[CONTRIBUTION NO. 217 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

STUDIES ON THE SCOPE OF THE REFORMATSKY REACTION

ROBERT E. MILLER AND F. F. NORD

Received December 7, 1950

The present study is concerned with the selection of an active condensing agent which will enable general usage of α-chloro- and β-bromo-esters in the Reformatsky reaction. The α-chloro-esters have the desirable advantage of being readily available in a wide variety, and lack the pronounced lachrimatory and vesicatory properties usually associated with their brominated analogs.

All experiments have been conducted in duplicate under identical conditions. The catalysts are evaluated in reactions of two hours' duration in which benzene-toluene is the usual solvent (1). Higher temperatures, or longer reaction times have been avoided in order to minimize the formation of high-boiling by-products. Due to the lower reactivity of these halogen esters, the standard experimental procedure has been slightly modified.

Only those reagents which significantly influence the yield of the β-hydroxy ester or its dehydration product are reported. No attempt has been made to isolate by-products in the reaction.

REACTION OF α-HALOGEN ESTERS

Zinc is preferable to magnesium as the condensing agent in the Reformatsky reaction because of the greater tendency of the latter metal to react with the carboxylate group of the halogen esters. Zinc, however, fails to effect significant condensation of α-chloroesters or β-bromoesters with either aldehydes or ketones under the experimental conditions used. Various metals have also been employed in conjunction with the zinc; gallium, sodium, and aluminum in 2–3 gram-atom % quantities are totally ineffective.

In an earlier modification (2) it is stated that copper powder, when added to the reaction mixture containing zinc, increases the yield of the β-hydroxy ester or its dehydration product. It has been pointed out by Kon and Nargund (3), however, that the reactions which occur in the presence of copper powder also take place in its absence. In a previous paper (4), we have reported that 2-acetothienone reacts inadequately with ethyl chloroacetate in the presence of this catalyst. Reexamination of this modification indicates that neither acetophenone nor 2-acetothienone react in the presence of copper. Benzaldehyde, however, gives 50% of methyl cinnamate on reaction with methyl chloroacetate in the presence of the zinc-copper mixture; in the absence of copper powder the yield is less than 10%.

With benzyl chloroacetate similar results have been obtained, although in the initial experiments the yield of benzyl cinnamate was poor (less than 10%). When the benzene-toluene solvent is replaced by toluene to aid the reaction of the high-boiling (133°/10 mm.) benzyl chloroacetate, the yield is substantially increased.

TABLE I
REFORMATSKY REACTIONS WITH CHLOROESTERS

CARBONYL COMPONENT[i]	α-HALOGEN ESTER	CONDENSING AGENT	SOLVENT	PRODUCT[a]	B.P., °C.	MM.	YIELD[g] %	DERIVATIVE[a, e]	M.P., °C.[h]
A	Methyl chloroacetate	Zn + $CuCl_2$	B–T	Methyl β-methylcinnamate[b]	121–123	6	26.3	β-Methylcinnamic acid	96.5–97
A	Methyl chloroacetate	Zn + CuCl	B–T	Methyl β-methylcinnamate	121–123	6	21.7	β-Methylcinnamic acid	96.5–97
A	Methyl chloroacetate	Mg + $HgCl_2$	B–T	Methyl β-methylcinnamate	118–121	3	46.8	β-Methylcinnamic acid	96.5–97
A	Methyl chloroacetate	Mg + $HgBr_2$	B–E	Methyl β-methylcinnamate[b]	129–131	9	68.3	β-Methylcinnamic acid	96.5–97
A	Methyl chloroacetate	Mg + I_2	B–E	Methyl β-methylcinnamate[b]	120–122	4	59.0	β-Methylcinnamic acid	96.5–97
A	Methyl chloroacetate	Blaise reagent (11)	B–T	Methyl β-methylcinnamate	122–124	6	37.2	β-Methylcinnamic acid	96.5–97
Bzd	Methyl chloroacetate	Zn + Cu	B–T	Methyl cinnamate[b]	123–125	3	50.9	Cinnamic acid	131.5–132
Bzd	Methyl chloroacetate	Mg + $HgCl_2$	B–E	Methyl β-phenyl-β-hydroxypropionate	141–142	8	64.1	Cinnamic acid	131.5–132
Bzd	Benzyl chloroacetate	Mg + $HgCl_2$	T	Benzyl cinnamate	174–178[c]	3	46.9	Cinnamic acid	131.5–132
C	Ethyl chloroacetate	Gilman reagent (12)	B–E	Ethyl β-methyl-β-(2-thienyl)-acrylate[b]	118–120	4	40.0	β-Methyl-β-(2-thienyl)-acrylic acid	112–112.5
C	Ethyl α-bromoisovalerate	Mg + $HgCl_2$	T	Ethyl α-isopropyl-β-methyl-β-(2-thienyl)acrylate[b]	115–118[d]	3	43.4	α-Isopropyl-β-methyl-β-(2-thienyl)acrylic acid[f]	53–53.5
C	Ethyl bromomalonate	Mg + $HgCl_2$	B–E	Ethyl α-carbethoxy-β-methyl-β-(2-thienyl)acrylate[b]	158–163	2	30.0	β-Methyl-β-(2-thienyl)-acrylic acid	112–112.5

