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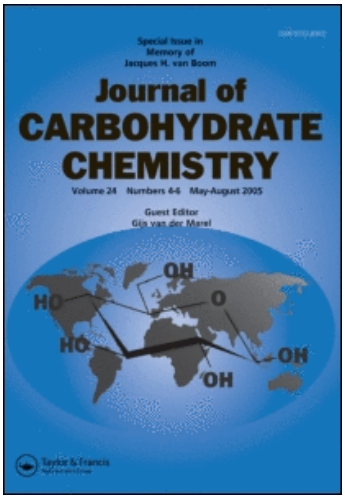

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Selective Deprotection of Fully Benzoylated Nucleoside Derivatives

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Selective Deprotection of Fully Benzoylated Nucleoside Derivatives

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CONTENTS

ABSTRACT

Selective deprotection of benzoylated hydroxyl groups is one of the crucial problems in the synthesis of nucleoside analogues as well as of other polyfunctional molecules.

Key Words: Selective deprotection; Benzoylated groups; Nucleoside analogues.

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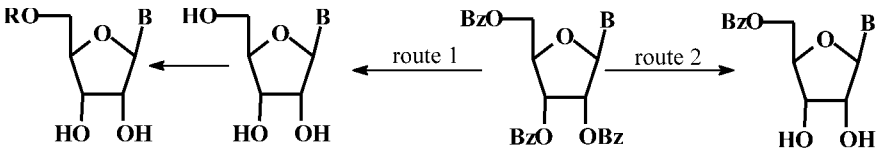

Scheme 1. Access to 2′,3′-dihydroxy nucleosides.

RESULTS AND DISCUSSION

So far, two methods have been reported for the preparation of 2′,3′-dihydroxy nucleosides (Sch. 1).

The first method includes at least two steps (route 1). First, protecting acyl groups are removed by treatment with a solution of sodium methoxide or ammonia in methanol at rt.[1] Then the primary hydroxyl function at C-5′ of the sugar residue is protected selectively, for instance by silylation. This reaction is highly selective if bulky protecting groups, such as *tert*-butyldiphenylsilyl (TBDPS) or *tert*-butyldimethylsilyl (TBDMS), are used.[2,3] The other option is to deprotect selectively the 2′ and 3′ positions (route 2). Only one method, reported by Nishino et al.,[4] has appeared in the literature. Benzoyl groups protecting secondary hydroxyls are removed selectively in THF in the presence of powdered sodium methoxide. The mixture has to be rigorously dried otherwise a complete deprotection of the hydroxyl groups occurs.

During the course of our investigations on the synthesis of nucleoside analogues, we became interested in the selective deprotection of benzoylated secondary hydroxyl groups. As reported above, total deprotection is well described by using ammonia in methanol. However, we have found that secondary hydroxyl groups can be efficiently and selectively generated from their benzoylated form by controlling the amount of NH_3, reaction time and temperature (see Table 1). This method requires no particular precaution and implies an easy workup (concentration of the reaction mixture) unlike the method with sodium methoxide. The reaction is stopped by evaporation (under reduced pressure) in an ice bath. The applicability of this selective deprotection reaction to benzoylated nucleoside analogues was investigated using nucleoside derivatives **1–3** (see Fig. 1).

Table 1. Selective debenzoylation of compounds **1**–**4**.

Entry	Substrate[a]	NH_3 (eq)	Time (hr)	Temperature (°C)	Product	Yield (%)[b]
1	**1**	25[c]	12	−15	**5**	68
2	**2**	25[c]	6	22	**6**	70
3	**3**	25[c]	6	−15	**7**	65
4	**4**	1.5[d]	6	22	**8**	65

[a]Conditions: substrate 0.5 mmol, solvent: MeOH (2 mL).
[b]Yield after purification by PLC.
[c]Eq per benzoyl protecting secondary hydroxy group, solution of ammonia (7 N).
[d]Eq per acetyl group.

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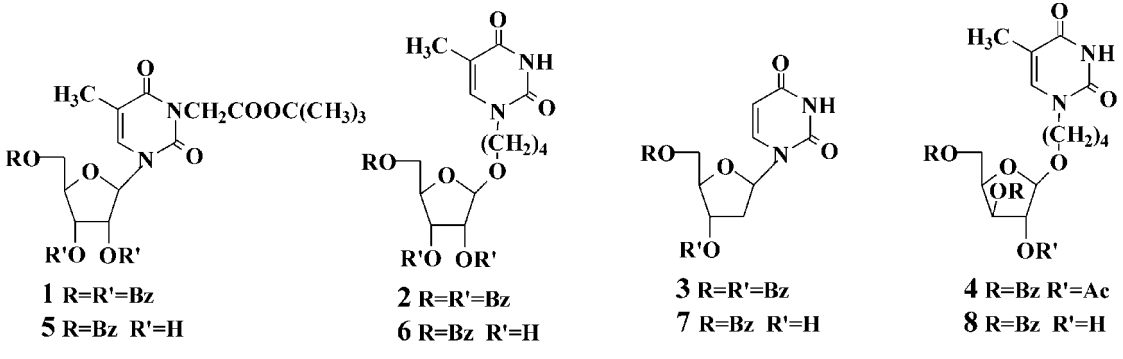
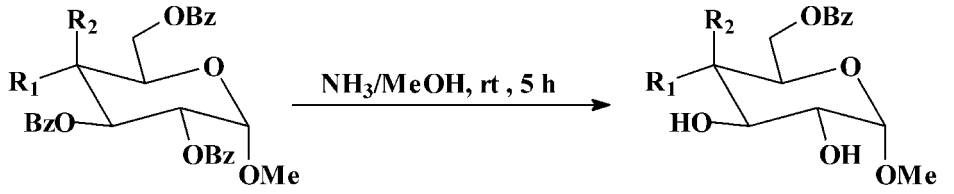


