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A simple one-pot synthesis of hydroxylated and carboxylated aryl alkyl sulfides from various bromobenzenes

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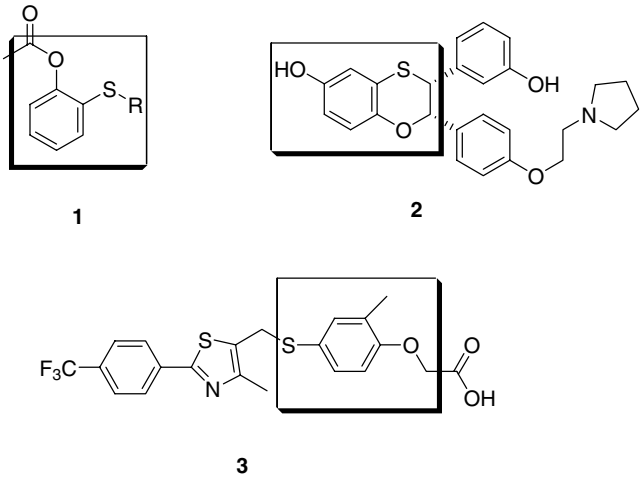
Abstract—A simple one-pot synthesis of aryl alkyl sulfides from various bromobenzenes containing a hydroxy, hydroxymethyl, hydroxyethyl, and carboxylic acid group at *-o*, *-m*, and *-p* positions is reported here. The reaction proceeds through, in sequence, in situ protection of the hydroxy or carboxylic acid group by reaction with a Grignard reagent, lithium-halogen exchange, the formation of lithium thiolates, and the nucleophilic attack of lithium thiolates on various electrophiles without isolation of the thiolates, in one vessel. This procedure required a very short reaction time (1–1.5 h) and gave the corresponding sulfides in 75–97% yields.

Aryl alkyl sulfides have a long and rich history as intermediates in organic synthesis.[1] In addition, aryl thiols and sulfides are incorporated into a number of natural products or compounds exhibiting biologically active properties.[2] In particular, many bioactive sulfides, such as cyclooxygenase-2 (COX-2) selective inhibitors, estrogen receptor (ER) selective modulators, and peroxisome proliferator-activated receptor (PPAR) agonists, contain a hydroxy functionality in their aryl moieties (Fig. 1).

In 1998, Marnett and co-workers reported on 2-acetoxyphenyl alkyl sulfides (**1**), a new class of selective COX-2 inhibitors.[3] The synthetic procedure included protection and deprotection reactions of the hydroxy functionality on the starting materials. Recently, the Merck research group reported the efficient asymmetric synthesis of a selective estrogen receptor modulator (SERM) that has a dihydrobenzoxathiin core structure (**2**) bearing two stereogenic centers.[4] They used 4-(benzyloxy)-2-mercaptophenol as a key intermediate and synthesized it through 3 steps from 1,4-benzoquinone. In addition, the research group of GlaxoSmithKline reported the discovery and synthesis of GW501516 (**3**), the most effective and selective ligand for PPARδ.[5] The core structure of GW501516 contained a hydroxylated aryl alkyl sulfide moiety. They used hydroxy acetophenone as a starting material to synthesize a mercaptophenol derivative. However, the procedure involved multiple



1 2 3

Figure 1. Important pharmaceutical drug candidates with aryl alkyl sulfides containing hydroxy functionality.

