

Electrophilic Substitution of Furo[3,2-*c*]pyridine

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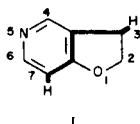
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Furo[3,2-*c*]pyridine (I) was nitrated to give 2-nitrofuro[3,2-*c*]pyridine (II). Bromination and chlorination of I gave, respectively, 2,3-dibromo-2,3-dihydrofuro[3,2-*c*]pyridine (III) and 2,3-dichloro-2,3-dihydrofuro[3,2-*c*]pyridine (IV). Oxidation of I with hydrogen peroxide afforded furo[3,2-*c*]pyridine 5-oxide (V) which was converted to I by phosphorus trichloride and to 4-chlorofuro[3,2-*c*]pyridine (VI) by phosphorus oxychloride.

The synthesis of furo[2,3-*b*]pyridine was reported from this laboratory in 1971 (1). In a continuing study of syntheses and reactions of the various furopyridines, we have undertaken the electrophilic substitutions on the furopyridines. In this paper, electrophilic substitutions and additions to another furopyridine isomer, namely furo[3,2-*c*]pyridine (I) are reported. The furo[3,2-*c*]pyridine has been synthesized by three different methods. Bourzat and Bisagni (2) synthesized I starting with 3-carboethoxy-2-formylfuran. Lhommet, Sliwa, and Maitte (3) used as starting material 3-(bromoacetyl)-4-ethoxy-pyridinium bromide. The procedure we have used is a modification of that reported by Eloy and Deryckere (4) in which furfural and malonic acid are the starting materials.

Nmr spectral studies of I (Tables I and II) revealed that in addition to the expected spin-spin couplings, long-range coupling occurred between H-4 and H-7 and also as previously reported (4) between H-3 and H-7. This long-range H-3 to H-7 coupling occurs over five bonds and has also been reported in benzofuran (5). The coupling in benzofuran was attributed to the geometrically fixed, all *trans* configuration, which results in favorable orbital overlap and thus favorable transmission of the proton spin-state information (6).

(favorable all *trans* configuration between H-3 and H-7)

The nitration of furo[3,2-*c*]pyridine (I) was effected in a mixture of fuming nitric and sulfuric acids below 0°. The product in 30.5% yield was 2-nitrofuro[3,2-*c*]pyridine (II). Evidence for nitration in the 2-position was the disappearance of H2-H3 coupling and the retention of

H3-H7 coupling (Tables I and II), thus indicating the absence of H2. Attributing the poor yield to a possible opening of the furan ring by the strong acid mixture, a mixture of acetic anhydride and nitric acid was used. While this mixture is known to give 2-nitrobenzofuran from benzofuran (7), no nitration product was obtained using I but rather 62% of I was recovered. The difference between reactivity of I and benzofuran toward the weaker nitrating mixture may be due to the fact that the furopyridine is undoubtedly protonated in acid. The protonated pyridine ring is strongly electron-withdrawing and deactivates the furan ring toward electrophilic attack. While 2-nitration occurred in the furopyridine (I), the thienopyridines are reported to give predominantly 3-nitration (8,9).

The ir spectrum of II showed strong NO₂ bonds at 1520 and 1350 cm⁻¹, and the nmr (Table I) showed the following absorptions: doublet δ 9.05 (H-4); doublet δ 8.67 (H-6); doublet δ 7.65 (H-3); multiplet δ 7.49 (H-7). Proton assignments were based on a comparison with those of the parent furo[3,2-*c*]pyridine (I) and decoupling data.

TABLE I

NMR Assignments (δ values) for Furo[3,2-*c*]pyridines

Compound No.	H-2	H-3	H-4	H-6	H-7
I	7.57d	6.70dd	8.89d	8.46d	7.32m
II	----	7.65d	9.05d	8.67d	7.49m
III	6.88s	5.75s	8.71s	8.53d	6.99d
IV	6.51s	5.52s	8.70s	8.56d	7.01d
V	7.78d	6.82dd	8.63dd	8.22dd	7.44m
VI	7.61d	6.80dd	----	8.18d	7.31dd

s = singlet; d = doublet; dd = double doublet; m = multiplet. Spectra were obtained in deuteriochloroform. Each absorption in Table represents one proton.

Halogenation (bromination and chlorination) of I in carbon tetrachloride gave the corresponding 2,3-dihalo-2,3-dihydrofuro[3,2-*c*]pyridines (III and IV). Reactions in ethanol and water gave essentially the same results. The addition rather than substitution of halogen was similar to the reaction of benzofuran (10), but somewhat different from thienopyridine (11) which gives both substitution and addition. On the basis of the disappearance of H2-H3 coupling in the halogenated furopyridines, the additions are believed to be *trans*. The *trans* products would have vicinal protons with dihedral angles close to 90°, and therefore near zero coupling constant (12,13).

The dihalofuropyridines were somewhat unstable at ambient temperatures. Hydrogen halide appeared to be evolved accompanied by discoloration of the residue (halogen values were low as shown in Experimental). The nmr absorptions are shown in Table I.

