

066
Organic Reactions

VOLUME I

EDITORIAL BOARD

ROGER ADAMS, *Editor-in-Chief*

WERNER E. BACHMANN

JOHN R. JOHNSON

LOUIS F. FIESER

H. R. SNYDER

ASSOCIATE EDITORS

A. H. BLATT

CHARLES R. HAUSER

F. F. BLICKE

MARLIN T. LEFFLER

NATHAN L. DRAKE

ELMORE L. MARTIN

REYNOLD C. FUSON

RALPH L. SHRINER

LEE IRVIN SMITH

JOHN WILEY & SONS, INC.
LONDON: CHAPMAN & HALL, LIMITED



E
1

COPYRIGHT, 1942

BY

ROGER ADAMS

All Rights Reserved

*This book or any part thereof must not
be reproduced in any form without
the written permission of the publisher.*

FIFTH PRINTING, APRIL, 1954

PRINTED IN THE UNITED STATES OF AMERICA

PREFACE

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. Volume I of *Organic Reactions* is a collection of twelve chapters, each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories. When all known examples of the reaction are not mentioned in the text, tables are given to list compounds which have been prepared by or subjected to the reaction. Every effort has been made to include in the tables all such compounds and references; however, because of the very nature of the reactions discussed and their frequent use as one of the several steps of syntheses in which not all of the intermediates have been isolated, some instances may well have been missed. Nevertheless, the

investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the book will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the index have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the index.

The success of this publication, which will appear periodically in volumes of about twelve chapters, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

CONTENTS

CHAPTER	PAGE
1. THE REFORMATSKY REACTION— <i>Ralph L. Shriner</i>	1
2. THE ARNDT-EISTERT SYNTHESIS— <i>W. E. Bachmann and W. S. Struve</i>	38
3. CHLOROMETHYLATION OF AROMATIC COMPOUNDS— <i>Reynold C. Fuson and C. H. McKeever</i>	63
4. THE AMINATION OF HETEROCYCLIC BASES BY ALKALI AMIDES— <i>Marlin T. Leffler</i>	91
5. THE BUCHERER REACTION— <i>Nathan L. Drake</i>	105
6. THE ELBS REACTION— <i>Louis F. Fieser</i>	129
7. THE CLEMMENSEN REDUCTION— <i>Elmore L. Martin</i>	155
8. THE PERKIN REACTION AND RELATED REACTIONS— <i>John R. Johnson</i>	210
9. THE ACETOACETIC ESTER CONDENSATION AND CERTAIN RELATED REACTIONS— <i>Charles R. Hauser and Boyd E. Hudson, Jr.</i>	266
10. THE MANNICH REACTION— <i>F. F. Blicke</i>	303
11. THE FRIES REACTION— <i>A. H. Blatt</i>	342
12. THE JACOBSEN REACTION— <i>Lee Irvin Smith</i>	370
INDEX.....	385

CHAPTER 1

THE REFORMATSKY REACTION

RALPH L. SHRINER

Indiana University

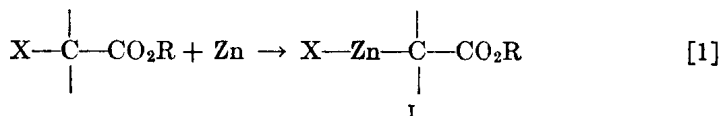
CONTENTS

	PAGE
GENERAL CONSIDERATIONS	2
Relative Reactivities of Reagents	4
Side Reactions	4
THE USE OF THE REFORMATSKY REACTION	5
Lengthening the Carbon Chain	6
Synthesis of Arylacetic Acids	9
Synthesis of β -Ketoesters	9
DEHYDRATION OF THE β -HYDROXYESTERS	11
Table I	13
SELECTION OF EXPERIMENTAL CONDITIONS. PROCEDURES	14
Ethyl β -Phenyl- β -hydroxypropionate	16
Ethyl 1-Hydroxycyclohexylacetate	17
Ethyl α -Methyl- β -phenyl- β -hydroxybutyrate	17
Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1-hydroxy-1,2,3,4-tetra- hydrophenanthrene-1-acetic Acid	18
EXAMPLES OF THE REFORMATSKY REACTION	19
Aldehydes. Table II	20
Ketones. Table III	24
Esters. Table IV	33
Substituted Amides	34
VARIATIONS OF THE REFORMATSKY REACTION.	34
Use of Halogen Compounds Other Than α -Haloesters	34
Table V	35
Use of Compounds Other Than Carbonyl Derivatives	36

