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ISOINDOLONE SYNTHESIS VIA INTRAMOLECULAR COUPLING OF BENZYLIC C-H BONDS WITH AMIDE N-H BONDS

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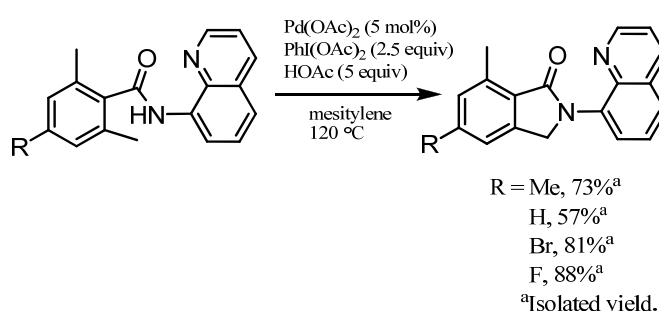
Abstract – Four 7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-ones were synthesized from 2,6-dimethyl-N-(8-quinolinyl)benzamides with excellent yields using Pd(OAc)₂ as a catalyst, iodobenzene as an oxidant and AgOAc as an additive.

Construction of heterocyclic scaffolds via C-H functionalization is an important strategy in heterocycle synthesis.^{1,2} In 2011, Chen³ and Daugulis⁴ reported independently a picolinamide directed intramolecular coupling of a sp³ C-H bond with a N-H bond, affording effectively four-, five-, and six-membered heterocycles. In 2013, Chen⁵ reported palladium-catalyzed 8-aminoquinoline carboxamide directed intramolecular amination of C(sp³)-H and C(sp²)-H bonds, constructing pyrrolidones and indolinones. In the same time, we also found palladium-catalyzed 8-aminoquinoline carboxamide directed intramolecular amination of C(sp³)-H bonds, affording a series of isoindolones.⁶ Recently, copper-catalyzed methods were reported,⁷ in which 8-aminoquinoline carboxamides were also used as directing groups, forming β-lactams via C(sp³)-H functionalization.

We are interested in C(sp³)-H functionalization. We reported synthesis of four 7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-ones from 2,6-dimethyl-N-(8-quinolinyl)benzamides via intramolecular direct amination of benzylic C-H bonds (Scheme 1).⁶ Based on previous work (Scheme 1),⁶ we intend to effect arylation/oxidation of benzylic C-H bonds with 2,6-dimethyl-N-(8-quinolinyl)benzamides as substrates according to literature methods,⁸ we obtained the cyclization products via intramolecular C-N coupling rather than arylation products (Scheme 2). Given

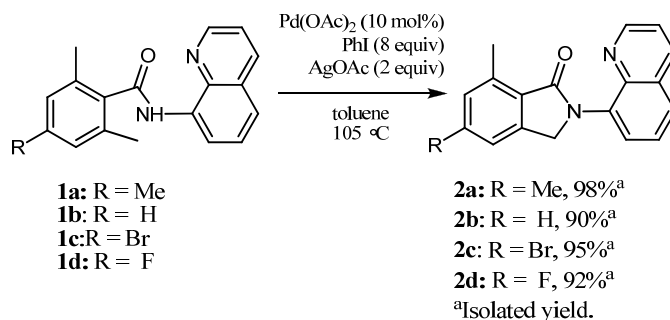
the isoindolone is an effective moiety in some medicines,⁹ the synthesis of their derivatives is important. In this paper, four 7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-ones were synthesized with excellent yields (90-98%) using Pd(OAc)₂ (10 mol%) as a catalyst, iodobenzene as an oxidant and AgOAc as an additive. The cyclization reactions did not occur in the absence of PhI or AgOAc. The amides **1e** and **1f** (Scheme 3) did not undergo the intramolecular cyclization under the reaction conditions as in Scheme 2. Under the reaction conditions, the amide **1e** probably formed a five-membered cyclometalated aryl-Pd(II) complex from sp² C-H activation on the benzene ring of the carboxylic acid, which probably is a stable intermediate. In this case, benzylic C-H activation did not occur.

