Reactions of Epoxides and Carbonyl Compounds Catalyzed by Anhydrous Copper Sulfate

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Anhydrous $CuSO_4$ and acetone have been used for many years to convert diols to acetonides. We have found that $CuSO_4$/acetone also converts many epoxides directly to acetonides at a convenient rate and in excellent yields. The following observations are pertinent to the mechanism and scope of this reaction: (*E*)- and (*Z*)-2,3-octene oxide each react completely stereoselectively to give the corresponding erythro or threo acetonide, respectively, the (*Z*)-oxide reacting ca. three times faster. In contrast, both (*E*)- and (*Z*)-β-methylstyrene oxide give identical mixtures of erythro (66%) and threo (34%) acetonides; no interconversion of the oxides or the acetonides was detectable. Competition kinetic studies show that para-substituted styrene oxides follow a Hammett relationship of the form $\log (k_X/k_H) = -2.63\sigma^+$, with $r = 0.9994$. Other observations pertaining to the scope, mechanism, and possible extension of these reactions are discussed.

Acetonide derivatives of diols are useful as protected synthetic intermediates, particularly in carbohydrate and steroid chemistry. They are also very well suited for GLC and/or mass spectral analysis of diols, because various geometrical isomers can easily be separated and because the dioxolane ring usually remains intact in the mass spectrometer whereas the diols cleave readily between the hydroxyl groups. Acetonides of diols are also easily prepared by a number of techniques, one of the most convenient being a direct condensation of the diol with acetone in the presence of anhydrous $CuSO_4$.[1-3] During our ^{18}O-tracer studies of the enzyme epoxide hydrase[4] a need arose for converting epoxides directly to acetonides for mass spectral determinations of their ^{18}O content. We found that anhydrous $CuSO_4$ in acetone cleanly and conveniently converts many epoxides directly to their corresponding diol acetonides. This is in contrast to anhydrous zinc[5] or magnesium[5,6] halides which give rearrangement products from epoxides, or anhydrous $FeCl_3$[7] or Me_3SiCl[8] which give chlorohydrin derivatives. In this paper, we describe our studies on the mechanism of the epoxide–acetonide conversion as well as its scope, limitations, and prospects for extension to related reactions.

Results and Discussion

The conversion of an epoxide to a diol and then to an acetonide involves the addition of a molecule of water and its subsequent elimination in the presence of acetone, both reactions being subject to acid catalysis. It occurred to us that it should be possible to effect the overall process as a single step in the presence of a suitable acid catalyst. Our first attempts involved stirring *p*-phenylstyrene oxide **1** and tetradecene 1,2-epoxide **2** in acetone over anhydrous $CuSO_4$; the styrene oxide was quantitatively converted to acetonide within a few hours at room temperature but the alkene oxide remained unchanged after 22 h. This result roughly paralleled the expected behavior of these substrates toward acids, and so kinetic studies were undertaken to explore this possibility. It was found that small amounts of water greatly inhibited the reaction despite their effect in solubilizing the copper reagent. For example, $CuSO_4 \cdot 5H_2O$ dissolves slightly in acetone to produce pale-blue solutions. Epoxides dissolved in these solutions are converted to acetonides extremely slowly, even when stirred over a large excess of finely powdered $CuSO_4 \cdot 5H_2O$. In contrast, anhydrous $CuSO_4$ is not detectably soluble in acetone, and, although acetone decanted after stirring over anhydrous $CuSO_4$ does not convert epoxides to acetonides, epoxides in acetone stirred over anhydrous $CuSO_4$ are readily converted to acetonides. Furthermore, stirred reactions proceed much more rapidly than unstirred reactions, suggesting that the reaction is truly heterogeneous in nature.

In attempting to carry out kinetic studies, we found that, although individual reactions were linear with time, the reproducibility of reaction rates was poor, probably because of the heterogeneous nature of the reaction. However, by incorporating an inert internal standard (naphthalene) we were able to obtain reproducible *relative initial* rates for pairs of epoxides competing for catalyst. Using this approach we found the reactivities of para-substituted styrene oxides to increase in the order $Br < Cl < H < CH_3$. A Hammett plot of $\log (k_X/k_H)$ vs. σ^+ for these substituents yielded a straight line ($r = 0.9994$) with a slope (ρ^+) of −2.63. This amply confirmed our initial suspicions about Lewis acid catalysis and carbonium ionlike intermediates in this reaction.

