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Stereochemical Studies on the 1,3-Dipolar Cycloaddition of 3,4,5,6-Tetrahydropyridine 1-Oxide to 2(5*H*)-Furanones

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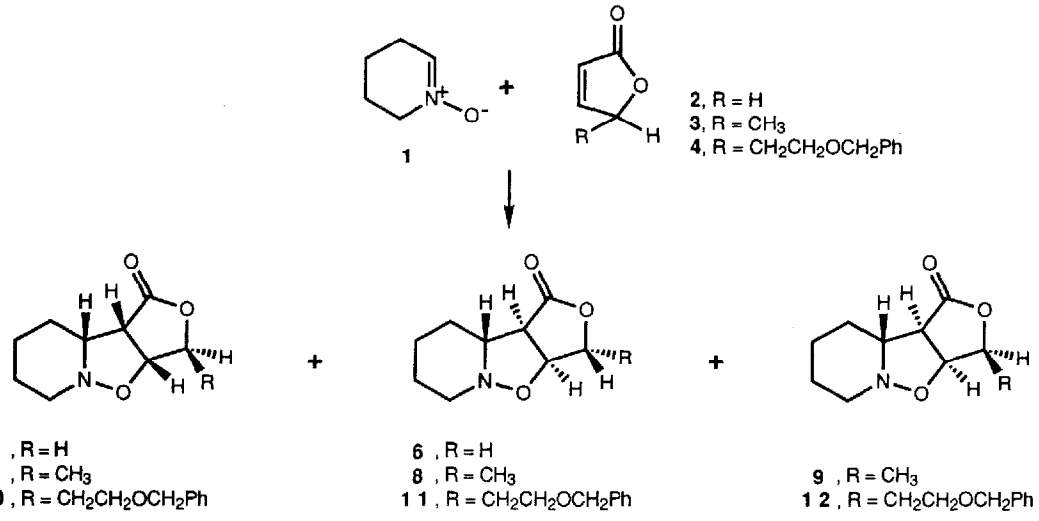
Abstract.- The 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydropyridine 1-oxide, **1**, to 2(5*H*)-furanones **2**, **3**, and **4** is investigated. Crucial nmr data are indicated to determine the conformational equilibria and stereochemistry of the adducts. The major products arise from *exo* transition states.

The 1,3-dipolar cycloaddition reaction of nitrones to alkenes is a widely employed method for the preparation of substituted isoxazolidines, which are useful intermediates for the synthesis of nitrogen-containing natural products.[1]

Our synthetic plans in the field of alkaloids required that we have some knowledge of the stereochemical course of the cycloaddition of 3,4,5,6-tetrahydropyridine 1-oxide, **1**, to β-substituted-α,β-unsaturated carboxylic acid derivatives. Under kinetic control conditions the stereochemistry of the products can be directly related to the *endo/exo* selectivity of the cycloaddition, but this stereochemistry is often difficult to establish due mainly to the conformational complexity that compounds containing the perhydroisoxazolo[2,3-*a*]pyridine system may present in solution.[2] Therefore stereochemical reassignment of some cycloadducts has been necessary.[3]

Steric as well as secondary orbital interactions have been usually invoked to explain the diastereoselectivity of the cycloaddition reaction of nitrones.[1,2b,2d,3,4] Recently the generally accepted assumption that secondary orbital interactions favour the *endo* mode of approach in the transition state has been questioned by Gandolfi and col.[5] These authors state that an "*endo* rule" does not hold for nitrone cycloadditions to electron-poor *Z*-dipolarophiles. At the beginning of our work only few examples of such type of reaction were described using a 2(5*H*)-furanone as the dipolarophile[6] and almost no stereochemical information was given. We previously reported the cycloaddition of dipole **1** to 5-methyl-2(5*H*)-furanone, **3**,[2b] and we describe now the reaction of **1** with crotonolactone, **2**, and 5-(2-benzyloxy)ethyl-2(5*H*)-furanone, **4**, (Scheme 1) and a straightforward methodology based on the observation of a few selected nmr data to assign the stereochemistry of the cycloadducts and therefore to deduce the diastereoselectivity of these reactions.

Compounds **1**[7] and **2**[8] were prepared according to literature procedures; lactone **3** was synthesized from phenylselenoacetic acid and (2-benzyloxy)ethyloxirane[9] following our previously described method[10] in a 61% overall yield. This highly functionalized C_6 synthon has recently received much attention as a useful intermediate in organic synthesis.[11]



Scheme 1

A first set of cycloaddition reactions were performed in $CHCl_3$ under mild temperature conditions to ensure a kinetic control with a high degree of diastereoselectivity. Then, the reactions were repeated in boiling toluene in order to allow isolation of the minor adducts. Reaction conditions and yields are given in Table 1. In all cases flash column chromatography of the crude afforded two different fractions of diastereoisomeric cycloadducts **5-12**. The less polar fraction was always the minor one and it contained a unique isomer identified as an *endo* adduct **5**, **7**, or **10** (*vide infra*). The more polar major fraction corresponded to *exo* adducts: **6** and non-separable mixtures of **8-9**, and **11-12**.

Table 1. Reactions of Nitrone **1** with 2(5*H*)-Furanones **2**, **3**, and **4**.

lactone	temp (°C)	reaction time	yield (%)	*exo/endo*	*exo anti/exo syn*[a]
2	4	30d	90	31	-
2	110	15h	79	6	-
3	40	17h	73	21	8
3	110	15h	84	7	2
4	25	18d	70	[b]	10
4	110	15h	78	14	6

[a]*anti*: **8** and **11**, *syn*: **9** and **12**; [b]only traces of adduct *endo* were detected.

