

Photoinitiated Synthesis of Sulfides in Water

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Herein, we report a synthetic route to obtain aryl sulfides using inexpensive and non-toxic reactants and water as solvent, that avoids the use of catalysts or heating. The photoinduced reaction between soluble substrates and a series of thiols in alkaline aqueous medium produces the corresponding sulfides in moderate to good yields.

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Introduction

Aryl sulfides are important structural motifs often found in biologically and pharmaceutically active molecules.^[1] For instance, aryl sulfides are present in compounds that are employed to treat Alzheimer's, Parkinson's, cancer, malaria, and HIV diseases.^[2] In the last few decades, a large number of transition metal-catalyzed cross-coupling reactions involving palladium,^[3] nickel,^[4] copper,^[5] cobalt,^[6] iron,^[7] or indium^[8] have been developed for the synthesis of aryl sulfides in high yields. However, these methods present some drawbacks such as the use of expensive and toxic metal catalysts. Thus, the development of new methodologies for the synthesis of these compounds represents an interesting challenge.

In light of this, radical nucleophilic reactions have been proposed as an attractive synthetic route to symmetrical and unsymmetrical sulfides. These photoinduced reactions take place between non-activated aryl halides and a variety of sulfur anions, such as arene and alkanethiolates, MeCOS⁻ and H₂N(HN)CS⁻.^[9–11] Most of the reported methods involve the use of liquid ammonia or DMSO as solvent. Thus, the replacement of these commonly used solvents by an environmentally friendly solvent could be of high value.

Considering that the design of sustainable protocols towards useful industrial applications represents an important target in chemistry nowadays, the use of a benign solvent such as water is of great interest due to the advantages associated with its intrinsic features (non-toxicity, low cost, safe handling, non-flammability, and easy isolation of final products).^[12,13] Recently, the synthesis of diaryl sulfides from aryl halides and potassium thiocyanate using water as the solvent and copper salts as a catalyst has been reported.^[14] However, these methods require either phase-transfer agents or solid supports.

We report, herein, a new metal-free synthetic route to obtain aryl sulfides in moderate to good yields based on photoinduced reactions between different water-soluble aryl halides (such as

1-bromo-2-naphthol) and a series of thiols in alkaline aqueous medium.

Result and Discussion

The photoinduced reactions of 1-bromo-2-naphthol (**1**) with different aromatic thiols (**2a–2d**) were first studied, and the results are summarized in Table 1. The reaction of 1-bromo-2-naphthol (**1**) with thiophenol (**2a**) and equimolar amount of base in a 1 : 9 : 9 ratio under nitrogen atmosphere formed 1-(phenylthio)-2-naphthol (**3a**) in 68 % yield (Table 1, entry 1). An increase in the yield was observed when the reaction was carried out with excess base (Table 1, entry 2). Then, different synthesis conditions were examined in order to optimize the product formation.

When the reaction time was reduced by half and the nitrogen atmosphere was replaced by air, the product **3a** was still formed in good yields. Under these conditions, the reaction between **2a** and **1** at a ratio of 4 : 1 formed **3a** in 67 % yield (Table 1, entry 3). When the ratio was decreased to 2 : 1, the yield of the product decreased by 10 % (Table 1, entry 4). Moreover, when KO^tBu was replaced by KOH (an inorganic and less expensive base), the yield of **3a** increased with respect to that observed in the previous reaction (Table 1, entry 5). The reaction does not occur in the absence of light (Table 1, entry 6), indicating that the photostimulation is necessary for the progress of the reaction. These results show that the product can be synthesized in good yields under mild conditions.

The substitution product 1-(2-naphthylthio)-2-naphthol (**3b**) was obtained in 77 % yield (Table 1, entry 7) through the reaction of **1** with 2-naphthalenethiol (**2b**). When the base used was KOH, the yield of **3b** increased (Table 1, entry 8). This increase was similar to that observed for the thiol **2a** (Table 1, entries 4 and 5).

