A Convenient Synthesis of 5-Fluoropyrimidines Using 1-(Chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane Bis(tetrafluoroborate)-SELECTFLUOR Reagent

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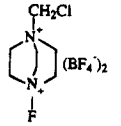
The pyrimidine bases uracil and thymine react with the titled reagent in water to generate the corresponding fluorohydrins. Uracil fluorohydrin provides 5-fluorouracil on sublimation. Triacetyluridine reacts similarly in the presence of H_2O, AcOH, or MeOH to form the respective adducts from which 5-fluorotriacetyluridine was obtained. The fluorohydrin of diacetylthymidine and the difluoromethoxy derivative of triacetylcytidine were also obtained by reaction of the nucleosides with 1-(chloromethyl)-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis(tetrafluoroborate)-SELECTFLUOR in H_2O and MeOH, respectively. This method represents a new practical and direct route to 5-fluoropyrimidine nucleoside.

Introduction

In the late 1950's, it was recognized that the replacement of a hydrogen atom by fluorine at C-5 of some pyrimidines resulted in a considerable enhancement of their medicinal activity. Noteworthy in this regard was the discovery of the significant tumor-inhibiting action of 5-fluorouracil and 5-fluoro-2′-deoxy-β-uridine (fluoruridine).[1a] It has been proposed that the metabolic product of these compounds inhibits the activity of the enzyme thymidylate synthetase and hence prevents DNA synthesis in tumor cells.[1b] Another 5-fluoropyrimidine, 5-fluorocytosine, has been found to be a very useful antifungal agent when applied orally for systemic infections.[1a] It has been suggested that flurocytosine is deaminated to 5-fluorouracil by bacteria and hence indirectly blocks DNA synthesis in these organisms.[1b]

The original synthesis of 5-fluorouracil and derivatives utilized the reaction of pseudourea and pseudothiourea salts with α-fluoro β-keto ester enolates.[2] Later investigators found that the direct fluorination of uracil with F_2 in the presence of CH_3COOH, CF_3COOH, or H_2O followed by addition of alcohol and elimination of the C-6 substituent provided a more cost effective synthesis of 5-fluorouracil. XeF_2[3e] and $C_{19}XeF_6$[3f] have also been used for the preparation of 5-fluorouracil from uracil. Barton and co-workers demonstrated quite nicely the efficacy of the electrophilic fluorinating agent CF_3OF for the synthesis of fluorinated uracils and pyrimidines.[3a,4a] This reagent was also successfully utilized by Robbins and coworkers for the fluorination of uracil and cytosine bases and nucleosides.[4b] They obtained various 5-fluoropyrimidines by an effective elimination of CF_3OH from the 5-fluoro-6-trifluoromethoxy derivatives.

Our interest in the development of safer and more facile fluorination methods prompted a study of the synthesis of fluorinated pyrimidine bases using the electrophilic fluorinating reagent 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1**)-SELECTFLUOR (F-TEDA-BF_4).[5] This compound which has been shown to be effective for the site-selective fluorination of a variety of organic substrates[6a-j] is a stable, easy to handle, nonhygroscopic solid which is now commercially available.[6k]



Results and Discussions

When an aqueous solution of uracil is heated at 90 °C with F-TEDA-BF_4, the fluorohydrin **2** is obtained as a diastereomeric mixture of products with the *trans* isomer predominating (*trans*/*cis* = 8:1): ^{19}F NMR ($CDCl_3$) δ −208 (d, *trans*), −202 (d, *cis*). Similar stereochemical results were observed with the products obtained from the reaction of uracil with F_2 gas in the presence of H_2O[3a] and CH_3COOH.[4a] The spent reagent which consisted of a mixture of fluoride, bifluoride, and tetrafluoroborate salts of 1-(chloromethyl)-4-protiotriethylenediamine, was separated from the aqueous solution by conversion to the

