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A copper-catalyzed approach for the synthesis of asymmetrical disubstituted 1,2,4-thiadiazoles via elemental sulfur-mediated decarboxylative redox cyclization

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ABSTRACT

The variety of asymmetrical disubstituted 1,2,4-thiadiazoles are smoothly prepared by copper-catalyzed approach, which employed arylacetic acids and amidines as substrates, and elemental sulfur to mediate decarboxylative redox cyclization. The advantages of this method are simple, efficient, and ligand-free. In addition, this method can provide products in moderate to good yields.

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Five-membered heterocyclic compounds, as pivotal roles in medicinal chemistry, have unique chemical properties [1]. 1,2,4-Thiadiazoles are broad existed in natural products, drug molecules, and functional materials. In particular, they have more extensive applications in pharmaceuticals industry owing to the improvement of liposolubility of medicine by sulfur atom [2]. The nucleus of 1,2,4-thiadiazoles is a fundamental constituent of synthetic products with biological activities, such as agonists [3], antibiotic [4] (Fig. 1), anticancer [5], analgesic [6], and inhibitor [7]. It is reported that 1,2,4-thiadiazoles possess hypoglycemic activity, and inhibition of Beta-secretase activity that can be used in treating Alzheimer's disease as a lead candidate [8].

According to these properties, many researchers focus on finding a simple, convenient, and efficient approach to obtain 1,2,4-thiadiazoles. The general synthetic ways of 1,2,4-thiadiazoles were to use thioamides as the starting material via oxidative dimerization, which use iodine reagents [9], dimethyl sulfoxide [10], oxone [11], oxygen [12] etc. as oxidant (Scheme 1a). Noei et al. have introduced a new synthetic method with aryl nitriles to produce 1,2,4-thiadiazoles, which main steps were activation of nitrile group and obtaining the thioamides by nucleophilic addition [13] (Scheme 1b). Later, a novel one-pot synthesis of asymmetrical disubstituted 1,2,4-thiadiazoles has been disclosed by Deng's group using amidines, elemental sulfur, and 2-methylquinolines or aldehydes as starting materials under transition-metal-free conditions [14] (Scheme 1c and d). Recently, Ling et al. used thioamides and nitriles as substrates to acquire asymmetrical disubstituted 1,2,4-thiadiazoles [15] (Scheme 1e). Though a large amount of synthetic researches about 1,2,4-thiadiazoles have been discovered, there were few reports for synthesis of asymmetrical disubstituted 1,2,4-thiadiazoles. Hence, it is crucial to explore a simple and efficient method to produce asymmetrical disubstituted 1,2,4-thiadiazoles.

Oxidative decarboxylation is a significant chemical reaction, which contribute to Heck reaction, forming carbon-heteroatom bonds, redox neutral cross-coupling reactions, and direct arylation processes [16,17]. In addition, the properties of arylacetic acids are easily available, low-cost, stable, and nontoxic. Previously, our group reported strategies constructing carbon-heteroatom bonds through decarboxylative redox cyclization of arylacetic acids [18,19], which laid the foundation for our new research. Based on previous research [14,20b], a synthetic method of asymmetrical 3,5-disubstituted 1,2,4-thiadiazoles was developed by using benzamidine hydrochloride and phenylacetic acid as starting materials (Scheme 1f).

Originally, our efforts were to explore the optimized reaction conditions using phenylacetic acid, benzamidine hydrochloride, and element sulfur as model reactants by varying diverse

