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Cyanation of  $\alpha,\beta$ -unsaturated enones by malononitrile in open air under metal-catalyst-free conditions†

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**Cyanation of  $\alpha,\beta$ -unsaturated enones by employing malononitrile as the organic cyanation source has been disclosed, which proceeds efficiently at room temperature in open air under metal-catalyst-free conditions.**

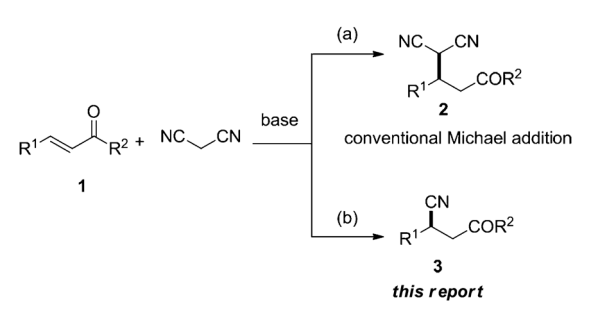
Conjugate addition of cyanide to  $\alpha,\beta$ -unsaturated enones has been extensively explored,<sup>1</sup> which has been demonstrated to be an efficient method toward synthesis of various substituted nitriles.<sup>2</sup> These existing reactions, while representing remarkable success in establishing general substrate scope and high asymmetric catalyst efficiency, require the use of various highly toxic cyanide sources in super-stoichiometric amounts.<sup>3</sup> Thus, the discovery of new sources of  $-\text{CN}$  generated from simple and readily available reagents is still an extremely attractive yet challenging goal.<sup>4</sup>

The Michael reaction is one of the most fundamental approaches for the formation of new carbon–carbon and carbon–heteroatom bonds.<sup>5</sup> As a typical Michael donor, malononitrile would, no doubt, react with  $\alpha,\beta$ -unsaturated enones, giving adduct **2** (Scheme 1a).<sup>6</sup> In our research on Michael-addition initiated cascade reactions, we disclose an unprecedented transformation into functionalized nitriles **3** via formal Michael addition by using malononitrile as the cyanide source (Scheme 1b). In 2005, Li and Li described copper-mediated oxidative coupling reaction of amines with malononitrile to give  $\alpha$ -amino nitriles.<sup>7a</sup> Recently, Zhou and co-workers reported copper-catalyzed

coupling reaction of aryl iodides with malononitrile to form aryl nitriles via copper-catalyzed cleavage of the C–CN bonds of malononitrile.<sup>7b</sup> To the best of our knowledge, reports on the utilization of malononitrile as an organic cyanation reagent via C–CN bond cleavage under metal-free conditions are scarce.<sup>8</sup> Compared with commonly used cyanation reagents such as MCN (M = Na, K, Cu, Zn),  $\text{K}_4[\text{Fe}(\text{CN})_6]$ ,<sup>9</sup> TMSCN,<sup>3a–c,10</sup> and acetone cyanohydrin,<sup>3d,11</sup> malononitrile as a new and alternative cyanide source has the distinct advantages of being relatively cheap, less toxic, stable and easy-to-handle. The reaction may proceed efficiently at room temperature in open air. This work would help to (i) obtain deep insight into traditional conjugation addition between Michael acceptors and malononitrile; (ii) present a more environmentally benign and potentially useful cyanation reagent; and (iii) provide an efficient and practical protocol for synthesizing functionalized nitriles.

Initially, the model reaction of chalcone **1a** with malononitrile was examined under basic conditions (Table 1). In the cases of using  $\text{K}_2\text{CO}_3$  as the base in solvents like DCE, THF, 1,4-dioxane and MeCN, the conventional Michael addition adduct **2a** was obtained in 92–97% yields at room temperature (Table 1, entries 1–4).

