Diastereoselective Synthesis of a Strawberry Flavoring Agent by Epoxidation of Ethyl *trans*-β-Methylcinnamate

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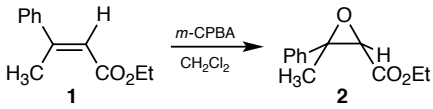
The epoxidation of alkenes is an important transformation that is discussed in virtually every introductory organic chemistry textbook. Yet, as has been noted before (*1*), there is a surprising paucity of experiments for undergraduate instruction that involve the synthesis of epoxides. Although this problem has been addressed to some extent in recent years by the publication of several elegant epoxidation experiments (*1–6*), few procedures designed for the undergraduate organic laboratory illustrate the common use of peracids to epoxidize alkenes (*4–6*). In this paper, we present an instructive experiment for the epoxidation of ethyl *trans*-β-methylcinnamate (**1**) with *m*-chloroperbenzoic acid (*m*-CPBA) to afford ethyl (*E*)-3-methyl-3-phenylglycidate (**2**, eq 1).[1] Epoxide **2**, commonly known by the strange name of "strawberry aldehyde", is a well-known food additive that imparts the flavor of strawberries; it is also used in the perfumery industry (*7*). The experiment is based on procedures published in the research literature (*8, 9*) and was developed by a group of Colby undergraduates as part of an independent project.[2] It was subsequently introduced with great success in our first-semester organic chemistry laboratory.



1 **2** (1)

The synthesis and purification of **2** is straightforward and may be accomplished with commonly available laboratory glassware and equipment. A particularly attractive feature of this exercise is the great flexibility it provides instructors for incorporating various components into the basic premise to suit individual needs. Thus, the experiment may be customized to highlight important aspects of organic chemistry such as chromatography, spectroscopy, stereochemistry, molecular modeling, and quantitative analysis. Some of the extensions that we have tried and suggestions for other possible variations are discussed later in the paper.

Experimental Procedure

A suspension of 85% *m*-CPBA (1.04 g, 5.12 mmol) in 5 mL of dichloromethane was stirred with a magnetic spin bar in a 20-mL disposable glass scintillation vial.[3] To this vial, a solution of ethyl *trans*-β-methylcinnamate (0.53 g, 2.79 mmol) in 2.5 mL of dichloromethane was slowly added with a pipet. The *m*-CPBA completely dissolved as the ethyl *trans*-β-methylcinnamate solution was added. When the solution became clear, the stir bar was removed and the vial was closed with its screw cap and placed in a refrigerator (7–8 °C) for a week.

The precipitated benzoic acid was removed from the reaction mixture by filtration. The filtrate was washed once with 10 mL of 10% sodium sulfite (Na_2SO_3). A strip of starch-iodide paper was used to test for the presence of any residual peracid. The organic layer was then washed twice with 10-mL portions of 5% sodium bicarbonate ($NaHCO_3$), dried over anhydrous sodium sulfate, and concentrated to give a clear, colorless liquid.

To purify the crude product, a 1 × 20-cm column was packed to a height of approximately 13 cm with a slurry of neutral alumina (80–200 mesh) in toluene. The sample was immediately loaded onto the column and eluted with toluene, and fractions of approximately 5 mL were collected. The epoxide elutes rapidly from the column and usually is found in fractions 2 through 6. The presence of the epoxide may be checked either by GC–MS or by TLC using a potassium permanganate dip (*6*). Fractions containing the product were combined and freed of solvent using a rotary evaporator to obtain ethyl (*E*)-3-methyl-3-phenylglycidate (0.34 g, 59% yield).

^{1}H NMR ($CDCl_3$, ppm) δ 7.37 (m, 5H), 4.30 (m, 2H), 3.46 (s, 1H), 1.77 (s, 3H), 1.33 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.6, 140.2, 128.5, 128.1, 125.2, 61.9, 61.5 (coincidental overlap of two carbons), 17.0, 14.3; IR (neat) 2981, 1751, 1201 cm^{-1}.

