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Peracid Oxidation of 1-Oxa-8-azabicyclo [3,3,0] octanes: An Entry to the cis-2,5-Disubstituted Pyrrolidines.

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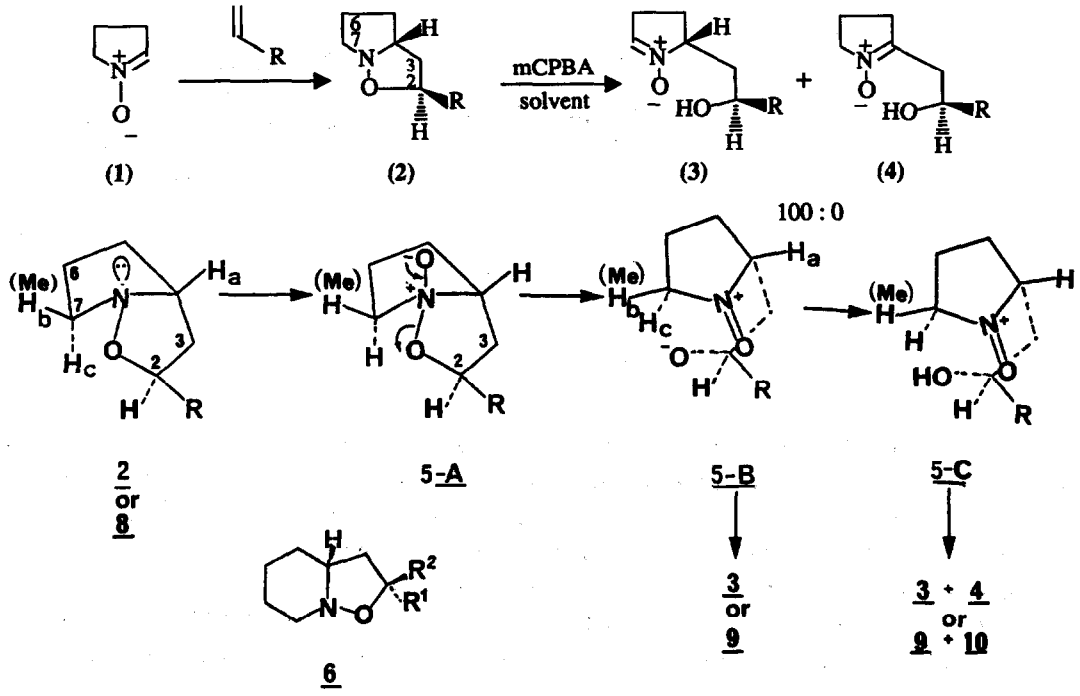
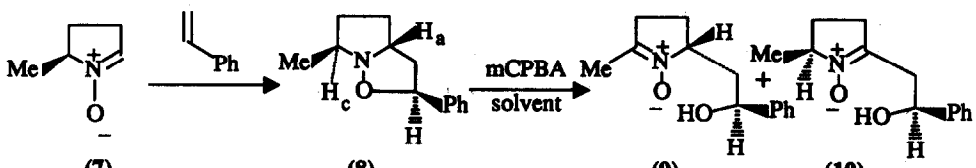
Abstract: Aldonitrones (3), generated by peracid induced ring opening of substituted 1-oxa-8-azabicyclo [3,3,0] octane (2), upon undergoing second cycloaddition, peracid oxidation, followed by hydrogenation, afforded *cis* -2,5-disubstituted pyrrolidine (17), stereoselectively in excellent yield.

Cycloadducts (2), obtained from addition of 1-pyrroline 1-oxide (1) to monosubstituted alkenes, upon treatment with peracid, result in the regiospecific formation of aldonitrones[1,2] (3). In our continuing efforts[1] to deduce the mechanism of the peracid oxidation, we report herein a closer look at the ring opening reaction. While the second cycloaddition involving the less substituted nitrone of the type (3) assures an excellent stereoselective route to *trans* -2,5-dialkylpyrrolidines[2] via the second cycloadducts, no nitrone-based approach is known to date to provide an entry to the corresponding *cis* counterpart. Our interest in alkaloids having *cis* 2,5-disubstituted pyrrolidine moiety[3] also led us to explore the possibility of converting the *trans* cycloadducts[2] to *cis*- 2,5 disubstituted pyrrolidines.



