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Aqueous DABCO, an efficient medium for rapid organocatalyzed Knoevenagel condensation and the Gewald reaction

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Abstract: In the presence of water and 1,4-diazabicyclo[2.2.2]octane, several aldehydes and cyclic ketones underwent efficient Knoevenagel condensation with malononitrile and ethyl cyanoacetate to produce the respective α,β-unsaturated systems within fairly short time periods. As a result, high yields of conjugated products were easily obtained. Products could be engaged in a Gewald reaction, either stepwise or in situ, to produce efficiently their respective 2-aminothiophenes within 4–7 h.

Key words: Knoevenagel condensation, Gewald reaction, organocatalysis, aqueous conditions, amine

1. Introduction

Although water has been known for a long time as the most inexpensive and nonhazardous solvent on earth, its presence as a medium in organic transformations has been avoided to a large extent, because careful use of dry reactants, additives, and solvents has always been practiced by synthetic chemists. This limited the use of water as a solvent for organic reactions until 3 decades ago, when the pioneering studies by Grieco[1,2] and Breslow[3,4] revealed that water can lead to unusual enhancements in the rate and selectivity of many organic reactions in comparison to the same reactions conducted under nonaqueous conditions. More importantly, the use of aqueous media in organic reactions has significantly lowered the environmental impacts associated with the use of regular organic solvents.

Knoevenagel condensation is one of the most commonly used reactions in synthetic organic chemistry to prepare electrophilic olefins from active methylene and carbonyl compounds.[5–7] The versatility of this reaction is due to its applications to access various target molecules.[8] In addition, products of this reaction are known as useful intermediates in other synthetic preparations such as the Gewald reaction, a process very useful for the synthesis of 2-aminothiophene derivatives.[9–11] Many alternative methods to the original Knoevenagel process have been developed in recent years so that the reaction proceeds under smoother conditions. In this regard, the use of ionic liquids,[12] nanocatalysts,[13] heterogeneous conditions,[14] and microwave irradiation[15] can be highlighted. Nevertheless, several of these methods still involve the use of expensive reagents, require relatively harsh conditions, or need extra additives to proceed.

In the framework of our studies on the chemistry of thiopyran-one structure[16] and its heterocyclic analogues,[17] and in continuation of our previous investigation on the development of aqueous mediated procedures,[18,19] we report herein the successful application of a H_2O/1,4-diazabicyclo[2.2.2]octane (DABCO)

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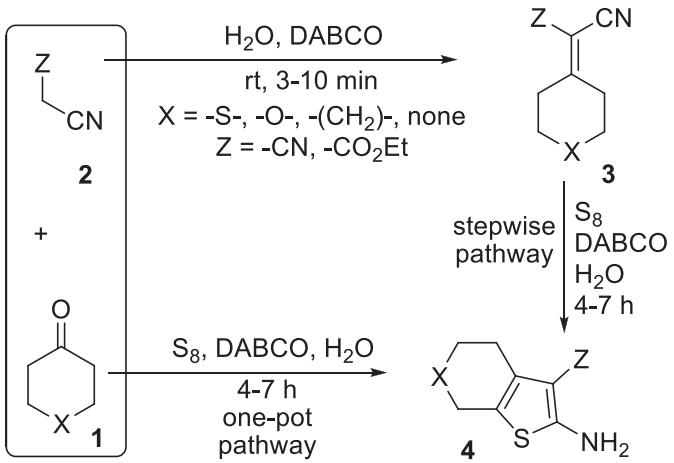
medium, which can cause rapid condensation of ketones **1** with malononitrile derivatives **2** to produce the Knoevenagel products **3** within a few minutes (3–10). The products can be further converted to 2-aminothiophenes **4**, either stepwise or in situ, to show the versatility of the method (Scheme).



Scheme. Aqueous mediated Knoevenagel condensation and Gewald reaction.

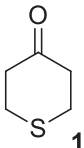
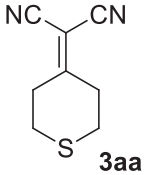
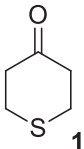
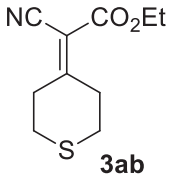
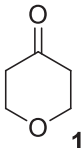
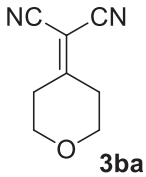
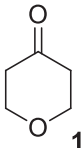
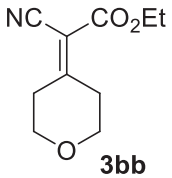
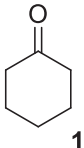
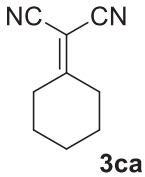
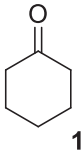
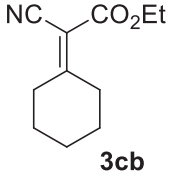
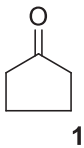
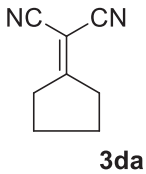
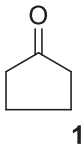
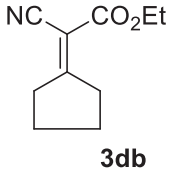
2. Results and discussion

