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Iron-Catalyzed Aerobic Oxidation and Annulation Reaction of Pyridine and α-Substituted Allenoate toward Functionalized Indolizine

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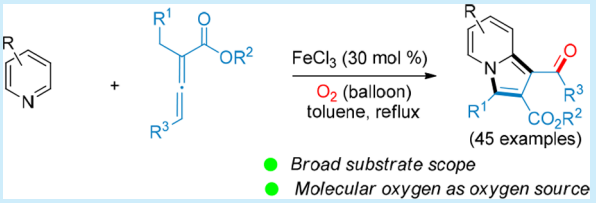
Supporting Information

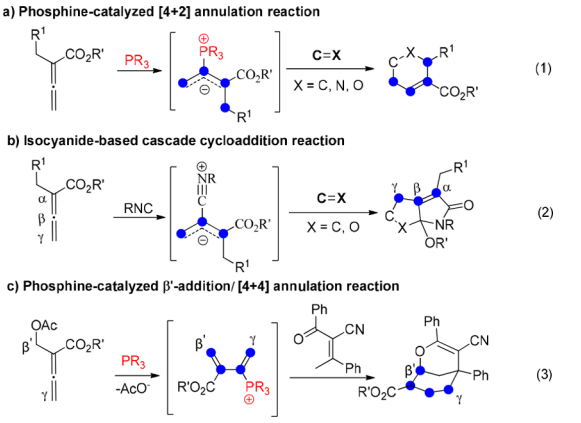
ABSTRACT: An iron-catalyzed reaction of pyridine and α-substituted allenoate has been disclosed. The present strategy incorporates the aerobic oxidation into annulation involving substituted allenoate, thus providing a new access to functionalized indolizine.



Indolizines represent privileged frameworks that are broadly found in a number of natural products and pharmaceuticals.[1] Compounds containing these core structures have displayed many important biological activities, including antitumor, antiviral, and anti-inflammatory activities.[2,3] Furthermore, many indolizines incorporated with different organic chromophores have found wide application in the photophysical and material fields.[4−6] A careful literature screening reveals that there are many successful strategies involving C2-functionalized pyridines.[7] Moreover, 1,3-dipolar cycloaddition of pyridinium *N*-methylides and electron-deficient species are also very popular.[8] While many new synthetic strategies have been developed, examples on the straightforward use of pyridine are still very rare.[9,10]

Since the pioneering work of Lu and co-workers in 1995,[11] the development of annulation reaction using allenoate as versatile building block has been well documented.[12] In particular, the transformation involving α-substituted allenoate provides a new opportunity for the construction of carbocycles and heterocycles. In 2003, Kwon and co-workers disclosed the first example of phosphine-catalyzed [4 + 2] annulation reaction of α-substituted allenoate and electron-deficient species to synthesize dihydropyridine derivatives (Scheme 1, eq 1).[13] Following these works, we have also started another isocyanide-based cascade cycloaddition reaction of α-substituted allenoate and electron-deficient species, which offers a new route to fused rings via *N*-acyliminium cation (Scheme 1, eq 2).[14] Remarkably, Tong and co-workers demonstrated that the reactivity of allenoate could be greatly changed when an acetate group was installed at the β′-position of 2,3-allenoate.[15] Accordingly, several interesting transformations including phosphine-catalyzed β′-addition/[4 + 4] annulation reaction were subsequently discovered (Scheme 1, eq 3). In addition, examples of γ-substituted allenoates to experience [4 + 2] and other related annulation were also reported by Huang and other groups.[16] To the best of our knowledge, the aerobic oxidation examples involving allenoate are still rare. As a continuation of our previous research,[17] herein we report an iron-catalyzed reaction of pyridine and substituted allenoate toward functionalized indolizine derivatives.

