SYNTHESES VIA REACTIONS OF ACTIVATED ORGANIC HALOGEN SUBSTRATES WITH TRANSITION METALS DISPERSED IN DIPOLAR APROTIC MEDIA

By

Byron C. Diehl

A Thesis submitted to the Faculty and the Board of Trustees of the Colorado School of Mines in partial fulfillment of the requirements for the degree of Master of Science.

Signed: Byron C. Diehl
Byron C. Diehl

Golden, Colorado

Date: Feb. 3, 1971

Approved: David W. Hall
Thesis Advisor

Head of Department

Golden, Colorado

Date: February 5, 1971

ABSTRACT

The reaction of α-halocarbonyl compounds with iron in dipolar aprotic solvents to form Reformatsky-type intermediates was investigated. Methods for making the reaction of these intermediates with carbonyl acceptor compounds a useful variation of the Reformatsky reaction were explored.

The reaction was shown to give conversions of the precursors comparable to the classical Reformatsky reaction. The problems encountered in isolating product could not be solved and prevented the development of a useful synthetic method. Organometallic intermediate-dipolar aprotic solvent complex formation and the wide solubility range of polar solvents were central experimental problems.

A possible solution to the solvent problem, using a co-solvent system, is described. A tentative investigation of furan formation from α-haloketones was made.

TABLE OF CONTENTS

ACKNOWLEDGMENTS

I gratefully thank the following for their assistance in helping me complete this thesis:

Dr. David W. Hall, my thesis advisor, for his patience and guidance throughout the work.

Drs. George B. Lucas, George H. Kennedy, and Kenneth W. Edwards for serving on my thesis committee.

The Colorado School of Mines Foundation, Inc., for the financial assistance which enabled me to attend graduate school.

Marathon Oil Company, for the donation of a gas chromatograph and reagents.

INTRODUCTION

The condensation reaction of an α-haloester and a carbonyl compound in the presence of zinc was first reported in 1887 by Fittig and Daimler[1] and Reformatsky.[2] The products of these first reactions were isolated as β-hydroxyesters.

In his first publication on the subject, Reformatsky suggested the following steps and intermediate for his reaction (Scheme I).

SCHEME I

$$(CH_3)_2C{=}O + ICH_2CO_2R + Zn \longrightarrow (CH_3)_2\overset{OZnI}{\overset{|}{C}}CH_2CO_2R \qquad (1)$$

$$\big\downarrow H_2O$$

$$ZnIOH + (CH_3)_2\overset{OH}{\overset{|}{C}}CH_2CO_2R \qquad (2)$$

In 1891 he extended the reaction to include other ketones[3] and in 1895[4] made the first report on the dehydration product, an α,β-unsaturated ester, and noted that aldehydes do not react with α-chloroesters, but that α-bromoesters will give a slow reaction.

A three-step pathway was proposed by Reformatsky[5] in 1896 (Scheme II; X may be Br or I).

SCHEME II

$$X\overset{R_1}{\underset{R_2}{C}}CO_2R + Zn \longrightarrow \underset{\text{I}}{XZn\overset{R_1}{\underset{R_2}{C}}CO_2R} \qquad (3)$$

$$\text{I} + \overset{R_3}{\underset{R_4}{C}}{=}O \longrightarrow \underset{\text{II}}{XZnO\overset{R_3}{\underset{R_4}{C}}-\overset{R_1}{\underset{R_2}{C}}CO_2R} \qquad (4)$$

$$\text{II} + H_2O \longrightarrow HO\overset{R_3}{\underset{R_4}{C}}-\overset{R_1}{\underset{R_2}{C}}CO_2R + XZnOH \qquad (5)$$

Dain[6] obtained a zinc and bromine analysis on an intermediate of Type I that was in fair agreement with the formula. Dippy and Parkins[7] obtained zinc and bromine analyses on intermediates of Type II. Their values agreed closely with theoretical values for several carbonyl acceptors which had been reacted with ethyl bromoacetate and ethyl α-bromopropionate.

Although Reformatsky proposed a pathway for the reaction in 1896, actual mechanistic studies were not undertaken until 1942. Newman,[8] working with acetomesitylene, methyl bromoacetate (MBrAc), and zinc, found that methyl acetate could be distilled from the reaction mixture before hydrolysis or following hydrolysis mesitylene and methyl acetate could be recovered. When no ketone was present a negligible amount of methyl acetate was isolated before hydrolysis. This led to a proposition in which the ketone dehalogenates the ester through an enolization process:

$$BrCH_2CO_2CH_3 + Zn \longrightarrow BrZnCH_2CO_2CH_3 \qquad (6)$$

$$BrZnCH_2CO_2CH_3 + (R)_2CH\overset{O}{\overset{\|}{C}}R \longrightarrow \overset{\oplus}{Br}Zn[(R)_2\overset{\ominus}{C}\text{---}\overset{O}{\overset{|}{C}}R] + CH_3CO_2CH_3 \qquad (7)$$

Subsequently, Hussey and Newman[9] found that other α-bromoesters react with zinc when no carbonyl acceptor is present to give reduced esters upon hydrolysis. A second

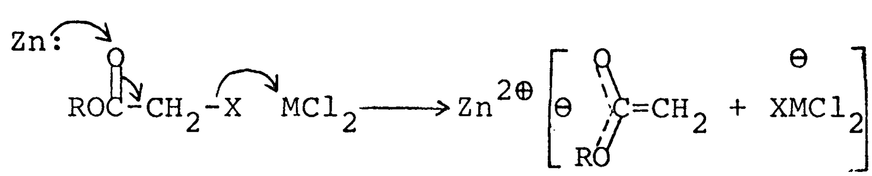
$$BrZn\overset{R}{\overset{|}{C}}HCO_2R + Br\overset{R}{\overset{|}{C}}HCO_2R \longrightarrow H_2\overset{R}{\overset{|}{C}}CO_2R + BrZn\overset{R}{\overset{|}{C}}BrCO_2R \qquad (8)$$

dehalogenation mechanism, in which the necessary proton is taken from a molecule of unreacted α-bromoester, was proposed (Formula 8).

