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Synthesis of 6-acyl phenanthridines by oxidative radical decarboxylation–cyclization of α-oxocarboxylates and isocyanides†

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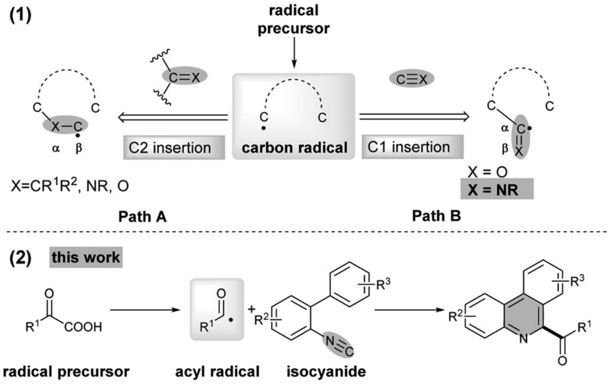
A silver catalysed synthesis of 6-acyl phenanthridines by oxidative radical decarboxylation–cyclization of α-oxocarboxylates and isocyanides was developed. This reaction provided a novel method to realize C1 insertion *via* a radical process and various functional groups were well-tolerated.

Radical chemistry has ushered in a new era in the development of chemistry and it has become an important and effective tool in organic synthesis in the past decades.[1] Among a wide variety of radical reactions, insertion reaction is one of the most useful reactions in synthetic chemistry because the carbon chain of the product can be extended.[2] In general, there are two pathways of insertion reactions for a carbon radical centre (Scheme 1(1)). The first is C2 insertion (path A): the carbon radical reacts with an acceptor to form a new β carbon radical centre thus leading to an increase of two atoms in chain propagation. In C2 insertion reactions, the acceptors mainly contain C–C multiple bonds like alkenes and alkynes, C–N double bonds like imines and C–O double bonds such as aldehydes, ketones and other carbonyl compounds. The other pathway is C1 insertion (path B): the carbon radical is inserted by an acceptor to increase one carbon atom in chain propagation and a new α carbon radical centre is formed. Among various C1 insertion reactions, CO is one of the most common acceptor which reacts with a radical to generate a new acyl radical by carbonylation.[3] Similar to CO, isocyanides can also act as radical acceptors to form imidoyl radicals, followed by bimolecular addition or cyclization.[4] However, only a few studies have been focused on this field and limited radical precursors were developed such as halides,[5] boronic acids,[6] CF_3 reagents,[7] aldehydes and diphenylphosphine oxide.[8] Therefore, it is still necessary to develop more radical precursors to realize isocyanide insertion *via* a radical process.



Scheme 1 (1) Two pathways of insertions: C2 insertion (path A) and C1 insertion (path B); (2) oxidative radical decarboxylation–cyclization of α-oxocarboxylates and isocyanides.

Transition metal catalysed decarboxylation of carboxylic acids has become an important method to form C–C and C–hetero bond in recent years.[9] For example, radical decarboxylation of α-oxocarboxylic acids can also act as a powerful and complementary synthetic method to provide an acyl radical, which presumably shows higher activity and more potential in acylation than traditional Friedel–Crafts acylation. Herein, we envisioned to realize this radical decarboxylation by utilizing α-oxocarboxylic acids as the acyl radical resources to construct 6-acyl phenanthridines, which demonstrate a plurality of biological and photochemical activities and show great potential in medical chemistry and materials applications.[10] To the best of our knowledge, this is the first example for realizing isocyanide insertion by using an acyl radical *via* the oxidative radical decarboxylation (Scheme 1(2)).

Initially, we started to evaluate the reaction parameters by employing 2-isocyanobiphenyl (**1a**) and potassium oxophenylacetate (**2a**) as model substrates. To our delight, the use of 10 mol% Ag_2CO_3 as the catalyst and $K_2S_2O_8$ as the oxidant in DMF at 100 °C could give the corresponding 6-benzoyl phenanthridine (**3a**) in 47% yield (Table 1, entry 1).

