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Three-component Process for the Synthesis of Some Thiophene Derivatives Using Water as a Green Media

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Abstract

A convenient and efficient three-component reaction to a one-pot synthesis of thiophene derivatives from activated acetylenic compounds and ethyl 2-chloroacetoacetate in the presence of tetramethyl thiourea in water lead to the formation of thiophenes in good yields.

Keywords: *One-pot reactions, Tetramethyl thiourea, Ethyl 2-chloroaceto acetate.*

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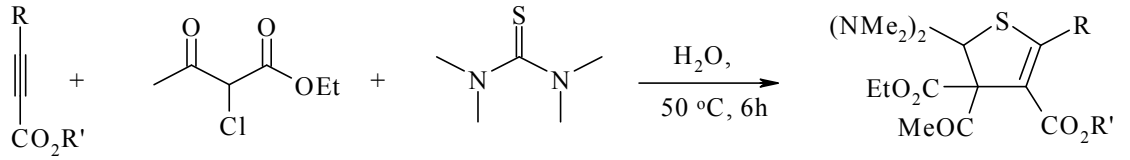
Introduction

The use of water as a green media for organic synthesis has become an important research area. Other than the economical and environmental benefits, water also exhibits unique physical and chemical properties which lead to unique reactivity and selectivity in comparison with organic solvents. Thus, the development of organic reaction in water medium is necessitating in the present days [1-8]. Thiophenes are a very important class of heterocyclic compounds. A variety of molecules containing the thiophene ring display a wide range of biological activity and find application as pharmaceuticals [9], fragrance compounds [10] or pharmacophoric entities [11] and to material sciences [12] due to their unique electronic properties. Moreover, they are also useful synthetic intermediates, such as, in the preparation of new conducting polymers [13] or nonlinear optical materials [14]. Substituted thiophenes can be prepared by proper functionalization of the thiophene ring, usually through α-metalation or α-halogenation [9]. 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 last approach [15]. Hence, we investigate an efficient one-pot three-component reaction between activated acetylenic compounds, ethyl 2-chloroacetoacetate and tetramethyl thiourea in water at 50 ^{o}C that produced thiophene derivatives **4** in good yields (Scheme 1).



1 **2** **3** **4**

1, 4	R'	R	Yield/ % of **4**
a	Me	CO_2Me	90
b	Et	CO_2Et	85
c	Iso-pro	CO_2-Iso-pro	73
d	Me	H	75
e	Et	H	74

Scheme 1. Synthesis of thiophene derivatives.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively, and were obtained for solutions in $CDCl_3$ using TMS as the internal standard or 85% H_3PO_4 as the external standard.

General procedure for preparation of compounds **4**

To a magnetically stirred mixture of activated acetylenic compounds **1** (2 mmol) and ethyl 2-chloroacetoacetate **2** (2 mmol) in water (5mL) was added tetramethyl thiourea **3** at 50 ^{o}C. After completion of the reaction [TLC (AcOEt/hexane 1:5) monitoring, 6h], the solid residue was filtered and washed by cold diethyl ether to afforded pure compounds **4**.

4-ethyl 2,3-dimethyl 4-acetyl-5,5-bis(dimethylamino)-4,5-dihydro-2,3,4-thiophenetricarboxylate **(4a)**

Pale yellow powder, m.p. 142-144°C, yield: 0.72 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1743, 1740, 1738, 1667, 1535, 1487, 1325, 1284 cm^{-1}. Anal. Calcd for $C_{17}H_{26}N_2O_7S$ (402.46): C, 50.73; H, 6.51; N, 6.96. Found: C, 50.84; H, 6.62; N, 7.12%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3 H, t, ^{3}J = 7.4, CH_3), 2.34 (3 H, s, Me), 2.42 (6 H, s, NMe_2), 2.48 (6 H, s, NMe_2), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.24 (2 H, q, ^{3}J = 7.4, CH_2O) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (Me), 27.8 (Me), 41.2 (NMe_2), 42.2 (NMe_2), 51.7 (MeO), 52.0 (MeO), 61.3 (CH_2O), 78.6 (C), 96.7 (C), 133.4 (C), 134.6 (C), 163.2 (C=O), 165.4 (C=O), 167.3 (C=O), 195.4 (C=O) ppm. MS, *m/z* (%): 402 (M^+, 20), 371 (88), 357 (68), 45 (96), 31 (100).

