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Mechanism of the Grignard Addition Reaction

VIII. Reaction Rates and Product Distribution for the Reactions of *t*-Butylmagnesium Chloride and Methylmagnesium Bromide with Substituted Benzophenones

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Benzophenone and substituted benzophenones react with *t*-butylmagnesium chloride yielding various ratios of 1,2-, 1,4-, or 1,6-addition products besides benzopinacols. While the product distribution is extremely sensitive to steric effects of substituents, the overall rate is not influenced by steric factors, and a linear Hammett plot is obtained. This suggests an initial rate limiting step, common to all four reactions. All evidence points to this step being a one electron transfer from the Grignard reagent to benzophenone with the formation of the *t*-butyl radical and the benzophenone ketyl radical anion.

A heterolytic mechanism is most likely for reactions of methylmagnesium bromide with unsubstituted benzophenone, but the radical mechanism is probably responsible for the conjugate addition observed with sterically hindered benzophenones under forcing conditions.

Generally, a radical mechanism seems to be implied when (i) conjugate addition to aromatic systems occurs, or (ii) Grignard addition reactions occur with rates which are much higher for reagents branched in the α-position than for those devoid of branching.

Traditionally benzophenone and its derivatives have been favourite substrates for mechanistic investigations of the Grignard addition reaction. As a result much knowledge has accumulated on this reaction, but many important problems concerning the detailed mechanism have remained unsolved.

A radical pathway for the reaction was first proposed in 1929 by Blicke and Powers[1] who found that many Grignard reagents reduce benzophenone rather than forming addition products. The initial step was suggested to be transfer of a single electron to benzophenone to give the magnesium benzophenone ketyl and the alkyl radical:

$$(C_6H_5)_2C=O + (CH_3)_3CMgCl \rightarrow (C_6H_5)_2\dot{C}-O^- + MgCl^+ + (CH_3)_3C\cdot$$

The radical pair would then (i) combine to form the tertiary alcohol, (ii) interact by mutual oxidation-reduction to form benzohydrol and alkene, or (iii) separate and recombine to form pinacol and hydrocarbons.

The formation of pinacol, the most direct support of the theory, was not observed, however, by Blicke and Powers,[1] but was noticed in 1932 by Arbuzov and Arbuzova [2] in the reaction of cyclohexylmagnesium iodide with benzophenone. Later, it was suggested [3] that the pinacol formation, observed by the Russian workers, was caused by the presence of metallic magnesium in the unfiltered reagent. Trace impurities of transition metals in the magnesium may likewise cause formation of benzopinacol in the reaction of, *e.g.*, methylmagnesium bromide with benzophenone.[4,5] Blomberg and Mosher,[6] however, obtained a 20 % yield of benzopinacol from the reaction of neopentylmagnesium chloride and benzophenone using magnesium-free reagent prepared from sublimed magnesium. Several workers,[7] including Blomberg and Mosher,[6] have verified the occurrence of benzophenone-magnesium ketyl during Grignard addition to benzophenone, by means of ESR technique.

Ketyl radicals are therefore without doubt involved in some, if not all, Grignard addition reactions with benzophenone, but the question remains whether they represent the main route, or rather result from unimportant side reactions.

In the present investigation a closer study has been made of the reaction of benzophenone and substituted benzophenones with *t*-butylmagnesium chloride and methylmagnesium bromide, both with regard to kinetics and distribution of reaction products.

The addition of *t*-butylmagnesium chloride to unsubstituted benzophenone has been reported by Kharash [8] to yield 63 % of the 1,2-addition product, diphenyl-*t*-butylcarbinol, and no reduction products (benzhydrol or benzopinacol). By NMR analysis of the crude reaction product it has now been found that 1,2-addition is, in fact, responsible for 44 % of the reaction, while

