Tetrahedron Letters 55 (2014) 5338–5341

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 6-carboxylated phenanthridines by oxidative alkoxycarbonylation–cyclization of 2-isocyanobiphenyls with carbazates

Gao Wang, Shan-Yong Chen *, Xiao-Qi Yu *

Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China

ARTICLE INFO

Article history:
Received 6 June 2014
Revised 7 July 2014
Accepted 14 July 2014
Available online 31 July 2014

Keywords:
Carbazates
Phenanthridines
Alkoxycarbonylation/cyclization

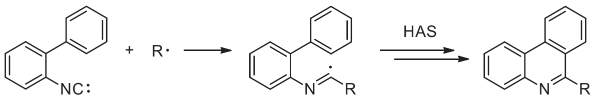
ABSTRACT

An iron-catalyzed synthesis of 6-carboxylated phenanthridines starting with readily prepared isocyanides and carbazates was developed. Reactions occurred via addition of alkoxycarbonyl radicals to the isocyanide group and subsequent intramolecular cyclization.

Phenanthridines are biologically important compounds by its widespread presence in natural products, drugs, or drug candidates.[1] Many phenanthridines show antibacterial, antitumoral, and cytotoxic activities.[2] They are also widely used in material science due to their significant optoelectronic properties.[3] Therefore, it is highly desirable to develop novel methods for the synthesis of diversified phenanthridines. Isocyanides are isoelectronic with carbon monoxide, and thus isocyanides can also act as radical acceptors to form imidoyl radicals, which can undergo bimolecular addition or cyclization.[4] A few studies have been focused on the addition of radicals to 2-isocyanobiphenyls followed by intramolecular cyclization to generate phenanthridines (Scheme 1). Radicals were limited within trifluoromethyl,[5] carbonyl,[6] alkyl,[7] and phosphoryl[8] .

On the other hand, carboxylic esters are valuable commodity chemicals and useful synthetic building blocks.[9] Using carbazates as the precursors of alkoxycarbonyl radicals, Taniguchi and Tian reported introducing alkoxycarbonyl groups to styrenes to obtain carboxylic esters.[10] Very recently, Du and our group reported the iron-catalyzed arylalkoxycarbonylation of N-arylacrylamides with carbazates independently, and various oxindole-3-acetates were obtained in good yields.[11] In 2014, Zhou reported a reaction about photosensitizer-catalyzed and oxygen-oxidated hydrazines to radical followed cyclization with 2-isocyanobiphenyls.[12] It provided a general and practical method for the construction of 6-substituted phenanthridines. But only one 6-carboxylated phenanthridine was mentioned with 56% yield after irradiation for 18 h. Considering the importance of esters, we reported an iron-catalyzed oxidative alkoxycarbonylation–cyclization of 2-isocyanobiphenyls with carbazates.[13,14]

Initially, we started to optimize reaction conditions by employing 2-isocyano-5-methylbiphenyl (**1a**) and methyl carbazate (**2a**) as model substrates. Using TBHP (*tert*-butyl hydroperoxide 70 wt % in water) as oxidant and $FeCl_2{\cdot}4H_2O$ as catalyst, the desired product **3a** was isolated in 56% yield after stirring in ethyl acetate (Table 1, entry 1). Without a catalyst, only a trace of the product was observed. Based on our previous results that ligands can coordinate with iron salt and influence the oxidation process of



Reported: R=CF_3, ArCO, alkyl, $Ph_2P(O)$ this work: R= CO_2R'

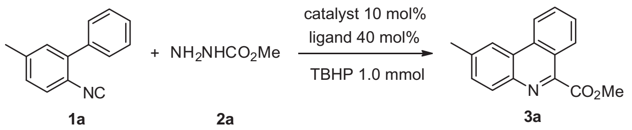
Scheme 1. Reported synthesis of phenanthridine derivates and our design.

---

* Corresponding authors. Tel./fax: +86 28 85415886.
E-mail addresses: chensy@scu.edu.cn (S.-Y. Chen), xqyu@scu.edu.cn (X.-Q. Yu).

http://dx.doi.org/10.1016/j.tetlet.2014.07.049
0040-4039/© 2014 Elsevier Ltd. All rights reserved.

Table 1
Optimization of the reaction conditions[a]



