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Regioselective synthesis of substituted pyrrolopyridines based on Pd(II)-mediated cross coupling and base induced heteroannulation

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Abstract—Novel pyrrolopyridines have been synthesized by an efficient, regioselective and catalytic method from commercially available and inexpensive 3-aminopyridine or 2-aminopyridine.

The palladium-catalyzed intramolecular cyclization reactions of various amines with alkynes and alkenes have been utilized for the synthesis of a number of nitrogen heterocycles including uracils,[1] pyrroles[2] and indoles[3] by the application of Sonogashira coupling. The catalytic coupling of aryl halides with alkynes has been applied in the synthesis of indoles, the final step in the procedure involving the palladium-catalyzed ring closure of N-protected arylamines, that is, by the implementation of the N-heteroannulation of acetylenic arylamines. In an effort to develop synthetic procedures for the preparation of substituted azaindoles, the synthesis and cyclization reactions of alkynyl amines were explored.[4]

Indole and azaindole heterocycles are prevalent substructures of naturally occurring and synthetic molecules displaying important biological and medicinal activity.[5] In particular, pyrrolopyridines bearing heterocycles have been used as modulators of kinase activity[6] and are frequently used in the treatment of allergic, autoimmune, inflammatory, proliferative and hyperproliferative diseases and immune mediated diseases including the rejection of transplanted organs or tissues and AIDS.[7] To our knowledge, there are only a few examples in the literature[4] on the synthesis of azaindoles via Sonagashira coupling followed by oxidative heteroannulation. Our aim was to prepare 2-substituted-5-bromo-1(*H*)-pyrrolo[3,2-*b*]pyridines and 2-substituted-5-bromo-1(*H*)-pyrrolo[2,3-*b*]pyridines so that a wide range of functionalities could be introduced at the 5-position such as by the reaction with aryl boronic acid, where an aryl group can be introduced via Suzuki coupling.[7] The recently reported synthesis of azaindole core moieties generally started with the dihalo compound followed by the replacement of one halo group with an amino group.[8] However, the development of substituted azaindoles from readily available and inexpensive 3-aminopyridine or 2-aminopyridine has not been investigated. In continuation of our efforts on the synthesis of biologically active heterocycles we undertook a study on the synthesis of pyrrolopyridines and herein we report the results of our investigation.

The required precursors **5a**,**b** were synthesized in 95–98% yields by the acylation of **4a**,**b** with trifluoroacetic anhydride in the presence of anhydrous K_2CO_3 in dry 1,4-dioxane at 25 °C for 1–2 h.[9] Compounds **4a**,[10] **b** were prepared in good yields (70–75%) by the regioselective cross coupling of alkynes **3** with 3-amino-2,6-dibromopyridine (**2**) under Sonogashira coupling[11] conditions. The dibromo compound **2** was prepared by bromination of 3-aminopyridine (**1**) with NBS in DMSO–water, mixed solvent at 0 °C[12] (Scheme 1).

For the heteroannulation of the internal alkynes, amino dibromopyridines **2** were acylated followed by Sonogashira coupling; however the coupling did not proceed well. The Sonogashira coupling was then attempted with amino dibromopyridine **2** using Pd $(PPh_3)_2Cl_2$ as a catalyst and CuI as a co-catalyst in dry DMF with Et_3N. The regioselective cross coupling[13] products **4** were

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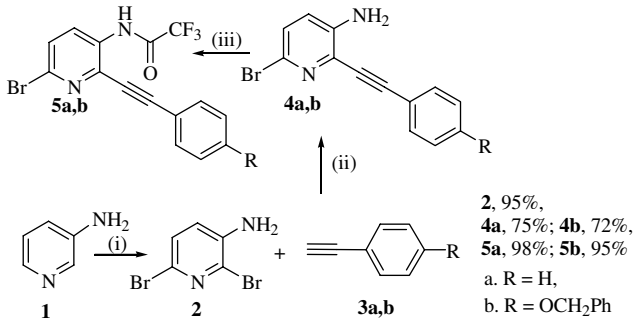
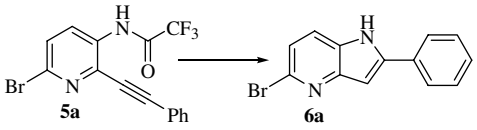


Scheme 1. Reagents and conditions: (i) NBS, DMSO, H_2O, 0 °C, 1 h; (ii) 5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 5:2 DMF–Et_3N, 110 °C, 2 h; (iii) trifluoroacetic anhydride, K_2CO_3, 1,4-dioxane, rt, 1–2 h.

