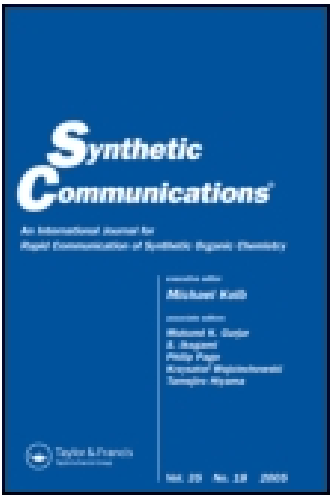

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Improved Synthesis of 7-(Alkyl/aralkyl)guanines

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Improved Synthesis of 7-(Alkyl/aralkyl)guanines

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ABSTRACT

A rapid and convenient preparation of 7-(alkyl/aralkyl)guanines from guanosine is described. Using this method, a series of 7-substituted guanines (compounds **2a–k**) was synthesized in good yields (51%–97%).

Key Words: Alkylations; Hydrolyses; Nucleotides; 7-(Alkyl/aralkyl)-guanines.

INTRODUCTION

The pharmacological profile of 7-(alkyl/aralkyl)guanines remains to be investigated, as these compounds could be potential inhibitors of DNA-glycosylases of the base excision repair system,[1,2] a major repair pathway

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involved in the emergence of drug-resistant tumor cells in patients under chemotherapy.[3,4] In order to examine this therapeutic activity, we undertook the synthesis of a series of 7-(alkyl/aralkyl)guanine derivatives, i.e., compounds **2a–k** (Fig. 1).

RESULTS AND DISCUSSION

To date, only few examples for such guanine derivatives have been reported and most concern 7-methylguanine (**2a**),[5–7] 7-ethylguanine (**2b**),[6] 7-benzylguanine (**2c**),[8] and 7-(2′-hydroxyethyl)guanine (**2d**).[9,10] These published syntheses for **2a–d** are two-step procedures consisting of: (i) the heating of guanosine (**1**) with an excess of alkylating agent in dimethylformamide or dimethylacetamide (acetic acid for **2d**), and then the isolation, with only low yields, of the resulting alkylated guanosine by precipitation with concentrated ammonia and filtration; (ii) the acid hydrolysis of this intermediary nucleoside to provide the target alkylated guanines. More recently, Piper and co-workers,[11] have developed a one-step procedure for some 7-substituted-benzylguanine derivatives, starting from guanosine. However, the intermediates 7-substituted-guanosines were not isolated but directly converted to 7-(alkyl/aralkyl)guanines by acid hydrolysis. Their method is effective, yet it still has its limitations: yields are very low, presumably due to the extraction and purification methods. Considering these previous works and their drawbacks, we set out to optimize the corresponding procedures by developing a one-step route mainly based on optimized reaction conditions and an efficient treatment.

The general method we adopted for the preparation of guanine derivatives **2a–k** from guanosine (**1**) was based on the preliminary treatment of **1** with excess alkylating agent in dimethylacetamide, according to experimental conditions precisely studied, and the subsequent cleavage of the glycosidic bond

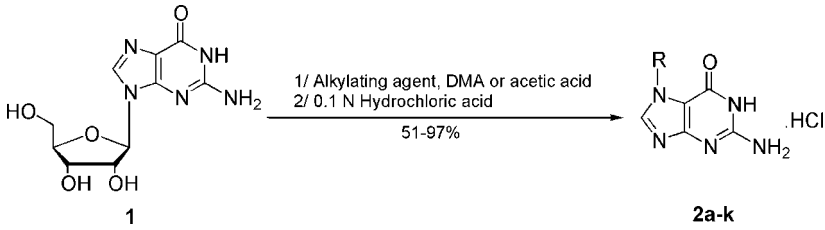

Figure 1.

of the alkylated guanosine by acid hydrolysis (0.1*N* hydrochloric acid). This procedure was modified compared with those previously reported[5–11] as follows: (i) the intermediary alkylated guanosine derivative was not isolated but directly engaged in the next step, (ii) after hydrolysis, the alkylated guanine was precipitated by neutralization (with 1*N* sodium hydroxide), filtered, and converted into its hydrochloride (with 2*N* ethanolic hydrochloric acid in dimethylacetamide). This strategy afforded good results, the desired 7-alkylated/aralkylated guanines, isolated as their hydrochloride salts, being obtained in good yield and excellent purity. The starting products, the conditions of alkylation, and the yield of the isolated compounds are reported in Table 1.

