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Technical Notes

Improved Stereoselective Synthesis of the β-Anomer of 1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-D-ribofuranosyl]-5-iodo-2-pyrimidinone

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Abstract:

The lack of stereochemical control has been a major hurdle in synthesizing β-nucleosides in large scale. This paper reports a study of the effects of different catalysts used in the synthesis of β-nucleosides. The effects of time and temperature on α- and β-anomers are illustrated in this paper. The yield and selectivity of the β-nucleoside have been improved vastly at temperatures between −30 and −40 °C and by using $SnCl_4$ as the catalyst.

Introduction

Current interest in synthesizing drugs active against antiviral[1−3] and antitumor[4,5] agents have concentrated on the synthesis of β-nucleosides. Since most ribonuclesides and 2-deoxyribonucleosides exist as a β-anomer in nature, stereoselective synthesis of the β-nucleosides has become an enormous challenge to all synthetic chemists. Increasingly, more drugs are nucleoside based, such as the dideoxynucleoside derivatives (e.g., AZT, ddC, ddl, 3TC) used in the treatment of AIDS.[6]

The most common nucleosides consist of pyrimidine bases coupled to a 2-deoxyribose sugar at the 1′ position. The pyrimidine bases coupled to cytosine and uracil derivatives have shown the most consistent activity against the virus.[7,8] As uracil compounds cannot be deaminated in vivo, there is a strong interest in their selectivity as well as their ability to form stable derivatives.[9] A method frequently used in the synthesis is the Vorbruggen coupling (Scheme 1).[10] However, this method seems to lack stereochemical control in forming the β-anomer. Since there are no methods of epimerization[11] nor any existing methods[12] to synthesize the β-anomer of 1-[3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-D-ribofuranosyl]-5-iodo-2-pyrimidinone (IPdR, **3**) in large scale, we were forced to reinvestigate conditions which would give a predominantly β-anomer.

Results and Discussion

In an attempt to find a procedure that increases the β content of the coupled reaction of **1** with the silylated 2-hydroxy-5-iodopyrimidine, the effects of three acid catalysts were examined. The catalysts were *p*-nitrophenol,[7] trimethylsilyltrifluoromethane sulfonate (trimethylsilyl triflate),[5] and stannic chloride.[5] The reactions were run initially at −20 °C for 3 h to examine the effects of the catalysts on the β/α ratio as well as the total conversion to the α- and β-anomers. The reaction was assayed by using reversed-phase (C_{18} column) HPLC. The results are summarized in Table 1.

Table 1 indicates that the best overall catalyst was stannic chloride for coupling of **1** with the silylated 5-iodopyrimidinone **2** to produce the β-anomer of IPdR (**3**). Good β/α ratios and excellent conversions were achieved using stannic chloride as the catalyst. TLC and HPLC assays indicate the near disappearance of starting materials.

While monitoring the coupling reaction with TLC using *p*-nitrophenol as the catalyst, it was observed that after 30 min of the reaction, the major product formed was the β-anomer, and only a trace amount of the α-anomer was detected. As the reaction continued, more α-anomer was produced. At the end of 3 h, the β/α ratio was 1.5/1—i.e., 60% β-anomer and 40% α-anomer. There was still a significant amount (60%) of unreacted protected sugar chloride remaining. However, it was obvious from this experiment that formation of the β-anomer was kinetically controlled, while the formation of α-anomer was thermodynamically controlled. This strongly suggests that the product distribution of these coupling reactions is dependent on thermodynamic and kinetic factors. Therefore, to under-

(1) Weygand, F.; Wacker, A.; Dellwag, Z. *Naturforsch, Teil B* **1952**, *7*, 19.
(2) Belts, R. E.; Visser, D. *J. Am. Chem. Soc*. **1955**, *77*, 736.
(3) Belts, R. E.; Viser, D.; Frisch, D. M. *Biochem. Pharmacol*. **1960,** *5*, 157.
(4) Heidelberg, C.; Griesbach, L.; Cruz, O.; Schnitter, R. J.; Grunberg, E. *Proc. Soc. Exp. Biol. Med.* **1958**, *97*, 470.
(5) Burchenal, J. H.; Holmberg, A. D.; Fox, J. J.; Hemphill, S. C.; Reppert, J. A. *Cancer Res.* **1959**, *19*, 497.
(6) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
(7) Prusoff, W. H.; Chen, M. S.; Fischer, P. H.; Lin, T. S. *Adv. Ophthalmol*. **1979**, *38*, 3.
(8) Cheng, Y. C.; Hoffman, P. J.; Ostrander, M. *Adv. Ophthalmol*. **1979**, *38*, 1976.
(9) Efange, S. M. N.; Alessi, E. M.; Shih, H. C.; Cheng, Y.; Bardos, T. *J. Med. Chem*. **1985**, *28*, 904.
(10) (a) Niedballa, U.; Vorbruggen, H. *J. Org. Chem*. **1974**, *39*, 3654. (b) Vorbruggen, H.; Bennua, B. *Chem. Ber*. **1981**, *114*, 1279.
(11) Lipshutz, B. H.; Hayakawa, H.; Kato, K.; Lowe, R. F.; Stevens, K. L. *Synthesis* **1994**, 1476.
(12) Okasuchi, T.; Kubota, H.; Narasaka, K. *Chem. Lett.* **1989**, 801.

