A Novel One-Pot Synthesis of Fully Substituted Thiophen-2(3*H*)-ones Using *N,N*-Disubstituted Thioamides

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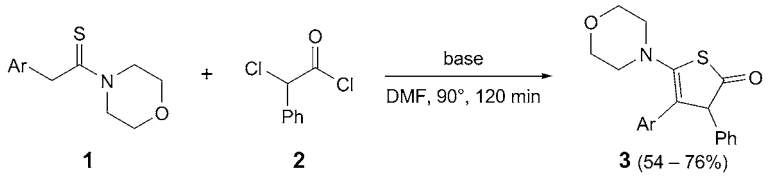
A new one-step synthesis of highly substituted thiophen-2(3*H*)-one derivatives was developed. 2-Aryl-1-(morpholin-4-yl)ethanethiones were reacted with 2-chloro-2-phenylacetyl chloride in DMF in the presence of a base to give the title compounds in moderate-to-good yields.

Introduction. – There has been considerable interest in the synthesis of highly substituted and functionalized thiophenes during the past few years due to their applications in medicinal chemistry [1–4] and industry [5–8]. The most general approaches for their preparation is the *Gewald* method [9], in which elemental sulfur in the presence of a secondary aliphatic amine is reacted with equimolar amounts of an activated MeCN and a carbonyl compound. Trisubstituted thiophenes have been prepared by the thio-*Claisen* rearrangement of *S*-propargylated thioacetomorpholides (=1-(morpholin-4-yl)ethanethiones) and *via* the ring closure of an α-allenyl thioacetomorpholide intermediate [10]. Also, fully substituted thiophenes have been successfully synthesized from the reaction of α-halocarbonyl compounds and tertiary thioamides in the presence of a base [11].

Here, for the first time, to the best of our knowledge, we report a one-step synthesis of new fully substituted thiophen-2(3*H*)-one derivatives.

Results and Discussion. – When a mixture of an 2-aryl-1-(morpholin-4-yl)ethanethione **1** and 2-chloro-2-phenylacetyl chloride **2** in DMF in the presence of a base was heated at 90°, fully substituted thiophen-2(3*H*)-ones **3** were obtained in moderate-to-good yields (54–76%; *Scheme 1*).

Scheme 1



1 **2** **3** (54 – 76%)

The study was initiated by running the reaction of 1-(morpholin-4-yl)-2-phenylethanethione (**1a**) as a test substrate with **2** in DMF and in the presence of Et_3N as a base. Under these conditions, only small amounts of the corresponding thiophene **3a**

(26%) were obtained. Therefore, we decided to examine various reaction conditions to find the optimal conditions for the highest yield of thiophen-2(3*H*)-one **3**. Hence, in addition of DMF and Et_3N, other solvents and bases were also tested in the reaction course, and the results are compiled in *Table 1*.

Table 1. *Screening of the Solvent and the Base in the Synthesis of Thiophene* **3a**

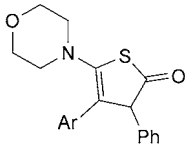
Entry	Solvent	Base	Yield[a]) [%]
1	DMF	DBU[b])	75
	dioxane		58
	MeCN		61
2	DMF	K_2CO_3	39
	dioxane		25
	MeCN		26
3	DMF	KOH	45
	dioxane		27
	MeCN		31

[a]) Yields of isolated products. [b]) DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

The results show that DBU in DMF led to the highest yield of the desired product. The effect of reaction temperature was also tested, and the results indicated that the best reaction temperature was 90°. At higher temperatures, the reaction mixture was contaminated with some colored or tarry materials.

After optimizing the conditions, we next examined the generality of these conditions to other substrates by using several 1-(morpholin-4-yl)ethanethiones (*Table 2*).

Table 2. *One-Step Synthesis of Highly Substituted Thiophen-2(3*H*)-ones*



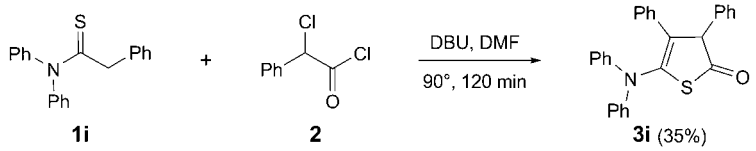
3a – 3h

Entry	Ar	Product[a])	Yield[b]) [%]
1	Ph	**3a**	75
2	4-Cl–C_6H_4	**3b**	69
3	4-Br–C_6H_4	**3c**	59
4	4-Me–C_6H_4	**3d**	76
5	4-MeO–C_6H_4	**3e**	64
6	4-Ph–C_6H_4	**3f**	60
7	Naphthalen-2-yl	**3g**	54
8	Pyridin-4-yl	**3h**	70

[a]) All products were characterized on the basis of their melting points, IR, and ^{1}H- and ^{13}C-NMR spectra. [b]) Yields of isolated products.

