYL-2-THIENYL)OXAZOLINE (263)[132]

To thienyl-oxazoline (261) (5.0 g, 27.62 mmol) dissolved in diethyl ether (150 ml) at -78°C was added ^nBuLi (30.39 mmol), and the mixture was stirred at -78°C for quarter of an hour and then at 0°C for half an hour. Methyl iodide (17.20 ml, 0.28 mol) was added and the mixture allowed to warm to room temperature. After stirring for

a further twelve hours, water (15 ml) was added and the layers separated. The ethereal layer was washed with water (2 x 20 ml) and brine (1 x 20 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the crude product as a light brown oil. Distillation under reduced pressure gave the pure compound (263) (5.0 g, 93%) (b.p., 105°C at 0.30 mmHg) as a white solid, m.p., 30 - 31°C; δ ($CDCl_3$), 7.27 (1H, d, J 4.99 Hz, thiophene 5-H), 6.86 (1H, d, J 4.99 Hz, thiophene 4-H), 4.03 (2H, s, OCH_2), 2.51 (3H, s, thiophene CH_3), 1.33 (6H, s, oxazoline CH_3); $\nu_{max.}$ (film), 2980, 2905, 1645, 1602, 1438 and 1050 cm^{-1}; m/z 195 (M^+, 81%), 180 (100), 152 (32), 124 (50 and 45 (54).

GENERAL METHODS FOR LITHIATION OF 4,4-DIMETHYL-2-(3-METHYL-2-THIENYL)OXAZOLINE (263)

METHOD A

^{n}BuLi or ^{s}BuLi, hexane or diethyl ether as solvent. To the oxazoline (263) (0.50 g, 2.56 mmol) in hexane or diethyl ether was added commercial ^{n}BuLi (2.82 mmol) in hexane (or ^{s}BuLi, 2.82 mmol, in cyclohexane) at the required temperature. The mixture was stirred under an inert atmosphere for the requisite time. The electrophile was added, the mixture allowed to warm to room temperature, and the mixture stirred for a further twelve hours unless otherwise stated. Water (5 ml) and then diethyl ether (60 ml) were added. If TMSCl was the electrophile then the mixture was basified to pH 11 (KOH aq., 40% w/w). The organic solution was separated, washed with water (3 x 10 ml) and brine (1 x 10 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure. If TMEDA was required, it was added immediately after, and in equimolar ratio to the organolithium reagent.

METHOD B

DME or thf as solvent. The procedure was the same as Method A, except that the solvent was removed under reduced pressure prior to the addition of water. Solids were then suspended in diethyl ether (60 ml).

METHOD C

Lithiations with LDA. To diisopropylamine (2.82 mmol) in the required solvent was added commercial ^{n}BuLi (2.82 mmol) at the requisite temperature. Oxazoline (263) (0.50 g, 2.56 mmol) in the required solvent (10 ml) was then added and the experiment continued as in Method A or B.

ATTEMPTED PREPARATION OF 4,4-DIMETHYL-2-(3-TRIMETHYLSILYLMETHYL-2-THIENYL)OXAZOLINE (264)

METHOD 1

To thienyl-oxazoline (261) (0.50 g, 2.76 mmol) in diethyl ether (30 ml) at -78°C was added ^{n}BuLi (3.04 mmol), and the mixture stirred at -78°C for quarter of an hour and then at 0°C for half an hour. Trimethylsilylmethyl-trifluoromethane sulfonate ($TMSCH_2Tf$) (0.61 ml, 3.04 mmol) was added and the mixture stirred at 0°C for one hour. The mixture was then allowed to warm to room temperature and stirred for a further eighteen hours. Triethylamine (0.58 ml, 4.14 mmol), water (5 ml) and diethyl ether (100 ml) were added. The organic solution was separated and washed with water (2 x 10 ml) and brine (1 x 10 ml). The organic solution was dried ($MgSO_4$) and evaporated to give a mixture of starting material (ca. 60%) and the trimethylsilyl-methyl-oxazoline (264) (ca. 40%) as judged by tlc and ^{1}H nmr analysis. Separation and characterisation of (264) was not attempted.

When trimethylsilylmethyl chloride or the corresponding iodide were used as electrophile in the above experimental procedure only starting material was recovered.

METHOD 2

The 3-lithio derivative of thienyl-oxazoline (261) (prepared as described in Method 1) was added to an equimolar mixture of HMPA and $TMSCH_2Tf$ in ether at 0°C. The reaction mixture was stirred and worked-up as in Method 1 to give a mixture of starting material (ca. 50%) and the trimethylsilylmethyl-oxazoline (264) (ca. 50%) as judged by tlc and ^1H nmr analysis.

3-[2-(4,4-DIMETHYLOXAZOLIN-2-YL)]THIENYL-ETHANOIC ACID (269)

To the 3-methyl-thienyl-oxazoline (263) (0.50 g, 2.56 mmol) in hexane (60 ml) at -78°C was added ^{S}BuLi (5.13 mmol) and the mixture stirred at -78°C for half an hour and then poured onto a slurry of crushed CO_2 and diethyl ether. The solvents were evaporated and the residual solids taken up in water (30 ml). The aqueous solution was then extracted with ether (2 x 30 ml). The aqueous phase was then acidified to pH 4 (conc. HCl) and extracted with ethyl acetate (2 x 60 ml). The organic solution was washed with water (2 x 20 ml) and brine (1 x 20 ml) and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude product which was recrystallised (ethyl acetate - light petroleum) to give the pure carboxylic acid (269) (0.47 g, 77%) as white needles, m.p., 116 - 118°C. (Found: C, 55.64; H, 5.51; N, 5.77. $C_{11}H_{13}NO_3S$ requires C, 55.21; H, 5.48; N, 5.85%); δ ($CDCl_3$), 7.52 (1H, d, J 5.02 Hz, thiophene 5-H), 7.14 (1H, d, J 5.02 Hz, thiophene 4-H), 4.25 (2H, s, CH_2-thiophene), 3.92 (2H, s, OCH_2), 1.45 (6H, s, CH_3); $\nu_{max.}$ (KBr), 3080, 2950, 1710, 1630,

1280, 1200, 1055, 820, 730 and 615 cm^{-1}; m/z 239 (M^+, 12%), 195 (65), 180 (100) and 110 (13).

