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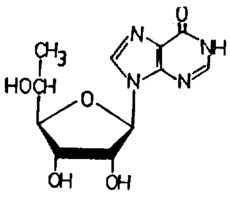
Synthesis of Chain-Extended Nucleosides

Kwan Soo Kim*, Sung Jung Kim, Jung Hee Kim, and Chi Sun Hahn

Department of Chemistry, Yonsei University, Seoul 120-749. *Received September 27, 1988*

As a group of compounds, nucleosides have few rivals in the vast realm of the natural products, with regard to diversity in biological function. A great number of synthetic nucleosides have been reported and their biological activities have been tested. Recent extensive studies on antiviral drugs have further promoted synthesis of new types of nucleosides one of which is the chain-extended nucleosides. For example, C-5′ modified nucleoside **1** strongly inhibit purine nucleoside phosphorylase.[1] Another chain-extended nucleoside **2**, which is a carboxyl analog of adenosine 5′-phosphate, is the substrate of AMP metabolizing enzymes.[2] Arabinonucleosides **3** and **4** are active against herpes simplex virus type I.[3] 4′-Homoara-C, **5**,[4] ethylenic nucleoside **6**,[5] and acetylenic nucleoside **7**[6] have also antiviral and antileukemic activities. Despite of the promising biological activities of the chain-extended nucleosides, their synthetic and biological studies are yet rather scarce compared with other types of modified nucleosides.

Herein we report the synthesis of several new chain-extended nucleosides as potential antiviral agents. We expected that heptofuranose nucleoside **8** would be readily obtained from nucleoside aldehyde **9** with ylide **10**. Suprisingly, however, Howgate and coworkers[7] have reported that no reaction occurred between **9** and **10**. We reinvestigated the reaction of **9** with **10**. Oxidation of **11** with dimethyl sulfoxide and dicyclohexylcarbodiimide afforded aldehyde **9**. Without isolation of **9**, it was allowed to react with ylide **10** for 24h at room temperature to afford pure **8** in 75% yield after chromatography. The reason for Howgate's failure to obtain **8** is not clear but we speculate that Howgate and co-workers might not detect and, therefore, could not isolate the desired produt actually generated in the reaction mixture because we found R_f value of the starting aldehyde **9** and that of the product **8** were same on the TLC plates using various eluents.



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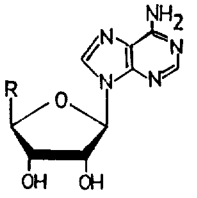
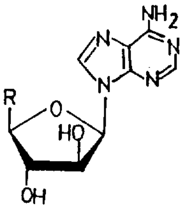
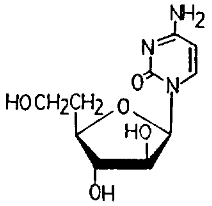


2 R=-$CH_2CH_2CO_2H$
6 R=-CH=CH_2

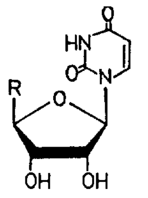


3 R=-$CH_2CH_2CH_2OH$
4 R=-$CH_2CH_2CONH_2$

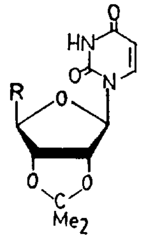


5

Hydrolysis with formic acid and subsequent catalytic hydrogenation of **8** gave another heptofuranose nucleoside **12** in 80% yield. Conversion of **8** to **13** was troublesome. Thus, reduction of **8** with lithium aluminum hydride at room temperature gave a complex mixture of products and the reaction was very slow at lower temperature. Lithium borohydride, however, nonselectively reduced **8** to **14** in 60% yield. But slow addition of DIBAL-H into the solution of **8** in THF at − 78 °C afforded **13** in 65% yield and the subsequent hydrolysis of isopropylidene group of **13** with formic acid afforded **15** in 90% yield. In order to obtain a bicyclic nucleoside **17**, lactonization of **12** under various conditions and with several reagents were attemp-

