CHEMISTRY LETTERS, pp. 605-606, 1994.

Facile Synthesis of 5-Substituted Arabinofuranosyluracil Derivatives

Hiroaki SAWAI, Hidekazu HAYASHI, and Sumie SEKIGUCHI
Department of Chemistry, Faculty of Engineering, Gunma University, Kiryu 376

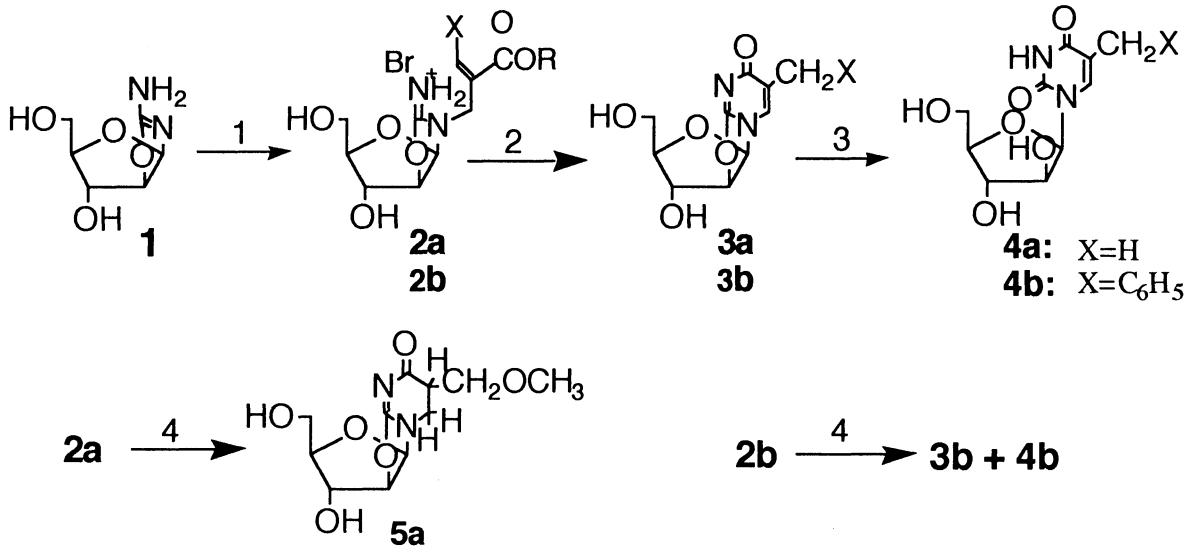
Arabinoaminooxazoline reacted readily with α-(bromomethyl)acrylate derivatives to afford the corresponding adduct. Potassium *tert*-butoxide- or sodium methoxide-catalyzed cyclization of the adduct gave 5-substituted 2,2'-anhydroarabinofuranosyluracil derivatives.

Previously, Sanchez and Orgel described a very simple synthesis of several β-arabinofuranosyl or α-ribofuranosyl cytosines and uracils from arabinoaminooxazoline or riboaminooxazoline and acetylenic compounds.[1] While this process uses no protecting group, β- or α-anomer of pyrimidine nucleosides can be obtained exclusively depending on the type of the starting sugar. Several studies have been reported on the synthesis of pyrimidine nucleosides by modification of the oxazoline method.[2] As a part of our program for the synthesis of 5-substituted pyrimidine nucleosides applicable to an antiviral agent or to a constituent of modified nucleic acids, we have explored a simple and stereoselective method for the 5-substituted pyrimidine nucleosides from arabinoaminooxazoline. Here we describe a facile synthesis of some 5-substituted uracil nucleosides from the reaction of arabinoaminooxazoline with α-(bromomethyl)acrylate derivatives.

The starting arabinoaminooxazoline **1** was prepared from D-arabinose and cyanamide in 96% yield by the modified procedure of the published method.[1] Reaction of **1** (1.0 g, 5.74 mmol) and ethyl α-(bromomethyl)acrylate[3] (1.87 g, 9.69 mmol) in dimethylacetamide (5 ml) at room temperature gave the adduct **2a**[4] (2.0 g, 95%). The adduct was isolated as white precipitates by pouring the reaction mixture into a dichloromethane-hexane solution with stirring. In a similar way, the adduct **2b** was obtained from **1** and methyl α-(bromomethyl)cinnamate[5] in 93% yield.

