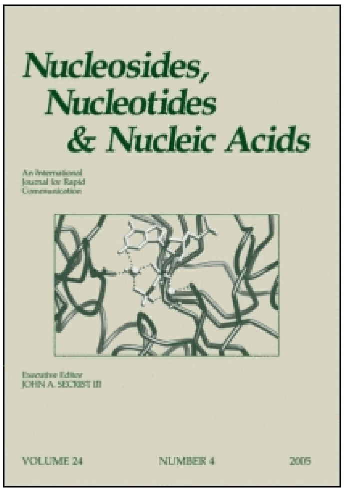

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SYNTHESIS OF C8-MODIFIED 2′-DEOXYADENOSINE WITH CARCINOGENIC ARYLAMINES

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□ *The synthesis of phosphoramidites of C8-modified 2′-deoxyadenosine with carcinogenic arylamines p-anisidine and 4-aminobiphenyl is described. Two different methods were studied related to the glycon and base protection groups.*

Keywords 2′-Deoxyadenosine; carcinogens; aromatic amines; c8-adducts

INTRODUCTION

Some aromatic amines are known carcinogens. Monocyclic aromatic amines such as aniline or *p*-anisidine are classified as borderline carcinogens, whereas polycyclic aromatic amines like 2-aminofluorene belong to the group of strong carcinogens. Poly- and monocyclic aromatic amines form covalently bonded adducts with DNA after metabolic activation and therefore may cause mutations and possible lead to cancer.[1] Predominantly, adduct formation was found with purine nucleosides. In in vivo studies C8- and N^6-arylamine adducts of 2′-deoxyadenosine (dA) **1, 2** were detected although the corresponding adducts of 2′-deoxyguanosine (dG) **3** were found to higher extents (Figure 1).[2a,b]

The synthesis of the adducted dA-nucleoside phosphoramidites is a prerequisite for the preparation of site-specifically C8-dA adduct modified oligonucleotides. These oligonucleotides can then be used to study the mutagenic effects, structure and DNA-repair of these lesions. In contrast to dG-adducts, no synthetic route towards these dA-adducts is known until today.[3] In 2001, Schoffers reported on the synthesis of C8-adducts of adenosine with several arylamines using the Buchwald-Hartwig-reaction, but neither phosphoramidites nor oligonucleotides were prepared.[4]

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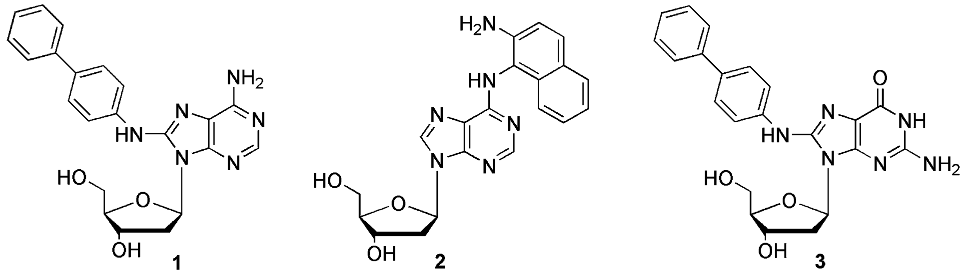


FIGURE 1 In vivo detected adducts of dA and dG.

RESULTS AND DISCUSSION

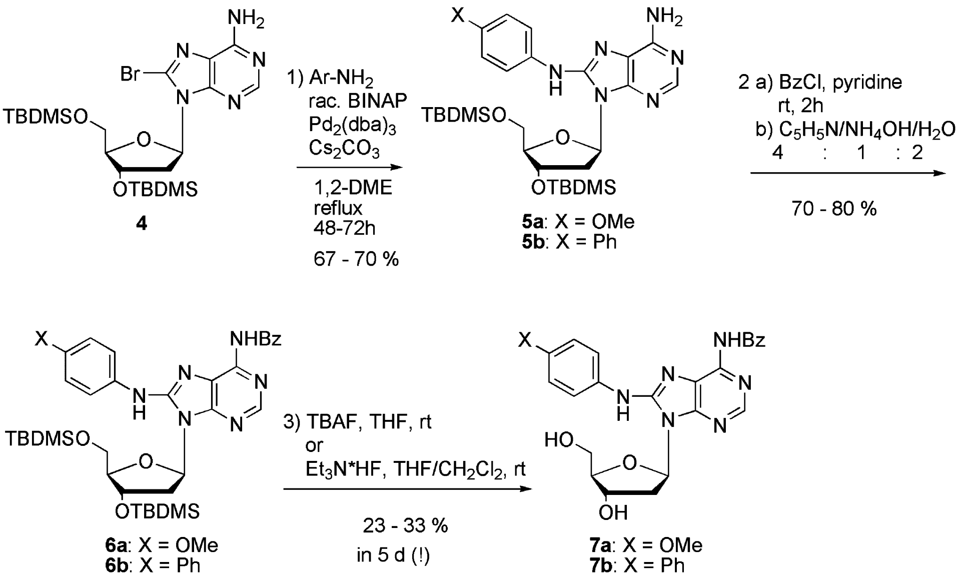
The first approach toward C8-adducted 2′-deoxyadenosine with carcinogenic arylamines was accomplished by using *tert*-butyldimethylsilyl (TBDMS) groups for blocking the 3′- and 5′-hydroxyl moieties in the Pd-catalyzed cross coupling reaction. Starting from the literally known silyl protected C8-brominated dA-derivative **4**[5,6] 8-*N*-(arylamino)-3′,5′-bis(TBDMS)-2′-dA **5a,b** were synthesized by a Pd-catalyzed reaction using 10 mol% tris(dibenzylidenacetone)-palladium(0), 30 mol% *racemic* BINAP, 1.5 equivalents of caesium carbonate and 1.5 equivalents of *p*-anisidine or 4-aminobiphenyl in refluxing 1,2-dimethoxyethane. Protection of the N^6-amino function could be achieved using benzoylchloride in pyridine followed upon treatment with a mixture of pyridine, water and 25% aq. ammonia (4:2:1).