Triethyl 4-acetyl-5,5-bis(dimethylamino)-4,5-dihydro-2,3,4-thiophene tricarboxylate **(4b)**

Yellow powder, m.p. 153-155 ^{o}C, yield: 0.73 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1740, 1735, 1684, 1562, 1447, 1354, 1237 cm^{-1}. Anal. Calcd for $C_{19}H_{30}N_2O_7S$

(430.51): C, 53.01; H, 7.02; N, 6.51. Found: C, 53.16; H, 7.14; N, 6.63%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (3H, t, ^3J = 7.4, CH_3), 1.32 (3H, t, ^3J = 7.3, CH_3), 1.38 (3H, t, ^3J = 7.5, CH_3), 2.34 (3 H, s, Me), 2.43 (6 H, s, NMe_2), 2.48 (6 H, s, NMe_2), 4.12 (2 H, q, ^3J = 7.3, CH_2O), 4.23 (2 H, q, ^3J = 7.4, CH_2O), 4.34 (2 H, q, ^3J = 7.5, CH_2O) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (CH_3), 14.0 (CH_3), 14.2 (CH_3), 28.7 (CH_3), 40.7 (NMe_2), 41.7 (NMe_2), 60.4 (CH_2O), 61.3 (CH_2O), 62.4 (CH_2O), 78.6 (C), 98.3 (C), 132.8 (C), 133.8 (C), 162.7 (C=O), 163.4 (C=O), 167.3 (C=O), 195.6 (C=O) ppm. MS, *m/z* (%): 430 (M^+, 20), 385 (58), 45 (100).

3-ethyl 2,3-diisopropyl 4-acetyl-5,5-bis(dimethylamino)-4,5-dihydro-2,3,4-thiophenetricarboxylate **(4c)**

White powder, m.p. 173-175 ^{o}C, yield: 0.67 g (73%). IR (KBr) (ν_{max}/cm^{-1}): 1744, 1742, 1738, 1686, 1527, 1458, 1364 cm^{-1}. Anal. Calcd for $C_{21}H_{34}N_2O_7S$ (458.57): C, 55.00; H, 7.47; N, 6.11. Found: C, 55.16; H, 7.58; N, 6.24%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, t, ^3J = 7.4, CH_3), 1.28 (6H, d, ^3J = 7.5, 2 CH_3), 1.32 (6 H, d, ^3J = 7.5, 2 CH_3), 2.35 (3 H, s, Me), 2.47 (6 H, s, NMe_2), 2.52 (6 H, s, NMe_2), 4.17 (2 H, q, ^3J = 7.5, CH_2O), 4.58 (1 H, m, CH), 5.04 (1 H, m, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.6 (CH_3), 21.4 (2 CH_3), 22.3 (2 CH_3), 29.2 (CH_3), 41.2 (NMe_2), 42.4 (NMe_2), 61.7 (CH_2O), 72.3 (CH), 73.0 (CH), 79.2 (C), 99.4 (C), 133.2 (C), 134.6 (C), 161.7 (C=O), 162.6 (C=O), 166.2 (C=O), 198.2 (C=O) ppm.

3-ethyl 4-methyl 3-acetyl-2,2-bis(dimethylamino)-2,3-dihydro-3,4-thiophenedicarboxylate **(4d)**

