**N,N-Dichloro poly(styrene-co-divinylbenzene) sulfonamide beads as an efficient, selective and reusable reagent for oxidation of thiols to disulfides**

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A novel method for oxidative coupling of thiols to their corresponding disulfides using N,N-dichloro poly(styrene-co-divinylbenzene) sulfonamide (PS-DVS) beads is described. PS-DVS beads act as novel and selective oxidative agents which efficiently reduce the reaction time, increase the product yield without producing over oxidized products and suitable under air atmosphere.

**Keywords**: Symmetrical disulfides, N,N-dichloropoly(styrene-co-divinylbenzene) sulfonamide beads, oxidative coupling, thiols, reusable

A macroporous poly(styrene-co-divinylbenzene) resin (PS-DVB) having N,N-dichloro sulfonamide groups have been used as a polymer supported reagent for chlorination, oxidation for residual sulfides, cyanides, thiocyanates, water disinfection, and some application in synthetic organic chemistry. In recent years, the use of recyclable reagents has received considerable interest in organic synthesis due to stringent environmental rules. This prompted us to explore the possibility of using a stable, non toxic, recyclable, easy to synthesize, cheap and efficient positive chlorine releasing reagent N,N-dichloro poly(styrene-co-divinylbenzene) sulfonamide. We have already reported N,N-dichloro poly (styrene-co-divinyl benzene) sulfonamide polymeric beads for decontamination of simulant of sulfur mustard (HD) and VX. Having established a commercially viable synthetic procedure for N,N-dichloro poly(styrene-co-divinylbenzene)-sulfonamide beads, we have recently explored its applications to synthesize dialkyl chlorophosphates from dialkyl phosphates and decontamination of chemical warfare agents. We investigated its use as an alternative reagent for oxidative coupling of thiols to their corresponding disulfides.

Disulfides have found industrial applications as vulcanizing agents and are important synthetic intermediates with many applications in organic synthesis. Disulfides are primarily produced from thiols, which are readily available and facile to prepare. Oxidative coupling of thiols to disulfides under neutral and mild conditions is of practical importance in synthetic chemistry and biochemistry. However, synthesis of disulfides from thiols sometimes can be problematic due to the over oxidation of thiols to sulfoxides and sulfones. On the other hand, many successful reagents such as 1,3-dibromo-5,5-dimethylhydantoin, cerium(IV) salts, permanganates, transition metal oxides, sodium chlorite, peroxides, halogens, solid acid reagents, monochloro poly(styrenehydantoin) beads, gold, N-phenyltriazolininedione, poly(N-bromomaleimide), and nano-catalysts have been developed for the synthesis of disulfides from thiols, under a range of experimental conditions.

**Experimental Section**

Sulfonated PS-DVB was purchased from Ion Exchange India Limited, Mumbai, India. SOCl₂, acetone, methanol, NH₃, acetic acid of AR grade were purchased from S.D. Fine-Chem Ltd., India. NaOCl was freshly prepared by passing chlorine gas at flow of 1 mL/min into NaOH solution (15%, 100 mL) for 30 min at 5°C.

**Synthesis of N,N-dichloro poly(styrene-co-divinylbenzene) sulphonamide**

Synthesis of N,N-dichloro poly(styrene-co-divinylbenzene) sulphonamide, was achieved in three steps (Scheme I) starting from sulfonated poly (styrene-co-divinylbenzene) (1a).
Chloro sulfonation of PS-DVB

Sulfonated PS-DVB (10 g) was mixed with 100 mL of SOCl₂ and refluxed for 4-6 h. SOCl₂ was distilled off after completion of the reaction.

The chloro sulfonated PS-DVB (1b) was washed with methanol.

**PS-DVB sulfonamides**

Chloro sulfonated PS-DVB (10 g) was refluxed with aqueous conc. ammonia (150 mL) for 4-6 h. The sulfonamide form of the beads was then filtered, washed with water and finally dried in air to get 1c.

