Silver Ion Mediated In Situ Synthesis of Mixed Diaryl Sulfides from Diaryl Disulfides

Prasanta Gogoi,[a] Sandhya R. Gogoi,[b] Mukul Kalita,[a] Pranjit Barman*[a]

[a] Department of Chemistry, National Institute of Technology, Silchar 788010, Assam, India
Fax +91(3842)224797; E-mail: barmanpranjit@yahoo.co.in

[b] Department of Chemical Science, Tezpur University, Tezpur 784028, Assam, India

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Abstract: The $AgNO_3$-mediated in situ scission of aromatic disulfides in the presence of electron-rich aromatic compounds results in the efficient synthesis of diaryl sulfides. Key features of this new methodology are high yields of aromatic and heteroaromatic sulfides, mild reaction conditions, simplicity, simple workup, and avoiding foul-smelling reactants like thiols.

Key words: in situ synthesis, disulfide, sulfenylation, metal-mediated

In recent years sulfenylation reactions of aromatic and heteroaromatic compounds have received much attention due to the wide range of applications of the resulting sulfides.[1] For example, heteroaromatic 3-thioindoles and 2-thiopyrroles are used in the treatment of diseases including obesity, cancer, heart disease and bacterial infections.[2] On the other hand, sulfenylated phenols have been employed as agrochemicals.[3] Sulfenylation of electron-rich heteroaromatic or aromatic systems with nucleophilic sulfenylating reagents like mercaptides, or thioethers is difficult and sulfenylation with electrophilic sulfenyl halides is impractical due to their moisture sensitivity and thermolability.[4,5] Metals like vanadium,[6] copper,[7] iron,[8] nickel,[9] cobalt,[10] palladium,[11] and indium[12] have been used in the preparation of diaryl sulfides. Though these are the convenient methods, they have their own limitations including harsh reaction conditions, poor yield of product and sometimes generation of disulfides as byproducts.[6] Very recently, in 2012, Ge and Wei reported an interesting procedure for an iodine-catalyzed sulfenylation reaction using indoles and disulfides as the reaction partners.[13] This novel reaction was limited to indoles only. In this paper we describe the preparation of aromatic and heteroaromatic sulfides by nucleophile-promoted reactions of disulfides with nucleophilic substrates. The methodology involves enhancing the electrophilicity of the disulfides so that they can serve as sulfenium-transfer agents to the electron-rich aromatic and heteroaromatic substrates. The side product of the reaction is the silver mercaptide that can be easily trapped with benzyl chloride or can be re-oxidized to the corresponding disulfide. The resulting benzyl thioethers may be used as precursors for sulfenyl halides[14] which, in turn, can be used as sulfenylating agents.[15] The main advantage of using silver salts is that the silver ion makes one sulfur atom of the disulfide group more electrophilic and this is preferentially attacked by nucleophiles. There are various merits of sulfenylation with disulfides. Other sulfenylating reagents such as sulfenyl halides are not easily available or are difficult to prepare, whereas disulfides can be easily prepared.[16] Sulfenyl halides are sensitive to hydroxylic solvents particularly at elevated temperature but disulfides are not. Finally, in the reaction with sulfenyl halides or thiols, the corresponding disulfides are formed as byproducts.[18]

At first we examined the reaction of β-naphthol **2f** with 2-nitrophenyl disulfide (**1b**) under various reaction conditions as shown in Table 1. We tried different solvents such as THF, MeCN, CH_2Cl_2, $CHCl_3$, EtOH, DMF–EtOH and water. However, it was found that DMF–EtOH in a 1:1 ratio was the best for phenolic substrates in terms of the percentage of the product yield and ethanol was best for amines.

The sulfenylation reaction was carried out with indole, β-naphthol, α-naphthol, aniline and phenol. It was found that for the phenolic substrates C-sulfenylation occurred, whereas for aniline, N-sulfenylation was observed (Table 2).

