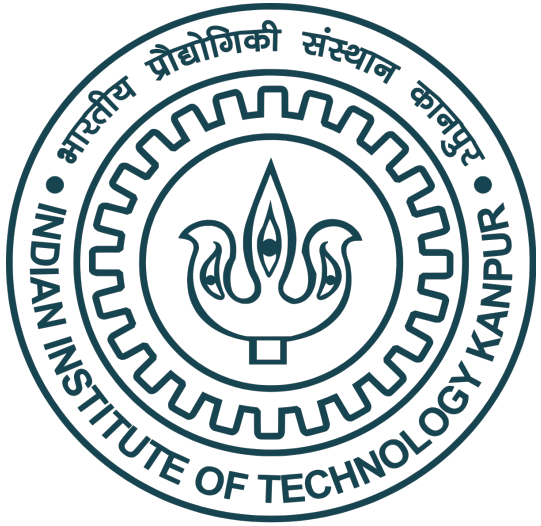
Lecture 17

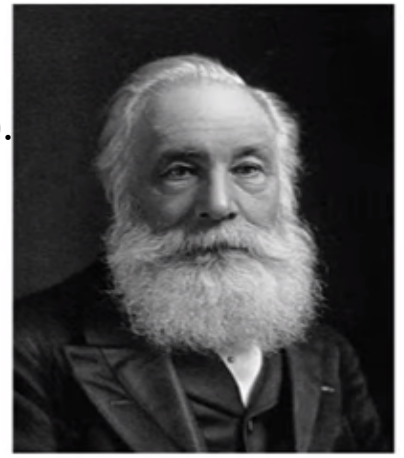
Fundamentals and Applications (CSO201A)



Dr. Srinivas Dharavath
Assistant Professor
Department of Chemistry
Indian Institute of Technology, Kanpur
Kanpur- 208016
E-mail: srinivasd@iitk.ac.in

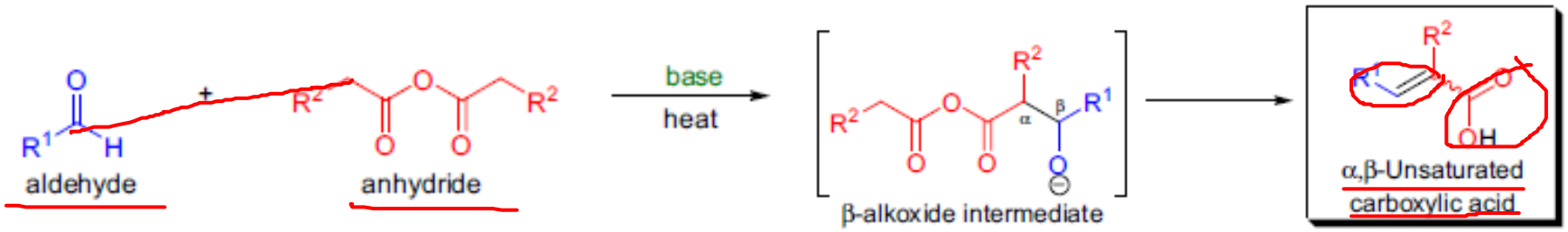
Perkin Reaction

The condensation of aromatic aldehydes with the anhydrides of aliphatic carboxylic acids in the presence of a weak base to afford α,β-unsaturated carboxylic acids is known as the *Perkin reaction* (or *Perkin condensation*).

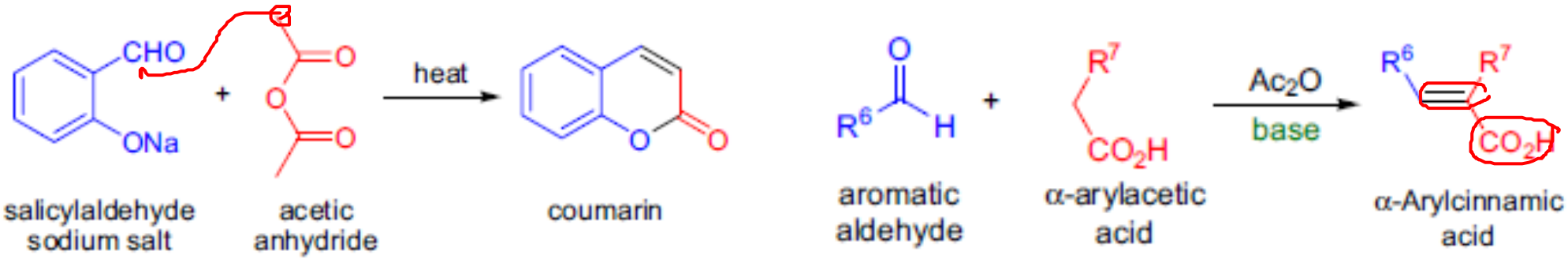


W H Perkin, British Chemi

(1838-1907)

