Conversion of Primary Amides to Nitriles by Aldehyde-Catalyzed Water Transfer

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The synthetic importance of the dehydration of primary alkyl- or arylamides to their corresponding nitriles has been thoroughly documented in the literature. As early as 1945[1] this reaction has been reviewed, and since that time alternate conditions and dehydration reagents providing higher yields have been introduced.[2] Many of these reported sequences, however, require the use of strong acids and bases or involve difficult procedures. Phosphorus pentoxide[3] is the most common dehydrating agent for this reaction, but many others including phosphorus oxychloride[4] or thionyl chloride[5] are usually employed.

More recently, dehydrating and alkylating reagents have been disclosed, permitting the reaction to proceed at lower temperature[6] and under neutral,[7] mild conditions[8,9] or in liquid triphasic systems.[10] Unfortunately,

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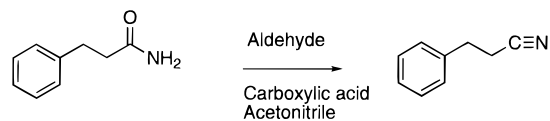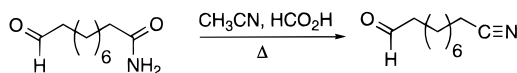
Scheme 1

Table 1

entry	RCHO	RCO$_2$H	isolated yield (%)
1	C$_7$CHO	HCO$_2$H	87
2	C$_7$CHO	CH$_3$CO$_2$H	0
3	C$_7$CHO	CF$_3$CO$_2$H	0
4	HCOH	HCO$_2$H	85

Scheme 2

these methods are generally limited to only arylamides and the reagents employed require special preparation.[11]

In our efforts toward the total synthesis of natural products and glycosidase inhibitors,[12] we explored the conversion of carboxamides to nitriles. The dehydration reaction of 3-phenylpropanamide, which proceeds in refluxing acetonitrile with formic acid, was interestingly catalyzed by an aldehyde (Scheme 1).

In contrast to the previously reported methods,[3−10] no strong dehydration or sophisticated reagent is needed and the reaction can be easily carried out on large scales.

Mechanistically, the trans amidation of an alkyl- or arylamide to its corresponding nitrile requires the transfer of water from the amide to acetonitrile. Experimentally, this transfer could be quantified upon replacement of acetonitrile with benzonitrile, which in addition to the desired nitrile produced 1 equiv of benzamide.

To understand this dehydration reaction and to investigate the role of the required acid and aldehyde, we varied the experimental conditions. The results are summarized in Table 1.

The reaction was very sensitive to the acid employed, with optimal yields being recognized when formic acid was used (entry 1, Table 1). As seen in entries 2 and 3 (Table 1), both acetic and trifluoroacetic acid were ineffective. The choice of the aldehyde, however, appears less critical (entry 4, Table 1). We noted that various aldehydes could be used and selected paraformaldehyde because of its ease of removal. The amount of aldehyde used did effect the reaction, and our studies show it to act in a catalytic fashion. For example, using 0.2 equiv of octanal (versus 3 equiv) resulted in a decrease in yield of the corresponding nitrile from 87% to 60%. The catalytic role of the aldehyde was further verified by the transformation of 10-oxodecanamide to its corresponding nitrile (80%) in the absence of any added aldehyde (Scheme 2). Here, the internal aldehyde moiety serves as the catalyst. In the absence of either the acid or aldehyde components, no products were isolated.

Furthermore, we observed that replacement of acetonitrile by benzonitrile leads to similar results, and in this case 1 equiv of benzamide is recovered at the end.

