New Addition Reactions. III. Addition of Aliphatic Epoxides to Nitriles

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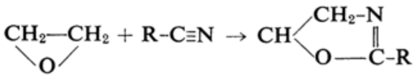
In a previous paper[1], the formation of oxazolidines by the cyclic addition of Schiff bases to epoxides in the presence of Lewis acid catalysts was described. In this connection, the early study of a similar addition of sodium cyanamide to ethylene oxide to yield 2-amino-2-oxazoline by Fromm et al.[2] is of interest.

We have now extended this addition to study the reactions of aliphatic or aromatic nitriles with aliphatic epoxides in concentrated sulfuric acid. The formation of the cyclic adduct is illustrated by the following equation. When a Lewis acid catalyst was employed, however, no product, except for a polymeric product of the epoxide, was obtained:



$R=CH_3$, C_6H_5, etc.

In this concentrated sulfuric acid medium, some competitive reactions — e.g., addition of water and sulfuric acid to the epoxide, and hydrolysis of the nitrile—may be expected. In fact, the reaction of ethylene oxide with phenylacetonitrile afforded a 37% yield of phenylacetamide, in addition to the desired adduct (5%) and the unchanged nitrile (51%). However, isolation of the by-products derived from the epoxide was difficult because of their water-soluble nature, but the observation that, in a blank experiment with epichlorohydrin, the loss amounted to roughly 80% and no water-insoluble product except for the unchanged epoxide was isolated, seems to support the possibility of the occurrence of the above-mentioned side-reactions.

In view of the appreciable loss of epoxide, all reactions were carried out in a molar ratio of 2 epoxide to 1 nitrile. The reaction temperature was maintained at 5~10°C. The results of several experiments are shown in Table I. At somewhat higher temperatures, a decrease in the yield of the desired product was observed. Moreover, an attempted reaction with styrene oxide was unsuccessful owing to its rapid hydration.

In the addition of propylene oxide to acetonitrile, two isomers of the product, i.e., 2, 4- and 2, 5-dimethyl-2-oxazolines, are possible. In fact, although only one basic fraction was obtained by distillation, vapor phase chromatographic analysis indicated that it was composed of 70% of the 2, 4-isomer and 30% of the 2, 5-isomer. A similar orientation was observed on the addition of the same epoxide to benzonitrile. Here, the authentic materials used for the assignments of structure were prepared by a condensation reaction[3]. The predominant ring-opening at secondary carbon suggests an S_N1-like mechanism[4] which involves a nucleophilic attack by nitrile on the carbonium ion resulting from the ring-opening of the protonated epoxide. On the other hand, the reaction of epichlorohydrin with acetonitrile afforded only one isomer which was chromatographically homogeneous; no characterization of it was made because of the failure of an attempted independent synthesis. If the orientation is much influenced by the electron-withdrawing chlorine atom, as is seen in other acidic additions to epichlorohydrin[5], the 2, 5-isomeric structure rather than the 2, 4-isomeric structure for the adduct would be more likely.

Experimental[6]

Illustrative examples are given below.

2-Phenyl-2-oxazoline.—Benzonitrile (51.5 g., 0.50 mol.) was gradually dissolved in 55 ml. of concentrated sulfuric acid at ca. 0°C. Into this solution 44.5 g. (1.00 mol.) of ethylene oxide was dropped over a period of 3 hrs. with stirring. The temperature was maintained at 5~10°C. After completion of this addition, stirring at 10°C was continued for 2 hr. The reaction mixture was then allowed to stand overnight below 10°C and poured slowly into ca. 200 ml. of ice and water. The solution was made slightly acidic below 20°C with aqueous sodium hydroxide, and the precipitated mixture of sodium sulfate and benzamide was filtered off. The filtrate was extracted with benzene to remove the unchanged nitrile and then made strongly basic by the addition of a concentrated sodium hydroxide solution. It was then extracted with three 100 ml. portions of ether. The combined ether extracts were washed with a saturated sodium chloride solution and

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[1] R. Oda, M. Okano, S. Tokiura and A. Miyasu, This Bulletin, **35**, 1216 (1962).

[2] E. Fromm et al., *Ann.*, **442**, 130 (1925).

[3] H. Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).

[4] Cf. R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 742 (1959).

[5] "Epichlorohydrin", Shell Chem. Corp., New York., N. Y. (1949).

[6] All boiling and melting points are uncorrected.

TABLE I. FORMATION OF 2-OXAZOLINES FROM ALIPHATIC EPOXIDES AND NITRILES

Epoxide	Nitrile	Product	B. p., °C (mmHg)	Yield[a] %	M. p. of picrate, °C
Ethylene oxide	Acetonitrile	2-Methyl-2-oxazoline	110[b]	7	162[c]
Ethylene oxide	Isobutyronitrile	2-Isopropyl-2-oxazoline	137~138[d]	21(29)	134[e]
Ethylene oxide	Phenylacetonitrile	2-Benzyl-2-oxazoline	136~137 (20)[f]	5(10)	141[g]
Ethylene oxide	Benzonitrile	2-Phenyl-2-oxazoline	121(13)[h]	19(42)	177[i]
Propylene oxide	Acetonitrile	Mixt. of 2,4- and 2,5-dimethyl-2-oxazolines (70 : 30)[j]	116~118[k]	8	
Propylene oxide	Benzonitrile	Mixt. of 4- and 5-methyl-2-phenyl-2-oxazolines (70 : 30)[j]	127~129 (22)[l]	5(12)	
Epichlorohydrin	Acetonitrile	4- or 5-Chloromethyl-2-methyl-2-oxazoline	73~75 (9)[m]	12	127[n]
Epichlorohydrin	Acrylonitrile	4- or 5-Chloromethyl-2-vinyl-2-oxazoline	92~93 (22)	2	

