COMMUNICATION

Synthesis of a new class of spin-labeled purine ribonucleosides and development of a novel nucleophilic reaction to form 2,6,8-trifunctionalized purine derivatives

Mariko Aso, Kouji Norihisa, Masakazu Tanaka, Noboru Koga and Hiroshi Suemune *

Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan. E-mail: suemune@lyra.phar.kyushu-u.ac.jp

Received (in Cambridge, UK) 2nd June 2000, Accepted 7th June 2000
Published on the Web 30th June 2000

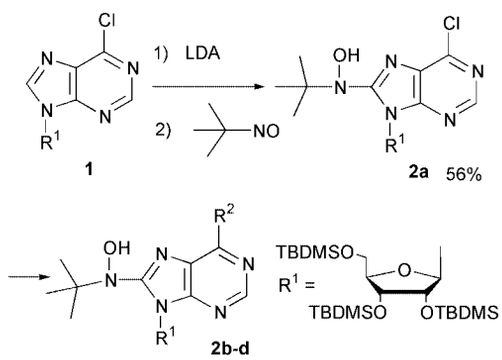
Novel purine ribonucleosides with a *tert*-butylhydroxyamino function at the C8-position of the purine nucleus were synthesized, and were oxidized to aminoxyl radicals by treatment with Ag_2O; after *O*-acylation of the *tert*-butylhydroxyamino group, nucleophilic substitution at the C2-position of the purine nucleus easily proceeded with elimination of the *N*-acyloxy group to provide a novel method for preparing C2-functionalized purine ribonucleosides.

The *tert*-butylhydroxyamino function has been focused on as the precursor of stable *N*-*tert*-butyl aminoxyl radicals for the construction of organic super-high-spin molecules with *m*-phenylene backbones.[1] We planned the introduction of a *tert*-butylhydroxyamino function into the purine nucleus of a ribonucleoside. The purposes of this work were as follows: 1. Synthesis of a new class of spin-labeled nucleoside, in which the spin source, an *N*-*tert*-butylaminoxyl radical, is directly attached to the nucleobase. In previous synthetic studies of spin-labeled nucleosides,[2] only 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and related compounds were used as a spin source; these were indirectly bonded to the nucleobase with the "linker" part. 2. The *tert*-butylhydroxyamino function could be considered to act as a radical scavenger, so that the new type of purine derivatives was expected to have such biological activity.

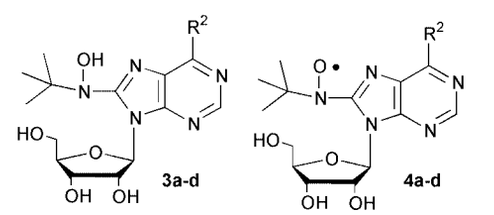
We wish to report here the synthesis of 8-(*tert*-butylhydroxyamino)purine ribonucleosides incorporating a novel reaction to introduce the nucleophilic functional group at the C2-position of the purine nucleus. Introduction of a *tert*-butylhydroxyamino group into the purine nucleus was carried out as follows: tri-*O*-silylated 6-chloropurine ribonucleoside **1**, prepared from inosine, was lithiated with 6 equiv. of LDA in dry ether at −78 °C,[3] and subsequent treatment with 2-methyl-2-nitrosopropane[4] at −20 °C gave the desired **2a** in 56% yield.[5] The position of the *tert*-butylhydroxyamino group was determined by ^{1}H-NMR spectrometry. The C2′-H of **2a** was observed at lower field (5.19 ppm) than that of **1** (4.59 ppm). The *syn*-glycosidic conformation of **2a** might cause an anisotropic deshielding of C2′-H by the nitrogen atom at the 3-position.†

Substitution reaction of **2a** at the C6-position proceeded easily to give 6-amino and 6-alkoxy derivatives without affecting the *tert*-butylhydroxyamino function at the C8-position. Heating **2a** in ammoniacal MeOH in a sealed tube (60 °C, 4 days) gave the 6-aminopurine derivative **2b** in 82% yield. The 6-alkoxy derivatives **2c** and **2d** were also formed with ease by treatment with sodium alkoxides at room temperature in 70% and 76% yields, respectively. Compounds **2a**–**d** were converted to the corresponding triols **3a**–**d** in 87–98% yields by heating (60 °C) with ammonium fluoride in MeOH (Scheme 1).

The *tert*-butylhydroxyamino group of **3a**–**d** was easily oxidized with Ag_2O in toluene to afford the corresponding aminoxyl



entry	reagent	solvent	temp.	product	R^2	yield (%)
1	NH_3	MeOH	60°C	**2b**	NH_2	82
2	NaOMe	MeOH	r.t.	**2c**	OMe	70
3	NaOEt	EtOH	r.t.	**2d**	OEt	76



Scheme 1

radicals **4a**–**d**, which was confirmed by EPR spectroscopy. Attempts to isolate the radicals **4a**–**d** were unsuccessful. But, for example, an EPR spectrum of **4b** is shown in Fig. 1 (g value = 2.005). Each triplet signal showed complex splitting due to delocalization of an unpaired electron of the aminoxyl radical in the purine nucleus. In addition, it was noted that the radical **4b** was stable over 24 h even in aqueous solution at room temperature.

