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Syntheses of aza and fluorine-substituted 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[*d*][1,3]diazepin-2(3*H*)-ones

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ABSTRACT

A practical and expedient synthesis of the title compounds is described. They were prepared by Stille reaction of nitro halopyridines **4** or nitro fluro-halobenzenes **10**, followed by Michael addition of *tert*-butyl 4-aminopiperidine-1-carboxylate to the resulting activated vinyl compounds **5** and **11**, hydrogenation ($-NO_2 \rightarrow -NH_2$), cyclic urea formation, Boc removal, and HCl salt formation. However, N3 and F1 analogs could not be made by this general strategy. Activated vinyl compounds **5a** and **5d** when reacted with *tert*-butyl 4-aminopiperidine-1-carboxylate did not stop at the desired Michael addition stage; but proceeded to produce azaindolines **8** and **9**. Michael addition did not occur to compound **11d**; instead, the fluorine atom was displaced.

We have used the GPCR recognition element,[1] 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[*d*][1,3]diazepin-2(3*H*)-one (1), in a recent medicinal chemistry program. However, the resulting compounds generally have poor aqueous solubility and poor bioavailability. Therefore, we hoped to improve on these by modifying the structure of **1** (Fig. 1).

By introducing a nitrogen atom into the fused phenyl ring, we hoped to improve both solubility and oral bioavailability of our target molecules.[2] In addition, the replacement of hydrogen atom(s) by fluorine in aromatic rings has been utilized to enhance solubility and bioavailability of pharmaceutically interesting molecules.[3] For these reasons, we hoped to generate aza- and fluoro- substituted analogs of **1** with all four possible regioisomers such as **2a–d** and **3a–d** to explore their effects on the pharmaceutical properties of the analogs which contain them.

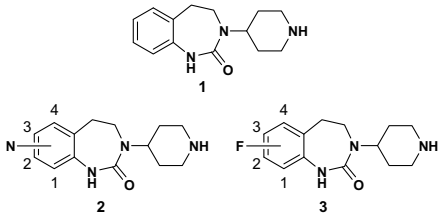

Figure 1. The targeted molecules.

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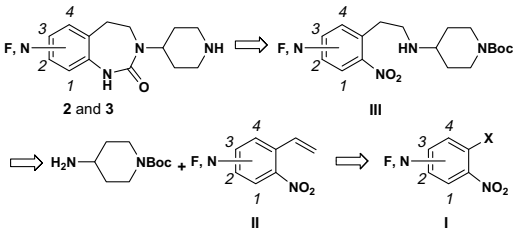
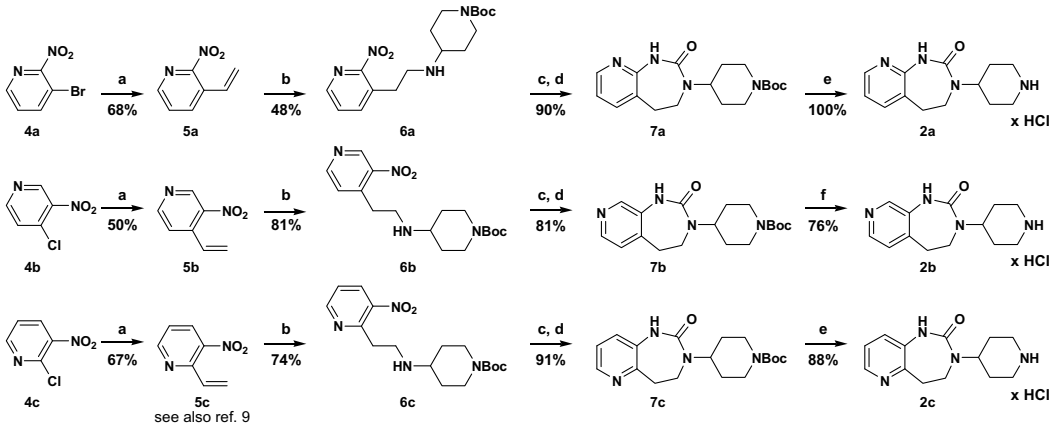


Figure 2. Retrosynthetic analysis.

The general retrosynthetic analysis is shown in Figure 2. Stille coupling of halide **I** with $Bu_3SnCHCH_2$ would provide nitro styrene **II**. Michael reaction of **II** with *tert*-butyl 4-aminopiperidine-1-carboxylate would afford nitro amine **III**. The reduction of $ArNO_2$ group to $ArNH_2$, and treatment of the resulting aminoethylaniline with CDI in the presence of Et_3N would afford cyclic ureas. Removal of the Boc-group would then afford the desired compounds **2** and **3**. In this letter, we report the successful synthesis of N1, N2, N4, F2, F3, and F4 analogs. This general strategy, however, failed to provide N3 and F1 analogs, as will be shown.

