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High-yield Synthesis of Nitriles by Oxidation of Aldehyde *N,N*-Dimethylhydrazones with Dimethyldioxirane†

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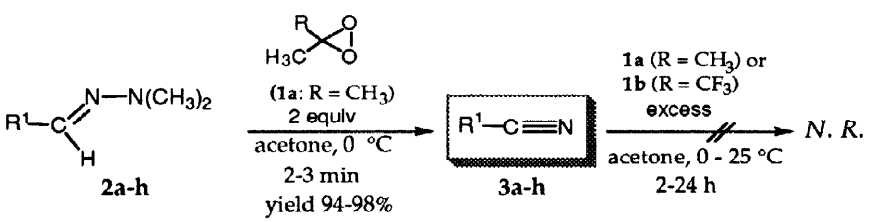
Abstract: Using dimethyldioxirane, the selective transformation of aldehyde *N,N*-dimethylhydrazones into the corresponding nitriles was achieved in high yield and under mild conditions. The determination of the substituent effect on rates, along with an estimate of the primary kinetic isotope effect using $PhCH{=}NNMe_2$ and $PhCD{=}NNMe_2$ provided useful hints concerning the reaction mechanism. It was also observed that the nitrile products do not undergo further oxidation, even with excess dioxirane.

Keywords: *Dioxiranes; Oxidation; N,N-dialkylhydrazones; Nitriles.*

Several procedures are available for carrying out the transformation of aldehydes into nitriles;[1] among these, particularly valuable is the oxidative conversion of aldehyde *N,N*-dialkylhydrazones using peracids, such as magnesium monoperoxyphtalate hexahydrate (MMPP).[1f]

Dioxiranes,[2] especially dimethyldioxirane (DMD) (**1a**)[3] and methyl(trifluoromethyl)dioxirane (TFD) (**1b**)[4] in the isolated form, have nowadays become well established as powerful oxidants. Indeed, these reagents can be employed to carry out a number of synthetically useful oxidative transformations,[5] including the easy regeneration of the carbonyl moiety from acetals and orthoesters.[6] In this context, we have shown that dioxiranes are excellent reagents for the selective regeneration of the C=O moiety from ketone hydrazones in neutral media and mild conditions.[7] We now report on the successful application of dimethyldioxirane (**1a**) for the clean, high-yield conversion of aldehyde *N,N*-dimethylhydrazones into nitriles (Scheme 1).



Scheme 1

Typical results in Table 1 show that representative hydrazones **2a-h** can be converted into the corresponding nitriles in almost quantitative yield and in a remarkably short reaction time.

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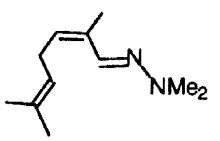
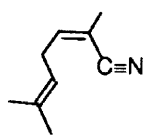
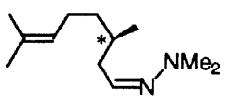
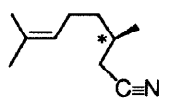
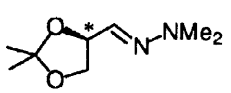
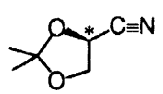
Table 1. Synthesis of nitriles by oxidation of *N,N*-dimethylhydrazones with dimethyldioxirane (**1a**) in acetone.[a]

entry	substrate(#)		relative rates [b]	product (#)		% yield [c]
1	*m*-$O_2NC_6H_4$-CH=N-N(Me)$_2$	(**2a**)	0.156	*m*-$O_2NC_6H_4$-C≡N	(**3a**)	97
2	*p*-ClC_6H_4-CH=N-N(Me)$_2$	(**2b**)	0.603	*p*-ClC_6H_4-C≡N	(**3b**)	98
3	C_6H_5-CH=N-N(Me)$_2$	(**2c**)	(1.000)	C_6H_5-C≡N	(**3c**)	97
3'	C_6H_5-CD=N-N(Me)$_2$	(**2c'**)	1.000[d]			
4	*p*-$MeOC_6H_4$-CH=N-N(Me)$_2$	(**2d**)	2.580	*p*-$MeOC_6H_4$-C≡N	(**3d**)	98
5	(*E*)-C_6H_5CH=CH-CH=N-N(Me)$_2$	(**2e**)	–	(*E*)-C_6H_5CH=CH-C≡N	(**3e**)	92
6		(**2f**)	–		(**3f**)	97
7		(**2g**) *(99%)*[e]	–		(**3g**) *(98%)*[f]	92
8		(**2h**) *(93.5%)*[e]	–		(**3h**) *(93%)*[f]	92

