# Nitrone Cycloaddition: Peroxy Acid Oxidation of 2-Phenyl-1-oxa-9-azabicyclo[4.3.0]nonane

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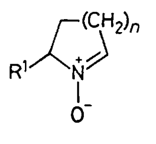
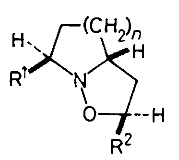
Oxidation of 2-phenyl-1-oxa-9-azabicyclo[4.3.0]nonane (**5**) with *m*-chloroperoxybenzoic acid is not regioselective, in contrast to the case with the corresponding 1-oxa-8-azabicyclo[3.3.0]octane (**2**; $n = 1$, $R^1 = H$, $R^2 = Ph$), affording mainly the keto-nitrone (**7**). On reaction with styrene in boiling toluene the latter forms the oxabicyclononane (**9**).

Cycloaddition of alkenes to 5-alkyl-$\Delta^1$-pyrroline-1-oxides (**1**; $n = 1$, $R^1$ = alkyl) and 2-alkyl-2,3,4,5-tetrahydropyridine-1-oxides (**1**; $n = 2$, $R^1$ = alkyl) followed by reductive cleavage of the resulting isoxazolidine (**2**; $n = 1$ or 2) provides a valuable stereoselective route to *trans*-2,5-dialkylpyrrolidines (**3**, $n = 1$) and *trans*-2,6-dialkylpiperidines (**3**, $n = 2$).[1,2] In the pyrrolidine series the scope and convenience of this sequence has been extended by the observation that isoxazolidines (**2**; $n = 1$, $R^1 = H$) are converted regioselectively into the less substituted nitrones (**4**) on oxidation with peroxy acids.[2] These nitrones can be employed in a second cycloaddition and this sequence has been successfully employed in the synthesis of a number of pyrrolidine alkaloids.[2,3]

In the piperidine series (**2**; $n = 2$, $R^1 = H$), however, we find that the reaction is less selective. It has been reported[2] that the adduct (**5**) from styrene and 2,3,4,5-tetrahydropyridine-1-oxide affords the nitrone (**6**) on oxidation with *m*-chloroperoxybenzoic acid, but in our hands the reaction gave a mixture of nitrones (**6**) and (**7**) in which (**6**) was the minor component (ratio *ca.* 1 : 2). As reported,[2] it reacted readily with a second molecule of styrene in boiling chloroform to give the adduct (**8**).



(1)



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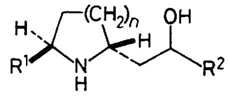

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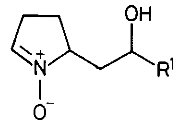

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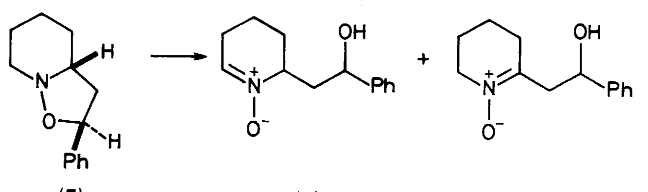
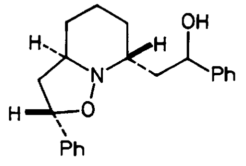
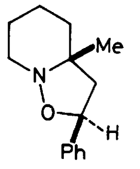


(5) (6) (7)



(8)



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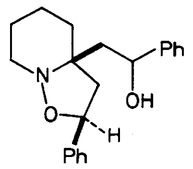
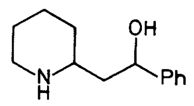


(10)



(11)

The main component of the oxidation of (**5**) was the more substituted nitrone (**7**) which was isolated and identified spectroscopically, particularly by a signal at δ 149.56 in the $^{13}C$ NMR spectrum indicating a vinylic quaternary carbon atom. Its structure was confirmed by an alternative preparation by tungstate-catalysed peroxide oxidation[4] of (**11**). In contrast to (**6**) the isomer (**7**) did not react with styrene in chloroform, but in boiling toluene it readily formed the unexpected product (**9**). The structure of this compound is supported by elemental analysis and the $^{1}H$ and $^{13}C$ NMR spectra, particularly by a signal at δ 62.84 in the $^{13}C$ NMR spectrum indicative of a non-aromatic quaternary carbon. In confirmation of the structure the same compound was obtained by reaction of 6-methyl-2,3,4,5-tetrahydropyridine-1-oxide with styrene in boiling toluene. The stereochemistry was established by nuclear Overhauser enhancement (NOE) experiments and is in line with the expected[3,5] *exo* addition of styrene to the nitrone. It is uncertain whether it arises by decomposition of the adduct (**10**) with elimination of benzaldehyde, detected in the reaction mixture by isolation of its 2,4-dinitrophenylhydrazone, or by retro-aldol reaction of the nitrone (**7**) to give 6-methyl-2,3,4,5-tetrahydropyridine-1-oxide followed by addition of styrene.

We have confirmed the high regioselectivity reported[2] for the oxidation of the pyrrolidine derivative (**2**; $n = 1$, $R^1 = H$, $R^2 = Ph$) but we can offer no convincing explanation for the difference found in the reaction with (**5**). It is clear, however, that the peroxy acid oxidation of isoxazolidines derived from tetrahydropyridine-1-oxide may not be so regioselective as has hitherto been supposed.

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