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A Facile One-Pot Preparation of Alkyl Aminoaryl Sulfides for the Synthesis of GW7647 as an Agonist of Peroxisome Proliferator-Activated Receptor α

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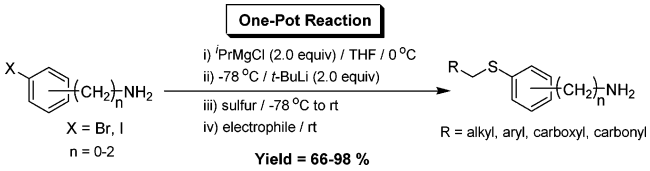

We have developed two simple and high yielding one-pot syntheses of alkyl aminoaryl sulfides containing a series of four-steps: in situ protection of the free amine by reaction with a Grignard reagent, halogen−lithium exchange, sulfur insertion, and a substitution reaction with various electrophiles. Through this protocol, we have successfully synthesized *tert*-butyl-2-[4-(2-aminoethyl)phenylsulfanyl]-2-methylpropanoate, a key intermediate for the synthesis of GW7647 and GW9578 (ureido-TiBAs), in 92% yield. Furthermore, we were able to improve the overall yield of GW7647 to 66%, 3 times the yield previously reported.

Alkyl aminoaryl sulfides are very useful moieties in many pharmaceutical compounds and are common building blocks to synthesize bioactive natural products in organic chemistry.[1] However, despite the importance of alkyl aminoaryl sulfides, streamlined methods for synthesizing these sulfides have not been fully investigated. Generally, most alkyl aminoaryl sulfides are prepared by a substitution reaction of electrophiles, such as organic halides and/or epoxides, etc., with alkali metal aminoaryl thiolate which is generated from 2-, 3-, and/or 4-aminothiophenol in the presence of strong alkaline bases.[2] Although these classical methods result in good yields, there is limited availability of aminothiophenol derivatives from commercial sources. In 1989, McKinnie and Ranken reported the synthesis of alkyl aminoaryl sulfides from aromatic amines and aliphatic disulfides in the presence of Lewis acid catalysts, such as $AlCl_3$ and CuI, at 130−170 °C.[3] Taniguchi et al. have shown that alkyl aminoaryl sulfides can be synthesized by nickel-catalyzed ($NiBr_2$-bpy/Zn) alkyl- or arylthiolation of aryl iodide with a disulfide in moderate yields.[4] However, the above methods are limited by their long reaction times and high reaction temperatures.

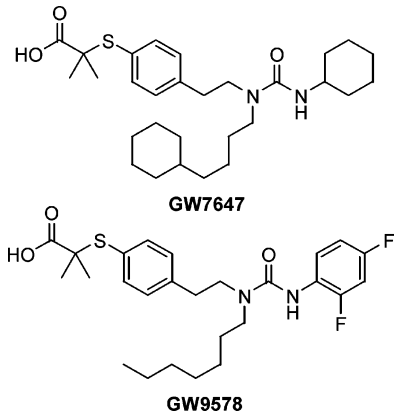

FIGURE 1. Chemical structures of GW7647 and GW9578 (ureido-TiBAs) as PPARα synthetic agonists.

Recently, the research group of GlaxoSmithKline discovered a series of urea-substituted thioisobutyric acids (ureido-TiBAs), such as GW7647 and GW9578, containing an alkyl aminoaryl sulfide bond (Figure 1), which are known to be highly selective agonists of peroxisome proliferator-activated receptor α (PPARα) and a potential therapeutic remedy for dyslipidemia.[5]

However, the synthesis of alkyl aminoaryl sulfide as the key intermediate in the preparation of GW7647 was complicated, and its yield was only 53%, so the target compound (GW7647) was obtained in only 20% overall yield. This demonstrates the need for a new method of synthesis of alkyl aminoaryl sulfides that can be easily used for the construction of new medicinal agents.