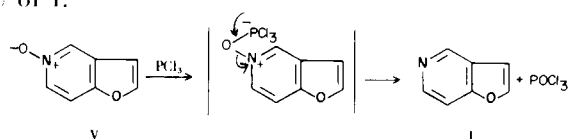
Attempts were made to acylate I using the systems acetyl chloride-aluminum chloride and acetic anhydride-boron trifluoride etherate. The only organic material isolated in either case was starting material. Inasmuch as benzofuran is acylated by the boron trifluoride system (14) and resinified by the aluminum chloride system (15), and furan is acylated under mild conditions (16), additional evidence was obtained for the deactivation of the furan ring of furopyridine.

Attempts at sulfonation of I using either concentrated sulfuric acid or pyridine-sulfur trioxide were unsuccessful. Use of the latter reagent resulted in recovery of starting material. Since furan (16) and benzofuran (17) are sulfonated using pyridine-sulfur trioxide, furopyridine is again shown to be less reactive than those compounds.

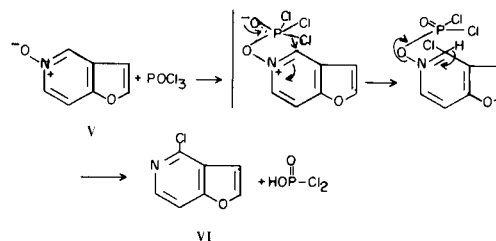
Furo[3,2-*c*]pyridine (I) was converted to furo[3,2-*c*]pyridine 5-oxide (V) by treatment with hydrogen peroxide. The *N*-oxide was found to be extremely hygroscopic and difficult to obtain in anhydrous form. The *N*-oxide was of interest because it is known that substitution on the pyridine ring is often changed when pyridine is converted to its oxide. For example, while electrophilic attack occurs at the 3-position in pyridine, it may occur at the 2- and 4-positions in pyridine *N*-oxide (18).

An attempt to acylate the *N*-oxide with acetyl chloride and aluminum chloride catalyst resulted in deoxygenation and conversion to furo[3,2-*c*]pyridine (I). The aluminum chloride probably complexes with oxygen causing its removal.

Deoxygenation of V also occurred when the *N*-oxide was heated with phosphorus trichloride (19,20), giving 94% of I.



Deoxygenation and concomitant chlorination occurred when the *N*-oxide (V) was treated with phosphorus oxychloride (20,21). The product was 4-chlorofuro[3,2-*c*]pyridine (VI) in 45% yield. Although the 6-chloro product is also possible, none was isolated. A likely mechanism for the reaction appears to be that below.



Attempts to brominate and chlorinate V resulted in formation of solids which became tars upon attempted purification.

TABLE II

Coupling Constants (J in H_2) for Furo[3,2-*c*]pyridines

Compound No.	$J_{2,3}$	$J_{3,7}$	$J_{4,6}$	$J_{4,7}$	$J_{6,7}$
I	2.25	1.1	---	0.8	5.6
II	---	0.9	---	1.0	5.6
III	---	---	---	---	5.5
IV	---	---	---	---	5.5
V	2.3	0.9	1.8	0.6	7.0
VI	2.2	1.0	---	---	5.5

EXPERIMENTAL

Elemental analyses were performed by the Midwest Microanalytical Laboratory, Indianapolis, Indiana. Melting points were determined on a Mel-Temp metal block and are not corrected. The infrared spectra were determined on a Perkin-Elmer Infracord and the nmr spectra on a Hitachi R-20 Spectrometer. Furo[3,2-*c*]pyridine (I) was synthesized by a modification of the method of Eloy and Deryckere (4).

2-Nitrofuro[3,2-*c*]pyridine (II).

To 8 ml. of stirred concentrated sulfuric acid at -20° was added dropwise during 5 minutes 1.78 g. (0.015 mole) of I. A mixture of 3 ml. of concentrated sulfuric acid and 8 ml. of 90% fuming nitric acid was then added at such a rate as to maintain the temperature at -10° . After 90 minutes at below 0° , the solution was poured onto 100 g. of ice and neutralized with small portions of solid sodium bicarbonate. The solution was extracted with eight 100-ml. portions of ether and the ether extracts dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave 0.75 g. (31%) of solid, m.p. $89-96^\circ$. Recrystallization from chloroform-petroleum ether yielded 0.42 g. (17%) of 2-nitrofuro[3,2-*c*]pyridine (II), m.p. $99.5-101.5^\circ$.

Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07. Found: C, 51.35; H, 2.70; N, 16.91.

An identical procedure to that above was used except a mixture of concentrated sulfuric acid and 70% nitric acid was used. The yield of II was 0.1 g. (4%).

2,3-Dibromo-2,3-dihydrofuro[3,2-c]pyridine (III).

To a solution of 1.78 g. (0.015 mole) of I in 15 ml. of carbon tetrachloride at -10° was added dropwise during 10 minutes a solution of 7.2 g. (0.045 mole) of bromine in 10 ml. of carbon tetrachloride. After the addition was complete the mixture was stirred at 0° for 2 hours. Solvent was removed under reduced pressure to yield a reddish-brown semi-solid (4.0 g.). The latter was washed with a cold solution of sodium sulfite until starch-iodide paper gave a negative test for bromine. The resulting acidic solution was neutralized ($\text{pH} \sim 8$) with sodium bicarbonate and the precipitated product filtered off and recrystallized from chloroform-petroleum ether ($30-60^{\circ}$). The tan crystals amounted to 1.9 g. (45%) of 2,3-dibromo-2,3-dihydrofuro[3,2-c]pyridine (III), m.p. $91-92^{\circ}$.

