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Palladium-Catalyzed Cascade Reactions of Isocyanides with Enaminones: Synthesis of 4-Aminoquinoline Derivatives

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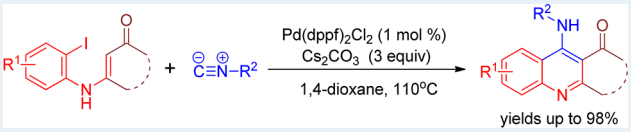
Supporting Information

ABSTRACT: A method for palladium-catalyzed cascade reactions of isocyanides with enaminones has been developed. This methodology provides a direct approach to 4-aminoquinoline derivatives under mild conditions with up to 98% yields.



KEYWORDS: *isocyanide, cascade reaction, amino quinoline, palladium*

The quinoline moiety is one of the most important skeletons found in numerous heterocycles, and many quinoline derivatives[1] have been employed in the manufacture of dyes, drugs, as well as important synthetic intermediates and building blocks.[2,3] Among them, 4-aminoquinolines have attracted special research interest[4−7] because they are useful antimalarial agents in treating erythrocytic plasmodial infections (Figure 1). For example, amodiaquine **IV** is used as an

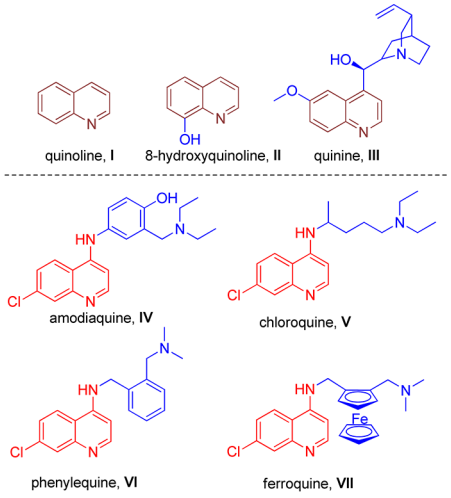
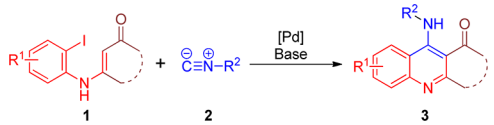


Figure 1. Representative examples of quinolone and 4-aminoquinoline.

antimalarial drug and anti-inflammatory agent.[4] Chloroquine **V** was discovered in 1934 and has been used as an antimalarial drug for more than half century.[5] Phenylequine **VI** shows good antimalarial activity.[6] The antimalarial ferroquine **VII** (FQ, SSR97193) is currently the most advanced organo-metallic drug candidate.[7]

During the past ten years, cascade reactions have been attracted great attention for their applications in the construction of complex molecules as well as natural products, which have undeniable advantages such as only a single workup procedure and purification step without the isolation of the intermediates and are looked upon as an atom and step economical benign strategy for the construction of complex molecules.[8,9] Recently, our group have been focused on the research of cascade reactions[10] based on isocyanides[11] to construct different molecules as well as complex heterocycles. As part of our research in this field, we herein report a practical synthetic strategy for the synthesis of 4-aminoquinoline derivatives by a palladium-catalyzed[12] [5 + 1] cascade annulation of isocyanides with functionalized enaminones (Scheme 1).

Scheme 1. Reaction of Indolyl Alcohol Derivatives with Nucleophiles



Initially, the model reaction of 3-((2-iodophenyl)amino)-5,5-dimethylcyclohex-2-enone **1a** (easily prepared from the corresponding amine with diketone) and *tert*-butyl isocyanide **2a** was performed in toluene at 110 °C for 12 h catalyzed by 10 mol % $Pd(OAc)_2$ in the presence of 2 equiv of K_2CO_3. To our delight, the desired [5 + 1] cascade annulation 4-aminoquinoline **3a** could be obtained in 53% LC yield (Table 1, entry 1). Only trace or poor yield of **3a** was obtained when the reaction was carried using Na_2CO_3, Et_3N, NaOAc, KOAc, or DABCO (Table 1, entries 2, 4, and 5). When other bases such as K_3PO_4, CsOAc, and Cs_2CO_3 were screened for this reaction, it was found that Cs_2CO_3 was the best additive for this reaction, and the LC yield of **3a** was increased to 76% (Table 1, entries 3, 7

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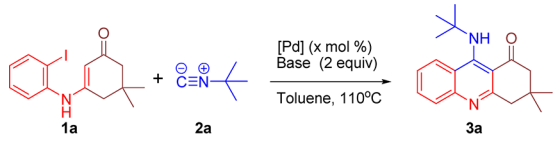
Table 1. Screening of Reaction Conditions: Effects of Catalyst and Base[a]



