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Graphical Abstract

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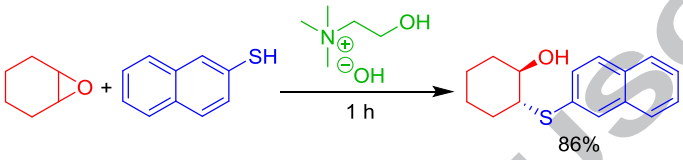

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Biodegradable choline hydroxide promoted environmentally benign thiolysis of epoxides

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ABSTRACT

An environmentally benign and rapid thiolysis of epoxides using a biodegradable, choline-based task-specific ionic liquid has been developed. The ring opening reaction of aryl and alkyl epoxides proceeded rapidly and afforded the corresponding β-hydroxysulfides in high yields with excellent regioselectivity. The protocol has the advantages of easy work-up, short reaction times, high yields and a biodegradable catalyst.

Task-specific, functionalized ionic liquids with unique physico-chemical properties have received increased attention over the last few years.[1] The incorporation of acidic or basic functional groups in the ionic liquid provides extra capacity to behave not only as a green reaction medium, but also as a recyclable promoter or catalyst in different organic reactions.[2] Despite the valuable properties of traditional task-specific ionic liquids based on imidazolium and pyridinium salts, they possess disadvantages such as toxicity, difficult preparation and high cost.[3] Choline hydroxide (ChOH) is a non-toxic and naturally abundant task-specific ionic liquid which can be used to carry the hydroxide ion into organic systems (Fig. 1). It is water-soluble and can be easily prepared from biodegradeable and low cost starting materials in high purity. Moreover, it is an excellent phase transfer catalyst in terms of activity and selectivity.[4]

The thiolysis of 1,2-epoxides under mild and eco-friendly conditions, is a useful method for the construction of the β-hydroxysulfide moiety[5] which are versatile intermediates in the synthesis of a variety of biological and pharmaceutically important products.[6] Sulfur-containing organic compounds have found various applications as antioxidants, chemotherapeutics, enzyme inhibitors, calcium channel antagonists, and antimicrobial agents.[7] Owing to their significance, the development of environmentally benign, high yielding, and clean epoxide thiolysis is still a challenge and has been extensively investigated.[8] The related work has focused on discovering environmentally friendly solvents, reagents and catalysts for the clean and fast ring opening of epoxides using thiol.[9] Although some of these reported procedures are environmentally friendly, to the best of our knowledge, there are no report of the thiolysis of epoxides using choline hydroxide.

In recent years, significant development has taken place in green chemistry using water and ionic liquids as an environmentally benign reaction media in place of traditional organic reaction media.[10]As a part of our research to develop green chemistry using deep eutectic solvents as reaction mediums,[11] herein, we report a simple, practical and effective process for synthesizing β-hydroxysulfides *via* the choline hydroxide promoted thiolysis of epoxides. The combination of using a green phase transfer promoter and solvent-free condition gives excellent yields and reduces the reaction times, making this a highly eco-friendly methodology to prepare β-hydroxysulfides.

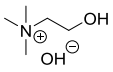

Fig. 1. Structure of choline hydroxide

Initially, we investigated the thiolysis of cyclohexene oxide with thiophenol as a model reaction in the presence of ChOH (Table 1). The reaction proceeded smoothly at room temperature in the presence of 50 mol% of ChOH, to give the desired product **3a** in quantitative yield after 30 minutes. When the amount of ChOH was decreased to 30 mol%, the yield of the product **3a** was reduced, and with 100 mol% loading of ChOH there was no improvement. Furthermore, without any ChOH only 40% yield was obtained with a much longer reaction time (Table 1, entry 1). Screening of different amounts of ChOH revealed that 50 mol%

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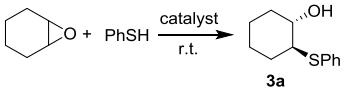
of ChOH was the most effective in terms of yields and time. Furthermore, the model reaction was carried out using common organic hydroxides such as Bu_4NOH, Me_4NOH, triton B, organic base (Et_3N) and a few commerically avaliable inorganic bases such as KOH and NaOH in order to substantiate the task-specific functionalized ionic liquids effect. All of the tested bases gave lower yields under the optimized reaction conditions (Table 1).

