Synthesis of Carbocyclic Pyrimidine Nucleosides Using the *Mitsunobu* Reaction: O^2- *vs.* N^1-Alkylation

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The *Mitsunobu* reaction is an important tool in carbocyclic nucleoside chemistry for the direct coupling of alcohols with heterocyclic bases under mild conditions. Chemical evidences for an unusual competitive O^2- *vs.* N^1-alkylation of 3-substituted pyrimidines is presented.

Introduction. – Carbocyclic analogues of nucleosides, in which a CH_2 group replaces the furan O-atom of nucleosides, are generally more stable to hydrolysis than the corresponding furanosyl compounds [1], and, in some cases, they have potent antiviral and/or anticancer activities [2].

On the other hand, removal of the OH groups in the 2′- and 3′-positions of the carbocycle has generated drugs of choice for treatment of certain viral infections, including human immunodeficiency virus (HIV) infection, which works by blocking viral reproduction, thus inhibiting reverse transcriptase [3].

Nucleoside analogues with six-membered carbocyclic rings, have been less extensively studied [4]. Nevertheless, research in this area has led to many new compounds, some of them with potent activities [5].

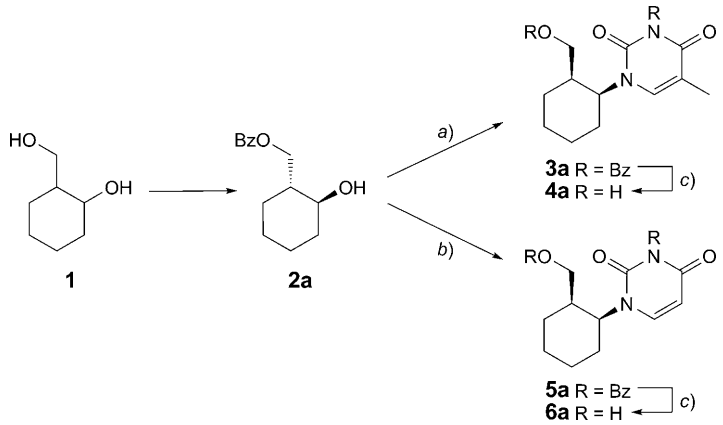
The common strategies used for the preparation of carbocyclic nucleosides can be subdivided into two categories [6]: *a*) the linear approach involves initial synthesis of a functionalized cycloalkylamine and a stepwise synthesis of the heterocyclic base, and *b*) the convergent approach; here, the appropriate heterocycle is coupled directly to a functionalized carbocyclic moiety, leading to a variety of carbocyclic nucleosides starting from one common carbocycle precursor.

During the last years, we have been working on six-membered 1,2-disubstituted carbocyclic nucleoside analogues, and we have published some comparative studies for the synthesis of some purine and pyrimidine derivatives of the nucleosides mentioned above using both of the synthetic strategies [7]. Considering that construction of the heterocyclic base on the amino group is a long way with low yield in several steps, in the present article, we report the synthesis of pyrimidine derivatives of (±)-*cis*/*trans*-2-

(hydroxymethyl)cyclohexane under conditions of the *Mitsunobu* reaction, taking into account the protecting group, the configuration of the carbocyclic moiety ((±)-*cis*/*trans*-2-(hydroxymethyl)cyclohexanol), and the substituents at C(5) of the pyrimidine base.

Results and Discussion. – The reaction of (±)-*trans*-(2-hydroxycyclohexyl)methyl benzoate (**2a**) [7] with N^3-benzoylthymine and N^3-benzoyluracil yielded (±)-*cis*-1-[2-(hydroxymethyl)cyclohexyl]thymine (**4a**) [8] and (±)-*cis*-1-[2-(hydroxymethyl)cyclohexyl]uracil (**6a**) [7] with yields of 20 and 16% after deprotection, respectively (*Scheme 1*).