In our previous report, we showed that various alkyl aryl sulfides could be easily obtained through the substitution reaction of various electrophiles and lithium aryl thiolates that

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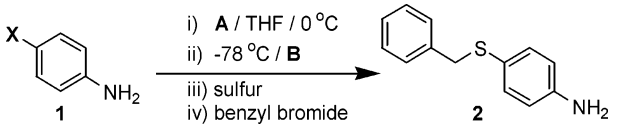
TABLE 1. Optimization of Reaction Conditions for the One-Pot Synthesis of Alkyl Aminoaryl Sulfide[a]



entry	X	**A** (equiv)	**B** (equiv)	% yield[b]
1	I	none	*n*-BuLi (3.0)	no reaction
2	I	none	*t*-BuLi (4.0)	no reaction
3	I	^{i}PrMgCl (3.0)	none	no reaction
4[c]	I	^{i}PrMgCl (2.0)	*n*-BuLi (1.0)	53
5	I	^{i}PrMgCl (2.0)	*t*-BuLi (2.0)	94
6	Br	^{i}PrMgCl (2.0)	*t*-BuLi (2.0)	88
7	Cl	^{i}PrMgCl (2.0)	*t*-BuLi (2.0)	no reaction

[a] Reaction conditions: 0.5 mmol of 4-haloaniline (**1**), 0.5 mmol of powdered sulfur, 0.5 mmol of benzyl bromide, dried THF (5 mL), 0 °C (added **A**), −78 °C (added **B**), −78 °C to room temperature (after addition of sulfur), 0 °C (added benzyl bromide), under N_2. [b] Yields were given for isolated products and average values of triplicate reactions. [c] 4-Butylsulfanylphenylamine as a side product was isolated in 32% yield.

were prepared in situ from the corresponding aryl bromides, *n*-BuLi, and sulfur powder.[6] On the basis of the previous work, we expected to find a new method for the formation of alkyl aminoaryl sulfides using aminoaryl halides as starting materials. In this paper, we wish to report a one-pot synthesis of alkyl aminoaryl sulfides from various aminoaryl halides and electrophiles. We also utilized this method in a formal synthesis of GW7647.

As a starting point, we needed to choose an appropriate amine protecting group in the various haloanilines used as starting materials. The protection group should be stable during the lithium−halogen exchange conditions and easily removed under neutral conditions at the end of the reaction. In this regard, a good way to protect the amine group of a haloaniline in situ would be by using a Grignard reagent. Indeed, Bumagin and Luzikova reported a protection method for free amine groups using Grignard reagent in 1997.[7] However, the strategic point of their report was not the preparation of sulfide derivatives but an alkyl aryl cross-coupling under palladium catalysis. Therefore, as a model reaction, we attempted to synthesize 4-benzylsulfanylphenylamine (**2**) through a one-pot reaction, including in situ protection of the amine group by reaction with a Grignard reagent. The results of the initial test are summarized in Table 1.

Initially, *n*-butyllithium (3.0 equiv), *tert*-butyllithium (4.0 equiv), or *iso*-propylmagnesium chloride was chosen for the in situ protection of the free amine and for the metal−halogen exchange. However, these reactions resulted in no reaction (Table 1, entries 1−3). On the other hand, when Grignard reagent (2.0 equiv) was used to pretreat the haloaniline before the metal−halogen exchange, we were able to obtain compound **2** in various yields depending on the lithium reagent used and the halide in the haloaniline (Table 1, entries 4−6). The best result was achieved with a combination of *iso*-propylmagnesium chloride (2.0 equiv) at 0 °C in the amine protection step and *tert*-butyllithium (2.0 equiv) at −78 °C in the halogen−lithium exchange step (Table 1, entry 5). From the reaction conditions, we were able to obtain the desired compound **2** in 94% yield. Concerning the reactivity of halides on **1** (Table 1, entries 5−7), 4-iodo- and 4-bromoaniline provided excellent yields of the respective sulfide compound (**2**). However, 4-chloroaniline did not undergo lithium−halogen exchange and resulted in recovered starting material. As might be expected, the in situ protection of the free amine by reaction with *iso*-propylmagnesium chloride was shown to be extremely stable under our reaction conditions and was easily removed by aqueous NH_4Cl solution at the end of reaction.

