SUSTAINABLE
CHEMICAL PROCESSES

**RESEARCH ARTICLE**

CrossMark

# Butadiene sulfone as 'volatile', recyclable dipolar, aprotic solvent for conducting substitution and cycloaddition reactions

Yong Huang[1,3†], Esteban E. Ureña-Benavides[1,3†], Afrah J. Boigny[1], Zachary S. Campbell[1], Fiaz S. Mohammed[1,3], Jason S. Fisk[4], Bruce Holden[4], Charles A. Eckert[1,2,3], Pamela Pollet[2,3*] and Charles L. Liotta[1,2,3*]

## Abstract

Butadiene sulfone has been employed as a "volatile", recyclable dipolar, aprotic solvent in the reaction of benzyl halide with metal azides to form benzyl azide (1) and the subsequent reaction of benzyl azide with *p*-toluenesulfonyl cyanide (3) to produce 1-benzyl-5-(*p*-toluenesulfonyl)tetrazole (2). Comparisons are made with the solvent DMSO and an analogous sulfolene solvent—piperylene sulfone. In addition, recycling protocols for butadiene sulfone and piperylene sulfone are also presented.

**Keywords:** Butadiene sulfone, Piperylene sulfone, Sulfolenes, Recyclable dipolar aprotic solvent, Tetrazoles, Sustainable, Green, DMSO

## Background

Dimethylsulfoxide (DMSO) is an outstanding solvent for conducting a wide variety of organic reactions. Its specific dipolar, aprotic properties allow for the dissolution of a range of organic molecules and ionic species. Unfortunately, the isolation of reaction products and the recyclability of the solvent is often times difficult as well as economically expensive. Recently a couple of sulfolene solvents have been proposed as possible recyclable substitutes for DMSO [1–6]. Piperylene sulfone is a liquid at room temperature and butadiene sulfone is a liquid at 64 °C. Both possess similar properties to that of DMSO. Unlike DMSO, however, each of these solvents can undergo a thermally promoted reversible retro-cheletropic process to form $SO_2$ and the respective diene (Fig. 1). This reversible characteristic provides a strategy for both solvent removal from the products of reaction as well as solvent recovery and reuse. Piperylene sulfone

undergoes a smooth reversal at 110 °C while butadiene sulfone requires temperatures in the 135–140 °C range. In both cases the gaseous diene and $SO_2$ can be captured by condensing at low temperatures (−76 °C) and reacting at room temperature to reform the original sulfolene solvent.
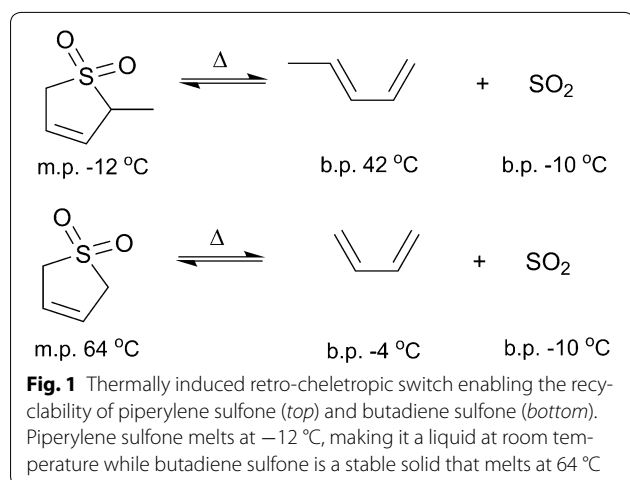
Several reports have employed sulfolenes as primary solvents for conducting various organic reactions along with the subsequent recycling of the solvent. Vinci et al. [5] reported the substitution reactions and associated rates of a wide variety of nucleophiles with benzyl chloride in both DMSO and in piperylene sulfone solvent. In general the reactions conducted in DMSO proceeded at faster rates than those in piperylene sulfone. It was discovered, however, that the addition of trace quantities of water (1–3 %) added to piperylene sulfone increased the rates of the nucleophilic substitution reactions. Furthermore, the reaction of benzyl chloride with thiocyanate ion in piperylene sulfone resulted in a 96 % isolated yield of benzyl thiocyanate upon reversal of piperylene sulfone to gaseous $SO_2$ and piperylene. The reformation and recovery of piperylene sulfone solvent was also demonstrated with 87 % efficiency [5]; a clear demonstration of the sulfolene's advantage over its DMSO counterpart. Ragauskas et al. [2] reported the TEMPO oxidation of

*Correspondence: pamela.pollet@chemistry.gatech.edu; charles.liotta@ chemistry.gatech.edu

†Yong Huang and Esteban E. Ureña-Benavides contributed equally as first-authors

3 Specialty Separations Center, Georgia Institute of Technology, Atlanta, GA 30332, USA

Full list of author information is available at the end of the article

Chemistry Central

Huang *et al. Sustain Chem Process* (2015) 3:13

Page 2 of 10



**Fig. 1** Thermally induced retro-cheletropic switch enabling the recyclability of piperylene sulfone (*top*) and butadiene sulfone (*bottom*). Piperylene sulfone melts at −12 °C, making it a liquid at room temperature while butadiene sulfone is a stable solid that melts at 64 °C

substituted benzyl alcohols to benzaldehydes in piperylene sulfone. Not only were the product yields as high as the reactions conducted in DMSO but, in addition, the turn-over frequencies (TOF) were greater.

Herein is reported a reaction sequence which exemplifies the potential superiority of sulfolene solvents over DMSO. Specifically, the synthesis of 1-benzyl-5-(*p*-toluenesulfonyl) tetrazole (2) in piperylene sulfone (PS) and butadiene sulfone (BS) via a two-step process is reported (Scheme 1). The first step involves the reaction of azide with benzyl chloride or benzyl bromide to form the corresponding benzyl azide. The second step involves the cycloaddition reaction of benzyl azide with *p*-toluenesulfonyl cyanide (TsCN, 2). Each of these reactions was investigated individually and in tandem in both DMSO and a sulfolene solvent. In addition, a detailed protocol is presented for the recycling of the sulfolene solvents (piperylene and butadiene sulfones).

