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THE REACTIONS OF BENZYLATED PYRROLE AND ADENINE RIBONUCLEOSIDES WITH GRIGNARD REAGENTS

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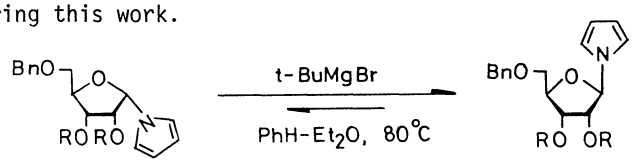
The anomerization of benzylated pyrrole nucleosides were found to proceed by the use of t-BuMgBr. These nucleosides also reacted with MeMgI to produce open-chain products. On the other hand, the reaction of a perbenzylated adenosine with the Grignard reagent gave rise to regioselective 2'-O-debenzylation.

Certain cyclic acetals are known to be cleaved by Grignard reagents in aromatic solvents at a high temperature.[1a-c] When benzene is used as a Grignard solvent instead of ether, the Grignard reagent comes to possess stronger affinities for the oxygen functions of compounds such as the acetal.[1a] Therefore, sugar derivatives including these functionalities are considered to be candidates appropriate for the Grignard reaction in benzene. For example, the anomeric region of a methyl furanoside is a kind of the cyclic acetal; recently we have found that methyl trans-1,2-pentofuranoside derivatives are converted into the respective cis-1,2-anomers by the use of MeMgI or t-BuMgBr via a route involving the furanose ring opening-reclosure.[2] These findings prompted us to investigate the behavior of these reagents on N-glycofuranosides. In this communication, the author wishes to report the first example of anomerization of ribonucleosides with the Grignard reagent and some observations made during this work.



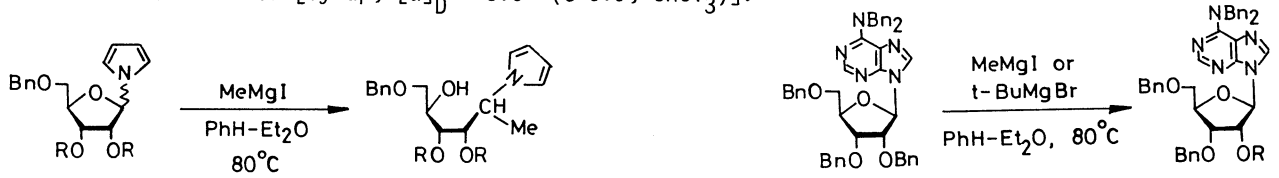
1α : R = H, 2α : R = Bn 1β : R = H, 2β : R = Bn

The starting materials,[3] 1-(5-O-benzyl-α- and -β-D-ribofuranosyl)pyrroles 1α [mp 81-82 °C; $[\alpha]_D^{21}$ +32.4° (c 1.0, $CHCl_3$)] and 1β [syrup; $[\alpha]_D^{25}$ -50.3° (c 0.9, $CHCl_3$)], were prepared by the reaction of 1-(2,3-O-isopropylidene-α- and -β-D-ribofuranosyl)pyrroles[4] with sodium hydride-benzyl chloride in N,N-dimethylformamide-benzene at 80 °C, followed by the deacetonation of the resulting 1-(5-O-benzyl-2,3-O-isopropylidene-α-D-ribofuranosyl)pyrrole [mp 113-114 °C; $[\alpha]_D^{20}$ -64.0° (c 0.9, $CHCl_3$)] and its β-anomer [mp 46-47 °C; $[\alpha]_D^{22}$ -51.9° (c 1.1, $CHCl_3$)] with 80% acetic acid at 80 °C, respectively. In a similar manner, the perbenzylation of 1α, 1β, and adenosine gave 1-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)pyrrole 2α [mp 63-64 °C; $[\alpha]_D^{19}$ +80.2° (c 1.0, $CHCl_3$)], the corresponding β-anomer 2β [syrup; $[\alpha]_D^{26}$ -23.4° (c 1.2, $CHCl_3$)], and N^6,N^6-dibenzyl-9-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl)adenine 5 [syrup; $[\alpha]_D^{25}$ -16.0° (c 1.2, $CHCl_3$); UV (EtOH) λ_{max} 278 nm (ε 25,000)], respectively. The positions of the benzyl groups in the adenine moiety have tentatively been assigned.

