3.1 Introduction

The success of regioselective acylation on monocyclic thiophene and furan molecules inspired us to experiment the same with a bicyclic system and explore its extent of application. For this we have selected benzothiophene, considering its derivatives to have wide range of applicability in the field of pharmacy. Benzothiophene with molecular formula C_8H_6S is a heterocyclic compound. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization. Being a heterocyclic compound, benzothiophene finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is found within the chemical structures of pharmaceutical drugs such as raloxifene, zileuton, and sertaconazole. It is also used in the manufacturing of dyes such as thioindigo.

Especially, benzothiophene derivatives having an acyl group as one of the substituents on the five membered rings have immense medicinal value due to their promising pharmacological properties. For example, raloxifen, [2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thiophen-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride (1), is representative of a class of compounds called as selective estrogen receptor modulators (SERMs) that has estrogen agonist-like actions on bone tissues and serum lipids while displaying potent estrogen antagonist properties on the breast and uterus. Another common example of SERM is tamoxifen which has been the therapy of
choice in the endocrine treatment of all stages of hormone-dependent breast cancer. Recently, raloxifene showed promising results in clinical trial and is hopeful to provide an alternative to current hormone replacement therapy (HRT) that has been casually linked to breast cancer.\(^2\) Another compound 2 was discovered as a thrombin inhibitor that can be utilized in the chronic treatment of thrombotic disorders.\(^3\)

![Chemical structures](image)

The compounds of the type 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-aminoethoxy)benzoyl]benzo[b]thiophenes (3) having pharmacological activity, in particular, coronary vasodilator activity are useful for the treatment of angina pectoris and intermediates for the preparation thereof. Derivatives of 2-phenyl-3-aroylbenzothiophenes (4) and 2-phenyl-3-aroylbenzothiophene-1-oxides, 2-aroyl-3-phenylbenzothio

phenes (5) and 2-aroyl-3-phenylbenzothiophene-1-oxide are useful as antifertility agents.\(^5\) Certain of these compounds also are useful in suppressing the growth of mammary tumors. 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, its ethers and esters, and the physiologically acceptable acid addition salts thereof, are valuable antiestrogens and antiandrogens.\(^6\)
Apart from medicinal importance, acyl derivatives of benzothiophene have synthetic value and a variety of diversity based benzothiophene derivatives have been prepared using these compounds.\textsuperscript{7-14}

### 3.2 Brief review of existing methodologies for acylation of benzothiophene

Yokoyama, Yasushi, Nakata and Hiroshi\textsuperscript{15} et al aroylated benzothiophene (7) with aroyl chloride (6) in the presence of anhydrous AlCl\textsubscript{3} catalyst and solvent CS\textsubscript{2} to give good yields of 3-aroyl benzothiophene (14, Scheme 1).

\[ \text{Scheme 1} \]

\[ \text{ArCOCl} + \text{7} \xrightarrow{\text{Anhy AlCl}_3, \text{CS}_2} \text{14} \]

Buu-Hoi, Cagniant & co-workers performed acylation of benzothiophene (7) by Friedel-Crafts acetylation\textsuperscript{4} using anhydrous aluminium chloride and acetyl chloride in DCM which was non regioselective and produced a mixture of 2- and 3- acetyl benzothiophene (8 & 14) in overall 78% (Scheme 2).
Ishiyama, Tatsuo & co-workers synthesized 3-benzoyl benzothiophene from 3-iodobenzothiophene (9), carbon monoxide and phenylboronic acid\(^{12}\) (10) with potassium carbonate, bistriphenylphosphine-palladium(II) chloride in various solvents at 80 °C (Scheme 3). T. Ishiyama, and his group performed the same reaction under 760 torr.\(^ {16}\)

Ludwig-Maximilians-Universitaet Muenchen\(^ {17}\) synthesized 3-arylm benzothiophene (14) from Grignard reagent (11) and aroyl chloride (6) (Scheme 4).

