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Preliminary communication

Intramolecular coordinative assistance in the addition of Grignard reagents to unconjugated carbon–carbon unsaturation

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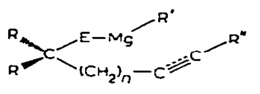
Our report of the first authenticated addition of a Grignard reagent to an unconjugated ethylene linkage[1] has raised considerable curiosity as to the scope, limitations and mechanism of this interesting reaction. Subsequent publications have shown the reaction to be feasible both with allylic[2], as well as homoallylic[1], alcohols. The present study brings forward results bearing not only on the generality of this novel Grignard reaction, but on its stereochemical and mechanistic aspects as well. Proceeding upon the tentative hypothesis offered in the original report[1], we have investigated the validity of intramolecular coordinative assistance by the carbinolate oxygen in bringing the carbon–magnesium bond in proximity to the carbon–carbon unsaturation (model I, E = O, n = 1, $C\overset{..}{=}CR$ = vinyl).



(I)

In order to test the generality of model I we have studied: (*a*) the reaction of allylmagnesium bromide with a series of ω-alkenyldiphenyl-carbinols (as carbinolates, I; R = C_6H_5; n = 0, 1, 2 or 4; $C\overset{..}{=}C$ = vinyl; E = O); (*b*) the reaction of allylmagnesium bromide with 1-(1-propynyl)- and 1-(2-butynyl)-cyclohexanols (as carbinolates, I, R,R = cyclohexylidene; n = 0 or 1; $C\overset{..}{=}C$ = 1-propynyl; E = O); (*c*) the reaction of allylmagnesium bromide with α-allylbenzhydryl methyl ether (I, R = C_6H_5; n = 1; $C\overset{..}{=}CR$ = vinyl; E = OCH_3) and with α-allylbenzhydrylaniline (as anilide, I, R = C_6H_5; n = 1; $C\overset{..}{=}C$ = vinyl; E = NC_6H_5); and (*d*) the individual reactions of allyldiphenylcarbinol (as carbinolate, I, R = C_6H_5; n = 1; $C\overset{..}{=}CR$ = vinyl; E = O) with benzylmagnesium bromide, tert-butylmagnesium bromide, phenylmagnesium bromide, diphenylmagnesium, and diallylmagnesium. In most of the foregoing cases addition of the carbon–magnesium bond to the olefinic or acetylenic linkage was realized by heating in refluxing ether or toluene. No addition could be observed, however, in the following cases: (*a*) allyldiphenylcarbinol with either phenylmagnesium bromide or diphenylmagnesium; (*b*) allylmagnesium bromide with ω-hexenyldiphenylcarbinol; and (*c*) allylmagnesium bromide with α-allylbenzhydrylaniline, where, instead, degradative cleavage to benzhydrylaniline ensued[3]. It is also relevant to note the inertness

TABLE 1

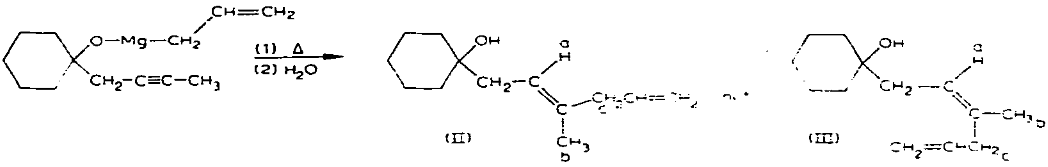
REACTION OF GRIGNARD REAGENTS WITH SUBSTRATES HAVING UNCONJUGATED CARBON–CARBON UNSATURATION

Substrate	Grignard reagents	Molar ratio (S/GR)	Solvent (temp.)	Time (h)	Product(s)[a] (Yield, %)
Vinyldiphenylcarbinol	C_3H_5MgBr	1/2.5	ether (r.t.)	240	1,1-Diphenyl-1,5-hexadiene, 13[e]
		1/2.5[b]	benzene (reflux)	120	1,1-Diphenyl-1,5-hexadiene, 54[e]
Allyldiphenylcarbinol	C_3H_5MgBr	1/2.5	ether (reflux)	60	1,1-Diphenyl-6-hepten-1-ol, 56
3-Butenyldiphenylcarbinol	C_3H_5MgBr	1/2.5	benzene (reflux)	60	1,1-Diphenyl-1,7-octadiene, 20[e]
					1,1-Diphenyl-1,4-pentadiene, 16[e]
					Two unidentified olefins[c]
5-Hexenyldiphenylcarbinol	C_3H_5MgBr	1/2.5[b]	benzene (reflux)	120	No reaction
1-(1-Propynyl)cyclohexanol	C_3H_5MgBr	1/2.5	toluene (reflux)	96	2-Allyl-2-methylvinylidene-cyclohexane, 80[e]
1-(2-Butynyl)cyclohexanol	C_3H_5MgBr	1/2.5	ether (reflux)	96	1-(3-Methyl-2,5-hexadienyl)-cyclohexanol, only II, 60
α-Allylbenzhydryl methyl ether	C_3H_5MgBr	1/2.5	toluene (reflux)	96	1,1-Diphenyl-1,6-heptadiene, 25[d,e]
					1,1-Diphenyl-2,6-heptadiene, 25[e]
α-Allylbenzhydrylaniline	C_3H_5MgBr	1/3.4	benzene (reflux)	144	Benzhydrylaniline, aniline, benzophenone anil, and others
Allyldiphenylcarbinol	$(C_3H_5)_2Mg$	1/1.25	benzene (r.t.)	96	5-Hexenyldiphenylcarbinol, 65
Allyldiphenylcarbinol	$C_6H_5CH_2MgBr$	1/2.5	ether (r.t.)	96	1,1,5-Triphenyl-1-pentene, 20[e]
Allyldiphenylcarbinol	$(CH_3)_3CMgBr$	1/2.5	toluene (reflux)	96	5,5-Dimethyl-1.1-diphenyl-1-hexene[e], 38
Allyldiphenylcarbinol	C_6H_5MgBr	1/2.5	benzene (reflux)	96	No reaction, 95% recovery
Allyldiphenylcarbinol	$(C_6H_5)_2Mg$	1/2.5	benzene (reflux)	96	No reaction, 95% recovery

