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DMAP-catalyzed cyanation of aldehydes and ketones with ethyl cyanoformate

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ABSTRACT

The cyanation of carbonyl compounds with ethyl cyanoformate is catalyzed by 4-dimethylaminopyridine (DMAP) to afford the corresponding cyanohydrin carbonates in excellent yields. The system provides a convenient method for cyanation of carbonyl compounds without using metal catalysts or solvents.

The nucleophilic addition of cyanide to carbonyl compounds is a powerful method for the construction of carbon–carbon bonds and represents an invaluable tool in organic synthesis.[1,2] Although hydrogen cyanide (HCN) is the simplest cyanide source for cyanation of carbonyl compounds, it is strongly toxic and difficult to handle. Several alternative cyanating reagents have been developed. Trimethylsilyl cyanide[3] has most commonly been used as a cyanide ion source because it is safer and easier to handle than hydrogen cyanide. Acyl cyanides[4] and alkyl cyanoformates[5] have been used as alternative cyanating reagents to afford the O-carbonylated cyanohydrins (Fig. 1). With these reagents, several methods using tertiary amines,[5] tributyltin cyanide,[6] or dimethyl sulfoxide[4b,7] as an activator have recently been reported. Here, we report a metal-free cyanation of aldehydes and ketones with ethyl cyanoformate in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP).

We initially examined the cyanation of 3-phenylpropanal (**4a**) with several cyanating reagents (**1–3**) in the presence of 1 mol % of DMAP in acetonitrile (Table 1).[8] Although the product yields were low for trimethylsilyl cyanide (**1**) and benzoyl cyanide (**2**) (entries 1 and 2), ethyl cyanoformate (**3**) gave the corresponding cyanohydrin carbonate (**7a**) in an excellent yield (97%) (entry 3).[9] No product was obtained in the absence of DMAP (entry 4), implying that DMAP was essential for cyanation with cyanoformate **3**. The concentration greatly influenced the rate of the cyanation. The reaction in 0.5 M acetonitrile completed within 0.5 h to afford the corresponding product (entry 5).

With the optimal conditions in hand, we explored the scope of aldehydes for the cyanation (Table 2).[10] Aliphatic aldehydes underwent cyanation in good to high yields in the presence of 1 mol % DMAP (entries 1–3), although the sterically congested aldehyde **4c** resulted in a moderate yield. In contrast, aromatic aldehydes were less reactive than aliphatic aldehydes (entries 5–10). Therefore, the use of 5 mol % catalyst was required for completion of the reaction. The cyanation of *p*-anisaldehyde (**4e**) bearing an electron-donating substituent was quite slow, but provided a good yield after 24 h (entry 5). Introduction of an electron-withdrawing group at the *para*-position increased the reactivity (entry 6). Products were obtained in excellent yields for the reaction of sterically hindered aromatic aldehydes, such as 1- or 2-naphthaldehyde (**4h**

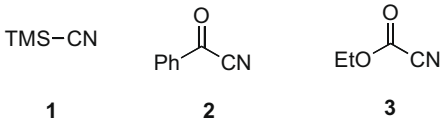
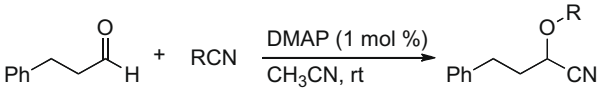


Figure 1. Cyanide sources.

Table 1
Cyanation of 3-phenylpropanal (**4a**) with cyanide sources (**1–3**)[a]



Entry	RCN	CH_3CN (mL)	Time (h)	Yield[b] (%)
1	**1**	5	2	<10
2	**2**	5	2	Trace
3	**3**	5	2	97
4[c]	**3**	5	2	0
5	**3**	1	0.5	96

[a] Unless otherwise noted, reactions were carried out by addition of a cyanide source (0.55 mmol) to a solution of 3-phenylpropanal (**4a**) (0.5 mmol) and DMAP (1 mol %) in CH_3CN at room temperature.
[b] Isolated yield.
[c] The reaction was conducted without catalyst.

