N-1 OXIDATION OF ADENINE SUBSTITUTED AT *N*-9 BY AN OLEFINIC CHAIN

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Abstract-The oxidation of 9-vinyladenine derivatives (**1a-c**) with *m*-chloroperoxybenzoic acid (MCPBA) leads selectively to the corresponding *N*-1 oxides (**2a-c**) and when the 6-amino group is protected, the oxidation occurs on the double bond of the olefinic chain to give the epoxides (**6a, b**) selectively.

There is a permanent interest for purine *N*-oxides, mostly because of potential therapeutic interest.[1] These compounds have been prepared by total synthesis,[1-3] by functional group transformation of purine *N*-oxide precursors[4-6] and, whenever chemoselectivity made it possible, by direct oxidation of purine derivatives.[7] For adenine[8a,b] and its *N*-7 or *N*-9 substituted derivatives[3,9] the direct oxidation was known to give preferentially *N*-1-oxides while it was recently reported[10] that oxidation of 3-benzyladenine unequivocally occurred at *N*-7. The oxidation of adenine carrying an unsaturated side chain at *N*-9 was unambiguously demonstrated[11] to take place at *N*-1 when the chain is *allylic*. To our knowledge, nothing was reported in the literature about the behavior of 9-vinylic adenine, and it appeared of interest to investigate oxidation of this little documented class of componds which became available from nucleophilic radical chain (SRN1) reactions.[12]

Treatment of 9-vinyl adenine derivatives (**1a-c**) with *m*-chloroperoxybenzoic acid (MCPBA) at room temperature selectively led to the corresponding *N*-1-oxide derivatives (**2a-c**) in high yields (Table 1). The reactions times were in a range of 14 to 48 h, but no clear relationship between the rate of oxidation at *N*-1 and the structure of the *N*-9 olefinic substituent emerged.

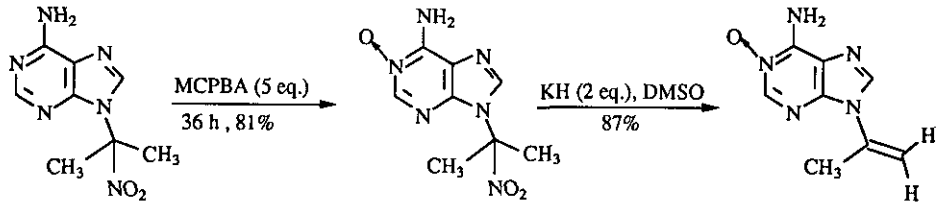
Table 1. Selective *N*-1 oxidation of adenine substituted at *N*-9 by an olefin chain.

	R_1	R_2	R_3	Time (h)	Recovered starting material %.	N_1-Oxide %
1a	CH_3	H	H	14	15	**2a** 72[a] (85)[b]
1b	CH_3	CH_3	CH_3	48	33	**2b** 62[a] (92)[b]
1c	CH_3	$-CH_2OCH(Ph)OCH_2-$		24	25	**2c** 60[a] (80)[b]

a) Pure isolated products; b) Yield calculated upon the converted starting material.

That oxidation of **1a** gave the *N*-1-oxide (**2a**) was shown by an alternative synthesis of this compound (Scheme 1). Consistently with oxidation of *N*-9 *alkyl* substituted adenine derivatives known to lead selectively to the corresponding to *N*-1 oxides.[9] MCPBA treatment of the *N*-9 *alkyl* derivative (**3**)[13] thus led to the *N*-1-oxide (**4**). Elimination of HNO_2 from **4** was performed by means of KH[12,13] to give **2a**, identical (mp, nmr) with the compound obtained by direct oxidation of **1a**.

