20 (disulfide), 90220-82-9; **20** (alkyl bromide), 27644-98-0; **21**, 88106-85-8; **21** (chloride), 88107-00-0; **21** (acid·Na), 90220-62-5; **21** (disulfide), 90220-65-8; **21** (alkyl bromide), 54877-27-9; **22**, 90220-24-9; **22** (chloride), 90220-72-7; **22** (acid·Na), 90220-63-6; **22** (disulfide), 90220-73-8; **22** (alkyl bromide), 14573-25-2; **23**, 88106-87-0; **24**, 88106-89-2; **25**, 88106-88-1; **26** ($X, R^1, R^2 = H$), 80639-72-1; **26** ($X, R^1 = H$; $R^2 = Me$), 90220-45-4; **26** ($X = H$; $R^1, R^2 = Me$), 90220-46-5; **26** ($X = 7,9\text{-}Me_2$; $R^1, R^2 = H$), 90220-47-6; **26** ($X = 6\text{-}Cl$; $R^1, R^2 = H$), 90220-49-8; **26** ($X, R^1, R^2 = H$; Tl(I) salt), 90220-55-6; **27** ($X = H$), 90220-51-2; **27** ($X = MeO$), 90220-52-3; **27** ($X = Cl$), 90245-52-6; **28**, 90220-76-1; **29**, 90220-77-2; **30**, 90220-54-5; **31**, 80639-67-4; **31** (amine, acid), 90220-56-7; **33c**, 90220-50-1; **34**, 90220-48-7; **36a**, 300-57-2; **36b**, 934-10-1; **36c**, 18321-36-3; **36d**, 77446-17-4; **36e**, 4810-05-3; **36f**, 1587-07-1; **36g**, 90220-53-4; **37a**, 635-46-1; **37b**, 19343-78-3; **37c**, 20364-31-2; **37d**, 41910-65-0; **37f**, 72995-16-5; **38**, 645-59-0; **39**, 10500-57-9; **44**, 5735-53-5; $3,5\text{-}Me_2C_6H_3(CH_2)_3OH$, 62343-68-4; $3,5\text{-}Me_2C_6H_3(CH_2)_2CO_2H$, 42287-87-6; $(2\text{-}NO_2C_6H_4(CH_2)_3)_2S_2$, 90220-66-9; $2\text{-}NO_2C_6H_4(CH_2)_3Br$, 63307-45-9; $(2\text{-}BrC_6H_4(CH_2)_3)_2S_2$, 90220-67-0; $2\text{-}BrC_6H_4(CH_2)_3Br$, 1075-28-1; $2\text{-}BrC_6H_4(CH_2)_3SO_2Cl$, 90220-71-6; $Ph(CH_2)_3SO_2NHBu\text{-}t$, 90220-75-0; $c\text{-}C_6H_{11}NH_2$, 108-91-8; $PhNH_2$, 62-53-3; quinoline, 91-22-5; 1,1,3,3-tetramethylguanidinium azide, 56899-56-0.

Supplementary Material Available: Details of the synthesis of new alcohols, halides, sulfonate salts, disulfides, sulfonyl chlorides, and azides and characterization data (elemental analytical data, NMR spectral data, IR data, etc.) for new compounds (17 pages). Ordering information is given on any current masthead page.

Effects of Reagent Concentrations and Solvents on Reactions of Organomagnesium and Lithium Reagents with *o*-Quinol Acetates. Differing Reaction Paths from Polymeric Grignards and from Dialkylmagnesiums or Monomeric Grignards

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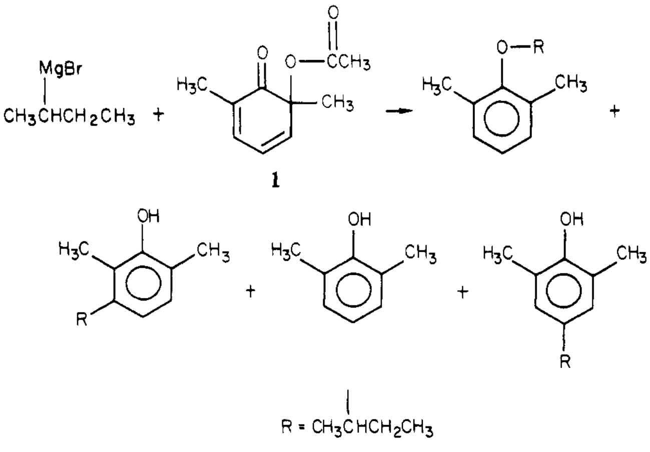
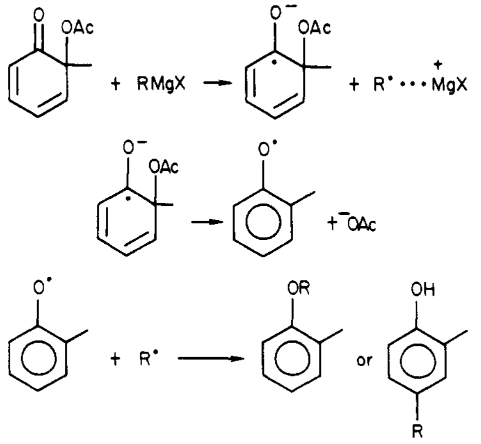
Studies of the reaction of 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (**2**) with isopropylmagnesium bromide showed that decreases in Grignard concentrations resulted in marked reductions in yields of the conjugate addition product, 3-isopropylmesitol (**5**), and increases in yields of isopropyl mesityl ether (**3**) and mesitol (**4**). Similar, though less pronounced, effects were observed with isopropylmagnesium chloride. Reaction of **2** with diisopropylmagnesium or diethylmagnesium resulted in large reductions in yields of **5** or of 3-ethylmesitol. Reactions with dialkylmagnesium reagents or with isopropyllithium were not significantly affected by changes in concentration. It is concluded that electron transfers from dialkylmagnesium reagents are the principal initial steps leading to formation of ethers and reduction products from reactions of *o*-quinol acetates with Grignard reagents, while non-electron-transfer reactions with the Grignards yield normal and conjugate addition products.

