Tetrahedron Vol. 45, No. 10, pp. 3183 to 3188, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

STEREOCONTROLLED EPOXY-EPIMINATION OF 1,3-CYCLOHEXADIENE

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In memoriam G. Kresze (1921-1987)

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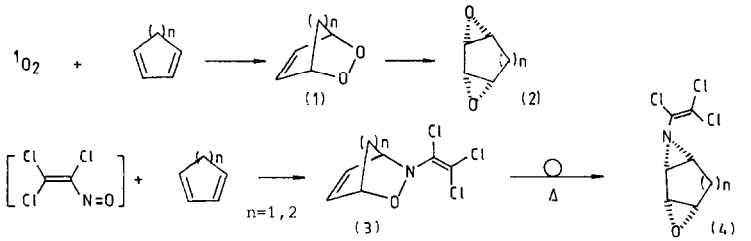
(*Received in Belgium* 20 *July* 1988)

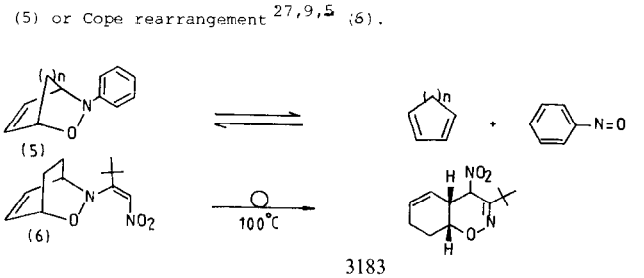
ABSTRACT. 1,3- cyclohexadiene yields with complete stereocontrol via oxazine (14) the new epoxy-epimine (15). The observed N-substituent effect, especially with the captodative vinyl group as oxazine isomerisation inducer, indicates a biradical mechanism. The use of this methodology permits enantiospecific cis epoxy-epimination of the four sp^2 carbon atoms of 1,3-cyclohexadiene.

Whereas the rearrangement of endoperoxides (1) to bisepoxides (2) has attracted considerable interest[1], there was no aza-analogous reaction until we discovered the rearrangement of oxazines carrying appropriate substituents on the ring nitrogen[2-5,7]. Thus oxazines (3) - formed by cycloaddition of trichloronitroso ethylene[6] to 1-3 cyclodienes rearrange thermally (n = 1 at 0°C, n = 2 at 80°C) to give the cis epoxy-epimines (4).

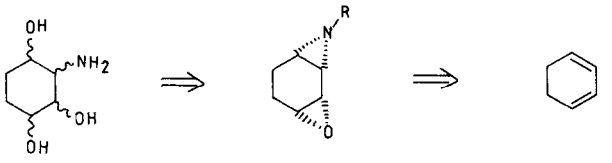


This reaction is mechanistically intriguing because of the pronounced effect of the substituents on the nitrogen; the size of the bicyclic oxazine is also of importance : adducts to non cyclic 1,3-dienes do not undergo the epoxy-epimination rearrangement, which succeeds with oxazines derived from 5, 6 and 7-membered cyclodienes[8].

Depending on their N-substituents, oxazines may undergo other reactions such as retro Diels-Alder[10,11] (5) or Cope rearrangement[2,7,9,5] (6).

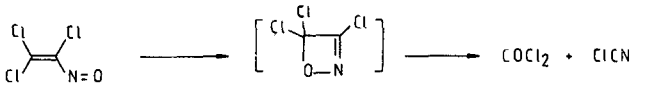


In order to achieve selectively the epoxy-epimination, the understanding of its reaction mechanism is a prerequisite. The application in synthesis permits stereocontrolled functionalization of cyclodienes. In fact, the epoxy- and epimine rings arise in cis arrangement to each other. This feature permits to use the epoxy-epimination as the key step of a new approach to the synthesis of aminocyclitol derivatives (7)[12].



