THE USE OF ORGANOCADMIUM REAGENTS FOR THE PREPARATION OF KETONES

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I. INTRODUCTION

The preparation of ketones by the reaction between an organocadmium compound and an acid chloride was first recommended by Gilman and Nelson (19) in 1936. The following reactions are involved in the preparation:

$$RBr + Mg \rightarrow RMgBr$$

$$2RMgBr + CdCl_2 \rightarrow RCdR + MgBr_2 + MgCl_2$$

$$RCdR + 2R'COCl \rightarrow 2R\underset{\underset{\displaystyle O}{\|}}{C}R' + CdCl_2$$

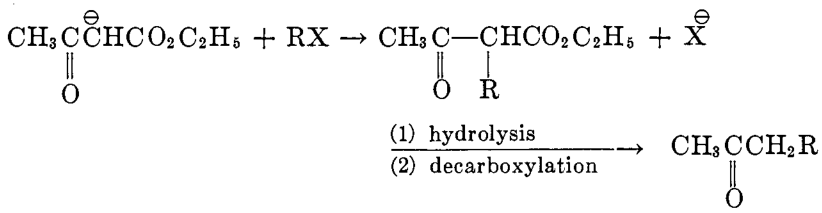
The cadmium reagent may be prepared from a lithium derivative instead of a Grignard reagent, if desired (19). This sequence may be carried through in a few hours without isolation of intermediates; however, the general utility of the method was not recognized for several years, possibly on account of experimental difficulties encountered in carrying out these reactions (*cf.* Section IV). At least one report (38) of a low yield in such a preparation has appeared. Since 1941, however, considerable information concerning this reaction has been gained, and the method may now be regarded as one of the best and most widely applicable procedures for laboratory-scale preparation of either simple ketones or various polyfunctional compounds containing a keto group. The required starting materials are relatively easily available, the experimental procedure is equivalent to a one-step process, and the yields are usually rather good.

II. Comparison with Other Methods

Although simple symmetrical ketones may be conveniently prepared from the appropriate acid or its salt, the most useful methods for preparing unsymmetrical ketones involve a Friedel–Crafts reaction, an enolate condensation, or some type of Grignard reaction. It is of interest, perhaps, to consider the relative merits of these methods as compared with the use of organocadmium reagents.

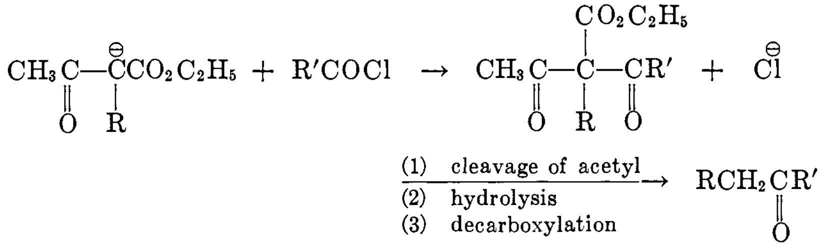
The Friedel–Crafts reaction is quite useful in cases where it is applicable. However, it is useful only in the aromatic series and with compounds containing no meta-directing groups; also, only certain orientations may be obtained. In the latter two categories mentioned above, the following general reactions may be considered:

(1)



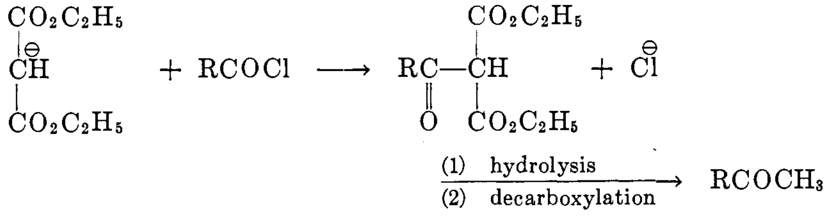
$$\mathrm{CH_3\underset{\underset{O}{\|}}{C}\overset{\ominus}{C}HCO_2C_2H_5 + RX \rightarrow CH_3\underset{\underset{O}{\|}}{C}{—}\underset{\underset{R}{|}}{C}HCO_2C_2H_5 + \overset{\ominus}{X} \xrightarrow[\text{(2) decarboxylation}]{\text{(1) hydrolysis}} CH_3\underset{\underset{O}{\|}}{C}CH_2R}$$

(2)



$$\mathrm{CH_3\underset{\underset{O}{\|}}{C}{—}\underset{\underset{R}{|}}{\overset{\ominus}{C}}CO_2C_2H_5 + R'COCl \rightarrow CH_3\underset{\underset{O}{\|}}{C}{—}\underset{\underset{R}{|}}{\overset{\overset{CO_2C_2H_5}{|}}{C}}{—}\underset{\underset{O}{\|}}{C}R' + \overset{\ominus}{Cl} \xrightarrow[\substack{\text{(2) hydrolysis}\\ \text{(3) decarboxylation}}]{\text{(1) cleavage of acetyl}} RCH_2\underset{\underset{O}{\|}}{C}R'}$$

(3)



$$\mathrm{\underset{\underset{CO_2C_2H_5}{|}}{\overset{\overset{CO_2C_2H_5}{|\ominus}}{CH}} + RCOCl \longrightarrow R\underset{\underset{O}{\|}}{C}{—}\underset{\underset{CO_2C_2H_5}{|}}{\overset{\overset{CO_2C_2H_5}{|}}{CH}} + \overset{\ominus}{Cl} \xrightarrow[\text{(2) decarboxylation}]{\text{(1) hydrolysis}} RCOCH_3}$$