CONCLUSION

In conclusion, we have developed a convenient, operational and simple one-pot procedure for the preparation of 7-substituted guanines **2a–k**, which are not easily obtained by other methods. In addition, the yields are high and the starting materials are commercially available. This efficient procedure avoids complications associated with extraction and purification of the intermediary alkylated guanosine. This method could therefore be extended to the preparation of other 7-(alkyl/aralkyl)guanines. Work on the potency of these compounds as glycosylases inhibitors is currently in progress.

EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and were used without further treatment, except when specified. Melting points (mp) were determined in open capillaries with an electrothermal digital apparatus and were uncorrected. Elemental analyses for carbon, hydrogen, nitrogen, and halogen were obtained from CNRS Service Central d'Analyse at Vernaison (France).

General Synthesis of Compounds 2a–k

Guanosine (**1**) (3 g, 9.34 mmol) was treated with the appropriate alkylating agent in dimethylacetamide (DMA) or acetic acid according to the reaction conditions summarized in Fig. 1. The solvent was then evaporated under reduced pressure, and the resulting residue was immediately refluxed for 1.5 hr

Table 1. Conditions of preparation of 7-substituted guanines **2a–k**.

Product	R	Alkylating agent	Conditions of alkylation	Yield (%)
2a	CH_3	Dimethyl sulfate (3 eq)	DMA, 6 hr, r.t.	96
2b	CH_2CH_3	Ethyl iodide (3 eq)	DMA, 24 hr, r.t.	97
2c	$CH_2C_6H_5$	Benzyl bromide (3 eq)	DMA, 24 hr, 60°C	92
2d	CH_2CH_2OH	Ethylene oxide (10 eq)	Acetic acid, 30 min, 100°C	95
2e	$CH_2CH_2CH_3$	Propyl bromide (3 eq)	DMA, 48 hr, 60°C	90
2f	$CH(CH_3)_2$	Isopropyl iodide (3 eq)	DMA, 48 hr, 60°C	81
2g	$CH_2[4\text{-}(CH_3)C_6H_4]$	4-Methylbenzyl bromide (3 eq)	DMA, 24 hr, 60°C	60
2h	$CH_2[3\text{-}(OCH_3)C_6H_4]$	3-Methoxybenzyl chloride (3 eq)	DMA, 30 min, 120°C	51
2i	$CH_2(4\text{-}FC_6H_5)$	4-Fluorobenzyl chloride (5 eq)	DMA, 1 hr, 60°C	90
2j	$CH_2CH = CH_2$	Allyl bromide (5 eq)	DMA, 2 hr, 70°C	85
2k	$CH_2COOCH_2CH_3$	Ethyl bromoacetate (3 eq)	DMA, 30 min, 100°C	88

in 0.1*N* hydrochloric acid (200 mL). The solution was concentrated under reduced pressure and treated with 1*N* sodium hydroxide to yield the intermediary base, which was converted into its hydrochloride **2a–k** by treatment with 2*N* ethanolic hydrochloric acid (10 mL) in DMA. After filtration, the guanine derivatives **2a–k** were washed with anhydrous ether, dried in vacuo, and recrystallized when necessary (from ethanol for **2e–k**) to give white solids (mp $> 300^{\circ}$C).

7-Methylguanine hydrochloride (2a). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.93 (s, 3H), 7.45 (s, 2H), 8.83 (s, 1H).[a] ^{13}C NMR (DMSO-d_6, 50 MHz) δ 34.6, 107.7, 139.2, 149.5, 153.1, 154.7. ES-MS m/z 166.06 (M^+): Anal. Calcd. for $C_6H_7N_5O.HCl \cdot 0.6\ H_2O$ (%): C, 34.14; H, 4.14; N, 32.69; Cl, 16.32. Found: C, 33.93; H, 4.36; N, 32.96; Cl, 16.69.

