An Efficient Synthesis of Nitriles from Aldoximes Using Diethyl Phosphorocyanidate under Mild Conditions

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*Received July 7, 2012, Accepted July 16, 2012*

Nitriles are valuable intermediates in organic synthesis not only because they serve as the appropriate precursors to various functional groups, but also because they are widely used as the key intermediates for pharmaceuticals, agrochemicals and various *N*-heterocyclic compounds.[1] The cyano group itself is also frequently found in many biologically important molecules.[2]

Therefore, a variety of synthetic routes to nitriles from diverse chemical precursors have been developed.[3] Among these routes, nitrile synthesis from aldoximes using an appropriate dehydrating agent has been a general and clean method. For this purpose, numerous reagents such as chlorosulfonyl isocyanate,[4a] di-2-pyridyl sulfite,[4b] Burgess reagent,[4c] [RuCl$_2$(*p*-cymene)]$_2$/MS 4A,[4d] BOP,[4e] Pd(OAc)$_2$/PPh$_3$,[4f] Cu(OAc)$_2$/ultrasound[4g] have been developed. These reagents, however, may have limitations in some respects such as harsh reaction conditions, use of expensive or less readily available reagents, low yields, and lack of generality. Therefore, there is still a need to develop mild and general method for this conversion.

Diethyl phosphorocyanidate (DEPC)[5] was initially introduced as an efficient peptide coupling reagent,[6a] and has been utilized for useful organic reactions.[6b,c]

Previously, we reported that 2-chloro-1-methylpyridinium iodide is an efficient and mild reagent for the dehydration of aldoximes to nitriles under mild conditions.[7] In continuation of our interest in developing mild method for the conversion of aldoximes to nitriles, we herein wish to report the first application of DEPC to the efficient synthesis of nitriles from aldoximes under mild conditions (Scheme 1).

R = alkyl, aryl, heteroaryl, vinyl
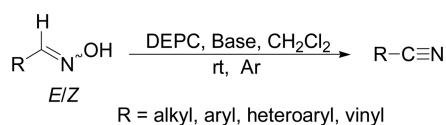
Scheme 1

In order to obtain the information regarding the optimum reaction conditions, 4-pyridine aldoxime (**1a**) was reacted with DEPC without base, and in presence of various base in CH$_2$Cl$_2$ at rt for a prolonged reaction time (20 h) (Table 1).

CH$_2$Cl$_2$ was chosen as reaction medium in this reaction due to the good solubility for both **1** and **3** in CH$_2$Cl$_2$, and also operational simplicity in extraction. When **1a** was

Table 1. Effect of various bases on the conversion of 4-pyridine aldoxime to 4-cyanopyridine with DEPC ar rt

Run	DEPC (eq.)	Base (eq.)	Time (h)	Yield (%)[a]		
				1a	**2a**	**3a**
1	1.0	None	20	84	13	0
2	1.3	Et$_3$N (1.1)	20	2	13	72
3	1.3	Et$_3$N (2.1)	20	0	0	85
4	1.3	(*i*-Pr)$_2$NEt (2.1)	20	0	23	58
5	1.3	DBU (2.1)	20	0	0	76[b]
6	1.3	K$_2$CO$_3$ (3.0)	20	0	82	0

[a]Isolated yield after flash column chromatography on silica gel.
[b]Relatively low yield may be due to the formation of unidentified, highly polar brown residue.

reacted with DEPC (1 eq.) in the absence of base, **1a** was recovered in 84% yield together with the reaction intermediate (**2a**) in 13% yield (run 1). The structural identity of **2a** was unambiguously corroborated by ^{1}H-NMR which showed a singlet peak for iminoyl-*H* at 8.32 ppm, and a doublet of triplet peak for -O$_2$P(OCH$_2$C*H$_3$*)$_2$ at 1.40 ppm.[8] With increasing amount of Et$_3$N added, the yield of **3a** was steadily improved up to 85% together with the gradual decrease of **1a** and **2a** (run 2, 3). (*i*-Pr)$_2$NEt, and especially K$_2$CO$_3$ failed to enforce the reaction to be completed most probably due to the ineffectiveness of the bases to abstract the iminoyl proton of **2a** (run 4, 6). Although DBU exhibited the similar reaction patterns to Et$_3$N, it gave relatively lower yield (76%) of **3a**, which may be attributable to the formation of unidentified, highly polar brown residue (run 5). Thus, the reaction conditions of (preferably run 3, or run 5 in some cases) using Et$_3$N or DBU as base were adopted as the standard conditions (DEPC (1.3 eq.), Et$_3$N (2.1 eq.), rt).