Anal. Calcd. for $\text{C}_7\text{H}_5\text{NOBr}_2$: N, 5.02. Found: N, 5.24.

2,3-Dichloro-2,3-dihydrofuro[3,2-c]pyridine (IV).

To a solution of 5.1 g. (0.072 mole) of chlorine in 30 ml. of cold (0°) carbon tetrachloride was added with stirring during 5 minutes a solution of 1.78 g. (0.015 mole) of I in 5 ml. of carbon tetrachloride. After 30 minutes of additional stirring at 0° and removal of solvent under reduced pressure, the resultant brown solid was treated with 20 ml. of water, followed by cold aqueous sodium sulfite solution until starch-iodide paper gave a negative test for chlorine. The resulting solution was neutralized with sodium bicarbonate to afford 1.8 g. (63%) of yellow solid, m.p. $61-68^{\circ}$. Recrystallization from chloroform-petroleum ether gave 0.97 g. (34%) of 2,3-dichloro-2,3-dihydrofuro[2,3-c]pyridine (IV), m.p. $70.5-72^{\circ}$. The nmr spectrum of IV indicated that the proposed structure was the correct one. Decomposition occurred resulting in poor elemental analyses. (Calcd. for N and Cl = 7.37 and 37.31; found were 8.22 and 35.54.)

Furo[3,2-c]pyridine 5-Oxide (V).

A solution of 11.9 g. (0.10 mole) of I in 30 ml. of glacial acetic acid and 34 ml. of 30% aqueous hydrogen peroxide solution was stirred and heated at 60° for 16 hours, and then cooled and poured onto 150 g. of ice. To the mixture was added cold, aqueous sodium carbonate solution until starch-iodide paper no longer gave a positive peroxide test. The solution was neutralized with sodium bicarbonate, extracted with ten 50-ml. portions of chloroform, the chloroform extracts dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The white solid residue was dried under vacuum over phosphorus pentoxide and amounted to 7.21 g. (50%) of furo[3,2-c]pyridine 5-oxide (V), m.p. $57-72^{\circ}$. The nmr spectrum indicated the presence of water (as hydrate). Therefore, the sample was dried for four days at 25° in a vacuum desiccator over phosphorus pentoxide, m.p. $91.5-94^{\circ}$; nmr indicating anhydrous V. Before analysis, however, the sample had absorbed up water.

Anal. Calcd. for $\text{C}_7\text{H}_5\text{NO}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 58.73; H, 4.22; N, 9.79. Found: C, 59.02; H, 4.38; N, 9.67.

Deoxygenation and Chlorination of V with Phosphorus Oxychloride.

A mixture of 0.675 g. (0.0045 mole) of V and 4.6 g. (0.030 mole) of phosphorus oxychloride was heated under reflux for 90 minutes. After cooling to 25° the mixture was poured onto 10 g. of ice and water. The solution was extracted with three 20-ml. portions of ether and the combined extracts dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave 0.31 g. (45%) of a colorless liquid which solidified upon standing, m.p. $40-41^{\circ}$, m.m.p. with 4-chlorofuro[3,2-c]pyridine (VI) $40-41^{\circ}$. The two samples also gave identical ir and nmr spectra.

Deoxygenation of V with Phosphorus Trichloride.

To a solution of 0.675 g. (0.0045 mole) of furo[3,2-c]pyridine 5-oxide (V) in 20 ml. of chloroform was added at 0° 2.75 g. (0.020 mole) of phosphorus trichloride. The mixture was heated under reflux for 2 hours, cooled to 25° , and slowly poured onto 20 g. of crushed ice. The acidic solution was neutralized to $\text{pH} 7$ with solid sodium carbonate and the solution extracted with five 50-ml. portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue was 0.51 g. (95%) of light brown oil, which was shown by ir and nmr to be furo[3,2-c]pyridine (I).

Attempted Acylation of V.

To a stirred mixture of 7.0 g. (0.053 mole) of anhydrous aluminum chloride and 20 ml. of carbon disulfide was added 2.03 g. (0.015 mole) of V portionwise at 5° over a period of 5 minutes. To this mixture was added a solution of 2.75 g. (0.035 mole) of acetyl chloride in 10 ml. of carbon disulfide at such a rate to maintain the reaction temperature below 10° . The mixture was heated under reflux 1 hour, cooled to 25° , and the carbon disulfide decanted from the grey semi-solid. The semi-solid was added to 50 ml. of ice water and the solution neutralized to $\text{pH} 7$ with solid sodium bicarbonate. The neutralized solution was extracted with six 50-ml. portions of ether, the ether extracts dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residue was 0.80 g. (45%) of furo[3,2-c]pyridine (I), identified by ir and nmr.

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