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t-Butyldimethylsilyloxymethyl Group, a Versatile Protecting Group of Adenine

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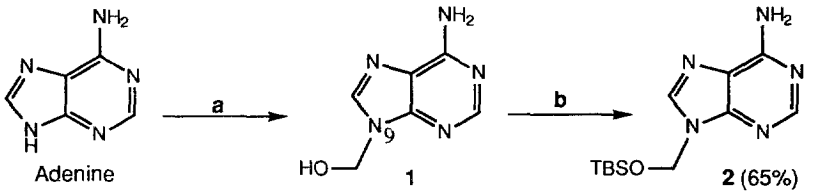
Abstract: The successive treatment of adenine with formaldehyde in basic conditions and with *t*-butyldimethylsilyl trifluoromethanesulfonate gave regioselectively 9-*t*-butyl-dimethylsilyloxymethyl-adenine **2** in a yield of 65%. This derivative **2** was soluble in most organic solvents. The silyl group was removed under acidic conditions. Copyright © 1996 Elsevier Science Ltd

In order to prepare nucleoside analogs, we needed an adenine derivative soluble in organic solvents in which the protecting group was stable under basic and reducing conditions, resistant to organometallic reagents and removable under specific conditions. Allyl,[1] benzyl,[2] cyanoethyl[3] and pivaloyloxymethyl[4] groups have been used as protecting groups of adenine. However, allyl and benzyl groups are sensitive to reducing reagents and cyanomethyl and pivaloyloxymethyl groups are unstable under basic conditions.[1-4] One of the most serious problems associated with the chemistry of adenine is its low solubility in most organic solvents.[5a] As an alternative 6-chloropurine more soluble than adenine in organic solvents,[5b] has been used as starting material.[6] Nevertheless, 6-chloropurine and its derivatives are sensitive to basic conditions.[6, 7] We report herein the use of *t*-butyldimethylsilyloxymethyl group as a protecting group of the N-9 position of adenine. The *t*-butyldimethylsilyloxymethyl group was introduced in two steps by successive treatment of adenine with formaldehyde in aqueous basic conditions and with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in pyridine. The corresponding modified adenine **2** was soluble in most organic solvents. Starting from compound **2**, a series of adenine analogs have been prepared.[8] This protective group has been proven to be stable under various conditions : LDA, $LiAlH_4$, and Pd catalyzed reactions (hydrogenation, Heck and Stille reactions). For instance, treatment at low temperature of **2** with LDA followed with iodine gave in good yield the corresponding C-8-iodo derivative.

Formaldehyde has been used as a protecting group for the heterocyclic NH of benzimidazole[9] and its reaction with adenine has been studied by ^1H and ^{13}C NMR in $^2H_6$-DMSO.[10] It was deduced from this study that the N-9 position of adenine was highly reactive with formaldehyde as almost half of the starting adenine disappeared within one hour; however, after several hours, a complex mixture of products has been observed.[10,11] Under basic conditions, the reactivity of the N-9 position should be enhanced. In order to obtain the best yield of hemiaminal **1**, we have studied the reaction of adenine with formaldehyde in water in various conditions of reagent concentration and reaction time (Table 1).



a) HCHO, H_2O, NaOH

b) TBDMSOTf (1.2 eq.), pyridine, 0 °C to 20 °C, 2 h

Table 1. Hydroxymethylation of Adenine under Various Conditions.

Entry	HCHO (eq.)[a]	NaOH (eq.)[a]	Reaction time	Yield of 1[b]
1	1.1	0.05	2 h	50%
2	1.1	0.05	24 h	55%
3	1.6	0.05	24 h	60%
4	1.6	0.1	2 h	75%
5	1.6	0.1	24 h	70%
6	**1.6**	**0.2**	**2 h**	**86%**
7	1.6	0.2	24 h	80%
8	1.6	0.4	24 h	65%
9	1.6	0.9	2 h	- [c]
10	3.3	0.05	24 h	- [c]

a) A stirred suspension of adenine in water was treated at 20 °C with the number of equivalents of formaldehyde and sodium hydroxide indicated in the table.

b) An aliquot of the reaction suspension was taken and dissolved in $^2H_6$-DMSO. The water signal was suppressed by a presaturation experiment. The ratio of hemiaminal 1 and adenine was deduced from the ^1H NMR spectrum by comparison of the integrations of the H-8 signals.

c) Complex mixture of compounds.[12]

The results of our study, summarized in Table 1, showed that the yield of compound **1** depended on base and formaldehyde concentration and reaction time. The highest yield was obtained with an excess of formaldehyde (1.6 eq.) and a catalytic amount of sodium hydroxide (0.2 eq) in 2 hours (entry 6).[13] A mixture of hemiaminal **1** (86%) and unreacted adenine (14%) was obtained under condition 6. The reaction was highly regioselective and none of the other N-3, N-6 or N-7 regioisomers could be observed by ^1H NMR.

