Deep eutectic mixture catalysed the synthesis of disulfides using Bunte salts as thiol surrogates

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Bunte salts, easily prepared from odourless sodium thiosulfates and various alkyl and aryl halides, acted as thiol surrogates for preparation of disulfides in the presence of hydrogen peroxide and a Brønsted-acidic deep eutectic mixture. The reaction proceeded smoothly to give the corresponding disulfide products in moderate to good yields, leaving odourless sodium bisulfite and water as the by-products. Moreover, this catalytic system could be readily recovered and reused several times without significant loss in activity.

Keywords: deep eutectic mixture, dialkyl disulfides, diaryl disulfides, Bunte salts, thiol surrogates, hydrogen peroxide

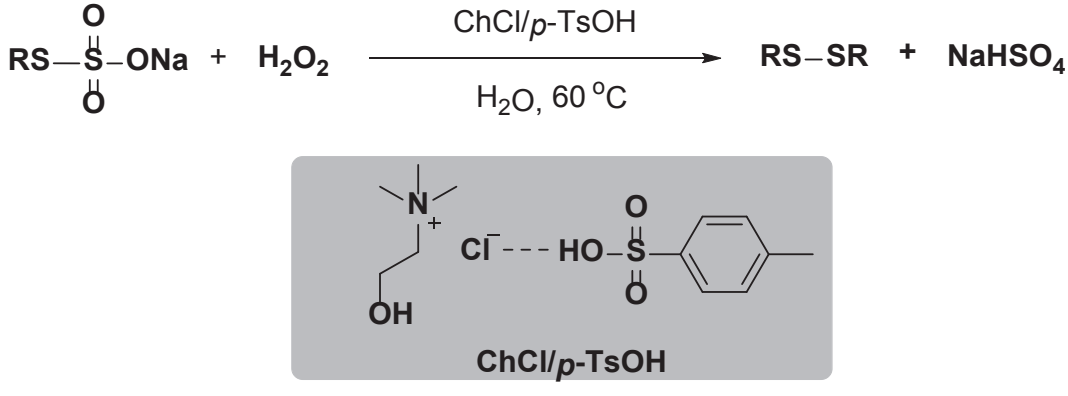
Application of a deep eutectic mixture as a "green" solvent or catalyst has invoked enormous interest in organic chemistry and other fields.[1] This kind of mixture exhibits similar properties to those of ionic liquids such as low vapour pressure, low flammability, biodegradability, ready availability and reusability. Compared to the preparation of ionic liquids, the preparation of a deep eutectic mixture is much easier. Generally, they are prepared by combining a cationic salt with a hydrogen-bond donor such as urea, a carboxylic acid, a sugar and an amide without further purification. The low cost and low toxicity make them alternatives to traditional organic solvents and ionic liquids. Subsequently, their ability to serve as catalysts as well as solvents has also been explored in the field of synthetic organic chemistry for C–C coupling reactions,[2,3] halogenation,[4] alkylation,[5] epoxide hydrolysis,[6] nitroaldol reactions,[7] multi-component reactions,[8] oxidative hydroxylation[9] as well as other useful transformations.[10,11]

On the other hand, organic disulfides play important roles in both biological and chemical processes.[12,13] Disulfides are also valuable organic intermediates for the preparation of sulfenyls,[14] sulfinyls[15] and thioethers by radical pathways.[16] Disulfides are generally prepared from thiols, and various reagents and oxidants have been employed including the halogens and their derivatives,[17,18] transition metal salts[19,20] and peroxides.[21,22] Despite considerable progress in this field, the use of malodourous and air-sensitive thiols, excess and/or expensive reagents, and hazardous solvents and oxidants, together with over oxidation and tedious work-up procedures are still issues to be addressed.

