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Novel syntheses of (*Z*)-alkene and alkane base-modified nucleosides

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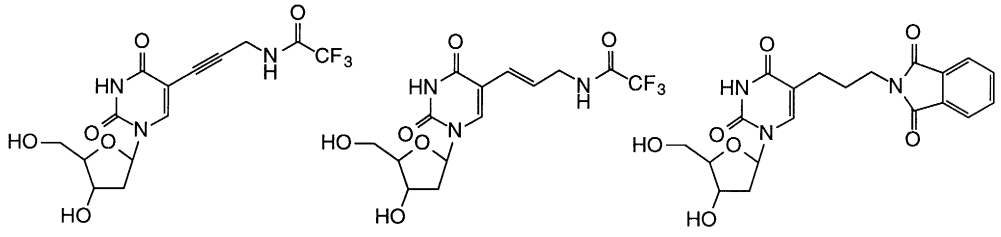
Abstract

The syntheses of 5-(*Z*)-(3-aminoallyl)- and 5-(3-aminopropyl)-substituted 2′-deoxyuridine and 2′-deoxycytidine are reported. These compounds were derived from the corresponding 5-propargylamine derivative. [Hobbs, F. W. *J. Org. Chem.* **1989**, *52*, 3420.] The catalyst we have employed for these reductions is a $NiCl_2/NaBH_4$ system, which we have found to be superior to the more conventional palladium-catalysts previously reported with similar compounds.

Keywords: pyrimidines; alkenes; nucleosides; reduction.

Pyrimidine nucleosides modified at the C5-position have been prepared previously as antiviral agents[1] and more recently, C5-amino-modified nucleosides have been utilised to stabilise DNA-triple helices[2] and for the attachment of reporter groups to oligonucleotides.[3] Examples include the attachment of a protected propargylamine[4] (e.g. **1**) or allylamine[5] (e.g. **2**) unit to the 5-position of the pyrimidine nucleoside using conventional palladium-coupling chemistry with the halogenated nucleoside. Analogous alkanes have also been synthesised (e.g. **3**) via hydrogenation of the alkyne, using palladium on carbon as a catalyst (no yield was reported for this reaction).[6]



1 **2** **3**

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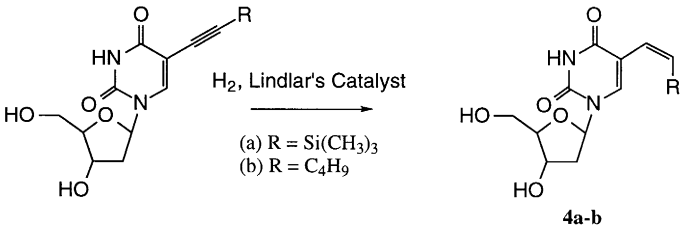
Direct coupling of the allyl unit to the nucleoside only allows access to the (*E*)-isomer of this compound. Since the positioning of the amino group relative to either the nucleobase or, when incorporated into a polymer, DNA, may be important in applications of these compounds, a facile synthesis of the (*Z*)-isomer would also be desirable. In 1983, Robins and Barr[7] reported formation of the *cis* isomers of the related uridine compounds **4a** and **4b** via a partial reduction of the alkyne derivative using a poisoned palladium catalyst as shown in Scheme 1. In the case of **4b**, 10% of the corresponding fully saturated material was also isolated.



Scheme 1.

We intended to repeat this procedure with compound (**1**) and found that although this reaction was successful,‡ it required precise optimisation of the reaction conditions for each batch of catalyst, and so was not routinely reproducible.

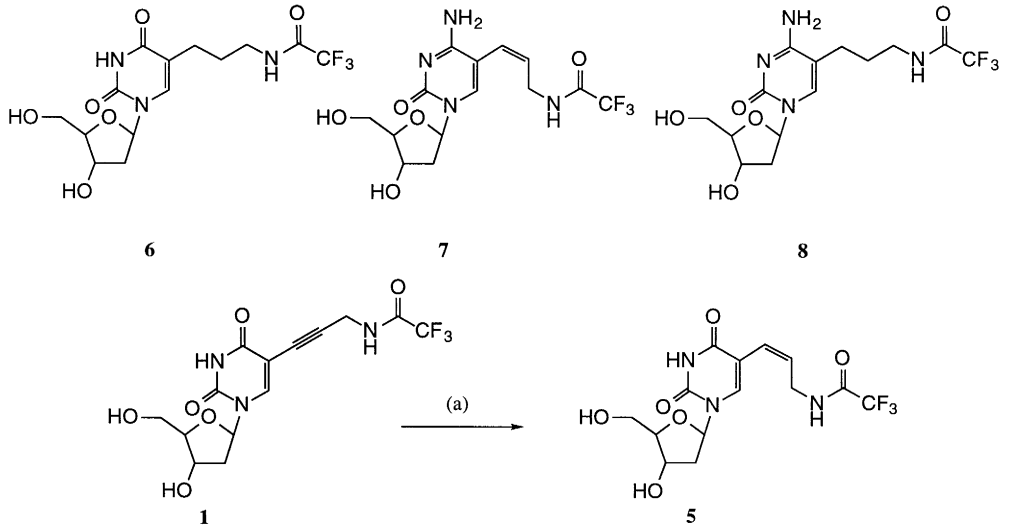
In order to overcome this problem we attempted the same reaction using $NiCl_2$ and $NaBH_4$, in place of palladium (Scheme 2), a reduction system which releases a known amount of hydrogen into the reaction mixture and transiently forms a hydrogenation catalyst in situ.[8] The immediate removal of this catalyst by column chromatography prevents the problems of further reduction and/or decomposition seen in the palladium catalysed reaction. The reaction to generate **5**§ produced reproducible yields of 55%, and also proved to be quite versatile. The corresponding uridine-alkane (**6**)¶ was synthesised from the (*Z*)-alkene