We first examined the Knoevenagel condensation of **1a** with **2a** (Z = CN) in the presence of several amines and water. The results are summarized in Table 1. Experiments showed that DABCO can cause convenient conversion of the 2 reactants to **3aa** at room temperature. Use of lower quantities of the amine (down to 20 mol%) was enough to obtain 80% of **3aa** after only 3 min (entry 1). Similarly, reaction of **1a** with **2b** (Z = CO_2Et) gave high yields of **3ab** within 4 min (entry 2). Pyran-4-one **1b** behaved equally well when it was reacted with **2a**–**b** to produce **3ba**–**bb** (entries 3 and 4). We next applied the conditions to the reactions of **1c**–**d** with **2a**–**b**. Due to the lower reactivities of these 2 ketones, their reactions were completed in slightly longer intervals giving 88%–92% of **3ca**–**db** in 7–10 min (entries 5–8). At the end of the reactions, most of the products precipitated spontaneously and could be separated by simple filtration.

Several independent studies suggest that in many cases the Gewald reaction proceeds through Knoevenagel intermediates.[20] Sabnis et al.[21] experimentally studied the Knoevenagel–Gewald pathway to 2-aminothiophene structures and the pathway was verified practically by others.[22,23] It is worthy of mention that although the one-pot Gewald strategy is more attractive from an operational perspective, the stepwise pathway involving the preparation of α,β-unsaturated nitriles followed by base catalyzed addition of sulfur to the Knoevenagel intermediate is also interesting, since it can usually lead to higher yields of the final products. On this basis, we were persuaded to study the behavior of products **3** in reaction with elemental sulfur under H_2O/DABCO conditions. To investigate this, we separately dispersed **3aa**, **3ba**, and **3ca** in the reaction medium and after the addition of S_8 we obtained the respective products **4aa**, **4ba**, and **4ca** in more than 80% yield within 4–7 h. Therefore, we envisaged that the mechanism of a 3-component Gewald reaction of **1** and **2** with S_8 can proceed through the respective Knoevenagel intermediates **3** to form products **4**. This is shown in the Figure for the synthesis of **4ca** via the reactions of S_8 with **3ca** (stepwise) or with **1c** and **2a** (one-pot).

To further verify this, we experimentally examined the 2-component Knoevenagel–Gewald pathway by the synthesis of various products **4** from their respective reactants by using the optimized H_2O/DABCO method

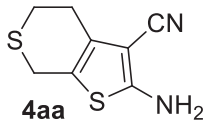
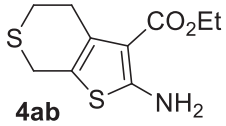
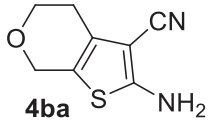
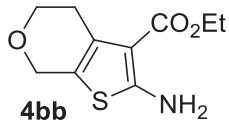
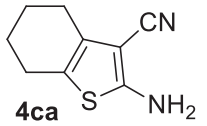
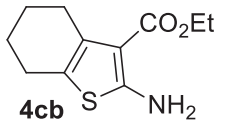
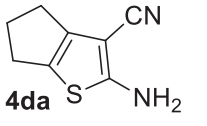
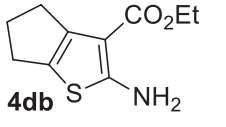
Table 1. Knoevenagel condensation of **1** with **2** in H_2O/DABCO medium.

Entry	Ketone	Product	Time (Min)	Yield (%)[a]
1	 **1a**	 **3aa**	3	80
2	 **1a**	 **3ab**	4	92
3	 **1b**	 **3ba**	3	75
4	 **1b**	 **3bb**	4	92
5	 **1c**	 **3ca**	7	89
6	 **1c**	 **3cb**	10	92
7	 **1d**	 **3da**	7	90
8	 **1d**	 **3db**	10	88

[a]Isolated yields.

(Table 2). As summarized in this table, all 4 types of the starting ketones react conveniently with malononitrile derivatives and S_8 to produce 87%–95% of the desired products. This occurs faster for the 2 heterocyclic ketones **1a** and **1b** due to the higher reactivities they show in the process.