The in situ sulfenylation of electron-rich aromatic and heteroaromatic systems such as, β-naphthol, α-naphthol, aniline, phenol, and indole with four different disulfides, 1,2-bis(phenyl) disulfane, 1,2-bis(2-nitrophenyl) disulfane, 1,2-bis(4-nitrophenyl) disulfane and 1,2-bis(4-chlorophenyl) disulfane in the presence of silver nitrate was performed. Except for aniline all other substrates gave thioethers, whereas aniline gave the corresponding sulfenamides (Table 2, entries 5, 10, 15 and 20). The effect of solvent polarity on the reaction was found to be substrate dependent. For example the DMF–ethanol mixture was found to be the best solvent for sulfenylation of phenols (Table 2, entries 4, 9, 14 and 19) whereas, ethanol was found to be the most suitable solvent for sulfenamide (Table 2, entries 5, 10, 15 and 20) formation.

These sulfenylations probably involve coordination of the Ag^+ ion with one of the two sulfur atoms of the symmetrical disulfide molecule with nucleophilic addition to the non-complexed sulfur leading to S–S bond scission in situ and formation of the products (Scheme 1) as first proposed by Davis et al.[19–21] The precipitate of the silver mer-

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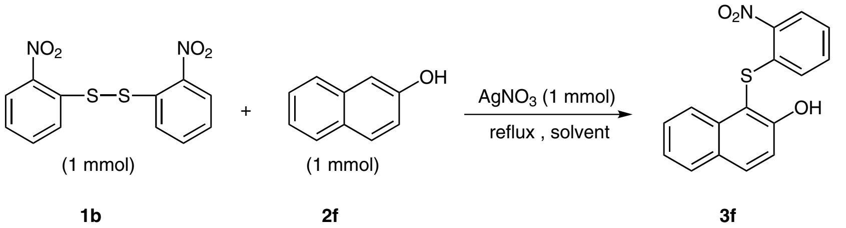
Table 1 Silver Ion Mediated Synthesis of 1-Sulfanyl-2-naphthol (**3f**) under Various Conditions[17]

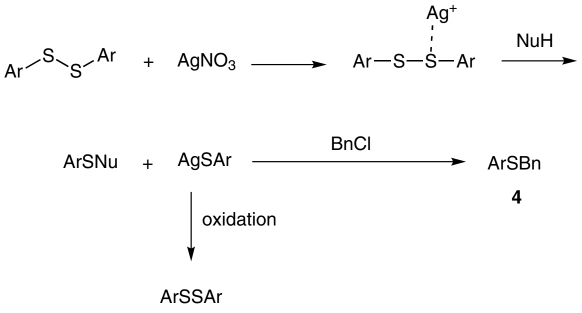


Entry	Solvent	Time (h)	Yield (%)[a]
1	CH_2Cl_2	10	50
2	MeOH	12	40
3	MeCN	10	20
4	DMF	10	60
5	EtOH	10	55
6	**DMF–EtOH**	**10**	**75**
7	$CHCl_3$	12	40
8	H_2O	12	trace

[a] Yield of isolated **3f**.

captide could be either trapped by benzylation to form aryl benzyl thioether **4** or converted to the starting disulfide by oxidation.[22]

In summary, silver nitrate is found to be an efficient reagent for sulfenylation of electron-rich aromatic and heteroaromatic systems. This method has added advantages of simple experimental procedure, mild and neutral reaction conditions and high yields of the desired products. In addition the resulting silver mercaptide can be easily trapped with benzyl chloride or oxidized back to the disulfide.



