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Synthesis of novel 4-substituted 1,2,3-thiadiazoles via iodine-catalyzed cyclization reactions

Weiwei Li [a], Xuezhen Li [a], Yijiao Feng [a], Ping Liu [a,*], Xiaowei Ma [a,*], Jixing Zhao [b]

[a] School of Chemistry and Chemical Engineering, The Key Laboratory for Green Processing of Chemical Engineering of Xinjiang, Bingtuan Shihezi University, Shihezi City 832003, China
[b] Analysis and Testing, Center of Shihezi University, Shihezi City 832004, China

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ABSTRACT

Iodine-catalyzed the reaction of substituted methyl ketone *N*-tosylhydrazones with elemental sulfur has been developed. The cyclizations of the ester-substituted *N*-tosylhydrazone substrates proceeded smoothly under optimal reaction conditions, and the corresponding products 4-alkyl-1, 2, 3-thiadiazoles are obtained. For the reaction of 4-arylbutan-2-one of *N*-tosylhydrazone substrates, (*E*)-4-styryl-1, 2, 3-thiadiazole derivatives were obtained with high selectivity through the control of reaction conditions. In addition, gram-scale synthesis and further transformation of the product were also investigated.

Introduction

Substituted 1, 2, 3-thiadiazoles are important heterocyclic compounds that frequently occur in pharmaceuticals and synthetic agrochemicals due to their unique bio-activities [1,2]. In addition, 1, 2, 3-thiadiazoles as versatile intermediates had been used widely in organic synthesis [3]. Therefore, the development of effective methods for constructing 1, 2, 3-thiadiazole backbones has received extensive attention. The classical methods mainly included Hurd-Mori reaction, Wolff synthesis, Pechmann synthesis, and so on [4–7]. However, these methods often suffer from limitations, such as the use of highly reactive reagents (the diazo compounds or azide), air-sensitive sulfur sources (SCl_2 or $SOCl_2$), and prefunctionalized substrates. To overcome these shortcomings, direct cyclization of readily available *N*-tosylhydrazones and various sulfur sources into 4-aryl-1, 2, 3-thiadiazoles under the action of iodine-catalysis, photo-catalysis or electrochemical-catalysis has been developed (Scheme 1**a**) [8]. But so far, there are few reports on the synthesis of alkyl-substituted thiadiazoles. Recently, Zhou *et al.* described I_2/DMSO-mediated one-pot cyclization reaction of enaminones, tosylhydrazine, and elemental sulfur for the synthesis of 5-acyl-1, 2, 3-thiadiazoles (Scheme 1**b**) [9]. Wu *et al.* reported I_2/$CuCl_2$-promoted one-pot synthesis of aliphatic or aromatic substituted 1, 2, 3-thiadiazoles from ketones, *p*-toluenesulfonyl hydrazide, and KSCN (Scheme 1**c**) [10]. With our continued interest in the development of *N*-tosylhydrazones [11], herein we developed a novel synthesis of aliphatic substituted 1, 2, 3-thiadiazoles functionalized with ester groups from ethyl 3-(2-tosylhydrazono)butanoate and elemental sulfur (Scheme 1**d**). Notable features of our findings include (i) the use of catalytic amount of elemental iodine, (ii) a novel 4-alkyl-1, 2, 3-thiadiazole skeleton was constructed, (iii) mild reaction conditions, and (iv) good reaction selectivity for different types of substrates.

Results and discussion

Our investigation of the 4-aliphatic-1, 2, 3-thiadiazoles began with ethyl (*E*)-2-benzyl-3-(2-tosylhydrazono)butanoate (**1a**) and elemental sulfur (**2a**) as model substrates to optimized the reaction conditions (Table 1). First, we investigated the effects of various iodine sources (20 mol%) such as NH_4I, KI, TBAI (tetrabutylammonium iodide), I_2, HI, and CuI in the presence of DMSO as solvent at 100 °C for 8 h. The results showed that the reaction could proceed smoothly, and the desired product ethyl 2-phenyl-2-(1, 2, 3-thiadiazol-4-yl)acetate **3a** was obtained in 47–54% yield (entries 1–6). Considering comprehensively, we chose elemental iodine as the catalyst for the next exploration. Unfortunately, increasing the amount of iodine did not promote the reaction (entries 7–9). Other solvents such as 1, 4-dioxane, DMA, DMF, MeCN, or toluene significantly inhibited the reaction (entries 10–14). Extending the reaction time to 18 h, the reaction yield did not increase significantly

* Corresponding authors.
E-mail addresses: liuping@shzu.edu.cn (P. Liu), mxw_tea@shzu.edu.cn (X. Ma).

