
: CHAPTER - I :

THE REFORMATSKII REACTION

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INTRODUCTION

The Reformatskii reaction is mild and versatile tool useful in Synthetic Organic Chemistry for the formation of carbon-carbon bonds. The Reformatskii reaction is the reaction of a carbonyl compound, usually an aldehyde or ketone, with an α -halo ester in the presence of zinc metal to yield, after hydrolysis,¹ a β -hydroxyester is routinely carried out to form an α,β -unsaturated ester. The literature pertaining to the Reformatskii reaction has been well documented²⁻⁵.

The course of the Reformatskii reaction with carbonyl compound is usually formulated as shown in the equations (1.2). Strong evidence exists for the formation of zinc alkoxides corresponding to (1.2). A number of these salts obtained from reactions of ethyl bromoacetate or ethyl α -bromo propionate with aldehydes and ketones have been isolated as pale-yellow solids with satisfactory analysis.

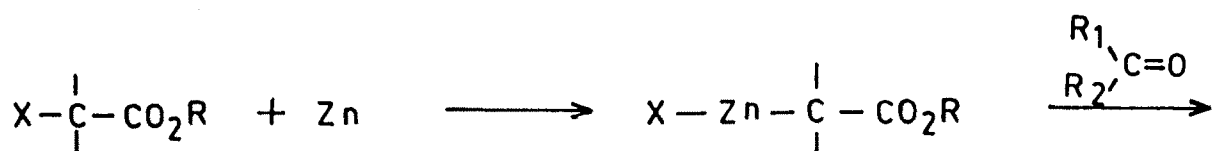
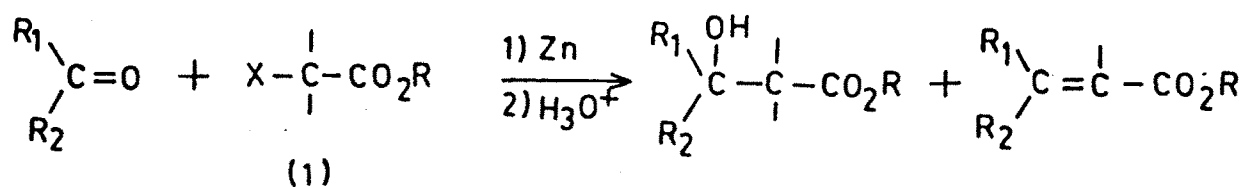
The Reformatskii reagent (1.5) is usually formulated with a zinc-carbon bond (1.3) because it reacts as a carbon rather than oxygen nucleophile. However, another formation i.e. zinc-oxygen bonded enolate (1.4) is possible. Reformatskii reaction is not a single step reaction² as it was thought initially. It was proved later on that two step process is possible⁶ with initial formation of Reformatskii reagent followed by its

addition to the carbonyl substrate. The infrared spectrum of the reagent obtained from ethyl α -bromoisobutyrate and zinc metal in an ether-benzene solvent possesses a strong band at 1525 cm^{-1} suggesting a zinc-oxygen bond⁷. A relatively weak band is observed in the ester carbonyl region (1730 cm^{-1}) and is due to unreacted bromoester. The chemical behaviour of the Reformatskii reagent (1.5) is completely analogous to that of the corresponding magnesium reagent (1.6), assumed to exist in enolate form^{8,16}. The adjacent carbonyl group can delocalise the negative charge on the carbon, so that the nucleophile is best described as zinc enolate. The enolate can then carry out a nucleophilic attack on the carbonyl group, in the same way, as an enolate formed by a deprotonation process. From nuclear magnetic resonance and infrared data obtained in a variety of solvents, carbon-bonded structures analogous to (1.3) are postulated for the reagent obtained from zinc and ethyl bromoacetate.

