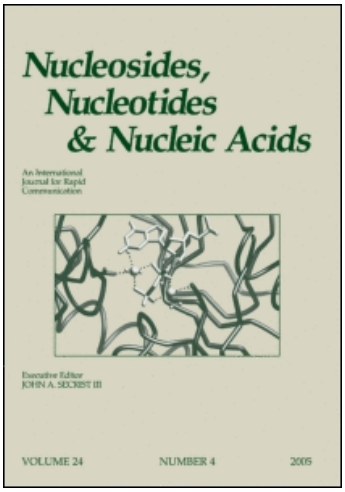

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7-SUBSTITUTED 8-AZA-7-DEAZAPURINES AND 2,8-DIAZA-7-DEAZA-PURINES: SYNTHESIS OF NUCLEOSIDES AND OLIGONUCLEOTIDES

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▫ *7-Substituted 8-aza-7-deazaadenosines* ***1a–e*** *were synthesized by Sonogashira cross coupling from the corresponding 7-iodo nucleoside in 36–79% yields. Starting from 7-bromo (or 7-iodo)-8-aza-7-deazaadenine,* ***2a,b*** *were obtained by acid-catalyzed glycosylation followed by deprotection in 53 and 35% yields, repectively. Compounds* ***2b*** *was applied to cross coupling reaction to give* ***2c–d*** *in 34–95% yield. Compounds* ***2a*** *and* ***4b*** *were further transformed to the phosphoramidites* ***5*** *and* ***6b*** *in 9 and 49% overall yields, which were incorporated into oligonucleotides.*

Keywords 7-Substituted 8-Aza-7-Deazaadenosine, Phosphoramidite, Sonogashira Cross Coupling, Glycosylation

INTRODUCTION

8-Aza-7-deazapurine (pyrazolo[3,4-d]pyrimidine) nucleosides have attracted attention due to their biological activities and as constituents of oligonucleotides[1,2] (Scheme 1).

Earlier, 7-substitutents, such as 7-halogeno and 7-alkynyl, have shown favourable effects on the stability of duplex DNA.[3] Herein we report on the synthesis of 7-substituted purine nucleoside analogs **1a–e**, **2a–e**, **3a,b**, and **4a,b**, as well as of the phosphoramidites **5** and **6b**.

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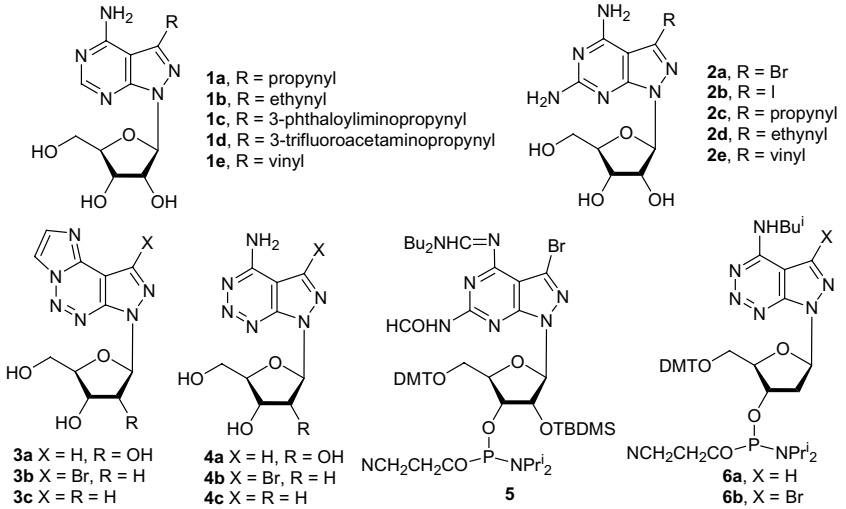
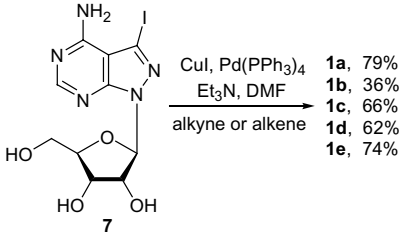


