[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Types of Reaction of Carboxylic Esters with Grignard Reagents[1]

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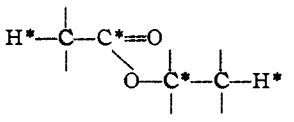
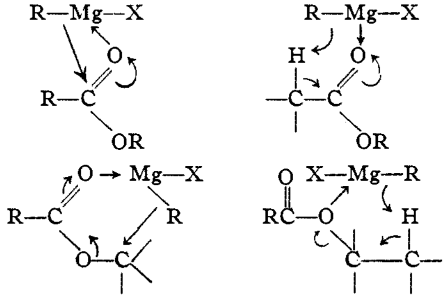
A strong base such as the amide ion[2] is capable of reacting with carboxylic esters at any of the four positions indicated by asterisks in the following general formula: at the carbonyl carbon, the α-hydrogen in the acyl portion, the α-carbon or the β-hydrogen in the alkoxy portion.



Since the strongly basic alkyl or aryl anion is potentially present in Grignard reagents these reagents should be capable of reacting at any of the four vulnerable positions of esters. Actually, reactions at three of these positions have been observed previously; reaction at the fourth position, the β-hydrogen, has been realized in this investigation.

The reactions of the potential alkyl or aryl anions of Grignard reagents at the four vulnerable positions of esters are of different types. Addition occurs at the carbonyl carbon to form a ketone or more often a tertiary alcohol[3]; the α-hydrogen is removed to form the magnesium halide derivative (enolate) of the ester which condenses with unchanged ester to form a β-keto ester (acetoacetic ester condensation); substitution takes place at the α-carbon to form a hydrocarbon; and the β-hydrogen is removed, accompanied by the elimination of the carboxylate group, to form an olefin (β-elimination). Because the magnesium atoms of Grignard reagents probably first coördinate with the carbonyl or alkoxy oxygen atoms of esters it is possible that these four types of reaction take place within the resulting coördination complexes. Indeed, the formation of the coördination complex should activate both the potential alkyl or aryl anion of the Grignard reagent and the electron accepting atom of the ester; moreover, these reactive centers should be brought in close contact within the coördination complex.[4] The electronic changes that may occur within the coördination complexes leading to the four types of reaction may be indicated as



It is well known that ethyl acetate and higher aliphatic homologs as well as ordinary aromatic esters such as ethyl benzoate exhibit mainly the carbonyl carbon reaction with most Grignard reagents. However, *t*-butyl acetate,[5] which has a relatively unreactive carbonyl carbon, and especially ethyl phenylacetate,[6] which has a relatively reactive α-hydrogen, are self-condensed by isopropylmagnesium bromide. With the more complex Grignard reagent, *t*-butylmagnesium chloride,[7] ethyl propionate mainly self-condenses, while with mesitylmagnesium bromide[8] even ethyl isovalerate and ethyl isobutyrate self-condense.

In this investigation ethylmagnesium bromide was found to effect the self-condensation of ethyl phenylacetate to the extent of only 8% under the conditions that have produced a 94% yield of the condensation product in the presence of the more complex isopropylmagnesium bromide.[6] Ethyl diphenylacetate was found to react to some extent with isopropylmagensium bromide in refluxing ethyl ether but neither the self-condensation product of the ester nor the carbonyl carbon product was obtained. Since treatment of the reaction mixture with benzoyl chloride gave some ethyl benzoyldiphenylacetate whereas none was obtained from the ester alone with benzoyl chloride, part of the ester must have been converted to its magnesium derivative by the Grignard reagent, thus

$$(C_6H_5)_2CHCO_2C_2H_5 \xrightarrow{(CH_3)_2CHMgBr} [(C_6H_5)_2CCO_2C_2H_5]MgBr \xrightarrow{C_6H_5COCl} C_6H_5COC(C_6H_5)_2CO_2C_2H_5$$

This appears to be the first case in which the magnesium derivative of an ester has been condensed with a component other than the original ester[9];

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(1) This work was supported in part by a grant from the Duke University Research Council.