Keywords: Hydroxylated and carboxylated aryl alkyl sulfides; Thioethers; Grignard reagent; Sulfur; Halogen lithium exchange; Lithium aryl thiolates.
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steps, resulted in a low yield, and was achieved under drastic conditions. Later the Kozikowski group reported a more efficient method for the synthesis of GW501516.[6] They synthesized the key intermediate, 4-mercapto-2-methylphenol, from *o*-cresol through two steps, performed the coupling reaction with thiazole chloride and obtained the corresponding aryl alkyl sulfide. Recently, Hartwig and co-workers reported palladium-catalyzed coupling of aryl chlorides with thiols using CyPF-*t*-Bu ligand.[7] Yet it is still inconvenient because of the involvement of unstable thiols. Therefore, a much simpler method, of greater efficiency, for the synthesis of aryl alkyl sulfides containing a hydroxy functionality has been required in organic and medicinal chemistry. Recently, we reported the general synthesis of aryl alkyl sulfides from aryl bromides and applied the methodology for the synthesis of an antiobestic drug, GW501516.[8] We then further extended our one-pot procedure to prepare hydroxylated and carboxylated aryl alkyl sulfides. In this letter, we want to report an efficient one-pot synthesis of aryl alkyl sulfides containing a hydroxy functionality such as hydroxy, hydroxymethyl, hydroxyethyl, and carboxylic acid group via in situ protection of the group by reaction with the Grignard reagent, isopropyl magnesium chloride. We obtained the corresponding sulfides in high yields (75–97%). The method overcame many problems encountered in other reports: being very quick, catalyst-free, and involving no unstable thiols.

We screened suitable bases and reagent equivalence for optimization of the reaction by using 4-bromophenol and benzyl bromide (Table 1).

When *n*-butyllithium (2.0 equiv) or *t*-butyllithium (3.0 equiv) was used, as a base to protect the phenolic hydroxy group and lithium-halogen exchange reagent, the reaction gave a low yield and resulted in many impurities (entries 1 and 2). However, in the case of a Grignard reagent, such as isopropyl magnesium chloride, being used as a base, the yield was high and the level of impurities decreased (entries 3 and 4). In entry 3, *n*-butyl bromide, which is formed by lithium-halogen exchange reaction, competed with benzyl bromide in nucleophilic substitution reaction, thus forming 4-butylsulfanylphenol as a side product. Therefore, the use of *n*-butyllithium as a lithium-halogen exchanger was not viable. In the case of entry 4 condition, 1 equiv of *t*-butyllithium was used for lithium-halogen exchange reaction and the rest of *t*-butyllithium (1 equiv) for the removal of *t*-butyl bromide formed during the lithium-halogen exchange.

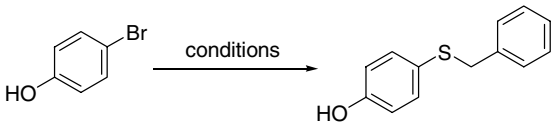
The general procedure for these reactions is as follows.

To a solution of aryl bromide at 0 °C, a solution of Grignard reagent (1.0 equiv) was added for the protection of the hydroxy group and then *tert*-butyllithium (2.0 equiv) was added to the reaction solution at −78 °C under nitrogen atmosphere. Through lithium-halogen exchange of bromide by *t*-butyllithium, an aryllithium salt was formed. Sulfur powder (1.0 equiv) was then added to the reaction mixture, thus forming lithium aryl thiolate. Because the generated lithium thiolate is a good nucleophile, after adding an electrophile, the corresponding aryl alkyl sulfide was obtained in a good yield.

We set up many reactions to explore the scope of this methodology with respect to various hydroxylated and carboxylated aryl bromides as substrates. The reaction was unaffected by the electronic factor of aryl bromides but moderately affected by the electrophilic affinity of alkyl halides reacting with various lithium aryl thiolates (see below). This one-pot procedure required very short reaction times (1–1.5 h) and gave the products in high yields (75–97%).

In the first part of this study, we applied this reaction to the coupling of hydroxylated aryl bromides and various electrophiles (Table 2). Phenols, having a bromide at -*o*, -*m*, or -*p* position, readily reacted with benzyl bromide to give the corresponding sulfides in high yields of 92%, 96%, and 92%, respectively, without regard to the electronic factor caused by the hydroxy functionality (entries 1–3). An electron withdrawing group such as a fluoride on aryl bromides did not affect the reactivity (entries 4–7, and entry 10). It was found that activated alkyl bromides gave the corresponding sulfides in slightly better yields than alkyl bromides did (entries 4, 6, and 7). Epoxide readily reacted with lithium thiolate, which was formed from bromophenol, to give the corresponding sulfide at a high yield (entry 10). In the case of bromo-resorcinol having two hydroxy functionalities,