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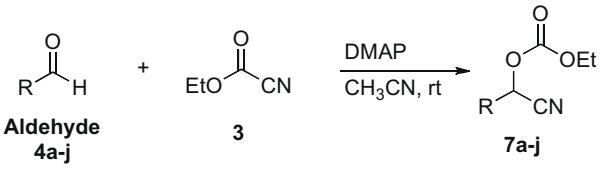
Table 2
Cyanation of various aldehydes (**4**) with ethyl cyanoformate (**3**) catalyzed by DMAP[a]



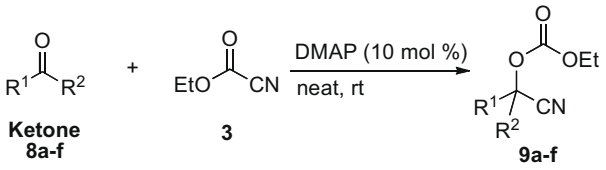
Entry	Aldehyde	DMAP mol%	Time (h)	Yield[b] (%)
1	$PhCH_2CH_2CHO$ **4a**	1	0.5	96
2	*i*PrCHO **4b**	1	1	83
3	*t*BuCHO **4c**	1	2	55
4	PhCHO **4d**	5	8	99
5	4-$MeOC_6H_4CHO$ **4e**	5	24	81
6	4-BrC_6H_4CHO **4f**	5	2	98
7	2-Furfural **4g**	5	8	97
8	1-Naphthaldehyde **4h**	5	6	97
9	2-Naphthaldehyde **4i**	5	8	99
10[c,d]	4-$HO_2CC_6H_4CHO$ **4j**	5	24	78

[a] Unless otherwise noted, reactions were carried out by addition of ethyl cyanoformate (0.55 mmol) to a solution of aldehydes (0.5 mmol) and DMAP in CH_3CN (1 mL) at room temperature.
[b] Isolated yield.
[c] The reaction was conducted using 2.5 equivalents of ethyl cyanoformate (**3**).
[d] EtOH (3 mL) was used instead of acetonitrile.

and **4i**). The reaction of aldehyde **4j**, which contains a carboxyl group, yielded the desired product in 78% yield using 2.5 equiv of cyanide source **3** (entry 10). It should be noted that the current method tolerates carboxyl groups. Furthermore, the current method is effective and convenient for the synthesis of cyanohydrin derivatives because simple extraction or chromatography affords the corresponding products.

Next, we investigated application of the DMAP-catalyzed cyanation to ketones (Table 3).[11] The reaction of cyclopentanone (**8a**) proceeded quite slowly to give the corresponding cyanohydrin in a low yield (entry 1). The reactivities of ketones were much lower than those of aldehydes. As shown in Table 1, concentration was important for this cyanation. The reaction of **8a** was performed using 10 mol % DMAP without solvent (entry 2). The reaction did proceed to afford the corresponding cyanohydrin carbonate in a good yield (85%). The reaction of cyclohexanone (**8b**) gave a quantitative yield for the same reaction time (entry 3). The reaction of

Table 3
Cyanation of various ketones (**8**) with ethyl cyanoformate (**3**) catalyzed by DMAP[a]



Entry	Ketone	Time (h)	Yield[b] (%)
1[c]	Cyclopentanone **8a**	24	20
2	Cyclopentanone **8a**	24	85
3	Cyclohexanone **8b**	24	99
4	Acetophenone **8c**	24	30
5	Cyclohexyl methyl ketone **8d**	24	87
6	Isopropyl methyl ketone **8e**	24	73
7	Pinacolone **8f**	48	44

[a] Unless otherwise noted, reactions were carried out by addition of ethyl cyanoformate (0.55 mmol) to a solution of ketones (0.5 mmol) and DMAP (10 mol %) without solvent at room temperature.
[b] Isolated yield.
[c] The reaction was conducted in acetonitrile (1 mL).

