Chapter 4

Synthesis of Functionalized Thiophenes from β-Oxothioamides

4.1 Introduction

Dithiocarboxylic acids and their esters, despite their offensive odour and instability, are extensively used by synthetic chemists worldwide; owing to their rich chemistry and relative ease of preparation. Our research group has reported several interesting synthetic transformations of these intermediates. In continuation of an ongoing project to explore the synthetic potentials of β-oxodithioesters, we have transformed them into corresponding β-oxothioamides, which are also recognized as important synthons in various synthetic protocols. The β-oxothioamides were subsequently converted into functionalized thiophenes in a one pot reaction via the intermediacy of the corresponding functionalized ketene-N,S-acetals.

4.1.1 β-Oxodithioesters: Synthesis

β-Oxodithioesters 3 are generally prepared by the reaction of enolizable carbonyl compounds 1 with dialkyl trithiocarbonates 2 in the presence of a base like sodium hydride (Scheme 1).

\[ \text{R}_1^1 \text{C}=\text{O} + \text{R}_2 \text{S}S\text{Me} \xrightarrow{\text{NaH}/\text{DMF}} \text{R}_1^1 \text{C}=\text{S}S\text{Me} \]

Scheme 1
Aryl substituted dithiocarboxylates 6 can be prepared from substituted acetophenones 4 by the addition of carbon disulfide in the presence of potassium t-butoxide and subsequent treatment with one equivalent of alkylating agent (Scheme 2).  

![Scheme 2]

Doubly activated active methylene ketones like 2,4-pentanedione 7 on treatment with dimethyl trithiocarbonate 2 in the presence of sodium acetate in DMF, afforded the corresponding dithiocarboxylates 8 in good yields (Scheme 3).

![Scheme 3]

The thioacyl-N-phthalimide derivative 10, derived from the thioamide 9 of N-(Boc)-β-alanine, was transformed into the corresponding ethyl dithioester 11 by treatment with ethanethiol and triethylamine at 0 °C (Scheme 4).

![Scheme 4]

4.1.2 β-Oxodithioesters: Synthetic Applications

β-Oxodithioesters 12 are known to react with a variety of electrophiles leading to the formation of several functionalized heterocycles. On treatment with
trimethyl silyl sulfide in presence of N-chlorosuccinimide and imidazole, they afford substituted 3-thioxo-1,2-dithiols 13 (Scheme 5).

\[ \text{Scheme 5} \]

The dithioester 14 derived from dimesone underwent selective addition of aniline to one of the carbonyl group to afford the \( \beta \)-phenylamino substituted \( \alpha,\beta \)-unsaturated dithioester 15 which cyclized to 16 on heating in diphenyl ether (Scheme 6).

\[ \text{Scheme 6} \]

Substituted 2H-thiopyran-2-thiones 18 and 19 were obtained by the reaction of \( \beta \)-oxodithiocarboxylic acid 17 with \( \alpha \)-acyctylinic ketones and \( \beta \)-chlorovinyl aldehydes respectively (Scheme 7).
When methyl aroyl dithioacetates 20 were treated with two equivalents of DCC 21 in the presence of DMAP in CH2Cl2, 4-arylmethylidene-3-cyclohexylimino-1,3-thiazetidines 22 were obtained (Scheme 8).^{8}

\[
\begin{array}{c}
\text{20} \\
\text{21} \\
\text{22} \\
X = \text{H, Me, Cl, Br}
\end{array}
\]

Scheme 8

Junjappa et al. have employed dithiocarboxylates in the synthesis of annulated heterocyclic systems 25 (Scheme 9).^{11}

\[
\begin{array}{c}
\text{23} \\
\text{24} \\
\text{25}
\end{array}
\]

