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Lipase-mediated Alkoxycarbonylation of Nucleosides with Oxime Carbonates.

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Abstract: *5'-O-carbonates of ribonucleosides and 2'-deoxyribonucleosides could be obtained by enzymatic alkoxycarbonylation with SP 435 lipase (from Candida antarctica) and oxime carbonates, which are easily prepared from chloroformates. Ribonucleosides gave as result two kind of 5'-O-carbonates depending on whether* ***alkoxy*** *or acetone oxime moiety acted as the leaving group. In the case of 2'-deoxynucleosides, the leaving group was always the acetonoxime moiety, giving rise to regioselective formation of the corresponding 5'-O-alkyl carbonates, together with small amounts of 3'-O-regiosiomer and diacylated compounds.*

INTRODUCTION

Modification of one out of several identical functional groups in a molecule is a fundamental challenge to organic chemists. With regards to nucleosides, selective reactions on their functional groups is an interesting subject of study,[1] since convenient advances in this field may lead to obtain new nucleoside analogues, which are compounds of high significance in some areas of medicinal chemistry,[2] showing antineoplasic[3] and antiviral activity.[4]

An important and synthetically relevant example of this problem is the selective alkoxycarbonylation of the sugar moiety of these compounds in order to obtain nucleoside carbonates, which play an important role in the synthesis of oligonucleotides[5] and other derivatives assayed in medicine such as dinucleoside carbonates.[6] The alkoxycarbonyl groups are commonly introduced using chloroformates,[7] but yields are low and regioselectivity is poor except when activated agents such as nitrophenyl[5a] or ß,ß,ß-tribromoethyl chloroformates[8] are used.

On the other hand, the synthetic potential of enzymes in organic solvents has been well documented in the last few years.[9] Esterification and especially transesterification reactions have been the processes most commonly used in organic synthesis, but on the contrary the alkoxycarbonylation reaction has scarcely been investigated:

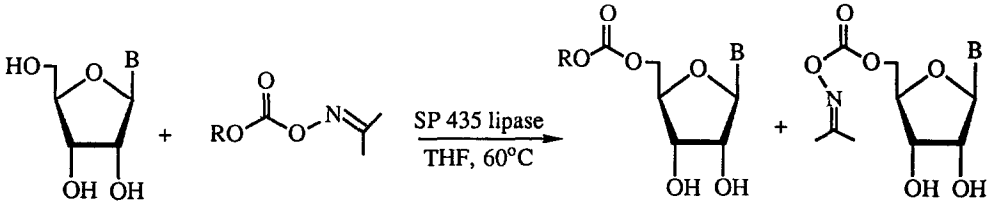
carbonates have been used in the synthesis of fatty carbonate esters,[10] and in the resolution of racemic alcohols.[11,12]

As a part of our program to design new regioselective enzymatic transformations of polyhydroxy compounds with oxime derivatives, we have described recently the preparation of 3'-*O*-carbonates from unprotected 2'-deoxynucleosides through an enzymatic alkoxycarbonylation reaction using *O*-alkoxycarbonyloximes and lipase from *Pseudomonas cepacia*.[13] Because of the immense potential of enzymes in regioselective transformations, we believed that other lipases could catalyze the regioselective alkoxycarbonylation of the primary hydroxyl group of nucleosides. In this paper it is shown that 5'-*O*-carbonates can also be obtained through an enzymatic reaction using *O*-alkoxycarbonyloximes.

RESULTS AND DISCUSSION

Alkoxycarbonylation of ribonucleosides: Our interest in the development of new alkoxycarbonylating reagents, which could be used in enzyme catalyzed reactions, led us to prepare *O*-alkoxycarbonyloximes, **2**, as appropriate agents for this purpose. These compounds were obtained from the corresponding chloroformates and acetonoxime in high yields (for physical and spectral data see Ref. 13).

