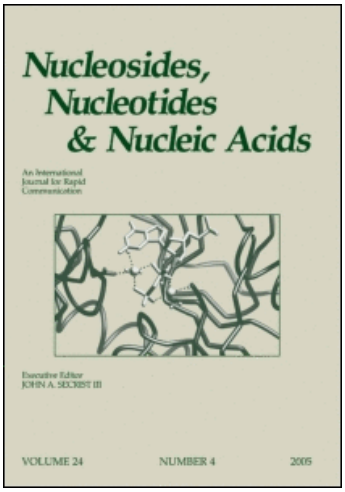
This article was downloaded by:
On: *26 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Oxidative Cyclization of 2',3'-O-Isopropylidene-Adenosines into 5'-O,8-Cycloadenosines with Lead Tetraacetate: Remarkable Effect of N^6-Substituents on the Oxidation

Yukio Kitade[a]; Tohru Makino[a]; Kosaku Hirota[a]; Yoshifumi Maki[a]
[a] Department of Medicinal Chemistry, Gifu Pharmaceutical University, Gifu, Japan

To cite this Article Kitade, Yukio , Makino, Tohru , Hirota, Kosaku and Maki, Yoshifumi(1992) 'Oxidative Cyclization of 2',3'-O-Isopropylidene-Adenosines into 5'-O,8-Cycloadenosines with Lead Tetraacetate: Remarkable Effect of N^6-Substituents on the Oxidation', Nucleosides, Nucleotides and Nucleic Acids, 11: 2, 365 — 372
To link to this Article: DOI: 10.1080/07328319208021710
URL: http://dx.doi.org/10.1080/07328319208021710

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

NUCLEOSIDES & NUCLEOTIDES, 11(2-4), 365-372 (1992)

OXIDATIVE CYCLIZATION OF 2',3'-*O*-ISOPROPYLIDENE-ADENOSINES INTO 5'-*O*,8-CYCLOADENOSINES WITH LEAD TETRAACETATE: REMARKABLE EFFECT OF N^6-SUBSTITUENTS ON THE OXIDATION†

Yukio Kitade, Tohru Makino, Kosaku Hirota, and Yoshifumi Maki*

Department of Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan

Downloaded At: 20:09 26 January 2011

Abstract

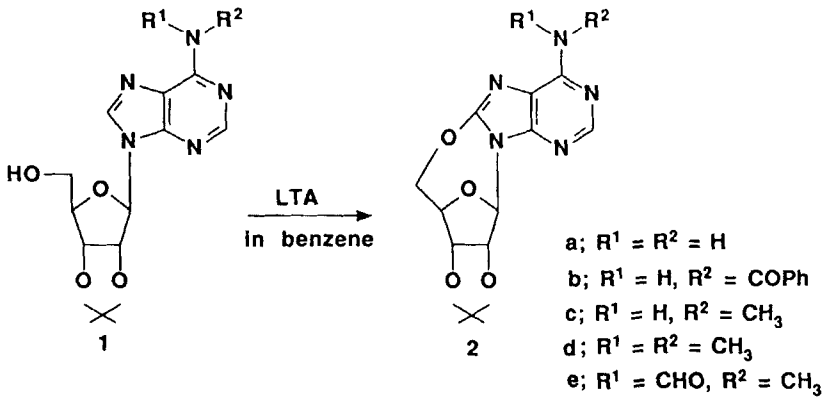
Oxidation of 2',3'-*O*-isopropylideneadenosines (**1**) with lead tetraacetate (LTA) in dry benzene resulted in the formation of the corresponding 5'-*O*,8-cyclo-2',3'-*O*-isopropylideneadenosines (**2**), which has a new methodological implication for the chemical modification of adenosines. The occurrence of the oxidative cyclization was remarkably affected by the nature of N^6-substituents: N^6-benzoyl substitution prominently accelerated the oxidative cyclization in comparison with none and dimethyl substitutions. In the oxidation of N^6,N^6-dimethyladenosine (**1d**), an intriguing oxidative demethylation was observed.