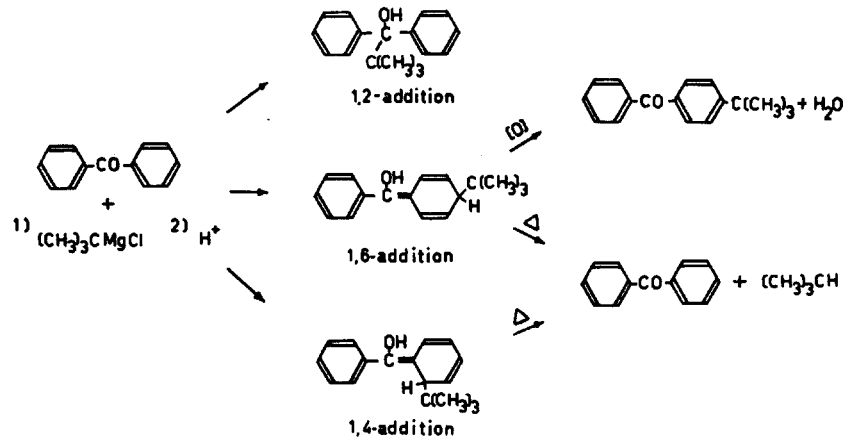

Fig. 1. Reaction paths by addition of *t*-butylmagnesium chloride to benzophenones; benzopinacol formation not included. Oxidative and thermal decompositions of the dihydrobenzophenones are shown.

50 % of the substrate is converted into an alkyldihydrobenzophenone as a result of 1,6-addition (see Fig. 1). Besides, a small amount of benzopinacol was isolated.

The conjugate addition of Grignard reagents to sterically hindered benzophenones is well-known, especially from the work of Fuson and coworkers.[8] The conjugate addition to benzophenone itself seems to have been overlooked, however, probably because *t*-butyldihydrobenzophenone is unstable and decomposes thermally at 80 – 90° with reformation of benzophenone (see Fig. 1). In the presence of oxygen or other oxidizing agents, such as bromine, it readily undergoes aromatization to give 4-*t*-butylbenzophenone. The vinylic proton pattern in the NMR spectrum of the dihydrobenzophenone supports the enolic 1,6-dihydro structure (Fig. 1). Thermolysis of *t*-butyldihydrobenzophenone accounts for the recovery of starting material in the reaction of benzophenone with secondary and tertiary Grignard reagents as reported by, *e.g.*, Arbuzov.[2]

Corresponding reactions with substituted benzophenones showed that the ratio between the three types of products, namely benzopinacol, 1,2-addition product, and conjugate addition products, is extremely sensitive to steric factors. For example, the presence of *t*-butyl groups in the *para* positions completely blocks 1,6-addition, while much 1,2-addition and some 1,4-addition take place (see Fig. 1). The absence of 1,6-addition in the present case was confirmed by reacting *p,p'*-di-*t*-butylbenzophenone with excess hexadeuterio-*t*-butylmagnesium chloride. After work-up it was shown that no deuterium was incorporated in the regenerated ketone. The formation of benzopinacol amounted to 21 % of the starting material.

Methyl groups in both *ortho* positions in one of the phenyl groups of benzophenone prevent addition of *t*-butylmagnesium chloride in a 1,2 fashion, and both 2,4,6-trimethylbenzophenone and 2,3,5,6-tetramethylbenzophenone yield exclusively the 1,6 conjugate addition products.

Methyl groups in both *para* positions of the substrate do not prevent 1,6-addition as do the *t*-butyl groups. In fact, 4,4'-dimethyl-4-*t*-butyl-1,6-dihydrobenzophenone is found together with equivalent amounts of the 1,2-addition product when 4,4'-dimethylbenzophenone is reacted with *t*-butylmagnesium chloride. In this case, 12 % of the starting material is converted into benzopinacol. The 4-methyl-4-*t*-butyldihydrobenzophenone is very thermolabile and reacts momentarily with oxygen to give *t*-butyl alcohol and the parent benzophenone.

