[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

Mechanisms of Grignard Reactions. I. Addition to Acid Halides. Metallic Halides as Lewis Acids[1]

BY ROBERT T. MORRISON AND MARVIN WISHMAN[2]

RECEIVED SEPTEMBER 15, 1953

It is proposed that addition of Grignard reagents to acid halides involves attack on a Grignard–acid halide complex by a second molecule of Grignard reagent; by acting as strong Lewis acids certain metallic halides can take the place of Grignard reagent in this complex and thus powerfully catalyze the reaction. These proposals account for the previously reported effects of order of mixing and of certain metallic halides on the reaction between mesitoyl chloride and methylmagnesium iodide, and are supported by results obtained when this reaction is carried out in the presence of well-recognized Lewis acids.

The fact that the order of reactivity of acid halides toward Grignard reagents is fluoride > chloride > bromide, rather than the reverse order characteristic of halide displacement reactions, led Entemann and Johnson[3] to propose that this reaction involves an initial addition to the carbonyl group, followed by elimination of magnesium halide. Fuson and Corse[4] have shown that in the case of mesitoyl chloride and methylmagnesium iodide reaction can proceed by two paths: (1) the expected *addition*, to form acetomesitylene (I), and (2) *dimerization*, to form mesitil (II) and ethane. Introduction of acid halide into Grignard reagent results exclusively in addition; inverse order of mixing favors dimerization. Kharasch, Morrison and Urry[5] found that traces of cuprous, manganous, or ferric chloride cause the reaction to proceed almost exclusively by addition even when inverse order of mixing is used; small amounts of cobaltous chloride favor dimerization (see Table I). They suggested that addition proceeds by some ionic mechanism whereas dimerization involves a free radical sequence (equations 4 to 6, M = Mg, X = I). The effect of cobaltous chloride was ascribed to the formation of an intermediate organocobalt compound which undergoes homolysis more readily than does the Grignard reagent (equations 3 to 6, M = Co, X = Cl).[6]

$$\mathrm{MesCOCl} + \mathrm{CH_3MgI} \longrightarrow \underset{\mathrm{I}}{\mathrm{MesCOCH_3}} + \mathrm{MgICl} \quad (1)$$

$$2\mathrm{MesCOCl} + 2\mathrm{CH_3MgI} \longrightarrow \underset{\mathrm{II}}{\mathrm{MesCOCOMes}} + \mathrm{C_2H_6} + 2\mathrm{MgICl} \quad (2)$$

$$\mathrm{Mes} = 2,4,6\text{-}(\mathrm{CH_3})_3\mathrm{C_6H_2}\text{-}$$

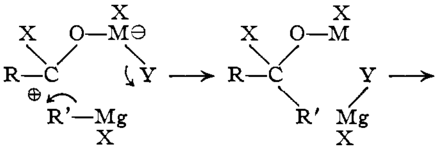
$$\mathrm{CH_3MgI} + \mathrm{MX_2} \rightleftarrows \mathrm{CH_3MX} + \mathrm{MgIX} \quad (3)$$

$$\mathrm{CH_3MX} \longrightarrow \mathrm{CH_3}\cdot + \mathrm{MX}\cdot \quad (4)$$

$$\mathrm{MX}\cdot + \mathrm{MesCOCl} \longrightarrow \mathrm{MXCl} + \mathrm{MesCO}\cdot \quad (5)$$

$$2\mathrm{MesCO}\cdot \longrightarrow \mathrm{MesCOCOMes} \quad (6)$$

To account for the effects of (a) order of mixing and (b) of cuprous, manganous and ferric chlorides described above, we propose the following mechanism for the addition of Grignard reagents to acid halides, and suggest a new catalytic role for metallic halides in Grignard reactions. Addition involves attack on a Grignard–acid halide complex by a second molecule of Grignard reagent, possibly *via* the cyclic transition state[7] shown in equation 7 (Y = R′, M = Mg). Other Lewis acids can take the place of Grignard reagent in the complex; a stronger Lewis acid permits a faster reaction by forming a higher concentration of a more reactive complex (*i.e.*, one with greater polarization of the carbonyl bond). When mesitoyl chloride is introduced into methylmagnesium iodide, there is always present in the reaction mixture a large excess of Lewis acid (Grignard reagent and/or the magnesium halide formed by the reaction); under these conditions, addition is much faster than dimerization.[8] During inverse order of mixing the concentration of Grignard reagent is always low,[9] but that of magnesium halide steadily increases; addition is slow at the beginning but rapid by the end of the reaction, and both products are formed. Cuprous, manganous and ferric chlorides, even at very low concentrations, powerfully catalyze addition by acting as very strong Lewis acids.



