This is to certify that the

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The Reformatsky Reaction Using a New Form of Highly Active Zinc

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Ezzeddine Bouhlel

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of the requirements for

PH.D. degree in Chemistry

Michael William Pattike
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THE REFORMATSKY REACTION USING A NEW FORM OF HIGHLY REACTIVE ZINC

By

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ABSTRACT

THE REFORMATSKY REACTION USING A NEW FORM OF HIGHLY ACTIVE ZINC

By

Ezzeddine Bouhlel

A fast and convenient procedure for the generation of highly activated zinc has been developed. The addition at 0°C of an ether solution of zinc chloride to a suspension of lithium (25 wt. % dispersion in mineral oil, containing about 0.5 % sodium) generates a highly activated form of zinc in a short period of time.

Twelve different zinc ester enolates (Reformatsky reagents) were generated from the corresponding α-bromoesters and the activated zinc in a first stage of a two step procedure. These reagents gave excellent yields of ß-hydroxy-esters when reacted in a second stage with benzaldehyde. Data on the stability of zinc and lithium ester enolates was obtained. Zinc ester enolates proved to be more stable than their lithium analogues. Lithium ester enolates reacted faster with the hindred ketone, 2-methyl cyclopentanone, than did the zinc ester enolates.

The regioselectivity of the Reformatsky reaction was briefly studied. The one step reaction of ethyl or trimethylsilyl 4-bromocrotonate esters with benzaldehyde in the presence of the activated zinc gave exclusively the alpha product. The two step procedure gave unidentified mixtures. Neither the one step nor the two step procedures gave the gamma product.

To My Family

ACKNOWLEDGEMENTS

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HIGHLY ACTIVATED ZINC

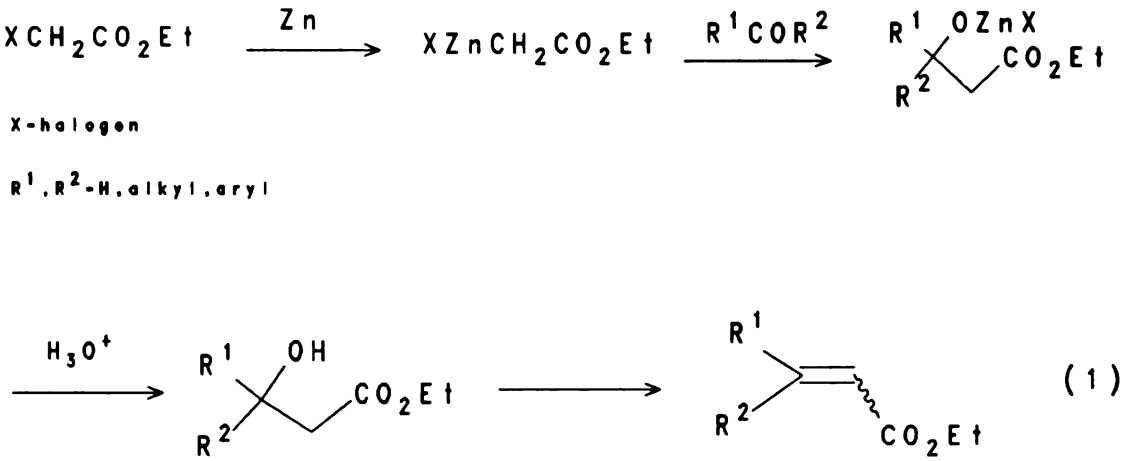
FROM

THE LITHIUM

REDUCTION OF ZINC CHLORIDE

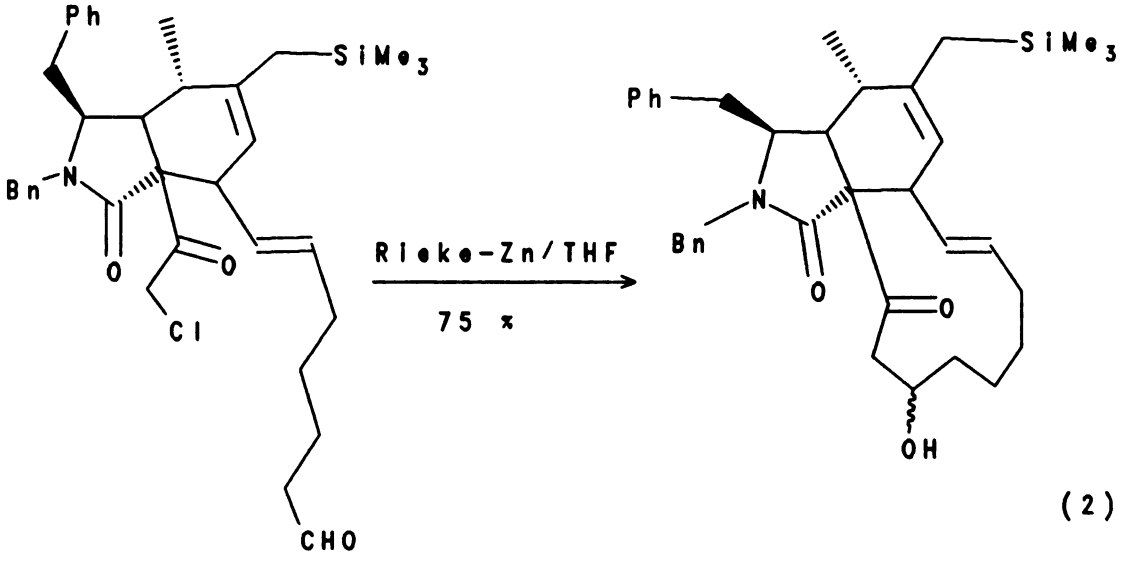
INTRODUCTION AND REVIEW OF LITERATURE

The Reformatsky reaction is one of the most generally applicable procedures for converting aldehydes and ketones to ß-hydroxyesters.[1] In this reaction an α-halocarbonyl compound, usually an α-bromoester, is reacted with zinc to give an enolate (the Reformatsky reagent). The enolate is subsequently reacted with an electrophile, usually an aldehyde or a ketone, to yield, after hydrolysis, a ß-hydroxyester. The ß-hydroxyester may be dehydrated in a further step to give an α,ß-unsaturated ester (eq 1).



(1)

A major advantage of this procedure over modern strong base procedures for generation of enolates is that most electrophiles, including aldehydes or ketones, do not react with zinc and may be present from the beginning of the reaction.[2] This allows the use of the intramolecular Reformatsky reaction in key steps in the selective synthesis of a wide variety of complex cyclic natural products and natural product precursors. The following cyclic transformation, yielding an 11-membered ring cytochalsin precursor[3], would be difficult to accomplish by a base promoted aldol reaction (eq 2).



(2)

The scope of the Reformatsky reaction has been extended to include a variety of α-halocompounds (esters, amides, ketones, nitriles, zinc salts of mono, di and trihaloalkanoic acids), a variety of electrophiles (imines, esters, acid chlorides and nitriles) and a variety of metals

other than zinc (magnesium, cadmium, nickel, indium, cerium and lithium).[2] A range of solvents (ethereal, aromatic hydrocarbons, mixtures of these, more polar solvents like acetonitrile, dimethylformamide, dimethylsulfoxide) have also been used.

The yield of ß-hydroxyesters in the classical method, using ordinary commercial zinc in refluxing benzene or benzene-ether, typically ranges from 50 to 89 %. For example, the reaction of ethyl α-bromoacetate with benzaldehyde in the presence of zinc dust gives a modest yield (61 %)[2] of ß-hydroxyester after twelve hours of refluxing in benzene (eq 3).

$$BrCH_2CO_2Et + PhCHO \xrightarrow[\text{reflux, 12hrs}]{\text{Zn, Benzene}} PhCH(OH)CH_2CO2Et \quad (3)$$

61 %

It has been shown that the reaction of ethyl α-bromoacetate with benzaldehyde in the presence of 20-mesh zinc at room temperature gives a higher yield (85 %)[4] than the corresponding reaction at reflux, (eq 4) versus (eq 3).

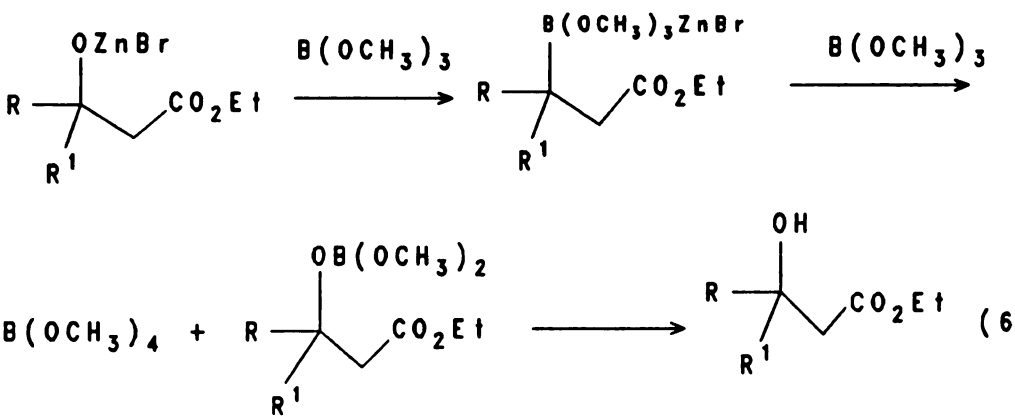
$$BrCH_2CO_2Et + PhCHO \xrightarrow[\text{12hrs at RT}]{\text{Zn, Benzene}} PhCH(OH)CH_2CO2Et \quad (4)$$

85 %

Base catalysed side reactions of the starting materials is a major factor responsible for the modest yields in the Reformatsky reactions. This is especially true in the case of aliphatic aldehydes, which can self-condense under the basic reaction conditions.[5] Higher yields (85 to 97 %) were obtained by conducting the Reformatsky reactions at room temperature in trimethylborate-benzene as a solvent system (eq 5). Trimethylborate[4] presumably serves to neutralize the basic alkoxide products, thus suppressing base catalysed condensations of the starting materials, especially in the case of the reactive aldehydes and cyclopentanone (eq 6).

$$BrCH_2CO_2Et + PhCHO \xrightarrow[12hrs\ at\ RT]{Zn,\ TMB\text{-}Benzene} PhCH(OH)CH_2CO_2Et \quad (5)$$

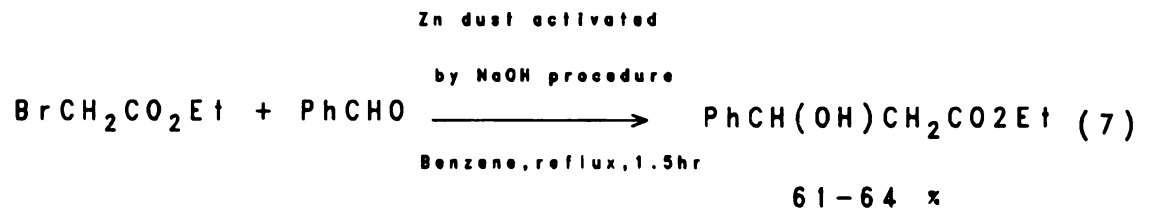
95 %



(6)

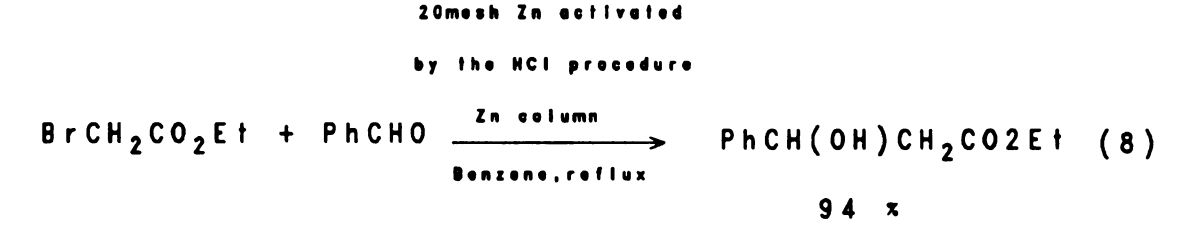
A more reactive form of zinc should increase the rate of formation of the Reformatsky reagent. Once the Reformatsky reagent is formed, it should react rapidly with carbonyl compounds to give, after hydrolyzis, the ß-hydroxyesters. This should lower the temperature at which the Reformatsky sequence can be completed, thus suppress side reactions and increase the yield.

Zinc metal is often activated before use in Reformatsky reactions.[6,2] This is usually accomplished by successively washing commercial zinc with different reagents to remove zinc oxides, exposing a fresh zinc surface, which reacts rapidly with α-bromoesters. One procedure for activating commercial zinc dust is to wash it successively with dilute sodium hydroxide solution, water, dilute acetic acid, water, ethanol, acetone and ether.[7] The zinc is then dried under vacuum at 100°C for two hours. For example the reaction of ethyl α-bromoacetate with benzaldehyde in the presence of zinc dust (activated by the sodium hydroxide procedure) gave a 61 to 64 % yield[7] of ß-hydroxyester in a shorter time than the reaction using unactivated zinc dust (eq 7).

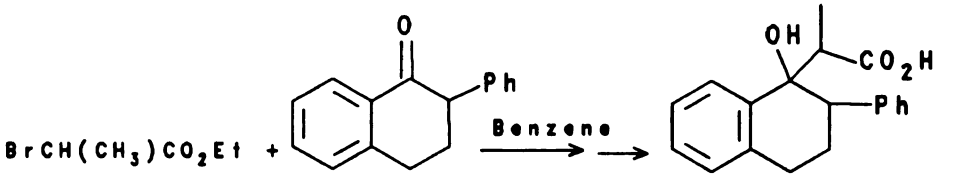


In a related procedure, zinc dust is stirred with a saturated ammonium chloride solution[8], followed by decantation and successive washings with water, ethanol, ether and dimethylformamide. Vaughan activated commercial 20-mesh zinc metal by heating it with a few drops of concentrated nitric acid[9] in concentrated sulfuric acid for 15 minutes at 100°C. The cooled zinc is washed free of acid with water followed by acetone and ether. The zinc is then dried at 110°C before use. In a more widely used procedure, 20-mesh zinc metal is washed successively with dilute hydrochloric acid,[10] then with water until neutral followed by acetone and ether. The washed metal is dried in a vacuum dessicator.

Even though the above procedures (sodium hydroxide, ammonium chloride, hydrochloric acid and nitric acid) help increase the yields slightly, and in some cases shorten the reaction times, they show limited success as general procedures for the activation of zinc metal. Usually these procedures are used in a preactivation step or in combination with another activation method (eq 8).[10]



A variety of materials has been added to Reformatsky reactions in attempts to increase the yields. A few promoters have been shown to increase the yields. Iodine[11] is probably the most frequently used promoter. Addition of about 10 mole % iodine to reaction mixtures was found in several cases to increase the yields slightly, as shown in the accompanying example (eq 9). A simple explanation for iodine promotion is that its reaction with zinc probably exposes a fresh metal surface.



(9)

38 % with I_2 activation
23 % without I_2
42 % recovered ketone

Another chemical method for zinc activation involves addition of about 10 mole % 1,2-dibromoethane[12] to commercial 20-mesh zinc metal, followed by a brief reflux. 1,2-dibromoethane probably reacts on the surface of the zinc to form a dihalozinc compound which decomposes in a further step to give zinc bromide, ethylene and a freshly exposed zinc surface (eq 10).

$$Br\text{-}CH_2\text{-}CH_2\text{-}Br \xrightarrow{Zn,\ reflux} Zn^* + ZnBr_2 + CH_2{=}CH_2 \quad (10)$$

Various other additives such as chlorotrimethylsilane,[13] copper (I) halides,[14] mercuric halide[15] or molecular sieves[14] have been used in Reformatsky reactions with limited success.

