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α-HALOENOLATES: THEIR PREPARATION AND SYNTHETIC APPLICATIONS*

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Summary

α-Haloenolates have been prepared by halogen—metal or hydrogen—metal interchange. Rearrangement of β-oxido carbenoids offers another useful route, whereas β-alkoxycarbenoids decompose via α- or β-elimination. Cu^I promotes the preparation of α-halomagnesium enolates. These organometallics undergo useful reactions as nucleophiles, but can also behave as electrophiles.

During the last decade we have studied the preparations and properties of mono- and poly-halomethyl Grignard reagents: they have been obtained by halogen—magnesium interchange or metalation in basic solvents (THF, HMPT) at low temperatures (—80°, —110°) for example:

$$CHBr_3 + i\text{-}PrMgCl \begin{cases} \xrightarrow{\text{THF, } -80^\circ} CHBr_2MgCl \\ \xrightarrow{\text{THF, HMPT, } -110^\circ} CBr_3MgCl \end{cases} \qquad [1]$$

They are stable in suitable basic solvents at low temperatures, and show the characteristic reactions of classical Grignard reagents (addition to carbonyl compounds, alkylation, etc.): in this respect they are as useful as the halomethyllithium reagents. Furthermore, they exhibit electrophilic behaviour towards nucleophilic substrates; e.g. divalent carbon transfer to olefins and to the C—metal bond of Grignards.

The synthetic utility of these carbenoid Grignard reagents led us to study the chemistry of α-haloenolates** derived from esters and ketones. We survey below, our main observations in the preparation and properties of these organometallics. They have been obtained through metalation or halogen—metal inter-

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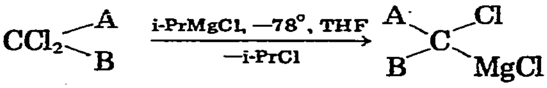
** The terms enolates, and enolato, do not imply that the metal is bonded to the oxygen atom, but merely designate α-keto or carbalkoxy organometallics.

change by use of alkaline, alkaline-earth organometallics or homocuprates, and also catalytically by use of Cu^I salts; yet another route involving rearrangements of β-alkoxy- and β-oxido-carbenoids is descirbed. The account is mainly concerned with the production of α-haloenolates, but we outline their synthetic utility.

Preparation of haloenolates

(1) By halogen—metal interchange

The greater the degree of halogen substitution in a polyhalomethane, the more facile is the exchange between one of the halogen atoms and the MgCl moiety of isopropylmagnesium chloride. It was therefore of interest to examine the reactivity of polyhalomethanes linked to other electron-withdrawing substituents, e.g. in alkyl trichloroacetates, trichloromethylketones, dichloromalonic esters or dichloroacetoacetates. In such compounds, the chlorine atoms should exhibit the characteristic "positive halogen" behaviour encountered in polyhalomethanes. A facile halogen—metal exchange is in fact observed:



$$CCl_2(A)(B) \xrightarrow[-i\text{-}PrCl]{i\text{-}PrMgCl,\ -78^\circ,\ THF} (A)(B)C(Cl)MgCl$$

(I) A = Cl, B = COOR [2]
(II) A = Cl, B = COR [3]
(III) A = COOR, B = COOR [4]
(IV) A = COOR, B = COR′ [4]

However, with trichloromethyl ketones, reduction of the carbonyl group may occur, and may even become the major pathway when R = phenyl [3]. With alkyl trichloroacetates, the use of THF as a solvent is necessary in order to avoid Claisen-type self condensation of the enolate. Addition of an ethereal solution of polyhalogenated carbonyl compounds to metal shavings has also been used for the preparation of "Reformatsky complexes", but this procedure is still restricted to reactions of alkyl trichloroacetates and dichloromalonates with zinc [4,5] in THF (—10°), magnesium promoting extensive polymerization.

(2) By hydrogen—metal interchange (metalation)

Haloenolates can be made by metalation by use of alkali dialkylamides. The induced acidity of the geminal protons facilitates a rapid hydrogen—metal interchange, and this has been utilized in the preparation of several haloenolates (M = Na, Li), initially by use of sodium bis(trimethylsilyl)amide in THF (—78°) e.g.:

$$HCXYCOOR \xrightarrow[-78^\circ]{(Me_3Si)_2NNa,\ THF} Na[CXYCOOR]$$

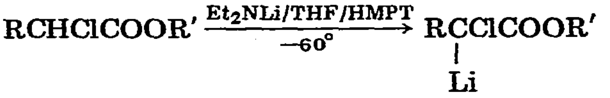
(V) X = H, Y = Cl, R = t-Bu
(VI) X = Me, Y = Cl, R = t-Bu, Et, Me
(VII) X = Me, Y = Br, R = Et
(VIII) X = Y = Cl, R = t-Bu
(IX) X = Y = Br, R = t-Bu
(X) X = Cl, Y = F, R = t-Bu

However, care must be taken that a Claisen-type self-condensation is avoided by t-butyl protection of the ester groups (as in V, VIII, IX, X). In contrast, methyl α-chloro- and α-bromo-propionic esters can be metalated to give the corresponding enolates without these side reactions [6].

The preparation of lithium haloenolates has been performed by use of lithium diethylamide, produced by the reaction of lithium metal with a HMPT—benzene—diethylamine mixture [7].

$$\mathrm{Li} \xrightarrow[\mathrm{Et_2NH}]{\mathrm{HMPT,\ C_6H_6}} \mathrm{Et_2NLi}$$

When diluted with THF, this reagent metalates (at —60°) isopropyl dichloroacetate and ethyl α-chloropropionate almost quantitatively:

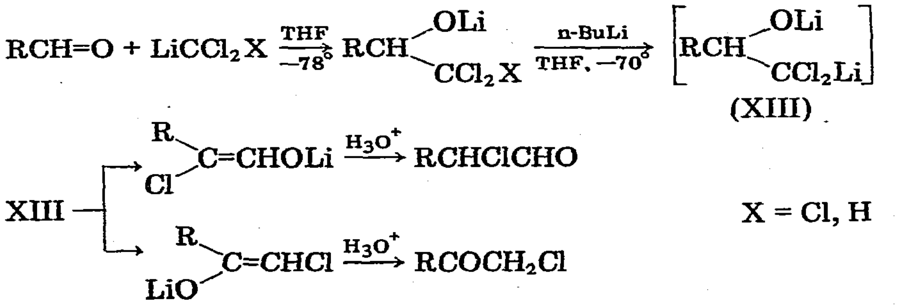


$$\mathrm{RCHClCOOR'} \xrightarrow[-60^\circ]{\mathrm{Et_2NLi/THF/HMPT}} \underset{\mathrm{Li}}{\mathrm{RCClCOOR'}}$$

(XI) $R = Cl, R' = i\text{-}Pr$ [8]
(XII) $R = Me, R' = Et$

(3) By rearrangement of β-oxidocarbenoids

Trichloro- and dichloro-methylcarbinols are easily made by coupling of trichloro- and dichloro-methyllithium with aldehydes and ketones. Subsequent metalation by n-butyllithium leads, via chlorine—lithium or hydrogen—lithium exchange, to the corresponding β-oxidocarbenoids, which are unstable even at —120°: they decompose by α-elimination with transfer to the carbenoid center of one of the two groups linked to the adjacent alcoholic carbon atom. Depending on the migratory aptitudes of these groups, two enolates are expected (see Table 1):



We first reported this reaction sequence by mid-1972 [9], at which time the late Professor G. Köbrich informed us of his independent study (then in the press) of the metalation of dichloromethylcarbinols by phenyllithium and lithium piperidide [10]. Similar experiments were described in a later publication by Taguchi, Yamamoto and Nozaki [11], who obtained results very similar to ours except that no competitive hydrogen—phenyl migration was detected with XIII ($R = C_6H_5$) in their experiments. We established the following sequence of migratory aptitude of groups adjacent to the carbenoid center: $H > C_6H_5 > R_3C = R_2CH > RCH_2 > CH_3$ and found that the H and Ph groups

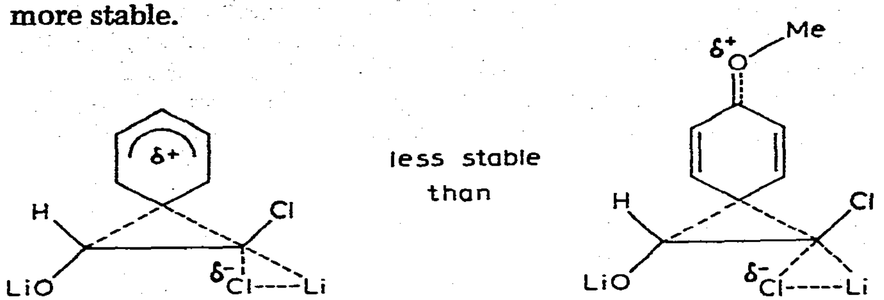
TABLE 1

REARRANGEMENTS OF β-OXIDOCARBENOIDS (ACTION OF BUTYLLITHIUM ON α,α-DICHLORO ALCOHOLS)

Substrate	Products[b]	Yield (%)
n-$C_4H_9CHOHCCl_3$	n-$C_4H_9COCH_2Cl$	80
$Me_2CHCHOHCCl_3$	$Me_2CHCOCH_2Cl$	57
$Et_2CHCH(OLi)CHCl_2$[a]	$Et_2CHCOCH_2Cl$ (92) $Et_2CHCH(Cl)CHO$ (8)	62
$Et_2CHCH(OH)CCl_3$	$Et_2CHCOCH_2Cl$ (80) $Et_2CHCH(Cl)CHO$ (20)	80
Cyclo-$C_6H_{11}CHOHCCl_3$	Cyclo-$C_6H_{11}COCH_2Cl$ (92) Cyclo-$C_6H_{11}CHClCHO$ (8)	83
$C_6H_5CH(OLi)CHCl_2$[a]	$C_6H_5COCH_2Cl$ (85) $C_6H_5CH(Cl)CHO$ (15)	70
$C_6H_5CH(OH)CCl_3$	$C_6H_5COCH_2Cl$ (60) $C_6H_5CH(Cl)CHO$ (40)	60

[a] The alcoholate was not isolated. [b] Relative yields in parentheses.

show migratory aptitude of the same order of magnitude. Furthermore a *para* or *ortho* substituent on the aryl group which can stabilize a positive charge (e.g. a methoxy group) promotes the migration of the aryl group and the α-chloroketone/α-chloroaldehyde ratio is then reversed compared with that from the unsubstituted phenyl probably because the phenonium intermediate is more stable.



As an example of an application of this reaction, cyclic (C_n) ketones undergo a facile ring enlargement [9] leading to α-chlorocyclanones (C_{n+1}) in good yields (Table 2).

