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FORMATION AND REARRANGEMENT OF THE GRIGNARD REAGENT FROM 2-PHENYLCYCLOBUTYLMETHYL BROMIDE

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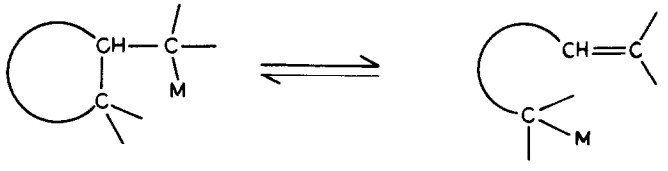
Summary

Reaction of *cis*- or *trans*-2-phenylcyclobutylmethyl bromide with magnesium produces the rearranged 5-phenyl-1-penten-5-ylmagnesium compound **7** in addition to the unrearranged Grignard reagent **6**. The former appears to result from very rapid rearrangement of a radical intermediate in the process of Grignard reagent formation. Rearrangement of **6** to **7** also occurs, at a rate which is accelerated by the phenyl group.

Introduction

Cycloalkylmethyl-organometallic compounds are interconverted with unsaturated open-chain isomers in a "ring-chain" rearrangement [1] (eq. 1). With three- or



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four-membered rings, the ring-opened isomer is usually favored. In previous work, we have concluded that a concerted four-center process provides the most probable mechanistic rationalization for this rearrangement with organomagnesium compounds [1a].

As part of a continuing effort to better understand the details of these rearrangements, we have examined the behavior of Grignard reagents from the 2-phenylcyclobutylmethyl halides. Some preliminary results for this system have been cited previously [1a]. Hydrolysis of a Grignard reagent prepared from 2-phenylcyclobutylmethyl chloride yielded only 5-phenyl-1-pentene and none of the unrearranged 2-phenyl-1-methylcyclobutane (eq. 2), suggesting that rearrangement of this Grig-

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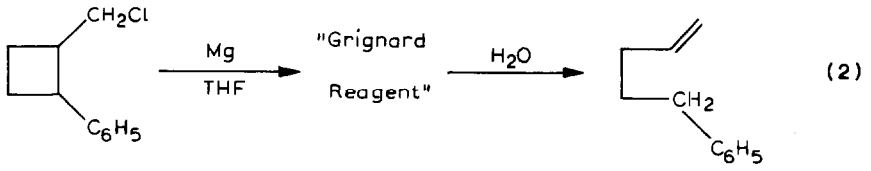


(2)

nard reagent occurs at a greatly accelerated rate. However, it is possible instead that rearrangement occurred entirely during formation of the Grignard reagent. We report here the outcome of further study of this system to clarify the nature of the rearrangement.

Results

2-Phenylcyclobutanecarboxylic acid was prepared following a route reported by Beard and Burger [2]. Small samples of nearly pure *cis* and *trans* isomers were separated by chromatography, but most of the study utilized a mixture containing an excess of the *trans*. The acid was routinely reduced to 2-phenylcyclobutylmethanol (**1-OH**) with lithium aluminum hydride, and then converted to the 2-phenylcyclobutylmethyl halides (**1-Cl** or **1-Br**) by reaction with thionyl chloride or triphenylphosphine/n-bromosuccinimide *. For comparison with hydrolysis products from the Grignard reagent, a mixture of the 1-methyl-2-phenylcyclobutanes (**2**) was made by reduction of the bromides with lithium triethylborohydride, and 5-phenyl-1-pentene (**3**) was prepared by coupling of 2-phenyl-1-ethylmagnesium bromide with allyl bromide. Spectroscopic properties of the various intermediates and products are listed in Table 1.

Grignard reagents were prepared from several samples of the 2-phenylcyclobutylmethyl halides and treated under various conditions. Gas chromatography allowed analysis of the hydrocarbons *cis*- and *trans*-**2** and **3** resulting from hydrolysis of the organometallic. Partial resolution of reaction products by small-scale molecular distillation also allowed identification of the dimeric hydrocarbon **4** produced by coupling of 5-phenyl-1-penten-5-yl radicals (mixture of diastereomers). From ^{13}C NMR spectra of intact Grignard reagent and of the unseparated hydrolysis mixtures, approximate analyses for the Grignard compounds **6** and **7**, hydrolysis products **2** and **3**, the dimer **4**, and the alcohol **5** (resulting from oxygenation) were obtained in several reactions. Signals attributable to the cyclic and open-chain organomagnesium compounds (**6** and **7**, respectively) were identified by comparison of spectra taken before and after hydrolysis, and from chemical shifts estimated from parameters published by Leibfritz, Wagner and Roberts [3]. ^{13}C NMR shifts of the organomagnesium compounds are included in Table 1, and the reaction pathways and products are summarized in Scheme 1.

Studies of Grignard reagent formation from the 2-phenylcyclobutylmethyl chloride mixture **1-Cl** in THF were inconclusive. Reaction of the chloride with magnesium required fairly lengthy periods of reflux, and commonly needed to be

* Some samples were contaminated with a small amount of the isomeric 5-halo-1-phenyl-1-pentene as a consequence of incomplete cyclization in the synthesis of the 2-phenylcyclobutanecarboxylic acid; other than producing small amounts of 1-phenyl-1-pentene on generation and hydrolysis of the Grignard reagent, it did not appear to influence the results in any way.

TABLE 1A

SPECTROSCOPIC PROPERTIES OF INTERMEDIATES AND PRODUCTS.