(2) Hauser, Shivers and Skell, THIS JOURNAL, **67**, 409 (1945).

(3) Obviously, the tertiary alcohol results from reaction with a second molecule of the Grignard but it is not clear whether the ketone is formed as an intermediate; see Gilman, "Organic Chemistry," Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 502–504.

(4) See Johnson, *ibid.*, Vol. II, pp. 1866, 1880; Young and Roberts, THIS JOURNAL, **68**, 649 (1946); Whitmore and George, Abstracts, Division of Organic Chemistry, Meeting of the American Chemical Society, Atlantic City, September, 1941.

(5) Hudson, Shivers and Hauser, THIS JOURNAL, **65**, 2051 (1943).

(6) Conant and Blatt, *ibid.*, **51**, 1227 (1929); see also Ivanov and Spassov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

(7) Zook, McAleer and Horwin, THIS JOURNAL, **68**, 2404 (1946).

(8) Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

(9) An unsuccessful attempt to benzoylate the magnesium derivative of ethyl isobutyrate, prepared by means of mesitylmagnesium bromide, was made previously in this laboratory; Hudson and Hauser, *ibid.*, **63**, 3157 (1941), note 8.

judging from previous results with diethylaminomagnesium bromide[10] the magnesium derivative of most esters condense very rapidly with the original ester. An attempt to carbonate the magnesium derivative of ethyl diphenylacetate failed, presumably because of the instability of the carbonation product.[11]

Substitution at the α-carbon in the alkoxy portion of esters has been observed with certain esters in which the carbonyl carbon is hindered and the α-carbon is attached to relatively strong electron releasing groups. Arnold and co-workers[12] have realized this type of reaction with certain allyl esters, for example allyl mesitoate, with which phenylmagnesium bromide gave a 70% yield of allylbenzene.[13] Fieser and Heymann[14] found that triphenylmethyl acetate reacts with methylmagnesium iodide to form α,α,α-triphenylethane in good yield. In the present investigation triphenylmethyl benzoate has been found to react similarly.

$$C_6H_5CO_2C(C_6H_5)_3 + CH_3MgI \longrightarrow (C_6H_5)_3CCH_3 + C_6H_5CO_2MgI$$

β-Elimination of esters with Grignards has apparently not been reported previously.[15] This type of reaction has been realized in the present investigation with α,β-diphenylethyl mesitoate in which the carbonyl carbon is hindered and the β-hydrogen is activated. With phenylmagnesium bromide in refluxing *n*-butyl ether this ester yielded the elimination products stilbene and mesitoic acid in yields of 80–90%; this was shown not to be merely a thermal elimination.

$$\text{Mes-}CO_2CH(C_6H_5)CH_2C_6H_5 + C_6H_5MgBr \longrightarrow C_6H_5CH{=}CHC_6H_5 + \text{Mes-}CO_2MgBr$$

With methylmagnesium iodide or ethylmagnesium bromide under similar conditions the yield of stilbene was only 30–40% and another product, 1,2,3,4-tetraphenylbutane, was obtained in 8–9% yield. The latter substance might be accounted for by the dimerization of the intermediate free α,β-diphenylethyl radical.[16] This type of reaction appears to have been observed by Stadnikoff[17] who found that benzhydryl acetate reacts with *n*-propyl- or *n*-butyl-magnesium iodide to form partly (6–10%) *sym*-tetraphenylethane along with the corresponding alkane and alkene from the Grignard. Since Kharasch and co-workers[18] have found that cobaltous chloride increases the free radical nature of certain Grignard reactions, α,β-diphenylethyl mesitoate and methylmagnesium iodide have been allowed to react in the presence of a catalytic amount of this salt. In agreement with the radical mechanism, the yield of the dimer was increased from 9% to 16% and no stilbene was found. However, the reaction of the ester with phenylmagnesium bromide and cobaltous chloride produced none of the dimer, although the yield of stilbene was reduced considerably. Actually the best yield (22%) of the dimer was obtained when the reaction was carried out with methylmagnesium iodide using a metal stirrer; no cobaltous chloride was added in this experiment. It might appear that the stilbene could be accounted for by the radical mechanism in which the α,β-diphenylethyl radical underwent disproportionation, but the other product of this reaction, dibenzyl, has not been found. Moreover, the yield of stilbene decreased as the conditions were made more favorable for the radical reaction.

