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CONVENIENT SYNTHESIS OF 2-AMINOTHIOPHENE DERIVATIVES BY ACCELERATION OF GEWALD REACTION UNDER ULTRASONIC AQUEOUS CONDITIONS

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Under ultrasound irradiation and in the presence of H_2O/Et_2NH, ethyl cyanoacetate or malononitrile can combine with α-methylene carbonyl compounds and elemental sulfur to efficiently yield 2-aminothiophene derivatives within a few minutes. Products are easily obtained by simple filtration because of their spontaneous precipitation in the reaction mixtures.

Keywords: 2-Aminothiophenes; aqueous conditions; Gewald reaction; ultrasound irradiation

In the past decade, several books,[1] reviews,[2] and papers[3] have been published that emphasize the extensive applications of ultrasonic irradiation in various types of organic transformations. Consequently, many protocols have been developed to carry out chemical reactions in shorter time periods and especially under more environmentally friendly conditions.[4] In another green chemistry front, multicomponent reactions (MCRs)[5] have increasingly gained popularity in synthetic organic chemistry[6] in recent years because they offer one-pot combinations of more than two reactants in one step, allowing direct access to complex target molecules. In this context, the one-pot cyclocondensation of ketones or aldehydes and β-substituted acetonitrile derivatives with elemental sulfur, known as the Gewald reaction,[7] has been one of the most well-studied MCRs in recent years. The reaction affords formation of 2-aminothiophenes with diverse pharmaceutical,[8] agrochemical,[9] and dye[10] properties. In addition, there are several natural products[11] and biologically active compounds[12] in which the 2-aminothiophene moiety serves as the basic structural framework. To extend the scope of the reaction, many alterations have been made to the original Gewald's base-catalyzed, two-component combination of α-mercapto ketones with cyanoacetate[13] by varying the components[14] and the conditions.[15] The usual long reaction time periods required in most of the published procedures

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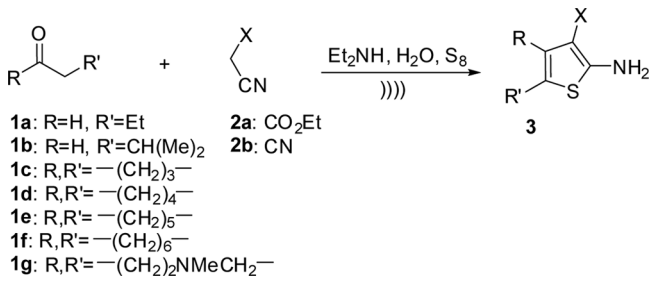


Scheme 1. Ultrasound-mediated Gewald reactions in water.

are dramatically decreased by the use of microwave irradiation in combination with the use of additional reagents and catalysts.[16] In the present work, ultrasound irradiation is employed to conduct various Gewald reactions under inexpensive and environmentally friendly H_2O/Et_2NH conditions (Scheme 1). The reaction times have been considerably decreased to a few minutes and, because of the high polarity of the medium, products precipitate spontaneously, which allows their solvent-free separation from the reaction mixtures.

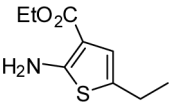
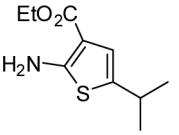
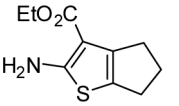
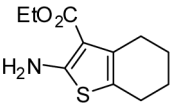
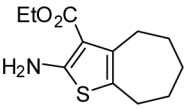
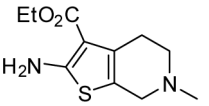
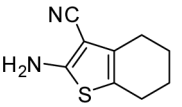
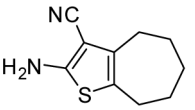
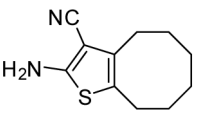
First, an equimolar mixture of 1-butanal **1a**, ethyl cyanoacetate **2a**, and sulfur was sonicated under various sets of conditions. The best results were obtained in the presence of H_2O/Et_2NH, leading to sole formation of ethyl 2-amino-5-ethylthiophene-3-carboxylate **3aa** within 5 min (Table 1, entry 1). The solid product precipitated by itself and was easily separated by simple filtration. A possible simultaneous thermal activation was excluded by conducting a temperature-controlled experiment. As a result, when a water bath was used to maintain the reaction temperature at $25 \pm 1\,^{\circ}C$, a similar yield was obtained for **3aa** after the same time period. Alternatively, in the absence of irradiation, the same mixture gave only low quantities of **3aa** after several hours, illustrating the crucial role of the sonication in the reaction. These observations suggest that the ultrasonic irradiation can significantly assist the reaction, presumably by providing the required energy of the transition state, as previously proposed by others.[17]

Reaction of 3-methylbutanal **1b** with **2a** proceeded equally well, leading to formation of **3ba** after 5 min of sonication (entry 2). Under the same conditions, cyclic ketones also gave their respective products in good yields (entries 3–6). The generality of the procedure was further shown by subjecting malononitrile to reaction with cyclic ketones, giving **3db**, **3eb**, and **3fb** in excellent yields (entries 7–9).