CYCLOBUTYL DERIVATIVES $C_6H_5\overline{CHCH_2CH_2CH}X$

X	Spectrum [a]
CO_2H	^{13}C NMR, *cis*: δ 179.7 (CO_2H), 140.2 (*ipso*), 127.5 and 126.7 (*meta* and *ortho*), 125.9 (*para*), 44.4 and 42.1 (C(1) and C(2), 45 and 41), 23.95 (C(3), 27), and 19.75 ppm (C(4), 22); *trans*: δ 180.5 (CO_2H), 143.2 (*ipso*), 127.7 and 125.7 (*ortho, meta, para*), 44.85 and 42.75 (C(1) and C(2)), 24.6 (C(3)), and 21.0 ppm (C(4)).
CH_3 (**2**)	^{13}C NMR, *cis*: δ 143 (*ipso*), 127.89 and 127.62 (*meta* and *ortho*), 125.48 (*para*), 42.27 (C(2), 47.4), 34.25 (C(1), 35.4), 25.76 and 22.91 (C(3) and C(4), 27.4 and 28.4) and 16.31 ppm (CH_3); *trans*: δ 145.25 (*ipso*), 128.20 and 126.50 (*meta* and *ortho*), 125.78 (*para*), 48.56 (C(2)), 39.30 (C(1)), 26.55 and 25.67 (C(3) and C(4)) and 20.98 ppm (CH_3); Mass spectrum (both isomers): (EI, 15 eV) 146(7), 118(10), 117(17), 115(9), 105(11); 104(100), 103(13), 91(11), 89(3), 86(4), 84(5), 78(12), 77(8), 65(3), 63(3), 51(7); (CI, CH_4) 145(10), 131(3), 105(7), 104(13), 91(9), 69(100).
CH_2OH (**1-OH**)	^{13}C NMR, *cis*: δ 140.84 (*ipso*), 128.1 and 127.1 (*meta* and *ortho*), 125.74 (*para*), 63.24 (CH_2OH, 64.3), 41.17 and 40.68 (C(1) and C(2), 44.3 and 37.3), 23.00 (C(3), 22.9), and 20.86 ppm (C(4), 20.8); *trans*: δ 144.68 (*ipso*), 128.07 and 126.42 (*meta* and *ortho*), 125.74 (*para*), 65.72 (CH_2OH, 69.0), 45.07 (C(1), 49.3), 42.59 (C(2), 43.6), 25.54 (C(3), 25.7) and 20.86 ppm (C(4), 21.5); Mass spectrum (both isomers): 162(0.5), 161(0.5), 144(1), 131(12), 120(3), 117(3), 116(4), 115(8), 105(13), 104(100), 103(11), 92(9), 91(12), 78(11), 77(7), 65(2), 63(2), 51(3).
CH_2Cl (**1-Cl**)	^{13}C NMR, *cis*: δ 139.9 (*ipso*), 128.3 and 127.5 (*ortho* and *meta*), 126.1 (*para*), 46.6 (CH_2Cl, 47.3), 41.6 (C(1) and C(2), 45.2 and 38.3), 23.0 and 22.5 (C(3) and C(4), 22.9 and 21.8); *trans*: δ 143.8 (*ipso*), 128.3 and 126.5 (*ortho* and *meta*), 126.1 (*para*), 48.3 (CH_2Cl, 52.0), 45.0 and 44.2 (C(1) and C(2), 50.3 and 44.6), 25.1 (C(3), 25.7), and 22.5 ppm (C(4), 22.5); ^1H NMR, mixture of isomers: four-line pattern centered at 3.5 ppm, characteristic of the center of the AB part of an ABX system; mass spectrum: (EI, 15 eV) 182(2), 180(6), 152(1), 145(5), 144(4), 131(6), 129(5), 128(5), 118 (6), 117(58), 116(10), 115(33), 105(22), 104(100), 103(13).
CH_2Br (**1-Br**)	^{13}C NMR, *cis*: δ 140.05 (*ipso*), 128.4 and 127.63 (*ortho* and *meta*), 126.4 (*para*), 42.29 and 41.76 (C(1) and C(2), 45.2 and 39.3), 36.14 (CH_2Br, 36.3) and 24.38 and 22.49 ppm (C(3) and C(4), 22.9 and 22.8); *trans*: δ 143.66 (*ipso*), 128.34 and 126.66 (*ortho* and *meta*), 126.28 (*para*), 45.71 and 45.13 (C(1) and C(2), 50.3 and 45.6), 37.78 (CH_2Br, 41.0), and 24.78 and 23.95 ppm (C(3) and C(4), 25.7 and 23.5); ^1H NMR ($CDCl_3$): *cis*, multiplet at δ 3.65 ppm (CH_2Br); *trans*, multiplet at 3.25 ppm characteristic of the AB portion of an ABX system.
CH_2MgBr (**6**)	^{13}C NMR (THF solution of mixed Grignard reagents, vs. TMS), *trans*: δ 147.7 (*ipso*, 147.5), 127.36 (*ortho* or *meta*), 125.49 (*para*, 124.7), 57.0 (C(2), 51.9 or 56.7), 50.25 (C(1), 46.2), 32.5 (C(4), 31), 24.75 (C(3), 26), and 17.45 ppm (CH_2Mg, 16.7); (ether solution of mixed Grignard reagents, vs. alkane reference), *trans*: δ 146.7, 126.7, 124.8, 55.7, 48.5, 31.3, 24.2, 17.7; *cis*: δ 128.48, 124.24, 46.9, 46, 25.5, 10.6 ppm (est. 46, 41, 30, 23, 11).

initiated, for instance, by addition of butyl bromide. Low yields of hydrolysis product and incomplete reaction of the chloride were found in most cases (gas chromatography and GC/MS). In most of the experiments, only the rearranged hydrolysis product **3** was detected. In two reactions initiated with the help of ethylene bromide (and probably hydrolyzed unintentionally by inefficient exclusion of moisture) the unrearranged hydrolysis product **2** predominated. In a reaction without an initiator, in which excess t-butyl alcohol was included to destroy Grignard reagent as it was formed, the ratio of *trans*-**2**/**3** was about 25/75.

TABLE 1B

SPECTROSCOPIC PROPERTIES OF INTERMEDIATES AND PRODUCTS.