In a typical experiment amide was solubilized in acetonitrile and an excess of formic acid and paraformaldehyde

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Scheme 3
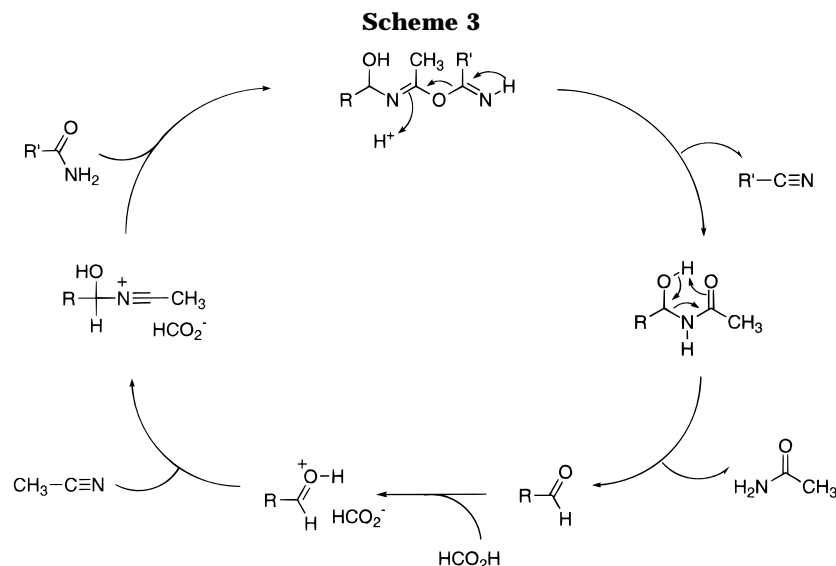
were successively added. The mixture was refluxed for 12 h and subjected to workup and purification.[13]

The results suggest a reaction mechanism in which the aldehyde serves as a relay for the water transfer from the amide to acetonitrile (solvent). We propose a set of equilibria to account for the reaction, although the fact that only formic acid allows the reaction was not yet fully understood (Scheme 3).

Addition of the protonated aldehyde to acetonitrile generates the intermediate nitrilium species, which subsequently undergoes addition by the primary amide. This intermediate can collapse through the release of the desired nitrile product to a β-hydroxy amide. Sigmatropic rearrangement liberates the aldehyde and acetamide. The net result is the transfer of one molecule of water from the amide to the acetonitrile.

The dehydration reaction gave the best results with primary arylamides (85−92%; entries 1−3, Table 2). The reaction was successful for primary alkylamides (64−92%; entries 4−7, Table 2), and functional groups including hydroxyl, carboxylic acid, and chloride were tolerated (entries 4−7, Table 2). Alkyne derivatives decomposed under the reaction conditions (entry 8, Table 2), and both tetrahydropyranyl ethers and *tert*-butyldimethylsilyl ethers (entries 9 and 10, Table 2) were unstable.

In conclusion, we reported herein the first conversion of primary alkyl- and arylamides to their corresponding

Table 2

Entry	Starting Amide	Product	Isolated Yield
1			85 %
2			87 %
3			92 %
4			64 %
5			68 %
6			87 %
7			92 %
8		Degradation products	
9		Degradation products	
10		Degradation products	

nitriles by aldehyde-catalyzed water transfer. The mild conditions and easy workup of this method will frequently offer significant advantages over former procedures, and this method should be a further interest in synthetic organic chemistry.

(13) Typical experimental procedure: To a stirred solution of 3-phenylpropanamide (50 mg, 0.34 mmol) in CH$_3$CN (0.8 mL) at room temperature were successively added formic acid (0.2 mL) and paraformaldehyde (50 mg, 1.67 mmol). The reaction mixture was then refluxed for 12 h, and the resulting solution was cooled to room temperature. Two workup procedures were used identically. Procedure A: The crude mixture was concentrated under reduced pressure and flash chromatography over silica gel (230−240 mesh) with hexanes/ethyl acetate (7:3): to yield 3-phenylpropanonitrile (37 mg, 85%). Procedure B: The reaction mixture was diluted with ethyl acetate (10 mL) and washed successively with a saturated solution of NaHCO$_3$ (5 mL) and water (5 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 10 mL). The organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated. The 3-phenylpropanonitrile crude was purified as described above (Procedure A). The spectral data were identical with those of commercially available product.