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Rapid Ring-Opening Reactions of Epoxides using Microwave Irradiation

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Abstract: Copper tetrafluoroborate catalyzes the ring-opening of epoxides with primary, secondary, and tertiary alcohols in short reaction times under microwave irradiation to give β -alkoxyalcohol products in excellent yields.

Keywords: β -alkoxyalcohols, copper tetrafluoroborate, microwave irradiation

Epoxides are highly versatile synthetic intermediates in organic synthesis and undergo ring-opening reactions to give β -substituted alcohols with a variety of nucleophilic species with high regio- and stereoselectivity.^[1] These reactions occur under a variety of conditions, although the most practical and widely employed strategy for the synthesis of these 1,2-bifunctional compounds utilizes Lewis acid promoters. However, the standard methods used are often far from ideal and suffer from disadvantages such as the highly toxic and corrosive nature of the promoter, high acidity, the requirement to use stoichiometric quantities of the promoter, long reaction times, and inconvenient handling procedures.^[2] Therefore, the introduction of new methods for the nucleophilic ring-opening of epoxides that work under mild conditions is an area of ongoing interest.

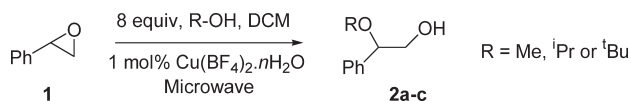
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The Lewis acid-catalyzed alcoholysis of epoxides to produce β -alkoxyalcohols provides an ideal example of these limitations, and their synthesis has attracted significant attention because of the synthetic utility of these materials.^[3] Although the use of alcohols in epoxide ring-opening reactions is a well-established route to β -alkoxyalcohols, the poor nucleophilicity of substrates other than primary alcohols means that these transformations often require harsh reaction conditions and lack regioselectivity.^[4] Significant and important progress has been made in the development of efficient catalytic methods that are successful under mild heterogeneous conditions;^[5] however, a number of these catalysts are not commercially available, are expensive, or have environmental implications. Barluenga recently reported the use of commercially available copper tetrafluoroborate ($\text{Cu}(\text{BF}_4)_2 \cdot n\text{H}_2\text{O}$) to catalyze epoxide ring-opening reactions under mild conditions.^[6] The reactions proceed at room temperature to give the β -alkoxyalcohol products in good to excellent yields, although sterically demanding alcohols or alkyl epoxides required extended reaction times (12–33 h).

Microwave dielectric heating has found increasing use in synthetic chemistry in recent years.^[7] Microwave-assisted procedures benefit from increased energy efficiency, higher product yields, and faster reaction rates and have been introduced for a wide range of synthetic transformations, which, with the advent of specialized instruments that focus microwaves in a monomodal cavity, are reliable, reproducible, and operationally facile.^[8] Microwave dielectric heating in pressurized systems can rapidly increase temperatures far above the boiling point of the solvent and leads to efficient energy transfer to the reactants. Indeed, the addition of 1-butanol to styrene oxide using supported acid catalysts on carbon has been shown to accelerate the addition reaction with varying degrees of success.^[9] Herein, we report that microwave irradiation dramatically accelerates the copper tetrafluoroborate-catalyzed epoxide ring-opening reaction under very mild conditions (35°C), even with sterically hindered alcohols, to give β -alkoxyalcohols in high yields (Scheme 1).

We initially investigated reaction conditions for the addition of methanol to styrene oxide (**1**) to ascertain the potential for microwave acceleration of this reaction (Scheme 1). Gratifyingly, good conversions to the β -alkoxyalcohol product (**2a**) were observed after irradiation at 35°C for 5–10 min under similar reaction conditions to those described by Barluenga (1 mol% catalyst with four equivalents of methanol). Disappointingly, however, attempts to further improve these yields by increasing the initial microwave



Scheme 1. Methanolysis of styrene oxide under microwave conditions.

power led to the production of substantial quantities of phenylacetaldehyde, generated in a competing rearrangement Meinwald reaction.^[10] This undesirable side reaction could be suppressed by simply increasing the number of equivalents of methanol. Therefore, under optimized conditions (35°C, 100 W initial power, 15 min), essentially quantitative conversions for the addition of methanol to styrene oxide were achieved using 8 equivalents of the alcohol (Table 1). Under similar conditions, the more synthetically challenging addition of sterically hindered alcohols such as *iso*-propanol and *tert*-butanol were successfully realized with excellent regioselectivity and in excellent overall yields. These yields were obtained in significantly shorter reaction times than those originally reported by Barluenga. The observed increase in the rate of reaction cannot be attributed to the elevated quantities of alcohol present nor the increase in bulk temperature, as control reactions proceeded in similar reaction times and produced yields comparable to those previously reported. Reaction of styrene oxide with 8 equivalents of *tert*-butanol at room temperature gave 78% conversion to compound **2c** after 12 h compared with 87% with 4 equivalents (see Ref: [6]). Reaction of styrene oxide with 4 equivalents of methanol at 35°C gave a 3:1 mixture of **2a** and starting material after 15 min.


