2-(4′-Fluorophenyl)imidazole. Nitration Studies

*J. S. Amato, V. J. Grenda, T. M. H. Liu and E. J. J. Grabowski**

Merck, Sharp & Dohme Research Laboratories, Merck & Company, Incorporated,
Rahway, New Jersey 07065 U.S.A.

Received March 27, 1979

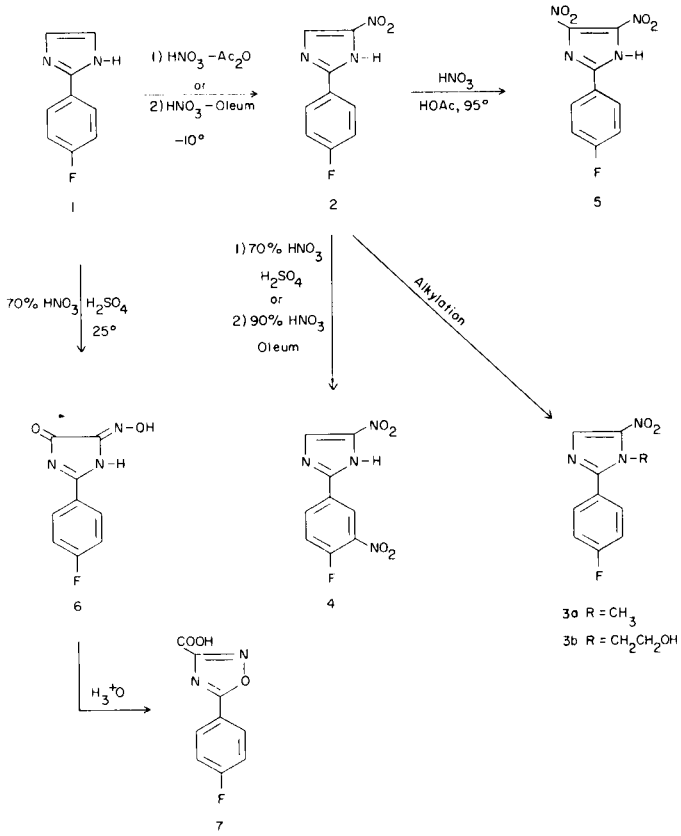
Reactions of 2-(4′-fluorophenyl)imidazole (**1**) and related compounds under various nitrating conditions are discussed. With 90% nitric acid in 20% oleum at -10°, **1** affords 2-(4′fluorophenyl)-4(5)-nitroimidazole (**2**) in 80% yield. Reaction of **2** with the same reagents at 25° affords 2-(4′-fluoro-3′-nitrophenyl)-4(5)-nitroimidazole (**4**) in 90% yield, whereas with 90% nitric acid in acetic acid at 95°, **2** affords 4,5-dinitro-2-(4′-fluorophenyl)imidazole (**5**) in 80% yield. Reaction of **1** with 70% nitric acid in concentrated sulfuric acid at 25° affords 2-(4′-fluorophenyl)-5-hyroximinoimidazolin-4-one (**6**), which rearranges and hydrolyzes to 5-(4′-fluorophenyl)-1,2,4-oxadiazole-3-carboxylic acid. A discussion of these reactions is presented.

J. Heterocyclic Chem., 16, 1153 (1979).

In connection with investigations directed towards the synthesis of compounds effective in the treatment of protozoan infections, a study of the nitration of 2-(4′-fluorophenyl)imidazole (**1**) was undertaken to prepare 2-(4′-fluorophenyl)-4(5)-nitroimidazole (**2**). This compound has proven to be an important intermediate in the synthesis, *via* alkylation, of **3a** and **3b**, which have shown utility in the treatment of these infections (1,2,3). Despite the significant advances which have been made in the understanding of the nitration of heteroaromatic compounds, and particularly imidazoles (4,5), the nitration of a specific heterocycle is often a unique problem because of its particular substituents and the effect they exert on nitration processes (6). Selective nitration of **1** was *a priori* an interesting problem since it contains a heterocyclic ring and an electron deficient phenyl ring. As the studies reported herein show, the site of nitration of **1** and its derivatives can be readily controlled by proper choice of reaction conditions. Also, this relatively simple system can be the source for unusual and useful chemical transformations.

