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A Ligand-Free Pd-Catalyzed Cascade Reaction: An Access to the Highly Diverse Isoquinolin-1(2*H*)-one Derivatives via Isocyanide and Ugi-MCR Synthesized Amide Precursors

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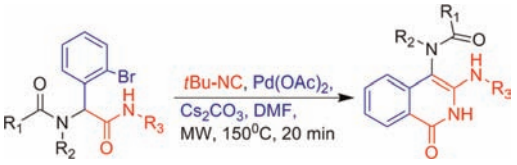
ABSTRACT



A novel ligand-free palladium-catalyzed cascade reaction for the synthesis of highly diverse isoquinolin-1(2*H*)-one derivatives from isocyanide and amide precursors synthesized by Ugi-MCR has been developed. A broad variety of acids, amines, and isocyanides were used as starting materials for Ugi-MCR leading to various amide precursors, which in turn provided entry into diverse isoquinolin-1(2*H*)-one derivatives. The reaction proceeds through tandem isocyanide insertion with intramolecular cyclization followed by a Mazurciewitcz–Ganesan type sequence to provide isoquinoline-1(2*H*)-one derivatives in moderate to good yields.

Isoquinolin-1(2*H*)-one is a frequently encountered structural subunit of numerous biologically active natural products such as narciclasine **1**, lycoricidine **2**, 7-deoxypancratistatin **3x**, dorianine **4**, ruprechstyril **5**, and thalifoline **6** depicted in Figure 1.[1] Isoquinolin-1(2*H*)-one derivatives have received significant attention owing to their antihypertensive and anticancer activities.[2] These are also known to inhibit enzymes such as topoisomerase I, Lck kinase, Rho-kinase, and JNK.[3]

However, there are several methods accessible for the preparation of isoquinolin-1(2*H*)-one derivatives,[4] but most of them suffer from a poor precursor scope with fewer points of diversity.

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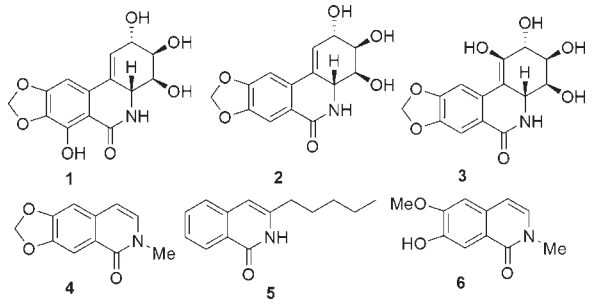


Figure 1. Biologically active natural products containing isoquinolin-1(2*H*)-one scaffold.

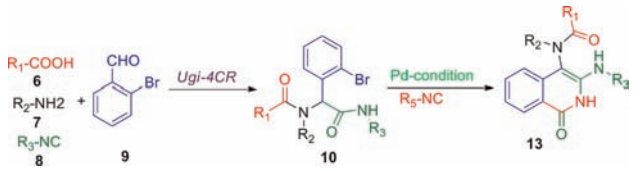
The broad range of biological activities exhibited by the isoquinolin-1(2*H*)-one derivatives make them an attractive and challenging synthetic target, and a concise synthetic methodology involving commercially available and cheap starting materials is still required for their viable synthesis. In this context, transition metal catalyzed synthesis of substituted isoquinolin-1(2*H*)-one derivatives has received noteworthy attention.[5] Thus, Yang and co-workers have reported the synthesis of isoquinolin-1(2*H*)-one derivatives via isocyanide based Ugi-MCR followed by a Heck reaction.[6] Furthermore, Fu and co-workers developed a copper catalyzed approach for the synthesis of isoquinolin-1(2*H*)-one derivatives.[7]

In the recent past, isocyanides have emerged as powerful building blocks in the construction of medicinally important molecules and natural products.[8] Isocyanides have an isoelectronic relationship with carbon monoxide,[9] which enables their inclusion into the organic molecules in transition metal catalyzed protocols.[10] The use of isocyanides in transition metal catalyzed reactions in place of CO has considerable advantages, such as simple handling, an extra diversity point, and possibilities for further elaboration using convertible isocyanide.[11]