Halogen-substituted benzophenones were shown to react by 1,2- as well as by 1,4- and 1,6-addition. When *t*-butyl entered a position carrying halogen, the adduct suffered immediate loss of magnesium halide, so that the overall reaction was substitution of halogen by *t*-butyl. The benzophenone thus formed was reattacked by the Grignard reagent, and from, *e.g.*, *p,p'*-dichlorobenzophenone the products identified included the three tertiary alcohols resulting from 1,2-addition solely, from 1,6-addition (substitution), followed by 1,2-attack, and from two 1,6-attacks (substitutions), followed by 1,2-addition. Other constituents of the crude product were: the parent dichlorobenzophenone, the *p*-*t*-butyl-*p'*-chlorobenzophenone, and the *p,p'*-di-*t*-butylbenzophenone. The presence of the ketones is explained by thermal decomposition of the 1,4-

Table 1. Approximate product distribution in the reactions of *t*-butylmagnesium chloride with substituted benzophenones. Ratios in per cent. See *Experimental.*

Benzophenone	Benzopinacol [a]	1,2-addition	1,4-addition	1,6-addition
Unsubstituted	6	44	0[b]	50
4,4'-Dimethyl	12	55	0[b]	33
4,4'-Di-*t*-butyl	21	40	39	0
4,4'-Dichloro	0	50	21	29
2,4,6-Trimethyl	0	0[b]	0[b]	100[c,d]
2,4,6,4'-Tetramethyl	0	0[b]	0[b]	100[d]
2,3,5,6-Tetramethyl	0	0[b]	0[b]	100[c,d]

[a] Isolated product. [b] The presence of trace amounts cannot be excluded by NMR. [c] The 1,6-addition products were aromatized in 80 % (trimethyl) and 76 % (tetramethyl) yields. [d] The sole product observed by NMR.

adducts, formed by conjugate addition of the Grignard reagent. It was not possible to isolate products with pinacol structure from this reaction.

The product distribution obtained by reaction of six benzophenones with *t*-butylmagnesium chloride is presented in Table 1.

Addition of cobalt(II) chloride to the *t*-butylmagnesium chloride employed in the reaction with benzophenone or 4,4'-dimethylbenzophenone gave no

Table 2. Pseudo first order rate constants and σ-values for substituted benzophenones (initial concentration 0.0100 M) reacting with 0.56 M *t*-butylmagnesium chloride (with 10.5 % $MgCl_2$) at 20° in diethyl ether (1 – 14), or at −30° (15 – 19).

No.	Substituents	k_{obs} (sec^{-1})	log k_{obs}	σ
1	2,4,6,4'-Tetramethyl	0.62	−0.208	−0.680
2	4-Dimethylamino	0.74	−0.13	−0.600
3	4,4'-Dimethoxy	1.65	0.218	−0.536
4	2,3,5,6-Tetramethyl	1.16	0.065	−0.478
5	2,4,6-Trimethyl	1.69	0.225	−0.510
6	4,4'-Di-*t*-butyl	11.2	1.049	−0.394
7	4,4'-Dimethyl	11.7	1.068	−0.340
8	2,4,6-Trimethyl-4'-chloro	13.4	1.127	−0.285
9	4-Methoxy	7.27	0.861	−0.268
10	4-Methyl	30.4	1.483	−0.170
11	Unsubstituted	94	1.971	0.00
12	4-Chloro-4'-methyl	84	1.483	0.057
13	3-Chloro-4'-methyl	424	2.63	0.203
14	3-Methoxy-4'-chloro	360	2.56	0.342
15	2,4,6-Trimethyl-4'-chloro	0.83	−0.083	−0.285
16	Unsubstituted	7.3	0.863	0.00
17	4-Bromo	33.5	1.525	0.232
18	4-Chloro-3'-methoxy	61	1.78	0.342
19	3-Chloro-3'-methoxy	152	2.182	0.488

increase in the yield of the benzopinacols. The ratio between 1,2-addition and conjugate addition was virtually unchanged.

Reaction of substituted benzophenones with *t*-butylmagnesium chloride were studied by means of the thermographic method.[9] First order kinetics were obtained for the disappearance of the substrate (starting concentration 0.01 M) when a large excess (0.56 M) of the Grignard reagent was used. From the first order rate plot, first order rate constants were obtained. The values are given in Table 2.

A Hammett plot of log rate *versus* σ-substituent values shows a linear distribution with a correlation coefficient of 0.974 (see Fig. 2). From the slope of the line a reaction constant of $\varrho = 3.0$ is obtained.

