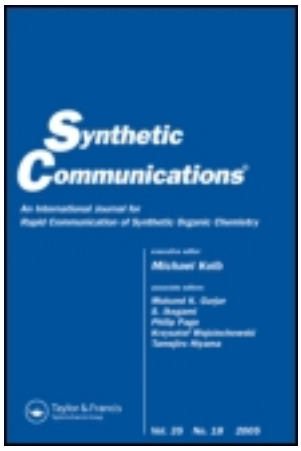

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A RAPID AND EFFICIENT SYNTHESIS OF SYMMETRICAL DISULFIDES UNDER MICROWAVE IRRADIATION CONDITIONS

Jin-Xian Wang [a] , Lijuan Gao [b] & Danfeng Huang [a]

[a] Department of Chemistry, Institute of Chemistry, Northwest Normal University, 95 An Ning Road (E.), Lanzhou, 730070, China

[b] Department of Chemistry, Ningxia University, Yinchuan, 75000, China

Published online: 21 Aug 2006.

To cite this article: Jin-Xian Wang , Lijuan Gao & Danfeng Huang (2002): A RAPID AND EFFICIENT SYNTHESIS OF SYMMETRICAL DISULFIDES UNDER MICROWAVE IRRADIATION CONDITIONS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:7, 963-969

To link to this article: http://dx.doi.org/10.1081/SCC-120003143

SYNTHETIC COMMUNICATIONS, 32(7), 963–969 (2002)

A RAPID AND EFFICIENT SYNTHESIS OF SYMMETRICAL DISULFIDES UNDER MICROWAVE IRRADIATION CONDITIONS

Jin-Xian Wang,[1,*] Lijuan Gao,[2] and Danfeng Huang[1]

[1]Institute of Chemistry, Department of Chemistry, Northwest Normal University, 95 An Ning Road (E.), Lanzhou, 730070 China
[2]Department of Chemistry, Ningxia University, Yinchuan, 75000 China

ABSTRACT

A rapid and general method for the synthesis of symmetrical disulfides involves reaction of sulfur with sodium hydroxide under PTC-microwave irradiation condition to give sodium disulfide, which reacts with alkyl halides to afford the disulfides in good to excellent isolated yields.

Disulfides are important organic sulfur compounds possessing a unique and rich chemistry in the synthetic and biochemical area. For example, large disulfide-linked aggregates are prevalent in proteins and many other bioactive molecules.[1] Industrially, disulfides find wide applications as vulcanizing agents for rubbers and elastomers, giving them excellent tensile strength.

*Corresponding author.

Several methods for the preparation of organic disulfide have been described.[2–6] Many reagents and catalysts have been introduced to oxidize thiols to disulfides under controlled conditions.[7–23] Disulfides can be easily prepared by electrochemical oxidation of the corresponding thiols in methanol/sodium methoxide solution under conditions of constant current,[24] thiol acetate with clayfen in the absence of solvent,[25] and oxidative cleavage of aryl or alkyl tertbutyl sulfides.[26] Recently, the catalytic coupling of thiols and new methods have been reported.[27] Although there are a number of methods available in the literature for the synthesis of disulfides, the most commonly employed method for the direct conversion of benzyl halides to disulfides has been using Na_2S_2 or Na_2S/S.[28] However, these methods suffer from severe disadvantages, such as long reaction times and operational complications.

In recent years, microwave-induced rate acceleration technology has become a powerful tool in organic synthesis, because of milder reaction conditions, reduction of reaction times, enhanced selectivity, and associated ease of manipulation. Microwave irradiation has also been applied to several organic reactions. It has been used for a great variety of organic reactions, such as Reformatsky, Knoevenagel, Bischler–Napieralski, etherification, esterification, oxidation, hydrolysis, Diels–Alder reactions and solid-phase peptide synthesis. Some important reviews have been published.[29] We have reported the synthesis of substituted glycerol selenide ether and chiral glycerol sulfide ethers under sulfur in base under PTC-microwave irradiation to afford the symmetrica disulfides in good to excellent isolated yields. The results are summarized in Table 1.

These results show that the phase transfer catalyst is not only involved in the formation of the disulfide ion in solution, but also catalyses the substitution reaction on the alkyl chlorides.

