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A general method for the preparation of 2,3,5-trisubstituted-furo[3,2-*b*]pyridines

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Abstract—The preparation of 2,3,5-trisubstituted-furo[3,2-*b*]pyridines via a Pd(0)-catalyzed intramolecular cyclization of methyl 4-(6-chloro-2-iodopyridin-3-yloxy)-substituted-butenoates **9a**–**f** is described. This approach was both efficient and general, and provided the highly functionalized heterocyclic ring system in high yield. Among the several examples provided is the preparation of 3-[2-(*N*,*N*-dimethylamino)ethyl]-5-(4-fluorobenzoyl)amino-2-methylfuro[3,2-*b*]pyridine **4**, a selective 5-HT_{1F} receptor agonist.

We have recently reported the identification of 5-HT_{1F} receptor ligands **1**–**3** (Fig. 1).[1] These selective agonists were active in the neurogenic plasma protein extravasation model of migraine,[2] and may be useful therapeutics for the treatment of acute migraine. In an effort to further advance the structure–activity relationship study of this series, we investigated a furopyridine ring system to determine if it served as a bioisosteric replacement for the indole nucleus.[3,4]

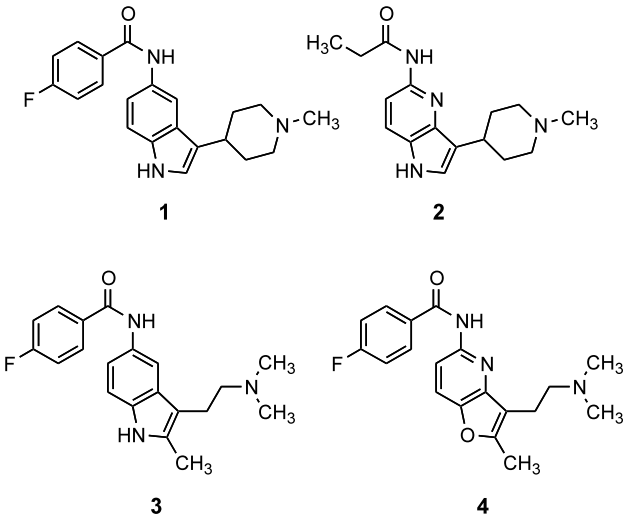

Figure 1.

We targeted 2,3,5-trisubstituted furo[3,2-*b*]pyridine analogues for evaluation. Methods to prepare the furo-[3,2-*b*]pyridine nucleus have been demonstrated. However the scope of substitution on the resulting bicyclic ring system was limited.[5] Recently, reports have focused on transition metal-mediated processes to form indole ring systems.[6] These methods typically utilized mild reaction conditions, and a variety of functional groups were tolerated in these cyclization processes. We report here an extension of this methodology, describing a general palladium-catalyzed cyclization reaction to form 2,3,5-trisubstituted furo[3,2-*b*]pyridines. Furthermore, we exemplify the utility of this method through the efficient synthesis of 5-HT_{1F} receptor agonist, 3-[2-(*N*,*N*-dimethylamino)ethyl]-5-(4-fluorobenzoyl)-amino-2-methylfuro[3,2-*b*]pyridine **4**.

The application of Pd(0)-catalyzed processes to form indoles and benzofurans has recently received much attention in the literature. Larock[7] and others[8] exploited the palladium-catalyzed heteroannulation of internal alkynes to prepare 2-substituted and 2,3-disubstituted indoles and benzofurans. This methodology has been expanded to include the synthesis of pyrrolopyridines as well as furopyridines.[9] In these reports, variation of substitution at C-2 versus C-3 had some limits, as the sterically more demanding substituent on the starting alkyne generally resided adjacent to the heteroatom (at position C-2) of the resulting heterocyclic ring system (Eq. (1)).[7,8c] Furthermore, in some cases the reaction was not regioselective, and where there was little steric difference between the substituents on the reacting alkyne, a mixture of regioisomers was reported.[7b,c,8e,9b]