Experimental[19]

Esters.—Ethyl diphenylacetate (m. p. 57°) was synthesized by the carbethoxylation of diphenylmethylpotassium as described previously.[20]

Triphenylmethyl benzoate was prepared by a modification of the method of Gomberg and Davis[21] for triphenylmethyl acetate. A mixture of 43.2 g. (0.15 mole) of triphenylchloromethane and 40.0 g. (0.15 mole) of silver benzoate in 500 ml. of dry benzene was stirred and heated on the steam-bath for six hours, filtered hot and the filtrate concentrated. The precipitate obtained on cooling was filtered off and recrystallized from ethyl acetate yielding 25 g. (50%) of the ester, melting at 162–163°.

Anal. Calcd. for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.35; H, 5.67.

α,β-Diphenylethyl mesitoate was prepared by stirring for four hours a mixture of 37 g. (0.22 mole) of phenylbenzylcarbinol and 40 g. (0.22 mole) of mesitoyl chloride[22] in 200 ml. of dry benzene. The benzene solution was extracted with sodium bicarbonate solution, dried with Drierite and the solvent distilled. The oily residue was recrystallized from 50% ethanol yielding 60 g. (82%) of the ester, melting at 55–57°.

Anal. Calcd. for $C_{24}H_{24}O_2$: C, 83.71; H, 7.03. Found: C, 83.36; H, 7.11.

Grignards.—These reagents were prepared under nitrogen in absolute ethyl or *n*-butyl ether. The solutions were decanted from unreacted magnesium and analyzed; when not used immediately they were stored under nitrogen in well stoppered flasks in the dark.

Apparatus.—The reactions of esters with Grignards were carried out in three necked round bottomed flasks (of suitable capacity) equipped through ground glass joints with a dropping funnel, a mercury sealed stirrer and a reflux condenser to which was attached a drying tube.

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[10] Hauser and Walker, THIS JOURNAL, **69**, 295 (1947).

[11] This half acid ester should be about as unstable as diphenylmalonic acid which is unknown in the free state; see Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1943, p. 1033.

[12] Arnold, Bank and Liggett, THIS JOURNAL, **63**, 3444 (1941); Arnold and Liggett, *ibid.*, **64**, 2875 (1942). See also, Arnold and Liggett, *ibid.*, **67**, 337 (1945).

[13] Fuson, Bottorf and Speck *ibid.*, **64**, 1450 (1942)) found that with methyl, butyl or benzyl mesitoate in refluxing *n*-butyl ether Grignards produce methyl, butyl or benzyl halide instead of the alkylation product.

[14] Fieser and Heymann, THIS JOURNAL, **64**, 376 (1942).

[15] Although *t*-butyl halides exhibit β-elimination relatively readily, *t*-butyl benzoate has failed to exhibit this type of reaction with phenylmagnesium bromide to form isobutylene; instead, the carbonyl carbon reaction occurred to form triphenylcarbinol (unpublished results of F. C. Frostick and Erwin Baumgarten in this Laboratory).

[16] See Waters, "Chemistry of Free Radicals," Oxford University Press, London, 1946, pp. 211–213.

[17] Stadnikoff, *Ber.*, **47**, 2135 (1914).

[18] See Kharasch and Fuchs, THIS JOURNAL, **65**, 504 (1943).

[19] Microanalyses are by Oakwold Laboratories, Alexandria, Va.

