with ice and water, then acidified to Congo Red. The aqueous phase was separated and extracted with three 15-ml. portions of ether. The original organic phase and the extracts were washed with two 30-ml. portions of water and one 30-ml. portion of saturated sodium chloride solution. After the total extracts had been dried over anhydrous sodium sulfate, the volume was adjusted to 100 ml. and aliquots of this solution were used for gas chromatography as described below.

Analysis of reaction mixtures by gas chromatography. Chromatography was on silicone grease partitioning agent, prepared as previously described[14]; column, 1.5 m. × 8 mm. o.d. Pyrex glass; temperature 190–225°; helium flow rate, 85–90 ml./min.; pressure, 16–17 cm. mercury. Quantitative analysis was based on comparison of areas under peaks obtained from the reaction mixture with areas under peaks obtained from injection of solutions of known concentration in the respective components. The reference solutions were always injected sequentially with the unknowns, and components for preparing these solutions were usually obtained by collecting samples corresponding to the respective peaks during gas chromatography of reaction mixtures. Separation of samples was usually accomplished by chromatography on a 3-m. × 15 mm. o.d. column. Purity of the collected material was checked by rechromatography.

Reactions with capryl chloride. Gas chromatography at 200° showed three peaks beyond the solvent peak. Peak 1, retention time (from point of injection to maximum in peak) 3:13 (min., sec.), gave the same retention time and peak shape as capric acid. Peak 2, retention time 6:23, showed a carbonyl band in the infrared at 5.84 μ and gave a negative test for unsaturation with bromine in carbon tetrachloride; so it was assigned to 5-tetradecanone. Peak 3, retention time 9:30 gave a positive test for unsaturation; so it was assigned to the mixture of olefins resulting from dehydration of the tertiary alcohol.

In runs in which methyl caprate was included, chromatography was carried out at 165° in order to permit good separation of the ester from the acid. Typical retention times were: methyl caprate, 6:18, capric acid, 8:21.

Reactions with 7-carbomethoxyheptanoyl chloride. Gas chromatography at 225° showed three peaks. Peak 1, retention time 3:18, had the same retention time and peak shape as methyl hydrogen suberate. Peak 2, retention time 5:42, showed carbonyl absorption in the infrared at 5.75 and 5.84 μ, and gave a negative test for unsaturation; so it was assigned to the keto ester. Peak 3, retention time 9:18, showed carbonyl absorption at 5.75 μ only and gave a positive test for unsaturation; so it was assigned to the unsaturated esters resulting from dehydration of the hydroxy ester.

Reactions with γ-carbomethoxybutyryl chloride. Chromatography at 190° gave four peaks. Peak 1, retention time 2:15, could be removed by extraction of the solution with sodium carbonate; so it was assigned to methyl hydrogen glutarate. Peak 2, retention time 4:03, showed carbonyl absorption in the infrared at 5.75 and 5.84 μ, and gave a negative test for unsaturation; thus it was assigned to the keto ester. Peak 3, retention time 7:12, showed carbonyl absorption in the infrared at 5.75 μ only, and gave a positive test for unsaturation; so it was assigned to the unsaturated esters resulting from dehydration of the hydroxy ester. Peak 4, retention time 12:45, was assigned to the hydroxy ester. On chromatography at higher temperature, peak 4 was diminished or eliminated, with a proportionate increase in Peak 3. The total from peaks 3 and 4 is reported as hydroxy ester in Table III.

Solubility behavior of ferric chloride and γ-carbomethoxybutyryl chloride in ether-toluene. An 0.55-g. sample of anhydrous ferric chloride was weighed under 3 ml. of dry toluene, then 20 ml. of dry ether was added to dissolve the ferric chloride. This solution was centrifuged, then the clear supernatant solution was added by pipette to a solution of 0.54 g. of γ-carbomethoxybutyryl chloride at room temperature. When the mixed solution was allowed to separate by standing, a small dark-colored liquid layer separated below the larger yellow layer. The dark layer was insoluble in ether, toluene, or water; however, the water with which the dark layer was shaken became yellow, and the organic layer became soluble in ether or toluene.

When the original two-phase solution was cooled with stirring to −60°, a homogeneous green solution was formed. Re-warming of the homogeneous solution caused separation into two phases again.

If initial mixing of the solution, as described above, were at −60°, the homogeneous solution formed directly, but separation into two phases occurred on warming.

BERKELEY, CALIF.

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(14) J. Cason and W. T. Miller, *J. Org. Chem.*, **24**, 1814 (1959).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

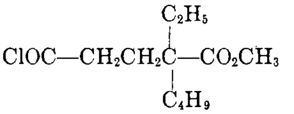
Mechanism of the Reactions of Grignard Reagents and of Organocadmium Reagents with Acid Chlorides in Presence of Ferric Chloride

JAMES CASON AND KENNETH W. KRAUS[1]

Received October 10, 1960

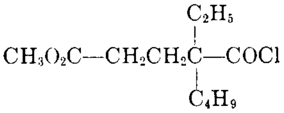
Both Grignard and organocadmium reagents, at −10° in presence of ferric chloride, will react with the ester acid chloride of an unsymmetrical dibasic acid without rearrangement, provided that the acid chloride function is unhindered. If the acid chloride is hindered, yield in the reaction is very low, and rearrangement occurs. These data are interpreted as indicating a dual reaction path. One route (leading to rearrangement) involves formation of an intermediate acylonium ion, as previously suggested, while the other route is an assisted reaction in which halogen is extracted by the Lewis acid from the acid chloride, as the alkyl of the organometallic reagent attacks the carbonyl carbon. It is proposed that inactivation of the components of these reactions at low temperature is caused by formation of a cyclic complex containing the acid chloride (or an ester), the Lewis acid, and the organometallic reagent. Use of the organocadmium reagent in presence of ferric chloride at low temperature appears to be the preferred method for avoiding rearrangement in reaction with the ester acid chloride of an unsymmetrical dibasic acid; however, the acid chloride function must be unhindered.