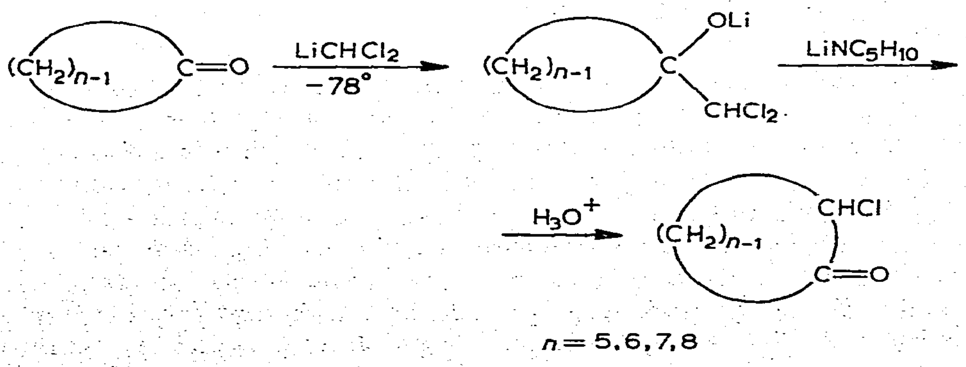
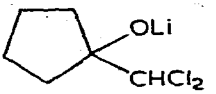
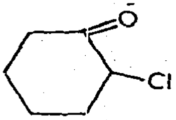
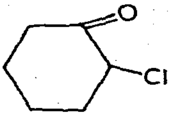
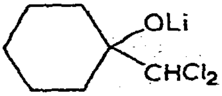
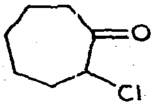
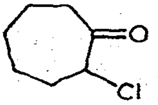
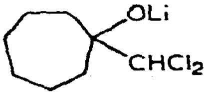
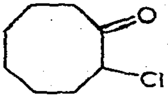
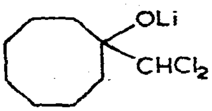
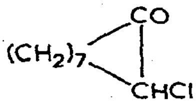
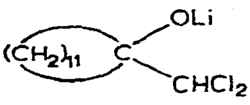
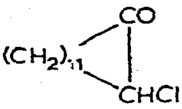
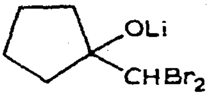
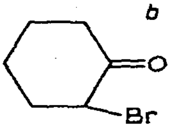
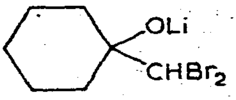
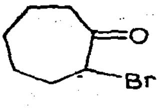


TABLE 2

RING ENLARGEMENT OF CYCLANONES

Initial product	Product (reaction performed with BuLi)	Global yield (%)	Product (reaction performed with $LiNC_5H_{10}$)	Global yield (%)
		64[a]		90
		41		70
				68
				48
		46[a]		
			[b] 	60
				53

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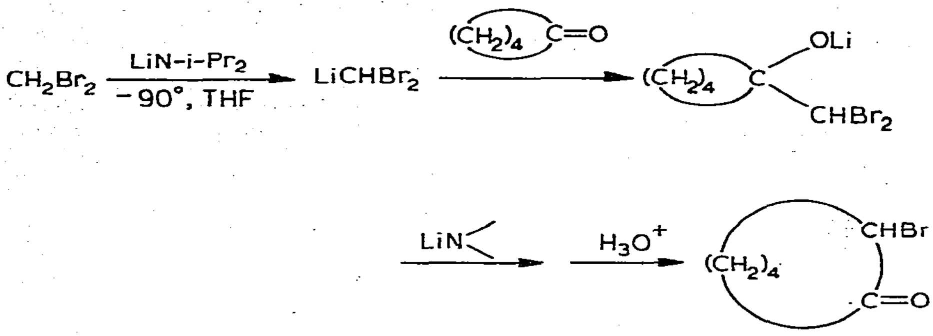
[a] Obtained by Yamamoto and al. [10]. [b] The lithium alcoholate was not isolated.

In these cases, lithium piperidide proved to be more effective than n-butyllithium, which gives substantial amounts of secondary products [12] (see Table 3). We obtained similar results with the bromoanalogs. For this work we devised a new route to dibromomethyl- and alkyl-lithium which involves the metalation of methylene bromide or 1,1-dibromoalkanes by lithium diisopropylamide in THF at —90° [13]. These reagents are easily condensed with aldehydes or ketones, and the resulting dibromomethyl-lithio alcoholates are further metalated by lithium diisopropylamide (or piperidide) to β-oxidodibromocarbenoids. These unstable species decompose via α-elimination and migration to yield α-bromoketoenolates [12].



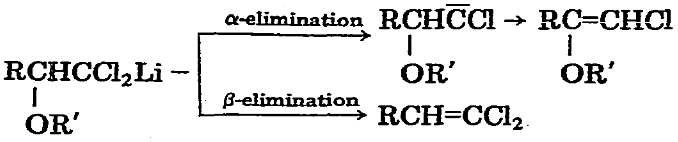
In contrast, the lithium α,α-dibromo alcoholates undergo bromine—lithium exchange when n-butyllithium is used and give non-halogenated enolates [9].

$$C_6H_5CHOHCHBr_2 \xrightarrow[\text{THF}, -70^\circ]{\text{2 BuLi}} \xrightarrow{H_3O^+} C_6H_5COCH_3 + C_6H_5CH_2CHO$$

A recent publication describes the application of this reaction to the ring enlargement of cyclanones [14].

(4) By haloketoenolates from alkoxycarbenoids

We have shown that β-alkoxycarbenoids can undergo either α- or β-elimination on heating [15,16].

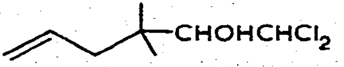
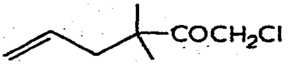


$$\underset{OR'}{RCHCCl_2Li} - \begin{cases} \xrightarrow{\alpha\text{-elimination}} \underset{OR'}{RCH\overline{C}Cl} \rightarrow \underset{OR'}{RC{=}CHCl} \\ \xrightarrow{\beta\text{-elimination}} RCH{=}CCl_2 \end{cases}$$

