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

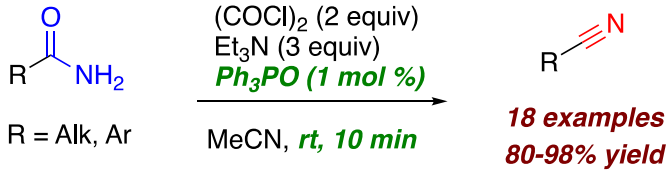
Sergei A. Shipilovskikh,[†] Vladimir Yu. Vaganov,[†] Elena I. Denisova,[†] Aleksandr E. Rubtsov,[*†] Andrei V. Malkov[*‡§]

† *Department of Chemistry Perm State University, Bukireva 15, Perm 614990, Russia*

‡ *Department of Chemistry, Loughborough University, Loughborough, Leics LE11 3TU, UK*

§ *Department of Organic Chemistry, RUDN University, 6 Miklukho-Maklaya Street, Moscow 117198, Russia*

Supporting Information Placeholder



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

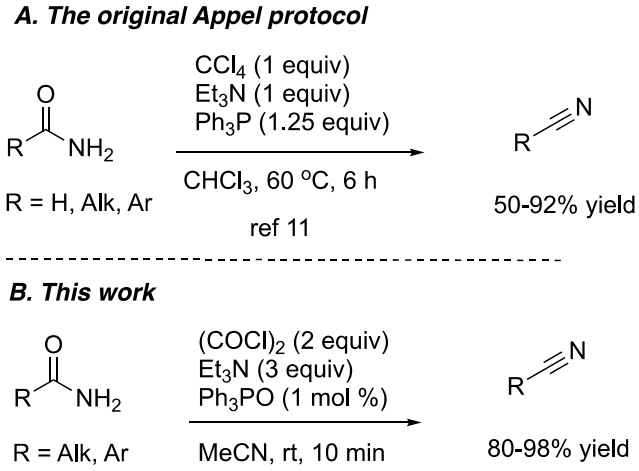
Chemical compounds with the nitrile functional group serve as useful precursors in the manufacture of a large variety of consumer products, such as polyamides, pigments and dyes, pharmaceuticals, agrochemicals and many other substances.[1] The nitrile group has a rich chemistry, since it can be conveniently 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 the 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 last few years, a number of new methods have emerged for carrying out an 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] were 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, slow 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[11] reaction, which employs a combination of Ph_3P, CCl_4 and Et_3N, belongs to a group of highly versatile tools that, among other useful transformation,[12] can be used for the synthesis of nitriles from amides (Scheme 1, A).



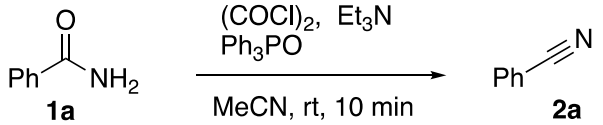
Scheme 1. Dehydration of amides to nitriles by Appel reaction.

However, the original Appel protocol has a number of weaknesses. First of all, exposure to CCl_4 can lead to kidney damage, it is also a suspected carcinogen. Furthermore, it contributes to depletion of the ozone layer and can no longer be used.[13] Secondly, 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, where CCl_4 as a source of chloride is replaced by a safer alternative, and the phosphorus reagent is used as an organic catalyst, while keeping the universal application scope of the original method, 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 chloride.

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

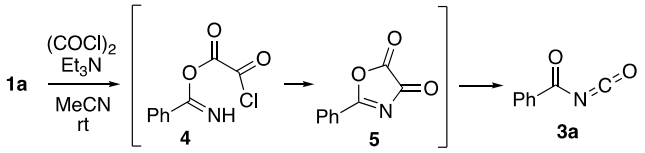
Table 1. Optimization of reaction conditions.[a]



entry	$(COCl)_2$ (equiv)	Ph_3PO (mol %)	Et_3N (equiv)	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: benzamide **1a** (0.25 mmol), Ph_3PO, Et_3N, dry MeCN (1ml), 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 nitrile **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%), benzoyl isocyanate **3a** (ca. 21%) and some unidentified by-products.

The investigation commenced with establishing the best conditions for the dehydration of amides which employ benzamide **1a** as a model substrate (Table 1). First, the role of each reagent was evaluated. Thus, oxalyl chloride on its own did not produce benzonitrile **2a** (entry 1). Instead, a slow formation of benzoyl isocyanate **3a** was observed, mirroring published data.[16] This reaction is likely to proceed through the initial *O*-acylation of **1a** to give oxalyl imidate **4** followed by cyclization into unstable 2-phenyloxazolin-4,5-dione **5**, which then forms benzoyl isocyanate **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 benzonitrile **2a** when benzamide **1a** was treated with oxalyl chloride in the presence of 2.6-lutidine.[16a]



Scheme 2. Formation of benzoyl isocyanate **3a**.