S-alkyl thiosulfates (Bunte salts) can be hydrolysed under acidic conditions to generate thiols. Other nucleophiles such as thiols[23] and Na_2S[24] also react with Bunte salts to give disulfides and trisulfides respectively. However, previous studies in this field only focused on alkyl Bunte salts. Recently, Reeves *et al.* reported[25] the the synthesis of sulfides by reaction of Grignard reagents with Bunte salts. The Bunte salts were readily prepared from alkyl, aryl or vinyl halides with odourless and inexpensive sodium thiosulfate. Jiang *et al.* also reported[26,27] one-pot synthesis of sulfides using $Na_2S_2O_3$ as a sulfurating reagent. Notably, all these procedures avoided the use of thiols or thiol-derived reagents, leaving odourless sulfites as the by-products. Thus, the importance of Bunte salts prompted us to explore other uses in organic synthesis. We now report a facile procedure for the synthesis of disulfides from Bunte salts catalysed by a recyclable Brønsted-acidic deep eutectic mixture in water (Scheme 1).

Results and discussion

Initially, sodium benzyl thiosulfate (**1a**) was selected as the model substrate to optimise the reaction conditions (Table 1). It was observed that no reaction took place in the absence of any catalyst. Different choline chloride (ChCl)-based eutectic mixtures such as choline chloride–urea, choline chloride–malonic acid, and choline chloride–glycerol did not promote the reaction. When the more acidic deep eutectic mixture ChCl/*p*-TsOH was employed, the corresponding product **2a** was obtained in 38% yield (Table 1, entry 5). However, when *p*-toluenesulfonic acid was used alone, 29% yield of product was obtained. The concentration of ChCl/*p*-TsOH was then examined. The results suggested 20% (*v*/*v*) of ChCl/*p*-TsOH in water was the best choice, providing **2a** in 55% yield. Since substrate **1a** was only soluble in a polar solvent, other solvents including methanol and ethanol were also checked, but only lower yields were obtained.



Scheme 1 Synthesis of disulfides catalysed by acidic deep eutectic mixture.

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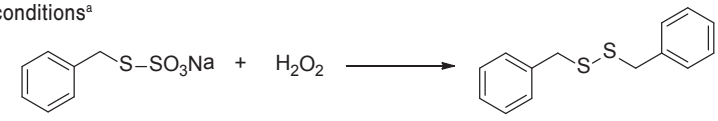
Table 1 Optimisation of reaction conditions[a]

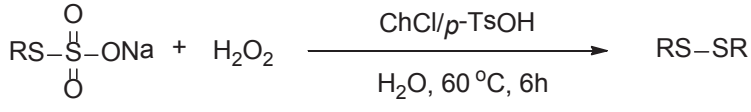


1a **2a**

Entry	Catalyst/%	Solvent	H_2O_2/equiv.	Temperature/°C	Yield/%[b]
1	–	H_2O	1	30	0
2	ChCl/urea (10)	H_2O	1	30	0
3	ChCl/malonic acid (10)	H_2O	1	30	0
4	ChCl/glycerol (10)	H_2O	1	30	0
5	ChCl/*p*-TsOH (10)	H_2O	1	30	38
6	*p*-TsOH (10)	H_2O	1	30	29
7	ChCl/*p*-TsOH (20)	H_2O	1	30	55
8	ChCl/*p*-TsOH (25)	H_2O	1	30	56
9	ChCl/*p*-TsOH (20)	MeOH	1	30	37
10	ChCl/*p*-TsOH (20)	EtOH	1	30	39
11	ChCl/*p*-TsOH (20)	H_2O	2	30	60
12	ChCl/*p*-TsOH (20)	H_2O	3	30	67
13	ChCl/*p*-TsOH (20)	H_2O	4	30	62
14	ChCl/*p*-TsOH (20)	H_2O	3	50	78
15	ChCl/*p*-TsOH (20)	H_2O	3	60	85
16	ChCl/*p*-TsOH (20)	H_2O	3	80	84
17	*p*-TsOH (20)	H_2O	3	60	76

[a] Reaction conditions: Bunte salt **1a** (2 mmol), solvent (10 mL), deep eutectic mixture (%, *v*/*v*), 6 h. For entry 6 and 17, catalyst amount is based on mol%.
[b] Isolated yield.