$$\mathrm{RR'CO} + \mathrm{YMgX} + \mathrm{MX_2} \quad (7)$$

(X = halogen
Y = R′ *or* halogen
M = Mg or other metal)

In agreement with this mechanism, the presence of certain well-recognized Lewis acids was found to increase the proportion of acetomesitylene in the reaction product, as shown in Table I. No exact comparison of catalytic activity can be made, because of the incomplete dissolution of some of the Lewis acids, and because of the formation of two layers[10] (each containing unknown concentrations of the reagents) in several instances where gross amounts of Lewis acids were used. However, it is

---

(1) Presented at the Los Angeles Meeting of the American Chemical Society, March, 1953.

(2) Based on a dissertation submitted by Marvin Wishman to the Graduate School of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) C. E. Entemann and J. R. Johnson, THIS JOURNAL, **55**, 2900 (1933).

(4) R. C. Fuson and J. Corse, *ibid.*, **60**, 2063 (1938).

(5) M. S. Kharasch, R. T. Morrison and W. H. Urry, *ibid.*, **66**, 368 (1944).

(6) This effect is consistent with results obtained in the extensive studies by Kharasch and his co-workers on the catalytic effect of this metallic halide on Grignard reactions, for a leading reference, see M. S. Kharasch and C. F. Fuchs, *ibid.*, **65**, 504 (1943).

(7) This mechanism is analogous to that suggested by C. G. Swain and H. B. Boyles, (*ibid.*, **73**, 870 (1951)) for the addition of Grignard reagents to ketones.

(8) It is assumed that Lewis acids do not catalyze dimerization, this is a reasonable assumption in view of the probable free radical nature of this reaction.

(9) R. T. Morrison and D. Wagner (unpublished work) found that even at −78° this reaction is too fast to be measured.

(10) The formation of layers is consistent with complex formation.

TABLE I

EFFECT OF LEWIS ACIDS ON REACTION BETWEEN MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE[a]

Catalyst	Molar ratio catalyst[b]	Yield based upon mesitoyl chloride, %		Catalyst	Molar ratio catalyst[b]	Yield based upon mesitoyl chloride, %	
		Acetomesitylene	Mesitil			Acetomesitylene	Mesitil
None[c,d]	..	83	0	$SnCl_4$	0.83	3	0[g,h]
None	..	28	59	$ZnCl_2$	.78	55	19[i]
MgI_2	0.78	55	34	$AlCl_3$	.93	18	14[g,j]
$MgBr_2$	0.78	57	33	$MnCl_2$[d]	.01	88	1
$MgBr_2$	2.25	85	5	$MnCl_2$[d]	.001	75	5
BF_3	0.26	84	0	$FeCl_3$[d]	.01	85	77
BF_3	0.84	50	0[e]	$CuCl$[d]	.01	85	2
BF_3	1.22	5	0[f]	$CoCl_2$[d]	.12	17	63
$SnCl_4$	0.05	8	76	$NiCl_2$	.01	10	75
$SnCl_4$	0.54	63	17[g]				

[a] Methylmagnesium iodide added to mesitoyl chloride plus catalyst unless otherwise specified. [b] Moles catalyst per mole mesitoyl chloride. [c] Mesitoyl chloride added to methylmagnesium iodide. [d] Data from reference 5. [e] 32% mesitoic acid, 4% ethyl mesitoate isolated. [f] 73% mesitoic acid, 10% ethyl mesitoate isolated. [g] Tar also formed. [h] 71% mesitoic acid, 7% ethyl mesitoate isolated. [i] 14% mesitoic acid isolated. [j] 45% mesitoic acid isolated.

evident that cuprous, manganous and ferric chlorides are much more effective than the other catalysts,[11] suggesting that some factor in addition to Lewis acidity is involved, possibly the steric requirements of the cyclic transition state proposed. Nickelous chloride and small amounts of stannic chloride, like cobaltous chloride, favor dimerization.

