A facile four-component Gewald reaction under organocatalyzed aqueous conditions

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Abstract
In the presence of water and triethylamine, a four-component process involving ethyl cyanoacetate, an α-methylene carbonyl compound, a primary or a secondary amine, and elemental sulfur leads to efficient room-temperature formation of 2-amino-3-carboxamide derivatives of thiophene in short time periods. The products, which precipitate from the reaction mixtures, are easily obtained by simple filtration and recrystallization from ethyl acetate/hexanes.

Keywords: Gewald reaction, four-component reaction, aqueous conditions, 2-aminothiophenes, organocatalysis

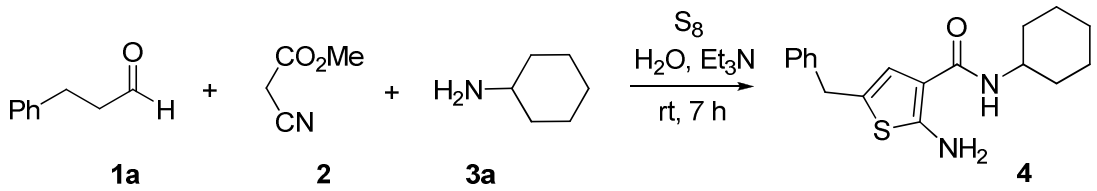
Introduction

A multicomponent reaction (MCR) is defined as a process that causes combination of three or more reactants to form a product, exclusively or in adequate yield, in a one-pot operation.[1,2] In an ideal case the process would take place highly selectively and a single product would form which retains all or the majority of the atoms of the reactants. These features have overwhelmingly led to numerous applications of MCRs in synthetic organic chemistry in recent years because MCRs allow direct access to complex target molecules and chemical libraries in a much more efficient and economical fashion.[3,4]

One of the best studied MCRs in recent decades has been the one-pot cyclocondensation of α-methylene carbonyl compounds and β-substituted acetonitriles with elemental sulfur,[5,6] a process which is named after its discoverer: the Gewald reaction.[7] The 2-aminothiophene products of the reaction exhibit agrochemical,[8] pharmaceutical,[9] mesogenic,[10] and dye[11] properties. In several cases they are also the key substructure of organic structures[12-14] and biologically active compounds.[15,16] The original two-component Gewald reaction between α-

mercaptoketones and cyanoacetate proceeds under basic catalysis.[7] The many modifications reported so far extend the scope of this reaction by altering the components[17-19] and the conditions.[20-23]

Another interesting feature of the Gewald reaction is the use of the 2-aminothiophene products in other organic transformations.[24,25] The growing use of MCRs in synthesis led us to examine the possibility of employing more than three components in the reaction so that we can access derivatized Gewald products in a one-pot operation. In the framework of our investigations on the development of one-pot synthetic procedures,[26-28] we herein report a simple method for conducting a four-component Gewald reaction under inexpensive and benign aqueous triethylamine conditions. As a result of this method, reactions proceed within relatively short time periods and 2-aminothiophene-*N*-alkyl products precipitate spontaneously, perhaps because of high polarity of the medium, allowing their solvent-free separation from the reaction mixtures. The overall process is exemplified in Scheme 1 for the reaction of 3-phenylpropanal (**1a**) with methyl cyanoacetate (**2**), cyclohexanamine (**3a**), and elemental sulfur. It is noteworthy that a literature survey shows little precedent for a four-component strategy in the Gewald reaction.[29]



Scheme 1. Four-component synthesis of **4.**

Results and Discussion

We first optimized the conditions by studying the reaction of **1a** with **2**, **3a**, and sulfur at room temperature (Table 1). Among various secondary or tertiary amines used in the reaction (entries 1-5), Et_3N caused a higher conversion of the reactants into **4**. In addition, the use of Et_3N led to precipitation of the product at the end of the process (entry 1). Conversely, hexyl-1-amine gave negligible quantities of the product (entry 6). In the absence of the amine (entry 7) or water (entry 8) no formation of product was noticed, even after a longer time period, illustrating the promoting effect of both additives.

