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# Synthetic Entries to Substituted Bicyclic Pyridones

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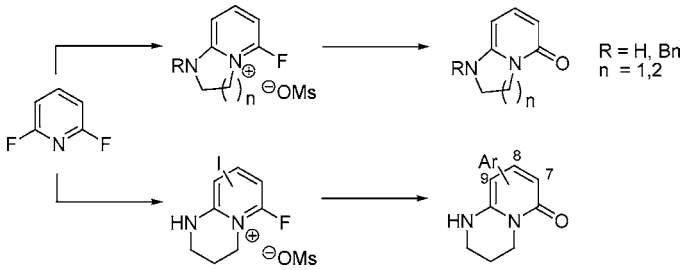
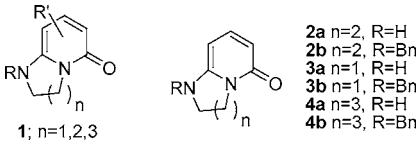
## ABSTRACT




**The synthesis of 6,6- and 5,6-bicyclic pyridone scaffolds has been completed using (*i*) an intramolecular Mitsunobu reaction and/or (*ii*) hydrolysis of a bicyclic pyridinium salt intermediate. Regioselective functionalization of the pyridone ring has been achieved via either direct lithiation or use of the "halogen dance" reaction. Suzuki coupling then allows introduction of aryl units at C(7)/C(9) or C(8) onto the bicyclic pyridone scaffold at either an early or late stage in the synthetic sequence. Suzuki couplings involving iodopyridinium intermediates are particularly effective.**

Bicyclic pyridones **1** are of general interest within medicinal chemistry, and a series of substituted variants of **1** ($n = 1,2$) have been reported as a basis for analgesics and anti-inflammatory agents.[1] Published methods for the synthesis of bicyclic pyridones **1** ($n = 1,2$) are based on three approaches: the cyclocondensation of ketenaminals,[2] the addition of diamines to cyanobutenoic esters,[1a,b] and the addition of diamines to halo-[1] or thiomethylpyridones.[3]




However, the range of variation available using these strategies is restricted as the diversity (i.e., substitution pattern) is set very early in the synthetic sequence. This, in turn, places limitations on the flexibility and subsequent applications of this chemistry.

In this paper, we report two strategies for the synthesis of the 5,6- and 6,6-ring bicyclic pyridones **2a/b** and **3a/b**. The introduction and exploitation of flexible functional groups (such as boronic acid or iodide) within these scaffolds is exemplified using the 6,6-ring system **2a**, and an ability to

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(1) (a) Kazuo, K.; Noriki, I.; Isao, S.; Yasuo, I.; Hiroshige, H.; Masuo, M. US 4186200, 1978. (b) Frohn, M.J.; Hong, F.-T.; Liu, L.; Lopez, P.; Siegmund, A.C.; Tadesse, S.; Tamayo, N. WO 2005070932, 2005. (c) Alonso-Alija, C.; Michels, M.; Schirok, H.; Schlemmer, K.-H.; Dodd, S.; Fitzgerald, M.; Bell, J.; Gill, A. WO 2003053967, 2003.

(2) (a) Huang, Z. T.; Liu, Z. R. *Heterocycles* **1986**, *24*, 2247−2254. (b) Huang, Z. T.; Wang, M. X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1085−1090. (c) Zhao, M. X.; Wang, M. X.; Huang, Z. T. *Tetrahedron* **2002**, *58*, 1309−1316. (d) Jones, R. C. F.; Smallridge, M. J. *Tetrahedron Lett.* **1988**, *29*, 5005−5008. (e) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Smallridge, M. J. *Tetrahedron* **1998**, *54*, 6191−6200. (f) Shiokawa, K.; Tsuboi, S.; Sasaki, S.; Moriya, K.; Hattori, Y.; Shibuya, K. EP 296453, 1988.