We found that potassium *tert*-butoxide-mediated cyclization of the adduct gave the target nucleosides. A solution of potassium *tert*-butoxide (15.3 mmol) and the adduct **2a** (1.7 g, 4.6 mmol) in *tert*-butanol (30 ml) was stirred for 20 h at 25 °C. The products were purified by silica gel column chromatography using 15% methanol-dichloromethane as an eluent to give 2,2'-anhydro-β-arabinofuranosylthymine (**3a**)[6] (354 mg, 32 %) and β-arabinofuranosylthymine (**4a**)[6] (163 mg, 14%). The compound **4a** was formed by hydrolysis of **3a** during the work up. Hydrolysis of **3a** with 1 M aqueous ammonia at 70 °C for 14 h afforded **4a** quantitatively. Similarly, treatment of **2b** with potassium *tert*-butoxide gave **3b** and **4b** in 7% and 18% yields, respectively.

Sodium methoxide also promoted cyclization of **2a** in methanol at room temperature, but in a different way. Sodium methoxide probably catalyzed the Michael-type addition of methanol to the olefinic double bond of **2a**, followed by cyclization to a new nucleoside **5a**[7] in 53% yield. On the other hand, **3b** and **4b** were obtained by sodium methoxide-mediated cyclization of **2b** in 30 and 11% yields, respectively.



1, $H_2C=C(CH_2Br)COOEt$ (**a**) or $PhHC=C(CH_2Br)COOMe$ (**b**); 2, *t*-BuOK; 3, NH_4OH; 4, MeONa

In conclusion, 5-substituted anhydro-nucleosides **3** were prepared steroselectively in a short reaction step without using any protecting group, though the yield of the cyclization step was moderate. The starting α-(bromomethyl)acrylate derivatives were synthesized from methyl acrylate and the corresponding aldehydes easily.[3,5] The anhydro-nucleoside **3** is considered to be a useful intermediate for the synthesis of 2'-deoxyribofuranosyl-, 2'-substituted-2'-deoxyribofuranosyl- and ribofuranosyl-5-substituted uracils, as in the case of uracil nucleosides.[8] The application of this approach for the synthesis of other 5-substituted pyrimidine nucleosides is now under progress.

References

1) R. A. Sanchez and L. E. Orgel, J. Mol. Biol., **47**, 531 (1970); D. H. Shannahoff and R. A. Sanchez, J. Org. Chem., **38**, 593 (1973).
2) C. M. Hall, G. Slomp, S. A. Mizsak, and A. J. Taylor, J. Org. Chem., **37**, 3290 (1972); A. Holy, Tetrahedron Lett., **1971**, 189; E. J. Hessler, J. Org. Chem., **41**, 1828 (1976); C. W. Murtiashaw, Eur. Pat. Appl. EP., 351126 (1990); Chem. Abstr., **113**, 41229b (1990); E. Abushanab and C. Vargeese, U. S. Patent, 5077403 (1991); Chem. Abstr., **116**, 194801u (1992); C. Vargeese and E. Abushanab, Nucleosides & Nucleotides, **11**, 1549 (1992).
3) J. W. Williers and H. Rambaud, Org. Syn., **66**, 220 (1987); S. E. Drewes, G. Loizou, and G. R. P. Roos, Syn. Commun., **17**, 291 (1987).
4) **2a**: mp:150-151.5°. ^{1}H-NMR(D_2O) 6.54, 6.12(2H, 2s, $=CH_2$), 6.06(1H, d, 1'-H), 5.34(1H, d, 2'-H), 4.58(1H, d, 3'-H), 4.39(2H, s, NCH_2-), 4.28(1H, m, 4'-H), 4.26(2H, q, $-CH_2$-), 3.59(2H, d, 5'-H), 1.31(3H, t, CH_3). MS(FD) *m/z* 287(M-Br).
5) F. Ameer, S. E. Drewes, N. D. Emslie, P. T. Kaye, and R. L. Mann, J. Chem. Soc., Perkin Trans. 1, **1983**, 2293.
6) I. L. Doerr, J. F. Codington, and J. J. Fox, J. Med. Chem., **10**, 247(1967).
7) **5a**: ^{1}H-NMR(D_2O) 6.07(1H, d, J = 5.3 Hz, 1'-H), 5.32(1H, d, 2'-H), 4.57(1H, s, 3'-H), 4.32(1H, m, 4'-H), 3.92-3.50(6H, m, OCH_2-, 5'-H, 6-CH_2-), 3.38(3H, s, OCH_3), 3.14-2.98(1H, m, 5-H). MS(FD) *m/z* 273(MH^+).
8) T. Ueda, "Chemistry of Nucleosides and Nucleotides," ed by L. B. Townsend, Plenum Press, New York (1984), p. 1; J. F. Codington, I. L. Doerr, and J. J. Fox, J. Org. Chem., **29**, 558 (1964).

(Received November 18, 1993)