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# Nickel-Catalyzed Cyclization of 2-Iodoanilines with Aroylalkynes: An Efficient Route for Quinoline Derivatives

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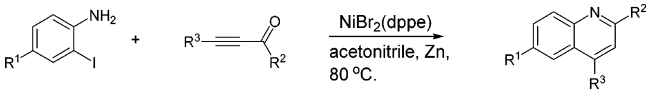
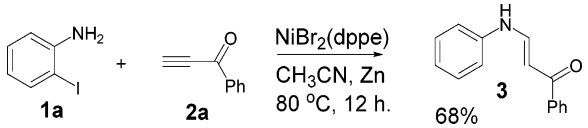



An efficient and convenient nickel-catalyzed cyclization of 2-iodoanilines with alkynyl aryl ketones to give 2,4-disubstituted quinolines was developed. The reaction can be employed for the synthesis of naturally occurring quinoline derivatives in good yields. On the basis of the regiochemistry of the products, the possible pathway for the reaction is via the formation of *o*-aminochalcone.

Quinolines are widely occurring natural alkaloids known to display a wide variety of pharmacological properties such as anesthetic, tumorcidal, angina pectoris, antihypertensive, and antibacterial activities and also act as insecticidal agents.[1] In addition, these compounds are well-known ligands for the preparation of OLED phosphorescent complexes.[2] Development of new synthetic methods for quinoline derivatives are in great demand because of the rise of the resistance level of malarial parasite in the use of Chloroquine, a widely used malarial drug.[1a] There are several synthetic methods[3,1a] available for the preparation of quinolines. The most popular method is the two-step Friedlander synthesis[4] based on Aldol condensation of unstable 2-aminobenzaldehydes generated in situ by reduction of 2-nitrobezaldehydes with ketones. This method is seriously limited by the availability of 2-nitrobenzaldehyde derivatives. Another crucial problem is the poor regioselectivity that often leads to isomers. Other methods generally require the use of strong acids, high temperature, and tedious reaction procedures and suffer from poor selectivity. Recently, several reports of transition metal-catalyzed synthesis of quinolines have appeared.[5] These included rhodium-catalyzed[5b,c] cyclization of anilines with styrenes and cyclization of trifluoroacetimidoyl chloride with alkynes and also the intramolecular cyclization of alkynyl imines catalyzed by tungsten carbonyl.[5d] In most of these cases, the regioselectivity and the scope of functionality on the quinolines are limited.

**SCHEME 1**




Our interests in developing new synthetic strategies using nickel catalysts[6,7] recently made possible the development of an efficient route for the preparation of isoquinolines and pyridines by the reaction of 2-iodobenzaldimines and 3-iodo-3-phenylacrylaldimines with alkynes, respectively. Herein, we wish to report a new convenient nickel-catalyzed synthesis of 2,4-disubstituted quinolines using the easily available 2-iodoanilines and 1-benzoylalkynes[8] as the starting materials under neutral conditions. The method for 2,4-disubstituted quinolines is important as most of the available methods are for the preparation of 2,3-disubstituted quinolines.

When 2-iodoaniline (**1a**) was treated with 1-benzoylethyne (**2a**) in the presence of $NiBr_2$(dppe) and zinc metal powder in acetonitrile, Michael addition-deiodination product **3** was obtained in 68% yield (Scheme 1). No expected quinoline was observed in this case. Fortunately, the use of internal alkyne, 1-benzoyl phenyl acetylene (**2b**), with **1a** in the presence of $NiBr_2$(dppe) and zinc metal powder in acetonitrile at 80 °C for 12 h gave the corresponding 2,4-diphenylquinoline (**4a**) in 56% yield (Table 1). Control experiments showed that in the absence of either nickel catalyst or zinc metal, no quinoline **4a** was observed.