(3) Hehemann, D. G.; Winnik, W. *J. Heterocycl. Chem.* **1994**, *31*, 393−396.

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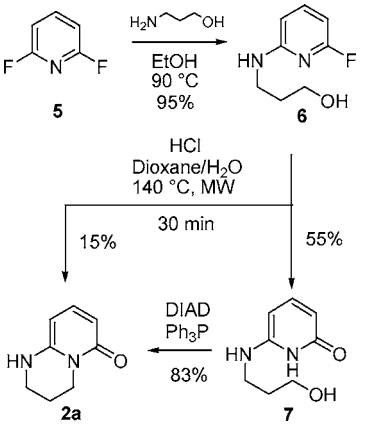
achieve aryl substitution at C(7), C(8), or C(9) is demonstrated.

Our route to the 6,6-pyridone (1,2,3,4-tetrahydro-6*H*-pyrido[1,2-*a*]pyrimidin-6-one) **2a** began with 2,6-difluoropyridine **5** which underwent nucleophilic substitution with 3-amino-1-propanol to provide **6** in 95% yield. Hydrolysis of **6** (0.1 M HCl, 140 °C, microwave irradiation) gave **7** in 55% yield along with 15% of the final target **2a**;[4] the intermediate pyridone **7** could be cyclized to **2a** under Mitsunobu cyclodehydration conditions[5] in 83% yield (Scheme 1).

**Scheme 1.** Mitsunobu Route to Bicyclic Pyridone **2a**



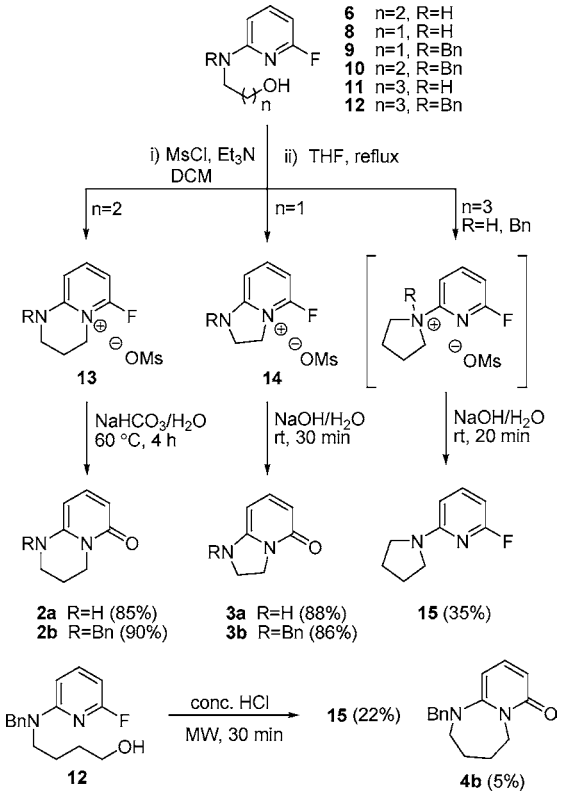

The scale associated with the chemistry shown in Scheme 1 was limited by the necessity for microwave irradiation (**6**→**7**) so a more efficient route was required. The key feature here was incorporation of a suitable leaving group on the aminoalcohol side arm to enable facile cyclization. After screening a variety of leaving groups and conditions, a one-pot procedure was identified (Scheme 2). This new methodology was also applicable to the *N*-benzyl and corresponding 5,6-variants **2b** and **3a/b**, respectively.

Aminoalcohol **6** was mesylated then cyclized (THF, reflux) to give the pyridinium salt **13** (R = H) as an isolable species. This reaction was readily monitored by $^1$H NMR, and the intermediacy of **13** was confirmed (see Supporting Information). Mild basic hydrolysis gave **2a** in 85% yield. Having established a more efficient method for generation of **2a**, the scope of this chemistry has been extended to the related 5,6-ring system represented by **3a/b**.

