

Regioselective Dye-Induced Photocleavage of Epoxides as an Alternative Mild Synthetic Route to a Targeted Alcohol Functionality

Anthony A. Provasas,^{A,B} Gary A. Epling,[†] James D. Stuart,^A
and Aliaksandr Yeudakimau^A

^AUniversity of Connecticut, Center for Environmental Sciences and Engineering,
3107 Horsebarn Hill Road Unit 4210, Storrs, Connecticut 06269-4210, USA.

^BCorresponding author. Email: anthony.provasas@uconn.edu

The regioselective cleavage of epoxides using visible light and a catalytic dye is reported in this study as an alternative mild synthetic approach. The epoxide radical anion is generated via visible light in an electron transfer reaction, induced by non-toxic dyes, leading to ring opening and formation of the corresponding alcohol with the hydroxyl group on the less substituted carbon in excellent yields.

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Introduction

Epoxides represent an interesting class of compounds, which are widely used in organic synthesis.^[1] Owing to the importance of epoxides as starting materials, much effort has been devoted to their study. Regioselective epoxidation followed by regioselective epoxide cleavage provides a powerful tool in designing specific functionalized molecules.

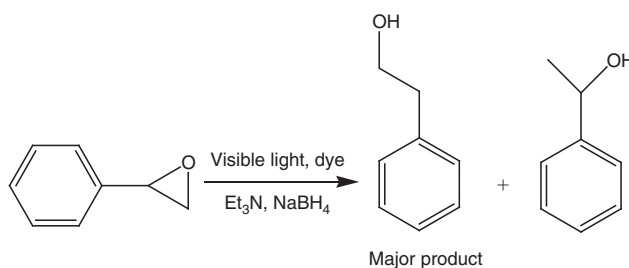
Considerable effort has focussed on the development of methods for regioselective epoxide cleavage.^[2] Among them are borohydride-catalyzed reaction of diborane with epoxides,^[3] regioselective reductive ring opening of epoxides via free radical,^[4] lithium triethylborohydride as a reagent for the reductive epoxide ring opening,^[5] regioselective cleavage of epoxides with cyanoborohydride and boron trifluoride etherate,^[6] and other methods as reported therein.^[7–10] In many of the above methods, low yields or poor regioselectivities have been observed. Reagents often predominantly yield the more substituted alcohol. Moreover, these methods use highly toxic reagents leading to toxic waste. Comparatively, very little has been done on epoxide ring opening using less toxic reagents and mild conditions. This can be achieved by using light to induce epoxide cleavage. Hasegawa et al. reported an ultraviolet (UV)-induced cleavage of α,β -epoxyketones in the presence of amines.^[11] After prolonged irradiation of the solution resulted in decomposition of the products, irradiation had to be terminated at low conversions. In a similar way, Cossy et al. conducted the photolysis of a series of α,β -epoxyketones in acetonitrile at 254 nm in the presence of triethylamine,^[12] and similarly reported decomposition of the photocleavage products after a prolonged irradiation period. Epling and Wang^[13] reported a photolytic method for the cleavage of epoxides,

which took place under mild conditions, gave good yields and high regioselectivities.

Results and Discussion

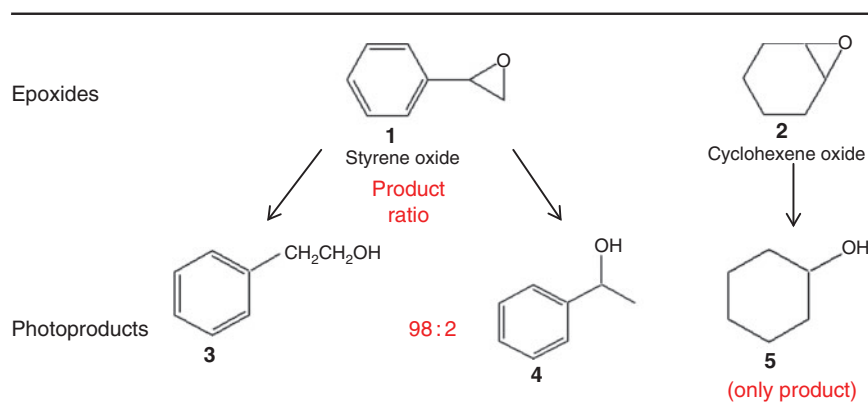
In this study, we report an efficient mild method for the regioselective cleavage of epoxides using visible light (or sunlight) and a catalytic dye. The radical anion of the epoxide could be generated via visible light-induced electron transfer reaction. This radical may lead to the formation of the corresponding alcohol with the hydroxyl group on the less substituted carbon. A typical photoreaction is depicted in Scheme 1.