## Experimental

### Materials

Piperylene (*cis-* and *trans-* mixutres) (97 %) was purchased from TCI America (Portland, OR, USA). Sulfur dioxide (>99.9 %) was purchased from Airgas (Kennesaw, GA, USA), Sigma-Aldrich (St. Louis, MO, USA) and Matheson (Montgomeryville, PA, USA). *p*-Toluenesulfonyl cyanide (>95 %) was purchased from AK Scientific, Inc (Union City, CA, USA) and Accel Pharmtech, LLC (East Brunswick, NJ, USA). Benzyl bromide (98 %), benzyl chloride (98 %), cesium azide (99.99 %), sodium azide (99.5 %) and dimethyl sulfoxide (99.9 %) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Butadiene sulfone (98 %) and all other chemicals were purchased from VWR International (Suwanee, GA, USA). All compounds were used as received. Authentic samples of benzyl azide were prepared in lab batches (see Additional file 1).

### Synthesis of piperylene sulfone (PS)

Piperylene sulfone was synthesized in large quantities (200–500 mL) from piperylene (*cis-* and *trans-* mixture) (200–630 mL) and sulfur dioxide (12 eq.) using 8-anilino-1-naphthalenesulfonic acid hemi-magnesium salt (0.012 eq.) as a polymerization inhibitor [3, 7]. The inhibitor was weighed and added to an Ace-Glass 5 L glass reactor. The experimental apparatus was then purged with $N_2$. The reactor was filled with 2 atm of vapour $SO_2$ and purged to remove $N_2$, this process was repeated three times. Liquid $SO_2$ was allowed to flow into the reactor while keeping the temperature at −30 °C or less. Once, all the desired amount of $SO_2$ was introduced, the piperylene was added into the reactor using an air tight syringe. The reactor was then sealed and allowed to warm up to room temperature around 21 °C.

The reaction was carried for at least 15 h after which the excess $SO_2$ was vented and collected in a bubbler containing 2.2 L of saturated potassium carbonate ($K_2CO_3$) solution, yielding an orange slurry product mixture. The mixture was sparged with $N_2$ to further remove residual $SO_2$. Water saturated with sodium chloride was added to the reactor and the aqueous phase was extracted with dichloromethane three times. Ethyl ether (1/3, v/v) was added to the combined organic phase as an anti-solvent to precipitate the inhibitor. The resulting liquid was dried over $MgSO_4$, and then filtered. A clear yellow liquid was obtained after evaporating the ethyl ether and dichloromethane under reduced pressure, affording 78 % yield of PS based on the trans isomer content. The resulting
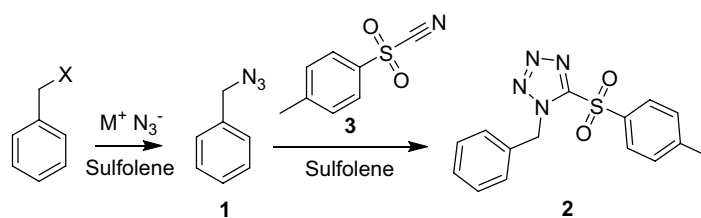


**Scheme 1** Overall reaction sequence in the synthesis of 1-benzyl-5-(4-toluenesulfonyl)tetrazole (2)

Huang *et al. Sustain Chem Process* (2015) 3:13

Page 3 of 10

piperylene sulfone was characterized by $^1$H and $^{13}$C NMR to verify nearly pure production.

**Recycling of sulfolenes**

The recycle of sulfolene solvents was demonstrated by beginning with a certain quantity of sulfolene, thermally decomposing it, and subsequently reforming it. The difference between the initial and final weights was designated as the percent recovery. The experiments were conducted in the prototype apparatus described in Fig. 2. Reactors R-1 and R-2 are Ace-Glass pressure tubes which could be easily removed and reattached to the setup. Both reactors were weighted before recycling. A desired amount of sulfolene was first added to R-1 (1 % by weight hydroquinone with regard to BS was added to R-2 for recycling of BS); the system was then purged with $N_2$. Liquid $SO_2$ was introduced into R-2, which was kept cold using a dry ice/isopropanol bath. When the desired amount of liquid $SO_2$ was introduced, the extra $SO_2$ was released through the base bath B-1. The decomposition flask was heated with an oil bath to the desired temperature, 120 °C for PS and 135 °C for BS. During the decomposition process, the reformation flask was kept between −76 and −55 °C (Table 1) to trap the volatile dienes and $SO_2$. $N_2$ was allowed to enter from V-5 towards B-1 to maintain a constant near atmospheric pressure and drive the decomposition products from R-1 to R-2. It should be noted that the line connecting R-1 to R-2 was heated during the decomposition process. In the case of PS, the tube was kept above 42 °C to prevent condensation of piperylene and polymerization in the lines; for BS, the tube was maintained at 70 °C to prevent
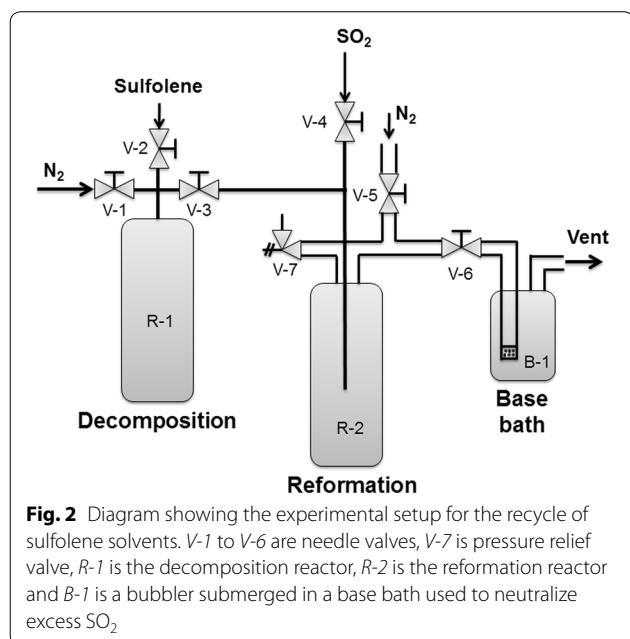


**Fig. 2** Diagram showing the experimental setup for the recycle of sulfolene solvents. *V-1* to *V-6* are needle valves, *V-7* is pressure relief valve, *R-1* is the decomposition reactor, *R-2* is the reformation reactor and *B-1* is a bubbler submerged in a base bath used to neutralize excess $SO_2$

**Table 1 Recycling results of sulfolene solvents**

| Entry | Solvent | Scale (mL) | $SO_2$/diene molar ratio | Cold bath (°C) | Recovered solvent (%) |
|---|---|---|---|---|---|
| 1 | PS | 5 | 8 | −55 | 89 ± 2 |
| 2 | PS | 20 | 6 | −60 | 98 ± 0 |
| 3 | BS | 20 | 6 | −76 | 95 ± 1[a] |

[a] Two replicates, one of them is added with inhibitor

clogging from solid BS reforming inside the tube. When reactor R-1 was completely empty, 100 mL/min of $N_2$ were allowed to enter from V-1 to further transport volatile products to R-2; this final wash was performed for at least 30 min. Reactor R-2 was then sealed and allowed to warm to room temperature.

