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Synthesis of 4,5-difluoroimidazole

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Abstract

5-Fluoroimidazole-4-carboxylic acid ethyl ester was converted to the corresponding hydrazide. Oxidation of the hydrazide to the carbonyl azide and Curtius rearrangement in *t*-butyl alcohol produced 4-*t*-butyloxycarbonylamino-5-fluoroimidazole. Dissolution of the *t*-butyl carbamate in 50% HBF_4, in situ diazotation of the resulting amine, and irradiation produced the target compound. © 2001 Elsevier Science B.V. All rights reserved.

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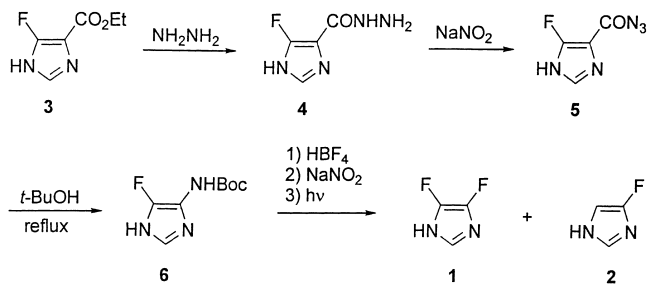
1. Introduction

We reported previously a study of the acid- and base-catalyzed hydrogen exchange of a series of fluoroimidazoles, including 4,5-difluoroimidazole (**1**) [1]. This molecule (**1**) is a rare example of imidazole with two fluorine atoms substituted on the heteroaromatic ring [2].[1] We had prepared this derivative as part of our investigation of the effects of ring-fluorination on the physical and chemical properties of imidazoles, and reported some of the physical properties of **1** [1]. The details of the synthesis of **1** are the subject of this note.

2. Chemistry

The synthesis of **1** is based on the photochemical Schiemann reaction, a reaction we developed in 1970 to prepare the first examples of ring-fluorinated imidazoles [3]. This procedure remains the only general method to prepare such derivatives. However, use of this strategy to prepare 4-fluoroimidazoles is complicated by the fact that, unless an electron-withdrawing substituent is present in the 5-position, the required starting 4-aminoimidazoles are unstable. In our synthesis of 4-fluoroimidazole (**2**), we circumvented this problem by generating 4-aminoimidazole in situ by HBF_4-mediated hydrolysis of the 4-*t*-butyloxycarbonylamino precursor [3]. Diazotation and in situ photolysis provided a convenient route to **2**. We used the analogous strategy to prepare **1**. 5-Fluoroimidazole-4-carboxylic acid ethyl ester (**3**), prepared as reported [3,4], was treated with hydrazine hydrate to give the corresponding hydrazide **4** in 81% yield. Oxidation with HNO_2 and heating of the resulting carbonyl azide **5** in *t*-butyl alcohol gave Boc-protected 5-amino-4-fluoroimidazole (**6**). This was dissolved in cold HBF_4 to generate the free amine. Addition of a concentrated aqueous solution of $NaNO_2$ and irradiation of the resulting diazonium tetrafluoroborate gave the target compound **1** (36% from **6**). In addition, 8% of 4-fluoroimidazole was isolated, presumably by reduction of a radical formed by homolytic extrusion of nitrogen.



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[1] 2,4-Difluoroimidazole-5-carboxylic acid ethyl ester and related compounds are other rare examples.

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3. Experimental details

^{1}H (300 MHz), ^{13}C (75.5 MHz) and ^{19}F NMR (282.3 MHz) spectra were obtained on a Varian Mercury 300 spectrometer. Coupling constants (J) are given in Hz. Chemical shifts (δ) are given in ppm relative to the following standards: TMS for ^{1}H and ^{13}C NMR, and $CFCl_3$ for ^{19}F NMR. Melting points (mp) were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Chemical ionization mass spectra were obtained on a Finnigan/extrel Model 1015 mass spectrometer with ammonia as reagent gas.

3.1. 5-Fluoroimidazole-4-carboxylic acid hydrazide (**4**)

To 5-fluoroimidazole-4-carboxylic acid ethyl ester (**3**) (1.57 g, 0.01 mol) in a 25 ml round bottom flask fitted with a reflux condenser was added 1.0 ml of hydrazine hydrate. This was stirred and heated in an oil bath at 100°C for 30 min. After about 10 min the mixture became nearly homogenous, and a new precipitate then formed. The mixture was cooled in an ice bath and the crystals were collected by suction filtration and washed with a small amount of cold water to give 1.17 g (81%) of **4**, homogenous by TLC and suitable for the next step. An analytical sample was prepared by recrystallization from ethanol/water: mp 225–235°C (dec.). ^{1}H NMR (DMF-d_7) δ 3.54 (vbs, 1H), 4.51 (bs, 2H), 7.61 (d, 1H, $^4J_{HF} = 1.5$, C*H*), 8.91 (bs, 1H); ^{13}C NMR (DMF-d_7) δ 105.17 (d, $^2J_{CF} = 33.4$, *C*–CF), 132.78 (d, $^3J_{CF} = 18.6$, *C*H), 156.38 (d, $^1J_{CF} = 238.8$, *C*F), 159.75 (d, $^3J_{CF} = 4.9$, *C*O); ^{19}F NMR (DMF-d_7) δ −126.4 (s). HRMS (EI): calculated for $C_4H_5FN_4O$, 144.0447; found, 144.0447.