In a previous report,[2] it was suggested that the Grignard reaction with an acid chloride in the presence of ferric chloride proceeds by a mechanism similar to that which had been proposed[3] for reaction of the organocadmium reagents. According to this mechanism, the function of the ferric chloride would be extraction of halogen from the acid chloride to give an acylonium ion as intermediate. The highly reactive acylonium ion would then react with Grignard reagent to yield ketone. It was further noted[2] that it might prove feasible to check the reality of this proposed mechanism by examination of the ferric chloride catalyzed Grignard reaction with one of the isomeric ester acid chlorides, I and II. It had been established[4] that the acylonium



$\mathrm{ClOC{-}CH_2CH_2}\overset{\mathrm{C_2H_5}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\mathrm{{-}CO_2CH_3}$

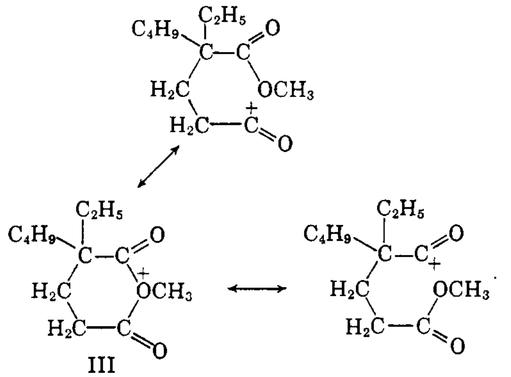
I



$\mathrm{CH_3O_2C{-}CH_2CH_2}\overset{\mathrm{C_2H_5}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\mathrm{{-}COCl}$

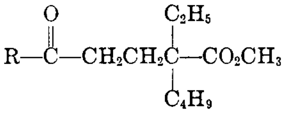
II

ion from either of these isomeric ester acid chlorides is best represented as the cyclic oxonium ion, III, which may react at either carbonyl function. In the organocadmium reaction, for example, either of the isomers, I and II, gives a mixture of the



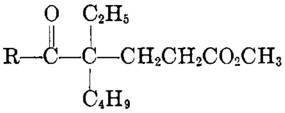
III

isomeric keto esters, IV and V. It follows that a mixture of keto esters would be expected from the



$\mathrm{R{-}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{-}CH_2CH_2}\overset{\mathrm{C_2H_5}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\mathrm{{-}CO_2CH_3}$

IV



$\mathrm{R{-}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{-}}\overset{\mathrm{C_2H_5}}{\underset{\mathrm{C_4H_9}}{\mathrm{C}}}\mathrm{{-}CH_2CH_2CO_2CH_3}$

V

ferric chloride catalyzed Grignard reaction if the oxonium ion, III, is indeed an intermediate in the reaction.

A necessary initial step in the present investigation is examination of the rearrangement of ester acid chlorides I and II in presence of ferric chloride, without presence of Grignard reagent. It has been reported[4] earlier that isomer II, in the presence of 1 mole per cent of ferric chloride and with no solvent, rearranges at room temperature to a mixture containing 39% of the isomer I. As shown by the data summarized in Table I, isomer I also rearranges rapidly at room temperature to approximately the same mixture previously obtained from isomer II. Both isomers rearrange at room temperature in ether-toluene solvent, although more slowly. At −55° to −60°, rearrangement occurs, but at such a slow rate that any rapid reaction at these temperatures must involve an assisted process for removal of halogen.

TABLE I
REARRANGEMENT OF ESTER ACID CHLORIDES

Mole % FeCl$_3$	Temperature	Rearrangement,[a] %
	Isomer I	
0^b	20–25°	0–2
4^b	20–25°	64
3	20–25°	47
3	−60°	0
25	−55°	6
	Isomer II	
0^b	20–25°	0
$1^{b,c}$	20–25°	39
20	20–25°	30
2.5	−55°	5
30	−55°	4

[a] The product was analyzed by esterification and use of gas chromatography, as described in Experimental. The precision of the analysis is believed to be about ±2%. [b] These runs without solvent; other runs in ether-toluene solvent. [c] Data from Ref. 4.

The Grignard reactions with ester acid chlorides I and II prove to give results that may be correlated with the behavior of these compounds in presence of ferric chloride, but the results cannot be correlated with a single reaction mechanism. As is summarized in Table II, ester acid chloride I gives yields of keto ester in consistency with the observations reported[5] for the unsubstituted ester acid chloride of glutaric acid. Best yield is obtained in concentrated solution, with excess of Grignard reagent, and with a rather large ratio of ferric chloride. It is of particular interest that *no rearranged keto ester was obtained* in any of the reactions.

In marked contrast to the behavior of ester acid chloride I, isomer II gives an extremely poor yield in the ferric chloride catalyzed Grignard reaction. Furthermore, some rearranged keto ester was always detected. When the temperature was raised from −60° to −10°, the yield was increased, and a majority of the product was rearranged.[6] The data

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(1) Recipient of a National Science Foundation Summer Fellowship, 1959, and Cooperative Fellowship, 1959, 1960.

(2) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1668 (1958).

(3) J. Cason, *J. Org. Chem.*, **13**, 227 (1948).

(4) J. Cason and R. D. Smith, *J. Org. Chem.*, **18**, 1201 (1953).

(5) J. Cason and K. W. Kraus, *J. Org. Chem.*, **26**, 1768 (1961).