On the basis of the preliminary study, we performed the one-pot synthesis of alkyl aminoaryl sulfides (**4**) with various haloanilines (**3**) and electrophiles. The results are summarized in Table 2.

In the reactivity test of *ortho*-, *meta*-, and *para*-haloanilines, yields of the target sulfides were shown to increase according to the order of *para* > *meta* > *ortho* under the same conditions (Table 2, entries 1−3). Although, *ortho*-substituted sulfides were obtained in a low yield (66%) when using 2-bromoaniline as the starting material, both *para*- and *meta*-substituted sulfides could be obtained in 81−94% yields from bromo- and/or iodoaniline(s).

In the synthesis of dialkyl-substituted aminoaryl sulfide using 2,4-dibromoaniline (Table 2, entry 4), despite all the reagents for 2,4-dibromoaniline being used at twice the amounts of those used in the previous cases, we were not able to obtain any of the desired product except for a monoalkyl-substituted aminoaryl sulfide, 4-benzylsulfanyl-2-bromophenylamine in 74% yield. Also, the presence of an electron-donating or -withdrawing group on the haloaniline or electrophile (Table 2, entries 5 and 6) did not affect yields of products (86 and 89%, respectively).

In the reactivity study of various electrophiles, activated alkyl halides, such as benzylic, allylic, carbonyl, or carboxyl (Table 2, entries 3, 7, 8, and 9), gave good yields (92−95%). By contrast, saturated alkyl bromides, such as 5-bromopentyl benzene (Table 2, entry 10) or bromomethyl cyclohexane (Table 2, entry 11), took longer (about 2 h) to complete the substitutions and gave lower yields under the same conditions (84 and 81%, respectively). Also, 1,2-epoxy-5-hexene (Table 2, entry 12) gave the desired sulfide in 87% yield.

Although we did not directly detect the generated intermediates during the one-pot synthesis of alkyl aminoaryl sulfide (**4**), we assumed the presence of those compounds at each step from the yields of the target compounds at the end of the reaction.

From the results of the alkyl aminoaryl sulfide reaction, we anticipated that our protocol could be expanded to the synthesis of alkyl (aminoalkyl)aryl sulfides (**6**), such as *tert*-butyl-2-[4-(2-aminoethyl)phenylsulfanyl]-2-methylpropanoate, which is a key intermediate of GW7647 (Figure 1). Although GW7647 is known to be a very effective and selective agonist of PPARα, the synthesis of the key intermediate sulfide consists of four steps and suffers from long reaction times, expensive reagents, such as Wilkinson's catalyst, and lower 53% overall yield.[5] The other method used sulfenylation of dimethyl ketene acetal with benzene sulfenyl chloride. Yet it required disulfide formation in the beginning and amination of the phenethyl chloride at the end.[8] We attempted a formal synthesis of GW7647 by applying the alkyl aminoaryl sulfide method. First, we performed the reaction using 4-bromobenzylamine hydrochloride and 4-bromophenethylamine (**5**) as starting materials (Table 3). Carrying

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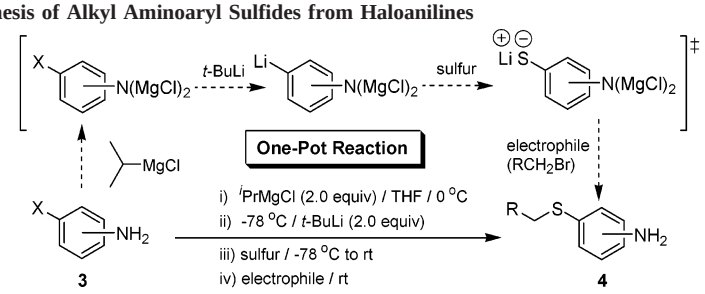
TABLE 2. Simple One-Pot Synthesis of Alkyl Aminoaryl Sulfides from Haloanilines