**Table 1** Optimization of the reaction conditions<sup>a</sup>

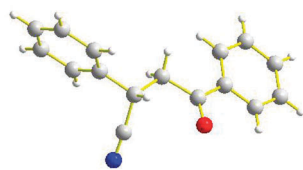


Entry	Solvent	Base	<i>T</i> (°C)	Time (h)	Yield <sup>b</sup> (%)	
					<b>2a</b>	<b>3a</b>
1	DCE	$\text{K}_2\text{CO}_3$ (1.1)	rt	12	97	0
2	THF	$\text{K}_2\text{CO}_3$ (1.1)	rt	12	94	0
3	1,4-Dioxane	$\text{K}_2\text{CO}_3$ (1.1)	rt	12	93	0
4	MeCN	$\text{K}_2\text{CO}_3$ (1.1)	rt	12	92	0
5	DMSO	$\text{K}_2\text{CO}_3$ (1.1)	rt	12	78	15
<b>6</b>	<b>DMF</b>	<b><math>\text{K}_2\text{CO}_3</math> (1.1)</b>	<b>rt</b>	<b>12</b>	<b>0</b>	<b>95</b>
7	DMF	NaOH (1.1)	rt	12	0	93
8	DMF	DBU (1.1)	rt	12	0	85
9	DMF	<i>t</i> -BuOK (1.1)	rt	12	0	92
10	DMF	Piperidine (1.1)	rt	12	98	0
11	DMF	DABCO (1.1)	rt	12	92	0
12	DMF	$\text{K}_2\text{CO}_3$ (1.1)	rt	6	49	47
13	DMF	$\text{K}_2\text{CO}_3$ (0.2)	rt	12	96	0

<sup>a</sup> Reactions were carried out with **1a** (1.0 mmol), malononitrile (1.1 equiv.) in solvent (4.0 mL) under basic conditions. <sup>b</sup> Isolated yield.

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Fig. 1 ORTEP drawing of **3a**.

When DMSO was used as the solvent, the yield of conjugate addition product **2a** decreased to 78%, along with the separation of cyanated product **3a** in 15% yield (Table 1, entry 5). The structure of **3a** was confirmed unambiguously by X-ray single crystal diffraction (Fig. 1). To our delight, upon switching the solvent to DMF, the yield of **3a** dramatically improved to 95% (Table 1, entry 6). Screening of different bases (Table 1, entries 7–11) showed that strong bases such as NaOH, DBU and *t*-BuOK afford **3a** in good to excellent yield (Table 1, entries 7–9), while weak organic bases like DABCO and piperidine gave adduct **2a** as the main product (Table 1, entries 10 and 11). Shortening the reaction time to 6 h led to a mixture of **2a** and **3a** in respective yields of 49% and 47% (Table 1, entry 12). Under otherwise identical conditions, upon cutting down the amount of  $K_2CO_3$  to 0.2 equiv., only **2a** was observed (Table 1, entry 13). Interestingly, products **2a** and **3a** can be prepared selectively by carefully controlling the reaction conditions, *e.g.* by selecting different bases, or merely changing the amount of the same base, or using different solvents.

Under the optimized conditions (Table 1, entry 6), a range of reactions were carried out with various  $\alpha,\beta$ -unsaturated carbonyl

