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STEREOSELECTIVITY IN INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS. NITRILE OXIDES VERSUS SILYL NITRONATES[1]

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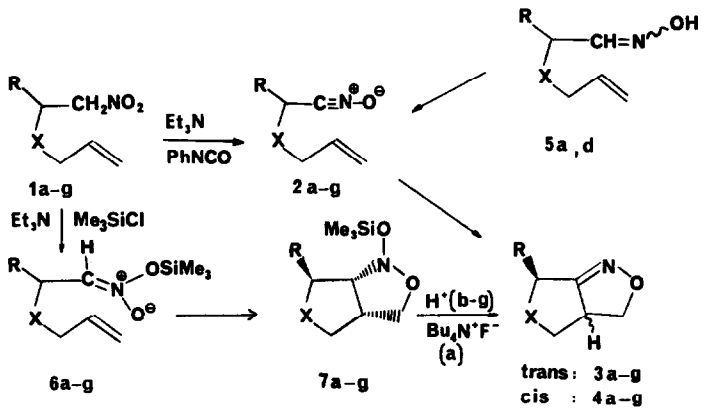
Abstract: Unlike nitrile oxides, silyl nitronates undergo highly stereoselective intramolecular cycloadditions to produce functionalized carbocyclic or heterocyclic rings.

C-C bond forming reactions leading to stereoselective ring closure are of pivotal interest in organic synthesis. Among these, the intramolecular nitrile oxide olefin cycloaddition (INOC) reaction has been studied extensively by various groups.[2] The resulting isoxazolines are versatile compounds, which can be converted to γ-amino-alcohols, β-hydroxy ketones and various other functional groups and provide a useful entry into natural product synthesis.[2] Whereas nitrones undergo stereospecific intramolecular cycloadditions to alkenes,[3] the stereochemistry of intramolecular silyl nitronate olefin cycloadditions have not been examined. Silyl nitronates can be considered as synthetic equivalents of nitrile oxides in their reaction with olefins,[4] since the resulting N-silyloxyisoxazolidines are readily transformed into isoxazolines upon treatment with acid or tetrabutylammonium fluoride.

We now report on the intramolecular silyl nitronate olefin cycloaddition (ISOC) and the high stereoselectivity observed in these reactions leading to stereoselectively functionalized heterocyclic and carbocyclic rings.

For comparison between INOC and ISOC stereochemistry, the unsaturated nitro compounds **1a-g**[5] were first treated with PhN=C=O and triethylamine at room temperature. This gave the reactive nitrile oxides **2**, which were not isolated, but cyclized to a mixture of trans- and cis-isoxazolines **3a-g** and **4a-g**, with the ratio of products **3** and **4** depending on the nature of the R substituent and the side chain.[6]

Allylether **1** (X:O) yielded a 2.4:1 mixture of **3a:4a**. The same ratio was observed earlier[7] starting from oxime **5**, which indicates that the nitrile oxide **2a** is the common intermediate. For thioethers **3** or **4** (b-e) the nitro route provides the only entry, since attempts to oxidize oxime **5d** to the nitrile oxide failed due to the sensitivity of the sulfur function. The greater selectivity in the ether over the thioether system



may be due to the larger sulfur atom allowing for a more flexible transition state with smaller differences between the trans and cis isomer. The stereoselectivity was reversed for cyclization to the carbocyclic system where cis-isomers 4f-g predominated.

The same unsaturated nitro compounds 1a-g were converted smoothly with Me_3SiCl/Et_3N at room temperature into silyl nitronates 6. These underwent a facile ISOC at room temperature to the N-trimethylsilyloxy isoxazolidines 7, which upon treatment with diluted HCl (7b-g) or tetrabutylammonium fluoride (7a) gave the trans isoxazolines 3a-g as the sole stereoisomers. The stereochemistry of the cycloaddition was determined by NOE experiments.