Solvent abbreviations: B = benzene; E = ether; T = toluene; F = tetrahydrofuran. [a] All compounds were analyzed. [b] Dehydrated with 6% aqueous oxalic acid before distillation. [c] M.p. 39–39.5°. [d] n_D^{20} 1.5190. The boiling point is incorrectly reported in Ref. (4) as 156–160°/1.5. [e] The esters were saponified by procedure *A*. [f] *Anal.* Calc'd for $C_{11}H_{14}O_2S$: C, 62.85; H, 6.71. Found: C, 63.10; H, 6.67. [g] Yields are based on the amount of carbonyl component used. [h] All melting points taken on a Fisher-Johns melting-point block. [i] A = acetophenone; Bzd = benzaldehyde; C = 2-acetothienone.

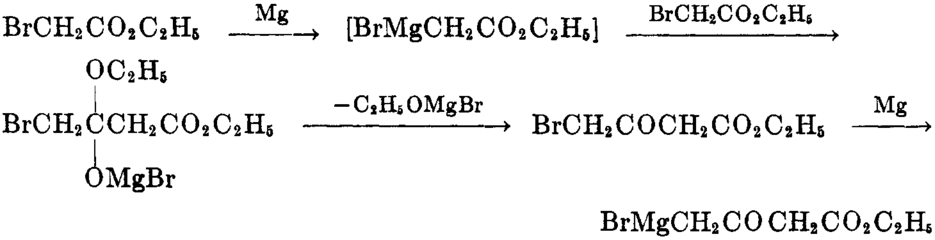
Zinc which has been immersed in a warm solution of cupric sulfate (5) and allowed to stand until a red-brown layer of copper deposits on the zinc granules, proves ineffective in promoting the condensation of acetophenone and methyl chloroacetate. It is probable that the active couple itself acts so rapidly on the water that the zinc is considerably oxidized. The experimental data would indicate that the use of copper metal as a composite of non-alloyed condensing agents is primarily limited to aldehyde condensations.

When 0.5–1.0 mole-% of a cuprous or cupric halide (2) is mixed with the zinc the condensation of ketones with α-chloroesters is only moderately successful, approximating 23% yields.

Aluminum, although a more electropositive metal than zinc, does not effect condensation (6).

There have been frequent reports in the literature concerning the substitution of magnesium for zinc in the Reformatsky reaction. In several cases (7) the yield has been greatly increased. In spite of these claims we have found that magnesium, like zinc, does not react appreciably with α-chloroesters.

When duplicate experiments are conducted with α-bromoesters, magnesium actually gives lower yields of the Reformatsky product than does zinc. Accordingly, the yields of the β-ketoesters resulting from the self-condensation of the bromoesters are approximately 10% higher. The explanation probably lies in the greater reactivity of magnesium with the carboxylate group, according to the reaction path previously suggested by Newman and Hussey (8).



$$BrCH_2CO_2C_2H_5 \xrightarrow{Mg} [BrMgCH_2CO_2C_2H_5] \xrightarrow{BrCH_2CO_2C_2H_5}$$

$$BrCH_2\overset{OC_2H_5}{\underset{OMgBr}{C}}CH_2CO_2C_2H_5 \xrightarrow{-C_2H_5OMgBr} BrCH_2COCH_2CO_2C_2H_5 \xrightarrow{Mg} BrMgCH_2COCH_2CO_2C_2H_5$$

When magnesium is treated with iodine following earlier directions (5, 9), the results are inconclusive. Although the activated metal gives an excellent yield of methyl β-methylcinnamate, the application of this reagent to polyhalogen esters and ethyl β-bromopropionate results in uniformly low yields.

Several zinc-copper alloys (10, 11) of varied composition and the magnesium-copper reagent, described by Gilman, Petersen, and Schulze (12), have also been utilized as condensing agents. The latter couple is suitable for use with α-chloroesters but fails with polyhalogen esters and β-bromoesters. The zinc-copper couples evidence a slight condensing action, but their application was discontinued because of the uncertainties involved in the preparation of the *most* reactive couple. This condition must be judged from the color, metallic appearance, luster, and length and intensity of heating of the mixture. The best results are obtained when the mixture acquires a yellowish, slightly lustrous appearance after heating for 10 to 15 minutes.

On the other hand, the exceptional activity of mercuric halides is remarkable. Although the use of mercuric halides in various organometallic condensations has been previously noted (13), our results have indicated that this is by far the most versatile and useful of the reagents investigated. For example, methyl chloroacetate and benzaldehyde react in the presence of magnesium and 0.5–1.0 mole-% mercuric chloride to yield 64% of methyl cinnamate; methyl β-methylcinnamate is obtained in 68% yield from acetophenone.

Furthermore, in the reactions of 2-acetothienone with ethyl α-bromoisovalerate and with ethyl bromomalonate, the yields of the respective Reformatsky products are double those reported in a previous paper (4).

