



Versatile and chemoselective transformation of aliphatic and aromatic secondary amides to nitriles



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ABSTRACT

Triflic anhydride in combination with 2-fluoropyridine effectively dehydrates secondary amides to afford nitriles under mild reaction conditions. The reaction is general in scope and compatible with the use of aliphatic, α,β -unsaturated, aromatic, and heteroaromatic amides bearing either secondary, tertiary, or benzylic *N*-alkyl groups. The reaction also shows good to excellent chemoselectivity for the secondary amide and tolerates several labile functional groups.

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1. Introduction

Nitriles participate in a wide range of transformations and are thus versatile and powerful synthetic intermediates for organic synthesis. For example, the cyano group serves as a good leaving group to generate reactive species such as iminium ions, carbanions, and radicals.¹ It stabilizes α -carbanion and allows the syntheses of amines^{1,2} and carbonyl compounds³ via umpolung.⁴ In addition, nucleophilic or radical addition to nitriles leads to several important classes of compounds including amines,⁵ ketones,⁶ and aldehydes.⁷

Nitriles are also widely present in natural products, bioactive compounds,^{8–10} and materials.¹¹ For these reasons, many methods have been developed for the synthesis of nitriles,^{12,13} most of which rely on cyanide addition or substitution reactions or dehydration of oximes^{13b–f} and amides.^{13d–u} Among the methods that have been developed for the dehydration of amides, reactions that employ secondary amides as substrates are rare.^{13o–t} Nonetheless, the classical Von Braun amide degradation using PCl_5 is suitable for the dehydration of secondary and tertiary benzamides.¹⁴ However, because of the vigorous conditions required, this reaction has rarely been used for the synthesis of nitriles. Gribble and Perni improved the protocol by using POCl_3 as the dehydration agent.¹⁵ But the

reaction requires *N*-*tert*-butylamides as the substrates. Recently, Prati and co-workers,^{13s} further optimized the reaction conditions by using $(\text{PhO})_3\text{P}$ -halogen (Br_2 or Cl_2) combination as the dehydration agents. This method accommodates secondary and tertiary amides with a wide variety of *N*-substituents including benzyl, allyl, tertiary and even primary alkyl groups. Although significant progress has been achieved for the synthesis of nitriles from amides, most of the reported methods still suffer from limited substrate scope and/or harsh reaction conditions. In addition, the chemoselectivity of the dehydration reactions has rarely been addressed.^{13t}

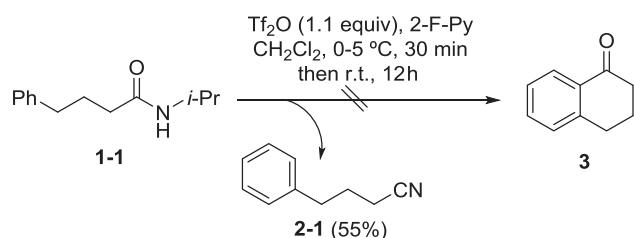
With our continued interest in developing synthetic methods employing readily available amides as the substrates,¹⁶ we report herein a convenient method for the dehydration of secondary amides to give nitriles using triflic anhydride ($\text{ Tf}_2\text{O}$)/2-fluoropyridine (2-F-Py).¹⁸

2. Results and discussion

Our discovery of the nitrile synthesis stemmed from an attempt to cyclize secondary amide **1-1** using $\text{ Tf}_2\text{O}$ /2-F-Py (Scheme 1). The reaction led to the formation of nitrile **2-1** in 55% yield instead of the desired ketone **3**. A survey of the literature showed that only two reports have used $\text{ Tf}_2\text{O}$ to convert secondary amides to nitriles. Kunz and Pleuss demonstrated in one reaction that $\text{ Tf}_2\text{O}$ transforms quantitatively *N*-glycosyl *p*-methoxybenzamide to *p*-

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methoxybenzoxonitrile.^{13q} However, no experimental procedure was provided and the protocol suffers from low atom economy. In their combinatorial synthesis of isoxazoles, Haino and Fukazawa employed a large excess of Tf₂O/pyridine to cleave a secondary amide linkage, leading to aryl nitriles.^{13r} Thus, we decided to develop a mild and general method for the direct transformation of secondary amides to nitriles using Tf₂O as the dehydration agent.



Scheme 1. Unexpected synthesis of nitrile **2-1** from secondary amide **1-1**.

