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A facile and practical one-pot synthesis of multisubstituted 2-aminothiophenes via imidazole-catalyzed Gewald reaction

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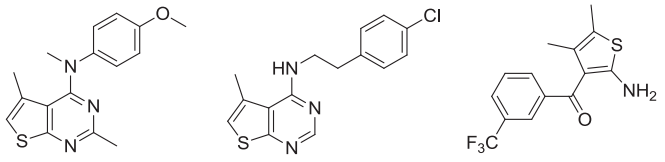
ABSTRACT

A simple and efficient procedure was developed for the synthesis of multisubstituted 2-aminothiophene derivatives. In the presence of catalytic amount of imidazole, ketones or aldehydes, dicyanomethane and elemental sulfur were converted into the corresponding 2-aminothiophene derivatives in moderate to high yields in DMF at 60 °C.

1. Introduction

Multisubstituted 2-aminothiophenes are privileged structures, which attracted considerable attention in the designing of biologically active molecules.[1] Moreover, they were found to have various biological applications, such as **1**,[1i] a potent apoptosis inducer; **2**,[1j] a potential anti-inflammatory and anti-osteoporosis agent; **3**,[1k] an agonist of allosteric enhancers (AE) at the adenosine A_1 receptor (A1AR) (Fig. 1). The prevalence of 2-aminothiophenes substituted compounds has resulted in a continuous demand for the development of general and flexible synthetic methods for this structural moiety.

The most popular approach to multisubstituted 2-aminothiophenes was Gewald reaction, which involves the multicomponents condensation of ketones or aldehydes, cyanoacetate, and elemental sulfur. Usually, the Gewald reaction was mediated by excess amount of base, such as morpholine, diethylamine, triethylamine, KF–alumina, etc.[2] Many modifications of this reaction have been developed recently, including using solid support,[3] microwave irradiation combined with insoluble polymer support[4] or soluble polymer support,[5] Lewis acid as catalyst,[1a] ionic liquid,[6] L-proline,[7] etc. In the course of our current research, we developed a facile and practical method to conduct one-pot Gewald reaction using catalytic amount of imidazole, which could give the desired products in moderate to high yield.



1 2 3

Fig. 1. Biologically important multisubstituted 2-aminothiophenes derivatives.

2. Results and discussion

On the basis of our previous results,[7] an effective catalytic base needs to be identified first. Therefore, the model reactions were conducted using butyraldehyde (**4**), dicyanomethane, and elemental sulfur in DMF under nitrogen atmosphere at 60 °C in the presence of various catalytic amount of bases. The screening results of the reaction were summarized in Table 1. Classical Gewald reaction bases, such as morpholine and diethylamine[2] were used to mediate the reaction, however, giving low yields (entries 1 and 2). The reaction also gave trace amount of desired product in the presence of triethyl phosphate[8] (entry 4). Several additional bases containing nitrogen atoms, such as isoquoline,[8] *N*-methylimidazole,[8] were tested to catalyze the multi-component condensation. The results showed that the yields were not significantly improved even prolonged the reaction time and increased the amount of catalyst (entries 3 and 5–9). By using L-/D-proline[7] and a prolonged reaction time up to 20 h, it could have a higher yield of

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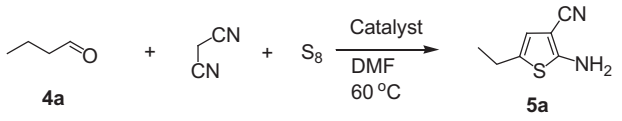
Table 1
Optimization of reaction conditions in the presence of catalytic amount of base



Entry	Catalyst	mol %	Time (h)	Yield[a] (%)
1	Morpholine	10	11	49
2	Diethylamine	10	10	43
3	*N*-Methylimidazole	10	12	48
4	Triethyl phosphite	10	12	Trace
5	*N*,*N*-Dimethylglycine	10	11	57
6	Isoquinoline	10	13	49
7	*N*,*N*-Dimethylglycine	20	18	35
8	*N*-Methylimidazole	20	12	59
9	Isoquinoline	20	22	52
10	D-Proline	10	10	67
11	L-Proline	10	20	74
12	L-Proline	10	10	64
13	Imidazole	10	10	75
14	Imidazole	5	11	52
15	Imidazole	20	11	51

[a] Isolated yield.