2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyridin-5-one **3a** was prepared from 2,6-difluoropyridine **5** by nucleophilic substitution with ethanolamine (to give **8**) followed by mesylation and cyclization as described for **2a**. Mild hydrolysis ($NaHCO_3$) of **14** (R = H) failed; however, aqueous NaOH (6 equiv, rt) converted **14** (R = H) to **3a** in 88% overall yield. Pyridone **3a** was unstable toward silica gel, but the efficiency of the hydrolysis procedure allowed **3a** to be isolated without recourse to chromatography.

(4) The primary chloride corresponding to **6** was isolated in 5% yield using a shorter reaction time (15 min), and it was then shown that this chloride cyclizes to give **2a** under the microwave reaction conditions used.

**Scheme 2.** Synthesis of Pyridones **2a/b**, **3a/b**, and **4b**




The *N*-benzyl variants **2b** and **3b** have also been prepared. Reaction of 2,6-difluoropyridine **5** with *N*-benzyl ethanolamine and *N*-benzyl 3-aminopropan-1-ol gave the *N*-benzylated adducts **9** and **10** in 81 and 87% yields, respectively. Subsequent *O*-mesylation and cyclization gave **3b** and **2b** in 86 and 90% overall yields, respectively. *N*-Benzyl pyridone **3b**, the structure of which was confirmed by X-ray crystallography (see Supporting Information), was more stable than **3a** under the reaction conditions used and in terms of its "shelf stability".

An entry to the 7,6-ring bicyclic pyridone (2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*][1,3]diazepin-7-one) **4a/b** has also been evaluated. Mesylation of **11** (obtained in 83% yield from **5** and 4-aminobutan-1-ol) led, after hydrolysis, to the pyrrolidine adduct **15**[6] as the only characterizable product in 35% yield, and a similar outcome was observed with the *N*-benzyl derivative **12**.[7] However, use of strongly acidic conditions (conc HCl, heating) did convert **12** to a separable mixture of **15** and the desired **4b** in 22 and 5% yields, respectively. Attempts to improve the yield of **4b** have not been successful,

(5) Weissman, S. A.; Lewis, S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 7459−7462.

(6) Following mesylation of **12** and heating in THF, the formation of the quaternary pyrrolidine salt shown in Scheme 2 was observed by $^1$H NMR but was not fully characterized. Debenzylation of this intermediate occurred on treatment with NaOH, and the apparently facile nature of this step may be associated with the enhanced leaving group ability of a 2-aminopyridine. The structure of **15** was confirmed by an alternative synthesis by reaction of **5** with pyrrolidine. See Supporting Information.

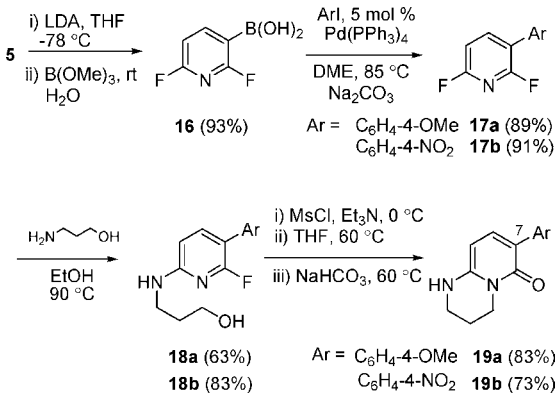
(7) Even under forcing conditions, we have not observed N-mesylation of **11** which limits our ability to deactivate the *exo*-amino function.

and when these acidic conditions were applied to the unsubstituted variant **11**, quantitative conversion to pyrrolidine **15** took place. The inability to generate efficiently the 6,7-scaffold (as in **4b**) represents a current limitation of this chemistry.

An ability to incorporate, for example, aryl substituents onto the pyridine core was another objective, and this is illustrated for derivatives of pyridone **2a**.

