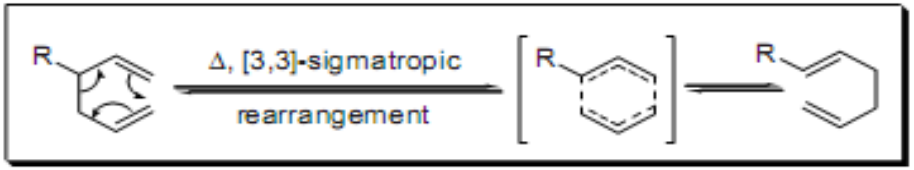
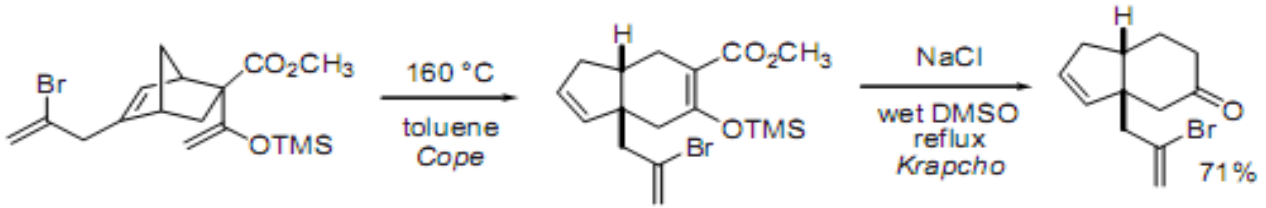
Cope rearrangement

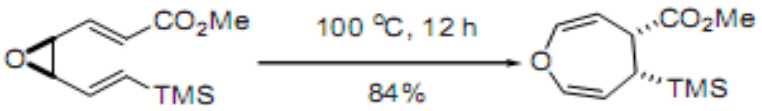
The Cope, oxy-Cope, and anionic oxy-Cope rearrangements belong to the category of *[3,3]-sigmatropic rearrangements*. Since it is a concerted process, the arrow pushing here is only illustrative. This reaction is an equilibrium process. *Cf.* Claisen rearrangement.



Example 1[4]



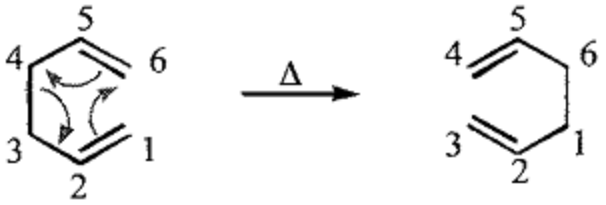
Example 2[6]



Cope and Related Reactions

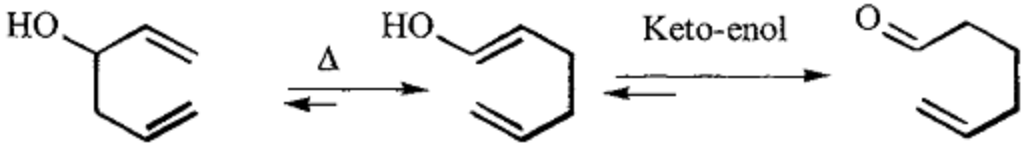
Aza-Cope Rearrangement

Cope Rearrangement



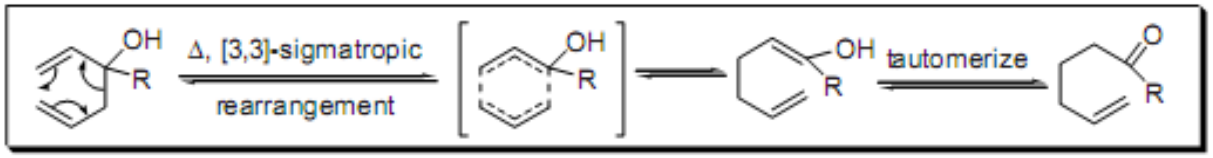
Azo-Cope Rearrangement

Oxy-Cope Rearrangement

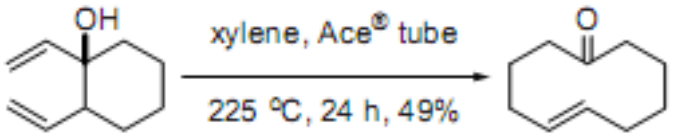


Oxy-Cope rearrangement

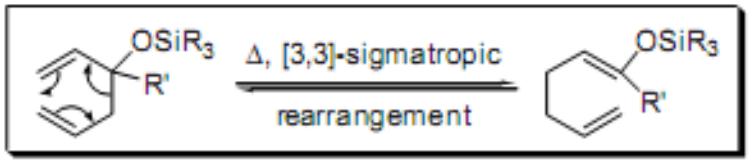
While the anionic oxy-Cope rearrangements work at low temperature, the oxy-Cope rearrangements require high temperature but provide a thermodynamic sink.



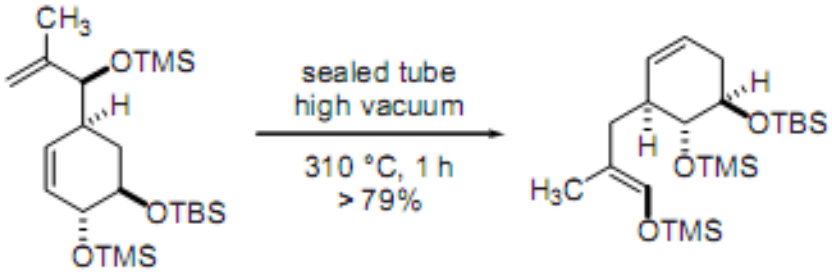
Example



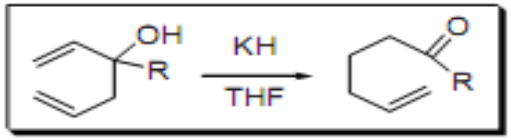
Siloxy-Cope rearrangement

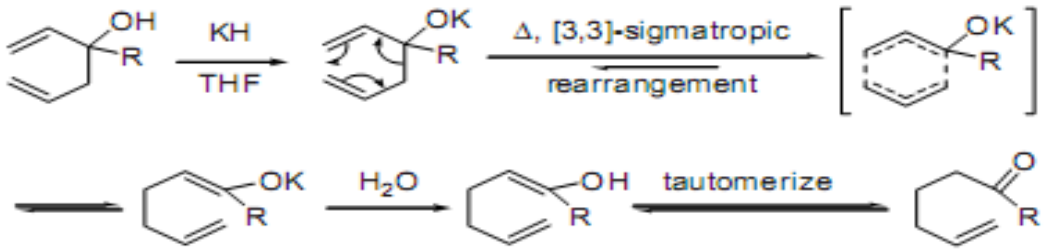


Example 1[1]

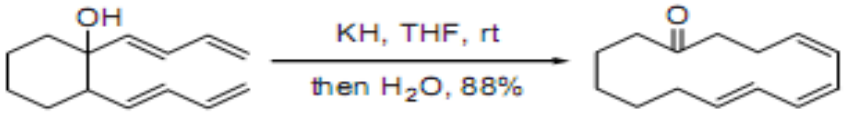


Anionic oxy-Cope rearrangement

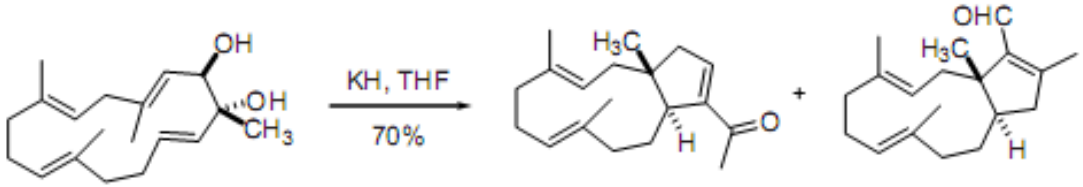




Example 1[1]



Example 2[4]

