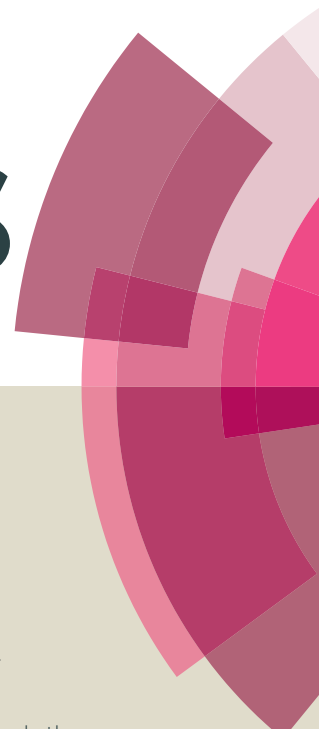


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Efficient Synthesis of Unsymmetrical Heteroaryl Thioethers and Chalcogenides by Alkali Hydroxide-Mediated S_NAr Reactions of Heteroaryl Halides and Dichalcogenides

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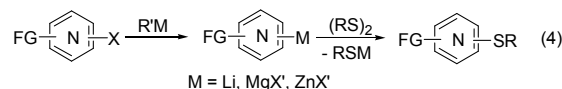
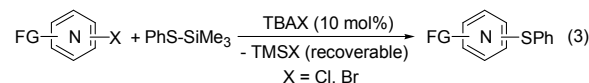
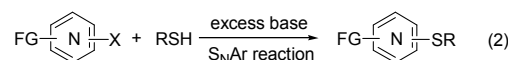
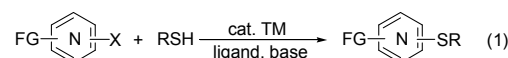
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An efficient alkali hydroxide-mediated S_NAr reaction of heteroaryl halides has been developed for practical synthesis of the useful unsymmetrical heteroaryl thioethers and chalcogenides. The usually odorless, easily available, lowly toxic, and easily stored and handled diorganyl dichalcogenides can be used as the safer and convenient chalcogen nucleophile precursors and a diverse unsymmetrical heteroaryl chalcogenides can be obtained in good to high yields by the method.

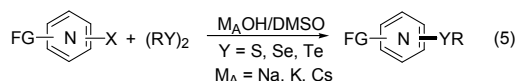
Thioethers are significant structural motifs abounding in natural products, biological, pharmaceutical, and agrichemical compounds.¹ They are also good ligands in transition metal (TM) catalyzed reactions,² key intermediates for the synthesis of the corresponding sulfoxides and sulfones,³ and even effective organocatalysts themselves in synthesis.⁴ Therefore, numerous methods have been developed for symmetrical and unsymmetrical thioethers, which can be mainly classified into TM-catalyzed Buchwald-Hartwig⁵ and copper-catalyzed Ullmann⁶ coupling reactions of aryl halides with thiols, TM-free super base media-promoted coupling of aryl halides and thiols via benzyne intermediates,⁷ as well as the TM-free nucleophilic aromatic substitution (S_NAr) reactions of the more reactive electron-withdrawing groups (EWG)-activated aryl halides and thiols.⁸ As to heteroaryl thioethers, although TM-catalyzed (Scheme 1, eq. 1)⁹ and S_NAr (eq. 2)¹⁰ methods have also been reported in recent years, the currently available methods are obviously much less than those for the usual aryl thioethers.⁵⁻⁸ Besides, these methods still employ thiols as the starting material, which are smelly and toxic, sensitive and not easy to handle. Therefore, there is still a great need in the field to

develop greener and more efficient methods for heteroaryl thioethers especially by using odorless and more easily-handled sulfur reagents instead of the thiols.

Known methods:



This work:



Scheme 1. Methods for heteroaryl thioether synthesis.

