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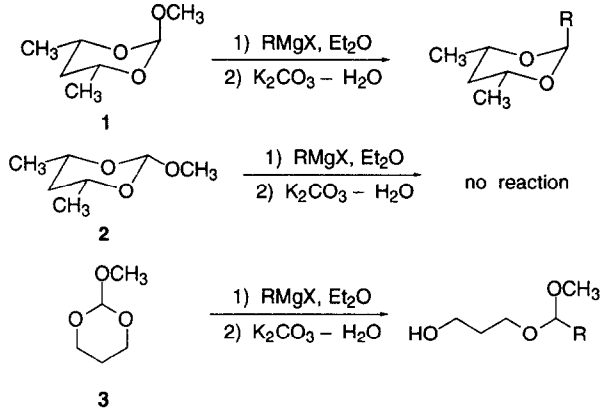
The Stereochemistry of the Grignard – Ortho Ester Reaction Revisited: Regioselective Endocyclic Cleavage in the Reaction of Grignard Reagents with *cis*-2-Methoxy-4-methyl-1,3-dioxane

William F. Bailey,* Allan A. Croteau and Alberto D. Rivera

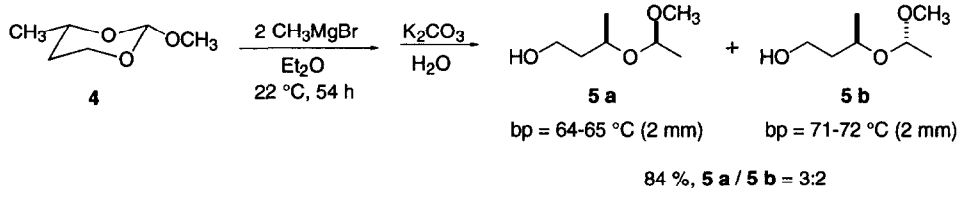
Department of Chemistry, University of Connecticut, Storrs, CT 06269-4060

Abstract: The reaction of *cis*-2-methoxy-4-methyl-1,3-dioxane (**4**) with Grignard reagents proceeds in a totally regioselective manner via rupture of the less congested C(2)–O(1) bond remote from the 4-methyl substituent. The analogous *r*-2-methoxy-*cis*-4,*cis*-6-dimethyl-1,3-dioxane (**2**) is totally inert to the action of Grignard reagents.

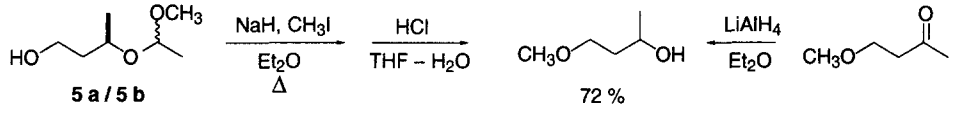
The conversion of an ortho ester to an acetal upon treatment with a Grignard reagent,[1] known as the Bodroux-Chichibabin reaction,[2] is a prototypical example of a stereoelectronically controlled transformation.[3] The stereochemistry of this process was elucidated by Eliel and Nader some twenty-five years ago in a study of the reaction of Grignard reagents with conformationally biased 2-methoxy-1,3-dioxanes (**1** and **2**).[4] As illustrated below, the axially substituted ortho ester (**1**) reacts rapidly with RMgX in diethyl ether at room temperature to afford the axially substituted acetal via exocyclic cleavage of the C(2)-OCH_3 bond with complete retention of configuration; the equatorial epimer (**2**) was found to be inert. In striking contrast to the results of this model study, the parent 2-methoxy-1,3-dioxane (**3**) was found to react slowly with Grignard reagents in diethyl ether at room temperature to give a 3-hydroxypropyl methyl acetal by endocyclic C(2)-O cleavage.[5] The failure of models **1** and **2** to reflect the behavior of 2-methoxy-1,3-dioxane (**3**) is due, in part, to the formation of a 1:1 complex between the less stable, equatorial isomer of **3** and a Mg^{2+} species ($RMgX$, R_2Mg, MgX_2)[6] prior to the cleavage step.[5,6] Indeed, the stereoelectronically favorable outcome of reaction between RMgX and a 1,3-dioxane bearing an equatorial 2-OCH_3 group is endocyclic C–O bond rupture.[3,5] The apparent dilemma is this: why is endocyclic C–O cleavage not observed in the reaction of **2** with Grignard reagents? As detailed below, the Grignard – ortho ester reaction is acutely sensitive to the presence of substituents adjacent to ring oxygens. Consequently, whereas **2** is totally inert to the action of RMgX, the analogous *cis*-2-methoxy-4-methyl-1,3-dioxane (**4**) reacts via a totally regioselective endocyclic cleavage of the C–O bond remote from the 4-methyl group.



