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THE REACTION OF PHENYLMAGNESIUM BROMIDE WITH DIETHYL ETHER DURING GRIGNARD PREPARATION

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Summary

To determine the Grignard products generated during the preparation of phenylmagnesium bromide in peroxide-free ether, the prepared compound was quenched with H_2O or D_2O and the products quantitatively determined by gas chromatography and gas chromatography coupled with mass spectrometry. Identified compounds showing no incorporation of deuterium were 1-phenylethanol, 1-ethoxy-1-phenylethane, 1-ethoxy-2-phenylethane, and phenol while those showing hydrogen and deuterium incorporation following D_2O quench included benzene, toluene, α-deuteroethylbenzene, biphenyl and terphenyls. Enrichment studies with phenetole suggested that, if produced, it is converted near-quantitatively to phenol while similar studies with 1-ethoxy-1-phenylethane suggested this compound was not the sole intermediate in the chemogenesis of 1-phenylethanol, ethylbenzene and phenetole. It is concluded that phenylcyclidene cosynthetics originate from new Grignard reagents formed by the reaction of the incipient phenylmagnesium bromide and the solvent diethyl ether.

Introduction

The carbon skeleton of the starting halides in Grignard preparations sometimes does not survive the synthetic process and the existence of free radicals during the preparation sequence has been proposed to account for the anomalous products. For example, following an aqueous quench of ethereal 2-methyl-2-phenylpropylmagnesium chloride, not only was the expected hydrocarbon found but up to 7% of rearranged products were present [$PhCH_2CH(CH_3)CH_3$, $PhCH_2C(CH_3)=CH_2$, $PhCH=C(CH_3)CH_3$]. The rearrangement was envisioned to occur during the Grignard formation via a 1,2-phenyl migration of the primary free radical intermediate to the more stable tertiary free radical [1]. Grovenstein and co-workers [2], using Fisher magnesium (see Experimental), also observed a significant amount of (1,2)-sigmatropic phenyl rearrangement in the preparation of 1,1,1-triphenylethylmag-

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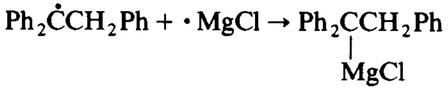
nesium chloride which they proposed derived from an analogous intermediate free radical as in

$$\mathrm{Ph_3CCH_2Cl \rightarrow Ph_3CCH_2^{\bullet} + {\cdot}MgCl \rightarrow Ph_3CCH_2MgCl}$$



$$\mathrm{Ph_2\dot{C}CH_2Ph + {\cdot}MgCl \rightarrow Ph_2\underset{\underset{\displaystyle MgCl}{|}}{C}CH_2Ph}$$

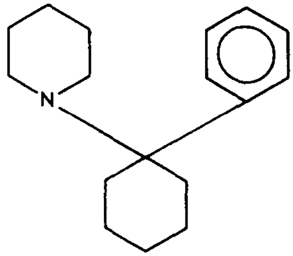
Gilman and Wood [3] reported the isolation of benzene, phenol, 2-phenylethanol, biphenyl, terphenyl and ethanol following an aqueous quench of the phenylmagnesium bromide prepared with magnesium of unspecified purity. They proposed that 2-phenylethanol originated from the "preliminary oxidation of the ether used as a medium". The Wurtz product, biphenyl, was subsequently attributed to free radical coupling [4]. The observed reduction of 7,7-dibromonorcarane with CD_3MgBr (magnesium source not described) to the nondeuterated monobromonorcarane even with a D_2O quench led Seyferth [5] to propose that the solvent (THF) donated a hydrogen to the intermediate free radical by a "polar or radical process".

