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# Efficient synthesis of highly substituted thiophenes from acetylenic esters, ethyl bromopyruvate, and tetramethylthiourea

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**Abstract** The reaction of acetylenic esters with ethyl bromopyruvate in the presence of tetramethylthiourea led to highly functionalized thiophenes in excellent yields.

**Keywords** Ethyl bromopyruvate; Activated acetylenes; Substituted thiophene; tetramethylthiourea.

## Introduction

Thiophenes are an important class of heterocyclic compounds. A variety of molecules containing the thiophene ring system display biological activity and find application as pharmaceuticals [1], fragrance compounds [2], or pharmacophoric entities [3, 4]. Moreover, they are also useful synthesis intermediates, in the preparation of new conducting polymers [5, 6] or nonlinear optical materials [7]. Substituted thiophenes can be prepared by proper functionalization of the thiophene ring, usually through $\alpha$-metalation or $\beta$-halogenation reactions [1]. However, annulation reactions of suitably substituted acyclic precursors represent an attractive alternative methodology, which may allow direct regioselective preparation of the target molecule. Recently, several new methods have been developed which illustrate the utility of the latter approach [8–11].

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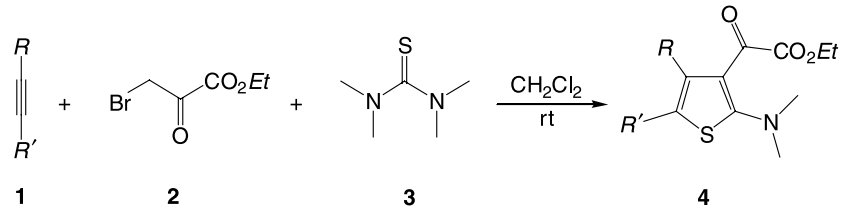
## Results and discussion

As part of our current studies on the development of new routes in heterocyclic synthesis [12–16], we now describe an efficient procedure for the direct synthesis of highly substituted thiophenes from the one-pot reaction of electron-deficient acetylenic esters with ethyl bromopyruvate in the presence of tetramethylthiourea at room temperature (Scheme 1).

The structures of **4a**–**4e** were deduced from their elemental analyses and their IR, $^1$H, and $^{13}$C NMR spectra. For example, the $^1$H NMR spectrum of **4a** exhibited three singlets for dimethylamino ($\delta =$ 3.12 ppm) and methoxy ($\delta = 3.78$ and 3.95 ppm) protons, together with characteristic multiplets for the ethoxy group. In the $^{13}$C NMR spectrum, the signals corresponding to ester and ketone carbonyl groups of the major isomer of **4a** were observed at $\delta = 161.9$, 162.5, 167.5, and 173.2 ppm. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 343$.

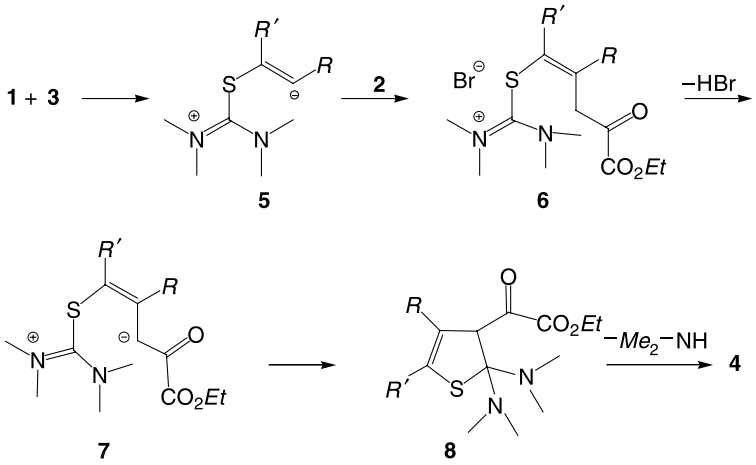
Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,5-dipolar intermediate **5** between tetramethylthiourea and the acetylenic compound, which reacts with ethyl bromopyruvate to produce **6**. Intermediate **6** is converted to the 1,6-diionic compound **7** *via* elimination of HBr. Cyclization of this intermediate leads to **8**, which is converted to **4** by elimination of dimethylamine (Scheme 2).

