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A Mild Hydration of Nitriles into Amides

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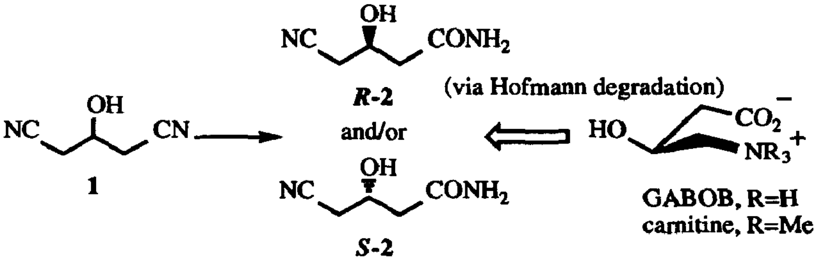
Abstract: *Stirring mixtures of β-hydroxynitriles with manganese dioxide, deposited onto silica gel for a few days at room temperature resulted in the formation of the corresponding amides in fair to good yields. The unprecedented conversion of 3-hydroxyglutarodinitrile into the corresponding monoamide has been performed by this methodology.*

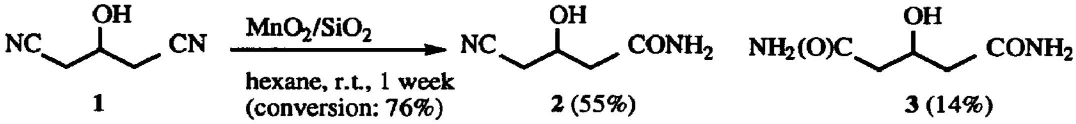
Our continued interest in the use of *meso* compounds in organic synthesis[1] led us to study desymmetrisation of compound **1**, a readily accessible dinitrile resulting from treatment of epichlorhydrin with potassium cyanide in water[2]. As it is shown below, the stereoselective hydration of only one of the two enantiotopic cyano groups should provide useful synthons for the preparation of such important compounds as carnitine and GABOB[3].



Though practised daily on a multi-ton scale to produce acrylamide[4], the nitrile-amide conversion is still being considered as a delicate operation at the laboratory scale, as attested by the continual flow of publications relating the discovery of improved processes or reagents[5]. More classical ones usually involve the use of either concentrated acids or hydrogen peroxide in alcaline medium. Nitrile **1** has been considered as an "intrinsically sensitive compound"[6], so that the use of these conditions seemed precluded. Furthermore, none of them should allow a selective monohydration of compound **1**. Silica gel-supported manganese dioxide[7] (MnO_2/SiO_2 in the remaining text) was accordingly selected as a possible reagent for our purpose. The stronger binding of a carboxamido group to the solid reagent, as compared to a cyano group, should prevent the monoamide from further hydration. Also encouraging was Dreiding's claim of an enantiomeric enrichment during an attempted purification of a racemic mixture by chromatography on silica gel[8].

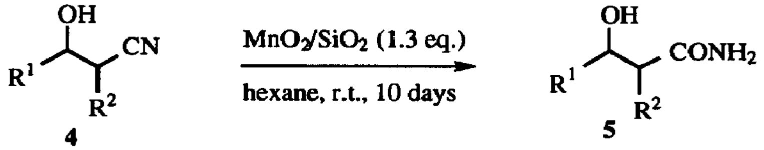
Supposing, on one hand, that a similar effect would take place in mixing **1** with the reagent, that is to say that compound **1** would interact with MnO_2/SiO_2 preferentially by one (pro*R* or pro*S*) of the two enantiotopic cyano groups and that, on the other hand, the "first-formed" molecules of amide would be preferentially bound to the solid, hydration of the remaining dinitrile molecules would then occur in an asymmetric context, with the possible result of a stereoselective hydration of **1** to the targeted amide. Though ***no optical activity has been detected so far*** in any of the chiral amides we have obtained in numerous experiments[9], we are pleased to report herein the remarkable ability of MnO_2/SiO_2 to convert β-hydroxynitriles into amides under very mild conditions.

The reagent was prepared as described[7] by pouring the purple powder resulting from impregnation of silica gel with $KMnO_4$ into an aqueous solution of $MnSO_4$[10]. The reported efficiency of MnO_2/SiO_2 was first verified by stirring benzonitrile with this reagent in refluxing hexane for 24 hours; benzamide (m.p.131°C) was isolated in very good yield (91%; lit[7]: m.p. 128-129°C, 98%). Under similar conditions the dinitrile **1** gave, after purification by flash-chromatography (silica gel, $MeOH/CH_2Cl_2$) the monoamide **2** as pale yellow crystals (m.p. 112-114°C; 36%) and the diamide **3** (m.p. 153-155°C; 24%). Lowering the temperature resulted in the formation of a substantial amount of amide **2** (55%). The diamide **3** (14%) and some unreacted dinitrile (24%) were also isolated[11a].