Following this study, the C–S coupling reaction was examined with heterocyclic thiols. The photoinduced reaction of the substrate **1** with 2-mercaptobenzoxazole (**2c**) in a 1 : 2 ratio

Table 1. Photoinduced reactions of thiols with 1-bromo-2-naphthol in water^A

Entry	Thiol [equiv.]	Base [equiv.]	Substitution product	Yield [%] ^B	
1 ^{C,D}		9		68	
2 ^{C,D}		12		82	
3		4		67	
4		2		57	
5 ^E		2		65	
6 ^F		9		– ^G	
7				8	77
8 ^E				16	82
9		9		68	
10 ^D		9		65	
11		1.5		57	
12		1.5		42	
13 ^E		1.5		52	
14 ^F		4		–	
15		5		51 ^H	
16 ^F		5		Trace	

^AReactions were carried out using 1-bromo-2-naphthol (0.25 mmol), thiol, and base (KO^tBu) in water (5 mL) for 3 h.

^BDetermined by gas-liquid chromatography (GLC) using the internal standard method on the basis of the concentration of **1**.

^CReaction carried out under N₂ atmosphere.

^DReaction time: 6 h.

^EBase: KOH.

^FIn the dark at 30°C.

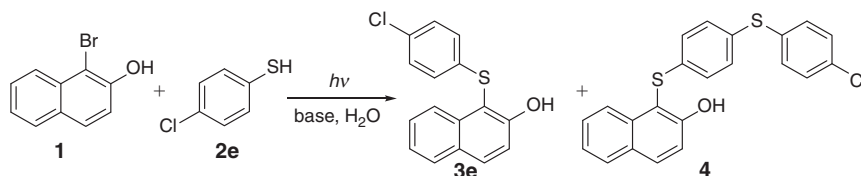
^GProduct not found.

^HIsolated yield.

and in the presence of an excess of base afforded the product **3c** in 68 % yield (Table 1, entry 9). A 2-fold increase in reaction time did not improve the yield (Table 1, entry 10). When the concentration of **2c** was decreased (Table 1, entry 11), there was almost no change in the yield of the product. Also, a dependence between the yield and the amount of base was observed (Table 1, entry 12). Moreover, in the reaction carried out with KOH as base, the product **3c** was obtained in moderate yield (Table 1, entry 13). In the reaction performed using 2-mercaptobenzothiazole (**2d**), the substitution product **3d** was formed in 57% yield. Again, the reactions did not occur in the dark, as shown in Table 1, entries 14 and 16. In summary, the photoinduced reaction of

1-bromo-2-naphthol with heterocyclic thiols **2c–2d** afforded the desired products in good yields, using water as the solvent.

Based on the promising results obtained with these thiols, we studied the reaction of 1-bromo-2-naphthol with 4-chlorothiophenol (**2e**) in water (Table 2). In the reaction of **1** with **2e** in a 1:3.5 ratio and with excess of base (Table 2, entry 1), the product **3e** was obtained in 18 % yield, and surprisingly, product **4** was also obtained in 40 % yield. This compound is the product of a substitution on the chlorine atom of **3e**. Considering that two C–S bonds are formed in a single step, we can say that the product **4** was obtained in very good yield. In addition, the remaining chlorine atom in **4** can be potentially substituted.

Table 2. Photoinduced reactions of 4-chlorothiophenol with 1-bromo-2-naphthol in water^A

Entry	Thiol [equiv.]	Base [equiv.]	Substitution product and yield [%] ^B
1		3.5	3e , 18; 4 , 40
2 ^C		3	3e , 12; 4 , 50
3 ^{C,D}		10	3e , 25; 4 , 53 ^E
4 ^F		9	— ^G

^AReactions were carried out using 1-bromo-2-naphthol (0.25 mmol), thiol, and base (KO^tBu) in water (5 mL) for 3 h.

^BDetermined by GLC using the internal standard method on the basis of the concentration of **1**.

