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A Simple Preparation of N-Protected Chiral α-Aminonitriles from N-Protected α-Amino Acid Amides

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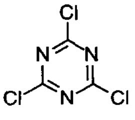
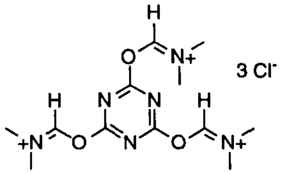
Abstract: N-protected α-amino-acid amides are dehydrated to N-protected α-aminonitriles in good yields and with excellent purities by reaction of the corresponding primary amides with cyanuric chloride in DMF. © 1997 Elsevier Science Ltd.

In a recent issue of this journal, a research group described the dehydration of primary amides to nitriles under Swern oxidation conditions.[1] The authors claim that their method is mild compared to many others taken from the literature. Undoubtedly, Swern oxidation conditions represent a mild procedure; however, they suffer from a serious drawback: methyl sulfide is generated as a by-product in the course of the reaction. This becomes of importance when the reaction is carried out on a large scale (stench), or when the next step involves a catalytic hydrogenation (catalyst poisoning).

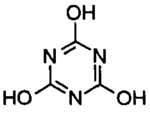
In 1980, Olah's group decribed the use of cyanuric chloride **1** as a mild dehydrating agent in the preparation of amides to nitriles.[2] It is most surprising that this method has not been utilized more extensively, as the reaction conditions (one third molar equivalent of cyanuric chloride in dimethylformamide at room temperature) are compatible with most sensitive functionalities. The reactive species is believed to be the dimethylformamide / cyanuric chloride adduct **2** depicted below.



1



2



3

Therefore, it is not surprising that the reaction goes to completion in the presence of only one third molar equivalent of cyanuric chloride. This is true when the reagent is freshly recrystallized. However, when using a less pure material, it is advisable to introduce c.a. half an equivalent. The excess reagent and the by-product of the reaction (cyanuric acid **3**) are easily removed by water or 5% sodium bicarbonate washings.

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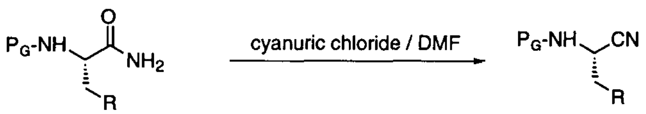
These observations prompt us to disclose our results regarding the synthesis of N-protected α-aminonitriles from N-protected α-amino-acid amides. It is worth mentioning that this method has been used in the past to generate N-protected α-amino acid cyanomethyl esters from the corresponding N-protected α-amino acid glycolamides.[3]

A typical procedure is as follows: To a stirred solution of a N-protected α-amino-acid amide (10 mmol.) in dimethylformamide (10 ml) at room temperature was added at once cyanuric chloride (Aldrich, 922 mg, 5 mmol.). Upon completion of the reaction (monitored by TLC, generally not more than 30 min.), water (c.a. 100 ml) was added. When the expected compound precipitated, the solid was collected by filtration on a sintered glass funnel, washed with 5% aqueous sodium bicarbonate, then with water, and dried in vacuo. When the expected product did not precipitate, the reaction mixture was partitioned between water and ethyl acetate, the organic layer washed with 5% aqueous sodium bicarbonate, then with water, dried over sodium sulfate and concentrated under reduced pressure. The product was then crystallized from the appropriate solvent.



The results are summarized in the table below.

Entry	Amide	Yield %	Mass Spec[a]	Mp °C	$[\alpha]_D$ c=1, DMF	HPLC purity %[b]
1	Boc-Phe-NH_2	91	246.30	115-118	-64	> 99
2	Z-Phe-NH_2	84	280.31	131-133	-44	> 97
3	Fmoc-Phe-NH_2	86	368.45	171-175	-58	> 95
4	Z-Asp(tBu)-NH_2	73[e]	304.33	49-51[c]	-28	> 99
5	Boc-Lys(Cl-Z)-NH_2	50[e]	395.87	90-92[d]	-30	> 98

a: either $M+H^+$ observed in ESI or FAB mass spec, or M^+ observed in EI mass spec. b: C18 A: 1% aqueous TEAP / B: acetonitrile; gradient 40% to 100% B in 20 min. c: crystallized from a mixture of diethyl ether and hexane. d: crystallized from diethyl ether. e: not optimized.

Under these conditions, the reaction proceeded in good yield and provided fairly pure crude material. Boc, Z and Fmoc protecting groups remained unaffected, whereas the yields and purities were comparable regardless of the nature of the protecting groups (see entries 1, 2 and 3). Polyfunctional amino acid amides were cleanly converted to nitriles as well (see entries 4 and 5), although the yields were somewhat lower. Since the process does not involve the chiral center, no epimerization was expected, and therefore, enantiomeric excesses have not been checked.

In summary, N-protected α-amino-acid amides are cleanly converted to N-protected α-aminonitriles in good yields and excellent purity. We hope that this short note will help to revive an excellent methodology published almost two decades ago.

References:

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