Selective Synthesis of Isocyanides from Secondary Alcohols by a New Type of Oxidation–Reduction Condensation

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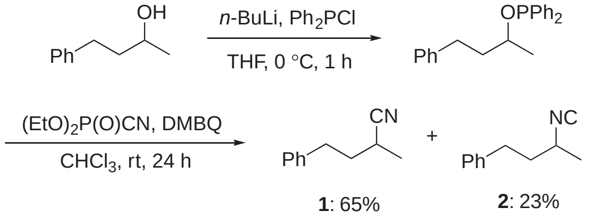
Selective synthesis of isocyanides from secondary alcohols via alkyl diphenylphosphinites is established by a new type of oxidation–reduction condensation in controlling the ambident reactivity of cyanide anion. In the presence of ZnO, isocyanides are obtained exclusively in moderate to high yields.

Isocyanides are the class of compounds which possess formally divalent carbon that exhibit unique reactivities.[1] By making the best use of their characteristics, isocyanides have been employed in multicomponent reactions such as Passerini[2] and Ugi[3] reactions, synthesis of heterocycles[4] as well as ligands of transition metal complexes.[5] Isocyanides can be prepared by various methods such as nucleophilic displacement of alkyl halides by silver cyanide,[6] dehydration of formamides,[7] carbylamine reaction,[8] or reduction of isocyanates or isothiocyanates.[9] Since these reactions are often carried out under basic conditions or at high reaction temperatures, it is desired to develop more convenient synthetic reactions that proceed under mild conditions.

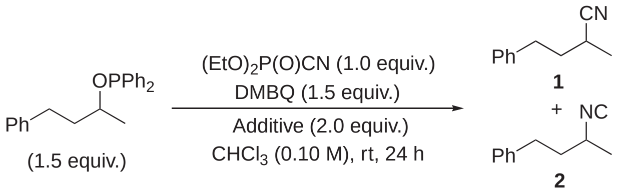
It was previously reported from our laboratory that the preparation of nitriles from primary alcohols was accomplished via a new type of oxidation–reduction condensation using 2,6-dimethyl-1,4-benzoquinone (DMBQ) and diethyl cyanophosphonate.[10] In the course of our study on the application of this condensation reaction to the secondary alcohols, formation of an isocyanide happened to be observed. This incident prompted us to study a selective preparation of isocyanides. In this communication, we would like to report a selective synthesis of isocyanides from the corresponding secondary alcohols via a new type of oxidation–reduction condensation process.

During the study on cyanation of 4-phenyl-2-butanol with diethyl cyanophosphonate in $CHCl_3$, it was found unexpectedly that the corresponding isocyanide **2** was formed in 23% yield along with the aimed nitrile **1** (Scheme 1). Formation of isocyanides by the conventional cyanations of the secondary alcohols with cyanide ion has not yet been known.[11] Since cyanide anion works as an ambident nucleophile[12] and upon considering the Pearson's HSAB principle,[13] it was figured that either nitriles or isocyanides would be formed selectively in the presence of an additive such as inorganic salt: that is, hard metal salts interact preferentially at the hard position of nitrogen of cyanide to provide niriles whereas soft metal salts interact at soft C-position to afford isocyanides.



Scheme 1.

Table 1. Additive effect



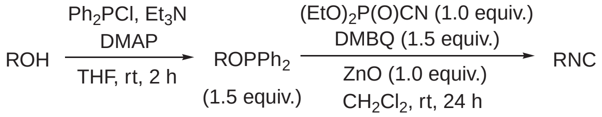
Entry	Additive	Yield (**1**:**2**)/%[a]	Entry	Additive	Yield (**1**:**2**)/%[a]
1	None	88 (74 : 26)	6	Ag_2O	0
2	Li_2SO_4	88 (79 : 21)	7	HgO	0
3	Na_2CO_3	80 (82 : 18)	8	CdO	68 (<5 : >95)
4	$Mg(OTf)_2$	72 (84 : 16)	9	ZnO	57 (<5 : >95)
5	CaO	48 (81 : 19)	10	ZnO	82[b,c] (<5 : >95)

