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Efficient synthesis of tetrasubstituted thiophenes by reaction of benzoyl isothiocyanates, ethyl bromopyruvate and enaminones

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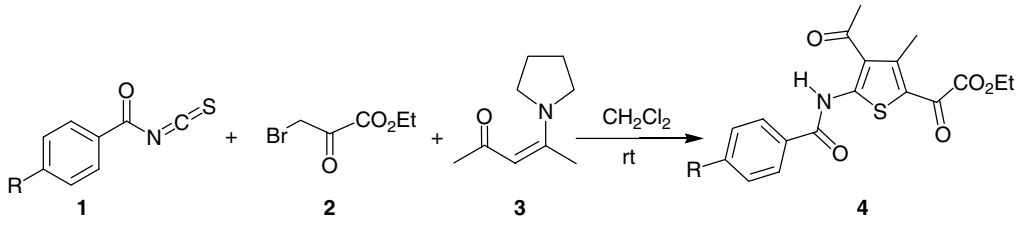
Abstract

An efficient synthesis of ethyl 2-(4-acetyl-5-benzoylamino-3-methyl-2-thienyl)-2-oxoacetates is described via reaction between benzoyl isothiocyanates and ethyl bromopyruvate in the presence of enaminones.

Keywords: Thiophene; Benzoyl isothiocyanate; Ethyl bromopyruvate; Enaminone

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 pharmacophores.[3] Moreover, they are useful synthetic intermediates in the preparation of new conducting polymers[4] or nonlinear optical materials.[5] Substituted thiophenes can be prepared by functionalization of the thiophene ring, usually through α-metalation or β-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.

As part of our current studies on the development of new routes in heterocyclic synthesis,[6–10] we report an efficient synthesis of tetrasubstituted thiophenes. Thus, the



1, 4	R	Yield (%) of 4
a	H	90
b	NO_2	85
c	Me	85
d	Br	80
e	Cl	75

Scheme 1. Synthesis of compounds **4**.

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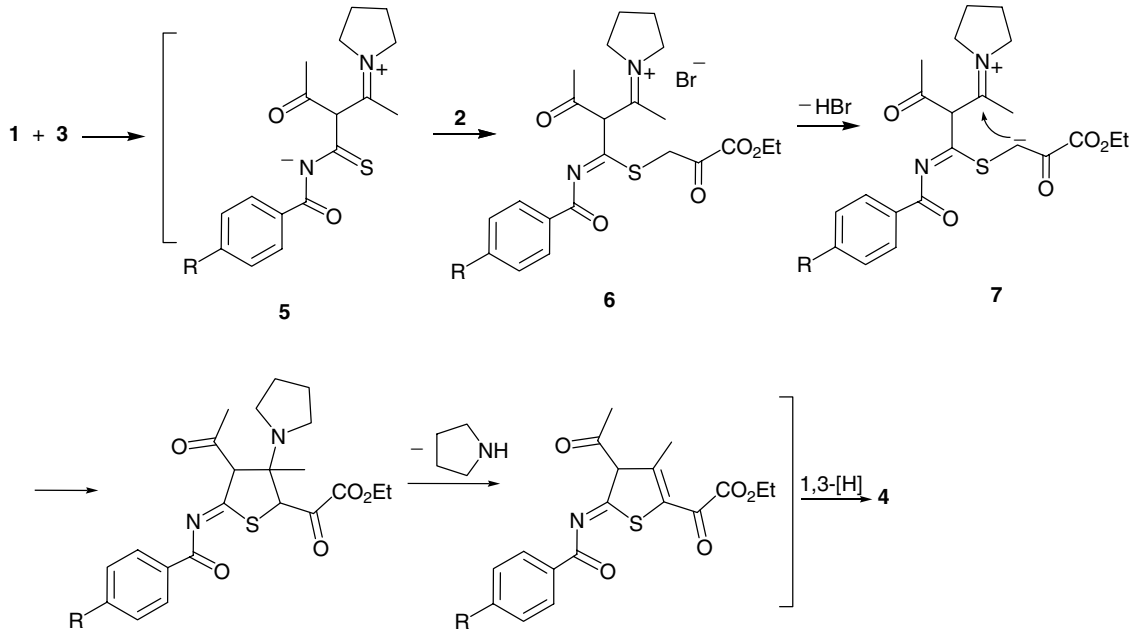
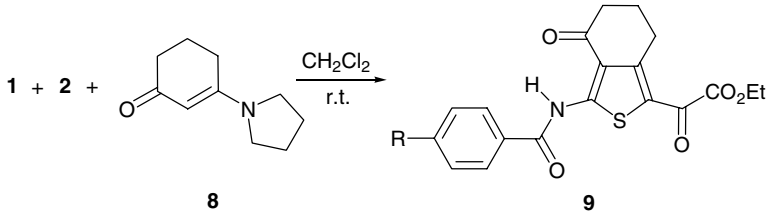


Scheme 2. Proposed mechanism for the formation of compounds **4**.