(6) In reactions with ester acid chloride II, both keto ester IV and hydroxy ester represent rearrangement, for the Grignard reagent could hardly add to the hindered keto group in keto ester V. It follows that about 85% of the product in Run 9 is rearranged; therefore, at low temperature, there is a significant effect of steric hindrance in determining rate of reaction at the respective carbonyl groups in the acylonium ion, III. At about 80°, the ratio of reaction at the unhindered carbonyl to that at the hindered carbonyl was somewhat less than 2:1.[3]

TABLE II

Ferric Chloride Catalyzed Grignard Reactions with Ester Acid Chlorides[a]

Run No.	Reaction Temp.	Reaction Time, Hr.	Mole % FeCl$_3$[b]	Ratio[b] of C$_4$H$_9$Br	Molar Concn.[c] Ester Acid Chloride	Yield data,[d] %		
						Keto Ester		Hydroxy Ester
						IV	V	
Isomer I (Unhindered Acid Chloride)								
1	−40°	1	1.5	1.10	0.26	12	0	3
2	−60°	3	2	1.18	.24	16	0	7
3	−60°	2.5	2	2.0	.21	16	0	31
4	−60°	1	55	1.8	.50	32	0	9
5	−60°	1	50	2.4	.50	40	0	21
Isomer II (Hindered Acid Chloride)								
6	−60°	1	50	1.8	.50	0.5[e]	1	0
7	−60°	1	50	2.4	.50	0.3[e]	4	2
8	−10°	0.5	35	2.0	.50	11[e]	4	6
9	−10°	0.5	35	2.0	.40	10[e]	3	9

[a] Reactions were carried out on 0.01 or 0.02 mole of ester acid chloride in ether-toluene solvent in the manner described in the Experimental. [b] Mole per cent of ferric chloride and ratio of butyl bromide are related to moles of ester acid chloride. [c] Molar concentration of ester acid chloride is based on total solvent, including that in which Grignard reagent is added. [d] Yield data were determined by gas chromatography, as described in Experimental. The limit of detection of one keto ester admixed with the other is about 2%, thus the maximum yield of rearranged keto ester that could escape detection in Run 1 is less than 0.25%. [e] A gas chromatography peak occurring just before the keto esters represented 2–5% of an unidentified compound.

are consistent with the view that a rapid reaction which gives keto ester without rearrangement is blocked by steric hindrance in isomer II. This allows the occurrence of a reaction which is slow at −60° and proceeds with rearrangement. An elevation of temperature causes a faster increase in the rate of the reaction route giving rearrangement than in the rate of the reaction proceeding by the other route. It is also necessary that the mechanism giving rise to rearrangement be one not subject to serious interference by steric hindrance.

It may be noted that the characteristics of the mechanism giving rearrangement are those of the previously suggested[2] one in which the acylonium ion is an intermediate. For example, the organocadmium reagent gives an equally facile reaction[3] with either isomer I or II at temperatures of 40° or higher, but the rate of reaction with either isomer is quite slow at temperatures below 20°. The data on the mechanism not giving rearrangement suggest a transition state of the form shown,[7] in VII, so that the dual routes may be formulated as shown in the accompanying chart. Although complexing of ferric chloride (and the several components of the Grignard reagent) probably occurs[10] with oxygen as well as with chlorine, the complex formulated in VII should give the transition state of lowest energy. Entrance of the alkyl group at the carbonyl carbon would be assisted by concurrent extraction of halogen by the strong Lewis acid. The possibility for such a concerted reaction offers a valid explanation of the observed discrimination of ferric chloride in promoting reaction with the acid chloride in preference to other carbonyl groups. In fact, most of the Grignard reagent is inactivated at −60° in unreactive complexes, in absence of ferric chloride. It is also apparent that reaction *via* transition state VII would be subject to steric hindrance, whereas reaction *via* VI would be relatively unaffected by hindrance. Indeed, formation of the new bond at the hindered site by reaction of the acylonium ion, III, would not be expected to be the rate-determining step by this route.

The dual reaction paths, involving transition states VI and VII, also are entirely consistent with the observation that the rate of the reaction route involving rearrangement changes more rapidly with temperature than does the rate by the other route. The transition state for the concerted reaction (VII) involves three molecules in an ordered arrangement, whereas VI involves only two molecules; therefore the negative entropy of activation would be much larger for reaction *via* VII. The large negative entropy of activation decreases the temperature coefficient of the rate of reaction; therefore, the concerted reaction would be expected to become more important as the temperature is lowered. Furthermore, the concerted reaction should become dominant at low temperature in absence of steric hindrance. It may be noted that

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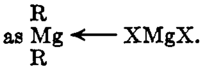
(7) The Grignard reagent is formulated as RMgX; however, RMgR may enter the transition state in similar fashion, as may various complexes such as  $\overset{R}{\underset{R}{Mg}} \longleftarrow XMgX$. Existence of the Grignard reagent as dimeric or higher complexes seems necessary to explain the observation[8,9] that reduction of and addition to the carbonyl group have the same kinetic order.

(8) J. Cason, K. W. Kraus, and W. D. MacLeod, *J. Org. Chem.*, **24**, 392 (1959).

(9) H. S. Mosher and J. A. Miller, *Am. Chem. Soc. 135th Meeting*, Paper 71-0 (1959).

(10) F. R. Jensen and H. C. Brown, *J. Am. Chem. Soc.*, **80**, 3039 (1958).

