Tetrahedron Letters No. 8, pp 585 - 588, 1975. Pergamon Press. Printed in Great Britain.

RING SIZE IN δ-EPOXYNITRILES CYCLIZATION

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(Received in UK 2 January 1975; accepted for publication 16 January 1975)

A recent publication by Stork and coworkers[1] on the cyclization of δ-epoxynitriles, promptsus to report some of our results. Interest in the syntheses of simple molecules related to prostaglandins lead us to investigate the feasibility of a stereoselective cyclization of cis or trans δ-epoxynitriles to furnish cyclopentane systems with three asymmetric carbons (Figure 1).

Figure 1

Intermolecular nucleophilic opening of epoxide ring is well known, however there are few examples of this type of the intramolecular reaction[2], especially on non-rigid molecules[3]. Very little attention has been devoted to the possible influence of the epoxide stereochemistry[4].

Pure cis 1a (R=-CH_3) was prepared by the successive alkylation of sodium acetylide by 1-bromo, 3-chloro propane and of the acetylide of the product with methyl iodide, followed by displacement of the chlorine by cyanide in dimethylsulfoxide. Reduction (H_2, 1 atm., Pd/Ba_2CO_3) furnished 1a. Epoxidation of 1a by peracetic acid (CH_2Cl_2/Drierite) gave 2a. Upon treatement of 2a with powdered sodium amide in tetrahydrofuran (4 hrs, 40°C) a mixture of two cyanoalcohols was obtained : 3a and 4a[5]. Oxidation by modified Collins reagent gave the corresponding methyl-ketones. I.R. (ν = 2234, 1725 cm^{-1}), NMR spectra (singlet at 2.16 δ,-CH_3) are consistent with structure 5a and 6a (Figure 2).

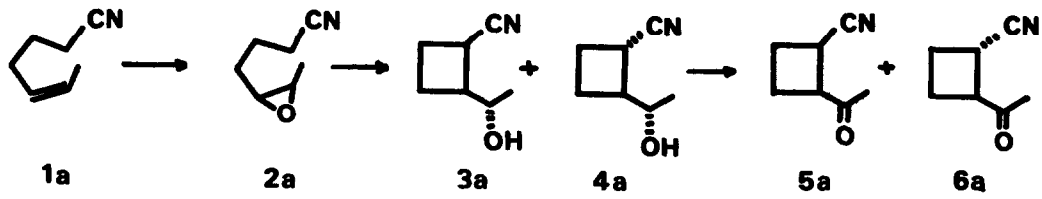
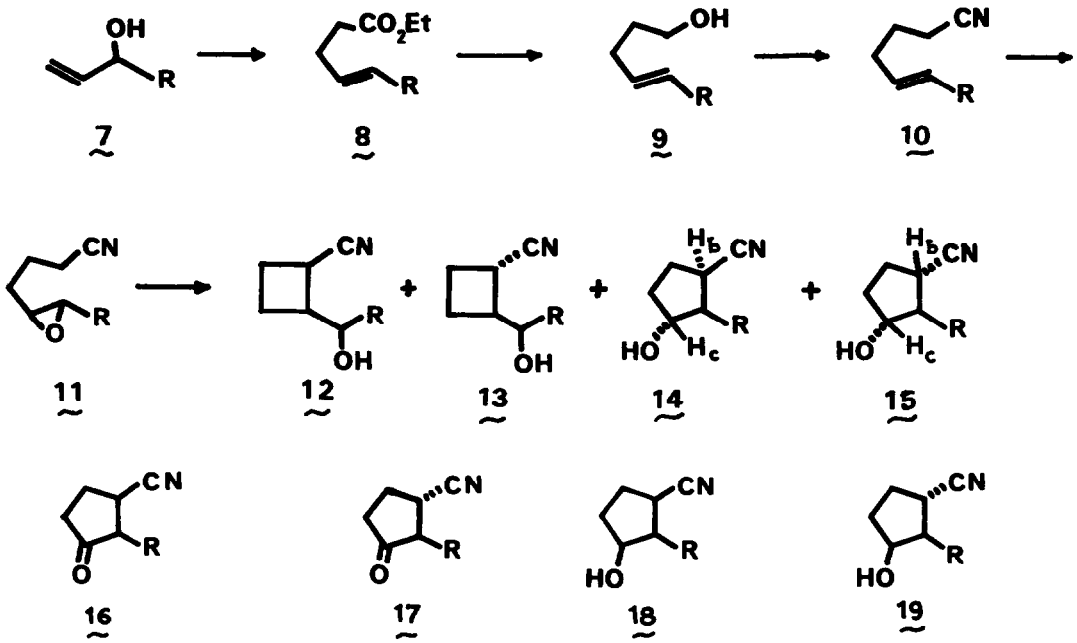


