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Synthesis of Highly Substituted Isoquinolone Derivatives by Nickel-Catalyzed Annulation of 2-Halobenzamides with Alkynes

Chuan-Che Liu, Kanniyappan Parthasarathy, and Chien-Hong Cheng*

Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan

chcheng@mx.nthu.edu.tw

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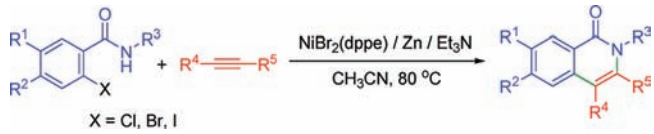
ABSTRACT



An efficient method for the synthesis of substituted 1(2*H*)-isoquinolone derivatives via nickel-catalyzed annulation of substituted 2-halobenzamides with alkynes is described. This protocol is successfully applied to the total synthesis of oxyavicine with excellent yield.

Highly substituted isoquinolones are versatile building blocks for many naturally occurring products[1a−f] and have attracted much attention due to their unique biological activities.[1g−i] Several approaches are available for the synthesis of isoquinolone derivatives such as base-promoted condensation of 2-(bromomethyl)benzonitriles,[2a] transformation of isocoumarins or 3-hydroxyphthalides,[2b] double metalation of arylbenzamides,[2c,d] and the cyclization of 2-chlorobenzonitriles with β-keto esters.[2e] In addition to these classical methods, efficient methods for the synthesis of various heterocyclic compounds catalyzed by metal complexes have been demonstrated recently.[3] A few examples of palladium-,[4a−i] copper-,[4j,k] and rhodium-catalyzed synthesis of isoquinolone derivatives were reported.[4l] An intermolecular nickel-catalyzed decarbonylation reaction of *N*-arylphthalimides with alkynes to form substituted isoquinolones was shown by Matsubara and Kurahashi in 2008.[5] At about the same time, Murakami et al. reported a nickel-

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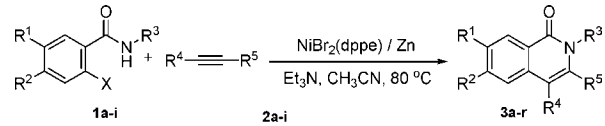
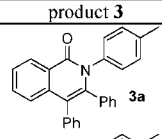
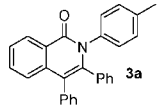
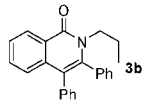
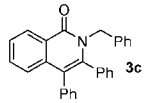
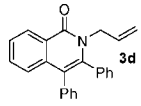
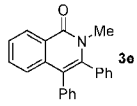
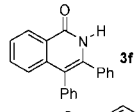
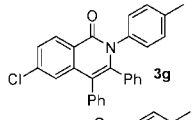
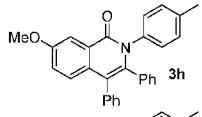
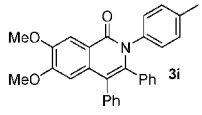
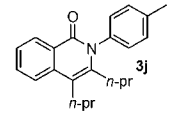
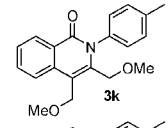
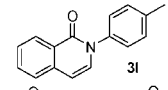
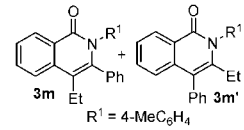
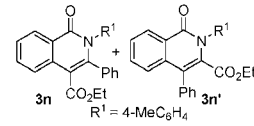
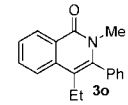
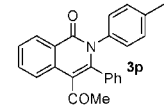
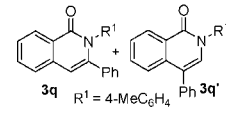
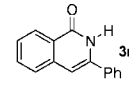
Table 1. Results of the Reaction of 2-Halobenzamides with Alkynes[a]



1a-i (R¹, R² = H)
1a: R³ = 4-MeC₆H₄, X = I
1a-Cl: R³ = 4-MeC₆H₄, X = Cl
1b: R³ = Propyl, X = I
1c: R³ = CH₂Ph, X = I
1d: R³ = Allyl, X = I
1e: R³ = Me, X = I
1f: R³ = H, X = I
X = Br, R³ = 4-MeC₆H₄
1g: R¹ = H, R² = Cl
1h: R¹ = OMe, R² = H
1i: R¹ = OMe, R² = OMe

