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A one-pot multicomponent synthesis of polysubstituted thiophenes via the reactions of an isocyanide, α-haloketones, and β-ketodithioesters in water

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ABSTRACT

An efficient synthesis of polysubstituted thiophene derivatives is achieved via the multicomponent reaction of β-ketodithioesters, α-haloketones, and cyclohexylisocyanide in aqueous medium.

Thiophenes are important targets for organic synthetic and medicinal chemists because of their applications in pharmaceuticals,[1] organic semi-conductors,[2] conducting polymers, organic light-emitting diodes (OLEDs),[3] and lasers.[4] The synthesis of highly substituted thiophenes has also attracted considerable attention in organic synthesis due to their significant biological activity. For example: adimanine(**I**) acts as an anti-inflammatory agent[5] and anticaine(**II**) is the most commonly used dental anesthetic in Europe[6] (Fig. 1). Moreover, monocyclic, bicyclic, and tricyclic thiophene derivatives have shown inhibition of protein tyrosine phosphatase 1B, which is a fascinating target for Type 2 diabetes treatment.[7]

Numerous synthetic routes to polysubstituted thiophene derivatives have been reported, such as the Fisselmane, Gewald, Hinsberg, and Paal–Knorr syntheses of thiophene.[8] Previously several synthetic methods for the synthesis of 2,3,4-trisubstituted thiophenes have been described. Asokan and co-workers reported the synthesis of highly functionalized thiophene derivatives via a two-component [3+2] cycloaddition/annulation,[9] while Singh and co-workers used two-component reactions.[10] The regioselective synthesis of polysubstituted thiophenes from Baylis–Hillman adducts has been carried out by Kim and co-workers.[11] To the best of our knowledge, there are only a few reports on the synthesis of 2,3,5-trisubstituted thiophenes.[12] In continuation of our research devoted to the synthesis of highly substituted thiophenes,[13] we sought to apply specific synthetic strategies to prepare such derivatives that could be utilized as possible therapeutic inhibitors and to disrupt certain protein–protein interactions. The application of β-ketodithioesters as substrates led to two distinct advantages. First, it allowed us to have a thiomethyl group as a masked methionine side chain. Second, owing to its leaving group ability, we found that (data not yet published), in the presence of appropriate nucleophiles, and with stepwise substitution and intramolecular condensation, the thiomethyl group and the nearby carbonyl can be utilized for the preparation of fused heterocycles. In addition, the presence of carbonyl groups enables us to introduce other amino acid side chains by converting the carbonyl group into the desired side-chain containing group. We herein report an efficient methodology for the preparation of highly substituted thiophenes via the one-pot, three-component reactions of β-ketodithioesters with an isocyanide and α-haloketones in water.

Initially, we prepared the starting β-ketodithioesters **3a–c** via the reaction of acetophenone derivatives **1a–c** with trithiocarbonate (**2**) in the presence of sodium hydride according to the reported procedure[14] (Scheme 1).

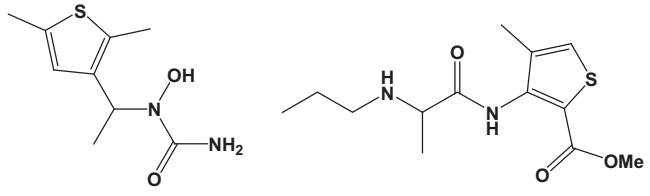

Figure 1. Biologically important molecules containing a polysubstituted thiophene skeleton.

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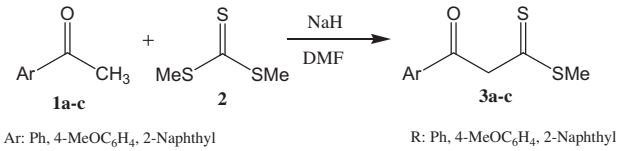
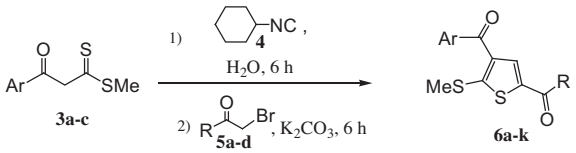


Scheme 1. Synthesis of β-ketodithioesters **3a**–**c**.



Scheme 2. Synthesis of polysubstituted thiophene derivatives **6a**–**k**.