The reformation reaction was carried for at least 40 h. During that time a pressure relief valve (V-7) ensured that the entire system was held under the pressure rating for the glass reactors. Upon conclusion, excess $SO_2$ was vented through B-1 until no bubbling was observed. The sulfolenes were sparged with $N_2$ to remove residual $SO_2$; BS had to be heated to 70 °C to prevent crystallization during sparging. The reformed sulfolene was weighted to obtain a recovery measurement. See Table 1 for recovery yields.

**Reaction of benzyl halide with azide**

Two concentrations for substitution reaction ($S_N2$) were investigated in this study. A lower concentration (0.7 M, 0.85 mmol) of benzyl halides was used to optimize reaction conditions and a higher concentration (2.5 M, 3.5 mmol) of benzyl halides was used to determine accurate isolated yields. Sodium or cesium azide (0.93 or 3.8 mmol), biphenyl (internal standard, 0.37 mmol) and liquid piperylene sulfone (1 mL) or solid butadiene sulfone (1.3 g) were first added to a two-dram vial. The heterogeneous mixture was heated at 60 °C with vigorous agitation for 2 h in order to precondition the salt. Benzyl chloride or benzyl bromide (0.85 or 4.2 mmol) was then introduced into the mixture to initiate reaction. Samples of 0.05–0.1 mL were taken hourly for the first 3 h. The samples were diluted with 1 mL of benzene and filtered with a syringe filter before GC-FID analysis. The GC oven temperature was ramped from 90.0 to 300 °C at a heating rate of 15 °C/min. The GC injector was held at a constant temperature of 300 °C. For NMR analysis, the same amount of sample was diluted with 0.5 mL of DMSO-$D_6$, and then filtered with a syringe filter. Reactions for synthesis of benzyl azide were all run in duplicate, and Table 2 includes the reaction yields.

**Reaction of benzyl azide (1) with *p*-toluenesulfonyl cyanide (3)**

Benzyl azide (1.09 g, 8.19 mmol), TsCN (1.63 g, 9.00 mmol) and BS (3.05 g, 25.81 mmol) were all added to

Huang *et al. Sustain Chem Process* (2015) 3:13

Page 4 of 10

a three neck round bottom flask and heated to the designated reaction temperature. At the end of the predefined reaction time, the reaction was cooled and the contents in the flask were dissolved in acetone. Samples for NMR analysis were taken from the acetone solution. A known amount of dimethyl sulfone was added to the samples as an internal standard for NMR quantitation.

Product isolation was carried out for selected high yield reactions. The post reaction mixture containing product was heated to 135 °C for approximately 2 h in order to promote the decomposition of the sulfolene; after approximately 2 h the bubbling had ceased. The product residue was a brown liquid which solidified upon cooling. Methanol (4 mL) and ethyl ether (1 mL) were added and stirred overnight to extract impurities from the solid. The mixture was cooled in an ice/water bath and filtered. The solid was then recovered and washed once more with the methanol-ether mixture. After filtration and drying, a cream colored powder (compound 3) was obtained (see Table 3 for yields and conversions). DSC: m.p. = 136 °C, $\Delta H = 106.0$ J/g. $^1$H NMR (DMSO-d$_6$, ppm): δ = 2.40 (s, 3H), 6.00 (s, 2H), 7.24–7.27 (m, 2H), 7.36–7.39 (m, 3H), 7.46 (d, $J = 8.1$ Hz, 2H), 7.83 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (DMSO-d$_6$, ppm): δ = 21.23, 52.67, 127.97, 128.67, 128.69, 128.91, 130.53, 133.56, 133.87, 147.46, 154.29. ESI–MS (*m/z*): 315 [M + H]$^+$, 332 [M + H$_2$O]$^+$.

### Tandem, two-step synthesis of 1-benzyl-5-(*p*-toluenesulfonyl) tetrazole (2)

Benzyl bromide (0.641 g, 3.75 mmol), sodium azide (0.269 g, 4.14 mmol), BS (1.315 g, 11.13 mmol) and biphenyl (0.06 g, GC internal standard) were added to a 2 dram vial. The reaction was allowed to react for 3 h at 60 °C. The reaction mixture was filtered hot using a syringe filter and added to a second vial containing TsCN (0.750 g, 4.14 mmol). The cycloaddition reaction was allowed to run for 2 days at 50 °C and 2 days at 60 °C. The reaction mixture was then cooled at which point the product solidified; dimethyl sulfone was added as an internal standard for NMR. The contents of the vial were dissolved in acetone and DMSO-d$_6$ and samples were analysed by NMR, and a yield of 72 ± 5 % 1-benzyl-5-(*p*-toluenesulfonyl) tetrazole (2) was obtained.

## Results and discussion
### Synthesis of benzyl azide (1)

Literature contains many examples of alkyl azide syntheses in a wide variety of solvents, using sodium azide and an alkyl halide [8, 9]. Alvarez et al. [8] reported high yields when the displacement reaction was conducted in DMSO. In particular, an isolated yield of 98 % was obtained in the reaction of benzyl bromide with sodium azide at ambient temperature. Nevertheless, while

this reported yield is excellent, solvent recycle was not addressed. Indeed, the post-reaction mixture in DMSO was quenched with water. The product was subsequently extracted with ethyl ether, followed by several washes with brine, drying, and finally ether solvent evaporation. Thus, while the isolated product was obtained in excellent yield, the DMSO solvent was no longer usable. This is almost always the case when DMSO is employed as the reaction medium. Since PS and BS have similar properties to those of DMSO and since they are recyclable, these solvents could represent a more sustainable approach to the production of alkyl azides.

