Straightforward Synthesis of 2-Acetyl-Substituted Benzo[*b*]thiophenes

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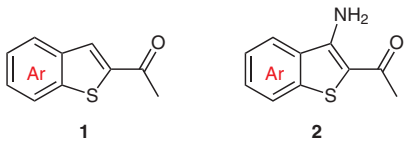
Abstract: Described herein is a green one-step protocol for the preparation of substituted 2-acetylbenzo[*b*]thiophenes from commercially available aromatic halides. This efficient method has the advantage of using water as the reaction medium, resulting in a high yield of pure cyclized products. Two scaffold types have been prepared using this general procedure: 2-acetylbenzo[*b*]thiophenes and 2-acetyl-3-aminobenzo[*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[*b*]thiophene, nucleophilic aromatic substitution, thiol, cyclization

Benzo[*b*]thiophene derivatives represent a major class of compounds displaying a wide range of biological activities, acting as selective estrogen modulators,[1] antagonists for a vascular 5-HT_{1B} receptor,[2] partial agonists at the benzodiazepine receptor,[3] and ligands for α1 and $5HT_{1A}$ receptors.[4] The development of new methods for the synthesis of sulfur-containing heterocycles is important in medicinal chemistry. Among these structures, benzothienopyridines were recently reported to be highly efficient inhibitors of Eg5 kinesin and also cell-cycle specific inducers of apoptosis in cancer cells.[5] Focusing on innovative methodologies to provide efficient access to the benzo[*b*]thiophene nucleus is consistent with the widespread presence of this skeleton in synthetic molecules.

In the laboratory, the functionalization of the benzo[*b*]thiophene skeleton has already been described at the C-2 position (through pallado-catalyzed direct arylation)[6] and the C-3 position (either by S_NAr or Friedel–Crafts acylation).[7] More recently, a new thematic direction was investigated to target molecules of major therapeutic interest, such as alkaline phosphatase inhibitors[8] or a Raloxifene synthetic intermediate.[9]

As a natural extension to our research projects, we investigated the direct access to 2-acetylbenzo[*b*]thiophenes **1** and 2-acetyl-3-aminobenzo[*b*]thiophenes **2** (Figure 1). Several methods have already been reported for the synthesis of 2-acetylbenzo[*b*]thiophene **1**, starting from 2-chlorobenzaldehyde,[10] 2-nitrobenzaldehyde,[11] 2-mercaptobenzaldehyde,[12] 2-mercaptobenzoic acid,[13] dihalobenzene derivatives[14] and thiophenol.[15] However, very little attention has been paid to 2-acetyl-3-aminobenzo[*b*]thiophene **2** that, according to the literature, is prepared in four steps from *o*-(benzylthio)benzoic acid, with an overall yield of 60%.[16]

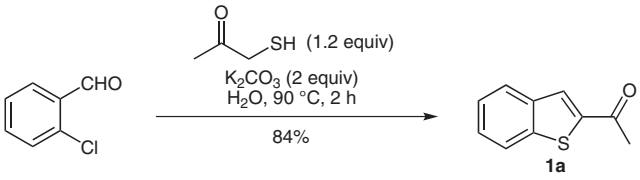


1 2

Figure 1 Structure of 2-acetylbenzo[*b*]thiophenes **1** and 2-acetyl-3-aminobenzo[*b*]thiophenes **2**

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[*b*]thiophenes.

In this Letter we present a new efficient methodology for the synthesis of substituted 2-acetylbenzo[*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[*b*]thiophene (**1a**) was isolated, in a high yield of 84%, by simple filtration (Scheme 1).[17] 2-Mercaptoacetone was also easily prepared, following the procedure described by Meakins.[18] Sodium hydrosulfide in water reacted with 2-chloropropanone, cooled to 0 °C for one hour, producing a 70% yield of 2-mercaptoacetone.