With aliphatic epoxides the rate of product formation is dependent on the nature of the substitution pattern on the oxirane ring, as shown by the data in Table I. Oxiranes from which a tertiary carbonium ion could be formed react significantly faster than those containing only secondary carbons, and monoalkyl-substituted oxiranes are essentially inert at room temperature, although they react cleanly, if slowly, at elevated temperatures. Although not indicated in Table I, small amounts of the cis and trans isomers of 2,3-epoxytetradecane which occurred as an impurity in **2** were observed to react in a fashion parallel to epoxides **4a** and **4b**. Thus, as already established in homogeneous reactions of epoxides with anhydrous metal ion Lewis acids,[5-7] carbonium ion forming ability plays an important role in governing the reactivity of epoxides in the heterogeneous $CuSO_4$/acetone system as well.

In order to determine the direction of epoxide ring opening, the acetonide derived from ^{18}O-enriched **1**[4] was subjected to mass spectral analysis and compared to unlabeled material. The major fragmentation occurred as shown in **7** with the base peak occurring at *m/e* 72. The origination of this peak as indicated by A in **7** is confirmed by its shift to *m/e* 74 in the mass spectra of the acetonides from both **1**-β,β-d_2 and **1**-^{18}O. The M^+ and $M - CH_3^+$ ions from **7** were, respectively, 25 and 20% of the base peak. In the spectrum of the acetonide from **1**-^{18}O, all three ions (A^+, $M - CH_3^+$, and M^+) contained the same atom-% excess ^{18}O. Therefore, acetonide formation must involve exclusive cleavage of the benzylic C–O bond, which also agrees with previous conclusions about the importance of carbonium ion intermediates.

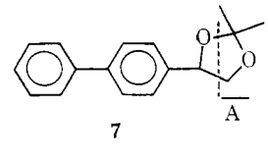

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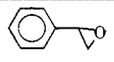
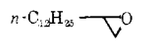
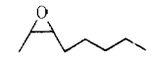
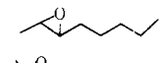
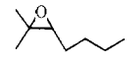
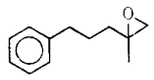
Table I. Relative Reactivities of Aliphatic and Aromatic Epoxides toward $CuSO_4$/Acetone

	Epoxide	Registry no.	Time, h[a]	% conversion
3		96-09-3	≤2	100
2		3234-28-4	22 7 (60 °C)	0 5
4a		23024-54-6	24	50
4b		28180-70-3	24	15–20
5		3776-34-9	24 3	95[c] 40
6		40463-17-0	6 (58 °C)	50

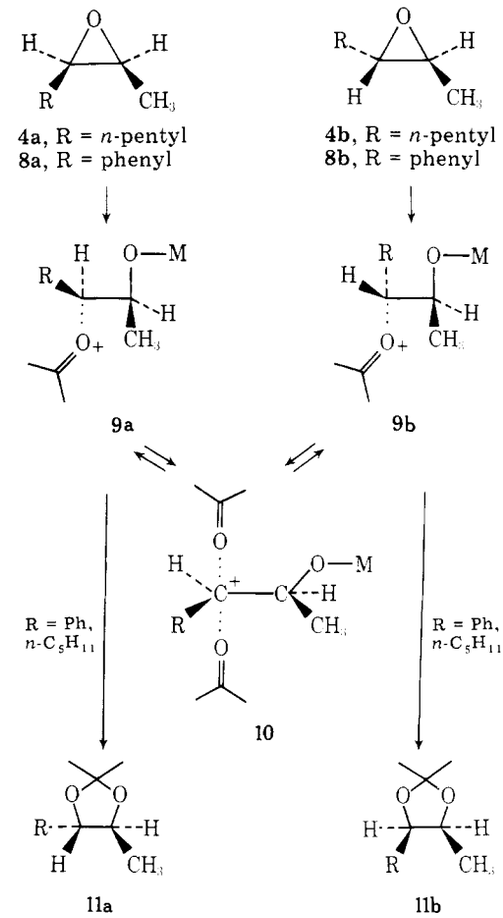
[a] Room temperature unless otherwise noted. [b] Sole product is the corresponding acetonide. [c] About 5% of non-acetonide products with short retention times was formed.

