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Palladium-catalyzed carbonylative synthesis of 3-arylquinolin-2(1*H*)-ones from benzyl chlorides and *o*-nitrobenzaldehydes

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ABSTRACT

A palladium-catalyzed carbonylative cyclization of benzyl chlorides with *o*-nitrobenzaldehydes has been developed for the synthesis of 3-arylquinolin-2(1*H*)-ones. $Mo(CO)_6$ played a dual role as both a CO surrogate and a reductant in this carbonylative transformation.

Quinolin-2(1*H*)-ones represent one of the most important *N*-heterocycles being found in natural products and synthetic molecules [1]. They have attracted much attentions because of their unique molecular skeletons and broad range of pharmaceutical activities [2-6]. For examples, nybomycin and deoxynybomyin, as promising antibiotics are found to be quite active against bacteria [2].[c] In addition, quinolin-2(1*H*)-ones are valuable building scaffolds, which could undergo further modifications in organic synthesis [7]. Therefore, various classical procedures, such as Vilsmeier-Haack [8], Knorr [9], and Friedlander reactions [10], together with modern methods, including transition-metal-catalyzed variation [11], as well as RCM[12] have been reported. Nevertheless, the exploration of novel strategy toward quinolin-2(1*H*)-ones remains of long-lasting interest.

In the last few decades, palladium-catalyzed carbonylation reaction provides an alternative access for the construction of *N*-heterocycles, and carbonylative protocols toward quinolin-2(1*H*)-ones have been reported [13]. On the other hand, the utilization of nitroarenes as a type of convenient nitrogen sources in recent years is becoming more and more popular because they are stable, less expensive, and easily available. Thus, the study of nitroarenes as nitrogen alternatives have been disclosed in a series of aminocarbonylation reactions [14]. For examples, Hu's group developed a nickel-catalyzed reductive aminocarbonylation of aryl halides with nitroarenes [14].[e] Cheung and Ma reported an aminocarbonylation reaction of arylboronic acid with nitroarenes using nickel metal as both a mediator and a reductant [14].[f] Herein, we wish to describe a new palladium-catalyzed carbonylative cyclization of benzyl chlorides with o-nitrobenzaldehydes toward the synthesis of 3-arylquinolin-2(1*H*)-ones.

Initially, *o*-nitrobenzaldehyde 1a (0.2 mmol) and benzyl chloride 2a (0.4 mmol) were used as model substrates to evaluate this carbonylative cyclization reaction. To our delight, 63% yield of desired product 3aa was obtained with $Pd(OAc)_2$ (5 mol%), DPEPhos (5 mol%), $Mo(CO)_6$ (1.0 equiv.), Et_3N (2.0 equiv.), $MgSO_4$ (1.0 equiv.), in DME at 100 °C for 22 h (Table 1, entry 1). Next, different ligands, involving PPh_3, SPhos, DPPP, and BINAP were examined, lower yields were observed (Table 1, entries 2–5). Catalysts screening showed that $Pd(OAc)_2$ was the optimal catalyst (Table 1, entries 6–8). The yield of 3aa increased to 76% by using DBU as the base (Table 1, entry 10), whereas other bases resulted in even lower yields (Table 1, entries 9, 11–12). When the reaction time was prolonged to 30 h, the target product was isolated in 92% yield (Table 1, entry 13). As the hydrogen source, H_2O played a significant role in this carbonylation reaction. However, extra H_2O will be generated as the reaction proceeding, which would affect the reaction. Hence, the amount of $MgSO_4$ was very important, only 48% yield of 3aa was resulted without $MgSO_4$ (Table 1, entry 14), while with 2 equivalent of $MgSO_4$, the corresponding product was produced in 99% yield (Table 1, entry 15).

With the optimal reaction conditions in hand, the scope and generality of this carbonylation reaction toward benzyl chlorides were studied. As summarized in Scheme 1, a broad range of benzyl chlorides were tolerated well to provide the corresponding quinolin-2(1*H*)-ones in moderate to excellent yields. Substrates with electron-donating groups,

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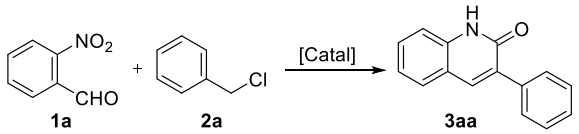
Table 1
Screening of Reaction Conditions.[a].



