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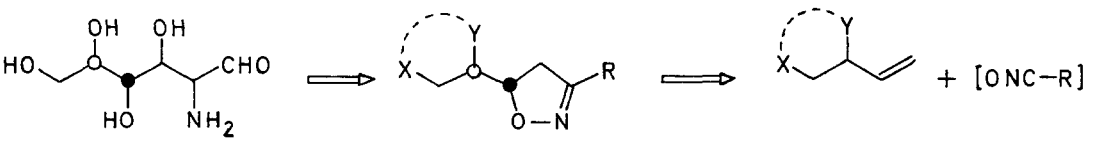
ASYMMETRIC INDUCTION IN NITRILE OXIDE CYCLOADDITIONS TO 3-BUTENE-1,2-DIOL AND DERIVATIVES[1]

Volker Jäger* and Rudolf Schohe
Institut für Organische Chemie der Universität Würzburg, Am Hubland, D-8700 Würzburg

Erich F. Paulus
Hoechst AG, D-6230 Frankfurt a. M. 80

Summary: *Nitrile oxide cycloadditions to 3-butene-1,2-diol and derivatives thereof show varying degrees of* erythro *selectivity, ranging from 0 to ca. 0.9 kcal/mol. Some of these results are rationalized qualitatively on the basis of the Felkin-Anh-Houk model.*

A concept to use the isoxazoline route[2] for the synthesis of amino sugars was detailed recently.[1,3] One of the problems associated is how to achieve stereocontrol concerning O-functionality at C-4/C-5 as present in 2-amino-2-de oxyhexoses 1, and a solution via nitrile oxide/furan adducts was presented.[1a] The C-4/C-5 part may also be related to isoxazolines 2, in turn accessible from nitrile oxides 4 and α-chiral olefins 3 such as 3-butene-2-ol (X = H, Y = OH) or 3-butene-1,2-diol (X, Y = OH). The success of this scheme then depends on the diastereoselectivity of the cycloaddition step, i. e. 3 + 4 → 2.[4]



1 2 3 4

In order to determine this, a variety of olefins 3 were reacted with various nitrile oxides 4.[1b,c,4-7] This letter gives a selection of results with the diol 3a and derivatives (see Table 1), with some reasoning concerning transition state conformations.[8] The relative configurations of diastereomers of 2 (except 2f) were determined by chemical and spectroscopic correlation with the main isomer of 2h,[9] which was shown by single crystal X-ray analysis to have erythro configuration.[10] This parallels recent results of Kozikowski's cycloaddition to 3g[5b] and Torssell's findings with 5-vinylisoxazolines.[5c]

In all cases, formation of the erythro *adduct is favoured* (see Table). Diastereomer ratios (d.r.s) exceeding or equal to 4 : 1, however, are found with vinyl-substituted 5-membered rings 3g - 3i only. Still useful selectivities (3 : 1) are exhibited by the cyclic boronate 3j, and the bis-silyl ether 3d. Derivatives with vinyl attached to rings of other sizes (3e, 3f, 3k) or open-chain alkenes (3a - c) are less or non-selective. Further, the diastereoselectivity found with 3g is *insensitive* to electronic and steric alterations in the nitrile oxide part, as the results with various dipoles 4 (R = CH_3,[5b] COOEt,[5b] mesityl,[1b] t-butoxymethyl,[1b,c,9b] diethoxymethyl[9b])

Table. Diastereomer ratio (d.r.) of isoxazolines 2 from benzonitrile oxide cycloadditions to butenediol and related olefins 3[9]

2	X	Y	yield[a,b] (crude; %)	d.r.[c] (*erythro* : *threo*)[d]	$\Delta\Delta G_T^{\ddagger}$ [b] (kcal/mol)
(a)	OH	OH	67	61 : 39	0.26
(b)	$OC(C_6H_5)_3$	OH	(quant.)[e]	54 : 46	0
(c)	$OSiMe_3$	$OSiMe_3$	65	75 : 25	0.64
(d)	OAc	OAc	67	53 : 47	0
(e)	-O-		99	69 : 31	0.47
(f)	-CO-NH-		78	59 : 41	0.2
(g)	$-O-CMe_2-O-$		88	85 : 15	0.94[d]
(h)	$-O-C(CH_2)_5-O-$		quant.	81 : 19	0.79[d]
(i)	-O-CO-O-		83	82 : 18	0.88
(j)	-O-BPh-O-		74	75 : 25	0.67
(k)	-O-CO-CO-O-		(38)[f]	66 : 34	0.39

a) Structures and configurations of 2 were secured by chemical/spectroscopic correlations; correct elemental analyses for 2a, 2c (for mixture and pure *threo*, m.p. 85 - 87°C), *threo*-2e (m.p. 88 - 91°C), 2f, 2g (for mixture, pure *erythro*, m.p. 80 - 81°C, and pure *threo*, 70 - 71.5°C), 2h (for mixture and pure *erythro*, m.p. 73.5°C).
b) Cycloadditions (Huisgen's *in situ* procedure) at 25°C (2g, 2h at 0°C). Alkenes were obtained commercially, as gifts or according to standard procedures.
c) Diastereomer ratios from 13C NMR integration of crude products, cp. ref. 11.
d) The term *erythro (threo)* corresponds to the relative configuration of erythrose (threose).
e) *Crude yield "107 %", with ca. 10 % of furoxan; F_3C-COOH detritylation gave 39 % of 2a.*
f) Over-all yield of 2g after hydrolysis and acetalization.

illustrate. Further, the diastereoselectivity of cycloadditions with 3a, 3c, and 3g is *not* subject to solvent effects, as was checked with CCl_4, *pyridine*, *acetonitrile*, *DMF*, *DMSO*, and *ethanol*.