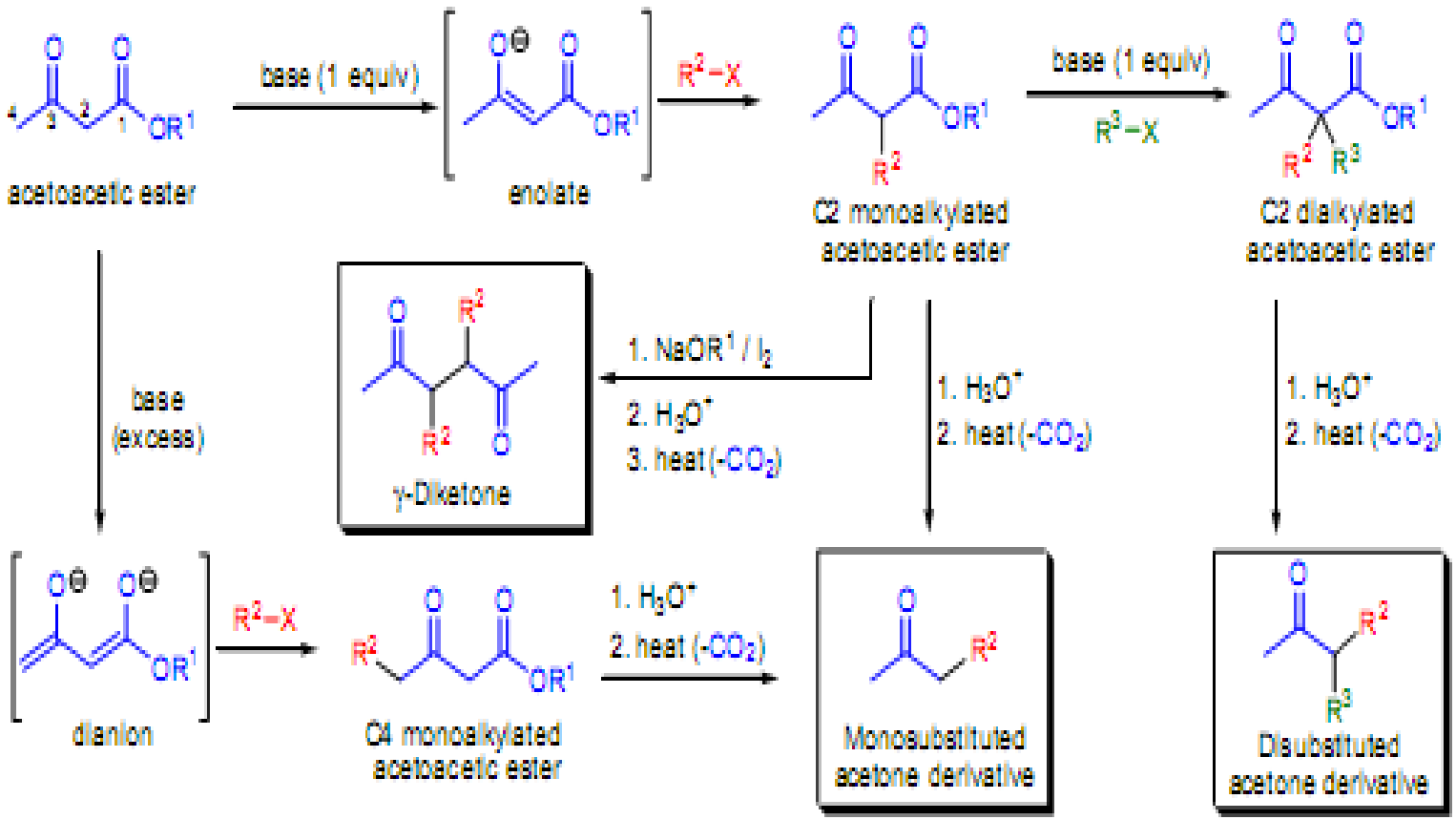


ACETOACETIC ESTER SYNTHESIS

Importance:

The preparation of ketones *via* the *C*-alkylation of esters of 3-oxobutanoic acid (acetoacetic esters) is called the *acetoacetic ester synthesis*. Acetoacetic esters can be deprotonated at either the C2 or at both the C2 and C4 carbons, depending on the amount of base used. The C-H bonds on the C2 carbon atom are activated by the electron-withdrawing effect of the two neighboring carbonyl groups. These protons are fairly acidic (pK_a ~11 for C2 and pK_a ~24 for C4), so the C2 position is deprotonated first in the presence of one equivalent of base (sodium alkoxide, LDA, NaHMDS or LiHMDS, etc.). The resulting anion can be trapped with various alkylating agents. A second alkylation at C2 is also possible with another equivalent of base and alkylating agent. When an acetoacetic ester is subjected to excess base, the corresponding dianion (extended enolate) is formed.[13-15,18,19] When an electrophile (e.g., alkyl halide) is added to the dianion, alkylation occurs first at the most nucleophilic (reactive) C4 position. The resulting alkylated acetoacetic ester derivatives can be subjected to two types of hydrolytic cleavage, depending on the conditions: 1) dilute acid hydrolyzes the ester group, and the resulting β-keto acid undergoes decarboxylation to give a ketone (mono- or disubstituted acetone derivative); 2) aqueous base induces a *retro-Claisen reaction* to afford acids after protonation. The hydrolysis by dilute acid is most commonly used, since the reaction mixture is not contaminated with by-products derived from ketonic scission. More recently the use of the *Krapcho decarboxylation* allows neutral decarboxylation conditions.[11,12] As with malonic ester, monoalkyl derivatives of acetoacetic ester undergo a base-catalyzed coupling reaction in the presence of iodine. Hydrolysis and decarboxylation of the coupled products produce γ-diketones. The starting acetoacetic esters are most often obtained *via* the *Claisen condensation* of the corresponding esters, but other methods are also available for their preparation.[5,8]

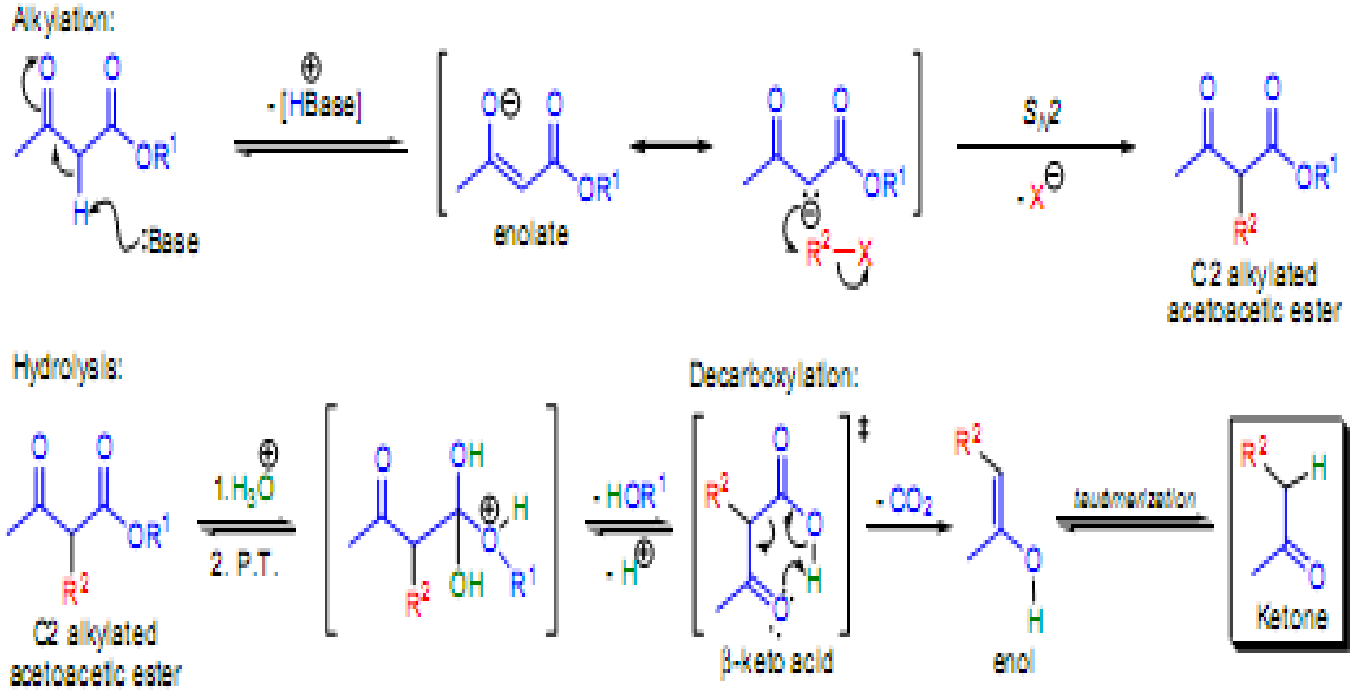
ACETOACETIC ESTER SYNTHESIS



R^1 = 1°, 2° or 3° alkyl, aryl; R^2 = 1° or 2° alkyl, allyl, benzyl; R^3 = 1° or 2° alkyl, allyl, benzyl; base: NaH, $NaOR^1$, LiHMDS, NaHMDS

Mechanism: [3,20]

The first step is the deprotonation of acetoacetic ester at the C2 position with one equivalent of base. The resulting enolate is nucleophilic and reacts with the electrophilic alkyl halide in an S_N2 reaction to afford the C2 substituted acetoacetic ester, which can be isolated. The ester is hydrolyzed by treatment with aqueous acid to the corresponding β-keto acid, which is thermally unstable and undergoes decarboxylation *via* a six-membered transition state.