Reactions where the solvent molecule is incorporated in the reaction products are known. Using THF as the solvent and rigorously excluding oxygen and moisture, Grootveld et al. found that reaction of 1-ethoxybromonorborane with magnesium (purity and source not specified) yielded, after deuterolysis, 1-ethoxydeuteronorborane (12%), 1-ethoxynorborane (36%), the dimer of 1-ethoxynorborane (12%), 1-ethoxy-7-(2-tetrahydrofuranyl) norborane (1.5%) and 2,2′-ditetrahydrofuran (6.0%) [6]. A "tight radical pair" intermediate Grignard, similar to that proposed by Walborsky and Young [7], was envisioned to react with the THF to account for the pronounced solvent-incorporated product. The presence of 1-(1-adamantyl)-1-ethoxyethane, n-butyladamantane and 2-(adamant-1-yl)tetrahydrofuran in addition to adamantane as byproducts in the "static" preparation of 1-adamantylmagnesium bromide in diethyl ether, di-n-butyl ether, and THF respectively was attributed to solvent trapping of the adamantyl radical [8], generated from the attack of adamantyl bromide on "highly active" magnesium prepared by the method of Rieke and Bales [9].

Other reactions in which the solvent is postulated to donate a hydrogen include the work of Walborsky and Aronoff [10]. On the basis of the distribution of deuterated products isolated in the carbonation of optically pure 1-methyl-2,2-diphenylcyclopropylmagnesium bromide in perdeuterated ether and THF, they concluded that little ether cleavage occurred to produce the corresponding hydrocarbon contrary to that observed in THF. The source of hydrogen present in the non-deuterated products was not unambiguously established although the possibility was suggested that the hydrogen was provided by the starting halide or compounds derived from it. It was determined that the purity of the magnesium had little effect on the optical purity of the carboxylic acids under study.

Reaction of the solvent with previously prepared Grignard reagents has been reported by Okuhara [11], who found that α-substituted diethyl ethers (substituents CF_2CCl_2H and $CF{=}CCl_2$) were produced when C_4H_9MgBr, produced with Grignard grade magnesium (purity > 99%) and n-C_4H_9Br, was treated with $CF_2{=}CCl_2$ in ether. However, when the Grignard reagent was prepared in ether, the ether removed, and the reaction completed with the difluorodichloroalkene in THF, only the analogously α-substituted tetrahydrofurans were found. It was concluded that the α-magnesium bromide of diethyl ether was not important but rather the products were derived from the solvent during the reaction of C_4H_9MgBr with the compound of interest.

We have investigated the preparation of 1-(1-phenylcyclohexyl)piperidine (**1**) from ethereal phenylmagnesium bromide and PCC (1-piperidinocyclohexane-carbonitrile) [12] and isolated and identified three new compounds: 1-[1-(phenylethyl)cyclohexyl]piperidine (**2**, 0.5%), 1-[1-(1,1′-biphenyl-4-yl)cyclohexyl]piperidine (**3**, 1%) and 1,1′(1,4-phenylenedicyclohexylidene)bis[piperidine] (**4**, 0.5%) [13].



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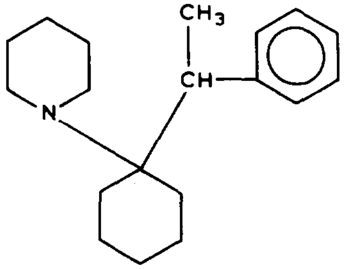

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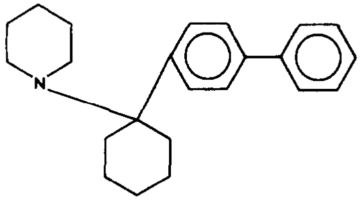

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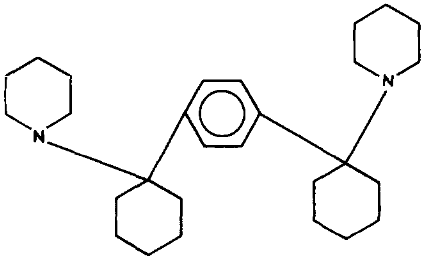


(4)

The preparation of the Grignard reagent involved the reaction of triply distilled bromobenzene with commercially available made-for-Grignard magnesium (see Experimental) and despite rigorous purification, these compounds and other as yet unidentified cosynthetics were always present, albeit varying in concentration from synthesis to synthesis [14]. Suggestive of involvement of the solvent diethyl ether was the phenethyl analogue **2**. To answer the question as to the origin and the time of insertion of the group, i.e. during the preparation of phenylmagnesium bromide in diethyl ether or during the addition of this product to the carbonitrile, we investigated the products formed by quenching the completed phenylmagnesium bromide (prepared using the same magnesium) synthesis with H_2O or D_2O. Identification and quantification of the resulting compounds was accomplished by GC and GC/MS and we now wish to report the results of our study.

