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DISPLACEMENT OF HALOGEN BY ORGANOCADMIUM REAGENTS IN ALPHA-HALO CARBONYL COMPOUNDS

JAMES RUPERT YOUNG

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DISPLACEMENT OF HALOGEN BY ORGANOCADMIUM REAGENTS

IN α-HALO CARBONYL COMPOUNDS

BY

JAMES RUPERT YOUNG

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Paul R. Jones

Gloria H. Lyle

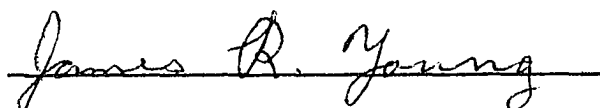_J. H. Weber_

Robert E. Lyle

Miyoshi Ikawa

May 19, 1967
Date

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James R. Young

TO THE FOUR GIRLS IN MY LIFE

My wife, Diana,

and

my daughters, Hilda, Mavis, and Argenta

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INTRODUCTION

Organomagnesium reagents have been used on occasion to replace a halogen atom vicinal to a carbonyl group with an alkyl or aryl substituent, but a great variety of products is possible because of the reactivity of the carbonyl group and the possibility of enolization. On the other hand, organocadmium reagents, being less reactive toward the carbonyl group, might be expected to effect replacement of the halogen without the attendant side reactions.

Following the observation by Crosby[1] that α-naphthylacetic acid was obtained in low yield (after saponification) by the reaction of ethyl bromoacetate and the α-naphthylcadmium reagent, the present work was undertaken to study the generality of this reaction.

-1-

HISTORICAL BACKGROUND

Grignard Reagents

When one equivalent of Grignard reagent is allowed to react with an α-halocarbonyl compound, four types of reactions are possible:[2] (a) replacement of the halogen atom by the alkyl or aryl group of the Grignard reagent; (b) addition of the reagent to the carbonyl double bond; (c) removal of the halogen with formation of the enolate of the non-halogenated carbonyl compound; and (d) removal of a proton with formation of the enolate of the halogenated carbonyl compound. The discussion that follows will be concerned primarily with reactions of the first two types.

There are many examples in the literature of reactions in which the <u>alpha</u> halogen atom of a ketone[3-16] or aldehyde[17] is replaced by the organic portion of the Grignard reagent.

As it was pointed out by Kharasch and Reinmuth[2], all of these replacements apparently involve reaction at the carbonyl, followed by rearrangement. Thus, Sackur[12] obtained 1-acetyl-1-phenylcyclohexane on treatment of 1-acetyl-1-chlorocyclohexane with phenylmagnesium bromide, and also on treatment of 1-benzoyl-1-chlorocyclohexane with methylmagnesium iodide.
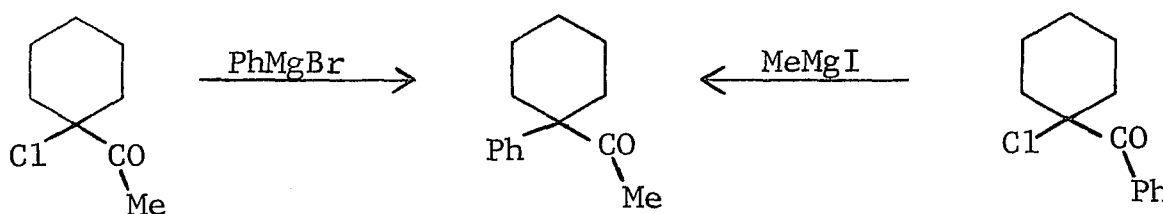
More recently, Ando[15] has amply demonstrated that
the products obtained on reaction of the Grignard reagent
with some α-chloroacetophenones depend on the relative migra-
tory tendency of the organic group of the reagent, compared
to the group attached to the carbonyl in the acetophenone.
The following examples illustrate variations in the course of
the reaction.

$$Ph-CO-CH_2Cl \; + \; RMgBr \; \rightarrow \; Ph-CO-CH_2-R$$

$$R = \underline{p}-MeO-C_6H_4 \; , \; \underline{p}-Me-C_6H_4$$

$$Ph-CO-CH_2Cl \; + \; RMgBr \; \rightarrow \; Ph-CO-CH_2-R \; + \; R-CO-CH_2-Ph$$

$$R = \underline{p}-F-C_6H_4$$

$$Ph-CO-CH_2Cl \; + \; RMgBr \; \rightarrow \; R-CO-CH_2-Ph$$

$$R = \underline{p}-Cl-C_6H_4, \; Me$$

$$\underline{p}-X-C_6H_4-CO-CH_2Cl \; + \; RMgBr \; \rightarrow \; R-CO-CH_2-C_6H_4-X$$

1) X = MeO , R = Ph

2) X = F , R = Me
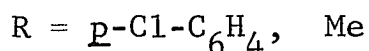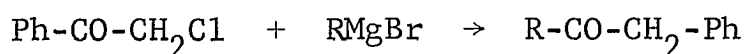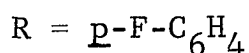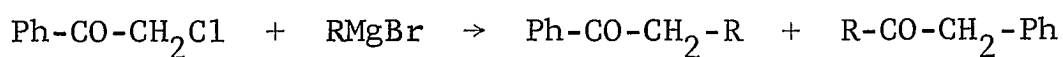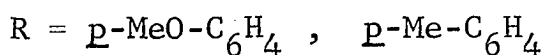
Apparently, the reaction proceeds in a similar manner with an α-halo ester. For example, Ando[18] found that the following reaction took place in yields of 50-60%.

$$Cl-CH_2-COOEt \xrightarrow{RMgBr} R-CH_2-CO-R$$

$R = Ph, \underline{p}-MeO-C_6H_4, \underline{p}-Me-C_6H_4, \underline{p}-F-C_6H_4, \underline{p}-Cl-C_6H_4.$
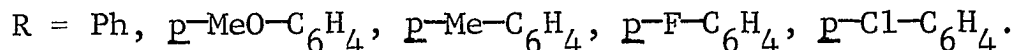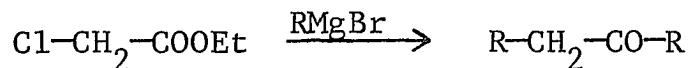
When two equivalents of methylmagnesium iodide were used, the only product isolated was 3-methyl-2-butanol.

$$Cl-CH_2-COOEt + MeMgI \rightarrow (CH_3)_2CH-\overset{\overset{\displaystyle OH}{\displaystyle |}}{C}HCH_3$$
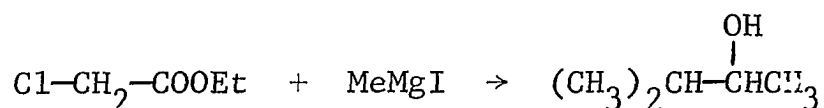
This can be rationalized as shown in Chart 1.

Chart 1

Reaction of Methylmagnesium Iodide
with Ethyl Chloroacetate
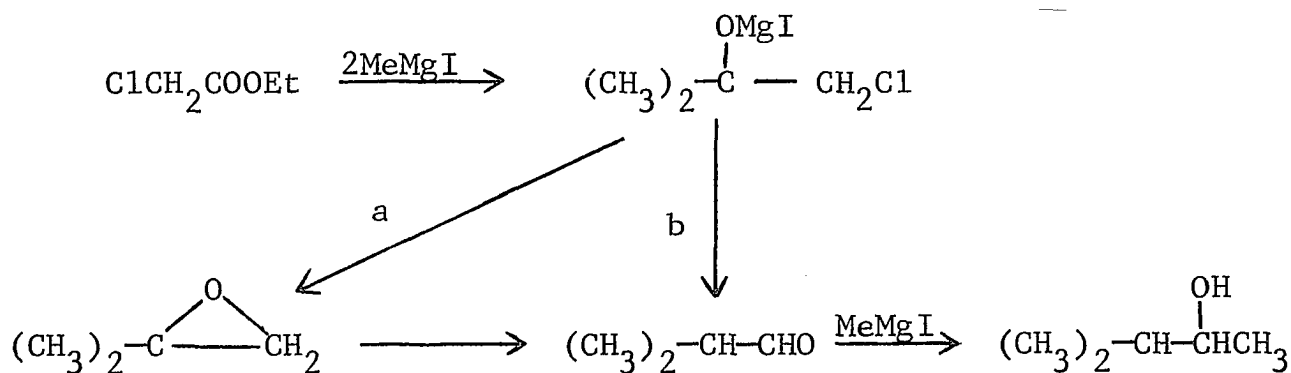
Although it is possible that the halohydrinate rearranges directly to the aldehyde (Path b), the epoxide intermediate (Path a) is postulated by Henry[19,20], who obtained the same product as above by reaction of methylmagnesium bromide with chloroacetone. Likewise, similar reactions of bromoacetone have been reported[21], and Crandall and Chang[22], among others, have shown that base-induced isomerizations of epoxides can

lead to carbonyl compounds.

By reaction at 0° of chloroacetic acid with two equivalents of Grignard reagent, Ando and coworkers[23] reported the formation (in 30-60% yields) of ketones of the type:

$Cl-CH_2-CO-R$ (R = Ph, $p-MeO-C_6H_4$, $p-Me-C_6H_4$, $p-Cl-C_6H_4$, $p-F-C_6H_4$, and $n-C_4H_9$). Fluoroacetic acid reacted similarly, but yields were lower because of formation of RCH_2COOH. The yield of this product increased with increasing migratory tendency of R.

Nitriles and amides with an α-chloro substituent react in a completely analogous manner, according to Smith[24], although low yields are reported. An example is the formation of phenyl benzhydryl ketone from either the nitrile or amide of α-chlorophenylacetic acid.

$$Ph-\underset{\underset{Cl}{|}}{CH}-CN \xrightarrow{PhMgBr} (Ph)_2-CH-COPh \xleftarrow{PhMgBr} Ph-\underset{\underset{Cl}{|}}{CH}-CO-NH_2$$
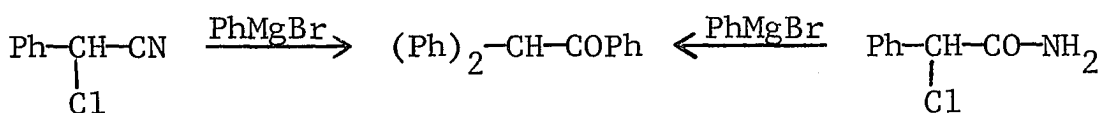
A most unusual and completely anomalous displacement reaction involving Grignard reagent was reported in 1925 by Kenyon and coworkers.[25] Although replacement of tosylate with an alkyl or aryl group via the Grignard is a well-known reaction[26,27,28], when the optically active p-toluene sulfonate of ethyl lactate was treated with either phenylmagnesium bromide or ethylmagnesium bromide, optically active ethyl α-bromopropionate with retention of configuration was isolated in good yield.

$$CH_3-\underset{\underset{OTs}{|}}{CH}-COOEt + \begin{matrix} PhMgBr \\ or \\ EtMgBr \end{matrix} \longrightarrow CH_3-\underset{\underset{Br}{|}}{CH}-COOEt$$
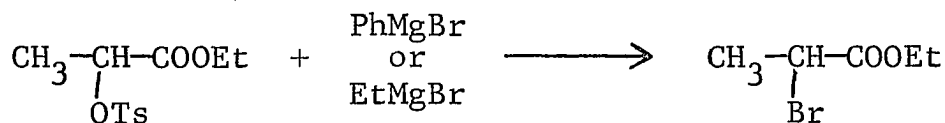
It is very probable, however, that this product did not arise through any action of the Grignard reagent, but is the result of a direct displacement of tosylate by bromide ion.[25,29]

Grignard reagents add normally to the carbonyl group of α-halocarbonyl compounds, although rearrangement may occur subsequently if the reaction mixture is heated. Thus if reaction conditions are kept mild, it is often possible to stop the reaction at the intermediate stage, which permits the isolation of the halohydrin.[7,19,20,30-40]

