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ScienceDirect
Tetrahedron 63 (2007) 2724–2728
Tetrahedron

A facile and convenient one-pot synthesis of polysubstituted thiophenes from 1,3-dicarbonyl compounds in water

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Received 30 October 2006; revised 26 December 2006; accepted 31 December 2006
Available online 4 January 2007

Abstract—A facile and convenient one-pot synthesis of polysubstituted thiophenes **2** and polysubstituted thieno[2,3-*b*]thiophenes **3** from 1,3-dicarbonyl compounds **1** has been achieved in high yields catalyzed by tetrabutylammonium bromide (TBAB) in the presence of K_2CO_3 in water. TBAB in the aqueous phase can be recycled after the separation of organic products.

1. Introduction

Thiophene derivatives represent a class of important and well-studied heterocycles.[1] The interest in this kind of heterocycles has spread from early dye chemistry[2] to modern drug design,[3] biodiagnostics,[4] electronic and optoelectronic devices,[5] conductivity-based sensors,[6] and self-assembled superstructures.[7] The general synthetic approaches to such kind of compounds either involve the functionalization at the positions α and β to the sulfur atom of the pre-constructed thiophene nucleus,[8] or the construction of thiophene ring from appropriately substituted open chain precursors.[9] The latter becomes much attractive for its general applicability to achieve more complicated substitution patterns.[10] Gewald and co-workers developed the synthesis of 2-aminothiophenes from the multicomponent condensation of ketones or aldehydes, cyanoacetate and elemental sulfur.[11] Later on, there are several reviews and papers reported on the variations and improvements on the originally published Gewald synthesis of polysubstituted thiophenes.[12] Some of the recent novel synthetic methods involve the cyclization of α-oxo ketene-(*S,S*)-acetals,[13] obtained from active methylene compounds and carbon disulfide, in basic media.[14] However, Gewald method requires long reaction time and suffers from harsh conditions such as strong base, high cost of catalyst and difficult purification, whereas the cyclization of α-oxo ketene-(*S,S*)-acetals is a two-step and low yielding reaction. Additionally, the related reactions are carried out in organic media.[11–14]

Very recently, we achieved a novel chemoselective thioacetalization using α-oxo ketene-(*S,S*)-acetals as thiol equivalents in water,[15] and developed a clean, facile and practical synthesis of α-oxo ketene-(*S,S*)-acetals and their aldol condensation with aldehydes in water.[16,17] Indeed, the use of water as a solvent in organic chemistry was rediscovered in 1980s in Breslow's work, which showed that hydrophobic effect could strongly enhance the rates of some organic reactions.[18] Obviously, water is an easily available, cheap, safe and environmentally benign solvent. Extensive research has revealed that a variety of organic reactions including aldol reaction, allylation reaction, Diels–Alder reaction, Michael reaction, Mannich-type reaction and even dehydration reaction can be realized in water, especially in the presence of various catalysts such as inverse phase-transfer catalysts and surfactant-type Lewis or Brønsted acids.[19–21] The importance of thiophenes and our continuing interest in organic reactions in water have inspired us to exploit the one-pot synthesis of thiophenes directly from 1,3-dicarbonyl compounds in aqueous media. We wish to report our findings herein.

2. Results and discussion

During the course of our studies on the synthesis and applications of α-oxo ketene-(*S,S*)-acetals,[22,23] we found that α-oxo ketene-(*S,S*)-acetals could be cleanly prepared from 1,3-dicarbonyl compounds catalyzed by tetrabutylammonium bromide (TBAB) in the presence of K_2CO_3 in water at room temperature.[16] Thus, we started the investigation with K_2CO_3 as a base and TBAB as a catalyst.