4,4-DIMETHYL-2-(3-METHYL-5-TRIMETHYLSILYL-2-THIENYL)OXAZOLINE (265)

To the 3-methylthienyl-oxazoline (263) (1.0 g, 5.13 mmol) in DME (60 ml) at -78°C was added ^{n}BuLi (5.64 mmol) and the mixture stirred at -78°C for one and a half hours. TMSCl (0.72 ml, 5.64 mmol) was added and the mixture allowed to warm to room temperature. The solvent was evaporated and the residue was taken up in ethyl acetate (100 ml) and water (10 ml). The organic layer was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent and bulb-to-bulb distillation of the residue gave the pure compound (265) (1.30 g, 95%) as a colourless oil, b.p., 140°C at 0.15 mmHg. (Found: C, 58.03; H, 7.95; N, 5.14. $C_{13}H_{21}NOSSi$ requires C, 58.37; H, 7.93; N, 5.24%); δ ($CDCl_3$), 6.99 (1H, s, thiophene 4-H), 4.34 (2H, s, OCH_2), 2.82 (3H, s, CH_3), 1.64 (6H, s, oxazoline CH_3), 0.59 (9H, s, TMS); $\nu_{max.}$ (film), 2960, 2920, 2890, 1635, 1248, 997 and 840 cm^{-1}; m/z 267.1105 (M^+, 56%, $C_{13}H_{21}NOSSi$ requires 267.1113), 252 (100), 224 (15), 196 (12), 180 (19), 84 (29), 73 (18) and 49 (13).

4,4-DIMETHYL-2-(3-ETHYL-5-TRIMETHYLSILYL-2-THIENYL)OXAZOLINE (272)

To 4,4-dimethyl-2-(3-methyl-5-trimethylsilyl-2-thienyl)oxazoline (265) (1.0 g, 3.75 mmol) dissolved in thf (60 ml) at -78°C was added ^{s}BuLi (7.50 mmol) and the mixture stirred at - 78°C for half an hour, after which methyl iodide (2.34 ml, 37.50 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was stirred for a further twelve hours and then the solvent was removed in vacuo. The residue was taken up in ethyl acetate (100 ml) and water (10 ml). The organic solution was washed with water (2 x 10 ml) and

brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent and then bulb-to-bulb distillation of the residue gave the chromatographically pure product 4,4-dimethyl-2-(3-ethyl-5-trimethylsilyl-2-thienyl)oxazoline (272) (0.70 g, 67%) as a colourless liquid, b.p., 160°C at 0.20 mmHg; δ ($CDCl_3$), 7.06 (1H, s, thiophene 4-H), 3.92 (2H, s, OCH_2), 2.86 (2H, q, $C\underline{H}_2CH_3$), 1.22 (6H, s, oxazoline CH_3), 1.12 (3H, t, $CH_2C\underline{H}_3$), 0.20 (9H, s, TMS); $\nu_{max.}$ (film), 2970, 1635, 1250 and 840 cm^{-1}; m/z 281.1265 (M^+, 100%, $C_{14}H_{23}NOSSi$ requires 281.1269), 266 (76), 73 (44).

4,4-DIMETHYL-2-(3-ETHYL-2-THIENYL)OXAZOLINE (274)

4,4-Dimethyl-2-(3-ethyl-2-thienyl)oxazoline (272) (0.50 g, 1.78 mmol) was stirred with CsF (0.80 g, 5.34 mmol) in acetontrile (15 ml) at room temperature for fourteen hours. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate (50 ml) and water (10 ml). The organic solution was washed with water (1 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation gave the chromatographically pure product 4,4-dimethyl-2-(3-ethyl-2-thienyl)-oxazoline (274) (0.35 g, 94%) as a colourless oil; δ ($CDCl_3$), 7.31 (1H, d, J 5.00 Hz, thiophene 5-H), 6.94 (1H, d, J 5.00 Hz, thiophene 4-H), 4.03 (2H, s, OCH_2), 3.06 (2H, q, $C\underline{H}_2CH_3$), 1.38 (6H, s, oxazoline CH_3), 1.24 (3H, t, $CH_2C\underline{H}_3$); $\nu_{max.}$ (film), 2980, 2900, 1645, 1600, 1435 and 1050 cm^{-1}; m/z 209.0875 (M^+, 100%, $C_{11}H_{15}NOS$ requires 209.0874), 194 (26), 105 (49) and 77 (42).

4,4-DIMETHYL-2-(3-TRIMETHYLSILYLMETHYL-5-TRIMETHYLSILYL-2-THIENYL)-OXAZOLINE (266)

METHOD 1

To 4,4-dimethyl-2-(3-methyl-2-thienyl)oxazoline (263) (2.0 g, 10.26 mmol) dissolved in thf (120 ml) at -20°C was added ^{s}BuLi (33.86

mmol) and the mixture stirred at -20°C for half an hour, after which time TMSCl (5.60 ml, 41.04 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for a further three and a half hours. The solvent was removed *in vacuo* and the residue taken up in diethyl ether (150 ml) and water (20 ml). The ethereal layer was washed with water (2 x 20 ml) and brine (1 x 20 ml) and then dried ($MgSO_4$). Evaporation of the solvent and bulb-to-bulb distillation of the residue gave the pure product 4,4-dimethyl-2-(3-trimethylsilylmethyl-5-trimethylsilyl-2-thienyl)oxazoline (266) (2.92 g, 84%), b.p., 175°C at 0.30 mmHg. (Found: C, 59.96; H, 8.77; N, 4.11. $C_{16}H_{29}NOSSi_2$ requires C, 56.57; H, 8.62; N, 4.12%); δ ($CDCl_3$), 6.81 (1H, s, thiophene 4-H), 4.34 (2H, s, OCH_2), 2.97 (2H, s, CH_2TMS), 1.68 (6H, s, oxazoline CH_3), 0.65 (9H, s, TMS), 0.33 (CH_2TMS); $\nu_{max.}$ (film), 2940, 1630, 1245 and 840 cm^{-1}; m/z 339.1512 (M^+, 23%, $C_{16}H_{29}NOSSi_2$ 339.1508), 324 (75), 266 (11), 234 (30) and 73 (100).