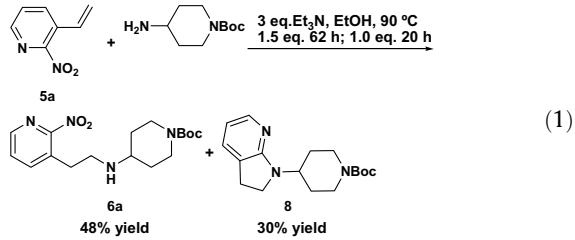
The synthesis of **2a–c** is summarized in Scheme 1. Stille coupling[4] of nitro bromide **4a** and $Bu_3SnCHCH_2$ (1.2 equiv) in the presence of $Pd(PPh_3)_2Cl_2$ (10%), TBAC (1.0 equiv) in MeCN at 90 °C for 2 h afforded nitro styrene **5a** in 68% yield. The Michael adduct **6a** was formed by the reaction of **5a** and *tert*-butyl 4-aminopiperidine-1-carboxylate (1.5 equiv), Et_3N (3.0 equiv) in EtOH at 90 °C for 24 h;[5] since some starting material was left at this point, more *tert*-butyl 4-aminopiperidine-1-carboxylate (1.5 equiv) was added, and the mixture was heated at 90 °C for 20 h to afford the final



Scheme 1. Syntheses of N1, N2, and N4 aza analogs of **2a**–**c**. Reagents and conditions. (a) 10% $Pd(PPh_3)_2Cl_2$, 1.2 equiv $Bu_3SnCHCH_2$, 1.0 equiv TBAC, MeCN, 90 °C, 2 h; (b) 1.5 equiv *tert*-butyl 4-aminopiperidine-1-carboxylate, 3 equiv Et_3N, EtOH, 90 °C, 24 h, then additional 1.5 equiv *tert*-butyl 4-aminopiperidine-1-carboxylate, 90 °C, 20 h; (c) H_2 (2 atm), 35% Pd/C (10%), MeOH, rt, 16 h; (d) 2.4 equiv CDI, 3.0 equiv Et_3N, MeCN, rt 16 h; then additional 1.2 equiv CDI, 3.0 equiv Et_3N, rt, 20 h; (e) (i) 20% TFA/CH_2Cl_2, rt, 4 h; (ii) 2 N HCl/Et_2O, CH_2Cl_2, 30 min; (f) 4 N HCl in dioxane.

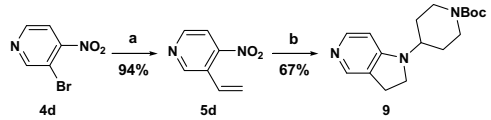
yield of 48%. The reduction of $-NO_2$ to $-NH_2$ was accomplished by hydrogenation [H_2 (2 atm), 35% Pd/C (10%), MeOH, rt, 16 h]. The resulting aminoethylaniline was treated with CDI (2.4 equiv) in the presence of Et_3N (3.0 equiv) in MeCN at rt for 16 h, followed by more CDI (1.2 equiv) and Et_3N (3.0 equiv) at rt for 20 h, to afford the cyclic urea **7a** in 90% yield (two steps).[6] The reaction of **7a** with 20% TFA in CH_2Cl_2 at rt for 4 h afforded a gummy semi-solid after removing TFA and CH_2Cl_2. This residue was re-dissolved in CH_2Cl_2 and was treated with 2 N HCl/Et_2O at rt for 30 min to afford **2a**·*x*HCl[7] as a white solid in 100% yield. While the synthesis of **2a**·*x*HCl had been reported previously,[8] the method reported herein is more direct (four steps vs seven steps) and results in a much higher overall yield (29.4% vs 3.7%). These same protocols were used to convert **4b** to **2b**·*x*HCl (25% yield for five steps, Scheme 1), and **4c** to **2c**·*x*HCl (40% yield for five steps, Scheme 1).[9]

It is interesting to note that the reaction of **5a** and *tert*-butyl 4-aminopiperidine-1-carboxylate under the reaction conditions used in Scheme 1 afforded both the desired Michael adduct **6a** in 48% yield, and azaindoline **8** in 30% yield (Eq. 1). Azaindoline **8** was presumably formed via **6a,** in which the nitro group acted as a leaving group in a S_NAr reaction. This indicated that the yield of **8** might be improved by raising the reaction temperature and by increasing reaction time, although this was not attempted.



