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Synthesis of α-cyanato-α′-carbonyl sulfoxonium ylides in water†

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A new strategy for direct access to unreported α-cyanato-α′-carbonyl sulfoxonium ylides is reported. The developed open-flask operation is a catalyst-, metal- and additive-free green process, which has good compatibility with various substituents and generally excellent yields. This protocol can be applied to gram-scale production and modification of bioactive drugs which demonstrate the practicality of this method.

Introduction

Over the past few decades, carbene has emerged as a highly appealing and potent tool in the field of organic synthesis.[1] In this context, diazo compounds have garnered significant attention as the most widely used carbene precursors. However, their toxicity, instability, and potential explosiveness have prompted the search for carbene precursors that meet the green chemistry criteria. Among these alternatives, sulfoxonium ylides have gained considerable interest.[2–4] Not only are they bench-stable and safer, but they can also be prepared on a larger scale with relative ease. In contrast to diazo compounds, which release N_2 as a byproduct during reactions, sulfoxonium ylides generate only DMSO, a high boiling point compound, thus avoiding an undesired increase in pressure within the reaction vessel.[5,6] Serving as greener alternatives to diazo compounds, sulfoxonium ylides have exhibited remarkable advancements since the seminal research conducted by Corey, Chaykovsky, and Johnson.[7–9] Functioning as versatile C1 or C2 synthons, sulfoxonium ylides have successfully facilitated the construction of various heterocyclic compounds and others. With their intriguing reactivity, the utility of sulfoxonium ylides can be further enhanced through the synthesis of novel derivatives.[10]

β-ketosulfoxonium ylides can be readily synthesized from trimethyl sulfoxide iodide by reacting it with various acyl chlorides.[11] However, the synthesis of bis-substituted sulfoxonium ylides remains challenging, which warrants the need for further research.[12] To address this challenge, several methods for C1-H functionalization of mono-substituted sulfoxonium ylides have been reported. Christophe Aïssàs group achieved palladium-catalyzed arylation using aryl bromides and triflates.[13] Antonio C. B. Burtoloso's group successfully realized the arylation *via* arynes as intermediates.[12] The synthesis of biscarbonyl sulfoxonium ylides is another strategy that has been explored. The Wu group developed an elegant palladium catalyst system for the synthesis of α,α′-dicarbonyl sulfoxonium ylides,[14] as well as α-carbonyl-α′-amide sulfoxonium ylides through an extra carbonyl insertion.[15] Satyendra K. Pandey group's achieved the synthesis of α-carbonyl-α′-amide sulfoxonium ylides through nucleophilic addition with isocyanates, under metal and additive-free conditions.[16] Zhang's group focused on the electrochemical synthesis of bis-substituted sulfoxonium ylides.[17,18] They successfully achieved electrochemically promoted C–H bond chlorination and thiocyanation of mono-substituted sulfoxonium ylides, enabling the gram-scale production of these two novel types of sulfoxonium ylides. Subsequent mechanistic studies have confirmed the involvement of a radical pathway in these reactions.

Despite the existence of a few elegant strategies for synthesizing bis-substituted sulfoxonium ylides, several significant issues remained unresolved in most cases. Firstly, in a certain number of processes, transition metal catalysts like Pd and Rh catalysts were required, which were expensive and might contribute to pollution. Secondly, these reactions typically required an argon or nitrogen atmosphere to prevent the adverse effects induced by air, which could lead to limited yields or even inhibit the reaction. This operational complexity was unfavorable for large-scale industrial production. Thirdly,