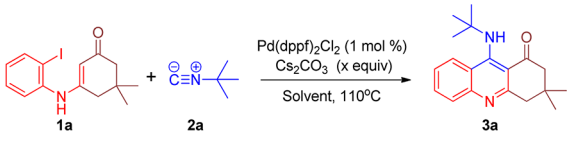
entry	cat. (x mol %)	base (2 equiv)	yield(%)[b]
1	$Pd(OAc)_2$ (10)	K_2CO_3	53
2	$Pd(OAc)_2$ (10)	Na_2CO_3	trace
3	$Pd(OAc)_2$ (10)	K_3PO_4	55
4	$Pd(OAc)_2$ (10)	Et_3N	trace
5	$Pd(OAc)_2$ (10)	NaOAc	trace
6	$Pd(OAc)_2$ (10)	KOAc	8
7	$Pd(OAc)_2$ (10)	CsOAc	52
8	$Pd(OAc)_2$ (10)	DABCO	5
9	$Pd(OAc)_2$ (10)	Cs_2CO_3	76
10	$Pd(PPh_3)_2$ (10)	Cs_2CO_3	67
11	$Pd(dba)_2$ (10)	Cs_2CO_3	70
12	$PdCl_2$ (10)	Cs_2CO_3	65
13	$Pd(PPh_3)_2Cl_2$ (1)	Cs_2CO_3	62
14	$Pd(dppf)_2Cl_2$ (1)	Cs_2CO_3	68
15		Cs_2CO_3	0

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (100 μL), toluene (3 mL), base (2 equiv), 12 h. [b]Yields were determined by LC with an internal standard (biphenyl) as the ratio between the formed products and the initial amount of limiting reactant.

and 9). We further tested other palladium catalysts including $Pd(PPh_3)_2$, $Pd(dba)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(dppf)_2Cl_2$ and found that 1 mol % $Pd(dppf)_2Cl_2$ was enough to catalyze this reaction and generated **3a** in 68% LC yield (Table 1, entry 14). The control experiment indicated that no product was formed in the absence of palladium catalyst (Table 1, entry 15). Satisfactorily, the change of the amount of Cs_2CO_3 to 3 equiv lead to **3a** in 79% LC yield (Table 2, entry 3). Further investigations by screening the solvent revealed that the yield of **3a** could be increased to 90% LC yield (88% isolated yield) when the reaction was carried out in 1.4-dioxane at 110 °C.

Under the optimized reaction conditions, the scope of this [5 + 1] annulation reaction was explored using various substituted

Table 2. Screening of Reaction Conditions: Effects of Solvent and Base[a]

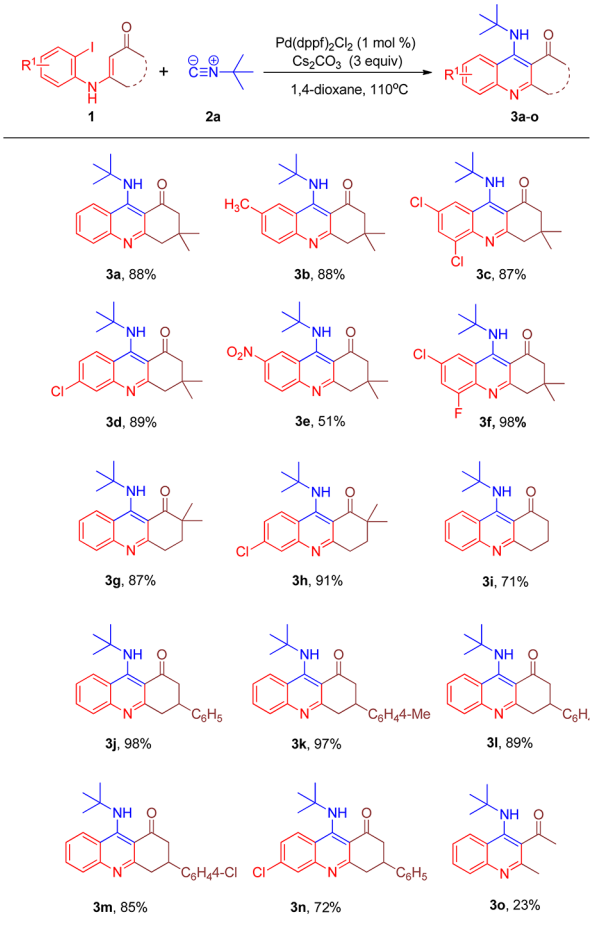


entry	solvent	Cs_2CO_3 (equiv)	yield (%)[b]
1	toluene	1	66
2	toluene	2	68
3	toluene	3	79
4	DMF	3	60
5	glycol	3	trace
6	1,4-dioxane	3	90 (88[c])

