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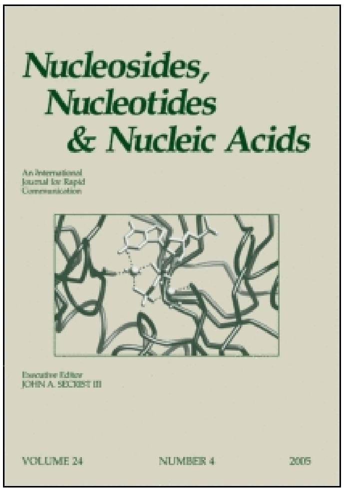

Nucleosides, Nucleotides and Nucleic Acids

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Unusual β-Elimination of Carbocyclic Ketonucleosides Catalyzed by Silica Gel

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UNUSUAL β-ELIMINATION OF CARBOCYCLIC KETONUCLEOSIDES CATALYZED BY SILICA GEL

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□ *β-elimination reactions occurred when carbocyclic ketonucleosides were treated with silica gel and α,β-unsaturated ketonucleosides were obtained. The positions of ketone groups did not affect the occurrance of the elimination reaction. The yields of the reaction were influenced by the properties of leaving groups.*

Keywords Carbocyclic nucleosides; elimination; silica gel

INTRODUCTION

Carbocyclic analogues of nucleosides have been of interest because these compounds sometimes had higher antiviral activities compared with the nucleosides with a "sugar" moieties and could usually avoid enzymatic degradation.[1] The analogues of carbocyclic nucleosides with a double bond inside or outside cyclopentane rings, such as Neplanocin A, Abcavir, and Entacavir, showed potent antiviral activities and low toxicities.[2] In some cases the antiviral activities of the carbocyclic nucleosides could be improved by the incorporation of such a double bond.

As a part of our program focused on the synthesis of carbocyclic nucleosides with a double bond outside the cyclopentane ring, **2a**, **b** were required as key intermediates. These two compounds were synthesized as shown in Scheme 1. The starting materials, **1c** and **1b**, were prepared by the known procedures.[3–5] *N*-Acetylation of **1c** produced **1a**. Compound **1a** and **1b** were oxidized with Dess-Martin reagents to obtain **2a**, **b**.[4,5] Surprisingly, when **2a** and **2b** were purified by column chromatography

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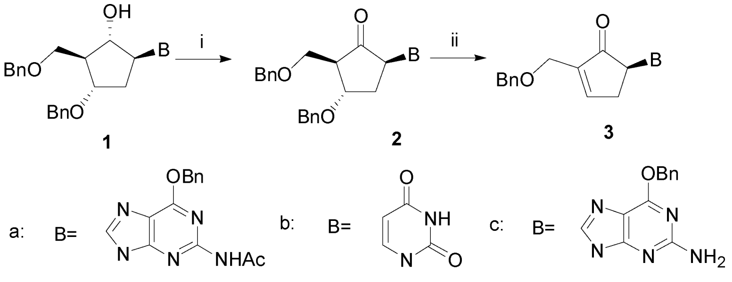
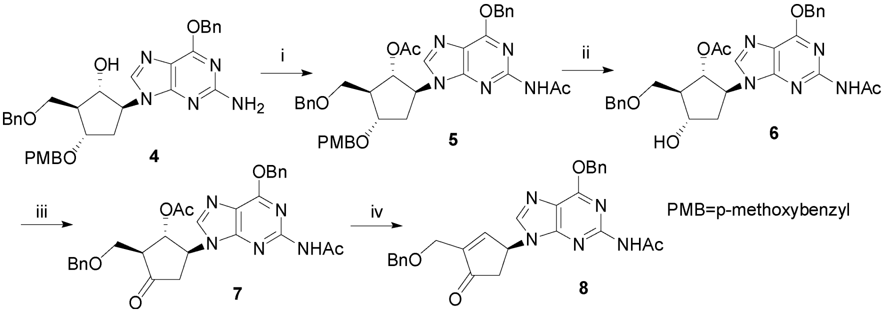


SCHEME 1 i, Dess-Martin reagent; ii, $CHCl_3$, silica gel.

with silica gel, compounds **3a**, and **3b** were isolated in 87% and 73% yields respectively. The same transformation could also be completed within one hour when compounds **2 a**, **b** were stirred with silica gel in $CHCl_3$.

The β-elimination of carbocyclic nucleosides in which the ketone groups were at the other positions was investigated as they were treated with silica gel. Compound **7** was designed and synthesized as shown in Scheme 2.



SCHEME 2 i, acetic anhydride, toluene, reflux; ii, DDQ, CH_2Cl_2, H_2 O; iii, Dess-Martin reagent, CH_2Cl_2, rt; iv, $CHCl_3$, silica gel.

Compound **4** was prepared by epoxide-opened reaction with O-benzylguanine.[6] After acetylating hydroxyl and amino groups, **5** was obtained. Compound **6** was synthesized by removal of the p-methoxybenzyl group of **5** with DDQ. Then **6** was oxidized with Dess-Martin reagent and **7** formed. Stirring **7** with silica gel in $CHCl_3$ for one hour produced **8** in 98% yield.