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**TABLE 1. Effect of the Catalyst and Solvent on the Synthesis of 4a from 1a and 2b[a]**

| entry[b] | catalyst | yield (%) | entry | catalyst | yield (%) |
|---|---|---|---|---|---|
| 1 | $NiBr_2$(dppe), $CH_3CN$ | 56 | 8 | $CoI_2$(dppe), $CH_3CN$ | 0 |
| 2 | $NiBr_2(PPh_3)_2$, $CH_3CN$ | 31 | 9 | $CoI_2$(dppe), $CH_3CN$, $H_2O$ | 0 |
| 3 | $NiBr_2$(dppm), $CH_3CN$ | trace | 10 | $PdCl_2(PPh_3)_2$, $CH_3CN$ | 0 |
| 4 | $NiBr_2$(dppp), $CH_3CN$ | trace | 11 | $Pd(PPh_3)_4$, DMF | 0 |
| 5 | $NiBr_2$(dppe), THF | 0 | 12 | $NiBr_2$(dppe), $CH_3CN$ | 83 |
| 6 | $NiBr_2$(dppe), *o*-xylene | 0 | 13 | $NiBr_2(PPh_3)_2$, $CH_3CN$ | 46 |
| 7 | $NiBr_2$(dppe), DMF | 12 | | | |

[a] All the reactions except in entries 12 and 13 were carried out in nitrogen atmosphere using **1a**, (0.10 mmol), alkyne **2b** (0.10 mmol), metal complex (0.0050 mmol), and Zn (0.20 mmol) in the solvent mentioned in each entry (3.0 mL) at 80 °C for 12 h. All the yields mentioned above are NMR yields using mesitylene as an internal standard. The reactions in DMF were followed by workup with aq $NH_4Cl$ solution to remove DMF. [b] An amount of 2 equiv of alkyne **2b** was used in entries 12 and 13.

To improve the product yield of the present catalytic reaction, the reaction conditions including the catalyst, solvent, and the ratio of the reagents used were varied. In addition to $NiBr_2$(dppe), other bidentate phosphine nickel complexes including $NiBr_2$(dppm) and $NiBr_2$(dppp) were tested giving **4a** in only a trace amount (Table 1). Monodentate phosphine nickel complex $NiBr_2(PPh_3)_2$ was also tested for the reaction affording **4a** in 31% yield. The use of $CoI_2$(dppe), $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$ as catalysts for the reaction of **1a** with **2b** showed no product formation, and the starting materials **1a** and **2b** were recovered. The yield of product **4a** for the reaction of **1a** with **2b** in the presence of $NiBr_2$(dppe) and zinc was further improved to 83% by using 2 equiv of alkyne **2b** (46% for $NiBr_2(PPh_3)_2$). The reaction of **1a** with **2b** in various solvents was investigated. Product **4a** was observed in $CH_3CN$ and DMF in 83 and 16% yields, respectively. In THF and *o*-xylene, the reaction did not yield the expected product **4a**. On the basis of the above studies, the reaction conditions using Ni(dppe)$Br_2$ in the presence of zinc at 80 °C in acetonitrile with 2 equiv of alkyne appeared to give the best yield of **4a** and were employed as the standard reaction conditions for other substrates shown in Table 2.

We next explored the scope and the possible mechanism of this nickel-catalyzed cyclization reaction. The product yields with various 2-haloanilines and aroylalkynes are summarized in Table 2. Similar to 2-iodoaniline, the corresponding 2-bromoaniline underwent cyclization with **2b** to give product **4a**, but in a lower yield of 48% (entry 2). Under the standard reaction conditions, 1-benzoyl-1-hexyne (**2c**) reacts smoothly with 2-iodoaniline (**1a**) to give 4-butyl-2-phenylquinoline (**4b**) in 86% yield (entry 3). The structure of **4b** was carefully assigned based on the NOE, $^1H$, and $^{13}C$ experimental data. The results clearly demonstrate that the phenyl group in **2c** is attached to the 2nd position of quinoline **4b** and the butyl group occupies the 4th position of the quinoline. The bulkier naphthoyl phenyl acetylene **2d** also reacted with **1a** to give **4c** in moderate yield of 59%.

