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Cobalt-Catalyzed Direct C−H Carbonylative Synthesis of Free (*NH*)-Indolo[1,2-*a*]quinoxalin-6(5*H*)-ones

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03900 Read Online

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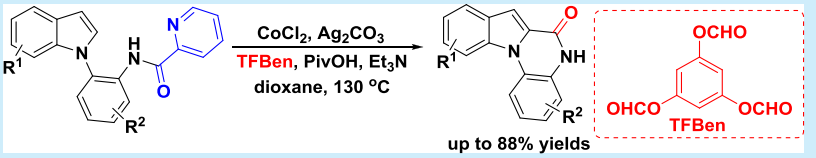
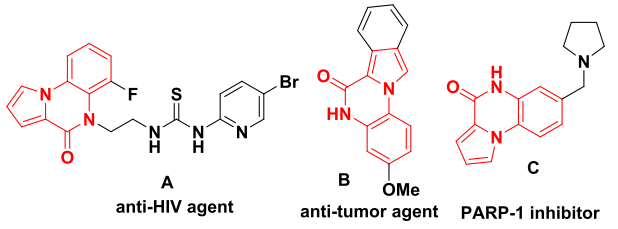


ABSTRACT: A cobalt-catalyzed direct C−H carbonylative reaction of *N*-(2-(1*H*-indol-1-yl)phenyl)picolinamides for the synthesis of (*NH*)-indolo[1,2-*a*]quinoxalin-6(5*H*)-one skeletons has been developed. Using benzene-1,3,5-triyl triformate (TFBen) as the CO source and picolinamide as the traceless directing group, various free (*NH*)-indolo[1,2-*a*]quinoxalin-6(5*H*)-ones were obtained in good yields (up to 88%). Additionally, a series of product derivatizations were demonstrated, and the core fragment of PARP-1 inhibitor **C** can be readily constructed by this protocol.

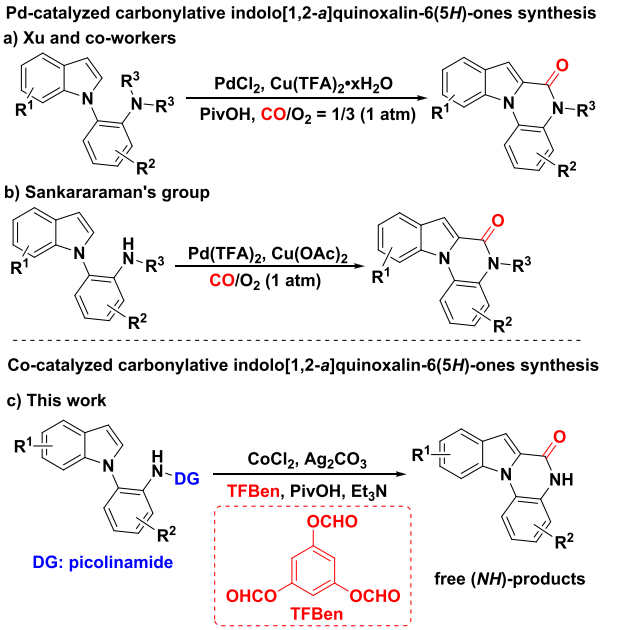
Pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones have been considered as a class of privileged scaffolds that are ubiquitous in a wide range of pharmaceuticals and bioactive compounds.[1−3] For instance, as shown in Scheme 1, compound **A** represents a type of anti-HIV agent by inhibiting the non-nucleoside reverse transcriptase.[1] Compound **B** was found to exhibit remarkable cytotoxic activity against a broad range of human tumor cell lines as a potent tubulin polymerization and topoisomerase I inhibitor.[2] Compound **C** serves as a poly(ADP-ribose)polymerase-1 (PARP-1) inhibitor with good enzymatic and cellular potency for cancer therapy.[3] Moreover, indolo[1,2-*a*]quinoxalin-6(5*H*)-ones comprise the core framework of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones and have also attracted the interests of many scientists due to their diverse biological activities.[4] To assemble the complicated indolo[1,2-*a*]quinoxalin-6(5*H*)-one scaffolds, a few synthetic methods have been realized.[5−8] The common methods involve the intramolecular condensation of amino carboxylates in multiple steps.[5]