The ribonucleosides employed were uridine and adenosine, as representatives of pyrimidine and purine nucleosides respectively. Since these compounds are hardly soluble in apolar organic solvents, commonly used in enzymatic esterifications, we chose a polar solvent such as THF to run the reactions (Scheme I). *Candida antarctica* SP 435 lipase was selected as catalyst because of its ability to acylate nucleosides at the primary hydroxyl group,[14] whereas other lipases (PPL, PSL, CCL) were not as effective as this one to achieve this goal.



1a-b **2 a-c** **3 a-c** **4 a-b**

1 a B = U
1 b B = Ad

2a R = CH_3-
2b R = Ph-CH_2-
2c R = CH_2=CH-

3a R = CH_3-
3b R = Ph-CH_2-
3c R = CH_2=CH-

4a B = U
4b B = Ad

Scheme I

Reactions were monitored by TLC and two products were observed together with starting material: compounds **3a-c** resulted as a consequence of the capability of oxime as leaving group, whereas in the case of

4a-b this role was adopted by alcohol moiety. As one can see in Table I, methoxy group is the worst leaving group (only 15% of **4** in entry 2) whereas vinyl group seems to be as good as acetone oxime (50% **3** and **4** in entry 2).

Table I. Reaction of nucleosides **1a-b** with **2a-c** and SP435 lipase in THF at 60°C

Entry	B	R	t (h)	Conv. (%)	Rate (%) **3**	**4**
1	U	Ph-CH_2-	72	75	60	40
2	U	CH_3-	72	80	85	15
3	Ad	CH_2=CH-	12	90	50	50

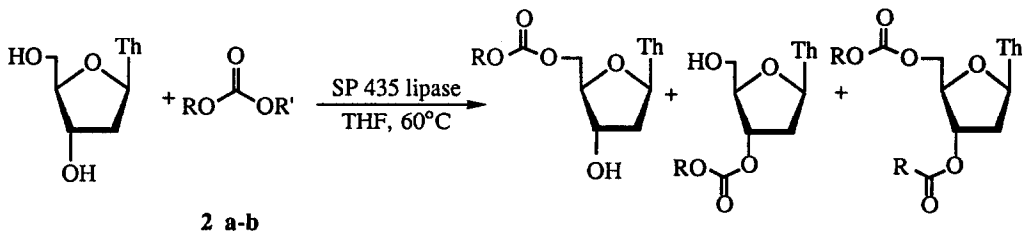
It is of note that acetonoxime was always the leaving group with PS lipase as catalyst, even when vinyl moiety was present.[13] Table I shows that three different alkyl groups have been introduced, as a proof of the versatility of the procedure, and when adenosine was employed, *N*-acylation of the base was not observed.

The structure of compounds **3** and **4** were determined on the basis of their spectral data. For example, ^{13}C-NMR for both compounds **3** and **4** showed a shift on C5' of *ca.* 7 ppm. towards lower fields with respect to the same carbon atom in the starting nucleosides **1a-b**. In addition, H5', H5" showed a shift of *ca.* 1.5 ppm. downfield with respect to the nucleosides **1a-b**.

Alkoxycarbonylation of deoxynucleosides: In this case, thymidine, **5**, was the representative compound of this kind of nucleosides and *O*-alkoxycarbonyloximes, **2a-b**, were used mainly as alkoxycarbonylating agents, together with methyl pyrocarbonate, **6**, employed in order to introduce methoxycarbonyl group (entry **1**, Table II) with higher yield that those reached with the acetonoxime counterpart. Pyrocarbonates seemed interesting reactives because of their analogy with anhydrides, which have been successfully used in enzymatic acylations,[15] but the lack of versatility (only some dialkyl pyrocarbonates are commercially available) and the proven instability of other ones prepared[16] limits their potential use as alkoxycarbonylating reagents.

Reactions were carried out in the manner of ribonucleosides, namely THF and 60°C with SP435 lipase (Scheme II). Table II gives the results obtained, and unlike with ribonucleosides, in this case only introduction of the alkyl moiety could be detected. High regioselectivity towards 5'-hydroxyl group was observed, other products are thymidine, 3'-*O*-carbonates, **8a-c**, and in some cases little amounts of diacylated compounds appeared too (**9a,b**).

