DMF-Catalysed Thermal Dehydration of Aldoximes: A Convenient Access to Functionalized Aliphatic and Aromatic Nitriles

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Abstract: *N,N*-Dimethylformamide was found to act as solvent and catalyst in the dehydration of aldoximes to nitriles. The reaction required heating at 135 °C and yields of nitriles were moderate to good. (Benzylideneaminooxy)formaldehyde was detected as an intermediate in one of the reactions.

Key words: aldoximes, dehydration, nitriles

Nitriles are particularly useful compounds endowed with rich chemistry that serve as precursors in several functional group transformations.[1] The cyano group is incorporated in the structure of several bioactive molecules[2a,b] and plays a significant role by hydrogen bonding to certain biological receptors.[2c–e] Although a number of protocols are available in the literature for their synthesis, new methods or their variants continue to appear. The most recently employed methods of synthesising nitriles are the metal-catalysed cyanation of aryl halides[3a–c] and triflates,[3d] cyanation of secondary amines and phenols with trichloroacetonitrile and boron trichloride,[3e] addition of hydrogen cyanide, generated in situ from acetone cyanohydrin, to alkenes,[3f] the oxidation of primary amines with $Ru–Al_2O_3/O_2$,[4] of hydrazones with *m*-chloroperbenzoic acid,[5a] HOF·MeN,[5b] $MeReO_3/H_2O_2$,[5c] or oxone® on wet alumina under microwave irradiation,[5c] the dehydration of unsubstituted amides by lithium chloride with a zirconium catralyst[6a] or by Bu_2SnO with microwave irradiation[6b] and the addition of the Schwartz's reagent[7] to isocyanides. However, by far the most widely used method to synthesise nitriles is the dehydration of aldoximes. In some examples aldoximes are prepared in situ from the corresponding aldehydes and the overall reaction to nitriles is a one-pot, two-step process. The majority of reactions entail the formation of an intermediate, O-derivative of the aldoxime. Acetic anhydride was one of the first reagents to be used in this transformation. Recently, a plethora of reagents effective under mild conditions has been described. Among these are $Na_2SO_4/NaHCO_3$ under microwave irradiation,[8a] Ph_3P/I_2,[8b] DABCO–$POCl_3$,[8c] ZnO/MeCOCl,[8d] basic Al_2O_3/PCl_5,[8e] (*S*,*S*)-dimethyldithiocarbonates,[8f] $MeSO_2Cl$/graphite,[8g] $AlCl_3·6H_2O$/KI/H_2O/MeCN,[6b] ruthenium catalyst,[8h] $NH_4OH/MgSO_4/MnO_2$,[8i] CS_2/Amberlyst A26 (OH^-),[8j] pyridine–$HCONH_2$,[8k] $TiCl_3(OTf)$,[8l] $SOCl_2$/benzotriazole,[8m] *N*-methylpyrrolidine,[8n] bacterial enzymes,[8o] TBSCl/imidazole,[8p] methyl or ethyl cyanoformate/Et_3N[8q] and Cl_3CCOCl/Et_3N.[8r] Isolation of the O-derivative of the aldoxime and then conversion into the nitrile has seldom been used to synthesise nitriles. One recent example is the conversion of aromatic oxime ethers into aromatic nitriles by reaction with $NiCl_2$/Zn.[9]

Formamide has been used by Sudalai and co-workers[8k] to convert aldehydes into nitriles. The reaction requires the use of equivalent amounts of formamide and pyridine with xylene as solvent and heating to reflux for several hours. The authors propose that the aldoxime reacts with the formamide to form an aldoxime formate intermediate, which subsequently undergoes thermal elimination to produce the nitrile with liberation of formic acid. DMF is a well-known Vilsmeier–Haack reagent and also a directed *ortho*-metalation (DoM)[10] formylating agent. It has been used, in one case, for the dehydration of a transient pyrrole oxime.[11] Based on these facts, we developed the idea that DMF could be used at an appropriate temperature to work three ways towards aldoximes, as a solvent, as a formylating agent and as a means of inducing thermal elimination of formic acid to give the nitrile.