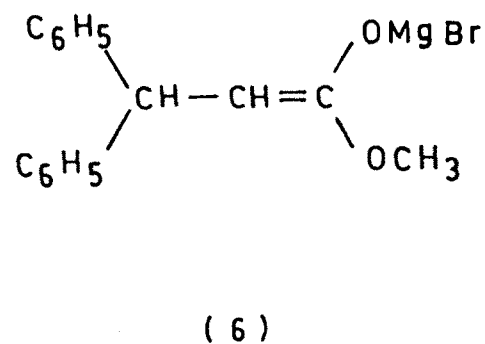
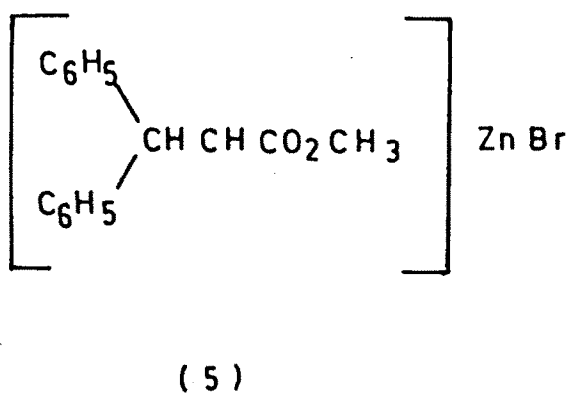
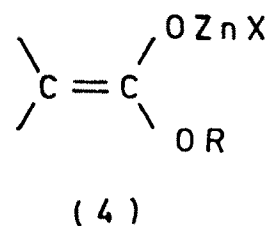
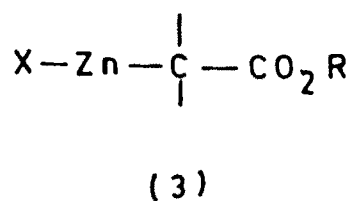
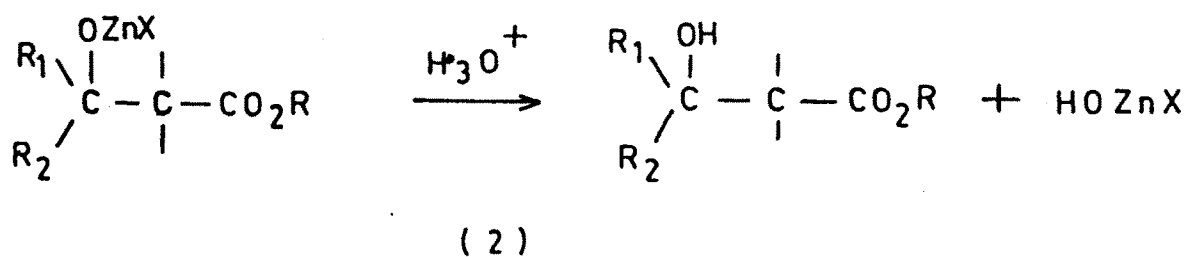
The reaction of optically active methyl α -bromopropionate with zinc and aromatic aldehydes produces optically active esters⁹. The structures of the products correspond to inversion at the asymmetric carbon. The preservation of optical activity estimated to be about 5% is explained by carbon-bonded structures analogous to (1.3) for the intermediate.

The Reformatskii reaction is subject to a number of side reactions. The most common side reactions are probably those of

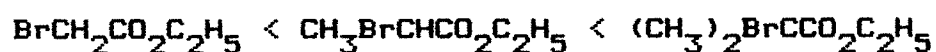
CHART-1



$X = \text{Cl, Br, I}$
 $R = \text{alkyl}$



the reagent with the carbonyl component to generate an aldehyde or ketone enolate or reaction to form β -ketoesters derived from the starting haloester. The importance of this condensation reaction is reported to increase in the order :



Reformatskii reagents prepared from ethyl α -bromo isobutyrate (2.1) and from methyl-2-bromo-3, 3-diphenyl propanoate (2.3) undergo a slow dimerization on heating or standing for long time^{7,8} to yield (2.2) and (2.4) respectively. The reaction may proceed via a ketene intermediate which reacts with a second molecule of reagent to furnish the condensation product.

The Reformatskii reaction often gives poor yield with aliphatic aldehydes due to self condensation that takes place under basic reaction conditions.¹⁰ Reversal of the Reformatskii reaction^{11,12} after extended refluxing may also lead to decreased yields by eventual self-condensation of the starting carbonyl substrate (2.5).

