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Aryl epoxide–halohydrin transformations: stereochemistry of reactions of aryl epoxides with lithium halide–acetic acid reagent

Jeanne-Marie Bartas-Yacoubou, Nkabuije Maduike, Sampson Kyere, Lanxuan Doan and Dale L. Whalen*

Department of Chemistry and Biochemistry, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, USA

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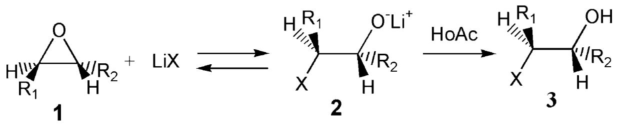
Abstract—The reactions of indene oxide (**4a**), 5-methoxyindene oxide (**4b**), 1,2,3,4-tetrahydronaphthalene-1,2-epoxide (**5a**) and 6-methoxy-1,2,3,4-tetrahydronaphthalene-1,2-epoxide (**5b**) with lithium halides in the presence of acetic acid (LiX/HOAc) yield mixtures of *cis* and *trans* halohydrins. These results are in contrast to those reported for the reactions of a series of aliphatic epoxides with LiX/HOAc, which proceed stereospecifically to yield only *trans* halohydrins. © 2002 Elsevier Science Ltd. All rights reserved.

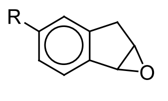
The reactions of a series of unsymmetrical epoxides with lithium halides and acetic acid (LiX/HOAc) in THF proceed with a high degree of regioselectivity to yield halohydrins in which the halogen group is located at the less substituted carbon.[1] The reactions are also stereospecific, yielding only halohydrins from *trans* epoxide ring opening. It was proposed that the mechanism for this reaction involves reversible epoxide ring opening by nucleophilic attack of halide ion, followed by protonation of the intermediate alkoxide ion, which drives the reaction to completion (Scheme 1).

anti-Benzo[a]pyrene 7,8-diol 9,10-epoxide (anti-BPDE), a carcinogenic metabolite of the environmental pollutant, benzo[a]pyrene, is also converted to its *trans* chlorohydrin by reaction with LiX/HOAc.[2] A number of aryl and vinyl epoxides react with chloride ion in water solutions to yield chlorohydrins[3–5] both by a mechanism similar to that in Scheme 1 and by capture of benzylic carbocations with chloride ion. Because of our interest in understanding the mechanisms of reaction of aryl epoxides and their chlorohydrins with nucleophiles, including nucleic acids, we attempted to prepare pure *trans* chlorohydrins from a number of aryl epoxides by their reactions with LiX/HOAc for mechanistic studies. Instead of obtaining pure *trans* chlorohydrins from these reactions, we have observed that both *cis* and *trans* chlorohydrins are formed.

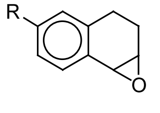


Scheme 1.

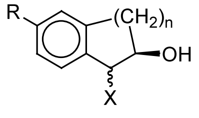
We have examined the reactions of indene oxide (**4a**), 1,2,3,4-tetrahydronaphthalene-1,2-epoxide (**5a**), and their 5- and 6-methoxy substituted derivatives **4b** and **5b** with LiCl/HOAc in THF. This procedure yielded chlorohydrin products with the chloro group substituted at the benzylic position (**6a**,**b**). When the published general procedure[1] for reaction of an epoxide with LiCl/HOAc was followed, the reactions of **4a** and **5a** each gave chlorohydrin product, but both *cis* and *trans* stereoisomers[6,7] were formed (Table 1). When this procedure, which involves dilution of the reaction mixture with water and extraction of the chlorohydrin product into diethyl ether, is followed for the reactions of methoxy-substituted epoxides **4b** and **5b** with LiCl/HOAc, however, chlorohydrin products could not be isolated. When the procedure was modified so that only a relatively small excess of acetic acid (1.4–1.5 equiv.) and a large excess of lithium chloride (9–12 equiv.) were used, and an aqueous workup was avoided, then chlorohydrin products were isolated.[8]



4a, R=H
b, R=OCH$_3$



5a, R=H
b, R=OCH$_3$



6a, R=H
b, R=OCH$_3$

Keywords: aryl epoxides; lithium halides; chlorohydrins; stereochemistry.

