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Dehydration of Amides to Nitriles under Conditions of a Catalytic Appel Reaction

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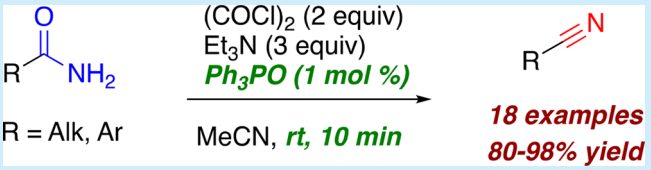
Supporting Information

ABSTRACT: A highly expedient protocol for a catalytic Appel-type dehydration of amides to nitriles has been developed that employs oxalyl chloride and triethylamine along with triphenylphosphine oxide as a catalyst. The reactions are usually complete in less than 10 min with only a 1 mol % catalyst loading. The reaction scope includes aromatic, heteroaromatic, and aliphatic amides, including derivatives of α-hydroxy and α-amino acids.



Chemical compounds with the nitrile functional group serve as useful precursors in the manufacture of a large variety of consumer products, such as polyamides, pigments and dyes, pharmaceuticals, agrochemicals, and many other substances.[1] The nitrile group has a rich chemistry since it can be conveniently converted to other functional groups.[2] Also, the nitrile pharmacophore plays a significant role in modulating the biological activity of synthetic medicinal drugs[3] and natural products.[4]

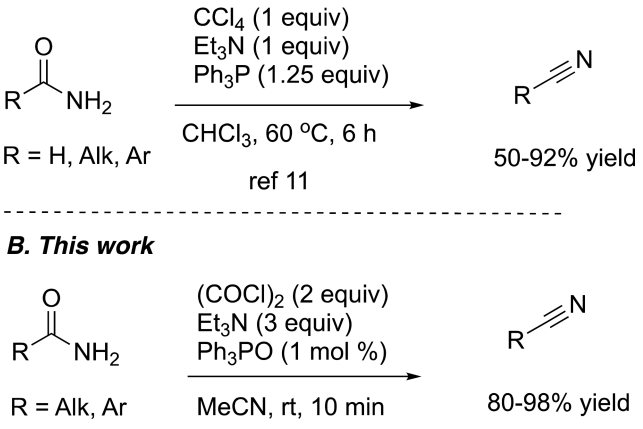
The synthesis of nitriles by dehydration of primary amides is a well-known process; numerous methods have been developed and used by practicing chemists for over a century.[5]

In the past few years, a number of new methods have emerged for carrying out efficient dehydration of amides to nitriles. Among the new reagents, $[Et_2NSF_2]BF_4$ (XtalFluor-E)[6] and silicotungstate $[n\text{-}Bu_4N]_4[\alpha\text{-}H_4SiW_{11}O_{39}]$[7] have been introduced. Also, metal-catalyzed dehydration has been carried out in the presence of silanes,[8] *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide,[9] and acetonitrile.[10]

However, in many instances the practicality of the methods is offset by the toxicity of the reagents, long reaction times, narrow scope, and the laborious workup needed to remove the side products. Therefore, the development of convenient, practical methods for converting amides to nitriles still holds its relevance.

The Appel reaction,[11] which employs a combination of Ph_3P, CCl_4, and Et_3N, belongs to a group of highly versatile tools that, among other useful transformations,[12] can be used for the synthesis of nitriles from amides (Scheme 1A). However, the original Appel protocol has a number of weaknesses. First of all, exposure to CCl_4 can lead to kidney damage, and it is also a suspected carcinogen. Furthermore, it contributes to depletion of the ozone layer and can no longer be used.[13] Second, stoichiometric use of Ph_3P results in the formation of large quantities of Ph_3PO, which complicates the isolation and purification of the target products. Therefore, the development of a catalytic version of the Appel dehydration of amides in which CCl_4 as a source of chloride is replaced by a safer alternative and the phosphorus reagent is used as an organic catalyst while the universal application scope of the original method is kept would make it significantly more attractive from the practical standpoint. Our work was inspired by the recent reports of Denton[14] and others,[15] who have demonstrated that running some reactions under the Appel conditions can be efficient using catalytic Ph_3PO in the presence of oxalyl

Scheme 1. Dehydration of Amides to Nitriles by Appel Reaction



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chloride. In this work, we present an adaptation of this protocol to the mild and facile conversion of amides to nitriles using as low as a 1 mol % loading of Ph_3PO (Scheme 1B).

