Mixed Carboxylic Anhydrides in the Grignard Reaction. I. Synthesis of Aldehydes from Formic Acetic Anhydride[1]

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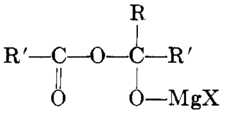
Reactions of formic acetic anhydride with Grignard reagents at −70° revealed a new method of aldehyde synthesis. Aldehydes predominated strongly over ketones in the products obtained with five aromatic Grignard reagents, less strongly with aliphatic ones. Initial study of the influences exerted by the structures of the reagents, and by reaction conditions, on the proportions of the products, indicated that both electronic and steric effects were significant.

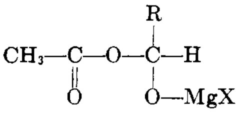
Newman and his co-workers[2] found that, when simple carboxylic anhydrides reacted with Grignard reagents at about −70°, good yields of ketones were obtained, with little or no appearance of the tertiary alcohols which, theoretically, might have been formed by further reaction with additional Grignard reagent. They attributed the suppression of such secondary reactions to the stabilities and the diminished solubilities, at low temperatures, of the complexes (see following)



$$\mathrm{R'{-}\underset{\underset{O}{\|}}{C}{-}O{-}\overset{\overset{R}{|}}{\underset{\underset{O{-}MgX}{|}}{C}}{-}R'}$$

formed by addition of one molecule of RMgX to one of the carbonyl groups of $(R'\text{-}CO)_2O$. Grignard reactions with a number of unsymmetrical cyclic anhydrides also have been reported.[3] The use of mixed carboxylic anhydrides in such reactions, however, does not appear to have received earlier attention. The present paper describes a study of the behavior of formic acetic anhydride with ten Grignard reagents at low temperatures; a later paper will deal with a similar study of higher mixed acetic anhydrides.

Formic acetic anhydride was of unique interest because in every instance one of the two possible carbonyl products of its primary reaction was an aldehyde. If this could actually be obtained, and if it could be made to predominate over the accompanying methyl ketone, the process might be regarded as a new method of aldehyde synthesis.[4] Recent attempts to prepare aldehydes with formic acetic anhydride by means of the Friedel–Crafts reaction were completely unsuccessful,[5] the only carbonyl compounds produced by that method being methyl ketones; but the probable mechanisms of the two reactions differ so fundamentally that this did not necessarily foreshadow a similar failure with the Grignard reaction. Success appeared to depend principally on two things: a preferential addition of the Grignard reagent to the formyl group rather than to the acetyl group, and a degree of stability of the complex



$$\mathrm{CH_3{-}\underset{\underset{O}{\|}}{C}{-}O{-}\overset{\overset{R}{|}}{\underset{\underset{O{-}MgX}{|}}{C}}{-}H}$$

at least comparable to the stabilities of other such complexes.

Table I shows the results obtained with aromatic Grignard reagents. The mole % of aldehydes and ketones in the total carbonyl products, determined by gas chromatography, are considered to be accurate. The estimated quantities are approximations, calculated from the weight ratios and from the weights of crude mixtures of both products.

Aldehydes predominated decidedly over ketones in all runs in which the solvent was ethyl ether. A small increase in both mole % and quantity of the aldehyde resulted when an excess of anhydride was used with phenylmagnesium bromide, the highest estimated quantities in any runs being obtained under such circumstances, but the *p*-tolyl Grignard reagent did not duplicate these increases.

Predominance of aldehydes over ketones may be attributed to the electronic and steric differences between hydrogen and methyl, which favored both the nucleophilic attack by R^- on the formyl carbon, and the stability of the resultant complex. The aldehyde–ketone ratio dropped sharply when tetrahydrofuran replaced ethyl ether as solvent, but without significant change in total quantity of carbonyl products, possibly indicating a substantial role for the steric factor.

An increased bias in favor of aldehydes was observed when phenyl was replaced, in the Grignard reagents, by the more nucleophilic tolyl groups. Presumably the drop in total quantity of carbonyl products, when the *o*-tolyl reagent was used, was caused by the steric obstacle placed by this group in the path of the formation of either of the two possible complexes with the anhydride. The diminished quantities of both products when *m*-chlorophenylmagnesium bromide was used, on the other hand, may be attributed at least partly to the weaker nucleophilic character of *m*-chlorophenyl, though this does not explain the failure to obtain more than a trace of ketone. The very low yields of both carbonyl products when the reaction was performed at 0° showed that a temperature much lower than this was as necessary for a successful aldehyde synthesis as it was for the ketone syntheses reported by Newman. The ratio of aldehyde to ketone was almost the same at 0° as in the runs made at −70°, but the quantities of both products were so small that this might be partly coincidence, particularly since the 0° runs were less consistent than the others.

