Fluorinated Heterocyclic Compounds. 4-Fluoro-2-pyridone

Clifford C. Leznoff*, Polina I. Svirskaya and Varda Yedidia

Department of Chemistry, York University,
Downsview, Ontario, Canada M3J 1P3

Jack M. Miller

Department of Chemistry, Brock University,
St. Catherines, Ontario, Canada L2S 3A1

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The uracil analog, 4-fluoro-2-pyridone was synthesized by ether cleavage of 4-fluoro-2-methoxypyridine with trimethylsilyl iodide. Improved procedures for the preparations of 2-methoxypyridine *N*-oxide hydrochloride and 2-methoxy-4-nitropyridine *N*-oxide are described.

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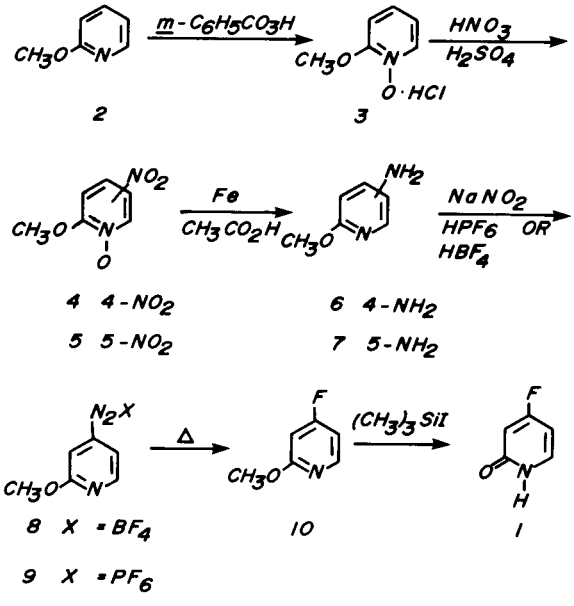
A large number of nucleoside analogs and nucleoside base analogs have been prepared for biological testing and many have been incorporated into modern drugs [1,2]. For example, 3-deazauridine [3] has pronounced antitumor and antiviral activity [4] and 5-fluorouracil [5] and 5-fluoro-2'-deoxyuridine [6] are widely used antitumor agents.

The very success of 5-fluorouracil and related compounds as antitumor drugs is seen as a demonstration of the efficacy of the proposal [5,7,8] that fluorine is a suitable replacement for *hydrogen* in designing drugs. Less well-known is the fact that a fluoro substituent can readily replace an *hydroxy* group. This principle has been particularly exploited in carbohydrate chemistry where a fluorine substituent replaces an hydroxy group in glucose and the resulting enzymatic effects have been studied [9,10]. Very few examples of drugs designed from the fact that a fluorine substituent could replace an *enolic hydroxy* group have been reported despite the fact that a fluoro substituent is much more similar to a hydroxy group than a hydrogen. Certainly, from recently calculated electronegativity figures [11], the value for the fluoro substituent (11.00) is even closer to that of oxygen (8.92) than the common oxygen replacement atom, sulfur (6.52). Ab initio calculations [12] on 2-fluoropyridine and 2-hydroxypyridine reveal that the C-F and C-O bond lengths at 1.35 and 1.39 Å respectively are very similar. The N_1-C_2-X bond angles where X is F (116°) or O (117°) are also exceedingly close [12].

With these considerations in mind we felt that the synthesis of pyridine and pyrimidine bases fluorinated in the appropriate positions where a fluoro group could replace an hydroxy substituent in the enolic form of pyridones and uracils, *i.e.* hydroxypyridines and hydroxypyrimidines were warranted. One of the simplest analogs of this type is 4-fluoro-2-pyridone (**1**), the nucleoside base analog of 3-deazauridine. Although 6-fluoro-2-pyridone [13], 5-fluoro-2-pyridone [14], 3-fluoro-2-pyridone [15] and most recently 1-fluoro-2-pyridone [16] have been described, the desired 4-fluoro-2-pyridone (**1**) was unknown. Since it was well documented that 4-fluoropyridine was an unstable elusive compound [7,18], there was concern that the related 4-fluoro-2-pyridone (**1**) would be difficult to prepare. Although some care must be exercised in the isolation of **1** (see Experimental), compound **1** was prepared using some of the methods related to those of Nesnow and Heidelberger [14] for the preparation of 5-fluoro-2-pyridone. Substantial modifications in the many steps of the synthesis gave highly improved yields.

