CHAPTER III

A NEW GENERAL METHOD FOR THE SYNTHESIS OF 2-ALKOXY/ARYLOXY THIOPHENES VIA SIMMONS-SMITH REACTION ON ACYLKETENE O,S-ACETALS.*

III.1 INTRODUCTION

While attempting cyclopropanation of the α-oxoketene dithioacetals 2 under the Simmons-Smith reaction conditions it was accidentally discovered that the course of reaction led to the development of a new method for the synthesis of corresponding thiophenes 4 in excellent yields¹,² (scheme 1).

Scheme - 1
The course of reaction followed the interaction of the divalent sulphur with an electrophilic carbenoid species to give the intermediate ylids 3A which on intramolecular aldol type of addition-elimination sequence followed by demethylation of the quarternary sulphonium salts 3B yield the product thiophenes 4. The interaction of divalent sulfur with carbenoid species to give the ylid was not very unusual since there were many examples reported in the literature that the divalent sulphur compounds attack the electrophilic carbene species to give the corresponding sulphonium ylids. However, the intermediate ylid participating in an intramolecular aldol type condensation to provide thiophene was not known. The first and the only example reported in the literature is the intramolecular aldol type condensation of the ylid 7 generated from the corresponding dimethyl (o-aceto-p-tolyl) sulfonium methylsulphonate 6 to give the corresponding sulphonium salt 8 which on demethylation yielded the corresponding dihydrobenzthiophene 9 (scheme 2). This example was reported in 1949 when the sulphur ylids were not discovered.

The new thiophene synthesis discovered in our laboratory by reacting α-oxoketene dithioacetals with Simmons-Smith reagent was a novel and versatile method since it was applicable to a large majority of the structural variants of α-oxoketene dithioacetals which could be derived from various active methylene ketones. In nut-shell, the method is the conversion of active methylene ketones to thiophenes in two
Scheme 2
steps via corresponding α-oxoketene dithioacetals. The thiophene synthesis using Simmons-Smith reagent was the first of its kind and there were no hitherto reported examples of thiophene synthesis involving Simmons-Smith reaction. The method was of general application which was demonstrated by selecting cyclic oxoketene dithioacetals 10, 12 and 14 (scheme 3) which yielded the corresponding annelated thiophenes 11, 13 and 15 respectively in high yields. The method was also extended to the cinnamoylketene dithioacetals 16 where the corresponding 4-vinylthiophenes 17 were formed in high yields. It was noted that in the presence of divalent sulphur the interaction of double bond with Simmons-Smith reagent was not observed. Also when dienyl and trienyl oxoketene dithioacetals 18 were reacted under Simmons-Smith reaction conditions yielded the corresponding 4-dienyl and trienyl thiophenes 19 in high yields. Here again the extended double bonds remain unaffected by Simmons-Smith reagent. The cyclopropyl oxoketene dithioacetals 20 also underwent smooth condensation to give the corresponding thiophenes 21 in high yields under similar reaction conditions. It may be noted again that the double bonds insulated by cyclopropane ring [R¹=C₆H₅, C₆H₅-CH=CH, also C₆H₅-(CH=CH)₂⁻] remained unaffected in the overall thiophene synthesis. Therefore, the method was extremely useful for the synthesis of various thiophenes from α-oxoketene dithioacetals with diverse functional groups which were otherwise sensitive to Simmons-Smith reagent in the absence of divalent sulphur group.
Scheme 3

10 \[ \text{Zn-Cu/CH}_2\text{I}_2 \rightarrow \text{Et}_2\text{O/THF} \]
\[ \text{n} = 1, 2, 3, 7 \]

12 \[ \text{Zn-Cu/CH}_2\text{I}_2 \rightarrow \text{Et}_2\text{O/THF} \]
\[ \text{n} = 1, 2 \]

14 \[ \text{Zn-Cu/CH}_2\text{I}_2 \rightarrow \text{Et}_2\text{O/THF} \]
\[ 14-15a, \text{R} = \text{H}; \text{X} = \text{O} \]
\[ b, \text{R} = \text{Me}; \text{X} = \text{S} \]
Scheme 4

16

\[
\text{Ar} = \text{C}_6\text{H}_5; 4-\text{Cl C}_6\text{H}_4; 2-\text{Cl C}_6\text{H}_4; 4-\text{MeO C}_6\text{H}_4; 3,4-(\text{MeO})_2 \text{C}_6\text{H}_3
\]
\[R^1 = R^2 = \text{H, Me}\]

17

18

\[n = 1; \text{Ar} = \text{C}_6\text{H}_5; 4-\text{MeO C}_6\text{H}_4; R^1 = \text{H, Me}; R^2 = \text{H, Me, n-Bu}\]
\[n = 2; \text{Ar} = \text{C}_6\text{H}_5; 3,4-\text{Methylene dioxy C}_6\text{H}_3; R^1 = \text{H}; R^2 = \text{H, Me}.\]

19

20

\[R^1 = \text{C}_6\text{H}_5; \text{C}_6\text{H}_5\text{CH = CH}; \text{C}_6\text{H}_5-(\text{CH = CH})_2^-.\]

Scheme 4
When this reaction was discovered in our laboratory, the $\alpha$-oxoketene dithioacetals were indeed already used for the synthesis of thiophenes by Marino and Kostusyk. The reaction involved deprotonation of the thiomethyl group cis to carbonyl group to give the corresponding sulphur stabilized carbanions which underwent intramolecular cyclization to give thiophenes in moderate yields (scheme 5). However the method suffered serious drawbacks in terms of yields of thiophenes. The overall yields were found to be low except that only in one case 55% of thiophene formation was observed. Also the method failed to give thiophenes when acylketene dithioacetals were used as substrates. The reason for the failure with acylketene dithioacetals was due to their competitive deprotonation of the acyl group to form the corresponding enolate anions in preference to methylthio group deprotonation (scheme 6). Thus the method was not suitable for the synthesis of 3-alkyl and 3,4-dialkyl thiophenes. Similarly it is doubtful whether the method could be used for the synthesis of 4-enylthiophenes due to competitive deprotonation of vinylic proton. Also the $\alpha$-position cannot carry the alkyl group which readily gives allyl anion although higher alkyl chains are tolerated to some extent.