Using mono- and poly-halogenated ethyl acetic esters, Miller and Nord[10] showed the ease of reaction of α-haloesters to be:

$$BrCH_2CO_2R >> ClCH_2CO_2R > Cl_2CHCO_2R > Cl_3CCO_2R$$

They concluded the halogen leaves the ester as an anion. In a better proof of this, McBee, et al.,[11] used ethyl bromofluoroacetate in reaction with carbonyl compounds to give α-fluoro-β-hydroxy esters. They proposed the following mechanism to form an enolate anion.

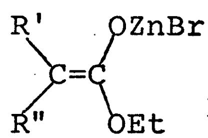


(9)

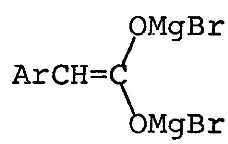
The yields obtained by varying the ester group have been studied by Fuson and Thomas[12] and Newman and Evans.[13]

Using substituted phenyl esters on straight-chain and branched alkyl systems, both research groups reached the same conclusion; i.e., the ester group has little electronic effect on reaction but the reaction is highly sensitive to steric effects from substituents in the ester position.

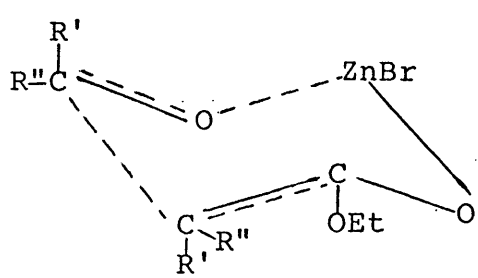
In working out the stereochemistry of the Reformatsky and Ivanov reactions, Zimmerman and Traxler[14] assumed both reactions to have similar intermediate organometallic structures:



III and



They gave a convincing proof of the configurations of the erythro-threo isomers (which are possible if the carbonyl acceptor is properly substituted at the carbonyl group and the α-haloester is properly substituted at the α-carbon atom so that upon reaction the two adjacent asymmetric centers are established). Working with the Ivanov reaction, they isolated both isomers in different yields. They proposed a six-membered ring transition state which would also apply to the Reformatsky reaction[15] (drawn in the chair



form).

That Zimmerman and Traxler were correct in assuming that the initial ester intermediate is a bromozinc enolate has been borne out by further work. Vaughn, et al.,[16] cite infrared studies and comment on differences of reactivities of zinc alkyls versus Reformatsky reagents toward carbonyl substrates. Gaudemar[17] and Gaudemar and Cure[18,19] concur in this; however, they point out that metal enolates cannot be characterized simply by infrared studies.

In a generalization, House[20] refers to the Reformatsky reaction as a type of aldol condensation. He is correct in that enolate anions are formed in both reactions and these anions will react with an electrophilic carbonyl-carbon atom. However, the anions differ in their mechanism of formation and in their subsequent reaction.

Shriner[21] and House[20] give brief discussions of the synthetic usefulness of the Reformatsky reaction. In recent years the definition of what constitutes a Reformatsky reaction has been greatly expanded to include, for example, α-halo amides[22] and nitriles.[23] It would be impractical in this introduction to mention all the work which has been done on the Reformatsky reaction. The remaining portion of the introduction is devoted to various studies and observations that apply or are pertinent in a direct manner to the development of the present work.

When synthesizing β-hydroxy amides, Cure and

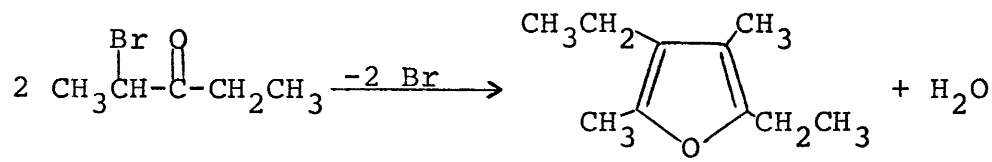
Gaudemar[19,22] found they could obtain satisfactory yields only if hexamethylphosphoramide (HMPA) was used as solvent in place of methylal.

While studying the reaction of organocadmium reagents with α-haloesters, Jones and Young[24] found increased yields when tetrahydrofuran (THF) was used as solvent in place of diethyl ether (ether).

In studying the formation of bromozinc enolates Vaughan, et al.,[16] recognized that the solvent system may be of great importance in obtaining a good yield of enolate. They referred to experiments being conducted in their laboratory, using THF in place of benzene, which have not yet been reported.

In their study of the Reformatsky reaction, Miller and Nord[10,25] observed the catalytic effect of metals and metal salts. They found no zerovalent metal that would help promote the reaction, but mercuric chloride and cuprous and cupric chloride, to a lesser extent, would speed up the reaction and give better yields. Other inorganic salts tested were $SnCl_2$, $SnCl_4$, $SbBr_3$, $MnCl_2$, $CrCl_3$, $CoCl_2$, and halides of iron and nickel. They noted that cuprous, cupric mercuric and presumably silver ions are substances which effectively activate reactions involving separation of a halide ion from an organic radical by complex formation. They explain the inactivity of iron and nickel halides by comments about the significance of relative sizes of donor and acceptor centers and steric factors.

In the course of studying the methylation of α-bromo ketones using methyl iodide and zinc, Spencer, et al.,[26] found furan formation with some α-bromocarbonyl compounds:

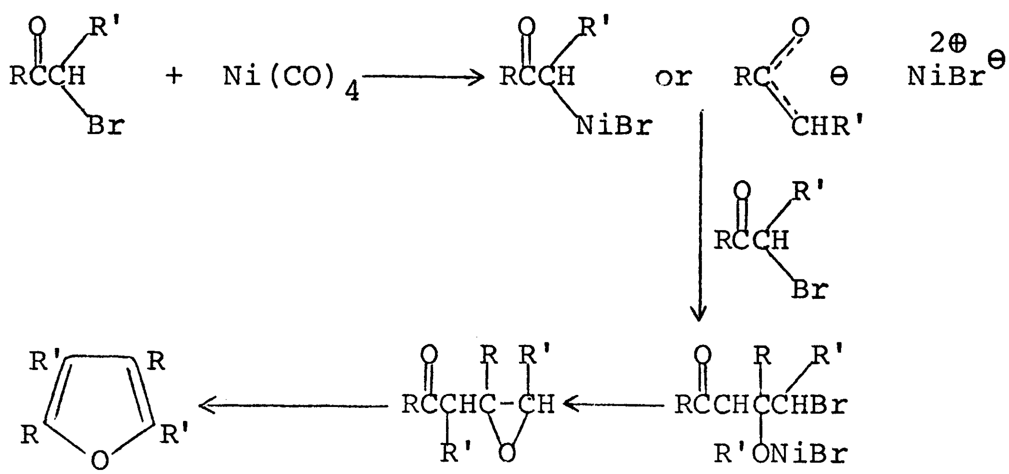


(10)

A 10% dimethylsulfoxide (DMSO)-benzene cosolvent system was used.