The 4-fluoro-2-pyridone (**1**) was prepared in six steps in an overall yield of 28% from commercially available 2-methoxypyrimidine (**2**) according to Scheme I. Thus **2** was oxidized with a peracid by the procedure of Den Hertog and Van Ammers [19] but using *m*-chloroperbenzoic acid instead of perbenzoic acid, higher temperatures and shorter reaction times resulting in the formation of 2-methoxypyridine *N*-oxide hydrochloride (**3**) in yields considerably higher (81 *vs* 61%) than those reported. Nitration of **3** yielded a *mixture* of 2-methoxy-4-nitropyridine

SCHEME I



N-oxide (**4**) and 2-methoxy-5-nitropyridine *N*-oxide (**5**) in 62 and 11% yields, respectively. The nitration of **3** had previously been reported [19] to give solely **4** in a crude yield of 55-60% but older crystallization techniques could not separate **4** from **5**. In fact, standard chromatography on silica can separate **4** from **5**. Again, higher reaction temperatures and longer reaction times gave higher yields for pure **4** than described [19]. The reduction [19] of **4** proceeded normally to give 4-amino-2-methoxypyridine (**6**) in 90% yield. Reduction of **5** yielded the known 5-amino-2-methoxypyridine (**7**) [20] and helped establish the identity of **5**. Diazotization of **6** with sodium nitrite and 48% fluoroboric acid [21] acid yielded 2-methoxypyridine-4-diazonium tetrafluoroborate (**8**). Diazotization using hexafluorophosphoric acid yielded 2-methoxypyridine-4-diazonium hexafluorophosphate (**9**). The diazonium salt **8** was decomposed *in situ* to give the unknown 4-fluoro-2-methoxypyridine (**10**). Decomposition [14] of **9** also yielded **10** but in lower yield. Attempts to cleave the methyl ether group of **10** following the procedure of Nesnow and Heidelberger [14] did give a very low yield of 4-fluoro-2-pyridone (**1**) but cleavage of the methyl ether of **10** under neutral conditions using trimethylsilyl iodide [22,23] gave **1** in 69% yield. Attempts to cleave the methyl ether group of **10** with boron tribromide [22-24] did give a trace of **1** but the major product was 4-hydroxy-2-pyridone (**11**). It is interesting to note that **1** is a quite stable compound that can be kept at room temperature for months, is soluble in water but does slowly decompose under aqueous conditions to give **11**. Biological testing of **1** and **10** are in progress.

EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra for protons were recorded on a Varian EM 360 spectrometer using deuteriochloroform (deuteriochloroform) as solvent and tetramethylsilane as the internal standard. Infrared spectra (ir) were recorded on a Unicam SP 1000 IR spectrophotometer as Nujol films between sodium chloride discs. Vapour phase chromatographs (vpc) were run on a 15 m × 0.25 mm i.d. column coated with DB5 having a film thickness of 0.25 μ. The temperature programming conditions were 50-200° held for 2 minutes to 200° at 12° min^{-1}. Computer acquired mass spectral data were recorded through a VG2025 data system interfaced to the gcms system at an ionizing energy of 70 eV in the EI mode at an ion source temperature of 200° and a scan rate of 1.5 sec per decade. Solvents were removed on a rotary evaporator, unless otherwise specified. Silica gel was used for all thin and preparative layer chromatography (tlc) and column chromatography. All melting and boiling points are uncorrected. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

2-Methoxypyridine *N*-Oxide Hydrochloride (**3**).

Oxidation of 21.8 g (0.12 mole) of 2-methoxypyridine with 100 g (0.46 mole) of *m*-chloroperbenzoic acid in dichloromethane was conducted overnight at room temperature, or at 40-45° for 6 hours and finally overnight at room temperature. The previous method [19] used perbenzoic acid in chloroform for four days at room temperature. The reaction mixture was treated with a 1:1 solution of concentrated hydrochloric acid and water and the acidic solution was evaporated *in vacuo* to dryness. The hydrochloride **3** was recrystallized twice from methanol-ether to give 25 g (81%) of **3** as white hygroscopic crystals, mp 122-123° (lit [19] mp 115°).