[a] All reactions routinely run at 0 °C, with dioxirane to substrate molar ratio ca. 2 to 1; in all cases, during 2-3 min a > 98% substrate conversion was achieved as determined (±2%) by GC (SPB-1, 0.25 μm film thickness, 30 m × 0.25 mm ID, capillary column). [b] From competition kinetic experiments (ref. 14). [c] Isolated yield. [d] Primary kinetic isotope effect (k_H/k_D) = 1.00, based on competition kinetic experiments (ref. 14). [e] Optical purity (o.p.) of the corresponding aldehyde starting material at 20 °C (Perkin-Elmer MC 241 spectropolarimeter). [f] O.p. from rotation of the given material at 20 °C.

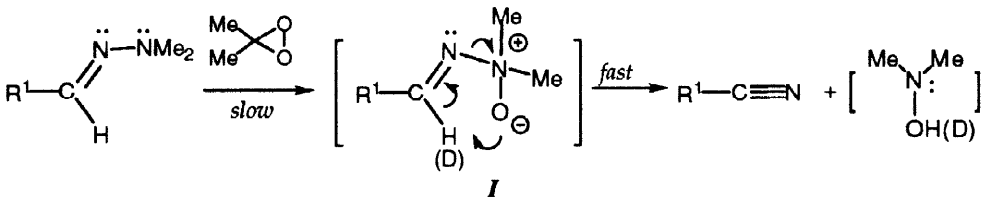
Substrates **2a-h**[8,9] were obtained starting with the corresponding aldehyde and *N,N*-dimethylhydrazine. To these, dioxirane **1a** was applied in the isolated form as acetone solution;[3-7] the latter was obtained according to described protocols.[3] In the simple general procedure, an aliquot (10-15 mL) containing 2 equiv of a standardized cold solution of dimethyldioxirane (**1a**) (ca. 0.1 M in acetone) was added to a stirred solution of 1 equiv of the hydrazone (0.5-0.7 mmol) in acetone (5 mL), kept at 0 °C. The nitriles **3a-h**[10] (Table 1) could be obtained in practically pure form simply upon removal of the acetone solvent in vacuo; they were identified upon comparison of their physical constants and spectral characteristics (MS, FT IR, and/or ^{1}H NMR, ^{13}C NMR) with those of authentic samples and/or literature data.[10,11]

Application of the more powerful methyl(trifluoromethyl)dioxirane (**1b**) to carry out the transformation at hand was less satisfactory than **1a**, yielding inferior nitrile yields and lower substrate conversions; seemingly, the hydrazones are capable of triggering the competitive decomposition of **1b**.[7]

It should be noted that — under the conditions adopted — the given nitriles were remarkably unreactive toward excess dioxirane **1a** or **1b** (Scheme 1). This is significant, since it has been recently reported on the facile conversion of nitriles into the corresponding amides using dimethyldioxirane (**1a**), either generated *in situ* or in the isolated form.[12] In our hands, *none* of the nitriles **3a-h** underwent this transformation in the attempted reaction with dioxirane **1a** excess (3 equiv) in acetone at 25 °C; after 24 h, GC and GC/MS monitoring revealed no detectable amount of amide and showed that the nitrile had remained unchanged. Similarly, we find that benzonitrile (**3c**) is not appreciably converted into benzamide even after exposure to aqueous caroate/acetone at pH 7.0-7.5 (*in situ* DMD)[2,5,13] under conditions similar to those reported.[12]

Examples in Table 1 illustrate the efficient transformation of *N,N*-dimethylhydrazones (convenient derivatives for aldehyde isolation and purification) into nitriles. Chemoselectivity of the -$NNMe_2$ → -C≡N oxidative conversion is illustrated by the fact that the C=C unsaturated functionalities in **2e-g**, and the *O,O*-isopropylidene group in **2h** are left unaltered; also, nitriles **3g** and **3h** are isolated with no loss of optical purity by the oxidation of hydrazone **2g** (derived from citronellal) or of the sugar derivative **2h**, respectively (Table 1, entry 7 and 8).

