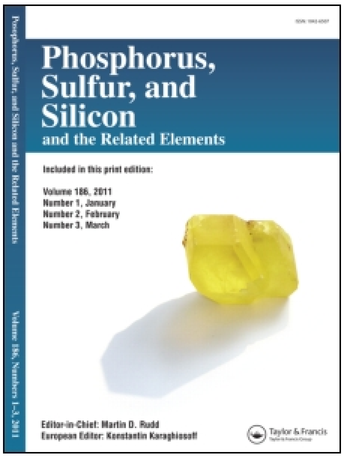


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

An Approach to Disulfide Synthesis Promoted by Sulfonyl Chloride in Sodium Bicarbonate Aqueous Media

Huilong Xiao[a]; Jiuxi Chen[a]; Miaochang Liu[a]; Huayue Wu[a]; Jinchang Ding[a]
[a] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, PR China

To cite this Article Xiao, Huilong , Chen, Jiuxi , Liu, Miaochang , Wu, Huayue and Ding, Jinchang(2009) 'An Approach to Disulfide Synthesis Promoted by Sulfonyl Chloride in Sodium Bicarbonate Aqueous Media', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 10, 2553 — 2559

To link to this Article: DOI: 10.1080/10426500802529051

URL: http://dx.doi.org/10.1080/10426500802529051

Phosphorus, Sulfur, and Silicon, 184:2553–2559, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802529051

An Approach to Disulfide Synthesis Promoted by Sulfonyl Chloride in Sodium Bicarbonate Aqueous Media

Huilong Xiao, Jiuxi Chen, Miaochang Liu, Huayue Wu, and Jinchang Ding
College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, PR China

A mild and efficient protocol for the synthesis of disulfides in aqueous media using mercaptans promoted by sulfonyl chloride is reported. This reaction offers the advantages of mild reaction conditions, short reaction time, high yields, and simple operation.

Keywords Aqueous media; disulfides; sulfonyl chloride

INTRODUCTION

The disulfide moiety exists in proteins and various natural products as well as pharmacologically active compounds.[1] For example, the synthesis of nucleotide derivatives,[2] addition reactions,[3] exchange reactions,[4] insert reactions,[5] and other applications[6] all exhibit chemistry associated with this group. Furthermore, polysulfide bonds have a well-known utility in the synthesis of polymers, such as rubber, and compounds that involve the disulfide moiety, which have been proved to be useful in the design of rechargeable lithium batteries.[7]

General methods for the synthesis of disulfides involve oxidation of mercaptans by various oxidants such as molecular oxygen,[8a] metal ions,[8b] $Bu_3SnOMe/FeCl_3$,[8c] nitric oxide,[8d] halogens,[8e–8h] sodium perborate,[8i] borohydride exchange resin (BER)-transition metal salt system,[8j] morpholine iodine complex,[8k] PCC,[8l] ammonium persulfate,[8m] $KMnO_4/CuSO_4$,[8n] H_2O_2,[8o] solvent-free permanganate,[8p] PVP-N_2O_4,[8q] and cesium fluoride-Celite,[8r] 2,6-dicarboxypyridinium

Received 8 July 2008; accepted 6 October 2008.

We are grateful to the Natural Science Foundation of Zhejiang Province (Y4080107) and Technology Program of Zhejiang Province (No. 2003C31026, 2005C31036) for financial support.

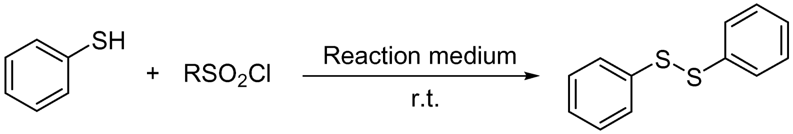
Address correspondence to Huayue Wu, College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325027, PR China. E-mail: hywu3@163.com

chlorochromate,[8s] and NH_4OH.[8t] Although a variety of catalytic systems have been explored for the synthesis of disulfides, some methods suffer from one or more disadvantages such as long reaction time, inefficient catalyst,[8b–c9] low yield, toxic solvent,[10] excess substrates or catalysts, and harsh reaction conditions. Moreover, in some cases they suffer from over-oxidation of the final product.[11] Therefore, the development of facile and environmental friendly methods for the synthesis of disulfides is essential for organic synthesis. In continuation of our interest in sulfur chemistry,[12] we herein wish to report a protocol for the synthesis of disulfides in aqueous media.