Table 2. Gewald reactions for the synthesis of **4** in H_2O/DABCO medium.

Entry	Reactants	Product	Time (h)	Yield (%)[a]
1	**1a** + **2a** + S_8	 **4aa**	4	87
2	**1a** + **2b** + S_8	 **4ab**	4	95
3	**1b** + **2a** + S_8	 **4ba**	5	88
4	**1b** + **2b** + S_8	 **4bb**	5	94
5	**1c** + **2a** + S_8	 **4ca**	7	88
6	**1c** + **2b** + S_8	 **4cb**	7	92
7	**1d** + **2a** + S_8	 **4da**	7	91
8	**1d** + **2b** + S_8	 **4db**	7	92

[a]Isolated yields.

With these results in hand, we decided to explore the potentials of this protocol further by examining the Knoevenagel condensation between aromatic aldehydes and malononitrile derivatives under the optimized conditions (Table 3). When a mixture of benzaldehyde and malononitrile was treated with water and DABCO, complete disappearance of the starting aldehyde occurred in less than 1 min and the ^{1}H NMR analysis showed the presence of compound **6a** as the sole product of the reaction (entry 1). Ethyl cyanoacetate showed a slightly slower reaction due to the lower activity it has (entry 2). Other aldehydes behaved in a similar manner and

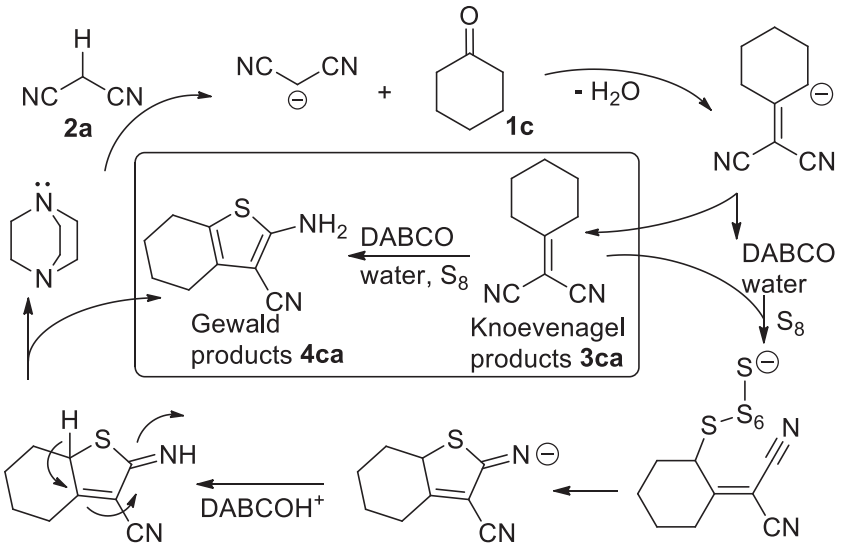
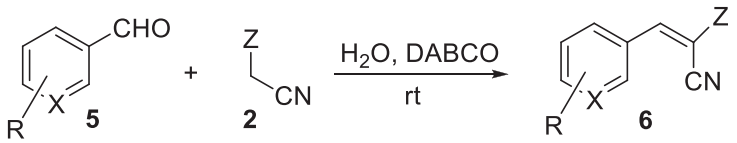
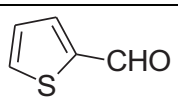


Figure. A plausible catalytic mechanism for both pathways.

produced high yields of their respective products (entries 3–14). In all reactions with **2b**, only geometric *E* isomers were obtained in high yields within 1–2 min.

Table 3. Knoevenagel condensation for the synthesis of **6** in H_2O/DABCO medium.



Entry	R, X	Z	Product	Time (Min)	Yield (%)[a]
1	H, CH	CN	**6a**	1	93
2	H, CH	CO_2Et	**6b**	1	95
3	4-Me, CH	CN	**6c**	1	87
4	4-Me, CH	CO_2Et	**6d**	1.5	85
5	4-OMe, CH	CN	**6e**	1	80
6	4-OMe, CH	CO_2Et	**6f**	1.5	80
7	4-Cl, CH	CN	**6g**	0.5	97
8	4-Cl, CH	CO_2Et	**6h**	1	95
9	4-NO_2, CH	CN	**6i**	0.5	92
10	4-NO_2, CH	CO_2Et	**6j**	1	98
11	H, N	CN	**6k**	0.5	93
12	H, N	CO_2Et	**6l**	0.5	90
13		CN	**6m**	1	91
14		CO_2Et	**6n**	1	95

[a]Isolated yields.

