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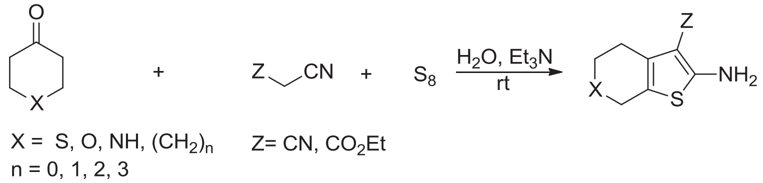
In a medium consisting of triethylamine and water, α-methylene ketones undergo room temperature Gewald reactions with elemental sulfur and ethyl cyanoacetate (or malononitrile) to yield 2-aminothiophene derivatives efficiently within short time periods. Because of the high polarity of the medium, products precipitate in the reaction mixtures spontaneously. This makes isolation of the products easy by simple filtration and avoids cumbersome chromatographic separations. Mechanistic studies suggest that the reactions proceed via a Knoevenagel condensation pathway.



Keywords: Gewald reaction; aqueous conditions; three-component reaction; thiophene; Knoevenagel condensation

1. Introduction

Although water is the most abundant chemical on our planet, its use has been neglected as a medium or a solvent in organic chemistry for many decades. This ignorance has been the result of the belief that water destroys many organic reagents and chemicals and is only safe to be used in workup procedures. This opinion was widespread until Grieco [1,2] and Breslow [3,4] demonstrated that aqueous media can cause Diels-Alder cycloadditions to proceed with extraordinary rate and selectivity enhancement. Since then, an overwhelming number of papers,[5–7] reviews,[8,9] and books [10,11] have been released discussing various synthetic reactions in water and more publications are expected to come.

Another green chemistry front that has witnessed remarkable development and found numerous applications in synthetic organic chemistry in recent decades has been multi-component reactions (MCRs).[12,13] The MCRs allow combination of more than two reactants in one-pot operations and allow direct access to complex molecules and chemical libraries.[14,15] In this regard, the

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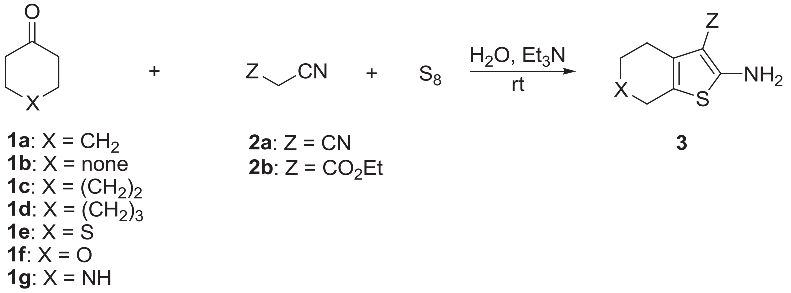
Gewald reaction has been one of the most interesting MCRs; a reaction that involves a one-pot cyclocondensation of ketones or aldehydes with β-substituted derivatives of acetonitrile and elemental sulfur.[16,17] The products of the reaction are derivatives of 2-aminothiophene that have diverse pharmaceutical,[18,19] agrochemical,[20] and dye [21] properties. Moreover, many synthetic or natural products [22] and biologically active molecules [23] are known to have the 2-aminothiophene backbone in their structures.

The original Gewald reaction is a two-component process that combines α-mercapto ketones with cyanoacetate under basic conditions.[24] The scope of the reaction is extended drastically by adopting multi-component modes [25–27] and altering the conditions.[28–31] Despite these developments, even some of newer reports still involve the use of relatively harsh conditions or require organic solvents during the reaction or workup stage. In the framework of our studies on the chemistry of heterocyclic systems [32–34] and in continuation of our previous investigations on the development of synthetic methods in aqueous media,[35,36] we would like to herein report an efficient protocol for Gewald reactions of several ketones with malononitrile derivatives and sulfur using triethylamine (Et_3N) under aqueous conditions (Scheme 1). As far as we know, this is one of the most inexpensive and environmentally friendly procedures offered so far for the Gewald reaction. The reaction times are shorter and due to high polarity of the medium, products precipitate spontaneously so that expensive and time-consuming chromatographic separations are avoided.



