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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Yue-jin Liu, Ting-yi Chu & Robert Engel (1992) A Synthetically Useful Regioselective Epoxide Ring-Opening Procedure, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:16, 2367-2371, DOI: <u>10.1080/00397919208019093</u>

To link to this article: http://dx.doi.org/10.1080/00397919208019093

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A SYNTHETICALLY USEFUL REGIOSELECTIVE EPOXIDE

RING-OPENING PROCEDURE

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ABSTRACT

The reaction of alcohols with epoxides in the presence of boron trifluoride etherate has been investigated and found to proceed with variable regioselectivity depending on the substituents attached to the oxirane ring.

INTRODUCTION

The opening of the epoxide ring of glycidyl tosylate by alcohols in the presence of boron trifluoride etherate has been used for the synthesis of analogues of platelet-activating-factor. ¹ In this acid catalyzed epoxide ring-opening process the alcohol exhibits a notable regioselectivity attacking the terminal carbon of the chain and giving the terminal ether product in 80% yield.

This general type of reaction has been of interest for our work in the preparation of a variety of phosphonic acid analogues of natural phosphates. For example, using the diisopropyl ester of (S)-(E)-3,4-epoxybut-1-enylphosphonic acid (1) as a substrate, reaction with stearic acid in the presence of boron trifluoride etherate has been observed to give the diisopropyl ester of (S)-(E)-4-octadecyloxy-3-hydroxybut-1-enylphosphonic acid (2) in 70% yield.² None of the alternative regioisomer product could be detected in the work-up of this reaction. The regioselectivity of this reaction was verified by subsequent acetylation to generate

the (S)-(E)-3-acetyloxy-4-stearoyloxybut-1-enylphosphonic acid diisopropyl ester (3) and the examination of the ¹H NMR spectra of the starting material and product.² This result and that previously reported ¹ prompted an investigation of the generality of the regioselective nature of the boron trifluoride induced opening of epoxides.



RESULTS AND DISCUSSION

This investigation has involved the study of a series of four additional epoxide substrates using methanol or 1-octadecanol as the nucleophilic agent. The epoxides investigated are illustrated as **4a-d** in Scheme 1. The ring-opening reactions were performed according to the general procedure as outlined in the Experimental section. In each instance the ring-opened product(s) obtained from the reaction mixture were subjected to HPLC for purification and quantification of their yields, and subsequent identification was performed by chemical transformation and investigation of their ¹H NMR and IR spectra.

For the reaction of methanol with 4a, a mixture of 5a and 6a was found with attack by the methanol at the terminal position of the epoxide being the dominant process (5a/6a = 1.62), although the degree of regioselectivity observed was significantly less than that noted in previous reactions. The materials 5a and 6a were identified by oxidation using the Sarett reagent³ and distinctive ¹H NMR spectra of the resulting ketone and aldehyde products When styrene oxide (4b) was used as the substrate with methanol as the nucleophile under the same conditions as used with 4a, a regiospecific reaction was observed in which the only product formed was 6b resulting from attack at the internal position of the epoxide.

REGIOSELECTIVE EPOXIDE RING-OPENING PROCEDURE



Scheme 1

Identification of the product was again made by investigation of the ¹H NMR spectra of the product and that of its derivative aldehyde produced by Sarett oxidation. This regiochemistry was opposite to that observed in the syntheses 1,2 previously noted.

When the epoxide substrate 4c was taken with methanol as the nucleophile under the same reaction conditions as used with 4a and 4b, the formation of a single product was again observed. This product was identified (by Sarett oxidation and ¹H NMR measurement) as 5c, that resulting from attack at the terminal position of the epoxide. Finally, the epoxide substrate 4d was allowed to react under the same conditions, using 1-octadecanol as the nucleophile. This reaction again exhibited a high degree of regioselectivity (98% yield of product, >49/1 5d/6d) in which attack by the nucleophile at the terminal position of the epoxide was favored.

In summary, regioselectivity is observed in the boron trifluoride etherate facilitated epoxide opening with alcohols, but it varies with the nature of the substituents of the oxirane ring. For those systems in which a substituent provides particular stabilization of charge by delocalization from the substituted site (as with a phenyl ring), attack at the internal position occurs exclusively and the reaction is of synthetic utility for the formation of a single regioisomer. Ordinary alkyl groups do not provide sufficient charge delocalization to result in a highly regioselective reaction. However, when a substituent is present which would disfavor the generation of a positively charged site, reaction occurs with a high regioselectivity at the unsubstituted position and is of synthetic utility for the production of a single regioisomer.

EXPERIMENTAL

Reagents were commercial materials used without further purification with the following exceptions: methylene chloride was distilled prior to use; 1-decene oxide was prepared using a standard procedure;⁴ benzyl glycidyl ether was prepared using a standard procedure;⁵ the 2-phenylethyl glycidyl ether was prepared from the corresponding diol by selective tosylation at the terminal position and ring closure with potassium carbonate. ⁶ The ¹H NMR spectra were measured using an IBM-Brucker WP200SY instrument, and IR spectra were measured using a Perkin-Elmer 1600 FTIR.

The general experimental procedure for the reaction of an epoxide with an alcohol in the presence of boron trifluoride etherate is as follows: In a 100 mL round-bottomed flask equipped with a magnetic stirrer and ice bath, maintained under a nitrogen atmosphere, is placed dry methylene chloride (25 mL), the epoxide (20 mmol), and alcohol (with methanol, 15 mL; with 1-octadecanol, 20 mmol). With cooling to 0° and stirring there is added dropwise 0.81 *M* boron trifluoride etherate in methylene chloride (1.0 mL). The reaction mixture is stirred at 0° for one hour, followed by stirring at ambient temperature for 18 hours. After this time volatile materials are removed under reduced pressure and the residue is subjected to flash chromatography for the isolation of products.

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(Received in USA 16 April, 1992)