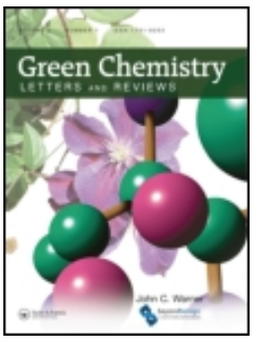

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RESEARCH LETTER

Glycerol as a recyclable solvent in a microwave-assisted synthesis of disulfides

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We present here a clean and fast synthesis of organic disulfides starting from thiols using glycerol as solvent under microwave irradiation. This efficient method is general for aromatic, aliphatic, and functionalized thiols, affording the corresponding disulfides in good to excellent yields after easy work up. Glycerol can be easily recovered and utilized for further oxidation reactions.

Keywords: glycerol; disulfides; green chemistry; microwave

1. Introduction

In organic synthesis, the choice of the solvent is a crucial step in a chemical reaction. The development of green solvents from renewable resources has gained much interest recently because of the extensive uses of solvents in almost all of the chemical industries and of the predicted disappearance of fossil oil (*1–6*). The wanted characteristics for a green solvent include no flammability, high availability, obtaining from renewable sources, and biodegradability (*6*). With the increase in biodiesel production worldwide, the market saturation of glycerol, a side product of biodiesel production, is inevitable (*7*). The peculiar physical and chemical properties, such as polarity, low toxicity, biodegradability, high boiling point, and ready availability from renewable feed stocks (*8*) prompted recently the use of glycerol (*9–12*) and their eutectics (*13*) as a green solvent in organic synthesis. Heck and Suzuki cross-couplings, ring closing metathesis of diolefins, multicomponent reactions, base- and acid-promoted condensations, catalytic hydrogenation, asymmetrical reduction, and cycloisomerization of (*Z*)-enynols into furans are some examples of the use of glycerol as a solvent in organic reactions (*9–12*).

On the other hand, thiols and disulfides are important in both biological (*14–19*) and chemical process (*20–22*). Disulfides are useful reagents in organic synthesis (*20–22*) and essential moieties of biologically active compounds for peptide and protein stabilization (*14–19*). As disulfides are relatively more stable to organic reactions such as oxidation, alkylation, and acylation compared to the corresponding free thiols, the thiol group can conveniently be protected as a disulfide. Besides, there are a large number of commercially available thiols and the interconversion between thiols and disulfides is easy (*23*). These aspects are responsible for the continuous interest in development of new, selective and efficient protocols for the preparation of disulfides (*20–22*, *24–34*). Recently reported procedures involve the use of stoichiometric amount of anhydrous potassium phosphate (*24*), potassium permanganate (*25*), molecular bromine supported on silica gel (*26*), *N*-phenyltriazolinedione (*27*), $VO(acac)_2$ (*28*), trichloroisocyanuric acid (*29*), nitric acid (*30*), 1,3-dibromo-5,5-dimethylhydantoin (*31*), basic alumina (*32*), CsF-Celite (*33*), and montmorillonite K10 (*34*).

The development of environmentally benign and clean synthetic methods for the synthesis of disulfides, including those involving solvent-free or the use of alternative solvents, such as water and ionic liquids, has increased in recent years (*27*, *35–44*). These methods involve the use of *N*-phenyltriazolinedione (*27*), pyridinium chlorochromate (*35*), 1,3-dibromo-5,5-dimethylhydantoin (*36*), SO_2Cl_2 (*37*), trichloronitromethane (*38*), $KMnO_4/MnO_2$ (*39*), $KMnO_4$ supported on montmorillonite K10 (*40*), catalytic amount of iodine and $CeCl_3 \cdot 7H_2O$ in graphite (*41*), KF/Al_2O_3 (*42*), $[bmim][SeO_2(OCH_3)]$ (*43*), and $[bmim][BF_4]$ (*44*).

