*Acta Chemica Scandinavica, 1999: 53: 280–283*
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ACTA
CHEMICA SCANDINAVICA
*ISSN 0904-213X*

# A Novel Route to $N^6$-Alkylated 2′-Deoxyadenosine Using Benzotriazole as a Synthetic Auxiliary

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El-Kafrawy, S. A., Zahran, M. A. and Pedersen, E. B., 1999. A Novel Route to $N^6$-Alkylated 2′-Deoxyadenosine Using Benzotriazole as a Synthetic Auxiliary. – Acta Chem. Scand. 53: 280–283. © Acta Chemica Scandinavica 1999.

The $N^6$-alkylation of 2′-deoxyadenosine is achieved by sodium borohydride reduction of the adduct formed from benzotriazole, an aliphatic, aromatic or heteroaromatic aldehyde and 2′-deoxyadenosine. In some cases ethoxy adducts are isolated and reduced to give the target $N^6$-alkylated-2′-deoxyadenosine.

*N*-Alkylaryl amines (ArNHR) can be prepared by the direct alkylation of primary aromatic amines with alkyl halides,[1,2] alkyl sulfonates,[3] dialkyl phosphites[4] or dimethyl oxalate[5] provided a large excess of the starting amine is used. However, the separation of the product from the reaction mixture is difficult because the *N*-alkylaryl amines produced as an alkylation product are more nucleophilic than the starting primary amines, and tertiary *N*,*N*-(dialkyl)arylamines are invariably by-products.[6–9]

To our knowledge, no direct route for the $N^6$-alkylation of 2′-deoxyadenosine using benzotriazole as a synthetic auxiliary has been published. In 1985 Katritzky and his group started an intensive investigation of the potential uses of benzotriazole chemistry[10] and reported the alkylation of adenine with 1-hydroxymethylbenzotriazole in 1987.[11] One of the reported routes for the alkylation of adenosine, cytidine and guanosine involved the reaction of the appropriate nucleoside with formaldehyde and *p*-thiocresol in boiling aqueous ethanol in the presence of acetic acid to give the corresponding *N*-(*p*-tolylthiomethyl) derivatives which led to the *N*-alkyl derivatives after heat treatment with sodium borohydride in 1,2-dimethoxyethane (glyme) or dimethyl sulfoxide (DMSO).[12,13]

The methylation of adenine, adenosine and nucleic acids have been extensively investigated and many mono-, di-, and trimethyl derivatives have been either isolated from the direct methylation or synthesized. There are two expected derivatives which have been described. These are the 3- and 7-substituted adenines, predicted to be labile nucleosides.[14] Moreover, the products of the ethylation of adenosine with diethyl sulfate and ethyl methanesulfonate in neutral aqueous solution are 1-ethyladenosine, $N^6$-ethyladenosine, and 7-ethyladenosine, plus unidentified products. Also the reaction of adenosine with anhydrous ethyl iodide or with methylating agents alkylate the 1- and 7-positions, but not the exocyclic amino group.[15] The isolation of $N^6$-alkyl-substituted deoxyadenosine and other derivatives of adenosine have been reported by Robins and Trip.[16] These reactions involved $N^1$-alkylation followed by a Dimroth rearrangement reaction to give the $N^6$-substituted compounds. Although 6-chloropurine riboside is commercially very expensive, it is used for the preparation of $N^6$-substituted purine ribosides. Many authors have described the preparation of several 6-substituted adenosines[17,18] by an amination reaction from the corresponding 6-chloropurine riboside.

In continuation of our investigation in the field of nucleoside synthesis,[19] our attention has been focused toward the facile application of this alkylation to 2′-deoxyadenosine, since $N^6$-alkylated adenosines have been found to have interesting biological, pharmacological as well as physiological activities.[20] Now we report a facile and novel direct alkylation of the unprotected 2′-deoxyadenosine via the use of benzotriazole as a synthetic auxiliary for $N^6$-alkylation.

