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Temperature controlled stereoselectivity in the synthesis of 5-halo-2′-deoxyuridine derivatives

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ABSTRACT

A series of α- and β-5-halo-2′-deoxyuridine derivatives were prepared with high anomeric selectivity using the conventional silylbase glycosylation method and taking advantage of the 3′-*O*-(*N*-acetyl)glycyl protection group and temperature control. Reactions performed at −7 °C gave as much as 87% of the β-anomers, while an overnight reaction at 30 °C gave up to 95% of the α-anomers.

Introduction

Nucleoside derivatives are commonly prepared through the Vorbrüggen method (also known as silylbase Hilbert–Johnson method), that is, through coupling of a silylated heteroaromatic base with a protected acyl or alkyl glycoside under Lewis acid catalysis.[1] Control of the coupling step stereochemistry is critical for the usefulness of the method. A significant effort in nucleoside synthesis has been aimed at preparing the naturally occurring β-anomers. In practice, β-ribonucleoside analogs can often be obtained with good selectivity by glycosylation of a peracylated D-riboside, taking advantage of the directing effect of the 2′-*O*-acyl group which coordinates through the carbonyl oxygen atom to the cationic anomeric carbon, blocking the α-face of the oxocarbenium intermediate (Scheme 1A).[2] In contrast, acylated 2′-deoxyribose derivatives lack this directing effect and the glycosylation reaction typically yields a mixture of β- and α-anomers in variable ratio. To overcome this problem, 3′-*O* protecting groups have been designed, which offer good β-directing effect. Recently Zhang and coworkers[3] reported a systematic study of this methodology and found that the 3′-*O*-(*N*-acetyl)glycyl protecting group efficiently facilitated production of the native β-anomers of 2′-deoxynucleosides under silylbase conditions (90–98% yield with approximately 90% β-anomer content). However, when we applied this methodology to the 3′-*O*-(*N*-acetyl)glycyl protected methyl 2-deoxy-D-riboside derivative **1** (Scheme 1B) for the preparation of 2′-deoxyuridine analogs, we found that the stereoselectivity was greatly affected by the 5-substituent of the uracil moiety. With 5-halouracil the stereochemical outcome was completely reversed, and after stirring overnight, more than 90% of the product consisted of the α-anomer. This behavior led us to conduct a more detailed and quantitative study on the substituent effects as well as other factors that may affect the outcome of the glycosylation reaction with 2-deoxyribosides.

Zhang and coworkers[3] tested several 3′-*O*-protecting groups in the glycosylation of silylated native nucleobases. The highest β-directing effect was found using the 3′-*O*-(*N*-acetyl)glycyl group, and the authors proposed this originated from the coordination of the amide moiety to the carbocationic center of the glycon intermediate (Scheme 1B, **I**). However, in an earlier study, Abdel Aleem et al.[4] employed an analogous type of protecting group, but obtained anomeric mixtures of pyrimidine nucleoside derivatives with an α/β ratio of ca. 3:1. More recently it has been shown with pyrimidone base analogs that the α/β ratio of glycosylation is susceptible to the reaction conditions, allowing in some cases selective formation of the kinetic and thermodynamic products by a small adjustment of temperature.[5,6] Another noteworthy publication by Sato et al.[7,8] showed that β-2′-deoxythymidine could be epimerized to its α-anomer by treatment with trimethylsilyl triflate.[8] Substituent and solvent effects on the conversion showed, for instance, that sterically demanding 5′-*O*-acyl substituents tended to enhance the epimerization and favor the α-anomer in the thermodynamic equilibrium.[8]