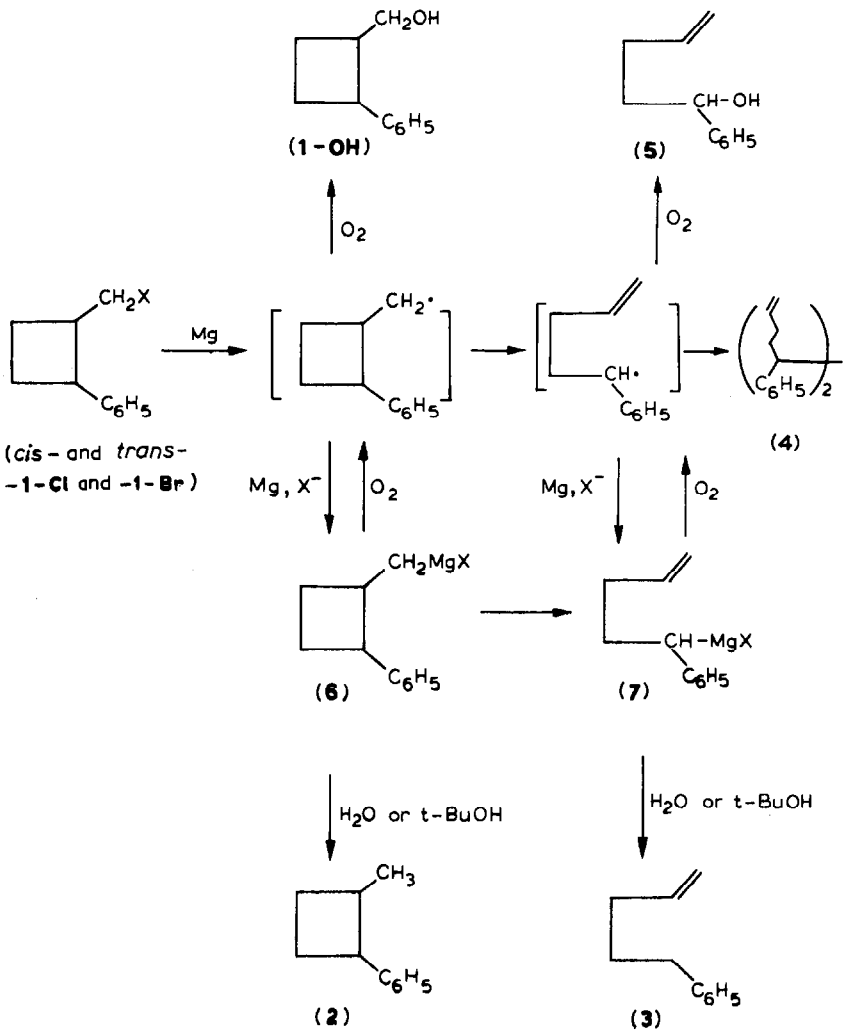
PENTENYL DERIVATIVES CH_2=$CHCH_2CH_2CH(Y)C_6H_5$

Y	Spectrum [a]
H (3)	^{13}C NMR: δ 142.47 (*ipso*), 138.56 (=CH), 128.33 (*ortho* and *meta*), 125.68 (*para*), 114.72 (=CH_2), 35.35 (C(5) 36.7), 33.30 (C(3), 34.0), 30.66 (C(4), 32.1); (ether solution of Grignard reagent): δ 143.0, 139.4, 128.99, 128.83, 126.28, 114.89, 35.98, 34.02, 31.56 ppm; ^{1}H NMR (CCl_4): δ 7.2–6.9 (m, 5, aromatic), 5.95–5.5 (m, 1, *J* 6.4, 10.1, 16.8 Hz, =CH), 5.1–4.84 (m, 2, =CH_2), 2.59 (t, 2, *J* 7.5 Hz, benzylic CH_2), ~ 2.05 (approx. q, *J* ≃ 6.5 Hz, allylic CH_2), ~ 1.7 ppm (approx. quintet, *J* ≃ 7.2 Hz, CH_2); Mass spectrum [b] (15 eV): 147(1.1), 146(9.2), 131(4.4), 118(2.4), 117(5.3), 106(1.6), 105(17.0), 104(100), 92(23.2), 91(23.7).
OH (5)	^{13}C NMR ($CDCl_3$, in mixture): δ 144.7 (*ipso*), 138.20 (=CH), 128.50 and 125.91 (*ortho* and *meta*), 127.60 (*para*), 144.97 (=CH_2), 74.09 (C(1), 76.3), 38.15 (C(2), 38.7) and 30.08 ppm (C(3), 28.3); (in ether solution of Grignard reagent): δ 75.1, 37.4, 30.1; Mass spectrum (GC/MS of product mixture) 162(2), 161(1), 160(2), 144(7), 133(5), 131(6), 129(7), 120(31), 108(9), 107(100), 105(36), 104(22), 92(3), 91(14), 79(62), 77(54), 65(4), 63(3), 55(7), 53(5), 52(4), 51(17).
MgBr (7)	^{13}C NMR (THF solution of mixed Grignard reagent, vs. TMS): δ 158.9 (*ipso*, 160.4), 141.53 (=CH, 140.9), 128.4 (*meta*, 127.6), 123.0 (*ortho*, 123.0), 116.2 (*para*, 116.7), 113.2 (=CH_2, 112.6), 38.25 and 36.9 (CH_2, 37.6 and 37.4), and 33.1 ppm (CHMg, 35.8); (ether solution of mixed Grignard reagent, vs. alkane reference): δ 156.6, 140.5, 123.3, 117.2, 112.6, 36.5, 36.9, and 33.9 ppm.
$C_{11}H_{13}$ [c] (4)	^{13}C NMR: δ 142.61, 144.15 (*ipso*), 138.71 (=CH), 129.05, 128.41, 127.58 (*ortho* and *meta*), 125.82, 126.20 (*para*), 114.46, 114.30 (=CH_2), 51.10, 51.69 (C(5)), 32.46 and 31.88, 33.63 and 31.58 ppm (C(3) and C(4)); (ether solution of mixed Grignard reagent): δ 144.1, 142.5, 138.4, 138.3, 128.9, 128.2, 127.6, 126.1, 125.7, 114.0, 113.8, 51.8, 51.2, 33.7, 32.6, 31.9, and 31.6 ppm; (THF solution of mixed Grignard reagent): δ 52.43, 51.83, 34.49 ppm; Mass spectrum (GC/MS of mixed reaction product) 290(1), 145(51), 144(44), 129(7), 117(3), 115(7), 104(8), 92(8), 91(100), 78(3), 77(5), 67(7), 65(3).