3.2. 5-Fluoroimidazole-4-carbonyl azide (**5**)

To a mixture of 1.00 g (6.9 mmol) of **4** and 4 ml of ice water in a 50 ml beaker was added 1.00 ml of 12N HCl. The mixture was stirred and cooled in an ice bath while a solution of 1.00 g of $NaNO_2$ in 2.00 ml of water was added dropwise over 15 min. After an additional 15 min of stirring, with occasional agitation with a spatula to decrease the effects of foaming, the solid was collected by suction filtration and washed with a small amount of cold water to give **5** (944 mg, 88%). The product was dried and used in the next step without purification: mp 144–146°C. ^{1}H NMR (CD_3OD) δ 7.60 (d, $^4J_{HF} = 1.7$, C*H*); ^{13}C NMR (CD_3OD) δ 105.45 (d, $^2J_{CF} = 29.8$, *C*–CF), 135.88 (d, $^3J_{CF} = 16.9$, *C*H), 160.38 (d, $^1J_{CF} = 252.8$, CF), 163.71 (d, $^3J_{CF} = 5.7$, *C*O); ^{19}F NMR (282 MHz, CD_3OD) δ −117.5 (s). HRMS (EI): calculated for $C_4H_2FN_5O$, 155.0291; found, 155.0238.

3.3. (5-Fluoroimidazol-4-yl)-carbamic acid t-butyl ester (**6**)

A solution of 944 mg (6.09 mmol) of **5** in 60 ml of anhydrous *t*-butyl alcohol was refluxed for 24 h. The reaction mixture was then concentrated to give 1.15 g (94%) of **6** of sufficient purity for the next step. A sample was chromatographed on silica gel (ethyl acetate/petroleum ether, 1:1) to give **6** as colorless crystals: mp 177–185°C (dec.). ^{1}H NMR ($CDCl_3$/CD_3OD 1:2) δ 1.50 (s, 9H), 7.05 (d, 1H, $^4J_{HF} = 1.4$, *C*H); ^{13}C NMR ($CDCl_3$/CD_3OD 1:2) δ 28.52 (*C*H_3), 81.63 (*C*$(CH_3)_3$), 104.90 (d, $^2J_{CF} = 30.3$, *C*–CF), 125.71 (d, $^3J_{CF} = 14.9$, *C*H), 148.12 (d, $^1J_{CF} = 231.6$, *CF*), 155.77 (s, *C*O); ^{19}F NMR ($CDCl_3$/CD_3OD 1:2) δ −144.6 (s). HRMS (FAB): calculated for $C_8H_{13}FN_3O_2$ (MH^+), 202.0992; found, 202.0985.

3.4. 4,5-Difluoroimidazole (**1**)

To 50 ml of 48% aqueous HBF_4, stirred and cooled to −5 to 0°C, was added 400 mg (2 mmol) of **6**. The solid dissolved and gas was evolved. After 10 min stirring, a solution of 200 mg of $NaNO_2$ in 1.0 ml of water was added dropwise. The presence of the diazonium salt was indicated by formation of a deep red color upon reaction with a basic solution of β-naphthol, and by the presence of a peak at 278 nm in the ultraviolet spectrum. After stirring at 0°C for an additional 15 min, the solution was irradiated for 1 h at 0°C with a Hanovia mercury vapor lamp, as described previously [3,4]. This resulted in the disappearance of the ultraviolet absorption maximum and the irradiated solution gave no visible reaction with basic β-naphthol. The solution was chilled in dry ice/acetone and neutralized with 40% aqueous NaOH. The mixture was then extracted three times with ethyl acetate, the ethyl acetate was dried (Na_2SO_4), and then concentrated to dryness. The residual white solid, containing product and $NaBF_4$, was chromatographed on silica gel (1:1 ethyl acetate/petroleum ether) to give 77 mg (36%) of **1** as a semi-crystalline solid. ^{1}H NMR ($CDCl_3$) δ 6.97 (s, C*H*), 12.53 (bs, N*H*); ^{13}C NMR ($CDCl_3$, dec. ^{1}H off) δ 118.83 (dt, $^1J_{CH} = 216.9$, $^3J_{CF} = 10.9$, *C*H), 130.90 (ddd, $^1J_{CF} = 244.8$, $^3J_{CH} = 8.2$, *C*F); ^{19}F NMR ($CDCl_3$) δ −160.1 (s). HRMS: calculated for $C_3H_2N_2F_2$, 104.0186; found, 104.0184. Further elution of the chromatographic column gave a fraction containing 22 mg (8%) of 4-flouoroimidazole (**2**), identical to material prepared previously. ^{1}H NMR ($CDCl_3$) δ 6.56 (d, $^3J_{CF} = 8.0$, 1H, C*H*=CF), 7.26 (s, 1H, N–C*H*=N), 10.95 (bs, 1H, N*H*); ^{13}C NMR ($CDCl_3$, dec. ^{1}H off) δ 94.38 (d, $^2J_{CF} = 37.8$, $^1J_{CH} = 196.6$, *C*H=CF), 128.85 (d, $^3J_{CF} = 15.9$, $^1J_{CH} = 211.7$, $^3J_{CH} = 8.3$, N–*C*H=N), 156.95 (d, $^1J_{CF} = 233.5$, $^2J_{CH} = 13.3$, $^3J_{CH} = 5.7$ *C*F); ^{19}F NMR ($CDCl_3$) δ −139.9 (d, 8.0).

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