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From aldehydes to nitriles, a general and high yielding transformation using HOF·CH₃CN complex

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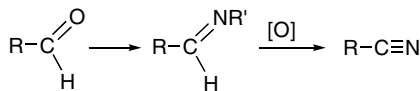*School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel*

Abstract—*N,N*-Dimethylhydrazones of aldehydes undergo a rapid oxidative cleavage to form nitriles in very high yields on reaction with HOF·CH₃CN under mild conditions. The reaction is chemoselective and proceeds rapidly without racemization. The nitriles were resistant to further oxidation, even when a large excess of the reagent was employed.
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The transformation of aldehydes to nitriles by reacting imines with certain oxidizing agents (Scheme 1) is an important topic in organic chemistry. Each of the procedures developed has its advantages and disadvantages. On the positive side most oxidants are commercial, however, not all reagents can be applied to all imines. The reactions are usually slow and certain oxidants are associated with health hazards as for example reactions with MCPBA or SeO₂,[1] heavy polluting metals such as molybdenum and tungsten[2] or expensive metals like rhenium.[3]

Dimethyldioxirane was employed using large quantities of organic solvents which generated large volumes of effluents.[4] Oxone supported on wet Al₂O₃ is an efficient reagent for this reaction too, providing microwave irradiation in dry media is used.[5] *N,N*-Dimethylhydrazones of aldehydes[6] could also be converted to the respective nitriles as well as the corresponding *N,N,N*-trimethylhydrazonium salts in basic media, using high temperatures and long reaction times.[7]

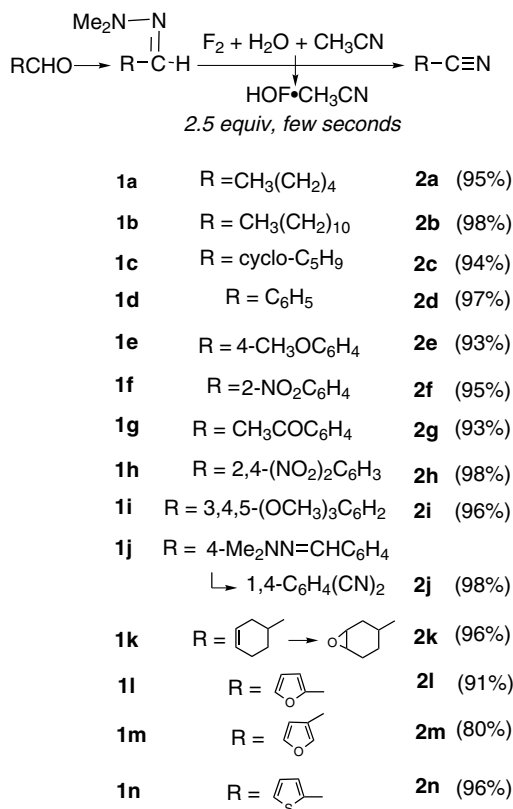We present here an additional route for the transformation of aldehydes to nitriles based on the very fast reaction of HOF·CH₃CN with *N,N'*-dimethylhydrazones of various aldehydes. This reagent, readily prepared from acetonitrile, water, and F₂,[8] is a powerful oxygen transfer agent. This stands alone in its ability to oxidize azides and vicinal diamines into the corresponding nitro[9] and dinitro[10] derivatives, forming a variety of *N*-oxides,[11] including the 1,10-phenanthroline-*N,N'*-dioxide derivatives which eluded chemists for so many decades,[12] quinoxalines,[13] and thiazoles.[14] This is also able to transfer oxygen atoms to episulfides,[15] thiophenes,[16] polythiophenes,[17] and can oxidize C═N-containing compounds,[18] among others.[19] The reaction with imines, which is the subject of this report, is general in nature and proceeds well with dimethylhydrazones of any aldehyde, being aromatic, heterocyclic, benzylic, aliphatic, or part of a sugar molecule. This is completed after a few seconds and the corresponding nitriles were formed under mild conditions and in almost quantitative yields.[20]

Reacting straight chain or cyclic *N,N'*-dimethylhydrazones such as **1a**, **1b**, and **1c**, obtained quantitatively from the corresponding aldehydes, with about 2.5 mol equiv of HOF·CH₃CN at 0 °C produced the corresponding nitriles **2a**, **2b**, and **2c** in a few seconds in 95%, 98%, and 94% yields, respectively (Scheme 2).

