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Multicomponent Coupling Reactions of Two *N*-Tosyl Hydrazones and Elemental Sulfur: Selective Denitrogenation Pathway toward Unsymmetric 2,5-Disubstituted 1,3,4-Thiadiazoles

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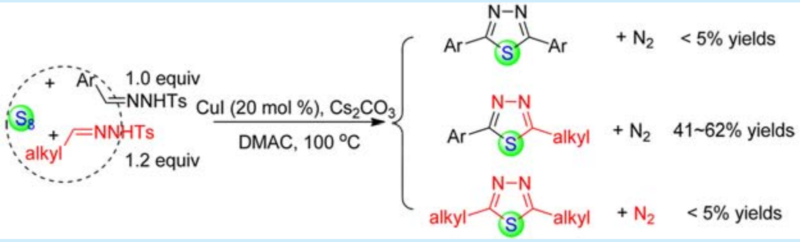
Supporting Information



ABSTRACT: A copper-mediated, three-component reaction between two different *N*-Ts hydrazones and elemental sulfur was developed, leading to a series of unsymmetric 2,5-disubstituted 1,3,4-thiadiazoles in moderate yields with good functional group compatibility. This procedure features the employment of elemental sulfur and the selective denitrogenation between aryl and alkyl aldehyde *N*-tosyl hydrazones, allowing rapid access to unsymmetric 2,5-disubstituted 1,3,4-thiadiazoles frameworks with chemical diversity and complexity.

1,3,4-Thiadiazoles possess a broad spectrum of biological activities.[1] For example, they could serve as antidepressant,[2] anxiolytic,[3] antimicrobial,[4] antituberculosis,[5] anti-inflammatory,[6] antidiabetic,[7] anticancer,[8] antihypertensive,[9] and antifungal drugs.[10] Therefore, numerous versatile and flexible approaches have been established to access 1,3,4-thiadiazoles, including the sulfuration of the corresponding 1,4-dicarbonyl and acyl precursors (in situ formed or not) by P_2S_5 or Lawesson's reagent,[11] cyclization of thiohydrazine,[12] and transformation from other heterocycles.[13] However, the sulfuration still suffers from harsh reaction conditions. P_2S_5 and Lawesson's reagent are sensitive to moisture have a strong odor, despite some modifications.[14] Moreover, the synthesis of *S*-substituted substrate was tedious and, in most cases, ineffective to access the 2,5-disubstituted analogues with carbon-centered groups. Therefore, the development of new methods to access 1,3,4-thiadiazoles via novel pathways and reaction partners remains an urgent goal for organic chemists.

The multicomponent coupling reactions (MCRs) between elemental sulfur and two *N*-tosyl hydrazones as readily available starting materials show that denitrogenation[15] is an ideal pathway toward such frameworks with chemical diversity and complexity.[16] However, in the case of two *N*-tosyl hydrazones, a great challenge arises from the selective denitrogen step between two *N*-tosyl hydrazone molecules, which may result in various distributions of two homoproducts and one cross-product.[17] Herein, we describe a three-component reaction of elemental sulfur toward unsymmetric 1,3,4-thiadiazoles with 2,5-disubstituted carbon-centered groups via a selective denitrogen pathway based on the reactivity discrimination between aryl and alkyl aldehyde *N*-tosyl hydrazones.

