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Simple and Efficient Conversion of N,N-Dimethylhydrazones and Aldehydes to Nitriles.

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Abstract: Aldehyde *N,N*-dimethylhydrazones undergo facile oxidative cleavage to nitriles on reaction with magnesium monoperoxyphtalate hexahydrate (MMPP) under very mild conditions. The reaction is high yielding, chemoselective and proceeds rapidly without racemization. Nitriles can be easily obtained in high yields in a 'one-pot' process starting from the corresponding aldehydes.

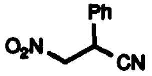
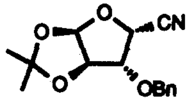
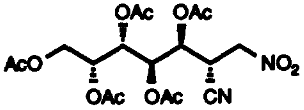
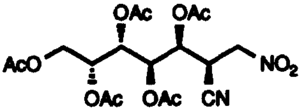
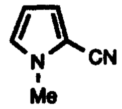
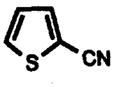
The versatility and usefulness of *N,N*-dialkylhydrazones as intermediates in organic synthesis have been shown in a number of reactions for carbon-carbon bond formation,[1] and therefore there has also been considerable interest in the development of mild methods for the transformations and cleavage of dialkylhydrazones. We have recently described the use of formaldehyde dimethylhydrazone as a new formyl anion equivalent through Michael addition to nitroolefins and cleavage of the dimethylhydrazone group.[2] As a further extension of the synthetic utility of *N,N*-dialkylhydrazones we have studied the reaction of aldehyde *N,N*-dialkylhydrazones with magnesium monoperoxyphtalate hexahydrate (MMPP). MMPP, a newly developed reagent with high stability at ambient temperature, has been shown to oxidize a wide range of compounds under mild conditions. The substrates include alkenes, ketones, sulphides, sulphoxides, pyridine and dipotassium *p*-tolylpentafluorosilicate.[3] It has been recently reported that *N,N*-dimethylhydrazones from ketones on treatment with MMPP undergo oxidative cleavage to ketones.[4] We wish to report here the successful application of this reagent for the transformation of aldehydes into nitriles *via* *N,N*-dimethylhydrazones.

We have investigated the reaction of MMPP with *N,N*-dimethylhydrazones **1**, which affords after a simple work-up nitriles **2** (Scheme 1).[5] The reaction is complete in a very short time (~ 5 min) and nitriles **2** are formed

$$\underset{\mathbf{1}}{\mathrm{RCH{=}NNMe2}} \xrightarrow[\text{0 °C, 5 min., 88-99\%}]{\mathrm{MMPP{\cdot}6H_2O,\ MeOH,}} \underset{\mathbf{2}}{\mathrm{RCN}}$$

Scheme 1

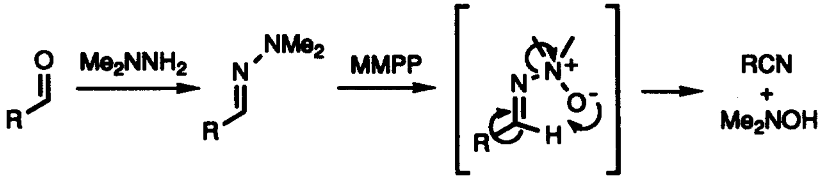
Table. Synthesis of Nitriles 2

Entry	Product 2	Method[a]	Yield of 2[b] (%)
a		A B	99 80
b		A B	90 88
c		A	90
d		A B	99[c] 84[c]
e		A	90[c]
f		A	92[c]
g	PhCN	A	93
h	4-MeOC$_6$H$_4$CN	A	97
i	4-MeC$_6$H$_4$CN	A	90
j	2,4,6-Me$_3$C$_6$H$_2$CN	A	98
k	4-NO$_2$C$_6$H$_4$CN	A[d]	91
l	4-ClC$_6$H$_4$CN	A	93
m		A	93
n		A	88

a) Method A: Transformation of *N,N*-dimethylhydrazones 1 into nitriles 2, ref. 5. Method B: 'One-pot' transformation of aldehydes to nitriles, ref. 7. b) Isolated yield. c) No racemization occured. d) The corresponding hydrazone 2k was not soluble in MeOH. The reaction was carried out in CH$_2$Cl$_2$:MeOH 1:1.

