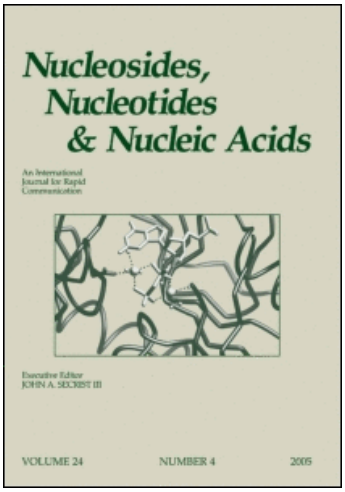

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A Convenient Approach to N-3 Alkylation of 9-Substituted Guanines

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A CONVENIENT APPROACH TO N-3 ALKYLATION OF 9-SUBSTITUTED GUANINES

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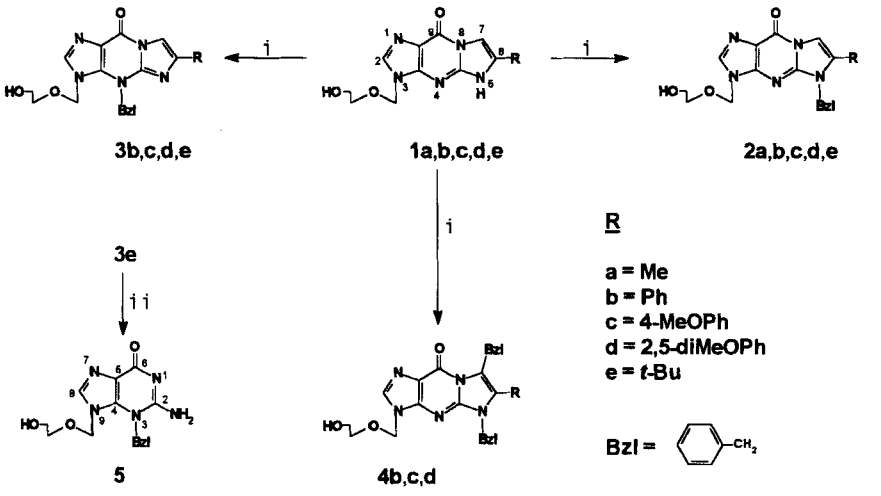
ABSTRACT: Aryl or *tert*-butyl substituent in the 6 position of 3,9-dihydro-3-[(2-hydroxy-ethoxy)methyl]-9-oxo-6-R-5*H*-imidazo[1,2-*a*]purine **1** directs the benzylation reaction partly into N-4 position to give **3**. Cleavage of the third ring of **3** gives 3-benzylacycloguanosine **5**, a first 3-aralkilo-9-substituted guanine.

No direct N-3 alkylation of monomeric 9-substituted guanine has been noted so far. We have previously found that N-3 methylation of guanine moiety in guanosine, 2'-deoxy-guanosine and 9-[(2-hydroxyethoxy)methyl]guanine (acycloguanosine) can be accomplished by a conversion into tricyclic 1,N^2-(prop-1-ene-1,2-diyl) derivatives, i.e. 3,9-dihydro-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine system. This tricyclic system which undergoes high yield N-4 methylation by means of cyclopropanation reagent[1] is easily split to 3-methylguaninederivatives.[2-4] The type of alkylation reagent however, does not allow for a variety of N-3substituents.

We present now further application of the tricyclic modification based on the observation that a substituent in the 6 position has an impact on the site of substitution with alkyl and aralkylhalides under alkaline conditions. Our attention was mainly focused on benzylation reactions of 3,9-dihydro-3-[(2-hydroxyethoxy)methyl]-9-oxo-6-R-5*H*-imidazo[1,2-*a*]purines **1**. When 6-methyl derivative **1a** in dry DMF was treated with K_2CO_3 followed by benzyl bromide, at room temperature for 5 hours, N-5 benzyl substituted **2a** resulted as a single product in over 80 % yield. Under analogous conditions the presence of 6-aryl groups (R = phenyl, 4-methoxyphenyl,2,5-dimethoxyphenyl in compounds **1 b**, **c**, **d**,

respectively) led to a mixture of products which were separated on silica gel column in chloroform - methanol gradient followed by rechromato-graphy of mixed fractions in ethyl acetate - ethanol. In addition to preponderant N-5 derivatives**2 b, c, d**; N-4, **3 b, c, d** (2-18 %); N-5,7, **4 b, c, d** (17-25 %) and 7,O[9] (3 %) substituted products were isolated. In the case of 6-*tert*-butyl substrate **1e**, the N-4 product **3e** became the major one (36 %). The structures of the compounds were assigned on the basis of ^{1}H and ^{13}C NMR, UV and mass spectra. ^{1}H and ^{13}C chemical shift values of benzyl methylene signal were particularly diagnostic (δ_H, δ_C; N-4 : ~5.9, ~49.0; N-5 : ~5.4, ~45.9; N-5,7 : ~5.2, 4.4, ~45.7, 29.7). The removal of the third ring of **3e** was accomplished with 30 % aq hydrogen peroxide in DMF at room temperature for 7 days. Crude product was acetylated with acetic anhydride in pyridine, separated by silica gel column chromatography in toluene - ethanol gradient and deblocked with methanolic ammonia to give 3-benzylacycloguanosine **5**. Similarly 3-(4-nitrobenzyl)acycloguanosine was prepared.

The N-4 directing effect of 6-substituents was weaker in the case of alkylation. On methylation and ethylation of **1b** the yields of N-4 substituted products were up to 10 %; **1e** did not react at N-4.



i: $C_6H_5CH_2Br$, DMF dry, K_2CO_3, r.t.; ii: 30% H_2O_2, DMF, r.t.

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