* Corresponding author. Tel.: 410-455-2521; fax: 410-455-2608; e-mail: whalen@umbc.edu

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Table 1. Summary of *cis*/*trans* chlorohydrin product ratios from reactions of aryl epoxides **4**(**a**,**b**) and **5**(**a**,**b**) with LiX[a]/HOAc in THF[b]

Cmpd-LiX	[LiX]:[HOAc]	Rxn time	% Rxn	*cis*:*trans*
4a-LiCl	2.0:3.6	13 h	72	12:88
4b-LiCl	12.5:1.35	11 min	>95	38:62
5a-LiCl	2.3:3.3	8 h	53	12:88
5b-LiCl	9.0:1.5	15 min	>95	61:39
4a-LiBr	2.0:3.3	12 h	>95	16:84
5a-LiBr	2.4:2.9	6.5 h	>95	26:74

[a] The lithium halides were dried at 100°C for >12 h.

[b] Tetrahydrofuran was freshly distilled from sodium metal before use.

We have observed that the rates of reaction of **4a** and **5a** with LiX/HOAc/THF depend markedly on whether the lithium salts are anhydrous. The reactions of **4a** and **5a** with lithium salts that were not dried before use were approximately 10 times faster than those with dry lithium halide salts, although the *cis*/*trans* halohydrin product mixtures were not significantly changed. The reaction of **5a** with LiCl that was not dried before use also yielded minor amounts (~10%) of other unidentified products.

The reactions of **4a** and **5a** with LiBr/HOAc are also significantly faster than with LiCl/HOAc, and give slightly greater yields of *cis* halohydrins (Table 1). Subsitiution of dimethyl malonate and other weak acids with pK_as less than that of an alcohol (~16) for HOAc in the reaction of phenyl glycidyl ether with LiI are reported to proceed in good yield.[1] However, when diethyl malonate is substituted for HOAc in the reactions of **5a** with LiCl and LiBr, <5% reaction occurs after 15 h.

The observation that reactions of aryl epoxides **4**(**a**,**b**) and **5**(**a**,**b**) with LiX/HOAc yield significant amounts of *cis* halohydrins can be attributed to the fact that acid-catalyzed epoxide ring openings of these epoxides yield resonance stabilized carbocations. The epoxides previously studied[1] that yield only *trans* halohydrins upon reaction with LiX/HOAc would yield unstable primary or secondary carbocations upon reaction with acids. Therefore, in the reactions of those epoxides[1] with LiX/HOAc the mechanism in Scheme 1 (and mechanisms involving concerted proton donation and nucleophile addition that also would give *trans* chlorohydrins) are favored over a mechanism involving a carbocationic intermediate.

Acknowledgements

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6. The ^{1}H NMR absorption's of the benzylic hydrogens alpha to the C–Cl bond in the *cis* chlorohydrins from **4a** and **5a** absorbed as doublets at δ 5.36 ($J = 5.1$ Hz) and 5.34 ($J = 3.0$ Hz), respectively ($CDCl_3$). The corresponding absorptions for the *trans* chlorohydrins from **4a** and **5a** absorbed as doublets at δ 5.12 ($J = 4.2$ Hz) and 5.02 ($J = 6.9$ Hz), respectively ($CDCl_3$).
7. Stirring biphasic solutions of mixtures of *cis* and *trans* indene chlorohydrins, mixtures of *cis* and *trans* indene bromohydrins and mixtures of *cis* and *trans* 1,2-dihydronaphthalene chlorohydrins in diethyl ether with aqueous 1.0 M NaOH solution led to formation of the corresponding epoxide and reduction is relative size of one of the ^{1}H NMR absorptions due to the benzylic hydrogens alpha to the halo group. The benzylic C–H absorption that disappeared more rapidly when the halohydrin mixture from each system was treated with base was assigned to the *trans* halohydrin. The assignment of stereochemistry to the methoxy-substituted halohydrins was based on the assumption that the relative chemical shifts and coupling constants of the benzylic alpha hydrogens parallel the relative chemical shifts and coupling constants of the known *cis* and *trans* halohydrins in the parent systems.
8. For reactions of **4b** and **5b** with LiCl/HOAc, 20–30 mg of epoxide in 0.5 mL of THF was added to a solution of LiX (9–12 equiv.) and HOAc (1.3–1.5 equiv.) in 4 mL of THF. After the time indicated (Table 1), the solvent was removed at aspirator pressure and 1.0 mL of $CDCl_3$ was added. The lithium salts were removed by filtration and the filtrate was analyzed by ^{1}H NMR.