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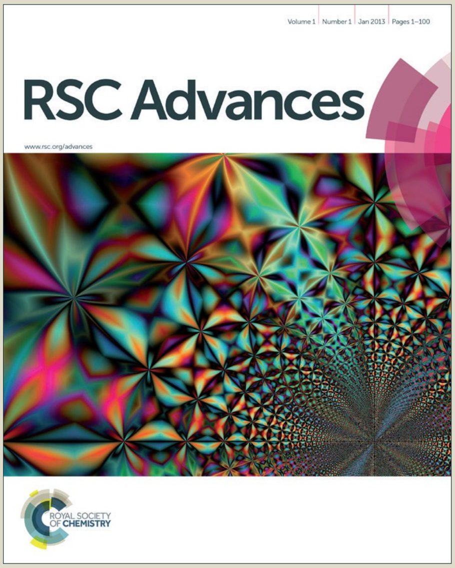

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Iodine-Mediated Thiolation of Phenol/Phenylamine Derivatives and Sodium Arylsulfinates in Neat Water

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An efficient and convenient protocol for iodine-mediated thiolation of Phenols/Phenylamines with sodium benzenesulfinates in water has been achieved. In this transformation, environment-friendly conditions (including metal-free and water as solvent) are employed under air condition, and a series of valuable thioethers are easily obtained in moderate to good yields.

The reactions for the construction of C–C and C–X (X = heteroatom) bonds via C–H functionalization have emerged as important research trend in organic synthesis.[1] In decades past, a good deal of novel and shortcut synthetic methods has been reported for the construction of C-C and C-X via C–H functionalization between two C–H/C–H and X–H centers. Among all C–H functionalization reactions, the formation of C−S bond has aroused people’s concern as an important field of research in contemporary synthetic organic chemistry.

Aryl sulfides are important compounds because they often appear in many natural products and are employed in total synthesis, in functional materials science, and in medicinal chemistry.[2] It is noteworthy that the diaryl sulfide are applied in numerous disease areas to cure HIV, allergies and cancer as well as Alzheimer’s and Parkinson’s diseases.[3] Compounds containing 2-naphthalenol are still an important part in all sorts of sulfocompounds because of their presence in many bioactive relevant molecules, including glycine transporter-1 (GlyT-1) inhibitions, and 4-hydroxy-3-(arylthio)-2*H*-chromen-2-ones exhibiting antibacterial and analgesic activities.[4] Over the past few decades, there are plenty of C-S cross-coupling reactions of aryl thiols and disulfides with aryl halides, boronic acids and triflates involving various transition metals, such as Pd,[5] Cu,[6] Ni,[7] In,[8] Fe,[9] Co[10] and so on. Nevertheless, many of these sulfur sources are often limited because of their expensiveness, instability and high-toxicity. Therefore, a new general and flexible approach under metal-free conditions and with increased efficiency and decreased energy and cost is still required. Sodium sulfinates as desirable sulfur source have been extensively used to construct the C−S bond because they are readily accessible and environment-friendly. We envisaged that sodium sulfinates might serve as feasible thiolating agents to couple with naphthols in the specified reaction conditions due to sodium sulfinates can be reduced to disulphides, which are classical sulfenylating agents. There is no doubt that many efficient methods have also made great progress, which have been reported by groups of Peddinti,[11] Huang, [12] Wang, [13] and others.[14] These urge us to report our own discovery. Herein we present a range of phenol/phenylamine derivatives readily experience thiolation with sodium arylsulfinates mediated by I_2–PPh_3 in water.[15]

