Pergamon

Tetrahedron Letters 40 (1999) 597–598

TETRAHEDRON LETTERS

# Synthesis of $N^2$- (2-Aminofluoren-3-yl) Adducts of 2′-Deoxyguanosine

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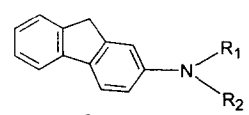
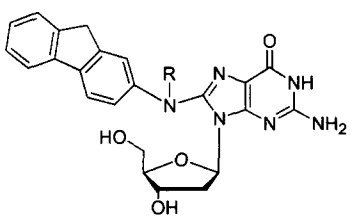
Received 22 September 1998; revised 17 November 1998; accepted 20 November 1998

**Abstract:** A direct route is described for the synthesis of $N^2$- (2-aminofluoren-3-yl)-2′-deoxyguanosine **3a** and $N^2$- (2-acetylaminofluoren-3-yl)-2'-deoxyguanosine **3b**.

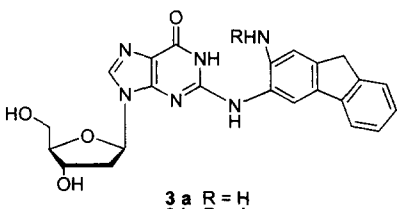

2-Aminofluorene (**1a**) one of the most extensively studied carcinogenic amines, and its *N*-acetyl derivatives (**1b**) are converted in vivo, mainly by hepatic enzymes, to a series of *N*-hydroxy metabolites (**1c-1f**). It is generally accepted that the latter compounds are the penultimate carcinogens and that they act via a solvolytic mechanism at near physiological pH, generating nitrenium ions. The latter are powerful electrophiles that react with DNA producing several adducts, the main compounds being the C-8 substitution products **2a** and its *N*-acetylated derivative **2b**.[1,2] The biology of these compounds has been well studied. A minor, but little investigated, adduct is $N^2$- (2-acetylaminofluoren-3-yl)-2′-deoxyguanosine (**3b**).[2,3]



**1 a** $R_1 = R_2 = H$
**b** $R_1 = H$; $R_2 = Ac$
**c** $R_1 = OH$; $R_2 = Ac$
**d** $R_1 = OAc$; $R_2 = Ac$
**e** $R_1 = OH$; $R_2 = OSO_3H$
**f** $R_1 = Ac$; $R_2 = OSO_3H$



**2 a** R = H
**2 b** R = Ac



**3 a** R = H
**3 b** R = Ac

In connection with our mutagenesis program we needed a practical synthesis of this latter type of carcinogenic amine adduct. Specifically, we were interested in a selective synthesis of the 2-aminofluorene derivatives **3a** and **3b** for eventual incorporation into oligomeric DNA. This letter now describes the first total synthesis of these adducts.

The method of preparation, outlined in **Scheme-I,** began with the treatment of 3′, 5′-bis-*O*-TBDMS-2′-deoxyguanosine (**4**) with two molar equivalents of 3-bromo-2-nitro-9-fluorenone[4] (**5**) in dry dioxane containing $K_2CO_3$ at reflux temperature. This led directly, after 10 days, to the desired coupled product **6** in 47% yield (it is interesting to note that 3-bromo-2-nitro fluorene was unreactive under these conditions). Reduction of the carbonyl group in **6** took place smoothly on treatment with $NaBH_4$ in 2-propanol to furnish $N^2$-(2-nitro-9-hydroxyfluoren-3-yl)-3′,5′-bis-*O*-TBDMS-2′-deoxyguanosine (**7**) in 83% yield. Hydrogenation of **7** over a $Pd(OH)_2/C$ catalyst effected double reduction and afforded $N^2$- (2-amino-9H-fluoren-3-yl)-3′,5′-bis-*O*-TBDMS-2′-deoxyguanosine (**8**) in

