Flow Synthesis of Symmetrical Di- and Trisulfides Using Phase-Transfer Catalysis

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Using mild conditions and short reaction times, symmetrical disulfides have been synthesized in flow chemistry using phase transfer catalysts to facilitate the substitution of organohalides with disodium disulfide. Also, the synthesis of symmetrical trisulfides was possible using this procedure with an additional equivalent of sulfur.

Keywords: flow chemistry, phase transfer catalysts, symmetrical disulfides, symmetrical trisulfides

1. Introduction

Disulfide linkages are important structural features in enzymes and peptidic structures, and also, disulfides themselves are important compounds in biochemistry. There are several established procedures for the chemical synthesis of disulfides. Widely used starting materials are thiols as they can undergo oxidative coupling reactions toward disulfides. Different catalysts can be used, such as anhydrous potassium phosphate [1], reusable ionic liquids [2], aluminium nitrate under heterogeneous reaction conditions [3], as well as metal-free nitrates [4], solid supported basic catalysts [5], the Burgess reagent [6], and others [7].

Using alkyl halides as an alternative precursor for the synthesis of disulfides is a safe and commercially viable alternative. Different methods and reagents as sulfur sources in such syntheses as benzyltriethylammonium tetracosathioheptamolybdate $[(C_6H_5CH_2N(Et)_3)_6Mo_7S_{24}]$ [8] or piperidinium tetrathiomolybdate [9] have been reported.

A promising procedure to develop disulfide synthesis in flow chemistry was reported by Sonavane et al. utilizing didecyldimethylammonium bromide (DDCB) as a transfer catalyst in the reaction between aqueous sodium disulfide and alkyl halides in chloroform to produce symmetrical disulfides under mild reaction conditions [10]. In this work, several other transfer catalysts, such as tetrabutylammonium bromide (TBAB), were screened. This method was investigated in batch and under flow chemistry conditions and extensively screened by reacting allyl bromide **1a** to diallyl disulfide **2a** as the target molecule. This compound is of large importance for the synthesis of garlic metabolites but not commercially available in pure form.

Diallyl trisulfide is another naturally occurring molecule in garlic [11], which has several health benefits through the release hydrogen sulfide [12]. In some cases, diallyl trisulfide has also shown greater effect on cancer cells compared to diallyl disulfide **2a** [13].

Sonavane et al. claimed that the reaction shown in Scheme 1 [10] is also suitable for the synthesis of other polysulfides. In the approach to synthesize the corresponding trisulfide, two equivalents of elemental sulfur were added to the disodium sulfide solution for the generation of disodium trisulfide. In preliminary batch reactions, however, a mixture of different polysulfides was generated. Also, dioxaphosphorinane derivatives have been used to synthesize both symmetrical [14] and unsymmetrical disulfides [15] as well as several novel aromatic and heterocyclic trisulfides in two-step reaction sequences starting from thiols.

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2. Results and Discussion

2.1. Synthesis of Symmetrical Disulfides in a Flow Reactor. Disodium disulfide (Na_2S_2) was generated by the reduction of sulfur by sodium sulfide at 50 °C in water. The resulting solution was then loaded onto a syringe pump, with the second syringe containing the alkyl bromide and tetra-*n*-butylammonium bromide (TBAB) in an organic solvent, as shown in Figure 1. After passing through a micromixer [16], the reaction occurs in the reactor coil (Teflon tubing, 0.8 mm diameter, 2 m length, and 1 mL volume) before being quenched with brine in the collection flask.

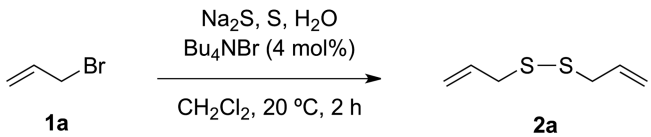
A low concentration (2 mM) of disodium disulfide was required to prevent the compound from precipitating in the flow setup. For optimization studies, a wide range of reaction conditions were investigated including different solvents, flow rates (residence times), and temperatures using allyl bromide **1a** as reactant. All reactions have been performed at 20 °C and are summarized in Table 1.