**Conversion of sulfonamide into chloro sulphonamide**

This final conversion (1d) was easily achieved by stirring PS-DVB sulfonamide (10 g) in 150 mL of freshly prepared sodium hypochlorite solution in acidic medium using acetic acid (99.5%) for 2-4 h at 5°C, filtered and dried in air.

**General experimental procedure for oxidative coupling of thiols to symmetrical disulfides using PS-DVS beads (Scheme II)**

Thiol (0.05 mol) was added to a suspension of \( N,N \)-dichloro poly(styrene-co-divinylbenzene) sulfonamide beads (containing 0.05 mol of active chlorine) in water (30 mL). The mixture was stirred at RT for 4 h and monitor by GC-MS. Then, the mixture was filtered, and the residue was washed with dichloromethane (DCM). The water was extracted with DCM (2 \( \times \) 25 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and the solvent evaporated to provide a disulfide.

**Characterization**

Thermal stability of commercial sulphonated cation-exchange resins (1a), corresponding sulphonyl chloride (1b), sulphonamide resins (1c) and macromolecular dichloroamine (1d) was studied by TA instrument Waters USA, TGA 2950 at a heating rate of 10°C/min using nitrogen. Fourier Transformation Infra Red spectra (FTIR) of all cation-exchange resins (1a-d) were recorded on a Perkin-Elmer BX-2 FT-IR spectrophotometer, USA.

Gas chromatography – mass spectrometry (GC-MS) analysis was performed by 7890 Agilent GC coupled with 5975C Mass Spectrometry (Agilent Technologies, San Jose, CA, USA) in El mode in order to identify the decontaminated products. The GC conditions used were as follows; column HP-5 (30 m \( \times \) 0.250 mm i.d., 0.25 μm film thickness) with a temperature programme of 50°C for 2 min followed by a linear
2 R—SH + SO₂NCl₂ → R—S—S—R + H₂O, r.t. Stirring, 4 h

Scheme II — Synthesis of disulfides from thiols

Table I — Synthesis of disulfides from thiols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (Thiol)</th>
<th>Product (Disulfide)</th>
<th>Yield(^a) (%)</th>
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<td><img src="image2.png" alt="image of product" /></td>
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<td>92</td>
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</tbody>
</table>

\(^a\) All products were identified by comparison of their physical data and spectral data with those reported in literature.

\(^b\) Isolated yield

gradient to 250°C at 10°C min⁻¹, and hold at 250°C for 5 min. The injector temperature was maintained at 250°C while the transfer line was at 280°C. The EI analysis was performed at 70 eV with ion source temperature at 200°C and emission current of 400 μA. The active chlorine content of PS-DVB beads were measured by standard iodometric titrations.\(^3\)

Spectral data for selected compounds

Bistolyl disulfide (Table I, entry 2)

White solid. m.p. 44-45°C (lit. 43-46°C). \(^1\)H NMR (CDCl₃/TMS 400 MHz): δ 2.25 (s, 6H), 7.03 (d, 4H), 7.30-7.35 (m, 4H); EI-MS: m/z 246 (M⁺), 213, 198, 182, 123, 108, 79, 77, 45.

2,2’-Dipyrimidyl disulfide (Table I, entry 4)

Pale yellow solid. m.p. 133-36°C. \(^1\)H NMR (CDCl₃/TMS 400 MHz): δ 7.20 (t, 2H), 8.63 (m, 4H); EI-MS: m/z 222 (M⁺), 158, 80, 79, 53.

