Tetrahedron Vol. 43, No. 17, pp. 4051 to 4056, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

STEREOSELECTIVE INTRAMOLECULAR NITRONE CYCLOADDITIONS TO CHIRAL ALLYL ETHERS

Rita Annunziata, Mauro Cinquini*, Franco Cozzi*,
and Laura Raimondi

Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, 20133 Milano, Italy.

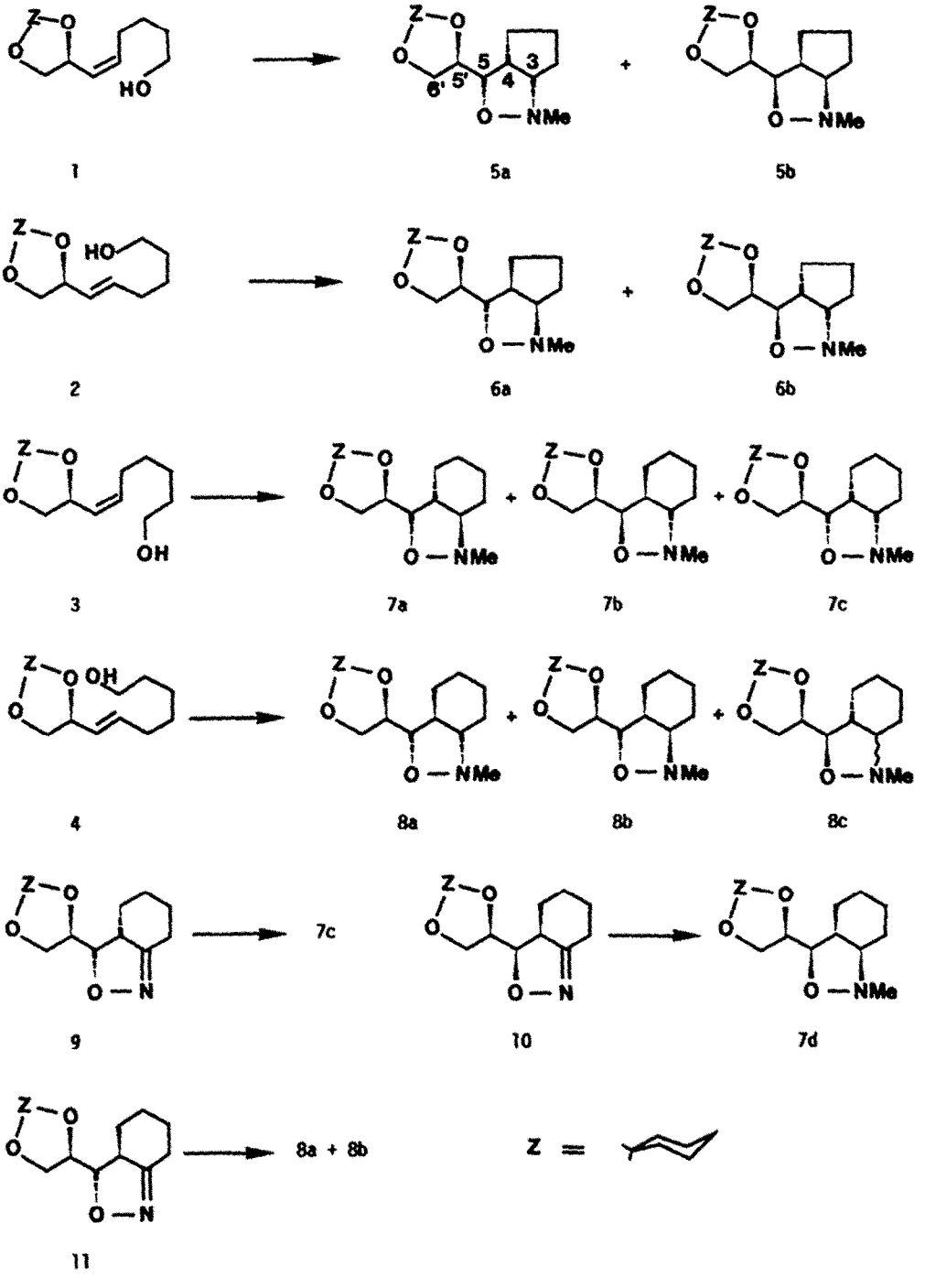
(*Received in UK* 29 *June* 1987)

Abstract. The intramolecular nitrone cycloadditions to Z and E chiral allyl ethers afford annulated isoxazolidines with good to excellent stereocontrol in favour of the C-5/C-5' anti isomers. The relative stereochemistry at the stereocenters in C-3/C-4 depends on the length of the chain connecting dipole and dipolarophile.