Scheme 1. Representative Reactivity Mode of Annulation Reactions Involving α-Substituted Allenoate



We initially chose pyridine (**1a**) and allenoate (**2a**) as model substrates to investigate the desired conversion. As shown in Table 1, with the aid of iron chloride, upon treatment with the mixture in the air gave rise to an interesting oxidative annulation product **3a** in 38% yield (Table 1, entry 4). Next, investigation on the effect of parameters including catalyst, catalyst loading, and solvent were performed to increase the yield of product. The experiment results revealed that the catalyst loading also had significant impact on the reaction

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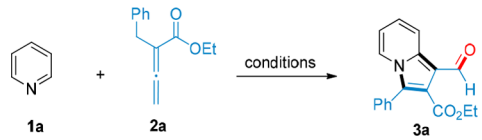
Table 1. Reaction Optimization[a]



entry	catalyst	equiv	solvent	yield[b] (%)
1[c]	*d*		toluene	0
2[c]	$Pd(OAc)_2$	0.2	toluene	0
3[c]	AgOTf	0.2	toluene	0
4[c]	$FeCl_3$	0.2	toluene	38
5	$FeCl_3$	0.2	toluene	51
6	$Fe(OTf)_3$	0.2	toluene	trace
7	$FeCl_2$	0.2	toluene	trace
8	$Fe(OAc)_2$	0.2	toluene	0
9	$Cu(OTf)_2$	0.2	toluene	trace
10	$FeCl_3$	0.1	toluene	trace
11	$FeCl_3$	0.3	toluene	68
12	$FeCl_3$	0.5	toluene	61
13	$FeCl_3$	1.0	toluene	30
14	$FeCl_3$	0.3	PhCl	28
15	$FeCl_3$	0.3	CH3CN	trace
16	$FeCl_3$	0.3	DCE	35
17	$FeCl_3$	0.3	DMF	15
18	$FeCl_3$	0.3	1,4-dioxane	trace

[a]Unless otherwise noted, all reactions were carried out with 0.5 mmol of pyridine **1a**, 0.5 mmol of allenoate **2a**, catalyst, O_2 balloon, in 5 mL of solvent, 20 h. [b]Isolated yield. [c]Reaction was conducted in air. [d]No catalyst was added.

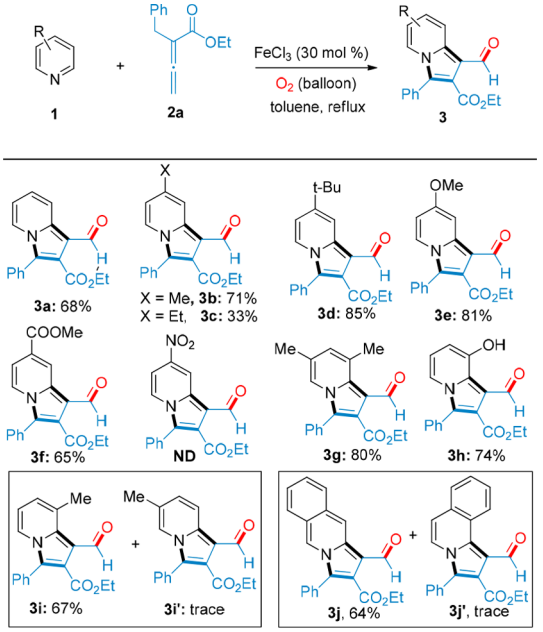
performance. Gratifyingly, the isolated yield of **3a** could be improved to 68% when the catalyst loading was increased to 30 mol % (Table 1, entry 11). Subsequent screening of other solvents including PhCl, CH_3CN, and DMF did not bring any improvement with respect to the yield of product **3a**.

With the optimized conditions in hand, we sought to briefly investigate the feasibility of substituted pyridines. As shown in Scheme 2, a series of substituents including methyl, *tert*-butyl, methoxyl, and oxycarbonyl groups were found to be particularly compatible under the optimized conditions. Isoquinoline as analogue of pyridine was also employed to react with allenoate **2a** under the similar conditions. The experimental result showed that compound **3j** was isolated in 64% yield and trace amount of **3j′** was obtained. In sharp contrast, reactions with pyridine **2** bearing substituent at position 2 failed to produce the desired product **3**, which might arise from the sterical hindrance. In the above-mentioned results, all the terminal position of allenoate was oxidized to aldehyde in the presence of molecular oxygen.[18]

After showing the scope of pyridine derivatives, we decided to examine the general applicability of substituted allenoates (Scheme 3). Since the presence of α-H in allenoate **2** was indispensable, allenoates **2** with substituted benzyl group at α-position were first attempted. Furthermore, the structure of compound **4c** was confirmed by single crystal X-ray analysis. Remarkably, allenoates **2** containing aliphatic substituents including methyl, ethyl, *n*-propyl, *n*-butyl groups at the α-position reacted smoothly to yield **4g−j**.

