DIRECT FLUORINATION OF ISOQUINOLINE COMPOUNDS[1]

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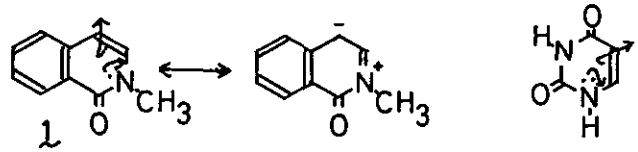
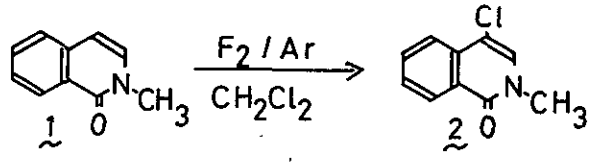
Abstract-Activation of isoquinoline for the direct fluorination was achieved by its conversion to 2-methylisocarbostyril. The fluorination of 2-methylisocarbostyril gave 4-fluoro compound in a satisfactory yield. The Reissert's compound was not reactive enough for the fluorination.

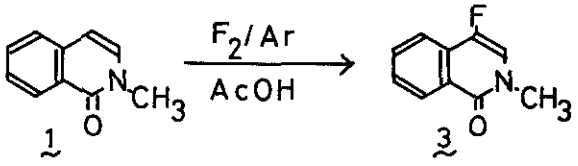
In our study of organic fluorine compounds, we attempted direct fluorination of heteroaromatic compounds with gaseous fluorine. However, the treatment of pyridine or its ring-fused derivatives with fluorine did not give fluorine compounds in practical yields but the starting materials were recovered quantitatively. Therefore, we tried to convert them to suitable derivatives. As the direct fluorination seemed to occur by the electrophilic attack of fluorine, we chose N-methylisocarbostyril (1) as a starting material. Its partial enamine structure seemed to be suitable for the fluorination. The previous success of fluorination of uracil might be due to the similar structure[2].



Bubbling of F_2 gas diluted to 10% with argon into a solution of 1 in methylene chloride, however, gave only 4-chloro-2-methylisocarbostyril (2)[3], ^{1}H-NMR $\delta(CDCl_3)$ 7.21 (1H, s, 3-H), m/e 193. Compound 2 might be produced by chlorination of 1 with chlorine, which was formed by the attack of fluorine on methylene chloride.



Next, F_2 gas (10% in argon, 50 ml per min) was bubbled into a solution of 1 (1 g) in AcOH (40 ml) at 30°C for 7 hr. After concentration of the reaction mixture under vacuum, the residue was taken up with methylene chloride. The methylene chloride solution was washed with dil. $NaHCO_3$ and dried over Na_2SO_4. After evaporation of the solvent, the residue was fractionated by high pressure liquid chromatography [column SiO_2, solvent C_6H_6-AcOEt (3 : 1)]. The first fraction gave 4-fluoro compound (3), 600 mg (54%), bp_{14}125-6°C, a pale yellow oil, which solidified on standing; ^{1}H-NMR δ($CDCl_3$) 3.53 (3H, s), 7.05 (1H, d, J_{HF} = 6.0 ppm); ^{19}F-NMR δ^4 94.5 (d-d, J_{HF} = 6.0 and 1.0 Hz). The starting material was recovered as a second fraction.



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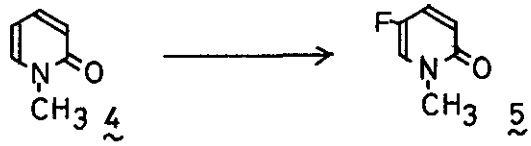
Similarly, N-methyl-2-pyridone gave 5-fluoro compound (5) in 43% yield, $bp_6$112-6 °C; ^{1}H-NMR δ($CDCl_3$) 3.57 (3H, s), 7.48 (1H, d, J = 10 Hz), 8.2 - 8.6 (2H, m); ^{19}F-NMR δ 85 (d-d, J = 10 and 5 Hz).



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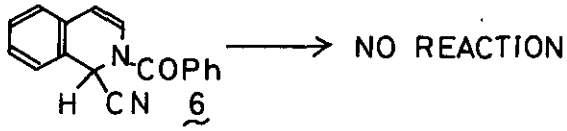
The fluorination of the so-called Reissert compound, 1-cyano-2-benzoyl-1,2-dihydroisoquinoline, which has the similar enamine part, afforded no fluorine compounds. This fact shows that the N-benzoyl group deactivates the enamine character strongly.



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References and Notes

1. Dedicated to Prof. Kyosuke Tsuda on the occasion of his 75th birthday.
2. Y. Kobayashi, I. Kumadaki, and A. Nalazato, Tetrahedron Lett., 1980, 21, 4605.
3. H. Riemlinger, J. J. M. Vandewalle, and W. R. F. Lingier, Chem. Ber., 1970, 103, 1960.
4. Benzotrifluoride was used as an external standard. Higher field is shown as plus.

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