Potential complications might have been expected with aromatic *N,N*-dimethylhydrazones, since HOF·CH₃CN is also capable of epoxidizing aromatic rings.[21] However, the initial attack of the reagent on the carbon–nitrogen double bond was fast enough to prevent any attack on the aromatic ring. This was demonstrated by the formation of benzonitrile **2d**, obtained in a few seconds

Scheme 1. Oxidation of imines to nitriles.

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1a	R = CH$_3$(CH$_2$)$_4$	**2a**	(95%)
1b	R = CH$_3$(CH$_2$)$_{10}$	**2b**	(98%)
1c	R = cyclo-C$_5$H$_9$	**2c**	(94%)
1d	R = C$_6$H$_5$	**2d**	(97%)
1e	R = 4-CH$_3$OC$_6$H$_4$	**2e**	(93%)
1f	R = 2-NO$_2$C$_6$H$_4$	**2f**	(95%)
1g	R = CH$_3$COC$_6$H$_4$	**2g**	(93%)
1h	R = 2,4-(NO$_2$)$_2$C$_6$H$_3$	**2h**	(98%)
1i	R = 3,4,5-(OCH$_3$)$_3$C$_6$H$_2$	**2i**	(96%)
1j	R = 4-Me$_2$NN=CHC$_6$H$_4$		
	↳ 1,4-C$_6$H$_4$(CN)$_2$	**2j**	(98%)
1k	R =	**2k**	(96%)
1l	R =	**2l**	(91%)
1m	R =	**2m**	(80%)
1n	R =	**2n**	(96%)

Scheme 2. Conversion of aldehyde *N,N*-dimethyl hydrazones to nitriles.

in a 97% yield, from benzaldehyde *N,N*-dimethylhydrazone **1d**.

Electron-donating or electron-withdrawing groups on the aromatic rings did not affect the speed of the reaction and nitriles **2e–i** were obtained from the corresponding *N,N*-dimethylhydrazones **1e–i** again in a few seconds and in excellent yields. No problems were encountered with the bifunctional 1,4-benzdialdehyde, which was converted almost instantaneously, via its bis(dimethylhydrazone) **1j** to 1,4-dicyanobenzene (**2j**) again in a practically quantitative yield.

It was of interest to expand the study to molecules with more than one potential reactive center. Aldehydes containing double bonds presented such an opportunity since the olefin function is known to undergo ready epoxidation.[22] Thus, reacting 3-cyclohexene *N,N*-dimethylhydrazone (**1k**) with 1 mol equiv of HOF·CH$_3$CN produced a mixture of products arising from an attack on both the nitrogen atom and the double bond. The addition of 4 mol equiv of the oxidizing agent resulted in the epoxynitrile **2k**[23] in a 96% yield.
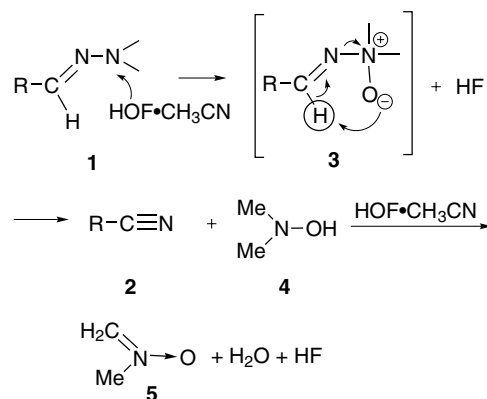
Heterocyclic aldehydes have potentially more than one reactive center and the question was whether these could be differentiated between to give clean products. Gratifyingly, furan derivatives such as the dimethylhydrazones of 2- and 3-furan aldehydes (**1l**) and (**1m**) were smoothly converted into the corresponding nitriles with HOF·CH$_3$CN in a few seconds at 0 °C forming 2- and 3-