In summary, we have reported a general procedure for efficient Knoevenagel and Gewald reactions by using only water and catalytic quantities of DABCO. Various 2-aminothiophene derivatives were successfully obtained from the reactions of different ketones with malononitrile derivatives and sulfur at room temperature. Reactions took place using an environmentally friendly medium consisting of water and DABCO. Preparation of single products in high yields within relatively short times, ease of operation, use of no harmful organic solvent, and no special handling requirements make this protocol an attractive addition to the present literature archive.

3. Experimental

3.1. General remarks

The 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 **1a** was prepared by a previously described method.[24] All other chemicals were purchased from commercial sources and were freshly used after being purified by standard procedures. The identity of the known products was confirmed by comparison of their physical and spectroscopic properties with those reported in the literature.[25–30]

3.2. Typical procedure for Knoevenagel condensation

A mixture of **1a** (232 mg, 2.0 mmol) and **2a** (132 mg, 2.0 mmol) in H_2O (0.5 mL) and DABCO (224 mg, 2.0 mmol) was stirred at room temperature for 3 min until TLC showed complete disappearance of the starting materials. The mixture was extracted by EtOAc (5 mL) and the organic layer was washed with saturated solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. Product **3aa** was obtained by evaporation of the volatile portion of the organic layer and was purified by recrystallization from EtOAc/hexane mixture. Product **3aa** was obtained in 80% yield (262 mg). The product was identified based on its physical and spectral characteristics. The remaining compounds **3ab**–**3db** were synthesized in a similar manner.

3.3. Typical procedure for the one-pot Gewald reaction

A mixture of **1a** (232 mg, 2.0 mmol) and **2a** (132 mg, 2.0 mmol) in H_2O (0.5 mL) and DABCO (224 μL, 2.0 mmol) was stirred at room temperature for 3 min and sulfur (64 mg, 2.0 mmol) was added to this mixture and stirring was continued at room temperature for another 4 h until TLC showed complete disappearance of the starting materials. The product **4aa**, which precipitated at the end of the reaction, was separated by filtration. The pure product was obtained by recrystallization of the precipitates using EtOAc/hexane mixture. Product **4aa** was obtained in 87% yield (341 mg). The product was identified based on its physical and spectral characteristics. The remaining compounds **4ab**–**4db** were synthesized in a similar manner.

3.4. Spectral data of the products

2-(2*H*-Thiopyran-4(3*H*,5*H*,6*H*)-ylidene)malononitrile (**3aa**). White solid, mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90–2.92 (m, 4H), 3.03–3.05 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.1, 36.6, 85.4, 111.4, 181.1 ppm; IR (KBr) ν 2920, 2854, 2250, 2220, 1573, 1276, 1004 cm^{-1}; MS m/z (%) 164 (M^+), 138

(M^+-CN), 118 (M^+-CH_2S), 46 (CH_2S), 26 (CN). Anal. Calcd. for $C_8H_8N_2S$ (Mw 164.23): C, 58.51; H, 4.91; N, 17.06. Found: C, 58.61; H, 5.02; N, 17.11%.

Ethyl 2-cyano-2-(2*H*-thiopyran-4(3*H*,5*H*,6*H*)-ylidene)acetate (**3ab**). Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 2.85–2.88 (m, 2H), 2.92–2.94 (m, 2H), 3.02–3.05 (m, 2H), 3.34–3.37 (m, 2H), 4.30 (q, J = 7.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 31.3, 31.5, 33.8, 48.6, 62.5, 104.7, 115.3, 161.9, 176.0 ppm; IR (KBr) ν 2978, 2916, 2308, 2223, 1653, 1028, 777 cm^{-1}; MS m/z (%) 211 (M^+), 182 (M^+-Et), 138 (M^+-CO_2Et), 29 (Et). Anal. Calcd. for $C_{10}H_{13}NO_2S$ (Mw 211.28): C, 56.85; H, 6.20; N, 6.63. Found: C, 56.66; H, 6.43; N, 6.41%.

2-(2*H*-Pyran-4(3*H*,5*H*,6*H*)-ylidene)malononitrile (**3ba**). White solid, mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81–2.83 (m, 4H), 3.87–3.89 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.5, 68.2, 84.4, 111.5, 179.0 ppm; IR (KBr) ν 2987, 2912, 2870, 2372, 2229, 1591, 1089 cm^{-1}; MS m/z (%) 148 (M^+), 122 (M^+-CN), 118 (M^+-CH_2O), 78 (M^+-70), 30 (CH_2O), 26 (CN). Anal. Calcd. for $C_8H_8N_2O$ (Mw 148.16): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.91; H, 5.52; N, 18.73%.

