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A Three-Component Approach to 3,5-Diaryl-1,2,4-thiadiazoles under Transition-Metal-Free Conditions

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Supporting Information

ABSTRACT: A novel route is disclosed for the synthesis of 1,2,4-thiadiazoles starting from amidines, elemental sulfur, and 2-methylquinolines or aldehydes under transition-metal-free conditions. This three-component approach affords efficient and rapid access to 3,5-diaryl substituted 1,2,4-thiadiazoles with good tolerance of a broad range of funcitional groups. Mechanistic studies reveal a radical-involved pathway.

The thiadiazole is an important five-membered heterocyclic motif containing two nitrogen atoms and a sulfur atom, which constitutes the key structures of many natural products, pharmaceutical drugs, and functional materials.[1] In particular, the 1,3,4-thiadiazoles which have a symmetrical core skeleton display a wide range of biological activities such as antituberculosis,[2] antimicrobial,[3] anti-inflammatory, and anti-cancer activity.[4] As an isomer of 1,3,4-thiadiazole, the 1,2,4-thiadiazole motif which has an unsymmetrical five-membered ring also showed a broad range of pharmacological activities, including cardiovascular, anti-inflammatory, and antibiotic activity.[5] Among them, cefozopran,[6] which contains a 3,5-disubstituted 1,2,4-thiadiazole motif, is a commercial drug with antibacterial activity. Despite their wide applications in pharmacology and organic synthesis, few methods for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles have been developed in the literature partially due to the unsymmetrical five-membered ring structure. The general methods for the synthesis of 1,2,4-thiadiazoles with identical substituents at positions 3 and 5 mainly rely on the oxidative dimerization reaction of thioamides.[7] A large number of oxidants such as thionyl chloride,[7a] hydrogen peroxide,[7b] nitrous acid,[7c] pyridinium salt-dimethyl sulfoxide (DMSO),[7d] HCl-DMSO,[7e] bis(acyloxyiodo)arenes,[7f] polymer-supported iodobenzene diacetate,[7g] *N,N′*-dibromo phenytoin,[7h] and 2,4,6-trichloro-1,3,5-triazine[7i] have been successfully employed for the conversion of thioamides as well as thiobenzamide derivatives to the corresponding 1,2,4-thiadiazoles. In recent years, few alternative methodologies have been developed using different starting materials such as aryl nitriles[8a] and 3,5-dichloro-1,2,4-thiadiazole[8b] (via the Suzuki–Miyaura coupling reaction).

So far, most of the previously mentioned procedures require strong oxidative reaction conditions or starting materials that are not readily available. More importantly, these methods are mainly suitable for preparation of 1,2,4-thiadiazoles with identical substituents at positions 3 and 5. It is highly desirable to develop an efficient method for the preparation of 1,2,4-thiadiazoles with different substituents at positions 3 and 5 using readily available raw materials in one pot. Methylarenes are cheap, commercially available, and easy to handle raw materials and widely used as the carbon source to assemble various heterocycles. In most cases, the methyl group attached to the aryl ring was oxidized in situ to an aldehyde group and used for further transformations. Therefore, it shows great advantages are to be gained by directly using methylarenes or aldehydes as the carbon as well as aryl source to construct substituted thiadiazoles under mild reaction conditions. As our continuing efforts on using readily available elemental sulfur to construct functionalized heterocycles,[9] herein, we disclose a novel base-promoted route for the synthesis of 1,2,4-thiadiazoles with different aryl substituents at positions 3 and 5 from amidines, elemental sulfur, and 2-methylquinolines or aldehydes under transition-metal-free conditions (Scheme 1). In this transformation, one substituent attached to 1,2,4-thiadiazoles comes from the amidines and the other one comes from 2-methylquinolines or aldehydes.