Most nmr spectra of these fractions at room temperature show broad absorptions due to the six-membered ring and nitrogen inversion processes (Figure 1). By lowering the temperature, two separate sets of well resolved signals can be observed for the *cis* and *trans* conformers. The chemical shift differences between the two protons attached to C_6 indicate a *cis* or *trans* fusion between rings A and B:[12] in the rigid *trans* invertomers differences of *ca.* 1 ppm are observed between equatorial and axial protons at C_6. The conformational equilibrium position, along with significant chemical shifts and coupling constant values for compounds **5-12** are given in Table 2.

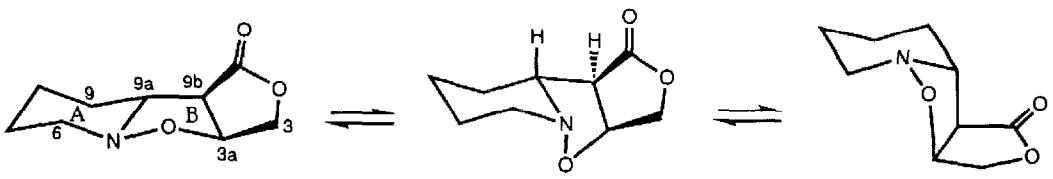


Figure 1. Conformational equilibrium of *exo* adduct **6**.

Table 2. Significant pmr Data (acetone-d_6, 400 MHz) for Adducts **5**-**12**.

Comp.	Temp.	A/B fusion	δH_{9a}	δH_{6ax}	δH_{6eq}	$J_{9a,9b}$	$J_{3,3a}$	% conf.
5	250K	*trans*	2.37	2.37	3.36	6.7	-	>98
6	250K	*trans*	2.17	2.49	3.36	8.4	-	25
		cis	3.42	3.25/3.00		1.9	-	75
7[2b]	253K	*trans*	2.35	2.35	3.33	7.2	2.0	>98
8[2b]	253K	*trans*	2.16	2.45	3.32	8.3	1.2	20
		cis	3.40	3.20/2.96		-	1.6	80
9[2b]	253K	*trans*	2.15	2.48	-	8.0	-	6
		cis	-	- /2.92		-	5.4	94
10	250K	*trans*	2.38	2.38	3.37	7.0	2.3	>98
11	270K	*trans*	2.20	2.50	-	8.3	1.2	25
		cis	3.43	3.25/3.09		2.0	1.7	75
12	270K	*cis*	-	-	-	-	5.0	-

For adducts **5** and **6** a complete pmr and cmr data assignment could be done with the help of SEFT, COSY, and $^1H/^{13}C$ correlation spectra. Presaturation of the signal corresponding to H_{9a} caused a nOe effect on H_{9b} of 6% and 2.5% for compounds **5** and **6** respectively. This experiment is consistent with the stereochemistry depicted in Scheme 1 for these cycloadducts. Thus, analysis of molecular models denotes that in *endo* stereoisomers protons H_{9a} and H_{9b} are almost eclipsed in both *trans* and *cis* conformers; by contrast, in *exo* adducts the former protons are close to an antiperiplanar arrangement in *trans* conformer, while in the two possible *cis* fused conformations the dihedral angle $H_{9a}CCH_{9b}$ has values of *ca.* 90° and 180°. Therefore, a small coupling constant value between H_{9a} and H_{9b} (*ca.* 2 Hz) is only compatible with an *exo* stereochemistry with a *cis* ring fusion. These observations were crucial since a perfect matching was found with the data encountered for the other compounds, allowing their unambiguous identification. It is noteworthy the predominance of the *cis* conformers in *exo* cycloadducts, since a *trans* fusion is usually preferred in indolizidine and related systems, when the piperidine ring has not additional substituents.[2a,12a]

Other critical data for the stereochemical assignment can be obtained from the cmr spectra (see Table 3): in *trans* conformers, C_9, C_{9a} and C_{9b} are upfield shifted in *endo* with respect to *exo* adducts, due to their position relative to the pseudoaxial carbonyl group.[13] Finally, the stereochemical relationship between C_3 and C_{3a} can be derived from $J_{3,3a}$: a small value in the range 1-2 Hz (compounds **7**, **8**, **10**, and **11**) is indicative of a *trans* geometry[14], namely an antifacial approach in the transition state.

In conclusion, we have presented new examples of nitrone cycloadditions to *Z*-1,2-disubstituted electron-deficient alkenes, where the *exo* transition state predominates. To establish the stereochemistry of the adducts, we suggest a careful investigation of their nmr spectra, looking for the significant data in the following sequence of steps: i) analysis of the *cis* and *trans* conformers separately; ii) observation of the $J_{9a,9b}$ for the *cis* invertomer: a small value in the range 0-2 Hz is indicative of *exo* stereochemistry; iii) comparison of the

^{13}C chemical shifts for C_9, C_{9a}, and C_{9b} in the *trans* invertomer: upfield values are observed in the *endo* stereoisomers related to the *exo*.

Table 3. Significant cmr Data (100 MHz, δ Values) of Compounds **5-11** in their *trans* A/B Fusion.

Comp.	Temp.	Solvent	C_9	C_{9a}	C_{9b}
5	298K	acetone-d_6	26.5	68.9	50.5
6	260K	acetone-d_6	29.5	71.9	53.7
7[2b]	298K	$CDCl_3$	25.9	68.6	51.0
8[2b]	270K	$CDCl_3$	28.5	70.4	53.1
9[2b]	270K	$CDCl_3$	28.9	71.2	-
10	298K	acetone-d_6	26.8	69.1	51.4
11	270K	acetone-d_6	29.8	-	54.2

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