(4) $\mathrm{RMgX + R'C{\equiv}N \rightarrow imine \xrightarrow{hydrolysis} RCOR'}$

(5) $\mathrm{RMgX + R'CONH_2 \rightarrow imine \xrightarrow{hydrolysis} RCOR'}$

(6) $\mathrm{RMgX + (CH_3CO)_2O \xrightarrow{-70°C.} RCOCH_3 + CH_3CO_2MgX}$

(7) $\mathrm{\begin{array}{c}RZnCl\\ or\\ R_2Zn\end{array} + R'COCl \rightarrow RCOR' + ZnCl_2}$

Method 1 has been widely used for the preparation of ketones; however, it involves two separate operations and the over-all yield of ketone rarely equals the yield obtained by use of the organocadmium reagent. This method may be extended to the preparation of keto acids (7, 32, 36) if a bromo ester is used instead of an alkyl halide; however, the difficult availability of most types of bromo esters is often a handicap. On the other hand, keto esters may be prepared in one step by the reaction of an organocadmium reagent with the ester acid chloride of a dibasic acid, $C_2H_5O_2C(CH_2)_nCOCl$, a type of starting material which is relatively easily obtained (11, 39). Method 1 has the advantage, however, that it may be used for the preparation of keto acids having a branching group between the keto and carboxyl groups.

The chief usefulness of method 1 is in the preparation of methyl ketones, for higher β-keto esters are obtainable (5, 30, 36) only by fairly laborious procedures. For this reason, method 2 has found considerable application in the preparation of other types of ketones, especially keto acids (32, 36). The chief difficulties with the method are that the over-all process is laborious and the yields are not especially good. Side reactions are oxygen-acylation and cleavage of the higher acyl group.

Method 3 is limited to the preparation of methyl ketones, for acylation of alkylmalonic esters (23, 40) gives a very poor yield, presumably owing to oxygen-acylation. For methyl ketones this method gives good yields, and it is about as useful as the cadmium method. For such ketones, there seems little basis for choice between the two methods.

Methods 4 (2, 17, 18) and 5 (17, 22, 38) give good yields of ketones, provided there is present in the molecule no other functional group which will react with the Grignard reagent. The nitrile and amide groups are among the least reactive toward this reagent. If this condition is met these methods give yields as good as or better than the cadmium method, and the experimental manipulations are similar. The scope of the cadmium method is much greater however, for the organocadmium reagents fail to react with most functional groups (*cf.* Section III,D).

Method 6 has been introduced only recently (27, 28) but seems quite promising as a general preparative method for methyl ketones. The yields are in the same range as those obtained from cadmium reagents. It is also reported that this method is satisfactory with secondary and tertiary alkyl halides, types which are not suitable for conversion to dialkylcadmium reagents.

Method 7 is identical with the preparation involving cadmium, except that zinc is used. Although Blaise (3) originally claimed excellent yields in this type of preparation, a succession of investigators (25, 26, 33, 34) has failed to obtain better than moderate yields. The superiority of the cadmium reagent arises from its much easier preparation and its lower reactivity toward the carbonyl group. Diethylzinc has been shown (19) to react with the carbonyl group about 3.5 times as fast as does diethylcadmium. A few ketones have been made from both cadmium and zinc reagents (15, 19), and in each case the yield was significantly larger when the cadmium reagent was used.

Thus, it seems safe to say that no other method of ketone preparation has the scope of the method utilizing the organocadmium reagents, and in relatively few specific cases are other methods superior. The actual scope and limitations of this method will be considered next.

III. Scope and Limitations of the Method

A. THE ALKYL OR ARYL HALIDE

1. The halogen

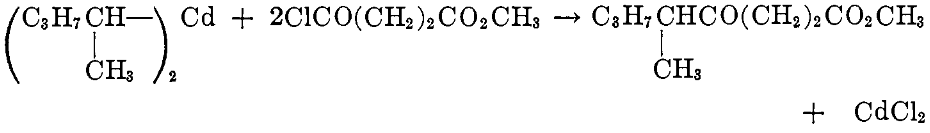
Several investigators (12, 16, 19) have reported that if the Grignard reagent from which the cadmium derivative is prepared is made from an iodide, the yield of ketone is much poorer than if the bromide is used. It has also been reported (12) that in the case of *n*-butyl halides the chloride is somewhat inferior to the bromide, although much better than the iodide. In the preparation of methyl 4-ketoöctoate from di-*n*-butylcadmium and β-carbomethoxypropionyl chloride, the yields were respectively 79.5, 63, and 45 per cent when the halides

$$\mathrm{(C_4H_9)_2Cd + 2ClCO(CH_2)_2CO_2CH_3 \rightarrow C_4H_9CO(CH_2)_2CO_2CH_3 + CdCl_2}$$

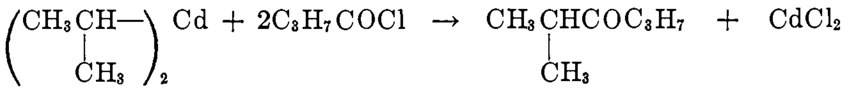
were butyl bromide, chloride, and iodide. Cole and Julian (15) reported the preparation of a methyl ketone using dimethylcadmium, and obtained the same yield when either methyl iodide or methyl bromide was used; however, a fivefold excess of cadmium reagent was used in this preparation, so the relative value of the halides may have been obscured. This seems probable, since De Benneville (16) reported methyl iodide inferior to the bromide.