In order to test the scope and efficiency of this idea we prepared, according to literature procedures, a number of aliphatic and aromatic aldoximes with variable substitution and stereochemistry. Conversion of aldoximes into nitriles took place by heating with anhydrous DMF in an oil bath at 135 °C for 48 hours (Table 1). The products obtained were purified by column chromatography and their structures were verified by comparing mp or bp, TLC, IR and NMR data with those of authentic samples. Although the yields of the nitriles obtained were moderate to good the advantages of this method are obvious. DMF acts both as a solvent and as a catalyst and due to its polarity a relatively small volume is needed to dissolve the aldoxime. No expensive catalysts or corrosive electrophiles are required to activate the aldoxime and the method does not need a solid support. We found that the reaction works for both aliphatic and aromatic aldehydes in the presence of nucleophilic substituents such as OH that in other cases may interfere with the reagent and render the reaction unfeasible or in any case limit its potential.

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Table 1 DMF-Catalysed Thermal Dehydration of Oximes to Nitriles

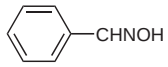
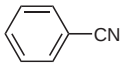
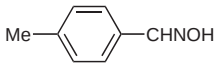
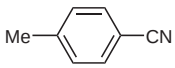
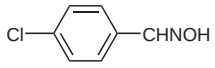
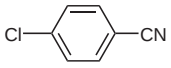
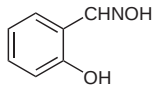
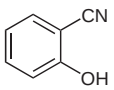
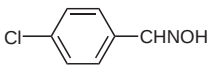
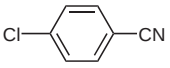
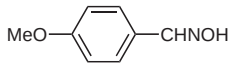
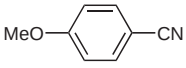
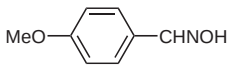
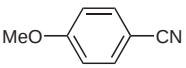
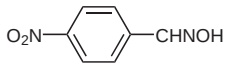
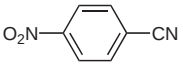
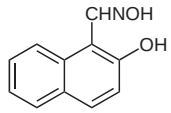
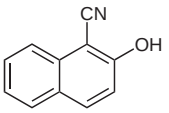
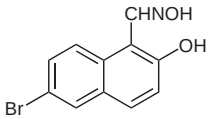
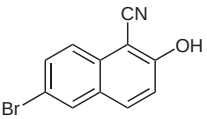
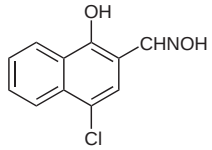
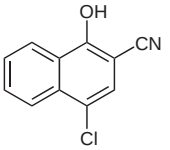
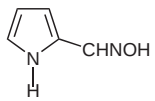
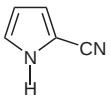
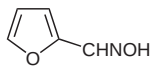
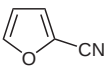
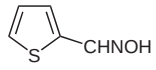
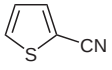
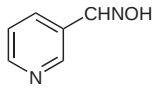
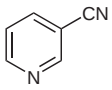
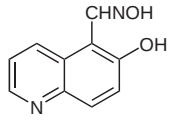
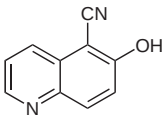
Entry	Substrate	Product[a]	Yields[b] (%)	Mp or bp (°C)/Torr (lit.)
1	*n*-PrCHNOH (*E*)	*n*-PrCN	76	120/760 (110/637)[8d]
2	*n*-BuCHNOH (*E*/*Z*)	*n*-BuCN	78	138–139 (138)[8d]
3	MeCH=CHCHNOH (*E*/*Z*)	MeCH=CHCN	66	123/760 (120/735)[13]
4	 (*E*/*Z*)		54	76/15 (60/6)[8r]
5	 (*E*)		69	29–30 (28)[8r]
6	 (*E*)		56	91–92 (91–92)[8n]
7	 (*E*/*Z*)		47	96–97 (95–97)[8k]
8	 (*Z*)		83	113–114 (112–114)[8k]
9	 (*E*)		80	58–59 (58)[8k]
10	 (*Z*)		76	58–59 (58)[8k]
11	 (*E*)		71	149–150 (148–150)[8i]
12	 (*E*/*Z*)		74	153–155 (153–154)[14]
13	 (*E*)		68	202–203[c]
14	 (*E*/*Z*)		50	188–190[c]
15	 (*E*/*Z*)		60	122–123/15 (120–123/15)[15]
16	 (*E*)		72	38/15 (146–148/760)[8n]