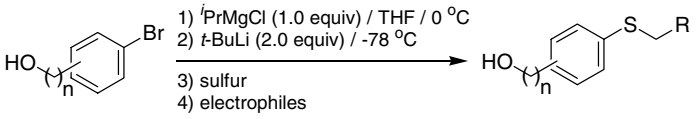
Table 1. Optimization of reaction conditions for one-pot synthesis of sulfide[a]

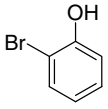
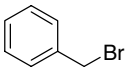
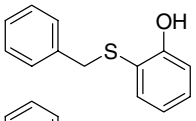
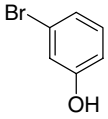
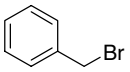
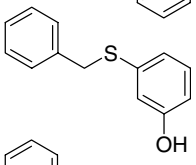
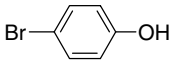
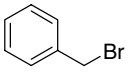
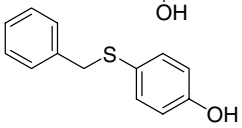
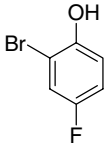
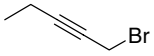
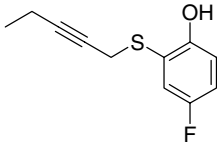
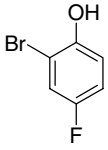
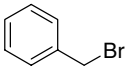
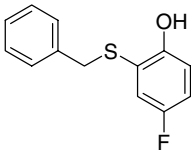
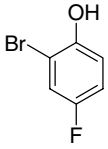
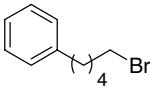
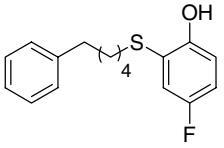
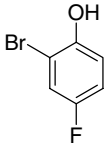
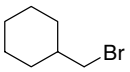
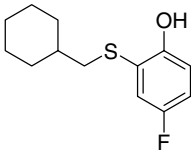
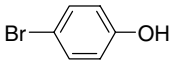
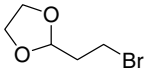
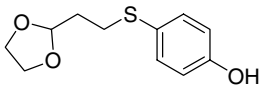
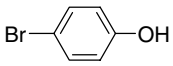
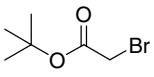
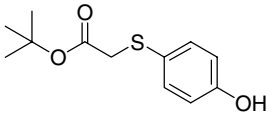
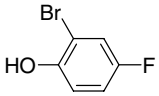
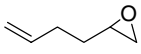
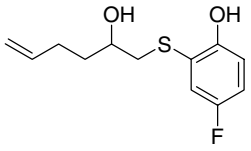


Entry	Conditions	% Yield[b]
1	*n*-BuLi (2.0 equiv), sulfur, benzyl bromide, THF	31
2	*t*-BuLi (3.0 equiv), sulfur, benzyl bromide, THF	39
3[c]	^{i}PrMgCl (1.0 equiv), *n*-BuLi (1.0 equiv), sulfur, benzyl bromide, THF	52
4	^{i}PrMgCl (1.0 equiv), *t*-BuLi (2.0 equiv), sulfur, benzyl bromide, THF	92

[a] All reactions were performed with 4-bromophenol (0.5 mmol), sulfur (1.0 equiv), and benzyl bromide (1.0 equiv).
[b] Yields refer to the average isolated yield of two runs.
[c] 4-Butylsulfanylphenol was isolated as a side product at 35% yield.

Table 2. A simple one-pot synthesis of hydroxylated aryl alkyl sulfides



Entry	Halophenol	Electrophiles	Products	% Yield[a]
1				92
2				96
3				92
4				89
5				95
6				83
7				81
8				78
9[10]				87
10				85
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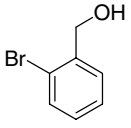
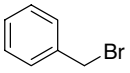
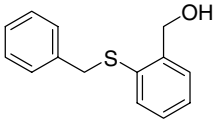
11				94