Scheme 1. Three-component Gewald reactions under H_2O/Et_3N conditions.

2. Results and discussion

We first optimized the conditions for the reaction of **1a** (1.0 mmol) with **2b** (1.0 mmol) and sulfur (1.0 mmol) to produce **3ab** (Table 1). Entry 1 shows that the best results are obtained when both water (0.3 mL) and Et_3N (1.0 mmol) are present in the mixture. In the absence of water, a dramatic rate decrease is observed illustrating the crucial role of the aqueous medium (Entry 2). The case gets even worst when Et_3N is omitted from the reaction mixture (Entry 3). Variation of the amounts of water (Entries 4 and 5) and the amine (Entries 6 and 7) lowers the yield of **3ab** suggesting that the optimum conditions are observed when 0.3 mL and 1.0 mmol of these two components of the medium are used, respectively. Reactions conducted in the presence of other amines (Entries 8–11) show that Et_3N is the most effective amine under our experimental conditions. The superiority of Et_3N coincides with both the basicity and the solubility of this amine in comparison with those of other amines in water.[37] Et_3N has a relatively higher basicity and remains partially undissolved in the mixture under the optimized conditions and is always available for more effective deprotonation of the starting materials. Therefore, Et_3N leads to the highest

Table 1. Optimization of the conditions for aqueous-mediated Gewald reactions.

Entry	H_2O (mL)	Amine (mmol)	Yield (%)[a,b]
1	0.3	Et_3N (1.0)	95
2	0.0	Et_3N (1.0)	30
3	0.3	Et_3N (0.0)	–
4	0.1	Et_3N (1.0)	78
5	0.5	Et_3N (1.0)	77
6	0.3	Et_3N (0.7)	47
7	0.3	Et_3N (3.0)	80
8	0.3	DABCO (1.0)	83
9	0.3	Morpholine (1.0)	75
10	0.3	Et_2NH (1.0)	47
11	0.3	$HexylNH_2$ (1.0)	9

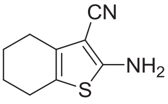
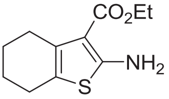
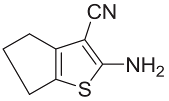
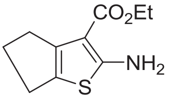
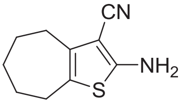
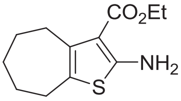
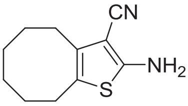
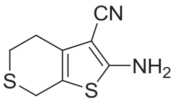
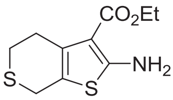
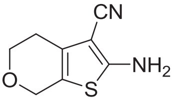
[a] Reaction times, 7 h.
[b] Isolated yield.

conversion of the reactants to **3ab**. In addition, when the amine of choice is Et_3N, spontaneous precipitation of the products is observed.

We next applied the optimum conditions to the reactions of various ketones with malononitrile derivatives and sulfur (Table 2). Cyclohexanone (Entries 1 and 2) and cyclopentanone (Entries 3 and 4) showed similar reactivities when subjected to the optimized conditions. As a result, high yields of the respective products were obtained within 6–7 h. Heavier cycloalkanones gave slightly lower yields of their products (Entries 5–7), perhaps due to their lower reactivities associated with their higher molecular weights. Due to our interests in the chemistry of thiopyran-4-one [33,35] and its other heterocyclic analogues,[38,39] we then applied the conditions to **1e** (Entries 8 and 9), **1f** (Entries 10 and 11), and **1g** (Entry 12) ketones. These ketones, especially **1g**, underwent the reactions more rapidly and gave high yields of their respective products in shorter time periods. To further demonstrate the generality of the method, we finally applied the conditions to an acyclic ketone (Entry 13) and an aliphatic aldehyde (Entry 14), where again high amounts of products **3hb** and **3ib** were obtained. In each case, formation of a single product was observed which precipitated from the reaction mixture and was separated by a simple filtration.

