

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

Julien Debray,<sup>\*a</sup> Marc Lemaire,<sup>a</sup> Florence Popowycz<sup>\*a,b</sup>

<sup>a</sup> Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, UMR-CNRS 5246, Equipe Catalyse Synthèse Environnement, Université de Lyon, Université Claude Bernard-Lyon 1, Bâtiment Curien, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France

<sup>b</sup> Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, UMR-CNRS 5246, Equipe Chimie Organique et Bioorganique, Institut National des Sciences Appliquées (INSA Lyon), Bâtiment Jules Verne, 20 Avenue Albert Einstein, 69621 Villeurbanne Cedex, France  
Fax +33(4)72438896; E-mail: florence.popowycz@insa-lyon.fr

Received: 12.09.2012; Accepted after revision: 26.10.2012

**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.

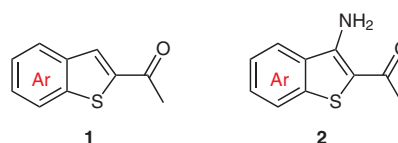
**Key words:** heterocycles, benzo[*b*]thiophene, nucleophilic aromatic substitution, thiol, cyclization

Benzo[*b*]thiophene derivatives represent a major class of compounds displaying a wide range of biological activities, acting as selective estrogen modulators,<sup>1</sup> antagonists for a vascular 5-HT<sub>1B</sub> receptor,<sup>2</sup> partial agonists at the benzodiazepine receptor,<sup>3</sup> and ligands for  $\alpha 1$  and 5HT<sub>1A</sub> receptors.<sup>4</sup> 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.<sup>5</sup> 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)<sup>6</sup> and the C-3 position (either by S<sub>N</sub>Ar or Friedel–Crafts acylation).<sup>7</sup> More recently, a new thematic direction was investigated to target molecules of major therapeutic interest, such as alkaline phosphatase inhibitors<sup>8</sup> or a Raloxifene synthetic intermediate.<sup>9</sup>

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,<sup>10</sup> 2-nitrobenzaldehyde,<sup>11</sup> 2-mercaptobenzaldehyde,<sup>12</sup> 2-mercaptobenzoic acid,<sup>13</sup> dihaloben-

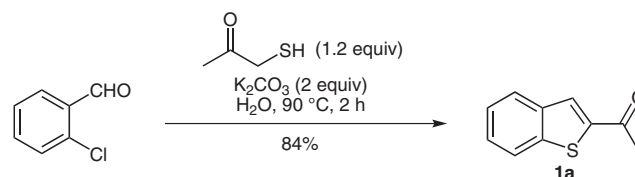
zene derivatives<sup>14</sup> and thiophenol.<sup>15</sup> However, very little attention has been paid to 2-acetyl-3-aminobenzo[*b*]thiophene **2** that, according to the literature, is prepared in four steps from *o*-(benzylthio)benzoic acid, with an overall yield of 60%.<sup>16</sup>



**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).<sup>17</sup> 2-Mercaptoacetone was also easily prepared, following the procedure described by Meakins.<sup>18</sup> Sodium hydrosulfide in water reacted with 2-chloropropanone, cooled to 0 °C for one hour, producing a 70% yield of 2-mercaptoacetone.



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

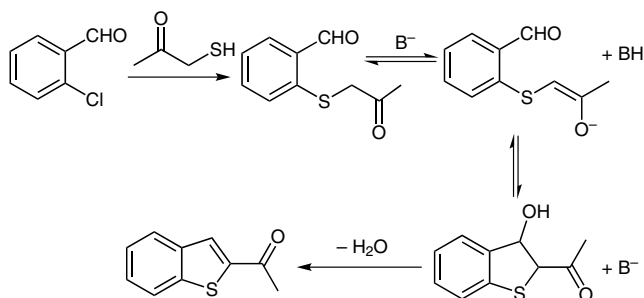
*SYNLETT* 2013, 24, 0037–0040

Advanced online publication: 28.11.2012

DOI: 10.1055/s-0032-1317674; Art ID: ST-2012-D0769-L

© Georg Thieme Verlag Stuttgart · New York

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).

