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An efficient and facile one-step synthesis of highly substituted thiophenes

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Abstract—An efficient one-step method for the synthesis of fully substituted thiophenes, from thiomorpholides and α-halo ketones, was developed. A mechanism has also been proposed for the course of reaction.
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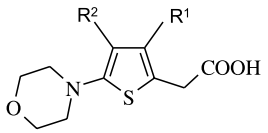
1. Introduction

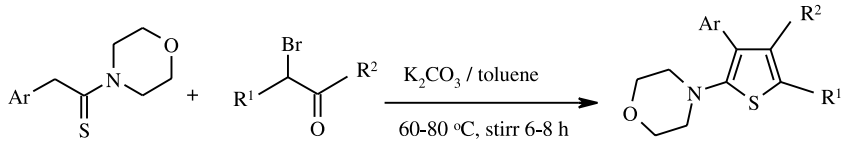
The synthesis of highly substituted thiophenes has attracted a great deal of interest over the years due to their presence in natural products,[1] as new conducting polymers[2] and isosteric replacement for phenyl group in medicinal chemistry.[3] Our interest in this class of compound was based on their use as novel anti-inflammatory and analgesic drugs having general formula (A).



(A)

However, the synthesis of highly substituted thiophenes is restricted by the lack of enough available methods to construct the desired ring bearing functionality in a controlled fashion. The most convenient method for preparing thiophenes with a high degree of functionality is by the Gewald method in which elemental sulfur is reacted with an activated acetonitrile and an aldehyde, ketone or 1,3-dicarbonyl compound in the presence of a base (equimolar quantities of each).[4] A modification of the Gewald method has been reported in which an alkoxyacetone is reacted with ethylcyanoacetate, sulfur, and morpholine producing 5-alkoxy thiophene derivatives in poor yields (19–39%).[5]

Thioamides have been used as useful synthons in the synthesis of heterocycles.[6] Thiazole derivatives are produced by the reaction of primary and/or secondary thioamides with α-haloketones. But, in contrast to the primary and secondary thioamides, the nitrogen atom of



1 a-i **2 a-i** **3 a-i**

55-80 %

a: Ar= phenyl, R^1= H, R^2= 4-bromophenyl
b: Ar= 4-chlorophenyl, R^1= H, R^2= 4-bromophenyl
c: Ar= 4-biphenyl, R^1= H, R^2= 4-bromophenyl
d: Ar= 2-naphthyl, R^1= H, R^2= 4 -bromophenyl
e: Ar= phenyl, R^1= phenyl, R^2= phenyl
f: Ar= 4-chlorophenyl, R_1= phenyl, R_2= phenyl
g: Ar= 2-naphthyl, R^1=phenyl, R^2= phenyl
h: Ar= 4-methoxyphenyl, R^1= phenyl, R^2= phenyl
i : Ar= phenyl, R^1=methyl, R^2=H

Scheme 1.

Keywords: Substituted thiophenes.
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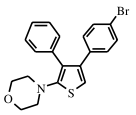
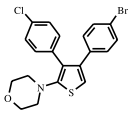
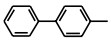
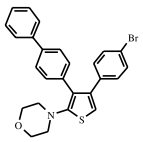
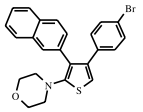
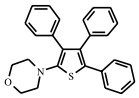
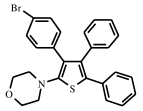
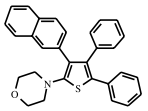
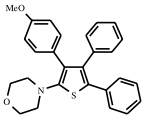
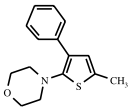
Table 1. Constraction of highly substituted thiophenes using thiomorpholides

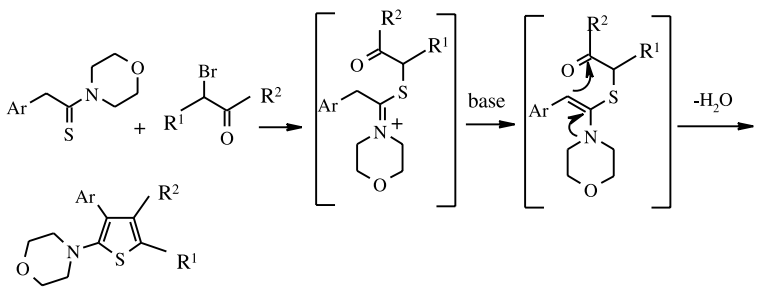
Entry	Ar	R^1	R^2	Product	Reaction time (h)	Temperature	Isolated yield (%)	Mp (°)
1		H			7	70	75	178
2		H			8	80	58	145
3		H			7	75	60	153
4		H			7	85	63	158
5					6.5	75	80	208
6					7	80	55	214
7					8	85	62	243
8					7	75	69	196
9		$-CH_3$	H		6	70	70	105

