Difluorinated carbaacyclonucleosides: synthesis and evaluation of antiviral activity

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J. Chem. Research (S), 2001, 311–312
J. Chem. Research (M), 2001, 0844–0856

The synthesis of 4-benzoyloxy-5,5-difluoropentan-1-ol from ethyl difluoroacetate is described; its condensation with pyrimidine bases gave carbaacyclonucleosides. which were evaluated, and found inactive, in a large variety of antiviral assays.

Keywords: difluorinated carbaayclonucleasides, antiviral activity

Allylation of carbonyl compounds under Barbier conditions is an important method in organic synthesis for C–C bond formation with simultaneous introduction of an –OH group and a C=C bond into a molecule. With indium powder in aqueous media the reaction proceeds smoothly at room temperature in the absence of acid catalysts or sonication.[15] Difluoroacetaldehyde ethyl hemiacetal acts as a difluoroacetaldehyde equivalent with metal reagents.[11] The resulting difluoromethylated carbinols are useful synthons for the building block approach to gem difluorinated compounds.

Many nucleoside analogues, including those in which the ribose ring has been replaced by a carbocycle or an alkyl side chain, exhibit biological activity as antiviral, antitumor and antifungal agents and many of these analogues contain one or more fluorine atoms.The discovery that 2′-deoxy-2′,2′-difluorocytidine, (gemcitabine)[3] shows antiviral and antitumoral activity has stimulated interest in gem-difluoro nucleosides.

In this paper, we report the synthesis of the difluorinated synthon 4-benzoyloxy-5,5-difluoropent-1-ol, **5b**, and its conversion into carbaacyclo nucleoside analogues: **8**, **9** and **10**.

Difluoroacetaldehyde ethyl hemiacetal **4** was prepared by partial reduction with sodium borohydride of ethyl difluoroacetate in a methanolic solution containing 1.1 equivalent of $CeCl_3.7H_2O$ at –15°C. The reaction was quenched by the addition of acetone and brine and extracted with ether. The dried ether extracts were evaporated at atmospheric pressure. The ^{19}F NMR of the residual methanolic solution showed that it contained two hemiacetal components (partial alkoxy exchange resulted in a mixture of methyl and ethyl hemiacetals) and difluoroethanol in a ratio of 10:1 (conditions not optimised). There was no signal corresponding to unreacted ester. The presence of the lanthanide ion protected the hemiacetals from further reduction; in the abscence of $CeCl_3.7H_2O$, difluoroethanol was the sole product.[12] The hemiacetal–alcohol mixture was used in the allylation step without further separation. Several allylation methods using Zn, Sn, Al or In with allyl bromide in aqueous media were investigated.[13] On a small scale (2 mmol) sonication at room temperature of **4** with tin in ethanol/water[14] gave good yields but the persistence of colloidal tin resulted in a tedious workup for larger scale synthesis. Use of indium powder in methanol/ water with stirring at room temperature[15] gave a clean workup. The crude allylation product **5a** was benzoylated and separated from difluoroethyl benzoate by column chromatography. The overall yield of the alkene **5b** from difluoroethyl acetate was 47%. Hydroboration of the alkene **5b** with 9- BBN in THF at room temperature followed by oxidation with hydrogen peroxide /sodium acetate[16] gave the alcohol **6**. At least 5 mmol of BBN per mmol of alkene were required for the reaction to go to completion at room temperature; use of ultrasound had no effect.[17] The alcohol **6** was converted into the tosylate **7** using Et_3N and catalytic $Me_3N.HCl$ in toluene.[18]