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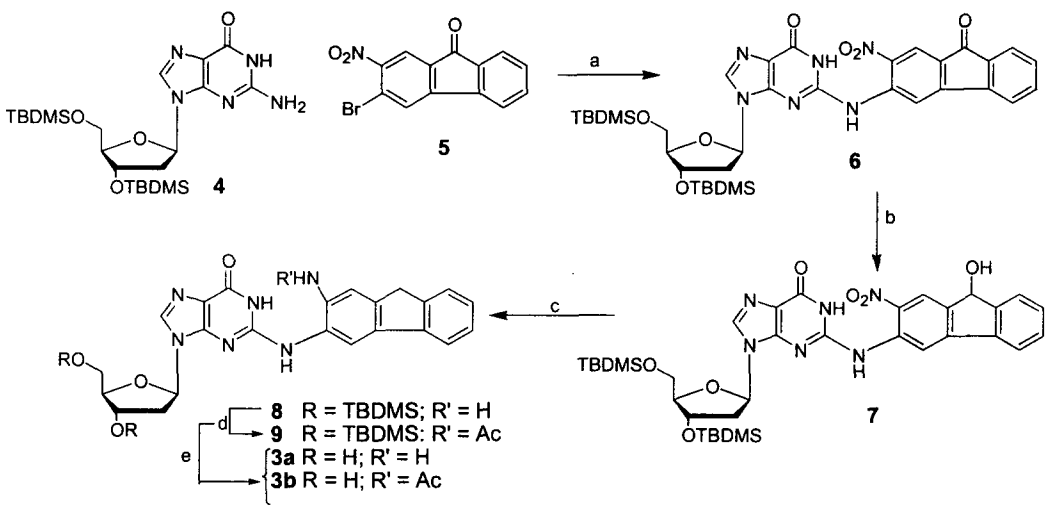
*PII:* S0040-4039(98)02502-7

78% yield. Although the reduction of nitro group was complete within 3 hrs, hydrogenolysis of the hydroxyl group required 48 hrs. Acetylation of the aromatic amino group in **8** using acetic anhydride in pyridine resulted in **9** in 90% yield. Finally removal of the TBDMS protecting groups from the sugar residues of compounds **8** and **9** by 1M solution of tetrabutyl ammonium fluoride in THF then provided the target compounds **3a** and **3b** both in 80% yield. The $^1$H NMR spectrum of **3b** proved to be identical to the reported spectrum of the material isolated from DNA that had been treated with **1b**.[3]

**Scheme-I**




**Scheme-I**: a) $K_2CO_3$/Dioxane, 115°C, 10days; b) $NaBH_4$ (4.0eq), 2-propanol, 24°C, 1h; c) $H_2$ (60.0 psi), $Pd(OH)_2/C$ (20%), Ethylacetate-Glacial Acetic Acid (1:4), 24°C, 60h; d) Acetic anhydride (1.2eq), Pyridine, 24°C, 24h; e) 1M solution of TBAF in THF (3eq), 24°C, 1h;

However, attempts to extend this approach to the synthesis of other *o*-nitro-aryl derivatives of dG using any of the known simpler *o*-halonitrobenzenes met with almost uniform failure. Only in the case of 2,4-dinitrofluorobenzene was any product obtained (70% yield). Thus it is obvious that double activation of the arylhalogen by strongly electrophilic groups is needed before the molecule is sufficiently reactive to arylate the $N^2$-group of deoxyguanosine. Despite the limited applicability of the synthetic pathway, the preparation of **3b** in particular is of interest because no practical syntheses of this type of adduct has been reported since[5] its initial discovery in the DNA of animals treated with **1a**, more than 25 years ago.[2]

**Acknowledgment:** We thank NIEHS (Grant ES0406812) in support of this work.

**References and Notes:**

1. Kriek, J.A.; Miller, W.J.; Miller, E.C.; *Biochemistry*, **1967**,*6*, 177.
2. Kriek, E.; *Cancer Research*, **1972**, *32*, 2042.
3. Westra, J.G.; Kriek, E.; Hittenhausen, H.; *Chem.Biol.Interact.*, **1976**,*15*,149.
4. Compound **5** (68% yield) was obtained by boiling 2-amino-3-bromo-9-fluorenone with m-chloro perbenzoic acid (mCPBA, 50-60%, about 4eq.) in 1,2-dichloroethane for 8hrs.
5. The synthesis of $N^2$-(2-aminophenyl) and $N^3$-(4-aminobiphenyl) derivatives of deoxyguanosine have been recorded[6] but the method requires the use of the difficulty accessible $O^2$-triflyl-$O^6$-allyl derivative of 2'-deoxyxanthosine and has not been applied to the synthesis of **3b**.
6. Edwards, C.; Boche, G.; Steinbrecher, T.; Scheer, S.; *J.Chem.Soc., Perkin Trans. 1*, **1997**, 1887.