Using the reaction of benzyl chloride with sulfur as an example, we investigated the effect of phase transfer catalysts (PTC) on the reaction. When PEG-400 was used as a phase transfer catalyst, the yield of the dibenzyl disulfide was high (91%). The efficiency of several PTCs studied is in the order PEG-400 $\cong$ PEG-600 > n-$C_{16}H_{33}NMe_3Br$ > Bu_4NBr > Me_4NI. The results are summarized in Table 2.

The effects of various solvents used in the formation of dibenzyl disulfide were studied and DMF was found to be the best solvent for the reaction. Because DMF is a polar solvent and its boiling point is high, it can efficiently absorb microwave energy. Other solvents were studied for these reactions and their suitability are in the order DMF > EtOH > butanol > acetone > benzene.

We have also investigated the effects of irradiation power and time on the reactions. It was found that the highest yield of compound **3** is obtained

$$2RX + 2S \xrightarrow[DMF,\ MW,\ 6-7\,min]{NaOH,\ PEG\text{-}400} RSSR$$

Table 1. Synthesis of Disulfides **3a-** Under PTC-Microwave Irradiation[a]

Entry	R	X	Product		Irradiation Condition Power (W)/ Time (min)	Yield[b] (%)
1	t-C_4H_9	Cl	$(t\text{-}C_4H_9S)_2$	(**3a**)	375/6	90
2	n-C_5H_{11}	Cl	$(n\text{-}C_5H_{11}S)_2$	(**3b**)	375/6	88
3	$CH_2=CH\text{-}CH_2$	Cl	$(CH_2{=}CH\text{-}CH_2S)_2$	(**3c**)	375/6	90
4	$C_6H_5CH_2$	Cl	$(C_6H_5CH_2S)_2$	(**3d**)	375/6	91
5	4-$ClC_6H_4CH_2$	Cl	$(4\text{-}ClC_6H_4CH_2S)_2$	(**3e**)	375/6	85
6	2-$BrC_6H_4CH_2$	Br	$(2\text{-}BrC_6H_4CH_2S)_2$	(**3f**)	375/6	81
7	4-$O_2NC_6H_4CH_2$	Br	$(4\text{-}O_2NC_6H_4CH_2S)_2$	(**3g**)	375/7	67
8	2-$O_2NC_6H_4CH_2$	Br	$(2\text{-}O_2NC_6H_4CH_2S)_2$	(**3h**)	375/7	65
9	2-$C_{10}H_7CH_2$	Br	$(2\text{-}C_{10}H_7CH_2S)_2$	(**3i**)	375/6	90

[a]The reactions were carried out in the presence of NaOH using PEG-400 as catalyst in DMF under microwave irradiation condition; [b]Isolated yield.

Table 2. Effect of Phase Transfer Catalyst on the Formation of (**3d**)[a]

Catalyst	$(C_4H_9)_4NBr$	n-$C_{16}H_{33}N(CH_3)_3Br$	PEG-600	PEG-400
Yield[b] (%)	76.2	82	89.3	91

[a]The reaction was carried out in DMF at a power level of 375 W for 6 min; [b]Isolated yield.

at a power level of 375 W for 6–7 min continuous irradiation. The results we summarized in Tables 3 and 4.

The impact of the PTC-microwave irradiation and PTC for the synthesis of compounds **3a–i** has been compared and results are summarized in Table 5. The results show that the synthesis of compounds **3a–i** under PTC-microwave irradiation are 34–40 times faster than under phase transfer conditions. This ratio between the reaction time using PTC and PTC-microwave irradiation ($t_p/t_{p\text{-}mw}$), under the same condition, quantifies the PTC-MW effect.

Table 3. The Effect of Microwave Irradiation Power[a]

Irradiation Power (W)	75	150	225	375	450
Yield[b] (%)	74.5	80.6	88.4	91	91

[a]The reaction was carried out in the presence of NaOH using PEG-400 as catalyst in DMF for 6 min; [b]Isolated yield.

Table 4. The Effect of Microwave Irradiation Time[a]

Irradiation Time (min)	3	4	5	6	7
Yield[b] (%)	64.2	75	85	88	88.4

[a]The reaction was carried out in the presence of NaOH using PEG-400 as catalyst in DMF at power level of 375 W under continuous irradiation conditions; [b]Isolated yield.

