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2-Amino-6-(1,2,4-triazol-4-yl)-purine: a useful intermediate in the synthesis of 9-alkylguanines

Karine Alarcon, Alain Martelli, Martine Demeunynck* and Jean Lhomme

Chimie Bioorganique, LEDSS, UMR CNRS 5616, Université Joseph Fourier, BP 53, 38041 Grenoble cedex 9, France

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Abstract

2-Amino-6-(1,2,4-triazol-4-yl)purine, prepared from 2,6-diaminopurine, was regioselectively alkylated at position 9. Subsequent alkaline hydrolysis afforded 9-alkylguanines in high yield.

Keywords: guanine; 2,6-diaminopurine; 1,2,4-triazole.

The continuous interest in antiviral drugs such as acyclovir and ganciclovir explains the constant search for new regioselective synthetic methods of 9-alkylguanines.[1,2] The major problem encountered is the control of N9 versus N7 alkylation of guanine. To overcome this problem, various methods were reported, involving either alkylation of 6-substituted 2-aminopurines, or ring closure of pyrimidine or imidazole derivatives. In the direct alkylation of purines, the presence of bulky substituents was shown to dramatically increase N9 regioselectivity and hence 6-chloro and 6-alkoxy derivatives have been successfully used. 2,6-Diaminopurine has also been used as starting material to prepare carbocyclic guanosine analogues. In 1984, Ogilvie[3] reported the synthesis of ganciclovir by alkylation of N^2,N^6-diacetyl-2,6-diaminopurine in 55% yield. The following steps involved the hydrolysis of the acetyl groups and the enzymatic conversion to ganciclovir using adenosine deaminase. In 1991, Jones[4] applied direct alkylation of 2,6-diaminopurine to prepare carbovir a carbocyclic nucleoside analogue. Introduction of the alkyl group was achieved regioselectively in 50% yield using sodium hydride in DMF. After selective protection of the 2-amino group by acetylation, the 6-amino group was converted into 6-hydroxyl via diazotation reaction. Herein, we present a new route to 9-alkylated guanines from 2,6-diaminopurines, by conversion of the 6-amino group to a bulky easily hydrolysable group, 1,2,4-triazole. Conversion of an amino group to 1,2,4-triazole has been previously reported to convert adenine[5] or adenosine analogues[6] to the corresponding 6-dimethylamino-, 6-methylthio- or 6-methoxy purines or nucleosides. A similar strategy was also used to functionalyze cytidine.[7] The (1,2,4-triazol-4-yl)

* Corresponding author. Tel: +33 476 51 44 29; fax: +33 476 51 43 82; e-mail: martine.demeunynck@ujf-grenoble.fr

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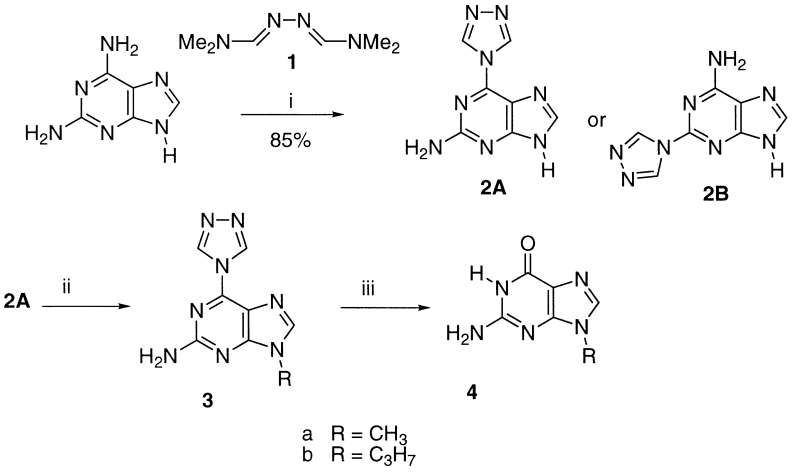
intermediates were obtained by treatment of the corresponding amino-heterocycles with 1,2-bis[(dimethylamino)methylene]hydrazine following the Bartlett and Humphrey's method.[8]