SCOPE OF THE REACTION :

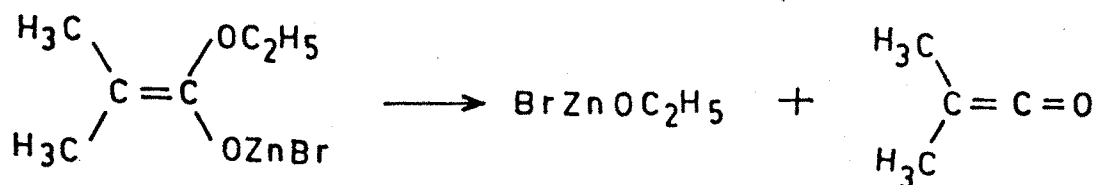
The Reformatskii reaction of α -haloester such as ethyl α -bromo propionate with aldehyde and ketones normally produces a mixture of two diastereomeric hydroxyesters¹³ (3.1) and (3.2). The various reaction conditions definitely affect

the ratio of erythro and threo isomers¹⁴⁻²¹. Most of the results can be rationalized with metal chelated structures of minimum steric interactions. The solvent appears to have a major influence on the ratio of isomers obtained. With rigid carbonyl systems, attack usually occurs from the less hindered side, as indicated from the predominance of exo isomer obtained from norborananone. Partial asymmetric synthesis of β -hydroxy esters have been obtained by the use of halo esters of optically active alcohols.

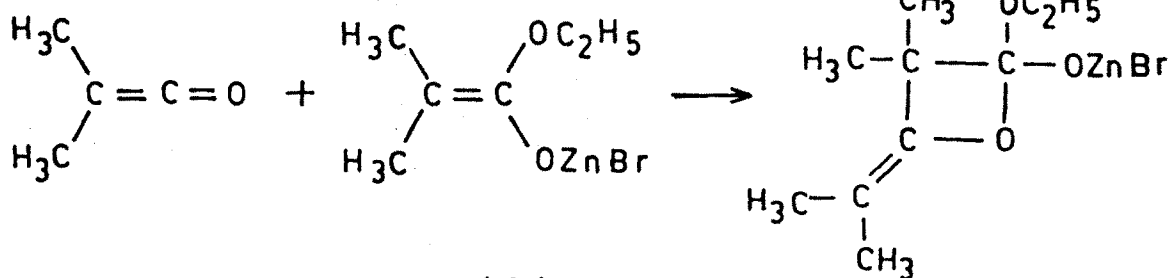
In a widely used procedure 20-mesh zinc metal²², zinc dust^{10,23} is used but freshly sand prepared zinc foil has also been used in Reformatskii reaction. The classical solvent for the Reformatskii reaction is benzene. With less reactive ketones, better yields are obtained in a mixture of benzene and ether. A mixed solvent of tetrahydrofuran and trimethyl borate provides increased yields of β -hydroxy esters from carbonyl compounds²⁴ susceptible to the self condensation. The zinc alkoxide formed in the reaction is neutralised by trimethyl borate. A mixed solvent of benzene and dimethoxy ethane is used for the Reformatskii reaction of keto acid.

The nature of the condensation product of the Reformatskii reaction of α,β -unsaturated haloesters was observed to change when the reaction solvent was changed from benzene or 1,2-dimethoxy ethane to ether. From the comparative results, Hudlicky and his group⁴² came to the conclusion that the tendency for ν -addition increases with decrease in polarity of