The \(^{13}\)C NMR spectrum of the product displays two signals at δ 26.2 and 28.2 ppm indicating a mixture of two regioisomers. The metallation of benzothiophene (7) with n-butyllithium in dry THF proceeds at -40 °C to -30 °C to get 2-lithiumbenzothiophene (12)
which reacts with dry acetic anhydride as electrophile in dry THF. Finally 66% 2-acetylbenzothiophene (8a) was isolated when the reaction mixture was heated under reflux for 1h (Scheme 5). The appearance of only one signal at δ 27.4 ppm in $^{13}$C NMR spectrum of the compound for –COCH$_3$ group indicates it is a C-2 regioisomer only.

Scheme 5

Kevin James Doyle and his group synthesized 2-propionyl benzothiophene$^{18}$ (8c) by adding n-butyllithium to benzothiophene (7) solution under nitrogen atmosphere followed by N-methoxy-N-methyl propionamide at an ambient temperature for 3 & 5h (Scheme 6).

Scheme 6

3-Acetylbenzothiophene (14a) was synthesized from Grignard reagent as shown below (Scheme 7).
There are innumerous methods which are known for the synthesis of acylbenzothiophenes.\textsuperscript{19-26} Out of them, many are however suitable for the preparation of certain specific compounds, like acetyl, propanoyl, and benzoyl derivatives. Some of the methodologies are quite complicated with complex reaction conditions e.g., unstable diazo compounds,\textsuperscript{24} or requirement of an expensive transition metal catalyst along with toxic carbon monoxide gas\textsuperscript{19} or tedious procedure like multi step synthesis of starting material,\textsuperscript{20} or pyrophoric BuLi.\textsuperscript{25,26}

### 3.3 Background

The simplest and convincing method for the synthesis of acylbenzothiophenes looked to be the Friedel-Crafts acylation\textsuperscript{27-30} which however has its own disadvantages like use of excess AlCl$_3$ which led to the formation of environmentally harmful gaseous HCl. Also, this procedure involves a) the use of moisture sensitive acyl chloride, b) requirement of large volume of chlorinated solvent, c) the formation of aluminium waste that needs to be disposed off and d) formation of unknown side products is very common in this reaction. Overall, the use of this method in large scale preparation might result major drawbacks. To overcome these difficulties, we have focused on the alternative methods available in the
literature\textsuperscript{31-34} that could direct a straightforward preparation of acylated benzothiophene derivatives via C-C bond forming reactions as a key synthetic step. It has been previously reported that the use of mixed anhydrides of trifluoroacetic acid for aromatic acylation was a useful alternative to the Friedel-Crafts acylation process and a variety of aromatic and aliphatic carboxylic acids were employed successfully. Inspired by these results, and a convincing work up with thiophene has led us in a direction to test the same on some bicyclic compound. Notably, while the use of various arenes/heteroarenes has been explored in the previous study,\textsuperscript{32-34} the use of benzothiophene has not been examined so far. Moreover, the wide application of acylated benzothiophene derivatives, in the field of medicine also grabbed our attention to focus on this compound.

Herein, we describe an efficient, simple and eco-friendly method for the preparation of acylbenzothiophenes (\textit{8} \& \textit{14}) that involves the first use of benzothiophene (\textit{7}) in the aromatic acylation mediated by mixed anhydrides of trifluoroacetic acid (\textbf{Scheme 8}). The results of this study are summarized in \textbf{Table 3.1} \& \textbf{3.2}.

\begin{center}
\textbf{Scheme 8}
\end{center}
3.4 Results & Discussion

3.4a Optimization of TFAA-H₃PO₄

The use of lower quantity of TFAA and H₃PO₄ was also examined and found to be less productive as the progress of the reaction was slow and the product yield was decreased significantly.