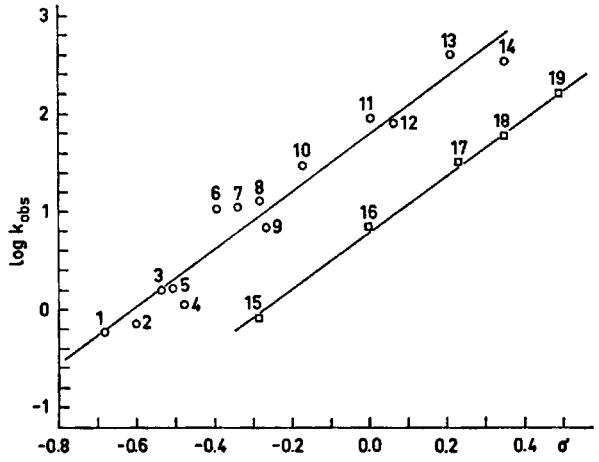

Fig. 2. Hammett *sigma* values *versus* log k_{obs} for the reaction of *t*-butylmagnesium chloride in diethyl ether and the substituted benzophenones tabulated in Table 2. Temperature 20° and −30°.

It can be seen from Table 1 that addition of *t*-butylmagnesium chloride to substituted benzophenones may yield from 0 to 55 % 1,2-addition product, from 0 to 39 % 1,4-addition product, from 0 to 100 % 1,6-addition product, and from 0 to 21 % benzopinacol. The rates of the formation of the four individual products are obviously controlled by steric factors. Nevertheless, a satisfactory Hammett plot is obtained for the sum of the four competing reactions, and steric factors have no influence on the rate of the overall reaction as measured by disappearance of the substrate.

The only reasonable rationalization of these findings is that the reactions are not independent, but proceed through a common rate limiting step, most probably the one-electron transfer from the Grignard reagent to the benzophenone to form the ketyl radical anion and the *t*-butyl radical. This would indicate that the radical path is not a side reaction, but rather constitutes the main, if not the only mechanism.

Since the Hammett equation is obeyed for a large number of combinations of substituents in the two aromatic rings (by summing up the substituent values) it may be concluded that the electron transfer occurs to the carbonyl group. The value of the reaction constant is partly dependent on the ease of transmission of electric effects to the reaction site; a regular Hammett plot therefore indicates that this is the same for all attacks (*in casu* the central carbonyl group).

The most surprising result of the rate studies is the absence of a steric effect from one or even two *ortho* methyl groups. The polar substituent value $\sigma^* = -0.17$, from the tabulation by Taft,[10] was applicable, which means that a *para* and an *ortho* methyl group has the same effect on the rate in this reaction. The simultaneous presence of methyl groups in all four *ortho*-positions, however, caused a breakdown of the regular Hammett rate law. In the case of 2,4,6,2',4',6'-hexamethylbenzophenone a high yield of 1,6-addition product was obtained, but only after a reaction time of several days.

The analogous Grignard addition reaction of methylmagnesium bromide to various substituted benzophenones was studied by means of the technique previously described.[11] A straight line Hammett plot with a slope of $\varrho = 1.1$

Table 3. Pseudo first order rate constants and σ-values for substituted benzophenones (initial concentration 0.00100 M) reacting with 0.100 M methylmagnesium bromide (0 % $MgBr_2$) at 20° in diethyl ether.

No.	Substituents	k_{obs} (sec^{-1})	log k_{obs}	σ
1	4,4'-Bisdimethylamino	0.0015	−2.829	−1.20
2	4,4'-Dimethoxy	0.0204	−1.69	−0.536
3	4,4'-Di-*t*-Butyl	0.0533	−1.273	−0.394
4	Unsubstituted	0.0825	−1.085	0
5	4,4'-Difluoro	0.084	−1.076	0.124
6	4-Chloro	0.123	−0.907	0.227
7	4,4'-Dichloro	0.231	−0.636	0.454
8	4,4'-Dibromo	0.169	−0.772	0.464

was obtained for *para*-substituted ketones (see Table 3 and Fig. 3). Attempts to fit *ortho*-methyl substituted benzophenones into the scheme were, however, futile. Even one *ortho* methyl group [12] caused a 5 – 6 fold reduction of the observed rate as compared with the expected value, while two *ortho* methyl groups block the reaction almost completely. The addition of methyl Grignard reagent to benzoyldurene or benzoylmesitylene is known to require forced conditions,[13] and while the normal addition product of methylmagnesium bromide to unhindered benzophenones is exclusively the 1,2-product, the hindered ketones under forced conditions yield 1,4- and 1,6- as well as 1,2-addition products.[13]