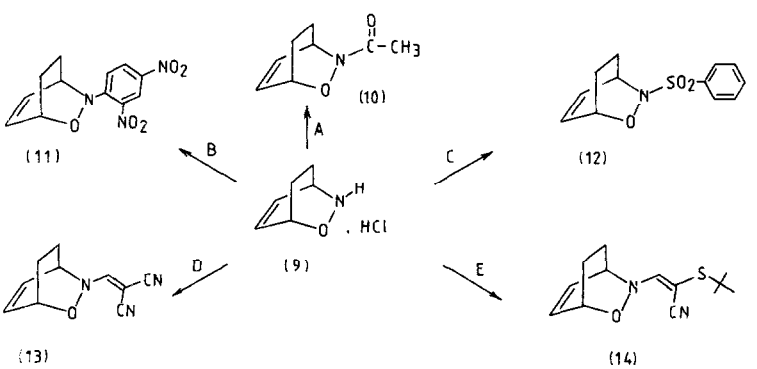
(7)

This work examines the preparation and the thermal behaviour of various N-substituted oxazines avoiding the fragile intermediate nitroso ethenes. Even though their hetero Diels-Alder reaction appears to be the most straightforward way to substituted oxazines, the synthesis of the requisite nitroso precursors is limited by their accessibility and by their inherent instability. Trichloronitroso ethylene, for example, fragments at room temperature to phosgene and to cyanogen chloride with oxazete (8) as the probable intermediate[5,13,14].



(8)

A complementary and more general approach to N-substituted oxazines starts from the easily available N-unsubstituted oxazine[15] (9), as examplified in scheme (1). Besides by acylation of (9) to (10)[25], this compound is also available by direct cycloaddition using acylnitroso compounds[17]. Dinitrophenylation of (9) produces the arylated oxazine (11), sulfonation leads to (12) and vinylation[16,26] furnishes the derivatives (13) and (14). The latter is of particular importance for this study concerning the desired epoxy-epimination rearrangement.



A = BENZYL CHLORIDE/PYRIDINE/CH_2Cl_2/R.T./81 %

B = 1-FLUORO 2,4-DINITROBENZENE/NEt_3/CH_2Cl_2/R.T./96 %

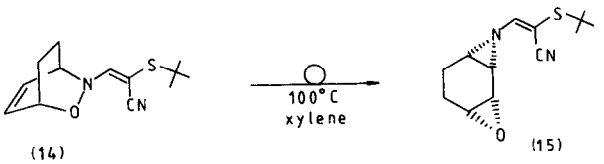
C = BENZENE SULFONYL CHLORIDE/NEt_3/CH_2Cl_2/R.T./83 %

D = 3-CHLORO 2-CYANO ACRYLONITRILE/NEt_3/CH_2Cl_2/R.T./79 %

E = 3-CHLORO 2-tBU.THIO ACRYLONITRILE/NEt_3/CH_2Cl_2/R.T./81 %

Scheme 1

It is remarkable and in agreement with the captodative-effect that among all the substituted oxazines (10)-(14), only the derivative (14) with captodative[18] vinyl substituent undergoes the smooth epoxy-epimination to (15).



(14) (15)

Scheme 2

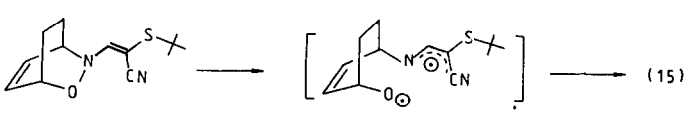
The kinetic study of this thermal isomerisation is feasible because it yields almost quantitatively the epoxy-epimine (15) which is stable under the conditions indicated in Scheme 2. The isomerisation is followed by NMR ^{1}H 200 MHz and shows a first order kinetic relationship practically without any solvent effect; changing from xylene to nitrobenzene and to dimethylsufoxide decreases the rate only by three. The activation energy in d-ortho-xylene is about 30 Kcal/mol and its activation enthropy is positive (10.e.U).

These kinetic results and the rather low nitrogen-oxygen bond energy in oxazines suggest that the epoxy-epimination proceeds by a biradical mechanism. Analogous reactions[19-21] support this idea; for example, the homolytic cleavage of the nitrogen-oxygen bond has also been assumed for the isomerisation of methylene isoxalidines (16) into pyrrolidone (17).

(16) (17)

Further, the kinetic study of the thermal isomerisation of the endoperoxides into bisepoxides also suggests a biradical mechanism[1]. However, since the nitrogen-oxygen bond is stronger and more polar than the oxygen-oxygen bond (E_{O-O} = 35 Kcal/mol, E_{N-O} = 53 Kcal/mol), this analogy is uncertain.

