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The Acid-Catalyzed and Uncatalyzed Hydrolysis of Nitriles on Unactivated Alumina

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Abstract: Nitriles are selectively converted into amides on unactivated alumina, with the surface hydroxyl groups serving as the source of water.

One of the best methods to synthesize carboxylic acids is the hydrolysis (acid- or base-catalyzed) of nitriles which occurs in two steps through the intermediate amide (eq. 1).[2] The selective hydrolysis of a nitrile to an amide is difficult to achieve, because the amide is often more easily hydroyzed than the nitrile from which it was formed.[1] Nonetheless several procedures have been developed to carry out this transformation.[1-3] We wish to report a new nitrile-to-amide synthesis which is particularly straightforward and which generates amides in high yield.

$$\mathrm{RCN} \xrightarrow{\mathrm{H_2O}} \mathrm{RCONH_2} \xrightarrow{\mathrm{H_2O}} \mathrm{RCOOH} \qquad (1)$$

The surface of unactivated alumina should provide an ideal environment in which to carry out a hydrolysis. The surface is polar[4] and contains a layer of hydroxyl groups (approximately 3.7 mmol of hydroxyls/g[5]) which could serve as the source of water in the reaction. In fact, Knözinger and Krietenbrink reported that acetonitrile, which was being used to probe (ir and Raman spectroscopy) the nature of the alumina surface, was converted into acetamide at less than 100°C and then into acetate at higher temperatures on δ-Al_2O_3.[6,7] Surprisingly, pivalonitrile was inert up to 200°C.[6]

The hydrolysis of nitriles in aqueous solution is acid-catalyzed.[1] This is also true on alumina. For example, when 3.00 mmol of acetonitrile and 0.1 mL of CF_3SO_3H on 15 g of unactivated, neutral alumina (Brockmann activity I; γ type) were heated at 60° for 24 hours, acetamide was isolated in 90% yield after extraction with methanol (Table 1).[8] Other aliphatic nitriles, when treated similarly, also yielded amides, but in lower yields. Aryl nitriles also yielded the corresponding amides in the presence of CF_3SO_3H, although the rates of their hydrolyses were slower than those for the aliphatic nitriles.[9] For the individual aryl nitriles, the rates of reaction were markedly dependent on the substituent; *p*-methyl and *p*-methyoxyl substrates reacted faster and *p*-nitro substrate reacted slower than benzonitrile. Thus, the relative rates of nitrile hydrolysis correlate linearly with anticipated nitrile basicity. This is in contrast to the results in H_2SO_4 where the reactivity is inversely related to basicity.[10] A plausible mechanism for the surface reaction is shown below.

$$\mathrm{RCN} + \mathrm{CF_3SO_3H} \rightleftarrows \mathrm{RCNH^+\ CF_3SO_3^-} \qquad (2)$$

$$\mathrm{RCNH^+} + \text{Surface } \mathrm{OH^-} \rightleftarrows \text{Adsorbed } \mathrm{RC(OH){=}NH} \qquad (3)$$

$$\text{Adsorbed } \mathrm{RC(OH){=}NH} \longrightarrow \text{Adsorbed } \mathrm{RCONH_2} \qquad (4)$$

For the less volatile nitriles the yields were corrected for recovered, unreacted substrate. In all instances the corrected yields were < 100%. The missing material was due to formation of the corresponding carboxylic acid (or its conjugate base), generated by the acid-catalyzed hydrolysis of the amide, which was not removed from the solid on methanol extraction.[11] As is the case in aqueous solution, the yield of amide on alumina is determined by the relative rates of nitrile and amide hydrolysis.

Table 1. Acid-Catalyzed Hydration of Nitriles on Unactivated Alumina[a]

RCN	Reaction		Recovered		%Corrected
(R)	Time (h)	Temp(°C)	RCN (mmol)	% Yield[b]	Yield
CH_3	24	60		90	
CH_3CH_2	24	60		47	
$(CH_3)_2CH$	24	60		18	
$CH_3(CH_2)_4$	24	60	0	26	26
C_6H_5[d]	120	60	0.41	80	87
p-$CH_3C_6H_4$	24	60	0.58	20	25
p-$CH_3OC_6H_4$	48	60	0.98	50	74
p-$NO_2C_6H_4$	168	100	0.90	60	90

a) 3.00 mmol of RCN + 0.1 mL of CF_3SO_3H on 15 g of Al_2O_3 (Brockmann, neutral, activity 1) unless noted. b) [Amide (mmol)/RCN_0(mmol)] x 100. c) {[Amide (mmol) - Recovered RCN (mmol)]/RCN_0(mmol)} x 100. d) 5.00 mmol of nitrile on 10 g of Al_2O_3.

