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Transition-Metal-Free Tandem Radical Thiocyanooxygenation of Olefinic Amides: A New Route to SCN-Containing Heterocycles

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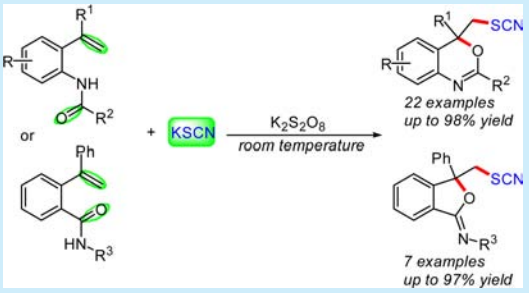
Supporting Information

ABSTRACT: A novel transition-metal-free tandem radical thiocyanooxygenation of olefinic amides with potassium thiocyanate has been developed under mild conditions. This method allows a reliable and practical access to diverse SCN-containing heterocycles bearing a wide range of functional groups in good to excellent yields. Furthermore, this tandem reaction provides a simple method for the construction of C−O and C−S bonds in one step.



Catalytic C−S bond formation reactions represent one of the most powerful methods for the synthesis of organosulfur compounds, which have found widespread applications in pharmaceuticals, agrochemicals, material science and nanotechnology.[1] To date, numerous sulfuration agents, including thiols, sulfur powder, thiourea, thioacetate and their derivatives have been utilized for C−S bond formations.[2] Among them, inorganic sulfosalts are the most attractive sulfur sources, especially for industrial scale, due to their easy availability, ease of use and low toxicity.[2c] Among the different inorganic sulfosalts, thiocyanate salts have been proven to be one of the most efficient and versatile sulfuration agents for the synthesis of various sulfur-containing compounds.[3] Although thiocyanate salts have been widely used in organic synthesis, the cascade oxidative coupling/cyclization of functionalized alkenes with thiocyanate salts remains relatively unexplored. Thus, developing new and efficient tandem thiocyanation reactions for the synthesis of diverse SCN-containing heterocycles is still highly desirable.

In the past decades, radical reactions have become a versatile and useful synthetic method for the carbon−carbon and carbon−heteroatom bond formations.[4] More recently, the tandem radical reactions, especially radical addition/cyclization of functionalized alkenes with different radicals have been developed as an attractive approach to various heterocycles.[5] In these transformations, the aromatic ring is usually utilized to trap the intramolecular alkyl radical intermediate, which is generated by radical addition to achieve the cyclization.[5] However, few examples of this cyclization completed with other trapping groups have been reported.[6] It is known that the thiocyanate anion could be easily oxidized by hypervalent iodine reagents, CAN or other oxidants to afford the thiocyanate radical.[7] However, the development of tandem thiocyanate radical reactions has received little attention, and there is no example of a tandem radical cyclization of thiocyanate radical with olefinic amides. As part of our ongoing work on tandem oxidative cyclization,[6e,8] we report herein a novel transition-metal-free tandem radical cyclization of olefinic amides with potassium thiocyanate under mild conditions (Table 1). The cyclization reaction proceeded via thiocyanation of an unsatured C=C bond followed by trapping the resulting alkyl radical with carbonyl group of amide to give a variety of SCN-containing heterocyclics.

At the outset of our investigation, we selected *N*-(2-isopropenyl-phenyl)-benzamide (**1a**) and potassium thiocyanate (**2a**) as a model reaction. In the presence of 2 equiv of oxone as the oxidant in MeCN at room temperature for 24 h, the desired benzoxazine **3a** was isolated in 33% yield (Table 1, entry 1). Several solvents such as $PhCF_3$, DCE and EtOAc were then screened, and no significant improvement was observed (entries 2−6). Gratifyingly, the yield of **3a** was dramatically increased to 84% by using HOAc as sole solvent (entry 7). To our delight, when $K_2S_2O_8$ was used instead of oxone, an excellent yield was obtained (entry 8). Further investigation showed that $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ were also effective for this reaction (entries 9 and 10). Other commercially available SCN sources such as NaSCN and NH_4SCN could also afford the desired product **3a**, but in lower yields (entries 11 and 12). Reducing the amount of $K_2S_2O_8$ to 1.5 equiv gave a cleaner reaction and better yield of **3a** (entry 13). However, the yield of **3a** was lowered to 54% when 1.0 equiv of $K_2S_2O_8$ was used (entry 14). Further investigation revealed that the amount of **2a** was crucial to obtaining higher yield of **3a** (entry 15). No reaction occurred in the absence of $K_2S_2O_8$ (entry 16).