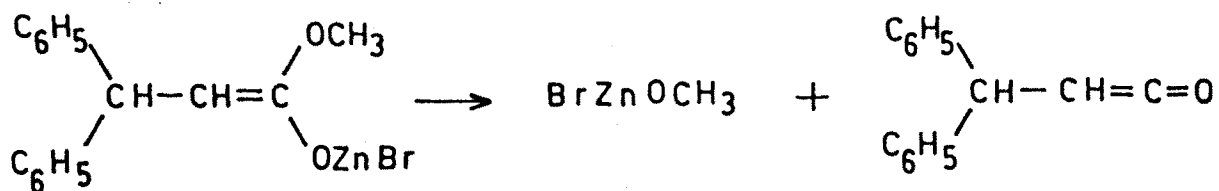
CHART-2



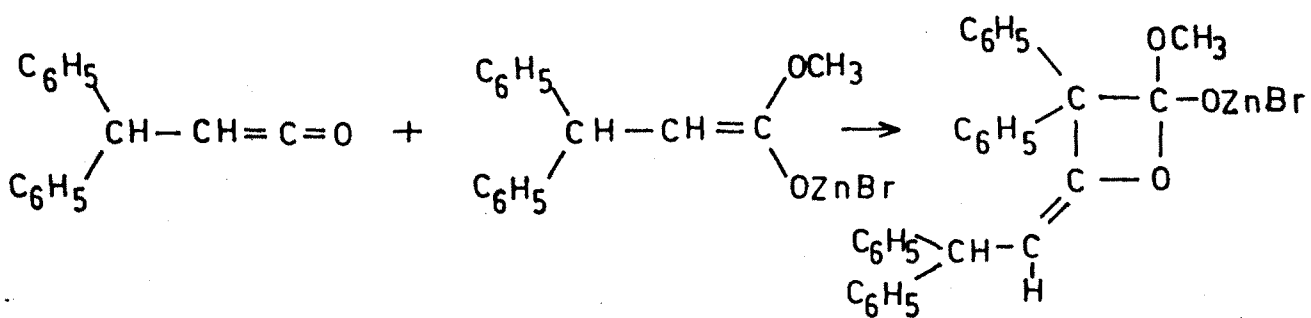
(1)



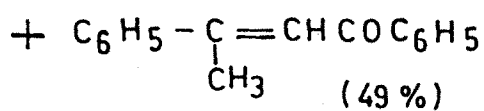
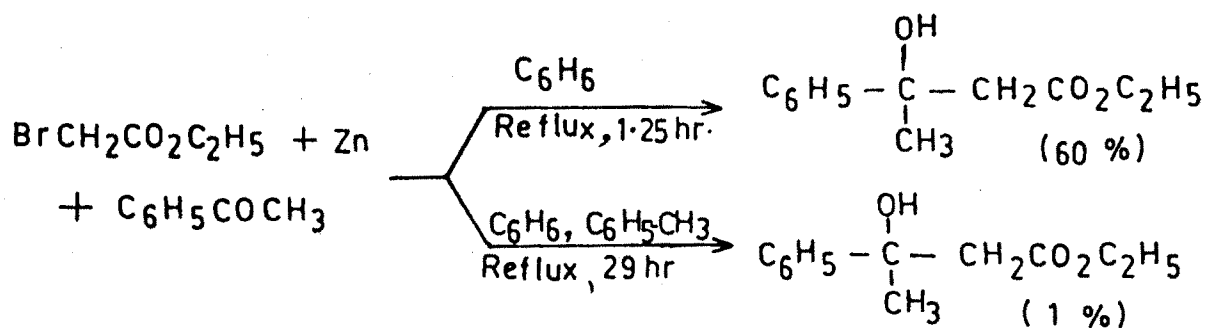
(2)



(3)



(4)



(5)

the solvent used. The exclusive α -addition can be obtained in ether by using Zn-Cu catalyst and traces of acetic acid while γ -addition predominates with anhydrous zinc in cyclohexane or tetrahydrofuran.

Thus variety of solvents have been utilised even though solvent like dimethyl ether, tetrahydrofuran, 1,4-dioxane or dimethoxy ethane are preferred. The mixture of these solvents with aromatic hydrocarbons or highly polar solvents like acetonitrile, dimethyl formamide (DMF), dimethyl acetamide, dimethyl sulfoxide (DMSO) or hexamethyl phosphoric triamide (HMPT) are selectively useful in specific transformations. Both the factors, the selection of proper solvent and the use of highly activated zinc helps to avoid various side reactions and to improve selectivity along with helping in preparation of separate zinc enolate.