2-Methoxy-4-nitropyridine *N*-Oxide (**4**) and 2-Methoxy-5-nitropyridine *N*-Oxide (**5**).

A crude mixture of **4** and **5** was obtained by nitration of **3** according to Den Hertog and Van Ammers [19]. The following modified procedure increased the yields of **4** relative to **5**. A solution of 26 g (0.16 mole) of *N*-oxide **3** in 60 ml of concentrated sulfuric acid at 0° was treated with 110 ml of a 3:1 mixture of fuming nitric and concentrated sulfuric acids. The mixture was heated for 3 hours at 90-100°. The solution was cooled, poured into 100 ml of ice-water and neutralized with concentrated ammonia to neutral *p*H, keeping the temperature below 10° in the neutralization step. The mixture was extracted five or six times with 250-300 ml portions of dichloromethane. The layers were separated, the organic layer dried over magnesium sulfate and evaporated to give 27 g of a crude product which exhibited three spots on tlc (eluting solvent, 2% methanol in dichloromethane). The crude mixture was separated into its components by chromatography on 400 g of silica gel. Elution with dichloromethane gave 5 g (20%) of 2-methoxy-5-nitropyridine [25] as white crystals: mp 110° (lit [20] mp 110°); ^{1}H nmr (deuteriochloroform): δ 4.10 (3H, s, OCH_3), 6.89 (1H, d, J = 8.0 Hz, H-3), 8.46 (dd, $J_{4,6}$ = 2.5 Hz, $J_{3,4}$ = 8.0 Hz, 1H, H-4), 9.16 (d, J = 2.5 Hz, 1H, H-6).

The major yellow fraction was then eluted with a 1:49 mixture of methanol-dichloromethane to give 17 g (62%) of 2-methoxy-4-nitropyridine *N*-oxide (**4**) as light yellow crystalline needles, mp 180-181° (lit [19] mp 154.5-158.5°); ir (potassium bromide): 1235 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.18 (3H, s, OCH_3), 7.76-7.95 (2H, m, H-3,5), 8.24-8,42 (m, 1H, H-6); ms: (70 eV), m/e (relative intensity) 170 (M^+, 77), 153 (57), 124 (59), 78 (100).

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.35; H, 3.55; N, 16.47. Found: C, 42.62; H, 3.55; N, 16.45.

A minor yellow fraction was next eluted with 1:9 and 1:4 mixture of methanol-dichloromethane to give 3 g (11%) of 2-methoxy-5-nitropyridine *N*-oxide (**5**) as a yellow solid: mp 161-162°; ir (potassium bromide): 1220 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.20 (s, 3H, OCH_3), 7.00 (d, J = 9 Hz, 1H, H-3), 8.15 (dd, J_{4-6} = 3 Hz, J_{3-4} = 9 Hz, 1H, H-4), 9.16 (1H, d, J = 3 Hz, H-6).

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.35; H, 3.55; N, 16.47. Found: C, 42.42; H, 3.94; N, 16.90.

4-Amino-2-methoxypyridine (**6**) and 5-Amino-2-methoxypyridine (**7**).

Reduction of 12.0 g (0.07 mole) of **4** by the reported method [19] gave 7.8 g (90%) of **6** as white crystals, mp 91-92° (lit [19] mp 91.5-92°); ir (Nujol): 3390, 3300, 3180 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.90 (s, 3H, OCH_3), 4.28 (br s, 2H, NH_2), 5.88 (d, J = 2.5 Hz, 1H, H-3), 6.18 (dd, J_{3-5} = 2.5 Hz, J_{5-6} = 7 Hz, 1H, H-5), 7.80 (d, J = 7 Hz, 1H, H-6).

Similarly, reduction of 1.7 g (0.01 mole) of **5** gave 1.1 g (89%) of **7** as a colourless oil [20] which on column chromatography yielded white crystals: mp 28-30°.

4-Fluoro-2-methoxypyridine (**10**). Method A.