Generation of the radical anion of the epoxide was possible through visible light-induced single-electron transfer reaction. The alcohol photoproduct was formed in high yields due to the mild photoreaction conditions. The epoxides used in this study were commercially obtained and are shown in Table 1. The alcohols that were observed as photoproducts from styrene epoxide **1** cleavage were 2-phenylethanol^[14] (**3**) and



Scheme 1.

[†]Deceased (September 9, 2001). This paper is dedicated to Professor Epling's memory.

Table 1. Epoxides used in this study with their corresponding photoproducts**Table 2. Experimental results of light-induced cleavage of epoxides**Et₃N, triethylamine; MG, methylene green; isol., isolated; BSA, bovine serum albumin

Substrate	Reaction	Concentration [mmol]	<i>t</i> [min]	Additive, dye	Conversion [%]	Yield [%]
1	1	8.33	100	Et ₃ N, NaBH ₄ /MG	100	96 (isol.)
2	2	10.2	90	Et ₃ N, NaBH ₄ /MG	100	95 (isol.)
2	3	8.33	100	Et ₃ N, NaBH ₄ /MG	75	
1	4	8.33	30	Et ₃ N, NaBH ₄ /MG	95	
1	5	8.33	15	Et ₃ N, NaBH ₄ /MG	100	96 (isol.)
1	6	16.6	15	Et ₃ N, NaBH ₄ /MG	87	
1	7	16.6	15	Et ₃ N, NaBH ₄ /MG	83	
1	8	16.6	15	NaBH ₄ /MG	12	
1	9	16.6	15	Et ₃ N/MG	18	
1	10	16.6	15	Et ₃ N, NaBH ₄ , BSA/D&C green #8 ^[16]	52	
1	11	16.6	15	Et ₃ N, NaBH ₄ , BSA/carmoisine	48	
1	12	16.6	15	Et ₃ N, NaBH ₄ , BSA/D&C yellow #10 ^[16]	31	
1	13	16.6	30	Et ₃ N, NaBH ₄	73	
1	14	166.6	240	Et ₃ N, NaBH ₄ /MG	100	94 (isol.)
			60		28	
			120		59	
			180		81	
1	15	166.6	120	Et ₃ N, NaBH ₄ , BSA/MG, carmoisine, D&C yellow #10	100	92 (isol.)
			30		36	
			60		73	

1-phenylethanol (4). The only photoproduct observed from the cleavage of cyclohexene oxide (2) was cyclohexanol^[15] (5).

The results in Table 2 illustrate the photosensitized cleavage of the epoxides 1 and 2. High isolated product yields and regioselectivity were observed. Reactions 1–12 (Table 2) were performed following small-scale Procedure 1, whereas Reactions 14 and 15 were performed using the large-scale Procedure 2. Reactions 1 and 2 afforded 100% conversion of the epoxide. A 96% yield of alcohol 3 was reported in 100 min for Reaction 1, and a 95% yield of alcohol 5 was reported in 90 min for Reaction 2. Reaction 3 afforded 75% conversion of the epoxide 1 in 100 min. Reaction 4 achieved a conversion of 95% of epoxide 1 in 30 min. Both Reactions 5 (100%) and 6 (87%) converted epoxide 1 in 15 min with a 96% isolated yield of alcohol 3 for Reaction 5. In Reaction 13, a moderate (73%) conversion of epoxide (1) was observed in 30 min following the UV irradiation (Procedure 3). Reaction 14 gave a 100% conversion and an isolated yield of 92% of alcohol 3 in 240 min.