tertiary thioamides could not take part in heterocyclization. However, the tertiary thioamides having an activated methylene group could react with α-halocarbonyl compounds in the presence of a base leading to the synthesis of 2-aminothiophene derivatives. For example, tertiary thioacetamides in benzene react with α-bromoketones in the presence of DBU yielding 2-amino-3-nitrothiophenes.[7] These reactions are restricted to the tertiary nitro thioacetamides as starting materials. Earlier we have reported a simple microwave-induced method for the preparation of thiomorpholides including aryl thioacetomorpholides.[8] The availability of such thiomorpholides provided a unique opportunity of examining their synthetic utility. We were especially intrigued by the possibility of their use in the synthesis of thiophene containing heterocyclic compounds especially aryl acetic acids. We hoped that such compounds would exhibit interesting analgesic and anti-inflammatory properties. As a preliminary result, recently we have reported a versatile one-pot synthesis of trisubstituted thiophenes from thiomorpholides via S-Claisen rearrangement.[9] In continuation of our research in this area and aiming to find new biologically active heterocyclic compounds, such as 2-aminothiophene derivatives, here we report our results on the reaction of aromatic thioacetomorpholides with α-bromoketones (Scheme 1).

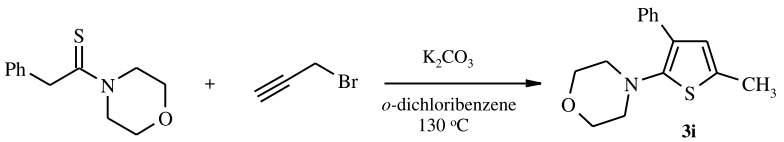
When the thiomorpholide **1** was treated with α-bromoketone **2** in toluene and stirred for 6–8 h at 60–80 °C in the presence of anhydrous K_2CO_3, the highly substituted thiophenes were obtained in good yields. Several examples have been investigated and Table 1 summarizes our results along with the melting points of the compounds.

A mechanism is proposed for the reaction course and shown in Scheme 2. Thiomorpholide undergoes first an *S*-alkylation with α-haloketone, then subsequent treatment with base leading to cyclization and formation of thiophene ring with water elimination.

For confirming the proposed mechanism, one of the model compounds (**3i**) was prepared by a reaction pathway for



Scheme 2.

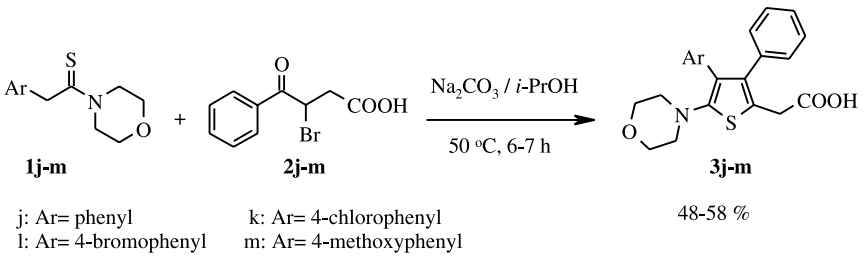


Scheme 3.

which the mechanism was known (Scheme 3).[9,10] Both reactions gave the same compound with fixed substitutes in thiophene ring.

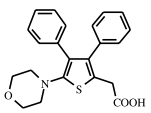
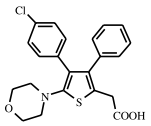
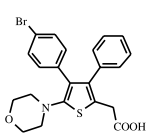
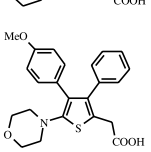
In order to obtain new aryl acetic acid derivatives, it was also found that the thiomorpholides could react with functionalized α-haloketones such as β-bromo-β-benzoyl propionic acid to give fully substituted thiophenes in one step and good chemical yields (Scheme 4). Table 2 resumes our results.

Surprisingly this reaction proceeded more conveniently in a polar solvent such as isopropanol in the presence of anhydrous Na_2CO_3 as base compared to the toluene/K_2CO_3 system. In toluene, the reaction proceeded sluggishly with low yield. These new aryl acetic acid



Scheme 4.

