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# Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/gpss20</u>

# LiOH-Catalyzed Simple Ring Opening of Epoxides Under Solvent-Free Conditions

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To cite this article: Najmedin Azizi , Alireza Khajeh-Amiri , Hossein Ghafuri & Mohammad Bolourtchian (2010): LiOH-Catalyzed Simple Ring Opening of Epoxides Under Solvent-Free Conditions, Phosphorus, Sulfur, and Silicon and the Related Elements, 185:7, 1550-1557

To link to this article: <u>http://dx.doi.org/10.1080/10426500903127573</u>

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#### LIOH-CATALYZED SIMPLE RING OPENING OF EPOXIDES UNDER SOLVENT-FREE CONDITIONS

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LiOH has been found to be a very simple and selective catalyst for the rapid and mild synthesis of  $\beta$ -hydroxy sulfides and  $\beta$ -hydroxyl nitriles by ring opening of epoxides with aromatic, aliphatic, and heterocyclic thiols and trimethylsilyl cyanide at room temperature under solvent free conditions. All the reactions proceeded satisfactorily in short times and afforded the corresponding products in good to excellent yields with high regioselectivity and chemoselectivity under mild reaction conditions.

**Keywords** Epoxide;  $\beta$ -hydroxy nitriles;  $\beta$ -hydroxy sulfide; lithium hydroxide; solvent free conditions; thiol

Epoxides have been recognized among the most versatile intermediates in organic synthesis. They can be easily prepared and due to their ring strain, which enhances their reactivity, and react with nucleophiles with high regioselectivity.<sup>1</sup> In this context, reactions with thionucleophiles play an important role, affording hydroxythio derivatives as useful building blocks for the synthesis of cyclic sulfides,<sup>2,3</sup> benzoxathiepines, benzothiazepines, and thioketones,<sup>4</sup> and as well as in organic chemistry, particularly in the pharmaceutical and natural product fields.<sup>5</sup>

A direct and practical approach to  $\beta$ -hydroxy sulfides is the ring opening of 1,2disubstituted epoxides using thiols as the nucleophile.<sup>6</sup> Thus, a variety of reagents and catalysts have been developed to achieve this simple process, which is testimony to the importance of this reaction,<sup>7</sup> although these problems were overcome to some extent by recently reported acid catalysts under solvent-free conditions.<sup>8</sup> Unfortunately, these processes turned out to involve stoichiometric or superstoichiometric amounts of toxic or hazardous catalysts, long reaction times, low yields, the use of volatile organic solvents, requirement of excess reagents or catalysts, and harsh reaction conditions. Furthermore, almost all procedures for the preparation of  $\beta$ -hydroxy sulfides reported so far are restricted to simple aromatic thiols.

Due to the growing concern for the influence of organic solvents on the environment as well as on the human body, organic reactions without the use of conventional organic solvents that employ a catalytic amount of an economic and readily available catalyst that

Received 7 April 2009; accepted 17 June 2009.

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does not contain a metal would be of great interest. In this context, during our ongoing studies of solvent-free conditions<sup>9</sup> in the presence of lithium salts, in this article we report a very mild, easy, and catalytic process for synthesizing  $\beta$ -hydroxysulfides under solvent-free conditions. Our approach is based on a simple thiolysis of epoxides under very mild conditions in the presence of a commercially available, catalytic amount of lithium hydrox-ide. The combination of using a simple catalysis and solvent-free conditions gave excellent yields of products and reduced the reaction times, which represents a highly ecofriendly approach.

#### **RESULTS AND DISCUSSION**

To find the optimal conditions for the ring opening, initial studies were performed by using LiOH as catalyst in the reaction of glycidyl phenyl ether with benzenethiol under various conditions at room temperature (Scheme 1). The reaction was slow in the absence of a catalyst, and reactions in solvents such as THF, CH<sub>2</sub>Cl<sub>2</sub>, acetone, DMF gave low yields of the desired product even after prolonged reaction time. Next, we optimized the quantity of the catalyst at room temperature under solvent-free conditions, and it was observed that the use of just 20 mol% is sufficient to produce an excellent yield of the product.