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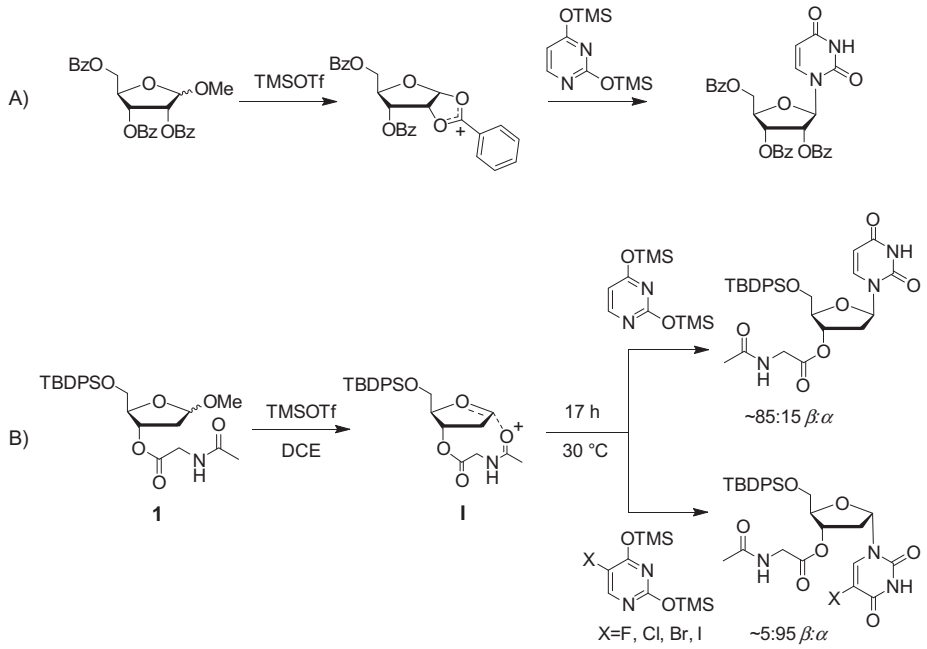


Scheme 1. Reaction scheme for the stereoselective preparation of uridine (A) in comparison with 2′-deoxyuridine and 5-halogenated 2′-deoxyuridine derivatives (B) after 17 h reaction at 30 °C.

Taking these earlier findings into account, we chose to examine the glycosylation of 5-substituted uracil derivatives by employing the (*N*-acetyl)glycyl group for 3-*O* protection and a *tert*-butyldiphenylsilyl group for 5-*O* protection. The bulkiness of the latter group was expected to enhance formation of the α-nucleoside in the proposed equilibration between the β- and α-anomers.[8]

In the present communication we wish to report the substituent effects on the anomeric ratio, and present a convenient temperature controlled glycosylation method for the stereoselective preparation of both the α- and β-anomers of 2′-deoxy-5-halouridines, in a stereoselective manner, from the same starting materials. The progress of the glycosylation of silylated uracil derivatives were followed on-line in a quantitative manner by ^{1}H NMR and with the aid of these results we were able to selectively control the formation of the two anomers, altering the product ratio by simple adjustment of the reaction temperature.

The present study is aimed at providing quantitative data for improving the synthesis of nucleoside analogs, which are widely applied in drug design and diagnostics. The 2′-deoxy-5-halouridines have been used as antivirals[9] (e.g., 2′-deoxy-5-fluorouridine known as Floxuridine) and as starting compounds in metal catalyzed carbon–carbon bond forming reactions.[10] The latter reactions are useful, for instance, in preparing fluorescent nucleoside derivatives which can be used as labeling compounds, and also be incorporated in DNA oligomers through the conventional phosphoramidite method.[11,12]

Results and discussion

The 2′-deoxyuridine derivatives with varying substituents at the pyrimidine C5 position were synthesized by the one-pot silylbase method using methyl 3-*O*-(*N*-acetyl)glycyl-5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-D-riboside **1** as the glycosyl donor and trimethylsilyl triflate as the Lewis acid in 1,2-dichloroethane. The preliminary results indicated that both the reaction temperature and the electron withdrawing substituent at the C5 position of uracil affected the formation of the α-anomer. In order to optimize the reaction conditions and assign the structure of the accumulating intermediates the progress of the glycosylation of 5-iodouracil was monitored by ^{1}H NMR at several temperatures (see Figs. 1 and 2, and details given in the ESI).[13,14] The 5-fluoro and 5-iodo-derivatives showed somewhat slower rates of conversion to the α-anomer than the 5-chloro and 5-bromo analogs. The β-nucleoside strongly prevailed in the initial product distribution (Fig. 1A), but soon passed the maximum accumulation point and began to diminish, while the amount of the α-nucleoside began to increase. Equilibrium between the anomers was reached after stirring overnight (*ca.* 17 h) at room temperature. When the reaction was carried out at 15 °C, less than half of the β-anomer was converted to the α-anomer after stirring overnight (Fig. 1B). By lowering the reaction temperature further to 3 °C or −7 °C (Fig. 1C and D, respectively), we were able to maximize formation of the β-anomer. The reactions were then carried out on a small preparative scale in order to ascertain the results with isolated products. The results in Table 1 demonstrate that the anomeric ratio obtained in the crude product mixture was in each case consistent with that obtained during NMR monitoring.