Both (*Z*)- and (*E*)-β-methylstyrene oxide (**8a** and **8b**) react with $CuSO_4$ and acetone to give the same mixture of threo and erythro acetonides (66:34). Acetonides formed under identical conditions from the corresponding erythro or threo diols show no interconversion, even after standing for days at room temperature. The loss of stereochemistry from the epoxides must therefore be due to the formation of a common symmetrical intermediate, such as **10** for example, from which both products could be formed. Interconversion of epoxides was not observed; thus, if it occurred it was much slower than the conversion of **9** to **11** as outlined in Scheme I. In contrast to this situation, acetonide formation from epoxides **4a** and **4b** is completely stereospecific, **4a** giving only threo acetonide and **4b** giving only erythro acetonide. This change of mechanism may be rationalized in terms of the strength of the $Me_2C{=}O{\cdots}C^+$ interaction in intermediate **9.** Thus, because of the greater stability of benzylic carbonium ions, formation of **9** from **8** requires relatively little mucleophilic assistance or solvation from acetone, and interconversion of **9a** and **9b** through **10** is not impeded by a strong $Me_2C{=}O{\cdots}C^+$ interaction. With the aliphatic epoxides, however, oxirane ring opening probably requires much more assistance from the carbonyl oxygen as a nucleophile, such that the strength of the $Me_2C{=}O{\cdots}C^+$ interaction which develops precludes facile interconversion of **9a** and **9b** when R = alkyl. Since the direction of ring opening from **4** is not known, similar arguments would apply to intermediates formed by attack of acetone at the methyl-substituted oxirane carbon; the overall result would of course be the same. The importance of the nucleophilic role of the solvent is also indicated by the fact that even styrene oxide is inert in acetonitrile over $CuSO_4$. Despite the highly polar nature of this solvent, which should help stabilize polar intermediates such as **9,** its low nucleophilicity prevents it from assisting the opening of the oxirane ring. In contrast, styrene oxide in methanol over $CuSO_4$ reacts rapidly to produce only 2-phenyl-2-methoxyethanol. Since $CuSO_4$ dissolves slightly in methanol to give pale blue solutions but does not dissolve noticeably in acetonitrile, it seems unlikely that the difference in reactivity of styrene oxide in these two solvents can be ascribed to attenuation of the catalyst by solvation.

The experiments described above clearly point to the importance of the Lewis acid property of anhydrous $CuSO_4$. However, $CuSO_4$ is also an effective dehydrating agent, much like $CaSO_4$ or $MgSO_4$, and both of these properties are important in its use to form acetonides from diols plus acetone. Many other organic reactions require acid catalysis with dehydrating conditions to shift an equilibrium in a useful direction, but the conversion of diols to acetonides is apparently the only one in which anhydrous $CuSO_4$ is used to advantage. As a start toward exploring the general utility of $CuSO_4$ as a reagent in organic chemistry, we examined its use in convering carbonyl substrates to 1,3-dioxolane and 1,3-dioxane derivatives in diol solvents. The carbonyl compounds were simply dissolved in the diol and stirred over an excess of $CuSO_4$ at room temperature. $CuSO_4$ dissolves in ethylene glycol to give a clear blue solution which converts benzaldehyde and acetophenone to their dioxolane derivatives in 45 and 5% yield, respectively, after stirring for 28 h. Although $CuSO_4$ does not dissolve detectably in propane-1,3-diol, benzaldehyde and acetophenone were converted to their 1,3-dioxane derivatives in yields of 98 and 10%, respectively, after stirring over $CuSO_4$ for 28 h. No attempts have yet been made to increase these yields by the use of larger amounts of $CuSO_4$, longer times, or higher temperatures. Nor is it known if these yields reflect the relative reactivities of the reactants (aldehyde > ketone; dioxane less strained than dioxolane) or an equilibrium under the conditions used. It is also possible that in solubilizing $CuSO_4$ ethylene glycol reduces its Lewis acidity and/or its affinity for water, thus contributing adversely at both the kinetic and thermodynamic levels. A parallel to this exists in the epoxide to acetonide conversion, where small amounts of water greatly decrease the effectivity of $CuSO_4$ as a catalyst despite increasing its solubility in acetone.