The initial study was performed on the reaction of 3-oxo-*N*-*o*-tolylbutanamide **1a** via a very simple procedure described as follows: to a suspension of **1a** (2.0 mmol), K_2CO_3

Keywords: 1,3-Dicarbonyl compound; Cyclization; α-Oxo ketene-(*S,S*)-acetals; Tetrabutylammonium bromide; Thiophenes; Water.
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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.090

(12.0 mmol) and TBAB (1.0 mmol) in water (5 mL) at room temperature was added CS_2 (2.2 mmol) under stirring. After the reaction mixture was stirred at room temperature for 1.0 h, ethyl 2-bromoacetate (4.0 mmol) was added. The mixture was warmed up to 60 °C and stirred for 1.2 h as indicated by TLC for completion of reaction. A white solid (80%) was obtained after workup and purification, and characterized as ethyl 5-(2-ethoxy-2-oxoethylthio)-3-methyl-4-(*o*-tolylcarbamoyl)thiophene-2-carboxylate (**2a**), a substituted thiophene, based on its spectral and analytical data (Table 1, entry 1).

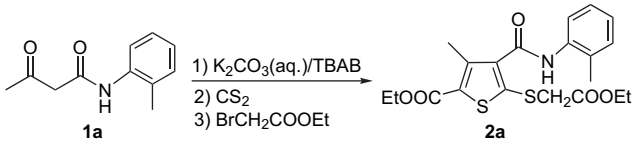
To optimize the reaction conditions, a range of reactions were carried out, in which the feed molar ratio of TBAB to **1a** was changed from 50/100 to 5/100, and the molar ratio of other reactants was kept constant. Some of the results are summarized in Table 1. There was nearly no change of the yields and rates of the reactions when the amount of TBAB was decreased from stoichiometric to catalytic amount (Table 1, entries 1–3). Very low feed molar ratio of TBAB/**1a**, 5 mol % for example, made the reaction a little sluggish with lower conversion (Table 1, entry 4). We then examined the effect of the feed amount of base on the reaction. The result revealed that 4.0 equiv of K_2CO_3 was effective for the cyclization reaction (Table 1, entry 5). It is worth noting that the reaction without TBAB can proceed to afford **2a** in 77% yield with prolonged reaction time (Table 1, entry 6). However, it did not proceed at room temperature (Table 1, entry 7). Therefore, it is assumed that the reaction takes place on the interface between inorganic phase and melting-like organic phase at high temperature without TBAB as a phase-transfer catalyst. When performed in *N,N*-dimethylformamide instead of water at 60 °C, the reaction could be completed in 1.0 h to produce **2a** in 68% yield. In this case, the slightly lower yield is attributed to the formation of byproducts observed by TLC. All the experiments indicate that the catalyst TBAB plays a key role in the reaction in water.

Bearing in mind the fact that the resulting aqueous filtrate still contained the catalyst TBAB after separation of the products, we investigated the possibility of recycling the catalyst. The reaction of **1a** with carbon disulfide (1.1 equiv), K_2CO_3 (4.0 equiv) and ethyl 2-bromoacetate (2.0 equiv) was carried out using the aqueous filtrate containing TBAB as reaction medium following the similar fashion as described in Table 1, entry 3. After the reaction was completed as indicated by TLC, workup and column chromatography of the resulting mixture furnished **2a** in 82% yield (Table 1, entry 8). Further study revealed that the recovered TBAB could attain very high catalytic activity even when it is used for the third time (Table 1, entry 9). The results demonstrate that the catalyst can be recycled, for several times, by reuse of the aqueous phase after the separation of organic products.

With optimized reaction condition in hand, we examined the scope of the substrates. Under the identical conditions as for **2a** (Table 1, entry 5), the reactions of selected β-oxo amides **1** with carbon disulfide and ethyl 2-bromoacetate in the presence of K_2CO_3 in water were carried out. Some of the results are summarized in Table 2. The reactions of all the selected β-oxo amides **1** can proceed smoothly to afford the corresponding polysubstituted thiophenes **2b–e** in high yields (Table 2, entries 2–5). In the same fashion, β-keto ester **1f** could be converted into polysubstituted thiophene **2f** in 75% yield (Table 2, entry 6). When β-diketones **1g** and **1h** were subjected to the similar conditions but with 6.0 equiv of K_2CO_3, the thieno[2,3-*b*]thiophenes **3g** and **3h** were obtained in very high yields (Table 2, entries 7 and 8).

