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AN EFFICIENT CHEMOSELECTIVE SYNTHESIS OF NITRILES FROM PRIMARY AMIDES

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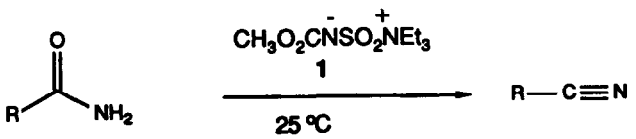
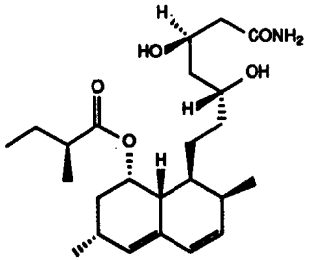
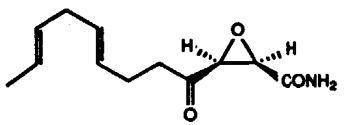
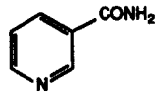
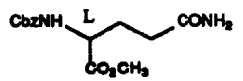
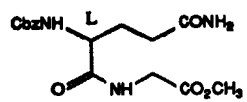
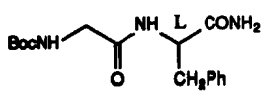
Abstract: An efficient chemoselective method for the preparation of nitriles from primary amides is described which utilizes methyl (carboxysulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent) as the dehydrating reagent.

The importance of nitriles as intermediates in organic synthesis is well established. More recently, the discovery of nitriles which are reversible inhibitors of thiol protease enzymes[1] has drawn our attention to developing a general and mild method for their preparation. The dehydration of primary amides offers a convenient approach to nitriles. Reagents which are often employed for this transformation are inappropriate in the presence of other functional groups, therefore requiring protection of intermediates or an entirely alternative synthesis.[1b, 2] We have discovered that Burgess reagent, 1, methyl (carboxysulfamoyl)triethylammonium hydroxide inner salt,[3] is a mild and efficient reagent for this transformation (Scheme 1).

Scheme 1



The original observation by Burgess[3] that secondary alcohols dehydrate using this reagent led us to explore its chemoselectivity. Under our reaction conditions, none of the secondary alcohol elimination products of mevinolin amide (entry 1 of table) could be detected by 300 MHz proton NMR of the crude reaction mixture. The table contains some of the other examples with which we have applied this methodology. The product obtained from cerulenin (entry 2) showed no sign

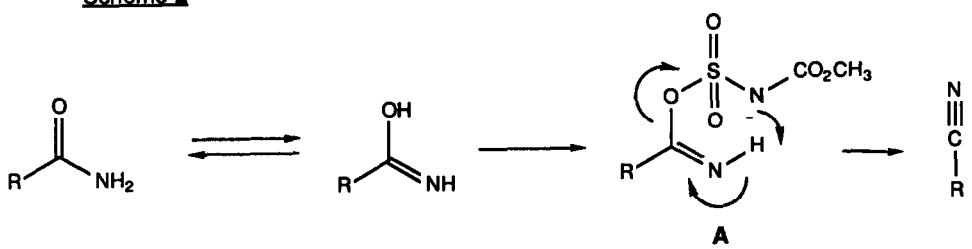
ENTRY	STARTING AMIDE	REACTION CONDITIONS[a]	ISOLATED YIELD[b]	NITRILE[c] MP °C (lit.)	[α]$_D$ (lit.)
1		3.0 equiv. Burgess reagent in CH_2Cl_2	82%	101-102.5	+211.0° $CHCl_3$ (c 0.10)
2		3.0 equiv. Burgess reagent in CH_2Cl_2	85%	<35	-15.0° $CHCl_3$ (c 0.20)
3		1.7 equiv. Burgess reagent in THF	92%	50-52 (50-52)	
4		2.8 equiv. Burgess reagent in CH_2Cl_2	92%	49-50 (42-43)[a]	-18.4° MeOH (c 0.50) (-21.0° MeOH (c 0.50))
5		2.0 equiv. Burgess reagent in THF	88%	118-119.5	-23.7° MeOH (c 1.00)
6		2.5 equiv. Burgess reagent in CH_2Cl_2	91%	100-101 (100-100.5)[1b]	-10.3° $CHCl_3$ (c 1.00)