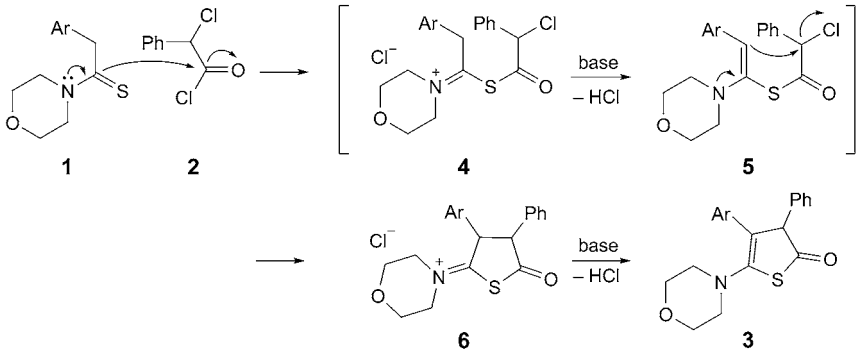
One of the advantages of the presented method is the simple isolation of the product. After completing the reaction (TLC), the mixture was poured in H_2O (except for **3g**), and the resulting precipitate was filtered and washed with MeOH to obtain pure compounds as white or light-yellow solids. To evaluate the scope of the reaction, the quite different thioamide **1i** was also used and reacted with **2** to obtain the sterically congested thiophen-2(3*H*)-one **3i** in low yield (35%; *Scheme 2*).

Scheme 2



A proposed mechanism for the reaction is outlined in *Scheme 3*. It seems likely that the *S*-acylated thioamide salt **4**, formed by the reaction of thioamide **1** with 2-chloro-2-phenylacetyl chloride **2** is the key intermediate in the reaction. This intermediate undergoes HCl elimination to give the next intermediate **5**, which undergoes cyclization to form the salt **6**, and **6** is finally transformed to the corresponding thiophen-2(3*H*)-one **3** *via* elimination of another HCl molecule.

Scheme 3



Conclusions. – We have developed for the first time a simple one-step method for the preparation of highly substituted thiophen-2(3*H*)-ones using *N*,*N*-disubstituted thioamides. Being a one-step reaction, requiring an easy workup and isolation of the product, and utilizing a general organic base for the reaction course are salient futures of the presented method.

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Experimental Part

General. All solvents used were dried and distilled before use according to standard procedures. Anal. TLC: silica gel (SiO_2; *Merck 60 F_{254}*) coated on aluminum plates; visualization with UV and aq.

$KMnO_4$ soln. M.p.: *Stuart SMP3* melting-point apparatus; uncorrected. IR Spectra: *UR-20* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker AMX-400* spectrometers; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz.

Caution: All experiments should be conducted in an efficient hood to avoid exposure to very corrosive vapors of 2-chloro-2-phenylacetyl chloride.

General Procedure for the Preparation of Highly Substituted Thiophenes **3**. 2-Aryl-1-(morpholin-4-yl)ethanethione **1** (1 mmol) and 2-chloro-2-phenylacetyl chloride (**2**; 1.2 mmol, 228 mg) were dissolved in DMF (1 ml), and DBU (1.06 mmol, 160 mg) was added dropwise. Then, the mixture was heated at 90° for 120 min. After completion of the reaction (TLC), the mixture was cooled to r.t. and poured in H_2O (10 ml). Then, the precipitated compound was filtered, and the solid residue was stirred for 10 min in warm (45°) MeOH (5 ml). The off-white thiophene precipitate was filtered and dried in vacuum desiccators. For the further purification, the solid was redissolved in a small amount of THF and reprecipitated with cold MeOH to obtain the pure product as white powder.

*5-(Morpholin-4-yl)-3,4-diphenylthiophen-2(3*H*)-one* (**3a**). IR: 3045, 1689, 1631, 1126. ^1H-NMR (400 MHz, $CDCl_3$): 7.23–7.40 (*m*, 10 H); 5.32 (*s*, 1 H); 3.69 (*t*, $J = 4.4$, 4 H); 2.93 (*t*, $J = 4.4$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.3; 136.8; 134.9; 134.3; 129.6; 129.3; 129.0; 128.6; 128.4; 127.9; 120.2; 62.0; 58.7; 52.9.

*4-(4-Chlorophenyl)-5-(morpholin-4-yl)-3-phenylthiophen-2(3*H*)-one* (**3b**). IR: 3011, 1693, 1629, 1122. ^1H-NMR (400 MHz, $CDCl_3$): 7.15–7.41 (*m*, 9 H); 5.31 (s, 1 H); 3.68 (*t*, $J = 2.4$, 4 H); 2.90 (*t*, $J = 2.4$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.8; 133.0; 131.4; 130.3; 129.4; 128.9; 128.8; 128.7; 128.0; 127.4; 127.3; 66.5; 58.6; 52.3.