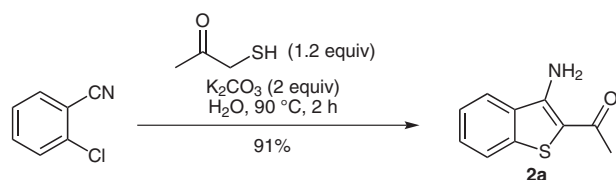


**Scheme 2** Suggested mechanism

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).<sup>19</sup> 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<sub>3</sub> in the Friedel–Crafts acylation of benzo[*b*]thiophene.<sup>20</sup> 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).<sup>17</sup>



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

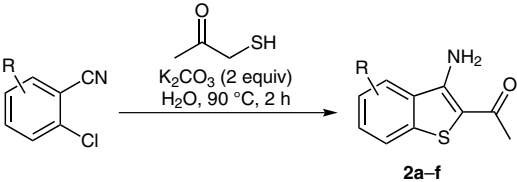
Using a similar approach, substituted chlorobenzonitriles were introduced into the same experimental procedures,

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

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

producing 2-acetyl-3-aminobenzo[*b*]thiophenes **2a–f** (Table 2).<sup>21</sup> 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-amino-benzo[*b*]thiophenes **2**


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

This research work was supported by a grant from Lyon Science Transfert to J.D. (Project N°705)

### References and Notes

- (1) (a) Qin, Z.; Kastrati, I.; Chandrasena, R. E. P.; Liu, H.; Yao, P.; Petukhov, P. A.; Bolton, J. L.; Thatcher, G. R. J. *J. Med. Chem.* **2007**, *50*, 2682. (b) Overk, C. R.; Peng, K.-W.; Asghodom, R. T.; Kastrati, I.; Lantvit, D. D.; Qin, Z.; Frasor, J.; Bolton, J. L.; Thatcher, G. R. J. *ChemMedChem* **2007**, *2*, 1520.
- (2) Moloney, G. P.; Garavelas, A.; Martin, G. R.; Maxwell, M.; Glen, R. C. *Eur. J. Med. Chem.* **2004**, 305.
- (3) Settimo, F. D.; Lucacchini, A.; Marini, A. M.; Martini, C.; Primofiore, G.; Senatore, G.; Taliani, S. *Eur. J. Med. Chem.* **1996**, 951.
- (4) Romeo, G.; Ambrosini, G.; Guccione, S.; De Blasi, A.; Russo, F. *Eur. J. Med. Chem.* **1993**, 499.

- (5) Vennemann, M.; Baer, T.; Groeger, G.; Braunger, J.; Gimmnich, P.; Maier, T.; Rothfels, H. WO 2006018435, **2006**.
- (6) (a) Popowycz, F.; Méta, E.; Lemaire, M. *C. R. Chim.* **2011**, *14*, 621. (b) Fournier Dit Chabert, J.; Joucla, L.; David, E.; Lemaire, M. *Tetrahedron* **2004**, *60*, 3221.
- (7) (a) Fournier Dit Chabert, J.; Chatelain, G.; Pellet-Rostaing, S.; Bouchu, D.; Lemaire, M. *Tetrahedron* **2006**, *47*, 1015. (b) David, E.; Perrin, J.; Pellet-Rostaing, S.; Fournier Dit Chabert, J.; Lemaire, M. *J. Org. Chem.* **2005**, *70*, 3569.
- (8) Chang, L.; Le Duy, D.; Mébarek, S.; Popowycz, F.; Pellet-Rostaing, S.; Lemaire, M.; Buchet, R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2297.
- (9) Liger, F.; Pellet-Rostaing, S.; Popowycz, F.; Lemaire, M. *Tetrahedron Lett.* **2011**, *52*, 3736.
- (10) (a) Chemburkar, S. R.; Anderson, D. G.; Reddy, R. E. *Synth. Commun.* **2010**, *40*, 1887. (b) Liu, Z.-Y.; He, X.-B.; Yang, Z.-Y.; Shao, H.-Y.; Li, X.; Guo, H.-F.; Zhang, Y.-Q.; Si, S.-Y.; Li, Z.-R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4167.
- (11) Guo, H.-F.; Shao, H.-Y.; Yang, Z.-Y.; Xue, S.-T.; Li, X.; Liu, Z.-Y.; He, X.-B.; Jiang, J.-D.; Zhang, Y.-Q.; Si, S.-Y.; Li, Z.-R. *J. Med. Chem.* **2010**, *53*, 1819.
- (12) Gallagher, T.; Pardoe, D. A.; Porter, R. A. *Tetrahedron Lett.* **2000**, *41*, 5415.
- (13) Hsiao, C. N.; Bhagavatula, L.; Pariza, R. L. *Synth. Commun.* **1990**, *20*, 1687.
- (14) Michellys, P.-Y.; D'Arrigo, J.; Grese, T. A.; Karanewsky, D. S.; Leibowitz, M. D.; Mais, D. A.; Mapes, C. M.; Reifel-Miller, A.; Rungta, D.; Boehm, M. F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1593.
- (15) Basha, A.; Brooks, D. W. *J. Org. Chem.* **1993**, *58*, 1293.
- (16) Hallas, G.; Towns, A. D. *Dyes Pigm.* **1997**, *35*, 219.
- (17) **Representative Procedure**  
Substituted 2-chlorobenzaldehyde or 2-chlorobenzonitrile (1 mmol) was stirred, in the presence of K<sub>2</sub>CO<sub>3</sub> (2 mmol) and 2-mercaptoacetone (1.2 mmol) suspended in H<sub>2</sub>O (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.
- (18) Brown, M. D.; Gillon, D. W.; Meakins, G. D.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1623.
- (19) **2-Acetyl-4-chlorobenzo[*b*]thiophene (1b)**  
White solid; mp 113–115 °C (Et<sub>2</sub>O); yield 88%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.05 (1 H, s, H<sub>arom</sub>), 7.74 (1 H, dd, *J* = 2.2, 6.6 Hz, H<sub>arom</sub>), 7.40–7.34 (2 H, m, H<sub>arom</sub>), 2.69 (3 H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 192.2 (C<sub>q</sub>), 144.8 (C<sub>q</sub>), 143.7 (C<sub>q</sub>), 137.7 (C<sub>q</sub>), 130.8 (C<sub>q</sub>), 128.1 (CH), 127.6 (CH), 125.0 (CH), 121.7 (CH), 26.9 (CH<sub>3</sub>). ESI-MS (MeCN): *m/z* calcd: 210 [M + H]<sup>+</sup>; found: 211. ESI-HMRS: *m/z* [M + Na]<sup>+</sup> calcd for C<sub>10</sub>H<sub>7</sub>ClNaOS: 232.9798; found: 232.9801.

