An Efficient New Procedure for the One-Pot Conversion of Aldehydes into the Corresponding Nitriles

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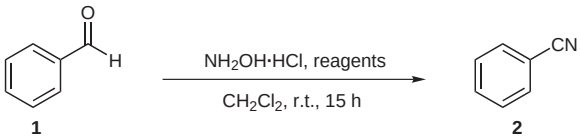
Abstract: A new and efficient procedure for the one-pot conversion of various aldehydes into the corresponding nitriles under mild reaction conditions has been developed. The ethyl dichlorophosphate/DBU-mediated dehydration of aldoxime intermediates was utilized as a key operation to effect the transformation.

Key words: aldehydes, nitriles, ethyl dichlorophosphate, DBU, dehydration

The conversion of aldehydes into the corresponding nitriles is an important functional group transformation due to the extensive utilities of nitrile compounds in synthetic chemistry.[1] Among numerous methods developed for this purpose,[2–6] those based on the dehydration of aldoximes generated from the condensation of aldehydes with hydroxylamine are the most widely employed ones. According to the literature reports,[6] many aldehydes can be directly converted into nitriles without the isolation of aldoxime intermediates upon the one-pot treatment with hydroxylamine hydrochloride ($NH_2OH·HCl$) in the presence of various dehydrating agents, such as *N*-methyl-2-pyrrolidinone,[6d] alumina/$MeSO_2Cl$,[6e] silica chloride,[6g] NaI,[6h] etc. However, these literature precedents often require drastic refluxing[6a,d,e,h,i] or microwave heating[6b,c,f,g] conditions to effect such one-pot transformation, and therefore practically may not be compatible with thermally unstable molecules. In addition, some of these methods have shown to be less efficient when applied to enolizable aliphatic aldehydes in giving unsatisfactory yields of aliphatic nitriles. With respect to these limitations, herein we report a novel protocol for the one-pot synthesis of a wide range of nitriles from the corresponding aldehydes by employing ethyl dichlorophosphate ($EtOPOCl_2$) combined with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[7] as a mild dehydrating system. In such an approach, the dehydration of aldoximes generated in situ can be greatly facilitated, conceivably via a process involving a coupling reaction of aldoximes with $EtOPOCl_2$ to form active intermediates, followed by a rapid DBU-promoted elimination to give the corresponding nitriles. In contrast to the previous requirement for heating conditions, this newly developed protocol permits the one-pot conversion of aldehydes into nitriles to occur smoothly at ambient temperature and, consequently, is endowed with a broad application scope.

Under different combinations, several bases (DBU, pyridine, Et_3N) and phosphorus-containing activating reagents, including $EtOPOCl_2$, diethyl cholorophosphate [$(EtO)_2POCl$] and *N*,*N*-dimethylphosphoramidous dichloride [$(CH_3)_2NPCl_2$], were initially investigated by using benzaldehyde (**1**) as a substrate (Table 1). We observed that on the treatment with $NH_2OH·HCl$ and DBU, followed by $EtOPOCl_2$ at room temperature in CH_2Cl_2, **1** could be converted into benzonitrile (**2**) in good yield (85%, Table 1, entry 1). However, switching $EtOPOCl_2$ to either $(EtO)_2POCl$ (entry 2) or Me_2NPCl_2 (entry 3) under similar reaction conditions caused the decreased yields of **2**, together with the notable isolation of *O*-diethylphosphinyloxime [$PhCH=NOPO(OEt)_2$] (entry 2, 22%) and aldoxime (PhCH=NOH; entry 3, 45%).[8] These results indicate that $EtOPOCl_2$ is far more effective than the other two attested reagents in promoting the dehydration process. A mechanistic study for disclosing the reason(s) of their divergent reactivity is currently under investigation.

Table 1 Optimization of the Reaction Conditions[a]



1 2

Entry	Reagents[b]	Yield (%)[c]
1	$EtOPOCl_2$, DBU	85
2	$(EtO)_2POCl$, DBU	53
3	Me_2NPCl_2, DBU	25
4	$EtOPOCl_2$, pyridine	15
5	$EtOPOCl_2$, Et_3N	5
6	DBU, $EtOPOCl_2$, MS 3 Å	96

[a] All reactions were performed using benzaldehyde (1 equiv), $NH_2OH·HCl$ (1.2 equiv), phosphorus-activating reagent (1.5 equiv) and base (5 equiv).
[b] All reagents were purchased from Fluka and Aldrich and used directly without further purification.
[c] Isolated yield of the purified product.