Rieke generated highly reactive metal powders[16,17] by reducing metal salts with alkali metals (eq 11).

$$MX_n + n\,A \longrightarrow M^* + n\,AX \qquad A: K, Na, Li \qquad (11)$$
$$X: Cl, Br$$

In this manner, metal powders of Mg, Ca, Zn, B, Al, Ga, In, Tl, Ge, Sn, Pb, Ti, V, Cr, Mn, Fe, Co, Ni, Pd, Pt, V, Cu and Cd have been prepared. A very reactive form of zinc[18] has been prepared as a fine black powder, by the reduction of anhydrous zinc chloride or bromide under an inert atmosphere. The reduction is carried out by potassium, sodium or lithium in an ethereal solvent, usually tetrahydrofuran (THF) or 1,2-dimethoxyethane (glyme). In the reduction of zinc chloride with potassium a mixture of anhydrous zinc chloride and potassium in THF is gently heated without stirring until the reaction starts on the surface of potassium metal. The heat is then removed and the mixture is stirred very slowly to keep the reaction under control. Finally the mixture is refluxed for two and half hours with rapid stirring to yield the reactive zinc powder

(eq 12).The yields of ß-hydroxyesters are much higher if the THF is removed after the reduction of zinc chloride is complete and exchanged for diethyl ether (Et_2O) to finish the Reformatsky sequence (eq 13).[18]

$$ZnCl_2 + 2K \xrightarrow[\text{reflux for 2.5 hrs}]{THF} Zn^* + 2KCl \qquad (12)$$

$$BrCH_2CO_2Et + PhCHO \xrightarrow[Et_2O,\ 60\ min\ at\ RT]{Zn^*(ZnCl_2/K)} PhCH(OH)CH_2CO2Et \qquad (13)$$

98 %

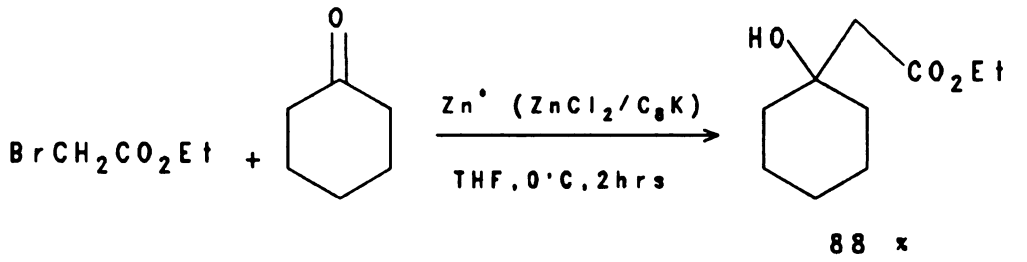
The Rieke procedure is often dangerous, tedious and time consuming. Since it involves the use of potassium, the reduction is very exothermic and THF has to be exchanged for diethyl ether (Et_2O) after the reduction.

After Rieke's initial work was published in 1975, other methods for generating reactive zinc powders were described. The procedure for reduction of zinc chloride with potassium-graphite (C_8K), developed by Ronchi[19], presents almost the same difficulties as the original Rieke method (eq 14).

$$8\,C + K \xrightarrow{150°C} C_8K$$

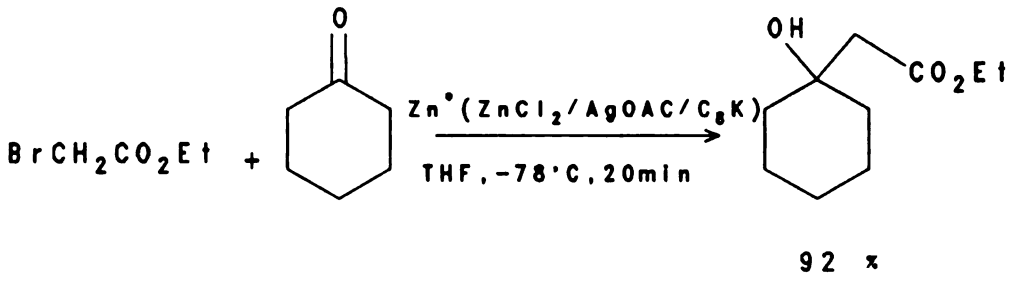
$$ZnCl_2 + 2C_8K \xrightarrow[\text{THF, reflux for 30 min}]{} C_{16}Zn + 2KCl \qquad (14)$$

After the generation of the reactive zinc powder, Ronchi conducted Reformatsky reactions at 0°C and obtained high yields of ß-hydroxyesters. For example, the reaction of ethyl α-bromoacetate with cyclohexanone at 0°C for two hours gave an 88 % yield of the adduct (eq 15).[19]



(15)

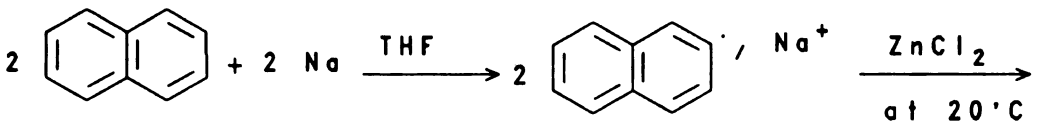
Weidman[20] developed a different method, which uses a zinc-silver couple obtained from equimolar amounts of potassium-graphite and zinc chloride/silver acetate (0.1 molar ratio). This procedure allowed Reformatsky reactions to be conducted at dry ice temeratures (-78°C), and shortened the time required for reaction from 120 minutes to 20 minutes, (eq 16) versus (eq 15).This procedure also involves the use of potassium, and thus presents the same drawbacks as in the previous two.

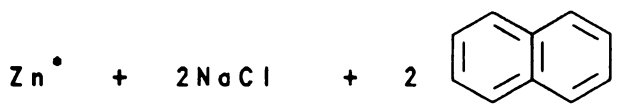


(16)

The fact that Reformatsky reactions can be conducted at ice or dry ice temperatures over short periods of time demonstrates that the reaction of zinc enolates with carbonyl compounds is very fast, and this suggests that the only purpose for conducting the classical reaction at reflux temperatures is to accomplish the formation of the zinc enolate.

In 1977, Arnold[21] developed a more convenient way of generating reactive zinc by reducing zinc chloride with sodium in THF, in the presence of naphthalene as an electron carrier (eq 17). In this procedure, a solution of sodium naphthalide is prepared under argon in an addition funnel. This solution is added dropwise with good stirring to a solution of anhydrous zinc chloride and a black suspension of finely divided zinc is formed in quantitative yield.This procedure is safe (sodium versus potassium), simple, convenient and fast; and the reduction solution is homogeneous at 20°C. The yield of ß-hydroxyester from the reaction of ethyl α-bromoacetate and benzaldehyde (75 %)[21] is not as high as in the procedures involving the use of potassium (eq 18).





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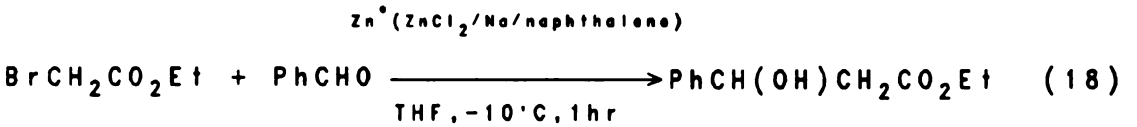
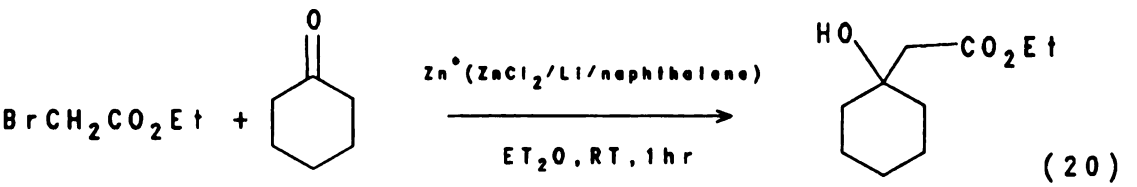


(18)

A modification of Arnold's procedure, using lithium instead of sodium was developed by Rieke[22] (eq 19). A typical reduction is carried out by adding lithium (99.9 %, rod, 1.27 cm diameter) to anhydrous zinc chloride and naphthalene (molar ratios, 1.2 : 2.5 : 0.25) in glyme, and stirring at room temperature until reduction is complete (about 15 hours). The reaction is conducted at room temperature and the yields are almost quantitative (95 to 98 %) for the reaction of ethyl α-bromoacetate and cyclohexanone (eq 20).[22]

$$ZnCl_2 + Li\,(rod,\ 1.27\ cm\ diam.) \xrightarrow[glyme,RT,15hrs]{naphthalene\ (cat.)} Zn^{*} + 2LiCl \qquad (19)$$



(20)

95-98 %

Despite improvements over previous methods (conducting the reduction at room temperature, using catalytic amount of naphthalene and obtaining better yields), this method presents many limitations: The reduction proceeds only in glyme, a very hydroscopic solvent, the glyme has to be removed and exchanged for ether to perform the Reformatsky reaction, and the generation of reactive zinc powder takes fifteen hours.

Boudjouk[23,24] found that low intensity ultrasound (from a laboratory cleaning bath) significantly increased the rates and yields of Reformatsky reactions. In early publications, Boudjouk used sonication with activated zinc dust (ammonium chloride procedure, iodine promoter). In a typical procedure a single-necked round-bottomed flask is charged with dioxane, benzaldehyde, ethyl α-bromoacetate and 10 mole %

iodine. The flask is then partially submerged in an ultrasonic bath. The progress of the reaction was monitored by ^1H NMR, and proved to be fast (five minutes) at room temperature, with quantitative yield of ß-hydroxyesters (eq 21).

$$BrCH_2CO_2Et + PhCHO \xrightarrow[\text{Dioxane, RT, 5 min}]{\substack{\text{Zn dust(NaOH washed)} \\ I_2/\text{Sonication} \\ (<10W/cm^2)}} PhCH(OH)CH_2CO2Et \quad (21)$$

98 %

Dioxane, a cancer suspect agent and high boiling solvent, was found to be the only satisfactory solvent. Neither benzene nor Et_2O (common Reformatsky reaction solvents) gave high yields, even after several hours of sonication.[23]

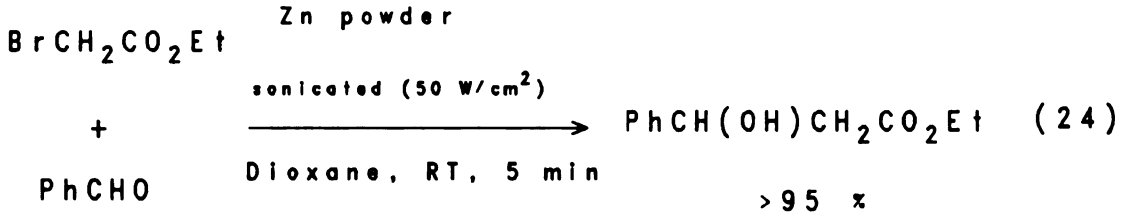
In 1986, Boudjouk[24] modified his original procedure to include reduction of zinc salts by metals. The reduction of zinc chloride to produce zinc powder can be accomplished in a short time with the aid of ultrasound energy (eq 22). This modification gives slightly lower yields,[24] involves exchanging THF for Et_2O and takes a longer time than the one using zinc dust (eq 23).

$$ZnCl_2 + \underset{(30\%\text{ in mineral oil})}{\text{Li dispersion}} \xrightarrow[\text{THF, RT, 40min}]{\text{Sonication}(<10 W/cm^2)} Zn^{\bullet} + 2LiCl \quad (22)$$

$$BrCH_2CO_2Et + PhCHO \xrightarrow[ET_2O, RT, 1hr]{Zn^{\bullet}(ZnCl_2/Li\ \text{dispersion in mineral oil/sonication})} PhCH(OH)CH_2CO_2Et \quad (23)$$

90 %

Recently, Suslick[25] examined the effects of ultrasonic irradiation on chemical reactivity, particle and surface morphology, and surface atomic composition of zinc powder. Suslick observed changes in particle morphology, aggregation, and surface composition, which he attributed to high-velocity interparticle collisions created by the ultrasonic irradiation. He also showed that the use of high intensity ultrasound from a direct immersion horn (≈ 50 W / cm^2) has a greater effect than an ultrasonic cleaning bath (< 10 W / cm^2). When a reaction mixture of benzaldehyde and ethyl α-bromoacetate in dioxane was irradiated, the yield was > 95 % after five minutes at 25°C (eq 24).[25] The use of iodine as a promoter had no effect on yield or reaction time.



(24)

Sonication has proved to be very useful in Reformatsky reactions. The yields typically range from 90 to 100 % and the reaction times from five minutes to three hours. The reactions are usually conducted at room temperature. The method is safe and usually inexpensive, since laboratory cleaning baths may be used for sonication. The drawback in the sonication procedures is that the highest yields require the use of dioxane as solvent.

Yields obtained by a variety of activation methods for commercial zinc are summarized in Table I, those obtained by methods of generation of reactive zinc powder are in Table II.

Over the past 20 years, major improvements in the classical Reformatsky reaction have been accomplished. It is clear from Table II that with reactive zinc powder the Reformatsky sequence is generally completed in short times and at low temperatures. The excellent yields obtained as shown in Table II (entries 1 and 3-6) support the supposition that side reactions (self-condensation of the bromoester or carbonyl compound, and elimination or retroaldolization of the intermediate) should be completely

suppressed when working at low temperatures. Table II also shows that each method of generation of reactive zinc powder suffers at least one drawback.

All the methods listed in Table I or in Table II have been used only in single step procedures, where a mixture of an α-haloester and a carbonyl compound is added to a suspension of zinc in an appropriate solvent. The Reformatsky reactions are probably conducted in this manner in an attempt to minimize problems associated with the stabilities of the zinc ester enolates.

The addition of a carbonyl compound to a preformed zinc ester enolate constitutes the two step Reformatsky reaction. such a procedure is especially useful for studying the properties of zinc ester enolates. The two step procedure is also useful for reaction with carbonyl compounds which are readily reducted by zinc metal.

There has been no published method that is useful, fast, safe and inexpensive for the generation of Rieke's highly reactive zinc powder. Therefore one of the objectives of study was to improve existing methods to incorporate the above characterestics. The zinc powder thus produced could be used to generate a serie of zinc ester enolates followed by an examination of the reactivities of the generated enolates towards carbonyl compounds in a second step. Another objective was to study the stability of the zinc ester enolates under various conditions, and to compare

these to the corresponding lithium ester enolates under similar conditions.

Activation of commercial zinc			Reaction with ethyl bromoacetate and benzaldehyde				
Run	Form of Zinc	Activation method	Solvent	t, °C	T, min	Yld	Ref.
1	dust	no activation	benzene	80	720	61	2
2	dust	NaOH	benzene	80	90	61-64	7
3	20-mesh	no activation	benzene	25	720	85	4
4	20-mesh (TMB-THF)	no activation	TMB-THF	25	720	95	4
5	20-mesh (zinc column)	HCl	benzene	80		94 by GC	10
6	dust/ Iodine/ ultrasound (<10W/cm^2)	NH_4Cl	dioxane	25	5	98 by NMR	23
7	powder/ ultrasound (50W/cm^2)	no activation	dioxane	25	5	>95	25
8	granular Zn-Cu	no activation	THF	66	60	82	26

TABLE I

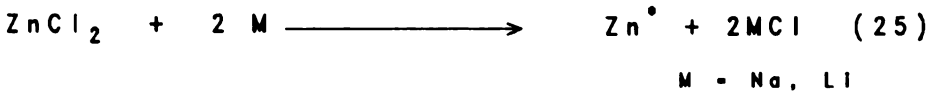
Reactive Zinc Powders from the Reduction of Zinc Chloride				Reaction with ethyl bromoacetate and a carbonyl compound					
Metal	Solv.	t_1, °C	T_1, min	Solv.	t_2, °C	T_2, min	Carbonyl Compound	Yld	Ref.
K	THF	66	150	Et_2O	25	80	PhCHO	98	18
$Na/C_{10}H_8$	THF	20	120	THF	-10	60		75	21
Li[a]	THF	25	60	Et_2O	25	60		90[c]	24
Li[b]/ $C_{10}H_8$	Glyme	25	960	Et_2O	25	60	CYCLO-HEXANONE	95-98	22
C_8K	THF	150 and 70	30	THF	0	120		88	19
C_8K/ AgOAc	THF	150 and 70	60	THF	-78	20		92	20

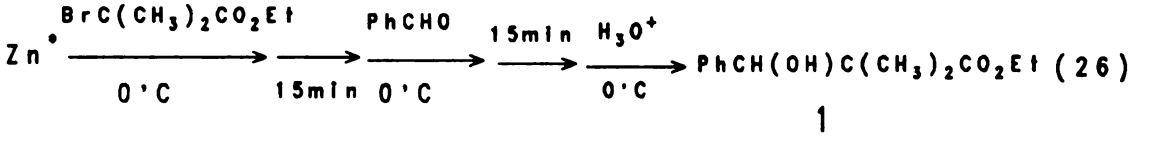
a) Lithium (dispersion) and sonication (<10W/cm^2).
b) Lithium (rod, 1.27 cm in diameter).
c) By G.C and ^{1}H-NMR.