α-Elimination is the rule when the *syn* or *anti* conformation of the CLi

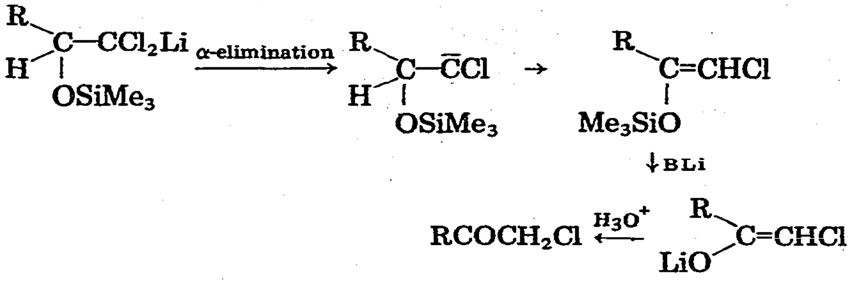
TABLE 3

COMPARISON BETWEEN BuLi AND $LiNC_5H_{10}$ USED FOR THE REARRANGEMENT OF β-OXIDOCARBENOIDS

Substrate	Product (reaction performed with BuLi)[c]	Global overall yield (%)	Product (reaction performed with $LiNC_5H_{10}$)[c]	Global overall yield (%)
$Me_2CHCHOLiCCl_2X$[a]	$Me_2CHCOCH_2Cl$	57	$Me_2CHCOCH_2Cl$	60
$Me_3CCHOLiCCl_2H$	Me_3CCOCH_2Cl	51	Me_3COOCH_2Cl	88
$BuCHOLiCCl_2X$[a]	$BuCOCH_2Cl$	80	$BuCOCH_2Cl$	80
$C_6H_5CHOLiCCl_2H$[b]	$C_6H_5COCH_2Cl$ (85) $C_6H_5CHClCHO$ (15)	70	$C_6H_5COCH_2Cl$ (35) $C_6H_5CHClCHO$ (65)	90
 CHOHCHCl2			 COCH2Cl	89

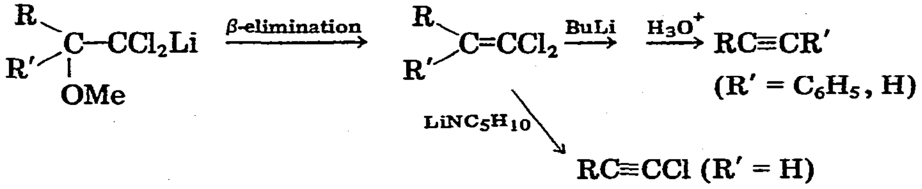
[a] X = Cl for the reaction with n-BuLi, X = H for the reaction with $LiNC_5H_{11}$. [b] The lithium alcoholate was not isolated. [c] Relative yields in parentheses.

and COR′ bonds are forbidden by steric hindrance, which precludes β-elimination. When R′ is the bulky trimethylsilyl group, and R is an α-branched alkyl, or *ortho*-methoxyaryl group, only α-elimination is found, and surprisingly exclusive migration of H or aryl is observed (this is only the predominant, not exclusive process in the case of β-oxido carbenoids). The resulting α-chlorotrimethylsilylenol ether is further cleaved by the excess of basic reagent (n-butyllithium or lithium piperidide) to the ocrresponding lithium enolate:



$B = n\text{-}C_4H_9,\ C_5H_{10}N$

When R is a linear alkyl group (or even a *p*-alkoxyphenyl group) β-elimination to dichloroalkene is the only route, and an excess of the reagent will convert it into a terminal alkyne or a 1-chloro-1-alkyne (when either n-butyllithium or lithium piperidide is used):



The replacement of the silyloxy group by a methoxy one leads to β-elimination in all studied cases. This is illustrated in Table 4.

TABLE 4

COMPETITION BETWEEN α- AND β-ELIMINATIONS FOR β-ALKOXY CARBENOIDS

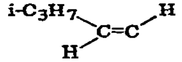
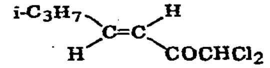
Substrate	Product obtained when R = $SiMe_3$ after hydrolysis	Yield (%)	Product obtained when R = Me after hydrolysis	Yield (%)
$Et_2CHCH(OR)CCl_3$	$Et_2CHCOCH_2Cl$	76[b]	$Et_2CHCH{=}CCl_2$	75[a]
			$Et_2CHC{\equiv}CH$	83[b]
Cyclo-$C_6H_{11}CH(OR)CCl_3$	Cyclo-$C_6H_{11}COCH_2Cl$	60[b]	Cyclo-$C_6H_{11}CH{=}CCl_2$	75[a]
			Cyclo-$C_6H_{11}C{\equiv}CCH_2OMe$	69[b,c]
o-$MeOC_6H_4CH(OR)CCl_3$	o-$MeOC_6H_4CHClCHO$	70[b]	o-$MeOC_6H_4CH{=}CCl_2$	93[a]
			o-$MeOC_6H_4C{\equiv}CH$	66[b]
n-$C_4H_9CH(OR)CCl_3$	n-$C_4H_9C{\equiv}CH$	60[b]	n-$C_4H_9C{\equiv}CH$	60[b]

[a] Addition of one equivalent of butyllithium at —110° followed by slow warming to —60°. [b] Addition of the substrate to 3 mol of butyllithium at —60°. [c] Methyl chloromethyl ether (one equivalent) was added to the lithium acetylide.

TABLE 5

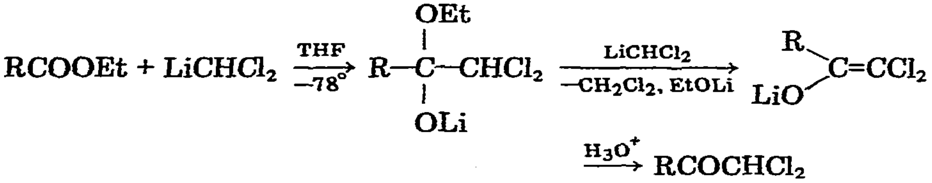
FORMATION OF DICHLOROMETHYL KETONE FROM THE COUPLING OF AN ESTER WITH 2 MOL OF $LiCHCl_2$

$RCOOR' + nLiCHCl_2 \rightarrow \xrightarrow{H_3O^+} RCOCHCl_2$

R	R	*n*	Dichloroketone	Yield (%)
Et	$i\text{-}C_3H_7$	2	$i\text{-}C_3H_7COCHCl_2$	70
Et	$t\text{-}C_4H_9$	1	$t\text{-}C_4H_9COCHCl_2$	21
	$t\text{-}C_4H_9$	2	$t\text{-}C_4H_9COCHCl_2$	69
Me	$o\text{-}CH_3OC_6H_4$	2	$o\text{-}CH_3OC_6H_4COCHCl_2$	75
Et		2		45
Et	$C_2H_5OCH_2$	2	$C_2H_5OCH_2COCHCl_2$	78
Me	CH_3CHCl	2	$CH_3CHClCOCHCl_2$	80

