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Efficient synthesis of 4-O- and C-substituted-7-azaindoles

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Abstract—6-Chloro-4-nitro- and 4,6-dichloro-1*H*-pyrrolo[2,3-*b*]pyridine are versatile building blocks that allow the synthesis of 4-substituted 7-azaindole derivatives by simple nucleophilic displacement of the 4-substituent. Herein, we report on their reaction with phenolates and activated methylene nucleophiles.

7-Azaindole is an indole surrogate of increasing interest in medicinal chemistry. It has been used as an indole bioisostere to improve physicochemical and pharmacokinetic properties of several drug candidates.[1] It is also an emerging pharmacophore in ATP competitive kinase inhibitors as it contains the typical motif (H-bond donor and acceptor in 1,3-position) to dock into the adenine binding pocket.[2,3]

The regioselective functionalization of the pyridine ring of 7-azaindole remains a major challenge, although some progress has been achieved starting from the N-oxide derivative,[4] and more recently using the Hemetsberger–Knittel reaction.[5] In the course of an ongoing research program, we required a general and efficient synthesis of 4-*O*-aryl-1*H*-pyrrolo-[2,3-*b*]pyridines, which to the best of our knowledge was unprecedented.

To permit a wide optimization program, we envisaged the synthesis of an activated 7-azaindole building block that could be substituted with phenols. 4-Chloro, 4-nitro, and 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine[6] proved to be inert when heated with 4-amino-2-fluorophenol in the presence of KO*t*-Bu. The corresponding N-oxides also did not afford any substitution product when reacted with 4-amino-fluorophenol under the same conditions.[7] The palladium or copper catalyzed coupling between either 4-chloro[8] or 4-bromo-1*H*-pyrrolo[2,3-*b*]-pyridine[4] and 4-N-protected-amino-2-fluorophenol also failed to afford an acceptable yield of the diarylether.[9]

Encouraged by the fact that 2,4-dichloropyridine readily undergoes nucleophilic substitution selectively at the 4-position,[10] we decided to use the corresponding 4,6-dichloro-1*H*-pyrrolo[2,3-*b*]pyridine (**3a**) as the acceptor. Compound **3a** was prepared following a published procedure (Scheme 1).[11] When heated overnight at 80 °C with 4-amino-2-fluorophenol and K_2CO_3 in DMSO, **3a** was completely converted to arylether **5**. Nevertheless, after a tedious workup of the tar-like reaction mixture and further chromatography, we isolated **5** in a 16% yield. Modification of the reaction conditions (KO*t*-Bu, DMF, 100 °C) did not significantly improve the isolated yield of diarylether **5**.

Relative to 2,4-dichloropyridine, the position 4 of compound **3a** should be less electrophilic due to the electron-donating effect of the fused pyrrole ring. Therefore, we reasoned that a more electron withdrawing leaving group would render the 4-position more electrophilic, thus accelerating the aromatic nucleophilic substitution. In fact, the reaction of the 6-chloro-4-nitro analogue **3b**, which was prepared by chlorination[12] of the known 4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine-*N*-oxide (**2**),[13] with 4-amino-2-fluorophenol was complete after 2 h. However, the isolated yield of **5** (29%) was not satisfying, and the difficult workup did not allow for an increase in scale. It is noteworthy that the 6-substitution product could not be detected in the reaction mixture.

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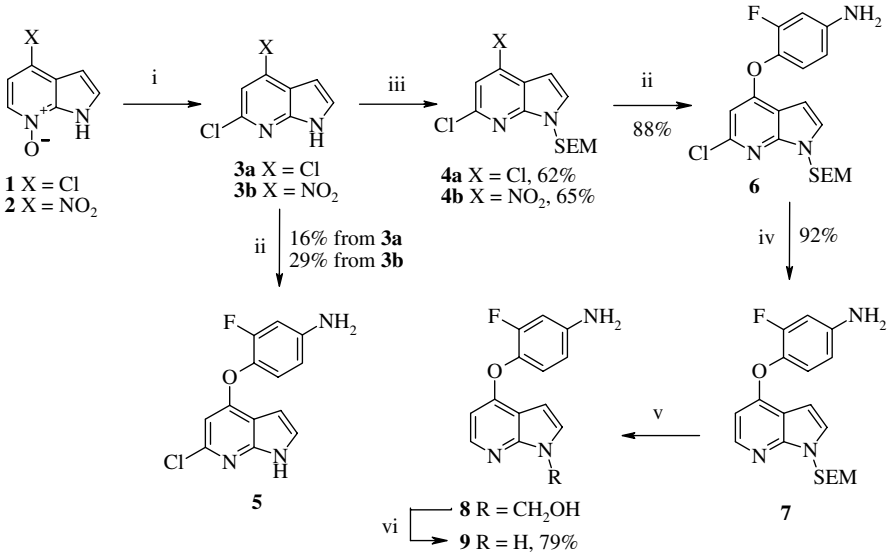


