Direct Bromination of Ethyl 5-Alkylthiophene-2-carboxylates

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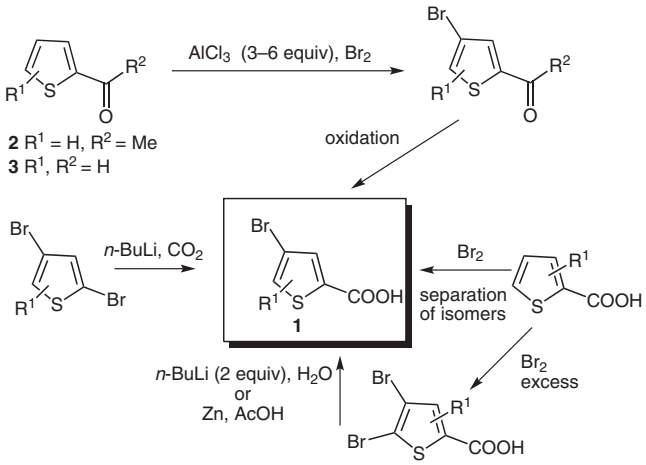
Abstract: Approaches to brominated thiophene-2-carboxylic acids by electrophilic bromination of the corresponding acids and esters were compared and investigated. A synthetic route was developed involving direct bromination of ethyl 5-alkylthiophene-2-carboxylates followed by saponification of the resulting ethyl 5-alkyl-4-bromothiophene-2-carboxylates. The key bromination step is selective in dichloromethane solution at 0–5 °C and furnishes the corresponding ethyl 5-alkyl-4-bromothiophene-2-carboxylates in excellent yields. No migration or isomerization of the alkyl substituents was observed.

Key words: bromine, esters, thiophenes, electrophilic aromatic substitutions, aluminum

Thiophene-2-carboxylic acids **1** brominated at the 4-position (Scheme 1) are of considerable interest, as they are key starting compounds in the synthesis of biologically active compounds (e.g., antitumor agents),[1a] nonlinear optics materials,[1b] and liquid crystals.[1c] Previously reported methods for the preparation of **1** include oxidation of the corresponding aldehydes or ketones,[1a] carboxylation of lithiated substituted 2,4-dibromothiophenes,[2a] or, alternatively, debromination of 4,5-dibromothiophene-2-carboxylic acids by using zinc and acetic acid[2b] or *n*-butyllithium (Scheme 1).[2c] It is worth noting that direct bromination of acids in the presence of bromine in various solvents has also been used for the preparation of 4-bromo or 4,5-dibromo derivatives.[1b,c,2d,e] However, many of the earlier described approaches to **1** have significant disadvantages, for example involving laborious, cumbersome operations, often requiring relatively uncommon starting materials, and tending to furnish the target acids **1** in low yields. Moreover, further scaling-up of certain key stages would be quite challenging.

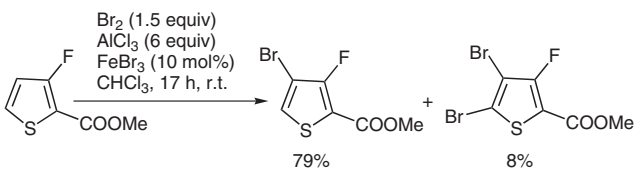
The bromination of 2-acetylthiophene (**2**) and thiophene-2-carbaldehyde (**3**) in the presence of a large excess of aluminum(III) chloride was investigated by Gol'dfarb (Scheme 1).[3a] Importantly, only 4-brominated products were formed under these conditions. Subsequently, this method, termed 'catalyst swamping conditions', has been used frequently for the preparation of various substituted 4-bromothiophenecarbaldehydes and ketones.[3b–e] In this context, it is rather surprising that no further attempts were made to expand the scope and applications of this method for obtaining thiophene-2-carboxylic acids and their derivatives. While catalytic quantities of iron(III) chloride have been used in the monobromination of 5-hexylthiophene-2-carboxylic acid[1c] and zinc(II) chloride has been used to catalyze the dibromination of ethyl thiophene-2-carboxylate,[3f] in all these cases an evaluation of the catalyst influence on the composition of the products is difficult, because under these conditions excessive bromination occurs at all the accessible positions.



