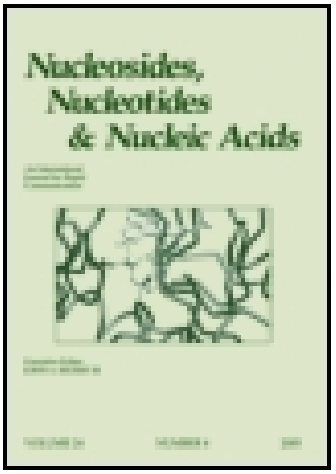

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A Highly Selective and Efficient Access to N-9 Alkylated Purine Derivatives via Radical SRN1 Chemistry

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A Highly Selective and Efficient Access to N-9 Alkylated Purine Derivatives *via* Radical $S_{RN}1$ Chemistry.

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Abstract: 6-Chloropurine and 2-amino-6-chloropurine were discovered to be efficient nucleophiles in $S_{RN}1$ reactions with various gem halonitroalkane derivatives as substrates to give high yield of N-9 alkylated purine derivatives in a N-9/N-7 ratio greater than 95/5 .

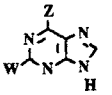
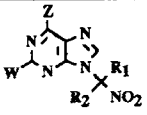
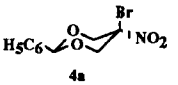
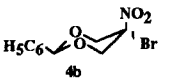
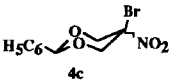
N-9 substitued 6-chloropurines are intermediates in the classical methodology for the synthesis of various 6-9 disubstitued purines from the commercially available 6-chloropurine and 2-amino-6-chloropurine[1]. Substitution at N-9 is often, but not always selective, so that mixtures of N-9 and of unwanted N-7 substituted derivatives are formed. Therefore the interest for selective methods is constant[2] and has increased when purine derivatives became needed as potentially useful antiviral drugs[3]. This prompted us to explore new developments based upon radical SRN1 chemistry which presents original features.

$S_{RN}1$ reactions in which a substrate $R_1R_2C(NO_2)X$ undergoes replacement of the halide X (Cl, Br) by a nucleophile Nu^- are very efficient and generally not (or little) subject to steric hindrance, but in contrast to the great number of carbon-carbon bond forming reactions where carbanions are the nucleophilic reagents[4], carbon-nitrogen bond formation is much less documented. Besides the preliminary report by N. Kornblum on amines[5], the only relevant contributions are those of R. Bowman's group on nitroimidazoles[6] and our's on imidazoles[7]. We report herein our first results on 6-chloropurine **1a** and 2-amino-6-chloropurine**1b** as nucleophiles in reactions with variously functionalized substrates (TABLE).

The photostimulated reactions between 6-chloropurine **1a** dissolved in a mixture of DMSO/CH_3CN (1:2) (heterogeneous system)[7,8] and the simple 2-bromo-2-nitropropane **2** or the monofunctionalized substrate[9] **3** gave a single product **5** or **6** (N.M.R; thin layer chromatography). Such was not the case with **4a** or **4b** since either of them yielded a mixture of two compounds **7a** and **7b** which were separated by

† . Deceased 02 August 1991.

TABLE

Nucleophiles[a]		Substrates	time (min)	Products (yield%)[b]	
					
1a Z=Cl W=H	2	$R_1 = R_2 = CH_3$	180	5	(96)
	3	$R_1 = CH_3$, $R_2 = CH_2OTHP$	120	6 (diastereoisomers)	(91)
		 4a	120	7a+7b (a/b:90/10)[c]	(60)
		 4b	90	7a+7b (a/b:90/10)[c]	(50)
		 4c	90	7a+7b (a/b:90/10)[c]	(81)
1b Z=Cl W=NH_2	2	$R_1 = R_2 = CH_3$	210	8	(88)
	3	$R_1 = CH_3$, $R_2 = CH_2OTHP$	105	9 (diastereoisomers)	(95)

a) 1.5 eq. Nu; 1.5 eq. K_2CO_3; DMSO/CH_3CN (1/2); illumination by HANAU 100W UV lamp . b) isolated pure products. c) ratio determinated from isolated pure products.

colum chromatography. A third experiment using **4c** (mixture of cis/trans isomers) gave also a mixture of **7a** and **7b** in a ratio similar to that determined in reactions from pure **4a** or **4b**.

