Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7291–7293

TETRAHEDRON LETTERS

Synthesis of 1-(dihydroxypropyl)-5-substituted uracils

Andrzej Gondela and Krzysztof Walczak*

Institute of Organic Chemistry and Technology, Silesian University of Technology, Krzywoustego 4, 44-100 Gliwice, Poland

Received 30 June 2003; revised 25 July 2003; accepted 1 August 2003

Abstract—Novel 1-(dihydroxypropyl)-5-substituted uracils were synthesized in the reaction of 1-(4-nitrophenyl)-5-substituted uracil derivatives with appropriate aminopropanediols under mild conditions. In the case of 3-amino-1,2-propanediol both racemic and enantiomerically enriched products were obtained. These compounds may be considered as new building blocks for oligonucleotide synthesis.

The acyclonucleosides, a group of compounds in which, the carbohydrate moieties are acyclic chains mimicking the sugar portion of naturally occurring nucleosides represent an important class of biologically active molecules.[1] Several acyclonucleosides are known to possess moderate antiviral activity (e.g. Acyclovir, (*S*)-HMPA, etc.).[1,2] Such analogues are of considerable interest as monomer precursors for the generation of antisense oligonucleotides.[3] On the other hand acyclonucleosides possessing two hydroxyl functions can be useful intermediates in the synthesis of 1,3-dioxolane and 1,3-dioxane derivatives.[4,5] Recently we have demonstrated, that 1,4-dinitroimidazoles can be easily converted into 3-(4-nitroimidazol-1-yl)-1,2-propanediols via the so-called 'degenerated imidazole ring transformation'.[6] Currently we have focused on other heterocyclic systems, which are able to undergo similar reactions. It is known from the literature that 3-methyl-5-nitro-1-(4′-nitrophenyl)uracil when treated with primary amines undergoes transformation into 1-alkyl derivatives.[7–9] 3-Methyl-1-phenyluracil-5-carboxamide undergoes the same reaction under forcing conditions.

In contrast, the biological activity of alkyl derivatives of 5-nitrouracil is rather less recognized in comparison with other uracil analogues. 5-Nitro-2′-deoxyuridine inhibits thymidylate synthetase,[10,11] and 5-nitro-1-[3-(5-nitro-2-furan-2-yl)-acroyl]uracil exhibits antitumor activity on leukemia P388 cells.[12] An inhibition effect on macrophage RAW 264.7 of 1-(2-hydroxy-3-methoxypropyl)-5-nitrouracil was also reported.[13]

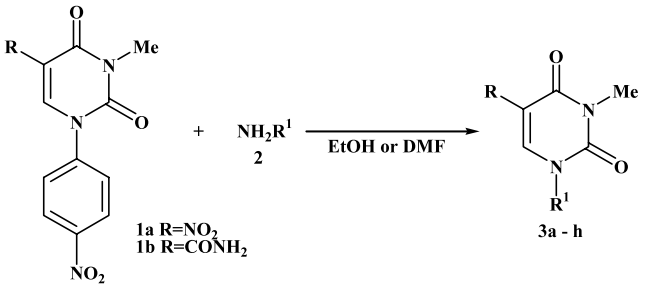
We report here a simple method for the synthesis of 5-substituted uracil propanediol derivatives. The direct nucleophilic addition of 3-methyl-5-nitrouracil to (hydroxymethyl)oxirane according to the method described by Acevedo[14] failed and the expected product was obtained in low yield (Table 1, entry 1). When

Table 1. Yields and properties of 1-(dihydroxypropyl)-5-substituted uracil derivatives

No.	Product	R	R^1	Yield (%)	Mp (°C)	$[\alpha]_D$ (*c* 0.5, MeOH)
1	**3a**	NO_2	(*RS*)-$CH_2CH(OH)CH_2OH$	18	186–188	–
2	**3a**	NO_2	(*RS*)-$CH_2CH(OH)CH_2OH$	75	187–188	–
3	**3b**	NO_2	(*R*)-$CH_2CH(OH)CH_2OH$	75	171–172	+50
4	**3c**	NO_2	(*S*)-$CH_2CH(OH)CH_2OH$	87	173–174	−46
5	**3d**	$CONH_2$	(*RS*)-$CH_2CH(OH)CH_2OH$	96	201–202	–
6	**3e**	$CONH_2$	(*R*)-$CH_2CH(OH)CH_2OH$	90	193–194	+55
7	**3f**	$CONH_2$	(*S*)-$CH_2CH(OH)CH_2OH$	92	192–194	−58
8	**3g**	NO_2	-$CH(CH_2OH)_2$	74	209–210	–
9	**3h**	$CONH_2$	-$CH(CH_2OH)_2$	70	236–237	–

Keywords: 1-(dihydroxypropyl)-5-substituted uracils; aminopropanediols; enantiomers.
* Corresponding author. Tel.: +4832-237-1792; fax: +4832-2372094; e-mail: walczak@polsl.gliwice.pl

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01872-0



Scheme 1.