The catalytic reaction also proceeded smoothly with 2-iodoanilines possessing various substituents. Iodoaniline derivative **1c** having a 4-methyl substituent reacted with alkyne **2b** to yield quinoline **4d** in excellent yield (91%, entry 5). Similarly, the reaction of **1c** with alkyne **2c** under the same conditions yielded quinoline **4e** in 76% yield (entry 6). Iodoaniline derivative **1d** having a para-substituted electron-withdrawing chloro group **1d** also reacted successfully with **2b** to give the corresponding cyclized product **4f** in good yield. In a similar manner, **1d** underwent cyclization with **2c** to give quinoline derivative **4g** in 83% yield. A key reason for the selection of halogen-substituted anilines as substrates for the present catalytic reaction is that the halogen-substituted derivatives of quinoline are of great interest[9,10] in medicinal chemistry. The catalytic reaction was successfully extended to 4-trifluoromethyl-2-iodoaniline **1e** with alkynes. The reaction of **1e** with alkyne **2b** and **2c** gave **4h** and **4i** in 68 and 87% yields, respectively. The structure of **4i** was determined by single-crystal X-ray diffraction. Finally, we also tested the reactivity of alkanoylalkyne for the present catalytic reaction. Under the standard conditions, acetyl-1-propyne (**2e**) successfully underwent cyclization with **1d** to give the corresponding quinoline **4j** albeit in a lower yield (56%).

The utility of this novel cyclization was further demonstrated by the synthesis of naturally occurring alkaloids **4m** and **4n** (Scheme 2). Under the standard conditions, treatment of 2-iodoaniline with piperonyloyl trimethylsilyl acetylene (**2f**) yields the corresponding quinoline **4k** in 79%. Dubamine[11a−c] (**4m**) was obtained by the cleavage of trimethylsilyl group in **4k** with TBAF at 60 °C in THF. In a similar manner **4l** was obtained in 74% yield using **1a** and alkyne **2g**, and the corresponding 2-phenylquinoline[11d] (**4n**) was obtained by further desilylation. These molecules have shown significant biological properties[10e] such as antioxidant, antiprotozoal, and cytotoxicity activities.

An intriguing feature of the present catalytic reaction is that the 1-aroylalkynes should be disubstituted in order for the catalytic reaction to proceed to obtain the quinoline products. Monosubstituted 1-aroylalkyne gave the hydroamination-dehalogenation product on reacting with 2-iodoaniline. Thus, the presence of a second substituent on the alkynyl group in 1-aroylalkynes appears to effectively block the attack of amino group in **1** at the $\beta$-alkynyl carbon. This is further evident by the results of reactions in Table 2 in which no hydroamination products were observed. Also in the reaction of **1a** with **2b** (Table 1) where no expected product **4a** was formed, there was no hydroamination product observed after heating the solution at 80 °C for 12 h; only the starting materials were recovered.

To explain how the nickel system catalyzes the present quinoline formation reaction, we propose the mechanism as shown in Scheme 3. The catalytic cycle is likely initiated by the reduction of Ni(II) to Ni(0) by zinc metal powder. The

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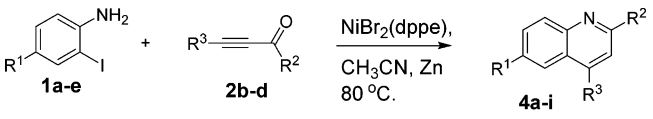
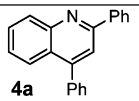
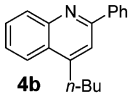
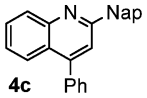
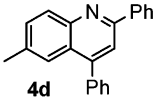
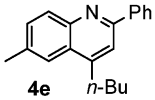
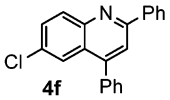
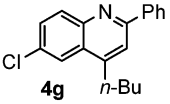
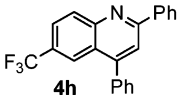
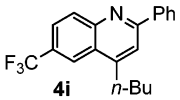
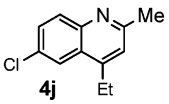
**TABLE 2. Nickel-Catalyzed Synthesis of Quinolines from 2-Iodoanilines and Aroylalkynes**[a]




**1a-e** **2b-d** **4a-i**

**1a**: $R^1$ = H, X = I
**1b**: $R^1$ = H, X = Br
**1c**: $R^1$ = Me, X = I
**1d**: $R^1$ = Cl, X = I
**1e**: $R^1$ = $CF_3$, X = I.

