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Short Communication

Synthesis of 5-(4-Nitroimidazol-1-yl)-2′-deoxyuridines

Krzysztof Walczak,[a] Erik B. Pedersen[a,*] and Claus Nielsen[b]

[a]Department of Chemistry, Odense University, DK-5230 Odense M, Denmark and [b]Retrovirus Laboratory, Department of Virology, Statens Seruminstitut, DK-2300 Copenhagen, Denmark

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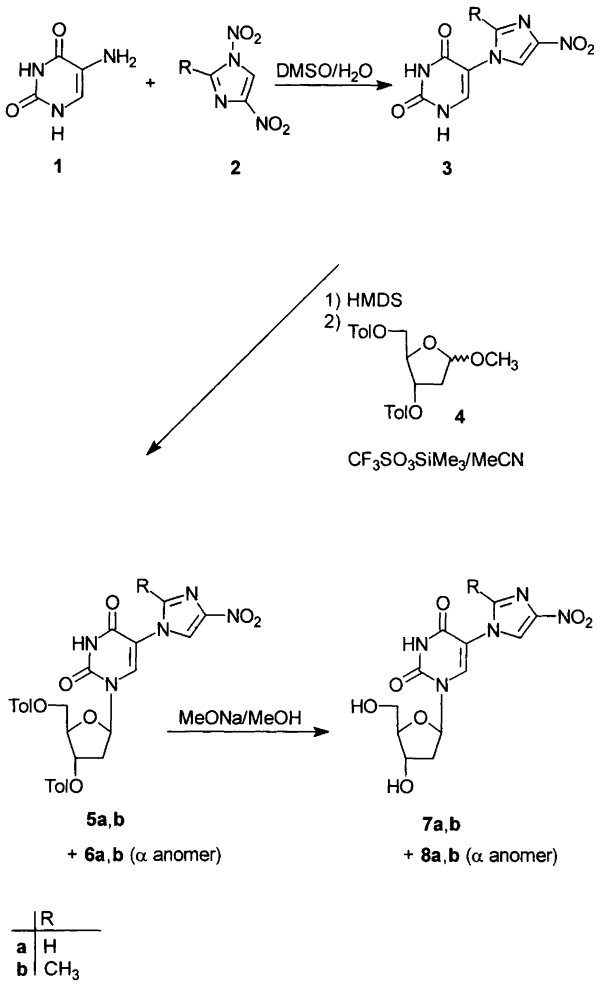
Since the discovery of 5-iodo-2′-deoxyuridine as a selective antiherpes agent[1] further search for effective inhibitors of herpes simplex virus (HSV) replication has led to the discovery of a variety of 2′-deoxynucleosides,[2,3] such as (*E*)-5-(bromovinyl)-2′-deoxyuridine. In the search for new active compounds, a number of 5-heteroaromatic 2′-deoxyuridines were synthesized from 5-iodo-2′-deoxyuridine using tetraorganotin reagents and palladium complexes as catalysts.[4–6] Earlier we found that certain compounds containing a primary amino group, also including sugar derivatives, react with 1,4-dinitroimidazoles in aqueous methanol to yield the corresponding 1-substituted 4-nitroimidazoles as a result of a degenerate transformation of the imidazole ring.[7,8]

Reaction of 5-aminouracil (**1**) with an equimolar amount of 1,4-dinitroimidazole[9] **2a** or **2b** in aqueous dimethyl sulfoxide (DMSO) afforded 5-(4-nitroimidazol-1-yl)uracils **3a** and **3b** in high yields (89% and 74%, respectively). The imidazolyl uracils **3a,b** were silylated according to standard procedure[10] and reacted with methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-α,β-D-*erythro*-pentofuranoside[11] (**4**) in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) as the catalyst[12,13] to give an anomeric mixture of β- and α-nucleosides **5** and **6** in 72–84% yield. Removal of the protecting groups with sodium methoxide gave the final nucleosides **7** and **8**. The structure assignment of the nucleoside anomers **7** and **8** was based on the deshielding effect of the nucleobase on 4′-H and 5′-H in the ^{1}H NMR spectra.[14]

Another strategy considered for the preparation of **7** was reaction of 5-amino-2-deoxyuridine with **2**. However, in an attempt to synthesize the required uridine by a convergent strategy we failed in deblocking the amino group prior to the reaction with **2**. At a first glance it looked very attractive to use the isobutyryl group as the protecting group of the 5-amino group since 1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-5-(isobutyrylamino)uracil could be precipitated as the pure β



Scheme 1.