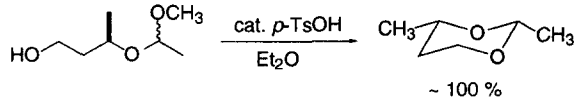
The conformationally homogeneous *cis*-2-methoxy-4-methyl-1,3-dioxane[4] (**4**) reacts cleanly, albeit very slowly, with an excess of MeMgBr in diethyl ether at room temperature under an atmosphere of dry nitrogen. While less than 5 % of the ortho ester is consumed on stirring for 3 h at ambient temperature, prolonged reaction (54 h at 22 °C) of **4** with ethereal MeMgBr gives an 84 % isolated yield of two isomeric products (**5a** and **5b**), in a ratio of ~3:2, derived from endocyclic C–O cleavage. The reaction is considerably faster when run at reflux in diethyl ether; a 76 % isolated yield of **5a** / **5b** (~ 3:2) results when **4** is heated at reflux for 14 h with 2 equiv of the Grignard reagent. Remarkably, the products are readily separated by distillation through a 3-ft spinning-band column (reflux ratio = 10:1). Despite the fact that cleavage of either endocyclic C–O bond in **4** would appear equally likely on purely stereoelectronic grounds,[3,5] both cleavage products, **5a** and **5b**, were derived via selective rupture of the C(2)–O(1) bond remote from the 4-methyl substituent. It should be noted that the reaction of **4** with MeMgBr is totally regioselective within the limits of detection by GC and ^{1}H NMR of the crude reaction mixture:[7] there was no evidence of any product resulting from cleavage of the C(2)–O(3) bond adjacent to the 4-methyl group.



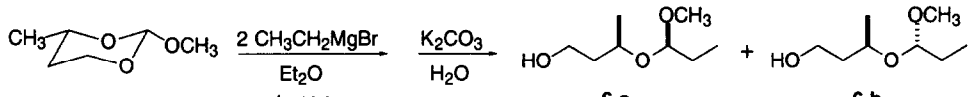
The ^{1}H NMR spectra of **5a** and **5b** in DMSO-d_6 revealed that both products are primary alcohols:[8] the OH resonance of each isomer appears as a well resolved triplet.[9] These constitutional assignments were confirmed, as illustrated below, by conversion of a 1:1 mixture of **5a** and **5b** to 4-methoxy-2-butanol in 72 % yield; the alcohol was identical in all respects to an authentic sample prepared by reduction of 4-methoxy-2-butanone.[10] Assignment of the relative configurations of **5a** and **5b** is more problematic: the materials are extremely acid sensitive (vide infra) and it has not proved possible to unambiguously correlate the stereocenters. Thus, the configurational assignments, which were made on the basis of subtle differences in ^{13}C NMR chemical shifts of the isomers[9] by analogy with hydrocarbon models,[11] are provisional; the major product, having the lower bp (**5a**), is tentatively formulated as the syn-diastereoisomer derived from C(2)–O(1) cleavage with retention of configuration at C(2).



Not surprisingly, the cleavage products are extremely labile. As shown below, a catalytic quantity (<1-mol %) of *p*-toluenesulfonic acid serves to convert an ethereal solution of either **5a** or **5b** to *cis*-2,4-dimethyl-1,3-dioxane in essentially quantitative yield.



The reaction of **4** with a variety of other Grignard reagents was surveyed with similar results. The reaction with EtMgBr, shown below, is illustrative of the general trend: rupture of the less congested endocyclic C–O bond is the exclusive mode of cleavage. It is of interest to note that the rate of these reactions (but not the mode of C–O cleavage) is a strong function of the solvent in which the reaction is conducted.



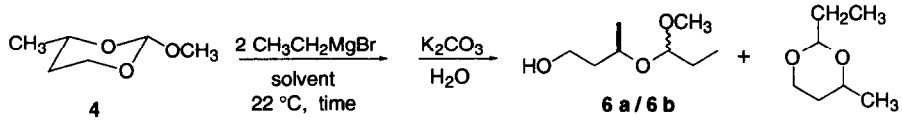
4 **6 a** **6 b**

bp = 72-73 °C (2 mm) bp = 80-81 °C (2 mm)

60 %, **6 a** / **6 b** = 4:3

As noted elsewhere, the rate of the Grignard – ortho ester reaction is dramatically dependent on the ability of the medium to compete with the ortho ester as a solvate for RMgX.[1,5] The data summarized in Table 1 reveal that **4** is inert to the action of EtMgBr in THF solution, but, in benzene containing the EtMgBr–(i-Pr)$_2$O complex,[12] a 36 % yield of **6a** and **6b** is realized after only 0.5 h at room temperature.