Table 1. Optimization of the model reaction



3a

Entry	Catalyst (mol%)	Time (min)	Yield (%)[a,b]
1	none	400	40
2	ChOH (1)	400	72
3	ChOH (5)	30	60
4	ChOH (10)	30	75
5	ChOH (30)	30	80
6	ChOH (50)	30	95
7	ChOH (100)	30	95
8	Et_3N (50)	30	65
9	KOH (50)	30	52
10	NaOH (50)	30	58
11	Bu_4NOH (50)	30	68
12	Me_4NOH (50)	30	56
13	triton B (50)	30	45

[a] Isolated yield. [b] Reaction conditions: cyclohexene oxide (1 mmol), thiophenol (1 mmol), catalyst, r.t..

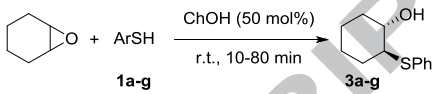
Having established suitable reaction conditions, various structurally diverese epoxides and arylthiophenols were applied to the synthesis of various β-hydroxyarylsulfides in order to investigate the reaction scope. It was observed that sterically, electronically and functionally diverse thiophenols reacted with cyclohexane oxide to give the corresponding products in good to excellent yields (Table 2). The reactions were chemoselective and epoxide cleavage with reactive functional groups such as -OH was not observed. Furthermore, the reactions were stereoselective and *trans* stereochemistry of the ring products were confirmed by the coupling constants of the C–H protons adjacent to the heteroatoms in the ^{1}H NMR spectra.

Next, the synthetic utility of this protocol was demonstrated by the use of various alkyl- and aryl-epoxides and thiol substrates. Thiolysis of alkyl- and aryl-epoxides such as phenyl 2,3-epoxypropyl ether, isopropyl-2,3-epoxypropyl ether, 1,2-epoxy butane, allyl-2,3-epoxypropyl ether and styrene oxide, with aryl thiols possessing different substituents (4-MeO, 4-Cl, 4-Br, and 4-Me) on the phenyl ring are shown in Table 3. The obtained results revealed that reaction of the epoxides and thiols proceed smoothly and afforded the corresponding β-hydroxysulfides in good to excellent isolated yield with high regioselectivity (Table 3).

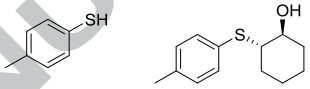
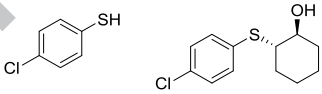
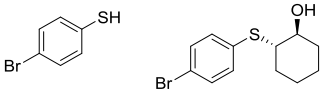
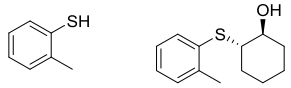
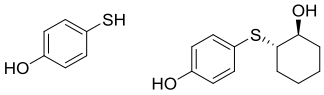
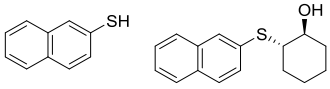
The regioselectivity in the reaction of unsymmetrical epoxides is governed by both steric and electronic effects. Selective nucleophilic attack of arylthiols occurred exclusively on the less substituted carbon atom of aliphatic epoxides. Styrene oxide undergoes regioselective nucleophilic attack at the benzylic position under electrophilic activation (i.e., Lewis acid catalysed epoxide ring opening) while under neutral or basic conditions leads to nucleophilic attack at the less hindered terminal position via a S_N2 mechanism.[9a,12] Styrene oxide reacted under standard reaction conditions with short reaction times and excellent yields. However, regioselectivity was not observed for this substrate, and both regio-isomers were formed. Their structures were confirmed by comparison of the ^{1}HNMR spectral data with those reported in the literature.[13]

In summary, a convenient, quick and green thiolysis of 1,2-epoxides with aromatic thiols using choline hydroxide as a environmentally benign catalyst has been developed. Using a biodegradable and inexpensive choline hydroxide under solvent free conditions provide a selective synthesis of β-hydroxysulfides in good to excellent yields.[14,15]

Table 2. Ring opening of cyclohexane oxide with thiols promoted by ChOH.



