Synthesis of C8-alkylamino substituted 2'-deoxyguanosine

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ABSTRACT

Synthesis of C8-alkynyl- and alkylamino substituted 2'-deoxyguanosine is described. Protected alkynylamines are coupled with 8-bromo-2'-deoxyguanosine by a Pd(0)-mediate Sonogashira coupling protocol. Hydrogenation of alkynyl derivatives over 10% Pd/C under atmospheric pressure gave 8-alkylamino guanosine derivatives in nearly quantitative yields.

INTRODUCTION

The incorporation of modified nucleosides into DNA have found widespread applications in nucleic acid labelling, stabilization of nucleic acid structures and many other purposes including DNA sequencing technologies.¹ Thus, there is a growing interest in design, synthesis, and introduction of functionalized nucleotide into a particular DNA sequence to offer modified oligonucleotide probes of improved applicability. An easy and alternative way to modify nucleic acid sequence is to incorporate a single nucleoside bearing a linker that contain a unique and universal functional group for attaching reporter molecules to nucleic acids in a easy and compatible manner.

There are many reports on the modification of the C5 carbon of the uridine and the corresponding modified oligonucleotides were shown to stabilize the duplex and triplexes.² Several methods have been reported for the functionalisation of the C8 position of purine nucleosides.³ Direct bromination at the C8 position and subsequent nucleophilic displacement was one of the earliest approaches.⁴ Synthetically more satisfactory is the lithiation of the C8 position of hydroxy protected purine nucleosides with lithium di-isopropylamide or n-butyl lithium and reaction with suitable electrophiles.⁵ Palladium catalysed coupling of alkynes with 8-bromo purine nucleosides has also been reported.⁶ However, there exists less importance in the literature for C8 functionalisation of 2'-deoxy guanosine bearing a modifiable universal functional group like amino functionality.⁷ In connection with our interest to get post-synthetically modifiable oligonucleotides,⁸ we required C8 functionalized 2'-deoxyguanosine having universal

![Chemical structure](https://example.com/structure.png)

(i) Ethyl trifluoroacetate/MethOH; (ii) MoCl₅/Et₂O; (iii) NaN₃/DMF; (iv) PPh₃·Et₂O·H₂O; (v) N-Bromosuccinimide, H₂O;
(vi) 6, 11 a,b·Pd[PPh₃]₄, Cul·Et₃N, DMF; (vii) NH₃/H₂O; (viii) MeOH, Pd/C, H₂

Scheme 1: Synthesis of C8-alkynyl- and alkylamino substituted 2'-deoxyguanosines.
functional group for attaching signaling molecules like reporter dye. Therefore, in this communication we report the synthesis of C8-alkynyl- and alkylamino substituted 2'-deoxyguanosines.

RESULTS AND DISCUSSION

To introduce the required C8-alkynylamino side chain, 2'-deoxyguanosine (12) was first converted to the corresponding C8-bromo derivative via treatment of N-bromosuccinimide in water for about 12 hours stirring at room temperature. Pd(0)-mediated Sonogashira coupling of 8-bromo-2'-deoxyguanosine, 13, with N-propargyltrifluoroacetamide afforded the target protected propargylamino substituted nucleoside 1a in 76% yield (Scheme 1).

Trifluoroacetyl protected higher homologs of alkynylamino substituted 2'-deoxyguanosines were prepared according to the Scheme 1 in a similar way. Thus, the homopropargyl alcohol 7a and its higher homologues 7b were converted to the corresponding mesylates 8a-b respectively in quantitative yields. The mesylates were then reacted with sodium azide in dry dimethylformamide to get azides 9a-b in 90% yields which were then converted to the corresponding amines 10a-b by reduction with triphenylphosphine and water and are protected with trifluoroacetyl derivatives 11a-b. The protected amines were then subjected to Sonogashira coupling to afford nucleosides 1b-c. The nucleosides with rigid trifluoroacetyl protected alkynylamino linker (1a-c) were then subjected to Pd/C catalysed hydrogenation in methanol to afford the flexible alkynylaminostituted guanosines (3a-c) in quantitative yield. We were tried to reduce the alkyne moiety of the 3'- and 5'-hydroxy protected C8-substituted guanosines by Pd/C catalyst but it failed. However, in the case of unprotected guanosine, the reduction proceeded smoothly at room temperature in a quantitative yield. Treatment of trifluoroacetyl protected nucleosides 1a-c and 3a-c with aqueous ammonia at room temperature for overnight afforded the corresponding alkylaminonucleosides 2a-c and 4a-c in quantitative yield.

CONCLUSION

In summary, we have described the efficient synthesis of C8-alkynylamino substituted 2'-deoxyguanosines. These modified guanosines can be incorporated into a variety of oligonucleotide sequences after being converted these nucleosides into their corresponding phosphoramide derivatives and subjected to automated DNA synthesizer. The unprotected aminofunctionality of the linkers can be coupled with reporter dyes or designed solvofluorochromic fluorophores via post synthetic modification and thus can be used widely as a C8 modified guanosine base in oligonucleotide chemistry.

REFERENCES


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