A REACTION OF N-FLUOROPYRIDINIUM CATION WITH DIAZOCARBONYL COMPOUNDS

Alexander S. Kiselyov and Lucjan Stękowski*

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, USA

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. It was Umemoto who showed for the first time these salts are not only reagents for fluorination of organic compounds but can also be used for the synthesis of 2-substituted pyridines in base-mediated reactions. Numerous reports on a facile preparation of pyridine derivatives by using Umemoto’s and similar approaches have been published.

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

![Scheme I](image-url)
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 KI/starch test, the dark red mixture was concentrated on a rotary evaporator and then treated with aqueous NaHCO₃ (1 mM, 10 ml). Extraction with CH₂Cl₂ (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 (4) or ester (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.\(^3\) 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

We thank NIH-NIAID (grant AI-27196) and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

REFERENCES AND NOTES


6. 1-Fluoro-1-(2-pyridyl)propan-2-one (4). Yield 31%, an oil; \(^1\)H nmr (CDCl\(_3\)): \(\delta\) 2.08 (s, 3H, CH\(_3\)), 5.82 (d, \(J = 48 \text{ Hz}, \text{ 1H, CHF}\)), 7.32 (t, \(J = 6 \text{ Hz}, \text{ 1H, H-5}\)), 7.64 (d, \(J = 8 \text{ Hz}, \text{ 1H, H-3}\)), 7.92 (dd, \(J = 8 \text{ Hz}, J = 6 \text{ Hz}, \text{ 1H, H-4}\)), 8.79 (d, \(J = 6 \text{ Hz}, \text{ 1H, H-6}\)); ms m/z (rel intensity): 78 (62), 93 (100), 135 (70), 153 (34, M\(^+\)). Anal. Calcd for C\(_8\)H\(_8\)NOF: 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$_3$): $\delta$ 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$_9$H$_{10}$NO$_2$F: C, 59.01; H, 5.50; N, 7.65. Found: C, 58.88; H, 5.61; N, 7.49.


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.

*Received, 29th September, 1993*