In the Reformatskii reaction, the initial exothermic reaction can be controlled by the use of a suitable solvent. By proper selection of the solvent or solvent mixture, it is often possible to keep the addition product in solution or to cause it to crystallise so that it is more readily removed from the metal by the stirrer. Thus, there is no formation of an oily product which may coat the zinc and stop the reaction.

The Reformatskii reactions can be carried out by using any kind of metal or metal salt insertion into sufficiently reactive halocarbonyl compound to obtain any kind of metal enolate in place of zinc. In order to extend scope and

selectivity variety of other metals and metal salts have been studied⁵.

The use of magnesium metal in place of zinc in the Reformatskii reaction normally results in self condensation²⁵ of the haloester. But the use of t-butyl haloesters²⁶ overcomes this difficulty and some times gives better yields. A similar use of magnesium was reported earlier for reactions of substituted haloesters. Reformatskii reactions with lithium²⁷ aluminium²⁸ cadmium²⁹, nickel,³⁰ indium³¹, lanthanoid metals³², like La, Ce, Nd, Sm, Lanthanoid salts³³ of Ce and Yb, tin³⁴ and Mn metal³⁵ have also been reported. Zinc/Silver-graphite³⁶ is highly useful in more complex. Reformatskii reactions due to its high synthetic potential. Thus due to the extraordinary high reactivity of zinc/silver graphite it enhances the diastereoselectivity of carbon-carbon bond forming carbonyl reactions. Zinc-Copper³⁷ and Zinc-Silver³⁸ couple were found to be most useful in preventing intermolecular reactions of Zn-homoenolates.

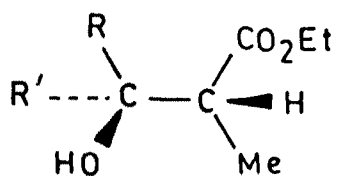
Many efforts have been reported to increase the yields of Reformatskii reactions by additions of variety of materials. These promoters activate the zinc and produce a faster reaction with haloester. Iodine is probably the most frequently used promoter. Addition of few crystals of iodine suppress enolization and leads to increased yields. Copper powder 10-20% of has been added to the zinc to give increased yields in some other reactions³⁹. Mercuric chloride was found to be one of the

more effective promoters. Recently it is reported that Zn-Tri-methyl chloro silane⁴⁰ promotes the conversion of aldehydes and ketones into enolates.

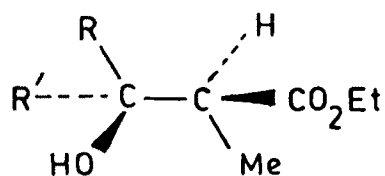
4-Bromo crotonate^{23,38,41-45} esters may undergo Reformatskii reaction with attack at either the 4-position to produce the normal product (3.4) or at the 2-position to produce the abnormal product (3.5). The hindered methyl ketones gives predominantly the normal product. But the aliphatic aldehydes gave a mixture of both isomers with branching in the alkyl position of the aldehydes favouring the normal product.

The reaction conditions also effect the product formed. Cyclohexanone⁴⁶ (4.1) reacts to give predominantly the normal product (4.2) in refluxing benzene and the abnormal product (4.3) in refluxing ether. With other ketones such as 2-methyl cyclohexanone (4.4) the normal product (4.5) is obtained in either solvent.

Detailed Reformatsky reaction studies of alkyl 4-bromo-2-butenates (4-bromo crotonates) with carbonyl compounds have indicated that α -substituted products are kinetically controlled and γ -substituted products are thermodynamically controlled²³. The α -substitution is preferred in low boiling solvents whereas γ -substitution required high temperature and longer reaction time; mostly in aromatic hydrocarbons. In order to ensure reaction at α -position acid-washed zinc copper couple in diethyl ether is useful. To obtain γ -substitution products unactivated zinc in higher boiling solvent is preferred. If Zn

CHART-3

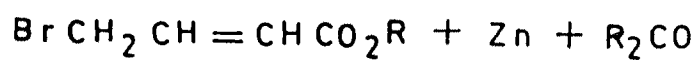
(1)



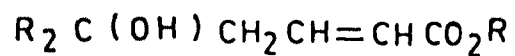
(2)

R = Alkyl or Aryl group .