Several important features should be noted in connection with the use of mercuric halides as promoters. The order of effectiveness seems to be $Mg\text{-}HgX_2 >$ $Zn\text{-}HgX_2 \gg Al\text{-}HgX_2$. The reaction proceeds equally well in benzene-ether and in toluene. While α-chloroesters usually do not react vigorously, in the presence of $Mg\text{-}HgX_2$ the characteristically vigorous reactions associated with the α-brominated esters are often encountered.

Of further significance is the fact that the mercuric halide *per se* is an essential component of the reaction mixture. In several experiments a magnesium amalgam had been employed as the condensing agent, but the results were entirely unsatisfactory. In view of the fact that Rochow (14) has shown that the reactivity of various magnesium amalgams is directly proportional to the percent of magnesium in the amalgam, it is probable that the function of the mercuric halide does not depend solely on its action as an amalgamating agent.

In the presence of other metallic and non-metallic halides, including $ZnCl_2$, $SnCl_2$, $SnCl_4$, $SbBr_3$, $MnCl_2$, $CrCl_3$ and $CoCl_2$, neither zinc nor magnesium significantly effect the reaction between acetophenone and methyl chloroacetate.

The failure of the magnesium-cobaltous chloride mixture to promote reaction is disappointing, in view of the pronounced effects which $CoCl_2$ has on the course of the Grignard reaction (15). A free radical reaction is not indicated. The absence of by-products is not unexpected, since the reaction does not become exothermic on addition of the metallic halide. The analogy between the Grignard and Reformatsky reactions cannot be carried too far, however. The exact influence of cobalt chloride on the nature and yield of the product and on the rate of the Reformatsky reaction is indeterminate, since the actual organomagnesium compound, $ClMgCH_2COOC_2H_5$, cannot be prepared.

REACTION OF β-BROMOESTERS

Relatively little is known concerning the use of β-bromoesters in the Reformatsky reaction. The general concept prevails, however, that the value of this reaction for synthesis is not promising. Fuson (16) reported that ethyl β-bromopropionate and γ-iodobutyrate react to give the expected products, although in only 1–3% yields. Haberland and Heinrich (17), using ethyl β-bromopropionate in the presence of magnesium and boiling toluene obtained a 22% yield of the desired ester upon reaction with 6-methoxy-1-tetralone. In other instances, the β-bromoesters are either unreactive (4) or are believed to give rise to products of unknown structure (18).

This investigation has indicated that zinc does not serve as an effective condensing agent for these esters. When acetophenone or benzaldehyde are reacted according to the procedure of Haberland and Heinrich, the products are viscous, high-boiling liquids. Upon trituration with petroleum ether, white crystalline solids are obtained. These substances could not be definitely characterized. They are largely unchanged upon treatment with 5 *N* alkali for five hours and do not give derivatives for carbonyl or alcohol functions. Treatment of these solids with aluminum chloride and chloroform produces a green color.

In general, the reaction as described above is difficult to initiate, maximum condensation occurring only when the reactants are introduced simultaneously into the boiling mixture of toluene and magnesium. Furthermore, during the course of the reaction the mixture becomes extremely viscous, and a thick oil settles out from the hot solvent. This material does not go into solution upon addition of the usual inert reaction solvents. When successive additions of magnesium are made, the metal is promptly coated by the viscous material, and rendered inactive.

Since it seemed quite possible that the nature of the mixture and not the unreactivity of the β-bromoester contributed chiefly to the inadequacy of the reaction, the selection of a new solvent was desirable. Tetrahydrofuran has been found to meet the requirements very satisfactorily. It permits a homogeneous solution, avoids excessively high temperatures, and allows the reaction to be carried out in the usual manner. The reaction, after initiation on a steam-bath, becomes exceedingly vigorous. The condensation products, which were not isolated, gave 30–35% of the expected acids after saponification.

$$\begin{tikzcd}
\mathrm{R_1R_2C{=}O} + \mathrm{BrCH_2CH_2COOCH_3} \arrow[r, "\mathrm{Mg}"] & {[\mathrm{R_1R_2C{=}CHCH_2COOCH_3}]} \arrow[d, "\mathrm{OH}"] \\
& \mathrm{R_1R_2C{=}CHCH_2COOH} + \mathrm{R_1R_2CH_2CH{=}CHCOOH}
\end{tikzcd}$$

Aliphatic aldehydes and ketones as well as cyclohexanone react in the expected manner. With benzaldehyde and acetophenone viscous products are again formed. The reaction products were saponified with 5 *N* alkali and the acids were characterized by suitable derivatives. No acid could be isolated from the reaction of acetophenone, however. These data are collected in Table II.

Ethyl β-iodopropionate has also been utilized in the reaction but the yields are not improved.

The utility of this reaction is readily indicated. The literature reveals that the synthesis of β,γ-unsaturated acids, especially of the aliphatic series, is infrequently accomplished by a direct approach. The question of the position of the double bond is, however, to a large degree dependent on the nature of the substituents. It has been shown that aliphatic acids of the type $R_1R_2C{=}CHCH_2COOH$ are isomerized by 25% alkali at 100° in a few hours, predominantly to α,β-unsaturated acids (19). Butenoic acids without a γ-substituent give the α,β-unsaturated compound exclusively. A substituent on the γ-carbon atom increases the stability of the β, γ-isomer, and a second γ-substituent still more.

