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Communication

Thiocarbonylation of C(sp^3)-H bonds in pyridylamines with CS_2: Facile synthesis of pyrido[1,2-*a*]pyrimidine-4-thiones

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ABSTRACT

Herein, a facile synthesis of valuable pyrido[1,2-*a*]pyrimidine-4-thiones is reported *via* novel thiocarbonylation of C(sp^3)-H bonds with carbon disulfide (CS_2). This reaction features easy availability of substrates, good functional group tolerance, high yields, facile scalability and atom economy. Mechanistic investigations indicate that sulfate anion and sulfuric anhydride anion might be involved in this reaction.

Construction of valuable thiocarbonyl-containing heterocycles has attracted much attention for long time due to their unique biological and pharmacological activities [1–3]. Traditionally, they are usually synthesized by using elemental sulfur, Lawesson reagent, isothiocyanates and phosphorus pentasulfide as sulfur source [4–8]. However, some drawbacks still exist for these sulfur sources, such as low atom- and step-economy, difficult-to-access substrates and/or low efficiency. Therefore, it is highly important to disclose an ideal thiocarbonyl source to synthesize valuable thiocarbonyl-containing heterocycles efficiently. Recently, metal sulfide species, such as potassium sulfide and sodium sulfide, have been used as sulfur source [9] to generate thiocarbonyl-containing compounds. However, in many cases, transition-metal catalysis (copper, ruthenium, *etc.*) is involved in the synthesis of sulfur-containing carbonyl heterocycles [10]. Therefore, it is very attractive to find another ideal sulfur source to construct a thiocarbonyl heterocycles, especially through transition-metal-free process. In addition to a buck chemical and common solvent in industry, carbon disulfide (CS_2) is also characterized as an ideal thiocarbonyl source due to the low cost, ready availability, stability and excellent solubility in organic solvent. In the past few decades, however, only few reports have documented CS_2 as a thiocarbonyl source to generate biologically active thiocarbonyl-containing heterocycles [11–15]. Therefore, novel application of CS_2 in constructing other important thiocarbonyl-containing heterocycles is highly appealing.

Pyrido[1,2-*a*]pyrimidine-4-thione is one key motif in many biological and pharmacological molecules (Fig. 1). In addition, as a bioisosteric [16] derivative of pyrido[1,2-*a*]pyrimidine-4-one that plays a vital role in many drug molecules and is widely investigated in medicinal chemistry [17], it also shows great biomedical potential. However, to the best of our knowledge, there are only a few methods to construct the pyrido[1,2-*a*]pyrimidine-4-thiones directly [18]. Early in 1975, Gilchrist [19] and coworkers reported the synthesis of pyrido[1,2-*a*]pyrimidin-4-thiones from sulfonamide and diphenylcyclopropene thione (Scheme 1A). Nonetheless, this reaction suffers from limited substrate scope and multi-step synthesis of substrates. What is more, the synthesis of diphenylcyclopropene thione relies on the use of Lawesson reagent or phosphorus pentasulfide, devoid of atomic economy. After a long time, in 2007 Britsun [20] and coworkers developed a novel method to obtain pyrido[1,2-*a*]pyrimidine-4-thiones from 3-oxopropanethioamides and 2-aminopyridine with acetic acid (Scheme 1B). Even so, the selectivity is governed exclusively by the structure of substituents and the condensation side reactions also exist. In view of above limitations, it remains desirable to develop a concise route to construct pyrido[1,2-*a*]pyrimidine-4-thiones efficiently. Therefore, we envisioned a novel synthesis of pyrido[1,2-*a*]pyrimidine-4-thione by using easily available ketoimines and CS_2 (Scheme 1C) through thiocarbonylation of C(sp^3)-H bonds. Nevertheless, this protocol is estimated to confront several challenges.