Experimental

Peroxide-free anhydrous diethyl ether was prepared by distilling reagent grade diethyl ether (Fisher Scientific Co.) from sodium hydride immediately before use.

Bromobenzene (Aldrich Chemical Co.) was triply distilled, the middle cut taken from each distillation. Gas chromatography (GC) was performed using an HP-5880A equipped with a Level IV microprocessor and capillary columns (fused silica, 12 m × 0.25 mm, SP-2100; 12 m × 0.25 mm SE-54; 30 m × 0.25 mm OV-17) to determine the final purity of the distilled products. For those experiments involving "untreated magnesium", weighed amounts of magnesium metal turnings (for "Grignard reaction", Catalogue No. M-11, Fisher Scientific Co. Atlanta, GA. Lot No. 783238 purity 99.8%) were washed three times with HPLC grade benzene (Burdick and Jackson), three times with a similar grade of acetone, dried for 20 min at 100°C in a heated vacuum dessicator and, upon cooling, used immediately. For "treated magnesium" experiments, the Fisher magnesium was prepared according to the method of Huber [15] and involved washing the magnesium rapidly in a sintered glass funnel with solvents in the following order: 1% HNO_3, distilled H_2O, 100% EtOH, reagent grade acetone, diethyl ether, and finally a solution of 5% wax, 0.1% I_2 in ether and evaporating off the ether. Stored in a heated vacuum dessicator, the magnesium was washed and treated as above before using.

Grignard reagent preparation. A 500 ml 3-necked flask (oven-dried) was fitted with a pressure-equalizing addition funnel through which either argon or nitrogen (Air Products and Chemicals Inc., Ultra-High Purity Grade, 99.998% and 99.998% purity, respectively.) entered the apparatus, a dry ice/acetone condenser, and the third neck of the flask was sealed with a rubber septum. The apparatus, after the addition of the weighed amount of magnesium, was gently heated with a Bunsen burner with inert gas flowing and exiting through the top of the reflux condenser. Flow rates of approximately 1 ml/min were maintained during the reaction and, prior to the addition of the other reactants, the apparatus was purged with inert gas for 15 minutes while cooling.

In general, the following procedure was employed using accurately weighed amounts of reactants: ca. 1.7 g prepared Mg (0.07 mol) were placed in the flask (vide supra) and of 11.0 g (0.07 mol) of warmed bromobenzene (to remove dissolved air), ca. 1 ml was added directly to the Mg, the remaining amount dissolved in 60 ml peroxide-free diethyl ether and placed in the addition funnel. A crystal of I_2 was added to the Mg/bromobenzene and the entire apparatus swept with inert gas for 5 minutes. With the addition of ca. 5 ml of the bromobenzene/ether solution and gentle stirring (Teflon coated magnetic stirring bar), the reaction proceeded smoothly. Gentle reflux was maintained by dropwise addition. The addition was usually completed in 30 minutes after which time the mixture was gently refluxed for 1 hour.

Aqueous quench. The mixture was cooled (ice bath) while maintaining a positive inert gas pressure and ca. 4 ml of H_2O was slowly added through the rubber septum via a cannula with vigorous stirring to control the otherwise vigorous evolution of gas. After addition was complete, 100 ml of 5% NH_4Cl was added slowly, followed by the addition of sufficient concentrated HCl (ca. 10 ml) to lower the pH to 1. The ether layer was removed, the water layer saturated with NaCl and extracted 3 × 25 ml with peroxide-free ether, the ether fractions combined and dried over $MgSO_4$. The dried ether solution (ca. 125 ml) was concentrated by carefully distilling (using a Vigreux distilling column) to a final volume of ca. 25 ml, transferring, and making up to exactly 50 ml with peroxide-free ether.