On the contrary, transition-metal-catalyzed C−H bond activation and carbonylation offer a direct and efficient

Scheme 1. Representative Pharmaceuticals and Bioactive Compounds of Pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones



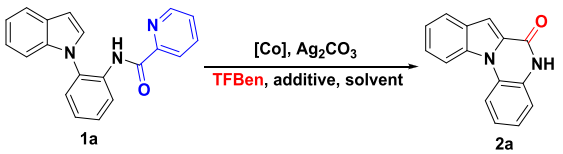
Scheme 2. C−H Carbonylative Synthesis of Indolo[1,2-*a*]quinoxalin-6(5*H*)-ones



Received: November 25, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03900
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening of the Reaction Conditions[a]



entry	[Co]	additive	solvent	yield (%)
1	$CoCl_2$	PhCOOH	dioxane	30
2	$Co(acac)_2$	PhCOOH	dioxane	25
3	$Co(OAc)_2{\cdot}4H_2O$	PhCOOH	dioxane	11
4	$CoCl_2$	AcOH	dioxane	31
5	$CoCl_2$	TFA	dioxane	n.r.
6	$CoCl_2$	PivOH	dioxane	45
7	$CoCl_2$	PivOH	toluene	42
8	$CoCl_2$	PivOH	DMF	40
9	$CoCl_2$	PivOH	DMSO	trace
10[b]	$CoCl_2$	PivOH	dioxane	60
11[b,c]	$CoCl_2$	PivOH	dioxane	66
12[b,c,d]	**$CoCl_2$**	**PivOH**	**dioxane**	**85**
13[b,c,d,e]	$CoCl_2$	PivOH	dioxane	53

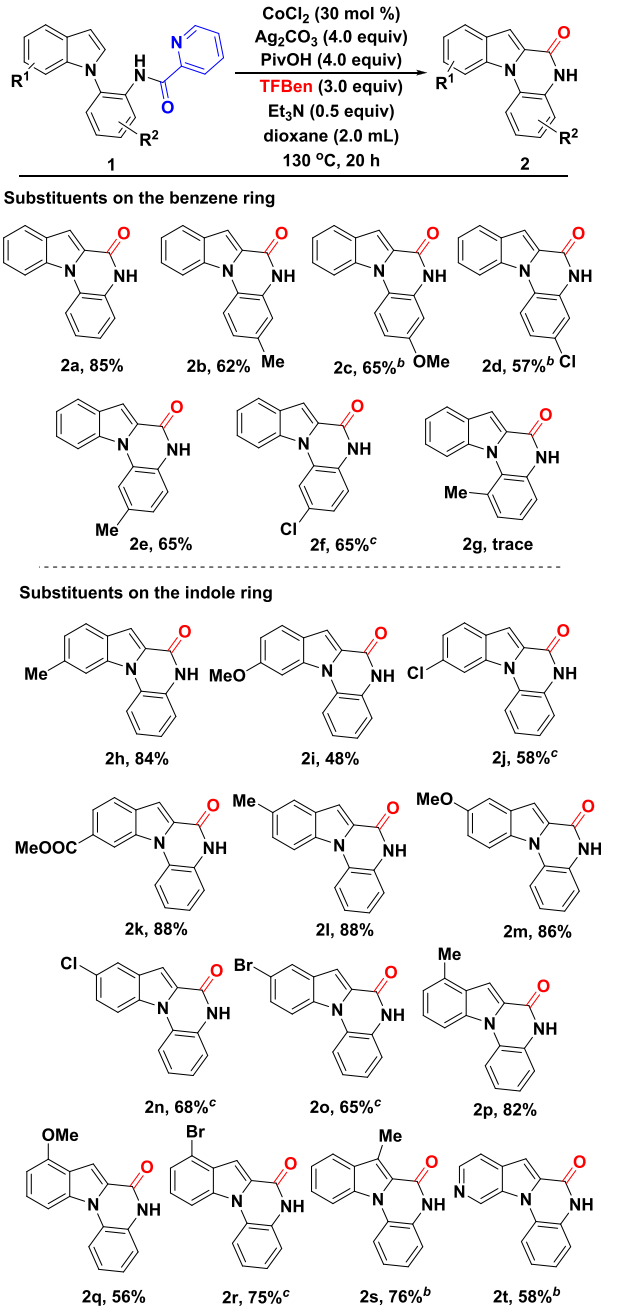
[a]Reaction conditions: **1a** (0.2 mmol), Co catalyst (30 mol %), Ag_2CO_3 (2.5 equiv), TFBen (3.0 equiv), additive (2.0 equiv), solvent (2.0 mL), 130 °C, 20 h, isolated yield. [b]Ag_2CO_3 (4.0 equiv). [c]Et_3N (0.5 equiv). [d]PivOH (4.0 equiv). [e]$CoCl_2$ (20 mol %).

