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Regioselective BH_3–hydride reduction of inosine derivatives

Kosaku Hirota,[a,*] Hironao Sajiki,[a] Ryuji Hattori,[a] Yasunari Monguchi,[a] Genzoh Tanabe[b] and Osamu Muraoka[b]

[a]*Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Gifu 502-8585, Japan*
[b]*Faculty of Pharmaceutical Sciences, Kinki University, Higashi-Osaka 577-0818, Japan*

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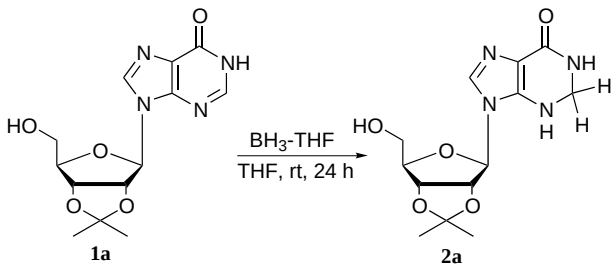
Abstract—Reaction of inosine derivatives with BH_3–THF resulted in the regioselective reduction of the purine nucleus to afford 2,3-dihydroinosine derivatives.

Chemically modified nucleosides are an important class of nonnatural molecules and they are receiving increasing attention in medicinal sciences as antitumor or antiviral agents. In the search for effective, selective, and non-toxic antiviral agents, a variety of strategies have been devised to design nucleoside analogs.[1] Therefore, novel and selective synthesis of modified nucleosides is of particular interest.

Previously we have reported[2] a facile synthetic method for the preparation of 9-D-ribitylpurines, acyclonucleosides, by the regioselective cleavage of the ribofuranosyl ring of 2′,3′-*O*-isopropylidene purine nucleosides using DIBAL-H reduction and it was applied for the preparation of diverse purine acyclonucleosides. During the course of our further study on the hydride reduction of purine nucleosides, we found that the reaction of 2′,3′-*O*-isopropylidene inosine **1a** with 5 equiv. of BH_3–THF at room temperature caused a novel and regioselective reduction of the C2–N(3) double bond in the hypoxanthine nucleus to give the corresponding 2,3-dihydroinosine derivative **2a** in 49% isolated yield together with recovery of **1a** (20%) (Scheme 1). The structure of **2a** was fully supported by spectral data and elemental analyses.[3] It was unambiguously determined by X-ray crystallography and Fig. 1 displays an ORTEP drawing.[4] The 2,3-dihydroinosine **2a** is stable in crystalline form, but in solution, was gradually oxidized into the inosine **1a** (10–20% over a week).



1a **2a**

Scheme 1. Regioselective BH_3–hydride reduction of **1a**.

2,3-Dihydroinosine derivatives **2** and its 5′-monophosphates are of interest as a transition state analog of inosine 5′-monophosphate (IMP) dehydrogenase that catalyzes the NAD-dependent oxidation at the C2 carbon of IMP to xanthosine 5′-monophosphate (XMP).[5,6]

Upon subsequently conducting a thorough literature search, we were able to locate a solitary pertinent paper on the reductive synthesis of dihydroinosines.[7] Although Itaya et al. reported[7] that a Pd/C catalyzed hydrogenation of 2′,3′-*O*-isopropylidene-3-methylinosine afforded the corresponding 1,2-dihydroinosine, the reduction of 3-unsubstituted inosines to dihydroinosines has been unprecedented.

The regioselective BH_3–THF reduction was successfully applied to various inosine derivatives[8] and related compounds **1** (Table 1). The reaction with 1-substituted inosine derivatives **1b**, **1c**, and **1g** smoothly proceeded to afford the corresponding 2,3-dihydro products in good to high yields (entries 2, 3 and 7). The BH_3–THF reduction of 2-methylinosine **1d** hardly proceeded (entry 4) while a 1,2-disubstituted inosine, 2′,3′-isopropylidene-1,2-dimethylinosine **1e**, which possesses a

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* Corresponding author. Tel.: +81-58-237-8572; fax: +81-58-237-5979; e-mail: hirota@gifu-pu.ac.jp