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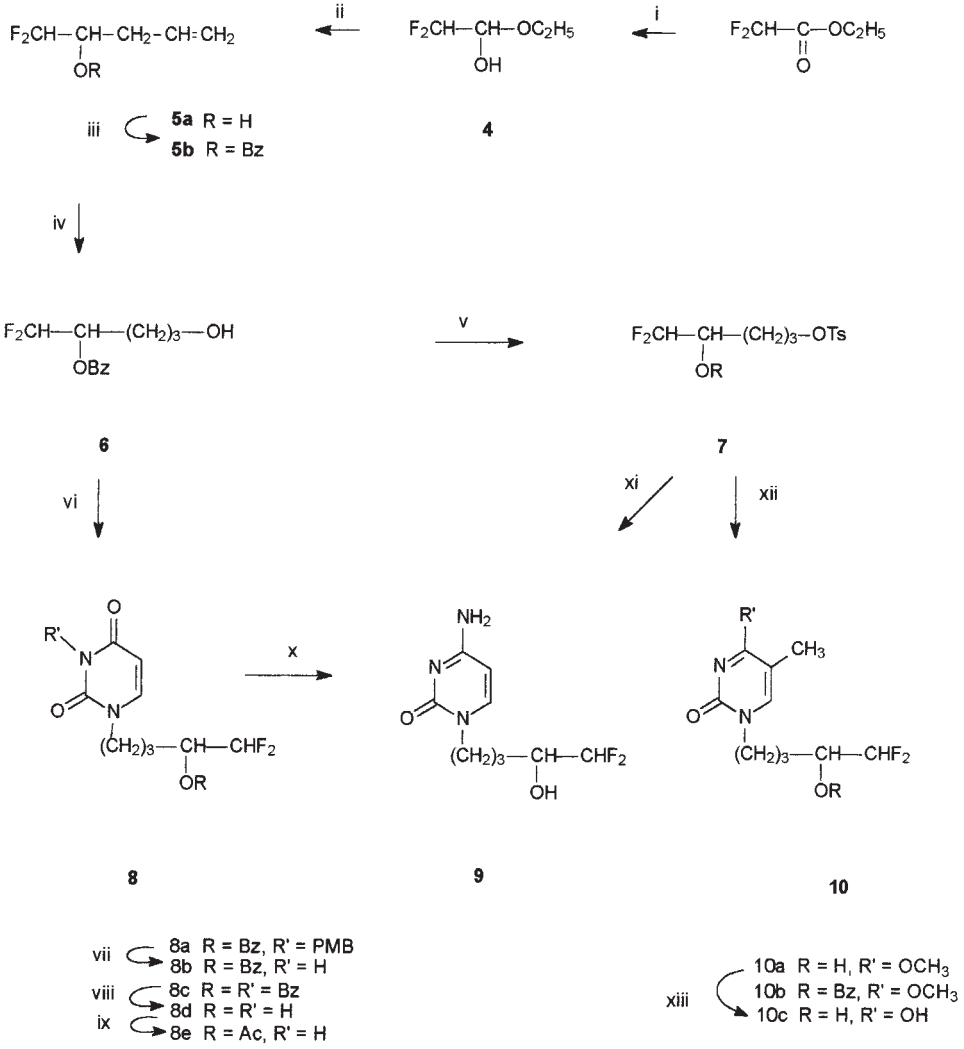
N^4-(2-methylpropanoyl)-1H-cytosine)[19] failed to react with **6** under Mitsunobu conditions[20] using DEAD and PPh_3 . N^3-4-methoxybenzyl (N^3-PMB) uracil [21,22] under the same conditions gave 80% yield of the condensation product **8a** without purification problems, but attempts to remove the PMB group were unsatisfactory – only a 46% yield of product **8b** was obtained after treatment with CAN in $CH_3CN–H_2O$ for 48h. at room temperature; none of the PMB derivative **8a** was recovered.