Acetylation of **2a** in the usual manner (Ac_2O, pyridine) afforded **5** (72%), which showed unexpected reactivity. Reaction of **5** with sodium azide in DMF at room temperature gave the 2,6-diazido-8-(*tert*-butylamino)purine derivative **6a** (70%), which was easily converted to the 2,6-diamino-8-(*tert*-butylamino)purine derivative **6d** (93%) by reduction with $NaBH_4$. This double introduction of an azide function was considered to be the sum of two independent reactions. One is nucleophilic substitution at the C2-position, which might take place concomitantly with elimination of the *N*-acetoxy group *via* an intermediate **A**. Subsequent aromatization might afford the C2-substituted product.[5] The other is the usual substitution

DOI: 10.1039/b004445h

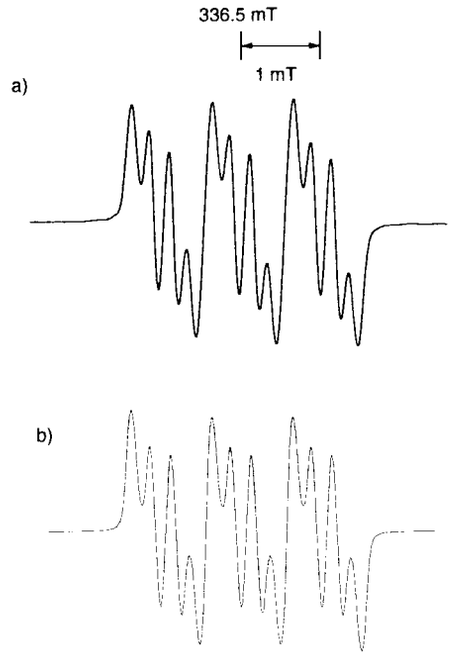
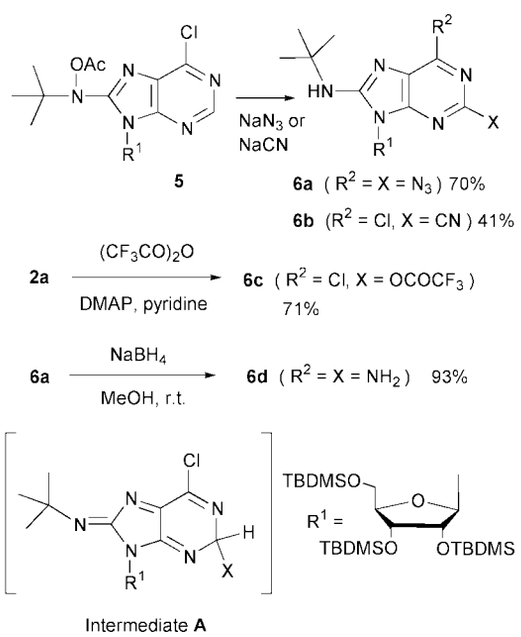


Fig. 1 a) EPR (9.44 GHz) spectrum of radical **4b** in toluene at 20 °C. b) The computer-simulated spectrum.‡



Scheme 2

reaction at the C6-position. Similar reaction of **5** with sodium cyanide in DMF at room temperature gave the 6-chloro-2-cyano-8-(*tert*-butylamino)purine derivative **6b** (41%), which possibly gives nucleosides with carbon functional groups at the C2-position of the purine nucleus by manipulation of the nitrile function. These results suggest that reaction at the C2-position was faster than that at the C6-position. The reactivity of **5**-type compounds was found to be affected by the nature of the leaving group on the nitrogen atom of the C8-substituent. That is to say, reaction of **2a** with trifluoroacetic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP) directly afforded **6c** in 71% yield**.** Introduction of an *N*-trifluoroacetoxy function as a leaving group resulted in smooth addition of the less nucleophilic trifluoroacetate anion (Scheme 2).

Thus, we successfully synthesized purine derivatives with a *tert*-butylamino group at the C8-position. Novel substitution reactions of **5**-type compounds enabled introduction of nitrogen, carbon, and oxygen functions at the C2-position to provide a new method for preparation of highly functionalized purine derivatives. Biological activities of the obtained compounds are currently under investigation.

Notes and references

† *Selected data* for **2a**: mp 144 °C (hexane). ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.62 (s, 1H), 6.98 (br s, 1H), 6.21 (d, J = 5.4 Hz, 1H), 5.19 (d, J = 5.1 Hz, 1H), 4.53 (t, J = 4.3 Hz, 1H), 4.04 (m, 1H), 4.01–3.72 (m, 2H), 1.46 (s, 9H), 0.96 (s, 9H), 0.86 (s, 9H), 0.78 (s, 9H). Anal. Calc. for $C_{32}H_{62}N_5O_5ClSi_3$: C, 53.64; H, 8.72; N, 9.77. Found: C, 53.80; H, 8.77; N, 9.77%.

‡ The splitting constants used are a_N = 10.50, 2.68, 1.16, 0.40 and 0.40 (G).

1 J. Fujita, M. Tanaka, H. Suemune, N. Koga, K. Matsuda and H. Iwamura, *J. Am. Chem. Soc.*, 1996, **118**, 9347 and references cited therein.
2 (*a*) J.-L. Duh and A. M. Bobst, *Helv. Chim. Acta*, 1991, **74**, 739 and references cited therein; (*b*) R. I. Zhdanov, V. A. Porotikova and E. G. Rozantsev, *Synthesis*, 1979, 267; (*c*) T. Gnewuch and G. Sosnovsky, *Chem. Rev.*, 1986, **86**, 203.
3 K. Kato, H. Hayakawa, H. Tanaka, H. Kuramoto, S. Shindoh, S. Shuto and T. Miyasaka, *J. Org. Chem.*, 1997, **62**, 6833.
4 T. Ishida and H. Iwamura, *J. Am. Chem. Soc.*, 1991, **113**, 4238.
5 For a method to introduce a functional group into the C2-position of the purine nucleus, see ref. 3 and A. Matsuda, M. Shinozaki, T. Miyasaka, H. Machida and T. Abiru, *Chem. Pharm. Bull.*, 1985, **33**, 1766 and references cited therein.