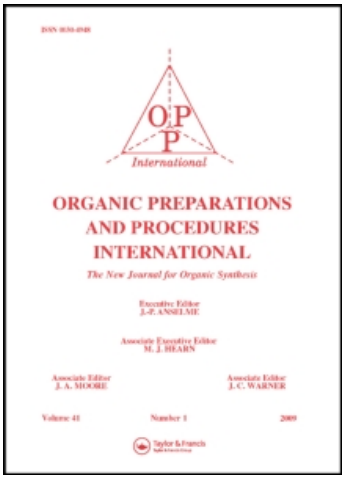


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A HIGHLY SELECTIVE EPOXY CLEAVAGE OF 1-(5'-*O*-BENZOYL-2',3'-EPOXY-β-D-LYXOSYL)URACIL WITH PYRIDINE HYDROCHLORIDE

Tadashi Sasaki[a]; Katsumaro Minamoto[a]; Naoto Kidokoro[a]
[a] Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Nagoya, Japan

To cite this Article Sasaki, Tadashi , Minamoto, Katsumaro and Kidokoro, Naoto(1973) 'A HIGHLY SELECTIVE EPOXY CLEAVAGE OF 1-(5'-*O*-BENZOYL-2',3'-EPOXY-β-D-LYXOSYL)URACIL WITH PYRIDINE HYDROCHLORIDE', Organic Preparations and Procedures International, 5: 2, 75 — 80
To link to this Article: DOI: 10.1080/00304947309356470
URL: http://dx.doi.org/10.1080/00304947309356470

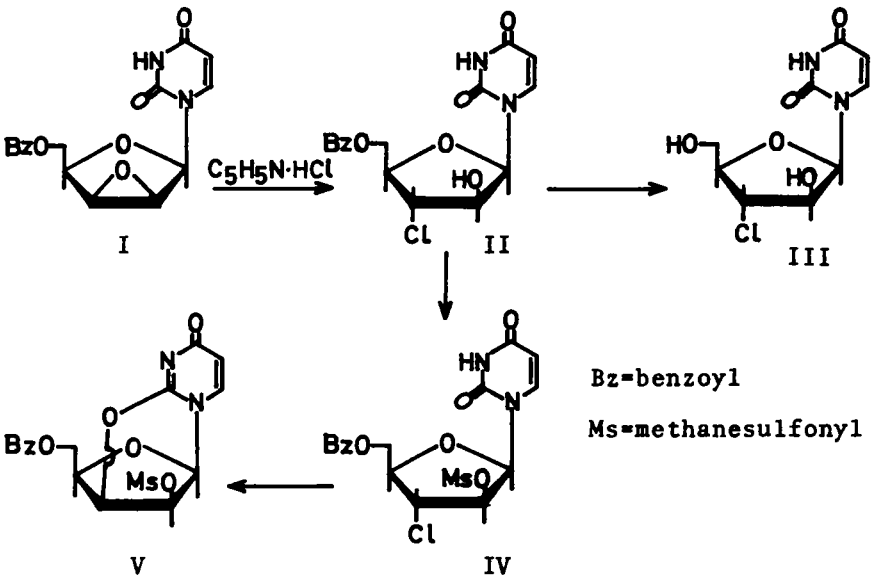
ORGANIC PREPARATIONS AND PROCEDURES INT. 5(2), 75-80 (1973)

A HIGHLY SELECTIVE EPOXY CLEAVAGE OF 1-(5'-*O*-BENZOYL-2',3'-EPOXY-β-D-LYXOSYL)URACIL WITH PYRIDINE HYDROCHLORIDE.

Tadashi Sasaki, Katsumaro Minamoto and Naoto Kidokoro

Institute of Applied Organic Chemistry,
Faculty of Engineering, Nagoya University,
Furo-cho, Chikusa-ku, Nagoya, Japan.

It is well known that in 2',3'-epoxy-β-D-lyxosyl nucleosides, the 3'-position is more vulnerable to the attack of nucleophiles, thus yielding 3'-substituted-β-D-arabinosyl nucleosides as main products with minor or trace amounts of their xylo isomers.[1-5] In this connection, Fox and co-workers



obtained 1-(3'-chloro-3'-deoxy-β-D-arabinosyl)uracil (III) in 67% yield from 1-(2',3'-epoxy-β-D-lyxosyl)uracil by treatment with aqueous hydrochloric acid.[6] We now describe a highly selective epoxy ring cleavage of 1-(5'-*O*-benzoyl-2',3'-epoxy-β-D-lyxosyl)uracil (I),[1] with the use of pyridine hydrochloride as a nucleophile, to give 1-(5'-*O*-benzoyl-3'-chloro-3'-deoxy-β-D-arabinosyl)uracil (II) in nearly quantitative yield.

