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Selective deacetylation using iodine–methanol reagent in fully acetylated nucleosides

Bo Ren, Li Cai, Liang-Ren Zhang, Zhen-Jun Yang and Li-He Zhang*

State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing 100083, PR China

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Abstract—Selective deprotection of primary acetyl ester in nucleosides and carbohydrates using 1% iodine–methanol solution (w/v) was described and the mechanism was also discussed.

5′-Hydroxyl of acetylated nucleosides or 6-hydroxyl of acetylated carbohydrates are key intermediates in the preparation of many biological active molecules.[1–3] In general, 5′-hydroxyl of acetylated nucleosides were obtained by selective protection of the 5′-hydroxyl first and followed by a multi-steps protection and deprotection (Scheme 1, method I). Regioselective deacetylation of fully protected nucleosides or carbohydrates had been investigated by several groups.[4–8] Nudelman[5] et al. reported selective deacetylation of anomeric sugar acetates with tin alkoxides, however, a mixture of 5′-hydroxyl and 3′-hydroxyl nucleoside was obtained in poor yield. Recently, Orita[6] et al. reported the high selective deacetylation of peracetylated carbohydrates with neutral $[t\mathrm{Bu_2SnOH(Cl)}]_2$, and also 5′-hydroxyl uridine and cytidine could be obtained in 89% and 77% yields, respectively (Scheme 1, method II). In addition, enzymatic methods had been used for selective deprotection of acetyl ester in nucleosides and carbohydrates,[9–11] even though the application is not yet widely available. Herein, we reported a new method for the facile regioselective deacetylation of fully acetyl protected nucleosides or carbohydrates in the presence of 1% (w/v) solution of iodine in methanol to give 5′-hydroxyl nucleosides or 6-hydroxyl carbohydrates in good yields.

The reaction system, iodine and methanol, was used to open oxirane rings then the same group described the application for the cleavage of acetals and dithioacetals in carbohydrates.[12] Ronald et al. reported that 5′-trityl group in nucleosides and carbohydrates could be removed with a solution of iodine in methanol.[13] We found that this system could cleave the trityl ether in the described condition. Furthermore, when the reaction was carried out at a higher temperature and longer time, this reagent could also remove the acetyl group at the other position of carbohydrate. After optimization of the reaction condition, peracetylated nucleosides **I**–**IV** and 3,4,6-tri-*O*-acetyl carbohydrates **VI**–**VIII** were treated with this system to give 5′-hydroxyl acetylated nucleosides **1**–**4** and 6-hydroxyl of protected carbohydrates **6**–**8** in reasonable yields (Table 1).

Fully acetyl protected nucleoside (0.100 g, 0.27 mmol) was dissolved into a solution of I_2 (200 mg, 0.79 mmol) in methanol (20 mL). The solution was heated and TLC (dichloromethane/methanol, 18:1) was used to monitor the reaction. Upon completion, a small quantity of sodium thiosulfate was added to quench the reaction. The solvent was removed and the residue was purified by column chromatography on silica gel (dichloromethane/methanol, 50:1) to give 5′-hydroxy-2′,3′-di-*O*-acetylnucleoside **1**–**4**.[14] The same procedure for the selective deacetylation of compounds **VI**-**VIII** gave compounds **6**–**8**.[14] All of the compounds (**1**–**8**) were identified by ^{1}HNMR and specific rotatory power compared to the authentic compounds.

Interestingly, when N^6-acetyl-2′,3′,5′-tri-*O*-acetyl-cytidine **V** was treated with 1% iodine in methanol at reflux for 5 h, a high yield of 2′,3′,5′-tri-*O*-acetyl cytidine **5**[14] was obtained. The selective deacetylation was carried

* Corresponding author. Tel.: +86 10 82801700; fax: +86 10 82802724; e-mail: zdszlh@mail.bjmu.edu.cn

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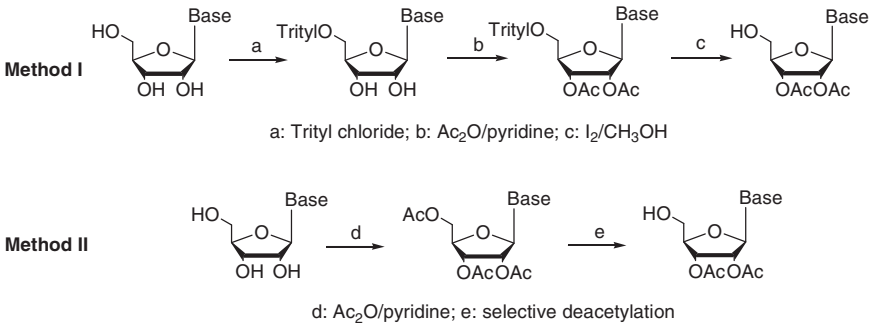


Scheme 1.