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

Next, the effect of the catalyst loading was investigated (entries 9-11). Pleasingly, Ph_3PO performed efficiently even when the loading was as low as 1 mol % (entry 11). With benzamide **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, 13), MeCN remained the best choice. Other solvents, such as toluene and dioxane, proved inferior (entries 14, 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, benzonitrile **2a** was isolated in a 98% yield. The reaction worked equally well on a 1 g (8.3 mmol) scale giving **2a** in a 92% yield. Aromatic amides **1b**-**1f** mirrored the reactivity of the model benzamide **1a** furnishing the respective nitriles **2b**-**2f** in high yields. A set of heterocyclic amides **1g**-**1j** 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 the 3-cyanotetrahydroisoquinoline derivative **2j** from the corresponding amide **1j**. This compound serves as a precursor to the respective 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**, 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 to 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 *t*-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.

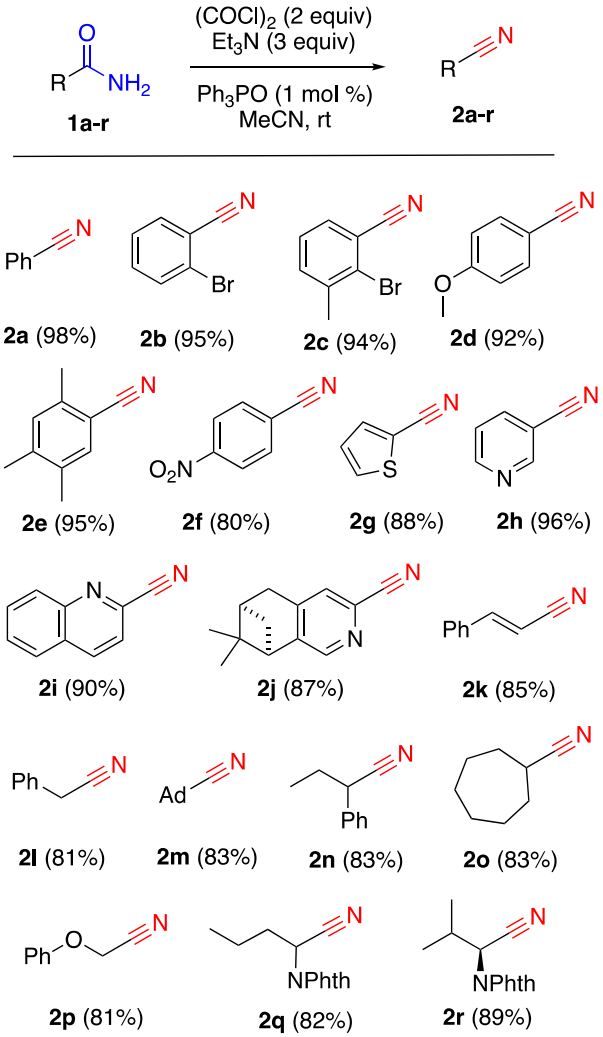
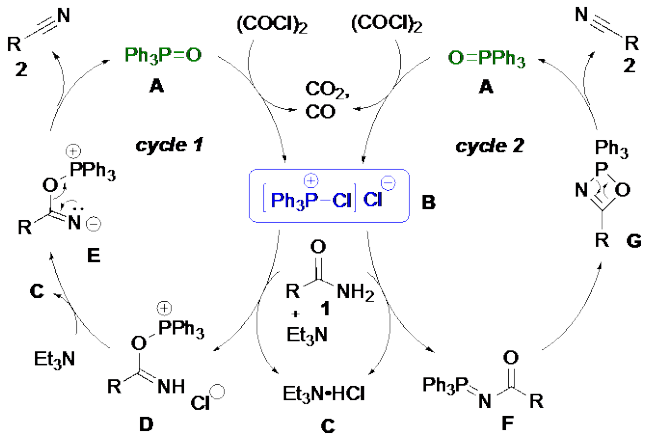


Figure 1. Catalytic dehydration scope. General conditions: amide **1** (2.0 mmol), Ph_3PO (1 mol %), Et_3N (3 equiv), dry MeCN (8 mL), dropwise addition of $(COCl)_2$ (2 equiv). The reactions were carried out for 10 min at rt. Yields of the isolated compounds are given.

Based on 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 2). Both cycles start with a quick formation of the intermediate chlorophosphomium 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 the 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 to regenerate triphenylphosphine **A**; such a sequence was proposed by Appel.[11] The pathway outlined in the catalytic cycle 2 that proceeds via formation of *N*-acyltriphenylphosphine imide **F** was originally rejected by Appel[11] because **F** was deemed too stable. Nonetheless, we decided to revisit this mechanistic option (see 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 $(COCl)_2$, a complete conversion to **2a** was achieved almost instantaneously, thus making this route highly probable. Currently, by monitoring the reaction by NMR, we were unable to distinguish whether it proceeds through the intermediacy of **D** or **F** (or both) due to fast reaction times. Therefore, both catalytic cycles could be considered viable options.[19]



Scheme 3. Possible catalytic cycles for dehydration of amides to nitriles mediated by phosphine oxide.

In conclusion, we have developed a highly expedient protocol for a 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) fast reaction times, (iv) mild conditions and (v) wide reaction scope that includes aromatic, heteroaromatic and aliphatic amides, including functionalized derivatives.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; ^1H and ^{13}C NMR spectra for new compounds.
The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*E-mail: A.Malkov@lboro.ac.uk
*E-mail: Rubtsov@psu.ru

Author Contributions

The manuscript was written through contributions of all authors.

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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 the imidate **4** was 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.