TABLE II

Reformatsky Reactions with β-Bromoesters

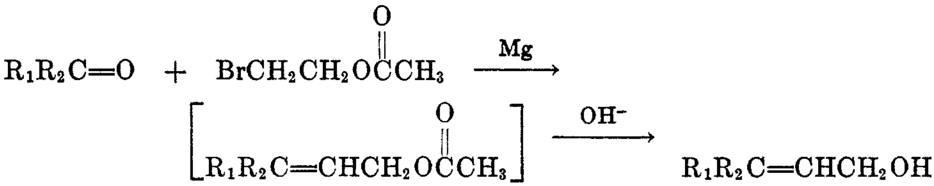
CARBONYL COMPONENT	β-HALOGEN ESTER[i]	SOLVENT	PRODUCT[a, b]	B.P., °C.	YIELD, %	DERIVATIVE[b]	M.P., °C.	REFERENCES
Benzaldehyde	EBP	F	4-Phenyl-3-butenoic acid	—[g]	31	Amide	86–87	19b
Benzaldehyde	EBP	B–F	4-Phenyl-3-butenoic acid	—	34	Amide	86–87	
Acetone	EBP	F	4-Methyl-3-pentenoic acid[c]	103–106/13	29.5	Anilide	105.5–106	19a, c
Acetaldehyde	EBP	F	2-Pentenoic acid[d]	192–194	20	Anilide	99.5–100	19a
Cyclohexanone	EBP	F	1-Cyclohexen-1-propionic acid	—[h]	31.5	*p*-Bromophenacyl ester	110–111	31
Benzaldehyde	BBA	T	Cinnamyl alcohol[e]	81–82/3	20	*p*-Nitrobenzoate	77.5–78	29
Benzaldehyde	BBA	B–T	Cinnamyl alcohol[f]	81–82/3	15	*p*-Nitrobenzoate	77.5–78	
Benzaldehyde	BBA	B–E	Cinnamyl alcohol	88–90/6	6	*p*-Nitrobenzoate	77.5–78	
Benzaldehyde	BBA	F	Cinnamyl alcohol	81–82/3	21	*p*-Nitrobenzoate	77.5–78	
Benzaldehyde	BBA	B–F	Cinnamyl alcohol	142–144/14	29	*p*-Nitrobenzoate	77.5–78	
Acetone	BBA	F	2-Methyl-2-buten-4-ol	140–141	25	Phenyl urethane	65–66	30
Butyraldehyde	BBA	F	2-Hexen-1-ol	155–156	35	α-Naphthyl urethane	75–76	32

[a] Unless otherwise specified a magnesium-mercuric chloride condensing agent was used. [b] All compounds were analysed. [c] 4-Methyl 2-pentenoic acid was also isolated in 5% yield; anilide, m.p. 119–119.5°. [d] 3-Pentenoic acid was isolated in 7% yield; anilide, m.p. 74.5–75°. [e] Saponification of the reaction mixture gave 3–9% benzoic acid in each case; *p*-bromophenacyl ester, m.p. 119°. [f] The condensing agent was zinc + cupric chloride. [g] M.p. 87–88°. [h] M.p. 103.5–104°; *Anal.* Calc'd for $C_9H_{14}O_2$: C, 70.12; H, 9.15. Found: C, 70.25; H, 9.02. [i] EBP = ethyl β-bromopropionate; BBA = β-bromoethyl acetate.

A second substituent on the β-carbon has less effect than the second γ-substituent.

Those acids where R_1 = phenyl are extremely difficult to isolate from the reaction mixture. This suggests that the phenyl group exerts a direct influence on the course of the reaction. This effect may be coupled with the ready tendency of β,γ-unsaturated acids to go over to lactones on distillation or upon treatment with alkali (20). Fittig has also shown that phenyl isocrotonic acid and γ-phenylbutyrolactone are polymerized to dimers by the action of alkali. Our experimental and analytical data indicate that a dimeric lactone may indeed be the primary reaction product. The product isolated from the reaction of benzaldehyde and methyl β-bromopropionate does not correspond to any of those reported by Fittig, however. The elucidation of the structure of these compounds is being continued and will be reported at a later date.

We have, moreover, carried the reaction of β-bromoesters a step further, leading to the eventual preparation of α,β-unsaturated alcohols and acetates. This novel reaction, which utilizes β-bromoethyl acetate and a carbonyl compound, gives 23–32% of the crude acetate after hydrolysis when carried out under the conditions described above.



$$R_1R_2C{=}O + BrCH_2CH_2O\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{Mg} \left[R_1R_2C{=}CHCH_2O\overset{\overset{O}{\|}}{C}CH_3\right] \xrightarrow{OH^-} R_1R_2C{=}CHCH_2OH$$

When the crude material is saponified with 25% aqueous potassium hydroxide, extracted with ether, and the ether extract distilled, two fractions are collected. The higher-boiling fraction contains the desired alcohol, isolated in 10–20% yield. The smaller fraction, which boils in the general range 70–95°, consists of a clear, unpleasant smelling liquid, which does not give alcoholic derivatives and which rapidly takes up bromine in the cold.