GENERAL CONSIDERATIONS

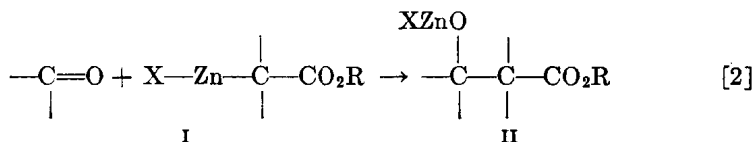
The reaction which takes place between a carbonyl compound such as an aldehyde, a ketone, or an ester and an α -haloester in the presence of zinc is commonly known as the Reformatsky reaction.¹ It represents an extension of the reactions of carbonyl compounds with a dialkylzinc or an alkylzinc halide, but possesses the advantage that the isolation of the organozinc compound is unnecessary. The process creates a new carbon-carbon linkage and appears to involve the following steps.²

1. Formation of an organozinc halide.

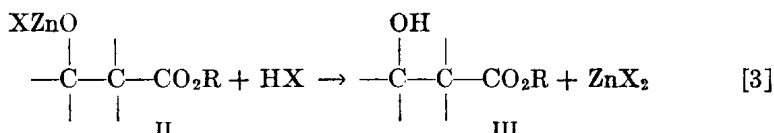


(X represents Cl, Br, I; R is an alkyl group.)

2. Addition to the carbonyl group of the aldehyde or ketone.

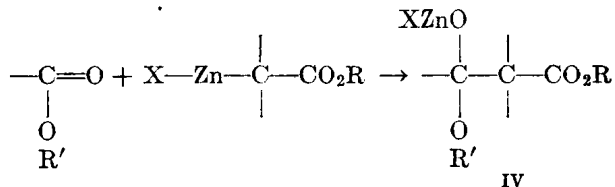


3. Decomposition by dilute acids.



Thus an aldehyde or a ketone leads to a β -hydroxyester (III) as the final product. Subsequent or simultaneous dehydration may produce an unsaturated ester.

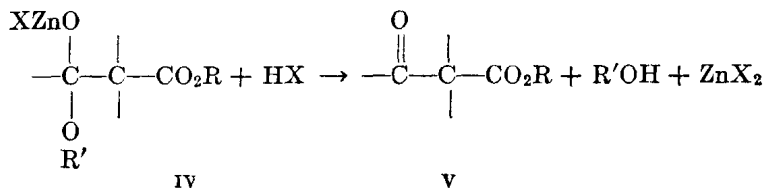
When an ester is used instead of an aldehyde or ketone the addition product IV is formed.



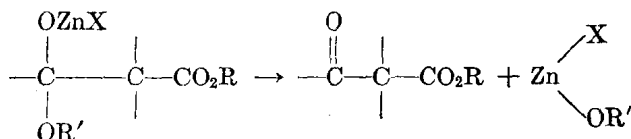
¹ Reformatsky, *Ber.*, **20**, 1210 (1887).

² Reformatsky, *J. prakt. Chem.*, **54**, 469 (1896).

If this addition complex is stable, then the product obtained by hydrolysis of the reaction mixture is a β -ketoester.

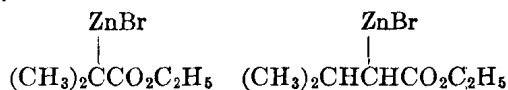


If the addition product decomposes spontaneously, the β -ketoester (V) may again be the final product.

