Straightforward Synthesis of 2-Acetyl-Substituted Benzo[\textit{b}]thiophenes

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Abstract: Described herein is a green one-step protocol for the preparation of substituted 2-acetylbenzo[\textit{b}]thiophenes from commercially available aromatic halides. This efficient method has the advantage of using water as the reaction medium, resulting in a high yield of pure cyclized products. Two scaffold types have been prepared using this general procedure: 2-acetylbenzo[\textit{b}]thiophenes and 2-acetyl-3-aminobenzo[\textit{b}]thiophenes, both crystallized directly from the reaction mixture, due to their low solubility with water, and without the need for an additional purification step.

Key words: heterocycles, benzo[\textit{b}]thiophene, nucleophilic aromatic substitution, thiol, cyclization

Benzo[\textit{b}]thiophene derivatives represent a major class of compounds displaying a wide range of biological activities, acting as selective estrogen modulators, antagonists for a vascular 5-HT\textsubscript{1B} receptor, partial agonists at the benzodiazepine receptor, and ligands for α1 and 5HT\textsubscript{1A} receptors. The development of new methods for the synthesis of sulfur-containing heterocycles is important in medicinal chemistry. Among these structures, benzothiopyridines were recently reported to be highly efficient inhibitors of Eg5 kinesin and also cell-cycle specific inducers of apoptosis in cancer cells. Focusing on innovative methodologies to provide efficient access to the benzo[\textit{b}]thiophene nucleus is consistent with the widespread presence of this skeleton in synthetic molecules.

In the laboratory, the functionalization of the benzo[\textit{b}]thiophene skeleton has already been described at the C-2 position (through pallado-catalyzed direct arylation) and the C-3 position (either by S\textsubscript{E}Ar or Friedel–Crafts acylation). More recently, a new thematic direction was investigated to target molecules of major therapeutic interest, such as alkaline phosphatase inhibitors or aRaloxifene synthetic intermediate.

As a natural extension to our research projects, we investigated the direct access to 2-acetylbenzo[\textit{b}]thiophenes 1 and 2-acetyl-3-aminobenzo[\textit{b}]thiophene 2 (Figure 1). Several methods have already been reported for the synthesis of 2-acetylbenzo[\textit{b}]thiophene 1, starting from 2-chlorobenzaldehyde, 2-nitrobenzaldehyde, 2-mercaptobenzaldehyde, 2-mercaptobenzoic acid, dihalobenzene derivatives and thiophenol. However, very little attention has been paid to 2-acetyl-3-aminobenzo[\textit{b}]thiophene 2, that, according to the literature, is prepared in four steps from \textit{o}-(benzylthio)benzoic acid, with an overall yield of 60%.

In all of these reported methods, hazardous reagents and/or solvents are widely used, and the synthetic strategies require multistep reaction sequence. This encouraged us to consider a direct water-mediated reaction for the synthesis of highly functionalized benzo[\textit{b}]thiophenes.

In this Letter we present a new efficient methodology for the synthesis of substituted 2-acetylbenzo[\textit{b}]thiophenes from simple aromatic and heteroaromatic halides. The strategy developed in the laboratory to access a library of compounds 1 and 2 is based on a one-step sequence between 2-mercaptoacetone and the corresponding aryl halides. An initial attempt involved commercially available 2-chlorobenzaldehyde (1 equiv) reacting with 2-mercaptoacetone (1 equiv), in the presence of potassium carbonate (2 equiv), in water at 90 °C. After only two hours of reaction, the desired benzo[\textit{b}]thiophene (1a) was isolated, in a high yield of 84%, by simple filtration (Scheme 1). 2-Mercaptoacetone was also easily prepared, following the procedure described by Meakins. Sodium hydrosulfide in water reacted with 2-chloropropanone, cooled to 0 °C for one hour, producing a 70% yield of 2-mercaptoacetone.
The first stage of the procedure is the nucleophilic aromatic substitution of the chlorine atom, promoted by an electron-withdrawing substituent in the ortho position. Next, an aldol-type cyclization is followed by dehydration and a complete rearomatization of the system (Scheme 2).