**Table 2** Direct cyanation of enones **1** by malononitrile *via* formal Michael addition<sup>a</sup>

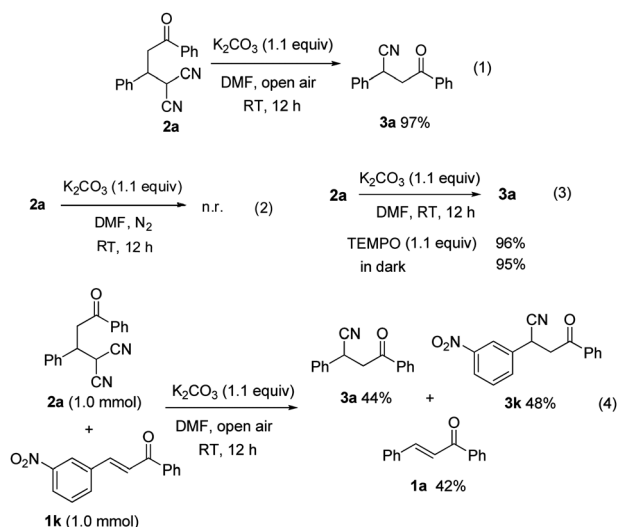
Entry	<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	<b>3</b>	Yield <sup>b</sup> (%)
1	<b>1a</b>	Ph	Ph	<b>3a</b>	95
2	<b>1b</b>	4-MeC <sub>6</sub> H <sub>4</sub>	Ph	<b>3b</b>	89
3	<b>1c</b>	2-MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>3c</b>	95
4	<b>1d</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>3d</b>	90
5	<b>1e</b>	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Ph	<b>3e</b>	91
6	<b>1f</b>	3,4-O <sub>2</sub> CH <sub>2</sub> Ph	Ph	<b>3f</b>	92
7	<b>1g</b>	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	<b>3g</b>	91
8	<b>1h</b>	2-ClC <sub>6</sub> H <sub>4</sub>	Ph	<b>3h</b>	90
9	<b>1i</b>	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	<b>3i</b>	96
10	<b>1j</b>	4-FC <sub>6</sub> H <sub>4</sub>	Ph	<b>3j</b>	89
11	<b>1k</b>	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	<b>3k</b>	51
12	<b>1l</b>	2-Furyl	Ph	<b>3l</b>	91
13	<b>1m</b>	2-Thienyl	Ph	<b>3m</b>	89
14	<b>1n</b>	<i>t</i> -Bu	Ph	<b>3n</b>	96 <sup>c</sup>
15	<b>1o</b>	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	<b>3o</b>	90
16	<b>1p</b>	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	<b>3p</b>	92
17	<b>1q</b>	Ph	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3q</b>	88
18	<b>1r</b>	Ph	2-Furyl	<b>3r</b>	93
19	<b>1s</b>	Ph	2-Thienyl	<b>3s</b>	97
20	<b>1t</b>	Ph	2-Pyridyl	<b>3t</b>	85 <sup>c</sup>
21	<b>1u</b>	Me	Ph	<b>3u</b>	— <sup>d</sup>

<sup>a</sup> Reactions were carried out with **1a** (1.0 mmol), malononitrile (1.1 equiv.), in the presence of  $K_2CO_3$  (1.1 equiv.) in DMF (4.0 mL) at room temperature for about 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> Run at 50 °C. <sup>d</sup> The product was not observed.

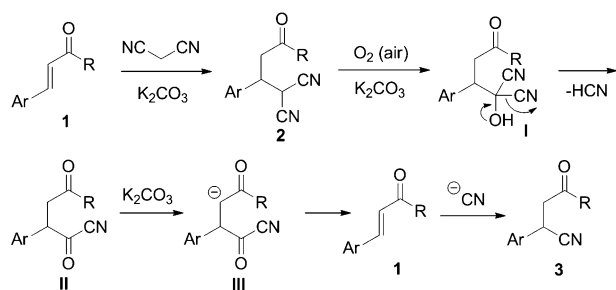
compounds **1** and malononitrile in the presence of  $K_2CO_3$  in DMF (Table 2). The reactions proceeded smoothly to afford the corresponding functionalized  $\alpha$ -aryl nitriles **3a–t** (except **3n**) in moderate to excellent yields (51–97%). The R<sup>1</sup> substituent of substrate **1** may be either electron-rich (Table 2, entries 1–6) or electron-deficient aryl (Table 2, entries 7–11), heteroaryl (Table 2, entries 12 and 13) and alkyl groups (Table 2, entry 14). The R<sup>2</sup> substituents were also broad, including electron-deficient aryl (Table 2, entries 15 and 16), electron-rich aryl (Table 2, entry 17) and heteroaryl (Table 2, entries 18–20). However, when it comes to the alkyl substituent like the Me group, the desired nitrile was not observed (Table 2, entry 21). It is worth noting that all the reactions were completely 1,4-selective, exhibiting a high regioselectivity.

