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Facile and Highly Selective Conversion of Nitriles to Amides via Indirect Acid-Catalyzed Hydration Using TFA or AcOH−H_2SO_4

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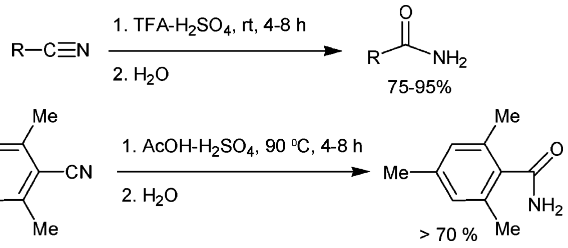
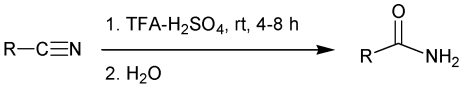


Both aliphatic and aromatic nitriles are conveniently and selectively converted in a single step, via an indirect acid-catalyzed hydration, into the corresponding amides in 1−8 h using a TFA−H_2SO_4 mixture as a reagent system. Although the same reagent did not work for the sterically hindered nitriles such as mesitonitrile, the transformation could be accomplished by changing TFA to AcOH at higher temperatures (>90 °C).

The hydration of nitriles constitutes a very important transformation to access amides,[1] whose applications lie at the core of organic synthesis as well as chemical industry as excellent intermediates and raw materials. Traditionally, the hydration is accomplished by acid[1,2] or base catalysis.[1,3] Unfortunately, each of these protocols is associated with certain debilitating disadvantages that include (a) formation of unwanted acids as side products, (b) high reaction temperatures, and (c) the failure, most importantly, with substrates that contain more than two nitrile groups. Thus, reagent systems that perform the selective conversion of nitriles to amides still continue to be hot pursuits. A variety of homogeneous catalysts based on transition metals such as Co, Pd, Rh, etc.[4] and heterogeneous catalysts such as KF/Al_2O_3, resins, MnO_2/SiO_2, Na/Fluorapatite, etc.[5,6] have been reported for selective conversion of nitriles to amides. Indeed, enzyme-mediated hydrations are also now known.[7]

In the course of our continuing studies on supramolecular self-assembly,[8] we needed to synthesize sterically hindered and strategically designed tetraamides starting from the precursor tetranitrile compounds. The precipitation of partially converted amides or lack of reaction using several of the procedures led us to explore new protocols. Herein, we wish to report that the reagent system consisting of a CF_3COOH−H_2SO_4 mixture accomplishes the conversion of nitriles to amides in a highly selective manner, via an indirect hydration mechanism, in excellent isolated yields (eq 1). In addition to the simplicity of the procedure, the conversions are found to occur in significantly short durations.



(eq 1)

Both aromatic and aliphatic simple nitrile compounds were found to react in TFA−H_2SO_4 medium at room temperature to afford the amides in 70 to >95% isolated yields (Table 1). The procedure involved simple stirring of 1−2 mmol of the substrate in a mixture of TFA−H_2SO_4 for 4−8 h at room temperature, followed by quenching of the reaction mixture with ice-cold water. In several cases, the insoluble amides were isolated by simple filtration (entries 2, 4−8, and 12). In an attempt to find the best reaction conditions, a systematic study was carried out on *p*-bromobenzonitrile as a representative case by varying the amount of the mineral acid and the reaction temperature. As can be seen from Table 1 (entry 2), the reaction occurred sluggishly (20 h) at room temperature (30 °C) with TFA/H_2SO_4 10:1 (v/v) combination, whereas it went to completion within 5−6 h with 1:0.25 equiv; indeed, the reaction was found to be much

