Tetrahedron Letters,Vol.28, No.3,pp 255-258,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

# DIRECT FLUORINATION OF SUBSTITUTED PYRIDINES

Michael Van Der Puy
Allied-Signal Corp., Buffalo Research Laboratory
Buffalo, New York, 14210, USA

The direct fluorination of pyridines bearing alkyl, halogen, ester, or ketone functions has been employed to prepare the corresponding 2-fluoro-substituted pyridines.

The direct fluorination of pyridine to 2-fluoropyridine first reported by Simons[1] has received little attention.[2] Although 2-fluoropyridine was a product of pyridine fluorination, it was claimed [1a] that at -20°C, pyridine or 2-fluoropyridine could be used as an unreactive solvent for the fluorination of benzenoid aromatics. For example, a solution of toluene in pyridine, when treated with $F_2$, reportedly gave fluorotoluenes, but no mention was made of fluoropyridines. In our hands, the addition of $F_2$ to a solution of toluene in pyridine at -25°C gave primarily 2-fluoropyridine and unreacted toluene at low conversions, while the fluorination of toluene in 2-fluoropyridine at 0°C gave monofluorotoluenes and a roughly equal amount of 2,6-difluoropyridine. These results indicated that the fluorination of pyridine and even electron deficient pyridines is kinetically competitive with ring and side chain fluorination of benzenoid aromatics. Consequently, it appeared that it should be possible to fluorinate substituted pyridines with some selectivity for fluorination at the 2-position. Indeed, the direct fluorination of substituted pyridines in $CF_2ClCFCl_2$ solution with approximately 10% $F_2$ in $N_2$ gave 2-fluoro-substituted pyridines as the major fluorination product in preparatively useful yields (Table). The results for alkyl-substituted pyridines (entries 1-6) can be contrasted with free-radical chlorination of alkyl pyridines which leads to side chain perhalogenation before substantial nuclear halogenation occurs.[3] The synthesis of 2-fluoro-substituted pyridines via direct fluorination is not limited to alkyl pyridines, but pyridyl ketones, esters, and some halides can be fluorinated successfully as shown by entries 7-10. Notable here are the satisfactory yields in spite of the higher reaction temperatures necessitated by the modest solubilities of the reactants in $CF_2ClCFCl_2$ at reduced temperatures. The direct fluorination of substituted pyridines thus offers a reasonable alternative to Balz-Schiemann reactions where the appropriate amine

may not be available, as well as an alternative to sluggish Cl-F exchange reactions in 2-chloropyridines lacking additional activating groups.[4]

Table Fluorination Of Substituted Pyridines

| No. | Substituent | Temp(°C) | % Yield(a) | Product | $^{19}F$ NMR(b) |
|---|---|---|---|---|---|
| 1 | 4-methyl | -25 | 31 | 2-F-4-Me | -70.3 |
| 2 | 4-ethyl | -25 | 32 | 2-F-4-Et | -69.9 |
| 3 | 4-isopropyl | -25 | 47 | 2-F-4-iPr | -69.6 |
| 4 | 4-benzyl | -25 | 25 | 2-F-4-Bz | -69.1 |
| 5 | 3-methyl | -25 | 43 | 2-F-3-Me(28%) | -72.5 |
| | | | | 2-F-5-Me(15%) | -73.6 |
| 6 | 3,5-dimethyl | 0 | 37 | 2-F-3,5-diMe | -78.5 |
| 7 | 3,5-dichloro | +25 | 46 | 2-F-3,5-diCl | -73.6 |
| 8 | 4-acetyl | 0 | 26(c) | 2-F-4-$COCH_3$ | -66.5 |
| 9 | 4-$COOCH_3$ | 0 | 61 | 2-F-4-$COOCH_3$ | -66.8 |
| 10 | 3-$COOCH_3$ | 0 | 36(d) | 2-F-5-$COOCH_3$(20%) | -61.9 |
| | | | | 2-F-3-$COOCH_3$(16%) | -62.3 |

(a) Crude isolated yields (GC purities >95%) based on $F_2$ added. (b) in ppm, recorded in $CDCl_3$ with internal $CFCl_3$. Negative values represent resonance upfield from $CFCl_3$. (c) Yield after recrystallization (d) in $CCl_4$.