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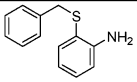
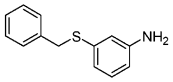
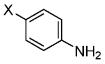
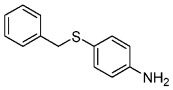
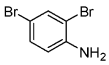
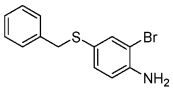
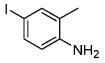
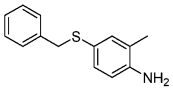
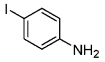
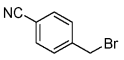
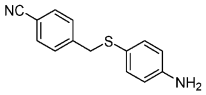
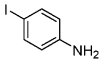
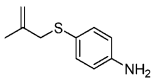
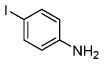
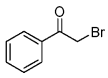
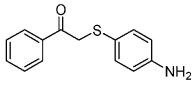
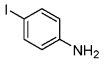
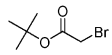
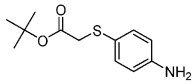
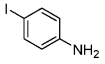
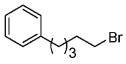
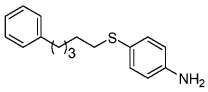
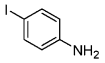
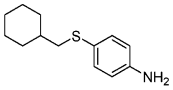
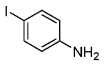
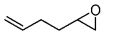
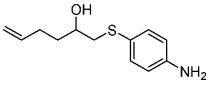
1				X = I 74 Br 66
2				X = I 83 Br 81
3				X = I 94 Br 88
4				74
5				86
6				89
7				93
8				92
9				95
10				84
11				81
12[b]				87

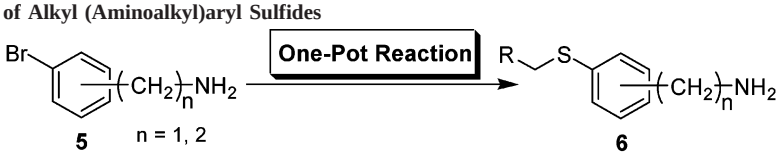
[a] Yields were given for isolated products. [b] Epoxide used as an electrophile was a racemic mixture.

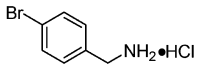
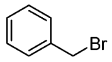
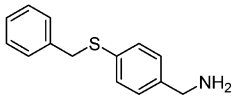
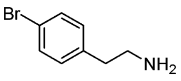
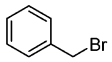
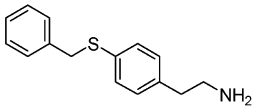
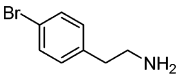
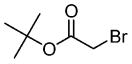
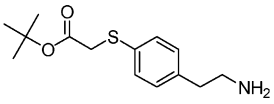
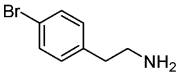
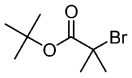
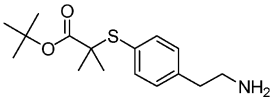
out the reaction with benzyl bromide (Table 3, entries 1 and 2), *tert*-butyl bromoacetate (Table 3, entry 3), and *tert*-butyl-α-bromoisobutyrate (Table 3, entry 4) as electrophiles gave the respective product in good yields (92−98%). When 4-bromobenzylamine hydrochloride was used (Table 3, entry 1), we added 1.0 equiv excess of *iso*-propylmagnesium chloride (3.0 equiv in total) to the reaction without an additional step for removing HCl from the starting material.

Although the *tert*-butyl-2-[4-(2-aminoethyl)phenylsulfanyl]-2-methylpropanoate was not obtained under the general conditions, we could successfully prepare the desired compound in 92% yield by changing the solvent from THF to methanol after formation of lithium thiolate, using KOH as a strong base, and refluxing for 1 h. After solving a problem of the key step, we completed the synthesis of GW7647 according to a modified procedure of GlaxoSmithKline's[5] and obtained the GW7647 in 66% overall yield (data not shown). Compared to the previous procedure, our one-pot synthesis is very quick, convenient, and economical.

