A REACTION OF *N*-FLUOROPYRIDINIUM CATION WITH DIAZOCARBONYL COMPOUNDS

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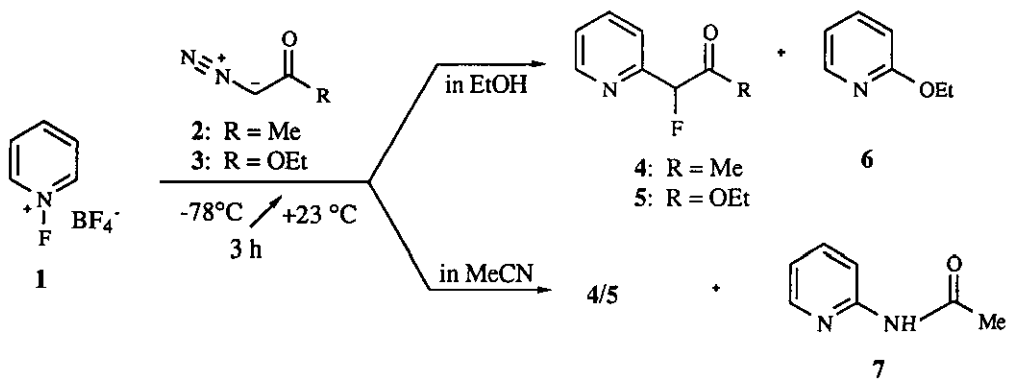
Abstract - 1-Fluoro-1-(2-pyridyl)propan-2-one (4) and ethyl fluoro(2-pyridyl)-acetate (5) are produced in the reaction of *N*-fluoropyridinium tetrafluoroborate with diazoacetone or ethyl diazoacetate, respectively.

N-Fluoropyridinium salts such as **1** are easily prepared, stable on storage, and safe in handling.[1] It was Umemoto who showed for the first time these salts are not only reagents for fluorination of organic compounds[1] but can also be used for the synthesis of 2-substituted pyridines in base-mediated reactions.[2] Numerous reports on a facile preparation of pyridine derivatives by using Umemoto's and similar approaches have been published.[3-5]

In this paper we describe a related albeit unusual reaction of **1** with α-diazocarbonyl compounds, such as **2** or **3**. The diazo functionality of **2** and **3** is eliminated as molecular nitrogen and the resultant carbonyl product (**4**) or (**5**), respectively, contains fluorine and a 2-pyridyl group at the α position (Scheme I).

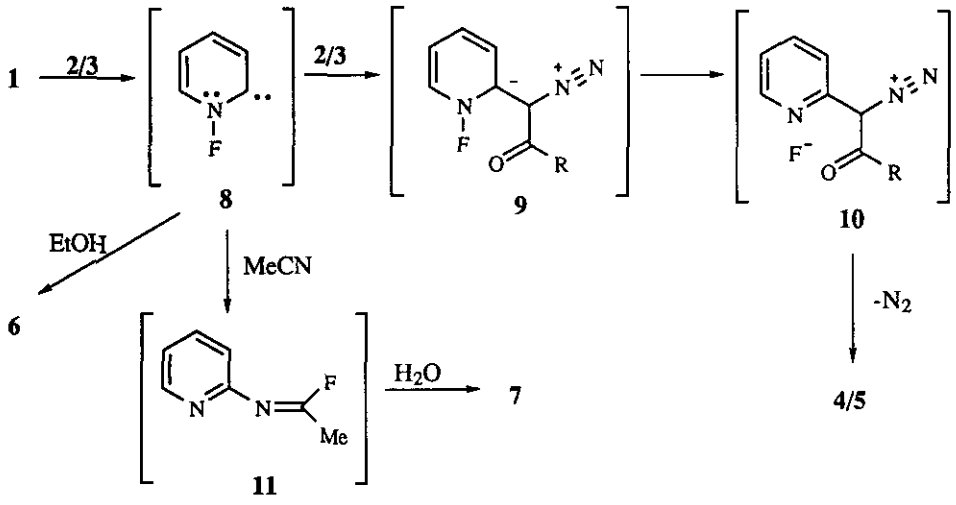
Scheme I



In a typical run a solution of 1 (0.92 g, 5 mmol) in absolute ethanol (15 ml) was stirred at -78 °C under a nitrogen atmosphere and treated dropwise with a solution of **2** or **3** (10 mmol) in ether (5 ml). The resultant yellow mixture was stirred at -78 °C for 1 h, and then the temperature was allowed to rise to 23 °C within 2 h. After the salt (**1**) had been consumed, as indicated by a KJ/starch test,[5] the dark red mixture was concentrated on a rotary evaporator and then treated with aqueous $NaHCO_3$ (1 mM, 10 ml). Extraction with CH_2Cl_2 (3x10 ml) followed by a standard workup and then chromatography on silica gel with hexane/ether (1:1) as an eluent gave 2-ethoxypyridine (**6**, yield 15-20%), which was eluted first, and ketone[6] (**4**) or ester[7] (**5**) as the major product (yield 31-37%).