Reaction of excess pyridine hydrochloride on I gave a monochlorinated compound II, the NMR spectrum of which exhibited the anomeric proton signal at 6.25 ppm as a doublet ($J_{1',2'}$ = 4.0 Hz), while the signals of H_2, H_5, merged in a broad multiplet. Compound II resisted atmospheric pressure reduction (H_2/Pd-C) to the known 1-(3-deoxy-β-D-*threo*-pentofuranosyl)uracil,[7] while hydrogenation in the presence of triethylamine gave 1-(3'-chloro-3'-deoxy-β-D-arabinosyl)-uracil (III),[6] the independent synthesis of which was abandoned for the sake of economy of material. Although structure II appeared to be evident on the basis of the coupling constant of the anomeric proton, 2'-hydroxyl was mesylated to cause a down-field shift of the H_2-signal for a more convincing structural assignment. The NMR spectrum of IV exhibited the expected doublet of doublets at 5.29 ppm ($J_{1',2'}$ = 4.8 Hz, $J_{2',3'}$ = 3.5 Hz, $H_{2'}$), which was distinctly separated from the signal envelope of $H_{3'}$, $H_{4'}$ and $H_{5'}$. Treatment of IV with excess sodium acetate gave 2,3'-anhydro-1-(5'-*O*-benzoyl-2'-*O*-mesyl-β-D-arabinosyl)uracil (V), the structure of which was supported by its UV spectrum (see

the experimental part) and the elimination of a molecule of hydrogen chloride instead of methanesulfonic acid in the anhydro-bridge formation.

The use of pyridine hydrochloride in the nucleophilic ring-opening of I thus represents an example of the promising use of mineral acids in their buffered forms which would preclude numerous side reactions expected in the nucleophilic reactions of nucleoside derivatives.

EXPERIMENTAL

All the melting points are uncorrected. The UV spectra were measured on a JASCO Model ORD/UV-5 spectrophotometer. The NMR spectra were recorded with a JNM C-60 HL spectrometer, TMS being used as an internal standard. WAKOGEL B-5 silica gel, supplied by the WAKO Pure Chemical Industries, LTD., was used for thin layer chromatography.

1-(5'-*O*-Benzoyl-3'-chloro-3'-deoxy-β-D-arabinosyl)uracil (II). —Compound I (470 mg, 1.42 mmol) and pyridine hydrochloride (1.1 g, 9.55 mmol) were combined in anhydrous pyridine (34 ml) and the mixture was heated to reflux for 3 hrs. After cooling, the solvent was evaporated *in vacuo*, and the residue was taken up in chloroform (60 ml). The chloroform solution was washed with dil. ammonia or sodium bicarbonate solution, and then with water with cooling. The solution was dried over sodium sulfate and concentrated to give a semi-solid residue, which was crystallized twice from methanol to colorless needles (470 mg, 90%), mp 234-235°; λ_{max}^{MeOH} nm (ε) 227 (15000) and 259 (10600); NMR ($CDCl_3$) δ 3.70 (1H, br. s, OH, D_2O-exchangeable), 4.18-4.92 (5H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$ and $2H_{5'}$), 5.37 (1H, d, $J_{5,6}$= 8.0 Hz, H_5), 6.25 (1H, d, $J_{1',2'}$= 4.0 Hz, $H_{1'}$), 7.4-8.6 (6H, m, Ph and H_6) and 10.65 (1H, br. s, NH).

Anal. Calcd. for $C_{16}H_{15}N_2O_6Cl$: C, 52.40; H, 4.12; N, 7.64. Found: C, 52.54; H, 4.16; N, 7.71.

