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CONCERNING THE FORMATION OF MAGNESIUM HYDRIDE IN THE PREPARATION OF GRIGNARD REAGENTS. THE ORIGIN OF 2-METHYLBENZHYDROL IN THE REACTION OF METHYLMAGNESIUM BROMIDE WITH 2-METHYLBENZOPHENONE[1]

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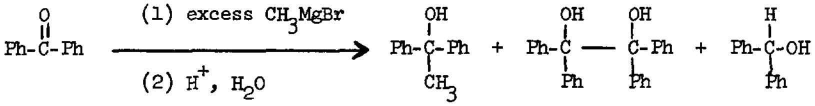
The reaction of methylmagnesium bromide with aromatic ketones has been the subject of intense mechanistic studies in recent years.[2] Since methylmagnesium bromide possesses no β-hydrogen atom, it is incapable of reducing ketones by β-hydrogen reduction and since aromatic ketones possess no α-hydrogen atom, enolization is not possible; thus, only addition product should be observed. However, addition of a large excess of methylmagnesium bromide to aromatic ketones has been shown to give significant yields of aromatic pinacols,[3-5] and hydrols,[5-6] as well as normal 1,2 addition product (eq. 1). The formation of aromatic pinacols has been shown to be

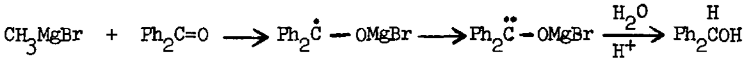


$$\mathrm{Ph{-}\overset{O}{\overset{\|}{C}}{-}Ph} \xrightarrow[\text{(2) } H^+,\ H_2O]{\text{(1) excess } CH_3MgBr} \mathrm{Ph{-}\underset{CH_3}{\overset{OH}{C}}{-}Ph} + \mathrm{Ph{-}\underset{Ph}{\overset{OH}{C}}{-\!-}\underset{Ph}{\overset{OH}{C}}{-}Ph} + \mathrm{Ph{-}\underset{Ph}{\overset{H}{C}}{-}OH} \qquad (1)$$

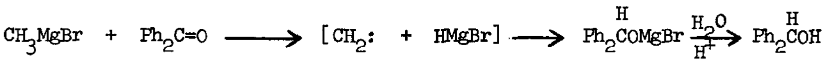
due to traces of transition metals, especially iron, present in various grades of magnesium metal[5,7] used to prepare the CH_3MgBr whereas the origin of aromatic hydrols has not been resolved

We wish to report that the formation of aromatic hydrols in the reaction of aromatic ketones with CH_3MgBr is due to reduction of the ketone by a small amount of magnesium hydride species (ca. 0.2%) formed in the preparation of CH_3MgBr from magnesium and CH_3Br.

The formation of hydrol in the reaction of CH_3MgBr with an aromatic ketone could possibly take place by any of the following pathways:



$$(1)\quad CH_3MgBr + Ph_2C{=}O \longrightarrow Ph_2\dot{C}{-}OMgBr \longrightarrow Ph_2\ddot{C}{-}OMgBr \xrightarrow[H^+]{H_2O} Ph_2\overset{H}{C}OH \qquad (2)$$



$$(2)\quad CH_3MgBr + Ph_2C{=}O \longrightarrow [CH_2{:} + HMgBr] \longrightarrow Ph_2\overset{H}{C}OMgBr \xrightarrow[H^+]{H_2O} Ph_2\overset{H}{C}OH \qquad (3)$$

$$\text{(3)}\quad Ph_2\dot{C}-OMgBr + (C_2H_5)_2O \longrightarrow Ph_2\overset{H}{C}OMgBr \xrightarrow[H^+]{H_2O} Ph_2\overset{H}{C}OH \qquad (4)$$

$$\text{(4)}\quad Ph_2\ddot{C}-OMgBr + (C_2H_5)_2O \longrightarrow Ph_2\overset{H}{C}OMgBr \xrightarrow[H^+]{H_2O} Ph_2\overset{H}{C}OH \qquad (5)$$

Pathway (1) was overruled on the basis that addition of D_2O to the reaction product did not produce $Ph_2C(D)OH$. Pathway (2) was overruled on the basis that reaction of CD_3MgBr with $Ph_2C{=}O$ did not result in the formation of $Ph_2C(D)OH$. Pathways (3) and (4) were overruled on the basis that generation of $Ph_2C-OMgBr$ by reaction of benzopinacol with a large excess of CH_3MgBr both in the presence and absence of addition product ($Ph_2C(CH_3)OMgBr$) did not produce even a trace of $Ph_2C(H)OH$ on hydrolysis.

The data in Table I show that preparation of CH_3MgBr in $(C_2H_5)_2O$ and subsequent reaction with 2-methylbenzophenone in the same solvent produces 59% $C_6H_5(C_7H_7)C(H)OH$ whereas the same series of reactions in $(CH_3CD_2)_2O$ produces $C_6H_5(C_7H_7)C(D)OH$ in 27% yield. This experiment shows that the hydrogen used in the reduction comes from the ether. The reaction in which CH_3MgBr is prepared in $(C_2H_5)_2O$ but then the solvent removed and replaced with $(CH_3CD_2)_2O$ before being allowed to react with the ketone, produces only $C_6H_5(C_7H_7)C(H)OH$. This result shows that the hydrogen abstraction from ether took place in the Grignard preparation and not in the reaction with the ketone. This is further proof that pathways 3 and 4 are not operable.