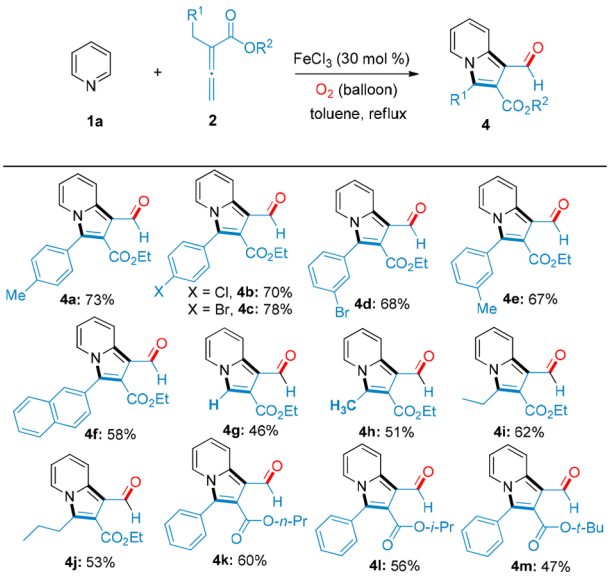
Unlike the usual mechanism, the present transformation also represents a novel β'-umpolung addition of nucleophile to substituted allenoate.[19]

Scheme 2. Scope of the Reaction with Respect to the Pyridine Substrate 1[a,b]



[a]Reaction conditions A: 0.5 mmol pyridine **1**, 0.5 mmol of allenoate **2a**, 30 mol % of catalyst, O_2 balloon, in 5 mL of solvent, 20 h. [b]Yields of product after silica gel chromatography. ND = not detected.

Scheme 3. Scope of the Reaction with Respect to the α-Substituted Allenoate Substrate 2[a,b]



[a]Reaction conditions A. [b]Isolated yields.

To further establish the scope and limitation of the present reaction, an investigation regarding the γ-substituted allenoates was carried out. As shown in Scheme 4, a γ-methyl-substituted allenoate **2** was first used to react with a variety of pyridines **1**. Gratifyingly, all reactions proceeded smoothly to yield the desired products **5a−h**. Other aliphatic substituents such as ethyl, propyl groups and aromatic substituent at the γ-position of allenoates were further proven to be compatible to produce **5i−o**.

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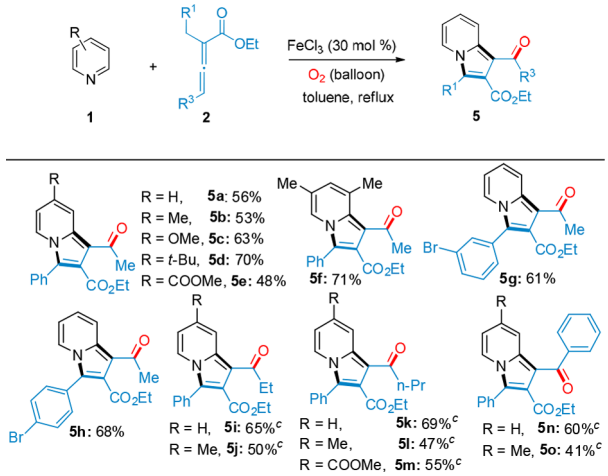
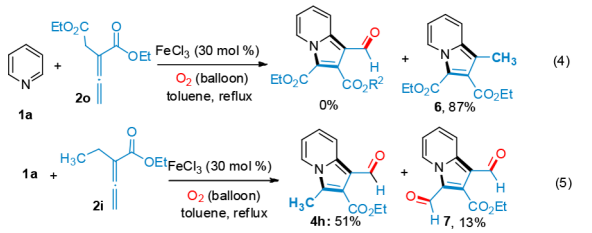
Scheme 4. Scope of the Reaction with Respect to the γ-Substituted Allenoate Substrate 2[a,b]



[a]Reaction conditions A. [b]Isolated yields. [c]In such case, 50 mol % of TBHP was used as extra additive under the otherwise identical conditions in a sealed tube.

