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Addition of Grignard Reagents to 4-O-TPS Pyrimidine Nucleosides: Synthesis of 6-Substituted 5,6-Dihydropyrimidine Nucleoside Derivatives

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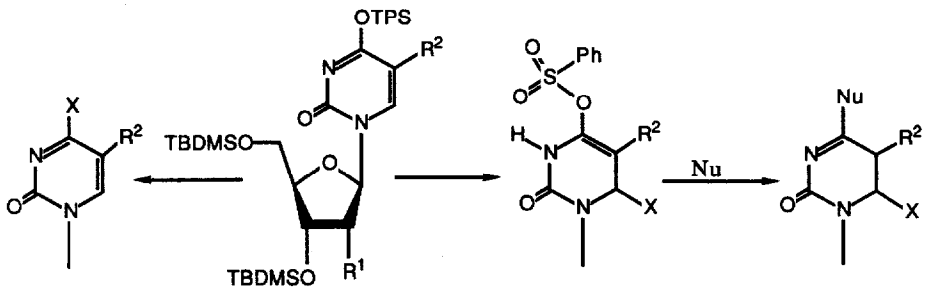
Summary - Methyl magnesium chloride, vinyl magnesium chloride and acetylides were found to add to 4-O-triisopropylphenylsulphonyl (TPS) uridine and thymidine derivatives at the 6-position leading to 6-substituted-3,6-dihydro-4-O-TPS pyrimidine nucleosides. Reaction with phenyl magnesium chloride resulted in addition at both the 6- and the 4-positions.

Nucleoside and nucleotide derivatives exhibit a wide range of biological effects, most notably antiviral and anticancer activities. Among the large number of nucleoside analogs prepared as potential agents against viral diseases and cancers, 6-C-substituted pyrimidine nucleosides have attracted relatively scant attention,[1] which may be due to their limited synthetic availability. Approaches to 6-C-substituted pyrimidine nucleosides include the glycosylation of 6-substituted pyrimidines,[2] photochemical methods,[3] addition of C-nucleophiles to 5-bromo uridines[4] or cyclouridines,[5] and lithiation of appropriately 5'-substituted uridine derivatives followed by treatment with electrophiles.[6] These methods are limited in scope and some suffer from low yields.



1 R^1=OTBDMS, R^2=H

2 R^1=H, R^2=CH_3

Figure 1.

We have recently shown[7] that t-butyldimethylsilyl (TBDMS) protected 4-O-triisopropylphenylsulfonyl (TPS) uridine 1 and thymidine 2 react with malonate type nucleophiles selectively at the 4-position to give 4-C-substituted pyrimidine nucleosides a (see Fig 1). Likewise, treatment with N- or O-nucleophiles results in attack at the 4-position leading to 4-N-cytidine- and 4-O-uridine (thymidine) analogs, respectively.[8] We now wish to report the addition of

organometallic reagents to 1 and 2, resulting unexpectedly in the formation of 6-substituted derivatives b. Compounds of type b react with N- and O-nucleophiles to give the 6-substituted cytidine and uridine analogs c.

When the 4-O-TPS uridine derivative 1 was treated with MeMgCl in THF a lower moving spot on TLC was formed after ~30 min at 0°C. After work up and chromatography on SiO_2 (ether/hexane gradient) a product could be isolated in 53% yield. Surprisingly this compound still contained the TPS moiety and was converted to a slower moving product on treatment with Et_2NH. On the basis of ^{1}H-NMR shifts and decoupling experiments this product was assigned structure 3 (see table, entry 1). It is a single stereoisomer and exists as the 4,5-double bond isomer due to the hydrogen bond formation between the 3-NH and the S=O group as has been found for related compounds.[7] Similarly, 1 was converted to the 6-vinyl compound 4 on treatment with vinyl magnesium chloride (entry 2). But, reaction of the thymidine derivative 2 with MeMgCl yielded the two isomeric compounds 5 and 6 (entry 3). The reaction of 1 with phenyl magnesium chloride proved to be an exception: it lead to the formation of both the 6-phenyl adduct 7 and the 4-phenyl pyrimidine 8 (entry 4).