Scheme 1

Eventhough the second cycloaddition sequence has resulted in the synthesis of several interesting alkaloids,[2] the peracid induced ring opening is limited mainly to a few cases of C-2 monosubstituted isoxazolidines (2). Orientation of the lone pair of electrons of nitrogen in the cis-fused sytem (2), dictates the regiochemical outcome of the peracid oxidation.[1] The mechanistic pathway this reaction traverses, envisages the intermediacy of the amine oxide intermediate **5-A** followed by nitroxonium salt **5-B** in which the secondary alkoxide ion finds H_c in its immediate vicinity for fast kinetic deprotonation to result in the exclusive formation of the less substituted nitrone (3). In the homologous series of isoxazolidine[4] (6), where the geometry permits *cis* ⇌ *trans* isomerism of the ring junction by nitrogen inversion,[1,5] peracid oxidation leads to a mixture of regioisomeric nitrones as reported earlier.[1] However, we were unable to offer any compelling evidence that would confirm the abstraction of the proton H_c instead of H_b in aprotic solvent. In order to substantiate the mechanism we synthesised the adduct (8) which is obtained stereoselectively by *exo* addition of styrene onto the less hindered face of the nitrone (7). It is a matter of concern whether the relatively bulky sec-alkoxide **5-B** (generated from isoxazolidine 8) would act fast enough to abstract the crowded tertiary proton H_c before being protonated by m-chlorobenzoic acid (which is produced in equivalent amount during the reaction). To our delight, the adduct (8) upon treatment with MCPBA in dichloromethane at -10°C for 10 min resulted in the exclusive and quantitative formation of the nitrone (9) by abstraction of the proton H_c. However, in the methanol solvent, the product-regiochemistry is changed dramatically owing to the intervention of the protonated specie **5-C** which tautomerizes under thermodynamic-controlled acid-catalysed process resulting in the formation of a mixture of the nitrone (9) and (10) in a 1 : 1 ratio. The proton NMR spectra readily identified the nitrone (9) and (10), the methyl protons of which appeared at δ2.04 (s, with fine splitting) and δ1.40 (d, J 6.0 Hz), respectively.



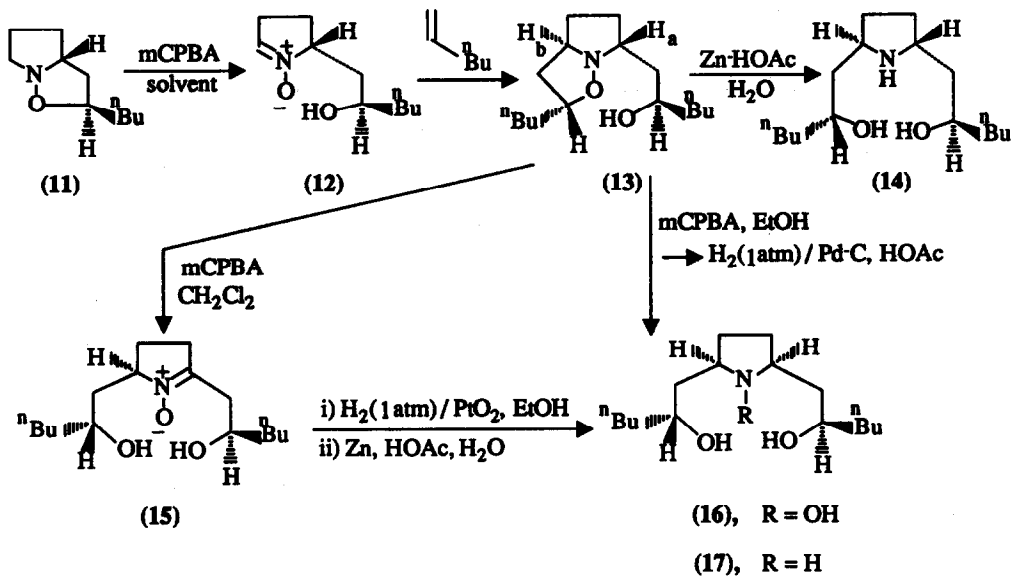
(7) (8) (9) (10)