Triphenylphosphine was often used as reducing agent in virtue of its inexpensiveness, wide material sources and application.[16] Inspired by this result, we began our investigation with the reaction of sodium benzenesulfinate with 2-naphthalenol (**2a**) as a model reaction to obtain the optimal reaction conditions and the results are presented in Table 1. 2-naphthalenol was treated with benzenesulfinic acid sodium salt (**1a**, 1.2 equiv.), iodine (1.0 equiv.) and triphenylphosphine (1.2 equiv.) in 2 mL of toluene at 100 °C for 10 h in the opening system. In a preliminary attempt, we were particularly pleased that the target product 1-(phenylthio)naphthalen-2-ol (**3a**) was obtained in 71% yield (Table 1, entry 1). Among the different solvents examined, water gave the best efficiency in terms of product yield (82% yield) and as an environment-friendly solvent (Table 1, entry 8). We further investigated the effect of the stoichiometry of I_2 and PPh_3. Unfortunately, obvious decreased yields of **3a** were observed when reducing the loads of iodine and triphenylphosphine (from 82% yield to 17% yield) (Table 1, entries 9–12). Furthermore, when the reaction was performed at lower temperature, the yield of **3a** was reduced as well (Table 1, entry 14). On the basis of the results shown in Table 1, the I_2/Ph_3P system at 100 °C in water for 10 h emerged as the optimized reaction conditions for follow-up studies.

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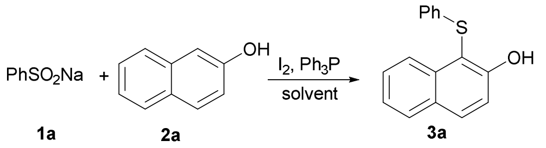
Table 1 Optimization of reaction conditions for I_2–PPh_3 mediated C1 thiolation reaction of 2-naphthalenol (**2a**)[a]



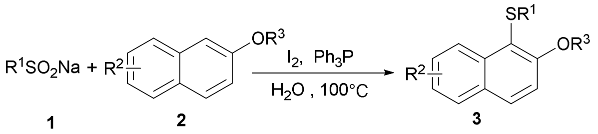
Entry	I_2 (equiv.)	PPh_3 (equiv.)	Solvent	temp (°C)	Yield[b] (%)
1	1	1.2	Toluene	100	71
2	1	1.2	CH_2Cl_2	100	58
3	1	1.2	THF	100	23
4	1	1.2	Dioxane	100	41
5	1	1.2	DMSO	100	trace
6	1	1.2	DMF	100	42
7	1	1.2	EtOH	100	18
8	1	1.2	H_2O	100	82
9	1	1.5	H_2O	100	79
10	1	1	H_2O	100	65
11	0.5	1.2	H_2O	100	17
12	1.5	1.2	H_2O	100	80
13	1	1.2	H_2O	80	47
14	1	1.2	H_2O	rt	trace

[a] Reaction conditions: **1a** (0.36 mmol) and **2a** (0.30 mmol) in 2 mL of solvent feflux for 10 h in air. [b] Yield of isolated product.

With the optimized conditions in hand, we next investigated the substrate scope of the sulfanylation of 2-naphthalenol (**2**) with various sulfinic acid sodium salts (**1**). The results were clarified in Table 2. It was exhilarating to find that a range of substituted sodium benzenesulfinates reacted with 2-naphthalenol to provide the corresponding products in good to excellent yields. It was important to note that both electron-withdrawing and electron-donating groups were introduced into the thiolation products by employing sodium benzenesulfinates bearing such groups on the aromatic ring. However, it was found that the effect of sodium benzenesulfinate with electron-withdrawing groups on the yield of target products were higher than that of naphthalenols on it. Obviously, when sodium 4-nitrobenzene sulfinate was employed under the standard conditions, only a trace amount of **3g** was detected by TLC. What interesting is that 2-methoxynaphthalene and 2-ethoxynaphthalene can be tolerated in this transformation, but 2 equiv of I_2 and 1 equiv of PPh_3 were needed, and the corresponding compounds were isolated in 71% and 75% yields, respectively.

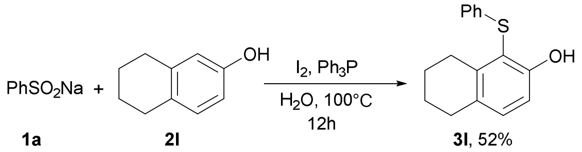
It's worth mentioning that when 5,6,7,8-tetrahydro-2-naphthol (**2l**) was subjected to the transformation under the optimal reaction conditions, the isolated yield of the corresponding product **3l** can reach 52%.

