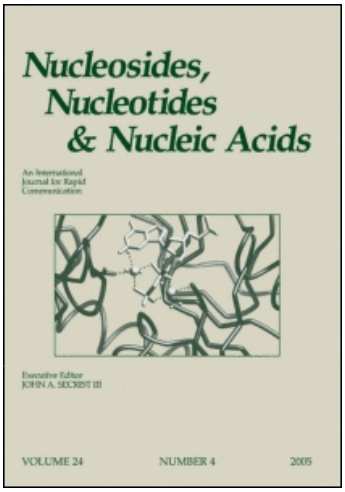

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INTRODUCTION OF AN AZIDO GROUP TO THE C-6 POSITION OF URIDINE BY THE USE OF A 6-IODOURIDINE DERIVATIVE

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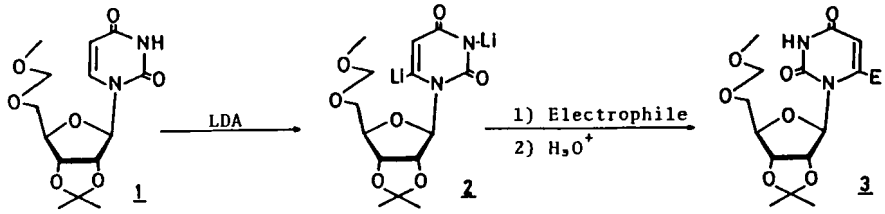
Abstract: Nucleophilic addition-elimination reaction of azide ion to 6-iodo-2',3'-O-isopropylidene-5'-O-methoxymethyluridine proceeded under mild conditions to give a 6-azidouridine derivative.

Recently, we have reported a series of papers on the lithiation of nucleosides which furnished a general access to the modification of their base moieties.[1-5] 6-Substituted uridines, which have thus far been difficult to synthesize, are now easily accessible by our method, the lithiation of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (1) with LDA (lithium diisopropylamide) and subsequent reactions of 2 with electrophiles (Chart 1).[1]



1 2 3

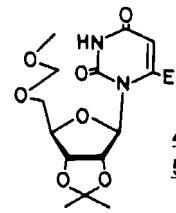
Chart 1

 0732-8311/85/0405-0607$3.50/0

Although 2 reacts with a wide range of electrophiles, introduction of an azido group to the C-6 position cannot be accomplished by this method.[6)]

In this paper, we would like to report on the preparation of 6-azidouridine, which could serve as a tool to elucidate nucleic acid-protein interactions and as an important intermediate to construct heterocyclic structures upon irradiation.[7)]

Despite the reported intramolecular cycloaddition-elimination reaction of 5'-azido-5'-deoxy-2',3'-O-isopropylidene-5-bromouridine,[8)] 5-bromouridine itself is inert toward external azide ion.[9)] On the other hand, a uridine derivative bearing a suitable leaving group at the C-6 position may be highly susceptible to the reaction of a nucleophile, as shown earlier in the case of 6-phenylthiouridine and its derivatives.[10)]



4 E= SPh
5 E= SePh

We examined the reactions of azide ion with 6-phenylthio, 6-phenylseleno, and 6-iodo derivatives of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine. These starting materials (4-6) were prepared in 76-83% yields by treatment of 2 with the corresponding electrophiles, diphenyl disulfide, diphenyl diselenide, and iodine.

The reaction of 4 with sodium azide (in DMF, at room temperature, overnight) gave an intractable mixture of products wherein a small amount of light-sensitive product was detected. This was also the case when 6-phenylseleno derivative (5) was employed as a starting material. The use of 6-iodo-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (6)[11)] appeared to effect the high-yield introduction of azido group to the C-6 position. Thus, treatment of 6 with 1.1 eq of sodium azide in DMF at room temperature for 1 h furnished 6-azidouridine derivative (7) in 90% yield after short column chromatography on silica gel. The presence of the azido group in 7 was clear from its IR spectrum (ν 2130 cm^{-1}). PMR ($CDCl_3$:

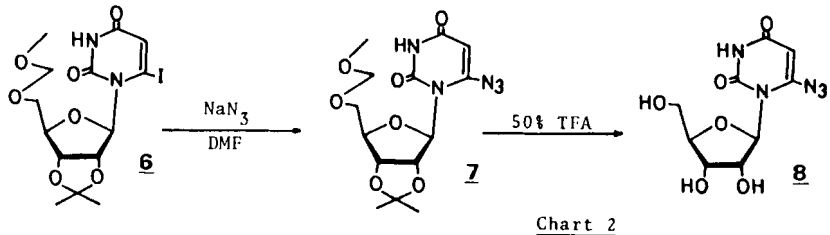


Chart 2

δ 5.52, H-5; δ 6.11, H-1'; δ 9.96, NH) and MS (M+1: m/z 370, M^+: m/z 369, M-Me: m/z 354, B+1: m/z 153) spectra were also in good agreement with the structure of 7.