METHOD 2

To 4,4-dimethyl-2-(3-methyl-5-trimethylsilyl-2-thienyl)oxazoline (265) (0.50 g, 1.87 mmol) dissolved in thf (30 ml) at -78°C was added ^sBuLi (3.74 mmol) and the mixture stirred at -78°C for half an hour, after which time TMSCl (0.47 ml, 1.87 mmol) was added. The mixture was allowed to warm to room temperature and stirred for a further two hours. The reaction was worked-up as for Method 1 to give, after distillation, the pure product (266) (0.58 g, 91%), spectroscopically identical to that formed under Method 1.

2-(3-TRIMETHYLSILYLMETHYL-5-TRIMETHYLSILYL-2-THIENYL)-3,4,4-TRIMETHYL-OXAZOLINIUM IODIDE (274)

4,4-Dimethyl-2-(3-trimethylsilylmethyl-5-trimethylsilyl-2-thienyl)oxazoline (266) (5.50 g, 16.22 mmol) was heated under reflux with methyl iodide (62 ml) and acetonitrile (60 ml) for twenty-four hours. Evaporation gave a yellow solid which was washed with light petroleum (6 x 30 ml) to give the pure salt 2-(3-trimethylsilylmethyl-5-trimethylsilyl-2-thienyl)-3,4,4-trimethyloxazolinium iodide (274) (7.02 g, 90%), m.p., 127 - 128°C (decomp.) (Found: C, 42.24; H, 6.73; N, 2.78. $C_{17}H_{32}INOSSi_2$ requires C, 42.39; H, 6.71; N, 2.91%); δ (d_6-DMSO), 7.21 (1H, s, thiophene 4-H), 5.27 (3H, s, $\overset{+}{N}CH_3$), 3.97 (2H, s, OCH_2), 3.34 (2H, s, $C\underline{H}_2TMS$), 1.97 (6H, s, oxazoline CH_3), 0.77 (9H, s, TMS), 0.40 (9H, s, $CH_2T\underline{M}S$); $\nu_{max.}$ (KBr), 2938, 2870, 1600, 1440, 1240, 1120, 1005 and 840 cm^{-1}; m/z 354 ($\underline{M}^+$, 14%), 339 (51) and 73 (100).

4,4-DIMETHYL-2-(5-METHYL-2-THIENYL)OXAZOLINE (280)

Commercial 5-methylthiophene-2-carboxylic acid (9.80 g, 69.01 mmol) was converted to the corresponding oxazoline by the method described for the parent oxazoline (261), distillation under reduced pressure gave the pure compound (280), b.p., 107°C at 0.15 mmHg as a white solid (11.10 g, 82%), m. p., 39 - 41°C (lit.,[132] 39 - 41°C) (Found: C, 61.40; H, 6.77; N, 7.09. Calculated for $C_{10}H_{13}NOS$, C, 61.52; H, 6.71; N, 7.18%); δ ($CDCl_3$), 7.31 (1H, d, J 3.28 Hz, thiophene 3-H), 6.65 (1H, d, J 3.28 Hz, thiophene 4-H), 4.01 (2H, s, OCH_2), 2.45 (3H, s, thiophene CH_3), 1.33 (6H, s, oxazoline CH_3); $\nu_{max.}$ (nujol mull), 2950, 2850, 1645, 1475, 1055 and 805 cm^{-1}; m/z 195 ($\underline{M}^+$, 80%), 180 (100), 152 (37), 125 (17), 124 (60) and 59 (84).

4,4-DIMETHYL-2-(3,5-DIMETHYL-2-THIENYL)OXAZOLINE (278)

METHOD 1

To 3-methylthienyl-oxazoline (263) (5.0 g, 25.64 mmol) dissolved in DME (150 ml) at -78°C was added ^{n}BuLi (28.21 mmol) and the mixture stirred at -78°C for one and a half hours. Methyl iodide (16.0 ml, 0.26 mol) was added and the mixture allowed to warm to room temperature. After stirring for thirteen hours the solvent was removed *in vacuo* and the residue taken up into diethyl ether (150 ml) and water (20 ml). The ethereal layer was washed with water (2 x 20 ml) and brine and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product as a white solid (5.35 g, 100%). A small sample was purified by sublimation to give the pure 4,4-dimethyl-2-(3,5-dimethyl-2-thienyl)oxazoline (278), m.p., 75 - 77°C. (Found: C, 63.00; H, 7.22; N, 6.46. $C_{11}H_{15}NOS$ requires, C, 63.14; H, 7.23; N, 6.69%); δ (C_6D_6), 6.26 (1H, s, thiophene 4-H), 3.61 (2H, s, OCH_2), 2.55 (3H, s, CH_3), 2.00 (3H, s, CH_3), 1.13 (6H, s, oxazoline CH_3); $\nu_{max.}$ (film), 2970, 1640, 1460, 1285, 1030, 830, 712 and 611 cm^{-1}; *m/z* 209 (M^+, 69%), 194 (100), 166 (27) and 138 (36).

METHOD 2

To thienyl-oxazoline (261) (1.0 g, 5.52 mmol) dissolved in thf (30 ml) at -20°C was added ^{s}BuLi (18.22 mmol) and the mixture stirred at -20°C for half an hour. Methyl iodide (11.34 ml, 0.18 mol) was added and the mixture allowed to warm to room temperature. The reaction was worked-up as for "Method 1" to give material (1.10 g, 96%), which was spectroscopically and chromatographically identical with that obtained using "Method 1".

METHOD 3

To 5-methylthienyl-oxazoline (280) (1.0 g, 5.13 mmol) dissolved in diethyl ether (60 ml) at -78°C was added ^{n}BuLi (5.64 mmol) and the mixture stirred for quarter of an hour at -78°C and half an hour at 0°C. Methyl iodide (3.20 ml, 51.30 mmol) was added and the mixture was allowed to warm to room temperature and stirred for a further twelve hours. The reaction was worked-up as for 3-methylthienyl-oxazoline (263), to give the crude compound (278) (0.99 g, 92%), spectroscopically and chromatographically identical to that produced from Methods 1 and 2.