It is difficult to account for the isolation of benzoic acid from the saponification of the mixture produced by reaction of benzaldehyde and β-bromoethyl acetate. Even when the crude product is steam-distilled prior to saponification, small amounts of benzoic acid are isolated. The formation of this acid may be due to the prolonged action of the hot alkali on the resonating allylic system, or the cinnamyl alcohol may be converted directly to benzaldehyde. This has been previously observed by Henriques (21). The alkali can then convert the aldehyde to benzoic acid.

REACTION OF POLYHALOGEN ESTERS

Information was also sought on the use of polyhalogen esters in the Reformatsky reaction. Darzens (22) has recently described the use of ethyl dichloroacetate in the glycidic ester synthesis, in which the condensing agent is a dilute magnesium amalgam. Excellent yields of α-chloro-β-hydroxy esters are obtained, which can be converted to the glycidic esters or to α-chloroacrylic esters.

TABLE III
REFORMATSKY REACTIONS WITH POLYHALOGEN ESTERS

CARBONYL COMPONENT	HALOGEN ESTER	CONDENSING AGENT	SOLVENT[k]	PRODUCT[a]	B.P., °C.	MM.	YIELD, %	DERIVATIVE[a]	M.P., °C.
Acetophenone	Ethyl dichloroacetate	Zn + $CuCl_2$	B–T	Ethyl β-phenyl-β-hydroxybutyrate	119–121[b]	4	28.5	β-Methylcinnamic[i] acid	96.5–97
Acetophenone	Ethyl dichloroacetate	Mg + $HgCl_2$	B–E	Ethyl β-phenyl-β-hydroxybutyrate	131–135	8	48	β-Methylcinnamic[i] acid	96.5–97
Acetophenone	Ethyl dibromoacetate	Zn + $CuCl_2$	B–T	Ethyl β-phenyl-β-hydroxybutyrate	118–123	3	32.5	β-Methylcinnamic[i] acid	96.5–97
Acetophenone	Ethyl trichloroacetate	Mg + $HgCl_2$	T	Ethyl β-phenyl-β-hydroxybutyrate	105–108	2	21.5	β-Methylcinnamic[i] acid	96.5–97
Benzaldehyde	Ethyl dichloroacetate	Mg + $HgCl_2$	B–E	Ethyl α-chloro-β-phenyl-β-hydroxypropionate	144–148[c]	4	49	α-Chlorocinnamic acid[h]	138.5–139
Benzaldehyde	Ethyl dichloroacetate	Zn + $HgCl_2$	B	Ethyl β-phenyl-β-hydroxypropionate	131–133	5	35	Cinnamic acid	132.5–133
Benzaldehyde	Ethyl trichloroacetate	Mg + $HgCl_2$	B–E	Ethyl β-phenyl-β-hydroxypropionate	—	-	25[g]	β-Phenyl-β-hydroxypropionic acid[h]	115–116
2-Acetothienone	Ethyl dibromoacetate	Zn + $CuBr_2$	B–T	Ethyl β-methyl-(2-thienyl)acrylate[d]	92–95	1	20	β-Methyl-(2-thienyl)-acrylic acid	112.5–113
2-Acetothienone	Ethyl dichloroacetate	Zn + $CuCl_2$	B–T	Ethyl β-methyl-(2-thienyl)acrylate[d]	109–113	3	19	β-Methyl-(2-thienyl)-acrylic acid	112.5–113
2-Acetothienone	Ethyl dichloroacetate	Mg + $HgCl_2$	B–T	Ethyl β-methyl-(2-thienyl)acrylate[d]	112–115	4	23	β-Methyl-(2-thienyl)-acrylic acid	112.5–113
Acetone	Ethyl dichloroacetate	Zn + $HgCl_2$	B	Ethyl 3-methyl-2-butenoate	153–154[e,f]	-	31	3-Methyl-2-butenoic acid	69–69.5[j]

[a] All compounds were analysed. [b] Ref. (6) gives 120°/4. [c] Ref. (33) gives 161–162°/4. [d] Dehydrated with 6% oxalic acid before distillation. [e] Ref. (28) gives 153–154°. [f] Approximately 2–3% of an ester boiling at 180–183° was also obtained. A syrupy acid was isolated after saponification which was not further characterized. [g] Based on yield of acid. [h] Saponified by method *B*; [i] Method *D*. [j] Ref. (27) gives 69.5–70°. [k] B = benzene; T = toluene; E = ether.

The use of the Reformatsky technique differs in two essentials—reaction temperature and duration of the reaction. The glycidic ester reaction as a rule is carried out at low temperatures, although Darzens (23) reported heating the mixture so obtained for 5–6 hours at 100°. The Darzens condensation requires reaction periods varying from six hours to a few days. Under the experimental conditions of the present paper the reaction is accomplished in either benzene, benzene-ether, or benzene-toluene (reaction temperature 90–95°) in only two hours.

It is necessary, however, to catalyse these reactions. Both zinc-cupric chloride and magnesium-mercuric chloride effect the condensation of either benzaldehyde or acetophenone with dihalogen esters. The latter condensing agent appears to be superior.

