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Novel synthesis of 4,4-difluoropyrido[4,3-*b*]indoles via intramolecular Heck reaction

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ABSTRACT

Various difluoropyridoindoles were synthesized via a palladium-catalyzed intramolecular Heck reaction as a key step. Thus, *ortho*-bromoanilines and difluoropiperidinone were treated with $(PPh_3)_2PdCl_2$ and base in pyridine to give the regioselective cyclized heterocycles in modest to satisfactory yields.

Nitrogen-containing heterocycles are one of the most important classes of medicinal compounds and are structural components of many bioactive natural products and organic materials.[1] Owing to the numerous applications of indoles in pharmaceutical research, the development of efficient and new synthetic protocols for their synthesis has attracted the attention of many chemists. Consequently, there is a strong driving force to design new and efficient strategies for making carbon–nitrogen (C–N) bonds.[2] And the unique properties of fluorine, selective introduction of fluorine atom(s), or fluorine-containing moieties into organic molecules often dramatically alter their stability, lipophilicity, bioavailability, and biopotency. It is estimated that as many as 30–40% of agrochemicals and 20% of pharmaceuticals on the market contain fluorine[3] as a result, difluoropiperidinone and o-haloanilines are included in the indole derivatives.

The intramolecular Heck reaction[4] is an important and powerful method for the construction of carbo- and heterocyclic compounds. The synthesis of indoles using this reaction has also been widely studied.[5,6] The application of the Hegedus–Mori–Heck reaction (intramolecular Heck reaction) to the synthesis of pyrido[3,2-*b*]indole was first explored on enamines with $NaHCO_3$ and $Pd(PPh_3)_4$ in HMPA at 140 °C.[7,8] Under these conditions, the scope of this palladium-catalyzed cross-coupling was limited to the preparation of 4-azaindoles. In a recent Letter, Joydev and others have described the synthesis of substituted R-carbolines involving a palladium coupling reaction with $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, DBU, DMA between aniline and 2,3-dihalopyridine by heating in a screw-capped sample vial at 145 °C for about 16 h.[9] Sarvesh et al., have described the synthesis of substituted pyrazolo[3,4-*b*]indoles involving a palladium coupling reaction with $Pd(OAc)_2$, *n*-Bu_4NBr, K_2CO_3 between aniline and 1-aryl pyrazole heating (2–30 h at 140 °C).[10] Nazaré et al., have reported the synthesis of substituted pyridoindoles involving a palladium coupling reaction with $Pd[P(t\text{-}Bu)_3]_2$ between chloroanilines and ketones by thermal heating in a sealed tube (4–16 h at 140 °C).[11]

In contrast to the well documented Fischer indole reaction applied to the azaindoles synthesis,[12–14] the Hegedus–Mori–Heck reaction has never been reported for the preparation of difluoropyridoindole. In this work, the authors have described the intramolecular Heck cyclization of difluoropiperidinone and *ortho*-bromoanilines which yields the corresponding 4,4-difluoropyrido[4,3-*b*]indoles.

To the best of our knowledge, a rapid and general synthesis of the isomeric difluoropyridoindole from readily accessible starting materials has not been described. As part of our medicinal chemistry research program, we needed an efficient route to difluoropyridoindole compatible with sensitive groups such as secondary amine. In this investigation, we wish to report for the first time a rapid one pot synthesis of difluoropyridoindole compounds using difluoropiperidinone employing sealed tube conditions via an intramolecular Heck reaction.