Figure 2

Alcohol 7 reacted with ethylorthoacetate[6] to give 8 which after reduction ($LiAlH_4$), formation of the tosylate and displacement of the tosylate by cyanide, lead to the pure unsaturated trans nitrile 10. Trans epoxide 11a (R=-CH_3) was prepared by usual methods and cyclised in presence of sodamide in dry tetrahydrofuran to furnish a mixture of the four isomeric cyanoalcohols 12a, 13a, 14a and 15a. The reaction failed with sodium or potassium amide in liquid ammonia or in benzene. Careful chromatography allows complete separation of the isomers. Cyclobutane derivatives 12a and 13a are readily identified by IR, NMR[5] and mass spectra. Oxidation furnished the corresponding ketones 5a and 6a (IR = 1725 cm^{-1}).

The two other isomers exhibit no visible coupling between the methyl protons and H_c in α-position of the hydroxy group and were identified as 14a (NMR -CH_3: doublet 1.13, H_b = 3.15, H_c = 3.95 δ) and 15a (NMR -CH_3 : doublet 1.18, H_b = 2.35 H_c = 3.75 δ). Oxidation of each isomer gave same mixture of cyanoketones 16a (30%, oil, NMR -CH_3 : doublet 1.31 δ) and 17a (70%, m.p. = 46°C, Lit.[7] 47-49°C, NMR -CH_3 : doublet 1.26 δ, carbonyl frequency : ν = 1752 cm^{-1}, cyclopentanone).

Reduction of the cyanoketone mixture ($NaBH_4$, MeOH) yields 14a and 15a with a smaller amount (24%) of other isomers 18a and 19a, and indicates that cyclization has been stereoselective with regards to the epoxide stereochemistry. Neither 18a or 19a were present in the reaction mixture arising during the original cyclization (NMR and GC).



Same reaction sequences allow preparation of 11b (R=-C_4H_9) and 11c (R= -C_5H_{11}). Cyclization under the same reaction conditions gave the corresponding cyclopentane and cyclobutane cyano alcohols. The yields and the cyclopentane/ cyclobutane ratios are summarized in Table I (calculated from G.C. and I.R. on ketones).

Table I

	C-5/C-4	Yields
R = -CH_3	72/28	90%
R = -C_4H_9	62/38	88%
R = -C_5H_{11}	65/35	88%
R = -H	no reaction	

From these results it is clear that stereoselective cyclization of trans δ-epoxynitriles into trisubstituted cyclopentane systems can be achieved in rather good yields. Stork's observation of preferential cyclobutane formation appears to be a consequence of the cis stereochemistry.

Although steric interactions in the transition state inhibit cyclopentane formation for cis 6-epoxynitriles, only statistical and geometrical factors are involved in the cyclization of the trans isomers. Thus, the C-5/C-4 ratio only varies slightly with the size of the R-group.

References and notes

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5 - Both compounds exhibited coupling between a proton α to the -OH group with the $-CH_3$ group. Hence these compounds are cyclobutanes 3a and 4a and not cyclopentanes.

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