We have been engaged in the preparation and synthetic and catalytic applications of organochalcogen compounds¹¹⁻¹² and heterocycle compounds¹² including the heteroaryl thioethers¹³ and chalcogen heterocycles.¹⁴ We have previously described a waste-free TBAX (X = Cl, Br)-catalyzed S_NAr reaction of heteroaryl halides with phenylthiotrimethylsilane (PhS-SiMe₃) via a fluorine-free halide ion-catalyzed S-Si bond activation process (Scheme 1, eq. 3).¹³ However, this method is mainly limited to heteroaryl phenyl thioethers due to the lower availability of other RS-SiMe₃ reagents than PhS-SiMe₃. We then considered using diorganyl disulfides as the alternative sulfur nucleophile precursors since they are not only as available as the corresponding thiols, but usually odourless, much lower in toxicity, and more easily stored and handled than the thiols. To our knowledge, although disulfides have been frequently used in aryl thioether synthesis by TM-

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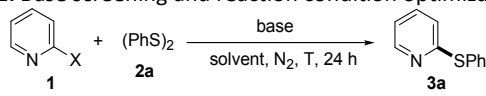
Electronic Supplementary Information (ESI) available: Experimental details, product characterization, and copies of ¹H NMR and ¹³C NMR spectra of the products. See DOI: 10.1039/x0xx00000x

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catalyzed coupling reactions with aryl halides,¹⁵ by benzyne-type reactions with aryl halides in super basic media,¹⁶ or by aromatic radical nucleophilic substitution ($S_{RN}1$) reaction with aryl halides in the presence of Sml_2 and $NaBH_4$,^{17,18} they have not been adopted in S_NAr reactions for heteroaryl thioether synthesis so far. Although heteroaryl thioethers could also be obtained from multi-step reactions of disulfides and heteroaryl halides,^{18,19} in these known methods the heteroaryl halides have to be converted first into the corresponding reactive and sensitive organometallic nucleophiles such as lithium, magnesium, and zincate reagents, which were then trapped by using disulfides as the sulfur electrophile (Scheme 1, eq. 4). Clearly, these methods have severe drawbacks such as the requirement of low temperature, strict anhydrous conditions, low tolerance of functional groups, and generation of wastes. Hence there is still much room for improvements in the synthesis of heteroaryl thioethers from disulfides and heteroaryl halides. As an ongoing interest in organochalcogen compounds^{11–13} and based-mediate/catalyzed synthesis of heterocycle derivatives,¹⁴ herein we report a new method for the synthesis of unsymmetrical heteroaryl thioethers by an efficient and practical NaOH-mediated S_NAr reaction of heteroaryl halides with disulfides (Scheme 1, eq. 5). This method can also be extended to the synthesis of unsymmetrical heteroaryl selenides and tellurides from the corresponding diselenides and ditellurides under similar conditions.

Various bases (2 equiv.) were initially evaluated in the model reaction of 2-chloropyridine (**1a**) and diphenyl disulfide (**2a**) in DMSO at 150 °C under nitrogen (Table 1).²⁰ Except the weak basic Na_2CO_3 that gave only a moderate yield of target product **3a** (run 1), strong basic alkali hydroxide bases all gave high yields of **3a** (runs 2–4). No obvious product formation was observed in the reaction without base (run 5), suggesting that base is crucial for the generation of the nucleophilic phenylthio anion (PhS^-) from $(PhS)_2$.^{15,16,20} Since NaOH is more economic, more available, lower in molecular weight, and easier to handle, it was used in further optimization of the reaction conditions. The reaction temperature and the amount of NaOH loaded could be reduced to 120 °C and 1.5 equiv. but still maintaining the high reaction efficiency (runs 6–7); while the reactions performed at lower temperatures or using even less amounts of NaOH only led to lower yields of **3a**. Solvent effect was also investigated at 120 °C using other usual solvents such as acetonitrile, toluene, DMF, etc. The results showed that DMSO is still the best one (runs 6, 8–10). For a control reaction under air, only a moderate yield of **3a** was obtained (run 11), most possibly because the in situ generated PhS^- is sensitive with air.¹⁵ The optimized conditions (run 7) could also be applied to 2-fluoro-, 2-bromo, and 2-iodopyridines, giving moderate to good yields of the product (runs 12–14). These results not only showed that all the heteroaryl halides are suitable substrates, but also suggested that the economic heteroaryl chlorides such as 2-chloropyridine (**1a**) are the most preferable ones.