Figure 1. Starting acylated nucleosides and corresponding products.



9 $R_1 = OBz$; $R_2 = H$ **11** $R_1 = OH$; $R_2 = H$

10 $R_1 = H$; $R_2 = OBz$ **12** $R_1 = H$; $R_2 = OH$

Scheme 2. Selective debenzoylation of compounds **9** and **10**.

In every case, the reaction was checked by TLC and stopped as soon as the trihydroxyl derivative appeared. After evaporation, the crude products were easily separated by preparative thin layer chromatography (silica gel, CH_2Cl_2/EtOH) and the main product[a] was isolated in good yield as shown in Table 1.

At rt, compound **2** yielded the partially deprotected nucleoside **6** in an acceptable yield (70%). The selective debenzoylation of compounds **1** and **3** at rt always gave the deprotected compounds **5** and **7** only in low yields also by varying the amounts of ammonia. The best results were obtained at $-15°C$ using 25 eq of ammonia

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[a] ^{1}H NMR data follow: **5** (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, *t*-Bu), 1.68 (bs, 3H, CH_3), 4.27 (dd, $J = 4$, 5 Hz, 1H, H-2′), 4.33 (t, $J = 5$ Hz, 1H, H-3′), 4.42 (m, 1H, H-4′), 4.53 (d, $J = 16.3$ Hz, 1H, CH_2), 4.54 (dd, $J = 3.8$, 12.5 Hz, 1H, H-5′), 4.58 (d, $J = 16.3$ Hz, 1H, CH_2), 4.74 (dd, $J = 2.5$, 12.5 Hz, 1H, H-5′), 5.82 (d, $J = 4$ Hz, 1H, H-1′), 7.3 (bs, 1H, H-6), 7.6 (m, 5H, Har). **6** (400 MHz, $CDCl_3$): δ 1.53 (m, 2H, CH_2), 1.68 (m, 2H, CH_2),1.89 (s, 3H, CH_3), 3.40 (dt, $J = 6.3$, 9.6 Hz, 1H, CH_2), 3.66 (t, $J = 7.7$ Hz, 2H, CH_2), 3.75 (dt, $J = 6.3$, 9.6 Hz, 1H, CH_2), 4.12 (d, $J = 4.7$ Hz, 1H, H-2′), 4.28 (dd, $J = 4.7$, 6.6 Hz, 1H, H-3′), 4.42 (m, 1H, H-4′), 4.44 (dd, $J = 5.7$, 12 Hz, 1H, H-5′), 4.58 (dd, $J = 3.5$, 12 Hz, 1H, H-5′), 5.0 (s, 1H, H-1′), 6.95 (s, 1H, H-6), 7.41 (t, $J = 7.7$ Hz, 2H, Har), 7.54 (t, $J = 7.5$ Hz, 1H, Har), 8.05 (t, $J = 7.5$ Hz, 2H, Har), 9.79 (s, 1H, N-H). **7** (400 MHz, DMSO): δ 2.56 (ddd. $J = 3.2$, 6.4, 14.4 Hz, 1H, H-2′); 2.64 (dd, $J = 7.2$, 14.4 Hz, 1H, H-2″); 4.51 (m, 1H, H-4′); 4.58 (dd, $J = 5.0$, 11.6 Hz, 1H, H-5′); 4.62 (dd, $J = 4.8$, 11.6, 1H, H-5′); 5.5 (m, 1H, H-3); 5.7 (d, $J = 8.0$ Hz, 1H, H-5); 6.28 (dd, $J = 6.8$, 7.2 Hz, 1H, H-1′); 7.72 (d, $J = 8.0$ Hz, 1H, H-6); 7.8 (m, 5H, Har). **8** (400 MHz, $CDCl_3$): δ 1.61 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 1.86 (d, $J = 0.84$ Hz 3H, CH_3), 3.50 (dt, $J = 6.10$, 9.64 Hz, 1H, CH_2), 3.65 (m, 2H, CH_2), 3.85 (dt, $J = 5.58$, 9.64 Hz, 1H, CH_2), 4.44 (bd, $J = 2.6$ Hz, 1H, H-2′), 4.62 (dd, $J = 5.9$, 12 Hz, 1H, H-5′), 4.63 (dd, $J = 5.9$, 12 Hz, 1H, H-5′), 4.88 (q, $J = 6$ Hz, 1H, H-4′), 5.07 (d, $J = 1$ Hz, 1H, H-1′), 5.42 (dd, $J = 2.6$, 6.2 Hz, 1H, H-3′), 6.88 (d, $J = 0.84$ Hz, 1H, H-6), 7.39 (m, 4H, Har), 7.54 (m, 2H, Har), 8.00 (m, 4H, Har), 8.99 (s, 1H, N-H). **11** (400 MHz, $CDCl_3 + CD_3OD$): δ 3.4 (dd, 1H, $J = 1.0$, 9.0 Hz, H-4), 3.42 (s, 3H, CH_3O), 3.45 (dd, $J = 3.7$, 9.2 Hz, 1H, H-2), 3.67 (t, $J = 9.2$ Hz, 1H H-3), 3.86 (ddd, $J = 2.1$, 6.0, 9.96 Hz, H-5), 4.45 (dd, $J = 6.0$, 11.8 Hz, 1H H-6a), 4.64 (dd, $J = 2.1$, 11.8 Hz, 1H, H-6b), 4,69 (d, $J = 3.7$ Hz, 1H, H-1), 7.47 (tt, $J = 1.5$, 7.5 Hz, 2H, Har), 7.60 (tt, $J = 1.5$, 7.5 Hz, 1H, Har), 8.04 (dd, $J = 1.5$, 7.5 Hz, Har). **12** (400 MHz, $CDCl_3 + CD_3OD$): δ 3.41 (s, 3H, CH_3O), 3.78 (dd, $J = 3.1$, 10.1 Hz, 1H, H-3), 3.83 (dd, $J = 3.5$, 10.1 Hz, 1H, H-2), 3.97 (dd, $J = 0.9$, 3.1 Hz, 1H, H-4), 4.13 (ddd, $J = 0.9$, 4.9, 7.5 Hz, H-5), 4.48 (dd, $J = 4.9$, 11.4 Hz, 1H, H-6a), 4.53 (dd, $J = 7.5$, 11.4 Hz, 1H, H-6b), 4,76 (d, $J = 3.5$ Hz, 1H, H-1), 7.47 (tt, $J = 1.5$, 7.5Hz, 2H, Har), 7.60 (tt, $J = 1.5$, 7.5 Hz, 1H, Har), 8.04 (dd, $J = 1.5$, 7.5 Hz, Har).