[a] Spectral and/or elemental data confirm the structures assigned. [b] Addition of 3 molar percent of anhydrous nickel(II) acetylacetonate was employed. [c] These olefins, similar to 1,1-diphenyl-1,7-octadiene in GLC retention times and in NMR characteristics, may be products of allylating olefinic bond in reverse sense. [d] The 1,1-diphenyl-2,6-heptadiene seems to be the initial product which then rearranges into the 1,6-heptadiene isomer. [e] The thermal elimination of MgO (or Mg_2OX_2) during the reaction proper is assumed.

of 1,1-diphenylbutadiene, indole and 2-allyl-1-methyl-1,2-dihydroquinoline[4] towards allylmagnesium bromide in refluxing benzene. These results are detailed in Table 1.

The substrate offering information on the stereochemistry of one of the Grignard reactions was 1-(2-butynyl)cyclohexanol. The hydrolysate product of the addition of allylmagnesium bromide is considered to be II, rather than III:



In addition to the usual analytical and spectral data confirming the formation of 1-(3-methyl-2,5-hexadienyl)cyclohexanol, the stereochemistry corresponding to that of II was suggested by the observation of the NMR doublet of the methyl group at 1.58 ppm (δ), J_{ab} 0.9 Hz. Structure III would be expected to display a larger vinyl *H*-β-allylic methyl splitting (J_{ab} = 1.2–1.7 Hz)*.

Two other observations, besides the stereochemistry and the structural constraints, bearing on the possible mechanism of these Grignard additions are the effects of donor solvents and the purity of the magnesium metal. Toward the most responsive substrate, allyldiphenylcarbinol, the action of allylmagnesium bromide** was the most rapid in ethyl ether (60% in 96 h) and the least rapid in benzene (4%) or in tetrahydrofuran (1%). Diallylmagnesium, on the other hand, reacted most rapidly with allyldiphenylcarbinol in benzene (65% in 96 h) and the least rapidly in ethyl ether (1%). Similarly, the use of allylmagnesium bromide of varying nickel content with allyldiphenylcarbinol gave the following yield of 1,1-diphenyl-6-hepten-1-ol after 84 h at 25°C: (*a*) ordinary Grignard magnesium (99.8%), 85%; (*b*) ordinary Grignard magnesium +3% of nickel(II)-acetylacetonate, 93%; and (*c*) triply sublimed magnesium, 62%***. Therefore, the presence of nickel and/or other transition metal salts clearly promotes the addition of allyl Grignard reagents to the olefinic linkage of allyldiphenylcarbinol (as well as to the acetylenic linkage of 1-(1-propynyl)cyclohexanol). However, the successful addition to the substrate of the Grignard reagent prepared from triply sublimed magnesium, albeit slower, does support the conclusion that the allyl-magnesium bond itself is able to add to the olefinic or acetylenic linkage of suitable donor-coordinating substrates.

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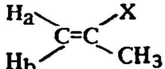
*While this coupling constant is small, it is based upon ample precedent with systems of known geometrical configuration[5,6]. For example, the NMR spectra of compounds of the type,



$(H_a)(H_b)C{=}C(X)(CH_3)$

where X = Cl, Br, I, OR and CH_2X display J_{ac} 0.6–1.2 Hz and J_{bc} = 1.2–1.7 Hz. Nevertheless, due to limits in the reliability of this NMR correlation we cannot rule out completely the possibility that structure III may be the actual product (H. Richey, private communication).