[a] Unless otherwise noted, proton and carbon NMR spectra are for solutions in $CDCl_3$, ppm downfield from internal $(CH_3)_4Si$. Assignments are given in parentheses. Estimated chemical shifts, included in parentheses in some cases, were based on model compounds, using additivity rules (refs. 3, 17, 18). Hydrocarbons *cis*- and *trans*-**2** and **3** were used as starting points for substituted derivatives. Mass spectra were obtained by electron impact with 70 eV electron unless otherwise noted. Results are reported as *m/e* (relative intensity). [b] Lit., K. Levsen, H. Heimbach, M. Bobrich, J. Respondek, and H. Schwarz, Z. Naturforsch. B., 32 (1977) 880. [c] Mixture of diastereomers.

Grignard reagents were prepared from the bromide in THF and in ether solutions. In general, preparation in THF led to a high yield of Grignard reagent; there was formation of very little of either monomeric or dimeric hydrocarbons **2**, **3** or **4**, but the Grignard reagent as initially observed was 60 to 80% rearranged. In no case was there any evidence for the presence of the *cis* isomer, either as Grignard reagent *cis*-**6** or as hydrocarbon *cis*-**2**, before or after hydrolysis. The subsequent rearrangement of the remaining *trans*-**6** was followed by NMR; after 21 h at 25°C, about half of the remaining *trans*-**6** had been converted to **7**, and after 4 h at 70°C, it was no longer detectable. In one experiment, *trans*-**1-Br** was allowed to react with magnesium in THF in the presence of an excess of t-butyl alcohol; about 78% of the monomeric hydrocarbon was rearranged.

A contrasting situation was found in Grignard reagent preparations from *trans*- or *cis*-**1-Br** in ether. In either case, half or more of the original alkyl groups ended up



SCHEME 1

as the dimeric hydrocarbon **4**, but the Grignard reagent formed was less extensively rearranged. The Grignard reagent initially formed from *trans*-**1-Br** in ether was 25% rearranged. Little change was observed over a period of 31 h at 25°C in a septum-capped NMR tube; after 15 days the Grignard reagent was 40% rearranged, but about a quarter of the original Grignard reagent had been lost. Hydrolysis of the Grignard reagent from *cis*-**1-Br** gave a mixture of *cis*-**2** and **3** which was 45% rearranged initially and 60% after 18 h of reflux. Reaction of *cis*-**1-Br** with magnesium in the presence of t-butyl alcohol produced 80% of dimer **4**, along with *cis*-**2** and **3** in a ratio of 75/25.

Grignard reagent from **1-Br** (*trans*/*cis* = 1.7/1) and sublimed magnesium in ether was sealed in an NMR tube. The dimer again formed in about 50% yield, and *cis*-**6**, *trans*-**6** and **7** were initially present in a ratio of 0.18/0.45/0.37. On heating at 52°C, signals attributed to *cis*-**6** decayed with a half-life of about an hour, and those from

trans-**6** with a half-life of about 140 h. After about a half-life for rearrangement of *trans*-**6**, the tube was opened, and the ether solvent was replaced with THF. Although the concentration of Grignard compound *trans*-**6** had been substantially reduced by prior rearrangement and some loss during solvent replacement, an approximate half-time of 18–36 h at 40°C could be estimated for its rearrangement in THF solution.

Since rearrangement to a considerable extent apparently occurred during formation of the Grignard reagent, it was of interest to investigate the behavior of 2-phenylcyclobutylmethyl radicals. This was done by reducing **1-Br** with tri-n-butyltin hydride in benzene solution utilizing ^{13}C NMR to identify products. Separate experiments were carried out on *trans* and *cis* isomers at 80°C, with a hydride concentration of 0.3 *M* (5-fold excess). In both reactions, disappearance of bromide was complete ($\geq 95\%$) and the only reduction product identified was the ring-opened **3**, with signals about one-third as intense as those of the co-product, tri-n-butyltin bromide. Neither *trans*- nor *cis*-**2** could be detected ($< 5\%$ and $< 2\%$, respectively, although there were some other minor unassigned resonances). When heated further with additional initiator, there was little change in the product signals *. A mixed sample of **1-Br** (*trans*/*cis* = 1.5/1) was also reduced in a solution approximately 3 *M* in the hydride. Weak signals appropriate to *trans*-**2** were present, corresponding to 6–8% of the yield of **3**. *Cis*-**2** was possibly present, but in an amount less than half as great. If it is assumed that the rate constant for transfer of hydrogen from tri-n-butyltin hydride to the *trans*-2-phenylcyclobutylmethyl radical is on the order of $3 \times 10^6\ M^{-1}\ s^{-1}$ at 80°C **, then the product mixture found implies a first order rate constant of about $8 \times 10^7\ s^{-1}$ for rearrangement of that radical, and an even greater rate for the *cis* isomer.

Discussion

In the formation and subsequent hydrolysis of a cyclobutylmethyl Grignard reagent, ring-opened product might result at either or both of two stages. The Grignard reagent itself may rearrange, or ring cleavage may occur earlier during formation of the reagent. In either case, it might be anticipated that a 2-phenyl substituent should have a major influence upon the rate of rearrangement. The results reported above indicate that both rearrangements are important in the 2-phenylcyclobutylmethyl system. The Grignard reagent formed from *trans*- or *cis*-**1-Br** in ether was 25–45% rearranged to **7** when first observed. Subsequent rearrangement is too slow to account for much of the initial **7** via rearrangement from **6**. Hence, most of the rearrangement in the freshly prepared reagent must have occurred in the process of formation. The situation is less clear in THF because of the higher temperature during preparation of the reagent, but it would appear that much of the rearranged **7** must again have been formed directly.

