# Selective oxidation of sulfides to sulfoxides catalysed by deep eutectic solvent with $H_2O_2$

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A Brønsted acidic deep eutectic solvent based on choline chloride and *p*-toluenesulfonic acid (ChCl/*p*-TsOH, 1:1) was prepared and utilised for the selective oxidation of sulfides with  $H_2O_2$  as the oxidant. Broad substrate compatibility, good yields and selectivities, the reusability of the catalyst as well as the gram-scale synthesis are the major advantages of this protocol. Moreover, the use of ChCl/*p*-TsOH, instead of neat *p*-TsOH, can greatly reduce the acid sewage especially in large-scale synthetic processes.

Keywords: sulfide, oxidation, deep eutectic solvent, hydrogen peroxide, chemoselectivity

Sulfoxides are important synthetic intermediates for the synthesis of various biologically active molecules.<sup>1</sup> The oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides, and a series of catalytic systems have been developed over the last decade for their preparation, including metal-containing catalytic systems,<sup>2–6</sup> metal-free protocols<sup>7,8</sup> as well as biocatalysts<sup>9</sup> in the presence of various oxidants.

While acknowledging the considerable progress in this field, the selective synthesis of sulfoxides remains a major challenge since the overoxidation of sulfoxides to sulfones is commonplace. Moreover, the reported methodologies also have drawbacks including complex catalytic systems,<sup>10,11</sup> need for excess of catalyst or oxidant,<sup>2,12</sup> harsh conditions and poor yields and selectivities.<sup>13</sup> To solve the problem, some acid catalysts such as camphorsulfonic acid,<sup>14</sup> glacial acetic acid,<sup>15</sup> sulfamic acid<sup>16</sup> and *p*-toluenesulfonic acid<sup>17</sup> have been reported which show good catalytic activities and selectivities. However, the non-recyclability and the acidic pollution greatly limit their large scale use. Thus, a simple, metal- and additive-free, and eco-friendly protocol for such a useful transformation is required.

Deep eutectic solvents (DESs), which are green solvents or catalysts, have received widespread attention due to their properties such as low vapour pressure, low flammability, biodegradability, non-toxicity, and cheapness. Also, one class of DES is readily prepared by just mixing choline chloride with a hydrogen bond donor, such as urea, or a Lewis or Brønsted acid. It is also worth noting that choline is a naturally occurring biocompatible compound and choline chloride is commercially produced on a large scale.<sup>18</sup> Many classes of DES have also shown potential applications as either solvents or catalysts in organic reactions such as the Still reaction,<sup>19</sup> halogenation,<sup>20</sup> alkylation,<sup>21</sup> epoxide hydrolysis,<sup>22</sup> nitroaldol reactions,<sup>23</sup> C–C coupling reactions<sup>24</sup> and oxidative hydroxylation.<sup>25</sup>

Moreover, the use of hydrogen peroxide has attracted much attention since it is readily available, cheap and environmentally benign, with water as the only byproduct. However, the oxidation reactions of sulfides with hydrogen peroxide are usually very slow, and the challenge is to identify suitable catalysts or reagents to activate hydrogen peroxide. As part of our programme for sustainable synthesis and catalysis,



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we found that some DESs could efficiently activate hydrogen peroxide through hydrogen bonding.<sup>26</sup> Here, we report a simple, efficient and reusable catalytic system for the selective oxidation of sulfides to sulfoxides using  $H_2O_2$  as the oxidant and a Brønsted acidic deep eutectic solvent (DES=ChCl/*p*-TsOH) as the catalyst (Scheme 1).

#### **Results and discussion**

Initially, the model reaction using benzyl phenyl sulfide (1a) as substrate and  $H_2O_2$  as the oxidant was carried out by using different eutectic mixtures based on choline chloride (ChCl) with H-donors such as urea, malonic acid, glycerol, hexafluoroisopropanol and *p*-toluenesulfonic acid (*p*-TsOH). The results are shown in Table 1 which clearly shows that ChCl/*p*-TsOH was the best DES, giving the corresponding product 2a in 89% yield after 4 h (Table 1, entry 5). Although ChCl/urea could efficiently activate the hydrogen peroxide by polarisation of the peroxide bond through hydrogen bonding,<sup>26</sup> a much lower yield of 32% was obtained for this combination; other types of DES were weakly effective or totally ineffective (Table 1, entries 1–4).