‡ Compound **1** was dissolved in dry MeOH (40 ml/mmol). Palladium on carbon was added (0.05 g/mmol) and the reaction mixture degassed. The reaction mixture was stirred under 1 atmosphere of H_2 at 38°C for 16 min then filtered through Celite and purified by recrystallisation from acetonitrile. The yield, after extensive optimisation, was 53% pure alkene (ca. 17% alkane, 0% alkyne in the crude mixture). Lindlar's catalyst caused decomposition of the nucleoside.

§ The nucleoside (0.150 g) was dissolved in excess dry methanol (20 ml) and cooled to −78°C. $NiCl_2$ (1 equiv.) was dissolved in hot MeOH (2 ml) and added to the reaction mixture. $NaBH_4$ (1.3 equiv.) was added to the reaction mixture portion-wise over 3 min and the reaction mixture held at −78°C for 30 min. The reaction mixture was then allowed to warm until it went black at which point silica was immediately added (an equal mass to that of the starting nucleoside). The reaction mixture was then adsorbed onto the silica, and purified by column chromatography (0–20% MeOH in EtOAc as eluent). Yield=55%. No alkane was observed in the crude reaction mixture. ^{1}H NMR data of **5**: (d_6-DMSO) δ 11.51 (1H, s, NH), 9.66 (1H, s, NH), 7.89 (1H, s, H6), 6.22 (1H, t, *J*=6.9 Hz, H1′), 6.20 (1H, d, *J*=10.4 Hz, CH), 5.58 (1H, m, CH), 5.26 (1H, m, OH), 5.12 (1H, m, OH), 4.25 (1H, m, H3′), 4.03 (2H, br. s, CH_2), 3.82 (1H, m, H4′), 3.58 (2H, m, H5′, H5′′), 2.15 (2H, m, H2′, H2′′); EI^+ ms *e/z* 379 (5 %, M^+).

¶ ^{1}H NMR data of **6**: (d_6-DMSO) δ 11.30 (1H, s, NH), 9.40 (1H, s, NH), 7.69 (1H, s, H6), 6.24-6.16 (3H, m, H1′, CH2), 5.25 (2H, m, CH_2), 5.12 (1H, m, OH), 5.01 (1H, m, OH), 4.24 (1H, m, H3′), 3.80 (2H, br. s, CH_2), 3.76 (1H, m, H4′), 3.56 (2H, m, H5′, H5′′), 2.27–2.13 (2H, m, H2′, H2′′); ES^+ ms *e/z* 404 (7.5%, $[M+Na]^+$), 382 (7.5%, $[M+H]^+$).

by the same method in 51% yield, and the corresponding (*Z*)-alkene (**7**)[‖] and alkane (**8**)[††] derivatives in the cytidine series were also successfully synthesised by this method in 59% and 58% yields respectively.



Scheme 2. (a) 1 equiv. $NiCl_2$, 1.3 equiv. $NaBH_4$, dry MeOH, −78°C, 30 min, 55%

In conclusion, we have developed a methodology for the preferential reduction of unsaturated side chains on modified pyrimidine nucleosides which does not require further optimisation in situ, and which is equally applicable to both cytidine and uridine nucleosides. Standard techniques should allow conversion of the (*Z*)-alkene and the alkane to the corresponding triphosphate or protected phosphoramidite for incorporation of these analogues into DNA.

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‖ ^{1}H NMR data of **7**: (d_6-DMSO) δ 9.73 (1H, s, NH), 7.84 (1H, s, H6), 7.41 (2H, s, NH_2), 6.22 (1H, d, *J*=11.3 Hz, CH) 6.19 (1H, t, *J*=7.0 Hz, H1′), 5.62-5.53 (1H, m, CH), 5.27 (1H, m, OH), 5.13 (1H, m, OH), 4.24 (1H, m, H3′), 3.97 (2H, br. s, CH_2), 3.80 (1H, m, H4′), 3.58 (2H, m, H5′, H5′′), 2.17–1.95 (2H, m, H2′, H2′′); ES^+ ms *e/z* 378 (5% $[M+H]^+$).

†† ^{1}H NMR data of **8**: (d_6-DMSO) δ 9.51 (1H, s, NH), 7.67 (1H, s, H6), 7.30 (2H, s, NH_2), 6.20–6.13 (3H, m, H1′, CH_2), 5.27 (1H, m, OH), 5.13 (1H, m, OH), 5.10 (2H, m, CH_2), 4.22 (1H, m, H3′), 4.10 (2H, br. s, CH_2), 3.75 (1H, m, H4′), 3.56 (2H, m, H5′, H5′′), 2.10–1.75 (2H, m, H2′, H2′′); EI^+ ms *e/z* 381 (5% $[M+H]^+$).

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