Anhydrous $CuSO_4$ can thus serve as a useful catalyst/reagent for several frequently encountered reactions of carbonyl compounds with diols or their epoxide equivalents. The reactions proceed under mild conditions, at rates comparable to those attainable with conventional acid catalysts (e.g., 0.05 M *p*-TsOH), and may be more convenient than other procedures involving azeotropic removal of water to shift an equilibrium.

Scheme I



Experimental Section

Epoxides. Styrene oxide was purchased from Aldrich; all other epoxides were prepared from the corresponding olefins by peracetic acid epoxidation in CH_2Cl_2 buffered with sodium acetate. Their purity was checked by TLC, GLC, and NMR and was >97% in all cases. Tetradec-1-ene and (*E*)- and (*Z*)-2-octene were obtained from Aldrich; 2-methyl-2-heptene (precursor for **5**) was obtained by Wolf–Kishner reduction of 6-methyl-5-hepten-2-one (Aldrich) followed by distillation (bp 120–121 °C); 1-phenyl-4-methylpent-1-ene (precursor for **6**) was obtained by Grignard coupling of 2-phenylethylmagnesium bromide and methallyl chloride in refluxing ether, followed by distillation (bp 90–95 °C, 34 Torr). Para-substituted styrenes were prepared from the corresponding acetophenones by borohydride reduction and dehydration as described previously.[9] *cis*-β-Methylstyrene was prepared by irradiation[10] of a 1% solution of the trans isomer (Aldrich) in benzene containing 2-acetonaphthone (2%) for 8 h under nitrogen in a Rayonet reactor with 350-nm lamps. GLC analysis on a DC-550 column showed that a photosteady state was reached at a cis/trans ratio of 82:18. The sensitizer was removed by filtering the solution through active silica gel. The mixture of isomers obtained after removing the benzene on a rotary evaporator was used without further purification.

$CuSO_4$-Catalyzed Reactions. Anhydrous $CuSO_4$ was prepared by *gently* heating the finely powdered pentahydrate in a bunsen flame until it turned very pale blue, cooling in a desiccator, and grinding in a mortar before use. Reactions were stirred at room temperature in screw-cap tubes to keep moisture out. In general, 100 mg of substrate epoxide (or carbonyl compound) was dissolved in 1 mL of acetone (or glycol solvent) and stirred with ca. 50 mg of $CuSO_4$; in more dilute solutions, the reactions proceeded very slowly. In all cases acetonides produced directly from epoxides were identical (GLC) to those produced from the corresponding diol.

Acetonides. The structures of many of the acetonides derived from epoxides **1–6, 8a,** and **8b** have been confirmed by mass spectroscopy.[4] All of the acetonides mentioned in this study have also been characterized by NMR spectroscopy, and these data are reported here together with their R_f on 0.25-mm silica layers eluted with 10% ethyl acetate in hexane. Each epoxide precursor had essentially the same R_f as its derived acetonide.

2,2-Dimethyl-4-(4′-phenylphenyl)dioxolane: from epoxide **1,** mp 62–65 °C, R_f 0.36; NMR ($CDCl_3$) δ 7.50 (m, arom), 1.49 and 1.55 (CMe_2), 5.10 (t, α-H), 4.30 (t, β-H), 3.72 (t, β-H).

2,2-Dimethyl-4-(*n*-dodecyl)dioxolane: From epoxide **2,** an oil, R_f 0.57; NMR ($CDCl_3$), δ 4.08 (ring CH_2), 3.50 (m, ring CH), 1.38 and 1.44 (CMe_2).

2,2-Dimethyl-4-phenyldioxolane: from styrene oxide, an oil, R_f 0.48; NMR ($CDCl_3$) δ 7.30 (arom), 5.05 (dd, α-H), 4.25 (dd, β-H), 3.66 (t, β-H).

erythro-2,2-Dimethyl-4-pentyl-5-methyldioxolane: from epoxide **4b,** an oil, R_f 0.55; NMR ($CDCl_3$) δ 4.15 (m, ring CH), 1.34 and 1.44 (CMe_2), 1.16 (d, J = 7 Hz, CH_3).

threo-2,2-Dimethyl-4-pentyl-4-methyldioxolane: from epoxide **4a,** an oil, R_f 0.55; NMR ($CDCl_3$) δ 3.60 (m, ring CH), 1.40 (CMe_2), 1.27 (d, J = 7 Hz, CH_3).