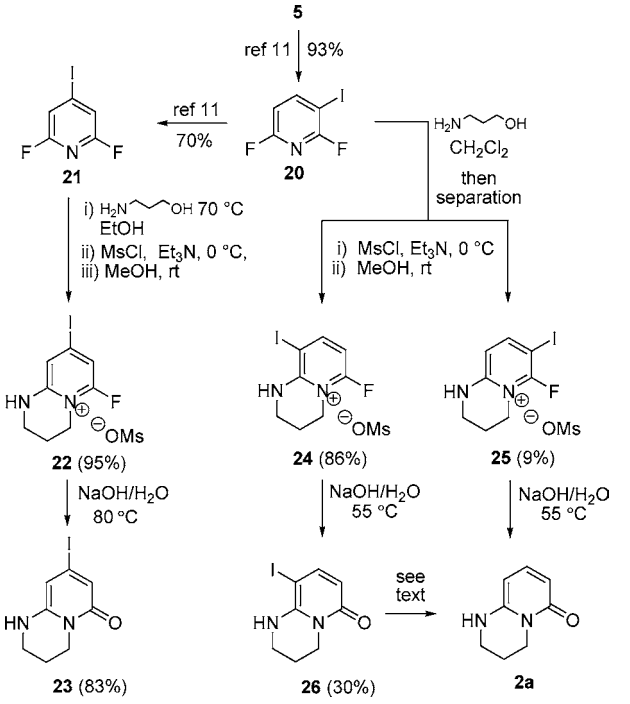
The capacity for fluorine to act as a directing group in orthometalation reactions has been used to introduce electrophiles regioselectively at the C(3) position of 2,6-difluoropyridine.[8] Deprotonation of **5** (LDA, −78 °C) followed by addition of trimethyl borate and basic hydrolysis provided boronic acid **16**[9] which gave the Suzuki adducts **17a** and **17b**. Aryl-substituted fluoropyridines **17a** and **17b** reacted with 3-amino-1-propanol giving **18a** and **18b** in 63 and 83% yield, respectively.[10] The one-pot cyclization conditions described previously were applied to **18a** and **18b** leading to aryl-substituted pyridones **19a** and **19b** in good yields (Scheme 3).

**Scheme 3.** Synthesis of C(7)-Arylated Variants



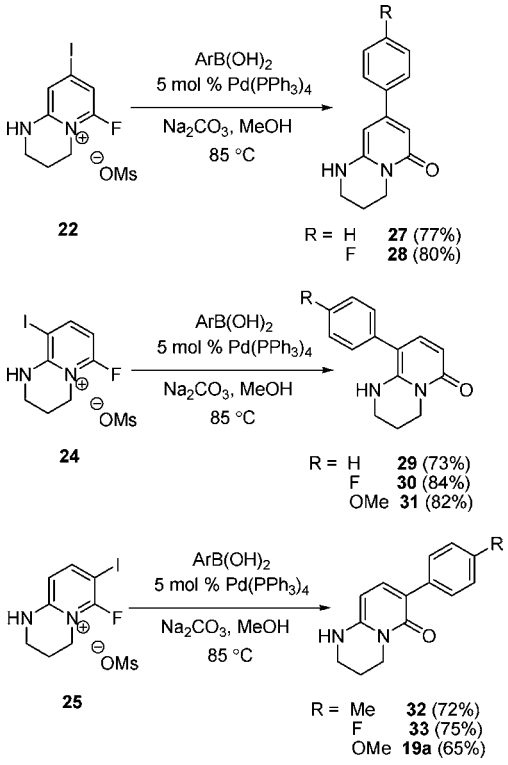

There are some limitations to this functionalization strategy: (*i*) substitution is limited to C(7), and (*ii*) the aryl substituent is still introduced at a relatively early stage. In order to address these issues, 3-iodo-2,6-difluoropyridine **20**[11] was employed. This was readily prepared by lithiation and iodination of **5**, and furthermore, **20** underwent clean isomerization (under "halogen dance" conditions[11]) to give the

**Scheme 4.** Approaches to Iodinated Pyridone Isomers




C(4) variant **21** (Scheme 4).[12] Exposure of **21** to 3-aminopropan-1-ol followed by mesylation and cyclization gave pyridinium salt **22** in 95% yield. In this case, it was necessary to use methanol (rather than THF) to achieve the cyclization

**Scheme 5.** Suzuki Couplings Based on Pyridinium Substrates




(8) For reviews of regioselective lithiation of pyridines, see: (a) Quéguiner, G.; Marais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−304. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090.