Scheme 1 A plausible mechanism for the formation of sulfides

Table 2 Synthesis of Mixed Diaryl Sulfides from Diaryl Disulfides

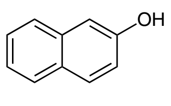
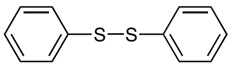
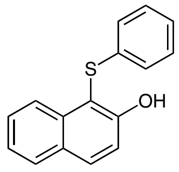
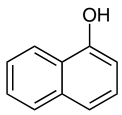
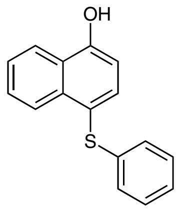
Entry	Substrate **2**	Disulfide **1**	Product **3**	Time (h)	Yield (%)[a]
1		 **1a**		8	78
2		**1a**		9	60

Table 2 Synthesis of Mixed Diaryl Sulfides from Diaryl Disulfides (continued)

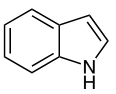
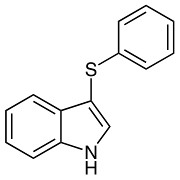
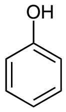
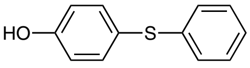
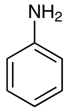
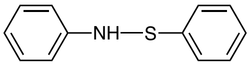
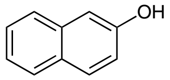
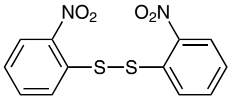
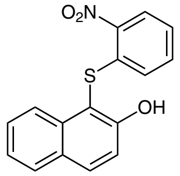
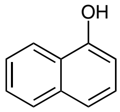
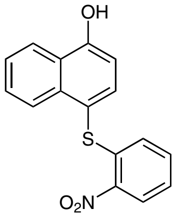
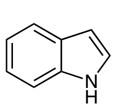
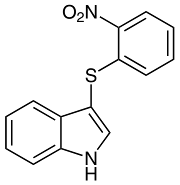
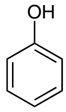
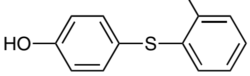
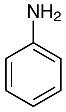
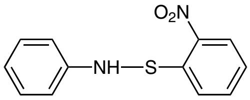
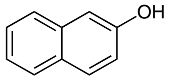
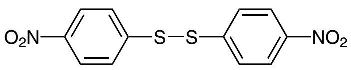
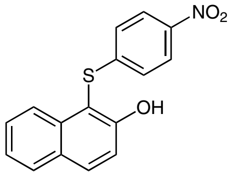
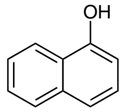
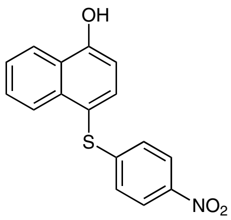
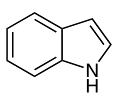
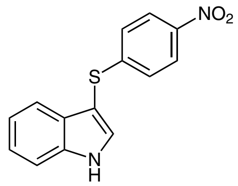
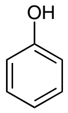
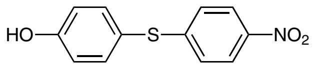
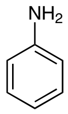
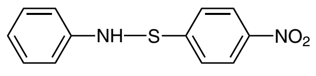
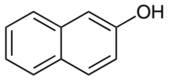
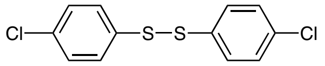
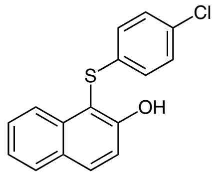
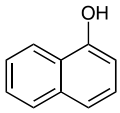
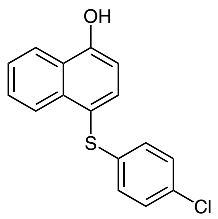
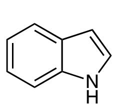
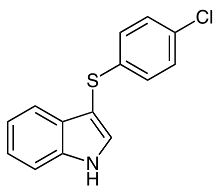
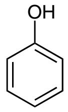
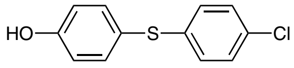
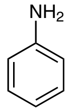
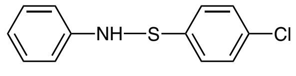
Entry	Substrate **2**	Disulfide **1**	Product **3**	Time (h)	Yield (%)[a]
3		**1a**		13	82
4		**1a**		4	85
5		**1a**		5	75
6		 **1b**		10	75
7		**1b**		12	30
8		**1b**		12	60
9		**1b**		6	80
10		**1b**		3	85
11		 **1c**		16	80
12		**1c**		20	45

