Received: 18 November 2019 | Revised: 26 December 2019 | Accepted: 5 January 2020

DOI: 10.1002/aoc.5513

FULL PAPER

Applied Organometallic Chemistry WILEY

Palladium-catalyzed cyclization reaction of N-(2-Haloaryl) alkynylimines: Synthesis of 3-acylindoles using water as the sole solvent and oxygen source

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 21572126, 21202095, 21172139, 21271125; Program for Science & Technology Innovation Talents in Universities of Henan Province, Grant/Award Number: 14HASTIT016; Program of Science and Technology Innovation Talents of Henan Province, Grant/Award Number: 2018JQ0011

A simple and efficient strategy for the preparation of 3-acylindoles via palladium-catalyzed cyclization reaction of *N*-(2-haloaryl)alkynylimines in water has been developed. The reaction tolerates a wide range of functional groups, and the corresponding 3-acylindoles were obtained in high yields using water as the sole solvent and oxygen sources. Additionally, this method could provide a short synthesis route for Pravadoline, a phase II analgesic drug.

KEYWORDS

3-acylindoles, *N*-(2-haloaryl)alkynylimines, palladium-catalyzed cyclization, water

1 | INTRODUCTION

Acylated indoles are ubiquitous in biologically active natural products and pharmaceutical compounds, and are also versatile precursors for the synthesis of alkaloids and other related heterocycles. In particular, 3-acylindoles are frequently reported as important leading compounds with diverse pharmacological effects, such as analgesic, tubulin polymerization inhibitor, and hypocholesterolemic activities. (Figure 1)[1] Consequently, much effort has focused on the synthesis of 3-acylindoles. In the past few years, the direct 3-acylation of indoles has been developed, and is well synthetic procedures of 3-acylindoles.[2] On the other hand, direct construction of the 3-acylindole skeleton from acyclic precursors has also got considerable attention, and some significant approaches have been achieved, such as intramolecular cyclization of enaminones,[3] direct intramolecular oxidative coupling or radical cyclization of aminoalkynes,[4] Rh-catalyzed annulation of N-phenylamidines with α-Cl ketones,[5] Ru- or Rh-catalyzed selective C-H activation/annulation of imidamides and

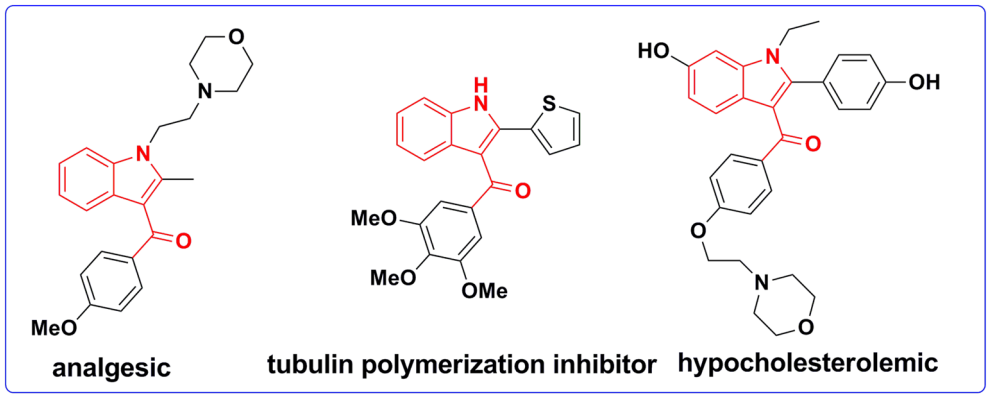
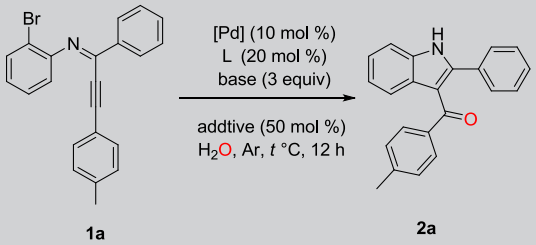


FIGURE 1 Selected examples of bioactive 3-acylindoles

TABLE 1 Optimization of reaction conditions[a]