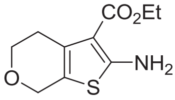
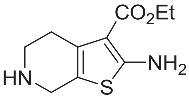
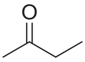
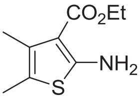
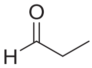
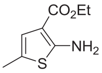
The mechanistic rationale for the efficiency of aqueous-mediated reactions is due to either hydrophobic interactions of the reactants in water [40] or to the hydrogen-bonded [41] activation of organic functional groups by H_2O molecules. Consequently, we then decided to study the mechanism of this water-mediated Gewald reaction. We designed several parallel experiments for the reaction of **1e** with **2b** and sulfur as summarized in Table 3. For meaningful conclusions, workup procedures were performed (after 2.5 h) before reactants had completely consumed. In the presence of optimum amounts of water and Et_3N only 45% of **3eb** was obtained (Entry 1). As expected, omission of water considerably decreased the yield (Entry 2). In the presence of solutions of NaCl (Entry 3) or LiCl (Entry 4), an ascending pattern in the yields was observed. This increase in the rate that is more obvious at higher concentrations of the two salts (Entries 5 and 6), is consistent with the “salt-out” [42] effect. In contrast, rates decreased when the reaction was conducted in the presence of guanidinium chloride (GnCl) (Entries 7 and 8) or $LiClO_4$ (Entries 9 and 10) solutions. These results suggest that the hydrogen-bonded association of the reactants with water does not have a major role in the catalysis of the reaction. On the other hand, these results can be rationalized by proposing an effective hydrophobic interaction of the starting organic molecules with water to force the reactants toward a Gewald reaction, as proposed by others to explain similar observations.[43,44] As a result of these observations, it can also be understood why a less soluble amine like Et_3N would behave better under the conditions governed by hydrophobic forces.

Table 2. Gewald reactions of various carbonyl compounds under the optimized conditions.

Entry	Reactants	Product	Time (h)	Yield (%)[a]
1	**1a** + **2a**	 **3aa**	6	89
2	**1a** + **2b**	 **3ab**	7	95
3	**1b** + **2a**	 **3ba**	6	90
4	**1b** + **2b**	 **3bb**	7	95
5	**1c** + **2a**	 **3ca**	7	80
6	**1c** + **2b**	 **3cb**	7	75
7	**1d** + **2a**	 **3da**	7	76
8	**1e** + **2a**	 **3ea**	4	98
9	**1e** + **2b**	 **3eb**	4	97
10	**1f** + **2a**	 **3fa**	5	77

(*Continued*)

Table 2. Continued.

Entry	Reactants	Product	Time (h)	Yield (%)[a]
11	**1f** + **2b**	 **3fb**	5	98
12	**1g** + **2b**	 **3gb**	2	94
13	 **1h** + **2b**	 **3hb**	7	82
14	 **1i** + **2b**	 **3ib**	3	86

[a] Isolated yield.

Table 3. Effect of different additives on the synthesis of **3eb** under aqueous conditions.

Entry	Additive	Yield (%)[a,b]
1	Water	45
2	–	15
3	NaCl (aq, 1.5 M)	51
4	LiCl (aq, 1.5 M)	47
5	NaCl (aq, 3.0 M)	63
6	LiCl (aq, 3.0 M)	55
7	GnCl (aq, 1.5 M)	23
8	GnCl (aq, 3.0 M)	10
9	$LiClO_4$ (aq, 1.5 M)	18
10	$LiClO_4$ (aq, 3.0 M)	5

[a] All reactions conducted in the presence of Et_3N (1 mmol).
[b] Isolated yield.