in almost quantitative yield. Table 1 lists several examples of this procedure including the synthesis of α,β-unsaturated (**2a**), simple (**2b**) and functionalized aliphatic (**2c-f**), aromatic (**2g-l**) and heterocyclic (**2m-n**) nitriles (Method A). Transformation of hydrazone **2a** (derived from cinamaldehyde) and sugar derivatives **2d-f** demonstrates the chemoselectivity of the process, and interestingly nitriles **2d**, **2e** and **2f** are isolated without racemization.

N,N-Dimethylhydroxylamine has been detected in the reaction mixtures, supporting the most probable Cope-type elimination mechanism (Scheme 2). This kind of process is not feasible in ketone hydrazones, which explains the different results obtained for these compounds.[4]



Scheme 2

Conversion of *N,N*-dialkylhydrazones into nitriles has been reported using different procedures:[6] the two steps synthesis *via* *N,N,N*-trimethylhydrazonium salts, the direct conversion in hyperbasic media, or the oxidative transformation using hydrogen peroxide or 3-chloroperbenzoic acid. The procedure here reported has the advantages of higher yields under milder conditions, being well-suited for the preparation of densely functionalized aliphatic nitriles, which are not easily accessible by other procedures.

Furthermore, the above reaction provides a new and easy 'one-pot' route to nitriles from aldehydes *via* *N,N*-dialkylhydrazones. Additional experiments have shown that these intermediates need not be isolated, and nitriles **2a**, **2b**, and **2d** have been obtained in high yields by reaction of the corresponding aldehyde with *N,N*-dimethylhydrazine and subsequent treatment of the reaction mixture with MMPP (Table, Method B).[7] Preparation of nitriles from aldehydes is usually achieved by dehydration of the corresponding aldoximes using classical reagents[8] or new mild ones.[9] Several more or less convenient procedures for the direct conversion of aldehydes into nitriles without isolation of nitrogen-containing intermediate are also known.[10] This new procedure for the conversion of an aldehyde to a nitrile *via* the hydrazone (often employed for its purification) has the following practical merits compared with the previously reported synthesis of aldehydes from nitriles: i) reagents (dimethylhydrazine and magnesium monoperoxyphtalate hexahydrate) are not expensive and very convenient to be used in both small and large-scale operations, ii) is quite simple to use without any particular care, iii) short reaction times and mild conditions, as the low temperature and not alkaline medium, allow the synthesis of rather unstable nitriles, iv) after a simple work-up nitriles are isolated in high yield for aromatic, heterocyclic, α,β-unsaturated and aliphatic nitriles, without isomerization of adjacent chiral centers.

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References and Notes

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5. General procedure (Method A): A solution of hydrazone **1** (5 mmol) in methanol (5 mL) is added dropwise to MMPP·$6H_2O$ (12.5 mmol) suspended in methanol (40 mL) at 0°C. The reaction mixture is stirred at 0°C until the hydrazone has completely reacted (~ 5 min, TLC control). Dichloromethane (125 mL) and water (125 mL) are added, the organic layer is separated and washed with saturated aqueous NaCl solution (2x125 mL). The organic layer is dried over $MgSO_4$ and evaporated at reduced pressure. The crude product is purified by column chromatography to give pure **2**.
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7. General 'one pot' procedure (Method B): *N,N*-Dimethylhydrazine (0.35 g, 5 mmol) is added to a solution of the aldehyde (3.5 mmol) in MeOH (20 mL) and the mixture is left at room temperature until the reaction is finished (TLC control). This solution of the hydrazone **1** is then added dropwise to MMPP·$6H_2O$ (8.3 mmol) suspended in methanol (12 mL) at 0°C. The reaction mixture is stirred at 0°C until the hydrazone has completely reacted (~ 5 min, TLC control) and then treated as in ref. 5.
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11. All new compounds were fully characterized by ^1H nmr, ^{13}C nmr, ir and high resolution mass spectroscopy and/or combustion analysis.

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