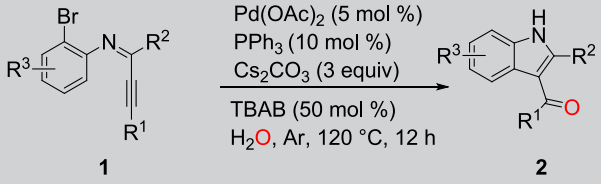


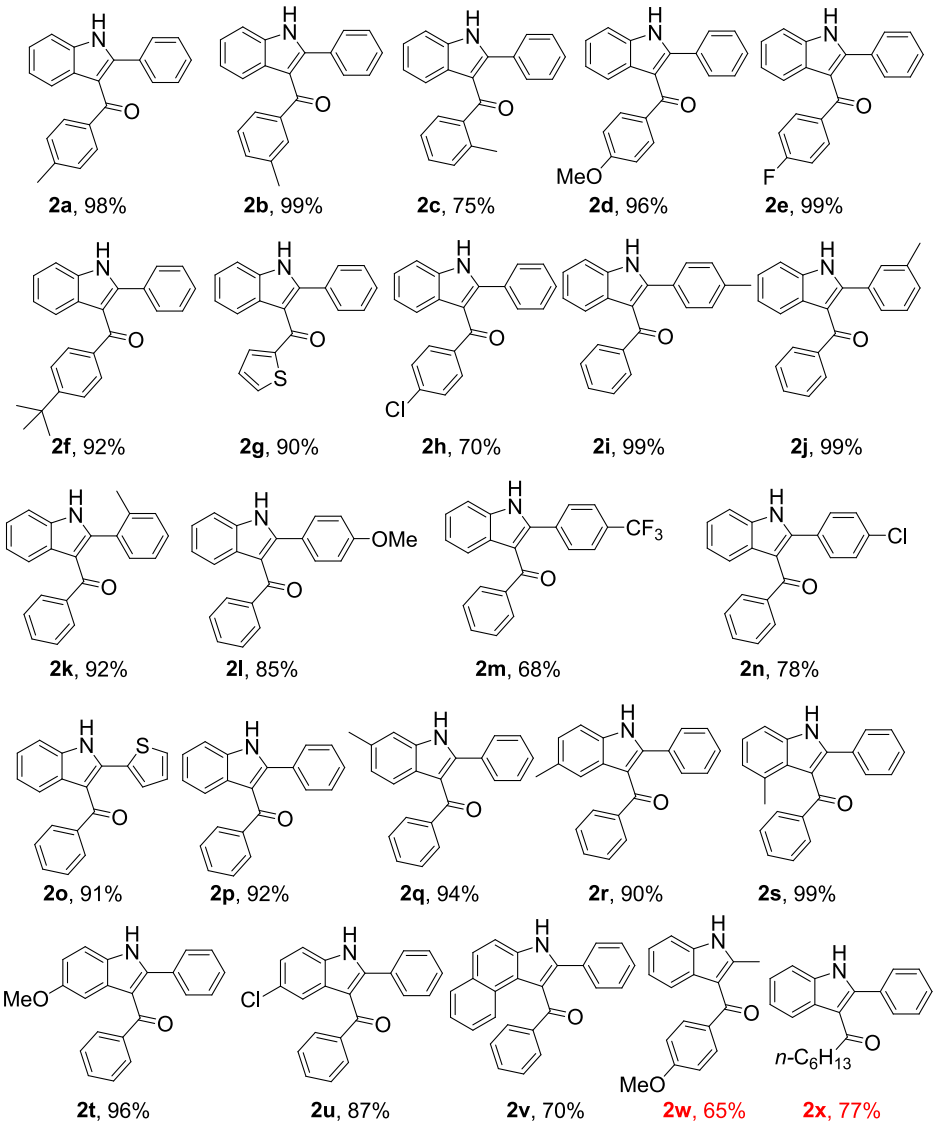
Entry	[Pd]	base	L	addtive	t [°C]	yield (%)[b]
1	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	--	110	80
2	$Pd(OAc)_2$	Cs_2CO_3	--	TBAB	110	trace
3	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	110	96
4	$PdCl_2$	Cs_2CO_3	PPh_3	TBAB	110	87
5	$Pd(dba)_2$	Cs_2CO_3	PPh_3	TBAB	110	88
6	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAI	110	93
7	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAC	110	83
8	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	100	76
9	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	120	99
10	$Pd(OAc)_2$	K_2CO_3	PPh_3	TBAB	120	97
11	$Pd(OAc)_2$	KOAc	PPh_3	TBAB	120	67
12	$Pd(OAc)_2$	Na_2CO_3	PPh_3	TBAB	120	89
13	$Pd(OAc)_2$	Cs_2CO_3	PCy_3	TBAB	120	22
14	$Pd(OAc)_2$	Cs_2CO_3	BINAP	TBAB	120	trace
15[c]	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	120	92
16[d]	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	120	99 (98)
17[e]	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	120	92
18[f]	$Pd(OAc)_2$	Cs_2CO_3	PPh_3	TBAB	120	84