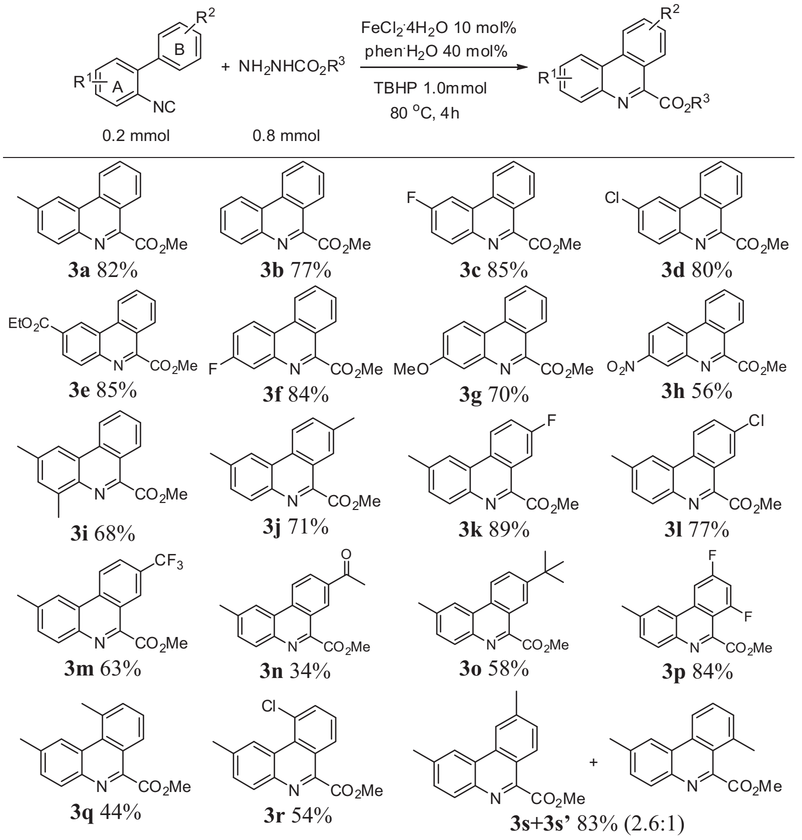
No.	Catalyst	mol %	Ligand	Solvent	Yield
1	$FeCl_2·4H_2O$	10	—	EA	56
2	—		—	EA	Trace
3	$FeCl_2·4H_2O$	10	Pyridine	EA	60
4	$FeCl_2·4H_2O$	10	TMEDA	EA	60
5	$FeCl_2·4H_2O$	10	18-Crown-6	EA	35
6	$FeCl_2·4H_2O$	10	2,2′-Bipyridine	EA	45
7	$FeCl_2·4H_2O$	10	2-Cyano-pyridine	EA	60
8	$FeCl_2·4H_2O$	10	Phen·H_2O	EA	76
9	$FeCl_3$	10	Phen·H_2O	EA	68
10	$FeSO_4·7H_2O$	10	Phen·H_2O	EA	68
11	$Cu(OAc)_2$	10	Phen·H_2O	EA	56
12	$Co(OAc)_2·4H_2O$	10	Phen·H_2O	EA	30
13	*n*-Bu_4NI	10	—	EA	42
14	*n*-Bu_4NI	5	—	EA	66[b]
15	$FeCl_2·4H_2O$	5	Phen·H_2O	EA	68[b,c]
16	$FeCl_2·4H_2O$	10	Phen·H_2O	EA	69[c]
17	$FeCl_2·4H_2O$	10	Phen·H_2O	EA	82[d]
18	$FeCl_2·4H_2O$	10	Phen·H_2O	MeOH	30[d]
19	$FeCl_2·4H_2O$	10	Phen·H_2O	MeCN	58[d]
20	$FeCl_2·4H_2O$	10	Phen·H_2O	DCE	72[d]

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (0.02 mmol), ligand (0.08 mmol), oxidant (1.0 mmol) in ethyl acetate (2 mL). After stirring well at 80 °C, **2a** (0.6 mmol) was added in portions for 20 min, and the reaction was exposed to air for 4 h at the same temperature.
[b] Reaction time is 24 h.
[c] 0.04 mmol phen·H_2O was used.
[d] 0.8 mmol **2a** was used.

carbazates, we studied the effect of ligands on this reaction. Experimental results show that 1,10-phenanthroline is the best ligand (entry 8 vs entries 3–7). It improved the yield significantly from 56% to 76% (entry 8 vs entry 1). After screening catalysts, we found that other catalysts were less efficient than $FeCl_2·4H_2O$ (entries 9–12 vs entry 8). Notably, this transformation could be catalyzed by an iodide catalyst. Using *n*-Bu_4NI as the catalyst, an acceptable yield (66%) was obtained after the extended reaction time (entries 13 and 14). Yields were slightly decreased when lessening the dosage of catalyst or ligand (entries 15 and 16). When 4 equiv of **2a** was added, the product **3a** was isolated in 82% yield (entry 17). The influence of solvents was also investigated. The reaction in ethyl acetate provided better result than that in methanol, acetonitrile, or 1,2-dichloroethane (entry 18 vs entries 19–20).

With optimal conditions in hand, we turned our attention to explore the substrate scope of this reaction. The results are summarized in Table 2. Substitutions on the benzene ring A did not affect this transformation significantly, and these 2-isocyanobiphenyls afforded the desired products **3a–i** in good yields. Different functional groups including fluoro, chloro, methyl, nitro, methoxyl, and ester are tolerable during the reaction process. Different 2-isocyanobiphenyls bearing a substituent on the ring B were then examined. Most of them worked well providing 6-carboxylated phenanthridines (**3j–p**) in moderate to good yields. Isocyanobiphenyls bearing an *ortho*-substituent on the benzene ring B gave lower yields than those bearing a *para*-substituent (**3q** vs **3j**; **3r** vs **3l**).[15] When **3s** bearing a *meta*-substitution on the benzene ring B was subjected to this reaction, two regioisomers (2.6:1) were isolated. Isocyanide with an anthracene ring instead of the benzene ring B is applicable

Table 2
Scope of the synthesis of 6-carboxylated phenanthridines[a]



3a 82% **3b** 77% **3c** 85% **3d** 80%
3e 85% **3f** 84% **3g** 70% **3h** 56%
3i 68% **3j** 71% **3k** 89% **3l** 77%
3m 63% **3n** 34% **3o** 58% **3p** 84%
3q 44% **3r** 54% **3s+3s’** 83% (2.6:1)

(*continued on next page*)