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

Ming Zhang,* Tianbao Chen, and Qinhua Liu

College of Chemistry and Key Laboratory of Functional Small Organic Molecule, Ministry of Education, Jiangxi Normal University (Yaohu campus), 99 Ziyangdadao, Nanchang, Jiangxi 330022, China

*Corresponding author: Ming Zhang. *Tel +86 (0791)18979135351; E-mail address*: zmchem@163.com

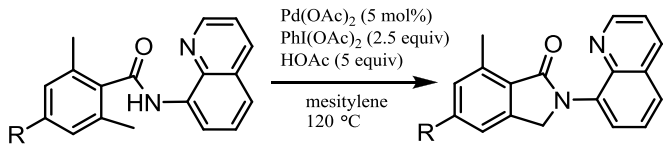
Abstract – Four 7-methyl-2-(8-quinolinyl)-2,3-dihydro-1H-isoindol-1-ones were synthesized from 2,6-dimethyl-N-(8-quinolinyl)benzamides with exellent yields using $Pd(OAc)_2$ as a catalyst, iodobenzene as an oxidant and AgOAc as an additive.

Construction of heterocyclic scaffolds via C-H functionalization is an important strategy in heterocycle synthesis.[1,2] In 2011, Chen[3] and Daugulis[4] reported independently a picolinamide directed intramolecular coupling of a sp^3 C-H bond with a N-H bond, affording effectively four-, five-, and six-membered heterocycles. In 2013, Chen[5] reported palladium-catalyzed 8-aminoquinoline carboxamide directed intramolecular amination of $C(sp^3)$–H and $C(sp^2)$–H bonds, constructing pyrrolidones and indolinones. In the same time, we also found palladium-catalyzed 8-aminoquinoline carboxamide directed intramolecular amination of $C(sp^3)$–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 $C(sp^3)$-H functionalization.

We are interested in $C(sp^3)$-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 intent 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 same 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 exellent 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 sp^2 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.

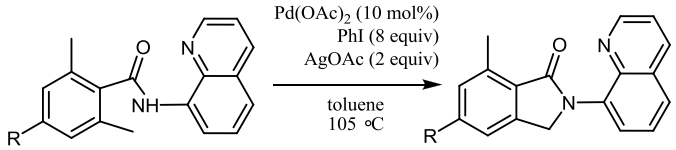
Our previous work[6]:



R = Me, 73%[a]
H, 57%[a]
Br, 81%[a]
F, 88%[a]
[a]Isolated yield.

Scheme 1

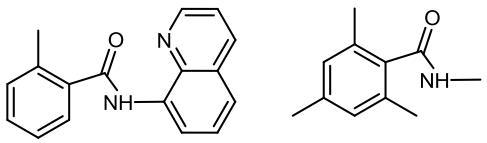
This work:



1a: R = Me
1b: R = H
1c:R = Br
1d: R = F

2a: R = Me, 98%[a]
2b: R = H, 90%[a]
2c: R = Br, 95%[a]
2d: R = F, 92%[a]
[a]Isolated yield.

Scheme 2

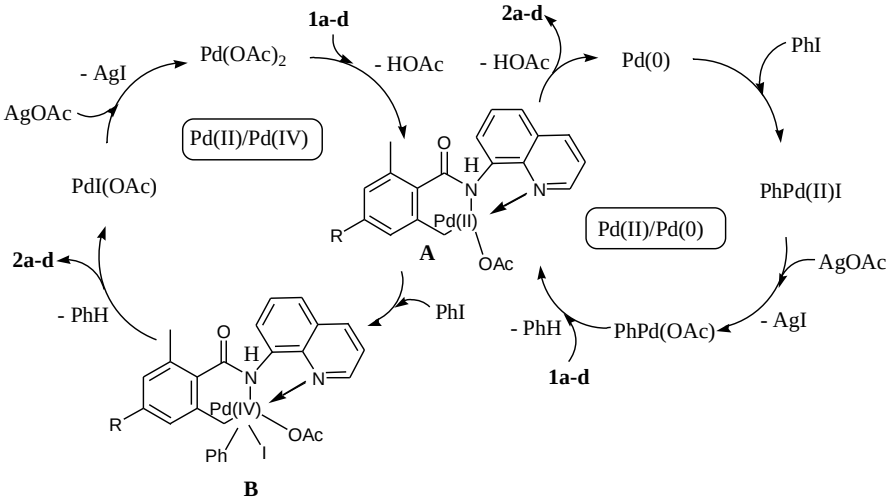


1e **1f**

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 exellent (90-98%).