Introduction

Since cyclonucleosides are generally regarded as versatile intermediates for the preparation of biologically important nucleosides and as tool for conformational studies of nucleosides,[1,2] many efforts have been made to explore a new methodology for the preparation of cyclonucleosides. Research in this field still has many untouched possibilities to explore. For example, although 5'-*O*,8-cyclo-2',3'-*O*-isopropylideneadenosine (**2a**) was synthesized by a conventional method involving the intramolecular cyclization of the corresponding 8-bromoadenosine in the presence of base,[3] we have found that 2',3'-*O*-isopropylideneadenosine (**1a**) undergoes an unprecedent-

†This contribution is dedicated to the late Professor Tohru Ueda with our deepest sympathy.

Copyright © 1992 by Marcel Dekker, Inc.



1 2

Scheme 1

Downloaded At: 20:09 26 January 2011

ed oxidative cyclization to give **2a** upon treatment with oxidants such as lead tetraacetate (LTA),[4] cupric chloride,[5] and *N*-halogenosuccinimide,[6] and by irradiation in the presence of pyrimido[5,4-*g*]pteridinetetrone 5-oxide.[7] The reaction mode of these intramolecular cyclizations obviously contains either a one-electron oxidation in two stages or a two-electron oxidation, and provides a clue for the development of new methods for the chemical modification of adenosines.

In this paper, we wish to describe in full detail[8] the oxidative cyclization of 2',3'-*O*-isopropylideneadenosines into the corresponding 5'-*O*,8-cyclo-adenosines with LTA, in particular, the remarkable substituent effect of N^6-substituents on the reaction, which sheds some light on the oxidation mode.

Results and Discussion

A stoichiometric study showed that the use of 1.2 equivalent of LTA is required for the smooth conversion of the 2',3'-*O*-isopropylidene derivative (**1a**) into the cycloadenosine (**2a**). Thus, refluxing **1a** with LTA (1.2 eq.) in dry benzene under argon for 2.5 h afforded **2a** in 93 % yield. The cycloadenosine (**2a**) was identical in all respects with an authentic sample.[3] The oxidative cyclization of adenosine itself with LTA did not give the expected 5'-*O*,8-cycloadenosine under the conditions employed. Therefore, 2',3'-*O*-isopropylidene protection of adenosines is a prerequisite for the oxidative cyclization.

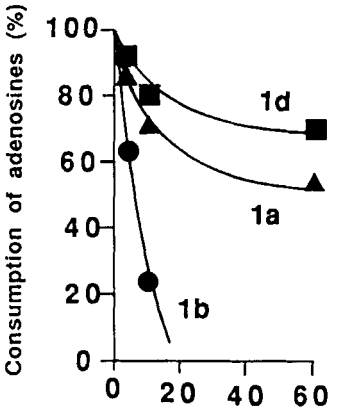
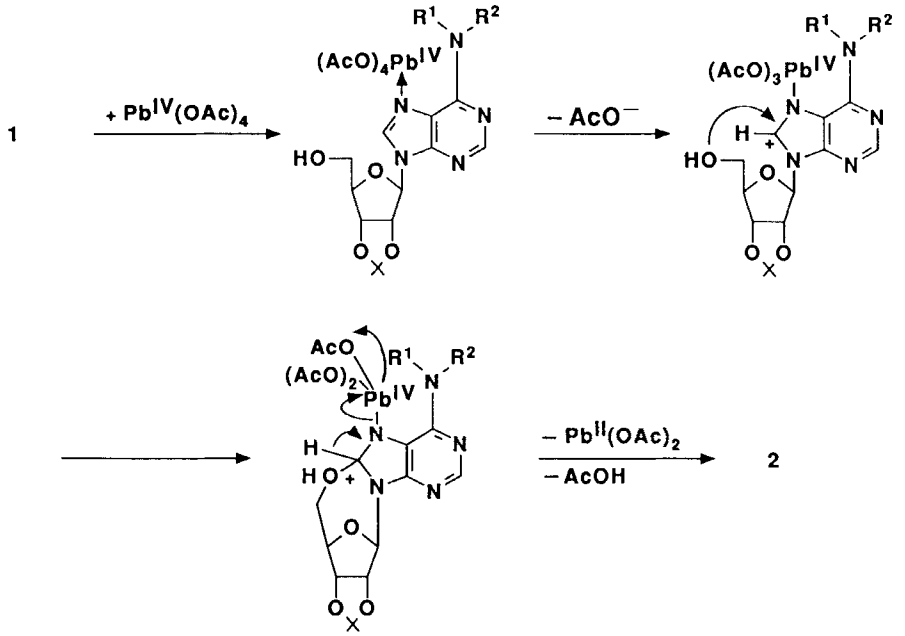


FIG.1.