The rate determining step of the epoxy-epimination would be the homolytic cleavage of the nitrogen-oxygen bond in the oxazines, followed by addition of the biradical to the C=C bond. Therefore, any substituent stabilising the intermediate biradical or destabilising the original oxazine would lower the activation energy of the epoxy-epimination. The cd-vinyl substituent on nitrogen appears to stabilise sufficiently the intermediate biradical (18) and the cyclic strain in (14) reduces its stability to permit the observed rearrangement.

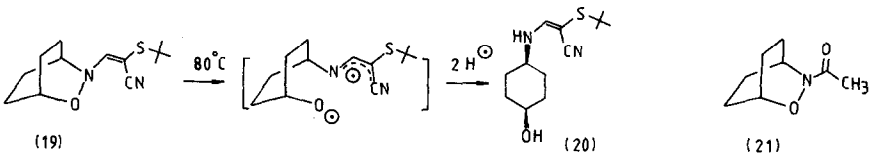


(14) (18) (15)

In order to check the proposed biradical mechanism for the rearrangement of (14) to (15), we have prepared the dihydro derivative (19) which cannot undergo epoxy-epimination. Nevertheless, this compound was expected to homolyse under the influence of the cd-vinyl group. This is indeed observed by hydrogen abstraction from xylene when (19) is heated to 80°C. Also the addition of triphenylmethane increased the rate of reduction to the amino-alcohol derivative (20).

In contrast, neither the N-acyl oxazine (10) nor its dihydro derivative[25] (21) reacted under these conditions.

These results indicate strongly the influence of the cd-vinyl group for homolytic bondbreaking[18].

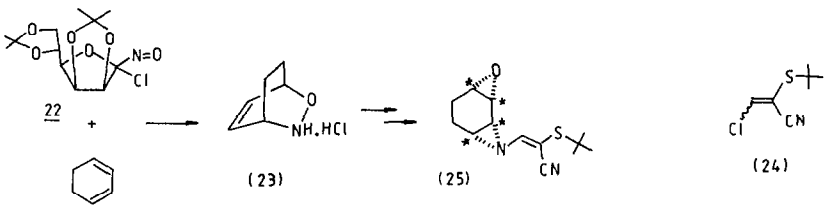


(19) (20) (21)

Applying the cd-vinyl-substituent as inducer of the rearrangement permits the enantiospecific synthesis of epoxy-epimines starting from cyclohexadiene. The chiral oxazine (23) is easily produced by cycloaddition of the chloro nitroso mannose bis-acetonide (22) to 1,3-cyclohexadiene, followed by the in situ solvolytic cleavage[22,23,16].

N-Substitution with β-chloro-α-tert-butylthioacrylonitrile[16] (24) on this oxazine followed by thermal isomerisation yields the epoxy-epimine (25) in 83 % chemical yield and in optical yield of at least 96 % ee, as determined by NMR ^{1}H using the Lanthanide shift reagents[24].

This transfer of chirality to all four originally dienic carbon atoms of cyclohexadiene is applicable to other cyclic dienes as will be described separately along with the new approaches to the synthesis of amino cyclitol derivatives.



22 (23) (25) (24)

EXPERIMENTAL

Melting points were determined on a Büchi (Dr. Tottoli) apparatus. ^{1}H NMR were recorded in a $CDCl_3$ or DMSO solution using TMS as internal reference at 200 MHz on a Varian GEMINI spectrometer, ^{13}C NMR recorded on a Varian GEMINI or XL-200 spectrometer. Infrared spectra were obtained on a Perkin-Elmer 297 instrument. Mass spectra were registered on a Varian AMT 44S spectrometer.

GENERAL PROCEDURE FOR N-SUBSTITUTED OXAZINES (11)(12)(13)(14).

To a suspension of N-unsubstituted oxazine (9) (10 mmol) in dry dichloromethane (50 ml) at 0°C triethylamine (22 mmol) and the electrophile (10 mmol) are added. The solution is left overnight at room temperature and is then extracted 3 times with dichloromethane (together 100 ml). The organic phase is washed with water (25 ml), dried over magnesium sulfate and the solvent evaporated under reduced pressure. The residue is purified by column chromatography yielding the corresponding N-substituted oxazines.