When 2'-deoxyadenosine was used as substrate, conversion was low and for this reason we have only referred to thymidine. This reaction proves to be an adequate complement to that reported recently by us[13] in which alkoxycarbonylation of secondary hydroxyls of unprotected 2'-deoxynucleosides was achieved.



2 a-b

5 **6** R' = MeOCO- **7 a-c** **8 a-c** **9 a-c**

Scheme II

Table II.Alkoxycarbonylation of thymidine with SP435 lipase in THF at 60°C

Entry	R	t (h)	Conv. (%)	Rate (%) 7	8	9
1	CH_3-	72	84	78	15	7
2	Ph-CH_2-	72	78	80	20	0
3	CH_2=CH-	12	92	66	25	9

The identification of nucleoside derivatives **7a-c** was accomplished specially by ^{13}C-NMR spectroscopy. Comparision with thymidine and with 3'-*O*-regioisomers already described,[13] gave no doubt about the structure of 5'-*O*-carbonates: C5' undergoes a *ca.* 8 ppm. downfield shift in the products with respect to thymidine. Assignment of C1' and C4' was readily made on the basis of the coupled ^{13}C-NMR spectra, since $^1J_{C1',H-C1'}$ exhibit values around 165 Hz whereas the other $^1J_{C,H}$ of the sugar moiety (for example, $^1J_{C4',H-C4'}$) are 15-20 Hz smaller.[17]

CONCLUSION

In the present work we described a easy and versatile method to obtain 5'-*O*-carbonates both of ribo and 2'-deoxyribonucleosides under mild conditions through a lipase-mediated alkoxycarbonylation. The procedure

represents an improvement to other methods and complements, from an enzymatic point of view, the one described by us to obtain regioselectively the 3'-*O*-carbonates of deoxynucleosides.[13] The introduction of different groups in the nucleoside, the importance of these compounds in some areas of medicinal chemistry and the simplicity and versatility of the procedure are noteworthy.

EXPERIMENTAL

Lipase from *Candida antarctica* SP 435 was kindly gifted by Novo Nordisk Company. Nucleosides and methyl pyrocarbonate were purchased from Aldrich Chemie. THF and 1,4-dioxane were distilled over $LiAlH_4$ in order to avoid moisture. Pre-coated TLC alumina sheets silica gel 60 F_{254} from Merck were used, and for column chromatography, Merck silica gel 60/230-400 mesh was used. Melting points were taken on samples in open capillary tubes using a Büchi melting-point apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Mattson 3000 FT spectrometer. NMR spectra were recorded using a Bruker AC300 spectrometer with DMSO-d_6 as solvent. Mass spectra were obtained on a Hewlett-Packard 5897A spectrometer. Microanalyses were performed on a Perkin-Elmer model 240 instrument. Oxime carbonates, **2**, were prepared in almost quantitative yields by treating acetone oxime with the corresponding chloroformate followed by vacuum-distillation.

General procedure for the synthesis of compounds 3a-c and 4a-b : 2 mmol of **1a-b**, 6 mmol of **2a-c** and 0.4g of lipase from *Candida antarctica* SP 435 was suspended in 15 mL of THF or dioxane under nitrogen atmosphere. The mixture was allowed to react at 60°C during the time indicated in Table I. Then, the enzyme was filtered off and washed with MeOH, the residue was evaporated under vacuum, and the product was subjected to flash chromatography (AcOEt : MeOH 92 : 8, for uridine nucleosides and CH_2Cl_2 : MeOH 9 : 1 for those from adenine). Crystallization was obtained from AcOEt or diethyl ether.