Following this encouraging result, we then made a survey of the effect of other parameters on the model reaction. The results are summarised in Table 2. The solvent played an important role in the reaction. Good yields were obtained when ethanol or acetonitrile was employed but not with solvents such as THF and  $H_2O$  (entries 1–4). This can be attributed to the fact that DES shows excellent solubility in polar solvents permitting the reaction to proceed in a homogeneous system. Increasing the amount of hydrogen peroxide from 2 to 15 equiv. is beneficial, affording the product **2a** with excellent yields and selectivities (entries 5–7). However, when excess hydrogen peroxide (20 equiv.) was used, a 5% yield of sulfone was detected. The temperature and the amount of catalyst were also evaluated. This

Table 1 Oxidation of benzyl phenyl sulfide 1a (R<sup>1</sup>=Ph, R<sup>2</sup>=Bn) to the corresponding sulfoxide with hydrogen peroxide and various types of DES (Scheme 1)<sup>a</sup>

DES	Molar ratio	Time/h	Yield/% <sup>b</sup>
ChCl/urea	1:2	12	15
ChCl/malonic acid	1:2	12	32
ChCl/glycerol	1:2	12	Trace
ChCI/HFIP°	1:1.5	12	Trace
ChCl/p-TsOH <sup>31</sup>	1:1	4	89

<sup>a</sup>Reaction conditions: Sulfide **1a** (1 mmol), DES (20 mol%), ethanol (3 mL), H<sub>2</sub>O<sub>2</sub> (2 equiv.), 30 °C.

<sup>▶</sup>Isolated yield.

°Hexafluoroisopropanol.

Table 2 Optimisation of reaction conditions for DES/H<sub>2</sub>O<sub>2</sub> oxidation of benzyl phenyl sulfide **1a** (R<sup>1</sup>=Ph, R<sup>2</sup>=Bn) to the corresponding sulfoxide (Scheme 1)<sup>a</sup>

Entry	ChCl/ <i>p-</i> TsOH /mol%	H <sub>2</sub> O <sub>2</sub> /equiv.	Solvent	Temp./⁰C	Time/h	Yield/% <sup>b</sup>
1	20	2	EtOH	30	4	89
2	20	2	MeCN	30	4	90
3	20	2	THF	30	4	6
4	20	2	H_0	30	4	0
5	20	5	EťOH	30	4	97
6	20	10	EtOH	30	2	94
7	20	15	EtOH	30	1	96
8	20	20	EtOH	30	1	95(5)°
9	20	2	EtOH	40	1	95
10	20	2	EtOH	50	1	96
11	_	2	EtOH	40	1	Trace
12	10	2	EtOH	30	4	80
13	30	2	EtOH	30	2	95
14	50	2	EtOH	30	2	97
15	100	2	EtOH	30	1	95
16	-	2	DES	30	4	30

<sup>a</sup>Reaction conditions: Sulfide **1a** (1 mmol), ChCl/p-TsOH (20 mol%),  $H_2O_2$ , solvent (3 mL).

<sup>b</sup>lsolated yield.

°Sulfone yield in parenthesis.

clearly showed that 40 °C is the optimum, giving the sulfoxide **2a** in 95% yield and 100% selectivity within 1 h (Table 2, entry 9). Generally, a greater amount of catalyst shortened the reaction times (entries 13–15), while only a 30% yield was obtained when ChCl/*p*-TsOH alone was used as solvent (entry 16). This may be attributed to a slow mass transfer that was caused by the viscosity of the reaction medium.<sup>27</sup>

To evaluate the scope and limitations of the current procedure, a series of sulfides were tested under the optimised reaction conditions. The results are summarised in Table 3. Dimethyl sulfide was more easily oxidised (30 min, 95%, entry 10) than other sulfides, which indicates that steric hindrance is very important for the reaction. Sulfides bearing an electrondonating group such as alkyl showed good reactivity while aryl sulfides bearing an electron-withdrawing group such as a chlorine atom gave relative lower yields (2 h, 88%, entry 5). This is due to the fact that electron-donating groups can increase the nucleophilicity of the sulfur atom and hence the reactivity of the substrates. Notably, other functional groups such as a double bond and a hydroxyl group survived the conditions, since neither epoxidation of the allyl phenyl sulfide (**2h**) nor oxidation of the hydroxyl group in the 2-hydroxymethyl substrates of **2i** was observed (entries 8 and 9). Although the oxidation of diphenyl sulfide **2g** (entry 7) was slower compared to aralkyl sulfides **2a**, **2d** and **2e**, the presented method still provides diphenyl sulfoxide relatively efficiently.

One of the most important advantages of employing a DES as a solvent or catalyst is their recyclability. Thus, recycling experiments were carried out using the oxidation of sulfide **1a** as the model reaction. After completion of the reaction, ethyl acetate was added and the mixture was stirred for 5 min. The ethyl acetate layer containing the starting substrate and product was separated and the DES was freed of water under vacuum at 80 °C and then reused for the next cycle. The results showed that the DES could be reused five times with only a gradual decrease in the yield to 95, 90, 88, 83 and 76%.

To further demonstrate the practicality and efficiency of the developed protocol, a scale-up reaction was performed using benzyl phenyl sulfide (1a) as substrate on a 20 mmol scale (Scheme 2). The reaction was initially carried out in an ice bath with slow addition of the hydrogen peroxide in order to control the exothermic reaction. After stirring for another 2 h at 40 °C, the product **2a** was obtained in 90% yield. It is worth noting that the use of ChCl/*p*-TsOH, instead of neat *p*-TsOH, could greatly reduce the acid sewage in such a large-scale synthetic process.