The reactions must be carried out at the reflux temperature of the solvent to insure adequate condensation. The most significant fact disclosed as a result of this study has to do with the reduction of the halogen atoms of the ester component during reaction. This is apparently a function of the boiling point of the mixture, and the ease of reaction of the carbonyl component.

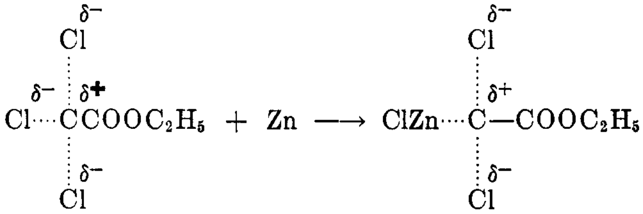
In the majority of experiments, therefore, the product is a non-halogenated β-hydroxy ester. No derivatives for α-keto or glycidic esters could be prepared. The reduction of the polyhalogen component in the Reformatsky reaction is supported by earlier work (24).

In general, the yields fall below those for the monohalogen esters. The optimum yield is 48–49%; and, as expected, ethyl trichloroacetate reacts less readily than the dichloroester.

The ease of reaction of α-halogen esters relative to the replacement of a halogen atom by the organometallic complex is of the order:

$$BrCH_2COOR \gg ClCH_2COOR > Cl_2CHCOOR > Cl_3CCOOR$$

Here the dominant effect is the increase in the carbon-halogen bond energy along the series. The effect of the three chlorine atoms in ethyl trichloroacetate for example, is to increase the partial positive charge on the adjacent carbon atom rendering more difficult the formation of an organometallic complex.



$$\overset{\delta-}{Cl}\cdots\underset{\underset{Cl}{\overset{\delta-}{\vdots}}}{\overset{\overset{\overset{\delta-}{Cl}}{\vdots}}{\overset{\delta+}{C}}}COOC_2H_5 + Zn \longrightarrow ClZn\cdots\underset{\underset{Cl}{\overset{\delta-}{\vdots}}}{\overset{\overset{\overset{\delta-}{Cl}}{\vdots}}{\overset{\delta+}{C}}}{-}COOC_2H_5$$

However, when one of the chlorine atoms does react with the metallic reagent, the effect is to decrease the partial positive charge on the carbon atom, due to the formation of the complex. The reaction of successive halogen atoms is consequently facilitated.

DISCUSSION

Since it has been shown that traces of the halides of iron, nickel, and cobalt do not exert a catalytic effect on the Reformatsky reaction, a free radical mechanism probably is inoperative. On the other hand, copper and mercury salts are effective in promoting the condensation. From a study of other reactions it can be seen that these salts are specific for reactions involving halogens. Copper and mercury salts are effective in the sense that they can enter into displacement reactions in such a way that the energy of formation of a new linkage contributes toward the rupture of the old.

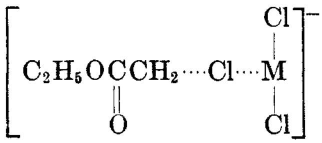
Substances such as copper, silver, or mercuric ions, which most effectively activate reactions involving the separation of a halide ion from an organic radical are characterized by their large affinity for a halide ion. The evidence for this is shown by the insolubility of silver halides, the small ionization of mercuric halides, and the fact that these substances form soluble complexes, such as AgI_2^-, which result from an excess of the halide ion (25).

The formation of a coordination complex by transition elements may be ascribed to the tendency of these elements to increase their valence shells by coordination with unshared electron pairs. The transition elements are particularly active acceptor centers. The relative sizes of the donor and acceptor centers and steric factors appear to be considerably significant. Stable complexes are more likely to be formed when the acceptor and donor centers are approximately of the same size.

It has also been shown that reactions between covalent molecules are greatly facilitated by the presence of media or catalysts that are capable of producing coordination complexes (26). Interchanges between covalent bonds may occur as the final stage of the mechanism.

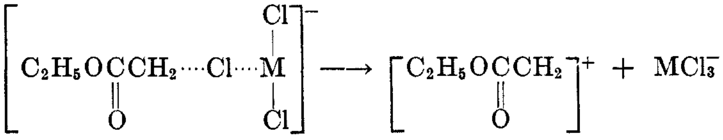
The formation of a coordination complex will influence polarization effects and increase the ability of unshared electron pairs to contribute. Electron mobility will be increased by the presence of an unstable electron shell in the complex, while the suitable approach of covalent molecules about the coordination center is dependent on the proximity of the reacting molecules.

