

Cycloaddition of Nitrile Oxides to Homochiral Vinyl Ethers

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In the [3 + 2] cycloaddition of a range of nitrile oxides with homochiral vinyl ethers the diastereoselectivity observed is dependent on the chiral auxiliary used; an X-ray structure determination of the major isomer of product **11a**, from the reaction of benzonitrile oxide and (*S*)-1-(2-naphthyl)-ethyl vinyl ether, is consistent with the proposed preferred conformation of the vinyl ether.

In nitrile oxide cycloaddition, a well established synthetic method,¹ substantial asymmetric induction has been observed in reactions with allyl silanes,² homochiral acrylates and crotonates,³ and addition to simple achiral vinyl ethers is known.⁴ Homochiral vinyl ethers have been used in Diels–Alder reactions,⁵ ketene and isocyanate cycloadditions,⁶ Bradsher cycloaddition,⁷ nitronc cycloaddition⁸ and tandem [4 + 2]/[3 + 2] cycloaddition.⁹ However, the corresponding nitrile oxide cycloaddition to chiral vinyl ethers has been observed, to the best of our knowledge in only one case, with a methylene sugar.¹⁰ We now report a study of nitrile oxide cycloadditions to homochiral vinyl ethers.

A series of homochiral vinyl ethers **1–4**, prepared by the exchange of the corresponding alcohol with butyl vinyl ether catalysed by mercury(II) acetate,¹¹ were allowed to react with benzonitrile oxide¹² to give the 4,5-dihydroisoxazoles **5–8** in 41–59% yield with diastereoisomer ratios ranging from 1.1:1 to 1.9:1 (see Table 1). Better diastereoselectivity was observed in the reaction of the homochiral vinyl ethers **9** and **10** as shown in Table 2.

In the case of the 4,5-dihydroisoxazole **11a**, the sense of the asymmetric induction was proved by an X-ray crystal structure† on the major diastereoisomeric product obtained after purification by column chromatography. Fig. 1 shows the result of this crystal structure determination. The absolute configuration of the chiral vinyl ether was *S*, and we found that the new asymmetric centre in the product **11a** has the *R* configuration. To explain this result we have followed the conclusions of extensive studies on the conformation of vinyl ethers.¹³ Clearly, steric factors may well override any inherent stereoelectronic preference in all but the most simple cases,

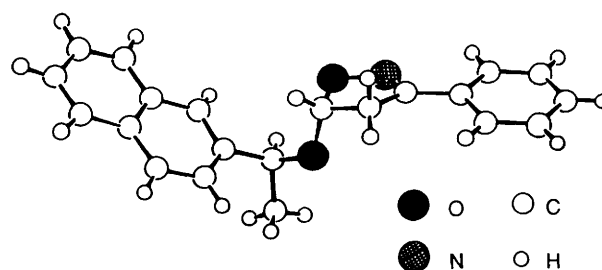
† Crystal Data for major diastereoisomer of compound **11a**. All crystals examined were composed of more than one component. The crystal used for data collection was split into two fragments of approximately equal intensity. Photographic data indicated sufficient resolution of the components to allow data collection without overlap. C₂₁H₁₉NO₂, *M* = 317.4, monoclinic, space group *P*2₁, *a* = 18.570(26), *b* = 5.829(2), *c* = 7.945(11) Å, β = 89.4(1)°, *U* = 860(2) Å³, *Z* = 2, *D*_c = 1.23 g cm⁻³, μ(Mo-*K*α) = 0.44 cm⁻¹, *F*(000) = 336, crystal dimensions 0.80 × 0.48 × 0.14 mm, data were collected at 293 K using Mo-*K*α X-radiation, λ = 0.7107 Å, on a Stoe STADI-2 Weissenberg diffractometer. The structure was solved using the TREF direct methods option of SHELXS-86.‡ All subsequent calculations were carried out using the program SHELX-76.§ Full-matrix least squares refinement of 217 parameters gave *R* 0.0584 (*R*_w 0.059) for 1159 independent reflections [*I* > 3σ(*I*)] in the range 7 < 2θ < 54°. The final residual Fourier map was featureless (±0.15 e Å⁻³). Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors, Issue No. 1.

