

0040-4039(95)02275-9

Formation of Non-Racemic Tricyclic Compounds by Intramolecular 1,3-Dipolar Cycloaddition of Nitrones

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Abstract: 3-Oxanitrones 10 and 3-azanitrones 11 were prepared starting from (S)-ethyl lactate 5 and (S)-N-benzyl alaninol 8, respectively. Both nitrones underwent spontaneously an intramolecular cycloaddition affording the tricyclic compounds 12 and 13. The diastereometric forms of 12 and of 13 were separated by column chromatography and identified by NMR spectroscopy.

The intramolecular 1,3-dipolar cycloaddition of δ -unsaturated nitrones makes 3-oxa-2-azabicyclo[3.3.0]octanes easily accessible.¹ Tricyclic compounds are formed by an analogous reaction if either the nitrone group or the unsaturated moiety or the tether between these two functional groups is part of a ring system. Thus, LeBel prepared 2-oxa-3-azatricyclo[5.3.1.0^{4.10}]undecane 2 (R = CH₃) by intramolecular cycloaddition of nitrone 1 in 1965.²



Roush et al. obtained a corresponding tricyclic compound 2 (R = Bz)substituted by a methyl and a butyl group at positions 9 and 10, respectively, in the synthesis of (-)-ptilocauline. As they found, the reaction proceeds with high asymmetric induction by the stereogenic center at position 4 of the nitrone giving an enantiomerically pure product in which the four protons at the bridgehead C-atoms are cis-orientated.³ Analogous nitrones with a cross-conjugated cyclohexadiene moiety afforded again an enantiomerically pure tricyclic compound as 2 with an additional double bond.⁴

Similar intramolecular cycloadditions were also performed with corresponding nitrile oxides giving tricyclic compounds with the same core including a C=N double bond function.⁵ Hassner et al. prepared the first compound of this type containing an additional O-atom in 6-position.⁶

Only recently, it was found that nitrones 3 formed in situ by a transesterification reaction give racemic tricyclic lactones 4 as single diastereomers.⁷



Our goal was the preparation of non-racemic 2.6-dioxa-3-azatricyclo $[5.3.1.0^{4.10}]$ undecanes 12 and 2-oxa-3.6diazatricyclo $[5.3.1.0^{4.10}]$ undecanes 13.⁸ Thus the ester 7 was prepared as diastereomeric mixture by reaction of (S)-ethyl lactate with racemic 1-bromo-2-cyclohexene in the presence of silver(I)-oxide. Reduction of 7 with DIBAL-H afforded the corresponding aldehyde which was treated with N-methylhydroxylamine to give nitrone 10. Compound 10 underwent spontaneously an intramolecular cycloaddition yielding a mixture of the two diastereomers 12A and 12B. These could be separated by column chromatography. Reaction of aminoalcohol 8 with racemic 1-bromo-2-cyclohexene afforded compound 9, which was subjected to Swern oxidation. Without isolation the aldehyde was treated with methylhydroxylamine to give nitrone 11. This underwent an intramolecular cycloaddition yielding a mixture of three diastereomers 13A, B and C. The diastereomers could be separated by chromatography.⁹

The tricyclic compounds 12 and 13 were shown to be optically active $(12A: [\alpha]_D^{22} = -23.2^\circ; 12B: [\alpha]_D^{22} = +54.5^\circ; 13A: [\alpha]_D^{22} = +61.9^\circ; 13B: [\alpha]_D^{22} = +56.9^\circ; 13C: [\alpha]_D^{22} = 85.6^\circ$, in ethanol). Since the formation of the corresponding bicyclic products under the same reaction conditions proceeded without racemization,⁹ it can be assumed that this is also true for the formation of compounds 12 and 13. Thus, these compounds should be enantiomerically pure. There are two stereogenic centers at C-2 and C-4 in the nitrones 10 and 11 formed as intermediates. Whereas in both diastereomers A and B the configuration at C-2 is equal they differ by their configuration at C-4. Certainly, the configuration at C-4 determines the side from which the cyclohexene ring is attacked by the nitrone group. Thus, the cis-relationship of protons 1-H, 11-H, 7-H and 4-H in the cycloadducts 12A/13A and 12B/13B results from an exo-approach of the Z-nitrone group.

The cis-relationship of 4-H and 5-H in compounds 12B/13B is unusual, since in the cycloadducts of nitrones with only one stereogenic center adjacent to the nitrone carbon atom the relative configuration at the comparable positions is opposite.¹⁰ However, in the case of diastereomers B the *cis*-relationship of 4-H and 5-H is caused by the dominating effect of the stereogenic center of the cyclohexene ring.