Our previous work⁶:

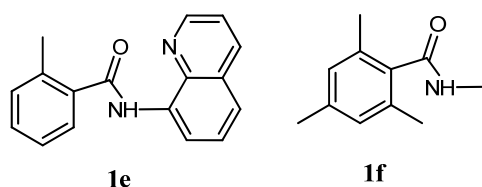


Scheme 1

This work:



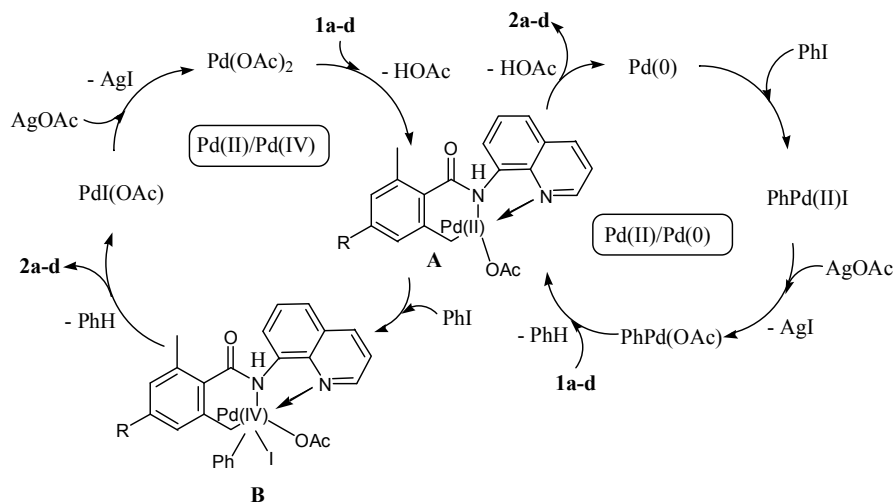
Scheme 2



Scheme 3

A possible mechanism involves benzylic C-H activation of **1a-d** to produce intermediate **A** (Scheme 4),⁶ then oxidative addition of **A** with PhI producing Pd(IV) species **B**, and reductive elimination to give the

product and Pd(II) so completing the catalytic cycle (Scheme 4). A Pd(II)/Pd(0) catalytic cycle is also possible. Reductive elimination of intermediate **A** gives the product and Pd(0), oxidation of Pd(0) to Pd(II) is effected by the oxidative addition of Pd(0) with PhI, and completing the catalytic cycle.



Scheme 4

In conclusion, we developed a new efficient method for synthesis of isoindolones, that is palladium-catalyzed 8-aminoquinoline carboxamide directed intramolecular amination of benzylic C-H bonds. It doesn't need an acidic additive, and yields are excellent (90-98%).

EXPERIMENTAL

Amides **1a-f** were prepared according to our previous methods.⁶ All reactions were performed under the atmosphere of nitrogen. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer with TMS as the internal standard and CDCl₃ as solvent. ¹⁹F NMR spectra were determined on a Bruker Avance 500 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Waters Micromass GCT Premier spectrometer.

General procedure for synthesis of 7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-ones (**2a-d**).

To a tube were added an amide **1** (0.138 mmol), Pd(OAc)₂ (10 mol%), PhI (8 equiv), AgOAc (2 equiv) and toluene (1 mL), then the reaction mixture was heated under an N₂ atmosphere at 105 °C for 24 h. After cooling to rt, the mixture was concentrated in vacuo, and the residue was purified by flash column chromatography with petroleum ether–EtOAc (3:1 for **2a**, and 4:1 for **2b-2d**) as the eluent to afford the product. The product crystals were obtained by recrystallization with a mixed solvent of hexane and EtOAc.

5,7-Dimethyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-one (2a)⁶: pale yellow solid; mp 166-168 °C (lit.⁶, 166-168 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.44 (s, 3H, Me), 2.75 (s, 3 H, Me), 5.18 (s, 2 H, CH₂), 7.07 (s, 1 H, ArH), 7.14 (s, 1 H, ArH), 7.41 - 7.44 (m, 1 H, ArH), 7.62 (t, *J* = 8 Hz, 1 H, ArH), 7.82 (app. d, *J*_{app.} = 8 Hz, 1 H, ArH), 7.91 (app. d, *J*_{app.} = 7.2 Hz, 1 H, ArH), 8.20-8.22 (m, 1 H, ArH), 8.87 - 8.89 (dd, *J* = 4, 1.6 Hz, 1 H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ = 17.38, 21.81, 53.09, 120.60, 121.44, 126.35, 127.12, 127.31, 128.90, 129.47, 130.96, 135.84, 136.42, 137.98, 141.87, 143.52, 144.51, 149.92, 169.73. HRMS (EI): *m/z* [M⁺] calcd for C₁₉H₁₆N₂O: 288.1263; found: 288.1265.