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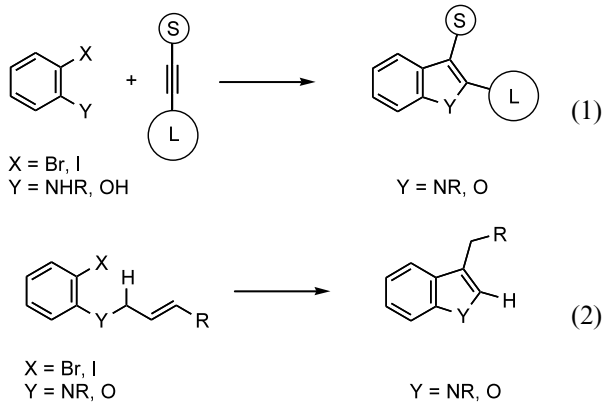
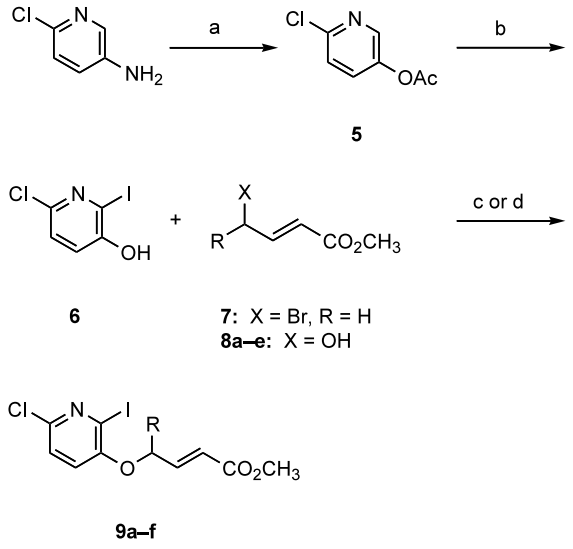
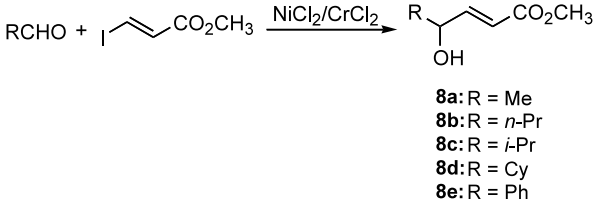


Alternatively, Pd(0)-catalyzed intramolecular cyclization of an *N*- or *O*-allyl *ortho*-haloaromatic circumvented the regioselective ambiguity of the previous reaction, as the C-2–C-3 substitution of the bicyclic product was pre-defined in the acyclic precursor (Eq. (2)).[10] Indoles and benzofurans substituted at C-3 were prepared through this method, but no examples to form 2,3-disubstituted products were reported.[11] We considered this strategy to be an attractive method to prepare desired target **4**, if we could demonstrate its feasibility to synthesize 2,3-disubstituted heterocyclic ring systems. In order to investigate this cyclization method, we prepared appropriately functionalized 2,3,6-trisubstituted pyridines. The Pd(0)-catalyzed cyclization of methyl 4-(6-chloro-2-iodopyridin-3-yloxy)-substituted-butenoates **9a**–**f** was subsequently explored.

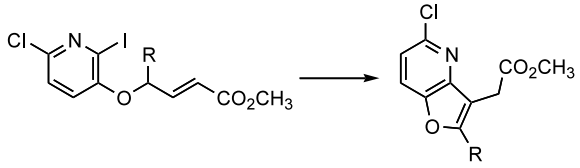


Scheme 1. *Reagents and conditions*: (a) i. $BF_3{\cdot}Et_2O$, *i*-BuONO, DME/CH_2Cl_2, 0°C; ii. Ac_2O, 75°C (62%, two steps). (b) i. K_2CO_3, MeOH, rt (94%); ii. I_2, Na_2CO_3, H_2O (95%). (c) **7**, K_2CO_3, DMF, 60°C (74%); (d) **8a**–**e**, PPh_3, DEAD, THF, rt.



Scheme 2.

Table 1. Pd(0)-catalyzed intramolecular cyclization of **9a**–**f**



9a–f **10a–f**

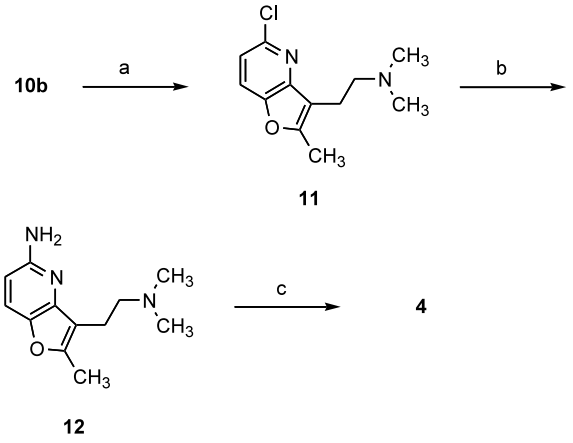
Aryl iodide	R	Conditions[a]	Yield (%)[b]	Product
9a	H	A	30	**10a**
9a	H	B	98	**10a**
9b	Me	B	98	**10b**
9c	*n*-Pr	B	97	**10c**
9d	*i*-Pr	B	94	**10d**
9e	Cy	B	78	**10e**
9f	Ph	B	34	**10f**

[a] Reaction conditions: (A) Na_2CO_3, $Pd(OAc)_2$, DMF, 80°C. (B) Na_2CO_3, *n*-Bu_4NCl, $Pd(OAc)_2$, NaO_2CH, DMF, 80°C.
[b] Isolated yield after column chromatography.

