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Difunctionalization of Alkenylpyridine *N*-Oxides by the Tandem Addition/Boekelheide Rearrangement

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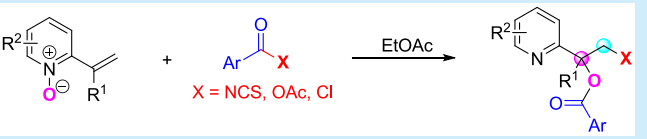
Supporting Information

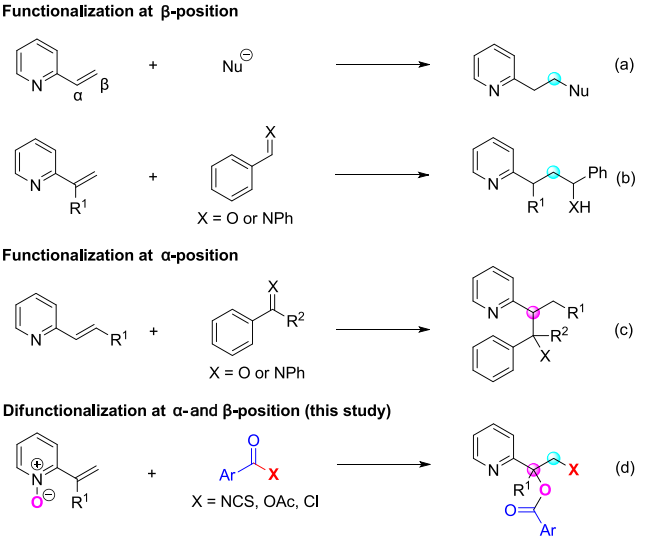
ABSTRACT: A convenient and efficient approach for the difunctionalization of alkenylpyridine *N*-oxides through the tandem addition/Boekelheide rearrangement has been developed. The C−O and C−X (S, O, Cl) bonds are constructed simultaneously at the α- and β-positions under mild reaction conditions in 100% atom economy, which complements previously reported α- or β-functionalizations.



Pyridines make up a versatile class of heteroarenes, which are commonly found in biologically active compounds including natural products, pharmaceuticals, and agrochemicals.[1] In addition, they are widely used as molecular materials in molecular recognition[2] and catalysts or ligands in asymmetric catalysis.[3] The traditional and common method to construct pyridine derivatives is based on the metal-mediated cycloaddition[4] or the modification of pyridine at the 2-position.[5] Due to their wide applications, it is of great importance to develop novel methods to modify the privileged structure, which would give access to new pyridine-containing architectures.

Alkenylpyridines are versatile synthetic intermediates and could be functionalized at the α- or β-positions. Normally, electrophilic alkenylpyridines functionalize at the β-position by the direct nucleophilic addition of strong nucleophiles (Scheme 1a).[6] Recently, Ngai[7] and Jiang[8] developed an umpolung strategy for the β-selective reductive coupling of alkenylpyridines with non-nucleophilic aldehydes, ketones, and imines (Scheme 1b). On the contrary, the functionalization of alkenylpyridines at the α-position is rare. Krische[9] and Lam[10] reported an elegant C−C coupling of alkenylpyridines at the α-position, in which the reaction proceeded with the first hydrogenation of the β-position, followed by the cascade coupling of the α-position to the electrophiles (Scheme 1c). On the other hand, difunctionalization of alkenes is an efficient tool for creating two new bonds in a single step. However, difunctionalization of alkenylpyridines at two positions has not been reported. The development of such a reaction would provide a complement to the reactivity of alkenylpyridines and give pyridine-containing architectures with structural diversity. In this study, we report the first difunctionalization of alkenylpyridines at the α- and β-positions, in which C−O and C−X (S, O, Cl) bonds are constructed simultaneously (Scheme 1d).

