Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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Firouz Matloubi Moghaddam[a]; Ghasem Rezanejade Bardajee[b]; Maliheh Dolabi[a]
[a] Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, Tehran, Iran [b] Department of Chemistry, Payame Noor University, Qazvin, Iran

Online publication date: 28 September 2010

To cite this Article Moghaddam, Firouz Matloubi , Bardajee, Ghasem Rezanejade and Dolabi, Maliheh(2010) 'An efficient one-pot synthesis of tri-substituted thiophenes via a multicomponent reaction in water', Journal of Sulfur Chemistry, 31: 5, 387 — 393
To link to this Article: DOI: 10.1080/17415993.2010.496129
URL: http://dx.doi.org/10.1080/17415993.2010.496129

Journal of Sulfur Chemistry
Vol. 31, No. 5, October 2010, 387–393

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An efficient one-pot synthesis of tri-substituted thiophenes via a multicomponent reaction in water

Firouz Matloubi Moghaddam[a]*, Ghasem Rezanejade Bardajee[b] and Maliheh Dolabi[a]

[a]*Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, PO Box 11155-9516, Tehran, Iran;* [b]*Department of Chemistry, Payame Noor University, Qazvin Branch, PO Box 878, Qazvin, Iran*

(*Received 25 April 2010; final version received 23 May 2010*)

An efficient one-pot synthesis of functionalized trisubstituted thiophenes via the reaction of 3-morpholino-3-thioxopropanenitrile, cyclohexyl isocyanide and α-haloketones is reported. This method provides a straightforward route to a variety of highly substituted thiophenes not easily accessible by conventional methods.

Keywords: amides; cyclization; multicomponent reaction; nitriles; thiophene

1. Introduction

Highly substituted thiophenes have attracted considerable attention in organic synthesis. They constitute an important class of natural compounds (*1*), show interesting biological activities and are used as a monomer in the synthesis of conducting polymers (*2*), isosteric replacements for phenyl groups in medicinal chemistry (*3*), flavor of food stuff comprising and optical chromophores (*4*). Certain thiophene derivatives occur as plant pigments and other natural products. For example, antihistamine methapyrilene (Thenylene), Biotin and certain other synthetic pharmaceuticals contain the thiophene nucleus. For instance, Banminth and Echino-thiophene are found in natural products (Figure 1) (*5*). Thus, several methods have been introduced for their syntheses which often consist of multistep reaction processes (*6–15*).

Although some methods such as Fisselmane, Gewald, Hinsberg and Paal were introduced and developed for the synthesis of various derivatives of thiophenes (*5*), finding new strategies for the synthesis of these structure motifs is still interesting. Furthermore, new routes for the functionalization of thiophenes for biological purposes are a challenge in thiophene chemistry. As one can see, a one step, straightforward and generally applicable reaction procedure for the synthesis of this functionalized scaffold would find significant utility in organic synthesis.

To the best of our knowledge, there are a few reports for the synthesis of nitrile functionalized thiophenes (*10*, *11*, *13*). Expensive reagents, multistep reaction process and uncommon reagents

*Corresponding author. Email: matloubi@sharif.edu

ISSN 1741-5993 print/ISSN 1741-6000 online

DOI: 10.1080/17415993.2010.496129
http://www.informaworld.com

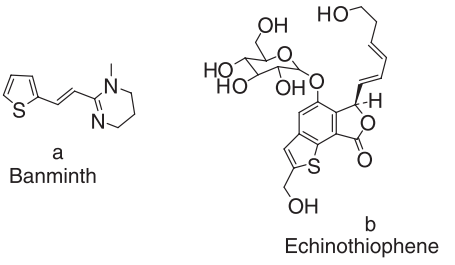


Figure 1. Thiophene containing natural products.

