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Cobalt-Catalyzed Carbonylative Cyclization of Pyridinyl Diazoacetates for the Synthesis of Pyridoisoquinolinones

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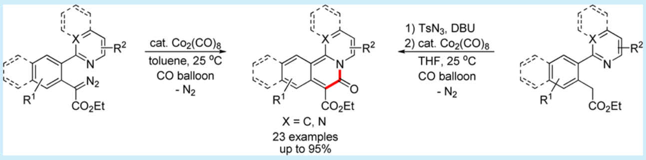
S *Supporting Information*

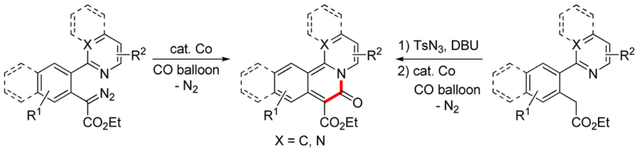
ABSTRACT: Dicobalt octacarbonyl-catalyzed carbonylative cyclization of pyridinyl diazoacetates is developed for the synthesis of pyridoisoquinolinones under mild conditions (room temperature) in a carbon monoxide atmosphere. Moreover, a synthetic method for various pyridoisoquinolinones from ethylpyridinyl aryl acetates is demonstrated through diazotization using TsN_3 and DBU followed by Co-catalyzed carbonylation to generate ketene intermediates, which can subsequently undergo intramolecular cyclization under mild conditions in a carbon monoxide atmosphere in a semi-one-pot fashion.



Transition-metal-catalyzed carbonylation using carbon monoxide is one of the significant methods to prepare a variety of carbonyl compounds.[1] In particular, Pd-catalyzed carbonylative cross-coupling is an important method for the synthesis of a large number of compounds having the carbonyl functional group. However, the carbonylation of metal carbenes is rarely reported due to the limitations of substrate scope and harsh conditions, such as the high pressure of carbon monoxide, high reaction temperature, and stoichiometric processes. Moreover, because the carbonylation of metal carbene furnishes ketenes, which are very important in organic synthesis, the development of streamlined synthetic methods to overcome these shortcomings is still highly attractive and challenging.

Recently, Ungváry[2] and Wang[3] reported the transition-metal-catalyzed carbonylation of metal carbenes derived from diazo compounds with carbon monoxide for the preparation of ketenes and the intermolecular addition of ketenes with nucleophiles such as alcohols and amines, resulting in the formation of a variety of carbonyl derivatives.[4] However, we are not aware of any reported examples of the transition-metal-catalyzed carbonylation of diazo compounds and sequential intramolecular cyclization. More recently, we demonstrated a robust synthetic method for a wide range of pyridoisoindoles from pyridinyl aryl diazoacetates under Cu-catalytic or metal-free conditions.[5] Inspired by our previous work, we envisioned that treatment of diazoacetate possessing a nucleophilic pyridinyl moiety with a transition-metal carbonyl catalyst, under a CO atmosphere or not, would result in the carbonylation of metal carbene to afford pyridinyl aryl-substituted ketene, which can be applicable in intramolecular cyclization reactions to provide pyridoisoquinolinones.[6] Herein, we report dicobalt octacarbonyl catalyzed carbonylative cyclization of pyridinyl diazoacetates for the synthesis of pyridoisoquinolinones under mild conditions (room temperature) in a carbon monoxide atmosphere (Scheme 1). Moreover, a useful synthetic method for a number of pyridoisoquinolinones from pyridinyl aryl acetates is demonstrated through diazotization using TsN_3 and DBU followed by Co-catalyzed carbonylation and the intramolecular cyclization of ketene with a tethering pyridinyl moiety under mild conditions in a carbon monoxide atmosphere in a semi-one-pot fashion.[7]

Scheme 1. Co-Catalyzed Carbonylative Cyclization for the Synthesis of Pyridoisoquinolinones



First, we investigated the scope and limitation of transition-metal carbonyl catalyzed carbonylative cyclization of pyridinylaryl diazoacetate **1a** as the substrate under a CO atmosphere (Table 1). A variety of pyridinylaryl diazoacetates were easily prepared from Rh-catalyzed alkylation[8] of 2-arylpyridines with Meldrum's acid and the diazotization reaction[9] of the corresponding pyridinyl aryl acetates (see the Supporting Information). Although $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, and $Fe_3(CO)_{12}$ (2.0 mol % each) were completely ineffective (entries 1−4), $Co_2(CO)_8$ (2.0 mol %) successfully produced pyridoisoquinolinone in 95% isolated yield in toluene at 25 °C under a CO atmosphere after CO bubbling for 2 min (entry 5). When $Co_2(CO)_8$-catalyzed carbonylative cyclization was carried out under a CO atmosphere without CO bubbling or under a N_2 atmosphere without CO bubbling, the cyclization reaction did not go to completion, and the desired product **2a** was obtained in 61% and 19% yields, respectively, along with