Scheme 2  Suggested mechanism

A series of substituted aryl halides underwent reactions with 2-mercaptoacetone, followed by cyclization into the corresponding benzo[b]thiophenes using this procedure (Table 1). In general, the reactions were efficient and gave excellent yields (more than 80%). Commercially available, but expensive, 2-acetylbenzo[b]thiophene (1a) was obtained with a good isolated yield of 84%. This sequence has the advantage of a high yield and purity and also avoids the use of BuLi, usually used for C-2 acylation or hygroscopic AlCl3 in the Friedel–Crafts acylation of benzo[b]thiophene. Substitutions, with a chlorine atom or a nitro moiety, gave an excellent yield of the cyclized adducts, respectively, in C-4 and C-5 positions. In the case of 1-chloro-2-naphthaldehyde, the compound 1d was almost obtained quantitatively whereas, in the case of 6-chloropiperonal, production was more limited with a moderate yield of 35% for the derivative 1e. Electronic factors strongly influence the scope of the reaction with a significant decrease in the electrophilicity of the aldehyde resulting in lower yields (1e, Table 1). The lack of reactivity explains the recovery of the starting material.

The reaction was extended successfully to 2-chloro-3-pyridinecarboxaldehyde, resulting in an almost quantitative yield of thieno[2,3-b]pyridine 1f. Replacing the 2-chlorobenzaldehyde with 2-chlorobenzonitrile resulted in a similar mechanistic pathway producing 2-acetyl-3-aminobenzo[b]thiophene (2a, Scheme 3).

Scheme 3 Synthesis of 2-acetyl-3-aminobenzo[b]thiophene (2a)

Using a similar approach, substituted chlorobenzonitriles were introduced into the same experimental procedures, producing 2-acetyl-3-aminobenzo[b]thiophenes 2a–f (Table 2). This provides a significant improvement in access to this family of compounds, which are rarely reported in the literature, and the one-step procedure described in this communication represents a significant breakthrough compared with other multistep methods that have been developed. When no substituent was introduced in the phenyl core, there was a 91% yield of compound 2a. Chlorine, nitro, or methyl substituents do not affect the scope of the reaction, with excellent yields obtained for 2b, 2c, and 2e, respectively. Again, the success of the condensation step was dependent on electronic factors, as shown in Table 1. Benzonitriles, substituted by electron-donating groups (2d) condensed in poor yields, lower than 15%. The replacement of the phenyl core by pyridine (with a lower electronic density) resulted in a yield of 96% for compound 2f.

In summary, a compound library of 12 highly substituted benzo[b]thiophenes is described in this paper. The reaction is compatible with a wide range of aromatic compounds based on a single step of condensation between 2-mercaptoacetone and either halobenzaldehydes or benzonitriles. Some interesting parameters have been highlighted, such as the water-mediated reaction conditions, short reaction times, and an easy purification process as the final products were usually isolated by simple filtration.

Table 1  Extension of the Scope of the Reaction to 2-Acetylbenzo[b]thiophenes 1

<table>
<thead>
<tr>
<th>Product</th>
<th>Isolated yield (%)</th>
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<tbody>
<tr>
<td>1a</td>
<td>84</td>
</tr>
<tr>
<td>1b</td>
<td>88</td>
</tr>
<tr>
<td>1c</td>
<td>86</td>
</tr>
<tr>
<td>1d</td>
<td>99</td>
</tr>
<tr>
<td>1e</td>
<td>35</td>
</tr>
<tr>
<td>1f</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 2  Extension of the Scope of the Reaction to 2-Acetylbenzo[b]thiophenes 2

<table>
<thead>
<tr>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
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<tr>
<td>2a</td>
<td>91</td>
</tr>
<tr>
<td>2b</td>
<td>88</td>
</tr>
<tr>
<td>2c</td>
<td>96</td>
</tr>
<tr>
<td>2e</td>
<td>96</td>
</tr>
<tr>
<td>2f</td>
<td>86</td>
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from the reaction mixture. Furthermore, the advantage of the procedure presented here is the similar synthetic approach used for the families of both compounds 1 and 2.

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### References and Notes


(17) **Representative Procedure**

Substituted 2-chlorobenzaldehyde or 2-chlorobenzonitrile (1 mmol) was stirred, in the presence of K2CO3 (2 mmol) and 2-mercaptoacetone (1.2 mmol) suspended in H2O (1 mL), at 90 °C, for 2 h. At the end of the reaction (TLC), the required product was either isolated by simple filtration of the mixture or extracted into EtOAc. The product was dried under vacuum at 50 °C.