Compound **3a**: Isolated yield 68%; mp 175-6°C; IR (KBr, cm^{-1}) 1757; $[\alpha]_{25}^{D}$ = -3.38 (c = 0.65, DMSO); ^{1}H-NMR (DMSO-d_6) δ 11.38 (1H, br, NH), 7.59 (1H, d, H6), 5.75 (1H, d, H1'), 5.65 (1H, d, H5), 5.51 (1H, d, 2'-OH), 5.33 (1H, d, 3'-OH), 4.29 (2H, m, H5', H5"), 4.07 (1H, m, H2'), 4.00 (2H, m, H3', H4'), 3.75 (3H, s, MeO); ^{13}C-NMR (DMSO-d_6) δ 163.37 (C4), 155.25 (C=O), 150.94 (C2), 141.01 (C6), 102.36 (C5), 88.94 (C1'), 81.27 (C4'), 72.84 (C2'), 70.05 (C3'), 67.59 (C5'), 55.18 (MeO); Anal. Calcd for $C_{11}H_{14}N_2O_8$: C, 43.71; H, 4.67; N, 9.27. Found: C, 43.50; H, 4.56; N, 9.41.

Compound **3b**: Isolated yield 45%; mp 135-6°C; IR (KBr, cm^{-1}) 1761; $[\alpha]_{25}^{D}$ = +6.0 (c = 0.6, DMSO); ^{1}H-NMR (DMSO-d_6) δ 11.41 (1H, br, NH), 7.62 (1H, d, H6), 7.40 (5H, s, Ph), 5.77 (1H, d, H1'), 5.60 (1H, d, H5), 5.49 (1H, br, 2'-OH), 5.35 (1H, br, 3'-OH), 5.18 (2H, s, CH_2), 4.35 (1H, m, H5'), 4.28 (1H, m, H5"), 4.09 (1H, m, H2'), 4.02 (1H, m, H4'), 3.95 (1H, m, H3'); ^{13}C-NMR (DMSO-d_6) δ 163.27 (C4), 154.53 (C=O), 150.89 (C2), 140.96 (C6), 135.62 (Ph), 128.76 (Ph), 128.69 (Ph), 128.48 (Ph), 102.26 (C5), 88.86 (C1'), 81.22 (C4'), 72.80 (C2'), 70.03 (C3'), 69.42 (CH_2), 67.64 (C5'); Anal. Calcd for $C_{18}H_{18}N_2O_8$:

C, 55.39; H, 4.65; N, 7.18. Found: C, 55.40; H, 4.56; N, 7.11.

Compound **3c**: Isolated yield 45%; mp 69-70°C; IR (KBr, cm^{-1}) 1763; $[\alpha]_{25}^{D}$ = -45.9 (c = 0.42, DMSO); ^{1}H-NMR (DMSO-d_6) δ 8.30 (1H, s, H8), 8.14 (1H, s, H2), 7.33 (2H, br, NH_2), 7.02 (1H, dd, CH), 5.92 (1H, d, H1'), 5.62 (1H, d, 2'-OH), 5.45 (1H, d, 3'-OH), 4.91 (1H, dd, CH_2), 4.67 (2H, m, CH_2, H2'), 4.44 (2H, m, H5', H5"), 4.26 (1H, m, H3'), 4.15 (1H, m, H4'); ^{13}C-NMR (DMSO-d_6) δ 156.26 (C6), 152.84 (C2), 152.10 (C=O), 149.51 (C4), 142.97 (CH), 139.84 (C8), 119.36 (C5), 87.96 (C1'), 81.39 (C4'), 73.01 (C2'), 70.39 (C3'), 68.30 (C5'); Anal. Calcd for $C_{13}H_{15}N_5O_6$: C, 46.29; H, 4.48; N, 20.76. Found: C, 46.40; H, 4.56; N, 20.61.

