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One-Pot Synthesis of Amine-Substituted Aryl Sulfides and Benzo[*b*]thiophene Derivatives

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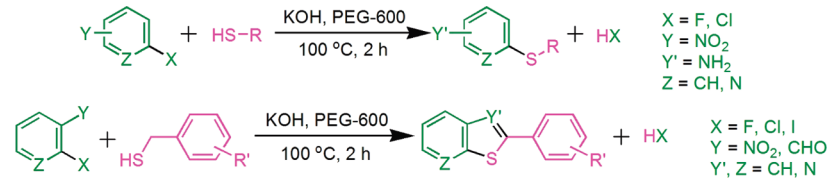
ABSTRACT



A series of amine-substituted aryl sulfides have been synthesized from nitroaryl halides via a simple one-pot procedure involving metal-free C−S cross-coupling and in situ nitro group reduction. Various nitroaryl halides were reacted with thiols in recyclable poly(ethylene glycol) to afford the amine-substituted aryl sulfides in high yield. Additionally, the cross-coupling reactions of nitro- and aldehyde-substituted aryl halides with benzyl thiols under the same reaction conditions were demonstrated to afford benzothiazole and phenylbenzo[*b*]thiophene derivatives.

Amine-substituted aryl sulfides are pivotal intermediates for the synthesis of biologically and pharmaceutically active molecules. A number of amine-substituted aryl sulfides have shown potential clinical applications as antitumor, antifungal, and anti-inflammatory agents.[1] In general, there are three approaches to synthesizing amine-substituted aryl sulfides. One is to directly couple aminoaryl halides with thiols to form the desired compounds.[2] The second approach is based on a two-step procedure involving synthesis of nitroaryl sulfides and subsequent reduction of the nitro group.[3] The third major approach relies on the cross-coupling of boronic acid derivatives with aminoaryl disulfides.[4] Despite their wide application in the synthesis of amine-substituted aryl sulfides, these approaches have limitations with regard to the need of either costly metal catalysts or multistep reactions. Adapa and co-workers have reported a one-step synthesis of aminoaryl sulfides in moderate yields by reacting aminoaryl halides with thiols in the absence of the metal catalyst, but this method requires relatively expensive iodide or bromide precursors and cesium hydroxide.[5] Here,

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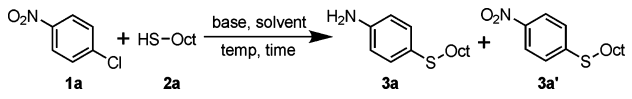
we report a convenient method that offers a one-pot synthesis of amine-substituted aryl sulfides directly from nitroaryl chloride or fluoride precursors by using poly(ethylene glycol)-600 (PEG-600)[6] and potassium hydroxide (KOH). In addition, we show that the reaction conditions can be extended to a one-pot synthesis of a variety of benzothiazole and phenylbenzo[*b*]thiophene derivatives via a novel synthetic pathway.

To identify optimum reaction conditions, we first investigated the C−S cross-coupling of 1-chloro-4-nitrobenzene and 1-octanethiol (1.5 equiv) in the absence of metal catalysts. Selected results from our screening experiments are summarized in Table 1. Without added base, the reaction in PEG-600 (3 mL) has

Table 1. Effect of Reaction Conditions[a]



1a 2a 3a 3a'

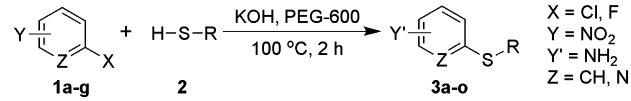
entry	base (equiv)	solvent	temp (°C)	time (h)	yield[b] (%) −NO_2	yield[b] (%) −NH_2
1		PEG	100	24	7	
2	KOH (3.0)	H_2O	100	24	42	
3	KOH (3.0)	PEG/H_2O (1:1)	100	24	65	
4	KOH (3.0)	DMF	100	5	90	<3
5	KOH (3.0)	PEG/DMF (1:1)	100	5	21	79
6	KOH (3.0)	DMSO	100	5		96
7	KOH (3.0)	PEG/DMSO (1:1)	100	5		96
8	KOH (1.0)	PEG	100	2	75	3
9	KOH (2.0)	PEG	100	2	28	72
10	**KOH (3.0)**	**PEG**	**100**	**2**		**98 (92)**
11	KOH (3.0)	PEG	80	5		90
12	KOH (3.0)	PEG	80	2	20	80
13	KOH (3.0)	PEG	50	4	90	<5
14	KOH (3.0)	PEG	rt.	24	90	<5
15	K_2CO_3 (2.0)	PEG	100	24	92	<3
16	K_2CO_3 (2.0)	DMSO	80	24	98 (89)	
17	K_2CO_3 (2.0)	DMSO	50	24	96	
18	K_2CO_3 (2.0)	DMSO	rt.	24	90	

