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Synthesis of spiro[4.4]thiadiazole derivatives via double 1,3-dipolar cycloaddition of hydrazonyl chlorides with carbon disulfide†

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An operationally simple and convenient synthesis method toward a series of diverse spiro[4.4]thiadiazole derivatives *via* double [3 + 2] 1,3-dipolar cycloaddition of nitrilimines generated *in situ* from hydrazonyl chlorides with carbon disulfide has been achieved under mild reaction conditions.

The spirocyclic compounds having cyclic structures connected through just one carbon atom have attracted much interest from synthetic chemists and medicinal chemists because of their ubiquitous presence in the core of a plethora of natural products and non-natural products, many of which display a broad range of pharmacological and biological activities.[1] Moreover, spiro-compounds are unique because of their rigidity and distinctly three-dimensional structure and have proved to be very interesting for medicinal chemistry or as ligand and catalyst motifs in asymmetric synthesis.[2] Due to the importance of the spirocyclic architectures, the methods for synthesis of the spirocyclic moiety are too many to enumerate. Some common strategies to afford spirocyclic scaffolds include radical cyclizations,[3] Diels–Alder reactions,[4] cycloaddition,[5] and ring expansion,[6] among others. Many of the known methods for synthesizing spiro structures are through constructing a new ring of which the substrates include a carbo- or heterocycle structure.[7] To the best of our knowledge, a few approaches have offered efficient ways on the formation of two rings through a double 1,3-dipolar cycloaddition in one pot for constructing spirocyclic scaffold.[8] Therefore, the design and development of innovative and efficient methodologies *via* double 1,3-dipolar cycloaddition under mild reaction conditions for synthesizing bioactive content spirocyclic scaffolds from readily available precursors is in great demand in both organic and medicinal chemistry.

On the other hand, the 1,3-dipolar cycloaddition reaction (1,3-DCs) has been one of the most prominent reactions to build five- or six-membered heterocycle in one step in the field of organic synthesis.[9] In particular, nitrilimines generated *in situ* from the corresponding hydrazonyl chloride in the presence of a base are highly active intermediates in organic synthesis and have been widely used as useful synthons for preparing bioactive nitrogen heterocyclic derivatives and spirocyclic compounds through the [3 + 2],[10] [3 + 3][11] and [3 + 4][12] cycloaddition reactions. In addition, the Lu group reported 1,3-dipolar cycloaddition of nitrilimines with carbon dioxide (CO_2), providing elegant access to 1,3,4-oxadiazole-2(3H)-ones derivatives.[13] Meanwhile, carbon disulfide (CS_2) that it is an analogue of CO_2, has been used for the synthesis of various sulfur-containing heterocyclic compounds for agricultural, medicinal, and pharmaceutical applications.[14] Based on the above literatures and in continuation of our interest in synthesis of heterocycles, we disclose a novel protocol for the synthesis of spiro[4.4]thiadiazole derivatives double 1,3-dipolar cycloaddition of nitrilimines generated *in situ* from hydrazonyl chlorides with carbon disulfide under mild conditions.

In our initial investigation, we chose the hydrazonyl chloride as the nitrilimine precursor with CS_2 as the model reaction to optimize the reaction conditions. The results of these experiments are summarized in Table 1. No product was observed when the reaction was performed in the absence of base (Table 1, entry 1). Usually, the active nitrilimine is generated *in situ* by dehydrohalogenation of the corresponding hydrazonyl halide in the presence of an equivalent base. Pleasingly, with the use of TEA as the base, the double 1,3-dipolar cycloaddition reaction proceeded very smoothly in CH_2Cl_2 to give spirothiadiazole product **3a** with 60% yield at room temperature (Table 1, entry 2). The product **3a** was obtained with 56% yield in the presence of DABCO (entry 3). However, the DBU base turned out to be inactive in the double 1,3-dipolar cycloaddition reaction (entry 4). Subsequently, we screened a series of inorganic base to improve the yield, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOH and KOH (entries 5–9). In comparison, the product **3a** was gave in

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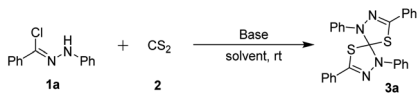
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Table 1 Optimization of reaction conditions[a]

Entry	Base	Solvent	Yield of 3a[b] (%)
1	None	CH_2Cl_2	0
2	TEA	CH_2Cl_2	60
3	DABCO	CH_2Cl_2	56
4[b]	DBU	CH_2Cl_2	Trace
5	Na_2CO_3	CH_2Cl_2	62
6	K_2CO_3	CH_2Cl_2	70
7	Cs_2CO_3	CH_2Cl_2	92
8	NaOH	CH_2Cl_2	90
9	KOH	CH_2Cl_2	88
10	Cs_2CO_3	$CHCl_3$	80
11	Cs_2CO_3	DCE	85
12	Cs_2CO_3	EtOAc	70
13	Cs_2CO_3	Toluene	61
14	Cs_2CO_3	THF	Trace
15	Cs_2CO_3	Et_2O	Trace
16	Cs_2CO_3	Dioxane	56
17	Cs_2CO_3	MeCN	62
18[c]	Cs_2CO_3	CH_2Cl_2	80
19[d]	Cs_2CO_3	CH_2Cl_2	92