3.4b Optimization of reaction time

Initially, we started with acylation of benzothiophene (7) with acetic acid in the presence of 85% H₃PO₄ and excess TFAA at room temperature (25-30 °C) for 30 min where no significant product formation was observed. Later, the reaction time was increased gradually, with continuous monitoring of TLC, for every half an hour. After 4h, considerable increase in the product formed was seen. This exercise resulted in isolation of acylated products and the best results were obtained when the reaction was carried out for 4h (Table 3.1). However, in spite of our sincere effort, our attempt to prepare a single regioisomer, as was obtained earlier with acylation of thiophene and furan, was not obtained. Instead, a mixture of 2- and 3- acylated benzothiophene was always isolated in every case. In fact, an attempt to prepare a single regioisomer by varying all the reaction parameters failed, perhaps due to the high reactivity of the benzothiophene ring under the conditions studied. A similar observation was seen during acetylation of benzothiophene using i) acetic anhydride in the presence of BF₃.Et₂O or ii) acetyl chloride in the presence of AlCl₃.
Table 3.1 Optimization of reaction time

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Product</th>
<th>Time</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>![Image of 8a and 14a]</td>
<td>1h</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td><strong>8a + 14a</strong></td>
<td>2h</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>AcOH</td>
<td><strong>8a + 14a</strong></td>
<td>3h</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>AcOH</td>
<td><strong>8a + 14a</strong></td>
<td>4h</td>
<td>70 (1:9)</td>
</tr>
</tbody>
</table>

In a typical procedure, to the compound benzothiophene (7, 2 g, 15 mmol) was added, TFAA (8.5 mL, 60 mmol) and acetic acid (0.9 g, 15 mmol) drop wise followed by 85% H₃PO₄ (1.46 mL, 15 mmol) with vigorous stirring at 0 °C. The mixture was then stirred at 25-30 °C for 4h and poured in to ice cold water (30 mL) with rapid stirring. The solid separated was first filtered, washed with petroleum ether (2×5 mL) and then dried to give the mixture of products 8a and 14a in 70% overall yield. Based on HPLC information, the isolated solid mixture was found to be in the ratio 1:9 of 8a and 14a respectively. After separating these compounds by column chromatography, the structures of 8a and 14a were confirmed by spectral data.

3.4c Optimization of reactants

The reactants benzothiophene (7) and acid (15) were initially taken in different proportions and % of yield of the products was observed in each case. It was identified that maximum yield was
obtained when the ratio of acid and benzothiophene was 1:1. Thus all
the reaction was carried out using 7 (1 equiv), acid (1 equiv), 85%
H₃PO₄ (1equiv), and TFAA (4 equiv) at 25-30 °C for 4-5h and the % of
yield shown in Table 3.2 represents isolated overall yields of products.

Table 3.2  Synthesis of acylbenzothiophenes (8 & 14) via acylation
of benzothiophene (7) with alkyl/aryl acids 15