Despite several advantages, the solvent-free methods are restricted to systems where at least one of the reagents is liquid at room temperature, whereas the uses of ionic liquids, especially imidazolium systems with PF_6 and BF_4 anions, have some drawbacks, such as the high cost and liberation of hazardous HF

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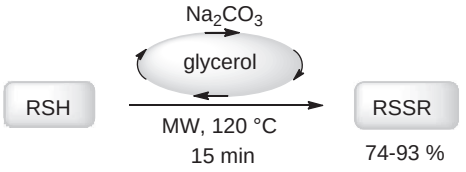


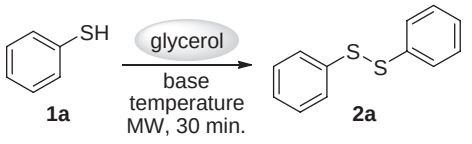
Scheme 1. General scheme of reaction.

during recycling (*45–48*). Thus, the use of alternative nonvolatile green solvents, such as glycerol, has been shown as an attractive way to cleaner synthesis of disulfides. According to our interest in the green protocols in organic chemistry (*42, 43*, *49–55*), we describe here the use of glycerol as a green solvent in the oxidation of thiols to disulfides (Scheme 1).

2. Results and discussion

Firstly, we reacted benzenethiol **1a** with K_2CO_3 as base, using glycerol as solvent at room temperature and under these conditions, no product was observed. When the reaction was performed at room temperature under microwave irradiation, product **2a** was formed in 15% yield after 30 minutes. Encouraged for this result, we performed this oxidation reaction in microwave irradiation under different temperatures (Table 1). To our satisfaction, increasing the temperature to 120°C the reaction proceeds smoothly, furnishing the disulfide **2a** in excellent yield (Table 1; entry 5) and the same result was obtained at 150°C (Table 1; entry 6).

Table 1. Optimization of oxidation reaction.[a]



1a **2a**

Entry	Temperature (°C)	Base	Yield of **2a** (%)[b]
1	30	K_2CO_3	15
2	50	K_2CO_3	20
3	80	K_2CO_3	45
4	100	K_2CO_3	83
5	120	K_2CO_3	89
6	150	K_2CO_3	89
7	120	Na_2CO_3	92
8	120	Cs_2CO_3	92
9	120	Na_3PO_4	56
10	120	K_3PO_4	80
11	120	KOH	86
12	120	LiOAc	70
13	120	NaOAc	69
14	120	Et_3N	82
15	120	–	–
16[c]	120	Na_2CO_3	85

[a]Reactions are performed in the presence of **1a** (1.0 mmol), base (1.1 mmol), glycerol (1 mL) in a microwave reactor (CEM Explorer).
[b]Yields are given for isolated product.
[c]Reaction performed using conventional heating for 12 h.

We observed that the nature of the base was critical for the success of the oxidation. When the reaction was carried out with different bases such as: Na_2CO_3, Cs_2CO_3, Na_3PO_4, K_3PO_4, KOH, LiOAc, NaOAc, and Et_3N, benzenethiol **1a** was successfully oxidated (Table 1; entries 7–14), and the best results were obtained using Na_2CO_3 and Cs_2CO_3 as base. Gratifyingly, the use of Na_2CO_3, an inexpensive base, resulted in the oxidation of benzenethiol **1a** in 92% isolated yield (Table 1; entry 7). It is also important to mention that when the reaction was performed without base no product was obtained (Table 1; entry 15). Reaction of benzenethiol **1a** with Na_2CO_3 in glycerol was performed using a conventional heating and the product **2a** was isolated in a good yield, however, in a longer reaction time comparing with microwave-assisted method (Table 1; entry 7 vs. 16).

To obtain an efficient methodology in terms of energy economy, we realized a study to establish the minimum time associated with a good reaction rate under the optimized conditions (Figure 1). Analyzing Figure 1, excellent conversion of benzenethiol in diphenyl disulfide **2a** was observed after 15 minutes of reaction. A further decrease in the reaction time (less than 15 minutes) was followed by a considerable reduction in the conversion rate of benzenethiol.