The *t*-butyldimethylsilyl group was introduced at the hydroxyl group of the intermediate **1** by treatment with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in pyridine.[14] The silylether **2** was isolated by crystallization as a pure compound in 65% yield in two steps from adenine. The *t*-butyldimethylsilyloxymethyl group of compound **2** and derivatives [8] was removed in quantitative yield by treatment with a mixture of trifluoroacetic acid and water (9:1) at 20 °C for 2 hours.

The ^1H NMR of **1** showed unambiguously that the 6-NH_2 was not substituted as the integration of its signal corresponded to two protons. The absorption spectrum and the chemical shifts of C-4 and C-5 in ^{13}C NMR of **1**[10] and of the silylether **2** were in agreement with the substitution at N-9 as compared with the spectral data of N-7 and N-9 methyladenine (Table 2).[15] In addition, long range heteronuclear coupling constants (HBMC)[16] between the methylene protons and the carbons C-2, C-4 and C-8 confirmed this assignment (data not shown).

Table 2. UV Absorption Data and ^{13}C Chemical Shifts of Selected Signals of *N*-Substituted-Adenine Derivatives.

Adenine derivatives	λmax (nm)[a)]	ε ($M^{-1}.cm^{-1}$)[a)]	δ (C-4)[b)]	δ (C-5) [b)]
9-Methyladenine	262	12500	149.9	118.7
7-Methyladenine	272	9500	159.8	111.7
1	-	-	149.1	118.6
2	262	16700	149.1	118.6

a) UV Absorption spectra in ethanol.

b) ^{13}C NMR spectra in $^2H_6$-DMSO; δ in ppm.

The hydroxymethylation of adenine in aqueous solution of sodium hydroxide (2 eq.) and formaldehyde (3.7 eq.) has been found to occur at N-6.[17] The N-6 hydroxymethyladenine was isolated after neutralization with a yield of 18%.[17] The ^1H and ^{13}C NMR spectra of the N-6 hydroxymethyladenine and of product **1** were different. The experimental conditions were however different. In particular, the reaction medium was homogeneous when an excess of base was used[17] and was heterogeneous when a catalytic amount of base was used as observed under our reaction conditions.

Extension of this new method of protection of adenine to the other bases is under way. The pKa of the other bases are similar to the pKa of adenine, thus their reaction with formaldehyde under appropriate conditions should occur with a regioselectivity comparable to that observed with adenine. Finally, the reaction of adenine should not be limited to formaldehyde and should be extended to other aldehydes. In particular, it could be the possible model of the first step of prebiotic pathway of nucleosides.[18]

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13. Typical procedure for the preparation of silylether **2**. A suspension of adenine (2 g) in water (65 mL) was treated with solid NaOH (0.2 eq.) and an aqueous solution of formaldehyde (2 mL, 1.5 eq.) (the pH of the 40% aqueous solution of formaldehyde was checked before use and adjusted to neutrality with a 1 N aqueous solution of NaOH). After stirring at 20 °C for 2 hours, the suspension, consisting of a mixture of adenine (14%) and **1** (86%) was filtered and the solid dried over P_2O_5. The solid was suspended with stirring at 4°C in dry pyridine (120 mL) and *t*-butyldimethylsilyl trifluoromethanesulfonate (1.2 eq.) was added. The reaction temperature was allowed to rise to 20°C and stirring was further continued for 3 hours. After evaporation of pyridine, **2** was extracted with $CHCl_3$ and the unreacted adenine was eliminated in the aqueous phase. The silylether **2** was obtained pure after washing with hexane and recrystallization in EtOH, in 65% yield for the two steps. m.p.=228-230°C; UV(EtOH): λmax=262 nm, ε=15700 M^{-1} cm^{-1}; ^1H NMR (200MHz, $CDCl_3$), δ (ppm) : 0.10 (6H, s, Si-CH_3); 0.88 (9H, s, $SiC(CH_3)_3$), 5.62 (2H, ls, NH_2), 5.75 (2H, s, CH_2), 7.97 (1H, s, H-2), 8.38 (1H, s, H-8); ^{13}C NMR ($^2H_6$-DMSO): -5.3 (p, Si-$\underline{C}H_3$), 17.6 (q, Si-$\underline{C}(CH_3)_3$), 25.4 (p, Si-C($\underline{C}H_3$)$_3$), 66.3 (s, CH_2), 118.5 (q, C-5), 140.6 (t, C-8), 149.1 (q, C-4), 153.3 (t, C-2), 155.4 (q, C-6); MS, CI (NH_4^+), (m/z) : 280.2 (MH^+,100), 222.0 (26), 135.9 (8); Anal. calcd. for $C_{12}H_{21}N_5OSi$, C 58, H 7.57, N 25.06; found C 51.51, H 7.72, N 25.18.
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