Scheme 1

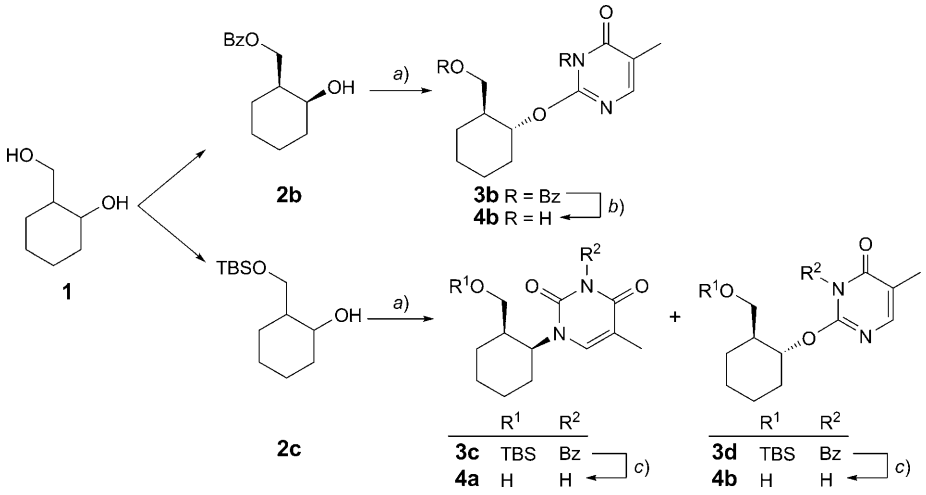


a) N^3-Benzoylthymine, Ph_3P, diethyl azodicarboxylate (DEAD), r.t., 12 h. *b*) N^3-Benzoyluracil, Ph_3P, DEAD, r.t., 12 h. *c*) MeONa, MeOH, r.t., 12 h.

On the other hand, when (±)-*cis*-(2-hydroxycyclohexyl)methyl benzoate (**2b**) [7] was reacted with N^3-benzoylthymine, only a small quantity (15% yield) of (±)-*trans*-O^2-[2-(hydroxymethyl)cyclohexyl]thymine (**4b**; after deprotection) was isolated (*Scheme 2*). However, the expected (±)-*trans*-1-[2-(hydroxymethyl)cyclohexyl]thymine could not be obtained [9]. To study the effect of the protecting group, we used then a protecting group on the diol with different steric and electronic effects: (±)-*cis*/*trans*-2-{[(*tert*-butyl)(dimethyl)silyloxy]methyl}cyclohexanol (**2c**) [7]. In this case, the mixture of *cis*/*trans*-isomers could not be separated by chromatography, and, after reaction with N^3-benzoylthymine, we identified the N^1-product **3c** and the O^2-product **3d**; this last one was probably formed from the *cis*-isomer of 2-(hydroxymethyl)cyclohexanol. From previous reactions, it became clear that the protecting group on the (±)-*cis*/*trans*-2-(hydroxymethyl)cyclohexane has not a major effect on the outcome of the *Mitsunobu* coupling.

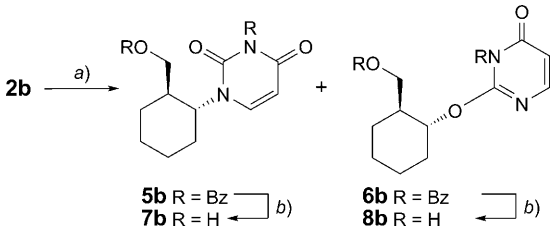
Reaction of **2b** with N^3-benzoyluracil yielded (±)-*trans*-1-[2-(hydroxymethyl)cyclohexyl]uracil (**7b**) and (±)-*trans*-O^2-[2-(hydroxymethyl)cyclohexyl]uracil (**8b**), after deprotection, in a very low yield (7 and 10%, resp; *Scheme 3*). Precursor **5b**, as **3a** and **5a**, could not be isolated by chromatography.

Scheme 2



a) N^3-Benzoylthymine, Ph_3P, DEAD, r.t., 12 h. *b*) MeONa, MeOH, r.t., 12 h, *c*) $MeCO_2H/H_2O$/THF 1.8 : 0.6 : 0.6 ml, r.t, 5 h, and MeONa, MeOH, r.t., 12 h.