4,4-DIMETHYL-2-(3-TRIMETHYLSILYLMETHYL-5-METHYL-2-THIENYL)OXAZOLINE (279)

To the 3,5-dimethylthienyl-oxazoline (278) (4.50 g, 21.53 mmol) dissolved in diethyl ether (150 ml) at -78°C was added ^{s}BuLi (23.68 mmol) and the mixture stirred at -78°C for half an hour, after which time it was quickly warmed to room temperature and TMSCl (3.0 ml, 23.68 mmol) was added. The mixture was stirred for six hours and then water (20 ml) was added. The ethereal layer was washed with water (2 x 20 ml) and brine (1 x 20 ml) and then dried. Evaporation of the solvent and distillation of the residue gave the pure 4,4-dimethyl-2-(3-trimethylsilylmethyl-5-methyl-2-thienyl)oxazoline (279) (5.00 g, 83%) as a colourless oil, b.p., 152°C at 0.20 mmHg. (Found: C, 59.78; H, 8.33; N, 4.86. $C_{14}H_{23}NOSSi$ requires C, 59.72; H, 8.25; N, 4.98%); δ ($CDCl_3$), 6.37 (1H, s, thiophene 4-H), 4.32 (2H, s, OCH_2), 2.88 (2H, s, CH_2TMS), 2.74 (3H, s, thiophene CH_3), 1.66 (6H, s, oxazoline CH_3), 0.31 (9H, s, TMS); $\nu_{max.}$ (film), 2960, 2910, 2880, 1635, 1295, 1245, 1040 and 850 cm^{-1}; m/z 281.1259 (M^+, 36%, $C_{14}H_{23}ONSSi$ requires 281.1269), 266 (100), 194 (19) and 73 (88).

2-(3-TRIMETHYLSILYLMETHYL-5-METHYL-2-THIENYL)-3,4,4-TRIMETHYLOXAZOLINIUM IODIDE (156)

4,4-Dimethyl-2-(3-trimethylsilylmethyl-5-methyl-2-thienyl)-oxazoline (279) (2.0 g, 7.12 mmol) was heated under reflux with methyl iodide (20 ml) and acetonitrile (35 ml) for twenty-four hours. Evaporation gave a yellow solid which was washed with light petroleum (4 x 50 ml) to give the pure salt 2-(3-trimethylsilylmethyl-5-methyl-2-thienyl)-3,4,4-trimethyloxazolinium iodide (156) (2.92 g, 95%), m.p., 121 - 121°C (decomp.). (Found: C, 42.66; H, 6.29; N, 3.30. $C_{15}H_{26}INOSSi$ requires C, 42.54; H, 6.20; N, 3.31%); δ (CD_3CN), 6.91 (1H, s, thiophene 4-H), 4.79 (2H, s, OCH_2), 3.45 (3H, s, $\overset{+}{N}CH_3$), 2.67 (2H, s, CH_2TMS), 2.58 (3H, s, thiophene CH_3), 1.55 (6H, s, oxazoline CH_3), 0.02 (9H, s, TMS); $\nu_{max.}$ (KBr), 2930, 1595, 1440, 1240, 1050, 920 and 850 cm^{-1}; m/z 296 (M^+, 11%), 281 (69), 73 (100).

2-METHYL-2-(METHYLAMINO)PROPYL-3,5-DIMETHYLTHIOPHENE-2-CARBOXYLATE (290)

A solution of salt (156) (0.50 g, 1.18 mmol) in acetontrile (20 ml) was added dropwise to a suspension of CsF (0.54 g, 3.54 mmol) in acetonitrile (10 ml) at 0°C. The mixture was then stirred at room temperature for thirteen hours, after which time the solvent was removed in vacuo and the residue taken up into ethyl acetate (50 ml) and saturated aqueous sodium carbonate (10 ml). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo to give the spectroscopically pure ester 2-methyl-2-(methylamino)propyl-3,5-dimethylthiophene-2-carboxylate (290) (0.28 g, 98%) as a colourless liquid, b.p., 220°C at 0.20 mmHg; δ ($CDCl_3$), 6.59 (1H, s, thiophene 4-H), 4.10 (2H, s, OCH_2), 2.50 (3H, s, NCH_3), 2.44 (3H, s, thiophene CH_3), 2.37 (3H, s, thiophene CH_3), 1.60 (1H, br., NH), 1.12 (6H, s,

oxazoline CH_3); $\nu_{max.}$ ($CHCl_3$), 2940, 1705, 1455, 1245, 1130 and 1075 cm^{-1}; m/z 241 (M^+, 100%), 86 (32) and 72 (8). When the above experiment is modified such that ethyl vinyl ether (10 ≡) or cyclohexene (10 ≡) is present in the reaction mixture, the outcome is the same.

3,5-DIMETHYLTHIOPHENE-2-CARBOXYLIC ACID (295)

METHOD 1

Ester (290) (0.19 g, 0.79 mmol) was heated under reflux with aqueous potassium hydroxide (40% w/w, 10 ml) and ethanol (10 ml) for twenty-four hours. After cooling, the bulk of the ethanol was evaporated and the residue acidified to pH 2 (conc. HCl). The solution was extracted with ethyl acetate (2 x 50 ml) and the organic solution was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). The solvent was removed in vacuo and the crude product recrystallised (ethyl acetate - light petroleum) to give the pure carboxylic acid (295) (0.11 g, 89%) as a white solid, m.p., 170 - 171°C (lit.,[179] 171 - 172°C). (Found: C, 53.71; H, 5.04. Calculated for $C_7H_8O_2S$, C, 53.84; H, 5.16%); δ ($CDCl_3$), 6.63 (1H, s, thiophene 4-H), 2.49 (3H, s, CH_3), 2.46 (3H, s, CH_3); $\nu_{max.}$ (KBr), 1662, 146, 1289 and 1142 cm^{-1}; m/z 156.0249 calculated for $C_7H_8O_2S$, 156.0245.

