Pergamon

Tetrahedron Letters, Vol. 35, No. 2, pp. 207-210, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0186-N

A Novel Synthesis of 2-Substituted Pyrido[1,2-a]-1,3,5-triazin-4-ones by the Reaction of *N*-Fluoropyridinium Salts with Cyanate Ion and Carbonitriles: Evidence in Support of a Carbene Intermediate

Alexander S. Kiselyov and Lucjan Strekowski*

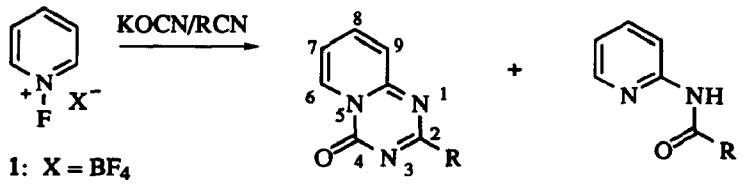
Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

Abstract: *A carbene 5" derived from N-fluoropyridinium cation is the suggested intermediate in the novel synthesis of pyridotriazines 3.*

N-Fluoropyridinium salts,[1] such as **1** and **2**, have emerged recently as an important new class of reagents for synthesis of substituted pyridines[2] by the reactions with nucleophiles. In these transformations the addition of some nucleophiles with *N*-fluoropyridinium cation is well documented,[2,3] and evidence has been growing that an SET pathway is involved in the reactions with nucleophilic species capable of an electron transfer.[4] The intermediary of ylid/carbene **5** has been suggested in several cases,[5] but this proposal remains controversial.[6]

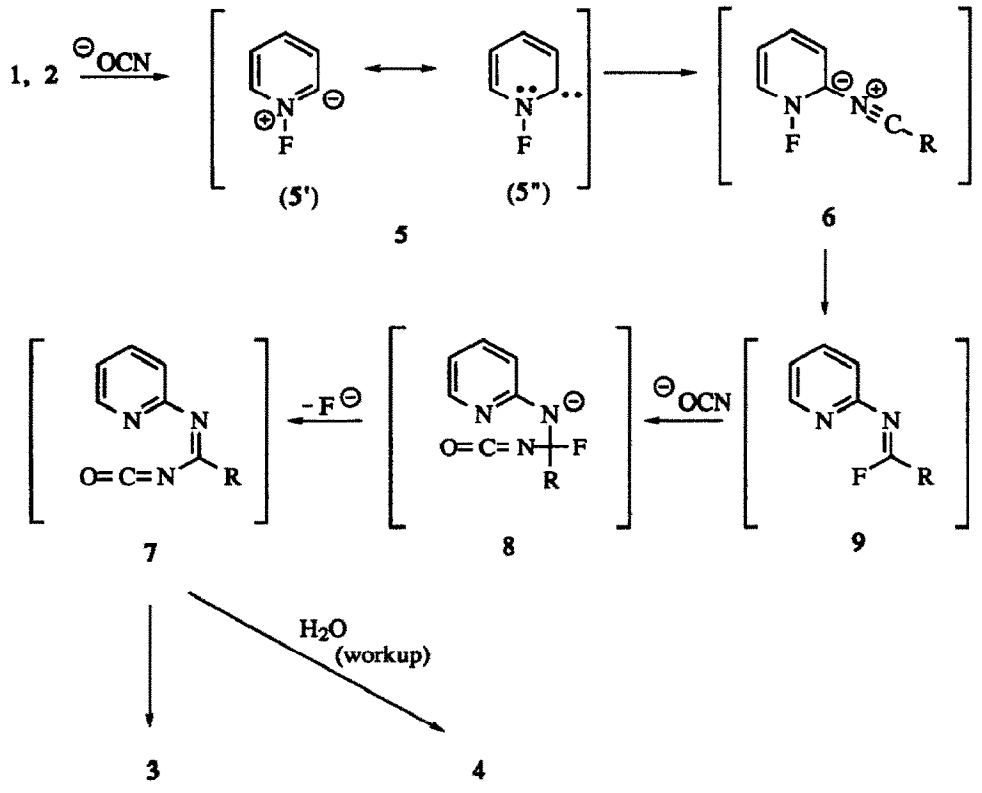
In this paper we present novel chemistry of *N*-fluoropyridinium salts **1**,**2** that leads to 2-substituted pyrido[1,2-a]-1,3,5-triazin-4-ones **3**, a previously unknown class of compounds. This is the first application of *N*-fluoropyridinium salts in the synthesis of a fused heterocyclic system. We also propose a mechanism which is fully consistent with the involvement of carbene **5"** as the major reaction intermediate.