Surprisingly, the limiting step in this reaction sequence was the desilylation of the 3′,5′-hydroxyl groups. A complete deprotection could not be achieved neither with tetrabutylammoniumfluoride nor triethylamine trihydrofluoride as deprotecting agent (Scheme 1).

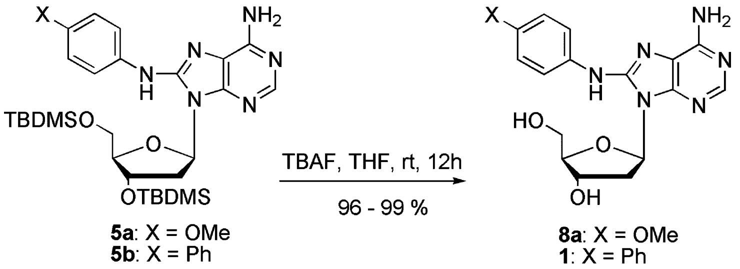
In contrast to the benzoyl protected adducts **6**, the adducts with unblocked N^6-amino group **5** could be deprotected in nearly quantitative yields within 12 h (Scheme 2). Nevertheless, this proves that fully deprotected C8-adducts of 2′-deoxyadenosine with carcinogenic arylamines are accessible by this method. Such compounds, of which **1** is known from in vivo[2a] and in vitro studies but was never synthesized chemically before, are important as analytical standards.

The fully deblocked adducts were then *N*-protected with the dimethylformamidine group which is used in the so called “fast deprotection chemistry” in oligonucleotide synthesis. After dimethoxytritylation, phosphitylation of **10** led to the corresponding phosphoramidite **11** in 70% yield (Scheme 3).

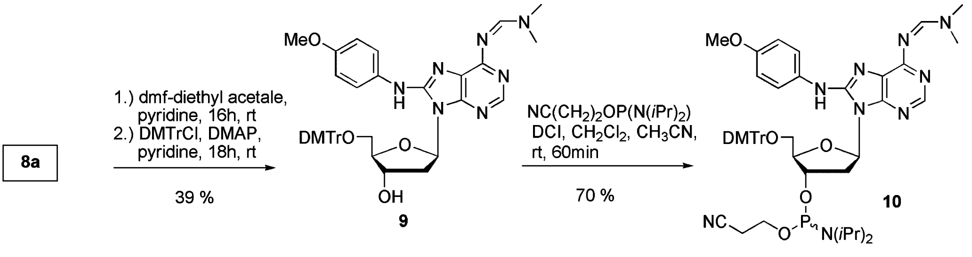
However, phosphoramidite **10** was very unstable and therefore unsuitable for further application in the automated DNA synthesis. In order to avoid the problems with the TBDMS groups, these were replaced by the



SCHEME 1 Synthesis of C8 adducted 2′-deoxyadenosine with carcinogenic arylamines.



SCHEME 2 Fully deprotected adducts.



SCHEME 3 Preparation of the phosphoramidite 10.

tetra*iso*propyldisilyloxane (TIPDS) protecting group in the synthesis. The cross coupling and the following benzoylation proceeded in nearly identical yields as described in Scheme 1. The following desilylation which was the crucial step in the first synthesis route gave the desired products in excellent yields like in the case of the desilylation of the N^6-unprotected compounds **5a,b** (Scheme 2). We recently reported on this new strategy that led to the C8-modified phosphoramidites in good yields.[7] A further difficulty was the dimethoxytritylation of the 5′-hydroxyl group of **7**, which showed only low regioselectivity and long reaction times and therefore led to an increasing amount of the 3′,5′-bis-dimethoxytritylated side product. According to Ogilvie who had similar difficulties in the dimethoxytritylation of N^6-bz-adenosine,[8] silver nitrate and 2,4,6-collidine were added to the reaction to enhance the regioselectivity by accelerating the reaction rate. Now yields up to 72% instead of 42–45% were obtained.

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