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (RCOOH)</th>
<th>Product</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me 15a</td>
<td>8a + 14a</td>
<td>70(1:9)</td>
</tr>
<tr>
<td>2</td>
<td>Et 15b</td>
<td>8b + 14b</td>
<td>73(1:9)</td>
</tr>
<tr>
<td>3</td>
<td>nC₄H₉ 15c</td>
<td>8c + 14c</td>
<td>68(1:9)</td>
</tr>
<tr>
<td>4</td>
<td>nC₅H₁₁ 15d</td>
<td>8d + 14d</td>
<td>67(1:3)</td>
</tr>
<tr>
<td>5</td>
<td>nC₇H₁₅ 15e</td>
<td>8e + 14e</td>
<td>70(2:3)</td>
</tr>
<tr>
<td>6</td>
<td>C₆H₅ 15f</td>
<td>8f + 14f</td>
<td>80(1:9)</td>
</tr>
</tbody>
</table>
All the products were identified by $^1$H NMR, IR and mass spectra. As shown in Table 3.2, both type of acids, namely, aliphatic and aromatic acids participated in the acylation of benzothiophenes. In all the cases, a mixture of acylated benzothiophene was isolated (entries 1-6, Table 3.2) and the 3-isomer was isolated as the major product irrespective of the nature of the carboxylic acid used. The ratio of regioisomers present in the crude product isolated from the reaction mixture was determined by analyzing the corresponding $^1$H NMR (Figure 3.1). The proton at the third place of compound 8a appeared in the region of $\delta$ 7.90-7.95 ppm (when R = alkyl) and $\delta$ 7.97-8.0 ppm (when R = aryl) whereas proton at 4$^{th}$ position of compound 14a appeared in $\delta$ 8.27-8.29 ppm (when R = alkyl) and $\delta$ 8.40-8.60 ppm (when R = aryl).
Similarly, when $^{13}\text{C}$ NMR of the mixture (Figure 3.2) was recorded then appearance of two carbonyl signals and two methyl signals clearly indicated the presence of two compounds.
Based on HPLC data the mixture was found to be a 1:9 mixture. HPLC conditions (column, mobile phase (range used), flow rate, detection wavelength, retention times): Luna C8 (150 x 4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in CH₃CN, gradient (T/% B) 0/10, 25/80, 25.1/10, 30/10, flow rate 1.5 mL/min, UV 230 nm, retention time 16.78 min for 8a, retention time 17.48 min for 14a.

The mixture was separated by column chromatography. ¹H NMR and ¹³C NMR were recorded for two regioisomers. The 3-keto compound (14a, Figure 3.3) showed characteristic multiplet for H₄ hydrogen at δ 8.74-8.79 (m, 1H); The H₂ appeared as singlet as expected at δ 8.28 ppm. The signal for keto methyl hydrogens at δ 2.65 ppm (14a, Figure 3.3) confirmed the incorporation of that group into benzothiophene.

Figure 3.3 ¹H NMR spectrum of 1-(benzo(b)thiophen-3-yl)ethanone (14a)
The $^1$H NMR was recorded for 2-keto compound obtained by column chromatography. The structure was confirmed by appearance of singlet for keto methyl group at $\delta$ 2.67 ppm. The singlet at $\delta$ 7.90 ppm confirmed H-3 hydrogen (8a, Figure 3.4).

**Figure 3.4** $^1$H NMR spectrum of 1-(benzo(b)thiophen-2-yl)ethanone (8a)
The $^{13}\text{C}$ NMR spectrum of C-2 regioisomer was recorded in CDCl$_3$. The resonance at δ 191.9 ppm due to keto carbonyl carbon and methyl signal at δ 26.7 ppm confirmed the structure. The three aromatic quaternary carbon atoms (C) appeared at δ 143.6, 142.2 and 138.8 ppm whereas resonance related to five aromatic methine carbon atoms (CH) were seen at δ 129.5, 127.1, 125.4, 124.6 and 122.6 ppm (Figure 3.5).

**Figure 3.5** $^{13}\text{C}$ NMR spectrum of 1-(benzo(b)thiophen-2-yl) ethanone (8a)
The molecular ion peak appeared at 177 (M+1) for compound 14a (Figure 3.6) and also for compound 8a (Figure 3.7) in their mass spectra.

**Figure 3.6** Mass spectrum of 1-(benzo(b)thiophen-3-yl)ethanone (14a)

**Figure 3.7** Mass spectrum of 1-(benzo(b)thiophen-2-yl)ethanone (8a)
3.4d Merits of this method

We have developed a simple and one pot synthesis for the preparation of acylbenzothiophenes. All the starting materials are readily available in the market and can be used directly. The process does not involve the use of any additional solvent but it requires the use of excess TFAA. But, the excess TFAA and TFA (trifluoroacetic acid produced during the reaction) can be easily removed by treating the reaction mixture with water, although, their removal by distillation is more appropriate for large scale preparations\textsuperscript{35} which allows the recovery of used TFAA, as TFA formed during the reaction can be converted back to TFAA via dehydration thus eliminating the acid waste. It is a known fact that TFAA is produced commercially via dehydration of TFA by using SO\textsubscript{3} as a dehydrating agent. However, P\textsubscript{2}O\textsubscript{5} is more convenient in small scale preparation of TFAA.

