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# Concise and Efficient Synthesis of 4-Fluoro-1*H*-pyrrolo[2,3-*b*]pyridine

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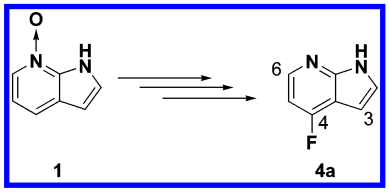
## ABSTRACT

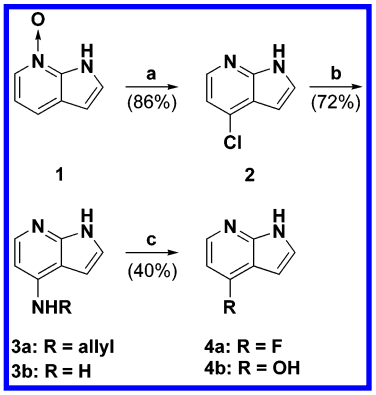



**Two routes describing the preparation of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (4a) from 1*H*-pyrrolo[2,3-*b*]pyridine *N*-oxide (1) are presented. Regioselective fluorination was achieved using either the Balz–Schiemann reaction or lithium–halogen exchange.**

Azaindoles are indole surrogates of great interest in synthetic organic and medicinal chemistry. While there are limited literature references on the chemical reactivity of 7-azaindoles, their synthesis has been the subject of a number of recent reviews.[1] The regioselective synthesis of 7-azaindoles, functionalized on the pyridine ring, remains a major challenge that has been addressed so far by two general approaches: (1) formation of the pyrrole ring via the cyclization of an appropriately functionalized pyridine precursor and (2) ring substitution starting from 7-azaindole *N*-oxide (**1**).[1] In the course of an ongoing research program, we required an efficient synthesis of 4-fluoro-1*H*-pyrrolo-[2,3-*b*]pyridine (**4a**), which to our knowledge was unprecedented (Scheme 1).

The challenge in the synthesis of compound **4a** resides in the need for selective aromatic fluorination at C-4. Aromatic fluorination reactions are usually achieved either by the Balz−Schiemann reaction[2,3] or via electrophilic fluorination.[4] The drawback of the electrophilic fluorination of neutral aromatics is that it typically gives mixtures of mono- and polyfluorinated products. On the other hand, the Balz−Schiemann reaction provides regioselective monofluorinated aryl fluorides via the controlled thermal decomposition of a diazonium tetrafluoroborate salt.

**Scheme 1**[a]




[a] Reagents and conditions: (a) $CH_3SO_2Cl$, DMF. (b) (1) *N*-allylamine, $Pd(OAc)_2$, (*o*-biphenyl)$PCy_2$, NaO*t*-Bu, 1,4-dioxane, 100 °C; (2) 10% Pd/C, $CH_3SO_3H$, EtOH, 80 °C. (c) 48% aq $HBF_4$, $NaNO_2$, 23 °C.

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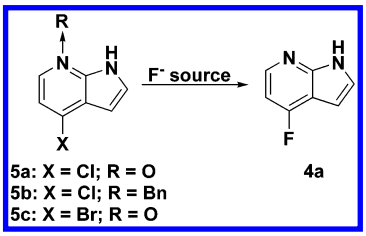
Our first approach to the synthesis of **4a** took advantage of a regioselective Balz-Schiemann fluorination reaction, which required the synthesis of the intermediate amine **3b**.[5] Recently, Benoît and Gingras have developed the regioselective chlorination at C-4 of 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (**1**), using methanesulfonyl chloride in DMF.[6] Attempted thermal nucleophilic substitution of the resulting chloride **2** using N-allylamine or sodium azide was unsuccessful. Cottam and co-workers[7] have demonstrated that the thermal nucleophilic substitution of chloride **2** worked only with secondary alkylamines or *N*-alkylanilines, from which deprotection to give the primary amine would not be trivial. It was therefore apparent to us that an alternative approach was necessary.

Fortunately, it was found that a Buchwald palladium-catalyzed amination[8] using chloride **2** and *N*-allylamine gave allylamine **3a** in 76% yield. Subsequent deallylation,[9] using palladium on carbon in acidic alcohol solution, provided 1*H*-pyrrolo[2,3-*b*]pyridin-4-ylamine **3b** in 95% yield, after purification on SCX-silica gel.[10] The amine **3b** was then submitted to the Balz-Schiemann reaction conditions. In previously reported Balz-Schiemann reactions, the diazonium tetrafluoroborate intermediate can typically be isolated and subsequent pyrolysis gives the desired fluoroaromatic compound.[2,3] In our case, diazonium tetrafluoroborate salt was generated from the amine **3b** at 0 °C[2b] and decomposition occurred spontaneously in the 48% tetrafluoroboric acid solution in water at room temperature, affording a 1:1.3 mixture of fluoride **4a** and 1*H*-pyrrolo[2,3-*b*]pyridine-4-ol (**4b**). This type of side reaction is typically not observed in the Balz−Schiemann transformation, because the dediazoniation step proceeds in the absence of water at high temperature.[2,3] However, in this case, the desired fluoride compound **4a** was isolated in 40% yield from the mixture by basic aqueous extractions. Using other reaction conditions, we were able to preclude the formation of alcohol **4b**, but this did not result in an improved isolated yield of **4a**. For example, when the diazonium tetrafluoroborate was isolated at low temperature (−5 °C) and the decomposition was carried out at 85 °C in toluene, only a 25% isolated yield of the fluoride **4a** was obtained. Similarly, other conditions using $HPF_6$,[2b] $NOBF_4$,[2b] $NOPF_6$,[2b] and *t*-BuONO[11] were attempted but did not improve the yield of fluoride **4a**. Nevertheless, the Balz−Schiemann route described above provided the first practical synthesis of 4-fluoro-1*H*-pyrrolo-[2,3-*b*]pyridine (**4a**) in a four-step sequence in 29% overall yield. Since a more efficient and scalable synthesis was required, alternative approaches were subsequently explored.