Scheme 3



a) N^3-Benzoyluracil, Ph_3P, DEAD, r.t., 12 h. *b*) MeONa, MeOH, r.t., 12 h.

The structures of O^2-alkylated compounds **4b** and **8b** were confirmed by ^{1}H- and ^{13}C-NMR, the chemical shifts of H–C(1′) of **4b** and **8b** were appreciably more downfield (5.42 and 5.49 ppm) compaired to those of the N^1-alkylated *Mitsunobu* products [10] (3.85 and 4.44 ppm for H–C(1′) of **4a** and **7b**, resp.).

In conclusion, while (±)-*cis*-1-[2-(hydroxymethyl)cyclohexyl]pyrimidines can be obtained in moderate yield from (±)-*trans*-2-(hydroxymethyl)cyclohexanol, the *Mitsunobu* reaction with (±)-*cis*-2-(hydroxymethyl)cyclohexanol and N^3-Bz-pyrimidines leads mainly to the corresponding *trans*-O^2-[2-(hydroxymethyl)cyclohexyl]pyrimidines.

Experimental Part

General. Flash chromatography (FC): silica gel (SiO_2; *Merck 60*, 230–400 mesh). Anal. TLC: plates precoated with silica gel (*Merck 60 F254*, 0.25 μm). M.p.: *Stuart Scientific* melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer 1640 FT* spectrophotometer (KBr disks, $\tilde{\nu}$ in cm^{-1}). ^{1}H- and

^{13}C-NMR spectra: *Bruker DPX* (250 MHz) and *Bruker AMX* (500 MHz) spectrometers, with TMS as internal standard (chemical shifts δ in ppm, J in Hz). EI-MS and HR-EI-MS: *Hewlett Packard 5988A* and *Micromass Autospec* spectrometer, resp.

Mitsunobu *Reaction. Typical Procedure.* To a soln. of N^3-benzoylpyrimidine (1.22 mmol), (2-hydroxycyclohexyl)methyl benzoate (2.03 mmol), and Ph_3P (2.03 mmol) in THF (5.0 ml) was added diethyl azodicarboxylate (DEAD; 2.03 mmol) dropwise at 0°. The mixture was stirred at r.t. for 12 h. The solvent was removed under reduced pressure, and the residue was purified by FC with hexane/AcOEt.

Influence of the solvent on the alkylation of N^3-benzoylthymine or N^3-benzoyluracil under *Mitsunobu* conditions was investigated [11]. Results obtained using MeCN or DMF were similar, in our case, to those obtained when THF was used as solvent.

(±)-trans-N^3-*Benzoyl*-O^2-*{[2-(benzoyloxy)methyl]cyclohexyl}thymine* (**3b**). Yield: 28%. Oil. IR: 3218, 3100, 2928, 1705, 1672, 1610, 1506, 1102, 810. ^{1}H-NMR ($CDCl_3$): 1.25 (*d*, J = 1.1, Me); 1.28–1.51 (*m*, 3 H); 1.61–1.63 (*m*, 1 H); 1.75–1.82 (*m*, 2 H); 2.12–2.21 (*m*, 3 H); 4.22–4.33 (*m*, CH_2O); 4.87–5.15 (*m*, H–C(1′)); 7.38–7.44 (*m*, 6 H); 7.97–8.05 (*m*, 5 H). EI-HR-MS: 446.1850 (M^+, $C_{26}H_{26}N_2O_5^+$; calc. 446.1842).

(±)-trans-N^3-*Benzoyl*-O^2-*(2-{[(*tert-*butyl)(dimethyl)silyloxy]methyl}cyclohexyl)thymine* (**3d**). Yield: 12%. Oil. IR: 2933, 2860, 1655, 1562, 1309, 1288, 1105, 708. ^{1}H-NMR ($CDCl_3$): 0.00 (*s*, 2 Me); 0.80 (*s*, *t*-Bu); 1.15–1.69 (*m*, 6 H); 1.70–1.80 (*m*, 2 H); 2.03 (*d*, J = 1.0, Me); 2.10–2.24 (*m*, 1 H); 3.39–3.71 (*m*, CH_2O); 5.40–5.50 (*m*, H–C(1′)); 7.41–7.61 (*m*, 2 H); 7.62–7.70 (*m*, 2 H); 8.10–8.20 (*m*, 2 H). EI-HR-MS: 456.2447 (M^+, $C_{25}H_{36}N_2O_4Si^+$; calc. 456.2444).