Scheme 9

4.1.3 β-Oxothioamides: Synthesis and Reactions

Due to the great practical and synthetic applicability of thioamides, their significance and impact on the development of chemistry is growing rapidly. Comprehensive reviews that have appeared earlier have recognized their importance as biologically active compounds, flotation and vulcanization agents, additives to lubricants and as interesting ligands in co-ordination chemistry.^{9} The general synthetic methods for thioamides include thioacylation reactions, addition of nucleophiles to isocyanates and thionation of amides. Simple thioamides can be prepared by thioacylation of amines employing thiocarboxylates, 3H-1,2-dithiol-3-ones, dithiocarboxylates, thietoketenes and carbon disulfide.
Nucleophilic attack on O-alkylthiocarboxylates 26 by ammonia or secondary amines provides thioamides 27 (Scheme 10). \(^\text{10}\)

\[
\begin{align*}
&R_1 OR \quad \text{HNRR}_3 \quad \text{R}_1 NR_3 \\
&26 \quad \longrightarrow \quad 27
\end{align*}
\]

Scheme 10

The S-S bond cleavage of 3H-1,2-dithiol-3-ones 28 by nucleophiles such as Grignard reagents afford malonic acid monothioamide 29 (Scheme 11). \(^\text{11}\)

\[
\begin{align*}
&\text{R}_1 \text{MgBr, THF} \quad \text{quench with H}_2\text{O} \\
&28 \quad \longrightarrow \quad 29
\end{align*}
\]

Scheme 11

Dianions of dithiocarboxylic acids 31 derived from active methylene compounds like camphor 30 on reaction with carbon disulfide followed by excess base on neutralization with HCl and addition of primary amines afforded the corresponding thioamides 32 (Scheme 12). \(^\text{12}\)

\[
\begin{align*}
&\text{NaNH}_2 \quad \text{CS}_2 \quad \text{HCl, RNH}_2 \\
&30 \quad \longrightarrow \quad 31 \quad \longrightarrow \quad 32
\end{align*}
\]

Scheme 12

Carbanions derived from active methylene compounds 33 underwent condensation with thiocarbamoyl chloride 34 to afford functionalized thioamides 35 (Scheme 13). \(^\text{13,14}\)
4.1.4 Thioamides: Applications in the Synthesis of Functionlized Thiophenes

Applications of thioamides in organic synthesis are well-documented. Over the years, these multifunctional synthons have been employed in a variety of synthetic transformations. Various routes to functionalized sulfur heterocycles like thiophenes have been developed based on these interesting intermediates. A short review including some select recent examples is given here.

γ,δ-Unsaturated thioamides are excellent synthons for thiophenes and pyrimidines. For example, the iodine induced cyclization of 36 proceeds as a region-(5-exo-trigonal) and chemoselective reaction. It yields iminothiolactones 37 which is converted to acetamidothiophenes 39 via dehydroiodination and N-acetylation (Scheme 14).

Nitrothioacetamides 40 in the presence of base reacted with α-bromoketones to give 2-amino-3-nitrothiophenes 41 (Scheme 15).
Different spiroheterocyclic systems 43 and 44 were formed in the two-step reactions of secondary thioamides 42 with arylidene malononitriles and nitroalkenes respectively (Scheme 16).\textsuperscript{17}

![Scheme 16](image)

4-Oxothioamides 45 when heated in carbon tetrachloride in the presence of concentrated sulfuric acid gave derivatives of 2-aminothiophenes 46 (Scheme 17).\textsuperscript{18}

![Scheme 17](image)

Hartman et al. have recently reported the synthesis of 2-amino-5-thiophene carboxylates from 3-aminothioacrylamides. Thus, N,N-disubstituted thioacrylamides 47 were reacted with alkyl haloacetates to yield the N,N-di substituted 1-amino-1-[9-(alkoxycarbonyl)methylthio]propeniminium salts 48 which were cyclized in situ in the presence of sodium methoxide to give 2-dialkylamino-5-thiophene carboxylates 49 (Scheme 18).\textsuperscript{19}

![Scheme 18](image)
When 3-aminothioacrylamides 50 were reacted with 2,2-dicyanoethenyl substituted bromomethyl alkanes, 5-tricyanoethenyl substituted 2-aminothiophenes 51 were obtained (Scheme 19).  

\[ \text{Scheme 19} \]

