Course CHEM 345 Instructor GELLMAN

Day FRIDAY Date 4/11/2014

Notes Taken By CHRIS Total # of Pages 5

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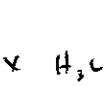
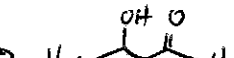
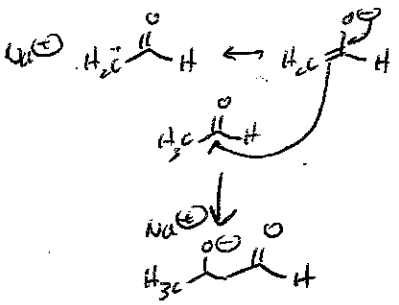
RECALL: ALDOL RXN

→ α-ACIDITY + CARBONYL ELECTROPHILICITY COMBINED

EX: 2 X  $\xrightarrow[H_2O]{NaOH}$ 

KEY MECHANISTIC STEP:



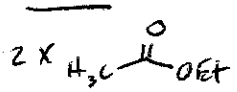
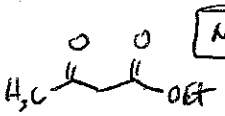
READ: SECTION 22.4D ON
SYNTHETIC USE OF ALDOL RXNS

CLAISEN CONDENSATION

ESTER ENOLATE = NUCLEOPHILE

ESTER = ELECTROPHILE

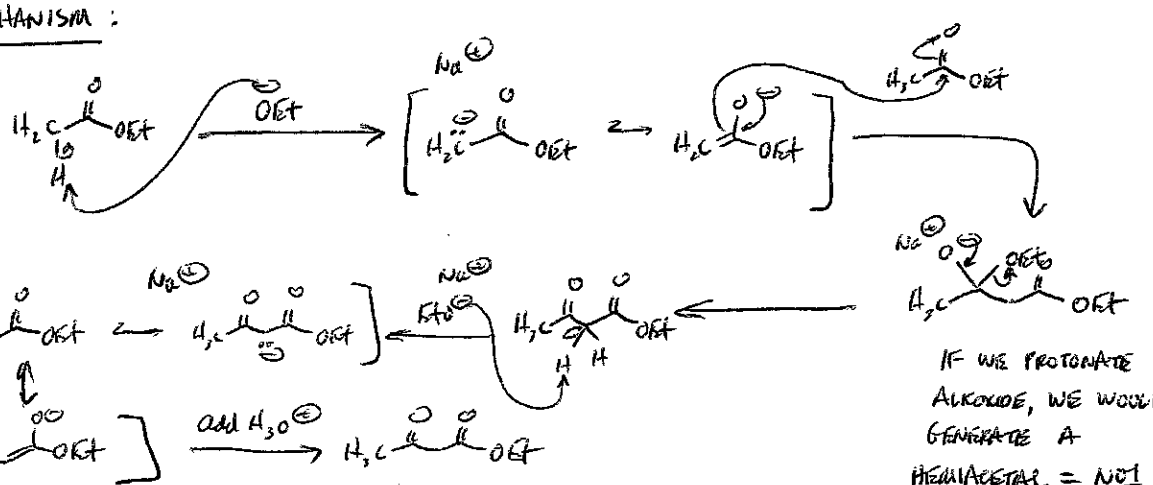
EX:

2 X  $\xrightarrow[2)\ H_3O^{\oplus}]{1)\ 1\text{ equiv. } NaOEt,\ EtOH}$ 

NEW C-C BOND

(a β-KETO ESTER)

MECHANISM:



IF WE PROTONATE THE ALKOXIDE, WE WOULD GENERATE A HEMIACETAL = NOT STABLE

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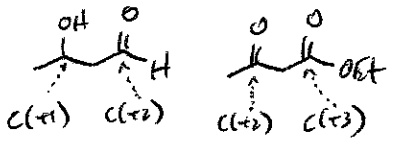
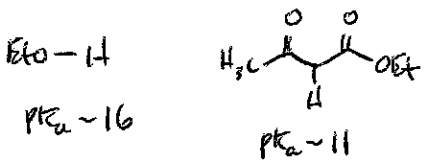
COMMENTS

1) COMPARE W/ ALDOL



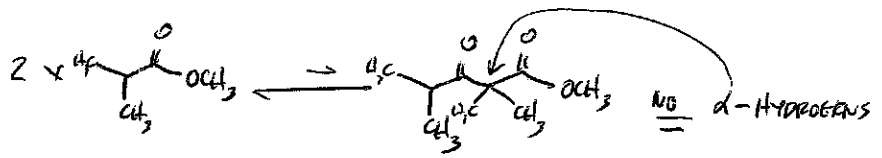
2) AS W/ ALDOL, CLAISEN COND. IS REVERSIBLE. THERMODYNAMICS FAVORS 2 ESTER MOLECULES VS. β-KETO ESTER

