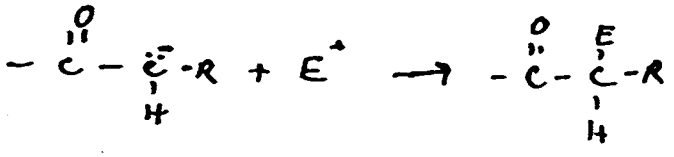
CHAPTER 22 ENOLS, ENOLATES AND SUBSTITUTION AT ALPHA CARBONS

THE PROTONS α TO A CARBONYL ARE SLIGHTLY ACIDIC. THEY WILL IONIZE IN THE PRESENCE OF BASE

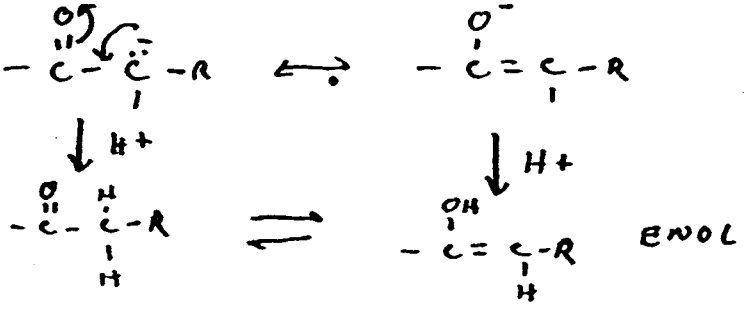
THIS ANION IS A STRONG NUCLEOPHILE AND WILL ADD TO ELECTROPHILES



THIS IS CALLED ALPHA SUBSTITUTION

KETO-ENOL TAUTOMERISM

THE ANION THAT RESULTS FROM α PROTONS AND BASE IS RESONANCE STABILIZED. IT IS CALLED AN ENOLATE ANION



THESE STRUCTURES ARE TAUTOMERS

THE EQUILIBRIUM USUALLY FAVORS THE KETO FORM, BUT CERTAIN CONDITIONS MAY FAVOR THE ENOL

ENOL STABILIZED BY HYDROGEN BONDING

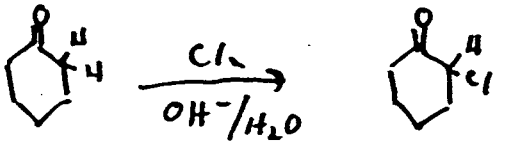
EVEN THOUGH THERE MAY BE ONLY A SMALL PERCENTAGE OF THE COMPOUND IN THE ENOLATE FORM, IT IS REACTIVE, AND REACTION REMOVES IT FROM THE EQUILIBRIUM. EVENTUALLY, ALL THE MOLECULES WILL REACT VIA THE ENOLATE

'E GENERALLY USE HYDROXIDE (OH^-) OR ALKOXIDE (^-OR) TO ABSTRACT N α HYDROGEN. BUT THESE 2 REAGENTS SOMETIMES INTERFERE WITH HE ADDITION OF AN ENOLATE TO AN ELECTROPHILE. THEN WE USE LDA ITHIUM DI ISOPROPYL AMIDE, WHICH IS A STRONG BASE, BUT A POOR NUCLEOPHILE