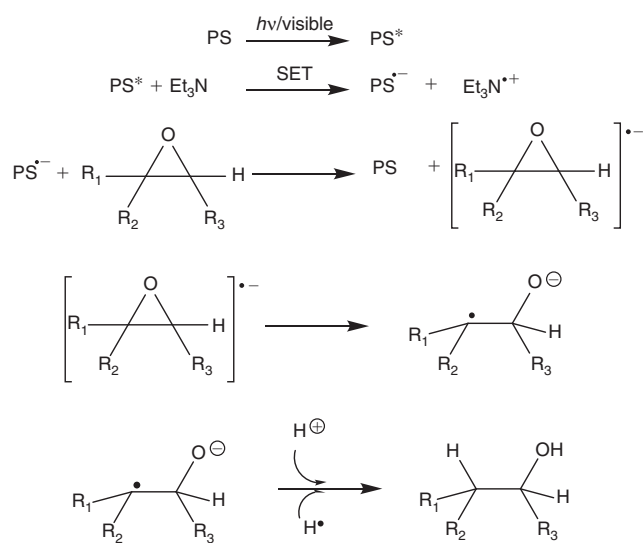
Reaction 15 was performed in the presence of bovine serum albumin (BSA) and the combination of three dyes in order to use the light more efficiently. A 100% conversion and 92% isolated yield of alcohol 3 were observed. Reaction 8 was performed in the absence of triethylamine thus, the conversion in 15 min was low compared with that achieved by Reaction 7 that was performed under the same conditions but in the presence of triethylamine. This finding agrees with the reported results of Epling and Wang,^[13] that the rate of reaction increased with increase in the sacrificial reductant (triethylamine) concentration. Reaction 9 was performed in the absence of sodium borohydride and as a result, the reaction rate was low. The observed conversion of 18% was very low compared with that achieved in Reaction 7 (83%). BSA was added to Reactions 10, 11, 12, and 15 in order to minimize the observed bleaching effect of the catalytic dye.

The use of non-toxic dyes, such as D&C dyes (employed in drugs and cosmetics), gave promising results. In order to use

Table 3. Photolytic stability of FD&C and D&C dyes
RT, room temperature

Dyes ^A , conditions	FD&C green #3	FD&C blue #1	D&C violet #2	Carmoisine	D&C green #8	D&C yellow #10
1 h, RT, 10 mM NaBH ₄ , no BSA	No bleaching	Bleached	Bleached	No bleaching	No bleaching	No bleaching
1 h, RT, 10 mM NaBH ₄ , 3.5 μM BSA	No bleaching	Low bleaching	Low bleaching	No bleaching	No bleaching	No bleaching
1 h, RT, 10 mM NaBH ₄ , 10 mM Et ₃ N, no BSA	No bleaching	Bleached	Bleached	No bleaching	No bleaching	No bleaching
1 h, RT, 10 mM NaBH ₄ , 10 mM Et ₃ N, 3.5 μM BSA	No bleaching	Low bleaching	Low bleaching	No bleaching	No bleaching	No bleaching
1 h, <i>hν</i> , 10 mM NaBH ₄ , 10 mM Et ₃ N, no BSA	No bleaching	Bleached	Bleached	No bleaching	No bleaching	No bleaching
1 h, <i>hν</i> , 10 mM NaBH ₄ , 10 mM Et ₃ N, 3.5 μM BSA	No bleaching	Low bleaching	Low bleaching	No bleaching	No bleaching	No bleaching

^AConcentration of dye: 1.0 mM.



the proper non-toxic dyes that would not bleach under the photoreaction conditions, experiments were performed in a 9 : 1 methanol/water solution in the absence or presence of BSA for each of the following dyes: FD&C (employed in food, drugs, and cosmetics) green #3, FD&C blue #1, D&C violet #2, carmoisine, D&C green #8, and D&C yellow #10, and methylene green (MG).^[16] The results are shown in Table 3.

Results from Table 3 indicated that dyes that could be used as photosensitizers in this epoxide cleavage study were FD&C green #3, carmoisine, D&C green #8, and D&C yellow #10. Carmoisine, D&C green #8, and D&C yellow #10 were used in Reactions 10, 11, 12, and 15 as shown in Table 2.

Based on the performed experiments, a mechanism for the cleavage of epoxides under these conditions is envisaged, as illustrated in Scheme 2. The proposed mechanism is similar to that proposed by Hasegawa et al.^[11] and Cossy et al.^[12] to explain the UV light-induced cleavage of epoxides. The initial step is the excitation of the photosensitizer (PS) in the presence of visible light. The dye-sensitized photocleavage of the epoxide is achieved by interaction of the excited dye (PS*) with the sacrificial reductant (triethylamine). The product of such single-electron transfer (SET) interaction is the photosensitized radical anion (PS^{•-}) that can react with the epoxide to give an epoxide radical anion and the ground state PS. Cleavage of the epoxide radical anion, and H[•] abstraction from the solvent may then occur. Then, the H⁺ abstraction from the solvent may lead to the alcohol product. Control experiments (Reactions 8, 9, and 13)

illustrated that the co-presence of the photosensitizer, sacrificial reductant, and sodium borohydride was essential in this process. Although slight bleaching of the dye was observed, it is believed that the function of the photosensitizer dye is catalytic. This was proven by a control experiment conducted in the absence of dye that did not lead to the conversion of the epoxide under light irradiation. UV-Visible spectra of the reaction mixture before and after the photolysis showed only slight bleaching of the photosensitizer. As mentioned above, BSA was added to assist this catalytic process. Sodium borohydride was believed to efficiently function as a radical scavenger of the radical intermediate. As a result, sodium borohydride minimized the formation of side products. The regioselectivity that this method provides depends on the radical anion formed from the ring opening of the radical anion of the epoxide. It is believed that the more stable radical is formed, leaving the hydroxyl group on the less substituted carbon atom.