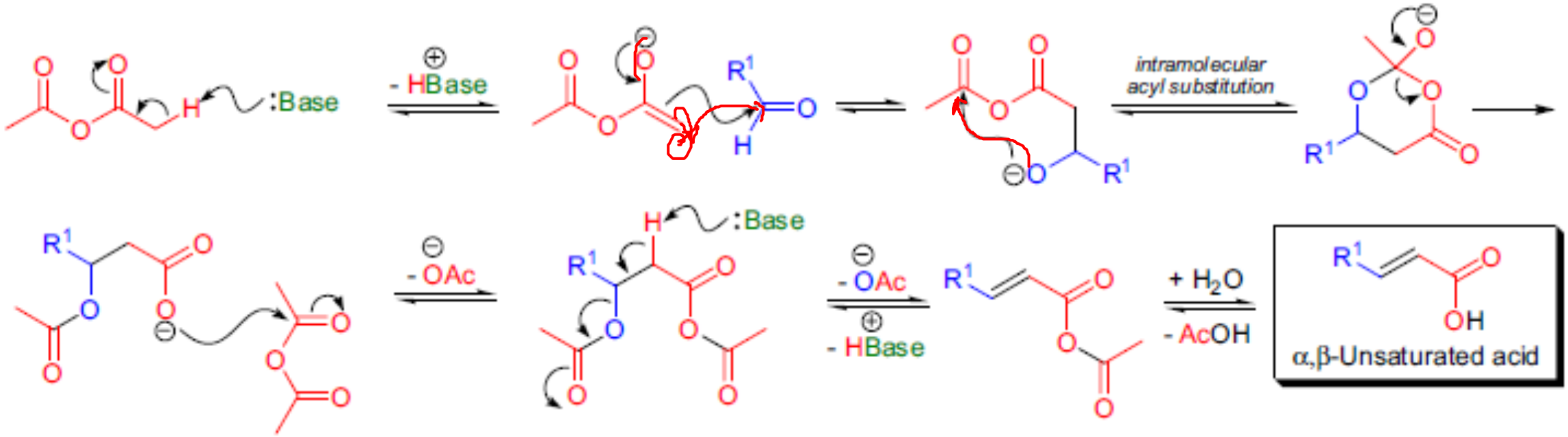


EWG enhances the reactivity

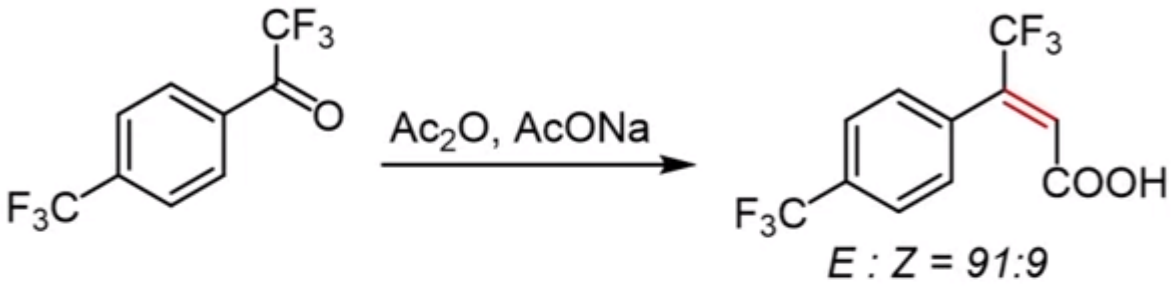


R^1 = aromatic, heteroaromatic, alkenyl, alkyl group with no α-hydrogen atom; R^2 = H, alkyl, aryl; R^6 = aryl, heteroaryl; base: NaOAc, KOAc, CsOAc, Et_3N, pyridine, piperidine, K_2CO_3

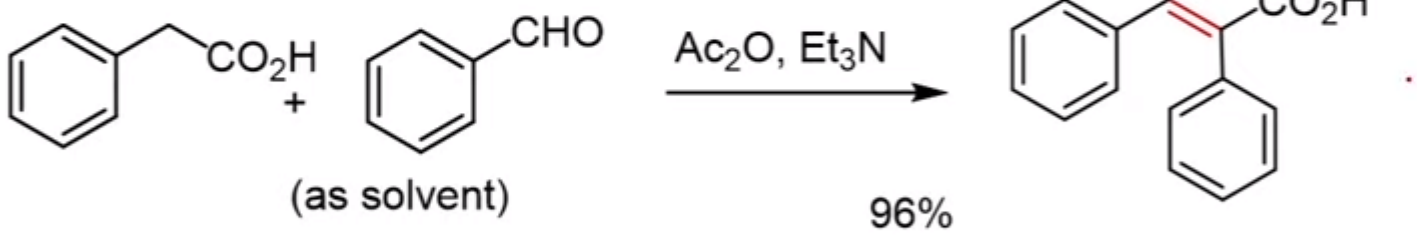
Mechanism


:Base
- HBase
intramolecular
acyl substitution
- OAc
:Base
- OAc
- HBase
+ H2O
- AcOH
α,β-Unsaturated acid

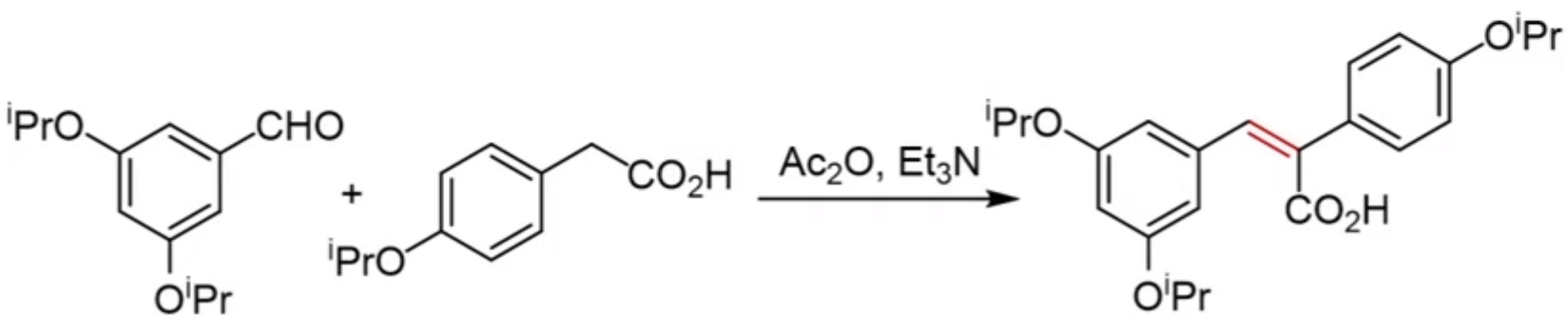
Examples



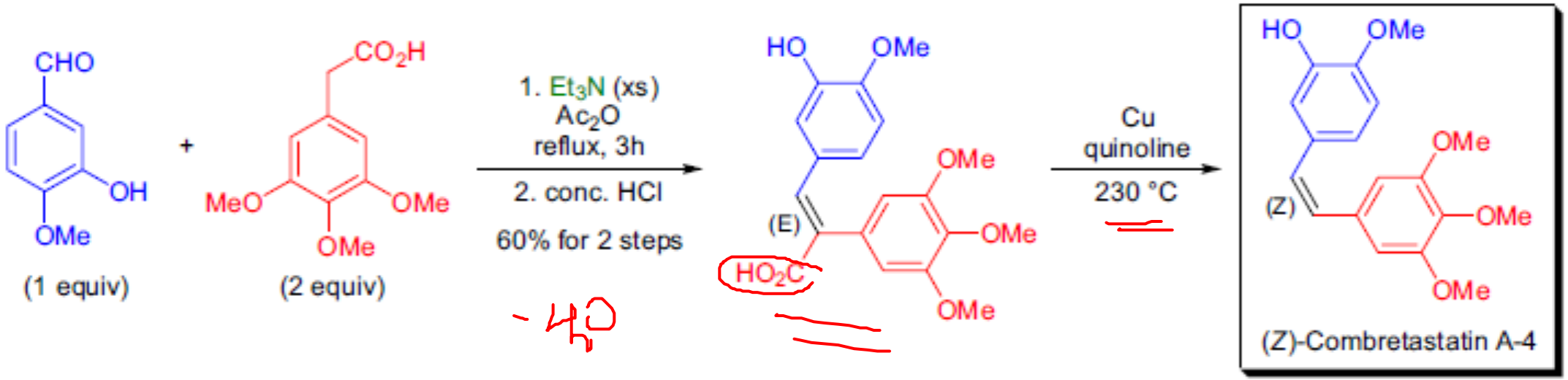
D. V. Sevenard, *Tetrahedron Lett.* **2003**, *44*, 7119.