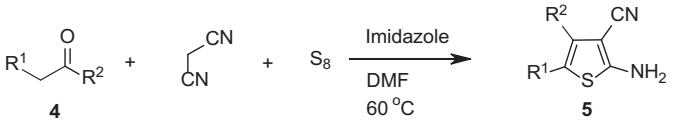
74% and 67%, respectively. However, if the reaction time was reduced to 10 h using L-proline, we only gained 64% yield (entries 10–12). When this reaction was conducted with 10 mol % imidazole, the yield could raise up to 75% in a shorter time (entry 13). We also found that the reaction gave lower yields when 5 mol % and 20 mol % of imidazole were used (entries 14 and 15). Therefore, we chose the optimized reaction condition of 10 mol % imidazole (entry 13) in the next step to investigate the scopes and the limitations of the imidazole-catalyzed Gewald reaction.

As shown in Table 2, the imidazole-catalyzed Gewald reactions proceeded smoothly with a wide range of ketones and aldehydes. Acetone **4k** known as its low boiling point together with other two unstable aldehydes, **4b** and **4c**, were challenged using our optimized reaction condition. These three compounds could give their corresponding products with moderate yield own to their instability (entries 2, 3, and 11). It can be seen that if the aldehyde bearing electron donating group at the β-position, the yield could be significantly increased as high as 88% (entries 5 and 6). We also found that along with the shorter carbon chain of aldehyde, our one-pot Gewald reaction could give a higher yield in a shorter reaction time (entries 1, 7, and 8). Next, some chain aliphatic ketones, which were difficult to produce 2-aminothiophenes in normal one-pot Gewald reaction, were also proceeded well under the optimized condition (entries 9–12). It was worth to notice that the asymmetric ketones of one-pot Gewald reaction showed some regioselectivity with the ratio of **5j**/**5j′** up to 14:1 (entry 10). Furthermore, some challenging aromatic ketones were also investigated (entries 13–18) especially with electron withdraw groups appearing on the benzene ring. Although these ketones could also proceed under the imidazole-catalyzed reaction condition to give the corresponding 2-aminothiophenes, the results showed that these electron withdraw groups had side-effects on the yield. In the cases of **5p** and **5q**, the yields were significantly lower than those of **5o** and **5r**. This significant difference could be caused by the strong electronegativity of fluorine atom.

3. Conclusions

In summary, we described a facile and practical method for the synthesis of multisubstituted 2-aminothiophenes in moderate to good yields through the reaction of aldehydes, or ketones with dicyanomethane and elemental sulfur in DMF in the presence of catalytic amount of imidazole.

Table 2
Synthesis of multisubstituted 2-aminothiophenes in the presence of imidazole via Gewald reaction[a]



Entry	4	R^1	R^2	5	Time (h)	Yield[b] (%)
1	**4a**	Et	H	**5a**	10	75
2	**4b**	Me	H	**5b**	12	37[c]
3	**4c**	C_6H_5	H	**5c**	18	38
4	**4d**	$C_6H_5CH_2$	H	**5d**	12	55
5	**4e**	*i*-Pr	H	**5e**	10	66
6	**4f**	*t*-Bu	H	**5f**	10	88
7	**4g**	*n*-C_7H_{15}	H	**5g**	15	41
8	**4h**	*n*-Bu	H	**5h**	11	56
9	**4i**	Et	Me	**5i**	12	56[d]
		H	Pr	**5i′**		
10	**4j**	Me	Me	**5j**	12	45[d]
		H	Et	**5j′**		
11	**4k**	H	Me	**5k**	12	39
12	**4l**	Me	Et	**5l**	11	57
13	**4m**	H	C_6H_5	**5m**	18	80[e]
14	**4n**	H	4-MeC_6H_4	**5n**	15	42[e]
15	**4o**	H	4-BrC_6H_4	**5o**	14	77[e]
16	**4p**	H	2-FC_6H_4	**5p**	13	27[e]
17	**4q**	H	4-Cl-3-FC_6H_3	**5q**	17	37[e]
18	**4r**	H	3,4-$Cl_2C_6H_3$	**5r**	17	46[e]