RESULTS AND DISCUSSION

Initially, we investigated the synthesis of phenyl disulfide in the presence of benzenesulfonyl chloride at room temperature under different conditions, and the results are listed in Table I.

TABLE I Synthesis of Phenyl Disulfide Under Different Reaction Conditions[a]

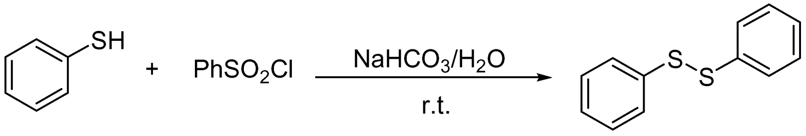


Entry	R	Reaction medium	Time (min)	Yield (%)[b]
1	C_6H_5	Pyridine	120	0
2	p-$CH_3C_6H_4$	Pyridine[11]	120	0
3	C_6H_5	Triethyl amine	120	80
4	C_6H_5	H_2O	120	10
5	C_6H_5	HCl/ H_2O (0.1 mol/L)	120	0
6	C_6H_5	$NaOH/H_2O$ (0.01 mol/L)	30	30
7	C_6H_5	$NaOH/H_2O$ (1 mol/L)	30	65
8	C_6H_5	$NaOH/H_2O$ (2.5 mol/L)	10	95
9	C_6H_5	$NaHCO_3/H_2O$ (Saturated)	10	96
10	C_6H_5	Na_2CO_3/H_2O (Saturated)	10	95
11	p-$CH_3C_6H_4$	$NaHCO_3/H_2O$ (Saturated)	10	95

[a] The reactions were performed starting from thiophenol (1 mmol) and sulfonyl chloride (0.5 mmol) in reaction medium (5 mL) at room temperature.

[b] Isolated yields.

TABLE II Synthesis of Phenyl Disulfide in the Saturated $NaHCO_3$ Solution at Room Temperature[a]



Entry	Sulfonyl Chloride (equiv.)	V/solvent (mL)	Yield (%)[b]
1	0.1	2	21
2	0.2	2	42
3	0.3	2	56
4	0.4	2	85
5	0.5	2	91
6	0.6	2	96
7	0.7	2	95
8	1.0	2	96
9	1.5	2	97
10	0.6	1	96
11	0.6	3	95
12	0.6	5	96

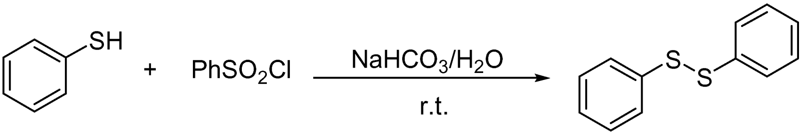
[a] Reaction conditions: thiophenol (1 mmol), room temperature, 10 min.
[b] Isolated yields.

Surprisingly, it was found that the phenyl disulfide (**2a**) was produced exclusively with excellent yields in alkaline aqueous media, such as $NaOH/H_2O$ (2.5 mol/L), saturated $NaHCO_3/H_2O$, and Na_2CO_3/H_2O for 10 min. However, a trace of **2a** was obtained using pyridine as solvent at the room temperature.[13] Encouraged by the results, subsequent studies were carried out to optimize the reaction. The results were summarized in Table II. It should be noted that 0.6 equiv benzenesulfonyl chloride and 1 mL solvent were efficient enough to promote the reaction. Increasing the amount of catalysts did not improve the yield significantly (Table II, entries 7–9). Finally, we achieved an optimized condition using 0.6 equiv benzenesulfonyl chloride in 1 mL saturated $NaHCO_3/H_2O$ solution at room temperature.

In the next stage, we studied the reaction scope for the synthesis of disulfides from various commercially available mercaptan derivatives under the optimized conditions (Table III).