Table 1: Ring Closure of 1a-g to trans 3a-g and/or cis 4a-g. [a]

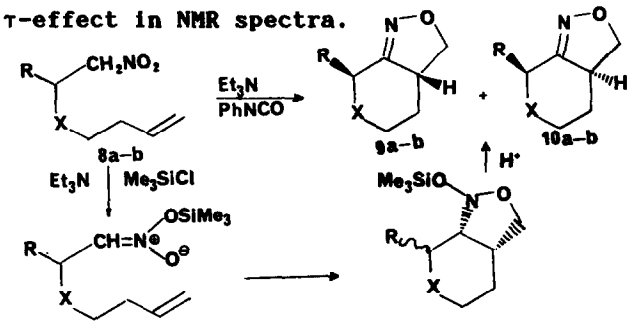
R	X	INOC reaction		ISOC reaction	
		yield %	ratio 3:4	yield %	ratio 3:4[a]
a Me	O	87	2.4:1	74	>99:1
b Me	S	84	1:1	89	>99:1
c iPr	S	90	1:1	84	>99:1
d Ph	S	80	3:2	85	>99:1
e 4-MeO-C_6H_4	S	63	3:2	87	>99:1
f Me	$C(COOMe)_2$	81	1:7	84	>99:1
g 4-MeO- C_6H_4	$C(COOMe)_2$	90	1:5	91	>99:1

(a) Isomer 4 below the NMR detection limit of 1%.

The ISOC reaction in deuterochloroform was followed by means of ^1H NMR spectroscopy. A spectrum taken 5 minutes after addition of Me_3SiCl and Et_3N to a deuterochloroform solution of 1a at room temperature showed clean conversion to 7a. No trace of starting material 1a, or silyl nitronate 6a was detected.

Under the same conditions (5 min) with nitro compound 1c the spectrum showed only silyl nitronate 6c. Gradually 6c underwent intramolecular cycloaddition to 7c. NMR spectra taken after several intervals of time permit the approximation of the half life for 6c of 1 hr at room temperature. Malonate 1f did silylate much slower because of steric hindrance. In this case the rate of silylation was of the same order as cycloaddition, so that only a trace of silyl nitronate 6f could be detected throughout the reaction, which takes about 4h to reach completion.

We were also able to use the ISOC reaction in the formation of 6-membered rings, although the cycloaddition was much slower and less stereoselective. Nevertheless, there was a marked effect of changing from nitrile oxide to silyl nitronate. While the INOC reaction of 8 gave a 1:5 mixture of 9:10, this ratio for the silyl nitronate pathway was 5:3. The assignment of stereochemistry to 9 and 10 was possible on the basis of the well known π-effect in NMR spectra.



Further applications of the high stereoselectivity of the ISOC reaction in the synthesis of 5- and 6-membered rings are being explored.

General procedure for the ISOC reaction

Nitroalkene 1e (253 mg, 1 mmol) was dissolved in 5 ml benzene. Triethylamine (0.12 g, 1.2 mmol) was added to the stirred solution, followed by 1.1 mmol (0.119g) of trimethylsilyl chloride. A precipitate formed and the resulting mixture was allowed to stand overnight at room temperature and treated with 5 ml of 5% HCl. The benzene layer was washed with water (10 ml) and brine (10 ml) and dried ($MgSO_4$). Evaporation gave an oil, which was chromatographed over silica gel to yield 87% of fused isoxazoline 3e. The product was crystallized from petroleum ether/ether, mp 112-113°C. ^1H NMR ($CDCl_3$, TMS) δ 2.90 (dd, J=10.5, 9.5, 1H, CH_2S), 3.18 (dd, J=10.5, 8.5, 1H, CH_2S), 3.80, (s, 3H, CH_3O), 4.10 (dd, J=10, 8, 1H, CH_2O), 4.28 (dddt, J=10, 9.5, 8.5, 1, 1H, $CH_2\underline{CH}CH_2$), 4.56 (dd, J=10, 8, 1H, CH_2O), 5.19 (s, $\underline{CH}$-Ar), 6.88 and 7.38 (dt, J=9, 2, Ar). ^{13}C NMR ($CDCl_3$, TMS) δ 31.64 (t, CH_2S), 42.85 (d, CH-Ar), 55.19 (d, $CH_2\underline{CH}CH_2$), 55.33(9, CH_3O), 74. 68 (t, CH_2O), 114.13 and 128.39 (d, Ar CH), 130.90 (s, Ar C1), 159.24 (s, Ar C4), 168.36 (s, C=N). MS (m/z, relative intensity, CI, NH_3)

253 (MNH_4^+, 68%), 236 (MH^+, 100%). Anal. Calcd. for $C_{12}H_{13}NO_2S$ C 61.28% H 5.53% N 5.96% Found C 61.40% H 5.42% N 5.60%.

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