[a] Unless noted otherwise, reactions were performed with hydrazonyl chloride **1a** (0.2 mmol), carbon disulfide (0.3 mmol, 1.5 equiv.), base (0.2 mmol, 1 equiv.) in solvent (1.0 mL) at rt for 12 h. [b] Isolated yield by chromatography on silica gel. [c] Reaction was performed with carbon disulfide (0.2 mmol, 1 equiv.) for 24 h. [d] Carbon disulfide (1.0 mmol, 5 equiv.).

moderate yields in the presence of TEA, Na_2CO_3 or K_2CO_3 (entries 2, 5 and 6). To our delight, the yield of the product **3a** was increased to 92% when used Cs_2CO_3 as the base (entry 7). Nevertheless, the yield was slightly reduced with the use of NaOH and KOH as the base (entries 8 and 9). Encouraged by this result, the reaction was examined with different solvents to improve the yield of **3a**. The reaction can be carried out in $CHCl_3$ and DCE to provide the expected product in 80% yield and 85% yield, respectively (entries 10 and 11). Whereas no the desired product formation take place upon using THF and Et_2O as the solvent (entries 14 and 15). The reactions run with either dioxane or MeCN resulted in moderate conversions (entries 16 and 17). It was found that CH_2Cl_2 was the best solvent for this transformation compared to $CHCl_3$, DCE, EtOAc, toluene, THF, Et_2O, dioxane and MeCN (entries 10–17). Moreover, when decreased the amounts of CS_2, the reaction time was prolonged and the yield of the product was lowered (entry 18). Whereas, the yield was not further improved when using 5.0 equiv. of CS_2 (entry 19). Therefore, the optimal reaction conditions have been determined which using Cs_2CO_3 as the base in CH_2Cl_2 at room temperature for 12 h (Table 2).

With the optimal reaction conditions in hand, we subsequently investigated the substrate scope and limitation of the nitrilimine precursors. The results are shown in Table 1. Under the optimized conditions, the double 1,3-dipolar cycloaddition reaction could tolerate a variety of hydrazonyl chlorides bearing different substituents, regardless of the electronic properties

**Table 2** Substrate scope of the double 1,3-dipolar cycloaddition[a]

[a] Unless noted otherwise, reactions were performed with hydrazonyl chloride **1** (0.2 mmol), carbon disulfide (0.3 mmol, 1.5 equiv.), base (0.2 mmol, 1 equiv.) in solvent (1.0 mL) at rt for 12 h. Isolated yield by chromatography on silica gel.

(such as electron-donating or electron-withdrawing) or the positions of substituents on the benzoyl chloride moiety, to generate the corresponding products **3** (**3a–i**) in high yields (92–96%). In addition, the structure of product **3h** (CCDC 2041891)[15] was further determined by single-crystal X-ray crystallography analysis. Furthermore, when using the fused aromatic and heteroaromatic hydrazonyl chlorides as the substrate reacted with CS_2, the reactions were also found to be compatible and gave the products (**3j–l**) in high yields. On the other hand, the hydrazonyl chlorides containing different substituents (such as methyl and chloro) on phenylhydrazone moiety also worked well in the reaction successfully to obtain the desired cycloadducts **3m** and **3n** in 90% and 93% yield, respectively. Nevertheless, the hydrazonyl chlorides bearing cyano or nitro group on the benzoyl chloride moiety were not suitable and the expected cycloadduct **3p** and **3q** were not formed. Moreover, the double 1,3-dipolar cycloaddition reaction also didn't work with aliphatic group (**3r**) at the hydrazonyl chloride.

Scheme 1 Scaled-up version of synthesis of **3a**.
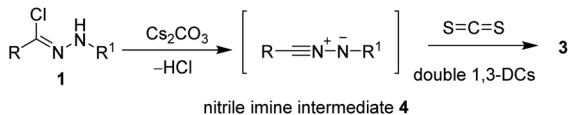
Scheme 2 Proposed mechanism of the double [3 + 2] cycloaddition.

To further exhibit the synthetic utility for spirocyclic compounds, under the optimized conditions, a gram scale experiment between 4 mmol of hydrazonyl chloride **1a** and 6 mmol of CS_2 proceeded smoothly to afford the desired product **3a** without a significant loss of efficiency (1.670 g, in 90% yield) (Scheme 1). The easy scale-up of this process shows the reaction to be a practical tool for the synthesis of structurally diversified natural product-like molecules possessing privileged scaffold for potential application in biomedical research and other research fields.

As shown in Scheme 2, a plausible mechanism was proposed. Firstly, the nitrilimine intermediate **4** generated *in situ* from the corresponding hydrazonyl halide **1** *via* eliminating of HCl in the presence of a base. Then, the nitrilimine **4** reacts with CS_2 through the double 1,3-dipolar cycloaddition reaction to give the desired product **3**.

In conclusion, we have developed an efficient and simple method to synthesize a broad range of diverse spiro[4.4]thiadiazole derivatives in high yields (up to 96%) through the double 1,3-dipolar cycloaddition of nitrilimines generated *in situ* with CS_2. This reaction proceeds with readily available starting materials, transition-metal free, the experimental simplicity, easy purification, and mild reaction conditions make this procedure highly appropriate for the synthesis of spiro[4.4]thiadiazole derivatives.

Conflicts of 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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15 CCDC 2041891 for **3h** contains the ESI crystallographic data for this paper.