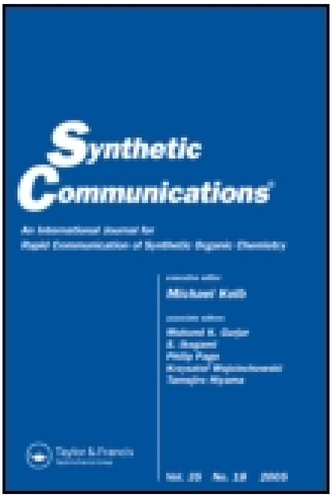

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Mild Organic Ammonium Tribromide-Mediated Regioselective Ring Opening of Epoxides with Alcohols, Water, Acetic Anhydride, and Amines Under Solvent-Free Reaction Conditions

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To cite this article: Sweety Singhal, Suman L. Jain & Bir Sain (2011) Mild Organic Ammonium Tribromide-Mediated Regioselective Ring Opening of Epoxides with Alcohols, Water, Acetic Anhydride, and Amines Under Solvent-Free Reaction Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:12, 1829-1837, DOI: 10.1080/00397911.2010.493259

To link to this article: http://dx.doi.org/10.1080/00397911.2010.493259

Synthetic Communications®, 41: 1829–1837, 2011
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ISSN: 0039-7911 print/1532-2432 online
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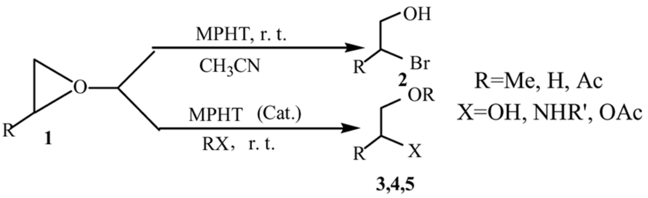
MILD ORGANIC AMMONIUM TRIBROMIDE–MEDIATED REGIOSELECTIVE RING OPENING OF EPOXIDES WITH ALCOHOLS, WATER, ACETIC ANHYDRIDE, AND AMINES UNDER SOLVENT-FREE REACTION CONDITIONS

Sweety Singhal, Suman L. Jain, and Bir Sain
Chemical Sciences Division, Indian Institute of Petroleum, Council of Scientific and Industrial Research, Dehradun, India

GRAPHICAL ABSTRACT



Abstract *Organic ammonium tribromide (OATB),* N-*methylpyrrolidine-2-one hydrotribromide (MPHT) was found to be an efficient catalyst for the regioselective ring opening of epoxides with various nucleophiles under solvent free conditions. This procedure occurs under neutral and mild reaction conditions with out adding any additive and afforded high yields of products.*

Keywords Metal free; MPHT; regioselective synthesis; ring opening; solid bromine

INTRODUCTION

Ring opening of epoxides with nucleophilic reagents is an important synthetic transformation as it offers a simple and straightforward approach for the synthesis of several regio- and stereoselective 1,2-difunctionalized ring-opened products.[1,2] The commonly used methods for the ring opening of epoxides with nucleophiles involve the use of strong acids or bases,[3,4] which have several limitations such as formation of undesirable side products mainly due to di- or polymerization of epoxides, lesser yields, and extended reaction times. Subsequently, several improved catalytic methodologies mainly using transition metal–based or metal-free catalysts under homogeneous or heterogeneous conditions have been developed for this

Received February 1, 2010.

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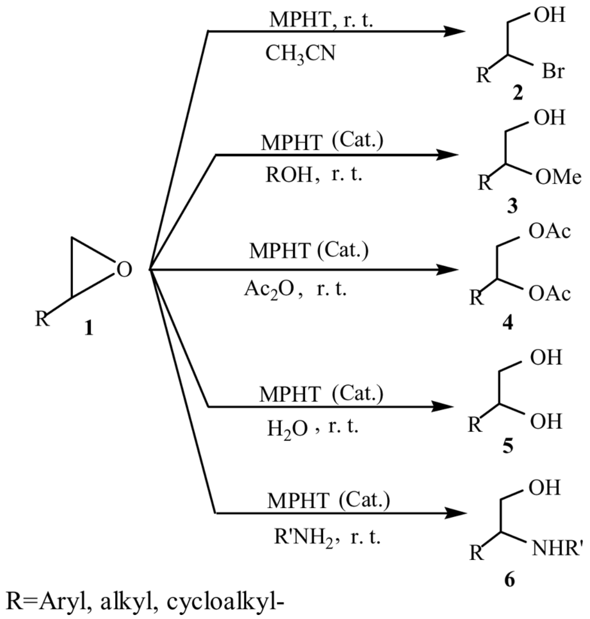


Scheme 1. Regioselective ring opening of epoxides.

transformation.[5–10] Although these methods generally lead to high yields with good regioselectivity, the use of toxic/expensive transition metals restrict their widespread applicability. In recent years, use of transition metal–free catalytic systems has become desirable, particularly for the preparation of compounds that do not tolerate metal contamination such as pharmaceuticals.