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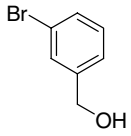
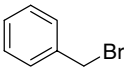
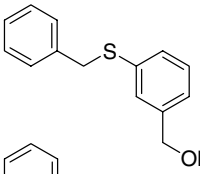
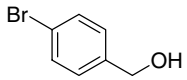
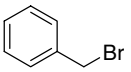
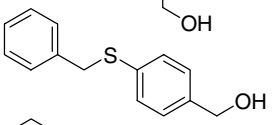
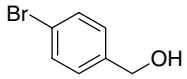
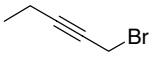
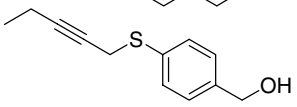
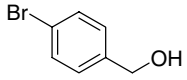
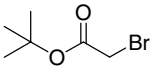
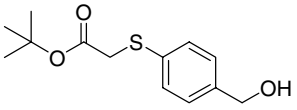
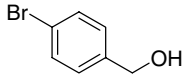
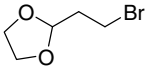
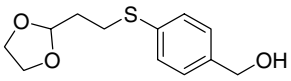
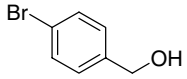
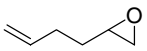
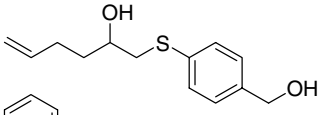
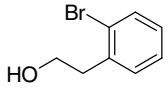
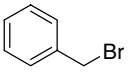
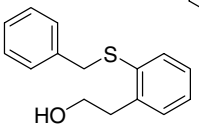
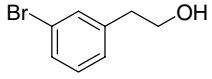
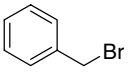
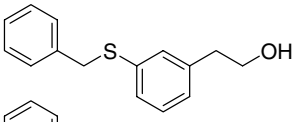
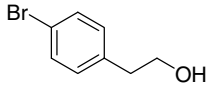
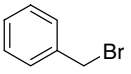
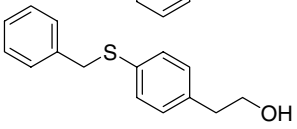
Table 2 (*continued*)

Entry	Aryl bromide	Electrophiles	Products	% Yield[a]
12				89
13				92
14				91
15				89
16				75
17				83
18[b]				91
19[b]				90
20[b]				90

[a] Yield refer to the average isolated yield of two runs.
[b] More reaction time was required (1.5 h).

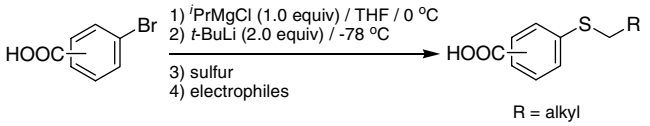
the lithium-halogen exchange reaction did not proceed because of the poor solubility of the dimagnesium salt formed by reacting the two hydroxy groups with isopropyl magnesium chloride in THF (data not shown).

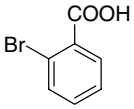
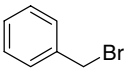
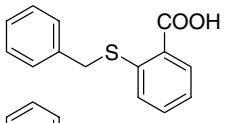
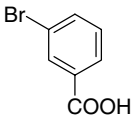
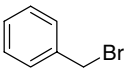
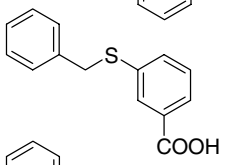
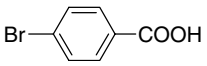
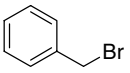
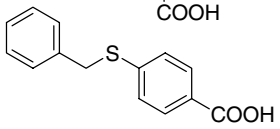
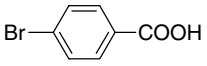
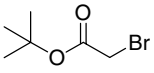
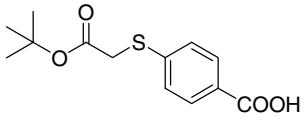
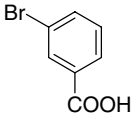
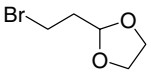
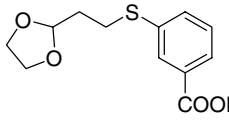
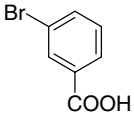
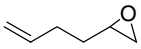
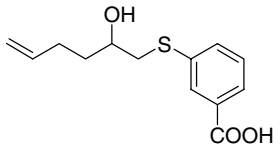
Like a reaction of bromophenol, the reaction was unaffected by electronic factor directed by the *ortho*, *meta*, and *para* positions of the hydroxylmethyl or hydroxyethyl group (entries 11–13, 18–20). In all cases, alkylation of the lithium thiolates with electrophiles leads to selective S-alkylation products (Table 2). In the case of hydroxyethyl bromobenzene (Table 2, entries 18–20), the solubility of the corresponding magnesium salt formed by its reaction with isopropyl magnesium chloride in THF was low and hence more reaction time was required for the lithium-halogen exchange reaction (about 1.5 h).

