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A FACILE ONE-POT SYNTHESIS OF 2,3′-ANHYDRO-2′-DEOXYURIDINES *via* 3′-*O*-IMIDAZOLYLSULFONATES

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ABSTRACT: Continued interests in the novel synthetic methods of the pivotal compound, 2,3′-anhydro-2′-deoxyribonucleosides (**7**) uncovered a facile one-pot conversion of **5** with 1,1′-sulfonyldiimidazole in basic conditions to **7** with almost quantitative yields (91-99 %).

For the transformation of 3′-OH of 2′-deoxyuridines (**4**) to biologically active functional moieties such as azido or fluoro, and dehydroxylation of 3′-OH to 2′,3′-dideoxy-2′,3′-didehydrouridines 2,3′-anhydro-2′-deoxyuridines (**7**) have been regarded as the inevitable intermediates.[1] For this pivotal intermediate **7**, synthetic methods such as 1) the classical methods of 3′-*O*-mesylate,[2] or 3′-iodo,[3] 2) reactions of 3′-OH with DAST or its anolog,[4] 3) reactions by way of 3′,5′-cyclic phosphate[5] or 3′,5′-cyclic sulfite,[6] or 4) one-step conversion with Mitsunobu type reaction[7] have been reported until recently. Our previous interest

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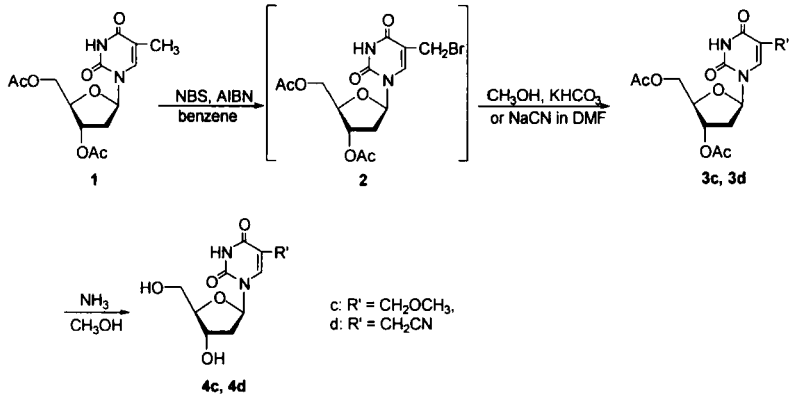
in the novel synthetic methods of 2,3′-anhydrothymidine were also reported in a communication[8] that the 3′-*O*-imidazolethiocarbonate to be the moderate to good leaving group under thermal or base-promoted conditions through the model compound of 5′-*O*-TBDMS-3′-*O*-(1*H*-imidazole-1-thiocarbonyl)thymidine. However, most of the recent synthetic methods were not compatible with the classical method of 3′-*O*-mesylate[2] due to low yields or expensive reagents. Therefore, we continued our efforts in searching for facile and practical methods to prepare 2,3′-anhydro-2′-deoxyuridines (**7**) including 2,3′-anhydrothymidine (**7b**) as an intermediate for the preparation of AZT and D4T, the reverse transcriptase inhibitors of HIV in clinical use.[1]

Application of the imidazolylsulfonate known by Hanessian, S. and Vatèle, J.-M.[9] as an effective and versatile leaving group to be complimentary to *O*-triflate in displacement reactions to the 5′-*O*-protected-5-(substituted)-2′-deoxyuridines (**5**) gave almost quantitative yields of 2,3′-anhydrouridines (**7**) in one-pot reaction with easy work-up process. We now we wish to report our preliminary results in this communication.

Preparations of 5-(methoxymethyl)-2′-deoxyuridine (**4c**) or 5-(cyano-methyl)-2′-deoxyuridine (**4d**) were done through 5-(bromomethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**2**) (Scheme 1). Selective monobromination of 3′,5′-di-*O*-acetyl-2′-deoxyuridine (**1**) was carried out with NBS and AIBN in refluxing benzene instead of the reported photo reactions of bromine in carbon

Scheme 1.