For example, Helferich and Speidel[33] reported the formation in good yield of 1-chloro-2-butanol from chloroacetaldehyde and ethylmagnesium bromide. Kirrmann and Chancel[38,39] have shown that bromoacetaldehyde also forms the halohydrin in high yield. In their study with α-bromo aldehydes, they found the yield of bromohydrin decreases sharply if the bromine is secondary or tertiary (in the latter case only minor amounts are isolated), whereas the yield of ketone formed by hydride transfer or the tertiary alcohol derived from the ketone increases in the same direction. These products are illustrated in the equations below. They also found that the yield of bromohydrin decreases as the reaction temperature is raised.

$$
\underset{\underset{Br}{|}}{\overset{\overset{R'}{|}}{R{-}C{-}CHO}} \quad \xrightarrow{R''MgX} \quad \underset{\underset{Br\ H}{|\ |}}{\overset{\overset{R'\ OMgX}{|\ \ \ |}}{R{-}C{-}C{-}R''}} \quad \longrightarrow \quad \underset{\underset{Br\ H}{|\ |}}{\overset{\overset{R'\ OH}{|\ \ |}}{R{-}C{-}C{-}R''}}
$$

$$
\underset{\underset{H}{|}}{\overset{\overset{R'\quad O}{|\quad //}}{R{-}C{-}C{-}R''}} \quad \xrightarrow{R''MgX} \quad \underset{\underset{H\ \ R''}{|\ \ \ |}}{\overset{\overset{R'\ \ OH}{|\ \ \ |}}{R{-}C{-}C{-}R''}}
$$
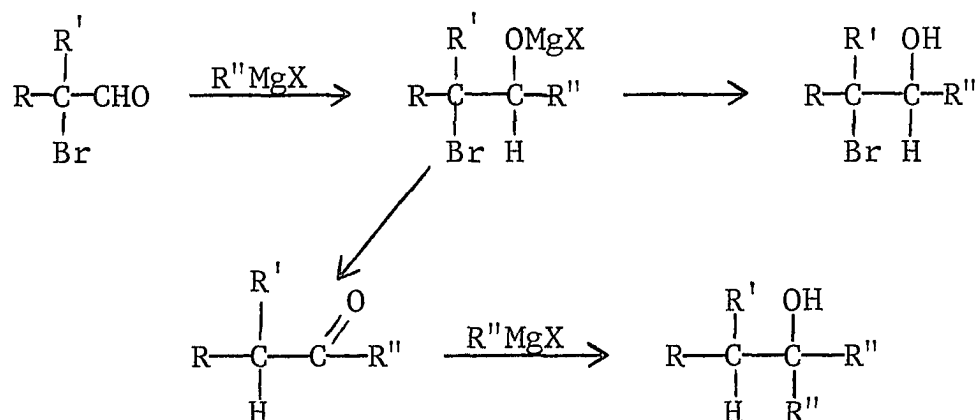
Cornforth and coworkers[40], in a comparison of the reactivity of α-chloro aldehydes and ketones with n-butylmagnesium bromide or n-butyllithium, reported the yields of

chlorohydrin shown in Table 1.

Table 1

Yield of Chlorohydrin from Chlorocarbonyl Compounds[40]

Chlorocarbonyl Compound	Yield (%) with n-BuLi	with n-BuMgBr
$CH_3-CH_2-CHCl-CHO$	65	68
$CH_3-CO-CH_2Cl$	30*	67
$CH_3-CH_2-CO-CH_2Cl$	25	75
$CH_3-CO-CHCl-CH_3$	79	65
$(CH_3)_2CCl-CHO$	63	25
$(CH_3)_2CCl-CO-CH_3$	68	10

*Light petroleum used as solvent; ether used in all others.

Their reagents were mixed at -70°, with a short reaction time (10-15 minutes), and acetic acid was used for hydrolysis of the complex. They stated that in the one (Grignard) reaction carried out at room temperature, as well as at -70°, the yield was lower at the higher temperature. They also stated that, in general, chlorohydrins were obtained in higher yields with the Grignard reagent than with butyllithium for ketones containing the group $-CO-CH_2Cl$, because the latter reagent caused self-condensation. The lithium reagent was superior with the hindered ketones because these were reduced by the Grignard reagent.

Organocadmium Reagents

Since the initial investigation of organocadmium com-
pounds by Gilman and Nelson[41], in which it was reported that
these reagents are reactive toward acid halides, there have
been comparatively few reports of their reaction with other
types of halides. Summerbell and Bauer[42] obtained in 44%
yield 2,3-dibutyl-1,4-dioxane by the reaction of dibutylcadmium
with the α-halo ether, 2,3-dichloro-1,4-dioxane. Hurd and
Holysz[43] extended this type of reaction to the carbohydrate
series. They found that tetraacetylglucopyranosyl bromide,
which may be visualized as an α-halo ether, coupled with di-
phenylcadmium in refluxing benzene solution to give tetra-
acetylglucopyranosylbenzene in 23% yield as shown below. The
mannose derivative behaved similarly, a 29% yield of the ex-
pected product being reported.
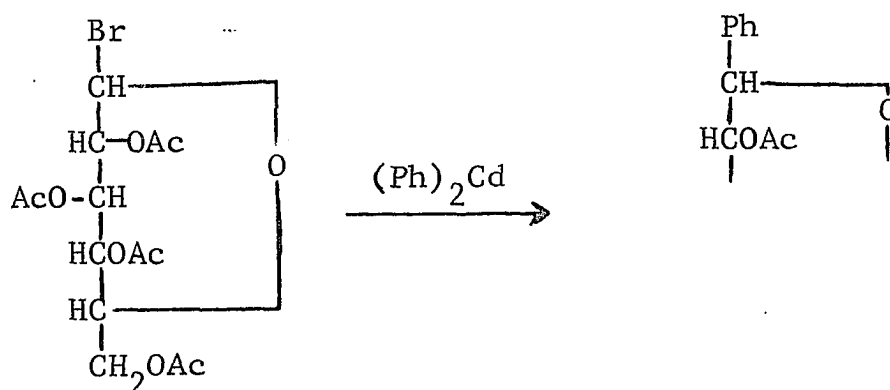
When dibutyl- or dibenzylcadmium was used, however,
entirely unexpected acetal-like products (a and b) were ob-
tained in 57% and 30% yield, respectively.

a) R = $C_6H_5CH_2$

b) R = C_4H_9
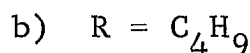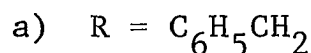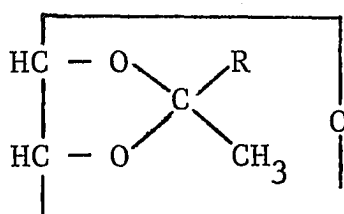
The authors offered the mechanistic scheme shown in Chart 2 as one possible course for the reaction.

Chart 2

Reaction of Cadmium Reagent with Halo Carbohydrate[43]
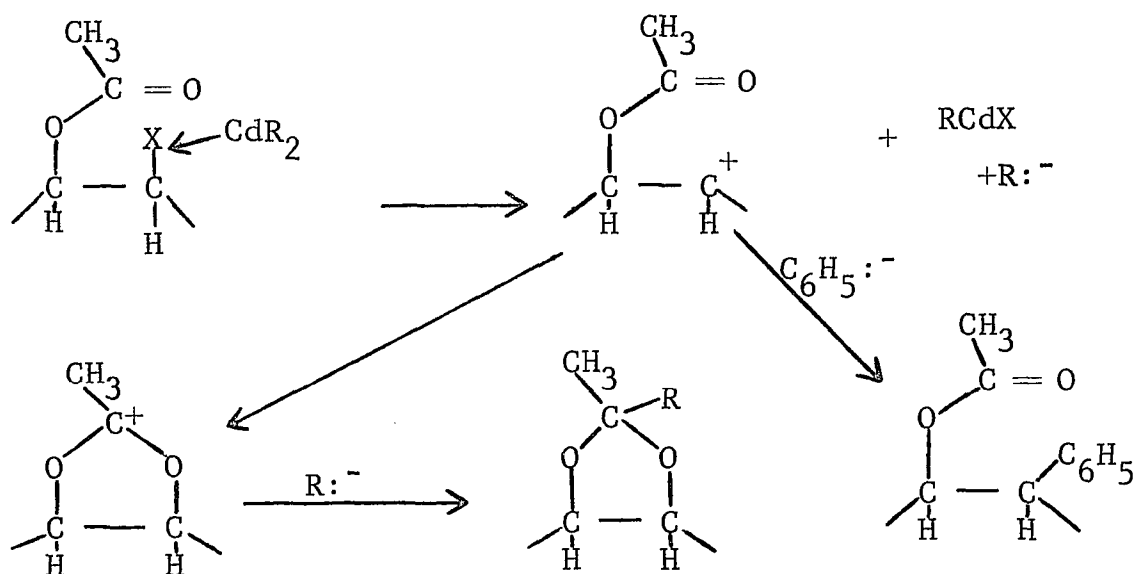
They state:

> If R is a highly electronegative group such as phenyl, then the normal coupling reaction apparently predominates. However, if R is a relatively less electronegative group such as butyl or benzyl, then inter-action of the deficient carbon and the electronegative carbonyl oxygen becomes significant.

Cason and Fessenden[44] have shown that there is no appreciable reaction between organocadmium reagents and allyl bromide or 2-iodooctane, nor is there coupling with tertiary chlorides. The latter are dehydrohalogenated.

Jones and coworkers[45,46], among others, have reported displacement of halogen and other substituents by organo-cadmium reagents in certain α'-substituted lactones and esters,

although the reagent does not normally attack the ester function itself.[47] A similar reaction has been reported for organozinc[48], for Grignard reagents[48,49], and for organomercury.[50]

For example, in the following reaction, the products were obtained in the yields shown in Table 2.
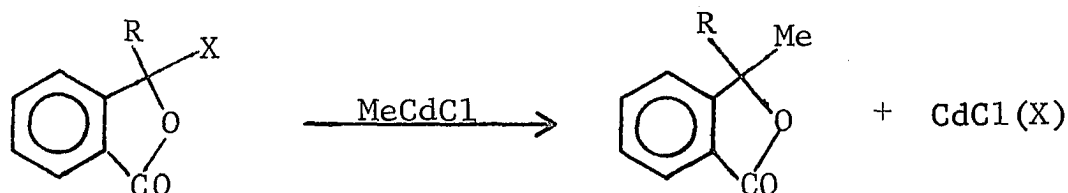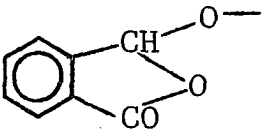
Table 2

Reaction of 3-Substituted Phthalides with Methylcadmium Chloride[45]

R	X	Yield (%) of Product
H	Br	90
H	OCH_3	9
H	OC_2H_5	9
H	OH	31[a]
H	$OCOCH_3$	0
CH_3	$OCOCH_3$	44
H		100[b]

a) Starting material was recovered to the extent of 41%.

b) Based on formation of two moles of product per mole of starting material.

In the only reported instance of displacement in α'-substituted acyclic esters[46], compounds I and II by reaction with phenylcadmium chloride yielded III, and IV yielded V.

$$C_6H_5\overset{\overset{O}{\|}}{C}O\underset{\underset{X}{|}}{C}HC_6H_5 \qquad\qquad C_6H_5\overset{\overset{O}{\|}}{C}O\underset{\underset{Cl}{|}}{C}HCH=CHC_6H_5$$

$$\text{IV}$$

I   X = Cl

II   X = $OCOC_6H_5$ $(C_6H_5)_2CHCH=CHC_6H_5$
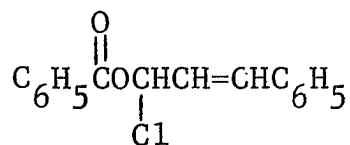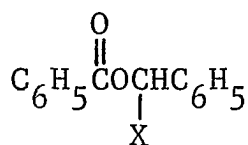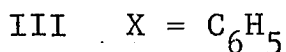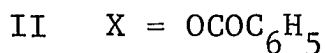
III   X = C_6H_5 V

It is interesting to note that the formation of V required displacement of both the benzoyloxy and the chloro group.