The possibility that the addition catalysts exert their effect through the formation of intermediate organometallic compounds seems quite unlikely since the organometallic compounds corresponding to the catalysts used are known to be *less* reactive than the Grignard reagent toward the carbonyl group,[12] and in the case of manganese and iron, *more* reactive with respect to free radical reactions. It is significant that magnesium iodide, which cannot give rise to a new organometallic compound, shows an effect comparable to the other Lewis acids. While there is no doubt that exchange 3 occurs, any organometallic compounds formed would be expected to act as Lewis acids, although somewhat weaker than the parent halides. The effect of magnesium bromide might be ascribed to the formation of methylmagnesium bromide (by reaction 3, $M = Mg$, $X = Br$), which is known[5] to react exclusively by addition; while this explanation cannot be ruled out, it also seems unlikely in view of the almost equal effects of the two magnesium halides.

Table I shows that the yield of acetomesitylene becomes very small at high molar ratios of boron trifluoride or stannic chloride; much of the acid chloride fails to react[13] and small amounts of ethyl mesitoate are isolated.[14] While no attempt was made to find an optimum ratio for the other Lewis acids, the isolation of mesitoic acid from the reactions involving aluminum chloride and zinc chloride indicates that the ratios used were above the optimum. Lewis acids at high ratios may hinder reaction by interaction with the Grignard reagent (reaction 3) to form less reactive organometallic compounds, or by interaction with the acid halide to form unreactive complexes; work to elucidate this point is in progress.

The factors determining which role—Lewis acid or free radical generator—a particular halide is likely to play are being investigated. It is already evident that this role can vary from reaction to reaction and even, with change in molar ratio, within the same reaction. Whereas cobaltous, nickelous, ferric and manganous chlorides all catalyze the free radical conversion of ketones to pinacols,[15] the latter two act as Lewis acids in the present reaction. At a low molar ratio stannic chloride catalyzes dimerization because of the homolytic instability of methyltin compounds; at a high molar ratio its acidity masks the free radical catalysis.

Work in this Laboratory indicates that other cases of metallic halide catalysis of Grignard reactions reported in the literature may also be attributed to the acidic nature of the halides. For example, Lewis acids show[16] the same effect as that reported for cuprous chloride on the reaction between trimethylacetyl chloride and *t*-butylmagnesium chloride (originally attributed to free radical formation[17]), and on the reaction between benzonitrile and phenylmagnesium bromide.[18] As in the present investigation, these results throw light on the mechanisms of the uncatalyzed reactions.

Experimental

Materials.—Dow sublimed magnesium, which has been shown[19] to be practically free of all heavy metals except lead, was used in the preparation of the Grignard reagent and the magnesium halides. Methyl iodide (reagent grade) was shaken with mercury and distilled just before use. Boron trifluoride etherate (The Matheson Co., technical grade) and stannic chloride (Fisher Scientific Co., reagent grade) were distilled just before use, and middle fractions taken. The following anhydrous reagent grade materials were used without further treatment: aluminum chloride (Baker and Adamson, sublimed), ferric chloride and zinc chloride (both Fisher Scientific Co.). Anhydrous nickelous chloride was pre-

---

(11) Boron trifluoride and aluminum chloride had no effect at molar ratios of 0.01.

(12) This is true for compounds of zinc, aluminum, tin, manganese, copper and boron. Little is known concerning the reactivity of organoiron compounds in this sort of reaction. See H. Gilman, "Organic Chemistry, An Advanced Treatise," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 542–566.

(13) That recovered mesitoic acid actually arises from unreacted acid chloride, and not from Lewis acid-catalyzed cleavage of acetomesitylene (*cf.* B. M. Perfetti and R. Levine, THIS JOURNAL, **75**, 626 (1953)) or ethyl mesitoate, is shown by the fact that when acetomesitylene or ethyl mesitoate was treated with boron trifluoride and methylmagnesium iodide under the conditions of the reaction, no mesitoic acid was obtained, and the ketone or ester was recovered.