Our study was initiated by choosing 2-methylquinoline (**1a**), benzamidine hydrochloride (**2a**), and elemental sulfur as the model system for the optimization of reaction conditions, which included base, solvent, temperature, and atmosphere (Table 1). No desired product was observed when the mixture in DMSO was stirred at 130 °C for 12 h in the absence of any

Scheme 1. New Strategy for the Synthesis of 3,5-Diaryl Substituted 1,2,4-Thiadiazoles

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Table 1. Optimization of Reaction Conditions[a]

entry	base	solvent	yield (%)[b]
1		DMSO	0
2	Cs_2CO_3	DMSO	trace
3	K_2CO_3	DMSO	trace
4	KOH	DMSO	61
5	K_2HPO_4	DMSO	52
6	K_3PO_4	DMSO	93
7	K_3PO_4	DMF	22
8	K_3PO_4	1,4-dioxane	33
9[c]	K_3PO_4	DMSO	63
10[d]	K_3PO_4	DMSO	31
11[e]	K_3PO_4	DMSO	93

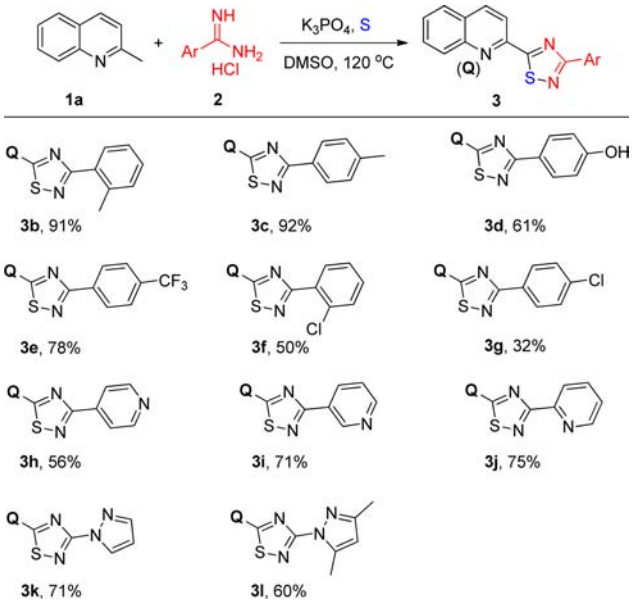
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2 equiv), S (1.0 mmol, 5 equiv), base (3 equiv), and solvent (0.6 mL) under air at 130 °C. [b]GC yield. [c]Reaction temperature of 100 °C. [d]S (0.8 mmol, 4 equiv). [e]Under argon.

additive (Table 1, entry 1). Subsequently, different bases were screened (entries 2−6). While carbonates such as Cs_2CO_3 and K_2CO_3 did not enable the desired transformation (entries 2−3), KOH and K_2HPO_4 gave a moderate yield of 3-phenyl-5-(quinolin-2-yl)-1,2,4-thiadiazole (**3a**) (entries 4−5). Then K_3PO_4 was proven to be the most effective base, which delivered **3a** in 93% yield (entry 6). Different reaction mediums (DMF and 1,4-dioxane) were investigated (entries 7 and 8). The results suggested that only DMSO gave a good yield for the reaction. No enhancement in yield was observed when the reaction was carried out at a reduced temperature or decreasing the amount of sulfur (entries 9 and 10). Notably, this reaction could not be affected by the reaction atmosphere (entry 11).

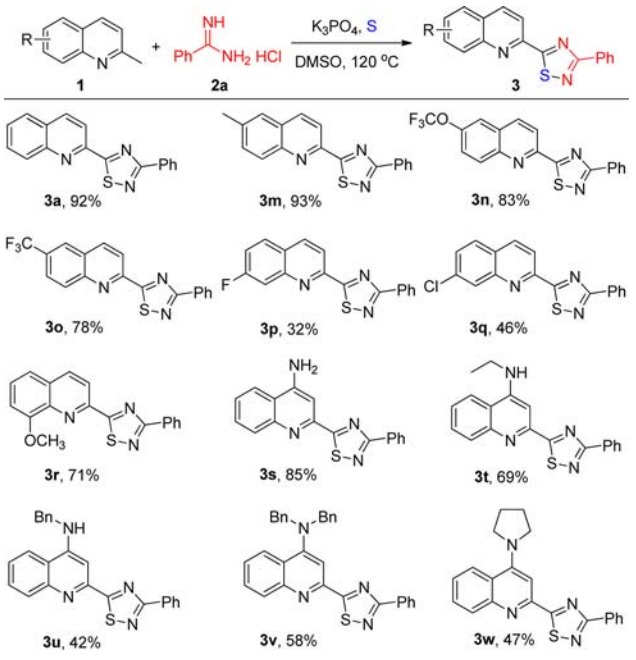
With these optimized conditions in hand, we next investigated the generality of the current procedure by first testing various amidine hydrochlorides with 2-methylquinoline (**1a**), and the results were summarized in Scheme 2. We were quite pleased to observe no steric effect. For example, the reactants with a methyl group at the para- and ortho-position of benzamidine salts were all tolerated well, delivering the target 1,2,4-thiadiazoles **3b** and **3c** in 91% and 92% yields, respectively. Furthermore, benzamidine hydrochlorides bearing either a typical electron-donating free OH group or a strong electron-withdrawing CF_3 group on the benzene ring provided good yields (**3d** and **3e**). However, for chloro- substituted benzamidines, decreased yields of the desired products (**3f** and **3g**) were obtained, which could probably be attributed to the coupling reactions of chloro-substituted benzamidines with elemental sulfur. Notably, pyridyl amidines were well tolerated in this reaction system, regardless of use of pyridyl-4-yl, pyridyl-3-yl, or pyridyl-2-yl, providing **3h**−**3j** in good yields. We then were pleased to find that guanidine derivatives, or 1*H*-pyrazole-1-carboximidamides, also worked well, giving 3-pyrazolyl-thiadiazoles (**3k** and **3l**) in good yields.