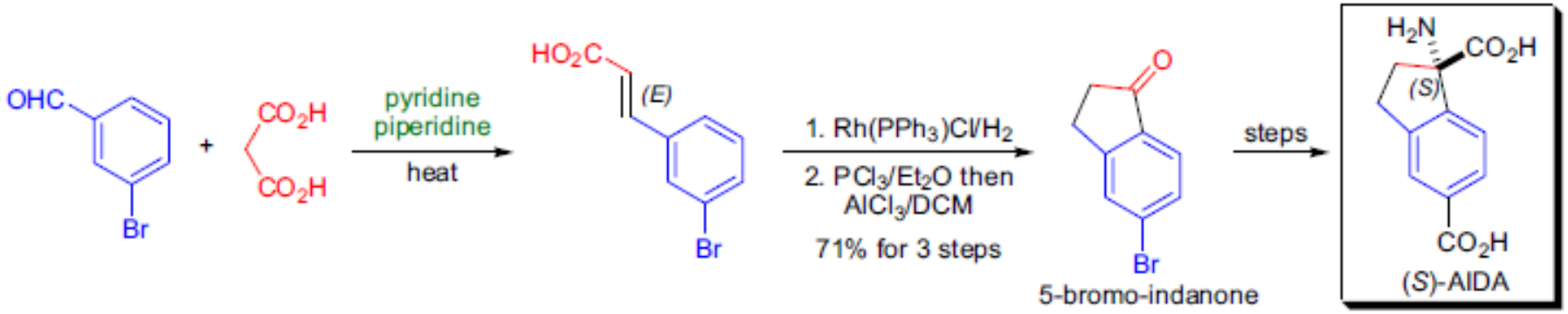
R. F. Buckles, J. A. Cooper,
J. Org. Chem. **1965,** *30*, 1588.



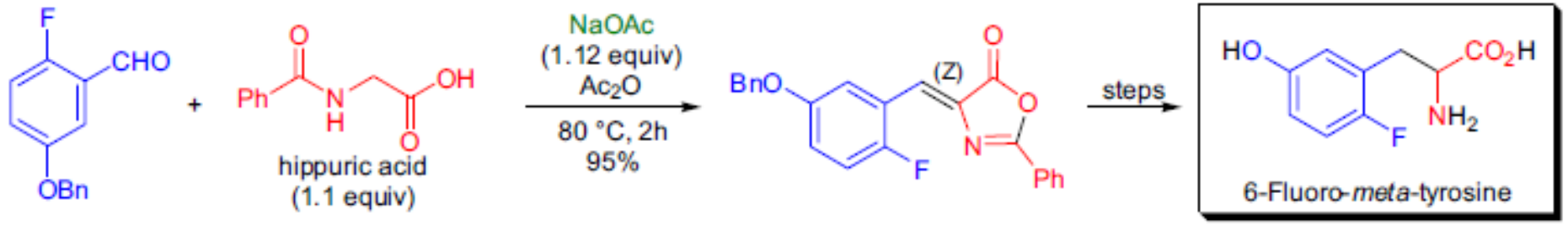
The combretastatins are a group of antimitotic agents isolated from the bark of the South African tree *Combretum caffrum*. A novel and highly stereoselective total synthesis of both the *cis* and *trans* isomers of combretastatin A-4 was developed by J.A. Hadfield and co-workers. The (*Z*)-stereoisomer was prepared using the *Perkin reaction* as the key step in which 3,4,5-trimethoxyphenylacetic acid and 3-hydroxy-4-methoxbenzaldehyde was heated with triethylamine and acetic anhydride at reflux for several hours. The α,β-unsaturated acid was isolated in good yield after acidification and had the expected (*E*) stereochemistry. Decarboxylation of this acid was effected by heating it with copper powder in quinoline to afford the natural product (*Z*)-combretastatin A-4.



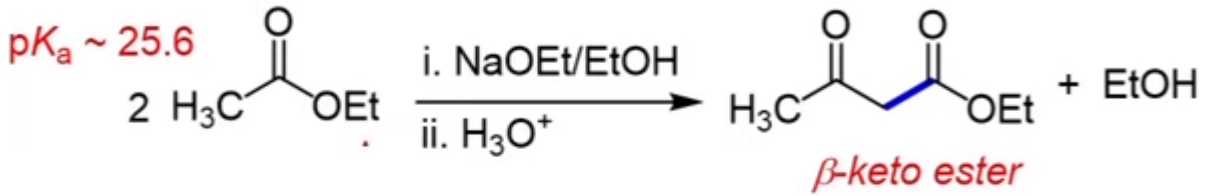
In the laboratory of D. Ma, the asymmetric synthesis of several metabotropic glutamate receptor antagonists derived from α-alkylated phenylglycines was undertaken. The preparation of (S)-1-aminoindan-1,5-dicarboxylic acid (AIDA) started with the Perkin reaction of 3-bromobenzaldehyde and malonic acid. The resulting (E)-cinnamic acid derivative was hydrogenated and the following intramolecular Friedel-Crafts acylation afforded the corresponding indanone, which was then converted to (S)-AIDA.



Fluorinated analogs of naturally occurring biologically active compounds, such as amino acids, often exhibit unique physiological properties, and therefore there is substantial interest in their convenient and high-yielding preparation. The research team of K.L. Kirk synthesized 6-fluoro-*meta*-tyrosine and several of its metabolites employing the *Erlenmeyer-Plöchl azlactone synthesis*. Hippuric acid and 2-benzyloxy-5-fluorobenzaldehyde were condensed in the presence of sodium acetate in acetic anhydride to isolate the corresponding azlactone, which was converted to the target fluorinated amino acid in three steps.

