Efficient New Protocols for Converting Primary Amides into Nitriles Initiated by P(NMe2)3, PCl3, or P(OPh)3

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Abstract: Three efficient and high-yielding procedures have been developed for the conversion of primary amides into nitriles, mediated by hitherto unexplored P(NMe2)3, PCl3, or P(OPh)3. The reactions were conducted under operationally simple and mild conditions and displayed broad substrate scope and good functional group tolerance.

Introduction

Nitriles are valuable structural motifs in organic chemistry. They can be easily converted to many other functional groups such as carboxylic acids, amines, and ketones and can be used as precursors of a large number of molecules of commercial significance such as pharmaceuticals, agrochemicals, polymers, and other material molecules.1-3 Moreover, the cyano group itself is present in a large number of biologically active molecules4,5 and in materials possessing important electronic and mechanical properties.6,7 For instance, many blockbuster nitrile-containing drugs, such as saxagliptin,8 anastrozole,9 and cimetidine,10 are prescribed for a diverse array of medical indications. The cyano group is also present in HIV protease and 5-lipoxygenase inhibitors and many other medicinally important molecules.11,12

Dehydration of primary amides is one of the most used methods for the preparation of nitriles.13 Traditionally, the dehydration reaction was achieved using basic dehydrating agents such as sodium hydroxide,14 lithium hydride,15 n-butyl lithium,16 and silazanes.17 The use of Lewis acids as dehydrating agents, such as P2O5,18 TiCl4,19 AlCl3/NaI,20 PdCl2,21 and ZnCl2,22 has been also documented. More recently, other dehydration systems giving higher yields have been introduced, such as EtOP(O)Cl2/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),23 (EO)3P(O)Cl2,24 silanes/transition metal catalysts,25 silicotungstate [n-Bu4N]4[Bα2H4SiW11O39],26 [Et2NSF2]BF4 (XtalFluor-E),27 and (COCI)/Et,N/Pb,PO3,28

Herein, we report three convenient and efficient protocols for the conversion of primary amides into nitriles mediated by P(NMe2)3, PCl3, or P(OPh)3. These new dehydration processes are facilitated by the ease of primary amides to undergo coupling with the highly electrophilic phosphorus-III reagents, tris(dimethylamino)phosphine, phosphorus trichloride, or triphenylphosphate, followed by rapid elimination with diethylamine or DBU to form the corresponding nitriles. While a wide variety of dehydrating agents were used to effect this transformation, the mild, readily available, and low-cost reagents, P(NMe2)3, PCl3, or P(OPh)3, applied in these newly developed protocols, to our knowledge, are unprecedented.

Results and Discussion

To establish the optimum conditions for the dehydration reaction, we used benzamide (1a) as the model substrate. The reaction was studied with three different commercially available and low-cost phosphorus-III promoters, P(NMe2)3, PCl3, or P(OPh)3, in combination with different bases, under various conditions. The results of these comparative experiments are summarized in Table 1. At the outset of the study, the reaction was performed in the absence of any promoter or base, but no desired product 2a was obtained in that case (Table 1, entries 1 and 2). When using P(NMe2)3 (2 equiv) as the promoter in the presence of triethylamine, pyridine, benzylamine, or DBU as the base (3 equiv), the reaction furnished the desired product in low to moderate yields (Table 1, entries 3–6). An improvement in the yield of 2a to 88% was, however, observed when employing diethylamine (3 equiv) as the base in refluxing CHCl3 (Table 1, entry 7). The best results were recorded with P(NMe2)3/Et2NH as the dehydration system prompted us to further investigate the effect of solvents on the reaction yield. A variety of solvents including CHCl3, toluene, EtOH, CH3Cl2, and MeCN were tested (Table 1, entries 7–11). The best results were recorded with CHCl3, which gave an 88% yield of 2a after 6 h at reflux temperature (Table 1, entry 7). Reducing the amounts of P(NMe2)3 and Et2NH to 1 and 2 molar equivalents, respectively, led to a diminished yield (Table 1, entry 12). On the other hand, performing the reaction under solvent-free conditions, with thermal heating or microwave irradiation, could not improve the reactivity, and lower than 50% yield was obtained in these cases (Table 1, entries 13 and 14).