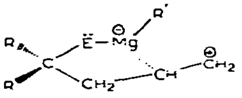
**For both the solvent and the nickel salt catalysis experiments a ratio of 2.5 equiv. of C_3H_5Mg groups (either of C_3H_5MgBr or $(C_3H_5)_2Mg$) to 1.0 equiv. of allyldiphenylcarbinol was employed. Although the volumes of solvent were identical, the systems were not always completely homogeneous.

***The triply sublimed magnesium, obtained from the Dow Chemical Company through the kind offices of Drs. Francis Johnson and Donald L. Leman, contained the following spectroscopically determined impurities (Mg >99.96%): %, Al <0.0011; Ca <0.01; Cu <0.001; Fe <0.0005; Mn <0.0005; Ni <0.0005; Pb <0.01; Si <0.01; Sn <0.01; and Zn <0.003.

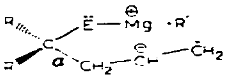
The most compatible mechanistic integration of the aforementioned findings is in terms of the intramolecular coordinative assistance depicted in model I[*]. As the vinyl group in ω-alkenyldiphenylcarbinol is removed farther from the carbinolate oxygen, the reaction slows down (I, $n = 2$) and then ceases altogether (I, $n = 4$). Even coordination at an ether oxygen, rather than carbinolate formation, apparently suffices to foster Grignard additions, as evidenced by the behavior of α-allylbenzhydryl methyl ether. Coordination of MgR' or RMgE on nitrogen, either as amide or amine complex (I, $E = NC_6H_5$ or NR_2), seems to suppress completely the ability of the allyl—magnesium bond to add to proximate olefinic unsaturation (indole and 2-allyl-1-methyl-1,2-dihydroquinoline). A further structural limitation on the reaction is the necessity of employing a Grignard reagent or derived diorganomagnesium of high reactivity[7], such as allylic or tert-alkyl representatives. Types of intermediate reactivity, such as phenylmagnesium reagents, are completely inert[**].

Consistent with the intramolecular view of this Grignard addition are the stereospecificity and regiospecificity of the allylation. The elements of Mg and C_3H_5 are added in a *cis*-fashion to the carbinolate of 1-(2-butynyl)cyclohexanol and the allyl group generally is found to be added to that olefinic or acetylenic carbon further removed from the complexing center E in model I. The solvent effects with allylmagnesium bromide and diallylmagnesium are not completely understood as yet, but it may be that, with diallylmagnesium in ether, model I ($E = O$, $R = C_3H_5$) is coordinated so firmly with ethyl ether molecules as to diminish attack on the olefinic bond. With allylmagnesium bromide in ether, the magnesium halide may play a Lewis acidic role in aiding attack on the olefinic bond. Use of tetrahydrofuran may quench this Lewis acid source by complexation; use of benzene may promote auto-complexation of the magnesium carbinolate—magnesium halide system and again quench the necessary Lewis acid sources.

These studies provide strong evidence favoring the intramolecular coordination of an organomagnesium moiety in proximity to an olefinic or acetylenic linkage as the basis for sucessful addition. Whether a polar or homolytic scission of bonds thereupon ensues cannot now be decided unambiguously. The results lend themselves to the proposal of either an electrophilic attack by Mg on the π-cloud (IV) or an electron-transfer pathway (V):



(IV)



(V)

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[*] The intermolecular mechanism, advocated by Felkin and coworkers in publications subsequent to ours (ref. 1, 2 and 8), may play a role in those reactions of allylic and related alcohols giving 2-alkyl-3-magnesio adducts (reverse of regio specificity observed here and in ref. 1; *cf.* Richey's accompanying communication. The reported stereoselectivity of analogous lithium reagents is the reverse of Grignard reagents in 2-alkyl-3-metallo additions to α-methylallyl alcohol [Li, 50/1 *vs.* Mg, 1/8]. The mechanisms of lithium reagent additions thus may be quite different from those of magnesium. Moreover, Felkin's magnesium results can also be reconciled with an intramolecular view.

[**] Other workers have found that even with the more reactive organolithium reagents, the presence of *N,N,N',N'*-tetramethylethylenediamine is often required to promote additions to alkenols[8].

In the accompanying communication, whose manuscript was kindly made available to us by Professor Herman Richey after our manuscript has been submitted, it is shown that vinyl Grignard reagent can add to the triple bond of 3-butyn-1-ol. It is well-known that C≡C linkages are generally more responsive to additions of metal (Na) or organometallic (RLi, R_3Al) reagents.

The inhibiting effect of donor solvents and nitrogen coordinating sites (IV, E = NR or NR_2) are consistent with electrophilic attack[9]. The orientation of R' addition to the terminal carbon atom (V), the nickel catalysis and the nature of those Grignard reagents able to add speak for an electron-transfer pathway (*cf.* the Blicke–Powers hypothesis[10]). Polar groups attached to C_α may stabilize proximate radical-anions, and it would be expected that allylic and tert-alkyl radicals would be more readily formed (V, $R'\cdot$) because of their relative stability[3]. Further work will scrutinize the mechanistic nuances of these views.

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