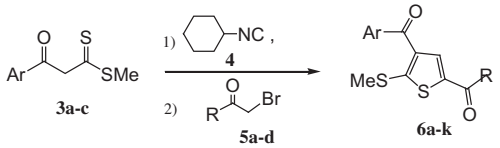
Next, we examined the three-component reaction of β-ketodithioester (**3a**), cyclohexylisocyanide (**4**), and phenacyl bromide (**5a**) as a model system. The conditions were optimized by screening various bases and using different solvents. The best results were obtained in water as the solvent with potassium bicarbonate as the base to afford polysubstituted thiophene **6a** in 74% yield (Scheme 2).

To investigate the scope of this procedure, we reacted β-ketodithioesters **3a**–**c** with cyclohexylisocyanide (**4**) and α-haloketones **5a**–**d** which gave the derivatives **6a**–**k** in good yields (Table 1).

The results showed that the reaction of β-ketodithioesters derivatives with a phenyl ring (**3a**,**b**) gave better yields compared to that with a naphthalene moiety (**3c**). This can be attributed to the low reactivity of naphthalene rings in comparison with phenyl rings.

In an effort to extend the applicability of this reaction, β-ketodithioester **3a** was reacted with α-chloroamides, α-chloroesters, or α-chloroacetone and cyclohexylisocyanide under the optimized

Table 1
Synthesis of polysubstituted thiophene derivatives **6a**–**k**



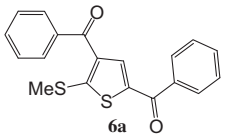
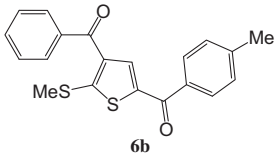
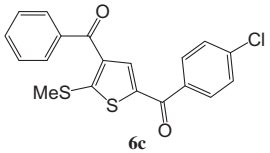
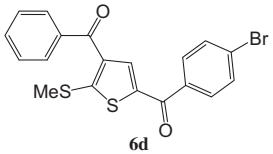
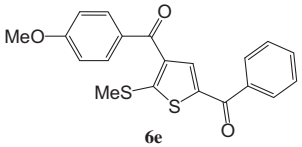
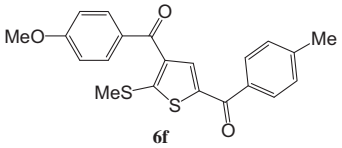
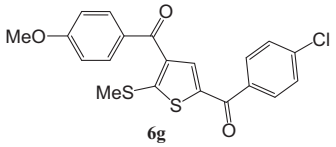
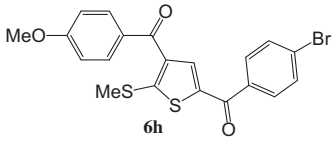
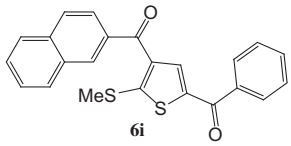
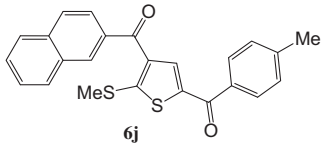
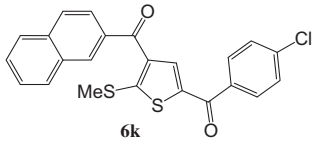
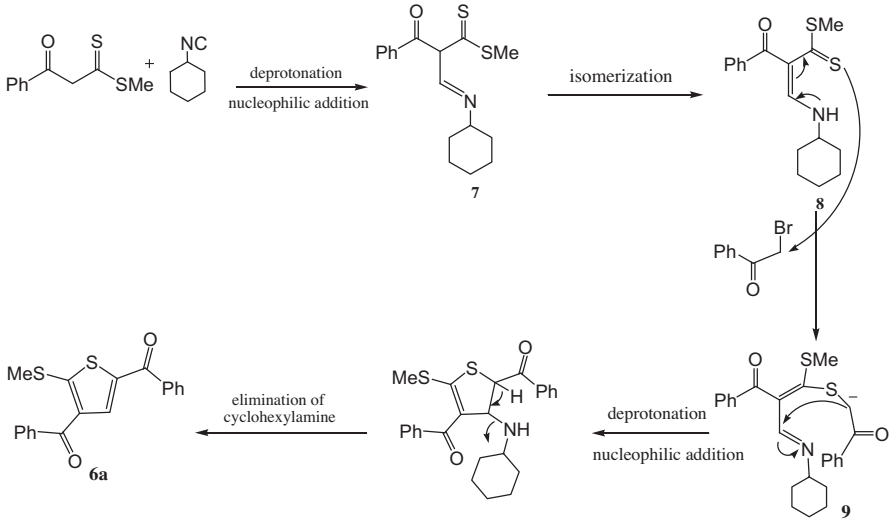
Entry	Ar	R	Product [a]	Yield [b] (%)
1	Ph	Ph	 **6a**	74
2	Ph	4-MeC$_6$H$_4$	 **6b**	70
3	Ph	4-ClC$_6$H$_4$	 **6c**	68
4	Ph	4-Br C$_6$H$_4$	 **6d**	73
5	4-MeOC$_6$H$_4$	Ph	 **6e**	69
6	4-MeOC$_6$H$_4$	4-MeC$_6$H$_4$	 **6f**	68