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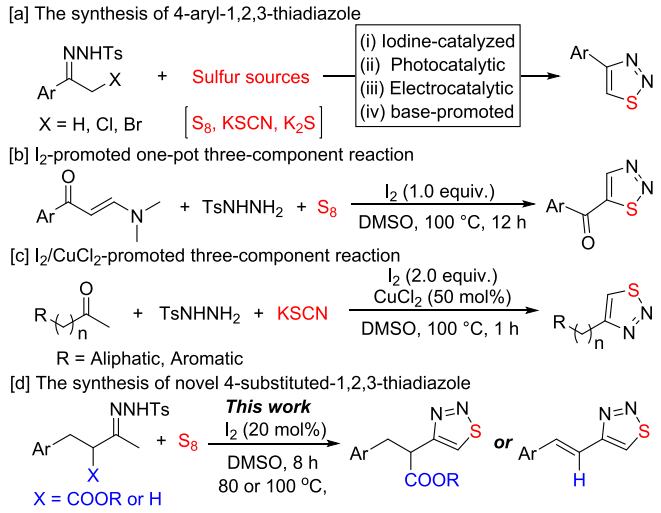
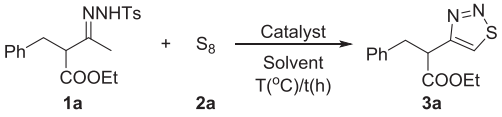


Scheme 1. The synthesis of various substituted 1, 2, 3-thiadiazoles.

(entry 15). To our delight, by adjusting the reaction temperature, the reaction yield was increased to 61% at 80 °C (entry 17 vs entries 16 and 18). Furthermore, increasing the amount of **2a** did not lead to a better yield (entry 19). On the contrary, when the amount of **2a** was reduced to 1.2 equivalents, the yield of **3a** could be increased to 68% (entry 20).

With the optimized conditions in hand (Table 1, entry 20), we next explored the substrate scope of α-ester ketone *N*-tosylhydrazones **1** (Table 2). The methyl (2-Me, 3-Me, and 4-Me) in different positions at the aryl ring were suitable for this protocol and provided the corresponding products **3b**, **3j**, and **3k** in good yields, but the yield of the product **3c** decreased to 47% when the electron-donating group 4-OMe was employed. In addition, a variety of electron withdrawing group substituted *N*-tosylhydrazones **1**

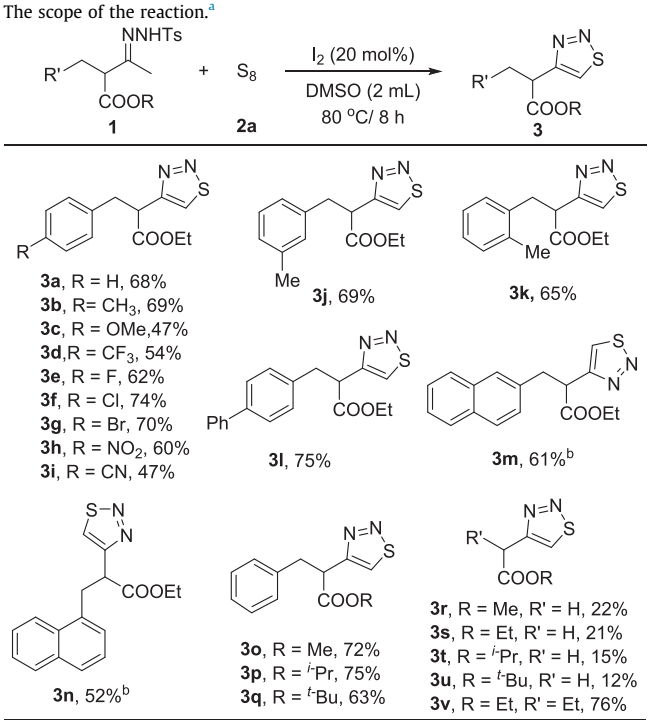
Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst/mol%	Solvent/mL	T/°C	Yield (%)[b]
1	NH_4I (20)	DMSO (2)	100	52
2	KI (20)	DMSO (2)	100	52
3	TBAI (20)	DMSO (2)	100	48
4	I_2 (20)	DMSO (2)	100	54
5	HI (20)	DMSO (2)	100	48
6	CuI (20)	DMSO (2)	100	47
7	I_2 (50)	DMSO (2)	100	47
8	I_2 (100)	DMSO (2)	100	38
9	I_2 (200)	DMSO (2)	100	16
10	I_2 (20)	1,4-dioxane (2)	100	trace
11	I_2 (20)	DMF (2)	100	8
12	I_2 (20)	DMA (2)	100	13
13	I_2 (20)	MeCN (2)	100	trace
14	I_2 (20)	toluene (2)	100	trace
15[c]	I_2 (20)	DMSO (2)	100	55
16	I_2 (20)	DMSO (2)	130	45
17	I_2 (20)	DMSO (2)	80	61
18	I_2 (20)	DMSO (2)	60	31
19[d]	I_2 (20)	DMSO (2)	80	62
20[e]	**I_2 (20)**	**DMSO (2)**	**80**	**68**

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (2 equiv.), catalyst (20 mol%), and solvent (2 mL) at 100 °C under air for 8 h. [b]Isolated yield. [c]Reaction time 18 h. [d]**2a** (3 equiv.). [e]**2a** (1.2 equiv.).

