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REACTIONS OF CAESIUM FLUOROXYSULPHATE WITH PYRIDINE

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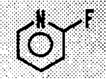
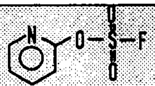
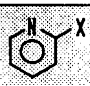
Abstract- Pyridine readily reacts with $CsSO_4F$ in various solvents at room temperature producing a mixture of up to three products (2-fluoropyridine, 2-pyridyl fluorosulphonate and 2-chloro or 2-alkoxypyridine), their distribution strongly depending on the solvent used. Reaction of 3-chloropyridine with $CsSO_4F$ in methanol leads regioselectively to 2-methoxy-3-chloropyridine, while 3-methylpyridine was converted into 2-methoxy-3-methyl and 2-methoxy-5-methylpyridine in a 2:1 relative ratio.

Introduction of a fluorine atom into organic molecules is a shared and important interest of organic chemists, and in view of the biological and chemical importance[1] of fluorine-containing organic molecules, a rapid development of new reagents and methods for selective fluorofunctionalization of organic compounds has taken place in the last few decades, most of this work being excellently reviewed recently[2]. Although new reagents and methods cover fluorination of almost the whole spectrum of organic compounds, for a long time relative little attention was paid to the fluorine organic chemistry of elementary heterocycles, such as pyridine. But quite recently, three independent reports related to direct fluorination or reactions of modern fluorinating agents with the pyridine ring appeared. The optimisation of the fluorination process by elementary fluorine produced 2-fluoropyridine derivatives in reasonable yield[3], while reactions of pyridine with fluorine, modified over in situ prepared acetyl hypofluorite[4], resulted in oxygenated, chlorinated or brominated pyridine derivatives, depending on the solvent used. Base initiated decomposition of N-fluoro pyridinium salts was reported[5] to result in 2-substituted pyridine derivatives, the structure and the distribution of the products being strongly dependent on the solvent used and the structure of the anionic part of the N-fluoro pyridinium salt.

We now report that when pyridine is treated with caesium fluoroxysulphate ($CsSO_4F$), one of the easiest handling[6] and selective of modern fluorination agents[7], in non-polar solvents, instantaneous reaction takes place, with oxygen gas evolution from the reaction mixture, while 2-fluoropyridine and 2-pyridylfluorosulphonate could be isolated in good yield after half an hour's reaction at room temperature. 2-Chloropyridine or 2-alkoxypyridine were also formed when reaction was carried out in CH_2Cl_2 and $CHCl_3$ or alcohols, respectively. The distribution of products isolated after 0.5-4 hour reactions of pyridine with $CsSO_4F$ at room or moderately increased temperature in various solvents is presented in the TABLE, and one can see that the course of the reaction is strongly dependent on the solvent, being the most selective in c-hexane or CCl_4 and in methanol or ethanol.

TABLE *Products distribution in reaction between pyridine and $CsSO_4F$* $^{a)}$

Solvent			
n-C_5H_{12}	56	44	-
$(CH_3CH_2)_2O$	61	39	-
c-C_6H_{12}	70	30	-
CCl_4	70	30	-
$CHCl_3$	47	17	36 ; X=Cl
CH_2Cl_2	26	12	62 ; X=Cl
$C(CH_3)_3OH$	64	18	18 ; $X=OC(CH_3)_3$
$CH(CH_3)_2OH$	22	7	71 ; $X=OCH(CH_3)_2$
CH_3CH_2OH	-	-	100 ; $X=OCH_2CH_3$
CH_3OH	-	-	100 ; $X=OCH_3$

a) determinated by GLC; in %; 2 mmol of pyridine, 4 ml of solvent, 4 mmol of $CsSO_4F$;T=22°C (50°C for $C(CH_3)_3OH$); reaction time 0.5-4 hours; all products were isolated by GLC or TLC and identified according to the spectroscopic data.

Further, we made a preliminary study of the effect of substituents on the reaction carried out in methanol or CCl_4. In methanol, 3-chloropyridine was converted by $CsSO_4F$ regioselectively to 2-methoxy-3-chloropyridine in over 80% yield, while the reaction carried out in CCl_4 failed and only the starting material could be isolated, even after 24 hours stirring at 35°C. The reaction of 3-methylpyridine was less selective and resulted in a 2.2:1 relative ratio of 2-methoxy-3-methyl and 2-methoxy-5-methylpyridine when the reaction was carried out in methanol, while the CCl_4 mediated reaction produced 2-fluoro-3-methylpyridine, 2-fluoro-5-methylpyridine, 2-(3-methylpyridyl)-fluorosulphonate and 2-(5-methylpyridyl)-fluorosulphonate in a 2:1:2:1 ratio.

As evident, once again it was shown that the course of the $CsSO_4F$ reaction with organic compounds strongly depends on the structure of the organic molecules and the functional groups present, solvent polarity, as well as the general reaction procedure. The testing of the reactivity of $CsSO_4F$ towards substituted pyridine derivatives and other elementary heterocycles is in rapid progress in order to define the limiting value and provide some mechanistic elucidation of this convenient, easy handling and mild method for direct functionalization of heterocyclic molecules.

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6 Caution: In handling dry $CsSO_4F$ any use of metallic equipment and mechanical pressure must be avoided, since decomposition or even explosion of the reagent may take place.

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