When the reactions were conducted in anhydrous acetonitrile under similar conditions *N*-(2-pyridyl)acetamide (**7**) was obtained as a major product (20-25%) with the ketone (**4**) or ester (**5**) (10-17%), and an increased amount of tar was observed. Similar reactions conducted in tetrahydrofuran produced tar exclusively. An increased amount of tar and ether (**6**) (up to 30%) with a concomitant decrease in the yield of **4** or **5** (to 12-15%) were also observed for the reactions conducted at 23 °C in ethanol. These results demonstrate that the formation of the desired products (**4**) and (**5**) is highly solvent- and temperature-dependent. They also strongly suggest the involvement of a highly reactive intermediate which does not discriminate between solvent and a diazocarbonyl compound at 23 °C but reacts preferentially with the diazo derivative at a lower temperature.

Scheme II



We believe that this intermediate is a carbene[2] (**8**) derived from the *N*-fluoropyridinium cation of **1** (Scheme II). The suggested formation of **8** requires proton abstraction from the cation by diazocarbonyl compounds which are known to be relatively basic.[8] The formation of **4** or **5** can be rationalized in terms of the reaction of **8** with **2** or **3** to give an adduct (**9**), then elimination of fluoride anion from **9** to give an ion pair (**10**) , and followed by nucleophilic substitution of the diazonium group in **10** by the fluoride anion. Carbene (**8**) may also react with ethanol to give **6** or with acetonitrile to give an intermediate fluoroimine (**11**) . Aqueous workup would result in hydrolysis of **11** to amide (**7**) , the observed product.[2]

In summary, the unified mechanism of Scheme II is consistent with the experimental data. An unusual feature in the proposed mechanistic pathway leading to **4** and **5** is the transfer of fluoride anion in the last step. This is in sharp contrast to other fluorination reactions with *N*-fluoropyridinium salts which are believed to proceed through an SET pathway.[1,9,10]

ACKNOWLEDGMENT

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REFERENCES AND NOTES

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6. **1-Fluoro-1-(2-pyridyl)propan-2-one (4).** Yield 31%, an oil; ^{1}H nmr ($CDCl_3$): δ 2.08 (s, 3H, CH_3), 5.82 (d, J = 48 Hz, 1H, CHF), 7.32 (t, J = 6 Hz, 1H, H-5), 7.64 (d, J = 8 Hz, 1H, H-3), 7.92 (dd, J = 8 Hz, J = 6 Hz, 1H, H-4), 8.79 (d, J = 6 Hz, 1H, H-6); ms m/z (rel intensity): 78 (62), 93 (100), 135 (70), 153 (34, M^+). Anal. Calcd for C_8H_8NOF: C, 62.74; H, 5.27; N, 9.15. Found: C, 62.55; H, 5.34; N, 9.01.

7. **Ethyl fluoro(2-pyridyl)acetate (5).** Yield 37%, an oil; ^{1}H nmr ($CDCl_3$): δ 1.24 (t, J = 7 Hz, 3H, CH_3), 4.21 (q, J = 7 Hz, 2H, CH_2), 5.87 (d, J = 48 Hz, 1H, CHF), 7.31 (t, J = 6 Hz, 1H, H-5), 7.70 (d, J = 8 Hz, 1H, H-3), 7.92 (dd, J = 8 Hz, J = 6 Hz, 1H, H-4), 8.64 (d, J = 6 Hz, 1H, H-6); ms m/z (rel intensity): 78 (41), 93 (100), 111 (15), 183 (37, M^+). Anal. Calcd for $C_9H_{10}NO_2F$: C, 59.01; H, 5.50; N, 7.65. Found: C, 58.88; H, 5.61; N, 7.49.

8. A.B. Smith, III, and R.K. Dieter, *Tetrahedron*, 1981, **37**, 2407 and references cited therein.

9. See reference 1 for arguments against *N*-fluoropyridinium salts as formal source of positive fluorine F^+ in fluorination reactions.

10. The SET and/or nucleophile addition pathways are plausible alternatives to the suggested intermediary of carbene (**8**)in the synthesis of **4** and **5**, and this possibility cannot be ruled out in light of the experimental results obtained. However, these additional mechanistic pathways cannot explain the formation of by-products (**6**)and (**7**). For example, see: A.S. Kiselyov, L. Strekowski, and V.V. Semenov, *J. Heterocycl. Chem.*, 1993, **30**, 329. Salt (1) is stable in acetonitrile and ethanol at 23 °C.

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