Initially, the reaction time was modified by increasing the length of the reactor coil, while the (total) flow rate was kept constant at 0.2 mL/min. The optimum reaction time was found to be 5 min (corresponding to a reactor coil length of 2 m, volume 1 mL), as shown in entries 1–3 in Table 1. Dichloromethane and chloroform are leading to a biphasic flow system resulting in segmented flow [17]. Microreactors can offer advantages by intense mixing of immiscible liquids. We have already shown that ester hydrolysis [18], performed under liquid–liquid biphasic reaction conditions or Heck reactions [19], can be accelerated in microreactors. In biphasic flow systems, mass transfer is accelerated as the fluid packets benefit from a continually refreshing interface between adjacent fluid segments and a rapid vortex flow within each fluid packet.

The reaction using ethanol or acetonitrile gave much lower yields compared to dichloromethane. Without TBAB as phase transfer catalyst, the reaction did not proceed and was less efficient when larger amounts of TBAB were used (Table 1, entries 9 and 10). A similar phase transfer catalyst, tetrabutylammonium iodide, was not as efficient (Table 1, entry 6). This protocol was then used to screen different substrates.

Other disulfides can be prepared efficiently, as shown in Table 2, but the reaction temperature had to be increased to 40 °C to ensure high yields within the 5-min reaction time. The

Scheme 1. Synthesis of diallyl disulfide **2a**



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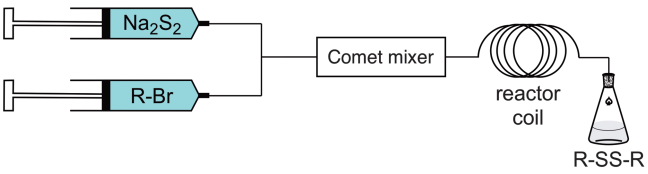


Figure 1. Flow reactor setup for disulfide synthesis

Table 1. Synthesis of diallyl disulfide **2a**

Entry	Solvent	TBAB (mol.%)	Reaction time (min)	2a Yield (%)
1	CH_2Cl_2	4	2.5	28
2	CH_2Cl_2	4	5	68
3	CH_2Cl_2	4	10	48
4	$CHCl_3$	4	5	10
5[a]	CH_2Cl_2	4	5	92
6[a]	CH_2Cl_2	4[b]	5	38
7	EtOH	4	5	44
8	MeCN	4	5	1
9	CH_2Cl_2	0	5	0
10	CH_2Cl_2	8	5	14

[a] Allyl chloride was used instead of allyl bromide.
[b] Tetrabutylammonium iodide was used instead of TBAB.

yields are lower compared to the batch experiments by Sonavane et al. [10]; however, the conditions are optimized for a different substrate.

2.2. Synthesis of Symmetrical Trisulfides in a Flow Reactor. For the synthesis of trisulfides, the corresponding trisulfide bisanion (S_3^{2-}) has to be generated first. The known equilibria between elemental sulfur and monosulfide (S^{2-}) lead to the formation of polysulfide dianions mixtures. For the optimization of the trisulfide synthesis, benzyl bromide **1e** was chosen as the model substrate as the product mixture was easy to analyze by proton nuclear magnetic resonance (^{1}H NMR). In this reaction, different amounts of dibenzyl disulfide **2e**, dibenzyl trisulfide **3e**, dibenzyl tetrasulfide **4e**, and dibenzyl pentasulfide **5e** are formed.

This reaction produced interesting results. Unlike the synthesis of the disulfide derivatives, which was selective, this procedure produces an array of polysulfides, as shown in Table 3. Forming the disulfide as the major product is a likely outcome as the reduction favored the formation of the disodium disulfide ion as a result of insufficient reduction by S^{2-} to form Na_2S_3. These results were reproduced with two different batches of disodium sulfide with minimal variation. The yield is improved with a reduced reaction time, and temperature is shown to have no substantial effect (Table 3, entries 3–6).

Other polysulfide mixtures using allyl bromide **1a**, propyl bromide **1b**, and pentyl bromide **1d** as starting materials have also been synthesized, as shown in Table 3, entries 7–9. The separation of the polysulfide products from these experiments was difficult and only possible using reverse phase C18 silica. Only the diallyl polysulfides were completely separated which lead to the isolation of diallyl tetrasulfide **4a**, pentasulfide **5a**, and some hexasulfide **6a**. These compounds have the identical ^{1}H NMR chemical shifts, and their assignment was only possible using mass spectrometric analysis. The structure of polysulfides **1b**, **1d**, and **1e** was also confirmed by high-resolution mass spectrometry.