Bis (2-hydroxyethyl) disulfide (Table I, entry 8)

Pale yellow liquid. b.p. 162-64°C (at 4 mm Hg). \(^1\)H NMR (CDCl₃/TMS 400 MHz): δ 2.63 (s, 2H, OH), 2.89 (t, 4H), 3.92 (t, 4H); EI-MS: m/z 154 (M⁺), 92, 79, 64, 45.
GUTCH & SHAIK: N,N-DICHLORO POLY(STYRENE-CO-DIVINYLBENZENE) SULPHONAMIDE REAGENT

Result and Discussion

Preparation of PS-DVS beads

N,N-Dichloro poly(styrene-co-divinylbenzene) sulphonamide beads were prepared by three step process, starting from a commercial available sulphonated PS-DVB cation-exchange resin via sulphonyl chloride and sulphonamide resins, a macromolecular dichloramine was prepared and active chlorine was found to be 8.2%.

TGA studies were carried out to characterize each step of synthesis of polymers (1a-d). TGA overlay thermogram of polymers (1a-d) (Figure 1) showed multi-step mass loss in all resins (1a-d). In starting sulphonated PS-DVB (1a), the mass loss up to 200°C was due to physically bound water and mass loss in the range of 200-300°C may be attributed to decomposition of sulfonic acid groups. The complete breakdown of polymer backbone takes place at 500°C. Thermal stability after substitution in 1a was found to be increase in polymers 1b to 1d and 50% decomposition in sulfonyl chloride of PS-DVB was found at 500°C and at 700°C residue left was found 35.5%. 10% weight loss in polystyrene sulphonamide was found at 298°C and at 700°C residue left was found 15.32%.

In the FT-IR spectra of N,N-dichloro poly(styrene-co-divinylbenzene) sulphonamide, absorption bands was observed at 2931 cm⁻¹ due to C-H. The other bands were observed at 1406 and 1159 cm⁻¹ due to stretching of SO₂ and 675 cm⁻¹ due to N-Cl bond.

Oxidative coupling of thiols to disulfides using PS-DVS beads

In this study, we have employed N,N-dichloro poly(styrene-co-divinylbenzene) sulphonamide beads in water for the conversion of thiols to symmetric disulfides. These polymeric beads did not over oxidize the thiols to sulfoxides or sulfones and the sole product isolated from these experiments was disulfides. Presumably, the reactions proceed through chlorine transfer from amide N-halamine to thiols to yield disulfides and hydrochloric acid (Scheme III). The proposed mechanism is in agreement with the experimental observation that water becomes acidic at the end of the reaction. In this method the synthesis of disulfides requires less time when compared to other recyclable reagents reported for this conversion and the progress of the reaction was monitored by GC-MS (Figure 2)
Scheme III — Plausible mechanism for formation of disulfides from thiols using the polystyrene divinylbenzene bound (PS-DVB) reagent

Figure 2 — Progress of reaction as monitored by GC-MS analysis at different time intervals
From Table I, it can be seen that the present method is of general applicability to aromatic (entries 1–4) and aliphatic thiols (entries 5–8), and also showed high efficiency and chemo selectivity in the case of bi-functional thiols (entry 8). As can be seen from entry 8, hydroxyl functionalities can be present in the substrate thiols and remain intact during the formation of the product disulfides. The observed inertness of the acidic hydroxyl–hydrogen (entry 8) is consistent with the higher acidity of S–H over O–H (Ref 38). Except for entry 7, excellent conversion of thiols to disulfides has been observed. The low yield using tert-butyl thiol may be due to low acidity of the tert-butyl thiol or to steric hindrance caused by the bulky tert-butyl group19.

This method has advantages over other earlier reported methods in terms of versatility, easily availability of reagent (PS-DVB), easy work-up. Furthermore, this method allows for the isolation of the parent, poly(styrene-co-divinylbenzene) sulfonamide, by simple filtration from the reaction mixture, which can be re-used in the regeneration of the reagent by known chlorination procedures.

Conclusions
In summary, we report a new, simple, and efficient method for the oxidation of thiols to symmetrical disulfides in good to excellent yields, utilizing the recyclable N,N-dichloro poly(styrene-co-divinylbenzene) sulfonamide beads as the oxidant.

References


