

SELECTIVE ELECTROCHEMICAL SYNTHESIS OF 4-FLUOROPYRIDINE USING $\text{Et}_3\text{N}\cdot 3\text{HF}$

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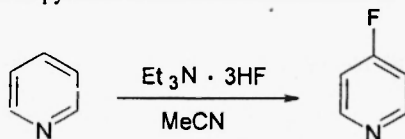
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Abstract: Pyridine was electrochemically fluorinated at platinum anode at constant voltage in acetonitrile solutions containing $\text{Et}_3\text{N}\cdot 3\text{HF}$, as supporting electrolytes and fluorine sources. The present electrolyte solution system was mild and suitable for the fluorination of pyridine. Thus, 4-fluoropyridine has been synthesized.

Introduction

It is well recognized that incorporation of fluorine atoms into the organic molecules used for medicines can significantly alter their biological function. Fluoro organic compounds have special chemical and physical properties. Especially, partially fluorinated compounds are useful in the fields of material science and medicinal chemistry⁽¹⁾. To date, many methods of fluoroorganics preparation of fluoroorganics have been developed⁽²⁾, the construction of ring-fluorinated heterocyclic systems has been less explored. Recently, selective electrochemical fluorination has been shown to be a highly efficient new tool for synthesizing various fluoroorganic compounds. The reaction can be carried out under mild conditions using relatively simple equipment and also avoiding hazardous or toxic reagents, which are necessary in chemical fluorination. However, only limited examples of selective anodic fluorination of heterocycles have been reported to date⁽³⁻⁵⁾, and in all cases, low yields and poor selectivities appear to be the major problems in electrochemical synthesis.

Because pyridine is very resistant to oxidation, it has been used as a solvent for electrochemical reactions. Huba (6) made 2-fluoropyridine as a by-product of electrolysis in pyridine/anhydrous hydrogen fluoride (AHF) mixtures (70/30 w/w) but that system requires special AHF-resistant equipment and is unsuitable for synthesis with pyridine derivatives and fluoride sources other than AHF. Later, James R. Ballinger⁽⁷⁾ reported that in his cell, the applied potential was 2.5 V and a supporting electrolyte solution was 0.5 M $\text{Me}_4\text{NF}\cdot 2\text{HF}$ in MeCN, 2-fluoropyridine has been synthesized in 22% yield by electrochemical fluorination of pyridine. His system requires special equipment and rigorous materials. In this paper, we disclose a practical and efficient selective anodic fluorination of pyridine obtained 4-fluoropyridine by using a conventional $\text{Et}_3\text{N}\cdot 3\text{HF}$ as both supporting electrolyte and the fluorine source. The result of anodic fluorination of pyridine is summarized in Scheme 1.



Scheme 1

Experiment

Acetonitrile (HPLC grade) is dried further by distillation from phosphorus pentoxide and from calcium hydride. Pyridine is distilled from KOH pellets. 2-Fluoropyridine and 3-Fluoropyridine are obtained from Acros Chemical Co. $\text{Et}_3\text{N}\cdot 3\text{HF}$ is obtained from Aldrich Chemical Co.

The electrolysis cell is a 50-ml glass beaker cooled by an enclosed ice-water jacket. Into the cell are placed a 4.3cm^2 platinum sheet anode and a 1.44cm^2 platinum sheet cathode, a magnetic stirring bar, a tube for bubbling NaOH-dried and MeCN-saturated nitrogen through the cell solution. The potential is controlled by a potentiostat with a digital coulometer (model HYL-A).

The electrolysis was performed at 2.5 V in 4ml $\text{Et}_3\text{N}\cdot 3\text{HF}/\text{MeCN}$ (45 ml) containing 0.4 ml pyridine. During the electrolysis, the temperature was maintained at ca. 20°C . Nitrogen bubbling is continued throughout the electrolysis to maintain slight positive pressure and minimize the amount of moisture that can enter the cell. After a calculated number of coulombs has passed, the reaction mixture was analyzed with gas chromatography MS (model Finnigan Tracc MS. HP-8 column, $80-200^\circ\text{C}$ $10^\circ\text{C}/\text{min}$), F-NMR (model Varian-360L).

As shown in Figure 1, the ^{19}F NMR of the reaction mixture has peak in -127ppm , it very approached the ^{19}F NMR of 4-fluoropyridine (-133.4ppm) exactly, and the MS showed extracts contained $\text{C}_5\text{H}_4\text{FN}$. M/e : 97(M^+ , 100%), 77, 70, 57, 50, 44. So we think 4-fluoropyridine is the only significant product and its identity is confirmed by gas chromatography analysis with 2-fluoropyridine (retention time 9.067 min) and 3-fluoropyridine (retention time 7.286 min).

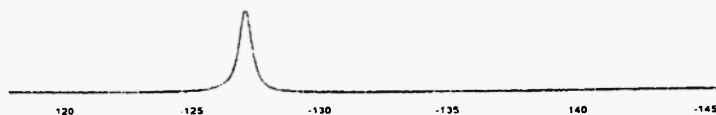
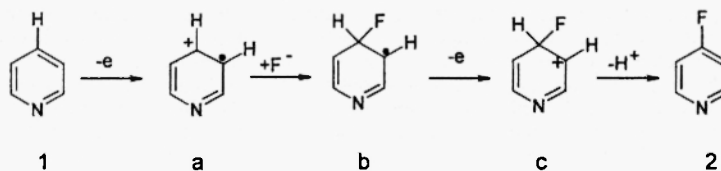


Figure 1

From the result, the reaction mechanism can be shown in Scheme 2, pyridine was oxidized to generate the radical cation intermediate (a). Then, this radical cation reacts with a fluoride ion followed by further oxidation to form cationic intermediate (c). Finally, the cationic intermediate loses a proton to give 4-fluoropyridine during the electrolysis.



Scheme 2

Fluoropyridine can be synthesized in higher yield by diazotization/fluorination of aminopyridine (8) and by fluoride exchange with chloropyridine (9). However, these methods require an appropriate precursor whereas electrochemical fluorination uses pyridine itself, this may be an important consideration in fluorination of pyridine derivatives: the lower yield of the direct electrochemical method may be higher than the overall yield of a procedure that requires synthesis of an intermediate.

Summary

In conclusion, we have successfully carried out highly regioselective anodic monofluorination of pyridine using $\text{Et}_3\text{N}\cdot 3\text{HF}$ /MeCN electrolytic solution.

Acknowledgement

We thank Science and technology key Project 00117 financial support by the Ministry of Education, China.

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Received on March 2, 2004.