JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 4, 158–162 (1991)

THE GRIGNARD REACTION OF α-DIKETONES. RADICAL INTERMEDIATES AS THE DETERMINANT OF CARBON- AND OXYGEN-ATTACKED PRODUCTS

KAZUHIRO MARUYAMA* AND TOSHIMASA KATAGIRI
Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

Although carbon (normal)- and oxygen (abnormal)-attacked products are usually afforded in the Grignard reaction of α-diketones, the relative ratio of the two are strongly dependent on the structure of the Grignard reagents. The product-determining factors are discussed on the basis of the intermediate radicals formed from α-diketones and Grignard reagents.

INTRODUCTION

In 1986 the present authors published a paper on the mechanism of the Grignard reaction with benzil (**1**).[1] Subsequently Holm[2] emphasized the formation of oxygen-attacked products (OAP) in addition to the normal carbon-attacked product (CAP) in similar reactions.

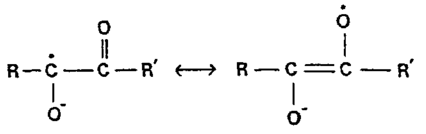
We have therefore reinvestigated the Grignard reactions of α-diketones. Two routes to the CAP and the OAP are discussed below. The Grignard reagents PhMgBr, MeMgBr and EtMgBr were used as representatives, because their C—Mg bond strengths have been well determined.[3]

RESULTS AND DISCUSSION

The reactions were undertaken under strictly dry and deaerated conditions. The results are summarized in Table 1. Products **2** and **3** are the normal CAP, but products **4** and **5** are the abnormal OAP.

In every case CAP **2** + **3** was the overwhelming product. However, in the reaction of *tert*-butyl phenyl diketone with EtMgBr, the reaction product (**6**), the reduction product, was predominant. In all of the reactions intermediate radicals were identified by ESR. The determined proton hyperfine splitting constants are given in Table 2 and typical ESR spectra are given in Figures 1–3.

As discussed in the previous paper,[1] all the results given above are compatible with the formation of the intermediate radical ion pair consisting of the radical anion of the α-diketone and the radical cation of the Grignard reagent. An alkyl (or aryl) radical transfers from the radical cation of the Grignard reagent to the radical anion to accomplish the addition reaction. Since the radical anion of α-diketone **I** exists in the resonance state, and is ion-paired with the counter cation radical of the Grignard reagent, the alkyl (or aryl) radical transfer from the radical cation moiety of the Grignard reagent can produce either CAP or OAP.



I

As discussed in the previous paper,[1] in the alkyl (or aryl) radical transfer step, assistance with aggregation by another Grignard molecule is required. This was clarified on the basis of kinetic measurements. However, there are two possible paths in the alkyl (or aryl) transfer to give sole CAP and mixture of CAP + OAP as discussed below. Especially the assistance with aggregation by another Grignard molecule to facilitate inner-spere R· transfer (see below) is essential in the reactions of the Grignard reagents which have a strong enough C—Mg bond [stronger than 210 kcal mol^{-1} (1 kcal = 4·184 kJ)] to keep $[\mathrm{RMgBr}]^{+\cdot}$ stable as the radical cation derived from PhMgBr (289 kcal mol^{-1}) or CH$_3$MgBr (251 kcal mol^{-1}). In the reactions of these Grignard reagents, stable contact ion-paired radicals

---

* Author for correspondence.

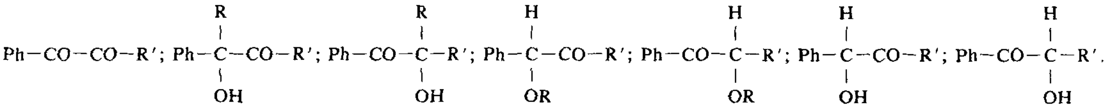
0894–3230/91/030158–05$05.00

Received 31 August 1990
Revised 6 October 1990

Table 1. Products of Grignard reactions with α-diketones[a]

