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“One-Pot” Two-Step Synthesis of Aryl Sulfur Compounds by Photoinduced Reactions of Thiourea Anion with Aryl Halides

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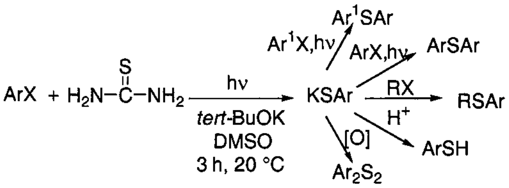
ABSTRACT



The photoinduced reactions of aryl halides with the thiourea anion afford arene thiolate ions in DMSO. These species without isolation, and by a subsequent aliphatic nucleophilic substitution, $S_{RN}1$ reaction, oxidation, or protonation, yield aryl methyl sulfides, diaryl sulfides, diaryl disulfides, and aryl thiols with good yields (50–80%). This is a simple and convenient approach which involves the use of the commercially available and inexpensive thiourea in a “one-pot” two-step process for the synthesis of aromatic sulfur compounds.

Organosulfur compounds are versatile reagents for organic synthesis and play an important role in biological systems.[1] Aryl thiols and alkyl aryl sulfides can be synthesized by aromatic nucleophilic substitution involving strong activated aryl halides and HS^- or RS^- anions.[2] For aromatic halides bearing only one electron-withdrawing group (EWG) or nonactivated, the employment of copper (CuI or Cu^0) or $(Ph_3P)_4Pd$ catalysis, high temperatures, and long reaction times is necessary to obtain from moderate to good yields.[3] Another possibility is the conversion of Grignard reagents.[2]

Radical nucleophilic substitution or $S_{RN}1$ has proven to be a versatile mechanism for the synthesis of aromatic sulfur derivatives with formation of a new C−S bond by reaction of arene and alkanethiolates, $MeCOS^-$ and $PhCOS^-$ ions.[4] These reactions proceed with nonactivated aryl derivatives. Among the sulfur nucleophiles described, RS^- ions give a mixture of substitution and fragmentation products, making this reaction of scarce synthetic value.[5] However, straightforward substitution products can be achieved by the reaction of RS^- with aromatic compounds, bearing EWGs (CN, CHO, $CONH_2$, COMe, and COPh) and heteroaromatic halides (70−90%).[6] Symmetrical and unsymmetrical diaryl sulfides can be synthesized in good yields by photostimulated reactions of arene and heteroarene thiolate ions with aryl halides.[4]

The electrochemically induced reactions of the thiourea anion (**1**) with aryl halides afford moderate yields of a mixture of aryl thiol, diaryl disulfide, and diaryl sulfide, ascribed to the fragmentation of the radical anions intermediates (Scheme 1).[7]

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[1] Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; John Wiley & Sons: Chischester, 1996.

[2] March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001.

[3] (a) Cu catalysis: Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (b) Pd catalysis: Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-I.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385−1389.

[4] Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71−167.

[5] Rossi, R. A.; Palacios, S. M. *J. Org. Chem.* **1981**, *46*, 5300−5304.

[6] Beugelmans, R.; Bois-Choussy, M.; Boudet, B. *Tetrahedron* **1983**, *39*, 4153−4161.

[7] Combellas, C.; Dellerue, S.; Mathey, G.; Thiébault, A. *Tetrahedron Lett.* **1997**, *38*, 539−542.

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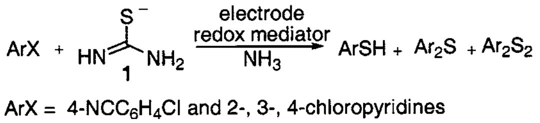
Scheme 1



On the other hand, the photochemical aromatic substitution of aryl halides by thiourea affords arylisothiuronium salts. These reactions proceed under UV irradiation and thermal hydrolysis, and oxidation of these salts leads to the formation of the corresponding diaryl disulfides.[8] For aryl derivatives bearing electron-donating substituents such as NH_2, NR_2, and OMe, variable yields of the disulfides are obtained (25−76%). However, 1-bromonaphthalene was unreactive under these reaction conditions.

We report herein the photoinduced reaction of **1** with haloarenes, as a "one-pot" method for the synthesis of aryl thiols, alkyl aryl sulfides, symmetrical or unsymmetrical diaryl sulfides, and diaryl disulfides from moderate to good yields.