approach to access carbonyl-containing compounds.[9,10] There are very limited reports on the direct C−H carbonylative synthesis of indolo[1,2-*a*]quinoxalin-6(5*H*)-ones.[11,12] In 2019, Xu and coworkers developed a palladium/copper-cocatalyzed C−H activation/*N*-dealkylative carbonylation of *o*-indolyl-*N*,*N*-dimethylarylamines under 1 atm (CO/O_2 = 1/3) mixed gas of CO and oxygen for the synthesis of various *N*-methyl indolo[1,2-*a*]quinoxalin-6(5*H*)-ones (Scheme 2, eq a).[11a] Recently, Sankararaman disclosed a palladium-catalyzed C−H carbonylation of *N*-substituted 2-(1*H*-indol-1-yl)anilines that proceeded well under a CO atmosphere to give *N*-substituted indolo[1,2-*a*]quinoxalin-6(5*H*)-ones (Scheme 2, eq b).[11b] It is important to mention that although oxygen or air is an ideal oxidant from an atom efficiency and sustainability point of view, the risk of explosion when combining CO and O_2 gases at a certain ratio should be kept in mind.[13] As a part of our continued interest in C−H carbonylation,[14] we now report a cobalt-catalyzed C−H bond carbonylative synthesis of free (*NH*)-indolo[1,2-*a*]quinoxalin-6(5*H*)-ones from *N*-(2-(1*H*-indol-1-yl)phenyl)picolinamides and TFBen (Scheme 2, eq c).

At the outset, the *N*-(2-(1*H*-indol-1-yl)phenyl)picolinamide **1a** was chosen as the model substrate and was reacted with TFBen (3.0 equiv) in the presence of $CoCl_2$ (30 mol %) as the catalyst, Ag_2CO_3 (2.5 equiv) as the oxidant, and PhCOOH (2.0 equiv) as the additive at 130 °C for 20 h. To our delight, the desired product **2a** was achieved in 30% yield (Table 1, entry 1). The reaction with $Co(acac)_2$ and $Co(OAc)_2{\cdot}4H_2O$ as the catalyst gave lower yields of **2a** (Table 1, entries 2 and 3). Then, a couple of additives were examined (Table 1, entries 4−6), and the yield was increased to 45% when PivOH was employed (Table 1, entry 6). Furthermore, using other solvents such as toluene, DMF, and DMSO gave reduced yields of **2a** (Table 1, entries 7−9). Notably, the reaction yield was enhanced to 60% when the amount of Ag_2CO_3 was increased (Table 1, entry 10). It was found that the addition of Et_3N could slightly promote the reaction to furnish **2a** in 66% yield (Table 1, entry 11). Gratifyingly, utilizing an increased loading of PivOH (4.0 equiv) significantly improved the yield of **2a** to 85% (Table 1, entry 12). Finally, a lower reaction yield (53%) was obtained when the catalyst loading was reduced (Table 1, entry 13). It is important to mention that $Cu(OAc)_2$, TBHP, and $Mn(OAc)_3$ were tested as oxidants in place of Ag_2CO_3 as well, but no target product could be detected from these tests.

Next, a series of *N*-(2-(1*H*-indol-1-yl)phenyl)picolinamides **1** were investigated under optimal reaction conditions, and the

Scheme 3. Scope of *N*-(2-(1*H*-Indol-1-yl)phenyl)picolinamides[a]



[a]Reaction condition: **1** (0.2 mmol), $CoCl_2$ (30 mol %), Ag_2CO_3 (4.0 equiv), TFBen (3.0 equiv), PivOH (4.0 equiv), Et_3N (0.5 equiv), dioxane (2.0 mL), 130 °C, 20 h, isolated yield. [b]150 °C, 20 h. [c]130 °C, 30 h.