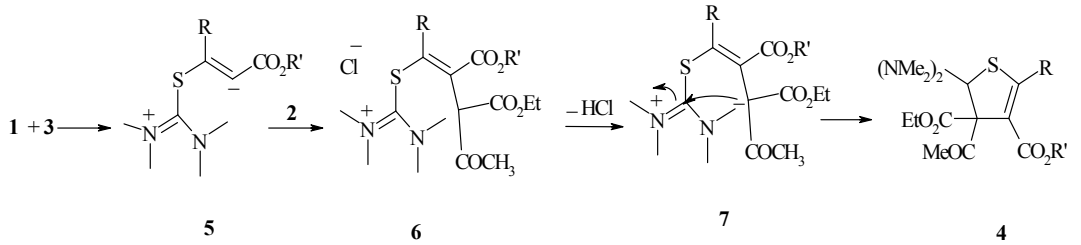
Yellow powder, m.p. 138-140 ^{o}C, yield: 0.52 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1737, 1686, 1564, 1452, 1373, 1243 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O_5S$ (344.42): C, 52.31; H, 7.02; N, 8.13. Found: C, 52.43; H, 7.15; N, 8.25%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (3 H, t, ^3J = 7.4, CH_3), 2.35 (3 H, s, Me), 2.45 (6 H, s, NMe_2), 2.53 (6 H, s, NMe_2), 3.75 (3 H, s, MeO), 4.25 (2 H, q, ^3J = 7.4, CH_2O), 6.87 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.6 (Me), 28.4 (Me), 42.3 (NMe_2), 42.8 (NMe_2), 52.3 (MeO), 62.4 (CH_2O), 79.3 (C), 97.6 (C), 128.3 (C), 132.3 (CH), 163.3 (C=O), 168.4 (C=O), 167.3 (C=O), 199.7 (C=O) ppm. MS, *m/z* (%): 344 (M^+, 20), 313 (78), 31(100).

Diethyl 3-acetyl-2,2-bis(dimethylamino)-2,3-dihydro-3,4-thiophenedicarboxylate **(4e)**

Yellow crystals, m.p. 145-147 ^{o}C, yield: 0.52 g (74%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1735, 1687, 1565, 1436, 1387, 1247 cm^{-1}. Anal. Calcd for $C_{16}H_{26}N_2O_5S$ (358.45): C, 53.61; H, 7.31; N, 7.82. Found: C, 53.73; H, 7.42; N,7.93%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3H, t, ^{3}J = 7.5, CH_3), 1.34 (3H, t, ^{3}J = 7.3, CH_3), 2.35 (3 H, s, Me), 2.40 (6 H, s, NMe_2), 2.45 (6 H, s, NMe_2), 4.16 (2 H, q, ^{3}J = 7.5, CH_2O), 4.25 (2 H, q, ^{3}J = 7.3, CH_2O), 6.87 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.6 (CH_3), 14.8 (CH_3), 29.3 (CH_3), 41.3 (NMe_2), 42.6 (NMe_2), 61.3 (CH_2O), 62.4 (CH_2O), 79.2 (C), 99.6 (C), 128.7 (C), 132.4 (CH), 163.8 (C=O), 164.6 (C=O), 198.3 (C=O) ppm.

Result and discussion

The three-component reaction between activated acetylenic compounds **1**, isothiocyanates **2** and ethyl 2-chloroacetoacetate **3** in the presence of tetramethyl thiourea **3** at 50 ^{o}C in water as the solvent produced thiophene derivatives **4** in good yields (Scheme 1). The structures of compounds **4a–e** were deduced from the ^{1}H NMR, ^{13}C NMR, Mass and IR spectra which are in agreement with the proposed structures. For example, the ^{1}H NMR spectrum of **4a** displayed five singlets for methyl protons at 2.34 ppm, two NMe_2 group protons at 2.42 and 2.48 ppm, and methoxy protons at 3.78 and 3.85 ppm. The carbonyl groups resonances in the ^{13}C NMR spectra of **4a** are appeared at 163.2 (C=O), 165.4 (C=O), 167.3 (C=O) and 195.4 (C=O) ppm. Also the mass spectra of **4a** displayed the molecular ion peak in the appropriate m/z values. A proposed mechanism for the formation of compound **4** is shown in Scheme 2. Apparently, the zwitterionic intermediate **5** formed from the reaction of activated acetylenic compound **1** and tetramethyl thiourea **3**. After adding ethyl 2-chloroacetoacetate **2** produced intermediate **6** that eliminate HCl and generate intermediate **7.** Finally, intramolecular cyclization of **7** produces compound **4**.



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

Conclusion

In conclusion, I investigate the reaction of activated acetylenic compounds with ethyl 2-chloroacetoacetate in the presence of tetramethyl thiourea that produce some thiophene derivatives at 50 ^{o}C in water as the solvent.

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