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A New Synthesis of Oxanosine and 2'-Deoxyoxanosine

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Abstract. An easy and more efficient synthesis of oxanosine and 2'-deoxyoxanosine has been developed, a key step in the reported synthesis is a new photochemical transformation by UV irradiation of 1-hydroxy derivatives of inosine.

Keywords: Nucleosides; Nitrones; Photochemistry.

Oxanosine **1** is a nucleoside antibiotic isolated from culture broths of *Streptomyces capreolus* MG265-CF3[1] showing interesting antimicrobial and carcinostatic activities.[2] Its analog 2'-deoxyoxanosine[3] **2** has been shown to be a stronger antimicrobial and antineoplastic agent than oxanosine. Two methods for the synthesis of **1** have already been reported in the literature,[4] both using 5-amino-1-(β-D-ribofuranosyl)imidazo-4-carboxyamide (AICAR) as precursor in the construction of imidazo-oxazinonic base of **1**. The most efficient synthesis[4a] furnishes **1** in 21 % overall yield from AICAR in four steps. 2'-Deoxyoxanosine **2** can be prepared either by direct deoxygenation of **1**[3] (27 % yield) or by nitrous acid treatment of 2'-deoxyguanosine[5] (21 % yield).

We here describe a profitable alternative route for the synthesis of **1** and **2** starting from inosine **3** or 2'-deoxyinosine **4**, respectively. A key step in the proposed synthesis is a new phototransformation of 1-hydroxyinosine **5** and 1-hydroxy-2'-deoxyinosine **6** by UV irradiation. During our studies on the reactivity of 1-N-substituted purine nucleosides,[6] we discovered this photoreaction when we were originally aiming at the photochemical transformation of the 1-hydroxy-hypoxanthinic nucleoside base of **5** and **6** in the xanthine ring of **7** and **8**. The photo-oxidation of the 2-carbon of the purine ring had been hypothesized on the basis of the well documented photoreactivity of the nitrone system[7] present in the tautomeric form of 1-hydroxy-hypoxanthine base. Furthermore, the photochemical oxidation of the 2-carbon of the purine base has been reported for the conversion of adenosine-1-oxide into isoguanosine.[8]

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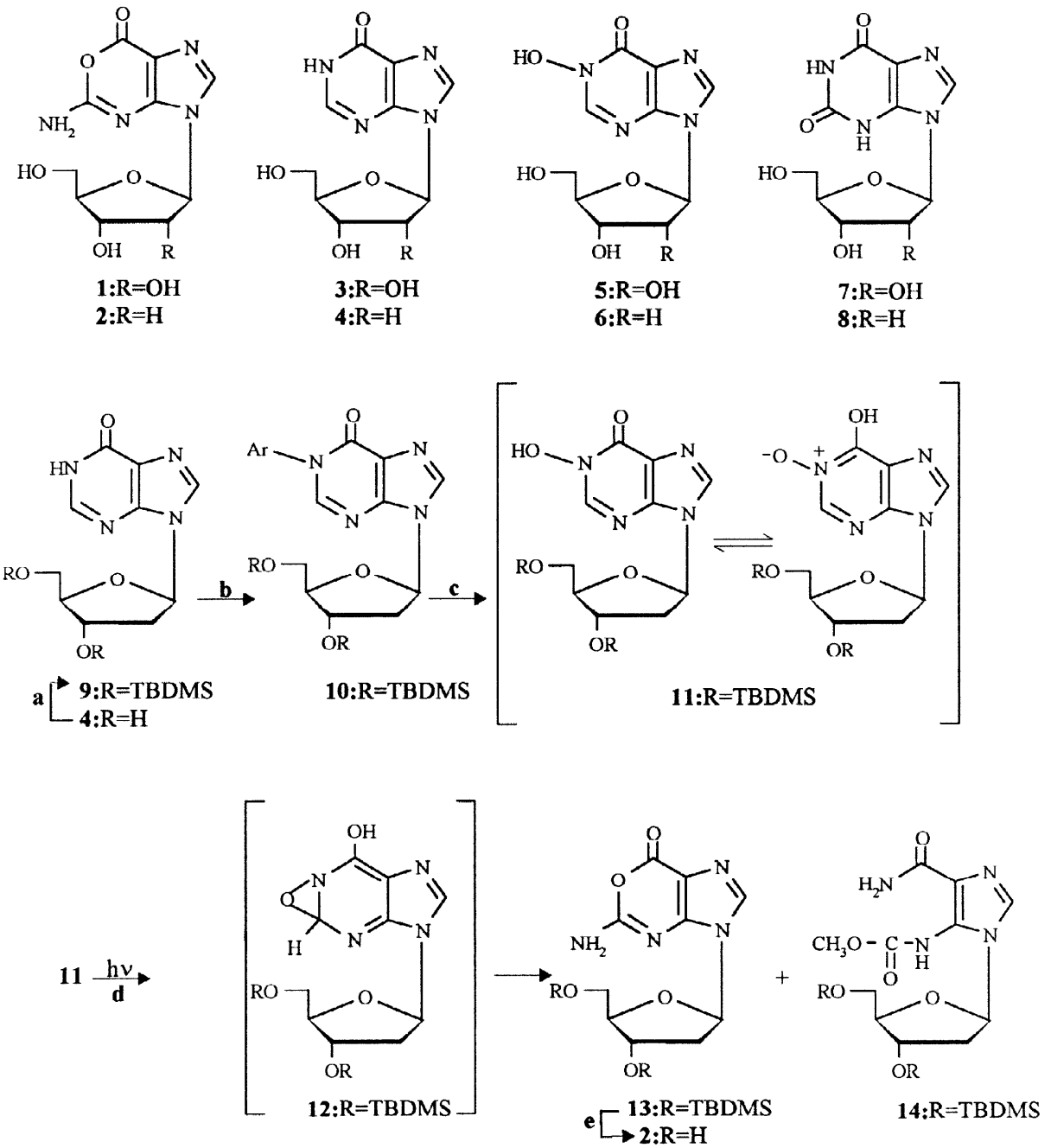