[a] Reaction conditions: 1-chloro-4-nitrobenzene (0.5 mmol), 1-octanethiol (0.75 mmol), KOH (3 equiv), PEG-600 (3 mL). [b] GC yield. Isolated yield is in parentheses.

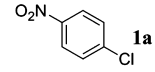
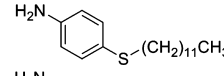
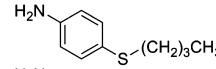
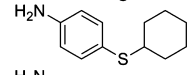
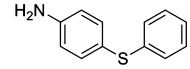
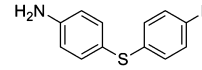
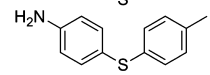
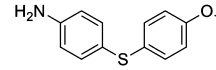
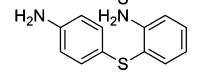
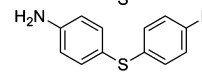
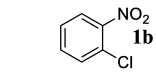
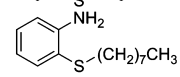
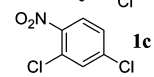
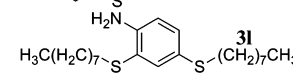
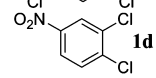
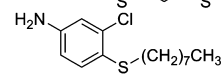
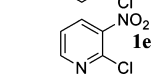
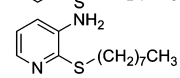
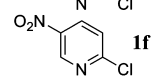
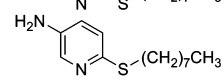
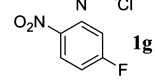
proven ineffective, affording less than 7% of the coupling product (Table 1, entry 1), whereas the reactions in the presence of stoichiometric amounts of KOH and PEG-600 (3 mL) resulted in high conversions of starting materials to amine- (**3a**) or nitro-substituted (**3a′**) aryl sulfide (Table 1, entries 8−14). Notably, the treatment of 1-chloro-4-nitrobenzene and 1-octanethiol in large excess of KOH (3 equiv) along with PEG-600 at 100 °C led to the desired amine-substituted aryl sulfide **3a** in 98% yield after 2 h (Table 1, entry 10). It should be noted that the PEG-600 solvent was recycled three times with no significant drop in reaction conversions (see the Supporting Information).

In a further set of experiments, a series of thiols and nitroaryl chlorides or fluorides were evaluated under the optimum reaction conditions, and the results are summarized in Table 2. The addition of different thiols to 1-chloro-4-nitrobenzene provided the corresponding products in moderate to excellent yields (Table 2, entries 1−9). The reaction protocol can tolerate both aliphatic thiols (Table 2, entries 1−3) and aromatic thiols with a variety of organic functional groups (Table 2, entries 4−9). Interestingly, the coupling reaction of 2- or 4-aminobenzenethiol with 1-chloro-4-nitrobenzene afforded the corresponding aminoaryl sulfides (**3i** and **3j**) in good yield (Table 2, entries 8 and 9), suggesting excellent chemselectivity of the reaction toward the thiol functional group.