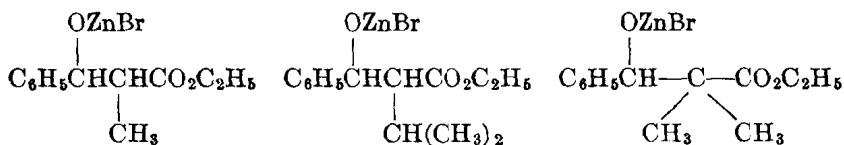


If the keto group in this ketoester is reactive and an excess of the organozinc halide (I) is present, further reaction may take place as in equation 2 above.

Evidence for the existence of the organozinc halide (I) as an intermediate was provided by G. Dain,³ who isolated and analyzed the following compounds.



Three addition products corresponding to the complex II were also obtained.



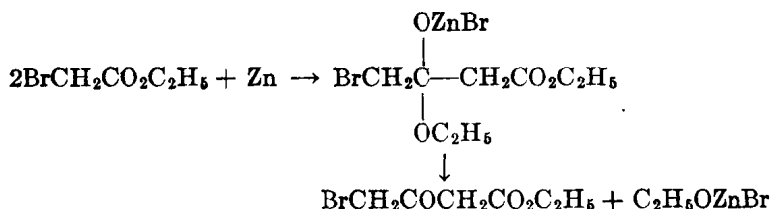
These complexes, therefore, parallel the intermediates formed in the well-known reactions involving the Grignard reagent or similar organometallic halides and carbonyl compounds. Indeed, magnesium may be used in place of zinc (p. 16), and apparently the intermediate complexes are analogous. Grignard reagents cannot be prepared from α -haloesters and magnesium alone; hence the Reformatsky reaction offers a pro-

³ Dain, *J. Russ. Phys. Chem. Soc.*, **28**, 593 (1896).

cedure by which the equivalent of a Grignard reagent from an α -haloester is available for synthetic work. In the subsequent discussion these intermediates will not always be written and only the reactants and main products will be shown. It is to be understood, however, that the steps shown above are always involved.

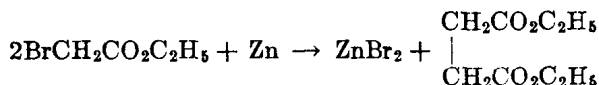
Relative Reactivities of Reagents. The order of reactivity of carbonyl compounds in the Reformatsky reaction is $\text{RCHO} > \text{R}_2\text{CO} > \text{RCO}_2\text{-C}_2\text{H}_5$. The order of reactivity of the haloacetates is $\text{ICH}_2\text{CO}_2\text{C}_2\text{H}_5 > \text{BrCH}_2\text{CO}_2\text{C}_2\text{H}_5 > \text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5$. The α -chloroacetic esters often react slowly or not at all, and the α -iodoesters are not readily available. Consequently, most Reformatsky reactions have been carried out with the α -bromoesters. Esters containing a secondary or tertiary α -chlorine atom are much more reactive than the corresponding primary derivatives and in some cases are reported to give good yields. The three types of α -bromoesters appear to react equally well.

Side Reactions. Various side reactions may be expected whenever the Reformatsky reaction is carried out. The intermediate organozinc halide may add to the carbonyl group of the α -haloester used as the reagent; for example, Hann and Lapworth^{4a} have reported that zinc and ethyl bromoacetate react to produce ethyl γ -bromoacetoacetate.



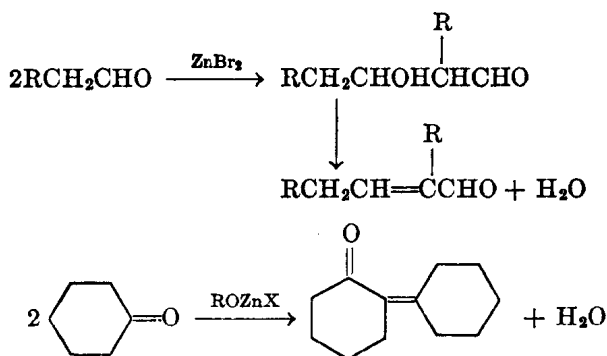
Since aldehydes and ketones possess far greater carbonyl reactivity than the ester group, this side reaction is not important when aldehydes and ketones are used. Moreover, its significance may be minimized by using an excess of the bromoester and adding the latter in successive portions.