Alkyl Grignard and lithium reagents react with *o*-quinol acetates (6-acetoxycyclohexa-2,4-dien-1-ones) to yield aryl alkyl ethers in addition to the expected products of conjugate and direct addition to the unsaturated carbonyl groups.[1] Reduction of the quinol acetates to their parent phenols always accompanies ether formation and addition reactions. When para positions of the cyclohexadienone rings are unsubstituted, para-substituted phenols may also be obtained. The four products shown below, for instance, were obtained from reaction of *sec*-butylmagnesium bromide with the quinol acetate **1**:[1a]



The yields of ethers and *p*-alkyl[1a] (or *p*-benzyl)[1b] phenols from these reactions were found to increase significantly with increasing electron-donating abilities of the organometallic reagents. It was therefore proposed[1] that electron donations from the Grignard or lithium reagents to the quinol acetates were the initial steps in formation of ethers and para-substituted phenols. Electron transfer was followed by the reaction sequence shown below:



Our earlier work appeared to indicate that the concentrations of the Grignard solutions did not affect the nature or relative yields of the products. We have since observed, however, that when a wider range of Grignard reagent concentrations is employed the relative yields of products *do* depend on the concentrations of the Grignard reagents.[2]

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(1) (a) Miller, B. *J. Org. Chem.* **1977**, *42*, 1402. (b) Miller, B. *Ibid.* **1977**, *42*, 1408.

0022-3263/84/1949-3121$01.50/0

Table I. Reactions of 2 with Isopropylmagnesium Bromide. Effects of Concentration of 2 on Reaction Products

concn of *i*-PrMgBr, mol/L	concn of 2, mol/L	reaction products					
		mol % 3	mol % 4	mol % 5	mol % "others"	%3/%4	%3/%5
0.63	0.208	40.6	30.9	26.2	2.4	1.31	1.55
0.63	0.104	39.8	33.2	24.9	2.1	1.20	1.60
0.63	0.052	41.3	31.7	25.0	2.0	1.30	1.65
0.24	0.068	44.0	35.7	19.2	1.1	1.24	2.30
0.24	0.034	44.1	34.9	19.4	2.0	1.26	2.27
0.24	0.017	42.0	38.5	19.4	0.1	1.09	2.16

Table II. Reactions of 2 with Isopropylmagnesium Bromide. Effects of Concentration of Grignard Reagent on Reaction Products[a]

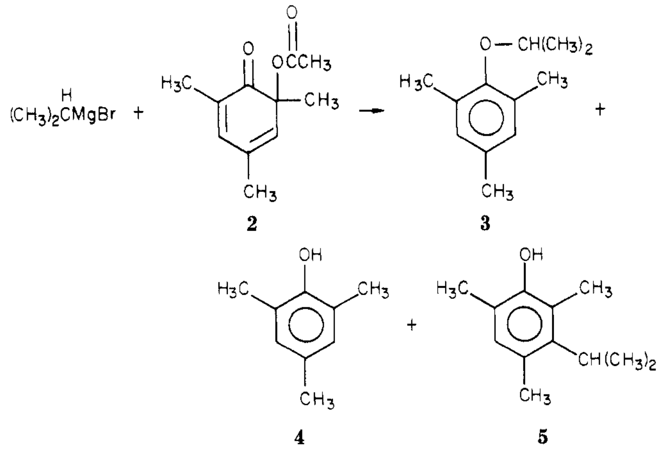
run	concn of *i*-PrMgBr, mol/L	reaction products					
		mol % 3	mol % 4	mol % 5	% "others"	%3/%4	%3/%5
3	1.35	40.5	34.0	23.8	1.8	1.19	1.70
6	0.80	41.4	33.7	24.5	0.2	1.23	1.69
9	0.60	39.9	35.9	24.2	0.1	1.11	1.65
12	0.40	40.9	34.7	22.7	0.2	1.18	1.80
15	0.20	44.1	35.8	18.4	0.7	1.23	2.40
18	0.15	46.6	34.8	16.6	1.9	1.34	2.80
21	0.10	46.6	38.8	12.6	1.7	1.20	3.60
24	0.080	47.9	37.7	12.3	2.1	1.27	3.90
27	0.072	51.8	38.4	9.4	0.4	1.35	5.51
30	0.060	54.0	38.8	6.1	1.0	1.39	8.86
	0.64[b]	41.1	34.2	24.0	0.7	1.20	1.71

[a] Results of each third run in order of decreasing Grignard concentration listed. The concentration of 2 was between 0.005 and 0.01 M in all reactions. [b] Solution was 0.3 M in added $MgBr_2$.

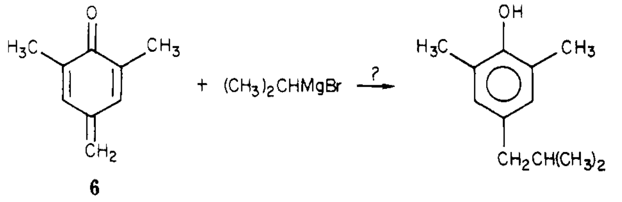
These observations, and further observations resulting from them, suggest a modification of the proposed mechanism for reactions of *o*-quinol acetates with Grignard reagents.

Reactions of Grignard Reagents with *o*-Quinol Acetates—Concentration and Solvent Effects. We chose to use secondary Grignard reagents—specifically, isopropylmagnesium bromide and chloride—because earlier work suggests that roughly comparable yields of ethers, *m*-alkylphenols, and reduction products should be obtained from these reactions. In addition, use of secondary Grignards minimizes 1,2-addition reactions, which occur to a major extent in reactions with primary Grignards.[1a] We used 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (2) as the substrate in all reactions in this study to avoid formation of both meta- and para-substituted phenols.

As expected, reaction of 2 with isopropylmagnesium bromide, prepared from magnesium of >99.99% purity, in ether gave isopropyl 2,4,6-trimethylphenyl ether (3), mesitol (4), and 3-isopropyl-2,4,6-trimethylphenol (5) as the principal products.