Reaction of 2,6-diaminopurine with 1,2-bis[(dimethylamino)methylene]hydrazine **1**[8] gave a single product in 85% yield. No other reaction product was detected. The NMR and mass spectra suggested the incorporation of one triazole moiety but the data were not sufficient to determine the regioselectivity of the reaction as both amino groups are susceptible to react. Furthermore, the literature data concerning the relative reactivity of the two amino groups of 2,6-diaminopurine are rather unclear. Acetylation in acetic acid[4] or using trichlorophenyl phenoxyacetate[9] were reported to occur at position 2, but Watkins and Rapoport described the regioselective mono-protection of the amine at position 6 by a CBZ group.[10] Nitrosation occurs preferentially at position 2.[11] To achieve the structural determination and distinguish between structures **2A** and **2B** (Scheme 1), we performed the alkaline hydrolysis of the amino-triazolo purine **2A**/**2B** and the reaction was followed by HPLC using a diode array detector. Depending on the position of the triazole at either position 6 or 2, guanine or isoguanine were expected to be formed respectively. As shown in Fig. 1, the retention time and the UV spectrum of guanine and isoguanine are very characteristic. Fig. 2 shows the HPLC profile obtained after hydrolysis of the amino-triazolo intermediate **2A**/**2B**. One peak is observed, and both the retention time and the UV spectrum correspond to guanine. Alkylation of **2A** was performed by reacting the sodium salt of **2A** with either methyliodide or 3-bromopropane in DMF. In both cases, a single alkylation product was formed in good to excellent yields (78 and 93%). The resulting compounds **3a** and **3b** were characterised by NMR and mass spectrometry. Alkaline hydrolysis of **3a** and **3b** was performed in 1N NaOH to give the corresponding 9-methyl or 9-propylguanines in good yields (67 and 85%). Their spectroscopic properties were identical to those reported in the literature data.[12–14]



Scheme 1. (i) **1**, DMF, 180°C, 18 h; (ii) ICH_3 or BrC_3H_7, NaH, DMF, rt, 1 h; (iii) 1N NaOH, 100°C, or DMSO–1N NaOH, 50°C

As a conclusion, the commercially available 2,6-diaminopurine was converted into 2-amino-6-(1,2,4-triazol-4-yl)purine, which may be considered as a cheaper alternative to 2-amino-6-chloropurine. The alkylation of this key-intermediate occurs regioselectively at position 9, this is probably due to steric hindrance introduced by the triazole that precludes alkylation at position 7.

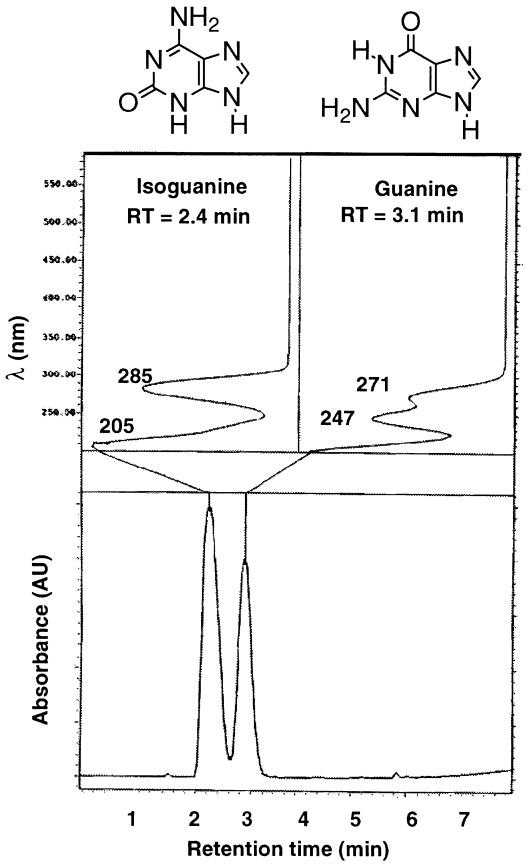


Figure 1. HPLC profile of a reference mixture of guanine and isoguanine (μ-bondapak-C_{18} reversed-phase column, methanol–water (pH 2.5, H_3PO_4) gradient)

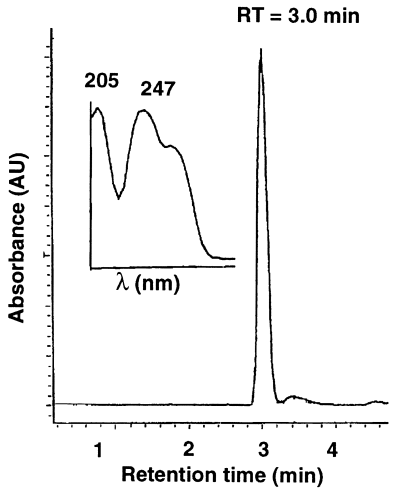


Figure 2. HPLC profile obtained after hydrolysis of **2A**

The corresponding substituted guanines are easily obtained by hydrolysis. Nucleophilic substitution of the triazole to prepare 9, N^6-dialkyl-2,6-diaminopurine is currently under investigation.

Synthetic procedures. 2-Amino-6-(1,2,4-triazol-4-yl)-9-*H*-purine **2**: A suspension of 2,6-diaminopurine (0.2 g, 1.3 mmol) and **1**[8] (0.38 g, 1.7 mmol) in DMF (50 mL) was refluxed for 8 h. The mixture was then cooled and the solvent removed under reduced pressure. The residue was co-evaporated with methanol three times. The solid was suspended in methanol, filtered and dried to give **2** (0.223 g, 85%), mp: >360°C. ^{1}H NMR (200 MHz, DMSO-d_6): δ ppm = 13 (br s, NH), 9.42 (2H, s, H triazole), 8.22 (1H, s, H-8), 6.77 (2H, s, NH_2). ^{13}C NMR (200 MHz, DMSO-d_6): δ ppm = 160.0 (C-2), 157.1 (C-4), 142.6 (C-6), 142.0 (C-8), 140.6 (2C, C triazole), 114.9 (C-5); ms (CI, ammoniac+isobutane): $M = 202$, m/z: 203 ($(M+1)^+$).