3.4e Demerits of this method

In spite of every effort, we failed to prepare a single regioisomer in this case. We always ended up with a mixture of 2- and 3- acylated benzothiophenes, though the 3-isomer was predominant.

3.4f Proposed mechanism

A proposed mechanism for the acylation of benzothiophene is shown in Scheme 9.\textsuperscript{29} According to which phosphoric acid plays a role of covalent catalyst which leads to the formation of acyl bis (trifluoroacetyl)phosphate from the acylation precursor acyl tri
fluoroacetate formed in situ. These formed acyl bis (trifluoroacetyl)phosphate then acylates the benzothiophene ring in the presence of phosphoric acid to give the products 8 and 14. Phosphoric acid acts as a source of proton and helps in activation. The fact that compound 14 being formed as a major product can be explained by the higher reactivity of C-3 over C-2 of the benzothiophene ring.

**Scheme 9**

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{CO}_2\text{H} \quad \text{H}_3\text{PO}_4 \\
\rightarrow & \quad \text{OCOCF}_3 \\
\rightarrow & \quad \text{OCOCF}_3 \\
\rightarrow & \quad \text{OCOCF}_3 \\
\rightarrow & \quad \text{S} \\
\rightarrow & \quad 8 & 14
\end{align*}
\]

**3.5 Conclusion**

In conclusion, we have described a general and single step synthesis of a wide range of acylated benzothiophenes via acylation of benzothiophene ring with in situ generation acyl trifluoroacetates. The striking features of this protocol are as follows: i) both alkyl and aryl carboxylic acids participated in trifluoroacetic anhydride-phosphoric acid mediated C-C bond forming reactions producing acylbenzothiophenes in good overall yields. ii) environmentally safe as the whole procedure is free from the use of inorganic Lewis acids, as well as chlorinated hydrocarbons as solvent and iii) simple operational procedure. However, as mentioned earlier, generation of a mixture of
regio-isomers is the major drawback of this protocol. For this reason, we have restricted ourselves from further study of the behavior of benzothiophene towards some anti-inflammatory drugs possessing carboxylic groups, like naproxen, ibuprofen etc, as we have done with thiophene in our previous chapter. Nevertheless, the present method is certainly superior to the classical Friedel-Crafts acylation technique and any other multi step synthesis.

3.6 Experimental

**General method for the synthesis of acylbenzothiophenes**

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added acid (15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temp at 0 °C, and then at 25-30 °C for 4h. The reaction mixture was poured in to ice cold water (30 mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product **a** and **b** in 70% overall yield. Based on HPLC data the isolated solid was found to be a mixture of **8** and **14**. After separating these compounds using column chromatography, the structures of **8** and **14** was confirmed by spectral data.
3.6.1 Synthesis of 1-(benzo(b)thiophen-2/3-yl)ethanone (8a & 14a)

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added acetic acid (0.9 g, 15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temperature at 0 °C, and then at 25-30 °C for 4h. Finally it was poured into ice cold water (30 mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product 8a and 14a in 70% overall yield. Based on HPLC data the isolated solid was found to be a 1:9 mixture. After separating these compounds using column chromatography, the structures were confirmed by spectral data. HPLC conditions (column, mobile phase (range used), flow rate, detection wavelength, retention times): Luna C8 (150 x 4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in CH$_3$CN, gradient (T/% B) 0/10, 25/80, 25.1/10, 30/10, flow rate 1.5 mL/min, UV 230 nm, retention time 16.78 min for 8a, retention time 17.48 min for 14a.