SCHEME 1

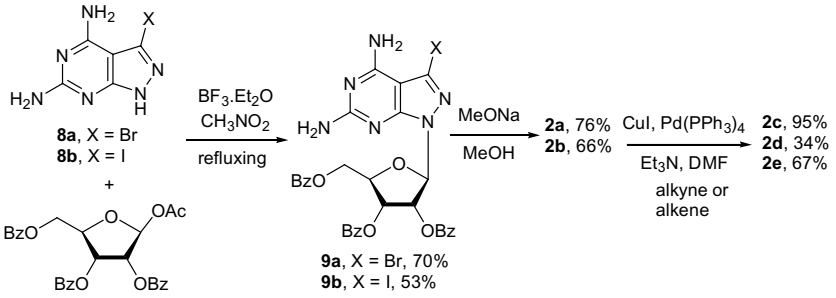
RESULTS AND DISCUSSION

7-Iodo-8-aza-7-deazaadenosine (**7**) was prepared according to Cottam et al.,[4] which was applied to Sonogashira coupling reaction with propynes to give **1a,c,d**.[5] Cross-coupling of **7** with trimethylsilylacetylene, followed by desilylation with K_2CO_3/MeOH furnished **1b** in 36% overall yield. The ethenyl nucleoside **1e** was obtained by coupling of **7** with tri-n-butyl-vinylstanane under the catalysis of a palladium catalyst and CuI in 74% yield (Scheme 2).

Compound **8a** was prepared from 8-aza-7-deaza-2,6-diaminopurine according to Taylor and Patel.[6] The preparation of **8b** was accomplished by iodination of 8-aza-7-deaza-2,6-diaminopurine with NIS in dichloroethane at refluxing in 65% yield. Glycosylation of **8a,b** with 1-acetyl-2,3,5-tribenzoyl-β-D-ribofuranose under catalysis of $BF_3 \cdot Et_2O$ resulted in **9a,b** in 70 and 53% yield, respectively. Deprotectin of the benzoyl groups in the presence of NaOMe/MeOH gave **2a,b**. Compound **2b** was further applied to cross coupling reaction to furnish **2c–e** in moderate to excellent yield (Scheme 3).



SCHEME 2



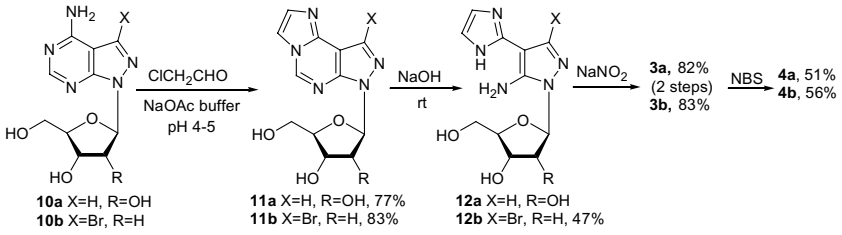
SCHEME 3

The syntheses of **4a,b** were accomplished from **10a,b** via their 1,N^6-etheno derivatives **11a,b**. Compounds **10a,b** were treated with chloroacetaldehyde in pH 4∼5 sodium acetate buffer at r.t. overnight to give **11a,b**. Treatment of **11a,b** with 0.5 M NaOH at ambient temperature overnight yielded **12a,b**, which were cyclized in the presence of $NaNO_2$ in 80% AcOH to give **3a,b**. Removal of the etheno group of **3a,b** by NBS afforded **4a,b** in 32 and 18% overall yield, respectively (Scheme 4).[7]