Table 2 Synthesis of disulfides from Bunte salts



1 **2**

Entry	Product	R	Yield/%[b]	M.p./°C[lit.]
1	**2a**	$PhCH_2$	85	69–70(69–71)[29]
2	**2b**	4-$ClC_6H_4CH_2$	87	59–61(58–60)[30]
3	**2c**	4-$FC_6H_4CH_2$	92	61–62(62.0–63.7)[31]
4	**2d**	4-$NO_2C_6H_4CH_2$	90	124–125(126.5)[32]
5	**2e**	4-$CNC_6H_4CH_2$	95	146–147(147.5)[33]
6	**2f**	4-$MeC_6H_4CH_2$	84	40–41(40–42)[34]
7	**2g**	4-$MeOC_6H_4CH_2$	83	75–77(76–80)[32]
8	**2h**	*n*-C_3H_7	86	Oil[33]
9	**2i**	*n*-C_8H_{17}	82	Oil[30]
10	**2j**	cyclohexyl	83	Oil[33]
11	**2k**	Ph	90	60–61(59–62)[29]
12	**2l**	4-MeC_6H_4	91	45–46(44–46)[29]
13	**2m**	3-MeC_6H_4	88	Oil[32]
14	**2n**	4-$MeOC_6H_4$	87	40–42(41–43)[35]
15	**2o**	2-$MeOC_6H_4$	85	114–116(118–119)[35]
16	**2p**	4-ClC_6H_4	91	72–73(72–74)[35]
17	**2q**	4-BrC_6H_4	90	89–90(90–92)[29]
18	**2r**	4-FC_6H_4	93	Oil[29]
19	**2s**	4-CNC_6H_4	92	168–170(172–173)[20]
20	**2t**	2-naphthyl	88	128–129(130–131)[32]

[a] Reaction conditions: Bunte salt **1** (2 mmol), H_2O (10 mL), deep eutectic mixture (20%, v/v), 30% H_2O_2 (3equiv.), 60 °C, 6 h.

Next, we investigated the concentration of the hydrogen peroxide. It was found that the yield increased along with the concentration of H_2O_2 and a 69% yield was obtained when 3 equiv. of H_2O_2 are used. Further addition of H_2O_2 led to lower product yields. Finally, variation of the reaction temperature clearly showed that 60 °C was optimum, affording the product in 85% yield. Again, we checked the activity of *p*-toluenesulfonic acid on its own; a relatively lower yield (76%) was obtained (Table 1, entry 17).

To evaluate the scope and limitations of the current procedure, a series of Bunte salts was tested under the optimised reaction conditions (Table 1, entry 15). The results are summarised in Table 2.

Since *S*-alkyl Bunte salts could be readily prepared from the corresponding alkyl halides and sodium thiosulfate, a series of *S*-alkyl Bunte salts was then subjected to the optimum reaction conditions. All the reactions proceeded smoothly to give the disulfides in good to excellent yields (**2a**–**j**, 82–95%). For the benzyl-substituted Bunte salts, those bearing electron-withdrawing substituents afforded the corresponding products in excellent yields. *S*-Aryl Bunte salts, prepared by coupling of aryl halides with sodium thiosulfate using a copper catalyst, showed good reactivity. *S*-Aryl Bunte salts with either electron-withdrawing or electron-donating substituents such as halide, OCH_3 or CN underwent the reaction in good to excellent yields (85–93%). The steric effect of an *ortho* –OCH_3 group was also negligible, with the product **2o** being obtained in 85% yield.

The reusability of the catalytic system was also an advantage of this protocol. For most of the reactions, the disulfide products precipitated out from the reaction mixture and were isolated by filtration. The filtrate containing the ChCl/*p*-TsOH, could be easily recovered and reused directly by the addition of a new substrate and oxidant. For the liquid disulfide products, the reaction mixture was extracted with ethyl acetate, followed by evaporation of the solvent to give the crude disulfide, which was further purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent. As above the aqueous system containing ChCl/*p*-TsOH could be reused directly for the next run. Using substrate **1a** as an example, it was found that the catalytic system could be readily recovered and reused without substantial loss in activity in six consecutive runs (85%, 85%, 84%, 82%, 80%, and 77% yield respectively, see Fig. 1).

Conclusion

In summary, a facile procedure for the synthesis of disulfides has been developed. *S*-Alkyl and *S*-aryl Bunte salts are employed as thiol surrogates and hydrogen peroxide is used as the oxidant, leaving only sodium bisulfite and water as the by-products. The workup procedure is simple and the products can be isolated by filtration. Moreover, the remaining aqueous system containing the deep eutectic mixture can be reused directly without further purification.

