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THE 1,3-DIPOLAR CYCLOADDITION OF 3-METHYL-5-PHENYLISOXAZOLINE N-OXIDE

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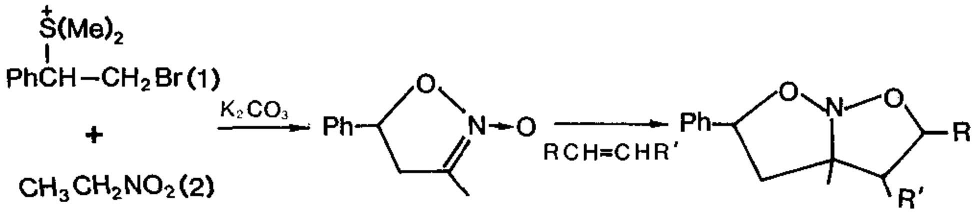
Abstract — The title isoxazoline N-oxide 3 underwent 1,3-dipolar cycloaddition with a number of electron deficient olefins regiospecifically to give isoxazolizidines 4. All four possible geometric approaches of addenda leading to successful cycloadditions occurred to give mixtures of products. A pressure at 1-2 KBar did accelerate the rate of the 1,3-dipolar cycloadditions significantly without improving the selectivity of geometrical orientations of approaches: the poor selectivity was ascribed to the lack of ground state molecular association in solution.

Isoxazoline N-oxides, such as 3, are cyclic derivatives of nitronic esters[1] that possess the structural feature of N-alkoxynitrones and have been shown to add to olefins in the 1,3-mode to give isoxazolizidines[2-4], such as 4, or the monocyclic analogues[5-8]. These reactions are analogous to those extensively studied 1,3-dipolar additions of nitrones that have contributed significantly to the synthesis of heterocyclic compounds[9-11] and mechanistic investigations[12,13]. The N-oxide 3 has been prepared readily by stepwise condensations of sulfonium salt[14] 1 and nitroethane 2 in our group[15]; this compound 3 possesses suitable features to examine the stereochemical consequence of its 1,3-dipolar cycloaddition. First of all, the geometry of the nitronate group is held rigid and the inversion at the N-center is not permitted. Second, the phenyl group in 3 serves as an internal marker to observe tortional movements of the methyl group (See Scheme 1.). In acetonitrile, N-oxide 3 and an electron deficient olefin reacted slowly at temperatures <100°C to give isoxazolizidine type compounds 4 without forming other by-products. Most of these adducts were isolated by HPLC



3

4

This paper is dedicated to Professor Sir Derek H.R. Barton on the occasion of his 70th birthday.

and/or column chromatography but their percentage yields, including those not isolated in the state, could be determined by HPLC and ^{1}H nmr analyses (Table 1). Dimethyl maleate, stilbene and vinyl acetate were shown to be unreactive with **3**. The products from the cycloaddition of vinyl methyl ketone and maleic anhydride to **3** decomposed rapidly during purification. The conditions and isolated 1,3-cycloaddition products **4** are summarized in Table 1 and their structures in Scheme 1.

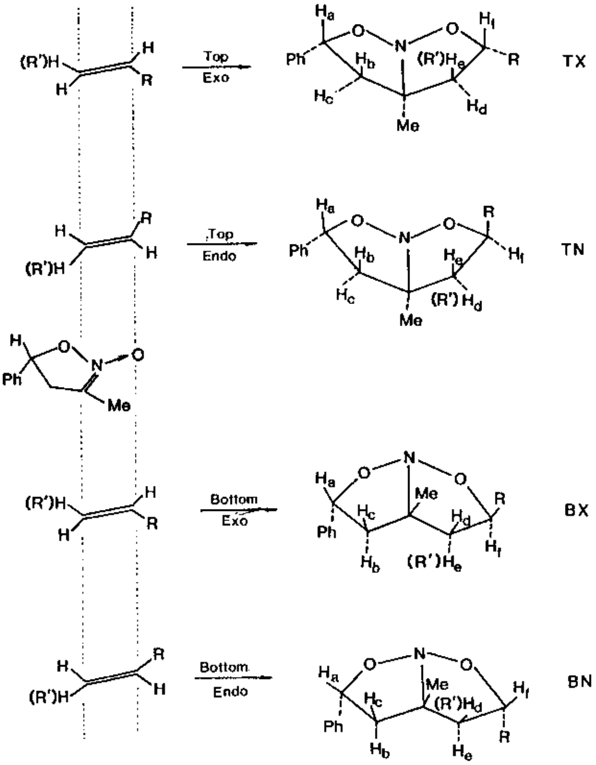
TABLE 1. 1,3-Dipolar cycloaddition of N-oxide **3** to olefins in acetonitrile.