furonitriles, (**2l**) and (**2m**), in 91% and 80% yields, respectively. We had doubts on the behavior of the thiophene ring since we had already shown that it could react with the acetonitrile complex of hypofluorous acid to produce the corresponding *S,S*-dioxides.[16,17] Fortunately, however, the dimethylhydrazone moiety reacted faster than the sulfur atom, and if one adheres strictly to 2.5 mol equiv of HOF·CH$_3$CN, the dimethylhydrazone of 2-thiophenecarboxaldehyde **1n** could be converted to 2-cyanothiophene (**2n**) in a few seconds at 0 °C in a 96% yield. If larger excess of the reagent was used, then the sulfur atom also reacted.
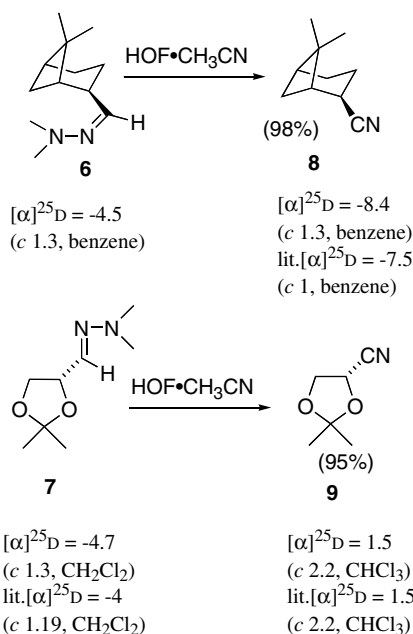
As mentioned above the oxidation of **1** required at least 2 mol equiv of HOF·CH$_3$CN. This fact supports the general mechanism proposed by Curci[4] and Rudler[3b] and involves an electrophilic oxygen (Scheme 3). The factor that makes a substantial difference as far as speed, yields and employment of mild conditions are concerned is the formation of HF along with oxide **3**, which is a very strong driving force for the reaction. It is thermodynamically favorable for **3** to transform immediately to nitrile **2** and dimethylhydroxylamine (**4**), which in turn is further oxidized by an additional molecule of HOF·CH$_3$CN, to *N*-oxide **5** and HF, this once again being a strong driving force for the whole process. We were able to detect both dimethylhydroxylamine (**4**) and *N*-oxide **5** by MS (EI) $m/z = 61$ (M)$^+$ for C$_2$H$_7$NO and $m/z = 59$ (M)$^+$ for C$_2$H$_5$NO. This procedure was not feasible for ketohydrazones.[18]

Transforming the *N,N*-dimethylhydrazone group to a nitrile moiety did not affect the stereochemistry around the nitrogen bonded carbon (Scheme 4). We have reacted dimethylhydrazone **6** (derived from (1*S*,2*S*, 5*S*)-(−)-myrtanal) and the *N,N*-dimethylhydrazone of (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (**7**) with HOF·CH$_3$CN for a few seconds and obtained the corresponding nitriles **8**[24] and **9**[4] without any racemization. It is worth noting that these reactions are fast enough such that rearrangement to the corresponding menthol derivatives did not occur as is usually the situation with this bicyclic system.

The retention of configuration and the chemoselectivity of this oxidation process, prompted us to explore the
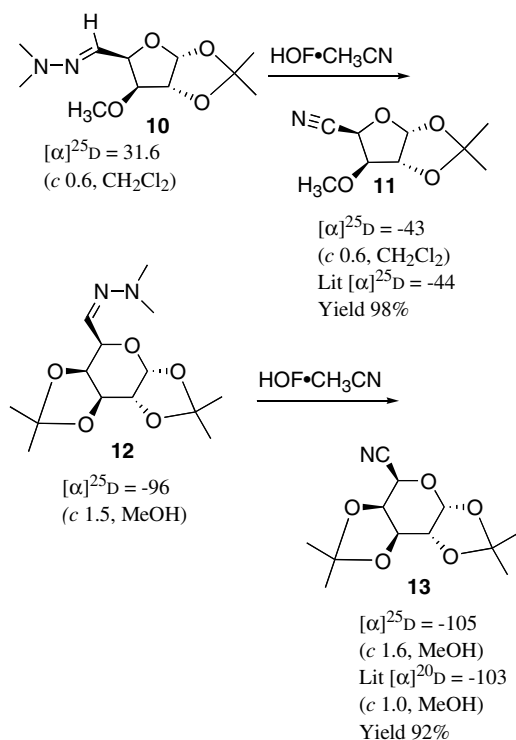

Scheme 3. The mechanistic route to nitrile formation.