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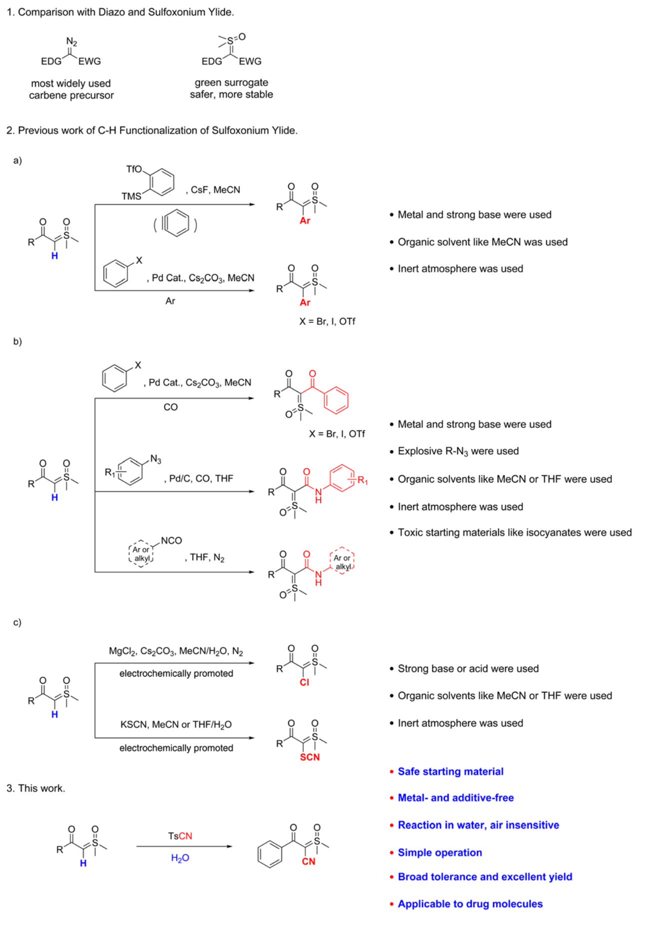
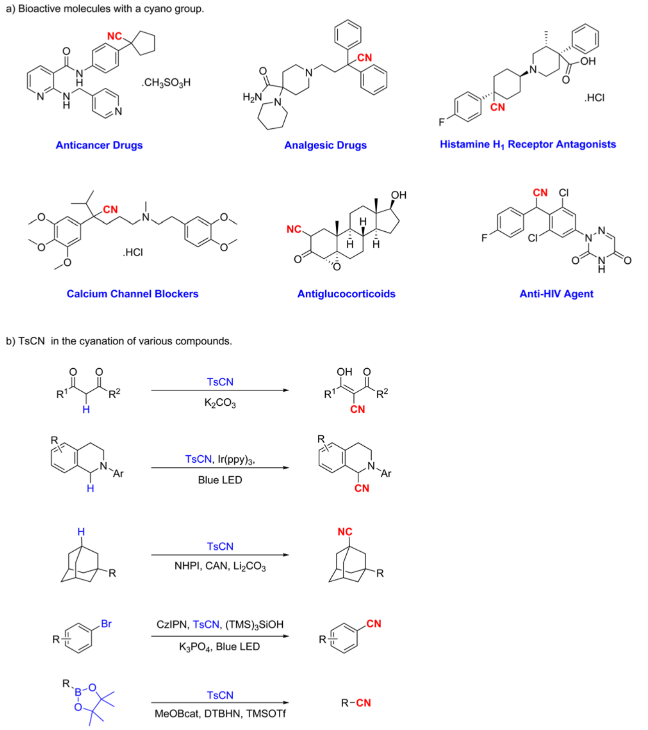
organic solvents like THF and MeCN were commonly used, which did not meet the green chemistry criteria. Besides, explosive azides and toxic isocyanates were used in some transformations. Therefore, it is highly desirable to develop a simple, efficient, additive- and catalyst-free C–H functionalization process of sulfoxonium ylides that can be operated under mild conditions in aqueous media. This approach would be more environmentally friendly and align with the principles of green chemistry (Scheme 1).