(±)-cis-N^3-*Benzoyl-1-(2-{[(*tert-*butyl)(dimethyl)silyloxy]methyl}cyclohexyl)thymine* (**3c**). Yield: 24%. Oil. IR: 3070, 2932, 2846, 2664, 1745, 1691, 1649, 1435, 1253, 831. ^{1}H-NMR ($CDCl_3$): 0.00 (*s*, 2 Me); 0.85 (*s*, *t*-Bu); 1.25–1.90 (*m*, 7 H); 1.95 (*d*, J = 1.1, Me); 2.01–2.29 (*m*, 1 H); 3.62–3.74 (*m*, CH_2O); 4.45–4.55 (*m*, H–C(1′)); 7.30–7.40 (*m*, 2 H); 7.55–7.65 (*m*, 1 H); 7.70–7.90 (*m*, 3 H). EI-HR-MS: 456.2449 (M^+, $C_{25}H_{36}N_2O_4Si^+$; calc. 456.2444).

(±)-trans-N^3-*Benzoyl*-O^2-*{2-[(benzoyloxy)methyl]cyclohexyl}uracil* (**6b**). Yield: 17%. Oil. IR: 3005, 2945, 2868, 1770, 1699, 1573, 1310, 1260, 1100. ^{1}H-NMR ($CDCl_3$): 1.28–1.40 (*m*, 2 H); 1.43–1.54 (*m*, 2 H); 1.75–1.79 (*m*, 1 H); 1.83–1.87 (*m*, 1 H); 1.97–2.01 (*m*, 1 H); 2.16–2.20 (*m*, H–C(2′)); 2.21–2.33 (*m*, 1 H); 4.36–4.45 (*m*, CH_2O); 5.10–5.18 (*m*, H–C(1′)); 6.90 (*d*, J = 5.2, H–C(6)); 7.37–7.41 (*m*, 2 H); 7.50–7.53 (*m*, 3 H); 7.65–7.68 (*m*, 1 H); 8.00–8.02 (*m*, 2 H); 8.14–8.18 (*m*, 2 H); 8.50 (*d*, J = 5.2, H–C(5)). EI-HR-MS: 432.1695 (M^+, $C_{25}H_{24}N_2O_5^+$; calc. 432.1685).

Deprotection Reaction. Typical Procedure. Hydrolysis of the Bz derivatives **3a**, **3b**, **5b**, and **6b** was performed with 1M MeONa/MeOH at r.t. overnight.

Compounds **4a** and **4b** were obtained by hydrolysis of the $TBSOCH_2$ derivatives **3c** and **3d** with MeCOOH/H_2O/THF (1.8 : 0.6 : 0.6 ml) at r.t. for 5 h, followed by hydrolysis of the benzoyl derivatives **3a**, **3b**, **5b**, and **6b** with 1M MeONa/MeOH at r.t. overnight.

(±)-cis-*1-[2-(Hydroxymethyl)cyclohexyl]thymine* (**4a**). Yield: 60% from **3a** and 54% from **3c**. M.p. 189–191°. IR (KBr): 3434, 2921, 1675, 1478, 1424, 1338, 1194. ^{1}H-NMR ($CDCl_3$): 1.29–1.33 (*m*, 2 H); 1.37–1.51 (*m*, 3 H); 1.59–1.63 (*m*, 1 H); 1.77–1.81 (*m*, 1 H); 1.84–1.88 (*m*, 2 H); 1.99 (*d*, J = 1.0, Me); 3.51 (br. *s*, OH); 3.84–3.86 (*m*, H–C(1′)); 4.06 (*dd*, J = 11.0, 5.1, 1 H, CH_2O); 4.60 (*dd*, J = 11.0, 5.1, 1 H, CH_2O); 7.54 (*q*, J = 1.0, H–C(6)); 11.08 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 12.3 (Me); 20.0; 22.5; 25.1; 32.0; 41.4 (C(2′)); 64.5 (C(1′)); 69.6 (C(7′)); 117.7 (C(5)); 150.7 (C(6)); 156.5 (C(2)); 164.9 (C(4)). EI-HR-MS: 238.1314 (M^+, $C_{12}H_{18}N_2O_3^+$; calc. 238.1317).

