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Solvent-free synthesis of 2-aminothiophene-3-carbonitrile derivatives using high-speed vibration milling

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The solvent-free synthesis of 2-aminothiophene-3-carbonitrile derivatives by high-speed vibration milling using the inexpensive and environmentally friendly Et_2NH as a catalyst was studied. The reaction conditions were optimised and the derivatives were obtained in good yield. This method has advantages in terms of short reaction time and facile conditions.

Keywords: solvent-free synthesis, high-speed vibration milling, 2-aminothiophene

High-speed vibration milling (HSVM) is a mechanical technique which is widely used for the grinding of minerals into a fine grain, and in the preparation or modification of inorganic solids,[1,2] in materials science[3] and in the pharmaceutical industry.[4] Recently, the technique of HSVM was applied successfully in solvent-free reactions in organic synthesis such as the functionalisation of fullerenes,[5] the Knoevenagel reaction,[6] the aldol condensation,[7] Heck-type cross-coupling reactions[8] and Horner–Wadsworth–Emmons reaction.[9]

The Gewald reaction[10,11] has been a well-studied multi-component reaction. It involves the reaction of a ketone with an activated nitrile in the presence of elemental sulfur to construct a poly-substituted 2-aminothiophene. Many methods have been examined to optimise the reaction conditions for the Gewald reaction. Madabhushi[12] had used microwave to synthesis target product with KF-alumina as catalyst and Mohammad[13] had realised this reaction under ultrasound irradiation with Et_2NH as catalyst. Yi Hu[14] increased the speed of the reaction with the ionic liquids as a new catalyst.

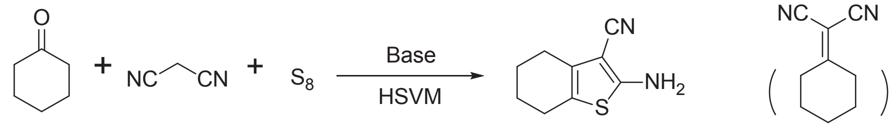
However, the application of HSVM to the Gewald reaction has not been reported. The one-pot cyclo-condensation of a variety of ketones and malononitrile with elemental sulfur has been used employing high-speed vibration milling with Et_2NH as the catalyst. The reaction times have been considerably decreased and the product was purified by a short column chromatography. Initial research was focused on the synthesis of 2-amino-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carbonitrile by the reaction of cyclohexanone and malononitrile in the presence of elemental sulfur and base. The reaction was conducted under HSVM, with a vibrational frequency of 30 Hz for 30 minutes.

In order to find the most effective catalyst, different common organic and inorganic bases were examined. As shown in Table 1, most of the bases improved the Gewald reaction to produce 2-aminothiophene-3-carbonitrile. The product **4a** was obtained in moderate yield in the presence of inorganic bases such as Na_2CO_3, KF, K_2CO_3, and $NaHCO_3$. The yield of **4a** reduced to 32% and 28% in the presence of NaOH and KOH and the by-products increased. The yield of **4a** was improved to 74% when the organic base Et_2NH was employed (Table 1, entry 9).

In further experiments, we found that the yield of **4a** was improved to 84% catalysed by 0.1 equiv. of Et_2NH. When we investigated the ratio of the reactants, the yield of **4a** was slightly increased to 88% with 1.2 equiv. of elemental sulfur.

To further optimise the reaction conditions, we have carried out this Gewald reaction at different vibration frequencies and reaction times. It was found that the vibration frequency had an effect on this reaction (Table 2). As shown in Table 2, higher vibration frequency of the vibration mill certainly accelerated the reaction. It is easy to understand that the faster milling vibration produces the higher energy, and therefore local pressure is applied to the reaction system. Furthermore, it was found that the best reaction time was vibration for 20 min

Table 1 Different catalysts on synthesis of **4a**



1a **2** **3** **4a** **5**

Entry[a]	Base	Product	Yield/%
1	KOH	**4a**	28
2	NaOH	**4a**	32
3	K_2CO_3	**4a**	43
4	DBU	**4a**	54
5	KF	**4a**	56
6	Piperidine	**4a**	60
7	Na_2CO_3	**4a**	63
8	Et_3N	**4a**	71
9	Et_2NH	**4a**	74
10	CH_3COOH	**5**	20

[a]The reaction: Cyclohexanone (0.0981 g, 1.0 mmol), malononitrile (0.0660 g, 1.0 mmol), elemental sulfur (0.0320 g, 1.0 mmol) was vigorously shaken with different bases by HSVM with 30 Hz for 30 min.