GC analysis was performed using a 30 m × 0.25 mm fused silica column coated with OV-17, programmed as follows: initial temperature 35°C, hold 5.0 min, programmed 7.5°/min to 240°C, 5.0 min hold. All analyses were done in triplicate. To determine the efficiency of the procedure for the recovery of benzene, the entire extraction/distillation procedure, followed by GC determination, was performed on 0.07 mol of benzene in ca. 250 ml diethyl ether. The average recovery of benzene (triplicate analysis) was 66.15% ± 5.5 and all benzene concentrations reported herein are corrected accordingly (Table 1).

Standard compounds (benzene, toluene, ethylbenzene, phenol, phenetole, 2-phenylethanol and biphenyl) were obtained from commercial sources and purified where necessary. Ethyl α-methylbenzyl ether (1-ethoxy-1-phenylethane) was prepared as described by Mislow [16].

Deuterium oxide quench. A glass syringe (oven-dried) equipped with a stainless steel needle was used to withdraw ca. 13.5 ml (ca. 15 g, 0.75 mol) of D_2O from a septum-capped bottle (Aldrich, 99.8% and verified by NMR) in a nitrogen-filled dry box. This was immediately added dropwise to the cooled ethereal phenylmagnesium bromide, as described above in the aqueous quench procedure. Extractions and analyses were performed as previously described.

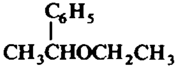
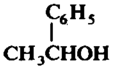
Quantification of the compounds incorporating deuterium was accomplished by gas chromatography/mass spectrometry (GC/MS) using a Hewlett Packard 5985B GC/MS/DS system equipped with a 25 m × 0.25 mm fused silica column deactivated with Carbowax 20m and coated with SP-2100 (Hewlett Packard), and mass spectra were accumulated at the rate of 2/sec. The amount of mono-deuterated benzene was estimated by utilizing C_6D_6 (Merck & Co., 98 atom% D) as an internal standard. Solutions were prepared by diluting 10.0 μl of the 50 ml concentrated quench solution plus 221.0 mg of C_6D_6 to 10 ml with peroxide-free ether. Chromatography was performed using the splitless injection mode (4 μl) with temperature programming from -20 to 240°C at 20°/min. Quantification calculations were performed by integrating the extracted ion current profiles of m/z 78, 79, and 84 corresponding to $C_6H_6{}^+$, $C_6H_5D^+$, and determining a response factor for m/z 84 based on the amount of C_6D_6 added. Corrections for contributions to m/z 79 from $C_6H_5D^+$ and $^{13}CC_5H_6{}^+$ were determined by repetitive analyses of purified C_6H_6. The ratios of C_6H_6/C_6H_5D thus obtained were then used to calculate the absolute amounts of non-deuterated and deuterated benzene previously obtained as total benzene by GC analysis (vide supra). For toluene and deuterated toluene, estimations were based on relative differences in the ratios of the intensity of the m/z values 92/93, ($C_7H_8{}^+/{}^{13}CC_6H_8$) obtained by repetitive injections of purified toluene. Differences in this ratio were attributed to $C_7H_7D^+$ in the experimental sample and the quantification of the toluene peak in the regular GC run, representing the total toluene present, was recalculated to reflect the amount of deuterated and non-deuterated toluene generated. In a similar manner, deuterated ethylbenzene was determined except that the ratio of the tropylium ion m/z 91 to the deuterated tropylium ion m/z 92 was used and the ^{13}C contribution was taken into account as above. The ratios agreed with those of the ethylbenzene M^+, $C_8H_{10}{}^+/C_8H_9D^+$. For biphenyl, the ^{13}C corrected ratios of $C_{12}H_{10}{}^+/C_{12}H_9D^+$ were used.