Based on the results shown in Scheme 1, a systematic survey of this reaction sequence to fused indoles was undertaken. The precursors required for the Heck reaction were prepared by nucleophilic substitution using 4-methoxy benzyl amine and

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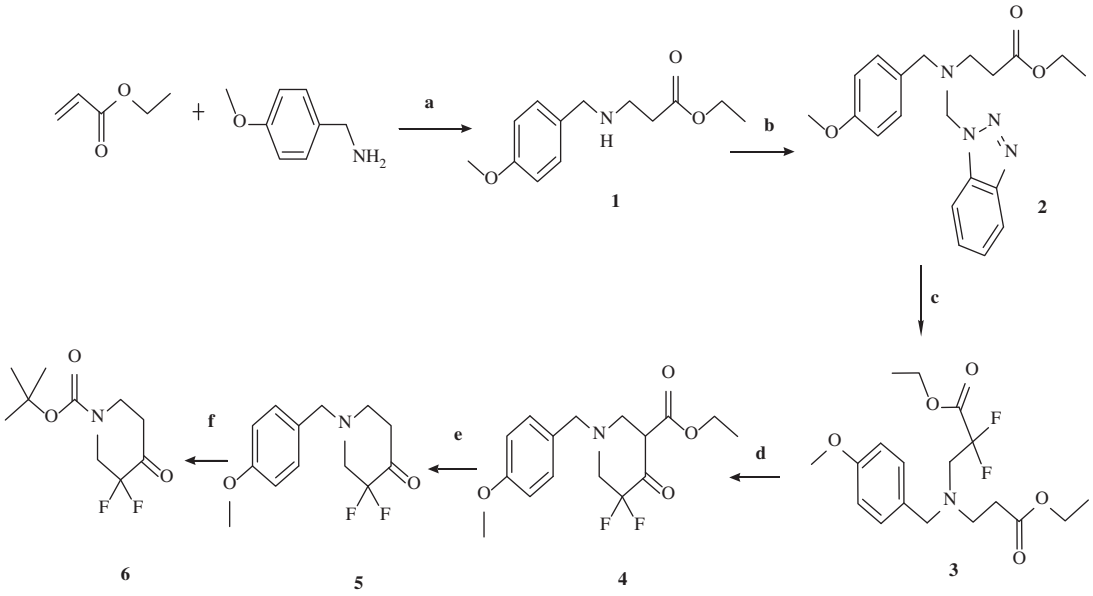
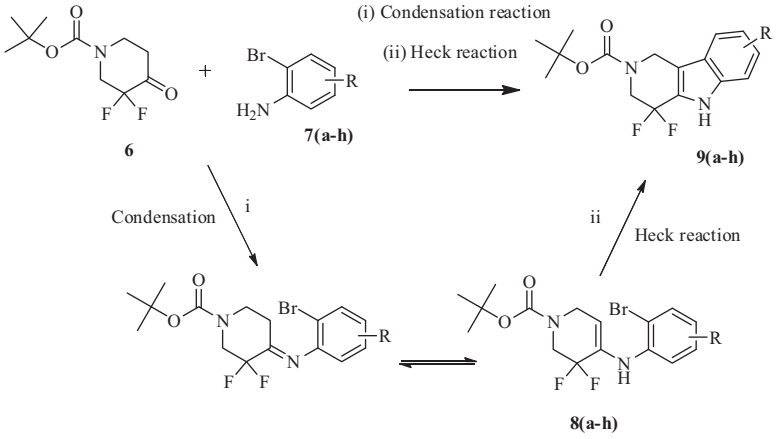


Scheme 1. Synthesis of precursor required for the Heck reaction. Reagents and condition: (a) ethanol, rt, 16 h; (b) formaldehyde, benzotriazole, methanol, rt, 16 h; (c) zinc, trimethylsilylchloride, ethylbromo difluoroacetate, tetrahydrofuran, rt, 18 h; (d) diisopropylamine, *n*-butyllithium, tetrahydrofuran, −78 °C, 16 h; (e) 18% HCl, reflux, 3 h; (f) 1-chloroethylchloroformate, 1,2-dichloroethane, 100 °C, 3 h; methanol, reflux, 6 h; triethylamine, boc anhydride, dichloromethane, rt, 18 h.

