Tetrahedron Letters No. 9, pp 615 - 618, 1975. Pergamon Press. Printed in Great Britain.

CYCLIZATIONS OF PHENYL SUBSTITUTED ALKENYL GRIGNARD REAGENTS

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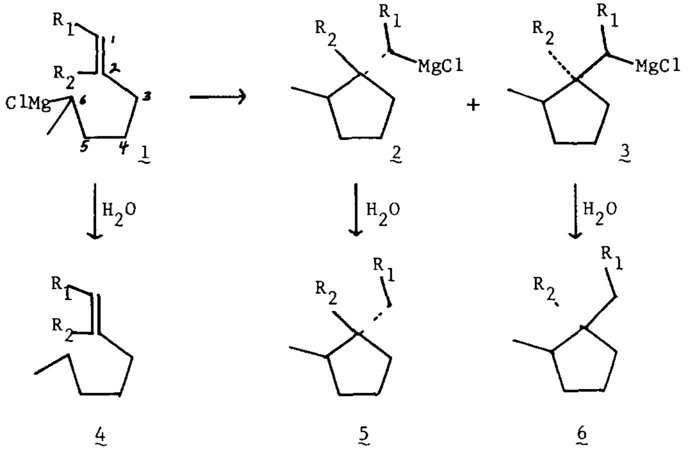
(Received in USA 17 July 1974; received in UK for publication 16 January 1975)

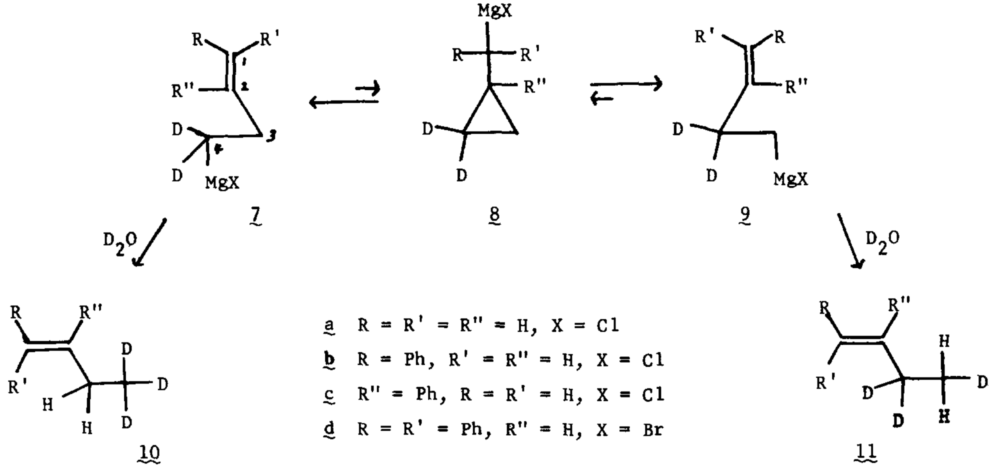
Cyclization of unsaturated Grignard reagents (or the reverse reaction, ring cleavage of strained cyclic Grignard reagents) has been studied in a range of systems,[1-12] but the detailed mechanism has yet to be established[13] We earlier reported that cyclization of **1a** is retarded *ca.*



a $R_1 = R_2 = H$
b $R_1 = CH_3$, $R_2 = H$
c $R_1 = H$, $R_2 = CH_3$ (**5c** = **6c**)
d $R_1 = Ph$, $R_2 = H$

1000-fold by either a C-2 (**1c**) or a *trans* C-1 (**1b**) methyl substituent[4f] It has since been reported that cyclization of **7** also is retarded significantly by a methyl substituent at C-2,[12c] by one (*trans*) or two methyl substituents at C-1,[12e] or by a chloro substituent at C-1[3f] However, early qualitative observations[1c] suggested that two phenyl substituents at C-1 greatly accelerated cyclization[14] Therefore, it seemed an important probe of mechanism to determine with certainty the effect of single phenyl substituents at each end of the double bond

Grignard reagents **1d**, **7b**, **9c**, and **7d** were prepared from the corresponding halides Cyclization of 7 or 9 leads to the less stable 8 that is not detected directly, but whose formation is the rate-determining step of the 7 ⇄ 9 isomerization The reactions were followed by glpc (for 1d) or nmr (for 7b, 9c, and 7d) analysis of the hydrocarbon mixtures obtained on hydrolysis (with D_2O for 7b, 9c, and 7d) of reaction aliquots. The first-order rates observed at 100° for ether solutions of 7b and 9c[15] were 29 x 10^{-6} and 14 x 10^{-6} sec^{-1}, respectively. Since the rate of 7a is 4 6 x 10^{-2} sec^{-1},[16] phenyl substitution at either carbon of the double bond leads to a substantial reduction in rate.[17,18] The equilibrium constant for the 7b ⇄ 9b isomerization was *ca* 1.39 [19] The lesser stability of 7b is not surprising since deuterium ordinarily acts as an "electron-releasing" substituent.