Table 1. Base screening and reaction condition optimization.^a


run	X	base (equiv.)	T(°C)	solvent	3a % ^b
1	Cl	Na_2CO_3 (2.0)	150	DMSO	56
2	Cl	NaOH (2.0)	150	DMSO	95
3	Cl	KOH (2.0)	150	DMSO	94
4	Cl	$CsOH \cdot H_2O$ (2.0)	150	DMSO	99
5	Cl	none	150	DMSO	trace
6	Cl	NaOH (2.0)	120	DMSO	96
7	Cl	NaOH (1.5)	120	DMSO	96 (80)
8	Cl	NaOH (2.0)	120	CH_3CN	79
9	Cl	NaOH (2.0)	120	Toluene	64
10	Cl	NaOH (2.0)	120	DMF	94
11 ^c	Cl	NaOH (2.0)	120	DMSO	54
12	F	NaOH (1.5)	120	DMSO	87 (68)
13	Br	NaOH (1.5)	120	DMSO	96 (75)
14	I	NaOH (1.5)	120	DMSO	99 (70)

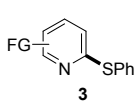
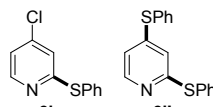
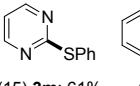
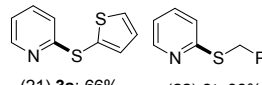
^a Unless otherwise noted, the mixture of **1** (0.5 mmol), **2a** (0.3 mmol), and base in a solvent (1.0 mL) was sealed under N_2 in a Schlenk tube, heated for 24 h, and monitored by TLC and/or GC-MS. ^b GC yields (isolated yield in parenthesis) based on **1**. ^c Under air.

The optimized conditions (Table 1, run 7) were then employed to extend the scope of the method. As shown in Table 2, both electron-donating and electron-withdrawing groups substituted 2-chloropyridines, including those with reactive groups such as amino, cyano, nitro, and chloro (runs 2, 5–8) that may undergo side reactions under strong basic conditions,^{7,8,21} could all react with **2a** efficiently to give the desired pyridyl phenyl thioethers **3a–3h** in moderate to good yields (runs 2–8). This suggested that, in above reactions with reactive groups (runs 2, 5–8), the potential side reactions in the NaOH/DMSO super base media^{7,16} might have been effectively avoided by the generation of the phenylthio anion (PhS^-) from $(PhS)_2$ and NaOH/DMSO, which in turn should be a rather efficient process to afford PhS^- , a more nucleophilic but less basic than the corresponding O- and N- nucleophiles.

In the cases of dichloropyridines with unreactive chloro groups at the 3- or 5-position (runs 7–8), the reactions were regiospecific and gave only the mono-substituted products under the standard conditions. While in reactions of dichloropyridines with reactive chloro groups at the 4- or 6-position (runs 9–12), a mixture of mono- and disubstituted products could be obtained under the standard conditions, with the mono-substituted product being the major one under the standard conditions (runs 9,11). When doubled amounts of **2a** and NaOH were used, the di-substituted products were obtained in high selectivities and in good yields (runs 10,12). In the case of 4-iodopyridine (**1k**), it also reacted smoothly with **2a** to give a moderate yield of the target **3k** (run 13), which may be attributed to the instability of the substrate. The same method could also be extended to other active heteroaryl halides such as 2-chloroquinoline, 2-chloropyrimidine, 2-chlorobenzothiazole, which gave good to high yields of the products (runs 14–16). Different to previous TBAX-catalyzed method that mainly limited to $PhS-SiMe_3$ and for the preparation of phenyl thioethers,¹³ the advantage of the

present methods is that various disulfides including diaryl, diheteroaryl, or dialkyl disulfides even dichalcogenides (R_2Se_2 , R_2Te_2) are all promising nucleophiles in the method. Thus, electron-rich disulfides without sterically bulky groups afforded good yields of the products (run 17, 19). In contrast, the reaction of di(2-aminophenyl) disulfide with steric hindrance from the *ortho*-amino group required a higher temperature to ensure a smooth reaction (run 18). The reaction of di(2-nitrophenyl) disulfide was not efficient at present most possibly due to its weak nucleophilicity attributed to the strong electron-withdrawing *ortho*-nitro group (run 20). Finally, diheteroaryl and dialkyl disulfides reacted efficiently with 2-chloropyridine to give good to high yields of the target thioethers under the standard conditions (runs 21–22).