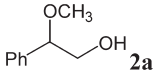

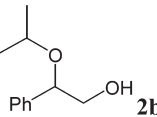

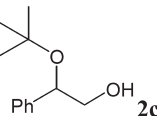

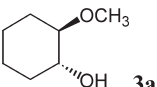

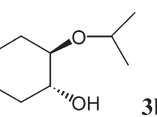

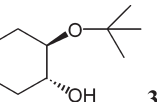
The generality of this methodology is illustrated by the successful addition of a range of alcohols to cyclohexene oxide to give β -alkoxyalcohol products (**3a–d**). In this case, no competing rearrangement reaction was observed, and the number of equivalents of the alcohol could be reduced without a noticeable reduction in yield or consequent increase in reaction times (entries 6 and 7). In keeping with previous literature observations,^[11] no regioselectivity was observed in the addition of alcohols to linear epoxides. Thus, approximately equal amounts of a mixture of regioisomers (**5a** and **5b**) were produced by the addition of *iso*-propanol to 1,2-epoxyhex-5-ene (**4**). However, under microwave-assisted conditions, this reaction proceeded rapidly to produce the corresponding addition products in excellent yield and in significantly shorter reaction times than those previously reported.^[6]


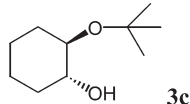

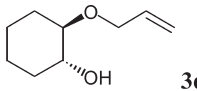
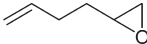
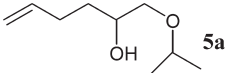
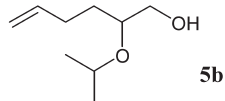
In conclusion, the copper tetrafluoroborate–catalyzed addition of alcohols to epoxides under microwave irradiation proceeds under mild reaction conditions, in excellent yields, and in significantly reduced reaction times. Furthermore, the high product purities obtained without chromatographic separation makes this a highly attractive alternative for the synthesis of β -alkoxyalcohols.

TYPICAL PROCEDURE

Copper tetrafluoroborate (1 mol%, 4 mg, 0.016 mmol) was added to a dichloromethane solution (5 ml) of styrene oxide (0.20 g, 1.66 mmol) and methanol (0.42 g, 13.28 mmol) in a Pyrex[®] tube. The vessel was sealed and irradiated inside a self-tunable microwave synthesizer (CEM Discover) under the stated reaction conditions. The reaction mixture was then diluted with water

Table 1. Cu(BF₄)₂ · nH₂O mediated additions to epoxides

Entry	Epoxide	Alcohol	Conditions ^c (°C/Watts/min)	Product ^{d,e}	Yield (%)
1		CH ₃ OH ^a	35/100/15	 2a	100
2		(CH ₃) ₂ CHOH ^a	35/100/15	 2b	78
3		(CH ₃) ₃ COH ^a	35/100/15	 2c	78
4		CH ₃ OH ^b	35/100/15	 3a	98
5		(CH ₃) ₂ CHOH ^b	35/100/15	 3b	95
6		(CH ₃) ₃ COH ^a	35/100/15	 3c	86

7		$(\text{CH}_3)_3\text{COH}^b$	35/100/15		85
8		$\text{CH}_2=\text{CHCH}_2\text{OH}^a$	35/100/15		84
9	 4	$(\text{CH}_3)_2\text{CHOH}^a$	35/100/15	 5a	90 ^f
				 5b	

^a8 Equivalents of alcohol.^b4 Equivalents of alcohol.^cPower indicates initial microwave power, which is modulated to maintain reaction temperature.^dAll products gave satisfactory spectroscopic data.^eRegioselectivity was determined from crude ¹H NMR spectra.^fIsolated as a 1.1:1 mixture of **5b**: **5a** as determined by ¹H NMR spectra of the crude reaction mixture.

(20 ml) and extracted with dichloromethane (3×20 ml). The combined extracts were dried over MgSO_4 and filtered, and the solvent was removed under reduced pressure to give 2-methoxy-2-phenylethanol (**2a**) as a colorless oil (250 mg, 100%), which was determined to be >98% pure by ^1H NMR spectroscopy. ^1H NMR (400 MHz; CDCl_3) δ = 7.44–7.29 (5H, m), 4.34 (1H, dd, J = 4 and 9 Hz), 3.74–3.59 (2H, m), 3.34 (3H, s), 2.45 (1H, dd, J = 4 and 9 Hz); ^{13}C NMR (100 MHz; CDCl_3) δ = 138.7, 129.4, 129.3, 128.9, 127.5, 127.4, 85.1, 67.8, 57.3; ν_{max} (film)/ cm^{-1} 3421, 2932, 2872, 1493, 1454, 1109, 1062, 1025, 865, 757, 699, 544; MS (EI) m/z 152 (M) $^+$; HRMS (CI, NH_3) calculated for $\text{C}_9\text{H}_{16}\text{NO}_2$ ($\text{M} + \text{NH}_4$) $^+$, 170.1176, found ($\text{M} + \text{NH}_4$) $^+$ 170.1176.

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