A Clean Conversion of Aldehydes to Nitriles Using a Solid-Supported Hydrazine

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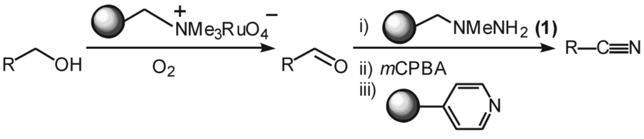
Abstract: A polymer-supported hydrazine reagent has been applied to the conversion of a range of aldehydes to nitriles, providing a clean and efficient route to more diverse building blocks for combinatorial chemistry programmes.

Key words: aldehydes, nitriles, polymer-supported reagents



Scheme

The inherent value of combinatorial chemistry as a preparative technique lies not only in the multitude of compounds that can be synthesised but, more importantly, in the structural diversity that can be realised through the combination of the correct monomer sets. Unfortunately, commercial supplies of many key starting materials for combinatorial chemistry programmes are limited. For example, at present there are approximately only 4,000 commercially available aldehydes,[1] while there are of the order of 76,000 available alcohols from which the corresponding carbonyl compounds can be obtained by oxidation.[2] Likewise, there are relatively few commercially available nitriles,[1] despite their common usage in the synthesis of agrochemical and drug-like fragments. It is known that aldehydes can be converted to the corresponding nitriles by the dehydration of aldoximes,[3] but current methods of converting aldehydes to nitriles tend to be based on solution phase oxidation of the aldimines, formed in situ by condensation of aldehydes and ammonia, with oxidants such as iodine,[4] lead tetraacetate,[5] nickel peroxide,[6] oxygen-copper (II) chloride,[7] copper powder and ammonium chloride[8] and tetrabutylammonium peroxydisulfate with a nickel copper formate catalyst.[9] These methods involve laborious work-up and so are unsuitable for generation of large monomer sets of nitriles for chemical library preparation. We reasoned that transferral to an immobilised system, via the application of solid supported reagents, could lead to a more efficient and cleaner route to these important starting materials.

We have previously demonstrated the application of polymer-supported reagents to the smooth, clean and high yielding conversion of alcohols to aldehydes.[10] Consequently a process that would perform a secondary transformation to the nitrile would allow access to many previously unknown components (Scheme).

For this study the resin bound hydrazine **1** was prepared[11] by substitution of the chloride of the Merrifield resin with the methylated nitrogen of *N*-methylhydrazine.[12] While it was not possible to quantify properly the loading of this immobilised hydrazine due to possible cross-linking or coupling via the non-methylated nitrogen, later reactions gave some indication of the high efficiency of this process.[13]

The immobilised hydrazine **1** was reacted with various aldehydes to give the hydrazones which underwent reactions with 3-chloroperbenzoic acid[14] (*m*CPBA) to give the *N*-oxide which eliminates to form the corresponding nitriles.[15] In order to obtain clean products it was found necessary to use an excess of *m*CPBA and then scavenge any unreacted oxidant by the addition of polyvinylpyridine. This process could be carried out sequentially by removal of the spent hydrazine resin, followed by addition of polyvinylpyridine. Alternatively, since the spent hydrazine resin cannot be recycled, the polyvinylpyridine could be added directly to the reaction mixture after oxidation, and both simultaneously removed by filtration. A final wash of the filtrate with aqueous bicarbonate ensured complete removal of 3-chlorobenzoic acid.

Following the general procedure, as described in the footnote,[16] a small collection of nitriles was prepared in parallel (Table). In all the reactions, except entries 5 and 6, which contained over-oxidation impurities, the nitriles were obtained in greater than 95% purity as determined by ^{1}H NMR.

The reaction conditions are sufficiently mild to be used on molecules without removing protecting groups such as TBS (entries 12 and 14). Chiral aldehydes (13 and 14) were also converted to nitriles without the loss of optical purity. The range of aldehydes investigated included aromatic (1, 7 and 8), substituted aromatic (2 and 9), heterocyclic (5, 6, 10 and 11) and aliphatic (3 and 4) aldehydes. While electron-withdrawing substituents such as a nitro group on an aromatic aldehyde reduced the yield, as might be expected from the mechanism of the reaction, the iso-