## Results and discussion

The target $N^6$-alkylated 2′-deoxyadenosines **6a–i** were prepared by reduction of the corresponding benzotriazole adducts **4a–f** and the adducts **5g–i** using 6 molar equivalents of sodium borohydride in tetrahydrofuran (THF) under reflux for 4–6 h. The adducts obtained **4a–f** and **5g–i**, were prepared according to Katritzky's method with the only modification that 5 molar equivalents of benzotriazole as well as the appropriate aldehyde were used to optimize the yield of the adducts instead

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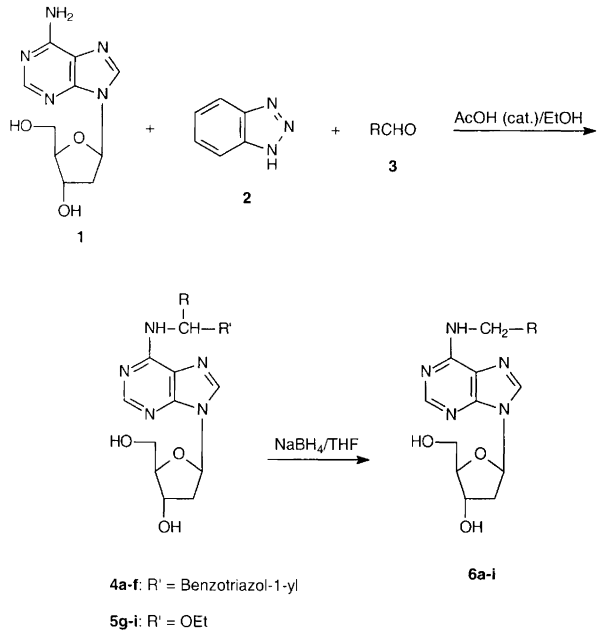
of 1 molar equivalent. Thus, the reaction of 2′-deoxyadenosine, benzotriazole and the appropriate aldehyde was carried out in refluxing ethanol using catalytic amounts of acetic acid. In the case of 2- and 4-pyridinecarboxaldehydes a catalytic amount of acetic acid afforded non-separable viscous raw materials. The catalyst was therefore omitted and the ethanol adducts **5h,i** were obtained. After the appropriate reaction times, the solvent was evaporated off and the residue was dissolved in chloroform and chromatographed with chloroform–methanol on silica gel to yield the desired adducts **4a–f** and **5g–i**. The $^1H$ as well as the $^{13}C$ NMR assignment of the adduct structures proved that all the adducts **4b–f** and **5g–i** are diastereomeric mixtures due to the presence of an asymmetric carbon atom at $N^6$. Thus, all the signals in the $^{13}C$ NMR spectra are duplicated. Many attempts were made to separate each isomer by column chromatography, but without success. Therefore, the reduction to **6b–i** was carried out directly on the diastereomeric mixtures using sodium borohydride in dry THF to give the target $N^6$-alkylated 2′-deoxyadenosine in good yields (67–88%), except for the pyridine derivatives (25–40%).




*Scheme 1.*

The adduct **4a** shows, in the $^1H$ and $^{13}C$ NMR spectra, the chemical shifts of the $N^6$-methylene group at 6.35 and 53.55 ppm, respectively, which are in accordance with the reported values for the adenine–benzotriazole adduct.[11] FAB MS also confirmed the assigned structures. The $^1H$ and $^{13}C$ NMR spectra of the isomeric adducts **5g–i** showed the absence of the benzotriazole moiety and the presence of an ethoxy group at around 1.2 ($CH_3$), 4.1 ($CH_2$) and 15.03 ($CH_3$), 62.9 ($CH_2$) ppm, respectively. To confirm the role of the benzotriazole as a synthetic auxiliary, a reaction was carried out between 2′-deoxyadenosine (**1**) and butyraldehyde, under the same conditions as for the formation of the ethanol adducts **5g–i**, but without the addition of benzotriazole. Instead of the possible formation of **4c** or a possible ethanol adduct, an unidentified product was isolated in high yield by filtration. FAB mass spectral analysis of compounds **6a–i** gave in all cases satisfactory results. The NMR data obtained for $N^6$-methyl-, $N^6$-ethyl-, and $N^6$-benzyl-2′-deoxyadenosine were found to be in accordance with the reported $^1H$ and $^{13}C$ NMR chemical shift values for **6a**[21,22] and **6b** and the reported $^1H$ NMR chemical shift values for **6f**.[23]