The cyano group is a widespread structural fragment distributed in many pharmaceutical compounds (Scheme 2a).[19–24] It is worth noting that the cyano group also serves as a versatile precursor for amino, carbonyl, and amide groups in organic transformation.[25–29] Most of the traditional cyanating reagents like metallic cyanides and TMSCN are highly toxic and environment-unfriendly. Recently, safe and effective *p*-toluenesulfonyl cyanide (TsCN) has been successfully employed in the cyanation of various compounds, such as 1,3-dicarbonyl compounds,[30] β-keto esters,[30] tetrahydroisoquinolines,[31] adamantane derivatives,[32,33] arenes,[34,35] alkenes,[36] and boron enolates (Scheme 2b).[37,38]

Based on our previous work and interest in sulfoxonium ylides,[39–42] we have developed a straightforward method for C–H bond cyanation of mono-substituted sulfoxonium ylides under mild and environmentally friendly conditions. Notably, this reaction does not require any additional catalyst or additives, and it exhibits good tolerance towards aromatic and aliphatic groups with diverse electronic properties and steric hindrance.



Scheme 1 Research background.

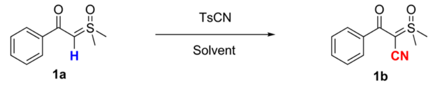


Scheme 2 (a) Bioactive molecules with a cyano group, (b) TsCN in the cyanation of various compounds.

Results and discussion

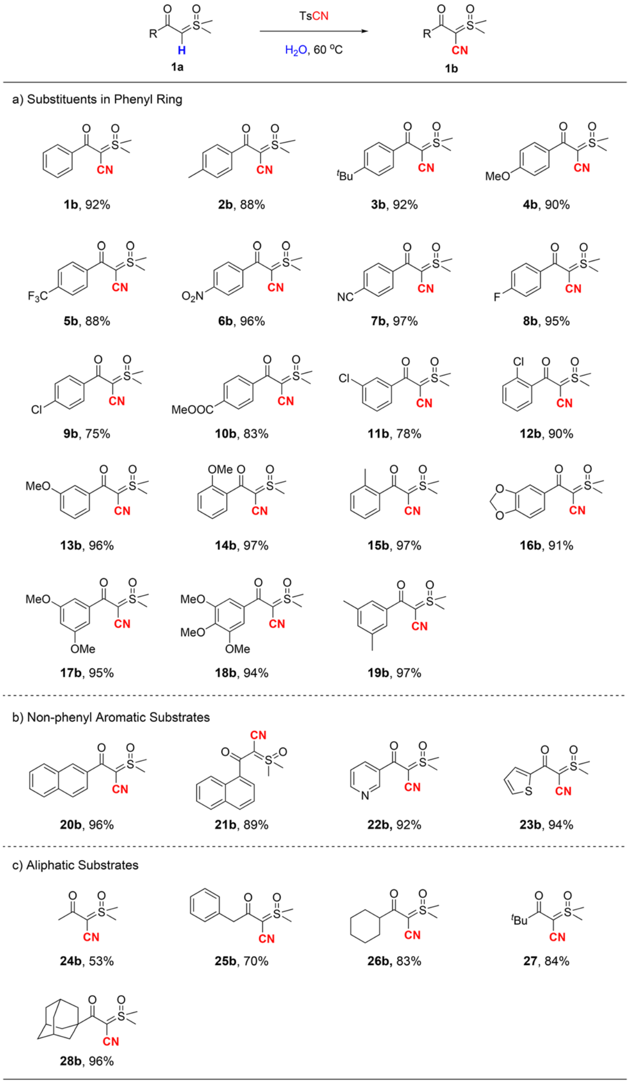
Our investigation began with the optimization of reaction conditions using β-ketosulfoxonium ylide **1a** as the model substrate. The results of this optimization were presented in Table 1. Based on a report by Satoshi Minakata,[43] tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) could activate TsCN through coordination of the cyano group to the boron center, making the cyano carbon center more electrophilic that could be attacked by an alkene. Sulfoxonium ylides are versatile zwitterionic compounds, and we hypothesized that the nucleophilic α-carbon of β-ketosulfoxonium ylides could undergo an electrophilic cyanation process as well. We initially employed $B(C_6F_5)_3$ as a catalyst, and toluene as the solvent (entry 1). This transformation was complete in 12 hours. However, upon further testing, we discovered that $B(C_6F_5)_3$ was not necessary for this reaction, albeit the yield was slightly lower and a longer time was needed, we speculated that it might be due to the more electrophilic attacking property of sulfoxonium ylides (entry 2). To explore the effect of solvents, a series of organic solvents were tested, and we found that both chloro-