In the absence of inorganic salts, the rate of formation of the organozinc halide is slow, especially with α-chloroesters because of the strong carbon-chlorine bond. The introduction of mercuric or cupric chloride makes possible the formation of an unstable complex such as:



$$\left[C_2H_5O\underset{\underset{O}{\|}}{C}CH_2\cdots Cl\cdots \overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{M}} \right]^- \quad \text{where M is Hg or Cu.}$$

It seems probable, therefore, that the function of the salts is simply to remove the halide ion, leaving the alkyl residue as a *carbonium* ion:



$$\left[C_2H_5O\underset{\underset{O}{\|}}{C}CH_2\cdots Cl\cdots \overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{M}} \right]^- \longrightarrow \left[C_2H_5O\underset{\underset{O}{\|}}{C}CH_2 \right]^+ + MCl_3^-$$

The driving force of the reaction is the tendency of the copper or mercury ion to attain a filled shell of valence electrons by sharing the electrons of the chlorine atom which carries three unshared pairs. Actually then this is an acid catalysis, in which the metal ion acts as an electrophilic reagent. The ability of metallic ions to act as electrophiles is common with all metals except the alkalies and alkaline earths. The attack of the metallic ion, therefore, is on the α-chloroester and not on the carbonyl compound.

Whether a carbonium ion is set free as an intermediate or an alkyl group transferred to a new linkage without actually being liberated has yet to be determined.

EXPERIMENTAL

Materials. The *2-acetothienone* was furnished through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Company, New York, N. Y. *Tetrahydrofuran* was obtained through the courtesy of the E. I. du Pont de Nemours Company, Wilmington, Del.

The *inorganic halides* were prepared in anhydrous condition by treating the hydrated salts with a stream of hydrogen chloride and were finally dried *in vacuo* at 100–150° for 20 hours.

Zinc-copper alloy (12). Zinc (9.0 g.) and 1.0 g. of copper were heated in a round-bottom flask bearing a capillary tube. The metals were mixed thoroughly and immersed in a free flame for 1–2 minutes. The mixture was agitated by continual shaking so that the filings lost their shape and acquired a yellowish tinge. If the manipulation was successful, a dark-gray granular mass without metallic luster was obtained. The formation of lustrous, semi-fluid shot is to be avoided.

Blaise reagent (13). In a liter flask were placed 120 grams of granulated zinc and 12 grams of electrolytic copper dust. The flask was equipped with a one hole stopper containing a glass stirring rod. The mixture was vigorously stirred while being heated over a free flame for several minutes. The red color of the copper disappeared, and at the melting point of the zinc a black powder suddenly formed. The stirring was continued without further heating until the mixture cooled.

Magnesium-copper alloy (14). A magnesium alloy (containing 13% copper) (5 g.) was mixed with iodine (1 g.) in a mortar and placed in a long-necked 200-cc. Pyrex flask. The flask was evacuated to 3 mm. and heated with shaking to 300° over a free flame. All the iodine disappeared in 8–10 minutes. The powder must not be allowed to melt to a granular mass. About 0.50 g. of the powder was used immediately to start the reaction and then the required amount of magnesium was added.

Von Baeyers' reagent (11). Magnesium filings (10 g.) were heated in a round-bottom flask over a free flame with continuous shaking. The temperature was regulated between 350–400°. Small portions of iodine were added so that each new addition was made when the previous portion had disappeared. The operation required 15–30 minutes. The active mass was formed as a grey powder, which turned brown after a time. The reagent was used immediately.

Lewinsohn's reagent (8). Granulated zinc was covered with a warm solution of copper sulfate. A layer of copper was deposited upon the zinc. The "couple" so formed was washed well with water, acetone, and finally dried in an oven at 100°. The warm activated condensing agent was used immediately.

Reformatsky reactions. The procedure for the reactions of α-chloroesters and polyhalogen esters was as follows: In a clean, dry 250-cc. three-necked flask with a stirrer and a reflux condenser protected from moisture was placed a large excess (usually five-fold) of the etched metal (or the freshly prepared alloy). A solution of a three-fold excess of the ethyl α-chloroester and 0.3–0.5 mole of the aldehyde or ketone in the appropriate solvent (benzene-ether, toluene, or benzene-toluene) was also added. The mixture was heated to reflux temperature and 0.1–0.5 mole-% of the inorganic halide was introduced. Refluxing and stirring were continued for two hours. The product was hydrolyzed and distilled in the usual way.

When tetrahydrofuran was employed as the solvent, the procedure was as described above, except that a few cc. of a solution of the halogen ester and the carbonyl compound in 100 cc. of tetrahydrofuran or benzene-tetrahydrofuran was added dropwise to 100 cc. of the boiling solvent containing the condensing agent. The reaction was initiated on a steam-bath and after the reaction set in, was allowed to proceed at such a rate that gentle refluxing occurred. After addition was complete, the mixture was refluxed for one hour on a steam-bath. The mixture was worked up in the usual manner.

Saponification. A. The products derived from reaction of α-chloroesters were saponified by refluxing 10 cc. of the ester with 5% aqueous potassium hydroxide for 1–2 hours. After cooling, the alkaline mixture was extracted with ether, and the aqueous layer then acidified with cold, dilute hydrochloric acid.

B. Alternately, the ester was dissolved in 50 cc. of ethanol containing 4 grams of potassium hydroxide and allowed to stand 48 hours. Some salt usually precipitated. The alcohol was evaporated completely and the salt was dissolved in the minimum of ice-water and acidified dropwise with 6 *N* acid.

C. The products derived from β-bromoester reactions were refluxed 2–4 hours with 25% aqueous potassium hydroxide, extracted with ether, and acidified. When the desired product was an alcohol, the ether extract was dried and distilled.