Scheme 2 shows the reaction of benzyl halide with inorganic azide salts in either PS or BS and Table 2 summarizes the results in these solvents. For comparison, the result from Alverez et al. for this same reaction in DMSO is included (Table 2, entry 1). When PS (Table 2, entry 2) was used as reaction medium, the substitution reaction afforded a 6 ± 0 % yield of benzyl azide in 3 h. However, employing the more thermally stable BS, a yield of 49 ± 5 % and 86 ± 4 % at 1 and 3 h, respectively, was obtained (Table 2, entry 3). The low yield in PS is attributed to the much lower solubility of azide salt in this solvent as compared to BS. It is postulated that the presence of the methyl group in the 2-position of PS sterically interferes with its ability to solvate the cationic portion of the salt and, as a consequence, results in reduced solubility. This steric factor is absent in BS. Several attempts were made to reduce the reaction time and increase the yield of benzyl azide in BS. For instance, the concentration of sodium azide was increased from 1.1 to 1.5 equivalents resulting in an increase of yield at 3 h reaction time from 86 ± 4 % to 93 ± 1 % (Table 2, entries 3, 4). Although the yield was marginally increased, the excess sodium azide presented concerns from both safety and atom-economy points of view. In addition, the excess azide might also interfere with the subsequent cycloaddition reaction step in the synthesis of 1-benzyl-5-(*p*-toluenesulfonyl) tetrazole (2) [10]. As mentioned previously it was discovered that trace amounts of water added to PS improved the rates of several nucleophilic substitution reactions [5]. Addition of 1 % water to DMSO did not appear to have any noticeable effect on the rate or the yield of benzyl azide (Table 2, entry 5). In contrast, addition of 1 % water to BS resulted in a 93 % yield of benzyl azide in a 1 h time period (from 49 % in anhydrous conditions). Extending further the reaction time to 3 h resulted in only a marginal increase in yield (Table 2, entry 6). The use of the more expensive cesium azide in place of the sodium salt also resulted in excellent yields (Table 2, entry 7). While these increased yields looked good, it was recognized that the addition of water to BS could potentially form small quantities of sulphurous

Huang *et al. Sustain Chem Process* (2015) 3:13

Page 5 of 10

acid which can subsequently react with azide to produce the extremely explosive and toxic hydrazoic acid. As a consequence, *the addition of water was avoided in further experiments.* Finally, by replacing benzyl chloride with its bromide counterpart a quantitative yield of benzyl azide was achieved in 1 h in BS in the absence of added water (Table 2, entry 8). This latter protocol provides a relatively less expensive and much safer procedure.

The next step in the reaction sequence involved the reaction of benzyl azide (BnAz, 1) with *p*-toluenesulfonyl cyanide (TsCN, 3) to form 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2). Tetrazoles have a broad range of applications. They are found in number of pharmaceutical compounds, they can be surrogates for peptides [11] and carboxylic acids [12], and they have been used to tag drug receptor proteins [13]. In addition, tetrazole ligands have also been used for fabricating coordination polymers [14, 15]. Moreover, the synthesis of tetrazoles with labile groups like the toluene sulfonyl substituent can enable their use as building blocks for further functionalization. As such, compounds like 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2) is of especial interest [10]. Demko and Sharpless synthesized 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2) in the absence of solvent from BnAz and TsCN with a near quantitative yield of product being reported [10]. The solid product, however, had to be chipped off the reactor. Although feasible on a laboratory scale, from an industrial standpoint, a scalable protocol that facilitates post-reaction processing and simultaneously minimizes waste is more desirable.

**Synthesis 1-benzyl-5-(*p*-toluenesulfonyl)tetrazole (2)**
Since excellent yields of benzyl azide were obtained in BS it was decided to conduct the second step in the synthetic sequence in the same solvent (Scheme 3). The results of the [2 + 3] cycloaddition of TsCN with benzyl azide (1) to form 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2) in both DMSO and BS are summarized in Table 3. The reaction in DMSO (Table 3, entry 1) at 50 °C for a period of 4 days produced a modest yield of 30 ± 1 %. In contrast, the reaction conducted in BS (Table 3, entry 3 and 4) resulted in yields of 50 % and 77 ± 1 % for reaction times of 1 and 4 h, respectively, under the same conditions. In both cases nearly all the TsCN cyanide is consumed at the end of 4 days. However, it is interesting to note that when DMSO is used, the conversion of benzyl azide is

**Table 2 Nucleophillic substitution reaction of benzyl halides with inorganic azide salts in sulfolenes and DMSO**

| Entry | Solvent | Reactants | Reaction time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | DMSO [8] | BnBr, NaAz | 1 | 98 |
| 2 | PS | BnCl, NaAz | 3 | 6 ± 0 |
| 3 | BS | BnCl, NaAz | 1 | 49 ± 5 |
| | | | 3 | 86 ± 4 |
| 4 | BS | BnCl, 1.5 NaAz | 1 | 65 ± 2 |
| | | | 3 | 93 ± 1 |
| 5 | DMSO (1 % H$_2$O)[b] | BnCl, NaAz | 1 | 97 ± 0 |
| 6 | BS (1 % H$_2$O) | BnCl, NaAz | 1 | 93 ± 1 |
| | | | 3 | 95 ± 1 |
| 7 | BS (1 % H$_2$O) | BnCl, CsAz | 1 | 96 ± 0 |
| 8 | BS | BnBr, NaAz | 1 | 100[c] |

[a] GC yield

[b] 1 % water by volume

[c] NMR yield, BnBr (2.5 M)

only 47 ± 1 % in contrast to a 91 ± 4 % conversion in BS. A control reaction was conducted: TsCN was added to DMSO at 50 °C; no benzyl azide was present. After 4 days most of the TsCN disappeared with the formation of a major product, and $^1$H NMR analysis of the control reaction at 2 and 4 days showed that the major product is a salt of *p*-toluenesulfonic acid (see $^1$H NMR spectra in Additional file 1: Fig. S1). The major product was precipitated from the DMSO solution upon the addition of water, and its exact mass analysis was consistent with the salt of *p*-toluenesulfonic acid [ion trap/orbitrap tandem mass spectrometer (*m/z*): calcd. for $C_7H_7O_3S$ 171.0110, found 171.0119 [M]$^-$]. It is clear that, in addition to the reaction of TsCN with benzyl azide to form the desired tetrazole (2), a competing reaction of TsCN with the solvent is taking place. As a consequence, *DMSO is not an appropriate solvent for this pericyclic process.* BS, in contrast, does not react with TsCN. In this particular case, therefore, BS is a dipolar, aprotic solvent alternative to DMSO.