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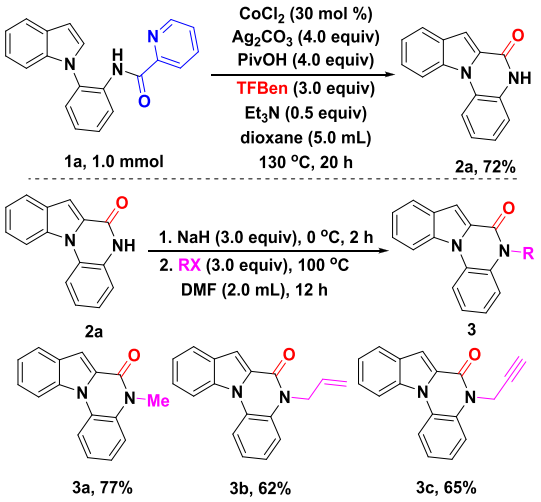
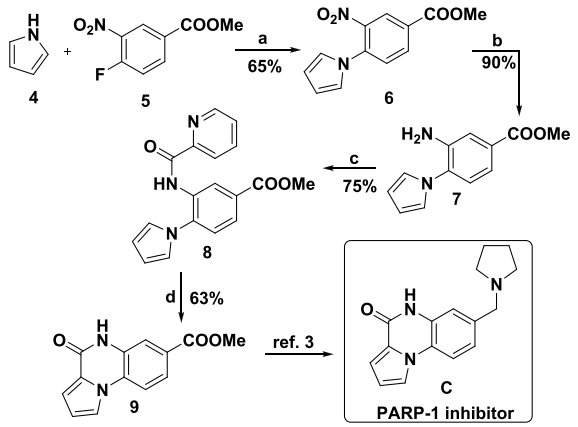
Scheme 4. Scale-up Reaction and Derivatization of the Product 2a



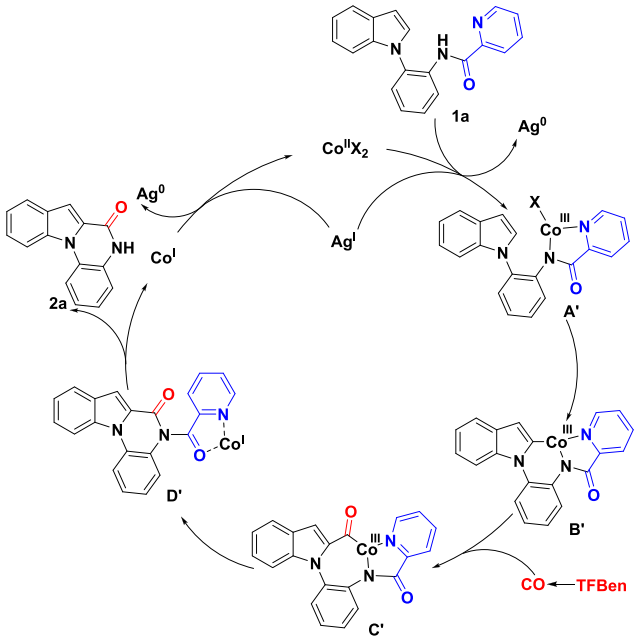
Scheme 5. Construction of the Core Skeleton 9 of PARP-1 Inhibitor C[a]



[a]Reagents and conditions: (a) Cs_2CO_3, DMF, 60 °C, 4 h. (b) Fe, NH_4Cl, H_2O, 4 h. (c) DMAP, picolinic acid, EDCI, DCM, 12 h. (d) $CoCl_2$, Ag_2CO_3, PivOH, TFBen, Et_3N, dioxane, 130 °C, 20 h.