    - · Apparent replacement of the chlorocarbonyl group has been reported by Cason and Schmitz.[51] Treatment of tri-phenylacetyl chloride with dimethylcadmium gave triphenyl ethane in approximately 40% yield, in addition to the other products (in lower yield) shown in the following equation.

$$(C_6H_5)_3C\text{--}COCl \xrightarrow{Me_2Cd} (C_6H_5)_3C\text{--}CH_3 + (C_6H_5)_3CH$$

$$+ (C_6H_5)_3C\text{--}CO\text{--}CH_3$$
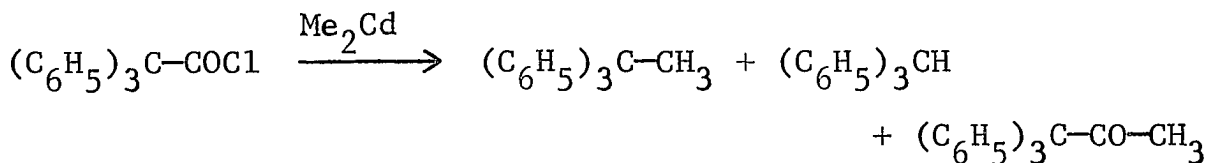
They accounted for the triphenyl ethane as follows: loss of chloride ion from the acid chloride yielded the acylonium ion which, in turn, lost carbon monoxide to form the trityl carbonium ion. This reacted with the cadmium reagent to yield the observed product. This is shown in the following equations:

$$(Ph)_3C\text{-}COCl \xrightarrow{\text{- }Cl^-} (Ph)_3C\text{-}\overset{+}{C}=O \xrightarrow{\text{- }CO}$$

$$(Ph)_3\overset{+}{C} \xrightarrow{(CH_3)_2Cd} (Ph)_3C\text{-}CH_3$$
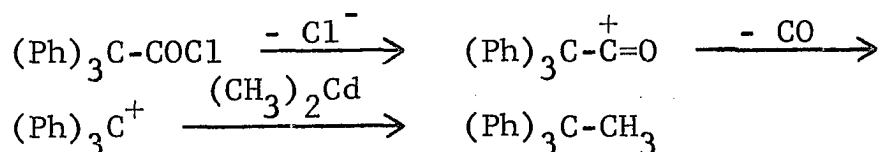
Reaction of organocadmium reagents with α-halocarbonyl compounds has not been previously reported to lead to displacement, except in the recent work of Gross and Freiberg.[52] However, as is seen in the following equation, the halocarbonyl compound is also an α-chloro ether, and the displacement reaction may be due to this fact alone. The product is formed in approximately 60% yield.

$$CH_3OCH-COOMe \quad \xrightarrow{(Ph)_2Cd} \quad CH_3OCH-COOMe$$
$$\underset{Cl}{|} \qquad\qquad\qquad\qquad \underset{Ph}{|}$$
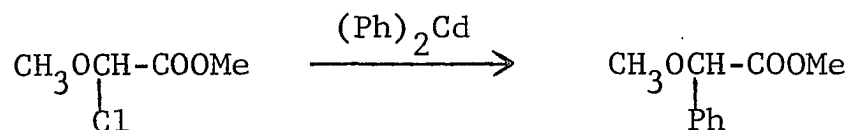
Bunnett and Tarbell[53] have reported the formation of α-chloro ketones in 8-29% yield as shown below.

$$ClCH_2-COCl \quad \xrightarrow{R_2Cd} \quad ClCH_2-CO-R$$

$$CH_3-CHCl-COCl \quad \xrightarrow{R_2Cd} \quad CH_3-CHCl-CO-R$$

R = alkyl
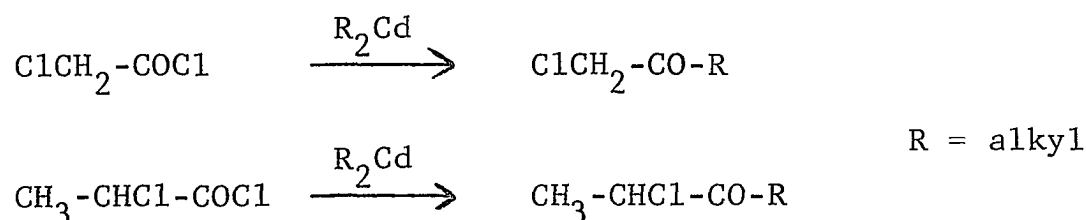
In the one case where diphenyl cadmium was used the yield was very low. In addition, it is not known what other products may have been formed, as no attempt was made to identify side-products of the reaction.

A study of the reaction of a variety of α-chloro ketones and aldehydes with organocadmium reagents has been made by Tatibouët and Fréon.[54] It was reported that there was no reaction in the case of monochloroketones and aldehydes. Both α,α- and α,α'-dichloro ketones, as well as α,α-dichloro aldehydes, suffered addition of the organocadmium reagent at the carbonyl to give the dichloro alcohol in yields of 30-65%. (The authors did not state which ketones and aldehydes were employed, nor did they specify the nature of the organocadmium reagents.) Likewise, from chloral they obtained trichloro alcohols in yields of 45-70%, as shown.

$$CCl_3\text{-}CHO + R_2Cd \longrightarrow CCl_3\text{-}CH(R)OH + CdX_2$$
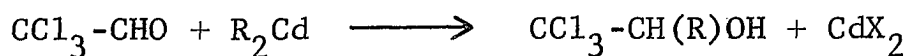
In no case did they report displacement of the halogen by the organocadmium reagent.

Alkylcadmium reagents have been shown to react with α-bromo esters under certain conditions to produce an alkyl bromide corresponding to the alkylcadmium reagent and a cadmium enolate of the ester.[44,55] Cason and Fessenden[44] found that this enolate undergoes the usual Claisen and Reformatsky condensations. Thus, as shown below, when di-butylcadmium was treated with ethyl α-bromoisobutyrate, there was obtained ethyl 2,2,4-trimethyl-3-oxopentanoate in 72% yield. The same product was obtained when dodecylcadmium reagent was used, and in this case, dodecyl bromide was also isolated in 62% yield.

$$(CH_3)_2C(Br)\text{-}COOEt \xrightarrow{R_2Cd} (CH_3)_2CH\text{-}CO\text{-}C(CH_3)_2\text{-}COOEt + RBr$$
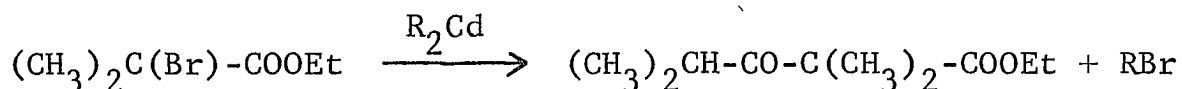
It was pointed out that the same keto ester is obtained by allowing magnesium to react[56] with ethyl α-bromoisobutyrate, but when the sodium enolate of ethyl isobutyrate interacts[57] with ethyl α-bromoisobutyrate, the product is diethyl tetra-methylsuccinate (VI).

$$(CH_3)_2\underset{|}{C}\text{-}COOEt$$
$$(CH_3)_2\overset{|}{C}\text{-}COOEt$$

VI
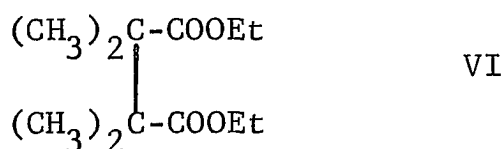
The authors[44] reasoned that if the cadmium enolate is actually present in the formation of the keto ester above, it should also condense with other carbonyl compounds. Such proved to be the case. When n-propylcadmium reagent was added to a mixture of ethyl α-bromoisobutyrate and 2-octanone,

the Reformatsky product, ethyl 2,2,3-trimethyl-3-hydroxynon-anoate, was formed in 83% yield, as shown below.

$$(CH_3)_2C(Br)\text{-}COOEt \;+\; C_6H_{13}\text{-}CO\text{-}CH_3 \;\xrightarrow{\;R_2Cd\;}\; C_6H_{13}\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}\text{-}C(CH_3)_2\text{-}COOEt$$
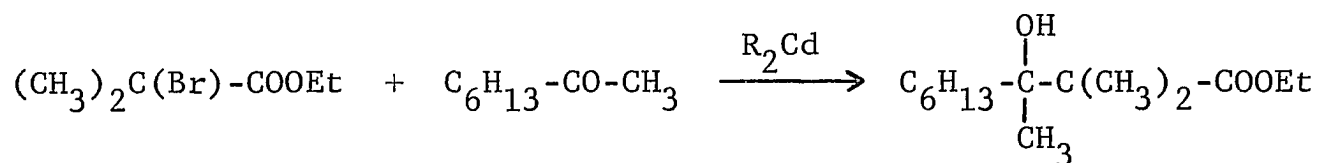
It was also found that ethyl α-bromopropionate forms the enolate, which likewise may be condensed with aldehydes or ketones.

DISCUSSION AND RESULTS

Displacement of halogen from certain α-halo ketones and esters by organocadmium reagents to yield the α-aryl or (in one case) α-alkyl substituted ketone or ester, as in the general equations shown below, has been investigated. The results are presented in Tables 3 and 4.

$$\text{Ph-CO-CH-R} \xrightarrow{\text{R'CdCl}} \text{Ph-CO-CH-R} + \text{CdCl(X)}$$
$$\overset{|}{X} \qquad\qquad\qquad\qquad \overset{|}{R'}$$

$$\overset{R'}{\underset{X}{\overset{|}{\underset{|}{R-C-COOEt}}}} \xrightarrow{\text{R''CdCl}} \overset{R'}{\underset{R''}{\overset{|}{\underset{|}{R-C-COOEt}}}} + \text{CdCl(X)}$$
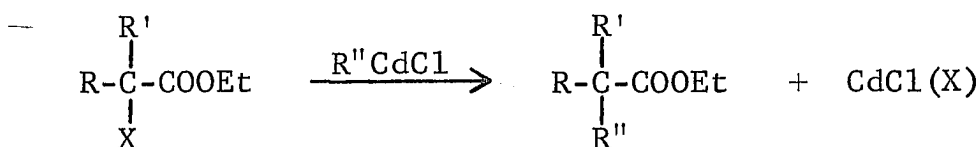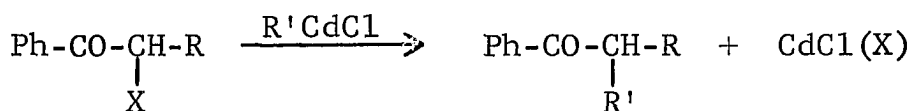
As was pointed out earlier, in similar displacements by Grignard reagents, the product appears to result from addition at the carbonyl, followed by rearrangement. That such may not be the case with organocadmium reagents is indicated by their low reactivity with carbonyl groups in general, and their order of reactivity with acid halides.[58] Thus, with the Grignard reagent, acid fluorides are the most reactive and acid iodides are least reactive, as would be expected for carbonyl addition. The reverse is true for organozinc, organocadmium, and organomercury compounds. Since these reagents follow the general order of reactivity of C-X bonds in displacement reactions[59], preliminary reaction at the carbonyl group apparently is not involved.

It was of great interest, therefore, to carry out the reaction of methylcadmium chloride and phenacyl bromide. Two alternate reaction paths, leading to entirely different

Table 3

Reaction of Organocadmium Reagents with α-Halo Ketones

Ketone Ph-CO-CH(X)R		Cd Reagent		Solvent	Reaction Temperature	Yield(%) Ph-CO-CH(R')R
R	X	R'	Ratio[a]			
H	Br	Me	2	THF	ice bath	15
H	Br	Ph	1	Ether	reflux	21
"	"	"	2	"	"	12[b]
"	"	"	1	"	"	7[c]
"	"	"	1	"	"	-[d]
"	"	"	1	"	"	17
"	"	"	1	"	"	12
"	"	"	2	THF	"	3
"	"	"	2	"	icebath	31
"	"	"	2	"	"	20
Ph	Cl	Me	2	"	"	0[e]

(a) Molar ratio of organocadmium reagent (R'CdCl) to halo ketone.
(b) 8% of 1,2-dibenzoylethane also isolated.
(c) 5% of 1,2-dibenzoylethane also isolated.
(d) Product was formed but not isolated in a quantitative manner.
(e) 92% of starting material was recovered.

