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REACTION OF 2-METHOXY-1,3-DIOXANE WITH GRIGNARD REAGENTS: REAGENT-SUBSTRATE COMPLEXATION AND STEREOELECTRONIC CONTROL.[1]

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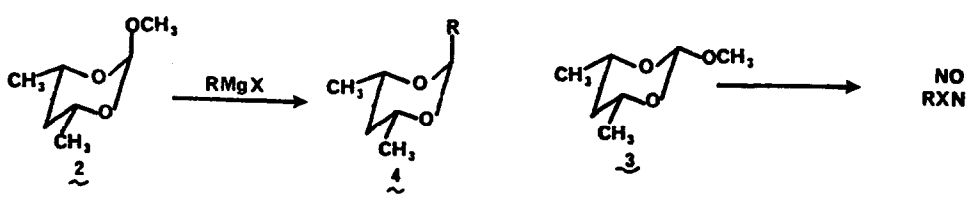
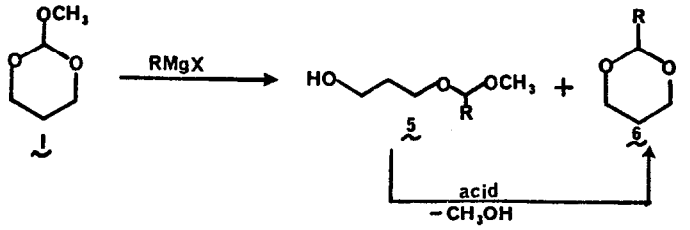
Abstract: The stereoelectronically controlled reaction of 2-methoxy-1,3-dioxane (1) with Grignard reagents does not follow the course suggested by the behavior of anancomeric models for the conformational isomers of 1. Treatment of 1 with RMgX leads to the predominant formation of acid labile 3-(1'-methoxyalkoxy)-1-propanols, derived from endocyclic cleavage of the ring C-O bond, and only minor amounts of the expected 2-R-1,3-dioxanes.

The fundamental importance of conformationally dependent stereoelectronic effects in the reactions of tetrahedral species bearing heteroatomic substituents has been demonstrated by recent experimental[2] and theoretical[3] work. The elegant investigations of Deslongchamps[4] have led to the formulation of a theory of stereoelectronic control which holds that the cleavage of a carbon-heteroatom bond is facile when there are at least two non-bonded electron pairs located antiperiplanar to the leaving group. Much of the experimental work in this area has, of necessity, focused on the stereochemical outcome of reactions involving conformationally biased (anancomeric) models. It has been assumed, albeit implicitly in most cases, that the behavior of conformationally mobile systems would follow the course suggested by such model studies. Herein we report on an investigation of the reaction of 2-methoxy-1,3-dioxane (1) with Grignard reagents which indicates that this assumption may not be valid when conformational changes may be occasioned by complexation of reagent with substrate prior to reaction.

The reaction of 1 with RMgX was expected to provide 2-substituted-1,3-dioxanes since 1 adopts a conformation (axial-OCH_3 favored by 0.62 kcal/mol in diethyl ether[5] due to the anomeric effect[6]) with the appropriate stereochemistry to allow for facile cleavage of the exocyclic C(2)-OCH_3 bond in a stereoelectronically controlled process. In fact, this classic Grignard-ortho ester reaction[7] has been probed by Eliel and Nader[8] using anancomeric substrates 2 and 3 as models for the two conformers of 1 and the results are consistent with stereoelectronic theory. The axially substituted ortho ester (2) reacts rapidly with RMgX in diethyl ether (1 hr at room temperature) to afford the axially substituted acetal (4) in a highly stereoselective reaction proceeding with retention of configuration.[8] The equatorial epimer (3) was found to be essentially inert under the reaction conditions employed.[8]





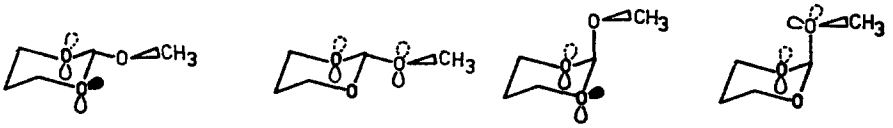
In striking contrast to the results of this model study, the parent ortho ester (1) reacts slowly with RMgX (mainly starting material material is recovered on stirring for 1 hr at ambient temperature in diethyl ether) and the major product is not the expected 2-substituted-1,3-dioxane. As shown below and in *Table 1*, the reaction affords high yields of the hitherto unknown 3-hydroxypropyl methyl acetals[9] (5) *via endocyclic C-O bond cleavage* along with minor amounts of the expected dioxanes[10] (6).