Recently, transition metal catalyzed reactions with the insertion of isocyanide for the synthesis of biologically important heterocycles[12] have been reported, e.g. Pd-catalyzed multicomponent synthesis of oxazoline and benzoxazole,[13] Pd-catalyzed synthesis of 4-aminophthalazin-1(2*H*)-one,[14] and synthesis of quinazolino[3,2-*a*]-quinazolines *via* a palladium-catalyzed three-component reaction.[15]

As part of our program to develop new strategies for the diversity oriented synthesis of biologically important heterocycles,[16] we have developed and reported herein the synthesis of highly diverse isoquinoline derivatives via a ligand-free Pd-catalyzed coupling cascade with the insertion of isocyanide into amide precursors obtained by Ugi-MCR under microwave conditions. To the best of our knowledge, it is the first report on the cascade reaction that involves isocyanide insertion with intramolecular cyclization followed by a Mazurciewitcz-Ganesan type procedure under ligand-free Pd-catalyzed conditions.

Scheme 1. General Strategy for the Synthesis of Isoquinolin-1(2*H*)-one



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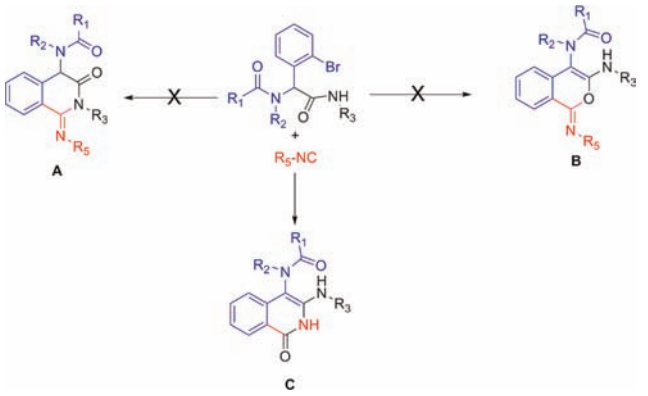
Scheme 2. Three Possible Structures in Pd-Catalyzed Coupling Conditions



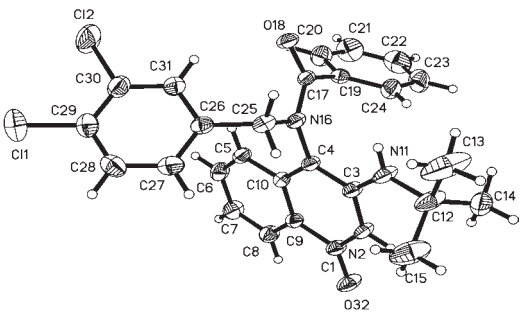


Figure 2. ORTEP diagram of compound **13e**.

As shown in Scheme 1, various acids, amines, and isocyanides can be used for Ugi 4-CR to prepare the corresponding amide precursors,[17] which were used as starting materials for the ligand-free palladium-catalyzed cascade reaction involving insertion and intramolecular cylization of an isocyanide. Further, as depicted in Scheme 2, there can be three probable products **A**, **B**, and **C** of the same molecular weight under Pd-catalyzed conditions. ^{1}H NMR, ^{13}C NMR, and X-ray crystallograhpy data of compound **13e** (Figure 2) confirmed that the products have the general structure **C**.

In the initial phase of the investigation, amide precursor **10a** was used as a substrate for the optimization of the palladium-catalyzed insertion and cyclization reaction of isocyanides. The reaction was carried out using different catalysts, ligands, bases, solvents, and temperature (Table 1). The reaction failed to proceed when palladium was excluded (Table 1, entry 1). Among the three catalysts ($PdCl_2$, $Pd(PPh)_3$, and $Pd(OAc)_2$) used, $Pd(OAc)_2$ was found to be the best and furnished the product **13a** in 89% yield in DMF as a solvent at 150 °C (Table 1, entry 4).