One of the important features that characterized all the $^1H$ and $^{13}C$ NMR spectral data was the chemical shift of the methylamino group; the intensity of this signal in all the spectra, either $^1H$ or $^{13}C$ NMR, were very low and sometimes hardly recognizable owing to line broadening. This may be due to the quadrapolar relaxation of the nitrogen atom or tautomerism.

*Table 1.* Yields of **4** and **6**.

| R | Adducts | Yield (%) | Adenosines | Yield (%) |
|---|---|---|---|---|
| H | **4a** | 65 | **6a** | 75 |
| $CH_3$ | **4b** | 70 | **6b** | 67 |
| $CH_2CH_2CH_3$ | **4c** | 75 | **6c** | 88 |
| $CH(CH_3)_2$ | **4d** | 70 | **6d** | 80 |
| $CH_2CH_2Ph$ | **4e** | 82 | **6e** | 80 |
| Ph | **4f** | 70 | **6f** | 71 |
| $CH_2(CH_3)Ph$ | **5g** | 75 | **6g** | 70 |
| 4-Pyridyl | **5h**[a] | 40 | **6h** | 40 |
| 2-Pyridyl | **5i**[a] | 13 | **6i** | 25 |

[a]The typical procedure was followed, but without addition of acetic acid.

## Experimental

NMR spectra were recorded at 300 MHz for $^1H$ and 75.5 MHz for $^{13}C$ NMR on a Varian Gemini 2000 300 MHz spectrometer; δ values are in ppm relative to tetramethylsilane as an internal standard. Positive FAB mass spectra were recorded on a Kratos 50TC spectrometer. Analytical silica gel TLC was performed on Merck precoated 60 $F_{254}$ plates. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck.

*$N^6$-(1-Benzotriazolylmethyl)-2′-deoxyadenosine* (**4a**). 2′-Deoxyadenosine (2.51 g, 10 mmol) was refluxed overnight in EtOH (40 ml) with benzotriazole (2.38 g, 20 mmol) and 2.6 ml (35 mmol) of 37% aq. formaldehyde in the presence of 5 drops of acetic acid as catalyst. The mixture was evaporated to dryness and the residue was chromatographed on a silica gel column using MeOH–$CHCl_3$ (2:98, v/v) as the eluent to obtain **4a** as a foam. Yield 2.86 g (75%). $^1H$ NMR (DMSO-$d_6$): δ 8.37 (s, H8), 8.28 (s, H2), 8.10 (d, Bt), 8.00 (d, Bt), 7.52 (t, Bt), 7.34 (t, Bt), 6.51 ($NCH_2N$), 6.35 (t, H1′), 5.29 (m, OH), 5.07 (m, OH), 4.40 (m, H3′), 3.84 (m, H4′), 3.58

(m, H5′), 2.24 (m, H2′). $^{13}$C NMR (DMSO-$d_6$): δ 153.56 (C6), 152.18 (C2), 149.99 (C4), 145.40 (Bt), 140.71 (C8), 132.42 (Bt), 127.29 (Bt), 124.05 (Bt), 119.97 (C5), 119.03 (Bt), 111.54 (Bt), 88.01 (C4′), 83.89 (C1′), 70.79 (C3′), 61.71 (C5′), 53.56 (NH–CH–N), 39.36 (C2′). FAB MS (DMSO + 3-nitrobenzyl alcohol): $m/z = 383$ ($M + H^+$).