Spectral data for compound 8a: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.90 (s, 1H), 7.87-7.84 (m, 2H), 7.45-7.38 (m, 2H), 2.67 (s, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 191.9 (C=O), 143.6, 142.2, 138.8, 129.5, 127.1, 125.4, 124.6, 122.6, 26.7 (CH$_3$); IR $\nu_{max}$/cm$^{-1}$(KBr): 3058, 2923, 1662, 1510; m/z (ES Mass) 177 (M+1, 50%), 161 (100%);
Compound **14a**: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 8.28 (s, 1H), 7.88-7.84 (m, 1H), 7.46-7.43 (m, 2H), 8.79-8.74 (m, 1H), 2.65 (s, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 192.7 (C=O), 139.6, 138.8, 137.3, 136.2, 135.1, 125.7, 125.1, 121.9, 26.4 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 2954, 2924, 1665; m/z (ES Mass) 177 (M+1, 100%).

**3.6.2 Synthesis of 1-(benzo(b)thiophen-2/3-yl)propan-1-one (8b & 14b)**

![Chemical Structure of 8b and 14b]

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added propanoic acid (1.1 g, 15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temperature at 0 °C, and then at 25-30 °C for 4h. Finally it was poured in to ice cold water (30 mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product **8b** and **14b** in 73% overall yield. Based on HPLC data the isolated solid was found to be a 1:9 mixture. After separating these compounds using column chromatography, the structures were confirmed by spectral data.

Spectral data for compound **8b**: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.94 (s, 1H), 7.90-7.84 (m, 2H), 7.53-7.35 (m, 2H), 3.03 (q, $J$ 7.3 Hz, 2H), 1.27 (t, $J$ 7.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 195.9 (C=O), 143.3, 142.1, 138.9, 128.5, 127.6, 125.5, 124.7, 122.7, 33.0 (CH$_2$), 8.3 (CH$_3$);
IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 3065, 2218, 1664, 1512; m/z (ES Mass) 191 (M+1, 100%);

Compound $14b$: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 8.77 (dd, $J$ 6.8, 1.0 Hz, 1H), 8.27 (s, 1H), 7.90-7.84 (m, 1H), 7.53-7.35 (m, 2H), 3.04 (q, $J$ 7.3 Hz, 2H), 1.28 (t, $J$ 7.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 195.0 (C=O), 139.6, 136.5, 136.1, 134.8, 125.7, 125.5, 125.1, 122.0, 32.2 (CH$_2$), 8.2 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 3063, 2871, 1665, 1512; m/z (ES Mass) 191 (M+1, 100%).

3.6.3 Synthesis of 1-(benzo(b)thiophen-2/3-yl)pentan-1-one (8c & 14c)

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added valeric acid (1.5 g, 15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temperature at 0 °C, and then at 25-30 °C for 4h. Finally it was poured in to ice cold water (30 mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product 8c and 14c in 68% overall yield. Based on HPLC data the isolated solid was found to be a 1:9 mixture. After separating these compounds using column chromatography, the structures of 8c and 14c were confirmed by spectral data.

Spectral data for compound 8c: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.96 (s, 1H), 7.91-7.85 (m, 2H), 7.49-7.39 (m, 2H), 3.00 (t, $J$ 7.3 Hz, 2H),
1.87-1.75 (m, 2H), 1.61-1.39 (m, 2H), 0.98 (t, 7.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 194.9 (C=O), 143.9, 142.4, 139.1, 128.7, 127.2, 125.8, 124.9, 122.9, 38.9, 26.8, 22.4, 13.8 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 2951, 2933, 1659, 1590; m/z (ES Mass) 219 (M+1$^+$, 100%).