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), solvent (3 mL), Cs_2CO_3 (x equiv), and $Pd(dppf)_2Cl_2$ (1 mol %), 12 h. [b]Yields were determined by LC–MS with an internal standard (biphenyl) as the ratio between the formed products and the initial amount of limiting reactant. [c]Isolated yield.

enaminone **1** with isocyanides **2**. As shown in Table 3, the 3-aryl enaminone bearing methyl group or Cl group participated

Table 3. Synthesis of 4-Aminoquinoline Derivatives[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), 1.4-dioxane (3 mL), Cs_2CO_3 (3 equiv), and $Pd(dppf)_2Cl_2$ (1 mol %). [b]Isolated yield.

in the annulation reaction equally efficiently, which furnished the desired 4-aminoquinoline derivatives **3b–d** in very similar good yields (87% to 89% yields). When disubstituted enaminone 3-((4-chloro-2-fluoro-6-iodophenyl)amino)-5,5-dimethylcyclohex-2-enone **1f** was subjected to the reaction, the desired product **3f** could be even obtained in 98% yield, which was further confirmed by X-ray analysis (Figure 2). When the 3-aryl enaminone **3e** bearing strong electron withdrawing group was applied to the reaction with **2a**, desired product **3e** could also be isolated in 51% yield.

The [5 + 1] annulation reactions of 9-(*tert*-butylamino)-2,2-dimethyl-3,4-dihydroacridin-1(2*H*)-one **1g** and 9-(*tert*-butylamino)-6-chloro-2,2-dimethyl-3,4-dihydroacridin-1(2*H*)-one **1h** with **2a** afforded the desired products **3g** and **3h** in 87% and 91% yields, respectively. Other substituted enaminones **1i–n** reacting with **2a** furnished the desired products **3i–n** in good to excellent yields (71% to 98%). It was also found that the reaction of 4-((2-iodophenyl)amino)pent-3-en-2-one **1o** with **2a** could also lead to the desired product **3o** in 23% yield, because of the poor stability of **1o**.

Subsequently, enaminones 3-((2-chlorophenyl)amino)-6,6-dimethylcyclohex-2-enone **1p** and 3-((2-bromophenyl)amino)-6,6-dimethylcyclohex-2-enone **1q** instead of **1a** were applied to

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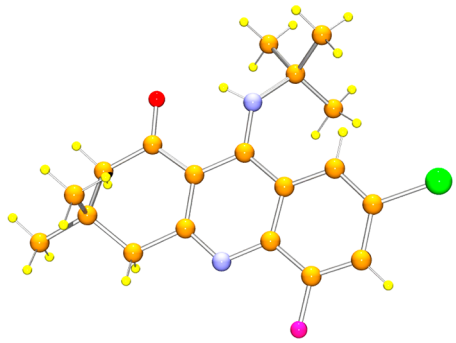
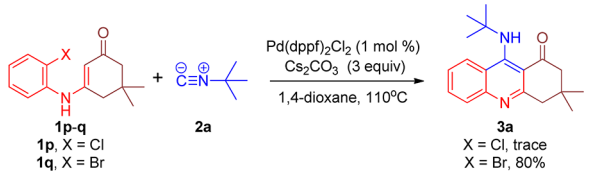


Figure 2. Crystal structure of **3f**.

reaction with **2a**. It was found that chloro-functionalized enaminone **1p** showed poor reactivity and bromo-functionalized enaminone **1q** showed competitive reactivity compared to iodo-functionalized enaminone **1a** (Scheme 2).

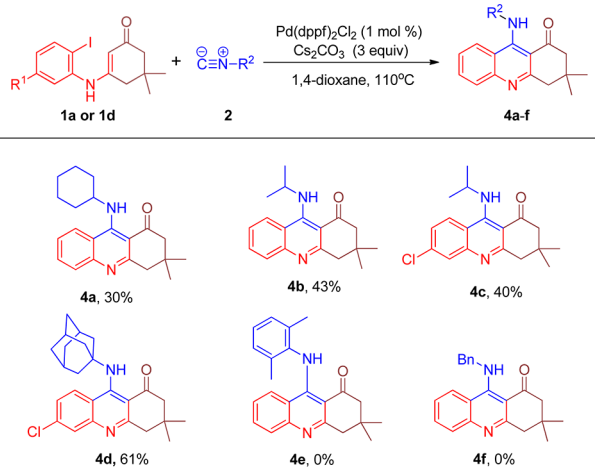
Scheme 2. Reaction of 1p−q with 2a



Additionally, the scope of isocyanides was investigated under the optimal conditions. However, when isocyanocyclohexane was subjected to the reaction with **1a**, only 30% desired product **4a** was obtained. When isocyanocyclohexane was replaced by 2-isocyanopropane **2b**, the desired products **4b** and **4c** could be obtained in 43% and 40% yields, respectively. When 1-adamantyl isocyanide was subjected to the reaction with **1d**, **4d** could be isolated in 61% yield. Unfortunately, some other isocyanides such as (isocyanomethyl)benzene and 2-isocyano-1,3-dimethylbenzene decomposed under the established conditions and no desired product was formed (Table 4).