Table 4

Reaction of Organocadmium Reagents with α-Halo Esters

| Ester R-C(R')(X)-COOEt | | | Cd Reagent | | Solvent | Reaction Temperature | Yield (%) R-C(R')(R")-COOEt |
R	R'	X	R"	Ratio[a]			
H	H	Br	Np[b]	1	Ether	reflux	16[c]
"	"	"	"	2	THF	ice bath	9[c]
"	"	"	"	2	"	room temp.	62[c]
"	"	"	Ph	1	Ether	reflux	--[d]
"	"	"	"	1	"	"	11[c]
"	"	"	"	2	THF	ice bath	53[e]
"	"	"	"	2	"	"	46
"	"	"	"	2	"	room temp.	26[c]
Me	"	"	"	2	Ether	reflux	40[c,f]
"	"	"	"	2	"	"	58[c]
"	"	"	"	2	THF	ice bath	0[g]
"	"	"	"	2	"	"	0[h]
CO₂Et	"	"	"	2	Ether	reflux	0[i]
CO₂Et	"	"	"	2	THF	room temp.	0[i]

-continued-

Table 4 (page 2)

Ester R-C(R')(X)-COOEt			Cd Reagent		Solvent	Reaction Temperature	Yield (%) R-C(R')(R")-COOEt
R	R'	X	R"	Ratio[a]			
Me	Me	Br	Ph	2	Ether	reflux	0[j]
"	"	"	"	2	THF	ice bath	0[k]
H	H	Cl	"	2	"	"	0[l]
Me	"	"	"	2	Ether	reflux	0[m]

(a) Molar ratio of organocadmium reagent (R"CdCl) to halo ester.
(b) Np = α-napthyl.
(c) Isolated as free acid.
(d) Some of product lost.
(e) Includes 4% isolated as free acid.
(f) Because difficulties were encountered in isolation, this does not represent an accurate yield.
(g) 50% of starting material recovered.
(h) 11% of 2,3-dimethysuccinic acid isolated.
(i) Approx. 75% each of diethyl malonate and bromobenzene isolated.
(j) Approx. 100% of starting material recovered.
(k) Unidentified acid obtained.
(l) 30% of starting material recovered.
(m) Lactic acid isolated after saponification.

products, present themselves:

$$\underset{\text{VII}}{\overset{\displaystyle \underset{\text{Ph-C-CH}_2\text{-CH}_3}{\overset{\text{O}}{\|}}}{}}\quad\xleftarrow{\;b\;}\quad\underset{}{\overset{\text{O}}{\underset{\|}{\text{Ph-C-CH}_2\text{-Br}}}} + \text{MeCdCl}\quad\xrightarrow{\;a\;}\quad \underset{\text{Ph}}{\overset{\text{OCdCl}}{\underset{|}{\underset{|}{\text{Me-C-CH}_2\text{-Br}}}}}\;\longrightarrow\;\underset{\text{VIII}}{\overset{\text{O}}{\underset{\|}{\text{CH}_3\text{-C-CH}_2\text{-Ph}}}}$$
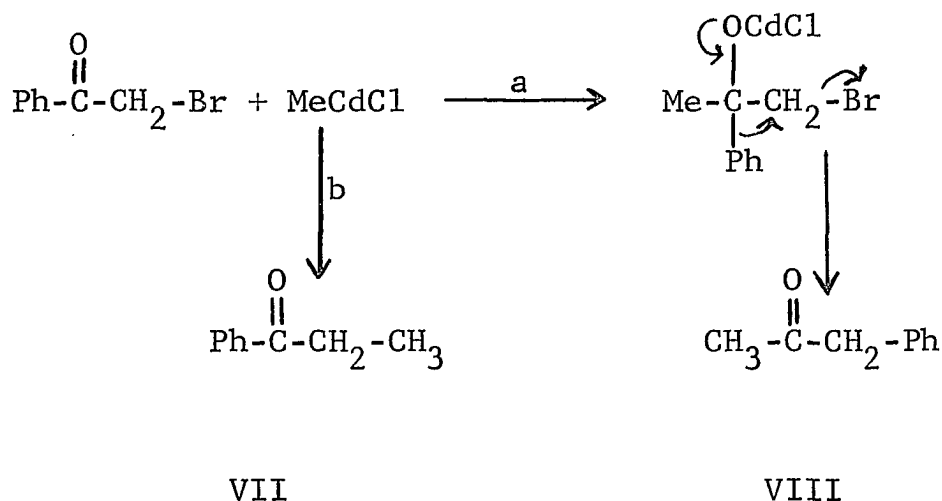
If the methylcadmium reagent were to add to the carbonyl (Path a), the group with the greater migratory tendency (in this case, the phenyl group) would migrate to the _alpha_ carbon; and the product would be acetonylbenzene (VIII). On the other hand, direct displacement by the methylcadmium reagent of bromide would lead to propiophenone (VII), which is the product obtained. Evidence against the presence of VIII includes the nmr and ultraviolet spectra, and the absence of a precipitate in the iodoform reaction.

Direct displacement does not necessarily involve prior dissociation of the organocadmium reagent to yield a carbanion. As Gould[60] and Hine[61] point out, it is highly improbable that more than a few reactions of organomagnesium and organolithium reagents proceed through carbanions. This would be even less probable for organocadmium reagents.

Even though there appeared to be no addition to the carbonyl in this reaction, the initial complex may involve the carbonyl, in a five-center mechanism of the type proposed by Puterbaugh and Readshaw[62] to explain the displacement of

halogen from α-halo acids by lithium enolates. In the present instance, the transition state may be represented as follows:

$$R \text{——} Cd \nearrow^{X}$$

$$C \text{——} C =\!\!\!=O$$

$$Br$$
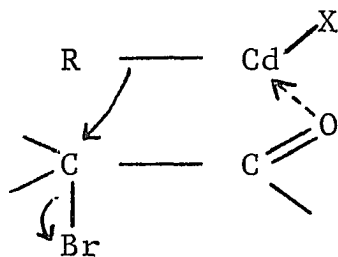
A mechanism that equally well explains the products obtained in this and in subsequent displacement reactions, both with bromo ketones and with bromo esters, also involves the metal as a Lewis acid. But in this case the metal coordinates with the bromide, leading to a four-center mechanism postulated by Dessy and Paulik[63] as common to organometallic reactions. The transition state for a concerted four-center mechanism should be intermediate between the limits S_N^2 - S_E^2, as shown below.

$$
\begin{array}{ccc}
\text{X----Y} & \text{X ---- Y} & \text{X------Y} \\
\text{|} & \text{|} \quad \text{|} & \text{|} \\
\text{|} & \text{|} \quad \text{|} & \text{|} \\
\text{E} & \text{E-----N} & \text{N} \\
\\
S_E^2 & S_F & S_N^2
\end{array}
$$
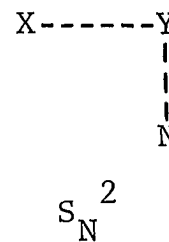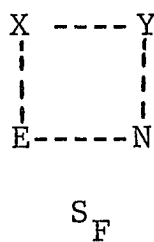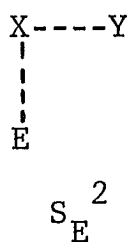
In the systems under consideration, the following diagram indicates the transition state.

$$
\begin{array}{c}
Br\text{-----}Cd \nearrow^{X} \\
| \qquad | \\
C\text{------}R \\
\diagdown \\
C = O
\end{array}
$$
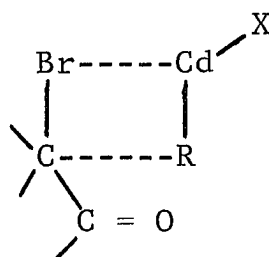
The stereochemistry of the product should be different in these two mechanisms; i.e., the five-center transition state leads to inversion of configuration whereas the four-center transition state gives retention of configuration. Therefore, further insight into the reaction mechanism undoubtedly can be gained by investigation of the reaction of an optically active substrate such as ethyl α-bromopropionate with phenylcadmium reagent. In the present work, the product from inactive ethyl α-bromopropionate and phenylcadmium reagent was obtained in good yield.

It should be pointed out that variations in the organocadmium reagent, solvent, and reaction conditions were not studied. The stoichiometry of the cadmium reagent was always such that it could be considered RCdX (or ArCdX); and, although α-naphthyl-, phenyl-, and methylcadmium reagents were used with various halo ketones or esters, the choice was generally a matter of convenience only. The methylcadmium reagent was used to study the course of the reaction with phenacyl bromide, so that known compounds would be obtained as products. In addition, a group of very different migratory tendency from phenyl was desired. It was felt that use of the α-naphthylcadmium reagent would aid the isolation of products because of the higher molecular weight, but low solubility of this reagent was a disadvantage and often the use of phenylcadmium reagent was more practical.

The organocadmium reagent was generally employed in 2:1 excess. In those reactions where it was employed on an equimolar basis, unchanged starting material was usually present at the end of reaction. Since most of the starting materials were lachrymatory, it was desirable to avoid this.

In the reaction of phenacyl bromide with phenylcadmium reagent as shown below, the coupling product, 1,2-dibenzoyl-

ethane (X), was isolated in addition to the normal displacement product, desoxybenzoin (IX), in certain instances.

$$Ph-CO-CH_2Br \xrightarrow{PhCdCl} Ph-CO-CH_2-Ph$$

IX

$$+ \quad Ph-CO-CH_2CH_2-CO-Ph$$
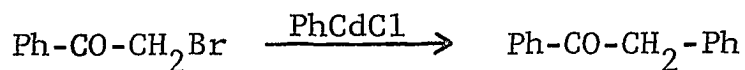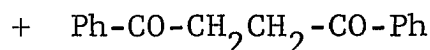
X

It was to decrease the yield of this type of by-product that most of the reactions were carried out under nitrogen and with excess magnesium removed. However, coupling was observed in certain instances even with these precautions, and will be discussed in more detail later.

It was expected, at first, that all reactions would be conducted in ether as solvent. However, the low yield of IX, above, as shown in Table 3, led to the consideration of tetrahydrofuran (THF) as a solvent. It was hoped that yields of displacement products would be higher, and that yields of coupling products would be lower, in this solvent system. Such was found to be the case only with primary bromides. An examination of Table 3 indicates that the yield of IX was approximately 10-20% when the reaction was carried out in ether, and 20-30% in THF. Likewise, in the reaction of ethyl bromoacetate with the organocadmium reagent followed by saponification as shown below, yields were much greater in THF.

$$\text{BrCH}_2\text{-COOEt} \xrightarrow[\text{3) H}^+]{\substack{\text{1) ArCdCl} \\ \text{2) OH}^-}} \text{ArCH}_2\text{COOH}$$
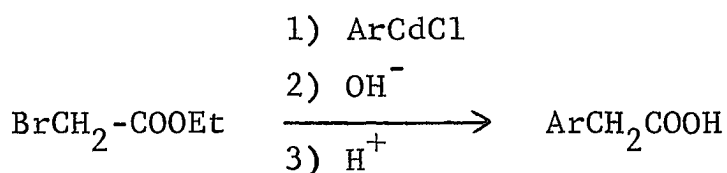
XI   Ar = α-naphthyl

XII   Ar = phenyl

As shown in Table 4, when the reaction was carried out in ether, XI was formed in 16% yield and XII in 11% yield. The same reactions in THF gave products XI and XII in 62 and 26% yields, respectively. In two other trials in THF, the ethyl ester of XII was formed in approximately 50% yield, but since the products were not converted to the acid, it is not known whether or not this represents an actual improvement in yield. One additional observation concerning this reaction should be noted here. The low (9%) yield of XI obtained when the reaction was carried out in THF cooled at ice-bath temperature is probably a reflection of the insolubility of the α-naphthylcadmium reagent under these conditions. This observation is based on the fact that the reaction mixture became so thick that effective stirring was not possible.

