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# Oxidative rearrangements of bicyclic 2-alkenyl aziridines

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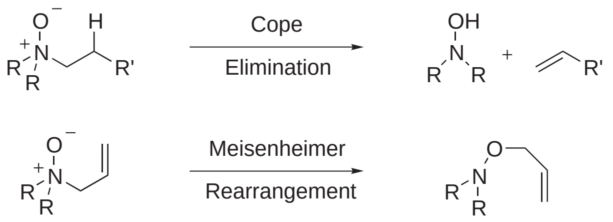
**Abstract**—Oxidation of a range of photochemically generated aziridines gave products arising from a [2,3] Meisenheimer rearrangement of the initial *N*-oxide, followed by further oxidation to give δ-hydroxynitrones. © 2001 Elsevier Science Ltd. All rights reserved.

Amine *N*-oxides are thermally labile species, which can undergo decomposition in a variety of ways.[1] Simple trialkyl *N*-oxides usually undergo Cope elimination upon heating to give a hydroxylamine and an olefin, whilst *N*-allylamine *N*-oxides tend to undergo a concerted [2,3] sigmatropic shift, commonly known as the Meisenheimer rearrangement (Scheme 1). The Meisenheimer rearrangement is perhaps of more interest from a synthetic point of view, as it allows the transfer of both functionality and stereochemical information; however it remains relatively under-utilised by synthetic chemists. In particular there have been no reports of Meisenheimer rearrangements of aziridine *N*-oxides, and only a handful of examples of azetidine *N*-oxides,[2] even though the relief of strain in such systems should provide an additional driving force for the reaction to proceed.

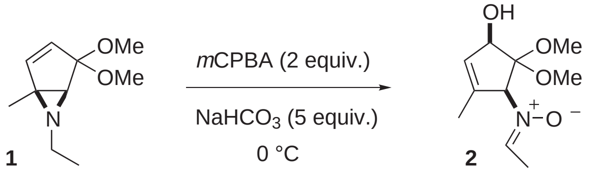


**Scheme 1.** Reactions of tertiary *N*-oxides.

Recent publications from our group[3] and others[4] have shown that the photosolvolysis of *N*-alkylpyridinium salts in water or methanol allows for the facile construction of bicyclic cyclopentenyl aziridines such as **1**. We felt that these conformationally restricted 2-alkenyl aziridines would provide an ideal starting point for a study into the behaviour of aziridine *N*-oxides.

It was found that under the first conditions we tried (portionwise addition of *m*CPBA to a cooled solution of **1** and excess $NaHCO_3$ in $CH_2Cl_2$), two equivalents of oxidant were required for the reaction to go to completion. The product was the nitrone **2**. Despite the low yield, we were encouraged by this result and reasoned that the highly polar *N*-oxide intermediate might be stabilised by the use of a more polar solvent. To our delight the yield improved considerably when the reaction was carried out in methanol or acetonitrile (Table 1).

**Table 1.** Oxidation of the aziridine **1**



| Solvent | Yield of 2 |
|---|---|
| $CH_2Cl_2$ | 26% |
| MeOH | 47% |
| MeCN | 69% |

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*Keywords*: amine oxide; aziridine; Cope elimination; Meisenheimer rearrangement; nitrone; oxidation; oxime.

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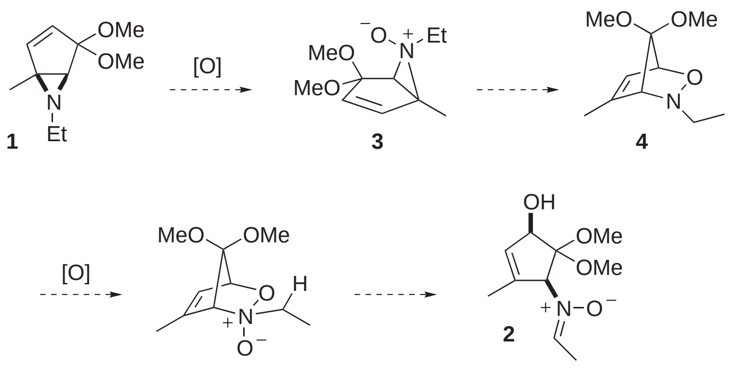
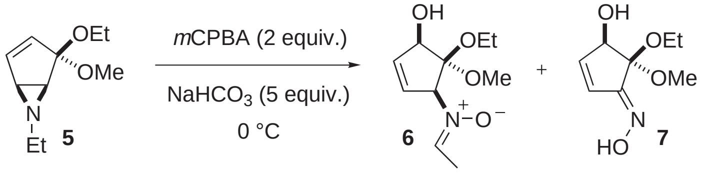