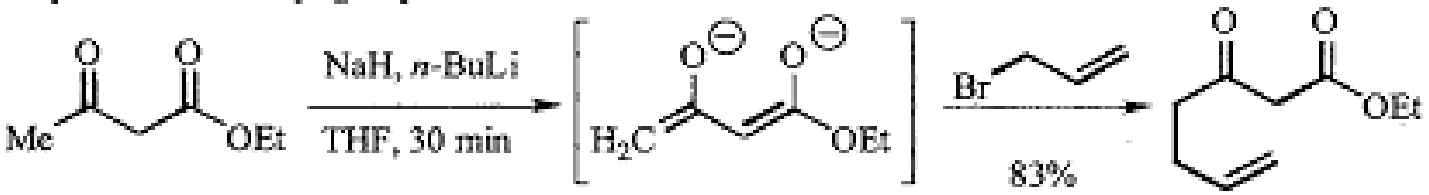
Notes:

Acetoacetic Ester can be prepared by the condensation of ethyl acetate, called the ***Acetoacetic Ester Condensation Reaction***, a ***Claisen Condensation***:

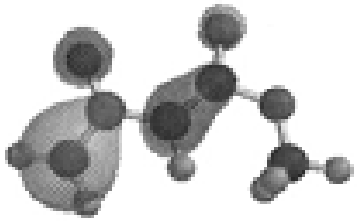
J. K. H. Inglis and K. C. Roberts
Organic Syntheses CV1, 235

See M. B. Smith, J. March in *March's Advanced Organic Chemistry*, 5th ed., John Wiley and Sons, Inc., New York, 2001, p 549; and C. R. Hauser, B. E. Hudson, Jr., *Organic Reactions* 1, 9

Weiler Modification: By using very strong bases, a dianion can be formed that will preferentially alkylate at the methyl group:



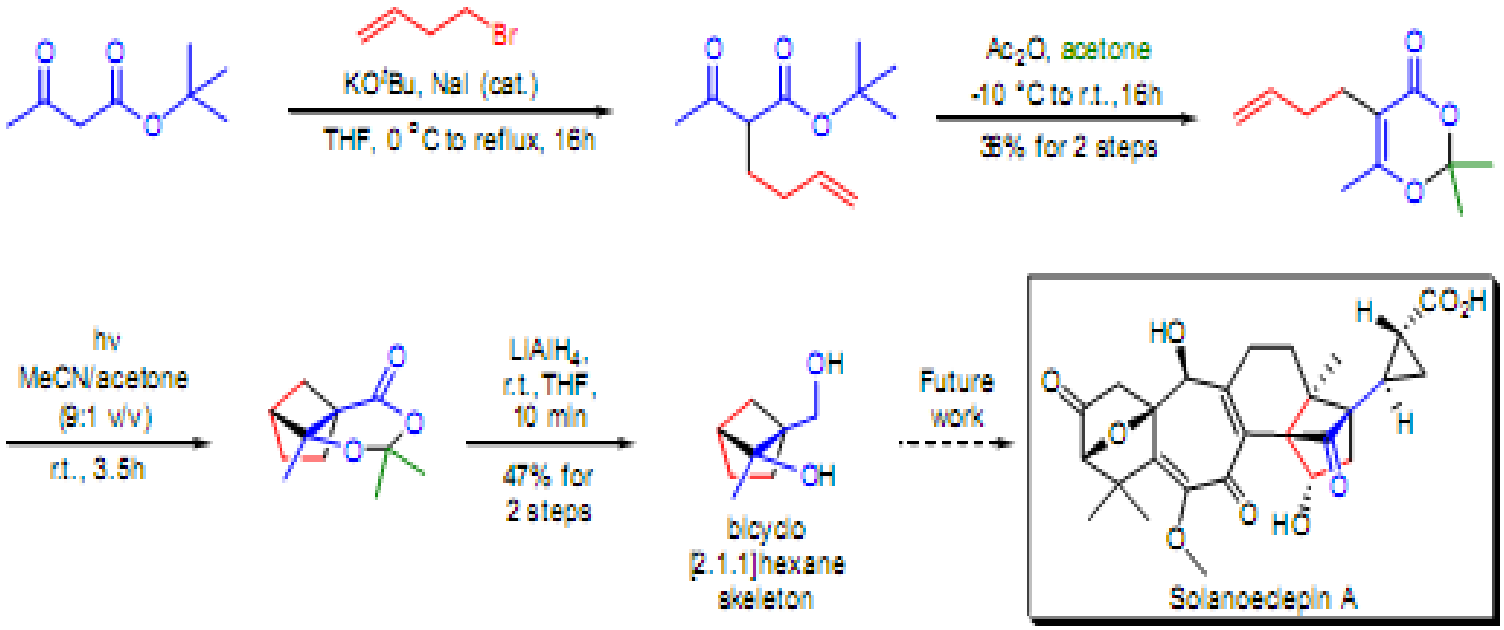
S. N. Huckin, L. Weiler *Journal of the American Chemical Society* **1974**, 96, 1082



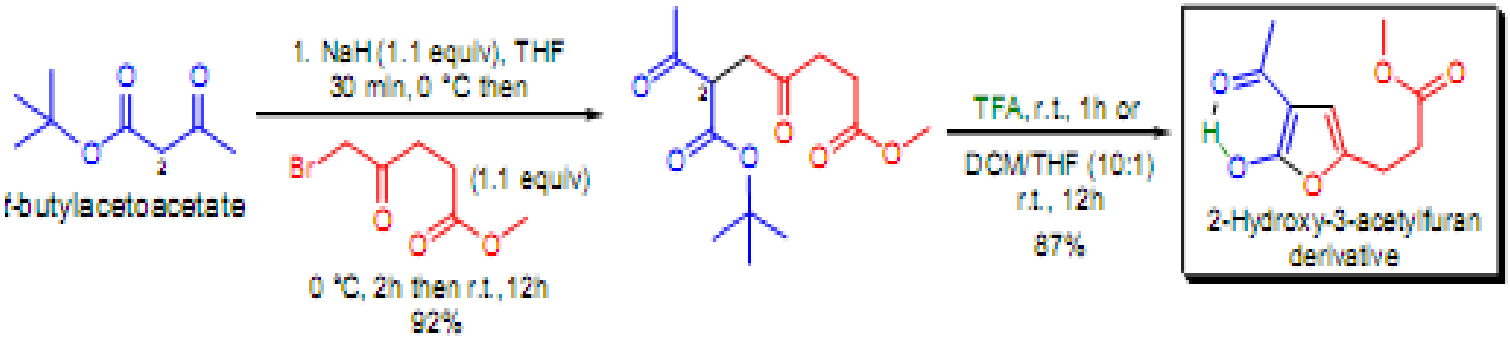
Simple AM1 calculation on Me ester shows the *HOMO* corresponding to the reactive intermediate

Synthetic Applications:

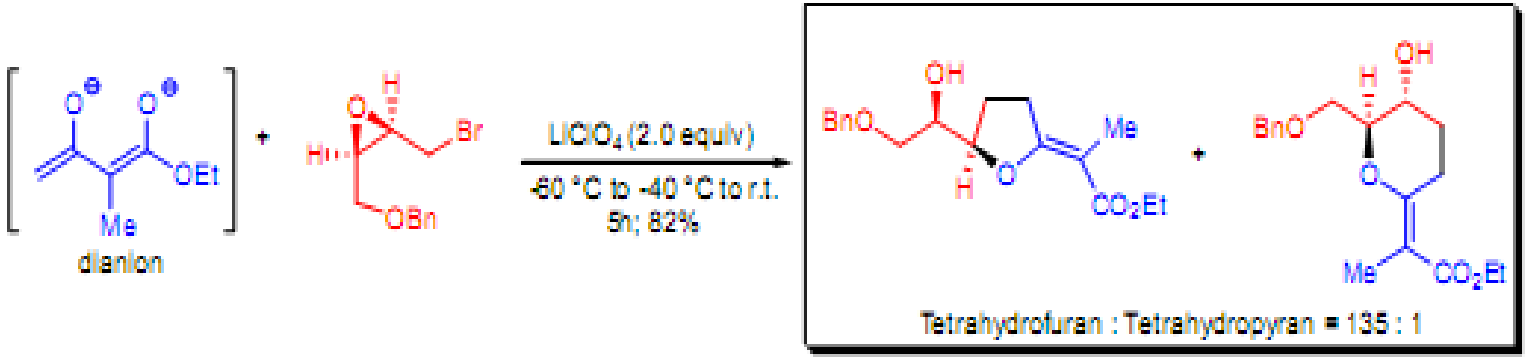
In the laboratory of H. Hiemstra, the synthesis of the bicyclo[2.1.1]hexane substructure of solanoaclepin A was undertaken utilizing the intramolecular photochemical dioxenone-alkene [2+2] cycloaddition reaction.[21] The dioxenone precursor was prepared from the commercially available *tert*-butyl acetoacetate using the *acetoacetic ester synthesis*. When this dioxenone precursor was subjected to irradiation at 300 nm, complete conversion of the starting material was observed after about 4h, and the expected cycloadduct was formed in acceptable yield.



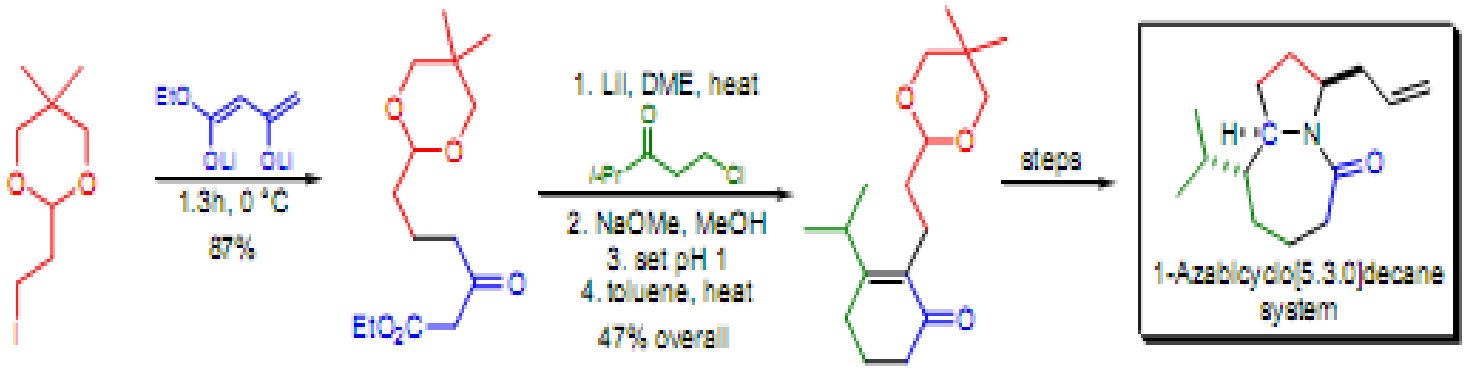
R. Naier et al. synthesized substituted 2-hydroxy-3-acetylfurans by the alkylation of *tert*-butylacetoacetate with an α-haloketone, followed by treatment of the intermediate with trifluoroacetic acid.[22] When furans are prepared from β-ketoesters and α-haloketones, the reaction is known as the *Feist-Bénary reaction*. A second alkylation of the C2 alkylated intermediate with various bromoalkanes yielded 2,2-disubstituted products, which upon treatment with TFA, provided access to trisubstituted furans.



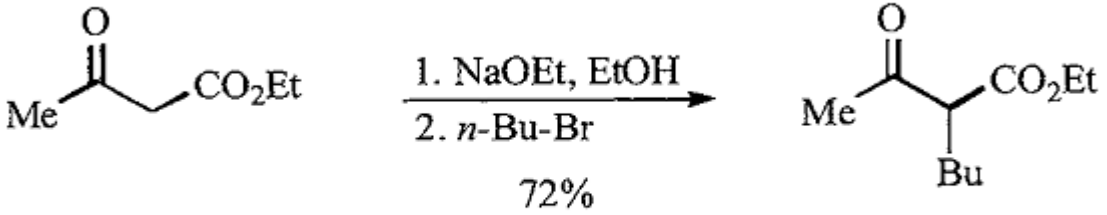
M. Nakada and co-workers developed a novel synthesis of tetrahydrofuran and tetrahydropyran derivatives by reacting dianions of acetoacetic esters with epibromohydrin derivatives.[23] The selective formation of the tetrahydrofuran derivatives was achieved by the use of $LiClO_4$ as an additive.



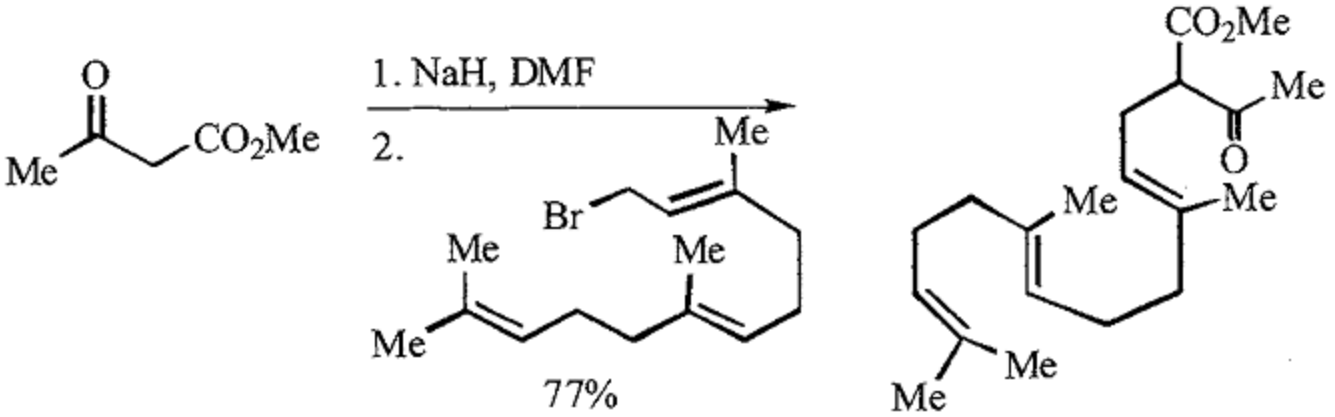
A synthetic strategy was developed for the typical core structure of the *Stemona* alkaloids in the laboratory of C.H. Heathcock.[24] The precursor for the 1-azabicyclo[5.3.0]decane ring system was prepared *via* the successive double alkylation of the dianion of ethyl acetoacetate.