The $\alpha$-oxoketene dithioacetals have been shown to be an alternate precursors for the synthesis of thiophenes which carry methylthio group at 2- or 5- position. The attempted selective desulphurization of methylthio group in the
Scheme 5

<table>
<thead>
<tr>
<th>Ar</th>
<th>R</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅</td>
<td>H</td>
<td>30</td>
</tr>
<tr>
<td>4-MeO C₆H₄</td>
<td>H</td>
<td>30</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>Et</td>
<td>55</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>MeO</td>
<td>42</td>
</tr>
</tbody>
</table>

**ArCH₃**
Scheme 6

\[ \text{R} = \text{H} \quad 22\% \\
\text{b, R} = \text{OMe} \quad 38\% \]
presence of Raney Nickel was not very satisfactory since desulphurized thiophenes were accompanied by open chain products. Also our attempts to desulphurise in the presence of nickel boride (\(NaBH_4/\text{NiCl}_2\)) failed as the unreacted methylthiothiophene 35 (scheme 7) was recovered. The reaction of Grignard reagent in the presence of triphenylphosphine nickel chloride complex also failed to give the corresponding thiophene 37 (scheme 7). Therefore one major limitation of this thiophene synthesis is retaining of the SMe group in the product thiophenes which could neither be removed nor be replaced.

In the present study doubly activated \(\alpha\)-carboalkoxyketene dithioacetals 38a-e were investigated with a view to observe the effect of the carbonyl moiety and also whether the reaction could be extended for the synthesis of 3-hydroxy/aminothiophenes. When 38a was examined under the Simmons-Smith reaction conditions, the corresponding dethiomethylated product ethyl 3-methylthio-2-phenyl propenoate 39a was obtained in 79% yield (scheme 8). The structure of 39a was established on the basis of its analytical and spectral data. It was analysed for \(C_{12}H_{14}O_2S\) and the molecular weight was confirmed by its mass spectrum with a peak at \(m/z\) 222 (\(M^+\), 100%). The compound showed a strong absorption in its IR (neat) spectrum at 1710 cm\(^{-1}\) indicating the presence of carbonyl function and other important peaks which are listed in the experimental section. The \(^1\)H NMR (\(CCl_4\)) of 39a exhibited a triplet at 51.10(3H, \(J=6\)Hz) was assigned to ester \(\text{CH}_3\) group. The singlet at
Scheme 7

35 \[ \xrightarrow{\text{NiCl}_2 \cdot 6\text{H}_2\text{O}} \] 36

35 \[ \xrightarrow{\text{NaBH}_4 / \text{EtOH}} \] 36

35 \[ \xrightarrow{\text{Ph}_3\text{P} / \text{NiCl}_2} \] 37

35 \[ \xrightarrow{\text{MeMgI / Et}_2\text{O}} \] 37
Scheme 8

\[
\begin{align*}
&\text{MeS-SMe} \quad \overset{\text{Zn-Cu/CH}_2\text{I}_2}{\longrightarrow} \quad \text{Et}_2\text{O}/\text{THF} \quad \text{R}^1\text{CO}_2\text{R}^2 \\
&\quad \downarrow \text{Zn-Cu/CH}_2\text{I}_2 \\
&\text{H}_5\text{C}_6\text{S} \quad \text{CO}_2\text{Et} \\
&\quad \text{H} \quad \text{SMe} \\
\end{align*}
\]

38-39

38-39 a, R\(^1\) = C\(_6\)H\(_5\); R\(^2\) = Et
b, R\(^1\) = CN; R\(^2\) = Et
c, R\(^1\) = CO\(_2\)Et; R\(^2\) = Et
d, R\(^1\) = COMe; R\(^2\) = Me
38 e, R\(^1\) = COC\(_6\)H\(_5\); R\(^2\) = Et
δ2.27(3H) was assigned for SMè protons. The ester CH₂ group was appeared as quartet at δ4.30(2H, J=6Hz). The broad singlet at δ7.27(5H), was assigned to phenyl protons. Similarly the di-thioacetals 38b-d afforded the corresponding dethiomethylated products 39b-d in 56-82% overall yields. All these compounds were characterised by their analytical and spectral data (experimental section).

Interestingly, when di-thioacetal 38e was treated with Simmons-Smith reagent, expected thiophene 40 was formed in 51% yield (scheme 8). The structure 40 was supported by its analytical and spectral data. It was analysed for C₁₄H₁₄O₂S and the molecular weight was confirmed from its mass spectrum with molecular ion peak at m/z 278 (M⁺, 100%). The compound had strong absorption in its IR (neat) region at 1710 cm⁻¹. The ¹H NMR (CCl₄) signal for ester CH₃ protons appeared at δ1.03(3H, J=6Hz) as triplet and the SMè protons appeared as singlet at δ2.57(3H). The quartet at δ4.08(2H, J=6Hz) was assigned to ester CH₂ protons. The thiophene ring proton appeared as singlet at δ6.97(1H). The phenyl protons appeared as singlet at δ7.28(5H).