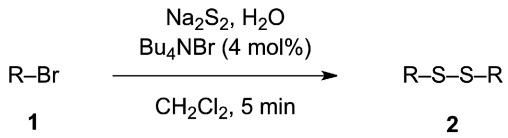
3. Conclusion

Several symmetrical disulfides can be synthesized efficiently in flow with high conversion and high throughput, requiring only an aqueous work-up and no additional purification. Symmetrical trisulfides were also successfully synthesized and isolated using similar reaction conditions; however, higher polysulfides were also produced.

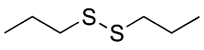
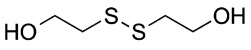
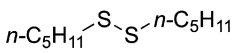
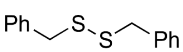
4. Experimental

4.1. General Procedure: Synthesis of Symmetrical Disulfides in Flow. Sulfur (0.258 g, 8 mmol) and anhydrous sodium sulfide (2.40 g, 10 mmol) were dissolved in water (5 mL) and stirred at 50 °C for 30 min. The alkyl halide (20 mmol) and TBAB (0.257 g, 0.8 mmol) were dissolved in EtOH (3.22 mL). The solutions were loaded into two separate 5-mL syringes and placed on a syringe pump with a flow rate of 0.1 mL/min, through a Comet mixer and a 0.8-mm diameter, 2-m-long polytetrafluoroethylene (PTFE) reaction coil. The reaction mixture was quenched by introducing the reactor outlet into brine. After the reaction, the mixture was extracted with diethyl ether

Table 2. Synthesis of dialkyl disulfides **2**

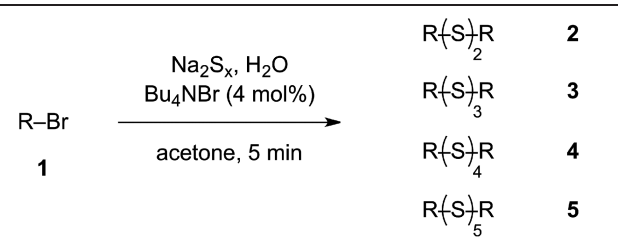


1 **2**

Entry	Substrate **1**[a]	Disulfide **2**	Reaction temperature (°C)	**2** Yield (%)
1	**1b**: R=*n*-C_3H_7	 **2b**	40	45
2	**1c**: R=CH_2CH_2OH	 **2c**	40	70
3	**1d**: R=*n*-C_5H_{11}	 **2d**	40	63
4	**1e**: R=CH_2Ph	 **2e**	30	43

[a] Reaction conditions: 4 mol.% TBAB, CH_2Cl_2, 5-min reaction time.

Table 3. Synthesis of polysulfides **2e**–**5e**



Entry	Substrate	Reaction time (min)	Temperature (°C)	2:3:4:5[a]	Combined yield (%)
1	**1e**	20	20	50:26:15:9	65
2	**1e**	10	20	51:25:15:9	83
3	**1e**	5	20	49:25:15:11	94
4	**1e**	5	30	49:27:15:9	92
5	**1e**	5	40	54:26:13:7	88
6	**1e**	5	50	53:25:14:8	92
7	**1a**	5	20	22:53:35[b]	72
8	**1b**	5	20	15:33:52[c]	87
9	**1d**	5	20	80:20[d]	80

[a] Ratios determined by ^{1}H NMR.
[b] Isolated compounds: **2a**: 1%, **3a**: 50%, **4a**: 15%, **5a**: 5%, **6a** (diallyl hexasulfide): 1%.
[c] 52% polysulfides.
[d] 20% polysulfides.

(3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over magnesium sulfate, and the solvents were removed in vacuo.