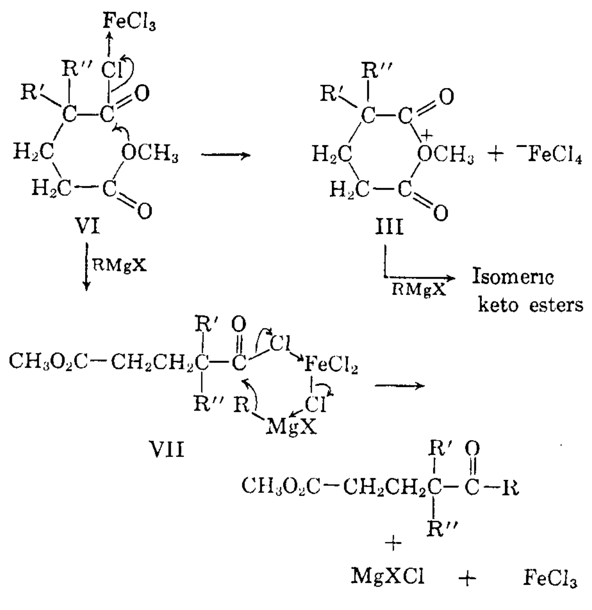
TABLE III

REACTION OF BUTYLCADMIUM REAGENT WITH ACID CHLORIDES[a]

Run No.	Reaction Temp.	Reaction Time, Hr.	Mole % $FeCl_3$[b]	Ratio[b] of C_4H_9Br	Yield Data,[c] % Keto ester		Yield Data,[c] % Recovered half ester
			γ-Carbomethoxybutyryl Chloride				
1	−10°	1	6	1.5	16		79
2	−5°	0.5	5	4	61		21
3	−60°	1	50	4	2[d]		62
4	−10°	0.5	7	4	55		—
5	−10°	2.5	8	3	56		38
6[e]	−10°	2.5	6	3	54		42
7	−10°	1	10[f]	3	54		42
			Isomer I (Unhindered Acid Chloride)		IV	V	
8	−60°	1	50	5	2[d]	0	95
9	−10°	0.5	55	6	61	0	20
10	+25°	3	50[g]	4	60	5	10
11	+25°	3	0	4	73	4	5
12	+38°[h]	3	0	4	80	10	3
			Isomer II (Hindered Acid Chloride)				
13	−10°	0.5	6.5	4	2[i]	2	79
14	−10°	.5	35	4	3[i]	4	71
15	−10°	.5	35	4	2[i]	5	65
16	−10°	4	50	4	5	4	68
17	[j]	[j]	37	4	5	5	—

[a] Reactions were carried out on 0.01–0.02 mole of ester acid chloride in 1:1 ether-toluene solvent, as described in Experimental. [b] Mole per cent of ferric chloride and ratio of butyl bromide are related to moles of ester acid chloride. [c] Yield data were determined by gas chromatography, as described in Experimental. Half ester was not determined in those runs where no value is indicated. In the cadmium reactions there was no evidence in the chromatography tracings of hydroxy ester or unsaturated esters from dehydration of hydroxy ester. [d] Just before the keto ester peak, there was a peak corresponding to 10–12% of an unidentified compound. [e] A reaction carried out with capryl chloride, under the same conditions as Run 6 except that reaction time was 0.5 hr., gave a 50% yield of 5-tetradecanone.[f] Run 7 was carried out as usual, with 5 mole per cent of ferric chloride, for a reaction time of 30 min., then an additional 5 mole per cent of ferric chloride was added and reaction was continued for 30 min. longer. [g] When ferric chloride was added to the cadmium reagent, the temperature rose rapidly to 35°, although the flask was immersed in a water bath at 25°. [h] In Run 12 the ester acid chloride was added to the solution of cadmium reagent at 5–6°, then the mixture was rapidly warmed to 38° and maintained at 38° ± 1° for 3 hr. [i] Just before the keto ester peaks, there was a peak corresponding to 1–3% of an unidentified compound. [j] Reaction 17 was carried out in ether solvent instead of the usual 1:1 mixture of ether and toluene. The reaction mixture was stirred at −10° for 45 min., then heated under reflux for 15 min.

all the data in Table II are consistent with the requirements of the proposed mechanisms.



It is not possible to investigate the Grignard reaction with acid chlorides at higher temperatures than those indicated in Table II on account of interference of the normal addition reaction to the carbonyl group, or reaction of ferric chloride with the Grignard reagent.[11] Even at −10°, a vigorous reaction occurs if the ferric chloride is added to the Grignard reagent.[12] In the synthesis of highly hindered ketones by use of the Lewis acid catalyzed Grignard reaction,[13] the temperature of boiling ether was used for the reaction, and a transition state corresponding to VI must have been involved, in view of the great steric hindrance which was overcome. It must be presumed that the ferric chloride survived long enough to promote the desired reaction on account of the use of *tert*-alkyl Grignard

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(11) B. Oddo, *Gazz. chim. ital.*, **44 II**, 268 (1914).

(12) In a run identical to Run 9, Table II, except that the ferric chloride was added to the Grignard reagent at −5° followed by the ester acid chloride, there was no yield of either keto esters or hydroxy ester.

(13) W. C. Percival, R. B. Wagner, and N. C. Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

reagents in all reactions. Of course steric hindrance would prevent normal addition to the carbonyl group of the ketone.

In contrast with the Grignard reaction, the reaction of organocadmium reagents with acid chlorides may be carried out successfully at higher temperatures in most instances, for such reagents add to the carbonyl group rather slowly. At temperatures above about 25°, the weak Lewis acids present in the reaction mixture (magnesium and cadmium halides, alkylcadmium halides) are able to extract halogen sufficiently rapidly to give a satisfactory rate of reaction.[13a] Such reactions give rearrangement with ester acid chlorides I and II; however, rearrangement has been reported[3] to be less at 40° than at 80°. At 80°, the same mixture of keto esters IV and V was obtained from either ester acid chloride; therefore, reaction must have been entirely by way of the acylonium ion. Although an increasing participation of a concerted mechanism at 40° is indicated for the cadmium reaction, in view of the decreased rearrangement, the rate becomes impractically slow if the temperature is lowered still further. On the other hand, if the above-cited deductions concerning mechanism be correct, the cadmium reaction should proceed at a faster rate at low temperature if a stronger Lewis acid such as ferric chloride were added. Below 0°, such a reaction with ester acid chloride I might well proceed without rearrangement, whereas isomer II should become subject to steric hindrance. As summarized by the data in Table III, these expectations have been realized. The hindrance encountered with isomer II, as well as the increase of rearrangement with temperature, indicate that a dual mechanism also applies to the cadmium reactions. Transition states similar to VI and VII would be involved. This circumstance had not been recognized previously because the reactions have always been run at temperatures at which the ionization route is dominant.

