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N-heterocyclic carbene catalyzed cyanation reaction of carbonyl compounds with ethyl cyanoformate and acetyl cyanide

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ABSTRACT

N-heterocyclic carbene (NHC) has been employed as an efficient catalyst for cyanation reaction of carbonyl compounds. Under catalysis of 1 mol % NHCs, various aldehydes and 2,2,2-trifluoroacetophenone coupled with ethyl cyanoformate in THF to provide cyanohydrins ethyl carbonates in excellent yields. While in the presence of 10 mol % catalyst, different types of aldehydes and 2,2,2-trifluoroacetophenone reacted with acetyl cyanide in dichloroethane to give acylated cyanohydrins in moderate to high yields.

The past decade has witnessed a dramatic growth in organocatalysis chemistry of N-heterocyclic carbenes (NHCs).[1] As one class of versatile nucleophilic organocatalyst, NHCs have been utilized broadly in a variety of important transformations, such as benzoin reaction,[2] Stetter reaction,[3] ring-opening reaction,[4] homoenolate transformations[5] and other reactions.[6] Recently, NHCs were found to be efficient catalysts for cyanosilylation of carbonyl compounds and aldimines, using trimethylsilyl cyanide as a cyanation reagent.[7]

Cyanohydrins serve as essential building blocks in biologically active compounds,[8] and tremendous efforts have been devoted to synthesizing this type of important compounds.[9] Hydrogen cyanide and trimethylsilyl cyanide are most commonly used as the sources of cyanide ions. However, the intrinsic high toxicity and the instability of *O*-trimethylsilyl cyanohydrins restrain their potential application sometimes. To overcome the unavoidable weakness of hydrogen cyanide and trimethylsilyl cyanide, alkyl cyanoformates and acyl cyanide have been applied as alternative cyanide sources, and different catalytic systems for these types of cyanations have been developed successfully in the recent years.[10] In contrast to the extensive exploration of chiral ligand-metal catalysis, the reactions promoted by organocatalysts were far less examined.[11] In line with our continue interest of NHCs chemistry,[12] we found that NHCs can be used as efficient catalysts for the cyanation of aldehydes with ethyl cyanoformate and acetyl cyanide, respectively. Herein, we would like to discourse our preliminary results on this topic.

Initially, the cyanoethoxycarbonylation reaction of benzaldehyde and ethyl cyanoformate was tested under catalysis of different kinds of NHCs. To our delight, we found that the reaction proceeded very smoothly in the presence of 10 mol % 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr, a stable NHC),[13] affording cyanohydrin ethyl carbonate **8a** in a moderate yield after 12 h (Table 1, entry 1). Interestingly, when we increased the amount of ethyl cyanoformate to 2.0 equiv, the reaction could be converted quantitatively within 30 min (Table 1, entry 2). Similar results were obtained with NHCs generated in situ from precursors **2** and **3** (Table 1, entries 3, 4), whereas NHCs derived from thiazolium and triazolium salts showed low catalytic activities (Table 1, entries 5–7). A brief survey of solvents revealed that dichloromethane, ether and toluene were all suitable reaction media (Table 1, entries 8–10). Surprisingly, lowered catalyst loading to 1 mol %, the excellent reaction yield can still be maintained (Table 1, entry 11). Even after decreasing catalyst loading to 0.5 mol %, the reaction finished in slightly lower yield within 2 h (Table 1, entry 12). Further reduced catalyst loading to 0.1 mol % led to a dramatic decrease of the yield (Table 1, entries 13, 14).

With the optimal reaction conditions in hand, a series of aldehydes were evaluated for the reaction and the results were summarized in Table 2.[14] It was found that both aromatic and aliphatic aldehydes were suitable electrophiles. Aromatic aldehydes with either electro-donating or withdrawing groups worked well, and the substituted groups showed a slight influence on the reaction yield (Table 2, entries 1–7). Additionally, the position of

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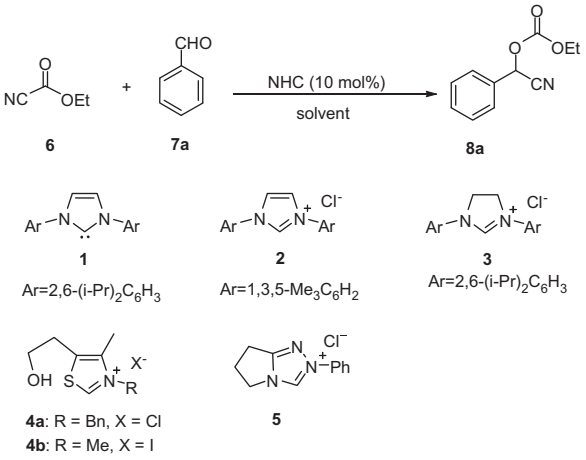
Table 1
NHCs catalyzed cyanation of benzaldehyde with ethyl cyanoformate[a]