The absence of steric hindrance by *ortho* methyl substitution in benzophenone in the reaction with *t*-butylmagnesium chloride, in contrast to the hindrance observed when using methylmagnesium bromide, is surprising in

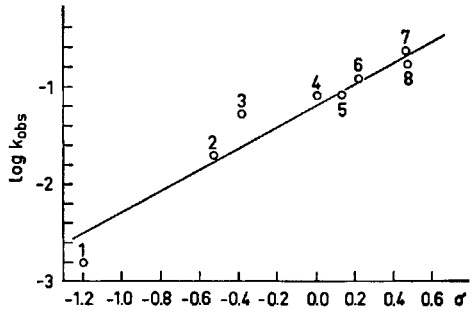

Fig. 3. Hammett *sigma* values *versus* log k_{obs} for the reaction of 0.56 M methylmagnesium bromide in diethyl ether and the substituted benzophenones of Table 3. Temperature 20°.

view of the greater bulk of the *t*-butyl group. The question is then whether the two reagents react by identical mechanisms. *A priori* methylmagnesium bromide would be expected to give up a single electron very reluctantly as compared with the *t*-butyl reagent, whereas heterolytic fission of the carbon-magnesium bond is much more likely to occur with the methyl reagent than with the *t*-butyl reagent. It is also acceptable that the transfer of an electron is less requiring sterically than the transfer of an ion. It may therefore be reasonable to suggest that methylmagnesium bromide reacts with hindered benzophenones, such as benzoyldurene, by the one electron transfer mechanism, but with unhindered benzophenones by a different, probably heterolytic, mechanism. Support for this conception may be obtained from three experimental facts. Thus the observation of conjugate addition to the hindered benzophenones, but clean 1,2-addition to unhindered benzophenone may in itself be an indication of different mechanisms. Furthermore, the kinetics of methylmagnesium bromide reacting with unhindered benzophenones are of a unique type (reactivity increasing roughly linearly with $[CH_3MgBr]$),[11] while the kinetics of the reaction of this reagent with hindered benzophenones or of *t*-butylmagnesium chloride reacting with any benzophenone (hindered or unhindered) are of the same general type. In the last mentioned reactions the rate shows a very low order with respect to Grignard reagent when the ketone is reacting under pseudo first order conditions with high concentrations of Grignard reagent (Fig. 4). Finally, it seems an indication of change of mechanism that the relative reactivity of methyl- and *t*-butylmagnesium bromide toward unsubstituted benzophenone is 10^{-2} (Ref. 11), but toward benzoyldurene of the order of 10^{-5}. The latter value is estimated from Fig. 4 (giving the value for methylmagnesium bromide at 100°) and from Fig. 2 (giving the value for *t*-butylmagnesium chloride at 20° and −30°, and allowing for extrapolation to 100°; the chloride is assumed to react faster by a factor of four).

For five differently substituted benzophenones, first order rate constants for the reaction with *t*-butylmagnesium chloride were determined at −30° (Table 2, Nos. 15 – 19), and the Hammett plot obtained (Fig. 2) gave a value for the reaction constant of $\varrho = 2.9$.

The Arrhenius energy of activation for the reaction of benzophenone with *t*-butylmagnesium chloride, based on the rates observed at 20° and at −30°, may be calculated to 3.60 kcal/mol. For methylmagnesium bromide, reacting

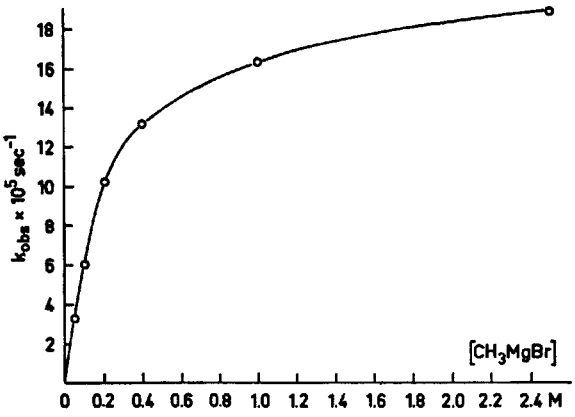

Fig. 4. Pseudo first order rate constants for benzoyldurene reacting with methylmagnesium bromide at 100° in diethyl ether. Initial concentration of substrate 0.0042 M.

with benzophenone, the activation energy was determined to 13.9 kcal/mol.[11]

It seems relevant at this point to reconsider the relative reactivity of various Grignard reagents toward benzophenone and toward aliphatic ketones and esters [11] in the light of the new findings.