In order to improve the yield of the tetrazole and reduce the reaction time, experiments were performed at slightly elevated temperatures. Since both the TsCN and the benzyl azide are thermally labile, the reaction temperatures employed had to be carefully adjusted. In addition, care had to be taken to avoid the retrochelotropic reaction of
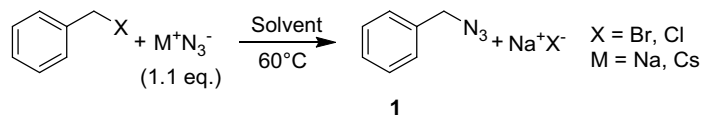


**Scheme 2** General reaction of benzyl halide with metal azide at 60 °C, to form the corresponding benzyl azide (1)
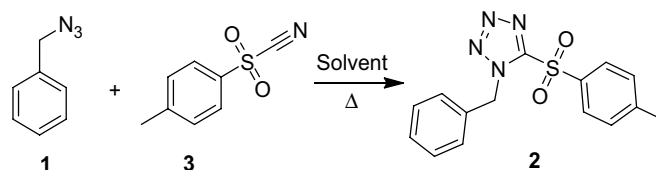
**Scheme 3** *p*-Toluenesulfonyl cyanide (3) reacting with benzyl azide (1) to form 1-benzyl-5-(*p*-toluenesulfonyl) tetrazole (2)

**Table 3  Synthesis of compound 3 through [2 + 3] cycloaddition of *p*-toluenesulfonyl cyanide (3) and benzyl azide (1)**

| Entry | Solvent | Temp (°C) | Time (days) | Yield (%) | Conv. 1 (%) | Conv. 2 (%) |
|---|---|---|---|---|---|---|
| 1 | DMSO | 50 | 4 | $30 \pm 1$ | $100 \pm 0$ | $47 \pm 1$ |
| 2 | BS | 70 | 1 | $70 \pm 2$ | $99.2 \pm 0.1$ | $89 \pm 1$ |
| 3 | BS | 50 | 1 | $50 \pm 1$ | $57 \pm 2$ | $51 \pm 2$ |
| 4 | BS | 50 | 4 | $77 \pm 1$ | $95 \pm 1$ | $91 \pm 4$ |
| 5 | BS | 50–60 | 4[a] | $82 \pm 2$[b] | $99 \pm 1$ | $93 \pm 2$ |

Yields and conversion were measured by NMR

[a]  Reaction was run 2 days at 50 °C, then 2 days at 60 °C
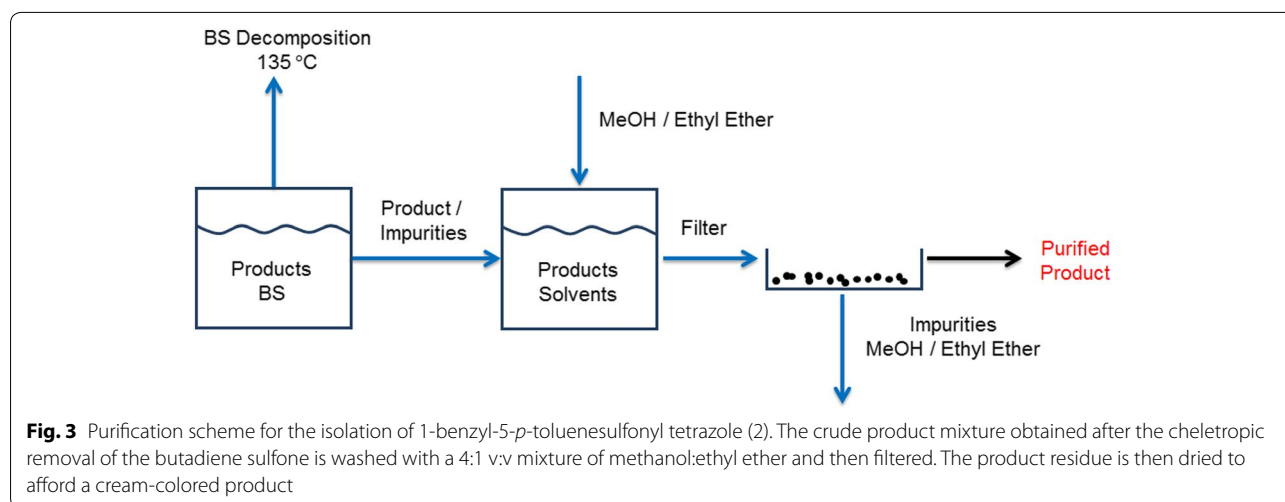
[b]  Isolated yield was $71 \pm 2$ %

the solvent. Fortunately, BS undergoes negligible decomposition up to 100 °C. The effect of heating from 50 to 70 °C was studied in BS (Table 3 entries 2 and 5). It was observed that after 1 day the yield at the higher temperature was $70 \pm 2$ %, while at the lower temperature it was $50 \pm 1$ %. Nevertheless, the conversion of TsCN at 50 °C was only $57 \pm 2$ %, and at 70 °C nearly all TsCN reacted within 1 day. The reaction at 50 °C proceeds slower than at 70 °C, but it can ultimately reach a higher yield since side reactions are not as competitive at the lower temperature. Temperature is also important on the phase behaviour of the reaction mixtures. Even though pure BS melts at 64 °C, the reaction mixture becomes a homogenous clear liquid at 45 °C. When the reaction is carried at 50 °C, some product precipitates with time and at the end of 4 days the mixture takes the appearance of a thick paste. However, if the temperature is raised to 60 °C after 2 days of reacting at 50 °C, the reaction mixture ends as a fluid slurry that can be easily poured out of the reaction flask. Table 3 shows that using entries 4 and 5 temperature scheme, the product yield is slightly increased from $77 \pm 1$ to $82 \pm 2$ %. It is postulated that the lower viscosity obtained by increasing the temperature favours the bimolecular cycloaddition reaction over the decomposition of the starting materials.