TABLE II

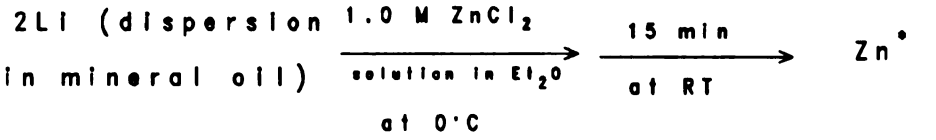
RESULTS AND DISCUSSION

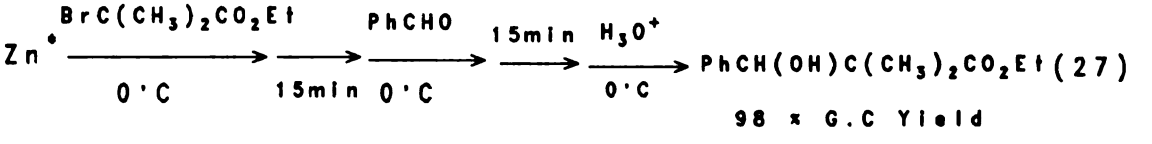
A survey of the reduction of zinc chloride, as a one molar solution in ether, to generate reactive zinc powders was conducted (eq 25). A two step Reformatsky reaction of ethyl α-bromoisobutyrate and benzaldehyde, conducted at 0°C for a total time of 30 minutes after generation of the zinc powder, was chosen as a standard reaction to compare the relative reactivity of each sample of zinc (eq 26). Ethyl α-bromoisobutyrate was chosen because it is not a lachrymator, as most α-haloesters are, and unlike many other α-bromoesters it is readily available. We chose benzaldehyde as a representative carbonyl compound because it reacts readily with nucleophiles and lacks enolizable protons which could lead to side reactions. The ease of spectroscopic identification of the ß-hydroxyester products of the reaction was another reason for choosing benzaldehyde as the carbonyl compound for our study.





G.C yields of ethyl 3-phenyl-3-hydroxyisobutyrate (1) are listed in table III. The highest (98 %) yield was obtained with a zinc powder generated by reduction of the zinc chloride solution at 0°C in diethyl ether (Et_2O) using lithium (dispersion in mineral oil) (eq 27).

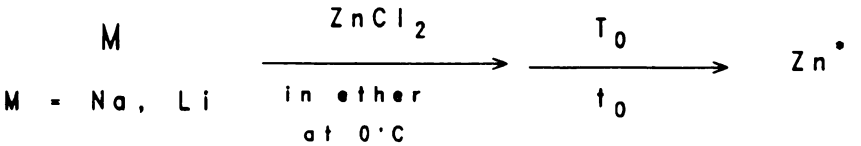


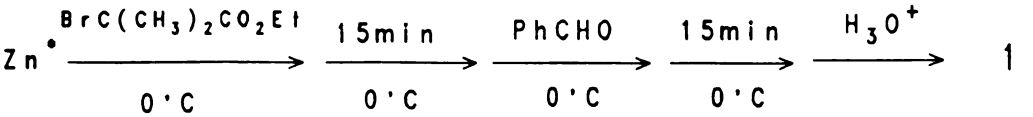


Generation of Reactive Zinc Powders from the Reduction a 1.0 M $ZnCl_2$ Solution in Ether					Two Step Reaction of $BrC(CH_3)_2CO_2Et$ and PhCHO	
Entry	Metal/Electron Carrier	Solvent	t_0, °C	T_0, min	Solvent	Yield of 1 (G.C)
1	Li[a]/Styrene	Et_2O	25	1080	Et_2O	69
2	Li[a]/Styrene	Et_2O	25	1080	THF	85
3	Li[a]/Styrene	THF	25	720	THF	76
4	Li[a]/Styrene	Glyme	25	720	Glyme	38
5	Na/Naphthalene	THF	25	15	THF	42
6	Li[b]/Styrene	Et_2O	0	15	Et_2O	65
7	Li[b]	Et_2O	0	15	Et_2O	94
8	Li[b]	Et_2O	25	15	Et_2O	98
9	Li[b]	Et_2O	25	15	Et_2O	65[c]
10[d]	Li[b]	Et_2O	25	15	Et_2O	83
11[d]	Li[b]	Et_2O	25	15	Et_2O	4[c]

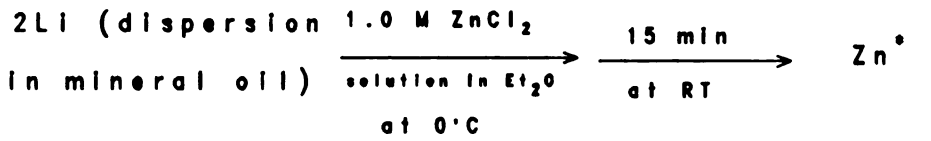
a) Lithium (rod,1.27 cm in diameter).
b) Lithium (25 % wt. dispersion in mineral oil).
c) The formation of the enolate and reaction with PhCHO were conducted at -78°C.
d) No $ZnCl_2$ added.

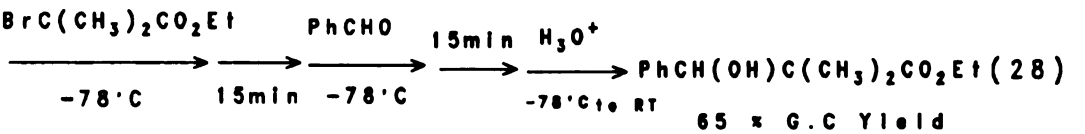
TABLE III





The dropwise addition at 0°C of a one molar zinc chloride solution in ether to lithium (dispersion in mineral oil) in ether resulted in the formation of a finely devided dark gray zinc powder. The zinc powder generated was highly reactive to α-bromoesters even at dry ice temperature. A 65 % yield (G.C) of ß-hydroxyester **1** was obtained for a two step Reformatsky reaction accomplished entirely at dry ice temperature (-78°C) in ether (eq 28). Unfortunately, stirring the heterogeneous solution at such low temperature was a problem which we believe contributed to the poor yield. We thought that the presence of mineral oil (from the lithium dispersion) was a factor in causing the reactions to stop stirring when cooled to -78°C. The mineral oil was easily removed by successive washings of the active zinc with pentane under a stream of argon. The reaction solvent (Et_2O) was then added to the washed zinc and the reaction sequence was completed as before. However, at dry ice temperature the zinc settles and attempts to stir the reactions failed.





In order to find a convenient procedure for generating reactive zinc, a systematic study of the reduction of zinc chloride using various reducing metals was undertaken. Data shown in table III illustrates the effectiveness of each procedure examined. Our conclusions about the relative reactivity of each form of zinc are based on the yields of 1 from a two step Reformatsky reaction involving ethyl α-bromoisobutyrate and benzaldehyde, conducted at 0°C for thirty minutes. Yields of 1 ranged from 38 % in the case of the zinc generated in glyme using lithium (rod, 1.27 cm diameter) in the presence of styrene (as an electron carrier) to 98 % in the case where lithium (dispersion in mineral oil) was used. Zinc generated from the reduction of zinc chloride in Et_2O or THF using lithium (rod, 1.27 cm diameter) in the presence of styrene (a slightly modified Rieke's procedure)[22] gave high yields of 1 (ranging from 69

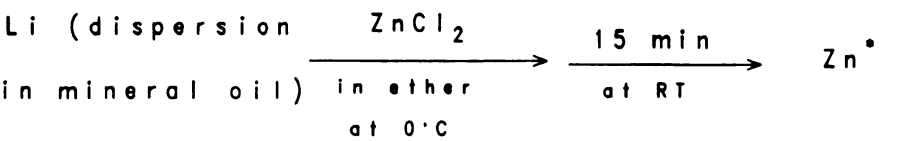
to 85 %). The drawback in this procedure is the length of time required to generate the reactive zinc (about 15 to 18 hours). The experiment that gave an 85 % yield required removal of the reduction solvent (Et_2O) and the use of THF.

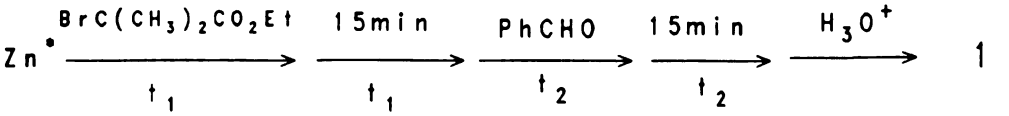
The convenience (short time required for the generation of reactive zinc and easy handling of the materials) along with the quantitative yield of 1 obtained by the lithium (dispersion in mineral oil) procedure prompted us to focus our efforts on studying other aspects and limitations of this newly discovered procedure. We decided to examine the use of tetrahydrofuran (THF) as a solvent for our procedure with the hope of improving the yields of the reaction at -78°C. Results of this study are shown in table IV. The reduction solvent (Et_2O) was removed and replaced by THF as the Reformatsky reaction solvent. We were encouraged by the fact that the reactions stirred better in THF at -78°C, but were disappointed by the moderate yields of 1 obtained see table IV. We concluded that Et_2O is the solvent of choice, especially because the procedure is not further complicated by an exchange of solvents as in both Rieke's procedures. A brief cross examination of our procedure using lithium (dispersion in mineral oil) with Rieke's[22] and Arnold's[21] methods of generation of reactive zinc powder is shown in table V. It is clear that the zinc powder generated by the lithium (dispersion in mineral oil) procedure is far more reactive than both the Rieke and Arnold zinc. A 65 % yield

	Preparation of the Reformatsky reagent		Reaction with benzaldehyde	
Entry	Solvent	t_1, °C	t_2, °C	G.C Yield of 1
1	Et_2O	0	0	98
2	Et_2O	0	-78	96
3	Et_2O	-78	-78	65 (48)[a]
4	THF	0	0	68
5	THF	0	-78	84
6	THF	-78	-78	57

a) G.C. Yield when the reaction was repeated under the same conditions.

TABLE IV





of **1** was obtained from the two step reaction at -78°C of ethyl α-bromoisobutyrate with benzaldehyde in the presence of reactive zinc generated using lithium (dispersion in mineral oil). Under the same conditions Rieke's zinc generated in glyme using lithium (rod, 1.27 cm in diameter) in the presence of naphthalene gave only 9 % yield of **1**. Arnold's zinc generated from the reduction of zinc chloride with a one molar sodium naphthalide solution in THF gave only 7 % yield of **1**.

No improvement in yield at -78°C was observed when 0.15 mole equivalent copper bromide or silver acetate (two classic Reformatsky reaction additives) were added to the lithium (dispersion in mineral oil) generated zinc powder see table V.

A brief study of the substitution of zinc by other metals was conducted. Corresponding metal salts were treated in a manner similar to zinc chloride, using lithium (dispersion in mineral oil) for generating the reactive metal powder. The results of this investigation for the two step reaction of ethyl α-bromoisobutyrate with benzaldehyde are shown in table VI. When lithium (dispersion in mineral oil) was used with no other metal salt added, an 83 % yield of **1** was obtained. This agrees with literature reports[27] that lithium can be used in Reformatsky reactions involving either branched chain α-haloesters or alkyl di- or trihalo-

	Generation of Reactive Zinc Powders from the Reduction of a 1.0 M $ZnCl_2$ Solution in Ether				Two step Reaction of $BrC(CH_3)_2CO_2Et$ with PhCHO	
Entry	Reducing Metal	Solvent	t_0, °C	T_0, min	Solvent	Yld of 1 (G.C)
1	Li[a]	Et_2O	25	15	Et_2O	65
2	Na/naphthalene	THF	25	720	THF	7
3	Li[b]/naphthalene	Glyme	25	960	Glyme	9
4[c]	Li[a]	Et_2O	25	15	Et_2O	4
5[d]	Li[a]	Et_2O	25	15	Et_2O	42
6[e]	Li[a]	Et_2O	25	15	Et_2O	24

a) Lithium (25 wt. % dispersion in mineral oil).
b) Lithium (rod, 1.27cm in diameter) was used, $ZnCl_2$ was purified by the $SOCl_2$ procedure and the two step procedure was conducted at -42°C.
c) No $ZnCl_2$ added.
d) 0.15 equivalent of $CuBr_2$ were added to the generated zinc.
e) 0.15 equivalent of AgOAc were added to the generated zinc.

TABLE V

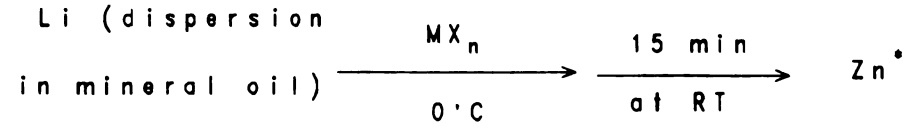
$$\underset{M = Na,\ Li}{M} \xrightarrow[\text{at } 0°C]{ZnCl_2 \text{ in ether}} \xrightarrow[t_0]{T_0} Zn^*$$

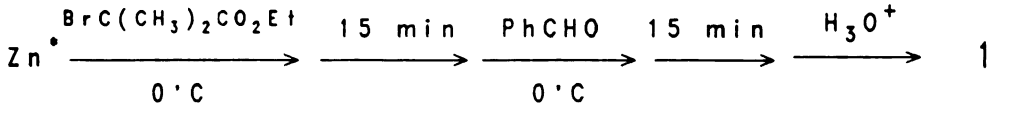
$$Zn^* \xrightarrow[\text{at } -78°C]{BrC(CH_3)_2CO_2Et} \xrightarrow{15 \text{ min}} \xrightarrow[-78°C]{PhCHO} \xrightarrow{15 \text{ min}} \xrightarrow{H_3O^+} 1$$

Substitution of Zinc Chloride by Other Metal Salts in the Two Step Reaction of Ethyl α-bromoisobutyrate with Benzaldehyde					
Entry	1	2	3	4	5
MX_n/Li^a	$MgCl_2/Li$	$CaCl_2/Li$	$MnBr_2/Li$	$AlCl_3/Li$	Li^b
Yield of 1 (G.C)	80	96	48	11	83

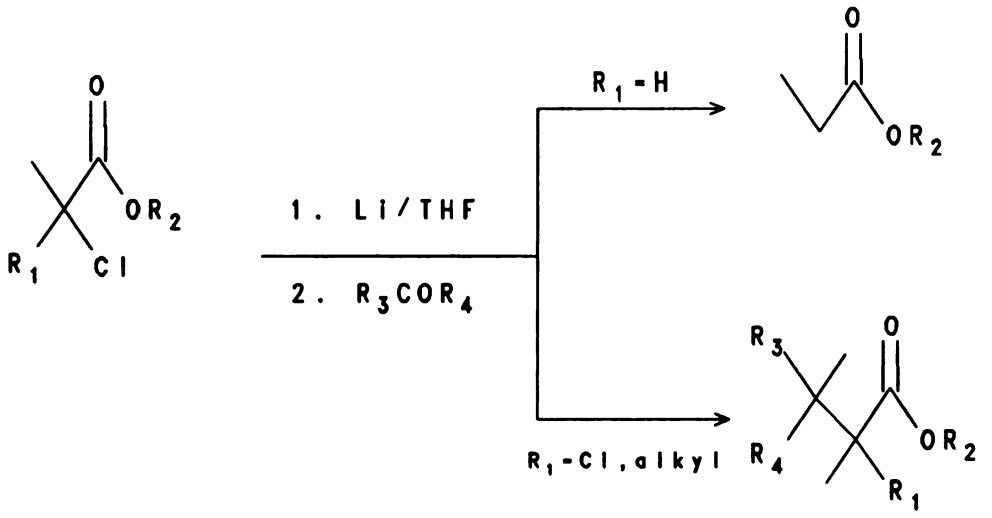
a) Lithium (25 wt. % dispersion in mineral oil).
b) No metal salt added to the lithium dispersion.