[a] Carbonyl compounds **4a**–**r** (3.0 mmol), dicyanomethane (3.3 mmol), sulfur (4.5 mmol), and imidazole (0.3 mmol) in 3 mL DMF at 60 °C under nitrogen.
[b] Isolated yield unless indicated otherwise.
[c] Actual reaction temperature at 50 °C.
[d] Ratio (**5i**/**5i′**=3.4:1) and (**5j**/**5j′**=14:1) determined by ^{1}H NMR.
[e] % conversion by SiO_2 gel.

4. Experimental

4.1. General information

Solvents and reagents were obtained from commercial sources and without purification. Column chromatography was carried out on silica gel (300–400 μm). Melting points were determined using a digital melting-point apparatus WRS-1B and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard. The ^{19}F NMR was measured with external CF_3CO_2H as the standard. Chemical shifts of protons were reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants are reported in Hertz (Hz). Infrared spectra were recorded on a Thermo FT-IR 200 Spectrometer. HRMS (ESI) data were determined using a mircoOTOF-Q II HPLC/MS instrument (Water). Elemental analyses were determined using a elementar vario El III Elemental Analyser.

4.2. Typical procedure for the synthesis of multisubstituted 2-aminothiophenes via imidazole-catalyzed Gewald reaction

A mixture of carbonyl compounds **4a**–**r** (3.0 mmol), dicyanomethane (3.3 mmol), sulfur (4.5 mmol), and imidazole (0.3 mmol) in DMF (3.0 mL) was stirred at 60 °C under nitrogen atmosphere for 10–18 h. The crude materials were directly purified through flash chromatography to give the desired products **5a**–**r**.

*4.2.1. 2-Amino-5-ethylthiophene-3-carbonitrile (**5a**)*[9]. Yellow solid; IR (KBr) ν_{max} 3420, 3229, 2973, 2202, 1626, 1522, 1388, 821, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 4.73 (br s, 2H), 2.60 (q, J=7.2 Hz, 2H), 1.20 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 132.0, 120.2, 115.9, 86.7, 23.0, 15.2.

*4.2.2. 2-Amino-5-methylthiophene-3-carbonitrile (**5b**)*[10]. Yellow solid; IR (KBr) ν_{max} 3420, 3332, 3227, 2916, 2199, 1626, 1519, 1385, 1276, 1106, 897, 812, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 4.72 (br s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 124.4, 122.0, 115.9, 86.8, 14.8.

*4.2.3. 2-Amino-5-phenylthiophene-3-carbonitile (**5c**)*[11]. Brown solid; IR (KBr) ν_{max} 3418, 3310, 3207, 2213, 1633, 1514, 1443, 1196, 826, 747, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.33 (m, 5H), 6.93 (s, 1H), 4.76 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 133.6, 129.4, 127.0, 124.5, 122.1, 116.7, 84.3.

*4.2.4. 2-Amino-5-benzythiophene-3-carbonitrile (**5d**)*[12]. Pale brown solid; IR (KBr) ν_{max} 3418, 3410, 3207, 2213, 1633, 1514, 1508, 1443, 1196, 826, 747, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 6.40 (s, 1H), 4.63 (br s, 2H), 3.93 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 139.1, 129.0, 128.7, 128.5, 126.9, 122.3, 115.7, 87.0, 35.9.

*4.2.5. 2-Amino-5-isopropylthiophene-3-carbonitrile (**5e**)*[13]. Light yellow solid; IR (KBr) ν_{max} 3425, 3331, 3221, 2972, 2956, 2195, 1619, 1518, 1387, 1272, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 1H), 4.66 (br s, 2H), 2.92–2.89 (m, 1H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 137.9, 118.9, 115.9, 86.8, 29.6, 24.0.