6

$[\alpha]^{25}_D = -4.5$
(*c* 1.3, benzene)

8

(98%)

$[\alpha]^{25}_D = -8.4$
(*c* 1.3, benzene)
lit.$[\alpha]^{25}_D = -7.5$
(*c* 1, benzene)

7

$[\alpha]^{25}_D = -4.7$
(*c* 1.3, CH$_2$Cl$_2$)
lit.$[\alpha]^{25}_D = -4$
(*c* 1.19, CH$_2$Cl$_2$)

9

(95%)

$[\alpha]^{25}_D = 1.5$
(*c* 2.2, CHCl$_3$)
lit.$[\alpha]^{25}_D = 1.5$
(*c* 2.2, CHCl$_3$)

Scheme 4. Synthesis of chiral nitriles using HOF·CH$_3$CN.

vast area of the carbohydrate chemistry. The dimethylhydrazone of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylopentodialdofuranose (1,4) (**10**) was reacted with HOF·CH$_3$CN to give 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranurononitrile (**11**)[25] in a quantitative yield without affecting any other center of the molecule. Six-membered ring sugars such as the dimethylhydrazone of 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-6-aldehyde (**12**) also reacted very well and the corresponding nitrile,

10

$[\alpha]^{25}_D = 31.6$
(*c* 0.6, CH$_2$Cl$_2$)

11

$[\alpha]^{25}_D = -43$
(*c* 0.6, CH$_2$Cl$_2$)
Lit $[\alpha]^{25}_D = -44$
Yield 98%

12

$[\alpha]^{25}_D = -96$
(*c* 1.5, MeOH)

13

$[\alpha]^{25}_D = -105$
(*c* 1.6, MeOH)
Lit $[\alpha]^{20}_D = -103$
(*c* 1.0, MeOH)
Yield 92%

Scheme 5. Synthesis of chiral sugar nitriles using HOF·CH$_3$CN.

1,2:3,4-di-*O*-isopropylidene-α-D-galacturononitrile (**13**)[26] was smoothly obtained (see Scheme 5).

In conclusion, we have described a method for converting aldehyde hydrazones to nitriles using HOF·CH$_3$CN, which is rapid, high yielding and ecofriendly (the released HF could be easily trapped by a base to produce a salt). Considering the commercial availability of premixed fluorine/nitrogen mixtures and the technical ease of the reaction (no special equipment is needed)[27], this method may become a method of choice for the above transformation.

Acknowledgment

References and notes

1. (a) Fernandez, R.; Gasch, C.; Lassaleta, J.; Llera, J.; Vazquezz, J. *Tetrahedron Lett.* **1993**, *34*, 141–144; (b) Said, S. B.; Skarzewski, J.; Mlochowski, J. *Synthesis* **1989**, 223–225; (c) Mlochowski, J.; Kloc, K.; Kubicz, E. *J. Prakt. Chem.* **1994**, *336*, 467–470.
2. Murahashi, S. I.; Shiota, T.; Imada, Y. *Org. Synth.* **1991**, *70*, 265–271.
3. (a) Stankovic, S.; Espenson, H. *Chem. Commun.* **1998**, 1579–1580; (b) Rudler, H.; Denise, B. *Chem. Commun.* **1998**, 2145–2146.
4. Altamura, A.; Daccolti, L.; Detomaso, A.; Dinoi, A.; Fiorentino, M.; Fusco, C.; Curci, R. *Tetrahedron Lett.* **1998**, *39*, 2009–2012.
5. Ramalingam, T.; Reddy, B. V. S.; Srinivas, R.; Yadav, J. S. *Synth. Commun.* **2000**, *30*, 4507–4512.
6. *General procedure for N,N-dimethylhydrazone preparation.* To an aldehyde derivative (usually 4–15 mmol) dissolved in 30 mL EtOH, *N,N*-dimethylhydrazine (12–45 mmol) was added in one portion and then stirred for 1 h. The reaction was terminated by pouring the mixture into water and was then extracted twice with CH$_2$Cl$_2$ and the combined organic layer was dried over MgSO$_4$. Evaporation of the solvent gave the target *N,N*-dimethylhydrazone derivative, which in certain cases was purified by flash column chromatography (petroleum ether/ethyl acetate as eluent). The yields of *N,N*-dimethylhydrazones varied between 90% and 95%.
7. (a) Smith, R. F.; Walker, R. E. *J. Org. Chem.* **1962**, *27*, 4372–4375; (b) Kamal, A.; Arifuddin, M.; Rao, N. V. *Synth. Commun.* **1998**, *28*, 4507–4512.
8. *General procedure for working with fluorine.* Fluorine is a strong oxidant and a corrosive material. It should be used only with an appropriate vacuum line.[11] For the occasional user, however, various premixed mixtures of F$_2$ in inert gases are commercially available, thereby simplifying the process. Unreacted fluorine should be captured by a simple trap containing a solid base such as sodalime located at the outlet of the glass reactor. If elementary precautions are taken, the work with fluorine is relatively simple and we had never experienced difficulties working with it.
General procedure for producing HOF·CH$_3$CN. The mixtures of 10–20% F$_2$ in nitrogen were used throughout this work. The gas mixture was prepared in a secondary container prior to the reaction[11] and passed at a rate of

