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Alkylation of Adenine with t-Propargyl Chlorides: Acetylene/Allene Ratio and N^9/N^7 Regioselectivity[1]

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Abstract: *Alkylation of adenine (**6**) with dialkylpropargyl chlorides **3a** and **3b** gave N^9- and N^7-acetylenes **7a**, **7b** and **9a**, **9b** accompanied by N^9-allenes **8a**, **8b**. Bromoallene **10a** gave only **7a** and **7b** but no allene **8a**. Reaction of propargyl chloride with **6** led only to N^9-propargyladenine (**7c**) whereas chloroallene **10b** afforded **7c** and allene **8c**. The possible reaction course will be discussed with emphasis on the influences of structure, reagent and solvent on acetylene/allene ratio and N^9/N^7 regioselectivity of alkylation. The nonequivalent methylene groups of **7b** and **9b** have $\Delta\delta$ 0.67 and 1.07, respectively, appearing as sextets in the ^1H NMR spectra.*

INTRODUCTION

Nucleic acid bases carrying an allenic residue are of interest as nucleoside analogues[2-4] with biological activity. Thus, adenallene (**1a**) and cytallene (**1b**) are effective agents[5-7] against human immunodeficiency virus (HIV), a cause of acquired immunodeficiency syndrome (AIDS). Allenols such as **1a** or **1b** were previously obtained[2] by a base-catalyzed isomerization of acetylenes **2a** or **2b** (Scheme 1). Obviously, such a method is not applicable for synthesis of allenes carrying two substituents at the C_3'. The purpose of this study was to investigate one possible route to such analogues.

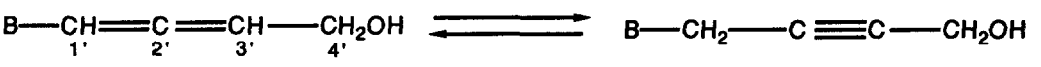
It is known[8,9] that alkylation of tertiary bases with 1,1-dialkylpropargyl chlorides (**3**) gives quaternary salts **4** derived from the starting halide and the respective allenic products **5** (Scheme 2). Thus, less bulky dimethyl derivatives **3a** favor formation of acetylenes **4a** whereas reactions with more hindered chlorides such as **3b** led predominantly to allenes **5b**. Because nucleic acid bases are nucleophiles which undergo alkylation with a variety of alkylating agents, it was of interest to study their reactions with t-propargyl halides. Our attention was focussed on the ratios of acetylene/allene products and regioselectivity of alkylation. The results obtained with adenine (**6**) and dialkylpropargyl chlorides **3a**, **3b** as well as related alkylations are the subject of this communication.

SYNTHESIS

Alkylation of sodium salt of adenine[10] (**6**) with dimethylpropargyl chloride[11] (**3a**) in hexamethylphos-

phoramide (HMPA) at 60°C for 36 h gave a mixture of N^9-(dimethylpropargyl)adenine (**7a**) and N^9-(3-methyl-1,2-butadien-1-yl)adenine (**8a**) in 24 % yield, inseparable by column chromatography, along with the N^7-isomer **9a** (9 %, Scheme 3). The ratio of allene **8a**/acetylene **7a**, as determined by ^{1}H NMR spectra, was 7 : 3. When the reaction of **3a** with **6** was performed in dimethylformamide (DMF) in the presence of K_2CO_3 at 60°C for 3 days, the yields of the mixture of **7a** + **8a** and acetylene **9a** were similar (30 and 5 %, respectively) but the **8a**/**7a** ratio (1.5 : 8.5) was reversed.