METHOD 2

2-Acetyl-3,5-dimethylthiophene (5.0 g, 32.46 mmol) was heated under reflux with commercial sodium hypochlorite (200 ml) and dioxan (50 ml) for twenty-four hours. After cooling, sodium metabisulphite (2.0 g) was added and the solution basified to pH 12 (KOH aq., 40% w/w). The solution was washed with diethyl ether (1 x 100 ml) and the aqueous phase was acidified to pH 1 (conc. HCl). This was

extracted with ethyl acetate (3 x 100 ml), which was dried ($MgSO_4$) and evaporated to give the crude product. Recrystallisation (ethyl acetate - light petroleum) afforded the pure carboxylic acid (295) (2.00 g, 39%), m.p., 170 - 171°C. This material was spectroscopically idential to that formed under Method 1.

ADDUCT (281) : REACTION OF o-XYLYLENE (157) WITH MVK

A solution of oxazolinium salt (156) (2.96 g, 7.00 mmol) in acetontrile (20 ml) was added dropwise to a mixture of CsF (3.16 g, 20.08 mmol), MVK (1.74 ml, 21.0 mmol) and acetonitrile (20 ml) at 0°C. The mixture was stirred at 0°C for five hours and then at room temperature for sixteen hours. The solvent was removed in vacuo and the residue taken up in diethyl ether (150 ml) and saturated aqueous sodium carbonate solution (30 ml). The ethereal layer was washed with water (1 x 20 ml) and brine (1 x 20 ml) and then dried ($MgSO_4$). Evaporation of the solvent gave the crude adduct (281) as a viscous gum (1.78 g, 87%); δ ($CDCl_3$), 6.39 (1H, s, thiophene 4-H), 3.77 (2H, dd, J 7.0 Hz, $OC\underline{H}_2$), 3.44 (1H, m), 3.15 (1H, m), 2.68 (1H, m), 2.38 (3H, s, NCH_3), 2.33 (1H, m), 2.26 (3H, s, thiophene CH_3), 2.22 (3H, s, $COC\underline{H}_3$), 1.95 (1H, m), 1.23 (3H, s, oxazoline CH_3), 1.07 (3H, s, oxazoline CH_3); $\nu_{max.}$ (CCl_4), 2990, 1725, 1465, 1365 and 910 cm^{-1}; m/z (CI), 294 (M+1, 100%), 223 (55) and 86 (19).

B-DIKETONE (282) : HYDROLYSIS OF ADDUCT (281)

Dilute aqueous HCl (5% v/v, 10 ml) was added to adduct (281), (0.80 g, 2.73 mmol) and the solution was stirred at room temperature for twenty-four hours. The solution was extracted with ethyl acetate (3 x 20 ml) and the organic phase was washed with water (1 x 10 ml) and brine (1 x 10 ml). The organic solution was dried ($MgSO_4$) and

the solvent removed in vacuo to give the β-diketone (282) (0.37 g, 65%); δ ($CDCl_3$), 15.68 (1H, s, OH); $\nu_{max.}$ (CCl_4), 3500 - 3000 (br.,), 2915, 1720, 1660, 1610, 1455 and 1285 cm^{-1}; m/z 208 (M^+, 100%), 193 (46) and 165 (52).

β-DIKETONE (283) : ALKYLATION OF β-DIKETONE (282)

To β-diketone (282) (0.35 g, 1.68 mmol) dissolved in acetone (4 ml) was added potassium carbonate (0.26 g, 1.85 mmol) and methyl iodide (1.0 ml, 16.80 mmol). The mixture was heated under reflux for twenty-four hours. After cooling the inorganic residues were removed by filtration and repeatedly washed with acetone. The combined acetone washings were evaporated to give the methylated β-diketone (283) (0.24 g, 64%); δ ($CDCl_3$), 6.62 (1H, s, thiophene 4-H), 2.97 - 2.55 (3H, m), 2.51 (3H, s, thiophene CH_3), 2.01 - 1.89 (1H, m), 1.41 (3H, s, $COCH_3$); ^{13}C, 206.54 (s), 191.05 (s), 153.00 (s), 151.41 (s), 133.67 (s), 126.92 (d), 59.73 (s), 33.60 (t), 26.27 (q), 23.10 (t), 20.41 (q), and 16.10 (q); $\nu_{max.}$ (CCl_4), 2985, 1712 and 1662 cm^{-1}; m/z 222.0717 (M^+, 16%, $C_{12}H_{14}O_2S$ requires 222.0714), 179 (100), 165 (47), 138 (36), 110 (27) and 43 (34).

ADDUCT (284) : REACTION OF o-XYLYLENE (157) WITH MALEIC ANHYDRIDE

A solution of oxazolinium salt (156) (1.48 g, 3.50 mmol) in acetonitrile (20 ml) was added dropwise to a mixture of CsF (1.58 g, 10.40 mmol), maleic anhydride (0.38 g, 3.85 mmol) and acetonitrile (15 ml) at 0°C. The mixture was stirred at 0°C for five hours and then at room temperature for sixteen hours. The solvent was removed in vacuo and the residue taken up in ethyl acetate (150 ml) and water (20 ml). The organic phase was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent gave

the crude product (0.91 g, 81%). Recrystallisation (ethyl acetate - light petroleum) afforded the pure adduct (284) as a white solid (0.87 g, 77%), m.p., 184 - 186°C. (Found: C, 59.76; H, 6.02; N, 4.00. $C_{16}H_{19}NO_4S$ requires C, 59.80; H, 5.96; N, 4.36%); δ ($CDCl_3$), 6.71 (1H, s, thiophene 4-H), 4.21 (2H, s, OCH_2), 4.10 (1H, d, J 5.0 Hz), 3.36 (1H, d, J 15.0 Hz), 3.12 (3H, s, NCH_3), 2.83 (2H, m), 2.47 (3H, s, thiophene CH_3), 1.42 (3H, s, oxazoline CH_3), 1.31 (3H, s, oxazoline CH_3); $\nu_{max.}$ (KBr), 2979, 1734, 1586, 1543, 1383, 1371, 1164 and 760 cm^{-1}; m/z (FAB) 322 (M^+, 100%), 304 (13), 27, 276 (95) and 136 (33).