[20] Yost and Hauser, THIS JOURNAL, **69**, 2325 (1947).

[21] Gomberg and Davis, *Ber.*, **36**, 3926 (1903).

[22] See Fuson, Corse and McKeever, THIS JOURNAL, **61**, 2010 (1939).

Ethyl Diphenylacetate with Isopropylmagnesium Bromide and Benzoyl Chloride.—To 143 ml. of the stirred ethyl ether solution containing 0.073 moles of isopropylmagnesium bromide was added 17.5 g. (0.073 mole) of ethyl diphenylacetate in 100 ml. of dry ether. Some gas was evolved. On stirring and refluxing for two days the solution became yellow and deposited a few crystals on the sides of the flask. Benzoyl chloride (14 g., 0.1 mole) was then added and the stirring continued for one-half hour. The mixture was decomposed with hydrochloric acid and crushed ice and the ether phase washed with water, dried and the solvent distilled. The brown oily residue was refluxed with 60 ml. of 47% hydriodic acid and 30 ml. of glacial acetic acid for three hours (to hydrolyze the benzoyl chloride and original ester but not the β-keto ester).[20] The resulting mixture was shaken with ether and the ether phase extracted with 2 *M* sodium hydroxide, dried and the solvent distilled. The white crystalline residue was recrystallized from 95% ethanol yielding 3.5 g. (14%) of ethyl benzoyldiphenylacetate, melting at 146° (and at 147° when mixed with an authentic sample,[20] m. p. 148°). Some (5 g., 29%) of ethyl diphenylacetate (m. p. 57°) was recovered from the ethanol filtrate; no attempt was made to recover the diphenylacetic acid that was undoubtedly present in the alkaline extract. The self-condensation product of the ester was not found.

A blank experiment with ethyl diphenylacetate and benzoyl chloride in ether yielded no ethyl benzoyldiphenylacetate. Some (30%) of the original ester was recovered; most of it was probably hydrolyzed in the hydriodic-acetic acid treatment.

In an attempt to effect carbonation the ether solution of equivalents of the Grignard and ester, after stirring and refluxing for two hours, was poured onto excess Dry Ice but no ethyl hydrogen diphenylmalonate was found; most (83%) of the original ester was recovered.

Triphenylmethyl Benzoate with Methylmagnesium Iodide.—To the stirred reagent from 13.5 g. (0.098 mole) of methyl iodide and 2.4 g. (0.098 g. at.) of magnesium in 400 ml. of ethyl ether, was added 6.0 g. (0.015 mole) of triphenylmethyl benzoate (partly as a suspension) in 350 ml. of dry ether. The resulting solution was stirred and refluxed for eight hours (producing a precipitate) and decomposed with ice and acid. The ether phase was extracted with sodium bicarbonate solution, dried and the solvent distilled. The residue (3.8 g.) melted at 65–75°. Recrystallization from 95% ethanol yielded 2.3 g. (45%) of α,α,α-triphenylethane, m. p. 93–94.5° (reported m. p. 93.8–95°).[14] Acidification of the bicarbonate extract yielded 1 g. (85%) of benzoic acid, m. p. 121°.

When triphenylmethyl benzoate was treated with excess diethylamino-magnesium bromide in ether[10] or with potassium amide in liquid ammonia, amines appeared to be formed but their hydrochlorides soon decomposed.

α,β-Diphenylethyl Mesitoate with Grignards. (A). With Phenyl-magnesium Bromide.—Since 75% of the ester was recovered when it was refluxed with the Grignard in ethyl ether for one hour and then allowed to stand overnight, the reaction was carried out in refluxing *n*-butyl ether (b. p. 142–143°). It was first shown that the ester may be refluxed alone in *n*-butyl ether for four hours and most (89%) of it recovered unchanged.