β-Oxothioamides prepared from β-oxodithioesters are very good precursors for the preparation of α-oxoketene-S,N-acetals. When active methylene ketones are refluxed with dimethyl trithiocarbonate in benzene in the presence of a base such as sodium hydride, respective β-oxodithiocarboxylates are formed. Benzoyldithioacetate 12 when refluxed with one equivalent of piperidine or morpholine in methanol gives the corresponding thioamides 52 which on treatment with methyl iodide gave excellent yields of corresponding-ketene S,N-acetals 53 (Scheme 20).

\[ \text{Scheme 20} \]

Studies from this laboratory on the synthetic potentials of β-oxothioamides have led to the development of some facile protocols to substituted aminothiophenes which will be discussed in the later part of this chapter.
4.1.5 Functionalized Thiophenes: General Synthetic Methods

Thiophenes and their derivatives have a myriad of uses in the field of medicinal, physical and material chemistry. The synthetic protocol developed by Gewald is considered one of the convenient methods for the synthesis of thiophenes with a high degree of functionality. In this method, elemental sulfur is reacted with an activated acetonitrile 54 and an aldehyde, ketone or a 1,3 dicarbonyl compound 55 in the presence of a base to afford substituted thiophenes 56 (Scheme 21).

\[
\begin{align*}
\text{EtO} & \quad \text{CN} \\
\text{O} & \quad \text{CN} \\
\text{S}_2 & \quad \text{Et}_2\text{NH}
\end{align*}
\]

\(54 \quad 55 \quad 56\)

Scheme 21

\(\alpha,\beta\)-Unsaturated carbonyl compounds 57 react with alkynyl lithium to afford the enynol 58 which is epoxidised using Bu′OOH/ VO(acac)_2 or MCPBA to give a mixture of syn and anti epoxy alcohols 59. The epoxy alcohols gave corresponding episulfides 60 on reaction with thiourea in sulfuric acid, which on treatment with Hg(II) in sulfuric acid afforded functionalized thiophenes 63 (Scheme 22).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_1
\end{align*}
\]

\(57 \quad 58 \quad 59 \quad 60 \quad 61 \quad 62 \quad 63\)

Scheme 22
Aromatic $\alpha$-mercaptoketones 64 derived from benzaldehyde dimethylthioacetal reacted with Michael acceptors like vinyl phosphonate to afford highly functionalized thiophenes 66 (Scheme 23).\(^\text{25}\)

\[
\begin{align*}
\text{64} & \xrightarrow{(E)} \text{65} & \text{DDQ} & \text{66}
\end{align*}
\]

**Scheme 23**

Reaction of lithiated propargylic amines with isothiocyanates followed by addition of $t$-BuOK, $t$-BuOH/ DMSO and methyl iodide afforded 2,5-bis($N,N$-dialkylamino)thiophenes 70 (Scheme 24).\(^\text{26}\)

\[
\begin{align*}
\text{67} & \xrightarrow{1 \text{ n-BuLi/THF}} \xrightarrow{2 \text{ RN=C=S}} \text{68} & \text{69} & \text{70}
\end{align*}
\]

**Scheme 24**

Thioaroylketene-$N,S$-acetals 71 reacted readily with silylenol ethers of enolizable ketones in the presence of mercury(II) acetate in CH$_2$Cl$_2$ to give 2- substituted 5-aryl-3-methyl aminothiophenes 73 via nucleophilic attack of the enolic carbon to the enaminocarbon atom of the intermediate 72 (Scheme 25).\(^\text{27}\)

\[
\begin{align*}
\text{67} & \xrightarrow{1 \text{ n-BuLi/THF}} \xrightarrow{2 \text{ RN=C=S}} \text{68} & \text{69} & \text{70}
\end{align*}
\]
2-Aminoisothioamunones 74 which contain a masked thiocarbonyl ylide in their structure underwent regiospecific 1,3 dipolar cycloaddition with methyl propiolate 75 to afford functionalized thiophenes 76 (Scheme 26).\(^\text{28}\)