From a mechanistic point of view, when a reaction rate is enhanced under aqueous conditions, the acceleration is attributed to either the repulsive forces arising from hydrophobicity of the reactants[30] or to activation of electron donating functional groups through H-bonding with water molecules.[31] To study the role of these effects in the present work, we next altered the composition of the aqueous medium to investigate the effect of different additives on the progress of the reaction (entries 9-14). In these cases, an early work-up procedure was used (after 0.5 h) so that a better comparison of the results could be concluded. Therefore, under

optimum conditions (H_2O/Et_3N), 65% of **4** was formed after 0.5 h (entry 9). When solutions of LiCl (entry 10) or NaCl (entry 11) were used, yields increased, suggesting that hydrophobic forces are responsible for the rate enhancement in this Gewald reaction. This was further confirmed by observing a greater rate increase at a higher concentration of NaCl (entry 12). In contrast, a descending pattern was noticed for a similar reaction conducted in the presence of guanidinium chloride (GnCl) (entry 13) or $LiClO_4$ (entry 14). This excluded intervention of hydrogen-bonds as being a driving force for the reaction. Thus, one can conclude that hydrophobic behavior of the reactants in water provides the driving force of the reaction. On this basis, it can also be justified that why Et_3N, which has the lowest solubility among the amines examined, causes a greater rate increase under the conditions, governed by hydrophobic effects.

Table 1. Optimization of the Gewald reaction for the synthesis of **4**

Entry	Medium	Amine	Time (h)	Yield (%)[a]
1	H_2O	Et_3N	1	95
2	H_2O	DBU	1	88
3	H_2O	DABCO	1	81
4	H_2O	morpholine	1	72
5	H_2O	Et_2NH	1	40
6	H_2O	hexyl-1-amine	1	7
7	-	Et_3N	6	0
8	H_2O	-	6	0
9	H_2O	Et_3N	0.5	65
10	LiCl (aq, 1.5 M)	Et_3N	0.5	68
11	NaCl (aq, 1.5 M)	Et_3N	0.5	70
12	NaCl (aq, 3.0 M)	Et_3N	0.5	75
13	GnCl (aq, 1.5 M)	Et_3N	0.5	30
14	$LiClO_4$ (aq, 1.5 M)	Et_3N	0.5	33

[a] isolated yields

Next, the generality of the method was investigated (Table 2). The optimum conditions under which **4** was formed in 95% yield and within 1 h (entry 1) were applied to the reactions of aldehydes **1a**-**b** with various amines, **2**, and sulfur. Thus, 92-97% of products **5**, **6**, and **7** were formed after 1-2 h (entries 2-4). Then, the conditions were used for similar reactions of cyclohexanone **1c** (entries 5-7). As a result, good to high yields of the respective products were obtained. For these entries, reaction times were relatively longer presumably due to lower reactivity of the starting ketone. Because of our interest in developing the chemistry of the

thiopyran-4-one system,[32,33] we subjected **1d** to the reaction conditions and obtained the expected products as shown in entries 8-10.