7-Ethylguanine hydrochloride (2b). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.42 (t, $J = 7.1$ Hz, 3H), 4.30 (q, $J = 7.1$ Hz, 2H), 7.43 (s, 2H), 8.92 (s, 1H).[a] ^{13C} NMR (DMSO-d_6, 50 MHz) δ 15.5, 43.3, 106.9, 138.3, 150.1, 152.9, 154.7. ES-MS m/z 180.09 (M^+): Anal. Calcd. for $C_7H_9N_5O.HCl \cdot 0.3\ H_2O$ (%): C, 37.96; H, 4.84; N, 31.62; Cl, 16.00. Found: C, 38.16; H, 4.72; N, 31.22; Cl, 15.83.

7-Benzylguanine hydrochloride (2c). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 5.52 (s, 2H), 7.37 (s, 5H), 7.54 (s, 2H), 8.94 (s, 1H), 12.00 (s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 52.0, 108.0, 128.6, 129.0, 129.5, 137.0, 141.1, 152.2, 154.2, 154.5. ES-MS m/z 242.15 (M^+): Anal. Calcd. for $C_{12}H_{11}N_5O.HCl \cdot 1.46\ H_2O$ (%): C, 47.39; H, 4.95; N, 23.03; Cl, 11.66. Found: C, 47.72; H, 4.75; N, 22.63; Cl, 11.35.

7-(2′-Hydroxyethyl)guanine hydrochloride (2d). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.71 (s, 2H), 4.30 (s, 2H), 5.00 (s, 1H), 7.42 (s, 2H), 8.91 (s, 1H), 11.88 (s, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 52.0, 59.7, 107.9, 140.1, 152.0, 153.9, 155.8. ES-MS m/z 196.06 (M^+): Anal. Calcd. for $C_{12}H_{11}N_5O.HCl \cdot 1.46\ H_2O$ (%): C, 47.39; H, 4.95; N, 23.03; Cl, 11.66. Found: C, 47.72; H, 4.75; N, 22.63; Cl, 11.35.

7-Propylguanine hydrochloride (2e). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 0.84 (t, $J = 7.0$ Hz, 3H), 1.85 (m, 2H), 4.25 (t, $J = 7.0$ Hz, 2H), 7.40 (s, 2H), 8.92 (s, 1H), 11.75 (brs, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 11.2, 23.8, 50.1, 107.5, 139.7, 151.6, 153.9, 155.4. ES-MS m/z 194.14

[a]The NH proton in **2a**, **2b**, **2g**, **2h**, **2i**, and **2k** were not distinctly observed in the ^{1}H NMR spectra presumably due to rapid exchange with traces of water.

(M^+): Anal. Calcd. for $C_8H_{11}N_5O.HCl \cdot 0.8\ H_2O$ (%): C, 39.07; H, 5.26; N, 28.36; Cl, 14.60. Found: C, 39.37; H, 5.61; N, 28.69; Cl, 14.52.

7-Isopropylguanine hydrochloride (2f). ^1H NMR (DMSO-d_6, 200 MHz) δ 1.50 (s, 6H), 4.89 (q, $J = 6.9$ Hz, 1H), 7.27 (s, 2H), 9.01 (s, 1H), 11.79 (brs, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 22.7, 52.5, 107.5, 137.6, 151.6, 153.8, 155.6. ES-MS m/z 194.14 (M^+): Anal. Calcd. for $C_8H_{11}N_5O.HCl \cdot 0.5H_2O$ (%): C, 40.03; H, 5.26; N, 29.51; Cl, 14.65. Found: C, 40.25; H, 5.49; N, 29.34; Cl, 14.85.