4.1.1. Diallyl Disulfide (2a). Compound **2a** was obtained as a clear yellow oil (0.769 g, 5.3 mmol) in 88% yield. ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ=5.81 (tdd, J=17.2, 9.9, 7.3 Hz, 4H), 5.21–5.09 (m, 2H), 3.34 (d, J=7.4 Hz, 4H) ppm; carbon nuclear magnetic resonance (^{13}C NMR) (125 MHz, $CDCl_3$, 298 K) δ=133.4, 118.4, 42.4 ppm; ν_{max} (NaCl): 3082, 3010, 2979, 2906, 1634, 1423, 1398, 1266, 1215, 987, 739 cm^{-1}; high-resolution mass spectrometry (HRMS) (electrospray ionization [ESI]): calculated for $C_6H_{10}S_2$ (M^+): 146.0224; found 146.0223.

4.1.2. Dipropyl Disulfide (2b). Compound **2b** was obtained as a clear oil (0.54 g, 3.6 mmol) in 45% yield. ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ=2.60 (dt, J=7.4, 3.1 Hz, 4H), 1.75–1.56 (m, 4H), 0.94 (dt, J=7.3, 2.6 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ=41.1, 22.5, 13.1 ppm; ν_{max} (NaCl): 2962, 2932, 2873, 1456, 1413, 1290, 1230, 1216, 760 cm^{-1}. HRMS (ESI): calculated for $C_6H_{13}S_2$ (M^+–H): 149.0453; found 149.0450.

4.1.3. 2,2′-Disulfanediyldiethanol (2c). Compound **2c** was obtained as a clear oil (0.517 g, 3.5 mmol) in 70% yield (5 mmol sulfur used in the general procedure). ^{1}H NMR (250 MHz, $CDCl_3$, 298 K) δ=2.82 (t, J=5.8 Hz, 4H), 3.84 (t, J=5.8 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ=60.4, 41.3 ppm; ν_{max} (NaCl): 3390, 3054, 2928, 2877, 1421, 1401, 1266, 1058, 1008, 739, 703 cm^{-1}; HRMS (ESI): calculated for $C_4H_{10}O_2S_2$ ($M+H^+$): 155.0200; found 155.0191.

4.1.4. Dipentyl Disulfide (2d). Compound **2d** was obtained as a clear oil (1.309 g, 5.0 mmol) in 63% yield. ^{1}H NMR (250 MHz, $CDCl_3$, 298 K) δ=2.67 (dd, J=7.5, 7.2 Hz, 4H), 1.81–1.60 (m, 4H) 1.42–1.26 (m, 8H), 0.94–0.86 (t, J=6.94 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ=39.1, 30.7, 28.9, 22.3, 13.9 ppm; ν_{max} (NaCl): 2957, 2927, 2871, 2858, 1465, 1413, 1378, 1341, 1297, 1271, 1254, 729 cm^{-1}; HRMS (ESI): calculated for $C_{10}H_{22}S_2$: 206.1163; found 206.1165.

4.1.5. Dibenzyl Disulfide (2e). Compound **2e** was obtained as a clear oil (0.834 g, 3.4 mmol) in 43% yield using half the equivalents of the general procedure. ^{1}H NMR (250 MHz, $CDCl_3$, 298 K) δ=7.50–7.37 (m, 10 H), 3.73 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K) δ=137.5, 129.5, 128.6, 127.5, 43.4 ppm; ν_{max} (NaCl): 3054, 2987, 1265, 739, 705 cm^{-1}; HRMS (ESI): calculated for $C_{14}H_{15}S_2$ ($M+H^+$): 247.0610; found 247.0608.

4.2. General Procedure: Synthesis of Symmetrical Trisulfides in Flow. Sulfur (0.641 g, 20 mmol) and anhydrous sodium sulfide (2.40 g, 10 mmol) were dissolved in water (5 mL) and stirred at 50°C for 30 min. The alkyl halide (20 mmol) and tetrabutylammonium bromide (0.257 g, 0.8 mmol) were dissolved in EtOH to a total volume of 5 mL. The solutions were loaded into two separate 5 mL syringes and placed on a syringe pump with a flow rate of 0.1 mL/min and attached to a Comet mixer which is connected to a PTFE reaction coil (length: 2 m, internal diameter: 0.8 mm). The reaction mixture was quenched by introducing the reactor outlet into brine. After the reaction, the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over magnesium sulfate, and the solvents were removed in vacuo.