The efficiency of the oxidation can be explained by the interaction between ChCl/*p*-TsOH and  $H_2O_2$ . The DES can form a strong hydrogen bond with  $H_2O_2$  and thereby increases the electrophilic ability of one of the peroxy oxygen atoms of  $H_2O_2$ .<sup>28</sup> Moreover, under these reaction conditions, hydrogen bonding may assist in controlling the chemoselectivity, because the hydrogen bond between the catalyst and the oxygen of the sulfoxides could decrease the nucleophilicity of the sulfur atom of the sulfoxides and prevent further oxidation of the sulfoxide to a sulfone.

Table 3 Selective oxidation of sulfides 1 to sulfoxides 2 (Scheme 1)<sup>a</sup>

Entry	Product	R <sup>1</sup>	R <sup>2</sup>	Time/h	Yield/% <sup>b</sup>	M.p./°C <sup>lit.</sup>
1	2a	Ph	Bn	1	95	120-122 (121-122)28
2	2b	Ph	CH	0.5	96	Oil <sup>29</sup>
3	2c	Ph	C <sub>2</sub> H <sub>5</sub>	1	93	Oil <sup>29</sup>
4	2d	4-Me-C <sub>6</sub> H <sub>4</sub>	Bn	1	95	121–122 (122–124) <sup>29</sup>
5	2e	4-CI-C <sub>6</sub> H <sub>4</sub>	Bn	2	88	126–127 (120–122) <sup>29</sup>
6	2f	Bn	Bn	1	92	135–136 (133–135) <sup>30</sup>
7	2g	Ph	Ph	2	81	70-72 (70)28
8	2h	Ph	Allyl	1	89	Oil <sup>29</sup>
9	2i	Ph	CH,CH,OH	1	90	150–152 (151–152) <sup>28</sup>
10	2j	CH	CH	0.5	95°	Oil <sup>28</sup>
11	2k	n-C₄H	n-Č₄H	1	92	Oil (29-33)28

<sup>a</sup>Reaction conditions: Sulfide **1** (1 mmol), EtOH (3 mL), 30% H<sub>2</sub>O<sub>2</sub> (2 equiv), ChCl/*p*-TsOH (20 mol%), 40 °C. <sup>b</sup>Isolated yield.

°GC yield.



Scheme 2

#### Experimental

All reagents were obtained from local commercial suppliers and used without further purification. Melting points were determined with a WRS-1B apparatus and were uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Advance 400 spectrometer. All the products are known compounds and were identified by comparing their physical and spectra data with those reported in the literature.<sup>28-30</sup>

#### Synthesis of DES: ChCl/p-TsOH

The DES ChCl/*p*-TsOH was readily prepared according to the literature<sup>31</sup> by mixing choline chloride (0.1 mol) with *p*-toluenesulfonic acid (0.1 mol) at 100 °C until a clear solution was obtained (40 min). This was used for reactions without further purification.<sup>31</sup> This method gave this DES with 100% atom economy since it completely forms a eutectic mixture with no by-product formation. Other DESs could be prepared in a similar way.

## Selective oxidation of sulfide 1a and the recovery of DES; typical procedure

A mixture of benzyl phenyl sulfide (0.2 g, 1 mmol), 30%  $\text{H}_2\text{O}_2$  (2 mmol), ethanol (3 mL) and ChCl/*p*-TsOH (20 mol%, four drops) was stirred at 40 °C for 1 h (monitored by TLC). After completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 5 mL). The organic layer was concentrated and the resulting crude product was further purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent, providing the sulfoxide **2a** in 95% yield. The DES was then readily recovered *via* evaporation under vacuum at 80 °C and reused for the next cycle. All the products are known compounds and fully characterised.

*Benzyl phenyl sulfoxide* (2a): White solid, m.p.  $120-122 \,^{\circ}C$ ;<sup>28</sup> IR (cm<sup>-1</sup>): 1027 (SO); <sup>1</sup>H NMR (400 Hz, CDCl<sub>3</sub>):  $\delta$  4.10 (2H, m, SOCH<sub>2</sub>), 7.02 (2H, m, Ph), 7.35 (3H, m, Ph), 7.46 (5H, m, Ph); <sup>13</sup>C NMR (100 Hz, CDCl<sub>3</sub>):  $\delta$  63.6, 124.5, 128.3, 128.5, 128.9, 129.1, 130.4, 131.2, 142.7.

#### Gram-scale synthesis of 2a

A reaction flask was charged with benzyl phenyl sulfide (4.0 g, 20 mmol), ethanol (30 mL) and ChCl/*p*-TsOH (1.25 g, 20 mol%), and the mixture was stirred in an ice bath. To this, 30%  $H_2O_2$  (4 mL) was added dropwise. After addition of  $H_2O_2$ , the mixture was stirred at 40 °C for 2 h. (monitored by TLC). After completion of the reaction, the reaction mixture was concentrated and extracted with EtOAc (3 × 20 mL). The organic layer was then concentrated and the resulting crude product was further purified by column chromatography on silica gel with petroleum ether/EtOAc as eluent to provide the sulfoxide **2a** (3.9 g, 90%). The DES layer was recovered using the method described above.

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