R' = Alkyl or Hydrogen .

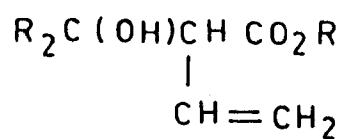


(3)



Normal Product

(4)



Abnormal Product

(5)

CHART-4

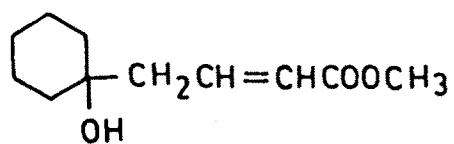


(1)

1) Zn
2) H_3O^+

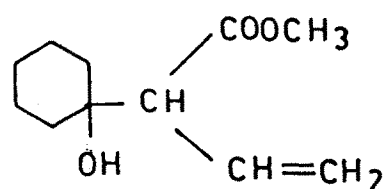
Boiling benzene

Boiling ether



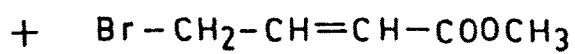
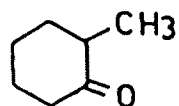
(Normal Product)

(2)



(Abnormal Product)

(3)

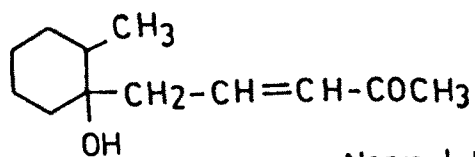


(4)

1) Zn
2) H_3O^+

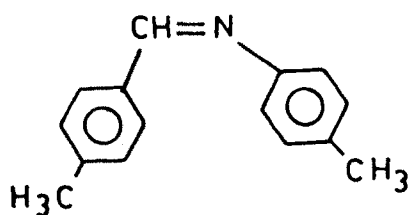
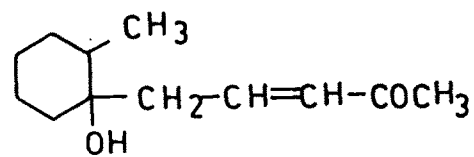
Boiling benzene

Boiling ether



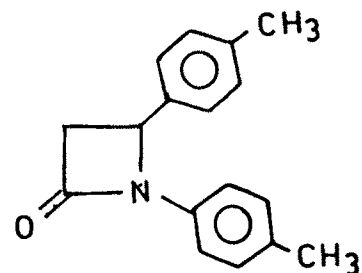
Normal Product

(5)



(6)

$\xrightarrow{\text{Zn}}$



is replaced by tin⁴⁷ or cerium⁴⁸ exclusively yields α -substituted products. In highly polar solvents like dimethyl sulfoxide 4-bromo crotonate undergo Wurtz-type dimerization⁴⁹.

The Reformatskii reaction with α , β -unsaturated carbonyl compounds e.g. ethyl-4-bromo-2-butenate⁴² may give either 1,2- or 1,4- addition products. Under controlled conditions four possible regioisomers, two resulting from 1,2- and one from 1,4- addition to the carbonyl system, were obtained in good selectivity in the end. Only 1,2- addition product is obtained by the reaction of variety of methyl vinyl ketones with bromoesters and zinc metal in refluxing ether. But the reaction of unsaturated ketenes with ethyl bromo isobutyrate and zinc in refluxing tetrahydrofuran gave 1,4- addition product. The hindered halo esters like ethyl α -bromo isobutyrate will generally give increased amount of 1,4- addition.

Reformatskii reaction involving zinc graphite promoted synthesis of β -hydroxy esters with improved yields is reported⁵¹ (Sonochemistry) chemical reactions are widely reported which is latest technique extensively used in synthetic chemistry; especially those involving organometallic reagents. The beneficial effects of ultrasonic irradiation on the Reformatskii reaction have also been observed.⁵²

The Reformatskii type reaction⁵³ of bromo acetate with diaryl Schiff's base and activated zinc in dioxane containing iodine catalyst at 25°C for 4 hr. under ultrasound irradiation

gave 95% lactam (4.6).