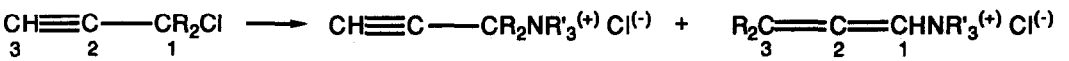
Scheme 1



1 2

1a, 2a: B = adenin-N^9-yl 1b, 2b: B = cytosin-N^1-yl

Scheme 2



3 4 5

Series a: R = CH_3, R' = alkyl; series b: R = CH_3CH_2, R' = alkyl; 3c: R = H; 4d: R = CH_3CH_2, R' = CH_3

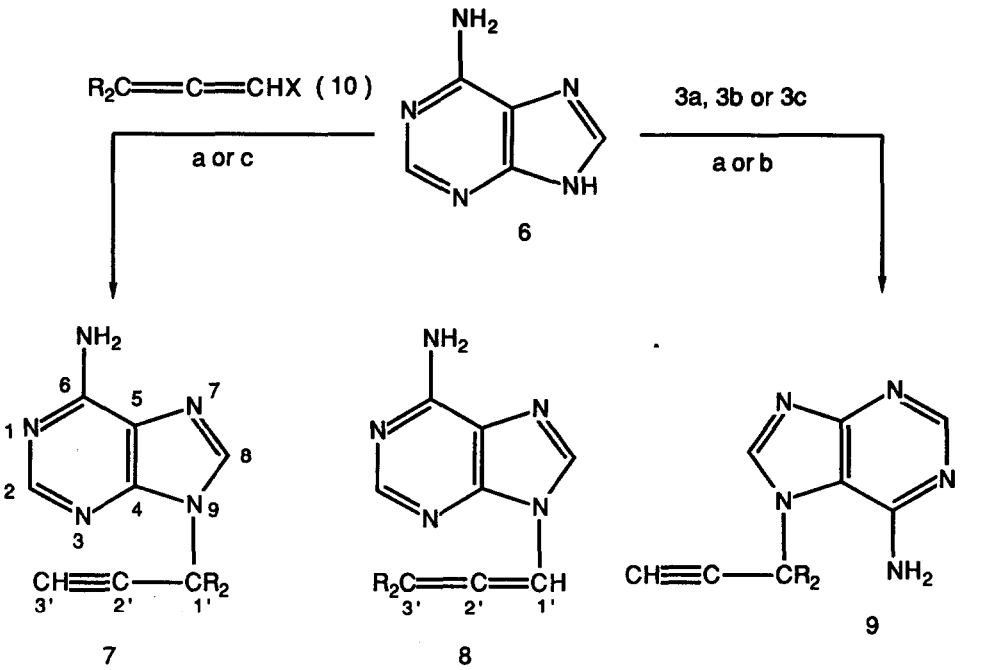
When sodium salt of adenine (**6**) was alkylated with diethylpropargyl chloride[11] (**3b**) in HMPA at 60°C for 2 days a 1 : 1 mixture of allene **8b** and acetylene **7b** was obtained in 30 % yield. The N^7-acetylene **9b** (5 %) was also obtained. All three products were also formed after reaction of **6** with **3b** in DMF in the presence of K_2CO_3 at 60°C for 3 days. The yields were as follows: 15 % (N^9-acetylene **7b**), 15 % (N^9-allene **8b**) and 9 % (N^7-acetylene **9b**). In contrast to alkylation of **6** with dimethylpropargyl chloride (**3a**), reagent and solvent (NaH/HMPA or K_2CO_3/DMF) have little effect on the ratio allene **8b**/acetylene **7b** but a distinct influence on the ratio of regioisomers **7b**/**9b**.

It is noteworthy that sodium salt of **6** and 1-bromo-3-methyl-1,2-butadiene[12] (**10a**) in DMF for 3 h at room temperature gave only acetylenes **7a** and **9a** in equal amounts (13 % yield of each). Allene **8a** was not formed and no improvement of yield was seen in a reaction catalyzed[13] with CuBr.