Entry	NHC	Solvent	Time (h)	Yield[b] (%)
1[c]	**1**, (10 mol %)	THF	12	63
2	**1**, (10 mol %)	THF	0.5	99
3	**2**, KOt-Bu (10 mol %)	THF	1.5	91
4	**3**, KOt-Bu(10 mol %)	THF	2	90
5	**4a**, KOt-Bu(10 mol %)	THF	24	11
6	**4b**, KOt-Bu(10 mol %)	THF	24	18
7	**5**, KOt-Bu(10 mol %)	THF	24	14
8	**1**, (10 mol %)	DCM	1	95
9	**1**, (10 mol %)	Et_2O	1	96
10	**1**, (10 mol %)	Toluene	1	85
11	**1**, (1 mol %)	THF	1	98
12	**1**, (0.5 mol %)	THF	2	89
13	**1**, (0.1 mol %)	THF	12	22
14	**1**, (0.01 mol %)	THF	12	—

[a] **6** (2.0 equiv), **7a** (1.0 equiv), solvent: 2.0 mL, r.t.
[b] Isolated yields.
[c] **6** (1.0 equiv).

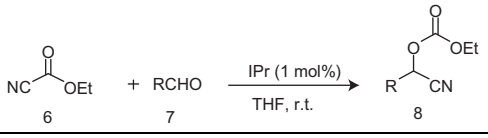
substituents had little effects on the reactions (Table 2, entries 8–15). On the other hand, aliphatic aldehydes such as cyclohexanecarboxaldehyde and 3-phenylpropionaldehyde were also good substrates for the additions (Table 2, entries 17, 18). Interestingly, 2,2,2-trifluoroacetophenone was also proved to be an excellent candidate, giving **8s** in a 64% yield (Table 2, entry 19).

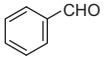
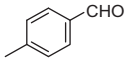
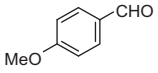
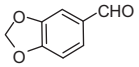
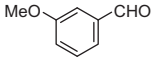
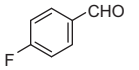
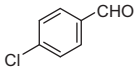
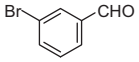
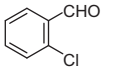
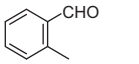
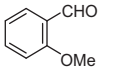
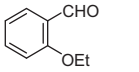
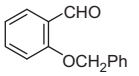
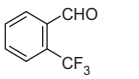
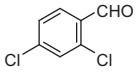
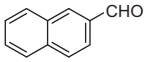
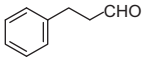
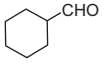
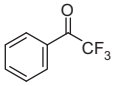
In the view of the high reactivity of ethyl cyanoformate observed, acetyl cyanide **9** was also tested.[15] This time, the solvent switched to DCE, and increasing the loading of IPr to 10 mol % proved to be optimal.[16] High yields were obtained for the most tested aromatic as well as the aliphatic aldehydes, although relatively long time was needed, presumably because of the stronger bond between the acetyl and cyanide groups in **9**. As expected, the reaction of aromatic aldehydes with electron-donating groups proceeded slowly and provided the desired products in moderate yields (Table 3, entries 1–17). Also, 2,2,2-trifluoroacetophenone was investigated, giving **10r** in low yield (Table 3, entry 18).

Based on the previous work of NHCs promoted cyanosilylation reaction of carbonyl compounds, two plausible mechanisms were illustrated in Scheme 1. Initially, the addition of NHC to aldehyde may initiate the following cyanation reaction (pathway **I**). Alternatively the addition was triggered through the activation of cyanation reagent by NHCs (pathway **II**).'

In summary, we have demonstrated a new method for NHCs-catalyzed cyanation of aldehydes and 2,2,2-trifluoroacetophenone with ethyl cyanoformate or acetyl cyanide. The low catalyst loading and mild conditions provide a valuable approach for the synthesis of O-protected cyanohydrins. Further studies toward the expansion of the scope, and using this method to other electrophiles are ongoing in our laboratory.

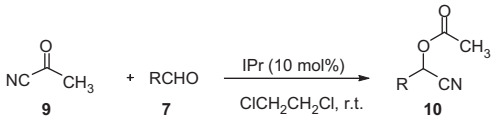
Table 2
NHCs catalyzed cyanation of aldehydes with ethyl cyanoformate[a]

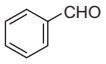
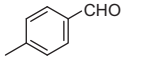
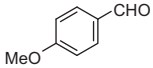
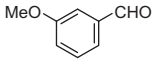
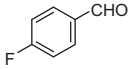
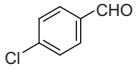
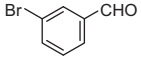
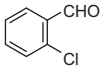
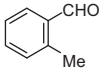
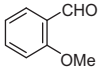
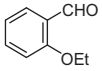
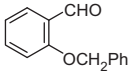
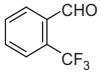
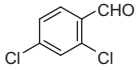
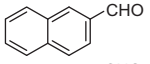
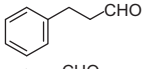
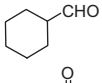
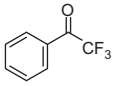