We first examined the effect of base on the reaction of substrate **1-1** in CH₂Cl₂. The substrate was treated with Tf₂O and a base at 0 °C for 30 min and then at 30 °C until the complete consumption of the substrate (monitored with TLC). In the absence of a base, the desired nitrile was obtained in only 13% yield (Table 1, entry 1). Trialkyl amines such as Et₃N and *i*-Pr₂NEt were not effective. Various pyridine-derived bases were tested and 2-chloropyridine (2-Cl-Py, entry 7) and 2-fluoropyridine (2-F-Py, entry 8) gave the best yields. The effect of these two bases on the nitrile formation was thus further investigated using *N*-isopropylbenzamide (**1-7**) as the substrate. The results show that 2-F-Py (yield: 71%, entry 10) is superior to 2-Cl-Py (yield: 51%, entry 9) as a base for the Tf₂O-promoted dehydration reaction.

A survey of the effect of substrate concentration on the reaction showed that 0.2 M of amide in CH₂Cl₂ gave the best yield (83%). Thus, the optimum conditions for the dehydration of secondary amides to nitriles involve the use of 1.1 equiv of Tf₂O and 1.2 equiv of 2-F-Py with a substrate concentration of 0.2 M in CH₂Cl₂. The reagents were mixed at 0 °C and the reaction mixture was kept at

Table 1
Screening of the base additive

$\text{R}^1\text{-C(=O)-NH-R}^2$ (1) $\xrightarrow[\text{then 30 }^\circ\text{C}]{\text{Tf}_2\text{O (1.1 equiv), Base (1.2 equiv), CH}_2\text{Cl}_2 (0.10\text{ M}), 0-5\text{ }^\circ\text{C, 30 min}}$ $\text{R}^1\text{-CN}$ (2)			
Entry	Amide	Base	2 (% Yield) ^a
1		—	13
2	 1-1	Et ₃ N	Trace
3		<i>i</i> -Pr ₂ NEt	Trace
4		Pyridine	8
5		2,6-Lutidine	Trace
6		DTBMP	44
7	 1-7	2-Cl-Py	58
8		2-F-Py	55
9		2-Cl-Py	51
10	 1-7	2-F-Py	71

^a Isolated yield.

the same temperature for 30 min, followed by at 30 °C until the disappearance of the substrate.

With the optimized reaction conditions defined, the scope of the reaction was investigated (Table 2). The dehydration reaction is compatible with the use of both aliphatic (entries 1–5, 73–85% yield) and aromatic amides (entries 7, 8, 11–14, 74–93% yield). Note that even hindered amide **1-5** reacted smoothly to give 1-adamantanecarbonitrile **2-5** in 73% yield. 2-Phenylacetamide **1-6** failed to afford the corresponding nitrile. The *N*-substituent has a dramatic effect on the reaction. Branched alkyl groups including isopropyl, cyclohexyl, cyclopentyl, *tert*-butyl or a benzyl group are well tolerated. In contrast, substrates bearing primary *N*-alkyl groups such as Me and *n*-Bu failed to form the desired nitriles (entries 9 and 10). For the naphthamides, both α - and β isomers reacted smoothly to give 1-naphthonitrile **2-13** and 2-naphthonitrile **2-14** in 93% and 85% yields, respectively. The chiral amide **1-15** also reacted without incident to give benzonitrile **2-15** in 74% yield. Finally, vinylogous benzamide derivative **1-16**^{19m} is also a viable substrate and reacted chemoselectively to produce the α,β -unsaturated nitrile **2-16** in 66% yield.

Table 2
Tf₂O-Activated transformation of secondary amides to nitriles

$\text{R}^1\text{-C(=O)-NH-R}^2$ (1) $\xrightarrow[\text{then 30 }^\circ\text{C}]{\text{one-pot Tf}_2\text{O (1.1 equiv), 2-F-Py (1.2 equiv), CH}_2\text{Cl}_2 (0.2\text{ M}), 0-5\text{ }^\circ\text{C, 30 min}}$ $\text{R}^1\text{-CN}$ (2)			
Entry	Substrate	Time (h)	Product (% yield) ^a
1	1-1	12	2-1 (79)
2	1-2	12	2-2 (76)
3	1-3	7	<i>n</i> -C ₁₀ H ₂₁ CN (85)
4	1-4	3	2-4 (78)
5	1-5	12	2-5 (73)
6	1-6	12	2-6 (trace)
7	1-7	12	2-7 (83)
8	1-8	3	2-7 (74)

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