Regioselective C–O bond cleavage reactions of acetals

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Abstract

Reactions of acetonide derivatives of monosaccharides with the Grignard reagent in benzene afford the corresponding monosaccharide derivatives having only one free hydroxy group. 1,4-di-alkoxy-(2S,3S)-2,3-butanediols are obtained from the reactions of 2S,3S-threitol bisketals with Grignard reagents or with LiAlH4/AlCl3. The reactions of benzylic acetals prepared from 1,4-dialkoxy-(2S,3S)-2,3-butanediols and aromatic aldehydes, with aryl or secondary or sterically hindered Grignard reagents give the corresponding ring-opening products in high diastereoselectivity. Other synthetic applications of such tunable chiral diols are briefly described.

MONOSACCHARIDE DERIVATIVES HAVING ONE FREE HYDROXY GROUP

The hydroxy functions in carbohydrates are conveniently protected by acetal groups. Selective deprotection of these acetals would be particularly valuable in the derivatization of carbohydrates. Reaction of 4 with MeMgI affords the corresponding diol 6 in 78% yield. It seems likely that the chelation with magnesium leading to intermediate 5 may play a key role in controlling such selectivity. At 60 °C, bisacetonide 7 is transformed to monohydroxy derivative 8. The two glucose acetonides are readily accessible by literature procedures. Treatment of 9 with the Grignard reagent in benzene-ether yields 11 exclusively. Interestingly, both anomeric α- and β-methoxy groups in 9 give the same cleavage pattern, liberating the 2-hydroxy derivatives 11. The chelation of OMe group and the neighboring oxygen
function at C2 with magnesium may account for the results. When 9 (α-OMe) is treated with MeMgI under refluxing toluene conditions for 36 h, diol 12 is isolated in 71% yield.

Methylation of 11 (R = Me) with MeI/NaH followed by treatment with MeMgI gives the corresponding 4-OH derivative 13 in 58% yield. The reaction of 10 (R = H) under the same conditions yields 14 having hydroxy groups at C3 and C5 positions. In a similar manner, treatment of 10 (R = Me) with MeMgI gives 14 (R = Me) exclusively in 68% yield. The presence of a β-hydroxy or β-methoxy group at C3 in 10 appears not to be essential for the selectivity of this ring-opening process. Thus, the reaction of allose derivative 15 also affords 54% yield of the corresponding 5-OH product 16. These results indicate that the chelation with the oxygen atom on the five-membered heterocycle may determine the selectivity in these reactions. The reaction with galactose derivative 17 furnishes the 4-hydroxy derivative 18 in 52% yield. Presumably, the chelation with the methoxy group at C6 controls the regioselectivity.

The transformations involving fructose derivatives are interesting. Thus, treatment of 19 with MeMgI under usual conditions gives selectively 21 in 75% yield. Apparently, the methoxy group at C1 would assist the cleavage reaction to occur at C2 giving a ketone intermediate 20 which further reacts with MeMgI stereoselectively to yield 21. In a similar manner, the hydroxy group at C3 also aids the regioselective ring-opening of the acetonide at C2 in the reaction of 22 to afford 24 via 23.
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**SELECTIVE DEPROTECTION OF ACETONIDES TO LIBERATE DIOLS**

Trimethylsilylethyl group is a useful protective group for alcohols and can readily be removed by treatment with BF₃. Upon treatment with Me₃SiCH₂MgCl, 11 yields the corresponding diol 25 selectively. Similarly, diol 26 is isolated from the reaction of 10 with Me₃SiCH₂MgCl. Presumably, intermediate 11 (R = Me₃SiCH₂) is involved; indeed, when PhMe₂SiCH₂MgCl is employed, the corresponding silyl ether 11 (R = PhMe₃SiCH₂) has been isolated. This transformation provides an unprecedented procedure for the regioselective deprotection of a ketal group under basic conditions.

**SYNTHESIS OF TUNABLE C₂-CHIRAL 1,2-DIOLS**

As described in the previous section, the reactions of a neighboring bis-acetonide with MeMgI afford the corresponding diols regioselectively. This strategy can be used for the synthesis of various tunable C₂-chiral diols. Thus, 1,4-di-tert-alkoxy-(2S,3S)-2,3-butanediols 28 (R² = alkyl) can be easily accessible from the corresponding L-tartaric acid-based bisketals 27. Reduction of the bisketals 27 with LiAlH₄-AlCl₃ yields the corresponding 1,4-di-sec-alkoxy-(2S,3S)-2,3-butanediols 28 (R² = H). Diols 28 might demonstrate certain unique properties to serve as an auxiliary in asymmetric synthesis. First, the size of the alkoxy substituents can be tuned. Second, the oxygen atom in the alkoxy substituent can act as an additional ligand for complexation with the metallic species which would result in the enhancement of the stereoselectivity of the reaction. This advantage has been made use of in the diastereoselective ring-opening reactions of chiral acetals 29 with Grignard reagents. Treatment of (4S,5S)-29 with cyclic secondary, aryl or sterically hindered Grignard reagents in refluxing benzene solution affords diastereoselectively the corresponding ring-opening products 30 in good yield.
Several interesting features about the ring-opening reactions with the Grignard reagent are worthy of comment. These results provide the first example on the highly diastereoselective ring-opening of chiral acetals using sterically hindered or secondary cyclic Grignard reagents. Interestingly, the diastereoselectivities for the reactions of 29 with MeMgI in the presence and in the absence of TiCl₂(OPr)₂ are opposite. Presumably, the titanium reagent competes with the Grignard reagent for complexation resulting in the discrepancy in selectivity.¹⁰ It is noteworthy that the selectivity of such titanium-promoted reaction parallels to those in the other substrates using similar conditions.³

As mentioned earlier, the oxygen atom in the alkoxy substituent can act as an additional ligand for complexation with the metallic species. Accordingly, complexation between the substrate 29 and the Grignard reagent may occur; and with bulky Grignard reagent, intermediate 33 would be more stable than its stereoisomer 34. Although the actual mode of the ring-opening reaction of acetals is not yet clear, retentive displacement of the C-O bond by an alkyl group from intermediate 33 is speculated.

In order to clarify the validity of this conjecture, the reaction of (4S,5S)-31, which does not have the oxygen atom on the side chain for chelation, with MeMgI under similar conditions gives 32 in 82% yield with 30% de in favor of (2S,3S,1'R)-32. The selectivity is just opposite to that observed for the reactions of 29. This discrepancy suggests that the chelation intermediate 33 may be involved in the reaction of 29 with Grignard reagents leading to the displacement of a C-O bond by a C-C bond.¹⁰

Other synthetic usage of the tunable chiral diols has been executed. For example, excellent diastereoselectivity (up to 98% de) has been observed in the Simmons-Smith cyclopropanation of the cyclic enone-ketals 35 to give 36.¹² Further applications on the asymmetric synthesis using such tunable chiral auxiliary are in progress in our laboratory.

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REFERENCES