The results of the ^{1}H NMR experiments may be interpreted as showing that the β-anomer was formed as the kinetic product, which was then almost completely converted to the thermodynamically more stable α-anomer in the subsequent step. As shown earlier[3] and confirmed here, the 3′-*O*-(*N*-acetyl)glycyl group favors formation of the β-anomer over the α-anomer. In our experiments the excess of the β-anomer was slightly lower than that reported by Zhang and coworkers[3] which may be due to the different protecting group employed at the 5′-*O* site. The proposed[3] coordination of the 3-*O*-protecting group to the anomeric carbon on the α-face of the intermediate oxocarbenium ion provides a sufficient explanation for the β-directing effect in the kinetically controlled reaction (Scheme 1, **I**).

In order to determine, if the structure of the protecting group had any effect on the equilibration step, we carried out the glycosylation reaction using various groups at the 3′-*O* site. The groups were chosen so that either a functional group was removed from

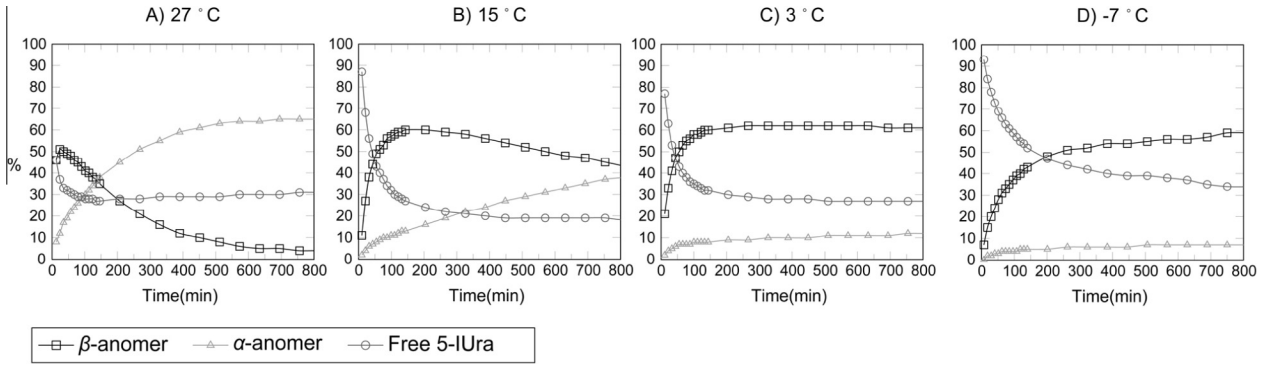


Figure 1. Time dependent product distributions as determined by ^{1}H NMR monitoring for the glycosylation of O^2,O^4-bis-trimethylsilylated 5-iodouracil at different temperatures.