COMPOUND (11) is prepared from oxazine (9) (1 g; 6.8 mmol), triethylamine (1,5 g; 14.8 mmol) and 1-fluoro 2,4-dinitrobenzene (1,26 g; 6.8 mmol). Yield : 1,8 g (96 %) as a red solid (m.p. 119°C). ^{1}H NMR ($CDCl_3$) δ 8.73(m,1H); 8.21(m,1H); 7.47(m,1H); 6.72(m,1H); 6.25(m,1H); 4.90(M,1H); 4.51(M,1H); 2.36(m,2H); 1.52(m,2H). ^{13}C NMR ($CDCl_3$) δ 150-119(olefinics and aromatics C); 70.2(CH); 56.1(CH); 22.1(CH_2); 19.9(CH_2). MS 277(M^+), 199, 181, 80, 77, 43. Anal. Calcd. for $C_{12}H_{11}N_3O_5$: C 52.0 %, H 4.0 %; found : C 52.1 %, H 4.1 %.

COMPOUND (12) is prepared from oxazine (9) (3 g; 20 mmol), pyridine (3,2 g; 40 mmol) and benzene sulfonyl chloride (3,6 g; 20 mmol). Yield : 4,2 g (83 %) as a white solid (m.p. 123°C). ^{1}H NMR ($CDCl_3$) δ 7.80(m,2H); 7.51(m,3H); 5.94(m,2H); 4.72(M,1H); 4.61(M,1H); 2.17(m,2H); 1.39(m,2H). ^{13}C NMR ($CDCl_3$) δ 137.1(Cq); 133.8(CH); 131.0(CH); 129.9(CH); 129.6(CH); 129.0(CH); 71.2(CH); 51.1(CH); 22.8(CH_2); 21.9(CH_2). MS 251(M^+), 173, 143, 80, 72. Anal. Calcd. for $C_{12}H_{13}NO_3S$: C 57.37 %, H 5.18 %, N 5.58 %, S 12.75 %; found : C 57.4 %, H 5.2 %, N 6.63 %, S 12.7 %.

COMPOUND (13) is prepared from oxazine (9) (0,64 g; 4.3 mmol), triethylamine (0,92 g; 9.1 mmol) and 3-chloro 2-cyano acrylonitrile (0,49 g; 4.3 mmol). Yield : 0,63 g (79 %) as a white solid (m.p. 202°C). ^{1}H NMR (DMSO) δ 7.76(s,1H); 6.71(m,2H); 5.25(M,1H); 4.90(M,1H); 2.15(m,2H); 1.53(m,2H). ^{13}C NMR (DMSO) δ 143.4(CH); 131.9(CH); 131.2(CH); 118.4(Cq); 116.4(Cq); 74.4(CH); 56.2(CH); 22.3(CH_2); 21.1(CH_2) (Cq olefinic carbon is not observed). MS 187(M^+), 79, 77, 68, 54. Anal. Calcd. for $C_{10}H_9N_3O_1$: C 64.16 %, H 4.85 %; found : C 63.9 %, H 4.89 %.

COMPOUND (14) is prepared from oxazine (9) (1 g; 6.8 mmol), triethylamine (1,44 g; 14 mmol) and 3-chloro tBu-thio acrylonitrile (1,18 g; 6.8 mmol). Yield : 1,36 g (81 %) as a white solid (m.p. 92°C). ^{1}H NMR ($CDCl_3$) δ 6.77(s,1H); 6.7(m,2H); 4.87(M,1H); 4.24(M,1H); 2.29(m,2H); 1.48(m,2H); 1.25(s,9H). ^{13}C NMR ($CDCl_3$) δ 153.6(CH); 131.9(CH); 131.3(CH); 120.3(Cq); 72.7(CH); 67.9(Cq); 55.7(CH); 47.0(Cq); 30.1(CH_3); 23.1(CH_2); 21.4(CH_2); $^{3}J_{cN}^{H}$ = 12Hz(E isomer). MS 250(M^+), 194, 149, 116, 80, 57, 43. Anal. Calcd. for $C_{13}H_{18}N_2O_1S_1$: C 62.37 %, H 7.25 %, S 12.8 %; found : C 62.21 %, H 7.08 %, S 12.6 %.