For the attractive biological properties of functionalized quinolines,[10] various substituted 2-methylquinolines under the optimized reaction conditions were then examined (Scheme 3). While substituents at the C6-position of quinolines, such as methyl, trifluoromethyl, and trifluoromethoxy, were all compatible (**3m**−**o**), halogen substituents such as F− and

Scheme 2. Reaction of 1a with Various Amidines (2)



Scheme 3. Reaction of 2a with Various 2-Methylquinolines (1)



Cl− at the C7-position of quinolines led to the corresponding products in lower yields (**3p**−**q**). The 2-methylquinoline with methoxy at the C8-position was also tolerated well, giving the corresponding 1,2,4-thiadiazole **3r** in good yield (71%). The substrate bearing a free amino group afforded an excellent yield of the desired product, with the free amino group being well reserved (**3s**, 85% yield). Other reactants with an alkyl amino or a dialkyl amino were also competent, albeit affording moderate yields of the target products (**3t**−**w**). These observations highlight the great significance of the present reaction system because the 4-aminoquinoline motif was widely found in drug molecules and natural products.[10b−e]

We speculate that the cyclization proceeds through an initial step of in situ oxidation of methylarenes to aldehydes.

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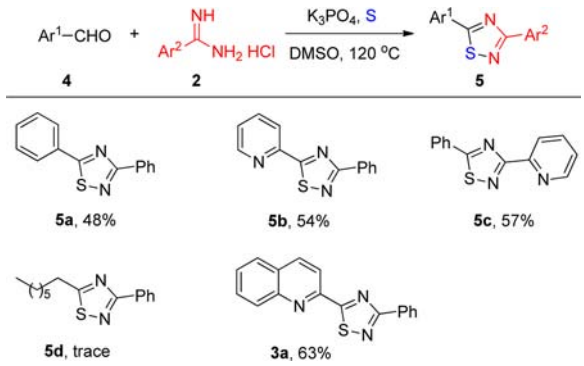
Therefore, a range of aromatic aldehydes were subjected to the present system (Scheme 4). Aldehydes employed such as

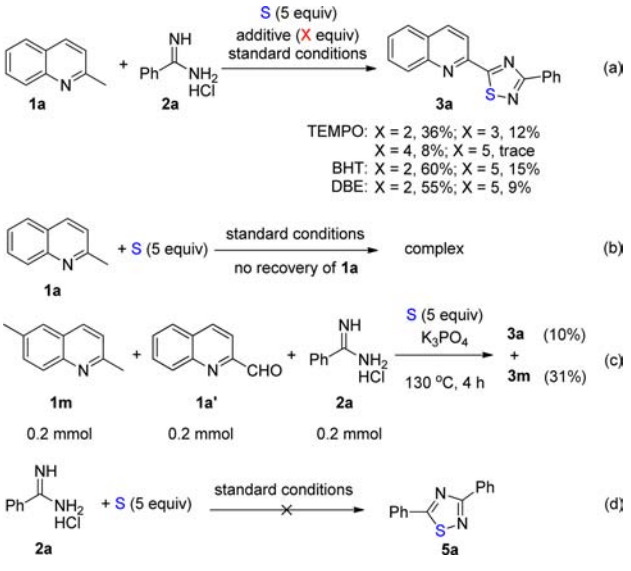
Scheme 4. Reaction of Aldehydes (4) with Amidines (2)