Diketones[b] (1)	Grignard reagent (RMgBr)	Products (%)[b] 2	3	4	5	6	7	1 (recovered)
PhCOCOPh	PhMgBr	97		3		—	—	—
(a)	EtMgBr	56		44		—	—	—
	MeMgBr	100		—		—	—	—
MeCOCOPh	PhMgBr	49	35	11	2	—	—	3
(b)	EtMgBr	38	18	7	6	13	11	7
	MeMgBr	58	42	—	—	—	—	—
t-BuCOCOPh	PhMgBr	99	—	—	—	—	—	1
(c)	EtMgBr	18	4	14	7	44	6	1
	MeMgBr	86	7	—	—	—	—	6

[a] Diketone/RMgBr molar ratio = 1·0; after mixing, allowed to stand for 3 days. RMgBr = 0·1 M. Solvent: THF. Reaction at room temperature.
[b] **a**, R′ = Ph; **b** R′ = Me; **c**, R′ = *t*-Bu.



$$\mathrm{Ph{-}CO{-}CO{-}R'};\ \mathrm{Ph{-}}\overset{\mathrm{R}}{\underset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}CO{-}R'};\ \mathrm{Ph{-}CO{-}}\overset{\mathrm{R}}{\underset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}R'};\ \mathrm{Ph{-}}\overset{\mathrm{H}}{\underset{\mathrm{OR}}{\mathrm{C}}}\mathrm{{-}CO{-}R'};\ \mathrm{Ph{-}CO{-}}\overset{\mathrm{H}}{\underset{\mathrm{OR}}{\mathrm{C}}}\mathrm{{-}R'};\ \mathrm{Ph{-}}\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}CO{-}R'};\ \mathrm{Ph{-}CO{-}}\overset{\mathrm{H}}{\underset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}R'}.$$

(1) (2) CAP (3) CAP (4) OAP (5) OAP (6) reduction (7) reduction

Table 2. Hyperfine splitting constants of radical intermediates. (reaction in THF)[a]

Ketone	RMgBr	Conditions	Hiperfine splittings (mT)		
PhCOCOPh	PhMgBr	r. t.	0·999 (6H)[b],	0·041 (4H)[c]	
		−20 °C	0·100 (6H),[b]	0·042 (4H)[c]	
		−40 °C	0·101 (6H),[b]	0·042 (4H)[c]	
	EtMgBr	r. t.	0·099 (6H),[b]	0·041 (4H)[c]	
		−20 °C	0·101 (6H),[b]	0·042 (4H)[c]	
		−40 °C	0·102 (6H),[b]	0·042 (4H)[c]	
MeCOCOPh	PhMgBr	r. t.	0·668 (3H),[d]	0·133 (3H),[b]	0·054 (2H)[c]
		−20 °C	0·635 (3H),[d]	0·133 (3H),[b]	0·057 (2H)[c]
		−40 °C	0·635 (3H),[d]	0·133 (3H),[b]	0·056 (2H)[c]
	EtMgBr	r. t.	0·668 (3H),[d]	0·131 (3H),[b]	0·053 (2H)[c]
		−20 °C	0·664 (3H),[d]	0·133 (3H),[b]	0·054 (2H)[c]
		−40 °C	0·656 (3H),[d]	0·139 (3H),[b]	0·055 (2H)[c]
t-BuCOCOPh	PhMgBr	r. t.	0·025 (9H),[e]	~0·101 (3H),[b]	~0·050 (2H)[c]
		−20 °C	—[f]	—[f]	—[f]
		−40 °C	—[f]	—[f]	—[f]
	EtMgBr	r. t.	0·025 (9H),[e]	~0·101 (3H),[b]	~0·050 (2H)[c]
		−20 °C	—[f]	—[f]	—[f]
		−40 °C	—[f]	—[f]	—[f]

[a] Mean values of three measurements. The standard deviation of values was smaller than 0·001 mT in room temperature (r. t.) measurements and smaller than 0·003 mT in −20 °C and −40 °C measurements.
[b] Due to phenyl *o*- and *p*-hydrogens.
[c] Due to phenyl *m*-hydrogens.
[d] Due to methyl hydrogens.
[e] Due to *tert*-butyl hydrogens.
[f] The hyperfine splitting constants cannot be determined because of the broad nature of the ESR spectrum.