(14) This Lewis acid-catalyzed reaction of acid halides with ethers is well-known; see, for example, R. L. Burwell, Jr., L. N. Elkin and L. G. Maury, *ibid.*, **73**, 2428 (1951).

(15) (a) M. S. Kharasch, S. C. Kleiger, J. A. Martin and F. R. Mayo, *ibid.*, **63**, 2305 (1941); (b) M. S. Kharasch and P. O. Tawney, *ibid.*, **63**, 2308 (1941); (c) M. S. Kharasch and F. L. Lambert, *ibid.*, **63**, 2315 (1941).

(16) R. T. Morrison and A. Koroscil, paper presented before the Meeting-in-Miniature of the Metropolitan-Long Island Subsection (New York Section) of the American Chemical Society, February 10, 1953; R. T. Morrison and A. Passannante, unpublished work.

(17) N. C. Cook and W. C. Percival, THIS JOURNAL, **71**, 4141 (1949). In a recent paper (*ibid.*, **75**, 3731 (1953)) W. C. Percival, R. B. Wagner and N. C. Cook have suggested that cuprous chloride is here acting as a Lewis acid.

(18) H. Gilman, E. L. St. John, N. B. St. John and M. Lichtenwalter, *Rec. trav. chim.*, **55**, 577 (1946).

(19) Reference 15a. This fact was confirmed by the manufacturer's analysis of the particular lot used.

pared by heating the hexahydrate (Baker's Analyzed, special, low in cobalt) at 210° in a stream of dry hydrogen chloride.

Magnesium bromide and magnesium iodide were prepared in ether solution from the elements by the method of Menschutkin.[20] The halide was used *in situ* in the experiment involving magnesium bromide at a molar ratio of 2.25. In all other cases the magnesium halide solutions were filtered and stored as described below for the Grignard reagent; the solutions were analyzed by titration with standard silver nitrate solution using dichlorofluorescein as an indicator.[21]

Mesitoyl chloride,[22] b.p. 125–126° (30 mm.), was stored in 0.1-mole portions in sealed ampules which were opened just before use.

Methylmagnesium iodide was prepared, filtered, stored and analyzed as described previously.[5]

Acetomesitylene, b.p. 118–120° (18 mm.), was prepared in 96% yield by the reaction of acetic anhydride with excess mesitylene in the presence of anhydrous aluminum chloride. Redistillation through a 45 cm. × 1.2 cm. column packed with Helipaks yielded material, b.p. 134.5–135° (31 mm.), n^{20}D 1.5158.

Ethyl mesitoate[23] was distilled through the above column, b.p. 143° (27 mm.), n^{20}D 1.5008.

Reaction of Methylmagnesium Iodide with Mesitoyl Chloride.—The reactions were carried out under a dry nitrogen atmosphere in a 1-l. three-neck flask equipped in the usual manner. Mesitoyl chloride (0.1 mole), diluted to 380 ml. with ether, was placed in the flask and cooled in an ice-bath; the catalyst was then added and the mixture stirred for one-half hour. Two liquid phases formed when the magnesium halides and zinc chloride were used; stannic chloride caused the separation of a solid phase. Methylmagnesium iodide (0.29 mole), diluted to 290 ml., was added during 1.5 hours; the same rates of addition and stirring were maintained in all experiments. After addition was complete the ice-bath was removed, the mixture stirred for an additional hour, and allowed to stand overnight. The reaction mixture was then poured onto ice and hydrochloric acid, the layers separated, and the aqueous layer extracted with ether; the aqueous layer was then rejected. The combined ether layers were extracted with aqueous sodium bisulfite and then with successive portions of aqueous sodium carbonate until all mesitoic acid had been removed. The combined aqueous extracts were acidified with hydrochloric acid and the mesitoic acid collected on a filter, dried and weighed. The ether solution was dried over sodium sulfate and the ether removed on the steam-bath; the residue was distilled at reduced pressure from a 125-ml. Claisen flask. The liquid product distilled cleanly within a five degree range which varied from 115–120° (15 mm.) for pure acetomesitylene to 125–130° (15 mm.) for pure ethyl mesitoate. This distillate was analyzed by comparing its refractive index with those of a series of synthetic mixtures of ketone and ester. Any mesitil remained in the Claisen flask, and was taken up in a small amount of 85% ethanol, collected on a filter, dried and weighed. These yellow crystals, m.p. 99–103°, could be recrystallized from petroleum ether to yield material of m.p. 119–120°.