Ethyl 2-cyano-2-(2*H*-pyran-4(3*H*,5*H*,6*H*)-ylidene)acetate (**3bb**). White solid, mp 65–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.5 Hz, 3H), 2.78–2.80 (m, 2H), 3.17–3.19 (m, 2H), 3.78–3.80 (m, 2H), 3.86–3.88 (m, 2H), 4.28 (q, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 32.8, 37.2, 62.4, 68.4, 68.7, 103.8, 115.4, 162.0, 173.8 ppm; IR (KBr) ν 2970, 2875, 2223, 1728, 1379, 1001 cm^{-1}; MS m/z (%) 195 (M^+), 166 (M^+-Et), 137 (M^+-HCOEt), 122 (M^+-CO_2Et), 29 (Et). Anal. Calcd. for $C_{10}H_{13}NO_3$ (Mw 195.22): C, 61.53; H, 6.71; N, 7.18. Found: C, 61.64; H, 6.88; N, 7.32%.

2-Cyclohexylidenemalononitrile (**3ca**). Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66–1.69 (m, 2H), 1.72–1.76 (m, 2H), 1.79–1.84 (m, 2H), 2.68 (dd, J= 6.0, 12.5 Hz, 2H) 2.99 (dd, J= 6.0, 12.50 Hz, 2H) ppm; IR (KBr) ν 2950, 2225, 1600 cm^{-1};gMS m/z (%) 146 (M^+), 120 (M^+-CN), 26 (CN). Anal. Calcd. for $C_9H_{10}N_2$ (Mw 146.19): C, 73.94; H, 6.89; N, 19.16. Found: C, 73.69; H, 6.97; N, 19.22%.

Ethyl 2-cyano-2-cyclohexylideneacetate (**3cb**). Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J= 7.5 Hz, 3H), 1.67–1.69 (m, 2H), 1.72–1.76 (m, 2H), 1.79–1.84 (m, 2H), 2.68 (dd, J= 6.0, 6.5 Hz, 2H) 2.99 (dd, J = 6.0, 6.5 Hz, 2H), 4.26 (q, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) ? 13.8, 25.5, 28.0, 28.5, 31.4, 36.6, 61.0, 101.7, 161.9, 180.0 ppm; IR (KBr disk) ν 2942, 2220, 1725 cm^{-1}; MS m/z (%) 193 (M^+), 165 (M^+-CO), 148 (M^+-HCO_2), 137 (M^+-C_4H_8), 121 (M^+-$CH_2CH_2CO_2$), 70 (C_5H_{10}). Anal. Calcd. for $C_{11}H_{15}NO_2$ (Mw 193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.58; H, 7.61; N, 7.26%.

2-Cyclopentylidenemalononitrile (**3da**). Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74–1.80 (m, 4H), 2.75 (dd, J = 7.0, 7.0, 2H), 2.93 (t, J = 6.0, 6.0 Hz, 2H) ppm;^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 35.5, 81.0, 112.5, 191.4; IR (KBr disk) ν 2930, 2220, 1641 cm^{-1}; MS m/z (%) 132 (M^+), 106 (M^+-CN), 105 (M^+-HCN), 26 (CN). Anal. Calcd. for $C_8H_8N_2$ (Mw 132.16): C, 72.70; H, 6.10; N, 21.20. Found: C, 72.59; H, 6.31; N, 21.29%.

Ethyl 2-cyano-2-cyclopentylideneacetate (**3db**). White solid, mp 49–51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3H), 1.75–1.82 (m. 4H), 2.75 (dd, J = 7.0, 7.5, 2H), 2.93 (t, J = 7.0, 7.5 Hz, 2H), 4.18–4.22 (q, J = 7.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 25.4, 26.9, 35.8, 38.1, 61.8, 101.2, 115.9, 162.2, 187.7 ppm; IR (KBr) ν 2190, 1725, 1605 cm^{-1}; MS m/z (%) 179 (M^+), 150 (M+-Et),

106 (M+-CO_2Et), 29 (Et). Anal. Calcd. for $C_{10}H_{13}NO_2$ (Mw 179.22): C, 67.02; H, 7.31; N, 7.82. Found: C, 67.21; H, 7.09; N, 7.55%.

2-Amino-5,7-dihydro-4*H*-thieno[2,3-c]thiopyran-3-carbonitrile (**4aa**). Light brown solid, mp 205–207 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.58–2.61 (m, 2H), 2.84–2.86 (m, 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, 116.7, 131.8, 163.0 ppm; IR (KBr) ν 3317, 3207, 2885, 2196, 1622, 1519 cm^{-1}; MS m/z (%) 196 (M^+), 168 (M^+-CH_2CH_2), 150 (M^+-CH_2S), 46 (CH_2S), 27 (HCN). Anal. Calcd. for $C_8H_8N_2S_2$ (Mw 196.29): C, 48.95; H, 4.11; N, 14.27. Found: C, 49.09; H, 4.28; N, 14.33%.