Several minor products of unknown structure, together usually comprising less than 2% of the total product yields, were also formed in all runs. They appeared as inseparable, overlapping peaks in GLPC analyses. Interestingly, when commercial "Grignard grade" magnesium turnings were used to prepare the Grignard reagent, significant amounts (ranging up to 10%) of 4-isobutyl-2,6-dimethylphenol were obtained. It seems likely that this product was formed by reaction of the Grignard with the quinone methide 6, formed by loss of acetic acid from 2. No 4-isobutylphenol was detected when the purer magnesium was used.



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The yields of reaction products at either of two concentrations of isopropylmagnesium bromide were essentially unaffected by the concentration of 2 (Table I). In a second series of studies (Table II), the Grignard concentrations were varied. Six different preparations of isopropylmagnesium bromide were employed and were diluted to the desired concentrations before each run. Consistent results were obtained from each of these preparations. The mole ratio of Grignard to 2 at the start of each reaction was at least 9:1, so that the Grignard concentrations were essentially constant throughout each reaction. A total of 30 runs were carried out, and the yield of each product was determined by GLPC analysis. The results only of each third run have been summarized in Table II to avoid a critical data overload.

At all concentrations of isopropylmagnesium bromide, the ratio of ether to mesitol formed (%3/%4) was essentially constant. In concentrated solutions (ca. 1.6 M–0.5 M) of the Grignard reagent, even large changes in concentration of isopropylmagnesium bromide did not markedly affect the reactions. In contrast, at Grignard

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(2) A preliminary report of part of this work has been published: Miller, B.; Matjeka, E. R.; Haggerty, J. G. *Tetrahedron Lett.* 1977, 323.

Table III. Reactions of 2 with Isopropylmagnesium Bromide in THF-Diethyl Ether Mixtures[a]

vol % THF	reaction products mol % 3	mol % 4	mol % 5	%3/%4	%3/%5
9.1	46.1	45.2	8.8	1.02	5.16
22.7	34.7	55.5	9.4	0.62	3.74
22.7	35.2	56.3	8.5	0.62	4.25
36.4	31.0	55.5	13.4	0.56	2.31
45.5	24.7	61.8	13.4	0.40	1.84
77.3	17.0	68.1	14.9	0.25	1.14
100	15.8	69.1	15.0	0.23	1.05
100	15.6	67.9	16.4	0.23	0.95

[a] Concentrations of isopropylmagnesium bromide were between 0.4 and 0.5 M in all runs. Concentrations of 2 were ca. 0.05 M in all runs.

concentrations below ca. 0.5 M the yield of the conjugate addition product 5 dropped sharply and consistently with decreasing concentration of the Grignard reagent. The results of all 30 runs are summarized in Figure 1, which shows plots of Grignard concentration vs. %3/%5 and %4/%5.

The curves shown in Figure 1 were each found to fit reasonably well ($r = 0.97$–0.98) to equations of the form

$$\frac{\%3}{\%5}\left(\text{or } \frac{\%4}{\%5}\right) = k[\mathrm{RMgBr}]^{-x} + k' \qquad (1)$$

when x lies between 1.5 and 2.0. A plot of the ratio %3/%5 vs. $[\mathrm{RMgBr}]^{-2}$ is shown in Figure 2.

The significance of these relationships will be considered in the Discussion section.

When reactions of isopropylmagnesium bromide with 2 were carried out in THF solution rather than diethyl ether yields of the ether 3 and the conjugate addition product 5 both dropped, while yields of the reduction product 4 increased to ca. 68% (Table III). Most interestingly, addition of small amounts (ca. 9% by volume of THF to ether solutions of isopropylmagnesium bromide resulted in marked decreases in yields of 5 but little changes in the relative yields of 3 and 4. Under these conditions, employing rather concentrated (ca. 0.45 M) Grignard solutions, the %3/%5 ratio is almost identical with the %3/%5 ratios from reactions using very low concentrations of isopropylmagnesium bromide in pure diethyl ether.

Yields of 5 from reaction of 2 with isopropylmagnesium chloride were significantly lowered at all Grignard concentrations, compared to those from reaction with isopropylmagnesium bromide, and yields of products other than 3, 4, or 5 increased to ca. 9–16% (see Table IV). The "other" products could still not be separated from each other but could be obtained as a mixture free of 3, 4, and 5 by preparative VPC. The spectra of these products resemble those of ketones obtained from reactions of 2 with methylmagnesium and ethylmagnesium bromides, which arise via initial 1,2-additions to the ring carbonyls.[1a]

As can be seen from the data in Table IV, the %3/%4 ratio from reaction of 2 with isopropylmagnesium chloride

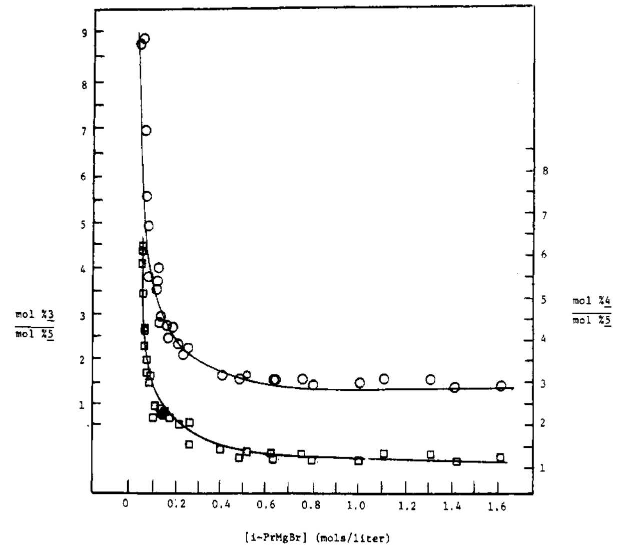


Figure 1. Effects of Grignard concentration on products from reaction of 2 with *i*-PrMgBr in ether: (○) mol % 3/mol %5; (□) mol %4/mol %5.

