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An alternatively metal-free synthesis of 1,3,5-triazines or 1,2,4-thiadiazoles from benzyl chlorides and benzylamines mediated by elemental sulfur

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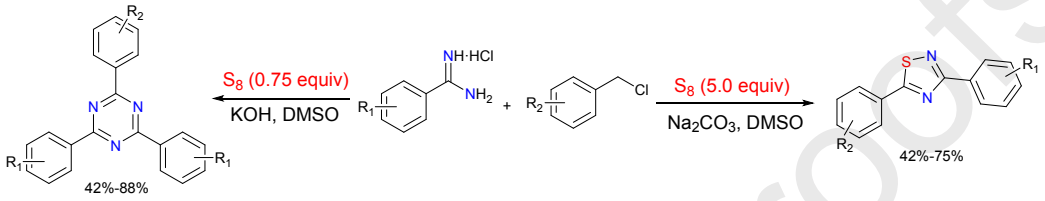

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An alternatively metal-free synthesis of 1,3,5-triazines or 1,2,4-thiadiazoles from benzyl chlorides and benzylamines mediated by elemental sulfur

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ABSTRACT

An elemental sulfur mediated reaction of benzyl chlorides with benzylamines is developed, which allows the practical synthesis of valuable 1,3,5-triazines. This protocol that is metal free, ligand free, and uses inexpensive elemental sulfur as oxidant or raw material displays mild reaction conditions, a broad substrate scope and moderate to good yields. Moreover, the modified sulfur-mediated reaction system can also be used to synthesize 1,2,4-thiadiazoles, by simply switching the stoichiometry of sulfur powder from 0.75 equivalents to 5 equivalnts.

Introduction

In recent decades, elemental sulfur has attracted much attention in organic synthesis since elemental sulfur exhibits non-toxic, low-cost, abundant, and stable properties under normal conditions. The elemental sulfur has been typically used as redox reagent, catalyst, building unit and so on, which depends on its numerous oxidation states, ranging from -2 to +6.[1] For instance, sulfur powder was reported to play an important role in the construction of C-C and C-N bonds, both as starting oxidant and reduced product.[2]

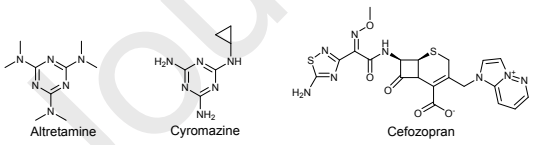
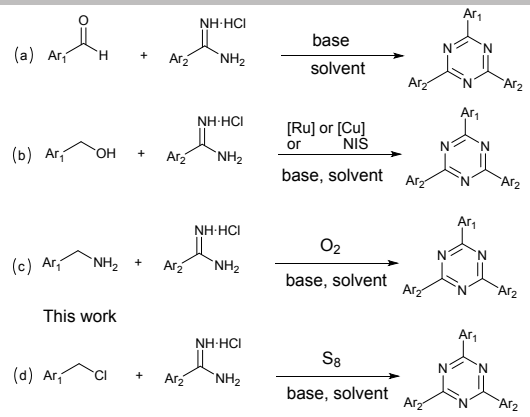


Figure 1. Biologically active 1,3,5-triazines and 1,2,4-thiadiazole

Nitrogen-containing heterocyclic compounds are privileged motifs frequently found in pharmaceutical and biologically active compounds.[3] Among these compounds, 1,3,5-triazines have attracted increasing attention since they are potentially scaffolds for the construction of many biologically active compounds, such as anticarcinogen, antiviral, and antibacterial.[4] At present, 1,3,5-triazines constitute the core units of many commercially drugs, such as the Altretamine[5a] which is used in the treatment of women with epithelial ovarian carcinoma, and Cyromazine[5b] can be used as insect growth regulator (Figure 1).