The uncatalyzed hydrolysis of nitriles also occurred smoothly on alumina (Table 2).[12] For example, when 3.00 mmol of pivalonitrile was heated on unactivated alumina at 60°C for 24 hours, pivalamide was formed in 87% yield. Other aliphatic and aryl nitriles also generated the corresponding amides in good to excellent yields.[13] These results are superior to those obtained in the acid-catalyzed reactions. The uncatalyzed hydrolysis thus represents a simple method to prepare and isolate amides. The likely mechanism by which the hydrolysis occurs is shown below.

$$\text{RCN} + \text{Surface OH}^- \rightarrow \text{Adsorbed RC(OH)=N}^- \tag{5}$$

$$\text{RC(OH)=N}^- + \text{Surface OH}^- \rightleftarrows \text{Adsorbed RC(OH)=NH} + \text{Surface O}^{-2} \tag{6}$$

$$\text{Adsorbed RC(OH)=NH} \longrightarrow \text{Adsorbed RCONH}_2 \tag{7}$$

Table 2. Uncatalyzed Hydration of Nitriles on Unactivated Alumina[a]

RCN (R)	Reaction Time (h)	Recovered RCN (mmol)	% yield[b]	%Corrected yield[c]	k_2/k_1[d]
CH_3	12		60		
CH_3CH_2	24		80		
$(CH_3)_2CH$	24		70		
$CH_3(CH_2)_4$	24	0.88	60	85	.23
$(CH_3)_3C$	24		87		
C_6H_5	72	0.23	83	90	.08
p-$CH_3C_6H_4$	24	0.50	69	82	.15
p-$CH_3OC_6H_4$	24	0.30	77	85	.10
p-$NO_2C_6H_4$	144	0.27	82	92	.06

a) 3.00 mmol RCN on 15 g of Al_2O_3 (Brockmann, neutral, activity 1) at 60°. b) [Amide (mmol)/RCN_0 (mmol)] x 100. c) {[Amide (mmol) - Recovered nitrile (mmol)]/RCN_0(mmol)} x 100. d) See text for explanation.

Three points are worth noting. First, the high yields in the uncatalyzed reactions are due to the fact that the rates of amide hydrolysis (k_2) are significantly slower than the rates of nitrile hydrolysis (k_1).

As seen in Table 2, k_2:k_1 ratios are all small.[14] In aqueous solution, the opposite is true.[15] Second, for the benzonitriles, the same relative reactivity was observed for the uncatalyzed reactions as was noted in the acid-catalyzed reactions. In solution, electron-withdrawing substituents accelerate the rates of base-catalyzed reactions.[16] More refined kinetics studies will clarify these dichotomies. Third, although the nitrile hydrolyses in water and on alumina are alike in many ways, their characteristics are different. This again illustrates that surface reactions occur by mechanisms that are subtly different than those which occur in solution.[17]

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References and Notes

1. a) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p. 788 and references cited therein. b) Schaefer, F. C. in *The Chemistry of the Cyano Group*; Rappaport, Z. ed.; Interscience: New York, 1970; p. 239.
2. Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; p. 994.
3. The following examples have recently been reported: a) MnO_2/SiO_2- Breuilles, P.; Leclerc, R.; Uguen, D. *Tetrahedron Lett.* **1994**, *35*, 1401. b) Enzyme (nitrile hydratase) - de Raadt, A.; Griengl, H.; Klempier, N. *J. Org. Chem.* **1993**, *58*, 3179. c) $RuH_2(PPh_3)_4$ - Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521. d) Urea/H_2O_2/carbonate - Balicki, R.; Kaczmarek, L. *Synth. Commun.* **1993**, *23*, 3149.
4. a) Pagni, R.M.; Kabalka, G.; Hondrogiannis, G.; Bains, S.; Tan, L. C.; Anosike, P.; Palmer, R. *Tetrahedron* **1993**, *49*, 6743. b) Michels, J. J.; Dorsey, J. G. *Langmuir* **1990**, *6*, 414.
5. Knözinger, H.; Ratnasamy, P. *Catal. Rev.-Sci. Eng.* **1978**, *17*, 31.
6. Knözinger, H.; Krietenbrink, H. *J. Chem. Soc., Faraday Trans. I* **1975**, *71*, 2421.
7. Acetonitrile is hydrolyzed to acetamide in zeolites at ≥ 200°: Haw, J. F.; Hall, M. B.; Alvarado-Swaisgood, A. E.; Munson, E. J.; Lin, Z.; Beck, L. W.; Howard, T. *J. Am. Chem. Soc.* **1994**, *116*, 7308.
8. HBr gas and CF_3COOH also catalyzed the hydrolyses.
9. See Pala Wilgus, C. M.S. Thesis, University of Tennessee, 1994, for details.
10. Deno, N. C.; Gaugler, R. W.; Wisotsky, M. J. *J. Org. Chem.* **1966**, *31*, 1967.
11. A variety of spectroscopic experiments demonstrated that the missing material was likely a carboxylic acid. Control experiments also demonstrated that adsorbed carboxylic acids were not removed from the surface by methanol extraction.
12. The reaction is more appropriately called uncatalyzed because the surface hydroxyls are consumed in the reaction. In the base-catalyzed reaction in solution, the OH^- is not consumed.
13. The yields have not been optimized.
14. The calculation (R. M. Pagni, unpublished results) assumes that both hydrolyses are bimolecular, i.e. first-order in substrate and first-order in hydroxyl. Both hydrolyses are bimolecular in solution.[1]
15. Rabinovitch, B. S.; Winkler, C. A. *Can. J. Chem.* **1942**, *20B*, 185.
16. Wiberg, K. B. *J. Am. Chem. Soc.* **1955**, *77*, 2519.
17. The catalyzed and uncatalyzed hydrolyses may occur by the same mechanism if the acid actually reacts with surface OH^- groups rather than the nitriles. Rate studies will clarify this issue.

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