Table 1. Selective deacetylation of protected nucleosides and carbohydrates

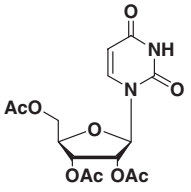
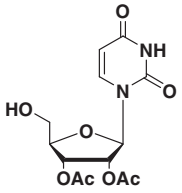
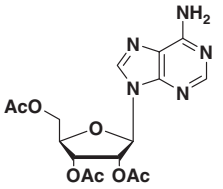
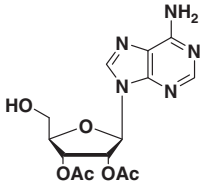
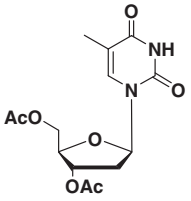
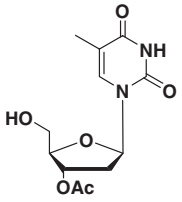
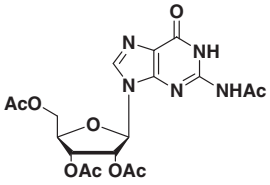
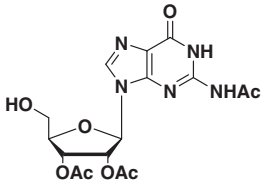
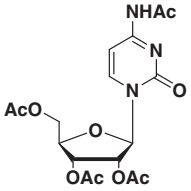
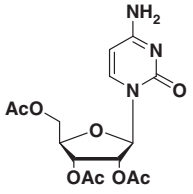
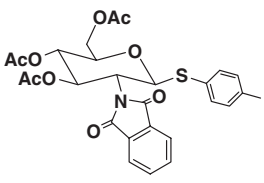
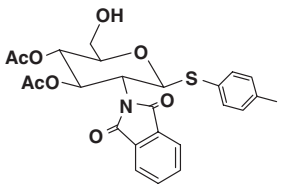
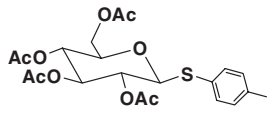
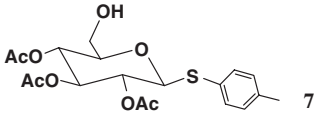
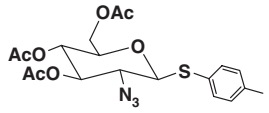
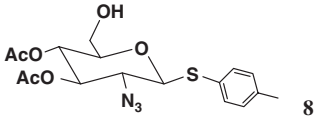
Compd	Substrate	Reaction temp. (°C)	Reaction time (h)	Product	Yield[a] (%)
I		68 °C[b]	14.5	 **1**	69
II		75–80 °C[c]	40	 **2**	60.5
III		78 °C[b]	9.5	 **3**	57.4
IV		67 °C[c]	30	 **4**	55.1
V		Reflux[b]	5	 **5**	78
VI		70 °C[b]	5.5	 **6**	42.8

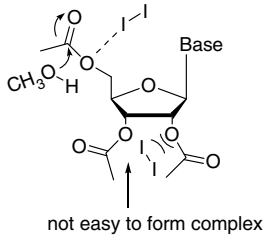
Table 1 (*continued*)

Compd	Substrate	Reaction temp. (°C)	Reaction time (h)	Product	Yield[a] (%)
VII		70 °C[b]	5.5	 **7**	38
VIII		70 °C[b]	5.5	 **8**	41

[a] Isolated yield.
[b] Open system.
[c] Closed system.

out at N^6 position and a small amount of 5-iodo-2′,3′,5′-tri-*O*-acetyl-cytidine was afforded as side product.

The mechanism of the reactions of acetal cleavage and deprotection of trityl group in carbohydrates by iodine–methanol reagent was proposed to be electrophilic attack of iodine on oxygen[12] or acid-catalyzed cleavage.[13] In our case, we found that the reaction can be carried out in the presence of base, therefore, the reaction is not an acid-catalyzed cleavage. We suggested that the deacetylation by iodine–methanol presumably involved initially a complexation of an iodine species with one of the oxygen atoms of the primary acetate in nucleoside and a subsequent nucleophilic attack with methanol would lead to the free alcohols. The steric hindrance of 2- and 3-*O*-acetyl- position may lead the selectivity (Scheme 2). Proposed mechanism:



Scheme 2.