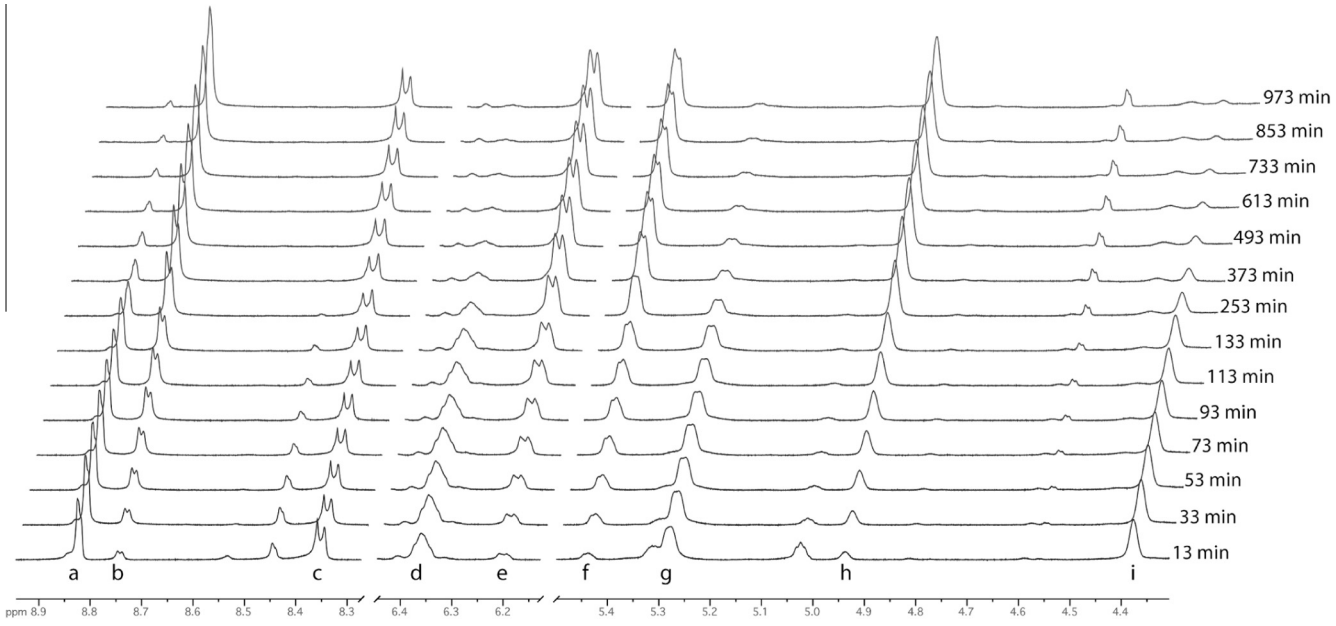


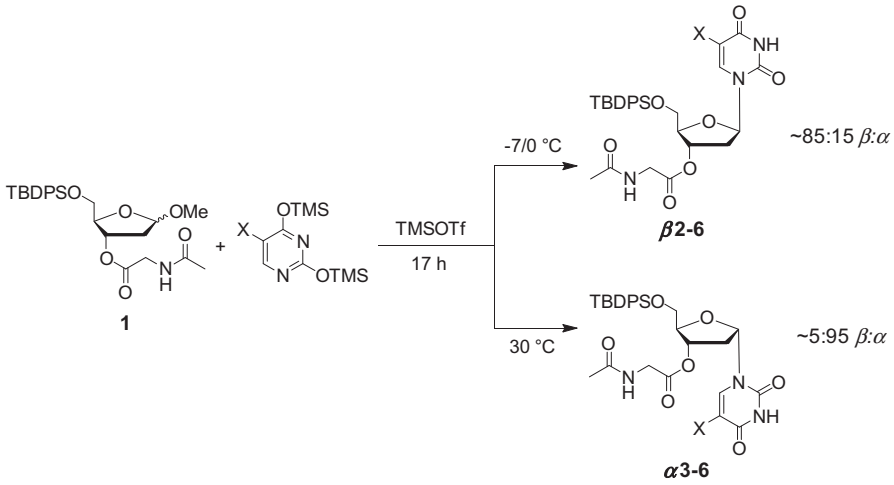
Figure 2. ^{1}H NMR monitoring of the glycosylation reaction of O^2,O^4-bis-trimethylsilylated 5-iodouracil at 27 °C. a: β6-H6, b: α6-H6, c: 5-IUra-H6, d: β6-H1′, e: α6-H1′, f: α6-H3′, g: β6-H3′, h: α6-H4′, i: β6-H4′.

the side chain (**8**, **9** and **10**) or the steric hinderance was increased (**8**). The results in Table 2 show that these changes had little effect on the thermodynamic equilibrium between the β- and α-anomers, although the (*N*-acetyl)glycyl group may slightly enhance the α-selectivity in comparison to the other 3′-*O*-groups tested. The present results do not allow a detailed discussion of the reasons and warrant further examination. One possible explanation could be an interaction between the amide carbonyl and the cationic pyrimidine moiety in the α-geometry.