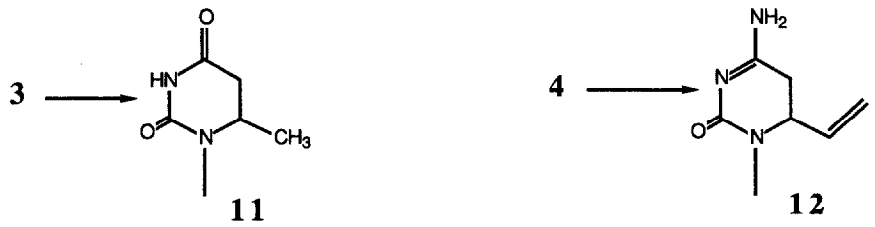


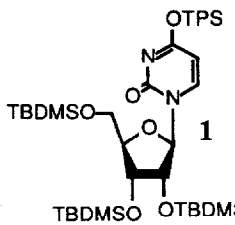
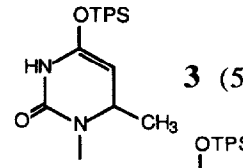
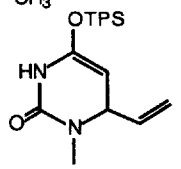
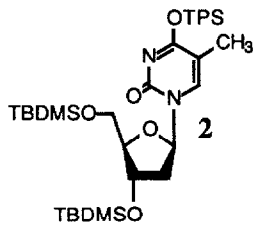
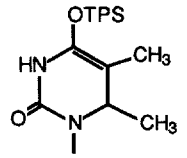
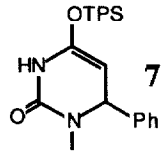
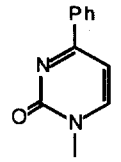
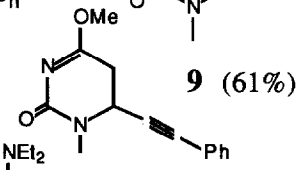
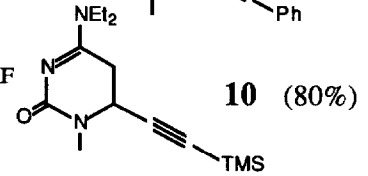
Figure 2.

In order to examine the reactivity of adducts 3 and 4 and to further prove their structures, both compounds were allowed to react with nucleophiles: 3 was converted to the 6-methyl-5,6-dihydro uridine 11 with tetrabutylammonium hydroxide in THF; 4 yielded the 6-vinyl-5,6-dihyro cytidine derivative 12 on treatment with anhydrous NH_3 (see Fig. 2). Subsequently the addition of the organometallic reagent and treatment of the resulting product with a nucleophile was carried out in a one pot procedure. Reaction of 1 with sodium phenyl acetylide and subsequent treatment of the crude reaction mixture with $MeOH/K_2CO_3$ gave 9 (entry 5). Treatment of 1 with potassium TMS-acetylide followed by Et_2NH produced 10 in good yield (entry 6).

A few other C-nucleophiles were also examined. Treatment of 1 with the lithium salts of t-butyl acetate or nitromethane led only to the formation of $(TBDMS)_3$-uridine. Reaction of 1 with methyl lithium or lithium dimethyl cuprate resulted in a complex mixture of products.

