

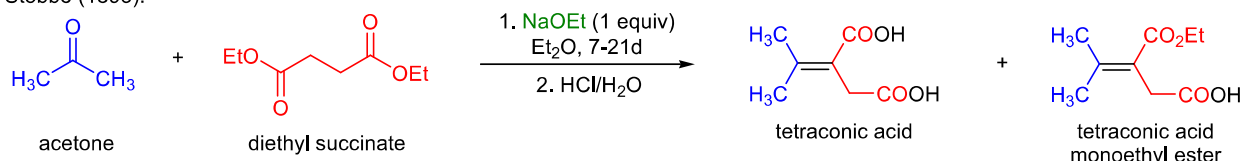
STOBBE CONDENSATION

(References are on page 689)

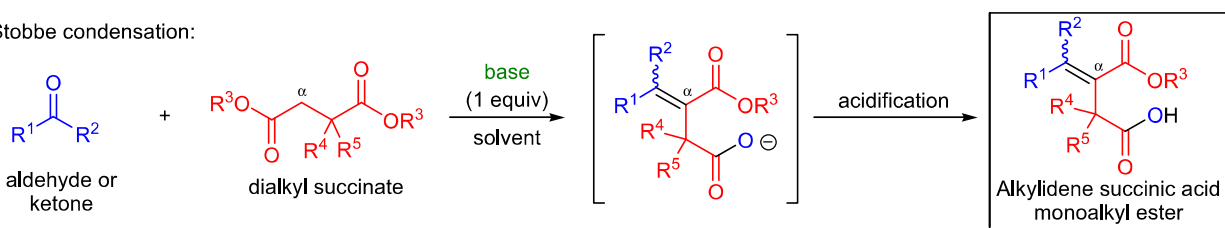
Importance:[Seminal Publications¹; Reviews^{2,3}; Modifications & Improvements⁴⁻¹⁶]

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:



R¹⁻² = H, alkyl, aryl, alkenyl, acyl, CH(R)CO₂alkyl, CH(R)CN; R³ = alkyl, aryl; R⁴⁻⁵ = H, alkyl, aryl, alkylidene; base: NaOR³, KO t -Bu, NaH, NaOEt, Na metal, NaCPh₃; solvent: Et₂O, 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 concomitant double bond formation upon deprotonation by the alkoxide ion. Under certain conditions the lactone intermediate can be isolated.