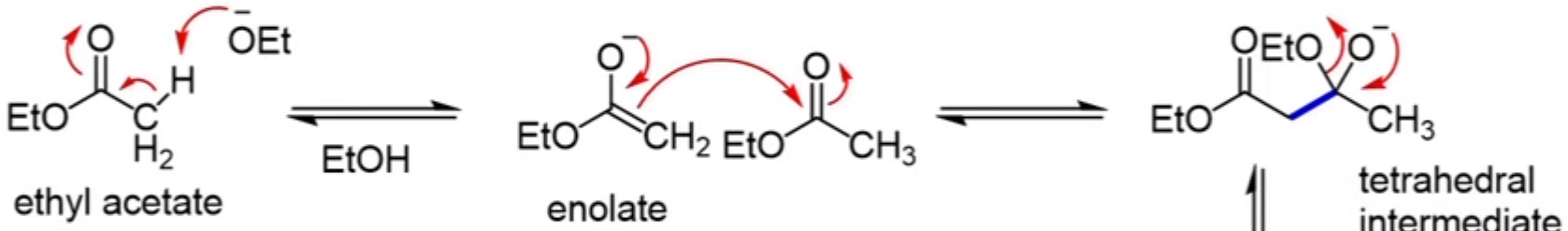


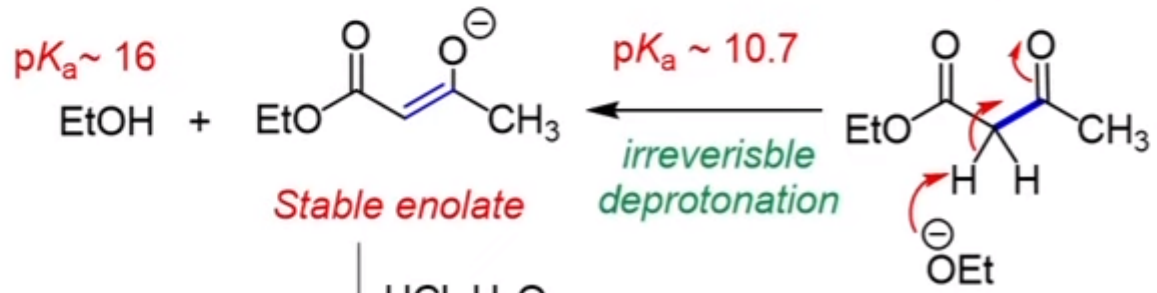
Claisen Condensation



Important: an equiv of amount base is to be used; unlike the Aldol Condensation

Mechanism

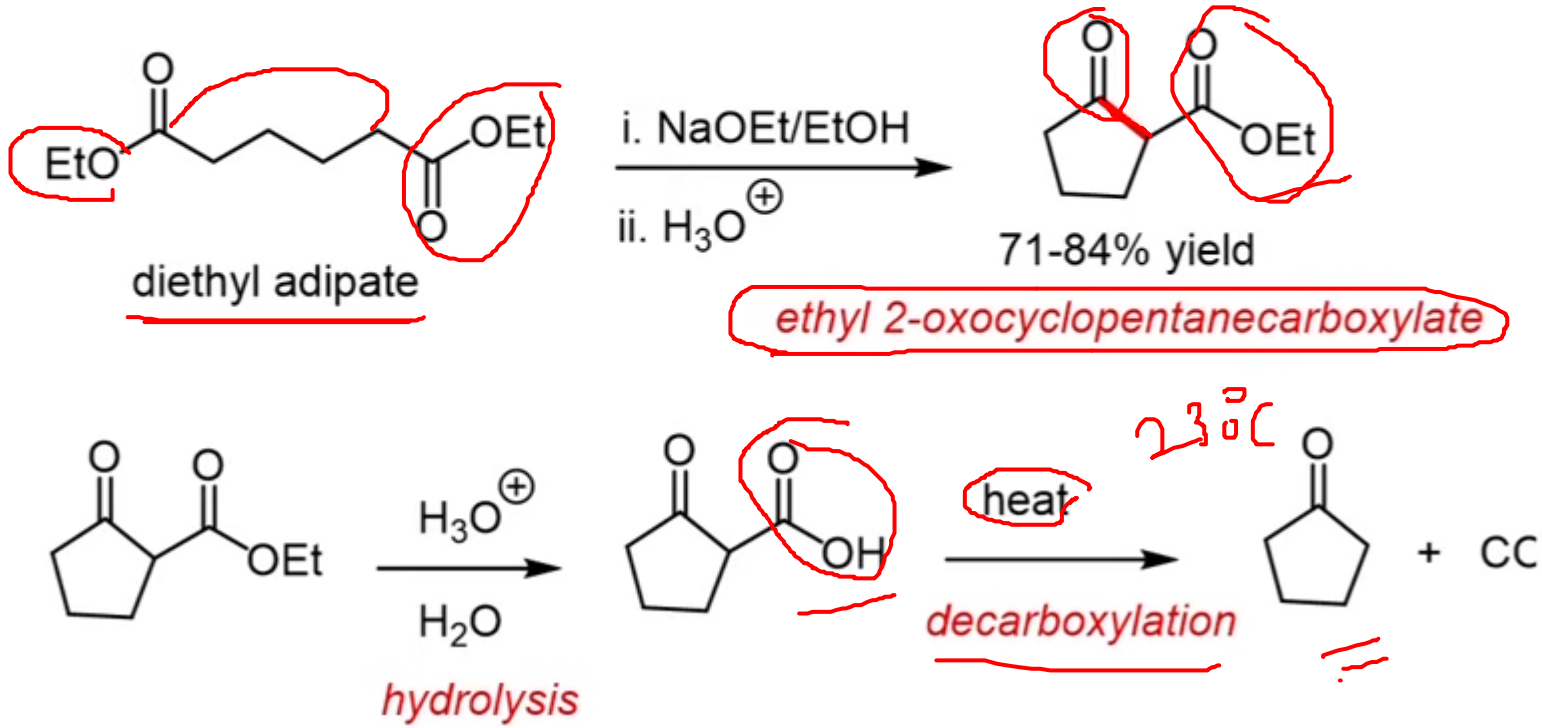




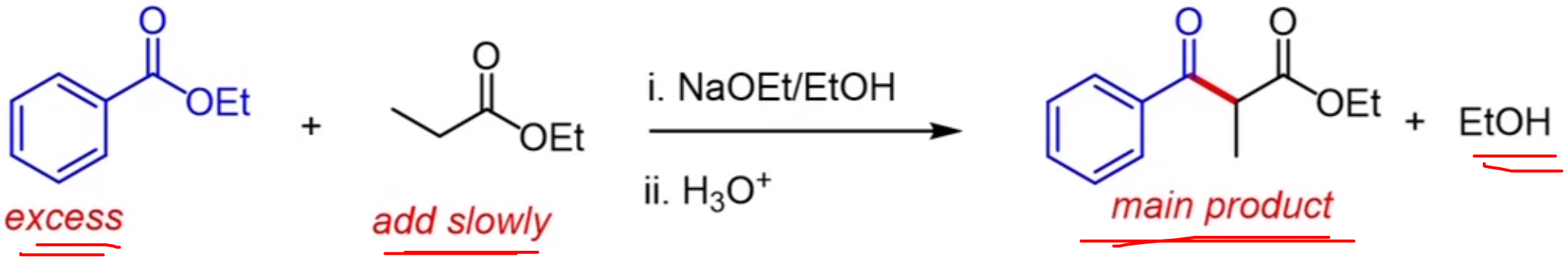
R. L. Claisen, German Chemist

(1851-1930)

Intramolecular Acylation:The Dieckmann Reaction

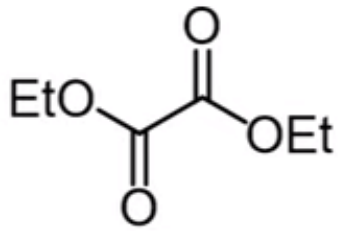


Crossed Claisen Condensation

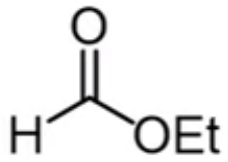


excess *add slowly* *main product*

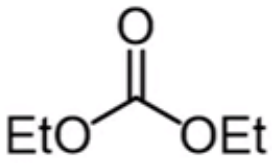
Esters that does not have acidic α-hydrogen