PhO	0, 0	-1	LiC	LiOH (x mol%)			^		
1 110		+ PhSH	I —	rt, 5 min		→ P	PhO Y S OH		
	X= Yields	200 97	100 97	50 97	20 97	10 80	5 50	1 10	_
									_

Sc	heme	]

We further explored the scope and limitation of this simple process by reaction of sterically, electronically, and functionally diverse epoxides and thiols under the optimized condition, and the results are summarized in Table I. Aliphatic as well as aromatic thiols reacted with different epoxides such as glycidyl phenyl ether, glycidyl isopropyl ether, 1,2-epoxy butane, 1,2-epoxy propane, and allyl 2,3-epoxypropyl ether to give the corresponding  $\beta$ -hydroxy sulfide in high to quantitative yield. Generally, aromatic thiols gave higher yields in short reaction time when compared with the aliphatic thiols. In all cases reported, the reactions proceeded smoothly at room temperature and typically afforded only one single product in high yield. Furthermore, the reaction with unsymmetrical epoxides was in most cases completely regioselective, since the only products isolated were those arriving from the attack of the nucleophile to the less hindered position of the epoxide with the exception of styrene oxide.

When styrene oxide was subjected to ring opening with the thiophenol, a mixture of both regioisomers was obtained in the ratio of 90:10, the major product resulting from the attack of nucleophile at the less-substituted carbon, which was confirmed by <sup>1</sup>H NMR analysis (Scheme 2).

The stereochemistry of the ring-opened products from bicyclic epoxides was found to be *trans* from the coupling constants of the ring hydrogens, as has been observed in most epoxide ring-opening reactions.



To establish the generality and scope of the present methodology, this study was further extended to TMSCN, which is expected to produce the corresponding  $\beta$ -hydroxy nitriles.  $\beta$ -hydroxy nitriles are useful synthetic intermediates in organic synthesis,<sup>10</sup> and it is a versatile moiety for the synthesis of 1,3-amino alcohols. The reaction of epoxides with different cyanide sources, such as hydrogen cyanide, cyanides,<sup>11</sup> and asymmetric ring opening with TMSCN in organic solvent,<sup>12</sup> or cyanide formed upon treatment of acetone cyanohydrin with various bases, are among the most direct methods for the preparation of these compounds.<sup>13</sup> The reaction of epoxides with NaCN, KCN, or HCN usually requires long reaction times, and protic and harmful solvents. They also lack appreciable regioselectivty when dealing with sensitive and bulky epoxides.

No reaction was observed in the absence of the lithium hydroxide. Reactions in solvents such as THF,  $CH_2Cl_2$ , acetone, and DMF gave lower yields of the desired product after prolonged reaction time. The best reaction condition was found when we used 20 mol% of commercially available LiOH under solvent-free conditions. The reactions were carried out with simple procedure by mixing directly the TMSCN (3.2 mmol), the epoxides (3 mmol), and solid LiOH (20 mol%) at 0°C to room temperature, under solvent-free conditions (Scheme 3).



Scheme 3

To show the generality and the scope of the lithium hydroxide–promoted  $\beta$ -hydroxy nitriles synthesis, the reaction was examined with various structurally diverse epoxides. The results are shown in Table II. The data clearly show that all reactions proceed smoothly under these conditions and afford the desired  $\beta$ -hydroxy nitriles in excellent yields with high regioselectivity. The regioselectivity for the unsymmetrical epoxides is governed by both steric and electronic effects. The regioselectivity was determined by <sup>1</sup>H NMR spectroscopy and by comparison with the known  $\beta$ -hydroxy nitriles.<sup>12</sup> Unsymmetrical oxiranes underwent cleavage by TMSCN with preferential attack at the less substituted carbon atom except for styrene oxide.

Furthermore, it is noteworthy that, in some cases, the product obtained after the routine workup was of sufficient purity for spectra analysis and did not require further purification.

The simple procedure described here appears to be highly efficient and competitive with the other methods reported in the literature. The ring-opening reaction of glycidyl phenyl ether in the presence of different catalysts is compared in Table III.

#### LIOH-CATALYZED RING OPENING OF EPOXIDES

Entry	Products	Yields (%) <sup>a</sup>	Time (mm)	Ref.
1	OH X=H	97	5	8c
2	X = Me	95	20	8q
3	X = Br	92	40	8p
4	X X = Cl	88	40	8q
5	X = EI	97	20	8m
6		82	100	8e
7	OH S	88	100	8s
8	OH S	80	120	8p
9	OH N	90	120	8p
10	C OH S S S	90	120	8q
11	он	97	20	8c
12	<b>→</b> <sup>0</sup> <b>→</b> <sup>S</sup> <b>→</b> X = H	95	30	8r
13	X = Br X X = Me	90	20	8r
14		05	10	0
14	OH	95	10	80 80
15	$\sim 0$ $\sim S$ $X = H$	90	50	op
16	X = Br X X = Me	92	30	8p
17	O OH S S N	85	120	8q
18	ŎН	97	20	80
19	0, , , , , , , , , , , , , , , , , , ,	93	15	8a
20	X = Me X X= Br	90	60	8q
21	ОН X = H	82	80	8c
22	S X = Me	80	60	8a
23	X = Br	78	100	8s