N$^6$-*[1-(1-Benzotriazolyl)ethyl]-2′-deoxyadenosine* (**4b**): *typical procedure for the synthesis of adducts* **4** *and* **5**. A mixture of 1.25 g (5 mmol) of 2′-deoxyadenosine, 1.19 g (10 mmol) of benzotriazole and 2.83 ml (50 mmol) of acetaldehyde was refluxed overnight in EtOH (25 ml) in the presence of 5 drops of acetic acid as catalyst. The EtOH was evaporated off and the residue was chromatographed on a silica gel column using MeOH–$CHCl_3$ (2:98, v/v) as the eluent, to obtain **4b**.

*Adenosines* **6b–i**: *general procedure for the reduction of adducts* **4a–f** *and* **5g–i**. The adduct was dissolved in dry THF (20 ml) and refluxed with a 6 molar excess of $NaBH_4$ for 5 h. The solution was cooled to room temperature, poured onto ice–water, neutralized with acetic acid and extracted with $CHCl_3$. The resulting mixture was chromatographed on a silica gel column to give **6a–i**.

N$^6$-*Butyl-2′-deoxyadenosine* (**6c**). $^1$H NMR ($CDCl_3$): δ 8.32 (s, H8), 7.79 (s, H2), 6.33 (m, H1′), 4.82 (m, OH), 4.23 (OH), 4.02 (m, H3′), 3.98 (m, H4′), 3.79 (m, H5′), 3.07 (m, H2′), 2.33 (m, H2′), 1.67 (m, $CH_2$), 1.45 (m, $CH_2$), 0.96 (t, $CH_3$). $^{13}$C NMR ($CDCl_3$): δ 155.43 (C6), 152.70 (C2), 149.01 (C4), 139.36 (C8), 124.76 (C5), 89.81 (C4′), 87.85 (C1′), 73.43 (C3′), 63.46 (C5′), 40.79 (C2′), 40.33 ($NCH_2$), 31.52 ($CH_2$), 19.88 ($CH_2$), 13.65 ($CH_3$). FAB MS ($CHCl_3$ + glycerol): $m/z = 308$ ($M + H^+$).

*2′-Deoxy-*N$^6$*-isobutyladenosine* (**6d**). $^1$H NMR ($CDCl_3$): δ 8.25 (s, H8), 7.80 (s, H2), 6.29 (m, H1′ + NH), 4.75 (d, OH), 4.56 (br s, OH), 4.19 (m, H3′), 3.88 (m, H4′), 3.72 (m, H5′), 3.41 (br s, HN–$CH_2$), 3.01 (m, H2′), 2.29 (m, H2′), 1.91 (m, CH), 0.95 (d, $2 \times CH_3$). $^{13}$C NMR ($CDCl_3$): δ 155.47 (C6), 152.61 (C2), 147.10 (C4), 139.20 (C8), 121.04 (C5), 89.57 (C4′), 87.54 (C1′), 72.84 (C3′), 63.25 (C5′), 47.87 (NH–$CH_2$), 40.75 (C2′), 28.36 (CH), 19.93 ($CH_2$). FAB MS ($CHCl_3$ + 3-nitrobenzyl alcohol): $m/z = 308$ ($M + H^+$).

*2′-Deoxy-*N$^6$*-(3-phenylpropyl)adenosine* (**6e**). $^1$H NMR ($CDCl_3$): δ 8.50 (s, H8), 7.75 (s, H2), 7.22 (m, Ph), 6.41 (m, H1′ + NH), 4.80 (m, OH), 4.21 (br s, H3′ + OH), 3.95 (m, H4′), 3.87 (m, H5′), 3.65 (NH–$CH_2$), 3.04 (H2′), 2.70 (m, $CH_2$Ph), 2.29 (m, H2′), 2.02 ($CH_2$). $^{13}$C NMR ($CDCl_3$): δ 155.29 (C6), 152.60 (C2), 141.34 (C4), 139.33 (C8), 128.47 (Ph), 128.37 (Ph), 126.03 (Ph), 121.12 (C5), 89.60 (C4′), 87.58 (C1′), 72.98 (C3′), 63.28 (C5′), 40.71 (C2′), 32.90 (NH–$CH_2$), 30.99 ($CH_2$Ph), 29.52 ($CH_2$). FAB MS ($CHCl_3$ + 3-nitrobenzyl alcohol): $m/z = 370$ ($M + H^+$).