When using PCl3 as the promoter at the optimized conditions obtained above [i.e., PCl3 (2 equiv), Et2NH (3 equiv), and

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CHCl₃ as the solvents at 62 °C, the desired product 2a was obtained with a better yield of 92% after 40 min (Table 1, entry 15).

Switching to triphenylphosphite, at the same reaction conditions, brought no improvement and only provided a 40% yield of 2a (Table 1, entry 18). However, performing the reaction under solvent-free conditions, with microwave irradiation, in the presence of DBU as the base, the reaction proceeded efficiently and afforded 2a in 91% isolated yield after 4 min at 150 °C (Table 1, entry 21).

Accordingly, three efficient and high-yielding methods could be deduced for the conversion of primary amides into nitriles, mediated by P(NMe₂)₃, PCl₃, or P(OPh)₃: Method A [P(NMe₂)₃ (2 equiv), Et₂NH (3 equiv), in refluxing CHCl₃ for 6 h], Method B [PCl₃ (2 equiv), Et₂NH (3 equiv), in refluxing CHCl₃ for 40 min], and Method C [P(OPh)₃ (2 equiv), DBU (3 equiv), neat, microwave irradiation at 150 °C for 4 min].

We next investigate the scope and generality of the three established methods by using a variety of structurally diverse primary amides. The results indicated that the three methods displayed wide substrate scope and good functional group compatibility, affording the desired nitriles in good-to-excellent yields (Table 2). The reactions proceeded efficiently with aliphatic, aromatic, and heteroaromatic carboxamides bearing electron-withdrawing or electron-donating groups. In general, aromatic amides bearing electron-donating groups gave slightly higher yields than those containing electron-withdrawing groups on the aromatic rings (Table 2, entries 1–4). This can be attributed to the substituent’s effects on the nucleophilicity of the imidic acid-tautomer oxygen atom (Scheme 1). Electron-donating groups on the aromatic ring would increase the nucleophilicity of that oxygen atom and therefore enhance the nucleophilic substitution rate between the phosphorus-III promoter and the imidic acid tautomer form. Aliphatic amides were also used in these protocols, affording the desired nitriles with good-to-high reaction yields (Table 2, entries 5 and 6). The three protocols were also found to be tolerant toward β-cyanoamines, malonamide, and α,β-unsaturated amides, allowing good yields of the corresponding nitriles (Table 2, entries 7–11). To further extend the scope and utility of these procedures, we examined the behavior of 2-aminothiophene-3-carboxamides (Table 2, entries 12–15). In all these cases, the reactions were compatible with the thiophene ring and the unprotected amine functionality and furnished the corresponding 2-aminothiophene-3-carbonitriles in moderate-to-good yields.

By comparison of the three developed protocols, it could be concluded from Table 2 that method B, which uses PCl₃ as the promoter, gave in general slightly higher yields than methods A and C. This can be attributed to the better reactivity of PCl₃ compared to P(NMe₂)₃ and P(OPh)₃. However, in the case of 2-aminothiophene-3-carboxamides (Table 2, entries 12–15), method C was found to be more suitable probably because of the fact that the P(OPh)₃ promoter used, which is less reactive than PCl₃ and P(NMe₂)₃, is more selective toward nucleophilic substitution with the imidic acid-tautomer oxygen atom (Scheme 1), therefore minimizing any competitive substitution with the NH₂ moiety on the thiophene ring.

It should be mentioned that under microwave conditions, the more stable and less volatile P(OPh)₃ promoter gave the best results (Table 1, entries 14, 17, 20, and 21), allowing for method C which, performed under microwave irradiation and in solvent-free conditions, offers significant advantages such as short reaction times, easy work-up, and environmental safety.