Initially, we tested the combination of benzaldehyde *N*-tosyl hydrazone (1.0 equiv), *n*-butanal *N*-tosyl hydrazone (1.2 equiv), and sublimed sulfur in the presence of CuI (20 mol %) and K_2CO_3 (2 equiv) in dimethylacetamide (DMAC, 2 mL) as the model reaction. To our delight, the cross-annulation product 2-phenyl-5-propyl-1,3,4-thiadiazole **3aa** via selective denitrogenation was isolated in 50% yield, and no homoannulated isomers were detected at 120 °C after 24 h under air (Table 1, entry 1). Subsequently, other bases such as Na_2CO_3, ^{t}BuONa, ^{t}BuOK, NaOH, Ag_2CO_3, and NaH_2PO_4, were examined. However, they were all inferior to K_2CO_3, generating **3aa** in lower yields (Table 1, entries 2−7). Pleasingly, Cs_2CO_3 worked well with an acceptable 62% yield (Table 1, entry 8). In the absence of copper, **3aa** was isolated in 44% yield (Table 1, entry 9). Other tested copper, such as CuCl (39%), and CuBr (36%), decreased the reaction efficiency (Table 1, entries 10 and 11). The tested solvents, such as DMF, CH_3CN, and dioxane, were inferior to DMAC (24−47%, Table 1, entries 12−14). The reaction efficiency decreased under elevated or lowered temperature (Table 1, entry 15), as did the procedure conducted under either N_2 or O_2, respectively (Table 1, entry 15). Thus, the optimized conditions were established as follows: benzaldehyde *N*-tosyl hydrazone (0.1 mmol), *n*-butanal *N*-tosyl hydrazone (0.12 mmol), and sublimed sulfur

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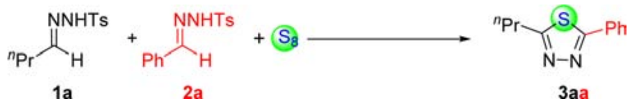
Table 1. Screening of the Optimized Reaction Conditions[a]



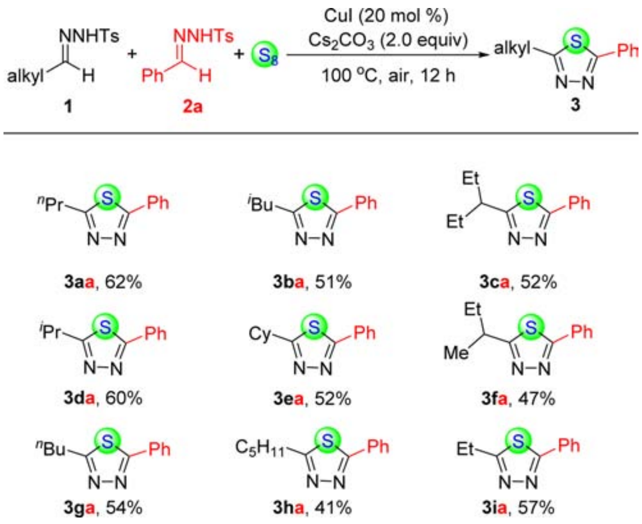
entry	copper	base	solvent	yield[b] (%)
1	CuI	K_2CO_3	DMAC	50
2	CuI	Na_2CO_3	DMAC	28
3	CuI	^{t}BuONa	DMAC	39
4	CuI	^{t}BuOK	DMAC	29
5	CuI	NaOH	DMAC	31
6	CuI	Ag_2CO_3	DMAC	<5
7	CuI	NaH_2PO_4	DMAC	24
8	CuI	Cs_2CO_3	DMAC	62
9		Cs_2CO_3	DMAC	44
10	CuCl	Cs_2CO_3	DMAC	39
11	CuBr	Cs_2CO_3	DMAC	36
12	CuI	Cs_2CO_3	DMF	47
13	CuI	Cs_2CO_3	CH_3CN	34
14	CuI	Cs_2CO_3	dioxane	24
15	CuI	Cs_2CO_3	DMAC	44,[c] 28,[d] 52,[e] 25[f]

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), S_8 (0.0625 mmol), CuX (20 mol %) in solvent (2 mL) under air at 100 °C. [b] Isolated yield. [c] 90 °C. [d] 110 °C. [e] Under N_2. [f] Under O_2.

(0.0625 mmol) in the presence of CuI (20 mol %) and Cs_2CO_3 (0.2 mmol) in dimethylacetamide (DMAC, 2 mL).