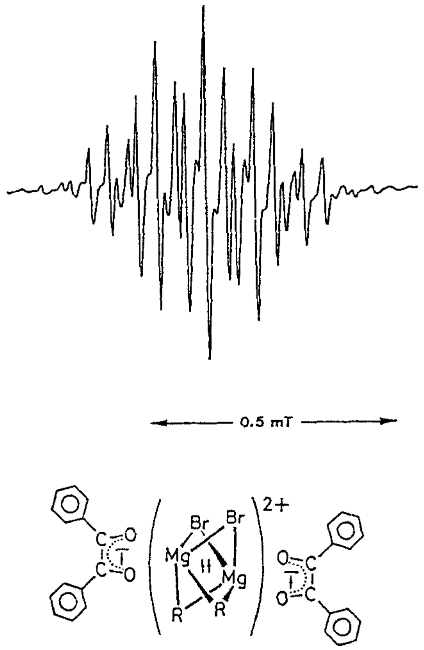


Figure 1. ESR spectrum observed in the Grignard reaction of benzil with PhMgBr in THF at r. t.

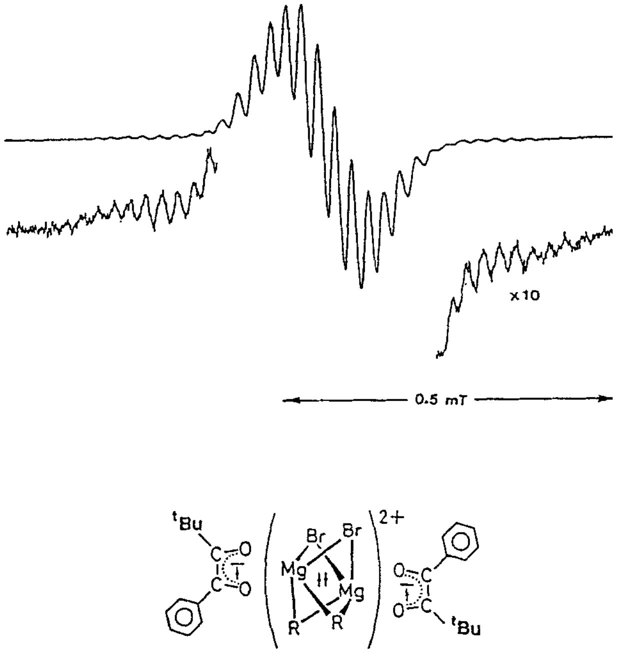


Figure 3. ESR spectrum observed in the Grignard reaction of *t*-BuCOCOPh with PhMgBr in THF at r. t.

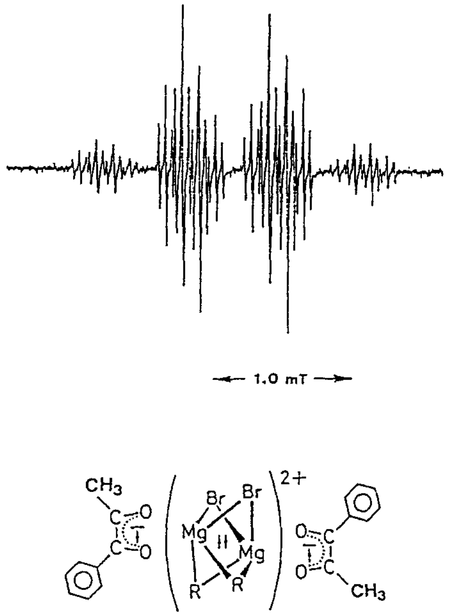
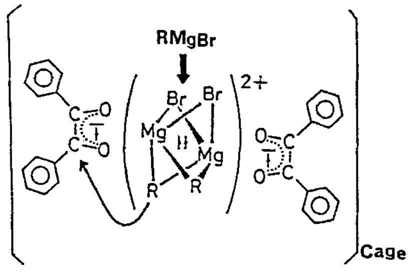


