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SYNTHESIS OF 4-C SUBSTITUTED PYRIMIDINE NUCLEOSIDES

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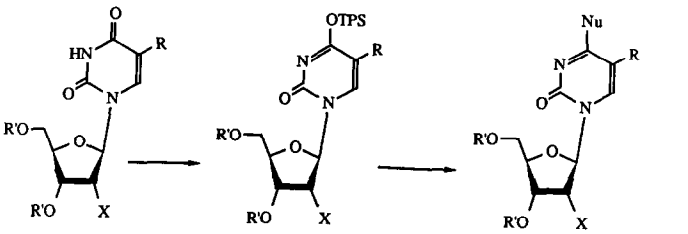
Abstract: t-Butyldimethylsilyl protected uridine and thymidine were converted to the 4-O-triisopropylphenylsulfonyl derivatives 3 and 4, respectively. 3 and 4 underwent clean displacements with malonate-type nucleophiles yielding the 4-C-substituted pyrimidine nucleosides in good yield.

Chemically modified nucleosides and nucleotides are continuing to attract interest due to their various biological effects, most importantly, their antiviral and anticancer activities[1]. Among the large number of known nucleoside analogs, 4-N-substituted pyrimidines are of interest as naturally occurring constituents of t-RNA[2] and 4-C-substituted analogs have been studied as potential cytidine deaminase inhibitors[3].

Synthetic approaches to 4-C substituted pyrimidine nucleosides include ribosylation of 4-C substituted pyrimidines[3,4] and the sulfur extrusion method[5]. In the latter 4-thiouridine is S-alkylated and subsequently transformed thermally or by base catalysis into the 4-C-derivative.

We wish to report a new method for adding C-nucleophiles to the 4 position of pyrimidine nucleosides by a simple two-step process starting from uridine (or thymidine) via the 4-O-triisopropylphenylsulfonyl derivatives.

Tris-(t-butyldimethylsilyl) uridine 1 and di-(t-butyldimethylsilyl) thymidine 2 were cleanly converted to their corresponding 4-O-triisopropylphenylsulfonyl (TPS) derivatives 3 and 4 by reaction with TPS-Cl/NaH in THF followed by aqueous workup[6]. 3 and 4 proved to be stable to chromatography on SiO_2 and were isolated in 87 percent and 93 percent yields, respectively. An alternative procedure using TPS-Cl/Et_3N/DMAP in CH_2Cl_2 resulted in low yields of 3 and 4 (64 percent and 49 percent, respectively). 3 and 4 could be stored at ambient temperature without any sign of decomposition after ~1 month.



Similarly, the 4-O-mesitylenesulfonyl derivatives were obtained, however, they were not as thermally stable showing ~50 percent decomposition (TLC) after ~1 week. Attempts to prepare the 4-O-diethylphosphoryl[7] or the 4-O-t-butyldiphenylsilyl[7] derivatives of 1 under a variety of reaction conditions did not yield any isolable products.

First we examined the reactivity of the sulfonates 3 and 4 towards O- and N-nucleophiles. 3 was stable in methanol but reacted cleanly and quantitatively in methanol/K_2CO_3 to give 5 in 78 percent yield[11]. Similarly, when treated with diethylamine, 3 was converted to 6 (95 percent yield) and 4 cleanly reacted with 2-(methylamino) ethanol to 7 (72 percent yield). As such, these reactions provide an alternative to the triazole[8] and methylimidazole[9] and other[10] methods for the preparation of 4-O-substituted uridine and thymidine and 4-N-substituted cytidine derivatives.

We next turned our attention to the addition of C-nucleophiles to 3 and 4. When treated with the sodium salts of diethylmalonate (entries 1 and 5), ethyl acetylacetate (entry 2), methyl cyanoacetate (entry 3), ethyl phenylacetate (entry 4) and malonitrile (entry 6) in THF solution, both 3 and 4 underwent clean displacements at ~0°C and the corresponding 4-C-substituted pyrimidine nucleosides were isolated in good to excellent yields (see Table). It is worth noting that the 5-methyl group of 4 did not exert any steric hindrance in the reaction with sodium diethylmalonate or with sodium malonitrile resulting in clean conversion to 12 and 13, respectively (entries 5 and 6).