The quantitative conversion of **7a** to the hypoxanthine derivative **10** (whose structure was unambigously determined by X Ray crystallography, FIG.) (scheme 1) indicates that *the substitution reaction was highly selective on N-9* and the comparison of the NMR spectra of **6**, **7a**, **7b** and **10** unambigously shows that **6** is a diastereoisomeric mixture and that **7a** and **7b** are conformationally stable isomers.

Comparative examination of NMR data of **7a** and **7b** indicated that the 6-chloropurine substituent of the minor product **7b** has *cis* equatorial configuration. In the chair conformation of the dioxane ring, the NO_2 group of the planar radical intermediate **4** is quasi equatorial and from the product distribution, one can assume that the attack from β face is favored over that from the α face in a ratio (9:1) which reflects the greater steric hindrance to the approach of $\mathbf{1a}^-$ caused by two axial hydrogen atoms on carbon C-4 and C-6 (scheme 2).

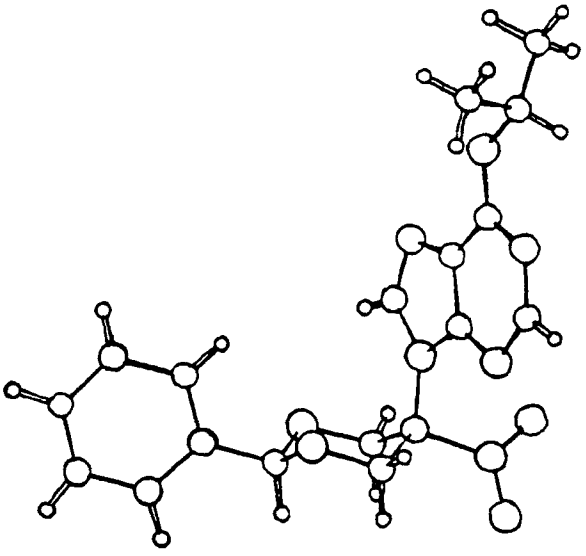
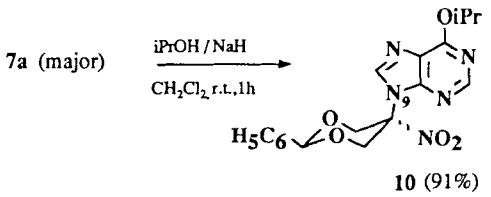


FIG.

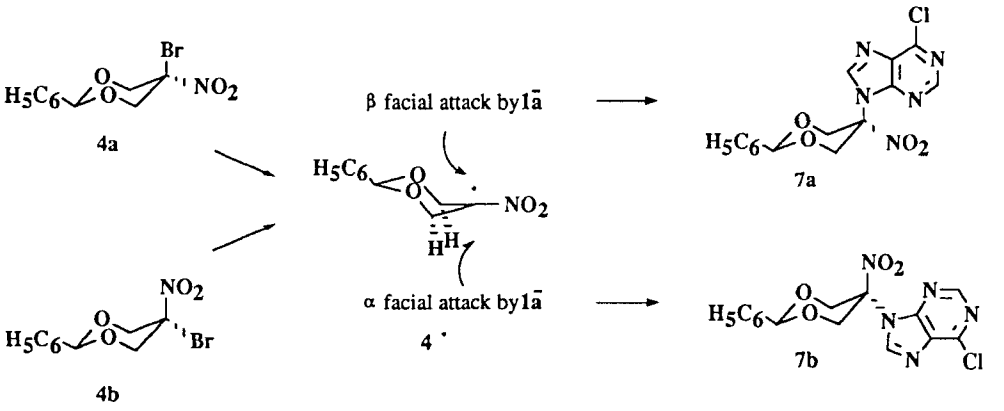


10 (91%)