5 $\xrightarrow[f]{h\nu}$ **1** (40%) + **7** (43%) + **3** (13%)

6 $\xrightarrow[f]{h\nu}$ **2** (42%) + **8** (40%) + **4** (15%)

Ar=2,4-dinitrophenyl
TBDMS=*t*-butyldimethylsilyl

Reagents and conditions: ***a***: TBDMSCl (2.2 eq), imidazole (4.0 eq), DMF, r.t., 16 h; ***b***: 2,4-dinitrochlorobenzene (2.5 eq), K_2CO_3 (2.5 eq), DMF, 80°C, 2.5 h; ***c***: hydroxylamine (10 eq), DMF, 80°C, 4 h; ***d:*** CH_3OH, r.t., 3 h; ***e:*** $Et_3N{\bullet}3HF$ (20 eq), THF, r.t., 24 h; ***f:*** H_2O, r.t., 2 h.

For the preparation of 1-hydroxy-3',5'-TBDMS-2'-deoxyinosine **11**, the chosen substrate for UV irradiation, we followed our previously reported strategy,[6b] using 3',5'-TBDMS-2'-deoxyinosine **9**, prepared in almost quantitative yields from **4** by reaction with *t*-butyldimethylsilyl-chloride following a standard procedure, as starting material. Compound **9** was converted by reaction with 2,4-dinitrochlorobenzene and K_2CO_3 in DMF to the corresponding 1-dinitrophenyl derivative **10**, which was obtained in 96 % yield as a 1:1 mixture of atropoisomers.[6b] Reaction of **10** with hydroxylamine afforded **11**[9] in 86 % yield through a rearrangement of the purine ring. UV irradiation of **11**, dissolved in CH_3OH (3 h, r.t. in quartz vessel), by using a UV lamp (500W, high pressure Hg, Helios italquartz) gave 3',5'-di-O-*t*-butyldimethylsilyl-2'-deoxyoxanosine **13**[9] (80 % yield) and the imidazo derivative **14**[9] (10 % yield). Finally **13** was deprotected at the 3'- and 5'-hydroxy functions by treatment with $Et_3N{\cdot}3HF$ leading to target compound **2**, which, after purification by silica gel chromatography, was obtained in 95 % yield (63 % overall yield from 2'-deoxyinosine). Crystallization from CH_3OH furnished pure **2**, m.p. 192-195 °C (lit.[3]: 193-196 °C), whose structure was confirmed by FAB MS spectra (m/z: 269, MH^+) and by comparison of its spectroscopic data (^1H, ^{13}C-NMR and UV) with those already reported in the literature.[3]

The isolation of compounds **13** and **14** confirmed the hypothesized high photoreactivity of 1-hydroxyhypoxanthine base, which has not been investigated so far. A possible mechanism for this reaction could involve the oxaziridine **12** (not isolated) as the first intermediate, which rearranged, as reported for adenosine-1-oxide,[8] to the imidazo-oxazinone ring of **13**, while the side product **14** could have been formed from a transient intermediate reacting with the solvent (CH_3OH). The observed chemical stability of isolated **13** (or **14**), when irradiated by UV light in the same reaction conditions used for **11**, excluded the possibility that one could be the precursor of the other.

