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Tetrahedron Letters 49 (2008) 3172–3175
Tetrahedron Letters

A one-pot synthesis of 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolines

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Received 11 October 2007; revised 3 March 2008; accepted 4 March 2008
Available online 7 March 2008

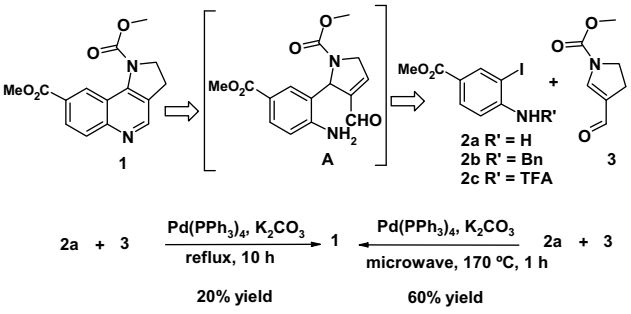
Abstract

A one-pot synthesis of the 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline core from substituted 2-iodoanilines and 2,3-dihydro-1*H*-pyrrole was achieved using 10 mol % $Pd(PPh_3)_4$, and K_2CO_3 in 1,4-dioxane at 170 °C for 1 h in a microwave oven. This reaction can be carried out on a gram scale. The proposed mechanism involves a Heck-coupling reaction followed by intra-molecular Schiff base formation and double bond migration.

Pyrrolo[3,2-*c*]quinoline ring system is a central core to a number of biologically active molecules. Derivatives from this class possess hypotensive,[1] anti-inflammatory,[2] anti-cancer,[3] and neuroprotective [4] activities. Moreover, 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolines, the sub-class of compounds described in this report, are potential therapeutic agents for peptic ulcer disease by acting as gastric H^+/K^+ ATPase 'proton pump' inhibitors.[5]

The two reported routes to 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]-quinolines involve as the key step the tandem radical cyclization of 4-(2-phenyl-4-isopropenyl-isoxalidine-3-yl)-2,3-dihydropyrrole[6] or the cyclization of symmetrical malonamides.[7] However, both of these approaches have narrow scope and involve multi step reactions resulting in low yields of final products. Herein, we would like to report a one-pot synthesis of 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinolines **1** which allows for the synthesis of gram quantities of this important tricyclic core.

According to the retro-synthetic analysis shown in Scheme 1, the target molecule **1**, 2,3-dihydro-1*H*-pyrrolo-[3,2-*c*]quinoline-1,8-dicarboxylate, can be obtained from intermediate **A** by an intra-molecular Schiff base formation and aromatization. Intermediate **A** was envisaged to come from the Heck coupling of 2-iodoaniline **2a** with methyl 4-formyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate, **3**.[8]



Scheme 1.

Our initial experiment demonstrated that a one-pot approach to this tricyclic core is feasible. Reaction of iodoaniline **2a** with pyrrole **3** (1 equiv) in the presence of $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 (2 equiv) in refluxing toluene for 10 h directly afforded the target molecule 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline **1**, in 20% yield (Scheme 1). In contrast, the corresponding reaction with secondary iodoanilines **2b** and **2c** only gave the dehalogenated starting materials. Promisingly, the yield of **1** could be increased to 44% by extending the refluxing of 2-iodoaniline **2a** and aldehyde **3** to 24 h. This yield is in line with that reported by Gurjar et al.[9] in their preparation of 1,2,5,9b-tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones via Heck coupling

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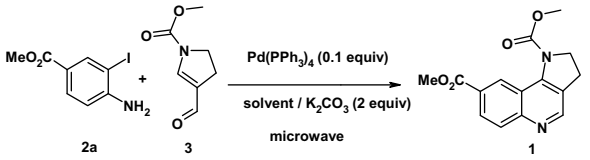
doi:10.1016/j.tetlet.2008.03.009

of 2-iodoaniline with 3-carbethoxy-4,5-dihydropyrrole. In order to shorten our reaction time and to potentially further improve the yield, we evaluated microwave conditions. Microwave irradiation has been reported to increase the rate and yield of Heck reactions.[10] Accordingly, microwave irradiation of **2a** and **3** (1.5 equiv) with $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 (2 equiv) at 170 °C in 1,4-dioxane for 1 h afforded compound **1** in 60% yield.