Under the standard conditions, various kinds of aldoximes were reacted with DEPC, and the representative results are summarized in Table 2.[9]

Various heteroaryl aldoximes (**1a-1d**) underwent dehydration reaction smoothly with DEPC (1.3-1.4 eq.) in the presence of Et$_3$N (2.1 eq.) to afford the corresponding nitriles (**3a-3d**) in 74-85% yields (run 1-4). Other types of aldoximes were also tested to examine the generality of this

Table 2. Efficient Conversion of Aldoximes to Nitriles using DEPC at rt

$$R\overset{\frown}{\underset{E/Z}{\text{N}}}\text{-OH} \quad \xrightarrow[\text{rt, Time (h), Ar}]{\text{DEPC, Base, CH}_2\text{Cl}_2} \quad R-C\equiv N$$

Run	R =	DEPC (eq.)	Base (eq.)	Time (h)	Yield (%)[a]
1	(**1a**)[b]	1.3	Et₃N (2.1)	10	85
2	(**1b**)[b]	1.3	Et₃N (2.1)	10	82
3	O₂N—S— (**1c**)[c]	1.4	Et₃N (2.1)	10	74
4	O₂N—O— (**1d**)[c]	1.4	Et₃N (2.1)	10	80
5	O₂N— (**1e**)[c]	1.3	Et₃N (2.1)	10	83
6	O₂N—Cl (**1f**)[c]	1.3	Et₃N (2.1)	10	86
7	Cl—Cl (**1g**)[c]	1.4	Et₃N (2.1)	10	84
8	(**1h**)[d]	1.4	Et₃N (2.1)	10	81
9	Ph (**1i**)[e]	2.3	Et₃N (2.1)	20	80
10	Ph (**1i**)[e]	1.3	DBU (2.1)	20	67
11	Ph–Me (**1j**)[f]	2.3	Et₃N (2.1)	20	72
12	Ph–Me (**1j**)[f]	1.3	DBU (2.1)	20	77
13	Me(10) (**1k**)[g]	2.5	Et₃N (2.1)	20	76[h]
14	Me(10) (**1k**)[g]	1.3	DBU (2.1)	20	68

[a]Isolated yield after flash column chromatography on silica gel. [b]Predominantly *Z*-isomer. [c]Predominantly *E*-isomer. [d]Mixture of (7:93) of *E*- & *Z*-isomer. [e]Mixture of (60:40) of *E*- & *Z*-isomer. [f]Mixture of (55:45) of *E*- & *Z*-isomer. [g]Mixture of (25:75) of *E*- & *Z*-isomer. [h]The reaction was carried out under reflux conditions.

reaction. Several aryl aldoximes (**1e-1h**) also exhibited the similar reaction patterns to **1a** under the standard conditions to provide the corresponding nitriles (**3e-3h**) in 81-86% yields (run 5-8). On the other hand, vinyl (**1i**) and alkyl aldoximes (**1j-1k**) were found to be less reactive toward DEPC. Under the standard conditions, aldoximes (**1i-1k**) were partially converted to the corresponding nitriles even after being stirred for 20 h. By using excess (2.3 eq.) of DEPC and extending the reaction time to 20 h, aldoximes (**1i**, **1j**) were converted to the corresponding nitriles (**3i**, **3j**) in 72-80% yields (run 9, 11). Aldoxime (**1k**), however, required refluxing for 20 h with more excess (2.5 eq.) of DECP to make the reaction proceed up to 76% yield (run 13). We also attempted DBU for these sluggish reactions as base to examine the base effect (run 10, 12, 14). Under the conditions of using DEPC (1.3 eq.) and DBU (2.1 eq.) ar rt for 20 h, aldoximes (**1i-1k**) were successfully converted to the corresponding nitriles (**3i-3k**) in good yields.

In conclusion, DEPC is a mild and practical reagent for the effective conversion of various aldoximes to nitriles.

Considering several advantages expected from this reaction, *e.g.*, commercial availability of DEPC at cheap price, good to excellent yields, mild reaction conditions, and wide scope of applicability, this new dehydrating protocol could be the method of choice in the synthesis of nitriles from various aldoximes.

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5. DEPC (90% purity) was purchased from Aldrich Chemical Co., and used directly without purification.
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8. **The reaction intermediate 2a:** pale-brown oil; ¹H-NMR (CDCl₃, 400 MHz) δ 1.40 (dt, 6H, J_1 = 7.2 Hz, J_2 = 1.1 Hz, -O₂P(OCH₂CH₃)₂), 4.24-4.34 (m, 4H, -O₂P(OCH₂CH₃)₂). 7.59 (d, 2H, *J* = 5.4 Hz, pyridinyl-*H*), 8.32 (s, 1H, -C*H*=N-), 8.73 (d, 2H, *J* = 5.4 Hz, pyridinyl-*H*).
9. **Typical procedure for the conversion of 1a to 3a:** To a stirred solution of 4-pyridinealdoxime (**1a**) (122.0 mg, 1.0 mmol) in CH₂Cl₂ (10 mL) were added DEPC (216.0 mL, 1.3 eq.) and Et₃N (293.0 mL, 2.1 eq.) by syringes, and the resulting mixture was stirred at rt for 10 h under Ar. The reaction was quenched with satd. NaHCO₃ solution (10 mL), and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (10 mL × 3), and the combined organic layers were dried over MgSO₄, filtered, and concentrated. Purification of the crude product by flash column chromatography on silica gel (CH₂Cl₂/EtOAc, 15/1) afforded 4-cyanopyridine (**3a**) (88.5 mg, 85%) as an off-white solid. mp 78-79 °C (lit.[10] 79 °C); R_f 0.50 (hexane/EtOAc, 1/1), IR (KBr) 2242 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz) δ 7.55 (d, 2H, *J* = 5.6 Hz), 8.83 (d, 2H, *J* = 5.6 Hz).
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