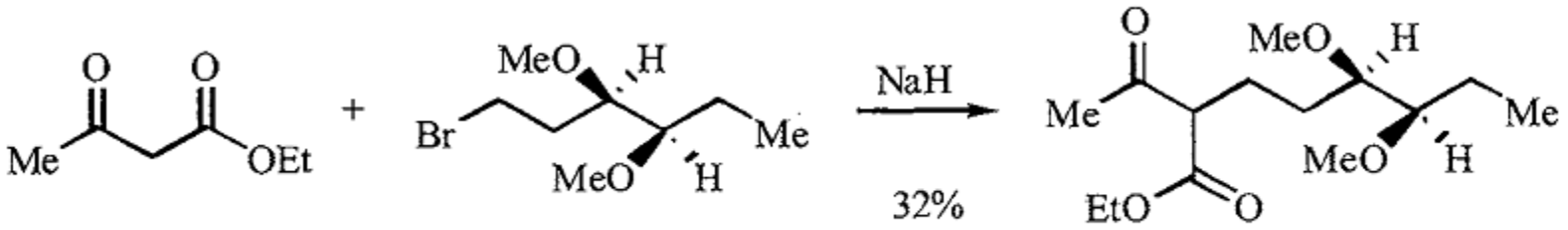
Examples:



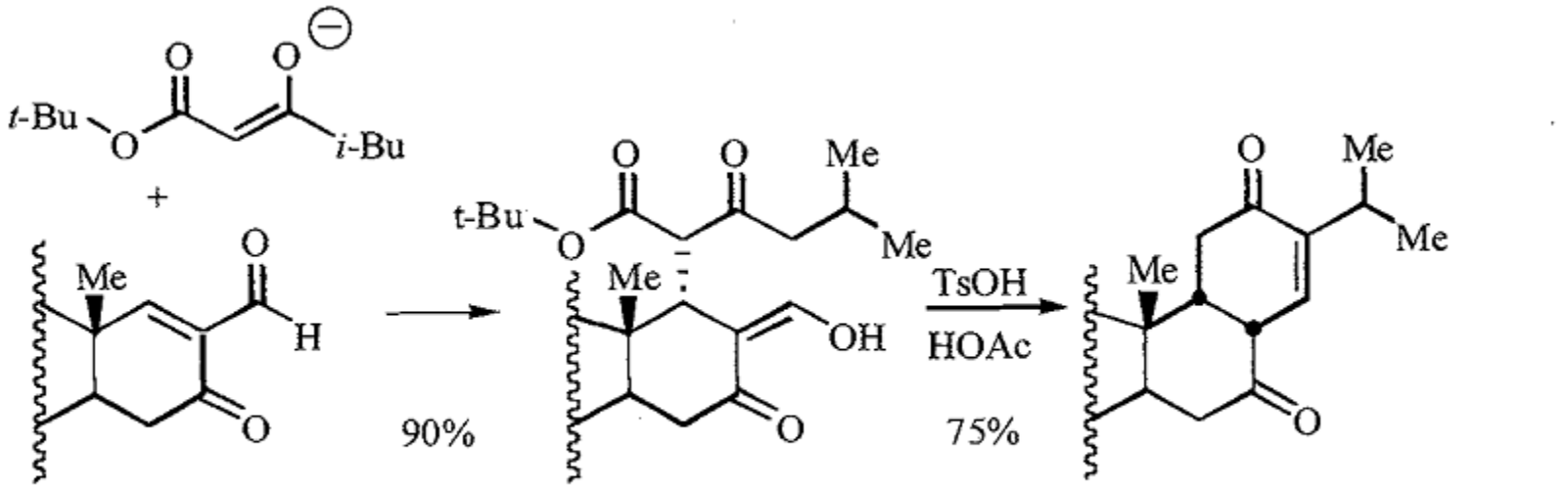
C. S. Marvel, F. D. Hager, *Organic Syntheses* **1941**, 1, 248



K. A. Parker, L. Resnick, *Journal of Organic Chemistry* **1995**, 60, 5726



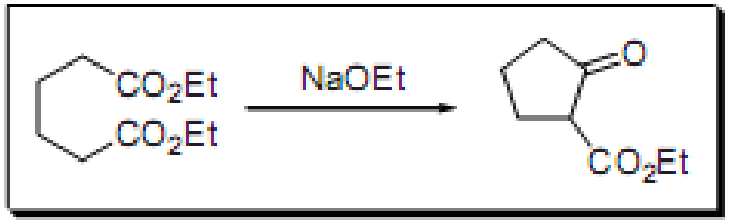
K. Mori, *Tetrahedron* **1974**, 30, 4223



W. L. Meyer, M. J. Brannon, C. da G. Burgos, T. E. Goodwin, R. W. Howard, *Journal of Organic Chemistry* **1985**, 50, 438

Dieckmann condensation

The Dieckmann condensation is the intramolecular version of the Claisen condensation.

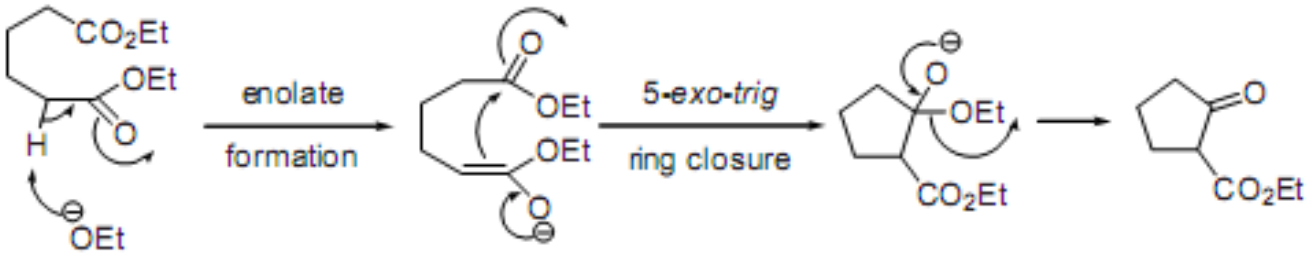


The base-catalyzed intramolecular condensation of a diester. The Dieckmann Condensation works well to produce 5- or 6-membered cyclic ß-keto esters, and is usually effected with sodium alkoxide in alcoholic solvent.

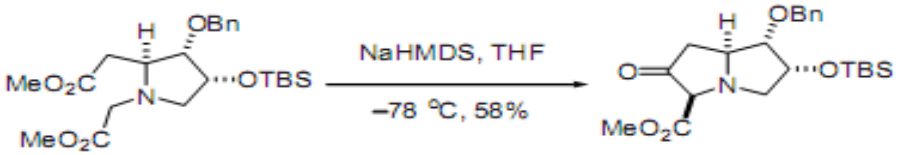
The yields are good if the product has an enolizable proton; otherwise, the reverse reaction (cleavage with ring scission) can compete. See the Claisen Condensation.

Mechanism

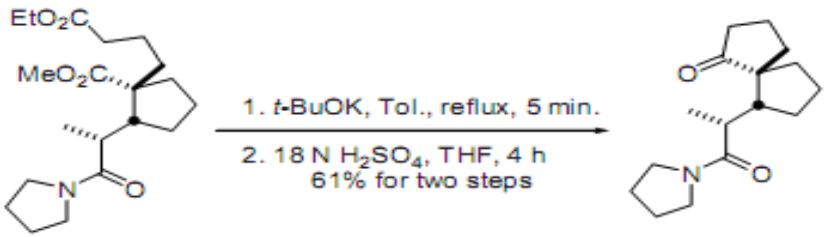
The mechanism is similar to the Claisen Condensation.



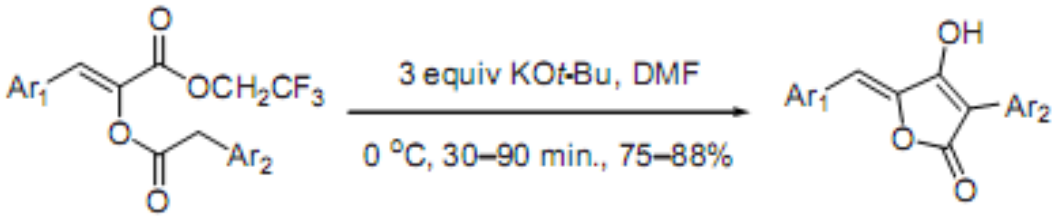
Example 1[6]



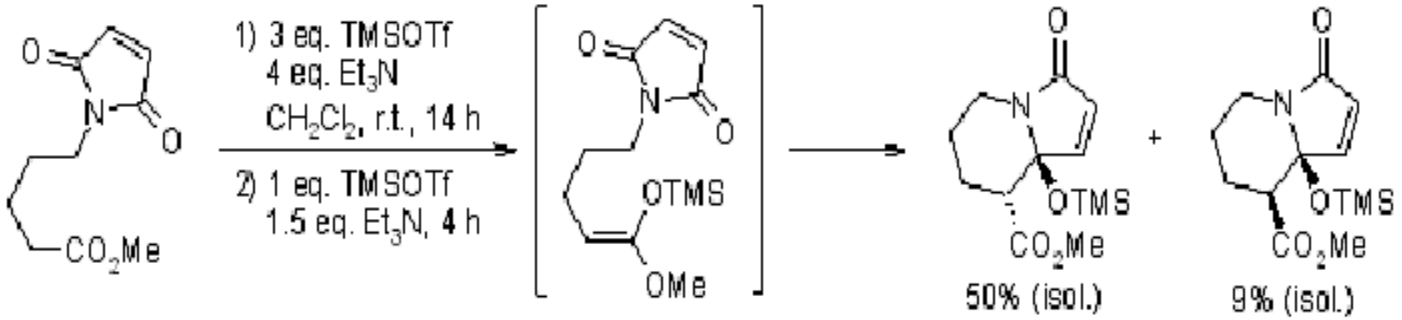
Example 2[8]