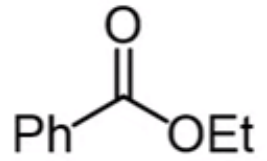
diethyl oxalate



ethyl formate

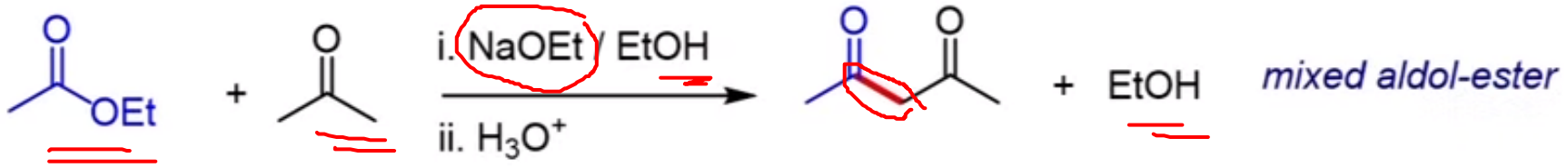


diethyl carbonate

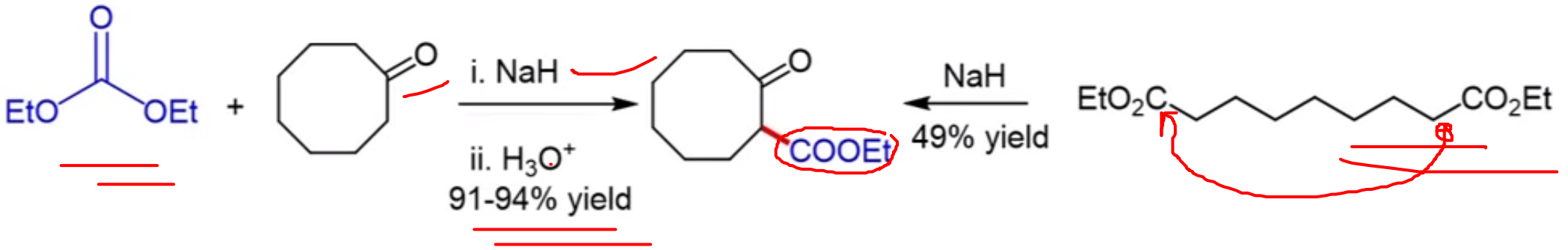


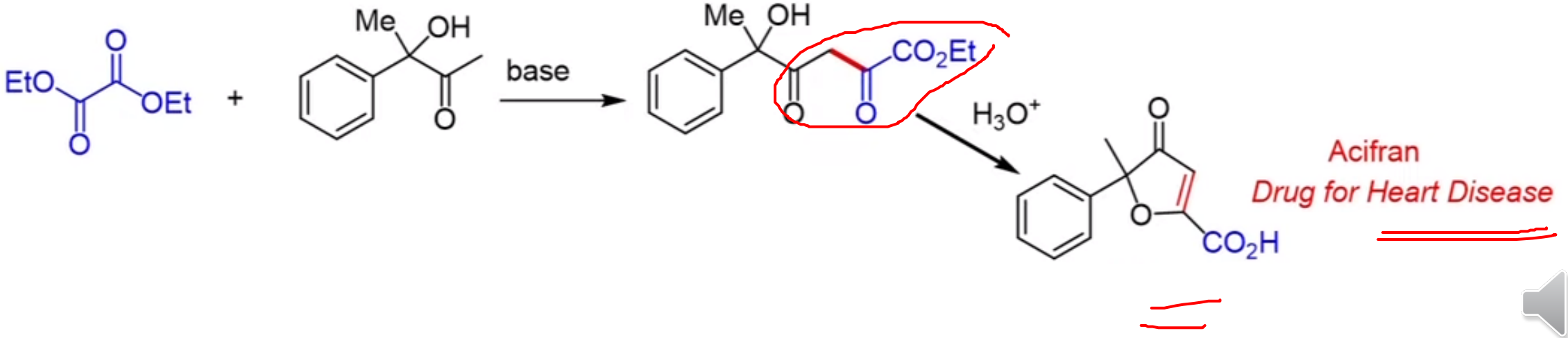
ethyl benzoate

Condensation of ketones with Esters



mixed aldol-ester

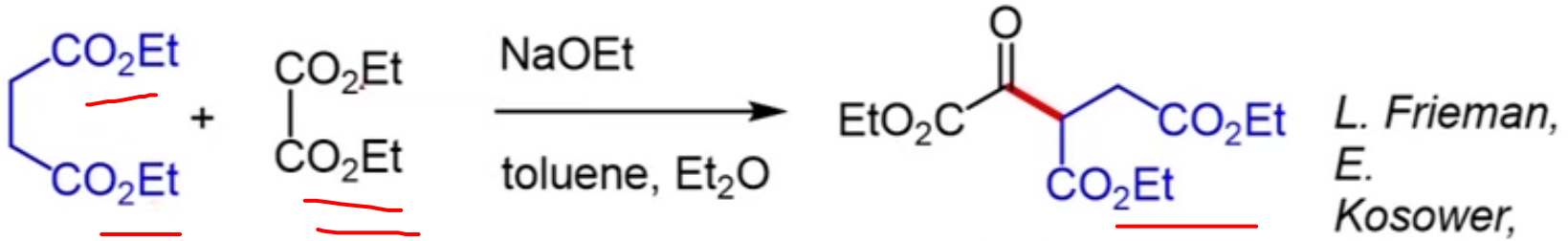




Acifran

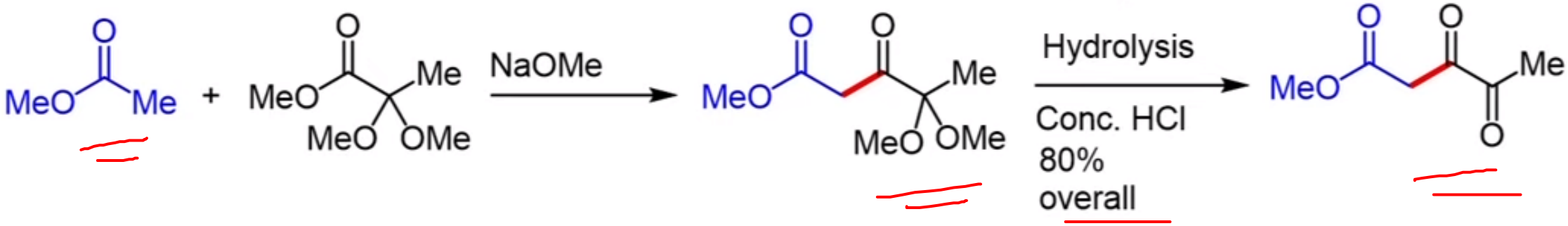
Drug for Heart Disease

Examples



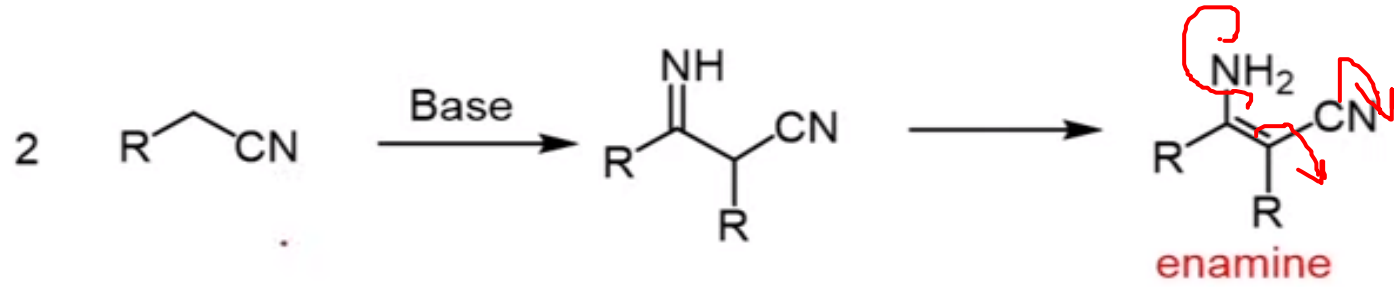