The salts **1** and **2** are conveniently crystallized from hot acetonitrile without any appreciable decomposition. Interestingly, the treatment of **1**,**2** in acetonitrile with 1 equiv. of a weak base, such as triethylamine or cyanide ion, at -10 °C for 48 h and followed by standard workup gave *N*-(2-pyridyl)-acetamide[5,7] (**4a**) in a 50-70% yield. The yield of **4a** was only 30% with cyanate ion used as a base under otherwise identical conditions, and a new fluorescent polar product was observed by TLC. This product could not be obtained in an analytically pure form and was not characterized. Similar reactions,[8] however,



a: R = Me; **b**: R = *n*-Pr; **c**: R = *t*-Bu; **d**: R = Ph

conducted in butyronitrile, pivalonitrile, or benzonitrile furnished products that were easily purified and the structure of which was shown as **3b-d**. Compounds[9] **3b-d** (30-41%) were accompanied by the corresponding amides[10] **4b-d** (12-30%). TLC and GC-MS analyses of crude mixtures revealed that compounds **3** and **4** were the major low molecular weight products. The GC-MS analysis of a crude mixture from the reaction conducted in pivalonitrile also gave a minor compound with an apparent molecular mass of 180 the fragmentation pattern of which was fully consistent with that expected for fluoro imine **9** (R = *t*-Bu). 2-Aminopyridine was also a minor product for these reactions conducted at -10 °C. On the other hand, all crude mixtures contained a significant amount of 2-aminopyridine and yields of **3** and **4** decreased sharply when the reactions were conducted at 23 °C. It was shown that amides **4** are stable during workup and purification and, therefore, the amides are not precursors to 2-aminopyridine found in crude mixtures. The ratios of **3** to **4** were not significantly affected by changes in temperature. These results strongly suggest that **3** and **4** are formed in related reaction pathways which are favored by the use of a low temperature. It can also be suggested that a precursor to 2-aminopyridine is formed in a competitive reaction pathway which becomes important at higher temperatures. We believe that this pathway involves nucleophilic addition of cyanate anion with N-fluoropyridinium cation to form an isocyanate derivative.



The addition reaction is suppressed at -10 °C, and the cyanate ion acts primarily as a base. It can regioselectively deprotonate *N*-fluoropyridinium cation at position 2 with the formation of an intermediate product **5**, for which two contributing structures, an ylid **5'** and a carbene **5"**, can be suggested. Our AMPAC calculations[11] on **5** and independent theoretical studies on related intermediate products[12] are in favor of the electrophilic carbene **5"** as the major contributor to the electronic structure of **5**.

The carbene can react with carbonitrile to give a nitrilium ylid **6**. An intramolecular shift of fluoride in **6** can be expected to give a fluoro imine **9**, the apparent product, as already mentioned. The cyanate ion may undergo an addition reaction with **9** to give an isocyanate adduct **8**. Elimination of fluoride from **8** and then intramolecular cyclization of the resultant isocyanato imine **7** would give pyridotriazine **3**, the observed product. The isocyanato imine **7** could also be hydrolyzed to amide **4**, the second major product.

In summary, it is highly likely that carbene **5"** is an intermediate product in the discussed synthesis of pyridotriazinones **3**. With a preliminary understanding of the mechanistic pathway our research efforts are now directed toward optimization of the synthesis of **3** and a possible extension of this novel chemistry to the preparation of related derivatives. Our continuing studies have been strongly encouraged by a recent report that compounds structurally similar to **3b-d** display potent 5-HT_2 antagonist activity.[13]

Acknowledgment. We thank NIH (grant AI-27196) and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. The Varian VXR-400 NMR spectrometer was obtained with partial support from an award by the NSF Chemical Instrumentation Program (CHEM-8409599).

References and Notes

1. For synthesis of *N*-fluoropyridinium salts and application as reagents for fluorination of organic compounds, see: (a) Umemoto, T.; Tomita, K.; Kawada, K. *Org. Synth.* **1990**, *69*, 129-139. (b) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563-8575; and references cited therein.
2. Kiselyov, A.S.; Strekowski, L. *J. Org. Chem.* **1993**, *58*, 4476-4478; and references cited therein.
3. (a) Gakh, A.A.; Kiselyov, A.S.; Semenov, V.V. *Tetrahedron Lett.* **1990**, *31*, 7379-7382. (b) Kiselyov, A.S.; Strekowski, L. *J. Heterocyclic Chem.* **1993**, *30*, in press.
4. (a) Kiselyov, A.S.; Strekowski, L.; Semenov, V.V. *J. Heterocyclic Chem.* **1993**, *30*, 329-332. (b) Kiselyov, A.S.; Strekowski, L.; Semenov, V.V. *Tetrahedron* **1993**, *49*, 2151-2158.
5. Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705-2708.
6. See, for example: Hebel, D.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 6298-6301.
7. Purification by silica gel chromatography, hexanes/ether (1:1).
8. A mixture of **1** or **2** (2 mmol) and oven-dried KOCN (0.81 g, 10 mmol) was stirred at -10 °C under a nitrogen atmosphere and treated dropwise with anhydrous butyronitrile or benzonitrile (5 mL). Pivalonitrile (5 mL) was diluted with hexanes (1 mL) before the addition in order to avoid solidification. The heterogeneous mixture was stirred at -10 °C for 24-48 h until a KJ/starch test (ref. 3a) showed the absence of **1,2**, and then treated with water-saturated CH_2Cl_2 (50 mL). Filtration and then concentration of a solution were followed by chromatography: **4b-d** (footnote 7), **3b-d** (Et_2O/CH_2Cl_2, 2:1).