1a

Scheme 1 One-step procedure to 2-acetylbenzo[*b*]thiophene (**1a**)

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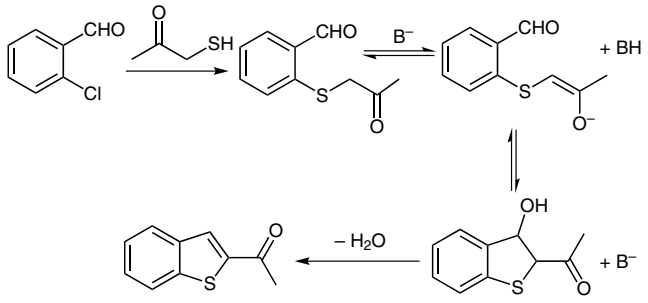
The first stage of the procedure is the nucleophilic aromatic substitution of the chlorine atom, promoted by an electron-withdrawing substituent in the *ortho* position. Next, an aldol-type cyclization is followed by dehydration and a complete rearomatization of the system (Scheme 2).

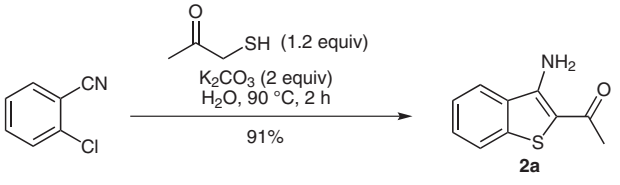


Scheme 2 Suggested mechanism

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).[19] 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 $AlCl_3$ in the Friedel–Crafts acylation of benzo[*b*]thiophene.[20] 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**.

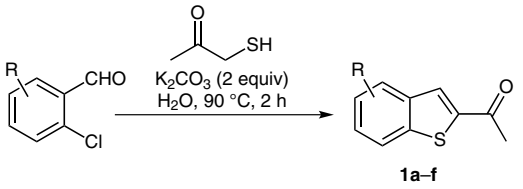
Replacing the 2-chlorobenzaldehyde with 2-chlorobenzonitrile resulted in a similar mechanistic pathway producing 2-acetyl-3-aminobenzo[*b*]thiophene (**2a**, Scheme 3).[17]

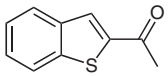
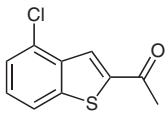
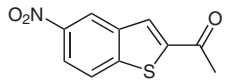
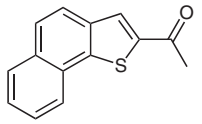
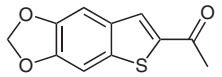
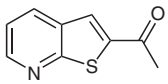


Scheme 3 Synthesis of 2-acetyl-3-aminobenzo[*b*]thiophene (**2a**)

Using a similar approach, substituted chlorobenzonitriles were introduced into the same experimental procedures,

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

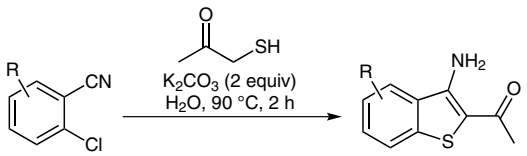


Product		Isolated yield (%)
1a		84
1b		88
1c		86
1d		99
1e		35
1f		86

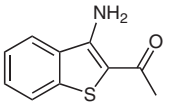
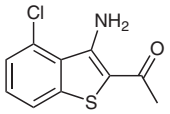
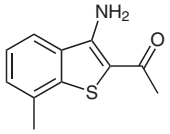
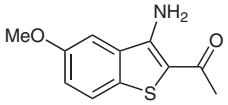
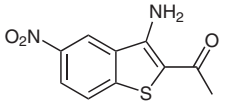
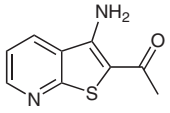
producing 2-acetyl-3-aminobenzo[*b*]thiophenes **2a**–**f** (Table 2).[21] This provides a significant improvement in access to this family of compounds, which are rarely reported in the literature, and the one-step procedure described in this communication represents a significant breakthrough compared 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 2 Extension of the Scope of the Reaction to 2-Acetyl-3-aminobenzo[*b*]thiophenes **2**



2a–f

Product		Isolated yield (%)
2a		91
2b		82
2c		90
2d		15
2e		99
2f		96

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**.

Acknowledgment

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References and Notes

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(17) **Representative Procedure**
Substituted 2-chlorobenzaldehyde or 2-chlorobenzonitrile (1 mmol) was stirred, in the presence of K_2CO_3 (2 mmol) and 2-mercaptoacetone (1.2 mmol) suspended in H_2O (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.