Earlier, the general methods for the synthesis of 1,3,5-triazines mainly relied on the cyclotrimerization of nitriles.[6] Later, amidines were frequently used as substrates to prepare 1,3,5-triazines. For example, amidine hydrochlorides have been reported to react with aryl aldehydes to afford 1,3,5-triazines by cyclodehydrogenation (Scheme 1a).[7] Alternatively method for the synthesis of 1,3,5-triazines was developed via ruthenium-promoted oxidative condensation of primary alcohols and amidines (Scheme 1b).[8] However, the using of expensive catalyst limited the further application of this method. Zhang and co-workers further improved this method by using low cost copper salt as catalyst under reflux conditions (Scheme 1b).[9] After that, a transition-metal free NIS-catalyzed oxidative cyclization of primary alcohols with amidines to 1,3,5-triazines has been employed by Bhanage and co-workers (Scheme 1b).[10] Recently, the method for synthesis of 1,3,5-triazines from benzylamines and amidines by employing O_2 as an oxidant has been reported (Scheme 1c).[11] Although those methods are efficiency, the reported approaches to the synthesis of 1,3,5-triazines are still rare in the literature. Therefore, developing an efficiency protocol for the synthesis of 1,3,5-triazines is still necessary. In continuation with our ongoing research in sulfur mediated reactions,[12] herein, we report a simple and efficient method for the synthesis of 1,3,5-triazines mediated by elemental sulfur (Scheme 1d), and the synthesis of 1,2,4-thiadiazoles via alternating the reaction conditions.

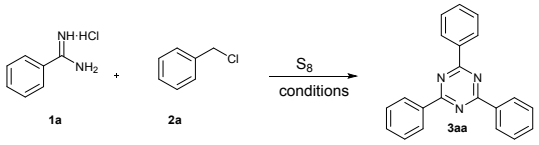


Scheme 1 Different routes for the synthesis of 1,3,5-triazines from benzamidine hydrochlorides.

Results and discussion

Considering that the benzyl chlorides could serve as carbon sources to construct heterocycles under an oxidative system, we chose benzamidine hydrochloride **1a** (1.0 equiv, 0.5 mmol) and benzyl chloride **2a** (1.0 equiv) as the model substrates to investigate the reaction conditions for construction of 1,3,5-triazines (Table 1). The use of Na_2CO_3 (3.0 equiv) as the base with sulfur powder (0.25 equiv) in dimethyl sulfoxide (DMSO) (2.0 mL) at 130 °C for 24 h provided the 1,3,5-triazine **3aa** in

Table 1 Optimization of 1,3,5-triazine synthesisa



Entry	S_8 (equiv)	Base	Temp (°C)	Solvent	Yield[b] (%)
1	0.25	Na_2CO_3	130	DMSO	45
2	0.5	Na_2CO_3	130	DMSO	50
3	0.75	Na_2CO_3	130	DMSO	68
4	1	Na_2CO_3	130	DMSO	61
5	0	Na_2CO_3	130	DMSO	41
6	0.75	Na_2CO_3	120	DMSO	56
7	0.75	Na_2CO_3	140	DMSO	66
8	0.75	Cs_2CO_3	130	DMSO	55
9	0.75	K_2CO_3	130	DMSO	78
10	**0.75**	**KOH**	**130**	**DMSO**	**82**
11	0.75	K_3PO_4	130	DMSO	56
12	0.75	NaOH	130	DMSO	69
13	0.75	KOH	130	Toluene	65
14	0.75	KOH	130	DMF	34
15	0.75	KOH	130	THF	11
16[c]	0.75	KOH	130	DMSO	72
17[d]	0.75	KOH	130	DMSO	60

[a] Reaction conditions: **1a** (1.0 equiv, 0.5 mmol), **2a** (1.0 equiv), sulfur powder, base (3.0 equiv), and DMSO (2.0 mL) at 130 °C for 24 h under air.

[b] Isolated yields.