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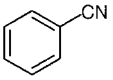
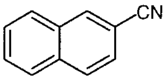
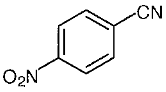
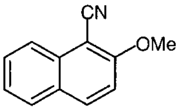
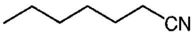
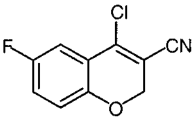
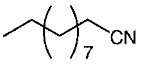
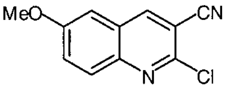
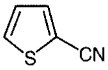
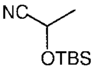
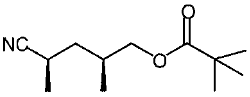
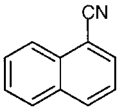
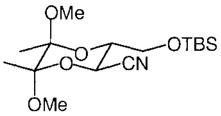
Table Nitriles[a] Prepared from Their Corresponding Aldehyde using a Solid-Supported Hydrazine.

Entry	Nitrile	Yield[b]	Entry	Nitriles	Yield[b]
1		55%	8		75%
2		43%	9		77%
3		76%	10		54%
4		100%	11		57%
5		43%[c]	12		43%
6		53%[c]	13		90%
7		77%	14		100%

[a] All new compounds were fully characterised.

[b] Yields are isolated yields; purity greater than 95% by ^1H NMR.

[c] Minor impurities present, ca. 90% purity by ^1H NMR.

lated yields also tended to be lower for the more volatile compounds, reflecting difficulties in isolation.

In summary, these examples demonstrate how polymer-supported reagents can be used in the clean conversion of aldehydes to nitriles avoiding conventional chromatography, distillation or crystallisation techniques.

Acknowledgement

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(1) Data courtesy of Available Chemicals Directory ACD 2001.

(2) For example by polymer-supported oxidation reagents, see: Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.

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(11) (a) Commercially available solid-supported hydrazines, such as PS-$TsNHNH_2$, whilst effective scavengers of aldehydes, did not oxidise upon treatment with *m*CPBA to release nitriles. (b) **Polymer-supported hydrazine**: Merrifield resin (Polymer Laboratories, 3.89 mmol/g, 18.60 g) was thoroughly washed [MeOH (50 mL), CH_2Cl_2 (50 mL), Et_2O (50 mL) this cycle was repeated 3 times] and dried in vacuo. The resin was cooled to 0 °C. Methyl

hydrazine (100 g, 2.171 mol, 30 equiv) was added drop wise and the temperature maintained at 0 °C. The resin was filtered to remove excess methyl hydrazine, and stirred in a 2:1 mixture of CH_2Cl_2–NEt_3 (200 mL) for 1 h. The resin was filtered, washed [MeOH (50 mL), CH_2Cl_2 (50 mL), Et_2O (50 mL) this cycle was repeated 10 times] and dried in vacuo.

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(13) The loading was determined by scavenging a 1:1 mixture of benzaldehyde and benzyl alcohol for 1 h and comparing the ratio of alcohol to aldehyde in the NMR spectra of the starting solution and recovered mixture. Loadings of approximately 3 mmol/g were obtained.

(14) Dimethyl dioxirane oxidation was also attempted but no oxidation was observed.

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(16) **Typical procedure:** Benzaldehyde (0.1 g, 0.942 mmol, 0.096 mL) was dissolved in CH_2Cl_2 (10 mL), and agitated for 1 h at r.t. with the polymer-supported hydrazine **1** (0.565 g, 1.130 mmol, 1.2 equiv). The polymer was separated from the reaction mixture by filtration, and the filtrate was concentrated in vacuo to yield recovered benzaldehyde (7.5 mg). The resin was washed thoroughly [MeOH (50 mL), CH_2Cl_2 (50 mL), Et_2O (50 mL) this cycle was repeated 3 times] then swelled in CH_2Cl_2 (10 mL), and agitated for 1 h at r.t. with *m*CPBA (0.358 g, 2.073 mmol, 2.2 equiv) and $NaHCO_3$ (50 mg). Polymer-supported polyvinylpyridine (Fluka, 0.545 g, 5.181 mmol, 5.5 equiv) was added to scavenge out remaining *m*CPBA and the reaction mixture was agitated for 1 h. The polymer was separated from the reaction mixture by filtration and the filtrate was washed with saturated sodium hydrogen carbonate (20 mL) to remove residual 3-chlorobenzoic acid. The organic fraction was concentrated in vacuo to yield the desired product, benzonitrile (0.049 g, 0.48 mmol, 55%) without further purification.