**2-Acetyl-5-nitrobenzo[*b*]thiophene (1c)**  
White-brown solid; mp 176–178 °C (from Et<sub>2</sub>O); yield 86%. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 8.86 (1 H, d, *J* = 1.5 Hz, H<sub>arom</sub>), 8.47 (1 H, s, H<sub>arom</sub>), 8.29–8.21 (2 H, m, H<sub>arom</sub>), 2.66 (3 H, s, CH<sub>3</sub>). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 192.4 (C<sub>q</sub>), 147.1 (C<sub>q</sub>), 146.7 (C<sub>q</sub>), 145.4 (C<sub>q</sub>), 139.0 (C<sub>q</sub>), 131.5 (CH), 124.5 (CH), 121.7 (CH), 121.1 (CH), 26.6 (CH<sub>3</sub>). ESI-MS (MeCN): *m/z* calcd: 221 [M + H]<sup>+</sup>; found: 222. HMRS (CI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>8</sub>NO<sub>3</sub>S: 222.0219; found: 222.0218.

**Acetylnaphtho[1,2-*b*]thiophene (1d)**  
White solid; mp 128–130 °C (from Et<sub>2</sub>O); yield 99%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.20–8.17 (1 H, m, H<sub>arom</sub>), 8.04 (1 H, s, H<sub>arom</sub>), 7.95–7.92 (1 H, m, H<sub>arom</sub>), 7.83–7.74 (2 H, m, H<sub>arom</sub>), 7.65–7.58 (2 H, m, H<sub>arom</sub>), 2.71 (3 H, s, CH<sub>3</sub>).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 191.9$  ( $\text{C}_q$ ), 142.9 ( $\text{C}_q$ ), 142.1 ( $\text{C}_q$ ), 137.0 ( $\text{C}_q$ ), 132.1 ( $\text{C}_q$ ), 130.6 (CH), 129.0 (CH), 128.7 ( $\text{C}_q$ ), 127.4 (CH), 127.2 (CH), 126.4 (CH), 124.2 (CH), 122.8 (CH), 26.8 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 226  $[\text{M} + \text{H}]^+$ ; found: 227. ESI-HMRS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{14}\text{H}_{10}\text{NaOS}$ : 249.0345; found: 249.0349.