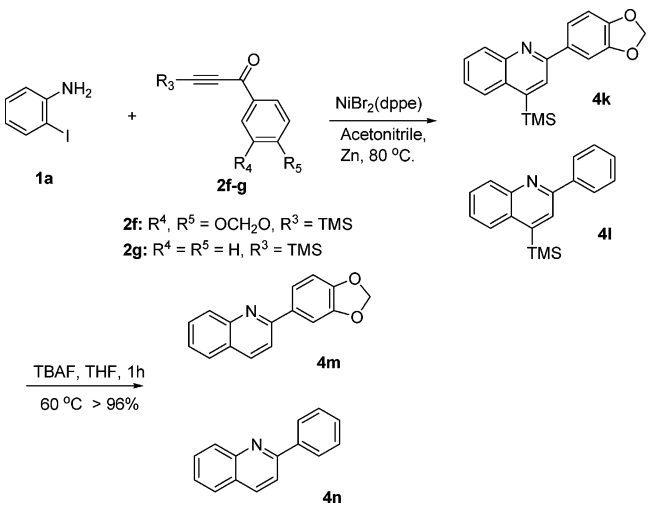
**2b**: $R^2$ = $R^3$ = Ph
**2c**: $R^2$ = Ph, $R^3$ = *n*-Bu
**2d**: $R^2$ = Naphthyl, $R^3$ = Ph
**2e**: $R^2$ = Me, $R^3$ = Et

| entry | 2-iodoaniline derivative | alkyne | product | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | **2b** |  **4a** | 74 (83)[c] |
| 2 | **1b** | **2b** | **4a** | 48 |
| 3 | **1a** | **2c** |  **4b** | 86 |
| 4 | **1a** | **2d** |  **4c** | 59 |
| 5 | **1c** | **2b** |  **4d** | 91 |
| 6 | **1c** | **2c** |  **4e** | 76 |
| 7 | **1d** | **2b** |  **4f** | 71 |
| 8 | **1d** | **2c** |  **4g** | 83 |
| 9 | **1e** | **2b** |  **4h** | 68 |
| 10 | **1e** | **2c** |  **4i** | 87 |
| 11 | **1d** | **2e** |  **4j** | 56 |

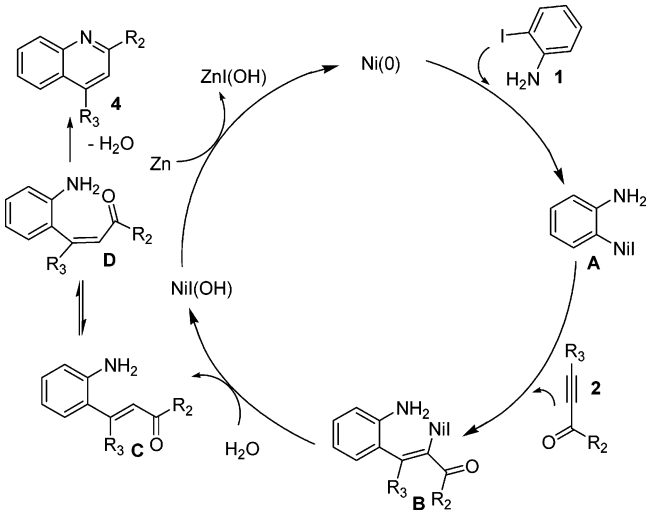
[a] All reactions were carried out under nitrogen atmosphere using **1** (0.10 mmol), alkyne (**2**, 0.20 mmol), $NiBr_2$(dppe) (0.0050 mmol), and Zn (0.20 mmol) in $CH_3CN$ (3.0 mL) at 80 °C for 12 h. [b] Isolated yields. [c] Measured by $^1H$ NMR using mesitylene as an internal standard.

oxidative addition of 2-iodoaniline to Ni(0) species affords an *o*-metalated aniline nickel complex **A**. Coordination of alkyne

**SCHEME 2**




**SCHEME 3**




and insertion of this alkyne into Ni-carbon bond of **A** generates intermediate **B**. Subsequent protonation with water yields amino chalcone **C** and a Ni(II) species. Further reduction of the Ni(II) species by zinc regenerates the catalyst Ni(0) along with a zinc-(II) derivative. The keto group and the *o*-amino group in the obtained amino chalcone **C** is expected to be trans to each other after protonation of intermediate **B**. Thus, trans to cis isomerization to yield *cis*-amino chalcone **D** should occur. Further condensation between the keto and the amino groups yields the final product **4**. The water thus generated is utilized in the protonation process of intermediate **B**. The pathway for the isomerization of α,*β*-unsaturated carbon−carbon double bond in **C** is not clear. A possible one is via a reversible addition of a base such as water, hydroxide, or the nearby amino group to the *β*-carbon of the α,*β*-unsaturated carbon−carbon double bond to give an anionic intermediate, followed by C−C bond rotation and elimination of the base. Such isomerization of α,*β*-unsaturated carbon−carbon double bonds before ring closure has been observed previously by us.[6c,12]

The other pathways with the keto group of **2** first undergoing condensation with the amino group in **1** to form an imine intermediate, followed by oxidative addition, insertion and protonation cannot be excluded totally.