We evaluated the influence of the palladium catalyst on this reaction. The three palladium catalysts, $Pd(dba)_2$, $Cl_2Pd(PPh_3)_2$, and $Pd(PPh_3)_4$, all gave similar yields of **1**, namely, 62%, 58%, and 60%, respectively.[11] Using the most economical catalyst of the three, $Pd(PPh_3)_4$, we examined the effect of catalyst loading. Increasing the loading of $Pd(PPh_3)_4$ from 2 to 5 to 10 mol % produced successively higher yields, 8%, 20%, and 40%, respectively, with 10% being the optimal loading. Increasing the number of equivalents of aldehyde **3** from 1 to 1.5 slightly improved the yield from 55% to 60% but there was no advantage in using 2 equiv of aldehyde. In subsequent optimization experiments we used 10 mol % of $Pd(PPh_3)_4$ and 1.5 equiv of **3** together with microwave irradiation at 170 °C.[12]

Next, studies were conducted to determine the optimal base and solvent combination. When K_2CO_3 was replaced by Et_3N (2 equiv), we observed only the de-halogenated starting material derived from **2a**. By switching to NaOH, we found only a small amount of the desired product **1** (ca. 5%) plus some decomposed aldehyde **3**. For the remainder of the studies K_2CO_3 (2 equiv) was used as the base. Of the seven solvents tried in this reaction (H_2O, CH_3CN, DMF, DMSO, THF, DME, and 1,4-dioxane), the best yields came from 1,4-dioxane and, secondly, from DME (Table 1). These two solvents may improve solubility of the reactants and catalyst, as well as, enhance the basicity of K_2CO_3. On the other hand, reactions carried out in H_2O, CH_3CN, DMSO, or DMF were totally ineffective.

Table 1
Solvent and reaction time study[a]



Entry	Solvent	Time (min)	Yield[b] (%)
1	1,4-Dioxane	120	58
2	1,4-Dioxane	60	60
3	1,4-Dioxane	30	29
4	1,4-Dioxane	15	20
5	DME	60	33
6	DME	30	28
7	DME	15	18
8	THF	15	13

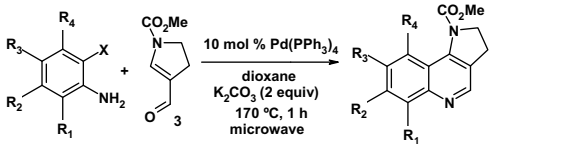
[a] Reactions conducted in microwave at 170 °C.
[b] Isolated yields following purification by preparative reverse-phase HPLC.

To determine the optimal microwave reaction time, a time course study was conducted using 1,4-dioxane and DME (Table 1, entries 1–7). When reactions were run for 30 min, both solvents gave comparable yields (entries 3 and 6), but noticeably better yields were obtained using 1,4-dioxane when the reaction time was extended to 1 h (entries 2 vs 5). Extending the reaction time to 120 min in 1,4-dioxane did not further improve the yield (entry 1 vs 2) and, as a result, a 1-h reaction time in 1,4-dioxane was used for the remainder of the experiments.

Having determined the optimal reaction conditions, we were interested in determining the scope of this one-pot reaction (Table 2).[13] Introduction of the electron-withdrawing group (CF_3, CO_2Me, or Cl) in position R_3, *para* to the NH_2 of the iodoanilines, afforded the highest yields (entries 1–8 vs entry 9 $R_3 = H$). It is important to note that these reactions can be scaled up to afford gram quantities of 2,3-dihydropyrrolo[3,2-*c*]quinolines (entries 2, 5, and 7). Introduction of a fluorine atom *ortho* to the NH_2 group (entry 6) and even a second fluorine atom in the meta position (entry 8) only slightly decreased the yield. On the other hand, the corresponding one-pot reactions with *ortho*-bromoanilines were less effective (entry 1 vs 10–12; entry 9 vs 13) with 35% being the best isolated yield using the strong electron-withdrawing fluorine atom in position R_3 (entry 11). *ortho*-Bromoanilines with an electron donating group in position R_3 gave none of the desired product (e.g., $R_1 = R_2 = R_4 = H$, $R_3 = -CH(CH_3)_2$, X = Br).