(5) Lithium α,α-dichloroketoenolates

The stable lithium salts of α,α-dichlorohemiacetals are easily obtained by treatment of dichloromethyllithium with esters. An excess of the basic reagent promotes a new metallation, followed by β-elimination of the alkoxy group, to give an α,α-dichloroketoenolate [17] (see Table 5), and thus provides a new route to dichloromethylketones:

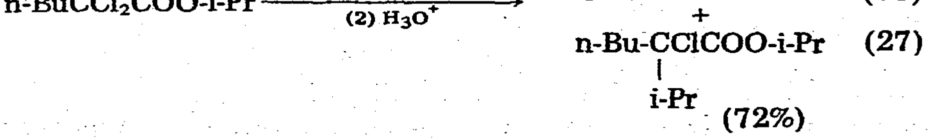


$$RCOOEt + LiCHCl_2 \xrightarrow[-78°]{THF} R\text{—}\overset{\overset{\large OEt}{|}}{\underset{\underset{\large OLi}{|}}{C}}\text{—}CHCl_2 \xrightarrow[-CH_2Cl_2,\ EtOLi]{LiCHCl_2} (R)(LiO)C{=}CCl_2 \xrightarrow{H_3O^+} RCOCHCl_2$$

(6) By Metal—halogen exchange of α,α-dihalo esters or ketones promoted by cuprates

The direct attack on isopropyl-2,2-dichlorohexanoate by magnesium in THF at 15° yields the corresponding chloromagnesium enolates (75% of α-monochloro ester after hydrolysis) but this reagent has the disadvantage that a large excess of metal must be employed, which impedes further alkylation, for example.

As for the reaction of an α,α-dichloro ester with a Grignard reagent, various reaction pathways are observed depending on the solvent and the nature (linear or branched) of the organometallics, and the alcoholic part of the ester. Thus, when both are secondary, exchange is favored:



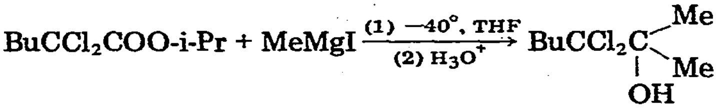
$$n\text{-}BuCCl_2COO\text{-}i\text{-}Pr \xrightarrow[(2)\ H_3O^+]{(1)\ i\text{-}PrMgCl,\ THF,\ -30°} \begin{array}{ll} n\text{-}BuCHClCOO\text{-}i\text{-}Pr & (73) \\ + & \\ n\text{-}Bu\text{-}\underset{\underset{\large i\text{-}Pr}{|}}{C}ClCOO\text{-}i\text{-}Pr & (27) \\ \quad (72\%) & \end{array}$$

Whereas ethyldichloro acetate in ether is alkylated at the electrophilic carboxylic center:

$$CHCl_2COOEt \xrightarrow[\text{ether, }-60^\circ]{RMgX} RCOCHCl_2$$

This represents another easy route to dichloromethyl ketones.

In THF, an excess of methyl Grignard reagent converts the dichlorohexanoate into the corresponding carbinol:



$$BuCCl_2COO\text{-i-Pr} + MeMgI \xrightarrow[(2)\ H_3O^+]{(1)\ -40^\circ,\ THF} BuCCl_2C(OH)(Me)_2 \qquad (90\%)$$

We have systematically investigated the reaction of α,α-dichloroesters and ketones with lithium and magnesium dialkylcuprates in view of the low reactivity of these derivatives towards carbonyl or carboxyl functions. In the reaction of lithium dialkylcuprates with α-haloketones there is doubt whether the reaction involves alkylation, metal—halogen exchange, or both.

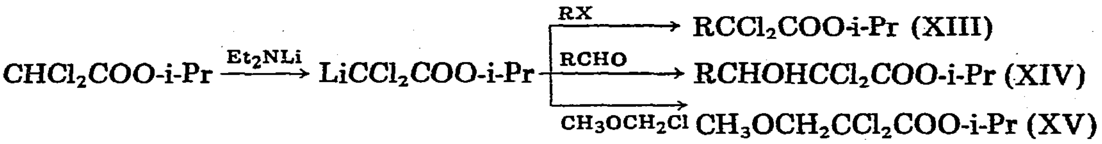
When two equivalents of lithium dialkylcuprate (in ether) or magnesium dialkylcuprate (in THF) are used, a nearly quantitative M—X exchange is obtained [18,19]:

$$BuCCl_2COO\text{-i-Pr} \xrightarrow[-60^\circ,\ 10min]{2\ Me_2CuM} BuCCl(M')COO\text{-i-Pr} \xrightarrow{H_3O^+} BuCHClCOO\text{-i-Pr}$$

M = MgBr (91%)
M = Li (95%)

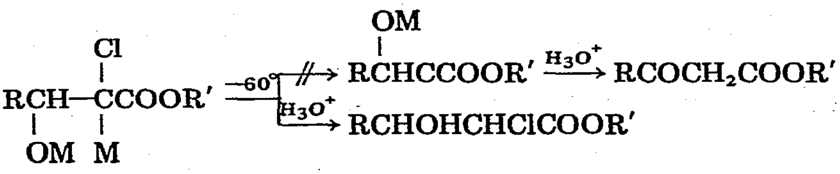
The absence of reaction when a mixture of 2 RMgBr + 1 CuI in ether is used leads us to doubt whether any cuprate is formed in this solvent.

This reaction represents a new route to α-monochloro esters, as α,α-dichloro esters are easily obtained in high yield from the lithioenolate of isopropyl dichloroacetate described above:



$$CHCl_2COO\text{-i-Pr} \xrightarrow{Et_2NLi} LiCCl_2COO\text{-i-Pr} \begin{cases} \xrightarrow{RX} RCCl_2COO\text{-i-Pr (XIII)} \\ \xrightarrow{RCHO} RCHOHCCl_2COO\text{-i-Pr (XIV)} \\ \xrightarrow[CH_3OCH_2Cl]{} CH_3OCH_2CCl_2COO\text{-i-Pr (XV)} \end{cases}$$

The influence of oxygenated functions on the course of metal—halogen exchange has been studied. The reaction of lithium dialkylcuprates with hydroxy derivatives (XIV) leads to α-chloro-β-hydroxy esters (*erythro* + *threo*); the high yields obtained point to a substantial stabilization of the intermediate alcoholate carbenoid at —60° (RCH(OM)CCl$_2$M [8] decompose below —120°).

