A convenient new procedure for converting primary amides into nitriles

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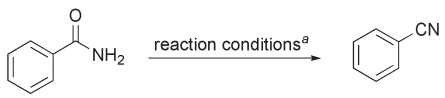
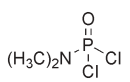
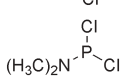
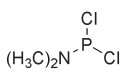
An operationally simple and high-yielding procedure has been developed for the conversion of primary amides to the corresponding nitriles, using ethyl dichlorophosphate/DBU as the mild dehydrating agent.

The conversion of the primary carboxamido functionality into the cyano group is an important process which has extensive utility in organic synthesis.[1,2] Herein, we wish to report a convenient new protocol for this operation. The new dehydration process is facilitated by the ease of primary amides to undergo coupling with ethyl dichlorophosphate ($EtOPOCl_2$) or phenyl dichlorophosphate ($C_6H_5OPOCl_2$) followed by rapid elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to form the corresponding nitriles. While a wealth of dehydrating agents are available to effect this transformation,[3–17] the mild reagent, either $EtOPOCl_2$ or $C_6H_5OPOCl_2$, applied in this newly developed methodology, to our knowledge, are unprecedented. Compiled in Table 1 are results for the initial model study by the use of benzamide (**1**) as a substrate under treatment with each hitherto unexplored dehydrating agents, including ethyl dichlorophosphate ($EtOPOCl_2$),† phenyl dichlorophosphate ($C_6H_5OPOCl_2$),† *N*,*N*-dimethylphosphoramidic dichloride [$(CH_3)_2NPOCl_2$],† and *N*,*N*-dimethylphosphoramidous dichloride [$(CH_3)_2NPCl_2$]† in the presence of different bases to afford benzonitrile (**2**). Accordingly, when accompanied with DBU as a base, ethyl dichlorophosphate is considered the reagent of choice to facilitate the dehydration reaction in terms of conversion rate and reaction time (Entry 3). As well, DBU was found to be more effective than other commonly used bases such as triethylamine and pyridine among the dehydration systems investigated (Entries 1, 2 and 3). The underlying cause of this remarkable base effect is still not fully understood. Other structure-related dehydrating agents such as $C_6H_5OPOCl_2$, $(CH_3)_2NPOCl_2$, and $(CH_3)_2NPCl_2$ were also examined. As shown in Table 1 (Entries 3 and 4), both $EtOPOCl_2$ and $C_6H_5OPOCl_2$ are equally effective for the transformation of carboxamide **1** into nitrile **2** in virtually quantitative yield (~98%). However, similar reaction conditions with $(CH_3)_2NPOCl_2$ or $(CH_3)_2NPCl_2$ as the coupling reagent merely gave rise to the desired product in 64% and 40%, respectively (Entries 5 and 6). In the case with $(CH_3)_2NPCl_2$, a low yield was obtained even after the reaction time was extended under refluxing conditions (Entry 7), presumably due to the less active phosphorus center compared to other coupling reagents examined. Thus, the system ($EtOPOCl_2$/DBU) indicated in Entry 3 is considered the method of choice, and the typical procedure is illustrated as follows. Benzamide (**1**) (0.121 g, 1.0 mmol) was treated with 3 equivalents of DBU (0.457 g, 3.0 mmol) in dichloromethane (5 mL) at room temperature for 10 min, at which time 2 equivalents of ethyl dichlorophosphate (0.326 g, 2.0 mmol) was then added, and the reaction was continued at the same temperature for additional 50 min. Addition of aqueous NH_4Cl followed by dichloromethane extraction and flash chromatography (silica gel, 10% ethyl acetate in *n*-hexane) afforded the corresponding nitrile **2**‡ (0.101 g, 98%) as a colorless oil. Its structure was verified by spectroscopy with spectral data (IR, ^1H NMR and ^{13}C NMR) identical to those of the authentic sample available from Aldrich. When the reaction was repeated with phenyl dichlorophosphate in place of ethyl dichlorophosphate, 97% yield of the pure product was isolated.