In contrast to the direct fluorination of benzenoid aromatics where the reaction products resulting from ring fluorination are difficult to separate from starting material, 2-fluoropyridines are readily separated from unreacted pyridines due to the pronounced reduction in basicity brought about by the presence of fluorine in the 2-position. Hence, simple extraction with 1 N HCl (2 N HCl for entries 8,9 and 10, 4 N for entry 7) cleanly separates product and unreacted starting material.

There is some evidence that pyridine difluorides ($Py \cdot F_2$) are intermediates in these fluorinations. Meinert[2] isolated pyridine difluoride as a white crystalline solid from the reaction of $F_2$ with pyridine at -80°C. It decomposed violently (to 2-fluoropyridine) at about 0°C. Umemoto has recently utilized difluorides of substituted pyridines (prepared with $F_2$ at -40°C) to synthesize N-fluoropyridinium salts.[5]

Electron withdrawing groups appear to stabilize the difluorides with respect to thermal decomposition, as the reaction mixtures may retain oxidizing power even after a nitrogen purge of the system to remove $F_2$. The oxidizing power in some cases was retained for several hours even at room temperatures, but only

when electron withdrawing groups were present.

An ionic structure, $PyF^+F^-$, has been proposed for pyridine difluoride.[2] A possible decomposition pathway leading to 2-fluoropyridines involves attack of $F^-$ on C-2(6) of the N-fluoropyridinium cation, followed by loss of HF. Decomposition of the difluoride of 2-chloropyridine might therefore be expected to result in Cl-F exchange by attack of fluoride on C-2. However, when $F_2$ was allowed to react with 2-chloropyridine at 0°C, the major reaction product was 2-chloro-6-fluoropyridine. By-products included 2,6-dichloropyridine, 2,6-difluoropyridine, and lesser amounts of dichlorofluoro- and chlorodifluoropyridines, but 2-fluoropyridine was not detected. Therefore, replacement of the hydrogen at C-6 by fluorine occurred preferentially to replacement of chlorine at C-2. The formation of a substantial amount of 2,6-difluoropyridine, but not 2-fluoropyridine, indicates that 2,6-difluoropyridine is the result of replacement of chlorine in 2-chloro-6-fluoropyridine by fluorine but not the result of fluorination of 2-fluoropyridine. This could arise via the addition of $F_2$ to the CCl=N bond, followed by loss of ClF.

The products formed in the fluorination of 2-chloropyridine and the increase in stability of pyridine difluorides bearing electron withdrawing groups [1b] are consistent with attack at C-2(6) by a reagent having electrophilic properties. Based on the data currently available, the decomposition of pyridine difluorides most likely occurs via the addition of $F_2$ to the most electron-rich C=N bond.

## EXPERIMENTAL

**Caution:** Potentially dangerous difluorides may precipitate during the reaction, especially if reaction temperatures are below -25°C. It is strongly recommended that prior to workup, the reaction mixture be allowed to warm slowly to room temperature, and tested for the presence of oxidizing material.

2-Fluoro-4-benzylpyridine: A solution of 25.0g 4-benzylpyridine in 20mL $CF_2ClCFCl_2$ was cooled to -25°C. $F_2$ (8 cc/min) diluted with $N_2$ (68 cc/min) was bubbled in subsurface for 3h (total $F_2$, 56 mmol). The reaction mixture was allowed to warm to room temperature and 150 ml ether added. The organic layer was washed with water, 1N HCl, and brine. After drying ($Na_2SO_4$), the volatiles were removed by rotary evaporation to give 2.6g (25% yield) amber oil (95% pure by GC) identified as 2-fluoro-4-benzylpyridine. Analytically pure material was obtained by chromatography on silica gel, eluting with $CH_2Cl_2$. Anal. Calcd. for $C_{12}H_{10}FN$: C, 76.96%; H, 5.38%; N, 7.51%; Found: C, 76.71%; H, 5.45%, N, 7.42%. NMR ($CDCl_3$) $\delta$ 8.1 (d, 1H), 7.0-7.4 (m, 6H), 6.7 (s, 1H), 3.96 (s,2H). Bp 77°C at 0.05 mm.