(19) **2-Acetyl-4-chlorobenzothiophene (1b)**

White solid; mp 113–115 °C (EtOH); yield 88%. 1H NMR (300 MHz, DMSO-d6): δ = 8.05 (1 H, s, Harrm), 7.74 (1 H, dd, J = 2.2, 6.6 Hz, Harrn), 7.40–7.34 (2 H, m, Harrn), 2.69 (3 H, s, CH3). 13C NMR (75 MHz, DMSO-d6): δ = 192.2 (Cq), 144.8 (Cq), 143.7 (Cq), 137.7 (Cq), 130.8 (Cq), 128.1 (Cq), 127.6 (CH), 125.0 (CH), 121.7 (CH), 269.3 (CH). ESI-MS (MeCN): m/z calecd: 210 [M + H]+; found: 211. ESI-HMRS: m/z [M + Na]+ calecd for C11H9ClN2O: 232.9798; found: 232.9801.

**2-Acetyl-5-nitrobenzo[b]thiophene (1c)**

White-brown solid; mp 176–178 °C (from Et2O); yield 86%. 1H NMR (300 MHz, DMSO-d6): δ = 8.86 (1 H, d, J = 1.5 Hz, Harrm), 8.47 (1 H, s, Harrn), 8.29–8.21 (2 H, m, Harrn), 2.66 (3 H, s, CH3). 13C NMR (75 MHz, DMSO-d6): δ = 192.4 (Cq), 147.1 (Cq), 146.7 (Cq), 145.4 (Cq), 139.0 (Cq), 131.5 (CH), 124.5 (CH), 121.7 (CH), 121.1 (CH), 26.6 (CH). ESI-MS (MeCN): m/z calecd: 221 [M + H]+; found: 222. ESI-HMRS: m/z [M + Na]+ calecd for C11H9N2O5S: 322.0219; found: 322.0218.

**Acyclonaphtho[b,1,2-]thiophene (1d)**

White solid; mp 128–130 °C (from Et2O); yield 99%. 1H NMR (300 MHz, DMSO-d6): δ = 8.20–8.17 (1 H, m, Harom), 8.17 (1 H, dd, J = 1.5 Hz, Harom), 7.74 (1 H, d, J = 1.5 Hz, Harom), 7.65–7.58 (2 H, m, Harrn), 7.65–7.58 (2 H, m, Harrn), 2.71 (3 H, s, CH3).
2-Acetyl-5,6-methylenedioxybenzo[b]thiophene (1f)

White solid; mp 120–122 °C (from Et2O); yield 86%. 1H NMR (300 MHz, CDCl3): δ = 7.34 (1 H, dd, J = 2.0, 8.8 Hz, Harom), 6.68 (2 H, br s, NH2), 2.66 (3 H, s, CH3). 13C NMR (75 MHz, CDCl3): δ = 192.7 (Cq), 149.9 (Cq), 142.4 (Cq), 130.7 (Cq), 128.9 (CH), 122.8 (CH), 26.8 (CH3). ESI-MS (MeCN): [M + Na]+ calcd: 226 [M + Na]+; found: 227. ESI-HRMS: m/z calcd: 226 [M + H]+; found: 227. ESI-HRMS: m/z [M + Na]+ calcd for C14H10NaOS: 249.0345; found: 249.0349.

2-Acetyl-3-amino-7-methylbenzo[b]thiophene (2d)

Brown solid; mp 110–111 °C (from Et2O); yield 15%. 1H NMR (300 MHz, CDCl3): δ = 7.59 (1 H, d, J = 2.0 Hz, Harom), 8.09 (1 H, d, J = 8.8 Hz, Harom), 7.16 (1 H, dd, J = 2.2, 8.8 Hz, Harom), 7.06 (1 H, d, J = 2.2 Hz, Harom), 3.85 (3 H, s, CH3), 2.45 (3 H, s, CH3). 13C NMR (75 MHz, CDCl3): δ = 193.4 (Cq), 157.6 (Cq), 148.4 (Cq), 132.4 (Cq), 132.1 (Cq), 124.5 (CH), 119.8 (CH), 110.4 (Cq), 103.5 (CH), 55.8 (CH3), 29.0 (CH3). ESI-MS (MeCN): m/z calcd: 221 [M + H]+; found: 222. ESI-HRMS: m/z [M + H]+ calcd for C11H11NNaOS: 222.0454; found: 222.0451.