In summary, we reported a selective deprotection of primary acetyl ester in nucleosides and carbohydrates using 1% iodine–methanol solution (w/v) in good yields. An iodine–acetate complex may involve in the mechanism of this reaction.

Acknowledgements

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Compd **4**: N^2-acetyl-2′,3′-di-*O*-acetylguanosine ^{1}H NMR (DMSO-d_6): δ 12.08 (br s, 1H), 11.73 (br s, 1H), 8.30 (s, 1H), 6.06 (d, 1H, $J = 7.0$ Hz, 1′-H), 5.75 (dd, 1H, $J = 7.0$, 5.5 Hz, 2′-H), 5.46 (dd, 1H, $J = 5.0$, 2.0 Hz, 3′-H), 5.39 (t, 1H, $J = 5.0$ Hz, –OH), 4.22 (d, 1H, $J = 2$ Hz, 4′-H), 3.64–3.73 (m, 2H, 5′-H), 2.19 (s, 3H), 2.13 (s, 3H), 1.99 (s, 3H).
Compd **5**: Saladino, R.; Mincione, E.; Crestini, C.; Mezzetti, M. *Tetrahedron* **1996**, *52*, 6759–6780.
Compd. **6**: *p*-methylphenyl 2-deoxy-2-phthalimido-3,4-di-*O*-acetyl-6-hydroxy-1-thio-β-D-glycopyranoside. ^{1}H NMR (DMSO-d_6): δ 7.91–7.94 (m, 4H, arom.), 7.26 (d, 2H, $J = 8.1$ Hz, arom.), 7.10 (d, 2H, $J = 8.1$ Hz, arom.), 5.68 (d, 1H, $J = 10.5$ Hz, 1-H), 5.63 (t, 1H, J=10.5Hz, 4-H), 4.94–5.03 (m, 2H, 3-H and –OH), 4.16 (t, 1H, J=10.5 Hz, 2-H), 3.57–3.60 (m, 1H, 5-H), 3.43–3.51 (m, 2H, 6-H), 2.26 (s, 3H), 2.00 (s, 3H), 1.77 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.1, 167.9, 138.9, 134.4, 134.3, 133.9, 131.2, 129.8, 126.8, 123.7, 83.0, 78.2, 71.5, 69.0, 61.6, 53.8, 21.2, 20.7, 20.4. Anal. Calcd for $C_{25}H_{25}NO_8S$: C, 60.11; H, 5.04; N, 2.80. Found: C, 60.03; H, 5.11; N, 2.75.

Compd. **7**: *p*-methylphenyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glycopyranoside.^{1}H NMR (DMSO-d_6): δ 7.37 (d, 2H, $J = 8.1$ Hz, arom.), 7.16 (d, 2H, $J = 8.1$ Hz, arom.) 5.29 (t, 1H, $J = 9.3$ Hz, 3-H), 5.14 (d, 1H, $J = 9.9$ Hz, 1-H), 4.85 (t, 1H, $J = 9.6$ Hz, 2-H), 4.82–4.88 (m, 1H, 6-OH), 4.75 (t, 1H, $J = 9.6$ Hz, 4-H), 3.74–3.81 (m, 1H, 5-H), 3.34–3.53 (m, 2H, 6-H), 2.30 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H).

Compd **8**: *p*-methylphenyl 2-deoxy-2-azido-3,4-di-*O*-acetyl-1-thio-β-D-glycopyranoside.^{1}H NMR (DMSO-d_6): δ 7.42 (d, 2H, $J = 8.1$ Hz, arom.), 7.18 (d, 2H, $J = 8.1$ Hz, arom.), 5.74 (d, 1H, $J = 6.0$ Hz, 1-H), 5.08 (t, 1H, $J = 9.6$ Hz, 3-H), 4.96 (t, 1H, $J = 9.6$ Hz, 4-H), 4.83–4.87 (m, 1H, 6-OH), 4.41 (dd, 1H, $J = 10.2$, 5.7 Hz, 2-H), 4.19–4.22 (m, 1H, 5-H), 3.31–3.53 (m, 2H, 6-H), 2.30 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H).