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

Brown solid; mp 170–172 °C (from  $\text{Et}_2\text{O}$ ); yield 35%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.78$  (1 H, s,  $\text{H}_{\text{arom}}$ ), 7.25 (1 H, m,  $\text{H}_{\text{arom}}$ ), 6.06 (2 H, s,  $\text{CH}_2$ ), 2.60 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 191.7$  ( $\text{C}_q$ ), 149.5 ( $\text{C}_q$ ), 147.6 ( $\text{C}_q$ ), 142.5 ( $\text{C}_q$ ), 138.2 ( $\text{C}_q$ ), 133.8 ( $\text{C}_q$ ), 129.5 (CH), 103.6 (CH), 101.9 ( $\text{CH}_2$ ), 101.8 (CH), 26.8 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 220  $[\text{M} + \text{H}]^+$ ; found: 221. ESI-HMRS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{11}\text{H}_8\text{NaO}_3\text{S}$ : 243.0086; found: 234.0079.

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

White solid; mp 120–122 °C (from  $\text{Et}_2\text{O}$ ); yield 86%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.67$  (1 H, dd,  $J = 1.5, 4.5$  Hz,  $\text{H}_{\text{arom}}$ ), 8.17 (1 H, dd,  $J = 1.5, 8.1$  Hz,  $\text{H}_{\text{arom}}$ ), 7.87 (1 H, s,  $\text{H}_{\text{arom}}$ ), 7.36 (1 H, dd,  $J = 4.5, 8.1$  Hz,  $\text{H}_{\text{arom}}$ ), 2.66 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 192.2$  ( $\text{C}_q$ ), 163.5 ( $\text{C}_q$ ), 149.7 (CH), 143.8 ( $\text{C}_q$ ), 133.7 (CH), 132.9 ( $\text{C}_q$ ), 127.0 (CH), 120.4 (CH), 26.8 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 177  $[\text{M} + \text{H}]^+$ ; found: 178. ESI-HMRS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_9\text{H}_7\text{NaNOS}$ : 200.0141; found: 200.0138.

- (20) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, 26, 1. (b) Kudo, H.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1985**, 22, 215. (c) Okuyama, T.; Tani, Y.; Miyake, K.; Yokoyama, Y. *J. Org. Chem.* **2007**, 72, 1634.

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

Yellow solid; mp 146–148 °C (from  $\text{Et}_2\text{O}$ ); yield 91%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.72$  (1 H, d,  $J = 8.1$  Hz,  $\text{H}_{\text{arom}}$ ), 7.67 (1 H, d,  $J = 8.1$  Hz,  $\text{H}_{\text{arom}}$ ), 7.49 (1 H, dd,  $J = 7.5$  Hz,  $\text{H}_{\text{arom}}$ ), 7.36 (1 H, dd,  $J = 7.5$  Hz,  $\text{H}_{\text{arom}}$ ), 6.52 (2 H, br s,  $\text{NH}_2$ ), 2.46 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 193.3$  ( $\text{C}_q$ ), 148.8 ( $\text{C}_q$ ), 139.9 ( $\text{C}_q$ ), 131.3 ( $\text{C}_q$ ), 129.0 (CH), 124.2 (CH), 123.6 (CH), 121.9 (CH), 108.8 ( $\text{C}_q$ ), 29.2 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 191  $[\text{M} + \text{H}]^+$ ; found: 192. ESI-HMRS:  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_{10}\text{NOS}$ : 192.0478; found: 192.0470.

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

Yellow solid; mp 101–103 °C (from  $\text{Et}_2\text{O}$ ); yield 82%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.59$  (1 H, d,  $J = 8.0$  Hz,  $\text{H}_{\text{arom}}$ ), 7.34 (1 H, dd,  $J = 7.8$  Hz,  $\text{H}_{\text{arom}}$ ), 7.27 (1 H, d,  $J = 7.5$  Hz,  $\text{H}_{\text{arom}}$ ), 2.43 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta =$

192.7 ( $\text{C}_q$ ), 149.9 ( $\text{C}_q$ ), 142.4 ( $\text{C}_q$ ), 130.7 ( $\text{C}_q$ ), 128.9 (CH), 126.8 ( $\text{C}_q$ ), 125.9 (CH), 122.4 (CH), 107.9 ( $\text{C}_q$ ), 29.3 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 225  $[\text{M} + \text{H}]^+$ ; found: 226. ESI-HMRS:  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_9\text{ClNOS}$ : 226.0088; found: 226.0093.