With the optimized reaction conditions in hand, the substrate scope of this transformation was investigated. As shown in

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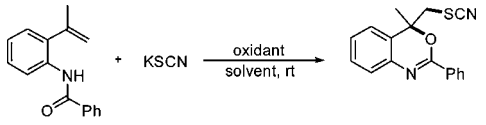
Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (equiv)	solvent	yield (%)[b]
1	oxone (2)	MeCN	33
2	oxone (2)	$PhCF_3$	34
3	oxone (2)	DMF	trace
4	oxone (2)	DCE	43
5	oxone (2)	EtOAc	29
6	oxone (2)	dioxane	n.r.[c]
7	oxone (2)	HOAc	84
8	$K_2S_2O_8$ (2)	HOAc	98
9	$Na_2S_2O_8$ (2)	HOAc	75
10	$(NH_4)_2S_2O_8$ (2)	HOAc	53
11	$K_2S_2O_8$ (2)	HOAc	66[d]
12	$K_2S_2O_8$ (2)	HOAc	42[e]
13	$K_2S_2O_8$ (1.5)	HOAc	98
14	$K_2S_2O_8$ (1)	HOAc	54
15	$K_2S_2O_8$ (1.5)	HOAc	55[f]
16	–	HOAc	n.r.[c]

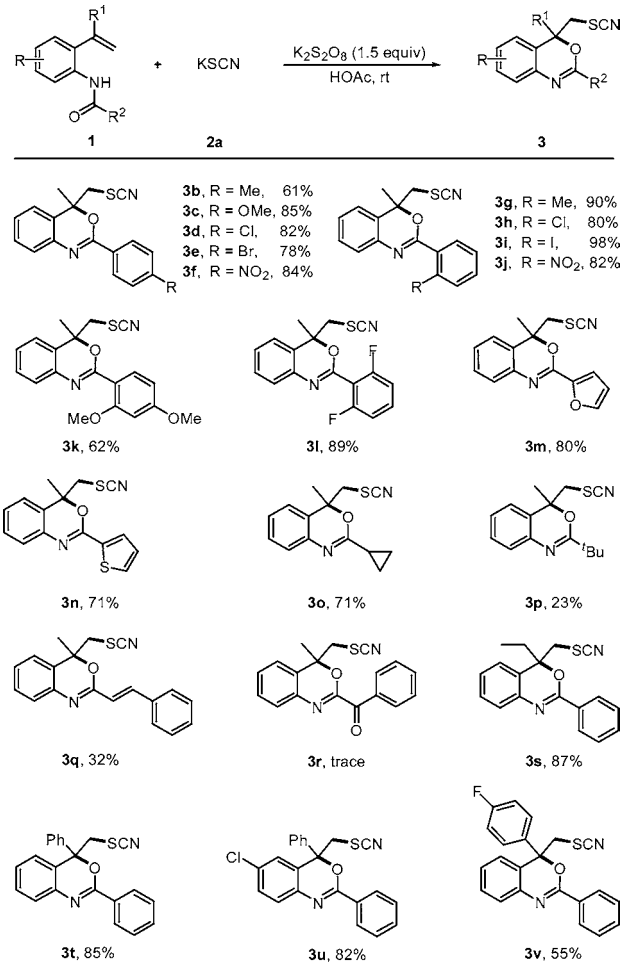
[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), solvent (1 mL), oxidant (2 equiv), rt, 24 h. [b]Yield of isolated product. [c]n.r. = no reaction. [d]NaSCN was used. [e]NH_4SCN was used. [f]**2a** (0.3 mmol, 1.5 equiv).

Scheme 1, olefinic amides derived from 2-vinyl arylamine and various carboxylic acids reacted smoothly to afford the desired 4-thiocyanatomethyl benzoxazines in moderate to high yields. Benzamides bearing electron-withdrawing or electron-donating substituents at the *para* (**3b–f**) and the *ortho* (**3g–j**) position of the benzoyl moiety worked well and led to functionalized benzoxazines in good to excellent yields. Notably, a wide range of functional groups such as bromo, iodo and nitro, etc., were tolerated well under the reaction conditions. Gratifyingly, heteroarylamides such as **1m** and **1n** also furnished the cyclized products in satisfactory yields. Aliphatic amides such as **1o** and **1p** were also compatible with the reaction conditions to give the desired products in 71 and 23%, respectively. Cinnamamide **1q** was also successfully converted to the desired product, albeit in low yield. However, no product was obtained for amide **1r** under the present conditions. Furthermore, substrates having ethyl or aryl group at the α position of the styrenyl system also furnished the corresponding benzoxazines in good yields (**3s–v**).

