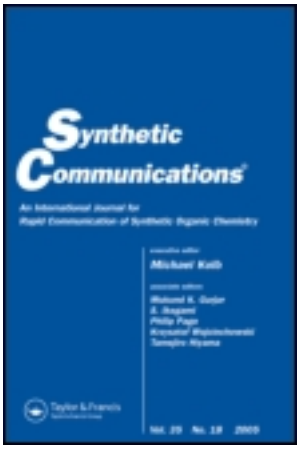

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Microwave-Assisted Synthesis of 2-Amino-thiophene-3-Carboxylic Derivatives Under Solvent-Free Conditions

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Abstract: Under microwave irradiation and solvent-free conditions, cyanoacetates (cyanoacetamides) react with ketones and sulphur in the presence of a small amount of morpholine to give 2-amino-thiophene-3-carboxylic derivatives. In particular, tetrahydro-benzo[b]thiophene-3-carboxylic acid *N*-aryl amides were synthesized in high yields of 84–95%.

Keywords: 2-Amino-thiophene-3-carboxylic derivatives, microwave irradiation synthesis, solvent-free

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INTRODUCTION

2-Amino-thiophene-3-carboxylic derivatives are known for their local anaesthetic activity.[1,2] Substituted 2-aminothiophenes have been used as starting materials in the synthesis of thienopyrimidines[3–6] and thienoimidazoles,[7] which display a variety of pharmacological activities, such as antimicrobial,[3] antiinflammatory,[4] anxiolytic,[5] and psychotropic[6] activity. Accordingly, developing more efficient, convenient, and environmentally friendly methods for synthesizing 2-aminothiophenes is of significance.

2-Amino-thiophene-3-carboxylic derivatives were synthesized previously by the Gewald method[8] from the reaction of ketones, cyanoacetates (cyanoacetamides), and sulphur (Scheme 1). Gewald et al. used a simplified one-pot procedure to synthesize these compounds instead of a two-step synthetic method. However, the yields of some compounds, such as 2-amino-4-methy-thiophene-3-carboxylic derivatives and tetrahydro-benzo[b]thiophene-3-carboxylic acid *N*-aryl amides, synthesized in this way are comparatively low. Moreover, this synthetic process needs long heating time and complicated handling.

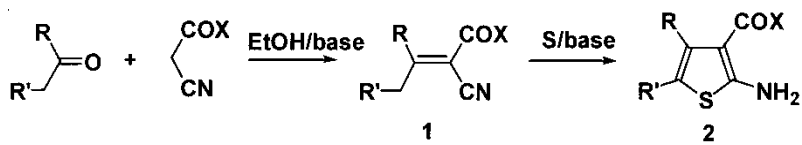
In the present communication, we report on an expeditious solvent-free method to prepare 2-amino-thiophene-3-carboxylic derivatives, which used microwave irradiation as the heating source and basic aluminum oxide as solid support. The results indicate that this synthetic method is easy and the yields of products are increased dramatically.

RESULTS AND DISCUSSION

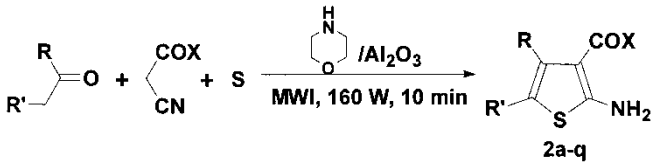
Treated with basic aluminium oxide as solid support and morpholine as base catalyst, ketones, cyanoacetates (cyanoacetamides), and sulphur were mixed and placed in an open vessel, and then the mixture was subjected to microwave irradiation for several minutes (Scheme 2). The purification of the reaction mixture by flash chromatography resulted in the exclusive isolation of 2-amino-thiophene **2a–q** in good yields.

The reaction conditions were optimized by testing several parameters, such as solid supports, power of microwave oven, and time of irradiation.

Solid supports such as various clays, aluminium oxides, and silica gel have been widely used in microwave-assisted organic synthesis to enhance substrates absorption of microwave energy. Using morpholine as base



Scheme 1.



Scheme 2.

catalyst, we compared the reaction yields of basic aluminium oxide with silica gel as solid supports during the synthesis of **2e**. The result indicated that basic aluminium oxide (87%) is more efficient than silica gel (59%). The reason of this result is probably due to the basicity of aluminium oxide, which enhances the catalytic effect of the base in the reaction.