These results showed that the β-elimination could occur though the ketone groups at different positions in carbocyclic nucleoside. The properties of the leaving groups influenced the yields in this transformation. The easier the leaving groups removed, the higher the yields were. The reaction proceeded in high yield when the leaving group was acetoxy, but the yield became lower for the benzyloxy group because of its reduced leaving activity.

There were some examples for β-elimination reactions of ketonucleosides, the eliminated groups at β-position of ketone included fluoro[7] and acetoxy,[8] all occurring under alkaline or enzymatic conditions. No report was found that β-elimination of carbocyclic ketonucleosides could be catalyzed by silica gel.

In this program, it was speculated at first that the acidity of silica gel induced the β-elimination reactions, but no change occurred when compound **2a** was treated for 24 hours with acetic acid or trifluoroacetic acid respectively. It seemed that the absorption on silica gel was important for this transformation. But the mechanism of this reaction was still unclear.

EXPERIMENTAL

Dess-Martin reagents was purchased from J&K Chemical Ltd. (Beijing, China). The ^{1}H-NMR spectra were recorded on a Varian Inova 600 (600 MHz) spectrometer. FT-ICR and FAB mass spectral data were measured with Bruker Daltonics. Inc. (National Center of Biomedical Analysis, Beijing, China). Apex II mass spectrometer and ZabSped mass spectrometer (National Center of Biomedical Analysis, Beijing, China).

[1 S-(1α, 2β, 3α, 5β)]-5-[(2-Acetylamido)-6-(phenylmethoxy)-9 H-purin-yl]-3-(phenyl- methoxy)-2-[(phenylmethoxy)methyl]cyclopentanol (1a). To the stirred solution of [1S-(1α, 2β, 3α, 5β)]-5-[2-amino-6-(phenylmethoxy)-9H-purin-yl]-3-(phenylmethoxy)-2-[(phenylmethoxy)methyl] cyclopentanol (1c)$^{[3-5]}$ (1 g, 1.81 mmol) in dry toluene (60 ml) at 60°C was added acetic anhydride (5 ml, 54.3 mmol) and the mixture was refluxed for 2 hours. The solvent was evaporated and the residue was dissolved in MeOH (100 ml). The solution was cooled in an ice-water bath and KOH (0.3 g, 4.39 mmol) was added. The mixture was stirred for 3 hours at 0–5°C, then the solvent was evaporated and the residue was extracted with water (100 ml)/ethyl acetate (200 ml) system. Organic phase was separated and dried with magnesium sulfate. After evaporating, **1a** (1.05 g, 99%) was obtained as a pale yellow gum. ^{1}H-NMR($CDCl_3$) δ 8.04–8.03 (d, 1H), 7.73 (s, 1H),7.46–7.24 (m, 15H), 5.58–5.51 (m, 2H),4.74–4.70 (m, 1H), 4.58–4.49 (m, 4H), 4.38–4.35 (t, 1H), 4.04–4.02 (t, 1H), 3.70–3.63 (m, 2H), 2.57–2.51 (m, 2H), 2.34–2.30 (m, 4H). Maldi-tof-MS m/z: $M+H^+$, 594.3. $C_{34}H_{35}N_5O_5$ requires $M+H^+$, 594.6.

5S-5-[(2-Acetylamido)-6-(phenylmethoxy)-9H-purin-yl]-2-en-2-[(phenylmethoxy)methyl]cyclopentanone (3a). Dess-Martin reagent (15% by weight, 3.9 ml, 2.04 mmol) was added to dry CH_2Cl_2 (15 ml) under N_2, and then dry *t*-butanol (0.19 ml, 2.04 mmol) was injected to the solution and stirred for 15 minutes at room temperature. A solution of **1a** (0.93 g, 1.57 mmol) in dry CH_2Cl_2 (15 ml) was added via cannula. The mixture was stirred under N_2 at rt for 1 hour and TLC showed **1a** was consumed. The mixture was diluted with 100 ml $CHCl_3$ and stirred vigorously with 10% sodium sulfite solution-saturated sodium bicarbonate solution (1:1, 150 ml) for 1 hour. The organic phase was separated and treated with silica gel (10 g) for 2 hours, and TLC showed that **2a** was disappeared. The mixture was filtered and the filtrate was concentrated to about 10 ml, then it was separated by column chromatography (chloroform-methanol, 100:1) and **3a** (0.66 g, 87%) was obtained as a pale yellow gum. [α] $^{20}{}_{D}$ = +8.4° (c 1.0, $CHCl_3$); ^{1}H-NMR($CDCl_3$,) δ 8.01 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.47–7.26 (m, 10H), 5.55 (s, 2H), 4.98–4.97 (q, 1H), 4.61 (s, 2H), 4.29–4.23 (m, 2H), 3.29–3.25 (q, 1H), 3.09–3.06 (d, 1H), 2.40 (s, 3H); ^{13} C-NMR($CDCl_3$) δ 200.1, 160.8, 156.5, 152.3, 151.9, 142.3, 141.2, 137.5, 135.7, 128.4, 128.4, 128.1, 128.1, 127.9, 127.7, 117.9, 73.4, 68.7, 63.8, 57.5, 33.8, 24.9; FT-ICRMS m/z M+H$^+$, 484.1983. Calc. for $C_{27}H_{26}N_5O_4$.