This reaction has also been run with magnesium;[27,28] but in addition to the furan (Formula 10) a β-hydroxy ketone was obtained and the reaction was not quantitative, based on α-halocarbonyl, as was the zinc reaction. In a review on metal carbonyls, Ryang[28] suggests the mechanism

SCHEME III



(11)

(12)

is similar to a nickel carbonyl reaction (Scheme III). Isolated intermediates have shown the epoxide structure and the reaction proceeds better in polar media.

During research on the transition metal promoted Wurtz coupling reaction of allylic and other potentially reactive halides, Hall and Hurley[29] observed that chloroacetone gave an unexpectedly low yield of 2,5-hexanedione, even though the conversion of chloroacetone was essentially complete. Hall and DePuy[30] showed that the reaction of iron metal in N,N-dimethylformamide (DMF) or N-methyl-2-pyrolidone (NMP) solvents leads to a Reformatsky-type organometallic intermediate. When the intermediate was allowed to react with benzaldehyde it gave 4-phenyl-4-hydroxy-2-butanone and the dehydrated product 4-phenyl-3-butene-2-one. In contrast to the above, bromoacetone has been reported not to react with zinc in traditionally used solvents to give Reformatsky products.[31]

Kim[32] found that using DMF in place of toluene or cyclohexane gave markedly increased yields when α-chloro acids and esters were allowed to react with zinc. He attributed the increased reactivity to increased solvation of the intermediate complex. With DMF as solvent no pretreatment of the zinc is required as in the usual procedures.[21]

Further experiments by Hall and Hurley using chloroacetone, methyl chloroacetate (MClAc) and benzaldehyde over iron brought out the following facts and observations. Chloroacetone reacts much more rapidly than MClAc, which requires sodium iodide or lithium bromide catalysis. This holds true whether or not the carbonyl acceptor is present.

If iron is not present, the reagents are stable under reaction conditions (DMF or NMP solvent, 120°C, 16 hrs). The reaction run in benzene shows no conversion of α-halocarbonyl. The consumption of iron is not related to consumption of α-halocarbonyl by a simple stoichiometric factor. There were varying amounts of by-products, e.g., in the chloroacetone case; 2,5-hexanedione (Wurtz coupling), a material tentatively identified as 5-chloro-4-methyl-4-hydroxy-2-pentanone (self condensation) and acetone. The previous literature contains no report of a Wurtz coupling product of an α-haloketone. In all cases the final reaction mixture either contained, or was, a dark tarry viscous liquid. This tar prevented isolation of the products in a yield comparable to that indicated by gas liquid chromatography (GLC), by which method most of the analyses were done. No effective work-up procedure was found, though Hall was slightly more successful than Kim, in his zinc activated reactions. The best yields obtained with the iron reaction were in the 50% range, compared to 50 to 80% for the classical reaction.[21]

Until the work of Hall and DePuy[30] and Kim[32] the Reformatsky reaction was limited to zinc, hydrocarbon or ether solvents, and almost exclusively α-bromo esters and amides. Because of the greater availability of α-chlorocarbonyl compounds it would be desirable to use them in place of α-bromocarbonyls. To use iron in place of zinc and to not have to pretreat the metal would also offer attractive synthetic possibilities.

It was the objective of the research described herein to develop a useful synthetic procedure based on the background knowledge presented above. It was also hoped to delineate the mechanism of the Reformatsky reaction and especially the mechanism of the dipolar aprotic solvent-iron modification of the reaction.

EXPERIMENTAL WORK

The experimental work required in this investigation consisted of the preparation and purification of reagents and solvents, the running of reactions, and analysis of these reactions during and after the reaction.

Reagents and Solvents

N,N-Dimethylformamide

DMF, reagent grade, from Eastman Kodak Company, was distilled, at atmospheric pressure, through a 40-cm Vigreux column into a receiving flask containing 5A moleculer sieves (Linde Company). A center cut (143 to 145°) was taken and the material stored in the stoppered flask until use.

N-Methyl-2-pyrrolidone

NMP, practical grade, from Eastman Kodak Company, was treated as in the DMF procedure (78 to 80° at about 15 torr).

Dimethylsulfoxide

DMSO, analytical reagent grade, from Mallinckrodt Chemical Works, was used as received.

Chloroacetone

Chloroacetone, technical grade, from Matheson Coleman and Bell Company was used. Upon distillation at atmospheric pressure, the material was shown to be decomposing in the Vigreux column. It was then distilled at 40° at a pressure of about 25 torr. This material became discolored upon standing. (No comment was found in the literature on chloroacetone decomposition.) A fresh distillation was made before each use.

Methylchloroacetate

MClAc, technical grade, from Matheson Coleman and Bell Company, was stirred over anhydrous magnesium sulfate, for 2 hr, filtered and distilled (41 to 42° at about 15 torr).

Methyl bromoacetate

MBrAc, reagent grade, from Eastman Kodak Company, was treated in the same manner as was MClAc (38 to 39° at about 10 torr).

Benzaldehyde

Benzaldehyde, reagent grade, from Eastman Kodak Company, was distilled at 73 to 75° at about 15 torr. A constant boiling point fraction was taken for use.

Iron

Iron, technical grade, from Baker and Adamson Company, 100 mesh, was used as received or treated by the method of Afanasyev and Tsyganova.[33] When treated, an amount slightly greater than needed was placed in a sintered glass Buchner funnel, washed consecutively with 10% hydrochloric acid, water, acetone, and ether. The iron was placed under a vacuum, at room temperature, until needed.

Zinc

Zinc, technical grade, from Baker and Adamson Company, 20 mesh, was treated by a procedure adapted from Shriner's review article.[21] The zinc is heated in concentrated sulfuric acid, to which a few drops of concentrated nitric acid have been added, at 110° for 15 min. The acid is decanted from the zinc and washed consecutively with water, acetone, and ether and then placed under a vacuum until used.

