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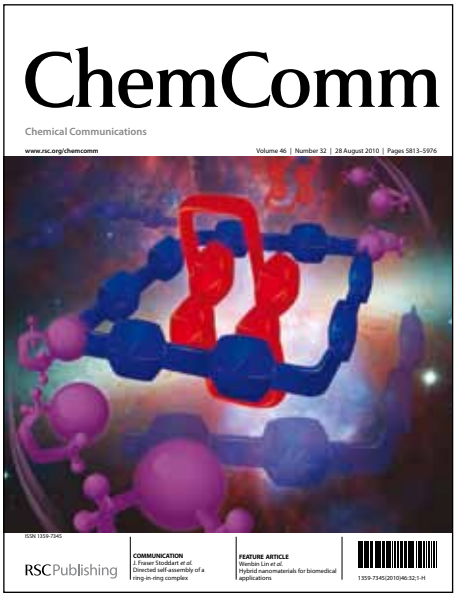

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ARTICLE TYPE

A Novel Protecting Group Methodology for Syntheses using Nitroxides

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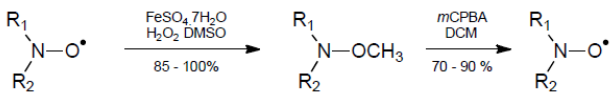
The methoxyamine group represents an ideal protecting group for the nitroxide moiety. It can be easily and selectively introduced in high yield (typically >90%) to a range of functionalised nitroxides using $FeSO_4.7H_2O$ and H_2O_2 in DMSO. Its removal is readily achieved under mild conditions in high yield (70-90%) using *m*CPBA in a Cope-type elimination process.

Nitroxides are versatile and stable free radical species that have been extensively studied for more than 50 years. The broad interest in nitroxides arises from their applications across a range of scientific disciplines including materials science, molecular biology, biophysics and medicine.[1] Nitroxides have been widely employed as initiators for the preparation of well-defined, functional and complex polymers[2] and nitroxide radical precursors are commonly used as stabilisers in materials.[3] The nitroxide moiety also provides an excellent synthetic handle for additional functionalization of polymers[4] and surfaces.[5] The use of nitroxides as spin-labels has enabled investigation into the molecular structure, dynamics and functional activity of various biomolecules.[1b,6] More recently, nitroxides have been exploited to prepare organic magnets[7] and as dynamic nuclear polarization agents for the enhancement of NMR signals.[8] The ability of nitroxides to undergo redox chemistry has further widened the scope of their applications. Their use as antioxidants in conditions involving oxidative stress is well documented[1b,9] and they display significant potential as redox mediators for dye-sensitised solar cells[10] and as cathodic materials in organic batteries.[11]

To cater for the diverse fields in which nitroxides are currently utilized, a number of synthetic strategies have been devised in order to develop tailored nitroxides for specific applications. Although the nitroxide moiety displays remarkable robustness in several different reaction types (e. g. Pd-catalysed cross-couplings,[12] the copper-catalysed azide-alkyne 1,3-dipolar cycloaddition reaction[13] and ring closing metathesis[14]), it is unstable in the presence of strong acid and base, radical driven reactions and strong oxidants and reductants.[15] To overcome the susceptibility of the nitroxide functionality to these conditions and extend nitroxide syntheses to access previously unobtainable structural variations, we sought an appropriate protecting group strategy. We herein report that the conversion to a methoxyamine group and cleavage under mild conditions in good yield represents a convenient and simple protecting group strategy for a range of nitroxide classes bearing different functionalities. (Scheme 1).



Scheme 1 Introduction and removal of the methoxyamine nitroxide protecting group.

In previous nitroxide syntheses, protection of the nitroxide moiety has been achieved using an acetate group which can be subsequently removed with strong base.[15b,16] However, this group may be unsuitable for a number of nucleophilic reactions as it contains a reactive ester moiety. Benzyloxyamines have also been employed as protecting groups but can provide low yields upon deprotection via hydrogenolysis in glacial acetic acid.[12c] The secondary amine precursor is a common synthetic intermediate for most hindered nitroxides, but these can be sensitive to autooxidation and can introduce difficulties in syntheses involving nucleophilic attack. Resolution on chromatography can also prove challenging for these amines.

We envisaged the methoxyamine group to be the ideal nitroxide protecting group as it imparts minimal structural change on the physical properties of the parent nitroxide, is stable under acidic and basic conditions and is inert to a number of typical functional group transformations. Furthermore, nuclear magnetic resonance analysis is facilitated through the introduction of a sharp 3H signal. (Nitroxides are paramagnetic and typically give significantly broadened NMR signals, so the reversible transformation to a functionality with a clear 3H integral aids structural elucidation).