In an optimized reaction, benzenethiol **1a** (1.0 mmol) and Na_2CO_3 (1.1 mmol) were dissolved in glycerol (1.0 mL) and reacted under microwave irradiation at 120°C for 15 minutes, yielding **2a** in 92% isolated yield.

After reaction optimization, a study regarding the recovering and reusing of glycerol was performed. After the total consumption of benzenethiol **1a**, the

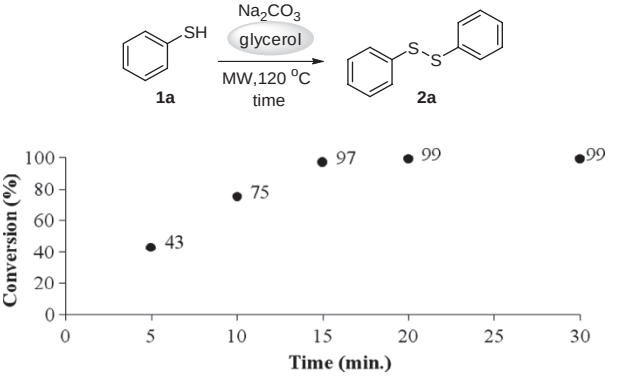
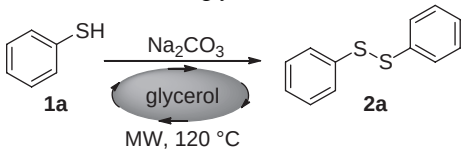


Figure 1. Plot of conversion vs. time for the oxidation of benzenethiol **1a**.

Table 2. Reuse of glycerol.[a]



Run	Time (minutes)	Yield of **2a** (%)[c]
1	15	92
2[b]	15	92
3[b]	15	90
4[b]	20	89
5[b]	30	88

[a]Reaction was performed in the presence of benzenethiol **1a** (1.0 mmol), Na_2CO_3 (1.1 mmol), glycerol (1 ml), at 120°C in a microwave reactor.
[b]Recovered glycerol was used.
[c]Yields are given for isolated products.

reaction mixture was diluted and extracted with a mixture of hexane/ethyl acetate 95:5 (3 × 3 mL). The upper phase was dried and the solvent evaporated. The inferior, glycerol phase was dried under vacuum and directly reused. We observed that the glycerol phase reused furnishing diphenyl disulfide **2a** in 89%. However, after second reuse, only traces of diphenyl disulfide **2a** were obtained. In view of this result, we performed the reuse studies using $NaCO_3$ in all runs, as shown in Table 2. It was observed that a good level of efficiency was maintained even after being reused four times. Diphenyl disulfide **2a** was obtained in 92%, 92%, 90%, 89%, and 88% yields after successive cycles, however, with an increase in the reaction time after the third run.

To demonstrate the generality of this method, we prepared a series of organic disulfides **2a**–**t** using aryl, heteroaryl or alkyl thiols, Na_2CO_3, and glycerol under microwave irradiation (Table 3). In most cases, the reactions proceeded fast and smoothly to give disulfides **2a**–**t** in good to excellent yields. A structurally diverse range of aryl thiols were oxidated to corresponding diaryl disulfides in excellent yields (Table 3; entries 1–12). Diaryl disulfides containing electron donating (EDG) (Table 3; entries 2–6) and electron withdrawing groups (EWG) (Table 3; entries 7–10) could be obtained in high yields. Both aryl thiols containing EDG and EWG have no significant influence on the reactivity of the process, because the products were obtained in comparable yields. Satisfactory yields of oxidation were achieved using 2-amino-4-chlorobenzenethiol, 2-naphthalenethiol, and 2-mercaptobenzothiazole (Table 3; entries 11–13). Good results were obtained using benzylic or furfuryl thiols yielding the corresponding disufides **2n**–**p** in 84–87%, but in 30 minutes reaction time (Table 3, entries 14–16). Finally, when we employed alkylic thiols, the corresponding dialkyl disulfides **2q**–**t** were synthesized in good yields (Table 3; entries 17–20).