Entry	[Pd]	Ligand	Base	Yield (%)
1	$Pd(OAc)_2$	DPEPhos	Et_3N	63
2	$Pd(OAc)_2$	PPh_3	Et_3N	trace
3	$Pd(OAc)_2$	SPhos	Et_3N	25
4	$Pd(OAc)_2$	DPPP	Et_3N	trace
5	$Pd(OAc)_2$	BNIAP	Et_3N	52
6	$Pd(tfa)_2$	DPEPhos	Et_3N	35
7	$Pd(acac)_2$	DPEPhos	Et_3N	52
8	$Pd(PPh_3)_4$	DPEPhos	Et_3N	42
9	$Pd(OAc)_2$	DPEPhos	DIPEA	43
10	$Pd(OAc)_2$	DPEPhos	DBU	76
11	$Pd(OAc)_2$	DPEPhos	$NaOCH_3$	23
12	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	40
13[b]	$Pd(OAc)_2$	DPEPhos	DBU	92
14[b,c]	$Pd(OAc)_2$	DPEPhos	DBU	48
15[b,d]	$Pd(OAc)_2$	DPEPhos	DBU	99

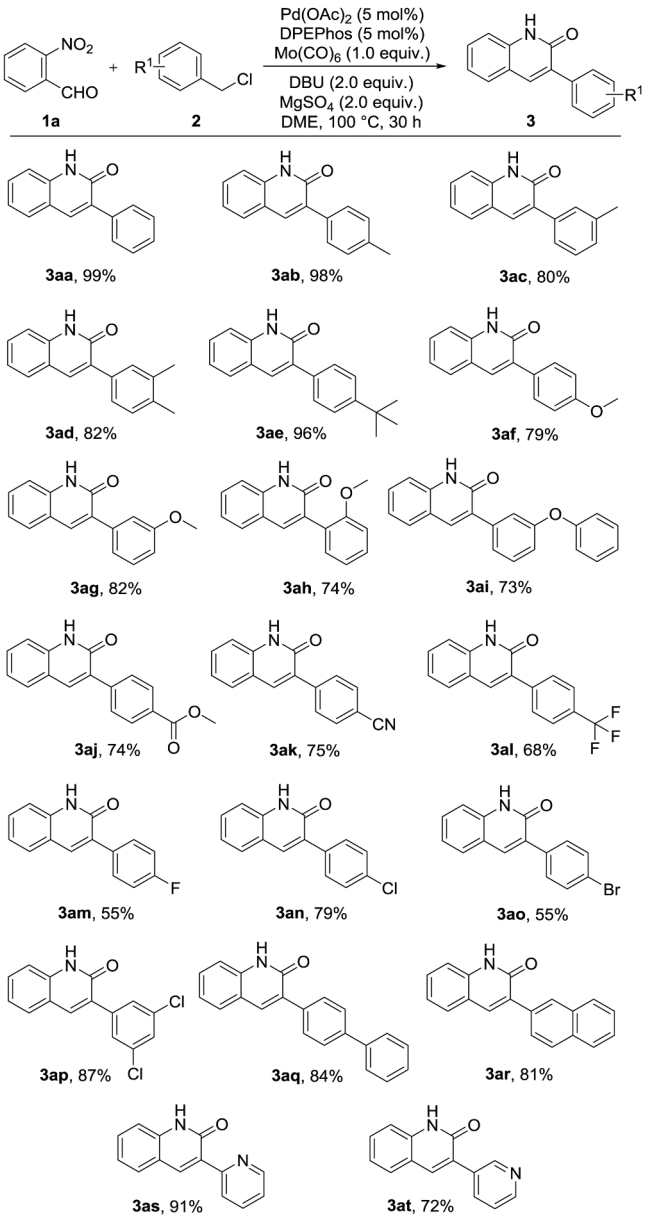
[a] Reaction conditions: *o*-nitrobenzaldehyde 1a (0.2 mmol), benzyl chloride 2a (0.4 mmol), [Pd] (5 mol%), ligand (10 mol% for monodentate ligand, 5 mol% for bidentate ligand), $Mo(CO)_6$ (1.0 equiv.), base (2.0 equiv.), $MgSO_4$ (1.0 equiv.), DME (1 mL), 100 °C, 22 h. Isolated yields. [b] 30 h. [c] Without $MgSO_4$. [d]$MgSO_4$ (2.0 equiv.).

including methyl, *tert*-butyl, methoxy, and phenoxy groups afforded the target products in good to high yields (3ab-3ai). The steric encumbered 3-(2-methoxyphenyl)quinolin-2(1*H*)-one product could be synthesized without significant effect on the yield (3ah). Electron-withdrawing groups, such as ester, cyano, and trfluoromethyl moieties were all well tolerated, the desired products were obtained in good yields (3aj-3al). Halogen substituents were tolerated as well, the final products were formed in moderate to excellent yields (3am-3ap). Moreover, biphenyl and naphthyl related substrates were also reacted with *o*-nitrobenzaldehyde 2a successfully to afford the quinolin-2(1*H*)-one products in 84%, 75% and 81% yields (3aq-3at). In addition, pyridine groups could be incorporated into quinolin-2(1*H*)-ones as well, the expected products were resulted in 91% and 72% yields (3as-3at).