Table 2. Unsymmetrical heteroaryl thioether synthesis.^a















$FG-\text{N} \begin{array}{c} \diagup \diagdown \\ \text{X} \end{array} + (RS)_2 \xrightarrow[\text{DMSO, N}_2, 120^\circ\text{C, 24 h}]{\text{NaOH (1.5 equiv.)}} FG-\text{N} \begin{array}{c} \diagup \diagdown \\ \text{SR} \end{array}$	
 (1) 3a : H, 80% (2) 3b : 3-NH ₂ , 67% ^b (3) 3c : 4-Me, 66% (4) 3d : 5-Me, 51% (5) 3e : 5-CN, 57% ^c (6) 3f : 5-NO ₂ , 77% ^c (7) 3g : 3-Cl, 79% (8) 3h : 5-Cl, 75%	 (9) 3i : 4-Cl, 69% (3i/3i' 90/10) (10) 3i' : 4-SPh, 79% (3i/3i' <1/99) ^d (11) 3j : 6-Cl, 80% (3j/3j' 99/1) (12) 3j' : 6-SPh, 78% (3j/3j' <1/99) ^d (13) 3k : 45% ^e (14) 3l : 90%
 (15) 3m : 61% (16) 3n : 88% (17) 3o : 61% (18) 3p : 52% ^f	 (19) 3q : 75% (20) 3r : trace (21) 3s : 66% (22) 3t : 88%

^a Unless otherwise noted, see run 7 of Table 1 for reaction conditions and X = Cl. FG = substituted functional group. Isolated yields of **3** were based on **1**. Ratios of the products in some reactions were determined by GC. ^b 60 h. ^c 150 °C, 60 h. ^d **1** (0.5 mmol), **2a** (0.6 mmol, 2.4 equiv.), NaOH (3.0 equiv.). ^e X = I. ^f 150 °C.

The reactions of diorganyldichalcogenides were then tested to extend the scope of the method for the synthesis of the corresponding unsymmetrical heteroaryl chalcogenides (Table 3). When the above standard conditions were initially applied to the reaction of 2-chloropyridine (**1a**) and diphenyldiselenide ($(PhSe)_2$ (**4**), the reaction was found not complete and gave only a moderate yield of the target 2-pyridyl phenyl selenide (**5a**). Base screening showed that, by simply replacing NaOH with KOH, the same reaction could proceed more efficiently to ensure full conversion of the reactants to give a high 88% isolated yield of **5a** (Table 3, run 1). Other halopyridines such

as electron-rich 5-methyl 2-chloropyridine (run 2), electron-deficient 2,3-dichloropyridine (run 3), and 4-iodopyridine (run 4) all reacted efficiently with $(PhSe)_2$ to give the target products. Similarly, other heteroaryl halides such as 2-chloroquinoline (run 5) and 2-chlorobenzothiazole also gave the target unsymmetrical heteroaryl phenyl selenides in good yields under the same conditions (run 5–6). Finally, the reactions of diphenyl ditelluride $(PhTe)_2$ was investigated, which gave only a very low yield of the target heteroaryl telluride under the above conditions (run 7). Using $CsOH \cdot H_2O$ as the base instead of KOH and conducting the reaction at 150 °C improved the product yield to 29% (run 8).

Table 3. Unsymmetrical heteroaryl chalcogenide synthesis.^a

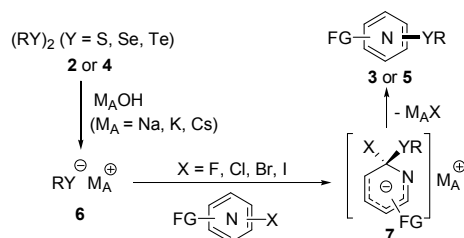
TABLE 1. General method for heteroaryl pyridines synthesis			
$\text{FG}-\text{N} \begin{array}{c} \diagup \diagdown \\ \text{X} \end{array} + (\text{PhY})_2 \xrightarrow[\text{DMSO, N}_2, 120^\circ\text{C, 24 h}]{\text{KOH (1.5 equiv.)}} \text{FG}-\text{N} \begin{array}{c} \diagup \diagdown \\ \text{YPh} \end{array}$			
Y = Se, Te			
run	1	5	Yield (%) ^b
1	 1a	 5a	88
2	 1d	 5b	88
3	 1g	 5c	86
4	 1k	 5d	42
5	 1l	 5e	77
6	 1n	 5f	70
7	 1a	 5g	9
8 ^c	1a	5g	29

^a Unless otherwise noted, the mixture of **1** (0.5 mmol), **4** (0.3 mmol), and KOH (0.75 mmol, 1.5 equiv.) in DMSO (1 mL) were stirred under N₂ at 120 °C for 24 h. ^b Isolated yield based on **1**. ^c $CsOH \cdot H_2O$ (0.75 mmol, 1.5 equiv.), 150 °C.