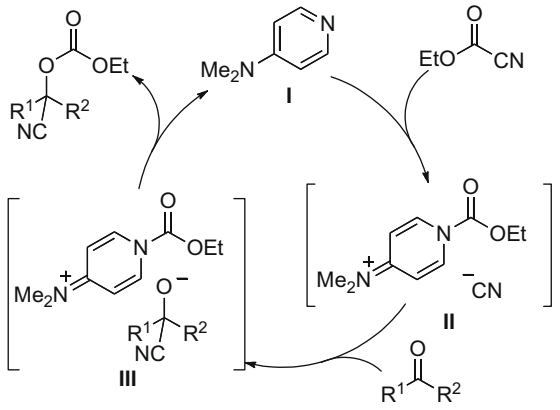


Figure 2. Proposed reaction mechanism for cyanation catalyzed by DMAP.

acetophenone (**8c**), an aromatic ketone, gave the cyanohydrin derivative in a low yield (entry 4). Acyclic ketones (**8d** and **8e**) gave the cyanohydrins in 87% and 73% yields, respectively (entries 5 and 6), although the cyanation of a sterically hindered ketone, pinacolone (**8f**), was slow (entry 7).

A proposed mechanism for the cyanation catalyzed by DMAP is shown in Figure 2. First, the nitrogen atom of the pyridine ring of DMAP (**I**) attacks the carbonyl carbon of ethyl cyanoformate to form the cationic carbamate intermediate (**II**).[12] Next, the released cyanide anion reacts with aldehydes or ketones, and the alkoxide anion of the cyanohydrin (**III**) is generated. Finally, the alkoxide is carboxylated to afford the corresponding cyanohydrin carbonate, and DMAP is regenerated to participate in a subsequent catalytic cycle (**I**).

In conclusion, we successfully demonstrated the effective and convenient cyanation of various aldehydes and ketones using DMAP as a nucleophilic catalyst. The system provides an effective method for cyanation of carbonyl compounds without metal catalysts or solvents. Investigations to clarify the detailed reaction mechanism and to develop asymmetric version are currently underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.123.

References and notes

1. For recent reviews on synthesis and reactions of cyanohydrins, see: (a) North, M. *Synlett* **1993**, 807–820; (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; (c) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; (d) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752–2778; (e) Chen, F.-X.; Feng, X. *Synlett* **2005**, 892–899.
2. For recent asymmetric cyanations, see: (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642; (b) Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405–2409; (c) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413; (d) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691–694; (e) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805–814; (f) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; (g) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636–3638; (h) Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589–2592; (i) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 4505–4507; (j)

Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; (k) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197–200; (l) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021–3024; (m) Abiko, Y.; Yamagiwa, N.; Sugita, M.; Tian, J.; Matsunaga, S.; Shibasaki, M. *Synlett* **2004**, 2434–2436; (n) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413–3422; (o) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592–11593; (p) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776–10777; (q) Wentao, W.; Shaohua, G.; Xiaohua, L.; Xiaoming, F. *Synlett* **2007**, 2875–2878; (r) Gou, S.; Wang, J.; Liu, X.; Wang, W.; Chen, F.-X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 343–349; (s) Chinchilla, R.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2008**, *19*, 265–268; (t) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776–1780; (u) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Prathap, K. J.; Jasra, R. V. *Eur. J. Org. Chem.* **2008**, 4511–4515; (v) Chinchilla, R.; Nájera, C.; Ortega, F. J.; Tari, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2279–2286; (w) Wang, J.; Wang, W.; Li, W.; Hu, X.; Shen, K.; Tan, C.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 11642–11659; (x) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Pathak, K.; Bajaj, H. C. *Chirality* **2010**, *22*, 153–158.