To 100 ml. of the stirred *n*-butyl ether solution containing 0.1 mole of phenylmagnesium bromide (prepared from an ethyl ether solution of the reagent by adding the butyl ether in an atmosphere of nitrogen and distilling off the ethyl ether) was added 13 g. (0.05 mole) of α,β-diphenylethyl mesitoate in 100 ml. of butyl ether. The mixture was stirred and refluxed for four hours and then hydrolyzed with ice and acid. The ether phase was extracted with bicarbonate, washed with water, dried and the solvent distilled. The oily residue on recrystallization from ethanol yielded 5.5 g. (68%) of *trans*-stilbene, m. p. and mixed m. p. 124°. From the ethanol filtrate there was obtained 1.1 g. (13%) of *cis*-stilbene, b. p. 148° (14 mm.) (reported b. p. 148–9° (17 mm.), 145° (13 mm.)).[23] The *trans*- and *cis*-stilbene gave the same dibromide, m. p. 237°.[24] Acidification of the bicarbonate extract yielded 7.3 g. (90%) of mesitoic acid, m. p. 151°.

When the reaction was carried out in the presence of 3 mole per cent. of anhydrous cobaltous chloride[18] (which was first refluxed with the Grignard before adding the ester) the yields of stilbene and mesitoic acid were only 38–40% but other products were not found.

(B) With Methylmagnesium Iodide.—The reaction of 35 ml. of a *n*-butyl ether solution containing 0.045 mole of methylmagnesium iodide (prepared in the butyl ether) with 5 g. (0.02 mole) of α,β-diphenylethyl mesitoate in 100 ml. of butyl ether was carried out as in (**A**). The residue obtained on distilling the solvent consisted of 2 g. of yellow solid from which two products were isolated by fractional crystallization from 95% ethanol. The more soluble substance (1.0 g., 30%) was *trans*-stilbene (m. p. and mixed m. p. 124°). The less soluble substance (0.3 g., 9%) was 1,2,3,4-tetraphenylbutane, m. p. 177–179°,[25] which after treatment with chromic anhydride in glacial acetic acid for five hours was recovered unchanged.

Anal. Calcd. for $C_{28}H_{26}$: C, 92.85; H, 7.18. Found: C, 92.52; H, 7.21.

Acidification of the bicarbonate extract gave 2.6 g. (78%) of mesitoic acid, m. p. 152°.

When the reaction was carried out in the presence of 3 mole per cent. of anhydrous cobaltous chloride[18] the yield of 1,2,3,4-tetraphenylbutane (m. p. 178°) was increased to 16%, a 40% yield of mesitoic acid was obtained but no stilbene or dibenzyl was found. Some (25%) of the original ester was recovered.

(C) With Ethylmagnesium Bromide.—The reaction of 22 ml. of a *n*-butyl ether solution containing 0.04 mole of ethylmagnesium bromide (prepared in the butyl ether) with 6.8 g. (0.028 mole) of α,β-diphenylethyl mesitoate in 100 ml. of butyl ether was carried out as in (**A**). The residue obtained on distillation of the solvent consisted of 2.5 g. of yellow solid from which was isolated 0.3 g. (8%) of 1,2,3,4-tetraphenylbutane (m. p. 178°) and 1.5 g. (45%) of a mixture of *cis*- and *trans*-stilbene (in approximately equal proportions) each of which was converted to the dibromide (m. p. 237°).[24] A 76% yield of mesitoic acid, m. p. 151°, was obtained.

Summary

1. Any of four positions of a carboxylic ester may react with the Grignard reagent. Reaction at one of these, the β-hydrogen in the alkoxy portion of an ester, has been realized for the first time. New examples of reactions at two other positions have also been described.

2. The influence of structure on the four courses of reaction and mechanisms have been considered.

3. Dimerization of the alkyl group in the alkoxy portion of an ester (apparently by a radical mechanism) has been realized.

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(23) Ref. 11, Vol. III, 1938, p. 640.

(24) Huntress and Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 514.

(25) Smith and Hoehn, THIS JOURNAL, **63**, 1184 (1941).