Example 3[9]

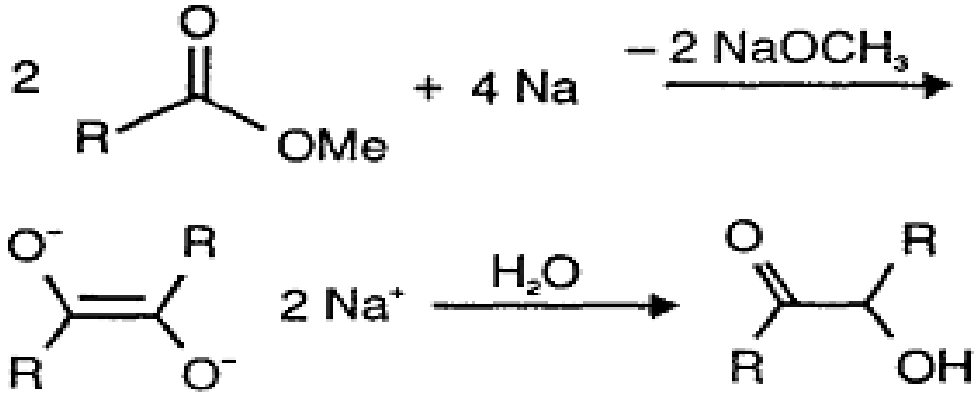


Recent Literature

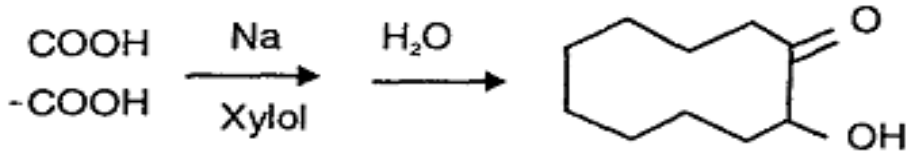


Silylative Dieckmann-Like Cyclizations of Ester-Imides (and Diesters)
T. R. Hoye, V. Dvornikovs, E. Sizova, *Org. Lett.*, **2006**, *8*, 5089-5091.

ACYLOIN CONDENSATION



The bimolecular reductive coupling of carboxylic esters by reaction with metallic sodium in an inert solvent under reflux gives an α-hydroxyketone, which is known as an acyloin. This reaction is favoured when R is an alkyl. With longer alkyl chains, higher boiling solvents can be used. The intramolecular version of this reaction has been used extensively to close rings of different sizes, e.g. paracyclophanes or catenanes.

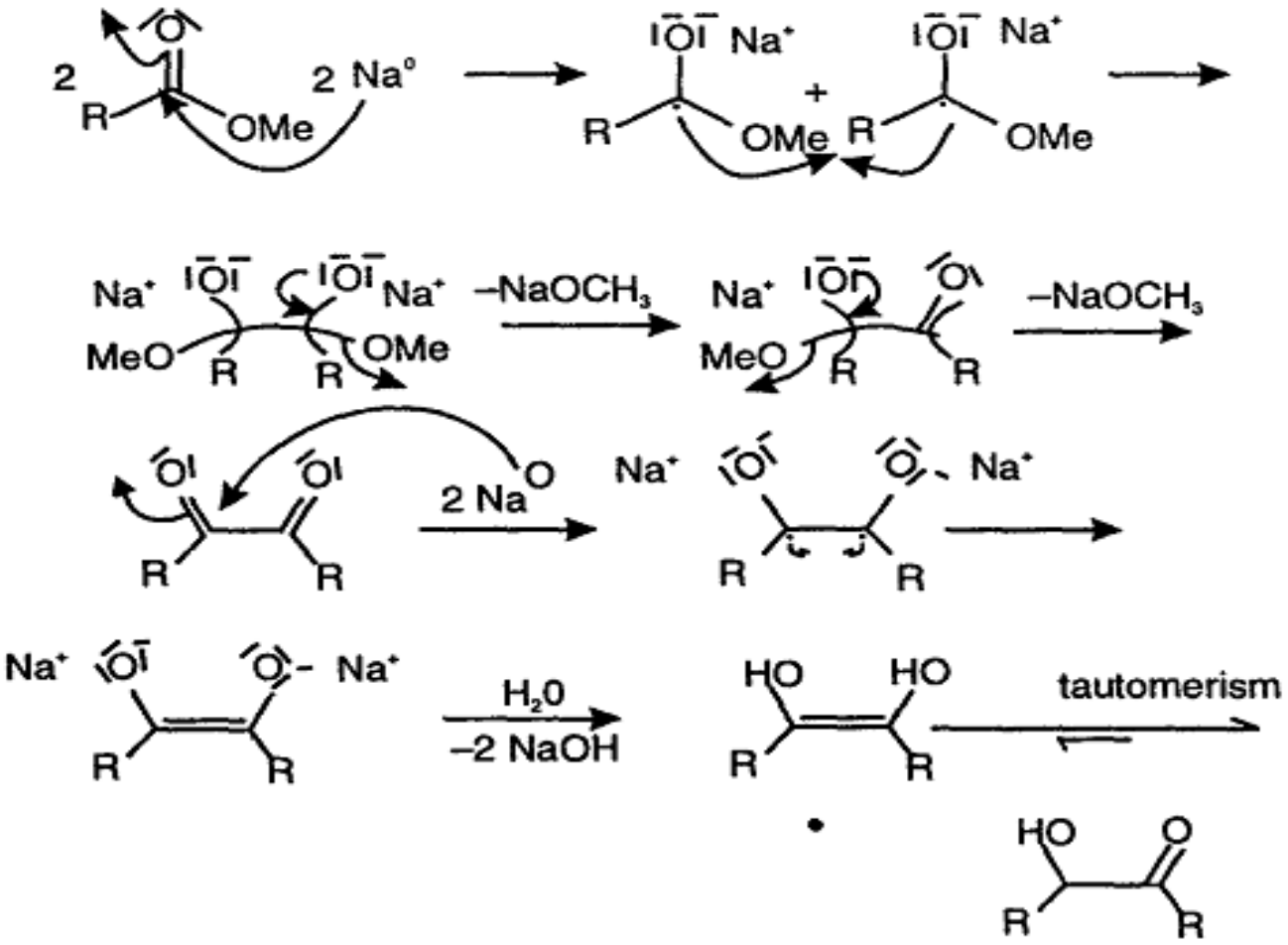


If the reaction is carried out in the presence of a proton donor, such as alcohol, simple reduction of the ester to the alcohol takes place (Bouveault-Blanc Reduction).

The Benzoin Condensation produces similar products, although with aromatic substituents and under different conditions.

When the acyloin condensation is carried out in the presence of chlorotrimethylsilane, the enediolate intermediate is trapped as the bis-silyl derivative. This can be isolated and subsequently is hydrolysed under acidic condition to the acyloin, which gives a better overall yield.

Mechanism

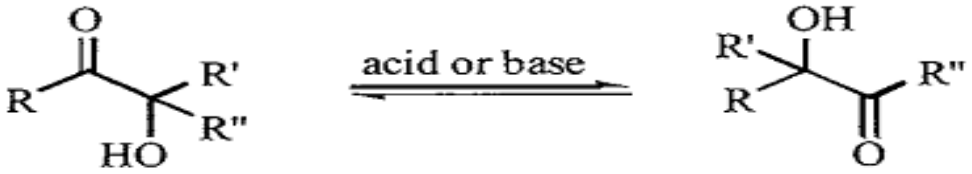


If two moles of a base are added in the first step, the hydrogen of the more acidic methylene group, and in the next step the hydrogen of the methyl group (ambident nucleophiles), reacts with the base. The hydrogenated methyl group is, however, more acidic than the hydrogenated methylene group. The reaction with alkylation agent in the following step gives a product substituted at methyl

group. This can be synthetically used to prepare selectively ketones of different types.