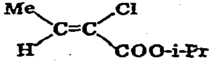
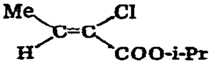
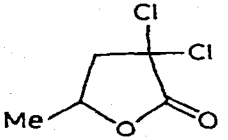
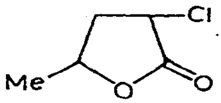


$$RCH(OM){-}C(Cl)(M)COOR' \xrightarrow{-60^\circ} \begin{cases} \not\rightarrow RCH(OM)CCOOR' \xrightarrow{H_3O^+} RCOCH_2COOR' \\ \xrightarrow{H_3O^+} RCHOHCHClCOOR' \end{cases}$$

The presence of a β-methoxy group in XV promotes elimination (probably *syn*) to a β-substituted α-chloroacrylate (*Z*).

TABLE 6

ACTION OF LITHIUM DIMETHYLCUPRATE ON α,α-DICHLOROCARBONYL COMPOUNDS

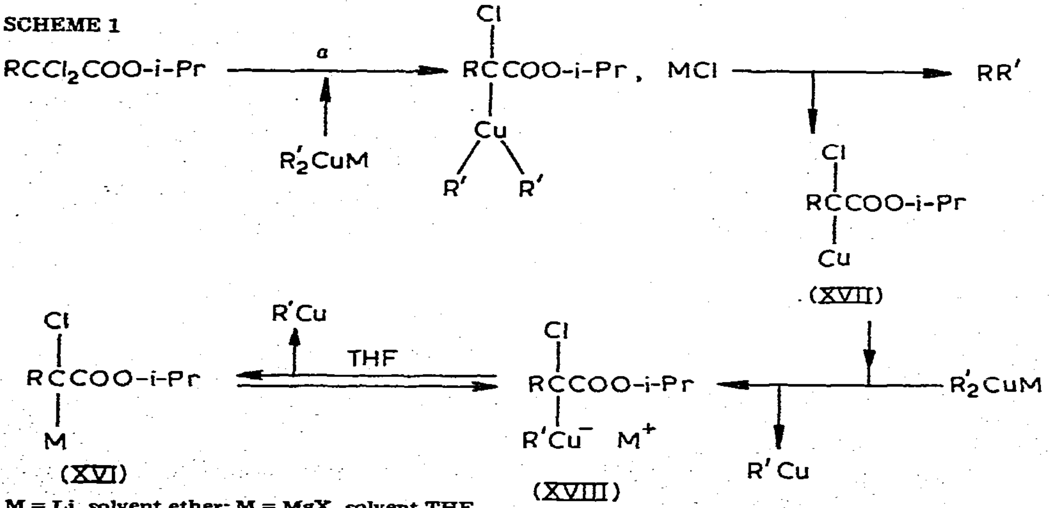
Substrate	T(°C)	Time (min)	Product after hydrolysis	Yield (%)
n-BuCCl$_2$COO-i-Pr	—60	10	n-BuCHClCOO-i-Pr	95
n-BuCCl$_2$COOMe	—60	10	n-BuCHClCOOMe	78
n-C$_6$H$_{11}$CCl$_2$COO-i-Pr	—60	10	n-C$_6$H$_{11}$CHClCOO-i-Pr	96
CH$_2$CHCH$_2$CCl$_2$COO-t-Bu	—60	10	CH$_2$=CHCH$_2$CHClCOO-t-Bu	90
MeCHOHCCl$_2$COO-i-Pr	—60	120	MeCHOHCHClCOO-i-Pr	80
PhCHOHCCl$_2$COOMe	—60	120	PhCHOHCHlCOOMe	85
i-PrCHOHCCl$_2$COO-t-Bu	—60	120	i-PrCHOHCHClCOO-t-Bu	86
i-PrOCH$_2$CCl$_2$COO-i-Pr	—90	30	i-PrOCH$_2$CHClCOO-i-Pr H$_2$C=CClCOO-i-Pr	60 [a]
i-PrOCH(Me)CCl$_2$COO-i-Pr	—90	15	i-PrOCH(Me)CHClCOO-i-Pr 	41 50 } 91
MeOCH$_2$CCl$_2$COO-i-Pr	—80	30	H$_2$C=CClCOO-i-Pr	[a]
MeOCH(Me)CCl$_2$COO-i-Pr	—80	15		90
	—90	10	 [b]	50
n-BuCCl$_2$COMe	—60	15	n-BuCHClCOMe	93

[a] Not determined. [b] *trans/cis* = 10/1.

Exchange with lithium dimethylcuprate in ether has been successfully applied to dichloro ketones and lactones (see Table 6).