Scheme 1. Reagents and conditions: (i) Cl_3CCOCl, $(Me_3Si)_2NH$, THF, 1 h; (ii) 4-amino-2-fluorphenol, K_2CO_3, DMSO, 100 °C, 2 h; (iii) SEMCl, NaH, THF, 1 h; (iv) H_2, 10% Pd/C, EtOH, rt, 24 h; (v) TFA 50% in DCM, 2 h; (vi) AcONa, EtOH, 1 h.

To avoid possible side reactions associated with the partial deprotonation of the pyrrolic nitrogen under the reaction conditions, we decided to examine the reaction using a protecting group for this position. 1-[2-(Trimethylsilyl)ethoxy]methyl group (SEM) proved to be the best choice among the available indole-protecting groups. To our delight, the SEM-protected 6-chloro-4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**4b**) reacted with 4-amino-2-fluorophenol to afford diarylether **6** in 88% yield. The 4-chloro analogue **4a** gave comparable yields as well.[14]

As can be seen in Table 1, the reaction yields correlate with the nucleophilicity of the reacting phenolate. Only phenols of very low nucleophilicity like methyl salicylate do not give any product (entry 5). In general, the 4-nitro derivative **4b** produced better yields than the 4-chloro

Table 1.

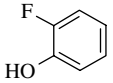
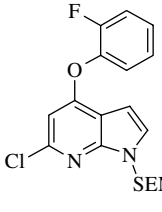
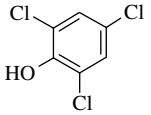
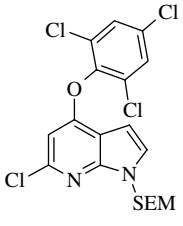
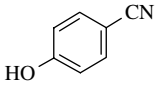
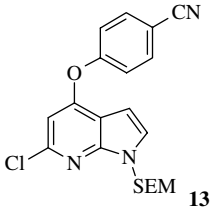
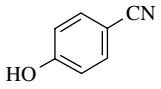
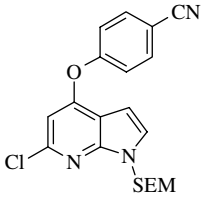
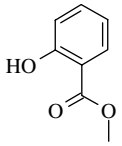
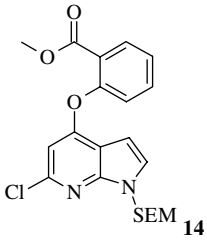
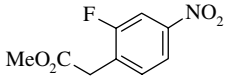
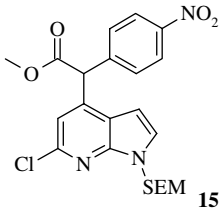
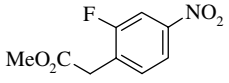
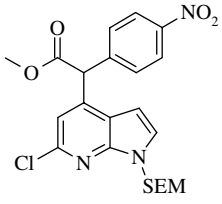
Entry	Phenol	Acceptor	Product	Yield[a] (%)
1		**4a**	 **11**	91
2		**4a**	 **12**	63
3		**4a**	 **13**	49

Table 1 (*continued*)

Entry	Phenol	Acceptor	Product	Yield[a] (%)
4		**4b**		71
5		**4b**	 **14**	0
6		**4a**	 **15**	0
7		**4b**		93

[a] Isolated yields.

analogue **4a**, when phenols carrying electron withdrawing groups were used (entries 4 and 5).

Moreover, we found that when using a suitable carbon nucleophile, it was also possible to make carbon analogues of compound **6**. Consequently, the 4-nitro derivative **4b** reacted with the sodium salt of methyl 2-(4-nitro-2-fluorophenyl)acetate (entry 7) to produce the 4-benzyl-derivative **15** in 93% yield.[15] Surprisingly, the reaction did not proceed with the 4-chloro-analogue **4a** (entry 6).

Compound **6** was cleanly converted into **7** by a hydrogenolytic removal of the chlorine atom (Scheme 1). The SEM group was cleaved in reasonable yield following a two-step procedure. First, treatment of compound **7** with 50% trifluoroacetic acid in dichloromethane at room temperature for 2 h afforded an equimolar mixture of hemiaminal **8** and deprotected compound **9**. This mixture was then quantitatively converted to **9** after stirring it for 1 h with sodium acetate in ethanol. After column chromatography, the target compound **9**[16] could be isolated in 79% yield. This route was performed on a 100 g scale.