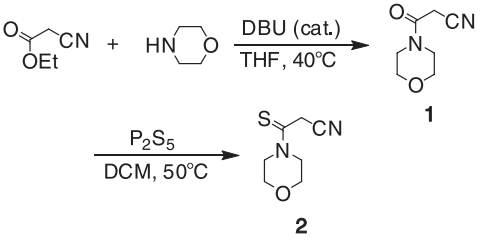
are major disadvantages of the reported methods. As a favorable functional group with the potential for converting to other biological important moieties such as amides, carboxylic acids and amines, the synthesis of nitrile-substituted thiophenes in the course of the reaction will be interesting.

Continuing our foregoing efforts in the construction of highly functionalized thiophene derivatives (*16*, *17*), herein we report a new methodology to construct functionalized thiophene derivatives by applying isocyanides through a one-pot procedure in water.

2. Results and discussion

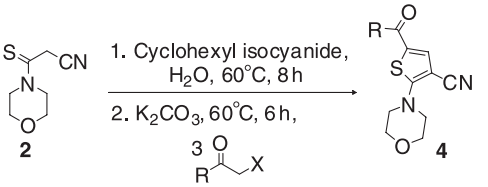
The approach involved the use of 3-morpholino-3-thioxopropanenitrile (cyanothioacetamide) **2** and cyclohexyl isocyanide followed by the addition of an α-haloketone to produce the desired thiophene derivatives in water. This protocol takes advantage of readily accessible starting materials, one-pot construction of thiophene building blocks and simple procedures. In this regard, cyanoacetamide **1** was synthesized by a direct amidation of alkyl cyanoacetates using DBU according to a recently reported procedure with a little modification (Scheme 1) (*18*). The thionation of compound **1** in the presence of P_2S_5 gave the desired product **2** in good yield (Scheme 1) (*8*, *12*).

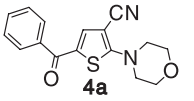
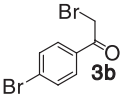
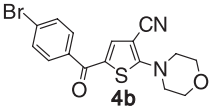
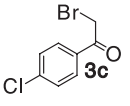
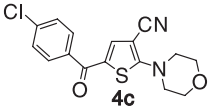
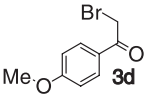
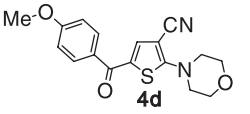
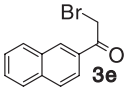
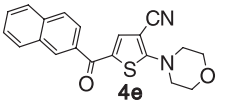
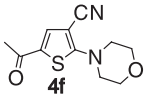
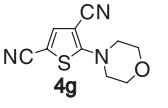
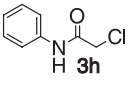
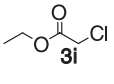
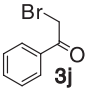
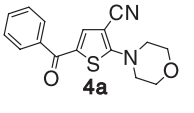
To test the feasibility of this reaction, we initially investigated the reaction of cyanothioacetamide **2**, cyclohexyl isocyanide and phenacyl chloride **3a** under various reaction conditions. To this end, different solvents and bases were examined. While with ethanol, DMSO, acetonitrile, DMF and diethyl ether low yield of the desired product was obtained, water as a solvent improved the reaction yield. A base screen (carbonates, sodium methoxide, ammonia and triethyl amine) revealed that carbonate bases such as potassium and cesium carbonate result in higher reactivity in this cyclization reaction. Accordingly, when thiomorpholide **2** (0.6 mmol, 1 equiv.) and cyclohexyl isocyanide (0.6 mmol, 1 equiv.) in water (3 mL) were treated with phenacyl chloride (0.6 mmol, 1 equiv.) in the presence of K_2CO_3 (0.7 mmol, 1.2 equiv.) for about 6 h at 60°C, the three-substituted thiophene **4a** was obtained in 65% yield (Table 1, Entry 1).



Scheme 1. The general route for the synthesis of compound **2**.

Table 1. One-pot conversion of thiomorpholide **2** to highly functionalized thiophenes **4**.



