The Reaction of Grignard Reagents with Diphenoquinones

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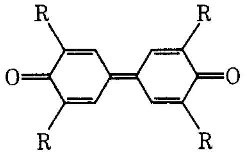
Many reactions of organometallic reagents with various kinds of quinones have been reported to give products normally expected from the addition to α,β-unsaturated carbonyl compounds. Frequently, considerable amounts of intractable tarry materials were also formed; and in a few cases, products resulting from hydrocarbon coupling were reported. Thus, Worrall and Cohen[1] found *p*-quaterphenyl and hydroquinone as major products from the reaction of 4-biphenylylmagnesium bromide with *p*-benzoquinone. Similarly, Smith and Crawford[2] obtained biphenyl and durohydroquinone from the reaction of phenylmagnesium bromide with duroquinone. Another noteworthy example, reported by Wittig,[3] involved the reaction of anthanthrone with phenyllithium. This led to reduction of the quinone and formation of biphenyl.

As far as we are aware, there have been no previous reports of reactions of diphenoquinones with organometallics. Diphenoquinones, in general, are relatively powerful oxidizing agents[4] and several 3,3′,5,5′-tetrasubstituted diphenoquinones have now been made readily available *via* oxidative coupling of appropriate 2,6-disubstituted phenols.[5] In connection with some other studies, it was recently of interest to examine the reaction of various Grignard reagents with the diphenoquinones **1**, **2**, and **3**.



1, R = CH_3
2, R = C_6H_5
3, R = $(CH_3)_3C$

When 2 mol of phenylmagnesium bromide was allowed to react with 1 mol of 3,3′,5,5′-tetramethyldiphenoquinone (**1**) in purified tetrahydrofuran, a rather complicated mixture of products, which included a yield of biphenyl of *ca.* 27%, was obtained. Phenyllithium, under the same conditions, gave no biphenyl. With 3,3′,5,5′-tetraphenyldiphenoquinone (**2**), phenylmagnesium bromide gave a yield of biphenyl of *ca.* 38% along with other products. In contrast to **1** and **2**, 3,3′,5,5′-tetra-*t*-butyldiphenoquinone (**3**) gave a 75–94% yield of biphenyl and an 88–95% yield of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butylbiphenyl (**4**).

Similarly, the Grignard reagent from 4-bromobiphenyl gave *ca.* 15% and *ca.* 20% yields of *p*-quaterphenyl by reaction with **1** and **2**, respectively, while a 79% yield was obtained with **3**. Several other Grignard reagents and phenyllithium were also treated with **3**. All of the results are tabulated below.

In the reaction of phenylmagnesium bromide with **3**, oxidation–reduction occurred to the virtual exclusion of Grignard additions to the α,β-unsaturated carbonyl group. That is, the organometallic compound transferred electrons to the oxidizing agent **3**, possibly giving phenyl radicals which then coupled to give biphenyl; **3** was simultaneously reduced to **4**.

Electron-transfer reactions between Grignard or alkyllithium reagents and ketones have been detected previously[6,7] by esr techniques. In fact, much organometallic–ketone chemistry[8] can be quite satisfactorily rationalized by assuming an initial electron-transfer step. If the initial phase of the reaction sequence involved coordination of magnesium to the carbonyl oxygen of **3**,[9] a reasonable mechanism leading to the observed products can be formulated which is similar to a sequence suggested[10] to explain some ketone reductions by phenyl Grignard reagents.

It was noted that the amount of biphenyl produced in the above reaction was not reduced by adding a large excess of cumene. Since it was anticipated that phenyl radicals could be trapped as benzene by reaction with cumene, this may indicate that the formation and subsequent coupling of phenyl radicals occurred within a solvent cage from which cumene had been excluded.

Since quantitative coupling was not observed in the phenyl case, it is possible that some of the phenyl radicals reacted with α hydrogens of the ether solvent (either those solvent molecules complexed to the magnesium atoms or those which comprised the "cage" for the reacting species) to give benzene.