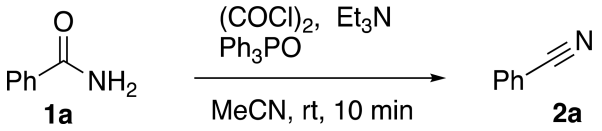
The investigation commenced with establishing the best conditions for the dehydration of amides, employing benzamide (**1a**) as a model substrate (Table 1). First, the role of each reagent was evaluated. Oxalyl chloride on its own did not produce benzonitrile (**2a**) (entry 1). Instead, slow formation of benzoyl isocyanate (**3a**) was observed, mirroring published data.[16] This reaction is likely to proceed through initial *O*-acylation of **1a** to give oxalyl imidate **4** followed by cyclization to form unstable 2-phenyloxazolin-4,5-dione (**5**), which then forms **3a** (Scheme 2). Addition of triethylamine to the reaction mixture did not alter the reaction outcome (entry 2), which contrasts with the previously reported formation of **2a** when **1a** was treated with oxalyl chloride in the presence of 2,6-lutidine.[16a]

The use of stoichiometric quantities of Ph_3PO and $(COCl)_2$ without triethylamine resulted in low conversion of **1a** into **2a** (Table 1, entry 3). With 10 mol % Ph_3PO and 1 equiv each of oxalyl chloride and trimethylamine, **2a** was formed in 14% conversion (entry 4), which increased to 29% and 45% when triethylamine was used in 2- and 3-fold excess, respectively (entries 5 and 6). Full conversion was achieved when the amount of $(COCl)_2$ was doubled to 2 equiv (entry 7). It should be noted that the reaction was complete in less than 10 min. A 3-fold excess of triethylamine appears to be crucial, as reducing the amount of Et_3N to 2 equiv slowed the reaction (entry 8).

Next, the effect of the catalyst loading was investigated (Table 1, entries 9–11). Pleasingly, Ph_3PO performed efficiently even when the loading was as low as 1 mol % (entry 11). With **1a** the catalyst content could be further reduced, but for investigating the reaction scope, 1 mol % proved to be most suitable. The influence of the solvent was briefly assessed (entries 12–15). Despite some good conversions achieved in Et_2O and CH_2Cl_2 (entries 12 and 13), MeCN remained the best choice. Other solvents, such as toluene and dioxane, proved to be inferior (entries 14 and 15). Thus, the conditions in entry 11 were taken as optimal.

To investigate the reaction scope, the substrates were selected to represent diverse compound classes. The results are collected in Figure 1. On a standard 2 mmol scale, **2a** was

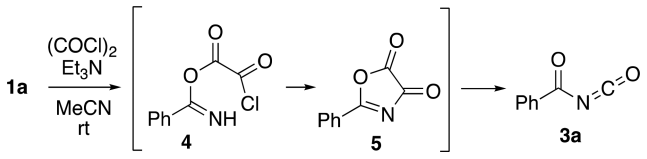
Table 1. Optimization of the Reaction Conditions[a]



entry	equiv of $(COCl)_2$	mol % Ph_3PO	equiv of Et_3N	solvent	conv. (%)[b]
1	1	–	–	MeCN	0[c]
2	1	–	1	MeCN	0[d]
3	1	100	–	MeCN	25
4	1	10	1	MeCN	14
5	1	10	2	MeCN	29
6	1	10	3	MeCN	45
7	2	10	3	MeCN	100
8	2	10	2	MeCN	75
9	2	5	3	MeCN	100
10	2	2	3	MeCN	100
11	2	1	3	MeCN	100
12	2	1	3	Et_2O	87
13	2	1	3	CH_2Cl_2	85
14	2	1	3	toluene	77
15	2	1	3	dioxane	31

[a]General conditions: **1a** (0.25 mmol), Ph_3PO, Et_3N, dry MeCN (1 mL), dropwise addition of neat $(COCl)_2$. The reactions were carried out for 10 min at rt before an aliquot (50 μL) was taken, quenched with aqueous MeCN (1 mL), and analyzed by GC. [b]Conversion to **2a** was calculated from GC. [c]After 10 min, according to GC, the reaction mixture contained **1a** (70%) and benzoyl isocyanate (**3a**) (ca. 25%). [d]After 10 min, according to GC, the reaction mixture contained **1a** (60%), **3a** (ca. 21%), and some unidentified byproducts.