As expected, this reaction proceeded smoothly, and the desired products were obtained with yields ranging from good to excellent. A

TABLE III Synthesis of Disulfides[a]



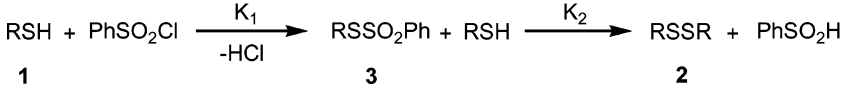
Entry	R	Product	Yield (%)[b]	Found Mp (°C) (Lit.)
1	C_6H_5	**2a**	97	55–57 (58–60)[15a]
2	$4\text{-}CH_3C_6H_4$	**2b**	96	38–40 (45–46)[15b]
3	$2\text{-}CH_3C_6H_4$	**2c**	91	Liquid[15c]c
4	$3\text{-}CH_3C_6H_4$	**2d**	90	Liquid[15d]d
5	$2,4\text{-}(CH_3)_2C_6H_3$	**2e**	98	Liquid[15e]e
6	$2\text{-}CH_3CH_2C_6H_4$	**2f**	93	Liquid[15f]f
7	$4\text{-}(CH_3)_2CHC_6H_4$	**2g**	90	Liquid[15g]g
8	$4\text{-}BrC_6H_4$	**2h**	83	89–90 (88–90)[15b]
9	$4\text{-}ClC_6H_4$	**2i**	89	68–70 (70–73)[15h]
10	$4\text{-}FC_6H_4$	**2j**	94	Liquid[15i]i
11	$4\text{-}OHC_6H_4$	**2k**	95	145–147 (149–150)[15j]
12	$2\text{-}NH_2C_6H_4$	**2l**	94	87–88 (93)[15k]
13	$2,3\text{-}(Cl)_2C_6H_3$	**2m**	91	144–146 (no report)[15l]
14	$4\text{-}CH_3OC_6H_4CH_2$	**2n**	86	91–93 (99)[15m]
15	$4\text{-}ClC_6H_4CH_2$	**2o**	95	50–52 (58–59)[15c]
16	$2\text{-}ClC_6H_4CH_2$	**2p**	94	85–87 (89–90)[15n]
17	$2\text{-}BrC_6H_4CH_2$	**2q**	82	66–68 (86–88)[15o]

[a] Reaction conditions: thiophenol (1 mmol), sulfonyl chloride (0.6 mmol), saturated $NaHCO_3$ solution (1 mL), room temperature, 10 min.

[b] Isolate yields.

series of mercaptans with electron-donating or electron-withdrawing groups attaching to the aromatic ring were investigated. The substitution groups on the aromatic ring have no obvious effect on the yields (Table III, entries 2–4). Moreover, it is observed that the desired products **2n–2q** were obtained from aliphatic mercaptans in good yields (Table III, entries 14–17). When the substrates bearing different nucleophilic groups such as 4-mercaptophenol and 2-aminobenzenethiol were used, interestingly, the reaction was completed with nucleophilic attack of the thiohydroxy, and the hydroxy or amino group remained untouched (Table III, entries 11–12). The easy isolation of final products by either filtration or extraction from the crude mixtures rendered this method practical in industrial applications.

A tentative mechanism for the formation of disulfides was proposed in Scheme 1. We propose that the reaction involves two steps. In the first



$$\underset{\mathbf{1}}{RSH} + PhSO_2Cl \xrightarrow[-HCl]{K_1} \underset{\mathbf{3}}{RSSO_2Ph} + RSH \xrightarrow{K_2} \underset{\mathbf{2}}{RSSR} + PhSO_2H$$

step, one molecule of mercaptans **1** reacts with benzenesulfonyl chloride and produces the thiolsulfonates **3**. In the second step, the other molecule of **1** reacts with **3** and delivers disulfides **2** at the expense of the thiolsulfonates in the alkaline aqueous solution. The initially formed thiolsulfonates are more reactive with thiophenol than the benzenesulfonyl chloride ($K_2 \gg K_1$),[14] so the reaction produces disulfides exclusively. The $NaHCO_3$ plays a role to eliminate the byproduct of acids.

EXPERIMENTAL

All products were known compounds and identified by comparison with authentic samples. Melting points were measured on Digital Melting Point Apparatus WRS-1B and are uncorrected. IR spectra were recorded on a Avatar 370 FI-infrared spectrophotometer. All ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrophotometer in $CDCl_3$ or DMSO-d_6 as a solvent with TMS as the internal standard. *J* values are given in Hz.

General Procedure

To a mixture of saturated $NaHCO_3$ solution (1 mL) and thiophenol (1 mmol), benzenesulfonyl chloride (0.5 mmol) was added. The mixture was stirred at room temperature for 10 min, and the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water and dried over sodium sulfate. The organic layer was concentrated under reduced pressure to afford crystalline (or liquid) dialkyl disulfides. The pure liquid products were obtained by purification on a short silica gel column using petroleum ether as the eluent. The pure solid products were obtained by purification recrystallization from ethanol.