It should be noted that in all I_2-initiated reactions, a very small amount of iodobenzene was found. When the yields of reactions not using I_2 were compared with these, the differences were not statistically significant. Additionally no evidence of dideuteration was found in any of the mass spectral data obtained.

The analytical results are summarized in Table 1.

TABLE 1

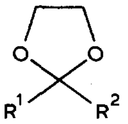
YIELDS OF PRODUCTS OBTAINED FROM ETHEREAL PHENYLMAGNESIUM BROMIDE D_2O/H_2O QUENCHES [a]

Compound	Treated magnesium H_2O quench	Treated magnesium D_2O quench (%O)	Untreated magnesium D_2O quench [b] (%O) [c]	Untreated magnesium phenetole added; H_2O quench [d]	Untreated magnesium phenetole added; D_2O quench [d] (%O)	Untreated magnesium 1-ethoxy-1-phenylethane added; H_2O quench [e]
C_6H_6	3158 ± 45.3	3208 ± 178 (72.5 ± 1.8)	3155 ± 350 (75.2 ± 1.0)	3272 ± 387	3053 ± 212 (74.4 ± 8.3)	3040 ± 270
$C_6H_5CH_3$	0.779 ± 0.032	0.754 ± 0.05 (53.3 ± 2.0)	1.803 ± 1.3 (57.2 ± 1.6)	1.133 ± 0.549	0.921 ± 0.262 (51.8 ± 21)	1.682 ± 0.43
$C_6H_5CH_2CH_3$	5.924 ± 0.304	5.328 ± 0.46 (27.3 ± 1.4)	1.453 ± 0.55 (34.2 ± 6.1)	6.702 ± 0.653	4.393 ± 2.08 (30.2 ± 3.3)	7.860 ± 1.50
C_6H_5Br	32.57 ± 44.7	17.0 ± 2.01 (0.00)	7.539 ± 2.3 (0.00)	28.23 ± 29.6	10.96 ± 12.4 (0.00)	20.55 ± 25
C_6H_5OH	19.22 ± 8.00	15.12 ± 4.43 (2.7 ± 1.5)	37.89 ± 21. (trace)	113.0 ± 19.9	116.8 ± 49.0 (49.0 ± 2.0)	85.64 ± 49
 $CH_3\overset{\overset{C_6H_5}{\vert}}{C}HOCH_2CH_3$	3.399 ± 0.808	3.391 ± 0.68 (0.00)	2.521 ± 0.17 (0.00)	3.113 ± 0.598	2.123 ± 0.319 (0.00)	67.89 ± 7.1
 $CH_3\overset{\overset{C_6H_5}{\vert}}{C}HOH$	13.42 ± 5.15	12.37 ± 4.02 (0.00)	25.88 ± 14 (0.00)	12.65 ± 7.47	17.86 ± 27.2 (0.00)	70.86 ± 40
$C_6H_5C_6H_5$	339.3 ± 58.3	289.7 ± 52.3 (20.3 ± 2.6)	371.5 ± 38 (16.8 ± 3.1)	371.7 ± 52.9	364.8 ± 130 (21.4 ± 3.5)	378.1 ± 160
Yield (%) of phenyl compounds	55.36 ± 1.40	55.9 ± 2.74	56.27 ± 4.0	57.70 ± 3.36	55.9 ± 2.30	57.58 ± 7.4
Yield (%) corrected	89.21 ± 1.40	89.83 ± 2.74	90.12 ± 4.0	91.55 ± 3.36	89.77 ± 2.30	91.43 ± 7.4

[a] Triplicate synthesis of approximately 0.07 mol bromobenzene reacted with 0.07 mol Mg in 250 ml peroxide-free ether (See Experimental). [b] mol $\times 10^5$ ± standard deviation. [c] See Experimental. [d] Triplicate reactions carried out with approximately 90×10^{-5} mol phenetole added. [e] Triplicate reactions carried out with approximately 83×10^{-5} mol 1-ethoxy-1-phenylethane added.

