

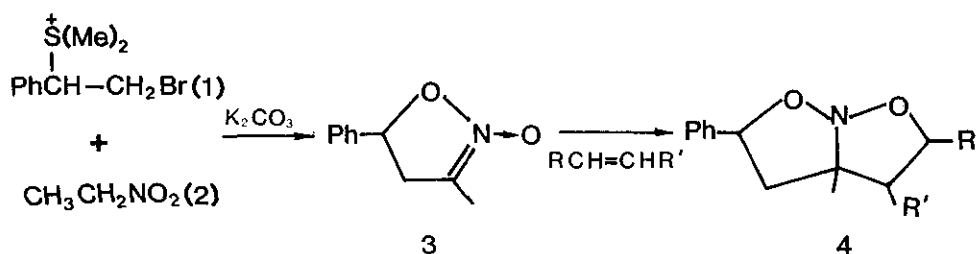
THE 1,3-DIPOLAR CYCLOADDITION OF 3-METHYL-5-PHENYLISOXAZOLINE N-OXIDE

Yuan L. Chow, Y. Yuen Shu, Bert H. Bakker, and K. Somasekharen Pillay

Department of Chemistry, Simon Fraser University, Burnaby, B.C. CANADA V5A 1S6

Abstract — The title isoxazoline N-oxide 3 underwent 1,3-dipolar cycloaddition with a number of electron deficient olefins regioselectively 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 esters¹ that possess the structural feature of N-alkoxynitrones and have been shown to add to olefins in the 1,3-mode to give isoxazolizidines²⁻⁴, such as 4, or the monocyclic analogues⁵⁻⁸. These reactions are analogous to those extensively studied 1,3-dipolar additions of nitrones that have contributed significantly to the synthesis of heterocyclic compounds⁹⁻¹¹ and mechanistic investigations^{12,13}. The N-oxide 3 has been prepared readily by stepwise condensations of



sulfonium salt¹⁴ 1 and nitroethane 2 in our group¹⁵; 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 torsional movements of the methyl group (See Scheme 1.). In acetonitrile, N-oxide 3 and an electron deficient olefin reacted slowly at temperatures $<100^\circ\text{C}$ to give isoxazolizidine type compounds 4 without forming other by-products. Most of these adducts were isolated by HPLC

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 ^1H 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.

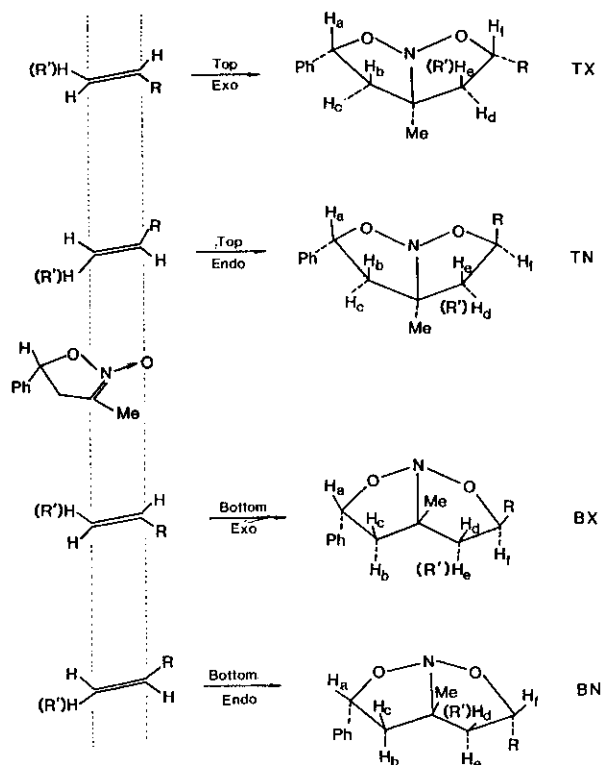
TABLE 1. 1,3-Dipolar cycloaddition of N-oxide 3 to olefins in acetonitrile.

Olefins	Conditions	Adducts	Relative Percentages (mp. °C)			
			TX	TN	BX	BN
$\text{CH}_2=\text{CHCO}_2\text{CH}_3$ (5)	45°, 144h	10	50(78-80)	19(71-74)	19(92-94)	(12) ^a
	2.07 KBar, 50h	10	46	19	24	(11)
$\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$ (6)	50°, 120h	11	54(140-143)	46(121-123)		0
$\text{CH}_2=\text{CHCN}$ (7)	95°, 120h	12	51(98-99)	(18) ^b	(20) ^b	(11) ^b
$\text{H}_3\text{CO}_2\text{CCH}=\text{CH}_2$ (8)	85°, 432h	13	50(96-98)	31(110-112)	0	(19) ^{c,d}
	2.07 KBar, 240h	13	63	25	0	(12)
$\text{NCCH}=\text{CHCN}$ (9)	82°, 168h	14	71(119-120)	(14) ^{c,e}	(10) ^c	(5) ^{c,e}
	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 specimens. 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 ^1H nmr spectroscopy using decoupling as well as NOE techniques. The interpretations of these data were greatly facilitated since the X-ray crystallographic structure of an isoxazolizidine⁴ 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 CH₃ 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 CH₃, 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 submitted¹⁵. 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 studies¹⁵. 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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Received, 21st July, 1988