Compound mixtures **2a**, **3a, 4a**, **5a**, and **6a** were obtained as a clear yellow oil (2.639 g) using twice of the amounts for all chemicals as described in the general procedure. From ^{1}H NMR, the sample contained 22% diallyl disulfide, 53% diallyl trisulfide, and 25% higher diallyl polysulfides. From the reaction mixture, 342 mg was purified on a Biotage Isolera system with a Telos Flash C18 column (12 g) using a solvent gradient (*v*:*v*) of water–methanol (50:50) to (20:80) for 25 column volumes (CV), then (20:80) to (0:100) for 15 CV, then (0:100) for 4 CV at a flow rate of 12 mL/min. This protocol also allowed a separation of **4a**, **5a**, and **6a**, which are indistinguishable by ^{1}H NMR. The amounts obtained after separation were as follows: **2a** (2 mg, 0.01 mmol), **3a** (206 mg, 1.16 mmol), **4a** (75 mg, 0.36 mmol), **5a** (28 mg, 0.12 mmol), and **6a** (10 mg, 0.04 mmol).

4.2.1. Diallyl Trisulfide (3a). ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ=6.00–5.81 (m, 2H), 5.32–5.16 (m, 4H), 3.52 (d, J=7.3 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ=133.0, 119.5, 42.0 ppm; ν_{max} (NaCl): 3082, 3010, 2979, 2906, 1634, 1423, 1398, 1217, 986, 191, 721 cm^{-1}; HRMS (ESI): calculated for $C_6H_{10}S_3$ (M^+): 177.9945; found 177.9940.

4.2.2. Diallyl Tetrasulfide (4a). ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ=5.89 (tdd, J=17.1, 9.9, 7.3 Hz, 4H), 5.24–5.11 (m, 2H), 3.51 (d, J=7.3 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ=132.4, 119.3, 42.0 ppm; ν_{max} (NaCl): 3084, 3011, 2980, 2908, 1634, 1423, 1398, 1219, 986, 909, 733 cm^{-1}; HRMS (ESI): calculated for $C_6H_{10}S_4$ (M^+): 209.9665; found 209.9661.

4.2.3. Diallyl Pentasulfide (5a). ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ=5.82 (tdd, J=17.1, 9.9, 7.3 Hz, 4H), 5.25–5.14 (m, 2H), 3.55 (d, J=7.3 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ=132.2, 119.9, 42.5 ppm; ν_{max} (NaCl): 3072, 3054, 2982, 2920, 1634, 1423, 1265, 1220, 988, 925, 739 cm^{-1}; HRMS (ESI): calculated for $C_6H_{10}S_5$ (M^+): 241.9386; found 241.9385.

4.2.4. Diallyl Hexasulfide (6a). ^{1}H NMR (250 MHz, $CDCl_3$, 298 K): δ=5.89 (tdd, J=17.2, 9.9, 7.3, 4H), 5.34–5.21 (m, 2H), 3.62 (d, J=7.3 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ=132.2, 120, 42.4 ppm; ν_{max} (NaCl): 3081, 2956, 2922, 2849, 1847, 1726, 1634, 1422, 1397, 1261, 1218, 1074, 1020, 945, 921, 859, 801, 720 cm^{-1}; HRMS (ESI): calculated for $C_6H_{10}S_6$ (M^+): 273.9107; found 273.9105.

Compounds **2b**, **3b**, **4b**, and **5b** were obtained as a yellow oil (1.3 g) using the amounts given in the general procedure. From ^{1}H NMR, the crude reaction product mixture contained 15% dipropyl disulfide, 33% dipropyl trisulfide, and 52% dipropyl polysulfides. From the product mixture, 200 mg was separated on a Biotage Isolera system with a Telos Flash C18 column (12 g) using a solvent gradient (*v*:*v*) of water–methanol (50:50) for 3 CV, then (50:50) to (24:86) for 32 CV, held at (24:86) for 13 CV, then (26:84) to (0:100) for 4 CV, then (0:100) for 13 CV at a flow rate of 12 mL/min. The amounts obtained after separation were as follows: **2b** (23 mg, 0.15 mmol), **3b**

(41 mg, 0.23 mmol), and an inseparable mixture of **3b**, **4b**, **5b**, and **6b** (121 mg, 0.56 mmol). Due to overlapping ^{1}H NMR signals, a ratio could not be determined.