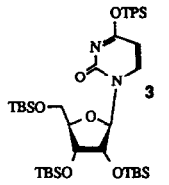
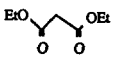
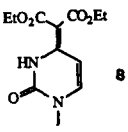
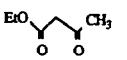
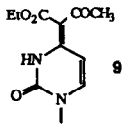
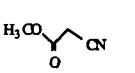
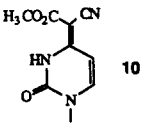
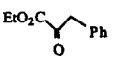
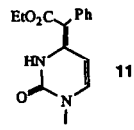
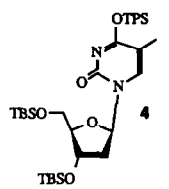
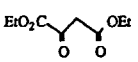
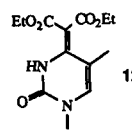
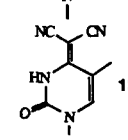
We believe that this method of synthesizing 4-C-substituted pyrimidine nucleosides offers advantages to existing methodologies in its shortness and simplicity. We are currently extending this work to other nucleophiles and to purine nucleosides.

Representative experimental procedures

Preparation of 4: To a suspension of NaH (250 mg; 10 mmol) in THF (20 ml) was added 2 (1.036 g; 2.1 mmol) followed after 30 min by TPS-Cl (1.1 g; 3.6 mmol). This mixture was stirred for 16 hours, quenched at 0°C (saturated NH_4Cl solution) and worked up. Chromatography (SiO_2; ether/hexane 1:20 to 1:3) yielded 4 as a foam (1.47 g; 93 percent).

Preparation of 8: To a suspension of NaH (70 mg; 2.9 mmol) in THF (5 ml) was added at 0°C a solution of diethylmalonate (216 mg; 1.35 mmol) in THF (2 ml) followed after 30 min by a solution of 3 (874 mg; 1.02 mmol)) in THF (4 ml). After 1 hour the mixture was quenched (saturated NH_4Cl solution), worked up and the crude product chromatographed (SiO_2; ether/hexane 1:5 to 1:3) yielding 8 as a foam (660 mg; 89 percent).

Table: Reaction of 3 and 4 with C-nucleophiles

Entry	Starting Material	Nucleophile	Product	Yield[11]
1	 3		 8	89 %
2	3		 9	68 %
3	3		 10	94 %
4	3		 11	94 %
5	 4		 12	88 %
6	4		 13	90 %

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11. All yields refer to isolated products after chromatography. All new compounds had ^{1}H-NMR, MS and UV-spectroscopical data consistent with the proposed structures. UV data (methanol solution):

3: λ_{max} = 290 (10,500), 235 (15,000); λ_{min} = 259 (1,900);

4: λ_{max} = 300 sh (7,000), 290 (7,500), 235 sh (10,000), λ_{min} = 260 (2,000);

5: λ_{max} = 278 (6,100); λ_{min} = 240 (1,300);

6: λ_{max} = 280 (18,000); λ_{min} = 240 (6,800);

7: λ_{max} = 290 (20,000); λ_{min} = 242 (7,500);

8: λ_{max} = 240 (7,000), 330 (24,000), 338 (24,000); 360 sh (12,000), λ_{min} = 278 (3,000);

9: λ_{max} = 235 (8,000), 339 sh (20,000), 352 (26,000); 365 sh (21,000), λ_{min} = 220 (7,000), 285 (2,000);

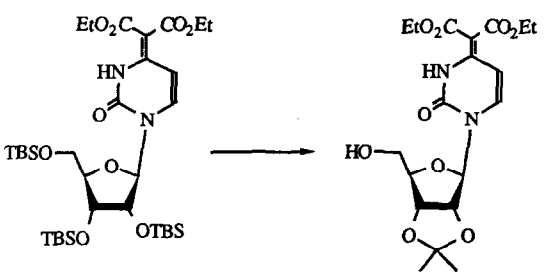
10: λ_{max} = 360 sh (14,000), 345 (22,000), 332 (20,000), 240 (5,500), λ_{min} = 280 (2,200);

11: λ_{max} = 335 (42,000), 250 (15,000), λ_{min} = 290 (11,000), 228 (11,000);

12: λ_{max} = 360 sh (11,000), 340 (20,000), 332 (21,000), 250 (9,000) λ_{min} = 280 (4,000);

13: λ_{max} = 372 sh (8,000), 345 (20,000), 252 (4,500); λ_{min} = 280 (2,500), 230 (2,500).

To further proof the structures, compound 8 was transferred in a two-step, one pot sequence (1. BF_3.MeOH/CH_2Cl_2, 2. 2,2-dimethoxypropane) into 14 (70 percent yield after chromatography) which had ^{1}H-NMR identical to that reported[7a] and Mp 125°C (Mp reported 123-124°C[7a]).



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