The mechanism of formation of dethiomethylated products 39a-d from doubly activated α-carboalkoxyketene di-thioacetals 38a-d under Simmons-Smith reaction conditions appears to be not very clear. The combination of Zn-Cu couple and diiodomethane was necessary for this transformation, since the starting material was recovered unchanged when 38a was refluxed with Zn-Cu couple alone in tetrahydrofuran under identical
conditions. Reductive dsulphurisation of α-phenylthioketones with zinc in the presence of trimethyl silyl chloride is reported in the literature. The methylthio group in these doubly activated ketene dithioacetals is more labile and less nucleophilic. Therefore the reaction appears to take different course under Simmons-Smith reaction conditions causing reductive dethiomethylation of the substrates.

Thus it was considered of interest to explore further the possibilities to alter the functional groups in the substrate molecules so that the desired substituents could be carried to the product thiophenes. However, such substitution should be highly configurationally favourable so that the lone SMe group should remain cis to the oxo group in the acetals. Thus for the displacement of SMe group, the oxoketene dithioacetals should necessarily be possessing 'Z' configuration so that the SMe group remains cis to the carbonyl group as desired. This has been successfully achieved by developing a methodology in this laboratory by condensing active methylene ketones 41 and 45 with alkylxanthates 39 (scheme 9) in presence of sodium t-butoxide to give corresponding thionoesters 43 and 46 in overall good yields. The thionoesters 43 and 46 were subsequently alkylated in the presence of potassium carbonate/acetone and methyliodide to give the corresponding α-oxoketene O-alkyl S-methylacetals 44a-d and 47 respectively in high yields. These O,S-acetals possess exclusive 'Z' geometry as confirmed by their NOE studies which is an
Scheme 9

H₅C₆CH₃ + MeS⁻ C⁻ OR¹ → H₅C₆ C-O⁻ OR¹

42a-d

42 - 44a, R¹ = Me
b, R¹ = Et
c, R¹ = n-Pr
d, R¹ = n-Bu

1. K₂CO₃ / Acetone
2. MeI

H₅C₆

44a-d

47
essential requirement for our efforts to develop suitable precursors for alkoxythiophenes.

However, the above described method of O,S-acetals could not be used for the synthesis of α-oxoketene O-aryl S-methyl acetals that were needed as starting materials in the present investigation. For this the best alternative method adopted has been formulated in scheme 10. The α-oxoketene dithioacetals 48 and 51 were conveniently quarternized by reacting with dimethyl sulphate followed by perchloric acid to the corresponding sulphonium salts 49 and 52 which are stable crystalline products as perchlorates. The sulphonium salts 49 and 52 underwent facile displacement with various phenols and alcohols to give the corresponding O,S-acetals 50a-f and 53. The configuration of all these O,S-acetals was assigned 'Z' geometry where the desired SMe group was cis to the carbonyl group.

The preliminary reaction of O,S-acetals under Simmons-Smith reaction conditions yielded the corresponding thiophenes in excellent yields. The synthesis of alkoxy and aryloxy thiophenes from the corresponding O,S-acetals described is the subject of this chapter. The development of an efficient method for the synthesis of alkoxy and aryloxy thiophenes was necessitated in view of the lack of good methods in the literature. There have been few attempts in the literature for the synthesis of alkoxy and aryloxy thiophenes which are briefly illustrated in the following section before the present new method is discussed.
Scheme 10

51

1. Me₂SO₄/Δ
2. HClO₄

52

K₂CO₃ / R¹OH
Acetone

53

50a-f

49a-f

48a-f

a, Ar = C₆H₅; R¹ = C₆H₅CH₂
b, Ar = C₆H₅; R¹ = n-C₁₂H₂₅
c, Ar = 4-MeO C₆H₄; R¹ = C₆H₅
d, Ar = C₆H₅

e, Ar = 4-MeO C₆H₄; R¹ = CO₂Et
f, Ar = 4-MeO C₆H₄; R¹ = CO₂Et
III.2 ALKOXY AND ARYLOXYTHIOPHENES: A BRIEF SURVEY

The earliest synthesis of 2-methoxythiophene 56 (scheme 11) appears to be reported by Hurd and Krenz in 1950. The thiophene magnesium bromide 54 was reacted with dry oxygen to give the corresponding 2-hydroxythiophene 55 which was alkylated with dimethyl sulphate in the presence of aqueous potassium hydroxide. Similarly 2-chloro-3-nitrothiophenes 57 were also shown to undergo facile displacement in the presence of potassium alkoxides to afford the corresponding 2-alkoxy-3-nitrothiophenes 58 (scheme 11).

Subsequently, Sice and Proft employed the 2-halothiophenes 59 under the conditions of Williamsons synthesis to obtain the corresponding 2-alkoxythiophenes 60 (scheme 12). They observed that the iodothiophenes gave better yields than the corresponding bromothiophenes while the corresponding chlorothiophenes failed to undergo this reaction. Improved yields of alkoxy thiophenes were obtained when the reaction was carried out in the presence of copper(II) salts rather than copper(I) salts (scheme 12).

