

STERIC EFFECTS IN THE REACTION OF DI(BROMOMAGNESIO)ALKANES WITH
CARBOXYLIC ESTERS

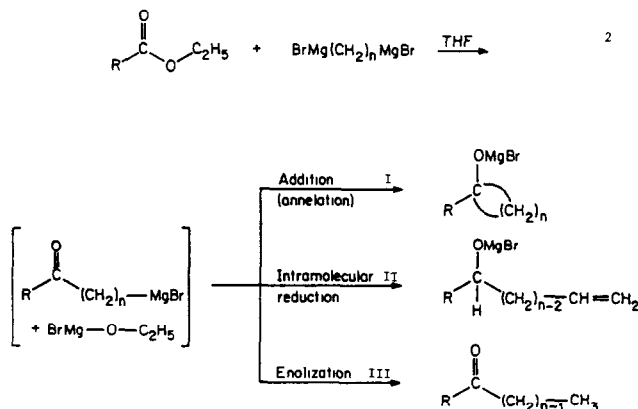
Perséphone Canonne*, Denis Bélanger and Gilles Lemay

Département de chimie, Université Laval, Québec Canada G1K 7P4

Summary. Largely different product distributions were observed on the action of various carboxylic esters with 1,4-di(bromomagnesio)butane and its homologue 1,5-di(bromomagnesio)pentane. The much larger yields of reduction product with the latter are the evidence for the structural geometric requirements for the annelation step.

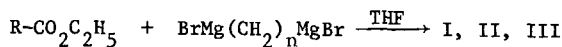
In preceding papers we have reported that the 1,4-di(bromomagnesio)butane and 1,5-di(bromomagnesio)pentane react with lactones and dicarboxylic anhydrides in presence of tetrahydrofuran solution, producing cyclopentane and cyclohexane compounds by two consecutive attacks of the nucleophilic compound¹⁻⁵. We observed that the formation of the cyclohexane ring is slightly more affected by steric factors than the cyclopentane, especially in the cases of monocyclic and hindered lactones or carboxylic acid anhydrides^{2,5}. More recent results show that the yields of the reactions of the two preceding di-Grignard reagents with bicyclic anhydrides in rigid systems are very high⁶. In fact in both reactions after work-up the spiro- γ -lactone crystallized and the ¹H-NMR spectra indicates that this lactone is the unique reaction product. Previously, it was noted that the reaction of the same di(bromomagnesio)alkanes with esters in the presence of diethylether solutions produced the corresponding cycloalkanol in lower yields⁷. These authors studied only the annelation products; their yields varied from 40 to 50%. With the pentane homologue the yields were always lower than with the butane homologue. More recently Ferles *et al.* reported a very low yield (< 10%) for the annelation product from the reaction of 1,4-di(bromomagnesio)butane on ethyl isonicotinate in THF solution.

In the present paper we report results on the reaction of these di-Grignard reagents with carboxylic esters in tetrahydrofuran solution. Various carboxylic esters have been studied in order to determine which factors affect the product distribution. For that purpose we investigated not only the addition products but also those of reduction and enolization. (scheme 1). Also the choice of cyclohexane carboxylic ester and ethyl benzoate allows comparison with those substrates which give good yields of annelation with lactones and cyclic anhydrides. Finally the reactions with the pyridine carboxylic esters enable a comparison with the results of Ferles.



Scheme 1

Table 1 : PRODUCT DISTRIBUTION IN THE REACTIONS OF 1,4-DI(BROMOMAGNESIO)BUTANE AND 1,5-DI(BROMOMAGNESIO)PENTANE WITH CARBOXYLIC ESTERS^a.



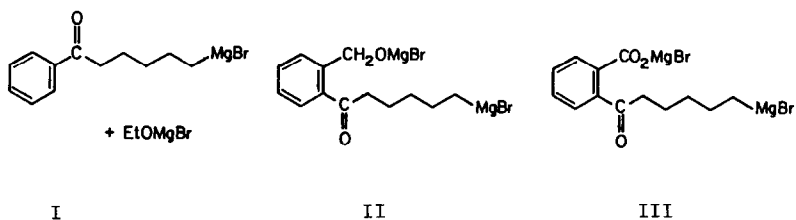
R	n	% Ann. I	% Red. II	% Enol.
methyl	4	94	6 ^b	
	5	88	6 ^b	6
phenyl	4	95	5 ^b	
	5	22	74 ^b	4
cyclohexyl	4	93	7 ^b	
	5	16	84 ^b	
2-pyridyl	4	92	8 ^b	
	5	19	69 ^c	12
3-pyridyl	4	90	10 ^b	
	5	9	86 ^b	5
4-pyridyl	4	92	8 ^b	
	5	6	88 ^b	6

a) Percentages determined by ¹H-NMR are believed accurate within 8%.

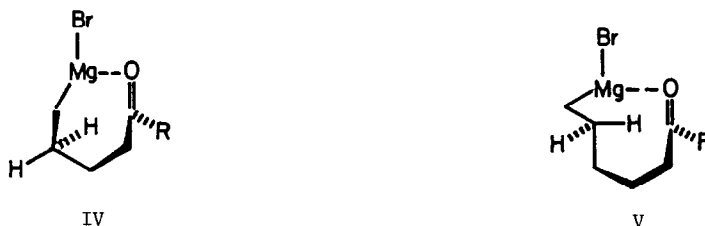
b) Evidence of some secondary alcohol from intramolecular reduction process.

c) Indication of two secondary alcohols formation: One unsaturated, from intramolecular reduction, the other saturated, from intermolecular reduction.

As may be gathered from Table 1 the two di-Grignard reagents show widely different product distribution in THF solution. Briefly, the 1,4-di(bromomagnesium)butane gives mainly addition products (cyclopentanols) whereas the 1,5-di(bromomagnesium)pentane gives mainly the reduction products (open chain secondary alcohols). Also the 1,5 Grignard derivative leads to enolization products. These results are in contrast with those from the corresponding lactones and cyclic carboxylic acid anhydrides. A plausible explanation is based on the structure of the intermediates (I, II, III) formed by the reactions of ethyl benzoate, phthalide, and phthalic anhydride with 1,5-di(bromomagnesium)pentane:



Furthermore, since there was no detectable amount of the initial ester among the reaction products, it follows that the addition is faster than the other competing processes. It is clear that the further addition leading into annelation is slower with 1,5-di(bromomagnesium)pentane. Likewise the same type of rationale, the oxoalkylmagnesium bromide intermediate must be responsible for the ratio of cyclic and open chain alcohols. The annelation reaction with 1,4-di(bromomagnesium)butane would be less affected by steric factor than that with its homologue. Accordingly, we suggest the two configurations (IV and V) for the two intermediates in the annelation step¹⁰.



As figures IV and V show the two intermediates are quite different. In the case of cyclohexyl ring formation the geometry favors the reduction via a six-membered transition state¹¹ rather than the addition. In contrast, in the cyclopentyl ring formation there is no steric hindrance to the addition reaction.

Experimental: The ethyl benzoate (0.06 mol) in anhydrous THF (50 ml) was added with vigorous stirring to the 1,5-di(bromomagnesium)pentane (0.07 mol) in anhydrous THF (150 ml) at room temperature and under nitrogen atmosphere. The mixtures were distilled. However, the two alcohols could not be separated as their boiling points are very close. The $^1\text{H-NMR}$ and IR spectra confirmed their presence and the lack of the initial product ethyl benzoate.

References.

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- 11) Inspection of a model of this reduction process indicated that a transition state of this type may be accommodated without serious strain by the inherent geometry.

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