ADDUCT (285) : REACTION OF o-XYLYLENE (157) WITH N-PHENYLMALEIMIDE

The experimental procedure described for adduct (284) was followed, with N-phenylmaleimide (10.50 mmol, 1.82 g) as dienophile. The work-up procedure differed only in the addition of saturated aqueous sodium carbonate solution (20 ml) to the residue obtained after solvent removal. Following the usual washing and drying procedures, solvent evaporation gave a dark grey solid (1.39 g, 100%). Recrystallisation (ethyl acetate - light petroleum) afforded the pure adduct (285) as a finely powdered pale grey solid, (1.02 g, 74%), m.p., 166 - 167°C. (Found: C, 66.66; H, 5.78; N, 6.89. $C_{22}H_{24}N_2O_3S$ requires C, 66.65; H, 6.10; N, 7.07); δ ($CDCl_3$), 7.33 (5H, m, aryl-H), 6.51 (1H, s, thiophene 4-H), 4.35 (1H, d, J 6.0 Hz, O-CH_2), 3.84 (1H, d, J 6.0 Hz, O-CH_2), 3.57 (2H, m, thiophene-CH_2-), 3.12 (2H, m, S-C-C-CH and S-C-C-C-CH), 2.43 (3H, s, NCH_3), 1.99 (3H, s, thiophene CH_3), 1.18 (3H, s, oxazoline CH_3), 1.01 (3H, s, oxazoline CH_3); $_{max.}$ (KBr), 2965, 2871, 1777, 1711, 1500, 1392 and 1194 cm^{-1}; m/z 396.1505 (M^+, 11%, $C_{22}H_{24}N_2O_3S$ requires 396.1508), 323 (66), 309 (22), 86 (100) and 58 (16).

ADDUCT (286) : REACTION OF o-XYLYLENE (157) WITH DIETHYL FUMARATE

A solution of oxazolinium salt (156) (1.48 g, 3.50 mmol) in acetonitrile (20 ml) was added dropwise to a mixture of CsF (1.58 g, 10.40 mmol), diethyl fumarate (1.72 ml, 10.50 mmol) and acetonitrile (20 ml) at 0°C. The mixture was stirred at 0°C for five hours and then at room temperature for sixteen hours. The reaction was worked-up as for adduct (281) to give the crude product as a viscous gum. Residual diethyl fumarate was removed by heating the gum (100°C) under vacuum (0.10 mmHg) to give the crude adduct (286) (1.18 g, 85%); m/z (CI), 396 (M^+, 12%), 242 (100), 86 (43) and 72 (25).

β-KETOESTER (287) : HYDROLYSIS OF ADDUCT (286)

Adduct (286) (1.28 g, 3.24 mmol) was hydrolysed using the procedure previously described for adduct (281). β-Ketoester (287) was obtained as a yellow solid (0.74 g, 74%), m.p., 121 - 123°C; $\nu_{max.}$ (CCl_4), 3500 - 3000 (br.,), 2975, 1735, 1675, 1460 and 1030 cm^{-1}; m/z 310 (M^+, 25%), 265 (20), 237 (100), 191 (66), 165 (84) and 72 (88).

β-KETOESTER (288) : ALKYLATION OF β-KETOESTER (287)

To β-ketoester (287) (0.18 g, 0.58 mmol), dissolved in acetone (5 ml) was added potassium carbonate (0.08 g, 0.64 mmol) and methyl iodide (1.80 ml, 29.0 mmol). The mixture was heated under reflux for twenty hours. The solvent was removed in vacuo and the residue taken up in ethyl acetate (100 ml) and water (10 ml). The organic solution was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent gave the chromatographically pure methylated β-ketoester (288) as a colourless liquid (0.18 g, 96%); δ ($CDCl_3$), 6.69 (1H, s, thiophene 4-H), 4.17 (4H, m, 2 x CH_2-CH_3), 3.40 (1H, m), 3.14 (2H, m), 2.53 (3H, s, thiophene CH_3), 1.60

(3H, s, CH_3), 1.23 (6H, m, 2 x $CH_2\underline{C}H_3$); $\nu_{max.}$ (CCl_4), 2980, 1735, 1665, 1460, 1175 and 1020 cm^{-1}; m/z 324.1034 (M^+, 14%, $C_{16}H_{20}O_5S$ requires 324.1031), 279 (22), 251 (100), 237 (26) and 72 (74).

4,4-DIMETHYL-2-(2-FURYL)OXAZOLINE (298)

The furyl-oxazoline (298) was synthesised from 2-furoic acid (20 g, 0.18 mol) using the procedure described for the analogous thiophene compound (261). The furyl-oxazoline (298) (24.65 g, 83%) was obtained as a waxy solid, m.p., 36 - 37°C (lit.,[132] 36 - 37°C); δ ($CDCl_3$), 7.53 (1H, dd, J 0.67, 1.68 Hz, furan 5-H), 6.94 (1H, dd, J 0.67, 3.38 Hz, furan 3-H), 6.49 (1H, dd, J 1.68, 3.38 Hz, furan 4-H), 4.09 (2H, s, OCH_2), 1.36 (6H, s, CH_3); m/z 165 (M^+, 14%), 150 (100), 122 (17), 95 (16) and 94 (31).

4,4-DIMETHYL-2-(5-METHYL-2-FURYL)OXAZOLINE (299)

Furyl-oxazoline (298) (1.0 g, 6.06 mmol) dissolved in thf (10 ml) was added to a solution of LDA (6.66 mmol) and TMEDA (6.66 mmol) in thf (30 ml) at -78°C. The mixture was stirred at -78°C for one hour and then methyl iodide (3.77 ml, 60.60 mmol) was added. The mixture was allowed to warm to room temperature and stirred for a further four hours. The solvent was removed in vacuo and the residue taken up in ethyl acetate (100 ml) and water (20 ml). The organic phase was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent and bulb-to-bulb distillation of the residue gave the chromatographically pure oxazoline 4,4-dimethyl-2-(5-methyl-2-furyl)oxazoline (299) (0.92 g, 85%), b.p., 135°C at 0.25 mmHg; δ ($CDCl_3$), 6.82 (1H, d, J 3.95 Hz, furan 3-H), 6.09 (1H, d, J 3.95 Hz, furan 4-H), 4.06 (2H, s, OCH_2), 2.37 (3H, s, furan CH_3), 1.36 (6H, s, oxazoline CH_3); $\nu_{max.}$ (film), 2950, 2910, 1660, 1640, 1295 and

1050 cm^{-1}; m/z 179.0943 (M^+, 24%, $C_{10}H_{13}NO_2$ requires 179.0946), 164 (100), 136 (28) and 108 (45).