Table 2. H_2O/Et_3N catalyzed four-component Gewald reactions

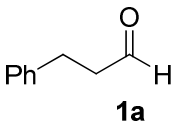
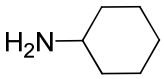
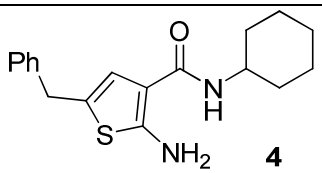
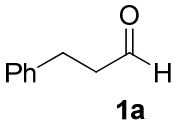
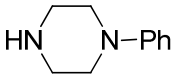
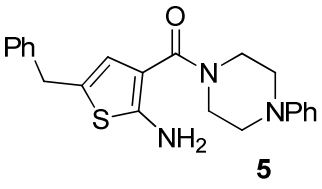
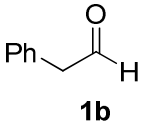
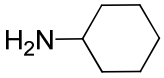
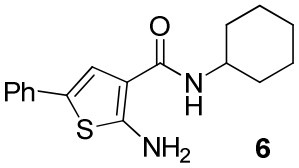
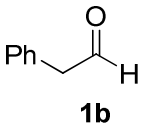
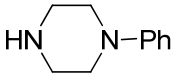
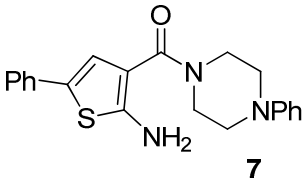
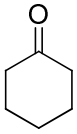
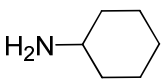
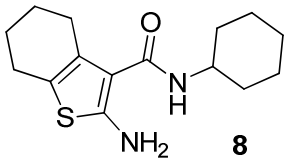
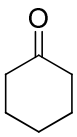
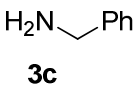
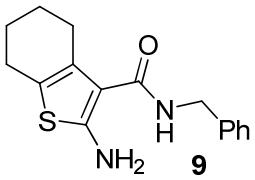
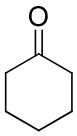
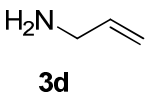
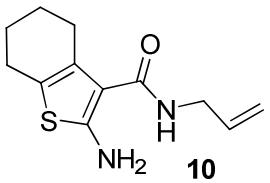
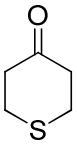
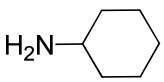
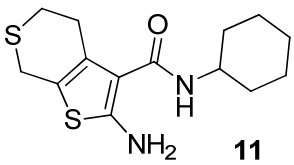
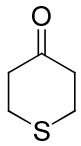
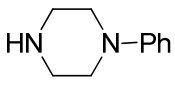
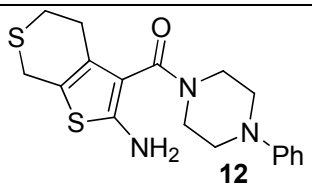
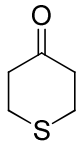
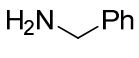
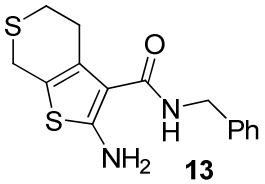
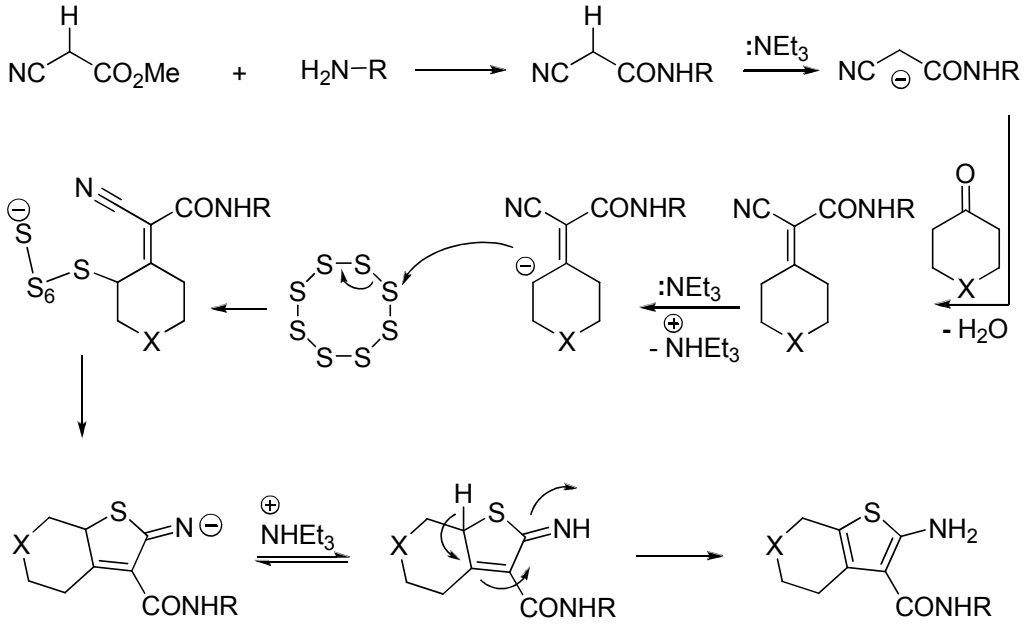
Entry	Ketone or aldehyde	Amine	Product	Time (h)	Yield[a] (%)	Mp (ºC)
1	 **1a**	 **3a**	 **4**	1	95	178-180
2	 **1a**	 **3b**	 **5**	2	92	164-166
3	 **1b**	 **3a**	 **6**	1	97	191-193
4	 **1b**	 **3b**	 **7**	2	95	195-197
5	 **1c**	 **3a**	 **8**	7	78	142-144
6	 **1c**	 **3c**	 **9**	7	81	113-115
7	 **1c**	 **3d**	 **10**	7	82	116-118
8	 **1d**	 **3a**	 **11**	5	77	131-133

Table 2. Continued

Entry	Ketone or aldehyde	Amine	Product	Time (h)	Yielda (%)	Mp (ºC)
9	 **1d**	 **3b**	 **12**	5	79	155-157
10	 **1d**	 **3c**	 **13**	5	75	130-134

[a] isolated yields.