Ethyl 2-amino-5,7-dihydro-4H-thieno[2,3-c]thiopyran-3-carboxylate (**4ab**). Orange solid, mp 86–89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 2.88–2.90 (m, 2H), 3.03–3.05 (m, 2H), 3.59 (s, 2H), 4.27–4.21 (q, J = 7.0 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; IR (KBr) ν 3412, 3304, 2978, 2943, 2895, 1651, 1568, 1483 cm^{-1}; MS m/z (%) 243 (M^+), 197 (M^+-CH_2S), 170 (M^+-CO_2Et), 46 (CH_2S), 29 (Et), 27 (HCN). Anal. Calcd. for $C_{10}H_{13}NO_2S_2$ (Mw 243.35): C, 49.36; H, 5.38; N, 5.76. Found: C, 49.48; H, 5.44; N, 5.89%.

2-Amino-5,7-dihydro-4*H*-thieno[2,3-c]pyran-3-carbonitrile (**4ba**). Yellow solid, mp 215–218 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.82–2.84 (m, 2H), 3.91–3.93 (m, 2H), 4.56 (s, 2H), 6.11 (br s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.5, 63.8, 64.0, 84.1, 114.0, 115.7, 130.8, 163.3 ppm; IR (KBr) ν 3411, 2201, 1620, 1525 cm^{-1}; MS m/z (%) 180 (M^+), 152 (M^+-CH_2CH_2), 150 (M^+-CH_2O), 27 (HCN). Anal. Calcd. for $C_8H_8N_2OS$ (Mw 180.23): C, 53.31; H, 4.47; N, 15.54. Found: C, 53.52; H, 4.31; N, 15.66%.

Ethyl 2-amino-5,7-dihydro-4H-thieno[2,3-c]pyran-3-carboxylate (**4bb**). Yellow solid, mp 117–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 2.82–2.85 (m, 2H), 3.90–3.92 (m, 2H), 4.25 (q, J = 7.0 Hz, 2H), 4.56 (s, 2H), 6.11 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 28.1, 60.0, 65.0, 65.5, 105.6, 115.1, 130.7, 162.7, 166.2 ppm; IR (KBr) ν 3433, 3325, 2945, 2902, 2846, 1654, 1587, 1265, 1083, 1018 cm^{-1}; MS m/z (%) 227 (M^+), 198 (M^+-Et), 73 (CO_2Et), 29 (Et). Anal. Calcd. for $C_{10}H_{13}NO_3S$ (Mw 227.28): C, 52.85; H, 5.77; N, 6.18. Found: C, 52.58; H, 5.61; N, 6.00%.

2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (**4ca**). White solid, mp 147–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78–1.83 (m, 4H), 2.49–2.52 (m, 4H), 4.7 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 23.8, 24.5, 24.9, 88.8, 116.0, 120.9, 132.7, 160.6 ppm; IR (KBr) ν 3450, 3325, 2200 cm^{-1}; MS m/z (%) 178 (M^+), 177 (M^+-1), 150 (M^+-CH_2CH_2). Anal. Calcd. for $C_9H_{10}N_2S$ (Mw 178.25): C, 60.64; H, 5.65; N, 15.72. Found: C, 60.43; H, 5.79; N, 15.48%.

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (**4cb**). White solid, mp 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 1.75–1.77 (m, 4H), 2.45–2.48 (m, 2H), 2.70–2.72 (m, 2H), 4.24 (q, J = 7.0 Hz, 2H), 6.00 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 23.3, 23.7, 25.0, 27.4, 59.8, 106.2, 118.1, 132.9, 162.1, 166.5 ppm; IR (KBr) 3405, 3300, 1650, cm^{-1}; MS m/z (%) 225 (M^+), 196 (M^+-Et), 179 (M^+-HCOOH), 29 (Et). Anal. Calcd. for $C_{11}H_{15}NO_2S$ (Mw 225.31): C, 58.64; H, 6.71; N, 6.22. Found: C, 58.66; H, 6.77; N, 6.45%.

2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (**4da**). White solid, mp 147–148 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.3–2.4 (m, 2H), 2.7–2.8 (m, 2H), 2.8–2.9 (m, 2H), 5.9 (s, 2H) ppm; IR (KBr) ν 3440, 3335, 2190 cm^{-1}; MS m/z (%) 164 (M^+), 148 (M^+-NH_2), 28 (CN). Anal. Calcd. for $C_8H_8N_2S$ (Mw 164.23): C, 58.51; H, 4.91; N, 17.06. Found: C, 58.66; H, 4.80; N, 16.89%.