Based on the above mentioned results together with our previous study,[16] a mechanism for the reaction of **1** with carbon disulfide and ethyl 2-bromoacetate is proposed as depicted in Scheme 1. Deprotonation of 1,3-dicarbonyl compound **1** followed by nucleophilic attack of enolate **4** on CS_2 near the interface should afford thiolate salt **5**. The double S-alkylation with ethyl 2-bromoacetate would afford α-oxo ketene-(*S,S*)-acetal **6**. The activated methylene group of thioalkyl chain in **6** should undergo deprotonation and subsequent intramolecular cyclization reaction, leading to the final product,

Table 1. Preparation of **2a** from 3-oxo-*N*-*o*-tolylbutanamide **1a** in water

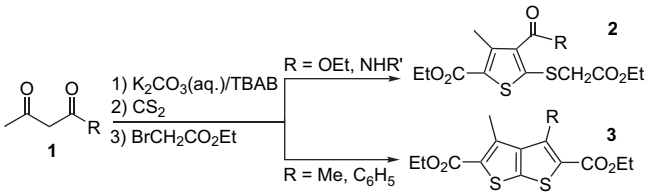


1a **2a**

Entry	TBAB (equiv)	K_2CO_3 (equiv)	*T* (°C)	Time[a] (h)	Yield **2a**[b] (%)
1	0.50	6.0	60	1.2	80
2	0.20	6.0	60	1.0	81
3	0.10	6.0	60	1.5	85
4	0.05	6.0	60	2.0	76
5	0.10	4.0	60	1.5	83
6	0	4.0	60	3.5	77
7	0	4.0	20	10	0
8[c]	Second use	4.0	60	1.0	82
9[d]	Third use	4.0	60	1.5	78

[a] Time recorded after the addition of ethyl 2-bromoacetate.
[b] Isolated yields.
[c] Aqueous filtrate from entry 5.
[d] Aqueous filtrate from entry 8.

Table 2. Preparation of polysubstituted thiophenes **2** and **3** from 1,3-dicarbonyl compounds **1** in water

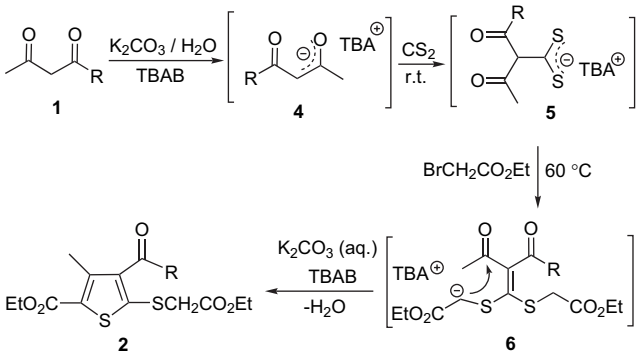


1 **2** **3**

Entry	Substrate **1**	R	Product	Time (h)	Yield[a] (%)
1	**1a**	2-MePhNH	**2a**	1.5	85
2	**1b**	PhNH	**2b**	2.0	80
3	**1c**	NH_2	**2c**	2.0	83
4	**1d**	2-MeOPhNH	**2d**	2.5	76
5	**1e**	4-ClPhNH	**2e**	3.0	82
6[b]	**1f**	OEt	**2f**	2.2	75
7[c]	**1g**	Me	**3g**	2.0	91
8[c]	**1h**	Ph	**3h**	2.1	90

[a] Isolated yields.
[b] At room temperature.
[c] In these cases, 6.0 equiv of K_2CO_3 was employed.

polysubstituted thiophene **2**. In the aqueous reaction, TBAB plays a role as a phase-transfer catalyst.



Scheme 1. A proposed mechanism for the preparation of polysubstituted thiophenes **2** from 1,3-dicarbonyl compounds **1** in water.