per benzoyl protected secondary hydroxyl group (Table 1, entries 1 and 3). The composition of the final mixture was analyzed and the compound structures were determined by 400-MHz ^{1}H NMR spectroscopy. In any case, about 10% of starting nucleosides and 5% of the fully deprotected product remained. By comparison with the starting nucleosides, ^{1}H NMR data show an important shielding in low field (-1.5 ppm) for H-2′ and H-3′.

In order to investigate the effect of selective deprotection, acetylated nucleoside **4** was used (Fig. 1). An excess of ammonia increased a ratio of the 2′,3′-deprotected nucleoside. However, the use of 1.5 eq of ammonia in methanol at rt, yielded the selective deacetylated nucleoside **8** in 65% yield (Table 1, entry 4). The IR spectrum displays the expected hydroxyl band at 3400 cm^{-1}. ^{1}H NMR indicates the disappearance of the acetyl proton and the presence of two benzoyl groups.

This new method offers an easy access to 2′,3′ unprotected nucleosides in good yields. Noteworthy, we equally succeeded in deprotecting acetylated secondary hydroxyl group at C-2′ without affecting the benzoyl group at C-3′.

In order to evaluate to what extent this method can be generalized, we used it for selectively deprotecting methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (**9**) and methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranoside (**10**). In agreement with our results in the nucleoside series, using 25 eq of ammonia per benzoyl protected secondary hydroxyl group at rt during 5 hr, we obtained compounds **11** and **12** in 65% yield (Sch. 2).

In summary, these results indicate for the first time that the use of a well-define concentration of ammonia and a specific reaction temperature resulted in selective debenzoylation of secondary hydroxyl groups. The convenient method disclosed herein does not need any specific treatment or precaution. As exemplified, the present strategy may be easily used for other carbohydrate derivatives.

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REFERENCES

1. Holy, A. Nucleic acid components and their analogs. Preparation of 2′-deoxy-L-ribonucleosides of the pyrimidine series. Collect. Czech. Chem. Comm. **1972**, *37* (12), 4072–4087.
2. Hanessian, S.; Lavallee, P. Preparation and synthetic utility of *tert*-butyldiphenylsilyl ethers. Can. J. Chem. **1975**, *53* (19), 2975–2977.
3. Corey, E.J.; Venkateswarlu, A. Protection of hydroxyl groups as *tert*-butyldimethylsilyl derivatives. J. Am. Chem. Soc. **1972**, *94* (17), 6190–6191.
4. Nishino, S.; Rahman, M.A.; Takamura, H.; Ishido, Y. Partial protection of carbohydrate derivatives. Part 18. Simple preparative procedure for 5′-*O*-acylribonucleosides; highly regioselective O-deacylation at 2′ and 3′ positions of fully acylated purine and pyrimidine ribonucleosides with the sodium methoxide-THF system. Tetrahedron **1985**, *41* (23), 5503–5506.

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