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Synthesis of 6-aroyl phenanthridines by Fe-catalyzed oxidative radical cyclization of 2-isocyanobiphenyls with benzylic alcohols

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ABSTRACT

A practical method for the synthesis of 6-aroyl phenanthridine derivatives by Fe-catalyzed oxidative radical cyclization of 2-isocyanobiphenyls with benzylic alcohols is described. In addition, this cyclization could be occurred by using toluene as aroyl source. The procedure tolerates various functional groups under simple conditions. A single-electron-transfer pathway is proposed according to mechanistic studies.

1. Introduction

Phenanthridines have attracted great attention due to their prominent applications in pharmaceuticals, natural products as well as organic materials.[1] These heterocycles exhibit various interesting biological activities such as antibacterial, antitumoral, and antileukemic properties.[2] For instance, benzo[*c*]phenanthridine alkaloid NK109 shows anticancer activity.[3] Therefore, the development of practical synthetic approaches to construct the framework of phenanthridine and its derivatives is highly valuable.

A great deal of routes have been reported for the synthesis of phenanthridines, including the classic Pictet-Hubert reactions,[4] transition metal-catalyzed domino reactions,[5] radical cascade reactions,[6–13] and other protocols.[14] Among these methods, considerable efforts have been made to synthesize 6-substituted phenanthridines from 2-isocyanobiphenyls by radical mediated cyclization reactions in the past decades. In this transformation, a great number of radical precursors have been investigated to provide various 6-position functionalized phenanthridines, including 6-alkylated,[7] 6-fluoroalkylated,[8] 6-arylated,[9] 6-phosphorylated,[10] 6-aroylated,[11] 6-carboxylated,[12] and 6-silylated[13] phenanthridine derivatives. For instance, in 2013, Studer and co-workers described the efficient synthesis of 6-aroylated phenanthridines from 2-isocyanobiphenyls and aromatic aldehydes using ^{t}BuOOH (TBHP) as oxidant and $FeCl_3$ (0.4 mol%) as initiator via base-promoted homolytic aromatic substitution (BHAS) (Scheme 1, eq. 1).[11a] In 2014, Lei and co-workers demonstrated the synthesis of 6-acyl phenanthridines in the presence of Ag_2CO_3 and $Na_2S_2O_8$ using potassium oxophenylacetate as radical precursor through an oxidative radical decarboxylative process.[11b]

As we all know that aromatic aldehydes can be readily obtained from corresponding substituted benzyl alcohols or toluene derivatives in the presence of oxidant (such as TBHP, O_2 or air).[15,16] Recently, transition metal-catalyzed direct oxidative acylation of (hetero)arenes with a directing group, such as pyridine, amide, benzoxazole, benzothiazole, benzo[h]quinoline, O-methyl aldoxime, phosphate, azoxybenzene, and azoarenes, etc., have been significantly investigated with alcohols[15] and toluene derivatives[16] as acyl equivalents (Scheme 1, eq. 2). Based on these transformations[6–16] and our previous work,[15e] we tried to study the synthesis of 6-aroyl phenanthridines by Fe-catalyzed oxidative radical cyclization of 2-isocyanobiphenyls with benzylic alcohols or toluene derivatives (Scheme 1, eq. 3).

2. Results and discussion

Initially, we focused on optimizing reaction conditions of 2-isocyanobiphenyl (**1a**) with benzylic alcohol (**2a**) in the presence