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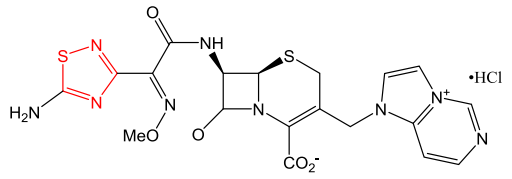
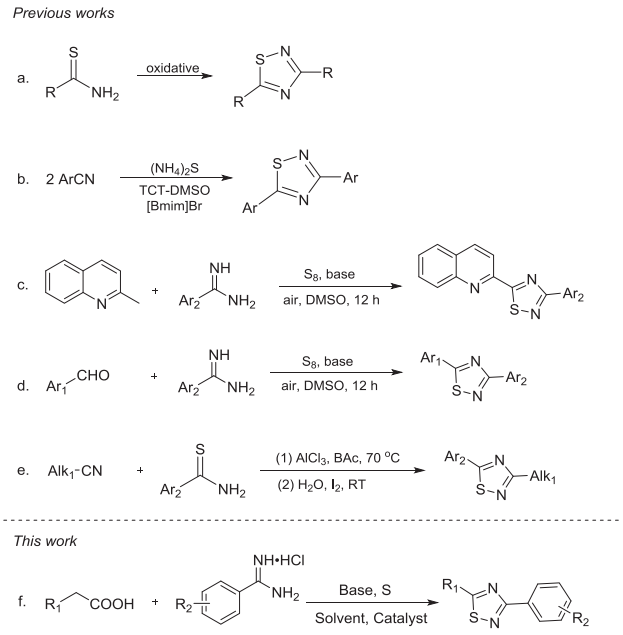


Fig. 1. Antibiotic drug: cefozopran.

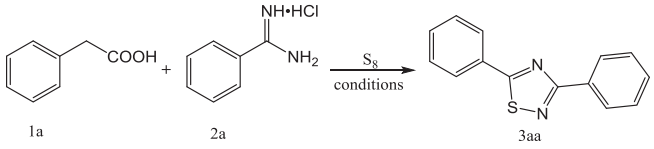


Scheme 1. Synthetic methods of 1,2,4-thiadiazoles.

parameters that include catalyst, base, temperature, solvent, reaction time, and equivalent (Table 1). As shown in Table 1, the best catalyst was CuI, which provided desired product 3,5-diphenyl-1,2,4-thiadiazole (**3aa**) in 51% yield (entries 1–5). Among the various bases tested, Na_2CO_3 was optimal choice, and few product was found using NaOH and KOH (entry 1 VS entries 6–9). Decreasing and increasing reaction time, the yields were not increased, respectively (entry 1 VS entries 10–11). With the study of solvent, DMF, PEG-400, and NMP were inferior to DMSO (entry 1 VS entries 12–14). Temperature also had influence in yields (entries 15–16). Delightfully, the yield was improved to 60% under nitrogen atmosphere (entry 17). Finally, the effect of sulfur equivalent on yields was tested (entries18-21). When the equivalent of sulfur was increased to 6.0, the yield was improved to 72%. Continuing to add the amount of sulfur, there was no increment in the yield. In addition, the target product is only 32% yield without CuI catalyst. Therefore, it was inferred the optimized reaction conditions: phenylacetic acid **1a** (2.0 equiv, 1.0 mmol), benzamidine hydrochloride **2a** (1.0 equiv), element sulfur (6.0 equiv), CuI (20 mmol%), and Na_2CO_3 (2.0 equiv) in DMSO (2.0 mL) at 130 °C for 24 h under a nitrogen atmosphere (entry 20).

With the optimized reaction conditions in hand, various aryl acetic acids were used to investigate the adaptability of reaction (Table 2). Phenylacetic acids with electron donating group, such as methyl and methoxy, were provided moderate to good yields (**3ca–3ea, 3ia–3ka**) except o-methyl (**3ba**). The yields of halogen substituents were poor (**3fa–3ga**). And there is no target product when using o-halophenylacetic acids as substrates, possibly since o-halophenylacetic acids are prone to substitution reaction. The strong electron withdrawing group (-CF_3) probably had beneficial effects on the reaction that the isolated yield of **3ha** was improved to 82%. Then, 2-thiopheneacetic acid, 2-naphthaleneacetic acid and 2-biphenylacetic acid reacted with benzamidine hydrochloride respectively led to moderate and good yields (**3la–3na**). There is

Table 1
Optimization of 3,5-diphenyl-1,2,4-thiadiazole synthesis.[a]