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$B(C_6F_5)_3$	Tol	12	64
2		Tol	24	50
3		DMF	24	56
4		Acetone	24	88
5		EtOH	24	30
6		EA	24	49
7		DCE	24	51
8		MeCN	24	28
9		$CHCl_3$	24	90
10		DMSO	24	90
11		H_2O	24	93
12[b]		**H_2O**	**24**	**92**

[a] Reaction conditions: **1a** (0.2 mmol), TsCN(0.4 mmol, 2 eq.), catalyst (5 mol%) in 2 mL of solvent at 60 °C under air. [b] TsCN (0.3 mmol, 1.5 eq.).



Reaction conditions: **1a** (0.2 mmol, 1 eq), TsCN (0.3 mmol, 1.5 eq) in 2 mL H_2O at 60 °C for 24 h.

Scheme 3 Scope of substrates.

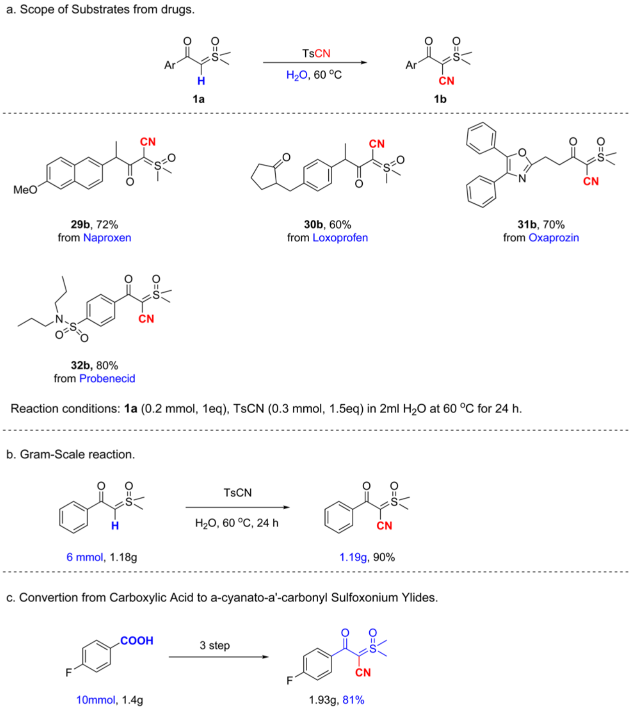
form ($CHCl_3$) and dimethyl sulfoxide (DMSO) gave the desired product **1b** in 90% yields. Inspired by this result and considering our previous work on the insertion of sulfoxonium ylides into arylamines in water,[41] we performed the model reaction in water, leading to the formation of the desired product **1b** in 93% yield. After the screening of equivalents of TsCN, optimal reaction conditions were obtained. When sulfoxonium ylide was treated with 1.5 eq. of TsCN at 60 °C for 24 h in water, we obtained product **1b** in 92% yield (more information in the ESI†).

With the optimal reaction conditions in hand, we proceeded to investigate the substrate generality of our reaction. Firstly, we presented the results obtained by testing various substituents on the phenyl ring of β-ketosulfoxonium ylide (Scheme 3a). Remarkably, our reaction exhibited good tolerance towards substrates bearing electron-donating, electron-withdrawing, halogen, and sterically bulky groups at the *para*-position. This enabled the formation of α-cyanato-α′-carbonyl sulfoxonium ylides **2b–10b** with yields ranging from 75% to 97%. To compare the yields of substrates with the same group at different positions, we further examined substrates **11b–14b**. We found that *ortho*-substituted β-ketosulfoxonium ylides afforded higher yields than their *para*-/*meta*-substituted analogues. Moreover, substrates bearing a methyl group at the *ortho* position afforded product **15b** in a near stoichiometric yield. We also explored the reactivity of polysubstituted substrates. Encouragingly, substrates with at least two electron-donating groups on the phenyl ring were fully compatible, leading to the formation of products **16b–19b** in excellent yields.

