DARZENS GLYCIDIC ESTER CONDENSATION

(References are on page 571)

Importance:

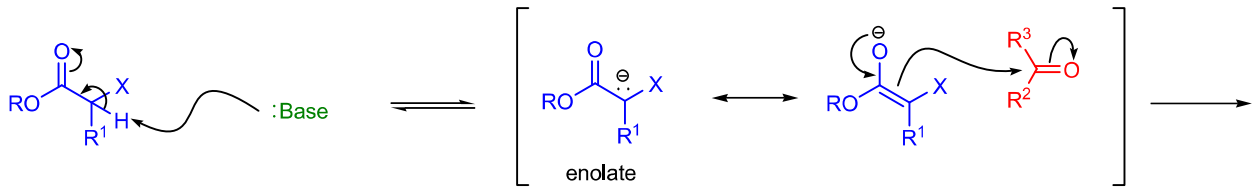
[*Seminal Publications*[1-3]; *Reviews*[4-7]; *Modifications and Improvements*[8-16]]

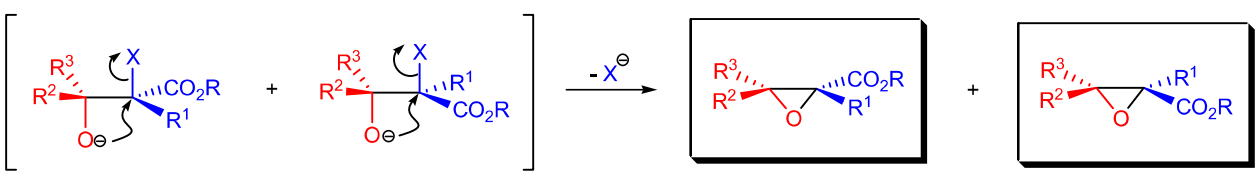
The formation of α,β-epoxy esters (glycidic esters) from aldehydes and ketones and α-halo esters under basic conditions is known as the *Darzens glycidic ester condensation*. The first report of this transformation was published by E. Erlenmeyer, and he described the condensation of benzaldehyde with ethyl chloroacetate in the presence of sodium metal.[1] During the early 1900s G. Darzens developed and generalized the reaction and found that sodium ethoxide (NaOEt) was a very efficient condensing agent.[3] Sodium amide[2] and other bases such as *N*-ethyl-*N*-(tributylstannyl)carbamate[17] can also be used to bring about the *Darzens condensation*. The reaction is general, since aromatic aldehydes and ketones, aliphatic ketones as well as α,β-unsaturated and cyclic ketones react smoothly and give good yields of the expected glycidic esters. Aliphatic aldehydes usually give lower yields, but the deprotonation of the α-halo ester with a strong kinetic base prior to the addition of the aldehyde results in acceptable yields.[18] α-Chloro esters are preferable to bromo or iodo esters, since they give higher yields. In addition to α-halo esters, α-halo sulfones,[19,15] nitriles,[20,16] ketones,[17] ketimines,[21] thiol esters,[22] or amides[14,16] can also be used to obtain the corresponding glycidic derivatives. A useful extension of the reaction is the *Darzens aziridine synthesis* (*aza-Darzens reaction*) when the α-halo esters are condensed with imines.[8] Newer versions of the *aza-Darzens reaction* allow the preparation of aziridines in optically pure form.[11,12] Glycidic esters are versatile synthetic intermediates: the epoxide functionality can be opened with various nucleophiles and upon thermolysis the intermediates undergo decarboxylation to afford the corresponding one carbon homologue of the starting aldehyde or ketone.[23]

R^1 = alkyl, aryl; X = Cl, Br, I; EWG = CO_2R, CN, SO_2R, $CONR_2$, C(=O), C(=NR); R^2 = alkyl, aryl, H; R^3 = alkyl, aryl; Y = O, NR;
base = Na, NaOEt, $NaNH_2$, NaOH, K_2CO_3, NaO*t*-Bu;
when Y = O and EWG = CO_2R then the product is called glycidic ester

Mechanism:[24-26,6,27-29]

The first step of the mechanism is an *aldol reaction*: the base deprotonates the α-halo ester in a rate-determining step and the resulting carbanion (enolate) attacks the carbonyl group of the reactant aldehyde or ketone. The resulting intermediate is a halohydrin that undergoes an S_Ni reaction in the second step to form the epoxide ring. The strereochemical outcome of the *Darzens condensation* is usually in favor of the *trans* glycidic derivative. However, changing the solvents, bases, and the substituents can give either the *cis* or *trans* diastereomers. The stereochemistry of the product is determined by the initial enolate geometry and the steric requirements of the transition state.[29]





