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A versatile one-pot synthesis of 2,3,5-tri-substituted thiophenes from thiomorpholides

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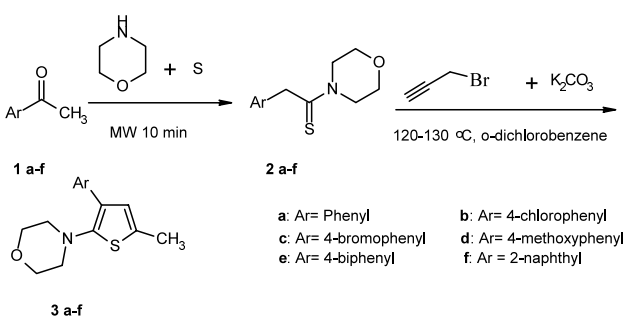
Abstract—An efficient method for the preparation of 2,3,5-trisubstituted thiophenes in a one-pot synthesis from thiomorpholides via the thio-Claisen rearrangement was developed.

Highly substituted thiophenes have attracted a great deal of interest, due to their presence in natural products,[1] as novel conducting polymers,[2] isosteric replacements for phenyl groups in medicinal chemistry[3] and as optical chromophores.[4] The thio-Claisen rearrangement has been an excellent method for the formation of C–C bonds and is useful for the construction of heterocyclic ring system.[5] In continuation of our recent work on microwave-assisted Claisen rearrangement of propargyl naphthyl ethers to pyrans and furans,[6] here we report a simple and one-pot method for the preparation of substituted thiophenes.

When the thiomorpholide **2a** as a model was treated with propargyl bromide in the presence of anhydrous K_2CO_3 in *o*-dichlorobenzene and heated at 120–130°C for about 4 h, the three-substituted thiophene **3a** was obtained in 76% yield (Scheme 1). *o*-Dichlorobenzene was found to be a versatile solvent for conducting this type of Claisen rearrangement. A mechanism has been proposed for this type of transformation and is shown in Scheme 2. Thiomorpholides undergo an initial enolization, then *S*-propargylation followed by Claisen rearrangement.



Scheme 1.

Several further examples have been investigated and Table 1 summarizes our results along with the melting points of the compounds. In conclusion, this is a facile one-pot synthesis of substituted thiophenes. The generality of the method has been demonstrated by the successful conversion of six substrates (**2a–f**) into 2-morpholinothiophenes (**3a–f**) in good isolated yields. These materials have the potential to be used as drugs.[7] The methodology described here seems to be the simplest one for the synthesis of these compounds.

Experimental

The substrates (**2a–f**) were prepared from substituted styrenes[8] or arylketones[9] by our previously published procedures.

General procedure for the one-pot preparation of substituted thiophenes: To a stirred solution of thiomorpholide (2 mmol) in *o*-dichlorobenzene (4 ml), anhydrous K_2CO_3 (0.552 g, 4 mmol) was added. Then, freshly distilled propargyl bromide (0.36 ml, 4 mmol) was added dropwise during about 15 min. The reaction mixture was heated to 60°C for 1 h and was then raised to 120–130°C for 4 h. The progress of the reaction was monitored by TLC. After the necessary time, the reaction mixture was filtered, washed with water (3×5 ml) and dried over anhydrous $MgSO_4$. The solvent was removed and the crude reaction mixture was purified by

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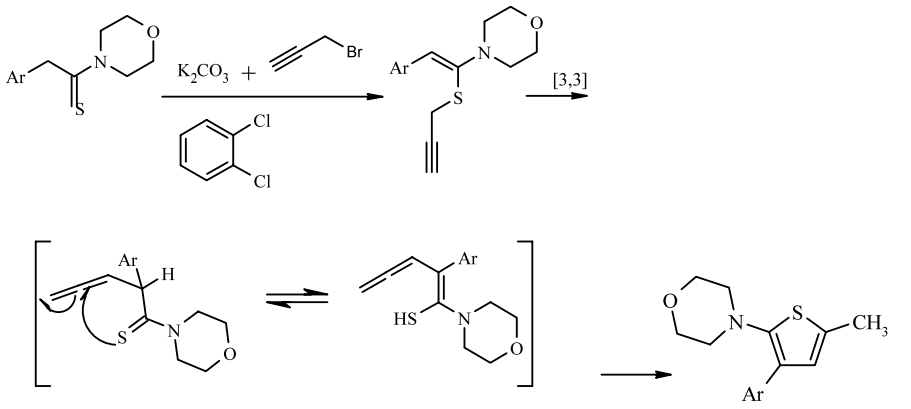
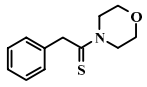
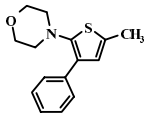
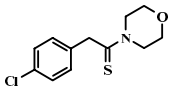
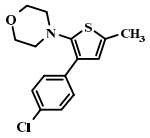
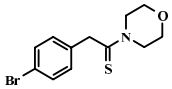
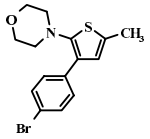
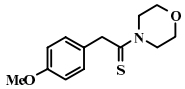
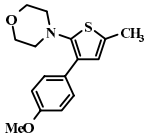
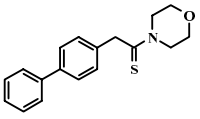
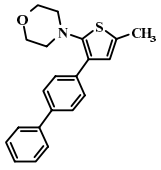
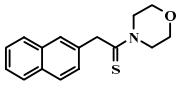
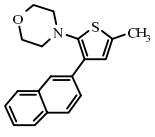