TABLE VI





acetates, but can cause reductive dehalogenations of straight chain monoesters (eq 29). Thus it is possible to use lithium with ethyl α-bromoisobutyrate, and the high yield (83 %) of **1** is not surprising. Using magnesium or calcium chloride instead of zinc chloride gave 80 % and 96 % yields of **1** respectively. We suspect that this may actually be due to reaction of the lithium with the α-bromoester, to form the ester enolate in a first step, followed by reaction with benzaldehyde in a second step. This is supported by the fact that both the magnesium and calcium salts reacted slowly with the lithium, and were still present prior to quenching the reactions. The reaction of aluminum chloride with lithium (dispersion in mineral oil) was very exothermic and the mixture turned black instantly; however the yield of ß-hydroxyester was very low (11 %). Manganese bromide did not appear to react with the lithium and the yield of **1** was only moderate (48 %).



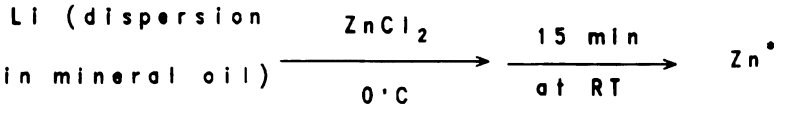
(29)

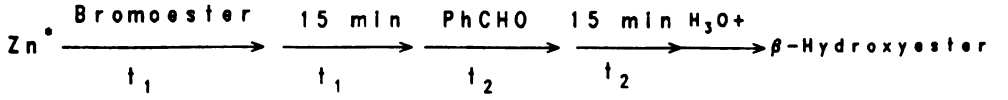
Encouraged by the results obtained with ethyl α-bromoisobutyrate, we extended our examination of the reactivity of the generated zinc powder to include other α-bromoesters. Due to the problems encountered in stirring the reactions at -78°C, we elected to study our two step reactions at 0°C. Results shown in table VII present data obtained from Reformatsky reactions of twelve different α-bromoesters, each reacting with active zinc to form the twelve corresponding zinc ester enolates in a first step. The resulting Reformatsky reagent is then reacted with benzaldehyde in a second step to yield, after quenching, the corresponding ß-hydroxyester. Excellent to quantitative G.C yields were obtained with methyl-, ethyl-, isopropyl- and tert-butyl bromoacetates and bromopropionates. To our surprise the corresponding bromoisobutyrates gave only

Two Step Reformatsky Reactions of a serie of α-bromoesters ($BrR_1R_2CCO_2R$) with Benzaldehyde using the Reactive Zinc Generated from the Lithium[a] Reduction of $ZnCl_2$ in Ether.						
Entry	1	2	3	4	5	6
α-bromoester	R_1=H R_2=H R=Me	R_1=H R_2=H R=Et	R_1=H R_2=H R=i-Pr	R_1=H R_2=H R=t-Bu	R_1=Me R_2=H R=Me	R_1=Me R_2=H R=Et
G.C Yield at t_1=t_2=0°C	100	90	89	98	100	94
Isolated Yld		78	60	72		
Entry	7	8	9	10	11	12
α-bromoester	R_1=Me R_2=H R=i-Pr	R_1=Me R_2=H R=t-Bu	R_1=Me R_2=Me R=Me	R_1=Me R_2=Me R=Et	R_1=Me R_2=Me R=i-Pr	R_1=Me R_2=Me R=t-Bu
G.C Yield at t_1=t_2=0°C	81	100	54	61	60	65
Isolated Yld	81	80	69	54		
G.C Yield at t_1=0°C, t_2=-78°C		31		48[b]	55	37

a) Lithium (25 wt. % dispersion in mineral oil).
b) G.C.yield for t_1=t_2=-78°C

TABLE VII





moderate to good G.C yields. Extensive efforts were made to reproduce the excellent yields obtained earlier with ethyl α-bromoisobutyrate. Again G.C yields ranging only from 50 to 70 % were obtained with the four bromoisobutyrate esters. Later, we discovered that a sample of 1, pure based on its ^{1}H-NMR spectrum, when injected on the G.C, displayed more than one peak. This is probably due to decomposition of the ß-hydroxyester in the injector port of the G.C. Lowering the injector temperature and washing the injector port with different solutions did not overcome the problem of decomposition of the isobutyrate hydroxyesters. The decomposition products observed by G.C analysis were usually the parent starting ester and benzaldehyde, probably due to a retro-aldol reaction. Furthermore, a crude sample of nearly pure ß-hydroxyester (^{1}H-NMR) gave a mixture of products upon vacuum distillation.

Despite the problems encountered in the G.C analysis and purification of the reaction products, a convenient procedure for the generation of highly reactive zinc powder has been developed. This reactive zinc powder is easily obtained by lithium (dispersion in mineral oil) reduction of zinc chloride in ether. The ß-hydroxyesters are usually obtained quantitatively in almost pure form and require no further purification. The fact that the highly branched α-bromoisobutyrates reacted readily with the zinc powder is a proof of the high reactivity of this form of zinc.

In conclusion, we believe that we have accomplished our main goal, which was to develop a convenient procedure for the generation of reactive zinc powder that could be used to overcome the rather harsh classical Reformatsky reaction conditions.

EXPERIMENTAL SECTION

I. General

All the reactions were conducted under an atmosphere of argon in round bottom flasks, each equipped with a side arm, a septum inlet and a teflon coated magnetic stirrer.

Gas Chromatography.

Qualitative G.C analysis was performed on a 5880A Hewlett-Packard Gas Chromatograph, using helium as carrier gas, and equipped with a flame ionization detector and a 30 meter fused silica capillary column (ID 0.32 mm). G.C yields were determined using hydrocarbons as internal standards.

Nuclear Magnetic Resonance.

Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on one of the following: a Varian T-60 at 60 MHz in $CDCl_3$, a Bruker WM-250 at 250 MHz in $CDCl_3$ or on a Varian GEMINI 300 spectrometer at 300 MHz in $CDCl_3$. Chemical shifts are reported in parts per million (δ scale) from the internal standard, tetramethylsilane (TMS). Data are reported as follow: chemical shifts (multiplicity: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (Hz).

Melting and Boiling Points.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected.

II. Materials

Solvents.

Diethyl ether (Et_2O) was taken from a freshly opened can of anhydrous ether. All other solvents were distilled and stored under argon before use. Tetrahydrofuran (THF) was distilled from calcium hydride, and 1,2-Dimethoxyethane (glyme) was distilled from lithium aluminum hydride.

Metals and Metal Salts.

Lithium (25 wt. % dispersion in mineral oil containing about 0.5 % sodium); zinc chloride, 1.0 M solution in diethyl ether; lithium (99.9 %, rod, 1.27 cm diameter) and sodium lumps in mineral oil were purchased from Aldrich Chemical Company. Zinc chloride, aluminum chloride and calcium chloride were obtained from M.C.B reagents. Cupric bromide and naphtalene were supplied by J.T.Baker Chemical Company. Magnesium chloride was obtained from Mallinkrodt, and was dried in an abderhalden flask over refluxing xylene

at 0.3 torr, and stored in a dessicator. Manganese bromide was purchased from Alfa Inorganics.

Benzaldehyde.

Benzaldehyde was washed successively with 10 % Na_2CO_3 (until no more CO_2 was evolved), saturated Na_2SO_3 and water; then dried over $MgSO_4$. It was then distilled at reduced pressure and stored under argon.

α-Bromoesters.

Methyl, ethyl, isopropyl and tert-butyl α-bromoacetates, ethyl α-bromopropionate and ethyl α-bromoisobutyrate were purchased from Aldrich Chemical Company. Methyl α-bromoisobutyrate was easily prepared by the reaction of α-bromoisobutyric acid and methanol in the presence of a trace of sulfuric acid. Isopropyl α-bromoisobutyrate was prepared from bromoisobutyryl bromide and isopropyl alcohol in the presence of N,N-dimethylaniline by the procedure described in Org. Syn. Coll. Vol. III, 142. Methyl, isopropyl and tert-butyl α-bromoisobutyrate were prepared by reaction of bromoisobutyryl bromide with the corresponding alcohol in the presence of pyridine by the procedure of L.A.Carpino, J. Am. Chem. Soc., 82, 2725 (1960).

Purification of Zinc Chloride.

Zinc chloride (granular) obtained from M.C.B reagents was dried by refluxing in thionyl chloride ($SOCl_2$) until gas evolution ceased. The excess $SOCl_2$ was removed under reduced pressure (15 mm), and the anhydrous zinc chloride was stored in a dessicator over potassium hydroxide under vacuum (0.25 mm) for twelve hours. It was then transferred to a dry bottle and stored in a dessicator over P_2O_5. All transfers of zinc chloride were carried out under a stream of argon.

III. Generation of Reactive Zinc

A. General Procedure for the Generation of Reactive Zinc from the Lithium (dispersion in mineral oil) Reduction of Zinc chloride in Ether.

Lithium (25 wt. % dispersion in mineral oil, 0.0832 g, 3 mmoles) was directly weighed in a dry 10 mL round bottom flask. A 0.5 mL portion of anhydrous diethyl ether was then added, and the flask was cooled to 0°C, using an ice bath. A 1.0 M zinc chloride solution in ether (1.5 mL) was added dropwise with stirring, instantenous reduction of zinc chloride occurs via a noticeable exothermic reaction, and a dark gray zinc powder is formed. The ice bath was removed and the mixture is stirred for fifteen minutes to ensure complete reaction.

B. Rieke's Procedure.[22]

Lithium (99.9 %, rod, 1.27 cm diameter) was cut under oil, rinsed in hexane then weighed (0.0208 g, 3 mmoles) and transferred under a stream of argon to a 10 mL round bottom flask. Zinc chloride (0.2044 g, 1.5 mmole), naphtalene (0.038 g, 0.3 mmole) and 1 mL of glyme are added to the flask. The mixture was stirred at room temperature until reduction of zinc chloride was complete (about 15 hours). The activated zinc appeared as a fine black powder which settled down after the stirring was stopped.

C. Arnold's Procedure.[21]

A solution of sodium naphtalide is prepared, under argon, in a 10 mL round bottom flask by adding small pieces of preweighed sodium (0.0689 g, 3 mmoles) to a solution of naphtalene (0.387 g, 3 mmoles) in dry THF (2 mL). The mixture is stirred overnight at room temperature. The prepared solution is then added dropwise with stirring to a second 10 mL round bottom flask containing a solution of anhydrous zinc chloride (0.2044 g, 1.5 mmole) in dry THF (1 mL). The dark green color of the naphtalide solution is discharged instantly and a black suspension of finely devided zinc was formed in quantitative yield.

IV. The Use of Reactive Zinc in the Two Step Reformatsky Reactions of a Serie of α-Bromoesters with Benzaldehyde.

A. General Procedure Used in the Two Step Reformatsky Reactions.

The corresponding α-bromoester (1 mmole) is added to a 10 mL round bottom flask containing stirred reactive zinc (generated from the lithium, dispersion in mineral oil, reduction of 1.5 mL of a 1 M zinc chloride in ether). The reaction mixture becomes more homogeneous and a change in color (from dark gray to dark brown) occurs upon the complete addition of the bromoester to the zinc. The mixture is stirred at 0°C for fifteen minutes. Benzaldehyde (0.101 mL, 1 mmole) is then added dropwise to the zinc ester enolate and allowed to react with it at 0°C for an additional fifteen minutes. 2 mL of a 1 N HCl solution are then added at 0°C to quench the reaction. The mixture is stirred and allowed to reach room temperature. One mmole of hydrocarbon (used as internal standard for G.C analysis) is added. The organic layer is then extracted with ether (3 x 2 mL). The organic extracts are washed with a saturated sodium chloride solution then combined and dried over sodium

sulfate. An aliquot is taken and Gas Chromatoghraphically analysed for the corresponding ß-hydroxyester.

B. Isolation of the Products ß-Hydroxyesters.

The two step Reformatsky reactions of the different α-bromoesters were conducted on a 30 mmole scale similarly to the 1 mmole scale reactions, but without the addition of a standard. After evaporation of the solvent (Et_2O), the residues were distilled under reduced pressure.

Methyl 3-Phenyl-3-Hydroxyacetate.

^1H NMR (250 MHz) ($CDCl_3$): δ 2.75 (dd, 2H), 3.05 (bs, 1H), 3.70 (s, 3H), 5.15 (dd, 1H), 7.35 (m, 5H).

Ethyl 3-Phenyl-3-Hydroxyacetate.

Kugelrohr distillation gave a clear viscous oil (78 %). ^1H NMR (60 MHz) ($CDCl_3$): δ 1.3 (t, 3H), 2.75 (dd, 2H), 3.30 (bs, 1H), 4.20 (q, 2H), 5.15 (dd, 1H), 7.35 (m, 5H).

Isopropyl 3-Phenyl-3-Hydroxyacetate.

Short path distillation gave a clear viscous oil (60 %), bp : 120°C (1 torr). ^1H NMR (250 MHz) ($CDCl_3$): δ 1.25 (d, 6H), 2.75 (dd, 2H), 3.25 (bs, 1H), 5.00-5.20 (m, 3H), 7.35 (m, 5H).

t-Butyl 3-Phenyl-3-Hydroxyacetate.

Kugelrohr distillation gave a clear viscous oil (72 %), bp : 150°C (0.1 torr). ^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.45 (s, 9H), 2.75 (dd, 2H), 4.10 (bs, 1H), 5.15 (dd, 1H), 7.35 (m, 5H).

Methyl 3-Phenyl-3-Hydroxypropionate.

^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.05 (t, 3H), 2.70-3.00 (m, 1H), 3.05 (bs, 1H), 4.70 (d) combined with 5.15 (d) make 1H, 7.35 (m, 5H).

Ethyl 3-Phenyl-3-Hydroxypropionate.

^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.15 (m, 6H), 2.70-3.00 (m, 1H), 3.10 (bs, 1H), 4.20 (m, 2H), 4.70 (d) combined with 5.15 (d) make 1H, 7.35 (m, 5H).

Isopropyl 3-Phenyl-3-Hydroxypropionate.

Short path distillation gave a clear viscous oil (81 %), bp : 122 (1 torr). ^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.10 (m, 9H), 2.6-2.9 (m, 1H), 3.10 (bs, 1H), 4.70-5.15 (m,2H), 7.35 (m, 5H).

t-Butyl 3-Phenyl-3-Hydroxypropionate.

Kugelrohr distillation gave a clear viscous oil (80 %), bp : 132°C (0.1 torr). ^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.10 (m,

3H), 1.40 (d, 9H), 2.5-2.8 (m, 1H), 3.15 (bs, 1H), 4.70 (d) combined with 5.15 (d) make 1H, 7.35 (m, 5H).

Methyl 3-Phenyl-3-Hydroxyisobutyrate.

White solid (69 %), mp : 68-69°C. ^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.15 (d, 6H), 3.05 (bs, 1H), 3.7 (bs, 3H), 4.9 (bs, 1H), 7.35 (m,5H).

Ethyl 3-Phenyl-3-Hydroxyisobutyrate.

Short path distillation gave a clear viscous oil (54 %), bp : 107°C (0.1 torr). ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.15 (d, 6H), 1.25 (t, 3H), 3.20 (bs, 1H), 4.20 (q, 2H), 4.9 (bs, 1H), 7.35 (m, 5H).

Isopropyl 3-Phenyl-3-Hydroxyisobutyrate.

^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.10-1.30 (m, 12H), 3.30 (bs, 1H), 4.9 (bs, 1H), 4.80-5.15 (m, 1H), 7.35 (m, 5H).

t-Butyl 3-Phenyl-3-Hydroxyisobutyrate.

Solid mp : 67-68°C. ^{1}H NMR (60 MHz) ($CDCl_3$): δ 1.15 (bs, 6H), 1.50 (bs, 9H), 3.20 (bs, 1H), 4.80 (bs, 1H), 7.35 (m, 5H).