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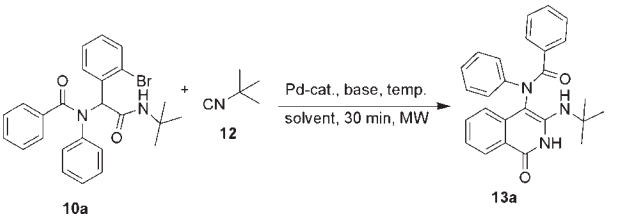
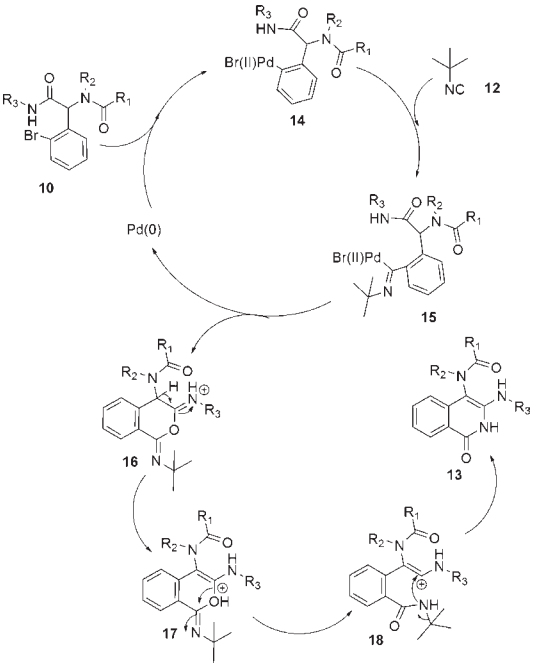
Table 1. Survey of the Reaction Conditions for Pd-Catalyzed Coupling Reaction[a]



entry	catalyst	base	solvent	temp (°C)	yield[b] (%)
1	–	Cs_2CO_3	DMF	150	0[c]
2	$PdCl_2$	Cs_2CO_3	DMF	150	trace
3	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	150	12
4	**$Pd(OAc)_2$**	**Cs_2CO_3**	**DMF**	**150**	**89**
5	$Pd(OAc)_2$	K_2CO_3	DMF	150	61
6	$Pd(OAc)_2$	K_3PO_4	DMF	150	49
7	$Pd(OAc)_2$	KO^t*Bu*	DMF	150	31
8	$Pd(OAc)_2$	Na_2CO_3	DMF	150	40
9	$Pd(OAc)_2$	Cs_2CO_3	DMSO	150	72
10	$Pd(OAc)_2$	Cs_2CO_3	Toluene	150	13
11	$Pd(OAc)_2$	Cs_2CO_3	CH_3CN	150	19
12	$Pd(OAc)_2$	Cs_2CO_3	DMF	120	35
13	$Pd(OAc)_2$	Cs_2CO_3	DMF	150	39[d]

[a] Reaction conditions: substrate **10a** (1 mmol), *tert*-butyl isocyanide (1.2 mmol), catalyst (10 mol %), base (2 mmol), solvent (2 mL) under nitrogen atmosphere, reaction temperature (150 °C), reaction time (20 min). [b] Isolated yield. [c] No addition of catalyst. [d] Loading of catalyst (5 mol %).

Scheme 3. Proposed Mechanism of the Reaction



On the other hand $PdCl_2$ and $Pd(PPh)_3$ resulted in poor yields of **13a** (Table 1, entries 2 and 3). With $Pd(OAc)_2$ as a

