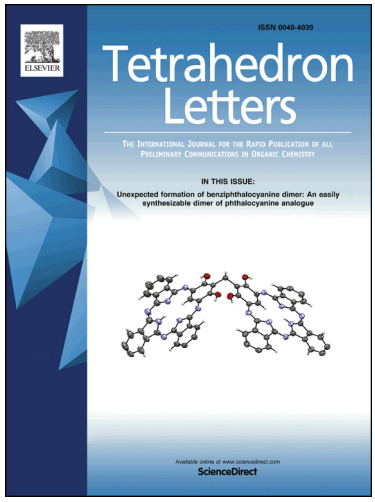

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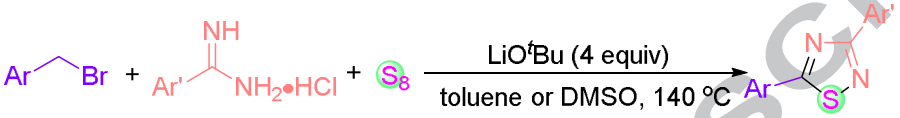

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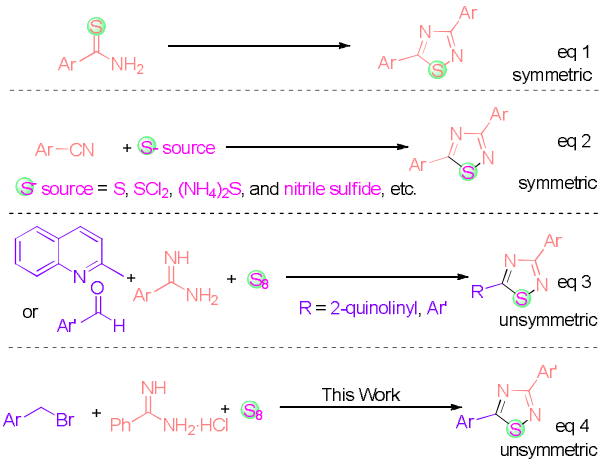
ABSTRACT

A base-promoted three-component reaction between arylmethyl bromides, arylamidines and elemental sulfur was developed, leading to unsymmetric 3,5-diaryl-1,2,4-thiadiazoles in moderate to good yields with chemical diversity and complexity. This procedure shows broad substrates scope by employing elemental sulfur and commercially available starting materials under transition-metal free conditions.

1,2,4-Thiadiazoles are important five-membered heterocycles with broad biological and pharmaceutical activities.[1,2] Among which, the 3,5-diaryl- analogues serve as sphingosine 1-phosphate receptor agonists,[3] antifungal agents,[4] and antibacterial reagents.[5] Compared with the intramolecular cyclization toward such frameworks,[6] the intermolecular pathway features the simplicity for preparing starting materials as well as diversity of the final products. For example, the oxidative dimerization of either thioamides (Scheme 1, eq 1),[7] or the annulation of aryl nitriles with sulfur,[8] SCl_2,[9] $(NH_4)_2S$[10] and nitrile sulfide[11] (Scheme 1, eq 2) allowed rapidly to construct symmetric 3,5-diaryl-1,2,4-thiadiazole. Unfortunately, the cross-dimerization of two kinds of thioamides resulted in the distribution of four 1,2,4-thiadiazole with extremely low selectivity.

From both diversity and complexity points of view, either the development of methodologies or the proper substrate design toward unsymmetric 3,5-diaryl-1,2,4-thiadiazole kept highly desired goal for organic chemists, yet challenging. And no examples were reported till Deng developed the annulation between amidines, elemental sulfur, and 2-methylquinolines (or aromatic aldehydes) under transition-metal-free conditions (Scheme 1, eq 3).[12] As our continuous interest in the synthesis of thiadiazole,[13] herein, we wish to report a three-component reaction between arylmethyl bromides, arylamidines and elemental sulfur toward unsymmetric 3,5-diaryl-1,2,4-thiadiazole (Scheme 1, eq 4). This procedure features: 1) high chemical diversity and complexity of the products by multicomponent reaction; 2) the employment of elemental sulfur[14] and commercially available starting material under transition metal-free conditions; 3) wide substrates scope.