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Scheme 1

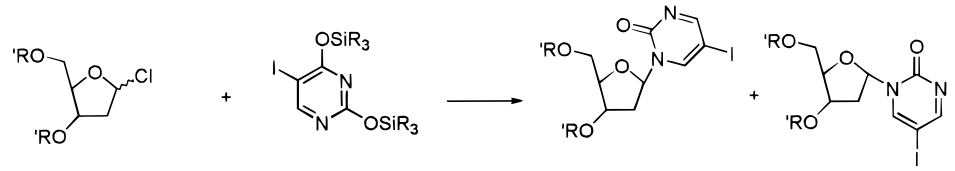

Table 1. **Effect of catalysts at −20 °C on *β*-selective synthesis of 1-[3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-D-ribofuranosyl]-5-iodo-2-pyrimidinone (IPdR, 3)**

catalyst	β/α-anomers	$\%\,\beta/(\alpha+\beta)$	$\%\,(\alpha+\beta)$
p-nitrophenol	1.5/1	60	40
trimethylsilyl triflate	0.43/1	30	15
stannic chloride	1.5/1	60	90

stand the product optimization between the α- and *β*-anomers, a mathematical model was used to estimate the product distribution due to kinetic and thermodynamic control at any time, *t*. This model is meant to be predictive and not used to interpret the mechanistic aspect of the reaction. In other words, by controlling the process, it should be possible to improve and optimize the *β*-anomer yields. To produce a simple mathematical model, it was assumed that the reaction was first order and that the rate-determining step was the disappearance of the protected sugar chloride S.

This reaction is ordinarily expressed as a competitive reaction sequence of the type

$$\beta \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} \mathrm{S} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \alpha \tag{1}$$

where the reactant S proceeds competitively toward products α and *β* until a final equilibrium is reached. The time evolution of the product ratio is determined by two parameters: the rate coefficients and the thermodynamics. In eq 1, *β* is the *kinetically* controlled product, while α is *thermodynamically* stable. Under the condition of low temperature, the product *β* is favored, for its low activation energy speeds up the change of S to *β*. In contrast, for long reaction times, the thermodynamic product α tends to dominate, as it is energetically more stable than the kinetic product *β*. At high temperature, the increase of temperature raises the rate coefficients and facilitates the reaction equilibrium; this favors the thermodynamic product.

Based on reaction 1 and assuming first-order kinetics throughout, the following kinetic equations were set up:

$$\frac{-\mathrm{d}[\mathrm{S}]}{\mathrm{d}t} = (k_1 + k_2)[\mathrm{S}] - k_{-1}[\beta] - k_{-2}[\alpha] \tag{2}$$

$$\frac{\mathrm{d}[\beta]}{\mathrm{d}t} = k_1[\mathrm{S}] - k_{-1}[\beta] \tag{3}$$

$$\frac{\mathrm{d}[\alpha]}{\mathrm{d}t} = k_2[\mathrm{S}] - k_{-2}[\alpha] \tag{4}$$

By using the matrix method, these coupled differential equations may be solved analytically.[10] The following secular equation,

$$\begin{bmatrix} k_{-1}-\lambda & -k_1 & 0 \\ -k_{-1} & k_1+k_2-\lambda & -k_{-2} \\ 0 & -k_2 & k_{-2}-\lambda \end{bmatrix} = 0 \tag{5}$$

yields the particular solutions, $\exp(-\lambda_i t)$, where λ_i is the eigenvalue of the equation and $i = 1$, 2, or 3. Thus,

$$\lambda_1 = 0$$

and

$$\lambda_{2,3} = \frac{b \pm \sqrt{b^2 - 4c}}{2} \tag{6}$$

where

$$b = k_1 + k_2 + k_{-1} + k_{-2}$$

and

$$c = k_1k_{-2} + k_{-1}k_2 + k_{-1}k_{-2}$$

Substituting the summation of particular solutions into eqs 2−4, and applying initial conditions $S = S_0$, $\alpha = \beta = 0$ at $t = 0$, the general solution is obtained:

$$[\mathrm{S}] = [\mathrm{S}]_0\left[\frac{k_{-1}k_{-2}}{\lambda_2\lambda_3} + \frac{(k_{-1}-\lambda_2)(\lambda_2-k_{-2})}{\lambda_2(\lambda_3-\lambda_2)}\mathrm{e}^{-\lambda_2 t} + \frac{(k_{-2}-\lambda_3)(k_{-1}-\lambda_3)}{(\lambda_3-\lambda_2)}\mathrm{e}^{-\lambda_3 t}\right] \tag{7}$$

$$[\beta] = [\mathrm{S}]_0\left[\frac{k_1k_{-2}}{\lambda_2\lambda_3} + \frac{k_1(\lambda_2-k_{-2})}{\lambda_2(\lambda_3-\lambda_2)}\mathrm{e}^{-\lambda_2 t} + \frac{k_1(k_{-2}-\lambda_3)}{\lambda_3(\lambda_3-\lambda_2)}\mathrm{e}^{-\lambda_3 t}\right] \tag{8}$$

$$[\alpha] = [\mathrm{S}]_0\left[\frac{k_2k_{-1}}{\lambda_2\lambda_3} + \frac{k_2(k_{-1}-\lambda_2)}{\lambda_2(\lambda_2-\lambda_3)}\mathrm{e}^{-\lambda_2 t} + \frac{k_2(k_{-1}-\lambda_3)}{\lambda_3(\lambda_3-\lambda_2)}\mathrm{e}^{-\lambda_3 t}\right] \tag{9}$$

Early on in the reaction, the reaction scheme reduces to

$$\beta \overset{k_1}{\longleftarrow} \mathrm{S} \overset{k_2}{\longrightarrow} \alpha \tag{10}$$

The product α- and *β*-anomers depend only on the forward reaction rate. That is, in the early reaction, the reverse routes may be neglected, since the products of α- and *β*-anomers are not significantly accumulated to compete with the forward reaction rates. Thus, we can show that in the early stages of the reaction, the following conditions exist:

$$[S] \sim [S]_0 e^{-(k_1+k_2)t} \tag{11}$$

$$[\beta] \sim \frac{k_1[S]_0}{k_1+k_2}[1 - e^{-(k_1+k_2)t}] \tag{12}$$

$$[\alpha] \sim \frac{k_2[S]_0}{k_1+k_2}[1 - e^{-(k_1+k_2)t}] \tag{13}$$

For long-term reactions, i.e., $t \rightarrow \infty$, eqs 8 and 9 are replaced by

$$[\beta] \sim \frac{k_1 k_{-2}[S]_0}{k_1 k_{-2} + k_{-1}k_2 + k_{-1}k_{-2}} \tag{14}$$

$$[\alpha] \sim \frac{k_2 k_{-1}[S]_0}{k_1 k_{-2} + k_{-1}k_2 + k_{-1}k_{-2}} \tag{15}$$

The concentration of product is invariant, and the system reaches equilibrium. In this case, the product ratio becomes

$$\frac{[\beta]}{[\alpha]} = \frac{k_1/k_{-1}}{k_2/k_{-2}} = \frac{K_1}{K_2} \tag{16}$$

and depends only on the equilibrium constants K_1 and K_2. The process is dominated by thermodynamics, and the products are thermodynamically or equilibrium controlled.

The time evolution at different temperatures of S and α- and β-anomers is depicted in Figure 1. The rates for the reactions were arbitrarily assigned on the basis of experiments monitored every 30 min up to 3 h using stannic chloride as the catalyst. In this manner, the curves very closely fit the experimental data. The mathematical model extrapolates data beyond the 3-h time period. It can be seen from the curves that the equilibrium concentration factors are quite different from the corresponding "early stage" values. The curves demonstrate how the product composition changes with time at constant temperature. The product composition, defined as $[\beta]/[\alpha]$, is seen to remain constant at about 10 min during the early stage of reaction but then drops until it assumes a final equilibrium value between 1000 and 5000 min. The curves also show that a decrease in temperature will decrease all rate constants and correspondingly alter the equilibrium constants. The principal effect of decreasing the temperature is to increase the time taken to reach equilibrium, thereby providing a means for obtaining the kinetically controlled product β-anomer.

For example, if at a temperature of −30 °C the reaction is quenched after 10 min, then the reaction composition will be

$$[\beta] = 0.88$$

$$[\alpha] = 0.12$$

with β-anomer as the main product. During this period of time, events are controlled almost exclusively by the values of the rate constants k_1 and k_2. In these circumstances, the reactions are under kinetic control, i.e., $k_1 > k_2$.