3. Conclusion

In summary, a facile and convenient one-pot synthesis of polysubstituted thiophenes **2** and polysubstituted thieno[2,3-*b*]thiophenes **3** based on the reactions of 1,3-dicarbonyl compounds **1** with carbon disulfide and ethyl 2-bromoacetate catalyzed by TBAB in the presence of K_2CO_3 in water has been developed. The simple procedure, mild conditions, high yields and especially environmental friendliness make this protocol much attractive for academic research and practical applications.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on an FTIR spectrophotometer in the range of 400–4000 cm^{-1}.

4.2. Typical procedure

Preparation of **2a** is described as an example: to a solution of 3-oxo-*N*-*o*-tolylbutanamide **1a** (2 mmol), K_2CO_3 (8.0 mmol) and TBAB (0.2 mmol) in water (5 mL) at room temperature was added CS_2 (2.2 mmol). After the reaction mixture was stirred at room temperature for 1.0 h, ethyl 2-bromoacetate (4.0 mmol) was added. The mixture was warmed up to 60 °C and stirred for about 1.5 h as indicated by TLC for a complete conversion. Then the resulting mixture was cooled down to room temperature and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with saturated aqueous NaCl (20 mL) and water (2×20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a white solid. Purification was carried out by flash silica gel chromatography using petroleum ether/ethyl acetate (15:1, v/v) as eluent to give product **2a** (0.72 g, 85%).

Compounds **3g** and **3h** are known, and their ^{1}H NMR and IR spectra, and elemental analysis data are in good agreement with those in literature [Ref. 13i]. Selected data for compounds **2a–f** are as follows.

4.2.1. Ethyl 5-(2-ethoxy-2-oxoethylthio)-3-methyl-4-(*o*-tolylcarbamoyl)thiophene-2-carboxylate (2a). White solid, mp 125–126 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.22 (t, J=6.0 Hz, 3H), 1.37 (t, J=6.0 Hz, 3H), 2.38 (s, 3H), 2.64 (s, 3H), 3.79 (s, 2H), 4.14 (q, J=7.0 Hz, 2H), 4.33 (q, J=7.0 Hz, 2H), 7.14 (t, J=7.5 Hz, 1H), 7.23–7.26 (m, 2H), 7.83 (d, J=7.5 Hz, 1H), 8.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=14.2, 14.5, 15.1, 18.6, 40.1, 61.5, 62.7, 124.5, 126.1, 126.8, 130.4, 131.0, 131.3, 135.7, 137.5, 143.5, 145.9, 161.8, 162.5, 169.6; IR (KBr, neat): ν=3234, 1708, 1643, 1533, 1370, 1296, 672 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_5S_2$: C 56.99, H 5.50, N 3.32; found: C 56.86, H 5.58, N 3.37.

4.2.2. Ethyl 5-(2-ethoxy-2-oxoethylthio)-3-methyl-4-(phenylcarbamoyl)thiophene-2-carboxylate (2b). White solid, mp 88–89 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.26 (t, J=7.0 Hz, 3H), 1.35 (t, J=7.0 Hz, 3H), 2.62 (s, 3H), 3.82 (s, 2H), 4.21 (q, J=7.0 Hz, 2H), 4.33 (q, J=7.0 Hz, 2H), 7.14 (t, J=7.5 Hz, 1H), 7.36 (t, J=7.5 Hz, 2H), 7.75 (d, J=8.0 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=14.3, 14.5, 15.0, 40.6, 61.5, 63.0, 120.1, 124.6, 129.2, 130.7, 137.3, 138.6, 143.9, 146.1, 161.8, 162.1, 170.4; IR (KBr, neat): ν=3338, 1736, 1711, 1641, 1596, 1443, 1305, 1247, 689 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C 56.00, H 5.19, N 3.44; found: C 56.25, H 5.22, N 3.53.

