

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

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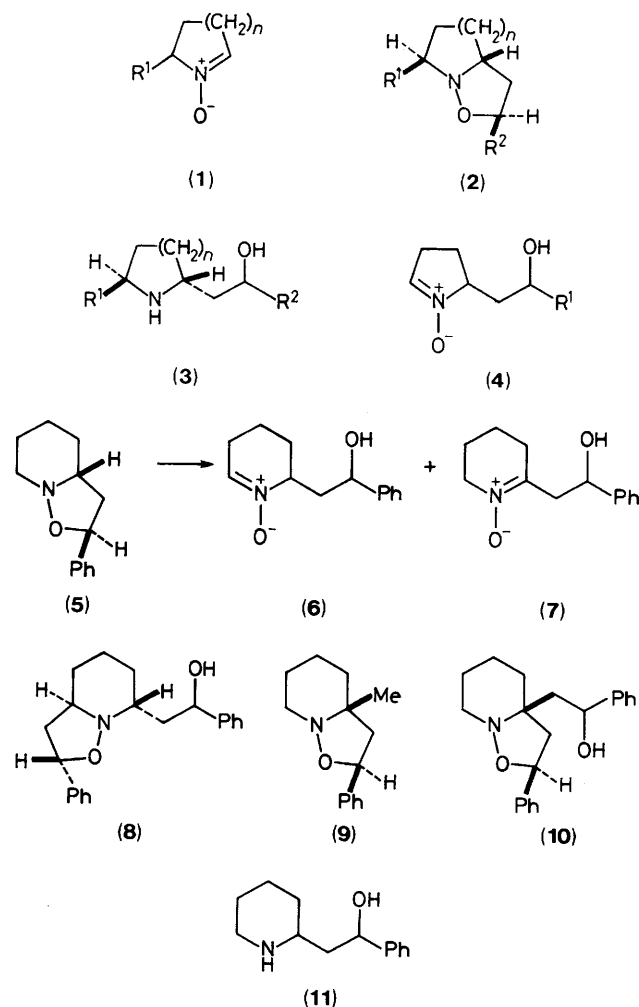
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Oxidation of 2-phenyl-1-oxa-9-azabicyclo[4.3.0]nonane (**5**) with *m*-chloroperoxybenzoic acid is not regioselective, in contrast to the case with the corresponding 1-oxa-8-azabicyclo[3.3.0]octane (**2**; $n = 1$, $R^1 = H$, $R^2 = Ph$), affording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

Cycloaddition of alkenes to 5-alkyl- Δ^1 -pyrroline-1-oxides (**1**; $n = 1$, $R^1 = \text{alkyl}$) and 2-alkyl-2,3,4,5-tetrahydropyridine-1-oxides (**1**; $n = 2$, $R^1 = \text{alkyl}$) 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 reported² 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**).



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 ¹³C NMR spectrum indicating a vinylic quaternary carbon atom. Its structure was confirmed by an alternative preparation by tungstate-catalysed peroxide oxidation⁴ 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 ¹H and ¹³C NMR spectra, particularly by a signal at δ 62.84 in the ¹³C 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 nitron. 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 nitron (7) to give 6-methyl-2,3,4,5-tetrahydropyridine-1-oxide followed by addition of styrene.

We have confirmed the high regioselectivity reported² for the oxidation of the pyrrolidine derivative (2; *n* = 1, R¹ = H, R² = 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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