CHEMISTRY LETTERS, pp. 235-238, 1989.

The Synthesis of 2'-Deoxyadenosine *via* Stereospecific Coupling Reaction

Hiroshi KAWAKAMI,* Hajime MATSUSHITA, Yoshitake NAOI,†
Kazuo ITOH,† and Hajime YOSHIKOSHI†
Life Science Research Laboratory, Japan Tobacco Inc.,
6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227
†Tokyo Research Laboratory, Yuki Gosei Kogyo Co., Ltd.,
3-37-1 Sakashita, Itabashi-ku, Tokyo 174

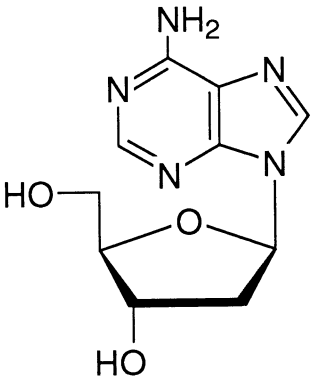
The coupling reaction of the sodium salt of adenine, which could be easily prepared by deprotonation with sodium hydroxide or sodium methoxide, with 1-α-chloro-2-deoxyribose derivative proceeded in a good stereospecific manner in acetone as a solvent to give the β-anomer of the corresponding acylated adenosine.

Much attention has recently been paid to 2'-deoxyadenosine(**1**) as a material for genetic engineering and as a source of many pharmacologically potent materials. For example, **1** is easily converted to 2',3'-dideoxyadenosine,[1] which shows a significant antivirus activity against HTLV-III which causes Acquired Immune Deficiency Syndrome (AIDS).[2] Because of no practical method for the chemical preparation, **1** is supplied in limited quantities only by separation from the hydrolized products of DNA of natural source. On a laboratory scale, the following two methods of the chemical preparation of **1** are known: One is the deoxygenation of adenosine,[3] and the other is coupling reactions between adenine derivatives and 2-deoxyribose derivatives.[4] Since it is difficult to differentiate the two secondary hydroxyl groups of adenosine, the former method is not useful for the practical purpose. In general, coupling reactions between 2-deoxyribose derivatives and nucleic bases with catalysts, especially Lewis acids, proceed in a non-stereospecific manner to give anomeric mixtures. In recent years, the coupling reactions between activated nucleic bases and 1-α-chloro-2-deoxyribose derivatives, for example 1-α-chloro-2-deoxy-3,5-di-O-(p-toluoyl)-D-ribose(**2**) which could be obtained as the pure form, were reported to proceed efficiently in S_N2 mode at the C-1 position in the sugar to give only β-anomers. As activated nucleic bases, silylated uracil derivatives[5] and the sodium salts of heterocyclic compounds, which are prepared *in situ*,[6] have been reported. Especially, Robins et al. have reported the preparative method of 2'-deoxyadenosine derivatives by the coupling reaction between **2** and the sodium salts, prepared by *in situ* deprotonation of 6-chloropurine derivatives with NaH followed by the amination.[6a] However, this method is not convenient for the preparation of 2'-deoxyadenosine **1**, because 6-chloropurine derivatives are rather expensive and the amination step requires somewhat higher pressure. In order to accomplish the

synthesis of **1** more efficiently, the coupling reaction between **2** and the salts of adenine derivatives was examined under various conditions.

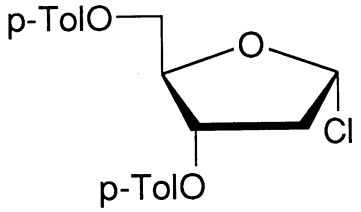
At first, the coupling reaction between adenine and chlorosugar **2** was carried out under the conditions reported by Robins et al. (*in situ* deprotonation by NaH, acetonitrile as a solvent). However, the desired N-9 coupling products were obtained as the anomeric mixture in 35% yield. Since the H-9 proton of adenine is known to be sufficiently acidic (pKa=9.80) for deprotonation by NaOH or NaOMe, we tried to isolate the Na salt of adenine (**3a**). Addition of one equivalent of NaOH or NaOMe to a suspension of adenine in methanol resulted in disappearance of the solid. After removal of the solvent, white solid **3a**, which was stable to air and moisture, was obtained and used for the coupling reactions. The results are summarized in Table 1.

As the result of solvent effects (entries 2-10), the good anomeric specificities were achieved in moderate polar solvents, for instance, acetone and 1,2-dimethoxyethane (entries 8 and 9). These results were reasonable in terms of the following facts; the chlorosugar **2** was easily anomerized in polar solvents which was reported by Walker et al.,[5a] and the Na salt **3a** was not soluble in non-polar organic solvents. However, the yields of N-9 coupling products were not so high because of low solubility of Na salt **3a**, therefore, we intended to raise the solubility. Benzoylation of the amino function made no remarkable change in yield (entries 11-15). The stereospecificities were lowered by the change of the counter cations of the salts (entries 16 and 17) or the addition of phase transfer catalysts (entries 1