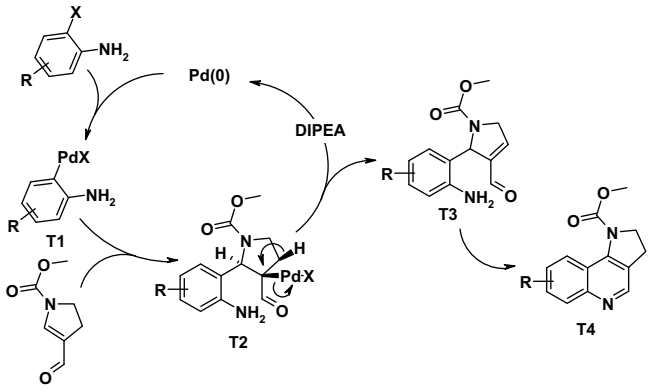
The mechanism leading to 2,3-dihydropyrrolo[3,2-*c*]-quinolines likely involves a Heck cross-coupling followed by an intramolecular cyclization (Scheme 2). The oxidative addition of palladium(0) to the aryl halide is followed by

Table 2
Synthesis of several 2,3-dihydro-pyrroloquinolines[a]



Entry	R1	R2	R3	R4	X	Yield[a] (%)
1	H	H	Cl	H	I	73
2	H	H	Cl	H	I	74[b]
3	H	H	CO_2CH_3	H	I	61
4	H	H	CF_3	H	I	60
5	H	H	CF_3	H	I	64[b]
6	F	H	Cl	H	I	50
7	F	H	Cl	H	I	38[b]
8	F	H	Cl	F	I	49
9	H	H	H	H	I	24
10	H	H	Cl	H	Br	14
11	H	H	F	H	Br	35
12	H	CF3	H	H	Br	26
13	H	H	H	H	Br	13

[a] Isolated yields following purification by preparative reverse-phase HPLC.
[b] Isolated yields of products (scale of 1 g of aryl halide) following purification by silica gel column chromatography.

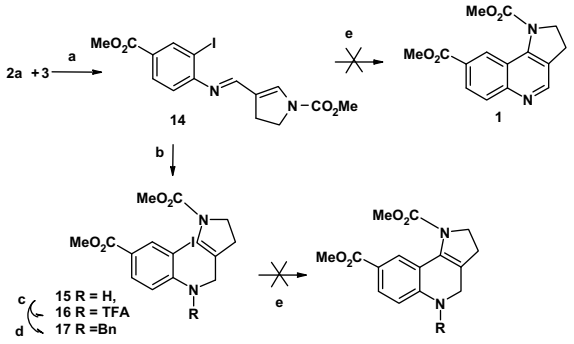


Scheme 2.

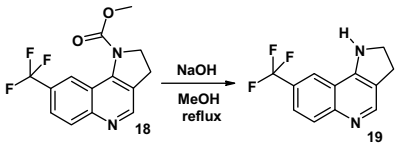
syn addition of this organopalladium species across the carbon–carbon double bond of aldehyde **3** generating intermediate **T2**. *syn*-Palladium hydride elimination can only occur in one direction producing **T3**, the Heck coupled product. This intermediate can then undergo double isomerization followed by cyclization or alternative cyclization followed by double bond migration.

An alternate mechanistic hypothesis involving first imine bond formation followed by Heck coupling seems less likely. To explore this possibility, we pre-formed the Schiff base **14** and subjected it to the Heck coupling conditions but it did not afford the cyclized product **1** (Scheme 3). Interestingly, even when the 2,3-dihydro-1*H*-pyrrolo and 2-iodoanilino motifs are tethered by an sp^3 carbon atom, as in compounds **15**–**17**, the Heck cyclization does not occur. Apparently, the tether in these systems (**14**–**17**) likely prevents the attainment of the required reaction geometry.

Removal of the methyl carbamate protecting group on the pyrrolo-1*H*-[3,2-*c*]quinoline **18** was accomplished by hydrolysis in NaOH and methanol (Scheme 4).[14] 2,3-Dihydropyrrolo-1*H*-[3,2-*c*]quinolines such as **19** represent a class of valuable building blocks amenable for further diversification.



Scheme 3. Reagents and conditions: (a) Reactants on K-10 Clay, microwave, 150 °C, 20 min; (b) $NaBH(OAc)_3$, CH_2Cl_2, 90%; (c) TFAA, DMAP, CH_2Cl_2, 85%; (d) PhCHO, $NaBH(OAc)_3$, HOAc, CH_2Cl_2, 95%; (e) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 170 °C, 1 h, microwave.



