SHORT PAPER

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Reinvestigation of the reaction of 8-bromoguanine derivatives with sodium thiosulfate†

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A convenient method for the synthesis of 8-thioguanine derivatives using sodium thiosulfate has been reinvestigated on different 8-bromoguanine-containing precursors.

Keywords: purines, thiodehalogenation, thiosulfate

Nucleophilic halide displacement to thio group with sodium thiosulfate is a widely used method in organic chemistry particularly for the preparation of alkyl and aryl thiols. In 1989 this method was introduced into the synthesis of 6-thio- and 8-thio-derivatives of adenosine, inosine and guanosine[1] as well as some of their acyclic analogues[2] from the corresponding 6-chloro- or 8-bromopurine precursors. The use of aluminium chloride as a catalyst of the reaction substantially facilitated the process and increased the yields of products, especially in the case of the acyclic nucleoside analogues.[2] Despite some limitations, *e.g.* concurrent full O-deacetylation of blocked nucleosides[1] or possible formation of cyclic by-products,[2,3] the thionation with sodium thiosulfate has been selected by us for the synthesis of a series of 8-thio-9-substituted guanines required for our studies on the preparation and investigation of multifunctional guanine derivatives.

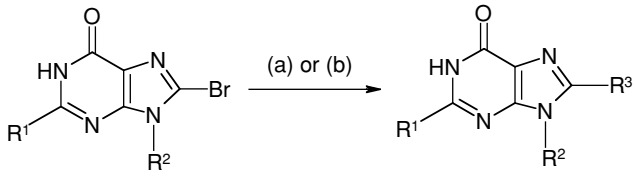
The preparation of the desired 8-thio-9-substituted guanines started from the corresponding 8-bromo-N^2-acetyl intermediates **1a–c, f, g**. The N^2-acetyl group in the derivatives was expected to increase the solubility of the reaction products, thus facilitating their purification and further modification. The reaction of compounds **1a–c** with sodium thiosulfate (4 equiv.) in the refluxing water suspension in the presence of aluminium chloride proceeded smoothly, affording the target 8-thio-9-(2-acetoxyethoxymethyl)-, 8-thio-9-[2-(3-carboxypropionyl)oxyethoxymethyl]- and 8-thio-9-benzyl-N^2-acetylguanine (**2a–c)** in 64–77% yield. No splitting of N^2- or O-acetyl protecting groups presented in substrates **1a-c** was observed in this case. The O-acetyl groups were also retained during the thionation of blocked nucleoside, *e.g.* 8-bromo-9-(2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl)guanine (**1d)** if the reaction was carried out in the presence of a catalytic amount of aluminium chloride. On the other hand, the thionation of the N^2-(*N*,*N*-dimethylamino)methylene function containing substrate **1e** afforded 8-thio-9-(2-hydroxyethoxymethyl)guanine (**2e**)[2a,4] in a quantitative yield supporting the instability of this protecting group under the reaction conditions.

Not all of our attempts to transform 8-bromo-9-substituted guanines into the corresponding 8-thio compounds using sodium thiosulfate were successful. Only the starting material was isolated after a prolonged heating of substrate **1f** with the combination of inorganic salts mentioned above. Taking into account the possibility that the failure of **1f** to react with sodium thiosulfate may be a solubility phenomenon, water as the reaction medium was replaced by ethanol or a water-ethanol mixture although without any success. The desired 8-thio-9-(2-octyloxymethyl)-N^2-acetylguanine (**2f)** was finally obtained in 50% yield using thiourea in ethanol,[5] *i.e.* under the conditions usually less efficient for the thionation of 8-bromo-9-alkoxyalkyl guanines.

The treatment of substrate **1g** with sodium thiosulfate with or without the addition of aluminium chloride resulted in the splitting of the tetrahydrofuryl cycle and formation of 8-bromo-N^2-acetylguanine (**2g**).[6] No thionation occurred in this case The resistance of halogen to the nucleophilic displacement in derivative **2g** was confirmed by unsuccessful attempts to substitute it by a thio group either with sodium thiosulfate-aluminium chloride in water or thiourea in *N*, *N*-dimethylformamide.[4]

The structures of 8-thioguanines obtained were confirmed by data of ^{1}H PMR spectra as well as elemental analysis.