Scheme 2.

Table 1. One-pot conversion of thiomorpholides to three-substituted thiophenes

Entry	Substrate	Product	(%)Yield [a]	mp (°C)
1			76	105
2			50	119
3			66	135
4			65	75
5			62	139
6			53	128

[a]All yields refer to isolated products.

column chromatography (silica gel, eluent: ethyl acetate:hexane, 1:4).

Spectroscopic data for Compound **3a**: white powder (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), 2.94 (t, $J=4.6$ Hz, 4H), 2.48 (s, 3H); IR (KBr) 2964, 2907, 2860, 1643, 1501, 1429, 1117 (cm^{-1}).

Compound **3b**: yellow crystals (EtOH); mp: 119°C; ^{1}H NMR ($CDCl_3$, 500 MHz) 7.71 (d, $J=6.6$ Hz, 2H), 7.37 (d, $J=6.6$ Hz, 2H), 6.71 (s, 1H), 3.77 (t, $J=4.6$

Hz, 4H), 2.89 (t, $J=4.6$ Hz, 4H), 2.44 (s, 3H); IR (KBr) 2964, 2856, 2825, 1501, 1441, 1117 (cm^{-1}).

Compound **3c**: light yellow crystals (EtOH); mp: 135°C; ^1H NMR ($CDCl_3$, 500 MHz) 7.64 (d, $J=8.5$ Hz, 2H), 7.49 (d, $J=8.5$ Hz, 2H) 6.71 (s, 1H), 3.77 (t, $J=4.5$ Hz, 4H), 2.89 (t, $J=4.5$ Hz, 4H), 2.45 (s, 3H); IR (KBr) 2954, 2912, 2845, 1563, 1501, 1444, 1114 (cm^{-1}).

Compound **3d**: light yellow crystals (EtOH); mp: 75°C; ^1H NMR ($CDCl_3$, 500 MHz) 7.69 (d, $J=8.7$ Hz, 2H), 6.92 (d, $J=8.7$ Hz, 2H), 6.72 (s, 1H), 3.85 (s, 3H), 3.77 (t, $J=4.6$ Hz, 4H), 2.90 (t, $J=4.6$ Hz, 4H), 2.44 (s, 3H); IR (KBr) 2949, 2846, 1650, 1393, 1120 (cm^{-1}).

Compound **3e**: yellow powder; (EtOH); mp: 139°C; ^1H NMR ($CDCl_3$, 500 MHz) 7.86 (d, $J=8.2$ Hz, 2H), 7.66 (d, $J=7.5$ Hz, 2H), 7.63 (d, $J=8.2$ Hz, 2H), 7.47 (t, $J=7.5$ Hz, 2H), 7.37 (t, $J=7.2$ Hz, 1H), 6.81 (s, 1H), 3.81 (t, $J=4.6$ Hz, 4H), 2.95 (t, $J=4.6$ Hz, 4H), 2.47 (s, 3H); IR (KBr) 2959, 2912, 2851, 1640, 1511, 1449, 1115 (cm^{-1}).

Compound **3f**: light brown crystals (MeOH); mp: 128°C; ^1H NMR ($CDCl_3$, 500 MHz) 8.01 (s, 1H), 7.65–7.85 (m, 3H), 7.35–7.50 (m, 3H), 6.89 (s, 1H), 3.86 (t, $J=4.6$ Hz, 4H), 2.94 (t, $J=4.6$ Hz, 4H), 2.49 (s, 3H); IR (KBr) 2964, 2846, 2805, 1619, 1511, 1443, 1116 (cm^{-1}).

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