Table 5. Comparison of Time and Yields in Synthesis of Compounds **3a–i** Using PTC-Microwave Irradiation and Phase Transfer Catalysis

Phase Transfer Catalysis[a]			PTC-Microwave Irradiation			
Product	t (h)	Yield (%)	Power (W)	t (min)	Yield[b] (%)	$t_p/t_{p\text{-}mw}$
3a	4	50	375	6	90	34
3b	4	76	375	6	88	34
3c	4	80	375	6	90	34
3d	4	95	375	6	91	34
3e	4	97	375	6	85	34
3f	4	70	375	6	81	34
3g	4	80	375	7	67	40
3h	4	75	375	7	65	40
3i	4	90	375	6	90	34

[a]The reaction was carried out in the presence of NaOH using PEG-400 as catalyst at 65–70°C; [b]Isolated yield.

EXPERIMENTAL

IR spectra were measured for KBr discs using an Alpha centauri FT-IR spectrophotometer. ^{1}H-NMR spectra (80 MHz) were recorded in $CDCl_3$ or $[(CD_3)_2CO]$ using an FT-80 spectrometer. Microanalyses were

measured using a Carlo Erba 1106 microelemental analyzer. Microwave irradiations were carried out with a modified Galanz WP 750B commercial microwave oven at 2450 MHz.

General procedure: Sulfur powder 0.4 g (12.5 mmol) was added to a mixture of PEG-400 0.2 g (0.005 mmol), sodium hydroxide 2 g (50 mmol) and DMF (20 ml) after which the reaction mixture was irradiated at 375 W for 3 min. The solution changed from colorless to blue. Then the alkyl halides (10 mmol) were added and the reaction mixture was irradiated for 3–4 min under the same irradiation power. When the blue color disappeared in the solution, the reaction was completed. The solid inorganic salt was separated by filtration and solvent was removed by evaporation under reduced pressure to afford a crystalline (or liquid) dialkyl disulfide. The pure solid products were obtained by recrystallization from ethanol, and pure liquid products were obtained by a short silica gel column using petroleum ether as the eluent.

***Bis*(*t*-Butyl)disulfide 3a:** oil; b.p.: 66–68°C/5 mmHg (Lit.[31] 88°C/12 mmHg). ^{1}H-NMR ($CDCl_3$): δ 1.32 (s, 18H, $2 \times CH_2)_3$. IR ν (KBr): 2959, 2862, 697, 615, 466.

***Bis*(*n*-Pentyl)disulfide 3b:** oil; b.p.: 118–119/7 mmHg (Lit.[31] 119°C/7 mmHg). ^{1}H-NMR ($CDCl_3$): δ 2.64 (t, 4H, $2 \times CH_2S$), 1.21–1.62 (m, 12H, $2 \times (CH_2)_3$), 1.20 (t, 6H, $2 \times CH_3$). IR ν (KBr): 2957, 2870, 507, 419.

***Bis*(Allyl)disulfide 3c:** oil; b.p.: 88–90°C/22 mmHg (Lit.[31] 78–80°C/16 mmHg). ^{1}H-NMR ($CDCl_3$): δ 5.8 (q, 2H, $2 \times$ =CH-), 5.01 (q, 4H, $2 \times CH_2$=C-), 2.82 (d, 4H, $2 \times$ -Ch_2S). IR ν (KBr): 3082, 2987, 579, 429.

Dibenzyldisulfide 3d: m.p.: 71–72°C (Lit.[31] 71–72°C). ^{1}H-NMR ($CDCl_3$): δ 7.20–7.79 (m, 10H, $2 \times$ ArH), 3.80 (s, 4H, $2 \times CH_2S$). IR ν (KBr): 3051, 2964, 2909, 708, 564, 465. Anal. calcd for $C_{11}H_{14}S_2$: C, 68.29; H, 5.73. Found: C, 68.58; H, 5.82.