The lower reactivity of the cadmium reagent, as compared to the Grignard reagent, is evidenced by the failure of the cadmium reagent to give significant amounts of ketone at −60° (Run III-3). In addition, the cadmium reagent is more handicaped than the Grignard reagent by formation of inactive complexes at low temperature. Moderately good yields of ketone are obtained from the cadmium reagent at low temperature only when a very large excess of reagent is used (compare Runs III-1 and III-2). Although ferric chloride appears to react rapidly with the cadmium reagent at 25° (Run III-10), this side reaction must be a minor factor at lower temperature; otherwse, increasing the ratio of cadmium reagent could hardly effect such a marked improvement in yield. If the cadmium reagent gives a reaction with ferric chloride of the sort that has been reported[11] for the Grignard reagent, the following equation would apply:

$$\text{R—Cd—R} + 4\,\text{FeCl}_3 \longrightarrow 2\,\text{RCl} + \text{CdCl}_2 + 4\,\text{FeCl}_2$$

Run III-17 was examined for butyl chloride, and this substance was found to be present; so occurrence of reaction between the cadmium reagent and ferric chloride is supported; however, very little of such a reaction occurred. The yield of butyl chloride, based on butyl bromide used for the reaction, was only 1.2%; therefore, less than 10% of the ferric chloride used in Run III-17 could have been destroyed by this route. The small amount of butyl chloride is of particular interest as Run III-17 was heated under reflux for 15 minutes after the reaction period at low temperature, whereas Run III-10 was exothermic when ferric chloride was added initially to the cadmium reagent at 25° prior to addition of acid chloride. Furthermore, heating of Run III-17 after an initial reaction period at −10° did not yield significant amounts of keto ester. In absence of ferric chloride, excellent yields are obtained in the cadmium reaction at 35–40°.[14]

When an acid chloride is added to the cadmium reagent at low temperature, in presence of ferric chloride, an exothermic reaction occurs during a few minutes, then little if any further reaction occurs on long stirring (compare Runs III-4 and III-6). Furthermore, when a second charge of ferric chloride was added after a brief reaction time (Run III-7), there was no effect at all on the yield of the reaction. All the data indicate that, although ferric chloride catalyzes reaction of an

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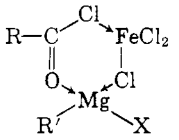
[13a] Note added to manuscript, Nov. 23, 1960. Since the submission of this manuscript there has appeared a report by J. Kollonitsch [*Nature*, **188**, 140 (1960)] in which there is described a "salt effect" on the reactivity of organocadmium reagents. In particular, it was found that R_2Cd is unreactive toward acid chlorides unless there is added an "activator" such as a magnesium halide; and it was claimed that this effect had not been previously recognized or included in discussions of mechanisms of reactions of organocadmium reagents. It seems clear that the reported effect is not a salt effect in the sense in which this term has been used (*e.g.*, *cf.* E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, pp. 185–187). In contrast, it is entirely consistent with presently reported work and considerable earlier work to ascribe the effect observed by Kollonitsch to action of Lewis acids. In fact, reactions of organocadmium reagents have been widely interpreted as involving Lewis acids in the reaction mixtures (*e.g.*, *cf.* Ref. 2 and references cited therein); so the observation that R_2Cd is indeed unreactive in absence of Lewis acids would appear to offer support to the previously proposed mechanisms and those in the present paper. The suggestion by Kollonitsch that his discovery of the "salt effect" invalidates previous proposals concerning reaction mechanisms for organocadmium reagents [ref. 2; W. G. Dauben and J. W. Collette, *J. Am. Chem. Soc.*, **81**, 968 (1959); and others] can be rationalized only as a failure to recognize this effect as an example of the role of Lewis acids in these reactions.

[14] Yields of 75–80%, as previously reported,[3] would not be expected after only fifteen minutes under reflux; however, there should have been substantial improvement over the yield observed, unless ferric chloride were interfering with the reaction in some way.

acid chloride with cadmium reagent, one mole of ferric chloride can also inactivate many moles of acid chloride towards reaction with cadmium reagent, even at 30–40°. There has been demonstrated in other ways[5] formation of a stable complex between one mole of ferric chloride and at least five moles of an acid chloride. Apparently, an initial complex between a mole of acid chloride and one of ferric chloride may react with cadmium reagent to give an activated complex analogous to VII, and this leads to ketone. A competing reaction with additional acid chloride, to give a complex inert to the cadmium reagent, becomes dominant, however, unless a large excess of cadmium reagent is present to compete for the initial complex. Further investigation of factors such as slow addition of acid chloride is anticipated.

Although the data indicate that the ferric chloride–acid chloride complex is inert to reaction with a cadmium reagent, a rather different situation is observed with the Grignard reagent. In the Grignard reactions, especially in presence of an ester group (*cf.* Table II, also ref. 5), a larger ratio of ferric chloride improves the yield more effectively than does a large excess of Grignard reagent. Even in this reaction, however, if the temperature is kept below zero, some acid chloride and/or Grignard reagent becomes inactivated soon after addition is complete. Subsequent heating causes utilization of all the Grignard reagent. It is possible that the complex which is inert at low temperature involves the same components as does VII, but has the different conformation shown in VIII. One or two additional moles of acid chloride could be complexed similarly. If such a complex were stable to further reaction at low temperature, ketone would be formed only if the conformation in VII were reached prior to that in VIII. The previously reported data[5] also indicate that, at −60°, a stable complex similar to VIII may be formed from normal components of the Grignard reagent. Furthermore, an ester seems especially effective at forming such inactive complexes at low temperature.