For example, we intensively examined alternative chlorine displacement reactions using 4-chloro-1*H*-pyrrolo[2,3-*b*]-pyridine-7-oxide (**5a**) and 7-benzyl-4-chloro-1*H*-pyrrolo[2,3-*c*]pyridin-7-ium bromide[12] (**5b**) together with various nucleophilic fluorine sources (Scheme 2).[13,14] These attempts proved to be unsuccessful, with either starting material recovery or decomposition occurring. We then tried increasing the leaving group capacity from a chloride to a bromide. Adapting the regioselective chlorination conditions found by Benoît and Gingras,[6] we synthesized 4-bromo-1*H*-pyrrolo-[2,3-*b*]pyridine (**6**) by treating the *N*-oxide **1** with methanesulfonyl bromide[15] in DMF. Interestingly, this bromination was not as regioselective as the corresponding chlorination and the desired bromide **6** was obtained in only 13% yield. The *N*-oxide[16] **5c** was prepared from **6**, but unfortunately all attempts to displace the bromide failed.

**Scheme 2**




We then decided to use bromide **7** in a lithium−halogen exchange reaction, followed by treatment with electrophilic fluorine reagent, to generate a 4-fluoro derivative (Scheme 3).[17] As part of this approach, the development of an improved preparation of **6** was undertaken. It was found that treatment of *N*-oxide **1** with methanesulfonic anhydride and tetramethylammonium bromide in DMF gave a mixture (8:1:1) of the 4-bromo-, 6-bromo- and 4,6-dibrominated compounds. The desired 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**6**) crystallized from the reaction mixture in 54% yield, following addition of water and neutralization to pH 7 using aqueous

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(10) On a larger scale, purification could also be done using Dowex 50W X 4 resin.

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(16) *N*-Oxide was formed in 94% yield upon treatment of 4-bromo-7-azaindole **6** with a solution of 32% peracetic acid/acetic acid in ethyl acetate.

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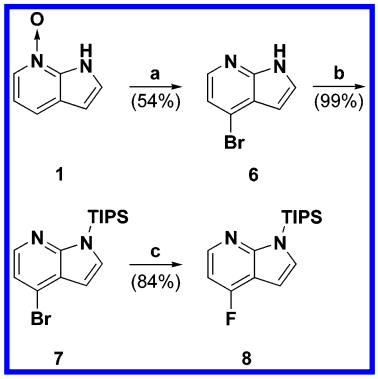
**Scheme 3** [a]




[a] Reagents and conditions: (a) $(CH_3SO_2)_2O$, $(CH_3)_4NBr$, DMF; (b) NaH, TIPS−Cl, THF, 65 °C; (c) *t*-BuLi, NFSI, THF, −78 °C.

sodium hydroxide. Bromide **6** was then protected (to avoid subsequent lithiation at C-2[18]) as the *N*-triisopropylsilyl derivative in quantitative yield. Lithium−halogen exchange of bromide **7** using *tert*-butyllithium[19] in THF at −78 °C, followed by addition of *N*-fluorobenzenesulfimide,[17] gave fluoride **8** in 84% yield. It is worth noting that the yield obtained for this heteroaryllithium fluorination is particularly high in comparison with related examples reported in the literature.[17] Finally, deprotection using tetrabutylammonium fluoride provided fluoride **4a** in quantitative yield. This route provided rapid, efficient, and scalable access to 4-fluoro-7-azaindole **4a** in 45% overall yield.

In conclusion, two routes have been developed for the synthesis of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (**4a**). The first synthetic approach features a Balz−Schiemann transformation proceeding at room temperature. A second approach features efficient lithium−halogen exchange of the corresponding bromide **7**, followed by quenching with an electrophilic fluorine source. These approaches afford new fluorinated azaindoles for which there is very little precedent in the literature. Further studies on the use of 4-fluoro-7-azaindole **4a** and related compounds will be reported in due course.

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**Supporting Information Available:** Detailed experimental procedures and full characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) A >1.5 M solution of *tert*-butyllithium in pentane was used to avoid the precipitation of *N*-fluorobenzenesulfimide.