

AN EFFICIENT METHOD FOR SYNTHESIZING [d₆]-BUTADIENE MONOEPOXIDE

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SUMMARY

Epoxides are known mutagenic and carcinogenic metabolites of alkenes. During current toxicological investigations in our laboratory, we have monitored *in vivo* epoxide levels using gas chromatography/mass spectroscopy isotope dilution assays. These assays require the use of deuterated analogues for the expected epoxide metabolites. To determine whether butadiene monoepoxide is formed *in vivo* following inhalation of 1,3-butadiene, deuterated butadiene monoepoxide, a compound that is not commercially available, was needed. To meet this need, we developed a method using monoperoxyphthalic acid to synthesize [d₆]-butadiene monoepoxide from [d₆]-1,3-butadiene with a reaction time of 50 min and a 94% yield.

Key Words: 1,3-Butadiene, Butadiene Monoepoxide, [d₆]-1,3-Butadiene, [d₆]-Butadiene Monoepoxide, Monoperoxyphthalic Acid, Epoxidation

INTRODUCTION

1,3-Butadiene is a high-volume chemical used in industry (1). The standards for occupational exposure to 1,3-butadiene are currently under

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review by the Occupational Safety and Health Administration due to its reported carcinogenicity in rodents. Carcinogenicity of 1,3-butadiene is believed to be due to epoxide metabolites, but few studies have quantitated the *in vivo* concentration of butadiene monoxide and diepoxide following inhalation exposure to butadiene (2,3).

We have shown the utility of using gas chromatography/mass spectroscopy (GC/MS) isotope dilution assays to monitor *in vivo* blood propylene oxide levels following inhalation exposure to propylene (4). In that study, commercially available [d₆]-propylene oxide was used as the internal standard. An analogous investigation of 1,3-butadiene required synthesis of [d₆]-butadiene monoepoxide, a compound that is not commercially available. Brougham *et al.* (5) and Querci and Ricci (6) have described methods using monoperoxyphthalic acid (MMPP) to synthesize epoxides from alkenes with good yields. In both reports, the liquid alkene was added to a mixed-solvent system containing the MMPP and stirred for relatively short periods of time. Our synthesis differs from these methods in that our alkene substrate is a gas at room temperature. Thus, we have modified the method of Brougham *et al.* (5) to synthesize [d₆]-butadiene monoxide from [d₆]-1,3-butadiene.

EXPERIMENTAL

Chemicals. MMPP (magnesium salt hexahydrate, 80% pure), 1,3-butadiene, butadiene monoepoxide (98% pure), and butadiene diepoxide (95% pure) were purchased from Aldrich Chemical Corporation (Milwaukee, WI). Deuterated 1,3-butadiene (98.99 % D) was purchased from MSD Isotopes (Rahway, NJ).

Synthesis of Butadiene Monoepoxide. MMPP (0.5 g, 0.81 mmoles) was stirred into 5 ml water (pH 5.5) contained in a 25-ml, three-neck flask at room temperature. Attachments for gas introduction were fitted on two necks, and a 14/20 joint capped by a rubber septa was attached to the third neck as a sampling port. The internal volume of this assembly was ca. 100 ml. The reaction flask was evacuated and the synthesis begun by adding 1 atmosphere of 1,3-butadiene (\approx 3.4 mmoles at 620 Torr in Albuquerque) into the flask. During the 50-min synthesis, 1- μ l aliquots of the aqueous mixture were tested at various times for butadiene monoepoxide formation using a GC/MS (Hewlett-Packard, GC model 5890 series II, 5970 series Mass Selective Detector) equipped with a 40-meter, 180-micron, DB-Wax capillary column (J & W Scientific, Folsom, CA). The GC/MS was operated under the following conditions: isothermal column temperature, 100°C; injector temperature, 220°C; and head pressure, 200 kPa. We used selective ion monitoring for the GC/MS detection (ions 39, 42, and 69 for [H_6]-butadiene monoepoxide; ions 42, 48, and 74 for [d_6]-butadiene monoepoxide; ions 29, 55, and 85 for [H_6]-butadiene diepoxide; and ions 30, 58, and 90 for [d_6]-butadiene diepoxide). The elution time for the butadiene monoepoxide was 4.2 min and for the butadiene diepoxide, 9.4 min. The concentration of butadiene monoepoxide was determined from a calibration curve of known concentrations of pure butadiene monoepoxide. This synthesis was repeated seven times, five using using 1,3-butadiene and twice using [d_6]-1,3-butadiene.