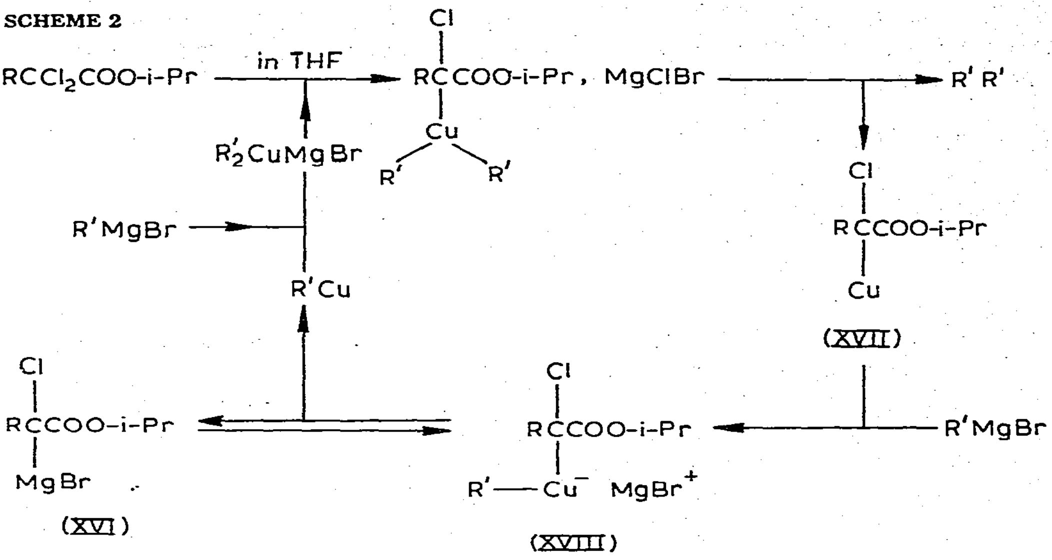
We have proposed the following mechanism which accounts for (i) the need to use two equivalents of dialkylcuprate, (ii) the precipitation of alkyl copper, (iii) the liberation of stoechiometric amounts of alkane R′—R′, and (iv) the stability and reactions of the end product (XVIII) (see Scheme 1):

SCHEME 1

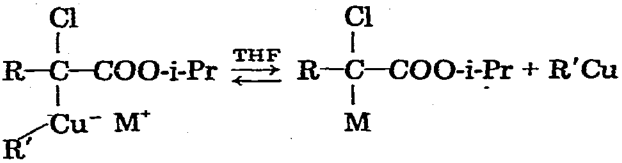


[a] M = Li, solvent ether; M = MgX, solvent THF.

SCHEME 2



Since XVII exhibits characteristic electrophilic properties (see below) which are not observed with our reaction mixture, we conclude that it must react very rapidly with the cuprate, which is used in excess to form an enolatoalkylcuprate (XVIII). The salt XVIII with M = Li, prepared in ether, does not react with methyl iodide, but addition of THF promotes the alkylation. On the other hand XVIII (M = MgBr) prepared in THF is methylated as rapidly as directly prepared (XVI). These facts suggest that this polar solvent promotes an equilibrium between XVIII and XVI:



$$R{-}\overset{\displaystyle Cl}{\underset{\displaystyle Cu^- M^+ (R')}{C}}{-}COO\text{-}i\text{-}Pr \overset{THF}{\rightleftharpoons} R{-}\overset{\displaystyle Cl}{\underset{\displaystyle M}{C}}{-}COO\text{-}i\text{-}Pr + R'Cu$$

(XVIII) (XVI)

In the light of this reaction scheme, it can be expected that if the four successive reactions leading to XVI have a higher rate than the direct attack of R—M on the substrate (such attack occurs at the carboxylic function) then a catalytic process should be possible. This has proved to be the case with the less nucleophilic Grignard reagent (the alkyllithium gives rise to both types of reaction). Thus, addition of two equivalents of Grignard to a mixture of 0.1 equiv. copper bromide and 1.0 equiv. of the α,α-dichloro ester in THF, at —40° yields, after hydrolysis, 0.91 equiv. of the α-monochloro ester [19]:

$$n\text{-}BuCCl_2COO\text{-}i\text{-}Pr + 2\ MeMgBr \xrightarrow[(2)\ H_3O^+]{(1)\ THF,\ 0.1\ CuBr} n\text{-}BuCHClCOO\text{-}i\text{-}Pr \qquad (91\%)$$

The catalytic process is shown in scheme 2. We assume that the Grignard reagent plays two roles: to form an heterocuprate XVIII, and to form the homocuprate R'_2CuM, any loss of alkylcopper thus being avoided. It should be noted that the absence of any alkylcopper at the end of the reaction means that only one equivalent of the electrophile (e.g.: R—X) need be used when further use of XVI is desired whereas for Scheme 1 four equivalents are necessary.

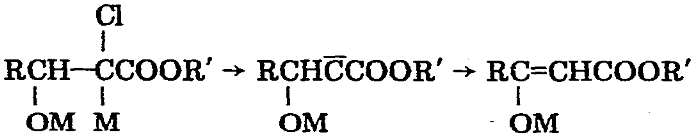
Properties of α-haloenolates

α-Haloenolates can be viewed as keto- or carbalkoxy-carbenoids and can thus exibit both electrophilic and nucleophilic behaviour.

Electrophilic behaviour

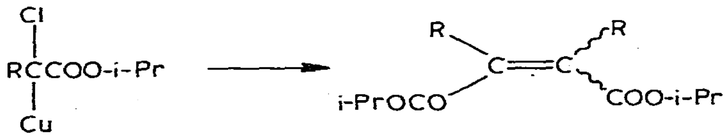
The delocalization of the negative charge minimizes the metal—halogen interaction. Consequently most of these enolates, e.g. (M = MgCl or ZnCl but not M = Cu) exhibit no electrophilic reactivity; e.g. they undergo no reactions with olefins or organometallics. Furthermore, some of them are quite stable at room temperature or even in boiling THF.

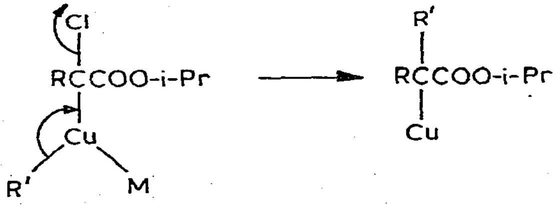
We have seen that β-oxido-α-haloenolates XVIII are stable at —60°, but they decompose at room temperature by an α-elimination—transposition mechanism:



$$\underset{OM}{RCH}-\overset{Cl}{\underset{M}{C}}COOR' \rightarrow \underset{OM}{RCH}\overline{C}COOR' \rightarrow \underset{OM}{RC}=CHCOOR'$$

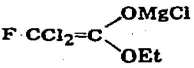
We found [20] that copper carbenoids are quite unstable; for instance, addition of 1/1000 equivalent of a copper bromide triethylphosphite complex to dichloromethyllithium in THF results in an almost explosive decomposition (at —85°). α-Halocupro enolates of type XVII decompose at room temperature to substituted maleates and fumarates while another type of carbenoid decomposition is observed with enolatocuprates XVIII: an intramolecular substitution may be involved in this case.





