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Regio-Controlled Radical Substitution of 9-Substituted Purines.

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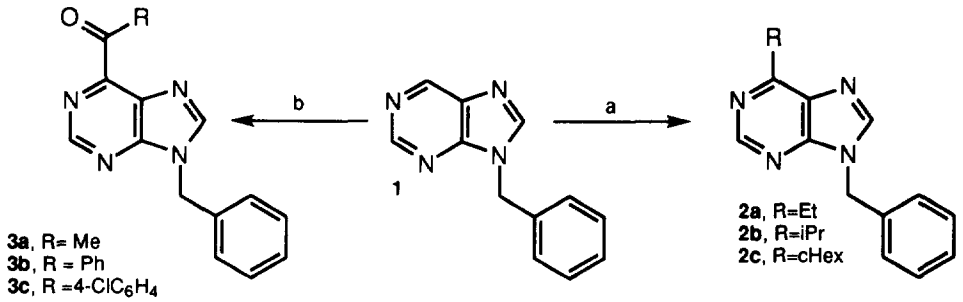
Abstract: 9-benzylpurine undergoes facile radical alkylation and acylation under standard Minisci 's conditions affording regioselectively 6-substituted derivatives.

The introduction of various substituents at the 6-position of 9-alkylpurines have been mainly achieved previously via nucleophilic substitution reactions of the corresponding 6-chloropurines, or the more reactive 6-methylsulphonylpurines using stabilized carbanions[1-3]. Moreover 6-alkynylpurines have been prepared by palladium-catalyzed coupling reactions of 6-chloropurines with alkynes,[4] and 6-methylpurines by ring closure of 4,5-diamino 6- methylpyrimidines[5].

We report here convenient homolytic alkylation and acylation reactions of 9-benzylpurine **1** using the Minisci's procedure[6]. The latter compound, prepared by catalytic hydrogenation of the corresponding 6-chloropurine, was submitted to radical subtitution. Alkyl radicals generated from alkyl iodide and t-BOOH as radical source[7](method A) react with 1 yielding the mononadduct **2** with 43-61% yields.The formation of a diadduct was not observed.

The 6-ethyl derivative **2a** has been prepared by an unambiguous method. For this purpose 6-chloropurine has been cross-coupled with trimethylsilylacetylene according to Koyama et al.[4], deprotected and catalytically hydrogenated. The obtained compound exhibits the same physical characteristics (^{1}H-NMR, ^{13}C-NMR, m.p.), than those found for the compound prepared previously by radical substitution.

The 9-benzylpurine **1** reacts also with acyl radicals generated from the corresponding aldehyde[8], using the $NH_4S_2O_8$- Fe^{2+} redox system (method B).The monoadducts 3 are obtained with 36-59 % yields[9]. Sodium borohydride reduction of **3a** afforded the awaited **2a**[9].



a : R-I, tBuOOH, $FeSO_4$, H_2SO_4 / AcOH, H_2O, 10°C ; **b** : RCHO, $(NH_4)_2S_2O_8$, $FeSO_4$, H_2SO_4 / AcOH, H_2O, 10°C

Scheme 1

PRODUCT	R	method*	yield (%)
2a	Et	A	43
2b	i-Pr	A	56
2c	c-Hex	A	61
3a	Me	B	36
3b	Ph	B	51
3c	4-ClC_6H_4	B	59

*Method A: alkyl iodide, conc. H_2SO_4, t-BuOOH, $FeSO_4$,H_2O-AcOH, 10°C.

Method B: aldehyde, conc. H_2SO_4, $(NH_4)_2S_2O_8$, $FeSO_4$,H_2O-AcOH, 10°C.

Table 1: homolytic substitution of 9-benzyl purine

Three different modes of preparation of 6-ethyl-9-benzyl purine were described. Two of them involved regioselective radical substitution of 9-benzyl purine. The reaction occurs on the pyrimidine ring of the purine. When the 6-position of the pyrimidine nucleus is already substituted (adenines, hypoxanthines, inosines), it has been shown that radical alkylation affords a mixture of C-8 (as major isomer), and C-2 substituted derivatives.[10,11]. Moreover, when compared to our results, similar regioselectivity has been earlier observed, when C-6 unsubstituted purines were submitted to photochemical reaction with alcohols[11-13] and amines.[14]

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9. **2a:** mp 58-59°C. ^{1}H-NMR $CDCl_3$ δ(selected data) : 8.94 (s, 1H), 8.02 (s, 1H), 5.43 (s, 2H), 3.26 (q, 2H). ^{13}C-NMR ($CDCl_3$) : 12.0, 25.9, 46.7, 127.4, 128.0, 128.6, 131.6, 134.9, 143.2; 150.3, 152.1, 163.3. Anal. Calculated for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51. Found : C, 70.43; H, 5.77; N, 23.43.

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