The 1,3 - dipolar cycloaddition of nitrones to alkenes[1] is widely exploited for the synthesis of various classes of natural products such as alkaloids,[2] antibiotics,[3] and aminosugars.[4] While several attempts to control the relative and the absolute stereochemistry relied on the use of chiral , non-racemic nitrones,[3-5] cycloadditions to enantiomerically pure alkenes received much less attention.[3c,6] As a part of our studies[7] on the stereoselectivity of intramolecular 1,3-dipolar cycloadditions, we here report that chiral allyl ethers undergo intramolecular C-alkenylnitrone cycloaddition to give annulated[1,8] isoxazolidines with good to excellent stereocontrol, depending on alkene geometry and ring size.

Suitable substrates were prepared as described in the Scheme. (R) - Alcohols 1-4[7a,7c] were converted by Swern oxidation in the corresponding aldehydes, which, by reaction with N-methylhydroxylamine in refluxing toluene,[9] gave the products 5-8 as mixtures of diastereoisomers in good chemical yield (Table 1). Three stereocenters are formed in these cycloaddition reactions. The relative stereochemistry at C-4 and C-5 is pre-determined by the alkene geometry.[1] Thus, from Z- and E- alkenylnitrones C-4/C-5 syn[10] (5 and 7) and C-4/C-5 anti[10] (6 and 8) isoxazolidines were obtained, respectively.

In each of the fused cyclopentane forming reactions only two products were produced with excellent diastereoselectivity.Since it has been shown[1,8] that intramolecular cycloaddition of N-alkyl-C-5-hexenylnitrones occurs in a



1 5a 5b

2 6a 6b

3 7a 7b 7c

4 8a 8b 8c

9 10 7d

11

completely stereoselective mode to deliver cis fused products, the C-3/C-4 syn configuration was assigned to 5 and 6. On the reasonable assumption that nitrones and nitrile oxides cycloadditions proceed with the same sense of diastereoselection,[11,12] the C-5/C-5' anti relative stereochemistry can be assigned to the major isomers 5a and 6a, and the syn one to 5b and 6b.[7,13] These attributions were confirmed by ^{13}C and ^{1}H NMR spectroscopy (Table 2). Thus, in these cases, the allylic stereocenter promotes the highly selective formation of

Table 1. Synthesis of isoxazolidines 5-8

Starting material	Product	Yield[a] %	Diastereoisomeric[b] ratios	C-5/C-5' anti:syn ratios
Z-1	5	71	96:4	96:4
E-2	6	64	92:8	92:8
Z-3	7	85	88:8:4	92:8
E-4	8	66	53:45:2	98:2

[a] Overall yield from the aldehydes. [b] As determined by ^{1}H and ^{13}C NMR spectroscopy.

three contiguous stereocenters in a predictable way.

Three isoxazolidines were obtained in the fused cyclohexane forming reactions. Intramolecular cycloaddition of N-alkyl-C-6-heptenylnitrones are known to proceed less stereoselectively than those of their lower homologues to give a predominance of trans fused derivatives, the trans:cis ratio depending on alkene substitution.[1,8] For the Z-alkene derived products 7a, 7b, and 7c, obtained in 88:8:4 ratio, structural assignment was based on inspection of ^{13}C and ^{1}H NMR spectra (Table 2), and chemical correlation. Indeed isoxazoline 9[7a,7c] gave ($Me_3O^+BF^-_4$ in $MeNO_2$; then $NaBH_4$ in EtOH, 55% yield)[14] 7c, while 10[7a,7c] afforded 7d (57% yield), an all-syn compound that was not produced by the cycloaddition. The overall anti:syn selectivity is thus 96:4 (7a+7b:7c) at C-3/C-4, and 92:8 (7a+7c:7b) at C-5/C-5'.

The E-alkene derived products 8a,8b, and 8c were obtained in a 53:45:2 ratio. Once again structural elucidation resided on NMR evidence and chemical correlation. Since isoxazoline 11[7a,7c] upon N-methylation and reduction (see above) afforded a 4:1 mixture of isoxazolidines 8a and 8b (60% yield), the C-5/C-5' anti relative configuration was assigned to 8a and 8b, and the syn one to 8c. As a consequence the cycloaddition proceeded with an overall C-5/C-5' anti:syn selectivity as high as 98:2 (8a+8b:8c), while the degree of stereocontrol at C-3 was low. Thus, the reported data indicate that the tendency to give C-5/C-5' anti products is independent of the double bond geometry and of the forming ring size.

As far as the stereocontrol at C-5/C-5' is concerned, the intramolecular nitrone cycloadditions favourably compare with those of the corresponding

nitrileoxides,[7a,7c] for which anti steroselection up to 86:14 were observed. This was not unexpected,[11,12] although the two cycloadditions were carried out at very different temperatures.[15]

Table 2. Relevant ^{1}H and ^{13}C NMR data for isoxazolidine 5-8.