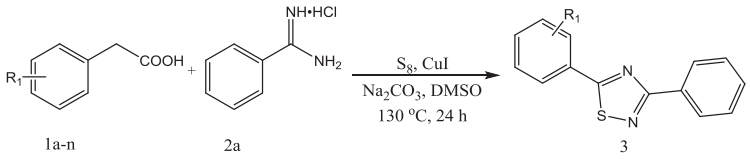


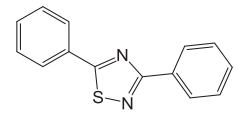
1a 2a 3aa

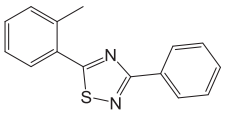
Entry	Catalyst	Base	S_8 (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CuI	Na_2CO_3	4.0	DMSO	130	24	51
2	$Cu(OAc)_2·H_2O$	Na_2CO_3	4.0	DMSO	130	24	40
3	CuO	Na_2CO_3	4.0	DMSO	130	24	41
4	$Cu(OAc)_2$	Na_2CO_3	4.0	DMSO	130	24	47
5	Cu	Na_2CO_3	4.0	DMSO	130	24	42
6	CuI	NaOH	4.0	DMSO	130	24	Trace
7	CuI	K_2CO_3	4.0	DMSO	130	24	26
8	CuI	KOH	4.0	DMSO	130	24	Trace
9	CuI	$NaHCO_3$	4.0	DMSO	130	24	21
10	CuI	Na_2CO_3	4.0	DMSO	130	18	33
11	CuI	Na_2CO_3	4.0	DMSO	130	30	25
12	CuI	Na_2CO_3	4.0	DMF	130	24	11
13	CuI	Na_2CO_3	4.0	PEG-400	130	24	14
14	CuI	Na_2CO_3	4.0	NMP	130	24	20
15	CuI	Na_2CO_3	4.0	DMSO	120	24	27
16	CuI	Na_2CO_3	4.0	DMSO	140	24	45
17[c]	CuI	Na_2CO_3	4.0	DMSO	130	24	60
18[c]	CuI	Na_2CO_3	3.0	DMSO	130	24	37
19[c]	CuI	Na_2CO_3	5.0	DMSO	130	24	64
20[c]	**CuI**	**Na_2CO_3**	**6.0**	**DMSO**	**130**	**24**	**72**
21[c]	CuI	Na_2CO_3	7.0	DMSO	130	24	68
22[c]	–	Na_2CO_3	6.0	DMSO	130	24	32

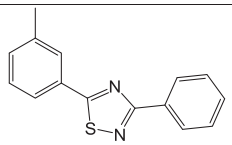
[a] Reaction conditions: 1a (2.0 equiv, 1.0 mmol), 2a (1.0 equiv), sulfur powder, base (2.0 equiv), catalyst (20 mmol%) and solvent (2.0 mL) under air.
[b] Isolated yields.
[c] Under nitrogen atmosphere.

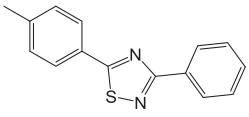
Table 2
Substrate scopes with various aryl acetic acids.[a]

