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

Yoshimasa FUKUDA, Yuka MAEDA, Kazuhiro KONDO,* and Toyohiko AOYAMA*

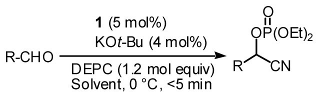
Graduate School of Pharmaceutical Sciences, Nagoya City University; 3–1 Tanabe-dori, Mizuho-ku, Nagoya 467–8603, Japan.
Received October 18, 2005; accepted December 12, 2005; published online December 14, 2005

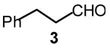
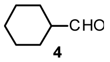
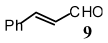
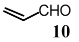
The first method for cyano-phosphorylation of aldehydes with diethyl cyanophosphonate in the presence of *N*-heterocyclic carbene prepared from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and KO*t*-Bu, as a nucleophilic catalyst, is described.

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.

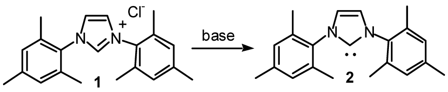
Table 1. Cyano-Phosphorylation of Various Aldehydes with **2** as a Catalyst[a)]



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]

∗ To whom correspondence should be addressed. e-mail: kazuk@phar.nagoya-cu.ac.jp; aoyama@phar.nagoya-cu.ac.jp

References and Notes

1) For review: César V., Bellemin-Laponnaz S., Gade L. H., *Chem. Soc. Rev.*, **33**, 619—636 (2004).

2) For review: Herrmann W. A., *Angew. Chem., Int. Ed.*, **41**, 1291—1309 (2002).

3) For review: Nair V., Bindu S., Sreekumar V., *Angew. Chem. Int. Ed.*, **43**, 5130—5135 (2004).

4) For review: Grasa G. A., Singh R., Nolan S. P., *Synthesis*, **2004**, 971—985.

5) For example: Connor E. F., Nyce G. W., Myers M., Möck A., Hedrick J. L., *J. Am. Chem. Soc.*, **124**, 914—915 (2002).

6) For example: Grasa G. A., Kissling R. M., Nolan S. P., *Org. Lett.*, **4**, 3583—3586 (2002).

7) For example: Suzuki Y., Toyota T., Imada F., Sato M., Miyashita A., *Chem. Commun.*, **2003**, 1314—1315.

8) For example: Singh R., Kissling R. M., Letellier M.-A., Nolan S. P., *J. Org. Chem.*, **69**, 209—212 (2004).

9) For example: Sohn S. S., Rosen E. L., Bode J. W., *J. Am. Chem. Soc.*, **126**, 14370—14371 (2004).

10) For example: Burstein C., Glorius F., *Angew. Chem., Int. Ed.*, **43**, 6205—6208 (2004).

11) For example: Kano T., Sasaki K., Maruoka, K., *Org. Lett.*, **7**, 1347—1349 (2005).

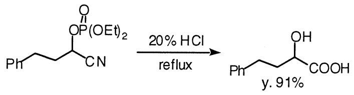
12) Fukuda Y., Maeda Y., Ishii S., Kondo K., Aoyama Y., *Synthesis*, **2006**, 589—590.

13) Green T. W., Wuts P. G. M., "Protective Groups in Organic Synthesis," 3th ed., John Wiley and Sons, Inc., New York, 1999, pp. 348—349.

14) Rasmussen J. K., Heilmann S. M., Krepski L. R., "Advances in Silicon Chemistry," Vol. 1, ed. by Larson G. L., Jai Press Inc, England, 1991, pp. 75—86.

15) Harusawa S., Yoneda R., Kurihara Y., Hamada Y., Shioiri T., *Chem. Pharm. Bull.*, **31**, 2932—2935 (1983).

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).

18) For asymmetric cyano-phosphorylations of aldehydes, see: Abiko Y., Yamagiwa M., Sugita M., Tian J., Matsunaga S., Shibasaki M., *Synlett*, **2004**, 2434—2436.

19) Baeza A., Nájera C., Sansano M. J., Saá M. J., *Chem. Eur. J.*, **11**, 3849—3862 (2005).

20) Micó I., Nájera C., *Tetrahedron*, **49**, 4327—4332 (1993).

21) Kurihara T., Miki M., Harusawa S., Yoneda R., *Chem. Pharm. Bull.*, **34**, 4620—4628 (1986).