CHAPTER II

STABILITY AND REACTIONS

OF

ZINC ESTER ENOLATES

INTRODUCTION AND REVIEW OF LITERATURE

Though the Reformatsky reaction has been known for over a century[1] and over 500 research articles and 6 reviews[2] have been published on the reaction, little data on the stability or structure of zinc ester enolates (Reformatsky reagents) is available. This is probably due to the fact that the reaction is usually conducted in a single operation by adding a mixture of α-haloester and a carbonyl compound to a suspension of zinc in an appropriate solvent (eq 30).

The Reformatsky reaction was effected in a sequence of two discrete steps for the first time in 1953.[28] Siegel and Keckeis prepared the Reformatsky reagent of ethyl α-bromoacetate in ether and then, in a separate step, reacted this reagent with a variety of carbonyl compounds (eq 31). The yields were moderate.

$$Zn \xrightarrow[BrCH_2CO_2Et]{R_1COR_2} \xrightarrow{H_3O^+} R_1R_2COHCH_2CO_2Et \quad (30)$$

$$Zn \xrightarrow[ether]{BrCH_2CO_2Et} [Reformatsky\ reagent] \xrightarrow{R_1COR_2} \xrightarrow{H_3O^+} R_1R_2COHCH_2CO_2Et \quad (31)$$

Since the work of Siegel, solutions of the Reformatsky reagents have occasionally been prepared and used in this fashion. Newman and Evans[29] slightly modified this procedure by using a 1:1 ether-benzene solvent mixture instead of ether as a reaction solvent. Yields of Reformatsky reagents are usually based on yields of reduced esters, the products of hydrolysis of the zinc ester enolates, (eq 32). When enolizable carbonyl compounds are used, the reduced esters were also formed as a result of zinc ester enolate induced enolization of the carbonyl compound (eq 33).[30] Based on the yields of reduced esters, Newman and Evans deduced the yields of Reformatsky reagents from a series of alkyl α-bromopropionates, ranging from 16 to 25 % when R=Me, Et or Pr and even lower when R=i-Pr, t-Bu or neopentyl. Ethyl α-bromoacetate gave a better yield (45 %) of the Reformatsky reagent. Along with the reduced ester (from the Reformatsky reagent) a ß-ketoester, the so called "condensed ester", is

usually formed. In an earlier work, Newman and Hussey[31] determined the stochiometry of the "condensed ester" that of (eq 34). They suggested that one possible path was a self-condensation reaction (eq 35), and that the importance of this reaction increases in the order $BrCH_2CO_2Et$ < $CH_3CHBrCO_2Et$ < $(CH_3)_2CBrCO_2Et$.

$$BrZnCH_2CO_2Et \xrightarrow{H_3O^+} CH_3CO_2Et \qquad (32)$$

Reduced ester

$$RCOCH_2R + BrZnCH_2CO_2Et \longrightarrow \underset{R}{\overset{OZnBr}{\overset{|}{C}}}=\underset{CH-R}{CH} + CH_3CO_2Et \qquad (33)$$

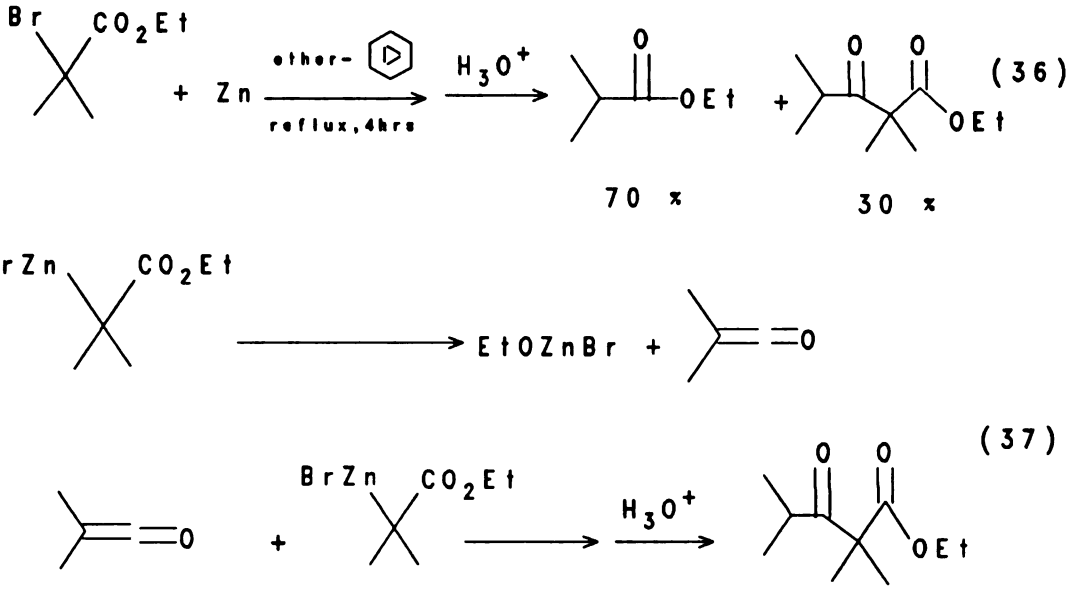
$$2(R)_2CBrCO_2Et + 2Zn \longrightarrow [(R)_2CCOC(R)_2CO_2Et]ZnBr + BrZnOEt \qquad (34)$$

$$[(R)_2CCO_2Et]ZnBr + (R)_2CBrCO_2Et \longrightarrow (R)_2CBrCOC(R)_2CO_2Et$$

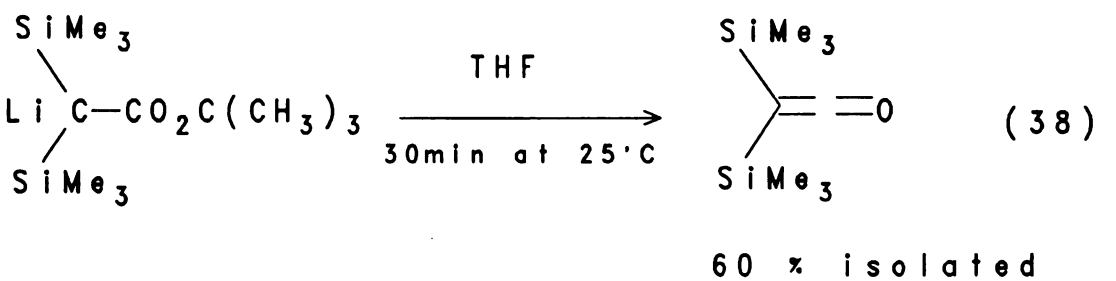
$$\xrightarrow{Zn} \xrightarrow{H_3O^+} (R)_2CHCOC(R)_2CO_2Et \qquad (35)$$

"condensed ester"

Vaughan and coworkers[9] were the first to thoroughly study the behavior of a specific Reformatsky reagent. They examined a solution of the reagent prepared from ethyl α-bromoisobutyrate and zinc (activated by the nitric acid procedure) in ether-benzene solvent mixture, and found that hydrolysis of the freshly prepared solution gave 70 % ethyl isobutyrate (reduced ester from the Reformatsky reagent) and 30 % of "condensed ester", ethyl isobutrylisobutyrate (eq 36). An increase in the amount of "condensed ester", with a corresponding decrease in ethyl isobutyrate, was observed when the solution was refluxed for longer periods prior to hydrolysis. Vaughan and coworkers concluded that the Reformatsky reagent decomposed by loses of EtOZnBr to give a ketene intermediate, followed by reaction with another molecule of the reagent to generate, after hydrolysis, the "condensed ester"(eq 37).[32]

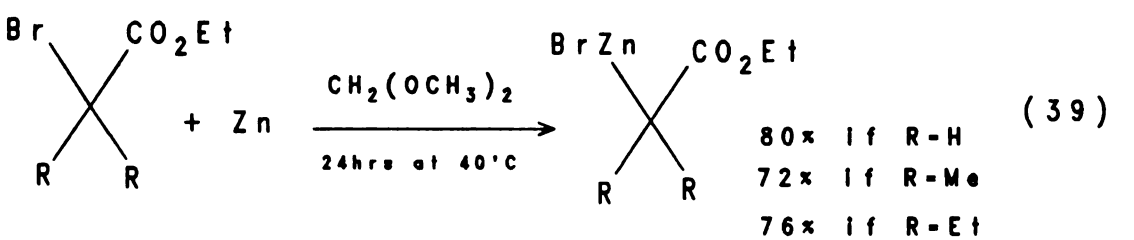


Ketenes are well known to be intermediates in the self-condensation of lithium ester enolates.[33,34] Bis(trimethylsilyl)ketene was isolated by vacuum distillation, after warming a tetrahydrofuran solution of lithio tert-butyl bis(trimethylsilyl)acetate to 25°C (eq 38).[33]



Although the ketene mechanism is plausible, further work needs to be done to determine which pathway (ketene, Claisen condensation or both) is followed in the formation of the "condensed ester".

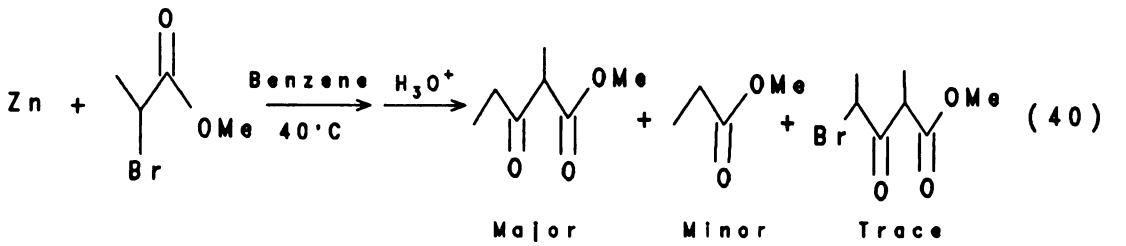
After testing different solvents, Gaudemar and Cure[12,35] discovered that dimethoxymethane was particularly effective for two step reactions. They prepared three different Reformatsky reagents in yields ranging from 70 to 80 % based on the reduced ester obtained by hydrolysis of the reagents (eq 39). In the case of ethyl α-bromoisobutyrate, Gaudemar reported a 10 % distillation residue and related that to the instability of the reagent compared with that from ethyl α-bromoacetate. In the case of ethyl α-bromodiethylacetate, he found that the formation of the Reformatsky reagent was slower than in the two previous cases, probably due to steric hindrance. Unfortunately, ethyl α-bromopropionate, methyl α-bromophenylacetate and phenyl α-bromoisobutyrate gave unsatisfactory results under Gaudemar's conditions. The authors stated that the solvent must be dimethoxymethane and that the reaction with zinc stops if the temperature is lowered below 40°C.



(39)

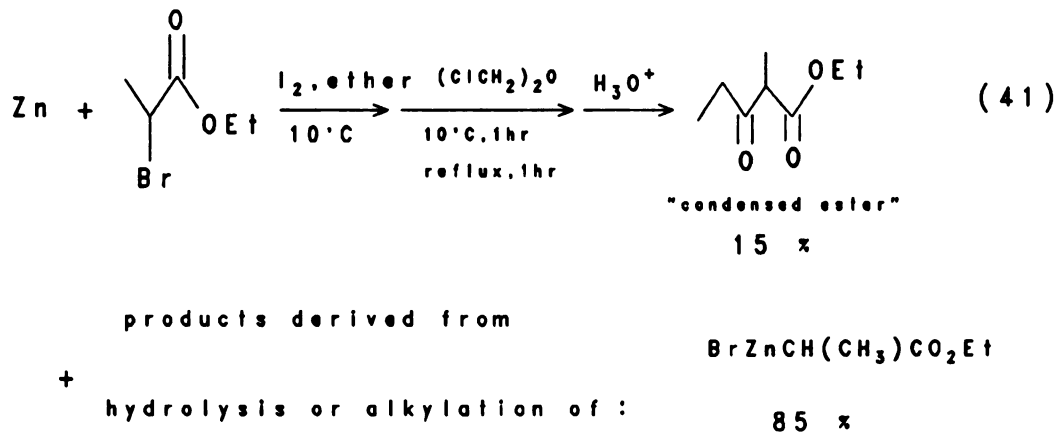
The Reformatsky reagents prepared by Gaudemar were generally used directly after preparation and no attempt was made to study their stabilities in dimethoxymethane.

In 1982, Orsini and coworkers[35] published the first article describing the isolation of a solid Reformatsky reagent. They obtained $BrZnCH_2CO_2C(CH_3)_3$.THF in 80 % yield, as a colorless microcrystalline solid, from the reaction of t-butyl α-bromoacetate and zinc wool in tetrahydrofuran. The reagent remained mostly unchanged for at least four to six days in different solvents. A slow hydrolysis to t-butylacetate was observed. However the authors were not able to isolate reagents from ethyl α-bromoacetate and methyl-, ethyl- or t-butyl α-bromopropionate. For example, in the case of methyl α-bromopropionate the "condensed ester" was the main product after hydrolysis (eq 40).



(40)

Johnson and Zitsman,[37] using powdered zinc (activated by iodine) and working at lower temperature in ether, obtained the Reformatsky reagent from ethyl α-bromo-propionate in good yield (eq 41).

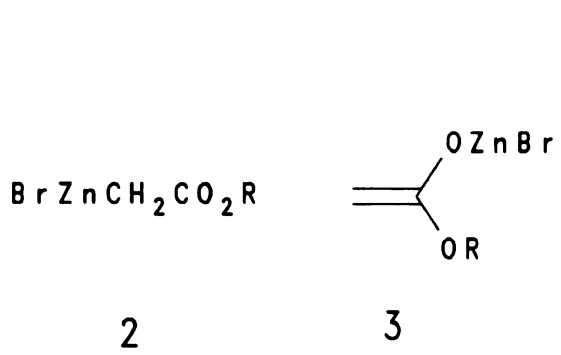


(41)

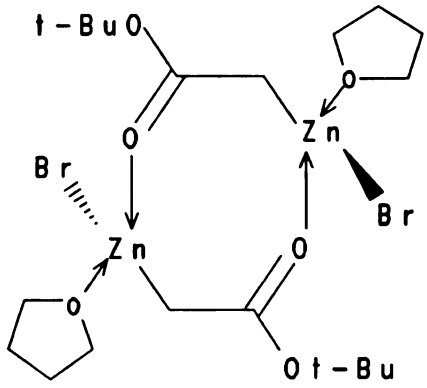
In 1984, Orsini and coworkers[38] extended their early work to the isolation of two more Reformatsky reagents, $BrCH(CH_3)CO_2C(CH_3)_3$ and $BrZnC(CH_3)_2CO_2C(CH_3)_3$, as the THF complexes. The former was obtained in 85 % yield as a colorless microcrystalline solid, which afforded quantitatively t-butyl propionate when treated in an ethereal solution with dilute HCl. The latter reagent, $BrZnC(CH_3)_2CO_2C(CH_3)_3$.THF, was isolated as a foamy colorless compound which, when treated with acid, behaved as expected for the Reformatsky reagent and afforded quantitatively t-butyl isobutyrate. Both reagents were described by the authors as stable in THF solution for a few hours, and in pyridine and in DMSO for about 10 to 15 minutes. Decomposition gave a precipitate of $BrZnOC(CH_3)_3$.

In order to have a better understanding of the behavior of the zinc ester enolates and to expand our knowledge of

the Reformatsky reaction mechanism, structural characterization of these reagents was necessary. Zinc ester enolates may be formulated as analogs of the classical Grignard reagent, with a zinc-carbon bond (**2**) or as the bromozinc enolate of an ester, with a zinc-oxygen bond (**3**). Both structures have been proposed on the basis of spectroscopic data. In 1983, Boersma and coworkers[39] obtained an X-ray structure of the Reformatsky reagent, prepared and crystallized according to Orsini's procedure. The authors found a carbon-bonded dimeric structure (**4**), in which the zinc is tetrahedrally surrounded by the anionic carbon, the carbonyl oxygen of the second ester molecule, the bromide ion and tetrahydrofuran. Based on ebulliometric and cryoscopic molecular weight measurements, this molecular arrangement was found to be favored in solvents of medium coordinating power (THF, DME, dioxane, dimethoxymethane and pyridine), but not in strongly coordinating ones (HMPT, DMSO), where the data is consistent with a monomeric structure.