2-Bromo-3-pentanone

A method adapted from two previous preparations by Pauly[34] and Rappe and Kumar[35] was used for the preparation of 2-bromo-3-pentanone. The method was basically that of Pauly (addition of bromine to a hydrobromic acid solution of 3-pentanone). However, the work-up procedure was that of Rappe and Kumar, which used carbon tetrachloride extraction of the reaction mixture and product isolation by distillation. The N-bromosuccinimide synthesis of Rappe and Kumar gave an impurity, which was not separable with the distillation apparatus at hand. The product was identified by infrared analysis and the purity was determined by GLC analysis. The 2-bromo-3-pentanone decomposed rapidly upon standing in the nearly pure form and, therefore, was freshly distilled before use. A distillation cut of greater than 98% purity could be obtained if a careful distillation procedure was followed, using a 40-cm Vigreux column and reduced pressure. The final fraction was taken at 58° at 15 torr.

2,4-Diethyl-3,5-dimethylfuran

The method of Spencer, Britton, and Watt[26] was used to prepare 2,4-diethyl-3,5-dimethylfuran. Fifty ml of benzene, 5 ml DMSO, 16.5 g 2-bromo-3-pentanone (0.100 mole), and 6.59 g zinc (0.100 g-atom) were placed in a 250 ml three-necked flask, under a nitrogen atmosphere. The mixture was stirred at room temperature for 24 hr with a magnetic stirrer. At this time GLC analysis showed the disappearance of 2-bromo-3-pentanone and appearance of a compensating product peak. This material was isolated by repeated fractionation (46°, 1 to 4 torr). An infrared spectrum of this material showed nothing contrary to the expected structure and a proton magnetic resonance (PMR) spectrum was in complete agreement with the data given by Dubois and Itzkowitch[27] for this compound.

The remaining materials used, such as acids, drying agents, inert solvents, etc., were analytical grade reagents and used as received unless otherwise noted.

Instrumentation

Infrared

Infrared spectra were obtained on a Perkin-Elmer 521 Grating Infrared Spectrophotometer. Solution analyses were made using sodium chloride or Irtran-4 matched cells of 0.2-mm path length. Carbon tetrachloride was used as the reference solvent. Spectra of liquid smears were obtained using sodium chloride plates for some of the non-lachrymatory compounds.

Proton Magnetic Resonance

PMR spectra were obtained on a Varian model A-60A instrument. Carbon tetrachloride was used as a solvent and tetramethylsilane as an internal standard.

Gas Liquid Chromatography

Chromatographic analyses were done on an F & M model 720 dual column instrument. The columns used were made of 0.25-in. stainless steel (12 ft). The solid support was Chromosorb-P (Hewlett-Packard no. 8501-6119). The stationary phase was either 15% Silicone Fluid SF-96 (Hewlett-

Packard no. 8501-3420) or 10% Bentone 34 (organic substituted bentonite clay) (Hewlett-Packard no. 8501-0360).

All GLC analyses were done with the injection block and thermoconductivity detector at 250°.

Extensive use was made of the programmed column temperature feature of the instrument, with column temperatures varying from room temperature to 180°.

Apparatus and Technique

In general, the reaction apparatus was a 3-necked, round-bottomed flask fitted with a condenser, nitrogen inlet, and thermometer. To the top of the condenser was attached either a drying tube packed with Drierite, or a dry ice trap. In cases where temperature control was required, a Therm•O•Watch (I^2R Corporation, model L-6) was connected to the thermometer. Stirring was accomplished by a Teflon blade overhead electric motor in the reactions in which iron was used. A water-cooled ground glass stirrer bushing was employed. A magnetic stirring bar was employed when iron was not present. If addition of a reagent at an elevated temperature was required, a pressure equalizing addition funnel was added to the top of the condenser. Heating was done by a heating mantle connected to a variable transformer, which could be controlled by the Therm•O•Watch.

A generalized reaction procedure follows: The required apparatus was set up and flame dried with a rapid flow of nitrogen sweeping the flask. The solvent, metal, and carbonyl acceptor, if used, were added at room temperature and heated to the reaction temperature. The α-halocarbonyl compound was added rapidly from the addition funnel. The reaction temperature was carefully observed to check for exothermic reaction. Samples for GLC analyses were taken initially and throughout the reaction as required by means of an eyedropper. These samples were stored in 5-ml vials. After the reaction was terminated, the reaction mixture was allowed to cool with enough time given for the solids to settle. The reaction mixture was decanted from the metal into an erlenmeyer flask or filtered through a sintered glass Buchner funnel and collected. When iron was used, a magnet was held on the outside of the flask to retain the iron. The metal was then rinsed with a weighed amount of the same solvent used in the reaction and added to the reaction mixture. The metal was washed with acetone and ether and then dried under vacuum and weighed.

The GLC analyses gave, to this point in the procedure, the relative amounts of solvent, non-metallic reactants, and non-organometallic products. Many of the experiments were taken no further than this, either because no reaction had taken place or the desired information had been obtained. Where reaction mixtures were worked up or where various work-up procedures were tried they will be described with the particular experiment.

α-Halocarbonyl-Metal Reactivity Experiments

A series of reactions, using no carbonyl acceptor, was made to test for reaction of different α-halocarbonyl compounds with iron in DMF and NMP solvents. The reactions were run for 300 minutes and contained 0.200 ± 0.002 gram atoms iron and 0.100 ± 0.005 moles α-halocarbonyl.

The results are outlined in table I.

A similar reaction using zinc and MClAc, at 100°, showed a consumption of 0.084 gram atoms of zinc.

The final reaction mixtures of the reactions in which there was a measurable loss of iron were darkly colored and viscous and could be filtered only with difficulty.