Figure 2. ESR spectrum observed in the Grignard reaction of MeCOCOPh with PhMgBr in THF at r. t.

can be formed under appropriate conditions. [In general, the highest concentrations of the stable radical ion pair (DIP) were observed in the reaction solution when Grignard reagent and α-diketone in a 2 : 1 molar ratio were mixed at room temperature; see also Ref. 4 in which the change from (MIP) to (DIP) was discussed.] This kind of contact ion-paired radicals is so stable that one can store the solution without any change in the concentration of the radicals for at least 3 years under dark, dry and deaerated conditions at room temperature. An example of this type of very stable radical ion pair is the dimer radical ion pair (DIP),[1,4] which is produced by rapid dimerization of 1 : 1 mono-radical ion pair (MIP) consisting of [diketone]$^{-\cdot}$ and [Grignard reagent]$^{+\cdot}$. This type of R$^{\cdot}$ transfer could be done in the contact ion-paired and solvent-separated ligating inner sphere. In DIP, the dimer of the contact ion-paired [RMgBr]$^{+\cdot}$ moiety with [α-diketone]$^{-\cdot}$, the two carbonyl oxygens could be blocked strongly by counter dimer radical cations of the Grignard reagent. Therefore, the subsequent R$^{\cdot}$ transfer in the DIP induced by participation of another RMgBr molecule could result in the predominant (or almost exclusive) formation of CAP. Thus, in the reactions of MeMgBr and PhMgBr processes (1) and (2) (see below) proceed almost exclusively (see **II**). The concept of the inner sphere in Grignard-type reactions has also been proposed by Okubo *et al.*[5]



II

In contrast, when the C—Mg bond of the Grignard reagents is not strong enough to keep MIP stable to form DIP at the reaction temperature, as with EtMgBr, PrMgBr, *i*-PrMgBr, or BuMgBr, the three processes (2) → (4) and (3) become competitive.

$$\text{Grignard reagent} + \text{diketone} \xrightarrow{\text{electron transfer}} \text{MIP} \tag{1}$$

$$\text{MIP} \xrightarrow{\text{MIP}} \text{DIP} \tag{2}$$

$$\text{MIP} \xrightarrow{\text{decomp.}} \text{R}^{\cdot}(\text{free radical}) + \text{MgBr}^{+} + (\text{diketone})^{-\cdot} \longrightarrow \text{CAP} + \text{OAP} + \text{others} \tag{3}$$

$$\text{DIP} \xrightarrow{\text{RMgBr}} \text{CAP} + \text{MgBr}^{+} + \text{MIP} + \text{RMgBr} \tag{4}$$

At the other extreme, in the reaction of *t*-BuMgBr (C—Mg bond strength 176 kcal mol^{-1}), process (3) is predominant, and the product is a complex mixture of small amounts of addition products (CAP + OAP) (or in some cases none of the addition products), the reduction products of α-diketone, isobutene and other products. (Even in the reaction with benzil, none of stable radical ion pair was found in the reaction solution, but *t*-BuMgBr was consumed completely. After work-up, most of benzil was recovered together with a small amount of 4-*tert*-butyl-substituted benzil and benzoin. A reasonable amount of isobutene was identified gas chromatographically.)

In the reactions of EtMgBr, PrMgBr, *i*-PrMgBr and BuMgBr the reactions are intermediate between the above two extremes and the three processes (2), (3) and (4) could proceed competitively, resulting in the formation of a mixture of CAP, OAP, acyloin and other minor products.

