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Efficient preparation of highly substituted thiophenes and thiophene-based arylacetic acids

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Efficient preparation of highly substituted thiophenes and thiophene-based arylacetic acids

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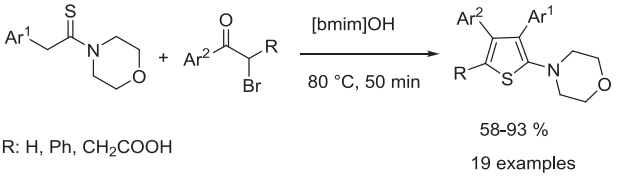
An efficient and one-step method for the preparation of highly substituted thiophenes and thiophen-2-yl-acetic acid derivatives was developed. Hence, thioacetomorpholides were smoothly reacted with α-bromo carbonyl compounds in [bmim]OH as an efficient dual catalyst-reaction medium to produce the title compounds in good yields.



Keywords: arylacetic acids; ionic liquids; sulfur heterocycles; thioamides; thiophenes

1. Introduction

There has been considerable interest in the synthesis of highly substituted and functionalized thiophenes during the years due to their huge applications in medicinal (*1–4*) chemistry and industry (*5–8*). The most known method for the preparation of highly substituted thiophenes is the Gewald method (*9*) in which, elemental sulfur is reacted with equimolar amounts of an activated acetonitrile and a carbonyl compound in the presence of a base. Earlier, we have shown that a one-pot thio-Claisen reaction and ring closure of thioacetomorpholides with propargyl bromide leads to trisubstituted thiophenes via an α-allenyl thioacetomorpholide intermediate (*10*). Following that we reported an efficient method for the synthesis of fully substituted thiophenes using thioacetomorpholides (*11*). However, preparing the desired thiophenes in an unfriendly solvent (toluene) and in long reaction times (6–8 h) was the main disadvantage of the method.

Herein, we have developed an efficient method for the preparation of highly substituted thiophenes using [bmim]OH as a task-specific ionic liquid. It was found that the reaction of

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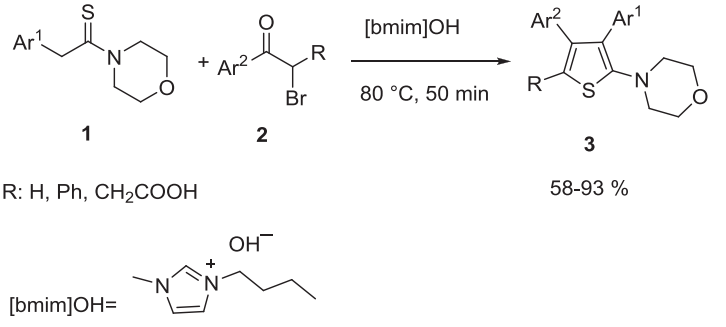
thioacetomorpholides with α-bromocarbonyl compounds in [bmim]OH proceeds smoothly at 80°C and produces moderate to excellent yields (58–93%) and in a relatively short time (50 min, Scheme 1).



Scheme 1. Preparation of highly substituted thiophenes.

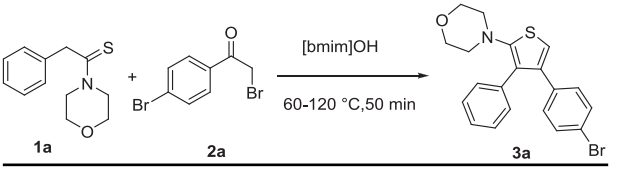
2. Results and discussion

Basic ionic liquids are environmentally friendly and recoverable solvents and catalysts with high activity. In this study, [bmim]OH was used to replace traditional bases such as KOH, NaOH, K_2CO_3, $NaHCO_3$, NaOAc, triethylamine, or tetrabutylammonium acetate. Using the traditional bases generally suffered from disadvantages such as waste production, corrosion, and environmental problems. Basic ionic liquids suggest a new feasibility for developing environmentally benign basic catalysts due to the combination of the benefits of inorganic bases and the striking solubilizing power of ionic liquids.