By-Product and Work-Up Experiments

Three by-products were reported[30] for the chloroacetone reaction (pg 9). The identification of 2,5-hexanedione and acetone was definite; however, the structure of what was called 5-chloro-4-hydroxy-4-methyl-2-pentanone was not proved conclusively. In the chloroacetone reactivity experiments above, a trace amount of 2,5-hexanedione and a small amount of acetone were identified by GLC analysis of reaction mixture samples containing

TABLE I. α-Halocarbonyl-Iron Reactivity

Run no.	α-Halo-carbonyl	Solvent	NaI Catalyst (g)	Reaction Temp. (°C)	Consumption Iron (g-atom)	Consumption α-Halocar-bonyl (mole)	Consumption Fe ÷ α-Halo carbonyl
1	MClAc	NMP	none	100	0.000	0.000	——
2	MClAc	NMP	1.0	100	0.000	0.000	——
3*	MClAc	DMF	1.0	100	0.020	0.047	0.42
4	MBrAc	NMP	none	100	0.026	0.046	0.56
5	MBrAc	DMF	1.0	100	0.000	0.018	0.00
6*	MBrAc	DMF	1.0	100	0.036	0.066	0.54
7*	Chloro-acetone	DMF	none	100	0.019	0.038	0.50
8*	Chloro-acetone	DMF	none	130	0.052	0.097	0.53

*Fe treated as outlined on pg 13

authentic samples of these materials (spiking). The chromatograms contained an unknown peak which could possibly be 5-chloro-4-hydroxy-4-methyl-2-pentanone.

If an effective work-up procedure could be found, these by-products could be isolated and the structure of 5-chloro-4-hydroxy-4-methyl-2-pentanone could be proved conclusively.

The reactions were made using 200 ml DMF or NMP, 46.3 g chloroacetone (0.500 mole) and 27.9 g untreated iron (0.500 g-atom) and were run at 130° for 5 hours.

After the first reaction run in DMF was shut off, the GLC showed less than 3% of the chloroacetone remaining. The iron consumed amounted to 0.267 gram atoms. About 90% of the DMF and the low-boiling material was stripped off using a rotary evaporator. A total of 3.8 g (0.07 mole) of acetone was recovered from the dry ice trap and rotary distillation. GLC analysis of the distillate showed three peaks. The first (<1%) was identified as 2,5-hexanedione by spiking. Judging from GLC elution times, one of the unknowns (unknown A) would have a molecular weight similar to that of 2,5-hexanedione and the other (unknown B) would be a much higher molecular weight compound. Together they constituted less than 4% of the distillate. These two unknowns were left unidentified since it was assumed at that point the bulk of the chloroacetone reaction products were in the residue; this could not be proved as it was impossible to obtain a chromatograph of this tarry material and the unhydrolyzed organometallic compounds would not elute from the GC if a chromatogram were possible.

The residue was poured into 300 ml of 10% H_2SO_4 and stirred for 22 hr to hydrolyze the intermediate. The solution was neutralized by slow addition of 37.4 g of sodium carbonate.

The entire mixture was placed in a continuous extractor and extracted with ether for a total of 7 days. During this period the ether extractant was changed twice. These extractant fractions were dried over sodium sulfate and let stand to allow the ether to evaporate.

After the first three days of extraction, NaCl was added to the extraction vessel. This caused a third tarry phase to settle to the bottom.

The beaker containing the first two evaporated ether extraction fractions (still over sodium sulfate) was extracted with benzene and filtered. A chromatograph of this material showed only benzene and DMF, although the benzene extractant was darkly colored.

A chromatograph of the final ether fraction was obtained and showed only ether, DMF, and H_2O. The experiment was discontinued at this point.

A second experiment, run in an identical manner except that NMP was substituted for DMF, was carried out. The consumption of iron was 0.162 gram atoms and GLC analysis showed less than 6% of the chloroacetone remaining. GLC analysis of the reaction mixture showed no 2,5-hexanedione or unknown A. A small peak, which eluted between unknowns A and B, was present, but amounted to only a trace of material.

In an attempt to accomplish hydrolysis of the organometallic intermediate and the product separation in one step the reaction mixture was steam distilled. The distillation was done using a 1-liter, 3-necked flask fitted with distillation head, condenser and an addition funnel, to add make-up water. The distillate contained water, acetone, chloroacetone and NMP. No unknown was present in large enough quantity to isolate and identify.

To a third run, done in NMP solvent, was also added 53.1 g (0.500 mole) of benzaldehyde. After 393 minutes at 130° less than 2% of the chloroacetone remained. The conversion of benzaldehyde was 34%. A chromatogram showed a peak identified as 4-phenyl-3-butene-2-one, by spiking.

The reaction mixture was steam distilled. Upon phase separation the organic layer weighed 12.3 g and contained 62% of 4-phenyl-3-butene-2-one (an 8% yield). The material left in the steam distillation pot was acidified with 100 ml of 10% H_2SO_4 and then stirred for 90 min. Continued steam distillation gave no more product.

Reaction of 2-Bromo-3-pentanone with Iron

The reaction of 2-bromo-3-pentanone with zinc in DMSO-benzene solvent to give 2,4-diethyl-3,5-dimethylfuran is contrary to what Hall and Hurley[29] found for the reaction of α-haloketones with iron, in DMF or NMP.

Experiments were run to determine whether iron does give a different product than zinc or whether longer chain length α-haloketones give the furan but chloroacetone does not.

A reaction identical with the preparation of 2,4-diethyl-3,5-dimethylfuran (see Reagents and Solvents) with the exception that 5.58 g (0.100 g-atom) of treated iron was substituted for zinc, was conducted.

The reaction was run at room temperature for 19 hr, at which time GLC analysis showed no change in composition of the reaction mixture. The reaction was refluxed (81°) for 3 hr. After this treatment no 2-bromo-3-pentanone or 2,4-diethyl-3,5-dimethylfuran could be found by GLC. The iron recovered was 5.27 g, which is a quantitative recovery within the limits of experimental technique. The disappearance of 2-bromo-3-pentanone was attributed to decomposition, to which, as noted in Reagents and Solvents, this compound is prone.

A second reaction using 120 ml of NMP solvent, 16.5 g (0.100 mole) of 2-bromo-3-pentanone and 11.2 g (0.200 g-atom) of treated iron was run at 130°.

After 2 hr the reaction was terminated; GLC analysis showed complete conversion of 2-bromo-3-pentanone. A trace (<0.5%) of material eluted identically with a spike of authentic 2,4-diethyl-3,5-dimethylfuran. The amount of iron consumed was 3.19 g (0.057 mole).

A third reaction, set up as the second, was run at 75° for 150 min. GLC analysis showed more than 98% of the 2-bromo-3-pentanone had disappeared and no formation of 2,4-diethyl-3,5-dimethylfuran. A quantitative recovery of iron was made.