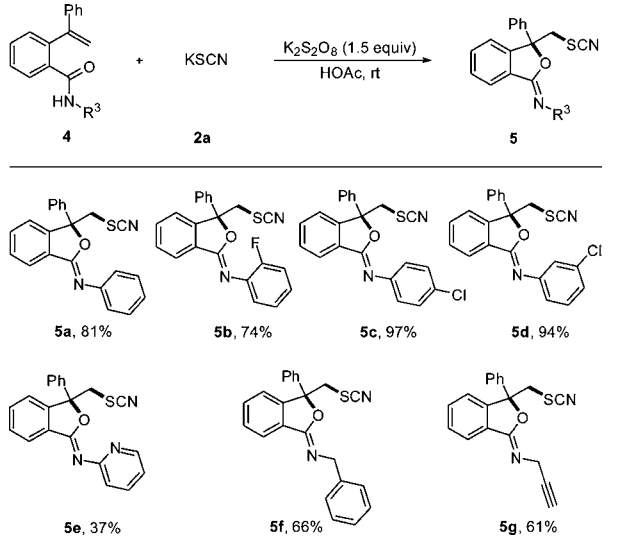
To further broaden the scope of this transformation, 2-vinylbenzamides **4** were then examined under the same conditions (Scheme 2). Satisfactorily, a series of 2-vinylbenzamides underwent the similar cyclization process smoothly to provide the corresponding imino-isobenzofurans **5a–g** in good yields. Herein, the benzamides could derive from a variety of amines such as arylamines, 2-aminopyridine and benzylamine (**5a–d**, **5e** and **5f**). It is noteworthy that the alkynyl group was also tolerant well under the reaction conditions, thereby offering good opportunities for further synthetic transformations (**5g**). In addition, the (*Z*)-configuration of the product **5g** was confirmed by NOESY experiment.

Furthermore, the potential synthetic utilities of **3** were also investigated (For details see the Supporting Information). As shown in Scheme 3, the SCN group of the product **3a** could be

Scheme 1. Substrate Scope of Amide Derivatives 1



Scheme 2. Substrate Scope of Amide Derivatives 4



hydrolyzed by sulfuric acid, giving access to thiocarbamate **7a** in 58% isolated yield. In the presence of $ZnCl_2$, the SCN group could also undergo cycloaddition reaction with NaN_3 to afford thiotetrazole **6a** in 94% yield. Finally, product **5a** containing imino group could be further transformed to the benzofuran-1-one **8a** in 98% yield by acid hydrolysis, which further confirmed

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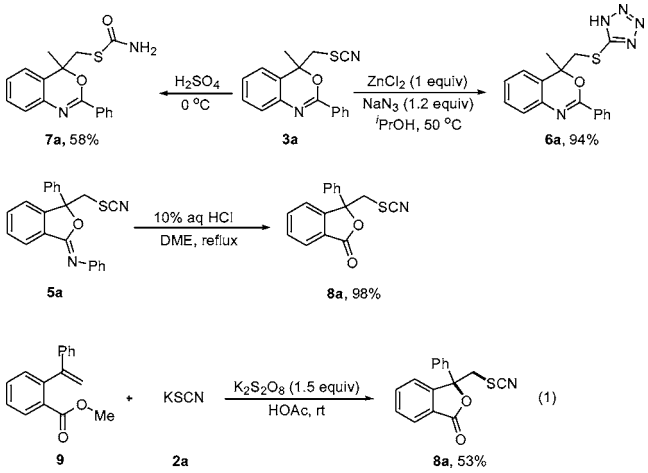
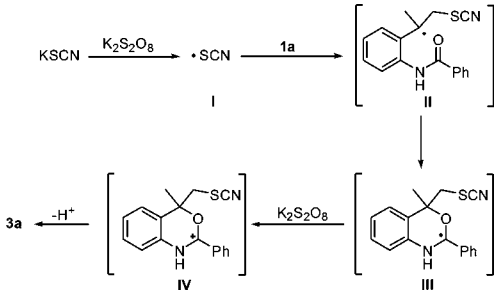
Scheme 3. Derivatization of Products 3a and 5a



the structure of **5**. Interestingly, the ester **9** could also react smoothly with **2a** under the standard conditions to produce the cyclized product **8a** in 53% yield (eq 1).

A preliminary mechanism investigation suggested that the reaction probably involved a thiocyanate radical which was consistent with previous reports.[7] When radical scavengers, such as TEMPO and BHT were added to the reaction of **1a** and **2a**, the yields of **3a** were decreased dramatically (for details see the Supporting Information), which indicated that the reaction probably proceeded via a free radical process. On the basis of the above results and previous investigations, a plausible mechanism was proposed in Scheme 4. First, the

Scheme 4. Proposed Mechanism



oxidation of thiocyanate anion by $K_2S_2O_8$ generates an electrophilic thiocyanate radical **I**,[7] which then adds to the C=C bond of amide **1a** to give the alkyl radical **II**. Second, **II** undergoes a radical cyclization to provide the radical intermediate **III**.[9] Finally, the radical **III** was further oxidized to the corresponding carbocation by oxidant followed by deprotonation to afford the benzoxazine **3a**. However, a cationic cyclization cannot be excluded completely at present, in which the intermediate **II** is further oxidized to carbocation, and subsequently trapped by the carbonyl group of amide.

In summary, a novel and efficient tandem thiocyanooxygenation of olefinic amides has been developed for the synthesis of functionalized benzoxazines and imino-isobenzofurans. The readily available starting reagents, broad substrate scope and mild reaction conditions are the characteristic features of this protocol. Importantly, the SCN group in the products could be easily converted into various functional groups, which would make these products more useful in organic synthesis. Preliminary mechanistic studies suggest that a tandem radical process is involved in the current transformation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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