EXPERIMENTAL

Amides **1a-f** were prepared according to our previous methods.[6] All reaction were performed under the atmosphere of nitrogen. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer with TMS as the internal standard and $CDCl_3$ as solvent. ^{19}F 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 N_2 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). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H, Me), 2.75 (s, 3 H, Me), 5.18 (s, 2 H, CH_2), 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{19}H_{16}N_2O$: 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). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79 (s, 3H, Me), 5.23 (s, 2 H, CH_2), 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{14}N_2O$: 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). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (s, 3H, Me), 5.20 (s, 2 H, CH_2), 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{13}{}^{79}BrN_2O$: 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). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77(s, 3H, Me), 5.20 (s, 2 H, CH_2), 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.43, 52.99 (d, $^4J_{F-C}$ = 2.8 Hz), 107.34 (d, $^2J_{F-C}$ = 23.7 Hz), 117.20 (d, $^2J_{F-C}$ = 22.3 Hz), 121.40, 125.77, 126.39, 127.49, 128.82, 129.49, 135.45, 136.39, 141.22 (d, $^3J_{F-C}$ = 9.3 Hz), 144.40, 145.49 (d, $^3J_{F-C}$ = 10.5 Hz), 150.03, 163.56, 167.36 (d, $^1J_{F-C}$ = 262 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ = - 108.19. HRMS (EI): *m/z* [M^+] calcd for $C_{18}H_{13}FN_2O$: 292.1012; found: 292.1008.

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REFERENCES AND NOTES

1. For reviews about heterocycle synthesis via C-H functionalization: (a) P. Thansandote and M. Lautens, *Chem. Eur. J.*, 2009, **15**, 5874; (b) M. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 2243; (c) T.-S. Mei, L. Kou, S. Ma, K. M. Engle, and J.-Q. Yu, *Synthesis,* 2012, 1778; (d) M. Zhang, A.-Q. Zhang, and Y. Peng, *J. Organomet. Chem.*, 2013, **723**, 224.
2. For a review about ligands directed C-H functionalization: T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147.
3. E. T. Nadres and O. Daugulis, *J. Am. Chem. Soc.,* 2012, **134**, 7.
4. G. He, Y. Zhao, S. Zhang, C. Lu, and G. Chen, *J. Am. Chem. Soc.,* 2012, **134**, 3.
5. G. He, S.-Y. Zhang, W. A. Nack, Q. Li, and G. Chen, *Angew. Chem. Int. Ed.,* 2013, **52**, 11124.
6. M. Zhang, *J. Chem. Res.,* 2013, 606.
7. (a) X. Wu, Y. Zhao, G. Zhang, and H. Ge, *Angew. Chem. Int. Ed*., 2014, **53**, DOI: 10.1002/anie.201311263; (b) Z. Wang, J. Ni, Y. Kuninobu, and M. Kanai, *Angew. Chem. Int. Ed.,* 2014, **53**, DOI: 10.1002/anie.201311105.
8. Y. Xie, Y. Yang, L. Huang, X. Zhang, and Y. Zhang, *Org. Lett*., 2012, **14**, 1238.
9. M. Ball, A. Boyd, G. Churchill, M. Cuthbert, M. Drew, M. Fielding, G. Ford, L. Frodsham, M. Golden, K. Leslie, S. Lyons, B. McKeever-Abbas, A. Stark, P. Tomlin, S. Gottsching, A Hajar, J. Jiang, J. Lo, and B. Suchozak, *Org. Process Res. Dev.,* 2012, **16**, 741.