ethylacrylate in ethanol to give the ester **1**[15] with good yields. Ester **1** was reacted with formaldehyde and benzotriazole in methanol afforded the benzotriazole derivative **2**,[16,17] which on treatment with ethyl bromodifluoro acetate in the presence of zinc and trimethylsilyl chloride afforded the difluoro-diester **3**. Dieckmann cyclization of **3** using diisopropylamine in tetrahydrofuran resulted in the formation of keto-ester **4**.[18] Hydrolysis of keto-ester **4** followed by decarboxylation using HCl gave the desired compound **5**.[19] The benzyl group was deprotected using 1-chloroethylchloroformate in 1,2-dichloroethane and methanol to form amine,[20] which was protected with boc anhydride to get an amine **6** which is having difluoro moiety in the piperidone ring as difluoropiperidinone.[21]

Preliminary studies focused on optimization of the intramolecular Heck reaction (**8a**–**h**) → (**9a**–**h**). The enamine was selected as the model substrate to explore the palladium catalyzed coupling reaction (Scheme 2). Several palladium catalysts {$Pd(OAc)_2$, $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$}, bases (*i*-Pr_2NEt, *i*-Pr_2NH, NEt_3, Cy_2NMe), solvent pyridine and temperature range (110–160 °C for 4–18 h) were examined in degassed sealed tube reactions. Investigation of the palladium source and the solvent effect revealed that $(PPh_3)_2PdCl_2$ and pyridine with diisopropylethylamine are the most appropriate reagents to perform this intramolecular Heck reaction under sealed tube.

From the above conditions, the Heck coupling was carried out with boc protected difluoropiperidinone **6** and *o*-bromoanilines (**7a**–**h**) in the presence of a catalytical amount of *p*-toluenesulfonic acid in toluene as a solvent, resulting in the formation of the corresponding imines.[22,23] During the reaction, the imines undergo tautomerism to form an enamine,[4a,24] which is an active intermediate to undergo Heck reaction. When the enamines (**8a**–**h**) were heated at 120 °C with bis(triphenylphosphine) palladium(II)dichloride in the presence of pyridine as solvent with diisopropylethylamine as base resulted in the formation of difluoropyridoindoles (**9a**–**h**). Under these conditions, yields of the desired *tert*-butyl 4,4-difluoro-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate derivatives ranged from 85% to 98%. Also, heating the reaction at a higher temperature (above 120 °C) led to lower yields of difluoropyridoindoles (**9a**–**h**) with increased decomposition.

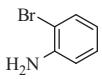
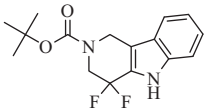
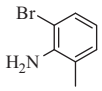
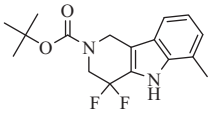
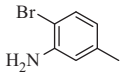
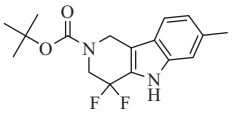
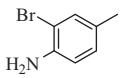
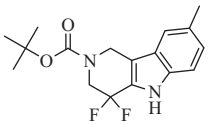
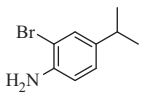
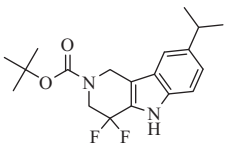
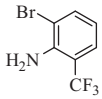
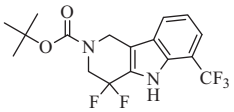
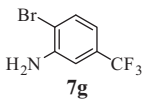
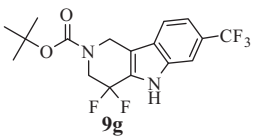
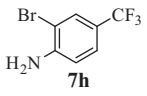
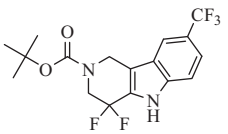


Scheme 2. One-pot synthesis of difluoropyridoindole (**9a**–**h**) from the reaction of **6** with (**7a**–**h**). Reagents and condition: (i) 2-bromo-aniline, *para* toluene sulfonic acid, benzene, reflux, 3 h; (ii) dichloro-bis(triphenylphosphine) palladium(II), diisopropylethylamine, pyridine, 120 °C, 16 h.