^CReaction time: 6 h.

^DAmount of 1-bromo-2-naphthol: 1 mmol.

^EIsolated yield.

^FIn the dark at 30°C.

^GProduct not found.

Table 3. Thermal reactions of thiols with 1-bromo-2-naphthol (1) in water^A

Entry	Thiol [equiv.]	Base [equiv.]	Temperature [°C]	Time [h]	Substitution product and yield [%] ^B
1	2b , 5	12	120	24	3b , 97
2	2b , 5	12	120	6	3b , 96
3	2b , 5	12	120	3	3b , 83
4	2b , 5	12	120	1	3b , 54
5	2b , 2.5	12	120	6	3b , 94
6	2b , 2.5	12	80	6	3b , 78
7 ^C	2c , 2	12	80	6	3c , —
8 ^C	2d , 2	12	80	4	3d , —
9 ^{C, D}	2e , 3	5	80	6	3e , 36; 5^E , 18
10 ^C	2e , 3	4	120	7	3e , 25; 5^E , 35

^AThermal reactions conducted in closed system in the absence of N₂ atmosphere using 0.5 mmol of **1** and KOH as base.

^BDetermined by GLC using the internal standard method on the basis of the concentration of **1**.

^CAmount of 1-bromo-2-naphthol: 0.3 mmol.

^DBase: KO^tBu.

^E**5**: 2-Naphthol.

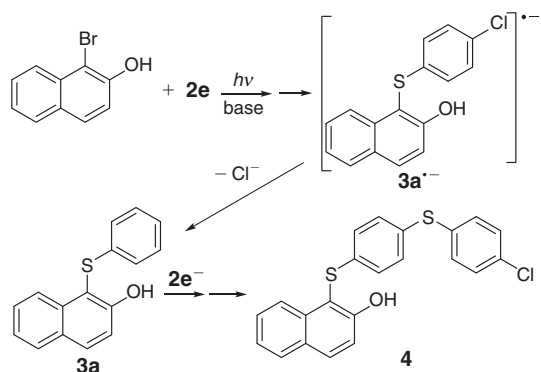
In order to analyze the product distribution, the ratio of **1** : **2e** and the concentration were modified (Table 2, entries 3 and 4). However, no change in the yield was observed. In all cases, **4** was the major product. The reaction performed in the dark did not lead to the formation of any products (Table 2, entry 4), suggesting that the reaction requires photostimulation to proceed.

To evaluate the contribution of polar mechanism to our results,^[15] thermal reactions were performed (Table 3). At temperatures below 50°C, the reaction products were observed in traces, demonstrating that there is no competition between thermal and photoinduced reactions in water. At 120°C, product **3b** is formed, and its yield depends on reaction time and the ratio of **1/2b** (Table 3, entries 1–5); at 80°C, the yield of **3b** decreased (Table 3, entry 6). The products of the reactions involving heterocyclic thiols were not observed under these conditions (Table 3, entries 7 and 8).

The thermal reaction using thiol **2e** gave product **3e** only. With an increase in the temperature, the yield of **3e** did not increase, but the amount of the substrate-decomposition product (2-naphthol) increased (Table 3, entries 9 and 10). In both reactions, product **4** was not observed.

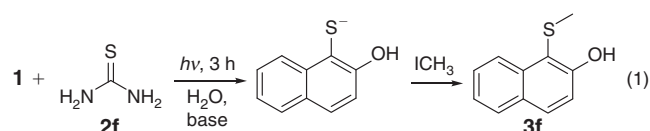
In view of the results, we attempted to explore the mechanism of the photoinduced reaction. For this purpose, the reaction using product **3e** as substrate and thiol **2e** in the presence of base and light irradiation was carried out. Under these conditions, only product **4** was formed. This result, the lack of reaction in the dark (Table 2, entry 4), and the results of the thermal reactions (Table 3, entries 9 and 10) suggest a photoinduced electron transfer mechanism, in which the radical anion **3e^{•-}** acts as an intermediate (Scheme 1).^[16]

Based on the good results mentioned above, and with the aim of obtaining an aryl-alkyl sulfide, the one-pot, two-step method

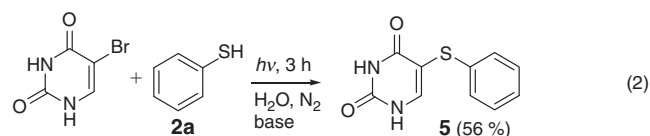


Scheme 1. Proposed mechanism.