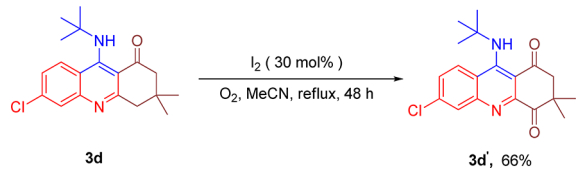
To explore the diversity application of the prepared 4-aminoquinoline derivative **3**, we tried the reaction of **3d** catalyzed by I_2 under O_2 conditions. It was found dicarbonyl functionalized 4-aminoquinoline derivative **3d′** could be easily obtained in 66% yield (Scheme 3).

Table 4. Reaction of 1a with Other Isocyanides[a]



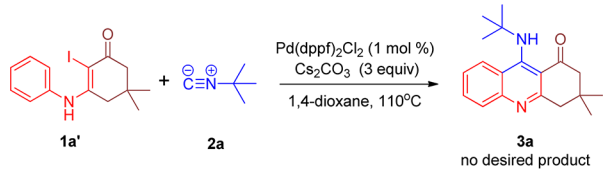
[a]Isolated yields.

Scheme 3. Iodine-Promoted Reaction of 9-(*tert*-butylamino)-6-chloro-3,3-dimethyl-3,4-dihydroacridin-1(2*H*)-one 3d under O_2 Condition



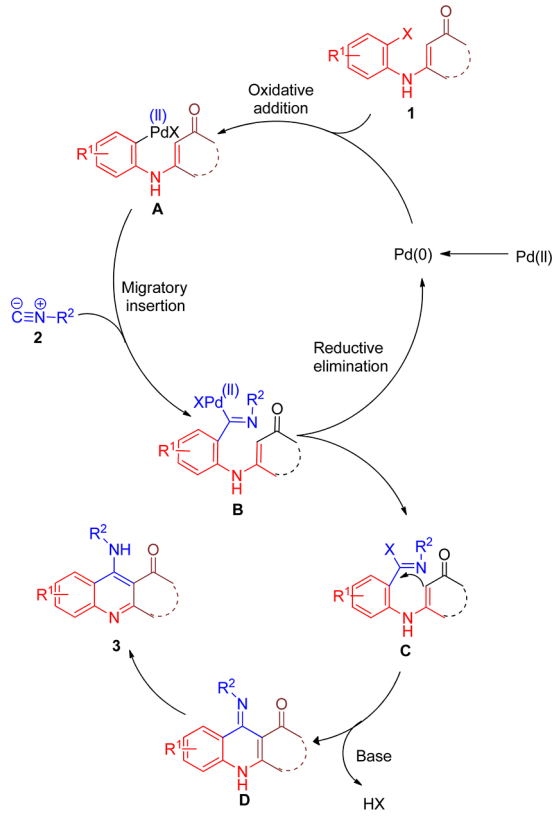
To better understand the mechanism of the reaction, we tried the reaction of **1a′** with **2a** under identical reaction conditions. It was found that no desired product **3a** was found when enaminone **1a′** was used instead of **1a** (Scheme 4).

Scheme 4. Control Experiment



On the basis of the above results and the related literatures,[12,13] a plausible mechanism is proposed in Scheme 5. A palladium(II) complex **A** was formed via the oxidative addition of **1a** to the Pd(0) catalyst. The insertion of isocyanide

Scheme 5. Plausible Mechanism



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leads to the formation of palladium(II) complex **B**, followed by the reductive elimination to give the intermediate **C** and Pd(0) catalyst. Subsequently, the sp^2 C−H bond at α-position of carbonyl group is activated under the base conditions to generate the new 6 member ring complex **D**. After cascade 1,5-H shift, the desired [5 + 1] cyclization product 4-aminoquinoline derivative is formed.

In summary, we have developed palladium-catalyzed cascade reactions of isocyanides with enaminones for the [5 + 1] cyclization reaction of enaminones with isocyanides. This protocol provides a new and straightforward approach to 4-aminoquinoline derivatives under mild conditions. This protocol also opens a way to explore new drugs based on 4-aminoquinoline derivatives for their potential high antimalarial activities.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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