After the exploration of the reaction conditions, we focused our attention on optimizing the isolation of the reaction product(s). It was noted that on using an aqueous work-up for the isolation of difluoropyridoindoles (**9a**–**h**), a lower yield than the conversion determined by HPLC was obtained. Therefore, we thought of non-aqueous work-up conditions since we suspected **9a**–**h** to be sparingly water-soluble. The optimized purification protocol involves a direct column chromatography over silica gel (10–15% EtoAc in hexane) of the reaction mixture followed by triturate with hexane, to get the desired difluoropyridoindoles (**9a**–**h**).

Having established rapid and high yielding conditions for the palladium cross-coupling of enamines (**8a**–**h**) to difluoropyridoindoles (**9a**–**h**), we wanted to examine the scope of this method. Table 1 summarizes the results of difluoropyridoindole syntheses starting from *ortho*-bromoanilines. Most of these condensed starting materials required for our studies were prepared following literature procedures.[7,8,25] Surprisingly, under these conditions and with higher temperatures or longer reaction time, *o*-bromoanilines remains unreacted in the presence of a small amount of difluoropiperidinone.

Table 1
Annulation reaction with acyclic ketones

Annulated precursor	Annulated product[a]	Yield[b] (%)
 **7a**	 **9a**	98
 **7b**	 **9b**	85
 **7c**	 **9c**	91
 **7d**	 **9d**	92
 **7e**	 **9e**	91
 **7f**	 **9f**	86
 **7g**	 **9g**	88
 **7h**	 **9h**	92

[a] Reaction conditions: 1.0 equiv ketone, 1.1 equiv aniline, 4 equiv *i*-Pr_2NEt, 0.1 equiv $(PPh_3)_2PdCl_2$, in pyridine.
[b] Yield of isolated products with >95% purity by ^1H NMR and HPLC.

Having established the optimal reaction conditions, the scope of this reaction was examined with respect to anilines by varying systematically the electronic properties of the aromatic ring. As shown in Table 1, the reaction turned out to be very general and is applicable to both electron-rich and electron-deficient *o*-bromoanilines. When *meta* and *para* methyl *o*-bromoanilines with electron releasing group in benzene ring increases the yield whereas *meta* and *para* trifluoromethyl *o*-bromoanilines with electron withdrawing group in benzene ring decreases the yield. Steric hindrance was also studied, when both 2-bromo-6-methylaniline (**7b**) and 2-bromo-6-(trifluoromethyl)aniline (**7f**) were used to produce less yield, thus, the use of 2 equiv of aniline was required for the reaction of **9b** and **9f**. The product yield trends of the (*ortho*/*meta*/*para*) methyl and trifluoromethyl derivatives may provide some evidence that the reaction yield is influenced by substituent electronic effects, the correlation could be considered over reaching due to the small scale synthesis.

In conclusion, we have developed an efficient synthesis of highly functionalized indoles by a palladium-catalyzed annulation reaction between *ortho*-bromoanilines and difluoropiperidinone. The intramolecular Heck reaction of enamines under sealed tube conditions provides good yields of difluoropyridoindole. The present method, therefore, provides general synthetic approaches for these heterocylic frameworks and is compatible with a range of electron-donating and electron-withdrawing substituents on the aryl group. This methodology provided an array of difluoropyridoindole in modest to satisfactory yields and will facilitate the synthesis of additional derivatives that can be used for various applications, including screening for biological activities. This method provides a new entry into interesting heterocycles containing a piperidine ring. Finally, this Letter is the first to describe the synthesis of difluoropyridoindole using difluoropiperidinone compound via an intramolecular Heck reaction.

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Supplementary data

Supplementary data (synthetic procedures and analytical data for all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.115.