Scheme 1. Synthetic Pathways toward 3,5-Diaryl-1,2,4-Thiadiazoles



Initially, we tested the reaction of (4-tolyl)methyl bromide (**1a**), benzamidine hydrochloride (**2a)** and sublimed sulfur in toluene at 140 °C under N_2 in the presence of 4 equivalent of K_2CO_3 as the model reaction. To our delight, 3,5-diaryl-1,2,4-thiadiazole **3aa** was isolated in 19% yield (Table 1, entry 1). Replacing K_2CO_3 with NaO^{t}Bu increased the yield to 34% (Table 1, entry 2). A comparable 31% yield was obtained in the case of KO^{t}Bu (Table 1, entry 3). The yield dramatically increased to

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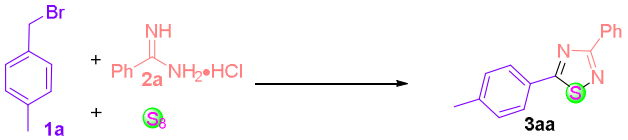
66% by using LiO^{t}Bu (Table 1, entry 4). Under an air or O_2 atmosphere, the reaction efficiency significantly decreased to 47% and 23%, respectively. So did the procedure under elevated (59%, 150 °C) or lower (51%, 130 °C) reaction temperature (Table 1, entry 4). The solvent tests demonstrated toluene was the best (66%), though DMSO provided the product **3aa** in an acceptable 58% yield (Table 1, entries 5-9). The practicability of this procedure was further increased since **3aa** was isolated in a comparable 62% yield in a 1 mmol scale reaction.

Table 1. Selected Results for Screening the Optimized Reaction Conditions[a]

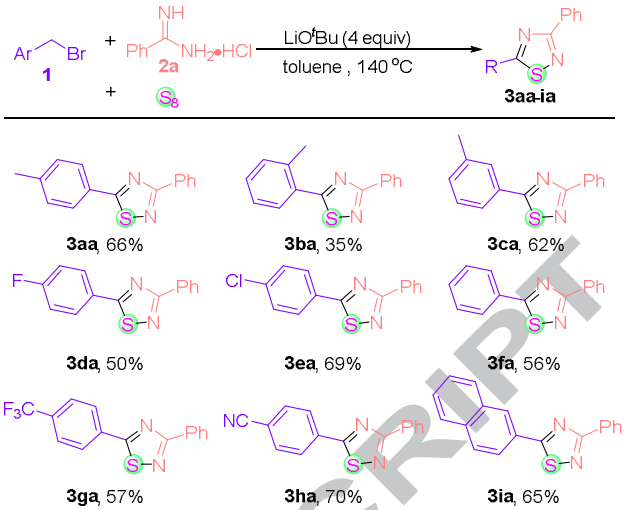


entry	base	solvent	yield[b] (%)
1	K_2CO_3	toluene	19
2	NaO^{t}Bu	toluene	34
3	KO^{t}Bu	toluene	31
4	LiO^{t}Bu	toluene	66,47[c],23[d],51[e],59[f]
5	LiO^{t}Bu	DMAC	33
6	LiO^{t}Bu	DMF	26
7	LiO^{t}Bu	DMSO	58
8	LiO^{t}Bu	xylene	51
9	LiO^{t}Bu	diglyme	13

[a] Reaction conditions: (4-tolyl)methyl bromide **1** (0.12 mmol), benzamidine hydrochloride **2** (0.1 mmol), S_8 (0.1 mmol), base (0.4 mmol), solvent (2.0 mL), N_2, at 140 °C for 12 h, in a sealed Schlenk tube. [b] Isolated yield. [c] air. [d] O_2. [e] 130 °C. [f] 150 °C. DMAC = dimethylacetamide; DMF = *N,N*-dimethylformamide; DMSO = dimethyl sulfoxide.

After the establishment of the optimized reaction conditions, the scope and limitation of arylmethyl bromides in the reaction with benzamidine hydrochloride and sublimed sulfur were tested, as shown in Fig. 1. As expected, this procedure was applicable for arylmethyl bromides bearing both *para*-, *meta*- and *ortho*-substitutents in the phenyl ring (**3aa**-**ea** and **3ga**-**ia**), albeit with low yield for *ortho*-substituted analogue (**3ba**, 35%). Some functional groups, such as fluoro (**3da**, 50%), chloro (**3ea**, 69%), trifluoromethyl (**3ga**, 57%), and cyano (**3ha**, 70%), survived under this procedure, providing handles for further transformation.

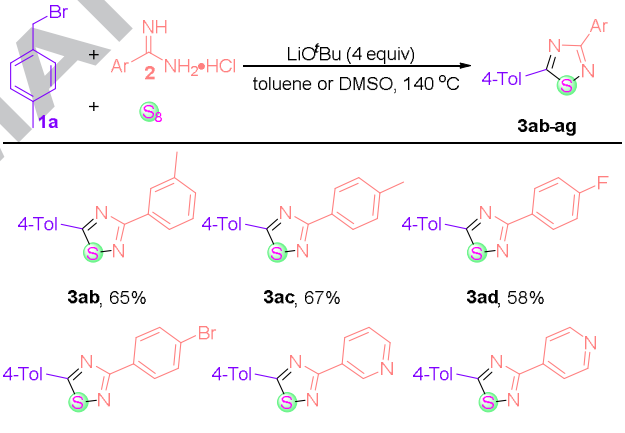
Figure 1. Scope of substituted benzyl bromides[a]



[a] Reaction conditions: arylmethyl bromide **1** (0.12 mmol), benzamidine hydrochloride **2a** (0.1 mmol), S_8 (0.1 mmol), LiO^{t}Bu (0.4 mmol), toluene (2 mL), N_2, 140 °C, 12 h.