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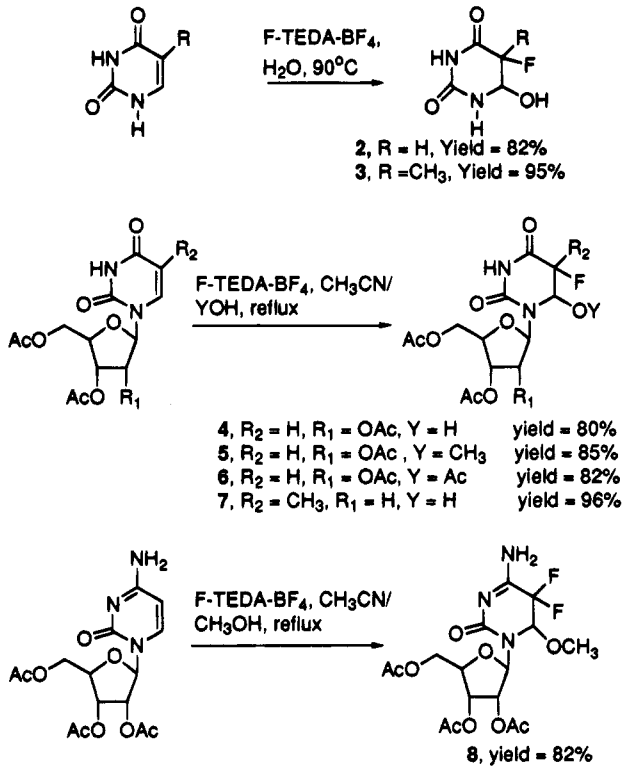
Scheme 1. Fluorination of Pyrimidine Bases with F-TEDA-BF$_4$



water insoluble salt 1-(chloromethyl)-4-protiotriethylenediamine bis(tetraphenylborate) on reaction with potassium tetraphenylborate. The aqueous filtrate was evaporated to dryness and the residue sublimed at 210–220 °C (0.5 mm) to obtain pure 5-fluorouracil.[3a] The fluorohydrin of thymine (**3**) was obtained in a similar manner by reaction of thymine with F-TEDA-BF$_4$ in H_2O at 90 °C. The spectral and stereochemical characteristics of this product were identical with those obtained by the reaction of thymine with F_2 gas in H_2O.[4a] A mixture of the fluorohydrins of cytosine and uracil was obtained on reaction of cytosine with F-TEDA-BF$_4$ in H_2O at 90 °C. The ease of hydrolysis of cytosine fluorohydrin to uracil fluorohydrin made it extremely difficult to isolate a pure product from the reaction mixture.[7]

It has been reported that the reaction of 2′,3′,5′-triacetyluridine with F_2/AcOH afforded the 5-fluoro-6-acetoxy adduct.[8] Robbins and co-workers obtained the fluoromethoxy derivative on reaction of triacetyluridine with CF_3OF in MeOH.[4b] The fluorination of triacetyluridine with F-TEDA-BF$_4$ also proved to be quite facile. Reactions conducted with triacetyluridine and F-TEDA-BF$_4$ in refluxing CH_3CN containing respectively AcOH, MeOH, or H_2O afforded high yields of the corresponding fluorohydrin[9] (**4**), fluoromethoxy[4b] (**5**), and fluoroacetoxy[8] (**6**) products. The fluoromethoxy and fluoroacetoxy adducts were converted to 2′,3′,5′-tri-*O*-acetyl-5-fluorouridine by heating in pyridine at 80 °C for 2 h.[8] Conversion of the fluorohydrin to the fluoroacetoxy derivative with Ac_2O/pyridine followed by elimination also afforded 2′,3′,5′-tri-*O*-acetyl-5-fluorouridine.[8]

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Other pyrimidine nucleosides were also readily fluorinated with F-TEDA-BF$_4$. The reaction of 3′,5′-di-*O*-acetylthymidine with F-TEDA-BF$_4$ in refluxing CH_3CN containing H_2O afforded 3′,5′-di-*O*-acetyl-5-fluoro-6-hydroxy-5,6-dihydrothymidine (**7**) with ^{19}F NMR spectral characteristics similar to those of the fluorohydrin of thymine. The reaction of 2′,3′,5′-tri-*O*-acetylcytidine with F-TEDA-BF$_4$ followed a different pathway from that observed for tri-*O*-acetyluridine. Fluorination carried out in refluxing CH_3CN containing CH_3OH afforded only the 5,5-difluoro-6-methoxy adduct (**8**). This presumably results from a rapid elimination of CH_3OH to generate initially 5-fluorocytidine followed by further fluorination at the 5,6-double bond. These results are in accord with the findings of Visser and co-workers[7] who obtained only the 5,5-difluorinated product on reaction of cytosine with F_2 and CH_3COOF in AcOH or H_2O.