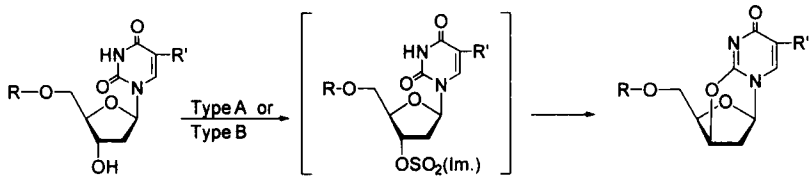


tetrachloride.[10] This modified radical bromination with NBS came out to be an effective method not only because of easy work-up process including hot filtration of succinimide followed by evaporation of the solvent, benzene, but also the selective monobromination (90–94 % yield of monobromo product **2** relative to the reported 78 % of photo reaction[10]). The yield of monobrominated product **2** was based on the integrations at 3.92 ppm for 5-CH_2Br and 6.35 ppm for 5-$CHBr_2$ of the dibromo compound in ^1H NMR of the crude product after evaporation of benzene due to the sensitivity of the bromide **2** to moisture.[10] The monobromo intermediate **2** was used directly without purification for next substitutions. In methanol with $KHCO_3$ **3c** was formed with satisfactory 72 % overall yield of the two steps (bromination and alkoxy substitution). However, cyanomethyl product **3d** was possible with only 36 % of the two-step overall yield by the reaction of **2** with NaCN in DMF (Scheme 1). Deacetylation followed by *O*-silylation or *O*-

tritylation of **3c** and **3d** as usual gave 5′-*O*-TBDMS-uridines (**5c,d**) or 5′-*O*-trityl-uridines (**5g,h**), respectively. The 5-hydroxyl groups of commercially available 2′-deoxyuridine and thymidine were also protected with *tert*-butyldimethylsilyl chloride (**5a,b**) or trityl chloride (**5e,f**).

Reactions of **5** with 1.5 eq. of 1,1′-sulfonyldiimidazole and NaH in DMF at room temperature (type A in Scheme 2) were completed within 4 hr when monitored by tlc. Isolated yields (94 – 99 %, Table) of each product (**7a-h**) after silica gel column chromatographic separation eluted with chloroform and methanol (25:1) were almost quantitative without any presence of the intermediate **6**. Electronic natures of the substituents at 5-carbon of uracil did not influence significantly on both reaction times and yields of the corresponding product **7** under this given conditions. When reactions were carried out with 1.5 eq. of K_2CO_3 in acetonitrile (type B in Scheme 2) it took 9.5–17 hrs to be completed at refluxing temperature. However, except **7c** and **7e** yields of the other products (**7a**, **7b**, **7d**, and **7f-h**) after column chromatography were slightly lower than those of the type A reaction (Table) though they could be considered within experimental error range. In addition, for a easier work-up process than the purification by silica gel chromatography direct isolations of **7** from the reaction mixture were tried. After neutralization of the solution with 1N HCl extraction with dichloromethane followed by triturations of each product with hexane did not diminish the isolated yields in Table.

Scheme 2.



5 6 7

a: R = TBDMS, R' = H
b: R = TBDMS, R' = CH_3
c: R = TBDMS, R' = CH_2OCH_3
d: R = TBDMS, R' = CH_2CN
e: R = Trityl, R' = H
f: R = Trityl, R' = CH_3
g: R = Trityl, R' = CH_2OCH_3
h: R = Trityl, R' = CH_2CN

Table. Formations of 2,3′-Anhydro-2′-deoxyuridines (7)