7 8 9

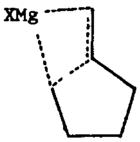
10 11

a R = R' = R'' = H, X = Cl
b R = Ph, R' = R'' = H, X = Cl
c R'' = Ph, R = R' = H, X = Cl
d R = R' = Ph, R'' = H, X = Br

The observation that a phenyl group at C-1 greatly decreased the rate of cyclization of 7a led us to reinvestigate the earlier conclusion that two phenyl substituents at C-1 led to a rapid equilibration (7d ⇄ 9d) that was complete by the time of first observation. After reaction of the bromide (corresponding to 7d) with magnesium at 0°, rearrangement was substantial *but not complete*, the ratio 7d 9d was *ca* 58 42 [21] Further rearrangement proceeded only slowly After two weeks at 100° a composition of *ca*. 45 55 was attained,[21] and equilibrium still had not been achieved. Although precise rate and equilibrium constants could not be obtained, the rate constant must be within a factor of 2 or 3 from 1 x 10^{-6} sec^{-1}. Therefore, the diphenyl system cyclizes even more slowly than the monophenyl systems The initial rapid rearrangement (observed, although to lesser extents, in the preparations of the other Grignard reagents used in this study) probably is due to a radical intermediate that intervenes during Grignard reagent preparation.[22]

By contrast, the phenyl substituent in **1d** does not decrease the rate. The rates observed at 100° for tetrahydrofuran solutions are 27 x 10^{-8} sec^{-1} for **1d** and[4f] 3.7 x 10^{-8} sec^{-1} for **1a**. The differing effects of a C-1 phenyl substituent in **1** and **7** suggest the interplay in the cyclizations of at least two effects of the phenyl substituent — most probably a rate-increasing electronic effect and a rate-decreasing steric effect.[13]

Immediately following preparation of the Grignard reagent, the ratio (**5d** **6d**) of *trans* and *cis* isomers (that arise from a rapid cyclization during Grignard reagent formation) was *ca*. 0.28[23] Within experimental error, the subsequent cyclization was completely *trans*, the *trans* *cis* ratio certainly exceeded 25.[24] The predominant formation of the *trans* isomer is one piece of evidence not necessarily accomodated by the concerted pathway (**12**, the requisite bond formations and



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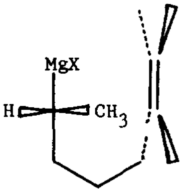

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cleavages being relatively synchronous) that has been used with considerable success[3g] to rationalize the effects of structure on cyclizations of unsaturated Grignard reagents. A large steric interaction (see **13**, but the interaction is even more evident if models are examined) develops between the methyl group at the α-carbon and the internal carbon of the double bond along a concerted (*syn*-*syn*) pathway leading to the *trans* isomer This interaction can decrease only as the old C-Mg bond cleaves sufficiently to allow the methyl substituent to pivot into the *trans* position that it will occupy in the product. The corresponding interaction along the pathway leading to the *cis* isomer involves the α-H rather than the α-CH$_3$ and will be much smaller.

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(13) It is assumed that the same reaction pathway is followed by all unsaturated Grignard reagents

(14) The diphenyl system had X = Cl, but the parent system X = Br However, the difference between chlorides and bromides has been small whenever both have been studied $^{3a\ 3g,4b,4d,4g}$

(15) A rate *ca* 10-fold larger has been reported for the rearrangement of **7c** (X = Br) to **9c** ^{12c}

(16) Extrapolated from data^{1a} obtained at lower temperatures

(17) It has been shown for the 5-hexen-1-yl system in tetrahydrofuran that cyclization is first-order both in RMgX and in RMgR, that RMgR is *ca* 50 times more reactive than RMgBr, and that significant amounts of both species are present in solution^{4h} Therefore, it is apparent that comparison of rates of different systems could be misleading to the extent that the Schlenck (or polymerization) equilibria differ or that different concentrations of excess halogen (MgX$_2$ is produced by side reactions during Grignard reagent formation) are present However, effects due to such complications probably are negligible compared to the large effects of substituents

(18) The effect of a phenyl group at C-4 on the rearrangement of the 3-cyclohexen-1-yl Grignard reagent is small,^{3g} but the exact magnitude of the effect is not certain

(19) Because the hydrocarbon obtained by hydrolysis with D$_2$O of the **7c**-**9c** mixture contained a constant amount (*ca* 30%) of dideuterated material,^{20} the areas of the methyl and methylene nmr absorptions do not correspond exactly to the relative amounts of **9c** and **7c** Values of *ca* 1 48 have been reported for the corresponding dialkylmagnesium compound, but of only *ca* 1 10 (at 80°) for the 3-methyl-3-buten-1-yl Grignard reagent (X = Br) ^{12c}

(20) The dideuterated material arose most probably by attack on solvent by intermediates present during the preparation of the Grignard reagent

(21) Because of *ca* 15% of dideuterated material in the hydrocarbon obtained by hydrolysis with D$_2$O,^{20} this ratio does not correspond exactly to the relative amounts of **7d** and **9d**

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(23) The configurations of **5d** and **6d** have been established [R M Bension, unpublished observations]

(24) Preferential formation of *trans* isomers was noted before,^{4f} but the data did not permit assigning such a high minimum to the *trans cis* ratio