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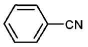
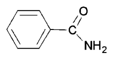
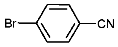
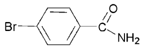
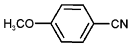
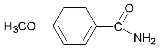
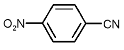
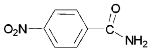
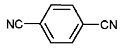
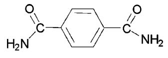
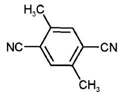
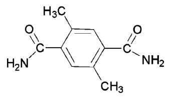
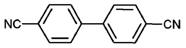
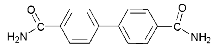
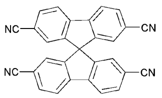
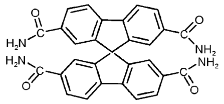
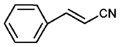
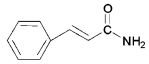
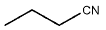
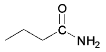
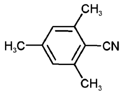
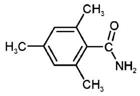
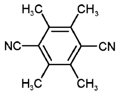
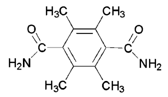
10.1021/jo048240a CCC: $30.25

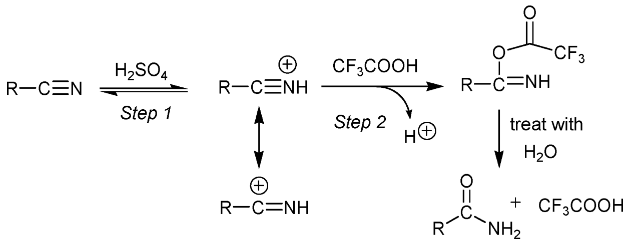
TABLE 1. Results of Conversion of Nitriles to Amides Using TFA/AcOH−H_2SO_4[a]

Entry	Substrate	Reagent system	Duration (h)	Temperature (°C)	Product	Yield (%)
1		TFA-H_2SO_4 (1:0.25)	4.0	30		87
2		TFA-H_2SO_4 (1:0.1)	20.0	30		77
		TFA-H_2SO_4 (1:0.25)	5.5	30		75
		TFA-H_2SO_4 (1:0.5)	3.5	30		75
		TFA-H_2SO_4 (1:1)	2.0	30		90
		AcOH-H_2SO_4 (1:1)	48.0	30		80
3		TFA-H_2SO_4 (1:0.25)	9.0	30		> 90
4		TFA-H_2SO_4 (1:0.25)	5.0	30		81
5		TFA-H_2SO_4 (1:0.25)	1.5	75[b]		> 95
6		TFA-H_2SO_4 (1:0.25)	5.0	75[b]		> 95
		TFA-H_2SO_4 (1:1)	48.0	30		> 95
7		TFA-H_2SO_4 (1:0.25)	1.0	75[b]		81
8		TFA-H_2SO_4 (1:0.25)	2.5	75[b]		77
9		TFA-H_2SO_4 (1:0.25)	5.5	30		> 90
10		TFA-H_2SO_4 (1:0.25)	5.0	30		80
11		TFA-H_2SO_4 (1:1)	5.0	75[b]		c
		AcOH-H_2SO_4 (1:0.5)	1.0	120[b]		35
		AcOH-H_2SO_4 (1:0.5)	7.0	90		70
12		AcOH-H_2SO_4 (1:0.5)	1.5	120[b]		90

[a] Isolated yields, see text for details. Conversion in all cases was 100%. [b] At reflux conditions. [c] No reaction was observed.

more rapid for a dinitrile (entry 6) on heating at reflux (75 °C). A good compromise between the duration of the reaction at room temperature and the amount of the mineral acid introduced into the reaction medium was judged to be 1:0.25 (v/v), and this combination was thus employed for conversion of all of the nitriles to amides. A perceptible dependence of the reaction durations on the electronic factors is noteworthy. For the reactions at room temperature, the unsubstituted benzonitrile (entry 1), *p*-bromobenzonitrile (entry 2), and *p*-nitrobenzonitrile (entry 4) underwent complete conversion (100%) in a comparable time (4−6 h), whereas the *p*-methoxy analogue (entry 3) was found to react in a relatively longer duration (9 h). Remarkably, the dinitrile compounds, viz., 1,4-dicyanobenzene (entry 5), 2,5-dimethyl-1,4-dicyanobenzene (entry 6), and 4,4′-dicyanobiphenyl (entry 7), and even a spirobifluorene tetranitrile (entry 8) underwent conversion to the corresponding di/tetraamides in excel-

SCHEME 1. Mechanism of Conversion of Nitriles to Amides Using TFA−H_2SO_4



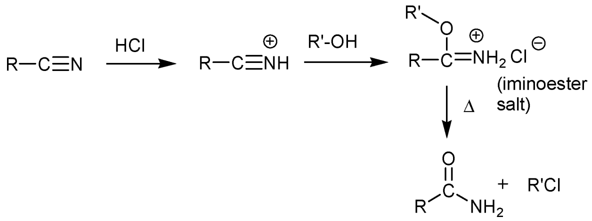
lent isolated yields; in all of these cases, the spectroscopically pure amides were isolated by simple filtration.