In summary, we have extended the procedure of thionation with sodium thiosulfate for the preparation of novel 8-thio-9-substituted guanine derivatives. It has been demonstrated that an addition of a catalytic amount of aluminium chloride to the reaction mixture not only facilitates the process, but also prevents the splitting of both *O*- and *N*-acetyl protecting groups in the substrate. At the same time, such functions as N^2-(*N*,*N*-dimethylamino)methylene and N^9-tetrahydrofuryl are unstable under the mild thionation reaction conditions. The insertion of a substituent at N-9 is essential for the successful halogen displacement to a thio group at C-8. However, its influence on the overall electron distribution in the purine system can also prevent the proceeding of the reaction as it was observed in the analogue with an increased length alkyl side-



1a–g **2a–g**

1a R^1 = NHCOCH$_3$, R^2 = $CH_2OCH_2CH_2OCOCH_3$
b R^1 = NHCOCH$_3$, R^2 = $CH_2OCH_2CH_2OCOCH_2CH_2COOH$
c R^1 = NHCOCH$_3$, R^2 = $CH_2C_6H_5$
d R^1 = NH_2, R^2 = 2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl
e R^1 = $NCHN(CH_3)_2$, R^2 = $CH_2OCH_2CH_2OH$
f R^1 = NHCOCH$_3$, R^2 = $CH_2OC_8H_{17}$
g R^1 = NHCOCH$_3$, R^2 = tetrahydro-2-furyl
2a R^1 = NHCOCH$_3$, R^2 = $CH_2OCH_2CH_2OCOCH_3$, R^3 = SH
b R^1 = NHCOCH$_3$, R^2 = $CH_2OCH_2CH_2OCOCH_2CH_2COOH$, R^3 = SH
c R^1 = NHCOCH$_3$, R^2 = $CH_2C_6H_5$, R^3 = SH
d R^1 = NH_2, R^2 = 2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl, R^3 = SH
e R^1 = NH_2, R^2 = CH_2CH_2OH, R^3 = SH
f R^1 = NHCOCH$_3$, R^2 = $CH_2OC_8H_{17}$, R^3 = SH
g R^1 = NHCOCH$_3$, R^2 = H, R^3 = Br

Scheme 1 Reagents and conditions:
(a) $Na_2S_2O_3{\cdot}5H_2O$, $AlCl_3{\cdot}6H_2O$, H_2O, reflux (64–77%);
(b) thiourea, EtOH, reflux (50 %).

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chain. Further studies on the mechanistic aspects and application of the method on the related substrates are in progress.

Experimental

M.p.s are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WH-90/DS spectrometer in DMSO-d_6 with TMS as an internal standard. All reactions were monitored by TLC carried out on silica gel 0.2 mm Merck silica gel plates ($60F_{254}$), using UV light and chloroform-ethanol (10:1) as solvent. Column chromatography was performed on 0.063–0.200 (70–230 mesh ASTM) silica gel 60 with chloroform-ethanol (40:0.5) as eluent.

Starting 8-bromo-N^2-acetylguanines **1a**,[7a] **1c**,[6] **1d**,[7b] **1f**[7a] and **1g**[7c] were prepared according to published procedures. Derivative **1b** was synthesised from 8-bromo-9-(2-hydroxyethoxymethyl)-N^2-acetylguanine and succinic anhydride following the literature method.[7d] The crude product was recrystallised from ethanol. Yield 64%; m.p. 200–201°C; ^{1}H NMR: δ 2.17 (s, 3H, $NCOCH_3$), 3.36 (s, 4H, CH_2CH_2COOH), 3.76 (m, 2H, CH_2), 4.12 (m, 2H, CH_2), 5.45 (s, 2H, NCH_2O), 12.17 (br. s, 2H, NH); Found: C, 37.74; H, 3.53; N, 15.58%. $C_{14}H_{16}BrN_5O_7$ requires C, 37.68; H, 3.61; N, 15.69%. Substrate **1e** was synthesised by treatment of 8-bromo-9-(2-hydroxyethoxymethyl)guanine with DMF dimethyl acetal following the published method[7e] and purified by crystallisation from ethanol. Yield 78%; m. p. 240–241°C; ^{1}H NMR: δ 3.06 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.54 (s, 4H, CH_2CH_2), 4.64 (s, 1H, OH), 5.43 (s, 2H, NCH_2O), 8.61 (s, 1H, CH), 11.42 (s, 1H, NH); Found: C, 36.62; H, 4.28; N, 23.60%. $C_{11}H_{15}BrN_6O_3$ requires C, 36.78; H, 4.21; N, 23.40%.