Downloaded At: 20:09 26 January 2011

When N^6-benzoyladenosine derivative (**1b**) was employed as a substrate, the oxidative cyclization smoothly proceeded to give the corresponding 5'-*O*,8-cycloadenosine (**2b**), quantitatively. Under the analogous conditions, the oxidative cyclization of N^6-methyladenosine (**1c**) and N^6,N^6-dimethyladenosine (**1d**) gave the corresponding 5'-*O*,8-cycloadenosines (**2c**) and (**2d**) in 65% and 40% yield, respectively. In the case of **1d**, the formation of small amounts of other oxidized products was observed (*vide infra*). The structures of **2b-d** were fully supported by mass, ^{1}H-NMR, and microanalytical results.

Figure 1 shows consumption of **1a**,**1b**, and **1d** in the reaction with LTA as a function of reaction time, indicating clearly that the ease of the oxidation is in the order of **1b** > **1a** > **1d**. The prominent substituent effect of theN^6-benzoyl group on the present conversion is unequivocal. The relative increase of the nucleophilicity of the imidazole ring nitrogen (N^7) in comparison with the pyrimidine nitrogen (N^1) by virtue of the introduction of N^6-acyl group in the adenosines has been manifested by concrete observations, e.g. contrary to the adenosines, protonation and alkylation of N^6-acyladenosines predominantly occur at the N^7-position rather than the N^1-position.[9] Thus, the accelerative effect of the N^6-benzoyl group on the present conversion can be explained in terms of the preferential coordination of lead ion at the N^7-position of **1d** for the oxidative cyclization. A conceivable reaction sequence for the present oxidative cyclization by lead ion is outlined in the manner of an intramolecular oxidative nucleophilic substitution[11] involving a two-electron oxidation as depicted in Scheme 2.



Scheme 2

Downloaded At: 20:09 26 January 2011

Reaction of the N^6,N^6-dimethyladenosine (**1d**) with LTA (1.2 eq.) under reflux in dry benzene for 2 h resulted in the formation of the corresponding cycloadenosine (**2d**)(40%) and demethylated products (**2c**)(5%) and (**1c**)(2%) together with a trace amount of N^6-formyl-N^6-methylcycloadenosine (**2e**). The structure of **2e** was fully supported by its ^{1}H-NMR and high-resolution mass spectrum, e.g. the NMR spectrum of **2e** showed the presence of only one methyl group (δ 3.55, s, 3H) and the *N*-formyl group (δ 10.10, s, 1H). When a mixture of **1d** and LTA (3 eq.) in large excess in benzene was refluxed for 1.5 h, the yields of demethylated products increased to some extent: **2c** (26%) and **1c** (8%). In the oxidation of **1d** under an oxygen atmosphere, no distinct change in both the products distribution and the consumption rate of **1d** was observed. Analogous treatment of **2d** with LTA gave a mixture of **2c** and **2e** in 60% and ca. 3% yield, respectively.

Endo and Zemlicka[12] have reported that the oxidation of N^6,N^6-dimethyl-2',3',5'-tri-*O*-acyladenosine with ruthenium tetroxide gives selectively the corresponding N^6-formyl-N^6-methyl derivative. Oxidation of the N^6,N^6-dimethyl

group in **1d** with LTA has an interesting mechanistic implication in connection with the previous observation.[12] Special attention will be paid to the occurrence of competitive oxidation with LTA in both the N^6,N^6-dimethyl group and the imidazole ring in **1d** in order to clarify the detailed oxidative mechanism.

In summary, the present study provided a basic observation which is applicable to the development of new methodology for the chemical modification of purine nucleosides.

Experimental Section

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were carried out at the microanalytical laboratory of our university. All UV measurements were carried out with a Shimadzu 260 spectrometer. ^{1}H-NMR spectra were recorded at 270 MHz on a JEOL JNX-270 spectrometer in $CDCl_3$. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, and m = multiplet). Mass spectra (MS) were measured at 70 eV with a JEOL JMS-D300 spectrometer. TLC for the assay of adenosines was performed on Silica gel 60 plates (Merk, art 5715) by using chloroform-methanol (5:1) as an eluent and TLC-scanning was carried out with a Shimadzu CS-9000 dual-wavelength flying-spot scanner (detection, the corresponding maximum peak of adenosines). Column chromatography was carried on silica gel (Wako gel C-200).