Scheme 1. Alternative access to *N*-1-oxide (**2a**)

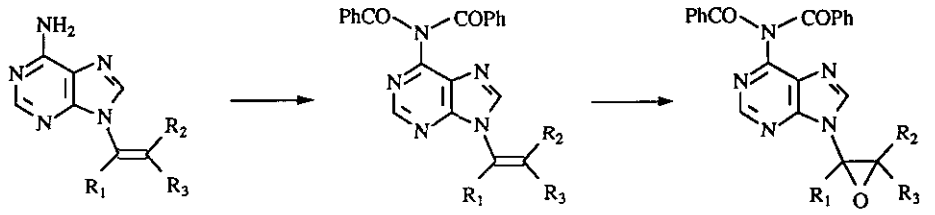


3 **4** **2a**

Thus, adenine derivatives substituted at *N*-9 by a vinylic chain (**1a-c**), or by an alkyl chain (**3**) are oxidized at *N*-1 due to the strong electron releasing 6-NH_2 group. It was therefore felt of interest to know if deactivation of this group might divert oxidation to another site available on the adenine skeleton. On treatement with MCPBA, the *N*-6 dibenzoyl derivatives (**5a, b**) were found to give the corresponding epoxy derivatives (**6a, b**)

with no trace of other *N*-oxide derivatives (Scheme 2). Thus the decrease of electron density, together with possible hindrance of *N*-1 by the closely located 6-*N,N* -dibenzoyl group prevent oxidation to take place on the purine ring, *and* facilitate oxidation of the vinyl bond.

Scheme 2. Preparation and oxidation of *N*-6 protected adenine derivatives (**5a,b**)



	R_1	R_2	R_3		
1a	CH_3	H	H	**5a** 89%	**6a** 51%
1b	CH_3	CH_3	CH_3	**5b** 92%	**6b** 86%

In this study, we have shown that 6-NH_2 unprotected adenine compounds substituted at *N*-9 by a *vinylic* chain are selectively oxidized at *N*-1 and that the vinylic double bond can be selectively epoxidized when the amino group is protected.

EXPERIMENTAL

General procedure for oxidation: The oxidation was performed on compounds (**1a-c**, **3** and **5a,b**) (1 mmol) using MCPBA (5mmol) in methylene chloride (20 ml). The organic phase was washed with aq. $NaHCO_3$, dried over sodium sulfate and concentrated. Column chromatography on silica gel (methylene chloride, methanol 5%) gave the oxides.

9-(Propen-2-yl)adenine 1-oxide (2a):

-from (1a)

mp 178-180°C, 70% aq. EtOH; ^{1}H nmr ($CDCl_3$ + CD_3OD, 250 MHz) δ: 2.40 (s, 3H, CH_3), 5.23 and 5,70 (s, 1H each, CH_2=C), 8.15 and 8,57 (s, 1H each, H_2-H_8 adenine); ms (CI)*m/z* : 192 $(MH)^+$, 176 $(MH^+ -(O) + H)$,

136 (adenine + H)$^+$; uv λ_{max} (95% aq. EtOH) 236 nm (ε 13500), 261 (9500). Anal. Calcd for $C_8H_9N_5O$: C 50.26; H 4.71; N 36.65. Found: C 59.96; H 4.8; N 36.18.

-from (4)

Potassium hydride (0.120 g, 3 mmol) obtained from a 35% oil suspension placed in a 50 ml flask and washed under argon atmosphere with *n*-pentane was added with DMSO (15 ml). The mixture was stirred for 15 min, then the nitroalkane (**4**) (0.357 g, 1.5 mmol) in DMSO (1 ml) was added by syringe. Reaction progress was monitored by *TLC* and after cosumption of the substrate, the reaction medium was poured into iced water (50 ml), neutralized with 5% HCl and extracted with methylene chloride (3x30 ml). The organic phase was dried and concentrated. Purification of the residual oil by column chromatography on silica gel (methylene chloride, methanol 5%) gave **2a** (0.249, 87%) identical (mp; nmr) with the compound obtained from **1a**.