In their patent Beranek et al.[8] claimed the synthesis of 5-fluorouridine by the reaction of triacetyluridine with F_2 gas followed by hydrolysis of the acetyl groups. It has been shown that CF_3OF can be used to introduce the fluorine atom at C-5 of pyrimidines.[4a,b] However, the difficulty in handling and the toxicity and high reactivity of F_2 and CF_3OF have curtailed their utility. The F-TEDA-BF$_4$ reagent provides a convenient, safe, and simple alternative for the preparation of 5-fluoropyrimidines.

Experimental Section

The pyrimidine bases and nucleosides were obtained from Sigma Chemical Co. and used as received. The reagents sodium tetraphenylborate, AcOH, MeOH, pyridine, and Ac_2O were obtained from Aldrich Chemical Co. and used without further purification. The solvent CH_3CN was dried with CaH_2 prior to use. Other solvents, hexane, and ethyl acetate were used without further purification.

(a) Fluorination of Uracil and Thymine. (i) 5-Fluorouracil.[3a] A suspension of uracil (896 mg, 8 mmol) in H_2O (25 mL) was treated with F-TEDA-BF$_4$ (2.83 g, 8 mmol) and heated in an N_2 atmosphere for 4 h at 90 °C. On cooling, a solution of sodium tetraphenylborate (6.08 g, 17.79 mmol) in H_2O (25 mL) was added, and the resulting precipitate was filtered. The filtrate was evaporated in vacuo, and the residue was sublimed at 210–220 °C (0.5 mm) to obtain 853 mg (82% yield) of product: ^1H NMR (DMSO-d_6) δ 11.5 (s, br, 1H), 10.7 (s, br), 7.75 (d, 1H); ^{19}F NMR (DMSO-d_6) δ −170 (d).

(ii) 5-Fluoro-6-hydroxy-5,6-dihydrothymine[4a] **(3).** A solution of thymine (1.000 g, 8 mmol) in H_2O (20 mL) was treated with F-TEDA-BF$_4$ (2.83 g, 8 mmol) and heated under N_2 at 90 °C for 3 h. On cooling a solution of sodium tetraphenylborate (6.08 g, 17.79 mmol) in H_2O (25 mL) was added, and the resulting precipitate was filtered. The filtrate was evaporated in vacuo, and the residue was recrystallized from 2 mL of H_2O to obtain 1.23 g (95% yield) of pure product: ^1H NMR (DMSO-d_6) δ 10.5 (s, br, 1H), 8.45 (s, br, 1H), 6.6 (d, 1H, J = 2 Hz), 4.7 (s, br, 1H), 1.50 (d, 3H, J = 22.5 Hz); ^{19}F NMR (DMSO-d_6) δ −170 (q, 22.5 Hz).

(b) Fluorination of Pyrimidine Bases in Nucleosides. (i) General Procedure for 2′,3′,5′-Tri-*O*-acetyl-5-fluorouridine. A solution of 2′,3′,5′-tri-*O*-acetyluridine (740 mg, 2 mmol) in CH_3CN (15 mL) containing the counternucleophile YOH (2 mL; Y = Ac, Me, or H) under N_2 was treated with F-TEDA-BF$_4$ (1.062 g, 3 mmol) and refluxed for 3 h. On cooling, the solution was poured into EtOAc (50 mL), washed with H_2O (2 × 25 mL) and saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to obtain respectively 5-fluoro-6-hydroxy-2′,3′,5′-tri-*O*-acetyl-5,6-dihydrouridine[9] (**4**), 5-fluoro-6-methoxy-2′,3′,5′-tri-*O*-acetyl-5,6-dihydrouracil[4b] (**5**), and 6-acetoxy-5-fluoro-2′,3′,5′-tri-*O*-acetyl-5,6-dihydrouridine[8] (**6**). The crude 6-acetoxy-5-fluoro-2′,3′,5′-tri-*O*-acetyl-5,6-dihydrouridine was dissolved into pyridine (3 mL) and heated at 80 °C for 2 h. The solution was evaporated in