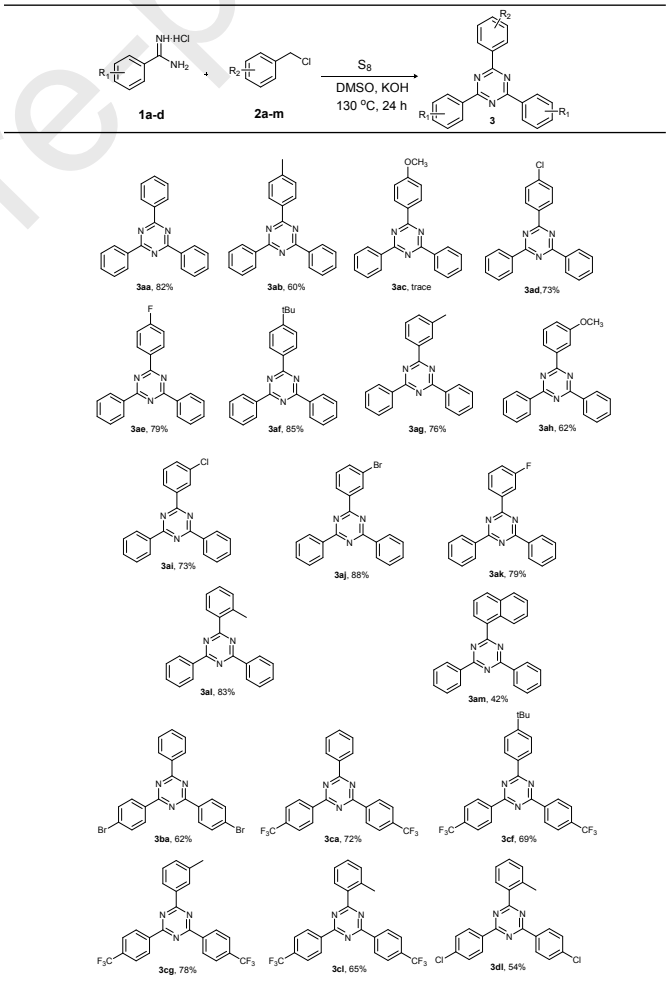
[c] 18 h.

[d] 36 h.

45% yield (entry 1). To our delight, increasing the amount of sulfur powder could promote the formation of product **3aa** the product **3aa** in 68% yield (entry 3). With further increasing of sulfur powder from 0.75 to 1.0 equiv, the yield of **3aa** was decreased. And the yield of **3aa** decreased to 41% in the absence of elemental sulfur (entry 5). Then optimization focused on the reaction temperature, changing the reaction temperatures to 120 °C or 140 °C both resulted the decreased yields of **3aa** (entry 3 vs entries 6-7). Furthermore, the influence of various bases and solvent on the yields of product **3aa** was investigated, which showed that KOH was the best choice base (entry 10 vs entries 3, 8-9, 11-12) and DMSO was the best choice solvent(entry 10 vs entries 13-15). Finally, changing the reaction time to 18 h or 36 h both provided lower yields of **3aa** (entry 10 vs entries 16-17). Thus, the optimized reaction conditions for 1,3,5-triazines were confirmed: benzamidine hydrochloride **1a** (1.0 equiv , 0.5 mmol), benzyl chloride **2a** (1.0 equiv), sulfur powder (0.75 equiv) and KOH (3.0 equiv) in DMSO (2.0 mL) at 130 °C for 24 h (entry 10).

With the optimized reaction conditions in hand, an investigation of the substrate scopes for the 1,3,5-triazines formation was carried out. The results were summarized in Table 2. The benzyl chloride with various substituents at different positions ranging from simple methyl (**3ab**, **3ag**, **3al**), methoxy (**3ah**), tertiary butyl (**3af**) to halogens such as F (**3ae**, **3ak**), Cl

Table 2 Substrate scopes for 1,3,5-triazines synthesis[a]



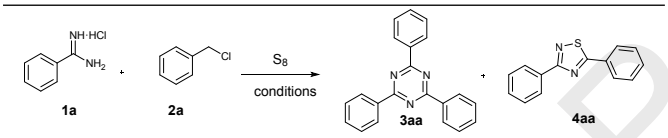
[a]Reaction conditions: **1** (1.0 equiv, 0.5 mmol), **2** (1.0 equiv), KOH (3.0 equiv), sulfur powder (0.75 equiv) and DMSO (2.0 mL) at 130 °C for 24 h under air. All reported yields are isolated yields.