2. The organic radical

Aromatic Grignard reagents form cadmium derivatives readily (12, 15, 16, 19) and give good yields of aromatic ketones. If the organic radical is alkyl, then it must be primary in order for the preparation to be useful. This seems to be the chief limitation of the organocadmium reagents. Gilman and Nelson (19) first reported that secondary and tertiary cadmium derivatives are stable only at low temperature. Other investigators (12, 14) have found that in the preparation of methyl 4-keto-5-methyloctoate from di-2-amylcadmium and β-carbomethoxypropionyl chloride, the yield of keto ester is nearly zero if the reaction temperature is allowed to rise somewhat above 0°C. (12a), and the yield is only 21.5 per cent when the reaction is conducted at $-5°$ to $-10°$C. Diisopropylcadmium seems to be somewhat more stable, for Gilman and Nelson, operating at 0°C., obtained *n*-propyl isopropyl ketone in 60 per cent yield:



$$\left(\underset{\mathrm{CH_3}}{\mathrm{C_3H_7\underset{|}{C}H}}\text{—}\right)_2\mathrm{Cd} + \mathrm{2ClCO(CH_2)_2CO_2CH_3} \rightarrow \mathrm{C_3H_7}\underset{\mathrm{CH_3}}{\mathrm{\underset{|}{C}H}}\mathrm{CO(CH_2)_2CO_2CH_3} + \mathrm{CdCl_2}$$



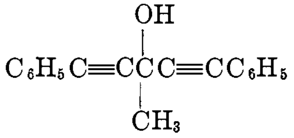
$$\left(\underset{\mathrm{CH_3}}{\mathrm{CH_3\underset{|}{C}H}}\text{—}\right)_2\mathrm{Cd} + \mathrm{2C_3H_7COCl} \rightarrow \mathrm{CH_3}\underset{\mathrm{CH_3}}{\mathrm{\underset{|}{C}H}}\mathrm{COC_3H_7} + \mathrm{CdCl_2}$$

Di-*tert*-butylcadmium has been used in the reaction with acetyl chloride (19) at −70°C. to give a 17 per cent yield of ketone. De Benneville (16) reported a 40 per cent yield (based on anhydride) in the reaction, at −70°C., between di-*tert*-butylcadmium and benzoic anhydride; however, in view of the low reactivity of cadmium reagents toward anhydrides (*cf.* Section III,C) and the preparation of ketones from Grignard reagents and anhydrides at −70°C. (27), it seems quite possible that the ketone obtained in this case resulted from Grignard reagent rather than cadmium reagent.

It may be mentioned at this point that Nightingale and Wadsworth (29) attempted the conversion of phenylethynylmagnesium bromide (I) to the corresponding cadmium derivative. After stirring for 1 hr. in ether the test for Grignard reagent was still positive, and when the resultant mixture was treated with acetic anhydride or acetyl chloride the only product isolable (in 14 per cent yield) was that expected from the Grignard reagent, bis(phenylethynyl)methylcarbinol (II).

$C_6H_5C\equiv CMgBr$

I



$$C_6H_5C\equiv C\overset{\displaystyle OH}{\underset{\displaystyle CH_3}{C}}C\equiv CC_6H_5$$

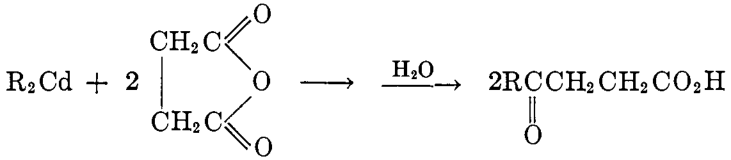
II

B. THE CADMIUM HALIDE

It has been shown (19) that cadmium chloride is at least as effective as is cadmium bromide for preparing the cadmium reagents. Since the bromide is more expensive and much more hygroscopic, the chloride is always used. It has also been reported (19) that the yields are approximately the same from a dialkylcadmium compound and an alkylcadmium halide; so the former is customarily used, since it requires only half as much cadmium chloride.

C. THE ACID CHLORIDE OR ANHYDRIDE

Organocadmium reagents will react with acid anhydrides (10, 12, 14, 16); however, the reaction seems to be uniformly inferior to that obtained with acid chlorides. The most interesting reaction with anhydrides is that with cyclic anhydrides. Unfortunately, the yields of keto acids (on the basis of alkyl or aryl halide) in this reaction have been only 25–30 per cent; so unless the halide is quite cheap, it seems profitable to convert the anhydride to the half-ester and this to the ester acid chloride (11, 39). Reaction of the latter compound with the cadmium reagent gives the keto ester corresponding to the keto acid obtained



from the anhydride (*cf.* equation on page 18). An exception is the phthalic anhydride type, for the ester acid chlorides of such dibasic acids are unstable (45).

Both aliphatic and aromatic acid chlorides react smoothly, the aliphatic ones being more reactive. This preparation of ketones has been very useful in the sterol series (15, 21, 21a, 29a), and a good yield has been obtained from a substituted acid chloride in the cyclohexane series (23). An aliphatic acid chloride of as high molecular weight as stearyl chloride has been found to react satisfactorily (19, 35). A considerable number (*cf.* table 2) of keto esters have been obtained in good yield from ester acid chlorides of dibasic acids. There has been one report (29) of the use of α,β-unsaturated acid chlorides in the reaction with an organocadmium reagent. The reaction between cinnamoyl chloride and diphenylcadmium gave about as good a yield as normal for the conditions used; however, several dialkylcadmium reagents gave only viscous oils in the reaction with cinnamoyl chloride, crotonyl chloride, or phenylpropiolyl chloride.