Table 1. Reaction of **4** with EtMgBr in Various Solvents at Room Temperature.



4 **6 a / 6 b**

entry	solvent	time, h	products, % yield [a]		
			6 a / 6 b		recovered **4**
1	THF	20	0	0	96
2	Et_2O	3	3	4	82
3	(i-Pr)$_2$O	1.5	31	22	36
4	C_6H_6[b]	0.5	36	24	25

[a] Yields were determined by GC and are corrected for detector response. [b] The reagent was prepared from the EtMgBr–diisopropyl ether complex; see ref. 12.

The totally regioselective cleavage of the C(2)–O(1) bond remote from the 4-methyl group observed when **4** is treated with a Grignard reagent demonstrates that the Grignard – ortho ester reaction of a 1,3-dioxane bearing an equatorial 2-OCH$_3$ group is acutely sensitive to steric effects engendered by a substituent located adjacent to a ring oxygen. Moreover, these results are fully consistent with the report by Eliel and Nader that *r*-2-methoxy-*cis*-4,*cis*-6-dimethyl-1,3-dioxane (**2**) is inert to the action of Grignard reagents in diethyl ether

solution.[4] Indeed, treatment of **2** with an excess of EtMgBr in diethyl ether at reflux for 12 h, or with the EtMgBr–diisopropyl ether complex in benzene solution for 2 h, does not result in any observable cleavage of the endocyclic C–O bond.[13] Thus, the failure of **2** to participate in the Grignard – ortho ester reaction is attributable to the presence of substituents at both C(4) and C(6). In this connection, it might be noted that similar regioselectivity of steric origin has been documented in the acylative cleavage of substituted 1,3-dioxanes with acetic anhydride or acetyl chloride.[14]

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

References and Notes

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7. In addition to **5a** and **5b**, the reaction of **4** with MeMgBr affords variable amounts (5 - 15 %) of *cis*-2,4-dimethyl-1,3-dioxane. This cyclic acetal is most probably the result of facile ring-closure of the cleavage products in the presence of adventitious acidic species present in the reaction mixture or introduced inadvertently on work-up.
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9. Satisfactory exact mass spectroscopic molecular weights have been determined for all previously unreported compounds. NMR spectra of highly acid-sensitive products were obtained in both DMSO-d_6 solution and in $CDCl_3$ solution to each of which a drop of dry pyridine had been added to neutralize any adventitious acid. **5a**: ^{1}H NMR (DMSO-d_6) δ 1.07 (d, J = 6.12 Hz, 3 H), 1.17 (d, J = 5.26 Hz, 3 H), 1.45–1.72 (m, 2 H), 3.20 (s, 3 H), 3.40–3.46 (m, 2 H), 3.71–3.92 (m, 1 H), 4.33 (t, J = 5.10 Hz, *OH*),4.65 (q, J = 5.26 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.07 (q), 20.27 (q), 39.61 (t), 52.39 (q), 59.81 (t), 70.56 (d), 99.17 (d). **5b**: ^{1}H NMR (DMSO-d_6) δ 1.12 (d, J = 6.29 Hz, 3 H), 1.16 (d, J = 5.21 Hz, 3 H), 1.40–1.72 (m, 2 H), 3.19 (s, 3 H), 3.33–3.94 (overlapping patterns, 3 H), 4.36 (t, J = 5.02 Hz, *OH*), 4.62 (q, J = 5.21 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.94 (q), 21.15 (q), 39.40 (t), 51.87 (q), 59.64 (t), 71.63 (d), 100.42 (d).
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13. The only product detected from prolonged reaction of **2** with EtMgBr was a small and variable amount of *r*-2-ethyl-*trans*-4,*trans*-6-dimethyl-1,3-dioxane bearing an axial 2-Et group. This acetal is undoubtedly produced, as noted by Eliel and Nader,[4] via epimerization of **2**, to give the thermodynamically more stable axial 2-OCH_3 isomer, followed by facile cleavage of the exocyclic C–O bond with retention of configuration.
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