Based on these results, a mechanism, as depicted in Figure 1, can be suggested for the process. The starting amine, which is first mixed with **2**, forms the corresponding amide. This amide then produces an α,β-unsaturated nitrile intermediate via a Knoevenagel condensation. The Knoevenagel intermediate then reacts with sulfur to produce the final thiophene skeleton, after a ring closure and an aromatization rearrangement.



Scheme 2. A suggested mechanism

Conclusions

In summary, we have reported a general and efficient protocol for the preparation of various 2-aminothiophene-3-carboxamide derivatives resulted from a four-component Gewald reaction. Thus, various ketones can combine with methyl cyanoacetate, an amine, and sulfur at room temperature in a one-pot process. Reactions occur using the H_2O/Et_3N environmentally safe medium, single products are rapidly formed in high yields, no complex operation or handling is required, and use of toxic organic solvents is avoided. These features make the present method an attractive addition to the present literature archive.

Experimental Section

General. Reactions were monitored by TLC using silica-gel coated plates and ethyl acetate/hexanes solutions as the mobile phase. Melting points are uncorrected. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) instrument 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 analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. Compound **1d** was prepared using available methods.[34] All other chemicals were purchased from commercial sources and were used after being freshly purified by standard procedures. Products **4**, **7**, **10**,[35] and **9**[16] are known. Other products were new and were characterized based on their spectral and physical data.

Typical procedure. A mixture of methyl cyanoacetate (**2**) (297 mg, 3 mmol) and cyclohexylamine (**3a**) (343 μL, 3 mmol) was stirred at room temperature for 15 minutes. To this mixture was added 3-phenylpropionaldehyde (**1a**) (400 μL, 3 mmol), sulfur (96 mg, 3 mmol), water (1.0 mL), and Et_3N (418 μL, 3.0 mmol) sequentially and stirring was continued at room temperature for another 45 minutes or until TLC showed complete disappearance of the starting materials. The product which solidified at the end of the reaction was separated by filtration and recrystallized from EtOAc/hexanes mixture. Product **4** was obtained in 95% yield (895 mg). The product was identified based on its physical and spectral characteristics.

(2-Amino-5-benzylthien-3-yl)(4-phenylpiperazin-1-yl)methanone (5). Yellow solid, mp 164-166 ºC (EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 3.23 (t, *J* 5.0 Hz, 4H), 3.83 (t, *J* 5.0 Hz, 4H), 3.98 (s, 2H), 5.37 (br s, 2H), 6.45 (s, 1H), 6.94-7.00 (m, 3H), 7.26-7.30 (m, 3H), 7.32-7.37 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.4, 45.5, 50.2, 109.8, 117.0, 121.0, 123.1, 126.4, 127.1, 128.9, 129.0, 129.1, 129.7, 140.4, 159.4, 167.7 ppm; IR (KBr) 3387, 3290, 1624, 1597

cm^{-1}; MS 377 (M^+), 258, 216, 161, 132, 91; Anal. Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14. Found: C, 70.24; H, 6.16 %.

2-Amino-*N*-cyclohexyl-5-phenylthiophene-3-carboxamide (6). Pink solid, mp 191-193 ºC (EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.24-1.28 (m, 3H) 1.43-1.46 (m, 2H), 1.67-1.69 (m, 1H), 1.77-1.81 (m, 2H), 2.03-2.06 (m, 2H), 3.90-3.93 (m, 1H), 5.69 (s, 1H), 5.72 (br s, 2H), 6.99 (s, 1H), 7.23 (t, *J* 7.5 Hz, 1H), 7.35 (t, *J* 7.5 Hz, 2H), 7.46 (d, *J* 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.0, 33.9, 48.5, 110.9, 118.5, 125.1, 126.2, 127.1, 129.3, 134.4, 159.8, 165.3 ppm; IR (KBr) 3439, 3298, 1608, 1571 cm^{-1}; MS *m/z* 300 (M^+), 201, 146, 130; Anal. Calcd for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71. Found: C, 68.14; H, 6.66 %.