In stark contrast to alkylation of adenine (**6**) with t-propargyl chlorides **3a** and **3b**, the reaction with propargyl chloride **3c** in DMF (K_2CO_3) at room temperature for 15 h gave only N^9-propargyladenine (**7c**) in 75 % yield. 1-Chloroallene[14] (**10b**) and sodium salt of **6** in HMPA for 15 h furnished **7c** (33 %) and N^9-allenyladenine (**8c**, 10 %).

At a first glance, it would seem that these results can simply be interpreted in terms of 1,3-elimination of HX from **3a** or **3b** and formation of a delocalized carbene **11** (Scheme 4)[15]. Thus, adenine (**6**) is neither small nor too large a nucleophile and, therefore, formation of both acetylenic and allenic products can be expected. However, the latter reaction course was observed only in case of bases significantly stronger than adenine (**6**).

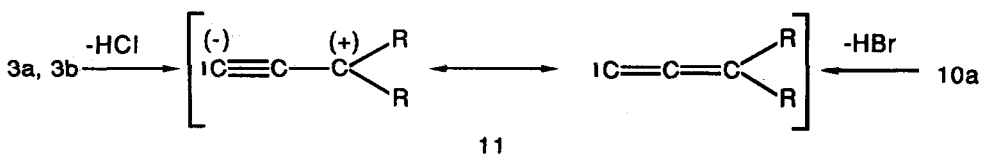
Scheme 3



7a - 9a: R = CH_3, 7b - 9b: R = CH_3CH_2, 7c, 8c: R = H, 10a: R = CH_3, X = Br, 10b: R = H, X = Cl

a. NaH, HMPA. b. K_2CO_3, DMF. c. NaH, DMF.

Scheme 4



With more powerful nucleophiles (thiophenoxide) a combination of S_N2 and S_N2' mechanisms was observed[15]. In addition, a similar product composition should result from the reaction of adenine (**6**) with acetylenic and allenic halides **3a**, **10a**. A lack of allene **8a** after alkylation of adenine (**6**) with **10a** as well as the reagent- and solvent-dependent acetylene/allene ratio in case of **3a** may indicate interference of other mechanisms. In particular, a surprising lack of N^9/N^7 regioselectivity observed in alkylation of **6** with **10a** as well as a high proportion of N^7-alkylation in all other cases could conceivably be explained by an S_N1 mechanism. Such a reaction course may be disfavored in dipolar aprotic solvents[16] structural factors (relief of steric hindrance at a branched carbon of allylic type) may provide the necessary driving force. Thus, 3-chloro-3-methyl-1-(trimethyl-

silyl)-1-butyne was solvolyzed 2.3 times faster[17] than t-butyl chloride. It is also likely that carbonium ion will attack N^7- and N^9-position rather indiscriminately. A complete lack of formation of the N^7-isomers of allenes is then more in line with an S_N2-like mechanism than S_N1-type of attack. Also, no N^7-isomers were formed in alkylation of adenine (**6**) with propargyl and allenic chlorides **3c**, **10b**. In this case, an S_N1 substitution is disfavored by the absence of a tertiary carbon atom.

STRUCTURE ASSIGNMENT AND NMR SPECTROSCOPY

The assignments of N^9-regioisomers **7a**, **7b**, **8b** vs. N^7-derivatives **9a**, **9b** were based on UV and NMR spectra along with electrophoretic mobilities. The N^7-isomers have a bathochromically shifted UV maxima relative to N^9-alkyl derivatives[18]. Compounds **7a** and **9a** have an equal mobility on paper electrophoresis at pH 3.7 which excludes the possibility that compound **9a** is a significantly more basic[18] N^3-isomer. An attempt to prepare the latter by alkylation of adenine (**6**) with **3a** following the procedure described for allylic halides[19] (heating in DMF at 70°C for 5 hours) was unsuccessful. The UV spectrum of allene **8b** is very similar to adenallene[2] (**1a**) except for a slight but expected bathochromic shift. It is interesting that the purine H_2 and H_8 signals of allene **8b** are overlapped as in adenallene[2] (**1a**). Comparison of the ^1H and ^{13}C chemical shifts of heterocyclic moieties and C_1's was of limited value for isomeric assignment because most of compounds previously studied were guanine derivatives[20,21]. Nevertheless, the C_8, C_2 and $C_{1'}$ chemical shifts of **7a**, **7b** and **9a**, **9b** follow the trend observed for N^9- and N^7-methyladenine[22]. The differences in C_5 chemical shifts are too small to be of significance. It is important to note that the NH_2 signals of N^9-isomers **7a**, **7b** are shifted upfield from those of N^7-derivatives **9a**, **9b** in contrast to 2-aminopurines[21]. Also, $\Delta\delta$ values for H_2 and H_8 signals of N^7-isomers **9a**, **9b** are much greater than those of N^9-isomers **7a**, **7b**. The assignment of H_8 in N^7 isomer **9a** followed from the ^1H NMR spectrum after deuterium exchange[23]. The acetylenic proton ($H_{3'}$) was completely deuterated.