While the TFA−H_2SO_4 mixture worked very well for the conversion of cinnamonitrile to cinnamamide (entry 9), the reaction failed with the sterically hindered mesitonitrile even at reflux (ca. 65 °C, entry 11). Gratifyingly, mesitonitrile could be reacted at slightly elevated temperatures by changing to acetic acid as the medium. Although the reaction was found to be rapid at reflux, the yield was found to be rather low. The reaction at a relatively low temperature, i.e., 90 °C, was found to afford the amide in a respectable yield, albeit in a longer duration (entry 11). However, for the dinitrile, i.e., 2,3,5,6-tetramethylterephthalonitrile, the reflux conditions led to the corresponding diamide in a 90% yield (entry 12). Encouraged by the finding that AcOH works nicely for the sterically hindered substrates at elevated temperatures, we returned to examine the reaction course for simple nitriles at the room temperature. Surprisingly, we found that *p*-bromobenzonitrile took 48 h for complete conversion, while the reaction in TFA was complete under similar conditions in 2 h (entry 2). Given that AcOH is a better nucleophilic solvent than TFA, the observed reactivity for the conversion of *p*-bromobenzonitrile in the latter is intriguing.

Scheme 1 shows a plausible mechanism for the conversion of a nitrile to an amide, which entails protonation of the nitrile by the strong mineral acid (step 1) followed by the nucleophilic capture by the organic acid, i.e., TFA or AcOH. The active acetate ester thus formed decomposes readily on treatment with water to the corresponding amide. Thus, the mechanism is basically the addition of an organic acid to the nitrile and its decomposition at the end externally with H_2O. Overall, the reaction involves a formal addition of water, but in an indirect manner. The disadvantage with carrying out hydration directly in the presence of water is that the amide formed can undergo further hydrolysis to the acid.[9,10] Indeed, the amides undergo hydration (to yield the tetrahedral intermediate that decomposes to the corresponding acid) faster than nitriles.[1c] Thus, the formation of acids is an inevitable side reaction.

The intriguing reactivity observed with the variation of TFA to AcOH is clearly suggestive of the dependence of the reaction on hard and soft nature of the nucleophilic solvents. Considering that the nitrile is a soft nucleophile, the transition state leading to the imino ester should be better stabilized with a soft trifluoroacetate anion than the acetate anion. This bears a close resemblance to the reactivity of OH^- and $CF_3CH_2O^-$ ions with nitroso and carbonyl compounds;[11] the OH^- has been found to react faster than $CF_3CH_2O^-$ with carbonyl compounds, whereas the opposite is observed with nitroso compounds.

SCHEME 2. Mechanism of Indirect Hydration of a Nitrile Using R′OH−HCl



The addition of a nucleophilic acid such as TFA or AcOH in the presence of a strong mineral acid may be contrasted with that of the Pinner reaction involving addition of an alcohol to a nitrile in the presence of HCl (Scheme 2) to yield imino esters.[12] In this instance, however, the iminoester/imidate salts are first isolated (step 1) and subjected to further decomposition separately (step 2). The two-step procedure thus yields the amides in 60−80%. In comparison, the advantages with the present TFA−H_2SO_4 are the following: (i) the active acetate ester decomposes readily on treatment with water, leading to amides in much better yields and thereby causing the procedure to be practically a *single-step* one, and (ii) the mechanism does not allow for the formation of the acid as long as water is excluded from the medium whereby the amide in situ formation is obviated. Further, the unique advantage with the reagent system is the remarkable property of TFA or AcOH to function as an excellent solvent, which is particularly crucial when polynitrile compounds are sought to be converted to the corresponding polyamides.[13] As mentioned earlier, precipitation of the partially transformed amides from the reaction media preclude complete conversions. The facile conversion of the tetranitrile to the corresponding tetraamide in 77% isolated yield (entry 8, Table 1) clearly attests to the ease with which the reagent system works.