Spectral data for compound 14c: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 8.70-8.65 (m, 1H), 8.24 (s, 1H), 7.95-7.85 (m, 1H), 7.57-7.32 (m, 2H), 3.01 (t, J 7.3 Hz, 2H), 1.85-1.75 (m, 2H), 1.60-1.39 (m, 2H), 0.97 (t, J 7.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 194.7 (C=O), 139.4, 138.8, 137.3, 136.2, 135.6, 125.8, 125.1, 121.4, 38.7, 26.5, 22.1, 13.5 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 2954, 2935, 1657, 1589; m/z (ES Mass) 219 (M+1$^+$, 100%).

3.6.4 Synthesis of 1-(benzo(b)thiophen-2/3-yl)hexan-1-one (8d & 14d)

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added hexanoic acid (1.75 g, 15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temperature at 0 °C, and then at 25-30 °C for 4h. Finally it was poured in to ice cold water (30 mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product 8d and 14d in 67% overall yield. Based on HPLC data the isolated solid was found to be a 1:3 mixture. After separating these compounds using column chromatography, the structures were confirmed by spectral data.
Spectral data for compound 8d: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.90 (s, 1H), 7.87-7.82 (m, 2H), 7.40-7.24 (m, 2H), 2.34 (t, $J$ 7.3 Hz, 2H), 1.64 (t, $J$ 7.3 Hz, 2H), 1.37-1.25 (m, 4H), 0.90 (t, $J$ 6.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 194.8 (C=O), 143.8, 142.2, 139.0, 128.6, 127.1, 125.6, 124.8, 122.8, 39.1, 31.3, 24.2, 22.4, 13.8 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 2955, 2931, 1655, 1585; m/z (ES Mass) 233 (M$^+$1$^+$, 100%);

Compound 14d: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 8.77 (dd, $J$ 6.9, 0.9 Hz, 1H), 8.27 (s, 1H), 7.90-7.84 (m, 1H), 7.53-7.35 (m, 2H), 2.35 (t, $J$ 7.3 Hz, 2H), 1.65 (t, $J$ 7.3 Hz, 2H), 1.37-1.31 (m, 4H), 0.90 (t, $J$ 6.4 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 195.7 (C=O), 139.7, 136.5, 136.2, 135.1, 125.7, 125.5, 125.2, 122.0, 40.0, 31.4 (CH$_2$), 24.3, 22.4, 13.8 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 3063, 2871, 1665, 1512; m/z (ES Mass) 233 (M$^+$1$^+$, 100%).

3.6.5 Synthesis of 1-(benzo(b)thiophen-2/3-yl)octan-1-one (8e & 14e)

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added octanoic acid (2.1 g, 15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temperature at 0 °C, and then at 25-30 °C for 4h. The reaction mixture was poured in to ice cold water (30 mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product 8e and 14e in 70%
overall yield. Based on HPLC data the isolated solid was found to be a 2:3 mixture. After separating these compounds using column chromatography, the structures were confirmed by spectral data.

Spectral data for compound 8e: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 7.95 (s, 1H), 7.87-7.84 (m, 2H), 7.45-7.37 (m, 2H), 3.10-3.07 (m, 2H), 1.79-1.69 (m, 2H), 1.35-1.25 (m, 8H), 0.88-0.78 (m, 3H); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 2957, 2930, 1650, 1579; m/z (ES Mass) 260 (M$^+$, 100%).

Spectral data for compound 14e: $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 8.80-8.76 (m, 1H), 8.27 (s, 1H), 7.88-7.85 (m, 1H), 7.46-7.37 (m, 2H), 3.09-3.01 (m, 2H), 1.79 (m, 2H), 1.35-1.24 (m, 8H), 0.89 (t, $J$ 6.8 Hz, 3H); IR $\nu_{\text{max}}$/cm$^{-1}$(KBr): 2948, 2935, 1661, 1582; m/z (ES Mass) 260 (M$^+$, 100%).