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[1] This paper was abstracted from part of the Ph.D. thesis of K. P. K., Jr., Louisiana State University, May, 1962.

[2] (a) M. S. Newman and W. T. Booth, Jr., *J. Am. Chem. Soc.*, **67**, 154 (1945); (b) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

[3] (a) M. S. Newman and C. D. McCleary, *J. Am. Chem. Soc.*, **63**, 1542 (1941); (b) M. S. Newman and C. W. Muth, *ibid.*, **72**, 5191 (1950); (c) M. S. Newman and P. G. Scheurer, *ibid.*, **78**, 5004 (1956).

[4] See L. J. Smith and J. Nichols, *J. Org. Chem.*, **6**, 489 (1941), for a survey of other ways of preparing aldehydes by use of Grignard reagents; see also A. Sisti, J. Burgmaster, and M. Fudim, *ibid.*, **27**, 279 (1962).

[5] (a) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **82**, 2380 (1960); (b) W. R. Edwards, Jr., and E. C. Sibille, *J. Org. Chem.*, **28**, 674 (1963).

TABLE I

RELATIVE AMOUNTS OF ALDEHYDES AND KETONES FROM FORMIC ACETIC ANHYDRIDE AND AROMATIC GRIGNARD REAGENTS, RMgBr[a]

R	Solvent	Molar ratio, anhydride–RMgBr	Temp., °C.	Mole % of each component in total carbonyl product		Estimated quantities, % of theory	
				Aldehyde	Ketone	Aldehyde	Ketone
Phenyl	Ether	1:1	−70	82.9	17.1	35.8	7.4
o-Tolyl	Ether	1:1	−70	97.1	2.9	24.1	0.7
m-Tolyl	Ether	1:1	−70	97.1	2.9	33.3	1.0
p-Tolyl	Ether	1:1	−70	97.7	2.3	34.5	0.8
m-Chlorophenyl	Ether	1:1	−70	100(−)	0(+)	13.8	Trace
Phenyl	THF	1:1	−70	53.5	46.5	23.8	20.6
Phenyl	Ether	2:1	−70	85.2	14.8	39.1	6.8
p-Tolyl[b]	Ether	2:1	−70	97.8	2.2	33.6	0.8
Phenyl	Ether	1:1	0	84.0	16.0	7.0	1.3

[a] Figures are averages of three or more reasonably agreeing runs, except where otherwise noted. Usual quantity of anhydride in each run was approximately 0.13 mole. [b] Averages of two runs.

TABLE II

RELATIVE AMOUNTS OF ALDEHYDES, KETONES, AND ALCOHOLS FROM FORMIC ACETIC ANHYDRIDE AND ALIPHATIC GRIGNARD REAGENTS, RMgX[a]

R	Mole % of each component in total carbonyl and hydroxyl products				Mole %, total formyl product[b]	Mole %, total acetyl product[c]	Estimated quantities, % of theory	
	Aldehyde	Ketone	*sec*-Alcohol	*t*-Alcohol			Aldehyde	Ketone
Ethyl	0(+)	0(+)	53.1	46.9	53.1	46.9	Trace	Trace
Propyl	28.6	15.9	26.1	29.4	54.7	45.3	9.0	5.0
n-Butyl	48.0	27.6	7.8	16.6	55.8	44.2	26.8	15.4
n-Butyl[d]	36.5	21.6	17.9	24.0	54.4	45.6	21.9	13.0
Isobutyl	59.7	33.4	4.6	2.3	64.3	35.7	34.1	19.2

[a] Temp., −70°; solvent, ethyl ether; equimolar proportions of anhydride and Grignard reagent; quantity of each reagent, about 0.13 mole. Except where otherwise noted, X was bromine, and figures are averages of three or more runs. [b] Sum of mole % of aldehyde and secondary alcohol. [c] Sum of mole % of ketone and tertiary alcohol. [d] Grignard reagent was chloride instead of bromide; figures are averages of two runs.