Table 2 Synthesis of Mixed Diaryl Sulfides from Diaryl Disulfides (continued)

Entry	Substrate **2**	Disulfide **1**	Product **3**	Time (h)	Yield (%)[a]
13		**1c**		15	65
14		**1c**		7	87
15		**1c**		2	78
16		 **1d**		12	70
17		**1d**		19	35
18		**1d**		16	60
19		**1d**		4	85
20		**1d**		6	75

[a] Yield of isolated **3**.

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Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291. (c) Silvestri, R.; De Martino, G.; La Regina, G.; Artico, M.; Massa, S.; Vargiu, L.; Mura, M.; Loi, A. G.; Marceddu, T.; La Colla, P. *J. Med. Chem.* **2003**, *46*, 2482. (d) Campbell, J. A.; Broka, C. A.; Gong, L.; Walker, K. A. M.; Wang, J.-H. *Tetrahedron Lett.* **2004**, *45*, 4073.

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(17) (a) **Typical Procedure**: $AgNO_3$ (0.17 g, 1 mmol), and disulfide **1b** (0.30 g, 1 mmol), were added to EtOH (1.0 mL) and DMF (1.0 mL) and stirred at r.t. for 5 min. After that, β-naphthol **2f** (0.14 g, 1 mmol) was added. Then the contents were refluxed with stirring for 10 h at 110 °C. The precipitated silver mercaptide was filtered and the solvent removed at reduced pressure. The residue obtained was extracted with CH_2Cl_2 and dried over anhyd Na_2SO_4. Removal of the CH_2Cl_2 under reduced pressure gave sulfide **3f** which was purified by column chromatography (EtOAc–hexane, 1:9).
(b) **Synthesis of Aryl Benzyl Thioethers 4**: Silver mercaptide (0.26 g, 1 mmol) and benzyl chloride (0.15 g, 1.2 mmol) in EtOH (5 mL) were refluxed for 6 h. Then NaOH (0.2 g, 5 mmol) was added and reflux continued for an additional 2 h. Upon cooling, NaOH (2 M, 30 mL) was added to the reaction mixture followed by extraction with CH_2Cl_2. The organic phase was washed with NaOH (2 M, 2 × 25 mL), H_2O (25 mL) and brine (25 mL), dried over anhyd Na_2SO_4, filtered and the solvent removed under reduced pressure to give the aryl benzyl thioether.
Representative Analytical Data; 1-(2-Nitrophenylthio)napthalen-2-ol (3f): The title compound was prepared according to the typical procedure in 75% yield (0.223 g) as a yellow solid (mp 170–171 °C). IR (KBr): 3435, 2905, 2845, 1588, 1545, 1497, 1335, 1055, 940, 865, 746, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.27$ (d, $J = 7.9$ Hz, 1 H), 8.16 (d, $J = 8.6$ Hz, 1 H), 7.86–7.97 (m, 6 H), 7.23 (s, 1 H), 6.84 (d, $J = 7.6$ Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.2$, 156.3, 155.3, 153.1, 148.6, 143.5, 138.4, 136.7, 130.2, 129.1, 128.5, 127.2, 118.6, 117.4, 115.0. HRMS (ESI): m/z $[M + H^+]$ calcd for $C_{16}H_{11}NO_3S$: 298.0460; found: 298.0463. Anal. Calcd for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.58; H, 3.91; N, 4.88.

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