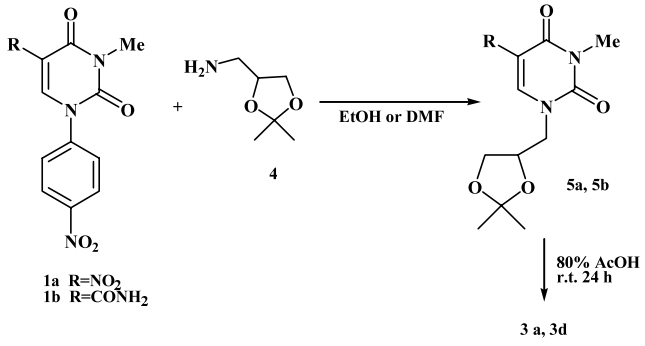
3-methyl-1-(4-nitrophenyl)uracil[7] **1a** and (±)-3-amino-1,2-propanediol were refluxed in anhydrous ethanol for 6 h, 1-(2,3-dihydroxypropyl)-3-methyl-5-nitrouracil **3a** was isolated in 75% yield (after column purification and crystallization from methanol) (Scheme 1, Table 1, entry 2).

In order to avoid racemization during the reaction, the experiments in which we applied pure enantiomers (*R* or *S*) of 3-amino-1,2-propanediol were performed in anhydrous DMF at room temperature. After 4–5 h, the corresponding products **3b** and **3c** were obtained in satisfactory yields (entries 3, 4).[15]

3-Methyl-(4-nitrophenyl)uracil-5-carboxamide **1b** was prepared from 1-(4-nitrophenyl)-5-cyanouracil[16] by *N*-3 methylation with methyl iodide followed by partial hydrolysis of the cyano group.[17]

Compound **1b** reacted smoothly with 3-amino-1,2-propanediol (*RS*, *R* or *S*) and gave the desired products **3d–f** in excellent yields (entries 5–7).[18] The optical purity of a single enantiomer depended on the optical purity of the starting 3-amino-1,2-propanediols. According to the reaction mechanism and mild reaction conditions racemization during synthesis can be prevented. The optical purity of the obtained compounds is not less than 94 (*ee*) as calculated from the enantiomeric composition of the starting amino-propanediols.

Under the same conditions, **1a** or **1b** treated with symmetrical 2-amino-1,3-propanediol gave the desired products **3g**,**h** in satisfactory yields (entries 8, 9). In order to obtain 1-(2,3-dihydroxypropyl)-3-methyl-5-substituted uracils the reaction of the appropriate uracil **1a** or **1b** with 4-aminomethyl-2,2-dimethyl-1,3-dioxolane **4** was performed (Scheme 2). Application of the same conditions (as above) gave intermediate products 1-(2,2-dimethyl-[1,3]-dioxolan-4-ylmethyl)-3-methyl-5-nitrouracil[17] **5a** and 1-(2,2-dimethyl-[1,3]-dioxolan-4-ylmethyl)-3-methyluracil-5-carboxamide[19] **5b** in satisfactory yields (68% and 86%, respectively). Cleavage of the dioxolane ring using 80% aq. acetic acid gave **3a** or **3d** in almost quantitative yield (>92%).



Scheme 2.

In conclusion, two parallel methods have been used for the syntheses of 1-(dihydroxypropyl)-5-substituted uracil derivatives. We have obtained both racemic and enantiomerically enriched products in all the reactions studied. We believe that the acyclonucleosides described will be of interest, both as synthetic intermediates and propane-2,3-diol monomers, having non-hydrogen bonded bases in oligonucleotide synthesis.[20–23]