One of the greatest advantages of sulfolene solvents is the simplicity of product isolation. Figure 3 shows the scheme employed for the isolation of 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2). Heat was used to decompose BS, leaving a liquid mixture containing the product and some unreacted starting materials. The residual impurities

were extracted from the product residue with a 4/1 v/v mixture of methanol/ethyl ether (Fig. 3). This simple purification scheme gave an isolated yield of $71 \pm 2$ % for the highest yielding reaction conditions in Table 3 (entry 5). The cream-colored product was analysed and its structure confirmed by $^1$H NMR, $^{13}$C NMR, ESI–MS and DSC. The product was also subjected to column chromatographic purification. While this mode of purification is not attractive for an industrial process, it was conducted in order to see if there are any differences between the "cream colored" product and the product derived from column chromatography. Figure 4 shows a comparison of the $^1$H NMR spectra of the product prior to and after the column chromatographic procedure. No appreciable differences were observed suggesting that comparable purities can be obtained using the simple isolation scheme described above without the need for subsequent column chromatography.

### Tandem two step synthesis of 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2)

In order to demonstrate the broad utility of BS as a recyclable DMSO substitute, the synthesis of 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2) was performed in tandem starting from the nucleophilic substitution reaction of benzyl bromide and sodium azide and followed by the reaction of the resulting benzyl azide (1) with TsCN (Scheme 1). The first step was carried out at 60 °C without addition of trace quantities of water. After a period of 3 h the reaction was completed and the sodium bromide precipitated and excess sodium azide were separated
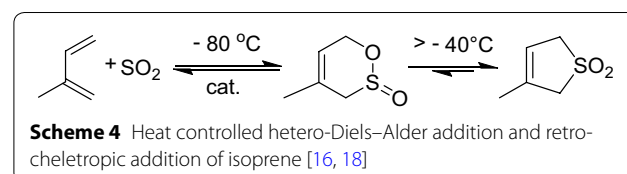
Huang *et al. Sustain Chem Process* (2015) 3:13

Page 7 of 10



**Fig. 3** Purification scheme for the isolation of 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2). The crude product mixture obtained after the cheletropic removal of the butadiene sulfone is washed with a 4:1 v:v mixture of methanol:ethyl ether and then filtered. The product residue is then dried to afford a cream-colored product



**Fig. 4** $^1$H NMR of 1-benzyl-5-*p*-toluenesulfonyl tetrazole (2). The purity of the isolated tetrazole obtained using the purification scheme outlined in Fig. 3 is compared to the isolated tetrazole product obtained via traditional purification techniques. **a** cheletropic switch, followed by extraction and **b** column chromatography. Peak labelled *asterisk* corresponds to d-DMSO and peak labelled *double asterisk* corresponds to water

the concentration used for the cycloaddition experiments depicted in Table 3. The reaction solution was then heated to 50 °C for 2 days and subsequently to 60 °C for an additional 2 days. At the end of the tandem process NMR analyses showed that all the benzyl bromide was consumed and only traces of ($3 \pm 2$ %) of benzyl azide remained. The conversion of TsCN (3) was $93 \pm 5$ %. Compound 2 (based on the initial moles of benzyl bromide) was obtained in $72 \pm 5$ %: a yield comparable to that obtained in the single step process (Table 3 entry 5, $82 \pm 2$ %).

**Recycling of sulfolenes**

There are a number of reports dealing with the reaction of conjugated dienes with $SO_2$ as well as the reverse process. Two simple addition products have been reported for the reaction of piperylene with $SO_2$ (Scheme 4). One is the product of a hetero-Diels–Alder process which produces a 6-membered ring sultine. This product is the result of a [4 + 2] cycloaddition. The other product is the expected 5-membered ring sulfone- the result of a [4 + 1] cycloaddition. Deguin and Vogel reported that at temperatures ranging from −80 to −60 °C the hetero-Diels–Alder sultine product can be obtained in the reaction of a 0.3 M solution of (E)-piperylene in $CD_2Cl_2/SO_2$ in the presence of an acid catalyst (0.2 M of $CF_3COOH$). In contrast, however, the reaction of butadiene or (Z)-piperylene did not produce the sultine products under

from the solution by filtration. At this juncture the benzyl azide product was not isolated. TsCN was added to the filtered reaction solution and then diluted to match



**Scheme 4** Heat controlled hetero-Diels–Alder addition and retro-cheletropic addition of isoprene [16, 18]

Huang *et al. Sustain Chem Process* (2015) 3:13

Page 8 of 10

the same conditions [16]. The latter results are not surprising since the necessary syn-conformation of the Z-piperylene is relatively high in energy due to steric factors. More recent studies revealed that at the same temperatures the reaction of dimethylidenecycloalkanes with variable ratios of $CD_2Cl_2/SO_2$ produce sultine products without employing acid catalysis. It was also reported that the sultine products isomerized into the corresponding sulfolenes at temperatures above $-40\ °C$ [17, 18].

Cheletropic reactions of $SO_2$ and a diene are often carried in the presence of radical inhibitors in order to avoid undesired polymerization of the dienes [19]. Morris and Finch proposed that organic peroxides, often present in dienes feedstock, are the major cause for polymerization. They claimed that a diene free of organic peroxides allows the cheletropic reaction to occur in the absence of polymerization inhibitors [20]. Staudinger et al. reported that reaction between $SO_2$ and butadiene at room temperature produced an amorphous product in 11 % yield and the crystalline cyclic sulfone in 89 % yield. The amorphous solid was identified as a linear polysulfone [21]. Finally, it has been reported that the rate of cheletropic and retrocheletropic reactions is affected by polarity of solvents. Polar solvents, like methanol, slow down the decomposition process, but accelerate the reformation reaction; the opposite occurs with non-polar solvents [22]. In this study, it is the pure sulfolene solvent which is thermally decomposed while the reformation process (the reaction of the conjugated diene with $SO_2$) takes place in liquid $SO_2$.

Sulfolene solvents have been proposed as recyclable substitutes for DMSO. The reversible reaction between a conjugated diene and $SO_2$ (cheletropic reaction) shown in Fig. 1 is the basis for the recyclability of these solvents. Initial experiments concerning the decomposition process of piperylene sulfone, trapping the volatile compounds, and reforming the solvent has previously been reported. As mentioned before, an 87 % recovery yield was obtained [5]. The loss of 13 % of the solvent was attributed to the small scale (5 mL) of the recycle process and the accompanying material loss due to surface adhesion to the tubing in the recycling apparatus. It was appropriate therefore to demonstrate the efficiency of the recycle process on a scale and in equipment which would minimize material losses. The results for the recycling of PS and BS reported here were conducted in the apparatus described in the "Experimental" section (Fig. 2). Each of the pure sulfolenes was allowed to undergo a thermal retro-cheletropic process at a specific temperature for a specified length of time. PS and BS undergo decomposition at a reasonable rate at 120 and 135 °C, respectively [23]. The pertinent processes were conducted on a 20 mL scale and compared to results conducted on a 5 mL scale.