If the bromide of the halo ester is secondary, as in the equation below, the difference introduced by solvent is even more dramatic. When this reaction is carried out in

$$\text{CH}_3\text{-CHBr-COOEt} \xrightarrow[\text{3) H}^+]{\substack{\text{1) PhCdCl} \\ \text{2) OH}^-}} \text{CH}_3\text{-CHPh-COOH}$$
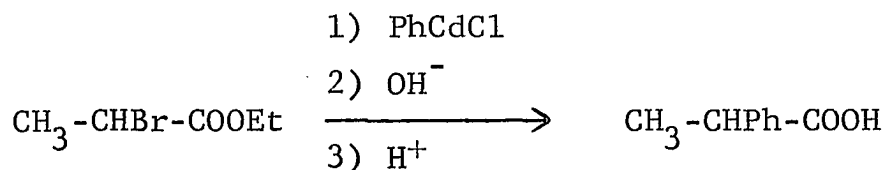
XIII

ether the displacement product, hydratropic acid (XIII), is
obtained in nearly 60% yield. In THF, the only product
isolated is the coupling product, 2,3-dimethylsuccinic acid
(XIV). It is highly probable that this arises through

$$CH_3-CH-COOH$$
$$|$$
$$CH_3-CH-COOH$$
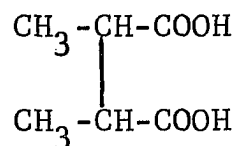
XIV

formation of the enolate, followed by attack of this enolate
on a molecule of ethyl α-bromopropionate. As was previously
mentioned, Cason and Fessenden[44] have shown that ethyl α-
bromopropionate forms an enolate when treated with alkyl-
cadmium reagent under the proper conditions. The reaction
of the enolate of ethyl isobutyrate with ethyl α-bromoiso-
butyrate to form a coupling product similar to XIV has been
discussed.[57]

It was hoped that if the bromide of the halo ester
were **alpha** to two carbonyl groups, as in the case of diethyl
bromomalonate, the presence of the two carbonyl groups would
activate the bromide for facile replacement. Instead, diethyl
malonate (XV) and bromobenzene (from the phenylcadmium reagent)
are isolated in equimolar quantities, as shown in the following
equation.

$$BrCH(COOEt)_2 \quad \xrightarrow[\text{2. } H^+]{\text{1. } PhCdCl} \quad CH_2(COOEt)_2 + PhBr$$
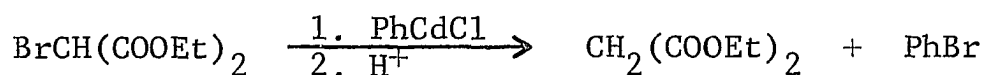
XV

Cason and Fessenden[44] postulate a six-center transi-
tion state for this type of halide-metal interchange, which is

probably best represented as follows.
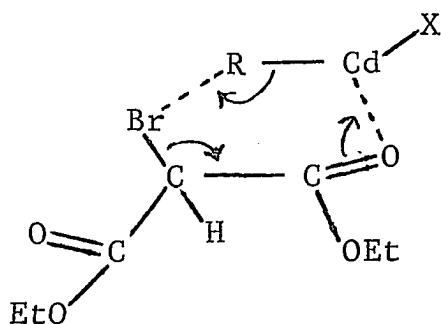
That this enolate does not react further is somewhat surprising, but may be due to additional stabilization by the presence of the other carbonyl, thus:
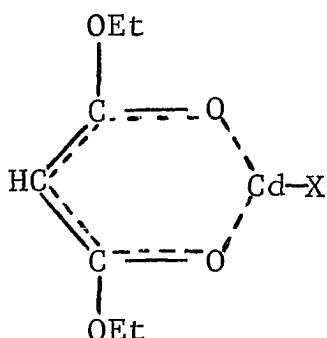
The only tertiary halide studied was ethyl α-bromo-isobutyrate. Neither in ether nor in THF was any displacement product obtained following treatment with phenylcadmium reagent. From the reaction carried out in THF, a very small amount of an unidentified acid was isolated after saponification. The melting point, infrared and nmr spectra, and combustion analysis fail to supply sufficient evidence to identify this product. They do indicate, however, that the material was not the displacement product, the coupling product, the product of dehydrohalogenation, nor the Claisen-type β-keto acid discussed earlier.[44,56]

It was assumed that in this displacement reaction the α-chloro ketones and esters would be less reactive than their bromo counterparts. So pronounced was this effect, however, that the chlorides failed entirely to react. This was not wholly expected, especially in the case of desyl chloride (Table 3). It was felt that the chloro group might be more easily replaced, since it is benzylic as well as _alpha_ to the carbonyl. No explanation for the failure of this reaction can be offered at this time, besides the fact that chloride is known to be less easily displaced than bromide.[64]

In summary, then, in the reaction of organocadmium reagents with α-halo ketones and esters the following observations can be made: (1) In THF, only primary bromides can be displaced. (2) In ether, secondary bromides are more reactive than primary, but both can be displaced. Tertiary bromides are not displaced. (3) Chlorides do not react under conditions which have been employed.

This work also allows one to draw certain conclusions with regard to the order of reactivity of Grignard reagents _versus_ organocadmium reagents with selected substrates, either by addition or displacement. Thus the order for Grignard reagents is assigned:

$$\text{R—CO—X} \;>\; \begin{array}{c} \text{R—CO—OR} \\ \text{R—CO—R} \end{array} \;>\; \begin{array}{c} \text{R—CH(X)—CO—OR} \\ \text{R—CH(X)—CO—R} \end{array}$$
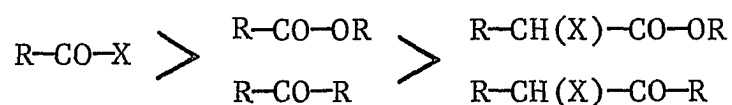
By contrast, for organocadmium reagents the order is:

$$\text{R—CO—X} > \text{R—CH(X)—CO—OR} > \text{R—CH(X)—CO—Ar} > \text{R—CO—R} > \text{R—CO—OR}$$
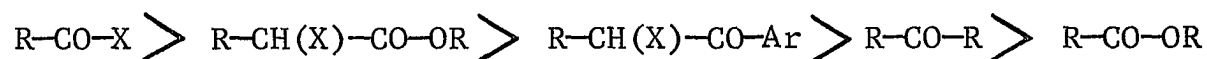
EXPERIMENTAL

All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen, except those marked with an asterisk (*). Reagent-grade anhydrous ether (Fisher Scientific Company) was dried over sodium wire for a minimum of 24 hr. before use. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride and stored over sodium wire until use. In some cases, Grignard reagents were filtered through a glass-wool plug to remove excess magnesium before conversion to the cadmium reagent, as noted by "magnesium removed" in parentheses.

Yields are based on the α-halocarbonyl compound, except where yields of naphthalene or biphenyl are given. These are based on the aryl bromide used in making the cadmium reagent. Yields obtained from glpc charts were determined by comparison of the peak area of the product with the peak area of a calibrated sample.[65] Yields were calculated from nmr spectra with toluene as internal standard.[66]

Infrared spectra were obtained with a Perkin-Elmer Model 337 grating spectrophotometer or with a Perkin-Elmer Model 21 recording spectrophotometer (the latter spectra are indicated by the number "21" preceding the spectrum number). Double mulls were prepared with halocarbon for the region 4000-1300 cm^{-1}, and Nujol for the region 1300-650 cm^{-1}. Ultraviolet spectra were obtained with a Perkin-Elmer Model 4000 recording spectrophotometer. Nuclear magnetic resonance spectra were determined with a Varian A-60 spectrometer and are reported in parts per million (ppm) downfield from tetramethylsilane. Gas liquid partition chromatography (glpc) was carried

out with an F & M Scientific Corp. Model 300 instrument on a 4' x 1/4" column containing 5% Silicone Oil 200 on Halo-port F; or with an Aerograph Model A 90-P3 instrument on a 5' x 1/4" column containing 20% SE-30 on Chromosorb W. Chromatographic charts are numbered with Roman numerals. Thin layer chromatography (tlc) was carried out on 20 cm-long silica gel plates and on microscope slides (micro tlc) (G. Merck, Type G, GF, H, or HF). Thickness varied from 300 to 500 microns. Chloroform and mixtures of chloroform containing up to 10% petroleum ether or methanol were used as eluents. Thick layer chromatography was carried out in a similar manner on 20 x 20 cm plates made from 24 g Silica Gel GF.

Melting points and boiling points are uncorrected. Unless otherwise noted, microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Formation of α-Naphthyl- and Phenylcadmium Reagents in Ether.

A 1-1., three-necked, round-bottomed flask was fitted with a reflux condenser, a mechanical stirrer, and an addition funnel. Nitrogen, when indicated, was introduced both at the top of the addition funnel and at the top of the condenser (so that the system was maintained under a positive pressure of nitrogen, without being swept). The Grignard reagent was prepared from equimolar amounts (0.1 or 0.2 mole, as noted) of magnesium and aryl bromide, and enough dry ether to make the solution 1.0-1.5 molar. After all the aryl bromide was added, the reaction mixture was allowed to reflux for one-half hour and was then filtered from excess magnesium as noted. The cadmium reagent was prepared by the addition of an equimolar portion of anhydrous cadmium chloride over a period of 15 minutes. In all cases a Gilman test[67] showed

the absence of Grignard reagent as soon as all of the cadmium chloride had been added.

Formation of α-Naphthyl- and Phenylcadmium Reagents in THF.

The Grignard reagent was formed in a manner essentially identical to that in ether, except that anhydrous THF was used as solvent. After one-half hour at reflux, the Grignard reagent was filtered from magnesium and cooled to room temperature or to ice-bath temperature as noted. Some difficulty was experienced here, because of the decreased solubility of the α-naphthyl Grignard reagent. The cadmium reagent was prepared by addition over a period of 15 minutes of an equimolar portion of anhydrous cadmium chloride to the cooled Grignard reagent. As before, a Gilman test showed the absence of Grignard reagent as soon as all of the cadmium chloride had been added.

Reaction of Methylcadmium Reagent with Phenacyl Bromide.

In THF.

A solution of 19.0 g (0.2 mole) of methyl bromide in 100 ml of THF, 4.86 g (0.2 mole) of magnesium, and an additional 100 ml of THF were used to prepare the Grignard reagent. After one-half hour at reflux, the Grignard reagent was filtered from excess magnesium, cooled in an ice bath, and 36.7 g (0.2 mole) of anhydrous cadmium chloride was added over about 15 minutes. Immediately after the addition was complete, the Gilman test was negative. A solution of 19.9 g (0.1 mole) of phenacyl bromide in 75 ml of THF was added slowly, with stirring, to the cooled mixture. The mixture was stirred at ice-bath temperature for approximately 8 hr. and then allowed to warm slowly to room temperature.

A solution of 21.4 g (0.4 mole) of ammonium chloride in 50 ml of water was added, and stirring was continued for 1.5 hr. The inorganic solids were removed by filtration, washed well with ether, and the washings added to the filtrate. The filtrate was concentrated to about one-fourth its original volume, and the layers were separated. The aqueous layer was extracted with ether and the extracts combined with the organic layer. Immediately, solid began to form in the organic layer. After storage overnight in the refrigerator, 0.44 g of solid was removed, mp 207-210°, darkens at 205° (IR 3432). The nmr spectrum was not obtained because of the low solubility of this solid in the common solvents. The supernatant solution was dried over calcium sulfate and evaporated under reduced pressure to yield an oil and 1.80 g of a straw-yellow solid, mp 152-160° (IR 3435). The solid was triturated with boiling 95% ethanol, yielding an almost white solid, mp 157-158° (IR 3452). Micro tlc using 2 drops methanol in 3 ml chloroform as eluent gave just one spot. The substance did not absorb bromine from carbon tetrachloride even upon heating for 5 minutes. Again, solubility was too low to permit one to obtain the nmr spectrum. Since a liquid product was expected, the solids were not examined further.

An attempt to analyze the oil (IR 3431) by glpc was unsuccessful. An iodoform test on the oil was negative. Thin layer chromatography gave three fractions, A, B, and C in order of elution, whose ultraviolet spectra had $\lambda_{max}^{CHCl_3} = 247,247$, and 249 m$\mu$, respectively (lit. values: acetonyl-benzene[68], $\lambda_{max}^{CHCl_3} = 287(2.25)$; propiophenone[69], $\lambda_{max}^{EtOH} = 242$ (4.13). Distillation of the oil gave 2.02 g (15%) of a yellow liquid subsequently identified as propiophenone, bp 80° (0.4-0.6 mm) (IR 3532 and 21-6482), very small amounts of two higher boiling fractions, and a large amount of tar.