The photoinduced reactions of **1** with 1-bromonaphthalene (**2**) were first studied, and the results are summarized in Table 1. The general procedure for these reactions is as follows: To a solution of the bidentate anion **1** obtained by deprotonation of thiourea with *t*-BuOK in an appropriate solvent was added the aryl halide, and then the solution was irradiated for 3 h or the indicated time. After irradiation, the arene thiolate ion obtained by the $S_{RN}1$ reaction was quenched by methyl iodide.[9]

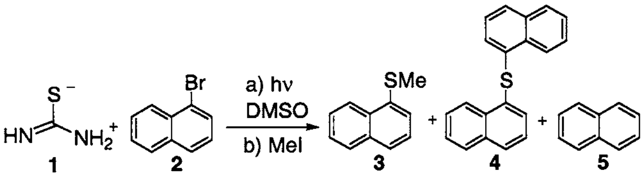
Table 1. Photoinduced Reactions of **1** with 1-Bromonaphthalene[a]

	conditions			product yield[b] (%)			
entry	solvent	time (h)	conv (%)	MB	ArH	ArSMe[c]	Ar_2S
1	DMSO	3	100	84	13	37	32
2[d]		3	100	83	9	50	22
3[d]		1	100	92	11	54	24
4[d]		0.25	91	87	9	48	19
5[d,e]		0.25	25	94	2	9	8
6[d,f]		3	0				
7[d]	DMF	3	100	90	39	33	18
8	MeCN	3	24	88	7.5	0.2	4
9	NH_3	3	94	62	9	15	31
10	EtOH	3	45	95	35	1.5	3
11[d]	HMPA	3	98	94	65	17	9

[a] ArX, 0.05 M; **1**, 0.25 M. After irradiation under nitrogen atmosphere, the reaction was quenched with MeI. [b] Determined by GC using the internal standard method, error 5%. The conversion was determined by quantification of the unreacted substrate. Mass balance (MB). [c] Together with ≤3% of the 2-(methylthio)naphthalene from the 2-bromonaphthalene present as impurity of **2**. [d] Nucleophile/ArX ratio of 10:1. [e] In the presence of 0.01 M DTBN. [f] In the dark.

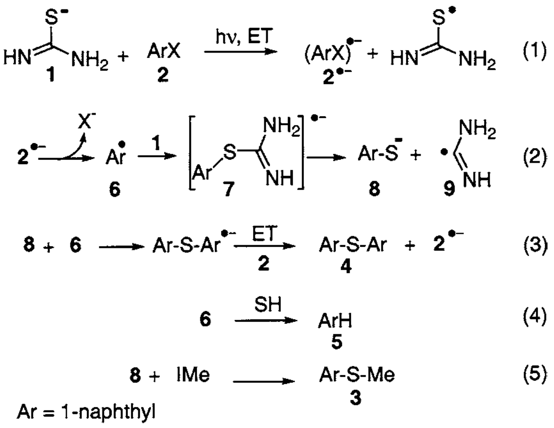
Following this approach, the main product in the reaction of **1** with **2** was the 1-(methylthio)naphthalene (**3**) with a smaller amount of bis(1-naphthyl) sulfide (**4**) and naphthalene (**5**) (Scheme 2).

Scheme 2



The ratio **3**/**4** was improved when the reaction was performed with a 10-fold excess of **1**. Similar results were obtained after 1 h of irradiation, and even after only 15 min, the conversion was almost complete. This photochemical reaction was inhibited by the presence of di-*tert*-butyl nitroxide (DTBN), a radical trap. This result, the lack of reaction in the dark after 3 h (Table 1, entries 1−5), and the presence of naphthalene suggest a radical chain mechanism for this reaction and can be rationalized as follows (Scheme 3): The reaction is initiated by a photoinduced electron-transfer reaction from **1** to the substrate to yield the corresponding radical anion **2**$^{\bullet-}$, which fragments to give radical **6**. Addition of **1** to radical **6** affords the radical anion intermediate **7**$^{\bullet-}$, which fragments into the thiolate ion **8** and radical **9** (step 2). To account for the chain reaction, two

Scheme 3



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(8) Frolov, A. N.; Klokova, E. M.; El'tsov, A. V. *J. Org. Chem. USSR (Engl. Transl.)* **1981**, *17*, 1926−1935.

(9) **Representative Experimental Procedure.** The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with nitrogen gas inlet and magnetic stirrer. The tube was dried under vacuum, filled with nitrogen, and then loaded with 10 mL of dried DMSO. 5.5 mmol of *t*-BuOK, 5 mmol of the thiourea, and 0.5 mmol of the aryl halide were added to the degassed solvent under nitrogen. After 3 h of irradiation with a medium-pressure Hg lamp emitting maximally at 350 nm, the reaction was quenched with addition of methyl iodide (6 equiv) and 30 mL of water, and then the mixture was extracted with methylene chloride (3 × 20 mL). The organic extract was washed twice with water and dried, and the products were quantified by GLC with the internal standard method.

different radical anion intermediates are possible. Deprotonation of **9** would render cyanamide radical anion which by electron transfer to **2** may continue the $S_{RN}1$ cycle.[7] Another possibility is that coupling of ion **1** with radical **9** would form a new radical anion able to continue the chain propagation. In any case, the products after ET would probably be water soluble and hydrolyze during workup. Further studies are in progress in order to clarify this step in the propagation cycle. The thiolate ion **8** is able to add to radical **6** and follows a new cycle of $S_{RN}1$ reaction to afford the disubstitution product **4** (step 3). Hydrogen atom abstraction from the solvent by naphthyl radicals gives the reduction product naphthalene (**5**) (step 4). After irradiation, the reaction mixture was quenched by methyl iodide to afford the 1-(methylthio)naphthalene (**3**) (step 5).