Scheme 1 Possible approaches to brominated thiophene-2-carboxylic acids **1**

To the best of our knowledge, there is only one example of the use of catalyst swamping conditions for the bromination of methyl 3-fluorothiophene-2-carboxylate (Scheme 2).[1b] This ester did not undergo bromination even in the presence of 600 mol% of aluminum(III) chloride, so that the addition of 10 mol% of iron(III) chloride was required to promote the reaction. A mixture of mono- and dibrominated compounds was obtained, but no further investigation of this reaction was carried out.

As one of the current research projects in our group focuses on thiophene-based dyes with nonlinear optic proper-



Scheme 2 Bromination of methyl 3-fluorothiophene-2-carboxylate

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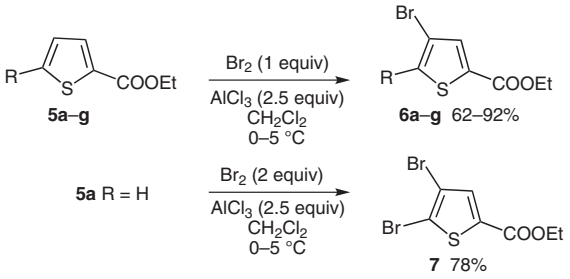
ties, we report here on a convenient and versatile method for the preparation of ethyl 5-alkyl-4-bromothiophene-2-carboxylates **6** (Scheme 3). This route is also perfectly suitable for various 5-alkylated thiophene acids. Gratifyingly, this new procedure, in our view, is readily applicable to the preparation of multigram quantities of the target compounds.



Scheme 3 Bromination of ethyl 5-alkylthiophene-2-carboxylates

We found that 5-alkylthiophene-2-carboxylates **5** can be selectively brominated to form 4-substituted derivatives under catalyst swamping conditions. The maximum yields of the brominated derivatives **6** were obtained when the molar ratio of ester to aluminum(III) chloride was 1:2.5. The yields reach 90–95% if the bromination is run in chlorinated solvents such as dichloromethane, chloroform, or 1,2-dichloroethane and the reaction temperature is maintained around 0–5 °C.

It is remarkable that under these conditions neither the thiophene side chain nor the ester group is affected. The experiments carried out with the ethyl esters of 5-substituted thiophene-2-carboxylic acids clearly show that migration and isomerization of the 5-substituent do not occur, even in the presence of a large excess of aluminum(III) chloride.

In addition to the high selectivity and yields obtained by this method, the reaction workup and the separation of the products are very convenient. Firstly, smooth decomposition of the aluminum complex is induced by the addition of ice-cold diluted hydrochloric acid. Secondly, by appropriate extraction of the products from the resulting mixture, esters **6** can in most cases be obtained in sufficiently pure form (at least 90% GC assay) simply after evaporation of the solvent. The reaction can easily be run on a two-mole scale without deterioration of the yield (Table 1).

When unsubstituted ethyl thiophenecarboxylate (**5a**) was brominated with one equivalent of bromine in the presence of aluminum(III) chloride, a mixture of products was obtained. The GC-MS analysis of the crude reaction mixture indicated the presence of four main components: (i) the unreacted ethyl thiophenecarboxylate (**5a**) (6.9%), (ii) ethyl 5-bromothiophene-2-carboxylate (3.2%), (iii) ethyl 4-bromothiophene-2-carboxylate (**6a**) (77.8%), and (iv) ethyl 4,5-dibromothiophene-2-carboxylate (**7**) (12.1%). Pure ethyl 4-bromothiophene-2-carboxylate (**6a**) was separated from this mixture by careful rectification on an efficient column (approximately 10 theoretical plates). Importantly, when *two* equivalents of bromine were used, ester **7** was obtained quantitatively (Scheme 3).