What are the factors causing π-facial selectivity of up to 0.9 kcal/mol? The absence of solvent effects indicates, that both hydrogen bond (with 2a, 2b) and dipole interactions[12,13] are not responsible. Related cases reported recently - a Diels-Alder addition[7b] and a nitrile oxide cycloaddition (to 3g)[5b] - have been interpreted on the basis of Houk's generalized Felkin-Anh[14] transition state model of allylic substituents being staggered with respect to forming bonds,[15] cp. fig. 1. With α-chiral allyl compounds 3 the question is, which substituent preferentially will occupy the *anti*-periplanar position, the alkyl group CH_2X (the *Large* substituent) or the oxy substituent (*Medium*). It has been assumed, that *anti* alignment of alkoxy dominates, due to less unfavourable secondary orbital interactions of *syn* alkoxy *vs. syn* alkyl.[7b] Further, the relation to nucleophilic additions to carbonyl compounds *anti* to the group having the lowest energy σ^* (C_2-X) orbital has been invoked.[5b,13]

Houk's calculations do show the *anti* position of a methyl substituent in 1-butene reactions to be the preferred one throughout, but the relative steric requirements of outside (ⓞ) and inside (ⓘ) methyl positions are reversed for nucleophilic and electrophilic additions (H^-, trajectory angle 123°, ⓘ preferred; BH_3, 73°, ⓘ most hindered!)[15]. However, the nitrile oxide/alkene case is considered a mildly electrophilic reaction, with an O····C trajectory angle of around 100° (the

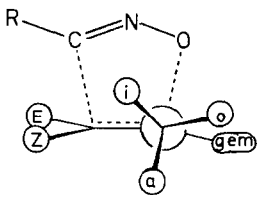
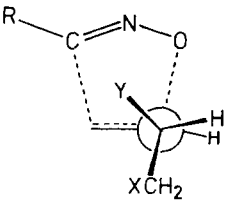
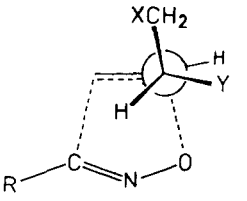


Fig. 1



erythro-2



threo-2

Fig. 2

C-4, C-5, O angle in 2h is 105.4° from the X-ray data). An assessment of relative preferences of CH_2X *vs.* Y groups for *anti*, ⓘ and ⓞ alignment (cp. fig. 1,2) in the competing transition states therefore is *not possible on this basis.*

Nevertheless, experimental results (Table 1) suggest, that transition state conformations with *anti*-periplanar alignment of the large group CH_2X are the preferred ones in the pathways to both *erythro* and *threo* diastereomers of 2 as depicted in fig. 2: First, electronic variation of the C-X bond (entries a - c; g - i) did not cause significant d.r. changes as expected when σ^* orbitals of *anti* Y substituents were involved.[16,17] Second, steric arguments are in favour of *anti* alignment of the large group CH_2X:[17b] the trityl derivative 3b shows a d.r. close to that of the parent diol 3a and the diacetate 3c. This is in accord with *anti* arrangements, but not with placement in one of the sterically more demanding positions, ⓘ or ⓞ . On the other hand, bis-silylation increases stereoselectivity by ca. 0.6 kcal/mol (3d *vs.* 3c), indicating a sterically more hindered position for Y in the *threo* transition state. Finally, any TS conformation with CH_2X placed *inside* should be discriminated when opposed to an o-methyl group of mesitonitrile oxide as seen from Dreiding models; however, the experimental d.r. remained unchanged (with 3g, see above). Still, more data both from experiment and computation are necessary to rationalize these relatively small effects (in particular those from variations of the X----Y bridge) in a more quantitative way. For example, fig. 1 shows, that variation of substituents in position Ⓩ and (gem) of the α-chiral olefin should allow for specific changes of relative minima (and rotational barriers) of competing transition state conformations.[17] Studies relating to this are in progress, as well as studies concerning chiral nitrile oxides.[18]

As a synthetic consequence, *erythro*-selective routes to various cleavage products of isoxazolines 2 are at hand. A recent example is a synthesis of 2-deoxy-D-ribose from Kozikowski's group;[5b] in the context of the present program the reduction of respective isoxazolines 2 gave access to amino sugars like DL- and D-lividosamine derivatives of type 1.[9b]

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1) Syntheses *via* Isoxazolines, 12.; (a) part 11: I. Müller, V. Jäger, *Tetrahedron Lett.*, 4777 (1982); (b) part of the Diploma (1980) and Ph.D. Thesis (planned, 1983) of R. S.; (c) some of these results were presented at the Chemiedozententagung, Tübingen, March 1981.