7-Methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-one (2b)⁶: colorless solid; mp 169-170 °C (lit.⁶, 169-170 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.79 (s, 3H, Me), 5.23 (s, 2 H, CH₂), 7.24 (m, 1 H, ArH), 7.33 (app. d, *J*_{app.} = 7.6 Hz, 1 H, ArH), 7.41 - 7.49 (m, 2 H, ArH), 7.61-7.65 (m, 1 H, ArH), 7.82-7.84 (dd, *J* = 8.4, 1.2 Hz, 1 H, ArH), 7.91-7.93 (dd, *J* = 7.6, 1.2 Hz, 1 H, ArH), 8.20-8.23 (m, 1 H, ArH), 8.88-8.89 (dd, *J* = 4, 1.6 Hz, 1 H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ = 17.41, 53.21, 120.12, 121.35, 126.38, 127.44, 128.88, 129.49, 129.63, 129.86, 131.28, 135.79, 136.35, 138.35, 143.07, 144.50, 150.00, 169.63. HRMS (EI): *m/z* [M⁺] calcd for C₁₈H₁₄N₂O: 274.1106; found: 274.1108.

5-Bromo-7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-one (2c)⁶: pale yellow solid; mp 245-246 °C (lit.⁶, 245-246 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.75 (s, 3H, Me), 5.20 (s, 2 H, CH₂), 7.40 - 7.43 (m, 2 H, ArH), 7.48 (s, 1 H, ArH), 7.60-7.64 (m, 1 H, ArH), 7.81-7.83 (dd, *J* = 8, 1.2 Hz, 1 H, ArH), 7.89-7.91 (dd, *J*₁ = 7.6, 1.2 Hz, 1 H, ArH), 8.19-8.21 (m, 1 H, ArH), 8.86-8.87 (dd, *J* = 4, 1.6 Hz, 1 H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ = 17.18, 52.73, 121.45, 123.46, 125.85, 126.37, 127.62, 128.68, 128.84, 129.47, 132.94, 135.28, 136.39, 140.20, 144.32, 144.81, 150.08, 168.75. HRMS (EI): *m/z* [M⁺] calcd for C₁₈H₁₃⁷⁹BrN₂O: 352.0211; found: 352.0212.

5-Fluoro-7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-one (2d)⁶: colorless solid; mp 178-179 °C (lit.⁶, 178-179 °C). ¹H NMR (400 MHz, CDCl₃): δ = 2.77(s, 3H, Me), 5.20 (s, 2 H, CH₂), 6.94-7.01 (m, 2 H, ArH), 7.40-7.43 (m, 1 H, ArH), 7.61 (t, *J* = 8 Hz, 1 H, ArH), 7.81 (app. d, *J*_{app.} = 7.6 Hz, 1 H, ArH), 7.90 (app. d, *J*_{app.} = 7.6 Hz, 1 H, ArH), 8.18-8.21 (m, 1 H, ArH), 8.86-8.88 (m, 1 H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ = 17.43, 52.99 (d, ⁴*J*_{F-C} = 2.8 Hz), 107.34 (d, ²*J*_{F-C} = 23.7 Hz), 117.20 (d, ²*J*_{F-C} = 22.3 Hz), 121.40, 125.77, 126.39, 127.49, 128.82, 129.49, 135.45, 136.39, 141.22 (d, ³*J*_{F-C} = 9.3 Hz), 144.40, 145.49 (d, ³*J*_{F-C} = 10.5 Hz), 150.03, 163.56, 167.36 (d, ¹*J*_{F-C} = 262 Hz). ¹⁹F NMR (470 MHz, CDCl₃): δ = - 108.19. HRMS (EI): *m/z* [M⁺] calcd for C₁₈H₁₃FN₂O: 292.1012; found: 292.1008.

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