Hazards

Due caution should be exercised in the use of *m*-CPBA, and the workup protocol recommended in the procedure should be followed to destroy any excess of this reagent. This reagent should be stored in the refrigerator.

Results and Discussion

The reaction is easily set up and, within a week, nearly all of the cinnamate ester is consumed. The isolation and purification process and the acquisition of a ^{1}H NMR spectrum may be accomplished in a single 4-hour laboratory session. In fact, the ^{1}H NMR spectrum of the epoxide presents several interesting puzzles that can help reinforce some key concepts of NMR spectroscopy. For instance, the signal for the methylene group in the ester moiety turns out to be a complex multiplet instead of the simple quartet that most students expect. This phenomenon serves to illustrate the diastereotopic nature of protons, an idea that is sometimes difficult for beginning students to grasp.[4]

This experiment also encourages students to think in terms of reaction mechanisms and their influence on the stereochemical outcome of reactions. Furthermore, some of

the practical differences between diastereomers and enantiomers are underscored. While the concerted mechanism of epoxidation ensures the diastereoselectivity of the process, the diastereomer itself is formed as a mixture of enantiomers, as the oxygen can be transferred to the top or bottom face of the alkene. However, the NMR spectrum, which is obtained under achiral conditions, only shows the presence of a single diastereomer without revealing its racemic composition.

In a related issue, one might ask the students how they would distinguish between the two diastereomers by ^{1}H NMR spectroscopy. This is an instructive question that highlights the shielding effect of the aromatic ring current. The point can be emphasized easily by examining the ^{1}H NMR spectrum of a commercially available[5] 50:50 mixture of diastereomers. Thus, in ethyl (*E*)-3-methyl-3-phenylglycidate, the signal for the proton on the oxirane ring, which is somewhat shielded by the neighboring phenyl group, is slightly more upfield (δ 3.46 ppm) than its counterpart in the Z isomer (δ 3.67 ppm). Similarly, the ethyl group, which is less shielded in the E isomer, has more downfield signals (δ 4.3 ppm for methylene and 1.33 for methyl) than the corresponding protons in the Z isomer (δ 3.92 and 0.90 ppm).

We also asked our students to model both diastereomeric epoxides using the semiempirical AM1 method. This was performed quite rapidly, within a matter of minutes, and led to the conclusion that the two isomers had comparable heats of formation, the E form being slightly more stable than Z.

The product epoxide obtained by the students was of very good purity. The most common contaminant was residual toluene resulting from incomplete removal of solvent at the rotary evaporator. In fact, we put this observation to good use by asking the students to estimate the ratio of epoxide to toluene by comparing the relative integrals of the methyl singlet in the two compounds. Quantitative estimation of yield using an internal standard is also planned as a future modification to this experiment.

Anecdotal feedback from the students was overwhelmingly positive. Aside from the fact that the experiment worked well and illustrated many key aspects of organic chemistry, the students seemed to be excited about synthesizing a pleasant-smelling substance that actually had applications in real life.

Acknowledgments

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[W]Supplemental Material

A list of chemicals and equipment, notes for the instructor, and a student handout are available in this issue of *JCE Online*.

Notes

1. The synthesis of **2** is more efficiently but less stereoselectively carried out by a Darzens condensation of acetophenone and ethylchloroacetate in base (*10*). The epoxidation of **1** with *m*-CPBA, however, proceeds with greater stereoselectivity, albeit in modest yields.

2. At Colby, the second-semester laboratory component of the two-semester organic chemistry course culminates in an independent project that students undertake in consultation with the faculty. This experiment evolved out of one such project.

3. Purchased from Fisher Scientific. Erlenmeyer or round-bottomed flasks may be also used instead of the vials.

4. Indeed, when we carried out a simple 1-D homonuclear decoupling experiment with the decoupler set to the methyl triplet at δ 1.33 ppm, the signal for the two protons of the methylene group collapsed to a pair of closely spaced AB-type doublets. Acquisition of the decoupled spectrum was not part of our instructional lab but we plan to include it in future versions of the experiment. More background information on the decoupling experiment may be found in ref *11*.

5. Obtained from Acros Organics.

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