Second, we evaluated the role of the base in the reaction. The reaction was respectively performed on the two solid supports without morpholine. Cyano-(4-methyl-cyclohexylidene)-acetic acid ethyl ester (**1e**) was obtained as the product of the reaction on basic aluminium oxide, but no product was determined on silica gel. This demonstrated the slight alkalinity of basic aluminium oxide and its effect on this procedure. Morpholine as an inexpensive and readily available secondary amine was used and found to be the most suitable in this reaction conditions.

In addition, the employed power of microwave oven and the irradiation time were investigated. When the power increased to 320 W, byproducts were observed on TLC and the yield was reduced in the synthesis of **2e**. No target product was observed in the synthesis of **2f** at 320 W for 5 min. We compared the irradiation time of 5 min, 10 min, and 15 min at 160 W in the synthesis of **2e**, and the corresponding yields are 73%, 87%, and 61%, respectively (Table 1).

Based on the studies described, the optimized condition of this procedure is basic aluminium oxide as solid support, microwave irradiation at 160 W, and reaction for 10 min. Compounds **2a–q** were synthesized under these conditions and the results are listed in Table 2.

Table 1. Procedure optimization of compound **2e** under microwave irradiation and solvent-free conditions

Solid support	Power (W)	Irradiation time (min)	Yield (%)
Silica gel	160	10	59
Basic Al_2O_3	160	5	73
Basic Al_2O_3	160	10	87
Basic Al_2O_3	160	15	61
Basic Al_2O_3	320	5	52
Basic Al_2O_3	320	10	46
Basic Al_2O_3	320	15	41

Table 2. Comparison of yields of 2-amino-thiophene-3-carboxylic derivatives **2a–q** obtained under thermal and microwave conditions

Compd.[a]	R	R′	X	Yield (%) Thermal condition[b]	Yield (%) Microwave condition
2a	CH_3	$COCH_3$	–OMe	31[8]	51
2b	CH_3	CO_2Et	–OEt	32[8]	80
2c	$-(CH_2)_3-$		–OEt	45[8]	77
2d	$-(CH_2)_3-$		$-NHC_6H_4$-*o*-Me	51[8]	73
2e	$-CH_2CH_2CH(CH_3)CH_2-$		–OEt	70[9]	87
2f	$-(CH_2)_4-$		$-NH_2$	61[8]	71
2g	$-(CH_2)_4-$		$-NHC_6H_5$	21[10]	93
2h	$-(CH_2)_4-$		$-NHC_6H_4$-*o*-Me	34[10]	93
2i	$-(CH_2)_4-$		$-NHC_6H_4$-*p*-Me	32[10]	95
2j	$-CH_2CH_2CH(CH_3)CH_2-$		$-NHC_6H_5$	67[6]	91
2k	$-CH_2CH_2CH(CH_3)CH_2-$		$-NHC_6H_4$-*p*-Me	—	85
2m	$-(CH_2)_4-$		$-NHC_6H_3$-3-Cl-4-F	—	86
2n	$-CH_2CH_2CH(CH_3)CH_2-$		$-NHC_6H_3$-3-Cl-4-F	—	84
2p	$-(CH_2)_4-$		$-NHC_6H_4$-*p*-OCF_3	—	84
2q	$-CH_2CH_2CH(CH_3)CH_2-$		$-NHC_6H_4$-*p*-OCF_3	—	86

[a]Compounds **2k–2q** are new chemicals.
[b]Taken from references [6], [8], [9], [10].

Compared with the Gewald method,[8] the yields of the present method were greatly improved. In particular, the yields of tetrahydro-benzo[b] thiophene-3-carboxylic acid *N*-aryl amides were increased from 21–67% to 84–95% (Table 2).

In conclusion, we have found an efficient method to prepare the title compounds by solvent-free microwave-assisted reaction. This method is also quite suitable for the synthesis of various tetrahydro-benzo[b] thiophene-3-carboxylic acid *N*-aryl amides.

EXPERIMENTAL

Melting points were tested on a melting point apparatus (SGW X-4) and are uncorrected. NMR spectra were obtained on a Bruker AMX-400 instrument in $CDCl_3$ or DMSO-d_6. MS spectra were recorded on a MAT-95 spectrometer. Microwave experiments were carried out in a domestic microwave oven (Galanz WG800DSL20II-K6).