Table I Ring opening of epoxide with thiols

(Continued on next page)

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Entry	Products	Yields (%) <sup>a</sup>	Time (mm)	Ref.
24	ОН	84	100	8m
25	S X = Me	76	85	8m
26	∽°~ <sup>OH</sup> s	70	180	8q
27	C OH S	76	200	8c
28	OH s	78	200	8c
29	OH S	80	200	8q
30	SPh MOH	86	120	8q
31	OH Br	78	120	8m

Table I Ring opening of epoxide with thiols (Continued)

<sup>a</sup>NMR yields.

In summary, we have developed an efficient and very simple methodology for the ring opening of epoxides with aromatic and aliphatic thiols and TMSCN that provides access to useful and synthetically challenging  $\beta$ -hydroxy sulfides and  $\beta$ -hydroxy nitriles. The use of inexpensive and readily available reagents, chemical efficiency, water tolerance of the catalyst, operational simplicity, simple workup, and high regioselectivity make this process particularly attractive. Additionally, the most important advantage was that when pure reactants were used, the products were always obtained in quantitative yields and a workup was not required in most cases. Consequently, these reactions were completely solvent-free, atom economic, and sustainable, and no waste was produced.

#### EXPERIMENTAL

All chemicals were purchased and used without any further purification. NMR spectra were recorded at 500 MHz for proton and at 125.7 MHz for carbon nuclei in (CDCl<sub>3</sub>/CCl<sub>4</sub>) or (CDCl<sub>3</sub>). The products were purified by column chromatography carried out on silica gel by using ethyl acetate/petroleum ether mixtures if necessary. All the epoxides used are known, and products obtained are known compounds.

#### LIOH-CATALYZED RING OPENING OF EPOXIDES



Table II LiOH catalyzed reactions of epoxides with TMSCN under solvent free-conditions

<sup>a</sup>NMR yields.

#### General Procedure for Aqueous Ring Opening of Epoxides with Thiols Catalyzed by LiOH

To a stirred solution of epoxide (5 mmol) and LiOH (20 mol%) in a test tube, thiols (5 mmol) were added, and the resulting mixture was stirred at room temperature for 5–200 min. Then water (5 mL) was added, and the organic materials were extracted with diethyl ether (2  $\times$  10 mL). The organic layer was separated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>,

	0, 0 +	SH	$\rightarrow$	OH S	
Entry	Catalyst (mol%)	Solvent	Time (min)	Yields (%)	Ref.
1	$InCl_3(1)$	SFC	10	85	8a
2	p-TsOH (5)	SFC	1080	73	8a
3	$K_2CO_3(5)$	SFC	120	95	8a
4	$n-Bu_{3}P(5)$	SFC	1200	95	8a
5	ZnCl <sub>2</sub> (10)	Water	20	100	8f
6	TBAF (10)	SFC	30	98	8d
7	Et <sub>3</sub> N (100)	MeOH	240	99	7h
8	MgClO <sub>4</sub> (75)	CH <sub>3</sub> CN	150	99	7h
9	$LiClO_4$ (12)	SFC	20	98	8c
10	Borax (20)	Water	540	90	8j
11	$ZnClO_4$ (5)	SFC	60	98	8b
12	$In(OTf)_3(1)$	SFC	20	80	8i
13	$Ga(OTf)_3(1)$	SFC	30	98	8q
14	LiOH (20)	SFC	5	97	This work

Table III Comparison of the catalytic activity of LiOH with other methods in the literature

and the solvent was removed under reduce pressure to give the pure product. Evaporation of the solvent afforded the desired pure product in most cases. In a few cases, the crude product was further purified by flash column chromatography to provide the corresponding pure product. All compounds were characterized on the basis of their spectroscopic data (IR, NMR) and by comparison with those reported in the literature.

#### General Procedure for the Preparation of $\beta$ -Hydroxy Nitriles

To mixture of epoxide (3 mmol) and LiOH (20 mol%) in a test tube, TMSCN (3.1 mmol) was added, and the mixture was stirred at 0°C for few min and then at room temperature for 20–180 min. The reaction was monitored with TLC or GC. Then water (5 mL) was added, and the organic materials were extracted with diethyl ether (2 × 10 mL). The organic layer was separated and dried over anhydrous MgSO<sub>4</sub>, and the solvent was removed to give the  $\beta$ -hydroxy nitriles in the pure product.

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