Based on these observations, a mechanism can be proposed for the process (Figure 1), where an α,β-unsaturated nitrile intermediate is formed via a Knoevenagel condensation.[45] Then, the Knoevenagel intermediate **I** adds to S_8, a ring closure process occurs, and the final aromatization rearrangement takes place to produce the thiophene skeleton. To support this mechanism, the intermediate **I** was prepared separately (for reactants **1a**,**f** and **2b**) and subjected to the same reaction conditions with S_8. The result was the formation of products **3ab** and **3fb** in comparable yields and time periods indicated in Table 2.

3. Conclusion

We have reported a general and efficient protocol for the preparation of various 2-aminothiophene derivatives by the Gewald reactions of different ketones with malononitrile derivatives and sulfur

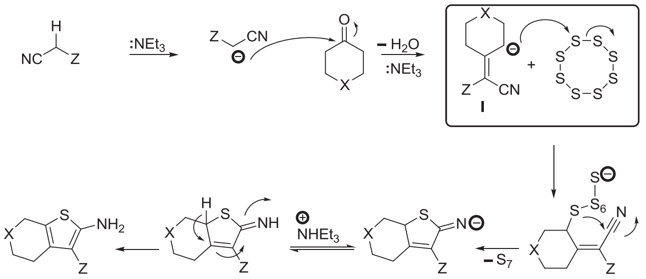


Figure 1. The proposed mechanism.

at room temperature. Reactions takes place using an environmentally friendly medium consisted of water and Et_3N. Preparation of single products in high yields within relatively short time periods, ease of operation, the absence of harmful organic solvent, and no special handling requirements makes this protocol an attractive addition to the present literature archive. This conclusion is further supported by comparison of the results of the present work with those of other recent studies. As shown in Table 4, the Et_3N/H_2O method (Entry 1) offers higher yields of the products in relatively shorter time periods under fairly inexpensive conditions and by using a one-pot operation.

4. Experimental

Reactions were monitored by TLC. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions were reported as wave numbers (cm^{-1}). NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) as $CDCl_3$ or DMSO-d_6 solutions and the chemical shifts were 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 by a Thermo Finnigan Flash EA 1112 instrument. Compound **1e** was prepared using available methods.[48] All other chemicals were purchased from commercial sources and were freshly used after being purified by standard procedures.

4.1. *Typical procedure*

A mixture of **1a** (311 µL, 3 mmol), **2a** (198 mg, 3 mmol), and sulfur (96 mg, 3 mmol) in H_2O (0.9 mL) and Et_3N (418 µL, 3.0 mmol) was stirred at room temperature for 6 h until TLC showed complete disappearance of the starting materials. The product, which precipitated at the end of the reaction, was separated by filtration. The pure product was obtained by recrystallization of

Table 4. Comparison of the present method with some other recent-related procedures.

Entry	Conditions	Time	Reference
1	Et_3N, H_2O, rt	2–7 h	This work
2	(i) NH_4OAc, AcOH, benzene, reflux; (ii) S, Et_2NH, MeOH (abs), 35–40°C	17–42 h	[46]
3	(i) $MeCO_2NH_4$, $MeCO_2H$, benzene, reflux, (ii) S_8, Et_2NH, EtOH, 50°C	>24 h	[31]
4	Imidazole, DMF, 60°C	10–17 h	[28]
5	nano ZnO, 100°C	6 h	[30]
6	KF-alumina, MW	6 min	[47]

the precipitates using EtOAc/hexane mixture. Product **3aa** was obtained in 89% yield (475 mg). The product was identified based on its physical and spectral characteristics.