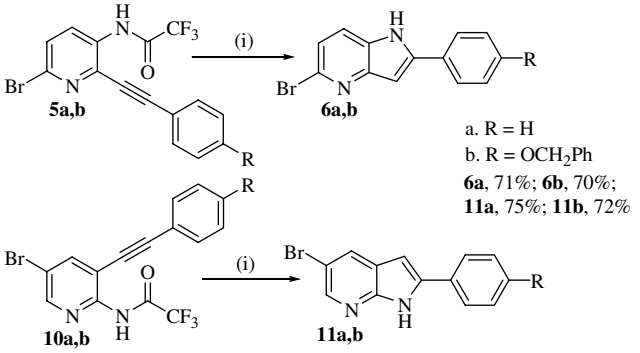
obtained exclusively. Compounds **10a**,**b** were obtained by the same procedure (Scheme 2). No cyclization product was detected in the reaction mixture. This result suggested that the nitrogen was not nucleophilic enough to permit cyclization. To obtain the cyclization product in one-pot, trifluoroacetic anhydride (TFAA) was added to the reaction mixture, which was heated for a further 1 h at 100 °C. Thus the cyclized product was isolated in only 10% yield. To increase the yield of the cyclized product, the acylated alkyne products **5** and **10** were first isolated and then heated for 1 h at 100 °C under the same Sonogashira coupling conditions as stated earlier. The desired cyclized products **6** and **11** were obtained in relatively good yields (50–55%). TFAA was used as the electron withdrawing group on the nitrogen to facilitate this transformation because deprotection of the acyl group was readily achieved via hydrolysis of the amide bond during the reaction and/or work-up.[14] In order to determine whether the cyclization reaction was Pd-catalyzed, Cu-catalyzed or a result of base induced cyclization, we performed the cyclization reaction under different conditions (Table 1).

From the results obtained we conclude that the heteroannulation occurred via base promoted cyclization, as the reaction did not occur without triethylamine even when heated at 100 °C for 5 h. Hence, the cyclization reactions were performed in *N*,*N*-dimethylformamide (DMF) using triethylamine as base under a nitrogen atmosphere at 100 °C for 1 h to afford[16] products **6a**,**b** and **11a**,**b** in 70–75% yields (Scheme 3).

Table 1. Various cyclization conditions[15]

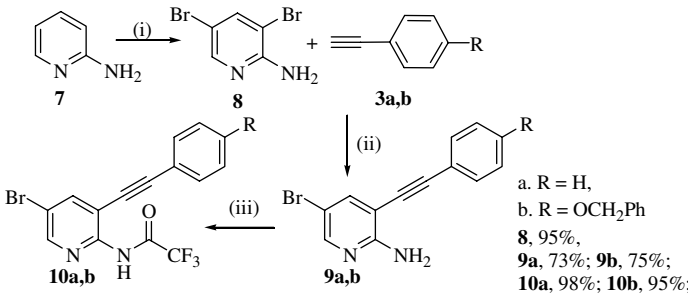


Entry	Reaction conditions	Time (h)	Yield (%)
1	5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 100 mol % Et_3N, DMF, rt	12	22
2	10 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 100 mol % Et_3N, DMF, rt	12	22
3	5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 100 mol % Et_3N, DMF, 100 °C	1	56
4	5 mol % $Pd(PPh_3)_2Cl_2$, 100 mol % Et_3N, DMF, 100 °C	1	52
5	10 mol % CuI, 100 mol % Et_3N, DMF, 100 °C	1	57
6	100 mol % Et_3N, DMF, 100 °C	1	70
7	50 mol % Et_3N, DMF, 100 °C	1	71
8	DMF, 100 °C	5	0



Scheme 3. Reagents and conditions: (i) DMF, 50 mol % Et_3N, 100 °C, 1 h.