References

1. Garg, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C. *Chem. Rev.* **1999**, *99*, 3525–3601.
2. Abushanab, E. In *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K.; Baker, D. C., Eds.; Plenum Press: New York, 1993; pp. 159–171.
3. Seeberger, P. H.; Caruthers, M. H. In *Applied Antisense Oligonucleotide Technology*; Stein, C. D.; Krieg, A. M., Eds.; *Modified Oligonucleotides as Antisense Therapeutics*; Wiley-Liss: New York, 1998; Chapter 3, pp. 51–72.
4. Efimtseva, E. V.; Mikhailov, S. N.; Meshkov, S.; Hankamaki, T.; Oivanen, M.; Lonberg, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1409–1415.
5. Cadet, G.; Chan, Ch. S.; Daniel, R. Y.; Davis, C. P.; Guiadeen, D.; Rodriguez, G.; Thomas, T.; Walcott, S.; Scheiner, P. *J. Org. Chem.* **1998**, *63*, 4574–4580.
6. Suwiński, J.; Szczepankiewicz, W.; Świerczek, K.; Walczak, K. *Eur. J. Org. Chem.* **2003**, 1080–1084.
7. Hirota, K.; Kitade, Y.; Sajiki, H.; Maki, Y. *Tetrahedron Lett.* **1986**, *27*, 3263–3266.
8. Hirota, K.; Kitade, Y.; Sajiki, H.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 367–373.
9. Senda, S.; Hirota, K.; Notani, J. *Chem. Pharm. Bull.* **1972**, *20*, 1389–1396.
10. Washtien, W. L.; Santi, D. V. *J. Med. Chem.* **1982**, *25*, 1252–1255.
11. Trusule, M.; Kupce, E.; Augustane, I.; Verovskii, N. V.; Lukevics, E.; Baumane, L.; Gavars, R.; Stradins, J. *Khim. Geterocycl. Soedin.* **1991**, *12*, 1687–1694.
12. Kranz, P.; Lee, C. S.; Gero, A. M.; O'Sullivan, W. J. *Biochem. Pharmacol.* **1989**, *38*, 3785–3789.
13. Copik, A.; Suwinski, J.; Walczak, K.; Bronikowska, J.; Czuba, Z.; Król, W. *Nucleosides, Nucloetides Nucleic Acids* **2002**, *21*, 377–383.
14. Acevedo, O. L.; Andrews, R. S. *Tetrahedron Lett.* **1996**, *37*, 3931–3934.
15. Synthesis of 1-(dihydroxypropyl)-3-methyl-5-substituted uracils (general procedure): To a solution of (*R*)-(+)-3-

amino-1,2-propanediol **2** (1.1 mmol) in anhydrous DMF (10 ml) **1a** or **1b** was added (1 mmol) in one portion while stirring. The resulting yellow-reddish solution was stirred until the substrate had been consumed and then concentrated under reduced pressure. The oily residue was purified on a silica gel column using methanol–chloroform mixture (1:9) as eluent.

3b: (*R*)-(+)-1-(2,3-dihydroxypropyl)-3-methyl-5-nitrouracil: ^{1}H NMR, (DMSO-d_6): δ (ppm) = 3.22 (s, 3H, CH_3), 3.27–3.48 (m, 2H, H-3′$_{a,b}$), 3.64–3.71 (m, 2H, H-1′$_a$, H-2), 4.21 (d, 1H, J = 10.8 Hz, H-1′$_b$), 4.78 (t, 1H, J = 5.7 Hz, OH-3′), 5.13 (d, 1H, J = 5.1 Hz, OH-2′), 9.12 (s, 1H, H-6). ^{13}C NMR, (DMSO): δ (ppm) = 28.15, 53.45, 63.37, 68.24, 124.00, 149.48, 149.53, 154.35. Anal. calcd for $C_8H_{11}N_3O_6$ (245.2): %C, 39.39; %H, 4.52; %N, 17.14. Found: %C, 39.30; %H, 4.52; %N, 16.95.