At the inception of this work the only reported nitration of **1** employed acetyl nitrate at steam bath temperatures (1). Compound **2** was the only reported isolated product, however, the yield was poor and the reaction was not amenable to large scale production. Our study of a variety of nitrating conditions revealed that nitration of **1** in 20% oleum at -10° using 90% nitric acid afforded **2** in 80% isolated yield. Compound **2** obtained via this procedure was identical with that obtained via the acetyl nitrate procedure (1). Its ^{1}H-nmr spectrum displayed an intact 4-fluorophenyl group and a low field imidazole proton.

Nitration of **2** with 90% nitric acid in oleum at 25° or 70% nitric acid in concentrated sulfuric acid afforded dinitro compound **4** in 90% yield. In addition to the low field imidazole proton, the chemical shifts and coupling constants for the three aryl protons of **4** compared favorably to those reported for 1-fluoro-2,4-dinitrobenzene (7), confirming the structural assignment for **4**. Conversely, nitration of **2** with 90% nitric acid in acetic acid at 95° afforded the 4,5-dinitroimidazole **5** in 80% yield. The ^{1}H-nmr spectrum of **5** showed an intact 4-fluorophenyl group and one exchangeable proton. Compound **5** was strongly acidic and readily dissolved in sodium bicarbonate. Additional analytical and spectral data for **5** are presented in the Experimental.



0022-152X/79/061153-03$02.25

Finally, the nitration of **1** was attempted with 70% nitric acid in concentrated sulfuric acid. Oxidation proved to be the major process under these conditions, affording a product whose structure has been assigned as **6**. In addition to the appropriate molecular ion, compound **6** showed an intact 4-fluorophenyl group and an exchangeable proton by ^{1}H-nmr analysis. By ir analysis in Nujol peaks at 3150 cm^{-1} and 1720-1735 cm^{-1} were noted and are in accord with **6**. Most characteristically, compound **6** on standing in aqueous acid rearranged and hydrolyzed to 5-(4′-fluorophenyl)-1,2,4-oxadiazole-3-carboxylic acid (**7**). Ruccia and Vivona (8) have already noted this rearrangement in analogous 5-hydroximinoimidazolin-4-ones. Their analogs of **6** were prepared by the nitrosation of imidazolin-4-ones under basic conditions. Thus, treatment of **1**, as described above, represents a new and ready conversion of 4,5-unsubstituted imidazoles into 1,2,4-oxadiazole-3-carboxylic acids.

The results of this study can be understood if one considers both reaction conditions and substrate structure. It has been suggested that nitration with nitric acid in acetic anhydride occurs on the substrate free base (5,9); thus, the nitration of **1** under these conditions would reflect the competition between the imidazole ring and the electron poor aryl ring, with the former being more effective. Also, under these conditions initial *N*-nitration remains a possible site controlling factor (5). It is unlikely that nitration occurs on the free base during the formation of **2** in 20% oleum. Undoubtedly, nitration occurs on protonated **1**, and the fact that **2** forms reflects the greater stability of the dipositively charged nitration intermediate when nitronium ion addition occurs to the imidazole ring instead of the aryl ring. The nitration of **2** to produce **5** using 90% nitric acid in acetic acid undoubtedly occurs by reaction of the free base with acetyl nitrate. Compound **2** is a poor base and the reaction conditions are only weakly acidic. Again, *N*-nitration may be the controlling factor. The nitration of **2** to afford **4** in strongly acidic media results via reaction of the nitronium ion. The product (**4**) probably reflects the ability of the fluorinated aryl ring to stabilize the nitration intermediate in an electron deficient system. The fact that **2** undergoes aryl nitration under the same conditions under which **1** undergoes imidazole oxidation reflects the electron deficient character of the imidazole ring in **2** relative to that in **1**. Oxidations during attempted nitrations are not uncommon. Thus, although *a priori* an uncertain problem, the reaction of **1** and its analogs under various nitrating conditions can be controlled to produce a variety of new products in good yields.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 251 spectrophotometer. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Nmr spectra were recorded on Varian A60A and T-60 spectrometers, and are reported relative to TMS at δ = 10.00 ppm.

2-(4′-Fluorophenyl)-4(5)-nitroimidazole (**2**).