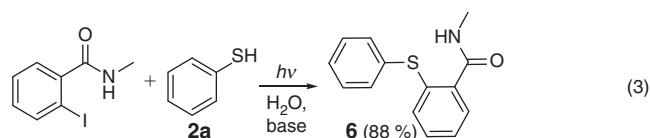
was studied.^[11] The photoinduced reaction of 1-bromo-2-naphthol with thiourea in a 1:10 ratio was carried out (Eqn 1). After irradiation, the ArS^- ions obtained by the aromatic substitution was quenched with methyl iodide, affording product ArSMe (**3f**) in 67% yield in a one-pot procedure. Different alkyl moieties can be introduced through this reaction if methyl iodide is replaced by other primary alkyl halides. In order to improve the reaction conditions, inexpensive reactants (sodium sulfide as nucleophile and KOH as base) were used. Under these conditions, a 63% yield of **3f** was obtained. These reactions did not occur in the dark.



Finally, in an attempt to expand the substrate scope, other water-soluble halides were studied. The photoinduced reaction of 5-bromouracil with thiophenol **2a** was performed in water under nitrogen atmosphere (Eqn 2), producing a 56% yield of the product **5**.^[17] The synthesis of this product using microwave heating and different organic solvents has been reported with comparable yield.^[18]



In the reaction of the substrate 2-iodo-N-methylbenzamide with thiophenol **2a** and base (1:9:9 ratio), the product **6** was obtained in 88% yield (Eqn 3). The yield of product was similar to that obtained from the reaction carried out in nitrogen atmosphere (80%). As in the previous cases, products **5** and **6** were not obtained under dark conditions.



Conclusions

We have reported a simple and inexpensive method for the metal-free formation of aryl-sulfur bonds at room temperature using water as a solvent. The studied reactions afforded diaryl,

aryl-alkyl, and aryl-heteroaryl sulfides in good yields. The current findings represent an improvement over previous protocols, which require the presence of copper-containing catalysts or a solid support in water.

The method reported in this manuscript can generate unsymmetrical sulfides under mild conditions. Experimental evidence is in accordance with a photoinduced electron transfer mechanism, and the results demonstrate that there is no competition between this mechanism and polar mechanism under the conditions investigated herein.

Experimental

Materials and Methods

All starting materials were purchased from Sigma-Aldrich. They were used without further purification. DMSO was dried and stored under molecular sieves (4 Å). ¹H NMR and ¹³C NMR spectra were recorded on 400 MHz nuclear magnetic resonance spectrometers. Gas chromatography analyses were performed on a chromatograph (Hewlett Packard 6890 series) equipped with a flame ionization detector and an HP-5 capillary column (30 m × 0.32 mm × 0.25 μm film thickness). Gas chromatography mass spectrometry analyses were carried out on a Shimadzu GC-MS QP 5050 spectrometer, using a Vf-5 ms 30 m × 0.25 mm × 0.25 μm column. High-resolution mass spectrometry (HRMS) was conducted on a Bruker MicroTOF Q II, operated with an electrospray ionization (ESI) or atmospheric pressure photoionization source operated in positive or negative mode, using nitrogen as nebulizing and drying gas and 10 mM sodium formate as internal standard for calibration purposes. Irradiation was conducted in a reactor equipped with two 400-W lamps emitting at a maximum of 350 nm (Philips Model HPT; air- and water-refrigerated). Column chromatography was performed on silica gel (70–270 mesh).