After the establishment of the optimized reaction conditions, the substrates scope and limitation of alkyl aldehyde *N*-tosyl hydrazones in the reaction with benzaldehyde *N*-tosyl hydrazone and sublimed sulfur were tested, as shown in Scheme 1. As expected, besides *n*-propyl, this procedure allowed rapid construction of 2-phenyl-1,3,4-thiadiazoles substituted with 5-primary carbon groups, such as *n*-butyl (**3ga**, 54%), *n*-pentyl (**3ha**, 41%), and ethyl (**3ia**, 57%) in moderate yields (**3ga**–**ia**). Importantly, the secondary carbon groups, such as isobutyl (**3ba**, 51%), isopropyl (**3da**, 60%), 2-ethylethyl (**3ca**, 52%), cyclohexanyl (**3ea**, 52%), and (2-methyl)ethyl (**3fa**, 47%) were facilely introduced to the 5-position of 2-phenyl-1,3,4-thiadiazoles.

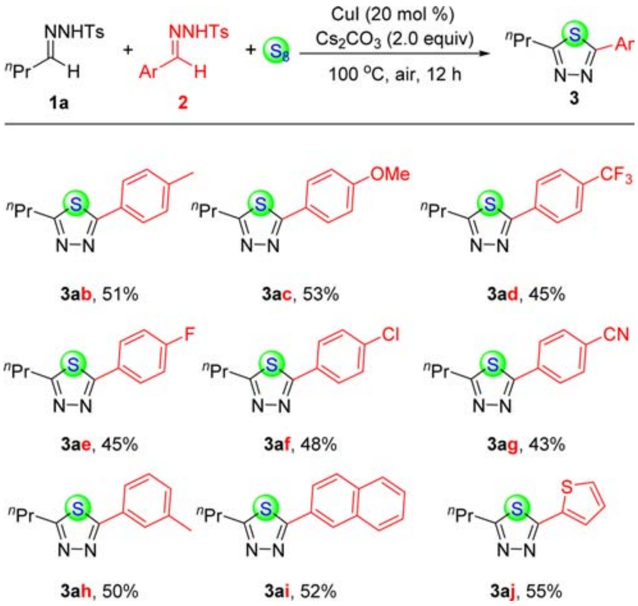
Scheme 1. Substrate Scope of Alkyl Aldehyde *N*-Tosyl Hydrazones[a]



[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), S_8 (0.0625 mmol), Cs_2CO_3 (0.2 mmol), CuI (20 mol %), DMAC (2 mL), air, 100 °C, 12 h.

Next, the scope of aromatic aldehyde *N*-tosyl hydrazones in the reaction with *n*-butanal *N*-tosyl hydrazone and sublimed sulfur was studied (Scheme 2). This procedure was compatible with some functional groups on the phenyl ring, such as methyl (**3ab**, 51%), methoxy (**3ac**, 53%), trifluoromethyl (**3ad**, 45%), fluoro (**3ae**, 45%), chloro (**3af**, 48%), and cyano (**3ag**, 43%), which provided a facile handle for potentially further functionalization. 2-Naphthaldehyde *N*-tosyl hydrazine was also a good reaction partner, giving the corresponding product **3ai** in 52% yield. Notably, 2-thienaldehyde *N*-tosyl hydrazone served as a reaction partner, and **3aj** was isolated in 55% yield.

Scheme 2. Substrate Scope of Aryl Aldehyde *N*-Tosyl Hydrazones[a]

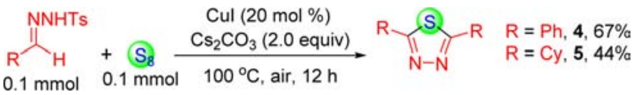


[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), S_8 (0.0625 mmol), Cs_2CO_3 (0.2 mmol), CuI (20 mol %), DMAC (2 mL), air, 100 °C, 12 h.

Notably, this procedure was also applicable in the synthesis of symmetric 1,3,4-thiadiazoles (Scheme 3). For example, 2,5-diphenyl-1,3,4-thiadiazoles **4** and 2,5-dicyclohexyl-1,3,4-thiadiazoles **5** were isolated in 67% and 44% yields under the standard procedure, respectively.

