Chemoselective Arylation of 2′-Deoxyguanosine at N-2 with Organoiron Complexes

Gerard A. Potter, Raymond McCague*† and Michael Jarman

Drug Development Section, Cancer Research Campaign Laboratory, Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK

2′-Deoxyguanosine has been directly and chemoselectively arylated at the N^2-amino function by treatment with tricarbonyl(η^5-cyclohexadienylium)iron or tricarbonyl[η^5-2-(n-butyl)cyclohexadienylium]iron cations, followed by decomplexation and dehydrogenation, providing a rapid route to N^2-aryl-2′-deoxyguanosine nucleosides.

N^2-Aryl-2′-deoxyguanosine nucleosides have been found to be inhibitors of mammalian DNA polymerases[1] and viral thymidine kinases.[2] It is the potential of their 5′-diphosphates to inhibit DNA synthesis *via* interaction at the negative allosteric effector site of ribonucleotide reductase[3] that attracted us to these compounds.[4]

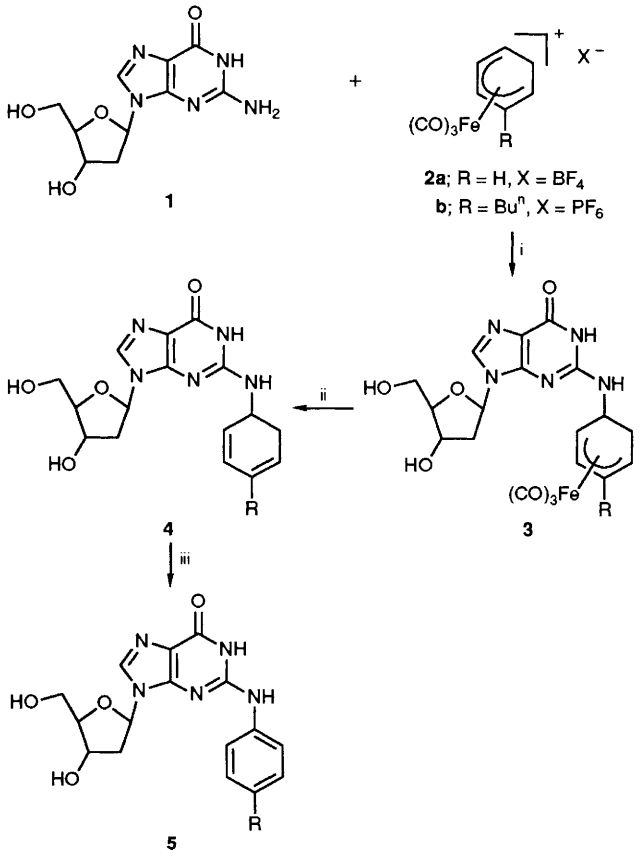
The reported classical synthetic route[1] is a lengthy multi-step process from primitive purine precursors that requires demanding control of both regioselectivity (N^7 *vs.* N^9) and stereoselectivity (α *vs.* β anomers) in the sugar coupling reaction as well as the need for masked functionality in the purine base and protecting groups on the ribose.

We report here a rapid route to these important compounds employing an organometallic aryl cation equivalent with 2′-deoxyguanosine itself as starting material, that avoids the use of protecting groups despite the multifunctional and highly polar nature of the nucleoside (Scheme 1).

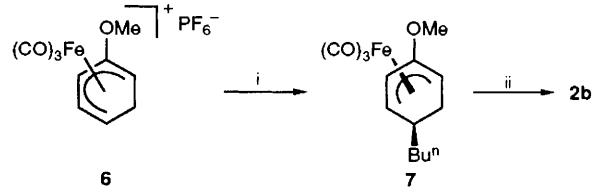
In the crucial transformation, reaction of 2′-deoxyguanosine **1** with the electrophilic phenyl cation equivalent[5,6] tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate **2a** (1.1 equiv.) in acetonitrile containing 2,6-di-*tert*-butyl-4-methylpyridine (1.1 equiv.) gave a respectable 37% yield (69% based on unrecovered **1**) of the complex **3a**‡ as pale-yellow crystals [m.p. 184 °C (decomp.)] in which the N^2-*H* appears in the ^{1}H NMR spectrum at δ 6.46 as a doublet (J = 7.2 Hz) owing to coupling with the adjacent cyclohexadiene 1-*H* proton.

† *Present address*: Chiros Ltd, Science Park, Cambridge CB4 4WE, UK.

‡ New compounds gave satisfactory elemental analysis and spectral data; all of the nucleoside derivatives were obtained as hydrates.



Scheme 1 *Reagents and conditions*: i, 2,6-di-*tert*-butyl-4-methylpyridine, MeCN, 20 °C; ii, Me_3NO, $MeCONMe_2$, 90 °C; iii, $(MeCN)_2PdCl_2$, Et_3N, $MeCONMe_2$, 80 °C



Scheme 2 *Reagents and conditions*: i, $Bu^nCu(Me_2S)$, tetrahydrofuran (THF); ii, H_2SO_4 then NH_4PF_6

The chemoselectivity for the N^2-amino group, despite its very weak nucleophilicity, has been achieved by virtue of the soft, reasonably hindered, yet strong electrophilic character[7] of the organoiron complex **2**, which reacts preferentially with the softest unhindered nucleophile available. In this respect it is noteworthy that attempts to arylate **1** using tricarbonyl(η^4-cyclohexa-2,4-dienone)iron or tricarbonyl(η^5-1-ethoxycyclohexadienylium)iron tetrafluoroborate[8] were unsuccessful, attributed to the insufficient electrophilicity of these complexes. The non-nucleophilic base used was necessary to prevent reversal of the reaction and to protect the acid-labile glycosidic bond from cleavage.