The ^1H NMR spectra of diethylpropargyladenines **7b** and **9b** show a nonequivalency of methylene groups[24] which appear as sextets[25]. As shown for **9b**, this spin-coupling pattern was not changed by heating the probe up to 120°C. The signals of methyl groups form sharp triplets (**7b**, **9b**) or, in case of dimethylpropargyl adenines **7a** and **9a**, singlets. Interestingly, a differential interaction of methylene functions with adenine ring, may be responsible for the observed large differences of chemical shifts ($\Delta\delta$ 0.67 and 1.07, respectively) of methylene groups in crowded molecules of **7b** and **9b**. The rotation of adenine rings is severly restricted in both isomers. The computer-minimized structures (Chem 3D Plus, Version 3.0) indicate that one of the methylene groups of N^9-isomer could be deshielded with the N_3 atom of the purine ring. A similar but stronger deshielding effect observed in N^7-isomer may then be primarily caused by the N^9 with some assistance from the N_3 and exocyclic amino group. Such factors can account for large downfield shifts of one set of methylene groups in both isomers. Also, this selective interaction can create an asymmetric environment at the relevant methylene functions and, consequently, $C_{1'}$. The protons of the methylene groups of **7b** and **9b** are then diastereotopic. The ^{13}C spectra of **7b** and **9b** exhibit only single signals for both methylene carbons and $C_{1'}$. It should be perhaps noted that a similar stereoselective interaction of methylene groups could generate axial dissymmetry of allenic system in **8b** and thus diastereotopicity along the lines mentioned for **7b** and **9b**. However, the molecule of **8b** is not crowded and the adenine moiety can rotate freely. The ^1H NMR spectra of **9a** and **9b**

also indicate that the rotation of NH_2 group is significantly impeded. Thus, the latter function forms two singlets in both **9a** and **9b** whereas in **7a** and **7b** only a single peak was observed. This splitting is a further confirmation of assignments for **9a** and **9b** as N^7-isomers.

BIOLOGICAL DATA

Allene **8b** inhibited the growth of murine leukemia L1210 cells in a clonogenic assay with IC_{50} 100 μM. It was also marginally cytotoxic at 500 μg/disk in a zone assay (soft agar colony formation) toward mouse colon C38, human lung tumor H125 and low malignancy cell lines.