1, 9	R	Yield (%) of 9
a	H	80
b	Br	75

Scheme 3. Synthesis of compounds **9**.

reaction of benzoyl isothiocyanates **1** with ethyl bromopyruvate (**2**) in the presence of enaminone **3** led to ethyl 2-(4-acetyl-5-benzoylamino-3-methyl-2-thienyl)-2-oxoacetates (**4**) in good to excellent yields[11] (Scheme 1).

The structures of compounds **4a–e** were assigned by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited characteristic signals for the ethoxy (δ 1.43 and 4.42), methyl (δ 2.68 and 2.85), and NH (δ 13.47) protons, along with multiplets (δ 7.53–8.02) for the aromatic protons. The carbonyl group resonances in the ^{13}C NMR spectrum of **4a** appeared at 163.0, 164.9, 178.1, and 198.5 ppm. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 359$.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of the 1:1 adduct **5** from the enaminone and benzoyl isothiocyanate, which is subsequently attacked by ethyl bromopyruvate to produce **6**. Intermediate **6** undergoes HBr elimination, cyclization, and a 1,3-[*H*] shift to generate **4**.

Under similar conditions, the reaction of benzoyl isothiocyanate **1** with ethyl bromopyruvate **2** in the presence of enaminone **8** led to ethyl 2-[3-(benzoylamino)-4-oxo-4,5,6,7-tetrahydro-2-benzothiophen-1-yl]-2-oxoacetates (**9**) in good yields[12] (Scheme 3).

In conclusion, we have reported a novel transformation involving benzoyl isothiocyanates and ethyl bromopyruvate in the presence of enaminones, which affords tetrasubstituted thiophenes. The advantage of the present procedure is that the reaction is performed under neutral conditions. The simplicity of the present procedure makes it an interesting alternative to other approaches.