Furan Formation from Chloroacetone

Because of furan formation from 2-bromo-3-pentanone, and considering Ryang's mechanism, it would seem possible to obtain 2,4-dimethylfuran from chloroacetone.

A reaction identical with the preparation of 2,4-diethyl-3,5-dimethylfuran, with the exception of substitution of 9.25 g (0.100 mole) of chloroacetone for the 2-bromo-3-pentanone, was set up. The reaction was stirred at room temperature for 24 hr. At this time, no product peak was evident in the GLC analysis. The benzene and chloroacetone could not be separated by the GLC technique then being used. A few drops of CH_3I were added and after 5 hr the reaction mixture had the cloudy appearance noted in the case of the 2-bromo-3-pentanone reaction with zinc. After 17 hr a new peak was present on the reaction mixture chromatogram; however, it could not account for more than about 20% of the original chloroacetone. By visual observation, it seemed very little of the zinc had reacted. An additional 8.97 g of chloroacetone was added and the mixture taken to reflux (80°). After a few minutes, a white, powdery precipitate was observed in the flask which was no longer present after 2 hr; however, a brown viscous layer was now present on the bottom of the reaction flask, along with only a few grains of zinc.

After decantation of the upper layer a vacuum (<1 torr) was applied to the residue in the reaction flask, as it was warmed in water at about 55°. Infrared spectra of this residue were obtained as a smear and as reference spectra in carbon tetrachloride and DMSO. A spectrum of DMSO in carbon tetrachloride was also obtained. The smear and DMSO reference spectra show a strong wide band at 1700 cm^{-1} not present in the DMSO in carbon tetrachloride spectrum. The DMSO in carbon tetrachloride and smear spectra show narrow medium bands at 2950 cm^{-1} and 3,000 cm^{-1} not present in the residue in DMSO spectrum. The residue when placed in H_2O forms a white precipitate, which disappears upon addition of a few drops of acid. An experiment set up as above, but containing 50 ml of benzene, 5 ml DMSO, and 13.6 g (0.100 g-atom) of zinc chloride, was run at reflux. The same brown viscous lower layer formed. When this material was treated as the above, it gave similar infrared spectra and the same qualitative tests.

The upper layer, which had been decanted, was placed in a micro-ware distillation apparatus and fractionated. The GLC analyses of these fractions showed a product to be present. However, the product was extremely difficult to separate from benzene and decomposed during the distillations and was lost.

Another similar experiment was run to attempt to isolate and identify the product. A GLC technique that would separate benzene and chloroacetone was developed. After 3 hr at reflux, no product or chloroacetone was present. Another 9.25 g of chloroacetone was added and refluxing continued for 3 hr more. Upon fractionation (38 to 39°, at about 8 torr) the same decomposition and separation problems were encountered. Since the product could not be separated from benzene, an infrared spectrum of the material was obtained using benzene as the reference solvent. A comparison to the spectrum of pure 2,4-diethyl-3,5-dimethylfuran indicates the product is 2,4-dimethylfuran.

On further attempts at purification, it was noticed that water was forming in the distillation column. This could be indicative of the dehydration step to form the furan; however, the instability of the compound is not indicative of a furan.

An experiment was made to test the reactivity of iron with the DMSO-benzene solvent mixture using chloroacetone. After 24 hr of refluxing there was no reaction of chloroacetone, as shown by GLC analysis, and a quantitative recovery of iron was made.

Decomposition Under Reaction Conditions

In the previous work with the iron-dipolar aprotic solvent system it was mentioned that decomposition or elimination reactions are occurring. For example there was acetone formation in the chloroacetone work and disappearance of 2-bromo-3-pentanone, with no visible product formation, in the 2-bromo-3-pentanone reactions.

Hall and Hurley[29] found the reacted iron to be Fe^{2+} in their work in coupling allylic halides. This series of experiments was done to determine if Fe^{2+} will promote decomposition or elimination reactions.

A reaction using 50.0 ml NMP, 9.25 g (0.100 mole) chloroacetone and 19.9 g $FeCl_2 \cdot 4\ H_2O$ (0.100 mole) was conducted. (Ferrous chloride was available only in the hydrate form, $FeCl_2 \cdot 4\ H_2O$.) The reaction was intended to be run at 130°; however, a component refluxing in the condenser held the temperature at 112°. The refluxing material was assumed to be H_2O formed from ligand displacement on the $FeCl_2 \cdot 4\ H_2O$.

The $FeCl_2 \cdot 4\ H_2O$ dissolved in the NMP formed a greenish-brown syrupy mixture. GLC analysis showed no change in the chloroacetone concentration after 5 hr of refluxing; benzene was used as an internal GLC standard.

2-Bromo-3-pentanone can form an elimination product, 1-pentene-3-one, whereas chloroacetone cannot form an elimination product. A reaction was set up as the previous one, but with the substitution of 16.5 g (0.100 mole) of 2-bromo-3-pentanone for the chloroacetone. In following the reaction by GLC, disappearance of 2-bromo-3-pentanone was simultaneous with the appearance of an unknown peak. After 240 min at reflux (118°) both peaks had disappeared and no other product peak could be found.

Running the reaction in the same manner at 130° but with no $FeCl_2 \cdot 4\ H_2O$ gave the same results. A likely explanation is that the unknown peak was due to 1-pentene-3-one and that this material polymerized after an extended reaction time.

RESULTS AND DISCUSSION

The reactivity experiments in Table I show that bromoesters are more reactive than chloroesters towards iron. However, neither ester is as reactive towards iron as the chloroester is towards zinc. The data indicate that the presence of sodium iodide is a critical factor for reaction of MClAc and that pretreatment of the iron is beneficial, under the reaction conditions.

As the reaction products of the reactivity experiments were not reacted with a carbonyl acceptor, it cannot be stated that these reactivities apply to formation of the Reformatsky intermediate. Bernstein[36] developed a method, using 9-fluorenone, for titrating the primary intermediate. This method could not be applied here because it relied on the yellow color of the ketone for an end point, which would not have been visible in these mixtures. He reported that 69 to 74% of the consumed α-halocarbonyl could be accounted for as the primary intermediate (bromozinc enolate), using his titration method. The validity of applying this to reactions involving iron has not been shown; however, the low yield of Wurtz-type products indicates a parallel situation. With an α-halocarbonyl that contains a proton on a β-carbon atom, which makes elimination reactions possible, the analogy would not be expected to hold.