7-(4-Methylbenzyl)guanine hydrochloride (2g). ^1H NMR (DMSO-d_6, 200 MHz) δ 2.27 (s, 3H), 5.46 (s, 2H), 7.15 (d, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 7.7$ Hz, 2H), 7.51 (s, 2H), 8.94 (s, 1H).[12] ^{13}C NMR (DMSO-d_6, 50 MHz) δ 21.5, 50.9, 107.9, 128.8, 130.1, 133.5, 138.6, 140.6, 151.1, 153.9, 155.1. ES-MS m/z 256.16 (M^+): Anal. Calcd. for $C_{13}H_{13}N_5O.HCl \cdot 0.8\ H_2O$ (%): C, 50.87; H, 5.17; N, 23.01; Cl, 11.60. Found: C, 51.00; H, 5.14; N, 22.87; Cl, 11.58.

7-(3-Methoxybenzyl)guanine hydrochloride (2h). ^1H NMR (DMSO-d_6, 200 MHz) δ 3.72 (s, 3H), 5.47 (s, 2H), 6.93 (m, 3H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.56 (s, 2H), 8.92 (s, 1H).[a] ^{13}C NMR (DMSO-d_6, 50 MHz) δ 51.0, 55.9, 107.9, 114.4, 114.7, 120.8, 130.8, 137.7, 140.8, 150.7, 153.8, 155.0, 160.2. ES-MS m/z 272.15 (M^+): Anal. Calcd. for $C_{13}H_{13}N_5O_2.HCl \cdot 1.0\ H_2O$ (%): C, 47.70; H, 5.01; N, 21.82; Cl, 11.11. Found: C, 47.93; H, 4.95; N, 21.50; Cl, 10.88.

7-(4-Fluorobenzyl)guanine hydrochloride (2i). ^1H NMR (DMSO-d_6, 200 MHz) δ 5.49 (s, 2H), 7.18 (d, $J = 8.8$ Hz, 1H), 7.23 (d, $J = 8.9$ Hz, 1H), 7.45 (s, 2H), 7.49 (m, 2H), 8.90 (s, 1H).[a] ^{13}C NMR (DMSO-d_6, 50 MHz) δ 50.3, 107.9, 116.2, 116.6, 131.1, 131.3, 140.8, 151.7, 154.0, 154.9, 160.4, 165.2. ES-MS m/z 260.20 (M^+): Anal. Calcd. for $C_{12}H_{10}N_5OF.HCl \cdot 1.0\ H_2O$ (%): C, 45.95; H, 4.11; N, 22.67; Cl, 11.62. Found: C, 45.94; H, 4.18; N, 22.32; Cl, 11.30.

7-Allylguanine hydrochloride (2j). ^1H NMR (DMSO-d_6, 200 MHz) δ 4.93 (d, $J = 5.56$ Hz, 2H), 5.05 (d, $J = 15.7$ Hz, 1H), 5.25 (d, $J = 9.86$ Hz, 1H), 6.06 (m, 1H), 7.76 (s, 2H), 8.87 (s, 1H), 12.10 (brs, 1H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 50.2, 108.2, 119.7, 133.3, 140.5, 151.9, 153.9, 155.1. ES-MS m/z 192.11 (M^+): Anal. Calcd. for $C_8H_9N_5O.HCl \cdot 0.5\ H_2O$ (%): C, 40.96; H, 4.73; N, 29.76; Cl, 14.67. Found: C, 40.60; H, 4.68; N, 29.59; Cl, 14.98.

7-(Ethoxycarbonylmethyl)guanine hydrochloride (2k). ^1H NMR (DMSO-d_6, 200 MHz) δ 1.21 (t, $J = 7.1$ Hz, 3H), 4.17 (q, $J = 7.1$ Hz, 2H), 5.23 (s, 2H), 7.65 (s, 2H), 8.58 (s, 1H)[a]. ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.8, 48.8, 62.5, 108.6, 142.6, 150.5, 153.7, 154.6, 167.9. ES-MS m/z 238.10 (M^+): Anal. Calcd. for $C_9H_{11}N_5O_2.HCl \cdot 1.2\ H_2O$ (%): C, 36.62; H, 5.15; N, 23.46; Cl, 11.57. Found: C, 36.38; H, 4.88; N, 23.57; Cl, 11.93.

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