results are shown in Scheme 3. For compounds bearing either electron-donating or -withdrawing substituents at the C4 position of the benzene ring, the reaction afforded the desired products **2b**–**d** in 57–65% yields. It was found that the reaction of compounds with substituents at the C5 position proceeded well to give the products **2e**–**f** in high yields. Surprisingly, only trace product **2g** was observed when the substrate **1g** with a methyl group at the C6 position was tested. Here one possible reason for this phenomenon is the steric effect from the *ortho*-methyl group, which makes the indole ring and the aniline not in the same plane and leads to difficulty in forming a new C–N bond. In addition, when compounds had substituents such as Me, OMe, Cl, and COOMe at the C6 position of the indole ring, the reaction gave the corresponding products **2h**–**k** in moderate to good yields (48–88%). It was shown that good yields (65–88%) of the products **2l**–**o** were obtained when substrates with functional groups at the C5 position were subjected to the reaction system. Also, C4-substituted compounds could undergo the reaction smoothly to give the products **2p**–**r** in high yields (56–82%). Furthermore, the C3-Me-substituted

Scheme 6. Plausible Mechanism



compound **1s** was successfully transformed to the product **2s** in 76% yield. However, the reaction failed when the C3 position of the indole ring was substituted with a phenyl ring. Notably, the substrate **1t** containing a 6-azaindole unit could be converted to the expected product **2t** in 58% yield as well.

Then, a scale-up reaction and a series of derivatization of the product **2a** were performed to demonstrate the utility of this method (Scheme 4). When the *N*-(2-(1*H*-indol-1-yl)phenyl)-picolinamide **1a** (1.0 mmol) was subjected to the standard reaction conditions, a 72% yield of the product **2a** was achieved smoothly. The treatment of **2a** with NaH at 0 °C followed by the addition of alkyl halides could provide various *N*-alkyl-substituted indolo[1,2-*a*]quinoxalin-6(5*H*)-ones **3**. The reaction of **2a** with methyl iodide gave a good yield (77%) of compound **3a**. When **2a** was reacted with allyl bromide and propargyl bromide, compounds **3b** and **3c** were obtained in 62 and 65% yield, respectively.

Furthermore, the core skeleton of PARP-1 inhibitor **C** can be easily established by this protocol as well (Scheme 5). The coupling reaction of pyrrole **4** and the fluoride **5** led to the formation of the nitro compound **6** in 65% yield. The subsequent reduction of **6** with iron gave an excellent yield (90%) of the amine **7**, which was then reacted with picolinic acid to access the picolinamide **8** in 75% yield. Gratifyingly, the direct C–H carbonylative reaction of **8** under our standard conditions could successfully construct the crucial pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one skeleton **9** in 63% yield. Finally, according to the known procedures,[3] PARP-1 inhibitor **C** can be synthesized via the reduction of **9** followed by amination.

On the basis of our results and previous reports,[14,15] a plausible mechanism for this cobalt-catalyzed C–H carbonylation of *N*-(2-(1*H*-indol-1-yl)phenyl)picolinamides is proposed as shown in Scheme 6. Initially, the coordination of the Co(II) catalyst with the *N*-(2-(1*H*-indol-1-yl)phenyl)-picolinamide **1a** followed by the oxidation of the Ag(I) salt forms the Co(III) species **A′**. Then, C–H bond activation at the C2 position of **A′** generates the Co(III) complex **B′**. Subsequently, the insertion of CO that is released from TFBen

https://dx.doi.org/10.1021/acs.orglett.0c03900
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gives the acyl Co(III) intermediate **C′**, which can be converted to the Co(I) complex **D′** via reductive elimination. Finally, the hydrolysis of **D′** leads to the formation of the target product **2a** and releases the Co(I) species. The Co(I) species is then oxidized by the Ag(I) salt to regenerate the active Co(II) catalyst for the next catalytic cycle.

In conclusion, we have developed a facile and convenient approach to access free (*NH*)-indolo[1,2-*a*]quinoxalin-6(5*H*)-ones via a cobalt-catalyzed C−H carbonylation of *N*-(2-(1*H*-indol-1-yl)phenyl)picolinamides with TFBen as the CO source and picolinamide as the traceless directing group. This method also provides an efficient alternative for the establishment of the core skeleton of PARP-1 inhibitor **C**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03900.

General information, procedures, analytic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Joint Funds of Zhejiang Natural Science Foundation and Taizhou (LTY21B020001) and the National Natural Science Foundation of China (21772177).

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