Interesting results were also obtained when reactions with differently substituted allenoates were conducted. As shown in Scheme 5, when allenoate **2o** was used no desired product was

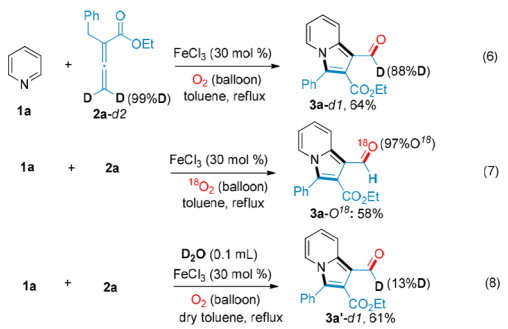
Scheme 5. Reactions with Differently Substituted Allenoates



detected and a new compound **6** was isolated as the major product (Scheme 5, eq 4). On the other hand, the reaction of α-ethyl-substituted allenoate **2i** and **1a** essentially produced the desired product **4h** in 51% yield (Scheme 5, eq 5). At the same time, a new compound **7** was also isolated in 13% yield, which might indicate that the methyl group in compound **4h** can be further oxidized to formyl group.

To gain more insight into the present oxidative cyclization reaction, several preliminary mechanistic experiments were conducted next. An isotope-labeling experiment was carried out with the reaction of **1a** and **2a**-d_2 (Scheme 6, eq 6). To find out

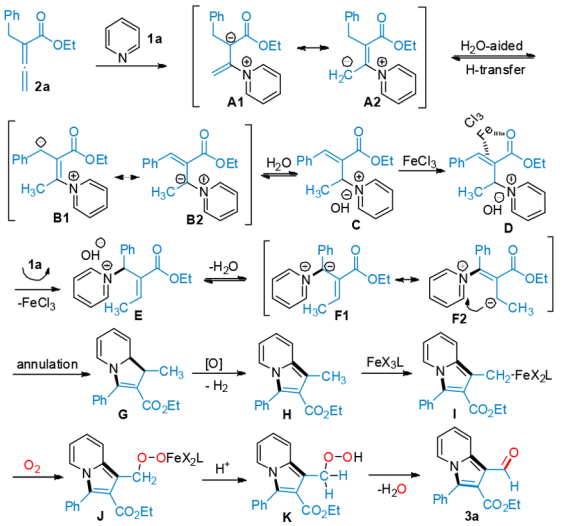
Scheme 6. Preliminary Mechanistic Study



the real oxygen source, we performed the reaction of **1a** and **2a** using $^{18}O_2$ as the oxidant (Scheme 6, eq 7). The experimental outcome established that the oxygen atom in the resultant aldehyde group of product **3a**-^{18}O originated from molecular oxygen, which was different with the reported literatures.[20,21] Furthermore, 13% deuterium was incorporated into product **3a′**-d_1 when additional D_2O was introduced into the reaction of **1a** and **2a** under the otherwise identical conditions (Scheme 6, eq 8). This result suggested that water was also involved in the present reaction.

On the basis of the aforementioned results and previous reports,[18] a plausible reaction mechanism is depicted in Scheme 7. With the aid of water, hydrogen transfer occurs to yield

Scheme 7. Proposed Mechanism



intermediate **B**,[22] from which intermediate **C** is produced via protonation. The reactivity of the olefin in intermediate **D** is enhanced by the coordination of iron chloride,[23] thus facilitating the following S_N2'-type process. In the presence of Fe(III), intermediate **H** is then converted to **I**, which then undergo molecular oxygen insertion to generate intermediate **J**.[18] Protonation then takes place followed by the O−O bond cleavage of **K**. Finally, elimination of a molecular of H_2O essentially leads to the formation of oxidation product.

In conclusion, we have described a selective oxidation and annulation reaction of pyridine and substituted allenoate, thus providing quick access to functionalized indolizine derivatives. This reaction also represents the first example to incorporate the aerobic oxidation into annulation of allenoate. The present strategy is also distinguished by unusual β′-umpolung addition, the employment of molecular oxygen as green oxidant, and the wide substrate scope. Further study and application of the present reaction including the biological detection are still underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03696.

Experimental procedures and full characterization of all compounds, spectral data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Accession Codes

CCDC 1567140 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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