Scheme 2. Formation of Benzoyl Isocyanate (3a)



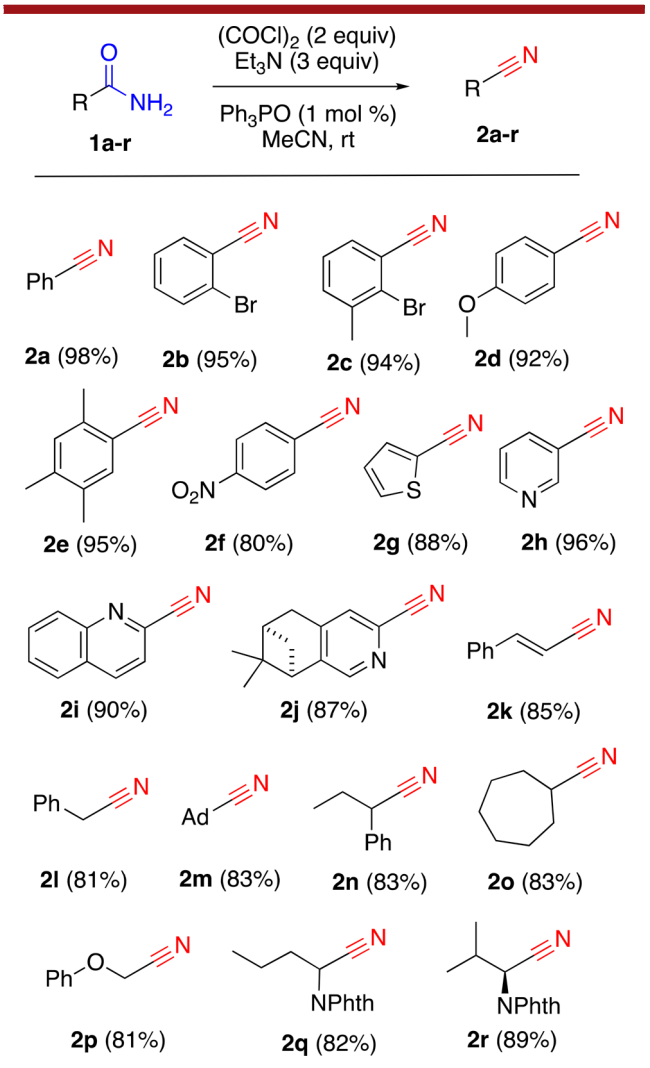


Figure 1. Catalytic dehydration scope. General conditions: amide **1** (2.0 mmol), Ph_3PO (1 mol %), Et_3N (3 equiv), dry MeCN (8 mL), dropwise addition of $(COCl)_2$ (2 equiv). The reactions were carried out for 10 min at rt. Yields of the isolated compounds are given.