* To whom correspondence should be addressed.

anomer in 78% yield from the reaction mixture on coupling of trimethylsilylated 5-butyrylaminouracil with **4** using the same procedure as above for the synthesis of **5** and **6**.

The nucleosides **7a,b**, and **8a,b** did not show any significant activity at 100 μM against HIV-1 in MT-4 cells and against herpes simplex virus, type 1 (HSV-1), strain McIntyre when tested in African green monkey kidney cell line Vero.

Experimental

5-(4-Nitroimidazol-1-yl)uracils **3a,b** *(general procedure).* To a solution of 1,4-dinitroimidazole (0.79 g **2a**[9] and 0.86 g **2b**,[9] 5 mmol) in DMSO–H_2O (5:1) was added 5-aminouracil (**1**) (0.64 g, 5 mmol). The resulting suspension was stirred overnight at room temperature and poured onto ice (100 g). The precipitated solid was filtered off, rinsed with cold water (2 × 10 ml) and dried. **3a**: yield 1.0 g (89%), m.p. 316 °C (decomp.). **3b**: yield 0.88 g (74%), m.p. 325 °C (decomp.).

*1-(2-Deoxy-*D*-*erythro*-pentofuranosyl)-5-(4-nitroimidazol-1-yl)uracils* **7**, **8** *(general procedure).* Compound **3** (4 mmol), NH_4SO_4 (0.02 g, 0.15 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (20 ml, 97 mmol) were refluxed for 6 h. Excess HMDS was removed *in vacuo* at 25 °C. The solid residue was dissolved in anhydrous MeCN (20 ml) and **4**[11] (2.3 g, 6 mmol) was added. The solution was cooled to −20 °C and trimethylsilyl triflate (1.2 ml, 6.6 mmol) was added dropwise with stirring. After 1 h at −20 °C, and 1 h at room temperature analytical TLC (MeOH–CH_2Cl_2, 3:97, v/v) showed that the starting material **3** had disappeared. The reaction mixture was diluted with CH_2Cl_2 (100 ml) and quenched with sat. aq. solution of $NaHCO_3$ (25 ml). The organic layer was washed with water (2 × 15 ml), dried (Na_2SO_4) and evaporated to dryness. The residue was purified on a silica gel column (MeOH–CH_2Cl_2, 3:97, v/v) to give pure anomers. **5a**: yield 0.94 g (41%), m.p. 153–154 °C. **6a**: yield 1.0 g (43%), m.p. 132–133 °C. **5b**+**6b**: yield 1.7 g (72%) were separated into the pure anomers in the ratio 6:1. Nucleosides **5** or **6** (1 mmol) were dissolved in a methanolic solution of sodium methoxide, prepared *in situ* from sodium (0.12 g) and MeOH (25 ml). The solution was stirred at 25 °C until TLC (MeOH–CH_2Cl_2, 10:90, v/v) showed that the starting material had disappeared (10–15 min). The mixture was neutralized with 4 M aq. HCl and evaporated to dryness. The residual oil was separated on a silica gel column (MeOH–CH_2Cl_2, 10:90, v/v) to give pure anomers **7** and **8**. **7a**: yield 0.32 g (93%), m.p. 183–184 °C (decomp.). **8a**: yield 0.29 g (85%), m.p. 158–160 °C (decomp.). **7b**: yield 0.29 g (83%), m.p. 191–192 °C (decomp.). **8b**: yield 0.05 g (14%), m.p. 165–166 °C. **7a**: ^{1}H NMR (DMSO-d_6): δ 12.06 (s, 1 H, NH), 8.53 (s, 1 H, H-6), 8.50 (d, 1 H, J = 1.5 Hz, H-5_{im}), 7.96 (d, 1 H, J = 1.5 Hz, H-2_{im}), 6.18 (t, 1 H, J = 6.3 Hz, H-1′), 5.27 (d, 1 H, J = 4.0 Hz, 3′-OH), 5.10 (t, 1 H, J = 5.0 Hz, 5′-OH), 4.29 (ddd, 1 H, J = 3.0, 5.0, 8.0 Hz, H-3′), 3.82 (dd, 1 H, J = 3.0, 7.0 Hz, H-4′), 3.62 (m, 2 H, H-5′), 2.20 (m, 2 H, H-2′). ^{13}C NMR (DMSO-d_6): δ 159.08 (C-4), 149.36 (C-2), 146.34 (C-4_{im}), 137.85 (C-6), 137.22 (C-2_{im}), 122.46 (C-5_{im}), 111.88 (C-5), 87.73 (C-1′), 85.05 (C-4′), 69.68 (C-3′), 60.71 (C-5′), 40.58 (C-2′). PDMS: m/z = 340 (M^+ + 1). **8a**: ^{1}H NMR (DMSO-d_6): δ 12.10 (s, 1 H, NH), 8.46 (d, 1 H, J = 1.5 Hz, H-5_{im}), 8.74 (s, 1 H, H-6), 7.94 (d, 1 H, J = 1.5 Hz, H-2_{im}), 6.13 (dd, 1 H, J = 2.2, 7.1 Hz, H-1′), 5.34 (br s, 1 H, 3′-OH), 4.84 (t, 1 H, J = 5.5 Hz, 5′-OH), 4.27 (m, 2 H, H-3′, H-4′), 3.40 (m, 2 H, H-5′), 2.59 (dd, 1 H, J = 7.1, 14.2 Hz, H-$2'_{\beta}$), 2.08 (dd, 1 H, J = 2.2, 14.2 Hz, H-$2'_{\alpha}$). ^{13}C NMR (DMSO-d_6): δ 159.23 (C-4), 149.42 (C-2), 147.06 (C-2_{im}), 138.84 (C-6), 137.80 (C-2_{im}), 122.48 (C-5_{im}), 111.20 (C-5), 89.59 (C-1′), 86.85 (C-4′), 70.38 (C-3′), 61.59 (C-5′), 48.62 (C-2′). Anal. $C_{12}H_{13}N_5O_7 \times 0.5\ H_2O$: C, H, N.