As for the reaction mechanism, relative rate data for the series of ring-substituted aryl hydrazones **2a-d** under identical conditions (Table 1, entry 1 to 4) yield an Hammett's ρ of ca. -1.22,[14] suggesting that the oxidation involves *electrophilic O*-transfer from the dioxirane to the substrate. Then, on a parallel with the mechanism invoked for the oxidation of aldehyde hydrazones by peracids,[1f] for the case at hand one could advance the stepwise two-electron process in Scheme 2.



I

Scheme 2

Thus, subsequent to electrophilic *O*-transfer to the distal nitrogen atom of the -$NNMe_2$ functionality, the labile intermediate ***I*** would break down to yield the nitrile and hydroxylamine;[1f] the latter is further oxidized, most likely via the corresponding *N*-oxide (consuming further dioxirane).[15] Obviously, a key feature of the mechanism consists in the *H*-transfer occurring in the second step, as sketched in Scheme 2. Using benzaldehyde *N,N*-dimethylhydrazone (**2c**) and its deutero derivative **2c'**, we were able to estimate a primary kinetic isotope effect (k_H/k_D) = 1.00;[14] this suggests that the C-H bond breaking does not occur in the rate determining step. Therefore, if the mechanism in Scheme 1 applies, the slow step should be represented by the crucial *O*-transfer by the dioxirane to the substrate -$NNMe_2$ moiety.

Be the mechanistic details as it may, the results reported herein suggest that dioxirane oxidation constitutes a substantial new entry into the high-yield synthesis of nitriles via *N,N*-dialkylhydrazones, alternative to using peracids. For instance, under comparable conditions we could achieve the conversion of the sugar derivative **2h** into the corresponding nitrile in just 75% yield during 2 h using MMPP,[1f] as compared to 92% yield and 3 min reaction time with DMD (Table 1, entry 8). Besides, product isolation is attractively simple using DMD since it merely involves removal of the volatile acetone that is both the solvent and the reduced form of the oxidant.