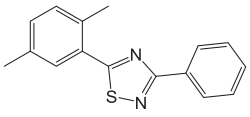


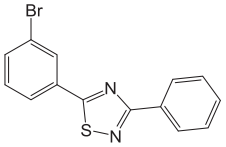

3aa 72%


3ba 20%

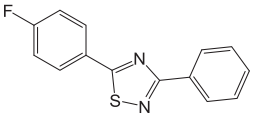

3ca 49%


3da 61%

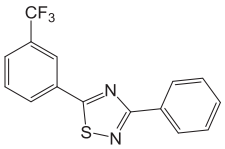

3ea 58%



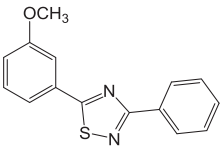
3fa 36%



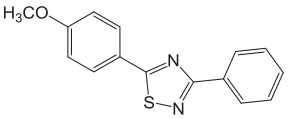
3ga trace



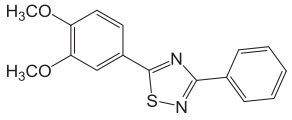
3ha 82%



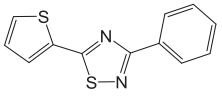
3ia 72%

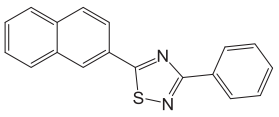


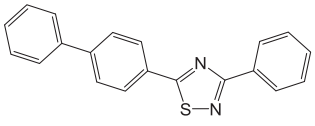
3ja 50%



3ka 69%

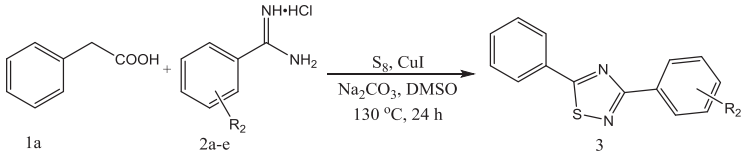

3la 46%

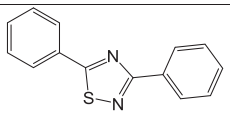

3ma 77%

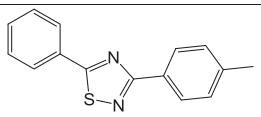

3na 80%

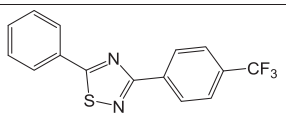
[a] Reaction conditions: 1 (2.0 equiv, 1.0 mmol), 2 (1.0 equiv), S (6.0 equiv), Na2CO3 (2.0 equiv), CuI (20 mmol%) and DMSO (2.0 mL) under N2 at 130 oC for 24 h.

Table 3
Substrate scopes with various benzamidine hydrochlorides.[a]

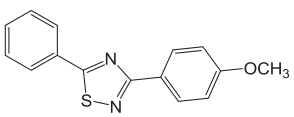



3aa 72%

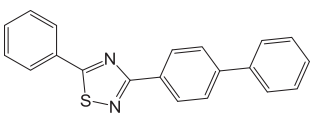

3ab 63%



3ac 43%



3ad trace

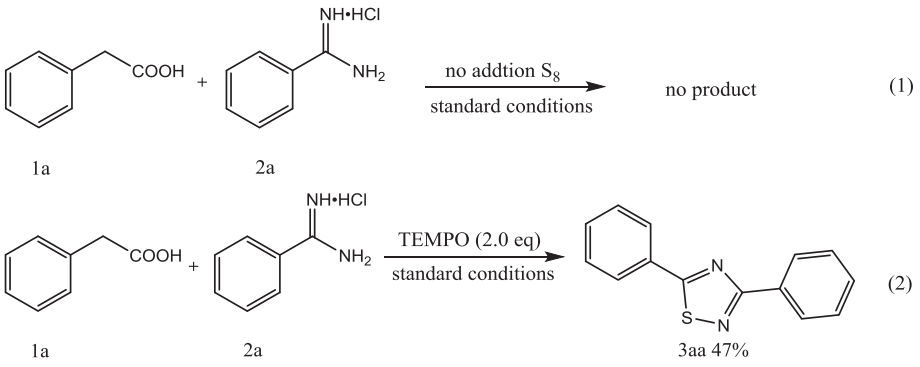

3ae 75%

[a] Reaction conditions: 1 (2.0 equiv, 1.0 mmol), 2 (1.0 equiv), S (6.0 equiv), Na2CO3 (2.0 equiv), CuI (20 mmol%) and DMSO (2.0 mL) under N2 at 130 oC for 24 h.