General Procedure for Reactions of 1-Bromo-2-naphthol and Thiols

The following procedure is representative of all the reactions of 1-bromo-2-naphthol with thiols. The reactions were carried out in a 25-mL three-neck round-bottom flask equipped with nitrogen inlet and magnetic stirrer. To degassed water (5 mL; using a rotary evaporator), potassium *t*-butoxide (280 mg, 2.5 mmol) was added. After total dissolution of the base, thiophenol (275 mg, 2.5 mmol) was added and stirred for 5 min. Then, 1-bromo-2-naphthol (111 mg, 0.5 mmol) was added. The reaction mixture was irradiated for 3 h. After that, it was quenched with an excess of ammonium nitrate and water (10 mL) was added. It was then extracted with dichloromethane (3 × 10 mL). The organic layer was dried over MgSO_4 , filtered, and concentrated to give a residue, which after radial chromatography on silica gel (petroleum ether/acetone) gave 1-phenylthio-2-naphthol (**3a**) as a white solid.

A similar procedure was used in the case of reactions in the absence of nitrogen atmosphere. The system was closed but not purged of atmospheric oxygen.

Compound Characterization

Products were isolated by column or radial chromatography (hexane/ethyl acetate: 1:1 or 1.5:1).

1-(Phenylthio)-2-naphthol (**3a**):^[19] white solid, mp 61.5–63.5°C.

1-(2-Naphthylthio)-2-naphthol (**3b**):^[20] white solid, mp 96–97°C.

2-(2-Mercaptobenzoxazolyl)-2-naphthol (3c): δ_{H} (CDCl₃, 400 MHz) 7.21–7.29 (2H, m), 7.34–7.44 (3H, m), 7.49–7.60 (3H, m), 7.82 (1H, d, *J* 8.1), 7.96 (1H, d, *J* 8.9), 8.33 (1H, d, *J* 8.8). δ_{C} (CDCl₃, 100.62 MHz) 111.70, 117.6, 120.9, 122.0, 124.1, 124.4, 124.6, 126.3, 127.2, 128.5, 128.7, 129.6, 134.4, 134.9, 135.6, 154.0, 157.6. *m/z* (EI, 70 eV) (%) 63 (11), 64 (7), 69 (9), 102 (27), 103 (10), 114 (12), 115 (18), 145 (13), 146 (52), 147 (47), 158 (13), 232 (18), 233 (24), 252 (13), 260 (57), 261 (19), 276 (33), 293 (100), 294 (19). HRMS (ESI⁻) *m/z* 292.0442; calcd for C₁₇H₁₀NO₂S 292.0432.

2-(2-Mercaptobenzothiazolyl)-2-naphthol (3d): δ_{H} (CDCl₃, 400 MHz) 7.32–7.49 (4H, m), 7.52–7.60 (2H, m), 7.86 (1H, d, *J* 8.2), 7.90 (1H, d, *J* 8.2), 8.01 (1H, d, *J* 8.9), 8.33 (1H, d, *J* 8.5). δ_{C} (CDCl₃, 100.62 MHz) 111.70, 117.6, 120.9, 122.0, 124.1, 124.4, 124.6, 126.3, 127.2, 128.5, 128.7, 129.6, 134.4, 134.9, 135.6, 154.0, 157.6. *m/z* (EI, 70 eV) (%) 63 (20), 69 (16), 77 (11), 87 (11), 88 (11), 102 (27), 103 (16), 108 (22), 113 (13), 114 (22), 115 (32), 135 (14), 140 (18), 144 (10), 145 (20), 146 (33), 147 (29), 148 (10), 247 (10), 248 (26), 249 (21), 268 (11), 276 (100), 277 (46), 278 (18), 281 (10), 292 (74), 293 (20), 309 (49), 310 (17). HRMS (ESI⁻) *m/z* 308.0216; calcd C₁₇H₁₀NOS₂ 308.0204.