Acknowledgment

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References and notes

1. *The Chemistry of Heterocyclic Compounds: Thiophene and its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1991; Vol. 44.
2. Bertram, H. J.; Emberger, R.; Güntert, M.; Sommer, H.; Werkhoff, P. In *Recent Developments in Flavor and Fragrance Chemistry*; Hopp, R., Mori, K., Eds.; VCH: Weinheim, 1993.
3. Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723–740.
4. Roncali, J. *Chem. Rev.* **1992**, *92*, 711.
5. Nalwa, H. S. *Adv. Mater.* **1993**, *5*, 341.
6. Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghazanfarpour-Darjani, M. *Monatsh. Chem.* **2007**, *138*, 677.
7. Yavari, I.; Ghazanfarpour-Darjani, M.; Sabbaghan, M.; Hossaini, Z. *Tetrahedron Lett.* **2007**, *48*, 3749.
8. Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Ghazanfarpour-Darjani, M. *Tetrahedron* **2007**, *63*, 9423.
9. Yavari, I.; Djahaniani, H. *Tetrahedron Lett.* **2006**, *47*, 2953.
10. Yavari, I.; Moradi, L. *Helv. Chim. Acta* **2006**, *89*, 1942.
11. *General procedure for the preparation of compounds* **4**: To a stirred solution of benzoyl isothiocyanate (2 mmol) and ethyl bromopyruvate (0.39 g, 2 mmol) in CH_2Cl_2 (15 mL) was added enaminone **3** (2 mmol) at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/EtOAc 10:1) to afford the pure title compounds. Compound **4a**: Pale yellow powder, yield: 0.65 g (90%), mp 122–124 °C. IR (ν_{max}/cm^{-1}) (KBr): 1729, 1713, 1700, and 1632 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.43 (3H, t, $^3J = 7.2$, Me), 2.68 (3H, s, Me), 2.85 (3H, s, Me), 4.42 (2H, q, $^3J = 7.2$, OCH_2), 7.53 (2H, t, $^3J = 7.2$, 2CH), 7.61 (1H, t, $^3J = 7.2$, CH), 8.02 (2H, d, $^3J = 7.3$, 2CH), 13.47 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 17.4 (Me), 32.2 (Me), 62.8 (OCH_2), 122.3 (C), 124.2 (C), 127.8 (2CH), 129.1 (2CH), 131.5 (C), 133.3 (C), 148.1 (C), 157.6 (C), 163.0 (C=O), 164.9 (C=O), 178.1 (C=O), 198.5 (C=O). MS (EI, 70 eV) *m*/*z*: 359 (M$^+$, 15); 239 (56); 105 (100); 120 (66); 45 (64). Anal. Calcd for $C_{18}H_{17}NO_5S$ (359.39): C, 60.16; H, 4.77; N, 3.99. Found: C, 60.10; H, 4.70; N, 4.01. Compound **4b**: Yellow crystals, yield: 0.69 g (85%), mp 155–157 °C. IR (ν_{max}/cm^{-1}) (KBr): 1722, 1715, 1710, and 1630 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.43 (3H, t, $^3J = 7.2$, Me), 2.70 (3H, s, Me), 2.89 (3H, s, Me), 4.44 (2H, q, $^3J = 7.2$, OCH_2), 8.20 (2 H, d, $^3J = 7.2$, 2CH), 8.39 (2H, d, $^3J = 7.3$, 2CH), 13.69 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 17.4 (Me), 32.3 (Me), 62.9 (OCH_2), 122.8 (C), 124.3 (2CH), 124.6 (C), 128.9 (2CH), 136.8 (C), 148.1 (C), 150.6 (C), 156.6 (C), 162.8 (C=O), 162.9 (C=O), 177.8 (C=O), 198.9 (C=O). MS (EI, 70 eV) *m*/*z*: 404 (M$^+$, 5); 331 (25); 150 (100); 120 (30); 104 (100); 76 (65); 45 (46). Anal. Calcd for $C_{18}H_{16}N_2O_7S$ (404.39): C, 53.46; H, 3.99; N, 6.93. Found: C, 53.40; H, 3.90; N, 6.90. Compound **4c**: Yellow powder, yield: 0.63 g (85%), mp 130–132 °C. IR (ν_{max}/cm^{-1}) (KBr): 1739, 1714, 1710, and 1620 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.41 (3H, t, $^3J = 7.2$, Me), 2.40 (3H, s, Me), 2.64 (3H, s, Me), 2.82 (3H, s, Me), 4.40 (2H, q, $^3J = 7.2$, OCH_2), 7.29 (2H, d, $^3J = 7.2$, 2CH), 7.86 (2H, d, $^3J = 7.3$, 2CH), 13.38 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 17.4 (Me), 21.6 (Me), 32.2 (Me), 62.7 (OCH_2), 122.2 (C), 124.0 (C), 127.8 (2CH), 128.6 (C), 129.8 (2CH), 144.2 (C), 148.2 (C), 157.6 (C), 163.0 (C=O), 