4,4-DIMETHYL-2-(3,5-DIMETHYL-2-FURYL)OXAZOLINE (300)

To 5-methylfuryl-oxazoline (299) (0.90 g, 5.03 mmol) dissolved in thf (30 ml) at -78°C was added ^nBuLi (7.54 mmol), and the mixture stirred at -78°C for half an hour, after which time, methyl iodide (3.13 ml, 50.30 mmol) was added. The mixture was stirred at -78°C for half an hour and then allowed to warm to room temperature and stirred for a further four hours. The solvent was removed in vacuo and the residue taken up in ethyl acetate (100 ml) and water (10 ml). The organic solution was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent and bulb-to-bulb distillation of the residue gave the chromatographically pure oxazoline 4,4-dimethyl-2-(3,5-dimethyl-2-furyl)oxazoline (300) as a colourless liquid (0.72 g, 74%), b.p., 120°C at 0.15 mmHg; δ ($CDCl_3$), 5.93 (1H, s, furan 4-H), 4.03 (2H, s, OCH_2), 2.29 (3H, s, furan CH_3), 2.23 (3H, s, furan CH_3), 1.32 (6H, s, oxazoline CH_3); $\nu_{max.}$ (film), 2960, 1660, 1640, 1230 and 1050 cm^{-1}; m/z 193.1099 (M^+, 53%, $C_{11}H_{15}NO_2$ requires 193.1103), 178 (100), 150 (35) and 122 (43).

4,4-DIMETHYL-2-(3-TRIMETHYLSILYLMETHYL-5-METHYL-2-FURYL)OXAZOLINE (301)

To the 3,5-dimethylfuryl-oxazoline (300) (0.70 g, 3.63 mmol) dissolved in thf (30 ml) at -78°C was added ^sBuLi (3.63 mmol) and the mixture stirred at -78°C for half an hour. The solution was quickly warmed to room temperature and TMSCl (0.51 ml, 3.99 mmol) was added. The solution was stirred for half an hour and then the solvent was removed in vacuo. The residue was taken up in ethyl acetate (100 ml)

and water (10 ml). The organic phase was washed with water (2 x 10 ml) and brine (1 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent and bulb-to-bulb distillation of the residue gave the chromatographically pure oxazoline 4,4-dimethyl-2-(3-trimethylsilylmethyl-5-methyl-2-furyl)oxazoline (301) as a colourless liquid (0.69 g, 72%), b.p., 150°C at 0.20 mmHg; δ ($CDCl_3$), 5.76 (1H, s, furan 4-H), 4.31 (2H, s, OCH_2), 2.55 (3H, s, furan CH_3), 2.43 (2H, s, CH_2TMS), 1.65 (6H, s, oxazoline CH_3), 0.36 (9H, s, TMS); $\nu_{max.}$ (film), 2960, 1660, 1640, 1240, 1040 and 840 cm^{-1}; m/z 265.1498 (M^+, 50%, $C_{14}H_{23}NO_2Si$ requires 265.1498), 250 (44), 193 (23), 178 (34) and 73 (100).

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APPENDIX

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2,3-DIMETHYLENE-2,3-DIHYDROTHIOPHENE: THE THIOPHENE ANALOGUE OF ORTHO-XYLYLENE

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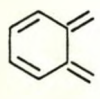
Abstract: The hitherto unknown 2,3-dimethylene-2,3-dihydrothiophene (the thiophene analogue of ortho-xylylene) and a substituted derivative have been prepared in solution and trapped as Diels-Alder adducts in good to excellent yields.

ortho-Xylylene 1 has found wide application in organic chemistry, notably in the synthesis of natural products including steroids,[1] alkaloids,[2] and anthracyclinones.[3] We have now developed routes to the hitherto unreported§ thiophene analogue of o-xylylene 2 (and to a substituted congener) based upon a directed metallation strategy for the construction of appropriate precursor molecules.



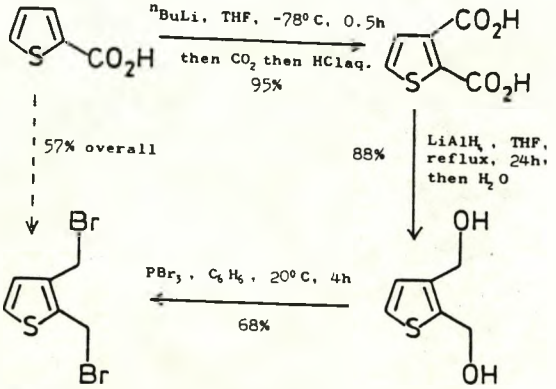
1

2

Our first approach utilizes the mono-anion of thiophene-2-carboxylic acid to direct lithiation into the β (3) position.[4] This permits the synthesis of 2,3-di(bromomethyl)thiophene 3 from thiophene-2-carboxylic acid in three, simple, steps (Scheme I). Treatment of the bis-bromide 3 with sodium iodide in dimethylformamide at 80°C in the presence of a dienophile[5] leads to the generation of 2,3-dimethylene-2,3-dihydrothiophene 2 which is trapped as its Diels-Alder adduct in good yield (Table I). Xylylene adducts 4 and 5

§ Dr. Jan Skramstad, Department of Chemistry, University of Oslo, has advised us that he will shortly be reporting the synthesis and trapping of a phenyl-substituted derivative of this system.

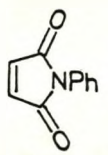
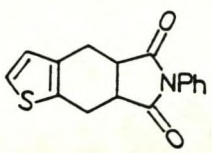
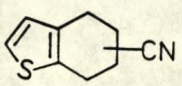
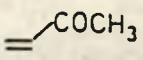
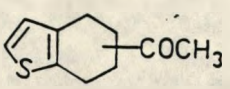
are obtained as mixtures of regioisomers. In the absence of dienophile, only polymeric material results.