Lawesson and co-worker attempted to prepare the methoxy thiophenes 66 from the corresponding thiolene-2-ones 64 using the corresponding thallium salts 65 (scheme 13). However, the thallium salts on alkylation gave a mixture of products including O- and C-alkylated products. The required thiolene-2-ones 64 were prepared from metallation of thiophenes 61 followed by treatment of anion 62 with t-butylperoxy ester to
\[
\begin{align*}
\text{Scheme-11} \\
\end{align*}
\]
Scheme 12

ROH/Δ or RONa

Catalyst

X = Cl, Br, I,

; R = Me, Et, C₆H₅

S

59

S

60

OR
**Scheme 13**

51 \[\text{n-BuLi} \rightarrow \text{52} \]

62 \[\text{1. Mg Br}_2 \rightarrow \text{63} \]

\[\text{2. Ph-COOBu} \rightarrow \text{64} \]

\[\text{PTSA} \]

56 \[\text{Mel} \rightarrow \text{55} \]

\[\text{55} \rightarrow \text{54} \]

R = H, Me.
afford the corresponding t-butoxy thiophenes 63 which were hydrolysed with p-toluene sulphonic acid to afford 64. The thallium salts 65 were obtained by treatment of thiolene-2-ones 64 with thallium ethoxide which on alkylation with methyl iodide afforded 2-methoxythiophenes 66.

Ashby and co-workers\textsuperscript{13} reacted 3-bromothiophene 67 with salicylate 68 in the presence of potassium carbonate and copper bronze to afford the corresponding ether 69 which was subsequently cyclized to give the corresponding xanthone 70 (scheme 14).

Subsequently, Watthey and Desai\textsuperscript{14} reacted 2-bromothiophene 71 with ethylsalicylate 72 essentially under similar reaction conditions reported by Ashby and co-workers\textsuperscript{13} to get the ether 73 but only in 8\% yield (scheme 15). The corresponding ether after hydrolysis of the ester group was cyclized to the corresponding xanthone 75 in the presence of polyphosphoric ester.

Brunet and Paquer\textsuperscript{15} prepared the ethoxy thiophenes 77 by treating the β-ketoesters 76 with hydrogen sulphide in the presence of hydrochloric acid (scheme 16).

Recently, Brandsma and co-workers\textsuperscript{16} have investigated copper (I) halide catalysed synthesis of alkyl, aryl and alkyl heteroaryl ethers and found that 2-bromothiophene tended to undergo reduction rather than displacement with alkoxy group. However, they found that the displacement reaction is favoured when the alkoxide concentration in the reaction
Scheme 14

K₂CO₃/Cu-bronze / Δ / 7 days

68

67

69

70
Scheme 15

EtO₂C

K₂CO₃/Cu-bronze

8%

EtO₂C

H₂O

+ 

Br

Scheme 15
mixture is high. They also observed that 2,3-dibromothiophene undergoes both displacement and reductive transformation in varying degrees as shown in scheme 17. Maximum yield of 3-methoxy thiophene 79 (60%) was obtained by the reduction of the 2-bromo group along with 3% of completely reduced thiophene 82 and the complete conversion required prolonged heating under reflux.

From these examples described above, it is apparent that the methods available in the literature for the synthesis of alkoxy thiophenes are not many and most of them suffer from serious limitations. Besides all the methods have employed halothiophenes which are to be prepared from the corresponding thiophenes. Therefore, a direct method for the synthesis of alkoxy and aryloxy thiophenes will be of great synthetic importance. In the present investigation it has been successfully demonstrated that the easily accessible O,S-acetals as described earlier have the requisite geometrical (Z) configuration suitable for the alkoxy thiophene synthesis under Simmons-Smith reaction conditions. These results are described as follows.

III.3 RESULTS AND DISCUSSION

The O,S-acetal 87a (scheme 18) when treated with Zn-Cu/methylene iodide in the presence of ether and tetrahydrofuran the reaction mixture after work-up yielded the corresponding 2-methoxy-4-phenylthiophene 89a in 66% yield. The methoxythiophene was not reported earlier and had melting point 40-41°C. It was analysed for C_{11}H_{10}OS and its molecular
Scheme 17:

\[ \text{MeOH, 10\% Cu Br} \]

\[
\begin{align*}
\text{Br} & \quad 78 \\
\text{S} & \quad \text{S} \\
\text{Br} & \quad \text{OMe} \\
83 & \\
\text{Br} & \quad \text{OMe} \\
84 & \\
\text{S} & \quad \text{S} \\
80 & \\
\text{S} & \quad \text{OMe} \\
81 & \\
\text{S} & \quad \text{OMe} \\
82 & \\
\text{S} & \quad \text{S} \\
85 & \\
\text{S} & \quad \text{Br} \\
86 & \\
\end{align*}
\]
weight was confirmed by its mass spectrum with a peak at m/z 190 (M⁺, 19%). In its IR(KBr) spectrum it showed strong bands at 1620, 1600, 1507, 1465 and 1218 cm⁻¹. Its structure was further confirmed from its ¹H NMR (CDCl₃) spectrum. The singlet at δ3.84(3H) was assigned to methoxy protons. The doublet at δ6.55(1H, J=1.5Hz) was assigned to H-3 ring proton which showed 1,3-coupling with the H-5 proton. The H-5 proton was found at δ6.88(1H), as a doublet with coupling constant J=1.5Hz. The phenyl protons appeared as multiplet between δ7.22-7.29 (5H). The other alkoxy thiophenes 87b-e were similarly obtained under the described reaction conditions in 32-72% overall yields. The structure of 87b-e were established by their analytical and spectral data (experimental section). Similarly the oxoketene O-dodecyl S-methylacetal 87f also underwent thiophene ring formation to give the 2-dodecylthiophene 89f in 59% yield (scheme 18). The structure of 89f was confirmed by its spectral and analytical data (experimental section).