The nmr spectrum (1398) of the yellow liquid had a triplet at 1.15, a quartet at 2.9, and aromatic protons centered around 7.5 ppm, as well as a triplet at 1.4, a singlet at 2.5, and a doublet at 4.45 ppm. The nmr spectrum (1399) of the next higher boiling fraction contained exclusively the four latter peaks.

The 2,4-dinitrophenylhydrazone of the yellow liquid was prepared, mp 190-192° after two recrystallizations from ethanol-ethyl acetate; lit.[70] mp for the 2,4-dinitrophenyl-hydrazone of propiophenone, 191°. The derivative did not react with 30% potassium hydroxide. The reagent itself decomposes under these conditions.

Reaction of Phenylcadmium Reagent with Phenacyl Bromide.

In Ether

*A. To 0.1 mole of phenylcadmium reagent in refluxing ether 19.9 g (0.1 mole) of phenacyl bromide dissolved in 75 ml of ether was added slowly with stirring. The mixture was stirred at reflux for approximately 10 hr., cooled in an ice bath and hydrolyzed with 100 ml of 6 N hydrochloric acid, and then briefly steam distilled. The odor of phenacyl bromide was very strong in the distillate, but because of its lachrymatory nature, no attempt was made to recover it. The residual oil was extracted with ether; the ether was removed, and the oil was distilled under aspirator vacuum (approximately 15 mm). In addition to the formation of a large amount of tar, there was collected at 195-210° 4.03g(21%) of a material which partially crystallized. The crystals were removed by filtration, washed once with ice-cold ethanol, and air-dried, mp 50-56°; recrystallized from ethanol, mp 59-60° (IR 1981), mixture mp with a similarly recrystallized commercial sample of desoxybenzoin, 59-60°. The oily residue was not examined

further. The infrared spectrum (1614) indicates it to be largely desoxybenzoin.

*B. A solution of 19.9 g (0.1 mole) of phenacyl bromide in 100 ml of benzene was added dropwise with stirring to 0.2 mole of the phenylcadmium reagent in refluxing ether. After 10 hr. at reflux, the mixture was cooled in an ice bath and 100 ml of 6 $\underline{N}$ hydrochloric acid was added. The organic layer was separated, washed with saturated sodium bicarbonate until there was no evidence of further reaction, then once with distilled water, and dried over calcium sulfate. When the solvent was removed a few mushy crystals formed, but these were not removed. The mixture was taken up in methanol and treated with Norit at the boil. After storage overnight in the refrigerator, 1.0 g (8%) of a solid subsequently identified as 1,2-dibenzoylethane had crystallized; recrystallized from acetone, mp 141-142°. The infrared spectrum (2008) is consistent for this compound, as is the nmr spectrum (1050), which has a singlet at 3.10 and an aromatic multiplet centered around 7.5 ppm. The material was recrystallized to constant mp (145-146°) from benzene-$\underline{n}$-hexane (lit.[71] mp 147°) and gave just one spot on micro tlc.

<u>Anal</u>. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.93. Found: C, 80.58; H, 6.01.

<u>The oxime</u> was prepared by the general procedure of Shriner, Fuson, and Curtin[72], mp 202-203°; lit.[71] mp 204°.

The filtrate obtained above by removal of the 1,2-dibenzoylethane was concentrated and the oil dissolved in ether. The ether solution was filtered from a solid, which had formed after several days. The solvent was removed, and the oil was analyzed by glpc (II), which indicated a 12% yield of desoxybenzoin.

The solid was taken up in acetone, the insoluble portion being discarded. From the acetone, by addition of water, was obtained 0.1 g of a white solid, which was dried under aspirator vacuum, mp 136-137° (IR 2632). The nmr spectrum (3100) has a singlet at 3.46 and two aromatic multiplets centered at 7.55 and 8.08 ppm. Integration of these peaks is in the ratio 2:3:2, respectively.

<u>Anal</u>. Found: C, 81.43, 81.20; H, 5.95, 6.17. (F & M, Model 185; C, H, N Analyzer).

*C. The reaction was carried out as in A (magnesium removed). After about 2 hr., the mixture had solidified, so that further stirring was impossible. The mixture was allowed to cool. After about 8 hr., the solid mass was broken up as much as possible and the mixture was again brought to reflux. After 1 hr. it was cooled in an ice bath and hydrolyzed with 100 ml of 6 <u>N</u> hydrochloric acid. The organic layer was removed, washed successively with saturated sodium bicarbonate and water, and dried over calcium sulfate. Removal of the solvent left an oil from which a small amount of solid separated; 0.6 g (5%) of 1,2-dibenzoylethane, mp 140-143°. The oil was analyzed by glpc (I), which indicated a 7% yield of desoxybenzoin.

D. The reaction was carried out as in A (magnesium removed). The mixture thickened up as the phenacyl bromide was added; and shortly after all of the phenacyl bromide had been added, the mixture became a solid mass. Heat was removed and the mixture was allowed to stand overnight. Hydrolysis and work-up were carried out as in C. Analysis of the organic portion by glpc (II) showed qualitatively that desoxybenzoin was a product, but the yield was so low that quantitative analysis was not attempted.

E. The reaction was carried out as in A (magnesium removed). After 10 hr., hydrolysis and work-up were carried out as in C. Analysis of the organic portion by glpc (V) indicated a 17% yield of desoxybenzoin.

F. The reaction and hydrolysis were carried out as described in A (magnesium removed). During work-up, 0.17 g of a yellow solid separated and was removed. The solid was triturated with benzene and with acetone, mp 185-190°d (IR 2633). The nmr spectrum was not obtained because of the low solubility of this solid in the common solvents.

The remainder of the organic portion was analyzed by glpc (VI) for an indicated yield of desoxybenzoin of 11%. Analysis of the same mixture by nmr (1085) indicated a 12% yield.

In THF

A. A solution of 19.9 g (0.1 mole) of phenacyl bromide in 100 ml THF was added dropwise with stirring to 0.2 mole of phenylcadmium reagent (magnesium removed) in refluxing THF. After 8 hr., the mixture was cooled in an ice bath and hydrolyzed with 100 ml of 6 $\underline{N}$ hydrochloric acid. The mixture was concentrated on the rotary evaporator until two layers formed. The organic layer was removed and combined with ether extracts of the aqueous layer. This solution was washed with saturated sodium bicarbonate and dried over calcium sulfate. Removal of the solvent and analysis of the residual oil by glpc (XXII) indicated a 3% yield of desoxybenzoin. An attempt to separate the oil into its major components by column chromatography on neutral alumina was unsuccessful. As shown by glpc (XIII), there was very little separation.

B. To 0.2 mole of phenylcadmium reagent (magnesium removed) cooled in an ice bath was added dropwise, with stirring, 19.9 g (0.1 mole) of phenacyl bromide in 75 ml of THF.

After 8 hr. at ice-bath temperature a solution of 21.4 g
(0.4 mole) of ammonium chloride in 50 ml of water was added,
and stirring was continued for 1.5 hr. The inorganic solids
were removed, washed with ether, and the washings combined
with the filtrate. The organic layer was combined with the
ether extracts of the aqueous layer and dried over calcium
sulfate. The solvents were removed, and analysis of the
residual oil by glpc (XIV) indicated a 24% yield of desoxy-
benzoin. Two analyses of the oil by nmr (1055 and 1067)
indicated yields of 25 and 31%, respectively.

C. The reaction and work-up were carried out as in
B. Analyses by nmr (1120 and 1147) indicated yields of 18
and 20%. The infrared spectrum (3066) was consistent for
desoxybenzoin.

Attempted Reaction of Methylcadmium Reagent with Desyl Chloride.

In THF

The Grignard reagent was prepared from 4.86 g (0.2
mole) of magnesium, 19.0 g (0.2 mole) of methyl bromide dis-
solved in 100 ml of THF, and an additional 100 ml of THF as
solvent. After all of the methyl bromide solution was added,
the reaction mixture was allowed to reflux for one-half hour
and was then filtered from excess magnesium. The cadmium
reagent was prepared by the addition over a period of 15
minutes of 36.7 g (0.2 mole) of anhydrous cadmium chloride
to the mixture cooled in an ice bath. Immediately after the
addition was complete, the Gilman test was negative.

A solution of 23.1 g (0.1 mole) of desyl chloride in
60 ml of THF was added slowly, with stirring, to the cold
mixture. The mixture was stirred at ice-bath temperature for
approximately 8 hr.; then a solution of 21.4 g (0.4 mole) of
ammonium chloride in 50 ml of water was added. Difficulty

was experienced because of the liberation of a gas (believed
to be methane), which caused considerable foaming of the
mixture. The mixture was stirred for 1.5 hr.; then the in-
organic solids were removed by filtration, washed well with
ether, and the washings were added to the filtrate. The
organic layer was removed from the filtrate and combined with
the ether extracts of the aqueous layer. After removal of
the solvent there was recovered 21.2 g (92%) of the starting
material, desyl chloride, mp 57-61°. The infrared (3128)
and nmr (1218) spectra were similar to those of authentic
material (3129 and 1221, respectively). The retention time
on glpc (XVI) was the same for the sample and for authentic
material.

Reaction of α-Naphthylcadmium Reagent with Ethyl Bromoacetate.

*In Ether

To 0.1 mole of α-naphthylcadmium reagent in refluxing
ether 16.7 g (0.1 mole) of ethyl bromoacetate was added drop-
wise with stirring. The mixture was stirred at reflux for
approximately 10 hr., then cooled in an ice bath and hydrolyzed
with 100 ml of 20% sulfuric acid. The layers were separated;
the aqueous layer was extracted with ether and the extracts
combined with the organic layer. After removal of the ether
on a rotary evaporator a dark colored oil remained. To the
oil was added 100 ml of 10% sodium hydroxide, and the mixture
was heated at reflux with magnetic stirring for 2.5 hr. The
mixture was cooled, filtered to remove a dark yellow solid,
and acidified with 20% sulfuric acid. There was removed by
filtration 2.9 g (16%) of α-naphthylacetic acid, mp 125-129°
(IR 1226); recrystallized from benzene-ligroin, mp 131-132.5°,
mixture mp with a commercial sample 131-132°. The nmr spectrum

(2068) is consistent for α-naphthylacetic acid.

The dark yellow solid obtained above partially dissolved in benzene. The insoluble portion did not melt below 300° and was discarded. Evaporation of the benzene yielded 4.7 g (37%) of naphthalene, mp 75-80°.

In THF

A. A solution of 16.7 g (0.1 mole) of ethyl bromoacetate in 15 ml THF was added dropwise, with stirring, to 0.2 mole of α-naphthylcadmium reagent (magnesium removed) cooled in an ice bath. At this time, the mixture was so thick that it was very difficult to stir. The mixture was stirred at ice-bath temperature for 10 hr. During this time the mixture had become so thick that effective stirring was not possible.

Approximately 50 ml of THF was added, and the mixture was heated at reflux for 15 minutes. Considerable darkening occurred. The mixture was again cooled in an ice bath, and 50 ml of 6 $\underline{N}$ hydrochloric acid was added. About 100 ml of ether was added, the organic layer was separated and combined with the ether extracts of the aqueous layer. The odor of ethyl bromoacetate was very strong in the mixture. Because of the extremely lachrymatory nature of the starting material, no attempt was made to recover it; instead, the solvents and the bromo ester were removed under vacuum, leaving a very dark semisolid mass. To this mixture was added 100 ml of 10% sodium hydroxide and 100 ml of ethanol, and the mixture was heated at reflux with magnetic stirring for 10 hr. After cooling, 300 ml of ether was added; the mixture was filtered from an inorganic solid, and the layers were separated. Evaporation of the ether and recrystallization from ethanol yielded 22.8 g (89%) of naphthalene, mp 74-78° (IR 3839).

The aqueous layer after treatment at the boil with Norit was acidified with concentrated hydrochloric acid. There was obtained 1.7 g (9%) of α-naphthylacetic acid, mp 123-130°.