9. Satisfactory microanalyses (C, ± 0.3; H, ± 0.1; N, ± 0.2) were obtained for **3b-d**. ^{1}H NMR (400 MHz) and ^{13}C NMR (68 MHz) spectra reported below were taken in $CDCl_3$/TMS solutions. Coupling constants J (Hz) are for adjacent protons only. Proton decoupling and NOE experiments (lack of interaction between the C2-substituent and protons at the pyridine moiety) and comparison of the spectral data with that reported for other pyrido[1,2-a]-1,3,5-triazines [(a) Usui, H.; Watanabe, Y.; Kanao, M. *J. Heterocyclic Chem.* **1993**, *30*, 551-552. (b) Okide, G.B. *J. Heterocyclic Chem.* **1992**, *29*, 1551-1555] were used in the structure determination.
3b. Mp 116-117 °C, yield 30%; ^{1}H NMR: δ 1.03 (t, J = 7.6, Me), 1.88 (sext, J = 7.6, CH_2), 2.76 (t, J = 7.6, CH_2), 7.34 (t, J = 6.8 Hz, H-7), 7.60 (d, J = 8, H-9), 8.03 (dd, J = 8, J = 6.8, H-8), 9.05 (d, J = 6.8, H-6); ^{13}C NMR: δ 13.6, 20.8, 41.6, 117.3, 124.5, 129.4, 141.2, 150.4, 154.9, 178.7; MS: m/z 189 (M^+, 100); IR: ν 1700 cm^{-1}.
3c. Mp 147-148 °C, yield 41%; ^{1}H NMR: δ 1.41 (s, *t*-Bu), 7.30 (t, J = 6.8, H-7), 7.62 (d, J = 8.4, H-9), 8.00 (dd, J = 8.4, J = 6.8, H-8), 9.05 (d, J = 6.8, H-6); ^{13}C NMR: δ 28.8, 39.4, 117.3, 125.1, 129.6, 141.4, 151.8, 155.6, 185.4; MS: m/z 188 (100), 203 (26, M^+); IR: ν 1700 cm^{-1}.
3d. Mp 154-155 °C, yield 34%; ^{1}H NMR: δ 7.33 (t, J = 6.8, H-7), 7.53 (m, H-3', H-4', and H-5' of Ph), 7.71 (d, J = 8.4, H-9), 8.06 (dd, J = 8.4, J = 6.8, H-8), 8.59 (d, J = 8, H-1' and H-6' of Ph), 9.09 (d, J = 6.8, H-6); ^{13}C NMR: δ 118.9, 125.6, 128.4, 129.6, 130.0, 132.7, 135.9, 141.7, 151.2, 155.5, 186.0; MS: m/z 222 (100), 223 (44, M^+); IR: ν 1702 cm^{-1}.
10. **4b** and **4c**: Katritzky, A.R.; Vanden Eynde, J.J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 639-642; **4d**: Kravchenya, N.A. *Vesti Akad. Navuk BSSR, Ser. Khim. Navuk* **1987**, 111-113 (C.A. **1987**, *108*, 75189a).
11. The calculated dipole moments for *N*-fluoropyridinium radical $(C_5H_5NF)^+$ and **5** are 4.01 D and 3.89 D, respectively. The lower polarity of **5** is not consistent with the ylid structure **5'**.
12. Grigg, R.; Wallace, L.; Morley, J.O. *J. Chem. Soc., Perkin Trans. 2* **1990**, 51-56.
13. Watanabe, Y.; Usui, H.; Kobayashi, S.; Yoshiwara, H.; Shibano, T.; Tanaka, T.; Morishima, Y.; Yasuoka, M.; Kanao, M. *J. Med. Chem.* **1992**, *35*, 189-194.

(*Received in USA* 15 *September* 1993; *revised* 26 *October* 1993; *accepted* 5 *November* 1993)