A common side reaction is the coupling of the haloester by the zinc.

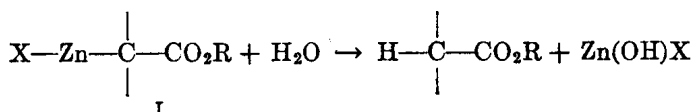


When aliphatic aldehydes or aliphatic or alicyclic ketones are used, these may undergo aldolization under the influence of the zinc salts.

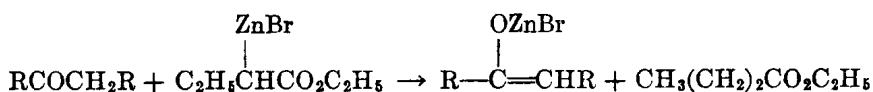
^{4a} Hann and Lapworth, *Proc. Chem. Soc.*, **19**, 189 (1903).



Not only does aldolization use up the aldehyde or ketone, but also the dehydration of the aldol produces water which decomposes the intermediate organozinc halide (I).



The organozinc compound may also induce enolization.^{4b}



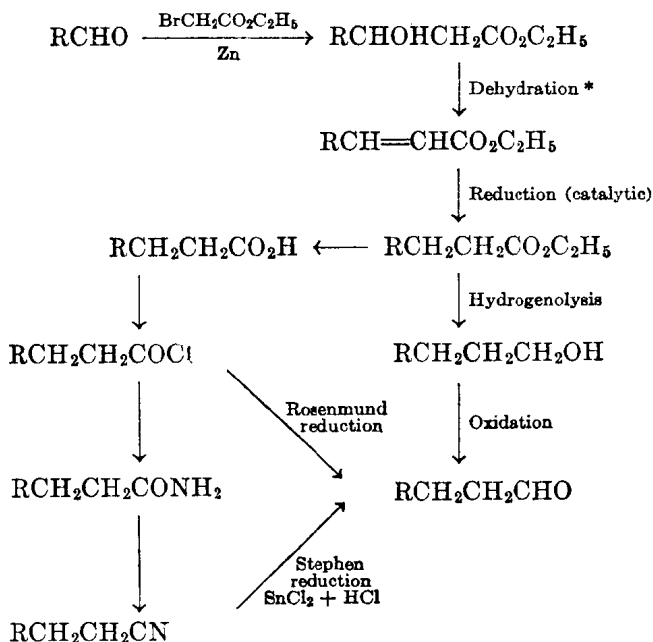
Subsequent hydrolysis of the bromozinc enolate regenerates the original ketone. This reaction accounts for the recovery of appreciable amounts of the starting material and the presence of ethyl *n*-butyrate among the reaction products.

THE USE OF THE REFORMATSKY REACTION

From a synthetic point of view the Reformatsky reaction not only constitutes a method for preparing β -hydroxyesters and the corresponding unsaturated esters and acids but also is a valuable procedure for lengthening the carbon chain by two carbon atoms. The chain may be branched on the α -, β -, or α - and β -carbon atoms by proper choice of reactants. Since the product contains the carbethoxy group, it is possible by a proper sequence of reactions to repeat the chain-lengthening process. Several examples have been chosen to illustrate the utility of the condensation and to point out the part played by the Reformatsky reaction in a synthetic sequence.

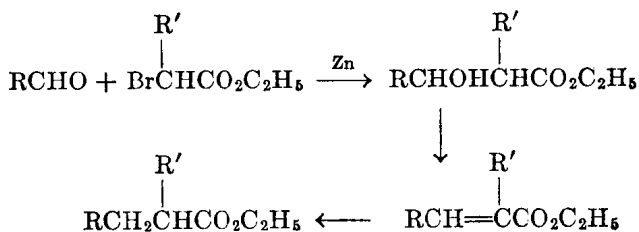
^{4b} Newman, *J. Am. Chem. Soc.*, **62**, 870 (1940).

Lengthening the Carbon Chain. *Lengthening the Carbon Chain of an Aldehyde without Branching the Chain.*

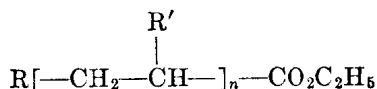


The process may be repeated, leading to $\text{R}(\text{CH}_2)_4\text{CHO}$.