In summary, we have developed a straightforward synthetic strategy that permits access to novel 4-substituted 7-azaindole derivatives, using a nucleophilic aromatic substitution as the key step.

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S.; Galgóczya, K.; Horvátha, C.; Farkasa, S.; Domány, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3953–3956.
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14. In a typical experiment, **5a** or **5b** and the corresponding phenol (1.5 equiv) were dissolved in DMSO, 2 equiv of K_2CO_3 was then added and the suspension was stirred at 100 °C until the starting azaindole was consumed. After being cooled, the reaction was poured into ice water and the product was extracted with ethyl acetate. The organic extracts were combined and washed with brine. After removal of the solvent, the residues were purified by column chromatography. ^{1}H NMR: compound **6** (300 MHz, DMSO-d_6): $\delta = -0.09$ (s, 9H), 0.82 (t, $J = 8.2$ Hz, 2H), 3.51 (t, $J = 8.2$ Hz, 2H), 5.53 (s, 2H), 6.32 (d, $J = 3.5$ Hz, 1H), 6.34 (s, 1H), 6.44 (dd, $J = 8.5$, 2.6 Hz, 1H), 6.52 (dd, $J = 13.2$, 2.6 Hz, 1H), 7.06 (t, $J = 9.1$ Hz, 1H), 7.54 (d, $J = 3.5$ Hz, 1H); compound **11** (300 MHz, DMSO-d_6): $\delta = -0.11$ (s, 9H), 0.82 (t, $J = 8.1$ Hz, 2H), 3.50 (t, $J = 8.1$ Hz, 2H), 6.33 (d, $J = 3.6$ Hz, 1H), 6.36 (s, 1H), 6.86 (m, 1H), 6.95 (t, 1H, $J = 7.8$), 7.05 (m, 2H), 7.55 (d, $J = 3.6$ Hz, 1H); compound **12** (300 MHz, DMSO-d_6): $\delta = -0.09$ (s, 9H), 0.81 (t, $J = 8.2$ Hz, 2H), 3.51 (t, $J = 8.2$ Hz, 2H), 6.35 (d, $J = 3.5$ Hz, 1H), 6.37 (s, 1H), 7.27 (s, 2H), 7.55 (d, $J = 3.5$ Hz, 1H); compound **13** (300 MHz, DMSO-d_6): $\delta = -0.10$ (s, 9H), 0.81 (t, $J = 8.1$ Hz, 2H), 3.51 (t, $J = 8.1$ Hz, 2H), 6.34 (d, $J = 3.6$ Hz, 1H), 6.37 (s, 1H), 6.97 (d, $J = 8$ Hz, 2H), 7.57 (d, $J = 3.6$ Hz, 1H), 7.62 (d, $J = 8$ Hz, 2H).
15. Methyl 2-(4-nitro-2-fluorophenyl)acetate (908 mg, 4.26 mmol) was dissolved in DMF (10 mL) and sodium hydride (60% in mineral oil, 170 mg, 4.26 mmol) was added. The mixture was stirred at rt for 30 min. Compound **5b** (698 mg, 2.13 mmol) in DMF (5 mL) was then added and the reaction was heated to 70 °C and further stirred for 2 h. After being cooled, the solution was poured into ice water and the suspension was extracted with ethyl acetate. The organic extracts were combined and washed with brine. After removal of the solvent, the residue was purified by column chromatography. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = -0.12$ (s, 9H), 0.80 (t, $J = 8.1$ Hz, 2H), 3.52 (t, $J = 8.1$ Hz, 2H), 3.74 (s, 3H), 5.57 (s, 2H), 6.02 (s, 1H), 6.60 (d, $J = 3.6$ Hz, 1H), 7.15 (s, 1H), 7.57 (t, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 3.6$ Hz, 1H), 8.05 (dd, $J = 8.5$, 2.2 Hz, 1H), 8.17 (dd, $J = 10.0$, 2.2 Hz, 1H).
16. ^{1}H NMR: compound **9** (DMSO-d_6, 300 MHz): $\delta = 5.40$ (s, 2H), 6.23 (dd, $J = 3.5$, 1.8 Hz, 1H), 6.29 (dd, $J = 5.3$, 0.8 Hz, 1H), 6.43 (ddd, $J = 8.7$, 2.4, 1.7 Hz, 1H), 6.52 (dd, $J = 13.5$, 2.4 Hz, 1H), 7.01 (t, $J = 9.0$ Hz, 1H), 7.32 (dd, $J = 3.3$, 2.6 Hz, 1H), 8.03 (d, $J = 5.3$ Hz, 1H), 11.65 (s, 1H).