B. To 0.2 mole of α-naphthylcadmium reagent cooled to room temperature was added 16.7 g (0.1 mole) of ethyl bromoacetate in 15 ml of THF. After about one-half of the bromo ester had been added, the mixture began to thicken so that stirring was difficult. The mixture was warmed only sufficiently to keep it semifluid. After 8 hr. 100 ml of 3 N hydrochloric acid was added. The organic layer was removed and combined with chloroform extracts of the aqueous layer. (Chloroform did not seem to emulsify as readily as ether.) The solution was concentrated on the rotary evaporator and saponified as in A. After a similar work-up there was obtained 11.5 g (62%) of α-naphthylacetic acid, mp 110-120°. A sample of the acid was dissolved in saturated sodium bicarbonate, treated with Norit, precipitated with concentrated hydro-chloric acid, and recrystallized from benzene-ligroin, mp 130-132°, mixture mp with a commercial sample 130-132°.

Reaction of Phenylcadmium Reagent with Ethyl Bromoacetate.

In Ether

*A. To 0.1 mole of phenylcadmium reagent in reflux-ing ether was added dropwise, with stirring, 16.7 g (0.1 mole) of ethyl bromoacetate. After 10 hr. at reflux, the mixture was cooled in an ice bath and 100 ml of 20% sulfuric acid was added. A sudden bumping of the mixture caused some loss of material, so the following results are not quantitative. The layers were separated; the aqueous layer was extracted with ether, and the extracts were combined with the ether layer. Removal of the ether on a rotary evaporator left a dark colored

oil. To the oil was added 100 ml of 10% sodium hydroxide
and the mixture was heated at reflux for 2 hr. The mixture
was cooled and filtered from a yellow solid. The solid was
washed with 1% sodium hydroxide, and the washings were added
to the filtrate. The solid was taken up in benzene, the in-
soluble portion being discarded. Evaporation of the benzene
yielded about 1 g of biphenyl; recrystallized from ethanol-
water, mp 65-69°.

The filtrate obtained above was cooled in an ice bath
and acidified with concentrated sulfuric acid, then stored
overnight in the refrigerator. Oily droplets separated but
did not crystallize, so the mixture was extracted with ether.
After several extractions with ether, the aqueous layer was
discarded and the extracts were combined. The dark oil re-
maining after removal of ether was dissolved in 5% sodium hy-
droxide and treated with Norit at the boil. The charcoal was
removed by filtration; the basic filtrate was washed with ether
and with chloroform, acidified with concentrated sulfuric acid
and stored overnight in the refrigerator. The dark, semisolid
material which separated was not removed, and this aqueous
mixture was distilled. Extraction of the distillate with ether
and evaporation of the ether yielded a white, waxy solid. The
solid was recrystallized from benzene-ligroin and dried under
aspirator vacuum; mp 77-78°. The infrared spectrum (1366) is
identical with that of a commercial sample of phenylacetic
acid (IR 1374), and the mixture mp is not depressed.

*B. The reaction was carried out as described in A.
Following reaction, the mixture was cooled in an ice bath,
and 100 ml of ice-cold 6 $\underline{N}$ hydrochloric acid was added. The
mixture was diluted by addition of 200 ml of water and then
steam distilled. Extraction of the distillate with ether and
removal of the ether gave a light yellow oil (IR 1472), to

which was added 100 ml of 10% sodium hydroxide; and the mixture was heated at reflux for 5 hr. The basic solution was cooled, extracted with ether to remove biphenyl, and acidified with 6 $\underline{N}$ hydrochloric acid. The soft, fine crystals which formed were not readily separated, so the mixture was extracted successively with several portions of ether and two of chloroform. The extracts were combined and after removal of the solvents, there remained 1.5 g (11%) of phenylacetic acid, mp 68-75°; recrystallized from benzene-ligroin, mp 77-78.5, mmp 77-78.5°.

In THF

A. A solution of 16.7 g (0.1 mole) of ethyl bromoacetate in 15 ml THF was added dropwise, with stirring, to 0.2 mole of phenylcadmium reagent (magnesium removed), which was cooled in an ice bath. After 10 hr. at ice-bath temperature, a solution of 21.4 g (0.4 mole) of ammonium chloride in 50 ml of water was added. The mixture was stirred for one hour and then steam distilled.

A first fraction of about 150 ml contained exclusively THF; evaporation on a steam bath left no residue. About 400 ml more of distillate was collected. This contained an almost colorless oil which was extracted with ether and dried over magnesium sulfate. By removal of the ether there was obtained 8.0 g (49%) of ethyl phenylacetate, bp 66-71° (0.6-1.0 mm) (IR 3586). The nmr spectrum (1453) is consistent for this compound.

The distillate above, after removal of the ethyl phenylacetate, was found to have a very high $\underline{p}$H. It was acidified with concentrated hydrochloric acid, extracted with ether, and the extracts dried over magnesium sulfate. Removal of the ether yielded 0.6 g (4.4%) of an orange oil which appeared to be largely phenylacetic acid. The infrared

spectrum (3609) is similar to that of an authentic sample
(1374), and the major spot on micro tlc had the same R_f as
authentic phenylacetic acid. Much weaker spots correspond-
ing to ethyl phenylacetate and biphenyl were also observed.

The amide was prepared as follows. A small sample
of the ethyl phenylacetate was saponified by heating at re-
flux with 5% sodium hydroxide. The basic solution was acidi-
fied with concentrated hydrochloric acid and extracted with
ether. The oily residue after removal of the ether was dis-
solved in excess thionyl chloride, and the solution was
stirred overnight. After 1 hr. at reflux excess thionyl
chloride was removed by distillation, and the acid chloride
was poured into a large excess of concentrated aqueous ammonia.
The flocculent tan precipitate was washed with cold water and
recrystallized from water after treatment with Norit, mp 154-
154.5°. An authentic sample of α-phenylacetamide had mp 155-
156°; mixture mp 155-156°.

B. The reaction was carried out as described in A.
Following reaction, 50 ml of cold water was added and the mix-
ture was steam distilled. Work-up of the distillate as in A
yielded 7.6 g (46%) of ethyl phenylacetate.

C. To 0.2 mole of phenylcadmium reagent cooled to
room temperature was added 16.7 g (0.1 mole) of ethyl bromo-
acetate in 10 ml of THF. After 8 hr. 100 ml of 3 $\underline{N}$ hydro-
chloric acid was added. The organic layer was removed and
combined with chloroform extracts of the aqueous layer. The
solution was concentrated on the rotary evaporator and saponi-
fied by heating at reflux with 100 ml of 10% sodium hydroxide
in 50% ethanol for 8 hr. The mixture was cooled and filtered
from biphenyl; 100 ml of chloroform was added and the layers
were separated. The aqueous layer was washed with chloroform;
the washings were discarded. After treatment with Norit

at the boil, the aqueous solution was acidified with concentrated hydrochloric acid. The solution was cooled, and there was removed 3.5 g (26%) of phenylacetic acid, mp 70-75°. A small amount of the acid was purified by sublimation; mp 76.5-77°, mixture mp with a commercial sample, 76-77°.

Reaction of Phenylcadmium Reagent with Ethyl α-Bromopropionate.

In Ether

*A. A solution of 18.1 g (0.1 mole) of ethyl α-bromopropionate in 15 ml of ether was added slowly to 0.2 mole of phenylcadmium reagent in refluxing ether. After 10 hr. at reflux, the mixture was cooled in an ice bath and hydrolyzed with 100 ml of 6 $\underline{N}$ hydrochloric acid. The organic layer was removed and combined with ether extracts of the aqueous layer. The solution was concentrated; 100 ml of 10% sodium hydroxide was added, and the mixture was stirred at reflux for 10 hr. At the end of this time material floating on the aqueous layer, assumed to be biphenyl, was extracted with ethyl acetate. Contrary to expectation, the aqueous layer had pH 6 by Alkacid Test Ribbon (Fisher Scientific Company). The mixture was made strongly acidic with about 10 ml of concentrated hydrochloric acid, extracted repeatedly with ethyl acetate and the extracts combined with the biphenyl extract obtained above. The solution was concentrated on a rotary evaporator; 200 ml of 5% sodium hydroxide was added, and the mixture was heated at reflux for 5 hr. After the mixture was cooled, 4.2 g (30%) of biphenyl, mp 65-69°, was removed.

The aqueous solution was acidified with concentrated hydrochloric acid, extracted with ethyl acetate, and the extracts combined. After removal of the solvent under vacuum there was obtained 6.1 g (40%) of hydratropic acid (α-phenylpropionic acid), bp 115-117° (1.0 mm). The infrared spectrum

(2813) is consistent for this compound, and glpc (X and XI) indicates that the product contains relatively minor amounts of impurities.

The amide was formed as follows: A 1.0 g sample of the acid was stirred overnight with a large excess of thionyl chloride. After 1 hr. at reflux excess thionyl chloride was removed by distillation and the acid chloride was poured into 25 ml of concentrated aqueous ammonia. The flocculent tan precipitate was washed with cold water and recrystallized from water after treatment with Norit. There was obtained 0.53 g of snow-white crystals, mp 92-92.5° (IR 5312), mixture mp 92-92.5°.

B. The reaction was carried out as described in A. Following reaction, the mixture was cooled in an ice bath and hydrolyzed with 100 ml of 3 $\underline{N}$ hydrochloric acid. The organic layer was removed, washed with saturated sodium bicarbonate, and concentrated on the rotary evaporator. To the oil remaining was added 100 ml of 10% sodium hydroxide. The mixture was heated at reflux for 10 hr. and cooled; after extraction of the biphenyl with ether, the solution was made acidic with hydrochloric acid. It was extracted repeatedly with ether, the extracts combined and dried over magnesium sulfate. After removal of the ether there remained 8.75 g (58%) of hydratropic acid. The infrared spectrum (5695) is essentially identical to that of the acid obtained in A. The nmr spectrum (2952) is consistent for this compound, but contains also minor peaks for ether (as shown by Nmr 2971), and for a trace of propionic acid (Nmr 2968).

The amide was made as in A from 1.0 g of the acid. There was produced 0.62 g of the purified amide, mp and mmp 92-92.5°. The nmr spectrum (2969) has a doublet at 1.50, a quartet at 3.58, and a singlet at 7.32 ppm.

In THF

A. A solution of 9.05 g (0.05 mole) of ethyl α-bromo-propionate in 10 ml of THF was added dropwise to 0.1 mole of phenylcadmium reagent (magnesium removed) in 200 ml of THF cooled in an ice bath. The mixture was stirred at ice-bath temperature for 10 hr. and then warmed slowly to room tempera-ture. Following reaction, 50 ml of cold water was added, and the mixture was steam distilled. The distillate was extracted successively with chloroform and ether, and the extracts were dried over calcium sulfate-magnesium sulfate. Evaporation of the solvents yielded 5.3 g (59%) of the starting material (ethyl α-bromopropionate). A sodium fusion test[73] was positive for bromine, and alcoholic silver nitrate[74] gave a precipitate after 4 minutes at room temperature. Bromobenzene does not react in the latter test. The infrared spectrum (5235) is nearly identical to that of the authentic material (5310); the nmr spectra (2188 and 2293, respectively) indicate that the sample is almost pure bromo ester containing a very small amount of an aromatic substance, very likely biphenyl.

B. To 0.2 mole of phenylcadmium reagent (magnesium removed), cooled in an ice bath, was added 18.1 g (0.1 mole) of ethyl α-bromopropionate in 15 ml of THF. The mixture was stirred at ice-bath temperature for 10 hr., then hydrolyzed with 100 ml of 3 N hydrochloric acid. To the mixture was added 50 ml of ether; the organic layer was removed and com-bined with the ether extracts of the aqueous layer, washed successively with saturated sodium bicarbonate and water, and dried over magnesium sulfate. Removal of the solvents left an oil (IR 5393), which was steam distilled. A first fraction, A, was collected until solid started forming in the distillate. The receiver was changed, and a second fraction,

B, was collected. Both fractions and the still-pot residue were extracted with ether and the extracts dried over magnesium sulfate.

From the still-pot extract, by removal of ether, there was obtained 4.0 g of dark-red oil. The infrared spectrum (5413) indicated it to be an acid; however, attempts to prepare the amide through treatment with thionyl chloride and ammonia led only to water-soluble products.