*2′-Deoxy-*N$^6$*-(2-phenylpropyl)adenosine* (**6g**). $^1$H NMR ($CD_3OD$): δ 8.22 (s, H8), 8.20 (s, H2), 7.19 (m, Ph), 6.39 (m, H1′), 4.56 (m, H3′), 3.80 (m, H4′), 3.82 (m, H5′), 3.75 (m, NH–$CH_2$), 3.14 (m, H2′), 2.77 (m, CHPh), 2.38 (m, H2′), 1.32 (d, $CH_3$). $^{13}$C NMR ($CD_3OD$): δ 155.25 (C6), 152.55 (C2), 143.99 (C4), 139.36 (C8), 128.72 (Ph), 127.25 (Ph), 126.75 (Ph), 121.06 (C5), 89.57 (C4′), 87.55 (C1′), 73.00 (C3′), 63.28 (C5′), 47.14 (NH–$CH_2$), 40.69 (C2′), 39.60 (CHPh), 19.21 ($CH_3$). FAB MS ($CHCl_3$ + 3-nitrobenzyl alcohol): $m/z = 370$ ($M + H^+$).

*2′-Deoxy-*N$^6$*-(4-pyridylmethyl)adenosine* (**6h**). $^1$H NMR (DMSO-$d_6$): δ 8.44 (d, Pyr), 8.38 (s, H8), 8.18 (s, H2), 7.27 (d, Pyr), 6.35 (m, H1′), 5.35 (m, NH–$CH_2$), 4.70 (m, OH), 3.87 (m, H3′), 3.51 (m, H4′), 3.34 (m, H5′), 2.72 (m, H2′), 2.25 (m, H2′). $^{13}$C NMR (DMSO-$d_6$): δ 154.50 (C6), 152.43 (C2), 149.58 (Pyr), 148.50 (C4), 146.31 (Pyr), 139.92 (C8), 123.05 (C5), 122.12 (Pyr), 88.05 (C4′), 83.96 (C1′), 70.93 (C3′), 61.83 (C5′), 42.95 (NH–$CH_2$), 39.36 (C2′). FAB MS (DMSO + 3-nitrobenzyl alcohol): $m/z = 343$ ($M + H^+$).

*2′-Deoxy-*N$^6$*-(2-pyridylmethyl)adenosine* (**6i**). $^1$H NMR (DMSO-$d_6$): δ 8.50 (m, Pyr), 8.37 (s, H8), 8.20 (s, H2), 7.69 (m, Pyr), 7.25 (m, Pyr), 6.35 (m, H1′), 5.30 (m, NH–$CH_2$), 4.81 (br s, OH), 4.42 (m, H3′ + OH), 3.88 (m, H4′), 3.60 (m, H5′), 2.75 (m, H2′), 2.25 (m, H2′). $^{13}$C NMR (DMSO-$d_6$): δ 158.84 (C6), 154.31 (C4), 152.18 (C2), 148.68 (Pyr), 148.12 (Pyr), 139.57 (C8), 136.50 (Pyr), 121.81 (C5), 120.52 (Pyr), 119.05 (C5), 87.91 (C4′), 83.82 (C1′), 70.81 (C3′), 61.75 (C5′), 45.05 (NH–$CH_2$), 39.95 (C2′). FAB MS ($CHCl_3$ + 3-nitrobenzyl alcohol): $m/z = 343$ ($M + H^+$).

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Received October 2, 1998.