(1)

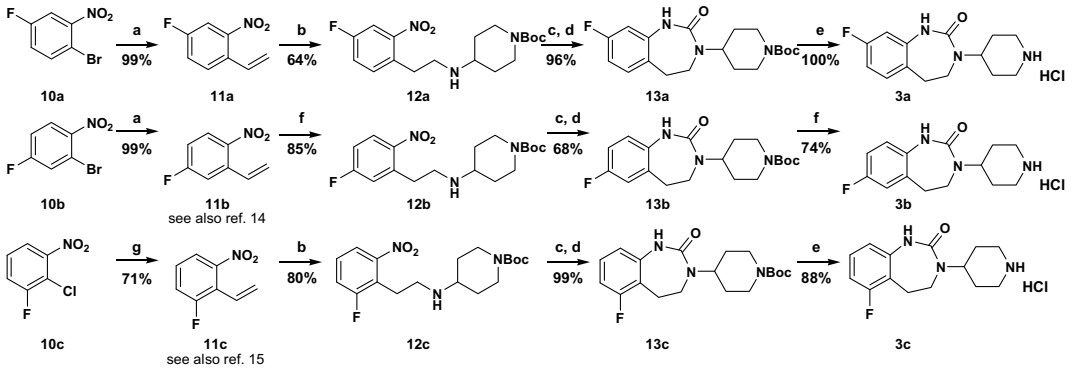
Efforts toward the synthesis of N3 aza analog **2d** are summarized in Scheme 2. The Stille coupling[4] of nitro bromide **4d**[10] and



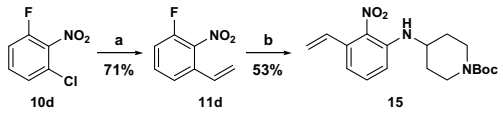
Scheme 2. Efforts toward synthesis of N3 aza analog. Reagents and conditions: (a) 10% $Pd(PPh_3)_2Cl_2$, 1.2 equiv $Bu_3SnCHCH_2$, 1.0 equiv TBAC, MeCN, 90 °C, 2 h; (b) 1.5 equiv *tert*-butyl 4-aminopiperidine-1-carboxylate, 3 equiv Et_3N, EtOH, 90 °C, 24 h.

$Bu_3SnCHCH_2$ (1.2 equiv) in the presence of $Pd(PPh_3)_2Cl_2$ (10%), TBAC (1.0 equiv) in MeCN at 90 °C for 2 h afforded nitro styrene **5d** in 94% yield. Reaction[5] of **5d** with *tert*-butyl 4-aminopiperidine-1-carboxylate (1.5 equiv), Et_3N (3.0 equiv) in EtOH at 90 °C for 2 h afforded azaindoline **9** exclusively in 67% yield. We were unable to discern whether attack of the NH_2– of *tert*-butyl 4-aminopiperidine-1-carboxylate occurred first at C4 of the pyridine or at the vinyl group. No intermediates could be detected by varying the reaction temperature (rt, 60 °C). No reaction is observed at rt, while slow formation of **9** occurs at 60 °C. Nitro groups on pyridines have been reported as leaving groups in S_NAr reaction by amines.[11] The procedures that are described in (Eq. 1) and Scheme 2 can be utilized to prepare azaindolines (**8** and **9**), whose syntheses have not been reported.