3. For cyanations with trimethylsilyl cyanide, see: (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56; (b) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, *49*, 4929–4932; (c) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, *20*, 537–540; (d) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, *20*, 541–544; (e) Golinski, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1993**, *58*, 159–164; (f) Saravanan, P.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3823–3824; (g) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Tetrahedron Lett.* **2001**, *42*, 3041–3043; (h) Córdoba, R.; Plumet, J. *Tetrahedron Lett.* **2003**, *44*, 6157–6159; (i) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949–952; (j) Amurrio, I.; Córdoba, R.; Csaky, A. G.; Plumet, J. *Tetrahedron* **2004**, *60*, 10521–10524; (k) Chen, F.-X.; Wolfert, M. A.; Moore, J. N.; Boons, G.-J. *Chem. Eur. J.* **2004**, *10*, 4790–4797; (l) Liu, X. H.; Qin, B.; Zhou, X.; He, B.; Feng, X. M. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965; (m) Qin, B.; Liu; Xiaohua; Shi, J.; Zheng, K.; Zhao, H.; Feng, X. *J. Org. Chem.* **2007**, *72*, 2374–2378; (n) Wang, X.; Tian, S.-K. *Tetrahedron Lett.* **2007**, *48*, 6010–6013; (o) Shen, K.; Liu, X.; Li, Q.; Feng, X. *Tetrahedron* **2008**, *64*, 147–153; (p) Matsukawa, S.; Sekine, I.; Iitsuka, A. *Molecules* **2009**, *14*, 3353–3359.
4. For cyanations with acyl cyanides, see: (a) Okimoto, M.; Chiba, T. *Synthesis* **1996**, 1188–1190; (b) Watahiki, T.; Ohba, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 2679–2681; (c) Li, F.; Widyan, K.; Wingstrand, E.; Moberg, C. *Eur. J. Org. Chem.* **2009**, 3917–3922.
5. For cyanations with alkyl cyanoformates, see: (a) Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807–1810; (b) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423–1425; (c) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995–6003; (d) Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191–7194.
6. Scholl, M.; Lim, C.-K.; Fu, G. C. *J. Org. Chem.* **1995**, *60*, 6229–6231.
7. Iwanami, K.; Hinakubo, Y.; Oriyama, T. *Tetrahedron Lett.* **2005**, *46*, 5881–5883.
8. The solvent has a great influence on the cyanation of aldehydes. Propionitrile and neat condition afforded the product in excellent yield (97% and 96%, respectively), while other solvents gave unsatisfactory results; toluene (trace), THF (45%), CH_2Cl_2 (29%) and EtOH (56%).
9. The ethyl carbonate group of **7a** could be removed with 1% K_2CO_3 in MeOH to afford the corresponding cyanohydrin in 93% yield.
10. Typical procedure for cyanation of aldehydes catalyzed by DMAP (Table 1, entry 5): To a stirred solution of aldehyde **4a** (0.066 mL, 0.5 mmol, 1.0 equiv) and DMAP (0.61 mg, 0.005 mmol, 1 mol %) in acetonitrile (1 mL) was added ethyl cyanoformate (**3**) (0.055 mL, 0.55 mol, 1.1 equiv) at room temperature under argon atmosphere. The mixture was stirred at the same temperature for 30 min and then brine. The mixture was extracted with EtOAc (10 mL) and the organic layer was dried over Na_2SO_4. After concentration, the crude material was purified by column chromatography (silica gel: 6 g, hexane–EtOAc: 6/1) to give the product **7a** (115.0 mg, 96% yield) as a colorless solid.
11. Typical procedure for cyanation of ketones catalyzed by DMAP (Table 3, entry 3): To a stirred mixture of ketone **8b** (0.45 mmol, 1.0 equiv.) and DMAP (5.5 mg, 0.045 mmol, 10 mol %) was added ethyl cyanoformate (**3**) (0.049 mL, 0.5 mol, 1.1 equiv) at room temperature under argon atmosphere. The mixture was stirred at the same temperature for 24 h. The mixture was purified by column chromatography (silica gel: 6 g, hexane–EtOAc: 4/1) to give the product **9b** (88.0 mg, 99% yield) as a colorless oil.
12. Pyridine and *N*,*N*-dimethylaniline did not promote the cyanation. Therefore, the nucleophilicity of DMAP plays an important role in the cyanation, as observed in DMAP-promoted acylation of alcohols.