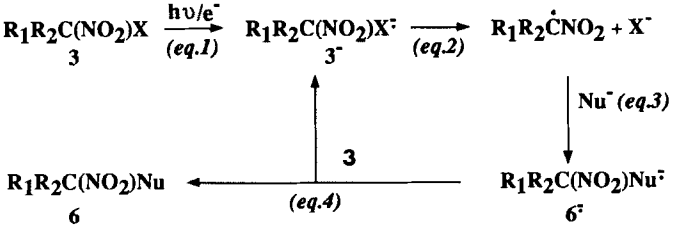
scheme 1

We then turned our attention to the 2-amino-6-chloropurine **1b** as a nucleophile in these reactions, since it is molecule of major importance for the syntheses of guanine derivatives. The $S_{RN}1$ reaction carried out between the derived anion $\mathbf{1b}^-$ and the substrates **2** and **3** gave the corresponding N-9 alkylated products **8** and **9** in high yield. Thus, the electron releasing 2-amino group does not affect the nucleophilic behaviour of **1b** as compared with **1a**.

Since neither of these purine derived anions were used before as nucleophiles in $S_{RN}1$ reactions, we have performed classical experiments supporting the four step mechanism (scheme 3) on a model reaction between **1** and **3**.



scheme 2



scheme 3

For the same reaction time (120 min) it was observed that -*i*) In the dark, no substitution product was obtained, since illumination which initiates the chain by providing the activation energy for the monoelectronic transfer to $R_1R_2C(NO_2)X$ and formation of the radical anion $R_1R_2C(NO_2)X^{\cdot-}$ was suppressed. -*ii*) Under illumination, but in presence of a catalytic amount of *para* dinitrobenzene (5%) acting as an electron trap towards the two radical anions $R_1R_2C(NO_2)X^{\cdot-}$ and $R_1R_2C(NO_2)Nu^{\cdot-}$ the yield of $R_1R_2C(NO_2)Nu$ was significantly diminished (16% instead of 91%). -*iii*) Under illumination, but in the presence of galvinoxyle which acts as a radical scavenger towards $R_1R_2\dot{C}NO_2$, no substitution product was formed.

Conclusion. For the first time, 6-chloro **1a** or 2-amino-6-chloropurine **1b** are demonstrated to be efficient nucleophiles for $S_{RN}1$ reaction with gem bromo-nitro derivatives leading to N-9 alkyled purines. Thus, radical $S_{RN}1$ reactions which are highly regioselective and furthermore compatible with chlorine borne on C-6 of purines are promising for the synthesis of various adenine and guanine derivatives. The scope and limitations of this methodology are currently under active investigation.

Experimental Section:

Reagents. All chemical reagents and solvents were purchased from Aldrich (France) and were used without further purification.

General Methods. Melting point was obtained on a Reichert apparatus. The IR spectra were recorded on a Nicolet (205, FT-IR) spectrometer. The UV spectra were obtained on a Perkin-Elmer lambda 5 UV/VIS spectrophotometer. The mass spectra were recorded on a AEI.MS-50 (MS-EI) or EI.MS-9 (MS-CI) spectrometer. The proton and carbon NMR spectra were recorded on either a Bruker spectrometer 4.7 T (200 Mz) or 9.4 T (400 Mz). Chemical schifts are reported in δ units, parts per million (ppm) downfield from TMS for ^1H NMR (δ = 0) and from $CDCl_3$ for ^{13}C NMR (δ = 77.14). Column chromatography utilized silica gel 60 (230-400 mesh) from E. Merck laboratories as the solid phase.