EXPERIMENTAL

General Methods. See[2, 26]. Starting halides were either obtained from commercial sources (**3c**) or they were prepared as described[11,12,14] (**3a**, **3b**, **10a** and **10b**). The column chromatography and TLC were performed in the following solvent systems: S_1 - EtOAc - Me_2CO (1 : 1), S_2 - CH_2Cl_2 - MeOH (9 : 1), S_3 - EtOAc - MeOH (95 : 5), S_4 - EtOAc - MeOH (9 : 1). All NMR spectra were determined in $(CD_3)_2SO$ unless stated otherwise. Starting materials: ^1H and ^{13}C NMR ($CDCl_3$) **3b**: δ 2.63 (s, 1, H_1), 1.95 (q, 4, CH_2), 1.14 (t, 6, CH_3); 84.03 (C_3), 74.37 (C_1), 68.18 (C_2), 37.12 (CH_2), 9.63 (CH_3). **10a**: δ 5.99 (1, t, H_1), 2.10 (m, 4, CH_2), 1.03 (t, 6, CH_3); 198.49 (C_2), 120.21 (C_3), 73.91 (C_1), 25.91 (CH_2), 11.88 (CH_3). **10b** + **3c** (9 : 1), **10b**: δ 6.06 (m, 1, H_1), 5.21 (m, 2, H_3); 207.49 (C_2), 88.69 (C_1), 84.75 (C_3); **3c**: δ 4.11 (m, 2, H_3), 2.26 (m, H_1).

A. Alkylation of Adenine (6) with 1-Bromo-3,3-dimethylallene (10a). Reagent **10a** (326 mg, 2.22 mmol) was added to a stirred mixture of adenine (**6**, 150 mg, 1.11 mmol) and NaH (60 %, 89 mg, 2.22 mmol) in DMF (5 mL). The stirring at room temperature was continued for 3 h. The mixture was evaporated in vacuo and the residue was chromatographed in solvent S_1 to give compound **7a** (30 mg, 13 %), mp. 195 - 196°C (transition point 165 - 166°C). UV max nm (ethanol) 261 (ε 12,400). ^1H NMR δ 8.21 and 8.11 (2s, 2, H_2 + H_8), 7.24 (s, 2, NH_2), 3.74 (s, 1, $H_{3'}$), 1.95 (s, 6, CH_3). ^{13}C NMR 156.84, 152.60, 149.68, 139.01, 120.83 (adenine), 85.38 ($C_{2'}$), 76.58 ($C_{3'}$), 53.35 ($C_{1'}$), 29.31 (CH_3). EI-MS 201 (M, 100.0). Anal. Calcd for $C_{10}H_{11}N_5$: C, 59.69; H, 5.50; N, 34.80. Found: C, 59.59; H, 5.47; N, 34.49.

Elution with solvent S_2 afforded compound **9a** (30 mg, 13 %), mp. 205 - 207°C (transition point 195 - 196°C). UV max nm (ethanol) 277 (ε 10,000). ^1H NMR δ 8.66 (s, 1, H_2), 7.76 (s, 1, H_8), 8.09 and 7.99 (2s, 2, NH_2), 4.11 (s, 1, $H_{3'}$), 2.08 (s, 6, CH_3). ^{13}C NMR 155.01, 152.02, 148.21, 140.64, 121.25 (adenine), 83.32 ($C_{2'}$), 80.48 ($C_{3'}$), 59.00 ($C_{1'}$), 28.17 (CH_3). EI-MS 201 (M, 44.2). Exact mass calcd 201.114, found 201.111. Anal. Calcd. for $C_{10}H_{11}N_5$: C, 59.69; H, 5.50; N, 34.80. found: C, 59.74; H, 5.51; N, 34.65.

Compounds **7a** and **9a** have identical mobilities towards cathode on paper electrophoresis[26] in citrate buffer (pH 3.7).

Acetylene **9a** (10 mg) was refluxed[23] in D_2O (99.8 %, 6 mL) for 5 h and the solution was evaporated to dryness. The decreases of integrated intensities of the following signals relative to δ 8.66 were observed in the ^1H NMR spectrum: 7.76 (83 %), 8.09, 7.99 (93 %) and 4.11 (100 %).