Bunnett and Tarbell (8) recently reported the interesting synthesis of α-chloro ketones by the reaction of organocadmium compounds with α-chloro acid chlorides, and more recently (12) the yields in such preparations have been improved considerably. The process is illustrated by the synthesis of 1-chloro-2-hexanone (III):

$$(C_4H_9)_2Cd + 2ClCH_2COCl \rightarrow \underset{\text{III}}{2C_4H_9COCH_2Cl} + CdCl_2$$

1-Chloro-2-hexanone

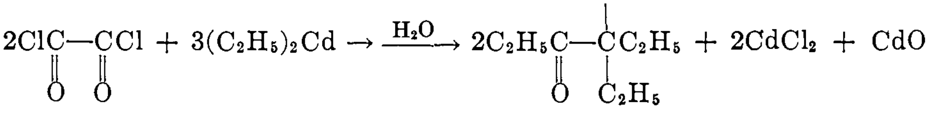
This preparation of α-chloro ketones is much simpler and safer than that involving an intermediate diazoketone (1, 4), especially if considerable quantities of such ketones are desired.

D. REACTION OF CADMIUM REAGENTS WITH OTHER GROUPS

1. Carbonyl groups

An isolated carbonyl group reacts with the cadmium reagent, but very slowly indeed. After 0.03 mole of benzaldehyde had been allowed to stand in a sealed tube for five months with excess diethylcadmium, there was obtained only 1.3 g. of ethylphenylcarbinol (19). Thus, the preparation of ketones by adding the acid chloride to the cadmium reagent results in very little addition of the cadmium reagent to the carbonyl group. It is true, however, that in some cases (12) the yield is improved somewhat by making the above addition at a low temperature and warming the mixture after all the acid chloride has been added.

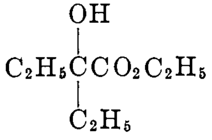
If the carbonyl group is activated by an adjacent group such as an ester group, the cadmium reagent may add to the activated carbonyl. For example (19), the reaction between oxalyl chloride and diethylcadmium gives a 27 per cent yield of diethylpropionylcarbinol:



$$2Cl\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle O}{\|}}{C}Cl + 3(C_2H_5)_2Cd \rightarrow \xrightarrow{H_2O} 2C_2H_5\underset{\underset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}}C_2H_5 + 2CdCl_2 + CdO$$

2. Ester groups

Diethylcadmium reacts with diethyl oxalate to give ethyl α-ethyl-α-hydroxybutyrate (IV) (19); however, cadmium reagents appear not to react at an appreciable rate with isolated ester groups, even formates (21). In the preparation of ethyl 10-ketohendecanoate from dimethylcadmium and ω-carbethoxynonoyl chloride (14) there was isolated a small amount of 2,11-dodecanedione (V), and it was suggested that this may have arisen from some reaction of dimethylcadmium with the ester grouping in ethyl 10-ketohendecanoate. This now seems highly improbable, and the trace of diketone very likely resulted from reaction of the dimethylcadmium with a small amount of sebacyl dichloride (VI) present in the ester acid chloride. The ester acid chloride was made from ethyl hydrogen sebacate, and half-esters disproportionate to some extent, on long standing, to the diacid and diester (12).



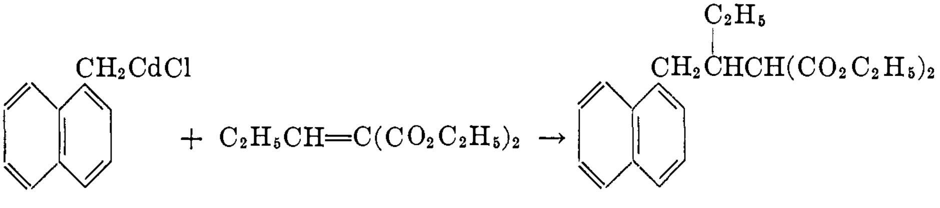
$$C_2H_5\overset{\displaystyle OH}{\underset{\displaystyle C_2H_5}{C}}CO_2C_2H_5$$

IV

$$(CH_3)_2Cd + 2ClCO(CH_2)_8CO_2C_2H_5 \rightarrow \underset{\text{Ethyl 10-ketohendecanoate}}{2CH_3CO(CH_2)_8CO_2C_2H_5} + CdCl_2$$

$CH_3CO(CH_2)_8COCH_3$	$ClCO(CH_2)_8COCl$
V	VI
2,11-Dodecanedione	Sebacyl dichloride

It has recently been reported (31) that cadmium reagents add in a 1,4-manner to alkylidenemalonic esters. In fact, the yields obtained in several such reactions were better than those obtained when the corresponding Grignard reagent was used. A representative reaction is the following, which gave a 65 per cent yield:



3. Miscellaneous groups

Only limited data are available concerning the reaction of cadmium reagents with other groups than those mentioned; however, it may be safely assumed that this reagent will not add to an amide or nitrile grouping. Gilman and Nelson (19) investigated several groupings and found that (*a*) coupling with *tert*-butyl chloride did not occur; (*b*) reaction with phenyl isocyanate did not occur (the isocyanate polymerized); (*c*) reaction with benzenesulfonyl chloride was according to the following equation:

$$2C_6H_5SO_2Cl + (C_6H_5)_2Cd \rightarrow C_6H_5SO_2C_6H_5 + C_6H_5SO_2H + C_6H_5Cl$$

Coupling does occur readily (37) with the α-chloro ether, 2,3-dichloro-1,4-dioxane, and the yield of 2,3-dialkyl-1,4-dioxane is much better than when the Grignard reagent is used. There seems to be no report concerning the reactivity of cadmium reagents toward the aromatic nitro grouping.