9-(3-Methyl-2-buten-2-yl)adenine 1-oxide (2b):

mp 124-142°C (amorphous solid); ^{1}H nmr ($CDCl_3$ + CD_3OD, 200 MHz) δ: 1.50 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 7.89 and 8.73 (s, 1H each, H_2-H_8 adenine); ms (CI) *m/z* : 220 (MH)$^+$, 204 (MH$^+$ -(O)), 136 (adenine + H)$^+$; uv λ_{max} (95% aq. EtOH) 236 nm (ε 16500), 261 (11000). Anal. Calcd for $C_{10}H_{13}N_5O$: C 54.79; H 5.93; N 31.96. Found: C 55.10; H 6.28; N 31.61.

9-[1-Methyl-2-(2-phenyl-1,3-dioxane)-ethen-1-yl]adenine 1-Oxide (2c):

mp 192-194°C, 70% aq. EtOH; ^{1}H nmr ($CDCl_3$ + CD_3OD, 200 MHz) δ: 1.88 (s, 3H, CH_3), 4.22, 4.47, 4.76 and 4.98 (d, 1H each, J= 12 Hz, CH_2O dioxane), 5.53 (s, 1H, OCH(Ph)O), 7.21-7.53 (m, 5H, C_6H_5), 7.99 and 8.63 (s, 1H each, H_2-H_8 adenine); ms (CI) *m/z* : 340 (MH)$^+$, 324 (MH$^+$ -(O)), 136 (adenine + H)$^+$. Anal.Calcd for $C_{17}H_{17}N_5O_3$: C 60.17; H 4.26; N 17.54;. Found: C 60.24; H 3.98; N 17.21.

9-[2-Nitropropan-2-yl)adenine 1-oxide (4):

mp 110-128°C (amorphous solid); ^{1}H nmr ($CDCl_3$ + CD_3OD, 200 MHz) δ: 2.45 (s, 6H, $(CH_3)_2$), 8.53 and 8.63 (s, 1H each, H_2-H_8 adenine); ^{13}C nmr (Me_2SO-d_6, 50 MHz) δ: 150.68 (C6), 145.59 (C2), 145.35 (C4), 143.96 (C8), 121.00 (C5), 98,45 ($(CH_3)C(NO_2)$), 26,04 (CH_3); ms (CI) *m/z* : 239 (MH)$^+$, 223 (MH$^+$ -(O)), 192 (MH$^+$ -(HNO_2)), 136 (adenine + H)$^+$. Anal. Calcd for $C_8H_{10}N_6O_3$: C 40.33; H 4.20; N 35.29. Found: C 40.08; H 4.48; N 34.92.

General procedure for dibenzoylation: The benzoylation was carried out on compounds (**1a-b**) (1mmol) which were treated in THF (5 ml) with sodium hydride (0.100 g, 2.5 mmol) obtained from a 60% oil suspension washed with *n*-pentane and then with benzoyl chloride (0.295 g, 2.1 mmol). Addition of water (30 ml) containing HCl (5%) and extraction with methylene chloride gave the crude compounds which were crystallized.

6-(*N,N*-Dibenzoyl)-9-(propen-2-yl)adenine (5a):

mp 173-175°C, Methylene chloride; ^{1}H nmr ($CDCl_3$, 200 MHz) δ: 2.35 (s, 3H, CH_3), 5.12 and 5.66 (s, 1H each, CH_2=C), 7.11-7.51 and 7.65-7.90 (m, 10H, 2x C_6H_5), 8.10 and 8.61 (s, 1H each, H_2-H_8 purine); ^{13}C nmr ($CDCl_3$, 50 MHz) δ: 172.38 (C=O amide), 152.97, 152.49, 152.18 143.27, 137.20, 134.20, 133.08, 129.57, 128.80, 128.14, 109.17, 20.96 (CH_3); ms (IE) *m/z* : 383 $(M)^+$, 355 $(M^+ - CO)^+$, 278 $(M^+ - C_6H_5CO)^+$, 122, 105 $(C_6H_5CO)^+$, 77 $(C_6H_5CO - CO)^+$. Anal.Calcd for $C_{22}H_{17}N_5O_2$: C 68.93; H 4.38; N 18.27. Found: C 69.11; H 4.24; N 17.92.