NEW YORK, N. Y.

---

[20] B. N. Menschutkin, *Z. anorg. Chem.*, **49**, 34 (1906).

[21] I. M. Kolthoff and E. B. Sandell, "Textbook of Inorganic Quantitative Analysis," The Macmillan Co., New York, N. Y., 1943, p. 571.

[22] R. P. Barnes, *Org. Syntheses*, **21**, 77 (1941).

[23] M. S. Newman, THIS JOURNAL, **63**, 2431 (1941).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INSTITUTE OF POLYMER RESEARCH, POLYTECHNIC INSTITUTE OF BROOKLYN]

Monomer Synthesis.[1] Synthesis of a Vinyltriazine and a Study of the Reaction of Phenylbiguanide with Acrylate Esters

BY C. G. OVERBERGER AND SEYMOUR L. SHAPIRO[2]

RECEIVED AUGUST 27, 1953

Reaction of phenylbiguanide with acrylyl chloride in an alkaline aqueous acetonitrile solution gave I, $X = CH{=}CH_2$. The structure was determined by hydrogenation to give the known ethyl derivative, I, $X = C_2H_5$. The products of the reaction of phenylbiguanide with methyl, ethyl and octyl acrylates with alkoxide catalysts have been determined. Derivatives of I, $X = CH_2{-}CH_2OR$, have been obtained and it has been demonstrated that the β-alkoxy group is derived from the alkoxide catalyst. Reaction of methyl β-methoxypropionate and ethyl β-ethoxypropionate with phenylbiguanide gave the corresponding alkoxy compounds, I, $X = CH_2{-}CH_2OR$.

We have initiated a study of the polymerization of specific types of vinyl monomers within the body, particularly within the cell. These monomers are of the vinylpyrimidine or vinyltriazine type containing an amino or substituted amino group. This paper describes the preparation of a vinyltriazine and the course of the reaction and products from the reaction of phenylbiguanide with methyl, ethyl and octyl acrylates with alkoxide catalysts. Reactions of phenylbiguanide with β-alkoxypropionic acid esters with alkoxide catalysts are also described.

We have been able to prepare I, $X = CH{=}CH_2$, by the reaction of phenylbiguanide and acrylyl chloride in an alkaline aqueous acetonitrile solution. Quantitative hydrogenation gave the ethyl derivative, $X = C_2H_5$, identical with a known sample (infrared and physical properties). Infrared spectra indicated the disappearance of the double bond frequency at 10.15 μ and 6.1 μ[3] after hydrogenation.

As an alternate route to I, $X = CH{=}CH_2$, we investigated the reaction of I, $R = C_2H_5$, with N-bromosuccinimide and benzoyl peroxide according to the directions of Wenner[4] who prepared *o,o'*-bis-(bromomethyl)-biphenyl in this way. Miller and co-workers[5] have reported that phenylsuccinic anhydride was converted to phenylmaleic anhydride in 57–64% yield by a similar reaction. When I, $X = C_2H_5$, was treated under the above condi-

---

[1] This is the eighth in a series of articles concerned with the synthesis and polymerization of vinyl monomers. For the preceding paper, see S. L. Shapiro and C. G. Overberger, THIS JOURNAL, **76**, 97 (1954).

[2] A portion of a thesis by Seymour L. Shapiro, submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[3] F. C. Shaefer, J. R. Dudley and J. T. Thurston, THIS JOURNAL, **73**, 3004 (1951), have reported double bond frequencies for 2-N-vinylanilino-4-hydroxy-6-ethoxy-*s*-triazine at 3090 cm.$^{-1}$ (3.22μ) 1620 cm.$^{-1}$ (6.17μ) and 905–1000 cm.$^{-1}$ (10–11μ).

[4] W. Wenner, *J. Org. Chem.*, **17**, 523 (1952).

[5] L. E. Miller, H. B. Staley and D. J. Mann, THIS JOURNAL, **71**, 374 (1949).