	(9)	(10)
CH_2Cl_2	100	0
MeOH	50	50

Scheme 2

The nitrone (12), obtained exclusively by peracid oxidation of the nitrone (1) - 1 -hexene cycloadduct (11), underwent second cycloaddition reaction (benzene, 75°C , 12 h) to give the adduct (13) (70%) by exo-mode of attack from the less hindered face of the nitrone (12). Precedent literature[2] and this work unambiguously confirms the *trans* orientation of the 2,5-substituents in (13), which on treatment with zinc and aqueous acetic acid afforded the amine (14) by cleavage of the N-O bond. The substituents were chosen judiciously so that the resulting amine has a C_2 symmetry and as such the carbon NMR spectra revealed the presence of eight well separated carbon signals from sixteen carbons. The proton NMR spectrum revealed the

presence of a multiplet at δ 3.50 assigned to the two equivalent protons at 2 and 5 positions of the pyrrolidine ring. Likewise the equivalence of the protons attached to the carbon bearing the hydroxyl groups is demonstrated by a single multiplet at δ 3.78. In line with the earlier finding (*vide supra*) the second cycloadduct (13) upon second sequence of peracid treatment in dichloromethane afforded the nitrone (15) in quantitative yield by the abstraction of the proton marked as H_a. This second sequence of peracid reaction on a second cycloadduct does indeed represent the first such example in the nitrone cycloaddition chemistry. We were highly gratified to obtain a single hydroxylamine (16) by hydrogenation of the nitrone (15). The *cis* - orientation of the 2,5 substituents is expected since the hydrogenation would take place from the less hindered face. The carbon and the proton NMR spectra confirm the *cis* geometry of the compound (16), which, being unsymmetrical, has non equivalent protons H_a, H_b and H_c, H_d. These four protons appeared as distinct well separated peaks at δ 2.99, 3.20, 3.70, and 3.95. (The proton NMR spectrum was recorded at 55°C in $CDCl_3$ in order to avoid any complication arising out of the nitrogen lone pair inversion in (16).) The only other



Scheme 3

hydrogenation product would be the *trans* isomer with a C_2 symmetry.The absence of the *trans* isomer is confirmed by conversion of the hydroxylamine (16) into the *cis* amine (17) by treatment with zinc and aqueous acetic acid. The NMR spectrum revealed the presence of four non equivalent protons H_a, H_b, H_c, H_d, which appeared at δ 3.30, 3.49, 3.68, 3.84. Both the proton and carbon spectra of the cis amine (17) failed to detect the presence of the trans amine (14). The overall yield for the three steps (13 ---> 16) was found to be 85%. In a separate experiment, the cycloadduct (13) was converted into the amine (17) without isolation of the intermediates (15) and (16). Thus, (13) upon peracid treatment in ethanol followed by

hydrogenation in ethanol-acetic acid mixture afforded the amine (17) as a colourless oil in 92% yield after chromatographic purification (silica, 98:2 ether - methanol saturated with NH_3). (It is to be noted that the abstraction of the proton H_a or H_b would give the dl-pair of the same nitrone 15). The nitrone-based approach thus provides an excellent entry to the trans - as well as the *cis* - 2,5 dialkylpyrrolidines. To the best of our knowledge the synthesis of the amine (17) represents the first utilization of intermolecular nitrone cycloaddition and probably the most efficient way to introduce *cis* substituents at 2 and 5 positions. The scope and convenience of this sequence may very well be extended to construct piperidine derivatives, an important system in great many alkaloids.

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