Concurrent deprotection of the isopropylidene and methoxymethyl groups was carried out in 50% aqueous trifluoroacetic acid (TFA) at room temperature without any appreciable side reaction to afford 6-azidouridine (8) as crystals (mp 174-176 °C) in 89% yield.

Photochemical reactions of 7 and 8 are presently under investigation.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. PMR spectra were measured with an appropriate internal standard of TMS (tetramethylsilane) or DSS (sodium-2,2-dimethyl-2-silapentane 5-sulfonate), with a JEOL JNM-FX 100 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV and IR spectra were recorded on a Shimadzu UV-240 and a JASCO IRA-I spectrophotometers, respectively. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by diphenylacetic acid in THF. THF was distilled from sodium benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). TLC was performed on silica gel (precoated silica gel plate F_{254}, Merck).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (4)—— For the preparation and physical data of 4: see reference 1.

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-(phenylselenenyl)uridine (5)—— LDA (15.1 mmol) in THF (30 ml) was placed in a three-necked flask equipped with a gas inlet adaptor, thermometer and rubber septum. To this, a solution of 1 (2.0 g, 6.1 mmol) in THF (20 ml) was added, under positive pressure of dry argon, at a rate such that the temperature did not exceed -70 °C. After the mixture was stirred for 1 h, a THF (15 ml) solution of diphenyl diselenide (3.8 g, 15.1 mmol) was added, while maintaining the temperature below -70 °C. The reaction mixture was stirred for 1 h, quenched with AcOH (0.9 ml), and evaporated to dryness. The residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and evaporated to give 5 (2.3 g, 79%) as a solid. Crystallization from acetone-hexane gave an analytical sample (mp 139-140 °C). Anal. Calcd. for $C_{20}H_{24}N_2O_7Se$: C, 50.02; H, 4.95; N, 5.92. Found: C, 49.82; H, 5.00; N, 5.79. MS m/z: 483 (M^+), 267 (B+1). UV absorption in MeOH: max 286 nm (ε 9000) and 271 nm (ε 8600), min 277 nm (ε 8200) and 250 nm (ε 5100). PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.59 (3H, s, isop.Me), 3.37 (3H, s, CH_2OCH_3), 3.69-3.87 (2H, m, CH_2-5'), 4.19-4.42 (1H, m, H-4'), 4.67 (2H, s, CH_2OCH_3), 4.88 (1H, dd, H-3'), 5.18 (1H, d, H-5), 5.24 (1H, dd, H-2'), 5.91 (1H, d, J= 1.5 Hz, H-1'), 7.34-7.73 (5H, m, Ph), 9.23 (1H, br, NH).

6-Iodo-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (6)—— This compound was prepared by the procedure for the conversion of 1 to 5. The following amounts of reagents and 2.87 g (8.7 mmol) of 1 in THF (20 ml) were used: LDA (22.0 mmol) in THF (100 ml), iodine (5.7 g, 19.0 mmol as I_2). The iodination reaction was continued for 1.5 h below -70 °C. Short column chromatography (1% EtOH in $CHCl_3$) on silica gel gave 6 (3.04 g, 76%) which was crystallized

from acetone-hexane (mp 204-205 °C). Anal. Calcd. for $C_{14}H_{19}N_2O_7I$: C, 36.92; H, 4.33; N, 6.49. Found: C, 37.02; H, 4.22; N, 6.17. MS m/z: 455 (M+1), 439 (M-Me). UV absorption in MeOH: max 267 nm (ε 9100), min 237 nm (ε 4400). PMR ($CDCl_3$) δ: 1.35 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 3.36 (3H, s, $CH_2OC\underline{H}_3$), 3.74 (2H, m, CH_2-5'), 4.30 (1H, m, H-4'), 4.66 (2H, s, $C\underline{H}_2OCH_3$), 4.85 (1H, dd, H-3'), 5.18 (1H, dd, H-2'), 6.13 (1H, d, J= 1.5 Hz, H-1'), 6.44 (1H, d, H-5), 9.23 (1H, br, NH).

