Preparation of Nitriles from Primary Alcohols by a New Type of Oxidation-reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone and Diethyl Cyanophosphonate

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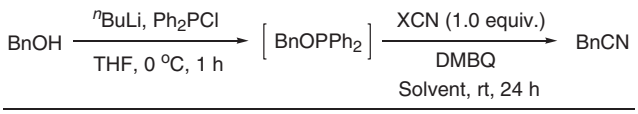
Cyanation of alkoxydiphenylphosphines, in situ prepared from ^{n}BuLi and various primary alcohols, with 2,6-dimethyl-1,4-benzoquinone (DMBQ) and diethyl cyanophosphonate provided the corresponding nitriles in high yields.

Oxidation-reduction condensation is known as one of very convenient and useful synthetic reactions in organic synthesis.[1] Various esters and ethers can be prepared in excellent yields under mild conditions by the combined use of alkoxydiphenylphosphines and quinones.[2] Further, successful syntheses of tertiary alkyl esters[3] and dialkyl ethers[4] were performed by the above procedure although it had been known difficult to work them out by conventional oxidation-reduction condensations. Then, some new versatile synthetic methodologies for carbon–oxygen bond formation were requested. In order to extend the scope of condensation reaction, our attention was next focused on carbon–carbon bond formation by using cyanide ion which is the most simple carbon nucleophile.

Preparation of nitriles from the corresponding alcohols is important in organic synthesis from the viewpoint of carbon chain elongation. In order to perform the above transformation, two-step procedure which involves prior conversion of alcohols into their halides or sulfonates and the following substitution with inorganic cyanides has generally been employed. When secondary and tertiary alcohols were used in this reaction, however, some reaction conditions such as high temperature and the use of strong bases often caused undesirable elimination reaction. Therefore, procedures such as one-pot cyanation of alcohols by using Mitsunobu reaction were devised to let the transformation go through under mild conditions.[5,6] Very recently, a conversion of alcohols into nitriles by using PPh_3/DDQ/^{n}Bu$_4$NCN system was reported.[7] However, there are some limitations in applying this system to other cyanation since it was too strong to use DDQ as an oxidant and too difficult to use extremely hygroscopic ^{n}Bu$_4$NCN. Here, a new type of oxidation-reduction condensation using a combination of milder oxidizing agent, 2,6-dimethyl-1,4-benzoquinone (DMBQ), and easy-to-handle cyanating agent, diethyl cyanophosphonate, is described for the preparation of nitriles from primary alcohols.

In the first place, cyanation reaction of benzyloxydiphenylphosphine, in situ formed from ^{n}BuLi-treated benzyl alcohol and chlorodiphenylphosphine, with TMSCN by using DMBQ was tried in CH_2Cl_2. The desired nitrile, however, was not obtained at all (Table 1, Entry 1). When acetone cyanohydrin was used as a cyanating agent, the yield of nitrile was still 20% (Table 1, Entry 2). While the use of diethyl cyanophosphonate also gave it in 35% yield (Table 1, Entry 3). After screening several reaction conditions, the nitrile was obtained eventually in 82% yield when 1.5 equiv. of benzyloxydiphenylphosphine and 1.5 equiv. of DMBQ in $CHCl_3$ were used (Table 1, Entries 4–6).

Table 1. Cyanation of benzyl alcohol with various cyanides and DMBQ



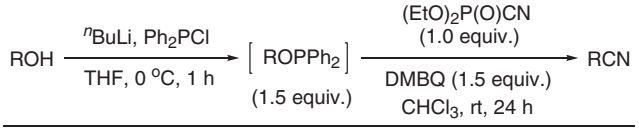
Entry	BnOPPh$_2$ /equiv.	XCN	DMBQ /equiv.	Solvent /mL	Yield /%[a]
1	1.0	TMSCN	1.0	CH_2Cl_2 /0.50	0
2	1.0	HO, CN	1.0	CH_2Cl_2 /0.50	20
3	1.0	$(EtO)_2P(O)CN$	1.0	CH_2Cl_2 /0.50	35
4	1.0	$(EtO)_2P(O)CN$	1.0	$CHCl_3$ /0.50	49
5	1.5	$(EtO)_2P(O)CN$	1.5	$CHCl_3$ /0.50	73
6	1.5	$(EtO)_2P(O)CN$	1.5	$CHCl_3$ /1.5	82