In conclusion, we have demonstrated a new convenient synthetic approach for the preparation of 2,4-disubstituted quinolines. This nickel-catalyzed reaction is interesting, since most of the synthetic methods available are for the preparation of 2,3-disubstituted quinolines. The method tolerates a range of functional groups and utilizes nonexpensive catalysts and easily available reagents. We have prepared halogen derivatives which are of particular interest in medicinal chemistry. The possibility of application in the synthesis of naturally occurring alkaloids by the present method is described.

## Experimental Section

**General Procedure for the Preparation of Quinolines. Synthesis of 2,4-Diphenylquinoline (4a).** A round-bottom sidearm flask (25 mL) containing $NiBr_2$(dppe) (3.1 mg, 0.0050 mmol), 2-iodoaniline (**1a**) (0.10 mmol), alkyne **2b** (0.20 mmol), and zinc powder (13 mg, 0.20 mmol) was subjected to the Schlenk-line procedures of evacuation and purging of nitrogen for three cycles. Freshly distilled acetonitrile (3.0 mL) was added to the reaction system, and the reaction mixture was stirred at 80 °C for 12 h. Then the reaction mixture was cooled to room temperature and diluted with dichloromethane. The mixture thus obtained was filtered through a silica gel pad and washed thoroughly with dichloromethane. The filtrate was concentrated in a rotary evaporator, and the residue was separated on a silica gel column using a mixture of hexanes and ethyl acetate as eluent to afford the desired pure product **4a** in 74% yield. White solid. Mp = 102 °C. $R_f$ = 0.57 (10% ethyl acetate in hexanes). $^1$H NMR $\delta$: 7.44−7.48 (m, 2H), 7.50−7.57 (m, 7H), 7.72 (t, $J$ = 7.5 Hz, 1H), 7.81 (s, 1H), 7.90 (d, $J$ = 3.0 Hz, 1H), 8.18 (d, $J$ = 8.0 Hz, 2H), 8.24 (d, $J$ = 9.0 Hz, 1H). $^{13}$C NMR $\delta$: 119.4, 125.6, 125.8, 126.3, 127.6, 128.4, 128.6, 128.8, 129.3, 129.5, 129.6, 130.1, 138.4, 139.7, 148.8, 149.2, 156.9. HRMS (EI+): 281.1195 (calcd for $C_{21}H_{15}N$, 281.1204). IR: 1357, 1489, 1590, 3053 cm$^{-1}$.

**4-Butyl-2-phenylquinoline (4b).** Alkyne **2c** was used to prepare this material using the same procedure described for **4a**. After chromatography, the compound was dried under vacuum to yield **4b** (86%). Viscous liquid. $R_f$ = 0.60 (10% ethyl acetate in hexanes). $^1$H NMR $\delta$: 0.98 (t, $J$ = 7.0 Hz, 3H), 1.46−1.50 (m, 2H), 1.75−1.80 (m, 2H), 3.12 (t, $J$ = 7.8 Hz, 2H), 7.44 (t, $J$ = 6.8 Hz, 1H), 7.49−7.53 (m, 3H), 7.67−7.70 (m, 2H), 8.03 (d, $J$ = 8.5 Hz, 1H), 8.13 (d, $J$ = 8.5 Hz, 2H), 8.18 (d, $J$ = 8.0 Hz, 1H). $^{13}$C NMR $\delta$: 13.9, 22.8, 32.3, 32.3, 118.8, 123.4, 126.0, 126.6, 127.6, 128.5, 128.8, 129.2, 130.4, 139.9, 148.4, 149.4, 157.1. HRMS (EI$^+$): 261.1512 (calcd for $C_{19}H_{19}N$, 261.1517). IR: 1353, 1447, 1551, 1597, 2957 cm$^{-1}$.

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**Supporting Information Available:** Experimental procedures, spectral data and $^1$H and $^{13}$C NMR spectra of all compounds, CIF of compound **4i** and NOE data of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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