In conclusion, the reaction of dialkyl acetylenedicarboxylates or alkyl propiolates with ethyl bromopyruvate in the presence of tetramethylthiourea led




| 1, 4 | R | R′ | Yield/% of 4 |
|---|---|---|---|
| a | $CO_2Me$ | $CO_2Me$ | 90 |
| b | $CO_2Et$ | $CO_2Et$ | 85 |
| c | $CO_2Me$ | H | 73 |
| d | $CO_2Et$ | H | 75 |
| e | *Ph* | $CO_2Et$ | 74 |

**Scheme 1**




**Scheme 2**

to substituted thiophenes. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

## Experimental

Compounds **1–3** were obtained from Fluka and were used without further purification. Mp: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. $^1$H and $^{13}$C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz; $\delta$ in ppm, $J$ in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in $m/z$. Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer; their results agreed favorably with the calculated values.

*General procedure for the preparation of compounds* ***4***

To a stirred solution of 2 mmol **1** and 0.39 g **2** (2 mmol) in 15 cm$^3$ $CH_2Cl_2$ was added 0.26 g tetramethylthiourea (2 mmol) at rt. The reaction mixture was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography ($SiO_2$; *n*-hexane:*Ac*O*Et* 10:1) to afford pure **4**.

*Dimethyl 2-(dimethylamino)-3-(2-ethoxy-2-oxoacetyl)-thiophene-4,5-dicarboxylate* (**4a**, $C_{14}H_{17}NO_7S$)

Yellow oil; yield: 0.62 g (90%); IR (KBr): $\bar{\nu} = 1721$, 1636, 1529, 1453, 1366, 1254 cm$^{-1}$; EI-MS: $m/z$ (%) = 343 ($M^+$, 10), 312 (65), 299 (64), 284 (42), 59 (84), 31 (100); $^1$H NMR: $\delta = 1.35$ (t, $^3J = 7.2$ Hz, *Me*), 3.08 (s, N*Me*$_2$), 3.78 (s, O*Me*), 3.95 (s, O*Me*), 4.33 (q, $^3J = 7.2$ Hz, $OCH_2$) ppm; $^{13}$C NMR: $\delta = 13.9$ (*Me*), 41.2 (N*Me*$_2$), 51.8 (O*Me*), 52.6 (O*Me*), 62.6 ($OCH_2$), 128.6 (C), 130.6 (C), 148.2 (C), 154.2 (C), 161.9 (C=O), 162.5 (C=O), 167.5 (C=O), 173.2 (C=O) ppm.

*Diethyl 2-(dimethylamino)-3-(2-ethoxy-2-oxoacetyl)thiophene-4,5-dicarboxylate* (**4b**, $C_{16}H_{21}NO_7S$)

Yellow oil; yield: 0.58 g (78%); IR (KBr): $\bar{\nu} = 1716$, 1654, 1474, 1429, 1369, 1304, 1231, 1105 cm$^{-1}$; EI-MS: $m/z$ (%) = 371 ($M^+$, 15), 326 (75), 298 (56), 292 (62), 73 (82), 45 (100); $^1$H NMR: $\delta = 1.28$ (t, $^3J = 7.2$ Hz, *Me*), 1.34 (t, $^3J = 7.2$ Hz, *Me*), 1.40 (t, $^3J = 7.2$ Hz, *Me*), 3.04 (s, N*Me*$_2$), 4.34 (q, $^3J = 7.2$ Hz, $OCH_2$), 4.38 (q, $^3J = 7.2$ Hz, $OCH_2$), 4.41 (q, $^3J = 7.2$ Hz, $OCH_2$) ppm; $^{13}$C NMR: $\delta = 13.9$ (*Me*), 14.1 (*Me*), 14.3 (*Me*), 43.9 (N*Me*$_2$), 61.5 ($OCH_2$), 61.9 ($OCH_2$), 62.4 ($OCH_2$), 127.5 (C), 129.7 (C), 149.1 (C), 152.7 (C), 162.7 (C=O), 163.4 (C=O), 168.6 (C=O), 175.4 (C=O) ppm.