Phenythioacetemorpholide 77 derived from acetophenone reacted with triethyl orthoformate and morpholine to afford the 3-morpholino-2-phenylthioacrylic acid morpholide 78 which underwent alkylation and subsequent cyclization to afford functionalized thiophenes 79 (Scheme 27).\(^\text{29}\)

\(\beta\)-Oxothioamides 80 bearing a tertiary amino group, upon alkylation with propargyl bromide afforded 2-amino-3-acyl-4-methyl thiophenes 82 via the intermediate ketene-N,S-acetal 81 (Scheme 28).\(^\text{30}\)
Another approach towards the construction of the thiophene skeleton employs the reaction of the dianion 83 derived from the dithioic acid of methyl cyanoacetate, with \( \alpha \)-chloroacetamide. The reaction proceeds under acidic conditions and the intermediate formed from the initial S-alkylation underwent cyclization which involved addition to the nitrile group (Scheme 29).\(^{31}\)

```
\[
\begin{align*}
\text{MeO} & & \text{CN} \\
\text{Na} & & \text{S} \\
\text{S} & & \text{Na}
\end{align*}
\]
```

Scheme 29

When the alkylation of the dithiolate anion 85 was carried out with two equivalents of \( \alpha \)-halocarbonyl compounds or \( \alpha \)-halonitriles, substituted thienothiophenes 87 were formed (Scheme 30).\(^{32}\)

```
\[
\begin{align*}
\text{R} & & \text{CN} \\
\text{S} & & \text{S} \\
\text{Y} & & \text{Y}
\end{align*}
\]
```

Scheme 30

The thiolate anion derived from simple \( \beta \)-oxodithiolates 12 on reaction with 1,2-bielectrophiles afforded functionalized ketenedithioacetals 89, which were later cyclized in the presence of glacial acetic acid to substituted thiophenes 90 (Scheme 31).\(^{33}\)
3-Oxothioamides 91 were found to undergo a base catalysed S-alkylation with methyl-4-bromocrotonate followed by intramolecular condensation to afford the corresponding 5-amino-2-thienyl propanoates 92 (Scheme 32).34

Reactions of \( \beta \)-oxothioamides, where the intermediate is a ketene-N,S-acetal 93 also lead to cyclizations to the respective 2-amino substituted thiophenes 94 (Scheme 33).35

Earlier studies from our research group on various modes of cyclization of functionalized ketene-N,S-acetals have led to the synthesis of substituted aminothiophenes 97 and 100 (Scheme 34).36
In continuation of our explorative studies on the synthetic utility of \( \beta \)-oxothioamides, we have treated them with 1,2-bielectrophiles like phenacyl bromide, ethyl bromoacetate, etc., which has led to a facile one pot strategy towards synthesis of 5-aminothiophene derivatives.

### 4.2 Results and Discussion

Our continued interest in the synthetic manipulations employing functionalized thioamides prompted us to explore the chemistry of the thioamides derived from \( \beta \)-oxodithioesters and cyclic amines like morpholine and piperidine.

#### 4.2.1 Reactions of \( \beta \)-Oxothioamides with Phenacyl Bromide

Earlier studies from this laboratory on the base catalyzed cyclizations of \( \alpha \)-oxoketene-N,S-acetals have led to the formation of various substituted thiophenes and oxathiols. The \( \alpha \)-oxoketene-N,S-acetals were derived from the reaction of enolates of active methylene ketones with aryl or alkyl isothiocyanates followed by alkylation. We next contemplated on the studies of the reactivity patterns of the ketene-N,S-acetals, which could in principle afford substituted thiophenes. With this idea in mind, we have subjected the \( \beta \)-oxothioamides derived from the corresponding dithioesters, with 1,2 bielectrophiles like phenacyl bromide and ethyl bromoacetate. But the intermediate ketene-N,S-acetal formed underwent in situ cyclization to afford the corresponding 5-aminosubstituted thiophenes in excellent
yields. Our attempts to isolate the intermediate ketene-N,S-acetal were not successful even when the reaction was carried out at room temperature.