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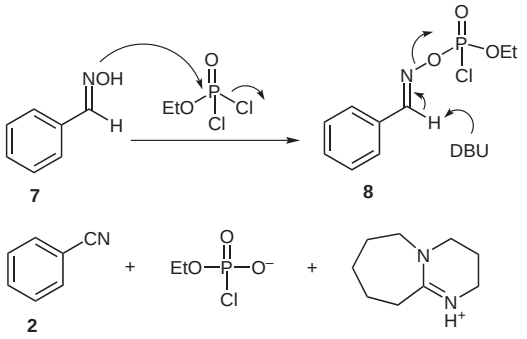
In addition, the replacement of DBU in entry 1 with pyridine (entry 4) or triethylamine (entry 5) also led to poor conversion even after reaction time was extended to a few days.

The recovery of intact **1** in both cases (entry 4, 67%; entry 5, 80%) implies that DBU may also play an essential role in the condensation reaction between **1** and $NH_2OH{\cdot}HCl$. Moreover, based on the conditions of entry 1, it was found that significant improvement (85% to 96%) could be further achieved by the addition of a certain amount of 3 Å molecular sieves (MS)[9] to the reaction mixture (entry 6), resulting in the formation of **2** in almost quantitative yield (96%). Therefore, as an optimal choice, the reagent combination indicated in entry 6 ($EtOPOCl_2$, DBU, 3 Å MS) was subsequently applied into our general procedure.

Having established the optimized conditions of the method, we turned to investigate its generality by probing an array of structurally diverse aldehydes. As outlined in Table 2, on the subjection to similar treatment, a broad range of substrates, including aromatic (Table 2, entries 1–4), heteroaromatic (entry 5 and 6), α,β-unsaturated (entry 7), cyclic (entry 8) and aliphatic (entry 9) aldehydes, were all uniformly transferred into the corresponding nitriles[10] in high to quantitative yields (83–98%). The yields of these nitrile products obtained from our studies are shown to be comparable or better than those of related literature methods. Additionally, this newly developed protocol was also applied to (*S*)-2-(*tert*-butoxycarbonylamino)propanal (**3**)[11] and (*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanal (**5**), the molecules bearing the labile stereogenic centers and *N*-*tert*-butoxycarbonyl amino protecting group. In both cases, **3** and **5** underwent ready conversion into the corresponding nitriles **4** (entry 10, 87%) and **6** (entry 11, 80%) with the maintenance of the steric integrity, demonstrating that the current procedure, in consistency with its mild reaction conditions, appears to be an attractive approach for the preparation of labile nitrile compounds that are otherwise difficult to obtain through related methods involving refluxing conditions. The *N*-Boc-protected amino nitriles **4** and **6** are the useful building blocks for synthesizing biologically interesting peptidomimetic compounds.[12,13] Their identities were unambiguously confirmed by the comparison of spectral data[13,14] and [α] values[14,15] with those previously described in the literature.[16]

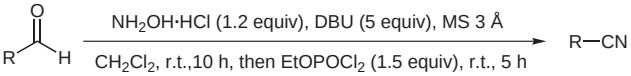
By taking the case of converting benzaldehyde (**1**) into benzonitrile (**2**) as an example, a proposed mechanism of the crucial $EtOPOCl_2$/DBU-mediated aldoxime dehydration process is illustrated in Scheme 1. At first, the in situ generated aldoxime **7** couples with $EtOPOCl_2$ to form an active intermediate **8**. Following this, **8** can undergo a rapid elimination reaction promoted by DBU to afford the corresponding nitrile **2**.

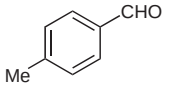
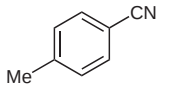
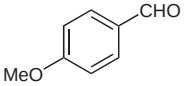
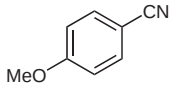
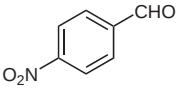
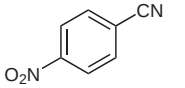
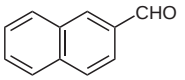
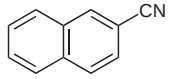
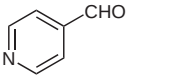
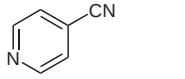
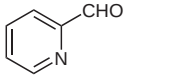
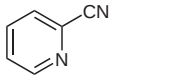
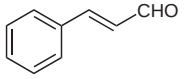
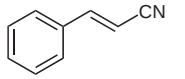
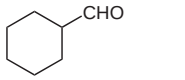
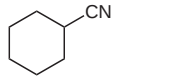
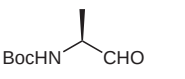
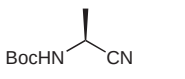
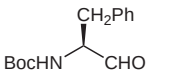
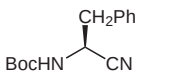
In conclusion, we have described a novel and efficient procedure for the one-pot conversion of aldehydes into the corresponding nitriles, using ethyl dichlorophosphate/DBU as a highly effective agent for the dehydration of



