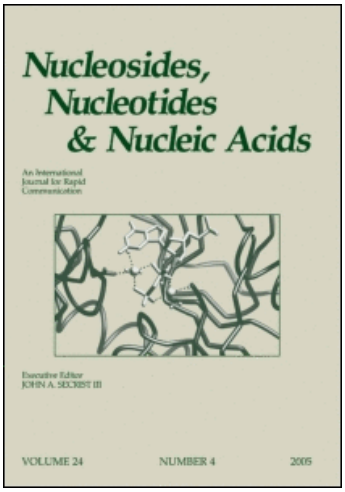

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Synthesis of Oligonucleotide Building Blocks of 2′-Deoxyguanosine Bearing a C8-Arylamine Modification

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ABSTRACT

C8-Arylamine-dG adducts were synthesized by palladium-catalyzed cross-coupling reactions. The corresponding 5′-*O*-DMTr-3′-*O*-phosphoramidite-C8-arylamine-dG adducts were synthesized as potential building blocks for the automated synthesis of site-specifically modified oligonucleotides.

Key Words: Arylamine-adducts; Palladium-catalyzed; Cross-coupling.

INTRODUCTION

Poly- and monocyclic aromatic amines belong to the class of chemical carcinogens that form covalently bonded adducts with DNA after metabolic activation. If these damages are not repaired, they can compromise the fidelity of DNA replication and cause mutations and possibly cancer. The predominant site of reaction is the C8-position of 2′-deoxyguanosine (dG). To properly study the mutagenic effects,

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structure and repair of these adducts, a strategy for the site-specific incorporation of dG-carcinogen adducts into oligonucleotides had to be developed.

RESULTS

In contrast to other research groups who were interested in investigating adducts of highly cancerogenic substances as for example 2-aminofluorene (AF) or 4-aminobiphenyl, our interest is related to DNA-adducts of so-called borderline carcinogens like toluidine or anisidine.

The synthesis of C8-arylamine-dG adducts by electrophilic amination has been reported but only low yields were obtained.[1] Thus this approach was unsuitable for the synthesis of the phosphoramidites. Direct nucleophilic substitution of protected 8-Br-dG with arylamines was also unsuccessful due to depurination.[2]

We decided to use the Buchwald-Hartwig reaction for the C-N bond formation. The key reaction is a Pd-catalyzed cross-coupling reaction of the protected dG-derivative.

N^2-*i*-Butyryl-O^6-benzyl-8-bromo-3′,5′-*O*-(*t*-butyldimethylsilyl)-2′-dG was treated with $Pd_2(dba)_3$ (10 mol%), *rac*-BINAP (30 mol%), 1.5 equivalents of K_3PO_4 and 2 equivalents of arylamine in 1,4-DME at 80°C. The yields obtained for different arylamines and heteroarylamines were between 60% and 81%.[3] By use of double amount or half amount of catalyst and ligand, the yields could be improved slightly (2%–6% improvement), but for lower catalyst quantities, the reaction time had to be doubled. With higher catalyst quantities, the reaction rate increased. Since the yields

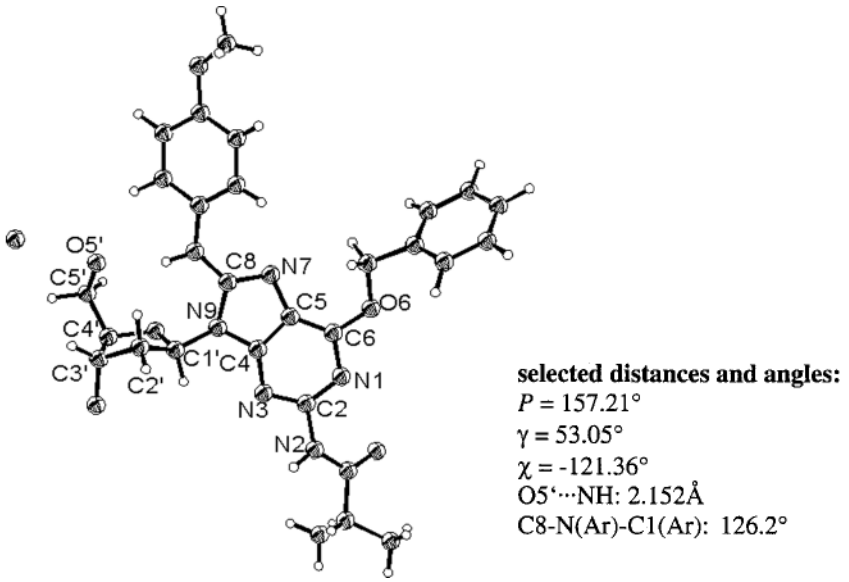

Figure 1. Crystal structure of N^2-*i*-butyryl-O^6-benzyl-8*N*-(4-methoxyphenylamino)-2′-deoxyguanosine.

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could be improved only slightly and due to the high costs of catalyst and ligand, we decided to use the original conditions. Stronger bases as NaOtBu led to decomposition of the starting material. The adducts were deprotected and converted into the 5′-*O*-DMTr-3′-*O*-phosphoramidites as published before.[3] After desilylation, crystals could be obtained from the anisidine-adduct. The crystal structure is shown in Fig. 1.

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