There appeared to be little if any formation of alcohols by secondary reactions, when using aromatic Grignard reagents at −70°. No indication of methyldiphenylcarbinol was observed on the chromatogram of any run with phenylmagnesium bromide, though tests made with samples to which small amounts of this alcohol had been added showed that it would have been revealed if present. The authors were not able to detect diphenylcarbinol chromatographically, as it failed to show a recognizable peak; a small amount of it was isolated by distillation and recrystallization from the products of the 0° runs, but none could be isolated by similar procedure from any run made at −70°. The chromatograms of the products obtained from the tolylmagnesium bromides, and from *m*-chlorophenylmagnesium bromide, did not show any unidentified peaks which might have suggested the presence of alcoholic products of secondary reactions; but, since the chromatographic characteristics of these alcohols were not determined, the possibility that they may have been present, but undetected, cannot be excluded. However, the residues which should have contained any such alcohols, after distillation of the aromatic aldehydes and ketones, were very small in all runs made at −70°.

Table II shows the results of reactions of formic acetic anhydride with aliphatic Grignard reagents. In most of these there was substantial alcohol formation. Relative molar proportions of all four possible products (aldehydes, ketones, and secondary and tertiary alcohols) were determined chromatographically; the estimated quantities, as before, are approximations. In this table, the sum of the mole % of each aldehyde and of its corresponding secondary alcohol has been regarded as the true measure of the total initial attack of the Grignard reagent on the formyl carbon atom, and had been tabulated under "Mole %, total formyl product." Similarly "Mole %, total acetyl product," combining ketone and tertiary alcohol, is a measure of the entire initial attack on the acetyl carbon. The data in these two columns give further evidence of steric influences. The bias in favor of the combined products of formyl attack was small and nearly constant, increasing very slightly with increase in the size of R, as long as R was an unbranched alkyl group. It increased substantially with isobutyl, with its moderately greater steric potential, but still fell short of the pronounced bias in favor of the aldehyde which was observed whenever R was an aryl group and the solvent was ethyl ether.

Estimated quantities of both carbonyl products of the alkylmagnesium bromides increased in the order ethyl < propyl < *n*-butyl < isobutyl, while alcohols decreased, rather irregularly, in the same order. The extreme minuteness of the amounts of carbonyl products which were obtained from the ethyl and propyl reagents is not readily explained. It is possible that the complexes formed by the two smallest alkyl groups used in this work were much more soluble at −70° than the others, and were, therefore, more exposed to further attack by additional Grignard reagent; this is in harmony with Newman's theory[2] that low solubilities of the complexes were largely responsible for the good ketone yields which he and his co-workers obtained with simple anhydrides.

Butylmagnesium bromide and the analogous chloride gave almost identical ratios of total formyl product to total acetyl product, revealing an apparent indifference to the identity of the halogen in the initial attack. Alcohol production by secondary attack, however, was appreciably greater with the chloride. It may be significant that here again the secondary reaction increased with decrease in size of the Grignard reagent.

Although use of the reaction as a practical means of aldehyde synthesis seems at present to be somewhat remote, it is possible that further work with this or other mixed formic anhydrides may discover special situations in which, because of higher yields than those described here, or unsuitability of other methods, it might find such application. Tentatively, a relatively good yield appears most likely when the Grignard reagent is aromatic, when it possesses appreciable but not extreme hindering potential, and when its aryl group is distinctly nucleophilic.

A possible hazard accompanying the use of formic acetic anhydride was revealed when small samples of two different batches of it, stored under laboratory conditions in sealed glass tubes (one for 4 months, the other for about 1 week) were sent away for elemental analysis. The analyst[6] reported that both exploded violently as the tubes were opened. No similar behavior has been shown by unconfined formic acetic anhydride, or, with perhaps one exception,[7] by other mixed acetic anhydrides, either in the present work or in any earlier work with which the authors are familiar.

Experimental

Formic Acetic Anhydride.—This reagent was made by passing slightly more than the theoretical amount of ketene into reagent grade formic acid in an absorption vessel immersed in an ice–water bath.[8] The crude anhydride was subjected to suction (45 mm. at 0° for 10 min.) to remove excess ketene. It was then distilled at the same pressure, and the fraction collected at 44.5–46.5° was used immediately in a Grignard reaction. Results of a typical preparation were yield of anhydride, 39.4%; $n^{20}\text{D}$ 1.3882, lit.[9] $n^{20}\text{D}$ 1.3880; neut. equiv. 44.7 (calcd., 44.03). Fractional distillations of the anhydride were made with a vacuum-jacketed Vigreux-type column, 9 cm. high and 11 mm. in diameter. Similar columns of appropriate size were used for distillation of the products of the subsequent Grignard reactions.