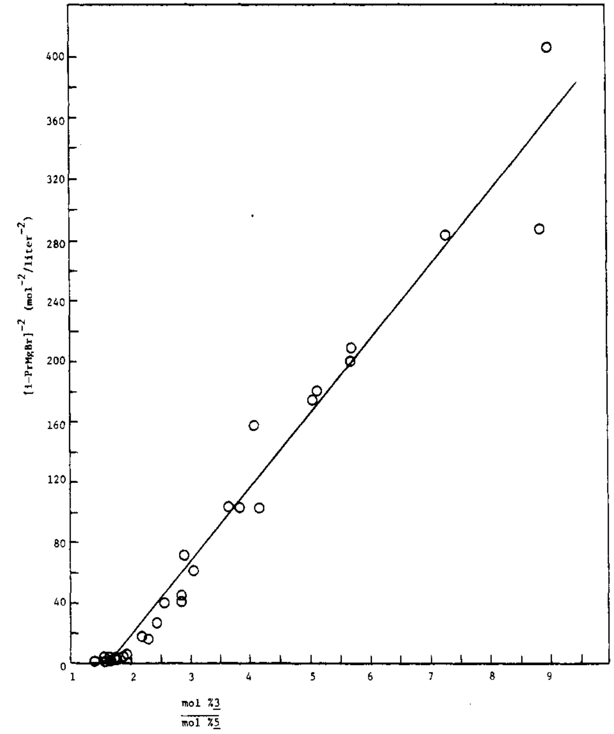


Figure 2. Fit of data to equation mol %3/mol %5 = $k[i\text{-PrMgBr}]^{-2} + k'$.

is similar to that from reaction with isopropylmagnesium bromide and is essentially invariant with Grignard concentration. However, the yields of 5 again drop sharply with decreasing Grignard concentration. The same is true of yields of "other" products. Interestingly, the combined yields of 5 and "other" products, and the variation of their

Table IV. Reactions of 2 with Isopropylmagnesium Chloride in Ether. Effects of Grignard Concentration on Reaction Products

concn of *i*-PrMgCl, mol/L	reaction products mol % 3	mol % 4	mol % 5	mol % "others"	%3/%4	%3/%5	%3/(%5 + % others)
0.76	39.9	37.3	7.1	15.7	1.07	5.6	1.75
0.41	41.9	38.9	5.6	13.8	1.08	7.5	2.16
0.22	44.2	42.0	4.8	12.2	1.05	9.2	2.60
0.11	41.0	42.0	4.1	13.0	0.98	10.0	2.4
0.056	45.1	42.9	2.9	9.4	1.05	15.6	3.67

Table V. Reactions of 2 with Diisopropylmagnesium

concn of (i-Pr)$_2$Mg, mol/L	solvent	reaction products %3	%4	%5	%3/%5	%3/%4
0.24[a]	diethyl ether	34.4	63.7	1.8	18.5	0.54
0.13[a]	diethyl ether	32.7	65.4	1.8	17.8	0.50
0.06[a]	diethyl ether	34.6	64.0	1.5	23.2	0.54
0.30[b]	10 vol % dioxane in ether	45.5	51.1	3.32	13.7	0.89
0.21[c]	9–45 vol % dioxane in ether	49.5 ± 1[d]	49.4 ± 1[d]	2.18 ± 1.1[d]	22.5 ± 6[d]	0.98 ± 0.03[d]

[a] (i-Pr)$_2$Mg dried at 65 °C before use. [b] Solution filtered free of MgBr$_2$ before reaction with 2. [c] Solution not filtered free of MgBr$_2$ before reaction with 2. [d] Average of five runs.

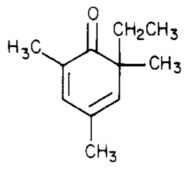
combined yields with Grignard concentration, are quite similar to yields of 5 from reaction of 2 with isopropylmagnesium bromide.

Reactions of 2 with Dialkylmagnesium Reagents. Solutions of diisopropylmagnesium were prepared by adding dioxane to ethereal solutions of isopropylmagnesium bromide. In several runs, reaction of the resulting mixture with 2 was carried out without filtering off the precipitated magnesium bromide. In other reactions, the solutions were filtered free of precipitate. This resulted in partial evaporation of ether, which was replaced with fresh ether to bring the solution back to its original volume. Finally, in several runs the solvent (after filtration) was evaporated, and the product was dried under vacuum at 65 °C. It was then redissolved in ether for reaction with 2.

Reaction of 2 with solutions of diisopropylmagnesium gave products 3–5, with almost no "other" products formed. The results of these studies are summarized in Table VI. It can be seen from comparison with Table II that all of these reactions showed a dramatic decrease in yields of the conjugate addition product 5 compared to reaction with isopropylmagnesium bromide. The %3/%5 ratio from reaction of 2 with diisopropylmagnesium averaged 22.5/1, compared to ratios between 1.6/1 and 9/1 from reactions with isopropylmagnesium bromide. The %3/%4 ratios from reactions with diisopropylmagnesium were only slightly increased compared to reactions with Grignard reagents if the diisopropylmagnesium was not dried and heated before use. Evaporation of the solvent and drying, however, resulted in a significant further increase in the yield of 4. This may result from partial decomposition of diisopropylmagnesium during removal of the solvent to form magnesium hydride. Magnesium hydride has been shown to be an effective reducing reagent in other reactions.[3]

Reaction of 2 with diethylmagnesium yielded ca. 25% of ethyl 2,4,6-trimethylphenyl ether, compared to ca. 4% obtained from reaction with ethylmagnesium bromide.[1a] The yield of the reduction product, mesitol, rose in a proportionate degree to ca. 40% from 7%. As shown in Table VI, the yields were not affected by the concentration of the diethylmagnesium nor by small differences in dioxane concentration. Diethylmagnesium was prepared from diethylmercury by reaction with magnesium in ether to determine whether traces of dioxane remaining even after evaporation of solvent could affect the relative yields of products. Aside from a slight decrease in the yield of the reduction product, the results of this reaction closely resemble those from reaction with diethylmagnesium prepared from the Grignard reagent.

In contrast to reaction of 2 with diisopropylmagnesium, its reaction with diethylmagnesium did form ca. 18% of products other than those from ether formation, reduction, and conjugate addition. Although the "other" products could not be obtained completely pure, they seemed to consist largely of a single compound, whose spectra suggested it to be a linearly conjugated cyclohexadienone, most likely 6-ethyl-2,4,6-trimethylcyclohexa-2,4-dien-1-one (**6**). This ketone presumably arises via pinacol rearrangement of the 1,2-addition product 7.