4.2.5. Dipropyl Trisulfide (3b). ^{1}H NMR (400 MHz, $CHCl_3$, 298 K) δ=2.92 (m, 4H), 1.80 (m, 4H), 1.02 (t, J=7.33, 7.33 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CHCl_3$, 298 K) δ=41.3, 22.3, 13.1 ppm; ν_{max} (NaCl): 2962, 2929, 2872, 1455, 1411, 1377, 1337, 1290, 1231, 1089, 1051, 897, 781 cm^{-1}; HRMS (ESI): calculated for $C_6H_{14}S_3$: 182.0258; found 182.0257.

4.2.6. Dipropyl Tetrasulfide (4b). HRMS (ESI): calculated for $C_6H_{14}S_4$: 213.9978; found 213.9977.

4.2.7. Dipropyl Pentasulfide (5b). HRMS (ESI): calculated for $C_6H_{13}S_5$: 245.9699; found 245.9702.

4.2.8. Dipropyl Hexasulfide (6b). HRMS (ESI): calculated for $C_6H_{14}S_6$: 277.9420; found 277.9420.

Compounds **2d**, **3d**, **4d**, and **5d** were obtained as a yellow oil (165 mg) using 10% of the amounts given in the general procedure. From ^{1}H NMR, the sample contained 80% dipentyl disulfide and 20% dipentyl polysulfides. Unfortunately, these could not be separated, and due to overlapping ^{1}H NMR signals, a ratio could not be determined. Their presence was confirmed by high-resolution mass spectrometry of the polysulfide mixture.

4.2.9. Dipentyl Trisulfide (3d). HRMS (ESI): calculated for $C_{10}H_{22}S_3$: 238.0884; found 238.0889.

4.2.10. Dipentyl Tetrasulfide (4d). HRMS (ESI): calculated for $C_{10}H_{22}S_4$: 270.0604; found 270.0606.

4.2.11. Dipentyl Pentasulfide (5d). HRMS (ESI): calculated for $C_{10}H_{22}S_5$: 302.0325; found 302.0331.

4.2.12. Dipentyl Hexasulfide (6d). HRMS (ESI): calculated for $C_{10}H_{22}S_6$: 334.0046; found 334.0039.

Compounds **2e**, **3e**, **4e**, and **5e** were obtained as a yellow oil (2.4 g) using the amounts given in the general procedure at 33 °C. From ^{1}H NMR, the sample contained 14% dibenzyl disulfide **2e**, 71% dibenzyl trisulfide **3e**, and 14% dibenzyl polysulfides. A purification of the dibenzyl polysulfides was impossible; however, their existence was detected and verified by mass spectrometry of the mixture. From the product mixture, 261 mg was separated on a Biotage Isolera with a Telos Flash C18 column (12 g) using a solvent gradient (*v*:*v*) of water–methanol (30:70) for 3 CV, (30:70) to (20:80) for 25 CV, then (20:80) to (0:100) for 15 CV, then (0:100) for 4 CV at a flow rate of 12 mL/min. The amounts obtained after separation were as follows: **2e** (21 mg, 0.09 mmol), **3e** (70 mg, 0.25 mmol), and an inseparable mixture of **3e**, **4e**, **5e**, and **6e** (104 mg).

4.2.13. Dibenzyl Trisulfide (3e). ^{1}H NMR (400 MHz, $CHCl_3$, 298 K) δ=7.65–7.51 (m, 10H), 4.31 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CHCl_3$, 298 K) δ=129.4, 128.6, 127.5, 136.4, 43.1 ppm; ν_{max} (NaCl): 3074, 3061, 3028, 2914, 1601, 1494, 1453, 1230, 1199, 1070, 914, 765, 967, 658 cm^{-1}; HRMS (ESI): calculated for $C_{14}H_{14}S_3$: 278.0258; found 278.0262.

4.2.14. Dibenzyl Tetrasulfide (4e). HRMS (ESI): calculated for $C_{14}H_{14}S_4$: 309.9978; found 309.9981.

4.2.15. Dibenzyl Pentasulfide (5e). HRMS (ESI): calculated for $C_{14}H_{14}S_5$: 341.9699; found 341.9695.

4.2.16. Dibenzyl Hexasulfide (6e). HRMS (ESI): calculated for $C_{14}H_{14}S_6$: 373.9420; found 373.9419.

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