Scheme 1 outlines the preparation of cyclization substrates **9a**–**f**. Commercially available 5-amino-2-chloropyridine was subjected to diazotization, then quenched with acetic anhydride to provide acetate **5**. Hydrolysis followed by iodination afforded **6** as the sole product. Alkylation with methyl-4-bromocrotonate **7**, or a Mitsunobu reaction with **8a**–**e** provided substrates **9a**–**f**. We found the Nozaki coupling reaction to be an attractive and general method to prepare the allylic alcohols **8a**–**e** required in the Mitsunobu reaction (Scheme 2).[12] Treatment of (*E*)-methyl 3-iodopropenoate[13] with the requisite aldehyde in the presence of $CrCl_2$ and a catalytic amount of $NiCl_2$ provided **8a**–**e** in good to excellent yields (65–92%).

We used the conditions described by Larock to effect the Pd(0)-catalyzed cyclization of **9a**–**f**.[10c] As reported, addition of both sodium formate and the phase transfer reagent *n*-Bu_4NCl were critical to obtain products **10a**–**f** in reproducibly high yields. For example, cyclization of **9a** in the absence of these additives provided **10a** in only 30% yield, whereas with these reagents, we obtained product virtually quantitatively. Table 1 illustrates the effectiveness of this method to prepare 2,3-disubstituted furo[3,2-*b*]pyridines.[14] Small alkyl, including branched alkyl, substituents (**9b**–**e**) cleanly underwent the cyclization process. On the other hand, the aromatic-substituted substrate (**9f**) provided only a modest isolated yield of product **10f**, yielding a significant amount of the C–O-cleavage by-product **6**. We made no effort to optimize the conversion of this particular substrate.

Cyclization product **10b** was suitably substituted for conversion to target molecule **4**, the synthesis of which is outlined in Scheme 3. The C-3 methyl acetate moiety



Scheme 3. *Reagents and conditions*: (a) Me_3Al, $Me_2NH{\cdot}HCl$, CH_2Cl_2, rt (97%); ii. $LiAlH_4$, THF, 30°C (64%). (b) Benzophenone imine, $Pd_2(dba)_3$, (±)-BINAP, NaO*t*-Bu, toluene, 80°C; ii. 1N HCl/THF (1:1), rt (88%, two steps). (c) 4-Fluorobenzoyl chloride, pyridine, 55°C (96%).

was converted to the *N*,*N*-dimethylaminoethyl side chain in two steps, which included amide formation using Weinreb's protocol,[15] followed by $LiAlH_4$ reduction to provide **11**. Conversion of the C-5 chloro group of **11** to the corresponding amine through a Pd-catalyzed amination reaction, employing benzophenone imine as an ammonia equivalent,[16] followed by acid hydrolysis, generated primary amine **12**. Acylation of **12** subsequently provided target compound **4**.

The Pd(0)-catalyzed intramolecular cyclization of *O*-allyl-substituted *ortho*-iodopyridines provided an attractive method to prepare 2,3-disubstituted furo[3,2-*b*]pyridines. We believe that this method is general and can be applied to the synthesis of other disubstituted heterobicyclic ring systems. Using this approach, we efficiently prepared 5-HT_{1F} receptor agonist **4**. The biological activity of this compound will be described elsewhere in due course.

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14. **Typical procedure**. Preparation of **10b**: To a solution of **9b** (2.00 g, 5.4 mmol) dissolved in 60 mL of DMF was added 1.44 g of Na_2CO_3 (13.6 mmol), 0.37 g of sodium formate (5.4 mmol), 1.66 g of n-Bu_4NCl (6.0 mmol), and 0.06 g of $Pd(OAc)_2$ (0.3 mmol). The reaction mixture was heated at 80°C for 3 h, then cooled, and partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O, and the combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, then concentrated. Upon column chromatography (hexane–80% EtOAc/hexane), the desired compound was isolated as an ivory solid (1.3 g, 98%): mp 166–167°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, $J=8.4$ Hz, 1H), 7.13 (d, $J=8.8$ Hz, 1H), 3.73 (s, 2H), 3.72 (s, 3H), 2.47 (s, 3H) ppm; MS m/z: 240 (M^+). Anal. calcd for $C_{11}H_{10}ClNO_3$: theory: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.18; H, 4.07; N, 6.07%.
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