Table 1 Synthesis of Ethyl 5-Alkyl-4-bromothiophene-2-carboxylates **6a–g**[a]

Entry	R	6	Yield[b] (%)
1	H	**6a**	62[c]
2	Me	**6b**	89
3	Et	**6c**	91
4	*n*-Pr	**6d**	77
5	*i*-Pr	**6e**	78
6	*t*-Bu	**6f**	69
7	*i*-Bu	**6g**	92

[a] Reaction conditions: **5** (10 mmol), $AlCl_3$ (2.5 equiv), Br_2 (1 equiv), CH_2Cl_2, 0–5 °C, 1.5 h.
[b] Isolated yield.
[c] Reaction was carried out on a 200 mmol scale.

A further study of the bromination of the free thiophenecarboxylic acids in the presence of aluminum(III) chloride showed that only complex mixtures of brominated products along with unidentifiable tarry material can be obtained. Therefore, this one-step procedure unfortunately cannot compete with the proposed two-step method for the preparation of brominated acids **1**, which involves the bromination of the corresponding esters **5** and subsequent saponification of the bromo esters **6** by using a solution of potassium hydroxide in water–ethanol.

In conclusion, we have shown that the bromination of ethyl 5-alkylthiophene-2-carboxylates **5** in the presence of 2.5 equivalents of aluminum(III) chloride selectively leads to the substitution at the 4-position of the thiophene fragment and is therefore an excellent preparative method for the preparation of 5-alkyl-4-bromothiophene-2-carboxylic acids **1** and their esters **6**.

All manipulations were performed in dry air. Anhyd $AlCl_3$ (powder) and solvents (synthetic grade) were purchased from Merck KGaA (Germany) and Acros Organics (Belgium). Esters **5a–g** were purchased from ArtChem GmbH (Campus Berlin-Buch, Germany). ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded at 25 °C on a Bruker AC-300 spectrometer operated at 300 MHz and 75 MHz, respectively. All ^1H chemical shifts are reported in ppm relative to TMS (0.00 ppm); ^{13}C shifts are reported in ppm relative to $CDCl_3$. Mass spectra were recorded on a Finnigan INCOS-50 instrument (EI, 70 eV, direct insertion). GC-MS analysis was performed on a Thermo Focus DSQ II instrument with an HP-5MS column. GC analysis was performed on a Varian 3700 instrument equipped with FID and a 15 m × 0.53 mm × 0.5 μm Zebron ZB-5 capillary column (Phenomenex, USA) using helium (5 mL·min^{-1}) in temperature-programming mode.

Ethyl 4-Bromothiophene-2-carboxylates 6a–g; General Procedure

A soln of the appropriate ester **5** (10 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred suspension of $AlCl_3$ (3.3 g, 25 mmol) in

CH_2Cl_2 (10 mL) at 0 °C; the reaction mixture was then stirred for an additional 30 min. A 2 M soln of Br_2 in CH_2Cl_2 (5 mL, 10 mmol) was added at the same temperature and the stirring was continued for 1 h. The reaction mixture was poured onto acidic crushed ice [ice (5 g), concd aq HCl (2 mL)] and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed successively with brine (10 mL) and sat. aq $NaHCO_3$ (10 mL) and subsequently dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was distilled; this gave the corresponding product **6**.

Ethyl 4-Bromothiophene-2-carboxylate (6a)
Colorless oil; bp 107–108 °C (3 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (s, 1 H, H-5), 7.68 (s, 1 H, H-3), 4.35 (q, *J* = 11.1 Hz, 2 H, CH_2), 1.35 (t, *J* = 9.9 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 134.9, 134.4, 131.2, 109.7, 61.4, 14.0.

