STOBBE CONDENSATION

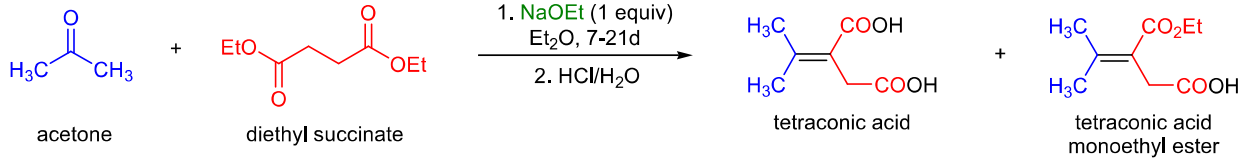
(References are on page 689)

Importance:

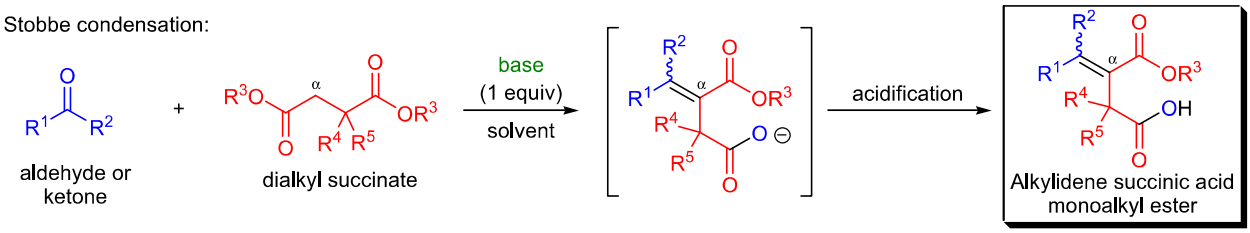
[*Seminal Publications*[1]; *Reviews*[2,3]; *Modifications & Improvements*[4-16]]

In 1893, H. Stobbe reported an unexpected reaction between acetone and diethyl succinate in the presence of a full equivalent of sodium ethoxide.[1] Upon acidification of the reaction mixture the major isolated product was found to be tetraconic acid, an α,β-unsaturated carboxylic acid, and its monoethyl ester. This result was surprising since the authors expected the formation of a 1,3-diketone *via* a *Claisen reaction*. A subsequent extensive study by Stobbe and co-workers revealed that the transformation was general for esters of succinic acid with aldehydes and ketones. The formation of alkylidene succinic acids or their monoesters by the base-mediated condensation of ketones and aldehydes with dialkyl succinates is known as the *Stobbe condensation*. The general features of the reaction are: 1) there is no restriction on the carbonyl component it may have hydrogens at its α-position; 2) aromatic-, α,β-unsaturated aldehydes and ketones as well as aliphatic ones are commonly used; 3) the diesters are mainly limited to succinic esters and their substituted derivatives, but certain α,ω-diesters that do not undergo competitive *Dieckmann condensation* will afford Stobbe products; 4) upon mild acidic work-up the primary product is an alkylidene succinic acid monoester; 5) when symmetrical ketones are condensed, only one alkene stereoisomer is formed, but unsymmetrical ketones afford a mixture of alkene stereoisomers; and 6) when the carbonyl component has α-protons, a variety of products may be formed as a result of double bond migration under the reaction conditions. There are a few drawbacks of the *Stobbe condensation*: 1) self-condensation of the aldehyde or ketone substrate; 2) *Cannizzaro reaction* of aromatic aldehydes; 3) if the ketone is highly enolizable under the reaction conditions yields tend to be low; 4) too reactive ketones may undergo acylation (*Claisen reaction*) at their α-position by the dialkyl succinate; 5) when NaOEt is used as the base, substantial reduction of the ketone substrate is usually observed due to the oxidation of ethoxide to acetaldehyde (this side reaction is minimized by using KO*t*-Bu).

Stobbe (1893):



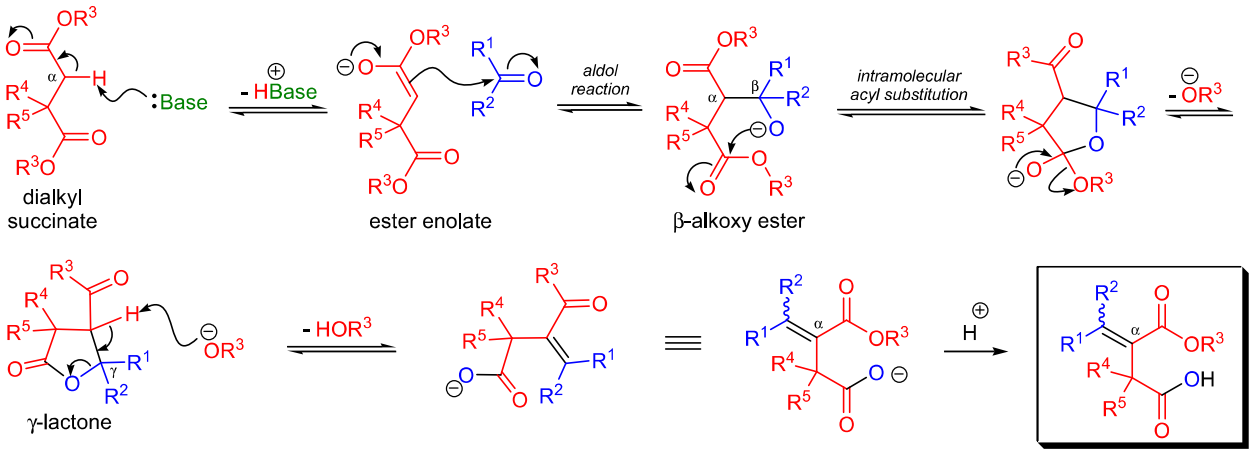
Stobbe condensation:



R^{1-2} = H, alkyl, aryl,alkenyl, acyl, CH(R)CO_2alkyl, CH(R)CN; R^3 = alkyl, aryl; R^{4-5} = H, alkyl, aryl, alkylidene; base: $NaOR^3$, KO*t*-Bu, NaH, NaOEt, Na metal, $NaCPh_3$; solvent: Et_2O, EtOH, *t*-BuOH

Mechanism:[17-22]

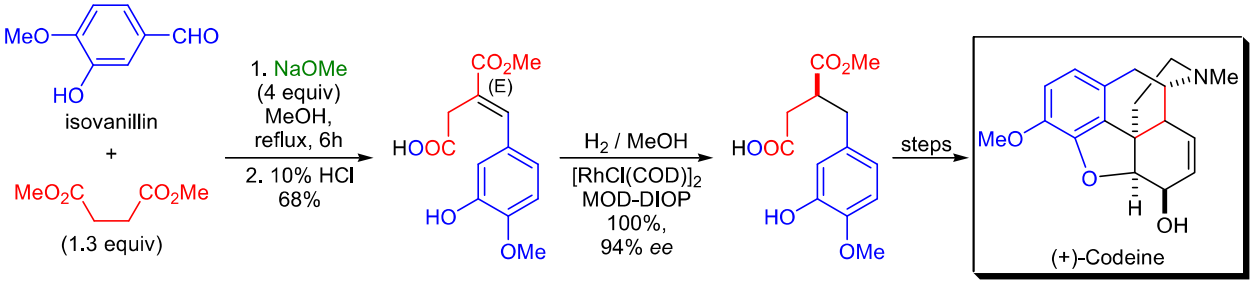
The first step of the *Stobbe condensation* is the deprotonation of the succinate at the α-carbon to afford an ester enolate that *in situ* undergoes an *aldol reaction* with the carbonyl compound to form a β-alkoxy ester intermediate. The following *intramolecular acyl substitution* gives rise to a γ-lactone intermediate which undergoes ring-opening and concomittant double bond formation upon deprotonation by the alkoxide ion. Under certain conditions the lactone intermediate can be isolated.



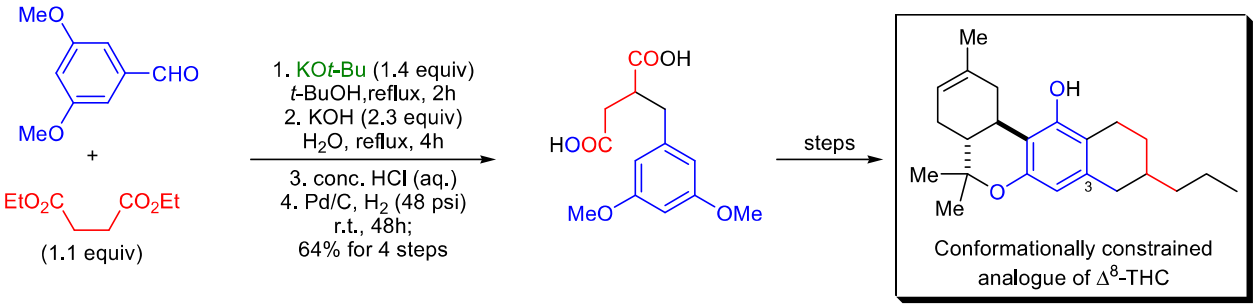
STOBBE CONDENSATION

Synthetic Applications:

The asymmetric total synthesis of (+)-codeine, the unnatural enantiomer, was accomplished by J.D. White and co-workers using an *intramolecular carbenoid insertion* as the key step.[23] The first stereogenic center that directed all subsequent stereochemical events was installed by the *asymmetric hydrogenation* of an alkylidene succinate that was obtained using the *Stobbe condensation*. Dimethyl succinate and isovanillin were reacted in the presence of excess sodium methoxide at reflux and the resulting reaction mixture was acidified to obtain the monomethyl ester.



The SAR data regarding the potency of various cannabinoids show that one of the most important variables is the length and substitution pattern of the alkyl side chain at C3. In order to investigate the effect of side chain conformation upon receptor affinity, J.W. Huffman et al. designed and synthesized a conformationally constrained analog of Δ^8-THC.[24] The *Stobbe condensation* was applied to prepare the tetralin moiety of the target by reacting diethyl succinate in *tert*-butyl alcohol and using KO*t*-Bu as the base. The initially formed alkylidene compound was not purified but immediately subjected to *in situ* catalytic hydrogenation, and the resulting diacid was cyclized to afford a substituted tetralone, which was subsequently converted to the target.



In the laboratory of J. Liu it was shown unambiguously by single crystal X-ray diffraction, that the *Stobbe condensation* of diphenylmethylenesuccinate with aromatic aldehydes proceeded with perfect (*E*)-stereoselectivity.[25] For many decades, the product of this reaction was believed to have the (Z) stereochemistry on the basis of extreme steric crowding. The authors demonstrated that the nature and the position of the substituents on the aromatic rings of substituted benzaldehydes had no effect on the stereoselectivity of the reaction. This result was surprising, since the product was highly crowded but apparently a noncovalent π stacking interaction was operational between the two stacked aromatic rings. The condensation of ethyl methyl diphenylmethylenesuccinate with 3,5-*bis*(trifluoromethyl) benzaldehyde was carried out in benzene using sodium hydride as the base. Upon acidic work-up the corresponding diacid was obtained, which was immediately subjected to dehydration employing neat acetyl chloride.