The β-oxothioamide 52a and 52b prepared from the methyl-3-oxo-3-phenylpropanedithiolate 12 by refluxing in methanol with the corresponding amines for 4-5 h. The thioamide was stirred in acetone in the presence of anhydrous K₂CO₃ for 10 minutes. Phenacyl bromide (1 equiv.) was added to the reaction mixture and then refluxed for 30 minutes. The crude reaction mixture was filtered and the solvent evaporated off. Subsequent purification by column chromatography over silica gel using hexane:ethyl acetate (9:1) afforded the corresponding 2-amino-3-aryloyl-4-phenyl thiophenes 101a-c in good yields (Scheme 35).

<table>
<thead>
<tr>
<th>52, 101</th>
<th>R</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₅</td>
<td>O</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>C₆H₅</td>
<td>CH₂</td>
<td>67</td>
</tr>
<tr>
<td>c</td>
<td>p-NO₂C₆H₄</td>
<td>CH₂</td>
<td>55</td>
</tr>
</tbody>
</table>

Scheme 35

The structure of the substituted thiophene 101a was confirmed on the basis of spectral data. The ¹H NMR spectrum (CDCl₃) of 101a shows two triplets integrating for four protons at δ 3.34 (J = 6 Hz) and 3.85 ppm (J = 5 Hz) due to the morpholine ring. The proton connected to C-2 of the thiophene ring appears as a singlet at δ 6.16 ppm. The aromatic protons appear as a multiplet of seven protons at 7.01 ppm, a triplet of one proton at δ 7.2 (J = 7 Hz) and as a doublet of two protons at δ 7.39-7.42 (J = 8 Hz). The ¹³C NMR (75 Mz, CDCl₃) shows signals at δ 49.82 and 66.38 ppm due to morpholine ring. The aromatic and alkenic protons appear at δ 108.87, 123.52, 127.79, 127.92, 128.09, 129.45, 129.64, 131.14, 136.89, 139.16,
Fig. 1 $^1$H NMR(300 MHz, CDCl$_3$) Spectrum of Compound 101a

Fig. 2 $^{13}$CNMR(75 MHz, CDCl$_3$) Spectrum of Compound 101a
**Fig. 3 IR Spectrum of Compound 101a**

**Fig. 4 Mass Spectrum (GCMS) of Compound 101a**
150.3, and 164.2 ppm respectively. The carbonyl group shows peak at 189 ppm. The mass spectrum (EIMS) showed a peak at 349(M+1).

A probable mechanism for the formation of the thiophene derivatives 101a-c can be depicted as follows. The β-oxothioamide in presence of base undergoes alkylation on the addition of phenacyl bromide to afford the intermediate ketene-N,S-acetal 102. This intermediate, owing the presence of electron donating morpholine or piperidine ring in their skeleton, undergoes in situ cyclization to afford the corresponding substituted thiophenes in 55-70 % yields (Scheme 36).

4.2.2 Reactions of β-oxothioamides with ethyl bromoacetate

We next examined the reactions of β-oxothioamide 52b with ethyl bromoacetate. In this case, the intermediate ketenedithioacetal adopted a different mode of cyclization to afford 3-phenyl 5-pipyridino thiophene carboxylate 103 in 60 % yields (Scheme 37).
The structure of the thiophene carboxylate 103 was confirmed on the basis of spectral data. The $^1$H NMR spectrum (300 MHz, CDCl$_3$) shows a triplet integrating for four protons at $\delta$ 1.15 ($J = 7$ Hz) and a multiplet at 1.58 ppm which could be due to the piperidine ring. The ethoxy group appears as a three proton triplet at $\delta$ 3.23 ppm ($J = 5.5$ Hz) and a two proton quartet at $\delta$ 4.10 ppm ($J = 7$ Hz). The proton connected to C-4 of the thiophenyl ring appears as a singlet at $\delta$ 5.99 ppm. The aromatic protons appear as a multiplet of five protons at $\delta$ 7.31 ppm. The $^{13}$C NMR (75 Mz, CDCl$_3$) shows signals at $\delta$ 14.68, 23.99, 25.34, 51.1, 60.4, 108.2, 110, 127.9, 128, 129.4, 137, 150.8, 162.7 ppm. The ester carbonyl appears at $\delta$ 162.9 ppm. The IR spectrum showed peaks at 1654, 1466, 1380, 1288, 1121, 900, 851, 806, 755, 632 cm$^{-1}$ respectively.