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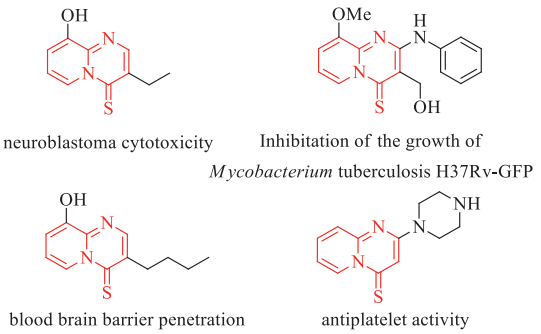
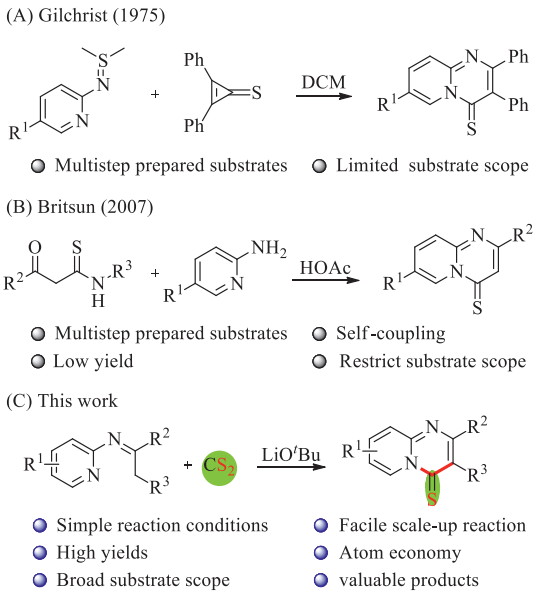


Fig. 1. Selected examples of bioactive pyrido[1,2-*a*]pyrimidine-4-thiones.

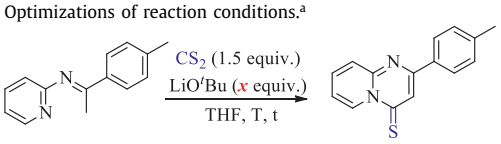


Scheme 1. Methods of synthesizing pyrido[1,2-*a*]pyrimidine-4-thiones.

First, to the best of our knowledge, in contrast to limited progress on thiocarbonylation of C(sp^2)-H bonds [13,14], the utilization of CS_2 to achieve the thiocarbonylation of C(sp^3)-H bonds has not been reported yet. Second, dearomatization of pyridines may occur during the reaction, rendering such processes even more delicate. Third, CS_2 is of relatively low reactivity thus requiring proper activation. Herein, we report a novel and efficient approach to directly synthesize pyrido[1,2-*a*]pyrimidine-4-thiones *via* thiocarbonylation of C(sp^3)-H bonds in pyridylamines with CS_2.

We started the project by investigating the thiocarbonylation reaction of *N*-(2-pyridyl)ketoimine **1a** with CS_2 (Table 1). At the beginning, we systematically screened different bases and solvents (more details see Table S1 in Supporting information). We found lithium *tert*–butoxide (LiO^{t}Bu) as the optimal base and tetrahydrofuran (THF) as the optimal solvent. The desired product could be obtained in 99% with 4.5 equiv. of LiO^{t}Bu in THF at 130 °C for 24 h (Table 1, entry 1). In order to realize this reaction under milder reaction conditions, we further screened the dosage of base, reaction temperature and time, respectively. The screening of the amount of LiO^{t}Bu demonstrated that 2.5 equiv. was the best choice (Table 1, entries 1–5). Notably, only trace product was observed when no base was added, highlighting the importance of base (Table 1, entry 5). Moreover, the reaction temperature of 100 °C was found to give the optimal outcome (Table 1, entries 3, 6, 7). The reaction time was then successfully compressed from 24 h to 10 h (Table 1, entries 6, 8, 12). Control experiments indicated that the yield would decrease to 61% when 1.0 equiv. of H_2O was added,

Table 1
Optimizations of reaction conditions.[a]