Conclusions

In summary, a mild, practical, and convenient method of regioselective photocleavage of epoxides has been developed and can be used as an alternative to existing methods. The alcohol product with the hydroxyl group on the less substituted carbon atom was isolated in high yield and regioselectivity. High conversions of the epoxide to the corresponding alcohol (up to 100 %) were observed. Control experiments illustrated that the presence of the photosensitizer dye, sodium borohydride, and light was crucial. Furthermore, the presence of triethylamine in the photoreaction mixture was necessary to increase the reaction rate and percentage yield of the corresponding alcohol. The presence of BSA and the use of non-toxic D&C dyes as photosensitizers in the photoreaction mixture gave promising results. Bleaching of the dyes was observed, but the use of BSA reduced this effect. The combination of MG, carmoisine, and D&C yellow #10 as photosensitizers along with triethylamine, sodium borohydride, and BSA was needed to achieve a high isolated yield of the corresponding alcohol in a large scale set-up. In comparison, UV irradiation of the epoxide substrate gave a high conversion to the alcohol but the photoreaction mixture did not appear to be clean as determined by gas chromatography mass spectrometry (GC-MS). In the presence of visible light, light absorption only occurs by the catalytic dye. In the UV-assisted photocleavage, if a complex substrate is being irradiated, there is a chance of light absorption by one of the possible chromophores present, leading to the initiation of unwanted photochemical reactions.

The proposed epoxide photocleavage method was specifically developed to use visible light from inexpensive sources (sunlight). The purpose of this study was to introduce

a convenient, efficient, and mild alternative synthetic route to epoxide ring opening and primarily to investigate the optimal conditions of this approach. Consequently, further investigation of photocleavage of other epoxides was beyond the scope of this study.

Experimental

General Procedures

Procedure 1: Small-Scale Photosensitized Cleavage of Epoxides Using Visible Light

A solution of 2.0 g epoxide, 1.0 mM (final concentration in solution) dye, 10 mM triethylamine, 10 mM sodium borohydride, and 3.5 μ M BSA in 250 mL methanol/water (9 : 1) in a 250-mL pyrex round-bottom flask, equipped with a reflux condenser and stirring bar magnet, were irradiated with a 150 W spot light for 15–240 min. Nitrogen was purged through the solution 15 min before and during irradiation. The distance between the centre of the flask and the spotlight was 6 cm with a reaction temperature of 68°C. The reaction was monitored by TLC. After irradiation, 10 % phosphoric acid was added in the amount needed to quench the excess sodium borohydride. The solution was then saturated with sodium chloride, and extracted with ethyl acetate three times. The combined ethyl acetate layers were dried over anhydrous sodium sulfate and concentrated to give the crude product. Finally, flash chromatography gave the spectroscopically pure product. The structures were confirmed by GC–MS and NMR.

Procedure 2: Large-Scale Photosensitized Cleavage of Epoxides Using Visible Light

A solution of 20.0 g epoxide, 1.0 mM (final concentration in solution) dye, 10 mM triethylamine, 10 mM sodium borohydride, and 10.5 μ M BSA in 2000 mL methanol/water (9 : 1) in a crystallizing dish, 190 \times 100 mm, equipped with a stirring bar magnet were irradiated with a 150 W spot light for 2 h. Nitrogen was purged through the solution 15 min before and during irradiation. The distance between the surface of the solution and the spotlight was 48 mm. The reaction was monitored by TLC. After irradiation, 10 % phosphoric acid was added in the amount needed to quench the excess sodium borohydride. The solution was then saturated with sodium chloride, and extracted with ethyl acetate three times. The combined ethyl acetate layers were dried over anhydrous sodium sulfate and concentrated to give the crude product. Finally, flash chromatography gave the spectroscopically pure product. The structures were confirmed by GC–MS and NMR.