Lengthening the Carbon Chain with Branching on the α -Carbon Atom.

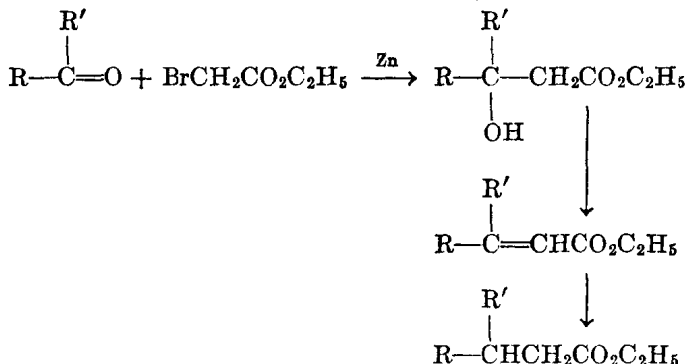


Use of the sequence of reactions outlined under the first example to convert the ester group into an aldehyde group leads to the synthesis of branched-chain esters of the following type.

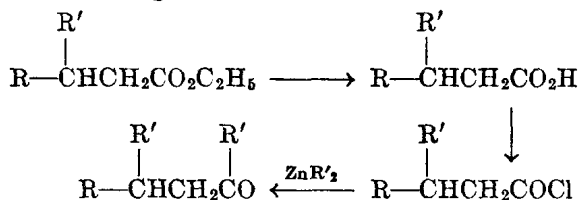


* The dehydration of β -hydroxyesters frequently produces a mixture of α,β - and β,γ -unsaturated esters (see p. 12). Both may be reduced catalytically to the saturated ester.

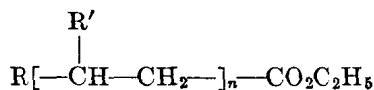
Lengthening the Carbon Chain with Branching on the β -Carbon Atom.



The ester group of the final product may be converted into a keto group by the following reactions.

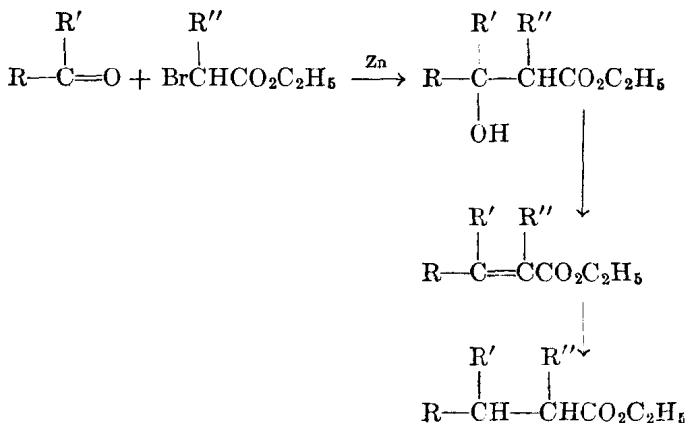


Repetition of these sequences of reactions leads to the preparation of a second type of branched-chain ester.



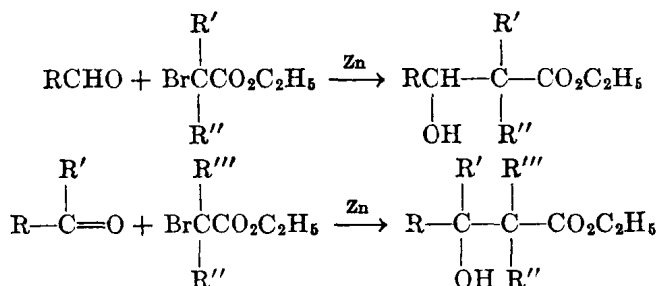
The nature of the R' group is determined by the starting ketone and the zinc alkyl used in converting the acid chloride into the final ketone. The R' groups may be alike or different.

Lengthening the Carbon Chain with Branching on Both α - and β -Carbon Atoms.