*4.2.6. 2-Amino-5-(tert-butyl)thiophene-3-carbonitrile (**5f**)*[14]. White solid; IR (KBr) ν_{max} 3416, 3332, 3229, 2961, 2201, 1626, 1524, 1450, 1248, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 4.61 (br s, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 142.2, 118.4, 115.9, 34.2, 31.8.

*4.2.7. 2-Amino-5-heptylthiophene-3-carbonitrile (**5g**).* Yellow solid, mp 119 °C; IR (KBr) ν_{max} 3422, 3331, 3225, 2956, 2927, 2853, 2200, 1621, 1520, 1465, 1392, 1261, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (s, 1H), 4.51 (br s, 2H), 2.58 (t, J=8.0 Hz, 2H), 1.58–1.55 (m, 2H), 1.30–1.27 (m, 8H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 130.6, 120.9, 115.8, 87.0, 31.7, 30.9, 29.6, 28.9, 28.9, 22.5, 14.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{19}N_2S$: 223.1269; found: 223.1270. Anal. Calcd for $C_{12}H_{18}N_2S$: C, 64.82; H, 8.16; N, 12.60. Found: C, 64.97; H, 8.09; N, 12.40.

*4.2.8. 2-Amino-5-butylthiophene-3-carbonitrile (**5h**).* Yellow solid, mp 91–93 °C; IR (KBr) ν_{max} 3419, 3333, 3225, 2964, 2928, 1410, 2201, 1625, 1518, 1463, 1390, 813, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 4.20 (br s, 2H), 2.59 (t, J=7.6 Hz, 2H), 1.60–1.52 (m, 2H), 1.41–1.32 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 130.8, 121.0, 115.7, 87.3, 33.0, 29.3, 21.9, 13.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_9H_{13}N_2S$: 181.0799; found: 181.0796. Anal. Calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54. Found: C, 60.24; H, 6.23; N, 15.39.

*4.2.9. 2-Amino-5-ethyl-methylthiophene-3-carbonitrile (**5i**) and 2-amino-4-propylthiophene-3-carbonitrile (**5i′**), (**5i**/**5i′**=3.4:1)*[15]. Compound (**5i**) ^1H NMR (400 MHz, $CDCl_3$) δ 4.81 (br s, 2H), 2.54 (q, J=6.4 Hz, 2H), 2.0 (s, 3H), 1.14 (t, J=6.8 Hz, 3H); compound (**5i′**) ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1H), 4.80 (br s, 2H), 2.50–2.46 (m, 2H), 1.64–1.61 (m, 2H), 0.94 (t, J=7.2 Hz, 3H).

*4.2.10. 2-Amino-4,5-dimethylthiophene-3-carbonitrile (**5j**)*[16]. Brown solid; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (br s, 2H), 2.16 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 129.6, 117.2, 115.9, 90.6, 12.7, 12.3.

*4.2.11. 2-Amino-4-methylthiophene-2-carbonitrile (**5k**)*[17]. Yellow solid; IR (KBr) ν_{max} 3418, 3310, 3207, 2213, 1633, 1514, 1508, 1443, 1195, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.67 (br s, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.3, 135.7, 115.4, 105.1, 90.6, 15.3.

*4.2.12. 2-Amino-4-ethyl-5-methylthiophene-3-carbonitrile (**5l**)*[18]. Yellow solid; IR (KBr) ν_{max} 3431, 3322, 3214, 2974, 2936, 2874, 2199, 1632, 1524, 1388, 1326, 1297, 498 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.0 (br s, 2H), 2.49 (q, J=7.6 Hz, 2H), 2.18 (s, 3H), 1.16 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 136.1, 116.6, 116.0, 89.1, 20.9, 14.3, 12.1.

*4.2.13. 2-Amino-4-phenylthiophene-3-carbonitrile (**5m**)*[1d]. Yellow solid; IR (KBr) ν_{max} 3428, 3307, 3209, 3104, 2208, 1629, 1509, 1400, 1193, 943, 774, 720, 661, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.44–7.40 (m, 2H), 7.38–7.34 (m, 1H), 6.32 (s, 1H), 5.02 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 139.9, 134.2, 128.8, 128.2, 127.2, 116.2, 105.9, 88.0.