1 **2** (55%) **3** (14%)

It is worth noting that direct conversion of nitrile **1** into the amide **2** has never, as far as we know, been described. Hydration of other hydroxylated nitriles proceeded similarly (hexane, r.t., 10 days) (table)[11].



4 **5**

substrate		**5**, yield (%) (reacted **4**, %)	m.p., °C
4a, R^1= H	R^2= H	92 (76)	oil
4b, R^1= CH_3-CH_2-	"	90 (51)	"
4c, R^1= Ph	"	68 (40)	125
" "	"	80 (58)*	"
4d, R^1= Ph-CH=CH-	"	15 (5)	113
4e, R^1= Ph-CH_2-CH_2-	"	40 (21)	110-112
4f, R^1= CH_3-CH=CH-	"	60 (21)	86-88
4h, R^1= Ph-CH(CH_3)-	R^2= CH_3	74 (42)	70-72**

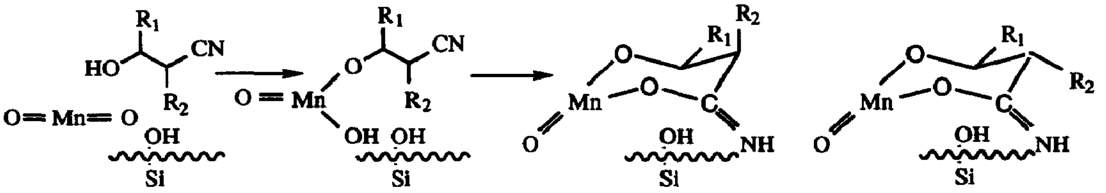
* under sonication

** 32/68 mixture of diastereomers (^1H NMR)

Noteworthy, the simpler 3-hydroxypropionitrile, **4a**, gave the corresponding amide in 92% yield. Though the conversion was low in some cases, yields in amide are overall acceptable, similar in magnitude to those observed with related nitriles and in using enzymes[12]. The reason for the low reactivity of nitrile **4d** remains unclear. Interestingly, the hydration competes with oxidation of the alcohol functionality in either **4c** or **4f**.

Benzonitrile proved much less reactive at r.t., giving benzamide in only 23 % yield, to be compared with the 91% yield observed in refluxing hexane. The higher reactivity of β-hydroxynitriles was clearly established in treating as above a 1:1 mixture of butyronitrile with nitrile **4a**: the only product formed was amide **5a**. This selectivity could arise from a stronger binding of the more polar hydroxynitrile to the reagent. The transient formation of a manganic ester could also be postulated. Should such an intermediate operate, the relative rates of hydration of diastereomeric 2,3-disubstituted hydroxynitriles will be dependent on the relative configuration of the substituents (Scheme 1).

Scheme 1



Both threo and erythro isomers of 3-hydroxy-2-methylbutyronitrile ($R_1=R_2=$methyl in Scheme 1) react at approximately the same rate. However, the result is not very conclusive since the expected effect could not have been very strong[13]. More probing results emerged when the hydroxynitriles **6** were treated with MnO_2/SiO_2. The affinity for the reagent should be of the same order of magnitude for each substrate whereas the participation of a neighbouring MnOH group as above should be less important for substrates **6c-e** than for substrates **6a** and **6b**. The resulting data (table) seem to validate the hypothesis. Furthermore, the cyanohydrin of 3-phenylpropanal gave with MnO_2/SiO_2 the corresponding α-hydroxyamide in good yield (75% isolated, m.p. 132°C).

$$\underset{\mathbf{6}}{HO\text{-}(CH_2)_n\text{-}CN} \xrightarrow[\text{hexane, r.t., 8 days}]{MnO_2/SiO_2} \underset{\mathbf{7}}{HO\text{-}(CH_2)_n\text{-}CONH_2}$$

nitrile	**7**, % / reacted **6**, %
6a, n= 2	92/76
6b, n= 3	12/83*
6c, n= 4	42/33
6d, n= 5	58/29
6e, n= 6	49/30

*butyrolactone (54%)
is the main product

In summary, the MnO_2/SiO_2 reagent proved suitable for preparing hydroxyamides from nitriles, allowing for instance the monohydration of the sensitive 3-hydroxyglutarodinitrile, **1**. In some cases, the conversion and hence the yield in isolated product are rather low. This could result *inter alia* from a stronger binding of the product to the catalyst, which obviously slows down the process. Fixation of MnO_2 on silica gel modified -i.e. of inverted polarity- should be a convenient means to improve the conversion. Preparation of such new reagents as well as formation of optically active amide **2** are now being investigated.