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. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 analyser in chloroform-d ($CDCl_3$) and D_2O using TMS as an internal standard. High-resolution mass spectrometry (HRMS) was performed on an Agilant 6540 Q-TOF instrument with an ESI source.

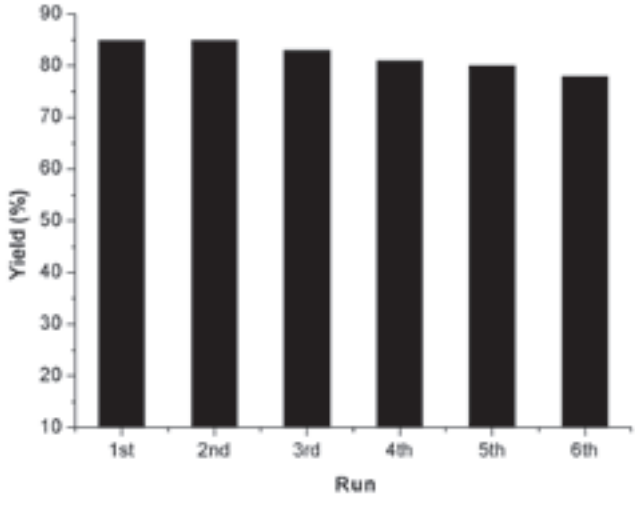


Fig. 1 Recycle study.

Synthesis of deep eutectic mixture

The deep eutectic mixture was readily prepared according to the literature[28] by mixing the choline chloride (0.1 mol) with *p*-toluenesulfonic acid (0.1 mol) at 100 °C until a clear solution was obtained (40 min) which was used for reactions without any purification or waste products.

Synthesis of Bunte salts

The Bunte salts were prepared according to the literature.[25] For the *S*-alkyl Bunte salts, the reaction of alkyl bromides (20 mmol, 1.0 equiv.) and sodium thiosulfate pentahydrate (24 mmol, 1.2 equiv.) in water (10 mL) and MeOH (20 mL) for 3–24 h at 65 °C provided the corresponding salts as white solids. For the *S*-aryl Bunte salts, a 100 mL flask was charged with aryl iodides (10 mmol, 1.0 equiv.), anhydrous sodium thiosulfate (15 mmol, 1.5 equiv.) and CuI (1 mmol, 0.10 equiv.). The flask was sealed with a septum, evacuated and filled with nitrogen. DMSO (10 mL) was charged using a syringe followed by *N*,*N*'-dimethylethylenediamine (DMEDA, 2 mmol, 0.20 equiv.). The mixture was stirred for 5 min at rt and then heated at 80 °C for 4–12 h. The reaction mixture was cooled to room temperature. Then saturated aqueous NaCl (30 mL) was added and the resultant slurry was stirred vigorously at rt for 1 h. The mixture was filtered and the solid was washed successively with saturated aqueous NaCl and hexanes. The solid was dried under reduced pressureat 50 °C for 6 h to provide the corresponding salts.

Melting points ranges are not provided for the Bunte salts, since they contain variable amounts of residual NaCl and also because the salts, even in the absence of residual NaCl, did not display a melting point but rather decomposition. For new Bunte salts, NMR spectra and HRMS data are provided.

Sodium S-*(*m*-tolyl) sulfurothioate* **(1m):** White solid. ^{1}H NMR (400 MHz, D_2O): δ 7.53–7.50 (m, 2 H), 7.14 (d, *J* = 7.6 Hz, 1 H), 7.01–6.97 (m, 1 H), 2.31 (s, 3 H); ^{13}C NMR (100 MHz, D_2O) δ 140.8, 134.9, 132.4, 130.5, 130.1, 129.7, 21.2. HRMS-ESI: calcd for $C_7H_8NaO_3S_2$ $[M+H]^+$: 226.9807; found: 226.9819.

