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NUCLEOSIDIC ENOL ESTERS A VERSATILE TOOL FOR THE SYNTHESIS OF 3'-CARBON-SUBSTITUTED NUCLEOSIDES

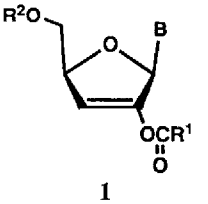
KAZUHIRO HARAGUCHI, HIROMICHI TANAKA, YOSHIHARU ITOH, AND TADASHI MIYASAKA*
School of Pharmaceutical Sciences, Showa University,
Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan

Summary Enol esters of uracil and adenine nucleosides prepared by selenoxide fragmentation of the corresponding 3'-phenylseleno derivatives have been shown to yield 3'-carbon-substituted products upon reacting with MeLi followed by electrophiles, providing the first example of the aldol reaction in this field.

For the carbon-carbon bond formation in the base moiety of nucleosides, both nucleophilic and electrophilic reactions are available and recently developed lithiation strategy constitutes a latter example of high generality.[1] In contrast to this, there has been a limited variety of methods for the introduction of carbon functionalities to the sugar portion and hence the vast majority of reports have been utilizing either the Wittig reaction[2] or nucleophilic addition using keto or aldehyde derivatives.[3] While cleavage of nucleosidic oxirane[4] and oxetane[5] with carbanions can be used in this context, no method seems to have been disclosed based on the use of carbon electrophiles. Our survey of the literature revealed that even the aldol reaction, a basic approach to construct C-C bond, has no precedent in this field, presumably due to instability of the keto derivatives under basic conditions [6]

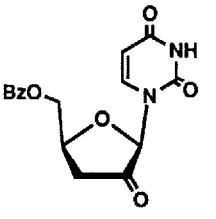
As a part of our studies aiming to devise C-C bond forming reactions applicable to nucleosides,[7] we were interested in exploiting an aldol reaction at the 3'-position, the result of which is the subject of this communication.

For the present purpose, we reasoned that enol esters of a general structure 1 would be a suitable substrate, since 2'-keto nucleosides such as 2 are susceptible to anomerization[8] and thus undesirable enolate formation is anticipated. The enol ester of uracilnucleosides can be prepared by reacting 3[9] with a phenylselenide anion followed by oxidative elimination. While the greater part of 3 was recovered when reacted with $(PhSe)_2/LiAlH_4$ (refluxing in dioxane overnight) according to our recently published method,[10-12] the use of $(PhSe)_2/NaBH_4$ (refluxing in EtOH-THF overnight) gave the desired "3'-up" selenide (4)[13] in high yield (Chart 1 isolated yields of products are shown in parentheses). Subsequent depivaloylation, regioselective silylation, and 3'-O-acylation led to 5, which was then subjected



1

B = a nucleobase
R^1 = alkyl or aryl
R^2 = a protecting group



2

Bz = Benzoyl

to selenoxide syn-fragmentation When 5 was treated with MCPBA (1.2 equiv) in CH_2Cl_2, the incipient selenoxide could not be detected but instead the enol ester was formed directly under mild conditions (at room temperature for 8 h). The enol acetate[14] derived from 5a was found to be unstable during chromatographic purification, forming the 2'-keto derivative 6 On the other hand, the bulkier acyl derivative 5b enabled isolation of the expected enol ester 7.

The generation of enolate was accomplished by treating a THF solution of 7 with MeLi at −78 °C, wherein 5 equiv of the reagent were necessary for complete disappearance of 7. It deserves a comment that the MeLi is not consumed for lithiation of the base moiety, as confirmed by deuteration.

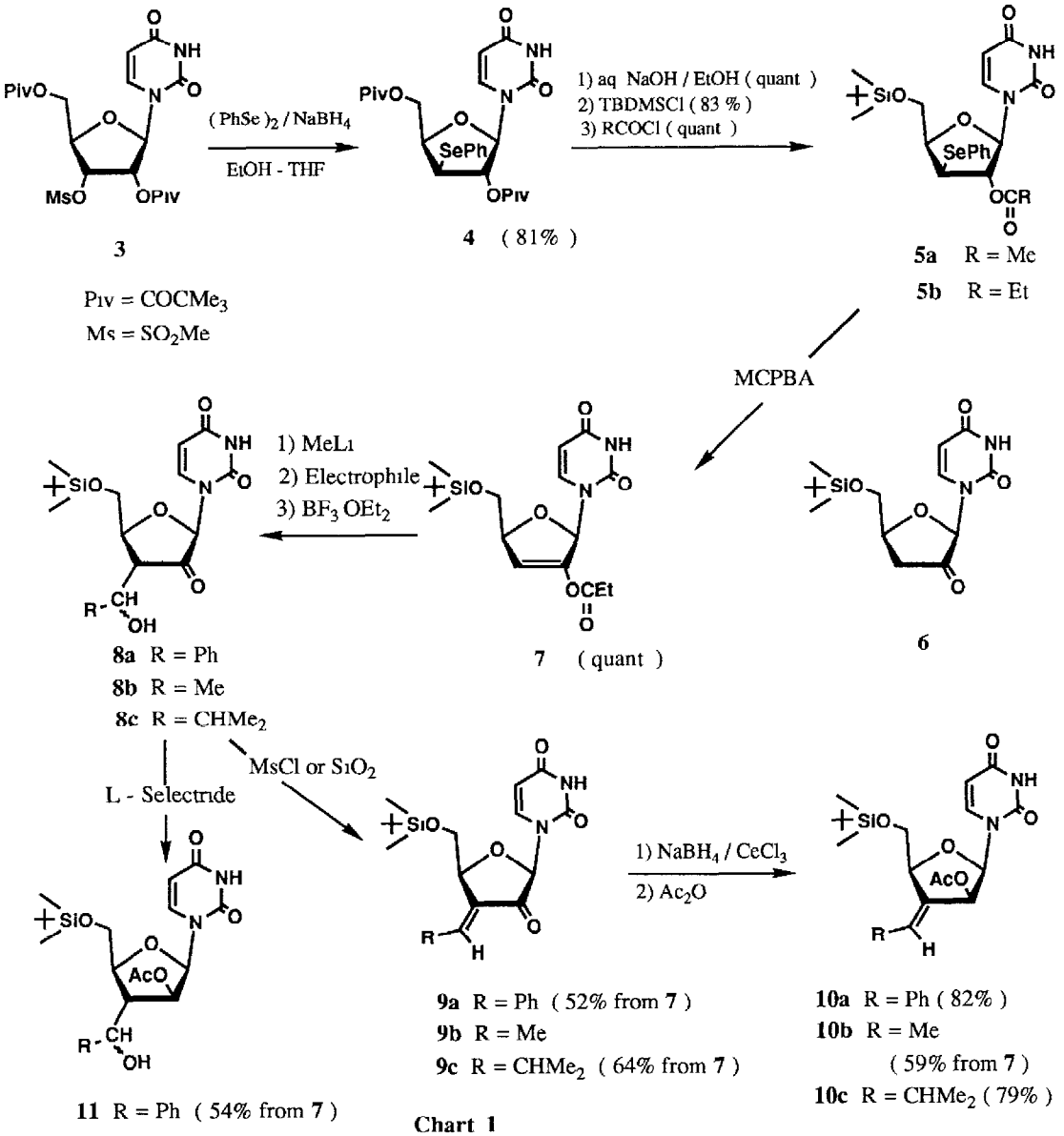
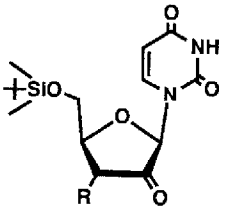


