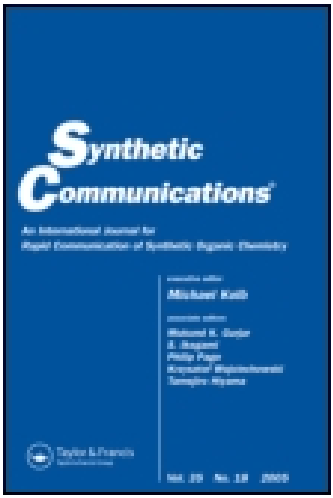

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New Aspects on the Reactivity of Radicals Generated from 5′-Deoxy-5′-iodoadenosine Derivatives

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NEW ASPECTS ON THE REACTIVITY OF RADICALS GENERATED FROM 5'-DEOXY-5'-IODOADENOSINE DERIVATIVES

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Abstract: Acrylonitrile can serve as a trap for a 5'-centered radical derived from adenosine affording the corresponding three carbon extended adenosine derivative **8** together with the known 5',8-cyclization product **9**.

Radicals, whatever their chemical or radiolytical origin, are very effective nucleobase damaging agents being able to interact with both purines and pyrimidines.[1] In the case of purines there is evidence indicating that position 8 and, to a minor extent, position 2 (adenine and inosine) are the major reaction sites.[2]

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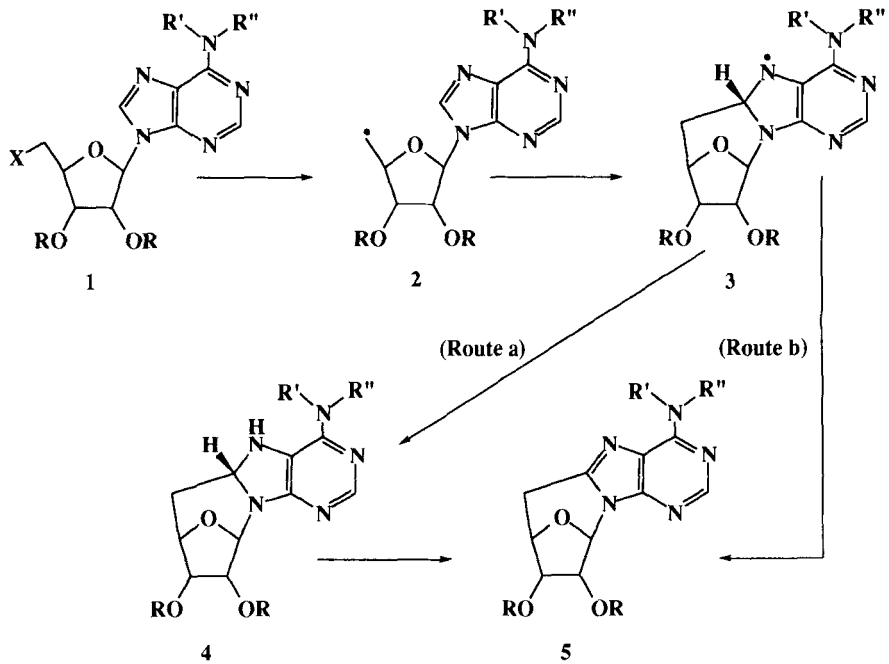
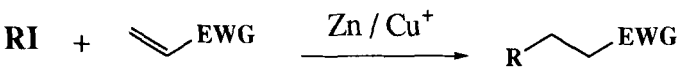
Of particular interest is the well documented formation of 5',8-cyclo-5'-deoxyadenosine derivatives by means of radical cyclization.[3] Thus, starting from an appropriate adenosine derivative **1** there is a number of ways to trigger the formation of the corresponding 5'-centered radical **2** which is postulated as an intermediate in these reactions. Addition of the C-5' radical at the C-8 position of the adenyl moiety occurs in a stereoselective manner and gives the new radical **3** whose stabilization can be accomplished either by reduction (Route a) or radical exchange[3d] (Route b), depending on the reaction conditions, to afford **4** or **5**, respectively. In one instance, the use of chloranil for the quantitative dehydrogenation of **4** to yield **5** has been proposed.[3b]