Compd.	R	R′	Reaction type[a]	Time hr	Product	Yield[b] %
5a	TBDMS	H	A	4	**7a**	94
			B	14		92
5b	TBDMS	CH_3	A	2	**7b**	98
			B	15		91
5c	TBDMS	CH_2OCH_3	A	2	**7c**	94
			B	10		95
5d	TBDMS	CH_2CN	A	2.5	**7d**	98
			B	15		96
5e	Trityl	H	A	3.5	**7e**	94
			B	16		96
5f	Trityl	CH_3	A	2	**7f**	98
			B	17		91
5g	Trityl	CH_2OCH_3	A	2.5	**7g**	95
			B	16		92
5h	Trityl	CH_2CN	A	3	**7h**	99
			B	9.5		93

[a]A: 1,1′-Sulfonyldiimidazole (1.5 eq.), NaH (1.5 eq.)/DMF, r.t.; B: 1,1′-Sulfonyldiimidazole (1.5 eq.), K_2CO_3 (1.5 eq.)/CH_3CN, reflux. [b]Isolated yields after silica gel column chromatographic separation with chloroform: methanol (25:1).

In summary, the above mentioned two types of the reaction for the formation of 2,3′-anhydro-2′-deoxyuridines (**7**) *via* 3′-*O*-imidazolylsulfonate were proved to be one of the most practical methods because of the two steps in one-pot reaction, quantitative isolated yields of products **7**, and easy work-up process. Further

studies including *in situ* formation of 1,1′-sulfonyldiimidazole followed by addition of **5** are now under progress and will be reported in near future.

Experimental

Synthesis of 5-(Methoxymethyl)-2′-deoxyuridine (4c) from 3′,5′-Di-*O*-acetylthymidine (1): After addition of NBS (2.0 g, 11.2 mmol) and AIBN (100 mg) to the refluxing solution of 3′,5′-di-*O*-acetylthymidine[3] (**1**, 3.0 g, 9.2 mmol) in 200 ml of dry benzene stirring with refluxing was kept for 5 hrs with monitoring the progress of bromination by tlc (acetone:toluene = 1:2). Hot filtration of benzene solution to remove solid particles through ordinary filter paper followed by evaporation of benzene gave 3.40 g of crude monobromo-interemdiate **2** (8.39 mmol, 91 %). The crude intermediate pure enough to give the same ^{1}H NMR spectroscopy and extreme sensitivity to moisture with a previous report[10] was used directly for the next step of methoxylation. To 3.40 g of the crude monobromo-intermediate **2** in 60 ml of the anhydrous methanol 1.10 g (11.0 mmol) of potassium bicarbonate were added. Stirring the solution at room temperature was continued until the disappearance of monobromo compound **2** on tlc (acetone:toluene = 1:2). Filtration of solid and evaporation of the corresponding alcohol gave crude product **3c** which was transferred to flash silical gel column chromatography eluted with hexane:ethyl acetate = 1:2 to give the pure 3′,5′-di-*O*-acetyl-5-(methoxymethyl)-2′-deoxyuridine (**3c**) with two steps (bromination and methoxylation) overall yields of 72 %. After deacetylation of **3c** following the general procedure with methanolic ammonia[11]

5-(methoxymethyl)-2′-deoxyuridine (**4c**) gave the physical data of reported m.p.s' and ^{1}H NMRs'.[12]

Synthesis of 5-(Cyanomethyl)-2′-deoxyuridine (4d) from 5-(Bromomethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (2): To 35 ml of anhydrous DMF solution of the monobromo-intermediate **2** (3.40 g) NaCN (540 mg, 11.0 mmol) was added and stirred at 90 °C for 10 hrs. After evaporation of DMF, water (30 ml) was added and from the aqueous layer extracted the crude product with chloroform (30 ml x 2). The crude product was transferred to silica gel column chromatography eluted with hexane:ethyl acetate = 1:1 which afforded 1.17 g (36 % of two-step overall yield from **1**) of pure 5-(cyanomethyl)-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**3d**). After deacetylation of **3d** by methanolic ammonia 5-(cyanomethyl)-2′-deoxyuridine (**4d,** 640 mg, yield = 72 %) was identified according to the reported data.[13]