Table 2. One-step synthesis of thiophene acetic acid derivatives

Entry	Ar	Product	Reaction time (h)	Temprature	Isolated yield (%)	Mp (°)
1			6	65	58	172
2			7	65	52	228
3			7	60	50	190
4			6	55	48	185

derivatives have promising analgesic and anti-inflammatory effect.

In conclusion we have developed a new general efficient and simple method for the preparation of highly substituted thiophenes. The generality of the method has been demonstrated by the successful conversion of twelve substrates into tri or tetra substituted morpholino thiophenes in good yields. The base is rather cheap and readily available in all chemistry laboratories. The method was easily extended to the synthesis of thiophenes (see Table 2) bearing an acetic acid unit at position 5. These materials especially 2-morpholino-5-acetic acid substituted thiophenes have the potential to be used as analgesic and anti-inflammatory drugs. The methodology described here seems to be the simplest one for the one-step synthesis of these compounds.

2. Experimental

The compounds gave satisfactory all spectroscopic data. FT IR spectra were recorded as KBr pellets on a Nicolet spectrometer (Magna 550). A Bruker (DRX-500 Avance) NMR was used to record the ^{1}H NMR spectra. All ^{1}H NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were determined on a Büchi B540 apparatus.

2.1. General procedure for the one-pot preparation of compounds (a–i)

To a stirred solution of thiomorpholide (4 mmol) in toluene (5 ml), anhydrous K_2CO_3 (0.552 g, 4 mmol) was added. Then a solution of bromoketone (4 mmol) in toluene (~3 ml) was added dropwise over 10 min. The reaction mixture was heated at 75 °C for about 7 h. The solvent was evaporated to half volume. After cooling a precipitate was appeared. The precipitate was filtered and crystallized from a suitable solvent.

2.2. General procedure for the one-pot preparation of compounds (j–l)

To a stirred solution of thiomorpholide (4 mmol) in 2-propanol (3 ml), β-bromo-β-benzoyl propionic acid (4 mmol) was added. Then reaction mixture was heated to 70 °C for about 1 h. Then, anhydrous Na_2CO_3 (0.212 g, 2 mmol) was added and stirred overnight. The solvent was removed under vacuum and the residue was dissolved in ether (20 ml), washed with 2×5 ml NaOH (5%). The aqueous solution was acidified with HCl (5%) and extracted with diethyl ether. The solvent was evaporated and the solid residue was recrystallized from ethanol.

2.3. Spectroscopic data for compounds (3a–3m)

Compound **3a**: white powder (EtOH), mp: 178 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.33 (d, J=8.2 Hz, 2H), 7.29 (d, J=9.4 Hz, 2H), 7.27 (t, J=5.4 Hz, 1H), 7.23 (t, J=5.4 Hz, 2H), 6.96 (d, J=8.2 Hz, 2H), 6.86 (s, 1H), 3.67 (t, J=4.3 Hz, 4H), 2.87 (t, J=4.3 Hz, 4H); IR (KBr) 3100, 2915, 1645, 1500, 1123, 830 (cm^{-1}).

Compound **3b**: white powder (EtOH), mp: 145 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.36 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.18 (d, J=8.5 Hz, 2H), 6.95 (d, J=8.4 Hz, 2H), 6.87 (s, 1H), 3.68 (t, J=4.6 Hz, 4H), 2.86 (t, J=4.6 Hz, 4H); IR (KBr) 3050, 2953, 1584, 1500, 1123, 830 (cm^{-1}).

Compound **3c**: light yellow crystals (EtOH), mp: 153 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.65 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.0 Hz, 2H), 7.46 (t, J=7.6 Hz, 2H), 7.36 (t, J=8.1 Hz, 1H), 7.34 (d, J=8.1 Hz, 2H2), 7.31 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.2 Hz, 2H), 6.88 (s, 1H), 3.70 (t, J=4.4 Hz, 4H), 2.91 (t, J=4.5 Hz, 4H); IR (KBr) 3060, 2845, 1638, 1500, 1123, 830 (cm^{-1}).

Compound **3d**: yellow powder (EtOH), mp: 157 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.83 (d, J=7.3 Hz, 1H), 7.77, (d, J=8.5 Hz, 1H), 7.72 (d, J=8.5 Hz, 1H), 7.70 (s, 1H), 7.45–7.50 (m, 2H), 7.41 (d, d, J=8.4, 1.5 Hz, 1H), 7.29 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 6.90 (s, 1H), 3,64 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3110, 2950, 1610, 1445, 1123, 700 (cm^{-1}).