VIII

For synthetic applications, the use of a Lewis acid with the cadmium reagent at low temperature appears specifically useful for avoiding rearrangement in reaction with the ester acid chloride of an unsymmetrical dibasic acid, provided that the acid chloride function is unhindered. If a large excess of cadmium reagent is used, the yield of ketone is better than may be obtained from the ferric chloride catalyzed Grignard reaction. At higher temperatures, where the ionization route becomes dominant, the cadmium reagent is no longer subject to hindrance, and yields are considerably improved, but rearrangement occurs in unsymmetrical situations.

EXPERIMENTAL

γ-Carbomethoxybutyryl chloride was prepared as described previously.[5]

α-Butyl-α-ethyl-γ-carbomethoxybutyric acid. α-Butyl-α-ethylglutaric acid was prepared and esterified as described previously,[3] to give the half ester from which acid chloride II was prepared. This half ester proved to be prone to pass in small amount to α-butyl-α-ethylglutaric anhydride during fractional distillation,[15] and this could not be prevented entirely by distillation at low pressure, or by adding magnesium oxide to the distillation pot. When the small amount of diester was removed by topping in a fractional distillation column, and the residual half ester was distilled rapidly at 1 mm. pressure in a Claisen flask, there was obtained half ester containing less than 1% anhydride. Such a sample, obtained in 85% yield, had b.p. 149–151°/1 mm., n_{D}^{25} 1.4527, infrared absorption 5.76, 5.90 μ. The anhydride absorbs at 5.55, 5.68 μ. Most accurate analysis of mixtures is by gas chromatography on silicone grease.[16] In a 1.5-m column, at 225°, with flow rate of 65 ml./min., retention times for anhydride and half eser, respectively, were 6:40 (min., sec.) and 8:40. Anhydride is no serious disadvantage in half ester to be used for preparing diester; however, anhydride-free samples were used for preparing acid chloride for rearrangement studies or for reaction with organometallic reagents.

α-Butyl-α-ethyl-γ-carbomethoxybutyryl chloride (II) was prepared with thionyl chloride, below 40°, as previously described.[3] A distilled sample, obtained in 90% yield, had b.p. 113–116°/1 mm., n_{D}^{25} 1.4577; however, all samples used for rearrangement studies or reaction with organometallic reagents were not distilled or heated above 40°. Infrared absorption is at 5.57, 5.76 μ; so small amounts of anhydride (5.55, 5.68 μ) cannot be detected. As gas chromatography of the ester acid chloride is unsuccessful, use of pure half ester is essential when pure ester acid chloride is required.

Dimethyl α-butyl-α-ethylglutarate. As direct esterification of the half ester proceeds very slowly and in poor yield,[3] and use of diazomethane for large amounts is undesirable, the acid chloride, II, was converted to diester by treatment with excess methanol. From dropwise addition of 0.15 mole of II to 0.5 mole of methanol, with stirring, there was obtained a 59% yield of diester, b.p. 127–128°/3 mm., n_{D}^{25} 1.4416, infrared absorption 5.77, 5.82 μ (two ester groups). There was also recovered a 35% yield of half ester.[17]

Use of a base (diethylaniline) during the reaction lowered the yield somewhat.

γ-Carbomethoxy-γ-ethylcaprylic acid was prepared by controlled saponification of the diester, as previously described,[3] in yields of 89–91%, b.p. 161–163°/3 mm., n_{D}^{25} 1.4500, infrared absorption 5.82, 5.88 μ (note different absorption of

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[15] The analytical sample, which had been saved from the earlier work,[3] proved to be free of anhydride (infrared and gas chromatography); however, in the present work, anhydride content of successive samples from fractional distillation varied erratically from <1% to >10%, and the content of the distilling pot was usually entirely free of anhydride. A premixed sample of anhydride (lower-boiling than half ester) and half ester could be separated by fractional distillation (no evidence of azeotrope formation).

[16] J. Cason and W. T. Miller, *J. Org. Chem.*, **24**, 1814 (1959).

[17] Subsequent investigation, to be published, has shown that this half ester does not arise in major part from anhydride present in the originally used half ester.

isomeric half ester). No difficulty was experienced with anhydride formation during distillation of this isomer.

γ-Carbomethoxy-γ-ethylcaprylyl chloride (I) was prepared and manipulated below 40°, as noted for the isomer II; infrared absorption 5.55, 5.80 μ. Anhydride may be readily detected in this isomer by its infrared absorption at 5.68 μ, in contrast with isomer II which exhibits absorption at 5.76 μ.

Rearrangement of ester acid chlorides I and II. The pertinent results from these experiments are tabulated in Table I. For the reactions without solvent, the anhydrous ferric chloride was added to the pure ester acid chloride, and the mixture was stirred for 2 hr. at room temperature in an atmosphere of nitrogen. Hydrolysis and analysis was as described below.