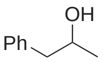
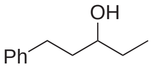
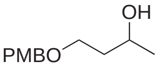
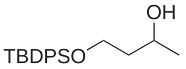
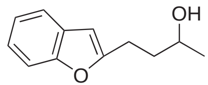
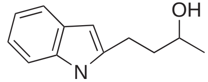
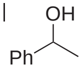
[a]Isolated as a mixture of isomers. Numbers in parentheses are ratios of isomers determined by comparing the peak of the methine proton of each isomer in ^{1}H NMR analysis. [b]The reaction was carried out in CH_2Cl_2 (1.0 M). [c]1.0 equiv. of ZnO was used.

The effect of inorganic salts was then examined in order to form either nitrile or isocyanide selectively (Table 1). In the first place, reactions were tried by using various alkali metal and alkaline earth metal salts (Table 1, Entries 2–5). However, the desired nitrile was not obtained in a good yield, which was contrary to our expectation. Then, the same reaction was carried out in the presence of heavy metal salts (Table 1, Entries 6–9), and to our surprise, it was found that the corresponding isocyanide was obtained exclusively when ZnO and CdO were used as additives (Table 1, Entries 8 and 9). Despite CdO afforded the isocyanide in higher yield, further optimization of the case with ZnO was tried from the environmental-benign point of view. Under the optimized conditions (1.0 M of CH_2Cl_2 and 1.0 equiv. of ZnO), the desired isocyanide was obtained in 82% yield (Table 1, Entry 10).

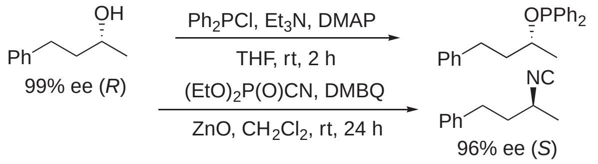
Next, cyanation of several secondary alcohols was tried under the optimized conditions (Table 2). Alkyl diphenyl phosphinites derived from 1-phenyl-2-propanol and 1-phenyl-3-pentanol provided the corresponding isocyanides in good yields

Table 2. Selective formation of isonitriles from various secondary alcohols with ZnO as an additive



Entry	ROH	Yield/%	
		ROPPh$_2$	RNC
1		quant.	63^a
2		95	89
3		82	63
4		quant.	72
5		71	78
6		86	81
7		99	40^b

^{a}1.5 mL of CH_2Cl_2 was used. ^{b}The reaction time was 3 h.



Scheme 2.

(Table 2, Entries 1 and 2). Monoprotected diols having *p*-methoxybenzyl group or *tert*-butyldiphenylsilyl group also provided the desired isocyanides in satisfactory yields (Table 2, Entries 3 and 4). On the other hand, heterocyclic rings such as benzofuran and *N*-methyl indole were not affected under the above conditions (Table 2, Entries 5 and 6). The corresponding isocyanide was obtained in 40% yield from 1-phenylethanol (Table 2, Entry 7).

Cyanation of an optically active secondary alcohol was next examined in order to know for certain the stereochemistry of the reaction. It was found then that the inversion of configuration was observed if (*R*)-4-phenyl-2-butanol was used as the substrate (Scheme 2).[14]

Typical experimental procedure is as follows: to a stirred suspension of dry ZnO (3N5, purchased from KANTO KAGAKU) (0.50 mmol), alkyl diphenylphosphinite[15] (0.75 mmol) and diethyl cyanophosphonate (0.50 mmol) was added a dichloromethane solution (0.50 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 aqueous $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and then with brine, and was dried over anhydrous sodium sulfate. After filtration and evaporation, the resulted residue was purified by preparative TLC to afford the corresponding isocyanide.

Thus, selective synthesis of isocyanides from secondary alcohols by a new type of oxidation–reduction condensation was achieved in the presence of ZnO.[16] Further study on this type of selective condensation reaction is now in progress.

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14 The absolute configuration of the isocyanide was determined by conversion to the known amine and comparison of the sign of specific rotation.
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16 Cyanation of a primary alcohol such as 3-phenyl-1-propanol gave ca. 2:1 ratio of the corresponding isocyanide and nitrile.