Downloaded At: 20:09 26 January 2011

5'-*O*,8-Cyclo-2',3'-*O*-isopropylideneadenosine (2a). A mixture of 2',3'-*O*-isopropylideneadenosine (**1a**) (154 mg, 0.5 mmol) and lead tetraacetate (90%) (LTA) (296 mg, 0.6 mmol) in dry benzene (60 mL) was refluxed for 2.5 h under argon. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform-methanol (30:1). The appropriate fractions containing the product were collected and the solvent was removed under reduced pressure to give **2a** (143 mg, 93%), which was identical in every respect with an authentic sample prepared by base-catalyzed cyclization of 8-bromo-2',3'-*O*-isopropylideneadenosine.[3]

***N*^{6}-Benzoyl-5'-*O*,8-cyclo-2',3'-*O*-isopropylideneadenosine (2b).** A mixture of N^6-benzoyl-2',3'-*O*-isopropylideneadenosine (**1b**) (123 mg, 0.3 mmol) and LTA (90%) (177 mg, 0.36 mmol) in dry benzene (10 mL) was

refluxed for 15 min. under argon. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform-methanol (40:1). The appropriate fractions containing the product were collected and the solvent was removed under reduced pressure to give **2b** (120 mg); m.p. 234-236 °C. ^{1}H NMR: δ 1.36 (s, CH_3), 1.57 (s, CH_3), 4.26 (d, 1H, J = 13.2 Hz, C_5'-H), 4.55 (d, 1H, J = 13.2 Hz, C_5'-H), 4.76 (m, 2H, C_3'-H and C_4'-H), 5.09 (d, 1H, J = 5.86 Hz, C_2'-H), 6.49 (s, 1H, C_1'-H), 7.48 (t, 2H, J = 7.32 Hz, C_2-H) 7.57 (t, 1H, J = 7.32 Hz), and 8.01 (d, 2H, J = 7.32 Hz). Anal. Calcd. for C, 58.68; H, 4.68; N, 17.11: Found C, 58.45; H, 4.75: N, 16.91; High-resolution mass spectrum: 409.1417 (M^+, $C_{20}H_{19}N_5O_5$ requires 409.1414).

5'-*O*,8-Cyclo-2',3'-*O*-isopropylidene-*N*^{6}-methyladenosine (2c). A mixture of 2',3'-*O*-isopropylidene-*N*^{6}-methyladenosine (**1c**) (438 mg, 1.36 mmol) and LTA (90%) (802 mg, 1.63 mmol) in dry benzene (15 mL) was refluxed for 2 h under argon. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform-methanol (30:1). The appropriate fractions containing the product were collected and the solvent was removed under reduced pressure to give **2c** (282 mg, 65%). ^{1}H NMR: δ 1.35 (s, CH_3), 1.56 (s, CH_3), 3.22 (d, 3H, N^6-H), 4.17 (d, 1H, J = 12.82 Hz, C_5'-H), 4.47 (d, 1H, J = 12.82 Hz, C_5'-H), 4.71 (br, 1H, C_4'-H), 4.75 (d, 1H, J = 5.55 Hz, C_2'-H), 5.08 (d, 1H, J = 5.55 Hz, C_2'-H), 5.86 (s, 1H, N^6-H), 6.40 (s, 1H, C_1'-H), and 8.35 (s, 1H, C_2-H); High-resolution mass spectrum: 319.1285 (M^+, $C_{14}H_{17}N_5O_4$ requires 319.1284).

Reaction of 2',3'-*O*-isopropylidene-*N*^{6},*N*^{6}-dimethyladenosine (1d) with LTA. A mixture of **1d** (100 mg, 0.3 mmol) and LTA (90%) (177 mg, 0.36 mmol) in dry benzene (10 mL) was refluxed for 2 h under argon. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform-methanol (40:1). The first fraction gave 5'-O,8-cyclo-2',3'-*O*-isopropylidene-*N*^{6}-formyl-*N*^{6}-methyladenosine (**2e**) (< 1%). ^{1}H NMR: δ 1.25 (s, CH_3), 1.37 (s, CH_3), 3.55 (s, 6H, N^6-CH_3), 4.26 (d, 1H, J = 12.21 Hz, C_5'-H), 4.45 (d, 1H, J = 12.21 Hz and 2.20 Hz, C_5'-H), 4.77 (m, 2H, C_3'-H and C_4'-H), 6.53 (s, 1H, C_1'-H), 8.63 (s, 1H, C_2-H), and 10.18 (1H, s, N^6-CHO); High-resolution mass spectrum: 347.1216 (M^+, $C_{15}H_{17}N_5O_5$ requires 347.1218).