benzaldehyde and picolinaldehyde afforded the desired products in moderate yields (**5a**–**c**). Unfortunately, aliphatic aldehydes such as *n*-octylaldehyde did not work in the present system (**5d**). Then, the treatment of quinoline-2-carbaldehyde gave the corresponding product **3a** in a moderate yield (63%). This observation indicated that, besides the in situ formation of aldehyde followed by condensation to give a C═N bond, the reaction of methylquinolines would undergo an alternative pathway to directly generate the C–N bond.

To understand the mechanism of the reaction, we performed a number of radical trapping and control experiments (Scheme 5). First, the addition of 2,2,4,4-tetramethyl-1-piperidinyloxy

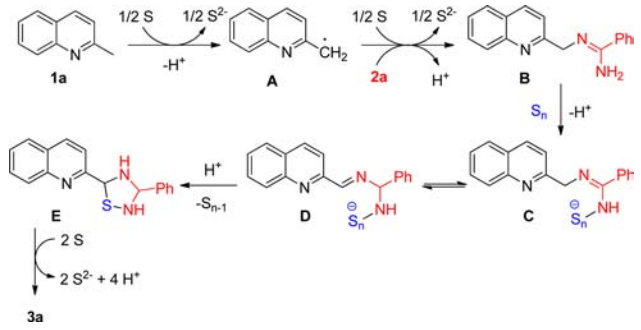
Scheme 5. Mechanistic Study



(TEMPO), butylated hydroxytoluene (BHT), or ethene-1,1-diyldibenzene (DBE) obviously inhibited the reaction under the standard conditions (Scheme 5a), thereby suggesting the involvement of a radical pathway. The starting material **1a** was not recovered when the reaction was carried out in the absence of **2a** (Scheme 5b), which indicates that the interaction of **1a** and sulfur may be the initial step. When a competitive reaction between **1m** and **1a**′ with **2a** was carried out within 4 h, the corresponding products **3a** and **3m** were determined by GC in a 1:3 ratio (Scheme 5c), while almost the same yields were obtained when using the two methylquinolines (Scheme 3, **3a** and **3m**). This further demonstrates that the aldehyde-involved procedure is not the predominant pathway when using methylquinolines. Finally, the reaction of benzamidine hydrochloride with elemental sulfur in the absence of either methylquinoline or aldehyde could not give the 3,5-diphenyl-1,2,4-thiadiazole **5a** in the present system (Scheme 5d).

On the basis of the experimental observations and reports, a proposed mechanism is outlined in Scheme 6. In the presence

Scheme 6. Tentative Mechanism



of elemental sulfur and a base, 2-methylquinoline (**1a**) could generate radical intermediate **A** via the more active enamine.[11] While the intermediate **A** would be oxidized into the corresponding quinolyl aldehyde for further transformation, more directly, it couples with **2a**, followed by a single-electron transfer with elemental sulfur to afford intermediate **B**.[12] The next steps would be the activation of elemental sulfur to form a C–S bond by a nucleophilic attack of intermediate **B** on the S_8 ring, generating intermediate **C**.[13] Then, imine isomerization of intermediate **C** produces intermediate **D**, which undergoes intramolecular nucleophilic addition to give 4*H*-thiadiazole **E**.[14] Finally, **E** was oxidized to **3a** by 2 equiv of sulfur.

In summary, we have developed straightforward and efficient access to 3,5-diarylsubstituted-1,2,4-thiadiazoles from amidines, elemental sulfur, and methylarenes or benzaldehydes under transition-metal-free conditions. The methyl group attached to quinolines and aldehydes successfully served as the carbon source, and elemental sulfur acted as the sulfur source to selectively assemble the five-membered 1,2,4-thiadiazole moiety. Functional groups such as halogen and trifluoromethyl were well tolerated under the optimized reaction conditions. This three-component approach affords a facile route for the rapid synthesis of unsymmetrical 3,5-diaryl substituted 1,2,4-thiadiazoles. The detailed mechanism and synthetic application of this reaction are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

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General experimental procedure and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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