**Scheme 2.** Possible mechanism of the oxidative rearrangement.

**Table 2.** Oxidation of the aziridine **5**



| Solvent | Yield of 6 | Yield of 7 |
|---|---|---|
| $CH_2Cl_2$ | 32% | 16% |
| MeCN | 66% | 8% |
| MeOH | - | 44% |

It seems likely that the reaction proceeds via the mechanism shown below (Scheme 2). Initial oxidation of the aziridine gives the *endo*-*N*-oxide **3**, which undergoes rapid Meisenheimer rearrangement to the bridged bicycle **4**. Further oxidation of the nucleophilic nitrogen, followed by base catalysed N–O bond cleavage gives the nitrone **2**.

The mixed aziridinyl acetal **5** was prepared by the photosolvolysis of 3-ethoxy-1-ethyl-pyridinium tetrafluoroborate in methanol. Upon oxidation of this in $CH_2Cl_2$, we were surprised to observe a mixture of the nitrone **6**[5] and the oxime **7**[6] as products. Switching the solvent to acetonitrile gave an improved yield and selectivity for the nitrone **6**, whilst carrying out the reaction in methanol gave a complete reversal of selectivity, with only the oxime **7** being observed (Table 2).

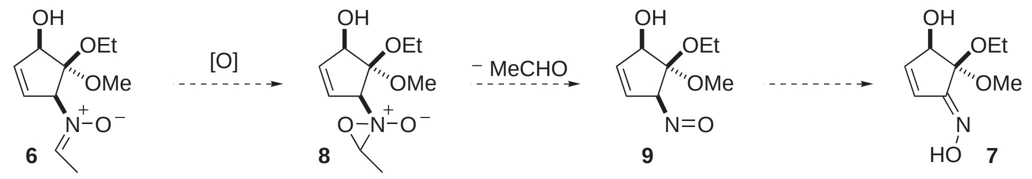
The oxime **7** appears to be a product of over-oxidation of the nitrone **6**. This is supported by the observation that pure **6** is converted to **7** upon treatment with *m*CPBA in methanol. This oxidative cleavage of nitrones has not previously been reported and the likely mechanism would involve oxidation of the nitrone to the oxaziridine **8**, which then loses acetaldehyde to give the nitroso compound **9**. This then tautomerises to the oxime **7** (Scheme 3).

An alternative mechanism involving initial hydrolysis of the nitrone followed by further oxidation was considered unlikely, because the nitrone **6** showed no sign of hydrolysis upon treatment with $NaHCO_3$ in damp methanol.

For good selectivity to be observed, the oxidation of the aziridine **5** would have to be faster than the oxidation of the nitrone **6**. The initial oxidation step is likely to involve a larger increase in dipole moment than the second, hence a polar solvent such as acetonitrile would be expected to improve the selectivity for the nitrone **6**. Methanol is also a very polar solvent; however the aziridinyl nitrogen lone pair of **5** would be deactivated towards oxidation by hydrogen bonding to the solvent. This would reduce the rate of the initial oxidation and perhaps account for the reversal of selectivity. It is possible that the extra steric protection afforded to the nitrone **2** prevents the over oxidation competing in reactions of **1**.