4.2.3. Ethyl 4-carbamoyl-5-(2-ethoxy-2-oxoethylthio)-3-methylthiophene-2-carboxylate (2c). White solid, mp 123–124 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.25 (t, J=7.5 Hz, 3H), 1.36 (t, J=7.5 Hz, 3H), 2.61 (s, 3H), 3.77 (s, 2H), 4.17 (q, J=7.0 Hz, 2H), 4.32 (q, J=7.5 Hz, 2H), 5.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=14.3, 14.5, 15.0, 40.2, 61.5, 62.7, 130.1, 138.5, 141.9, 145.7, 161.8, 166.2, 169.6; IR (KBr, neat): ν=3363, 1747, 1711, 1645, 1613, 1530, 1374, 1259, 689 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_5S_2$: C 47.11, H 5.17, N 4.23; found: C 47.25, H 5.06, N 4.15.

4.2.4. Ethyl 5-(2-ethoxy-2-oxoethylthio)-4-[(2-methoxyphenyl)carbamoyl]-3-methylthiophene-2-carboxylate (2d). White solid, mp 138–140 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.24 (t, J=7.0 Hz, 3H), 1.37 (t, J=7.0 Hz, 3H), 2.64 (s, 3H), 3.73 (s, 2H), 3.88 (s, 3H), 4.17 (q, J=7.0 Hz, 2H), 4.33 (q, J=7.0 Hz, 2H), 6.91 (d, J=8.0 Hz, 1H), 7.02 (d, J=7.5 Hz, 1H), 7.08–7.10 (m, 1H), 8.46–8.48 (m, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=14.3, 14.6, 15.1, 39.4, 56.0, 61.4, 62.3, 110.4, 120.5, 121.3, 124.7, 127.5, 129.2, 139.9, 141.9, 145.3, 148.6, 161.8, 162.0, 168.6; IR (KBr, neat): ν=3439, 1706, 1642, 1560, 1460, 1366, 1219, 757 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_6S_2$: C 54.90, H 5.30, N 3.20; found: C 54.84, H 5.43, N 3.15.

4.2.5. Ethyl 4-[(4-chlorophenyl)carbamoyl]-5-(2-ethoxy-2-oxoethylthio)-3-methylthiophene-2-carboxylate (2e). White solid, mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz):

δ=1.28 (t, J=7.0 Hz, 3H), 1.37 (t, J=7.0 Hz, 3H), 2.62 (s, 3H), 3.84 (s, 2H), 4.22 (q, J=7.0 Hz, 2H), 4.33 (q, J=7.0 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H), 7.33 (d, J=8.5 Hz, 2H), 9.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=14.3, 14.6, 15.0, 40.8, 61.6, 63.2, 121.3, 129.2, 129.4, 131.0, 137.2, 137.3, 143.7, 146.2, 161.7, 162.0, 170.7; IR (KBr, neat): ν=3281, 1738, 1713, 1633, 1594, 1526, 1308, 1246, 691 cm^{-1}. Anal. Calcd for $C_{19}H_{20}ClNO_5S_2$: C 51.64, H 4.56, N 3.17; found: C 51.56, H 4.73, N 3.23.

4.2.6. Diethyl 5-(2-ethoxy-2-oxoethylthio)-3-methylthiophene-2,4-dicarboxylate (2f). White solid, mp 141–143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.30 (t, J=7.0 Hz, 3H), 1.36 (t, J=7.0 Hz, 3H), 1.40 (t, J=7.0 Hz, 3H), 2.73 (s, 3H), 3.83 (s, 2H), 4.24 (q, J=6.5 Hz, 2H), 4.31 (q, J=7.0 Hz, 2H), 4.37 (q, J=7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=14.3, 14.5, 14.6, 15.7, 37.6, 61.3, 61.4, 62.4, 125.0, 148.3, 153.1, 161.8, 163.7, 168.1, 170.9; IR (KBr, neat): ν=1738, 1529, 1413, 1374, 1226, 760 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_4S_2$: C 58.60, H 4.63; found: C 58.71, H 4.66.

Acknowledgements

Financial support of this research by the National Natural Science Foundation of China (20572013), the Ministry of Education of China (105061 and 10412) and the Department of Science and Technology of Jilin Province (20050392) is greatly acknowledged.

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