The yields of coupling products from phenylmagnesium bromide and 4-biphenylylmagnesium bromide are strongly dependent on the diphenoquinone used. As can be seen in the table, relatively low yields were obtained with **1** and **2**, while high yields were obtained with **3**. This is certainly in no way related to the oxidation potentials which would be predicted for the three diphenoquinones on the basis of substituent effects[11] ($\mathbf{2} > \mathbf{3} \approx \mathbf{1}$). If one compares, with Stuart–Briegleb molecular models, the closeness of approach that is possible for a phenyl carbanion to each of the diphenoquinones, it is readily seen that the approach to bonding distance for 1,2 or 1,4 addition is only

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[2] L. I, Smith and H. M. Crawford, *ibid.*, **50**, 869 (1928).

[3] G. Wittig in "Newer Methods of Preparative Organic Chemistry," Vol. I, W. Foerst, Ed., Interscience Publishers, New York, N. Y., 1948, p 589.

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[7] K. Maruyama, *Bull. Chem. Soc. Jap.*, **37**, 897 (1964).

[8] (a) R. C. Fuson, M. D. Armstrong, and S. B. Speck, *J. Org. Chem.*, **7**, 297 (1942); (b) R. C. Ruson and J. Corse, *J. Amer. Chem. Soc.*, **60**, 2063 (1938); (c) R. C. Fuson and A. I. Rachlin, *ibid.*, **68**, 343 (1946); (d) Löwenbein and Schuster, *Ann.*, **481**, 106 (1930); (e) Malmgren, *Ber.*, **36**, 2608 (1903); (f) R. E. Lutz and W. G. Reveley, *J. Amer. Chem. Soc.*, **63**, 3178 (1941); (g) A. Schönberg and A. F. A. Ismail, *J. Chem. Soc.*, 201 (1945); (h) H. Gilman and R. E. Fothergill, *J. Amer. Chem. Soc.*, **51**, 3149 (1929); (i) G. Wittig, M. Leo, and W. Wiemer, *Ber.*, **64**, 2405 (1931); (k) W. Schlenk and R. Ochs, *ibid.*, **49**, 608 (1916); (l) J. Schmidlin, *ibid.*, **43**, 1137 (1910); (m) R. C. Fuson and J. P. Freeman, *J. Amer. Chem. Soc.*, **76**, 911 (1954).

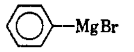
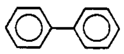
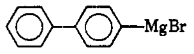
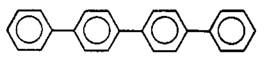
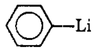
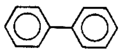
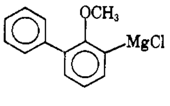
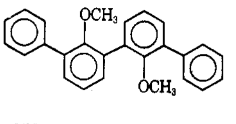
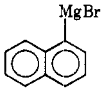
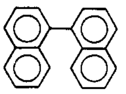
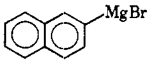
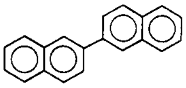
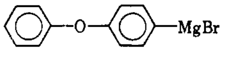
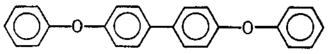
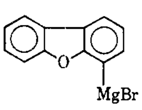
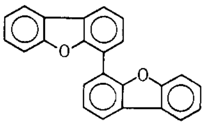
[9] S. G. Smith and G. Su, *J. Amer. Chem. Soc.*, **88**, 3995 (1966).

[10] R. Runge, "Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1944, p 394.

[11] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 595.