Table 2. Synthesis of Various Amine-Substituted Aryl Sulfides[a]



1a-g 2 3a-o

entry	1	product 3		yield [%][b]
1	 **1a**		**3b**	95
2	**1a**		**3c**	96
3	**1a**		**3d**	83
4	**1a**		**3e**	90
5	**1a**		**3f**	50
6	**1a**		**3g**	87
7	**1a**		**3h**	84
8	**1a**		**3i**	85
9	**1a**		**3j**	87
10	 **1b**		**3k**	82
11	 **1c**		**3l**	68
12	 **1d**		**3m**	80
13	 **1e**		**3n**	75
14	 **1f**		**3o**	61
15	 **1g**	**3a**		91
16	**1g**	**3e**		82

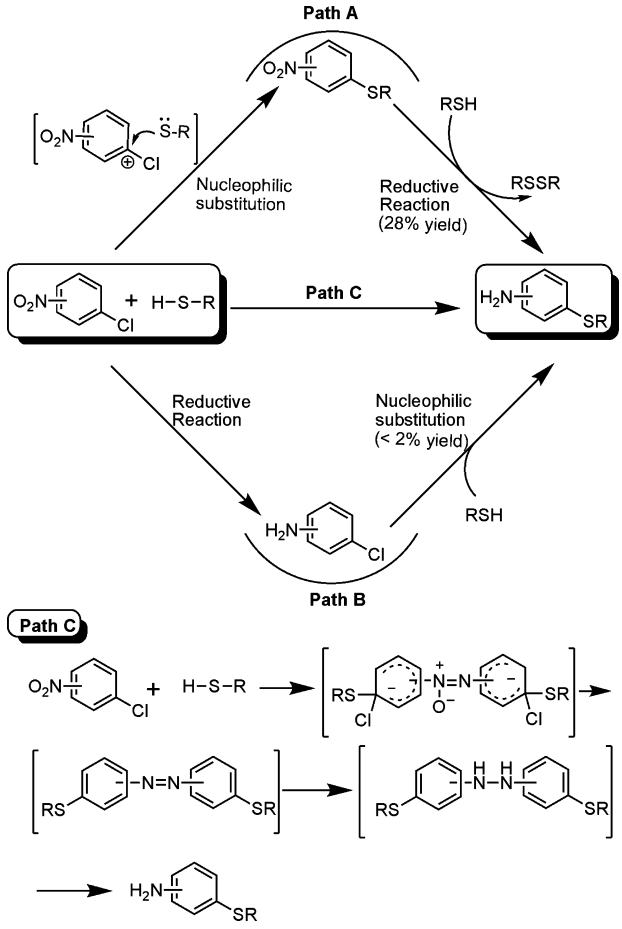
[a] All the reactions were carried out with aryl halides (0.5 mmol) and thiols (0.75 mmol) in the presence of KOH (3 equiv) and PEG-600 (3 mL). [b] Yields of isolated products are the average of at least two experiments.

The addition of 1-octanethiol to aryl halides with a nitro group in the ortho or para position furnished the amine-substituted

products (**3k** and **3l**) in good yield (Table 2, entries 10 and 11). In stark contrast, aryl chloride with a nitro group in the meta position did not react with 1-octanethiol (Table 2, entry 12). Furthermore, nitroheteroaryl chlorides and nitroaryl floride were quite effective and provided the corresponding amine-substituted aryl sulfides in high yield (Table 2, entries 13−16).

To provide insight into the one-pot synthesis of amine-substituted aryl sulfides through use of nitroaryl halides, we performed several control experiments. As shown in Scheme 1, reduction of 1-nitro-4-octylthiobenzene by 1-octanethiol only

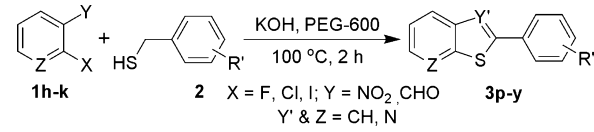
Scheme 1



afforded the amine-substituted aryl sulfide product in 28% under the preparation and cross-coupling conditions (path A, step 2). In contrast, the direct coupling of 4-chloraniline with 1-octanethiol did not proceed under the same reaction conditions (path B, step 2). On the basis of these results, we reasoned that the reduction of the nitro group and the C−S cross-coupling occur simultaneously in the one-pot reaction (path C).[7] It was well-known that nitrosobenzene rapidly dimerizes to form azodioxy compound in basic solution.[8] Indeed, we observed the formation of azoxylbenzene and azobenzene intermediates by GC/MS analysis through reduction of nitrobenzene with 1-octanethiol (Supporting Information). Nitrobenzene was reduced by PEG-600 in low yield in the absence of the alkyl thiol. Upon addition of increasing amounts of the alkyl thiol to the reaction the product yield increased dramatically.