To a solution at −10° of 5.96 g (0.04 mole) of **6** in 15 ml of 48% fluoroboric acid was added 5.0 g (0.07 mole) of sodium nitrite in small portions, keeping the temperature below −5°. After the addition was complete, the mixture was stirred for 45 minutes at 0° and finally warmed slowly during 30 minutes to room temperature to decompose the intermediate diazonium salt **8**. The temperature of the solution rose to 30-35° and nitrogen was evolved for about 30 minutes. The solution was cooled to −10° and neutralized with 3*M* sodium hydroxide precooled to 0-5°. The temperature of the solution must remain below 0° during this procedure [26]. The mixture was extracted with 50 ml of ether, washed with 5 ml of cooled water and dried over anhydrous potassium fluoride. The ether solvent was distilled through a small 15 cm column and final distillation *in vacuo* in which the receiver flask was cooled in dry ice acetone yielded 4.6 g of **10** (90%) as a pure (99.7% by vpc analysis) colorless

oil, bp 22-23° (2 torr); ^{1}H nmr (deuteriochloroform): δ 3.96 (s, 3H, OCH_3), 6.2-6.8 (m, 2H, H-3,5), 8.14 (dd, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 5.5 Hz, 1H, H-6); ms: (70 eV), m/e (relative intensity) 127 (M^+, 70), 97 (100), 70 (70).

Anal. Calcd. for C_6H_6FNO: C, 56.68; H, 4.75; N, 11.01; F, 14.94. Found: C, 56.68; H, 4.71; N, 11.04; F, 14.96.

Method B.

Using the method of Nesnow and Heidelberger [14] 3.4 g (0.027 mole) of **6** yielded 5.7 g (79%) of 2-methoxypyridine-4-diazonium hexafluorophosphate (**9**), mp 66-67°. Decomposition of 5.7 g of **9** by the described procedure [14] yielded 1.2 g (35% from **6**) of **10**. Compound **10** (>99% pure by vpc) was identical to **10** prepared by Method A.

4-Fluoro-2-pyridone (**1**).

To a solution of 5.08 g (0.04 mole) of **10** in 20 ml of dry dichloromethane under argon was added 9.0 g (0.045 mole) of iodotrimethylsilane in 5 ml of dichloromethane. The mixture was stirred for 4 hours at room temperature, 1 hour at 40°, and overnight at room temperature. The reaction was complete as evidenced by the lack of methoxyl proton absorbances in the nmr spectrum of the brown reaction mixture. The mixture was evaporated *in vacuo*, 10 ml of dry dichloromethane was added and the solvent evaporated again. The resulting solid was dissolved in dichloromethane and some wet crystals of sodium thiosulfate were added. Stirring was continued until the brown color disappeared from both the solid and solution. The dichloromethane solution was filtered, dried (magnesium sulfate) and the solvent evaporated to give 2.1 g of 4-fluoro-2-pyridone (**1**) as a white precipitate. The residue of inorganic salt was treated with methanol to dissolve further product trapped in the salts. The methanol was filtered and evaporated to give a white powder which was recrystallized from dichloromethane-ether to give an additional 1.0 g of white crystals of **1**. The total yield of **1** was 3.1 g (69%), mp 176-177°; ir: 1660, 1600 cm^{-1}; ^{1}H nmr: δ 6.3-6.0 (m, 2H, H-3,5), 7.60-7.28 (m, 1H, H-6); ms: m/e (relative intensity) 113 (M^+, 100), 85 (24), 66 (19), 57 (100).

Anal. Calcd. for C_5H_4FNO: C, 53.09; H, 3.65; N, 12.38; F, 16.80. Found: C, 52.89; H, 3.60; N, 12.57; F, 17.02.

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[25] The presence of 2-methoxy-5-nitropyridine in the product mixture is definitely not due to unreacted **2** present in the preparation of **3** as **3** used in this nitration step was completely free of **2**.

[26] If the temperature during the neutralization step was maintained only at 0 to +10°, the yield of **10** was only 70-80% and from the residue in the distillation flask was isolated 5-15% of 2-methoxy-4-hydroxypyridine, mp 135° (lit [27] mp 133.5-134°).

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