TABLE I

ORGANOMETALLIC REAGENTS AND COUPLING PRODUCTS FROM REACTIONS WITH DIPHENOQUINONES

Organometallic reagent[a]	Registry no.	Coupling product	Registry no.	Yield, %	Diphenoquinone
	100-58-3			27 38 75–94	1 2 3
	3315-91-1			15 20 79	1 2 3
	591-51-5			∼0 13[b]	1 3
	21472-99-1		21473-04-1	56	3
	703-55-9			44	3
	21473-01-8			33	3
	21473-02-9			29	3
	21473-03-0			11	3

[a] The structure given does not imply the actual structure in solution. [b] N,N,N′,N′-tetramethylethylenediamine added in this reaction did not change the yield.

difficult in the case of **3**. This is not true in the cases of **1** and **2**, where the carbonyl groups appear to be fairly well exposed. Therefore, it is possible that the lower yields of coupling products observed with **1** and **2** result from the loss of Grignard reagent in competing addition-reaction pathways.

In connection with the other Grignard reagents used, it may be argued that the bulkier the aryl radicals, the more difficult it would be for them to rotate within the solvent "cage" into the correct configuration for bonding. That is, they might be expected to preferentially abstract a hydrogen atom from a nearby solvent molecule. The amount of coupling observed with the Grignard reagents from 2-chloro-6-phenylanisole, 1-bromonaphthalene, 2-bromonaphthalene, and 1-bromodibenzofuran seem consonant with this hypothesis (see Table I). However, it does not seem likely that this could be the explanation for the difference in the amount of coupling observed for 4-bromobiphenyl and 4-bromodiphenyl ether.[12]

Experimental Section

Tetrahydrofuran (THF) was distilled under nitrogen from lithium biphenyl complex and stored under nitrogen. All reactions were carried out under nitrogen; melting points are uncorrected.

3 and Phenylmagnesium Bromide.—A 9.0-ml sample of 2.27 *M* phenylmagnesium bromide in diethyl ether (0.0204 mol of "C_6H_5MgBr") was diluted with 100 ml of THF. While this solution was stirred at room temperature, a solution of 3.40 g (0.00833 mol) of **3** in 100 ml of THF was added dropwise (15 min). As each drop was added, its color changed rapidly from red to green to yellow. After 5 min, 200 ml of 3 *N* hydrochloric acid and 200 ml of diethyl ether were added and the system was shaken vigorously. The organic phase was extracted with three 200-ml portions of water and 200 ml of saturated sodium chloride, dried ($MgSO_4$), filtered, and concentrated to dryness, giving 4.69 g of solid. Analysis by vpc (2-ft 20% SE-30 column, helium flow 72 ml/min, isothermal at 101° for the biphenyl determination and at 216° for the determination of **4**) showed a 92% yield[13] of biphenyl (based on **3**) and an 88% yield of **4**.

When the same reaction was carried out by inverse addition, the yields of biphenyl and **4** were 94[13] and 89%, respectively.

Subsequently, when different samples of **3** were used, difficulty was encountered in trying to obtain the same high yield (92–94%) of biphenyl as was found in the original reactions. Many variations in the exact details of the procedure were investigated with the hope of duplicating the original results. It was found that by maintaining the temperature between −4 and 0°, one could reproducibly obtain a 75% yield of biphenyl.

For example, 11.20 ml of 1.97 *M* "C_6H_5MgBr" in THF was added dropwise (15 min) to a stirred solution of 4.49 g (0.0110 mol) of **3** in 100 ml of THF at −4 to 0°. This system was worked up as described above and the solid product mixture (5.77 g) was analyzed by vpc on two different columns (2-ft 10% SE-30 and 2-ft 10% polyphenyl ether columns). These analyses indicated that a 75 ± 3% yield of biphenyl and a 95 ± 3% yield of **4** were obtained. The nmr spectrum (CCl_4) of the reaction mixture indicated that the ratio of **4** to biphenyl was 100:86. The nmr spectrum of **4** in this mixture was identical with that of an authentic sample of **4**: τ 8.53 [s, 36 H, $(CH_3)_3C$], 5.05 (s, 2H, OH), and 2.83 (s, 4 H, ArH).

