

Eleventh Symposium on Nucleic Acids Chemistry

held in Tokyo, Japan

November 1st–2nd, 1983

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Compiled by Angela E. Pritchard

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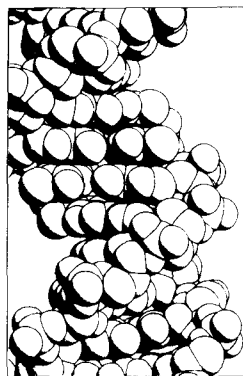
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α -Oxyalkylation and α -amidoalkylation of nebularine tri-O-benzoate via homolytic processes

Hiroshi Suemune and Tadashi Miyasaka

School of Pharmaceutical Sciences, Kyushu University, Maedashi 3-1-1, Higashi-ku, Fukuoka-shi 812, and School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

ABSTRACT

A series of new purine ribonucleoside derivatives having oxyalkyl or amidoalkyl functionality at the 6-position have been synthesized from nebularine tri-O-benzoate by Minisci-type homolytic processes using ammonium persulfate as the radical initiator.

INTRODUCTION

Our recent research on chemical modification of natural nucleosides concerning introduction of a carbon-function into the base moiety ^{1,2} revealed some interesting features in the reactivity as well as biological activity of 6-dicyanomethyl-9- β -D-ribofuranosylpurine and 3-amino-2-(9- β -D-ribofuranosylpurine-6-yl)acrylonitrile. ^{1,3} As a facile C-alkylation method, Minisci reaction was utilized by Kawazoe *et al.* ⁴ Thus, methylation of adenosine with *t*-butyl hydroperoxide as a radical source afforded 8-methyl- and 2,8-dimethyladenosine. Elad *et al.* examined photochemical alkylation of the purine base to deduce reactivity sequence: C-6 > C-8 > C-2. ^{5,6} We expected that Minisci reaction would offer a facile and regiospecific method to introduce a functionalized alkyl group at the 6-position of nebularine tri-O-benzoate which seemed stable and soluble enough in the acidic reaction media. ^{7,8}

RESULTS

Treatment of nebularine tri-O-benzoate (**1**) with 30% H₂O₂, *t*-BuOOH, and MeOH in aqueous H₂SO₄-FeSO₄ did not give good result, however, when acetic acid was used in stead of sulfuric acid, 6-hydroxymethyl-9-(2,3,5-tri-O-benzoyl- β -D-ribofuranosyl)-

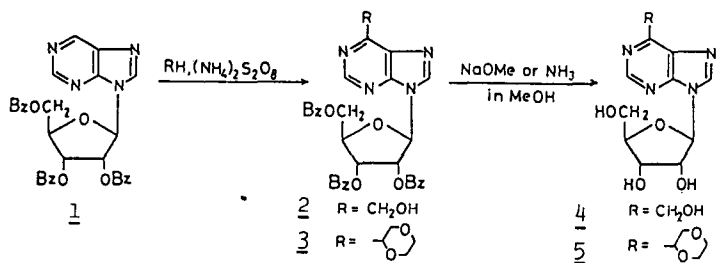


TABLE I

No.	R	C ₂ -H	C ₆ -H	C ₈ -H
1	- H	8.96	9.22	8.39
2	-CH ₂ OH	8.82	-	8.23
3	(a cyclic structure)	8.86	-	8.29

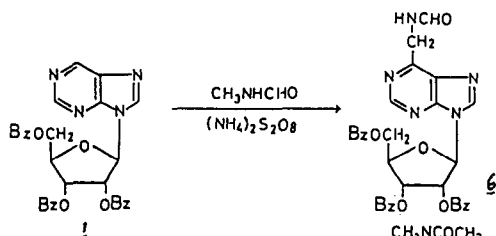
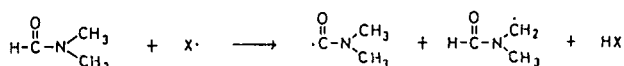


TABLE II

R	No.	I (%)	No.	II (%)
1 -CH ₂ N(Me)COCH ₃	7	73	8	24
2 -CH ₂ NHCOCH ₃	9	74	10	6
3 (a cyclic structure)	11	84	-	-
4 -CH ₂ N(Me)P(O)(NMe) ₂	12	73	-	-

purine (2) was obtained in low yield (23%). Treatment of 1 with 30% H_2O_2 and dioxane in H_2SO_4 - FeSO_4 solution afforded 6-(dioxane-2-yl)purine ribonucleoside (3) in 49% yield. Hydroxymethylation of 1 in less acidic medium with ammonium persulfate (5 eq.) in methanol by heating at 60°C for 20 minutes gave 2 in 74% yield. In the same procedure with dioxane, 3 was obtained in 82% yield. Debenzoylation in the usual manner furnished 6-hydroxymethyl-9- β -D-ribofuranosylpurine (4) and 6-(dioxane-2-yl)-9- β -D-ribofuranosylpurine (5) in 61 and 95% yield respectively. The absence of the pmr-signals at around 9.2 ppm indicates the substitution occurred at the 6-position of the purine nucleus. (TABLE I).