Scheme 1. Related Research and This Work



At the outset our study, we chose benzoyl isothiocyanate[11] as a model substrate to react with the alkenylpyridine, since it contains both nucleophilic and electrophilic sites. After many attempts, the reaction still did not work, probably due to the low reactivity of the alkenylpyridine. At this time, the Boekelheide rearrangement, in which an *N*-oxide oxygen transfers to the α-position via the 1-acetoxypyridin-1-ium intermediate, came to our horizon (Scheme 2).[12] We speculated the introducing an oxygen atom to form alkenylpyridine *N*-oxide[13] would (1) enhance the reactivity of alkenyl group and (2) function as an oxygen nucleophile to react with the electrophilic site of benzoyl

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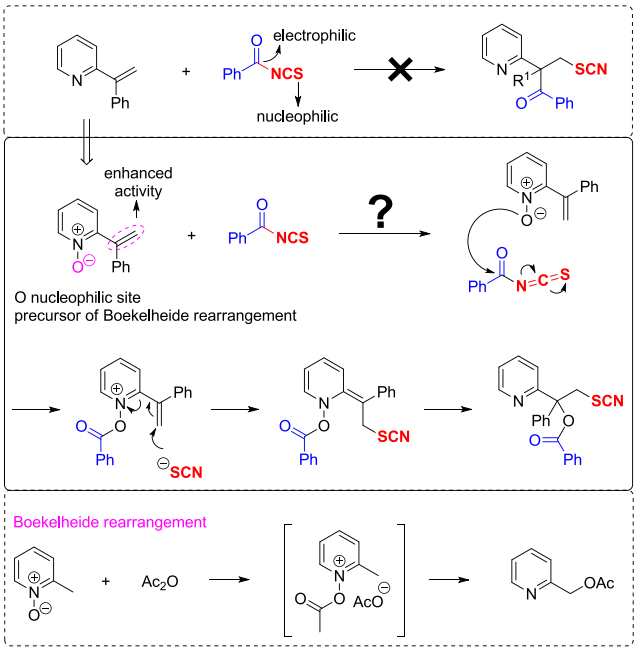
Scheme 2. Our Strategy

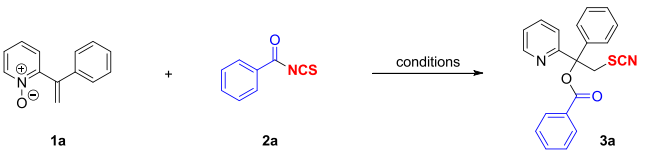


isothiocyanate to form the precursor of Boekelheide rearrangement. By a cascade direct addition−Boekelheide rearrangement, the reaction of alkenylpyridine *N*-oxide with benzoyl isothiocyanate would give a formal difunctional product of alkenylpyridine. As far as we know the reactivity of alkenylpyridine *N*-oxides has not been investigated, so we believed that this investigation should be of great interest.

Initial optimization was performed using alkenylpyridine *N*-oxide **1a** with benzoyl isothiocyanate **2a** (Table 1). The reaction was stirred in the presence of 20 mol % of $CuBr_2$ in THF at room temperature for 6 h and proceeded smoothly to afford the corresponding product **3a** in 55% yield, which was confirmed by X-ray. We next examined some other catalysts including CuCN, $Yb(OTf)_3$, $Sc(OTf)_3$, NMI, $PhCO_2H$, and Cs_2CO_3, but none of them gave better results than $CuBr_2$ (Table 1, entries 1−7). Interestingly, when the reaction was conducted in the absence of any catalyst, the reaction gave a comparable yield of 58% (Table 1, entry 8). Then, the solvents were screened without any catalyst. We found the reaction worked equally well when EtOAc was applied (Table 1, entry 15). We also examined some other conditions like the reaction temperature and the ratio of two substrates, and no obvious improvement of yield was observed. Thus, conducting the reaction in EtOAc at room temperature was used for all subsequent studies.

We then surveyed the substrate scope of alkenylpyridine *N*-oxides **1** and isothiocyanates **2** (Scheme 3). The reaction proceeded smoothly to afford the desired difunctionalization products **3** in modest yields. The aromatic ring of benzoyl isothiocyanates with a variety of substituents was well-tolerated (**3c**−**3j**), although better yields were observed for those with electron-withdrawing substituents (**3c**−**3f**). The reaction also worked well for thiophene-3-carbonyl isothiocyanate to give **3k** in 55% yield. With regard alkenylpyridine *N*-oxides, the pyridine ring with 5-Me substituent afforded **3b** in 60% yield, whereas the 6-Br substituent did not work in this reaction. Alkenylpyridine *N*-oxides with aromatic substituents at the α-position were effective substrates, leading to the desired products (**3l**−**3n**) in moderate yields.