In other experiments, lower yields of biphenyl were obtained if the reaction was carried out above 25° or below −30°. Changing the solvent system from THF to Et_2O or to mixtures of these, changing the initial concentration of "C_6H_5MgBr" from *ca.* 0.2 *M* to *ca.* 2.2 *M*, or varying the rate of mixing during the reaction had essentially no effect on the yield of biphenyl. No

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[12] Clearly, further experiments must be conducted to attempt to identify all of the products from these reactions, especially those resulting from reaction of the aryl radicals with the solvent.

[13] Control experiments were run to determine the amount of biphenyl in the starting organometallic reagent solution.

change in the yield of biphenyl was observed if the reaction was run in the presence of a large excess of cumene.

3 and Phenyllithium.—Under the same conditions used for the reaction of **3** with phenylmagnesium bromide, phenyllithium gave only a 13% yield[13] of biphenyl. This same low yield of coupling product was obtained when phenyllithium was allowed to react with **3** in the presence of N,N,N′,N′-tetramethylethylenediamine.

3 and 4-Biphenylylmagnesium Bromide.—A solution of 4-biphenylylmagnesium bromide was prepared from 7.76 g (0.0333 mol) of 4-bromobiphenyl, 10 g (0.41 g-atom) of magnesium turnings, and a trace of iodine in 200 ml of THF. To this solution was added 6.80 g (0.0167 mol) of **3** in 200 ml of THF (*ca.* 15 min, same color changes as noted in the "C_6H_5MgBr" experiment). During the addition, a solid precipitated. The system was filtered and the solid obtained was triturated with three 250-ml portions of 2 *N* hydrochloric acid, two 250-ml portions of water, and two 100-ml portions of diethyl ether. After traces of solvent had been removed, 4.01 g (79%) of *p*-quaterphenyl was obtained, mp 313–316° (lit.[14] mp 312–313°). The ir spectrum (KBr) of this material was identical in all respects with that of an authentic sample of *p*-quaterphenyl. No change in the yield of *p*-quaterphenyl was noted if the reaction was carried out with a large excess of cumene.

3 and (2-Methoxy-3-phenyl)phenylmagnesium Chloride.—A solution of 20.00 g (0.0916 mol) of 2-chloro-6-phenylanisole in 50 ml of THF was converted into a Grignard reagent by refluxing for 12 hr with 2.43 g (0.100 g-atom) of magnesium. The resulting solution was cooled to *ca.* 15°. Then, with continuous stirring, a solution of 18.70 g (0.0458 mol) of **3** in 175 ml of THF was added dropwise (1 hr). (Each red-colored drop rapidly decolorized as it was added to the Grignard solution until *ca.* 85% of the reagent had been added. A precipitate began to appear after *ca.* 35% of the reagent had been added.) The usual work-up afforded 36.1 g of a mixture of products (vpc). This mixture was recrystallized twice from 98% ethanol; 9.36 g (56%) of 2′,2″-dimethoxy-*m*-quaterphenyl was obtained, mp 137.3–138.8°. Vpc (2-ft 20% SE-30, isothermal at 240°, helium flow 72 ml/min) showed this compound to be homogeneous (t_r = 24.9 min). The ir spectrum showed strong absorptions as 1223 (aryl ether vibration[15]), 1459, 1454, 1409, 1007, 1001, 993, 800, 768, 759, and 695 cm^{-1} (monosubstituted benzene[15]). The nmr spectrum ($CDCl_3$) was consistent with the assigned structure: τ 2.2–3.0 (m, 16 H, ArH), and 6.75 (s, 6 H, OCH_3).

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.23; H, 6.01. Found: C, 85.3; H, 6.1.