To demonstrate the versatility of the methoxyamine group as a suitable nitroxide protecting group, we examined its introduction to, and removal from, a variety of functionalised nitroxides (containing halides, amines, carbonyls, alkynes and conjugated systems). The selection was largely based upon the isoindoline class of nitroxides due to the presence of an inherent chromophore which aided chromatographic analysis of the reaction, however 4-benzyloxy-2,2,6,6-tetramethylpiperidin-1-oxyl (**8**) was also selected to examine the applicability of this method towards the piperidine class of nitroxides.

The synthesis of methoxyamine derivatives of nitroxides has been previously achieved via two main methods: reaction with methyl radicals (generated either though Fenton chemistry in DMSO[17] or the CuCl-catalysed decomposition of

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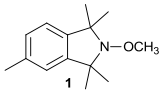
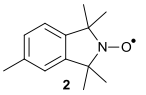
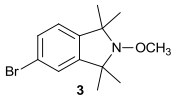
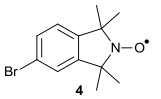
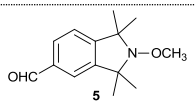
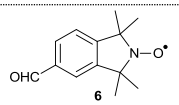
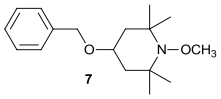
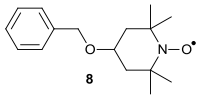
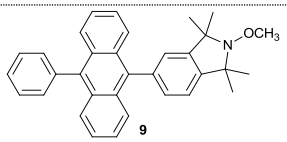
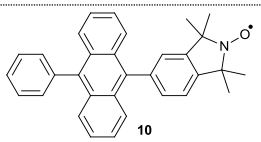
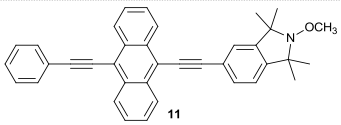
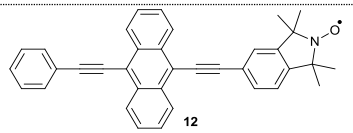
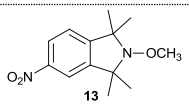
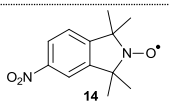
Table 1 Formation of methoxyamines from nitroxides using H_2O_2 and $FeSO_4.7H_2O$ in dimethylsulfoxide and deprotection with *m*CPBA.

Entry	Methoxyamine Formation	Isolated yield	Nitroxide Regeneration	*m*CPBA (equiv.)	Time (hr)	Isolated yield
1	 **1**	74%[a]	 **2**	2.1	0.5	85%
2				4.2	0.1	80%
3	 **3**	96%	 **4**	2.1	0.5	88%
4				4.2	0.1	86%
5	 **5**	88% (from **3**[b])	 **6**	3.0	2.0	88%
6	 **7**	68%[a]	 **8**	2.5	1.0	84%
7	 **9**	85-95% (80% over 2 steps[c])	 **10**	2.5	1.0	75%
8				3.0	8.0	37%
9	 **11**	95%	 **12**	2.1	0.5	67%
10	 **13**	87%	 **14**	3.0	1.0	85%

[a] Compounds **1** and **7** are formed in high yield from the nitroxides **2** and **8** , however they are volatile and provide lower isolated yields due to loss of product upon workup *in vacuo*. Successful protection and deprotection for the even more volatile parent TEMPOL was also achieved, details of which are provided in the Supplementary Information.

[b] See Supplementary Information for synthetic procedure.

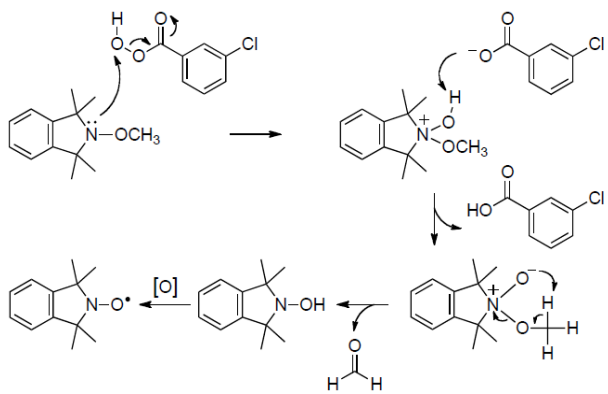
[c] Compound **9** can be formed from the nitroxide in good yield or synthesised from the arylhalide in two steps as previously described.[12c]

aldehyde/ketone peroxide intermediates[18]) or reduction of the nitroxide to the corresponding hydroxylamine and subsequent reaction with an alkyl halide.[19] Our preference has been to use Fenton chemistry as the reaction is fast, tolerates a wide range of functional groups and does not require an inert atmosphere. Accordingly, a range of methoxyamines **1**, **3**, **5**, **7**, **9**, **11** and **13** were prepared in high yield (typically over 90%) by reacting the corresponding nitroxides with $FeSO_4.7H_2O$ and H_2O_2 in DMSO.