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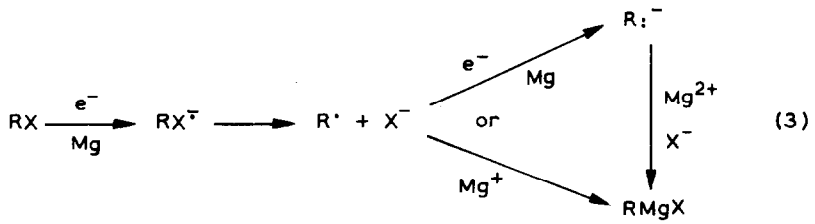
* The *cis* sample did show considerable further loss of hydride, perhaps via accidental introduction of oxygen.

** A value of $3.4 \times 10^6\ M^{-1}\ s^{-1}$ for reaction of primary alkyl radicals with tri-n-butyltin hydride may be calculated from a set of Arrhenius parameters preferred by Ingold [4]. A slightly lower rate is calculated using alternative parameters [5].

A number of lines of evidence [6] implicate free radicals in the formation of Grignard reagents, possibly via steps shown in eq. 3. Rearranged Grignard reagent



(3)

may result when the radical is prone to rearrange, and does so rapidly enough to compete with the subsequent reduction or recombination step.

It is known that cyclobutylmethyl and cyclopropylmethyl radicals rearrange, with rate constants of about 10^4 and about 10^8 s^{-1}, respectively *. *Trans*- and *cis*-2-methyl substituents accelerate the former cleavage by factors of 7 and 40, respectively [7], and 2-phenyl substitution might be expected to have a still larger effect. Indeed, the results of the tri-n-butyltin hydride reduction indicate that the *trans*-2-phenylcyclobutylmethyl radical has a first order rate constant of about 8×10^7 s^{-1} for rearrangement at 80°C, comparable with that of the cyclopropylmethyl radical.

In Grignard reagent formation, it is found that cyclobutylmethyl chloride and bromide react to form reagent with 98% or more of cyclobutylmethyl structure [12]. However, cyclopropylmethyl Grignard reagent formation is accompanied by about 50% of ring cleavage to produce the 3-buten-1-yl Grignard reagent [13]. It is likely that the cyclopropylmethyl radicals may rearrange rapidly enough to compete with reaction on the surface or in a radical pair. In addition, those radicals which diffuse away and subsequently return to complete the process will have a much higher probability of rearranging during their extended lifetime. It appears that a similar situation exists for 2-phenylcyclobutylmethyl radicals.

In the present study, a significant difference was observed between reactions in THF and ether. In THF, a good yield of Grignard reagent was obtained, but most of the reagent formed was of rearranged structure. In ether, less than half of the reagent as formed was rearranged, but half or more of the original alkyl groups ended up in the hydrocarbon dimer **4**. In the total reaction product, however, the fraction of original alkyl groups which have rearranged is similar in the two solvents, despite the difference in product distribution. Perhaps, the radicals which diffuse away from the magnesium surface (and therefore have more time to rearrange) primarily return to complete the reaction in THF, but couple in ether; alternatively, reduction of the rearranged benzylic radicals may be more difficult in ether. The absence of mixed rearranged-unrearranged dimer probably implies coupling of only those radicals which have diffused away from the surface.

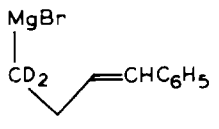
Some experiments were performed in which t-butyl alcohol was included in the reaction between **1-Cl** or **1-Br** and magnesium. The t-butyl alcohol is intended to

* For rearrangement of the cyclobutylmethyl radical, published Arrhenius parameters lead to rate constants at 25 and 80°C of 2.1×10^4 and 4.8×10^5 s^{-1} derived from EPR measurements [4a] and 9.1×10^2 and 3.5×10^4 s^{-1} derived from tri-n-butyltin hydride reductions [4a,7]. For the cyclopropylmethyl radical, minimum rates on the order of 6×10^7 s^{-1} at 25°C [8,9] and 3×10^7 s^{-1} at 80°C [10] have been estimated variously from kinetic data, and values of 1.3×10^8 and 6.4×10^8 s^{-1} at 25 and 80°C are calculated from Arrhenius parameters derived from EPR data at much lower temperatures [11].

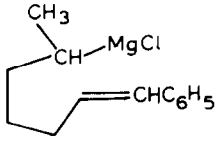
trap Grignard reagent before it has the opportunity to rearrange, but yet not interfere with formation of the reagent (as by reacting with radical intermediates) [6d,13]. However, our results suggest that the presence of the alcohol may be influencing the amounts of rearrangement and coupling which occur during Grignard reagent formation. For instance, in the reaction of *trans*-**1-Br** with magnesium in THF, a lower yield of unrearranged *trans*-**2** was obtained in the presence of the alcohol, whereas efficient trapping of newly formed Grignard reagent would be expected to result in an increased yield. In contrast, the reaction of *cis*-**1-Br** in ether did give an increased yield of *cis*-**2**, although rearrangement under those conditions appears to be too slow to influence the initial product distribution. The dimer yield also increased. We therefore recommend caution in the quantitative interpretation of such trapping experiments.