REFERENCES

[1] (a) F. Freeman, M. Aregullin, and E. Rodriguez, *Rev. Heteroat. Chem.*, **9,** 1 (1993) (b) Y. Kishi, S. Nakatsuga, T. Fukuyama, and M. Havel, *J. Am. Chem. Soc.*, **95,** 6493 (1973) (c) S. Ito, A. Ota, H. Suhara, K. Tabashi, and Y. Kawashima, *Chem. Pharm. Bull.*, **41,** 1066 (1993).

[2] T. Mukaiyama and M. Hashimoto, *J. Am. Chem. Soc.*, **94,** 8528 (1972).

[3] (a) T. Kondo and T. A. Mitsudo, *Chem. Rev.*, **100,** 3205 (2000) (b) S. Kumar and L. Engman, *J. Org. Chem.*, **71,** 5400 (2006).

[4] (a) K. Tanaka and K. Ajiki, *Tetrahedron Lett.*, **45,** 5677 (2004) (b) R. D. Bach, O. Dmitrenko, and C. Thorpe, *J. Org. Chem.*, **73,** 12 (2008).

[5] (a) J. Dowsland, F. McKerlie, and D. J. Procter, *Tetrahedron Lett.*, **41,** 4923 (2000) (b) A. Z. Rys and D. N. Harpp, *Tetrahedron Lett.*, **41,** 7169 (2000).

[6] (a) K. Hiroi, H. Miura, K. Kotsuji, and S. Sato, *Chem. Lett.*, **10,** 559 (1981) (b) I. Nakagawa and T. Hata, *Tetrahedron Lett.*, **16,** 1409 (1975) (c) G. A. Russell and S. V. Kulkarni, *J. Org. Chem.*, **58,** 2678 (1993) (d) T. Mukaiyama, K. Goto, R. Matsueda, and M. Ueki, *Tetrahedron Lett.*, **11,** 5293 (1970).

[7] T. Maddanimath, Y. B. Khollam, M. Aslam, I. S. Mulla, and K. Vijayamohanan, *J. Power Sources*, **124,** 133 (2003).

[8] (a) K. T. Liu and Y. C. Tong, *Synthesis*, 669 (1978) (b) T. J. Wallace, *J. Org. Chem.*, **31,** 3071 (1966) (c) T. Sato, J. Otera, and H. Nozaki, *Tetrahedron Lett.*, **31,** 3591 (1990) (d) W. A. Pryor, D. F. Church, C. K. Govindan, and G. Crank, *J. Org. Chem.*, **47,** 156 (1982) (e) J. R. Schaeffer, C. T. Goodhue, H. A. Risle, and R. E. Stevens, *J. Org. Chem.*, **32,** 392 (1967) (f) J. Drabowicz and M. Mikolajczyk, *Synthesis*, 32 (1980) (g) M. H. Ali and M. McDermott, *Tetrahedron Lett.*, **43,** 6271 (2002) (h) T. Aida, T. Akasaka, N. Furukawa, and S. Oae, *Bull. Chem. Soc. Jpn.*, **49,** 1441 (1976) (i) A. McKillop, D. Koyuncu, A. Krief, W. Dumont, P. Renier, and M. Trabelsi, *Tetrahedron Lett.*, **31,** 5007 (1990) (j) J. Choi and N. M. Yoon, *J. Org. Chem.*, **60,** 3266 (1995) (k) K. Ramadas and N. Srinivasan, *Synth. Commun.*, **26,** 4179 (1996) (l) P. Salehi, A. Farrokhi, and M. Gholizadeh, *Synth. Commun.*, **31,** 2777 (2001) (m) R. S. Varma, H. M. Meshram, and R. Dahiya, *Synth. Commun.*, **30,** 1249 (2000) (n) N. A. Noureldin, M. Caldwell, J. Hendry, and D. G. Lee, *Synthesis*, 1587 (1998) (o) B. J. Evans, J. T. Doi, and W. K. Musker, *J. Org. Chem.*, **55,** 2337 (1990) (p) A. Shaabani and D. G. Lee, *Tetrahedron Lett.*, **42,** 5833 (2001) (q) N. Iranpoor, H. Firouzabadi, and A. R. Pourali, *Tetrahedron*, **58,** 5179 (2002) (r) S. T. A. Shah, K. M. Khan, M. Fecker, and W. Volter, *Tetrahedron Lett.*, **44,** 6789 (2003) (s) M. Tajbakhsh, R. Hosseinzadeh, and A. Shakoori, *Tetrahedron Lett.*, **45,** 1889 (2004) (t) M. Carril, R. SanMartin, E. Dominguez, and I. Tellitu, *Green Chem.*, **9,** 315 (2007).