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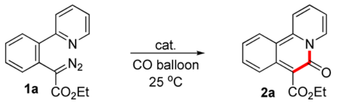
Table 1. Reaction Optimization[a]



entry	cat. (mol %)	solvent	time (h)	yield[b] (%)
1	$Cr(CO)_6$ (2.0)	toluene	12	0
2	$Mo(CO)_6$ (2.0)	toluene	12	0
3	$W(CO)_6$ (2.0)	toluene	12	0
4	$Fe_3(CO)_{12}$ (2.0)	toluene	12	0
5	$Co_2(CO)_8$ (2.0)	toluene	5	97 (95)[c]
6[d]	$Co_2(CO)_8$ (2.0)	toluene	5	61 (35)[e]
7[f]	$Co_2(CO)_8$ (2.0)	toluene	5	19 (70)[e]
8	$Co_2(CO)_8$ (1.0)	toluene	24	56
9	$Co_2(CO)_8$ (2.0)	DCE	12	57
10	$Co_2(CO)_8$ (2.0)	CH_3CN	12	30
11	$Co_2(CO)_8$ (2.0)	THF	5	88

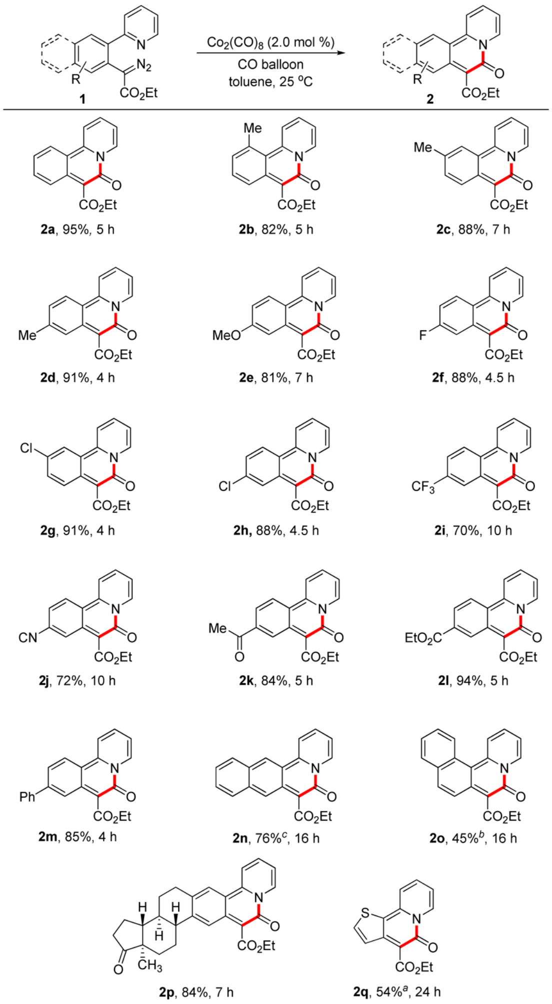
[a]Reactions were carried out with **1a** (0.2 mmol) and metal carbonyl (1.0−2.0 mol %) in solvent (1.25 mL) at 25 °C. After CO bubbling for 2 min, the reaction mixture was stirred under CO atmosphere. [b]NMR yield using dibromomethane as an internal standard. [c]Isolated yield. [d]Under CO atmosphere without CO bubbling. [e]Recovery yield of **1a**. [f]Under N_2 atmosphere without CO bubbling.

recovery of **1a** (entries 6 and 7). These results indicate that the CO bubbling and atmosphere are essential for the carbonylative cyclization. The use of 1.0 mol % of $Co_2(CO)_8$ gave inferior results compared to 2.0 mol % (Table 1, entries 5 and 8). Toluene gave the best result among the solvents (DCE, CH_3CN, and THF; entries 9−11). Screening of a series of Pd and Rh catalysts did not give satisfactory results (see the Supporting Information).