In order to elucidate the possible mechanism for the conjugate cyanation reaction, several control experiments were carried out (Scheme 2). It was found that Michael adduct **2a** was converted into **3a** in 97% yield in open air (eqn (1)), but no reaction was observed if the reaction was conducted under a N<sub>2</sub> atmosphere (eqn (2)). This indicates that dioxygen in air may participate in the reaction. The conversion reaction from **2a** to **3a** was scarcely influenced by the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO 1.1 equiv.) (96% yield) or in the dark (95% yield), which fundamentally ruled out a radical mechanism (eqn (3)). In an isolated reaction of a mixture of **2a** and **1k** under standard conditions, two cyanated products **3a** and **3k** were isolated in 44% and 48% yields, respectively (eqn (4)). Meanwhile, enone **1a** (which is supposed to be derived from **2a**) was separated in 42% yield. The cross-over experiment, along with the result obtained under a N<sub>2</sub> atmosphere (eqn (2)), suggests that an aerobic oxidation<sup>12</sup> and subsequent elimination may be involved in the reaction.

Based on all the results described above, a plausible mechanism for the efficient one-pot transformation into functionalized nitriles **3** is proposed in Scheme 3. Firstly, Michael addition of enone **1** with malononitrile furnishes adduct **2**. Secondly, oxidation of tertiary C–H in **2** by dioxygen in air in the presence of a base provides cyanohydrin **I**.<sup>13,14</sup> Thirdly, elimination of hydrogen cyanide and formyl cyanide



Scheme 2 Control experiments.



**Scheme 3** A plausible reaction mechanism.

(I → II → III → 1) regenerates enone 1.<sup>15</sup> Finally, Michael addition by cyanide affords product 3.

In conclusion, cyanation of  $\alpha,\beta$ -unsaturated enones by malononitrile has been disclosed, which enables a variety of functionalized  $\alpha$ -aryl nitriles to be obtained in high yields under extremely mild conditions (room temperature, dioxygen in air as the oxidant, and metal-free). Further exploration of malononitrile as an organic cyanation reagent in other types of reactions is ongoing.