General procedure for the preparation of gem nitro-N-9-(6-chloro or 2-amino-6-chloropurine)alkanes:

A solution of **1a** or **1b** (1.5 eq) in a mixture of dry DMSO/CH_3CN (ratio 1:2 and 10 ml/mmol) was stirred with K_2CO_3 (1.5 eq) about 30 min under argon. The gem bromonitroalkane (1 eq), dissolved in 2 ml of DMSO/CH_3CN, was then added by syringe to the heterogeneous mixture. After exposure to 100W fluorescent light (HANAU), under argon (reaction monitored by TLC silica gel), the mixture was poured onto ice-water and extracted twice by CH_2Cl_2. The organic layer was dried and the solvent was removed. The crude product was purified by silica gel column chromatography (Ether/pentane/methanol: 70/25/5).

6-chloro-9-(2-nitro-propane-2-yl)-purine **5**

Oil.

SM (CI): m/z 242, 244 (MH^+), 195, 197 (MH^+-HNO_2), 155,157 (6-chloro-purine+H)$^+$.

^1H NMR ($CDCl_3$): δ (ppm) 2.54 (s, 6H), 8.31 (s,1H, H_8 purine), 8.67 (s, 1H, H_2 purine).

^{13}C NMR(DMSO-D_6): δ (ppm) 151.8 (C2), 145.7 (C8), 97.1, 24.9.

Anal. Calc. for $C_8H_8N_5ClO_2$: C: 39.75; H: 3.31. Found: C: 39.91; H: 3.51.

6-chloro-[2-nitro-1-(2-oxy-tetrahydropyrannyl)-propane-2-yll-purine **6.**

1st diastereoisomer:

Oil

IR ($CDCl_3$): ν (cm^{-1}) 1030, 1130, 1200, 1220, 1290, 1340, 1560 (NO_2), 1580, 2940.

SM (CI): m/z 342-344 (MH^+), 295-297 (MH^+- HNO_2), 155-157 (6-chloro purine), 85 (THP)$^+$, 57.

UV (CH_3OH): λ max (nm) 263.

^1H NMR ($CDCl_3$): δ (ppm) 1.33-1.90 (large, 6H), 2.55 (s, 3H), 3.55 (m, 1H), 3.83 (m, 1H), 4.60 (d, 1H, J=10Hz), 4,63 (broad s, 1H), 4.72 (d, 1H, J=10Hz), 8.66 (s, 1H, H_8 purine), 8.80 (s, 1H, H_2 purine).

^{13}C NMR ($CDCl_3$): δ (ppm) 152.25 (C6), 151.95 (C2), 151.6 (C4), 144.4, (C8), 131.95 (C5), 100.2, 97.65, 69.8, 63.45, 30 , 24.9, 21.5, 19.4.

2nd diastereoisomer:

Oil

IR ($CDCl_3$): ν (cm^{-1}) 1030, 1130, 1200, 1220, 1290, 1340, 1560 (NO_2), 1580, 2940.

SM (IC): m/z 342-344 (MH^+), 295-297 (MH^+- HNO_2), 155-157 (6-chloro purine), 85 $(THP)^+$, 57.

UV (CH_3OH): λ max (nm) 263.

^{1}H NMR ($CDCl_3$): δ (ppm) 1.48-1.68 (large, 6H), 2.56 (s, 3H), 3.45-3.55 (m, 2H), 4.3 (d, 1H, J=10Hz), 4.78 (m, 1H), 4.88 (d, 1H, J=10Hz), 8.52 (s, 1H, H_8 purine), 8.75 (s, 1H, H_2 purine).

^{13}C NMR ($CDCl_3$): δ (ppm) 151.95 (C2), 151.83 (C6),145.87 (C4), 144.15 (C8), 151.8 (C6), 98.95, 97.42, 69.07, 62.5, 29.9, 24.7, 21.4, 18.7.

6-Chloro-9-(5-nitro-2-phenyl-1,3-dioxanne-5-yl)purine:

Trans isomer **7a**:

Oil.

IR ($CDCl_3$), ν (cm^{-1}): 1123, 1220, 1311, 1410, 1484, 1565 (NO_2), 1590, 2887, 3134.

M.S.(IE): m/z: 316-314 (M^+ –HNO_2), 270, 209, 157-155 (6-chloropurine), 105, 77.