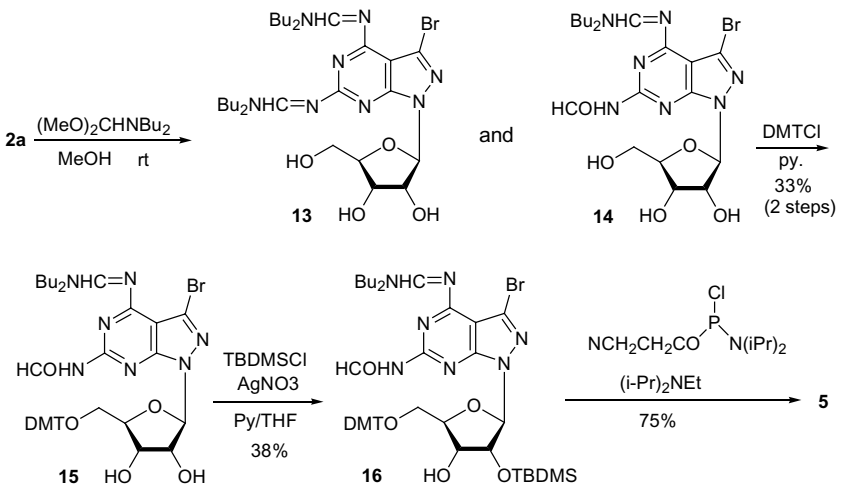
Treatment of **2a** with N,N-di-n-butylformamide dimethyl acetal at r.t. gave a mixture of **13/14**, which was further treated with DMTCl in pyridine to yield **15** in 33% overall yield. Because of the unstability of the imino group in N2, the formamide was obtained in these two steps. Treatment of **15** with TBDMSCl and $AgNO_3$ provided **16** (38% yield), along with its 3′-OTBDMS isomer which could be removed by careful column chromatography. At last, the phosphoramite **5** was obtained in 75% yield (9% overall yield from **2a**) according to the standard procedure (Scheme 5).

Treatment of **4b** with N,N-dimethylformamide dimethyl acetal at r.t. gave **17** in 75% yield. The introduction of the 4,4′-dimethoxytrityl group followed the standard protocol giving compound **18** in 83% yield. Subsequent phosphitylation with chloro-(2-cyanoethoxy)-N,N-(diisopropylamino)phosphine gave the phosphoramidite **6b** in 79% yield (Scheme 6).

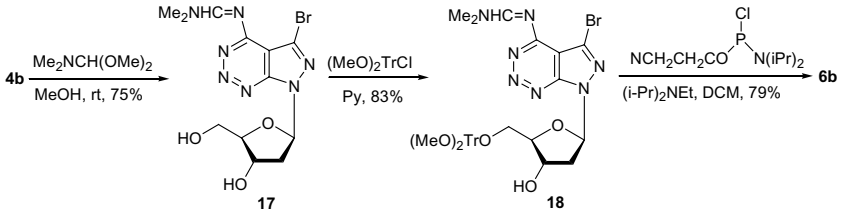
Compounds **5** and **6a** were employed in solid-phase oligonucleotide synthesis. Base pairing studies on **4c**, incorporated in a 12-mer duplex, showed that this



SCHEME 4



SCHEME 5



SCHEME 6

adenine nucleoside analogue forms a strong base pair with dG [5′-d(TAG GTC A**4c**T ACT) · 3′-d(ATC CAG T**G**A TGA), T_m = 46°C comparable to 5′-d(TAG GTC A**A**T ACT) · 3′-d(ATC CAG T**G**A TGA), T_m = 44°C] by forming a face to face base pair because of the absence of N7. This novel base pair is as stable as that of the canonical dA-dT pair. However, **4c** could not form a stable base pair with dT, dA, and dC.

In conclusion, 8-aza-7-deazapurine nucleosides **1,2**, as well as 2,8-diaza-7-deazapurine nucleosides **3a,b** and **4a,b** were prepared in good to excellent yield. Studies on the biological activities are under way. Compound **2a** and **4b** were also transformed to the oligonucleotide building blocks **5** and **6b**. Their incorporation into oligonucleotides is in progress.

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