2,2,4,4-Tetramethyl-5-butyldioxolane: from epoxide **5,** an oil, R_f 0.62; NMR ($CDCl_3$) δ 3.70 (t, J = 6 Hz, ring CH), 1.10, 1.24, 1.33, and 1.41 (methyls).

2,2,4-Trimethyl-4-(3-phenylpropyl)dioxolane: from epoxide **6,** an oil, R_f 0.41; NMR ($CDCl_3$) 7.14 (s, arom), 3.65 (s, ring CH_2), 2.60 (m, benzylic CH_2), 1.34 and 1.38 (CMe_2), 1.27 (s, CH_3).

erythro-2,2,4-Trimethyl-5-phenyldioxolane: from epoxides **8a** and **8b,** an oil, R_f 0.53; NMR ($CDCl_3$) 7.29 (arom), 5.19 (d, J = 7 Hz, benzylic H), 4.6 (m, ring H), 1.45 and 1.62 (CMe_2), 0.79 (d, J = 6 Hz, CH_3).

threo-2,2,4-Trimethyl-5-phenyldioxolane: from epoxides **8a** and **8b,** an oil, R_f 0.53; NMR ($CDCl_3$) 7.34 (arom), 4.46 (d, J = 9 Hz, benzylic H), 3.92 (m, ring H), 1.50 and 1.55 (CMe_2), 1.25 (d, J = 6 Hz, CH_3).

Kinetic Studies. Solutions of the styrene oxides were prepared (ca. 0.08 M) in acetone containing 10 mg/mL naphthalene as an internal standard. Reaction solutions were prepared by combining a 1.0-mL aliquot of each of two such solutions. Reactions were monitored by GLC on either 3% SE-30 (6 ft × ⅛ in. at 85 °C) or 5% DC-550 (10 ft × ⅛ in. at 140 °C). After calibrating the digital integrator on the GLC with two injections of the epoxide/naphthalene solution, 20–50 mg of powdered anhydrous $CuSO_4$ was added and the mixtures were stirred rapidly at room temperature in sealed vials. At 5–10-min intervals, aliquots were analyzed by GLC, and the slope of a plot of epoxide remaining vs. time was taken as the rate of reaction. Due to the heterogeneous nature of the reaction, rates for individual epoxides were poorly reproducible from run to run. However, when two epoxides were competing for the same catalyst, their *relative* rates were quite reproducible. Relative to styrene oxide (1.00) the rates of reaction of *p*-methyl-, *p*-chloro-, and *p*-bromostyrene oxide were 7.65, 0.50, and 0.43, respectively. The Hammett plot of these data is described in the text.

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Registry No.—**1,** 36099-26-0; **8a,** 4541-87-1; **8b,** 23355-97-7; 2,2-dimethyl-4-(4′-phenylphenyl)dioxolane, 64216-04-2; 2,2-dimethyl-4-(*n*-dodecyl)dioxolane, 64216-03-1; 2,2-dimethyl-4-phenyldioxolane, 52129-03-0; *erythro*-2,2-dimethyl-4-pentyl-5-methyldioxolane, 64216-08-6; *threo*-2,2-dimethyl-4-pentyl-5-methyldioxolane, 64216-07-5; 2,2,4,4-tetramethyl-5-butyldioxolane, 64216-09-7; 2,2,4-trimethyl-4-(3-phenylpropyl)dioxolane, 64235-91-2; *erythro*-2,2,4-trimethyl-5-phenyldioxolane, 64216-06-4; *threo*-2,2,4-trimethyl-5-phenyldioxolane, 64216-05-3; 2-methyl-2-heptene, 627-97-4; 6-methyl-5-hepten-2-one, 110-93-0; 1-phenyl-4-methylpent-1-ene, 15314-20-2; 2-phenylethyl bromide, 103-63-9; methallyl chloride, 563-47-3; *p*-methylstyrene oxide, 13107-39-6; *p*-chlorostyrene oxide, 2788-86-5; *p*-bromostyrene oxide, 32017-76-8; acetone, 67-64-1.

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