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Magnesium Bromide Promoted Barbier-Type Intramolecular Cyclization of Halo-Substituted Acetals, Ketals, and Orthoesters

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Abstract: Although acetals, ketals and orthoesters are commonly used as protective groups against organometallic reagents, Grignard reagents derived from halo-acetals, ketals, or orthoesters cyclize intramolecularly under $MgBr_2$ promoted conditions, giving rise to the corresponding cycloalkanol and cycloalkanone derivatives. Our results also suggest a Lewis acid catalyzed push-pull mechanism operating for the cyclization. © 1999 Elsevier Science Ltd. All rights reserved.

Because of their high stability towards Grignard reagents, protection of carbonyl compounds as acetals or ketals becomes a very common and valuable tactic during synthesis.[1] However, on treatment of ω-haloacetals with magnesium, formation of unexpected intramolecular cyclization products is occasionally observed.[2,3e] This observation prompted us to investigate the details of this one-step cyclization. A survey of the chemical literature, as well as our preliminary experimental results, revealed that the relevant Grignard reagents could be effectively prepared in THF.[3] In diethyl ether, however, the reaction is in general difficult to initiate. Although addition of 1,2-dibromoethane as a promoter does trigger the reaction, formation of the intramolecular cyclization product is inevitable. More interesting is the fact that the yield of the cyclization product **1a** from **1** (Table 1) increased with increasing amounts of $BrCH_2CH_2Br$ used. Maximum yield was obtained when over 4 equivalents of $BrCH_2CH_2Br$ were employed. In addition, polymerization does not occur under these conditions. Since $MgBr_2$ is generated from $BrCH_2CH_2Br$ during the course of reaction,[4] the success of the cyclization is likely attributable to a Lewis-acid assisted mechanism.[5]

Under our conditions, as the results in Table 1 show, the three and five membered ring precursors **1-5** deliver cyclized products in higher yields. In addition, the ω-haloalkyl-1,3-dioxolanes **3** and **8** cyclize more effectively than the corresponding 1,3-dioxane precursors **2** and **7**. The difference in cyclization behavior of these systems clearly outlines the reaction mechanism. The order of 3~5 > 4 for the ring-closures is in good agreement with the general trend for kinetically-controlled intramolecular cyclization,[6] indicating that the ring-closure process is the rate-determining step. On the other hand, our experimental results also suggested that the acetal ring opening process should be involved in the transition state. Strain released from ring-opening of the

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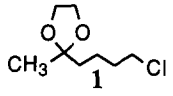
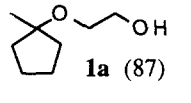
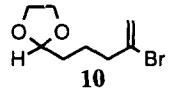
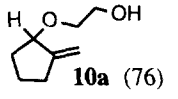
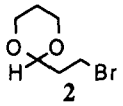
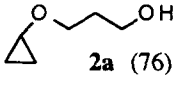
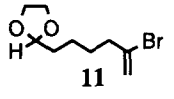
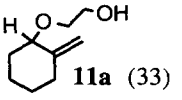
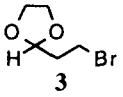
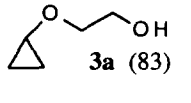
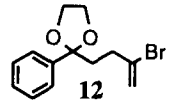
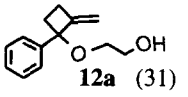
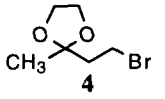
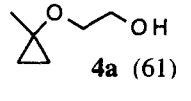
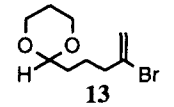
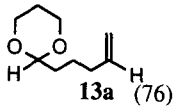
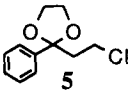
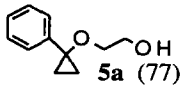
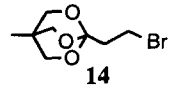
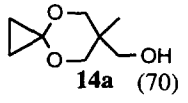
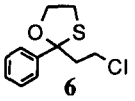
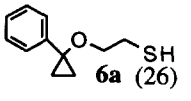
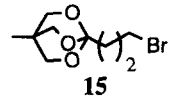
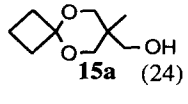
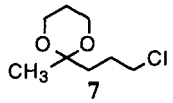
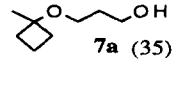
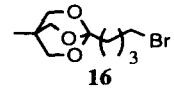
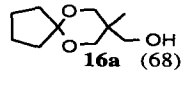
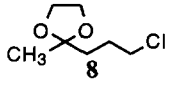
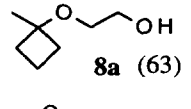
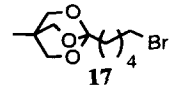
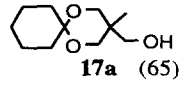
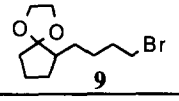
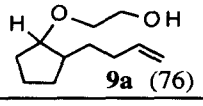
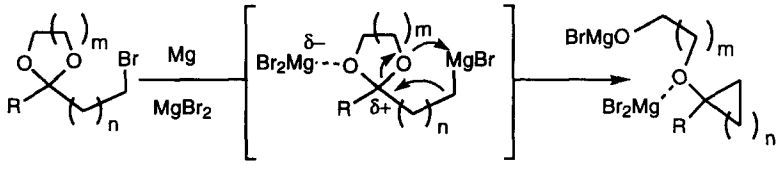
Table 1: Magnesium Bromide Promoted Barbier-Type Intramolecular Cyclization of Halo-Substituted Acetals, Ketals, and Orthoesters