MS (EI, 70 eV): *m*/*z* (%) = 81 (55), 82 (100), 189 [^{79}BrM – C_2H_5O]$^+$ (67), 191 [^{81}BrM – C_2H_5O]$^+$ (68), 204 (75), 206 (75), 234 [^{79}BrM]$^+$ (21), 236 [^{81}BrM]$^+$ (23).

Anal. Calcd for $C_7H_7BrO_2S$: C, 35.76; H, 3.00; S, 13.64. Found: C, 36.13; H, 3.21; S, 14.22.

Ethyl 4-Bromo-5-methylthiophene-2-carboxylate (6b)
Light yellow oil; bp 80–82 °C (2 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1 H, H-3) 4.34 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.36 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 142.1, 135.6, 130.61, 110.1, 61.3, 15.4, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 69 (93), 96 (75), 203 [^{79}BrM – C_2H_5O]$^+$ (97), 205 [^{81}BrM – C_2H_5O]$^+$ (100), 248 [^{79}BrM]$^+$ (39), 250 [^{81}BrM]$^+$ (41).

Anal. Calcd for $C_8H_9BrO_2S$: C, 38.57; H, 3.64; S, 12.87. Found: C, 38.64; H, 3.89; S, 12.71.

Ethyl 4-Bromo-5-ethylthiophene-2-carboxylate (6c)
Light yellow oil; bp 105–106 °C (1 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, H-3), 4.35 (d, *J* = 7.2 Hz, 2 H, CH_2), 2.82 (d, 2 H, *J* = 7.2 Hz, CH_2), 1.34 ('t', *J* = 8.5 Hz, 6 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.35, 155.35, 133.50, 130.93, 124.46, 60.86, 23.81, 15.64, 14.36.

MS (EI, 70 eV): *m*/*z* (%) = 69 (100), 95 (67),110 (58), 217 [^{79}BrM – C_2H_5O]$^+$ (28), 219 [^{81}BrM – C_2H_5O]$^+$ (51),247 [^{79}BrM – Me] (20), 249 [^{81}BrM – Me]$^+$ (21), 262 [^{79}BrM]$^+$ (19), 264 [^{81}BrM]$^+$ (21).

Anal. Calcd for $C_9H_{11}BrO_2S$: C, 41.08; H, 4.21; S, 12.19. Found: C, 41.33; H, 4.29; S, 12.46.

Ethyl 4-Bromo-5-propylthiophene-2-carboxylate (6d)
Light yellow oil; bp 144–1146 °C (5 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, H-3), 4.3 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.8 (t, *J* = 7.9 Hz, 2 H, CH_2), 1.7 (sext, *J* = 7.2 Hz, 2 H, CH_2), 1.4 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.0 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.38, 147.64, 135.64, 130.5, 109.35, 61.38, 31.78, 23.70, 14.36, 13.65.

MS (EI, 70 eV): *m*/*z* (%) = 69 (46), 95 (81), 219 (59), 221 (59), 231 [^{79}BrM – C_2H_5O]$^+$ (22), 233 [^{81}BrM – C_2H_5O]$^+$ (23), 247 [^{79}BrM – C_2H_3] (98), 249 [^{81}BrM – C_2H_3]$^+$ (100), 276 [^{79}BrM]$^+$ (40), 278 [^{81}BrM]$^+$ (39).

Anal. Calcd for $C_{10}H_{13}BrO_2S$: C, 43.33; H, 4.73; S, 11.57. Found: C, 43.49; H, 4.60; S, 11.69.