vacuo and the residue chromatographed on silica gel in EtOAc/hexane (7:3) to obtain 5-fluoro-2′,3′,5′-tri-*O*-acetyluridine[9] (636 mg, 82%). Similar treatment of 5-fluoro-6-methoxy-2′,3′,5′-tri-*O*-acetyluridine[9] afforded 5-fluoro-2′,3′,5′-tri-*O*-acetyluridine (660 mg, 85%). The crude 5-fluoro-6-hydroxy-2′,3′,5′-tri-*O*-acetyl-5,6-dihydrouridine was heated at 80 °C for 2 h under N_2 in a mixture of Ac_2O (3 mL) and pyridine (2 mL). After removal of solvents in vacuo, the residue was chromatographed on silica gel as above to obtain 630 mg (80%) of 5-fluoro-2′,3′,5′-tri-*O*-acetyluridine:[9] ^{1}H NMR ($CDCl_3$) δ10.0 (s, br, 1H), 7.60 (d, 1H, J = 7.3 Hz), 6.10 (d, 1H, J = 6.6 Hz), 5.5–5.2 (m, 2H), 4.6-4.2 (m, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −163 (d).

(ii) 3′,5′-Di-*O*-acetyl-5-fluoro-6-hydroxy-5,6-dihydrothymidine (7). A solution of 3′,5′-di-*O*-acetylthymidine (652 mg, 2 mmol) in CH_3CN (15 mL) containing H_2O (2 mL) was treated with F-TEDA-BF_4 (1.06 g, 3 mmol) and refluxed for 3 h under N_2. On cooling, the solution was poured into EtOAc (50 mL), washed with H_2O (2 × 25 mL) and saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Chromatography on silica gel in ethyl acetate/hexane (7:3) afforded 695 mg (96% yield) of product as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$), δ9.0 (s, br, 1H), 6.25 (t, 0.4H, J = 6 Hz), 6.15 (dt, 0.6H, J = 6, 2 Hz), 5.15 (s, br, 2H), 4.4-4.15 (m, 2.4H), 4.15-3.95 (m, 1.6H), 2.5-2.3 (m, 0.8H), 2.15-1.95 (m, 1.2H), 2.05 (s, 6H), 1.55 (d, 1.8H, J = 18 Hz), 1.45 (d, 1.2H, J = 18 Hz); ^{19}F NMR ($CDCl_3$) δ −170.5 (q, 0.6F), −171.5 (q, 0.4F; HRMS calcd for $C_{14}H_{19}N_2O_8F$, $(M + Na)^+$ = 385.1023, found $(M + Na)^+$ = 385.1017.

(iii) 5,5-Difluoro-6-methoxy-2′,3′,5′-tri-*O*-acetyl-5,6-dihydrocytidine (8). A solution of cytidine (337 mg, 0.91 mmol) in CH_3CN (10 mL) containing MeOH (2 mL) was treated with F-TEDA-BF_4 (644 mg, 1.82 mmol) and refluxed for 4 h. On cooling, the solution was poured into EtOAc (50 mL), washed with H_2O (25 mL) and saturated $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Flash chromatography on silica gel in EtOAc/hexane (3:2) afforded 313 mg (82% yield) of product: ^{1}H NMR ($CDCl_3$) δ 9.15 (dd, 1.0H), 5.90 (dd, 1.0H, J = 7, 36 Hz), 5.5–5.15 (m, 2H), 5.0–4.85 (m, 1.0H), 4.50–4.20 (m, 3H), 3.60 (s, 1.5H), 3.45 (s, 1.5H), 2.15 (s, br, 9H); ^{19}F NMR ($CDCl_3$) δ −109 (dd), −131 (dd); MS *m/z* (rel intensity) 89 (100), 259 (14.0), 439 (M^+, 4.33), 440 (M + 1, 0.80), 441 (M + 2, 0.19). HRMS calcd for $C_{16}H_{23}F_2N_3O_9$ M^+ = 439.3715, found M^+ = 439.3723.

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Supporting Information Available: Copies of ^{1}H and ^{19}F NMR spectra for compounds **7** and **8** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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