Results and discussion

Using the commercially available magnesium for the preparation of phenylmagnesium bromide followed by an aqueous quench and extraction, we identified by comparison of retention times with authentic compounds and confirmed by GC/MS benzene, bromobenzene, iodobenzene, toluene, ethylbenzene, phenol, 1-phenylethanol, 1-ethoxy-1-phenylethane, and biphenyl. Traces of methyl substituted phenols, a methyl substituted styrene, 2-ethoxy-1-phenylethane, 1-hydroxyl-1-phenylpropane and three terphenyls were suggested by GC/MS alone and small amounts of two dioxolanes having the structure **5** (where R^1, and R^2 were CH_3, CH_3CH_2, and H, $(CH_3)_2CH$) were also indicated.



(**5**)

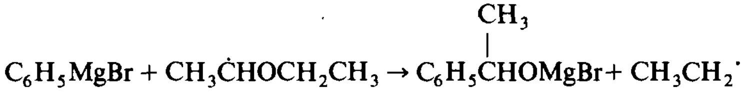
To ascertain those compounds derived from any Grignard reagent present, the ethereal product solution was quenched with D_2O and the amount of incorporated deuterium for each compound determined by GC/MS. The major compounds showing deuterium incorporation (Table 1) were benzene (74.0%) average), toluene (54.1% average), ethylbenzene (30.6% average), phenol (2.2% average), biphenyl (19.5% average), and, in trace amounts only, terphenyls. In the case of ethylbenzene, 30.6% of the ethylbenzene present originated from the α-ethylbenzenemagnesium bromide as indicated by an intense 92 m/z deuterotropylium ion ($C_7H_7D^+$). The remaining 69.4%, having no deuterium, is considered to originate from the corresponding free radical abstraction of a hydrogen from the solvent [8,10]. This Grignard reagent, when treated with 1-piperidylcyclohexylcarbonitrile (PCC), would produce the identified PCP cosynthetic, 1-[1-(phenethyl)cyclohexyl]piperidine (**2**) [12]. Similarly, the deuterated biphenyl suggests the precursor of **3** to be biphenylmagnesium bromide. This does not, however, indicate the ring position of the attached magnesium bromide and more recent studies on the isolated biphenyl analogue of PCP suggest that two isomers are indeed present [17].

An examination of the compound classes identified, excluding iodobenzene, reveals that the only four classes of compounds were found; hydrocarbons, ethers, phenols, and alcohols. Those compounds containing phenyl groups would apparently derive from phenyl radicals generated in one of the processes described by Whitesides and his group [18]. Not inconceivably, a "tight radical pair" similar to that proposed by Walborsky and co-workers [6,10] can also be envisioned as a participant. The data in Table 1 show that the yields of the compounds selected for study were essentially constant and independent of the type of magnesium used, i.e., "treated" or "untreated" (see Experimental). In those experiments comparing the product distribution following H_2O or D_2O quench of the two types of magnesium, the "untreated" magnesium resulted in slightly higher quantitites of oxygen-containing compounds. Although the differences are not statistically significant, the possibility of oxide coating on the "untreated" magnesium effecting the yields [15] must be considered.

The mechanistic origin of 1-phenylethanol, proposed by Hock and co-workers [19] to occur as follows, seems reasonable:

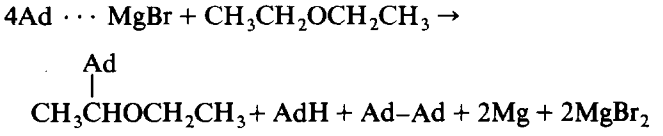
$$2C_6H_5^{\cdot} \rightarrow C_6H_5C_6H_5 \qquad (1)$$

$$C_6H_5^{\cdot} + CH_3CH_2OCH_2CH_3 \rightarrow C_6H_6 + CH_3\dot{C}HOCH_2CH_3 \qquad (2)$$



$$C_6H_5MgBr + CH_3\dot{C}HOCH_2CH_3 \rightarrow C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}HOMgBr + CH_3CH_2^{\cdot} \qquad (3)$$