Scheme 1 Proposed mechanism of the dehydration of aldoximes

Table 2 One-Pot Conversion of Various Aldehydes into Nitriles



Entry	Substrate[a]	Product	Yield (%)[b]
1			90
2			98
3			87
4			85
5			83
6			90
7			98
8			92
9	*n*-C_7H_{15}—CHO	*n*-C_7H_{15}—CN	98
10	 **3**	 **4**	87
11	 **5**	 **6**	80

[a] All substrates are commercially available except for that in entry 10.[11]
[b] Isolated yield of purified product.

aldoxime intermediates. The mild reaction conditions of this method enabled us to prepare a large variety of nitriles from readily available aldehydes in high to excellent yields. As a supplement to those existing one-pot protocols, the current procedure appears to be particularly valuable for synthesizing the nitriles bearing labile functionalities.[16]

Acknowledgment

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(8) Both PhCH=NOPO(OEt)$_2$ and PhCH=NOH were obtained as the single stereoisomers. The stereochemistry remains to be determined.
(9) An optimized amount of 3 Å MS was used. It was found that at least 120 mg of 3 Å MS was required for a quantitative conversion of 1.50 mmol of benzaldehyde (**1**) into benzonitrile (**2**).
(10) Satisfactory spectral and LC-MS analytical data were obtained for all products; all known nitriles showed physical and spectral properties identical to those reported in the literature.
(11) For the preparation of compound **3**, see: Falorni, M.; Giacomelli, G.; Porcheddu, A.; Teddei, M. *J. Org. Chem.* **1999**, *64*, 8962.
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(16) A representative experimental procedure is described for the preparation of benzonitrile (**2**). To a solution of benzaldehyde (**1**, 0.2 g, 1.88 mmol) in CH_2Cl_2 (8 mL), powdered 3 Å MS (120 mg), 1.2 equiv of $NH_2OH{\cdot}HCl$ (0.157 g, 2.26 mmol) and 5 equiv of DBU (1.43 g, 9.42 mmol) were successively added in one portion. The reaction mixture was stirred at r.t. for 10 h, cooled in an ice-water bath to 5 °C, and 1.5 equiv of $EtOPOCl_2$ (0.46 g, 2.83 mmol) were added. Then, stirring at r.t. was continued for an additional 5 h. The mixture was then quenched with aq NH_4Cl, extracted with CH_2Cl_2 and subjected to chromatographic purification on silica gel (15% EtOAc in hexane) to afford **2** in 96% yield (0.186 g), whose spectral data (IR, ^{1}H NMR and ^{13}C NMR) were identical to those of the authentic sample.
Benzonitrile(**2**): IR (KBr): 2228, 1701, 1597, 1583, 1489, 1447 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 3 H), 7.43–7.32 (tm, *J* = 7.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.8, 132.0, 129.1, 118.8, 112.2. GC-MS: *m/z* = 103.5 [M]$^+$.
(*S*)-2-(*tert*-Butoxycarbonylamino)propanenitrile (**4**): IR (KBr): 3317, 2979, 2260, 1680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 1.53 (d, *J* = 7.2 Hz, 3 H), 4.61 (br s, 1 H), 4.99 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 28.2, 37.6, 81.2, 119.6, 154.1. LC-MS (ES): *m/z* = 193 [M + 23]$^+$; mp 105–106 °C; $[\alpha]_D^{25}$ –24.5 (*c* 2.5, $CHCl_3$) {Lit.[15] $[\alpha]_D^{20}$ –24.6 (*c* 2.5, $CHCl_3$)}.
(*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanenitrile (**6**): IR (KBr): 3353, 3065, 2248, 1691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 3.08 (m, 2 H), 4.84 (m, 1 H), 4.95 (m, 1 H), 7.25–7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 39.2, 43.4, 81.3, 118.4, 127.9, 129.0, 129.5, 133.9, 154.1. LC-MS (ES): *m/z* 246 [M]$^+$; mp 114–115 °C; $[\alpha]_D^{25}$ –16.4 (*c* 0.98, dioxane) {Lit.[14] $[\alpha]_D^{25}$ –16.4 (*c* 0.98, dioxane)}.