[a]Reaction conditions: 1a (0.20 mmol), in the 4 ml H_2O, at the indicated temperature under an argon atmosphere.
[b]Yields of 2a were measured by ^1H NMR with dibromomethane as the internal standard. Isolated yield is in parentheses.
[c]Cs_2CO_3 (1.5 equiv).
[d]$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %).
[e]Using 2 ml toluene and 2.5 equiv H_2O as the solvent.
[f]Using 2 ml toluene and 10.0 equiv H_2O as the solvent.

sulfoxonium ylides,[6] iodine-mediated tandem *aza*-michael addition/C-H functionalization of aniline and α,β-ynones,[7] copper-catalyzed cyclization of *N*-(2-iodoaryl)enaminones,[8] visible light induced intramolecular radical cyclization of *N*-[2-(alkynyl)phenyl]trifluoroacetimidoyl chlorides,[9] Pd-catalyzed isocyanide insertion and oxypalladation of alkyne,[10] visible-light-induced oxidant and metal-free

TABLE 2 Substrate scope[a,b]





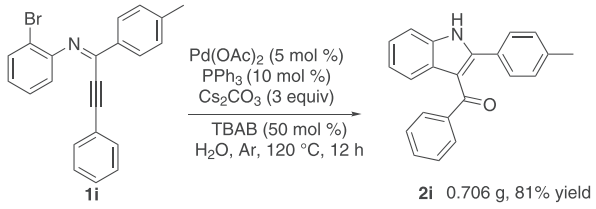
[a]Reaction conditions: 1 (0.2 mmol), Pd $(OAc)_2$ (5.0 mol %), PPh_3 (10.0 mol %), Cs_2CO_3 (3.0 equiv.), TBAB (50.0 mol %) and H_2O (4.0 ml), at 120 °C for 12 hr under an argon atmosphere.
[b]Isolated yield.

dehydrogenative cascade trifluoromethylation and oxidation of 1,6-enynes with water,[11] as well as palladium-catalyzed cyclization reaction of *N*-(*o*-haloaryl) alkynylimines producing 2-trifluoromethylindole derivatives.[12] From the perspective of green chemistry, water is an ideal solvent since it is a non-toxic, abundant, cost-effective and environmental-friendly solvent.[13] Water as the sole solvent and oxygen sources represents one of the best strategies for green chemistry. Herein, we report a simple strategy for the preparation of 3-acylindoles via palladium-catalyzed cyclization reaction of *N*-(2-haloaryl) alkynylimines using water as the sole solvent and oxygen sources and its application in concise synthesis of Pravadoline, a phase II analgesic drug.

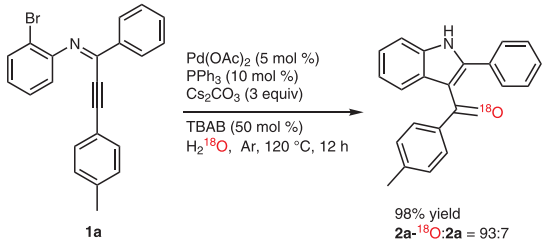
2 | RESULTS AND DISCUSSION

Initially, our initial efforts focused on optimization of the reaction conditions, using (Z)-2-bromo-N-(1-phenyl-3-(p-tolyl)prop-2-yn-1-ylidene)aniline (1a) as a model substrate (Table 1). Treatment of 1a with 10 mol% Pd $(OAc)_2$, 20 mol% PPh_3 and 3 equiv of Cs_2CO_3 in H_2O at 110 °C under argon atmosphere gave the 3-acylindoles 2a in 80% yield (Table 1, entry 1). The addition of 50 mol% of TBAB accelerated the reaction and increased the yield of 2a to 96% (Table 1, entry 3). Next, different palladium sources and additives were screened, and preliminary results showed that the use of Pd $(OAc)_2$ and TBAB gave best yield of the product (Table 1, entries 3–7). To improve the yield, the temperature was examined, resulting in the optimal one at 120 °C (Table 1, entry 3, entries 8–9). Among the bases and ligands studied, Cs_2CO_3 and PPh_3 provided the best result (Table 1, entries 9–14). Lowering the amount of the catalyst did not significantly influence the yields (Table 1, entry 16). We then probed the solvent effect and found that water as the sole solvent was superior to a mixed solvent of toluene and a small amount of water (Table 1, entries16–18). The conditions used in entry 16 were therefore the best for this reaction.