From the data in this section it is seen that, with the exception of groups containing active hydrogen, very few groups interfere with the preparation of ketones from cadmium reagents.

E. SIDE REACTIONS

1. Ester formation

It is known that acid chlorides will react with diethyl ether in the presence of anhydrous magnesium halide (10, 41, 42):

$$\mathrm{RCOCl} + (\mathrm{C_2H_5})_2\mathrm{O} \xrightarrow{\mathrm{Mg}^{++}} \mathrm{RCO_2C_2H_5} + \mathrm{C_2H_5Cl}$$

Since there is present in the mixture during a cadmium reaction a full molar equivalent of magnesium halide, the conditions for reaction of the acid chloride with ether are good. Although Gilman and Nelson (19) indicated that this reaction occurs to a very small extent, later workers (10, 12, 14, 29a) obtained appreciable quantities of ester when the reaction was carried out in ether. If the ether solution of the cadmium reagent is distilled to dryness and the reaction with the acid chloride is carried out in benzene solution, ester formation is greatly reduced, but there is still obtained 0.5–2.5 per cent of ester. This is true even if, after distillation of ether to dryness, benzene is added and distilled.

This small amount of ester is ordinarily of no great significance. It may be separated, if desired, by fractional distillation unless the cadmium reagent contains methyl or ethyl radicals. Methyl and ethyl ketones boil very near the corresponding ethyl esters. In such cases, a pure sample of ketone may be obtained by saponification and removal of the resultant acid.

If butyl ether is used as solvent (12) for preparation of the cadmium reagent, ester formation is reduced by the lower reactivity of butyl ether; also, the resulting butyl ester may be separated by fractional distillation from the corresponding methyl or ethyl ketones. Unfortunately, these advantages are nullified by the fact that the yields obtained in butyl ether are low (in the case reported), and Grignard reagents react very sluggishly with cadmium chloride in butyl ether. In the preparation of ethyl 10-ketohendecanoate (*cf.* page 21) in benzene as solvent the yield was 84 per cent, whereas in butyl ether it was only 57 per cent.

2. Addition to carbonyl

As stated in Section III,D,1, this reaction occurs, but to only a small extent unless the carbonyl is activated.

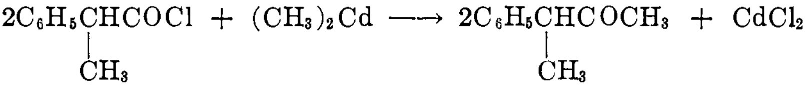
3. Enolization

The reaction of the cadmium reagent with the enol form of the ketone being prepared is always a potential side reaction. Gilman and Nelson (19) showed that benzaldehyde may be condensed with acetophenone in the presence of diethylcadmium:

$$C_6H_5CHO + CH_3COC_6H_5 \xrightarrow[\text{21 per cent yield}]{(C_2H_5)_2Cd} C_6H_5CH{=}CHCOC_6H_5$$

It was suggested that an —OCd type of compound might be involved in this reaction.

For most ketones it seems apparent that reaction of the enol form with cadmium reagent is a very minor side reaction. In fact, Campbell and Kenyon (9) carried out the following reaction, using *d*-methylphenylacetyl chloride:



$$2C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCOCl + (CH_3)_2Cd \longrightarrow 2C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCOCH_3 + CdCl_2$$

Since no significant racemization occurred during this reaction, it may be assumed that the concentration of the enol form of the ketone was very small. It should be pointed out that retention of asymmetry in the ketone may have resulted from the fact that nearly all the enol formed during the reaction was lost by condensation with another molecule of ketone. This is consistent with the fact that the good yields obtained in the preparation of simple ketones indicate very little loss of cadmium derivative by enolization.

In the case of α-chloro ketones, the loss by enolization becomes rather serious (12), so that the yields obtained in this type of preparation are lower than normal, 40–60 per cent. This, presumably, is due to the presence of the halogen atom in the α-position, promoting enolization. The occurrence of this reaction during the preparation of α-chloro ketones was established by isolation and characterization of the hydrocarbon formed by reaction of the cadmium derivative with the enol. When the preparation of 2-chloro-3-heptanone was carried out in ether,

$$(C_4H_9)_2Cd + 2CH_3CHClCOCl \longrightarrow 2C_4H_9COCHClCH_3 + CdCl_2$$

2-Chloro-3-heptanone

the yield was lower than when the preparation was carried out in benzene, and the yield of butane was greater in the case where the yield of ketone was lower. This indicates that enolization is more serious in ether as solvent than in benzene.

It was also found (12) that 1-chloro-2-hexanone (III) reacts rapidly and exothermically with di-*n*-butylcadmium, and there was evolved an amount of butane which, after purification, was equivalent to 70 per cent of the butyl bromide used for preparing the dibutylcadmium. When this reaction was worked up, very little of the 1-chloro-2-hexanone was recovered, most of it having been converted to higher-boiling materials. This could result from condensation of the cadmium enolate with another molecule of the chloro ketone.

IV. EXPERIMENTAL CONSIDERATIONS

Yields in the preparation of ketones from cadmium reagents can be greatly reduced by an incorrect experimental procedure, and it is probably in order to make some reference to the critical study of these factors which has been made (12). Certain general factors concerning experimental procedures were mentioned in Section III.