3. Experimental section

3.1. General remarks

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz on a Bruker DPX-200 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million, referenced to the solvent peak of $CDCl_3$ or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant *(J)* in Hertz, and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 50 MHz on a Bruker DPX-200 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million, referenced to the solvent peak of $CDCl_3$. Column chromatography was performed using Merck Silica Gel (230–400 mesh) following the standard methods. Thin layer chromatography (TLC) was performed using Merck Silica Gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were placed under ultraviolet light, stained with iodine vapor, or acidic vanillin. The reactions were monitored by TLC for disappearance of starting material. All microwave reactions were conducted using a CEM Discover, mode operating systems working at 2.45 GHz, with a power programmable from 1 to 300 W.

3.2. General procedure for the oxidation of thiols using glycerol

In a 10 mL glass vial equipped with a small magnetic stirring bar, containing Na_2CO_3 (0.116 g; 1.1 mmol) and glycerol (1 mL), thiol (1.0 mmol) was added. The vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated in a microwave reactor (CEM Explorer) for 15 minutes at 120°C (temperature was measured with an IR sensor on the outer surface of the reaction vial), using an irradiation power of 100 W and pressure of 100 psi (the ramp temperature rate was 45 sec). After the reaction was complete, the product was extracted by successive washings with a mixture of hexane/ethyl acetate (95:5) (3 × 3 mL) and concentrated under vacuum. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluent.

1,2-diphenyl disulfide **2a** (*56*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.41–7.39 (m, 4*H*); 7.22–7.07 (m,

Table 3. Scope and generality of the synthesis of disulfides **2a**–**t** using glycerol as solvent.[a]

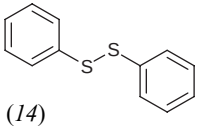
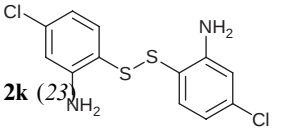
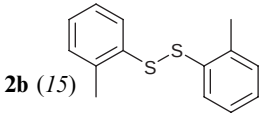
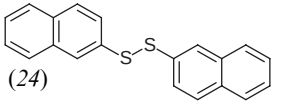
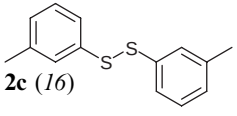
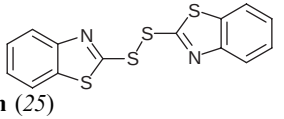
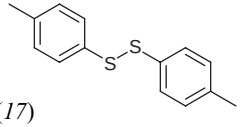
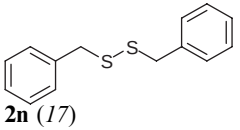
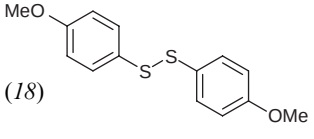
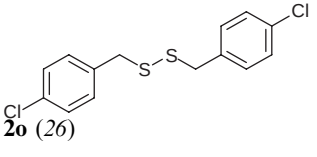
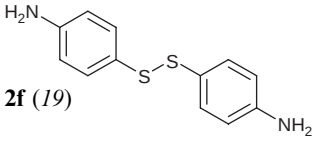
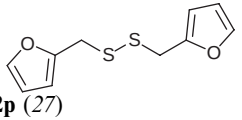
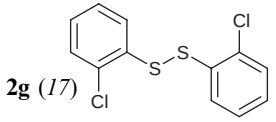
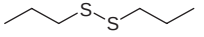
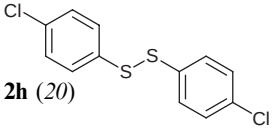
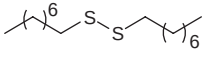
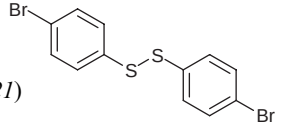
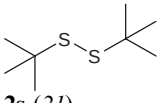
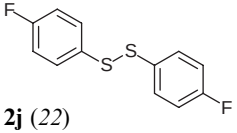
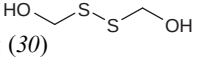
Entry	Product (Ref.)	Yield (%)[b]	Entry	Product (Ref.)	Yield (%)[b]
1	 **2a** (*14*)	92	11	 **2k** (*23*)	85
2	 **2b** (*15*)	87	12	 **2l** (*24*)	88
3[c]	 **2c** (*16*)	87	13	 **2m** (*25*)	89
4	 **2d** (*17*)	91	14[c]	 **2n** (*17*)	87
5	 **2e** (*18*)	92	15[c]	 **2o** (*26*)	86
6	 **2f** (*19*)	88	16[c]	 **2p** (*27*)	84