(**3ad**,**3ai**) and Br (**3aj**) were tested and provided 1,3,5-triazines in moderate to good yields. However, a trace amount of

corr es the phenyl ring of benzyl chloride at the *para*- position. Also, electron-donating groups at the *meta*- position on the phenyl ring of benzyl chloride afforded higher yield of the corresponding products than that at *para*- position (**3ag** vs **3ab**, **3ah** vs **3ac**). This suggested the position of the substituents affected the reaction. As aromatic substrate, 2-(chloromethyl) naphthalene gave the corresponding product **3am** in 42% yield. The reaction of *para*-chlorobenzamidine, *para*-bromobenzamidine, *para*-trifluoromethyl benzamidine with various arylmethyl chlorides also processed smoothly to provided 1,3,5-triazines (**3ba-3dl**) in moderate to good yields (54%-78%).

In the process of our exploring the synthesis of 1,3,5-triazines, in an accidental opportunity, by changing the stoichiometry of sulfur powder, a novel method for 1,2,4-thiadiazoles synthesis was established. 1,2,4-Thiadiazoles which have an unsymmetrical five-membered rings display a wide range of applications in medicinal chemistry.[13] For example, Cefozopran[14] is a commercial drug used to against several bacterial infections, which contains a 3,5-disubstituted 1,2,4-thiadiazole scaffold (Figure 1). In addition, 1,2,4-thiadiazoles are useful as thiol trapping agents, pesticides, and corrosion inhibitors.[15] Cheng and co-workers reported a method for the synthesis of 1,2,4-thiadiazoles from arylmethyl bromides, arylamidine hydrochlorides and elemental sulfur under nitrogen atmosphere in 2017.[16]

Table 3 The selectivity variation of the cyclization reactions and the optimization of 1,2,4-thiadiazole synthesisa



Entry	S_8 (equiv)	Base	Temp (°C)	Solvent	Yield[b] (%)	
					3aa	**4aa**
1	0.25	Na_2CO_3	130	DMSO	45	trace
2	0.5	Na_2CO_3	130	DMSO	50	trace
3	0.75	Na_2CO_3	130	DMSO	68	trace
4	1	Na_2CO_3	130	DMSO	61	19
5	2	Na_2CO_3	130	DMSO	50	21
6	3	Na_2CO_3	130	DMSO	31	23
7	4	Na_2CO_3	130	DMSO	21	34
8	5	Na_2CO_3	130	DMSO	21	50
9	6	Na_2CO_3	130	DMSO	20	51
10	5	K_3PO_4	130	DMSO	19	41
11	5	*t*-BuOK	130	DMSO	12	28
12	5	KOH	130	DMSO	9	9
13	5	K_2CO_3	130	DMSO	18	50
14	5	NaOH	130	DMSO	20	40
15	5	Na_2CO_3	130	Toluene	25	trace
16	5	Na_2CO_3	130	THF	13	25
17[c]	5	Na_2CO_3	130	DMSO	14	60
18[c]	**5**	**Na_2CO_3**	**120**	**DMSO**	**15**	**60**
19[c]	5	Na_2CO_3	110	DMSO	18	44

[a]Reaction conditions: **1a** (1.0 equiv, 0.5 mml), **2a** (1.0 equiv), sulfur powder, base (3.0 equiv), and DMSO (2.0 mL) at 130 °C for 24 h under air.

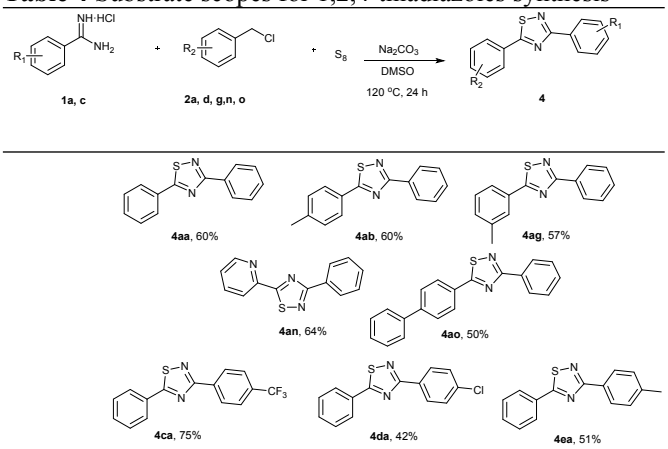
[b]Isolated yields.