The nature of the R and R' groups is determined by the ketone and that of the R'' group by the haloester.

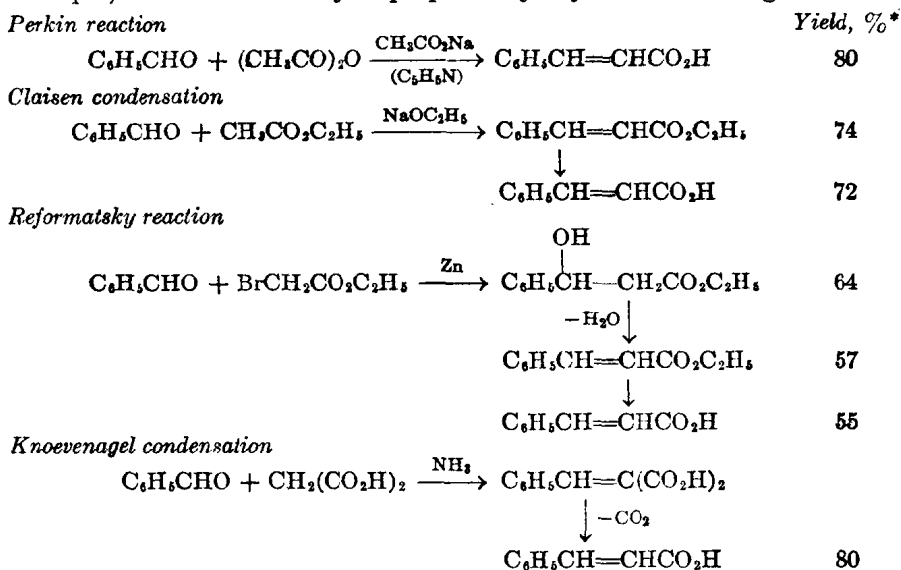
Lengthening the Carbon Chain with Double Branching on the α -Carbon Atom.



Occasionally, hydroxyesters of this type may be dehydrated to β,γ -unsaturated esters which can then be reduced to the saturated esters. However, conversion of these α,α -disubstituted- β -hydroxyesters to the saturated esters is usually best effected by refluxing with phosphorus and hydriodic acid.

These five general types of reactions therefore constitute methods for synthesizing straight-chain and branched-chain hydroxyesters and unsaturated and saturated esters and acids.

Whether or not the Reformatsky reaction is the best method for lengthening a given carbon chain depends on a number of factors. For example, cinnamic acid may be prepared by any of the following reactions.



*These figures represent the over-all yields of the products shown, based on benzaldehyde.

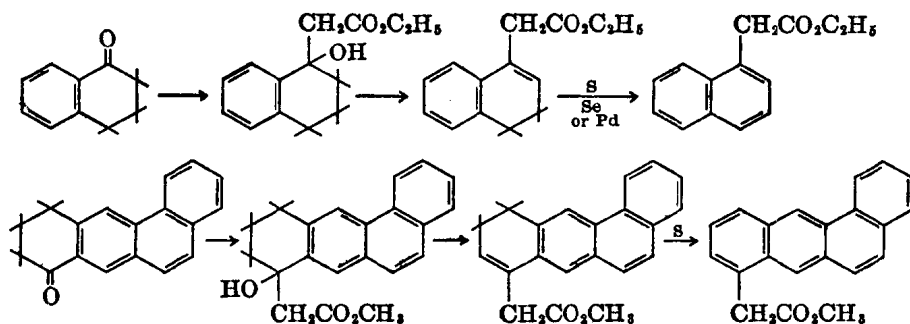
On the basis of yields alone, the Knoevenagel or Perkin condensation would be preferred for preparing cinnamic acid. From an economic point of view, the reaction chosen would depend on the relative cost of the reagents and the time involved in the preparation. The Reformatsky reaction would not be selected.