Product Purification. The reaction flask was attached to a high vacuum line and cryogenically distilled (3,7) using four removable U-tubes. These U-tubes were specially constructed for this research with Teflon

stopcocks at both ends, and an additional sampling port was added directly at the center of the bend in the tube. The first U-tube following the reaction flask was immersed in a *o*-xylene slush (-22 - -24°C) to collect water as well as side products, such as butadiene diepoxide and 1-butene-3,4-diol. The second U-tube was immersed in a *m*-xylene slush (-45°C) to trap any unanticipated volatile materials passing the first trap (there were none). The third U-tube was immersed in a toluene slush (-95°C) to collect butadiene monoepoxide. The fourth U-tube was immersed in liquid nitrogen (-196°C) and trapped unreacted 1,3-butadiene. Following distillation, air was introduced into the collection tubes, and a sample from each U-tube was analyzed by GC/MS.

RESULTS

The concentration of butadiene monoepoxide in the aqueous solution increased over the first 40-50 min and then leveled off. The results from the five trials using 1,3-butadiene are shown in Figure 1. Analogous results were obtained using $[\text{d}_6]$ -1,3-butadiene as substrate. We obtained a $94 \pm 20\%$ ($x \pm \text{SE}$, $n = 5$) yield of the butadiene monoepoxide by the end of a 50-min reaction period. This yield is based on the MMPP used in our synthesis. Under the conditions used, little ($< 1\%$) butadiene diepoxide was formed as determined by GC/MS.

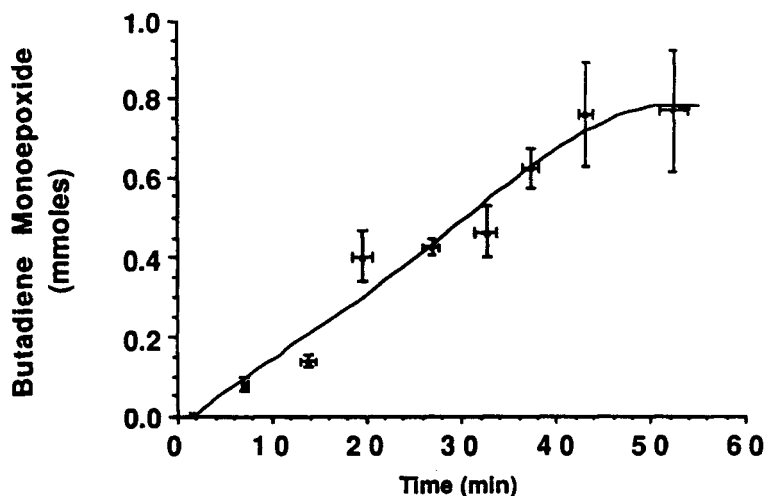


Fig. 1 The extent of butadiene monoepoxide formation with time during synthesis from 1,3-butadiene. Points shown represent the mean \pm SE for five determinations of the amount of butadiene monoepoxide formed within the specified time range (mean \pm SE) in the aqueous reaction mixture.

DISCUSSION

To our knowledge, this is the first example of an epoxide being synthesized from a gaseous alkene substrate using MMPP. Butadiene boils at -4.4°C and has a Henry's law constant of $7.46 \text{ kPa m}^3/\text{mol}$ corresponding to a water/air partition coefficient of 0.322 (8). The concentration of

aqueous butadiene during the reaction, based on the partition coefficient and the amount reacted, was initially 0.011 M and finally 0.008 M. Butadiene monoxide boils at 65°C (9), and we determined the water/air partition coefficient to be approximately 25 at 25°C (based on GC headspace analysis of aqueous solutions). The aqueous concentration of butadiene monoxide ranged from zero initially to \approx 0.12 M at the completion of the reaction. Even though the aqueous concentration of butadiene monoxide must exceed that of butadiene during a substantial part of the reaction period, relatively little was oxidized to butadiene diepoxide. This result indicates that the rate constant for epoxidation of butadiene is substantially greater than that for butadiene monoxide.

Preliminary work in our laboratories with other gaseous alkenes, such as isobutylene, has produced good epoxide yields in a minimal amount of time, suggesting wide applicability of this method. Thus, this method of synthesis provides a simple and inexpensive means for the microsynthesis of epoxides from gaseous substrates.

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