Mitsunobu condensation of N^3-benzoyluracil [23] with **6** gave 60% of **8c** after repeated chromatography to remove Ph_3PO, with which it co-eluted. Use of 1,2-bis(diphenylphosphino)ethane (DPPE) /DEAD[24] or DPPE / DIAD as alternative coupling reagents resulted in reduced yields of **8c** (20%), together with unreacted **6** contaminated with the dialkyl hydrazinedicarboxylates. Treatment of **8c** with NH_3- methanol removed both benzoate groups to give **8d** which was acetylated to **8e.** Attempted conversion of **8e** to the cytosine analogue **9** using the 1,2,4-triazole / $POCl_3$ / aqueous ammonia method[25] gave none of the required product and 55% of **8e** was recovered. Conversion using the 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) – Et_3N-DAMP system[26] followed by treatment with concentrated aqueous ammonia (33%) gave a cytosine – TPSOH salt mixture from which the pure cytosine compound was isolated in 20% yield from **8e** by means of Amberlite-120 resin.[27] The cytosine analogue was obtained more easily by the direct alkylation of cytosine with the tosylate **7** in DMF with Cs_2CO_3 as base. A mixture of O^2- and N^1-regioisomers resulted, which were readily separated by column chromatography. The N^1- isomer, obtained as the tosylate salt was adsorbed onto Amberlite I.R-120 (H) resin from which the pure cytosine compound **9** was released with excess ammonia solution.[27] The yield was 31% based on the tosylate **7**.

The O^4-methylthymine analogue **10a** was obtained by condensation of **7** with 4-methoxy-5-methyl-2-pyrimidinone in DMF with K_2CO_3 and catalytic CsF as base.[28] Addition of MeOH to the crude residue after evaporation of the DMF resulted in removal of the benzoate group,whereas use of ethanol left it intact to give **10b**. Hydrolysis of **10a** with 1M HCl gave **10c**. The values for the UV max and for the ^1H and ^{13}C chemical shifts of the pyrimidine derivatives were in agreement with the published values for the N^1 – isomers. The ^{13}C and ^1H NMR signals were assigned by means of HMQC and DEPT spectra and the characteristic ^{19}F coupling patterns. Use of NOE and of the HMBC protocol for measurements of long range ^1H-^{13}C interactions for compounds **8b, 8c, 9** and **10b** showed correlation between the pyrimidine proton H-6 and C-1′ of the alkyl chain and so confirmed the required N^1-alkylated structures.

We thank Professor T. Brian H. Mc Murry for his encouragement and for his suggestions on the presentation of the manuscript. We are grateful to Dr John O'Brien for the NMR spectra and his assistance in their interpretation; to Dr Martin Feeney for the mass spectra; to Trinity College Dublin for use of the facilities in the University Chemical Laboratory. We thank S.P.



Scheme 1 *Reagents and conditions:* (i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH-H_2O, –15 °C, 1h; (ii) In, CH_2=CH–CHBr, MeOH-H_2O, 20 °C,17 h; (iii) BzCl, Et_3N, DMAP, toluene, 20 °C,17 h; iv, BBN, THF, 0 °C 4 h; then H_2O_2, NaOAc, 20 °C, 17h; v, p-TsCl, Et_3N, Me_3N.HCl, toluene, 20 °C, 4 h; (vi) DEAD, PPh_3, THF, 20°C, 22 h; (vii) CAN, CH_3CN-H_2O, 20 °C, 48h; (viii) NH_3-MeOH,20°C, 18 h; (ix) Ac_2O, pyridine, 20 °C C, 2 h; (x) TPSCl, DMAP, Et_3N, CH_3CN, 20 °C, 3 h; then NH_3-H_2O 33%, 20 °C, 17h; (xi) cytosine, Cs_2CO_3, DMF, 20 °C, 24 h; (xii) 5-methyl-4-methoxy-2-pyrimidinone, K_2CO_3, CsF, DMF, 20 °C, 24h; (xiii) 1M HCl-EtOH,78 °C, 90 min

Graham Ltd. for a grant to cover the cost of materials. The excellent technical assistance of Anita Camps, Frieda De Meyer, Kristien Erven, Cindy Heens, Lies Vandenheurck and Anita Van Lierde with the bio-assays is gratefully acknowledged.

Techniques used: ^1H, ^{13}C and ^{19}F NMR, UV and IR

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Schemes 1

Received 12 April 2001; accepted 21 June 2001
Paper 01/836

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