For reactions using solvent, 4–8 mmoles of ester acid chloride was dissolved in 8 ml. of anhydrous ether and 4 ml. of dry toluene contained in a 60-ml. round bottomed flask equipped with sealed stirrer, thermometer, and provision for a nitrogen atmosphere. Ferric chloride was weighed under 1 ml. of toluene, then dissolved by addition of 2 ml. of ether. This solution was added to the cooled solution of ester acid chloride, and the mixture was stirred for 2–2.5 hr. as the reaction temperature was maintained to ±2°. At the end of the reaction period, 5 ml. of water was added to the cold solution with stirring, the mixture was allowed to warm to room temperature, then the organic layer was separated and washed with two 15-ml. portions of water. The residue remaining after solvent removal was hydrolyzed to half ester(s) with sodium carbonate according to the procedure worked out previously.[4]

Although it was possible to separate the isomeric half esters by chromatography on silicone grease[16] the separation was not sufficiently good to allow detection of less than about 10% of one isomer in the other. For this reason, the isomeric composition of the half ester mixture was determined by use of esterification, which rapidly attacks the unhindered carboxyl and very slowly attacks the hindered carboxyl. The mixture obtained by following the previously used esterification procedure[4] could be analyzed more accurately than by distillation, for the gas chromatography tracing goes to baseline between diester and the half ester with hindered carboxyl (fortunately, this half ester has the longer retention time of the two). In a typical chromatography on a 1.5-m. silicone column at 205°, flow rate 75 ml./min., the respective retention times for diester and half ester were 4:21 and 6:09. Presence of less than 2% of half ester may be detected. Quantitative data were obtained, as usual,[5] by comparing sequential tracings of the reaction mixtures with those from known amounts of the components. A correction was applied for the determined fact that the esterification procedure leaves 6% of the unhindered carboxyl unesterified, and causes esterification of 4% of the hindered carboxyl. Although equal weights of the isomeric half esters give rather different areas under the chromatography tracings, this is not sufficient to be significant when the half ester with hindered carboxyl contains a small amount of the isomer. The over-all precision of the analysis is believed to be about ±2%.

Grignard reactions in presence of ferric chloride were carried out by the same procedure that has been described previously,[5] and the quantitative analysis of the reaction mixtures was by gas chromatography. Data are summarized in Table II, and specific details of the analyses are described below for each isomer.

Grignard reactions with γ-carbomethoxy-γ-ethylcapryl chloride (I). The reaction mixture was worked up in the normal manner,[5] and aliquots were injected for gas chromatography. The half ester, from hydrolysis of unchanged acid chloride, could be detected on silicone grease partitioning agent, but the isomeric keto esters (IV and V) were not separated on this agent. The half ester is not recorded in chromatography on Reoplex-400 or on diethylene glycol succinate (DEGS), but the isomeric keto esters are separated sufficiently well to allow detection of 2% of one keto ester in the other. Most of the quantitative data were determined by chromatography on a 1.5-m. diethylene glycol succinate column at a temperature of 180°.

For assignment of bands, there were examined the fractions corresponding to the four peaks obtained by chromatography on a 1.5-m. silicone grease column, temperature 215°, helium flow 60 ml./min. Peak 1, retention time 2:50 (min., sec., from time of injection to maximum in peak), gave the same shape of peak and same retention time as the half ester with unhindered carboxyl; this peak did not appear in chromatography on poly-esters. Peak 2, retention time 4:17, showed carbonyl absorption in the infrared at 5.78 and 5.84 μ, gave a negative test for unsaturation, and had the same retention time as methyl 2-butyl-2-ethyl-5-ketononanoate[3] (IV). Chromatography of a sample collected from this peak was carried out on Reoplex-400 at 200°, to give a peak at 12:30; times for authentic samples of IV and V were 12:15 and 14:10. An authentic sample of keto ester IV shows carbonyl absorption at 5.78 and 5.84 μ, while the isomer V shows absorption at 5.74 and 5.87 μ.

Peak three, retention time 5:38, showed carbonyl absorption in the infrared at 5.78 μ only, and gave a positive test for unsaturation; thus it was assigned to the unsaturated esters resulting from dehydration of the hydroxy ester. Peak 4, retention time 9:00, was rechromatographed to give either peak 3 or a mixture of peaks 3 and 4. As the temperature was raised, the ratio of peak 4 decreased. Peak 4 was accordingly assigned to the hydroxy ester, and the total of peaks 3 and 4 are recorded as hydroxy ester in Table II. For reasons which are not entirely clear, any cracking of the hydroxy ester appears to occur immediately on injection. Any gradual cracking during passage through the column would result in loss of material in the analysis, for such material would not appear in any band; however, injections at different temperatures, giving different ratios of peaks 3 and 4, gave comparable values for the total of the two peaks. In addition, Run II-5 (0.02 mole of ester acid chloride I) was extracted with carbonate for removal of half ester, then fractionally distilled, to give the following data:

Fraction	B.P./1 Mm.	Wt., G.	$n_D^{25.5}$	Yield, %
1	100–125°	0.22	1.4423	
2	125°	1.71	1.4472	36
3	125–144° (mostly 125°)	0.24	1.4477	
4	144–152° (mostly 144–145°)	0.21	1.4530	3.4
5	152–153.2°	1.05	1.4562	16

Fraction 2 has the properties recorded for the keto ester,[3] and Fraction 3 is largely keto ester. Fraction 4, which gave a positive test for unsaturation, and exhibited a single carbonyl band in the infrared at 5.78 μ, was judged to consist largely of unsaturated ester. Fraction 5, which gave a negative test for unsaturation, and gave infrared absorption at 2.81 and 5.78 μ, was judged to be hydroxy ester. It will be noted that the yield data determined by distillation are in good agreement with that in Table II for Run 5, especially if allowance be made for keto ester IV in Frac. 1.