N-Alkoxyamines have been previously cleaved using diammonium cerium(IV) nitrate at elevated temperatures (70 °C), however over-oxidation results in the formation of the oxoammonium species which may readily decompose.[20] We now report that removal of the methyl protecting group can be readily facilitated by oxidation with 3-chloroperoxybenzoic acid (*m*CPBA) in DCM in a Cope-type elimination reaction that precludes other functional group modification and provides high yields of the desired nitroxide (Table 1).

Typically, *m*CPBA has been used synthetically as an oxidant in the oxidation of ketones, amines and sulfides, most notably in the Baeyer-Villiger and Rubottom oxidations, as well as being utilised in the Prilezhaev epoxidation of alkenes.[21] Furthermore, *m*CPBA has been demonstrated to be a mild oxidant capable of producing *N*-oxides via electrophilic attack at nitrogen.[22] Subsequent oxygen transfer yields a substrate that is primed for Cope elimination.[23] The mechanism for the application in this context is proposed in Scheme 2. GCMS evidence for the formation of formaldehyde is provided in the Supplementary Information.

In the absence of sensitive functionalities, such as the simple alkyl substituted aryl system **1**, the *m*CPBA promoted deprotection occurs more readily when larger amounts of *m*CPBA are used (Table 1, entries 1 and 2).



Scheme 2 Proposed deprotection mechanism via *N*-oxidation and subsequent Cope-type elimination.

Similarly, the presence of aryl halides has little impact on the nitroxide yield when using excess *m*CPBA (Table 1, entries 3 and 4). Notably, deprotection of the methoxyamine **5** occurs in high yield (88%) even in the presence of aldehydes (Table 1, entry 5). The TEMPO-based methoxyamine **7** also underwent efficient deprotection in high yield (Table 1, entry 6), and this result

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further highlights that benzyl ethers remain unaffected under these conditions. In the case of anthracene methoxyamines such as **9**, deprotection was observed to produce the nitroxide **10** in good yield (75%), however small amounts of fluorescent side-products were also detected (Table 1, entry 7 and 8). These products are expected to arise from partial oxidation of the anthracene core to give substituted anthraquinones, perhaps via the corresponding endoperoxides.[24] Notably, the formation of by-products could be minimised using shorter reaction times and decreased equivalents of *m*CPBA. In the presence of anthracenes with alkyne side-chains, such as in **11**, the deprotection gave the desired nitroxide **12** in reasonable yield (67%) along with similar fluorescent by-products as were seen with **9**. These by-products may also include small amounts of peracid oxidation of the alkyne (Table 1, entry 9).[25] Again, these side reactions could be minimised by immediate quenching of the reaction upon consumption of the starting material (followed via TLC). The nitro group was shown to be quite stable under the deprotection conditions with a high yield (85%) of nitroxide **14** arising from the treatment of methoxyamine **13** (Table 1, entry 10). However, attempted deprotection of 5-amino-2-methoxy-1,1,3,3-tetramethylisoindoline by *m*CPBA gave multiple products after only a few minutes, as indicated by TLC, consistent with competitive oxidation of the primary aryl amine.

We have shown the methoxyamine group to be a highly efficient, chemically robust protecting group for nitroxide syntheses. The introduction of the methyl group was achieved for a variety of nitroxides under mild conditions and in high yield using methyl radicals generated from DMSO, ferrous ions and hydrogen peroxide. Removal of the methyl protecting group was readily achieved using *m*CPBA in DCM in the presence of a variety of functional groups. The facile nature of the Cope-type elimination allows for the methyl ether to be readily cleaved before any significant side reactions occur. If side reactions are possible through over oxidation, then careful monitoring of the reaction and the use of limited amounts of *m*CPBA can still provide the nitroxide in good yield. In this way, deprotection can be induced in good to high yields (67-88%). This new nitroxide protecting group strategy should now enable a large range of synthetic transformations that were not previously possible in the presence of the nitroxide radical and thereby substantially broaden the scope of possible nitroxide applications.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Full experimental procedures; ^{1}H and ^{13}C NMR spectra for compounds **1, 3, 5, 7** and **13**; HPLC chromatograms for compounds **1**, **2**, **5**-**8**, **13** and **14**]. See DOI: 10.1039/b000000x/

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