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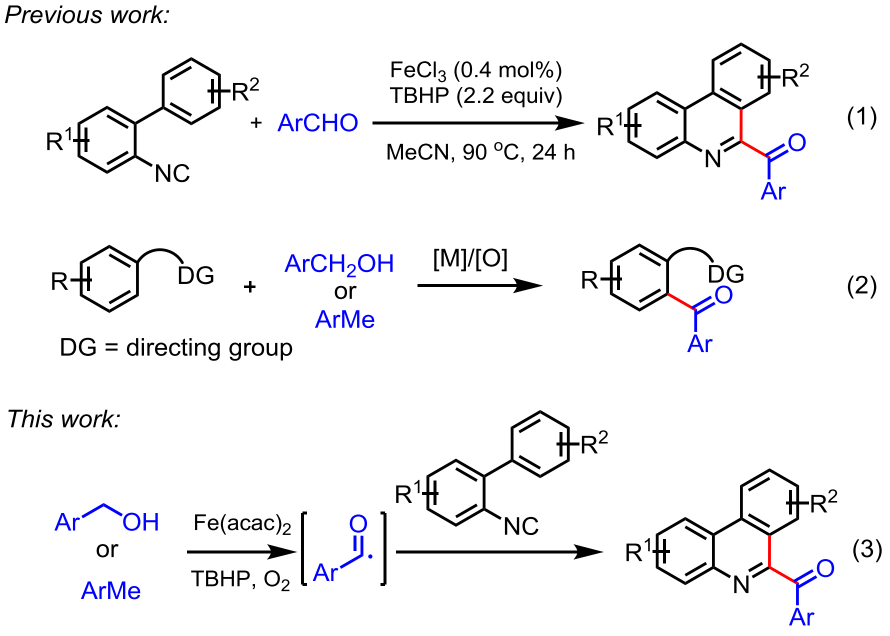
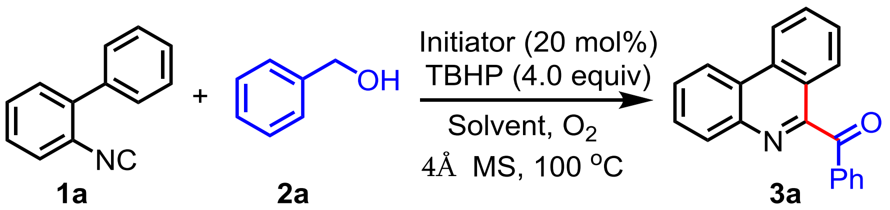


Scheme 1. Transition metal-catalyzed aroylation.

of TBHP using $FeCl_3$ as radical initiator. To our delight, the desired 6-aroyl phenanthridine (**3a**) was obtained in 10% isolated yield (Table 1, entry 1). The screening of some commonly used radical initiators demonstrated that CuI, $CuCl_2$, $Cu(OAc)_2$, $Cu(TFA)_2$, $CoSO_4{\cdot}7H_2O$, $Co(acac)_2$, $CoCO_3$, $Co(OAc)_2$, and $CoCl_3{\cdot}5NH_3$ were inferior to $FeCl_3$ (Table 1, entries 2–10). Fortunately, while $Mn(OAc)_2$, $Mn(OAc)_3$, $Fe(OAc)_2$, $Fe(acac)_3$, and $Fe(acac)_2$ were efficient initiators for this radical transformation, and $Fe(acac)_2$ provided the best yield (80%, Table 1, entry 15). Then we investigated the influence of solvents. In methyl *tert*-butyl ether (MTBE) and

Table 1
Optimization of reaction conditions.[a]



Entry	Initiator	Solvent	Yield (%)[b]
1	$FeCl_3$	MeCN	10
2	CuI	MeCN	n.d.
3	$CuCl_2$	MeCN	Trace
4	$Cu(OAc)_2$	MeCN	Trace
5	$Cu(TFA)_2$	MeCN	Trace
6	$CoSO_4{\cdot}7H_2O$	MeCN	Trace
7	$Co(acac)_2$	MeCN	Trace
8	$CoCO_3$	MeCN	9
9	$Co(OAc)_2$	MeCN	Trace
10	$CoCl_3{\cdot}5NH_3$	MeCN	Trace
11	$Mn(OAc)_2$	MeCN	70
12	$Mn(OAc)_3$	MeCN	68
13	$Fe(OAc)_2$	MeCN	40
14	$Fe(acac)_3$	MeCN	74
15	$Fe(acac)_2$	MeCN	80
16	$Fe(acac)_2$	MTBE	50
17	$Fe(acac)_2$	Toluene	60
18	$Fe(acac)_2$	1,4-dioxane	n.d.
19	$Fe(acac)_2$	THF	n.d.
20	$Fe(acac)_2$	DMF	n.d.

[a] Reaction conditions: 2-isocyanobiphenyls **1a** (0.2 mmol, 1.0 equiv), benzylic alcohol **2a** (0.8 mmol, 4.0 equiv), initiator (20 mol%), TBHP (4.0 equiv), 4 Å MS (100 mg), solvent (2 mL), 100 °C, n.d.: not detected. MTBE: methyl *tert*-butyl ether.

[b] Isolated yields.