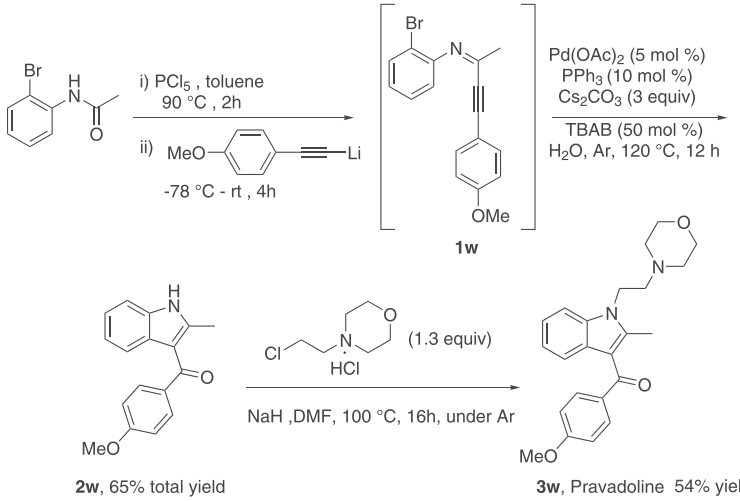
The substrate scope was investigated under the optimized conditions and the results are summarized in Table 2. A variety of *N*-(*2*-haloaryl)alkynylimine substrates, containing electronically or different substituents, were converted into the corresponding products in good to excellent yield. The effect of R^1 groups was first studied. In general, the desired products were obtained with decent yields regardless of electric effects of R^1 (Table 2, 2a-2h, 2x). However, the substrate with electron-withdrawing group such as 4-chlorophenyl gave the product 2 h in slightly lower yield. The sterically hindered substrate bearing 2-methylphenyl group gave the product 2c in relatively lower, but pretty good, yield. It is worth noting that product 2 g with thiophen-2-yl