1a **2a**

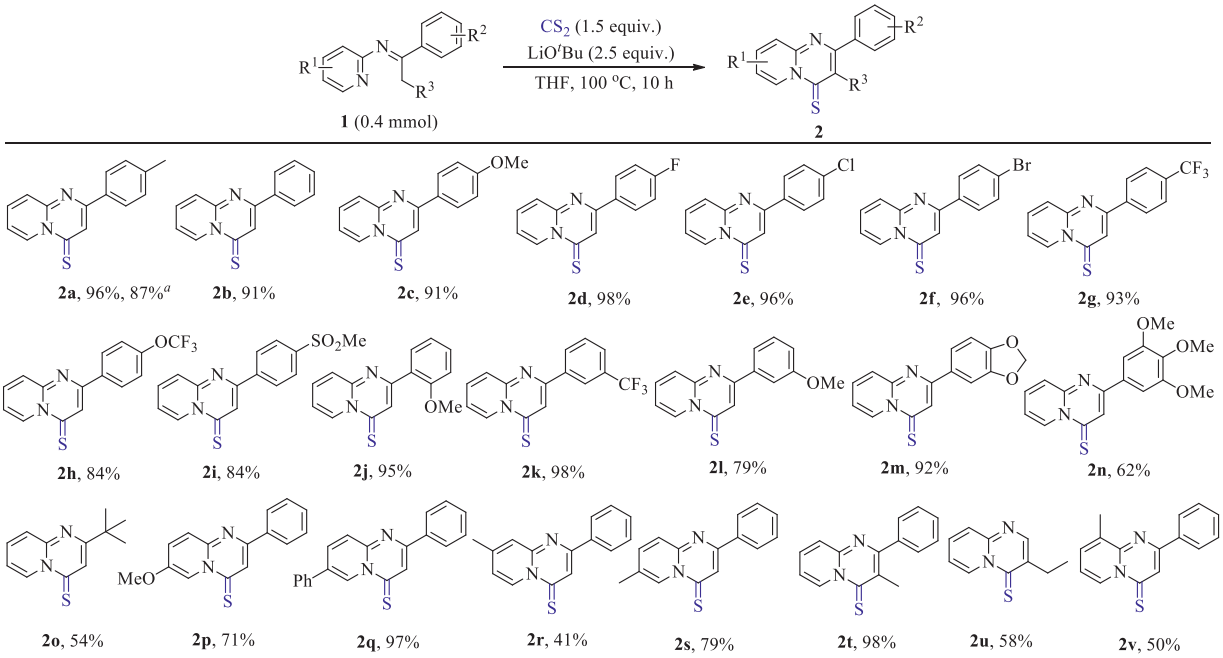
Entry	*x*	T (°C)	t (h)	Yield (%)[b]
1	4.5	130	24	99
2	3.0	130	24	93
3	2.5	130	24	98
4	2.0	130	24	83
5	0	130	24	trace
6	2.5	100	24	96
7	2.5	80	24	83
8	2.5	100	12	96
9	2.5	95	12	95
10	2.5	90	12	87
11	2.5	r.t.	12	66
12	2.5	100	10	96[d]
13	2.5	95	10	92
14	2.5	90	10	86
15[c]	2.5	100	10	61

[a] Reaction conditions: **1a** (0.2 mmol), CS_2 (1.5 equiv., 0.3 mmol), THF (2 mL).
[b] Isolated yield.
[c] H_2O (1.0 equiv., 0.2 mmol) was added.
[d] Yield same as the scale of 0.4 mmol.

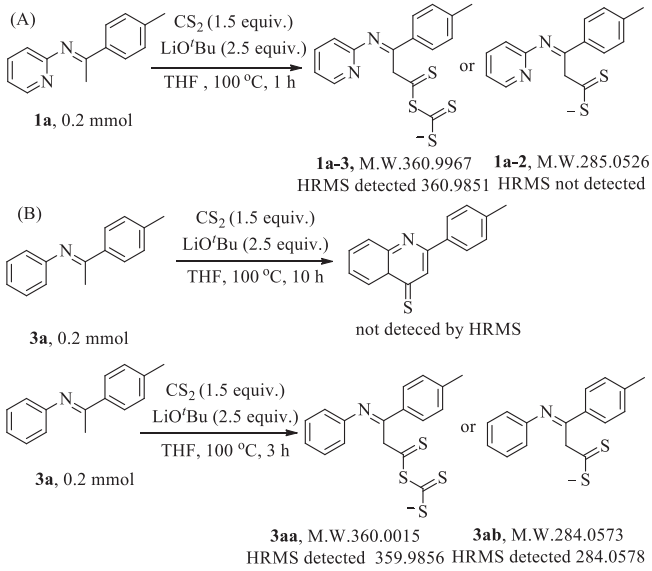
demonstrating the significant influence of water on the transformation (Table 1, entry 15). To our delight, this reaction could also afford **2a** in 66% yield under room temperature (Table 1, entry 11).

