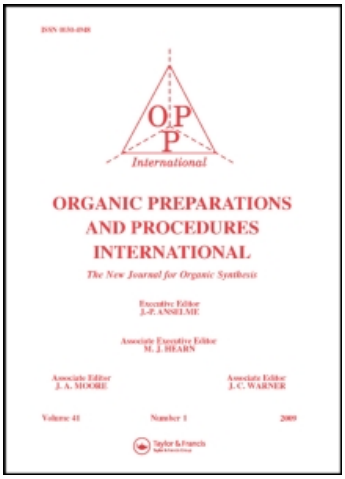

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2-(1-AZETIDINYL)- AND 2-(1-PYRROLIDINYL)PYRIDINE *via* S_NAr REACTIONS OF 2-FLUOROPYRIDINE AND 2-PYRIDINYL TRIFLATE

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(09/06/99)

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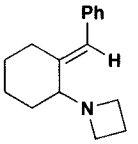
Aminopyridines have attracted attention as acylation catalysts,[1] potassium channel blockers[2] and as key intermediates for pharmaceutical and agricultural chemicals.[3] Significantly, 4-aminopyridine is reported to improve symptoms of multiple sclerosis.[4] The azetidinyl group has appeared in natural products[5] and in synthetic medicinal agents.[6] In the latter, it has been used to mimic a dimethylamino or a pyrrolidinyl group. In the case of tazadolene (**1**) this led not only to enhancement of biological activity,[7] but also to a preferred mode of metabolism due to the formation of the β-alanine derivative **2**,[8] as compared to the complex metabolism of the dimethylamino moiety.[9] Another instructive example of enhancement of biological activity due to the azetidine moiety is provided by oxotremorine analogs.[10] We report here the preparation of 2-azetidinylpyridine, which to our knowledge, has not been reported previously.



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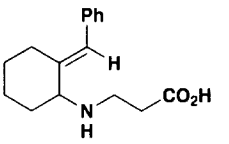


2

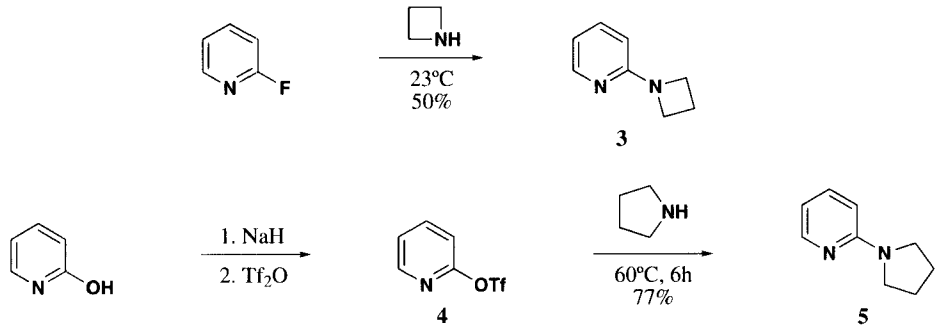
General methods exist for the preparation of all possible regioisomers of mono- and dialkylamino pyridines. Two major approaches to these compounds are alkylation of unsubstituted aminopyridines and reaction of halopyridines[11] and pyridyl pyridinium hydrochlorides[12] with amines. Unfortunately, these methods were unsuitable for our particular needs. The bisalkylation route to azetidines[13] unsubstituted at carbon is known to give very low yields in the case of arylamines[14] due to competing side reactions such as dimerization and elimination. The nucleophilic aromatic substitution route used previously for the preparation of dialkylaminopyridines employed harsh conditions (heat, acid) to which the azetidine nucleus is known to be sensitive.