1S-1-[2-oxo-3-en-3-[(Phenylmethoxy)methyl]cyclopentyl]-2,4(1H, 3H)-pyrimidinedion (3b). [1 S-(1α, 2β, 3α, 4β)]-1-[2-Hydroxy-4-(phenymethoxy)-3-[(phenylmethoxy)methyl] cyclopentyl]-2,4(1H,3H)-pyrimidinedion (**1b**)[3,4] was treated with Dess-Martin reagent and silica gel successfully as **1a** was treated, **3b** was obtained in 73% yield as amorphous solid; [α] $^{20}{}_{D}$ = +5.8° (c 1.0, $CHCl_3$); ^{1}H-NMR($CDCl_3$,) δ 8.37 (br, 1H), 7.62 (s, 1H), 7.37–7.29 (m, 5H), 6.97–6.96 (d, 1H), 5.74–5.73 (q, 1H), 4.61–4.59 (t, 3H), 4.26–4.25 (m, 2H), 3.18–3.13 (m, 1H), 2.84–2.79 (m, 1H); FAB-MS m/z calcd for M+H$^+$ 313.3, found 313.0.

[1S-(1α, 2β, 3α, β)]-N-Acetyl-6-(phenylmethoxy)-9-[2-acetoxy-4-(4-methoxybenzyloxy)-3-[(phenylmethoxy)methyl]cyclopentyl]-9H-purin-2-amine (5). To a stirred solution of [1S-(1α, 2β, 3α, 5β)]-5-[2-amino-6-(phenylmethoxy)-9H-purin-yl]-3-(4-methoxybenzyloxy)-2-[(phenylmethoxy)methyl]cyclopentanol (**4**) (1 g, 1.72 mmol) in pyridine (20 ml), DMAP (0.05 g) and acetyl chloride (0.5 ml, 6.88 mmol) were added, then the mixture was stirred for 2 hours at rt and stood overnight. Pyridine was evaporated in vacuo. The residue was dissolved in chloroform (200 ml) and washed successively with saturated aqueous sodium bicarbonate solution (100 ml) and brine (250 ml). After dried with magnesium sulfate and evaporated, **5** (1.12 g, 96%) was obtained as a white amorphous solid.

[1S-(1α, 2β, 3α, 4β)]-4-[(2-Acetylamido)-6-(phenylmethoxy)-9H-purin-yl]-3-acetoxy-2-[(phenylmethoxy)methyl]cyclopentanol (6). To a stirred solution of **5** (1.1 g, 1.65 mmol) in dichloromethane-H_2O (19:1, 40 ml), DDQ (0.56 g, 2.48 mmol) was added. The mixture was stirred vigorously for 14 hours, then was diluted with CH_2Cl_2 (100 ml) and washed with saturated aqueous sodium bicarbonate solution (100 ml). The aqueous solution was extracted with CH_2Cl_2 (100 ml), the combined organic phase was dried by magnesium sulfate. After evaporated, a dark oily residue was produced, which was purified by column chromatography (chloroform-methanol, 20:1) and **6** (0.72 g, 80%) was obtained as a yellow amorphous solid. ^{1}H-NMR($CDCl_3$)δ 7.83 (br, 1H), 7.77 (s, 1H), 7.48–7.26(m, 10H), 5.58 (s, 2H), 5.56–5.54 (t, 1H), 5.04–5.00 (q, 1H), 4.56 (s, 2H), 4.52–4.50 (q, 1H), 3.77–3.75 (q, 1H), 3.68–3.65 (t, 1H), 2.70–2.65 (m, 1H), 2.54 (s, 3H), 2.34–2.27 (m, 2H), 1.95 (s, 3H). FAB-MS m/z M+H$^+$, 546.2. $C_{29}H_{31}N_5O_6$ requires M+H$^+$, 546.6.

4S-4-[(2-Acetylamido)-6-(phenylmethoxy)-9H-purin-yl]-2-en-2-[(phenylmethoxy)methyl]cyclopentanone (8). Compound **6** (0.4 g, 0.74 mmol) was oxidized with the same procedure as **1a**, then treated with silica gel (10 g). Compound **8** (0.35 g, 98%) was obtained as a yellow gum. $[\alpha]\ ^{20}{}_{D} = +6.5°$ (c 1.0, $CHCl_3$); ^{1}H-NMR($CDCl_3$,) δ 8.03 (br, 1H), 7.76 (s, 1H), 7.51–7.26 (m, 10H), 5.72–5.71 (m, 1H), 5.60 (s, 2H), 4.62 (s, 2H), 4.32–4.32 (t, 2H), 3.17–3.13 (q, 1H),2.76–2.72 (dd, 1H), 2.49 (s, 3H), 2.09 (s, 1H); FAB-MS m/z calcd for $M+H^+$ 484.2, found 484.5.

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