Table 1 (*continued*)

Entry	Ar	R	Product [a]	Yield[b] (%)
7	4-$MeOC_6H_4$	4-ClC_6H_4	 **6g**	70
8	4-$MeOC_6H_4$	4-BrC_6H_4	 **6h**	73
9	2-Naphthyl	Ph	 **6i**	60
10	2-Naphthyl	4-MeC_6H_4	 **6j**	59
11	2-Naphthyl	4-ClC_6H_4	 **6k**	56

[a] The products were characterized by IR and NMR spectroscopy and by elemental analysis.
[b] Isolated yield after recrystallization.



Scheme 3. A plausible mechanism for the formation of thiophenes **6**.

conditions, but unfortunately the desired products were not obtained.

The structures of products **6a–k** were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy and by elemental analysis.[15] For example, the IR spectrum of cycloadduct **6a** showed characteristic absorptions at 1630 and 1705 cm^{-1} corresponding to the carbonyl groups. In the ^1H NMR spectrum of **6a** two singlets appeared at δ 2.74 and δ 7.81 for the SCH_3 and CH of the thiophene ring, respectively. In the ^{13}C NMR spectrum of **6a**, the thiomethyl and two carbonyl carbons resonated at δ 19.3, δ 187.0, and δ 188.7.

A proposed mechanism for the reaction is shown in Scheme 3. The first step is the abstraction of the acidic proton of the β-keto-dithioester by cyclohexyl isocyanide followed by nucleophilic attack on the positively charged ion obtained from the isocyanide to generate imine **7**, which easily isomerizes into enamine **8**. Next enamine **8** undergoes an S-alkylation with the α-haloketone to

afford the iminium ion **9**. Finally, intramolecular cyclization with the elimination of cyclohexylamine yields the thiophene **6a**.

In conclusion, we have developed a novel and efficient procedure for the synthesis of polysubstituted thiophene derivatives via the reaction of β-ketodithioesters, cyclohexylisocyanide, and α-haloketone derivatives. The reaction was performed in aqueous medium and proceeds via a catalyst-free procedure. Other advantages include good yields of products and a simple work-up, which should make it a useful and attractive method for the synthesis of polysubstituted thiophenes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.014.

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15. *Typical procedure for the synthesis of polysubstituted thiophenes **6a–k**:* a mixture of β-ketodithioester **3a** (0.5 mmol) and cyclohexylisocyanide (**4**) (0.6 mmol) in H_2O (6 ml) was stirred at 50 °C for 6 h. After completion of the reaction, the halocarbonyl compound (0.6 mmol) in MeCN (2 ml) and K_2CO_3 (0.6 mmol) was added. The progress of the reaction was monitored by TLC using petroleum ether–EtOAc (4:1) as the eluent. After completion of the reaction (5 h) the mixture was extracted with CH_2Cl_2 (3 × 6 ml). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was recrystallized with EtOH to afford pure [5-(methylthio)thiene-2,4-diyl]bis(phenylmethanone) (**4a**): yellow powder, mp 135–137 °C, ^{1}H NMR δ = 2.74 (3H, s, SMe) 7.49 (2H, t, *J* = 7.2 Hz, ArH) 7.51 (2H, t, *J* = 7.2 Hz, ArH) 7.59 (1H, t, *J* = 7.5 Hz, ArH) 7.61 (1H, t, *J* = 7.4 Hz, ArH) 7.77 (2H, d, *J* = 7.5 Hz, ArH) 7.81 (1H, s, ArH) 7.84 (2H, d, *J* = 7.5 Hz, ArH) ^{13}C NMR δ = 19.3, 104.2, 129.1, 129.4, 131.6, 131.8, 132.9, 134.7, 137.7, 137.8, 139.1, 163.5, 187.0, 188.7; IR (KBr): 1630,1705, 2956, 3059 cm^{-1}; Anal. Calcd for $C_{19}H_{14}O_2S_2$: C, 67.43; H, 4.17; N, 18.95. Found: C, 67.61; H, 4.09; N, 18.90.