In a number of experiments, we noted that storage of Grignard reagent in a septum-capped NMR tube for periods of days led to slow destruction of Grignard reagent, with formation of the oxygenation product **5**. Similar reaction apparently occurred more rapidly when small residual amounts of reagent were kept in the preparation vessel (under nitrogen) and in one case during syringe transfer. The oxygenation was generally accompanied by partial hydrolysis, and also by production of increased amounts of dimer **4**. It is likely that initial interaction of Grignard reagent with O_2 generates free radicals by electron transfer. Depending upon the concentration of O_2 present, the radicals may be trapped by O_2 (to eventually produce the alcohol), rearrange, or couple. With 2-phenylcyclobutylmethyl radicals, rearrangement appears to be sufficiently rapid that all products formed in this fashion at low oxygen concentration are of rearranged structure.

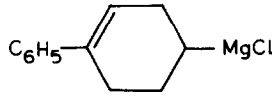
Once formed, 2-phenylcyclobutylmethylmagnesium bromide rearranges to its open chain isomer. Approximate half-lives for rearrangement, based on NMR or hydrolysis product compositions may be compared with observed or estimated half-lives for cyclobutylmethylmagnesium bromide [1a,14] (given in parentheses) as follows: *trans*-**6** in THF, 20 h at 25°C (65 000 h) or 18–36 h at 40°C (4800 h); *trans*-**6** in ether, 140 h at 52°C (150 h) or > 1200 h at 25°C (13 000 h); *cis*-**6** in ether, 1 h at 52°C (150 h) or 45 h at 36°C (1900 h). It may be seen that the *cis* isomer rearranges at an accelerate rate, as does the *trans* isomer in THF, though rearrangement of the *trans* isomer in ether occurs at a rate similar to that of the unsubstituted compound. An increase in the rate of the rearrangement may be attributed to benzylic resonance stabilization in **7**, and additionally to relief of steric repulsion in the *cis* isomer. While the acceleration is not unexpected, in view of the increased stability of the product, it was not a foregone conclusion that 2-phenyl substitution must accelerate the rearrangement. It has been reported earlier [1a,15] that the phenyl substitution in **8**, **9**, and **10** either decelerates or only slightly accelerates cyclization.



(**8**)



(**9**)

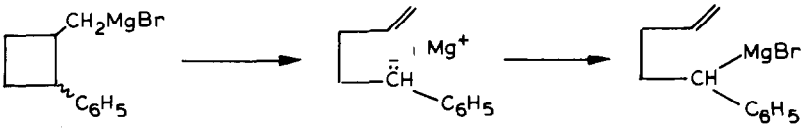


(**10**)

Furthermore, in a study of the effects of 2-methyl and 2,4-dimethyl substitution on the cleavage reaction of cyclobutylmethyl Grignard reagents, it was suggested that a

rate-decreasing methyl substituent effect may be largely steric rather than electronic in nature [16].

Another pertinent observation is that the rearrangement of *trans*-**6** occurs more rapidly in THF than in ether. This result contrast with previous observations [1a] of more rapid organomagnesium rearrangements in ether. The results may imply an increase in transition state polarity with 2-phenyl substitution. It is reasonable that the 2-carbon should become substantially more carbanionic in the transition state because of resonance stabilization of the developing charge; the immediate product of cleavage may even be ionic in nature:



A decreased rate in ether might also result from the increased amount of coupling during formation of the reagent in that solvent. The increase in concurrently formed magnesium bromide would shift the Schlenk equilibrium away from the more reactive dialkylmagnesium [1a,15b] and hence lead to a slower rate of reaction.

Most of the experiments reported in this paper utilized commercial grade magnesium turnings "for Grignard reaction". Solutions obtained, after setting, were clear and essentially colorless. The potential does exist for effects of trace transition metal impurities, particularly in inducing radical formation. However, there is no indication that any such influence was important in the results of this study. Formation of the Grignard reagent in ether produced a 50% yield of hydrocarbon dimer with either the commercial turnings or with turnings from a bar of sublimed magnesium. It has been previously reported that the rearrangement of cyclobutylmethylmagnesium chloride is slightly slower when the Grignard reagent is prepared from sublimed magnesium [1a]. However, the rate-enhancing effects of phenyl and the difference in rate between THF and ether are far larger than the effects of magnesium purity previously observed.

Experimental

Melting and boiling points are uncorrected. Nuclear magnetic resonance spectra were obtained on Varian Associates HA-100 and EM-360 (^{1}H) and Varian CFT-20 and Bruker WP 250 (^{13}C) spectrometers. Chemical shifts are reported relative to internal tetramethylsilane; in Grignard reagent solutions, shifts were referenced either directly to TMS, or indirectly vs. an alkane reference or the higher-field solvent resonance. Assignments of ^{13}C shifts were assisted by single frequency off-resonance decoupled spectra and comparisons with estimates based upon additive or substitution parameters [3,17,18]. Mass spectra were obtained on a Hewlett-Packard 5985 gas chromatograph-mass spectrometer, using a 74 cm × 2 mm column packed with 2% OV-101 and 0.2% Carbowax 20M on 100/120 mesh Chromosorb W-HP, by Mr. F. Laib. Other gas chromatograms were obtained on a Varian Aerograph A90-P3 instrument, using an 8 ft × 1/4 in column of 10% Ucon 50-HB-2000 on 60/70 mesh Chromosorb W (AW-DMC). Spectroscopic data are collected in Table 1. Elemental analyses were performed by Mr. K. Krumnow and by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Tetrahydrofuran (THF) and diethyl ether for Grignard reactions were distilled from sodium benzophenone or lithium aluminum hydride under nitrogen. Magnesium used for most experiments was Fisher Scientific magnesium turnings "for Grignard reaction". One experiment utilized a sample of sublimed magnesium which had been received as a gift several years earlier from the Dow Metal Products Company. Grignard reagents were prepared under nitrogen or argon in a flask sealed to a condenser, with a side-arm above the condenser for connection with an inert gas or vacuum line. Transfers of solvent or Grignard reagent were made by syringe, maintaining the inert atmosphere with a brisk flow of nitrogen or argon through the top of the apparatus. NMR spectra of Grignard reagents were obtained in either sealed or septum-capped 10-mm NMR tubes.