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(19) **2-Acetyl-4-chlorobenzo[*b*]thiophene (1b)**
White solid; mp 113–115 °C (Et_2O); yield 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (1 H, s, H_{arom}), 7.74 (1 H, dd, *J* = 2.2, 6.6 Hz, H_{arom}), 7.40–7.34 (2 H, m, H_{arom}), 2.69 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2 (C_q), 144.8 (C_q), 143.7 (C_q), 137.7 (C_q), 130.8 (C_q), 128.1 (CH), 127.6 (CH), 125.0 (CH), 121.7 (CH), 26.9 (CH_3). ESI-MS (MeCN): *m/z* calcd: 210 $[M + H]^+$; found: 211. ESI-HMRS: *m/z* $[M + Na]^+$ calcd for $C_{10}H_7ClNaOS$: 232.9798; found: 232.9801.
2-Acetyl-5-nitrobenzo[*b*]thiophene (1c)
White-brown solid; mp 176–178 °C (from Et_2O); yield 86%. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.86 (1 H, d, *J* = 1.5 Hz, H_{arom}), 8.47 (1 H, s, H_{arom}), 8.29–8.21 (2 H, m, H_{arom}), 2.66 (3 H, s, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 192.4 (C_q), 147.1 (C_q), 146.7 (C_q), 145.4 (C_q), 139.0 (C_q), 131.5 (CH), 124.5 (CH), 121.7 (CH), 121.1 (CH), 26.6 (CH_3). ESI-MS (MeCN): *m/z* calcd: 221 $[M + H]^+$; found: 222. HMRS (CI): *m/z* $[M + H]^+$ calcd for $C_{10}H_8NO_3S$: 222.0219; found: 222.0218.
Acetylnaphtho[1,2-*b*]thiophene (1d)
White solid; mp 128–130 °C (from Et_2O); yield 99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.17 (1 H, m, H_{arom}), 8.04 (1 H, s, H_{arom}), 7.95–7.92 (1 H, m, H_{arom}), 7.83–7.74 (2 H, m, H_{arom}), 7.65–7.58 (2 H, m, H_{arom}), 2.71 (3 H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9 (C_q), 142.9 (C_q), 142.1 (C_q), 137.0 (C_q), 132.1 (C_q), 130.6 (CH), 129.0 (CH), 128.7 (C_q), 127.4 (CH), 127.2 (CH), 126.4 (CH), 124.2 (CH), 122.8 (CH), 26.8 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 226 $[M + H]^+$; found: 227. ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{10}NaOS$: 249.0345; found: 249.0349.

2-Acetyl-5,6-methylenedioxybenzo[*b*]thiophene (1e)

Brown solid; mp 170–172 °C (from Et_2O); yield 35%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (1 H, s, H_{arom}), 7.25 (1 H, m, H_{arom}), 6.06 (2 H, s, CH_2), 2.60 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7 (C_q), 149.5 (C_q), 147.6 (C_q), 142.5 (C_q), 138.2 (C_q), 133.8 (C_q), 129.5 (CH), 103.6 (CH), 101.9 (CH_2), 101.8 (CH), 26.8 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 220 $[M + H]^+$; found: 221. ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_8NaO_3S$: 243.0086; found: 234.0079.

2-Acetylpyrido[2,3-*b*]thiophene (1f)

White solid; mp 120–122 °C (from Et_2O); yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (1 H, dd, *J* = 1.5, 4.5 Hz, H_{arom}), 8.17 (1 H, dd, *J* = 1.5, 8.1 Hz, H_{arom}), 7.87 (1 H, s, H_{arom}), 7.36 (1 H, dd, *J* = 4.5, 8.1 Hz, H_{arom}), 2.66 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2 (C_q), 163.5 (C_q), 149.7 (CH), 143.8 (C_q), 133.7 (CH), 132.9 (C_q), 127.0 (CH), 120.4 (CH), 26.8 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 177 $[M + H]^+$; found: 178. ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for C_9H_7NaNOS: 200.0141; found: 200.0138.

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(21) **2-Acetyl-3-aminobenzo[*b*]thiophene (2a)**

Yellow solid; mp 146–148 °C (from Et_2O); yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (1 H, d, *J* = 8.1 Hz, H_{arom}), 7.67 (1 H, d, *J* = 8.1 Hz, H_{arom}), 7.49 (1 H, dd, *J* = 7.5 Hz, H_{arom}), 7.36 (1 H, dd, *J* = 7.5 Hz, H_{arom}), 6.52 (2 H, br s, NH_2), 2.46 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.3 (C_q), 148.8 (C_q), 139.9 (C_q), 131.3 (C_q), 129.0 (CH), 124.2 (CH), 123.6 (CH), 121.9 (CH), 108.8 (C_q), 29.2 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 191 $[M + H]^+$; found: 192. ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}NOS$: 192.0478; found: 192.0470.