In summary, we have developed a simple one-pot synthesis of alkyl aminoaryl sulfide through in situ protection of the free amine by reaction with a Grignard reagent. Using this method, we have successfully obtained *tert*-butyl-2-[4-(2-aminoethyl)-phenylsulfanyl]-2-methylpropanoate, which is a key intermediate

TABLE 3. One-Pot Synthesis of Alkyl (Aminoalkyl)aryl Sulfides



entry	5	electrophile	Product (6)	yield (%)[a]
1[b]				96
2				98
3				94
4[c]				92

[a] Yields were given for isolated products. [b] Reaction was performed in the presence of 3.0 equiv of ^{i}PrMgCl. [c] See Experimental Section for detailed reaction conditions.

of GW7647 and GW9578 (ureido-TiBAs), in 92% yield. Finally, we were able to obtain the desired compound (GW7647) in 66% overall yield. Therefore, our method could be a useful protocol for the preparation of pharmaceutical drugs and their intermediates containing various alkyl aminoaryl sulfides.

Experimental Section

General Procedure for the Formation of Alkyl Aminoaryl Sulfides (Table 2). To a solution of haloanilines (2.0 mmol) in anhydrous THF (30 mL) was added a solution of ^{i}PrMgCl (2.0 M solution in diethyl ether, 4.0 mmol) at 0 °C under N_2 atmosphere, and a solution of *t*-BuLi (1.7 M solution in pentane, 4.0 mmol) was slowly added for 15 min at −78 °C. After 30 min, sulfur powder (2.0 mmol) was then added, and the reaction mixture was slowly warmed to room temperature for 30 min. Finally, alkyl halide (2.0 mmol) was added at 0 °C. The reaction was monitored by thin-layer chromatography. After the reaction was complete, it was quenched with aqueous NH_4Cl (35 mL). The organic layer was separated, and then the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product. The crude compound was purified by chromatography on silica gel to obtain the desired product.

General Procedure for the Formation of Alkyl (Aminoalkyl)-aryl Sulfides (Table 3). To a solution of 4-bromobenzylamine hydrochloride or 4-bromophenethylamine (2.0 mmol) in anhydrous THF (30 mL) was added a solution of ^{i}PrMgCl (2.0 M solution in diethyl ether, 4.0 mmol) at 0 °C under N_2 atmosphere, and then a solution of *t*-BuLi (1.7 M solution in pentane, 4.0 mmol) was slowly added for 15 min at −78 °C. After 30 min, sulfur powder (2.0 mmol) was added, and the reaction mixture was slowly warmed to room temperature for 30 min. Finally, alkyl halide (2.0 mmol) was slowly added. The reaction was monitored by thin-layer chromatography. After the reaction was completed, the reaction mixture was quenched with aqueous NH_4Cl (35 mL). The organic layer was separated, and then the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined extract was washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product. The crude compound was purified by chromatography on silica gel to obtain the desired compound.

Preparation of *tert*-Butyl-2-[4-(2-aminoethyl)phenylsulfanyl]-2-methylpropanoate (Table 3, entry 4). To a solution of 4-bromophenethylamine (400.2 mg, 2.0 mmol) in anhydrous THF (30 mL) was slowly added ^{i}PrMgCl (2.0 M solution in diethyl ether, 2.0 mL, 4.0 mmol) at 0 °C for 10 min under N_2. After 30 min, *t*-BuLi (1.7 M solution in pentane, 2.4 mL, 4.0 mmol) was slowly added at −78 °C for 20 min, and the reaction mixture was stirred for an additional 30 min. Sulfur powder (64 mg, 2.0 mmol) was added at once, and the reaction mixture was slowly warmed to room temperature for 30 min. After the reaction was complete, the solvent was completely removed by an evaporator under the atmosphere. To a solution of the residual product in MeOH (30 mL) was added KOH (117.8 mg, 2.1 mmol). The reaction mixture was heated at 60 °C for an additional 1 h. After that time, the reaction mixture was poured into a NH_4Cl solution (35 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with H_2O, dried ($MgSO_4$), filtered off, and then concentrated on a rotary evaporator. The crude compound was purified by chromatography (eluent: 5% MeOH in CH_2Cl_2) on silica gel to obtain the desired compound (544 mg, 92%).

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Supporting Information Available: Experimental procedures, spectral characterization, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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