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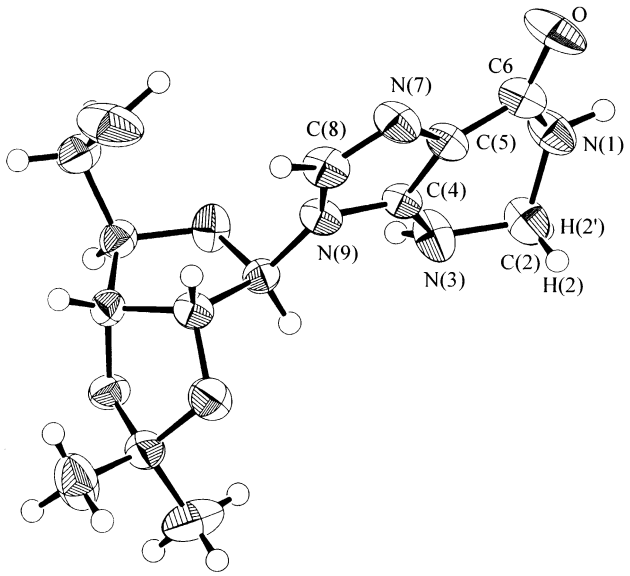
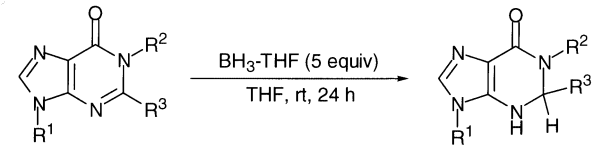


Figure 1. An ORTEP drawing of **1a** with 50% probability ellipsoids. Selected bond lengths (Å) and angles (°): N(1)–C(2) 1.478(8), C(2)–N(3) 1.444(9), N(3)–C(4) 1.363(7), C(4)–N(9) 1.410(7), C(5)–N(7) 1.386(8), N(7)–C(8) 1.293(8), C(8)–N(9) 1.386(7); H(2)–C(2)–H(2′) 109.6, N(1)–C(2)–N(3) 111.3(6), N(3)–C(4)–C(5) 124.0(6), N(1)–C(6)–C(5) 112.8(5), N(3)–C(4)–N(9) 128.6(5), N(7)–C(8)–N(9) 114.2(5).

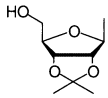
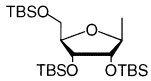
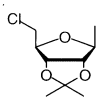
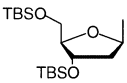
substituent at both N1 and C2 positions, was reduced (entry 5). Consequently, the present regioselective BH_3–THF reduction is accelerated by the introduction of a substituent to the N1 position, whereas the reduction was strongly depressed by the presence of a substituent at the C2 position. Inosine derivatives without a free 5′-hydroxy group **1f**–**1i** were also reduced to give the 2,3-dihydroinosines **2f**–**2i** (entries 6–9). Although the yield could not be improved in the cases of **1f**, **1h** and **1i** (entries 6, 8, 9), the introduction of a methyl substituent to the N1 position accelerated the reaction and the yield was improved to 58% (entry 7). Analogous reduction of 2′-deoxyinosine derivative **1j** and 9-benzyl hypoxanthine **1k** afforded the reductive products **2j** and **2k**, respectively (entries 10, 11).

With the use of N1-unsubstituted inosine derivatives **1a**, **1d**, **1f**, and **1h**–**1k** as the starting material, the unreacted starting material was always observed by the TLC analysis. In these cases, the yield of the reaction was not improved by the use of much more equivalents of BH_3–THF (e.g. 10 equiv.). The reaction sequence for the formation of 2,3-dihydroinosine derivatives **2** is outlined in Scheme 2 on the basis of the above observations. The alternative initial step of the N1-unsubstituted (R = H) inosines would be formation of a borane ester complex **3**. This complex is inactive toward the BH_3 reduction because of the aromatization of the pyrimidine ring. In the case of the N1-substituted (R ≠ H) inosines or a part of the N1-unsubstituted inosines, the borane complex **4** could be formed. A subsequent hydride attack on the electron poor C2 carbon and methanolic work-up gave the corresponding 2,3-dihydroinosine **2**.

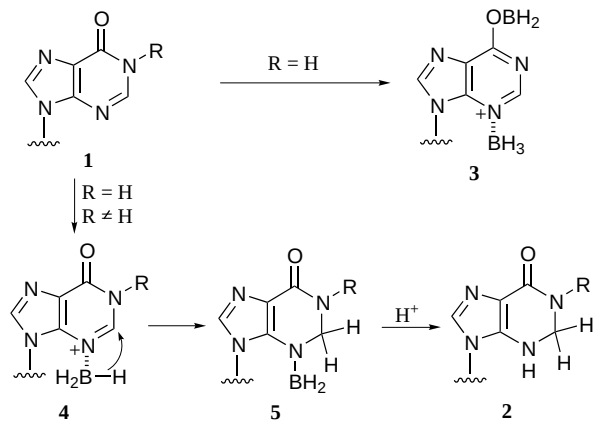
Table 1. BH_3–THF reduction of inosines to 2,3-dihydroinosines



1 2

Entry	Compd.	R^1	R^2	R^3	Yield (%)[a,b]
1	**a**		H	H	49
2	**b**		Me	H	92[c]
3	**c**		Bn	H	75[c]
4	**d**		H	Me	0[d]
5	**e**		Me	Me	30
6	**f**		H	H	30
7	**g**		Me	H	58
8	**h**		H	H	35
9	**i**		H	H	23
10	**j**		H	H	30
11	**k**	Bn	H	H	51

[a]All reactions were carried out in distilled THF at room temperature using 5.0 equiv BH_3-THF solution. [b]Unreacted starting material **1** was always observed by the TLC analysis except Entries 2, 3 and 7. [c]The reaction was completed within 3 h. [d]18% of 2',3'-*O*-isopropyridene-7,8-dihydroinosine was obtained.