Next, the scope of substrates in this carbonylative cyclization reaction was examined with pyridinyl aryl diazoacetates (**1**) possessing a wide range of substituents on the aryl groups under the optimal conditions (Scheme 2). Electronic modification of the substituents at the aryl moiety of **1** had little effect on the reaction efficiency. The substrates possessing both electron-donating groups (R = Me and MeO) and electron-withdrawing groups (R = F, Cl, CF_3, CN, CH_3CO, and EtO_2C) on the aryl moiety were well tolerated under the reaction conditions and provided the corresponding products **2b**−**l** in good to excellent yields ranging from 70% to 94%. When 2,3-naphthyl-substituted pyridinyl diazoacetate (**1n**) underwent the Co-catalyzed carbonylative cyclization, the desired benzopyridoisoquinolinone **2n** was produced in 76% yield. However, 1,2-naphthyl-substituted pyridinyl diazoacetate (**1o**) was cyclized to **2o** in 45% yield. This decreased efficiency was attributed to the steric congestion of the bent polycyclic aromatic compound. When pyridinyl diazoacetate (**1p**) possessing an estrone moiety was employed as the substrate, the carbonylative cyclization product **2p** was satisfactorily obtained in 84% yield. Moreover, the arene is not limited to a benzene skeleton. Heteroaromatic diazoacetate **1q** obtained from (thiophene-2-yl)pyridine was applied to the present Co-catalyzed carbonylative cyclization, affording **2q** in 54% yield.

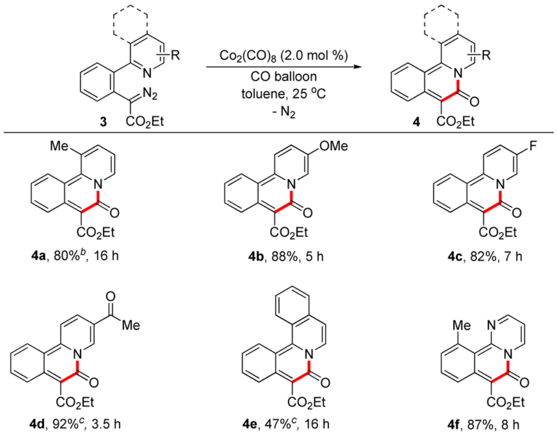
In addition, modification of a wide range of substituents (R = Me, MeO, F, and CH_3CO) on the pyridine moiety was tolerated without notably affecting the catalytic effectiveness (Scheme 3, **4a**−**d**). Diazoacetate (**3e**) possessing an isoquinoline moiety showed moderate reactivity in this transformation due to the steric congestion arising from the intramolecular cyclization. Pyrimidine-substituted diazoacetate (**3f**) is appli-

Scheme 2. Scope of Aryl Groups[a]



[a]Reactions were carried out with **1** (0.2 mmol, 1.0 equiv) and $Co_2(CO)_8$ (2.0 mol %) in toluene (1.25 mL) at 25 °C under CO atmosphere after CO bubbling. [b]$Co_2(CO)_8$ (5.0 mol %) was used. [c]$Co_2(CO)_8$ (15.0 mol %) was used.

Scheme 3. Scope of Pyridyl Groups[a]

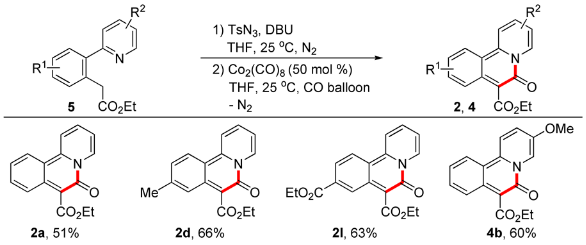


[a]Reactions were carried out with **3** (0.2 mmol) and $Co_2(CO)_8$ (2.0 mol %) in toluene (1.25 mL) at 25 °C under CO atmosphere after CO bubbling. [b]$Co_2(CO)_8$ (15.0 mol %) was used. [c]$Co_2(CO)_8$ (5.0 mol %) was used.

cable to the present transformation, providing the corresponding cyclic product (**4f**) in 87% yield.