Procedure 3: Ultraviolet Irradiation of Epoxides

To a quartz irradiation tube (5 \times 40 cm) was added 2.0 g epoxide. Then, 225 mL methanol, 25 mL water, 10 mM triethylamine, and 10 mM sodium borohydride were added to the epoxide-containing tube. After the solution was stirred, nitrogen gas was bubbled through the solution gently for 15 min. The solution was then irradiated for 30 min using the Rayonet preparative UV reactor equipped with 254-nm lamps (model RPR-208). The nitrogen gas was bubbled through the solution during photolysis. The reaction was monitored by TLC. After irradiation, 10 % phosphoric acid was added to quench the excess sodium borohydride. The solution was then saturated with sodium chloride and extracted with ethyl acetate three times. The combined ethyl acetate layers were dried over anhydrous sodium sulfate and concentrated to give the crude

product. Finally, flash chromatography gave the spectroscopically pure product. The structures were confirmed by GC–MS and NMR.

All reagents were purchased from commercial suppliers and used without further purification.

Analytical Instrumentation

Gas Chromatography–Mass Spectrometry

GC–MS analysis was done on a Hewlett-Packard 5890A GC/MSD 5970B with a Hewlett-Packard HP-1 12 m \times 0.20 mm of 0.33 μ m film thickness methyl silicone capillary column. The carrier gas was helium and flow rate was 1.0 mL min⁻¹. For sample analysis, the following temperature program was used: start at 100°C (hold 2 min), then ramped to 270°C at a rate of 20°C min⁻¹; transfer line at 270°C; injector splitless at 270°C; 1.0 μ L injection volume.

Nuclear Magnetic Resonance Spectroscopy

Proton spectra were recorded at 270 MHz on a Bruker AC270 spectrometer. Chemical shifts were recorded relative to TMS as internal standard. The samples were prepared in CDCl₃ and 10-mm tubes, and spectra were recorded at ambient temperature. Splitting patterns are given as s, singlet; d, doublet; t, triplet; m, multiplet.

Thin Layer Chromatography

TLC analysis was done on Merck silica gel 60F254 pre-coated on plastic sheets, with a layer thickness of 0.22 mm. Visualization was done using UV light.

Flash Chromatography

Flash chromatography was done using Baker flash chromatography silica gel, with an average particle size of 40 μ m. The column used was purchased from Air Glass (part #25; outer diameter, 2.5 cm).

Ultraviolet–Visible (UV–Visible) Spectroscopy

UV–Visible spectra were recorded on a Hewlett-Packard HP8452A diode array spectrophotometer. All analyses were done using 10-mm path length quartz UV cells.

Yields of Photochemical Reactions

All photochemical reactions performed were monitored by TLC and GC–MS. Percentage conversion and the percentage yield of the alcohol were calculated based on the integrals and/or the weight of the isolated alcohol.

Acknowledgements

This research project would not have been possible without the invaluable support and guidance of the late Professor Gary Epling. He was a 1967 graduate of MIT and received his Ph.D. from the University of Wisconsin (Zimmerman 1972). His post-doctoral work was done at Yale in 1973. He was a Professor at Fordham University from 1973 to 1978, when he came to the Chemistry Department at the University of Connecticut as Professor and served as its Head. He was profiled in the October 15, 2001 edition of C&E News and has published over 70 peer-reviewed photochemistry papers.

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- [14] 2-Phenylethanol: δ_{H} (CDCl₃, 270 MHz) 7.36–7.23 (5H, m), 3.82 (2H, t), 2.87 (2H, t), 2.10 (1H, br s).
- [15] Cyclohexanol: δ_{H} (CDCl₃, 270 MHz) 3.70–3.45 (1H, m), 2.61 (1H, br s), 0.9–2.05 (5H, m).
- [16] Chemical properties of the organic dyes used as photosensitizers are as follows (FD&C are colorants approved by the Food and Drug Administration for use in food, drugs, and cosmetics; D&C are colorants used in drugs and cosmetics, but not food). (1) FD&C green #3: formula weight (FW) 808.86, λ_{max} 624 nm, class – triphenylmethane, type – anionic; (2) D&C violet #2: FW 329.36, λ_{max} 570 nm, class – anthraquinone, type – neutral; (3) D&C yellow #10: FW 579.31, λ_{max} 411 nm, class – quinoline, type – anionic; (4) D&C green #8: FW 524.39, λ_{max} 403 nm, class – phenanthrene, type – anionic; (5) Carmoisine: FW 502.00, λ_{max} 515 nm, class – monoazo, type – anionic; (6) MG: FW 433.00, λ_{max} 657(618) nm, class – thiazine, type – cationic; and (7) FD&C blue #1: FW 791.00, λ_{max} 628 nm, class – triphenylmethane, type – anionic.