2a-i
2a: R⁴ = Ph, R⁵ = Ph
2b: R⁴ = *n*-Pr, R⁵ = *n*-Pr
2c: R⁴ = CH₂OMe, R⁵ = CH₂OMe
2d: R⁴ = H, R⁵ = H
2e: R⁴ = Et, R⁵ = Ph
2f: R⁴ = CO₂Et, R⁵ = Ph
2h: R⁴ = COMe, R⁵ = Ph
2i: R⁴ = H, R⁵ = Ph

3a-r

entry	1	2	product 3	yield (%)[b]
1	**1a**	**2a**	 **3a**	92
2	**1a**-Cl	**2a**	 **3a**	71[c]
3	**1b**	**2a**	 **3b**	80
4	**1c**	**2a**	 **3c**	77
5	**1d**	**2a**	 **3d**	79
6	**1e**	**2a**	 **3e**	77
7	**1f**	**2a**	 **3f**	73
8	**1g**	**2a**	 **3g**	56
9	**1h**	**2a**	 **3h**	82
10	**1i**	**2a**	 **3i**	76
11	**1a**	**2b**	 **3j**	63
12	**1a**	**2c**	 **3k**	92
13	**1a**	**2d**	 **3l**	70
14	**1a**	**2e**	 **3m** **3m'** R^1 = 4-MeC₆H₄	65/13
15	**1a**	**2f**	 **3n** **3n'** R^1 = 4-MeC₆H₄	82/8
16	**1e**	**2e**	 **3o**	72
17	**1a**	**2h**	 **3p**	74
18	**1a**	**2i**	 **3q** **3q'** R^1 = 4-MeC₆H₄	67/16
19	**1f**	**2i**	 **3r**	81

[a] Unless otherwise mentioned, all reactions were carried out with 2-halobenzamide **1** (1.00 mmol), alkyne **2a** (1.50 mmol), Ni(dppe)Br_2 (5 mol %), Zn (3.00 mmol), Et_3N (2.00 mmol), and CH_3CN (3.0 mL) at 80 °C for 16 h under N_2. [b] Isolated yields. [c] Reaction was carried out for 36 h.

catalyzed synthesis of functionalized isoquinolones via denitrogenative addition of triazinones with alkynes.[6] Very recently, we observed a nickel-catalyzed reaction of 2-halobenzaldimines with alkynes to give isoquinolinium salts, which were easily converted to isoquinolones.[7g] However, the nickel catalysts used were generally air- and moisture-sensitive and must be stored under an inert atmosphere at low temperature to prevent their decomposition.

Our continued interest in the nickel-catalyzed cyclization reactions[7a−c] and synthesis of heterocyclic compounds[7d−h]

prompted us to explore the possibility of using air-stable nickel complexes as catalysts for the reaction of substituted 2-halobenzamides with alkynes. Herein, we wish to report a very efficient method for the synthesis of highly substituted isoquinolones. Moreover, the method can be used for the synthesis of isoquinolinone alkaloid natural products.

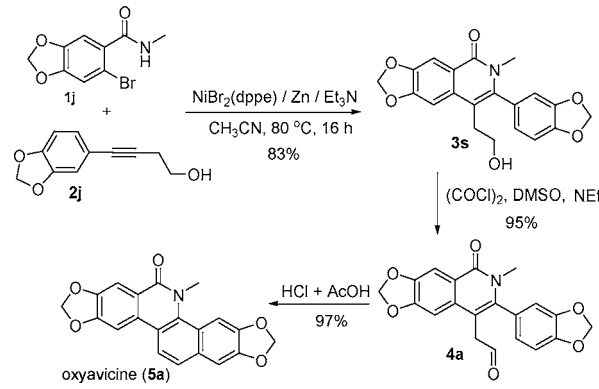
The reaction of *N*-*p*-tolyl-2-iodobenzamide **1a** with diphenyl acetylene **2a** in the presence of [Ni(dppe)Br_2], Zn, and Et_3N in acetonitrile at 80 °C for 16 h gave isoquinolone **3a** in 92% isolated yield (Table 1, entry 1). Product **3a** was thoroughly characterized by its ^1H and ^{13}C NMR and mass spectral analysis.