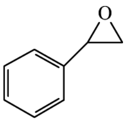
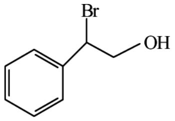
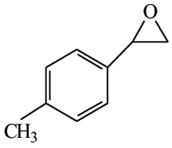
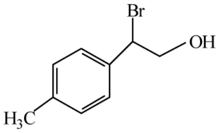
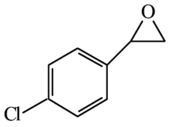
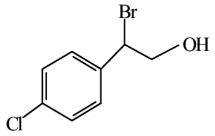
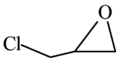
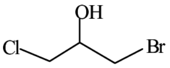
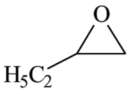
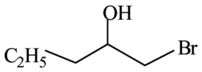
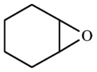
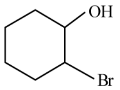
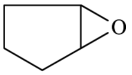
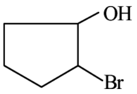
Organic ammonium tribromides (OATB),[11,12] also referred to as solid bromines because of their crystalline nature, ease of synthesis/handling, better storage stability, and capacity to maintain the desired stoichiometry, have proven to be safer and promising alternatives to toxic molecular bromine and anhydrous HBr in organic reactions. The use of these compounds for bromination of organic compounds is well documented, but little is known about their catalytic potential for organic transformations.

In the present article, we report a simple methodology for the regioselective ring opening of epoxides with various nucleophiles such as alcohols, water, acetic anhydride, and amines to afford corresponding β-alkoxy alcohols, 1,2-diols, 1,2-diacetates, and β-amino alcohols in the presence of a catalytic amount of *N*-methylpyrrolidine-2-one hydrotribromide (MPHT)[13] without adding any additive under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

Initially, we studied the nucleophilic ring opening of various epoxides with equimolar amounts of MPHT (1:1.2) in acetonitrile at room temperature. These results are presented in Table 1. All the epoxides smoothly underwent regioselective

Table 1. Ring opening of epoxides with MPHT in acetonitrile[a]

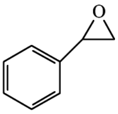
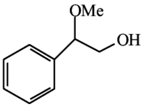
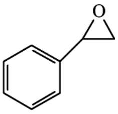
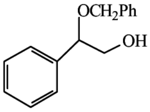
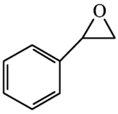
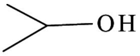
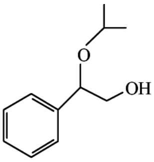
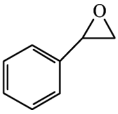
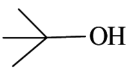
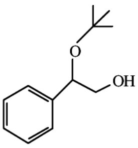
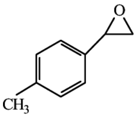
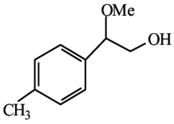
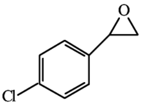
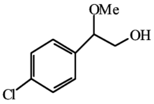
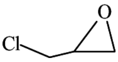
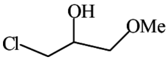
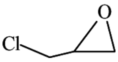
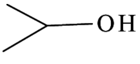
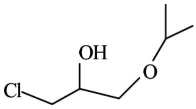
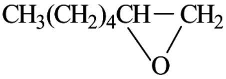
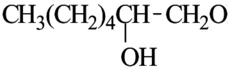
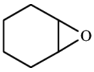
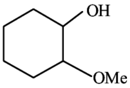
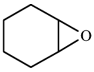
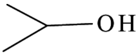
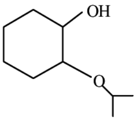
Entry	Epoxide **1**	Product **2**	Yield (%)[b]
1			98
2			94
3			95
4			96
5			94
6			98
7			98

[a] Reaction conditions: epoxide (1 mmol), MPHT (1.2 mmol), acetonitrile (3 ml); reaction time 15–20 min at room temperature.

[b] Isolated yields.

