NUCLEOSIDE SYNTHESIS FROM FURANOID GLYCALS

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Abstract --- Reaction of furanoid glycals with PhSCl afforded 1-chlorosugars, which were used for condensation reaction with silylated uracil in the presence of SnCl4. These two reactions proceeded in a highly stereoselective manner.

2',3'-Dideoxynucleosides and 2',3'-didehydro-2',3'-dideoxynucleosides are known to be active compounds against HIV, which causes AIDS. To prepare these nucleosides, we have focused on the stereoselective condensation reaction between sugars and nucleic bases, since this reaction can be used to synthesize a wide variety of structurally related compounds.

In the course of this study, we have clarified the effect of the phenylthio group on sugar C-2 as a stereocontrolling element. The condensation reaction between 2-α-phenylthio-2,3-dideoxyribose (1) and silylated pyrimidine bases in the presence of SnCl4 as a catalyst afforded the anomeric mixture of nucleosides in a ratio of α : β = 1 : 9. The phenylthio group on the sugar moiety was used as a hand hold to introduce the carbon-carbon double bond of 2',3'-didehydro-2',3'-dideoxynucleosides. This method, however, has a serious disadvantage. The stereoselectivity of the phenylsulfonylation of γ-lactone...
(2) to 3, which is the starting material for 1, is rather low \((\text{trans} : \text{cis} = 2 : 1)\). 3, 4, 6 In recent years, there have been reported some instances in which the electrophilic sulfonylation reaction of glycals was used directly for the \(\Omega\)-glycosylation reaction. 7 In this paper, we report a novel and stereoselective condensation reaction between silylated uracil and furanoid glycals (4) by the aid of benzenesulfonyl chloride (PhSCI). 8

There have been two reports concerning the reaction of furanoid glycals with PhSCI used for the carbon-carbon bond formation. 9 In both cases, the existence of chlorotetrahydrofuran (similar to 5) was assumed. As 5 could be considered the equivalent of 2-phenylthio sugar (1), we at first examined the condensation reaction between 5 and silylated uracil (6). After 2,3-dihydrofuran (4a) was treated with PhSCI at \(-50^\circ\text{C}\) for 30 min to generate 5 \textit{in situ}, 9b 5 was subjected to reaction with 6 in the presence of SnCl4 as a catalyst at \(0^\circ\text{C}\) for 2 h. The condensation products (7) were isolated in the ratio of \(\text{trans} : \text{cis} = 99 : 1\) in 80% yield (Scheme 1). Although we have not determined the diastereomeric ratio of 5, \textit{trans} isomer is thought to be the major isomer when the reaction mechanism is taken into account. It was also supported that the condensation reaction without SnCl4 proceeded to give 7 in the ratio of \(\text{trans} : \text{cis} = 15 : 85\) (82% yield), under which conditions 1-chlorosugars react with 6 in \(\text{SN}_2\) mode. 2, 10

![Scheme 1.](image)

4a was also reported to react with PhSeCl to yield 8. 9a We examined the condensation reaction of 8 with 6 in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) or SnCl4 as a catalyst, since the phenyl-selenyl group on sugar C-2 was useful as the stereocontrolling element. 5 In the reaction with 8, better stereoselectivity was achieved in the presence of SnCl4 (\(\text{trans} : \text{cis} = 98 : 2\)) than with TMSOTf (\(\text{trans} : \text{cis} = 85 : 15\)). In both cases, however, the yields of the condensation products (9) were not as good (up to 38%) as those for
the reaction with PhSCI. This results could be attributed to the more radical character of PhSeCl than PhSCI, which caused the various side reactions.\textsuperscript{7c}

As a new route for nucleosides from 4a was at hand, we turned our attention to the stereoselectivity of the reaction with the substituted glycal (4b).\textsuperscript{11} The condensation reaction between silylated uracil (6) and substituted 1-chlorosugar (10),\textsuperscript{12} which was prepared \textit{in situ} from 4b and PhSCI, was performed under the same conditions as those for 4a. Three stereoisomers (11 - 13) were obtained, as indicated in Scheme 2. The ratio was determined by hplc, and the stereochemistry of each was determined by comparison with the samples previously prepared from 1 and its $\beta$-phenylthio isomer.\textsuperscript{3} It was pointed out by the ratio of 11 to 12 that stereo-selectivity in the condensation reaction between 10a and 6 was as much high as that with 1-chlorosugar (5) derived from 4a ($\alpha : \beta = 2 : 98$). It was also revealed that electrophilic addition of PhSCI to 4b proceeded unexpectedly in a highly stereoselective manner (10a : 10b = 96 : 4) when the ratio of 13 was compared to the sum of those of 11 and 12. The latter selectivity was not strongly affected by the reaction temperature. In fact, the mixture of 11 - 13 was obtained in similar ratio when the addition step of PhSCI was carried out at 0°C (11 : 12 : 13 = 94 : 3 : 3).

\begin{center}
\begin{tikzpicture}
  \node [draw, rectangle] (a) at (0,0) {4b};
  \node [draw, rectangle, fill=white] (b) at (2,0) {10a};
  \node [draw, rectangle, fill=white] (c) at (4,0) {10b};
  \node [draw, rectangle] (d) at (6,0) {6};
  \node [draw, rectangle] (e) at (8,0) {11};
  \node [draw, rectangle] (f) at (10,0) {12};
  \node [draw, rectangle] (g) at (12,0) {13};
  \node [draw, rectangle] (h) at (14,0) {U=uracil-1-yl};
  \node [draw, rectangle] (i) at (16,0) {U=uracil-1-yl};

  \draw [->] (a) -- node [above] {PhSCI} (b);
  \draw [->] (b) -- node [above] {CH\textsubscript{2}Cl\textsubscript{2}} (c);
  \draw [->] (d) -- node [above] {Me\textsubscript{3}SiO} (e);
  \draw [->] (e) -- node [above] {SnCl\textsubscript{4}} (f);
  \draw [->] (f) -- node [above] {CH\textsubscript{2}Cl\textsubscript{2} / 0\textdegree C} (g);
  \draw [->] (g) -- node [above] {Yield 80\%} (h);

  \draw [->] (i) -- node [above] {11 : 12 : 13 = 94 : 2 : 4} (j);

  \node [draw, rectangle] (j) at (18,0) {U=uracil-1-yl};

\end{tikzpicture}
\end{center}
After purification with hplc, β-nucleoside (11) was converted to protected 2',3'-didehydro-2',3'-dideoxyuridine (15) by oxidation with mCPBA followed by thermal elimination of benzenesulfenic acid (Scheme 3). In conclusion, a novel and stereoselective route for the 2-phenylthionucleosides was established. In this route, a key step is the electrophilic addition of PhSCl to furanoid glycal.

REFERENCES AND NOTES


12. The numbering system in this paper is based on that for the sugar system, except for 2,3-dihydrofuran (4a).

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