Ethyl 2-amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (**4db**). White solid, mp 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 2.28–2.33 (m, 2H), 2.68–2.72 (m, 2H), 2.84–2.87 (m, 2H), 4.26 (q, J = 7.0 Hz, 2H), 5.90 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 27.6, 29.3, 31.2, 59.8, 103.4, 121.7, 143.1, 166.2, 166.8 ppm; IR (KBr)gν 3415, 3290, 1625, cm^{-1}; MS m/z (%) 211 (M^+), 165 (M^+-HCOOH), 137 (M^+-HCOOEt). Anal. Calcd. for $C_{10}H_{13}NO_2S$ (Mw 211.28): C, 56.85; H, 6.20; N, 6.63. Found: C, 56.97; H, 6.43; N, 6.39%.

2-Benzylidenemalononitrile (**6a**). White crystals, mp 83–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.68 (m, 3H), 7.79 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H) ppm; IR (KBr disk) ν 2225, 1560 cm^{-1}; MS m/z (%) 154 (M^+), 128 (M^+-CN), 77 (Ph), 26 (CN). Anal. Calcd. for $C_{10}H_6N_2$ (Mw 154.17): C, 77.91; H, 3.92; N, 18.17. Found: C, 77.71; H, 4.09; N, 17.99%.

(*E*)-Ethyl 2-cyano-3-phenylacrylate (**6b**). White crystals, mp 49–51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, J = 7.0 Hz, 3H), 4.35 (q, J = 7.0 Hz, 2H), 7.48–7.51 (m, 3H), 7.87–7.90 (m, 2H), 8.20 (s, 1H); IR (KBr disk) ν 2225, 1730 cm^{-1}; MS m/z (%) 201 (M^+), 173 (M^+-CO), 129 (M^+-$CO_2CH_2CH_2$), 29 (Et). Anal. Calcd. for $C_{12}H_{11}NO_2$ (Mw 201.22): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.79; H, 5.75; N, 6.81%.

2-(4-Methylbenzylidene)malononitrile (**6c**). White crystals, mp 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.41 (d, J = 8.0 Hz, 2H), 7.75 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H) ppm; IR (KBr disk) ν 2222, 1593 cm^{-1}; MS m/z (%) 168 (M^+), 153 (M^+-CH_3), 142 (M^+-CN), 26 (CN). Anal. Calcd. for $C_{11}H_8N_2$ (Mw 168.19): C, 78.55; H, 4.79; N, 16.66. Found: C, 78.76; H, 5.01; N, 16.80%.

(*E*)-Ethyl 2-cyano-3-*p*-tolylacrylate (**6d**). White crystals, mp 90–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 2.40 (s, 3H), 4.35 (q, J = 7.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 8.18 (s, 1H); IR (KBr disk) ν 2215, 1722 cm^{-1}; MS m/z (%) 215 (M^+), 200 (M^+-CH_3), 141 (M^+-HCO_2Et). Anal. Calcd. for $C_{13}H_{13}NO_2$ (Mw 215.25): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.71; H, 5.91; N, 6.75%.

2-(4-Methoxybenzylidene)malononitrile (**6e**). Light yellow crystals, mp 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.03 (d, J = 8.0 Hz, 2H), 7.65 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H) ppm; IR (KBr disk) ν 2220, 1600 cm^{-1}; MS m/z (%) 184 (M^+), 169 (M^+-CH_3), 154 (M^+-CH_2O). Anal. Calcd. for $C_{11}H_8N_2O$ (Mw 184.19): C, 71.73; H, 4.38; N, 15.21. Found: C, 71.51; H, 4.62; N, 15.43%.

(*E*)-Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (**6f**). Yellow crystals, mp 82–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3H), 3.90 (s, 3H), 4.33 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 7.0 Hz, 2H), 7.97 (d, J = 7.0 Hz, 2H), 8.08 (s, 1H); IR (KBr disk) ν 2218, 1720 cm^{-1}; MS m/z (%) 231 (M^+), 186 (M^+-CO_2H), 159 (M^+-$CO_2CH_2CH_2$). Anal. Calcd. for $C_{13}H_{13}NO_3$ (Mw 231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.73; H, 5.44; N, 6.14%.

2-(4-Chlorobenzylidene)malononitrile (**6g**). White crystals, mp 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 2H), 7.72 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H) ppm; IR (KBr disk) ν 2222, 1585 cm^{-1}; MS m/z (%) 188 (M^+), 162 (M^+-CN), 26 (CN). Anal. Calcd. for $C_{10}H_5ClN_2$ (Mw 188.61): C, 63.68; H, 2.67; N, 14.85. Found: C, 63.79; H, 2.81; N, 14.65%.