Importantly, the newly developed reaction conditions can be extended to the synthesis of 2-substituted benzo[*b*]thiophene or benzothiazole compounds that are important in dye and the pharmaceutical industry.[9] Conventional methods typically rely on Suzuki−Miyaura coupling of 2-benzo[*b*]thiophene boronic acid with aryl halides.[10] Alternatively, the benzothiophene compounds can be synthesized via a palladium(II)-catalyzed direct arylation of heteroarenes.[11] In contrast, the cross-coupling reactions of 2-chlorobenzaldehyde with benzyl thiol and its derivatives under our standard conditions afforded benzothiophene compounds in high yield (Table 3, entries 1−8). The procedure was also applicable to large-scale synthesis (Table 3, entry 1) and heteroaromatic substrate (Table 3, entry

Table 3. the Scope of the One-Pot Conversion of Heterocyclic Compounds[a]



entry	1	2	product 3		yield [%][b]
1	**1h**			**3p**	81 (78[c])
2	**1h**			**3q**	86
3	**1h**			**3r**	87
4	**1h**			**3s**	75
5	**1h**			**3t**	74
6	**1h**			**3u**	85
7	**1h**			**3v**	82
8	**1i**			**3p**	72
9	**1j**			**3w**	70
10	**1k**			**3x**	46
11	**1k**			**3y**	40

[a] All the reactions were carried out with aryl halides (0.5 mmol) and thiols (0.75 mmol) in the presence of KOH (3 equiv) and PEG-600 (3 mL). [b] Yields of isolated products are the average of at least two experiments. [c] Large-scale reaction was carried out in the presence of 2-chlorobenzaldehyde (5 mmol) and benzylmercaptan (7.5 mmol) for 4 h.

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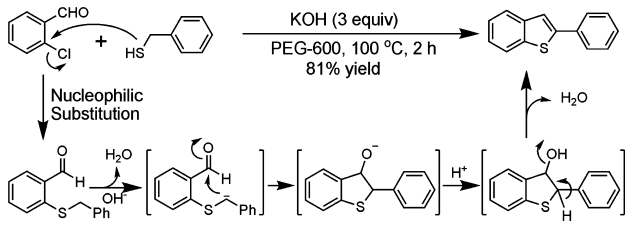
9). In addition, benzothiazole compounds (**3x** and **3y**) can be synthesized in moderate yield via the same procedure (Table 3, entries 10 and 11).[12]

The formation of 2-substituted benzo[*b*]thiophene compounds can be attributed to a tandem cross-coupling/intramolecular cyclization process that involves a probable aryl sulfide intermediate (Scheme 2). The C−S cross-coupling reaction results in the formation of the aryl sulfide intermediate, which then undergoes an intramolecular reaction[13] by preferential attack on the benzyl carbon in the presence of a base. Subsequent acidification and dehydration give rise to the 2-substituted benzothiophene product. The relatively low yield of the benzothiazole compound is probably caused by the high tendency of nitrobenzene dimerization in basic solution.[12]

Scheme 2



In summary, we have demonstrated that a combination of KOH and PEG-600 allows for an efficient generation of amine-substituted aryl sulfide, benzo[*b*]thiophene, and benzothiazole compounds. The one-pot conversion of nitroaryl chlorides (or florides) to the corresponding aminoaryl sulfides in large-scale synthesis via our method may be of industrial relevance due to the replacement of expensive transition metal catalysts with cheaper, recyclable PEG solvent. Further studies of the reaction scope and mechanism are currently underway in our laboratory.

Acknowledgment. This work was supported by ARF (R-143-000-317). X.L. is grateful to the National University of Singapore for a Young Investigator Award (R-143-000-318).

Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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