We then investigated the photochemical behaviour of unprotected 1-hydroxy-2'-deoxyinosine **6** using H_2O as the solvent. UV light irradiation (2 h, r.t.) led to the desired 2'-deoxyoxanosine **2** (42 %), together with 2'-deoxyxanthosine **8** (40 %) and 2'-deoxyinosine **4** (15 %), identified on the basis of their spectroscopic data and by comparison with authentic samples. Analogously, **5** subjected to the same irradiation, gave a mixture of oxanosine **1**, xanthosine **7** and inosine **3** in similar ratios (40, 43 and 13 % yield, respectively). Notwithstanding the photoreactions in H_2O of **5** and **6** produced lower yields of target compounds **1** and **2**, this route is of interest since the synthesis of oxanosine could be achieved in only two steps starting from commercially available adenosine-1-oxide, directly converted to 1-hydroxyinosine by treatment with $NaNO_2$/acetic acid (56 % yield from the literature[10]).

In conclusion, we have developed an alternative and more efficient route for the synthesis of oxanosine **1** and 2'-deoxyoxanosine **2**, based on the photochemical rearrangement of the base of 1-hydroxyinosine. When using a sugar protected form of 1-hydroxy-2'-deoxyinosine **11**, UV irradiation

in CH_3OH gave 2'-deoxyoxanosine derivative **13** in 80 % yield (63 % overall yield from 2'-deoxyinosine). The same photochemical transformation performed in H_2O on unprotected **5** and **6** gave **1** and **2** in 40 and 42 % yield, respectively. In addition we have demonstrated the feasibility of the desired conversion of inosine into xanthosine by a photochemical oxidation of 2-carbon. This reaction, so far not investigated, may be a useful entry to several nucleoside base transformations.

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9. ^{1}H NMR data: **11** (250 MHz, CD_3OD) δ: 8.50 (1H, bs, H-2); 8.25 (1H, s, H-8); 6.36 (1H, dd, J= 6.3 and 6.3 Hz, H-1'); 4.70 (1H, m, H-3'); 4.00 (1H, m, H-4'); 3.85 (2H, AB part of ABX system H_2-5'); 2.75 and 2.40 (1H, each, m's, H_2-2'); 1.05 and 0.95 (9H each, s's, *t*-butyl); 0.15 and 0.05 (6H each, s's, CH_3). HRMS (FAB), *m/z* $(M+1)^+$ 497.2620, calcd. 497.2616 for $C_{22}H_{40}N_4O_5Si_2 + H^+$. **13** (250 MHz, $CDCl_3$) δ: 7.80 (1H, s, H-2); 6.14 (1H, dd, H-1'); 5.49 (2H, s, exchangeable in D_2O, NH_2); 4.56 (1H, m, H-3'); 3.97 (H, m, H-4'); 3.76 (2H, m, H_2-5'); 2.38 (1H each, m's, H_2-2'); 0.30 (18H, s, *t*-butyl); 0.10 and 0.08 (6H each, s's, CH_3). FAB-MS 497 *m/z* $(MH)^+$. **14** (250 MHz, DMSO-d_6) δ: 9.20 (1H, bs, NH); 7.85 (1H, s, H-2); 7.35 and 7.15 (1H each, s's, exchangeable in D_2O, NH_2); 5.85 (1H, dd, J = 6.8 and 6.8 Hz, H-1'); 4.45 (1H, m, H-3'); 3.85 (1H, very sharp AB part of ABX system, apparent doublet, H-4'); 3.75 (2H, m, H_2-5'); 3.65 (3H, s, CH_3O); 2.48 and 2.28 (1H each, m's , H_2-2'); 0.99 (18H, s, *t*-butyl); 0.10 and 0.05 (6H each, s's, CH_3). HRMS (FAB) *m/z* $(M+1)^+$ 529.2883, calcd. 529.2878 for $C_{23}H_{44}N_4O_6Si_2 + H^+$.
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