2-Amino-*N*-cyclohexyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (8). Yellow solid, mp 142-144 ºC (EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.18-1.24 (m, 3H) 1.37-1.43 (m, 2H), 1.59-1.62 (m, 1H), 1.67-1.71 (m, 2H), 1.78-1.80 (m, 4H), 1.94-2.03 (m, 2H), 2.52-2.54 (m, 2H), 2.65-2.66 (m, 2H), 3.88-3.95 (m, 1H), 5.56 (d, *J* 7.0 Hz, 1H), 6.00 (br s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 23.5, 25.0, 25.2, 26.1, 27.7, 33.8, 40.0, 109.6, 119.4, 129.2, 158.8, 166.0 ppm; IR (KBr) 3298, 1585, 1650, 1564 cm^{-1}; MS *m/z* 278 (M^+), 196, 179, 151, 83; Anal. Calcd for $C_{15}H_{22}N_2OS$: C, 64.71; H, 7.96. Found: C, 64.87; H, 7.69 %.

2-Amino-*N*-cyclohexyl-5,7-dihydro-4*H*-thieno[2,3-*c*]thiopyran-3-carboxamide (11). Brown solid, mp 131-133 ºC (EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 3H), 1.40-1.47 (m, 2H), 1.62-1.66 (m, 1H), 1.70-1.75 (m, 2H), 1.97-2.00 (m, 2H), 2.89-2.91 (m, 4H), 3.65 (s, 2H), 3.90-3.96 (m, 1H), 5.51 (d, *J* 7.0 Hz, 1H), 6.00 (br s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.2, 25.7, 26.0, 26.4, 29.3, 33.7, 48.3, 111.2, 115.6, 129.7, 157.3, 165.5 ppm; IR (KBr) 3361, 3298, 1635, 1590, 1564 cm^{-1}; MS *m/z* 296 (M^+), 197, 170, 152, 41; Anal. Calcd for $C_{14}H_{20}N_2OS_2$: C, 56.72; H, 6.80. Found: C, 56.61; H, 6.73 %.

(2-Amino-5,7-dihydro-4*H*-thieno[2,3-*c*]thiopyran-3-yl)(4-phenylpiperazin-1-yl)methanone (12). White solid, mp 155-157 ºC (EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 2.68-2.78 (m, 2H), 2.79-2.87 (m, 2H), 2.88-2.92 (m, 2H), 2.93-2.95 (m, 2H), 3.21-3.23 (m, 4H), 3.67 (s, 2H), 3.84 (s, 2H), 6.93-6.96 (m, 3H), 7.25-7.31 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 34.6, 36.5, 42.5, 47.3, 50.0, 50.3, 106.5, 114.8, 117.4, 121.5, 128.0, 129.8, 151.0, 161.2, 164.7 ppm; IR (KBr) 3265, 3062, 2823, 1637, 1498, 1026 cm^{-1}; MS *m/z* 359 (M^+), 327, 278, 179, 132; Anal. Calcd for $C_{18}H_{21}N_3OS_2$: C, 60.14; H, 5.89. Found: C, 60.11; H, 5.75 %.

2-Amino-*N*-benzyl-5,7-dihydro-4*H*-thieno[2,3-*c*]thiopyran-3-carboxamide (13). Brown solid, mp 130-134 ºC (EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 2.85-2.87 (m, 2H), 2.88-2.92 (m, 2H), 3.63 (s, 2H), 4.58 (d, *J* 7.0 Hz, 2H), 5.88 (br s, 2H), 5.97 (t, *J* 7.0 Hz, 1H), 7.29-7.39 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 26.3, 29.3, 43.9, 110.4, 115.5, 127.9, 128.1, 129.2, 129.7, 139.0, 158.1, 166.4 ppm; IR (KBr) 3265, 3062, 2823, 1637, 1498, 1026 cm^{-1}; MS *m/z* 304 (M^+), 197, 170, 152, 104, 91; Anal. Calcd for $C_{15}H_{16}N_2OS_2$: C, 59.18; H, 5.30. Found: C, 59.33; H, 5.41 %.

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