A NOVEL RING FORMATION OF 1,2-DIHYDROQUINOXALINES

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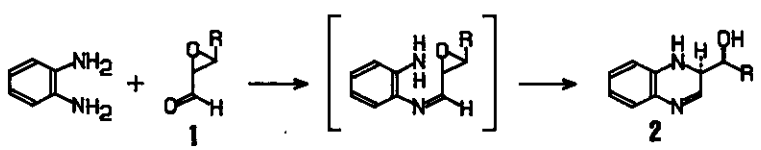
Abstract——Reaction of o-phenylenediamine with 2,3-epoxyaldehydes gives 2-hydroxyalkyl-1,2-dihydroquinoxalines, while the reaction with 2,3-epoxyesters gives either dihydroquinoxaline derivative or the uncyclized hydroxyamino ester.

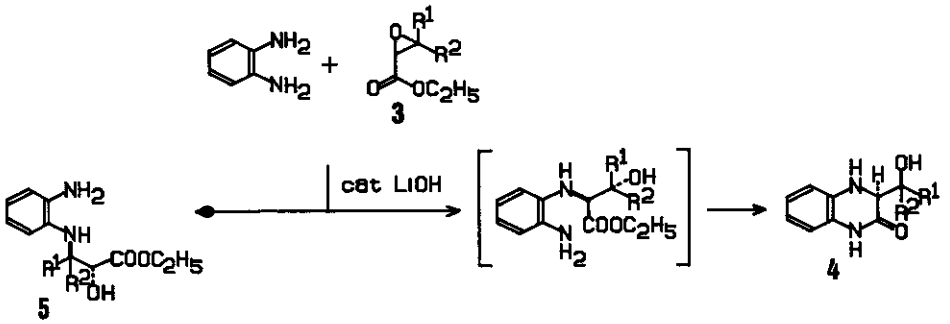
Although 2,3-epoxycarbonyl compounds seem to be widely applicable as the trifunctionalized precursor for stereocontrolled organic syntheses, these molecules have been little taken into account for syntheses of heterocycles.[1] In this paper, we describe the synthetic utilities of 2,3-epoxyaldehydes and -esters for quinoxalines,[2] which may develop an effective procedure for biologically active pteridines, e.g. biopterin[3] and neopterin.

Stereospecific ring opening of 2,3-epoxycrotonaldehyde and -cinnamaldehyde [1] by o-phenylenediamine gave the respective erythro-2-hydroxyalkyl-1,2-dihydroquinoxalines [2]. The reaction proceeded stepwise via a Schiff base formation followed by an intramolecular nucleophilic ring opening of epoxide.



2a: R = CH_3, 69%; **2b**: R = Ph, 78%

On the contrary, ring opening of 2,3-epoxyesters 3 by o-phenylenediamine required the LiOH catalysis, which could activate both epoxide oxygen as a Lewis acid and nitrogen as a base. Since ring opening occurred at the first step rather than the amide formation, the products were strongly influenced by the position of the bond cleavege. In the cases of ethyl esters of 2,3-epoxycrotonic, -pentenoic,



4a: $R^1 = CH_3$, $R^2 = H$, 78%; **4b**: $R^1 = C_2H_5$, $R^2 = H$, 65%; **4c**: $R^1 = R^2 = CH_3$, 81%
5a: $R^1 = R^2 = H$, 46%; **5b**: $R^1 = Ph$, $R^2 = H$, 53%

and -3,3-dimethylacrylic acids, carbon-oxygen bond cleaveges on the α-carbon and the subsequent intramolecular aminolysis gave the quinoxalines **4**. Because of a less steric hindrance or benzylic activation on the β-carbon, the amino group attacked to β-carbons of 2,3-epoxyacrylate and -cinnamate to give 3-amino-2-hydroxyesters **5** in which the intramolecular cyclization hardly proceeded.

The following procedures are representative. A mixture of o-phenylenediamine (0.22 g, 2 mmol) and trans-2,3-epoxycrotonaldehyde (0.17 g, 2 mmol) in CH_3OH (2 ml) was stirred at 25 °C for 3 h. After removal of the solvent, column chromatography on silica gel eluting with 10% EtOAc in CH_2Cl_2 gave erythro-2-(1-hydroxyethyl)-1,2-dihydroquinoxaline (**2a**, 0.24 g, 69%) as yellow oil. Ethyl trans-2,3-epoxycrotonate (0.26 g, 2 mmol) was heated with o-phenylenediamine (2 mmol) under presence of LiOH (0.02 g) in C_2H_5OH (2 ml) at 80 °C for 48 h. From the mixture erythro-2-(1-hydroxyethyl)-3-hydroxy-1,2-dihydroquinoxaline (**4a**, 0.30 g, 78%) was obtained as colorless crystals (mp 200-202 °C) by a silica-gel column.

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(1) 2,3-Epoxycrotonaldehyde was once employed for synthesis of a heterocycle, see: W. C. Lumma, Jr. and J. P. Springer, J. Org. Chem., 1981, **46**, 3735.

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(3) E. L. Patterson, R. Milstrey, and E. L. R. Stockstad, J. Am. Chem. Soc., 1956, **78**, 5868.

Received, 8th December, 1986