Structures 5a-d are seen to be the intermediates in the widely used transacetalization of dimethyl acetals with 1,3-propanediol to produce 6 and, as such, it is not surprising that they are extremely acid labile: a catalytic quantity of *p*-TsOH serves to convert 5 to 6 in quantitative yield. For this reason, it is entirely possible that the 1,3-dioxanes are produced by ring closure of 5 catalyzed by adventitious acid rather than as direct products of the reaction.[11] Moderate to good yields of 5a-d may be isolated (*Table 1*) by careful hydrolysis of the reaction mixture at 0°C with saturated, aqueous K_2CO_3.

The disparate behavior of 1 vis-a-vis the models 2 and 3 is perhaps best discussed within the framework of stereoelectronic theory.[4] Examination of the orbital interactions for exocyclic and endocyclic C-O bond cleavage from each conformation of 1 (Figure; following Deslongchamps[4]), reveals that they should display different modes of C-O cleavage: predominant loss of the $-OCH_3$ group from the axial conformer in a stereoelectronically facile reaction (as found for 2)[11] and exclusive endocyclic C-O bond rupture from the equatorial conformation in a much less favorable process. On this basis, the reaction of 1 with RMgX presents a seeming paradox: unbiased 1 shows no propensity for presumably facile loss of $-OCH_3$ from the axial conformer but rather undergoes predominant endocyclic ring cleavage in a slow reaction!

A clue as to the reason for this behavior is provided by the data in *Table 2*. The rate of reaction of 1 with EtMgBr (but not the mode of C-O cleavage) is dramatically dependent on the ability of the reaction medium to solvate RMgX: 1 is inert to the Grignard reagent in THF solution, but, in benzene containing the EtMgBr-diisopropyl ether complex[12], 1 is converted to 5b in 59% yield after only 30 min. These results indicate that a competition exists between 1 and solvent for solvation of the reagent and we suggest[13] that complexation between 1 and RMgX gives a species in which the $2\text{-}OCH_3$ moiety is effectively "locked" in a nonaxial position. The fact that model compound 3 is inert to the action of RMgX in all solvents[14] indicates that either: (i) the $2\text{-}OCH_3$ group of 1 is not equatorially situated on a chair conformation in the complex, or; (ii) the steric pertubation engendered by equatorial methyl substituents at C(4) and C(6) of the model renders 3 incapable of forming the necessary complex with RMgX. Experiments designed to distinguish between these two possibilities are in progress.

Figure: Examination of the orbital interactions for C-O bond cleavage.



EXOCLEAVAGE	ENDOCLEAVAGE	EXOCLEAVAGE	ENDOCLEAVAGE
No Primary Interaction!	Primary No Secondary	Primary 2 Secondary	Primary 1 Secondary

Table 1. Reaction of 1 with Grignard Reagents in Diethyl Ether.

RMgX	Conditions[a]	Yield[b,c] of 5, %	Yield[b] of 6, %	Recovered[b] 1, %
CH_3-	1.2 eq, 30 hrs, room temp	67 (61)	11	14
CH_3-	2.0 eq, 12 hrs, reflux	71	17	3
C_2H_5-	1.2 eq, 24 hrs, room temp[d]	34	24	26
C_2H_5-	2.0 eq, 15 hrs, reflux	70 (56)	22	1
$(CH_3)_2CH$-	2.0 eq, 15 hrs, reflux[e]	40 (35)	35	9
Ph-	1.2 eq, 18 hrs, room temp	65	28	4
Ph-	2.0 eq, 12 hrs, reflux	33	58	∿0

[a]Number of equivalents of RMgX, time, temperature. [b]Absolute yields determined by glc analysis of the reaction mixture and correction for detector response. [c]Isolated yields in parenthesis. [d]The reaction also afforded an 8% yield of 7b, see Ref. 10. [e]The reaction also afforded a 12% yield of 7d, see Ref. 10.

Table 2. Reaction of 1 with 1.2 Equivalents of EtMgBr in Various Solvents.