The products of the decomposition (the conjugated diene and $SO_2$) were captured and allowed to react to reform the original sulfolene. The overall process was meant to demonstrate the recyclability of these solvents. In this latter part of the process specific ratios of diene to $SO_2$ were investigated in the absence and in the presence of polymerization inhibitors. Table 1 summarizes the final results obtained for both PS and BS. Entries 1 and 2 show the effect of reaction scale for the recycle of PS. It is observed that increasing the amount of starting PS from 5 to 20 mL increased the recovery from an acceptable $89 \pm 2$ % to a near quantitative $98.3 \pm 0.3$ %. In addition, it is interesting to note that even though the molar ratio of $SO_2$ to piperylene in the reforming step was reduced from 8 to 6, the yield of PS was still excellent. Vinci's result of 87 % recovery was performed at a 5 mL scale [5]. The results reported herein are consistent with his data.

First, the recycling process was investigated in the absence of any polymerization inhibitor. For recycling of PS, when the $SO_2$/diene molar ratio was 6 or higher, minimal or no polymerization was detected. Minimal polymerization could be observed in the tubing connecting two reaction vessels; however it did not affect the recovery yields due to negligible volume of connecting tubing. Lower $SO_2$/diene molar ratios yielded significant amounts of polymers which had to be removed by antisolvent precipitation using a 3/1 mixture of dichloromethane and ethyl ether. For recycling of BS, the same procedure was performed six times in the absence of a polymerization inhibitor. Only one of these experiments was successful—a 94 % recovery yield was obtained. The other five experiments resulted in the formation of the white amorphous polysulfone polymer [24]. However, with the addition of 1 % of the polymerization inhibitor hydroquinone (by weight with respect to butadiene sulfone) to reformation flask, 96 % yield of butadiene sulfone was obtained.

In our recycle experiments for both PS and BS, the dienes/$SO_2$ mixture is kept at temperature between $-55$ and $-76$ °C for at least 2–3 h. The temperatures at which the hetero-Diels−Alder products in Fig. 2 [16, 18] were observed are the same used here to trap the products of the retrocheletropic decomposition. The kinetic product (hetero-Diels−Alder) may be favoured at low temperature in this case; but at higher temperatures, the more thermodynamically stable sulfolene is formed. It is hypothesized that if kinetic products were formed at low temperatures, the undesired polymerization of dienes would be significantly reduced upon warming up to room temperature.

Figure 5 shows a schematic diagram of the desired process. The reactants for nucleophilic reaction or cycloaddition reaction are introduced to a reactor in which the synthesis is performed, followed by the retrocheletropic decomposition of BS, and leaving the desired product
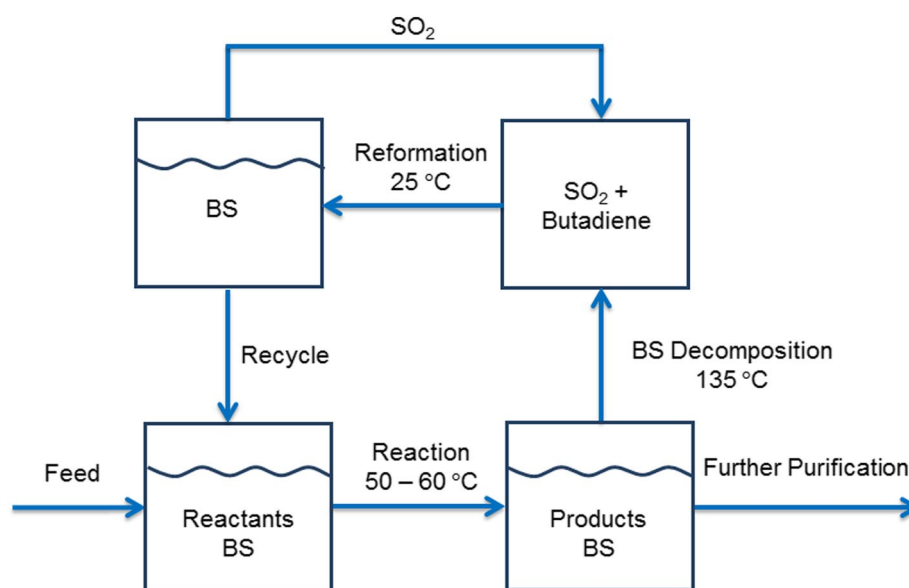
Huang *et al. Sustain Chem Process* (2015) 3:13

Page 9 of 10

**Fig. 5** Process diagram for the synthesis of tetrazoles using butadiene sulfone. The reactants are introduced to a reactor in which the synthesis is performed. Post reaction, the retrocheletropic decomposition of Butadiene sulfone leaves the desired product (and side products) behind. These can then further purified using techniques described in Fig. 3. The volatile SO$_2$ and butadiene are trapped in the presence of excess SO$_2$. The neat reformation (cheletropic) reaction is performed at room temperature; after which SO$_2$ is vented. Any residual SO$_2$ can be separated by bubbling N$_2$ through the sulfolene. Since SO$_2$ has a very low vapour pressure compared to N$_2$, it can be easily condensed and recycled

(and side products) behind. The volatile SO$_2$ and butadiene are trapped in the presence of excess SO$_2$. The neat reformation (cheletropic) reaction is performed at room temperature; after which SO$_2$ is vented. Any residual SO$_2$ can be separated by bubbling N$_2$ through the sulfolene. Since SO$_2$ has a very low vapour pressure compared to N$_2$, it can be easily condensed and recycled. In this study, only small scale two step synthesis (1 mL) was performed due to safety concern, and recycling of sulfolene solvents in larger scale (20 mL) were conducted separately.

## Conclusions

In conclusion, piperylene sulfone and butadiene sulfone have been shown to be recyclable solvents as a consequence of the reversible reactions between SO$_2$ and the respective diene. They are dipolar, aprotic solvents and serve as potential substitutes for DMSO. This is especially true for BS in the synthesis of organic azides by nucleophilic substitution and, tetrazoles by the reaction of organic azides with *p*-toluenesulfonyl cyanide (3). Both reactions using sulfolene solvent have noticeable advantages: operational simplicity, low cost and environmental safety.

