Tetrahedron Letters, Vol. 34, No. 30, pp. 4835-4836, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Reductive Cleavage of the Ribose Moiety in Purine Nucleosides Using Diisobutylaluminum Hydride: A New Method for the Preparation of Acyclonucleosides

Yukio Kitade, Kosaku Hirota, and Yoshifumi Maki
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University,
5-6-1 Mitahora-higashi, Gifu 502, Japan

Abstract: Reaction of purine nucleosides, such as 2',3'-*O*-isopropylideneinosine **1a** and 2',3'-*O*-isopropylideneadenosine **1c**, with diisobutylaluminum hydride in dry tetrahydrofuran resulted in the reductive cleavage of the ribose moiety at the anomeric position to give the corresponding 9-(2',3'-*O*-isopropylideneribityl)purines **2a, c** in good yields.

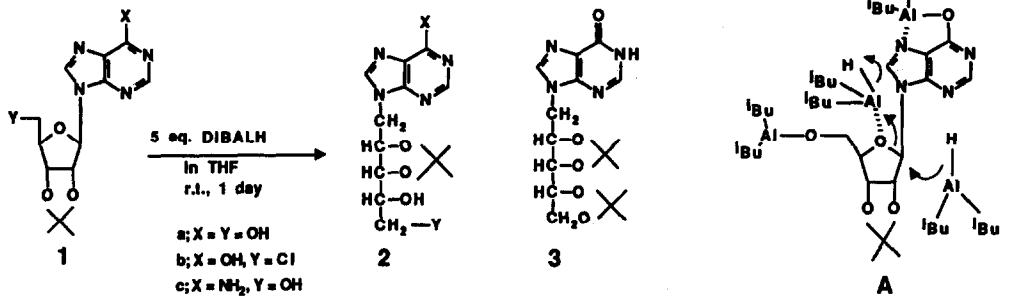
Much attention has been donated to synthesis and biological property of acyclonucleosides since the discovery of acyclovir, 9-[(2-hydroxyethoxy)methyl]guanine, as an antiviral agent for the treatment of certain herpes virus infections.[1] Among the acyclonucleosides, (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA][2] and 9-[(2-phosphonomethoxy)ethyl]adenine (PMEA)[3] have been evaluated to have broad-spectrum antiviral activities. Conventional and common synthetic methods for the preparation of acyclic nucleosides and nucleotides involve the coupling-reaction of bases with acyclic sugar moieties,[4] except for an example of the oxidative cleavage of the 2',3'-*cis*-diol portion of ribonucleosides with $NaIO_4$.[5]

In this context, we wish to report the efficient conversion of purine nucleosides into acyclonucleosides, 9-ribitylpurines, by the reductive cleavage[6] at the anomeric position of the ribose moiety in purine nucleosides with diisobutylaluminum hydride (DIBALH).

Reaction of 2',3'-*O*-isopropylideneinosine **1a** with DIBALH[6,7] (5 eq.) in dry THF under Ar for 1 day at room temperature gave 9-(2',3'-*O*-isopropylideneribityl)hypoxanthine **2a** in 86% yield. The stoichiometric study showed that the use of excess DIBALH is requisite for the smooth conversion of **1a** into **2a**. The structure of **2a** was fully supported by spectral data (^1H NMR, ^{13}C NMR, and mass) and microanalytical result.[8] Further proof of the structure of compound **2a** rests upon its conversion into 9-(2',3',4',5'-di-*O*-isopropylideneribityl)hypoxanthine **3**.

Analogous treatment of 5'-chloro-5'-deoxy-2',3'-*O*-isopropylideneinosine **1b** having no 5'-hydroxy group also smoothly gave the corresponding acyclic product **2b** in 97% yield. The compound **2b** was identical in every respect with the product prepared by the chlorination of **2a** with CCl_4/PPh_3 in DMF. The result means no crucial participation of 5'-hydroxy group[9] in the

reductive cleavage. Under the analogous conditions, 2',3'-*O*-isopropylideneadenosine **1c** was converted into the corresponding 9-ribityladenine derivative **2c** in 57% yield.



Taking the above facts into consideration, the reductive ring-opening reaction is likely explained in terms of the initial formation of a Lewis complex A: the anomeric position (1') can be activated by the coordination of DIBALH with the furanose ring-oxygen, to facilitate the nucleophilic attack of hydride anion at the position. The selectivity of the reductive cleavage at the anomeric position is obviously governed by virtue of the coordination of aluminum atom with the ring-oxygen. The detailed mechanism of this reaction, however, is not clear at present.

To the best of our knowledge, the present reductive cleavage of the ribose moiety in purine nucleosides with DIBALH is unprecedented and is of great interest for the preparation of antiviral acyclonucleosides.

References and Notes

1. H. J. Schaeffer, L. Beauchamp, P. De Miranda, G. B. Elion, D. J. Bauer, and P. Collins, *Nature* (London), 1978, **272**, 583; R. J. Remy and J. A. Secrist III, *Nucleosides & Nucleotides*, 1985, **4**, 411; R. Pauwels , J. Balzarini, D. Schols, M. Baba, J. Desmyter, I. Rosenberg, A. Holy, and E. De Clercq, *Antimicrob. Agents Chemother.*, 1988, **32**, 1025.
2. E. De Clercq, J. Descamps, P. De Somer, and A. Holy, *Science*, 1978, **200**, 563.
3. J. Balzarini, L. Naesens, P. Herdewijn, I. Rosenberg, A. Holy, R. Pauwels, M. Baba, D. G. Johns, and E. De Clercq, *Proc. Natl. Acad. Sci. USA*, 1989, **86**, 332.
4. C. K. Chu and S. J. Cutler, *J. Heterocycl. Chem.*, 1986, **23**, 289 and references cited therein.
5. L. M. Lerner, *Carbohydr. Res.*, 1984, **127**, 141; M. Bessodes and K. Antonakis, *Tetrahedron Lett.*, 1985, **26**, 1305.
6. The analogous selective cleavage of 1,3-dioxane or 1,3-diazine derivatives by DIBALH has already been reported - see; H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, 1981, **103**, 4186; A. Mori, J. Fujiwara, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, 1983, **24**, 4581.
7. E. Winterfeldt, *Synthesis*, **1975**, 617; K. Maruoka and H. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, 1985, **24**, 668.
8. All new compounds showed satisfactory spectral and analytical data; selected data for **2a**: mp 238 °C (EtOH), ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.20 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 3.42 (1 H, dd, J = 10 and 5 Hz, H5'), 3.86-3.89 (2 H, m, H4' and H5'), 4.14 (1H, dd, J = 10 and 5 Hz, H3'), 4.25 (1 H, dd, J = 13 and 10 Hz, H1'), 4.50-4.57 (2 H, m, H1' and H2'), 4.64 (1 H, brt, C_5-OH), 5.12 (1 H, d, J = 6 Hz, C_4-OH), 8.02 (2H, s, H-2 and H-8), and 12.28 (1 H, s, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.6, 28.0, 44.3, 63.8, 69.3, 75.1, 75.9, 108.6, 123.8, 140.9, 145.4, 148.5, 156.7.
9. K. Green and D. M. Blum, *Tetrahedron Lett.*, 1991, **32**, 2091.

(Received in Japan 16 March 1993)