Entry	α-Haloketone (**3**)	Product (**4**)	Yield[a] (%)
1	 **3a**	 **4a**	65
2	 **3b**	 **4b**	72
3	 **3c**	 **4c**	74
4	 **3d**	 **4d**	59
5	 **3e**	 **4e**	64
6	 **3f**	 **4f**	62
7	 **3g**	 **4g**	66
8	 **3h**	–	–
9	 **3i**	–	–
10	 **3j**	 **4a**	65

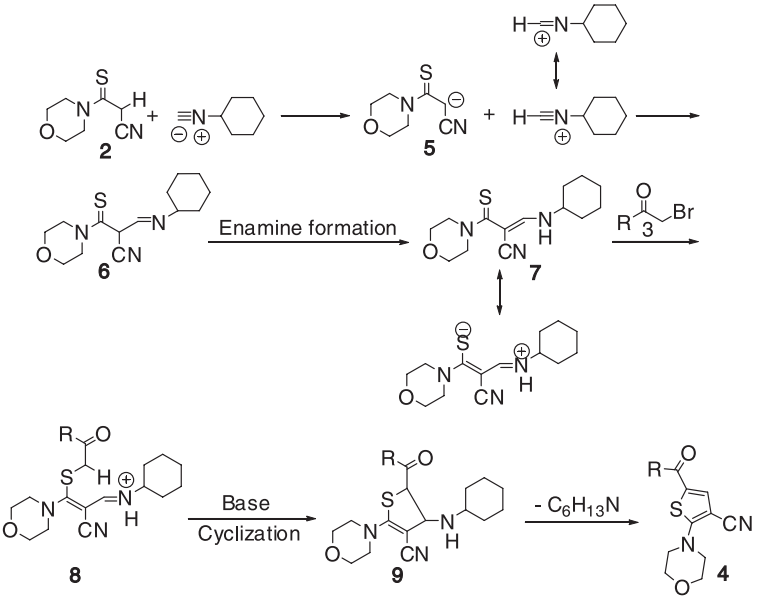
Note: [a]Isolated yields.

We next used these optimal reaction conditions to investigate the scope of the reaction with a range of α-haloketones. The results showed that a variety of substituents were tolerated under the reaction conditions. While the *para*-bromophenacyl bromide **3b** and *para*-chlorophenacyl bromide **3c** resulted in the corresponding thiophenes **4b** and **4c** in 72% and 74% yields, respectively, the *para*-methoxyphenacyl bromide **3d** afforded product **4d** in lower yield (Table 1, Entries 2–4). This dissimilarity of yields can be attributed to the different abilities of halides and methoxy substitutions on the phenyl rings in the stabilization of related anions. In continuation, we expanded the scope of the reaction to include naphthalene rings. Compound, **3e** gave the desired product with a satisfactory yield (64%, Table 1, Entry 5). As well, the possibility of the reaction was investigated by using the aliphatic partner of α-haloketones **3f** and a comparable yield was obtained (Table 1, Entry 6). The structure of the products was confirmed by analytical data, FT-IR, ^{1}H NMR and ^{13}C NMR spectra (*17*).

It was also desirable to test whether α-halonitriles, α-haloamides and α-haloesters could be applied in the reaction. While with the chloroacetonitrile **3g**, comparable results were obtained (Table 1, Entry 7), 2-chloro-*N*-phenylacetamide and ethyl-2-chloroacetate failed to take part in this methodology (Table 1, Entries 8 and 9).