(±)-trans-O^2-*[2-(Hydroxymethyl)cyclohexyl]thymine* (**4b**). Yield: 55% from **3b** and 50% from **3d**. M.p. 137–139°. IR (KBr): 3501, 3315, 2900, 2730, 1698, 1590, 1300, 1018. ^{1}H-NMR ($CDCl_3$): 1.25–1.39 (*m*, 3 H); 1.55–1.61 (*m*, 3 H); 1.70–1.90 (*m*, 2 H); 1.95 (*d*, J = 1.1, Me); 2.00–2.10 (*m*, 1 H); 3.23 (*dd*, J = 11.0, 4.5, 1 H, CH_2O); 3.40 (*dd*, J = 11.0, 4.5, 1 H, CH_2O); 4.42 (br. *s*, OH); 5.41–5.43 (*m*, H–C(1′)); 7.52 (*q*, J = 1.1, H–C(6)); 10.9 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 12.2 (Me); 20.5; 23.1; 24.9; 30.6; 43.6 (C(2′)); 62.8 (C(7′)); 74.8 (C(1′)); 117.8 (C(5)); 150.3 (C(6)); 156.6 (C(2)); 164.7 (C(4)). EI-HR-MS: 238.1322 (M^+, $C_{12}H_{18}N_2O_3^+$; calc. 238.1317).

(±)-trans-*1-[2-(Hydroxymethyl)cyclohexyl]uracil* (**7b**). Yield: 60%. M.p. 177–179°. IR (KBr): 3450, 3010, 2922, 1698, 1478, 1424, 1338, 1281, 1194. ^{1}H-NMR ($CDCl_3$): 1.25–1.37 (*m*, 3 H); 1.46–1.58 (*m*, 3 H); 1.84–2.16 (*m*, 3 H); 3.38–3.50 (*m*, CH_2O); 4.32–4.56 (*m*, H–C(1′)); 5.76 (*d*, J = 10.0, H–C(5));

7.23 (*d*, *J* = 10.0, H–C(6)); 8.99 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 22.7; 24.7; 25.5; 29.7; 35.0 (C(2′)); 51.0 (C(1′)); 63.2 (C(7′)); 102.9 (C(5)); 140.4 (C(6)); 151.9 (C(2)); 162.3 (C(4)). EI-HR-MS: 224.1169 (M^+, $C_{11}H_{16}N_2O_3^+$; calc. 224.1161).

(±)-trans-O^2-*[2-(Hydroxymethyl)cyclohexyl]uracil* (**8b**). Yield: 58%. M.p. 144–146°. IR (KBr): 3550, 3010, 2933, 1702, 1488, 1400, 1308, 1280, 1184. ^{1}H-NMR ($CDCl_3$): 1.25–1.35 (*m*, 3 H); 1.48–1.62 (*m*, 3 H); 1.80–1.96 (*m*, 2 H); 2.11–2.19 (*m*, 1 H); 3.26 (*dd*, *J* = 10.0, 4.5, 1 H, CH_2O); 3.44 (*dd*, *J* = 10.0, 4.5, 1 H, CH_2O); 4.85 (br. *s*, OH); 5.44–5.54 (*m*, H–C(1′)); 5.68 (*d*, *J* = 6.2, H–C(5)); 7.50 (*d*, *J* = 6.2, H–C(6)); 11.4 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 20.8; 22.9; 25.2; 30.8; 42.6 (C(2′)); 61.8 (C(7′)); 73.9 (C(1′)); 113.9 (C(5)); 154.6 (C(6)); 156.6 (C(2)); 168.7 (C(4)). EI-HR-MS: 224.1171 (M^+, $C_{11}H_{16}N_2O_3^+$; calc. 224.1161).

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