BUT, FINAL DEPROTONATION IS ESSENTIALLY IRREVERSIBLE



3) BECAUSE OF FINAL DEPROTONATION (BEFORE $H_3O^{\oplus}$ ADDITION), CLAISEN COND. CONSUMES 1 EQUIV. OF NaOEt

4) CLAISEN CONDENSATION DOES NOT OCCUR IF β-KETO ESTER LACKS AN ACIDIC H BETWEEN THE CARBONYLS



INTRAMOLECULAR CLAISEN CONDENSATIONS – PARTICULARLY USEFUL FOR 5- & 6-MEMBERED RINGS

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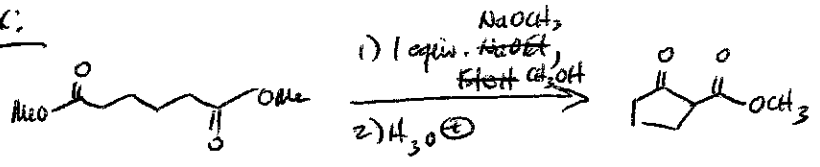
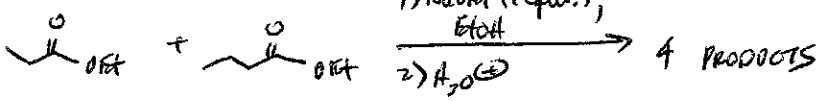
EX:



CROSSED CLAISEN CONDENSATION? OFTEN, CROSSED CLAISEN CONDENSATIONS LEAD TO MULTIPLE PRODUCTS

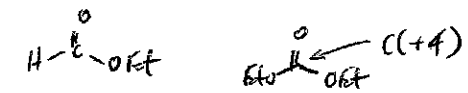
EX:



4 PRODUCTS

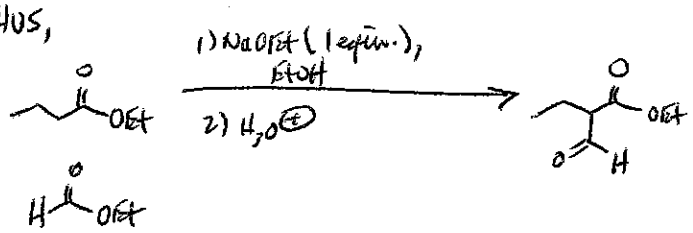
SOME CROSSED CLAISEN CONDENSATIONS ARE SELECTIVE

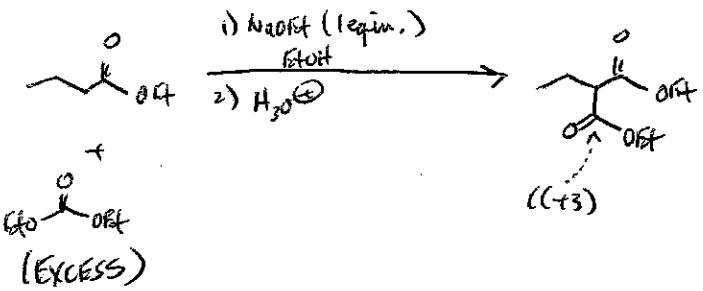
1) ONE ESTER LACKS α-HYDROGENS (∴ CAN'T SERVE AS ELECTROPHILE)



"ETHYL FORMATE" DIETHYL CARBONATE

THUS,





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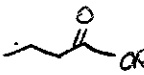
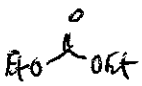
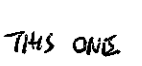
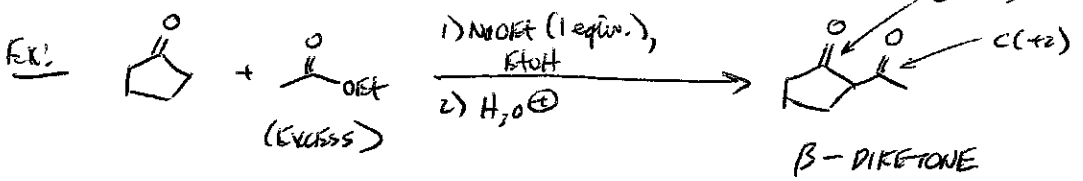
NOTE: HOW TO AVOID SELF-CONDENSATION OF  ?

 HIGH INTRINSIC ELECTROPHILIC REACTIVITY (LACK OF STERIC HINDRANCE + "ELECTRONICS")

 USE EXCESS TO ENSURE THAT THIS ONE IS ELECTROPHILE (NOT )

2) USE KETONE AS NUCLEOPHILE

EX: 

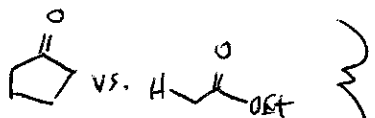
(EXCESS)

β-DIKETONE

ORIGIN OF SELECTIVITY ?

1) KETONE AS NUCLEOPHILE & ELECTROPHILE (i.e., ALDOL) ? KETONE ALDOL PRODUCTS ARE NOT STABLE (BASIC CONDITIONS)

2) ESTER AS NUCLEOPHILE & ELECTROPHILE (i.e., CLAISEN SELF-CONDENSATION)
NOT A PROBLEM, BECAUSE OF RELATIVE ACIDITIES...



$pK_a \sim 19$ $pK_a \sim 25$

∴ KETONE ENOLATE FORMS IN VAST PREFERENCE TO ESTER ENOLATE

⇓

ESTER CAN SERVE AS ELECTROPHILE

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READ SECTION 22.5D ON SYNTHETIC APPLICATIONS

READ SECTION 22.6 (FOR FUN)