16. Wolfbeis, O. S. *Liebigs Ann. Chem.* **1982**, 182–185.
17. **1b**. 3-Methyl-(4-nitrophenyl)uracil-5-carboxamide: To the suspension of 1-(4-nitrophenyl)-5-cyanouracil[16] (9.0 g, 33 mmol) in water (0.6 ml, 33 mmol), concd sulphuric acid (41 ml, 98%) was added. The reaction mixture was stirred at 50°C for 3 h and then poured onto crushed ice (210 g). The precipitated solid was filtered off, rinsed with water and finally with methanol and crystallized from acetone. Yield 9.5 g (98%); mp 286–288°C. ^{1}H NMR, (DMSO): δ (ppm) = 3.28 (s, 3H, CH_3), 7.22 (bd, 1H, J = 3 Hz, NH_2), 7.81 (d, 2H, J = 9.3 Hz, Ar), 8.22 (bd, 1H, J = 3 Hz, NH_2), 8.37 (s, 1H, H-6), 8.38 (d, 2H, J = 9.3 Hz, Ar).
18. **3e**: (*R*)-(+)-1-(2,3-dihydroxypropyl)-3-methyluracil-5-carboxamide: ^{1}H NMR, (DMSO): δ (ppm) = 3.23 (s, 3H, Me), 3.28–3.47(m, 2H, H-3′), 3.59 (dd, 1H, J = 13.2 Hz, 9.3 Hz, H-1′$_a$), 3.65–3.76 (m, 1H, H-2′), 4.16 (dd, 1H, J = 13.2 Hz, 2.7 Hz, H-1′$_b$), 4.74 (t, 1H, J = 5.7 Hz, 3′-OH), 5.04 (d, 1H, J = 5.4 Hz, 2′-OH), 7.53 (d, 1H, J = 3.6 Hz, NH), 8.22 (s, 1H, J = 3.6 Hz, NH), 8.41 (s, 1H, H-6). ^{13}C NMR, (DMSO): δ (ppm) = 27.84, 53.17, 63.56, 68.62, 103.44, 150.50, 150.75, 162.52, 163.26. Anal. calcd for $C_9H_{13}N_3O_5$ (243.22): %C, 44.44; %H, 5.40; %N, 17.28. Found: %C, 44.46; %H, 5.61; %N, 16.97.
19. Synthesis of 1-(2,2-dimethyl-[1,3]-dioxolane-4-ylmethyl)-3-methyl-5-substituted uracils (general procedure): To the solution of 4-aminomethyl-2,2-dimethyl-[1,3]-dioxolane **4** (1.1 mmol) in anhydrous DMF (10 ml) **1a** or **1b** was added (1 mmol) in one portion while stirring. The resulting yellow-reddish solution was stirred until the substrate had been consumed and then concentrated under reduced pressure. The oily residue was crystallized from methanol.

5a: Yield 68%; mp 167–168°C; ^{1}H NMR, ($CDCl_3$): δ (ppm) = 1.34 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.41 (3H, s, N-CH_3), 3.73 (1H, dd, J = 9.0 Hz, 5.7 Hz, H-5′$_a$), 3.84 (1H, dd, J = 13.8 Hz, 7.2 Hz, CH_{2a}), 4.16 (1H, dd, J = 9.0 Hz, 6.6 Hz, H-5′$_b$), 4.28 (1H, dd, J = 13.8 Hz, 2.7 Hz, CH_{2b}), 4.40–4.50 (1H, m, H-4′), 8.81 (1H, s, H-6). ^{13}C NMR, ($CDCl_3$), δ (ppm) = 24.78, 26.66, 28.93, 52.54, 66.11, 72.88, 110.47, 124.96, 147.64, 149.88, 154.24. Anal. calcd for $C_{11}H_{15}N_3O_6$ (285.3): %C, 46.32; %H, 5.30; %N, 14.73. Found: %C, 46.37; %H, 5.01; %N, 14.67.

5b: Yield 86%; mp 199–200°C; ^{1}H NMR, (DMSO): δ (ppm) = 1.25 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.25 (s, 3H, N-CH_3), 3.68 (dd, 1H, J = 8.6 Hz, 5.6 Hz, H-5′$_a$), 3.94–4.14 (m, 3H, CH_{2a}, CH_{2b}, H-5′$_b$), 4.29 (m, 1H, H-4′), 7.56 (bd, 1H, J = 3.5 Hz, NH_2), 8.19 (bd, 1H, J = 3.5 Hz, NH_2), 8.47 (s, 1H, H-6). ^{13}C NMR, (DMSO): δ (ppm) = 25.16, 26.44, 28.02, 51.21, 65.82, 73.03, 103.94, 108.94, 150.17, 150.65, 162.32, 162.96.

20. Kool, E. T. *Acc. Chem. Res.* **2002**, *35*, 936–943.
21. Loakes, D. *Nucleic Acids Res.* **2001**, *29*, 2437–2447.
22. Kool, E. T. *Biopolymers* **1998**, *48*, 3–17.
23. Berger, M.; Wu, Y.; Ogawa, A. K.; McMinn, D. L.; Schultz, P. G.; Romesberg, F. E. *Nucleic Acids Res.* **2000**, *28*, 2911–2914.