TABLE 1

Simple ketones and α-chloro ketones

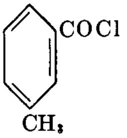
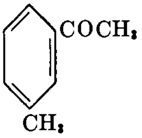
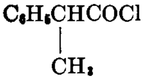
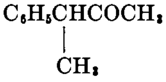
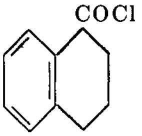
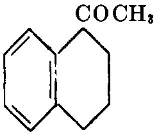
HALIDE	ACID CHLORIDE OR ACID ANHYDRIDE	KETONE	YIELD *per cent*	REFERENCE
C_2H_5Br	CH_3COCl	$C_2H_5COCH_3$	50	(19)
n-C_4H_9Br	CH_3COCl	$C_4H_9COCH_3$	74	(19)
n-C_4H_9Br	$(CH_3CO)_2O$	$C_4H_9COCH_3$	56	(16)
$(CH_3)_3CBr$	CH_3COCl	$(CH_3)_3CCOCH_3$	17	(19)
$(CH_3)_2CHBr$	C_3H_7COCl	$(CH_3)_2CHCOC_3H_7$	60	(19)
C_6H_5Br	CH_3COCl	$C_6H_5COCH_3$	83	(19)
CH_3Br	C_6H_5COCl	$C_6H_5COCH_3$	85	(19)
C_6H_5Br	$(CH_3CO)_2O$	$C_6H_5COCH_3$	75	(16)
C_6H_5Br	C_2H_5COCl	$C_6H_5COC_2H_5$	81	(12, 19)
C_2H_5Br	C_6H_5COCl	$C_6H_5COC_2H_5$	84	(12, 19, 38)
C_6H_5Br	$(C_2H_5CO)_2O$	$C_6H_5COC_2H_5$	68	(16)
C_2H_5Br	$(C_6H_5CO)_2O$	$C_6H_5COC_2H_5$	53	(16)
$C_6H_5CH_2Cl$	CH_3COCl	$C_6H_5CH_2COCH_3$	18	(19)
CH_3Br			83	(19)
CH_3Br	 $C_6H_5\underset{\underset{CH_3}{\mid}}{C}HCOCl$	 $C_6H_5\underset{\underset{CH_3}{\mid}}{C}HCOCH_3$	78	(9)
C_6H_5Br	$((CH_3)_2CHCO)_2O$	$C_6H_5COCH(CH_3)_2$	72	(16)
$(CH_3)_2CHBr$	$(C_6H_5CO)_2O$	$C_6H_5COCH(CH_3)_2$	44	(16)
CH_3Br			65	(28)

TABLE 1—*Continued*

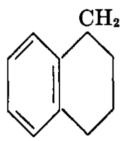
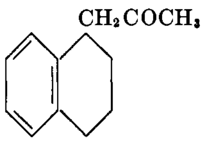
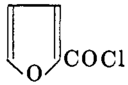
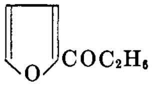
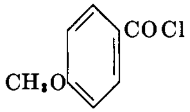
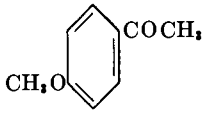
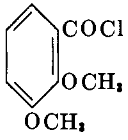
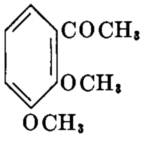
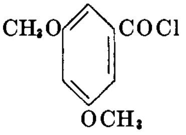
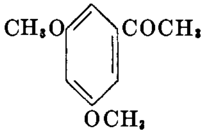
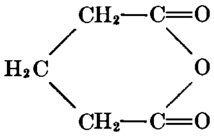
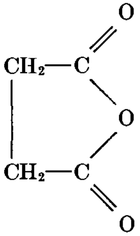
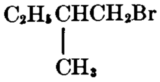
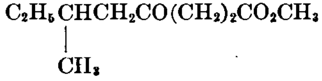
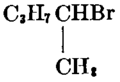
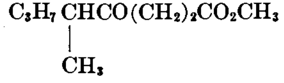
HALIDE	ACID CHLORIDE OR ACID ANHYDRIDE	KETONE	YIELD *per cent*	REFERENCE
CH_3Br			69	(28)
C_6H_5Br	C_6H_5COCl	$C_6H_5COC_6H_5$	57	(19)
C_6H_5Br	$C_6H_5CH{=}CHCOCl$	$C_6H_5CH{=}CHCOC_6H_5$	44	(29)
C_2H_5Br	n-$C_{17}H_{35}COCl$	$C_{17}H_{35}COC_2H_5$	65	(19)
$C_6H_5(CH_2)_2Br$	n-$C_{17}H_{35}COCl$	$C_{17}H_{35}CO(CH_2)_2C_6H_5$	65.5	(35)
n-C_4H_9Br	$CH_2ClCOCl$	$C_4H_9COCH_2Cl$	63.5	(8, 12)
n-$C_5H_{11}Br$	$CH_2ClCOCl$	$C_5H_{11}COCH_2Cl$	24	(8)
n-C_4H_9Br	$CH_3CHClCOCl$	$C_4H_9COCHClCH_3$	53	(12)
n-$C_{12}H_{25}Br$	$CH_2ClCOCl$	$C_{12}H_{25}COCH_2Cl$	18	(8)
n-$C_{12}H_{25}Br$	$CH_3CHClCOCl$	$C_{12}H_{25}COCHClCH_3$	13	(8)
n-$C_{14}H_{29}Br$	$CH_2ClCOCl$	$C_{14}H_{29}COCH_2Cl$	41	(8, 12)
C_2H_5Br			61	(19)
CH_3Br			84	(19)
CH_3Br			71	(44)
CH_3Br			84	(44)
CH_3Br	$C_6H_5O(CH_2)_3COCl$	$C_6H_5O(CH_2)_3COCH_3$	78	(6)