*Methyl 2-(dimethylamino)-3-(2-ethoxy-2-oxoacetyl)thiophene-4-carboxylate* (**4c**, $C_{12}H_{15}NO_5S$)

Yellow oil; yield: 0.42 g (73%); IR (KBr): $\bar{\nu} = 1725$, 1696, 1627, 1574, 1469, 1399, 1226 cm$^{-1}$; EI-MS: $m/z$ (%) = 285 ($M^+$, 5), 254 (55), 241 (64), 226 (76), 59 (84), 31 (100); $^1$H NMR: $\delta = 1.31$ (t, $^3J = 7.2$ Hz, *Me*), 3.01 (s, N*Me*$_2$), 3.76 (s, O*Me*), 4.38 (q, $^3J = 7.2$ Hz, $OCH_2$), 7.30 (s,

CH) ppm; $^{13}$C NMR: $\delta = 13.9$ (*Me*), 45.4 (N*Me*$_2$), 51.8 (O*Me*), 62.3 ($OCH_2$), 115.9 (C), 132.8 (CH), 136.3 (C), 155.0 (C), 163.2 (C=O), 167.1 (C=O), 179.1 (C=O) ppm.

*Ethyl 2-(dimethylamino)-3-(2-ethoxy-2-oxoacetyl)thiophene-3-carboxylate* (**4d**, $C_{13}H_{17}NO_5S$)
Yellow oil; yield: 0.45 g (75%); IR (KBr): $\bar{\nu} = 1693$, 1633, 1605, 1556, 1509, 1399, 1307, 1260 cm$^{-1}$; EI-MS: $m/z$ (%) = 299 ($M^+$, 10), 255 (64), 254 (45), 226 (66), 73 (62), 45 (100); $^1$H NMR: $\delta = 1.31$ (t, $^3J = 7.2$ Hz, *Me*), 1.41 (t, $^3J = 7.2$ Hz, *Me*), 3.06 (s, N*Me*$_2$), 4.22 (q, $^3J = 7.2$ Hz, $OCH_2$), 4.29 (q, $^3J = 7.2$ Hz, $OCH_2$), 7.31 (s, CH) ppm; $^{13}$C NMR: $\delta = 14.1$ (*Me*), 14.2 (*Me*), 45.2 (N*Me*$_2$), 60.7 ($OCH_2$), 61.8 ($OCH_2$), 116.4 (C), 133.0 (CH), 137.5 (C), 160.3 (C), 160.5 (C=O), 164.5 (C=O), 178.2 (C=O) ppm.

*Ethyl 2-(dimethylamino)-3-(2-ethoxy-2-oxoacetyl)-5-phenylthiophene-4-carboxylate* (**4e**, $C_{19}H_{21}NO_5S$)
Yellow oil; yield: 0.45 g (75%); IR (KBr): $\bar{\nu} = 1700$, 1692, 1634, 1609, 1502, 1310, 1268, 1153, 1076 cm$^{-1}$; EI-MS: $m/z$ (%) = 375 ($M^+$, 10), 330 (75), 302 (60), 298 (44), 77 (85), 73 (80), 45 (100); $^1$H NMR: $\delta = 1.23$ (t, $^3J = 7.2$ Hz, *Me*), 1.36 (t, $^3J = 7.2$ Hz, *Me*), 3.12 (s, N*Me*$_2$), 4.10 (q, $^3J = 7.2$ Hz, $OCH_2$), 4.26 (q, $^3J = 7.2$ Hz, $OCH_2$), 6.85 (t, $^3J = 8.2$ Hz, 2CH), 7.42 (t, $^3J = 8.2$ Hz, CH), 8.15 (d, $^3J = 8.2$ Hz, 2CH) ppm; $^{13}$C NMR: $\delta = 13.8$ (*Me*), 14.2 (*Me*), 44.5 (N*Me*$_2$), 61.2 ($OCH_2$), 62.0 ($OCH_2$), 114.2 (C), 127.3 (C), 128.5 (2CH), 129.4 (CH), 130.5 (2CH), 131.7 (C), 137.8 (C), 156.3 (C), 160.1 (C=O), 165.2 (C=O), 178.2 (C=O) ppm.

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