^{1}H NMR ($CDCl_3$,): δ (ppm) 4.93 (d, 2H, J= 13Hz, H ax.), 5.43 (d, 2H, J= 13Hz, H eq.), 5.83 (s, 1H, O-CH-O), 7.26 (br s, 5H, H ar), 8.63 (s, 1H, H_8 purine), 8.76 (s, 1H, H_2 purine).

^{13}C NMR ($CDCl_3$): δ (ppm) 152.47, 152.15, 151.6, 143.9, 135.1, 132.15, 130, 128.5, 126.05, 103.15, 69.45.

Anal. Calcd. for $C_{15}H_{12}ClN_5O_4$: C (49.81), H (3.34). Found: C (49.48), H (3.42).

Cis isomer **7b**:

Oil.

IR ($CDCl_3$), ν (cm^{-1}): 1134, 1233, 1296, 1388, 1441, 1569 (NO_2), 1595, 2874, 3107.

M.S.(EI): m/z: 316-314 (M^+ –HNO_2), 270, 209, 157-155 (6-chloropurine), 105, 77.

^{1}H NMR ($CDCl_3$): δ (ppm) 4.75 (d, 2H, J= 13Hz, H ax.), 5.8 (d, 2H, J= 13Hz, H eq.), 5.8 (s, 1H, O-CH-O), 7.45 (br s, 5H, H ar), 8.33 (s, 1H, H_8 purine), 8.8 (s, 1H, H_2 purine).

^{13}C NMR ($CDCl_3$): δ (ppm) 153, 151.7, 141.3, 135.3, 131.65, 130, 128.8, 126.35, 101.7, 89.85, 68.2.

2-Amino-6-chloro-9-(2-nitro-propane-2-yl)purine **8**

m.p.:163°C.

IR ($CDCl_3$), ν (cm^{-1}): 1275, 1567, 1620, 2975, 3425.

M.S. (IC): m/z 259-257 (MH^+), 212-210 (MH^+-HNO_2), 172-170 (2-amino-6-chloropurine+H)$^+$.

^{1}H NMR (DMSO d6): δ (ppm) 2.36 (s, 6H), 7.05 (large s, 2H, NH_2), 8.5 (s, 1H, H_8 purine).

^{13}C NMR (DMSO d6,): δ (ppm) 159.5, 153.7, 150.15, 140.6, 123.75, 96.5, 24.85.

Anal. Calcd. for $C_8H_9N_6O_2$: C: 36.99; H: 3.47. Found: C: 37.06; H: 3.56.

2-Amino-6-chloro-9-[2-nitro-1-(2-oxy-tétrahydropyranyl)-propane-2-yl]purine **9**

Oil.

1st diastereoisomer:

IR ($CDCl_3$): ν (cm^{-1}) 1020, 1060, 1110, 1120, 1160, 1280, 1320, 1490, 1560, 1600, 2925, 3000-3500, 3400, 3500.

SM (IC): m/z 359-357 (MH^+), 314-312 (MH^+- HNO_2), 172-170 (2-amino 6-chloropurine), 85 $(THP)^+$

57.

UV (CH_3OH): λ max (nm) 254.

^{1}H NMR ($CDCl_3$): δ (ppm) 1.33–1.76 (large, 6H), 2.43 (s, 3H), 3.6 (m, 1H), 3.83 (m, 1H),

4.48 (d, 1H, J=10Hz), 4.6 (d, 1H, J=10Hz and s, 1H), 5.26 (broad s, 2H, NH_2), 8.21 (s, 1H, H_8 purine).

^{13}C NMR ($CDCl_3$): δ (ppm) 158.95 (C2), 144.35 (C4), 140.95 (C8), 124.9 (C5), 100.2, 97.4, 69.85, 63.3, 30.15, 25.05, 21.45, 19.30.

Anal. Calcd. for $C_{13}H_{17}ClN_6O_4$: C: 43.51; H: 4.74. Found: C: 43.38; H: 4.65.

2nd diastereoisomer:

SM (IC): m/z 359-357 (MH^+), 314-312 (MH^+- HNO_2), 172-170 (2-amino 6-chloropurine), 85 $(THP)^+$,

57.