Oxidative decomplexation to the arene proved troublesome owing to sensitivity of both the ribose and purine groups to oxidation. Two steps were necessary. First, treatment with an excess of trimethylamine *N*-oxide (10 equiv.) in dimethylacetamide[6] gave the diene **4a**‡ as a white powder in 60% yield [m.p. 138 °C (decomp.)]. This was dehydrogenated with bis(acetonitrile)palladium(II) chloride[9] (1 equiv.) in dimethylacetamide at 80 °C to give N^2-phenyl-2′-deoxyguanosine **5a** in 28% yield as white crystals, m.p. 230 °C (decomp.), (lit.[2] m.p. 228–231 °C).

The greatest activity against mammalian enzymes assessed to date[1,3] has been observed not for the N^2-phenylnucleoside but for the N^2-[4-(n-butyl)phenyl] derivative. The appropriate cationic organoiron complex **2b** was prepared (Scheme 2) from the commercially available tricarbonyl(2-methoxycyclohexadienylium)iron complex **6** so as to provide the necessary regiochemistry. Treatment of **6** with the low-order butylcopper(dimethyl sulfide) complex[10] gave the butylated iron diene in over 90% yield as predominantly the required C-5 regioisomer (C-5:C-1 = 60:1), and the pure C-5 regioisomer **7**[11] was obtained following chromatography in 86% isolated yield. On treatment of **7** with sulfuric acid diene relocation necessarily preceded methoxy elimination[12] to give, in 94% yield, the requisite 4-(n-butyl)phenyl cation equivalent tricarbonyl[η^5-2-(n-butyl)cyclohexadienylium]iron hexafluorophosphate **2b**‡ exclusively as the 2-butyl regioisomer [m.p. 190 °C (decomp.)]. It is clear that other *para*-substituents could be incorporated using the appropriate low-order organocopper complex.[10]

Reaction of **2b** under the conditions described above gave **3b**‡ as yellow crystals, m.p. 128–130 °C [δ(dimethyl sulfoxide) of N^2-*H* doublet = 6.36, *J* 7.4 Hz]. The lower yield of 24% obtained using **2b** (46% based on unrecovered 2′-deoxyguanosine) is due presumably to the electron releasing inductive effect of the alkyl substituent decreasing the electrophilicity of this complex compared with **2a**. Decomplexation (42% yield) and dehydrogenation (26% yield) afforded the target compound N^2-[4-(n-butyl)phenyl]-2′-deoxyguanosine **5b** as white crystals, m.p. 193–196 °C (lit.[1] m.p. 196–197 °C).

Thus, N^2-arylated nucleosides have been reached directly from the parent 2′-deoxyguanosine by a three-step sequence performed entirely on the unprotected nucleoside. Although yields remain to be improved, the overall yield compares very favourably with the multistep approaches used to date. The intermediate dienes **4** are not only precursors to the aromatic targets, but should also provide versatility for transformation into several unusual nucleoside analogues.

This study was supported by a grant to the Institute of Cancer Research (Royal Cancer Hospital) from the Cancer Research Campaign. The Cancer Research Campaign is also acknowledged for the provision of a studentship (to G. A. P.).

Received, 23rd January 1992; Com. 2/00383J

References

1 G. E. Wright and L. W. Dudycz, *J. Med. Chem.*, 1984, **27**, 175; G. E. Wright, L. W. Dudycz, Z. Kazimierczuk, N. C. Brown and N. N. Khan, *J. Med. Chem.*, 1987, **30**, 109.
2 F. Focher, C. Hildebrand, S. Freese, G. Ciarrocchi, T. Noonan, S. Sangalli, N. Brown, S. Spadari and G. E. Wright, *J. Med. Chem.*, 1988, **31**, 1496.
3 J. G. Cory, A. Sato, and N. C. Brown, *Adv. Enzyme Regul.*, 1986, **25**, 3.
4 G. A. Potter, PhD Thesis, University of London, 1991, p. 186.
5 A. J. Birch, A. J. Liepa and G. R. Stephenson, *Tetrahedron Lett.*, 1979, **37**, 3565.
6 L. F. Kelly, A. S. Narula and A. J. Birch, *Tetrahedron Lett.*, 1980, **21**, 2455; A. J. Birch, L. F. Kelly and A. S. Narula, *Tetrahedron*, 1982, **38**, 1813.
7 T. Ghazy and L. Kane-Maguire, *J. Organomet. Chem.*, 1988, **338**, 47.
8 A. J. Birch and I. D. Jenkins, *Tetrahedron Lett.*, 1975, **2**, 119.
9 B. Bierling, K. Kirschke, H. Oberender and M. Schulz, *J. Prakt. Chem.*, 1972, **314**, 170.
10 G. A. Potter and R. McCague, *J. Chem. Soc., Chem. Commun.*, preceding communication.
11 A. J. Pearson, *Aust. J. Chem.*, 1977, **30**, 345.
12 A. J. Birch and M. A. Haas, *J. Chem. Soc. C*, 1971, 2465; A. J. Birch and L. F. Kelly, *J. Organomet. Chem.*, 1985, **285**, 267.