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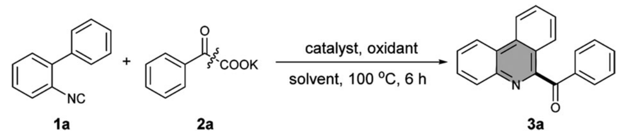
Table 1 Optimization of conditions for the reaction of 2-isocyanobiphenyl (**1a**) and potassium oxophenylacetate (**2a**)[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	Ag_2CO_3	$K_2S_2O_8$	DMF	47
2	Ag_2O	$K_2S_2O_8$	DMF	42
3	AgOAc	$K_2S_2O_8$	DMF	41
4	$AgNO_3$	$K_2S_2O_8$	DMF	39
5	—	$K_2S_2O_8$	DMF	6
6	Ag_2CO_3	$K_2S_2O_8$	DMSO	69
7[c]	$\mathbf{Ag_2CO_3}$	$\mathbf{Na_2S_2O_8}$	**DMSO**	**75(71)**
8	Ag_2CO_3	$(NH_4)_2S_2O_8$	DMSO	37
9	Ag_2CO_3	O_2	DMSO	Trace

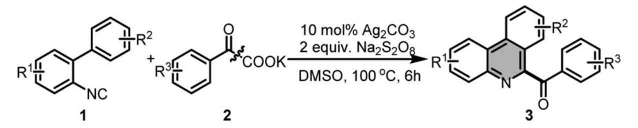
[a] Reaction conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), catalyst (10 mol%), oxidant (0.5 mmol), solvent (1.5 mL), 100 °C, N_2, 6 h. [b] Yield determined by GC analysis. [c] Yield in the parentheses is isolated yield.

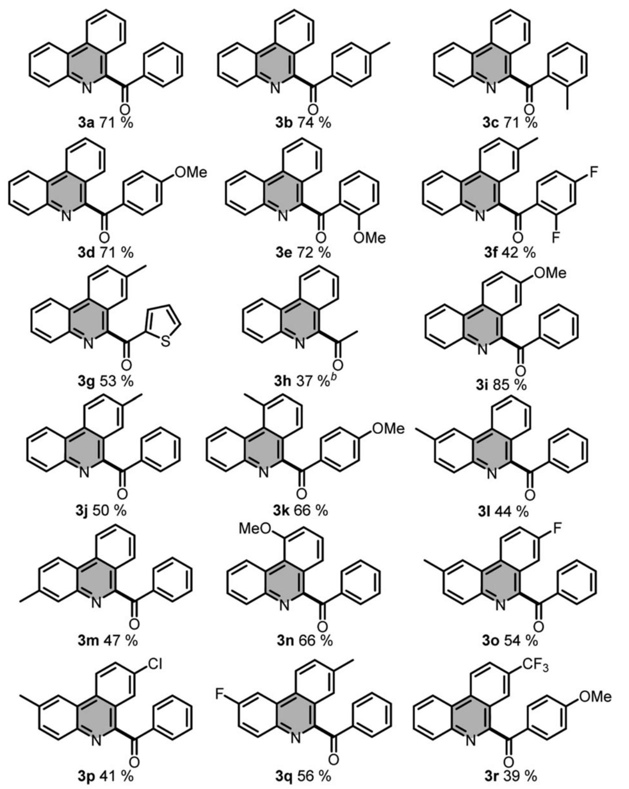
Then we tried other silver salts, such as Ag_2O, AgOAc and $AgNO_3$, and slightly lower yields were obtained (entries 2–4). It is noteworthy that Ag salts might play a critical role in the blank experiment (entry 5). When the solvent was changed to DMSO, the yield was increased up to 69%. The reaction also proceeded in the presence of various oxidants such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$ and dioxygen (1 atm) (entries 7–9), and $Na_2S_2O_8$ gave the best result to promote this reaction.

With the optimal conditions established, various α-oxocarboxylates **2** were tested to react with 2-isocyanobiaryls **1** to form the corresponding 6-acyl phenanthridines products **3** (Table 2). This reaction was successfully amenable to a wide range of α-oxocarboxylates, and moderate to good yields were achieved with substrates bearing various functional groups such as Me (**3b** and **3c**), OMe (**3d** and **3e**) and F (**3f**). In addition, heterocyclic α-oxocarboxylates like thiophene was found to be favoured in this catalytic system to afford the corresponding products (**3g**). It is noteworthy that aliphatic α-oxocarboxylates were compatible in this reaction as well and gave moderate yields (**3h**). Furthermore, the reactivities of different isocyanides were also investigated. Isocyanides bearing both electron-rich (**3i** to **3n**) and -deficient groups (**3r**) underwent this oxidative radical decarboxylation–cyclization process smoothly to afford the desired products in moderate to good yields. In addition, this transformation also showed satisfactory tolerance with halogen groups (**3o** to **3q**) which provided useful handles for further transformations through traditional cross coupling reactions.