References and notes

1. (a) Yuhong, J.; Rajender, S. V. *Org. Lett.* **2005**, *7*, 2409; (b) Brown, E. G. *Ring Nitrogen and Key Biomolecules*; Kluwer: Boston, MA, 1998; (c) Negwar, M. *In Organic Chemical Drugs and Their Synonyms (An International Survey)*, 7th ed.; Akademie Verlag Gmbh: Berlin, 1994.
2. Tom, H. H.; Hsieh, V. M. D. *Tetrahedron* **2009**, *65*, 3062.
3. Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.
4. (a) Maruyama, J.; Yamashita, H.; Watanabe, T.; Arai, S.; Nishida, A. *Tetrahedron* **2009**, *65*, 1327; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
5. Mori, M.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 1037.
6. Synthesis of indoles by intramolecular Heck reaction involving formal 5-endo cyclization of *N*-alkenyl-*o*-haloanilines, see: (a) Fuwa, H.; Sasaki, M. *Org. Lett.* **2007**, *9*, 3347; (b) Jia, J.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826; (c) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678.

7. Blache, Y.; Sinibaldi-Troin, M. E.; Voldoire, A.; Chavignon, O.; Gramain, J. C.; Teulade, J. C.; Chapat, J. P. *J. Org. Chem.* **1997**, *62*, 8553.
8. Blache, Y.; Sinibaldi-Troin, M. E.; Hichour, M.; Benezech, V.; Chavignon, O.; Gramain, J. C.; Teulade, J. C.; Chapat, J. P. *Tetrahedron* **1999**, *55*, 1959.
9. Joydev, K. L.; Philip, P.; Gregory, D. C. *J. Org. Chem.* **2009**, *74*, 3152.
10. Sarvesh, K.; Hiriyakkanavar, I.; Hiriyakkanavar, J. *J. Org. Chem.* **2009**, *74*, 7046.
11. Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526.
12. Abramovitch, R. A.; Adams, K. A. H. *Can. J. Chem.* **1962**, *40*, 864.
13. Kelly, A. H.; Parrick, J. *J. Chem. Soc. C* **1970**, 303.
14. Mann, F. G.; Prior, A. F.; Willcox, T. J. *J. Chem. Soc.* **1959**, 3830.
15. Sean, P. B.; Hughes, D. L.; Nicholas, J. P.; Vladimir, S.; Katy, M. S.; Martin, A. W. *Chem. Commun.* **2006**, 4338.
16. Fujimoto, T.; Tomata, Y.; Kunitomo, J.; Hirozane, M.; Marui, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6409.
17. Remen, L.; Bezencon, O.; Richard, B. S.; Bur, D.; Prade, L.; Corminboeuf, O.; Boss, C.; Grisostomi, C.; Sifferlen, T.; Strickner, P.; Hess, P.; Delahaye, S.; Treiber, A.; Weller, T.; Binkert, C.; Steiner, B.; Fischli, W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6762.
18. Bezencon, O.; Sifferlen, T.; Bur, D.; Fischli, W.; Weller, T.; Remen, L.; Richard-Bildstein, S. WO2005040120, 2005.
19. Zavoianu, D. *Rev. Chim.* **1983**, *34*, 699.
20. Sukumar, S.; Istvan, J. E.; Alan, P. K.; Wahiduz, A. Z.; Kenneth, M. J.; Shaomeng, W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495.
21. Fan, X.; Zhang, F. H.; Al-Safi, R. I.; Zeng, L. F.; Shabaik, Y.; Debnath, B.; Sanchez, T. W.; Odde, S.; Neamati, N.; Long, Y. Q. *Bioorg. Med. Chem.* **2011**, *19*, 4935.
22. Jun, M.; Hiromichi, Y.; Takeshi, W.; Shigeru, A.; Atsushi, N. *Tetrahedron* **2009**, *65*, 1327.
23. Blache, Y.; Marie-Eve; Sinibaldi-Troin; Aline, V.; Olivier, C.; Jean-Claude, G.; Jean-Claude, T.; Jean-Pierre, C. *J. Org. Chem.* **1997**, *62*, 8553.
24. Lachance, N.; April, M.; Joly, M. A. *Synthesis* **2005**, *15*, 2571.
25. Couture, A.; Deniau, E.; Grandclaudon, P.; Simion, C. *Synthesis* **1993**, 1227.