The O-aryl S-methyl acetalts were next examined for thiophene synthesis. Thus O,S-acetal 87g (scheme 19) on treatment under the Simmons-Smith reaction conditions yielded the corresponding 4(4'-methoxyphenyl)-2-phenoxythiophene 89g in 66% yield. It was analysed for C₁₇H₁₄O₂S and the molecular weight was confirmed from its mass spectrum with a peak at m/z 283 (M⁺, 100%). It showed in its IR(KBr) spectrum bands at 1619, 1608, 1583, 1486, 1252, and 1214 cm⁻¹. The structure was further confirmed from its ¹H NMR (CDCl₃)
Scheme 18

\[ \text{Ar} \quad \overset{\text{Zn-Cu/CH}_2\text{I}_2}{\text{Et}_2\text{O}/\text{THF}/\Delta} \quad \text{Ar} \]

87a-e

87 - 89a, Ar = C_6H_5; R^1 = Me
b, Ar = C_6H_5; R^1 = Et
c, Ar = C_6H_5; R^1 = n-Pr
d, Ar = C_6H_5; R^1 = n-Bu
e, Ar = C_6H_5; R^1 = C_6H_5 \text{CH}_2

88A

88B

89a-e

87f, \overset{\text{Zn-Cu/CH}_2\text{I}_2}{\text{Et}_2\text{O}/\text{THF}/\Delta} \quad \text{H}_5\text{C}_6

Scheme 18
spectrum. The singlet at 53.78(3H), was assigned to p-methoxy protons of phenyl group. The thiophene ring protons at 3 and 5 positions (H-3 and H-5) were submerged with aromatic two protons in a multiplet at 56.76-7.00 (4H). The other aromatic protons appeared as multiplet between 57.03-7.57 (7H). Similarly the O,S-acetal 87h prepared by reacting the dimethylsulphonium perchlorate salt of the corresponding oxoketene S,S-acetal with ortho-chlorophenol under the Simmons-Smith reaction conditions afforded the corresponding thiophene 89h in 62% yield (scheme 19). The structure of 89h was in accordance with its analytical and spectral data (expermental section).

The O,S-acetals 87i and 87j obtained by the reaction of dimethylsulphonium salts of the corresponding S,S-acetals with methylsalicylate were also found to undergo thiophene ring closure to afford the corresponding thiophenes 89i and 89j under Simmons-Smith reaction conditions in 78% and 84% yields respectively (scheme 19). The structure of thiophenes 89i and 89j were in accord with their analytical and spectral data (experimental section).

It may be noted here that these aryloxy thiophenes with orthocarbomethoxy group in aryl group are important starting materials for the corresponding xanthone synthesis\textsuperscript{14}. The present method therefore is of practical importance for the synthesis of a number of xanthones by appropriately carrying the substituents in the substrate O,S-acetals.
Scheme 19

\[
\begin{align*}
\text{Ar} & \quad \text{X} \\
\text{S} & \quad \text{O} \\
\text{Me} & \quad \text{CH}_2 \text{I}_2 \\
\text{Zn-Cu} & \quad \text{Et}_2\text{O} / \text{THF/}\Delta \\
\text{Ar} & \quad \text{X} \\
\text{S} & \quad \text{O} \\
\text{Me} & 
\end{align*}
\]

87g, h, 87–89g, Ar = 4-MeO C\text{C}_6\text{H}_4 ; X = H

87h, Ar = C\text{C}_6\text{H}_5 ; X = Cl

87i, j, 87–89i, Ar = C\text{C}_6\text{H}_5

87j, Ar = 4-MeO C\text{C}_6\text{H}_4
The O,S-acetal 87k obtained from the sulphonium salt of corresponding S,S-acetals and β-naphthol also underwent thiophene ring closure under Simmons-Smith reaction conditions to afford the corresponding 2-(β-naphthoxy)-4-(4'-methoxyphenyl) thiophene 89k in 76% yield. Similarly O,S-acetal 87l from tetralone gave the corresponding condensed thiophene 89l under similar reaction conditions in 34% yield (scheme 20). The structure of 89k and 89l were established by their analytical and spectral data (experimental section).

Apparently, the O,S-acetals which can be easily prepared by either one of the methods described are shown to be excellent precursors for the synthesis of 2-alkoxy and 2-aryloxy thiophenes in attractive yields. However, when the method was extended to N,S-acetal 90 under similar reaction conditions the corresponding aminothiophene 91 could not be obtained and the reaction mixture resulted in intractable tar.

III.4 CONCLUSION

In conclusion, it may be inferred that the O,S-acetals including alkoxy and aryloxy groups are excellent precursors for the synthesis of the corresponding 2-alkoxy and 2-aryloxythiophenes. The aryloxythiophenes could be of further importance to synthesize the condensed thiophene derivatives with appropriate functional groups placed in the ortho position of the aryl group. The method certainly suffers a
Zn-Cu/CH₂I₂  
Et₂O/THF/Δ  
Ar = 4-MeOC₆H₄

Scheme - 20
limitation that it failed to undergo thiophene ring closure with S,N-acetals to afford the corresponding aminothiophenes.

III.5 EXPERIMENTAL

Melting points were determined on a 'Thomas Hoover' capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer. The $^1$H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in CDCl$_3$ or CC1$_4$ using TMS as internal standard. While $^{13}$C NMR spectra were recorded on a Bruker WM-400 spectrometer and chemical shifts are expressed in $\delta$(ppm) units downfield from TMS. Mass spectra were obtained on a Jeol JMS-D 300 spectrometer. Elemental analysis were performed on a Heraeus CHN-O-Rapid Elemental Analyzer.

Starting Materials

Commercially available ketones and esters were purchased and were used as supplied without further purification. Zinc-Copper couple was purchased (ventron) and was dried at 120°C for 24 hr prior to use. Methylene iodide was distilled before use. Diethylether and tetrahydrofuran were dried over sodium wire and distilled prior to use.