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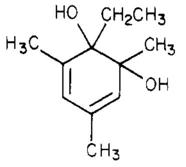

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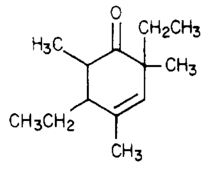

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The principal "other" product from reaction of 2 with ethylmagnesium bromide was ketone 8,[1a] presumably formed by further reaction of 6 with the Grignard. The differences between these products suggests that pinacol rearrangement of 7 (presumably catalyzed by magnesium halide) occurs during the course of the Grignard reaction, but during workup of the diethylmagnesium reaction.

Finally, we investigated the reactions of 2 with solutions of isopropyllithium in pentane solution. These consistently gave product mixtures containing 3, 4, 5, and "other" products in the ratios 20:10:50:20. Essentially identical product mixtures were obtained from isopropyllithium solutions ranging in concentration from 0.8 to 0.16 M and from reagents prepared either from high purity lithium ribbon or from "commercial" lithium wire.

Discussion

As was shown above, the %3/%5 ratio from reaction of 2 with isopropylmagnesium bromide is related to the concentration of the Grignard reagent by the equation:

$$\frac{\%3}{\%5} = k[\mathrm{RMgBr}]^{-x} + k' \qquad (1)$$

where x lies in the range 1.5–2.0. A similar relationship holds for the %4/%5 ratio.

Kinetic relationships of this type would result if conjugate addition to form 5 proceeds by rate law 2,

$$\frac{\mathrm{d}[5]}{\mathrm{d}t} = k^{\mathrm{II}}[\mathrm{RMgBr}]^{y}[2] \qquad (2)$$

while ether formation and reduction each proceeds by a two function rate law (eq 3). Alkylmagnesium bromides,

$$\frac{\mathrm{d}[3]}{\mathrm{d}t}\left(\text{or } \frac{\mathrm{d}[4]}{\mathrm{d}t}\right) = k^{\mathrm{III}}[\mathrm{RMgBr}][2] + k^{\mathrm{IV}}[\mathrm{RMgBr}]^{y}[2] \qquad (3)$$

where y lies between 2.5 and 3.0

except for the most dilute solutions, exist largely in asso-

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[3] Ashby, E. C.; Wiesemann, T. L.; Bowers, J. S. Jr.; Laemmle, J. T. *Tetrahedron Lett.* **1976**, 21. Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1557, 1560, 1564.

ciated forms (dimers and higher order forms) in ether solution.[4] It seems highly improbable that formation of compounds **3**–**5** actually involve third-order reactions with the monomeric Grignard reagent. Instead, these reactions seem almost certain to involve associated forms of the Grignard reagent. Equations 2 and 3 may thus be rewritten in the kinetically equivalent forms:

$$\frac{d[5]}{dt} = k^{II}[(RMgBr)_y][2] \tag{2a}$$

$$\frac{d[3]}{dt} = k^{III}[RMgBr][2] + k^{IV}[(RMgBr)_y][2] \tag{3a}$$

The important observation that product ratios from reaction of **2** with isopropylmagnesium bromide at very low concentrations become increasingly similar to those from reaction with diisopropylmagnesium suggests that the dialkylmagnesium reagent may play a role in formation of ethers and reduction products. Since the ratios of monomeric Grignard reagents to dialkylmagnesium in the Schlenk equilibrium, $2RMgX \rightleftharpoons R_2Mg + MgX_2$,[5] should be essentially independent of concentration, rate laws 4 and 5 would hold as well as 2 and 3 provided that diisopropylmagnesium exists largely as its monomer over the entire range of Grignard concentrations.

$$\frac{d[5]}{dt} = k^{V}[R_2Mg][2] \tag{4}$$

$$\frac{d[3]}{dt} = k^{VI}[R_2Mg][2] + k^{VII}[(RMgBr)_{2.5-3}][2] \tag{5}$$

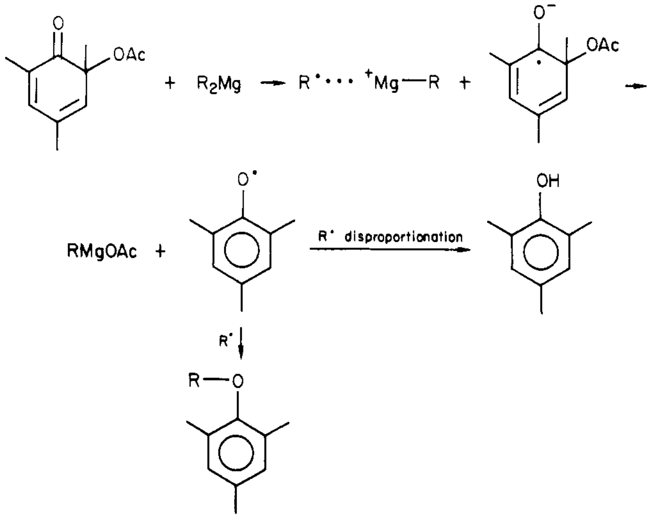
There seems to be no published data in regard to the degree of association of diisopropylmagnesium in ether solutions. However, Walker and Ashby have shown that diethylmagnesium (but not dimethylmagnesium) exists largely as the monomer at all concentrations in diethyl ether.[4] It seems highly probable that diisopropylmagnesium similarly exists largely in the monomeric form.

Since the effects of Grignard concentrations on product ratios from reactions with quinol acetates would be the same whether monomeric Grignards or dialkylmagnesiums are involved in ether formation and reduction, we cannot conclusively decide between the two mechanisms. However, we have shown in this paper that dialkylmagnesium reagents, essentially or completely free of Grignard contaminants, give high yields of ethers and reduction products from reactions with quinol acetates. Very dilute Grignard solutions give product ratios which approach those obtained from the dialkylmagnesiums. It is possible that monomeric Grignard reagents and dialkylmagnesiums give similar product mixtures. However, it is not necessary to assume such a coincidence. Instead, we favor the hypothesis that ethers and reduction products are formed principally from reactions with dialkylmagnesiums, while products of conjugate and normal additions to the unsaturated ketones result principally from reactions with the Grignards.