The basic problem in working up a reaction that has been run in a dipolar aprotic solvent, such as DMF or NMP, is that these solvents are extremely soluble in both water and the normal organic solvents. In the classical Reformatsky work up the hydrolysis is accomplished by pouring the reaction mixture into an acid solution and then stirring. The product remains with the organic phase and is separated after hydrolysis. Any product remaining in the water phase can be extracted with a low boiling immiscible solvent and added to the organic phase. The product is obtained by evaporation and distillation.

In working up the reactions done in this work there were other problems as well. Both the Reformatsky intermediate hydrolysis product (reduced starting α-halocarbonyl) and the Reformatsky addition reaction hydrolysis product (β-hydroxy carbonyl) are very soluble in polar solvents. Outwardly, distillation would seem to be the answer; however, by the time the tarry mixture has been poured into dilute acid and the acid neutralized the mixture is extremely difficult to work with. This is particularly true because the mixture now has a high content of inorganic salts in and out of solution.

There is also a problem in the monitoring of these reactions by GLC. The injection block of the chromatograph is at a high temperature (250° for these analyses) and reactions can take place here or on the columns. For the analysis to be quantitative it is necessary to have a direct relationship between the material placed on the injection block and the response of the instrument to the components of the material; i.e., the chromatogram. For example, the fate of the unhydrolyzed organometallic intermediates has not been determined and no GLC experiments were done to determine the extent to which dehydration reactions take place in the chromatograph.

Although Hall and DePuy[30] report moderate success in isolating a final product, 4-phenyl-3-butene-2-one, by ether extraction of the hydrolysis mixture, this method failed to give comparable results when applied to isolating hydrolyzed intermediates in this work. Steam distillation was slightly better than ether extraction for isolating hydrolyzed intermediates but cannot be termed successful. When steam distillation was used to isolate final product, the results were disappointing.

Failure to find an effective work-up procedure was central to not being able to investigate the thesis problem more deeply; i.e., there was no effective way of determining yields of hydrolyzed intermediates and products so the solvent conditions, temperatures, reaction times, etc. could not be optimized.

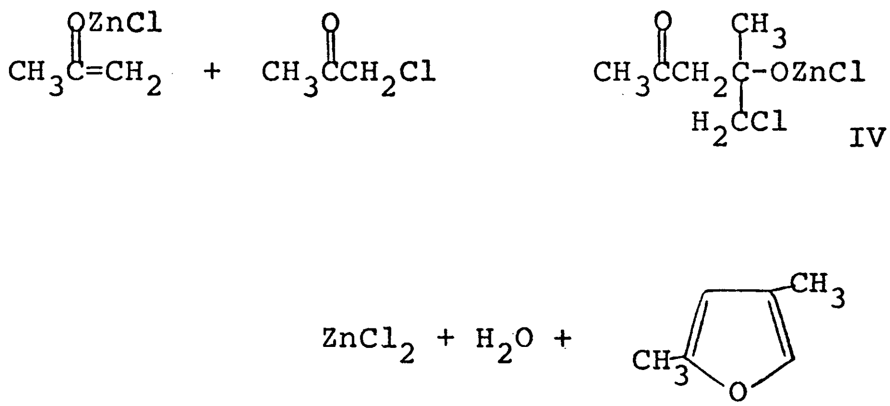
The separation of complexed polar solvent from inert solvent, as occurred in the furan reactions, was noted too late in the work to allow investigation of iron reactions in this medium. It is the author's opinion that if the iron-polar solvent system is made into a feasible reaction, it will be by this method.

The method seems ideal as the inert solvent, containing the product, can be decanted or distilled from the complexed metal (tar). The decantated material can then be fractionated or treated as in the classical Reformatsky work-up procedure.

A trace of Reformatsky product, 2,4-diethyl-3,5-dimethylfuran, in the reaction of 2-bromo-3-pentanone with iron in DMSO-benzene solvent is not outstanding but is enough to encourage further experimentation with the mixed solvent systems. That decomposition, or an elimination reaction followed by polymerization, is what is accounting for the consumption of 2-bromo-3-pentanone is borne out by the disappearance of this compound in a simple mixture of dipolar aprotic solvent at 130° (Decomposition of α-Halocarbonyl Experiments).

That 5-chloro-4-hydroxy-4-methyl-2-pentanone was reported in the earlier chloroacetone-iron-dipolar aprotic solvent work[30] is interesting. This compound is the equivalent of what would be the hydrolyzed form of Ryang's intermediate (formula 12) in furan formation. The unhydrolyzed

SCHEME IV



product (structure IV) is shown in the reaction outlined in Scheme IV. It is possible that 5-chloro-4-hydroxy-4-methyl-2-pentanone could also form the furan; the products being 2,4-dimethylfuran, H_2O and HCl.

Another possible explanation of what is taking place in this reaction is the reaction of the bromozinc enolate with acetone. Acetone was a demonstrable by-product in the earlier experimental work with chloroacetone. The product of this reaction would be 4-methyl-4-hydroxy-2-pentanone. However, the electron withdrawing effect of the chlorine atom of chloroacetone would be expected to make chloroacetone the more reactive electrophile.

The paper that led to the furan work[26] was found at a late date in this project. This is unfortunate since there seems to be a great deal of interesting chemistry here and time did not allow even the proper completion of the few experiments the investigator was able to make. Before any further speculation is attempted, the reaction should be run on a quantitative basis, which was not done in these experiments.

From the earlier chloroacetone work[30] it is known that chloroacetone is stable in NMP (120° for 16 hr gave no change in composition). Because chloroacetone has been shown to be stable in a ferrous chloride solution of NMP, in this work, the products and by-products of the chloroacetone reaction all seem to involve zerovalent iron. The reaction should be run with anhydrous ferrous chloride to prove this.

The decomposition, or elimination reaction, of 2-bromo-3-pentanone appears to be autocatalytic as it decomposed while standing in the pure state (Reagents and Solvents). Parker[37] mentions that higher homologues of α-halocarbonyl compounds eliminate HX in dipolar aprotic solvents.