In an attempt to find mild conditions to connect the azetidinyl nucleus to the pyridine ring, our attention turned to nucleophilic aromatic substitution. It has been established in aromatic S_NAr reactions of haloarenes that the order of reactivity is F>>Cl>Br>I with the reactivity of the last three halides being essentially equal.[15] In fact, successful aromatic S_NAr reactions of azetidine (excess) with 2- and 4-fluoronitrobenzene have been demonstrated. From this study azetidine was found to undergo

this substitution at double the rate of pyrrolidine and 300-times as fast as aziridine.[16]

The order of reactivity for the halopyridines in these S_NAr reactions is 4=2>>3.[17] The commercial availability of 2- and 3-fluoropyridines further encouraged us to explore the use of these reagents. Unfortunately, 4-fluoropyridine is not available commercially, but can be synthesized by a modified Balz-Schiemann reaction.[18] A second possibility involved the use of a triflate leaving group. Although unactivated aryl triflates typically undergo predominant S-O cleavage in their non-catalyzed reactions with nucleophiles, some examples of selective S_NAr displacement of the triflate group have been reported for nitrophenyl triflates.[19] Studies in these labs have shown that the corresponding triflate is more readily displaced than the chloride in 9-chloro-1,2,3,4-tetrahydroacridine.[20]

For initial study we chose to work with 2-fluoropyridine and 2-pyridinyl triflate (**4**).[21] Under very mild conditions, it was found that azetidine did react with 2-fluoropyridine to give 2-(1-azetidinyl)pyridine (**3**) in 50% isolated yield. The efficiency of this reaction is likely due to the high reactivity of 2-fluoropyridine towards S_NAr displacement together with the potent nucleophilicity of azetidine. In order to probe its reactivity, 2-pyridinyl triflate (**4**) it was combined with pyrrolidine and heated at 60° in 1,2-dichloroethane. After 24 h a 1:1 mixture of 2-(1-pyrrolidino)pyridine (**5**) and **4** was recovered. However, heating pyrrolidine and **4** neat at 60° gave a clean conversion to **5** in 5 h.



EXPERIMENTAL SECTION

All reactions were conducted under a N_2 atmosphere. ^1H NMR spectra were recorded (δ, ppm) using a Magnachem-200 spectrometer with TMS as an internal reference in $CDCl_3$. Coupling constants (J) are given in hertz. Mass spectra were obtained on a Mat CH-5-DF(FAB), a Finnigan 8230 B(EI), a Kratos MS-80 (HR EI) and a Mat CH-7(Cl) mass spectrometers. 2-Fluoropyridine was used as received from Aldrich. Azetidine[22] and 2-pyridyl triflate (**4**)[19] were prepared according to the literature procedures.

2-(1-Azetidinyl)pyridine (3).- A mixture of azetidine (169 mg, 2.96 mmol), 2-fluoropyridine (287 mg, 2.96 mmol), and Na_2CO_3 (160 mg, 1.51 mmol) was stirred at room temperature for 72 h. The partially solidified reaction mixture was partitioned between ether and sat. aq. Na_2CO_3. The layers were separated and the aqueous layer was back extracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated to give 200 mg (50%) of **3** as a colorless liquid (bp 65°, 1 torr): ^1H NMR δ 2.38 (m, 2 H), 4.03 (t, J = 8, 4 H), 6.26 (m, 1 H), 6.57 (m, 1 H), 7.43 (m, 1 H),

8.14 (m, 1 H); MS (EI) m/z at 134 (M^+).

For analytical purposes a *bis*-succinate salt, mp 99-100° was prepared.

Anal. Calcd for $C_8H_{10}N_2 \cdot 2C_4H_6O_4$: C, 51.89; H, 5.99; N, 7.56. Found: C, 51.67; H, 6.00; N, 7.23

2-(1-Pyrrolidino)pyridine (5).- 2-Pyridyl triflate (**4**) (100 mg, 0.44 mmol) and pyrrolidine (61 mg, 0.88 mmol) were stirred neat at 60° for 5 h. Isolation as described above gave 50 mg (77%) of **5** as a yellow oil. The ^{1}H NMR spectra of this compound was identical to that reported previously.[1]

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