$(IPR)_2N:^- Li^+$ POOR NUCLEOPHILE DUE TO STERIC HINDRANCE

α-HALOGENATION

TREAT A KETONE WITH BASE AND A HALOGEN

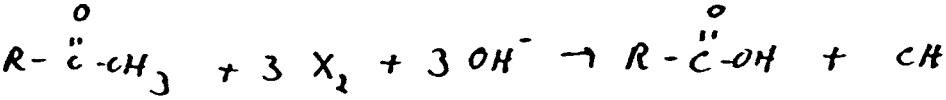


THE ENOLATE NUCLEOPHILE DISPLACES Cl FROM Cl_2

BECAUSE THE NEW HALOGEN ATOM STABILIZES THE FORMATION OF MORE ENOLATE, MULTIPLE HALOGENATION OCCURS

METHYL KETONES, WITH 3 α H, UNDERGO THE HALOFORM REACTION

3 α HALOGENATIONS FOLLOWED BY BASIC HYDROLYSIS

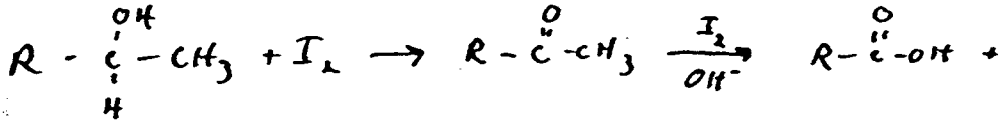


CHLOROFORM, BROMO-, IODO-

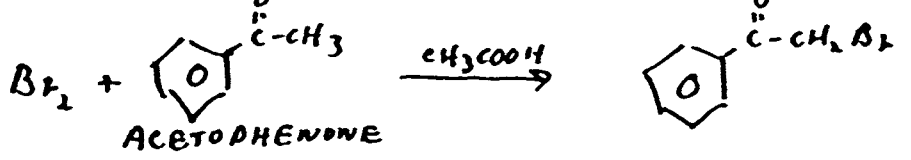
IN ORGANIC QUAL ANALYSIS WE USE IODINE TO IDENTIFY METHYL KETONES

A YELLOW PRECIPITATE OF CHI_3 IS IODOFORM

WITH IODINE, 2 METHYL ALCOHOLS ALSO TEST POSITIVE, DUE TO OXIDATION

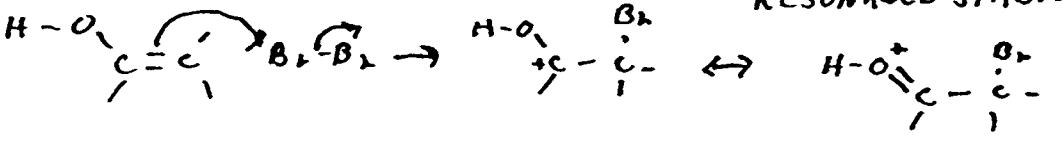


α HALOGENATION IS ALSO DONE WITH ACID CATALYSIS. MONO HALOGENATED PRODUCTS RESULT

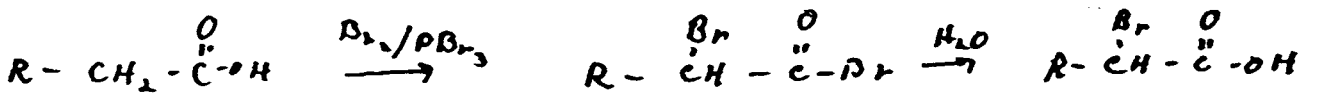


USING 2 EQUIVALENTS OF BROMINE GIVES THE DI BROMO PRODUCT

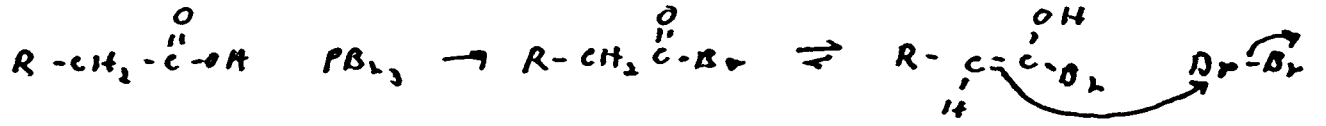
THE MECHANISM OF ACID CATALYSED α HALOGENATION INVOLVES ATTACK OF THE ENOL FORM ON THE HALOGEN. THE CARBOCATION INTERMEDIATE IS RESONANCE STABILIZED

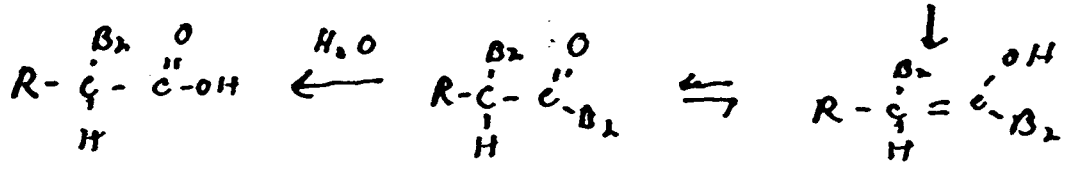


α BROMINATION OF ACIDS HUZ REACTION



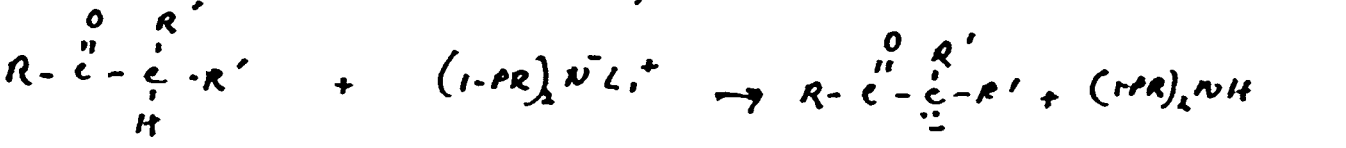
AGAIN, THE ENOL FORM OF THE ACYL BROMIDE IS THE NUCLEOPHILE



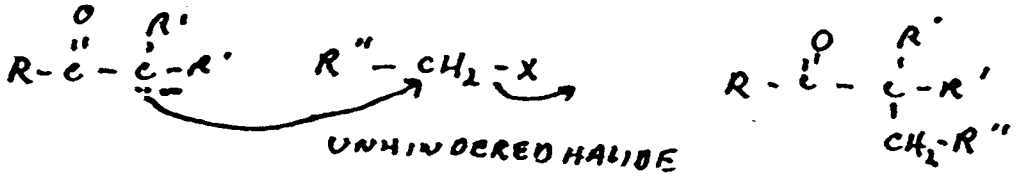


ALKYLATION OF ENOLATE IONS

ENOLATE ANIONS MAKE GOOD NUCLEOPHILES FOR S_N2 REACTIONS WITH UNHINDERED HALIDES OR TOSYLATES



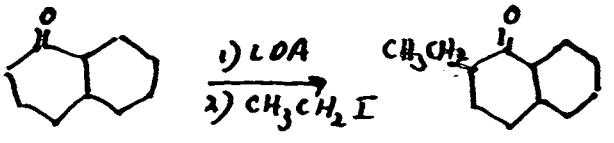
ENOLIZABLE KETONE ENOLATE DIISOPROPYLAMINE



UNHINDERED HALIDE

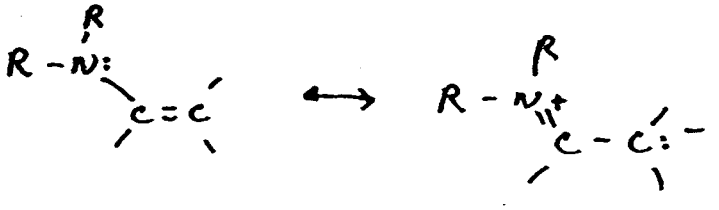
O-ALKYLATION IS POSSIBLE, USUALLY MINOR

EXAMPLE



FORMATION AND ALKYLATION OF ENAMINES

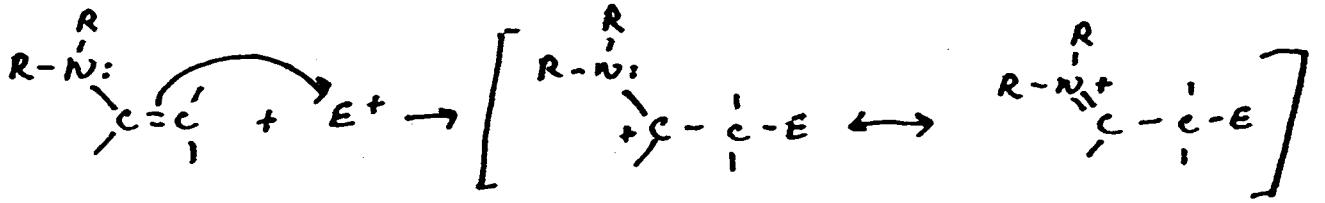
AN ENAMINE IS THE NITROGEN ANALOG OF AN ENOL



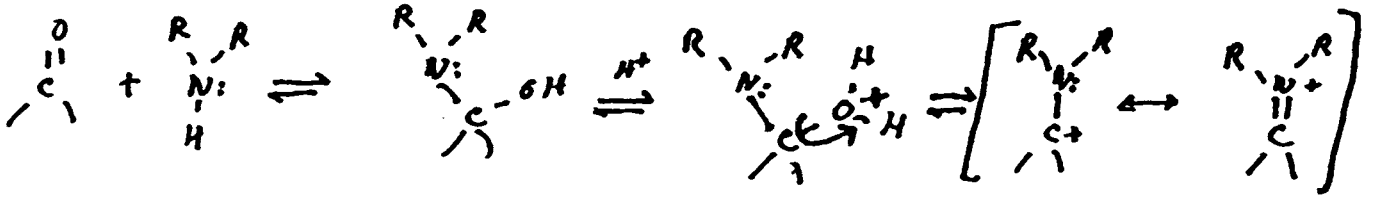
RESONANCE STABILIZATION OF AN ENAMINE

ENAMINES ATTACK ELECTROPHILES TO GIVE A RESONANCE STABILIZED CATIONIC INTERMEDIATE

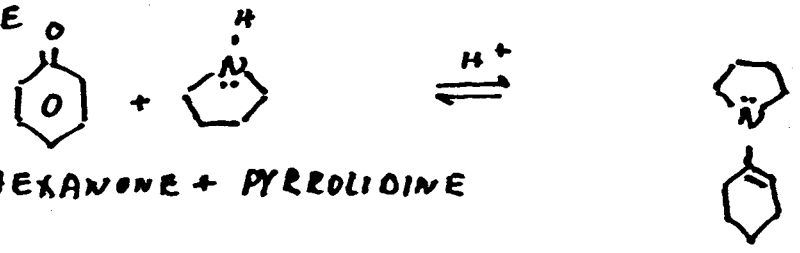
ENAMINES



ENAMINES ARE MADE FROM KETONES AND SECONDARY AMINES

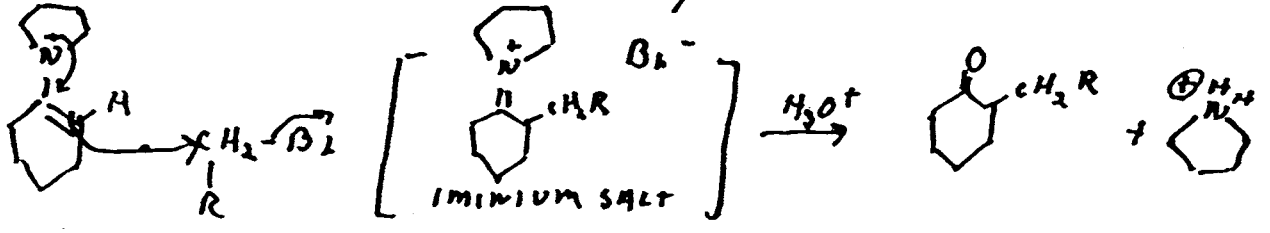


EXAMPLE

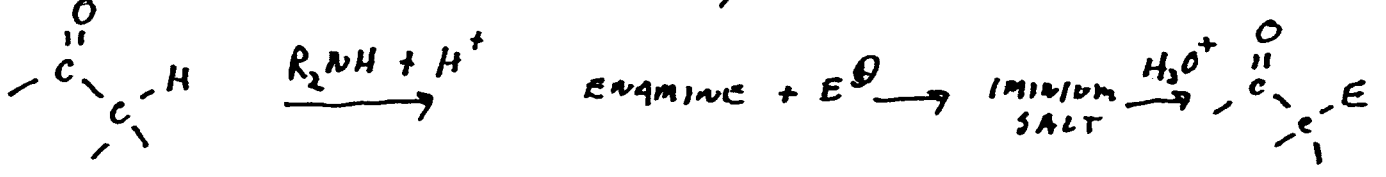


CYCLOHEXANONE + PYRROLIDINE

THE ENAMINE THEN DISPLACES AN ALKYL HALIDE

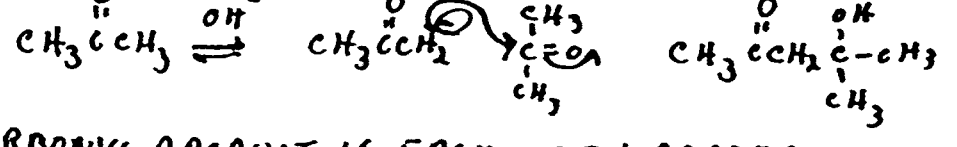


ITS COMPLICATED, BUT THE OVERALL REACTION IS SIMPLE, JUST AN α ALKYLATION

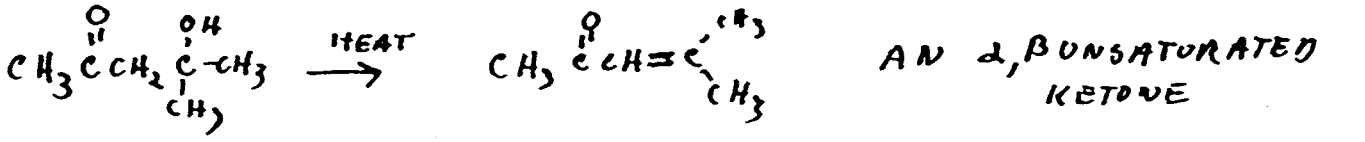


LOOL CONDENSATION

A CONDENSATION REACTION COMBINES TWO MOLECULES. THIS IS AN α SUBSTITUTION WHERE THE ELECTROPHILE IS ANOTHER CARBONYL COMPOUND. THE PRODUCT IS A β-HYDROXY KETONE OR ALDEHYDE

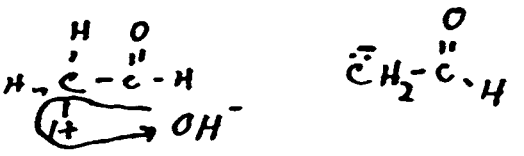
FOR ACETONE 

THE β-HYDROXY CARBONYL PRODUCT IS EASILY DEHYDRATED

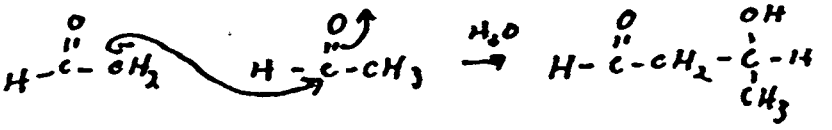


HE TWO-STEP MECHANISM

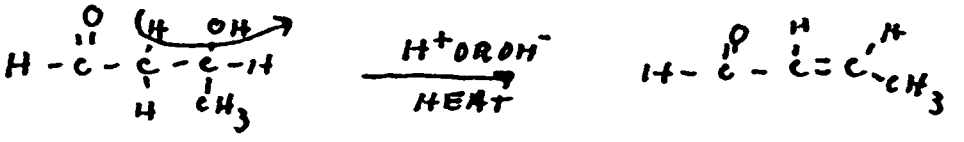
1) FORM ENOLATE



2) ENOLATE ATTACKS CARBONYL



HEATING THE ALDOL PRODUCT IN EITHER ACID OR BASE CAUSES IT TO DEHYDRATE



ROSSED ALDOL CONDENSATIONS

INVOLVE 2 DIFFERENT CARBONYL COMPOUNDS

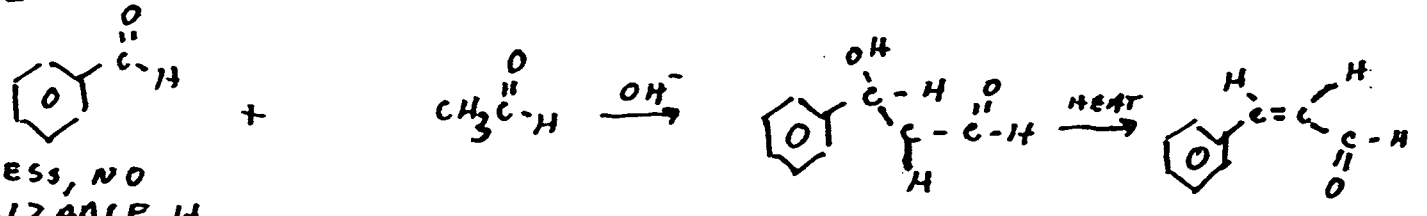
ITS POTENTIALLY POSSIBLE TO GET 4 PRODUCTS,

2 SELF-CONDENSATION PRODUCTS AND 2 CROSSED CONDENSATIONS

WE AVOID THIS PROBLEM BY

1) ONLY ONE CARBONYL CAN HAVE ENOLIZABLE PROTONS
2) ADD THE ENOLIZABLE COMPOUND TO A BASIC SOLUTION OF THE NON-ENOLIZABLE ONE

XAMPLE



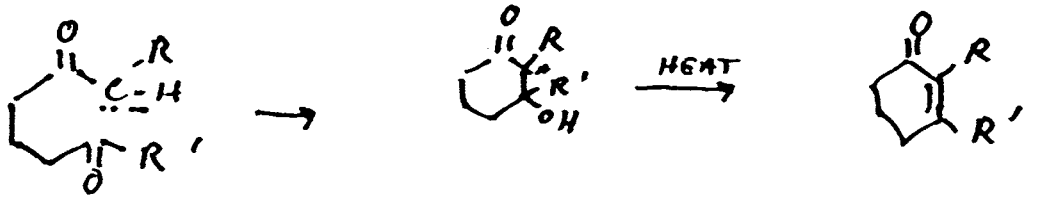
EXCESS, NO ENOLIZABLE H

CINNAMALDEHYDE

OL CYCLIZATIONS

1,4 DIKETONES → CYCLOPENTENONES

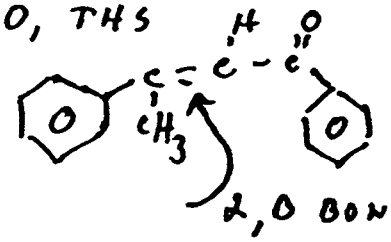
1,5 DIKETONES → CYCLOHEXENONES

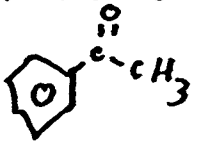


ENOLATE OF A 1,5 DIKETONE

I FINAL WORD ON ALDOL CONDENSATIONS

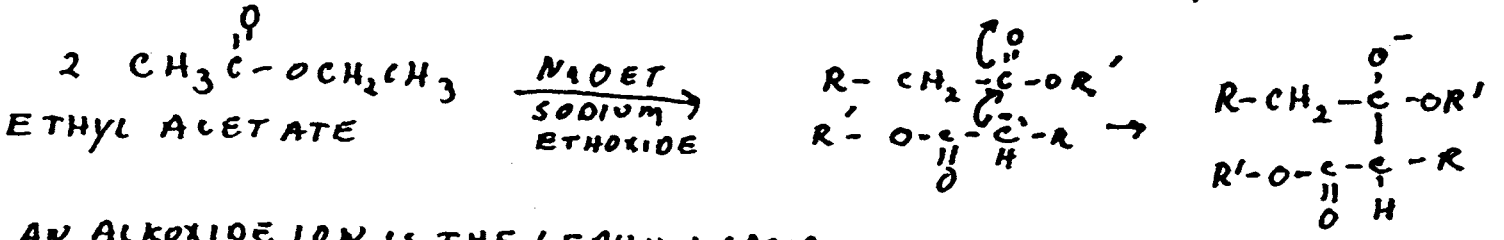
ALDOL PRODUCTS ARE β-HYDROXYL ALDEHYDES AND KETONES OR α,β-UNSATURATED ALDEHYDES AND KETONES. TO DISSECT AN ALDOL PRODUCT INTO ITS STARTING MATERIALS, MENTALLY BREAK THE α,β BOND (MAY BE A DOUBLE BOND)

SO, THIS 

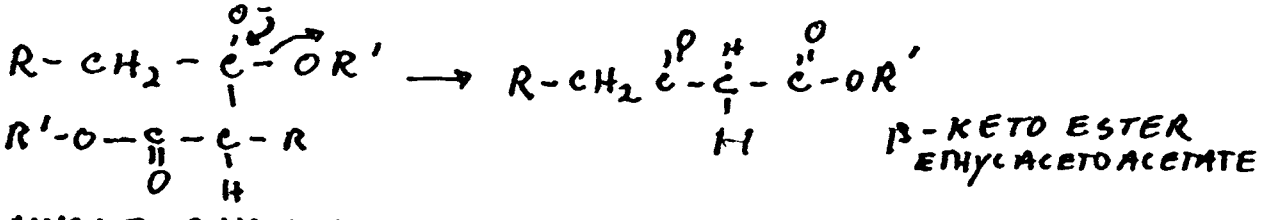
CAME FROM THIS 

IE CLAISEN ESTER CONDENSATION

α-HYDROGENS OF ESTERS ARE ACIDIC ENOUGH TO PRODUCE ENOLATES. WHEN 2 MOLES OF AN ESTER ARE PUT IN BASIC CONDITIONS, AN ALDOL-LIKE CONDENSATION OCCURS. THE PRODUCT IS A β-KETO ESTER