Solvent	Rxn. Time, hrs.	Yield[a] of 5b, %	Yield[a] of 6b, %	Recovered[a] 1, %
THF	20	∿0	∿0	99.6
Et_2O	3[b]	5	3.5	65.5
$(i\text{-}Pr)_2O$	1.5	51	25	20
C_6H_6[c]	0.5	59	32	9

[a]Absolute yield, see footnote b, *Table 1*. [b]The reaction in diethyl ether under these conditions also afforded a 17% yield of 7b, see Ref. 10. [c]The reagent was prepared from the EtMgBr-diisopropyl ether complex, see Ref. 11.

References and Notes

1. Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

2. See for example, (a) P. Deslongchamps, N. Beaulieu, R. Chenevert, and R. A. Dickinson, *Can. J. Chem.*, 58 1051 (1980); (b) A. J. Kirby and R. J. Martin, *J. C. S. Chem. Commun.*, 803 (1978); (c) O. Bouab, C. Moreau, and M. Zen Ako, *Tetrahedron Lett.*, 61 (1978).

3. See for example, (a) J. M. Lehn and G. Wipff, *J. Am. Chem. Soc.*, 96, 4048 (1974); (b) G. Wipff, *Tetrahedron Lett.*, 3269 (1978); (c) J. M. Lehn, G. Wipff, and H. B. Burgi, *Helv. Chim. Acta*, 57, 493 (1974).

4. (a) P. Deslongchamps, *Tetrahedron*, 31, 2463 (1975); (b) P. Deslongchamps, *Pure Appl. Chem.*, 43, 351 (1975); (c) P. Deslongchamps, U. O. Cherigan, A. Guida, and R. J. Taillefer, *Nouv. J. Chim.*, 1, 235 (1977); (d) P. Deslongchamps, *Heterocycles*, 7, 1271 (1977).

5. F. W. Nader and E. L. Eliel, *J. Am. Chem. Soc.*, 92, 3050 (1970).

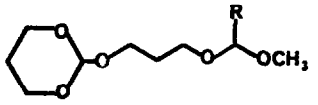
6. W. F. Bailey and E. L. Eliel, *J. Am. Chem. Soc.*, 96, 1978 (1974).

7. M. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances"; Prentice-Hall, New York, 1954, pp 586 ff.

8. E. L. Eliel and F. W. Nader, *J. Am. Chem. Soc.*, 92, 584 (1970).

9. Acetals having the structure of 5 would be named 3-(1'-methoxyalkoxy)-1-propanols. A few substituted acetals bearing strongly electron withdrawing groups have been observed to resist ring closure to cyclic acetals when treated with diols. These special cases provide the only unambiguous examples of the isolation of species analogous to 5. See, for example, the report of McElvain and Curry (*J. Am. Chem. Soc.*, 70, 3781 (1948)) on the reaction of chloral diethyl acetal with glycols.

10. In several instances the reaction of 1 with EtMgBr or i-PrMgBr in diethyl ether afforded low and erratic yields of mixed acetal-ortho esters identified as 2-[3'-(1"-methoxyalkoxy)propoxy]-1,3-dioxanes [R = C_2H_5 and R = $CH(CH_3)_2$].



These compounds are presumably generated *in situ* from 5b or 5d and unreacted 1 in the presence of a catalytic quantity of adventitious acid as evidenced by the fact that 7 may be prepared in moderate yield by the ZnI_2 catalyzed transacetalization of 1 with 5.

11. As reported in Ref. 8, 2 reacts with RMgX under the conditions employed in the present study to give high yields of axially substituted acetals (4). This reaction could *not* involve endocyclic C-O cleavage of 2 to give an anolog of 5 followed by ring-closure to the acetal since such a process would invariably lead to the thermodynamically more stable equatorial epimer (Ref. 5, 6 and 8) rather than 4 as observed.

12. G. Westera, C. Blomberg, and F. Bickelhaupt, *J. Organometal. Chem.*, 82, 291 (1974).

13. The suggested formation of a complex between 1 and RMgX prior to C-O bond cleavage is supported by the observation that an oily precipitate forms almost immediately upon addition of 1 to the Grignard reagent. The oil (stoichiometry unknown) affords unreacted 1 and alkane when hydrolyzed by the addition of saturated, aqueous K_2CO_3.

14. Compound 3 was treated with RMgX under each of the reaction conditions employed in this study (*Tables 1* and *2*) and we have been unable to detect any evidence for endocyclic C-O cleavage.

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