AN S_NAr-BASED PREPARATION OF 1-(2-, 3-, AND 4-PYRIDYL)INDOLES USING POTASSIUM FLUORIDE/ALUMINA[1]

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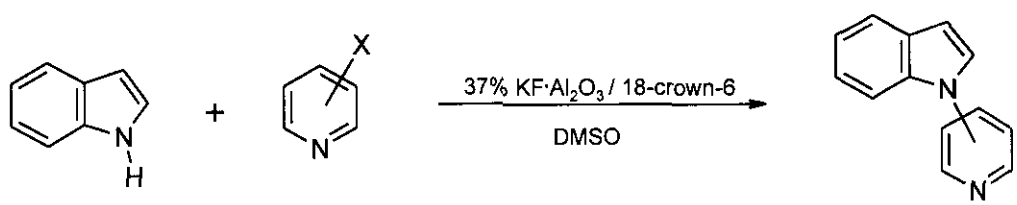
Abstract - The reaction of indole with 2-, 3-, and 4-halopyridines in the presence of potassium fluoride/alumina and 18-crown-6 in DMSO at 120 °C is effective in producing 1-(2-, 3-, and 4-pyridyl)indoles in moderate to good yields.

In a previous communication[2] we described a selective method for the 1-arylation of indoles mediated by 37% potassium fluoride on alumina, which represented an extension of our earlier work developing KF/alumina as an effective reagent for an S_NAr-based synthesis of diaryl ethers, thioethers, and diarylamines.[3] In the course of developing this method for the construction of 1-arylindoles, it was found that even reticent electrophiles, such as 3-chlorobenzonitrile, could be coupled to indole at the 1-position in good yields. This current report details a logical extrapolation of this methodology to encompass the synthesis of 1-pyridylindoles (Scheme 1), which are associated with an extensive patent and periodical

Scheme 1



literature featuring potentially important medicinal agents such as antidiabetics,[4] anti-HIV-1 agents,[5] and σ_2 ligands.[6] While Ullmann[7] and photochemical techniques[8] developed for the synthesis of 1-pyridylindoles include disadvantages ranging from low yields to poor regio- and

chemoselectivity, the S_NAr work of Seki and co-workers[9] has clearly demonstrated conditions for efficient coupling of indoles to 2- and 4-halopyridines. However, their sodium hydride/DMF protocol mediated the formation of 1-(3-pyridyl)indole from indole and 3-fluoropyridine in only 12% yield. An indirect formation of 1-(2-pyridyl)indoles, involving heterocyclization of masked cyclopalladated secondary amine and ketone complexes, has also been reported.[10]

These reports prompted us to conduct a short investigation beginning with the addition of indole to 2-fluoropyridine (Table, Example 1). Similar to the results of Seki *et al.*, addition of indole to

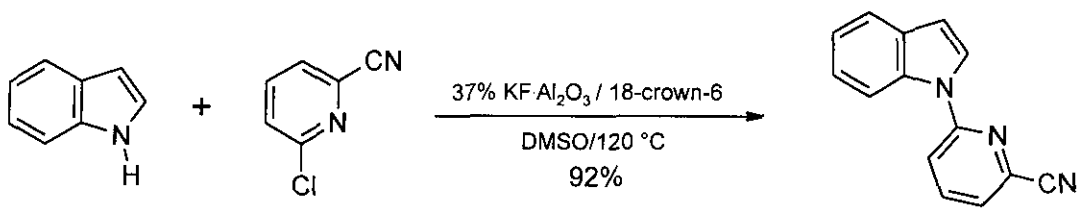
Table. The reaction of indole with halopyridines mediated by 37% KF/Al_2O_3 and 18-crown-6 in DMSO at 120 °C.

Example	Pyridine Substitution	Yield (%)
1	2-fluoro	90
2	2-chloro	61
3	4-chloro	52
4	3-fluoro	38
5	3-chloro	27

2-fluoropyridine mediated by potassium fluoride/alumina and 18-crown-6 in hot DMSO provided 1-(2-pyridyl)indole in 90% chromatographed yield. When using 2-chloropyridine as the electrophile, a 61% yield was obtained (Example 2) in contrast to sodium hydride/DMF, which gave only a 14% yield.[9] A more interesting result involved the addition of indole to 4-chloropyridine, which failed to provide the expected product with sodium hydride/DMF. With potassium fluoride/alumina (Example 3), a 52% yield of 1-(4-pyridyl)indole was obtained. Example 3 is particularly important considering the ready commercial availability of 4-chloropyridine relative to 4-fluoropyridine, which does react under the sodium hydride/DMF protocol. Noting the low yield reported for the addition of indole with 3-fluoropyridine using sodium hydride/DMF (12%), we repeated the addition with potassium fluoride/alumina and realized a 38% yield of the expected product (Example 4), while less expensive 3-chloropyridine gave a somewhat lower yield (Example 5).

These results provide support for potassium fluoride/alumina as an effective mediator for the synthesis of unsubstituted 1-(2-, 3-, and 4-pyridyl)indoles. From our previous experience with this reaction,[2,3] the combination of indole and halopyridines substituted with electron-withdrawing groups should represent an even more facile process. Indeed, the addition of indole to 2-chloro-6-cyanopyridine (Scheme 2) proceeded to the predicted product in high yield.

Scheme 2



This particular result includes incorporation of a versatile nitrile functionality, which may serve as a convenient handle for further synthetic elaboration.[11]

Other solvents, such as acetonitrile, have been successfully used in place of DMSO, but are not as reliable when unfavorable substitution patterns are present in the reactants. Solvents such as DMF proved problematical due to decomposition at the reaction temperature employed. Most of the S_NAr reactions we have examined proceed faster in the presence of 18-crown-6. Other catalysts, such as tetra-*n*-butylammonium bromide, are effective in shortening the reaction times, but do not perform as well as 18-crown-6.[3]

EXPERIMENTAL

Representative procedure (synthesis of 1-(6-cyanopyridin-2-yl)indole): A suspension of indole (3.00 g, 25.6 mmol), 2-chloro-6-cyanopyridine (3.55 g, 25.6 mmol), 37% w/w potassium fluoride on alumina (6.00 g),[12] and 18-crown-6 (677 mg, 2.56 mmol) in dry DMSO (25 mL) was heated at 120 °C under a nitrogen atmosphere for 6 h. The mixture was cooled to rt, diluted with ethyl acetate, and filtered. The filtrate was washed once with water and once with saturated sodium chloride solution. The organic layer was separated, dried (sodium sulfate), filtered, and concentrated *in vacuo*. Chromatography (silica gel, ethyl acetate/hexane) provided

5.16 g (92%) of the title product as off-white crystals: mp 82-84 °C. ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J = 9 Hz, 1 H), 7.88 (t, J = 9 Hz, 1 H), 7.63 (m, 3 H), 7.46 (d, J = 9 Hz, 1 H), 7.34 (t, J = 9 Hz, 1 H), 7.24 (t, J = 9 Hz, 1 H), 6.73 (d, J = 5 Hz, 1 H); MS FD m/e 219 (p); IR ($CHCl_3$, cm^{-1}) 3020, 2230 (w), 1590, 1467 (s). Anal. Calcd for $C_{14}H_9N_3$: C, 76.60; H, 4.14; N, 19.17. Found: C, 76.78; H, 4.29; N, 19.29.

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