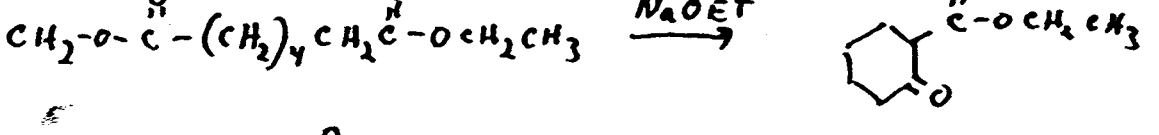


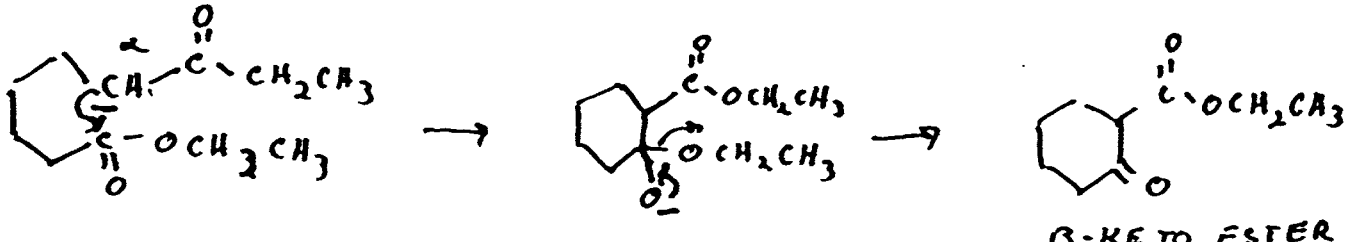
AN ALKOXIDE ION IS THE LEAVING GROUP



THIS IS NUCLEOPHILIC ACYL SUBSTITUTION BY AN ENOLATE

HE CLAISEN CONDENSATION CAN ALSO GIVE CYCLIC PRODUCTS



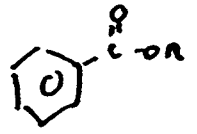


THIS IS CALLED THE CLAISEN CONDENSATION

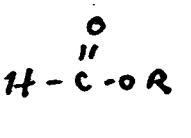
CROSSED CLAISEN CONDENSATIONS

ONE ESTER WITHOUT α HYDROGENS CONDENSES WITH ANOTHER ESTER THAT DOES HAVE ENOLIZABLE PROTONS

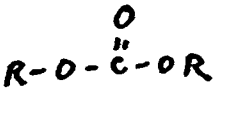
USEFUL ESTERS INCLUDE



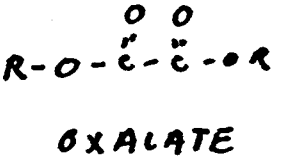
BENZOATE



FORMATE

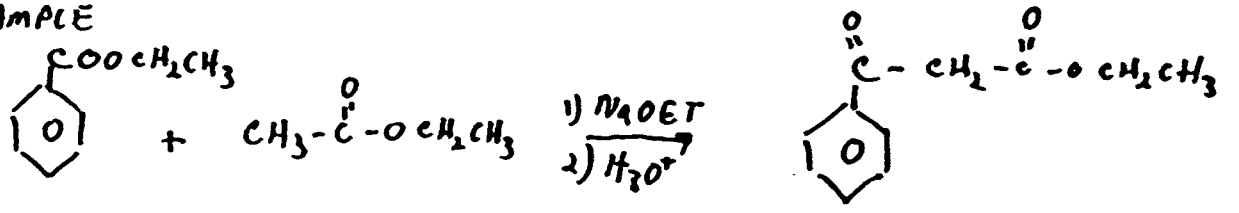


CARBONATE

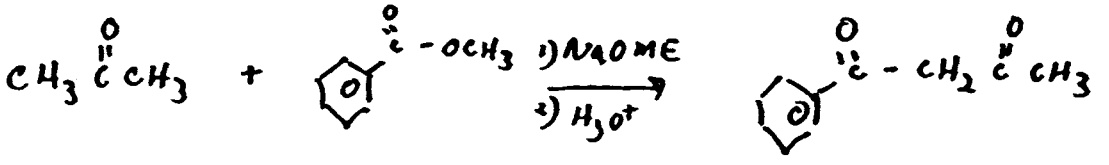


OXALATE

FOR EXAMPLE



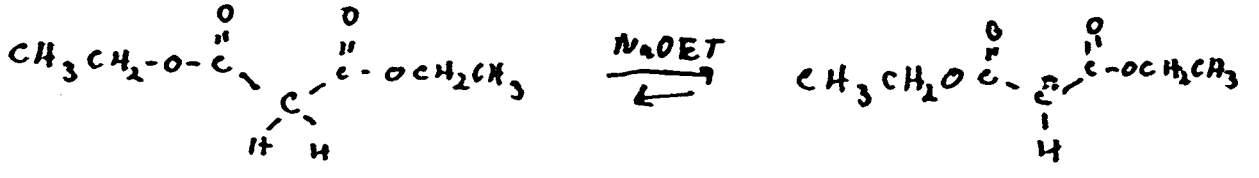
CROSSED CLAISEN CONDENSATIONS MAY ALSO HAPPEN BETWEEN ESTERS AND KETONES



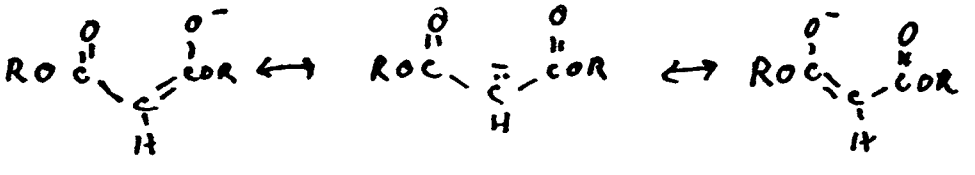
SYNTHESIS USING β-DICARBONYL COMPOUNDS

β-DICARBONYL COMPOUNDS HAVE MANY ADVANTAGES IN SYNTHESIS MOSTLY BECAUSE THEY ENOLIZE EASILY AND COMPLETELY

THE ENOLATE IS ESPECIALLY STABLE DUE TO THE TWO CARBONYLS



STABILIZED BY RESONANCE

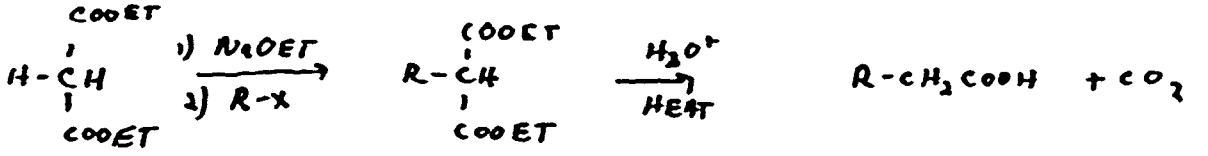


THIS ENOLATE IS USED AS A NUCLEOPHILE IN THE MALONIC ESTER SYNTHESIS

THE MALONIC ESTER SYNTHESIS

THE PRODUCTS OF MALONIC ESTER SYNTHESIS ARE SUBSTITUTED ACETIC ACIDS

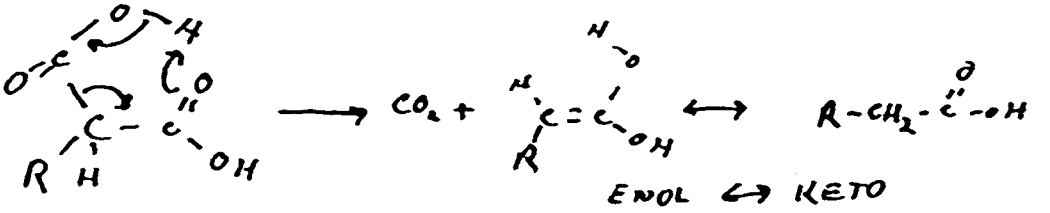
AFTER ALKYLATION, THE SECOND ESTER GROUP IS REMOVED BY DECARBOXYLATION



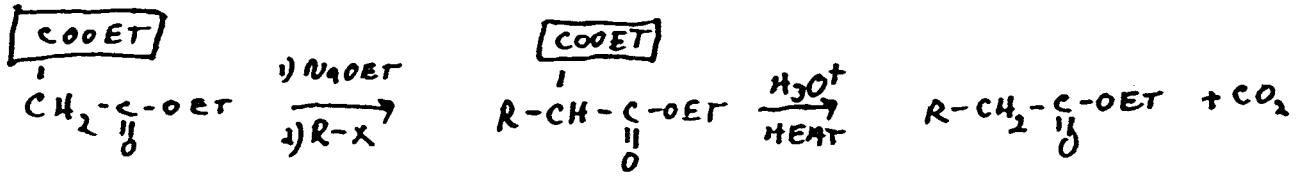
MALONIC ESTER IS COMPLETELY DEPROTONATED BY SODIUMETHOXIDE. THE ENOLATE REACTS WELL WITH ANY GOOD S_N2 SUBSTRATE