B. With Dimethylpropargyl Chloride (3a) and NaH in HMPA. Reagent **3a** (228 mg, 2.22 mmol) was added to a stirred mixture of adenine (**6**, 100 mg, 0.74 mmol) and NaH (60 %, 59 mg, 15 mmol) in HMPA (10 mL). The stirring was then continued for 36 h at 60°C. The progress of alkylation was followed by TLC in S_2 and S_3 (double development). The most of HMPA was removed in vacuo (oil pump) and repeated column chromatography in solvent S_1 gave a mixture of compound **8a** and **7a** in the ratio of 7 : 3 as determined by ^1H NMR spectroscopy, 30 mg (24 %), mp. 150 - 157°C. IR (KBr) 1965 - 1970 cm^{-1}, C=C=C), ^1H NMR δ 8.21, 8.14, 8.13 and 8.12 (2s, 2, H_2 + H_8), 7.29, 7.23 (2s, 2, NH_2), 7.07 (s, $H_{1'}$ of **8a**), 3.70 (s, $H_{3'}$ of **7a**), 1.95 (s, CH_3 of **7a**), 1.84 (s, CH_3 of **8a**).

Continued elution of the column with solvent S_2 afforded N^7-acetylene **9a**, 13 mg (9 %) which was identical with a sample prepared by method A.

C. With Dimethylpropargyl Chloride (3a) and K_2CO_3 in DMF. Reagent **3a** (455 mg, 4.44 mmol) was added to a stirred mixture of adenine (**6**, 0.2 g, 1.48 mmol) and K_2CO_3 (flame-dried before use, 413 mg, 2.96 mmol) in DMF (15 mL). The stirring was continued for 72 h at 60°C. The mixture was evaporated and chromatographed as described in Method A and B to give a mixture of **8a** + **7a** (1.5 : 8.5, 90 mg, 30 %) and compound **9a** (15 mg, 5 %). The latter was identical with a sample prepared by Method A.

D. With Diethylpropargyl Chloride (3b) and K_2CO_3 in DMF. The reaction was performed as in Method C but with reagent **3b** instead of **3a** and on a half scale. After the usual work-up, chromatography in solvent S_1 afforded a 1 : 1 mixture of N^9-acetylene **7b** and N^9-allene **8b** (55 mg, 30 %). Elution with S_2 gave N^7-isomer **9b** (15 mg, 9 %), mp. 198-200°C. UV max nm (ethanol) 275 (ε 10,600). ^1H NMR δ 8.60 (s, 1, H_2), 7.72 (s, 1, H_8), 8.12 and 8.07 (2s, 2, NH_2), 4.24 (s, 1, $H_{3'}$), 3.06 and 2.04 (2sx, 4, CH_2), 0.66 (t, 6, CH_3). ^{13}C NMR 155.59, 152.66, 147.74, 142.45, 120.92 (adenine), 83.66 ($C_{2'}$), 80.43 ($C_{3'}$), 69.38 ($C_{1'}$), 31.41 (CH_2), 8.89 (CH_3). EI-MS 229 (M, 18.1). Exact mass calcd 229.1327, found 229.1331. Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.58; N, 30.54. Found: C, 62.77; H, 6.55; N, 30.70.

The mixture of **7b** and **8b** was rechromatographed in solvent S_4. The N^9-isomer **7b** was eluted first (26 mg, 15 %), mp. 198-200°C. UV max nm (ethanol) 261 (ε 12,000). ^1H NMR δ 8.14 and 8.07 (2s, 2, H_2 + H_8), 7.28 (s, 2, NH_2), 3.96 (s, 1, $H_{3'}$), 2.65 and 1.98 (2sx, 4, CH_2), 0.68 (t, 6, CH_3). ^{13}C NMR 156.86, 152.61, 149.12, 140.88, 120.97 (adenine), 81.69 ($C_{2'}$), 80.09 ($C_{3'}$), 63.58 ($C_{1'}$), 32.06 (CH_2), 9.00 (CH_3). EI-MS 229 (M, 5.7). Exact mass calcd 229.1327, found 229.1329. Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.58; N, 30.54. Found: C, 63.02; H, 6.64; N, 30.60.