2 3

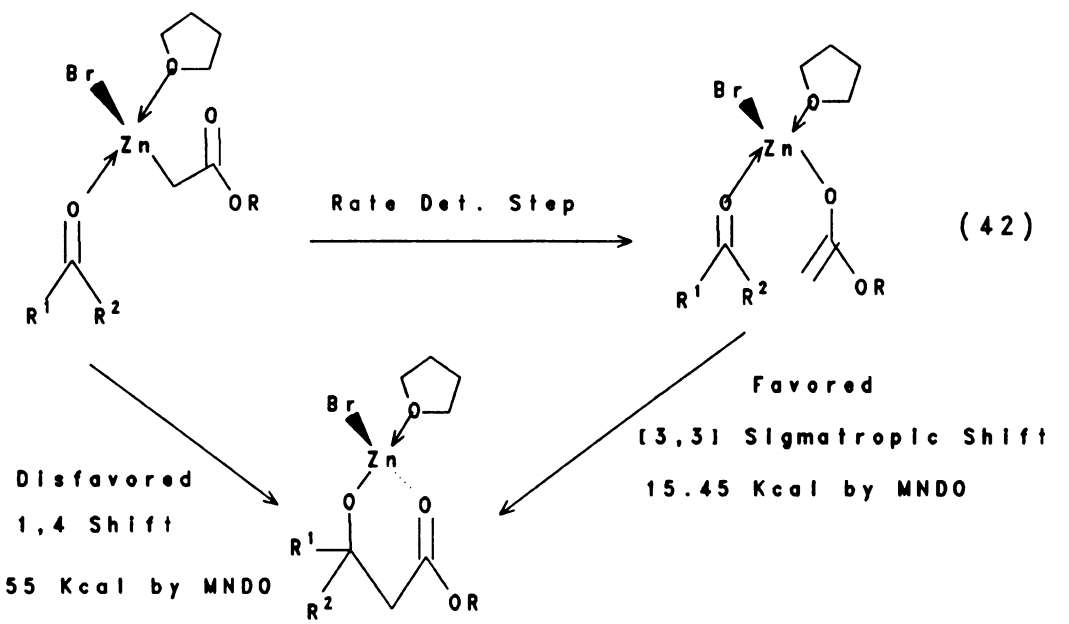


4

Based on IR and NMR studies of the reagent from ethyl α-bromoacetate, Gaudemar and Martin[40] determined that the reaction solvent has a strong influence on the structure of Reformatsky reagents. They suggested that in solvents of medium coordinating power the zinc is coordinated to a carbonyl oxygen of a carbon-bonded structure (as confirmed by Boersma's crystal structure) and in strongly coordinating solvents this coordination to oxygen is absent.

Recent molecular mechanics calculations by Dewar and coworkers[41] not only confirmed the dimeric structure of zinc ester enolates but also provided additional information on the mechanism of the Reformatsky reaction. According to Dewar's MNDO calculations, the thermodynamically favored dimeric complex dissociates on interaction with of a carbonyl compound, and converts in the rate determining step from a carbon to an oxygen metallated species. This allows

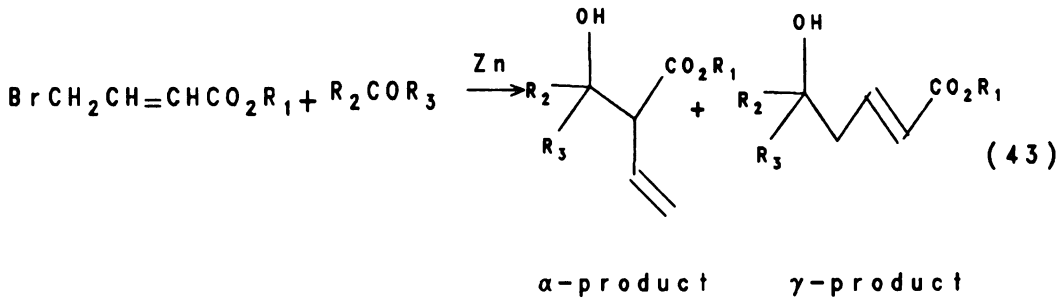
the formation of a six-electron (aromatic) cyclic transition state for the reaction with the carbonyl compound (eq 42). The four-electron (antiaromatic) path required by the carbon metallated species is less favored. Dewar classified the carbon-carbon bond forming step as a metallo [3,3] sigmatropic shift (or metalloClaisen). Other authors[42,43] had previously proposed that the Reformatsky reaction can proceed by a pericyclic mechanism without identifying it as a [3,3]-sigmatropic shift process.



(42)

The question of whether the Reformatsky reaction of 4-bromocrotonate esters with carbonyl compounds would give

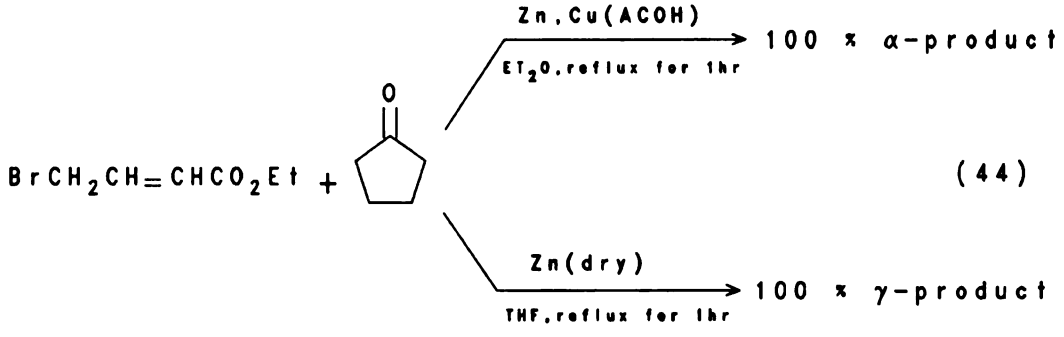
selectively alpha or gamma products (eq 43) has been the subject of many recent studies.[2]



(43)

α-product γ-product

Hudlicky and coworkers[44] examined the reaction of ethyl 4-bromocrotonate with a serie of carbonyl compounds. They described conditions for obtaining alpha or gamma products (eq 44).



(44)

Gaudemar and coworkers[44] reacted trimethylsilyl esters of 4-bromocrotonic and 4-bromosenecioic acids with benzaldehyde (eq 45). They found that in the case of the one step procedure, alpha products are favored at low temperatures while gamma products are produced at higher temperature or longer reaction times. Gaudemar concluded that the former condition favor kinetic control while the latter proceeds with thermodynamic control. Gamma products were the only products in the case of the two step Reformatsky reaction of trimethylsilyl 4-bromocrotonate with benzaldehyde. When the reaction was conducted at -40°C Gaudemar obtained an overall 53 % yield of gamma product exclusively (eq 46). This result is surprising because under such low temperature conditions the alpha product would be expected to predominate in a kinetically controlled process. The authors explained these findings by postulating the existence of two different zinc enolates (eq 47). In the case of a one step reaction, the initially formed enolate (**5**) reacts with benzaldehyde to give alpha product. In the case of the two step reaction, **5** rearranges to a different enolate (**6**) which then reacts to give gamma products.

$BrCH_2C(CH_3)=CHCO_2Si(CH_3)_3$ — 100 : 0 (α : γ) (−40°C, 120 hrs)

+

PhCHO

$\xrightarrow[THF]{Zn}$ 92 : 8 (α : γ) (reflux, 1hr)

42 : 58 (α : γ) (reflux, 96 hrs) (45)

$BrCH_2CH=CHCO_2Si(CH_3)_3$

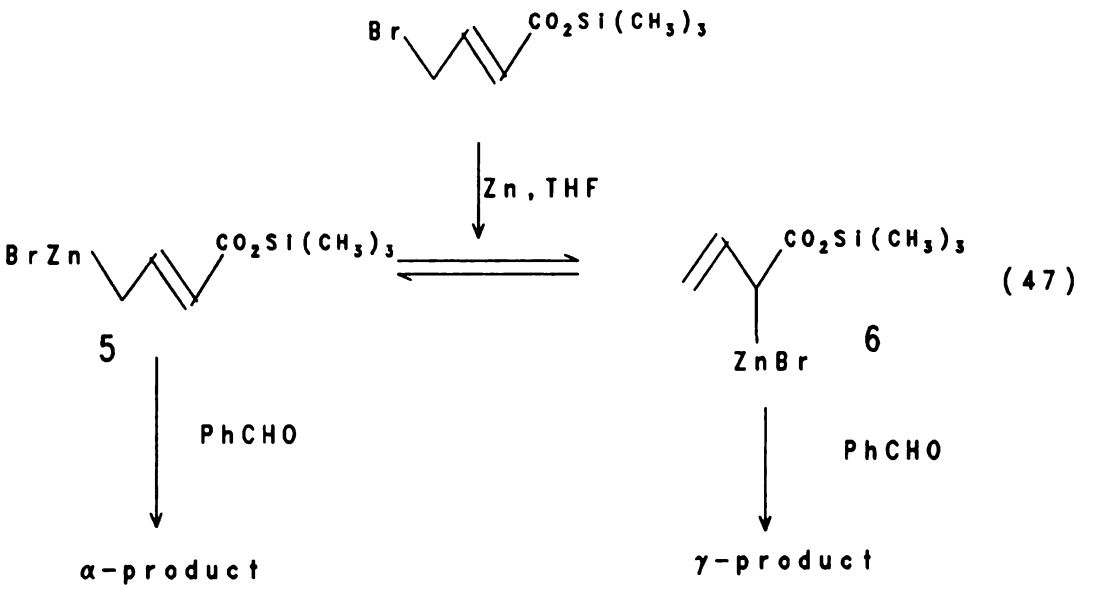
+

Zn

$\xrightarrow[-40°C, 48\ hrs]{THF}$ Zinc Enolate $\xrightarrow[-40°C, 48\ hrs]{PhCHO}$ 0 : 100 (α : γ) (46)

75 %

53 % Overall



(47)

It seemed to us that our procedure for generating highly reactive zinc would allow us to quantitatively prepare a series of Reformatsky reagents in short times and at low temperatures. These could then be used in the two stage reaction. We also planned to examine the stabilities of these reagents under various conditions. By doing so, we should get a clearer idea of the behavior of these reagents, especially since other researchers focused on structural elucidations and neglected other useful information concerning stabilities and reactivities of the zinc ester enolates. We also planned, using the same procedure, to search for conditions to selectively generate either the alpha or the gamma products from the Reformatsky reactions

of 4-bromocrotonate esters with carbonyl compounds in both the one and two stage procedures.

RESULTS AND DISCUSSION

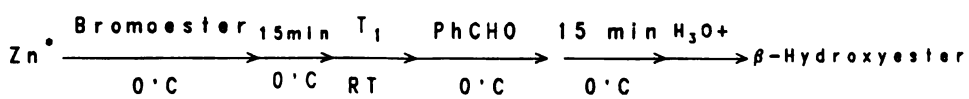
Stability of Zinc Ester Enolates:

The relative stabilities at 25°C of twelve different zinc ester enolates were examined. Data from this study are presented in table VIII. The zinc ester enolates were each generated by the addition at 0°C of the corresponding α-bromoester to a suspension of reactive zinc powder (prepared by the lithium, dispersion in mineral oil, reduction of zinc chloride in ether, as described in chapter I). The generated zinc ester enolates were stirred at 25°C, cooled again to 0°C, and then reacted with one equivalent of benzaldehyde. The reactions were maintained at 0°C for an additional period of time, and then quenched and analyzed by gas chromatography (eq 48).

$$\underset{\text{in ether}}{Zn^{*}} \xrightarrow[\text{at } 0^{\circ}C]{\text{Bromoester}} \xrightarrow[0^{\circ}C]{15\text{ min}} \xrightarrow[\text{at RT}]{T_1} \xrightarrow[\text{at } 0^{\circ}C]{PhCHO} \xrightarrow[0^{\circ}C]{15\text{ min}} \xrightarrow[0^{\circ}C \text{ to RT}]{H_3O^{+}} \beta\text{-Hydroxyester} \qquad (48)$$

Reaction of Zinc Ester Enolates with Benzaldehyde			
Entry	Starting α-Bromoester	G.C Yield for T_1=12 hrs at RT	G.C Yield for T_1=24 hrs at RT
1	$BrCH_2CO_2Me$	45	41
2	$BrCH_2CO_2Et$	70	0
3	$BrCH_2CO_2iPr$	45	32
4	$BrCH_2CO_2tBu$	97	77
5	$BrCH(CH_3)CO_2Me$	30	17
6	$BrCH(CH_3)CO_2Et$	66	17
7	$BrCH(CH_3)CO_2iPr$	56	12
8	$BrCH(CH_3)CO_2tBu$	93	58
9	$BrC(CH_3)_2CO_2Me$	24	22
10	$BrC(CH_3)_2CO_2Et$	31	3
11	$BrC(CH_3)_2CO_2iPr$	34	24
12	$BrC(CH_3)_2CO_2tBu$	26	28

TABLE VIII



The Reformatsky reagents proved to be quite stable. Zinc ester enolates derived from tert-butyl α-bromoacetate and α-bromopropionate showed almost no decomposition after stirring at room temperature for twelve hours. This is evidenced by the exceptionally high G.C yields of ß-hydroxyesters (97 and 93 % respectively). Even after 24 hours of continuous stirring at 25°C both reagents were still present in significant amounts (77 and 58 % yields of products respectively). Difficulties in analyzing the isobutyrate ß-hydroxyesters did not allow us to obtain reliable data for the relative stabilities of the corresponding zinc ester enolates. Nevertheless, the isobutyrate zinc reagents followed the same qualitative stability pattern found for the acetate and propionate reagents, as evidenced by the last four entries in table VIII. The ethyl zinc ester enolates were still present in appreciable amounts (70 and 66 % yields respectively in the case of the acetate and propionate esters) after 12 hours of continuous stirring at 25°C. However, ethyl zinc ester enolates gave very little or no expected ß-hydroxyesters when stirred for 24 hours at 25°C.

Stability of Lithium Ester Enolates:

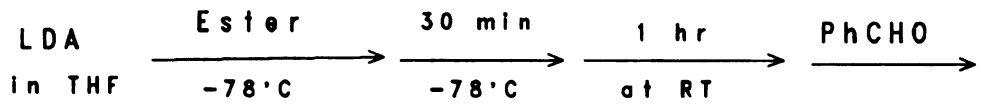
Data presented in table IX concerning stability and reactivity of lithium ester enolates was obtained as

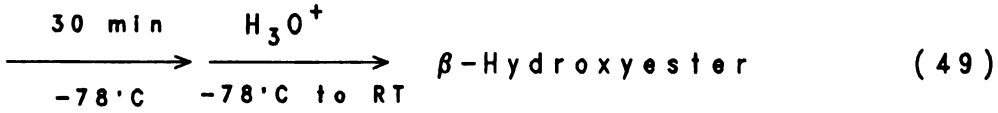
follows: The lithium reagents, obtained at dry ice temperature by slow addition of the corresponding ester to lithium diisopropylamide (LDA) in THF, were reacted separately at -78°C with benzaldehyde to yield after quenching the expected ß-hydroxyesters. The G.C yields of the corresponding ß-hydroxyesters obtained from the reactions of four different lithium ester enolates with benzaldehyde ranged from 77 to 100 %. In a separate set of experiments the lithium ester enolates were warmed to 25°C, stirred for one hour then cooled again to -78°C, and reacted with benzaldehyde for an additional thirty minutes (eq 49). Peaks corresponding to starting materials and the internal standard were observed exclusively during the G.C analysis of the quenched reactions. Only a 2 % yield of ß-hydroxyester was obtained in the case of the lithium ester enolate of tert-butyl acetate. These results clearly show the higher stability of zinc ester enolates over their lithium analogues (table VIII versus table IX). Thus the zinc ester enolates are much more convenient to use than their lithium analogues, especially since the zinc reagents can be prepared, stored and used when needed. This is not the case with the lithium ester enolates which have to be used freshly prepared, due to their fast decomposition.