Table 1 DMF-Catalysed Thermal Dehydration of Oximes to Nitriles (continued)

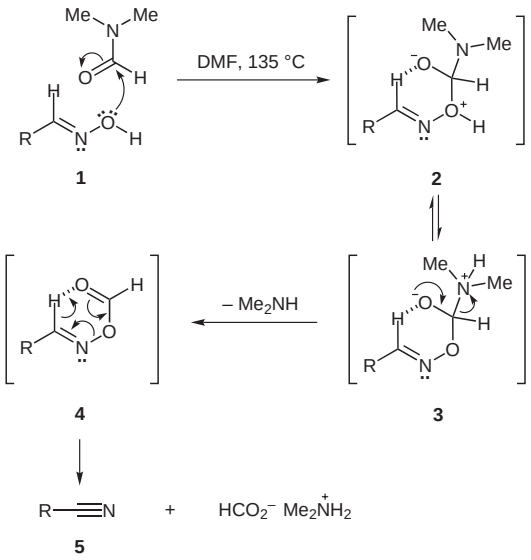
Entry	Substrate	Product[a]	Yields[b] (%)	Mp or bp (°C)/Torr (lit.)
17	 (*E*)		75	80/15 (72–73/10)[8r]
18	 (*E*)		83	50 (47)[8d]
19	 (*E*)		55	292–293 (293)[16]

[a] The products were characterized by comparison of their mp or bp, TLC, IR and ^{1}H NMR data with those of authentic samples.
[b] Yields of the isolated pure compounds.
[c] See experimental section.[17]

Mechanistically it is proposed (Scheme 1) that the reaction takes place by way of initial attack by the hydroxyl group of the oxime **1** on the carbonyl group of DMF to give the cyclic intermediate **2**. This relatively stable intermediate can lose the hydroxyl proton that can be transferred to the nitrogen atom of intermediate species **3**. The deprotonation–protonation between species **2** and **3** is conceivably reversible, although protonation–deprotonation of the imine nitrogen cannot be ruled out. The strong intramolecular hydrogen bond of species **2** and **3**, under the circumstances, would logically be unaffected by the electrophilic proton. Loss of dimethylamine from intermediate **3** would give the intramolecularly hydrogen-bonded aldoxime formate intermediate **4**. Subsequent thermal elimination of formic acid would produce the nitriles **5**. Although the reaction works for both (*E*)- and (*Z*)-aldoximes it is very probable that the isomers interconvert under the reaction conditions[12] and only the (*E*)-aldoximes that are dehydrated to the nitriles. Although this may seem to be the case according to the proposed mechanism, the possibility of the (*Z*)-aldoxime itself undergoing dehydration cannot be ruled out.