The possible mechanism for this conversion is summarized in Scheme 2. The first step involves the deprotonation of compound **2** by cyclohexyl isocyanide via an acid–base reaction. Then, the nucleophilic addition of carbanion to positively charged ion obtained from cyclohexyl isocyanide leads to **6** which easily isomerizes to enamine **7**. The S-alkylation of component **7** with α-haloketone **3** via an S_N2 reaction affords the iminium ion **8**. Subsequent cyclization followed by cyclohexylamine elimination affords the corresponding thiophene **4**. The improved yield of the reaction in water can be explained by this mechanism. As the starting materials as well as the intermediates involving in this reaction are polar compounds in organic chemistry, the more polarity of water relative to other examined solvents can result in higher homogeneity of the reaction mixture and in more stability of relating intermediates.

In order to determine whether nucleophilic addition of compound **7** to α-haloketones is the rate-determining step, phenacyl bromide (**3j**) was used instead of phenacyl chloride (**3a**), and no



Scheme 2. The plausible mechanism for the formation of substituted thiophenes.

variation in yield was observed (Table 1, Entry 10). This result suggests that the conversion of intermediate **7** to **8** is not the rate-determining step which is attributed to the steric and mainly to electronic effects (*19*).

3. Conclusion

In summary, we have developed a straightforward and general one-pot approach to highly functionalized thiophenes using readily accessible α-haloketones and cyanothioacetamide. We have investigated the possibility of this methodology for the construction of these structural patterns not easily available by other methods. Expansion of the derived methodology for the preparation of similar functionalized heterocycles is under investigation.

4. Experimental

4.1. *Synthesis of cyanoacetamide 1*

Compound **1** was synthesized according to a recently reported method with a little modification (*16*). DBU (1.73 mL, 11.48 mmol) and morpholine (2.00 mL, 22.96 mmol) were added to tetrahydrofuran (8 mL) and the reaction temperature was maintained at 40°C. Ethyl cyanoacetate (4.89 mL, 45.91 mmol) was added and the mixture was stirred for 4 h. The mixture was concentrated and purified by column chromatography (SiO_2; 2% methanol in methylene chloride) to give of an off-white crystalline solid (62%).

4.2. *Synthesis of thiocyanoacetamide 2*

Cyanothioacetamide **2** and α-halocarbonyl compounds **3** were prepared according to previously reported procedures (*8, 12, 20, 21*). In a typical procedure for the synthesis of cyanothioacetamide **2**, certain amount of P_2S_5 (0.05 mol) was added gradually to a stirring mixture of cyanoacetamide **1** (0.1 mol) in dichloromethane (250 mL) at room temperature. In continuation, the mixture was refluxed for 5 h, and after cooling to room temperature, it was subsequently triturated with water in an efficient fume hood. After stirring overnight, the organic layer was separated, dried with $CaCl_2$ and concentrated in vacuum. The solid product was triturated with methanol and isolated by filtration and stored in a refrigerator for further reactions.

4.3. *Typical experimental procedure for the synthesis of substituted thiophenes (4)*

In a round-bottomed flask equipped with a magnet and a condenser, cyclohexyl isocyanide (0.6 mmol, 1 equiv.) was added to a stirred suspension of cyanothioacetamide **2** (0.6 mmol, 1 equiv.) in H_2O (3 mL). The reaction mixture was stirred at 60°C for 8 h. After completion of the reaction, α-halocarbonyl compound **3** (0.6 mmol, 1 equiv.) in acetonitrile (2 mL) and K_2CO_3 (0.7 mmol, 1.2 equiv.) was added to the mixture. The reaction mixture was stirred at 60°C for further 6 h. The course of the reaction was monitored using TLC on silica gel with dichloromethane as an eluent. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. The residue was subjected to column chromatography on SiO_2 (dichloromethane) to obtain pure products. Representative analytical data: *Compound* **4a**: Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (t, $J = 5.0$ Hz, 4H), 3.92 (t, $J = 5.0$ Hz, 4H), 6.61 (s, 1H), 742 (d, $J = 6.8$ Hz, 2H), 747 (m, 2H),