Table 3 (*Continued*)

Entry	Product (Ref.)	Yield (%)[b]	Entry	Product (Ref.)	Yield (%)[b]
7	 **2g** (*17*)	89	17[c]	 **2q** (*28*)	86
8	 **2h** (*20*)	93	18[c]	 **2r** (*29*)	82
9	 **2i** (*21*)	92	19[c]	 **2s** (*21*)	81
10[c]	 **2j** (*22*)	92	20	 **2t** (*30*)	81

[a]Reactions are performed in the presence of thiol (1.0 mmol), Na_2CO_3 (1.1 mmol), glycerol (1 mL), at 120°C in a microwave reactor for 15 minutes.
[b]Yields are given for isolated product.
[c]Reactions are performed in 30 minutes.

6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 136.33, 129.10, 127.50, 127.30.

1,2-bis(2-tolyl) disulfide **2b** (*57*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.52–7.49 (m, 2*H*); 7.15–7.10 (m, 6*H*); 2.42 (s, 6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 137.42, 135.40, 130.31, 127.78, 127.29, 126.75, 21.08.

1,2-bis(3-tolyl) disulfide **2c** (*58*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.34–7.21 (m, 8*H*); 2.13 (s, 6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 139.92, 137.19, 130.52, 129.89, 128.22, 127.75, 21.82.

1,2-bis(4-tolyl) disulfide **2d** (*59*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40 (d, $J = 8.3$ Hz, 4*H*); 7.12 (d, $J = 8.3$ Hz, 4*H*); 2.33 (s, 6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 139.02, 131.89, 130.78, 128.91, 21.01.

1,2-bis(4-methoxyphenyl) disulfide **2e** (*60*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40 (d, $J = 8.1$ Hz, 4*H*); 6.84 (d, $J = 8.1$ Hz, 4*H*); 3.80 (s, 6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 159.91, 132.67, 128.42, 114.61, 55.36.

bis(4-aminophenyl) disulfide **2f** (*61*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.20 (d, $J = 8.5$ Hz, 4*H*); 6.53 (d, $J = 8.5$ Hz, 4*H*); 3.73 (bs, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 144.75, 130.55, 127.95, 118.60.

1,2-bis(2-chlorophenyl) disulfide **2g** (*59*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.55 (dd, $J^1 = 7.6$ Hz, $J^2 = 1.5$ Hz, 2*H*); 7.35 (dd, $J^1 = 7.6$ Hz, $J^2 = 1.5$ Hz, 2*H*); 7.23–7.11 (m, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 134.33, 132.37, 131.32, 129.29, 128.98, 124.75.

1,2-bis(4-chlorophenyl) disulfide **2h** (*62*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40 (d, $J = 7.8$ Hz, 4*H*); 7.13 (d, $J = 7.8$ Hz, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 135.07, 132.19, 130.43, 128.74.

1,2-bis(4-bromophenyl) disulfide **2i** (*63*).^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.42 (d, $J = 8.2$ Hz, 4*H*), 7.33 (d, $J = 7.8$ Hz, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 133.03, 131.31, 130.24, 128.61.