In summary, we have shown that a variety of aliphatic, aromatic and allylic mono-to-tetranitrile compounds can be converted, in a single step, into their corresponding amides selectively using a TFA− or AcOH−H_2SO_4 reagent system that excludes water. Although the conversion to the amide is formally by addition of water, the transformation is accomplished in an indirect way. We believe that the methodology based on indirect hydration of nitriles reported herein is simple and surpasses the existing ones based on acid catalysis in terms of selectiv-

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(9) Fuson, R. C.; Bertetti, J. W.; Ross, W. E. *J. Am. Chem. Soc.* **1932**, *54*, 4380.

(10) For conversion of aliphatic nitriles to the corresponding amides using 85% H_2SO_4−AcOH (3:1) at 140 °C, see: Tsai, L.; Miwa, T.; Newman, M. S. *J. Org. Chem.* **1957**, *22*, 2530. The acid is invariably an associated side product under these conditions. Note that the conditions of the reactions are drastic.

(11) (a) Iglesias, E. *J. Am. Chem. Soc.* **1998**, *120*, 13057. (b) Iglesias, E.; Casado, J. *Int. Rev. Phy. Chem.* **2002**, *21*, 37.

(12) (a) McElvain, S. M.; Tate, B. E. *J. Am. Chem. Soc.* **1951**, *73*, 2233. (b) Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1963**, *28*, 3255.

(13) Indeed, it has been shown by Barber and Slack that even the Pinner reaction is not applicable to the polynitrile compounds due to precipitation of the partially converted imidate salts from the reaction medium; see: Barber, H. J.; Slack, R. *J. Chem. Soc.* **1947**, 82.

ity, ease of operation, and isolated yields even from polynitrile compounds.

Experimental Section

General Procedure for Conversion of Nitriles to Amides. A solution of 5.0 mmol of the nitrile in a ca. 7.0 mL mixture of TFA$-$H$_2$SO$_4$ (4:1, v/v) was stirred either at room temperature or at an elevated temperature depending upon the substrate. For sterically hindered nitriles, the AcOH$-$H$_2$SO$_4$ mixture (2:1, v/v) was used as the reagent mixture and the reaction was conducted at elevated temperatures (see Table 1). The progress of the reaction in each case was monitored by TLC analysis. After completion of the reaction, the reaction mixture was poured into ice-cold water. In cases where the product precipitated out, the solid material was filtered off. Otherwise, the reaction mixture was extracted with ethyl acetate, and purified by silica gel chromatography. The products obtained were characterized spectroscopically. All the known compounds were characterized by comparison of their melting point and spectroscopic data with those of the commercially available amides and literature-reported values.[14]

A representative procedure is described below for the preparation of 2,5-dimethylterephthalamide.

2,5-Dimethylterephthalamide. A solution of 2,5-dimethylphthalonitrile (5.0 mmol) in ca. 7.0 mL of TFA$-$H$_2$SO$_4$ (4:1, v/v) mixture was heated at reflux (75 °C). The progress of the reaction was monitored by TLC analysis. After completion of the reaction (5 h), the reaction mixture was poured into ice-cold water. The product thus precipitated out was filtered to obtain colorless powder of the amide in >95% yield, mp >280 °C: IR (KBr) cm^{-1} 1403, 1618, 1659, 3179, 3342; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 6H), 7.19 (s, 2H), 7.33 (s, 2H), 7.67 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 19.0, 129.1, 132.1, 137.5, 170.5.

Acknowledgment. We thank the Department of Science and Technology (DST), India for financial support. N.S. is grateful to C.S.I.R. for a junior research fellowship.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of 2,5-dimethylterephthalamide, 1,1′-biphenyl-4,4′-dicarboxamide, spirobifluorene-tetraamide, and 2,3,5,6-tetramethylterephthalamide. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048240A

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[14] Shie, J. J.; Fang, J.-M. *J. Org. Chem.* **2003**, *68*, 1158.