3.6.6 Synthesis of benzo(b)thiophen-2/3-yl(phenyl)methanone (8f & 14f)

To a mixture of benzothiophene (7, 2 g, 15 mmol) in TFAA (8.5 mL, 60 mmol) was added benzoic acid (1.8 g, 15 mmol) dropwise followed by 85% H$_3$PO$_4$ (1.46 g, 15 mmol) with vigorous stirring maintaining the temperature at 0 °C, and then at 25-30 °C for 4h. The reaction mixture was poured in to ice cold water (30mL) with rapid stirring. The solid separated was filtered, washed with petroleum ether (2×5 mL) and dried to give the mixture of product 8f and 14f in 80% overall yield. Based on HPLC data the isolated solid was found to be a 1:9
mixture. After separating these compounds using column chromatography, the structures were confirmed by spectral data.

Spectral data for compound 8f: \(^{1}\text{H NMR (CDCl}_3, 200 \text{ MHz}} \) \(\delta 7.97 \text{ (s, 1H), 7.88-7.80 (m, 4H), 7.55-7.32 (m, 5H)}\); IR \(\nu_{\text{max}}/\text{cm}^{-1}(\text{KBr})\): 2920, 1644, 1598; m/z (ES Mass) 239 (M^+, 100%).

Spectral data for compound 14f: \(^{1}\text{H NMR (CDCl}_3, 200 \text{ MHz}} \) \(\delta 8.59-8.55 \text{ (m, 1H), 7.89-7.79 (m, 4H), 7.55-7.32 (m, 5H)}\); IR \(\nu_{\text{max}}/\text{cm}^{-1}(\text{KBr})\): 3016, 2928, 1645, 1598; m/z (ES Mass) 239 (M^+, 100%).
3.7 References


3.8 Some important spectra of the compounds

Fig 3.8 $^1$H NMR spectrum of 1-(benzo(b)thiophen-2/3-yl)propan-1-one (8b & 14b)

Fig 3.9 $^1$H NMR spectrum of 1-(benzo(b)thiophen-2-yl)propan-1-one (8b)
Fig 3.10 $^1$H NMR spectrum of 1-(benzo(b)thiophen-3-yl)propan-1-one (14b)

Fig 3.11 $^{13}$C NMR spectrum of 1-(benzo(b)thiophen-2/3-yl) propan-1-one (8b & 14b)
Fig 3.12 $^{13}$C NMR spectrum of 1-(benzo(b)thiophen-3-yl)propan-1-one (14b)

Fig 3.13 $^1$H NMR spectrum of 1-(benzo(b)thiophen-2-yl)pentan-1-one (8c)
Fig 3.14 $^{13}$C NMR spectrum of 1-(benzo(b)thiophen-2-yl)pentan-1-one (8c)

Fig 3.15 $^1$H NMR spectrum of 1-(benzo(b)thiophen-3-yl)pentan-1-one (14c)
Fig 3.16 $^1$H NMR spectrum of 1-(benzo(b)thiophen-2-yl)hexan-1-one (8d)

Fig 3.17 $^1$H NMR spectrum of 1-(benzo(b)thiophen-2/3-yl)octan-1-one (8e & 14e)
Fig 3.18 $^1$H NMR spectrum of 1-(benzo(b)thiophen-3-yl)octan-1-one (14e)

Fig 3.19 $^1$H NMR spectrum of 1-(benzo(b)thiophen-2-yl)octan-1-one (8e)
Fig 3.20  Mass spectrum of 1-(benzo(b)thiophen-2-yl)octan-1-one (8e)

Fig 3.21  $^1$H NMR spectrum of benzo(b)thiophen-2/3-yl(phenyl) methanone (8f & 14f)
Fig 3.22  Chromatogram of benzo(b)thiophen-2/3-yl(phenyl) methanone (8f & 14f)

Fig 3.23  $^1$H NMR spectrum of benzo(b)thiophen-2-yl(phenyl) methanone (8f)

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Fig 3.24  IR spectrum of benzo(b)thiophen-2/3-yl(phenyl)methanone (8f & 14f)