SCHEME 1 Gram-scale preparation

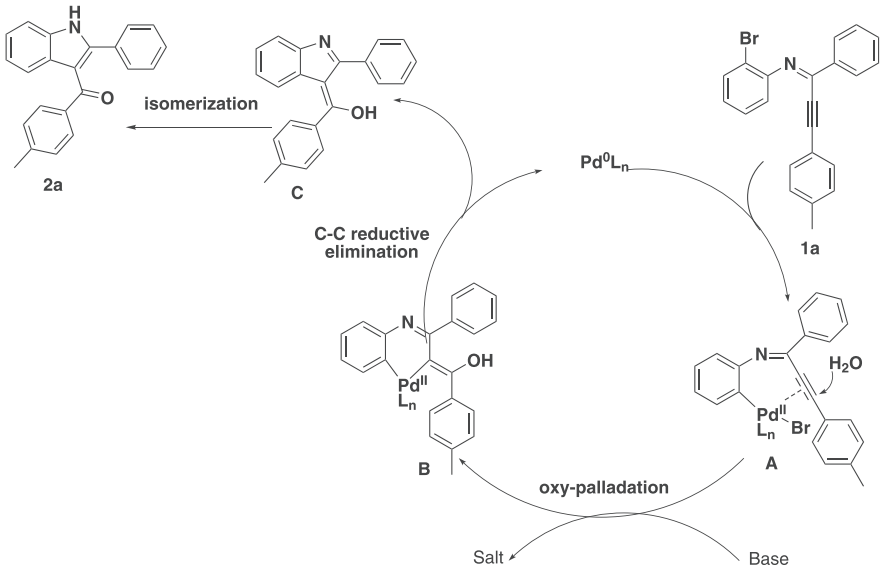


SCHEME 3 Mechanistic studies



SCHEME 2 Conversion of the product

SCHEME 4 Proposed reaction mechanism



group was generated in excellent yield and the alkyl substituted substrate 1x was converted into the corresponding product 2x in 77% of isolated yield. Then the substrates with different R^2 groups were then checked (Table 2, 2i-2p). The excellent yields of products 2i-2 k, with methyl group at different positions of R^2, indicated that the steric effect of R^2 has no obvious influence on the yield. N-(2-Haloaryl)alkynylimine bearing electron-withdrawing groups produced products 2 m and 2n in satisfactory, but slightly lower, yields. In addition, thiophen-2-yl group was also tolerated here generating 2o in 91% of isolated yield. Finally the substrates with different R^3 groups were also suitable for the reaction affording the corresponding products 2p-2v successfully in good to excellent yields.

Furthermore, the potential application of this method was illustrated by gram-scale synthesis. Under the standard conditions, the desired 3-acylindoles product 2i was obtained with a yield of 81% when the reaction was carried out at a 2.8 mmol scale (Scheme 1). Significantly, our protocol could provide a short synthesis route for Pravadoline, a phase II drug, which was recognized as a cannabinoid CB1 receptor agonist with a strong analgesic effect (IC_{50} = 4.9 μM).1h Its synthetic protocol was provided in Scheme 2. Firstly, a concise synthesis of 1w was achieved by one-pot two steps reactions from N-(2-bromophenyl)acetamide which was then converted to 2-methyl-3-acylindoles 2w in 65% total yield without isolation. Finally, Pravadoline was obtained in easily in 54% isolated yield.

We also performed labeling experiments to identify the oxygen source in product 2a (Scheme 3). The ^{18}O incorporated product 2a-^{18}O was formed with $H_2{}^{18}O$ as the solvent, and the ratio of 2a-^{18}O:2a was 93:7. It is indicated that the carbonyl oxygen originated from H_2O.

On the basis of our results and previous reports,[10,12] a plausible mechanistic pathway for the formation of 2a is depicted in Scheme 4. Initially, oxidative addition of Pd(0) to aryl halide generates arylpalladium bromide A. Under the activation of arylpalladium, the oxy-palladation of the internal alkyne with H_2O, takes place to give the six-membered palladacycle B. C-C reductive elimination regenerates the Pd(0) species and affords compound C, which isomerizes to the desired product D.

3 | CONCLUSIONS

In conclusion, we have developed an efficient strategy for the synthesis of biologically important 3-acylindoles from the *N*-(2-haloaryl)alkynylimines in water. Notably, the solvent of this cyclization reaction is water, which represents a low-cost, environmentally friendly and sustainable medium. The method shows remarkable features, including extensive substrate compatibility and gram-scale synthesis. In addition, a concise synthesis of Pravadoline, a phase II drug demonstrate the synthetic utility of this protocol.

4 | EXPERIMENTAL SECTION

4.1 | General procedure for the synthesis of 3-acylindoles

A 10 ml Schlenk-type sealed tube was charged with *N*-(2-haloaryl)alkynylimines (0.2 mmol), Pd $(OAc)_2$ (2.3 mg, 0.01 mmol, 5.0 mol %), PPh_3 (5.3 mg, 0.02 mmol, 10.0 mol %), Cs_2CO_3 (195.5 mg, 0.6 mmol, 3.0 equiv.), TBAB (32.2 mg, 0.1 mmol, 50.0 mol %) and H_2O (4.0 ml).

The reaction mixture was stirred at 120 °C for 12 hr under an argon atmosphere. After the reaction was complete, then cooled to the room temperature. The reaction mixture was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2/petroleum ether = 1/1, *v*/v) to afford the desired 3-acylindoles (data of 3-acylindoles see details in the Supporting Information).

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 21572126, 21202095, 21172139, 21271125), Program of Science and Technology Innovation Talents of Henan Province (2018JQ0011), and the Program for Science & Technology Innovation Talents in Universities of Henan Province (14HASTIT016).

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SUPPORTING INFORMATION

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How to cite this article: Zhang A-A, Meng T, Wang W, Liu X, Zhu Y, Liu L. Palladium-catalyzed cyclization reaction of N-(2-Haloaryl) alkynylimines: Synthesis of 3-acylindoles using water as the sole solvent and oxygen source. *Appl Organometal Chem*. 2020;e5513. https://doi.org/10.1002/aoc.5513