At the outset of our study, phenyl acetomorpholide **1a** was used as a test substrate and reacted with 2-bromo-1-(4-bromophenyl)ethanone **2a** in [bmim]OH and at various reaction temperatures to produce 4-[4-(4-bromophenyl)-3-phenyl-2-thienyl]morpholine **3a**. Our investigations revealed that the reaction proceeds efficiently and cleanly at 80°C to produce the desired thiophene product in excellent yield (93%, Table 1).

However, when aryl thioacetomorpholides were reacted with 3-bromo-4-oxo-4-phenylbutanoic acid derivatives in [bmim]OH, the corresponding thiophen-2-yl acetic acids were produced in fair to good yields (58–77%).

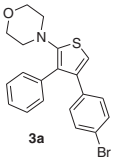
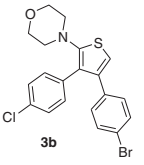
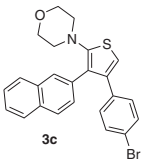
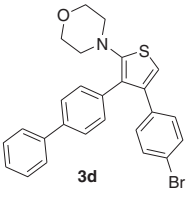
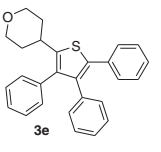
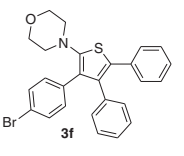
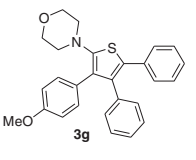
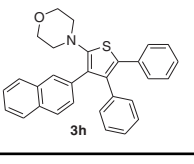
Table 1. Temperature screening in the synthesis of thiophenes.



Entry	Product	T (°C)	Yield (%)[a]
1	**3a**	60	71
2	**3a**	80	93
3	**3a**	95	90
4	**3a**	120	84[b]

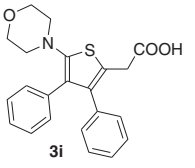
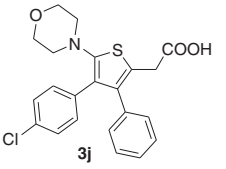
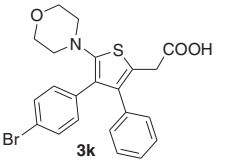
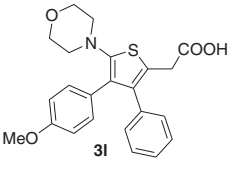
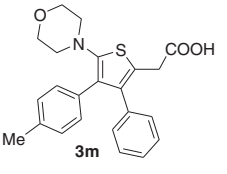
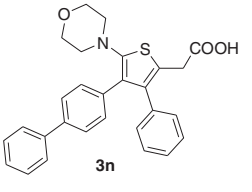
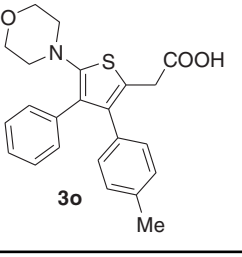
Notes: [a]Isolated yields.
[b]Formation of some tarry and colored materials was observed.

Table 2. Efficient synthesis of highly substituted thiophenes.

Entry	Ar^1	Ar^2	R	Product[a]	Yield[b] (%)
1	Ph	4-BrC_6H_4	H	 **3a**	93
2	4-ClC_6H_4	4-BrC_6H_4	H	 **3b**	85
3	2-Naphthyl	4-BrC_6H_4	H	 **3c**	87
4	4-PhC_6H_4	4-BrC_6H_4	H	 **3d**	83
5	Ph	Ph	Ph	 **3e**	90
6	4-BrC_6H_4	Ph	Ph	 **3f**	81
7	4-$MeOC_6H_4$	Ph	Ph	 **3g**	84
8	2-Naphthyl	Ph	Ph	 **3h**	80

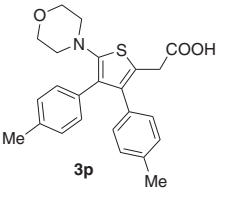
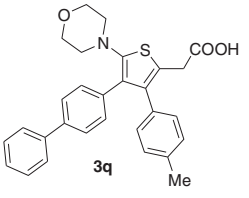
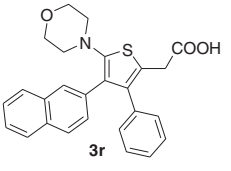
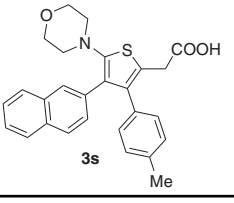
(*Continued*)

Table 2. Continued.