1,2-bis(4-fluorophenyl) disulfide **2j** (*64*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40 (m, 4*H*); 6.95 (t, $J = 8.6$ Hz, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 163.28 (d, $J = 246.5$ Hz), 133.84 (d, $J = 2.9$ Hz) 132.78 (d, $J = 8.6$ Hz), 118.00 (d, $J = 21.1$ Hz).

6,6′-disulfanediyl bis(3-chloroaniline) **2k** (*65*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.15–6.76 (m, 6*H*); 5.60 (bs, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 144.98, 132.52, 128.06, 123.86, 123.36, 123.23.

2-Naphthyl disulfide **2l** (*66*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.99 (d, $J = 0.9$ Hz, 2*H*), 7.81–7.72 (m, 4*H*), 7.65–7.61 (m, 2*H*), 7.49–7.42 (m, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 134.03, 133.51, 132.55, 128.91, 127.84, 127.54, 126.73, 126.60, 126.21, 125.70.

1,2-bis(2-benzothiazolyl) disulfide **2m** (*67*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.37 (dd, $J^1 = 3.5$ Hz, $J^2 = 0.9$ Hz, 2*H*); 7.32–7.25 (m, 4*H*); 7.25–7.21 (m, 2*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 149.26, 145.86, 133.61, 127.24, 125.14, 120.86, 120.69.

1,2-dibenzyl disulfide **2n** (*59*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.36–7.22 (m, 10*H*); 3.60 (s, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 137.20, 129.20, 128.20, 127.20, 43.32.

1,2-bis(4-chlorobenzyl) disulfide **2o** (*68*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.29–7.27 (m, 4*H*); 7.15–7.13 (m, 4*H*); 3.57 (s, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 134.60, 133.02, 130.11, 127.96, 43.16.

1,2-difurfuryl disulfide **2p** (*69*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.40–7.38 (m, 2*H*); 6.34–6.32 (m, 2*H*); 6.22 (d, $J = 3.2$ Hz, 2*H*); 3.69 (s, 4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 149.46, 142.01, 111.85, 107.46, 35.99.

1,2-di(n-propyl) disulfide **2q** (*70*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 2.41 (t, $J = 7.2$ Hz, 4*H*); 1.46 (quint, $J = 7.2$, 4*H*); 0.88 (t, $J = 7.2$ Hz, 6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 41.26, 22.56, 13.12.

1,2-di(n-octyl) disulfide **2r** (*71*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)): 2.65 (t, $J = 8.0$ Hz, 14*H*); 1.77–1.18 (m, 24*H*); 0.87 (t, $J = 7.2$ Hz, 6*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 39.84, 32.14, 29.72, 29.38, 28.63, 28.28, 22.72, 14.10.

1,2-di(t-butyl) disulfide **2s** (*63*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.29 (s, 18*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 45.71, 30.51.

1,2-bis-hydroxymethyl disulfide **2t** (*72*). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.64 (s, 2*H*), 4.32 (4*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 64.81.

3.3. General procedure for the recycle of glycerol

In a 10 mL glass vial equipped with a small magnetic stirring bar, containing Na_2CO_3 (0.116 g; 1.1 mmol) and glycerol (1 mL), thiol (1.0 mmol) was added. The vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated in a microwave reactor (CEM Explorer, mode operating systems working at 2.45 GHz) for 15 minutes at 120°C (temperature was measured with an IR sensor on the outer surface of the reaction vial), using an irradiation power of 100 W and pressure of 100 psi. After the reaction was complete, the product was extracted by successive washings with a mixture of hexane/ethyl acetate (95:5) (3 × 3 mL) and concentrated under vacuum. The residue was purified by

column chromatography on silica gel using hexane/ethyl acetate as the eluent.

4. Conclusion

In conclusion, glycerol has proved to be an efficient solvent for the oxidation of aromatic, aliphatic, and functionalized thiols under microwave irradiation. The reactions proceeds quickly, and the desired disulfides were obtained in good to excellent yields. In addition, glycerol can be easily recovered and utilized for further oxidation reactions and is particularly appropriate to the green chemistry concept.

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