The extreme reactivity of branched alkylmagnesium halides toward benzophenone (as opposed to the relative inertness of these reagents toward acetone and aliphatic esters) may now be interpreted in terms of a single electron transfer as the rate limiting step. The reactions are fast because of the ease of formation of both the ketyl radical anion and of the branched alkyl radical. Whether the radical mechanism applies also to the reaction of benzophenone with unbranched, aliphatic and aromatic Grignard reagents remains undecided, although the possibility is attractive. These reagents would produce extremely reactive and unstable radicals compared with the *t*-butyl radical. The pair of radicals obtained by electron transfer would probably combine or react before any conjugate addition or benzopinacol formation takes place.

The radical mechanism certainly plays an important role in the reaction of neopentylmagnesium chloride with benzophenone. The radical combination in this case is slowed down because of steric bulk, with the result that the neopentyl radical attacks the solvent, while the ketyl radicals combine to form a pinacol.[6]

No evidence has been presented for a radical mechanism in the reaction of Grignard reagents with saturated aliphatic esters and ketones. Toward these substrates branched alkyl reagents like *t*-butylmagnesium chloride are of low relative reactivity. However, one may possibly assume that whenever a Grignard reagent branched in the α-position reacts faster than a Grignard reagent devoid of branching, a one electron transfer mechanism is operating in the former case. Examples, other than benzophenones, include typical electron acceptors such as azobenzene,[14] nitrobenzene,[15] pyridazines,[16] and, possibly, acetylenes.[17]

The benzyl and allyl Grignard reagents are usually of relative high reactivity, but may react either by homolytic or heterolytic mechanisms. Both types of reagent may yield conjugate addition products with aromatic substrates, and it seems a reasonable generalization that conjugate aromatic addition of Grignard reagents is always of a radical type mechanism.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained on a Varian A-60 instrument. Gas chromatography was performed on an Aerograph 1520 using a 120 cm silicone column.

The benzophenones were prepared from acid chlorides and hydrocarbons by Friedel-Crafts syntheses or from acid chlorides and arylcadmium compounds. They were distilled *in vacuo* and recrystallized.

The Grignard reagents were prepared from Dow sublimed magnesium with strict precautions against contamination with moisture or air. The solutions were analysed for the content of chloride; this was compared with the base titer to evaluate competition from side reactions in the preparation of the Grignard reagents.

Addition reactions. In a typical preparative run 5 mmol of the benzophenone were dissolved (or dispersed) in 5 ml of dry ether in an evacuated vessel. *t*-Butylmagnesium chloride (7.5 ml, 1.00 M in ether) was added by means of a syringe with cooling, each drop giving a characteristic red to brown coloration until the Grignard reagent was in excess. In the case of slow reactions, the color disappeared only gradually; thus the red color from 2,4,6,2′,-4′,6′-hexamethylbenzophenone and excess *t*-butylmagnesium chloride persisted for more than 24 h. If substitution could take place as in 4.4′-dichlorobenzophenone, more Grignard reagent had to be added. The adducts were decomposed with water (2 ml) and aqueous ammonium chloride (2 ml saturated) while cooling in ice water to diminish thermal decomposition of any dihydrobenzophenones present. Argon pressure was applied to the vessel, the ether layer removed with a syringe, and transferred to an evacuated vessel, from which the ether was removed *in vacuo*. The crude mixture thus obtained was analysed.