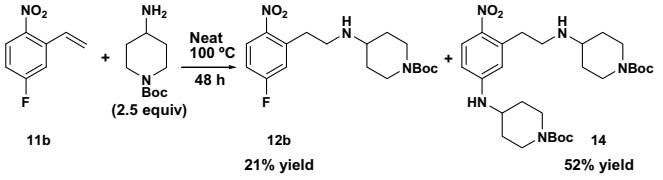
The preparation of **3a–c** is summarized in Scheme 3. The Stille coupling of nitro bromide **10a** with $Bu_3SnCHCH_2$ (1.2 equiv) under conditions described by Fu[12] for ArBr [2.5% $Pd(P^tBu_3)_2$, 2.5% $Pd(dba)_2$, PhMe, rt, 36 h] afforded the nitro styrene **11a** in 99% yield. Various reaction conditions utilizing base-catalyzed hydroaminations of styrene[13] failed to provide the desired Michael adduct **12a** from **11a** and *tert*-butyl 4-aminopiperidine-1-carboxylate. We were delighted to find that the mixture of **11a** and *tert*-butyl 4-aminopiperidine-1-carboxylate (2.5 equiv), when heated *neat* at 100 °C for 48 h, afforded Michael adduct **12a** in 64% yield. Hydrogenation [5% PtO_2, H_2 (60 psi), MeOH, rt, 16 h] afforded the desired reduction product ($-NO_2 \rightarrow -NH_2$) cleanly without removal of fluorine. Treatment[6] of the resulting aminoethylaniline with CDI (1.2 equiv), Et_3N (1.5 equiv) in MeCN at rt for 16 h produced cyclic urea **13a** in 96% yield (two steps). Reaction of **13a** in CH_2Cl_2 with 4 N HCl/dioxane produced **3a** in 100% yield. The procedures used to prepare **3a** from **10a** were also employed to prepare **3b** from **10b** (42% yield for five steps)[14] and **3c** from **10c** (49% yield for five steps)[15] with minor modification. The conversion of **11b**→**12b** was performed by simply mixing **11b** and *tert*-butyl 4-aminopiperidine-1-carboxylate (1.5 equiv) in CH_2Cl_2 at rt. Then, CH_2Cl_2 was removed in vacuo, and the residue was stirred at rt for 48 h to afford **12b** in 85% yield after flash chromatography. Under the reaction conditions for converting **11a** to **12a** [*tert*-butyl 4-aminopiperidine-1-carboxylate (2.5 equiv), neat, 100 °C, 48 h], **11b** was converted to **12b** in 21% yield along with bis-substitution product **14** in 52% yield (Eq. 2). The conversion of **10c** to **11c** employed Fu conditions[12] reported for ArCl [5%$Pd(P^tBu_3)_2$, 1.2 equiv $Bu_3SnCHCH_2$, 1.2 equiv CsF, dioxane, 100 °C, 24 h], since nitro chloride **10c** was less reactive than nitro bromides **10a,b** toward the Stille coupling reaction.



Scheme 3. Syntheses of F2-, F3-, and F4- substituted analogs of **3a–c**. Reagents and conditions. (a) 2.5%Pd(P^tBu_3)$_2$, 2.5% Pd(dba)$_2$, 1.2 equiv $Bu_3SnCHCH_2$, PhMe, rt, 36 h; (b) 2.5 equiv *tert*-butyl 4-aminopiperidine-1-carboxylate, neat, 100 °C, 48 h; (c) 5% PtO_2, H_2 (60 psi), MeOH, rt, 16 h; (d) 1.2 equiv CDI, 1.5 equiv Et_3N, MeCN, rt, 16; (e) 4 N HCl/dioxane, CH_2Cl_2, rt; (f) 1.5 equiv *tert*-butyl 4-aminopiperidine-1-carboxylate, CH_2Cl_2; the two reactants were formed a solution in CH_2Cl_2; all CH_2Cl_2 was removed and the resulting oil was stirred at rt for 48 h; (g) 5%Pd(P^tBu_3)$_2$, 1.2 equiv $Bu_3SnCHCH_2$, 1.2 equiv CsF, dioxane, 100 °C, 24 h.



Scheme 4. Efforts toward synthesis of F1 substituted analog. Reagents and conditions: (a) 5% Pd($^tBu_3$)$_2$, 1.2 equiv $Bu_3SnCHCH_2$, 1.2 equiv CsF, dioxane, 100 °C, 24 h. (b) 2 equiv *tert*-butyl 4-aminopiperidine-1-carboxylate, neat, 100 °C, 24 h.



(2)

The efforts toward synthesis of F1 analog **3d** are summarized in Scheme 4. Nitro styrene **11d** was formed in 71% yield using the conditions that were used for converting **10c** to **11c**. A mixture of **11d** and *tert*-butyl 4-aminopiperidine-1-carboxylate (2.0 equiv) was heated at 100 °C (neat) for 24 h to afford nitroaniline **15** in 53% yield with no desired product observed. The results of Eq. 2 and Scheme 4 indicated that the S_NAr reaction of amines with 2-F-nitrobenzene is more facile than with 4-F-nitrobenzene, in accordance with literature reports.[16]

In summary, aza analogs **2a–c** and F-substituted analogs **3a–c** of 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[*d*][1,3]diazepin-2(3*H*)-one (1) have been synthesized in high yields in five steps from the corresponding nitro halides, via Stille coupling, Michael addition, hydrogenation, cyclization, and Boc removal, in a straightforward manner. Although the protocols developed above cannot be applied to the synthesis of N3 and F1 analogs, some interesting previously unreported azaindolines by-products **8** and **9** were obtained.

Supplementary data

Representative experimental procedures. ^1H, ^{13}C NMR (data and spectra), and LRMS data for representative compounds are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.012.

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