Based on these observations, a mechanistic pathway as depicted in Scheme 2 can be proposed in which an α-β-unsaturated nitrile intermediate is formed via a Knoevenagel condensation.[8a,18] This intermediate further adds to S_8 to form the thiophene structure after a ring-closure process, followed by an aromatization rearrangement.

In summary, we have furnished a rapid and efficient method for the preparation of substituted 2-aminothiophenes via condensation of carbonyl compounds with elemental sulfur and ethyl cyanoacetate or malononitrile under ultrasonic irradiation. The H_2O/Et_2NH medium is inexpensive, no extra additive or catalyst is required, and the conditions are environmentally safe and green. We can reach

Table 1. Ultrasound-promoted Gewald reactions

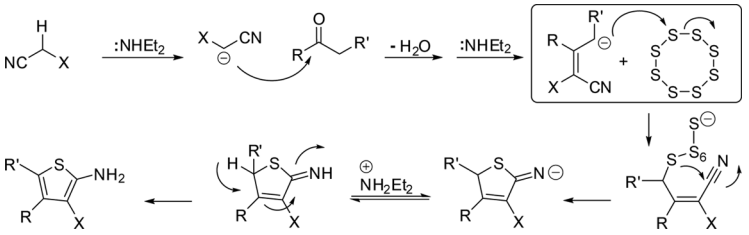
Entry	Substrate	Product	Time (Min.)	Yield (%)[a]
1	**1a** + **2a**	 **3aa**	5	91
2	**1b** + **2a**	 **3ba**	5	89
3	**1c** + **2a**	 **3ca**	5	96
4	**1d** + **2a**	 **3da**	5	97
5	**1e** + **2a**	 **3ea**	7	88
6	**1 g** + **2a**	 **3ga**	3	87
7	**1d** + **2b**	 **3db**	5	96
8	**1e** + **2b**	 **3eb**	8	90
9	**1f** + **2b**	 **3fb**	8	87

[a]Isolated yields.

a better conclusion by comparing the performance of the present work with some other reports available in the literature as illustrated in Table 2.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC) and gas chromatography (GC). Fourier transform–infrared (FT-IR) spectra were recorded using



Scheme 2. The proposed mechanism.

KBr disks on a Bruker Vector-22 IR spectrometer, and absorptions are reported as wave numbers (cm^{-1}). NMR spectra were obtained on a FT-NMR Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz as $CDCl_3$ solutions, and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analysis was performed for compound **3ba** using a Thermo Finnigan Flash EA 1112 instrument. Aldehydes were purified using standard procedures prior to use. All other chemicals and reagents were purchased from commercial sources and were used without further purification. Sonication was performed using a Sartorius Ultrasonic homogenizer Labsonic P 230-V/50-Hz instrument with a frequency of 24 KHz and nominal power of 460 W/cm^2. In all reactions, the tip of the sonotrode was located in the same position just under the liquid surface in order to obtain optimal sonication and reproducible results.

Typical Procedure for the Synthesis of 3aa

A mixture of **1a** (360 mg, 5 mmol), **2a** (565 mg, 5 mmol), and sulfur (160 mg, 5 mmol) in H_2O (1 mL) and Et_2NH (0.3 mL) was sonicated in a 10-mL test tube for an appropriate length of time (as indicated in Table 1) until TLC showed complete disappearance of the starting materials. In temperature-controlled experiments, reactions were performed in a water bath at $25 \pm 1\,^{\circ}C$. The product precipitated upon completion of the reaction. The pure product was obtained by recrystallization of the precipitates using an EtOAc/hexane mixture. Products were identified based on their melting points and spectral characteristics.

Table 2. Ultrasound-mediated Gewald reaction in comparison with some other methods

Energy type	Solvent requirement	Reference
Ultrasonic	H_2O	Present work
Thermal	MeOH, Et_2O	Gütschow et al.[14b]
Thermal	EDDA,[a] Et_2O	Hu et al.[15a]
Microwave	Toluene, MeOH, CH_2Cl_2, DMF	Hoener et al.[16b]
Microwave	EtOH, CH_2Cl_2	Sridhar et al.[16c]
Electrochemical	MeCN	Feroci et al.[15d]

[a]Ethylenediammonium diacetate.

Data

Ethyl 2-Amino-5-ethylthiophene-3-carboxylate (3aa). Mp 73 °C (reported mp. 73 °C)[16c]; ^{1}H NMR ($CDCl_3$) δ 6.64 (s, 1H), 5.84 (s, 2H), 4.25 (q, 2H, $J = 7.1$ Hz), 2.60 (q, 2H, $J = 7.5$ Hz), 1.33 (t, 3H, $J = 7.1$ Hz), 1.22 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 165.5, 161.2, 128.5, 120.6, 106.2, 59.6, 23.0, 15.4, 14.5; IR (KBr) 3407, 3305, 1660, 1254 cm^{-1}; MS m/z (%) 200 (M^+, 25), 199 (100), 184 (80), 138 (86).