The effects of addition of small amounts of THF to solutions of isopropylmagnesium bromide in diethyl ether can be accounted for as due either to an increase in concentration of the monomeric Grignard or of diisopropylmagnesium (or of both). Grignard reagents have been demonstrated to exist largely in monomeric forms in THF solutions at all concentrations, presumably due to enhanced solvation of the monomers by the relatively basic cyclic ether.[4] In addition, the Schlenk equilibrium is shifted toward the dialkylmagnesium.[4] The reason for the increased formation of reduction products with higher concentrations of THF is not yet clear.

Reactions with isopropylmagnesium chloride show concentration effects similar to those of isopropylmagnesium bromide, although isopropylmagnesium chloride appears to exist largely in dimeric forms at all except quite low concentrations.[4] Since the concentrations of dialkylmagnesiums in solutions of isopropylmagnesium chloride would thus be low, the high yields of reduction and ether formation from the Grignard suggest that addition reactions with isopropylmagnesium chloride are appreciably slower than with isopropylmagnesium bromide.

Our results show that products from reactions of *o*-quinol acetates with Grignard reagents may be divided into two classes—those prinicpally derived from polymeric Grignards and those derived from monomeric reagents, including dialkylmagnesiums. Of the latter products, ethers have been shown to be formed by initial electron transfer from the organometallic reagent to the quinol acetate. The relatively constant %**3**/%**4** ratio over a wide range of conditions suggests that reductions of *o*-quinol acetates to their parent phenols also proceed by electron transfer. (The simplest mechanism for reduction would then be disproportionation between the resulting phenoxy and alkyl radicals:



However, our data are insufficient to exclude other possible mechanisms, such as a hydrogen transfer to the intermediate radical anion.) The enhanced formation of ether and reduction products from dialkylmagnesiums is thus readily explained, since electron transfer from dialylmagnesiums should be appreciably easier than from Grignard reagents, in which electronegative halogen atoms are bonded to magnesium. In contrast, complexing of the cyclohexadienone oxygen with Grignard reagents (or magnesium halides in a Grignard solution) appears to favor addition reactions proceeding by polar pathways. (The copper-catalyzed conjugate additions observed in reactions of Grignards with unsaturated ketones are not observe with quinol acetates, since addition of copper or other trace metal salts leads exclusively to reduction.[1])

Electron-transfer processes have frequently been proposed for additions of Grignards and other "carbanionoid"

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(4) Walker and Ashby (Walker, F.; Ashby, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 3945) have shown that the degrees of association of both ethylmagnesium bromide and *tert*-butylmagnesium bromide increase from ca. 1.0 to ca. 2.5 as the concentrations of the Grignards increase from near zero to ca. 1.5 M. We have not been able to locate any published evidence in regard to the degree of association of isopropylmagnesium bromide, but there seems no reason to believe it would differ appreciably from the degrees of association of ethyl and *tert*-butylmagnesium bromides.

(5) Ashby, E. C. *Q.R. Chem. Soc.* **1967**, *21*, 259. Wakefield, B. J. *Organomet. Chem. Rev.* **1966**, *1*, 131.

Table VI. Reaction of 2 with Diethylmagnesium

concn of $(Et)_2Mg$ mol/L	solvent (vol % dioxane in ether)	reaction products					
		% ethyl mesityl ether	%4	% 3-ethylmesitol	% other	%3/%4	%3/%5
0.33	12	24.4	40.7	18.1	21.7	0.60	1.35
0.17	6	24.6	39.4	17.7	18.5	0.62	1.38
0.09	3	25.3	39.0	16.7	19.0	0.65	1.51
0.07[a]	~0	20.0	50.0	15.4	14.4	0.40	1.30
0.29[b]	0	27.6	33.1	19.5	19.6	0.83	1.42
(ca. 0.5 M EtMgBr)[c]	0	4	7	52	31	0.57	0.08

[a] $(Et)_2Mg$ dried at 65 °C before use. [b] $(Et)_2Mg$ solution prepared from $(Et)_2Hg$. [c] Data from ref 1a.

organometallic reagents to carbonyls.[6] Indeed, we have observed evidence for such processes in reactions of *o*-quinol acetates bearing electronegative substitutents. For *o*-quinol acetates lacking such substituents, however, our evidence is completely in accord with a mechanism in which ether formation and reduction proceed principally by electron transfer from dialkylmagnesium reagents, and in which addition reactions proceed principally via Grignard processes similar to carbanion additions to carbonyls.

Experimental Section

General Methods. NMR spectra were taken on a Perkin-Elmer R12A instrument in deuteriochloroform solution, using Me_4Si as an internal standard. IR spectra were taken on a Perkin-Elmer 237B spectrometer. GLPC analyses were carried out on a Varian Model 202c gas chromatograph, using a $^1/_4$ in. × 6 ft column packed with 5% DEGS on Chromosorb W. Preparative runs were carried out on a $^3/_8$ in. × 6 ft column with the same packing.

Solvents. Anhydrous diethyl ether was distilled into the reaction flask from lithium aluminum hydride immediately before use. Dioxane was refluxed with aqueous hydrochloric acid under a stream of nitrogen, dried over potassium hydroxide pellets, passed through a column of activated alumina, and distilled from sodium under a nitrogen atmosphere just prior to use. Tetrahydrofuran was refluxed with cuprous chloride, distilled, dried over potassium hydroxide pellets, passed through a column of activated alumina, and distilled from lithium aluminum hydride just before use. Benzene was distilled from sodium under a nitrogen atmosphere just prior to use. Pentane was washed with a mixture of concentrated sulfuric and nitric acids and then with a solution of potassium permanganate in 10% sulfuric acid, washed several times with water, dried over anhydrous calcium chloride, and passed through a column of activated alumina. It was distilled from lithium aluminum hydride into the reaction flask.