Steric factors around both the carbonyl group and the radical centre of R$^{\cdot}$ could also be the important controlling factor of the reaction. In the reaction of benzil with *t*-BuMgBr, neither CAP nor OAP was found in the products, but benzoin, isobutene and recovered benzil were the major components. According to the literature[6] the reactions of *t*-BuMgBr with 2, 4, 6-trimethyl-, 2, 4, 6, 4′-tetramethyl- and 2, 3, 5, 6-tetramethyl-benzophenones gave *p*-*tert*-butyl-substituted benzophenones as the sole product. The results given in Table 1 reflect well the above discussion.

To explore in more detail the nature of the DIP, we added CuBr in the Grignard reaction of benzil with PHMgBr. As expected, a drastic change in the product distribution was observed. Figure 4 illustrates the results. Even the addition of 0·1% (w/w) of CuBr vs PhMgBr reduced the yield of CAP to 45%, and increased the amounts of OAP (7%), benzoin (12%), biphenyl (15%) and recovered benzil (35%). The yield of OAP reached at the maximum (10%) on adding 0·3% (w/w) of CuBr. Further increases in CuBr increased the formation of biphenyl and recovered benzil, but led to a continuing decrease in CAP and OAP. Hence the presence of a minute amount of CuBr in the reaction system induces prompt decomposition of DIP to give 'free R$^{\cdot}$' + MgBr^{+} by a recycling process (Cu$^{\text{I}}$ ⇆ Cu$^{\text{II}}$ + e). The salt, CuBr, should be considered as a 'free radical' promoter. Other heavy metal ions such as Co$^{\text{III}}$, Mn$^{\text{II}}$, Fe$^{\text{II}}$ and Ce$^{\text{II}}$ have a similar ability via repetitive redox processes. Synthetic applications of heavy metals in Grignard reactions and other analogous

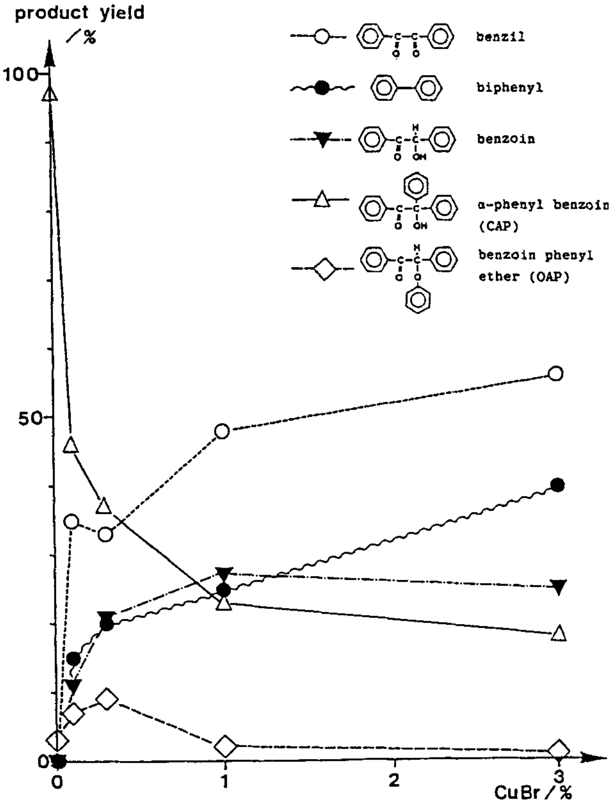


Figure 4. Drastic variation of products induced by adding CuBr in the Grignard reaction (benzil + PhMgBr)

organometallic reactions to control the product distribution are empirically well known. Especially copper ion is likely to have an outstanding ability to prolong the lifetime of 'free $R^{\cdot}$' via ligation. The Gomberg reaction,[7] the Ullmann reaction,[8] 1,4-addition to —C=C—CO— bonds and 1,6-addition to —C=C—C=C—CO— bonds in organometallic reactions in the presence of heavy metal ions and others[9] are in this category.