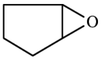
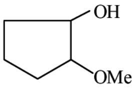
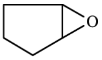
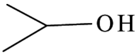
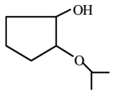
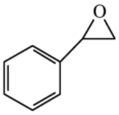
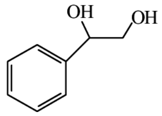
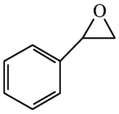
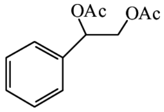
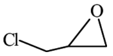
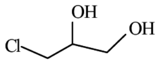
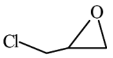
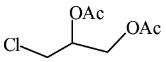
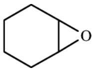
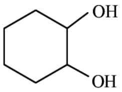
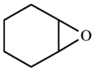
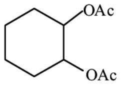
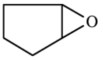
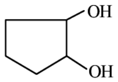
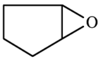
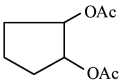
ring opening and afforded β-bromohydrins selectively without any evidence of the formation of by-products. 2-Arylepoxides, for example, styrene oxide, underwent regioselective ring cleavage with the preferential attack at the benzylic position, probably because of formation of stabilized benzylic cation as a reactive intermediate during the reaction (Table 1, entries 1–3). In the case of 2-alkyl epoxides, ring-opening products were formed by cleavage at the terminal position with the preferential attack of nucleophile from the less-hindered side (Table 1, entries 4 and 5). Cycloalky epoxides such as cyclohexane epoxide and cyclopentane epoxide were efficiently reacted with MPHT and yielded the corresponding 2-bromo cyclohexanol and 2-bromocyclopentanol respectively in good yields (Table 1, entries 6 and 7). Further, we studied the regioselective ring opening of epoxides with alcohols, acetic anhydride, amines, and water in the presence of a catalytic amount of MPHT under solvent-free condition (Scheme 1). A variety of epoxides reacted smoothly

Table 2. MPHT-catalyzed ring opening of epoxides with alcohols, water, and acetic anhydride[a]

Entry	Epoxide **1**	Nucleophile	Product **3**, **4**, **5**	Time (h)	Yield (%)[b]
1		MeOH		1.0	96
2		$PhCH_2OH$		3.5	75
3				1.5	90
4				2.5	85
5		MeOH		1.5	92
6		MeOH		2.0	94
7		MeOH		1.5	89
8				2.5	80
9	 $CH_3(CH_2)_4CH{-}CH_2$ (O bridge)	MeOH	 $CH_3(CH_2)_4\underset{OH}{CH}{-}CH_2O$	2.0	84
10		MeOH		3.0	92
11				1.5	89

(*Continued*)

Table 2. Continued

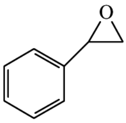
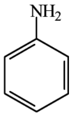
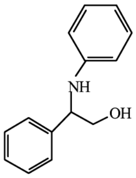
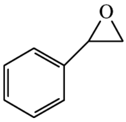
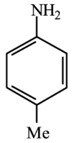
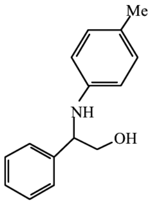
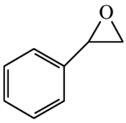
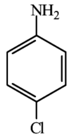
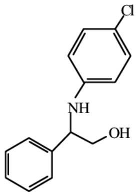
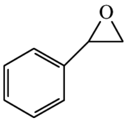
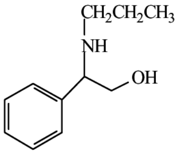
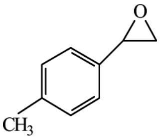
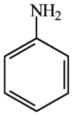
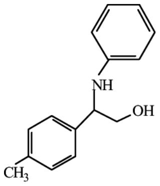
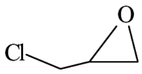
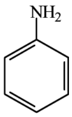
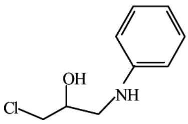
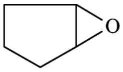
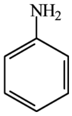
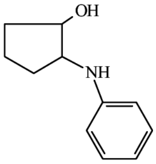
Entry	Epoxide **1**	Nucleophile	Product **3**, **4**, **5**	Time (h)	Yield (%)[b]
12		MeOH		1.0	93
13				1.0	87
14		H_2O		1.0	97
15		Ac_2O		1.5	97
16		H_2O		2.0	94
17		Ac_2O		2.0	92
18		H_2O		1.5	97
19		Ac_2O		1.5	97
20		H_2O		1.5	97
21		Ac_2O		1.5	97

[a] Reaction conditions: Epoxide (1 mmol), nucleophile (2 mmol), and MPHT (10 mol%) at room temperature.