‡ G. M. Sheldrick, 'SHELXS-86, Program for the Solution of Crystal Structures', University of Göttingen, Germany, 1986.

§ G. M. Sheldrick, 'SHELX-76, Program for the Solution of Crystal Structures', University of Cambridge, England, 1976.

Table 1

R ¹	Yield (%)	Diastereoisomer ratio of products 5–8
1 (–)-Menthyl	41	1.4:1
2 8-Phenylmenthyl	51	1.9:1
3 Isopinocampheyl	45	1.3:1
4 (<i>R</i>)-PhCH(CO ₂ Me)	59	1.1:1

Fig. 1 Crystal structure of major diastereoisomer of compound **11a**

however we propose structure **13** as a possible transition state for the 1,3-dipolar cycloaddition. In the vinyl ether **13**, the bulky naphthyl group is *anti* to the vinyl group, and the oxygen lone pairs are *anti* to the olefin group leading to a more effective overlap according to the bent bond theory.¹⁴ The modest diastereoselectivity observed results from attack on the least hindered side of the double bond, which explains the *R* configuration of the new asymmetric centre in the major diastereoisomer.

Experimental

The general procedure used for all the cycloadditions was as follows. The oxime (8.2 mmol), *N*-chlorosuccinimide (9.0 mmol) and pyridine (2 drops) in chloroform (30 cm³) were heated under reflux for 20 min. The reaction mixture was cooled to room temperature and solutions of the vinyl ether (8.2 mmol) and triethylamine (9.0 mmol) in chloroform (both 5 cm³) were added consecutively in a dropwise fashion, after which the mixture was heated under reflux for 1 h. After removal of the solvent under reduced pressure, the product was purified using silica flash chromatography [10:1 light petroleum (b.p. 40–60 °C)–diethyl ether].

All new compounds gave satisfactory spectroscopic data, elemental analyses and/or accurate mass measurements.

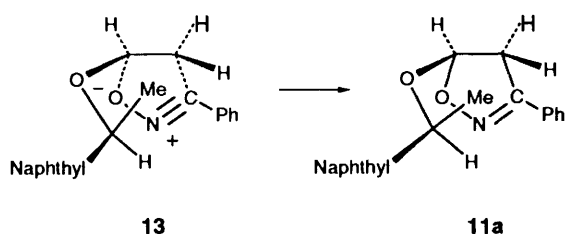
Table 2

$\text{R}^2\text{O}-\text{CH}=\text{CH}_2 \xrightarrow{\text{R}^3\text{CNO}} \text{R}^2\text{O}-\text{CH}(\text{R}^3)-\text{CH}=\text{N}-\text{O}$

9,10 **11a-g or 12a-g**

R ³	11a-g R ² = (S)-2-NaphthylCH(Me)		12a-g R ² = (S)-PhCH(Pr)	
	Crude ratio* of diastereoisomers	Isolated yield (%) of major diastereoisomer	Crude ratio* of diastereoisomers	Isolated yield (%) of major diastereoisomer
a Ph	3:1	43	2:1	33
b PhCH ₂ CH ₂	3:1	28	4:1	44
c 4-NO ₂ C ₆ H ₄	4:1	26	1:1	23
d Bu ^t	3:1	53	4:1	47
e Pr	4:1	37	3:1	39
f Et	3:1	40	4:1	35
g Me	3:1	37	4:1	53

* The ratio of the two diastereoisomers of **11a-g** and **12a-g** was measured from several peaks in the ¹³C NMR spectrum of the crude product. In the case of **11a** the ratio was confirmed by ¹H NMR spectroscopy and by isolation of both diastereoisomers. In **11b-g** and **12a-g** the major isomer was isolated and fully characterised.



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