	^{1}H						^{13}C			
Compound	3	4	5	5'	6'$_A$	6'$_B$	3	4	5	5'
5a	3.23	3.03	4.00	4.06	4.06	4.06	74.9	50.3	79.8	73.5
5b	3.35	2.91	4.15	4.26	3.63	4.11	74.6	49.8	80.4	75.1
6a	3.03	2.83	3.49	4.06	3.85	4.06	75.4	52.1	84.9	76.5
6b	3.03	2.60	3.61	4.18	3.79	4.02	75.4	50.3	84.9	76.1
7a	1.98	2.16	3.87	3.86	3.80	4.03	70.3	50.6	79.0	74.9
7b	2.16	2.30	3.96	3.96	3.76	3.96	70.1	50.5	77.7	75.7
7c	2.85	2.43	4.03	4.06	3.81	4.06	67.2	45.3	80.4	73.0
7d	2.85	2.23	4.10	4.20	3.55	4.08	67.3	45.3	81.5	75.5
8a	2.00	1.86	3.61	4.03	3.90	4.03	73.7	53.3	80.6	78.2
8b	2.66	2.53	3.56	3.93	3.83	4.06	65.7	44.6	83.4	77.4
8c	-[a]	-[a]	3.68	4.15	4.00	4.15	-[a]	51.0	81.1	-[a]

[a] Undetermined.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 247 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer in $CDCl_3$ as solvent. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. All reactions employing dry solvents were run under Argon. Alcohols 1-4 were prepared as previously described.[7a,7c]

General procedure for the synthesis of cycloadducts 5-8. These products were prepared from alcohols 1-4 by a sequence of reaction involving: a) Swern oxidation to the aldehydes;[7a,7c] b) conversion of the aldehydes into the nitrones and intramolecular cycloaddition.

Synthesis of aldehydes: to a stirred solution of oxalyl chloride (1.2 mmol, 0.103 ml) in CH_2Cl_2 (15 ml) cooled at -65°C, DMSO (2.5 mmol, 0.180 ml) was added and the mixture stirred at -65°C for 20 min. A solution of alcohol (1.0 mmol) in CH_2Cl_2 (5ml) was then added and the reaction allowed to warm-up to -50°C. After 15 min stirring triethylamine (5 mmol, 0.7 ml) was added, and the mixture allowed to warm-up to room temperature in about 20 min and kept at that temperature for additional 20 min. Usual work-up gave crude aldehydes that were generally used without further purification. Typical yields were in the range 70-90%.

Synthesis of nitrones and intramolecular cycloadditions.

A mixture of crude aldehyde (1 mmol), N-methylhydroxylamine hydrochloride (1.5 mmol, 0.125 g), anhydrous K_2CO_3 (3 mmol, 0.414 g) in dry toluene (10 ml) was refluxed (3-6 h) under vigorous stirring. The reaction mixture was cooled, filtered, and concentrated under vacuum, and the crude product purified by flash chromatography (eluant diethylether: hexanes 1:1 mixture, and then diethylether).

Yields, diastereoisomeric ratios, and relevant NMR data are collected in Tables 1 and 2.

Cycloadducts 5a,b. Found: C%67.41;H%9.41; N%5.29.$C_{15}H_{25}NO_3$ requires: C% 67.38; H% 9.43; N% 5.24.

Cycloadducts 6a,b. Found: C% 67.33; H%9.39; N% 5.24. $C_{15}H_{25}NO_3$ requires: C% 67.38; H% 9.43; N%.5.24.

Cycloadducts 7a,bc. Found: C%68.19; H%9.72; N% 5.01. $C_{16}H_{27}NO_3$ requires: C% 68.29; H% 9.67; N% 4.98.

Cycloadducts 8a,b. Found: C% 68.23; H% 9.64; N% 4.94. $C_{16}H_{27}NO_3$ requires: C% 68.29:H% 9.67;N% 4.98.

General procedure for the conversion of isoxazolines into N-methyl isoxazolidines. To a stirred solution of isoxazoline [7a,7c] (0.5 mmol) in dry nitromethane (10 ml), cooled at 0°C, $Me_3O^+BF_4^-$ (0.5 mmol, 0.074 g) was added in one portion. The mixture was allowed to warm-up to room temperature, and stirred for 2.5 h. The solvent was then evaporated under vacuum at 25°C. To the residue, dissolved in abs. EtOH (10ml), $NaBH_4$ (9mmol , 0.342 g) was added and the mixture stirred overnight at room temperature. Usual work-up followed by flash chromatography gave the products in 55-60% yield. Relevant NMR data for compound 7d are reported in Table 2.

NMR analysis.