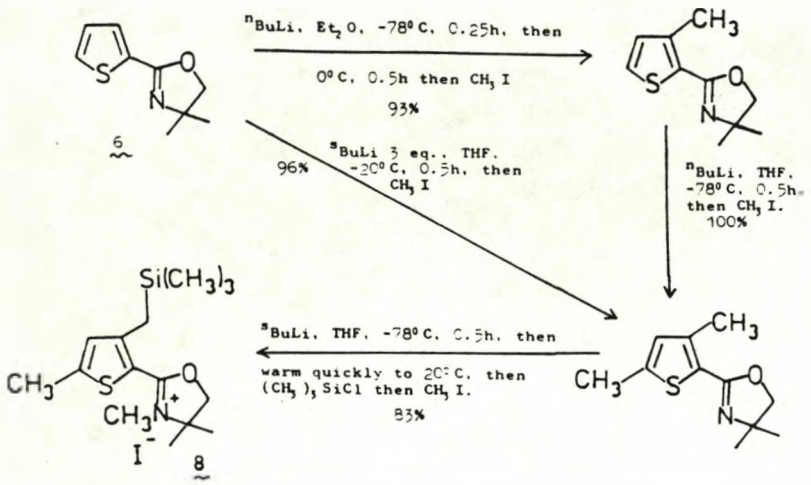
3

Scheme I

Table I Diels-Alder Trapping Experiments on o-Xylylene Analogue 2

Dienophile	Product	Yield (%)
		60
		60
4		
		50
5		

In a second approach to the thiophene o-xylylene system, oxazoline-directed metallation of 4,4-dimethyl-2-(2-thienyl)oxazoline[6] 6 provides access to the key, β-substituted, intermediates (Scheme II).



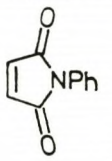
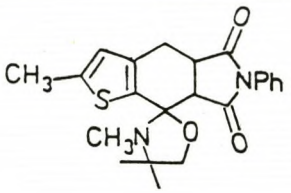
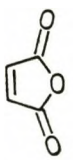
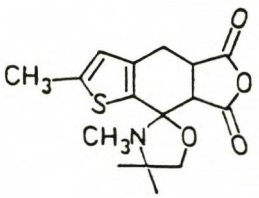
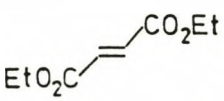
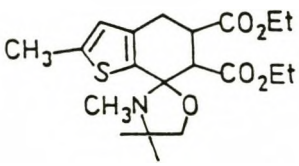
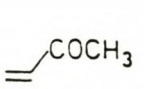
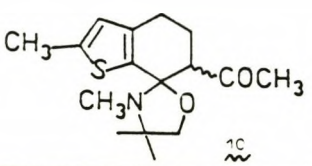
Scheme II

Lithiation of the 3,5-dimethyl-2-thienyloxazoline 7 occurs exclusively at the 3-methyl group. Reaction of the lithio-intermediate with chlorotrimethylsilane and methylation of the oxazoline nitrogen yields the required o-xylylene precursor 8. Treatment of this with caesium fluoride and acetonitrile in the presence of a dienophile[7] leads to the generation of a derivative of 2,3-dimethylene-2,3-dihydrothiophene bearing electron-donating substituents 9 which is trapped as its Diels-Alder adduct in high yield (Table II). Adduct 10 is obtained as a 1:1 mixture of diastereomers but is a single regioisomer.

We are currently applying these approaches to the preparation of other heterocyclic analogues of o-xylylene and investigating their synthetical utility.

Acknowledgment. A.P. is indebted to the SERC for the award of a studentship.

Table II Diels-Alder Trapping Experiments on o-Xylylene Analogue 9

Dienophile	Product	Yield (%)
		74
		77
		85
		87

10

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(2) Oppolzer, W. and Keller, K. J.Am.Chem.Soc. 1971, 93, 3836-7.

(3) Kerdesky, F.A.J., Ardecky, R.J., Lukshmikanthon, M.V., and Cava,M.P. J.Am.Chem.Soc. 1981, 103, 1992-6.

(4) Carpenter, A.J. and Chadwick, D.J. Tetrahedron Lett. 1985, 26, 1777-80.

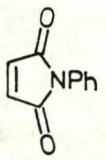
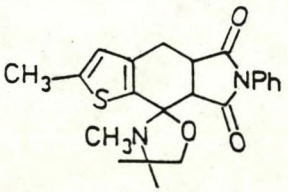
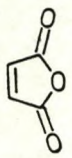
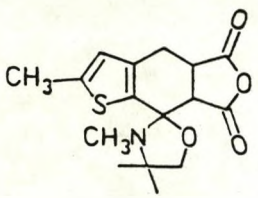
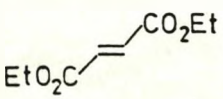
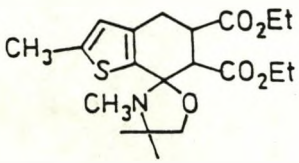
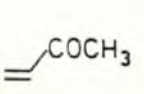
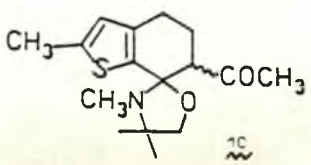
(5) Saroja, B. and Srinivasan, P.C. Tetrahedron Lett. 1984, 25, 5429-30.

(6) Carpenter, A.J. and Chadwick, D.J. J.Chem.Soc. Perkin Trans. I 1985, 173-181.

(7) Ito, Y., Amino, Y., Nakatsuka, M. and Saegusa, T. J.Am.Chem.Soc. 1983, 105, 1586-90.

(Received in UK 7 October 1987)

Table II Diels-Alder Trapping Experiments on o-Xylylene Analogue 9

Dienophile	Product	Yield (%)
		74
		77
		85
		87

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(1) Funk, R.L. and Vollhardt, K.P.C. Chem.Soc.Rev. 1980, 9, 41-61; Oppolzer, W. Synthesis 1978, 793-802; Kametani, T. and Nemoto, H. Tetrahedron 1981, 37, 3-16; Djuric, S., Sarkar, T., and Magnus, P. J.Am.Chem.Soc. 1980, 102, 6885-6.

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(5) Saroja, B. and Srinivasan, P.C. Tetrahedron Lett. 1984, 25, 5429-30.

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