General Procedure for the Preparation of Acylketene O,S-Dialkylacetals (87a-d).

(a) Preparation of $\beta$-Oxothionoesters.

To an ice cold stirring suspension of sodium t-butoxide (38.4 g, 0.4 mol, prepared from 9.2g, 0.4 atom of sodium) in t-
butylalcohol (150 ml), a mixture of dialkyl xanthate (0.2 mol) and respective ketones (0.2 mol) was added dropwise and the resulting mixture was stirred at room temperature for 8-10 hr. (monitored by tlc). It was then poured on to crushed ice (200 g), acidified with 50% HCl (50 ml), extracted with benzene (3 x 100 ml) and the combined extracts were washed with water (3 x 150 ml), dried (Na₂SO₄) and concentrated to give the crude thionoesters, which were purified by column chromatography over silica gel using hexane as eluent.

(b) Preparation of Acylketene O,S-Dialkylacetals (87a-d).

A suspension of β-oxothiono esters (0.2 mol) and anhydrous K₂CO₃ (52.59 g, 0.4 mol) in dry acetone (100 ml) was refluxed with stirring for 3 hr. and then cooled to room temperature. Appropriate alkyl halide (0.25 mol) was added dropwise with stirring at 0-5°C and the resulting reaction mixture was further stirred at room temperature for 8-10 hr. (monitored by tlc). It was then filtered, washed the precipitate with acetone (2 x 25 ml) and the combined filtrate was concentrated on a water bath. The residue was cooled to room temperature and poured onto crushed ice (200 g), extracted with CHCl₃ (2 x 100 ml). The combined extracts were washed with water (3 x 100 ml), dried (Na₂SO₄) and evaporated to give the crude O,S-acetals 87 which were purified by column chromatography over silica gel using EtOAc/hexane (1:99) as eluent.

General Procedure for the Preparation of Acylketene O-Alkyl/Aryl S-Methylacetals (87e-1).
A suspension of the appropriate alcohols or phenols (0.03 mol) and anhydrous K$_2$CO$_3$ (12.50 g, 0.09 mol) in anhydrous acetone (100 ml) was refluxed with stirring for 2-3 hr. The resulting mixture was cooled to 0-5°C and the dimethyl sulphonium perchlorate salt (0.01 mol) was added in small portions with stirring. The reaction mixture was further stirred for 7-8 hr. and filtered. Washed the precipitate with acetone (2 x 25 ml) and the combined filtrate was concentrated on water bath. The residue was cooled to room temperature and poured onto crushed ice (200 g), extracted with CHCl$_3$ (2 x 100 ml). The organic layer was washed with 10% NaOH solution (3 x 50 ml) and then with water (3 x 100 ml), dried Na$_2$SO$_4$ and evaporated to give crude O,S-acetals, which were purified by column chromatography over silica gel using EtOAc/hexane (1:99) as eluent.

General Procedure for Simmons-Smith Reaction: Synthesis of β-Methylthio-α,β-unsaturated esters (39a-d) and 2-Alkoxy/Aryloxythiophenes (89a-l).

To a well stirred suspension of Zinc-Copper couple (4.0 g, 0.03 mol) in dry ether (25 ml), under nitrogen atmosphere, a small crystal of iodine and methylene iodide (6.70 g, 0.025 mol) were added and the reaction mixture was refluxed for 45 minutes. A solution of the respective α-oxoketene O,S- or S,S-acetal (0.01 mol) in dry THF (25 ml) was added in one lot into the reaction mixture, which was further refluxed with stirring for 8-12 hr (monitored by tlc). The solvent was removed under reduced pressure and the residue was
diluted with chloroform (150 ml) and water (200 ml). The extract was filtered and the residue was washed with chloroform (2x25 ml). The chloroform layer was separated and washed with saturated NH₄Cl solution (2x25 ml), water (2x100 ml), dried over sodium sulphate and concentrated to give the crude esters (39a-d) and thiophenes (89a-l) which were purified by column chromatography over silica gel using hexane as eluent.

**Ethyl 3-methylthio-2-phenylpropenoate (39a).** Yellow viscous liquid; yield 79%; IR (neat) 1710, 1570, 1230 cm⁻¹; δH (CDCl₃) 1.10 (3H, t, J = 6Hz, OCH₂CH₃), 2.27 (3H, s, SCH₃), 4.30 (2H, q, J = 6Hz, OCH₂CH₃), 7.27 (5H, brs, arom), 7.61 (1H, s, =CH); m/z 222 (M⁺, 100%), 175 (60) (Anal. Calcd. for C₁₂H₁₄O₂S: C, 64.83; H, 6.35. Found: C, 65.11; H, 6.61%)

**Ethyl-2-cyano-3-methylthiopropenoate (39b).** Yellow crystals (CHCl₃/hexane); yield 82%; m.p. 51-52°C; IR (KBr) 2218, 1712, 1540, 1300, 1245 cm⁻¹; δH (CDCl₃) 1.34 (3H, t, J = 6Hz, OCH₂CH₃), 2.68 (3H, s, SCH₃), 4.28 (2H, q, J = 6Hz, OCH₂CH₃), 8.50 (1H, s, =CH); m/z 171 (M⁺, 100%) (Anal. Calcd. for C₇H₅NO₂S: C, 49.10; H, 5.30. Found: C, 49.37; H, 5.56%)