In the final stage of the reaction, equilibrium is attained, and the final composition will be

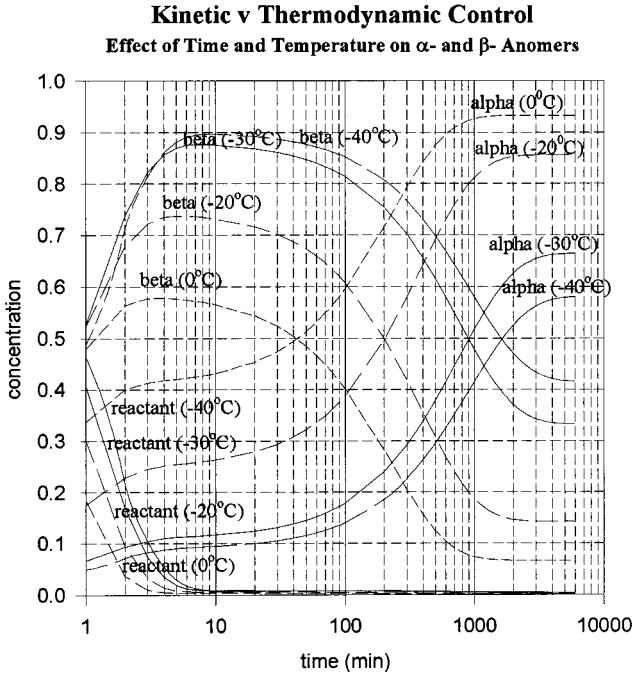

Figure 1. **Time evolution of reactant S and product α- and β-anomers at different temperatures.**

$$[\beta]_{eq} = 0.33$$

$$[\alpha]_{eq} = 0.67$$

with the α-anomer being the main product. The final state of the system is exclusively controlled by the values of the equilibrium constants K_1 and K_2, and the reactions are said to be under equilibrium or thermodynamic control, i.e., $k_2/k_{-2} > k_1/k_{-1}$.

Thus, according to the kinetic equation, the chemical system will favor the kinetic products at the early stage of the reaction and then will gradually shift to the thermodynamic products as the reaction time is increased. This requires a reversible channel connecting the reactants and products. As the concentration of the kinetic product β in reaction 1 increases, the reverse rate increases so that S will apparently produce the thermodynamic product α. Consequently, to increase β, the reverse reaction must be decreased by either removing the product β or isolating it in terms of a protective reaction. Accordingly, the β/α ratio decreases to zero as the reverse S ⇜ α is blocked. This is shown in Figure 1. In this way, either the kinetic or thermodynamic product may be controlled. The graphs in Figure 1 demonstrate that the optimum temperature for obtaining high yields of the β-anomer is between −30 and −40 °C using stannic chloride as the catalyst. The reaction time should not exceed 1.5 h. Table 2 summarizes HPLC results of experiments run at different temperatures using stannic chloride as the catalyst. In all cases, the reactions were terminated at 1.5 h with saturated $NaHCO_3$. Acid catalysis will also affect both the kinetic and thermodynamic factors of the coupling reaction by accelerating the rate constants and thereby reducing the time it takes to reach equilibrium. Complete destruction of the acid catalyst is essential for maximizing the yields of the β-anomer.

Table 2. **Effect of temperature on β-selective synthesis of 1-[3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-D-ribofuranosyl]-5-iodo-2-pyrimidinone (IPdR, 3)**

temp (°C)	β/α-anomers	% $\beta/(\alpha+\beta)$	% $(\alpha+\beta)^a$	% β^b
0	0.35/1	25.8	89.5	23.1
−20	1.56/1	60.9	88.9	54.2
−30	4.72/1	82.5	92.1	76.0
−40	6.89/1	87.4	79.3	69.3

[a] Percent of α- and β-anomers in residue. [b] Percent of β-anomer in residue.