When a mixture of 1α (0.73 mmol) and t-BuMgBr (7.6 mmol) in benzene (15 ml)-ether (10 ml) was heated at about 80 °C to remove the ether from a reaction vessel[2b] for 30 min under an atmosphere of dry nitrogen (Method A), a rapid anomerization occurred. The usual work-up gave a 35:65 mixture of 1α and 1β. Starting from the latter, we also obtained an anomeric mixture (α/β=24:76).

However, the prolonged reactions of 1α and 1β with this reagent caused the increase of formation of by-products under these conditions. In the reactions of 2α and 2β, the conditions were slightly modified; after the ether had been evaporated at 80 °C for about 45 min, the reaction mixture was heated at the same temperature for 0.5-2 h under refluxing conditions (Method B). An anomeric mixture was also produced in a ratio (α/β) of 33:67 (from 2α) or 22:78 (from 2β).

On the other hand, the reaction of 1α (0.73 mmol; Method B) or 1β (0.76 mmol; Method A) with MeMgI (3.8 mmol) in benzene (10 ml)-ether (5 ml) predominated the cleavage of its furanose ring to give diastereomeric open-chain products 3, one of the isomers being isolated as crystalline form [mp 106.0-106.5 °C; $[\alpha]_D^{20}$ +18.6° (c 1.1, $CHCl_3$)] in 48 or 63% yield, respectively. Analogously, the treatment (Method B) of 2α or 2β with MeMgI afforded diastereomeric open-chain products 4 in a ratio of 63:37 or 67:33, respectively: the major diastereomer [mp 49-50 °C; $[\alpha]_D^{20}$ +30.4° (c 0.9, $CHCl_3$)]; the minor diastereomer [syrup; $[\alpha]_D^{18}$ +5.0° (c 0.9, $CHCl_3$)].



1α ; 1β : R = H — 3 : R = H — 5 — 6 : R = H

2α ; 2β : R = Bn — 4 : R = Bn — 7 : R = Ac

When a mixture of 5 (1.0 mmol) was treated with t-BuMgBr (20 mmol) in benzene-ether under conditions similar to the Method B, neither the corresponding α-anomer nor open-chain products could be detected, but we isolated the corresponding 3',5'-di-O-benzyl derivative 6 [glass; $[\alpha]_D^{28}$ -51.4° (c 0.9, $CHCl_3$); UV (EtOH) λ_{max} 278 nm (ε 22,000)] as a main product (69%), in which the 2'-O-benzyl group was lacking. When MeMgI was used in place of t-BuMgBr, 5 underwent a complex reaction to give a small amount of 6. The structure of 6 was confirmed by spin decoupling studies using its acetate 7 [glass; $[\alpha]_D^{24}$ -29.6° (c 0.9, $CHCl_3$); UV (EtOH) λ_{max} 277 nm (ε 22,000); ^{1}H NMR ($CDCl_3$) δ 2.12 (s, $COCH_3$), 5.76 (dd, $J_{1',2'}$=4 Hz, $J_{2',3'}$=6 Hz, H-2'), 6.27 (d, $J_{1',2'}$=4 Hz, H-1')].

Recently, Ishido et al.[5] have found the regioselective 2'-O-deacylation of the peracylated ribonucleosides. The present observations also suggest the potential of the selective removal of nucleoside protecting groups with the Grignard reagents. Work now in progress is designed to provide additional information about the anomerization and deprotection with the Grignard reagents.

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