***Bis*(4-Chlorobenzyl)disulfide 3e:** m.p. 59–60°C (Lit.[32] 60–66°C); ^{1}H-NMR ($CDCl_3$): δ 7.36–7.60 (q, 8H, $2 \times$ ArH), 3.81 (s, 4H, $2 \times CH_2S$). IR ν (KBr): 3080, 2980, 2879, 679, 519, 464. Anal. calcd for $C_{14}H_{12}C_{12}S_2$: C, 53.23; H, 3.81. Found: C, 52.98; H, 3.74.

***Bis*(2-Bromobenzyl)disulfide 3f:** m.p. 87–88°C (Lit.[32] 87–88°C); ^{1}H-NMR ($CDCl_3$): δ 7.37–7.89 (m, 8H, $2 \times$ ArH), 3.94 (s, 4H, $2 \times CH_2S$). IR ν (KBr): 3079, 2879, 699, 666 528, 486. Anal. calcd for $C_{14}H_{12}Br_2S_2$: C, 41.60; H, 2.97. Found: C, 41.50; H, 2.99.

***Bis*(4-Nitrobenzyl)disulfide 3g:** m.p. 109–111°C (Lit.[32] 111–113°C); ^{1}H-NMR ($CDCl_3$): δ 7.34–8.01 (m, 8H, $2 \times$ ArH), 4.06 (s, 4H, $2 \times CH_2S$). IR ν (KBr): 3080, 2872, 622, 539, 473. Anal. calcd for $C_{14}H_{12}N_2O_4S_2$: C, 50.00; H, 3.57; N, 8.33. Found: C, 50.25; H, 3.50; N, 8.21.

***Bis*(2-Nitrobenzyl)disulfide 3h:** m.p. 105–106°C (Lit.[32] 106–107°C); ^{1}H-NMR ($CDCl_3$): δ 7.28–7.59 (m, 8H, $2 \times$ ArH), 3.94 (s, 4H, $2 \times CH_2S$).

IR ν (KBr): 3075, 2940, 2872, 657, 572, 439. Anal. calcd for $C_{14}H_{12}N_2O_4S_2$: C, 50.00; H, 3.5 N, 8.33. Found: C, 50.09; H, 3.56; N, 8.31.

***Bis*(2-Naphthylmethylene)disulfide 3i:** m.p. 116–117°C (Lit.[32] 116–117°C). ^{1}H-NMR ($CDCl_3$): δ 7.22–7.81 (m, 14H, $2 \times C_{10}H_7$), 3.92 (s, 4H, $2 \times CH_2S$). IR ν (KBr): 3080, 2980, 2879, 645, 579, 479. Anal. calcd for $C_{22}H_{18}S_2$: C, 76.30; H, 5.20. Found: C, 76.04; H, 5.20.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China and the Northwest Normal University Science and Technology Development Foundation of China.

REFERENCES

1. Bodzansky, M. *Principles of Peptide Synthesis*. Springer-Verlag: Berlin, 1984, Chap. 4.
2. (a) Parry, R.J. Tetrahedron **1983**, *39*, 1215; (b) Karchmer, J.H. *The Analytical Chemistry of Sulfur and Its Compounds*. Wiley: New York, 1972; (c) Kuhle, E. *The Chemistry of the Sulfenic Acids*. Georg Thieme Verlag: Stuttgart, 1973; (d) Douglass, I.B.; Norton, R.V. J. Org. Chem. **1968**, *33*, 2104; (e) Douglass, I.B. J. Org. Chem. **1974**, *39*, 563; (f) Suter, C.M. *The Organic Chemistry of Sulfur and its Compounds*. Wiley: New York, 1972; (g) Oae, S. *Organic Chemistry of Sulfur*. Plenum Press: New York, 1977.
3. (a) Ohe, H. Bull. Chem. Soc., Jpn. **1983**, *56*, 3813; (b) Babu, J.R.; Bhatt, M.V. Tetrahedron Lett. **1986**, *27*, 1073; (c) Dhar, P.; Ranjan, R.; Chandrasekaran, S. J. Org. Chem. **1990**, *55*, 3728.
4. Tadashi, O.; Tomoki, N.; Takayuki, F. Tetrahedron Lett. **1990**, *31*, 1017.
5. Dhar, P.; Chandrasekaran, S. J. Org. Chem. **1989**, *54*, 2998.
6. Capozzi, G. Tetrahedron Lett. **1989**, *30*, 2995.
7. Olah, G.A.; Arvanaghi, M.; Vankar, Y.D. Synthesis **1979**, 721.
8. Drabowica, J.; Mikotaczyk, M. Synthesis **1980**, 32.
9. Firouzabadi, H.; Iranpoor, N.; Parhan, H.; Sardarian, A.; Toofan, J. Synth. Commun. **1984**, *14*, 717.
10. Mahieu, Jean-Pierre; Gosselet, M.; Sebill, B.; Beuzard, Y. Synth. Commun. **1986**, *16*, 1709.
11. Pemriashvili, K.A.; Usov, V.A.; Larik, M.F.; Voronkov, M.G. Zh. Org. Khim. **1986**, XXII, 454.