**Ethyl 2-carboethoxy-3-methylthiopropenoate (39c).** Yellow viscous liquid; yield 56%; IR (neat) 1710, 1554, 1242 cm⁻¹; δH (CDCl₃) 1.08-1.43 (6H, m, OCH₂CH₃), 2.40 (3H, s, SCH₃), 3.89-4.32 (4H, m, OCH₂CH₃), 7.90 (1H, s, =CH); m/z 218 (M⁺,
Methyl 2-acetyl-3-methylthiopropenoate (39d). Pale yellow crystals (CHCl₃/hexane); yield 69%; m.p. 57°C; IR (KBr) 1711, 1644, 1493, 1343, 1201 cm⁻¹; δ_H (CDCl₃) 2.48 (3H, s, SCH₃), 3.80 (3H, s, OCH₃), 8.50 (1H, s, =CH); m/z 174 (M⁺, 100) (Anal. Calcd. for C₇H₁₀O₃S: C, 48.26; H, 5.79. Found: C, 48.51; H, 6.02%).

Ethyl 2-methylthio-4-phenylthiophene-3-carboxylate (40) was obtained by Simmons-Smith reaction on 38e under similar reaction conditions as described in the general procedure. Yellow viscous liquid; yield 51%; IR (neat) 1710, 1600, 1482, 1420, 1310, 1245 cm⁻¹; δ_H 1.03 (3H, t, J = 6Hz, OCH₂CH₃), 2.57 (3H, s, SCH₃), 4.08 (2H, q, J = 6Hz, OCH₂CH₃), 6.97 (1H, s, H-5), 7.28 (5H, s, arom); m/z 278 (M⁺, 100%) (Anal. Calcd. for C₁₄H₁₄O₂S²: C, 60.40; H, 5.07. Found: C, 60.67; H, 5.35%).

2-Methoxy-4-phenylthiophene (89a). Colourless solid (hexane); yield 66%; m.p. 40-41°C; IR (KBr) 1620, 1600, 1507, 1465, 1218 cm⁻¹; δ_H (CCl₄) 3.84 (3H, s, OCH₃), 6.55 (1H, d, H-3, J = 1.5Hz), 6.68 (1H, d, H-5, J = 1.5 Hz), 7.22-7.69 (5H, m, ArH); m/z 190 (M⁺, 19%) (Anal. Calcd. for C₁₁H₁₀OS: C, 69.44; H, 5.30. Found: C, 69.67; H, 5.49%).

2-Ethoxy-4-phenylthiophene (89b). Viscous liquid; yield 72%; IR (neat) 1600, 1580, 1549, 1502, 1465, 1388 cm⁻¹; δ_H (CCl₄) 1.37 (3H, t, J = 6Hz, OCH₂CH₃), 4.09 (2H, q, J = 6Hz,
OCH<sub>2</sub>CH<sub>3</sub>), 6.45 (1H, d, J = 1.5 Hz, H-3), 6.63 (1H, d, J = 1.5 Hz, H-5), 7.12-7.64 (5H, m, ArH); m/z 204 (M<sup>+</sup>, 62%), 176 (100) (Anal. Calcd. for C<sub>12</sub>H<sub>12</sub>OS: C, 70.55; H, 5.92. Found: C, 70.36; H, 5.70%).

2-Propyloxy-4-phenylthiophene (89c). Colourless solid (hexane): yield 58%; m.p. 35-36°C; IR (KBr) 1562, 1520, 1481, 1203 cm<sup>-1</sup>; δ<sub>H</sub> (CCl<sub>4</sub>) 1.07 (3H, t, J = 6 Hz, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.75 (2H, sext, J = 6 Hz, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.98 (2H, t, J = 6 Hz, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 6.54 (1H, d, J = 1.5 Hz, H-3), 6.67 (1H, d, J = 1.5 Hz, H-5), 7.23-7.67 (5H, m, ArH); m/z 218 (M<sup>+</sup>, 39%), 176 (100) (Anal. Calcd. for C<sub>13</sub>H<sub>14</sub>OS: C, 71.52; H, 6.46. Found: C, 71.35; H, 6.27%).

2-Butyloxy-4-phenylthiophene (89d). Colourless solid (hexane): yield 72%; m.p. 43-44°C; IR (KBr) 1622, 1602, 1570, 1522, 1481, 1396 cm<sup>-1</sup>; δ<sub>H</sub> (CCl<sub>4</sub>) 0.88 [3H, t, J = 7 Hz, OCH<sub>2</sub> (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 1.17-1.88 [4H, m, OCH<sub>2</sub> (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 4.02 [2H, t, J = 7 Hz, OCH<sub>2</sub> (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>], 6.58 (1H, d, J = 1.5 Hz, H-3) 6.69 (1H, d, J = 1.5 Hz, H-5), 7.27-7.79 (5H, m, ArH); m/z 232 (M<sup>+</sup>, 24%), 176 (100) (Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>OS: C, 72.37; H, 6.94. Found: C, 72.64; H, 7.12%).

2-Benzylxy-4-phenylthiophene (89e). Colourless crystals (hexane/ether): yield 32%; m.p. 82-83°C; IR (KBr) 1562, 1518, 1472, 1400, 1201 cm<sup>-1</sup>; δ<sub>H</sub> (CDCl<sub>3</sub>) 5.08 (2H, s, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 6.62 (1H, d, J = 1.5 Hz, H-3), 6.70 (1H, d, J = 1.5 Hz, H-5), 7.19-7.73 (10H, m, ArH); m/z 266 (M<sup>+</sup>, 14%), 175
(15), 91 (100) (Anal. Calcd. for C_{17}H_{14}O_S : C, 76.66 ; H, 5.30. Found : C, 76.92 ; H, 5.45%).

