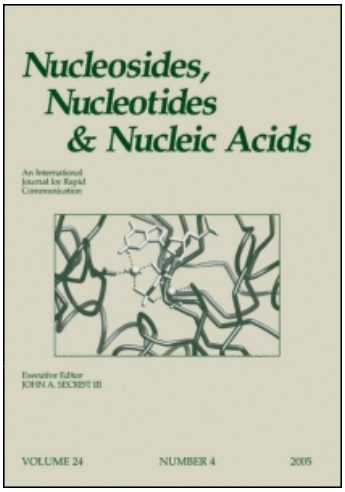

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A CONVENIENT APPROACH TO THE SYNTHESIS OF AZIDO-ACYCLIC NUCLEOSIDES

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Abstract

The azidation of unprotected acyclic nucleosides (4) was carried out in a one-pot reaction by means of the reagent triphenylphosphine-carbon tetraiodide-sodium azide to give the corresponding mono-azido-acyclic nucleosides (6) in good yields without by-products such as the di-azido-acyclic nucleosides.

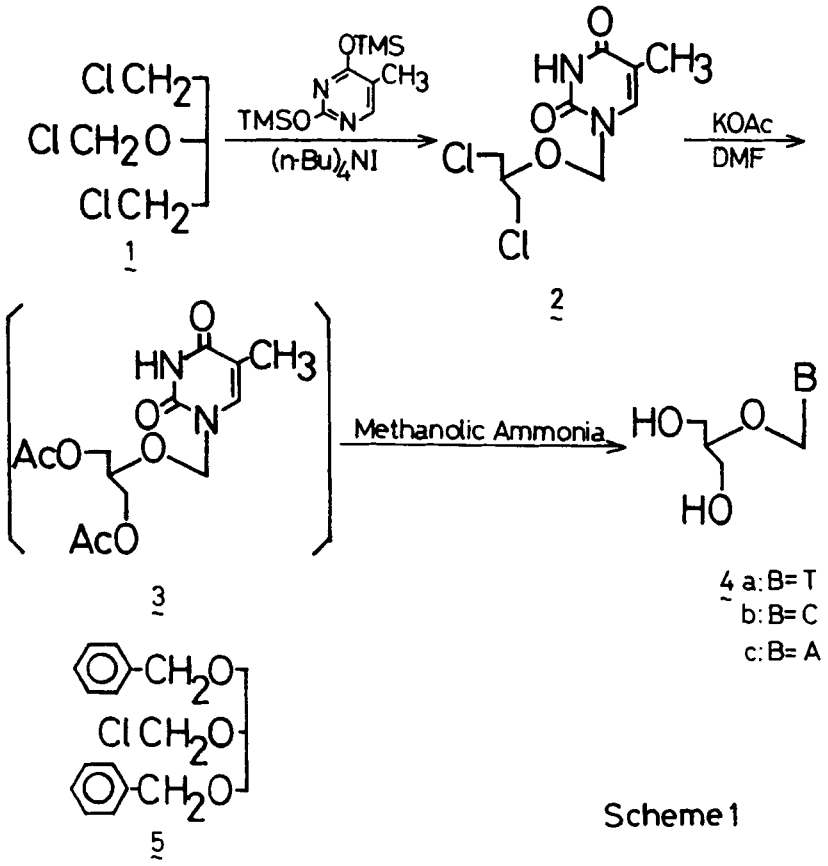
INTRODUCTION

A number of acyclic nucleoside analogues have been reported to be active against herpe simples virus.[1] Recently, we have also reported that some acyclic nucleoside cyclic phosphoroamidate derivatives showed inhibitory effects on the proliferation of tumor cells.[2] On the other hand, 3'-azido-2',3'-dideoxythymidine (AZT) is a potent and selective inhibitor of the replication of HIV, the human immunodeficiency virus responsible for AIDS.[3,4]

We now wish to report a convenient approach for the synthesis of azido-acyclic nucleoside derivatives (6), which were evaluated for their anti-HIV activity.