Compound **4a**: Isolated yield 30%; mp 177-8°C; IR (KBr, cm^{-1}) 1770; $[\alpha]_{25}^{D}$ = -6.1 (c = 0.43, DMSO); ^{1}H-NMR (DMSO-d_6) δ 11.40 (1H, s, NH), 7.68 (1H, d, H6), 5.78 (1H, d, H1'), 5.65 (1H, d, H5), 5.53 (1H, d, 2'-OH); 5.36 (1H, d, 3'-OH), 4.38 (2H, m, H5', H5"), 4.09 (1H, m, H2'), 4.04 (1H, m, H4'), 3.93 (1H, m, H3'), 1.98 (6H, s, 2 x Me); ^{13}C-NMR (DMSO-d_6) δ 164.80 (C=N), 163.28 (C4), 153.07 (C=O); 150.92 (C2), 140.97 (C6), 102.27 (C5), 88.70 (C1'), 81.29 (C4'), 72.80 (C2'), 70.12 (C3'), 67.88 (C5'), 21.34 (Me), 16.69 (Me); Anal. Calcd for $C_{13}H_{17}N_3O_8$: C, 45.48; H, 4.99; N, 12.24. Found: C, 45.34; H, 4.76; N, 12.11.

Compound **4b**: Isolated yield 45%; mp 90-100°C; IR (KBr, cm^{-1}) 1770; $[\alpha]_{25}^{D}$ = -40.3 (c = 0.59, DMSO); ^{1}H-NMR (DMSO-d_6) δ 8.33 (1H, s, H8), 8.15 (1H, s, H2), 7.33 (2H, br, NH_2), 5.94 (1H, d, H1'), 5.62 (1H, d, 2'-OH), 5.45 (1H, d, 3'-OH), 4.66 (1H, m, H2'), 4.43 (2H, m, H5', H5"), 4.26 (1H, m, H3'), 4.15 (1H, m, H4'), 1.95 (3H, s, Me), 1.91 (3H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 164.63 (C=N), 156.25 (C6), 152.87 (C2), 153.09 (C=O), 149.61 (C4), 139.70 (C8), 119.29 (C5), 87.83 (C1'), 81.65 (C4'), 73.28 (C2'), 70.53 (C3'), 67.92 (C5'), 21.32 (Me), 16.67 (Me); Anal. Calcd for $C_{14}H_{18}N_6O_6$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.05; H, 4.86; N, 22.71.

General procedure for the synthesis of compounds 7a-c: 2 mmol of **5**, 6 mmol of **2a-b** or **6** and 0.4g of lipase from *Candida antarctica* SP 435 was suspended in 15 mL of THF or dioxane under nitrogen atmosphere. The mixture was allowed to react at 60°C during the time indicated in Table II. Then, the enzyme was filtered off and washed with MeOH, the residue was evaporated under vacuum, and the product was subjected to flash chromatography (AcOEt : MeOH 100 : 1). Crystallization was obtained from diethyl ether. Compounds **8a-c** were previously described by us.[13]

Compound **7a**: Isolated yield 67%; mp 159-160°C; IR (KBr, cm^{-1}) 1757; $[\alpha]_{25}^{D}$ = +10.4 (c = 0.45, MeOH); ^{1}H-NMR (DMSO-d_6) δ 11.31 (1H, s, NH), 7.44 (1H, s, H6), 6.18 (1H, t, H1'), 5.44 (1H, d, 3'-OH), 4.24 (3H, m, H3', H5', H5"), 3.90 (1H, m, H4'), 3.71 (3H, s, MeO), 2.20 (2H, m, H2',H2"), 1.77

(3H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 163.94 (C4), 155.24 (C=O), 150.70 (C2), 136.09 (C6), 110.05 (C5), 84.07 (C1'), 83.68 (C4'), 70.38 (C3'), 67.56 (C5'), 55.12 (MeO), 38.76 (C2'), 12.38 (Me); Anal. Calcd for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.90; H, 5.36; N, 9.41.

Compound **9a**: ^{1}H-NMR (DMSO-d_6) δ 11.35 (1H, s, NH), 7.49 (1H, s, H6), 6.16 (1H, t, H1'), 5.15 (1H, m, H3'), 4.33 (2H, m, H5', H5"), 4.24 (1H, m, H4'), 3.72 (6H, s, 2 x MeO), 2.40 (2H, m, H2',H2"), 1.78 (3H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 163.82 (C4), 155.04 (C=O), 154.56 (C=O), 150.60 (C2), 135.96 (C6), 110.22 (C5), 84.18 (C1'), 80.78 (C4'), 77.54 (C3'), 67.22 (C5'), 55.15 (2 x MeO), 35.62 (C2'), 12.33 (Me); Anal. Calcd for $C_{14}H_{18}N_2O_9$: C, 46.93; H, 5.06; N, 7.82. Found: C, 47.11; H, 5.16; N, 7.71.