Table 1. Reaction Optimization[a]



1a 2a 3a

entry	catalyst	solvent	yield (%)[b]
1	$CuBr_2$	THF	55
2	CuCN	THF	52
3	$Yb(OTf)_3$	THF	48
4	$Sc(OTf)_3$	THF	50
5	NMI	THF	53
6	$PhCO_2H$	THF	51
7	Cs_2CO_3	THF	52
8		THF	58
9		toluene	48
10		CH_2Cl_2	48
11		CH_3CN	55
12		DMF	46
13		Et_2O	47
14		1,4-dioxane	50
15		EtOAc	58
16[c]		EtOAc	36
17[d]		EtOAc	53

[a]The reaction was carried out on the scale of **1a** (0.10 mmol), **2a** (0.12 mmol), and catalyst (10 mol %) in solvent (1.0 mL) at room temperature for 6 h. [b]Isolated yield. [c]T = 0 °C. [d]T = 65 °C. NMI: *N*-methylimidazole.

Encouraged by the positive results of benzoyl isothiocyanates, we then tested some potential difunctional reagents such as carbonyl chlorides **4** and acetic anhydride **6** to examine the compatibility of this method. Among the tested carbonyl chlorides, all of them could deliver the desired products **5** in moderate yield, though slightly lower than that of the corresponding isothiocyanates, probably due to the lower nucleophilicity of chlorine (Scheme 4). Carbonyl chlorides with electron-withdrawing groups (**5a**,**5b**) at the benzene ring gave higher yield, whereas electron-donating groups (**5c**,**5d**) gave lower yields. 2-Naphthoyl chloride (**5e**) and thiophene-3-carbonyl chloride (**5f**) were also compatible in this reaction. In the case of acetic anhydride **6**, the reaction proceeded well to give the desired product **7** in 80% yield under the reflux conditions (Scheme 5).

To further demonstrate the practicality of this reaction, we tested the three-component reaction of alkenylpyridine *N*-oxide **1a**, benzoyl chloride **4a**, and KSCN, as multicomponent reactions could efficiently construct complex molecules in a one-pot operation and reduce purification steps (Scheme 6). We were pleased to find the three-component reaction underwent the SCN addition/Boekelheide rearrangement to give **3a** in 60% yield (Scheme 6). We also carried out some derivatizations of product **3a** to demonstrate the synthetic utility of this method. As the sulfur atom of thiocyanate possesses the electrophilic character, when treated with PhMgBr in THF, it afforded the thioether **9** in 72% yield. The treatment of **3a** with NaOMe in MeOH readily underwent the domino hydrolysis/cyclization sequence to give 2-imino-1,3-oxathiolane **8** in 67% yield.

In summary, we have developed the first difunctionalization of alkenylpyridine *N*-oxides at the α- and β-positions, which provides a convenient and efficient approach for the construction of new pyridine-containing architectures through

