Synthesis of 2′,3′-dideoxynucleosides from 2-(methylsulfanyl)uracils

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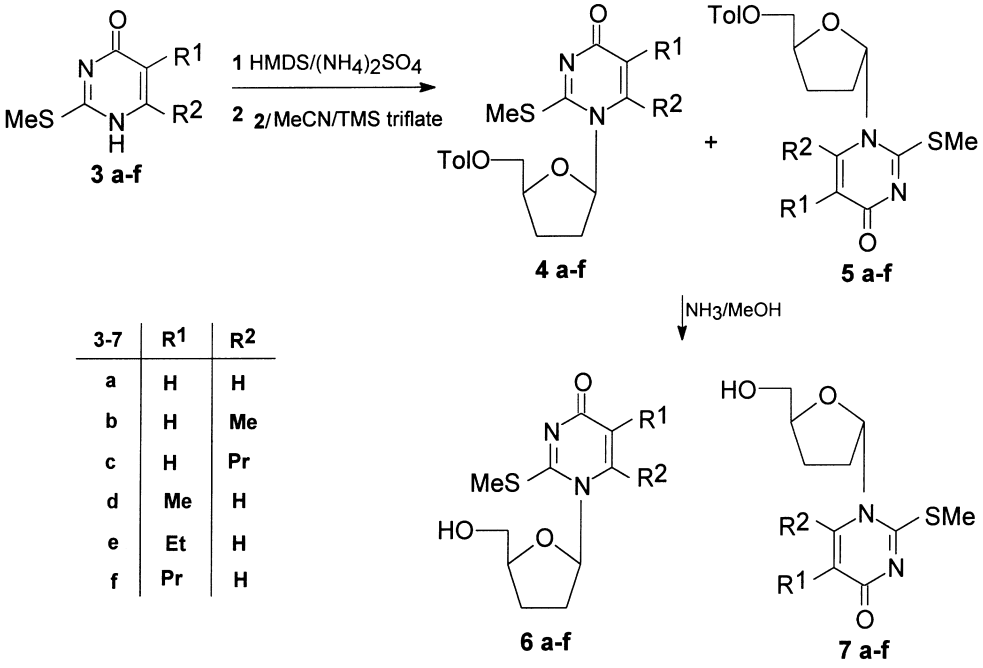
Silylated 2-(methylsulfanyl)uracils were condensed in the presence of TMS triflate with methyl 2,3-dideoxy-5-*O*-(4-methylbenzoyl)-D-*glycero*-pentofuranoside (**2**) to give, after deprotection, the corresponding nucleosides **6a–f** and **7a–f**.

Keywords: 2′,3′-dideoxynucleosides, 2-(methylsulfanyl)uracils

Since the discovery of the human immunodeficiency virus (HIV) as the cause of AIDS,[1] intense efforts have been made to find potential drugs that can selectively inhibit the replication of HIV.[2-4] As a result, some compounds have been identified as having an inhibitory effect. Among these, 2′,3′-dideoxycytidine (ddC), 3′-azido=3′-deoxythymidine (AZT) and 3′-deoxy-3′-fluorothymidine (FddThd) are the most potent drug candidates.[5] In the case of AZT, the key toxicity is the suppression of bone marrow, whereas in the case of ddC, the key toxicity is peripheral neuropathy. However, their usage is limited due to their side effects.[6] Hence, there is a need to design and synthesise new analogues of these molecules with less prominent side effects.[6] The continued interest of our research group in the synthesis of *S*-alkylated 2-thiouracil nucleoside analogues[7-14] has prompted us to synthesise novel 2′,3′-dideoxynucleoside analogues of 3′-dideoxythymidine (ddThd), where the 2-oxo group has been replaced by methyulsulfanyl group in the nucleobase moiety and to test their antiviral activity. The results are presented here.

2-(Methylsulfanyl)uracils **3a–f** were synthesised according to Brown *et al.*[15] Silylation of the nucleobase with hexamethyldisilazane (HMDS) was carried out according to Vorbrüggen *et al.*[16] by refluxing the nucleobase in HMDS in the presence of catalytic amounts of ammonium sulfate. Coupling of the dideoxy sugar **2** with the silylated 2-(methylsulfanyl)uracils **3a-f** was carried out under the Vorbrüggen conditions[17] in dry acetonitrile, using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a catalyst, to give the corresponding anomeric mixtures. Condensation of 2,3-dideoxyribofuranosides with silylated pyrimidines in the presence of TMS triflate produce the corresponding nucleosides in which the major anomer has the α configuration.[18] However, substituents such as CN, N_3, or SPH at 2- or 3-position in the dideoxy sugars increase the formation of β-anomer.[19] We have previously reported, [9] the condensation of 2,3-dideoxy-3-iodo ribofuranoside derivative with silylated 2-(ethylsulfanyl)-5-methyluracil according to the method described by Vorbrüggen *et al.*[16] to give the β-anomer as the only anomer together with the acyclic derivative arising by a neighbouring group interaction between the iodo substituent and the silylated 2-(ethylsulfanyl)-5-methyluracil. This phenomena is the reason for the stereoselectivity with preferential attack on the β face of the sugar ring. Herein, we disclose our latest findings on the use of 2-(methyulsulfanyl)uracils in the condensation with unsubstituted sugar *i.e.*, 2,3-dideoxy sugar. The results of the anomeric selectivity are presented. In all cases the β/α ratio was close to 2:3. The β-anomers **4a-f** were obtained in 21–35% yields and the α-anomers **5a-f** in 42–51% yields, after purification by column chromatography on silica



3-7	R1	R2
a	H	H
b	H	Me
c	H	Pr
d	Me	H
e	Et	H
f	Pr	H

Scheme 2

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gel. Treatment of **4a–f** or **5a–f** with a 1:1 mixture of methanol and conc. ammonia at room temperature overnight resulted in complete deprotection of the 5′-OH group to give **6a–f** in 55–58% yields or the corresponding α-anomers **7a–f** in 56–68% yields.

The assignment of the anomeric configuration of the deprotected 2′,3′-dideoxynucleosides are based on NOE data. The NOE of H-C (4′) upon irradiation of H-C (1′) can be used for the assignment of the β-configuration.[19,20] In the case of **6b**, a NOE of 2.5% was observed, while a smaller NOE in the case of **7b** (0.1%), indicating that **6b** was the β-anomer and **7b** the α-anomer. In similar way, the β-configuration of compounds **6a,e** were assigned by the presence of NOE on H-C (4′) (2.1%), while the α-configuration of **7a,e** were confirmed by the absence of NOE on H-C (4′).

Compounds **6a–f** and **7a–f** were tested for their activity against Hepatitis B virus (HBV) in Hep G_2 2.2.15 cell. Compounds **6a–f** and **7b** showed moderate inhibition activity and high cytotoxicity, while compounds **7a,c–f** showed low inhibition activity and high cytotoxicity.

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Techniques used ^{1}H and ^{13}C NMR including 2D NMR and EIMS

Schemes: 2

References: 20

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