TABLE 2

Keto acids and keto esters

HALIDE	ACID CHLORIDE OR ACID ANHYDRIDE	KETONE	YIELD	REFERENCE
			per cent	
CH_3Br	$ClCO(CH_2)_4CO_2C_2H_5$	$CH_3CO(CH_2)_4CO_2C_2H_5$	76	(14, 24)
C_4H_9Br	$ClCO(CH_2)_2CO_2CH_3$	$C_4H_9CO(CH_2)_2CO_2CH_3$	80	(12)
n-C_4H_9Br		$C_4H_9CO(CH_2)_3CO_2H$	30.5	(12)
$(CH_3)_2CH(CH_2)_2Br$	$ClCO(CH_2)_2CO_2CH_3$	$(CH_3)_2CH(CH_2)_2CO(CH_2)_2CO_2CH_3$	79	(10, 12, 14)
$(CH_3)_2CH(CH_2)_2Br$		$(CH_3)_2CH(CH_2)_2CO(CH_2)_2CO_2H$	31	(14)
 $C_2H_5CH(CH_3)CH_2Br$	$ClCO(CH_2)_2CO_2CH_3$	 $C_2H_5CH(CH_3)CH_2CO(CH_2)_2CO_2CH_3$	60	(14)
 $C_3H_7CH(CH_3)Br$	$ClCO(CH_2)_2CO_2CH_3$	 $C_3H_7CH(CH_3)CO(CH_2)_2CO_2CH_3$	21.5	(12, 14)

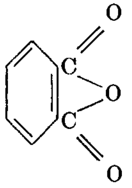
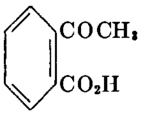
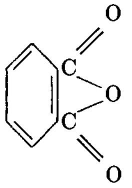
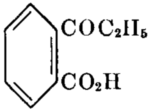
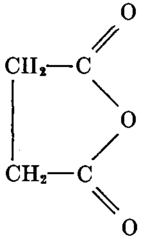
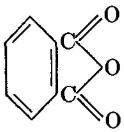
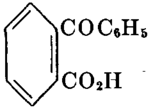
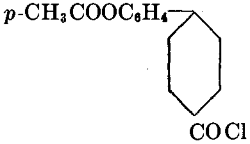
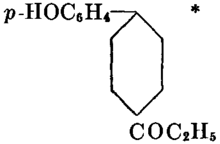
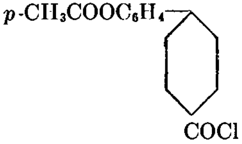
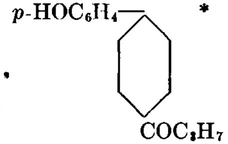
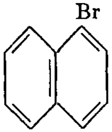
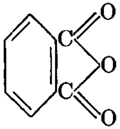
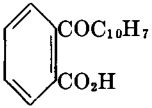
CH_3Br			62	(16)
C_2H_5Br			67	(16)
C_6H_5Br		$C_6H_5CO(CH_2)_2CO_2H$	30	(16)
CH_3Br	$ClCO(CH_2)_7CO_2C_2H_5$	$CH_3CO(CH_2)_7CO_2C_2H_5$	64	(24)
CH_3Br	$ClCO(CH_2)_8CO_2C_2H_5$	$CH_3CO(CH_2)_8CO_2C_2H_5$	84	(12, 14)
$(CH_3)_2CH(CH_2)_2Br$	$ClCO(CH_2)_4CO_2CH_3$	$(CH_3)_2CH(CH_2)_2CO(CH_2)_4CO_2CH_3$	84	(43)

TABLE 2 — *Continued*

HALIDE	ACID CHLORIDE OR ACID ANHYDRIDE	KETONE	YIELD	REFERENCE
			per cent	
C_6H_5Br			64	(16)
C_2H_5Br		 *	63	(23)
n-C_3H_7Br		 *	75	(23)
$(CH_3)_2CH(CH_2)_2Br$	$ClCO(CH_2)_8CO_2C_2H_5$	$(CH_3)_2CH(CH_2)_2CO(CH_2)_8CO_2C_2H_5$	85	(14)
			57	(16)
$(CH_3)_2CH(CH_2)_6Br$	$ClCO(CH_2)_8CO_2C_2H_5$	$(CH_3)_2CH(CH_2)_6CO(CH_2)_8CO_2C_2H_5$	46	(10)