Table I. Formation of 2-Methylbenzhydrol at 400:1 Grignard to Ketone Ratio

Grignard[a] Formed In	Reaction Carried Out In	% Yield Reduction Product[b]	
		$C_6H_5(C_7H_7)CHOH$	$C_6H_5(C_7H_7)CDOH$
$CH_3CH_2-O-CH_2CH_3$	$CH_3CH_2-O-CH_2CH_3$	59	--
$CH_3CD_2-O-CD_2CH_3$	$CH_3CD_2-O-CD_2CH_3$	0	27
$CH_3CH_2-O-CH_2CH_3$	$CH_3CD_2-O-CD_2CH_3$	65	0

a. CH_3MgBr prepared from Dow Doubly Sublimed magnesium.

b. Normalized as - % 1,2 Addition + % Reduction = 100%.

Analysis of Dow doubly sublimed magnesium[8], shows no trace elements in sufficient concentration (~0.2%) to produce the amount of metal hydride in CH_3MgBr necessary to form benzhydrol in 59% yield. Therefore the active reducing agent must be a magnesium hydride species. The following data will attempt to establish this point.

Table II illustrates the striking similarity in selectivity between reduction of an equimolar mixture of 2-methylbenzophenone and acetone with CH_3MgBr prepared from Dow doubly sublimed magnesium and reduction of the same mixture with methylmagnesium bromide prepared from ROC/RIC magnesium crystals with added MgH_2. In the former case, reduction product is almost exclusively 2-methylbenzhydrol (98%) and in the latter case the results are similar. These results are very meaningful considering that CH_3MgBr prepared from ROC/RIC crystals yields no reduction product without added MgH_2. The fact that considerable reduction is observed in such a large excess of alkylating agent indicates what a powerful reducing agent the MgH_2 species in the Grignard reagent is toward ketones.

Table II. Selectivity of Reduction of an Equalmolar Mixture of 2-Methylbenzophenone and Acetone with CH_3MgBr and $CH_3MgBr + MgH_2$.[a]

Grade of Magnesium Used To Prepared CH_3MgBr	1,2 Addition Products (%)	Reduction Products (%) 2-Methylbenzhydrol	Isopropanol
Dow (DS)	74.5	25.0	0.5
ROC/RIC	100.0	0	0
ROC/RIC + MgH_2	74.0	24.5	1.5

a. Millimoles of each ketone = 0.3; mmol CH_3MgBr = 120; mmol MgH_2 = 0.2

b. Yields normalized as % 1,2 Addition + % Reduction = 100%.

Further evidence that MgH_2 in the Grignard reagent is the source of the observed reduction is indicated by the similarity in observed stereochemistry when CH_3MgBr that gives reduction (Dow doubly sublimed) reduces 4-t-butycyclohexanone compared to CH_3MgBr that normally does not give reduction (ROC/RIC) except when MgH_2 is added to the reagent. The data in Table III show

Table III. Stereochemistry of Reduction of 4-tert-butycyclohexanone (0.3 mmol) With CH_3MgBr (120 mmol) and $CH_3MgBr + MgH_2$.

Grade Mg Used	mmol MgH_2	Alkylation (%) Total[a]	Axial[b] Alcohol	Equatorial[b] Alcohol	Reduction (%) Total[a]	Axial[b] Alcohol	Equatorial[b] Alcohol
Dow (DS)	0	84	66	34	16	11	89
ROC/RIC	0	100	59	41	0	--	--
ROC/RIC	0.2	92	62	38	8	21	79
------	0.3	--	--	--	--	68	32

a. Normalized as - % Alkylation alcohols + % Reduction alcohols = 100%

b. Normalized as - % Axial alcohol + % Equatorial alcohol = 100%

that the reaction of CH_3MgBr (Dow doubly sublimed) with 4-t-butylcyclohexanone yields the reduction product in 89:11 ratio (equatorial:axial alcohol). On the other hand, CH_3MgBr prepared from ROC/RIC magnesium which normally does not give any reduction product, produced a 79:21 ratio of alcohols (equatorial:axial) when MgH_2 was added. The similarity of the above stereochemistry is even more striking when compared to MgH_2 alone which gives a 32:68 ratio.

The large variation in the amount of hydrol formed from CH_3MgBr prepared from different grades of magnesium has been traced not to the purity of the various grades, but to the size of the crystals or shavings. Those grades of magnesium that consisted of fine shavings gave the most hydrol and those grades of much coarser material gave the least hydrol. We have shown that MgH_2 is normally produced as a by-product (~0.2%) in CH_3MgBr formation and that the MgH_2 is destroyed when allowed to react with excess CH_3Br. Since the reaction of CH_3Br with magnesium (fine shavings) is very rapid, the by-product MgH_2 survives when the reaction is carried out in excess magnesium. On the other hand, the reaction of CH_3Br with magnesium (coarse shavings) is slow and the concentration of CH_3Br builds up in the reaction mixture destroying the by-product MgH_2 even when the reaction is carried out in excess magnesium.

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8. PPM trace elements in Dow Doubly Sublimed Mg by spark source mass spectrometry: B-0.005, N-2.9, O-420, F-0.01, Na-8.9, Al-ND, Si-2, P-ND, S-1, Cl-25, K-0.85, Ca-1.8, Ti-ND, Cr-ND, Mn-ND, Fe-0.1, Co-ND, Ni-ND, Cu-0.1, Zn-25, Ga-ND, Sr-ND, Y-ND, Zr-ND, Pb-ND. Analysis by Micro-Trace Analytical Services, Industry Calif., 91746 (ND = Not Detectable).