In conclusion, the described chemistry outlines a method by which a range of highly functionalized pharmaceutically important 5-bromopyrrolopyridines can be rapidly accessed, regioselectively and in high yield. The novelty in our synthesis lies (1) with the use of readily



Scheme 2. Reagents and conditions: (i) NBS, DMSO, H_2O, 0 °C, 1 h; (ii) 5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 5:2 DMF–Et_3N, 110 °C, 2 h; (iii) trifluoroacetic anhydride, K_2CO_3, 1,4-dioxane, rt, 1–2 h.

available, inexpensive 3-amino- or 2-aminopyridine as starting materials, (2) regioselective cross coupling of the alkyne group, and (3) mild base induced cyclization. In comparison, Cacchi et al. used K_2CO_3 in 1,4-dioxane at 110 °C for 24 h with 2,2,2-trifluoro-*N*-(3-(2-phenylethynyl)quinoxalin-2-yl)acetamide to obtain only a 22% yield of the cyclized product.[8]

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10. *Compound* **4a**, *(6-bromo-2-(2-phenylethynyl)pyridine-3-amine)*: White solid, mp 120–122 °C, yield 75%. IR (KBr, cm^{-1}) ν_{max}: 3455, 3312; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.94 (d, 1H, Ar*H*, $J = 8.6$ Hz), 7.20 (d, 1H, Ar*H*, $J = 8.5$ Hz), 7.33–7.37 (m, 3H, Ar*H*), 7.56–7.58 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 84.3, 96.4, 122.1, 124.2, 128.3, 128.7, 129.4, 132, 144.1; MS (*m*/*z*): 272 (M^+) 274. Anal. Calcd for $C_{13}H_9BrN_2$: C, 57.17; H, 3.32; N, 10.26. Found: C, 57.03; H, 3.33; N, 10.39.
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15. *Compound* **6a**, (*5-bromo-2-phenyl-1H-pyrrol[3,2-b]pyridine*): White solid, mp above 245 °C, yield 71%. IR (KBr, cm^{-1}) ν_{max}: 3135; ^1H NMR (DMSO-d_6, 400 MHz) δ: 7.05 (d, 1H, C*H*═C, $J = 1.4$ Hz), 7.23 (d, 1H, Ar*H*, $J = 8.4$ Hz), 7.40 (t, 1H, Ar*H*, $J = 7.3$ Hz), 7.51 (t, 2H, Ar*H*, $J = 7.5$ Hz), 7.72 (d, 1H, Ar*H*, $J = 8.4$ Hz), 7.92 (d, 2H, Ar*H*, $J = 7.5$ Hz), 12.04 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 98.8, 119.5, 120.8, 125.7, 128.4, 128.8, 129.1, 131.4, 133.8, 142.5, 147.5; HRMS ($C_{13}H_9BrN_2$) Calcd: 273.0027 (M+H (^{79}Br)), 275.0007 (M+H (^{81}Br)). Found: 273.0022 (M+H (^{79}Br)) (M+H (^{81}Br)). Anal. Calcd for $C_{13}H_9BrN_2$: C, 57.17; H, 3.32; N, 10.26. Found; C, 57.33; H, 3.18; N, 10.22.
16. *General procedure for the synthesis of compounds* **6a**,**b** and **11a**,**b**: Triethylamine (0.18 mL, 50 mol %) was added to a solution of compound **5a** (1 g, 2.70 mmol) in dry DMF (10 mL) and the reaction was heated for 1 h at 100 °C. After cooling the reaction mixture, water (30 mL) was added and stirring continued for 3 h. The resulting solid precipitate was filtered and dried over $CaCl_2$, to afford **6a** (0.517 g, 71%) as a white solid. Similarly, the other substrates **5b** and **10a**,**b** were subjected to the same reaction conditions to give products **6b** and **11a**,**b**.