2) (a) V. Jäger, H. Grund, *Angew. Chem.* 88, 27 (1976); *Angew. Chem., Int. Ed. Engl.* 15, 50 (1976); (b) cp. also previous papers in this series; (c) for a collection of references to related work by other groups see lit. 1a.

3) V. Jäger, W. Schwab, V. Buß, *Angew. Chem.* 93, 576 (1981); *Angew. Chem., Int. Ed. Engl.* 20, 601 (1981).

4) At the outset of this work, some 30 reports on nitrile oxide cycloadditions to chiral olefins were known; however, in most cases with acyclic alkenes diastereoselectivities were not determined or found to be low. Meanwhile, several examples with α-chiral, acyclic olefins exhibiting useful diastereoselectivity have been reported (ref. 5), including cycloadditions of 4 (R=COOEt, CH_3) to S-2g by Kozikowski and Gosh (ref. 5b).

5) (a) A. A. Hagedorn, III, B. J. Miller, O. J. Nagy, *Tetrahedron Lett.* 229 (1980); (b) A. P. Kozikowski, A. K. Gosh, *J. Am. Chem. Soc.* 104, 5788 (1982); (c) P. A. Wade, M. K. Pillay, S. M. Singh, *Tetrahedron Lett.*, 4563 (1982); (d) N. B. Das, K. B. G. Torssell, *Tetrahedron* 39, 2247 (1983).

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7) Cp. Diels-Alder additions to olefins of type 3, f. e. (a) D. Horton, T. Machinami, *J. Chem. Soc., Chem. Commun.*, 88 (1981); (b) R. W. Franck, T. V. John, K. Olejniczak, J. F. Blount, *J. Am. Chem. Soc.* 104, 1106 (1982).

8) Results of a joint study with butenol and the like, and a computational model developed in Prof. Houk's group: S. R. Moses, Y.-D. Wu, N. G. Rondan, K. N. Houk, R. Schohe, V. Jäger, F. R. Fronczek, to be submitted.

9) (a) Details concerning experimental and correlations will be reported in the full paper; for the synthesis of 2g, 2h see (b) V. Jäger, R. Schohe, *Tetrahedron*, submitted.

10) 2h: m.p. 73.5°C (from heptane); monoclinic, space group $P2_1/C$, 4 molecules in the unit cell with a = 16.806 (2), b = 5.827 (1), c = 16.560 (2) Å; β = 109.26 (1)°; 2070 [$>1\sigma(I)$] of 3722 independent reflexes; R_w = 5.4%, w = $1/\sigma^2$ (F).

11) V. Jäger, V. Buß, *Liebigs Ann. Chem.* 101 (1980).

12) Solvent effects are noted with butenols (ref. 8) and cyclic alkenes: P. Caramella, G. Cellerino, *Tetrahedron Lett.* 229 (1974); G. Bianchi, C. De Micheli, A. Gamba, R. Gandolfi, *J. Chem. Soc., Perkin Trans.* 1, 137 (1974); C. De Micheli, A. Gamba Invernizzi, R. Gandolfi, L. Scevola, *J. Chem. Soc., Chem. Commun.* 246 (1976).

13) For a related case of stereoselective, nucleophilic addition to an α-chiral olefin see J. Mulzer, M. Kappert, *Angew. Chem.* 95, 60 (1983); *ibid., Int. Ed. Engl.* 22, 63 (1983); *ibid., Suppl.*, 23 (1983).

14) For a review see N. T. Anh, *Top. Current Chem.* 88, 145 (1980).

15) (a) P. Caramella, N. G. Rondan, M. N. Paddon-Row, K. N. Houk, *J. Am. Chem. Soc.* 103, 2438 (1981); (b) M. N. Paddon-Row, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* 104, 7162 (1982); and references cited therein.

16) Cp. results with 3-chloro-1-butene: T. G. Burrowes, W. R. Jackson, S. Faulks, I. Sharp, *Austr. J. Chem.* 30, 1855 (1977); and ref. 8.

17) (a) Nitrile oxide cycloadditions to *cyclic* α-X-substituted alkenes show more pronounced substituent effects (ref. 12), indicating transition state conformers different from those operative in the *acyclic* cases of the present work. (b) A recent study on C-chiral nitrone cycloadditions states a large preference for a TS conformation with *anti* R and outside OR' alignment (ref. 6c).

18) Variation of positions Ⓩ, (gem) in 3 led to interesting, but preparatively not useful (< 3 : 1) d.r. changes: ref. 1b and B. Häfele, Diploma Thesis, Würzburg 1983. Likewise, use of α-chiral nitrile oxide derived from glyceronitrile oxide gave low d.r.s: unpublished results with B. Häfele; see also K. Torssell et al., *Acta Chem. Scand.*, in press.

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