Entry	Ar^1	Ar^2	R	Product[a]	Yield[b] (%)
9	Ph	Ph	CH_2COOH	 **3i**	77
10	4-ClC_6H_4	Ph	CH_2COOH	 **3j**	65
11	4-BrC_6H_4	Ph	CH_2COOH	 **3k**	58
12	4-$MeOC_6H_4$	Ph	CH_2COOH	 **3l**	60
13	4-MeC_6H_4	Ph	CH_2COOH	 **3m**	78
14	4-PhC_6H_4	Ph	CH_2COOH	 **3n**	73
15	Ph	4-MeC_6H_4	CH_2COOH	 **3o**	71

(*Continued*)

Table 2. Continued.

Entry	Ar^1	Ar^2	R	Product[a]	Yield[b] (%)
16	4-MeC_6H_4	4-MeC_6H_4	CH_2COOH	 **3p**	68
17	4-PhC_6H_4	4-MeC_6H_4	CH_2COOH	 **3q**	69
18	2-Naphthyl	Ph	CH_2COOH	 **3r**	67
19	2-Naphthyl	4-MeC_6H_4	CH_2COOH	 **3s**	62

Notes: [a]All products were characterized by IR, ^{1}H NMR, and CHNS elemental analysis.
[b]All yields refer to pure isolated products.

The generality of the method has been confirmed by successful synthesis of 19 different thiophene derivatives in moderate to excellent yields (58–93%), and Table 2 summarizes our results.

To assess the feasibility of applying this method on a preparative scale, we carried out the reaction of thioamide **1a** with 2-bromo-1-(4-bromophenyl)ethanone **2a** on a 40-mmol scale. It was found that the reaction proceeded smoothly, similar to the case in a smaller scale (Table 2, Entry 1), and the requested thiophene **3a** was obtained in 89% isolated yield.

3. Conclusions

In conclusion, we have developed an efficient method for the preparation of highly substituted thiophenes using a task-specific ionic liquid, which plays the role of a basic catalyst as well as the solvent. Easy work-up, isolation, purification of product, mild reaction conditions, short reaction time, and high yield of product are salient futures of the method. It is also expected that the synthesized thiophen-2-yl acetic acids show potential anti-inflammatory and/or analgesic properties.

4. Experimental

4.1. *General procedure for the preparation of highly substituted thiophenes*

Aryl thioacetomorpholide (2 mmol) and α-bromocarbonyl compound (2 mmol) were dissolved in [bmim]OH (1 ml) and heated to 80°C for 50 min. After that, the reaction mixture was cooled to room temperature and poured in water (10 ml). Then, the precipitated compound was filtered and the solid residue was stirred for 10 min in cold MeOH (5 ml). The off-white thiophene precipitate was filtered and dried in a vacuum desiccator. For further purification, the solid was redissolved in the minimum amount of THF and reprecipitated with cold MeOH to obtain the pure product as white powder.

4.2. *General procedure for the preparation of highly substituted thiophen-2yl-acetic acids*

Thioacetomorpholide (2 mmol) and α-bromo-β-aroylpropionic acid derivative (2 mmol) were dissolved in [bmim]OH (1 ml) and heated to 80°C for 50 min. After that, the reaction mixture was cooled to room temperature, poured into dilute HCl (5%, 10 ml), and the precipitated product was filtered. Then, the semi-solid residue was dissolved in diethyl ether (20 ml) and extracted with NaOH (1 M, 2 × 10 ml). The aqueous layer was separated and treated with HCl (1 M, 22 ml) and the resulting precipitate was filtered, washed with water (2 × 5 ml), and dried in a vacuum desiccator to obtain thiophen-2-yl-acetic acids as white to light yellow solids.