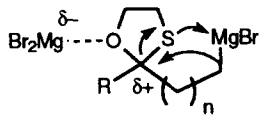
Haloacetals, ketals or orthoesters	Cyclization Product (yield)	Haloacetals, ketals or orthoesters	Cyclization Product (yield)
 **1**	 **1a** (87)	 **10**	 **10a** (76)
 **2**	 **2a** (76)	 **11**	 **11a** (33)
 **3**	 **3a** (83)	 **12**	 **12a** (31)
 **4**	 **4a** (61)	 **13**	 **13a** (76)
 **5**	 **5a** (77)	 **14**	 **14a** (70)
 **6**	 **6a** (26)	 **15**	 **15a** (24)
 **7**	 **7a** (35)	 **16**	 **16a** (68)
 **8**	 **8a** (63)	 **17**	 **17a** (65)
 **9**	 **9a** (76)		

five-membered 1,3-dioxolane could partially compensate for the activation energy and therefore be beneficial for the cyclization. On the contrary, the less strained 1,3-dioxanes are relatively stable and therefore sluggish towards the acetal ring-opening process. All these observations are indeed consistent with a Lewis acid catalyzed push-pull mechanism.

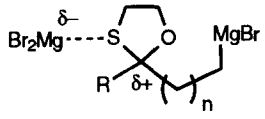


When 1,3-oxothiolane derivative **6** reacts under the same conditions, the C-S bond is cleaved regioselectively to give **6a** as the product. Since $MgBr_2$ is a hard Lewis acid, it is expected to complex preferentially to the hard

oxo atom and therefore the C-S bond is cleaved selectively through the cyclic transition state. This result agrees with the previous model proposed for the 1,3-dioxolane system.

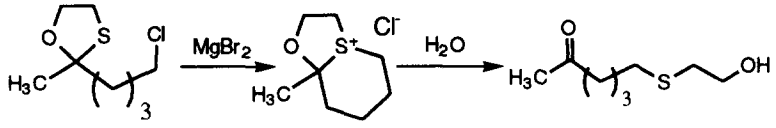


Favored hard acid-hard base interaction



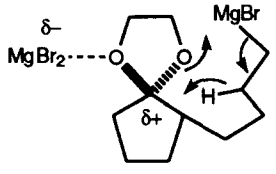
Disfavored hard acid-soft base interaction

For **18**, instead of the cyclization product, thioethanol **18a** was isolated in high yield. We tentatively attributed this to the formation of sulfonium salt **19** that would be hydrolyzed finally to afford **18a** as the major product.



18 **19** **18a**

In the case of spiro-ketal **9**, perhaps due to ring-strain in the transition state, hydride transfer preferentially occurs to give terminal olefin **9a** as the major product. Hydride transfer commonly occurs in the reaction of sterically hindered alkyl magnesium halides with ketones, giving rise to alcohols as the reduction products.[7]



Following the success of previous cyclizations, our attention turned next to the 2-bromoalkenyl derivatives **10-13**. Again the five-membered ring precursor **10** cyclized most effectively under our conditions to afford **10a** in high yield. In addition, when the less strained six-membered 1,3-dioxane precursor **13** was employed, no cyclization product could be isolated.

Under no condition could the one-step cyclization of ω-haloalkylesters be performed, according to previous literature,[7] our reaction conditions were successfully applied to ω-haloalkylorthoesters **14-17** to give protected cycloalkanones **14a-17a** in moderate yields. This reaction is particularly useful for preparing cyclopropanone derivatives in one step.

In summary, our Lewis-acid catalyzed reaction conditions provide a mild and effective way for the Barbier type one-step cyclization. Application of this reaction to other systems is under investigation.

A general procedure is described as follows: To a suspension of Mg powder (1.6 g, 65 mmol) and iodine (catalytic amounts) in ether (6 mL) was added slowly $BrCH_2CH_2Br$ (9.3 g, 44 mmol) in ether (15 mL). The reaction is exothermic and should be cooled in an ice-bath. After complete addition of $BrCH_2CH_2Br$, a solution of **1** (1.78 g, 10 mmol) in ether (5 mL) was added dropwise. The reaction mixture was then kept at reflux temperature for 25 h, quenched by addition of aqueous NH_4Cl, extracted with CH_2Cl_2, chromatographed on silica gel, using ethyl acetate-hexanes (1:4 to 1:3) as eluent to give a colorless oily product **1a** (1.25 g, 87 %).

Acknowledgements

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References and Notes

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