Both ethyl (z)- and (E)-4-bromo-3-methyl butenoate (5.1) and (5.2) upon reaction with carbonyl compounds in presence of zinc form 5,6-dihydro-2-pyrone (5.3) derivative which is explained by α to γ - rearrangement accompanied by an E to Z inversion⁵⁴.

Recently triethyl borane⁵⁵ mediated and indium(I) iodide⁵⁶ and palladium (0) complexes⁵⁷ mediated reactions are also reported. In stereoselective Reformatskii type reaction $TiCl_4$ ⁵⁸ is found to be most applicable. In electrochemically supported Reformatskii reaction sacrificial zinc electrode⁵⁹ is widely used. There is also evidence for Ni-Zn transmetalation⁶⁰. Recently Zn, Sn, Al, In and Fe⁶¹ metals are used as sacrificial anodes in the electrochemically assisted Reformatskii reaction of ethyl-2-bromo alkanates with succinic anhydride has been reported.

Most recently Reformatskii type reaction of α -halo ester with carbonyl compounds in the presence of low-valent tantalum⁶² prepared readily from tantalum(V) chloride and activated zinc to afford β -hydroxy esters has been reported.

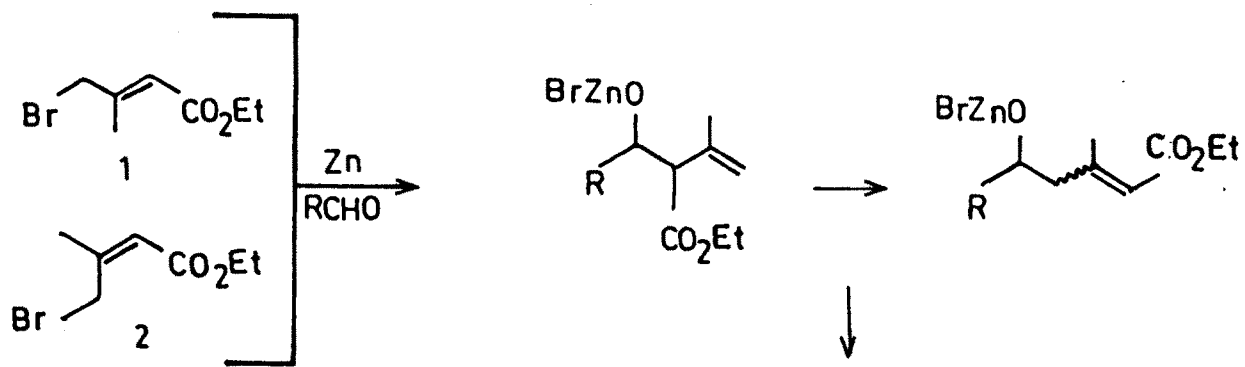
The Reformatskii reaction has wide applications in the selective synthesis of large numbers of new compounds by changing the starting material and variation in the structure of reagents, including complicated natural products. The intramolecular reactions giving regioselective enolate is recently

gaining increasing importance. Thus the Reformatskii reaction is genuine alternative to fast developing base induced aldolization.