## Additional file

**Additional file 1.** Supplementary information.

**Author details**
[1] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA. [2] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA. [3] Specialty Separations Center, Georgia Institute of Technology, Atlanta, GA 30332, USA. [4] The Dow Chemical Company, Midland, MI 48674, USA.

Huang *et al. Sustain Chem Process* (2015) 3:13

Page 10 of 10

### References

1. Donaldson ME, Mestre VL, Vinci D, Liotta CL, Eckert CA (2009) Switchable solvents for in-situ acid-catalyzed hydrolysis of beta-pinene. Ind Eng Chem Res 48(5):2542–2547. doi:10.1021/ie801149z
2. Jiang N, Vinci D, Liotta CL, Eckert CA, Ragauskas AJ (2008) Piperylene sulfone: a recyclable dimethyl sulfoxide substitute for copper-catalyzed aerobic alcohol oxidation. Ind Eng Chem Res 47(3):627–631. doi:10.1021/ie070616y
3. Marus GA, Vyhmeister E, Pollet P, Donaldson ME, Llopis-Mestre V, Faltermeier S et al (2010) Sustainable and scalable synthesis of piperylene sulfone: a "volatile" and recyclable DMSO substitute. Ind Eng Chem Res 50(1):23–27
4. Pollet P, Eckert CA, Liotta CL (2011) Switchable solvents. Chem Sci 2(4):609–614. doi:10.1039/c0sc00568a
5. Vinci D, Donaldson M, Hallett JP, John EA, Pollet P, Thomas CA et al (2007) Piperylene sulfone: a labile and recyclable DMSO substitute. Chem Commun 14:1427–1429. doi:10.1039/b616806j
6. de Frias JA, Feng H (2013) Switchable butadiene sulfone pretreatment of Miscanthus in the presence of water. Green Chem 15(4):1067–1078
7. Marus GA (2011) The application of green chemistry and engineering to novel sustainable solvents and processes [Dissertation]. Georgia Institute of Technology, Atlanta
8. Alvarez SG, Alvarez MT (1997) A practical procedure for the synthesis of alkyl azides at ambient temperature in dimethyl sulfoxide in high purity and yield. Synthesis 1997(04):413–414. doi:10.1055/s-1997-1206
9. Zeng HY, Tian Q, Shao HW (2011) PEG 400 promoted nucleophilic substitution reaction of halides into organic azides under mild conditions. Green Chem Lett Rev 4(3):281–287. doi:10.1080/17518253.2011.571717
10. Demko ZP, Sharpless KB (2002) A click chemistry approach to tetrazoles by Huisgen 1,3-dipolar cycloaddition: synthesis of 5-sulfonyl tetrazoles from azides and sulfonyl cyanides. Angew Chem Int Ed 41(12):2110–2113. doi:10.1002/1521-3773(20020617)41:12<2110:AID-ANIE2110>3.0.CO;2-7
11. Tymtsunik AV, Bilenko VA, Kokhan SO, Grygorenko OO, Volochnyuk DM, Komarov IV (2011) 1-Alkyl-5-((di)alkylamino) tetrazoles: building blocks for peptide surrogates. J Org Chem 77(2):1174–1180. doi:10.1021/jo2022235
12. Singh H, Singh Chawla A, Kapoor VK, Paul D, Malhotra RK (1980) 4 Medicinal chemistry of tetrazoles. In: Ellis GP, West GB (eds) Progress in medicinal chemistry. Elsevier, Amsterdam, pp 151–183
13. Otsuki S, Nishimura S, Takabatake H, Nakajima K, Takasu Y, Yagura T et al (2013) Chemical tagging of a drug target using 5-sulfonyl tetrazole. Bioorg Med Chem Lett 23(6):1608–1611
14. Sharifzadeh Z, Abedi S, Morsali A (2014) Fabrication of novel multi-morphological tetrazole-based infinite coordination polymers; transformation studies and their calcination to mineral zinc oxide nano- and microarchitectures. J Mater Chem A 2(13):4803–4810. doi:10.1039/C3TA14904H
15. Wang D-Z (2012) Zinc(II) and cadmium(II) coordination polymers with bis(tetrazole) ligands: syntheses, structures and luminescent properties. Polyhedron 35(1):142–148. doi:10.1016/j.poly.2012.01.012
16. Deguin B, Vogel P (1992) Hetero-diels-alder addition of sulfur dioxide to 1,3-dienes. Suprafaciality, regioselectivity, and stereoselectivity. J Am Chem Soc 114(23):9210–9211. doi:10.1021/ja00049a076
17. Fernandez T, Sordo JA, Monnat F, Deguin B, Vogel P (1998) Sulfur dioxide promotes its hetero-Diels–Alder and cheletropic additions to 1,2-dimethylidenecyclohexane. J Am Chem Soc 120(50):13276–13277. doi:10.1021/ja982565p
18. Monnat F, Vogel P, Sordo JA (2002) Hetero-Diels–Alder and cheletropic additions of sulfur dioxide to 1,2-dimethylidene-cycloalkanes. Determination of thermochemical and kinetics parameters for reactions in solution and comparison with estimates from quantum calculations. Helv Chim Acta 85(3):712–732. doi:10.1002/1522-2675(200203)85:3<712:aid-hlca712>3.0.co;2-5
19. Turk SD, Cobb RL (1967) Formation of five-membered cyclic sulfones. In: Hamer J (ed) 1,4-Cycloaddition reactions: the Diels–Alder reaction in heterocyclic syntheses. Organic chemistry: a series of monographs, vol 8. Academic Press, New York, pp 13–45
20. Morris RC, Finch HDV (1947) Production of cyclic mono-sulfones. Google Patents
21. Staudinger H, Ritzenthaler B (1935) Ber. 68B:445
22. Desimoni G, Faita G, Garau S, Righetti P (1996) Solvent effect in pericyclic reactions. X. The cheletropic reaction. Tetrahedron 52(17):6241–6248
23. Drake L, Stowe S, Partansky A (1946) Kinetics of the diene sulfur dioxide reaction1. J Am Chem Soc 68(12):2521–2524
24. Minoura Y, Nakajima S (1966) Polymerization of butadiene sulfone. J Polym Sci Part A-1 Polym Chem 4(12):2929–2944