BIBLIOGRAPHY

1. R. Fittig and C. Daimler, Ueber die Einwirkung von Chloressigsäureäther und Zink auf Oxaläther: Ber., 20, 202 (1887).

2. S. Reformatsky, Neue Synthese zweiatomiger einbasischer Säuren aus den Ketonen: Ber., 20, 1210 (1887).

3. S. Reformatsky, Action of zinc and ethyl chloroacetate on ketones and aldehydes: J. Chem. Soc., 60, 169 (1891).

4. S. Reformatsky, Die Einwirkung eines Gemengens von Zink und Bromoisobuttersäureester auf Isobutyraldehyd: Ber., 28, 2842 (1895).

5. S. Reformatsky, Ueber die Einwirkung von Jodpropyl und Zink auf Butyron: J. Prakt. Chem., 54, 469 (1896).

6. G. Dain, title unavailable: J. Russ. Phys. Chem. Soc., 28, 543 (1889); see reference 7.

7. J. Dippy and J. Parkins, An investigation of the course of the Reformatsky reaction: J. Chem. Soc., 1570 (1951).

8. M. Newman, Enolization in the Reformatsky reaction: J. Am. Chem. Soc., 64, 2131 (1942).

9. A. Hussey and M. Newman, Some observations on the Reformatsky reaction: J. Am. Chem. Soc., 70, 3024 (1948).

10. R. Miller and F. Nord, Studies on the scope of the Reformatsky reaction: J. Org. Chem., 16, 728 (1951).

11. E. McBee, O. Pierce and D. Christman, The Reformatsky reaction with ethyl bromofluoroacetate: J. Am. Chem. Soc., 77, 1581 (1955).

12. R. Fuson and N. Thomas, Extension of the Reformatsky reaction to new types of compounds: J. Org. Chem., 18, 1762 (1953).

13. M. Newman and F. Evans, The Reformatsky reaction: Effect of alkyl group in alkyl α-bromopropionates: J. Am. Chem. Soc., 77, 946 (1955).

14. H. Zimmerman and M. Traxler, The stereochemistry of the Ivanov and Reformatsky reactions: J. Am. Chem. Soc., 79, 1920 (1957).

15. L. Canonica, F. Pelizzoni and E. Fedeli, Reazioni di Reformatzky. - Nota V. ancora sugli aspetti stereochimici della reazione di Reformatzky: Gazz. Chim. Ital., 85, 130 (1955); see reference 14.

16. W. R. Vaughan, S. C. Bernstein and M. E. Lorber, The Reformatsky reaction. I. Zinc and ethyl α-bromoisobutyrate: J. Org. Chem., 30, 1790 (1965).

17. M. Gaudemar, Préparation et structure des complexes de Reformatsky issus des mono et dibromo malonates d'ethyle: Bull. Soc. Chim. France, 1966, #10, 3113.

18. M. Gaudemar and J. Cure, Sur la préparation la structure et les propriétés des complexes de Reformatsky: C. R. Acad. Sci., Paris, Ser. C, 262, 213 (1966).

19. J. Cure and M. Gaudemar, Sur la préparation, la structure et la réactivité du complexe de Reformatsky issu du N-diéthylbromacetamide: C. R. Acad. Sci., Paris, Ser. C, 264, 97 (1967).

20. H. O. House, Modern synthetic reactions: New York, W. H. Benjamin, chap. 8, p. 242 (1965).

21. R. Shriner, Organic reactions: New York, John Wiley & Sons, Inc., vol. 1, chap. 1, pp. 1-37 (1942).

22. J. G. Noltes, Zinc, annual survey covering the year 1967: Organometal. Chem. Rev. B, 4, 233 (1968).

23. L. Kh. Vinograd and N. S. Vul'fron, The Reformatsky reaction with α-halonitriles: Zhur. Obshchei Kihm., 29, 2690 (1959); Chem. Abstr., 54, 10940e (1960).

24. P. R. Jones and J. R. Young, Organocadmium reagents. V. Reaction with α-halo esters and ketones: J. Org. Chem., 33, 1675 (1968).

25. R. Miller and F. Nord, The application of the Reformatsky reaction to thiophene aldehydes and ketones: J. Org. Chem., 15, 89 (1950).

26. T. A. Spencer, R. W. Britton and D. S. Watt, Chemistry of enolates from zinc reduction of α-bromo ketones: J. Amer. Chem. Soc., 89, 5727 (1967).

27. J. D. Dubois and J. Itzkowitch, Furannisation et cetolisation mixtes inversees par echange "metal-hydrogene" entre enolate et cetone: Tetrahedron Lett., 2839 (1965).

28. M. Ryang, Metal carbonyls as stoichiometric reagents in organic synthesis: Organometal. Chem. Rev. A, 5, 67 (1970).

29. D. W. Hall and E. Hurley, Jr., Coupling of allylic halides promoted by iron metal dispersed in dimethyl formamide: Can. J. Chem., 47, 1238 (1969).

30. D. W. Hall and C. H. DePuy (to Marathon Oil Company), Chemical process for the production of carbonyl addition compounds: U. S. Patent 3,481,986 (Dec. 2, 1969).

31. J. F. Arens and D. A. Van Dorp, Some observations on the reactions of bromoacetone and bromoacetaldehyde and their acetals with metals: Rec. Trav. Chim., 65, 729 (1946); Chem. Abstr., 41, 5442 (1947).

32. Y. S. Kim, Reactions of organic halogen compounds with metals: Daehan Hwahak Howoejee, 7, #3, 216 (1963); Chem. Abstr., 62, 4047a (1965).

33. B. N. Afanosyev and P. A. Tsyganova, Reaction of metallic iron with ethyl bromide: Chem. Abstr., 45, 6109 (1951).

34. H. Pauly, Veber bromderivate des diaethylketons: Ber., 34, 1771 (1901).

35. C. Rappe and R. Kumar, Preparation of α-bromoketones using N-bromosuccinimide: Arkiv. för Kemi, 23, 475 (1965).

36. S. C. Bernstein, An investigation of the Reformatsky reaction: University of Michigan, Ann Arbor, Mich., (1963).

37. A. J. Parker, Dipolar Aprotic solvents as media for nucleophilic substitution reactions at a saturated carbon atom: J. Chem. Soc., 1328 (1961).