The compounds (**3a–3l**) are known materials (*11*):

(3m): m.p.: 179–181°C; ^{1}H NMR (400 MHz, DMSO): δ 11.35 (s, 1H), 7.14–7.21 (m, 3H), 7.05 (d, J = 6.4 Hz, 2H), 6.94–6.99 (m, 4H), 3.53 (t, J = 4.3 Hz, 4H), 3.21 (s, 2H), 2.73 (t, J = 4.3 Hz, 4H), 2.21 (s, 3H); Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56; S, 8.15. Found: C, 70.45; H, 5.73; N, 3.64; S, 8.03.

(3n): m.p.: 107–109°C; ^{1}H NMR (400 MHz, DMSO): δ 11.47 (s, 1H), 7.65 (d, J = 6.5 Hz, 2H), 7.52 (d, J = 6.5 Hz, 2H), 7.32–7.42 (m, 3H), 7.13–7.19 (m, 7H), 3.56 (t, J = 4.2 Hz, 4H), 3.22 (s, 2H), 2.77 (t, J = 4.2 Hz, 4H); Anal. Calcd for $C_{28}H_{25}NO_3S$: C, 73.82; H, 5.53; N, 3.07; S, 7.04. Found: C, 74.01; H, 5.36; N, 3.02; S, 6.98.

(3o): m.p.: 180–182°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.32 (s, 1H), 7.18 (t, J = 7.3 Hz, 2H), 7.02–7.12 (m, 3H), 6.99 (d, J = 7.7, 2H), 6.95 (d, J = 7.7, 2H), 3.52 (t, J = 4.3 Hz, 4H), 3.20 (s, 2H), 2.72 (t, J = 4.3 Hz, 4H), 2.24 (s, 3H); Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56; S, 8.15. Found: C, 70.36; H, 5.79; N, 3.77; S, 8.08.

(3p): m.p.: 256–258°C; ^{1}H NMR (400 MHz, DMSO): δ 11.28 (s, 1H), 6.98–6.94 (m, 8H), 3.53 (t, J = 4.4 Hz, 4H), 3.18 (s, 2H), 2.72 (t, J = 4.4 Hz, 4H), 2.24 (s, 3H), 2.22 (s, 3H); Anal. Calcd for $C_{24}H_{25}NO_3S$: C, 70.73; H, 6.18; N, 3.44; S, 7.87. Found: C, 70.91; H, 6.06; N, 3.62; S, 7.80.

(3q): m.p.: 127–129°C; ^{1}H NMR (400 MHz, DMSO): δ 11.41 (s, 1H), 7.65 (d, J = 7.4 Hz, 2H), 7.52 (d, J = 8.2, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 7.01 (m, 4H), 3.55 (t, J = 4.3 Hz, 4H), 3.44 (s, 2H), 2.76 (t, J = 4.3 Hz, 4H), 2.23 (s, 3H); Anal. Calcd for $C_{29}H_{27}NO_3S$: C, 74.17; H, 5.80; N, 2.98; S, 6.83. Found: C, 74.36; H, 5.69; N, 3.09; S, 6.72.

(3r): m.p.: 279–281°C; ^{1}H NMR (400 MHz, DMSO): δ 11.57 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.57 (s, 1H), 7.37–7.43 (m, 2H), 7.30 (d, J = 8.3 Hz, 1H), 7.11–7.17 (m, 5H), 3.52 (t, J = 4.2 Hz, 4H), 3.50 (s, 2H), 2.77 (t, J = 4.2 Hz, 4H); Anal. Calcd for $C_{26}H_{23}NO_3S$: C, 72.70; H, 5.40; N, 3.26; S, 7.47. Found: C, 74.76; H, 5.25; N, 3.37; S, 7.51.

(3s): m.p.: 227–229°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.51 (s, 1H), 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, 4H), 3.71 (s, 2H), 3.68 (t, $J = 4.4$ Hz, 4H), 2.88 (t, $J = 4.4$ Hz, 4H), 2.22 (s, 3H); Anal. Calcd for $C_{27}H_{25}NO_3S$: C, 73.11; H, 5.68; N, 3.16; S, 7.23. Found: C, 72.96; H, 5.55; N, 3.32; S, 7.15.

Acknowledgements

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