1-(3'-Chloro-3'-deoxy-β-D-arabinosyl)uracil (III).—A solution of II (310 mg, 0.83mmol) in methanol (30 ml), containing triethylamine (0.24 ml), was shaken with 6% palladium on charcoal (200 mg) under hydrgen overnight. The catalyst was filtered and the filtrate was evaporated *in vacuo* to a paste, which was submitted to preparative thin layer chromatography with the use of silica gel and a mixed solvent, chloroform: ethyl acetate (1:2, v/v) to give 75 mg (33.8%) of practically pure crystals (III) which melted at 175-176° after recrystallization from acetone, lit.[7] mp 178-179°; λ_{max}^{MeOH} 259 nm (ε 9300); NMR ($CDCl_3$ + DMSO) δ 3.86 (2H, br. s, $2H_{5'}$), 3.99-4.59 (5H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$, 5'-OH and 2'-OH), 5.37 (1H, d, $J_{5,6}$= 8.0 Hz, H_5), 6.25 (1H, d, $J_{1',2'}$= 4.0 Hz, $H_{1'}$), 7.4-8.6 (6H, m, Ph and H_6) and 10.65 (1H, br. s, NH).

Anal. Calcd. for $C_9H_{11}N_2O_5Cl$: C, 41.16; H, 4.22; N, 10.66. Found: C, 41.33; H, 4.24; N, 10.81.

1-(5'-*O*-Benzoyl-3'-chloro-3'-deoxy-2'-*O*-mesyl-β-D-arabinosyl) uracil (IV).—To a stirred ice-cold solution of II (367 mg, 1 mmol) in anhydrous pyridine (6 ml) was added methanesulfonyl chloride (0.48 ml, 6 mmol) and the mixture was left at 0° for 2 days. The mixture was treated with methanol (1 ml) at room temperature for 30 min, and evaporated *in vacuo* to give a paste, which was dissolved in methanol (5 ml) and poured into ice-water (100 ml) with vigorous stirring. The precipitate was filtered, washed with water and dried by

pressing on a porous plate. Repeated crystallization from chloroform gave 240 mg (54%) of fine needles of mp 139.5-140°. λ_{max}^{MeOH} nm (ε) 227 (11200) and 259 (7800); NMR ($CDCl_3$ + DMSO) δ 2.90 (3H, s, mesyl), 4.27-4.68 (4H, m, $H_{3'}$, $H_{4'}$ and $2H_{5'}$), 5.29 (1H, dd, $J_{1',2'}$ = 4.8 Hz, $J_{2',3'}$ = 3.5 Hz, $H_{2'}$), 5.50 (1H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.17 (1H, d, $J_{1',2'}$ = 4.8 Hz, $H_{1'}$), 7.27-8.0 (6H, m, Ph and H_6) and 10.07 (1H, br. s, NH).

Anal. Calcd. for $C_{17}H_{17}N_2O_8SCl$: C, 45.90; H, 3.85; N, 6.30. Found: C, 46.04; H, 3.74; N, 6.27.

2,3'-Anhydro-1-(5'-*O*-benzoyl-2'-*O*-mesyl-β-D-lyxosyl)uracil (V). —A mixture of IV (100 mg, 0.225 mmol) and sodium acetate (120 mg, 1.47 mmol) in N,N-dimethylformamide (12 ml) was stirred at 100-105° for 1 hr. The reaction mixture was evaporated *in vacuo* to a thick gum, which was dissolved in methanol (5 ml) and poured into ice-water (100 ml) with stirring. The precipitated product was filtered and the fitrate was concentrated to *ca.* 20 ml, whereupon another crop of product was obtained. The combined product was air-dried and repeatedly crystallized from acetone to give 36 mg (39.5%) of colorless needles (V), mp 213-215°; λ_{max}^{MeOH} nm (ε) 227 (22500) and 250 (8200, inflection).

Anal. Calcd. for $C_{17}H_{16}N_2O_8S$ + 1/2 CH_3COCH_3: C, 50.80; H, 4.38; N, 6.40. Found: C, 50.77; H, 4.41; N, 6.40.

REFERENCES

1. J. F. Codington, R. Fecher, and J. J. Fox, J. Org. Chem., 27, 163 (1962).

2. W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, J. Am. Chem. Soc., 82, 2648 (1960).

3. A. P. Martinez, W. W. Lee, and L. Goodman, J. Org. Chem., 31, 3263 (1966).

4. W. W. Lee and A. P. Martinez, *ibid.*, 32, 2538 (1967).

5. M. Hirata, Chem. Pharm. Bull.(Tokyo), 16, 291 (1968).

6. R. J. Cushly, J. F. Codington, and J. J. Fox, Can. J. Chem., 46, 1131 (1968).

7. J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, J. Org. Chem., 31, 205 (1966).

(Received April 8, 1973; in revised form May 14, 1973)