Overall, we have shown that unlike malonate type nucleophiles, Grignard reagents add to 4-O-TPS pyrimidine nucleosides preferentially at the 6-position leading to intermediates which can be easily transformed in a single reaction procedure to 4,6-substituted dihydropyrimidines. Thus, this methodology provides easy access to a variety of 6-substituted-5,6-dihydrouridine (thymidine) and cytidine analogs. Such 5,6-dihydropyrimidine nucleosides are interesting compounds from both the biochemical and structural point of view. They occur in t-RNA,[9] are implicated in the catabolism of pyrimidine bases (dihydroorotic acid) and they are the products of radiation damage of DNA.[10] 5,6-Dihydrouridine and cytidine have also been studied as cytidine deaminase inhibitors.[11]

Table: Addition of Organometallic Reagents to 4-O-TPS Pyrimidine Nucleosides

Entry	Starting Material	Reaction Conditions	Product(s)	Yield (%)[11]
1	 **1**	CH_3MgCl / THF	 **3**	(53%)
2	TBDMSO OTBDMS	 MgCl / THF	 **4**	(61%)
3	 **2**	CH_3MgCl / THF		Isomer A **5** (47%) Isomer B **6** (24%)
4	**1**	PhMgCl / THF	 **7** (37%)	 **8** (38%)
5	**1**	1. Ph—≡ / NaH / THF 2. MeOH / K_2CO_3	 **9**	(61%)
6	**1**	1. TMS—≡ / KH / THF 2. Et_2NH / ether	 **10**	(80%)

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8. This methodology has also been used by others, see: (a) References cited in 7. (b) Nyilas, A.; Chattopadhyaya, J. *Acta Chem Scand.* **1986**, B40, 826-830. (c) Zhou, X-X.; Chattopadhyaya, J. *Tetrahedron* **1986**, 42, 5149-5156.

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12. All yields refer to isolated products after chromatography. All new compounds had ^{1}H-NMR, MS and UV-spectroscopic data consistent with their structure. ^{1}H-NMR Data (300 MHz in $CDCl_3$) :

3: 7.22 (s,2H), 6.05 (NH), 5.68 (d,J=6.2,H1'), 4.39 (dxd,J1=2.7,J2=6.6,H5), 4.11-4.18 (m,2H), 4.05 (qui,J=6.3,2H), 3.99 (m,1H), 3.90 (m,1H), 3.68 (AB-system,J=11.1,A-part 3.63,split into d,J=2.7,B-part 3.73,split into d,J=3.3,2H5'), 2.93 (qui,J=6.9,1H), 1.25-1.28 (m,~18H), 1.13 (d,J=6.2,Me6), 0.85-0.89 (m,3tBu), 0.02-0.06 (m,6Me).

4: 7.20 (s,2H), 6.10 (NH), 5.75 (dxdxd,J1=2.4,J2=4.1,J3=16.1,1H), 5.62 (d,J=4.6,H1'), 4.98 (m,1H), 4.94 (d,J=4.6,1H), 4.67 (dxd,J1=5.3,J2=6.4,H6), 4.4 (dxd, J1=2.5,J2=6.4, H5), 4.17 (dxd,J1=4.6,J2=5.1,H2'), 4.05 (qui,J=6.7,2H), 4.01 (m,H3'), 3.90 (m,H4'), 3.68 (AB-system,A-part 3.61,split into d,J=2.4,B-part 3.74,split into d,J=3.2,2H5'), 2.92 (qui,J=6.8,1H), 1.25 (d,J=6.7,6Me),0.84-0.87 (m,3tBu), 0.02-0.05 (m,6Me).

5: 7.21 (s,2H), 5.99 (dxd,J1=5.4,J2=9.0,H1'), 5.70 (NH), 4.30 (m,1H), 4.02(qui,J=6.6, 3H), 3.73 (m,1H), 3.66 (m,2H5'), 2.92 (qui,J=6.6,1H), 1.61-1.95 and 2.02-2.11 (2m,2H2'), 1.17-1.27 (m,8Me), 0.86-0.89 (m,2tBu), 0.02-0.07 (m,4Me).

6: 7.21 (s,2H), 6.13 (dxd,J1=6.0,J2=8.7,H1'), 5.67 (s,NH), 4.30 (m,1H), 4.04 (qui,J=6.9,2H), 3.83 (qua,J=6.3,Me6), 3.77 (m,1H), 3.60 (m,2H5'), 2.92 (qui,J=6.6,1H), 1.76-1.86 and 1.95-2.16 (2m,2H2'), 1.17-1.28 (m,~8Me), 0.85-0.90 (m,2tBu), 0.03-0.05 (m,4Me).