This newly developed synthetic protocol for aryl alkyl sulfides was also applied to bromobenzoic acid (Table 3). Carboxylic acid group was more effectively protected by isopropyl magnesium chloride than by alkyllithium (Table 3). Generally, the carboxylic acid group on benzene ring acts as an electron withdrawing group. But, the electron withdrawing effect of carboxylic acid did not affect the reactivity of lithium-halogen exchange reaction in our method. In the case of bromobenzoic acid, the reaction gave a better yield for *m*-bromobenzoic acid than for the other two regioisomers (entries 1–3). Because of the low reactivity of saturated alkyl halide and epoxides as electrophiles the reactions gave lower yields than the reaction with benzyl bromide (entries 5 and 6). Bromoacetate readily reacted with lithium thiolate to give the corresponding sulfide at a high yield of 88% (entry 4).

In summary, we have developed a convenient one-pot procedure for the production of hydroxylated or carboxylated aryl alkyl sulfides from commercially available and inexpensive aryl bromides containing a hydroxyl or carboxylic acid functionality by in situ protection of the group by reaction with a Grignard

Table 3. A simple one-pot synthesis of aryl alkyl sulfides from various bromobenzoic acids[a]



Entry	Bromobenzoic aicds	Electrophiles	Products	% Yield[b]
1				88
2				97
3				92
4				88
5				82
6[11]				83

[a] The aqueous layer was acidified to approximately pH 3.0 with aqueous 1 N HCl.
[b] Yield refer to the average isolated yield of two runs.

reagent. With protection and deprotection steps being omitted through in situ protection by Grignard reagent, this method is easy to use and highly efficient in various synthetic occasions such as SERM.[9]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.056.

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9. The key intermediate ketosulfide was synthesized from 1,4-benzoquinone in 67% yield (3 steps, Ref. 4). However, the ketosulfide was prepared from 4-methoxyphenol in 90% yield by using our one-pot method (1 step from 2-bromo-4-methoxyphenol, patent pending, data not included).
10. All compounds' structures have been confirmed by ^{1}H, ^{13}C NMR and GC–MS. The selected spectroscopic data are reported below (Table 2).
tert-Butyl 2-(4-hydroxyphenylthio)acetate (entry 9) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.36 (m, 2H), 6.69–6.75 (m, 2H), 6.60 (br, 1H), 3.43 (s, 2H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 156.7, 134.9, 124.6, 116.6, 82.7, 40.2, 28.4. HRMS (ESI) calculated for $C_{12}H_{16}O_3S$, *m*/*z* 240.0820, found *m*/*z* 240.0826.
11. All compounds' structures have been confirmed by ^{1}H, ^{13}C NMR and GC–MS. The selected spectroscopic data are reported below (Table 3).
3-(2-hydroxyhex-5-enylthio)benzoic acid (entry 6) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09–8.10 (m, 1H), 7.92–7.94 (m, 1H), 7.58–7.62 (m, 1H), 7.37–7.42 (m, 1H), 5.76–5.82 (m, 1H). 4.95–5.07 (m, 2H), 3.75 (m, 1H), 3.18–3.24 (m, 1H), 2.91–2.99 (m, 1H), 2.17–2.24 (m, 2H), 1.63–1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 138.3, 137.1, 135.0, 131.2, 130.6, 129.5, 128.5, 115.6, 69.5, 42.1, 35.6, 30.3. HRMS (ESI) calculated for $C_{13}H_{16}O_3S$ *m*/*z* 252.0820, found *m*/*z* 252.0820.