760 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.0, 66.6, 91.4, 109.0, 117.1, 128.1, 128.7, 129.1, 134.7, 142.8, 169.0, 189.1; IR (KBr) 3086, 2201, 1514, 1382 cm^{-1}; Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.62; H, 4.86; N, 9.54; S, 10.83. *Compound* **4b**: Yellowish crystals; mp 151–153°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (t, $J = 4.9$ Hz, 4H), 3.93 (t, $J = 4.9$ Hz, 4H), 6.59 (s, 1H), 746 (d, $J = 8.4$ Hz, 2H), 760 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.9, 66.5, 109.1, 116.9, 123.0, 129.7, 130.5, 132.3, 132.5, 133.6, 144.1, 184.3; IR (KBr) 3044, 2922, 2207, 1670, 1497 cm^{-1}; Anal. Calcd for $C_{16}H_{13}BrN_2O_2S$: C, 50.94; H, 3.47; N, 7.43; S, 8.50. Found: C, 51.02; H, 3.64; N, 7.58; S, 8.62. *Compound* **4c**: Yellowish crystals; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 (t, $J = 4.9$ Hz, 4H), 3.91 (t, $J = 4.9$ Hz, 4H), 6.90 (s, 1H), 744 (d, $J = 8.6$ Hz, 2H), 789 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.1, 68.7, 113.3, 117.2, 127.7, 129.1, 130.5, 131.2, 131.3, 134.0, 140.6, 193.4; IR (KBr) 3055, 2964, 2209, 1683, 1502 cm^{-1}; Anal. Calcd for $C_{16}H_{13}ClN_2O_2S$: C, 57.74; H, 3.94; N, 8.42; S, 9.63. Found: C, 57.86; H, 4.08; N, 8.60; S, 9.77. *Compound* **4d**: Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (t, $J = 5.0$ Hz, 4H), 3.86 (s, 3H), 3.94 (t, $J = 5.0$ Hz, 4H), 6.48 (s, 1H), 6.92 (d, $J = 8.7$ Hz, 2H), 794 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.7, 56.2, 68.4, 111.6, 113.6, 114.5, 115.4, 127.8, 128.8, 129.4, 131.5, 164.2, 193.3; IR (KBr) 3042, 2958, 2188, 1656, 1512 cm^{-1}; Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53; S, 9.76. Found: C, 62.34; H, 4.75; N, 8.51; S, 9.87. *Compound* **4e**: Yellowish crystals; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (t, $J = 5.0$ Hz, 4H), 3.94 (t, $J = 5.0$ Hz, 4H), 6.63 (s, 1H), 754 (m, 2H), 785 (m, 4H), 8.12 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.2, 68.3, 110.8, 116.6, 124.0, 125.5, 125.8, 126.4, 126.8, 127.9, 128.8, 129.2, 129.5, 131.3, 132.5 134.7, 141.3, 187.5; IR (KBr) 3059, 2965, 2206, 1675, 1512, 1453 cm^{-1}; Anal. Calcd for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04; S, 9.20. Found: C, 69.12; H, 4.79; N, 8.21; S, 9.36. *Compound* **4f**: Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 3.44 (t, $J = 4.9$ Hz, 4H), 3.88 (t, $J = 4.9$ Hz, 4H), 6.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 51.6, 66.5, 107.4, 117.0, 130.1, 138.3, 164.1, 203.2; IR (KBr) 3086, 2968, 2205, 1716, 1502 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.10; H, 5.24; N, 11.73; S, 13.74. *Compound* **4g**: Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (t, $J = 5.0$ Hz, 4H), 3.69 (t, $J = 5.0$ Hz, 4H), 5.54 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.6, 66.2, 95.5, 110.4, 115.6, 129.8, 141.3, 157.6; IR (KBr) 3086, 2968, 2205, 1716, 1502 cm^{-1}; Anal. Calcd for $C_{10}H_9N_3OS$: C, 54.78; H, 4.14; N, 19.16; S, 14.62. Found: C, 54.89; H, 4.18; N, 19.34; S, 14.74.

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