*4.2.14. 2-Amino-4-p-totylthiophene-3-carbonitrile (**5n**)*[19]. Yellow solid; IR (KBr) ν_{max} 3440, 3334, 3213, 3104, 2206, 1623, 1512, 1414, 1187, 820, 738, 497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J=8.0 Hz, 2H), 7.23 (d, J=8.4 Hz, 2H), 6.31 (s, 1H), 4.85 (br s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 140.0, 138.1, 131.4, 129.4, 127.0, 116.0, 105.3, 88.4, 21.2.

*4.2.15. 2-Amino-4-(4-bromophenyl)thiophene-3-carbonitrile (**5o**)*[1d]. Yellow solid; IR (KBr) ν_{max} 3329, 3206, 2219, 1648, 1538, 1512, 1406, 1383, 1070, 1010, 817, 732, 691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J=8.0 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 7.29 (s, 2H), 6.56 (s, 1H), 4.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 137.5, 134.0, 132.0, 129.3, 121.5, 116.9, 106.1, 83.2.

*4.2.16. 2-Amino-4-(3-fluorophenyl)thiophene-3-carbonitrile (**5p**).* Pale white solid, mp 108–110 °C; IR (KBr) ν_{max} 3418, 3310, 3207, 2215, 1634, 1544, 1508, 1443, 1196, 826, 747, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.39 (m, 2H), 7.29–7.28 (m, 1H), 7.08–7.04 (m, 1H), 6.39 (s, 1H), 5.02 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 163.8, 161.4, 137.3, 137.1, 137.0, 131.1, 131.0, 123.4, 116.9, 115.1, 114.9, 113.9, 106.6, 83.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ −112.7 to −112.6 (m); HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{11}H_6FN_2S$: 217.0236; found: 217.0239. Anal. Calcd for $C_{11}H_7FN_2S$: C, 60.54; H, 3.23; N, 12.84. Found: C, 60.79; H, 3.18; N, 12.67.

*4.2.17. 2-Amino-4-(3-chloro-4-fluorophenyl)thiophene-3-carbonitrile (**5q**).* Light yellow solid, mp 149 °C; IR (KBr) ν_{max} 3418, 3310, 3207, 2213, 1633, 1544, 1508, 1443, 1196, 826, 747, 685 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.71–7.70 (m, 1H), 7.55–7.53 (t, J=8.8 Hz, 1H), 7.33 (s, 2H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 166.9, 158.4, 156.0, 136.1, 132.6, 129.2, 128.0, 127.9, 120.3, 120.1, 117.7, 117.4, 116.8, 106.6, 83.2; ^{19}F NMR (376 MHz, DMSO-d_6) δ −117.3 (s); HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{11}H_5ClFN_2S$: 250.9846; found: 250.9850. Anal. Calcd for $C_{11}H_6ClFN_2S$: C, 52.28; H, 2.39; N, 11.09. Found: C, 52.56; H, 2.66; N, 10.79.

*4.2.18. 2-Amino-4-(3,4-dichlorophenyl)thiophene-3-carbonitrile (**5r**).* Pale white solid, mp 190 °C; IR (KBr) ν_{max} 3418, 3310, 3207, 2213, 1633, 1546, 1508, 1445, 1195, 826, 747, 685 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J=2.0 Hz, 1H), 7.68 (d, J=8.4 Hz, 1H), 7.53 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.35 (s, 2H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 135.9, 135.3, 131.8, 131.2, 130.8, 128.9, 127.4, 116.8, 107.2, 82.9; HRMS (ESI): m/z $[M-H]^-$ calcd for

$C_{11}H_5Cl_2FN_2S$: 266.9551; found: 266.9555. Anal. Calcd for $C_{11}H_6Cl_2N_2S$: C, 49.09; H, 2.25; N, 10.41. Found: C, 49.56; H, 2.45; N, 10.26.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.061.

References and notes

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