(XVIII)

TABLE 7

NUCLEOPHILIC REACTIONS OF 

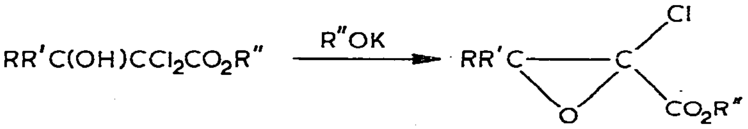
$CCl_2{=}C\begin{smallmatrix}OMgCl\\OEt\end{smallmatrix}$

Substrate	Product	Yield (%)
H_2O	$HCCl_2COOEt$	70
C_2H_5CHO	$C_2H_5CH(OH)CCl_2COOEt$	79
CH_3COCH_3	$(CH_3)_2C(OH)CCl_2COOEt$	68
$(CH_3CO)_2O$	CH_3COCCl_2COOEt	56
IC_4H_9	$n\text{-}C_4H_9CCl_2COOEt$ (in 20/80 HMPT/THF)	55
CH_3OCH_2Cl	$CH_3OCH_2CCl_2COOEt$	73
$C_2H_5OCHClC_2H_5$	$C_2H_5\underset{\underset{OC_2H_5}{\vert}}{C}HCCl_2COOEt$	78
$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2CCl_2COOEt$	73

Nucleophilic behaviour

All the α-haloenolates derived from esters exhibit nucleophilic behaviour such as addition to carbonyl compounds (M = ZnCl, MgCl, Li, Na), alkylation (M = MgCl, Li, Na), acylation, etc. Table 7 shows some typical reactions of the ethyl trichloroacetate-derived magnesium enolate with carbonyl compounds and organic halides [2].

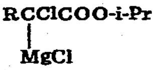
The functional dichloro carboxylate esters which are obtained in this way in high yields are valuable intermediates in chemical synthesis [21,22]. For example, the β-hydroxy-α,α-dichlorocarboxylate esters, obtained by addition of the magnesium enolate prepared from alkyl trichloroacetates to aldehydes and ketones, were the precursors used in the synthesis of α-chloro glycidic esters, which represent a new class of compounds [22].

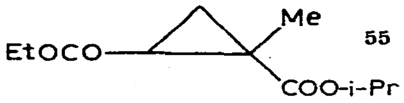
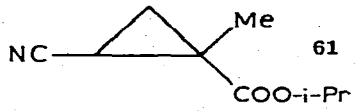


The synthetic utility of Grignard reagents derived from α-haloesters is exemplified by the reactions listed in Table 8 of the Grignard reagents XVI obtained by addition of two equivalents of methylmagnesium bromide on α,α-dichloroesters in the presence of a catalytic amount of cuprous bromide [8]. These reagents give α-monochloro esters on hydrolysis, but can also be alkylated to α-tertiary chloro esters; their hydroxyalkylation represents an extension of the Darzens condensation, while conjugate addition to α,β-unsaturated esters and nitriles yields substituted cyclopropanes as in the MacCoy condensation.

Some typical difference between lithium α-chloroenolates derived from either α-chloro esters or α-chloro ketones are worthy of mention: when the former are prepared by metalation via diethylamide in a THF—HMPT mixture, they can be alkylated in almost quantitative yield, even by alkyl bromides [8], whereas the latter (derived from the rearrangement of β-oxidocarbenoids) lead to substantial amounts of *O*-alkylation. We have not been able so far to C-alkylate them under satisfactory conditions; but our efforts are continuing.

TABLE 8

NUCLEOPHILIC REACTIONS OF  $R\underset{\substack{|\\ MgCl}}{C}ClCOO\text{-}i\text{-}Pr$ IN THF [8] R = n-Bu (A), R = Me (B)

Enolate	Substrate	T(°C)	Time (h)	Product	Yield (%)
A	H_3O^+	−60		n-BuCHClCOO-i-Pr	91
A	CH_3I	20	1	n-BuC(Me)ClCOO-i-Pr	85
A	$CH_2{=}CHCH_2Br$	20	3	n-BuC(All)ClCOO-i-Pr	72
B	n-C_4H_9I	20	4	n-BuC(Me)ClCOO-i-Pr	69
A	n-C_4H_9I	20	18	n-$Bu_2CClCOO$-i-Pr	49
A	$CH_3OCHClCH_3$	20	3	 $n\text{-Bu}\underset{\substack{|\\ CH_3CHOCH_3}}{C}ClCOO\text{-}i\text{-}Pr$	75
B	$C_6H_5CH_2Br$	20	1	$PhCH_2C(Me)ClCOO$-i-Pr	70
B	$HC{\equiv}CCH_2Br$	−10	3	$HC{\equiv}CCH_2C(Me)ClCOO$-i-Pr	62
B	CH_3CHO	−80	0.25	MeCHOHC(Me)ClCOO-i-Pr	85
B	CH_3COCH_3	−80	1	$Me_2COHC(Me)ClCOO$-i-Pr	79
B	$CH_3COCH{=}CH_2$	−80	1	$CH_2{=}CHC(Me)(OH)C(Me)ClCOO$-i-Pr	70
B	$CH_2{=}CHCOOEt$	−80	1.5		55
B	$CH_2{=}CHC{\equiv}N$	−80	3		61
B	$(CH_3CO)_2O$	−80	0.25	$CH_3CO{-}C(Me)ClCOO$-i-Pr	58

Conclusion

α-Haloenolates can be easily made by several routes. We have demonstrated the relative advantages and disadvantages between hydrogen—metal and halogen—metal exchange, depending on the substrate used, and the stabilities of these organometallics. An insight into organocopper chemistry enabled us to devise a catalytic route to them. They represent a powerful point of entry to the synthesis of many polyfunctionalised compounds. Electronegative groups other than the carbalkoxy moiety can stabilize carbenoids, and are being actively studied in our laboratories.

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