The effects of the solvent were studied in the reaction of ion **1** with **2** (Table 1, entries 7−11). From the dipolar aprotic solvents employed, DMSO gave the best results, with a product ratio for substitution/reduction of approximately 7. In DMF, the conversion was completed but naphthalene was produced in an amount similar to that of ArSMe. In this reaction, the product ratio for substitution/reduction was 1.3 due to a competitive hydrogen atom abstraction from the solvent with the coupling reaction.[10] Conversely, in the dipolar aprotic MeCN, the yields were low because of the lower solubility of *t*-BuOK. The reaction performed in liquid ammonia showed a poor mass balance, probably due to the low recovery of the naphthalene.[11] In comparison to the reaction carried out in DMSO, the ratio Ar_2S toward ArSMe increased. This finding can be ascribed to a higher selectivity of the naphthyl radicals toward the two competing anions (**1** and **8**) at lower temperature.[12] In EtOH and HMPA, the formation of the reduction product naphthalene notably increased in comparison to the coupling products. These reactions yielded a product ratio for substitution/reduction of 0.1 and 0.4, respectively. In *t*-BuOH or H_2O, thiourea and **2** are, respectively, slightly soluble but there was no reaction at all. In summary, DMSO is the most suitable solvent to perform these reactions.

The reactivity of thiourea anion toward 1-bromonaphthalene under irradiation has encouraged us to further explore the potential of this anion in the synthesis of sulfur compounds. Table 2 condenses the results obtained in the photoinduced reactions of **1** with a variety of aryl halides.

From Table 2, it is possible to conclude that this methodology is appropriate for substrates bearing one EWG or heteroaryl halides, providing, thus, more reactivity in the coupling reaction. In these cases, the arene thiolate ions obtained by the $S_{RN}1$ reaction were quenched by MeI to afford the ArSMe derivatives from moderate to good yields (50−83%). Nevertheless, these yields were considerably better than those reported by classical substitution mechanisms. For example, an alternative synthesis of 3-mercaptopyridine by a substitution reaction of the aryl bromide with KHS in propylene glycol required 20 h of heating at 175−190 °C and copper catalysis to produce only 14% yield of the thiol.[13]

Table 2. Photoinduced Reactions of **1** with Aryl Halides[a]

			products yield[b] (%)		
entry	ArX	conv (%)	ArH	ArSMe	Ar_2S
1	1-Br-naphthalene	100	9	50[c]	22
2	2-Br-naphthalene	100	7	54[d]	25
3[e]	PhI	f	f	28	26
4[e]	$4\text{-}IC_6H_4OMe$	100	62	21	7
5	$4\text{-}BrC_6H_4OMe$	96	60	20	8
6	$4\text{-}BrC_6H_4SMe$	100	14	42	23
7	$4\text{-}BrC_6H_4CN$	100	4	49	9
8[e]	$4\text{-}IC_6H_4NO_2$	100		77	
9[e]	$4\text{-}PhCOC_6H_4Br$	100	5	81	
10	$2\text{-}MeCOC_6H_4Br$	100	2	64	3
11	3-Cl-pyridine	100	f	58	15
12	2-Cl-pyridine	100	f	87	f
13[e]	2-Cl-quinoline	100	2	64	
14	2-Cl-pyrazine	100	f	83	
15	2-Cl-pyrimidine	100	f	36	

[a] ArX, 0.05 M; **1**, 0.50 M. After irradiation for 3 h under nitrogen atmosphere in DMSO, the reaction was quenched with MeI. [b] Determined by GC using the internal standard method, error 5%. The conversion was determined by quantification of the unreacted substrate. [c] Together with 2.5% of the methyl 2-naphthyl sulfide. [d] Together with 1% of the methyl 1-naphthyl sulfide. [e] Nucleophile/ArX ratio of 5:1. [f] Not quantified.

2-Chloropyrimidine gave modest yield of the 2-(methylthio)pyrimidine, and it was less reactive than 2-chloropyrazine. A similar difference on reactivity has been previously observed in the photoinduced reactions of both chlorides with potassium phenylacetonitrile[14] and ketone enolates.[15] These results were explained on the basis of the reduction potential difference of the halides.