On the basis of our experimental results and the known literature precedents, a mechanistic rationalization for protocols A, B, and C is provided in Scheme 1. First of all, the primary amide undergoes a selective O-phosphinylation, through its imidic acid tautomer, with the hard acid phosphorus-III promoter. The obtained intermediate permits rapid elimination in the presence of diethylamine or DBU as the base, to afford the final nitrile.

## CONCLUSIONS

In summary, we have successfully developed three efficient and simple methodologies for the conversion of primary amides into nitriles, mediated by the mild, readily available, and low-cost phosphorus-III reagents P(NMe₂)₃, PCl₃, or P(OPh)₃. These synthetic strategies offer significant advantages, such as good-to-excellent yields, wide substrate scope, good functional group compatibility, mild reaction conditions, short reaction times, easy work-up, and environmental safety, which make these protocols more amenable for high throughput library synthesis.

## EXPERIMENTAL SECTION

**General.** Commercially available analytical grade reagents and solvents were used without further purification. Melting

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Table 1. Optimization of the Reaction Conditions

| entry | promoter | base | solvent | temp. (°C) | time | yield (%) |
|-------|----------|------|---------|------------|------|-----------|
| 1     | none     | Et₂NH| CHCl₃   | 62         | 24 h | 0         |
| 2     | P(NMe₂)₃| none  | CHCl₃   | 62         | 24 h | 0         |
| 3     | P(NMe₂)₃| Et₂N | CHCl₃   | 62         | 14 h | 48        |
| 4     | P(NMe₂)₃| pyridine | CHCl₃ | 62         | 24 h | 39        |
| 5     | P(NMe₂)₃| N- NH₂| CHCl₃   | 62         | 24 h | 7         |
| 6     | P(NMe₂)₃| DBU  | CHCl₃   | 62         | 24 h | 52        |
| 7     | P(NMe₂)₃| Et₂NH| CHCl₃   | 62         | 6 h  | 88        |
| 8     | P(NMe₂)₃| Et₂NH| toluene | 111        | 12 h | 71        |
| 9     | P(NMe₂)₃| Et₂NH| EtOH    | 78         | 24 h | 10        |
| 10    | P(NMe₂)₃| Et₂NH| CH₂Cl₂  | 40         | 24 h | 60        |
| 11    | P(NMe₂)₃| Et₂NH| MeCN    | 82         | 24 h | 65        |
| 12    | P(NMe₂)₃| Et₂NH| CHCl₃   | 62         | 24 h | 35        |
| 13    | P(NMe₂)₃| Et₂NH| none    | 150        | 3 h  | 33        |
| 14    | P(NMe₂)₃| Et₂NH| none    | 150        | 15 min| 42        |
| 15    | PCl₃     | Et₂NH| CHCl₃   | 62         | 40 min| 92        |
| 16    | PCl₃     | Et₂NH| none    | 150        | 60 min| 15        |
| 17    | PCl₃     | P(NMe₂)₃| Et₂NH| 150  | 5 min | 0         |
| 18    | P(OPh)₃ | Et₂NH| CHCl₃   | 62         | 24 h | 40        |
| 19    | P(OPh)₃ | Et₂NH| none    | 150        | 30 min| 65        |
| 20    | P(OPh)₃ | Et₂NH| none    | 150        | 15 min| 52        |
| 21    | P(OPh)₃ | P(NMe₂)₃| DBU  | 4 min  | 91        |

"All reactions (except in entry 12) were conducted with 2 equiv of promoter and 3 equiv of base as optimized quantities. The progress of the reactions was monitored by thin layer chromatography (TLC). Isolated yield after purification by column chromatography. One equivalent of P(NMe₂)₃ and 2 equiv of Et₂NH were used. Entries 14, 17, 20, and 21 were conducted under microwave irradiation (150 °C, 300 W)."
The progress of the reactions was monitored by TLC. Isolated yield after purification by column chromatography.