2-Acetyl-3-amino-4-chlorobenzo[*b*]thiophene (2b)

Yellow solid; mp 101–103 °C (from Et_2O); yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (1 H, d, *J* = 8.0 Hz, H_{arom}), 7.34 (1 H, dd, *J* = 7.8 Hz, H_{arom}), 7.27 (1 H, d, *J* = 7.5 Hz, H_{arom}), 2.43 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.7 (C_q), 149.9 (C_q), 142.4 (C_q), 130.7 (C_q), 128.9 (CH), 126.8 (C_q), 125.9 (CH), 122.4 (CH), 107.9 (C_q), 29.3 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 225 $[M + H]^+$; found: 226. ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_9ClNOS$: 226.0088; found: 226.0093.

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

Brown solid; mp 110–111 °C (from Et_2O); yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.51 (1 H, m, H_{arom}), 7.35–7.31 (2 H, m, H_{arom}), 2.50 (3 H, s, CH_3), 2.49 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.3 (C_q), 149.6 (C_q), 140.2 (C_q), 133.0 (C_q), 131.2 (C_q), 129.2 (CH), 124.7 (CH), 119.4 (CH), 108.9 (C_q), 29.1 (CH_3), 19.8 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 205 $[M + H]^+$; found: 206. ESI-HMRS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{11}NNaOS$: 228.0454; found: 228.0451.

2-Acetyl-3-amino-5-methoxybenzo[*b*]thiophene (2d)

Brown solid; mp 116–117 °C (from Et_2O); yield 15%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (1 H, d, *J* = 8.8 Hz, H_{arom}), 7.16 (1 H, dd, *J* = 2.2, 8.8 Hz, H_{arom}), 7.06 (1 H, d, *J* = 2.2 Hz, H_{arom}), 3.89 (3 H, s, CH_3), 2.45 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.4 (C_q), 157.6 (C_q), 148.4 (C_q), 132.4 (C_q), 132.1 (C_q), 124.5 (CH), 119.8 (CH), 110.4 (C_q), 103.5 (CH), 55.8 (CH_3), 29.0 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 221 $[M + H]^+$; found: 222. ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{12}NO_2S$: 222.0593; found: 22.0589.

2-Acetyl-3-amino-5-nitrobenzo[*b*]thiophene (2e)

Orange solid; mp 290–292 °C (from MeOH); yield 99%. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.23 (1 H, d, *J* = 2.0 Hz, H_{arom}), 8.28 (1 H, dd, *J* = 2.0, 8.8 Hz, H_{arom}), 8.09 (1 H, d, *J* = 8.8 Hz, H_{arom}), 2.37 (3 H, s, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 191.7 (C_q), 150.0 (C_q), 145.0 (C_q), 144.9 (C_q), 131.7 (C_q), 124.9 (CH), 122.9 (CH), 120.2 (CH), 107.8 (C_q), 29.2 (CH_3). ESI-MS (MeCN): *m*/*z* calcd: 236 $[M + H]^+$; found: 237. HMRS (CI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_9N_2O_3S$: 237.0328; found: 237.0327.

2-Acetyl-3-aminopyrido[2,3-*b*]thiophene (2f)

Yellow solid; mp 194–196 °C (from Et_2O); yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (1 H, dd, *J* = 1.5, 4.7 Hz, H_{arom}), 7.98 (1 H, dd, *J* = 1.5, 8.0 Hz, H_{arom}), 7.33 (1 H, dd, *J* = 4.7, 8.0 Hz, H_{arom}), 6.68 (2 H, br s, NH_2), 2.49 (3 H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.9 (C_q), 160.8 (C_q), 151.3 (CH), 146.3 (C_q), 130.0 (CH), 125.5 (C_q), 119.2 (CH), 108.0 (C_q), 29.4 (CH_3). ESI-MS(MeCN): *m*/*z* calcd: 192 $[M + H]^+$; found: 193. ESI-HMRS: *m*/*z* $[M + H]^+$ calcd for $C_9H_9N_2OS$: 193.0430; found: 193.0432.