Synthesis of 2-amino-thiophene-3-carboxylic derivatives: general procedures are described as those of compound **2a**.

5-Acetyl-2-amino-4-methyl-thiophene-3-carboxylic acid methyl ester (**2a**). A one-neck 50-mL flask containing acetylacetone (0.3 g, 3 mmol), methyl cyanoacetate (0.2 g, 2 mmol), sulphur (0.11 g, 3.4 mmol), basic Al_2O_3 (0.2 g), and morpholine (0.2 g, 2.3 mmol) was placed into a microwave oven and irradiated at the power of 160 W for 10 min. After cooling, the residue was separated by column chromatography with silica gel using petroleum ether/ethyl acetate (8/1) as eluting solution. The product **2a** (0.22 g, yield 51%) was obtained as a solid upon evaporation. Mp 159–161°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H), 2.58 (s, 3H), 3.73 (s, 3H), 7.98 (s, 2H). m/z (EI): 213 (M^+), 166 (100%).

5-Amino-3-methyl-thiophene-2,4-dicarboxylic acid diethyl ester (**2b**). Mp 106–108°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, 3H, J = 7.2 Hz), 1.26 (t, 3H, J = 7.2 Hz), 2.58 (s, 3H), 4.12 (q, 2H, J = 7.2 Hz), 4.21 (q, 2H, J = 7.2 Hz), 7.90 (s, 2H). m/z (EI): 257 (M^+), 211 (100%).

2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylic acid ethyl ester (**2c**). Mp 91–92°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, 3H, J = 7.2 Hz), 2.19 (m, 2H), 2.59 (m, 2H), 2.69 (m, 2H), 4.11 (q, 2H, J = 7.2 Hz), 7.16 (s, 2H). m/z (EI): 211 (M^+), 165 (100%).

2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylic acid *o*-tolyl-amide (**2d**). Mp 153–155°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 2.31 (m, 2H), 2.67 (t, 2H, J = 7.2 Hz), 2.96 (t, 2H, J = 7.2 Hz), 7.02 (t, 1H, J = 7.2 Hz), 7.12–7.20 (m, 2H), 7.16 (s, 2H), 7.79 (d, 1H, J = 7.2 Hz), 7.91 (s, 1H). m/z (EI): 272 (M^+), 165 (100%).

2-Amino-6-methyl-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester (**2e**). Mp 109–110°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03

(d, 3H, J = 6.4 Hz), 1.32–1.36 (m, 1H), 1.35 (t, 3H, J = 7.2 Hz), 1.84 (m, 2H), 2.16 (m, 1H), 2.59 (m, 2H), 2.88 (m, 1H), 4.24 (q, 2H, J = 7.2 Hz). m/z (EI): 239 (M^+), 193 (100%), 151, 125.

2-Amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid amide (**2f**). Mp 187–189°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (m, 4H), 2.54 (m, 2H), 2.63 (m, 2H). m/z (EI): 196 (M^+), 179 (100%), 151.

2-Amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid phenyl-amide (**2g**). Mp 138–140°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.66 (m, 2H), 1.74 (m, 2H), 2.47 (m, 2H), 2.62 (m, 2H), 6.48 (s, 2H), 6.99 (t, 1H, J = 7.6 Hz), 7.25 (t, 2H, J = 7.6 Hz), 7.58 (d, 2H, J = 7.6 Hz), 8.91 (s, 1H). m/z (EI): 272 (M^+), 179 (100%), 151.

2-Amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid *o*-tolyl-amide (**2h**). Mp 118–120°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71 (m, 4H), 2.21 (s, 3H), 2.47 (m, 2H), 2.73 (m, 2H), 6.65 (s, 2H), 7.03 (t, 1H, J = 7.6 Hz), 7.12–7.19 (s, 2H), 7.62 (d, 1H, J = 7.6 Hz), 8.41 (s, 1H). m/z (EI): 286 (M^+), 179 (100%), 151,107, 91, 57.

2-Amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid *p*-tolyl-amide (**2i**). Mp 131–134°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.64 (m, 2H), 1.72 (m, 2H), 2.23 (s, 3H), 2.47 (m, 2H), 2.62 (m, 2H), 6.48 (s, 2H), 7.06 (d, 2H, J = 8.0 Hz), 7.47 (d, 2H, J = 8.0 Hz), 8.82 (s, 1H). m/z (EI): 286 (M^+), 179 (100%), 151,107, 91, 56.

2-Amino-6-methyl-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid phenyl-amide (**2j**). Mp 163–165°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (d, 3H, J = 6.8 Hz), 1.24–1.30 (m, 1H), 1.75–1.84 (m, 2H), 2.10 (m, 1H), 2.52–2.72 (m, 3H), 6.52 (s, 2H), 6.99 (t, 1H, J = 7.2 Hz), 7.25 (t, 2H, J = 7.2 Hz), 7.58 (d, 2H, J = 7.2 Hz), 8.91 (s, 1H). m/z (EI): 286 (M^+), 193, 151, 57 (100%).

2-Amino-6-methyl-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid *p*-tolyl-amide (**2k**). Mp 128–130°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (d, 3H, J = 6.8 Hz), 1.22–1.29 (m, 1H), 1.75–1.82 (m, 2H), 2.10 (m, 1H), 2.51–2.62 (m, 3H), 7.06 (d, 2H, J = 8.0 Hz), 7.47 (d, 2H, J = 8.0 Hz), 8.81 (s, 1H). m/z (EI): 300 (M^+), 193, 151, 56 (100%). m/z (high-resolution EI-MS): 300.1293 ($C_{17}H_{20}N_2OS^+$) calc. 300.1296.

2-Amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid (3-chloro-4-fluoro-phenyl)-amide (**2m**). Mp 99–100°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82–1.87 (m, 4H), 2.58 (m, 2H), 2.75 (m, 2H), 6.04 (s, 2H), 7.09 (t, 1H, J = 8.8 Hz), 7.32 (m, 1H), 7.49 (s, 1H), 7.72 (m, 1H). m/z (EI): 324 (M^+), 177 (100%), 166. m/z (high-resolution EI-MS): 324.0498 ($C_{15}H_{14}ClFN_2OS^+$) calc. 324.0499.

2-Amino-6-methyl-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid (3-chloro-4-fluoro-phenyl)-amide (**2n**). Mp 184–187°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, 3H, J = 6.8 Hz), 1.46–1.51 (m, 1H), 1.92–1.98 (m, 2H), 2.22 (m, 1H), 2.61–2.84 (m, 3H), 7.09 (t, 1H, J = 8.8 Hz), 7.32 (m, 1H), 7.54 (s, 1H), 7.72 (m, 1H). m/z (EI): 338 (M^+), 194 (100%), 151. m/z (high-resolution EI-MS): 338.0638 ($C_{16}H_{16}ClFN_2OS^+$) calc. 338.0656.

2-Amino-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid (4-trifluoro-methoxy-phenyl)-amide (**2p**). Mp 124–127°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84–1.87 (m, 4H), 2.58 (m, 2H), 2.76 (m, 2H), 6.02 (s, 2H), 7.17 (d, 2H, J = 8.0 Hz), 7.55 (d, 2H, J = 8.0 Hz). m/z (EI): 356 (M^+), 177, 166 (100%). m/z (high-resolution EI-MS): 356.0801 ($C_{16}H_{15}F_3N_2O_2S^+$) calc. 356.0806.

2-Amino-6-methyl-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid (4-trifluoro-methoxy-phenyl)-amide (**2q**). Mp 153–157°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, 3H, J = 6.8 Hz), 1.42–1.49 (m, 1H), 1.91–1.96 (m, 2H), 2.29 (m, 1H), 2.61–2.87 (m, 3H), 6.02 (s, 2H), 7.17 (d, 2H, J = 8.0 Hz), 7.55 (d, 2H, J = 8.0 Hz). m/z (EI): 370 (M^+), 194 (100%), 151. m/z (high-resolution EI-MS): 370.0951 ($C_{17}H_{17}F_3N_2O_2S^+$) calc. 370.0963.

Cyano-(4-methyl-cyclohexylidene)-acetic acid ethyl ester (**1e**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, 3 H, J = 6.8 Hz), 1.21–1.29 (m, 2H), 1.35 (t, 3H, J = 7.2 Hz), 1.73 (m, 1H), 1.90–2.05 (m, 2H), 2.15 (dt, 1H, J = 4.8, 12.8 Hz), 2.33 (dt, 1H, J = 4.8, 12.8 Hz), 3.03 (m, 1H), 3.85 (m, 1H), 4.26 (q, 2H, J = 7.2 Hz). m/z (EI): 207 (M^+), 179 (100%), 162, 135.

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