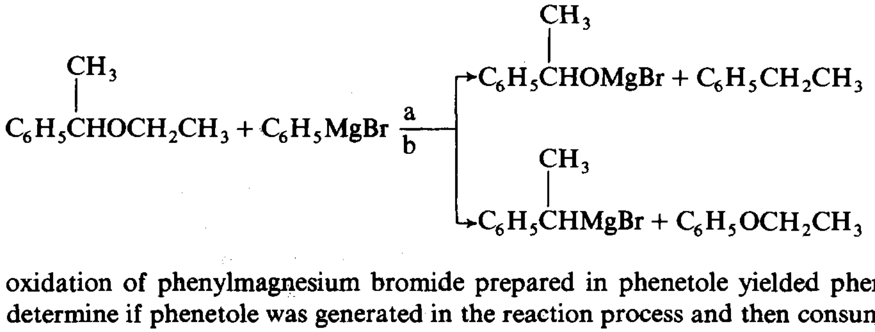
Molle and coworkers [8] studied the byproducts resulting from the solvent attack on adamantyl (Ad) Grignard reagents and proposed the magnesium surface-generated adamantyl free radical generation from the "loose-pair" radical Ad ··· MgBr reaction:



$$4Ad \cdots MgBr + CH_3CH_2OCH_2CH_3 \rightarrow$$
$$CH_3\overset{\overset{\displaystyle Ad}{|}}{C}HOCH_2CH_3 + AdH + Ad\text{–}Ad + 2Mg + 2MgBr_2 \qquad (4)$$

A radical of the type $CH_3\dot{C}HOCH_2CH_2$ was envisioned as being an intermediate in the process and the sequence seems reasonable for the phenylmagnesium bromide/ether production of the phenyl analogue, **6**, as well as the unlabeled benzene and diphenyl.

In accord with Okuhara's conclusion [11], the authors of both studies [8,19] did not propose the α-magnesium bromide of diethyl ether to be an intermediate in the reaction sequence and Muth and Benkeser [20] have shown that $MgBr_2$ is not the causative agent in the cleavage of di-n-butyl ether with ethylmagnesium bromide and does not participate further in the reaction. If 1-ethoxy-1-phenylethane (**6**) was a possible source for ethylbenzene, 1-phenylethanol or phenol, then the alternative pathways outlined in eq. 5 needed to be considered. Attack on **6** by phenylmagnesium bromide could yield 1-phenylethoxymagnesium bromide and ethylbenzene as indicated by path "a" in eq. 5. Alternatively since the observed α-deuteroethylbenzene must have originated from the corresponding α-magnesium bromide ethylbenzene, the alternative path "b" producing this Grignard reagent and phenetole must also be taken into account. Gilman and Wood [3] previously reported that the air



$$C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}HOCH_2CH_3 + C_6H_5MgBr \; \begin{cases} \xrightarrow{a} C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}HOMgBr + C_6H_5CH_2CH_3 \\ \xrightarrow{b} C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}HMgBr + C_6H_5OCH_2CH_3 \end{cases} \qquad (5)$$

oxidation of phenylmagnesium bromide prepared in phenetole yielded phenol. To determine if phenetole was generated in the reaction process and then consumed, we determined the product distribution of the deuterolysis and hydrolysis of phenyl-

TABLE 2

PRODUCT DISTRIBUTION IN PHENETOLE ENRICHED SYNTHESES [a]

	H_2O Quench			D_2O Quench		
	$C_6H_5OC_2H_5$		CH_6H_5OH produced	$C_6H_5OC_2H_5$		C_6H_5OH produced
	added [b]	remaining		added [b]	remaining	
Enriched	94.7 ± 2.44	0	113.0 ± 19.9 [b]	111.4 ± 17.4	0	116.8 ± 49.0 [b]
Unenriched	0	0	24.08 ± 3.8 [c]	0	0	24.08 ± 3.8 [c]
Net	94.7 ± 2.44	0	88.92(93.4%) [d]	111.4 ± 17.4	0	92.72(83.2%) [d]

[a] mol $\times 10^{-5}$. [b] Average of three syntheses ± standard deviation. [c] Average of nine unenriched syntheses, see Table 1. [d] Per cent yield based on amount of added phenetole.

magnesium bromide prepared in ether enriched with phenetole. The results are shown in Table 1 and 2.