So far the product distributions in the Grignard reactions have been disputed taxonomically on the basis of the oxidation potentials of Grignard reagents,[5,10] of the steric bulkiness around the carbonyl group[6,11] and of the C—Mg bond strength.[3,11] However, the Grignard reaction consists of more complicated processes as discussed above. The product distributions are the accumulative results of these processes, simple or complex, depending on the nature of both the ketone and the Grignard reagent and also the polarity of the solvents. (Product distributions, e.g. addition and reduction products, are much affected by solvent polarity. Relative amounts of the components in the well known equilibrium $2RMgBr \rightleftharpoons RMgBr \rightleftharpoons R_2Mg + MgBr_2$ are dependent on the solvent polarity.)

EXPERIMENTAL

Materials and methods. Grignard reagents using magnesium (99·995% pure) were prepared as described previously.[1] Benzil synthesized by air oxidation of benzoin was recrystallized twice from carbon tetrachloride, m.p. 95·2 °C. 1-Phenylpropane-1,2-dione, obtained by hydrolysis of isonitrosopropiophenone, was distilled twice (b.p. 120 °C/24 Torr). 3,3-Dimethyl-1-phenylbutane-1,2-dione prepared by HNO_3 oxidation of 3,3-dimethyl-1-hydroxy-1-phenylbutan-2-one was distilled twice (b.p. 53 °C/0·2 Torr). Pure tetrahydrofuran (THF) was distilled *in vacuo* from reservoirs containing sodium benzophenone ketyls.

A JEOL JES-FE1XG *X*-band ESR spectrometer, a JEOL JNM 100-MHz ^1H NMR spectrometer and a JEOL JNM 400-MHz FT-NMR spectrometer were used.

Reactions. Preparations of samples and ESR observations were undertaken as described in the previous paper.[1] After reaction the solutions were quenched and hydrolysed with 1·5 M aqueous ammonium chloride under deaerated conditions. Work-ups were done as usual, but under an argon atmosphere. Identifications of the products, qualitative and quantitative, were done straightforwardly by spectroscopic methods, because of the simplicity of their structures. If needed, products were separated by column chromatography.

Reactions in the presence of CuBr. An amount of guaranteed-grade CuBr weighed and dissolved in a THF solution of α-diketone. The solution and a solution of Grignard reagent, which were separated from each other by a breakable seal, were mixed in a vessel under strictly dry and deaerated conditions by breaking the seal. Work-ups of the products were done as usual, but under an argon atmosphere.

REFERENCES

1. K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.* **108**, 6263 (1986).
2. T. Holm, *Acta Chem. Scand. Ser. B* **41**, 278 (1987)
3. T. Holm, *J. Chem. Soc., Perkin Trans. 2* 464 (1981).
4. K. Maruyama and T. Katagiri, *Chem. Lett.* 731, 735 (1987).
5. M. Okubo, Y. Fukuyama, M. Sato, K. Matsuo, T. Kitahara and M. Nakashima, *J. Phys. Org. Chem.* **3**, 379 (1990).
6. T. Holm and I. Crossland, *Acta Chem. Scand.* **25**, 59 (1971).
7. (a) M. Gomberg, *J. Am. Chem. Soc.* **22**, 757 (1900); (b) H. Gilman, *J. Am. Chem. Soc.* **61**, 957 (1939).
8. (a) F. Ullman and J. Bielecki, *Chem. Ber.* **34**, 2174 (1901); (b) J. F. Bunnet and R. E. Zahler, *Chem. Rev.* **49**, 392 (51).
9. Y. Yamamoto, S. Yamamoto, H. Yatagai and K. Maruyama, *J. Am. Chem. Soc.* **102**, 2318 (1980); (b) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, *J. Org. Chem.* **47**, 119 (1982); (c) K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.* **99**, 8068 (1977).
10. M. Okubo and S. Ueda, *Bull. Chem. Soc. Jpn.* **52**, 3346 (1979); (b) M. Okubo, T. Tsutsumi and K. Matsuo, *Bull. Chem. Soc. Jpn.* **60**, 2085 (1987); (c) M. Okubo, *Bull. Chem. Soc. Jpn.* **48** 1327, 2057 (1975).
11. E. C. Ashby and T. L. Wiesemann, *J. Am. Chem. Soc.* **100**, 189 (1978).