1a-g **3a-g**

Entry	ArSH	**3a-3g**	Yield[a,b] (%)	Time (min)
1			95	10[9e]
2			95	10[9e]
3			88	60[9b]
4			90	45[9f]
5			80	35[9g]
6			76	80[6b]
7			86	60[8b]

[a] Isolated yields. [b] Reaction conditions: cyclohexene oxide (1 mmol), ArSH (1 mmol), ChOH (50 mol%), r.t.

Acknowledgments

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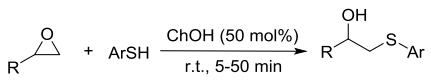
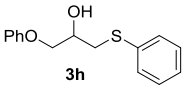
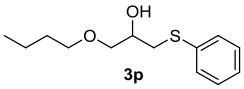
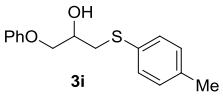
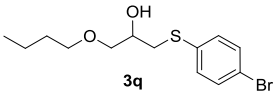
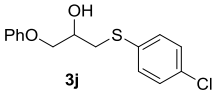
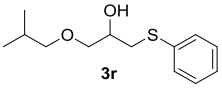
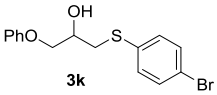
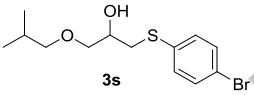
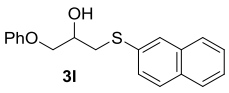
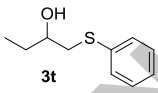
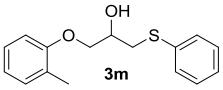
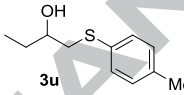
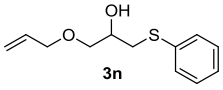
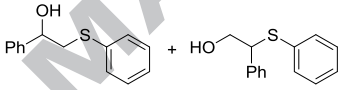
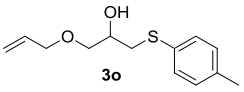
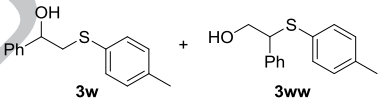
14. **Preparation of choline hydroxide:** The choline hydroxide based ionic liquid was prepared according to the literature.[4] Choline chloride (10 mmol) and KOH (10 mmol) in methanol (15 mL) were heated at reflux for 12 h under N_2. After cooling to room temperature, the reaction mixture was filtered to remove solid KCl and the solution was concentrated under vacuum to remove methanol. The residue was dissolved in water to prepare 40% by weight of the choline hydroxide solution which was used without any further purification.
15. **General procedure**: A test tube, equipped with a magnetic stir bar, was charged with epoxide (1.0 mmol), thiol (1.0 mmol), and ChOH (50 mol%). The resulting mixture was stirred at room temperature until the reaction was complete (5-80 min). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL) to remove the ChOH. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. In some cases, the crude products were purified by flash column chromatography using silica gel or recrystallization from ethanol or diethyl ether. All products are known compounds and the characterization data of these compounds were identical to literature reports.

Table 3. Ring-opening of various epoxides with thiols promoted by ChOH



1 2 3h-3w

Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **3h**	95[9b]	9	 **3p**	82[9b]
2	 **3i**	92[9b]	10	 **3q**	88[9h]
3	 **3j**	90[13c]	11	 **3r**	78[6a]
4	 **3k**	92[9h]	12	 **3s**	80[6a]
5	 **3l**	75[7b]	13	 **3t**	75[9e]
6	 **3m**	78[8b]	14	 **3u**	78[9i]
7	 **3n**	86[9a]	15[c]	 **3v** 54% **3vv** 46%	92[14a]
8	 **3o**	80[8a]	16[c]	 **3w** 58% **3ww** 42%	94[14c]

[a] Isolated yield. [b] Reaction Conditions: epoxide (1 mmol), ArSH (1 mmol), ChOH (50 mol%), r.t. [c] ^{1}H NMR yield