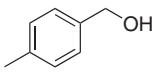
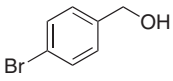
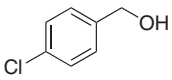
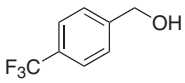
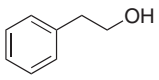
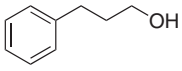
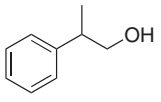
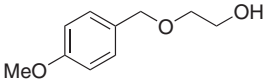
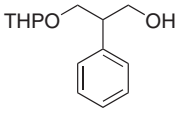
[a]A small amount of DMBQ was contained. Yield was determined by ^{1}H NMR analysis.

Next, cyanation of several primary alcohols using DMBQ and diethyl cyanophosphonate was tried (Table 2). When benzyl alcohols having various substituents were used, the corresponding nitriles were obtained in good yields (Table 2, Entries 1–4). Non-benzylic, hindered primary alcohols, and monoprotected diols having *p*-methoxybenzyl group or tetrahydropyranyl group also provided the desired nitriles in satisfactory yields (Table 2, Entries 5–9). On the other hand, substrates shown in Entries 8 and 9 did not provide the corresponding nitriles when subjected to the methods reported by Iranpoor[7] and Untch[6b] at all.

A proposed reaction mechanism is shown in Scheme 1: alkoxydiphenylphosphine reacted initially with DMBQ to form the adduct,[2] which in turn transformed to the phosphonium cyanide by the interaction with diethyl cyanophosphonate. Attack of the cyanide anion to a carbon atom adjacent to oxygen atom of the alkoxy group afforded the corresponding nitrile.

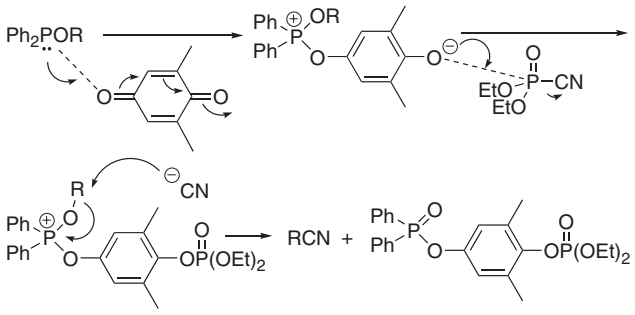
Table 2. Cyanation of various primary alcohols with $(EtO)_2$-P(O)CN and DMBQ



Entry	ROH	Yield /%
1		64
2		73[a]
3		86
4		70
5		97
6		94
7		81[b,c]
8[d]		96[a]
9[e]		83[a,b]

[a]Preparation of alkoxydiphenylphosphine was carried out at −78 °C. [b]The reaction was carried out in 5.0 mL of $CHCl_3$ for 48 h. [c]A small amount of DMBQ was contained. Yield was determined by ^{1}H NMR analysis. [d]Inanpoor's method mainly provided bis(*p*-methoxybenzyloxyethyl) ether of 2,3-dichloro-5,6-dicyanohydroquinone. [e]According to Untch's method, the corresponding diol, bis(tetrahydropyranyl) ether and 1,3-dioxane were obtained.

Typical experimental procedure is as follows: to a mixture of alkoxydiphenylphosphine[8] (0.75 mmol) and diethyl cyanophosphonate (0.50 mmol) was added a chloroform solution (1.5 mL) of 2,6-dimethyl-1,4-benzoquinone (0.75 mmol) at room temperature under argon atmosphere. After 24 h, the reaction mixture was quenched with saturated aq. $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with saturated aq. $NaHCO_3$ solution and then with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the resulted residue was purified by preparative TLC to afford the corresponding nitrile.



Scheme 1.

Thus, cyanation of alkoxydiphenylphosphines, in situ prepared from ^{n}BuLi and various primary alcohols, with 2,6-dimethyl-1,4-benzoquinone and diethyl cyanophosphonate provided the corresponding nitriles in high yields. Further study on this type of condensation reaction is now in progress.

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References and Notes

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8 Preparation of various alkoxydiphenylphosphines: See Refs. 2 or 3. The reactions were carried out at 0 °C.

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