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## Notes and references

- (a) W. Nagata and M. Yoshioka, *Org. React.*, 1977, **25**, 255; (b) J. Yang, Y. Shen and F.-X. Chen, *Synthesis*, 2010, 1325; (c) J. Yang and F. Chen, *Chin. J. Chem.*, 2010, **28**, 981; (d) T. Arai, Y. Suemitsu and Y. Ikematsu, *Org. Lett.*, 2009, **11**, 333; (e) L. D. S. Yadav, C. Awasthi and A. Rai, *Tetrahedron Lett.*, 2008, **49**, 6360; (f) H. Iida, T. Moromizato, H. Hamana and K. Matsumoto, *Tetrahedron Lett.*, 2007, **48**, 2037.
- Nitriles are ubiquitous structural motifs frequently found in natural products, pharmaceuticals, agrochemicals, and optoelectronic materials. (a) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications*, Georg Thieme, Stuttgart, Germany, 4th edn, 2001; (b) P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049.
- (a) C. Mazet and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2008, **47**, 1762; (b) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai and M. Shibasaki, *Tetrahedron*, 2007, **63**, 5820; (c) P. Bernal, R. Fernandez and J. M. Lassaletta, *Chem.-Eur. J.*, 2010, **16**, 7714; (d) H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2012, **51**, 4959; (e) A. V. Ushkov and V. V. Grushin, *J. Am. Chem. Soc.*, 2011, **133**, 10999; (f) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 8862; (g) X. Jia, D. Yang, S. Zhang and J. Cheng, *Org. Lett.*, 2009, **11**, 4716; (h) H.-J. Cristau, A. Ouali, J.-F. Spindler and M. Taillefer, *Chem.-Eur. J.*, 2005, **11**, 2483; (i) C. Yang and J. M. Williams, *Org. Lett.*, 2004, **6**, 2837.
- (a) J. Kim, J. Choi, K. Shin and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 2528; (b) S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374; (c) J. Velcicky, A. Soicke, R. Steiner and H.-G. Schmalz, *J. Am. Chem. Soc.*, 2011, **133**, 6948; (d) J. Kim and S. Chang, *J. Am. Chem. Soc.*, 2010, **132**, 10272; (e) P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519; (f) P. Anbarasan, H. Neumann and M. Beller, *Chem.-Eur. J.*, 2010, **16**, 4725; (g) G. Zhang, X. Ren, J. Chen, M. Hu and J. Cheng, *Org. Lett.*, 2011, **13**, 5004; (h) J. Wang, W. Li, Y. Liu, Y. Chu, L. Lin, X. Liu and X. Feng, *Org. Lett.*, 2010, **12**, 1280; (i) Z. Zhang and L. S. Liebeskind, *Org. Lett.*, 2006, **8**, 4331.
- (a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, 1992; (b) M. E. Jung, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, M. F. Pergamon, Oxford, 1991, vol. 4, pp. 1–67; (c) E. D. Bergman, D. Ginsburg and R. Pappo, *Org. React.*, 1959, **10**, 179; (d) N. Krause and A. Hoffmann-Roder, *Synthesis*, 2001, 171.
- For reviews on malononitrile, see: (a) F. Freeman, *Chem. Rev.*, 1980, **80**, 329; (b) F. Freeman, *Chem. Rev.*, 1969, **69**, 591.
- (a) Z. Li and C.-J. Li, *Eur. J. Org. Chem.*, 2005, 3173; (b) Z. Jiang, Q. Huang, S. Chen, L. Long and X. Zhou, *Adv. Synth. Catal.*, 2012, **354**, 589.
- Only one example with malononitrile as a cyanide source was found. See: X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2009, **74**, 74649.
- (a) P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 648; (b) G. Yan, C. Kuang, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 1052; (c) T. Schareina, A. Zapf and M. Beller, *Chem. Commun.*, 2004, 1388.
- (a) L. Lin, W. Yin, X. Fu, J. Zhang, X. Ma and R. Wang, *Org. Biomol. Chem.*, 2012, **10**, 83; (b) N. Kurono, N. Nii, Y. Sakaguchi, M. Uemura and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2011, **50**, 5541; (c) T. Mita, K. Sasaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 514; (d) X. Liu, B. Qin, X. Zhou, B. He and X. Feng, *J. Am. Chem. Soc.*, 2005, **127**, 12224; (e) G. M. Sammis, H. Danjo and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 9928; (f) G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442.
- (a) B. A. Provencher, K. J. Bartelson, Y. Liu, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2011, **50**, 10565; (b) T. Schareina, A. Zapf, A. Cotte, M. Gotta and M. Beller, *Adv. Synth. Catal.*, 2011, **353**, 777; (c) E. J. Park, S. Lee and S. Chang, *J. Org. Chem.*, 2010, **75**, 2760; (d) R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Pettersen and A. Ricci, *J. Org. Chem.*, 2006, **71**, 9869; (e) M. Sundermeier, A. Zapf and M. Beller, *Angew. Chem., Int. Ed.*, 2003, **42**, 1661.
- (a) S. S. Stahl, *Science*, 2005, **309**, 1824; (b) W. Adam, C. R. Saha-Mçller and P. A. Ganeshpure, *Chem. Rev.*, 2001, **101**, 3499.
- (a) D. Yang, H. Yang and H. Fu, *Chem. Commun.*, 2011, **47**, 2348; (b) K. Schröder, B. Join, A. J. Amali, K. Junge, X. Ribas, M. Costas and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 1425; (c) S. H. Kim, K. H. Kim and J. N. Kim, *Adv. Synth. Catal.*, 2011, **353**, 3335; (d) B. C. Giglio, V. A. Schmidt and E. J. Alexanian, *J. Am. Chem. Soc.*, 2011, **133**, 13320.
- A hydroperoxide intermediate can also not be completely excluded at this stage.
- For metal-catalyzed C–CN bond cleavage, see: (a) M. Tobisu and N. Chatani, *Chem. Soc. Rev.*, 2008, **37**, 300; (b) D. C. Koester, M. Kobayashi, D. B. Werz and Y. Nakao, *J. Am. Chem. Soc.*, 2012, **134**, 6544; (c) M. Tobisu, H. Kinuta, Y. Kita, E. Remond and N. Chatani, *J. Am. Chem. Soc.*, 2012, **134**, 115; (d) K. Nakai, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2011, **133**, 11066; (e) M. Tobisu, Y. Kita, Y. Ano and N. Chatani, *J. Am. Chem. Soc.*, 2008, **130**, 15982; (f) Q. Wen, J. Jin, B. Hu, P. Lu and Y. Wang, *RSC Adv.*, 2012, **2**, 6167.