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SYNTHESIS OF 6-ALKYL AND 6-ARYL SUBSTITUTED 9-β-D-RIBOFURANOSYL PURINES VIA THE NICKEL CATALYZED COUPLING OF GRIGNARD REAGENTS TO 2',3',5'-Tris-O-(t-BUTYLDIMETHYLSILYL)-9-β-D-RIBOFURANOSYL-6-CHLOROPURINE

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Summary: A series of 6-substituted purine nucleosides have been synthesized in moderate yield by the nickel catalyzed cross coupling reaction between alkyl- and aryl- Grignard reagents and 2',3',5'-tris-O-(t-butyldimethylsilyl)-9-β-D-ribofuranosyl-6-chloropurine.

Adenosine analogues with alkyl and aryl group linked to the amino group at C-6 show a considerable range of biological activity.[1] For example, N^6-cyclohexyladenosine strongly binds A_1-adenosine receptors[2] and N^6-(4-hydroxy-3-methyl-trans-butenyl)adenosine(zeatin riboside) is an active cytokinin.[3] The amino group at C-6 is not always necessary for activity. The most potent inhibitors of nucleoside transport in erythrocytes are purine nucleosides to which a substituted benzyl group is attached via sulfur to C-6.[4] A number of 6-alkylated purines[5] and their nucleoside analogues[6] show interesting biological activity. However, despite efforts to synthesize 6-alkyl and 6-aryl nucleoside analogues for biological testing no direct broadly useful synthetic route to this class of compounds has been developed. Until recently attempts to form carbon-carbon bonds at the 6-position through nucleophilic displacement of the corresponding chloropurine nucleosides were generally unsuccessful. A notable exception is the preparation of 2,6-dialkylpurine nucleosides[8] by the phosphorane alkylation method of Taylor and Martin.[9] Recently, a number of papers have appeared on the reactions of 9-(2',3',5'-tri-O-benzyl)-β-D-ribofuranosides of 6-chloropurine and 6-methylsulfonylpurine with the carbanions from the active methylene compounds diethyl malonate, ethyl cyanoacetate, malononitrile and nitromethane,[10] as a route to 6-alkylpurine ribonucleosides. Two rearrangement reactions, a photo-Claisen[11] and an Eschenmoser contraction[12] have also been used to create carbon-carbon bonds at C-6. None of these routes are of quite as broad scope, however, as the coupling reaction described here.

As part of our overall effort to synthesize modified nucleosides via organotransition metal chemistry we now report a short efficient synthesis of 6-substituted purine nucleosides. One other report of modification of purine nucleosides by organotransition metal intermediates has appeared recently. A palladium catalyzed reaction of Grignard reagents with the trimethylsilyl protected derivative of 8-bromoadenosine was used to prepare 8-alkyl- and aryl-adenosines.[13] Following the independent reports of Corriu and Masse[14] and Kumada et al[15] in 1972, that metal phosphine complexes catalyse the selective cross coupling of Grignard reagents with aryl and alkenyl halides, a series of papers[16] have appeared in the literature

on the synthetic utility of this reaction. Derivatives of 6-chloropurine would seem to be ideal candidates for substiution by this procedure.

2',3',5'-Tris-O-(t-butyldimethylsilyl)-9-β-D-ribofuranosyl-6-chloropurine (1) was prepared from the known 6-chloro-9-β-D-ribofuranosylpurine[17] by silylation with an excess of t-butyldimethylsilyl chloride, imidazole and DMF by the literature procedure.[18] Nucleoside 1 reacts readily with Grignard reagents via a nickel complex generated from dichloro[1,3-bis(diphenylphosphine)propane]nickel(II)[19] [$Ni(dppp)Cl_2$] (Scheme I). The products, following deprotection with tetra-n-butylammonium fluoride in THF and chromatographic purification, were isolated in 40-50% yield (Table I).[20] The scope of the reaction extends to Grignard reagents generated from 1° and 2° alkyl and aryl halides. Consequently this method has somewhat greater scope than other methods. The primary limitation is undoubtedly that imposed by the presence of functional groups reactive towards Grignard reagents.

In a typical procedure: To a mixture of 2',3',5'-tris-O-(t-butyldimethylsilyl)-9-β-D-ribofuranosyl-6-chloropurine (0.565 g, 1 mmole) and $Ni(dppp)Cl_2$ (0.075 g, 0.15 mmole) in anhydrous ether (75 ml) was added freshly prepared Grignard reagent (10 equivalents) at 0° under nitrogen atmosphere. The brown colored reaction mixture was allowed to stand at room temperature, with stirring, overnight. Hydrolysis with saturated aqueous NH_4Cl (25 ml) and extraction with ether followed by washing with water (2 x 50 ml), drying over anhydrous Na_2SO_4 and removal of the solvent at reduced pressure yielded, in all cases, a yellow viscous liquid.