CHEMISTRY

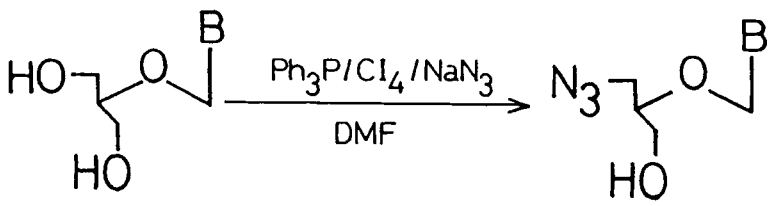
First, we examined the synthesis of acyclic nucleosides (4a) using the procedure of Ogilvie without the removal of benzyl groups of acyclic sugar moiety through catalytic hydrogenation (Scheme 1).[5] The chloromethyl derivative (1) was treated with trimethylsilylated thymine in the presence of n-Bu_4NI to give the corresponding product 2 in 42% yield. Compound 2 thus obtained was treated with potassium acetate in DMF to give the acetoxy derivative 3 which was then treated with methanolic



Scheme 1

ammonia to remove the acetyl groups. 1-[[2-Hydroxy-1-(hydroxymethyl)ethoxy]methyl]thymine (4a) was obtained in 10% yield after separation by silica gel chromatography. Compared with the route using compound 5 as a starting material, it is noted that yields of the desired acyclic nucleosides were undoubtedly low.

Next, we examined the direct conversion of unprotected acyclic nucleosides (4) to azido-acyclic nucleosides (6) using the procedure of Hata et al.[6]. Hata and coworkers reported[6] that the most effective combination was triphenylphosphine-carbon tetrabromide-lithium azide, which gave a good yield of 5'-azido-deoxythymidine. In this method, when sodium azide was used in place of lithium azide, 1-[[2-azido-1-(hydroxymethyl)-ethoxy]methyl]thymine (6a) was obtained in an unsatisfactory yield (12 %). More recently, Ogilvie et al.[7] reported that compound 4c was treated with a combination of triphenylphosphine-carbon tetrabromide-lithium azide to give the desired product 6c with



4 a: B=T
b: B=C
c: B=A

6 a: B=T
b: B=C
c: B=A

Scheme 2

9-[[2-azido-1-(azidomethyl)ethoxy]methyl]adenine as a by-product. However, we tried the reaction of 4a with triphenylphosphine-carbon tetraiodide-sodium azide in dry DMF at room temperature for 24 h; the corresponding azido-product (6a) was obtained in a good yield (75%) without by-products such as 1-[[2-azido-1-(azidomethyl)ethoxy]methyl]thymine. In a similar manner, the other azido-acyclic nucleosides (6b,c) were obtained in 66% and 68% yields, respectively. In these reactions, by-products such as cyclonucleosides were not detected at all.

Antiviral Activity

These compounds (6) have been evaluated for citotoxicity and inhibition of HIV replication in MT4 cells, but no activities were detected.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. Ultraviolet spectra were recorded on a Shimazu UV-200 spectrophotometer. The ^{1}H-NMR spectra were recorded on a JEOL JNM-MH 100 spectrometer in $CDCl_3$ with trimethylsilane as an internal standard. Thin-layer chromatography (t.l.c) was performed on plates of Kiesegel $60F_{254}$ (Merck). Column chromatography was performed on silica gel (BW-300; Fuji Davison Co. Ltd.).

1,3-Dichloro-2-chloromethoxypropane (1). This preparation is carried out by a modification of the procedure of Ogilvie et al.[5]. 1,3-Dichloro-2-propanol (14.8 ml, 155 mmol) was dis-

solved in CH_2Cl_2 (50 ml). Paraformaldehyde (9.8 g) was added and the mixture was cooled in an ice-salt bath. Dry HCl gas was bubbled into the solution with stirring for 8 h. Anhydrous $CaCl_2$ was added to the solution and the reaction mixture was filtered through Celite. The filtrate was evaporated in vacuo to give 24.8 g (90%) of compound 1 as a syrup. ^{1}H-NMR ($CDCl_3$) δ 3.75 (d, 4H, $\underline{CH_2}$-CH-$\underline{CH_2}$), 4.07 (m, 1H, CH_2-$\underline{CH}$-CH_2), 5.59 (s, 2H, CH_2Cl).

The product was used directly in coupling experiments without further purification.

1-[[2-Chloro-1-(chloromethyl)ethoxy]methyl]thymidine (2). Thymine (3.5 g, 27.7 mmol) was suspended in HMDS (20 ml) and ammonium sulfate (0.12 g, 0.9 mmol) was added. The mixture was heated under reflux temperature until a clear solution was obtained. The excess HMDS was removed under reduced pressure and the residue was dissolved in dry CH_2Cl_2 (30 ml) and 1 (12.3 g, 70 mmol) and $(n\text{-}Bu)_4NI$ (0.31 g, 0.83 mmol) were added. The solution was stirred at room temperature for 12 h. The mixture was quenched with addition of a mixture of MeOH and H_2O (4:1, v/v) and the solution was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (50 ml), washed with water(50 ml X 3), and dried over Na_2SO_4. The solvent was concentrated to a small volume (10 ml) and the solution was applied to a silica gel column which was eluted with a stepwise gradient of MeOH (0-10%) in CH_2Cl_2. The fractions containing the desired product were pooled and the solvent was evaporated in vacuo to give compound 3a (3.1 g, 42%) as a gum; UV λmax(MeOH) 264 nm; ^{1}H-NMR ($CDCl_3$) δ 1.91 (s, 3H, CH_3), 3.60 (s, 4H, $\underline{CH_2}$-CH-$\underline{CH_2}$), 3.90 (m, 1H, CH_2-$\underline{CH}$-CH_2), 5.20 (s, 2H, CH_2-N), 7.60 (s, 1H, H-6).
Anal. Calc. for $C_9H_{12}N_2O_3Cl_2$: C, 40,47; H, 4,53; N, 10,49. Found: C, 40,28; H, 4,31; N, 10.35.