We next went on our study on the substrate scope of *o*-nitrobenzaldehydes. As illustrated in Scheme 2, an array of *o*-nitrobenzaldehydes was carried out under the standard reaction conditions, affording the corresponding quinolin-2(1*H*)-ones in good to excellent yields. *o*-Nitrobenzaldehyde bearing methyl, ethoxy, ester and acetal substituents could react with 1a efficiently, the desired products were isolated in high yields (3ba-3ea). This protocol allowed various quinolin-2(1*H*)-ones to be synthesized with fluoro and chloro groups at different positions, resulting the expected products in good to high yields (3fa-3ia). Finally, o-nitroacetophenone was also tested with benzyl chloride and 15% yield of the corresponding product was detected with significant amount of o-aminoacetophenone formed.

In addition, a control experiment of *o*-aminobenzaldehyde 1a as reductant was performed (eq a). Under the standard conditions, the target product 3aa was obtained in 14% yield along with large amount of 1a remained. This is mainly due to the dimerization effect (condensation between aldehyde and amine groups) from *o*-aminobenzaldehyde.

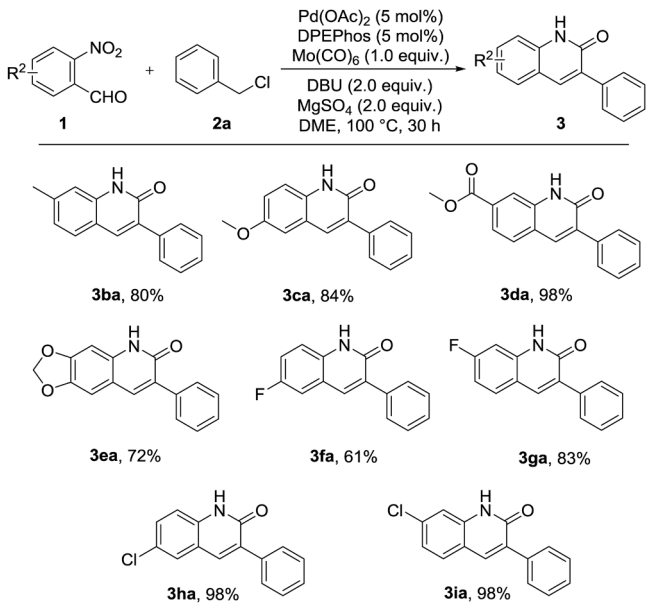
To further reveal the potential utility of this approach in organic synthesis, a late-stage modification of natural product was conducted (Scheme 3). L-Menthol was reacted with 4-(chloromethyl)benzoyl chloride to afford intermediate 4, followed by a carbonylative cyclization with *o*-nitrobenzaldehyde under the standard reaction conditions to deliver the corresponding quinolin-2-(1*H*)-one 5 in 74% isolated yield. It was a positive outcome, which might be applied as an efficient strategy in potent drug synthesis and discovery.



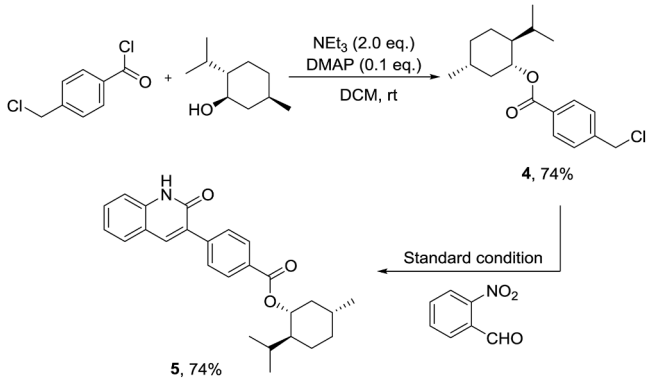
Scheme 1. Substrate Scope of Benzyl Chlorides. Reaction conditions: *o*-nitrobenzaldehyde 1a (0.2 mmol), benzyl chlorides 2 (0.4 mmol), $Pd(OAc)_2$ (5 mol %), DPEPhos (5 mol%), $Mo(CO)_6$ (1.0 equiv.), DBU (2.0 equiv.), $MgSO_4$ (2.0 equiv.), DME (1 mL), 100 °C, 30 h. Isolated yields.