General procedure for thionation of **1a–e** *with* $Na_2S_2O_3$*:* A mixture of the appropriate 8-bromoguanine derivative **1a–e** (1.0 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (4.0 mmol) and $AlCl_3{\cdot}6H_2O$ (0.2 mmol) in 15 ml of water was refluxed for 4 h. Any solid substance was filtered off and the filtrate was cooled to 5°C. The resulting precipitate was filtered, washed with cold water and. recrystallised from ethanol to give products **2a, c–e**. The water solution of product **2b** after cooling was acidified to pH 2 with 1N HCl and the white precipitate formed was collected by filtration and recrystallised from ethanol.

2a: Yield 75%; m. p. 158–160°C; ^{1}H NMR: δ 1.96 (s, 3H, $OCOCH_3$), 2.18 (s, 3H, $NCOCH_3$), 3.83 (m, 2H, CH_2), 4.14 (m, 2H, CH_2), 5.49 (s, 2H, NCH_2O), 11.89 (s, 1H, NH), 12.21 (s, 1H, NH); Found: C, 39.74; H, 4.64; N, 19.71; S, 8.73%. $C_{12}H_{15}N_5O_5S{\cdot}H_2O$ requires C, 40.11; H, 4.77; N, 19.49; S, 8.92%.

2b: Yield 64%; m. p. 121–122°C; ^{1}H NMR: δ 2.16 (s, 3H, $NCOCH_3$), 2.49 (m, 4H, CH_2CH_2) 3.83 (m, 2H, CH_2), 4.12 (m, 2H, CH_2), 5.53 (s, 2H, NCH_2O), 11.98 (s, 1H, NH), 12.27 (s, 1H, SH), 13.46 (s, 1H, NH); Found: C, 40.15; H, 4.47; N, 16.72; S, 7.80%. $C_{14}H_{17}N_5O_7S{\cdot}H_2O$ requires C, 40.29; H, 4.59; N, 16.78; S, 7.68%.

2c: Yield 80%; m. p. 200°C (dec.); ^{1}H NMR: δ 2.16 (s, 3H, $NCOCH_3$), 5.34 (s, 2H, NCH_2), 7.36 (m, 5H, C_6H_5); Found: C, 53.28; H, 4.20; N, 21.96; S, 10.29%. $C_{14}H_{13}N_5O_2S$ requires C, 53.32; H, 4.16; N, 22.21; S, 10.17%.

2d: Yield 77%; m. p. 168–170°C; ^{1}H NMR: δ 2.05 (s, 3H, $OCOCH_3$), 2.07 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 4.27 (m, 2H, 4′H-5′H), 5.69 (m, 1H, 3′H), 6.16 (m, 1H, 2′H), 6.47 (s, 1H, 1′H), 6.67 (s, 2H, NH_2), 11.16 (s, 1H, NH); Found: C, 41.76; H, 4.75; N, 15.15; S, 6.99%. $C_{16}H_{18}N_5O_8S \cdot H_2O$ requires C, 41.83; H, 4.61; N, 15.24; S, 6.98%.

Procedure for thionation of **1f** *with thiourea:* To a stirred solution of derivative **1f** (1.0 mmol) in 15 ml of abs. ethanol was added thiourea (5.0 mmol). The mixture was refluxed for 72 h (the reaction progress followed by TLC). Any solid substance was filtered off and the filtrate was evaporated at reduced pressure. The residue was purified by column chromatography. Product **2f** was crystallised from ethanol.

2f: Yield 50%; m. p. 222–224°C; ^{1}H NMR: δ 0.83 (t, 3H, CH_3), 1.18 (m, 12H, $(CH_2)_6$), 2.17 (s, 3H, $NCOCH_3$), 3.61 (t, 2H, CH_2), 5.49 (s, 2H, NCH_2O), 11.87 (s, 1H, NH), 12.32 (s, 1H, NH); Found: C, 52.48; H, 6.93; N, 19.18; S, 8.67%. $C_{16}H_{25}N_5O_3S$ requires C, 52.29; H, 6.86; N, 19.06; S, 8.73%.

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