Reagents. Alkyl halides were dried over potassium hydroxide pellets and distilled from phosphorus pentoxide under a nitrogen atmosphere before use. Magnesium chips of >99.99% purity (grade m4N) and lithium ribbon (>99.95% purity) were obtained from the Ventron Corporation and handled only with nonmetallic spatulas. Commerical "high purity" lithium wire was obtained from the Foote Mineral Company and magnesium metal turnings from the Fisher Scientific Company. Anhydrous magnesium bromide was prepared by the method of Ashby et al.[7]

Glassware. Schlenk tubes were cleaned in chromic acid, rinsed with a solution of 1% EDTA in 20% sodium hydroxide, and then washed repeatedly with distilled water. All glassware was dried for at least 2 h in an oven at 150 °C and cooled under a stream of nitrogen or argon.

Isopropylmagnesium Bromide. Several different solutions of isopropylmagesium bromide were employed in the runs listed in Tables I and II. The following procedure is typical.

Magnesium chips (1.60 g, 0.066 mol) in ether (50 mL) were stirred under argon. Isopropyl bromide (8.1 g, 0.066 mol) was added as rapidly as possible. The reaction commenced spontaneously and was moderated with an ice bath. After the reaction subsided, it was refluxed on a steam bath for 15 min and then transferred under a nitrogen atmosphere to a Schlenk tube, where it was filtered under continuing nitrogen pressure. The solution was titrated and stored under positive nitrogen pressure until used (within 5 days). **Isopropylmagnesium Chloride** was prepared in a similar manner.

Diethylmagnesium Dioxonate. According to the general procedure of Strohmeier and Seifert,[8] ethyl magnesium bromide was prepared from 7.18 g (0.658 mol) of ethyl bromide and 1.6 g (0.648 mol) of magnesium chips in 50 mL of ether. The solution was added drop by drop to a refluxing mixture of 150 mL of ether and 30 mL of dioxane. The mixture was refluxed for an additional 2 h after addition was complete and then stirred overnight at room temperature. The solids were then allowed to settle and the supernatant liquid transferred under nitrogen pressure to a Schlenk tube and filtered. The filtrate was collected in a distillation flask kept at 60 °C. After distillation of solvent was apparently complete, the residue was cooled and the flask maintained at 0.8 torr while being heated at 170 °C for 4 h. It was then maintained at 0.8 torr overnight to give a white powdery residue, which was washed 3 times with pentane. The residue was dried under vacuum and dissolved in 25 mL of ether. The solution was filtered in a Schlenk tube under nitrogen and titrated with hydrochloric acid. It was found to be 0.071 M.

Diisopropylmagnesium dioxonate was prepared according to the literature procedure,[9] except that the product was dried at 65 °C under vacuum to prevent excessive decomposition. After removal of solvent, the residual powder was dissolved in ether to give a cloudy solution, which was filtered under nitrogen in a Schlenk tube. The resulting clear solution was analyzed by addition of an aliquot to hydrochloric acid and back-titration with potassium hydroxide solution.

Solutions of **diethylmagnesium** in ether were prepared by reaction of diethylmercury, bp 62–64 °C (23 torr) (lit.[9] bp 53–56 °C (15 torr), with magnesium according to the procedure of Ashby and Arnott,[10] and tritrated as described above for diethylmagnesium dioxonate.

Isopropyllithium in pentane solution was prepared as described in the literature,[11] under an atmosphere of argon which had been passed through chambers containing concentrated sulfuric acid, potassium hydroxide pellets, and Drierite. Samples were filtered through Schlenk tubes and analyzed by titration before and after reaction with allyl bromide.[11]

Isopropyl 2,4,6-Trimethylphenyl Ether. To a solution of potassium *tert*-butoxide (1.12 g, 0.01 mol) in 20 mL of dimethyl sulfoxide was added 2,4,6-trimethylphenol (1.4 g, 0.010 mol). The mixture was shaken until a clear solution was obtained, and isopropyl bromide (1.4 g, 0.0114 mol) was added. After 10 min the solution was diluted with water and extracted with hexane. The hexane layer was washed 3 times with water, extracted with Claisen alkali, washed again with water, and dried over magnesium sulfate. The solvent was evaporated to give isopropyl 2,4,6-trimethylphenyl ether (1.4 g, 79%) as a pale yellow oil. Its NMR spectrum showed peaks at δ 1.15 (d, J = 8 Hz, 6 H), 2.07 (s, 9

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[6] Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* **1983**, *105*, 2922.

[7] Ashby, E. C.; Laemmle, J.; Neumann, L. M. *J. Am. Chem. Soc.* **1972**, *94*, 5421.

[8] Strohmeier, W.; Seifert, F. *Chem. Ber.* **1961**, *94*, 2356.

[9] Cowan, D. O.; Mosher, H. S. *J. Org. Chem.* **1962**, *27*, 1.

[10] Ashby, E. C.; Arnott; R. C. *J. Organomet. Chem.* **1968**, *14*, 1.

[11] Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862.

H), 4.00 (septet, J = 8 Hz, 1 H), and 6.60 (s, 2 H).

6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (2), mp 87.5–89 °C (lit.[12] mp 84 °C), was prepared in 51% yield by reaction of 2,4,6-trimethylphenol with lead tetraacetate in chloroform, according to the procedure employed for the preparation of 6-acetoxy-2,6-dimethylcyclohexa-2,4-dien-1-one.[13]

Reaction of 6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one with Isopropylmagnesium Bromide. The general procedure was as follows.