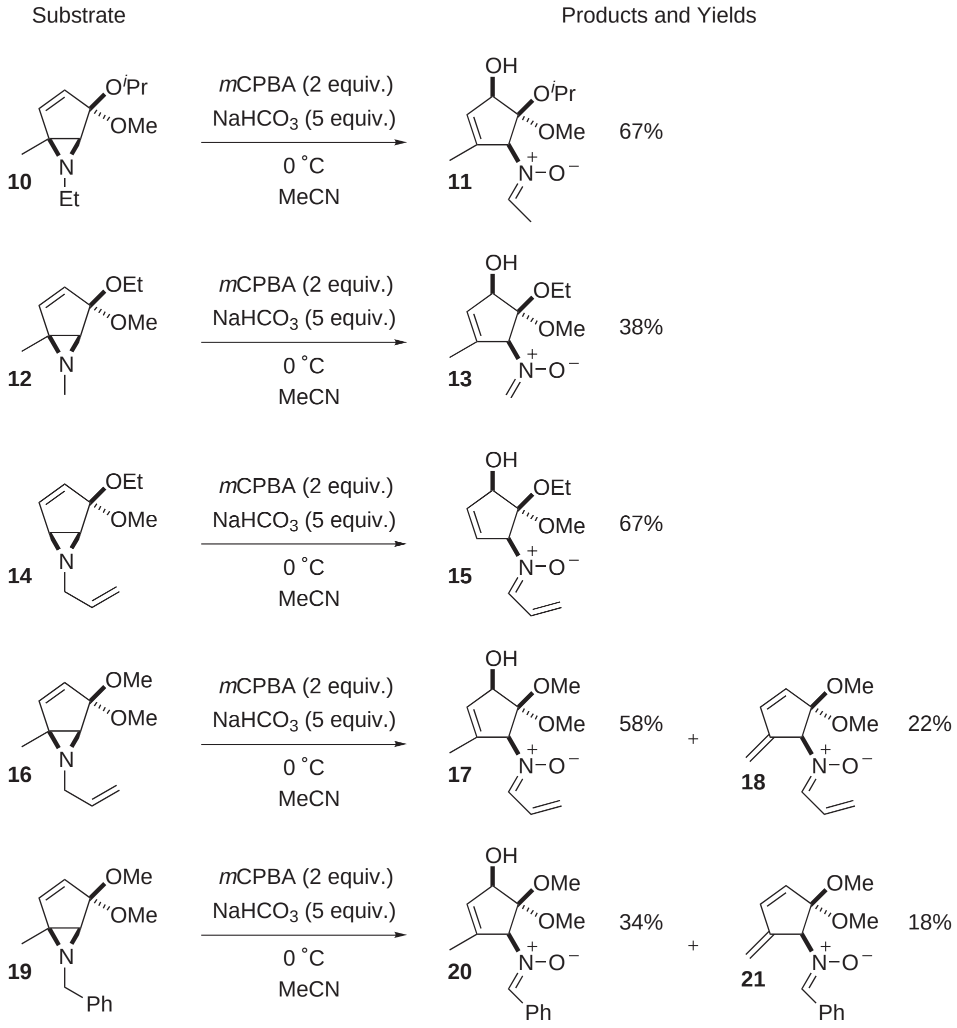
Having established acetonitrile as the best solvent in terms of both yield and selectivity, we carried out the reaction on a range of other aziridines (Table 3).

It is interesting to note that substrates **16** and **19** gave mixtures of products, with the side products **18** and **21**



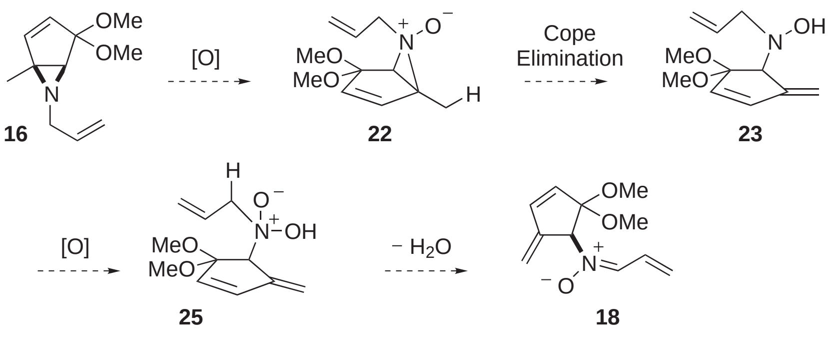
**Scheme 3.** Proposed mechanism for the oxidation of the nitrone **6**.

**Table 3.** Oxidation of a selection of other aziridines



apparently arising from the formation of an *exo* rather than an *endo* aziridine *N*-oxide. In the case of substrate **16** the *exo*-*N*-oxide **22** could form, which would be unable to undergo a Meisenheimer rearrangement. However, a Cope elimination of **22** would be possible and the resulting hydroxylamine **23** could be further oxidised to the nitrone **18** (Scheme 4).[7] The reason why an *exo* aziridine *N*-oxide should form is unclear, although it appears that the presence of an unsaturated group on the aziridine may play a role.

In conclusion we have shown that the oxidation of bicyclic cyclopentyl aziridines gives rise to a variety of rearrangements, including a previously unreported [2,3]



**Scheme 4.** Formation of the nitrone side-product **18** via a Cope elimination.

Meisenheimer rearrangement of an aziridine *N*-oxide and a novel oxidative cleavage of a nitrone to an oxime.[8]

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