However, in the synthesis of an unsaturated acid with branching on the β -carbon atom ($\text{C}_6\text{H}_5\text{C}=\text{CHCO}_2\text{H}$) from the ketone ($\text{C}_6\text{H}_5\text{COR}$)



the Reformatsky is the only method of these four which will give good yields; the Perkin reaction fails to take place, the Claisen condensation leads to an entirely different product (a 1,3-diketone), and the Knoevenagel condensation gives low yields for small R groups and fails if R is large. Branching of the chain on both α - and β -carbon atoms can be accomplished only by the Reformatsky method.

Synthesis of Arylacetic Acids. The Reformatsky reaction is also particularly well adapted to the synthesis of arylacetic acids or their esters. Thus, ketones such as 1-tetralone or 1-ketotetrahydrophenanthrene⁵ give hydroxyesters which are readily dehydrated to dihydroarylacetic esters. The latter may be easily dehydrogenated to the aromatic compounds.

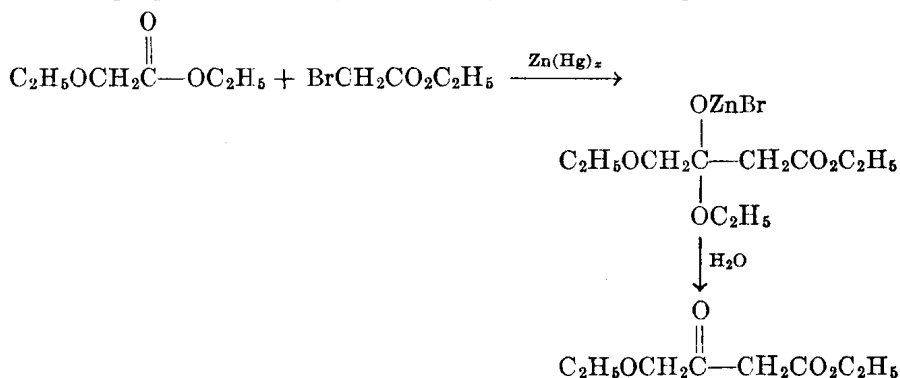


Synthesis of β -Ketoesters. Very few applications of the Reformatsky reaction to the synthesis of β -ketoesters by reactions involving the carbonyl group of an ester are recorded. Ethyl γ -bromoacetoacetate is formed by the action of zinc or magnesium on ethyl bromoacetate.^{4a} Hamel⁶ reported 56% yields of ethyl γ -chloroacetoacetate by the action of amalgamated magnesium on ethyl chloroacetate. Ethyl γ -ethoxyacetoacetate has been prepared in 10 to 33% yields from ethyl ethoxy-

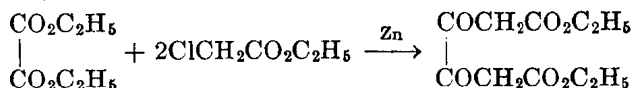
⁵ Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

⁶ Hamel, *Bull. soc. chim.*, [4] **29**, 390 (1921); Stolle, *Ber.*, **41**, 954 (1908).

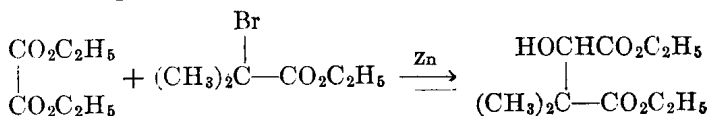
acetate and ethyl bromoacetate ⁷ by using amalgamated zinc. If ethyl α -bromopropionate is used, the α -methyl derivative is produced.⁸



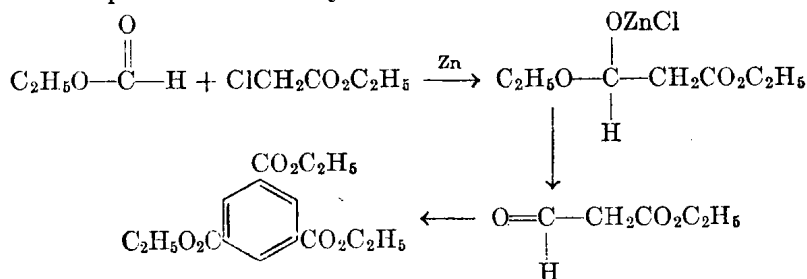
Ethyl 3,4-diketoadipate ⁹ has been obtained from ethyl oxalate, ethyl chloroacetate, and zinc.