Notably, ^{n}BuBr worked to some extent under this procedure to introduce the *n*-propyl to 5- position of 3-phenyl-1,3,4-thiadiazole (**3ja**, 21%). However, replacing ^{n}BuBr with ^{n}BuI did not have any positive effect on the reaction efficiency.

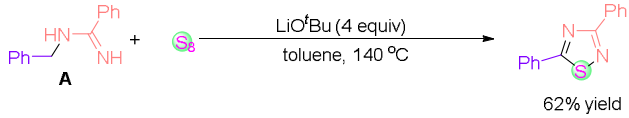
Figure 2. Scope of substituted benzamidine hydrochloride.[a]



[a] Reaction conditions: (4-tolyl)methyl bromide **1a** (0.12 mmol), arylamidine hydrochloride **2** (0.1 mmol), S_8 (0.1 mmol), LiO^{t}Bu (0.4 mmol), toluene (2 mL), N_2, 140 °C, 12 h. [b] DMSO (2 mL).

Next, the scope of (4-tolyl)methyl bromide in the reaction with arylamidine hydrochloride and sublimed sulfur was studied (Fig. 2). Once again, this procedure workedsmoothly, providing a series of 3-aryl-5-(4-tolyl)-1,3,4-thiadiazoles in moderate yields (**3ab**-**ae**, 56-67%). Notably, 3- and 4-pyridinyl were introduced into 3- position of 5-(4-tolyl)-1,2,4-thiadiazoles (**3af**, 45%; **3ag**,47%) by replacing toluene with DMSO as solvent.

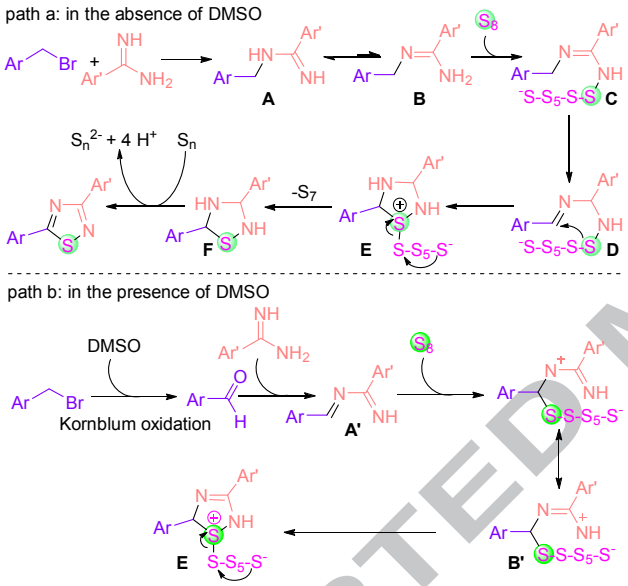
Scheme 2. Mechanism Study



To get insights into the mechanism, the presumed intermediate **A** was subjected to the procedure, and 3,5-diphenyl 1,2,4-thiadiazole was isolated in a comparable 62% yield, which indicated **A** may serve as intermediate during this tranformation.

Based on the experimental results, a proposed pathway of this reaction is outlined in Scheme 3. In step 1, in the presence of base, the reaction of arylmethyl bromide with arylamidine produces intermediate **A**, which tautomerizes to **B**. Then, the nucleophilic attack of elemental sulfur to nitrogen atom in amino takes place leading to intermediate **C**.[15] After the tautomerization of **C** to **D**, the intermolecular nucleophilic attack of sulfur atom to imino group provides cyclized intermediate **E**. Afterwards, intermediate **E** transforms to intermediate **F** by the elimination of S_7^-. Finally, the oxidation of intermediate **F** by sulfur furnishes the final product 3,5-diaryl-1,2,4-thiadiazone (path a). Alternatively, in the presence of DMSO, the Kornblum oxidation of benzyl bromide produces aldehyde,[16] which annulates with amidine to provide intermediate **A'**. Then, the nucleophilic attack of elemental sulfur takes place leading to intermediate **B'**. After that, the nucleophilic attack of sulfur atom to nitrogen atom provides intermediate **E** (path b).

Scheme 3. Proposed Mechanism



In conclusion, we have developed a base-promoted three-component reaction between arylmethyl bromides, arylamidine hydrochlorides and sublimed elemental sulfur leading to unsymmetric 3,5-diaryl-1,2,4-thiadiazoles in moderate to good yields with diversity and complexity. This procedure features with broad substrates scope as well as the employment of elemental sulfur and commercially available starting materials under transition-metal free conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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