This nickel-catalyzed annulation reaction depends greatly on the reaction conditions. To understand the nature of this reaction and to find the optimized reaction conditions, the effect of solvent, base, and nickel complexes was examined. First, the reaction of **1a** and **2a** in acetonitrile in the presence of Et_3N but without Zn metal powder or nickel complex was carried out at 80 °C for 16 h; no **3a** was observed in both cases. Under similar reaction conditions, nickel complexes with monodentate phosphine ligands, including [Ni(PPh_3)$_2Br_2$] and [Ni(PPh_3)$_2Cl_2$], showed some catalytic activity for the reaction, giving **3a** in only 12 and 18% yield, respectively. The use of bidendate nickel complexes greatly improves the product yield. Among the complexes examined, [Ni(dppe)Br_2] was most effective for the cyclization of **1a** with **2a**, furnishing **3a** in 92% yield. Other bidendate nickel(II) systems tested, including [Ni(Phen)Cl_2], [Ni(Phen)Br_2], [Ni(Bipy)Br_2], [Ni(dppe)Cl_2], [Ni(dppf)Cl_2], [Ni(dppp)Br_2], and [Ni(dppb)Br_2], were also active, giving **3a** in 45, 62, 41, 26, 35, 57, and 53% yield, respectively. The catalytic reaction did not proceed in the absence of a base. Various bases were used for the catalytic reaction. Among them, Et_3N gave the highest product yield of 92%. Other bases are less effective, giving **3a** in lower yields. The choice of solvents is also vital to the catalytic reaction. The best solvent is acetonitrile, in which **3a** was obtained in 92% yield. THF is also effective, giving **3a** in 53% yield. Other solvents such as DCE, DMF, and toluene were less effective for the catalytic reaction (see Supporting Information for details).

Under the same reaction conditions, 2-chloro-substituted benzamide (**1a**-Cl) also reacted well with **2a** to give **3a** in 71% yield, albeit a much longer reaction time of 36 h (entry 2) was required. In addition to **1a**, various N-substituted 2-iodobenzamides (*N*-propyl, **1b**; *N*-benzyl, **1c**; *N*-allyl, **1d**; *N*-methyl, **1e**) were tested for the reaction with **2a**, affording the corresponding N-substituted isoquinolones, **3b**−**e**, in 77−80% yield (entries 3−6). Interestingly, the nonsubstituted 2-iodobenzamide **1f** also reacted efficiently with **2a** to afford isoquinolone derivative **3f** in 75% yield (entry 7). In a similar fashion, *o*-bromobenzamides **1g**−**i** having 4-chloro, 5-methoxy, and 4,5-dimethoxy substituents on the aryl ring underwent cyclization with diphenyl acetylene **2a** smoothly to give the corresponding isoquinolones **3g**−**i** in moderate to good yields (entries 8−10). The present catalytic reaction was also successfully extended to aliphatic alkynes **2b**−**d**. Thus, **1a** reacted with oct-4-yne (**2b**) to give isoquinolone derivative **3j** in 63% yield (entry 11). In a similar manner, the reaction of 1,4-dimethoxy-2-butyne (**2c**) and acetylene gas (**2d**) with **1a** gave isoquinolones **3k** and **3l** in 92 and 70% yield, respectively (entries 12 and 13). To understand the regioselectivity of the present reaction, unsymmetrical alkynes **2e**−**h** were investigated. Thus, 1-phenyl-1-butyne (**2e**) and phenylpropiolate **2f** underwent cyclization successfully with **1a** to give regioisomeric products **3m** and **3m′** in 65 and 13% yield and **3n** and **3n′** in 82 and 8% yield, respectively (entries 14 and 15). In contrast, *N*-methyl *o*-iodobenzamide (**1e**) reacted with **2e**, affording regioisomer **3o** exclusively in 72% yield (entry 16). The regiochemistry of these isoquinolone isomers was confirmed by NOE experiments. Similarly, 4-phenyl-3-butyn-2-one (**2h**) also reacted with **1a** in a highly regioselective manner, providing isoquinolone derivative **3p** exclusively in 74% yield (entry 17). Encouraged by the above results, terminal alkynes were tested for the present cyclization reaction. Thus, phenylacetylene **2i** reacted well with **1a** to give regioisomeric products **3q** and **3q′** in 67 and 16% yield, respectively (entry 18). However, the reaction of 2-iodobenzamide **1f** with **2g** gave a single regioisomeric product **3r** in 81% yield (entry 19).