HYDROLYSIS OF THE ALKYLATED MALONATE GIVES A MALONIC ACID DERIVATIVE

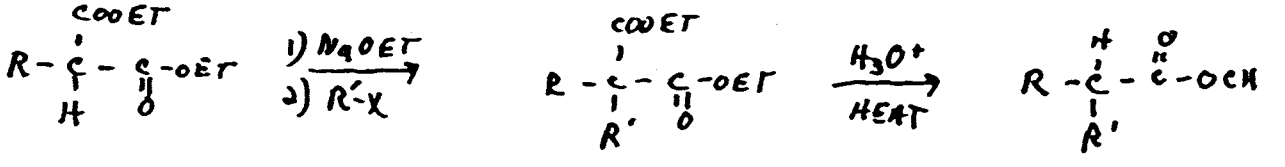
ANY β-CARBONYL CARBOXYLIC ACID IS PRONE TO DECARBOXYLATE



IN EFFECT, THE SECOND ESTER GROUP OF MALONIC ESTER IS TEMPORARY. IT PROMOTES ENOLIZATION AND ALKYLATION AND THEN IS REMOVED BY HYDROLYSIS AND DECARBOXYLATION

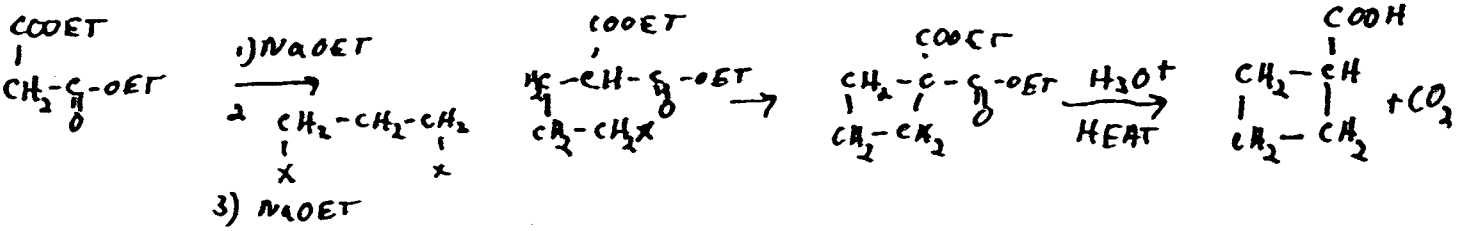


SINCE THERE ARE TWO PROTONS ON MALONIC ESTER THAT CAN IONIZE, DIALKYLATION IS POSSIBLE



SMALL RINGS CAN EVEN BE MADE FROM DIHALIDES

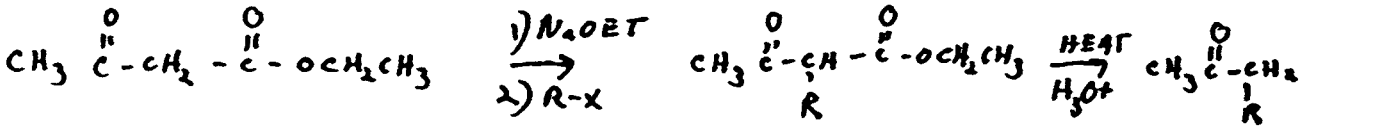
DI SUBSTITUTED ACETIC ACID



THE ACETOACETIC ESTER SYNTHESIS

VERY SIMILAR TO MALONIC ESTER SYNTHESIS

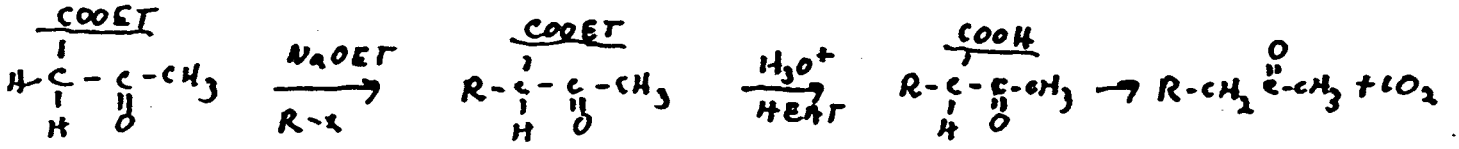
THE PRODUCTS ARE SUBSTITUTED ACETONES



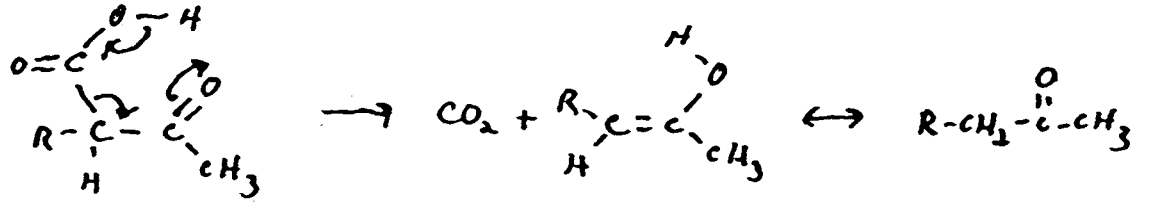
ETHYL ACETOACETATE — ALKYLATED ESTER — SUBSTITUTED ACETONE

AGAIN, YOU CAN THINK OF THE ESTER GROUP AS TEMPORARY,

DIALKYLATIONS ARE POSSIBLE, AND DECARBOXYLATION REMOVES THE ESTER



DECARBOXYLATION PROCEEDS BY THE SAME SIX MEMBERED RING MECHANISM

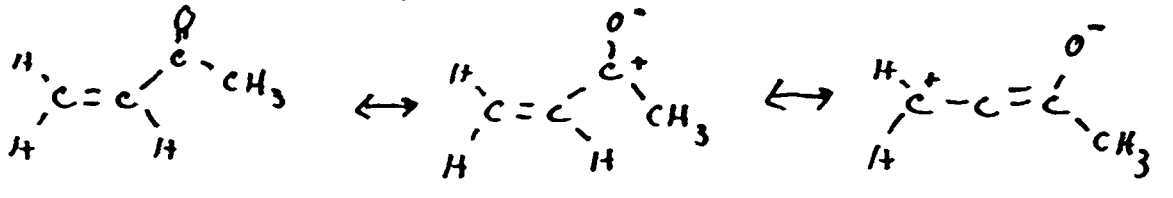


CONJUGATE ADDITIONS - THE MICHAEL ADDITION

CARBONYL CARBONS ARE ELECTRON DEFICIENT