			Relative Percentages (mp.°C)			
Olefins	Conditions	Adducts	**TX**	**TN**	**BX**	BN
$CH_2{=}CHCO_2CH_3$ (**5**)	45°, 144h	**10**	50(78-80)	19(71-74)	19(92-94)	(12)^a
	2.07 KBar, 50h	**10**	46	19	24	(11)
$C_6H_5CH{=}CH_2$ (**6**)	50°, 120h	**11**	54(140-143)	46(121-123)		0
$CH_2{=}CHCN$ (**7**)	95°, 120h	**12**	51(98-99)	(18)^b	(20)^b	(11)^b
H_3CO_2CCH (**8**)	85°, 432h	**13**	50(96-98)	31(110-112)	0	(19)^{c,d}
$\|$ $CHCO_2CH_3$	2.07 KBar, 240h	**13**	63	25	0	(12)
NCCH (**9**)	82°, 168h	**14**	71(119-120)	(14)^{c,e}	(10)^c	(5)^{c,e}
$\|$ CHCN	1.38 KBar, 50h	**14**	87	(7)	(4)^f	(2)

a) A mixture of **10BN**/**10TN** = 7/3; the structure of 10BN was not established. b) The spectral data were collected from mixtures of isomers and the structural assignments were not confirmed c) The structures were assigned based on the spectral data of impure speciments. d) The specimen was contaminated with a few % of other isomers. e) The specimen contains **14TX**, **14TN** and **14BN** in a ratio of 4:21:4. f) The specimen contains 14TX, 14TN, 14BX and 14BN in a ratio of 3:4:32:1.

The structures of the products were determined from the spectroscopic data and elemental analyses. In certain cases, impure samples were used for the spectroscopic measurements and the useful data could be obtained by subtraction techniques. All cycloadducts showed a common ir absorption at ca. 1000 cm^{-1} characteristic of the O-N-O group in addition to other absorptions. They also exhibited pertinent ^{13}C nmr and mass spectra that indicate the presence of expected functional groups. However, the stereochemistry of the cycloadducts was confirmed largely from ^{1}H nmr spectroscopy using decoupling as well as NOE techniques. The interpretations of these data were greatly fascilitated since the X-ray crystallographic structure of an isoxazolizidine[4] showed that the two fused five-membered rings had "envelope"

SCHEME 1



conformations. Isoxazolizidines 10 - 12 derived from monosubstituted olefins exhibit two similar ABX patterns with the X-proton in lower fields in their ^1H nmr spectra and comparable ^{13}C nmr chemical shifts for the C3 - C7 and C4 - C6 pairs. These leave no doubt that the substituent group is located at the C7-position as shown in Scheme 1. Using the styrene adducts **11** as models, one of the two products is **11TN** (which is identical to **11BX**) since it shows two sets of signals for these protons and carbons. The other product is **11TX**,(which is the diastereoisomer to **11BN**) since it shows only one set of ABX pattern and ^{13}C signals owing to the presence of a plane of symmetry. The relative orientations of the substituent groups in these two isoxazolizidines are clearly resolved from NOE and coupling constants determinations. The latter sample shows that H_c is located on the same side of the CH_3 group and *trans* to H_a (J_{ac} = 10 Hz) and can be assigned to **11TX** but not to **11BN**. The former sample (**11TN**) exhibits strong NOE enhancements, suggesting that the CH_3, H_f, H_c and H_d, but not H_a, are in the *cis* configuration to each other. Strong NOE enhancements also place the H_a-H_b and H_d-H_f pairs in the *cis*-relation in both samples (**11TX** and **11TN**). The stereochemical relations of other 1,3-dipolar cycloadducts in Table 1 are determined similarly and the pertinent data are summarized in the thesis submitted[15]. Also, all isoxazolizidines **13** and **14** derived from disubstituted olefins show one set each of ABX and AB systems; the protons in the latter AB system (H_d or H_e with respect to H_f) are shown to be in the *trans*-relations.

The stereochemical consequences described above lead to the following conclusions on the mechanism of the 1,3-dipolar addition of isoxazoline N-oxides. First of all, the addition of monosubstituted olefins is regiospecific in that the substituent group is located at the C7-position, i.e., closer to the oxide terminus. Second, as the *trans*-geometry of disubstituted olefins is completely retained in the final products, this suggests that the cycloaddition follows concerted pathway in analogy to most 1,3-dipolar additions[9,10,12,13]. Third, the stereoselectivity during the approach of addenda is not high although the least hindered approach (the top exo mode) generally dominates the reaction over other approaches (Scheme 1). The four possible geometrical assemblies of bringing addenda to productive approaches are shown in Scheme 1, each of them leads to the corresponding final product; they are arbitrarily designated as top exo(**TX**), top endo(TN), bottom exo(**BX**) and bottom endo(BN). The low stereoselectivity of the approach of addenda probably arises from the lack of ground state molecular associations between addenda as shown by uv spectroscopic studies[15]. The lack of molecular associations also explains the failure to improve the stereoselectivity in reactions at 1-2 KBar. It must be pointed out that the rate of the cycloaddition is considerably increased at these high pressures.

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