As models reveal an endo-approach of the nitrone group would be severely strained. Consequently, the transannulation of the two five-membered rings in 13C must be assumed to result from the attack of an E-nitrone group. The structural assignment of the tricyclic compounds 12 and 13 is based on the NMR spectra (¹H NMR data see Table 1). It is further confirmed by an X-ray analysis of 13A.¹¹

The ¹H NMR spectra of diastereomers A and B differ in particular by the coupling constants ³J 4-H/5-H and the chemical shifts of the protons 5-H, 7-H and the methyl groups at C-5 according to different conformations. Thus, the coupling constants J 4/5 <1 Hz of 12A and 13A certainly indicate the trans-configuration of 4-H and



5-H. In 12A and 13A the proton 5-H occupies a quasi-equatorial position according to the down-field shift of its

 $12 : X = O \qquad 13 : X = N - Bzl$

signal compared to the signal of the quasi-axial position of 5-H in 12B and 13B. For the methyl group at C-5 the situation is opposite.

The most striking data of 13C are the high coupling constant J 4/11 = 11.7 Hz and the signal of C-11 at lower field (55.9 ppm) compared to 13A and B (46.8 and 46.6 ppm, resp.). The trans-annulation of the two five-membered rings in 13C is confirmed by a NOESY spectrum which shows cross-peaks for the protons $4/CH_3$, 1/11 and 7/11 but not for the protons 4/11.¹²

δ	12A	12B	13A	13B	13C	
1-H	4.33	4.31	4.41	4.30	4.08	
4-H	3.40	3.44	3.13	3.16	3.07	
5-H	4.26	3.73	3.35	2.40	2.95	
7-H	4.15	3.77	2.94	2.43	2.88	
11 -H	2.99	2.91	3.02	2.75	3.21	
CH ₃ (5)	1.18	1.35	0.86	1.12	1.26	
³ J _{H-H}		- u				
1/11	7.1	6.5	~7	6.2	7.9	
4/5	<1	5.4	<1	8.0	8.9	
4/11	7.1	7.6	7.9	7.6	11.7	
7/11	7.1	6.3	~7	7.7	8.0	

Table 1. Characteristic ¹H NMR data of compounds 12 and 13 (in CDCl₃, δ in ppm, J in Hz)

We thank the Fonds der Chemischen Industrie for financial support.

References and Notes

- a) Tuffariello, J.J. In *1.3-Dipolar Cycloaddition Chemistry*, Padwa A. Ed.; Wiley Interscience: New York 1984; Chapter 9, pp. 116-119. b) Wade, P.A. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I.; Semmelhack, M.F. Eds., Pergamon: Oxford 1991, Vol.4, pp. 1113-1114.
- 2. LeBel, N.A. Trans. N.Y. Acad. Sci. 1965, 27, 858-867, (C.A. 1966, 64, 548h).
- 3. Walts, A.E.; Roush, W.R. Tetrahedron 1985, 41, 3463-3478.
- 4. Stanssens, D.; De Keukeleire, D.; Vandewalle, M. Tetrahedron Asymm. 1990, 1, 547-560.
- a) Wollenberg, R.H.; Goldstein, J.E. Synthesis 1980, 757-758. b) Knight, J.; Parsons, P.J. J. Chem. Soc., Perkin Trans 1, 1989, 979-984. c) Curran, D.P.; Jacobs, P.B. Tetrahedron Lett. 1985, 26, 2031-2034.
- 6. Hassner, A.; Murthy, K.S.K.; Padwa A.; Chiacchio, U.; Dean, D.C.; Schoffstall, A.M. J. Org. Chem. 1989, 54, 5277-5286.
- 7. Tamura, O.; Okabe, T.; Yamaguchi, T.; Gotanda, K.; Noe, K.; Sakamoto, M. Tetrahedron 1995, 51, 107-118.
- After preparation of the manuscript a paper appeared describing tetracyclic compounds which are similar to 12 and 13, insofar as they contain the same tricyclic frame but an additional oxygen atom in the six-membered ring: Hewson, A.T.; Jeffery, J.; Sczcur, N. *Tetrahedron Lett.* 1995, 36, 7731-7734.
- Using 1-bromo-2-cyclohexene instead of allyl bromide the same reaction procedures were followed as described before for the preparation of the corresponding bicyclic compounds: Aurich, H.G.; Biesemeier, F. Synthesis 1995, 1171-1178 (X = O); Aurich, H.G.; Gentes, C.; Harms, K. Tetrahedron 1995, 51, 10497-10512 (X = NR).
- 10. Bernet, B.; Vasella, A. Helv. Chim. Acta 1979, 62, 2411-2431.
- 11. The results of the X-ray analysis performed by Dr. K. Harms will be published later.
- 12. To the best of our knowledge only one example of two trans-fused five-membered rings containing an isoxazolidine moiety comparable to 13C has been described: Armstrong, P; Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W.J. Tetrahedron 1991, 47, 4495-4518.

(Received in Germany 2 November 1995; accepted 27 November 1995)