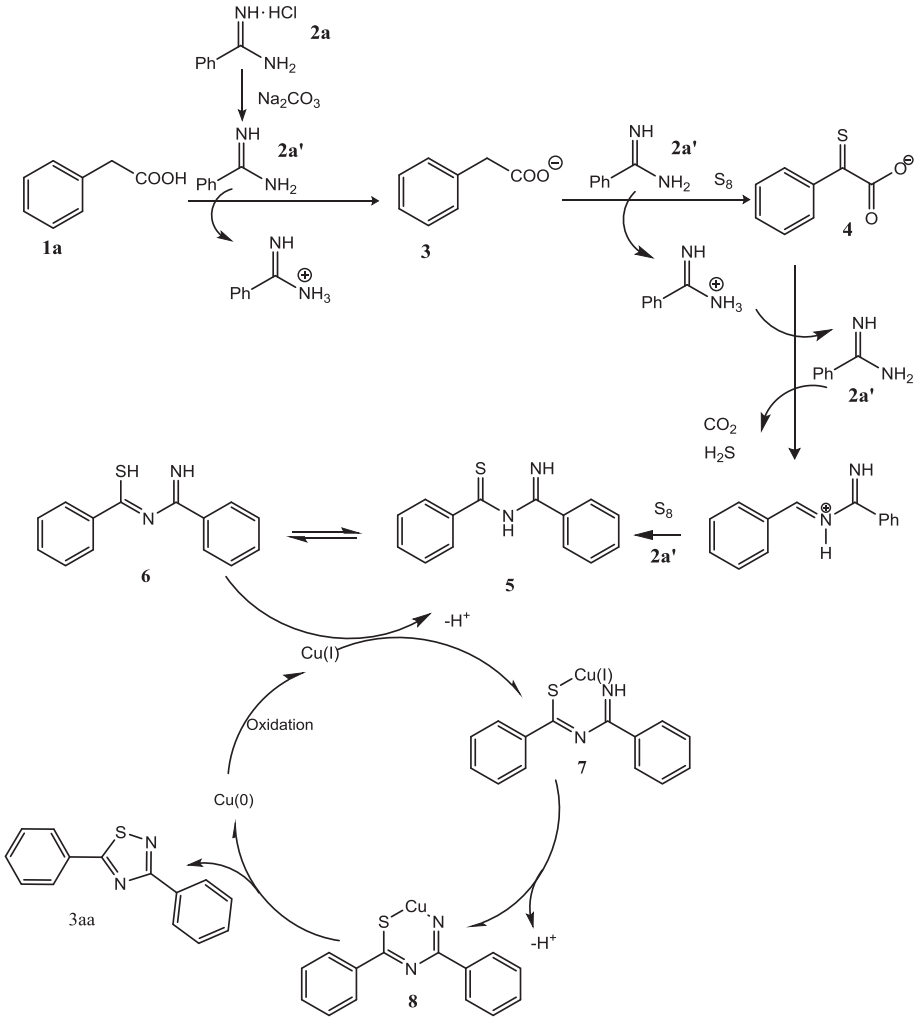
no product in the reaction with 2-bromoacetic acid and pivalic acid as substrates (**3oa–3pa)**. What's more, the scopes of benzamidine hydrochloride were also tested (Table 3). Methyl, trifluoromethyl, and phenyl benzamidine hydrochloride all have moderate to good yields (**3ab, 3ac, 3ae**), except methoxy benzamidine hydro-chloride (**3ad**).

In order to study proposed mechanism, the following control experiments were performed (Scheme 2). There is no product in absence of sulfur under the standard conditions (Scheme 2, Eq. 1). The sulfur is pivotal for the reaction and may play a key role in the beginning. The addition of 2,2,4,4-tetramethyl-1-piperidinyloxy (TEMPO) had no obvious differences in the yield of target product (Scheme 2, Eq. 2). It was concluded that the proposed reaction mechanism may exclude the radical pathway.

Based on the control experiments and consulting literatures [20], the proposed mechanism was disclosed in Scheme 3. First, under alkaline conditions, phenylacetic acid **1a** was transformed to **3** which reacted with sulfur to form sulfide **4**, and another



Scheme 2. Control experiments.



Scheme 3. Proposed Mechanism.

equivalent of base was applied for neutralize benezamidine hydrochloride to acquire bare amine **2a'**. Then, iminium ion was formed by decarboxylation with the release of H_2S and CO_2. There may be two path to obtain product. One path, iminium ion transformed to **A**, and the nucleophilic attack of elemental sulfur was taken to provide intermediate **B**/**C**. Then, the formation of **3aa** was the nucleophilic attack of sulfur atom to nitrogen atom (Path A). Another path, under the action of element sulfur and **2a'**, the intermediate **6** was provided. The formation of **7** was through enol isomerization, and the copper catalyzed to obtain intermediate **8**. Finally, the target product **3aa** was gained via the process of reductive elimination (Path B).

In conclusion, a synthetic method of asymmetrical 3,5-disubstituted 1,2,4-thiadiazoles was developed that used phenylacetic acid, benzamidine hydrochloride and sulfur as substrates under copper catalysis in moderate to good yields. Phenylacetic acid was carbon source through cyclization realized synthesis 1,2,4-thiadiazoles. It also had well tolerated of functional groups. Detail mechanism and wide range of applications about this method are researching currently.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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