In the case of alkylation of $\beta$-oxothioamide using ethyl bromoacetate, the intermediate ketene-N,S-acetal 104, in the presence of base forms the enolate at the carbon $\alpha$-to the sulfur atom, which via a nucleophilic attack at the carbonyl group of the phenacyl moiety affords the thiophene carboxylate. This reverse mode of cyclizations can be attributed to the diminished reactivity of the electrophilic centre of the ester carbonyl compared to the ketocarbonyl group in the case of the intermediate 102 (Scheme 38).

Scheme 38
The thiophene carboxylate 105 derived from the morpholine derivative of the thioamide 52a decomposed rapidly after purification by column chromatography to yield a complex NMR spectrum (Scheme 39).

![Scheme 39](image)

In conclusion, we have developed a new one-pot strategy for the synthesis of 4-aryl 5-amino thiophenes and 3-aryl 5 amino thiophene carboxylates employing the β-oxothioamides.

4.3 Experimental

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. Infra red spectra were recorded on Shimadzu IR-470 spectrometer and the frequencies are reported in cm⁻¹. Proton NMR spectra were recorded on a Bruker DRX-300 (300 MHz), Bruker WM 250 (250 MHz) or on a Bruker WM 200 (200 MHz) spectrometer in CDCl₃. Chemical shifts are expressed in parts per million downfield from internal tetramethyl silane. Coupling constants J are given in Hz. Electron impact Mass spectra were obtained on a Finnigen-Mat 312 instrument and FAB mass spectra on a Jeol SX-102 instrument.

4.3.1 General procedure for the Synthesis of (2-Morpholino-4-phenyl-3-thienyl)(phenyl)methanones 101a-b

A suspension of the thioamide 52(2 mmol) and anhydrous K₂CO₃ (3 g, 20 mmol) in dry acetone (30 ml) was refluxed with stirring for 10 minutes. The mixture was cooled and phenacyl bromide (0.4 g, 2 mmol) was added followed by further refluxing with stirring for 30 minutes. It was then filtered, the residue washed with acetone (25 mL), and the solvent evaporated to form the combined filtrate. The crude product thus obtained is purified by column chromatography.
over silica gel using hexane: ethyl acetate (98:2) as eluent to afford the title compounds 101a-b in 55 to 60% yields.

2-Morpholino-4-phenyl-3-thienyl)(phenyl) methanone 101a was obtained by the reaction of 3-morpholino-1-phenyl-3-thioxo-1-propanone 52a (0.5 g, 2 mmol) as pale yellow crystalline solid. Yield 0.38 g (60%), mp. 128-130 °C. \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 3.32(t, 4H, \( J = 6\) Hz, morpholine); 3.85 (t, 4H, \( J = 5\) Hz, morpholine); 6.16 (s, 1H, thienyl); 7.07(m, 7H, aromatic), 7.18(m, 1H, aromatic), 7.39(d, 2H, aromatic) ppm; \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 49.8, 66.3, 108.8, 123.5, 127.7, 127.9, 128.1, 129.5, 129.4, 131.4, 136.9, 139.6, 150.3, 164.2, 189.0 ppm; ElMS m/z (%) 349(M\(^+\), 100), 348 (41), 290 (17), 272 (15), 77 (12)