[c]**1a** (2.0 equiv, 1 mmol), Na_2CO_3 (4.0 equiv) .

formation, which was isolated as a side product in our initial studies (Table 3). Using Na_2CO_3 as the base, the increased yields of 1,2,4-thiadiazole **4aa** were observed with increasing amount of sulfur powder (entries 1-9), and we chose 5.0 equiv elemental sulfur as the best choice (entry 8). The effect of various bases on the product **4aa** yield was investigated, which indicated that Na_2CO_3 is the best choice (entry 8 vs. entries 10-14). Then majorization focused on the solvent, which referred that DMSO is the best choice (entry 8 vs entries 15-16). An increase in 60% yield of **4aa** occurred when using 2.0 equiv of benzamidine hydrochloride **1a**, 1.0 equiv of benzyl chloride **2a** and 4.0 equiv Na_2CO_3 (entry 17). Also, lowering the reaction temperature to 120 °C was not detrimental for the 1,2,4-thiadiazole formation (entry 18 vs entry 17). However, decreasing the reaction temperature further to 110 °C resulted in a lower yield of **4aa** (entry 19 vs entry 18). Thus, the best reaction conditions for 1,2,4-thiadiazole **4aa** were: benzamidine hydrochloride **1a** (2.0 equiv, 1.0 mmol), benzyl chloride **2a** (1.0 equiv), sulfur powder (5.0 equiv), Na_2CO_3 (4.0 equiv) and DMSO (2.0 mL) at 120 °C for 24 h (entry 14).

Furthermore, we explored the substrate scopes for the 1,2,4-thiadiazoles and the results were summarized in Table 4. As we can see, benzamidine hydrochloride was used to couple with 1-(chloromethyl)-4-methylbenzene and 1-(chloromethyl)-3-methylbenzene, providing 3-Phenyl-5-(p-tolyl)-1,2,4-thiadiazole **4ab** in 60% yield and 3-Phenyl-5-(m-tolyl)-1,2,4-thiadiazole **4ag** in 57% yield. Besides, benzamidine hydrochloride with halogen substituent such as Cl proceeded smoothly to form corresponding product **4da** in 42 % yield. When benzyl chloride with a phenyl group, 50% yield was obtained (**4ao**). As aromatic heterocyclic substrate, 2-(chloromethyl)pyridine offered the corresponding product **4an** in 64% yield. Moreover, the reaction of para-trifluoromethyl benzamidine with benzyl chloride gave the desired product **4ca** in 75% yield. Then, the reaction of p-methylbenzidine hydrochloride with benzyl chloride gave the product **4ea** in 51% yield.

Table 4 Substrate scopes for 1,2,4-thiadiazoles synthesis[a]



[a]Reaction conditions: 1 (2.0 equiv, 1 mmol), 2 (1.0 equiv), Na_2CO_3 (4.0 equiv), sulfur powder (5.0 equiv) and DMSO (2.0 mL) at 120 °C for 24 h under air. All reported yields are isolated yields.

To probe the mechanism of the reaction, the control experiments were performed (Scheme 2). When the reaction for the synthesis of 1,3,5-triazines took place under an atmosphere of nitrogen, an obviously decreased reactivity was observed (Scheme 2, eq 1). Thus, molecular O_2 might involve the reaction process for the synthesis of 1,3,5-triazines. And molecular O_2 was not important factor for 1,2,4-thiadiazole formation (Scheme 2, eq 2). On the other hand, a free radical control experiment was

