Intramolecular Cycloadditions of oxazoline N-oxides

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Abstract : Various 2-alkenyl oxazoline N-oxides $\underline{4}$ gave rise via a regio and stereoselective [2+3] cycloaddition to tricyclic compounds $\underline{6}$ and/or $\underline{7}$, precursors of functionalized cyclo alkanones.

In the last few years, the various [2+3] cycloaddition reactions received increasing interest as a valuable tool in natural products synthesis¹. Among the possible dipoles which can be used in these reactions, oxazoline *N*-oxides, a new class of cyclic nitrones, seemed to be very promising. These compounds which can be prepared either by oxidation of the corresponding oxazolines followed by isomerisation of the oxaziridine intermediates²⁻⁴ or by direct condensation of a β -hydroxylaminoalcohol with trialkyl orthoesters or amidoacetals⁵⁻⁶ (scheme 1) showed increasing reactivity when compared with the corresponding nitrones⁵. Moreover these compounds can be considered as equivalents of nitrile oxides. Although the intramolecular nitrile oxide-olefin cycloadditions (INOC) are well known⁷⁻⁹, nothing has been reported about the intramolecular cycloaddition of oxazoline *N*-oxides. As a part of a program directed toward the use of oxazolines in various cycloadditions¹⁰, we disclose in the present paper our preliminary results concerning the achiral version of this reaction.



Scheme 1

Thus 2-alkenyl oxazolines 2 were prepared from the commercialy available 4, 4, 2 - trimethyl - 4, 5 - dihydro oxazole 1 by deprotonation with butyllithium followed by alkylation¹¹ with various alkenyl bromides. Oxidation with MCPBA gave the corresponding oxaziridinooxazolidines 3 in high yields¹².

These compounds were in turn smoothly isomerized over silica gel² and gave rise to the anticipated oxazoline N-oxides 4 (scheme 2). However this isomerization was always followed by partial hydrolysis (z = 10%) of the oxazoline N-oxide moiety giving rise to hydroxylamine esters 5 (Table 1).

After several unsuccessful purifications, the crude mixture of $\underline{4}$ and $\underline{5}$ was directly heated in THF or toluene to give cycloadducts $\underline{6}$ and/or $\underline{7}$ (Table 2. Scheme 2).



Scheme 2

These results deserve some comments. In the cases of compounds $\underline{4a}$, $\underline{4b}$ and $\underline{4c}$ (n = 1) intramolecular cycloaddition were regioselective and gave rise exclusively to the formation of five membered ring adducts <u>6</u> (entries 1-6). Whereas compound $\underline{4d}$ (n = 2; $\mathbb{R}^1 = \mathbb{R}^2 = H$) afforded compound $\underline{7d}$ as the major adduct (entry 7). For the monosubstituted olefin $\underline{4a}$ (n = 1; $\mathbb{R}^1 = \mathbb{R}^2 = H$) cycloaddition occured both in refluxing THF and refluxing toluene to give <u>6a</u> (entries 1 - 2). Repeating these conditions on a mixture of *E* and *Z* isomers of <u>4b</u> afforded a mixture of two isomeric adducts in the same ratio (90:10), altough the more forcing condition (refluxing toluene), gave the better yield (entry 4)¹³.

Finally, it is worthy of note that the cycloaddition took place even with a trisubstituted olefin (entry 6). The resulting adduct <u>6c</u> (n = 1; $R^1 = R^2 = Me$) underwent spontaneous hydrolysis, leading to the less sterically, congested cyclopentanone derivative <u>8</u> when a trace of water was present.

R Br	<u>2</u> Yield %	<u>3</u> Yield %	4 ± 5 Ratio
$a:n=1 R^1=R^2=H$	62	89	86 : 14
$b: n = 1$ $R^1 = Me; R^2 = H$	76	97	90 : 10
$c: n = i R^1 = R^2 = Mc$	62	98	88 : 12
$\mathbf{d}:\mathbf{n}=2\mathbf{R}^1=\mathbf{R}^2=\mathbf{H}$	64	88	88 : 12

Table 1. Preparation of oxazoline derivatives 2, 3 and 4

Entry	Starting material	Solvent	Temp. (°C)	Time (h)	Yield (%) ^(a)		
	4 + 5				6	7	8
1	a	THF	66	4	85		-
2		Toluene	110	1	69	-	-
3	ь	THF	66	5	19	-	-
4		Toluene	110	1.5	62 ^(b)		-
5	u -	11	40 (US)	16	34	-	-
6	c	"	110	2.5	35	-	53
7	d	"	110	10	16	49	

a : overall yields from 3

b : mixture of two isomers <u>6b</u> $R^1 = Me$; $R^2 = H$ and $R^1 = H$; $R^2 = Me$ ratio : 90:10

Table 2. Cycloadditions of oxazoline N-oxides 4

In a preliminary experiment, hydrolysis and hydrogenolysis of the oxazolidinoisoxazolidino rings were studied on the major isomer of adduct <u>6b</u>. This sequence of reactions can be performed as a one pot process and gave rise to the cyclopentanone derivative 9 (47%) (Scheme 3) which showed the same spectral data than the compound previously described by Curran¹⁴. This correlation allowed the attribution of the relative configurations for this compound and corroborate the configurations deduced from the ¹HNMR spectrum of its precursor <u>6b</u>.





Further studies concerning the enantioselective version of this cycloaddition and the use of this reaction in synthesis are in development in our laboratory.

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