References

1. Prusoff, W. H. *Biochim. Biophys. Acta. 32* (1959) 295.
2. Herdewijn, P. A. M. M. *Antiviral Chem. Chemother. 5* (1994) 131.
3. Perigaud, C., Gosselin, J. L. and Imbach, J. L. *Nucleosides Nucleotides 11* (1992) 903.
4. Wigerinck, P., Kerremans, L., Claes, P., Snoeck, P., Maudgal, P., De Clercq, E. and Herdewijn, P. *J. Med. Chem. 36* (1993) 538.
5. Gutierres, A. J., Terhorst, T. J., Matteucci, M. D. and Froehler, B. C. *J. Am. Chem. Soc. 116* (1994) 5540.
6. Wigerinck, P., Pannecouque, C., Snoeck, R., Claes, P., De Clercq, E. and Herdewijn, P. *J. Med. Chem. 34* (1991) 2383.
7. Suwiński, J. and Szczepankiewicz, W. *Arch. Pharm. (Weinheim) 325* (1992) 317.
8. Walczak, K. and Suwiński, J. *Polish J. Chem. 67* (1993) 691.
9. Suwiński, J. and Salwińska, E. *Polish J. Chem. 61* (1987) 913.
10. Wittenburg, F. *Z. Chem. 4* (1964) 303.
11. Hoffer, M. *Chem. Ber. 93* (1960) 2777.
12. Vorbrüggen, H., Krolikiewicz, K. and Bennua, B. *Chem. Ber. 114* (1981) 1234.
13. Vorbrüggen, H. and Hoffe, G. *Chem. Ber. 114* (1981) 1256.
14. Okabe, M., Sun, R. Ch., Tam, S. Y.-K., Todaro, L. J. and Coffen, D. L. *J. Org. Chem. 53* (1988) 4780.

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