D. The attempted saponification of glycidic esters was carried out as follows: the ester (6.0 g.) was dissolved in 25 cc. of 10% alcoholic potassium hydroxide and kept at room temperature for 24 hours. The mixture was diluted with 100 cc. of water and acidified with 4 *N* phosphoric acid. The mixture was extracted with ether, washed with light petroleum ether (60–75°) and kept at 0° overnight. The precipitated solid was washed with petroleum ether and crystallized from chloroform-petroleum ether under an atmosphere of nitrogen in a dark bottle.

SUMMARY

1. The extension of the Reformatsky reaction to include the use of α-chloroesters, β-bromoesters, and polyhalogen esters has been described.

2. Mercuric chloride has been shown to be an excellent promoter for this reaction.

3. The reaction of β-bromoesters, previously unpromising, has been successfully carried out in 32% yields.

4. β-Bromoethyl acetate has been utilized in the Reformatsky reaction. As a result the direct synthesis of several α,β-unsaturated alcohols has been attained.

5. The reaction of polyhalogen esters in the presence of zinc and a carbonyl compound has resulted in the formation of reduced β-hydroxy esters.

New York 58, N.Y.

REFERENCES

(1) Natelson and Gottfried, *J. Am. Chem. Soc.*, **61**, 970 (1939).
(2) Nieuwland and Daly, *J. Am. Chem. Soc.*, **53**, 1842 (1931).
(3) Kon and Nargund, *J. Chem. Soc.*, 2461 (1932).
(4) Miller and Nord, *J. Org. Chem.*, **15**, 89 (1950).
(5) Lewinsohn, *Perfumery Essent. Oil Record*, **15**, 44 (1924).
(6) Ray and Dutt, *J. Indian Chem. Soc.*, **5**, 109 (1928) [*Chem. Zentr.*, I, 2371 (1928)].
(7) Zelinsky and Gutt, *Ber.*, **35**, 2140 (1902); Willstätter and Hatt, *Ann.*, **418**, 148 (1919).

(8) Hussey and Newman, *J. Am. Chem. Soc.*, **70,** 3024 (1948).

(9) von Baeyer, *Ber.*, **38,** 2759 (1905).

(10) Gladstone and Tribe, *J. Chem. Soc.*, **36,** 567 (1879).

(11) Krause and von Grosse, *Die Chemie der metall-organischen Verbindungen*, Edwards Bros., Inc., Ann Arbor, Mich., 1943, p. 63.

(12) Gilman, Petersen, and Schulze, *Rec. trav. chim.*, **47,** 19 (1928).

(13) Wachs, *Am. Perfumer Essent. Oil Rev.*, **44,** 25 (1942); Henbest, Jones, and Walls, *J. Chem. Soc.*, 2696 (1949); Sommelet and Hamel, *Bull. soc. chim.*, (4) **29,** 545 (1921).

(14) Rochow, *J. Am. Chem. Soc.*, **61,** 3591 (1939).

(15) Kharasch and others, *J. Am. Chem. Soc.*, **63,** 2305 (1941).

(16) Fuson, Arnold, and Cooke, *J. Am. Chem. Soc.*, **60,** 2272 (1938).

(17) Haberland and Heinrich, *Ber.*, **72,** 1222 (1939).

(18) Morita, personal communication, March 29, 1950.

(19) (a) Goldberg and Linstead, *J. Chem. Soc.*, 2354 (1928); (b) Linstead and Williams, *J. Chem. Soc.*, 2741 (1926); (c) Linstead, *J. Chem. Soc.*, 2506 (1929).

(20) Fittig and others, *Ann.*, **334,** 68 (1904); *Ann.*, **331,** 160 (1904).

(21) Henriques, *Z. angew. Chem.*, **10,** 399 (1898).

(22) Darzens, *Compt. rend.*, **203,** 1374 (1936).

(23) Darzens, *Compt. rend.*, **139,** 1215 (1904).

(24) Fuson and Farlow, *J. Am. Chem. Soc.*, **56,** 1593 (1934).

(25) Hammett, *Physical Organic Chemistry*, 1st ed., McGraw-Hill Book Co., Inc., New York, N.Y., 1940, p. 138.

(26) Meisenheimer and others, *Ann.*, **442,** 180 (1925); Meerwein, *Ann.*, **455,** 227 (1927).

(27) von Miller, *Ann.*, **200,** 264 (1880).

(28) Perkin, *J. Chem. Soc.*, **70,** 1471 (1896).

(29) Burton and Ingold, *J. Chem. Soc.*, 914 (1928); Hill and Nason, *J. Am. Chem. Soc.*, **46,** 2244 (1924).

(30) Courtot, *Bull. soc. chim.*, (3) **35,** 660 (1906).

(31) Nenitzescu and Przemetzky, *Bul. Soc. Chim. România*, (2) **1,** 333 (1929) [*Chem. Abstr.*, **35,** 6255 (1941)].

(32) Bouis, *Ann. chim.*, (10) **9,** 402 [*Chem. Zentr.*, II, 977 (1928)].

(33) Darzens and Lévy, *Compt. rend.*, **204,** 272 (1937).