2-Phenylcyclobutanecarboxylic acid was prepared by the route described by Beard and Burger [2]. This route involves alkylation of malonic ester with cinnamyl chloride, addition of hydrogen bromide, cyclization with sodium hydride, and hydrolysis followed by decarboxylation in refluxing xylene. Some preparations were varied by substitution of cinnamyl bromide; addition of hydrogen chloride to diethyl cinnamylmalonate did not occur readily. In our hands, the decarboxylation of 2-phenylcyclobutane-1,1-dicarboxylic acid in refluxing xylene required extended periods up to several days rather than the previously reported 1.5 h. In some preparations, therefore, decarboxylation was carried out with the neat diacid at 210–215°C under reduced pressure. A partial separation of the *cis*- and *trans*-isomers was achieved by chromatography as described by Beard and Burger [2]. Samples of the *cis* acid, which was eluted first, were isolated as a solid (m.p. 84.5–86°C; lit. [2] m.p. 84.5–85°C). The liquid *trans* acid was approximately 90% pure in small fractions; the remainder of the material was carried through subsequent stages as a mixture with *trans* predominating. Mixtures could be conveniently monitored with ^{13}C NMR. In some samples, small amounts of cinnamylacetic acid were recognized by ^{13}C NMR resonances ($CDCl_3$) at δ 176 (CO_2H), 137.0 (*ipso*), 130.8, and 129.1 (olefinic), 128.2–125.9 (aromatic), 33.4 and 27.7 ppm (CH_2).

2-Phenylcyclobutylmethanol (**1-OH**) was prepared by reduction of 2-phenylcyclobutanecarboxylic acid. In a typical preparation, 4.0 g (23 mmol) of the acid in 10 ml of anhydrous ether was added to 1.0 g (25 mmol) of lithium aluminum hydride in 40 ml of ether over a period of about 15 min. The mixture was stirred and refluxed for an additional 45 min and hydrolyzed by dropwise addition of 3 ml of saturated aqueous sodium chloride. The ethereal solution was filtered through filter cell, dried (K_2CO_3) and stripped to yield 2.7 g (73%) of the crude alcohol. The product boiled at 150–160°C (0.7 mmHg). Small amounts of 5-phenyl-4-penten-1-ol gave rise to ^{13}C NMR signals ($CDCl_3$) at 137.44 (*ipso*), 130.11 and 129.94 (olefinic), 128.26 and 126.69 (*ortho* and *meta*), 125.7 (*para*), 61.77 (CH_2OH), 31.98 and 29.06 ppm (CH_2) (est. 62.3, 33.1 and 24.5).

Anal. Found: C, 81.63; H, 9.10. $C_{11}H_{14}O$ calcd.: C, 81.44; H, 8.70%.

2-Phenylcyclobutylmethyl chloride (**1-Cl**). In a typical preparation, 1.97 g (12 mmol) of the alcohol and 0.94 g (12 mmol) of pyridine were dissolved in 10 ml of ether. A solution of 1.43 g (12 mmol) of thionyl chloride in 2 ml of ether was added dropwise with stirring and cooling in an ice bath. The mixture was allowed to warm to room temperature, the ether distilled, and the resulting dark mixture heated to 70°C for 1 h. On cooling, the liquid was washed from the solid pyridinium salts with pentane, and chromatographed on a small alumina column with pentane as eluent.

Evaporation of the solvent yielded 1.11 g (51%) of clear liquid product.

Anal. Found: C, 73.13; H, 7.55. $C_{11}H_{13}Cl$ calcd.: C, 73.13; H, 7.25%.

2-Phenylcyclobutylmethyl bromide (**1-Br**). In a typical preparation, 5.34 g (30 mmol) of *N*-bromosuccinimide was added in small portions to a solution of 3.47 g (21 mmol) of the alcohol and 7.87 g (30 mmol) of triphenylphosphine in 10 ml of anhydrous ether. The mixture refluxed spontaneously after each addition, and a yellow precipitate separated. After an additional hour of reflux, the precipitate was removed by filtration and washed with ether. The ether was evaporated under vacuum and the pentane-soluble portion was chromatographed on an alumina column, eluting with pentane. Evaporation of the pentane yielded 2.52 g (47%) of the bromide. In some preparations, the product was purified by molecular distillation at 65°C (pot temperature) and 2 mmHg in a small-scale molecular still. The presence of 1-phenyl-5-bromo-1-pentene was shown in the ^{13}C NMR of some preparations by resonances at δ 137.5 (*ipso*), 131.3 and 128.6 (alkene), 127.2 and 126.2 (aromatic), and 33.2, 32.3 and 31.4 ppm (CH_2) in a neat mixture.

Anal. Found: C, 59.06; H, 5.85. $C_{11}H_{13}Br$ calcd.: C, 58.70; H, 5.82%.

5-Phenyl-1-pentene (**3**). A Grignard reagent was prepared from 3.0 g (16 mmol) of 1-bromo-2-phenylethane in THF. Allyl bromide (2.4 g, 20 mmol) was added gradually, resulting in an exothermic reaction. After 3 h of further reflux, the reaction mixture was hydrolyzed with saturated aqueous sodium chloride, filtered, and distilled at 80°C (10 mmHg) (lit. [19] b.p. 77–78°C/10 mmHg).

1-Methyl-2-phenylcyclobutane (**2**). To 0.4 g (1.8 mmol) of 2-phenylcyclobutylmethyl bromide (*cis/trans* ~ 1/2) was added 5 ml of 1 *M* lithium triethylborohydride ("Superhydride"). After 2.5 h stirring under nitrogen, the mixture was hydrolyzed with saturated aqueous sodium chloride and extracted with ether. The solvent was evaporated under vacuum, and the residue was taken up in pentane and chromatographed on alumina. The pentane eluent was found by gas chromatography to contain principally two components in a ratio of 2/1; the order of elution is consistent with reported boiling points of the *trans* and *cis* isomers [20].