On the other hand, ethyl α -bromoisobutyrate is reported to react with ethyl oxalate to form ethyl α,α -dimethylmalate.¹⁰ It is evident that reduction takes place during this reaction.



The chief product from ethyl formate, ethyl chloroacetate, and zinc is ethyl trimesate.¹¹ Ethyl formate undergoes the normal Reformatsky reaction to produce the aldehydoester which then trimerizes.



⁷ Sommelet, *Bull. soc. chim.*, [4] **29**, 553 (1921); *Compt. rend.*, **154**, 706 (1912).

⁸ Johnson, *J. Am. Chem. Soc.*, **35**, 582 (1913); Johnson and Chernoff, *J. Am. Chem. Soc.*, **35**, 585 (1913); **36**, 1742 (1914).

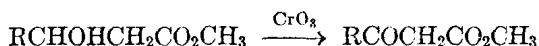
⁹ Fittig and Daimler, *Ber.*, **20**, 202 (1887).

¹⁰ Rassow and Bauer, *Ber.*, **41**, 963 (1908).

¹¹ Reformatsky, *J. Russ. Phys. Chem. Soc.*, **30**, 280 (1898); *J. prakt. Chem.*, **54**, 477 (1896).

With ethyl α -bromopropionate, the presence of the α -methyl group in the intermediate aldehydoester prevents the trimerization. Hence a second Reformatsky reaction occurs leading to ethyl 2,4-dimethyl-3-hydroxyglutarate.¹² Ethyl α -bromoisobutyrate, ethyl formate, and zinc react in a similar fashion to produce ethyl 2,2,4,4-tetramethyl-3-hydroxyglutarate.¹³

Oxidation* of the β -hydroxyesters, obtained by the Reformatsky reaction on aldehydes, by means of the calculated amount of chromic acid in glacial acetic acid as the solvent, produces β -ketoesters in low yields (30–50%).



Thus, β -ketoesters with no α -substituents may be obtained. This is useful since the Claisen condensation of esters (other than ethyl acetate) yields α -substituted β -ketoesters (see Chapter 9).

DEHYDRATION OF THE β -HYDROXYESTERS

If the temperature of the reaction mixture is high it occasionally happens that the product from the Reformatsky reaction is the unsaturated ester. However, if the reaction is run in the usual solvents, such as ether or benzene (p. 15), the chief constituent of the reaction mixture is the hydroxyester. Because of their tendency to lose water during distillation or saponification,¹⁴ the β -hydroxyesters and their derivatives can sometimes be isolated in the pure state only with difficulty and in poor yields, whereas dehydration of the crude reaction mixtures leads to higher yields of the unsaturated products.

Dehydration may be accomplished by heating the β -hydroxyester with acetic anhydride, acetic anhydride and acetyl chloride,¹⁵ fused potassium acid sulfate,¹⁶ 85% formic acid,¹⁷ anhydrous formic acid,^{5, 18, 19} zinc chloride in acetic acid,²⁰ or sulfuric acid²¹ of various strengths (20 to

*See p. 22, reference 48.

¹² Reformatsky, *Ber.*, **28**, 3262 (1895).

¹³ Blaise, *Compt. rend.*, **126**, 1808 (1898).

¹⁴ Schroeter, *Ber.*, **37**, 1090 (1904); **40**, 1589 (1907).

¹⁵ Stoermer and Frederici, *Ber.*, **41**, 324 (1908).

¹⁶ Wallach, *Ann.*, **365**, 255 (1909).

¹⁷ Rupe, *Ann.*, **369**, 321 (1909).

¹⁸ Cook, *J. Chem. Soc.*, 2524 (1931); Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2971 (1940).

¹⁹ Bergmann and Bograchov, *J. Am. Chem. Soc.*, **62**, 3617 (1940).

²⁰ Wallach, *Ann.*, **314**, 147 (1901); Tetry, *Bull. soc. chim.*, [3] **27**, 600 (1902).

²¹ Jaworsky and Reformatsky, *Ber.*, **35**, 3633 (1902).