Non-phenyl aromatic substrates could convert to the desired products in excellent yields as well (Scheme 3b). Both α- and β-naphthyl substrates underwent the desired transformation, resulting in the corresponding products **20b** and **21b** with yields of 96% and 89%, respectively. Heteroaromatic substrates, such as pyridinyl and thienyl, also proved amenable to the reaction, affording the desired products **22b** and **23b** with yields of 92% and 94%.

Sulfoxonium ylides with aliphatic substituents also showed high reactivity to our reaction (Scheme 3c). We tested sulfoxonium ylides bearing various common aliphatic substituents and the products were obtained in good to excellent yields (**25b–28b**). However, it was worth noting that the methyl substituent was an exception, affording a moderate yield of **24b**.

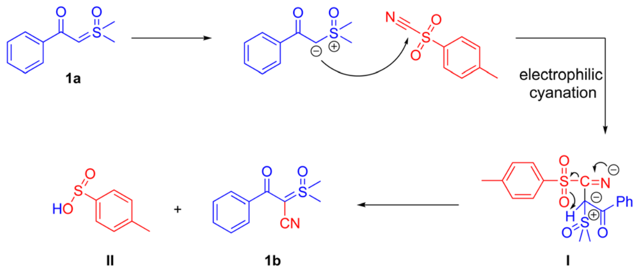
In Scheme 4a, we demonstrate the application potential of our reaction by testing it on pharmacologically active drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) were widely used,[44–48] and we successfully applied our reaction to substrates derived from naproxen,[46,48] loxoprofen,[44] and oxaprozin,[45] yielding the desired products **29b–31b** in 60% to 72% yields. Furthermore, substrate **32b** derived from probenecid which was widely used as an antigout drug,[49] underwent excel-



Scheme 4 Gram-scale reaction and applications.

lent conversion. A gram-scale reaction using the model substrate was performed (Scheme 4b). The product **1b** was obtained in 90% yield, demonstrating the feasibility of our reaction on a large scale. Carboxylic acids were readily available raw materials. To make this transformation more valuable and practical, we also explored the transformation from carboxylic acids to α-cyanato-α′-carbonyl sulfoxonium ylides with purification by column chromatography only once through three steps (Scheme 4c),[50–52] and **8b** was successfully isolated in 81% yield.

Following the practical synthesis of α-cyanato-α′-carbonyl sulfoxonium ylides from β-ketosulfoxonium ylides, a tentative reaction mechanism is proposed as shown in Scheme 5 based on the work of other research groups.[16,43] The nucleophilic sulfoxonium ylide **1a** reacts with TsCN, resulting in the formation of intermediate **I** through an electrophilic cyanation process. Subsequently, proton transfer leads to the formation of product **1b** following electron transfer. The by-product **II** was detected and identified through LCMS and GCMS analysis.



Scheme 5 The proposed mechanism.

Conclusions

In summary, we have developed a simple additive- and catalyst-free approach for the synthesis of α-cyanato-α′-carbonyl sulfoxonium ylides under green conditions. The reaction exhibited excellent tolerance towards β-ketosulfoxonium ylides bearing various functional groups, resulting in the formation of α-cyanato-α′-carbonyl sulfoxonium ylide derivatives in good to excellent yields. The operational procedure is simple, and the gram-scale reaction and transformation of drug substrates highlight the practical applicability of our method. Currently, some interesting applications of this new type of sulfoxonium ylide as building blocks are in progress, which will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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