83% yield

L. Frieman, E. Kosower, Org. Synth. CV3, 510.

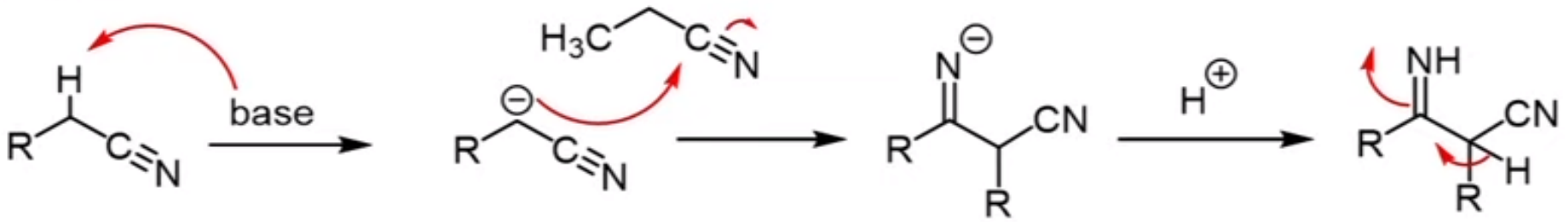


A. G. Cameron, A. T. Hewson, M. I. Osammur *Tetrahdron Lett.* **1884**, *25*, 2267.

Thorpe Reaction



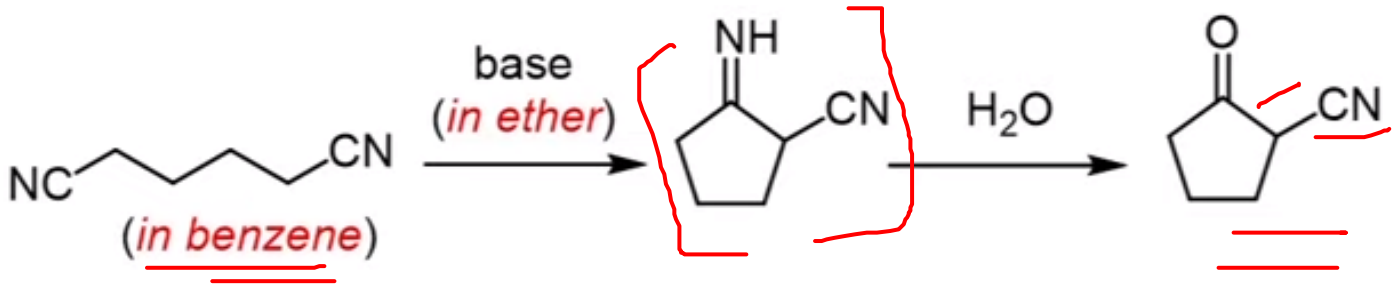
Mechanism



hydrolysis (if desired)

hydrolysis and decarboxylation (if desired)

Thorpe Ziegler Reaction



The *Thorpe reaction* is often better than the *Dieckmann Cyclization* ⟹ 5 and 6 membered rings for ring sizes > 7