Based on above results and the literatures on S_NAr reactions of EWG-activated aryl halides and heteroatom-activated heteroaryl halides,^{8,10,13} a mechanism depicted in Scheme 2 was proposed for the present S_NAr reactions of heteroaryl halides with dichalcogenides.²² Thus, dichalcogenides **2** or **4** was first transformed into the corresponding RY[−] anion **6** by the bases.^{15,16,20} **6** then added to the heteroaryl halides to form dearomatized anion **7**, which is relatively stable due to the stabilization of the anionic charge on the ring by the electronegative heteroatoms in the ring.⁸ The final leaving of halide anion and rearomatization of **7** completes a typical S_NAr reaction to give the target unsymmetrical thioethers **3** or chalcogenides **5**.

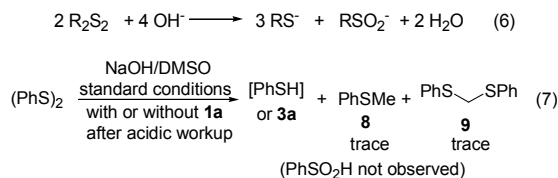
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Scheme 2. Proposed mechanism for M_AOH -mediated S_NAr reaction of heteroaryl halides with dichalcogenides.

However, how dichalcogenides are transformed into the corresponding RY^- anions **6** by the alkali bases and the stoichiometry between dichalcogenides and anions **6** are still not clear. Previous reports on the reactions of disulfides and bases provided no more insights on this subject.^{15,16} Whereas, a seminal work reported by Danehy and Hunter suggested that alkali treatment of aryl and alkyl disulfides may lead to 75% thiol and 25% sulfonic acid (eq. 6).^{18,22} However, although we tried many times on slightly different reactions under the standard conditions, and performed and analyzed the reactions with great care by means of NMR, GC-MS, TLC comparison with the authentic sample of sulfonic acid, even purification of the reaction residue containing the potential sulfonic acid, we could not isolate even merely observe any trace of sulfonic acid in these reactions.²³ In contrast, trace amounts of $PhSMe$ (**8**) and $PhSCH_2SPh$ (**9**) that are most possibly produced from the reactions of DMSO was detected in the reactions (eq. 7).^{24,25} This may suggest that in the media of alkali base and DMSO,^{15,16} generation of the thio anions does not follow Danehy and Hunter's proposal (eq. 6).^{22,23} Therefore, no more amounts of dichalcogenides than 0.3 mmol is needed in the reactions and usually good yields of the products could be obtained under the standard conditions.²⁰



In summary, an efficient NaOH-mediated S_NAr reaction of heteroaryl halides and disulfides has been developed for a practical synthesis of the useful unsymmetrical heteroaryl thioethers. The advantage of the method is that the usually odorless, easily available, lowly toxic, and easily stored and handled diorganyl disulfides can be used as the safer and more convenient sulfur nucleophile precursors instead of the smelling and toxic thiols, and a diverse unsymmetrical heteroaryl thioethers can be obtained in good to high yields by this method. Moreover, this method could also be extended to diselenides and ditellurides for the synthesis of unsymmetrical heteroaryl selenides and tellurides, largely extended the scope of the method in unsymmetrical heteroaryl chalcogenide synthesis. Further applications of the S_NAr method in

heteroaryl compound synthesis are still in progress in this group.

Acknowledgment

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Notes and references

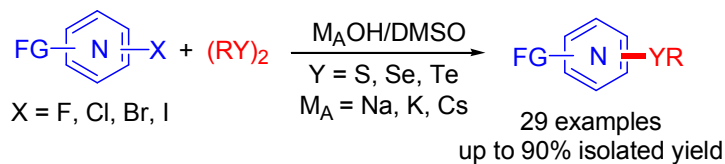
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Efficient Synthesis of Unsymmetrical Heteroaryl Thioethers and Chalcogenides by Alkali Hydroxide-Mediated S_NAr Reactions of Heteroaryl Halides and Dichalcogenides

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An efficient S_NAr reaction of heteroaryl halides and diorganyl dichalcogenides is developed for practical synthesis of the useful unsymmetrical heteroaryl thioethers and chalcogenides.