Table 1 Conversion of benzamide into benzonitrile with various dehydrating agents and bases



1 2

Entry	Dehydrating agent	Base	Time/h	Temp./°C	Yield (%)[b]
1		NEt_3	3	rt	63
2		Pyridine	3	rt	50
3		DBU	1	rt	98
4		DBU	1.5	rt	97
5		DBU	5	rt	64
6		DBU	3	rt	40[c]
7		DBU	8	reflux	54[c]

[a] All reactions were performed using amide **1** (1 equiv.), dehydrating agent (2 equiv.), and base (3 equiv.) in dichloromethane. [b] Yields are for isolated, chromatographically pure products. [c] Starting material was recovered intact in less than 10% along with an unidentified side product.

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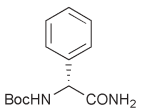
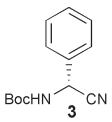
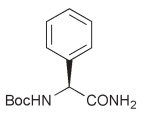
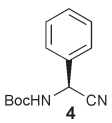
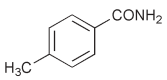
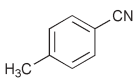
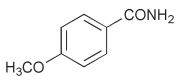
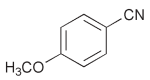
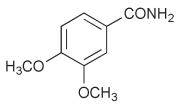
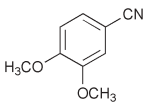
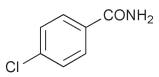
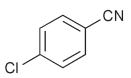
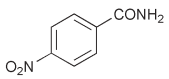
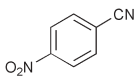
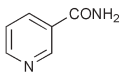
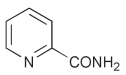
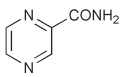
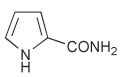
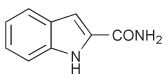
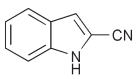
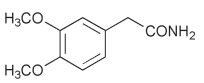
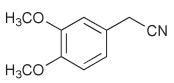
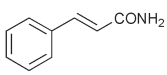
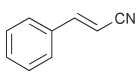
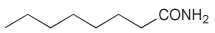
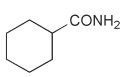
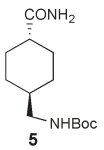
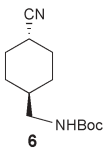
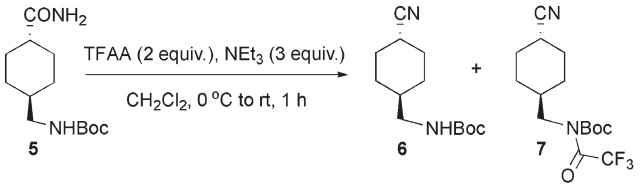
Table 2 Conversion of primary amides into nitriles with ethyl dichlorophosphate and DBU as base

$$RCONH_2 \xrightarrow[CH_2Cl_2,\ rt]{EtOPOCl_2\ (2\ equiv.),\ DBU\ (3\ equiv.)} RCN$$

Entry	Substrate[a]	Product	Time/h	Yield (%)[b]
1			2	85
2			2	86
3			3	92
4			3	94
5			2	91
6			3	95
7			2	93
8			1	90
9			1	88
10			3	73
11			1	78
12			1	81
13			2	92
14			3	92
15			2	88
16			3	80
17			2	92

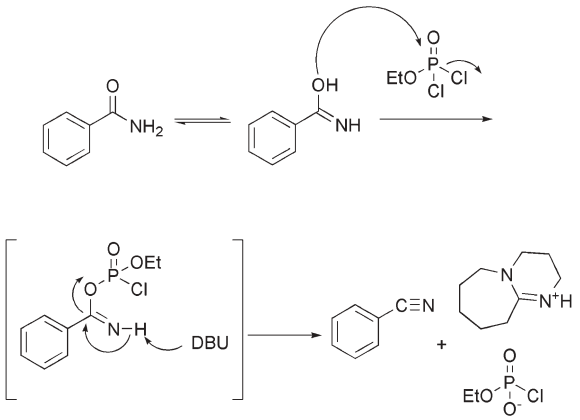
[a] All substrates are commercially available and used without further purification. [b] Yields are for isolated, chromatographically pure products.