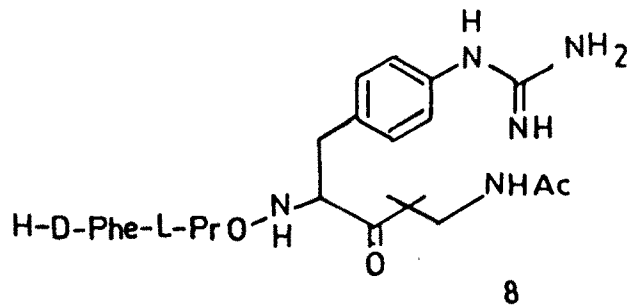
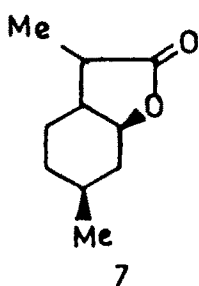
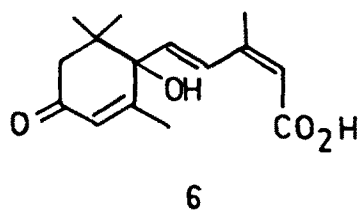
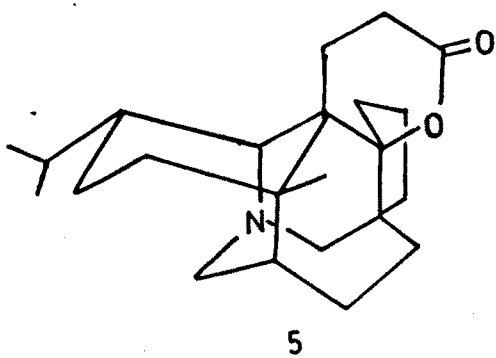
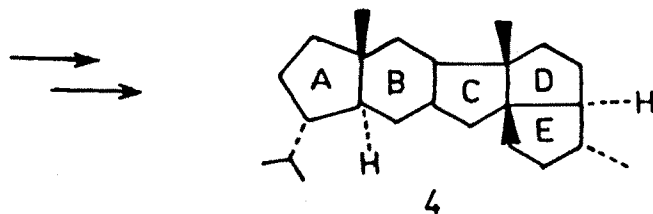
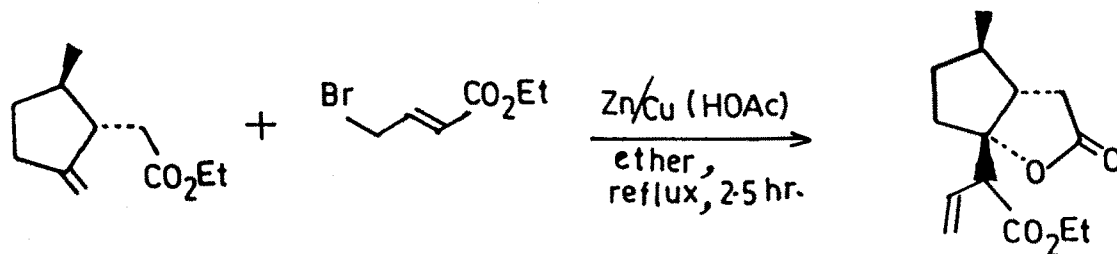
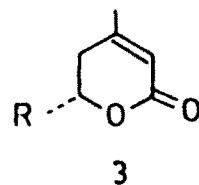
Reformatskii Reaction is widely used in the synthetic organic chemistry⁵ reaction of α -di and -trihalo esters are finding useful applications in the synthesis of derivatives of natural products like deoxy-fluoro sugars, difluoromevalonolactone, 2-fluorocitric acid, difluoro β -lactams and 7, 7-difluorothromboxane A₂ precursor. Reformatskii reaction of alkyl-2-bromo methyl -2-alkenoate specifically alkyl-2-bromomethyl-2-propenoate is widely employed in the synthesis of variety of natural products mainly the steroids and alkaloids.

Alkyl-4-bromo-2-butenolate is used successfully in the synthesis of natural products such as supinidine, retigeranic acid, (5.4) iso-and epiiso-cumenic acid and in annulation reactions to obtain polycondensed aromatic systems by regioselective γ -substitution. Also in synthesis of daphnilactone-A (5.5) by intramolecular reaction and in abscisic acid (5.6) synthesis in which it act as donor.

Recently it has been reported that Reformatskii reaction is useful in synthesis of (\pm) -mintlactone⁶³ (5.7) a butenolide (potential inhibitor of human thrombin⁶⁴ (5.8) in form of poly-functionalized fluoromethylene ketone retromides has been prepared through a Reformatskii type reaction.



(Major Product)



Thus from synthetic point of view, the Reformatskii reaction not only constitute a method for preparing β -hydroxy-esters and a corresponding unsaturated esters and acids but also is a mild and versatile method for the formation of carbon-carbon bond.

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