Dieckmann

⇩

2 RCOOR'

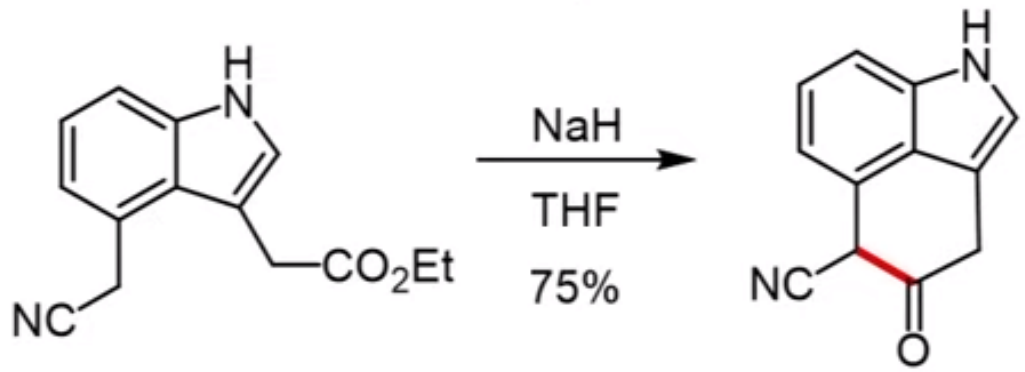
Nitrile and Ester

⇩

Thorpe

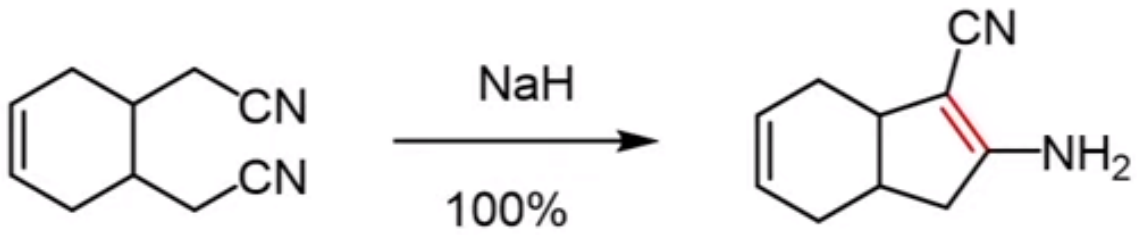
⇩

2 R-CN

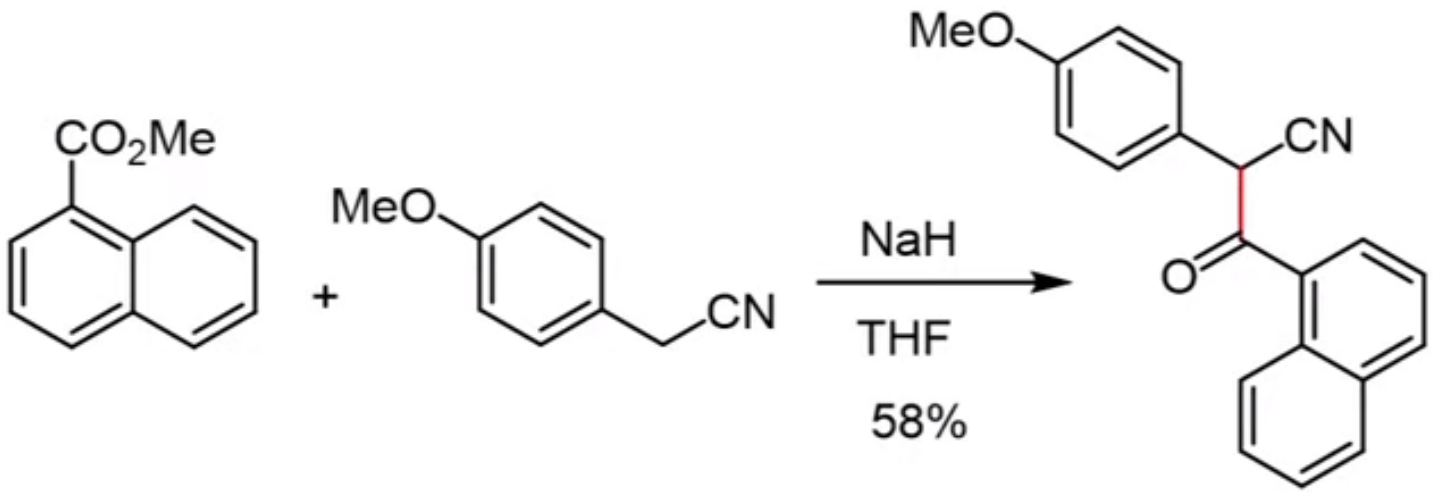


Thorpe Reaction:
7 membered ring 95%
8 membered ring 88%
9-15 membered <13%

Examples

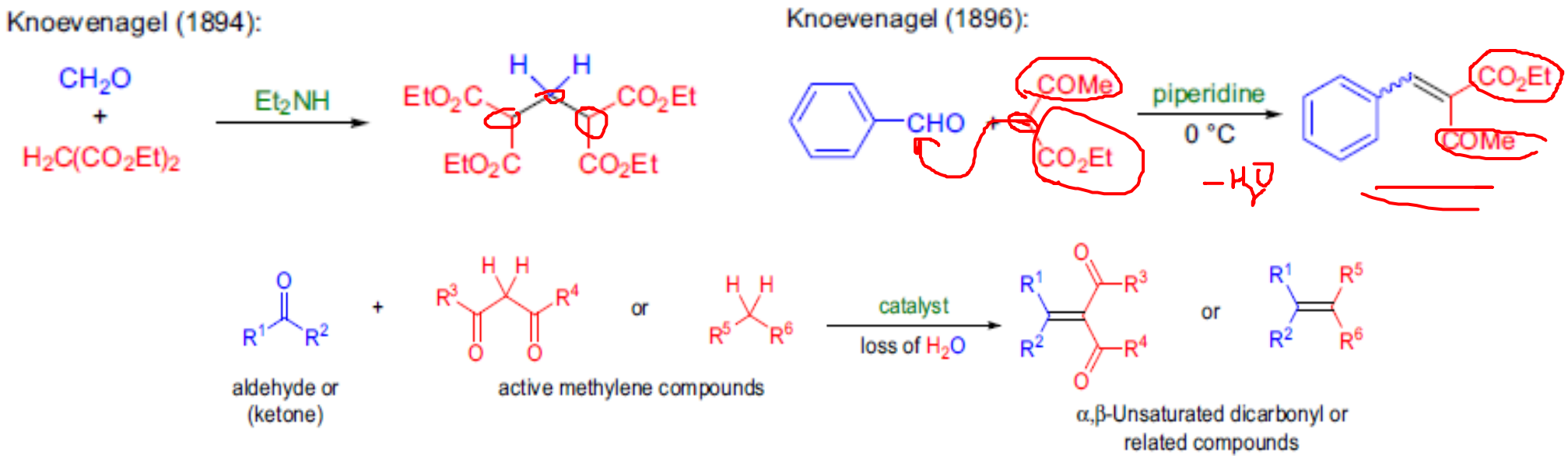


J. J. Bloomfield, P. V. Fennessey, *Tetrahedron Lett.* **1964**, *5*, 2273.



Knoevenagel condensation

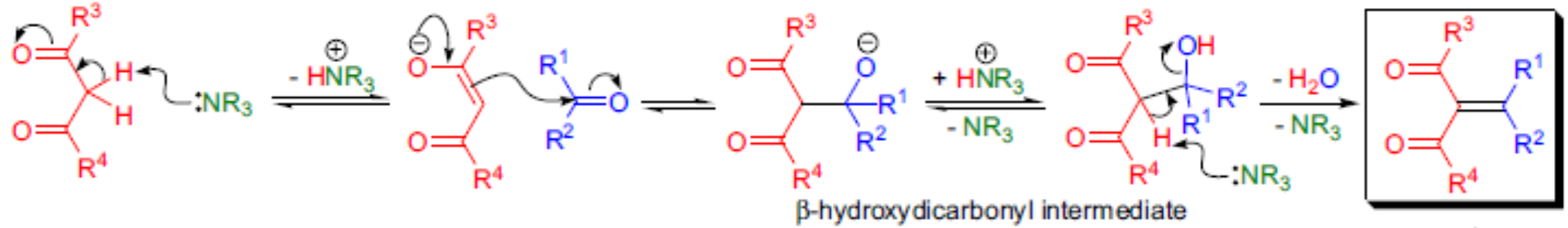
The reaction of aldehydes and ketones with active methylene compounds in the presence of a weak base to afford α,β-unsaturated dicarbonyl or related compounds is known as the *Knoevenagel condensation*.



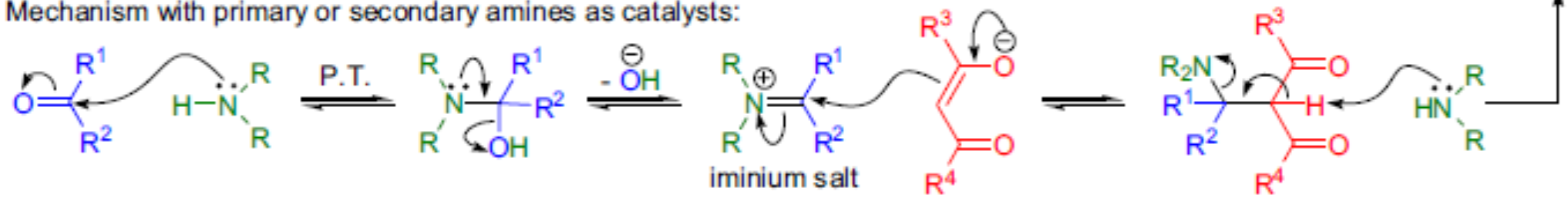
R^1 = H, alkyl, aryl; R^2 = H, alkyl, aryl; R^{3-4} = alkyl, aryl, OH, *O*-alkyl, *O*-aryl, NH-alkyl, NH-aryl *N*-dialkyl, *N*-diaryl; R^{5-6} = CO_2H, CO_2-alkyl, CO_2-aryl, C(O)NH-alkyl, C(O)NH-aryl, C(O)N-dialkyl, C(O)N-diaryl, C(O)-alkyl, C(O)-aryl, CN, $CNNR_2$, $PO(OR)_2$, SO_2OR, SO_2NR_2, SO_2R, SOR, SiR_3; catalyst: 1°, 2° or 3° amines, R_3NHX such as $[H_3NCH_2CH_2NH_3](OAc)_2$, piperidinium acetate/AcOH, NH_4OAc, KF, CsF, RbF, $TiCl_4/R_3N$ (*Lehnert modification*), pyridine/piperidine (*Doebner modification*), dry alumina (*Foucaud modification*), $AlPO_4/Al_2O_3$, xonotlite with KO*t*-Bu, $Zn(OAc)_2$