(*E*)-Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (**6h**). White crystals, mp 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 4.30 (q, J = 7.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H), 8.10 (s, 1H); IR (KBr disk) ν 2221, 1725 cm^{-1}; MS m/z (%) 235 (M^+), 208 (M^+-HCN), 190

(M^+-HCO_2), 162 (M^+-CO_2Et). Anal. Calcd. for $C_{12}H_{10}ClNO_2$ (Mw 235.67): C, 61.16; H, 4.28; N, 5.94. Found: C, 60.88; H, 4.37; N, 5.78%.

2-(4-Nitrobenzylidene)malononitrile (**6i**). Light yellow crystals, mp 160–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J= 9.0 Hz, 2H), 8.29 (d, J = 9.0 Hz, 2H), 8.46 (s, 1H) ppm; IR (KBr disk) ν 2225, 1600 cm^{-1}; MS m/z (%) 199 (M^+), 173 (M^+-CN), 153 (M^+-NO_2), 26 (CN). Anal. Calcd. for $C_{10}H_5N_3O_2$ (Mw 199.17): C, 60.31; H, 2.53; N, 21.10. Found: C, 60.44; H, 2.66; N, 21.36%.

(*E*)-Ethyl 2-cyano-3-(4-nitrophenyl)acrylate (**6j**). White crystals, mp 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3H), 4.37 (q, J = 7.0 Hz, 2H), 8.15 (d, J = 9.0 Hz, 2H), 8.28 (s, 1H), 8.35 (d, J = 9.0 Hz, 2H); IR (KBr disk) ν 2224, 1712 cm^{-1}; MS m/z (%) 246 (M^+), 200 (M^+-NO_2), 188 (M^+-HCOEt), 174 (M^+-$CO_2CH_2CH_2$), 29 (Et). Anal. Calcd. for $C_{12}H_{10}N_2O_4$ (Mw 246.22): C, 58.54; H, 4.09; N, 11.38. Found: C, 58.78; H, 4.32; N, 11.67%.

2-(Pyridin-4-ylmethylene)malononitrile (**6k**). White crystals, mp 156–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 7.5 Hz, 2H), 8.35 (d, J = 7.5 Hz, 2H), 8.79 (s, 1H); IR (KBr disk) ν 2220, 1600 cm^{-1}; MS m/z (%) 155 (M^+), 129 (M^+-CN), 26 (CN). Anal. Calcd. for $C_9H_5N_3$ (Mw 155.16): C, 69.67; H, 3.25; N, 27.08. Found: C, 69.88; H, 3.51; N, 27.12%.

(*E*)-Ethyl 2-cyano-3-(pyridin-4-yl)acrylate (**6l**). White crystals, mp 104–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, J = 7.0 Hz, 3H), 4.45 (q, J = 7.0 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H), 8.23 (s, 1H), 8.85 (d, J = 7.5 Hz, 2H); IR (KBr disk) ν 2220, 1600 cm^{-1}; MS m/z (%) 202 (M^+), 176 (M^+-CN), 129 (M^+-CO_2Et). Anal. Calcd. for $C_{11}H_{10}N_2O_2$ (Mw 202.21): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.54; H, 5.09; N, 13.78%.

2-(Thiophen-2-ylmethylene)malononitrile (**6m**). Brown crystals, mp 96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.30 (m, 1H), 7.83–7.86 (m, 1H), 7.88–7.90 (m, 2H) ppm; IR (KBr) ν 2225, 1575, 735 cm^{-1}; MS m/z (%) 160 (M^+), 134 (M^+-26), 26 (CN). Anal. Calcd. for $C_8H_4N_2S$ (Mw 160.20): C, 59.98; H, 2.52; N, 17.49. Found: C, 59.91; H, 2.55; N, 17.62%.

(*E*)-Ethyl 2-cyano-3-(thiophen-2-yl)acrylate (**6n**). Yellow crystals, mp 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, J = 7.0 Hz, 3H), 4.40 (q, J = 7.0 Hz, 2H), 7.30 (dd, J = 5.0, 4.0 Hz, 1H), 7.81 (d, J = 5.0 Hz, 1H), 7.85 (d, J = 4.0 Hz, 1H), 8.40 (s, 1H) ppm; IR (KBr disk) ν 2220, 1715, 1600 cm^{-1}; MS m/z (%) 207 (M^+), 181 (M^+-26), 133 (M^+-HCO_2Et). Anal. Calcd. for $C_{10}H_9NO_2S$ (Mw 207.25): C, 57.95; H, 4.38; N, 6.76%. Found: C, 57.88; H, 4.33; N, 6.62%.

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