In order to gain insights into this novel oxidative decarboxylation–cyclization, radical scavengers, such as TEMPO and BHT, were employed in the reaction (Table 3). As a result, the reactions were completely shut down, which could indicate that this transformation involved radical intermediates.

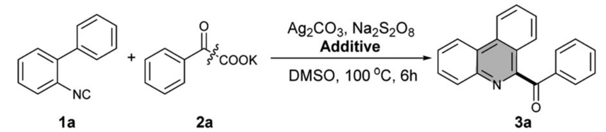
Table 2 Scope of oxidative cyclization of different α-oxocarboxylates **2** and 2-isocyanobiaryls **1**[a]





[a] Reaction conditions: **1** (0.75 mmol), **2** (0.5 mmol), Ag_2CO_3 (10 mol%), $Na_2S_2O_8$ (1.0 mmol), DMSO (3.0 mL), 100 °C, N_2, 6 h. [b] 0.5 mmol CH_3COCO_2Na was used.

Table 3 Radical inhibiting experiments



Additive	Yield of **3a** (%)
None	71
TEMPO (2 equiv.)	0
BHT (2 equiv.)	0

Moreover, although it is widely proposed that Ag(I) could be easily oxidized to Ag(II) in the presence of persulfates as the oxidants according to related reports,[11] recently Maiti's group has demonstrated a novel Ag(0)–Ag(I) catalytic circle in the presence of persulfates from XPS.[12] This result intrigued us to investigate the plausible oxidation state of Ag species in our reaction. Therefore, we tried to use electron paramagnetic resonance (EPR) to study this oxidative process. As shown in Fig. 1(a), no EPR signal was observed when AgOTf was tested alone in DMSO, 80 °C, N_2 for 2 hours.[13] However, when a mixture of AgOTf and $Na_2S_2O_8$ was used under the same conditions, a strong EPR signal could been detected (Fig. 1(b)). According to related reports, we may ascribe this obvious signal to Ag(II) species.[14] Therefore, this oxidative radical decarboxylation involved a Ag(I)–Ag(II) catalytic circle *via* a single electron transfer (SET) process.

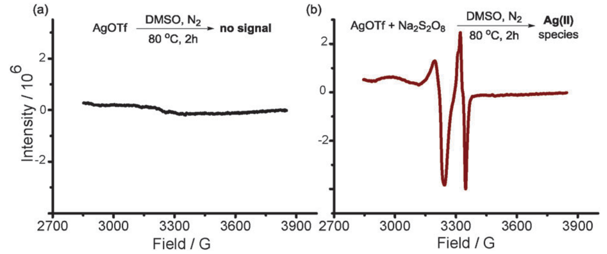
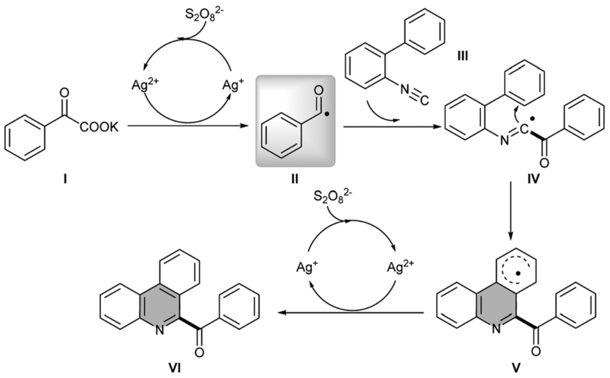


Fig. 1 Evidence of Ag(II) species in EPR spectra.



Scheme 2 Proposed mechanism.

According to the previous reports and above results,[3,11,15] a proposed mechanism is described in Scheme 2. In the presence of Ag_2CO_3 and $Na_2S_2O_8$, α-oxocarboxylates **I** underwent an oxidative radical decarboxylative process to generate the benzoyl radical **II**. The addition of the benzoyl radical to the isocyanide **III** generated the imidoyl radical **IV**, which next cyclized to the arene to form cyclohexadienyl radical **V**. Subsequently, a single electron transfer process happened between the cyclohexadienyl radical **V** and Ag(II) which finally gave the desired product 6-acyl phenanthridine **VI**.

In summary, we have demonstrated a novel approach for the silver catalyzed synthesis of 6-acyl phenanthridines by oxidative radical decarboxylation–cyclization of α-oxocarboxylates and isocyanides. This reaction provides a complementary method to realize C1 insertion *via* a radical process. In addition, this method presented a variety of functional group tolerance and showed promising potential in biological activities and pharmaceutical applications. The EPR experiments provided information that this reaction involved a Ag(I)–Ag(II) catalytic circle.

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