Chart 1

When PhCHO (5 equiv) was added to the enolate solution, no reaction took place but further addition of $BF_3 \cdot OEt_2$ (5 equiv) produced the corresponding aldol adduct (8a). Since 8a is prone to undergo retro aldol reaction to form 6, it was treated with MsCl/pyridine to give 9a (only the major geometrical isomers are depicted). To preclude anomerization taking place,[15] the 2'-keto function in 9a was reduced by $NaBH_4/CeCl_3$[16] in MeOH to afford 10a after acetylation.[17] It is also possible to reduce at the stage of 8a in a one-pot manner by adding a THF solution of L-Selectride® (2 5 equiv) After acetylation, 11[17] was obtained as a mixture of two diastereomers about CH(OAc)Ph.

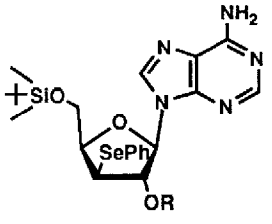
When aliphatic aldehydes (MeCHO and Me_2CHCHO) were employed as electrophiles, the aldol adducts (8b and 8c) could be dehydrated simply by passing through a silica gel column. The resulting 9b and 9c were reduced to 10b and 10c, respectively. Electrophiles other than the aldehydes, $BrCH_2CO_2Et$ and $PhCH_2Br$, also work with the reaction of the enolate, though yields of the products (12 and 13) are comparatively low During the preparation of 12 and 13, $ZnBr_2$ was used as a Lewis acid



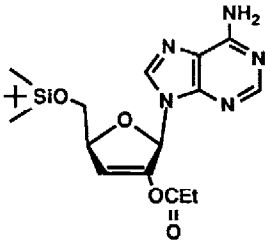
12 R = CH_2CO_2Et (43% from **7**)

13 R = CH_2Ph (9% from **7**)

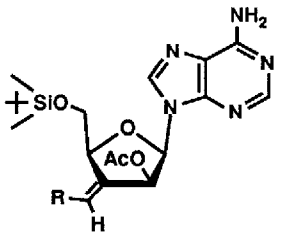
The aldol reaction can be extended to the synthesis of 3'-carbon-substituted adeninenucleosides. Preparation of the adenine counterpart of 7 was carried out starting from 9-[2,3-anhydro-5-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]adenine.[18] Regiospecific introduction of a phenylseleno group to the 3'-position was accomplished by treatment with $(PhSe)_2/LiAlH_4$ to give 14. Compound 14 was converted to 15 and then to 16 following the aforementioned sequence of reactions. Treatment of 16 with MeLi (5.5 equiv) produced the lithium enolate, which was subjected to the reaction with electrophiles, PhCHO and Me_2CHCHO, under similar conditions used



14 R = H (80%)
15 R = COEt (88%)



16 (quant)



17 R = Ph (31% from **16**)
18 R = $CHMe_2$ (33% from **16**)

for 7. The resulting aldol adducts have a higher propensity to undergo dehydration even the adduct derived from PhCHO gave the corresponding enone after silica gel column chromatography. The Luche reduction[16] of the enones and successive acetylation provided 17 and 18.

Although the reaction conditions and isolation procedure have not yet been optimized and can doubtless be improved,[19] the present study has disclosed a new C-C bond formation at the 3'-position of nucleosides, which may open a way to analogues possibly act as a chain terminator in nucleic acids biosynthesis.

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12) Under similar conditions, the corresponding 3'-mesylate with 2',5'-di-O-trityl protection gave the expected 3'-selenide in 83% yield.
13) The stereochemistry of 3 was confirmed by X-ray crystallographic analysis.
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