General procedures for the synthesis of 7

(a) Type A reaction: To 1.0 mmol of 5′-*O*-protected-5-(substituted)-2′-deoxy-uridines (**5a-h**) with 1.5 eq. of 1,1′-sulfonyldiimidazole in 20 ml of anhydrous DMF was added 1.5 eq of NaH and the solution was stirred at room temperature. DMF was evaporated under reduced pressure after completion of the reaction by monitoring with tlc. Water (20 ml) was added to the sticky mixture and it was neutralized by 1N HCl. The aqueous mixture was extracted with dichloromethane (20 ml x 3) and the organic layer was dried over $MgSO_4$. Filtration of the $MgSO_4$ followed by addition of n-hexane to the dichloromethane solution gave the

precipitates of 5′-*O*-protected-2,3′-anhydrouridines **7** as white solids after filtration. Products showed same mp's and ^{1}H NMR spectra with the reports (for **7a** and **7b**, see ref. 14; for **7e** and **7f**, see ref. 15). **2,3′-Anhydro-5-(methoxymethyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyuridine (7c):** mp 121.2-121.9 °C; IR (KBr) 1664, 1625, 1534, 1473, 1267, 1128 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14(t, J = 1.6Hz, 1H), 5.50(d, J = 3.7Hz, 1H), 5.20(br, s, 1H), 4.28(m, 3H), 3.78(m, 2H), 3.45(s, 3H), 2.60(br, d, J = 12.8Hz, 1H), 2.45(m, 1H), 0.87(s, 9H), 0.07(s, 3H), 0.06(s, 3H); ^{13}C NMR(125MHz, $CDCl_3$) δ 170.0, 153.6, 135.1, 119.4, 87.8, 85.8, 76.5, 67.6, 61.1, 59.0, 33.6, 25.7, 18.2, -5.5; HRMS calcd. for $C_{17}H_{28}N_2O_5Si$: 368.1767. Found: 368.1759. **2,3′-Anhydro-5-(cyanomethyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyuridine (7d):** mp 184.5-185.8 °C; IR (KBr) 2357, 2251, 1666, 1637, 1529, 1472, 1260, 1135 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34(br, s, 1H), 5.60(d, J = 3.5Hz, 1H), 5.26(br, s, 1H), 4.31(m, 1H), 3.85(dd, J = 5.9, 10.8Hz,1H) 3.73(dd, J = 7.7, 10.5Hz, 1H), 3.51(d, J = 1.2Hz, 2H), 2.65(br, d, J = 12.8Hz, 1H), 2.51(m, 1H), 0.88(s, 9H), 0.07(s, 3H), 0.06(s, 3H); ^{13}C NMR(125MHz, $CDCl_3$) δ 169.3, 154.3, 136.7, 116.7, 112.3, 88.0, 85.9, 76.8, 60.9, 33.6, 25.8, 18.2, 16.5, -5.5; HRMS calcd. for $C_{17}H_{25}N_3O_4Si$: 363.1614. Found: 363.1612.

(b) Type B reaction: A mixture of **5** (1.0 mmol), 1.5 eq. of 1,1′-sulfonyldiimidazole, and 1.5 eq. of K_2CO_3 in 30 ml of anhydrous CH_3CN was heated at 80 °C for hours until the disappearance of the starting material **5** on tlc. The reaction mixture was cooled to r.t. and the CH_3CN was evaporated. The

residue was treated with 50 ml of water and extracted with dichloromethane (20 ml × 3). The dichloromethane extracts were concentrated and transferred to silica gel column chromatography eluted with $CHCl_3$:MeOH (25:1) to give 5′-*O*-protected-2,3′-anhydrouridines **7** with given yields in Table with the same physical data of products from type A reaction.

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