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

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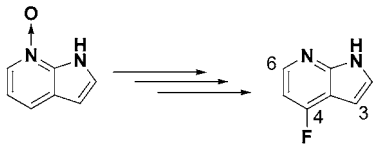
ABSTRACT

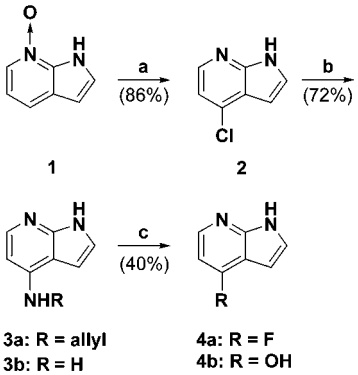


Two routes describing the preparation of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (4a) from 1*H*-pyrrolo[2,3-*b*]pyridine *N*-oxide (1) are presented. Regioselective fluorination was achieved using either the Balz–Schiemann reaction or lithium–halogen exchange.

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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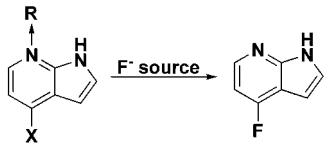
Our first approach to the synthesis of **4a** took advantage of a regioselective Balz-Schiemann fluorination reaction, which required the synthesis of the intermediate amine **3b**.[5] Recently, Benoît and Gingras have developed the regioselective chlorination at C-4 of 1*H*-pyrrolo[2,3-*b*]pyridine 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

Scheme 2



5a: X = Cl; R = O
5b: X = Cl; R = Bn
5c: X = Br; R = O

4a

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.

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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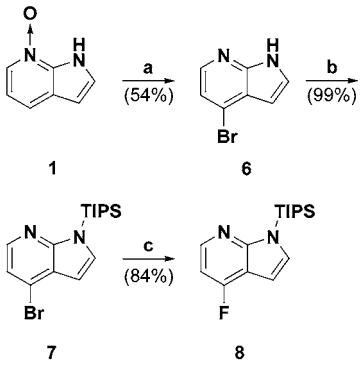
Scheme 3 [a]



[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.