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

Brown solid; mp 110–111 °C (from  $\text{Et}_2\text{O}$ ); yield 90%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.54$ – $7.51$  (1 H, m,  $\text{H}_{\text{arom}}$ ), 7.35– $7.31$  (2 H, m,  $\text{H}_{\text{arom}}$ ), 2.50 (3 H, s,  $\text{CH}_3$ ), 2.49 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 193.3$  ( $\text{C}_q$ ), 149.6 ( $\text{C}_q$ ), 140.2 ( $\text{C}_q$ ), 133.0 ( $\text{C}_q$ ), 131.2 ( $\text{C}_q$ ), 129.2 (CH), 124.7 (CH), 119.4 (CH), 108.9 ( $\text{C}_q$ ), 29.1 ( $\text{CH}_3$ ), 19.8 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 205  $[\text{M} + \text{H}]^+$ ; found: 206. ESI-HMRS:  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{11}\text{H}_{11}\text{NNaOS}$ : 228.0454; found: 228.0451.

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

Brown solid; mp 116–117 °C (from  $\text{Et}_2\text{O}$ ); yield 15%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.59$  (1 H, d,  $J = 8.8$  Hz,  $\text{H}_{\text{arom}}$ ), 7.16 (1 H, dd,  $J = 2.2, 8.8$  Hz,  $\text{H}_{\text{arom}}$ ), 7.06 (1 H, d,  $J = 2.2$  Hz,  $\text{H}_{\text{arom}}$ ), 3.89 (3 H, s,  $\text{CH}_3$ ), 2.45 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 193.4$  ( $\text{C}_q$ ), 157.6 ( $\text{C}_q$ ), 148.4 ( $\text{C}_q$ ), 132.4 ( $\text{C}_q$ ), 132.1 ( $\text{C}_q$ ), 124.5 (CH), 119.8 (CH), 110.4 ( $\text{C}_q$ ), 103.5 (CH), 55.8 ( $\text{CH}_3$ ), 29.0 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 221  $[\text{M} + \text{H}]^+$ ; found: 222. ESI-HMRS:  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ : 222.0593; found: 22.0589.

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

Orange solid; mp 290–292 °C (from MeOH); yield 99%.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 9.23$  (1 H, d,  $J = 2.0$  Hz,  $\text{H}_{\text{arom}}$ ), 8.28 (1 H, dd,  $J = 2.0, 8.8$  Hz,  $\text{H}_{\text{arom}}$ ), 8.09 (1 H, d,  $J = 8.8$  Hz,  $\text{H}_{\text{arom}}$ ), 2.37 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 191.7$  ( $\text{C}_q$ ), 150.0 ( $\text{C}_q$ ), 145.0 ( $\text{C}_q$ ), 144.9 ( $\text{C}_q$ ), 131.7 ( $\text{C}_q$ ), 124.9 (CH), 122.9 (CH), 120.2 (CH), 107.8 ( $\text{C}_q$ ), 29.2 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 236  $[\text{M} + \text{H}]^+$ ; found: 237. HMRS (CI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_9\text{N}_2\text{O}_3\text{S}$ : 237.0328; found: 237.0327.

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

Yellow solid; mp 194–196 °C (from  $\text{Et}_2\text{O}$ ); yield 96%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.72$  (1 H, dd,  $J = 1.5, 4.7$  Hz,  $\text{H}_{\text{arom}}$ ), 7.98 (1 H, dd,  $J = 1.5, 8.0$  Hz,  $\text{H}_{\text{arom}}$ ), 7.33 (1 H, dd,  $J = 4.7, 8.0$  Hz,  $\text{H}_{\text{arom}}$ ), 6.68 (2 H, br s,  $\text{NH}_2$ ), 2.49 (3 H, s,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 193.9$  ( $\text{C}_q$ ), 160.8 ( $\text{C}_q$ ), 151.3 (CH), 146.3 ( $\text{C}_q$ ), 130.0 (CH), 125.5 ( $\text{C}_q$ ), 119.2 (CH), 108.0 ( $\text{C}_q$ ), 29.4 ( $\text{CH}_3$ ). ESI-MS (MeCN):  $m/z$  calcd: 192  $[\text{M} + \text{H}]^+$ ; found: 193. ESI-HMRS:  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_9\text{H}_9\text{N}_2\text{OS}$ : 193.0430; found: 193.0432.