Phenyl(4-phenyl-2-piperidino-3-thienyl) methanone 101b was obtained by the reaction of 1-phenyl-3-piperidino-3-thioko-1-propanone 52b (0.5 g, 2 mmol) as deep yellow crystalline solid. Yield 0.48 g (67%), mp. 108-110 °C. IR \( \nu_{max}/cm^-1 \) 1657, 1595, 1528, 1498, 1446, 1384, 1263, 1199, 1168, 1116, 1070, 1025, 980, 922, 850. \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.3 (m, 1H, piperidine); 6.75 (s, 1H, thienyl); 7.18 (m, 5H, aromatic); 7.36 (m, 2H, aromatic); 7.48 (m, 1H, aromatic); 7.86 (d, 2H, \( J = 8\) Hz, aromatic) ppm.; \( ^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 14.5, 21.5, 56, 113, 125.7, 127.4, 128.2, 128.4, 128.5, 128.7, 129.9, 130.2, 133.0, 137.0, 138.4, 142.0, 162.9, 194.5 ppm.
4.3.2 General procedure for the synthesis of (2-morpholino-4-phenyl-3-thienyl)(phenyl)methanones 101a-c

A suspension of the thioamide 52 (2 mmol) and anhydrous K$_2$CO$_3$ (3 g, 20 mmol) in dry acetone (30 ml) was refluxed with stirring for 10 minutes. The mixture was cooled and $p$-nitro phenacyl bromide (0.42 g, 2 mmol) was added followed by further refluxing with stirring for 30 minutes. It was then filtered, the residue washed with acetone (25 mL), and the solvent evaporated to form the combined filtrate. The crude product thus obtained is purified by column chromatography over silica gel using hexane: ethyl acetate (98:2) as eluent to afford the title compounds 101c in 55 to 60% yields.

[2-Morpholino-4-((4-nitrophenyl)-3-thienyl](phenyl)methanone 101c was obtained by the reaction of 3-morpholino-1-phenyl-3-thioxo-1-propanone 52a (0.5 g, 2 mmol) as yellow crystalline solid. Yield 0.43 g (55%), mp. 170-172 °C. IR $\nu_{\text{max}}$/cm$^{-1}$ 1640, 1510, 1449, 1410, 1372, 1341, 1264, 1201, 1142, 1109, 1027, 986, 937, 901, 852, 738. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.99 (t, 4H, J = 6 Hz, morpholine), 3.45 (t, 4H, J = 5 Hz, morpholine), 6.93 (s, 1H, thienyl), 7.48 (m, 5H, aromatic), 7.82 (m, 2H, aromatic), 8.07 (m, 2H, aromatic) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 54.6, 66.6, 94.2, 105, 116, 126.5, 128.2, 128.7, 129, 133.7, 138.3, 140.3, 147.1, 162, 193 ppm.

4.3.3 General Procedure for the Synthesis of Ethyl 3-phenyl-5-piperidino-2-thiophene carboxylate 103

A suspension of the thioamide 52 (2 mmol) and anhydrous K$_2$CO$_3$ (3 g, 20 mmol) in dry acetone (30 ml) was refluxed with stirring for 10 minutes. The mixture was cooled and ethyl bromoacetate (0.33 g, 2 mmol) was added followed by further refluxing with stirring for 30 minutes. It was then filtered, the residue...
washed with acetone (25 mL), and the solvent evaporated to form the combined filtrate. The crude product thus obtained was purified by column chromatography over silica gel using hexane as eluent to afford the title compound 103 in 60 % yields.

*Ethyl 3-phenyl-3-piperidino-2-thiophene carboxylate 103* was obtained by the reaction of 3-morpholino-1-phenyl-3-thioxo-1-propanone 52a (0.5 g, 2 mmol) as crystalline solid. Yield 0.38 g (60%), mp.132-134 °C. IR $\nu_{\text{max}}$/cm$^{-1}$ 1654, 1466, 1380, 1288, 1121, 900, 851, 806, 755, 632 $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.1 (t, 4H, $J = 7$Hz, piperidine); 1.5 (m, 6H, piperidine); 3.2 (t, $J = 5.5$ Hz, 3H, -OEt); 4.1 (q, $J = 7$ Hz, 2H, -OEt); 5.99 (s, 1H, thienyl); 7.3 (m, 5H, aromatic) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.68, 23.99, 25.34, 51.1, 60.4, 108.2, 110, 127.9, 128, 129.4, 137, 150.8, 162.7, 162.9 ppm.
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9. 


10. 


11. 


12. 


13. 


15. 


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