1 3 4 5 2

Scheme 2. Tentative mechanism of the formation of 2,3-dihydroinosines **2** from inosine derivatives **1**.

In summary, we have developed a mild and efficient method for the regioselective conversion of inosines to 2,3-dihydro-inosines that proceeds at room temperature. The reaction is general for the hypoxanthine nucleus, and the products are of interest as transition state analogs of IMP dehydrogenase. Studies to further elucidate the scope of this method and biological activities are currently under way.

References

1. (a) *Antiviral Drug Development: A Multidisciplinary Approach*; De Clercq, E.; Walker, R. T., Eds.; Plenum Press: New York, 1988; Vol. 2; (b) *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: Greenwich, 1996.
2. (a) Kitade, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett*. **1993**, *34*, 4835–4836; (b) Kitade, Y.; Monguchi, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett*. **1993**, *34*, 6579–6580; (c) Hirota, K.; Monguchi, Y.; Sajiki, H.; Kitade, Y. *Synlett* **1997**, 697–698; (d) Hirota, K.; Monguchi, Y.; Kitade, Y.; Sajiki, H. *Tetrahedron* **1997**, *53*, 16663–16698; (e) Hirota, K.; Monguchi, Y.; Sajiki, H.; Sako, M.; Kitade, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 941–946; (f) Hirota, K.; Monguchi, Y.; Sajiki, H.; Yatome, C.; Hiraoka, A.; Kitade, Y. *Nucleosides Nucleotides* **1998**, *17*, 1333–1345.
3. *Spectroscopic data*: for **2a**: Mp 207–209°C; ^{1}H NMR (400 MHz; DMSO-d_6): 1.30 and 1.50 (each s, each 3H, isopropylidene *Me*), 3.35–3.62 (m, 2H, 5′-CH_2), 4.04–4.13 (m, 1H, 4′-C*H*), 4.27–4.41 (m, 2H, 2-CH_2), 4.84 (dd, J=2.4 Hz, 6.4 Hz, 1H, 3′-C*H*), 5.08 (dd, J=3.4 Hz, 6.4 Hz, 1H, 2′-C*H*), 5.22 (br, 1H, 5′-O*H*, D_2O exchangeable), 5.70 (d, J=3.4 Hz, 1H, 1′-C*H*), 6.32 (t, J=5.4 Hz, 1H, 1-N*H* or 3-N*H*, D_2O exchangeable), 7.05 (br, 1H, 1-N*H* or 3-N*H*, D_2O exchangeable), 7.60 (s, 1H, 8-C*H*); ^{13}C NMR (100 MHz, DMSO-d_6): 25.1, 26.9, 55.0, 61.1, 80.7, 82.8, 85.6, 88.9, 113.3, 118.2, 132.2, 144.8, 162.4. Anal. calcd for $C_{13}H_{18}N_4O_5$: C, 50.32; H, 5.85; N, 18.05. Found: C, 50.23; H, 5.85; N, 18.00%; FAB-MS (NBA) m/z 311 (M^++1, 30%), 238 (16%), 169 (100%).
4. *Crystal data* for **1a** at 25°C with Cu Kα radiation (λ= 1.54178 Å: $C_{13}H_{18}N_4O_5$, M=310.31, colorless prismatic, monoclinic, space group $P2_1$ (no. 4), a=6.065(1), b= 9.926(2), c=12.555(3) Å, β=96.860(2)°, V=750.4(3) Å^3, Z=2, D_c=1.373 g cm^{-3}, μ=9.06 cm^{-1}, $2\theta_{max}$=120.1°, 1320 total reflections, 1077 observed reflections [I> $3.00\sigma(I)$], R_1=0.048, R_w=0.073. CCDC reference number 168032
5. Hedstrom, L.; Wang, C. C. *Biochemistry* **1990**, *29*, 849–854.
6. Zhang, H.-Z.; Rao, K.; Carr, S. F.; Rapp, E.; Straub, K.; Wu, J. C.; Fried, J. *J. Med. Chem*. **1997**, *40*, 4–8.
7. (a) Itaya, T.; Matsumoto, H. *Tetrahedron Lett*. **1978**, *19*, 4047–4058; (b) Itaya, T.; Matsumoto, H. *Chem. Pharm. Bull*. **1985**, *33*, 2213–2219.
8. The reaction with an unprotected inosine in the sugar moiety did not proceed and the starting material was recovered. It seems likely that the poor solubility of the unprotected inosine suppresses the reduction.