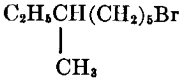
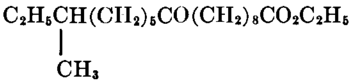
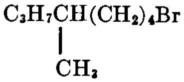
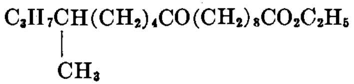
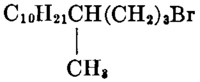
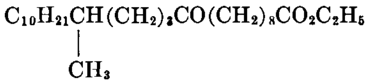
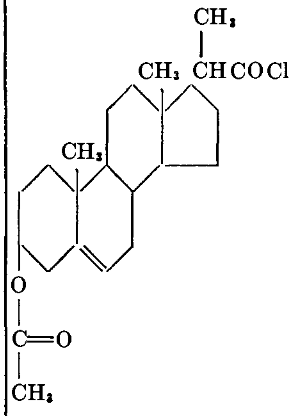
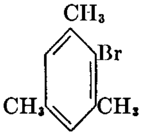
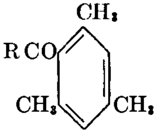
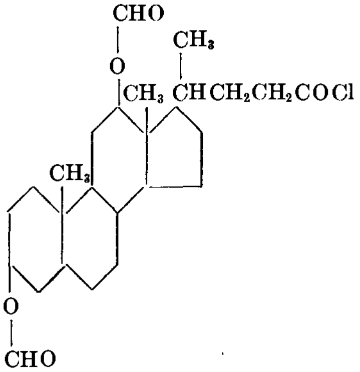
 $C_2H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_5Br$	$ClCO(CH_2)_8CO_2C_2H_5$	 $C_2H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_5CO(CH_2)_8CO_2C_2H_5$	76.5	(14)
 $C_3H_7\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_4Br$	$ClCO(CH_2)_8CO_2C_2H_5$	 $C_3H_7\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_4CO(CH_2)_8CO_2C_2H_5$	65	(13)
 $C_{10}H_{21}\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_3Br$	$ClCO(CH_2)_8CO_2C_2H_5$	 $C_{10}H_{21}\underset{\displaystyle CH_3}{\underset{\vert}{C}}H(CH_2)_3CO(CH_2)_8CO_2C_2H_5$	78	(13)
C_6H_5Br		$RCOC_6H_5$ (R = the sterol nucleus indicated)	98	(15)
CH_3I or CH_3Br	RCOCl	$RCOCH_3$	95	(15)
C_2H_5Br	RCOCl	$RCOC_2H_5$	93.5	(15)
$(CH_3)_2CH(CH_2)_2Br$	RCOCl	$RCO(CH_2)_2CH(CH_3)_2$	84	(15)

TABLE 2—*Continued*

HALIDE	ACID CHLORIDE OR ACID ANHYDRIDE	KETONE	YIELD	REFERENCE
			per cent	
	RCOCl		46	(15)
$(CH_3)_2CHBr$	RCH_2CH_2COCl	$RCH_2CH_2COCH(CH_3)_2$		(29a)
	(R = sterol nucleus indicated above)			
C_6H_5Br		$R'COC_6H_5$† (R′ = sterol nucleus indicated at left, except that the formyl esters at the 3- and 12-positions were hydrolyzed to give hydroxyl groups)	81	(21)

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* The keto ester obtained as the initial reaction product was hydrolyzed and this product was isolated.

† By the same process, phenyl ketones of seven other steroid derivatives were prepared by these authors. This preparation, only, was described "as an example", and yields were not reported for the other preparations. Jacobsen (21a) has also reported a similar preparation.

After the Grignard reagent has been prepared in ether it is allowed to react with solid cadmium chloride in this solvent, most conveniently at the boiling temperature unless a thermally unstable cadmium derivative is being prepared. The length of time required for this reaction varies considerably, even for the same preparation, probably owing to variation in particle size of the cadmium chloride. Thus, completion of this reaction should always be checked by testing for Grignard reagent (12, 19).

After formation of the cadmium derivative, it is desirable to remove ether by distillation and carry out the reaction with the acid chloride in benzene. This nearly eliminates ester formation (*cf.* Section III,E,1), reduces enolization (*cf.* Section III,E,3), and often has the additional advantage of preventing the reaction complex from agglutinating and stopping the stirrer, in cases where this happens in ether. Also, the higher reaction temperature makes possible the completion of the reaction in 10–60 min., whereas several hours are sometimes required in boiling ether.

The laborious procedures (6, 8, 37) for drying cadmium chloride that have been described are quite unnecessary. Drying to constant weight in an oven at 110°C. gives entirely reliable anhydrous cadmium chloride. It may be handled in air without absorbing significant amounts of moisture; however, it should be stored in a desiccator, for it slowly absorbs moisture from the air.

The organometallic compounds and metallic halides formed in this reaction always precipitate and form heavy sludges. Failure to continue adequate stirring to the end of the reaction lowers the yield significantly; so an efficient stirrer, such as the Hershberg type (20), and a powerful stirring motor should be used.

Since there is some loss in preparing the cadmium derivative from the alkyl or aryl halide *via* the Grignard reagent, there is no advantage in using an amount of acid chloride equivalent to the bromide. It has been found (12) that the maximum useful ratio of acid chloride to bromide is about 0.8. Use of a larger ratio of acid chloride does not increase the yield based on bromide. If methyl or ethyl bromide is used, some loss of dialkylcadmium occurs when the ether is distilled from the mixture, so it is advisable to use only a 0.5 molar equivalent of acid chloride if complete consumption of the acid chloride is to be assured. In cases where a very expensive acid chloride is used, a large excess of cadmium reagent is recommended for a maximum yield of ketone based on the acid chloride. In this manner, yields up to 98 per cent have been obtained (15).

V. KETONES PREPARED BY THE CADMIUM REACTION

An effort has been made to enter in tables 1 and 2 all the ketones prepared by the reaction of an organocadmium reagent with an acid chloride or acid anhydride; however, it is probable that isolated examples reported as part of a synthesis have been overlooked. Since the factors contributing to a maximum yield in this type of preparation have been investigated only recently, it is certain that many of the yields included in the tables lack much of being the maximum obtainable. The yields in the tables are based on acid chloride or acid anhydride.

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