Entry	Aldehyde	Time (h)	Product	Yield[b] (%)
1		1	**8a**	98
2		24	**8b**	90
3		24	**8c**	73
4		36	**8d**	83
5		2	**8e**	99
6		12	**8f**	96
7		4	**8g**	94
8		12	**8h**	94
9		24	**8i**	90
10		4	**8j**	97
11		4	**8k**	98
12		24	**8l**	97
13		4	**8m**	85
14		4	**8n**	94
15		8	**8o**	91
16		2	**8p**	99
17		36	**8q**	70
18		12	**8r**	82
19		12	**8s**	64

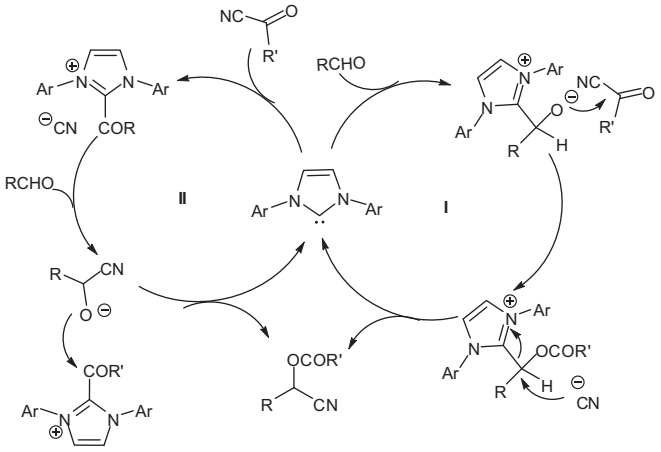
[a] Reaction conditions: **6** (2.0 equiv), **7** (1.0 equiv), IPr (1 mol %), THF 2.0 mL, r.t.
[b] Isolated yields.

Table 3
NHCs catalyzed cyanation of aldehydes with acetyl cyanide[a]



Entry	Aldehyde	Time (h)	Product	Yield[b] (%)
1		24	**10a**	83
2		36	**10b**	65
3		36	**10c**	62
4		36	**10d**	81
5		24	**10e**	78
6		12	**10f**	82
7		18	**10g**	76
8		12	**10h**	78
9		48	**10i**	82
10		48	**10j**	73
11		48	**10k**	71
12		48	**10l**	70
13		36	**10m**	84
14		8	**10n**	89
15		24	**10o**	82
16		36	**10p**	90
17		12	**10q**	71
18		36	**10r**	30

[a] Reaction conditions: **9** (2.0 equiv), **7** (1.0 equiv), IPr (10 mol %), solvent 2.0 mL, r.t.
[b] Isolated yields.



Scheme 1. Proposed mechanisms.

Acknowledgments

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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.2011.10.119.

References and notes

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14. *Typical procedure for cyanation of aldehydes with ethyl cyanoformate* (Table 2 entry 1): To a stirred solution of aldehyde **7a** (48.0 μL, 0.5 mmol, 1.0 equiv) in THF (2.0 mL) was added ethyl cyanoformate (98.0 μL, 1.0 mmol, 2.0 equiv) at room temperature under argon atmosphere. After that the solution was then cooled to 0 °C and IPr (2.0 mg, 1 mol %) was added. The mixture was stirred at room temperature until the starting aldehyde was fully consumed as indicated by TLC concentration and the crude material was purified by column chromatography (PE-EtOAc: 9:1) to afford product **8a** (100 mg, 98%) as a colorless oil. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.59–7.53 (m, 2H), 7.49–7.44 (m, 3H), 6.27 (s, 1H), 4.37–4.23 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.65, 131.45, 130.85, 129.50, 128.10, 115.96, 66.58, 65.85, 14.34; GC–MS (EI) m/z 205.0 $[M]^+$.
15. The addition of benzaldehyde to acetyl cyanide in THF under optimal conditions that are used for cyanation with ethyl cyanoformate, isolated only 35% yield of the product. After a brief survey of solvents, catalyst loading and other reaction conditions, we found that in the presence of 10 mol % IPr, the cyano-acylation of aldehydes worked well in dichloroethane and afforded acylated cyanohydrins in high yields. See Supplementary data for details of reaction procedure.
16. *Typical procedure for cyanation reaction with acetyl cyanide* (Table 3 entry 6): To a stirred solution of aldehyde **7f** (70.0 mg, 0.5 mmol, 1.0 equiv) in 1,2-DCE (2.0 mL) was added acetyl cyanide (80.0 μL, 1.0 mmol, 2.0 equiv) at room temperature under argon atmosphere. After that the solution was then cooled to 0 °C and IPr (19.4 mg, 10 mol %) was added. The mixture was stirred at room temperature until the starting aldehyde was fully consumed as indicated by TLC concentration, the crude material was purified by column chromatography (PE-EtOAc: 15:1) to afford product **10f** (92 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H), 7.45–7.41 (m, 2H), 6.38 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.78, 136.64, 130.26, 129.52, 129.27, 115.77, 62.15, 20.43; GC–MS: (EI) m/z 209.0 $[M]^+$.