Reaction of ***1-Br*** *with magnesium.* A Grignard reagent was prepared by addition of 0.51 g (2.3 mmol) of a sample of mixed isomers of the bromide (*trans/cis* 1.5/1) in 4 ml of THF to a reaction flask containing 0.088 g (3.6 mmol) of magnesium. The mixture was stirred without heating for 30 min, during which time it spontaneously warmed slightly and considerable corrosion of the magnesium surface was apparent. The flask was heated for 5 min in a 60°C oil bath and cooled. Two ml of the solution was transferred under nitrogen to a septum-capped 10 mm NMR tube. A spectrum was run, with accumulation completed approximately 1.5 h after the beginning of the reaction, and spectra were repeated periodically over the next 21 h, and again after heating in an oil bath at 70°C for 4 h. Signals attributed to Grignard reagents *trans*-**6** and **7**, in a ratio of about 1/3, were most prominent. Smaller amounts (on the order of 1% each) of hydrocarbons *trans*-**2**, **3** and **4** were present. Despite the appearance of several other minor unidentified resonances, there was no evidence for either *cis*-**2** or *cis*-**6**. The NMR sample was stored for several days in the capped NMR tube, during which time spectra were run after addition of a small amount of **3** and tetramethylsilane reference. The NMR solution was hydrolyzed by addition of D_2O. The solution remaining in the preparation flask was also hydrolyzed with D_2O after about 6 h at room temperature. Several other reactions in THF gave hydrolysis product mixtures shown by gas chromatography to contain up to

one third of *trans*-**2**. Some samples also had substantial amounts of alcohol **5** resulting from contact with air.

A sample of *trans*-**1-Br** (0.57 g, 2.6 mmol) was allowed to react with magnesium (0.090 g, 3.7 mmol) in 3 ml of ethyl ether. The solution was stirred for about 1 h, and a very gentle reflux was maintained by suspending the flask over an oil bath. About 2 ml of the solution was transferred to a 10 mm NMR tube, and the remainder was hydrolyzed. Several ^{13}C NMR spectra were run over a period of 30 h and again after 15 days at room temperature. The NMR spectrum indicated a 50% conversion to the dimer **4**. In addition to about 35% of Grignard reagents *trans*-**6** and **7**, there were small amounts of hydrolysis and oxygenation products. The reagent was hydrolyzed by addition of water, and a spectrum was again run. The hydrolyzed samples from this run were combined, extracted with pentane, washed, the solvent evaporated, and transferred to a small molecular still. Fractions were collected at a pressure of about 1.5 mm and bath temperatures of 70 and 110°C. ^{13}C NMR spectra of the fractions were obtained. The more volatile fraction (70°C) contained largely the monomeric hydrocarbons *trans*-**2** and **3**, along with alcohol **5** and probably a smaller amount of *trans*-**1-OH**. The less volatile fraction was composed mainly of an equal mixture of the two diastereomers of the dimeric hydrocarbon **4** as the major component. Partial crystallization of one isomer occurred, allowing assignment of resonances to the two isomers.

A Grignard reagent was similarly prepared from mixed isomers of **1-Br** (0.15 g, 0.67 mmol) and sublimed magnesium (0.029 g, 1.2 mmol) in about 2.5 ml of ether. The solution was sealed in a 10 mm NMR tube and observed after heating for various periods of time up to 130 h at 52°C. The tube was opened in an inert atmosphere bag and attached to an adapter which allowed the solvent to be removed under vacuum. The residue was dissolved in ether and transferred to a septum-capped NMR tube. Additional spectra were run after heating at 40°C for various periods of time. The spectra indicated some loss of reagent due to hydrolysis during the solvent replacement, but sufficiently strong resonances for *trans*-**6** remained that a very rough estimate of its rate of disappearance could be made.

A Grignard reagent was prepared by addition of *cis*-**1-Br** (0.38 g, 1.7 mmol) in 1.5 ml ether to magnesium (0.068 g, 2.8 mmol) and 1 ml of ether. No reaction was apparent during 20 min without heating, so the mixture was heated gently for 40 min. A sample was removed and hydrolyzed, and the remaining solution was hydrolyzed after heating at reflux for 16 h. Hydrolyzed samples were extracted with pentene, dried (K_2CO_3), the solvent was stripped on a rotary evaporator, and the residue was transferred in $CDCl_3$ to a 10 mm sample tube for ^{13}C NMR analysis.

A sample of *cis*-**1-Br** (0.23 g, 1.0 mmol) in 1 ml of ether was added to magnesium (0.045 g, 2.2 mmol) and t-butyl alcohol (0.17 ml, 2.0 mmol) in 1 ml of ether. This mixture was heated at reflux for 6 h and then worked up and analyzed as in the preceding experiment. Similar experiments were carried out with **1-Br** and **1-Cl** in THF.

Reaction of ***1-Br*** *with tri-n-butyltin hydride.* A stock solution was prepared from tri-n-butyltin hydride (0.87 g, 3.0 mmol) and 0.01 g of azobis(isobutyronitrile) (AIBN) in benzene (6 ml) which had been purged by a flow of nitrogen for several minutes. A 2 ml aliquot of this solution was transferred to a 10 mm NMR tube containing *trans*-1-Br (0.044 g, 0.2 mmol) in 1 ml of benzene with benzene-d_6 as a lock signal. Final concentrations of *trans*-**1-Br** and tri-n-butyltin hydride were about

0.06 and 0.30 *M*. The tube was heated for 45 min in an oil bath maintained at 80°C, and the ^{13}C NMR spectrum was run. In order to establish the stability of reaction products, an additional 3 mg of AIBN was added, and the tube was heated for an additional 50 min. A similar experiment was performed using *cis*-**1-Br**. Another reaction was run with mixed bromide isomers using neat tri-n-butyltin hydride in place of the stock solution; concentrations of bromide and hydride were about 0.09 and 3.0 *M*, respectively.

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