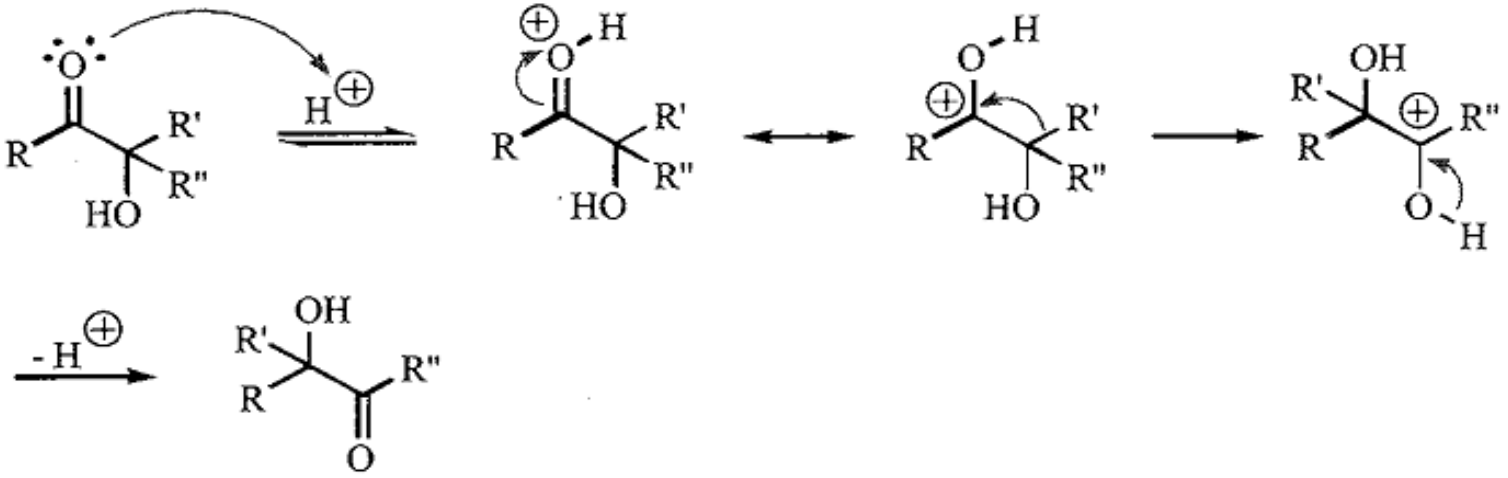
Acyloin Rearrangement

The Reaction:

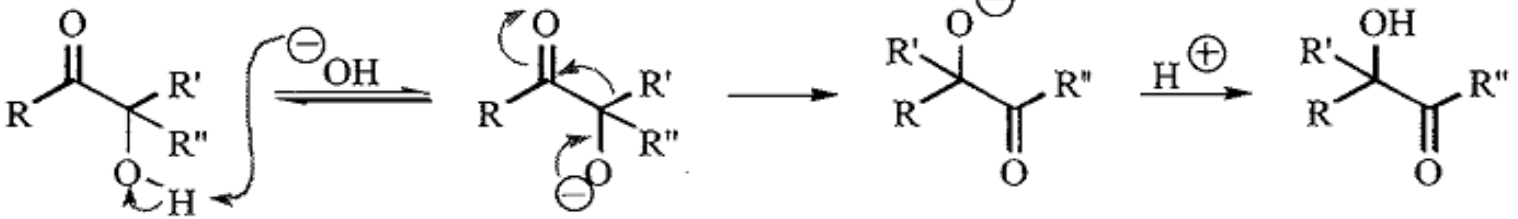


Proposed Mechanism:

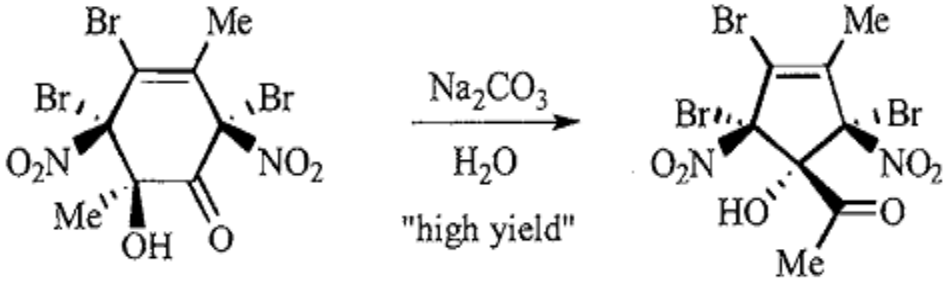
In acid:



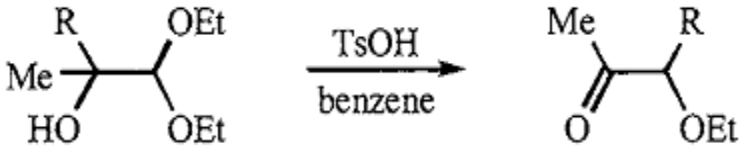
In base:



Examples:

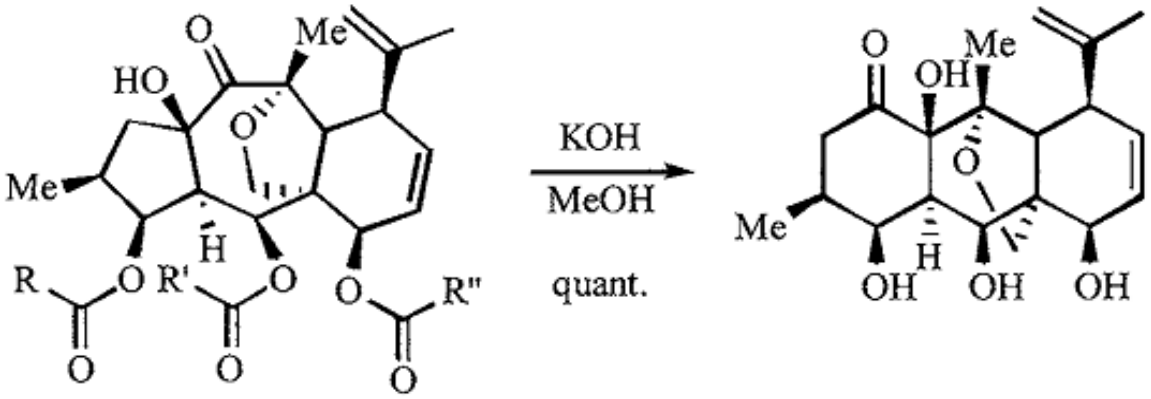


P. A. Bates, E. J. Ditzel, M. P. Hartshorn, H. T. Ing, K. E. Richards, W. T. Robinson, *Tetrahedron Letters* **1981**, 22, 2325



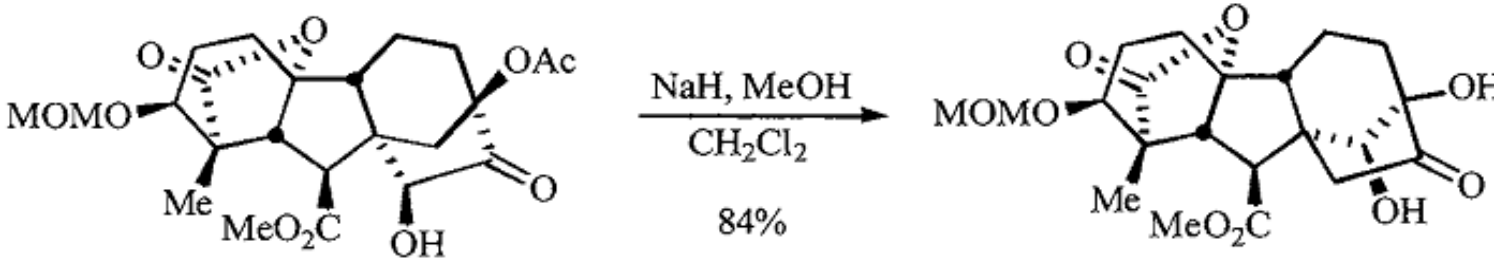
R = *i*-Pr 43%
R = Ph 80%

T. Sate, T. Nagata, K. Maeda, S. Ohtsuka, *Tetrahedron Letters* **1994**, 35, 5027



a mixture of acyl esters

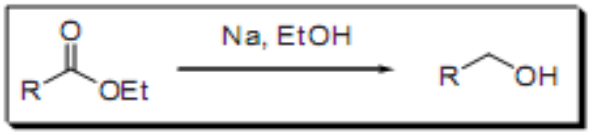
M. Rentzea, E. Hecker, *Tetrahedron Letters* **1982**, 23, 1785