1-(4-Chlorophenylthio)-2-naphthol (3e): [19] white solid, mp 105.0–106.0°C. δ_{H} (CDCl₃, 400 MHz) 6.85–6.88 (2H, d), 7.04–7.07 (3H, m), 7.28–7.32 (1H, m), 7.40–7.44 (1H, m), 7.73–7.75 (1H, d), 7.83–7.85 (1H, d), 8.07–8.09 (1H, d). δ_{C} (CDCl₃, 100.62 MHz) 107.64, 116.94, 124.03, 124.46, 127.65, 128.13, 128.69, 129.31, 129.55, 131.89, 133.13, 133.95, 135.21, 157.04. *m/z* (EI, 70 eV) (%) 63 (13), 69 (12), 73 (8), 75 (10), 82 (7), 99 (15), 108 (67), 143 (100), 144 (15), 145 (44), 222 (9), 286 (66), 287 (9), 288 (50), 289 (6), 290 (11).

1-(4-(4-Chlorophenylthio)phenylthio)-2-naphthol (4): δ_{H} (CDCl₃, 400 MHz) 6.89–7.00 (2H, m), 7.10–7.15 (2H, m), 7.16–7.24 (4H, m), 7.31–7.35 (1H, m), 7.37–7.42 (1H, m), 7.47–7.55 (1H, m), 7.82 (1H, d, *J* 8), 7.92 (1H, d, *J* 8.5), 8.18 (1H, d, *J* 8.5). δ_{C} (CDCl₃, 100.62 MHz) 107.49, 116.93, 123.99, 124.51, 127.14, 128.09, 128.67, 128.90, 129.35, 129.52, 130.11, 131.99, 132.05, 132.71, 133.10, 134.27, 135.11, 135.30, 157.03. HRMS (ESI⁻) *m/z* 393.0192 (395.0158); calcd for C₂₂H₁₄ClO₂S 393.0175 (395.0145).

1-Methylthio-2-naphthol (3f): [21] δ_{H} (ClCD₃, 400 MHz) 2.20 (3H, s), 7.16–7.19 (2H, m), 7.47–7.51 (1H, m), 7.69–7.72 (2H, d), 8.24–8.27 (1H, d). δ_{C} (CDCl₃, 100.62) 18.65, 112.56, 116.49, 123.52, 124.36, 127.61, 128.76, 129.41, 131.53, 134.88, 155.87. *m/z* (EI, 70 eV) (%) 69 (9), 73 (6), 77 (6), 95 (5), 102 (10), 103 (9), 115 (14), 145 (9), 147 (82), 148 (9), 175 (64), 176 (7), 190 (100), 191 (13).

5-(Phenylthio)uracil (5): [22] δ_{H} ((CD₃)₂SO, 400 MHz) 7.14–7.29 (5H, m), 7.92 (1H, s), 11.40 (2H, s). δ_{C} ((CD₃)₂SO, 100.62 MHz) 102.41, 125.99, 126.74, 129.43, 137.21, 149.46, 151.76, 162.81.

N-Methyl-2-(phenylthio)benzamide (7): [23] δ_{H} ((CD₃)₂SO, 400 MHz) 2.84–2.89 (3H, m), 6.88–7.76 (9H, m). δ_{C} ((CD₃)₂SO, 100.62 MHz) 26.72, 126.43, 127.08, 127.97, 128.37, 128.51, 129.47, 130.57, 130.93, 132.62, 134.33, 135.57, 136.07, 168.86. *m/z* (EI, 70 eV) (%) 51 (8), 77 (8), 107 (39), 108 (7), 139 (9), 150 (31), 152 (16), 166 (7), 184 (71), 185 (18), 213 (100), 214 (16), 243 (89), 244 (14), 245 (5).

Supplementary Material

¹H NMR and ¹³C NMR spectra and mass spectra of compounds **3c**, **3d**, and **4** are available on the Journal's website.

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