7: 7.09-7.32 (m,~7H), 6.18 (s,NH), 5.47 (d,J=4.5,H1'), 5.23 (d,J=6.3,H6), 4.50 (dxd,J1=2.4,J2=6.0,H5), 4.32 (m,1H), 4.08 (m,1H), 3.96 (qui,J=6.6,2H), 3.84 (m,1H), 3.46-3.57 (m,2H5'), 2.91 (qui,J=6.6,1H), 1.26, 1.20, 1.11 (3d,J=6.6,6Me), 0.80-0.89 (m,3tBu), 0.05-0.12 (m,6Me).

8: 7.23-7.35 (m,5H),5.82 (d, J=5.7,H1'), 5.25 (s,H5,H6), 4.32 (m,1H), 4.06 (m,1H), 3.78 (m,1H), 3.37 (s,2H5'), 0.89, 0.84, 0.79 (3s,3t-Bu), 0.02-0.06 (m,6Me).

9: (500 MHz): 7.26-7.34 (m,5H), 5.95 (s,H1'), 5.31 (dxd,J1=1.5,J2=6.5,H6), 4.38 (dxd,J1=4.5,J2=8.7,H3'), 4.28 (d,J=4.5,H2'), 4.02 (dxd,J1=2.1,J2=11.7,H5'), 3.96 (s,Me), 3.92 (dxt,J1=8.7,J2=2.0,H4'), 3.76 (dxd,J1=2.0,J2=11.7,H5'), 2.69 (AB-system,J=15.9,A-part 2.63,split into d,J=1.5,B-part 2.76,split into d,J=6.5,2H5), 0.95, 0.91, 0.82 (3s,3tBu), -0.13-0.26 (m,6Me).

10: (500 MHz): 5.94 (s,H1'), 4.89 (dxd,J1=1.8,J2=5.8,H6), 4.19-4.24 (m,2H), 3.97 (dxd,J1=2.0,J2=11.6,H5'), 3.87 (dxt,J1=8.4,J2=2.0,H4'), 3.80 (sext,J=7,1H), 3.74 (dxd,J1=2,J2=11.6,H5'), 3.58 (sext,J=6.7,1H), 3.39 (sext,J=7.3,1H), 3.29 (sext,J=7.6, 1H), 2.58 (AB-system,J=14.8,A-part 2.46,split into d,J=5.8,B-part 2.70,split into d,J=1.8,2H5), 1.19-1.25 (m,2Me), 0.90, 0.91, 0.92 (3s,3tBu), 0.07-0.26 (m,6Me).

11: 7.61 (NH), 5.63 (d,J=4.8,H1'), 4.16 (m,2H), 4.03 (m,1H), 3.98 (m,1H), 3.76 (AB-system,J=9.0,A-part 3.86,split into d,J=2.7,B-part 3.86,split into d,J=2.4,2H5'), 2.55 (AB-system,J=16.8,A-part 2.39,B-part 2.70,split into d,J=6.0,2H5), 1.26 (d,J=6.6,Me6), 0.87-0.9 (m,3tBu), 0.05-0.09 (m,6 Me).

12: 5.74 (dxdxd,J1=4.8,J2=10.5,J3=15.3,1H), 5.55 (d,J=3.3,H1'), 5.17, 5.13 (2m,2H), 4.65 (NH2), 4.18 (m,H2'), 3.97-4.05 (m,H3',H4',H6), 3.77 (AB-system,J=11.4,A-part 6.68,split into d,J=2.1,B-part 3.87, split into d,J=2.4,2H5'), 2.77 (AB-system,J=16.2,A-part 2.69,split into d,J=6.0,B-part 2.83,broadened,2H5),0.88-0.90 (m,3tBu), 0.03-0.14 (m,6Me).

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