Table 2 C-1 Sulfenylation of 2-naphthalenol derivatives with sodium sulfinates mediated by I_2–PPh_3 system[a]



Entry	R^1	R^2	R^3	Product, yield[b] (%)
1	C_6H_5	H	H	**3a**, 82
2	4-MeC_6H_4	H	H	**3b**, 89
3	2- MeC_6H_4	H	H	**3c**, 83
4	4-ClC_6H_4	H	H	**3d**, 85
5	4-BrC_6H_4	H	H	**3e**, 87
6	4-$MeOC_6H_4$	H	H	**3f**, 81
7	4-$O_2NC_6H_4$	H	H	**3g**, trace
8	C_6H_5	6-Br	H	**3h**, 91
9[c]	C_6H_5	7-OH	H	**3i**, 88
10[d]	C_6H_5	H	CH_3	**3j**, 71
11[d]	C_6H_5	H	C_2H_5	**3k**, 75

[a] Conditions: **1** (0.36 mmol), **2** (0.30 mmol), I_2 (1.0 equiv.), and PPh_3 (1.2 equiv.) in 2 mL of water reflux for 10 h in air. [b] Isolated yield after column chromatography (SiO_2). [c] The reaction of **1a** (0.30 mmol) with **2i** (0.36 mmol) under the standard conditions. [d] 2 equiv of I_2 and 1 equiv of PPh_3 were added in water (2 mL) .

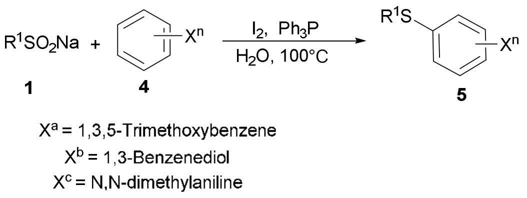


Scheme 1. Reaction of **2l** with sodium benzenesulfinate.

Then we explored the scope of the reaction with respect to a variety of sodium sulfinates with other phenols/phenylates (Table 3, entries 1-10). These compounds participated well to afford aryl sulfides in good to excellent yields under the optimized conditions (Table 3). Various sodium arylsulfinates having electron-withdrawing and electron-donating halo-groups at the 4-position were able to react with phenols/phenylates to give the desired products **5aa-5eb** in a few hours in moderate to high yields. Besides, We further tested this protocol with the carbon nucleophile *N,N*-dimethylaniline bearing an amino functionality providing the corresponding aryl sulfides **5ac-5ec** in good yields. In general, for substituted sodium benzenesulfinates, the substrates containing electron-donating groups showed higher reactivity than those with electron- withdrawing groups.

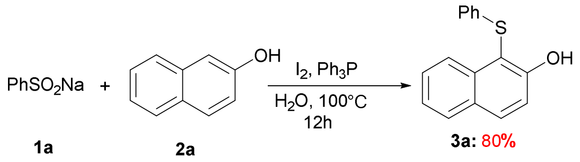
Inspired by these satisfactory results, we tried to probe the synthetic adaptability of the present method. The gram-scale reaction was completed between **1a** and **2a**, and the reaction afforded **3a** in 80% yield (Scheme 2). Consequently, this expedient protocol could be served as an efficient method for the synthesis of various thioether derivatives with hydroxy/amidogen/methoxyl groups.

Table 3 C-4 Sulfenylation of X[a] - X[c] with sodium sulfinates mediated by I_2–PPh_3 system[a]