Ethyl 4-Bromo-5-isopropylthiophene-2-carboxylate (6e)
Colorless oil; bp 136–137 °C (7 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, H-3), 4.4 (q, *J* = 6.6, 7.2 Hz, 2 H, CH_2), 3.35 (sept, *J* = 6.6 Hz, 1 H, CH), 1.4 (m, 9 H, 3 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 155.1, 135.7, 130.5, 107.8, 61.4, 30.3, 23.6, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 65 (68), 109 (63), 197 (47), 233 [^{79}BrM – C_3H_7]$^+$ (65), 235 [^{81}BrM – C_3H_7]$^+$ (47), 261 [^{79}BrM – Me] (98), 263[^{81}BrM – Me]$^+$ (100), 276 [^{79}BrM]$^+$ (35), 278 [^{81}BrM]$^+$ (35).

Anal. Calcd for $C_{10}H_{13}BrO_2S$: C, 43.33; H, 4.73; S, 11.57. Found: C, 42.99; H, 4.84; S, 11.18.

Ethyl 4-Bromo-5-*tert*-butylthiophene-2-carboxylate (6f)
Light yellow oil; bp 147–150 °C (4 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, H-3). 4.3 (m, 2 H, CH_2), 1.5 (s, 9 H, 3 CH_3), 1.38 (m, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 156.1, 138.3, 135.3, 61.3, 35.74, 32.31, 29.61, 14.38.

MS (EI, 70 eV): *m*/*z* (%) = 123 (64), 247 (41), 249 (29), 275 [^{79}BrM – Me] (100), 277 [^{81}BrM – Me]$^+$ (98), 290 [^{79}BrM]$^+$ (30), 292 [^{81}BrM]$^+$ (30).

Anal. Calcd for $C_{11}H_{15}BrO_2S$: C, 45.37; H, 5.19; S, 11.01. Found: C, 45.45; H, 5.03; S, 10.89.

Ethyl 4-Bromo-5-isobutylthiophene-2-carboxylate (6g)
Colorless oil; bp 147–150 °C (6 Torr).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, H-3), 4.34 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.69 (d, *J* = 7.2 Hz, 2 H, CH_2), 2.0 (sept, *J* = 6.6 Hz, 1 H, CH), 1.37 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.6 Hz, 6 H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.5, 135.6, 131.0, 110.1, 61.4, 38.6, 30.2, 22.3, 14.36.

MS (EI, 70 eV): *m*/*z* (%) = 95 (42), 219 (88), 221(87), 247 [^{79}BrM – C_3H_7]$^+$ (100), 249 [^{81}BrM – C_3H_7]$^+$ (100), 290 [^{79}BrM]$^+$ (60), 292 [^{81}BrM]$^+$ (62).

Anal. Calcd for $C_{11}H_{15}BrO_2S$: C, 45.37; H, 5.19; S, 11.01. Found: C, 45.67; H, 5.38 S, 11.19.

Ethyl 4,5-Dibromothiophene-2-carboxylate (7)
The same procedure as for **6** was applied, but 2 M Br_2 soln (10 mL, 20 mmol) was added. Crude solid ester was recrystallized from hexane.

Yield: 2.45 g (78%); mp 50–50.5 °C (Lit.[2d] 51.0–51.1 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (s, 1 H, H-3), 4.35 (q, *J* = 10.9 Hz, 2 H, CH_2), 1.35 (t, *J* = 10.9 Hz, 3 H, CH_3).

Large-Scale Preparation of 6b
A soln of **5b** (100 g, 0.59 mol) in CH_2Cl_2 (50 mL) was added over 30 min to an ice-cooled magnetically stirred suspension of $AlCl_3$ (196 g, 1.47 mol) in CH_2Cl_2 (400 mL). The resulting dark suspension was stirred for an additional 30 min at 0 °C and Br_2 (30.3 mL, 94 g, 0.59 mol) was added dropwise; this resulted in vigorous effervescence. The mixture was stirred on an ice bath for 2 h, poured onto a crushed ice (1000 g)–concd aq HCl (150 mL) mixture, and the combined organic solns were treated as above to yield, after distillation, pure **6b** as an oil.

Yield: 130 g (89%).

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