Removal of the ether from Fraction A left 4.8 g of a colorless oil (IR 5414). Saponification and treatment of the resulting acid with thionyl chloride and ammonia again led only to water-soluble products.

Fraction B yielded 5.7 g of a light-colored oil containing a few crystals (IR 5416). This was saponified by heating at reflux for 12 hr. with 20 ml of 10% sodium hydroxide. The basic solution was filtered from biphenyl and extracted with ether, after which it was made acidic with concentrated hydrochloric acid. The mixture was extracted with ether and the extracts dried over magnesium sulfate. After removal of the ether 1.8 g of an oil remained (IR 5666). The oil was again taken up in ether, and crystals began to form. There was removed by filtration 0.83 g (11%) of 2,3-dimethylsuccinic acid, mp 210-211° (lit.[75] mp 208°). The infrared (5690) and nmr (2904) spectra are consistent for this compound.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.16; H, 6.93.

Reaction of Phenylcadmium Reagent with Diethyl Bromomalonate.

In Ether

A solution of 23.9 g (0.1 mole) of diethyl bromomalonate in 25 ml of ether was added dropwise, with stirring, to 0.2 mole of phenylcadmium reagent in refluxing ether. The

mixture was stirred at reflux for 10 hr., then cooled in an ice bath and hydrolyzed with 100 ml of 3 $\underline{N}$ hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate and dried over magnesium sulfate. Removal of the ether on the rotary evaporator left 34.1 g of a dark oil. The infrared spectrum (5830) is similar to that of diethyl malonate (4685). Analysis of the nmr spectra (3022 and 3102) indicates that the mixture contained approximately 12 g (75%) of diethyl malonate (Nmr 1955), a trace of starting material (Nmr 2031), and an aromatic substance. Analysis of the mixture by glpc (XXI) indicated that bromobenzene was present in equimolar ratio with diethyl malonate.

In THF

To 0.2 mole of phenylcadmium reagent cooled to room temperature was added 23.9 g (0.1 mole) of diethyl bromo-malonate in 25 ml of THF. The mixture was stirred at room temperature for 10 hr., then cooled in an ice bath and hydro-lyzed by addition of a solution of 21.4 g (0.4 mole) of ammonium chloride in 50 ml of water. The mixture was stirred for 1 hr., then filtered from solid. The solid was washed with chloroform and discarded, the washings being added to the filtrate. The organic layer was removed, washed with water, and dried over calcium sulfate-magnesium sulfate. Removal of the ether and distillation of the residual oil under vacuum (3.5-4.0 mm) gave three fractions, A, B, and C, in order of increasing boiling points.

Fraction A, bp 40-70°, weighed 8.1 g. The infrared spectrum (4767) indicated it contained diethyl malonate (IR 4685) and an aromatic substance. Analysis by glpc (XIX) indicated it to be largely bromobenzene and a minor quantity of the ester. The nmr spectrum (1972) is consistent for this mixture.

Fraction B, bp 70-98°, 11.0 g (70%), was shown by glpc (XIX) to be nearly pure diethyl malonate containing a small amount of diethyl bromomalonate and a trace of bromobenzene. The infrared (4784) and nmr (1949) spectra support this analysis.

Fraction C, bp 98°, 1.8 g (8%), was shown by glpc (XIX) to be largely diethyl bromomalonate, a small amount of diethyl malonate, and a trace of bromobenzene. The infrared (4669) and nmr (1950) spectra are consistent for this analysis.

Attempted Reaction of Phenylcadmium Reagent with Ethyl α-Bromoisobutyrate.

In Ether

A solution of 19.5 g (0.1 mole) of ethyl α-bromoisobutyrate in 15 ml of ether was added dropwise, with stirring, to 0.2 mole of phenylcadmium reagent in refluxing ether. The mixture was heated at reflux for 10 hr., then cooled in an ice bath and hydrolyzed with 100 ml of 3 $\underline{N}$ hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate and dried over magnesium sulfate. Removal of the ether on the rotary evaporator left 21.6 g of a dark oil. The infrared spectrum (5810) is similar to that of the starting material (5316) but also contains other bands expected for biphenyl. The nmr spectrum (2993) is consistent for the bromo ester (Nmr 2210), but also contains minor peaks attributable to ether (as shown by Nmr 2971), and to a small amount of biphenyl (multiplet centered around 7.4 ppm).

Reaction of Phenylcadmium Reagent with Ethyl α-Bromoisobuty-rate.

In THF

A solution of 19.5 g (0.1 mole) of ethyl α-bromoiso-butyrate in 20 ml of THF was added dropwise to 0.2 mole of phenylcadmium reagent (magnesium removed) cooled in an ice bath. The mixture was stirred at ice-bath temperature for 10 hr., then warmed to room temperature. After 50 ml of cold water was added, the mixture was steam distilled. A first fraction, A, appeared to be mostly THF during collection. After all of the THF had been distilled, the receiver was changed and a second fraction, B, was collected until the organic portion of the distillate was solid.

The THF was distilled on a steam bath from Fraction A, leaving a small amount of an oil which was taken up in ether and dried over magnesium sulfate. After removal of the ether there was obtained 0.65 g of a light yellow oil, which appeared to be mostly starting material. The infrared spectrum (5315) is consistent for ethyl α-bromoisobutyrate (IR 5316), with biphenyl (IR 6062, 6063) as a minor component. The nmr spectrum (2211) is also consistent for the bromo ester (Nmr 2210) with biphenyl and ether as impurities.

Fraction B was extracted successively with chloroform and with ether and the extracts were dried over magnesium sulfate. Removal of the solvents yielded 7.7 g of a mixture of oil and crystals. A small amount of the crystals was removed and washed with cold methanol, mp and mixture mp with authentic biphenyl 69-70°. The oil appeared to be a mixture of starting material, biphenyl, and an unidentified component. The infrared spectrum (5317) can be satisfactorily accounted for as a mixture of starting material (ethyl α-bromoisobutyrate) and biphenyl. The nmr spectrum (2213) has a multiplet centered

around 7.45 ppm consistent for biphenyl; a quartet at 4.2, a singlet at 1.9, and a triplet at 1.3 ppm consistent for the starting material, and an unexplained singlet superimposed on the triplet at 1.3 ppm.

Fraction B was saponified by heating at reflux with 50 ml of 5% sodium hydroxide in 30% ethanol for 12 hr. The mixture was cooled and filtered from biphenyl. The basic solution was extracted with ether and the extracts discarded. The solution was made acidic with concentrated hydrochloric acid, extracted with ether, and the extracts dried over magnesium sulfate. Removal of the ether left a dark solid (IR 5359)(Nmr 2237), which was dissolved in dilute sodium hydroxide and treated twice with Norit at the boil. The clear solution was cooled in an ice bath and acidified with concentrated hydrochloric acid. After 5 hr. fine white crystals were removed, recrystallized from water to constant melting point, and dried 18 hr. at 56° (1.0 mm). The sample had mp 91.5-93° (IR 5759)(Nmr 2905).

Anal. Found: C, 54.69, 54.52; H, 7.68, 7.59.

Attempted Reaction of Phenylcadmium Reagent with Ethyl Chloroacetate.

In THF

To 0.2 mole of phenylcadmium reagent (magnesium removed) cooled in an ice bath, 12.3 g (0.1 mole) of ethyl chloroacetate in 15 ml of THF was added dropwise. The mixture was stirred at ice-bath temperature for 10 hr., then allowed to warm to room temperature. After 10 ml of cold water had been added, the mixture was steam distilled until solid began to form in the distillate. The solid did not possess a carbonyl group (IR 5703) and was not examined further. The distillate

was extracted with ether, and the extracts were dried over magnesium sulfate. After removal of the ether on the rotary evaporator there was obtained 3.7 g (30%) of unchanged ethyl chloroacetate. The infrared spectrum (5702) is consistent for the chloro ester (IR 5787), with additional bands for biphenyl; and the nmr spectrum (2327) is also consistent for this mixture (ethyl chloroacetate, Nmr 2943). Distillation of the mixture in a modified Babcock apparatus[76] effected a substantial reduction of the biphenyl content, as shown by the infrared (5789) and nmr (2946) spectra.

Attempted Reaction of Phenylcadmium Reagent with Ethyl α-Chloropropionate.

In Ether

To 0.2 mole of phenylcadmium reagent in refluxing ether, 13.7 g (0.1 mole) of ethyl α-chloropropionate in 15 ml of ether was added dropwise. The mixture was heated at reflux with stirring for 10 hr., then cooled in an ice bath and hydrolyzed with 100 ml of 3 $\underline{N}$ hydrochloric acid. The ether layer was separated and washed with saturated sodium bicarbonate. To the oil remaining after removal of the ether was added 100 ml of 10% sodium hydroxide, and the mixture was heated at reflux with magnetic stirring for 12 hr. The mixture was cooled, filtered from biphenyl, washed with ether, and acidified with concentrated hydrochloric acid. The solution was extracted with ether and the extracts dried over magnesium sulfate. Evaporation of the ether left 1.6 g of impure lactic acid. The infrared spectrum (5800) is very similar to that of authentic lactic acid (5801), but does contain certain additional bands associated with an aromatic compound. The nmr

spectrum (2995), although complex, indicates that the major portion of the material is lactic acid (Nmr 2994). The nmr spectrum does not indicate the presence of either the expected replacement product, hydratropic acid (Nmr 2964)[77], or of the coupling product, 2,3-dimethylsuccinic acid (Nmr 2904).

SUMMARY

Displacement of halogen from certain α-halo ketones and esters by organocadmium reagents to yield the α-aryl or α-alkyl substituted ketones and esters has been investigated. Unlike similar displacement reactions by Grignard reagents, in which the product appears to result from addition at the carbonyl followed by rearrangement, these reactions with organocadmium reagents apparently do not involve preliminary addition to the carbonyl group.

The reaction of methylcadmium chloride and phenacyl bromide led to propiophenone, and not to acetonylbenzene which would have resulted from attack at the carbonyl. The results obtained in this and in subsequent displacement reactions can be explained by a concerted mechanism involving either a four- or five-center transition state, as shown:
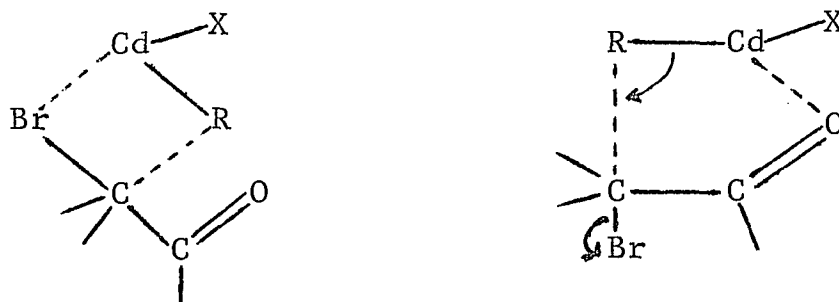
The displacement product, when obtained, could be isolated in moderate to good yield; but a solvent effect was noted in these reactions. In tetrahydrofuran, only primary bromides were displaced by the organocadmium reagents, whereas in ether both primary and secondary bromides were displaced, the latter being more reactive. Chlorides and tertiary bromides were not displaced under the conditions which have been employed.

In addition to the expected displacement product, coupling products were observed in certain cases. For example, in the reaction of phenacyl bromide with phenylcadmium reagent, in two instances in which ether was the solvent, 1,2-dibenzoylethane was isolated in low yield in addition to desoxybenzoin, the displacement product. A similar product was obtained when the reaction of ethyl α-bromopropionate with phenylcadmium reagent was carried out in tetrahydrofuran. The only product isolated (after saponification) was 2,3-dimethylsuccinic acid.

This type of product is believed to arise through a halogen-metal exchange leading to the enolate, which then displaces halogen in a molecule of the halo carbonyl compound. When diethyl bromomalonate was treated with phenylcadmium reagent, halogen-metal exchange appeared to be nearly complete and the enolate appeared to be quite unreactive, since diethyl malonate and bromobenzene were isolated in high yield.

The present work points up the difference in scope and mechanism between the reaction of α-halo carbonyl compounds with organocadmium and Grignard reagents.

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