With the optimal reaction conditions in hand, we attempted to expand the substrate scope of *N*-(2-pyridyl)ketoimines (Scheme 2). A series of (*E*)-1-aryl-*N*-(pyridin-2-yl)ethan-1-imines (**1a, 1c-1i**) underwent this transformation to corresponding products in excellent yields, including those bearing electron-withdrawing groups (EWGs) or electron-donating groups (EDGs) on the phenyl ring at *para*-position, such as methyl group, halogen groups (-F, -Cl, -Br), trifluoromethyl group, trifluoromethoxy group (-OCF_3). In addition, substrates with substituents at the *ortho*- (**1j**) or *meta*- (**1k, 1l**) positions of the phenyl ring also performed well. Besides monosubstituents, the substrates bearing di- (**1m**) or tri-substitutes (**1n**) on the phenyl ring could also undergo this transformation to provide the desired products in good to excellent yields. Delightedly, alkyl-substituted *N*-(2-pyridyl)ketoimine substrate **1o** was reactive in this reaction. Substrates with different substituents on the pyridine ring (**1p**-**1s**, **1v**) were also investigated, indicating that those with EDGs on pyridine ring performed better than those with EWGs. Besides the mono-substituted pyrimidinones, to our delight, we could also generate the disubstituted one (**2t**) in excellent yields. Moreover, **2u**, an important motif for synthetic biomedicine, could also be obtained in 58% yield in this transformation. To further showcase the utility of the transformation in organic chemistry, we carried out gram-scale reaction of **1a** and obtained the target product **2a** in 87% yield.

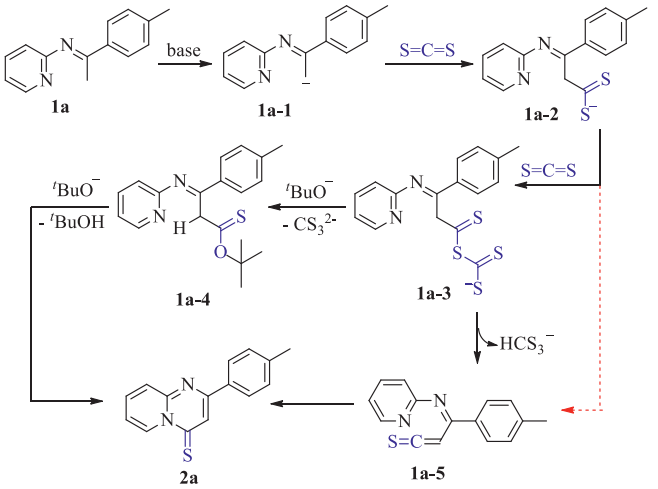
To get insight into this transformation, some control experiments were implemented (Scheme 3). Inspired by our previous work on carbonylation with CO_2 [18], we hypothesized that **1a-2** and **1a-3** might be the intermediates (Scheme 3A). We conducted the reaction and detected **1a-3** *via* HRMS, while **1a-2** was not detected probably due to its instability. So, we chose the hard-to-cyclize **3a** and conducted a similar reaction (Scheme 3B). Fortunately, we detected both **3aa** and **3ab**. Therefore, we speculated that **1a-2** and **1a-3** might be both involved in this transformation. It is worth noticing that the intermediates mentioned above could not be detected in the absence of CS_2.



Scheme 2. Substrate scope. **1a** (0.4 mmol scale), CS_2 (1.5 equiv., 0.6 mmol), LiO^{t}Bu (2.5 equiv., 1.0 mmol), THF (4 mL), 100 °C, 10 h. Isolated yields are shown. [a] The scale-up reaction, **1a** (5 mmol), CS_2 (1.5 equiv., 7.5 mmol), LiO^{t}Bu (2.5 equiv., 12.5 mmol), THF (50 mL), 100 °C, 10 h.



Scheme 3. Control experiments.



Scheme 4. Proposed mechanism.

Based on the current results and previous reports [18,21], a plausible mechanism was proposed (Scheme 4). Firstly, **1a** undergoes deprotonation in the presence of base to form **1a-1**, which can further react with CS_2 to generate intermediates **1a-2** and **1a-3** [22]. Then **1a-3** might react with ^{t}BuO$^-$ to generate **1a-4**, which further transforms to **2a** in the presence of a base. Furthermore, intermediate **1a-3** might be subjected to subsequent cyclization *via* **1a-5** [23] to obtain the desired product **2a**. Additionally, **1a-2** might transform into **1a-5** directly and then generate **2a** *via* cyclization [24].

In summary, we disclosed a novel thiocarbonylation of C(sp^3)-H bonds in pyridylamines with carbon disulfide (CS_2). By using this strategy, we manage to prepare valuable pyrido[1,2-*a*]pyrimidine-4-thiones in efficient and economical way. This protocol features broad substrate scope, good functional group tolerance, facile scalability, thus providing potential application in organic synthesis and pharmaceutical industry. Control experiments indicate that sulfate anion and sulfuric anhydride anion might be generated as intermediates in this reaction. Further mechanistic studies and application of this chemistry are underway in our lab.

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.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.05.055.

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