12. Nagano, T.; Yoshikawa, K.; Hirobe, M. Tetrahedron Lett. **1980**, *21*, 279.
13. Firouzabadi, H.; Mottghinejad, E.; Seddighi, M. Synthesis **1989**, 378.
14. Sato, T.; Otera, J.; Nozaki, H. Tetrahedron Lett. **1990**, *31*, 3591.
15. Kajigaeshi, S., et al. Chem. Express **1991**, *6*, 129.
16. Barton, D.H.R.; Chen Chen; Wall, G.M. Tetrahedron **1991**, *47*, 6127.
17. Akabori, S.; Takanohashi, Y.; Takagi, S. Synth. Commun. **1990**, *20*, 3187.
18. Mckillop, A.; Koyuncu, D. Tetrahedron Lett. **1990**, *31*, 5007.
19. Wu, G.; Hu, Z.; Huang, X. Chemical Reagents **1991**, *13*, 135.
20. Fujihara, H.; Mima, H.; Ikemori, M.; Furukawa, N. J. Am. Chem. Soc. **1991**, *113*, 6337.
21. Sakat, K.; Tachifuji, Y.; Hashimoto, M. Synth. React. Inorg. Met—Org. Chem. **1990**, *20*, 901.
22. Suzuki, H.; Kawato Sri-ichi; Nasu, A. Bull. Chem. Soc. Jpn. **1992**, *62*, 626.
23. Broin, B.O.; Darcy, R. Synth. Commun. **1993**, *23*, 1209.
24. Leite, S.L.S.; Pardini, V.L.; Hans, V. Synth. Commun. **1990**, *20*, 393.
25. Meshrain, H.M. Tetrahedron Lett. **1993**, *34*, 2521.
26. Dickman, D.A.; Chemburkar, S.; Konopacki, D.B.; Elisseou, E.M. Synthesis **1993**, 573.
27. Iranpoor, N.; Zeynizadeh, B. Synthesis **1999**, 49.
28. Amosova, S.V.; Nosyreva, V.V.; Sigalov, M.V. Zh. Org. Khim. **1992**, *28*, 927.
29. For recent reviews, see: (a) Caddick, S. Tetrahedron **1995**, *51*, 10403; (b) Strauss, C.R.; Trainor, R.W. Aust. J. Chem. **1995**, *48*, 1165; (c) Galema, S.A. Chem. Soc. Rev. **1997**, *26*, 233; (d) Loupy, A.; Petic, A.; Hamelin, J.; Fexier-Boullet, F.; Jacquault, P.; Mathe, D. Synthesis **1998**, 1213; (e) Varma, R.S. Green Chem. **1999**, 43.
30. (a) Wang, J.-X.; Wu, X.; Hu, Y.; Zaho, K.; Liu, Z. J. Chem. Res. (S) **1999**, 688; (M) **1999**, 3038; (b) Wang, J.-X.; Zhang, Y.; Huang, D.; Hu, Y. J. Chem. Res. (S) **1998**, 216; (c) Wang, J.-X.; Xi, Y.; Wu, X.; Hu, Y.; Du, Z. Synth. Commun. **1998**, *28*, 4619.
31. Buckingham, J.; Donaghy, S. *Dictionary of Organic Compounds*, 5th Ed.; p. 1524, p. 1688, p. 2294, Chapman and Hall: New York, 1982.
32. Wang, J.-X.; Cui, W.; Hu, Y. Synth. Commun. **1995**, *25*, 3572.

Received in the USA April 5, 2001