Cyano-Phosphorylation of Aldehydes Catalyzed by a Nucleophilic *N*-Heterocyclic Carbene

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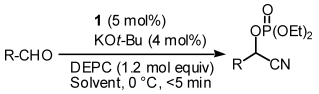
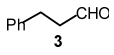
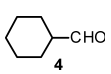
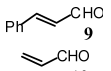
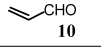
The first method for cyano-phosphorylation of aldehydes with diethyl cyanophosphonate in the presence of *N*-heterocyclic carbene prepared from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and KO*t*-Bu, as a nucleophilic catalyst, is described.

Key words cyano-phosphorylation; *N*-heterocyclic carbene; imidazolium salt; nucleophilic catalyst

N-Heterocyclic carbenes prepared from imidazolium salts and bases, have been used mainly in transition metal-catalyzed reactions as ligands.[1,2] However, their suitability as nucleophilic catalysts has been underdeveloped.[3—11] We recently reported a catalytic method leading to the synthesis of various cyanohydrins using *N*-heterocyclic carbene **2** prepared from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**1**) and KO*t*-Bu as a nucleophilic catalyst in cyanosilylation reactions.[12] Cyanohydrins and their trimethylsilyl ethers are versatile intermediates in organic synthesis,[13,14] but the instability of cyanohydrins and their trimethylsilyl ethers is sometimes problematic for further transformations. Therefore, the development of a one-pot cyanation-*O*-protection reaction with a stable protecting group is desirable. In 1983, the above one-pot reaction of carbonyl compounds with diethyl cyanophosphonate (DEPC) in the catalytic amount of lithium diisopropylamide has been reported by Shioiri *et al.*[15] Herein, we disclose the first catalytic method leading to the synthesis of various cyanohydrin-*O*-phosphonates using *N*-heterocyclic carbene **2** prepared from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**1**) and KO*t*-Bu as a nucleophilic catalyst in cyano-phosphorylation reactions.

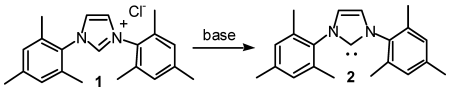
Table 1. Cyano-Phosphorylation of Various Aldehydes with **2** as a Catalyst[a]



Entry	Aldehyde	Solvent	Yield (%) of cyanohydrin-*O*-phosphonate[b]
1	 **3**	THF	91
2	 **4**	THF	94
3	*t*-Bu-CHO **5**	THF	98
4	Ph-CHO **6**	THF	94
5	**6**	DMF	91
6	4-Cl-C_6H_4-CHO **7**	THF	92
7	4-MeO-C_6H_4-CHO **8**	THF	90
8[c]	 **9**	THF	19[d]
9[e]	 **10**	THF	90

a) All reactions were performed with 5 mol% of **1**, 4 mol% of KO*t*-Bu and 1.2 mol eq of DEPC in the solvent (0.3 M solution of aldehydes). *b*) Isolated yield. *c*) Reaction conditions: rt, 30 min. *d*) Accompanied by recovery of the starting material (30%). *e*) Reaction conditions: rt, 15 min.

The cyano-phosphorylation of various aldehydes **3**—**10** was performed as shown in Table 1. The aldehydes except for *trans*-cinnamaldehyde (**9**) were reacted with *N*-heterocyclic carbene **2** prepared from 5 mol% of the imidazolium chloride **1** and 4 mol% of KO*t*-Bu, and 1.2 mol eq of DEPC in THF, affording the corresponding cyanohydrin-*O*-phosphonates in good yields.[16] A polar solvent such as DMF was also a suitable solvent (entry 5). The use of ketones such as acetophenone and methyl vinyl ketone afforded little or none of the desired products.



In summary, *N*-heterocyclic carbene **2** was found to function as catalyst in cyano-phosphorylation reaction of aldehydes with DEPC. Ongoing efforts are focused on developing an asymmetric version[17,18] of this reaction with a chiral *N*-heterocyclic carbene.

Experimental

IR spectra were measured on a JASCO IR Report-100 diffraction grating IR spectrophotometer. ^{1}H- (270 MHz) and ^{13}C-NMR (68 MHz) spectra were measured on a JEOL JNM-EX-270 NMR spectrometer. MS spectra were measured on a JEOL JMS-SX-102A instrument. Commercially available aldehydes and reagents were used without any purification. THF was distilled from Na/benzophenone ketyl under a nitrogen atmosphere. DMF was distilled from CaH_2 under reduced pressure. Silica gel column chromatography was performed on Fuji silysia PSQ 60B.

Representative Procedure for the Cyano-Phosphorylation Reaction To a stirred solution of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**1**) (5.1 mg, 15 μmol) in THF (1.0 ml) was added KO*t*-Bu (1.4 mg, 13 μmol) at rt and the mixture was stirred for 15 min at the same temperature. After dissolving the imidazolium chloride **1** completely, the mixture was cooled to 0 °C. Then, benzaldehyde (**6**) (32.1 mg, 0.302 mmol) and DEPC (59.0 mg, 0.362 mmol) were added to this mixture. The reaction mixture was stirred for 5 min at the same temperature, then quenched with water and extracted with EtOAc. The organic extracts were successively washed with water and brine, dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (hexane : EtOAc = 4 : 1) gave phosphoric acid cyano-phenyl-methyl ester diethyl ester (76.3 mg, 94%) as a colorless oil. The physical data were comparable to those reported.[19]

The physical data of the known cyanohydrin-*O*-phosphonates shown below were comparable to those of the corresponding literature: Phosphoric acid 1-cyano-3-phenyl-propyl ester diethyl ester.[19] Phosphoric acid cyano-cyclohexyl-methyl ester diethyl ester.[20] Phosphoric acid 1-cyano-2,2-dimethyl-propyl ester diethyl ester.[20] Phosphoric acid (4-chlorophenyl)-cyano-methyl ester diethyl ester.[19] Phosphoric acid cyano-(4-methoxyphenyl)-methyl ester diethyl ester.[19] Phosphoric acid 1-cyano-3-phenyl-allyl ester diethyl ester.[21] Phosphoric acid 1-cyano-allyl ester diethyl ester.[20]

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References and Notes

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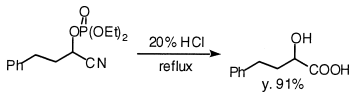
16) The cyanohydrin-*O*-phosphonate as shown below gave smoothly α-hydroxycarboxylic acid on treatment with 20% HCl.



17) For asymmetric cyano-phosphorylations of aldehydes, see: Baeza A., Casas J., Nájera C., Sansano M. J., Saá M. J., *Angew. Chem. Int. Ed.*, **42**, 3143—3146 (2003).
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