The amounts of benzene and biphenyl derived from both quenches were essentially unchanged from those of other studies shown in Table 1. An 83–93% yield of phenol from the phenetole enrichment was realized while the yield of ethylbenzene did not show a commensurate increase (Table 2). The results suggest that a simple phenetole phenylmagnesium bromide interaction is not occurring since this process would produce a proportionate increase in the amount ethylbenzene. The results do not rule out, however, the attack of $^{\cdot}$MgBr [10] on phenetole to yield C_6H_5OMgBr and the ethyl radical.

Attention was next directed to the product distribution predicted in eq. 5, pathways "a" and "b". To that end, the Grignard reagent was prepared in diethyl ether, enriched with 83.7×10^{-5} mol of 1-ethoxy-1-phenylethane and the product distribution determined (Tables 1 and 3). The amount of 1-phenylethanol and phenol showed an appreciable increase over that in the unenriched study, 64.1 and 73.5% yield respectively, based on the amount of added **6**. However, no similar increase in ethylbenzene was observed suggesting that the 1-ethoxy-1-phenylethane does not interact as depicted in eq. 5 but rather the mechanism proposed by Hock et al. [19] is the more accurate chemogenesis of 1-phenylethanol. The fact that 64.79×10^{-5} mol of **6** remained after the reaction was terminated and only 22.6% was consumed strongly suggests that some other concerted process was occurring to generate the phenol observed. The results offered here do not provide an unambiguous phenol source but certainly the presence of 1-ethoxy-1-phenylethane must be suspect.

It is concluded that the cosynthetics present in the Kalir synthesis of PCP, **1**, derive from the interaction of phenylmagnesium bromide with the solvent ether to produce new Grignard reagents that can react with PCC. The origin of **2** 1-[1-(phenylethyl)cyclohexyl]piperidine, does not appear to be associated with the product 1-ethoxy-1-phenylethane and is proposed to derive from some transition state or intermediate formed prior to this compound. No compounds were identified which could be envisioned as resulting in 1,1′-(1,4-phenylenedicyclohexylidene)bis[piperidine] (**4**), suggesting that this compound may result during the reaction of PCC and the Grignard reagent.

The results do indicate, however, that compounds prepared from ethereal phenyl-

TABLE 3

PRODUCT DISTRIBUTION IN 1-ETHOXY-1-PHENYLETHANE ENRICHED SYNTHESES [a]

	$C_6H_5\overset{CH_3}{\overset{\vert}{C}}HOCH_2CH_3$		$C_6H_5\overset{CH_3}{\overset{\vert}{C}}HOH$	$C_6H_5\overset{CH_3}{\overset{\vert}{C}}HOCH_2CH_3$	C_6H_5OH	$C_6H_5\overset{CH_3}{\overset{\vert}{C}}HOCH_2CH_3$
	added [b]	remaining	produced	originally [c]	produced	consumed
Enriched	83.74 ± 11.21	67.89 ± 7.1	70.86 ± 40	138.75	85.64 ± 20	18.93
Unenriched	0	3.10 [d]	17.22 [d]	20.32	24.08	
Net	83.74 ± 11.21	64.79	53.64(64.1%) [e]	118.42	(73.5%) [e]	

[a] mol $\times 10^{-5}$. [b] Average of three syntheses ± standard deviation. [c] Calculated assuming all the 1-ethoxy-1-phenylethane derived from 1-phenylethanol plus remaining 1-ethoxy-1-phenylethane. [d] Average of nine unenriched syntheses (see Table 1). [e] Per cent yield base on added 1-ethoxy-1-phenylethane.

magnesium bromide will contain small amounts of products originating from solvent-generated Grignards, heretofore not reported.

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