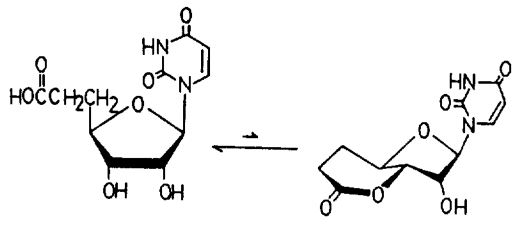


7 R=$-C{\equiv}CH$
12 R=$-CH_2CH_2CO_2Et$
15 R=$\mathrm{{}_{H}{>}C{=}C{<}^{H}_{CH_2OH}}$



8 R=$\mathrm{{}_{H}{>}C{=}C{<}^{H}_{CO_2Et}}$
9 R=$-CH{=}O$
11 R=$-CH_2OH$
13 R=$\mathrm{{}_{H}{>}C{=}C{<}^{H}_{CH_2OH}}$
14 R=$-CH_2CH_2CH_2OH$
22 R=$-CH{=}CHCH_2CH{=}CH_2$
23 R=$-CH{=}CHCH{=}C(CH_3)_2$
24 R=$-CH{=}CHPh$
25 R=$-CH{=}CHCH{=}CH_2$

Ph_3PCHR
10 R=$-CO_2Et$
18 R=$-CH_2CH{=}CH_2$
19 R=$-CH{=}C(CH_3)_2$
20 R=$-Ph$
21 R=$-CH{=}CH_2$



16 **17**

ted. We also prepared a carboxylic acid derivative, **16** by hydrolysis of **12** with potassium hydroxide in ethanol. However, lactonizations of compound **12** and **16** were not successful at all. Difficulty in lactonization of **12** and **16** should be attributable to the instability of **17** owing to the strain of the trans-fused bicyclic system.

It was not necessary to isolate aldehyde **9** from the reaction mixture in DMSO in its reaction with the stabilized ylide such as **10**. However, in the reaction with nonstabilized ylides, aldehyde **9** must be purified to some extent and thus the oxidation of **11** with DMSO-DCC is not appropriate because of difficulty in isolation of **9**. Pure **9** could be obtained in 85% yield by oxidation of **11** with chromium trioxide-pyridine complex in methylene chloride-dimethylformamide at room temperature and by precipitating **9** in benzene-hexane. The Wittig reactions of isolated **9** with ylides **18**-**21** in THF afforded chain-extended nucleosides **22**-**25** in high yields, respectively. The stereochemistry of newly generated double bonds varied with reaction condition and the ratios of the cis and trans isomers of **22**-**25** were not rigorously determined.

The results of the present work indicate that Wittig reactions employing both stabilized and nonstabilized ylides are generally applicable to synthesis of chain-extended nucleosides and that bicyclic lactone nucleoside **17** is unstable and rather exists in the carboxylic acid form, **16**. And interesting biological activities of the nucleosides synthesized in the present work are expected.

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An Improved Synthesis of Aldehydes from Carboxylic Acid Esters with Diisobutylaluminum Hydride in the Presence of *o*-Anisidine

Seong Heon Kim, Jeong Hyo Kim, and Nung Min Yoon*

Department of Chemistry, Sogang University, Seoul 121-742. *Received October 12, 1988*

The synthesis of aldehydes from carboxylic acid derivatives is one of the most important reactions in organic synthesis, and many useful reducing agents have been developed.[1] Recently thexylchloroborane-dimethyl sulfide[1a] and thexylbromoborane-dimethyl sulfide[1b] are reported to be excellent reagents for the partial reduction of carboxylic acids and their salts to the corresponding aldehydes. However only a few reagents are knwon for the transformation of carboxylic acid esters to the corresponding aldehydes. Representative metal hydrides for such purposes are diisobutylaluminum hydride[2] (DIBAH), lithium tri-*tert*-butylaluminum hydride[3] (LTBA), and bis(4-methylpiperazinyl) aluminum hydride[4,5] (BMPA). Of these reagents, LTBA reduces phenyl esters of aliphatic acids to aldehydes in yields of approximately 70%, however, can not be applied for aromatic acids. Although BMPA is effective for both aliphatic and aromatic esters, and gives 50-80% yields of aldehydes, the reaction requires the longer reaction