164.7 (C=O), 178.0 (C=O), 198.4 (C=O). MS (EI, 70 eV) *m*/*z*: 373 (M$^+$, 15); 239 (58); 119 (100); 134 (66); 45 (84). Anal. Calcd for $C_{19}H_{19}NO_5S$ (373.42): C, 61.11; H, 5.13; N, 3.75. Found: C, 61.10; H, 5.10; N, 3.70. Compound **4d**: White powder, yield: 0.70 g (80%), mp 152–154 °C. IR (ν_{max}/cm^{-1}) (KBr): 1736, 1715, 1714, and 1615 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.41 (3H, t, $^3J = 7.2$, Me), 2.65 (3H, s, Me), 2.84 (3H, s, Me), 4.41 (2H, q, $^3J = 7.2$, OCH_2), 7.66 (2H, d, $^3J = 7.2$, 2CH), 7.84 (2H, d, $^3J = 7.3$, 2CH), 13.47 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 17.4 (Me), 32.2 (Me), 62.9 (OCH_2), 122.4 (C), 124.2 (C), 128.5 (C), 129.2 (2CH), 130.2 (C), 132.5 (2CH), 148.2 (C), 157.2 (C), 162.9 (C=O), 163.9 (C=O), 177.9 (C=O), 198.4 (C=O). MS (EI, 70 eV) *m*/*z*: 438 (M$^+$, 10); 184 (100); 199 (76); 239 (44), 104 (85); 45 (36). Anal. Calcd for $C_{18}H_{16}BrNO_5S$ (438.29): C, 49.33; H, 3.68; N, 3.20. Found: C, 49.30; H, 3.65; N, 3.20. Compound **4e**: Yellow powder, yield: 0.59 g (75%), mp 165–167 °C. IR (ν_{max}/cm^{-1}) (KBr): 1741, 1714, 1690, and 1631 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.40 (3H, t, $^3J = 7.2$, Me), 2.67 (3H, s, Me), 2.85 (3H, s, Me), 4.40 (2H, q, $^3J = 7.2$, OCH_2), 7.65 (2H, d, $^3J = 7.2$, 2CH), 7.83 (2H, d, $^3J = 7.3$, 2CH), 13.45 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.9 (Me), 17.2 (Me),32.1 (Me), 62.7 (OCH_2), 122.2 (C), 123.9 (C), 128.2 (C), 128.9 (2CH), 130.5 (C), 132.6 (2CH), 148.1 (C), 157.5 (C), 162.5 (C=O), 163.8 (C=O), 177.8 (C=O), 198.2 (C=O). MS (EI, 70 eV) *m*/*z*: 393 (M$^+$, 10); 139 (100); 154 (56); 239 (44), 104 (38); 45 (64). Anal. Calcd for $C_{18}H_{16}ClNO_5S$ (393.84): C, 54.90; H, 4.09; N, 3.56. Found: C, 54.90; H, 4.10; N, 3.50.
12. Compound **9a**: Yellow powder, yield: 0.59 g (80%), mp 182–184 °C. IR (ν_{max}/cm^{-1}) (KBr): 1750, 1719, 1710, and 1665 cm^{-1}. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.34 (3H, t, $^3J = 7.2$, Me), 2.52 (2H, m, CH_2), 2.81 (2H, t, $^3J = 7.2$, CH_2), 3.28 (2H, t, $^3J = 7.2$, CH_2), 4.28 (2H, q, $^3J = 7.2$, OCH_2), 7.49 (1H, t, $^3J = 7.2$, CH), 7.68 (2H, t, $^3J = 7.3$, 2CH), 7.85 (2H, d, $^3J = 7.3$, 2CH), 13.45 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.5 (Me), 23.6 (CH_2), 28.5 (CH_2), 37.5 (CH_2), 61.8 (OCH_2), 126.5 (2CH), 128.9 (2CH), 130.8 (CH), 133.3 (C), 135.6 (C), 139.5 (C), 142.7 (C), 152.6 (C), 163.8 (C=O), 165.4 (C=O), 184.5 (C=O), 198.4 (C=O). MS (EI, 70 eV) *m*/*z*: 371 (M$^+$, 10), 266 (88), 221 (45), 105 (100), 45 (52). Anal. Calcd for $C_{19}H_{17}NO_5S$ (371.4): C, 61.44; H, 4.61; N, 3.77. Found: C, 61.40; H, 4.60; N, 3.75. Compound **9b**: Yellow powder, yield: 0.68 g (75%), mp 190–192 °C. IR (ν_{max}/cm^{-1}) (KBr): 1752, 1725, 1710, and 1668 cm^{-1}.^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.22 (3H, t, $^3J = 7.2$, Me), 2.57 (2H, m, CH_2), 2.79 (2H, t, $^3J = 7.2$, CH_2), 3.36 (2H, t, $^3J = 7.2$, CH_2), 4.22 (2H, q, $^3J = 7.2$, OCH_2), 7.64 (2H, d, $^3J = 7.2$, 2CH), 7.83 (2H, d, $^3J = 7.3$, 2CH), 13.58 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.6 (Me), 23.7 (CH_2), 28.9 (CH_2), 38.1 (CH_2), 62.9 (OCH_2), 126.8 (C), 129.4 (2CH), 130.7 (2CH), 131.6 (C), 137.6 (C), 138.2 (C), 143.9 (C), 155.8 (C), 162.3 (C=O), 164.9 (C=O), 185.8 (C=O), 199.6 (C=O). MS (EI, 70 eV) *m*/*z*: 450 (M$^+$, 5); 266 (78), 193 (46), 184 (100), 45 (56). Anal. Calcd for $C_{19}H_{16}BrNO_5S$ (450.30): C, 50.68; H, 3.58; N, 3.11. Found: C, 50.70; H, 3.60; N, 3.10.