The elution was continued with solvent S_4 to give allene **8b** (26 mg, 15 %), mp. 178-180°C. UV max nm (ethanol) 263 (ε 12,400), IR (KBr) 1965 cm^{-1} (weak, C=C=C). ^1H NMR δ 8.14 (2s, 2, H_2 + H_8), 7.32 (s, 2, NH_2), 7.28 (s, 1, $H_{1'}$), 2.14 (m, 4, CH_2), 0.98 (t, 6, CH_3). ^{13}C NMR 156.61, 153.51, 148.90, 138.49, 119.53 (adenine), 191.95 ($C_{2'}$), 122.63 ($C_{3'}$), 94.50 ($C_{1'}$), 26.59 (CH_2), 12.37 (CH_3). EI-MS 229 (M, 15.1, M). Exact mass 229.1327, found 229.1331. Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.86; H, 6.58; N, 30.54. Found: C, 62.74; H, 6.59; N, 30.58.

E. With Diethylpropargyl Chloride (3b) and NaH in HMPA. The Method B was followed on the same scale with **3b** instead of **3a**, reaction time 48 h. Separation of products was performed as in Methods B and D. The mixture of N^9-acetylene **7b** and allene **8b** (1 : 1, 50 mg, 30 %) was eluted first. It was followed by N^7-acetylene **9b** (10 mg, 5 %).

F. With Propargyl Chloride (3c). A mixture of adenine (**6**, 135 mg, 1 mmol), K_2CO_3 (276 mg, 2 mmol)

and **3c** (150 mg, 2 mmol) in DMF (20 mL) was stirred for 15 h at room temperature. The solution was evaporated in vacuo (oil pump) and and the residue was chromatographed in on a silica gel column in solvent S_2. Evaporation of appropriate fractions afforded compound **7c** (130 mg, 75 %), mp. 213-214°C after crystallization from solvent S_2. UV max nm (ethanol) 260 (ε 13,000). ^{1}H NMR δ 8.18 and 8.16 (2s, 2, H_2 + H_8), 7.28 (s, 2, NH_2), 5.01 (d, 2, $H_{1'}$), 3.43 (s, 1, $H_{3'}$). ^{13}C NMR 155.97, 152.67, 149.06, 140.07, 118.48 (adenine), 78.23 ($C_{2'}$), 75.75 ($C_{3'}$), 32.20 ($C_{1'}$). EI-MS 173 (M, 100.0). Exact mass calcd 173.0701, found 173.0703. Anal. Calcd for $C_8H_7N_5$ x 0.25 H_2O: C, 54.07; H, 4.27; N, 39.41. Found: C, 54.07, H, 4.40; N, 39.63.

G. With Chloroallene (10b). A mixture of adenine (**6**, 300 mg, 2.22 mmol), NaH (60 %, 178 mg, 4.4 mmol) and chloroallene (**10b**, 90 %, 320 mg, 4.4 mmol) in HMPA (7 mL) was stirred at room temperature for 15 h. After evaporation of most of HMPA, the residue was chromatographed as described in the previous experiment. Allene **8c** was eluted first (30 mg, 10 %), mp. 225-226°C after crystallization from ethanol. UV max nm (ethanol) 261 (ε 11,000). ^{1}H NMR δ 8.15 and 8.14 (2s, 2, H_2 + H_8), 7.40 (t, 1, $H_{1'}$), 7.30 (s, 2, NH_2), 5.75 (d, 2, $H_{3'}$). ^{13}C NMR 156.06, 153.07, 148.44, 138.43, 118.91 (adenine), 202.13 ($C_{2'}$), 92.49 ($C_{3'}$), 88.47 ($C_{1'}$). EI-MS 173 (M, 69.1). Exact mass calcd 173.0701, found 173.0699. Anal. Calcd for $C_8H_7N_5$: C, 55.48; H, 4.07; N, 40.44. Found: C, 55.32; H, 4.03; N, 40.50.

Continued elution gave compound **7c** (100 mg, 33 %), identical with a sample prepared from propargyl chloride (**3c**).

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