Heating of 1 with ammonium persulfate in formamide did not give good result. In the same reaction with N-methylformamide, 6-(N-formylaminomethyl)purine ribonucleoside (6) was obtained in 24% yield. N,N-Dimethylacetamide (DMA) which does not produce carbamoyl radical was applied in the same manner to give two compounds, 6-N-methylacetamidomethylpurine riboside (7) and the 6,8-disubstituted compound (8) in 73 and 24% yields, respectively. N-Methylacetamide, N-methylpyrrolidone and hexamethylphosphoric triamide (HMPA) were also applied to the reaction. (TABLE II). The pmr spectra indicated α -amidoalkylation occurred at the 6-position first. (TABLE III).

Debenzoylation furnished the corresponding triols.

TABLE
III

	R ¹	R ²	C ₂ -H	C ₆ -H	C ₈ -H
	-H	-H	8.96	9.22	8.39
<u>1</u>	-CH ₂ NHCHO	-H	8.77	-	8.37
<u>2</u>	-CH ₂ N(Me)COCH ₃	-H	8.78 8.80	-	8.25 8.30
<u>3</u>	-CH ₂ N(Me)COCH ₃	-CH ₂ N(Me)COCH ₃	8.75	-	-
<u>4</u>	-CH ₂ NHCOCH ₃	-H	8.76	-	8.25
<u>5</u>	-CH ₂ NHCOCH ₃	-CH ₂ NHCOCH ₃	8.67	-	-
<u>6</u>		-H	8.80	-	8.33
<u>7</u>	-CH ₂ N(Me)P(O)(NMe ₂) ₂	-H	8.85	-	8.35

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Introduction of carbon substituents at C-2 position of purine nucleosides

Akira Matsuda, Kazue Satoh, Hiromichi Tanaka and Tadashi Miyasaka

School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

ABSTRACT

A series of new purine nucleosides which have carbon substituents at their C-2 position were synthesized by non-aqueous diazotization/ deamination of 2-amino-6-chloro-9-(2,3,5-tri-O-acetyl- β -D-ribofuranosyl)purine(**1**) with isoamyl nitrite in aromatic solvents and by palladium-catalyzed alkynylation of 2-iodoadenosine(**4**) with terminal alkynes.

INTRODUCTION

Considerable effort has been devoted to the synthesis and biological evaluation of 2-substituted purine nucleosides, but few approaches have been reported on a carbon-carbon bond formation reaction at the C-2 position of intact purine nucleosides. Methods reported so far involve the cyclization of appropriately substituted imidazole nucleosides,¹ homolytic methylation,² and the substitution of a methylsulfonyl group at 2-position of adenosine with cyanide.³ We have been seeking to develop more general and versatile procedures for creation of carbon-carbon bonds to base moiety of nucleosides.

Phenylation and Heteroarylation of Purin-2-yl Radicals

2-Amino-6-chloro-9-(2,3,5-tri-O-acetyl- β -D-ribofuranosyl)purine(**1**) has been shown to be a useful intermediate for the synthesis of 2,6-dihalogenated purine nucleosides via the purin-2-yl radicals.⁴ This methodology was adopted to generating carbon-carbon bonds at the C-2 position of **1**.

When compound **1** was heated in benzene or heteroaromatic solvents in the presence of isoamyl nitrite and cuprous oxide, 2-phenyl or heteroarylated 6-chloropurine nucleosides(**2a-c**) were

obtained in moderate yields. Attempts to apply this method to olefins such as ethyl acrylate and acrylonitrile in the presence of cupric chloride (the Meerwein reaction⁵), met with little success.