Based on the above results and previous reports [10,15], a possible reaction pathway is proposed in Scheme 4. Firstly, an oxidative addition step of Pd^0L_n with benzyl chloride 2a occurred to give intermediate benzylpalladium complex I, followed by a coordination and insertion of CO (released from $Mo(CO)_6$) to provide acylpalladium complex II. Secondary, a reaction of acylpalladium complex II with *o*-aminobenzaldehyde 4a, which was generated from the reduction of *o*-nitrobenzaldehyde 1a in the presence of $Mo(CO)_6$ and H_2O [15], furnishing intermediate III and meanwhile releasing HCl which will be neutralized by DBU. Subsequently, a reductive elimination of intermediate III lead to intermediate IV and regenerated Pd^0L_n for the next catalytic cycle. Finally, the target product 3aa was obtained through an intramolecular condensation of intermediate IV assisted by DBU.

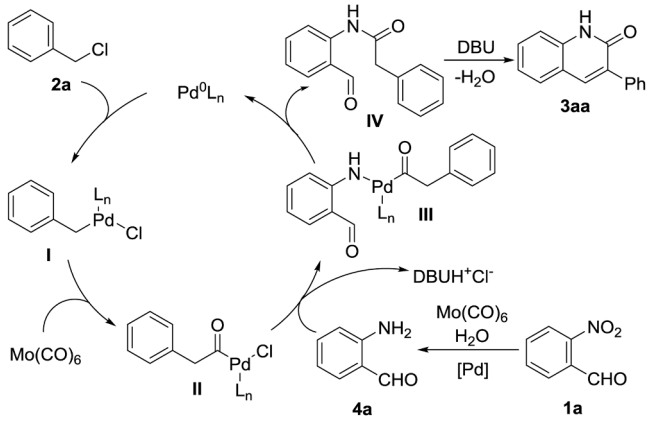
In summary, we have explored a general and straightforward synthesis of 3-arylquinolin-2(1*H*)-ones through a palladium-catalyzed aminocarbonylation reaction of benzyl chlorides with *o*-



Scheme 2. Substrate Scope of *o*-Nitrobenzaldehydes. Reaction conditions: *o*-nitrobenzaldehydes 1 (0.2 mmol), benzyl chloride 2a (0.4 mmol), $Pd(OAc)_2$ (5 mol%), DPEPhos (5 mol%), $Mo(CO)_6$ (1.0 equiv.), DBU (2.0 equiv.), $MgSO_4$ (2.0 equiv.), DME (1 mL), 100 °C, 30 h. Isolated yields.



Scheme 3. Late-stage Modification.



Scheme 4. Proposed Reaction Mechanism.

nitrobenzaldehydes. This protocol employed readily available *o*-nitrobenzaldehydes as stable nitrogen sources, using $Mo(CO)_6$ as both CO precursor and reductant, a variety of 3-arylquinolin-2(1*H*)-ones were prepared in moderate to high yields with good functional group compatibility. Moreover, the late-stage modification of natural species has been successfully conducted *via* this carbonylation process as well.

General procedure

o-Nitrobenzaldehydes 1 (0.2 mmol), $Pd(OAc)_2$ (5 mol%), DPEPhos (5 mol%), $Mo(CO)_6$ (0.2 mmol) and $MgSO_4$ (0.4 mmol) were added to an oven-dried tube (15 mL), which was then placed under vacuum and refilled with nitrogen for three times. Benzyl chlorides 2 (0.4 mmol), DBU (0.4 mmol) and DME (1 mL) were added into the tube via a syringe. The tube was sealed and the mixture was stirred at 100 °C for 30 h. After the reaction was completed, the crude mixture was filtered and concentrated under vacuum. The crude product was purified by column chromatography (DCM/EA = 20/1 to 5/1) on silica gel to afford the desired products 3.

Author statements

X.F.Wu and X. Qi supervised this project. X. Qi prepared the manuscript and X.F.Wu did the revision and corrections. J.L. Liu performed all the experiments. C.-Y. Hou purified part of the products.

Declaration of Competing Interest

There are no conflicts to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2021.111842.

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