The foregoing crude product, without purification, was treated with tetra-n-butylammonium fluoride (10 ml) 1 M in THF at 0° with the exclusion of moisture for 4 hr. THF was removed at reduced pressure and the black residue purified by chromatography on silica gel (MeOH-$CHCl_3$, 15:85 v/v) followed by Bio-gel P-2 (water). Lyophilization of the solution yielded colorless fluffy material in 40-50% overall yield. The actual yield of the coupling reaction is some what higher, but complete separation of the product from tetra-n-butylammonium salts and nickel catalyst requires chromatographic conditions that results in some loss of product. Studies are currently underway to assess the biological activity of these analogues.

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TABLE I Products from the Reaction of Nucleoside 1 with Grignard Reagents

Grignard Reagent	Product[21]	Overall Yield (%)	M.P.	Calcd. Mass ($M + H^+$)	Deviation (ppm)
EthylMgI	3a	45	105	281.124981($C_{12}H_{17}N_4O_4$)	1.8
CyclohexylMgBr	3b	47	99-100	335.171931($C_{16}H_{23}N_4O_4$)	1.0
PhenylMgBr	3c	40	93	329.124981($C_{16}H_{17}N_4O_4$)	0.8
2-PhenylethylMgBr	3d	50	67-70		
3-PhenylpropylMgBr	3e	48	62-63	371.17931($C_{19}H_{23}N_4O_4$)	1.6
4-Methyl-3-penten-1-ylMgBr	3f	42	48-49		

Scheme I

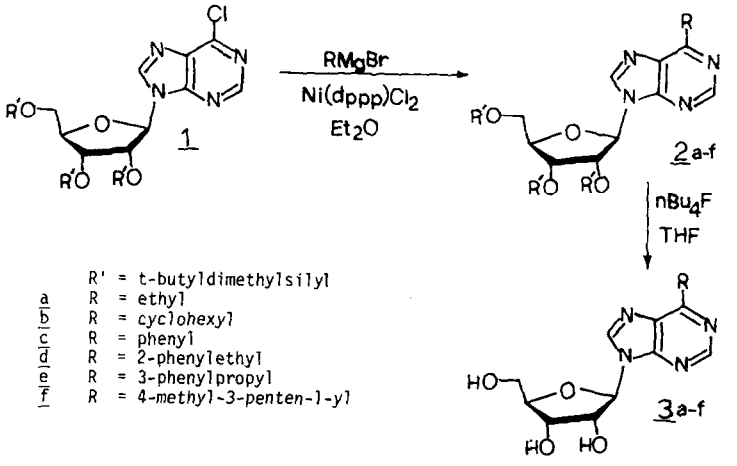
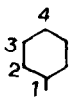
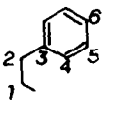
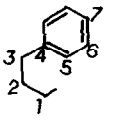
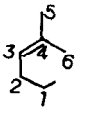


TABLE II ^{13}C NMR Spectra[a]

Carbon						
Purine	3a	3b	3c	3d	3e	3f
2	151.78	151.45	152.23	151.32	151.19	151.26
4	150.28	149.11	151.91	149.24	148.98	149.18
5	132.29	132.68	135.31	133.78	133.59	133.07
6	162.76	167.57	153.01	162.95	163.64	163.41
8	143.98	143.59	144.89	143.98	143.91	144.17
β-D-ribose						
1'	87.78	90.77	87.65	90.90	90.77	90.70
2'	73.75	73.62	73.68	73.62	73.49	73.75
3'	70.43	71.73	70.17	71.86	71.79	71.57
4'	85.77	87.00	85.64	87.00	87.00	87.00
5'	61.40	62.63	61.14	62.70	62.70	62.83
C-6 Substituent						
1	25.73	41.65	131.12	34.63	35.41	33.14
2	12.21	30.93	129.36	33.79	24.45	26.60
3		25.92	128.65	140.54	32.55	122.41
4		25.92	130.86	128.26	141.25	133.59
5				128.26	128.19	26.70
6				126.11	128.19	17.67
7					125.72	

[a]Spectra were run in $CDCl_3$ and are referenced to internal TMS.

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20. A shorter route, devised with J. Orwin, required only four steps. Inosine was protected at the three hydroxyl groups with t-butyldimethylsilyl and the protected derivative converted to nucleoside 1 with $SOCl_2$ in DMF. However, this latter reaction leads to side products which makes purification difficult and overall yields are low as a consequence.
21. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, UV, and Fast Atom Bombardment (FAB) low and high resolution Mass Spectrometry. Cf. D.H. Williams, C. Bradley, G. Bojesen, S. Santikarn, and L.C.E. Taylor, J. Am. Chem. Soc., 1981, 103, 5700.

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