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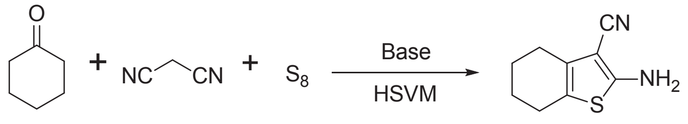
Table 2 The effect on the reaction of **1a**, **2** and sulfur



1a **2** **3** **4a**

Entry	**1**:**2**:**3**	Et$_2$NH/mmol	Vibration time/min	Speed/s^{-1}	Yield/%
1	1:1:1	1.0	30	30	74
2	1:1:1	0.2	30	30	82
3	1:1:1	0.1	30	30	84
4	1:1:1	0.05	30	30	40
5	1.2:1:1	0.1	30	30	84
6	1:1:1.2	0.1	30	30	88
7	1:1:1.5	0.1	30	30	88
8	1:1:1.2	0.1	20	30	88
9	1:1:1.2	0.1	15	30	79
10	1:1:1.2	0.1	30	20	83
11	1:1:1.2	0.1	20	20	83

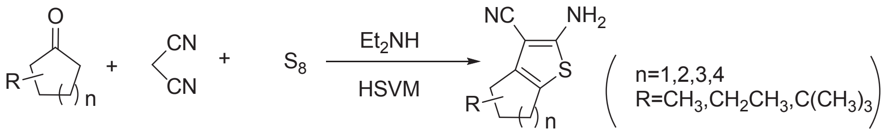
in 88% yield. The result indicated that the Gewald reaction proceeded in good yield in the presence of 0.1 equiv. Et$_2$NH under HSVM conditions.

The reaction conditions using a vibration frequency (30 Hz), reaction time (20 min) and 0.1 equiv. Et$_2$NH as catalyst and starting material mole ratio 1 : 1 : 1.2 were selected from the above results, for investigating the Gewald reaction with different cyclic ketone **1** and malononitrile with sulfur.

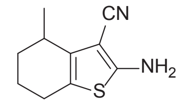
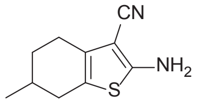
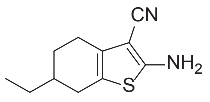
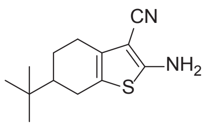
As shown in Table 3, the cyclic ketone gave the corresponding 2-aminothiophene-3-carbonitrile derivative in good yield. Cyclohexanone and substituted cyclohexanones gave excellent yields but the reaction of 2-methylcyclohexanone and 4-tertbutylcyclohexanone gave lower yields of 43% and 52% due to the steric hindrance of the *ortho*- substituent and ^{t}Bu-substituent (Table 3, entry 5, 9). Other cyclic ketones also gave the corresponding product in moderate yields of 42–61%.

In conclusion, we have developed a green and comparatively convenient way for the synthesis of 2-aminothiophene-3-carbonitrile derivatives by HSVM. The notable advantages of this strategy are its short reaction time, clean conditions and

Table 3 Synthesis of 2-aminothiophene-3-carbonitrile derivatives



1a **2** **3** **4a**

Entry[a]	Substrate	n	R	Product	Yield/%
1	**1a**	2	H	**4a**	88
2	**1b**	1	H	**4b**	42
3	**1c**	3	H	**4c**	61
4	**1d**	4	H	**4d**	52
5	**1e**	2	2-Methyl	 **4e**	43
6	**1f**	2	4-Methyl	 **4f**	81
7	**1g**	2	4-Ethyl	 **4g**	94
8	**1h**	2	4-t-Bu	 **4h**	52

[a]The reaction: Cyclic ketone (1.0 mmol), malononitrile (0.0660 g, 1.0 mmol), elemental sulfur (0.0384 g, 1.2 mmol) was vigorously shaken with Et$_2$NH (0.1 mmol) by HSVM with 30 Hz for 20 min.

inexpensive catalyst. We believe that this method has provided a better way to synthesise 2-aminothiophenes and will be an improvement over the existing methods for other organic reactions.

Experimental

All chemicals were purchased from commercial vendors and were used as received without further purification. The ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ using TMS as internal standard with a Bruker AM 500 spectrometer. The GC-MS was taken on Varian (GC431-MS210). The HSVM was achieved with Retsch MM301 (Retsch GmbH, Haan, Germany) equipment.

General procedure

Cyclohexanone (0.0981 g, 1.0 mmol), malononitrile (0.0660 g, 1.0 mmol), elemental sulfur (0.0384 g, 1.2 mmoL) was vigorously shaken by HSVM for a designated time.

The product was purified by chromatography on silica gel and eluted using CH_2Cl_2 as the eluent to afford the desired product 2-amino-5,6-dihydro-4H-cyclopenta[b]-thiophene-3-carbonitrile as colourless solid.

2-Amino-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carbonitrile **(4a):** Yield 88%; m.p. 146–147 °C (lit.[21] 145 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.61 (s, 2H, NH_2), 2.52–2.50 (m, 4H), 1.85–1.77 (m, 4H); HRMS (ESI-TOF) *m/z* calcd for $C_9H_{11}N_2S$ $[M+H]^+$ 179.0637; found 179.0637.