Table 2. Substrate Scope Studies

| Entry | Substrate | Product | Method A | Method B | Method C |
|-------|-----------|---------|----------|----------|----------|
|       |           |         | Time*    | Yield (%)| Time*    | Yield (%)| Time*    | Yield (%)|
| 1     |           |         | 6 h      | 88       | 40 min   | 92       | 4 min    | 91       |
| 2     |           |         | 6 h      | 89       | 45 min   | 90       | 3 min    | 90       |
| 3     |           |         | 5 h      | 86       | 45 min   | 93       | 3 min    | 92       |
| 4     |           |         | 8 h      | 65       | 50 min   | 51       | 5 min    | 88       |
| 5     |           |         | 8 h      | 90       | 35 min   | 94       | 5 min    | 93       |
| 6     |           |         | 7 h      | 82       | 45 min   | 91       | 5 min    | 89       |
| 7     |           |         | 9 h      | 77       | 30 min   | 89       | 6 min    | 85       |
| 8     |           |         | 10 h     | 72       | 45 min   | 80       | 6 min    | 81       |
| 9     |           |         | 7 h      | 85       | 40 min   | 91       | 4 min    | 89       |
| 10    |           |         | 8 h      | 81       | 30 min   | 92       | 5 min    | 88       |
| 11    |           |         | 7 h      | 69       | 40 min   | 89       | 4 min    | 84       |
| 12    |           |         | 12 h     | 76       | 4 h      | 45       | 6 min    | 88       |
| 13    |           |         | 12 h     | 79       | 4 h      | 45       | 6 min    | 89       |
| 14    |           |         | 12 h     | 55       | 5 h      | 40       | 6 min    | 70       |
| 15    |           |         | 12 h     | 64       | 4 h      | 40       | 7 min    | 72       |

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The progress of the reactions was monitored by TLC. 1H and 13C NMR spectra were recorded with CDCl3 as the solvent, on a Bruker AC-300 spectrometer operating at 300.1 MHz for 1H and 75.5 MHz for 13C. IR spectra were recorded on a Nicolet IR200 spectrometer. The progress of the reactions was monitored by TLC, using 5 × 20 cm plates with a layer thickness of 0.25 mm (silica gel 60 F254) and a mixture of ether and hexane (1:1) as the eluent. Purification of products was performed by column chromatography using silica gel (70–230 mesh size).
A mixture of primary amide (1 mmol), tris(dimethylamino)phosphine (2 mmol), and diethylamine (3 mmol) in CHCl₃ (5 mL) was stirred at reflux temperature for 6–12 h (Table 2). The reaction mixture was then cooled to room temperature and washed with a saturated NH₄Cl solution (5 mL) and then with water (2 × 5 mL). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The crude product obtained was purified by silica gel column chromatography using a mixture of ether and hexane (1:1) as the eluent.

Method B. To a mixture of primary amide (1 mmol) and diethylamine (3 mmol) in CHCl₃ (5 mL), cooled at 0 °C, phosphorus trichloride (2 mmol) was added dropwise with stirring within 15 min. The resulting mixture was then heated under reflux with constant stirring for 0.5–5 h (Table 2). After cooling to room temperature, the reaction mixture was washed with a saturated NH₄Cl solution (5 mL) and then with water (2 × 5 mL). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The crude product obtained was purified by silica gel column chromatography using a mixture of ether and hexane (1:1) as the eluent.

Method C. The primary amide (1 mmol), triphenylphosphite (2 mmol), and DBU (3 mmol) were placed in a 10 mL microwave reaction tube. The mixture was subjected to microwave irradiation (CEM Discover, 150 °C, 300 W) for 3–7 min (Table 2). After cooling to room temperature, the reaction mixture was diluted with CHCl₃ (5 mL) and washed with a saturated NH₄Cl solution (5 mL) and then with water (2 × 5 mL). The organic phase was dried over Na₂SO₄ and concentrated under vacuum. The crude product obtained was purified by silica gel column chromatography using a mixture of ether and hexane (1:1) as the eluent.

All synthesized nitriles are known compounds and showed physical and spectral properties identical to those reported in the literature.

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