2-Amino-9-alkyl-6-(1,2,4-triazol-4-yl)-9*H*-purin **3**: Sodium hydride (60%, 0.025 g, 0.60 mmol) was added to compound **2** (0.1 g, 0.50 mmol) dissolved in DMF (2.5 mL) under inert atmosphere. After 1 h stirring at room temperature, methyl iodide or 3-bromopropane (0.75 mmol) was added to the solution and the resulting mixture was stirred for 3 h. After dilution with water, the desired product was extracted with CH_2Cl_2. The organic layers were dried over sodium sulphate and concentrated. Precipitation was achieved by slow addition of diethylether.

Compound **3a**: (93% yield) mp: >350°C. ^{1}H NMR (200 MHz, TFA-D): δ ppm = 10.13 (2H, s, H triazole), 8.94 (1H, s, H-8), 4.09 (3H, s, CH_3). ^{13}C NMR (50 MHz, TFA-D): δ ppm = 156.6, 150.6, 141.8, 139.2, 138.8, 138.3, 106.8, 28.6 (N-CH_3).

Compound **3b**: (78% yield) mp: 248–250°C. ^{1}H NMR (200 MHz, CD_3OD): δ ppm = 9.62 (2H, s, H triazole), 8.11 (1H, s, H-8), 4.15 (2H, t, N-CH_2), 1.92 (2H, m, CH_2-CH_3), 0.96 (3H, t, CH_3). ^{1}H NMR (200 MHz, DMSO-d_6): δ ppm = 9.41 (2H, s, H triazole), 8.27 (1H, s, H-8), 6.90 (2H, s, NH_2), 4.05 (2H, t, N-CH_2), 1.81 (2H, q, CH_2-CH_3), 0.86 (3H, t, CH_3). ^{13}C NMR (50 MHz, DMSO-d_6): δ ppm = 160.0, 156.2, 144.0, 142.9, 140.7 (2C, triazole), 115.2, 44.5 (N-CH_2), 22.4 (CH_2-CH_3), 10.9 (CH_2-CH_3); ms (FAB(+),NBA): M = 244, m/z: 245 (100, $(M+1)^+$), 176 (M^+-triazole).

9-Propylguanine **4b**: A suspension of 9-propyl-6-triazolyl derivative **3b** (0.3 mmol) in 1N NaOH (1 mL) was stirred at 100°C for 10 min (or in DMSO–1N NaOH, 1:1 mixture at 50°C for 30 min). When all starting material had dissolved, the solution was cooled at room temperature and acetic acid was slowly added until precipitation of **4b**, which was thus isolated in 85% yield.

9-Methylguanine **4a**: The procedure described above was used for conversion of **3a**. Due to poor solubility of **3a**, hydrolysis required 45 min in boiling 1N NaOH. Compound **4a** was obtained in 67% yield. The structures of **4a** and **4b** were confirmed by comparison of their MS and NMR data with literature data.[12–14]

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References

1. Gao, H.; Mitra, A. K. *Synthesis* **2000**, 329–351.
2. Clausen, F. P.; Juhl-Christensen, J. *Org. Prep. Proced. Int.* **1993**, *25*, 373–401.
3. Ogilvie, K. K.; Nguyen-Ba, N.; Gillen, M. F.; Radatus, B. K.; Cheriyan, U. O.; Hanna, H. R.; Smith, K. O.; Galloway, K. S. *Can. J. Chem.* **1984**, *62*, 241–252.

4. Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2479–2484.
5. Samano, V.; Miles, R. W.; Robins, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 9331–9332.
6. Miles, R. W.; Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 5951–5957.
7. Miles, R. W.; Samano, V.; Robins, M. J. *J. Org. Chem.* **1995**, *60*, 7066–7069.
8. Bartlett, R. K.; Humphrey, I. R. *J. Chem. Soc. (C)* **1967**, 1664–1666.
9. Luyten, I.; Aerschot, A. V.; Rozenski, J.; Busson, R.; Herdewijn, P. *Nucleosides Nucleotides* **1997**, *16*, 1649–1652.
10. Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471–4477.
11. Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2608–2611.
12. Michael, M. A.; Cottam, H. B.; Smee, D. F.; Robins, R. K.; Kini, G. D. *J. Med. Chem.* **1993**, *36*, 3431–3436.
13. Alhede, B.; Clausen, F. P.; Juhl-Christensen, J.; McCluskey, K. K.; Preikschat, H. F. *J. Org. Chem.* **1991**, *56*, 2139–2143.
14. Browne, D. T.; Eisinger, J.; Leonard, N. J. *J. Am. Chem. Soc.* **1968**, *90*, 7302–7323.