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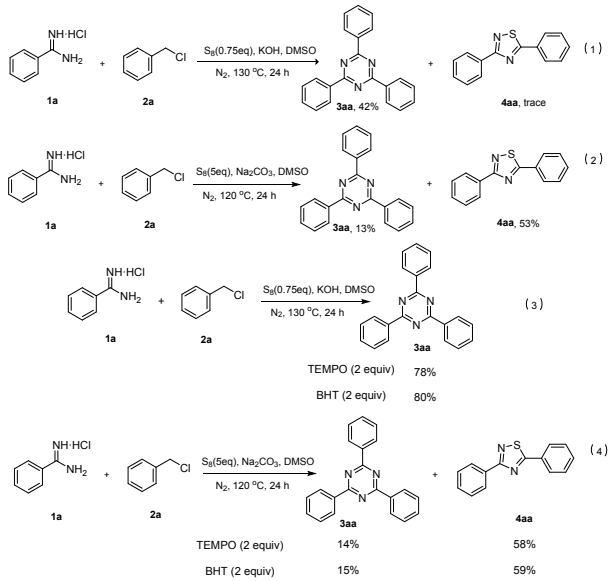
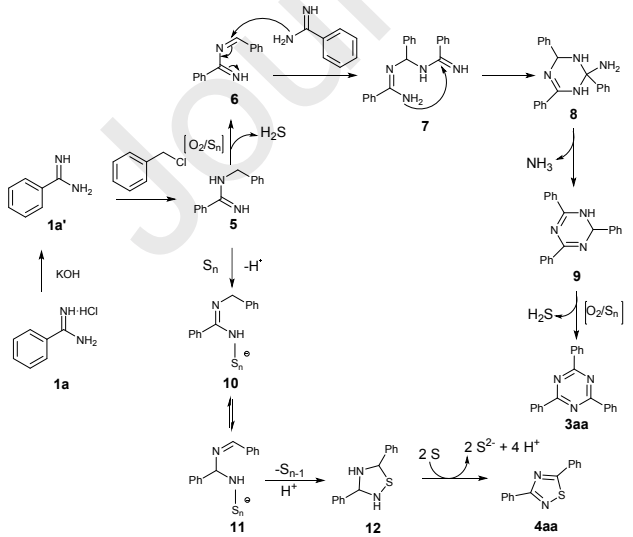
such as 2,2,6,6-tetramethylpiperidine oxynitride (TEMPO) or 2,6-di-tert-butyl-4 - Methylphenol (BHT), there was no significant decrease in the yield of 1,3,5-triazine product **3aa** or 1,2,4-thiadiazole **4aa**, which confirmed that the reaction process does not include free radical step (Scheme 2, eq 3 and eq 4).



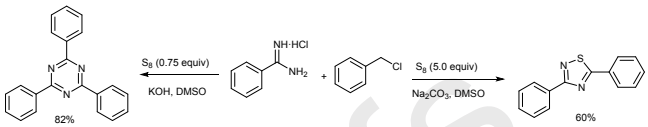
Scheme 2. Control experiments.

Based on the above findings, a plausible mechanism is proposed (Scheme 3).[11, 16, 17] Initially, the amidine **1a'** is neutralized by base from its hydrochloride salt. **1a'** and benzyl chloride form intermediate **5** which undergoes an elimination reaction to give intermediate **6**. The subsequent nucleophilic addition of the amino group to the electrophilic carbon center would afford intermediate **7** and racemic aminals **8**. Finally, the thermodynamically favourable deamination may release ammonia and dihydrotriazine **9**, followed by dehydrogenative aromatization to afford the product **3aa**. On the other hand, the intermediate **5** undergoes an isomerization reaction and reacts with elemental sulfur, generating intermediate **10**. Then, intermediate **10** undergoes imine isomerization reaction to give intermediate **11**, and 4H-thiadiazole **12** is obtained via intramolecular cyclization of **11** with a new C-S bond formed. Finally, dehydrogenation of **12** forms the desired product **4aa**.



Scheme 3. Plausible Mechanism.

In summary, we have reported a novel metal-free approach to the synthesis of 1,3,5-triazine derivatives in moderate to good yields by using elemental sulfur to promote the cyclization of benzyl chlorides and amidines. By changing the stoichiometry of benzyl chlorides, amidines, elemental sulfur and base, an effectively alternative approach to access 1,2,4-thiadiazoles has also been developed (Scheme 4). Detailed mechanistic studies and extension to other heteroaromatic substrates of this protocol are under way in our laboratory.



Scheme 4 The synthesis of 1,3,5-triazine and 1,2,4-thiadiazole.

Acknowledgments

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Supplementary Material

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alternatively prepared.

2.An selectively metal-free synthesis mediated by elemental sulfur.

3.The yield was moderate to good.

4.Good functional group tolerance.