2-(4′-Fluorophenyl)imidazole (32.4 g., 0.200 mole) was dissolved by portionwise addition to 20% oleum (116 ml.) at ≤ 20° with vigorous stirring under nitrogen. The resulting solution was cooled at -10° and 90% nitric acid (13.8 g., 0.200 mole) was added over 2.5 hours at -10°. The mixture was stirred for 15 min, poured onto 1.5 kg. of ice and stirred for 1 hour. The precipitate was filtered, reslurried in water (400 ml.) and the *p*H adjusted to 4 with 2.5*N* sodium hydroxide solution. The precipitate was filtered, washed with water (2 x 100 ml.) and dried at 60° *in vacuo* to afford 36 g. of crude **2**, m.p. 216-218°. A 32 g. portion of crude **2** was dissolved in acetone (256 ml.) and water (40 ml.) on a steam bath. The solution was treated with DARCO G-60 (3.2 g.) and filtered, and water (216 ml.) was added. The acetone was removed at reduced pressure. The resulting precipitate was filtered, washed with water (3 x 50 ml.) and dried at 60° *in vacuo* to afford pure **2**, 29.6 g. (80% yield based on **1**), m.p. 217-220.5°; nmr (acetone-d_6): 7.27 (mult, 2H, $H_{3'}$, $H_{5'}$), 8.08 (mult, 2H, $H_{2'}$, $H_{6'}$), 8.27 (s, 1H, imidazole-H). This material was identical with that reported previously (1).

2-(4′-Fluoro-3′-nitrophenyl)-4(5)-nitroimidazole (**4**).

To 20% oleum (120 ml.) was added **2** (30 g., 0.145 mole) over 10 minutes at 20-25° followed by the addition of 90% nitric acid (6.8 ml., 0.145 mole) over 20 minutes at 25°. The solution was stirred overnight at 25° and crude **4** was isolated as was crude 2. The crude product (35.7 g., m.p. 193-195°) was dissolved in hot methanol (40 ml.), treated with DARCO G-60 (3.5 g.), filtered and the product precipitated by the addition of water (114 ml.) over 25 minutes. Cooling, filtration, water washing (30 ml.) and drying (60°) *in vacuo* afforded pure **4** as its hemihydrate, 34.1 g. (0.131 mole, 90%), m.p. 194-196°; uv (methanol): λ max 311 nm (ϵ = 9,700), 252 (17,800); nmr (DMSO-d_6): 7.72 (q, 1H, $H_{5'}$, $J_{H5'H6'}$ = 9 Hz, $J_{H5'F}$ = 11), 8.37 (octet, 1H, $H_{6'}$, $J_{H2'H6'}$ = 2.5, $J_{H5'H6'}$ = 9, $J_{H6'F}$ = 4.5), 8.52 (s, 1H, imidazole-H), 8.72 (q, 1H, $H_{2'}$, $J_{H2'H6'}$ = 2.5, $J_{H2'F}$ = 7).

Anal. Calcd. for $C_9H_5FN_4O_4 \cdot \frac{1}{2}H_2O$: C, 41.4; H, 2.3; N, 21.5; M, 252. Found: C, 41.5; H, 2.2; N, 21.3; M, 252.

Similar results were obtained when the nitration was run in concentrated sulfuric acid using 70% nitric acid.

4,5-Dinitro-2-(4′-fluorophenyl)imidazole (**5**).

A solution of **2** (7.65 g., 36.9 mmoles) in acetic acid (30 ml.) and 90% nitric acid (2.0 ml.) was heated at 95° for 30 minutes. An additional 0.5 ml. of 90% nitric acid was added, followed by heating at 95° for another 30 minutes. The resulting solution was concentrated to an oil (60°) *in vacuo*, triturated with water (25 ml.), and the resulting precipitate filtered, washed with water (2 x 15 ml.) and dried. Recrystallization from chloroform (50 ml.) afforded pure **5**, 7.45 g. (29.6 mmoles, 80%), m.p. 151-154°; uv (methanol): λ max 328 nm (ϵ = 7,100), 277 (10,200), 240 (14,800); nmr (methanol-d_6): 7.20 (mult, 2H, $H_{3'}$, $H_{5'}$); 8.00 (mult, 2H, $H_{2'}$, $H_{6'}$); exchangeable proton of variable chemical shift.

Anal. Calcd. for $C_9H_5FN_4O_4$: C, 42.9; H, 2.0; N, 22.2; M, 252. Found: C, 42.7; H, 1.9; N, 22.0; M, 252.