Analysis of products. The presence of dihydrobenzophenones was shown by NMR technique. The crude product was dissolved in deuteriochloroform *in vacuo* immediately after removal of the ether and transferred under argon to the sample tube. The presence of vinylic protons and integration of *t*-butyl resonances gave qualitative and quantitative analyses of the dihydrobenzophenones present. Oxidation with bromine gave aromatized products (see below). The termal decomposition of the dihydrobenzophenones was shown to give isobutane and the parent benzophenone. Thus the crude products obtained from unsubstituted benzophenone decomposed at 80 – 90° to give stoichiometric amounts of isobutane (identified by NMR) and benzophenone (identified by GLC and NMR). Any benzophenones isolated after anaerobic work up were supposed to originate from 1,4- and 1,6-adducts. This was of particular value in the gas chromatographic analysis of the very complex mixture obtained from 4,4′-dichlorobenzophenone. The following six products were identified by gas chromatography (205°, flame detector); retention times and relative areas of the peaks are given: 4,4′-dichlorobenzophenone (3.2 min, 21 %), 4-chloro-4′-*t*-butylbenzophenone (5.5 min, 8 %), *bis*-*p*-chlorophenyl-*t*-butyl carbinol (7.4 min, 50 %), *p*-chlorophenyl-*p*′-*t*-butylphenyl-*t*-butylcarbinol (9.3 min, 13 %), 4,4′-di-*t*-butylbenzophenone (9.8 min, 4 %), and bis-*p*-*t*-butylphenyl-*t*-butylcarbinol (11.7 min, 4 %).

The presence of substituted benzopinacols was shown by dissolving the crude product in petroleum ether (25 ml) and allowing crystallization to take place at – 20° for several days. The addition of 1.5 mmol of cobalt(II) chloride or copper(I) chloride to 15 mmol of *t*-butylmagnesium chloride had no influence on the yield (6 %) of benzopinacol from 10 mmol of benzophenone.

Aromatization of the dihydrobenzophenone derivatives was observed by NMR when the samples were exposed to the atmosphere. For preparative or analytical work, excess bromine was added either to a chloroform solution of the crude product after work up, or directly to the Grignard reagent-benzophenone adduct in ether. Thus the adduct from

benzophenone (9.1 g) and *t*-butylmagnesium chloride (75 mmol) in ether gave a nearly colorless suspension by slow addition of bromine (2.0 ml) at the reflux temperature of the ether. Addition of water, extraction with ether, and concentration *in vacuo* gave a yellow oil (12.6 g). NMR (integration of the *t*-butyl groups) indicated the presence of 1,2-adduct (37 %) and of 4-*t*-butylbenzophenone (50 %). Benzopinacol (0.7 g) was isolated by crystallization from petroleum ether. A sample of the oil (2.2 g) and hydrogen bromide (1.8 M in acetic acid; 10 ml) was kept at reflux temperature for half an hour. Water was added and the products extracted with chloroform, washed with aqueous ammonia, dried and concentrated *in vacuo* to give a mixture (1.9 g) of alkenes and *t*-butylbenzophenone. The latter was adsorbed on silica gel from a petroleum ether solution and washed with petroleum ether. Extraction of the silica gel with chloroform gave a solution which was shown to consist of 4-*t*-butylbenzophenone contaminated with benzophenone (10 %; compared by NMR and gas chromatography on authentic samples).

The yields of 2,4,6-trimethyl-4′-*t*-butylbenzophenone (b.p. 163°/0.3) and of 2,3,5,6-tetramethyl-4′-*t*-butylbenzophenone (m.p. 123 – 125°, *cf.* 125 – 127° [8]), given in Table 1, note c, are based on isolated products. In both cases NMR revealed the characteristic AA′BB′-spin pattern of a *para* substituted benzophenone (aromatic protons).