Compound **7b**: Isolated yield 64%; mp 146-7°C; IR (KBr, cm^{-1}) 1747; $[\alpha]_{25}^{D}$ = +10.7 (c = 0.54, MeOH); ^{1}H-NMR (DMSO-d_6) δ 11.33 (1H, s, NH), 7.44 (1H, s, H6), 7.35 (5H, s, Ph), 6.20 (1H, t, H1'), 5.48 (1H, d, 3'-OH), 5.15 (2H, s, CH_2), 4.30 (3H, m, H3', H5', H5"), 3.94 (1H, m, H4'), 2.15 (2H, m, H2',H2"), 1.70 (3H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 163.86 (C4), 154.52 (C=O), 150.61 (C2), 136.00 (C6), 135.48 (Ph), 128.67 (Ph), 128.48 (Ph), 109.99 (C5), 83.99 (C1'), 83.59 (C4'), 70.25 (C3'), 69.39 (CH_2), 67.59 (C5'), 38.79 (C2'), 12.29 (Me); Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.59; H, 5.34; N, 7.41.

Compound **7c**: Isolated yield 61%; mp 147-8°C; IR (KBr, cm^{-1}) 1755; $[\alpha]_{25}^{D}$ = -7.8 (c = 0.5, MeOH); ^{1}H-NMR (DMSO-d_6) δ 11.32 (1H, s, NH), 7.44 (1H, s, H6), 7.05 (1H, dd, CH), 6.19 (1H, t, H1'), 5.47 (1H, d, 3'-OH), 4.91 (1H, dd, CH_2), 4.67 (1H, dd, CH_2), 4.38 (2H, m, H5', H5"), 4.27 (1H, m, H3'), 3.95 (1H, m, H4'), 2.15 (2H, m, H2',H2"), 1.78 (3H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 163.90 (C4), 152.15 (C=O), 150.06 (C2), 142.98 (CH), 136.06 (C6), 110.04 (C5), 98.68 (CH_2), 84.10 (C1'), 83.40 (C4'), 70.27 (C3'), 68.15 (C5'), 38.80 (C2'), 12.36 (Me); Mass spectra (70eV) m/z,%: 312 (M^+, 2), 127 (28), 81 (100), 43 (54); Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 49.90; H, 5.36; N, 9.11.

Compound **9c**: ^{1}H-NMR (DMSO-d_6) δ 11.41 (1H, s, NH), 7.51 (1H, s, H6), 7.06 (2H, dd, 2 x CH), 6.20 (1H, t, H1'), 5.29 (1H, m, H3'), 4.95 (2H, dd, 2 x CH_2), 4.73 (2H, dd, 2 x CH_2), 4.45 (2H, m, H5', H5"), 4.34 (1H, m, H4'), 2.46 (2H, m, H2',H2"), 1.78 (3H, s, Me); ^{13}C-NMR (DMSO-d_6) δ 163.82 (C4), 152.01 (C=O), 151.52 (C=O), 150.60 (C2), 142.95 (CH), 142.76 (CH), 136.04 (C6), 110.25 (C5), 98.87 (CH_2), 98.80 (CH_2), 84.28 (C1'), 80.34 (C4'), 78.22 (C3'), 67.76 (C5'), 35.44 (C2'), 12.34 (Me); Mass spectra (70eV) m/z,%: 382 (M^+, 1), 126 (9), 81 (100), 43 (22); Anal. Calcd for $C_{16}H_{18}N_2O_9$: C, 50.27; H, 4.75; N, 7.33. Found: C, 50.08; H, 4.56; N, 7.15.

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