In the past years, this radical chemistry has been applied for the syntheses of a number of nucleoside analogues having the base irreversibly blocked in the

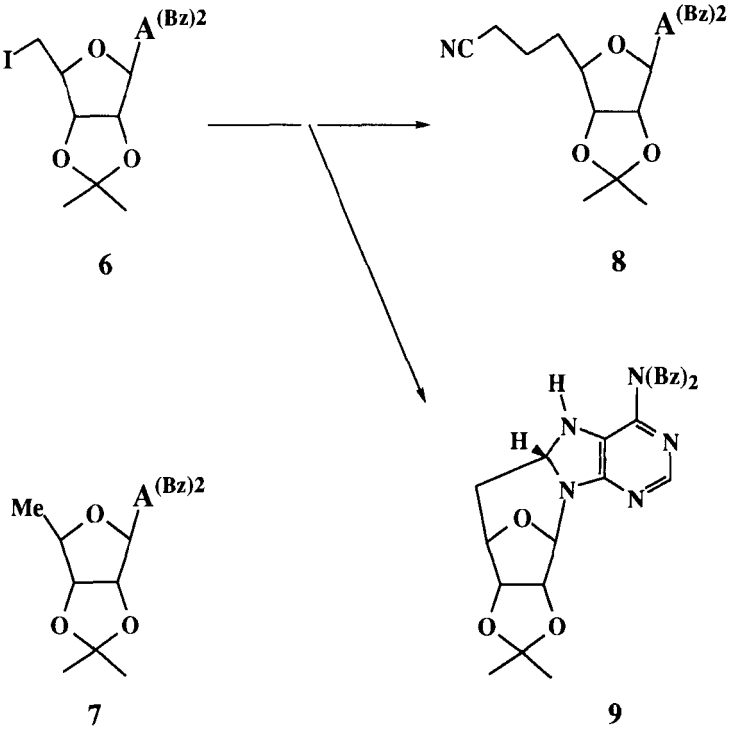
anti conformation. Such derivatives can be used for biological investigations (enzymatic transition states, base pairing...) where one needs to prove that the prefered anti conformation of nucleosides plays a crucial role.[4]

Recently, we have proposed an efficient alternative method to generate carbon radicals.[5,6] We showed that radicals can be produced by a simple treatment of an iodo derivative with either the (Zn/ Cu^{+})[5] or the (Zn/ Fe^{3+})[6] couple. The radicals obtained in this manner are nucleophilic and have the capacity to undergo addition to electron deficient olefins as depicted below:



Because of the current interest in radical reactions involving nucleosides we were prompted to submit the known 5'-deoxy-N^{6}-dibenzoyl-5'-iodo-2',3'-isopropylideneadenosine **6**[7] to our reaction conditions.[5] We wished to explore the chemical behaviour of the expected radical when generated by the Zn/Cu couple system [6] with the hope of finding some experimental conditions which might prevent its anticipated cyclization and instead favour the potentially useful addition reaction. To avoid 5',8-cyclization we were aware that a very efficient trap would be necessary. Indeed, to the best of our knowledge, the only encouraging precedent in the literature was the earlier observation of the partial reduction of **6** by tributyltin hydride in the presence of AIBN to give the corresponding 5'-deoxyadenosine derivative **7**.[3b]

Effectively, when a mixture comprising **6** and a moderate excess of acrylonitrile (3 equiv), used as the radical trap, was submitted to the Zn/Cu^{+} couple the 5',8-cycloderivative **9** was produced in 70% yield in the absence of any