Reaction of Lithium Ester Enolates with Benzaldehyde				
Ester	CH_3CO_2Et	CH_3CO_2iPr	CH_3CO_2tBu	$CH_3CH_2CO_2Et$
G.C Yield[a]	100	100	97	77
G.C Yield[b]	0	0	2	0

a. The reactions were conducted in THF for 1 hour at -78°C.
b. After 30 min at -78°C the lithium ester enolates were stirred for 1 hour at room temperature then cooled to -78°C, benzaldehyde was then added and the reactions were stirred at -78°C for another 30 min.

TABLE IX

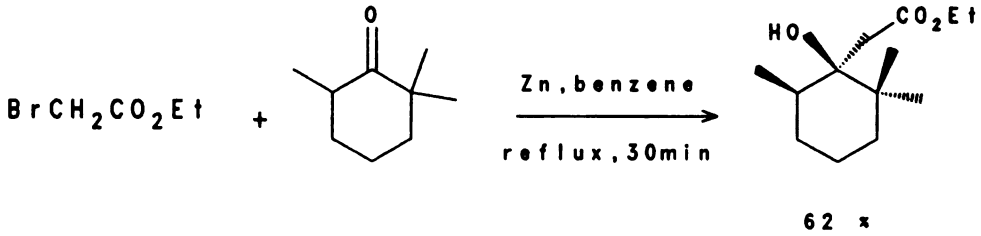




(49)

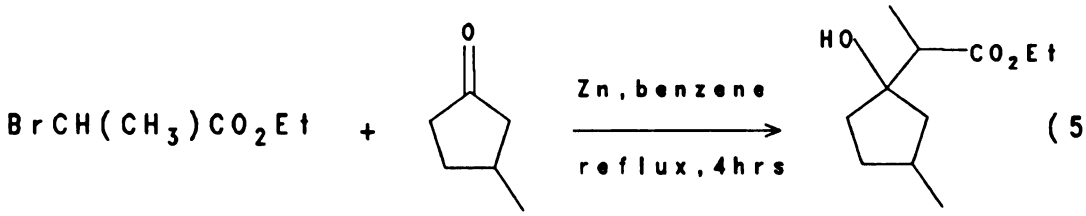
Reactions of Zinc and Lithium Ester Enolates with the Hindered Ketone 2-Methylcyclopentanone.

Based on the fact that the Reformatsky reaction is known to succeed with highly hindred ketones (eq 50)[46], and that it is a successful method for the addition of carbon nucleophiles to the ready enolizable cyclopentanone ring system (eq 51),[47] we studied the reactivity of the zinc ester enolate of ethyl α-bromoacetate with 2-methylcyclopentanone (a hindered and readily enolizable ketone) (eq 52). Results of this brief study are presented in table X.



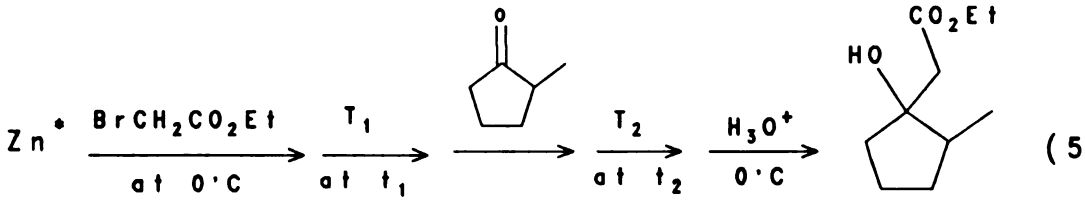
(50)

62 %



(51)

84 %



(52)

7

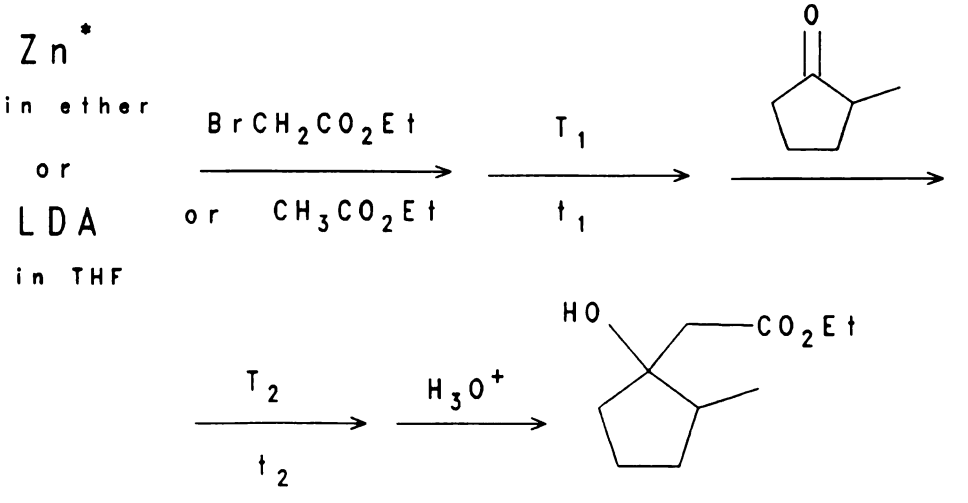
The zinc ester enolate of ethyl α-bromoacetate reacted sluggishly with 2-methylcyclopentanone at 0°C. No product was detected by G.C when the reaction was conducted entirely at -78°C. Moderate yields of the ß-hydroxyester (7) were obtained when this reation was conducted at room temperature. The highest (56 %) G.C yield of 7 was obtained when the zinc ester enolate was reacted with 2-methylcyclopentanone at room temperature for 22 hours. No further efforts were made to maximize the yields of 7. The lithium ester enolate generated at -78°C from ethyl acetate and lithium diisopropylamide (LDA) gave a 79 % G.C yield of 7 when reacted for two hours at -78°C with the same ketone.

It seems that the lithium ester enolate reacts much faster with 2-methylcyclopentanone than does the zinc

Reactions of Zinc and Lithium Ester Enolates with 2-Methyl Cyclopentanone							
Entry	Metal	Ester	t_1 in °C	T_1 in min	t_2 in °C	T_2 in min	G.C Yield of 7
1	Zn[a]	$BrCH_2CO_2Et$	0	15	0	15	32
2	Zn	$BrCH_2CO_2Et$	0	15	0	15	33
3	Zn	$BrCH_2CO_2Et$	0	15	RT	15	49
4	Zn	$BrCH_2CO_2Et$	0	30	0	15	26
5	Zn	$BrCH_2CO_2Et$	0	15	RT	60	46
6	Zn	$BrCH_2CO_2Et$	one step procedure 30 min at 0°C				9
7	Zn[b]	$BrCH_2CO_2Et$	-78	30	-78	30	0
8	Zn	$BrCH_2CO_2Et$	0	15	RT	1320	56 (52)[c]
9	Li	CH_3CO_2Et	-78	30	-78	30	72
10	Li	CH_3CO_2Et	-78	30	-78	120	79

a. The reactive zinc was generated during 30 min at RT instead of the usual 15 min.
b. The zinc was washed with pentane to remove the mineral oil.
c. Isolated yield.

TABLE X



reagent. This is especially clear from the results obtained at -78°C with both reagents. While the zinc ester enolate failed to react at -78°C, the lithium reagent gave a good yield of the ß-hydroxyester (7). This limits the use of the Reformatsky reaction in reactions involving hindered carbonyl compounds. In such cases lithium ester enolates are a better choice than their zinc analogues.

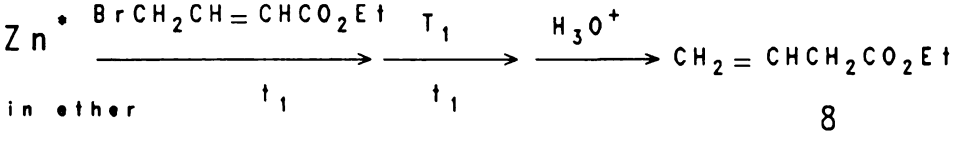
Reactions of 4-Bromocrotonate Esters with Benzaldehyde.

A survey was undertaken to find the best conditions for generating the zinc ester enolate of ethyl 4-bromocrotonate. Ethyl 4-bromocrotonate was reacted with the lithium (dispersion in mineral oil) generated reactive zinc under various conditions. Hydrolysis of the intermediate thus formed gave ester (8) (eq 53). ^{1}H-NMR yields of 8 are presented in table XI. High ^{1}H-NMR yields of 8 were obtained both at 0°C and at -78°C in ether. The highest yield (84 %) of 8 was obtained when the mineral oil was removed by washing the zinc with pentane and using anhydrous ether as the solvent. The zinc was allowed to react with the bromoester for a period of two hours at -78°C. When THF was used as the solvent, only an unidentified mixture of products was observed by ^{1}H-NMR.

Generation of the Zinc Ester Dienolate of Ethyl 4-Bromocrotonate				
Entry	Solvent	t_1, °C	T_1, min	Yield of **8** (^{1}HNMR)
1	Et_2O	0	15	62
2	Et_2O	0	60	80
3	Et_2O	0	1440	26
4	Et_2O	-78	15	53
5	Et_2O	-78	60	79
6	Et_2O[a]	-78	120	84
7	Et_2O	120 min at -78 then 60 min at 0°C		15
8	THF[a]	-78	60	unidentified materials

a) The generated zinc was washed with dry pentane to remove the mineral oil.

TABLE XI



$$Zn^{*} \xrightarrow{BrCH_2CH=CHCO_2Et} \xrightarrow[t_1]{T_1} \xrightarrow{H_3O^+} CH_2=CHCH_2CO_2Et \quad (53)$$

8

However, a one step reaction of ethyl 4-bromocrotonate with benzaldehyde in the presence of reactive zinc at -78°C in THF gave a quantitative yield (^{1}H-NMR) of alpha product (eq 54).

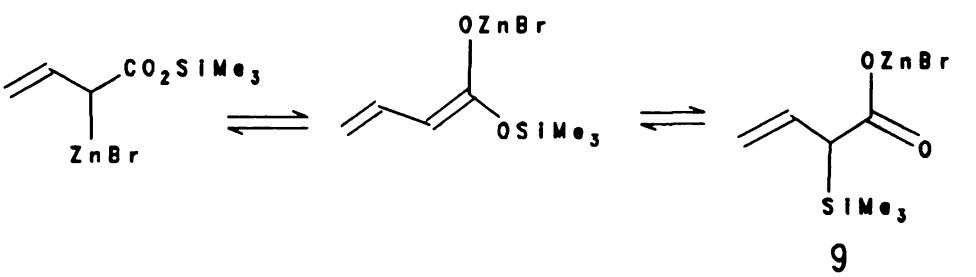
$$Zn^{*} \text{ in ether} \xrightarrow[\text{using pentane}]{\text{Removal of the mineral oil}} \xrightarrow{THF} \xrightarrow[2)\ BrCH_2CH=CHCO_2Et]{1)\ PhCHO \text{ at } -78^{\circ}C}$$

$$\xrightarrow[-78^{\circ}C]{2 \text{ hrs}} \xrightarrow[-78^{\circ}C \text{ to RT}]{H_3O^+} \begin{matrix} 100\ \% \text{ yield} \\ \text{of } \alpha\text{-product} \\ \text{by } ^1\text{HNMR} \end{matrix} \quad (54)$$

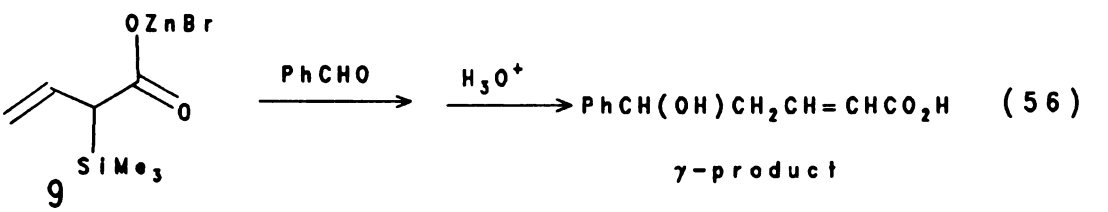
The two step Reformatsky reaction of ethyl 4-bromocrotonate with benzaldehyde under various conditions gave either unidentified products (reactions in THF), or the alpha product (reactions in Et_2O). No gamma product was detected by ^{1}H-NMR from these reactions. Data from the two

step reaction of ethyl 4-bromocrotonate with benzaldehyde are presented in Table XII.

It occured to us that the two step reaction described by Gaudemar[45], in which trimethylsilyl 4-bromocrotonate and 4-bromosenecioate were reacted with benzaldehyde, leading exclusively to gamma products, might occur through an α-silyl intermediate (9). The mechanism for the two step reaction may not involve a rearrangement of the zinc ester enolate, as described in eq (47), but rather the rearrangement shown in eq 55. Intermediate 9 could give the gamma product by attack of the electrophile at the gamma position, with loss of the silyl group (eq 56).We decided then to study the reactions of trimethylsilyl 4-bromocrotonate with benzaldehyde in both the one and two stage reactions.



9 (55)

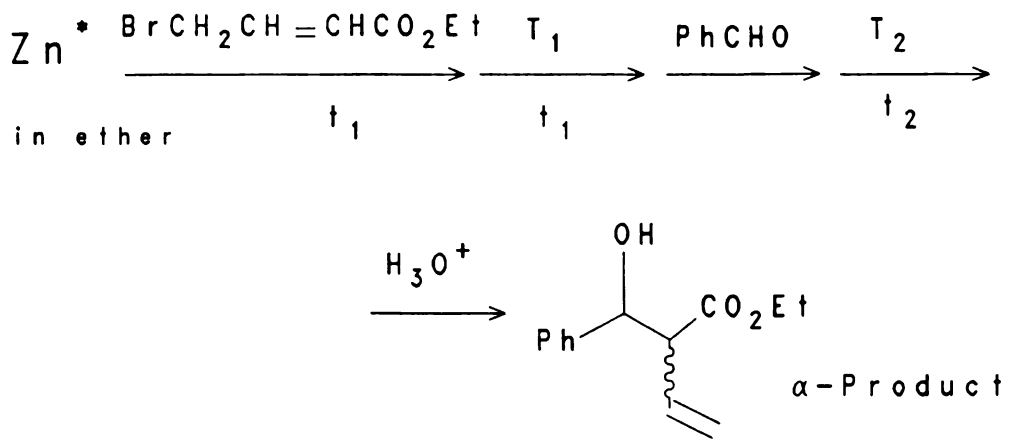


9 (56)

Two Step Reactions of Ethyl 4-Bromocrotonate with Benzaldehyde								
Entry	Solvent	t_1, °C	T_1, min	t_2, °C	T_2, min	Yld[a] of **8**	Yld of PhCHO	Yld of α-Pro.
1	THF[b]	-78	60	-78	60	unidentified mixture		
2		-78	30	-78	60	unidentified mixture		
3	Et_2O[b]	-78	120	-78	60	unidentified mixture		
4		-78	120	0	60		20	79
5	Et_2O	0	15	0	15		19	76
6		0	60	0	15	27	21	76
7		0	1440	0	15	16	59	43

a) ^{1}H-NMR yields.
b) The generated zinc was washed with dry pentane to remove the mineral oil.

TABLE XII



The one step reaction of trimethylsilyl 4-bromocrotonate with benzaldehyde gave a 96 % yield (^{1}H-NMR) of alpha product (eq 57).

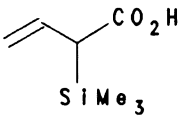
$$Zn^{*} \xrightarrow[\text{in ether}]{\text{1) PhCHO}\quad \text{2)}BrCH_2CH{=}CHCO_2SiMe_3} \xrightarrow[0^{\circ}C]{30\ min} \xrightarrow{NH_4Cl/H_2O} \begin{matrix}96\ \%\ yield \\ of\ \alpha\text{-product} \\ by\ ^1HNMR\end{matrix} \qquad (57)$$

The two step reaction in ether gave a mixture of unidentified products plus a 30 % yield (^{1}H-NMR) of unreacted benzaldehyde. Both the one and two step reactions gave mixtures of unidentified products plus 27 % and 42 % recovered benzaldehyde, when reacted in THF at 0°C. It appears that reactions conducted in THF at 0°C favor other reaction pathways (coupling, decomposition, ..etc) than the desired Reformatsky reactions. This phenomena has been observed throughout our study of the Reformatsky reaction. As mentioned in Chapter I we were faced with two limitations:

(1)-The reactions gave better results in ether but problems with stirring at low temperatures were usually encountered (even after removing the mineral oil).