[a] The figures in parentheses represent conversions based on consumed nitriles.
[b] Ref. 3 gives b. p. 111°C.
[c] Ref. 3 gives m. p. 163°C.
[d] Found: C, 63.49; H, 9.80; N, 12.60. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.39%.
[e] Found: C, 41.84; H, 3.79; N, 16.44. Calcd. for $C_{12}H_{14}N_4O_8$: C, 42.11; H, 4.12; N, 16.37%.
[f] Found: C, 74.81; H, 6.66; N, 8.81. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.
[g] Monohydrate. Found: C, 47.81; H, 4.24; N, 13.75. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.95; N, 13.72%.
[h] Ref. 3 gives b. p. 247°C.
[i] Ref. 3 gives m. p. 177°C.
[j] Determined by v. p. c. analysis.
[k] Found: C, 60.69; H, 9.19; N, 14.01. Calcd. for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13%.
[l] Found: C, 74.53; H, 6.80; N, 8.42. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69%.
[m] Found: C, 44.96; H, 6.13; N, 10.19; Cl, 26.62. Calcd. for C_5H_8NOCl: C, 44.95; H, 6.04; N, 10.49; Cl, 26.54%.
[n] Found: C, 36.77; H, 3.20; N, 15.63. Calcd. for $C_{11}H_{11}N_4O_8Cl$: C, 36.43; H, 3.06; N, 15.45%.

dried. The solvent was removed by evaporation, and the resulting oil was distilled to yield 13.9 g. (19%) of 2-phenyl-2-oxazoline, b. p. 121°C/13 mmHg. The recovered benzonitrile from the benzene extact weighed 28.4 g. (54%).

A Mixture of 2, 4- and 2, 5-Dimethyl-2-oxazolines.—Into a solution of 20.5 g. (0.50 mol.) of acetonitrile in 55 ml. of concentrated sulfuric acid, 58 g. (1.00 mol.) of propylene oxide was dropped over a period of 3 hr. at 5~10°C. Stirring was continued at 10°C for an additional 2 hr. After the solution had stood overnight below 10°C, the reaction mixture was gradually poured into 200 ml. of ice and water. The solution was then neutralized with aqueous sodium hydroxide, and the resulting precipitate was filtered off. The filtrate was made strongly basic with concentrated sodium hydroxide and extracted three times with 100 ml. of ether. After the removal of the ether, the residue was distilled and 4.1 g. (8%) of the product, b. p. 116~118°C, was obtained. Recovery of unchanged acetonitrile was difficult due to its water-solubility. A redistilled sample prepared for elemental analysis was chromatographed on a 2-meter column containing polyethylene glycol 4000-Celite 545 (3 : 7 by weight), with hydrogen as a carrier gas, at 70°C. Data showed that it was composed of 70% of 2,4-dimethyl-2-oxazoline (low retention) and 30% of the 2,5-isomer (high retention). Authentic 2,4- and 2,5-dimethyl-2-oxazolines used as references were prepared by the method of Wenker[3] from 2-amino-1-propanol and 1-amino-2-propanol with acetic acid respectively. The 2-amino-1-propanol used here was synthesized by esterification of *dl*-alanine[7], followed by reduction with lithium aluminum hydride[8]. 1-Amino-2-propanol was commercially available. The pure 2,4-isomer boiled at 116~117°C [lit.[9] 30°C/35 mmHg], and its picrate melted at 130~131°C (lit.[9] 130~135°C). The 2,5-isomer boiled at 117~118°C (lit.[10] 117~119°C), and its picrate at 114~115°C (lit.[10] 114~115°C).

***x*-Chloromethyl-2-vinyl-2-oxazoline and its Polymer.**—The procedure employed was similar to that used for the preparation of the above oxazoline except that a small amount of hydroquinone was added as a polymerization inhibitor. The product, b. p. 92~93°C/22 mmHg, easily polymerized on

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[7] S. D. Brewer and R. M. Herbst, *J. Org. Chem.*, **6**, 870 (1941).

[8] D. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948).

[9] N. V. Organon, Dutch Pat. 81868; *Chem. Zentr.*, **1959**, 3971.

[10] A. Uekinck, *Ber.*, **32**, 975 (1899).

standing. No effort was made to characterize the structure of the adduct. In the bulk polymerization using benzoyl peroxide as an initiator, a hard, clear, colorless polymer was obtained. This polymer is soluble in water and *m*-cresol, but insoluble in ethanol and benzene.

Found: C, 48.75; H, 5.43; N, 9.73; Cl, 24.15. Calcd. for $(C_6H_8NOCl)_n$: C, 49.50; H, 5.54; N, 9.62; Cl, 24.35%.

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