4.2. *Selected spectral data*

4.2.1. *2-Amino-5,7-dihydro-4H-thieno[2,3-c]thiopyran-3-carbonitrile (3ea)*

Light brown solid, mp: 205–207°C [49]; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.58–2.61 (t, $J = 5.81$, 11.45 Hz, 2H), 2.84–2.86 (t, $J = 5.74$, 11.59 Hz, 2H), 3.53 (s, 2H), 7.05 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.5, 25.4, 26.9, 84.6, 114.0, 116.6, 131.8, 163.0 ppm; (KBr, cm^{-1}) 3415, 3317, 3207, 2885, 2196, 1622, 1519, 1411 cm^{-1}; MS (70 eV): *m/z* 196 (M$^+$), 168, 150, 60, 45, 29, 27; Anal. Calcd for $C_8H_8N_2S_2$: C, 48.95; H, 4.11. Found: C, 49.03; H, 4.22.

4.2.2. *Ethyl 2-amino-5,7-dihydro-4H-thieno[2,3-c]thiopyran-3-carboxylate (3eb)*

Orange solid, mp: 86–89°C [49]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.34–1.37 (t, $J = 7.13$, 14.26 Hz, 3H), 2.88–2.90 (t, $J = 5.94$, 11.79 Hz, 2H), 3.03–3.05 (t, $J = 5.84$, 11.80 Hz, 2H), 3.59 (s, 2H), 4.27–4.21 (q, $J = 7.09$, 14.23, 21.32 Hz, 2H), 6.05 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.9, 25.4, 26.6, 29.1, 60.0, 106.5, 114.0, 132.7, 161.6, 166.2 ppm; (KBr, cm^{-1}) 3412, 3304, 2978, 2943, 2895, 1651, 1568, 1483, 1018 cm^{-1}; MS (70 eV): *m/z* 243 (M$^+$), 197, 170, 45, 29, 27; Anal. Calcd for $C_{10}H_{13}NO_2S_2$: C, 49.36; H, 5.38. Found: C, 49.43; H, 5.54.

4.2.3. *Ethyl 2-amino-5,7-dihydro-4H-thieno[2,3-c]pyran-3-carboxylate (3fb)*

Yellow solid, mp: 117–118°C [50]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.33–1.36 (t, $J = 7.12$, 14.23 Hz, 3H), 2.82–2.84 (m, 2H), 3.91–3.93 (t, $J = 5.59$, 11.19 Hz, 2H), 4.25–4.30 (q, $J = 7.11$, 14.22, 21.34 Hz, 2H), 4.56–4.57 (t, $J = 3.32$, 10.69 Hz, 2H), 6.11 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.8, 28.1, 59.9, 65.0, 65.3, 105.7, 115.0, 130.7, 162.8, 166.3 ppm. (KBr, cm^{-1}) 3433, 3325, 2945, 2902, 2846, 1654, 1587, 1265, 1083, 1018 cm^{-1}; MS (70 eV): *m/z* 229 (M^{+2}), 228 (M^{+1}), 227 (M$^+$), 198, 124, 125, 29; Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77. Found: C, 52.63; H, 5.80.

4.2.4. *Ethyl 2-amino-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (3gb)*

White solid, mp:119–120°C [51]; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.35–1.37 (t, $J = 7.14$, 14.23 Hz, 3H), 1.66 (s, 1.3H), 2.75–2.77 (m, 2H), 3.08–3.11 (t, $J = 5.84$, 11.67 Hz, 2H), 3.8 (t, $J = 1.8$, 3.58 Hz, 2H), 4.27–4.31 (q, $J = 7.1$, 14.23, 21.34 Hz, 2H), 6.02 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.9, 28.7, 43.9, 44.8, 59. 9, 106.2, 117.2, 131.7, 162.3, 166.4 ppm. MS (70 eV): *m/z* 226 (M$^+$), 197, 179, 125, 43, 29, 27; Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24. Found: C, 53.33; H, 6.40.

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