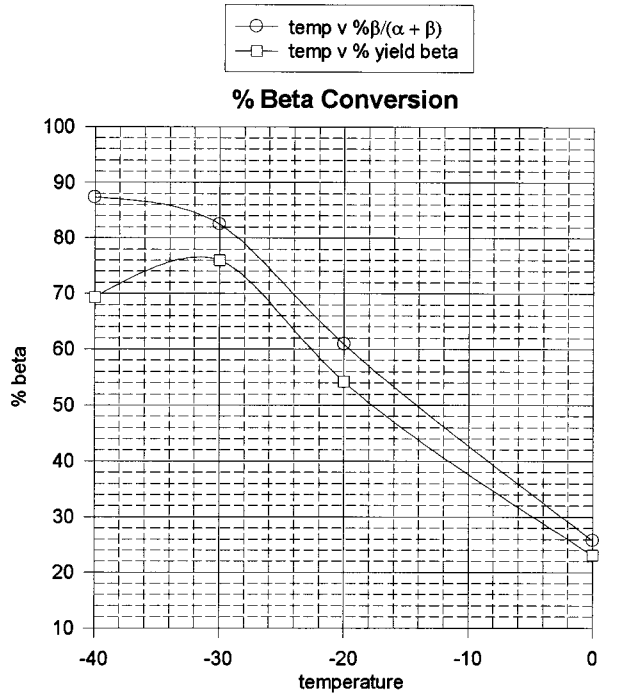

Figure 2. **Effect of temperature on β-anomer yields in IPdR.**

Table 2 shows the effect of decreasing the temperature on the β-anomer yields. The yields of β-anomer rapidly increase as the temperature is decreased. The optimum yields of β-anomer occur between −30 and −40 °C. Suprisingly, HPLC analysis indicates that almost all of the starting materials are reacted, even at −40 °C. 1,2-Dichloroethane was used as the solvent down to temperatures of −30 °C; methylene chloride was the solvent used at temperatures lower than −40 °C. An attempt was made to produce *IPdR* (**3**) at −60 °C. Only a 42% yield of the α- and β-anomers of IPdR was obtained, with 25.5% of the product being the β-anomer, approximately 33% unreacted starting materials, and the rest byproducts. Thus, at −60 °C, the reaction is incomplete and does not fit the model. The effect of temperature on yield of β-anomer is shown in Figure 2.

Experimental Section

All melting points are corrected. NMR spectra were run on a Varian VX-300 NMR. The chemical shifts are reported in parts per million (δ ppm) downfield from tetramethylsilane (TMS) which had been used as an internal standard.

Silylations. To 1.5 g (6.8 mmol) of 2-hydroxy-5-iodopyrimidine were added 15 mL of hexamethyldisilazane (HMDS) and 0.30 mL of chlorotrimethylsilane. The mixture was refluxed for 2 h (with exclusion of moisture), cooled, and concentrated in vacuo to yield a light brown oil. Removal of any remaining HMDS was accomplished with 2 × 25−50 mL of anhydrous xylene.

***β*-Selective Synthesis of 1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-D-ribofuranosyl]-5-iodo-2-pyrimidinone (IPdR, 3).** To the silylated 2-hydroxy-5-iodopyrimidine was added 50 mL of anhydrous 1,2-dichoroethane. The solution was cooled to −30 °C with stirring under a nitrogen atmosphere. The cooling bath used was an acetone−dry ice mixture. Just enough dry ice was added to the acetone to maintain a temperature between −30 and −35 °C. After the temperature was below −30 °C, 2.54 g (6.1 mmol) of the protected sugar chloride **1** was added. To the cooled solution was added dropwise a solution of 0.2 mL of $SnCl_4$ in 25 mL of anhydrous 1,2-dichloroethane while maintaining the temperature below −30 °C. Analysis by TLC (15% ethyl acetate in dichoroethane) showed that the reaction was essentially complete in 1.5 h.

Workup of IPdR. After 1.5 h, the mixture was poured into ice cold saturated $NaHCO_3$ solution (200 mL) and methylene chloride (300 mL) and stirred for 30 min to destroy all the acid catalyst. The mixture was filtered, if necessary, over Celite, the precipitate being washed 3 times with methylene chloride. The organic layer was washed with water (200 mL) and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure. Reversed-phase HPLC analysis of the residue showed that the major product was the β-anomer (82.5%), with 17.5% α-anomer (Figure 3). The pure β-anomer of IPdR (**3**) was obtained by crystallization from ethyl acetate, mp 158−160 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.59 (d, J = 3 Hz, 1H), 8.23 (d, J = 3, 1H), 8.00 (m, 4H), 7.43 (m, 4H), 6.25 (dd, J = 5.7, 2.1 Hz, 1H), 5.59 (d, J = 6.6 Hz, 1H), 4.73 (m, 1H), 3.18 (ddd, J = 1.5, 4.2, 7.5 Hz, 3H), 2.2 (m, 1H). Anal. Calcd for $C_{23}H_{17}Cl_2IN_2O$: C, 44.90; H, 2.79; Cl, 11.53; I, 20.63; N, 4.55. Found: C, 45.12; H, 2.87; I, 20.38; N, 4.38.

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