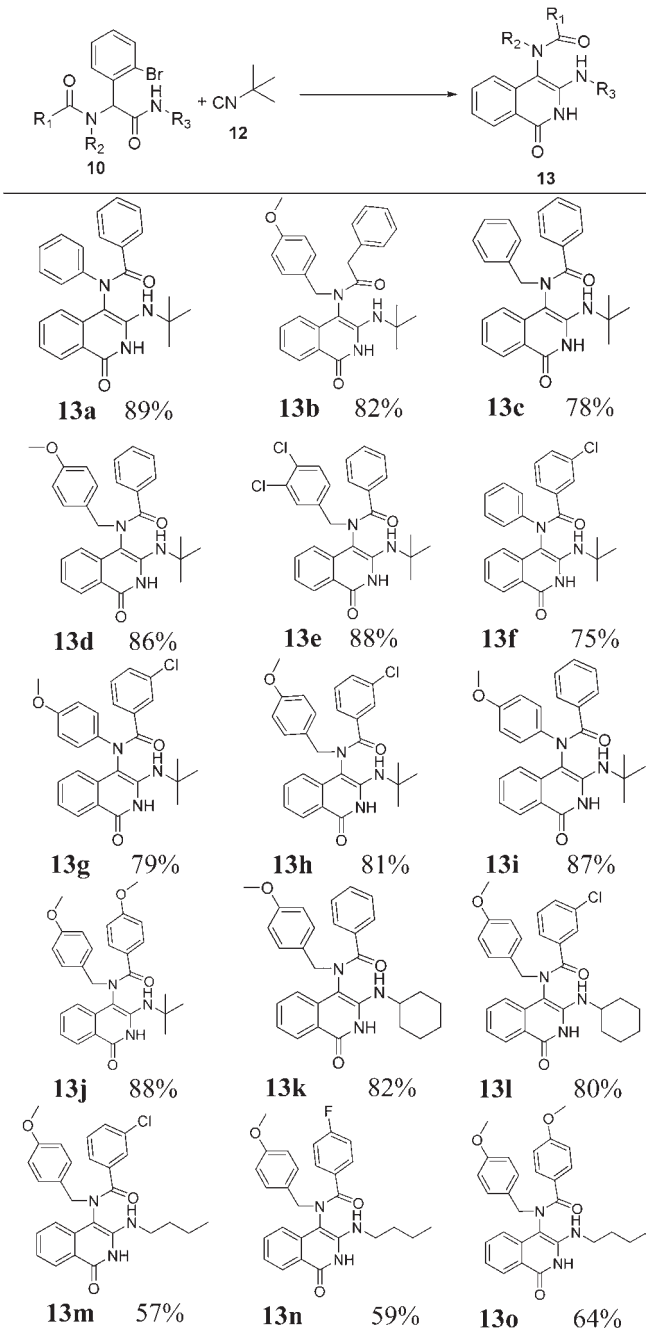


Figure 3. Synthesis of substituted isoquinolin-1(2*H*)-one *via* a Pd-catalyzed coupling reaction of amide **10** and isocyanide **12**. Conditions: $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2 mmol), DMF (2 mL), MW, 150 °C, reaction time 20 min. Yields refer to isolated products.

catalyst and DMF as solvent, lowering of the reaction temperature to 120 °C resulted in a significantly lower yield of **13a** (Table 1, entry 12). Also, various bases were screened in DMF at 150 °C, using $Pd(OAc)_2$ as a catalyst, and Cs_2CO_3 was found to be the most effective base (Table 1, entry 4). Using $Pd(OAc)_2$ as the catalyst and Cs_2CO_3 as the base in DMSO resulted in a slightly lower yield (Table 1, entry 9), while using toluene and CH_3CN under the same conditions provided **13a** in only poor yields (Table1, entries 10 and 11). The efficiency of transformation was affected when the catalyst loading was decreased from 10 to 5 mol % (Table 1, entry 13). The reaction proceeded to completion within 20 min under MW conditions at 150 °C, while in the absence of MW irradiation it took 4−5 h to reach completion (disappearance of amide precursour on TLC). With this standard protocol in hand, we extended it to the synthesis of various substituted isoquinolin-1(2*H*)-ones (**13a**−**13o**) via different Ugi-MCR synthesized amide precursors in moderate to good yields (Figure 3). Of the various isocyanides tested, only *tert*-butyl isocyanide was found to effectively undergo insertion and cyclization and, hence, was the only isocyanide used.[13−15]

A plausible mechanism for the synthesis of an isoquinolin-1(2*H*)-one of type **13** is depicted in Scheme 3. Thus, oxidative insertion of Pd to the amide precursor **10** leads to the intermediate **14** which on insertion of *tert*-butyl isocyanide leads to Pd(II) species **15**. Intermediate **15** via intramolecular cyclization followed by subsequent reductive elimination provides species **16**. Intermediate **16** then undergos a Mazurciewitcz-Ganesan type[18] procedure with de-*tert*-butylation to afford **13**.

In summary, we have developed an efficient method for the synthesis of highly diverse isoquinolin-1(2*H*)-one derivatives via isocyanide-based ligand-free Pd-catalyzed reactions. The strategy allows synthesis of biologically important molecules in a straightforward and atom-economical fashion. Additionally, a range of acids, amines, and isocyanides has been used in the reaction protocol, which offers an opportunity for the synthesis of highly diverse isoquinoline derivatives for combinatorial and medicinal chemistry.

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Supporting Information Available. Experimental procedure, characterization data of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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