Ethyl 2-Amino-5-isopropylthiophene-3-carboxylate (3ba). Mp 68 °C;^{1}H NMR ($CDCl_3$) δ 6.63 (s, 1H), 5.80 (s, 2H), 4.25 (q, 2H, $J = 7.1$ Hz), 2.95–2.86 (m, 1H), 1.34 (t, 3H, $J = 7.1$ Hz), 1.24 (d, 6H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 165.5, 161.0, 134.2, 119.1, 106.0, 59.6, 29.5, 24.1, 14.6; IR (KBr) 3441, 3334, 1677, 1590 cm^{-1}; MS m/z (%) 213 (M^+, 35), 198 (100), 152 (40). Calcd. for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09. Found: C, 56.44; H, 7.12.

Ethyl 2-Amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (3ca). Mp 90 °C (reported mp. 89–90 °C);[15c] ^{1}H NMR ($CDCl_3$) δ 5.83 (s, 2H), 4.25 (q, 2H, $J = 7.1$ Hz), 2.85–2.80 (m, 2H), 2.74–2.69 (m, 2H), 2.36–2.26 (m, 2H), 1.33 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.2, 165.8, 142.7, 121.4, 103.0, 59.4, 30.8, 28.9, 27.2, 14.4; IR (KBr) 3414, 3294, 1624, 1287 cm^{-1}; MS m/z (%) 211 (M^+, 100), 165 (70), 137 (15).

Ethyl 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3da). Mp 113 °C (reported mp. 115 °C)[15c]; ^{1}H NMR ($CDCl_3$) δ 6.01 (s, 2H), 4.25 (q, 2H, $J = 7.2$ Hz), 2.71–2.69 (m, 2H), 2.48–2.46 (m, 2H), 1.75–1.73 (m, 4H), 1.33 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 161.9, 132.4, 117.5, 105.5, 59.4, 27.0, 24.5, 23.3, 22.9, 14.5; IR (KBr) 3405, 3299, 1647, 1274 cm^{-1}; MS m/z (%) 225 (M^+, 100), 223 (90), 179 (51), 151 (24).

Ethyl 2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carboxylate (3ea). Mp 87 °C (reported mp 89 °C)[16c]; ^{1}H NMR ($CDCl_3$) δ 5.74 (s, 2H), 4.28 (q, 2H, $J = 7.2$ Hz), 3.00–2.96 (m, 2H), 2.60–2.56 (m, 2H), 1.82–1.78 (m, 2H), 1.68–1.62 (m, 4H), 1.35 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.0, 159.7, 137.9, 121.4, 107.6, 59.6, 32.2, 28.7, 28.6, 27.8, 27.0, 14.5; IR (KBr) 3398, 3301, 1651, 1277 cm^{-1}; MS m/z (%) 239 (M^+, 9), 193 (8), 83 (100).

Ethyl 2-Amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (3ga).[8c] Mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 6.18 (s, 2H), 4.22 (q, 2H, $J = 7$ Hz), 3.37 (s, 2H), 2.82 (m, 2H), 2.67 (m, 2H), 2.43 (s, 3H), 1.30 (t, 3H, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$) δ 165.9, 162.4, 130.5, 113.9, 104.9, 59.5, 53.1, 52.3, 45.2, 27.1, 14.4; IR (KBr) 3394, 3262, 1667 cm^{-1}.

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (3db). Mp 145 °C (reported mp. 146–147 °C)[15c]; ^{1}H NMR ($CDCl_3$) δ 4.7**1** (s, 2H), 2.48–2.46 (m, 4H), 1.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 160.1, 132.3, 120.6, 115.6, 88.5, 24.5, 24.1, 23.4, 22.1; IR (KBr) 3445, 3328, 2196, 1521 cm^{-1}; MS m/z (%) 178 (M^+, 85), 150(100).

2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[b]thiophene-3-carbonitrile (3eb). Mp 125 °C (reported mp. 126 °C)[16c]; ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 2H),

2.65–2.57 (m, 4H), 1.83–1.79 (m, 2H), 1.67–1.63(m, 4H); ^{13}C NMR ($CDCl_3$) δ 157.7, 136.9, 123.9, 115.9, 92.0, 31.9, 29.4, 29.2, 28.1, 27.2; IR (KBr) 3443, 3310, 2203 cm^{-1}; MS m/z (%) 192 (M^+, 100), 164 (35), 138 (25).

2-Amino-4,5,6,7,8,9-hexahydrocycloocta[b]thiophene-3-carbonitrile (3fb). Mp 107 °C (reported mp. 110 °C)[16c]; ^{1}H NMR ($CDCl_3$) δ 4.69 (s, 2H), 2.64–2.58 (m, 4H), 1.64–1.59 (m, 4H), 1.41–1.26 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 159.2, 135.1, 122.7, 115.8, 90.0, 31.5, 29.8, 26.1, 26.0, 25.8, 25.5; IR (KBr) 3428, 3334, 2194, 1619 cm^{-1}; MS m/z (%) 206 (M^+, 100), 178 (85), 163 (25).

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