Grignard Reaction.—Grignard reagents were made by methods similar to those outlined by Vogel,[10] and their strengths were determined by acid titration.[11] They were used, usually, within 1–2 hr.

In a typical run, a solution of about 0.13 mole of formic acetic anhydride, in 120 ml. of anhydrous ethyl ether or tetrahydrofuran, was placed in a 500-ml. round-bottomed flask equipped with stirrer, dropping funnel, and drying tubes. A temperature between −78° and −70° was maintained throughout the reaction by immersion in Dry Ice and acetone in a dewar flask. An equimolar quantity of Grignard reagent, in the same solvent as the anhydride, was added dropwise over a period of about 1 hr. The reaction was allowed to proceed, with continued cooling and stirring, for about 2 hr. after addition was complete. The reaction mixture was then allowed to warm to −10°, and hydrolyzed with saturated aqueous ammonium chloride. Separation of the organic phase, washing, extraction of aqueous phase and washings, and drying with anhydrous sodium sulfate were performed as described by Newman.[2] The combined ethereal solution was then concentrated, by distillation of ether, to a volume of 75–100 ml. Samples of this were analyzed by gas chromatography, to determine the relative proportions of aldehyde, methyl ketone, and (if present and measurable) secondary and tertiary alcohols. Reaction mixtures obtained from ethyl and propyl Grignard reagents were chromatographed both before and after distillation of ether, to ensure the detection of any volatile products.

Approximate estimates of the absolute quantities of aldehyde and ketone were then made, in most cases, by fractionally distilling the ethereal solutions at appropriate pressures, collecting the material which distilled over a range extending from slightly below the boiling point of the aldehyde to slightly above that of the ketone. This fraction was regarded as a crude mixture composed principally of the two carbonyl products, and the quantity of each one was calculated from the weight of the fraction, and from the ratio of the two which had been determined chromatographically. Corrections were made for any other component (such as unchanged halide) which could not be separated from the aldehyde–ketone mixture by distillation, and whose presence and quantity relative to aldehyde and ketone had been determined chromatographically. Estimated quantities of alcohols in Table II were calculated in a similar manner. In runs made with propylmagnesium bromide and isobutylmagnesium bromide, the total amount of aldehyde and ketone present in the reaction product was determined by the carbonyl titration method.[12] Because of the small quantities employed, complete recovery of the products was not attempted in the runs described here.

Most chromatographic measurements were made on a Beckman GC-2 gas chromatograph with a 6-ft. 20% silicon SF 96 on 30/60 Silocel column. This instrument did not give satisfactory resolution of unchanged *m*-chlorobromobenzene and the corresponding aldehyde; therefore, in runs involving the former, it was replaced by a Barber Colman IDS chromatograph Model 20 with a 200-ft. Apiezon L capillary column, and the high boiling material which would have clogged this column was removed by preliminary distillation. To validate identifications, and determinations of weight ratios, comparable runs were made with solutions (in ether or THF[13]) containing known amounts of authentic samples of the reaction products, including runs in which appropriate amounts of recognized impurities were also present. Materials used in these calibrations included all aldehydes, ketones, and aliphatic alcohols mentioned in the tables, and also methyldiphenylcarbinol.

Identifications of reaction products were based primarily on comparisons of their retention times with those of the authentic samples. In addition, relatively pure samples of those aldehydes, ketones, and alcohols which were formed in sufficient quantities were obtained by repeated fractional distillations of the crude mixtures from which their quantities had been calculated, and their identities were verified by determinations of boiling points, refractive indices, and melting points of derivatives. These were found to be in good agreement with values reported in the literature. Products which were further identified in this way included all aldehydes mentioned in the Tables except propanal; acetophenone, and all the aliphatic ketones except butanone; and diethyl- and dipropylcarbinols.

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(6) Galbraith Laboratories, Inc., Knoxville, Tenn.

(7) W. R. Edwards, Jr., and W. M. Henley [*J. Am. Chem. Soc.*, **75**, 3587 (1953)] reported an explosion during an attempt to prepare acetic oxalic anhydride from silver oxalate and acetyl chloride, undiluted, at room temperature.

(8) C. D. Hurd and A. S. Roe, *ibid.*, **61**, 3355 (1939).

(9) R. E. Dunbar and F. C. Garven, *ibid.*, **77**, 4161 (1955).

(10) A. Vogel, "Textbook of Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., London, 1956, pp. 257, 756.

(11) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923).

(12) W. M. Bryant and D. M. Smith, *ibid.*, **57**, 57 (1935).

(13) Tetrahydrofuran.