(9) Altenbach, R. J.; Black, L. A.; Chang, S.-J.; Cowart, M. D.; Faghih, R.; Gfesser, G. A.; Ku, Y.-Y.; Liu, H.; Lukin, K. A.; Nersesian, D. L.; Pu, Y.-M.; Sharma, P. N.; Bennani, Y. L. WO 2004043458, 2004.

(10) Reaction of **16** with 4-iodopyridine gave the corresponding 3-(4-pyridyl) adduct in 93% yield. Nucleophilic displacements on 2,6-difluoropyridine 3-carboxylates have been studied (Hirokawa, Y.; Horikawa, T.; Kato, S. *Chem. Pharm. Bull.* **2000**, *48*, 1847−1853). In our hands, nucleophilic substitution of **17** shows only moderate regioselectivity (8−2:1) depending on the nature of the aryl moiety. In the case of **17a**, the minor (of a 2:1 mixture) regioisomer (not shown) was converted to the corresponding C(9)-arylated bicyclic pyridone using the same methodology. See Supporting Information.

(11) Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018−1024.

step. Pyridinium **22** has other important applications (see below) but also underwent facile hydrolysis to give the target 8-iodopyridone **23**. The 3-iodo isomer **20** also underwent nucleophilic displacement with 3-aminopropan-1-ol, leading to regioisomeric adducts, the ratio of which varied between 2 and 8:1 depending on the solvent used (see Supporting Information). These were separable, and each was carried through to give pyridinium salts **24** and **25** in 86 and 9% yields, respectively, using dichloromethane as solvent for the initial nucleophilic displacement.

Hydrolysis of **24** (aq NaOH, 55 °C) gave **26** in moderate yield, but deiodination (to give **2a**) also occurred. When these hydrolysis conditions were applied to **25**, only deiodination was observed. Loss of the iodo function from **24/25** clearly complicates this approach, but the intermediate iodopyridinium species (**22**, **24**, and **25**) proved themselves to be excellent substrates for Suzuki coupling. In fact, using these pyridinium salts, we achieved *both* Suzuki coupling *and* hydrolysis to liberate the target pyridones **19a** and **27**−**33** in a "one-pot" operation (Scheme 5). The structure of adduct **31** was confirmed by X-ray crystallographic analysis (see Supporting Information).

(12) Regioisomeric iodopyridines **20** and **21** show significant volatility and care must be taken during work-up and purification.

In summary, we have developed efficient synthetic entries to bicyclic pyridones **2a** and **3a** and the corresponding *N*-benzylated variants **2b** and **3b**. Attempts to extend this to a larger ring system (as in **4a/b**) suffered because of the preference for 5- rather than 7-ring formation leading to **15** with **4b** only being obtained in very low yield. Strategies for the incorporation of additional (aryl) substituents onto these heterocyclic scaffolds at either an early or (preferably) late stage in the synthetic sequence have been evaluated. The use of iodinated substrates and Suzuki coupling is effective, and for these purposes, the use of the intermediate pyridinium species (as shown in Scheme 5) is particularly appropriate by avoiding the need to use sensitive iodinated pyridones.

**Acknowledgment.** Financial support from GSK, University of Bristol, and EPSRC is gratefully acknowledged.

**Supporting Information Available:** Complete experimental details, including crystallographic data for **3b** and **31**, and spectroscopic data for new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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