*4-(4-Bromophenyl)-5-(morpholin-4-yl)-3-phenylthiophen-2(3*H*)-one* (**3c**). IR: 3011, 1688, 1640, 1134. ^1H-NMR (400 MHz, $CDCl_3$): 7.23–7.90 (*m*, 9 H); 5.36 (*s*, 1 H); 3.74 (*t*, $J = 2.4$, 4 H); 2.96 (*t*, $J = 2.4$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.0; 134.7; 133.1; 129.3; 129.1; 128.9; 128.7; 128.5; 128.1; 127.3; 127.1; 66.6; 58.7; 52.2.

*4-(4-Methylphenyl)-5-(morpholin-4-yl)-3-phenylthiophen-2(3*H*)-one* (**3d**). IR: 3044, 1691, 1643, 1150. ^1H-NMR (400 MHz, $CDCl_3$): 6.94–7.29 (*m*, 9 H); 5.20 (*s*, 1 H); 3.58 (*t*, $J = 4.8$, 4 H); 2.82 (*t*, $J = 4.8$, 4 H); 2.29 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.3; 140.5; 136.8; 134.9; 129.6; 129.3; 129.0; 128.6; 128.4; 127.9; 120.2; 62.0; 56.5; 52.6; 20.9.

*4-(4-Methoxyphenyl)-5-(morpholin-4-yl)-3-phenylthiophen-2(3*H*)-one* (**3e**). Light-yellow powder. IR: 3022, 1701, 1631, 1110. ^1H-NMR (400 MHz, $CDCl_3$): 7.53 (*d*, $J = 8.9$, 2 H); 7.32–7.41 (*m*, 5 H); 7.12 (*d*, $J = 8.9$, 2 H); 5.23 (*s*, 1 H); 3.72 (*s*, 3 H); 3.54 (*t*, $J = 4.4$, 4 H); 2.88 (*t*, $J = 4.4$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.3; 140.5; 136.8; 134.9; 129.6; 129.3; 129.0; 128.6; 128.4; 127.9; 120.2; 69.2; 62.0; 56.5; 52.6.

*4-(1,1′-Biphenyl-4-yl)-5-(morpholin-4-yl)-3-phenylthiophen-2(3*H*)-one* (**3f**). IR: 3043, 1689, 1635, 1122. ^1H-NMR (400 MHz, $CDCl_3$): 7.36–7.89 (*m*, 9 H); 7.08–7.25 (*m*, 5 H); 5.24 (*s*, 1 H); 3.65 (*t*, $J = 4.3$, 4 H); 2.94 (*t*, $J = 4.3$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.3; 144.0; 133.7; 129.1; 128.7; 128.6; 127.9; 127.8; 127.6; 127.3; 127.2; 126.0; 121.6; 66.6; 58.6; 52.2.

*5-(Morpholin-4-yl)-4-(naphthalen-2-yl)-3-phenylthiophen-2(3*H*)-one* (**3g**). IR: 3053, 1688, 1633, 1101. ^1H-NMR (400 MHz, $CDCl_3$): 7.23–7.66 (*m*, 12 H); 5.33 (*s*, 1 H); 3.71 (*t*, $J = 4.4$, 4 H); 2.97 (*t*, $J = 4.4$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.0; 139.7; 131.6; 131.0; 129.3; 128.9;128.8; 128.7; 128.1; 127.5; 127.4; 127.3; 127.2; 127.0; 126.9; 66.5; 58.7; 52. 32.

*5-(Morpholin-4-yl)-3-phenyl-4-(pyridin-4-yl)thiophen-2(3*H*)-one* (**3h**). Light-yellow crystals. IR: 3033, 1698, 1648, 1106. ^1H-NMR (400 MHz, $CDCl_3$): 7.16–7.35 (*m*, 9 H); 5.23 (*s*, 1 H); 3.61 (*t*, $J = 4.4$, 4 H); 2.80 (*t*, $J = 4.4$, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 164.2; 131.7; 131.6; 130.5; 129.4; 128.9; 128.8; 128.0; 127.4; 127.1; 66.5; 58.6; 50.9.

*5-(Diphenylamino)-3,4-diphenylthiophen-2(3*H*)-one* (**3i**). Light-yellow powder. IR: 3015, 1690, 1641, 1156. ^1H-NMR (400 MHz, $CDCl_3$): 6.96–7.36 (*m*, 20 H); 4.86, (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.1; 135.1; 134.7; 129.1; 128.9; 128.8; 128.7; 128.4; 128.2; 127.8; 127.7; 127.6; 126.7; 123.0; 122.4; 53.1.

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