Table 2
The scope of the reaction.[a]



[a] Reaction conditions: **1a** (0.30 mmol), **2a** (1.2 equiv.), I_2 (20 mol%), and solvent (2 mL) at 80 °C for 8 h under air, isolated yield. [b]Reaction time 12 h.

reacted with S_8 smoothly to provide the corresponding products **3d**-**3i** in 47–74% yields. The structure of **3i** was further confirmed by single crystal X-ray diffraction (Fig. 1, CCDC: 2036307). It is worth mentioning that the halogen groups (-F, -Cl, and -Br) at the *para*-positions of the aryl ring were well tolerated, furnishing the desired products **3e**-**3g** in 62–74% yields. Furthermore, biphenyl and naphthyl substituted *N*-tosylhydrazones were also suitable substrate, delivering the desired products **3l**-**3n** in 52–75% yields. Moreover, the structure of the ester groups (–COOR, R = Me, *i*-Pr, and *t*-Bu) on the *N*-tosylhydrazones had no significant effect on the reactivity, and the desired products **3o**-**3q** were obtained in 63–75% yields. In contrast, the *N*-tosylhydrazones derived from acetoacetate esters can also react with S_8, affording the corresponding products **3r**-**3u** albeit with lower yields. To our delight, ethyl (Z)-2-ethyl-3-(2-tosylhydrazono)butanoate was utilized as a partner to furnish the desired product **3v** was obtained in 76% yield.

Interestingly, when the *N*-tosylhydrazones derived from 4-arylbutan-2-ones were used as reactants, the substituted (*E*)-4-styryl-1,2,3-thiadiazole **4aa** and **4ba** were obtained in 73% and 71% ^{1}H NMR of yields with high selectivity, accompanied by lower yields of the products substituted 4-phenethyl-1,2,3-thiadiazole **4ab** and **4bb** (Scheme 2**a**). The above results indicated that the ester group had a significant influence on the selectivity of the reaction. This speculation was further confirmed by the reaction of **4c** as a substrate with S_8, and the products **4ca** and **4cb** were obtained in 33% and 32% isolated yields, respectively (Scheme 2**b**). In addition, we found that the selectivity of the resulting product **4ab** was improved in the presence of 20 mol% NH_4I as catalyst and TBHP as oxidant (Scheme 2**c**). Next, the reaction of the mixture of **4aa** and **4ab** (the ratio of ^{1}H NMR = 5:1) was performed in the presence of I_2, the **4aa** and **4ab** ratio of ^{1}H NMR = 5:1 were increased to 8 : 1. The result showed that the product **4ab** can be further transformed into **4aa** under standard condition (Scheme 2**d**).

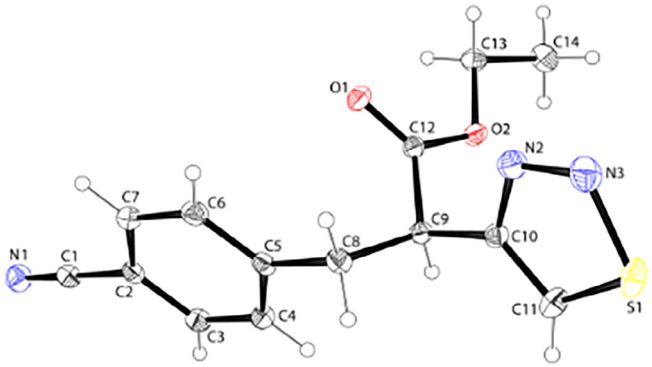
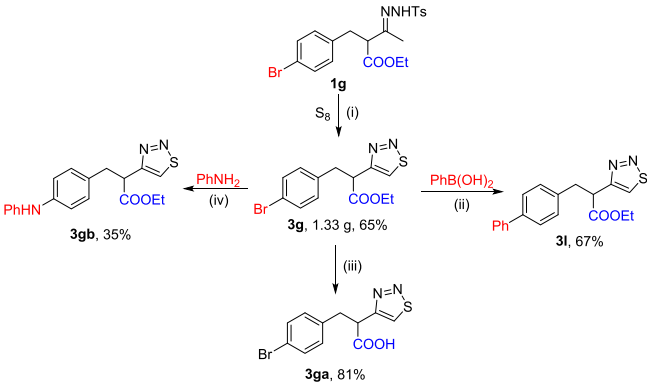
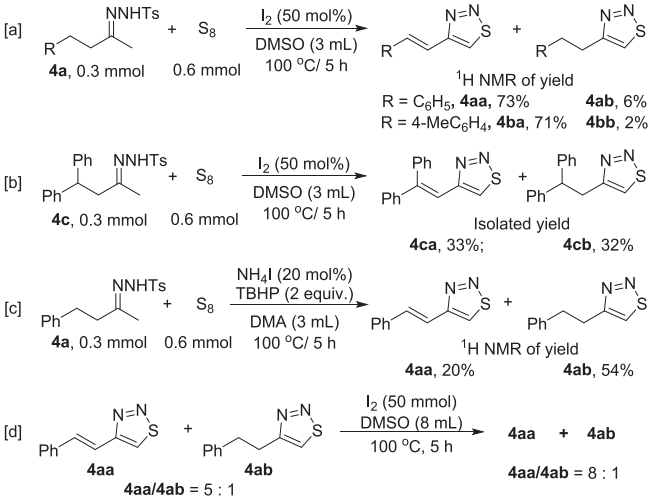