Downloaded At: 20:09 26 January 2011

The second fraction gave 5'-*O*,8-cyclo-2',3'-*O*-isopropylidene-N^6,N^6-dimethyladenosine (**2d**) (40 mg, 40%). ^{1}H NMR: δ 1.36 (s, CH_3), 1.56 (s, CH_3), 3.43 (s, 6H, N^6-dimethyl), 4.16 (d, 1H, J = 13.19 Hz, $C_{5'}$-H), 4.45 (d, 1H, J = 13.19 Hz, $C_{5'}$-H), 4.75 (d, 1H, J = 5.37 Hz, $C_{3'}$-H), 5.08 (d, 1H, J = 5.55 Hz, $C_{2'}$-H), 6.42 (s, 1H, $C_{1'}$-H), and 8.29 (s, 1H, C_2-H); High-resolution mass spectrum: 333.1452 (M^+, $C_{15}H_{19}N_5O_4$ requires 333.1452). The third fraction gave **2c** (5%), which was identical with the sample prepared above. The fourth fraction gave **1c** (2%), which was identical with the authentic sample.

Reaction of 2d with LTA. A mixture of **2d** (100 mg, 0.3 mmol) and LTA (90%) (177 mg, 0.36 mmol) in dry benzene (15 mL) was refluxed for 1 h under argon. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform-methanol (40:1). The early-eluting fraction gave **2c** (60 mg, 60%), which was identical in every respect with the sample obtained above. The later-eluting fraction gave **2e** (3 mg, 3%), which was identical in every respect with the sample obtained above.

Measurement of Consumption of 2',3'-*O*-isopropylideneadenosines (1a, 1b, and 1d) in the oxidation with LTA. A mixture of adenosines (**1a**, **1b**, or **1d**) (5mM) and LTA (6mM) in dry benzene (20 mL) was refluxed under argon. Consumption of the adenosines (**1a**, **1b**, and **1d**) was followed spectrophotometrically with a TLC scanner and was calculated by $A/A_0 \times 100$ (A_0 = the initial peak area of adenosines, A = the peak area of adenosines in the time course of the oxidation).

Downloaded At: 20:09 26 January 2011

Acknowledgments

This work was partly supported by a Grant-in-Aid for Scientific Research on Priority Areas No. 03242104 from the Ministry of Education, Science and Culture, Japan.

REFERENCES AND NOTES

1. M. Ikehara and T. Ueda, *J. Syn. Org. Chem. Jpn.*, **32**, 407 (1974).
2. M. Ikehara, *Acc. Chem. Res.*, **2**, 47 (1969).
3. M. Ikehara, M. Kaneko, and R. Okano, *Tetrahedron*, **20**, 5675 (1970).
4. K. Kameyama, M. Sako, K. Hirota, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, **1984**, 1658.

5. Y. Kitade, R. Nakanishi, M. Sako, K. Hirota, and Y. Maki, *Chem. Pharm. Bull.*, **39**, 1902 (1991).
6. Y. Maki, M. Sako, T. Saito, and K. Hirota, *Heterocycles*, **27**, 347 (1988).
7. M. Sako, K. Shimada, K. Hirota, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, **1986**, 1704.
8. These results were partly published in a preliminary form (cf. reference 4).
9. Y. Maki, K. Kameyama, M. Suzuki, M. Sako, and K. Hirota, *J. Chem. Res.*, **1984**, 388.
10. The present oxidative cyclization with LTA is applicable to other purine nucleoside derivatives such as inosines and guanosines.
11. R. A. Sheldon and J. K. Kochi, *"Metal-Catalyzed Oxidations of Organic Compounds,"* Academic Press, New York, 1981, p 130.
12. T. Endo and J. Žemlička, *J. Org. Chem.*, **44**, 3652 (1979).

Received 8/22/91
Accepted 12/4/91

Downloaded At: 20:09 26 January 2011