Scheme 4.

In summary, we report an efficient one-pot synthesis of the 2,3-dihydropyrrolo-1*H*-[3,2-*c*]quinolines, which allows for the synthesis of gram quantities of this important tricyclic core. The mechanism most likely involves a Heck cross-coupling reaction followed by an intramolecular Schiff base formation and aromatization.

Acknowledgments

We thank Mr. Chris Porter for HPLC analysis, and Dr. V. Santhakumar and Dr. Simon Woo for their helpful suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.009.

References and notes

1. Kiyohiko, M.; Michihiko, M.; Tadasu, T. Jpn. Kokai Tokkyo Koho, JP 49081398, 1974.
2. Pevarello, P.; Heidempergher, F.; Della, T. A.; Varasi, M.; Speciale, C. PCT Int. Appl., WO 9805660 A1, 1998.
3. (a) Ferlin, M. G.; Chiarelotto, G.; Gasparotto, V.; Via, L. D.; Pezzi, V.; Barzon, L.; Palù, G.; Castagliuolo, I. *J. Med. Chem.* **2005**, *48*, 3417–3427; (b) Aragon, P.-J.; Yapi, A.-D.; Pinguet, F.; Chezal, J.-M.; Teulade, J.-C.; Chapat, J.-P.; Blache, Y. *Chem. Pharm. Bull.* **2004**, *52*, 659–663; (c) Ferlin, M. G.; Via, L. D.; Gia, O. M. *Bio-org. Med. Chem.* **2004**, *12*, 771–777; (d) Mark, S.; Hylton, P. L. PCT Int. Appl., WO 2002068412 A1, 2002.
4. Rosenberg, P. A.; Zhang, Y. U.S. Patent 407698, 2003.
5. (a) Cheon, H. G.; Lim, H.; Lee, D. H. *Eur. J. Pharmacol.* **2001**, *411*, 181–186; (b) Cheon, H. G.; Lee, S. S.; Lim, H.; Lee, D. H. *Eur J. Pharmacol.* **2001**, *411*, 187–192.
6. Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warrington, J.; Saraiva, M. C. *Synlett* **1995**, 507.
7. (a) Leach, C. A.; Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Parsons, M. E.; Price, C. A.; Wiggall, K. J. *J. Med. Chem.* **1992**, *35*, 1845–1852; (b) Ife, R. J. Eur. Pat. Appl., EP307078, 1989.
8. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Tetrahedron Lett.* **1982**, *23*, 1201–1204.
9. Gurjar, M. K.; Pal, S.; Rao, A. V. R. *Heterocycles* **1997**, *45*, 231–234.
10. (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584; (b) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537–4542; (c) Qabaja, G.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 5317–5320; (d) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
11. Microwave irradiation of **2a** and **3** (1.5 equiv), Pd catalyst (10 mol %), and K_2CO_3 (2 equiv) at 170 °C in 1,4-dioxane for 1 h.
12. The influence of microwave reaction temperature was briefly explored. Microwave irradiation of **2a** and **3** (1 equiv) with $Pd(PPh_3)_4$

(10 mol %) and K_2CO_3 (2 equiv) at 170 °C in 1,4-dioxane for 1 h afforded **1** in 60% yield. Dropping the microwave temperature to 140 °C decreased the yield to 40% while increasing the microwave temperature to 200 °C led to a number of side products.

13. *General procedure for the synthesis of pyrroloquinoline compounds*: In a Smith Process Vial™ 1,4-dioxane (1 mL) was added to a mixture of aldehyde **3** (1.5 equiv), potassium carbonate (2 equiv), $Pd(PPh_3)_4$ (0.1 equiv), and the corresponding aniline (30 mg). The reaction vessel was sealed with cap and septum, placed in the Smith Synthesizer, and radiated at 170 °C for 1 h. The crude product was extracted with EtOAc and filtered to remove solids. After evaporation of solvent under reduced pressure, the product was purified by Gilson-HPLC using CH_3CN/H_2O (1–40% CH_3CN gradient) over 30 min. Products were analyzed by MS, ^1H, and ^{13}C NMR. The purity check was performed by HPLC using 40-min run monitoring three wavelengths: 215, 254, and 280 nM.
14. Yang, D.; Kim, S.-H.; Kahne, D. *J. Am. Chem. Soc.* **1991**, *113*, 4715–4716.