Knoevenagel condensation

The *Knoevenagel condensation* is a base-catalyzed *aldol-type reaction*, and the exact mechanism depends on the substrates and the type of catalyst used. The first proposal for the mechanism was set forth by A.C.O. Hann and A. Lapworth (*Hann-Lapworth mechanism*) in 1904. When tertiary amines are used as catalysts, the formation of a β- hydroxydicarbonyl intermediate is expected, which undergoes dehydration to afford the product. On the other hand, when secondary or primary amines are used as catalyst, the aldehyde and the amine condense to form an iminium salt that then reacts with the enolate. Finally, a 1,2-elimination gives rise to the desired α,β-unsaturated dicarbonyl or related compounds. The final product may undergo a *Michael addition* with the excess enolate to give a *bis* adduct.

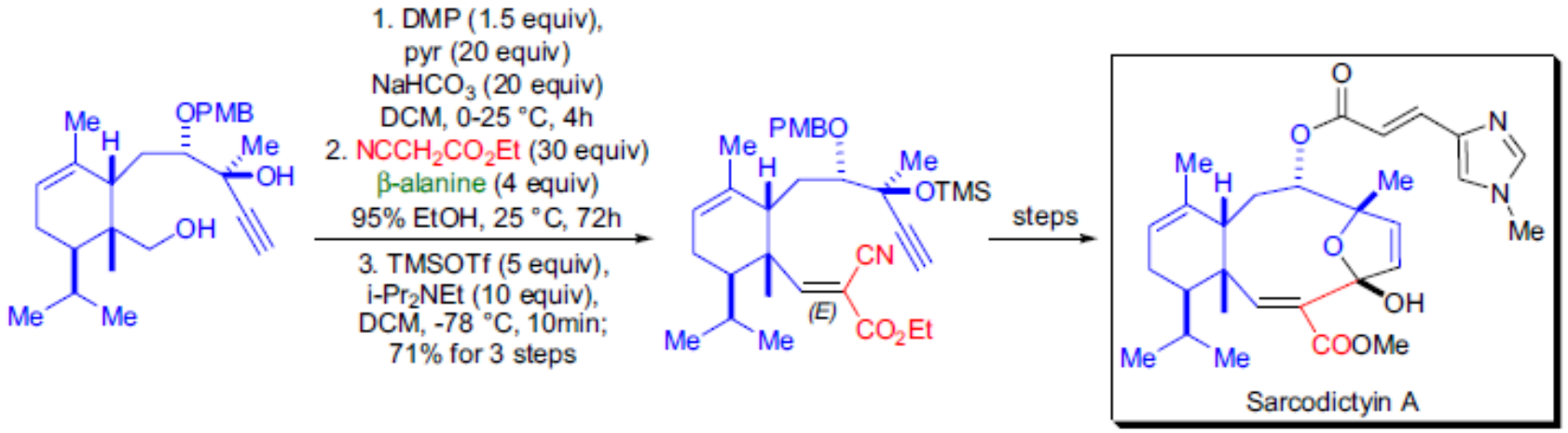


Mechanism with primary or secondary amines as catalysts:



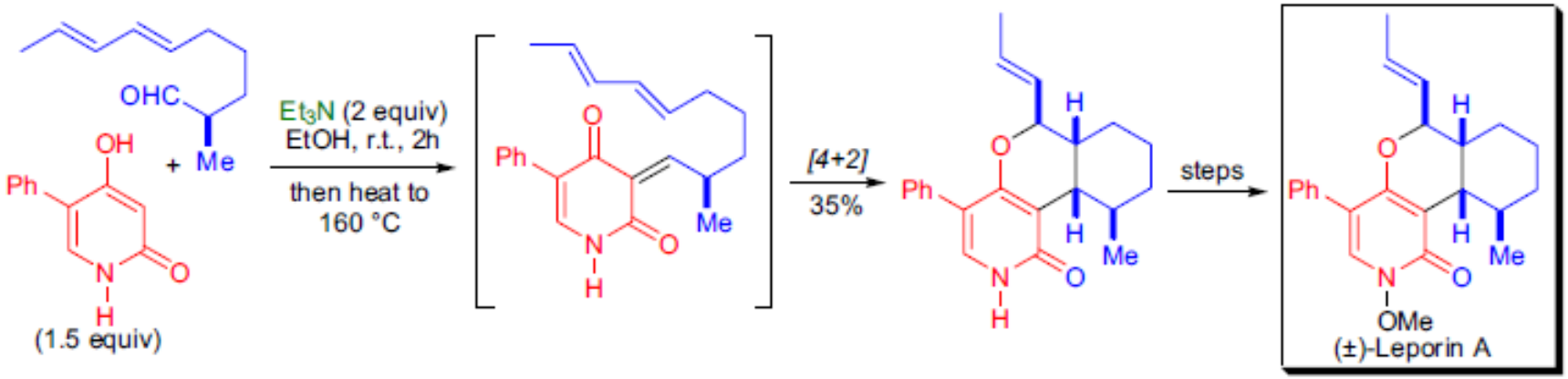
Examples

The total synthesis of the marine-derived diterpenoid sarcodictyin A was accomplished in the laboratory of K.C. Nicolaou. The most challenging part of the synthesis was the construction of the tricyclic core, which contains a 10- membered ring. This macrocycle was obtained by the intramolecular 1,2-addition of an acetylide anion to an α,β- unsaturated aldehyde. This unsaturated aldehyde moiety was installed by utilizing the *Knoevenagel condensation* catalyzed by β-alanine. The Knoevenagel product was exclusively the (*E*)-cyanoester.



Examples

During the total synthesis of (±)-leporin A, a tandem Knoevenagel condensation/inverse electron demand intramolecular hetero-Diels-Alder reaction was employed by B.B. Snider et al. to construct the key tricyclic intermediate. The condensation of pyridone with the enantiopure acyclic aldehyde in the presence of triethylamine as catalyst afforded an intermediate that underwent a [4+2] cycloaddition to afford the tricyclic core of the target.



The stereocontrolled total synthesis of (±)-gelsemine was accomplished by T. Fukuyama and co-workers using the *Knoevenagel condensation* to prepare a precursor for the key *divinylcyclopropane-cycloheptadiene rearrangement*. The use of 4 iodooxindole as the active methylene component allowed the preparation of the (*Z*)-alkylidene indolinone product as a single stereoisomer.