2-Dodecyloxy-4-phenylthiophene (89f). Colourless solid (hexane) ; yield 59% ; m.p. 34-35°C ; IR (KBr) 1559, 1518, 1478, 1196 cm^{-1} ; δ_H (CCl_4) 0.89 [3H, brt, J = 6Hz, OCH_2(CH_2)_10CH_3], 1.13-1.41 [20H, m, OCH_2(CH_2)_10CH_3], 4.10 [2H, t, J = 6Hz, OCH_2(CH_2)_10CH_3], 6.62 (1H, d, J = 1.5Hz, H-3), 7.76 (1H, d, J = 1.5Hz, H-5), 7.31-7.75 (5H, m, ArH) ; m/z 344 (M^+, 43%), 176 (100) (Anal. Caled. for C_{22}H_{32}O_S : C, 76.69 ; H, 9.36. Found : C, 76.97 ; H, 9.58%).

2-Phenoxy-4-(4'-methoxyphenyl)thiophene (89g). Colourless crystals (hexane/ether) ; yield 66% ; m.p. 97-98°C ; IR (KBr) 1619, 1608, 1583, 1486, 1255, 1214 cm^{-1} ; δ_H (CDCl_3) 3.78 (3H, s, OCH_3), 6.76-7.0 (4H, m, H-3, H-5 and ArH), 7.03-7.57 (7H, m, ArH) ; m/z 283 (M^+, 100%), 206 (46) (Anal. Calcd. for C_{17}H_{14}O_2S : C, 72.31 ; H, 5.00. Found : C, 72.49 ; H, 5.13%).

2-(2'-Chlorophenoxy)-4-phenylthiophene (89h). Colourless crystals (hexane) ; yield 62% ; m.p. 46-47°C ; IR (KBr) 1598, 1562, 1484, 1238 cm^{-1} ; δ_H (CCl_4) 6.80-6.93 (2H, m, H-3 and H-5), 7.07-7.63 (9H, m, ArH) ; m/z 286, 288 (M^+, 100, 30%), 252 (51) (Anal. Calcd. for C_{16}H_{11}ClO_S : C, 67.01 ; H, 3.87. Found : C, 67.28 ; H, 4.09%).

2-(2'-Carbomethoxyphenyl)-4-phenylthiophene (89i). Colourless crystals (ether/hexane) ; yield 78% ; m.p. 59.60°C ; IR (KBr) 1748, 1626, 1508, 1472, 1320, 1240 cm^{-1} ; δ_H (CDCl_3) 3.88 (3H, s, OCH_3), 6.82-6.97 (2H, m, H-3 and H-5), 7.10-7.63 (8H,
m, ArH), 7.96 (1H, d, J = 9Hz, ArH) ; m/z 310 (M<sup>+</sup>, 100%) 279 (9), 190 (55) (Anal. Calcd. for C<sub>18</sub>H<sub>14</sub>O<sub>3</sub>S : C, 69.66 ; H, 4.55. Found : C, 69.90 ; H, 4.76%).

**2-(2'-Carbomethoxyphenyl)-4-(4'-methoxyphenyl)thiophene (89j).** Colourless crystals (ether/hexane) ; yield 84% ; m.p. 69°C ; IR (KBr) 1721, 1602, 1500, 1482, 1442, 1298, 1217 cm<sup>-1</sup> ; δ<sub>H</sub> (CDCl<sub>3</sub>) 3.78 (3H, s, OCH<sub>3</sub>), 3.82 (3H, s, CH<sub>3</sub>0CO), 6.62-6.98 (4H, m, H-3, H-5 and ArH), 7.02-7.24 (2H, m, ArH), 7.26-7.53 (3H, m, ArH), 7.73-7.96 (1H, s, ArH) ; m/z 340 (M<sup>+</sup>, 17%), 399 (100), 205 (20), 135 (13) (Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>O<sub>4</sub>S : C, 67.04 ; H, 4.74. Found : C, 67.16 ; H, 4.83%).

**2-(2'-Naphthyloxy)-4-(4'-methoxyphenyl)thiophene (89k).** Colourless crystals (ether/hexane) ; yield 76% ; m.p. 149°C ; IR (KBr) 1621, 1530, 1478, 1310, 1276 cm<sup>-1</sup> ; δ<sub>H</sub> (CDCl<sub>3</sub>) 3.80 (3H, s, OCH<sub>3</sub>), 6.73-7.0 (4H, m, H-3, H-5 and ArH), 7.33-7.59 (6H, m, ArH), 7.64-7.83 (3H, m, ArH) ; m/z 332 (M<sup>+</sup>, 100%) (Anal. Calcd. for C<sub>21</sub>H<sub>16</sub>O<sub>2</sub>S : C, 75.88 ; H, 4.85. Found : C, 76.03 ; H, 4.96%).

**2-Phenoxy-3,4-dihydronaphtho[2-1-c]thiophene (891).** Colourless viscous liquid ; yield 34% ; IR (neat) 1620, 1510, 1238 cm<sup>-1</sup> ; δ<sub>H</sub> (CDCl<sub>3</sub>) 2.51-2.98 (4H, m, CH<sub>2</sub>), 6.97-7.19 (3H, m, H-5 and ArH), 7.20-7.49 (6H, m, ArH), 7.68 (1H, d, J = 4.5Hz, ArH) ; m/z 278 (M<sup>+</sup>, 50%), 201 (4), 185(14) (Anal. Calcd. for C<sub>18</sub>H<sub>14</sub>OS : C, 77.66 ; H, 5.07. Found : C, 77.95 ; H, 5.30%).
REFERENCES