3 and 1-Naphthylmagnesium Bromide.—A sample of 1-bromonaphthalene (2.07 g, 0.0100 mol) in 100 ml of THF was stirred overnight with 1.22 g (0.0500 g-atom) of magnesium turnings and a trace of iodine.[16] A solution of 2.04 g (0.0050 mol) of **3** in 40 ml of THF was added at room temperature. The red color of **3** completely disappeared. Following the usual work-up, 3.26 g of a dark yellow solid was obtained. This solid was stirred overnight at room temperature with 150 ml of isopropyl alcohol and then filtered, giving 0.56 g (44%) of 1,1′-binaphthyl, mp 156–158° (lit.[17] mp 157°). The ir spectrum of this compound and an authentic sample of 1,1′-binaphthyl were superimposable.

3 and 2-Naphthylmagnesium Bromide.—Using the same method as in the case of 1-bromonaphthalene, 2-bromonaphthylmagnesium bromide[16] gave 0.42 g (33%) of 2,2′-binaphthyl, mp 184.5–186.5° (lit.[18] mp 187°). The ir spectrum of this compound was superimposable on that of authentic 2,2′-binaphthyl.

3 and 4-Phenoxyphenylmagnesium Bromide.—By using the identical method as was used for 1-bromonaphthalene, 4-phenoxyphenylmagnesium bromide[16] gave 0.48 g (29%) of 4,4′-diphenoxybiphenyl, mp 152.5–154.5° (lit.[19] mp 151°). The ir spectrum of this compound contained many of the same intense absorption bands as an authentic sample of 4-phenoxybiphenyl: 690, 747 ± 3, 835 ± 7, 1256 ± 1, 1269 ± 1, 1490, and 1588 ± 1 cm^{-1}.

Anal. Calcd for $C_{24}H_{18}O_2$: mol wt 338. Found: mol wt 336.

3 and 1-Dibenzofuranylmagnesium Bromide.—The dimer 1,1′-bisdibenzofuranyl, mp 187–189.5° (lit.[20] mp 191°), was obtained in 11% yield from 1-dibenzofuranylmagnesium bromide[16] and **3** (same method as used for 1-bromonaphthalene except for trituration with 2-propanol). The ir spectrum of this compound contained many of the same intense absorption bands as a sample of dibenzofuran: 726 ± 3, 743 ± 3, 753, 840, 850 ± 2, 1196 ± 1, 1446 ± 2, 1452, and 1470 ± 1 cm^{-1}. It also contained prominent bands at 612, 1050, 1106, 1174, 1262, and 1395 cm^{-1}.

Anal. Calcd for $C_{24}H_{14}O_2$: mol wt 334. Found: mol wt 337.

Registry No.—**1**, 4906-22-3; **2**, 3550-01-4; **3**, 2455-14-3.

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(14) K. Brand and H. W. Stephen, *Ber.*, **72**, 2175 (1939).

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958.

(16) When an identical organometallic preparation was worked up by hydrolysis, vpc showed that no aryl bromide remained. Only the corresponding debrominated aromatic hydrocarbon was present.

(17) C. S. Schoepfle, *J. Amer. Chem. Soc.*, **45**, 1566 (1923).

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Improved Procedure for the Reformatsky Reaction of Aliphatic Aldehydes and Ethyl Bromoacetate

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Recently, we required a series of homologous, straight-chain β-hydroxy esters in large quantities and in a high state of purity. Because of its simplicity and the ready availability of the requisite reagents, the Reformatsky reaction appeared to be the best route to these compounds. Our early attempts with this well-known synthesis, however, were disappointing, not only because of the low yields obtained (10–40%), but also because of the difficulty we experienced in purifying the products. An examination of the literature revealed that our results were by no means unique; poor yields are generally the rule when the classical Reformatsky reaction is applied to aliphatic aldehydes.[1-3] Several investigations on the nature of the reaction[4] and on the side reactions encountered[1,5] help to explain the low yields. These workers and others[5,6] have proposed numerous variations of the Reformatsky reaction which have value in certain situations. However, none of these appeared attractive when applied to the large-scale syntheses we required. Consequently, we undertook a study of conditions for the Reformatsky reaction in hopes of improving the yields and quality of the products and with the view of tailoring the reaction for large-scale syntheses. We wish to report the results

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