Glycosylation of the silylated uracil and thymine compounds in an overnight reaction at 20 °C gave the kinetic β-nucleoside products in 85:15 anomeric ratio under the applied conditions (**β2** in Table 1). However, when the reaction was run at 27 °C for one week, conversion to the α-anomer was observed. Thus, the 5-halogen substituents have a strong rate increasing effect on this step. Since the electronegative halogen substituent may enhance the leaving group ability of the pyrimidine base, the finding is, in our opinion, in accordance with a mechanism involving a rate limiting loss of the silylated uracil base from the glycoside of the initially formed nucleoside derivative. The formed oxocarbenium-type glycon moiety, reacts with another uracil molecule in a subsequent step from the other face of the glycon.

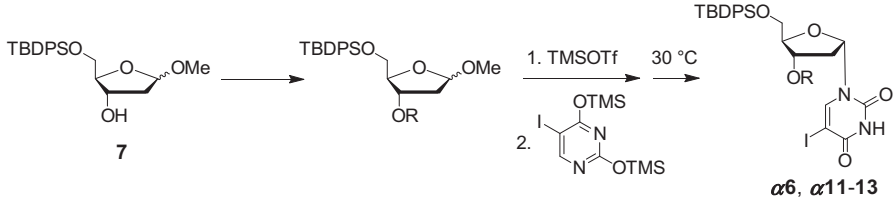
In conclusion, we have shown that α- and β-5-halo-2′-deoxyuridines can be prepared with good anomeric selectivity using the conventional silylbase glycosylation method and taking advantage of the 3′-*O*-(*N*-acetyl)glycyl protecting group and temperature control. We suggest this as a practical method for selective preparation of either the β- or α-anomer of 5-halo-2′-deoxyuridines from the same starting materials by a simple adjustment of reaction conditions. When the reaction temperature was kept at 0 °C or lower (Table 1, entries 3, 5, 7 and 9), the β-nucleoside could be isolated in 85:15 anomeric ratio, whereas an overnight reaction at 30 °C gave the α-anomer in more than 90:10 ratio (Table 1, entries 2, 4, 6 and 8). Although the purification methods were not optimized during this study, the anomeric purity could be further raised by careful chromatography. In contrast, the 5-unsubstituted uracil and 5-methyluracil derivatives were converted to the α-anomer much more slowly, and an anomeric mixture containing 85% of the β-form was isolated after an overnight reaction at 20 °C.

Table 1
Anomeric ratio and isolated yields for the glycosylation of trimethylsilylated 5-substituted uracils



Entry	X	*T* (°C)	Crude product α/β-ratio	Main product	Total yield (%)
1	H	20	15:85	**β2**	75
2	F	30	90:10	**α3**	74
3	F	0	20:80	**β3**	80
4	Cl	30	95:5	**α4**	72
5	Cl	−7	13:87	**β4**	73
6	Br	30	94:6	**α5**	76
7	Br	−7	13:87	**β5**	72
8	I	30	94:6	**α6**	76
9	I	0	14:86	**β6**	70

Table 2
Anomeric ratio and isolated yields for the glycosylation of trimethylsilylated 5-iodouracil with methyl 2-deoxy-D-ribose derivatives containing different 3′-*O*-protecting groups



Entry	R	Crude product α/β-ratio	Main product	Total yield (%)
1	*N*-AcGly (**1**)	94:6	**α6**	76
2	Pentanoyl (**8**)	89:11	**α11**	68
3	Acetyl (**9**)	87:13	**α12**	70
4	Methyl (**10**)	89:11	**α13**	64

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.061.

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13. The β- and α-anomers were distinguished with the aid of NOESY spectra of the enriched samples. The C1′- and C3′-protons showed couplings either with different C2′-protons (β-anomer) or with the same C2′-proton (α-anomer).
14. The relative concentrations (as shown in Fig. 1) were in most cases determined from the integrated resonance signals of uracil H6, which were usually the most readily distinguished signals between the anomers and thus gave the most reproducible results. The peak areas of the H6 resonances were related to the peak area of the H6 of the substituted uracil derivative in the starting mixture. This area was assumed to correspond to the sum of the peak areas of all the uracil derivatives present in the mixture at the appropriate time. In few cases, however, the product distribution could be more accurately determined from the signals of the anomeric protons. The uracil derivative was used in slight excess compared to the glycoside. Thus, part of the uracil derivative remains uncoupled, as is seen from the profiles in Figure 1.