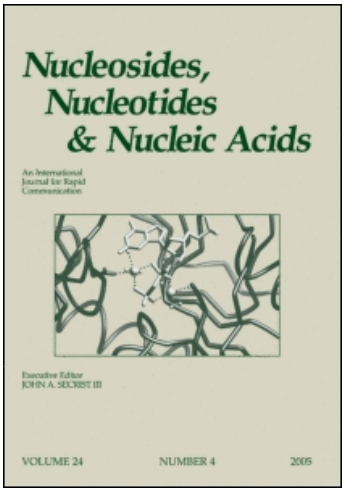

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Efficient Synthesis of 8-Thiosubstituted Guanine Derivatives as Potential Tools for Biochemical and Biological Studies

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ABSTRACT

A method for the selective introduction of the N^2-(dimethylamino)methylene group into 8-thio-9-(2-hydroxyethoxymethyl)guanine (**1**) has been developed. The effect of the N^2-amidine protection on the S-alkylation of **1** was studied.

Key Words: 8-Thioguanine derivates; N^2-Amidine protection; S-Alkylation.

In the search for new bioactive agents and tools for biological studies, many sulfur nucleoside analogues have been synthesised.[1] Among these compounds, 8-thiosubstituted guanine derivatives occupy significant position. Some of them present interesting therapeutic activities whereas others may serve as subunits of supramolecular arrays essential both in certain biological processes and as binding components in artificial systems.

Up to now, only a few alkylating agents have been successful in the S-alkylation of 8-thioguanosine and 8-thioguanine derivatives.[2] The attempts to diversify the alkylating agents structure resulted in moderate yields and low regioselectivity of the process.[3] The objective of this work was to develop a more efficient way for

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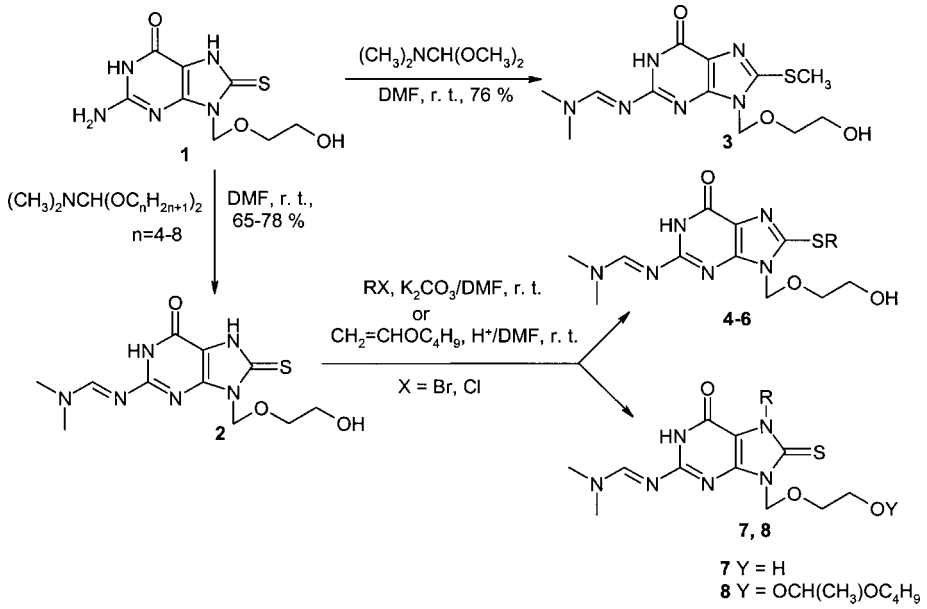

Scheme 1.

the synthesis of various 8-thiosubstituted guanines. Therefore, we decided to study the impact of the N^2-(dimethylamino)methylene protecting group in the guanine cycle on the S-alkylation of its 8-thio derivatives. Despite its common use in purine and pyrimidine chemistry,[4] to the best of our knowledge a (dimethylamino)methylene moiety has not been used with this purpose.

As starting material we chose 8-thio-9-(2-hydroxyethoxymethyl)guanine (**1**), which was transformed into the corresponding N^2-(dimethylamino)methylene derivative **2** by the reaction with DMF-dibutyl acetal or some of its higher homologues.

Table 1. Characteristics of products **4–8.**

					^{1}H NMR (DMSO-d_6), δ, ppm	
Product	R	Reaction time (h)	Yield (%)	Mp (°C)	SCH_2 (s, 2H)	N^7CH_2 (s, 2H)
4	$CH_2C_6H_5$	3	68(60)[b]	159–162	4.49	–
5	CH_2COOCH_3	3	94(11)	187–190	4.16	–
6	CH_2CH_2OH	8[a]	30(< 5)	168–170	3.49	–
7	$CH_2OC_8H_{17}$	4	53(30)	131–132	–	5.72
8	$CH(CH_3)OC_4H_9$	3.5	43(30)	184–186[c]	–	6.48[d]

[a]Reflux.
[b]For 8-thio-9-(2-acetoxyethoxymethyl)-N^2-acetylguanine alkylation (3).
[c]After N^2-deprotection with NH_4OH/EtOH.
[d]q, 1H.

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The widely used DMF-dimethyl acetal was unsuitable in our case as it behaved as a methylating agent affording 8-methylthio-9-alkoxyalkylguanine **3**. Benzyl and 2-hydroxyethyl bromides, chloromethyl octyl and n-butyl vinyl ethers as well as methyl chloroacetate were used for the alkylation of compound **2** to obtain the corresponding 8-alkylthio- (**4**–**6**) or 7-alkyl-8-thio-9-(2-hydroxyethoxymethyl)-N^2-[(dimethylamino)methylene]guanines (**7**, **8**) (Sch. 1). The synthesised compounds were purified by crystallisation from ethanol (products **4**–**6**) or by column chromatography on silica gel (products **7**, **8**). They were characterized by ^{1}H NMR spectra (Table 1) as well as elemental analyses.

In conclusion, the results obtained indicate that the presence of N^2-(dimethylamino)methylene protection in the molecule of 8-thio-9-alkoxyalkylguanine **1** had a beneficial effect on the alkylation of its imidazole cycle, as the yields of alkylation in this case were higher than those obtained with the alternative N^2-acetylated substrate (Table 1). Unfortunately, the amidine protecting group had little influence on the regioselectivity of compound **1** alkylation (*S* vs. *N*). The process was mainly directed by the structure of the alkylating agent used.

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