COMPOUND (15) is obtained by warming oxazine (14) (2 g; 8 mmol) at 100°C under nitrogen in xylene (150 ml) for 8 hours. After removal of the solvent by vacuum distillation, the residual oil is purified by column chromatography (Kieselgel/Ethylacetate - petroleum ether 50/50) yielding 1,6 g (83 %) of (15) as a white solid (m.p. 104°C). ^{1}H NMR ($CDCl_3$) δ 7.27(s,1H); 3.49(m,1H); 3.16(m,1H); 2.82(m,1H); 2.49(m,1H); 1.87(m,4H); 1.45(s,9H). ^{13}C NMR ($CDCl_3$) δ 162.0(CH); 121.2(Cq); 87.7(Cq); 50.0(Cq); 49.4(CH); 46.9(CH); 37.4(CH); 36.4(CH); 31.2(CH_3); 20.6(CH_2); 18.1(CH_2). $^{3}J_{cN}^{N}$ = 11Hz (E isomer). MS 250(M^+), 194, 137, 124, 110. Anal. Calcd. for $C_{13}H_{18}N_2O_1S_1$: C 62.37 %, H 7.24 %, S 12.8 %; found : C 62.16 %, H 7.20 %, S 12.39 %.

GENERAL PROCEDURE FOR DIIMIDE REDUCTION OF OXAZINE DERIVATIVES (19) and (21).

A solution of acetic acid (200 mmol) in methanol (100 ml) is added to the yellow slurry formed by oxazine (10 mmol), potassium azadicarboxylate (100 mmol) and methanol (100 ml); care is taken to keep the vigorous gas evolution under control. After complete addition of the acid, the slurry is stirred until it becomes white and gas evolution stops. Water (200 ml) is added to the residual mixture after removal of most of the methanol by vacuum distillation. The aqueous solution is then extracted 3 times with dichloromethane (together 100 ml). The organic phase is washed with a saturated sodium bicarbonate solution (50 ml) and then with water, dried over magnesium sulfate and dichloromethane evaporated under reduced pressure. The residue is purified by column chromatography yielding the corresponding saturated oxazine.

COMPOUND (19) is prepared from oxazine (14) (2,5 g; 10 mmol). Yield : 2,15 g (86 %) as a white solid (m.p. 73°C). ^{1}H NMR ($CDCl_3$) δ 6.77(s,1H); 4.36(M,1H); 3.76(M,1H); 2.20(m,4H); 1.82(m,4H); 1.28(s,9H). ^{13}C NMR ($CDCl_3$) δ 153.5(CH); 122.2(Cq); 73.7(CH); 61.9(Cq); 54.1(CH); 46.7(Cq); 29.8(CH_3); 24.7(CH_2); 24.4(CH_2). $^{3}J_{cN}^{H}$ = 13Hz (E isomer). MS 252(M^+), 212, 196, 169, 156, 81. Anal. Calcd. for $C_{13}H_{10}N_2OS$: C 61.9 %, H 7.94 %, N 11.11 %, S 12.7 %; found : C 61.9 %, H 8.01 %, N 11.14 %, S 12.13 %.

COMPOUND (21) is prepared from oxazine (10) (1,53 g; 10 mmol). Yield : 1.22 g (79 %) as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 4.58(M,1H); 4.23(M,1H); 2.11(s,3H); 1.93(M,8H). This known compound was synthetized via another methodology. For complete analytical characterisation of this compound, see ref. [25].

COMPOUND (20) is obtained from oxazine (17) (1 g; 4 mmol), by warming it in xylene (75 ml) for 8 hours. After removal of the solvent by vacuum distillation, the residual oil is purified by column chromatography (Kieselgel/Ethylacetate - petroleum ether 65/35) affording 0,19 g (19 %) yield of

white liquid (19) and 0,59 g of the starting material (17). ^{1}H NMR ($CDCl_3$) δ 7.35(m,1H); 5.92(M,1H); 3.93(M,1H); 3.24(M,1H); 1.70(M,8H); 1.35(s,9H). ^{13}C NMR ($CDCl_3$) δ 155.0(CH); 123.4(Cq); 77.0(Cq); 65.2(CH); 54.7(CH); 49.3(Cq); 30.8(CH_2); 30.6(CH_3); 28.3(CH_2). $^{3}J_{CN}^{H}$ = 11.8Hz (E isomer). MS 254(M^+), 198, 180, 171. IR ν cm^{-1} 3400, 3200, 2900, 2170, 1570, 1400.

ACKNOWLEDGEMENT

We thank Z. Janousek and R. Merényi for helpful discussion. We thank SPPS (Grant 86-91/94) and IRSIA for partial financial support of this work.

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