6-Azido-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (7)—— To 460 mg (1.0 mmol) of 6 in DMF (2.5 ml) was added 72 mg (1.1 mmol) of NaN_3, and the mixture was stirred at room temperature for 1 h, while protecting from light. The reaction mixture was taken up into EtOAc and washed with aqueous NaCl. The organic layer was dried with Na_2SO_4, evaporated and chromatographed on a silica gel column (1% EtOH in $CHCl_3$) to give 7 (337 mg, 90%) as foam. MS m/z: 370 (M+1), 369 (M^+), 354 (M-Me), 153 (B+1). IR (KBr) cm^{-1}: 2130 ($-N_3$). PMR ($CDCl_3$) δ: 1.34 (3H, s, isop.Me), 1.56 (3H, s, isop.Me), 3.36 (3H, s, $CH_2OC\underline{H}_3$), 3.57-3.87 (2H, m, CH_2-5'), 4.14-4.34 (1H, m, H-4'), 4.65 (2H, s, $C\underline{H}_2OCH_3$), 4.85 (1H, dd, H-3'), 5.15 (1H, dd, H-2'), 5.52 (1H, s, H-5), 6.11 (1H, d, J= 1.0 Hz, H-1'), 9.96 (1H, br, NH).

6-Azidouridine (8)—— Compound 7 (235 mg) in 50% TFA (4 ml) was stirred at room temperature overnight with protection from light. The reaction mixture was evaporated and the resulting residue was chromatographed on a silica gel column (5-6% EtOH in $CHCl_3$) to give 8 (161 mg, 89%), which was crystallized from EtOH (mp 174-176 °C). Anal. Calcd. for $C_9H_{11}N_5O_6$: C, 38.02; H, 3.82; N, 24.56. Found: C, 37.90; H, 3.89; N, 24.56. UV absorption in MeOH: max 285 nm (ε 10300), min 246 nm (ε 1800). IR (KBr) cm^{-1}: 2140 ($-N_3$). PMR (D_2O) δ: 3.62-4.01 (3H, m, CH_2-5' and H-4'), 4.39 (1H, t, H-3'), 4.74 (1H, dd, H-2'), 5.73 (1H, s, H-5), 6.03 (1H, d, J= 3.4 Hz, H-1').

REFERENCES

1) H. Tanaka, H. Hayakawa, and T. Miyasaka, Tetrahedron, 38, 2635 (1982).
2) H. Tanaka, Y. Uchida, M. Shinozaki, H. Hayakawa, A. Matsuda, and T. Miyasaka, Chem. Pharm. Bull., 31, 787 (1983).
3) H. Tanaka, H. Hayakawa, S. Iijima, K. Haraguchi, and T. Miyasaka, Tetrahedron, 41, 861 (1985).
4) H. Hayakawa, H. Tanaka, and T. Miyasaka, Tetrahedron, 41, accepted for publication.
5) H. Tanaka, M. Hirayama, A. Matsuda, T. Miyasaka, and T. Ueda, Chem. Lett., 1985, accepted for publication.
6) Although tosyl azide serves as a $^{+}NH_2$ synthetic equivalent reagent in the reaction of organolithium compounds, no reagent to introduce azido group has been known.
7) S. Senda, K. Hirota, T. Asao, and K. Maruhashi, J. Am. Chem. Soc., 100, 7661 (1978) and references cited therein.
8) T. Sasaki, K. Minamoto, T. Suzuki, and T. Sugiura, J. Org. Chem., 44, 1424 (1979).
9) T. Sasaki, K. Minamoto, M. Kino, and T. Mizuno, J. Org. Chem., 41, 1100 (1976).
10) H. Tanaka, S. Iijima, A. Matsuda, H. Hayakawa, T. Miyasaka, and T. Ueda, Chem. Pharm. Bull., 31, 1222 (1983).
11) H. Tanaka, A. Matsuda, S. Iijima, H. Hayakawa, and T. Miyasaka, Chem. Pharm. Bull., 31, 2164 (1983).

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