Since the analysis of standard ^1H NMR spectra was hampered by overlapping multiplets of relevant protons (Table 2), two-dimensional NMR techniques were used for structural assignment of isoxazolidines 5-8. The homonuclear double quantum filter COSY [16] revealed the ^1H-^1H interactions; the multiple quantum filtering was employed for selection of two/more-proton spin systems and for the N-methyl peak suppression without significantly affecting cross peaks. The two dimensional heterounuclear chemical shift ^1H-^{13}C correlation spectra, [17,18] together with standard coupled and decoupled ^{13}C NMR spectra, were used to establish the identity of connected carbons and protons.

The stereochemical assignment at C-5 and C-5' rested on the different chemical shift values of HC-5 and HC-5'. The resonances of syn isomers were observed at lower field than those of the corresponding anti products, as already found in related substrates. [7a,7c]. The very similar values of HC-5/HC-5' coupling constants (in the range of 6-9 Hz) could not be used to discriminate between anti and syn isomers. The ^{13}C chemical shift values of C-3 and C-4 were diagnostic for the attribution of the relative configuration at these stereocenters: in the case of syn isomers the resonances were at higher field than those of their anti counterparts.

References and notes.

1 J.J. Tufariello in "1.3-Dypolar Cycloaddition Chemistry", A. Padwa Ed.; Wiley, New York, 1984; vol. 2, p. 87.

2 a) W. Oppolzer, S. Silas, C.L. Snowden, B.H. Bakker, M. Petrzilka, Tetrahedron, 41, 3497, 1985; b) J.J. Tufariello, H. Meckler, K.P.A. Senaratne, Tetrahedron, 41, 3447, 1985.

3 a) T. Kametani, S. Chu, T. Honda, Heterocycles, 25, 241, 1987, and references therein; b) H. Iida, K. Kasahara, C. Kibayashi, J. Am. Chem. Soc., 108, 4647, 1986; c) S. Mzengeza, C.M. Yang, R.A. Whitney, J. Am. Chem. Soc., 109, 276, 1987.

4 a) P. De Shong, M. Dicken, J.M. Leginus, R.R. Whittle, J. Am. Chem. Soc., 106, 5598, 1984, and references therein; b) P.M. Wovkulich, M.R. Uskokovic, Tetrahedron, 41, 3455, 1985.

5 B. Bernet, E. Krawczyk, A. Vasella, Helv. Chim. Acta, 68, 2299, 1985, and references therein.

6 T. Koizumi, H. Hirai, E. Yoshii, J. Org. Chem., 47, 4005, 1982.

7 a) R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, J. Chem. Soc., Chem. Commun., 529, 1987; b) R. Annunziata, M. Cinquini, F. Cozzi, G. Dondio, L. Raimondi, Tetrahedron, 43, 2369, 1987; c) R. Annunziata M. Cinquini, F. Cozzi, C. Gennari, L. Raimondi, J. Org. Chem., in the press.

8 N.A. Le Bel, E.G. Banucci, J. Org. Chem., 36, 2440, 1971.

9 S.W. Baldwin, J.D. Wilson, J. Aubē, J. Org. Chem., 50, 4432, 1985.

10 S. Masamune, S.A. Ali, D.L. Snitman, D.S. Garvey, Angew. Chem., Int. Ed. Engl., 19, 557, 1980.

11 M.J. Fray, E.J. Thomas, D.J. Williams, J. Chem. Soc., Perkin Trans. 1, 2763, 1985.

12 P.M. Confalone, G. Pizzolato, D. Lollar Confalone, M.R. Uskokovic, J. Am. Chem. Soc., 102, 1954, 1980.

13 K.N. Houk, S.R. Moses, Y.-D. Wu, N.G. Rondan, V. Jäger, R. Schohe, F.R. Fronczeck, J. Am. Chem. Soc., 106, 3880, 1984; b) A.P. Kozikowski, Acc. Chem. Res., 17, 410, 1984; c) V. Jäger, I. Müller, R. Schohe, M. Frey, R. Ehrler, B. Hafele, D. Schröter, Lect. Heterocycl. Chem., 79, 1986.

14 A.P. Kozikowski, Y. Chen, B.C. Wang, Z. Xu, Tetrahedron, 40, 2345, 1985. The borohydride reduction of C-4/C-5 syn configurated isoxazolines is reported to be completely stereoselective, hydride attack occurring on the convex face of the molecule.

15 Hydrogenation of alcohol 1, oxidation to the aldehyde, and reaction with N-methylhydroxylamine afforded a nitrone that by n.O.e. experiments was shown to exist exclusively in the Z configuration.

16 U. Piantini, O.W. Sorensen, R.R. Ernst, J. Am. Chem. Soc., 104, 6800, 1982.

17 R. Freeman, G. A. Morris, J. Chem. Soc., Chem. Commun., 684, 1978.

18 A. Bax, R. Freeman, J. Magn. Res., 44, 542, 1981.