Grignard reactions with α-butyl-α-ethyl-γ-carbomethoxybutyryl chloride (II). These reactions were worked up in a normal manner, except that the hindered acid chloride was only partly hydrolyzed during the usual procedure. For this reason, the total initially-obtained product of the reaction was stirred overnight with aqueous sodium carbonate solution in order to hydrolyze the acid chloride. After this treatment, the organic phase was extracted and diluted for gas chromatography on a 1.5-m. diethylene glycol succinate column. Peaks observed were the same as for isomer I, except that both keto esters were present. Isomer IV results from rearrangement. In most runs, recovered half ester was determined by chromatographing on silicone the material recovered from the carbonate solution, but these data are not recorded in Table II.

Organocadmium reactions in presence of ferric chloride (Table III). The cadmium reagent was prepared (nitrogen atmosphere) from butyl bromide, by way of the Grignard reagent, in a usual manner[18] except that no ether was distilled from the solution. After a negative Gilman test had been obtained, there was added 5 ml. of toluene, the stirred reaction mixture was cooled to the desired reaction temperature, and the ether-toluene solution of ferric chloride was added. Immediately after the ferric chloride had been added, a toluene solution of the ester acid chloride was added during about 2 min. or as rapidly as was consistent with keeping the reaction temperature within the limit of ±2°. At the end of the reaction period, ice and sulfuric acid were added, the reaction mixture was worked up, and the products were determined by gas chromatography in the manner described for the Grignard reactions.

Reaction III-17 was carried out as usual for 45 min. at $-10°$, then it was heated under reflux for 15 min. as the condenser outlet was attached to a trap cooled in Dry Ice and acetone. No volatile products were collected in the trap. In addition to the analysis for the usual products by gas chromatography at high temperature, injections were also made at 48° in order to allow determination of butyl chloride. In a 2-m. silicone column, at a flow rate of 30 ml./min., retention time of butyl chloride from the reaction mixture was 10:48. Retention times of several of the compounds run for comparison in assigning the 10:48 peak were: ethanol, 3:18; butyl chloride, 10:30; butanol, 15:45; *n*-heptane, 16:48; butyl bromide, 20:06.

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[18] J. Cason and F. S. Prout, *Org. Syntheses*, 28, 75 (1948).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY]

Action of Grignard Reagents. XXI. Action of Organomagnesium Compounds on 4-Arylazo and of Lithium Aluminum Hydride on 4-Arylidene Derivatives of 1-Phenyl-3-methyl-5-pyrazolone

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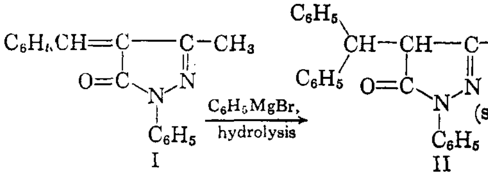
Treatment of 4-arylazo derivatives of 1-phenyl-3-methyl-5-pyrazolone with Grignard reagents does not effect hetero-ring opening and only the carbonyl group of III enters into reaction, followed by elimination of the elements of water on acidification, yielding colored products, believed to be derivatives of 1-phenyl-3-methyl-4-arylazo-5-arylpyrazole (IV). 1,5-Diphenyl-3-methyl-4-phenylazo-5-pyrazole (IVa) now has been obtained by the action of phenylmagnesium bromide on 1-phenyl-3-methyl-4-phenylazo-5-chloropyrazole (IVe), followed by hydrolysis.

Treatment of IVe and of 1-phenyl-3-methyl-4-arylidene-5-pyrazolones (Xa-d) with lithium aluminum hydride effects the formation of 1-phenyl-3-methyl-4-phenylazo-5-pyrazole (IVf) and 1-phenyl-3-methyl-4-arylmethyl-5-pyrazolones (XIa-d) respectively.

Recently, Mustafa and co-workers[1] showed that treatment of 1-phenyl-3-methyl-4-phenylazo-5-pyrazolone (I) with phenylmagnesium bromide, followed by hydrolysis, resulted in the addition of the reagent to the conjugation created by the attachment of an exocyclic double bond in the position 4 of a heterocyclic nitrogen ring having carbonyl function and yielded 1-phenyl-3-methyl-4-diphenylmethyl-5-pyrazolone (II).



I II (scheme A)

We now have undertaken the investigation of the effect of the introduction of the electron withdrawing group, namely, the phenylazo group in the 4-position of 1-phenyl-3-methyl-5-pyrazolone,[2] on the reactivity of the carbonyl group toward the action of organomagnesium compounds. When the highly colored 1-phenyl-3-methyl-4-arylazo-5-pyrazolones[3] (III) are treated with organomagnesium compounds, colored products of 1-phenyl-3-methyl-4-arylazo-5-arylpyrazoles (IV) are obtained (scheme B).

The assigned structure for the Grignard products (IVa-d) is inferred from: (1) the fact that they are colored,[4] (2) the identity of IVa with the product obtained by treating IVe with phenylmagnesium bromide, and (3) agreement of the ultimate analyses with those expected.

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[1] A. Mustafa, W. Asker, A. F. A. Shalaby, S. A. Khattab, and Z. Selim, *J. Amer. Chem. Soc.*, 81, 6007 (1959).

[2] The effect of the electron-withdrawing groups such as phenylazo in the 4-position, on the ease of replacement of a halogen in position 5 by nucleophilic reagents has been carefully studied with 1-phenyl-3-methyl-4-phenylazo-5-chloropyrazole (*cf.* P. Duquenois and H. Amal, *Bull. soc. chim. France*, (5) 9, 721 (1942); A. Michaelis and H. Klopstock, *Ann.*, 354, 102 (1907).

[3] The arylazo-derivatives may have the structure in III or one of the tautomeric structures (*cf.*, K. Auwers and A. Boennecke, *Ann.*, 378, 218 (1911)).

[4] The colored substituted 1-phenyl-3-methyl-4-arylazo-5-pyrazole, A. Michaelis and R. Leonhardt, *Ber.*, 36, 3597 (1903).