(2)-The reactions stirred much better in THF even at low temperatures but the results were usually disappointing (mixtures, low yields..etc).

Data from a brief search for the best conditions for generating the zinc ester enolate of trimethylsilyl 4-bromocrotonate are presented in table XIII. The data show that THF is a suitable solvent for the rearrangement of the enolate to give intermediate (**9**), and that this rearrangement does not occur in Et_2O. A 73 % yield of a compound whose ^{1}H-NMR spectrum is consistent with structure **10**.



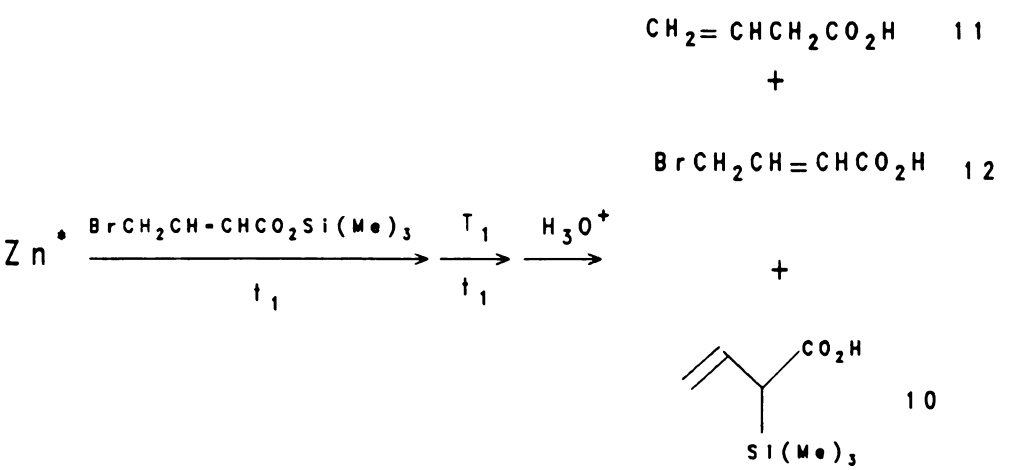
10

All attempts to isolate acid **10** failed. Efforts were made to generate the gamma product in the two step reaction of the silyl bromoester with benzaldehyde, using reactive zinc (from the lithium, dispersion in mineral oil, reduction of zinc chloride), under Gaudemar's and various other reaction conditions. No gamma product was detected by ^{1}H-NMR from any of the different trials. However gamma product was obtained when the same reaction was conducted using Gaudemar's activated zinc (1,2-dibromoethane procedure for activation) (eq 45). After many disappointing trials to reproduce Gaudemar results using our reactive zinc,

Generation of the Zinc Ester Dienolate of Trimethylsilyl 4-Bromocrotonate						
Entry	Solvent	t_1, °C	T_1, min	Yield[a] of 10	Yield[a] of 11	Yield[a] of 12
1	ET_2O	0	15	unidentified products		
2		-78	60	--	81	29
3	THF[b]	0	30	unidentified products		
4		0	60	73	--	--

a) ^{1}H-NMR yields.
b) The generated zinc was washed with dry pentane to remove the mineral oil.

TABLE XIII



generated from the lithium (dispersion in mineral oil) reduction of $ZnCl_2$, we conclude that the type of zinc is important in this reaction, and that the reactive zinc (from reduction of zinc chloride) reacts faster with the bromoester, generating a reactive enolate which in turn undergoes other reaction pathways (coupling, decomposition ..etc). On the other hand with Gaudemar's activated zinc the formation of the dieneolate is slow (two days). Once formed, the second step (reaction with benzaldehyde) is also slow and requires one day at 0°C.

EXPERIMENTAL SECTION

I. General

Gas Chromatography.

Qualitative G.C analysis was performed on a 5880A Hewlett-Packard gas chromatograph, using helium as carrier gas, and equipped with a flame ionization detector and a 30 meter fused silica capillary column (ID 0.32 mm). G.C yields were determined using hydrocarbons as internal standards.

Nuclear Magnetic Resonance.

Proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on one of the following : A Varian T-60 at 60 MHz in $CDCL_3$, on a Varian Gemini 300 at 300 MHz or on a Varian VXR 300 spectrometer at 300 MHz. Chemical shifts are reported in parts per million (δ scale) from the internal standard, tetramethylsilane (TMS). Data are reported as follows: Chemical shifts (multiplicity: s=singlet, bs=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet).

Spinning Band Distillation.

A Nester/Faust auto annular teflon spinning band distillation column was used to purify both ethyl and trimethylsilyl 4-bromocrotonate esters.

II. Materials

Diethyl ether (Et_2O), tetrahydrofuran (THF), benzaldehyde, the α-bromoesters, the 1.0M zinc chloride solution in ether and the lithium (25 % wt. dispersion in mineral oil containing about 0.5 % sodium) were purchased and or purified as described in the experimental section of Chapter I. Pyridine and carbon tetrachloride (CCl_4) were purshased from Fisher Scientific. Diisopropylamine was distilled from calcium hydride and stored under argon before use. n-Butyllithium (2.5 M solution in hexane), 2-methyl-cyclopentanone, crotonic acid (98 %), ethyl crotonate (96 %), methyl propionate, ethyl- and isopropyl acetates were available from Aldrich Chemical Company and were used without further purification. Benzoyl peroxide was purshased from Mallinckrodt. N-Bromosuccinamide (NBS) was available from MCB reagents. t-Butyl acetate was prepared from acetyl chloride and t-butyl alcohol in the presence of dimethyl-aniline by the procedure described in Org. Syn. Coll. Vol. III, 142.

Ethyl 4-Bromocrotonate.

This bromoester was prepared by the method of Bellasoued, Habbachi and Gaudemar.[48] 31.05 mL (0.25 mol) of Ethyl crotonate, 45 g (0.30 mol) of NBS, 1 g of benzoyl

peroxide and 325 mL of CCl_4 were placed in a 1 liter three-necked flask equipped with a reflux condenser and a gas inlet. The mixture was stirred for 15 min at 25°C then refluxed for 5 hours. The flask was cooled on ice and the floating suspension (succinamide) was filtered off. The filtrate was concentrated in vacuo and the crude product was distilled (short path) affording 30.7 g (64 %) of a mixture of 9:1 (gamma-bromo : alpha-bromo regioisomers). Spinning band distillation (reflux ratio 20:1) gave pure gamma regioisomer bp 52°C (0.2 torr). ^{1}HNMR (300 MHz) ($CDCl_3$): δ 1.65 (t, 3H), 4.0 (d, 2H), 4.10 (q, 2H), 6.0 (d, 1H), 7.0 (m, 1H).

Trimethylsilyl 2-Crotonate.

This ester was prepared by the method of Bellasoued, Habbachi and Gaudemar.[48] In a 2 liter three-necked flask equipped with a dropping funnel, a reflux condenser, a thermometer, an efficient mechanical stirrer and an argon inlet, 86.09 g (1 mole) of crotonic acid (98 %) was dissolved in ether (1 liter), 130 g (1.2 mol) of trimethylsilyl chloride was added and the mixture was stirred for 5 min. 82.8 g (1.2 mol) of pyridine was added dropwise with vigorous stirring while the temperature of the mixture was maintained at ≈ 35°C. After addition was complete, the mixture was heated at reflux temperature for 3 hours then cooled in an ice bath. The precipated pyridinium

chloride was filtered off and the residual ester was distilled (short path) affording 133.8 g (83 %) of trimethylsilyl 2-crotonate bp : 40°C (1.5 torr). ^{1}HNMR (300 MHz) ($CDCl_3$): δ 0.2 (s, 9H), 1.8 (d, 3H), 5.75 (d, 1H), 6.85 (m, 1H).

Trimethylsilyl 4-Bromocrotonate.

This bromoester was prepared also by the method of Bellasoued, Habbachi and Gaudemar[48] from trimethylsilyl 2-crotonate and NBS in the presence of a catalytic amount of benzoyl peroxide following the same procedure used to make ethyl 4-bromocrotonate. A spinning band distillation (reflux ratio 30:1) was required to remove the contaminating regioisomers. bp : 88°C (5 torr). ^{1}HNMR (300 MHz) ($CDCl_3$): δ 0.3 (s, 9H), 4.0 (d, 2H), 6.0 (d, 1H),6.95 (m, 1H).

III. Stability of Zinc Ester Enolates

A. Relative Stabilities of Twelve Different Zinc Ester Enolates.

Data presented in Table VIII was obtained using the following procedure: An ether solution of 1 mmole of zinc ester enolate, generated at 0°C from 1 mmole of the corresponding α-bromoester and 1.5 equivalent of reactive zinc (following the procedure described in Chapter I) was warmed to room temperature. The solution was allowed to

stirr at 25°C for either 12 hours or 24 hours then cooled to 0°C. 1 mmole of Benzaldehyde was added dropwise to the solution and the reaction was stirred at 0°C for 15 min. The reaction was then quenched with 2 mL of a 1 N HCl solution. After addition of a standard and workup the ether layer was analyzed by G.C for the corresponding ß-hydroxyester.

IV. Reactivity and Stability of Lithium Ester Enolates

A. Generation and Reactions of Lithium Ester Enolates.

To a THF solution of lithium diisopropylamide (LDA) (prepared at 0°C from 1.1 mmole of diisopropylamine and 1.1 mmole of n-butyllithium) was added at -78°C 1 mmole of the corresponding ester. The solution was maintained at -78°C for 30 min. One mmole of benzaldehyde was then added and the reaction mixture was maintained at -78°C for another 30 min. The reactions were then quenched with 2 mL of a 1 N HCl solution. After addition of the standard and workup the organic layer of each reaction was analyzed by G.C for the corresponding product.

B. Stability of Lithium Ester Enolates.

THF solutions of lithium ester enolates formed as above at -78°C in THF were each warmed to 25°C, stirred for 1 hour then cooled again to -78°C. One equivalent of benzaldehyde

was added to each solution and the reaction mixtures were stirred at -78°C for 30 min. After quenching, addition of standard and workup, the organic layer of each reaction was G.C analyzed for the corresponding ß-hydroxyester.

V. Reactions of Zinc and Lithium Ester Enolates with 2-Methylcyclopentanone

A. Reaction of the Zinc Ester Enolate of Ethyl Bromoacetate with 2-Methylcyclopentanone.

To an ether solution of 1 mmole of zinc ester enolate (generated at 0°C as in Chapter I from 0.11 mL of ethyl α-bromoacetate and 1.5 equivalent of reactive zinc) was added 0.10 mL (1mmole) of 2-methylcyclopentanone. The reaction was stirred for 22 hours at 25°C then quenched at 0°C with 2 mL of a 1 N HCl solution. After addition of the standard and workup the ether layer was G.C analyzed. A 56 % yield of product was observed by G.C.

When the reaction was repeated on a 10 mmole scale and after a short path distillation of the residue from workup, a 52 % isolated yield of a clear viscous oil (bp : 59°C at 0.2 torr) was achieved. ^{1}H NMR (60 MHz) ($CDCl_3$): δ 0.8-2.0 (m, 19H), 3.4 (bs, 1H), 4.15 (q, 2H).

B. Reaction of the Lithium Ester Enolate of Ethyl Acetate with 2-Methylcyclopentanone.

To a THF solution of 1 mmole of lithium ester enolate (generated at -78°C from 1.1 mmole of LDA and 0.2 mL (1 mmole) of ethyl acetate was added 0.1 mL (1 mmole) of 2-methylcyclopentanone. The reaction was maintained at dry ice temperature for 30 min then quenched with 2 mL of a 1 N HCl solution and allowed to reach 25°C while being stirred. After addition of standard and workup with ether, the ether layer gave a 76 % yield of product when analyzed by G.C.

VI. Reactions of 4-Bromocrotonate Esters with Benzaldehyde

A. Generation of Zinc Ester Dieneolate of Ethyl 4-Bromocrotonate.

Ethyl 4-bromocrotonate (0.138 mL, 1 mmole) was added at -78°C to a suspension of 1.5 equivalent of reactive zinc (the mineral oil was removed by washing several times the generated zinc with dry pentane, 2 mL of ether were added after removal of pentane under vacuum). After 2 hours of continuous stirring the enolate solution was quenched with 2 mL of a 1 N HCl solution. One equivalent of chlorobenzene (used as standard) was added. After workup with ether and removal of the solvent the residue was analyzed by ^{1}H NMR.

An 84 % yield of unconjugated ester **8** was observed. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.25 (t, 3H), 3.1 (d, 2H), 4.15 (q, 2H),5.15 (d, 1H), 5.85-6.0 (m, 1H).

B. <u>One Step Reformatsky Reaction of Ethyl 4-bromocrotonate with Benzaldehyde.</u>

To a suspension of 1.5 equivalent of reactive zinc (free of mineral oil) in 2 mL of THF was added at -78°C 0.1 mL (1 mmole) of benzaldehyde, 0.138 mL (1 mmole) of ethyl 4-bromocrotonate. The mixture was stirred for 2 hours at dry ice temperature. After quenching, addition of 1 equivalent of chlorobenzene (^{1}H NMR standard), workup with ether and removal of the solvent <u>in vacuo</u>; the residue was analyzed by ^{1}H NMR. A 100 % yield of pure α-product (hydroxyester). ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.05 (t) combined with 1.2 (t) make 3H, 2.9 (bs, 1H), 3.3 (t) combined with 3.4 (t) make 1H, 4.0 (q) combined with 4.15 (q) make 2H, 4.9-5.25 (m, 3H), 5.7 (m) combined with 5.9 (m) make 1H, 7.3 (m, 5H).

C. <u>Generation of Zinc Ester Dieneolate of Trimethylsilyl 4-Bromocrotonate.</u>

Trimethylsilyl 4-bromocrotonate (0.182 mL, 1 mmole) was added at -78°C to a suspension of 1.5 equivalent of reactive zinc (in 2 mL of THF and free of mineral oil). The mixture was stirred for 1 hour at dry ice temperature then quenched with 2 mL of a saturated ammonium chloride (NH_4Cl) solution.

After addition of 1 equivalent of standard, workup with ether and removal of the solvent <u>in vacuo</u>, the residue was analyzed by ^{1}H NMR. A 73 % yield of acid **10** was observed. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 0.05-0.30 (m, not clear), 3.15 (d, 1H), 5.15-5.3 (m, 2H), 5.8-6.0 (m, 1H).

D. <u>One Step Reformatsky Reaction of Trimethylsilyl 4-Bromocrotonate with Benzaldehyde.</u>

The same procedure as for Ethyl 4-bromocrotonate after (but in ether and without removal of the mineral oil). 96 % ^{1}H NMR yield of the α-product (hydroxyacid) was observed. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 3.40 (t, 1H), 4.8-5.30 (m, 3H), 5.65 (m) combined with 6.0 (m) make 1H, 7.40 (m, 5H).

E. <u>Generation of the Gamma Product using Gaudemar's Procedure.</u>

Gamma regioselectivity was achieved using the procedure of Bellassoued and Gaudemar.[45] Zinc metal (0.36 g, 5.5 mg-atoms) was placed in a 25 mL round bottom flask. The zinc was covered with 1.5 mL of THF; 0.1 g dibromoethane was added and the mixture was refluxed for 30 min. The flask was then cooled to -40°C, 0.94 mL (5 mmoles) of trimethylsilyl 4-bromocrotonate diluted in 2.5 mL of THF were added dropwise and the mixture was maintained at -40°C for 48 hours. The flask was warmed to 0°C and 0.406 mL (4 mmoles) of benzaldehyde were added dropwise to the zinc enolate. The

reaction mixture was stirred for 24 hours while at the temperature maintained at 0°C. The contenent of the flask was poured in a solution of NH_4Cl (10 mL of saturated NH_4Cl + 5 g of crushed ice). After extraction with ether, the organic layer was dried over sodium sulfate followed by removal of the solvents in vacuo. The residue was then analyzed by ^1H NMR. A ^1H NMR spectra pattern analogous to the one reported by Gaudemar was observed. ^1H NMR (300 MHz) (CD_3COCD_3): δ 2.65 (t, 2H), 4.90 (t, 1H), 5.85 (d, 1H), 7.10 (m, 1H), 7.45 (m, 5H).

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