This paper is dedicated to Sir John Cornforth on the occasion of his 75th birthday

References and Notes

1- Adjé N., Breuilles P., and Uguen D., *Tetrahedron Lett.*, **1993**, *34*, 4205-4208.

2- Johnson F., Panella J.P., and Carlson A.A., *J. Org. Chem.*, **1962**, *27*, 2241-2243; Johnson F., Panella J.P., *Organic Syntheses*, **1973**, *coll. vol. 5*, 614-616.

3- Kolb H.C., Bennani Y.L., and Sharpless K.B., *Tetrahedron: Asymmetry*, **1993**, *4*, 133-141, and references cited therein.

4- a) Matsuda F., *Chemtech*, **1977**, 306-308; b) Jensen C.M., and Trogler W.C., *J. Am. Chem. Soc.*, **1986**, *108*, 723-729.

5- a) Katritzky A.R., Pilarski B., and Urogdi L., *Synthesis*, **1989**, 949-950; b) Curtis N.J., and Sargeson A.M., *J. Am. Chem. Soc.*, **1984**, *106*, 625-630; c) *Comprehensive Organic Chemistry, vol. 2*, Sutherland I.O. Ed., Pergamon Press: Oxford, New-York, Toronto, Sydney, Paris, Frankfurt, 1979; pp. 528-550.

6- Berger B., de Raadt A.A., Griengl H., Hayden W., Hachtberger D., Klempier N., and Faber K., *Pure and Applied Chem.*, **1992**, *64*, 1085-1088; see also Johnson F., Panella J.P., Carlson A.A., and Hunneman D.H., *J. Org. Chem.*, **1962**, *27*, 2473-2478.

7- Liu K.-T., Shi M.-H., Huang H.-W., and Hu C.-J., *Synthesis*, **1988**, 715-717.

8- Apparently, this oral communication has not been followed by a printed report.

9- The yields reported herein correspond to average values, obtained through several (at least three) experiments. Search for enantiomeric excess in amide **2** has been performed by means of camphoratoeuropium-induced chemical shifts in ^{1}H NMR (racemic **2** gave two sets of well-resolved peaks in presence of the chiral reagent). It is doubtful, given the low magnitude of the expected effect (if any!), that this analytical tool could have been of some help in determining e.e..

10- After filtration and thorough washing with water, the brown powder was dried at 120°C for 2 hours in an oven. The free water content was shown to be c.a. 2 mmol per gram of reagent using Karl-Fischer titration.

11- a) typical experimental procedure: nitrile **1** (0.11 g, 1 mmol) was vigorously stirred in hexane (4 ml). The reagent (1.8 g, corresponding to 1.5 mmol of MnO_2, or 1.5 eq. in the text) was gradually added. Stirring was continued for the indicated time, after which the solvent was removed by filtration. The resulting brown solid was deposited onto a column of 60H silica gel (Merck). Flash-chromatography ($MeOH/CH_2Cl_2$) afforded successively: *i)* the unreacted nitrile **1** (0.026 g; conversion: 76%); *ii)* the amide **2** (0.07 g; 55%, 77% based on the reacted dinitrile); *iii)* the diamide **3** (0.021 g; 14%, 18%, based on the reacted dinitrile). On a 118 mmol scale, the amide **2** (6.48 g, 43%) was obtained as white crystals (m.p. 116-118°C) after two crystallisations from EtOH; ^{1}H NMR (D_6 acetone): 2.48 (dd; J7.1, 5 Hz), 2.69 (dd; J6.1, 4.9 Hz), 4.24-4.35 (m), 5.93 (s), 6.42 (s); ^{13}C NMR (MeOD): 26.15, 42.15, 65.5, 118.94, 175.43; b) yields reported in the tables have been obtained in dividing the yield of isolated product by the conversion (%). Significantly lower yields result from the use of either CH_2Cl_2 or water as solvent. Since much of our nitriles were sparingly soluble, the only role of hexane seems to help in dispersing the nitrile at the surface of the reagent, as does applying ultrasounds. With nitrile **4a**, similar results have been obtained in using MnO_2 deposited on other solid supports such as neutral alumina (Merck), montmorillonite KSF (Fluka), and quartz powder. Replacement of MnO_2 by lead dioxide or nickel peroxide gave very poor results.

12- de Raadt A.A., Klempier N., Faber K., and Griengl H., *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3179-3184.

13- Assuming that both the Mn=O and the NH groups are linked to silica, the hypothetical intermediate with a pseudo axial-equatorial substitution pattern should not be much disfavoured over its pseudo diequatorial isomer since the interaction between the lipophilic R_1-R_2 substituents and the hydrophilic support is minimised in the former.

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