Scheme 1

Under similar conditions, dehydration of several functionally diverse primary amides was further performed. The generality of the method is apparently demonstrated by results outlined in Table 2. Comparison of Entries 1 and 2 reveals that the labile stereogenic center adjacent to the carboxamido group remains intact, as evidenced by obtaining individual enantiomeric nitrile product in optically pure form,§ potentially rendering this mild dehydration system a great synthetic utility. Additional examples of substituted benzamides were also subjected to the transformation (Entries 3–7) and all resulted in excellent yields (91–95%) within 3 h, indicating that the reaction rate appears to be little affected by the stereoelectronic nature of the substitution. More intriguingly, N-containing heteroaromatic carboxamides including those containing a pyrrolic N-hydrogen (Entries 8–12) are readily converted into the corresponding nitriles in good to high yields. Especially, when nicotinamide (Entry 8) was employed as a starting substrate, a substantially high yield of the corresponding 3-cyanopyridine (90%) was obtained compared to other reported methods such as trichloromethyl chloroformate (0%),[17] trichloroacetyl chloride/triethylamine (77%),[15] and titanium tetrachloride/triethylamine (78%).[5] Alkyl or arakyl carboxamides bearing various functionalities are also allowed to provide the corresponding nitriles in high yields (80–92%) under this newly developed protocol (Entries 13–16). In addition, it is noteworthy that carboxamide **5** (Entry 17), under treatment with the titled method ($EtOPOCl_2$ (2 equiv.)/DBU (3 equiv.)), cleanly afforded the desired nitrile **6** in 92% yield; however, for comparison, when the same reaction was carried out using a classical system, trifluoroacetic anhydride (2 equiv.)/pyridine (3 equiv.),[10] nitrile **6** was formed in only 64% yield along with an over-acylated side product **7** in 23% yield (Scheme 1). The aforementioned example, again, demonstrates the usefulness and versatility of this new synthetic method.

A mechanistic rationale of the dehydration reaction is depicted in Scheme 2 by taking the conversion of benzamide into



Scheme 2

benzonitrile as a typical pathway. It is highly conceivable that the carboxamido group is initially coupled with ethyl dichlorophosphate to form an active intermediate which in turn undergoes elimination rapidly with DBU to give the corresponding cyano group.

As described above, the $EtOPOCl_2$/DBU system presents itself as a mild, highly effective dehydrating agent for the conversion of primary amides to the corresponding nitriles. In addition to high yields, enhanced reaction rates and operational simplicity, this newly developed process is expected to have broad synthetic utility, particularly for the preparation of thermodynamically labile nitriles.

We are grateful to the National Health Research Institutes and National Science Council of the Republic of China for financial support.

Notes and references

† $EtOPOCl_2$, $C_6H_5OPOCl_2$, $(CH_3)_2NPOCl_2$ and $(CH_3)_2NPCl_2$ were obtained from Aldrich or Acros and used without further purification.
‡ Satisfactory spectral and elemental or LC-MS analytical data were obtained for all new compounds; all known nitriles showed physical and spectral properties identical to those reported in the literature.
§ (*R*)-2-*N*-*tert*-butoxycabonylamino-2-phenylethanenitrile (**3**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H), 5.23 (br s, 1H), 5.78 (br s, 1H), 7.41–7.48 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 46.0, 81.5, 177.7, 126.8, 129.2, 129.4, 133.5, 154.2; EIMS: *m*/*z* 255 (M + 23); mp 119.5–120.2 °C; $[\alpha]_D^{24}$ −1.82 (*c* = 1.1, $CHCl_3$) {Lit.[18] $[\alpha]_D^{22}$ −1.9 (*c* = 1.1, $CHCl_3$)}. (*S*)-2-*N*-*tert*-butoxycabonylamino-2-phenylethanenitrile (**4**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 5.21 (br s, 1H), 5.77 (br s, 1H), 7.41–7.48 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 46.1, 81.5, 177.6, 126.9, 129.3, 129.4, 133.4, 154.2; EIMS: *m*/*z* 255 (M + 23); mp 120.5–121.3 °C; $[\alpha]_D^{24}$ + 1.83 (*c* = 1.09, $CHCl_3$).

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