Scheme

side product. As a consequence, we reasoned that for observing the desired addition reaction of the adenosine derived radical to acrylonitrile one should need a higher concentration of the trap and that the best conditions would be reached by using acrylonitrile both as a solvent and a reagent. Indeed, when the reaction was carried out in acrylonitrile solution two products were isolated. The minor one, formed in 21% yield, was identified to the previously isolated cyclic derivative **9**, whereas the major one which was isolated in 27% yield was found to be N^9-(7'-cyano-2',3'-*O*-isopropylidene-5',6',7'-trideoxy-β-D-heptafuranosyl)-N^6-dibenzoyladenine (**8**) on the basis of the analytical and spectral data.

Then, we examined the behaviour of N^6-benzoyl-5'-deoxy-2',3'-*O*-isopropylidene-5'-iodoadenosine[8] (**10**) in this addition reaction. It was found to be identical with that of the dibenzoyl derivative **6**.

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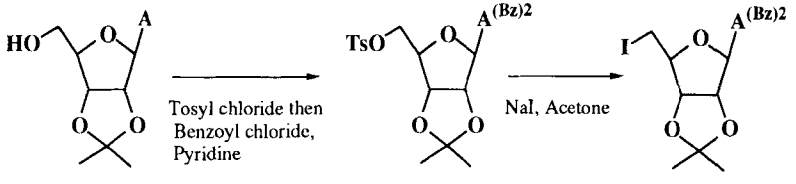
Compound 6 was obtained in two steps starting from 2',3'-*O*-isopropylideneadenosine:



8. Compound **10** was easily prepared by treatment of N^6-benzoyl-*O*-isopropylidene-adenosine with the Rydon reagent methyltriphenoxyphosphonium iodide (Landauer, S. R. and Rydon, H. N. *J. Chem. Soc.* **1953**, 2224-2234) in DMF.

9. To a suspension of a solid mixture composed of zinc powder (150 mg, 5.3 mmol) and CuI (150 mg, 0.96 mmol) in acrylonitrile/H_2O (8/2, 0.5 ml) containing BHT (50 mg) was added stepwise in five portions an acrylonitrile solution of the adenosine derivative **6** (160 mg, 0.25 mmol). The reaction

mixture was vigourously stirred under an argon atmosphere with a vibromixer until the disappearance of the starting material (4.5-5h). At that time the reaction mixture was diluted with ethyl acetate and filtered over Celite. The filtrate was washed with brine and evaporated to give a residue which was chromatographed over Silica gel to give compound **8** (amorphous solid) in 27% yield together with the known 5',8-cyclo derivative **9** (21% yield).

Selected spectral data:

Compound **8**: MS (CI, isobutane) m/z 553 $(M+H)^+$. ^1H NMR ($CDCl_3$) 8.68 (s, 1H, H-2); 8.13 (s, 1H, H-8); 7.5-7.3 (m, 5H, C_6H_5); 6.08 (d, 1H, H-1'); 5.45 (dd, $J_{1',2'}$= 2.5 Hz, $J_{2',3'}$= 2.5 Hz, 1H, H-2'); 4.86 (dd, $J_{3',5'}$= 4.3 Hz, 1H, H-3'); 4.19 (m, 1H, H-4'); 2.36 (m, 2H, H-7'); 1.91-1.73 (m, 4H, H-5' and H-6'); 1.61 (s, 3H, CH_3); 1.38 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) 171.7; 151.9; 143.5; 133.6; 132.5; 129.0; 128.2; 114.7; 89.8; 85.4; 83.4; 83.3; 31.6; 26.7; 24.9; 21.3; 16.4.

Compound **9**[3b]: MS (EI) m/z 499 (M^+). ^{13}C NMR ($CDCl_3$) 160.8; 152.0; 133.9; 131.1; 130.8; 129.0; 128.7; 123.6; 113.3; 85.1; 82.9; 81.6; 79.5; 71.3; 37.3; 26.0; 25.1.

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