The 1,4-addition of *t*-butylmagnesium chloride to 4,4′-di-*t*-butylbenzophenone was confirmed by adding bromine to the Grignard adduct, decomposing the carbinols present as above, and finally subjecting the resulting reaction mixture to chromatography (silica gel; eluent: carbon tetrachloride-benzene 2:1). NMR analysis of the crystalline product (m.p. 99 – 100° from ethanol) showed the presence of a third *t*-butyl group, an AA′BB′-spin pattern (four protons), and three more aromatic protons partly superimposed on the AA′BB′-system, indicating that the compound is 2,4,4′-tri-*t*-butylbenzophenone. The exclusion of any 1,6-addition involved an experiment with hexadeuterio-*t*-butylmagnesium chloride: hexadeuterioacetone (4.5 g) in ether (10 ml) was added to methylmagnesium bromide (40 ml, 2.5 M). After removal of ether *in vacuo*, hydrochloric acid (20 ml conc.) and calcium chloride were added, the organic layer was dried with calcium chloride and gave crude hexadeuterio-*t*-butyl chloride (2.6 g contaminated with 17 % ether). The chloride (1.3 g) was added in six portions to magnesium (1 g) in ether (12 ml) with stirring to give the Grignard reagent (12 ml, 0.35 M). 4,4′-Di-*t*-butylbenzophenone (0.8 g) was added, the adduct was decomposed with water, and the ether layer was concentrated *in vacuo*, finally at 100°, to ensure thermal decomposition of any dihydrobenzophenones present. The residue was taken up in petroleum ether, the tetra-*t*-butylbenzopinacol (177 mg) removed by filtration, and the residue was recrystallized from methanol to give 4,4′-di-*t*-butylbenzophenone (140 mg). The IR spectrum showed no C – D stretching in the 2000 – 2300 cm^{-1} range.

Kinetic measurements. Two 50 ml burettes with Teflon pistons were driven by a 60 rpm synchronous motor, each delivering 0.625 ml/sec. Substrate solution and Grignard reagent passed through 100 cm of 0.6 mm bore stainless steel cooling coils, kept at either 20° or −33° (liquid ammonia), and were mixed in a T of 0.6 mm bore stainless steel tubing. To the short (1.5 mm) exit of the T was fitted the reaction tube of 0.8 mm bore polyethene tubing. The liquid speed in the tube was 2380 mm/sec. A copper-constantan thermocouple junction (0.1 mm wire) was placed in the reaction tube, the distance from the mixing point being adjustable from 1.5 mm to 350 mm. Parallelly connected reference junctions were placed in the delivery tubes 5 mm ahead of the mixing point. For slow reactions a coiled 1200 mm reaction tube was used. During low temperature experiments the reaction tube was insulated. The thermocouple EMF was recorded and read to ±0.1 μV by the combination of a Philips 2460 microvoltmeter and a Servorgor recorder.

The first reading (T_0) was made as closely as possible (2 mm) to the mixing point. For fast reactions a series of readings (T_t) was obtained, which allowed the calculation of the fraction of unreacted benzophenone ($a-x$) at the time of observation (t). Good first order plots were obtained, and the first order rate constants were determined from the linear plots of

$$\ln \frac{T_\infty - T_0}{T_\infty - T_t} = \ln \frac{a}{a-x}$$

versus time. For slow reactions a single reading was made at $t = 0.5$ sec (~1185 mm). The final temperature (T_∞) was determined by thermometric titration (see below) or, in the case of very fast reactions, from the value of T after five or more half lives.

For measurements of the final temperature of slow reactions a Dewar flask calorimeter was used. To 40 ml of 0.5 M *t*-butylmagnesium chloride in ether, protected by dry argon, 0.4 mM of the ketone was added in a micro-weighing glass, while the temperature was recorded. The calorimeter was agitated by shaking.

The reaction of benzoyldurene with methylmagnesium bromide was followed kinetically at 100°. Ampoules were charged with 100 mg of benzoyldurene and stoppered. The ampoule was evacuated to < 0.1 mm, diethyl ether, freshly distilled from lithium aluminum hydride, and a calculated volume of a 2.50 M stock solution of ethereal methylmagnesium bromide were admitted through the rubber stopper by means of an injection needle, using a 50 ml Metrohm piston burette, to a final volume of 100 ml. The ampoule was sealed off and placed in the steam bath for one hour. After cooling, the solution was worked up without exposure to air (as above), and analysed by NMR. As only the phenyl group of the phenyl duryl ketone is attacked by the Grignard reagent, and as the remaining aromatic proton (of the duryl group) does not interfere with the aromatic protons in NMR, integration of the latter gives the fraction of unconsumed substrate. The methyl group introduced by the Grignard reagent does not interfere with the aromatic methyl groups, which therefore serve as an internal standard.

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