2-Fluoro-4-carbomethoxypyridine: Methyl isonicotinate (25.5g) was dissolved in 125 mL $CF_2ClCFCl_2$ and the mixture cooled in an ice bath. $F_2$ (8 cc/min) diluted with $N_2$ (80 cc/min) was then bubbled in for 4h (75 mmol $F_2$). After

allowing the mixture to warm to room temperature, it was washed with water, 2N HCl, water, and dried. A small amount of a third phase which formed during the extraction was removed by filtration and discarded. After removal of solvent there was obtained 7.1g (61%) of liquid, homogeneous by GC. Distillation gave 5.3g colorless oil, bp 82-85°C at 8 mm. IR (neat) 1745 $cm^{-1}$ (C=O); NMR ($CDCl_3$)$\delta$ 8.35 (d, J=5Hz, 1H), 7.73 (m, 1H), 7.47 (d, J=1-2Hz, 1H), 3.98 (s, 3H) MS, m/z 155 (parent), 124 (base).

The other compounds listed in the Table were prepared in a similar fashion. Products from entries 1 and 5 were commercially available. Physical and spectral data for the other products are as follows: 2-fluoro-4-ethylpyridine, Bp 79-81°C at 22 mm; MS, m/z 125 (parent and base); NMR ($CDCl_3$) $\delta$ 8.07 (d, 1H), 7.0 (m, 1H), 6.7 (s, 1H), 2.67 (q, 2H), 1.25 (t, 3H); 2-fluoro-4-isopropyl-pyridine, Bp 75°C at 15 mm; MS, m/z 139 (parent), 124 (base); NMR($CDCl_3$) $\delta$ 8.12 (d, 1H), 7.16 (m, 1H), 6.75 (s, 1H), 2.92 (heptet, 1H), 1.25 (d, 6H); 2-fluoro-3,5-dimethylpyridine, Bp 76°C at 24 mm; MS, m/z 125 (parent and base); NMR($CDCl_3$) $\delta$ 7.8 (bs, 1H), 7.45 (dd, 1H), 2.28,2.25 (6H); 2-fluoro-3,5-dichloropyridine, mp 41-42°C (lit.[6] 42-43°C). 2-fluoro-4-acetylpyridine, Mp 37.5-39°C; IR(nujol mull) 1710 $cm^{-1}$ (C=O); NMR ($CDCl_3$) $\delta$ 8.43 (d, 1H), 7.65 (m, 1H), 7.40 (bs, 1H), 2.67 (s, 3H). Anal. Calcd. for C7H6FNO: C, 60.43; H, 4.35; N, 10.07; Found: C, 60.34; H, 4.38; N, 9.91%; methyl 2-fluoronicotinate; Isomer ratios were determined by $^{19}F$ and $^{1}H$ NMR. $^{1}H$ NMR (mixture of isomers in $CDCl_3$): 2-F-5-$COOCH_3$,$\delta$8.9 (d, J=2 Hz, H6), 8.3-8.6 ($H_4$), 6.95 (dd, J=2 and 9 Hz, H3); 2-F-3-$COOCH_3$, $\delta$ 8.3-8.6 (H4 and H6), 7.2-7.4 (H5).

Acknowledgement: Dr. Richard E. Eibeck is gratefully acknowledged for suggesting this work.

References

(1) (a) J. H. Simons, U.S. Patent 2,447,717 (1948); (b) J. H. Simons, "Fluorine Chemistry", Vol. 1, Academic Press, New York, 1959 p 421.
(2) H. Meinert, Z. Chem. 1965, 5, 64.
(3) H. S. Mosher in "Heterocyclic Compounds", Vol. 1, Ed. R. C. Elderfield, John Wiley, New York, 1950, p 509 and references cited therein.
(4) M. M. Boudakian, J. Heter. Chem., 1967, 4, 381.
(5) T. Umemoto and K. Tomita, Tetrahedron Lett., 1986, 27, 3271.
(6) G. C. Finger et. al., J. Org. Chem., 1963, 28, 1666.

(Received in USA 15 October 1986)