Carbonyl Alpha Chem. II

Alkylation Reactions

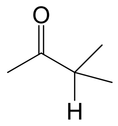
- malonic ester synthesis
- acetoacetic ester synthesis
- “direct alkylation”

Ref	(17: 7C; 19: 3 - 6)
Prob	19: 8, 12, 15
Adv Rdg	17: 4 – 7, 9b; 19: 9

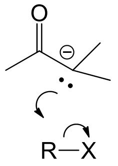
α Alkylation

(replace H by alkyl group at α pos^{n} of “Keto”)

General:



keto cmpd

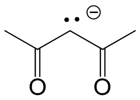


enolate;
acts as nucleophile in S_N2 rxn

gives alkylated "keto" cmpd

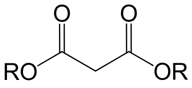
where R–X = 1° halide, tosylate, ...
(incl. allylic, benzylic)

“keto” works best (easiest)
if α C is doubly activated
i.e., β – dicarbonyl cmpds, such as

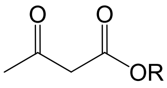


α Alkylation

esp.



malonic ester

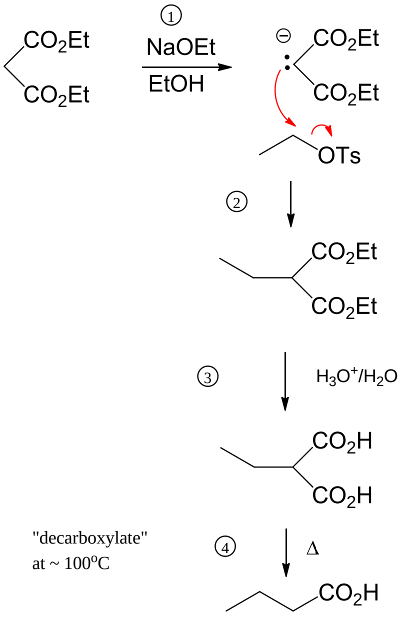


acetoacetic ester

can form enolates easily,
with “weak bases” , such as EtO^{-}
(consult pKa Tables , if needed)

1.) Malonic Ester Synthesis

Ex. Mech.:

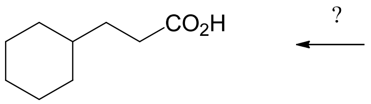


malonic ...

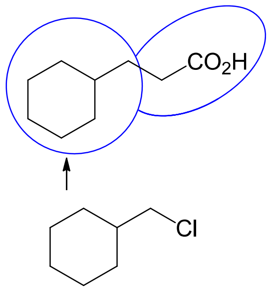
N.B. Adds $-CH_2CO_2H$ (2 C's)

to "1° substrate"

Practice: Retrosynthetic Analysis



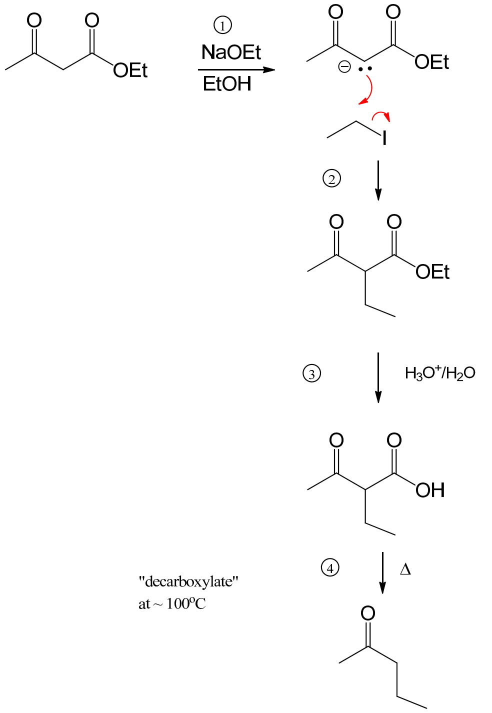
Ans.



from malonic ester

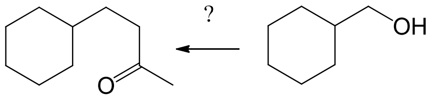
Do details as HMWK !

2.) Acetoacetic Ester Synthesis

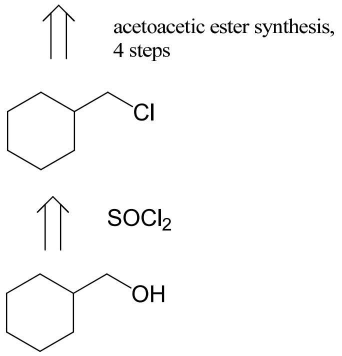


N.B. 3 C's added to substrate

Practice



Ans.



Do details as HMWK!

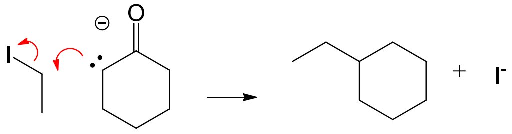
3.) "Direct Alkylation"

(*modern development*)

"1° substrate" + enolate of <u>mono</u>keto cmpd

→ "alkylated keto cmpd"

Ex.



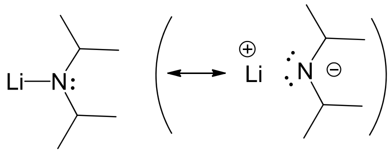
<u>Problems</u>

- need strong base (OR^- too weak) to make enolate
- side rxns (e.g. aldol) possible
- amide (e.g., NH_2^-)strong enough, but could attack carbonyl C (imine form^n)
- in ketones, 2 different α positions exist and could react

direct ...

Solution

Use LDA, lithium diisopropylamide, as base



- is very strong base (pKa of amine ≈ 40)
- “bulky”: does not form imine/enamine, forms enolate at less substituted α C

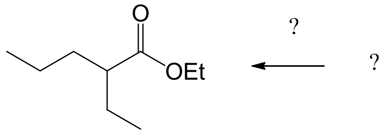
Suitable Conditions

1.) treat “keto cmpd” at -78°C w/ 1 equiv. of LDA / THF

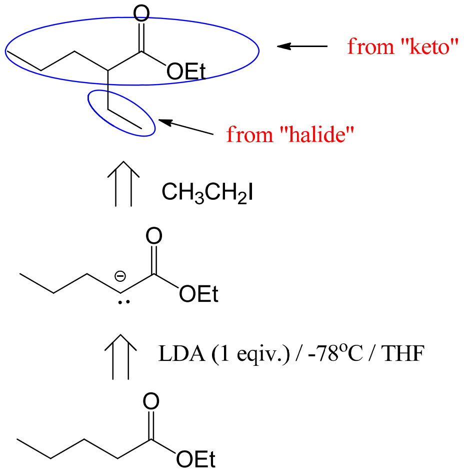
(makes enolate quantitatively, irreversibly, selectively at less substituted C)

2.) Add substrate (“halide”) and allow T↑ to r.t.

Practice



Ans.: α substituted ester; try "direct alkylation"



Potential Alternative: