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Microwave-assisted synthesis of 2-aminothiophene-3-carboxylic acid derivatives, 3*H*-thieno[2,3-*d*]pyrimidin-4-one and 4-chlorothieno[2,3-*d*]pyrimidine

Stéphanie Hesse,* Enrico Perspicace and Gilbert Kirsch

Laboratoire d'Ingénierie Moléculaire et Biochimie Pharmacologique, Institut Jean Barriol, Université Paul Verlaine—Metz, 1 Boulevard Arago, 57070 METZ Technopôle, France

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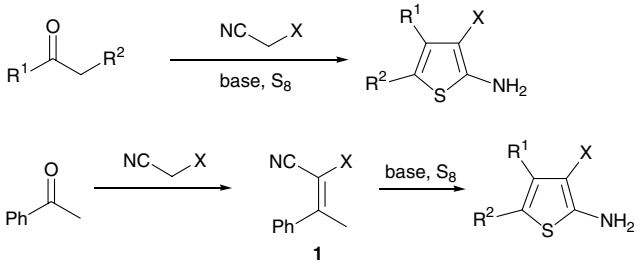
Abstract—A two-minute microwave irradiation allowed the synthesis of several 2-aminothiophene-3-carboxylic acid derivatives. Their efficient transformation to thieno[2,3-*d*]pyrimidin-4-one and the corresponding 4-chloro derivative is also reported under microwave irradiation.

2-Aminothiophenes have demonstrated a broad spectrum of uses including pharmaceuticals,[1] dyes and agrochemical applications. Traditionally, polysubstituted 2-aminothiophenes with an electron-withdrawing group such as cyano, carbethoxy or carboxamide in the 3-position and alkyl, aryl or hetaryl groups in the 4- and 5-positions are prepared via the Gewald reaction.[2] There are two common variations on this synthesis: a one-pot procedure in which ketones or aldehydes react with an activated nitrile and elemental sulfur and a two-step procedure in which alkene **1** produced by the Knoevenagel condensation is isolated prior to cyclization with sulfur and base (Scheme 1).



Scheme 1. Gewald reaction: the one-pot procedure and the two-step version.

In some cases, especially with alkylarylketones such as acetophenone, the two-step procedure is generally preferred and provided better yields. Recently a one-pot procedure was described on several substituted acetophenones, working with an excess of ethyl cyanoacetate and a careful portionwise addition of sulfur.[3]

Another improvement that can be made in the Gewald synthesis is the diminution of the reaction time by using microwave technology. Indeed, most published Gewald thiophene synthetic procedures required long reaction times that vary between 4 and 48 h for the condensation step. Microwave heating is an area of increasing interest in both academic and industrial laboratories because it can enhance the rate of reaction and in many cases improve product yields.[4]

Recently, two papers using microwave-assisted Gewald synthesis appeared. The first one,[5] published in 2003, reported the one-pot synthesis of tetrasubstituted 2-acylaminothiophenes using a commercially available polystyrene bound cyanoacetate. The Gewald reaction and the acylation of the resulting 2-aminothiophenes took place in less than 1 h and gave a high degree of purity. In 2005, a second paper[6] described the reaction of ketones (essentially cyclic ketones) with cyanoacetates and sulfur in the presence of a small amount of

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* Corresponding author. Fax: +33 387315801; e-mail: hesse@univ-metz.fr

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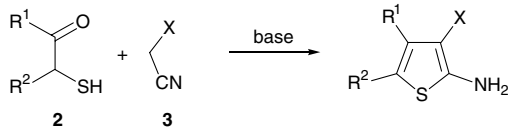
morpholine in solvent-free conditions. In this case, basic aluminium oxide was used as the solid support.

As a part of our research on the preparation of new polyheterocycles with pharmaceutical values, we were interested in synthesizing some 2-aminothiophenes without substituents in positions 4 and 5. In the very first version of the Gewald reaction,[7] an α-mercaptoaldehyde or an α-mercaptoketone **2** was treated with an activated nitrile **3** bearing electron-withdrawing groups such as malononitrile, methylcyanoacetate (Scheme 2).

This version has few drawbacks as the starting compounds **2** are unstable and difficult to prepare. Indeed, α-mercaptocarbonyl derivatives were often generated in situ by the reaction of alkali sulfides with the corresponding α-halocarbonyl compounds. In 1996, an efficient synthesis was described starting from 2,5-dihydroxy-1,4-dithiane **4** (thioacetaldehyde dimer).[8] Reaction of cyanoacetamide at 70 °C for 2 h allowed the formation of 2-aminothiophene-3-carboxamide in 62% yield (Scheme 3). This procedure was also used by Gütschow and Neumann in their synthesis of thieno[1,3]oxazin-4-ones as inhibitors of human leucocyte elastase.[9]

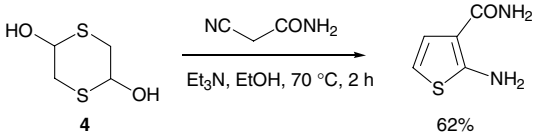
Here we reported an expedious synthesis of 2-aminothiophene-3-carboxylic acid derivatives under microwave irradiation. Transposition of reaction under focused microwave irradiation needs special attention. For this reason, we performed preliminary experiments in order to establish the optimal conditions. We decided to try the two types of microwave control: the first one was a 'transposition' of classical heating conditions with a control of temperature/time (the microwave controls the irradiation power to maintain the fixed temperature) and the second one was the power/time control with an infrared measurement of the temperature reached in the mixture. The first method was more satisfying and all the reactions were performed in a round bottom flask irradiated for 2 min at 50 °C. The results are presented in Table 1.

The next step we wanted to study and apply under microwave irradiation was the conversion of 2-aminothiophene-3-carboxylic acid derivatives to 3*H*-thieno[2,3-*d*]pyrimidin-4-one. Indeed, this thieno[2,3-*d*]-pyrimidine core is present in many compounds having pharmaceutical activities such as, for example, analgesic,[11] anticancer,[12] anti-angiogenic[13] and mGluR1 antagonists.[14]



2 **3**

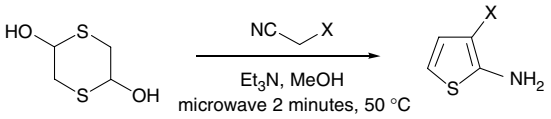
Scheme 2.



4

Scheme 3.

Table 1. Microwave-assisted synthesis of 2-aminothiophene-3-carboxylic acid derivatives starting from thioacetaldehyde dimer

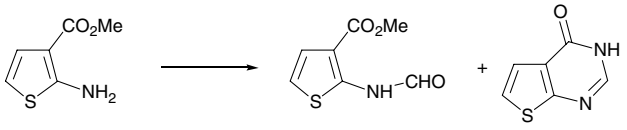


Entry	2-Aminothiophene		Yield (%)	Literature (%)
1	X = CO_2Me	**5**	82	46[7]
2	X = $CONH_2$	**6**	78	60[10]
3	X = CN	**7**	81	55[7]
4	X = CONHPh	**8**	87	
5	X = CO*t*Bu	**9**	60	

We first used classical conditions[15] to synthesize compound **10** in order to have some reference for TLC control. Aminothiophene **5** was refluxed with formamide for 1.5 h and left overnight under stirring at room temperature providing **10** in 53% yield. We next wanted to transpose this reaction under microwave heating. We have to be careful because formamide may decompose at a temperature above 200 °C with toxic gas emission. Our first attempt (2 min of microwave irradiation at 200 °C) gave after treatment a mixture of starting material **5** and intermediate **11** in a 3:2 ratio (Table 2, entry 1). Increasing the reaction time allowed the total consumption of **5** and the formation of compounds **11** and **10** (Table 2, entries 2–6). Addition of ammonium formate seems to accelerate the reaction (Table 2, entries 7 and 8). However, it was very difficult to find conditions providing **10** with no trace of intermediate **11**.

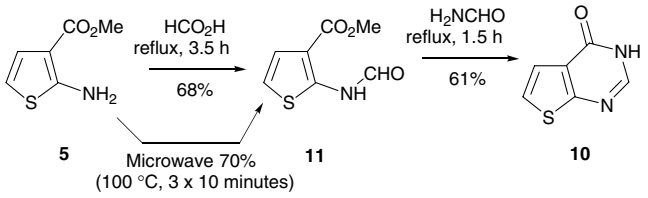
It must be noted that the structure of **11** was confirmed by its direct synthesis from aminothiophene **5** with for-

Table 2. Microwave-assisted synthesis of 3H-thieno[2,3-*d*]pyrimidin-4-one **10** starting from compound **5**

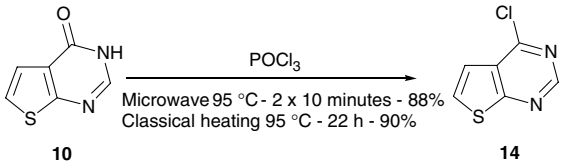


5 **11** **10**

Entry	Conditions	**5**	**11**	**10**
1	200 °C—2 min	3	2	
2	200 °C—10 min		3	1
3	210 °C—20 min		3	4
4	200 °C—20 + 10 min		1	3
5	200 °C—35 min		1	1
6	200 °C—3 × 10 min		2	5
7	150 °C—3 × 10 min 2.8 equiv HCO_2NH_4		1	1
8	190 °C—3 × 10 min 8 equiv HCO_2NH_4		1	6



Scheme 4.



Scheme 5.

mic acid under classical and microwave conditions (Scheme 4). When compound **11** was refluxed with formamide for 1.5 h, compound **10** was obtained in 61% yield.

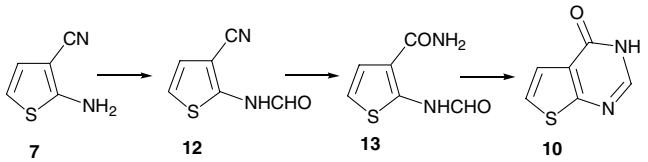
We next turned our attention to the conversion of 2-aminothiophene-3-carbonitrile **7** in thieno[2,3-*d*]pyrimidin-4-one **10**. We tried two different conditions described in the literature. In 2006, Cheong et al. reported the synthesis of some substituted furopyrimidines: 2-aminofuran-3-carbonitrile was stirred for 3 h with formic acid 85% in the presence of acetic anhydride at 0 °C and refluxed for 24 h to afford furopyrimidine in 72% yield.[16] Compound **7** was reacted with formic acid 99% and acetic anhydride and irradiated for 5 min at 100 °C. Compound **12** was isolated in 70% yield and characterized (Table 3, entry 1). This first result confirmed the mechanism proposed by Cheong. However, all the other essays made using this protocol always gave compound **12** and we never obtained thienopyrimidinone **10** by this way[17] (Table 3, entries 2–5).

We next tried some slightly different conditions:[18] compound **7** was reacted with formic acid in the presence of H_2SO_4 catalysis (Table 3, entry 6). The reaction was followed by TLC after, respectively, 5 min, 10 min and 15 min of microwave irradiation. We clearly observed the apparition and consumption of **12** and **13**. 3H-Thieno[2,3-*d*]pyrimidin-4-one **10** was obtained in 79% yield after 15 min of microwave irradiation. Moreover, reaction of 2-aminothiophene-3-carboxamide **6** with formic acid in the presence of H_2SO_4 catalysis under microwave irradiation (90 °C—3 × 10 min) also gave a mixture of **13** and **10** in a 1:2 ratio.

Finally we transformed 3*H*-thieno[2,3-*d*]pyrimidin-4-one **10** into 4-chlorothieno[2,3-*d*]pyrimidine **14** by the action of phosphorus oxychloride using both classical[19] and microwave heating (Scheme 5).

In conclusion, we have synthesized in very good yields some 2-aminothiophene-3-carboxylic acid derivatives **5**–**9** in 2 min thanks to microwave irradiation.[20] We have also prepared with success 3*H*-thieno[2,3-*d*]pyrimidin-4-one **10** under microwave irradiation. We have elucidated its mechanism of formation as we have isolated and characterized the two intermediate compounds **12** and **13**. Finally, conversion of **10** into the corresponding chloro derivative **14** was also performed in excellent yield under microwave irradiation in a short time (2 × 10 min).

Table 3. Microwave-assisted synthesis of 3*H*-thieno[2,3-*d*]pyrimidin-4-one **10** starting from compound **7**



Entry	Conditions	Results
1	HCO_2H 99%–Ac_2O MW 100 °C—5 min	**12** (70%)
2	HCO_2H 99%–Ac_2O MW 60 °C—10 min	**12** (59%)
3	HCO_2H 99%–Ac_2O MW 90 °C—2 × 15 min	**12** (55%)
4	HCO_2H 85%–Ac_2O MW 90 °C—3 × 10 min	**12** (56%)
5	HCO_2H 99%–Ac_2O Reflux—24 h	**12** (75%)
6	HCO_2H 99%–H_2SO_4 concd MW 90 °C—5 min	**13** (1) + **10** (2.5)
7	HCO_2H 99%–H_2SO_4 concd MW 90 °C—10 + 5 min	**10** (79%)

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20. All reactions were performed in the Open Vessel mode with a CEM Discover single mode microwave reactor equipped with a 300 W power source.

General procedure for the synthesis of 2-aminothiophenes: A mixture of 2,5-dihydroxy-1,4-dithiane (dimer of thioacetaldehyde) (5 mmol), activated nitrile (10 mmol), triethylamine (0.5 mL) and two drops of DMF in methanol (4 mL) was submitted to microwave irradiation for 2 min at 50 °C. After cooling, the reaction mixture was concentrated under reduced pressure and hydrolyzed. The precipitate was filtered off.

2-Amino-thiophene-3-carboxylic acid phenylamide **8**: Pale brown solid. Mp 139 °C. IR (KBr): 1616 (C=O), 3346, 3458 (NH_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 6.32 (d, 1H, $J = 5.8$ Hz), 6.98–7.05 (m, 1H), 7.25–7.34 (m, 3H), 7.38 (br s, 2H), 7.66 (d, 2H, $J = 7.5$ Hz), 9.31 (br s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 105.6 (CH), 106.8 (C), 120.3 (CH), 122.8 (CH), 124.2 (CH), 128.4 (CH), 139.3 (C), 162.9 (C), 164.3 (C).

1-(2-Amino-thien-3-yl)-2,2-dimethyl-propan-1-one **9**: Yellow solid. Mp 101 °C. IR (KBr): 1591 (C=O), 3266, 3370 (NH_2) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.30 (s, 9H, $3CH_3$), 6.15 (d, 1H, $J = 6$ Hz), 6.87 (br s, 2H), 7.19 (d, 1H, $J = 6$ Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 27.8 (CH_3), 43.7 (C), 105.4 (CH), 112.8 (C), 126.3 (CH), 166.3 (C), 202.2 (C=O).

3*H*-Thieno[2,3-*d*]pyrimidin-4-one **10**: Pale yellow solid. Mp 245 °C (dec) (lit.:[15] 264 °C). IR (KBr): 1652 (C=O) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 7.39 (d, 1H, $J = 5.8$ Hz), 7.57 (d, 1H, $J = 5.8$ Hz), 8.12 (s, 1H), 12.50 (br s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 121.8 (CH), 124.1 (CH), 124.7 (C), 145.3 (CH), 156.5 (C), 163.5 (C=O).

Methyl 2-formylaminothiophene-3-carboxylate **11**: Pale brown solid. Mp 88 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 3.85 (s, 3H), 7.03 (d, 1H, $J = 5.9$ Hz), 7.17 (d, 1H, $J = 5.9$ Hz), 8.54 (s, 1H), 11.31 (br s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 51.7 (CH_3), 113.0 (C), 117.2 (CH), 123.8 (CH), 145.7 (C), 159.8 (C=O), 163.8(C=O).

2-Formylaminothiophene-3-carbonitrile **12**: Brown solid. Mp 195 °C (dec). IR (KBr): 1678 (C=O), 2227 (CN), 3216 (NH_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 7.18 (s, 2H), 8.41 (s, 1H), 12.04 (br s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 92.8 (C), 114.4 (CN), 119.2 (CH), 124.6 (CH), 147.8 (C), 159.2 (CH).

2-Formylaminothiophene-3-carboxamide **13**: Pale brown solid. Mp 193 °C (dec). IR (KBr): 1648 (C=O), 1673 (C=O), 3262, 3339, 3446 (NH_2) cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ 6.98 (d, 1H, $J = 5$ Hz), 7.39 (d, 1H, $J = 5$ Hz), 7.49 (br s, 1H), 7.87 (br s, 1H), 8.51 (s, 1H), 12.03 (br s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 116.0 (C), 116.3 (CH), 123.1 (CH), 143.7 (C), 159.2 (CH), 166.3 (C).

4-Chlorothieno[2,3-*d*]pyrimidine **14**: Pale brown solid. Mp 85 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 7.57 (d, 1H, $J = 6$ Hz), 8.10 (d, 1H, $J = 6$ Hz), 8.92 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 119.6 (CH), 129.0 (C), 130.7 (CH), 152.8 (CH), 153.9 (C), 168.4 (C).