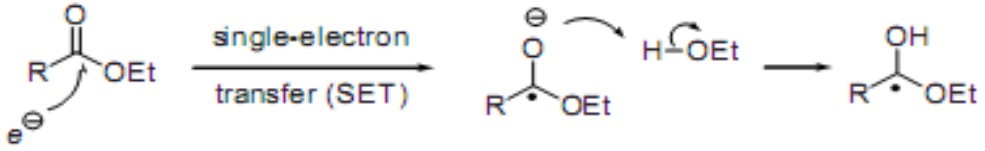


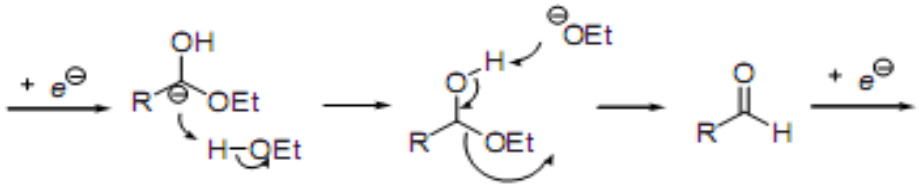
J. Liu, L. N. Mander, A. C. Willis, *Tetrahedron* **1998**, 54, 11637

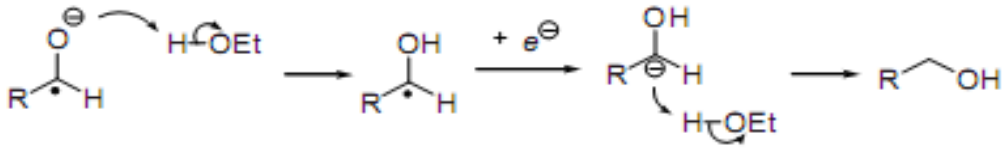
Bouveault–Blanc reduction

Reduction of esters to the corresponding alcohols using sodium in an alcoholic solvent.

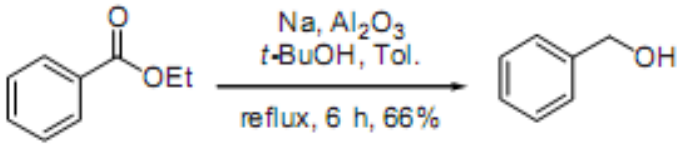








Example[2]

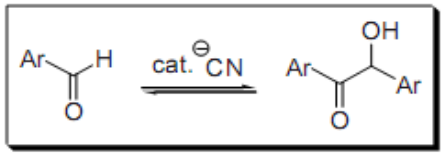


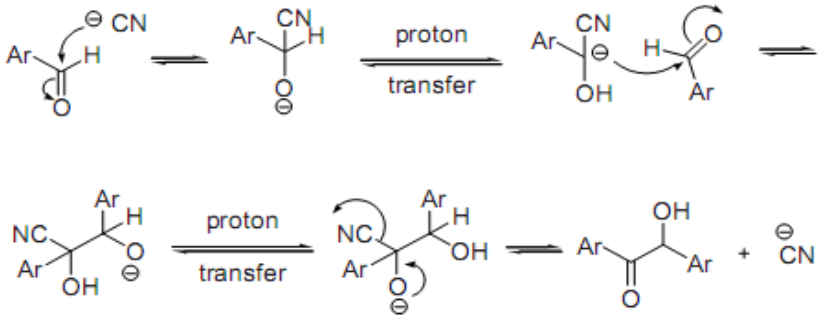
References

1. Bouveault, L.; Blanc, G. *Compt. Rend. Hebd. Seances Acad. Sci.* **1903**, *136*, 1676–1678.
2. Bouveault, L.; Blanc, G. *Bull. Soc. Chim.* **1904**, *31*, 666–672.
3. Rühlmann, K.; Seefluth, H.; Kiriakidis, T.; Michael, G.; Jancke, H.; Kriegsmann, H. *J. Organomet. Chem.* **1971**, *27*, 327–332.
4. Seo, B.-I.; Wall, L. K.; Lee, H.; Buttrum, J. W.; Lewis, D. E. *Synth. Commun.* **1993**, *23*, 15–22.
5. Singh, S.; Dev, S. *Tetrahedron* **1993**, *49*, 10959–10964.
6. Schopohl, M. C.; Bergander, K.; Kataeva, O.; Föehlich, R.; Waldvogel, S. R. *Synthesis* **2003**, 2689–2694.

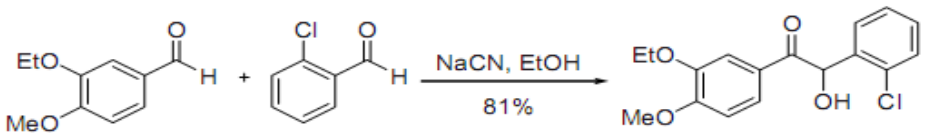
Benzoin condensation

Cyanide-catalyzed condensation of aryl aldehyde to benzoin. Now cyanide is mostly replaced by a thiazolium salt. *Cf.* Stetter reaction.

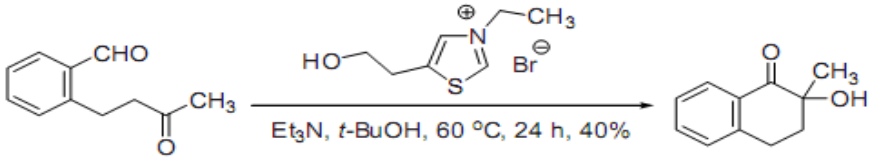




Example 1[2]

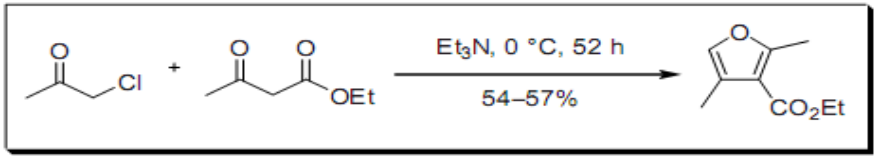


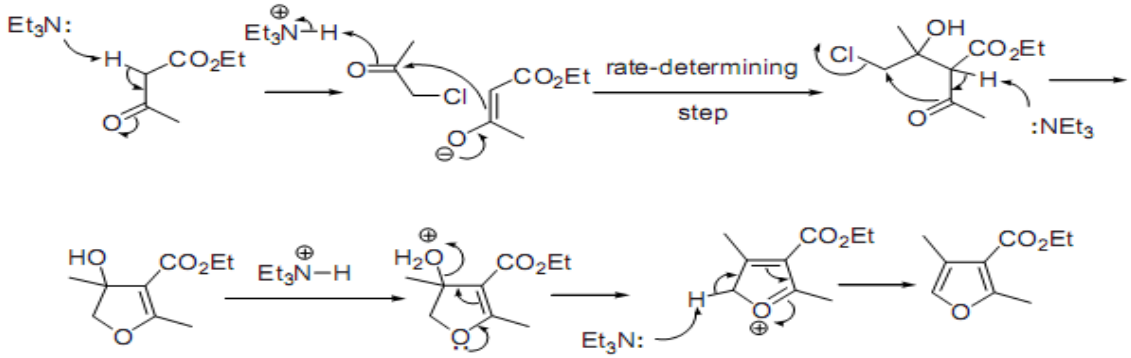
Example 2[7]



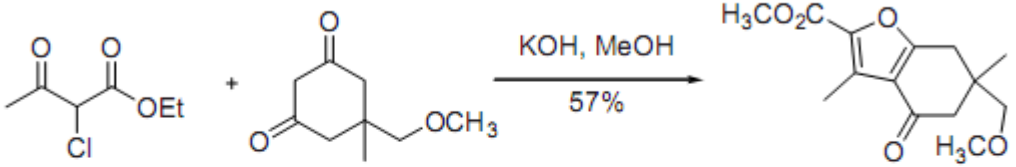
Feist–Bénary furan synthesis

α-Haloketones react with β-ketoesters in the presence of base to fashion furans.





Example 1[2,3]



Example 2[4]