CONJUGATED CARBONYL SYSTEMS HAVE ANOTHER SITE

OF ELECTRON DEFICIENCY AT THE β-CARBON



TWO NUCLEOPHILES CAN ATTACH AT EITHER THE CARBONYL CARBON

OR THE BETA CARBON, TERMED 1,4 ADDITION

ADDITION OF A STABILIZED ENOLATE TO THE DOUBLE BOND OF AN α,β-UNSATURATED

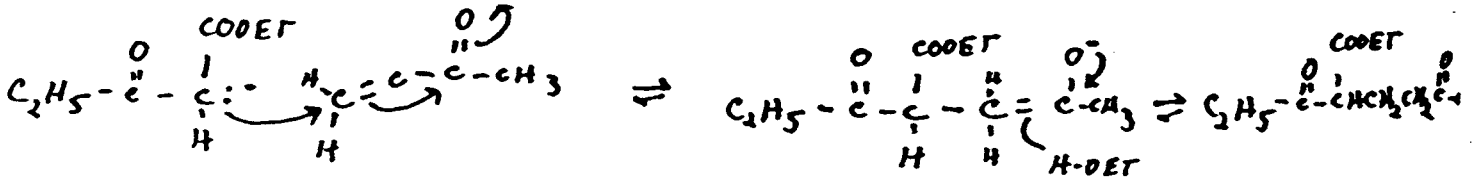
CARBONYL COMPOUND IS CALLED MICHAEL ADDITION

A MICHAEL ADDITION ALWAYS INVOLVES:

AN ELECTROPHILE (α,β-UNSATURATED CARBONYL COMPOUND) (MICHAEL ACCEPTOR)

A NUCLEOPHILE (STABILIZED ENOLATE) (MICHAEL DONOR)

ICHAEL ADDITION

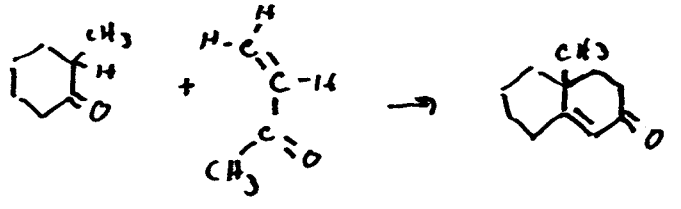


MALONIC ESTER ENOLATE — METHYL VINYL KETONE — 1,4 ADDITION PRODUCT

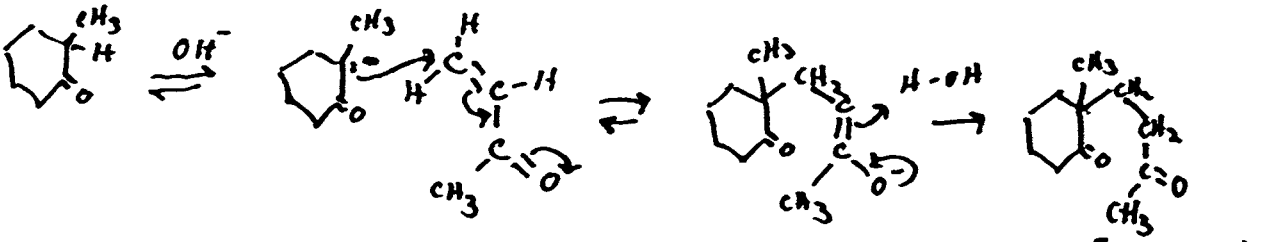
HYDROLYSIS AND DECARBOXYLATION LEAD TO A δ-KETO ACID

E ROBINSON ANNULATION - MICHAEL ADDITION PLUS ALDOL CONDENSATION

δ-KETOACIDS MAY UNDERGO A SPONTANEOUS INTRAMOLECULAR ALDOL CONDENSATION, FORMING A NEW RING

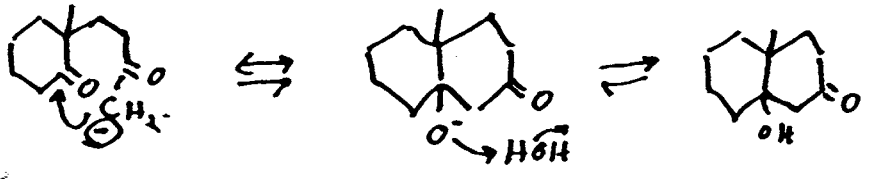


STEP 1 IS MICHAEL ADDITION

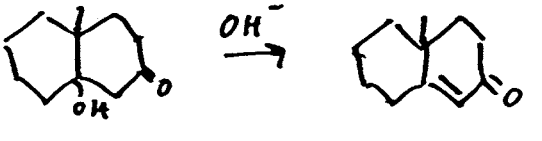


δ-DIKETO

STEP 2 IS ALDOL CONDENSATION TO FORM NEW RING



FINALLY, DEHYDRATION



CHAPTER 20

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