Subsequently, because pyridinyl aryl diazoacetates (**1** and **3**) were easily obtained from the diazotization reaction of the corresponding pyridinyl aryl acetates,[9] we envisioned that this carbonylative cyclization for the synthesis of pyridoisoquinolinones could be achieved directly through diazotization followed by the Co-catalyzed carbonylative cyclization from pyridinyl aryl acetates in a one-pot fashion (Scheme 4). First, after pyridinyl aryl diazoacetate **5a** was treated with TsN_3 and DBU in THF at 25 °C for 12 h, $Co_2(CO)_8$ catalyst (2.0 mol %) was added to the reaction mixture for carbonylative cyclization. However, because the remaining DBU in the reaction mixture deactivated the Co catalyst, the corresponding cyclic product **2a** was not produced. Accordingly, we attempted the synthesis of the pyridoisoquinolinone (**2** and **4**) in a two-step, semi-one-pot procedure.[7] After pyridinyl aryl diazoacetate **5a** was treated with TsN_3 and DBU in THF for 12 h, the reaction mixture was filtered through a short pad of silica, and the filtrate was used as the starting material in the following Co-catalyzed carbonylative cyclization at 25 °C under a CO atmosphere, leading to the formation of **2a** in 51% yield. Likewise, pyridinyl aryl diazoacetates (**5**) possessing a variety of substituents (R^1 = Me and EtO_2C, R^2 = MeO) on the aryl and pyridinyl groups are applicable in this modified method, providing the corresponding pyridoisoquinolinones (**2d**, **2l**, and **4b**) in good yields ranging from 60% to 63%.

Scheme 4. Synthesis of Pyridoisoquinolinones from Pyridinyl Aryl Esters in a Semi-One-Pot Fashion[a]

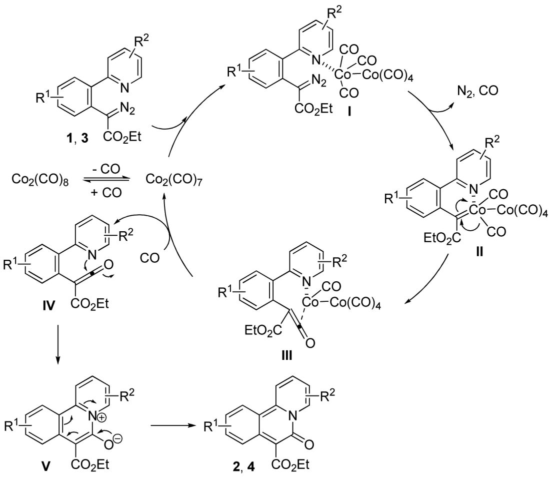


[a]Reactions were carried out with **5** (0.2 mmol, 1.0 equiv), TsN_3 (0.4 mmol), and DBU (0.4 mmol) in THF at 25 °C for 12 h. After the reaction mixture was filtered through a short pad of silica, $Co_2(CO)_8$ (50.0 mol %) in THF was added to filtrate at 25 °C for 6 h under CO atmosphere.

Because pyridoisoquinolinones (**2** and **4**) are fluorescent, their optical properties in CH_2Cl_2 solution were examined (see the Supporting Information). The pyridoisoquinolinone fluorophores displayed Stokes shifts ranging from 41 to 75 units. The extinction coefficients were variable from 67264 to 245677 $M^{-1}\cdot cm^{-1}$. The pyridoisoquinolinone (**2q**) affords high quantum yields and extinction coefficients, which are an attractive property for biological probes.[6]

Although the mechanism of the present reaction has not been completely established, a feasible reaction pathway is illustrated in Scheme 5. Coordination of the cobalt catalyst to the nitrogen atom in pyridinyl diazoacetate **1** and **3** results in the formation of the intermediate **I**, which is converted to a cobalt ethoxycarbonyl carbene complex **II** through dinitrogen extrusion. Migration of a CO from the Co carbene **II** affords the metal-complexed ketene intermediate **III**, which is followed by decomplexation to furnish ethoxycarbonyl ketene **IV** with regeneration of the cobalt catalyst.[2a,b,j−l] Subsequent intramolecular cyclization of the ketene group with the pyridinyl moiety in **IV** provides pyridinium enolate **V**, which is in resonance with pyridoisoquinolinone **2** and **4**. The elucidation of the detailed reaction mechanism must wait further study.

Scheme 5. Proposed Mechanism



In conclusion, we have successfully developed a dicobalt octacarbonyl catalyzed carbonylative cyclization of pyridinyl diazoacetates for the synthesis of pyridoisoquinolinones under a carbon monoxide atmosphere. Moreover, a useful synthetic method for a wide range of pyridoisoquinolinones from pyridinyl aryl acetates has been demonstrated through diazotization using TsN_3 and DBU followed by Co-catalyzed carbonylation and intramolecular cyclization of ketene with a tethering pyridinyl moiety under a carbon monoxide atmosphere in a semi-one-pot procedure. These transformations are attractive due to the use of an inexpensive and commercially available Co catalyst and an easily accessible starting material and the release of harmless N_2 under mild conditions (room temperature).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03340.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated to Professor Barry M. Trost (Stanford University) on the occasion of his 75th birthday.

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