2-(4′-Fluorophenyl)-5-hydroximinoimidazolin-4-one (**6**).

To a solution of **1** (0.50 g., 3.1 mmoles) in concentrated sulfuric acid (2.0 ml.) was added 70% nitric acid (0.13 ml., 3.1 mmoles) over 10 minutes at 0-5°. After stirring for 3 hours at 0-5° and 1 hour at 25°, the reaction was added to ice (20 g.) and extracted with ethyl acetate (25 ml.). The pinkish solid, insoluble in either phase, was filtered, washed with water and dried to afford **6**, 0.28 g. (1.35 mmoles, 44%), m.p. 178° dec (rate dependent); uv (methanol): λ max 333 nm (ϵ = 10,900), 271 (16,000), 238 (10,000), 232 (10,300); nmr (DMSO-d_6): 7.45 (mult, 2H, $H_{3'}$, $H_{5'}$), 8.23 (mult, 2H, $H_{2'}$ $H_{6'}$), 12.6 (broad s, 1H, OH).

Anal. Calcd. for $C_9H_6FN_3O_2 \cdot \frac{1}{2}H_2O$: C, 50.0; H, 3,3; N, 19.4; M, 207. Found: C, 50.3; H, 3.4; N, 19.1; M, 207.

In addition to the parent ion, ions at m/e 189, 163, 147 and 122 were noted on mass spectral analysis.

5-(4′-Fluorophenyl)-1,2,4-oxadiazole-3-carboxylic Acid (7).

To concentrated sulfuric acid (20 ml.), was added **1** (5.0 g., 31 mmoles) over 5 minutes. At 0-5°, 70% nitric acid (1.3 ml.) was added over 10 minutes. The resulting solution was warmed to 25° and held at 25° for 2 hours. It was poured onto ice (50 g.) and allowed to stand overnight to effect the rearrangement and hydrolysis. The resulting precipitate was filtered, washed with water (3 x 10 ml.) and dried to afford **7**, 2.6 g. (12 mmoles, 39%), m.p. 130-132° dec; ir (potassium bromide): υ max 1735 cm^{-1}; uv: λ max 256 nm (ϵ = 29,000); nmr (acetone-d_6): 7.48 (mult, 2H, $H_{3'}$, $H_{5'}$), 8.31 (mult, 2H, $H_{2'}$,$H_{6'}$), 11.6 (1H, exchangeable, COOH).

Anal. Calcd. for $C_9H_5FN_2O_3$: C, 51.9; H, 2.4; N, 13.5; M, 208. Found: C, 52.1; H, 2.4; N, 13.3; M, 208.

Compound **7** was soluble in sodium bicarbonate and its mass spectrum displayed a major peak at M-CO_2. It formed on letting **6** stand overnight in aqueous acid. It was identical with a sample prepared by independent synthesis (8).

Acknowledgment.

We thank Mr. J. Gilbert, Mr. J. Smith, Mr. R. Zerfing and Mr. D. Harris for assistance in obtaining the analytical and spectral data. We also thank Dr. A. W. Douglas for his comments and critical review of this manuscript.

REFERENCES AND NOTES

(1) L. H. Sarett, D. R. Hoff and D. W. Henry, U. S. Patent 3,399,211 (1968).

(2) J. Kollonitsch, U. S. Patent 3,471,511 (1969).

(3) E. J. J. Grabowski, T. M. H. Liu, L. Salce, and E. F. Schoenesaldt, *J. Med. Chem.*, **17**, 547 (1974).

(4) J. H. Ridd, *Z. Chem.*, **6**, 201 (1968).

(5) M. R. Grimmett, S. R. Hartshorn, K. Schofield and J. B. Weston, *J. Chem. Soc., Perkin Trans. II*, 1654 (1972).

(6) M. A. Iradyan, A. G. Torosyan, R. G. Mirzoyan and A. A. Aroyan, *Khim. Geterotsikl. Soedin.*, 1384 (1977).

(7) T. Schaefer, *Can. J. Chem.*, **40**, 431 (1962).

(8) M. Ruccia and N. Vivona, *Ann. Chim. (Rome)*, **58**, 484 (1968) and references cited therein.

(9) B. M. Lynch and Y.-Y. Hung, *Can. J. Chem.*, **42**, 1605 (1964).