Sodium S-*(4-methoxyphenyl) sulfurothioate* **(1n):** Tan solid. ^{1}H NMR (400 MHz, D_2O): δ 7.56 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 158.5, 135.9, 123.1, 116.5, 56.1. HRMS-ESI: calcd for $C_7H_8NaO_4S_2$ $[M+H]^+$: 242.9756; found: 242.9748.

Sodium S-*(2-methoxyphenyl) sulfurothioate* **(1o):** Tan solid. ^{1}H NMR (400 MHz, D_2O): δ 7.77 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.33–7.29 (m, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.75–6.69 (m, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 160.9, 134.6, 128.3, 127.5, 124.4, 118.6, 56.8. HRMS-ESI: calcd for $C_7H_8NaO_4S_2$ $[M+H]^+$: 242.9756; found: 242.9762.

Sodium S-*(4-bromophenyl) sulfurothioate* **(1q):** Tan solid. ^{1}H NMR (400 MHz, D_2O): δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 134.2, 133.9, 133.1, 121.3. HRMS-ESI: calcd for $C_6H_5BrNaO_3S_2$ $[M+H]^+$: 290.8756; found: 290.8767.

Sodium S-*(4-fluorophenyl) sulfurothioate* **(1r).** Tan solid. ^{1}H NMR (400 MHz, D_2O): δ 7.64-7.61 (m, 2H), 6.86-6.81 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 162.7 (d, *J* = 245.8 Hz), 138.9 (d, *J* = 7.7 Hz), 126.8, 117.7 (d, *J* = 22.0 Hz). HRMS-ESI: calcd for $C_6H_5FNaO_3S_2$ $[M+H]^+$: 230.9556; found: 230.9570.

Sodium S-*(4-cyanophenyl) sulfurothioate* **(1s):** Tan solid. ^{1}H NMR (400 MHz, D_2O): δ 7.85–7.82 (m, 2H), 7.36 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 137.3, 135.0, 129.7, 118.9, 110.0. HRMS-ESI: calcd for $C_7H_5NNaO_3S_2$ $[M+H]^+$: 237.9603; found: 237.9620.

Synthesis of disulfides; general procedure

The Bunte salt (2 mmol) was dissolved in water (10 mL) in a 25 mL round bottom flask. To this mixture, the deep eutectic mixture (2 mL) was added, followed by slow addition of 30% H_2O_2 (3 equiv.). The mixture was then stirred at 60 °C for 6 h. After completion of the

reaction, the precipitated disulfide was isolated by filtration. If the product was liquid, the reaction mixture was extracted with ethyl acetate, followed by evaporation of the solvent under reduced pressure to give the crude disulfide, which was further purified by column chromatography on silica gel using petroleum ether (60–90 °C)/EtOAc as eluent. The aqueous phase containing deep eutectic mixture could be reused directly for the next run. All the disulfides are known compounds and were identified by comparison of their physical and spectroscopic data with those reported in the literature.

1,2-Di(n-propyl) disulfide (**2h**):[33] Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (t, *J* = 7.6 Hz, 4H); 1.52–1.39 (m, 4H); 0.88 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.3, 22.6, 13.1.

*1,2-Di(*n*-octyl) disulfide* (**2i**):[30] Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (t, *J* = 8.0 Hz, 4H), 1.66–1.54 (m, 4H), 1.30–1.21 (m, 20H), 0.86 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 31.8, 29.2, 29.2, 29.1, 28.5, 22.6, 14.1.

1,2-Dicyclohexyl disulfide (**2j**):[33] Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77–2.72 (m, 2H), 1.9–1.94 (m, 4H), 1.71–1.58 (m, 3H), 1.57–1.53 (m, 3H), 1.37–1.13 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 37.8, 26.2, 25.2.

1,2-Di(3-tolyl) disulfide (**2m**):[32] Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 8H); 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 137.2, 130.5, 129.9, 128.2, 127.8, 21.8.

1,*2-Di(4-fluorophenyl) disulfide* (**2r**):[29] Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.43 (m, 4H), 7.10–6.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 245.7 Hz), 133.2 (d, *J* = 8.4 Hz), 131.2 (d, *J* = 8.3 Hz), 116.2 (d, *J* = 23.3 Hz).

Electronic Supplementary Information

References for the known Bunte salts and NMR spectra of the novel ones have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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