Conversion of 2 to 4a. Compound 2 (1.87 g, 11.5 mmol) was mixed with potassium acetate (4.53 g, 46 mmol) in dry DMF (30 ml) and the reaction mixture was heated at reflux for 3 h under nitrogen atmosphere. The mixture was filtered through Celite. The filtrate was evaporated in vacuo and the residue was treated with methanolic ammonia for 6 h. The solution was concentrated under reduced pressure and the residue was applied to a silica gel column which was eluted with CH_2Cl_2-MeOH (9:1, v/v). The fractions containing the desired product were collected and the solvent was evaporated in vacuo. The residue was crystallized from MeOH to give compound 4a (270 mg, 10%); mp 159-160 °C (lit[8] mp 155-156 °C); UV λ max(H_2O, pH 7.0) 264; ^{1}H-NMR (DMSO-

d_6) δ 1.73 (s, 3H, CH_3); 3.47 (d, 4H, $\underline{CH_2}$-CH-$\underline{CH_2}$); 4.01 (m, 1H, CH_2-$\underline{CH}$-CH_2); 5.18 (s, 2H, CH_2N); 7.57 (s, 1H, H-6).

Direct conversion of 4 to 6. To a mixture of acyclic nucleosides (2.0 mmol), triphenylphosphine (1.05 g, 4.0 mmol), and sodium azide (1.3 g, 4.0 mmol) in dry DMF (40 ml) was added carbon tetraiodide (2.0 g, 4.0 mmol). The mixture was stirred at room temperature for 24 h, MeOH (1 ml) was added, the solvent was removed in vacuo, and chromatography on a column of silica gel [eluted with a stepwise gradient of MeOH (0-10%) in CH_2Cl_2] gave mono-azido derivatives 6. Yields were 6a, 75%; 6b, 66%, and 6c, 68%.

6a: mp: 105-106 °C; UV λmax (MeOH) 262 nm; IR (KBr) ν 2102 cm^{-1} (N_3); ^{1}H-NMR (DMSO-d_6) δ 1.68 (s, 3H, CH_3), 3.50 (d, 4H, $\underline{CH_2}$-CH-$\underline{CH_2}$), 4.15 (d, 1H, CH_2-$\underline{CH}$-CH_2), 4.84 (br s, 1H, OH), 5.19 (s, 1H, CH_2N), 7.60 (s, 1H, H-6). Anal. Calcd for $C_9H_{13}N_5O_3$: C, 45,18; H, 5.47; N, 29,28. Found: C, 45,31; H, 5.52; N, 29,18.

6b: mp: 213-215 °C; UV λmax(MeOH) 265 nm; IR (KBr) ν 2091 cm^{-1} (N_3); ^{1}H-NMR (DMSO-d_6) δ 3.60 (m, 5H, CH_2-CH-CH_2), 4.21 (m, 1H, OH), 5.35 (s, 2H, CH_2N), 5.82 (d, 1H, $J_{5,6}$=7.5 Hz, H-5), 7.69 (d, 1H, $J_{5,6}$=7.5 Hz, H-6). Anal. Calcd for $C_8H_{13}N_6O_2$: C, 42,66; H, 5.82; N, 37,32. Found: C, 42,39; H, 5.94; N, 37.41.

6c: mp 198-200°C (lit[7] mp: 200-204°C); UV λmax(MeOH) 259 nm; IR (KBr) ν 2100 cm^{-1} (N_3); ^{1}H-NMR (DMSO-d_6) δ 3.57 (m, 5H, CH_2-CH-CH_2), 4.00 (m, 1H, OH), 5.79 (s, 2H, CH_2N), 7.25 (br s, 2H, NH_2), 8.21 and 8.31 (s, 2H, H-2 and H-8). Anal. Calcd for $C_9H_{12}N_8O$: C, 43,54; H, 4,87; N, 45,14. Found: C, 43,61; H, 4,98; N, 45.25.

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