[a]See text for procedure.
[b]Analytically pure samples.
[c]All compounds exhibited spectral data consistant with structure.

of epimerization of the cis epoxide and demonstrates the weakly acidic reaction conditions.[4] To our knowledge this is the first example of a dehydrative approach to α, β-epoxy-nitriles. The other examples in the table demonstrate the excellent chemoselectivity of this reagent and its tolerance of various functional groups.[2] Noteworthy is the product of entry 6, which demonstrates the ability to prepare C-terminal nitriles in protected peptides which are important intermediates for thiol protease inhibitors.[1] The reaction is also quite insensitive to solvent variation. However, this reagent is sensitive to moisture, and reactions must be run under standard anhydrous conditions.

The mechanism which we propose in Scheme 2 is consistent with the previous work of Burgess. The rate determining step for dehydration of alcohols is formation of the sulfonate ester followed by a much faster syn elimination. The observed chemoselectivity may be the result of kinetically faster formation of intermediate A versus the formation of a similar species for secondary alcohols.

Scheme 2



The reaction conditions for the conversion of Mevinolin amide to the corresponding nitrile are typical. Alternatively, an extractive workup may be used to provide crude products which are usually >95% pure by NMR.

Procedure: Mevinolin amide[6] (125 mg, 0.30 mm) was dissolved in 1.5 mL of anhydrous CH_2Cl_2 (distilled from CaH_2) and stirred at 25°C under argon. Methyl (carboxysulfamoyl)triethyl ammonium hydroxide inner salt (Burgess reagent) was added in five 50 mg portions (1.05 mm) over 2 h. Stirring was continued an additional 15 min, and the mixture applied directly to a silica gel column. Flash chromatography (50% ethyl acetate in hexane) gave 99 mg (82%) of the nitrile (entry 1) as a white crystalline solid.[7] A small amount of unreacted starting material was detected in the crude reaction mixture by TLC (10% methanol in methylene chloride) but was not recovered.

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References and Notes:

1) a) J. B. Moon, R. S. Coleman, and R. P. Hanzlik, J. Amer. Chem. Soc., 108, 1750 (1986). b) S. A. Thompson, P. R. Andrews, and R. P. Hanzlik, J. Med. Chem., 29, 104 (1986).

2) K. Mai and G. Patil, Tetrahedron Lett., 27, 2203 (1986) and references cited therein. This recent methodology was incapable of preparing 3-cyanopyridine from nicotinamide.

3) a) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, J. Org. Chem., 38, 26, (1973). b) E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, and W. M. Williams, Org. Synth., 56, 40 (1977).

4) Burgess Reagent (10 mg/mL) in H_2O gives PH = 5.6 after equilibration.

5) T. T. Van, E. Kojro, and Z. Grzonka, Tetrahedron Lett., 33, 2299, (1977).

6) Mevinolin amide was prepared according to a procedure developed by Dr. C. S. Rooney of our laboratories: Mevinolin was treated with excess anhydrous ammonia in ethanol (pressure flask) at 50°C for 2 h and 25°C overnight. Concentration and recrystallization from toluene provided 80% yield of analytically pure sample.

7) Physical data: Anal. Calcd for $C_{24}H_{37}NO_4$: C 71.43 H 9.24 N 3.47; found C 71.31 H 9.10 N 3.30. Rf = 0.22 (silica, 50% ethyl acetate in hexane) ^1H NMR (300 MHz., $CDCL_3$) δ = 0.89(d, J = 7.0 Hz, 3H) 0.90(t, J = 8.0 Hz, 3H) 1.11(d, J = 8.0 Hz, 3H) 1.13(d, J = 7.1 Hz, 3H) 1.20-2.05 (m, 11H) 2.20-2.56 (m, 4H), 2.53 (d, J = 6.4 Hz, 2H), 2.83 (d, J = 4.3 Hz, 1H, exchangeable), 3.82 (m, 1H), 4.14 (m, 1H), 4.31 (d, J = 1.4 Hz, 1 H, exchangeable) 5.51 (m, 2H), 5.78 (dd, J = 6.3, 10.0 Hz, 1H) 6.00 (d, J = 10.0 Hz, 1H) ppm. IR ($CHCl_3$) $\tilde{\nu}$ = 3490(m, OH), 2270 (w, nitrile), 1725 (s, ester carbonyl) cm^{-1}.

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