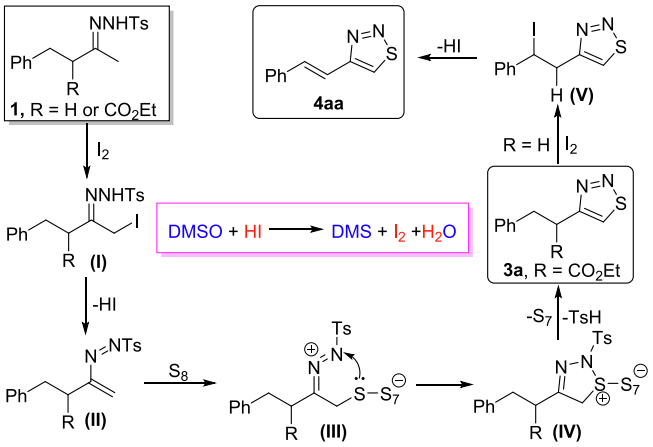
Fig. 1. The crystal structure of compound 3i.



Scheme 3. Gram-scale experiments and further conversion of 3 g.



Scheme 2. The reactions of other *N*-tosylhydrazones with S_8.



Scheme 4. Proposed reaction mechanism.

To demonstrate the practicality of this method, a gram-scale reaction was conducted under standard conditions. As shown in Scheme 3, the reaction could be easily scaled up with 6.0 mmol of **1g**, affording the product **3g** in 65% (1.33 g) yield. Importantly, the synthetic versatilities of **3g** as the substrate were demonstrated by the corresponding transformations. The compound **3g** and phenylboronic acid underwent the Suzuki – Miyaura reaction in the presence of $Pd(PPh_3)_4$ (0.2 mol%) and $PCy_3{\bullet}HBF_4$ (0.4 mol%), affording the desired product **3l** in 67% yield. Under the action of 10% NaOH, the hydrolysis reaction of the compound **3g** could be carried out to give the corresponding product **3ga** in 81% yield. In addition, under the catalysis of the $Pd_2(dba)_3$ (2 mol%) and Xphos (4 mol%), the C—N coupling reaction could proceed smoothly, providing the corresponding product **3gb** in 35% yield.

Based on the previous reports [8], a plausible mechanism was proposed (Scheme 4). First, elemental iodine reacts with **1** to form α-iodation of tosylhydrazone (**I**), and the elimination of HI provided azoalkene intermediate (**II**). Subsequently, the reaction of azoalkene intermediate (**II**) with S_8 affords zwitterionic intermediate (**III**), which underwent cyclization that furnished intermediate (**IV**). Furthermore, the elimination of S_7 and TsH led to the formation of the product **3a**. In addition, for non-ester substituted product **3**, the iodination will continue to form intermediate (**V**) under the action of I_2. Finally, this intermediate (**V**) loses one molecule of HI to obtain the product **4aa**. In the whole process, the released HI is oxidized by DMSO to I_2 for the next cycle of the reaction.

Conclusion

In conclusion, we have developed an iodine-catalyzed the reaction of the ester-substituted *N*-tosylhydrazones, the desired products 4-alkyl-1, 2, 3-thiadiazoles were obtained with good functional group tolerance. When the *N*-tosylhydrazones of 4-arylbutan-2-one were used as reactants, the (*E*)-4-styryl-1, 2, 3-thiadiazole derivatives were provided with high selectivity by adjusting the reaction conditions. The merits of this method include the use of catalytic amount of I_2, broad substrate scope, gram-scale synthesis, and further transformations.

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.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152824.

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