[9] M. Arisawa, C. Sugata, and M. Yamaguchi, *Tetrahedron Lett.*, **46,** 6097 (2005).

[10] S. C. Banfield, A. T. Omori, H. Leisch, and T. Hudlicky, *J. Org. Chem.*, **72,** 4989 (2007).

[11] (a) N. Iranpoor and B. Zeynizadeh, *Synthesis*, 49 (1999) (b) S. M. S. Chauhan, A. Kumar, and K. A. Srinivas, *Chem. Commun.*, 2348 (2003) (c) S. Patel and B. K. Mishra, *Tetrahedron Lett.*, **45,** 1371 (2004) (d) M. Hashemi, H. Ghafuri, and Z. Karimi-Jaberi, *J. Sulfur Chem.*, **27,** 165 (2006) (e) B. Karami, M. Montazerozohori, and M. H. Habibi, *Molecules*, **10,** 1358 (2005).

[12] (a) J. X. Chen, H. Y. Wu, C. Jin, X. X. Zhang, Y. Y. Xie, and W. K. Su, *Green Chem.*, **8,** 330 (2006) (b) W. K. Su, J. X. Chen, H. Y. Wu, and C. Jin, *J. Org. Chem.*, **72,** 4524 (2007) (c) W. K. Su, J. J. Li, Z. G. Zheng, and Y. C. Shen, *Tetrahedron Lett.*, **46,** 6037 (2005).

[13] F. I. Ali, I. A. Hashmi, B. S. Siddiqui, and M. Rasheed, *Synth. Commun.*, **37,** 2461 (2007).

[14] M. G. Ranasinghe and P. L. Fuchs, *Synth. Commun.*, **18,** 227 (1988).

[15] (a) P. Kielbasinski, J. Drabowicz, and M. Mikolajczyk, *J. Org. Chem.*, **47,** 4806 (1982) (b) H. W. Pinnick, M. A Reynolds, R. T. Mcdonald Jr., and W. D. Brewster, *J. Org. Chem.*, **45,** 930 (1980) (c) N. B. Islam, H. Kwart, and S. Khan, *J. Chem. Eng. Data*, **30,** 509 (1985) (d) G. D. Figuly and J. C. Martin, *J. Org. Chem.*, **45,** 3728 (1980) (e) S. Oae and H. Togo, *Bull. Chem. Soc. Jpn.*, **56,** 3813 (1983) (f) S. Krishnamurthy and

D. Aimino, *J. Org. Chem.*, **54,** 4458 (1989) (g) R. Silvestri, G. De Le Martino, G. La Regina, M. Artico, S. Massa, L. Vargiu, M. Mura, A. G. Loi, T. Marceddu, and P. La Colla, *J. Med. Chem.*, **46,** 2482 (2003) (h) M. Montazerozohori, S. Joohari, B. Karami, and N. Haghighat, *Molecules*, **12,** 694 (2007) (i) B. Karami, M. Montazerozohori, and M. H. Habib, *J. Chem. Res.*, **8,** 490 (2006) (j) A. Onoue, M. Kawamura, T. Nishi, M. Yoshikawa, and Y. Lida, J.P. Patent, **62,** 089, 655 A (1987) (k) G. Crank and M. I. H. Makin, *Tetrahedron Lett.*, **20,** 2169 (1979) (l) S. L. Colletti, J. R. Tata, H. C. Shen, F. X. Ding, J. L. Frie, J. E. Imbriglio, and W. C. Chen, W.O. Patent 2,006,057,922 A2 (2006) (m) V. I. Cohen, *Helv. Chim. Acta*, **59,** 840 (1976) (n) J. E. Christian, G. L. Jenkins, L. C. Keagle, and J. A. Crum, *J. Am. Pharm. Assoc.*, **35,** 328 (1946) (o) A. R. Kiasat, B. Mokhtari, F. Kazemi, S. Yousefi, and M. Javaherian, *J. Sulfur Chem.*, **28,** 171 (2007).