2-Amino-5,6-dihydro-4H-cyclopenta[b]-thiophene-3-carbonitrile **(4b):** Yield 42%; m.p. 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.69 (s, 2H, NH_2), 2.78–2.69 (m, 4H), 2.40–2.34 (s, 2H); HRMS (ESI-TOF) *m/z* calcd for $C_8H_9N_2S$ $[M+H]^+$ 165.0482; found 165.0481.

2-Amino-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carbonitrile **(4c)**: Yield 61%; m.p. 125–126 °C (lit.[21] 125 °C), ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.49 (s, 2H, NH_2), 2.63–2.59 (m, 4H), 1.85–1.81 (m, 2H), 1.68–1.63 (m, 4H); HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{13}N_2S$ $[M+H]^+$ 193.0792; found 193.0794.

2-Amino-4,5,6,7,8,9-hexahydrocycloocta[b]thiophene-3-carbonitrile **(4d)**: Yield 52%; m.p. 108–109 °C (lit.[21] 107 °C); ^{1}H NMR (500 MHz,$CDCl_3$): δ (ppm) 4.56 (s, 2H, NH_2), 2.65–2.61 (m, 4H), 1.69–1.59 (m, 4H), 1.45–1.38 (m, 4H); HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{15}N_2S$ $[M+H]^+$ 207.0950; found 207.0950.

2-Amino-4,5,6,7-tetrahydro-4-methyl-benzo[b]thiophene-3-carbonitrile **(4e)**: Yield 43%; m.p. 126–128 °C; ^{1}H NMR (500 MHz,$CDCl_3$): δ (ppm) 4.60 (s, 2H, NH_2), 2.85–2.79 (m, 1H), 2.53–2.43 (m, 2H), 1.90–1.73 (m, 3H), 1.57–1.54 (m, 1H), 1.28 (d, $J = 7$ Hz, 3H); HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{13}N_2S$ $[M+H]^+$ 193.0793; found 193.0794.

2-Amino-4,5,6,7-tetrahydro-6-methyl-benzo[b]thiophene-3-carbonitrile **(4f):** Yield 81%; m.p. 117–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.59 (s, 2H, NH_2), 2.62–2.46 (m, 3H), 2.18–2.12 (m, 1H), 1.96–1.85 (m, 2H), 1.44–1.34 (s, 1H), 1.07 (d, $J = 6.5$ Hz, 3H); HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{13}N_2S$ $[M+H]^+$ 193.0794; found 193.0794.

2-Amino-6-ethyl-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carbonitrile **(4g):** Yield 94%; m.p. 109–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.59 (s, 2H, NH_2), 2.63–2.58 (m, 2H), 2.51–2.12 (m, 2H), 1.95–1.64 (m, 2H), 1.48–1.34 (m, 3H), 0.96 (t, $J = 7.5$ Hz, 3H); HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{15}N_2S$ $[M+H]^+$ 207.0950; found 207.0950.

2-Amino-6-(1,1-dimethylethyl)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carbonitrile **(4h):** Yield 52%; m.p. 150–151; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.60 (s, 2H, NH_2), 2.68–2.53 (m, 2H), 2.46–2.26 (m, 2H), 2.03–1.28 (m, 3H), 0.93 (s, 9H); HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{19}N_2S$ $[M+H]^+$ 235.1261; found 235.1263.

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References

1 G. Kaupp, M.R. Naimi-Jamal, H. Ren and H. Zoz, *Res. Signpost. Kerala*, 2003, 83.
2 S. Kipp, V. Sepelak and K.D. Becker, *Chem Unsere Zeit*., 2005, **39**, 384.
3 V.P. Balema, K.W. Dennis and V.K. Pecharsky, *Chem. Commun*., 2000, **17**, 1665.
4 T.P. Shakhtshneider and V.V. Boldyrev, *Mol. Solid State*, 1999, **3**, 271.
5 K. Komatsu, *Top. Curr. Chem*., 2005, **254**, 185.
6 G. Kaupp, M.R. Naimi-Jamal and J. Schmeyers, *Tetrahedron,* 2003, **59**, 3753.
7 B. Rodriguez, A. Bruckmann and C. Bolm, *Chem. Eur. J*., 2007, **13**, 4710.
8 E. Tullberg, F. Schacher, D. Peters and T. Frejd, *Synthesis*, 2006, **7**, 1183.
9 A. Baron, J. Martinez and F. Lamaty, *Tetrahedron Lett*., 2010, **51**, 6246.
10 K. Gewald, *Chem. Heterocycl. Compd*, 1976, **12**, 1077.
11 R.W. Sabnis, *Sulfur Rep*., 1994, **16**, 1.
12 M. Sridhar, R.M. Rao, N.H.K. Baba and R.M. Kumbhare, *Tetrahedron Lett*., 2007, **48**, 3171.
13 M.M. Mojtahedi, M.S. Abaee, P. Mahmoodi and M. Adib, *Synth. Commun*., 2010, **40**, 2067.
14 Y. Hu, Z.C. Chen, Z.G. Le and Q.G. Zheng, *Synth. Commun*., 2004, **34**, 3801.