about 400 mL per minute through a cold ($-15\ °C$) mixture of 100 mL CH_3CN and 10 mL H_2O in a regular glass reactor. The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. The typical concentrations of the oxidizing reagent were around 0.4–0.6 mol/L.

9. (a) Rozen, S.; Carmeli, M. *J. Am. Chem. Soc.* **2003**, *125*, 8118–8119; (b) Carmeli, M.; Rozen, S. *J. Org. Chem.* **2006**, *71*, 4585–4589.

10. Golan, E.; Rozen, S. *J. Org. Chem.* **2003**, *68*, 9170–9172.

11. Dayan, S.; Kol, M.; Rozen, S. *Synthesis* **1999**, 1427–1430.

12. (a) Rozen, S.; Dayan, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3471–3473; (b) Rozen, S.; Carmeli, M. *J. Org. Chem.* **2005**, *70*, 2131–2134.

13. Rozen, S.; Carmeli, M. *J. Org. Chem.* **2006**, *71*, 5761–5765.

14. Amir, E.; Rozen, S. *Chem. Commun.* **2006**, *21*, 2262–2264.

15. Harel, T.; Amir, E.; Rozen, S. *Org. Lett.* **2006**, *8*, 1213–1216.

16. Rozen, S.; Bareket, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1959.

17. Amir, E.; Rozen, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7374–7378.

18. Carmeli, M.; Rozen, S. *Tetrahedron Lett.* **2006**, *47*, 763–766.

19. Rozen, S. *Eur. J. Org. Chem.* **2005**, 2433–2447.

20. The ^1H NMR and ^{13}C NMR were recorded at 200 and 50 MHz, respectively, with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The IR spectra were recorded in a $CHCl_3$ solution on an FTIR spectrophotometer. The MS were measured under CI, EI or FAB conditions. The typical spectroscopic data for the nitriles: IR (*CN*): 2250–2400 cm^{-1}; ^{13}C NMR (*CN*): 115–125 ppm.

21. Kol, M.; Rozen, S. *J. Org. Chem.* **1993**, *58*, 1593–1595.

22. (a) Rozen, S.; Kol, M. *J. Org. Chem.* **1990**, *55*, 5155–5159; (b) Rozen, S.; Golan, E. *Eur. J. Org. Chem.* **2003**, 1915–1917; (c) Golan, E.; Hagooly, A.; Rozen, S. *Tetrahedron Lett.* **2004**, *45*, 3397–3399.

23. Hopff, H.; Hoffmann, H. *Helv. Chim. Acta* **1957**, *164*, 1585–1594.

24. Sasson, R.; Rozen, S. *Org. Lett.* **2005**, *7*, 2177–2179.

25. (a) Brink, A. J.; Villiers, O. G.; Jordaan, A. *S. Afr. J. Chem.* **1978**, *31*, 59–65; (b) Talukdar, A. *Synth. Commun.* **2002**, *32*, 3503–3508.

26. Telvekar, V. N.; Akamanchi, K. G. *Synth. Commun.* **2004**, *34*, 2331–2336.

27. One of the referees who had very positive and constructive remarks, still expressed unfortunate common feelings amongst chemists regarding fluorine saying that it is 'surely one of the more evil reagents available'. We would like to differ. In our opinion and experience, comparing work with 10–15% F_2 in N_2, to chlorine reveals that it is more complicated to work with the latter since it tends to corrode the cylinders' heads. Working with bromine is associated with many accidents and fatalities. Experimenting with the widely used HCN, HF, perchlorates and alike is surely more dangerous. Diluted fluorine can be passed through copper, monel, stainless steel, or Teflon tubes without much trouble.