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References and Notes

1. For instance, see: (a) Barton, D.; Ollis, W. D. In *Comprehensive Organic Chemistry*; Pergamon: Oxford, UK, 1979; Vol 2, Chapter 8, pp 534-535. (b) Smith, R. F.; Albright, J. A.; Waring, A. M. *J. Org. Chem.* **1966**, *31*, 4100. (c) Suzuki, H.; Fuchita, T.; Iwasa, A.; Mishina, T. *Synthesis* **1978**, 905-908. (d) Olah, G. A.; Narang, S. C.; Garcia-Luna, A. *Synthesis* **1980**, 659. (e) Saednya, A. *Synthesis* **1983**, 748. (f) Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Llera, J.-M.; Vázquez, J. *Tetrahedron Lett.* **1993**, *34*, 141; and references therein.
2. For a recent review, see: Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.
3. (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699. (c) Adam, W.; Chan, Y.-Y; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.
4. (a) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749.
5. (a) Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; Chapter 4, pp 195-219. (b) Clennan, E. L. *Trends Org. Chem.* **1995**, *5*, 231.
6. (a) Curci, R.; D'Accolti, L.; Fiorentino, M.; Fusco, C.; Adam, W.; González-Nuñez, M. E.; Mello, R., *Tetrahedron Lett.* **1992**, *33*, 4225. (b) Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Rosa, A. *Tetrahedron Lett.* **1996**, *37*, 115.
7. Altamura, A.; Curci, R.; Edwards, J. O. *J. Org. Chem.* **1993**, *58*, 7289-7293.
8. Aldehyde hydrazones (**2a**),[9a] (**2b**),[9a] (**2c**) (^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63-7.54 (m, 1 H), 7.40-7.15 (m, 5 H), 2.95 (s, 6 H, NCH_3); MS (70 eV), *m/z* (r.i.): 148 (M^+, 100), 147 (24), etc.),[9a] (**2d**),[9a] (**2e**),[9b] (**2f**)[9b] gave physical constants and spectral data in agreement with literature. Reduction of PhCOCl with $(Ph_3P)_2CuBD_4$ in acetone gave benzaldehyde-d_1; the latter afforded **[1-D]Benzaldehyde *N,N*-dimethylhydrazone** (**2c'**):[9c] colorless oil, b.p. 84 °C/12 mmHg; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64-7.52 (m, 2 H), 7.40-7.15 (m, 3 H), 2.93 (s, 6 H, NCH_3); MS (70 eV), *m/z* (r.i.): 149 (M^+, 100), 134 (28), etc.. ***R*-3,7-Dimethyl-6-octenal *N,N*-dimethylhydrazone** (**2g**): b.p. 119-120 °C/3 mmHg [lit.[9d] b.p. 65 °C/0.1 mmHg]; $[\alpha]_D$=+1.77° (c 1.36, CH_2Cl_2). [*R*-(+)-Citronellal starting material: $[\alpha]_D$=+15.8° (neat), o.p. 99%]. **(+)-2,3-*O*-Isopropylidene-D-glyceraldeyde *N,N*-dimethylhydrazone** (**2h**):[9e] $[\alpha]_D$=-4.0° (c 1.19, CH_2Cl_2) [(+)-2,3-*O*-isopropylidene-D-glyceraldeyde starting material: $[\alpha]_D$=+59.2° (c 0.78, C_6H_6), lit.[9f] $[\alpha]_D$=+63.3°(c 1.27, C_6H_6), o.p. 93.5%].
9. (a) Wiley, R. H.; Slaymaker, S. C.; Kraus, H. *J. Org. Chem.* **1957**, *22*, 204. (b) Yamashita, M.; Matsumiya, K.; Nakano, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1759. (c) Nguyen, M. T.; Clarke, L. F.; Hegarty, A. F. *J. Org. Chem.* **1990**, *55*, 6177. (d) Wiley, R. H.; Irick, G. *J. Org. Chem.* **1959**, *24*, 1925. (e) Remuzon, P.; Dussy, C.; Jacquet, J.-P.; Roty, P.; Bouzard, D. *Tetrahedron Asymm.* **1996**, *7*, 1181. (f) Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337.
10. (**3a**),[11a] (**3b**),[11b] (**3c**),[11b] (**3d**),[11b] (**3e**),[11c] (**3f**),[11d] (**3g**) ($[\alpha]_D$=-9.80° (neat), lit.[11e] $[\alpha]_D$=-9.96° (neat), o.p. 98%). ***S*-4-Cyano-2,2-dimethyl-1,3-dioxolane** (**3h**) ($[\alpha]_D$=+1.36° (c 1.33, $CHCl_3$), lit.[11f] $[\alpha]_D$=+1.46° (c 2.2, $CHCl_3$), o.p. 93%).
11. (a) Smith, R. F.; Walker, L. E. *J. Org. Chem.* **1962**, *27*, 4372. (b) Sosnovsky, G.; Krogh, J. A.; Umhoefer, S. G. *Synthesis* **1979**, 722. (c) Ikeda, I.; Machii, Y.; Okahara, M. *Synthesis* **1978**, 301. (d) Düttmann, H.; Weyerstahl, P. *Liebigs Ann. Chem.* **1976**, 1753. (e) Herschmann, C. *Helv. Chim. Acta* **1949**, *32*, 2537. (f) Chelucci, G.; Cabras, M. A.; Saba, A. *Tetrahedron Asymm.* **1994**, *5*, 1973.
12. Bose, D. S.; Baquer, S. M. *Synth. Commun.* **1997**, *27*, 3119.
13. Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758.
14. In competition kinetic experiments the given substituted hydrazone and the reference hydrazone **2c** (X and H, respectively), both ca. 0.05 M in acetone, were allowed to react with ca. 0.05 M DMD, making $([X]_o+[H]_o) > [DMD]_o$); GC analyses (VOCOL, 3.0 μm film thickness, 60 m × 0.53 mm ID, capillary column) of the reaction mixture allowed to obtain relative rate (k_r) data as $(k_X/k_H) = \{\log([X]/[X]_o)/(\log([H]/[H]_o)\}$. In each experiment, at least two values were measured and averaged (estimated error ≤ ±2%). Essentially the same procedure was followed for the determination of the primary kinetic isotope effect, except that the ratio of concentrations of residual **2c** and deuteriated **2c'** was determined by ^{1}H NMR (500 MHz) upon integration of the $-N(CH_3)_2$ signals at δ 2.95 and 2.93, respectively (see also ref. 8). The estimated (k_H/k_D) = 1.00 was confirmed by GC/MS analyses; in fact, from the EI mass spectrum of the reaction mixtures, the relative abundance of the M^+ ions, i.e. *m/z* 148 and 149, corresponding to the coeluting isotopomers **2c** and **2c'** respectively, remained unchanged (i.e., 1:1, ±2%) with respect to the initial solution, prior to the addition of the dioxirane.
15. Murray, R. W.; Singh, M. *Tetrahedron Lett.* **1988**, *29*, 4677.