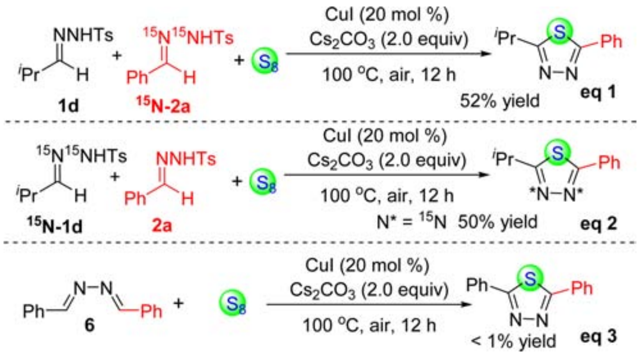
To gain insight into the mechanism, control experiments were conducted. No ^{15}N was detected in the 2-phenyl-5-isopropyl-1,3,4-thiadiazoles by the reaction of isobutanal *N*-tosyl hydrazone, ^{15}N-labeled benzaldehyde *N*-tosyl hydrazone, and sublimed sulfur under the standard procedure (Scheme 4, eq 1). However, ^{15}N was totally incorporated in 2-phenyl-5-

Scheme 3. Synthesis of Symmetric 1,3,4-Thiadiazoles[a]



[a] Reaction conditions: *N*-Ts hydrazone (0.1 mmol), S_8 (0.1 mmol), Cs_2CO_3 (0.2 mmol), CuI (20 mol %), DMAC (2 mL), air, 100 °C, 12 h.

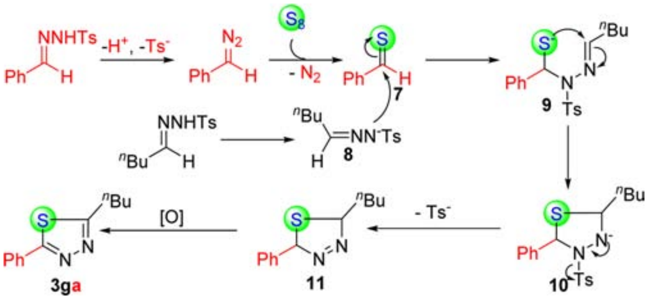
Scheme 4. Preliminary Mechanism Study



isopropyl-1,3,4-thiadiazoles by the reaction of ^{15}N-labeled isobutanal *N*-tosyl hydrazone, benzaldehyde *N*-tosyl hydrazone, and sublimed sulfur (Scheme 4, eq 2). This result confirmed the selective denitrogenation took place in benzaldehyde *N*-tosyl hydrazone rather than isobutanal *N*-tosyl hydrazone. Moreover, 1,4-diphenylformalazine **6** was subjected to the standard procedure and no 1,3,4-thiadiazoles was detected, ruling out the possibility of benzaldehyde 2-butylidenehydrazone as the intermediate (Scheme 4, eq 3).

On the basis of these experimental results, a tentative pathway of this reaction is outlined in Scheme 5. In the case of the blank experiment, in step 1, under basic conditions, the sequential elimination of proton and Ts$^-$ in benzaldehyde *N*-tosyl hydrazone took place leading to a diazo species, which transformed to carbene species by the extrusion of N_2.[17−19] Then, the reaction of carbene species with elemental sulfur produced benzothialdehyde **7**.[20] Meanwhile, in the presence of base, the anion species **8** was formed. In step 2, the nucleophilic attack of **8** to **7** provided intermediate **9**. Then, the intramolecular nucleophilic attack of **9** produced intermediate **10**. Finally, the elimination of Ts$^-$ in intermediate **10** delivered intermediate **11**, which transformed to the final product by aromatization. In the presence of CuI, the copper carbene may be involved in the procedure.

Scheme 5. Tentative Mechanism



In conclusion, we have developed a copper-promoted selective denitrogenation MCR between aryl aldehyde *N*-tosyl hydrazone, alkyl aldehyde *N*-tosyl hydrazone, and elemental sulfur toward 2-aryl-5-alkyl-1,3,4-thiadiazoles with chemical diversity and complexity in moderate yields. In this procedure, the selective denitrogenation took place in alkyl *N*-tosyl hydrazone rather than in aryl aldehyde *N*-tosyl hydrazine. Notably, this procedure was also applicable in the synthesis of symmetric 2,5-disubstituted-1,3,4-thiadiazoles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02583.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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