6-(*N,N*-Dibenzoyl)-9-(3-methyl-2-buten-2-yl)adenine (5b):

mp 178-179°C, Methylene chloride; ^{1}H nmr ($CDCl_3$, 200 MHz) δ: 1.48, 1.95 and 2.17 (s, 3H each, 3x CH_3), 7.17-7.71 and 7.79-8.17 (m, 10H, 2x C_6H_5), 8.07 and 8.70 (s, 1H each, H_2-H_8 purine); ^{13}C nmr ($CDCl_3$, 50 MHz) δ: 172.35 (C=O amide), 152.85, 152.47, 151.85, 145.44, 131.21, 133.63, 133.32, 132.98, 130.21, 129.48, 128.69, 128.35, 126.68, 122.53, 20.13, 19.98 and 18.65 (CH_3); ms (FAB) *m/z* : 412 $(MH)^+$, 308 $(MH^+ - C_6H_5CO + H)$, 105, 91, 77. Anal.Calcd for $C_{24}H_{21}N_5O_3$: C 70.07; H 5.1; N 17.03. Found: C 69.72; H 5.42; N 16.71.

6-(*N,N*-Dibenzoyl)-9-(2-methyloxiran-2-yl)adenine (6a):

mp 96-120°C (amorphous solid); ^{1}H nmr ($CDCl_3$, 250 MHz) δ: 2.03 (s, 3H, CH_3), 3.17 and 3.38 (d, 1H each, Jab= 4.5 Hz, CH_2O epoxide), 7.13-7.60 and 7.68-8.01 (m, 10H, 2x C_6H_5), 8.23 and 8.83 (s, 1H each, H_2-H_8 adenine); ^{13}C nmr ($CDCl_3$, 50 MHz) δ: 172.39 (C=O amide), 152.95, 152.49, 152.17, 142.61, 134.16, 133.15, 129.57, 128.84, 127.63, 65.66 and 53.95 (oxiranic carbons); 21.39 (CH_3); ms (FAB) *m/z* : 422 $(MNa)^+$, 400 $(MH)^+$, 386 $(MH^+ - CH_3 + H)$, 344 $(MH^+ - CH_2OC(CH_3) + H)^+$, 296 $(MH^+ - C_6H_5CO + H)^+$, 240 $(344 - C_6H_5CO + H)^+$, 105 $(C_6H_5)^+$; uv λ_{max} (95% aq. EtOH) 236 nm (ε 11000), 261 (5000) . Anal.Calcd for $C_{22}H_{17}N_5O_3$: C 66.16; H 4.26; N 17.54. Found: C 66.29; H 4.51; N 17.12.

6-(*N*,*N*-Dibenzoyl)-9-(2,3,3-trimethyloxiran-2-yl)adenine (6b):

mp 203-205°C, AcOEt; ^{1}H nmr ($CDCl_3$, 250 MHz) δ: 1.01, 1.59 and 1.97 (s, 3H each, 3x CH_3), 7.02-7.69 and 7.72-8.22 (m, 10H, 2x C_6H_5), 8.37 and 8.74 (s, 1H each, H_2-H_8 purine); ^{13}C nmr ($CDCl_3$, 50 MHz) δ: 170.77 (C=O); 152.60, 143.45, 134.84, 134.39, 133.87, 133.11, 131.39, 130.38, 129.90, 129.62, 128.78 and 128.42, 74.13 and 61.28 (oxiranic carbons), 20.34, 19.62 and 19.01 (CH_3); ms (FAB) *m/z* : 450 $(MNa)^+$, 428 $(MH)^+$, 344 (MH^+ - $(CH_3)_2COC(CH_3)$ + H), 324 (MH^+ -C_6H_5CO + H), 240 (324 - $(CH_3)_2COC(CH_3)$ + H or 344 - C_6H_5CO + H), 222, 105 $(C_6H_5CO)^+$; uv λ_{max} (95% aq. EtOH) 236 nm (ε 14400), 261 (4800) . Anal.Calcd for $C_{24}H_{21}N_5O_3$: C 67.44; H 4.91; N 16.39. Found: C 67.63; H 4.71; N 16.01.

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