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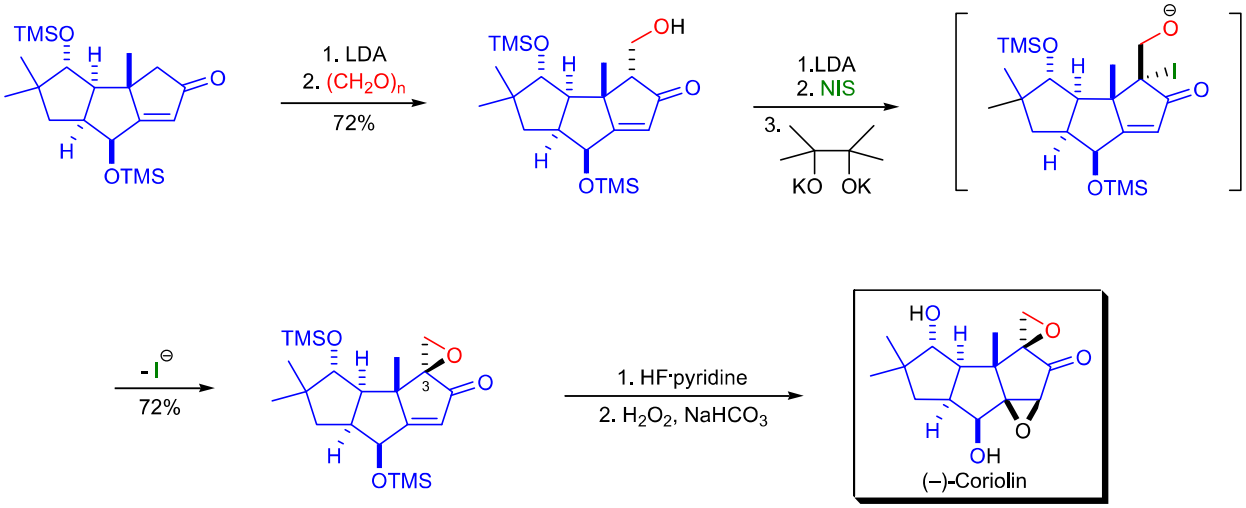
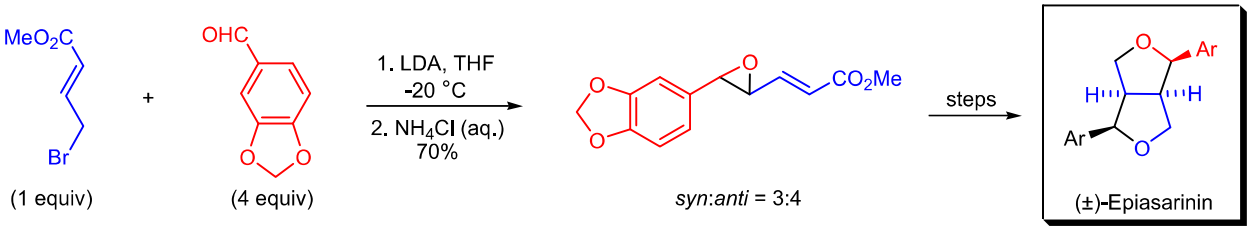
Synthetic Applications:

During the enantioselective total synthesis of (–)-coriolin, I. Kuwajima and co-workers used a *Darzens-type reaction* to construct the spiro epoxide moiety on the triquinane skeleton.[30] Interestingly, the usual *Darzens condensation* where the α-bromoketone was condensed with paraformaldehyde yielded a bromohydrin in which the hydroxymethyl group was introduced from the concave face of the molecule. This bromohydrin upon treatment with DBU gave the undesired stereochemistry at C3 (found in 3-*epi*-coriolin). To obtain the correct stereochemistry at C3, the substituents were introduced in a reverse manner. It was also necessary to enhance the reactivity of the enolate with potassium pinacolate by generating a labile potassium enolate in the presence of NIS. The *in situ* formed iodohydrin, then cyclized to the spiro epoxide having the desired stereochemistry at C3.



In the laboratory of P.G. Steel, a five-step synthesis of (±)-epiasarinin from piperonal was developed.[31] The key steps in the sequence involved the *Darzens condensation*, *alkenyl epoxide-dihydrofuran rearrangement* and a Lewis acid mediated cyclization. The desired vinyl epoxide intermediate was prepared by treating the solution of (*E*)-methyl-4-bromocrotonate and piperonal with LDA, then quenching the reaction mixture with mild acid (NH_4Cl).



A. Schwartz et al. synthesized several calcium channel blockers of the diltiazem group enantioselectively by using an auxiliary-induced asymmetric *Darzens glycidic ester condensation*.[32] The condensation of *p*-anisaldehyde with an enantiopure α-chloro ester afforded a pair of diastereomeric glycidic esters that possessed significantly different solubility. The major product was crystallized directly from the reaction mixture in 54% yield and in essentially enantiopure form. This major glycidic ester was then converted to diltiazem in a few more steps.