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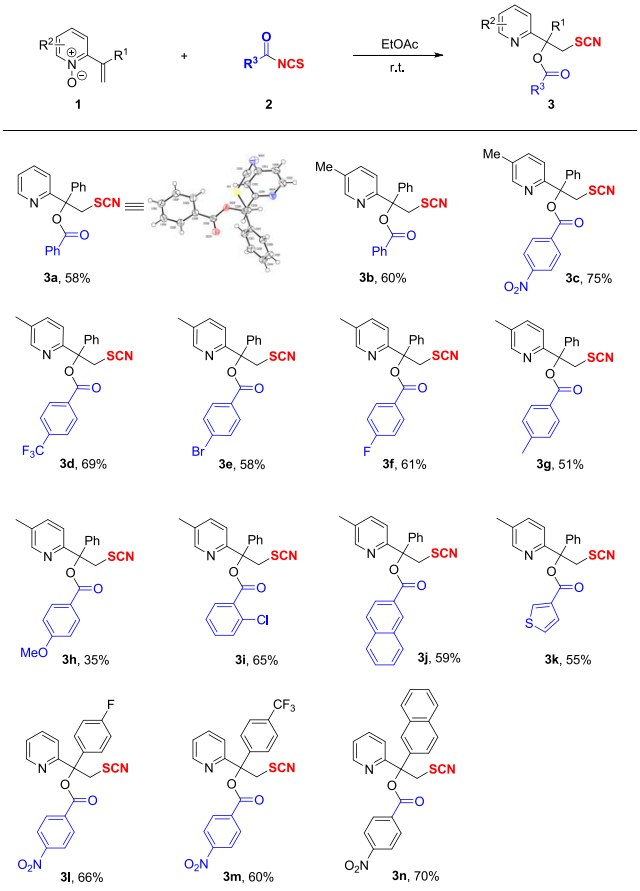
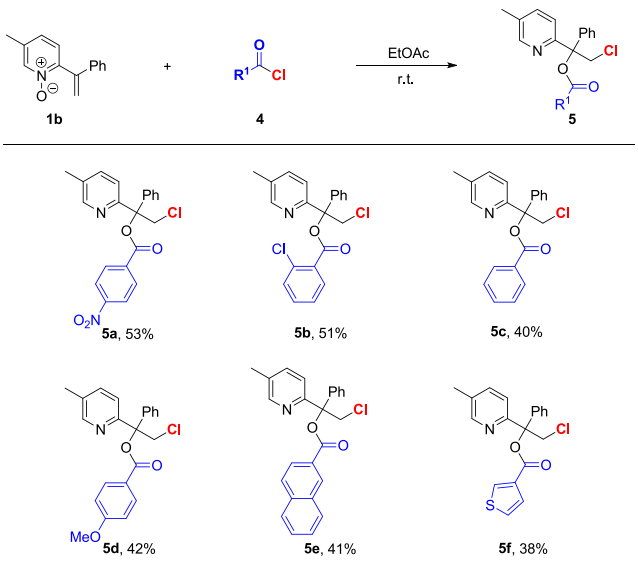
Scheme 3. Reaction of Alkenylpyridine *N*-Oxides 1 with Isothiocyanates 2

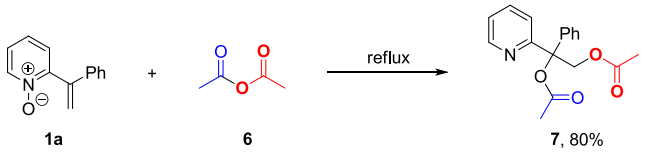


Scheme 4. Reaction of Alkenylpyridine *N*-Oxide 1b with Carbonyl Chlorides 4

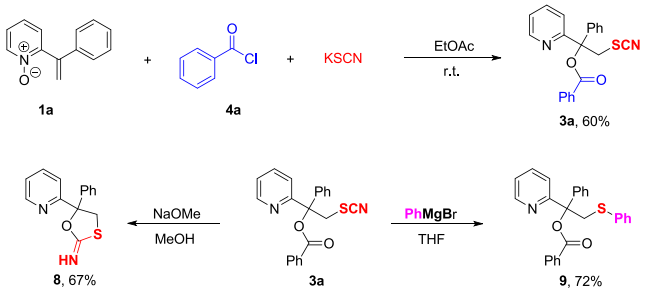


the tandem addition/Boekelheide rearrangement. With this method, the C−O and C−X (S, O, Cl) bonds are constructed simultaneously under mild reaction conditions in 100% atom economy. Importantly, the reaction could be conducted in a one-pot three-component reaction using inorganic KSCN, and the SCN group could easily be converted to other functional groups, which makes this method practical and useful in organic synthesis.

Scheme 5. Reaction of Alkenylpyridine *N*-Oxide 1a with Acetic Anhydride 6



Scheme 6. Three-Component Reaction and Transformations of 3a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03035.

Details of the experimental procedure, structural characterizations, and spectral data of all new compounds (PDF)

Accession Codes

CCDC 1919876 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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