Entry	R^1	X^n	Time (h)	Product yield[b] (%)
1	C_6H_5	a	8	**5aa**, 80
2	$4\text{-}MeC_6H_4$	a	8	**5ba**, 86
3	$4\text{-}ClC_6H_4$	a	8	**5ca**, 82
4	$4\text{-}BrC_6H_4$	a	8	**5da**, 80
5	$4\text{-}OMeC_6H_4$	a	8	**5ea**, 82
6	$4\text{-}O_2NC_6H_4$	a	12	**5fa**, 78
7	C_6H_5	b	8	**5ab**, 90
8	$4\text{-}MeC_6H_4$	b	8	**5bb**, 92
9	$4\text{-}BrC_6H_4$	b	8	**5db**, 88
10	$4\text{-}OMeC_6H_4$	b	8	**5eb**, 87
11	C_6H_5	c	10	**5ac**, 83
12	$4\text{-}MeC_6H_4$	c	10	**5bc**, 87
13	$4\text{-}BrC_6H_4$	c	10	**5dc**, 84
14	$4\text{-}OMeC_6H_4$	c	10	**5ec**, 82

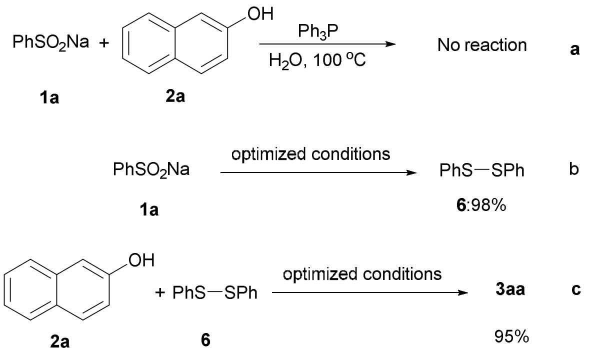
[a] Conditions: **1** (0.3 mmol), 4 (0.36 mmol), I_2 (1.0 equiv.), and PPh_3 (1.2 equiv.) in 2 mL of water reflux for 10 h in air. [b] Isolated yield.



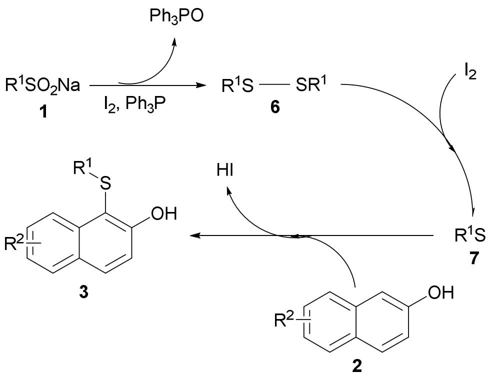
Scheme 2. Synthesis of **3a** on gram scale.

In order to gain further insight into the plausible reaction pathway of I_2-mediated thiolation of substituted phenols, several control experiments were conducted under various reaction conditions, as showed in Scheme 3. No reaction occurred upon treatment of benzenesulfinic acid sodium salt **1a** with 2-naphthalenol **2a** in the absence of iodine (Scheme 3, **a**). Only phenyl disulfide was produced in the standard conditions without 2-naphthalenol (Scheme 3, **b**). In the optimized conditions, 2-naphthalenol **2a** stably reacted with diphenyldisulfane **6** to give the desired product **3a** in 95% yield (Scheme 3, **c**).

On the basis of the experimental results described above and together with previous relevant mechanistic studies,[17] we proposed a plausible reaction pathway depicted in Scheme 4. Initially, sodium benzenesulfinate was reduced to diphenyldisulfane (**6**) in the presence of I_2 and PPh_3. Then, **6** reacts with I_2 to form 2 equiv of an electrophilic species PhSI (**7**), which is attacked by **2** to yield the desirable product **3** and HI.



Scheme 3. Control experiments.



Scheme 4. The plausible mechanism.

Conclusions

In conclusion, a metal-free and convenient way for the synthesis of diaryl sulfide derivatives via the I_2–PPh_3 system mediated thiolation of substituted naphthols/phenylamines in water under air condition has been described. The thiolation of naphthols/phenylamines and sodium benzene-sulfinate undergoes S-S bond formation, S–S bond cleavage, and C-S bond formation. In this program, using a range of arylsulfinic acid salts as sulfur source, structurally diversed naphthol/aniline thioethers can be smoothly produced in moderate to good yields. It is believed that this method would offer an efficient approach to thioethers containing hydroxy /amino/alkoxy groups.

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