The significance of this nickel-catalyzed annulation reaction is demonstrated by its application to the total synthesis of isoquinolinone alkaloid natural products. The synthesis of oxyavicine using this methodology is shown in Scheme 1. Thus,

Scheme 1. Application of Total Synthesis of Oxyavicine

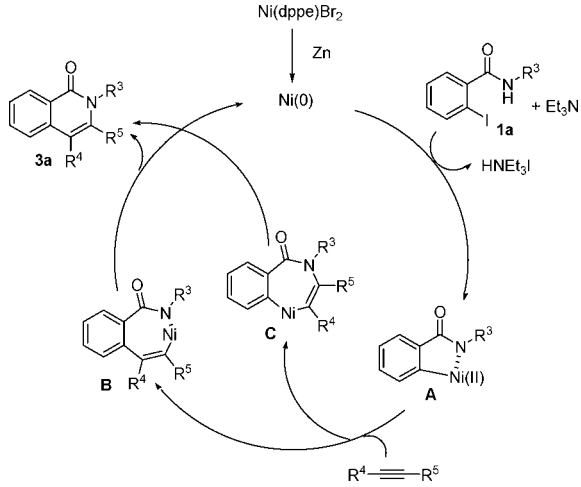


the reaction of benzamide **1j** with alkyne **2j** in the presence of [Ni(dppe)Br_2], Zn, and Et_3N in acetonitrile at 80 °C for 16 h provided isoquinolone derivative **3s** in 83% yield in a highly regioselective manner. No other regioisomer of **3s** was detected in this catalytic reaction. The regiochemistry of product **3s** was confirmed by NOE experiments. We then converted this isoquinolone intermediate to the corresponding aldehyde derivative **4a** in 95% yield by Swern oxidation.[8] After a successful acid-catalyzed ring-closing and dehydration reaction, we obtained oxyavicine (**5a**) in 97% yield. The procedure in Scheme 1 appears to be the most efficient method for the synthesis of oxyavicine, affording a total of 76% yield starting from **1j** and **2j**. Both **1j** and **2j** can be prepared in essentially quantitative yield from amidation of the corresponding acid of **1j** and the Sonogashira reaction of commercially available 5-bromobenzo[*d*][1,3]dioxole and 3-butyn-1-ol, respectively.[7g,9] It is

interesting to note that this natural product has exhibited analgesic and anti-inflammatory effects in the biological evaluation.[10] There are many isoquinolinone alkaloids existing in nature with a similar core structure as oxyavicine. As a result, the methodology shown in Scheme 1 should be very useful for the synthesis of these alkaloids.

On the basis of the known metal-catalyzed cyclization reactions and synthesis of heterocyclic compounds,[5−7] a possible reaction mechanism is proposed to account for the present nickel-catalyzed reaction (Scheme 2). The reaction

Scheme 2. Proposed Mechanism for the Cyclization Reaction of 2-Halobenzamides with Alkynes



likely starts with the reduction of Ni(II) to Ni(0) by zinc powder. The oxidative addition of 2-iodobenzamide **1a** to Ni(0) in the presence of Et_3N leads to the formation of a five-membered ring nickelacycle **A**. Coordinative insertion of alkyne into the nickelacycle to give seven-membered ring nickelacycle intermediates **B** and **C**. Reductive elimination of **B** and **C** affords the final isoquinolinone **3a** and the regeneration of the Ni(0) catalyst for the next catalytic cycle. There are two possible pathways for the insertion of a coordinated alkyne into nickelacycle **A**. We propose that a carbon−carbon triple bond can insert into the carbon−nickel bond or the nitrogen−nickel linkage in **A** depending on the nature of the alkynes.[7d,g]

In conclusion, we have demonstrated an easy and convenient nickel-catalyzed annulation of substituted 2-halobenzamides with alkynes to give the corresponding isoquinolinone in good yields. The present protocol is successfully applied to the total synthesis of oxyavicine with excellent yield. Further applications of this methodology in natural product synthesis are in progress.

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Supporting Information Available: General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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