Into each of six 50-mL three-necked flasks equipped with glass-coated magnetic stirring bars, reflux condensers leading to mercury traps, and nitrogen inlet tubes were pipetted aliquots of freshly prepared and standardized solutions of isopropylmagnesium bromide. These solutions were diluted with anhydrous ether to give a range of concentrations varying from ca. 0.08 to 1.8 M. To each solution was added a sample of the quinol acetate dissolved in 1 mL of anhydrous ether. The samples of quinol acetate did not exceed 0.11 times the number of moles of Grignard reagent employed. The reaction mixtures were stirred overnight at room temperature and were then quenched with either saturated ammonium chloride solution or 0.1 M hydrochloric acid solution. Each mixture was extracted 4 times with 10 mL of methylene chloride, washed with 10 mL of water, and dried over magnesium sulfate. The solvent was evaporated, the residual oil was weighed, and a known weight of hexamethylbenzene was added to act as an internal GLPC standard. GLPC analysis at 150 °C showed the presence of three major components with retention times of 1.0, 3.2, and 7.6 min. Comparison of the areas of these peaks (corrected for thermal conductivity differences, as determined from isolated samples) with that of hexamethylbenzene showed that these peaks comprised ca. 99 mol % of the product. Very minor peaks with retention times of 4–5 min were also observed.

The three components were isolated by preparative GLPC on column B. The components with retention times 1.0 and 3.2 min were identified as isopropyl 2,4,6-trimethylphenyl ether and 2,4,6-trimethylphenol, respectively by comparison with authentic samples. The component with a retention time of 7.6 min was identified as 3-isopropyl-2,4,6-trimethylphenol. Its NMR spectrum showed peaks at δ 1.30 (d, J = 8 Hz, 6 H), 2.11 (s, 3 H), 2.25 (s, 6 H), 3.39 (m, J = 8 Hz, 1 H), 4.59 (br s, 1 H), 6.71 (br s, 1 H). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.41; H, 11.40.

Reactions of 2 with solutions containing various percentages of dioxane or THF were carried out as described above, except that measured volumes of the other solvents were added to the ethereal Grignard solutions before reaction with 2. Reactions of 2 with diisopropylmagnesium were carried out in the same manner as reactions with isopropylmagnesium bromide.

Reactions of 2 with isopropylmagnesium chloride were carried out as described for reaction with isopropylmagnesium bromide. A sample of products with retention times on column A of ca. 4–5 min was isolated by preparative GLPC on column B. Its IR spectrum showed strong absorptions at 1710 and 1680 cm^{-1}. It had a very complex NMR spectrum.

Reactions of 2 with isopropyllithium in pentane were carried out and analyzed in a manner similar to that described for reaction with isopropylmagnesium bromide.

Reaction of 2 with Isopropylmagnesium Bromide Formed from Grignard Grade Magnesium. The reaction was carried out as described above by employing magnesium turnings ("for Grignard Reactions") obtained from the Fisher Scientific Co. The reaction was worked up and analyzed as usual. In addition to peaks for 3, 4, and 5, a peak with a retention time of 4.9 min was observed. This component was isolated by preparative GLPC as a pale yellow oil and identified as **2,6-dimethyl-4-isobutylphenol.** Its NMR spectrum showed peaks at δ 0.87 (d, J = 7.8 Hz, 6 H), 2.18 (m, 9 H), 4.47 (br s, 1 H), and 6.85 (s, 2 H). Addition of Eu(fod)$_3$ (4.85 × 10^2 mmol to 1.58 × 10^1 mmol of the phenol) converted the multiplet at δ 2.18 into peaks at δ 2.96 (s, 6 H), 2.50 (d, J = 7.8 Hz, 2 H), and 2.3 (m, 1 H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.04; H, 10.41.

Reaction of 2 with Diethylmagnesium. Reactions of 2 with diethylmagnesium were carried out in a manner similar to that described for reaction with isopropylmagnesium bromide. GLPC analysis (column A, 140 °C) of the reaction products after workup showed components with retention times of 1.1, 3.1, 4.1–5.2 (at least three overlapping peaks) and 6.8 min. The peaks with retention times of 1.1, 3.1, and 6.8 min were isolated by preparative GLPC and identified as ethyl 2,4,6-trimethylphenyl ether, mesitol, and 3-ethyl-2,4,6-trimethylphenol by comparison of their spectra with those of authentic samples.[1a] The products with retention times of 4.1–5.2 min could not be separated but were isolated as a mixture. Its IR spectrum showed strong peaks at 1667 and 1650 cm^{-1}. Its UV spectrum (in methanol) had a λ_{max} of 330 μm.

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Registry No. 2, 4906-82-5; 3, 13605-05-5; 4, 527-60-6; 5, 54337-56-3; 6, 91083-11-3; 8, 61248-71-3; (Et)$_2$Mg, 557-18-6; (i-Pr)$_2$Mg, 3536-97-8; i-PrMgCl, 1068-55-9; i-PrLi, 1888-75-1; i-PrMgBr, 920-39-8; ethyl 2,4,6-trimethylphenyl ether, 61248-63-3; isoproyl 2,4,6-trimethylphenyl ether, 13605-05-5; 2,6-dimethyl-4-isobutylphenol, 35993-75-0.

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Generation and [3 + 2] Cycloaddition Reactions of Oxazoline *N*-Oxides

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2,4,4-Trimethyloxazoline *N*-oxide (**6a**) and 2-ethyl-4,4-dimethyloxazoline *N*-oxide (**6b**) have been prepared by condensation of 2-(hydroxyamino)-2-methyl-1-propanol hydrochloride (**7**) with triethyl orthoacetate and orthopropionate. [3 + 2] Cycloaddition reactions of nitrones **6a** and **6b** and the related 2,5,5-trimethylpyrroline *N*-oxide (**12**) with phenyl isocyanate, dimethyl acetylenedicarboxylate, methyl phenylpropiolate, phenylpropiolonitrile, methyl acrylate, and acrylonitrile were carried out. Competition experiments demonstrated that **6a** is at least 6800 times more reactive than **12** towards phenyl isocyanate. The oxazoline *N*-oxide (**6a**) proved to be 160 times more reactive than the pyrroline *N*-oxide in similar competitive cycloadditions with dimethyl acetylenedicarboxylate. Reaction of **6a** with acrylonitrile afforded 3-substituted cycloadducts as major products (3:1 ratio of regioisomers) in contrast to **12** which gave only a 2-substituted cycloadduct under kinetically controlled conditions at room temperature.

Nitrones[1] readily undergo 1,3-dipolar cycloaddition reactions with multiply bonded dipolarophiles to yield synthetically useful heterocyclic derivatives.[2] For example, the inter- and intramolecular reactions of nitrone functions

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