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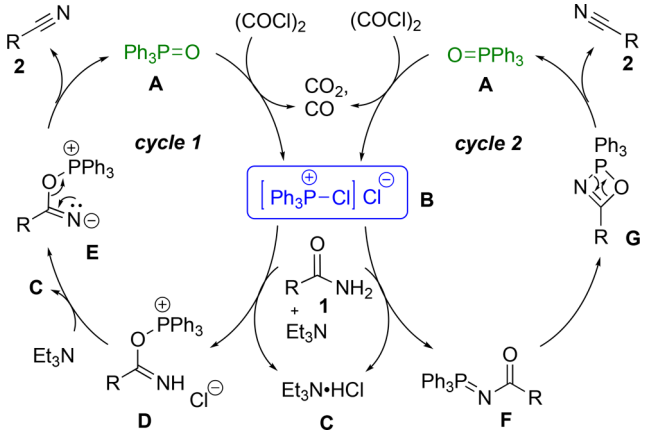
isolated in 98% yield. The reaction worked equally well on a 1 g (8.3 mmol) scale, giving **2a** in 92% yield. Aromatic amides **1b–f** mirrored the reactivity of the model amide **1a**, furnishing the respective nitriles **2b–f** in high yields. A set of heterocyclic amides **1g–j** were next assessed. 2-Cyanothiophene (**2g**), 3-cyanopyridine (**2h**), and 2-cyanoquinoline (**2i**) were accessed in high yields. In this series, it is worth highlighting the efficient synthesis of 3-cyanotetrahydroisoquinoline derivative **2j** from the corresponding amide **1j**. This compound serves as a precursor to the corresponding axially chiral tetrahydroisoquinoline-*N*,*N*′-dioxide, which belongs to a group of highly competent Lewis base catalysts for asymmetric crotylation of carbonyl compounds that are currently under investigation in our laboratories.[17] Unsaturated cinnamamide (**1k**) and aliphatic linear (**1l**, **1m**) and branched (**1n**, **1o**) amides were converted into the respective nitriles in good yields, though their reactivity was somewhat lower compared with the aromatic analogues. The same applied to the functionalized derivatives **1p–r**, which included phenoxyacetamide (**1p**) and phthalimide-protected amino acid amides **1q** and **1r**. It has to be noted that the corresponding Boc-protected amino acids did not give the desired nitrile. Instead, numerous side products were formed, which most likely resulted from the reaction of the *N*-Boc group with oxalyl chloride, similar to the reaction shown in Scheme 2.

On the basis of the experimental observations and the published data on the catalytic Appel reaction,[14,15] we suggest two possible mechanistic pathways for this dehydration reaction (Scheme 3). Both cycles start with quick formation of the

Scheme 3. Possible Catalytic Cycles for Dehydration of Amides to Nitriles Mediated by Triphenylphosphine Oxide



intermediate chlorophosphonium chloride (**B**) upon treatment of triphenylphosphine oxide (**A**) with $(COCl)_2$, as demonstrated by Denton with the aid of ^{31}P NMR spectroscopy.[14d] Next, in catalytic cycle 1, intermediate **B**, in the presence of Et_3N, reacts with amide **1** via oxygen to form first species **D** followed by species **E**, which then undergoes elimination to furnish nitrile **2** and regenerate **A**; such a sequence was proposed by Appel.[11] The pathway outlined in catalytic cycle 2, which proceeds via formation of *N*-acyltriphenylphosphine imide **F**, was originally rejected by Appel[11] because **F** was deemed to be too stable. Nonetheless, we decided to revisit this mechanistic option (see the Supporting Information for details). *N*-Benzoyltriphenylphosphine imide synthesized by a literature method[18] was first treated with 3 equiv of Et_3N in MeCN. After 10 min at rt, conversion to nitrile **2a** reached 30%. However, when Et_3N was used in a combination with 1 equiv of $(COCl)_2$, complete conversion to **2a** was achieved almost instantaneously, thus making this route highly probable. Currently, by monitoring the reaction by NMR spectroscopy, we were unable to distinguish whether it proceeds through the intermediacy of **D** or **F** (or both) because of the short reaction times. Therefore, both catalytic cycles could be considered viable options.[19]

In conclusion, we have developed a highly expedient protocol for catalytic Appel-type dehydration of amides to nitriles catalyzed by triphenylphosphine oxide. The salient features of the method are (i) operationally simplicity, (ii) low catalyst loading (1 mol %), (iii) short reaction times, (iv) mild conditions, and (v) wide reaction scope that includes aromatic, heteroaromatic, and aliphatic amides, including functionalized derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03862.

Experimental procedures and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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(19) One of the reviewers suggested another possible mechanistic scenario for the dehydration of amides using the same set of reagents: imidate **4** formed by *O*-acylation of **1** (Scheme 2) reacts with triphenylphosphine oxide to give the active intermediate **D**, which is then deprotonated by triethylamine to yield **2** (Scheme 3). While we cannot rule out such a possibility, our optimization experiments (Table 1, entries 1 and 2) suggest that if **4** were formed in appreciable quantities, we should have observed formation of the respective acyl isocyanates, which were not detected under the optimized reaction conditions. Therefore, this route appears to be less likely than the two shown in Scheme 3.

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