Palladium-Catalyzed Alkynylation of 2-Iodoadenosine with Terminal Alkynes

Recently much attention has been received for the convenient

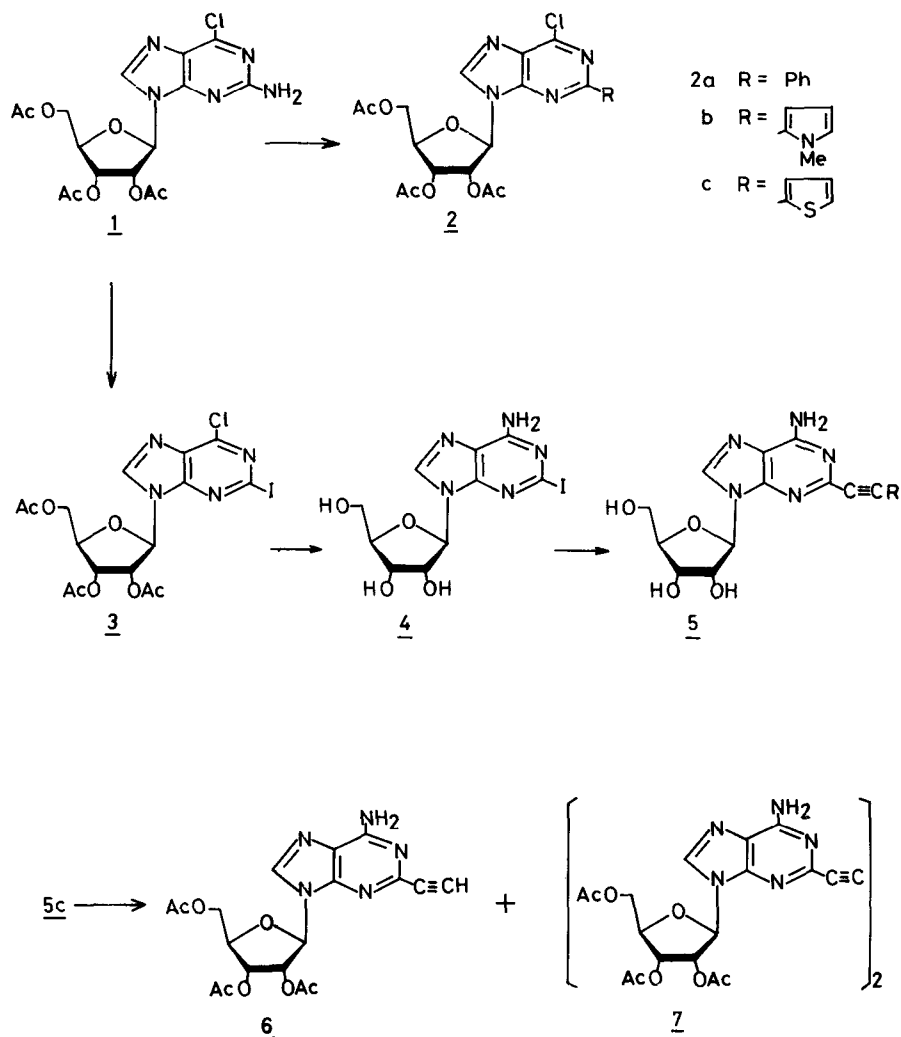


Table 1. Synthesis of 2-Alkynylated Adenosines

compd	R	isolated yield(%)	ir(KBr) (cm ⁻¹) $\nu_{C\equiv C}$	mp(°C)
5a	Ph	97	2210	146-7
5b	HOCH ₂	96	2230	152-5
5c	TMS	85	2160	156-8
5d	CH ₃ (CH ₂) ₃	85	2230	121-5
5e	CH ₃ (CH ₂) ₄	93	2230	113-5
5f	CH ₃ (CH ₂) ₅	84	2230	101-3

introduction of terminal alkynes into N-heteroarenes and base moiety of nucleosides,⁶ since acetylenes have the great versatility of their transformations. The modified method by Sonogashira et al.⁷ which was originally developed by Heck,⁸ was employed in this study for palladium-catalyzed cross-coupling reactions of 4 with terminal alkynes. As a starting material, 2-iodoadenosine (4), mp 141-4°C, was easily prepared in 90% yield upon treatment of 3 with methanolic ammonia.

When 4 was treated with a slight molar excess of phenylacetylene in the presence of catalytic amounts of bis(triphenylphosphine)palladium dichloride and cuprous iodide in triethylamine and N,N-dimethylformamide as a co-solvent at 80°C for one hour under argon atmosphere, the alkynylated product(5a) was isolated as a crystalline form after purification over a silica gel column chromatography. Analogous coupling reactions of 4 with several monosubstituted acetylenes were successfully carried out to give the corresponding 2-alkynylated adenosines(5b-f) in good to excellent yields(Table 1). In all cases these conversions were completed within one hour.

Desilylation of 5c into 6 was accomplished by treatment with methanolic sodium hydroxide at room temperature, followed by acetylation of the crude products. The desired 2-ethynyladenosine derivative 6, mp 174-6°C; $\delta \equiv CH$ (CDCl₃): 3.00 (s); $\nu_{C\equiv C}$: 2110 cm⁻¹, was isolated along with a small amount of fluorescent diyne 7, mp 239-42°C; $\nu_{C\equiv C}$: 2130 cm⁻¹. The by-product(7) was obtained in 86% yield upon oxidative coupling⁹ of 6 in the presence of cupric acetate in pyridine under oxygen atmosphere.

The isolated ethynyladenosine derivative 6 could serve as a

terminal alkyne to afford more complex nucleoside analogs. Transformations of alkynyl side chains to other functionalities are currently under investigation.

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