UV (CH_3OH): λ max (nm) 251.

^{1}H NMR ($CDCl_3$): δ (ppm) 1.33-1.75 (large, 6H), 2.43 (s, 3H), 3.5 (m, 2H), 4.23 (d, 1H, J=10Hz), 4.8 (d, 1H, J=10Hz and s, 1H), 5.26 (broad s, 1H, NH_2), 8.1 (s, 1H, H_8 purine).

^{13}C NMR ($CDCl_3$): δ (ppm) 159.1 (C2), 154.1 (C6), 151.95 (C4), 140.50 (C8), 125.25 (C5), 98.9, 97.2, 69.1, 62.35, 30, 24.9, 21.35, 18.7.

Synthesis of 6-isopropoxy-9-(5-nitro-2-phenyl-1,3-dioxanne-5-yl)purine **10**:

Sodium hydride (50 mg, 2 mmol washed twice by pentane), and CH_2Cl_2 (10 ml) introduced in a pyrex flask caped with a rubber septum are cooled in an ice bath and stirred for 10 min. under argon. Isopropyl alcohol (154 µl, 2 mmol) is slowly added by syringe and the mixture is kept at room temperature for 15 min. The purine derivative **7a** (723 mg, 2 mmol) dissolved in CH_2Cl_2 (10 ml) is then introduced by syringe and stirring is maintained at room temperature for 1 hour. After classical work-up, the crude product is purified by silica gel colum chromatography (CH_2Cl_2/MeOH : 95/5) to give **8**, white solid (700 mg, 91%) slowly recrytallized for several days in pure MeOH to yield the monocrystal required for X-ray crystallography.

m.p.: 180°C.

IR ($CDCl_3$), ν (cm^{-1}): 1113, 1155, 1250, 1315, 1470, 1566 (NO_2), 1600, 1610, 2915, 3050, 3075.

M.S.(EI): m/z : 385 (M^+), 339 (M^+ –NO_2), 297, 234, 191.

^{1}H NMR ($CDCl_3$): δ (ppm) 1.5 (d, 6H, J= 6Hz, $(C\underline{H}_3)_2CHO$), 4.9 (d, 2H, J= 13Hz, H ax.), 5.46 (d, 2H, J= 13Hz, H eq.), 5.68 (m, 1H, J= 6Hz, pur-O-C<u>H</u>), 5.82 (s, 1H, O-C<u>H</u>-O), 7.36 (br s, 5H, H ar), 8.42 (s, 1H, H_8 purine), 8.5 (s, 1H, H_2 purine).

Anal. Calcd. for $C_{18}H_{19}N_5O_5$: C (56.10), H (4.94). Found: C (56.08), H (4.73).

Crystal data: $C_{18}H_{19}N_5O_5$, M= monoclinic, space group C2/c, a= 21.411(9), b= 12.577(6), c= 15.032(7) Å, β= 112.88(7)°, U= 3729 $Å^3$. Dc= 0.8*0.4*0.4 mm^3. A Philips automatic diffractometer, graphite monochromator, λ= 0.7107 Å, ω= 0.025°. s^{-1}, larg. 1.4°, 3 reflexions /3hours. 3764 reflexions were recorded, of which 2856 unique reflexions were observed with I›3.0 σ (I).

Acknowledgements

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8 . In the "X philic" process, the halogen is transferred from the substrate to the nucleophile (N.S. Zefirov and D.I. Makhonkov, *Chem. Rev.*, **1982**, *82*, 615). In our case, the anion ($R_1R_2CNO_2^-$) thus formed would react with the substrate $R_1R_2C(NO_2)Br$ to afford the dimeric compound $(R_1R_2C(NO_2))_2$, diminishing the yield of the target compound $R_1R_2C(NO_2)Nu$. The heterogeneous system K_2CO_3/CH_3CN which generates a low, but sufficient concentration of the nucleophile prevents the side "X philic reaction" to take place.

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