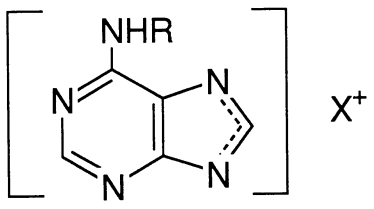


1

p-Tol=p-$CH_3C_6H_4C$(=O)-

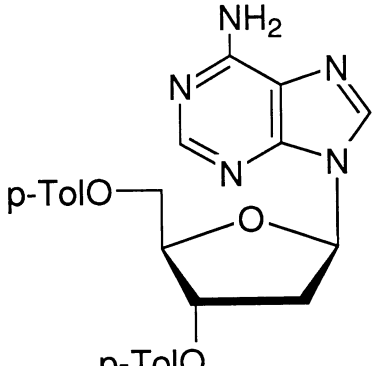


2



X^+

3a:R=H ;X=Na
3b:R=Bz;X=Na
3c:R=H ;X=K
3d:R=H ;X=Li



4

Table 1. The coupling reactions between chlorosugar **2** and salts of adenine derivatives **3**[a)]

Entry	Base	Solvent	Yield/%[b)] (α+β)	Stereospecificity[b)] (α:β)
1[c)]	**3a**	CH_3CN	35	16 : 84
2	**3a**	$CHCl_3$	14	36 : 64
3	**3a**	CH_2Cl_2	24	15 : 85
4	**3a**	PhH	14	64 : 36
5	**3a**	Et_2O	17	16 : 84
6	**3a**	THF	23	6 : 94
7	**3a**	EtOAc	20	5 : 95
8	**3a**	DME	40	8 : 92
9	**3a**	acetone	50	17 : 83
10	**3a**	DMF[d)]	35	41 : 59
11	**3b**	CH_3CN[d)]	37	21 : 79
12	**3b**	CH_2Cl_2	38	18 : 82
13	**3b**	EtOAc	36	4 : 96
14	**3b**	DME	46	5 : 95
15	**3b**	acetone	42	10 : 90
16	**3c**	CH_3CN[d)]	18	57 : 43
17	**3d**	CH_3CN[d)]	17	71 : 29
18[e)]	**3a**	CH_2Cl_2	48	36 : 64
19[f)]	**3a**	CH_2Cl_2	30	59 : 41
20[g)]	**3a**	CH_2Cl_2	51	56 : 44

a) Coupling reactions were carried out under the following conditions; 0.25 mmol scale, sugar:salt=1:2, in 10 ml solvent, room temperature, for about 24 h.

b) Yields and stereospecificities were determined by HPLC (UV detection, 260 nm; compared to uracil as an internal standard) after deprotection by concentrated aqueous ammonia in methanol.

c) Coupling reaction was carried out under Robins' conditions. The isolated yield of **4** and its α anomer was described. Stereospecificity was determined by ^{1}H-NMR.

d) In 2 ml solvent.

e) A catalytic amount of 18-crown-6 ether was added.

f) A catalytic amount of Bu_4NHSO_4 was added.

g) A catalytic amount of $BnEt_3NCl$ was added.

8-20). The best result was obtained when the coupling reaction was carried out between **2** and Na salt **3a** in acetone.

A typical procedure is as follows. To a suspension of Na salt **3a** (0.40 g, 2.5 mmol) in 25 ml of acetone (dried over molecular sieves 3A) was added 1-chloro-2-deoxy-3,5-di-O-(p-toluoyl)-α-D-erythro-pentofuranose (**2**) (0.49 g, 1.3 mmol). The reaction mixture was stirred at room temperature for 19 hours under anhydrous conditions, and poured into brine, and extracted with CH_2Cl_2. After drying over anhydrous $MgSO_4$, the organic layer was concentrated, and the residue was purified by

column chromatography (silica gel, CH_2Cl_2:acetone=50:50, v/v) to give 0.34 g of the anomeric mixture (yield 56%, α:β=20:80; determined by ^{1}H-NMR). Pure β-anomer **4** (0.29 g) was obtained in 43% yield by recrystalization from ethyl acetate. ^{1}H-NMR suggested that the crystals contained 1 molecule of ethyl acetate per 2 molecules of **4**.

In conclusion, we developed a simple procedure of the coupling reaction utilizing the sodium salt of adenine for the chemical preparation of 2'-deoxyadenosine. In moderate polar solvents such as acetone or 1,2-dimethoxyethane stereospecificities are rather good but yields are moderate. For increasing the yield further investigations are now under way.

References

1) E. J. Prisbe and J. C. Martin, Synth. Commun., 15, 401 (1985).
2) H. Mitsuya and S. Broder, Proc. Natl. Acad. Sci. U. S. A., 83, 1911 (1986).
3) See, for example, M. J. Robins, J. S. Wilson, and F. Hansske, J. Am. Chem. Soc., 105, 4059 (1983).
4) See, for example, G. Schramm, G. Lünzmann, and F. Bechmann, Biochim. Biophys. Acta, 145, 221 (1967).
5) a) A. J. Hubbard, A. S. Jones, and R. T. Walker, Nucleic Acids Res., 12, 6827 (1984); b) H. Aoyama, Bull. Soc. Chem. Jpn., 60, 2073 (1987).
6) a) Z. Kazimierczuk, H. B. Cottam, G. R. Revankar, and R. K. Robins, J. Am. Chem. Soc., 106, 6379 (1984); b) See, for example, F. Seela and H. Steker, J. Chem. Soc., Perkin Trans. 1, 1985, 2573.

(Received October 19, 1988)