Compound **3e**: white powder (EtOH), mp: 208 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.13–7.24 (m, 13H), 6.96 (d, d, J=7.4, 1.8 Hz, 2H), 3.61 (t, J=4.6 Hz, 4H), 2.88 (t, J=4.6 Hz, 4H); IR (KBr) 3090, 2970, 1620, 1500, 1123, 700 (cm^{-1}).

Compound **3f**: yellow powder (EtOH), mp: 214 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.14–7.23 (m, 8H), 7.10 (d, J=8.7 Hz, 2H), 6.97 (d, d, J=7.3, 2 Hz, 2H), 6.79 (d, J=8.7 Hz, 2H), 3.62 (t, J=4.6 Hz, 4H), 2.89 (t, J=4.6 Hz, 4H); IR (KBr) 3120, 2845, 1600, 1507, 1123, 753 (cm^{-1}).

Compound **3g**: light yellow powder (EtOH), mp: 243 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.75 (d, J=7.7 Hz, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.58 (s, 1H), 7.40–7.43 (m, 2H), 7.38 (d, J=8.5 Hz, 1H), 7.13–7.23 (m, 5H), 7.07–7.11 (m, 3H), 6.96 (d, J=6.5 Hz, 2H), 3.64 (t, J=4.4 Hz, 4H), 2.93 (t, J=4.4 Hz, 4H); IR (KBr) 3097, 2807, 1607, 1500, 1253, 836 (cm^{-1}).

Compound **3h**: light yellow crystals (EtOH), mp: 196 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.1–7.18 (m, 8H), 7.06 (d, J=8.6 Hz, 2H), 6.93 9m, 2H), 6.71 (d, J=8.6 Hz, 2H), 3.79 (s, 3H), 3.69 (t, J=4.4 Hz, 4H), 2.94 (t, J=4.5 Hz, 4H); IR (KBr) 3090, 2856, 1597, 1502, 1125, 830 (cm^{-1}).

Compound **3i**: white crystals (EtOH), mp: 105 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.79 (d, J=7.7 Hz, 2H), 7.41 (t, J=7.7 Hz, 2H), 7.27 (t, J=7.6 Hz, 1H), 6.79 (s, 1H), 3.81 (t, J=4.6 Hz, 4H), 2.97 (t, J=4.6 Hz, 4H), 2.48 (s, 3H); IR (KBr) 2964, 2907, 2860, 1643, 1505, 1117, 837 (cm^{-1}).

Compound **3j**: white powder (EtOH), mp: 172 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 9.45 (s, 1H), 7.24 (m, 3H), 7.11–7.19 (m, 5H), 7.05 (m, 2H), 3.72 (s, 2H), 3.67 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3738, 3050, 2923, 1707, 1446, 1253, 759 (cm^{-1}).

Compound **3k**: light yellow powder (EtOH), mp: 228 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 9.52 (s, 1H), 7.26 (m, 3H), 7.15 (d, J=8.5 Hz, 2H), 7.1 (d, J=8.5 Hz, 2H), 7.02–7.04 (m, 2H),

3.71 (s, 2H), 3.68 (t, J=4.4 Hz, 4H), 2.88 (t, J=4.4 Hz, 4H); IR (KBr) 3610, 3110, 2961, 1710, 1446, 1262, 707 (cm^{-1}).

Compound **3l**: light yellow crystals (EtOH), mp: 190 °C, ^1H NMR ($CDCl_3$, 500 MHz) 9.58 (s, 1H), 7.25 (m, 3H), 7.08 (d, J=8.6 Hz, 2H), 7.05 (m, 2H), 6.72 (d, J=8.6 Hz, 2H), 3.79 (s, 2H), 3.68 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3446, 2923, 1692, 1592, 1261, 769 (cm^{-1}).

Compound **3m**: yellow crystals (EtOH), mp:185 °C, ^1H NMR ($CDCl_3$, 500 MHz) 9.50 (s, 1H), 7.22–7.27 (m, 3H), 7.08 (d, J=8.7 Hz, 2H), 7.05 (d, J=7.7 Hz, 2H), 6.72 (d, J=8.7 Hz, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 3.68 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3455, 2937, 1702, 1595, 1257, 748 (cm^{-1}).

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