There is substantial evidence that a transient aldoxime formate is produced in this reaction. In one experiment, benzaldehyde oxime was heated with DMF at 135 °C for 12 hours followed by the work-up given in the general procedure.[17] The remaining oil was examined by LC–MS to give in the MS spectrum a $[M + Na]^+$ peak at m/z = 171.8 corresponding to (benzylideneaminooxy)formaldehyde and a $[M + H]^+$ peak at m/z = 186.8 corresponding to benzaldehyde *O*-acetyl oxime. Evidently the reaction had not reached completion and the remaining benzaldehyde oxime must have reacted with ethyl acetate during work-up. Sudalai and co-workers[8k] have reported a formamide-assisted one-pot conversion of aromatic aldehydes into the corresponding nitriles using stoichiometric amounts of hydroxylamine hydrochloride, pyridine and formamide in refluxing xylene. They suggest that dehydration to the nitrile occurs via an aldoxime formate but no evidence is given. Sarvari[8d] has reported the efficient synthesis of nitriles via dehydration of the corresponding aldoximes using zinc oxide and acetyl chloride as catalyst, under solvent-free conditions. An intermediate aldoxime acetyl is suggested but no proof has been given. Thomas and Greyn[8q] have described a procedure for obtaining nitriles by reacting aldoximes with methyl or ethyl cyanoformates. They propose that the intermediate is an alkoxy carbonyl aldoxime which loses thermally an alcohol and carbon dioxide. Both Sarvari[8d] and Thomas and Greyn[8q] support the theory that nitriles are produced by thermal dehydration of a cyclic intermediate similar to that proposed in Scheme 1.

In conclusion, we have developed a convenient new procedure for the conversion of aliphatic and aromatic aldoximes into the corresponding nitriles, in moderate to good yields. The method requires only DMF which acts both as solvent and dehydrating agent. An aldoxime



Scheme 1 Proposed mechanism of thermal dehydration of (*E*)- and (*Z*)-oximes to nitriles

formate intermediate was detected by mass spectrometry in one experiment which lends substantial support to the proposed mechanism. In comparison with others, this method is preferable since the use of several reagents that are more toxic or expensive is avoided.

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References and Notes

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(17) **Conversion of Aldoximes into Nitriles (Table 1); General Procedure**: The appropriate aldoxime (3 mmol) in anhyd DMF (10 mL) was heated at 135 °C for 48 h. After cooling, the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (25 mL) and then dried (Na_2SO_4). The solvent was removed under vacuo and the crude product was purified by column chromatography (EtOAc–hexane, 1:4) to give the corresponding nitrile. The structure of the products was confirmed by comparison of their mp or bp, TLC, IR or ^{1}H NMR data with authentic samples obtained commercially or prepared by literature methods.

Preparation of 6-Bromo-2-hydroxynaphthalene-1-carbonitrile (Table 1, entry 13):
Obtained as yellow microcrystals (EtOAc–hexane); yield: 0.48 g (68%); mp 202–203 °C. IR (Nujol): 3200, 2220 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.32 (d, J = 9.2 Hz, 1 H, H-3), 7.77–781 (m, 2 H, H-7, H-8), 8.08 (d, J = 9.2 Hz, 1 H, H-4), 8.24 (s, 1 H, H-5), 11.85 (br s, 1 H, OH). MS (EI, 70 eV): m/z (%) = 246 (96) [M$^+$], 221 (7), 192 (7), 140 (29), 113 (30), 87 (11), 70 (7), 63 (15), 50 (5). HRMS–EI: m/z [M$^+$] calcd for $C_{11}H_6BrNO$: 246.9633; found: 246.9628.

Preparation of 4-Chloro-1-hydroxynaphthalene-2-carbonitrile (Table 1, entry 14):
Obtained as yellow microcrystals (EtOAc–hexane); yield: 0.31 g (50%); mp 187–190 °C. IR (Nujol): 3200, 2200 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62–7.86 (m, 3 H, H-3, H-6, H-7), 8.11 (d, J = 7.0 Hz, 1 H, H-5), 8.40 (d, J = 8.4 Hz, 1 H, H-8), 8.62 (br s, 1 H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 93.78, 116.62, 121.38, 123.17, 123.71, 125.62, 126.23, 127.38, 130.66, 132.51, 158.07. MS (EI, 70 eV): m/z (%) = 203 (100) [M$^+$], 174 (9), 148 (21), 140 (50), 113 (32), 88 (15), 74 (17), 63 (21), 50 (17). HRMS–EI: m/z [M$^+$] calcd for $C_{11}H_6ClNO$: 203.0138; found: 203.0145.