[b] Isolated yields.

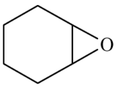
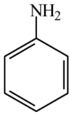
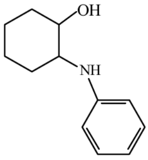
with various alcohols such as benzylic, primary, secondary, and tertiary in the presence of a catalytic amount of MPHT and yielded corresponding β-hydroxy ethers in good yields as shown in Table 2. Again, aryl epoxides underwent ring opening at the benzylic position regioselectively (Table 2, entries 1–4), whereas alkyepoxides such as epichlorhydrin and heptane oxide gave ring-opened products by cleavage at the terminal position because of the preferential attack of the nucleophile from the less-hindered side (Table 2, entries 7–9). However, the hydrolysis of epoxides in

Table 3. MPHT-catalyzed ring cleavage of epoxides with amines[a]

Entry	Epoxide **1**	Amine	Product **6**	Time (h)	Yield (%)[b]
1				2.5	80
2				3.0	80
3				5.0	72
4		$CH_3CH_2CH_2NH_2$		8.0	55
5				3.0	80
6				5.0	65
7				5.0	70

(*Continued*)

Table 3. Continued

Entry	Epoxide **1**	Amine	Product **6**	Time (h)	Yield (%)[b]
8				5.0	75

[a]Reaction conditions: Epoxide (1 mmol), amine (2.0 mmol), MPHT and (10 mol%) at room temperature.
[b]Isolated yields.

the presence of a catalytic amount of MPHT yielded corresponding *vic*-diols selectively in excellent yields under the described reaction conditions (Table 2, entries 14, 16, 18, and 20). Similarly, ring cleavage of epoxides in acetic anhydride using MPHT as catalyst yielded exclusively 1,2-diacetates in good yields (Table 2, entries 15, 17, 19, and 21).

To extent that the catalytic potential of the protocol developed, we studied the ring cleavage of styrene oxide with various aromatic and aliphatic amines by using MPHT as catalyst under similar reaction conditions. These results are presented in Table 3 (entry 1–4). All the reactions were found to be regioselective and yielded corresponding β-hydroxy amines by cleavage on the benzylic position. Alkyl amines in general were found to be less reactive than anilines in terms of the reaction times and yields of the cleaved product. Next we carried out the ring opening of various epoxides with aniline under the described reaction conditions (Table 3).

In summary, we have described the use of the MPHT, an easily accessible organic ammonium tribromide, as a stoichiometric reagent or catalyst for the ring opening of various epoxides with a number of nucleophiles under mild reaction conditions. MPHT can be considered to be a versatile reagent that has remarkable stability and does not decompose on storage at room temperature even after a long time. It is not corrosive and can easily be handled because of its crystalline nature. Furthermore, the use of solvent-free conditions makes this process more advantageous from environmental viewpoints.

EXPERIMENTAL

General Procedure for Ring Opening of Epoxides with MPHT in Acetonitrile

MPHT (1.2 mmol) was added to a stirred solution of an epoxide (1 mmol) in dry acetonitrile (3 ml), and the reaction was continued at room temperature for 15–20 min. After completion of the reaction, the solvent was evaporated under reduced pressure. The residue thus obtained was dissolved in dichloromethane and extracted with water (3 × 10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography using EtOAc/hexane (1:9) as eluent to afford pure β-bromohydrin. All the products were characterized by their physical and spectral analysis.

General Procedure for MPHT-Catalyzed Nucleophilic Ring Opening with Alcohols, Water, Acetic Anhydride, and Amines

Nucleophile (2 mmol) was added into a stirred mixture of an epoxide (1 mmol) and MPHT (10 mol%) in a 50-ml round-bottomed flask, and the reaction continued at room temperature for the appropriate time as mentioned in Tables 2 and 3. After completion of the reaction as indicated by thin-layer chromatography (TLC), the reaction mixture was quenched with water and extracted with dichloromethane (3 × 10 ml). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography to yield pure β-hydroxy product.

ACKNOWLEDGMENTS

We are grateful to the director, Indian Institute of Petroleum, for his kind permission to publish these results. S. L. J. and S. S. are thankful to the Council of Scientific and Industrial Research New Delhi, for the award of research fellowships.

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