For substrates giving both the mono- and disubstitution products (ArS^- and Ar_2S, respectively), optimization of the reaction conditions is possible to afford preferentially the symmetrical diaryl sulfide by increasing the amount of the aromatic halide or the arylthiol by increasing the amount of thiourea. Thus, the photoinduced reaction between 1-bromonaphthalene (**2**) and **1** with a ratio **2**/**1** of 1:1 yielded 38% of bis (1-naphthyl) sulfide after 3 h.

Different chemical transformations are possible for the arene thiolate ions formed in good yields in the $S_{RN}1$ reaction without isolation, namely oxidation to the diaryl disulfide, protonation to yield the aryl thiols, or subsequent $S_{RN}1$

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[10] The following hydrogen atom abstraction rates have been determined for 1-naphthyl radicals: $2.5 \times 10^5\ s^{-1}$ (MeCN), $3 \times 10^5\ s^{-1}$ (DMSO) and $8 \times 10^6\ s^{-1}$ (DMF). Helgee, B.; Parker, V. D. *Acta Chem. Scand.* **1980**, *34*, 129−156. Although for DMSO a k_H value of $1 \times 10^8\ s^{-1}$ determined by Saveánt (Andrieux, C. P.; Savéant, J.-M.; Su, K. B. *J. Phys. Chem.* **1986**, *90*, 3815−3823) seems to be more adequate.

[11] Part of naphthalene is lost during the reaction and with the evaporation of the solvent.

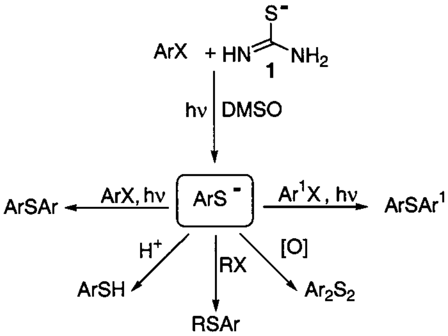
[12] The absolute rate constant for the coupling reaction of aryl radicals with **1** and benzene thiolate ion have been electrochemically measured in liquid NH_3. Toward 3-pyridyl radical (similar reactivity to naphthyl radical), benzene thiolate ion is 1 order of magnitude more reactive than ion **1** (ref 7).

[13] Wuest, H. M.; Sakal, E. H. *J. Am. Chem. Soc.* **1951**, *73*, 1210−1216.

[14] Hermann, C. K. F.; Sachdeva, Y. P.; Wolfe, J. F. *J. Heterocycl. Chem.* **1987**, *24*, 1061−1065.

[15] Carver, D. R.; Komin, A. P.; Hubbard, J. S.; Wolfe, J. F. *J. Org. Chem.* **1981**, *46*, 294−299.

Scheme 4



reaction with a different aryl halide to afford unsymmetrical diaryl sulfides. With this strategy, we synthesized a variety of sulfur compounds. Thus, a solution of 4-benzoylbenzene thiolate ion obtained by this methodology affords 4-mercaptobenzophenone (80%) by protonation under nitrogen atmosphere, bis(4-benzoylphenyl) disulfide (70%) after oxidation by KI_3, and by a subsequent photoinduced $S_{RN}1$ reaction with iodobenzene 4-phenylthiobenzophenone (35%).

Although no efforts have been made to optimize these reactions, they clearly show the versatility of the method to obtain several organosulfur compounds.

The $S_{RN}1$ reaction between MeCOSK and arenediazonium tetrafluoroborates in DMSO has been reported as a method for the "one-pot" access to aromatic sulfur derivatives, without isolation of the aryl thioesters.[16] This methodology implies the handling of the not always stable diazonium salts and the yields of the sulfur compounds were lower (31−66%) than the ones obtained in the present report.

In conclusion, the photoinduced reaction of thiourea ion (**1**) with aryl halides provides a very good alternative to introduce a sulfur functionality in aryl compounds by ipso substitution of an adequate leaving group (X = I, Br, or Cl). Further reactions of the thiolate ions yield a variety of sulfur compounds in a "one-pot" reaction. Scheme 4 summarizes all these possible transformations. The use of commercially available, easy to handle, inexpensive thiourea and the very mild conditions make this process a simple and convenient approach to obtain several sulfur aromatic compounds.

Further studies are in progress in order to optimize the synthesis of unsymmetrical diaryl sulfides, extend this methodology for the synthesis of sulfur compounds derived from substrates reactive in radical reactions such as bridgehead, neopentyl, and vinyl halides, as well as study the possibility of polysubstitution.

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Supporting Information Available: General methods, materials, experimental procedures, and literature references for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Petrillo, G.; Novi, M.; Garbarino, G.; Filiberti, M. *Tetrahedron* **1989**, *45*, 7411−7420.