

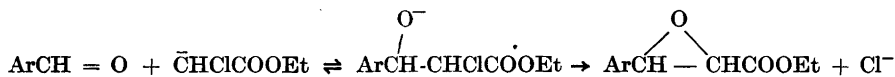
Darzens' Glycidic Ester Condensation. The Isolation of an Aldol Intermediate*

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The aldol-halohydrin type of product, which is generally postulated as an intermediate in the Darzens condensation process, has been isolated in the condensation of benzaldehyde with ethyl chloroacetate (and ethyl α -chloropropionate), by using diisopropylaminomagnesium bromide as the basic condensing agent.

For the Darzens glycidic ester condensation¹ of an aldehyde or a ketone and an α -haloester** in the presence of a basic reagent to form a glycidic ester, *e.g.* benzaldehyde and ethyl chloroacetate, with sodium ethoxide as the condensing agent, the following mechanism appears to be generally accepted***:



The base converts the ester partially into its anion which attacks the carbonyl carbon of the aldehyde to form an aldol-anion. This anion undergoes an intramolecular nucleophilic displacement of the halogen by the negatively charged oxygen. The aldol, whose anion is thus postulated as an intermediate, would be a halohydrin, and it appears quite reasonable that such a compound, in the basic medium, splits off hydrogen halide forming an epoxy compound. Furthermore, Darzens and Lévy⁵ prepared the aldol ester, ethyl α -chloro- β -

* An abstract of this work was presented at The 8th Scandinavian Chemical Meeting in Oslo, June 1953.

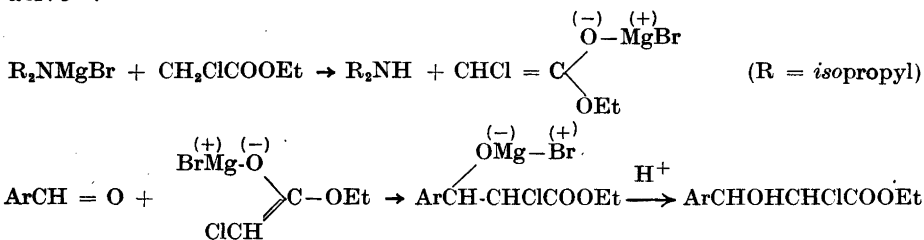
** The α -haloester may be replaced by α -haloketones, acylethylene-oxides being formed^{2,3}. Preliminary attempts during the present work to obtain an aldol intermediate in the reaction between benzaldehyde or 2,4-dichlorobenzaldehyde (m.p. 72°) and phenacyl chloride failed as no crystalline product could be isolated and the reaction products decomposed on attempted distillation.

*** In reference 1 further references concerning mechanisms and applications are given. A review of various mechanisms suggested is given by Fourneau and Billeter⁴ who, however, themselves favor a different mechanism.

hydroxy- β -phenylpropionate, independently, by a Grignard type of reaction from ethyl dichloroacetate and benzaldehyde, and they found that, by treatment with sodium ethoxide, it was transformed into phenylglycidic ester. Claisen⁶, using sodium amide as the condensing agent, observed that some ethyl α -chlorocinnamate was formed in addition to phenylglycidic ester. This corresponds to the usual Claisen-Schmidt cinnamic ester synthesis and is consistent with the intermediate formation of an aldol:



The aldol itself, however, has hitherto not been isolated from the reaction products. This has now been accomplished by using diisopropylaminomagnesium bromide as the basic reagent. This reagent was introduced by Frostick and Hauser⁷, and Hauser and Walker⁸ have suggested the mechanism for the action of this type of reagent. In the present investigation diisopropylaminomagnesium bromide was chosen, because it might be expected that the largely covalent magnesium derivative of the aldol would be less apt to undergo nucleophilic displacement than the highly ionic sodium derivative*:



The condensations were generally carried out as described below for the case of benzaldehyde and ethyl chloroacetate:

To 0.2 equivalents of diisopropylaminomagnesium bromide suspended in dry ether and prepared as previously described¹² was added, during 20–30 minutes, with stirring and frequent cooling in ice-water, an ether solution of a mixture of 0.2 moles each of the aldehyde and the ester. An oily precipitate was formed, and, after the addition of about half of the solution the precipitate became doughy and stirring was hindered. The lumps were broken up with a spatula to render further stirring possible. The inefficient stirring may, in part, explain the poor yield**. After stirring for about two hours at room

* While this work was in progress a report has been published⁹ describing the use of diethylaminomagnesium bromide and certain similar reagents for the condensation of ketones with esters to form β -hydroxyesters. Methylanilinomagnesium bromide has been used for the condensation of aldehydes with ketones¹⁰ and for the mixed condensation of ketones¹¹, to form ketols.

** Several variations in the procedure were tried in order to improve the yield. The basic reagent was isolated by filtration and then added in small portions to the mixture of the starting materials. By this procedure the obstacle of the doughy precipitate was avoided as the reaction mixture remained a suspension of solid material. The yield, however, was still less than that described. Excess of basic reagent, longer reaction time and refluxing for some hours was tried. The recovery of starting materials was decreased, but the amount of non-distillable residue was increased, and the yield of desired product was negligible. In order to decrease the attack on the carbonyl group of the ester, *t*-butyl chloroacetate was tried, but the product obtained decomposed completely on distillation.

temperature the mixture was cooled in ice-salt; then an excess of glacial acetic acid (0.5 mole) and water were added. Stirring was continued until all solid material dissolved. The organic layer was separated, washed with sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and the ether distilled. By fractional distillation *in vacuo* (2–3 mm) a fore-run, consisting of a mixture of the starting materials, was obtained below 80°. This amounted to 20–30 % of the total weight. By further distillation some fumes were evolved while material boiling at 130–160° passed over. The yield of this product was about 50 %. Then strong decomposition of the residue took place. This residue probably consists partially of products formed by attack of the base on the carbonyl groups of the esters. Diisopropylammonium chloride generally separated in the distillate. The distillate was, therefore, dissolved in ether, the ether solution successively washed with diluted hydrochloric acid, water, sodium bicarbonate solution and water, and dried. The solvent was distilled and fractional distillation now gave a product boiling at 145–150° at 3 mm, the over-all yield being about 40 %. Further redistillation rendered a fraction boiling at 148–150° at 3 mm, the over-all yield now amounting to 30 %. This fraction had a chlorine content of 14.5–15.5 % (calc. for the pure aldol Cl = 15.51) corresponding to an aldol content of 93–100 %. It is here assumed that the impurity is ethyl phenylglycidate. Partial crystallization was generally observed after 2–3 weeks; on seeding, crystallization started immediately. After standing, the crystals from several runs were collected by filtration, washed with ice-cold ethanol and recrystallized from ligroin (b.p. 60–100°), m.p. 72° (uncorr.).

$C_{11}H_{13}O_3Cl$ (228.69)	Calc. C 57.77	H 5.72	Cl 15.51
	Found » 57.91	» 5.95	» 15.44

In the case of ethyl α -chloropropionate, similar results were obtained. However, no crystallization took place, but two further redistillations gave a colorless oil, b.p. 158–60° at 5 mm, $n_D^{25} = 1.5256$, which analysed correctly for chlorine:

$C_{12}H_{15}O_3Cl$ (242.72)	Calc. Cl 14.61
	Found » 14.65

Compared with Claisen's observation⁶ of the formation of ethyl α -chlorocinnamate in addition to ethyl phenylglycidate, the chlorine content in the above mentioned condensation product could, of course, be due also to that ester. Claisen's experiment was repeated and his observations verified. 50 % yield of a water-white product boiling sharply at 131° at 5 mm was obtained. No higher boiling material and only very little distillation residue was encountered. Its chlorine content corresponded to about 20 % of ethyl α -chlorocinnamate*. The boiling point of this product was, however, about 20° lower than that of the aldol. Another possibility would be that the aldol obtained in the condensation is contaminated also with ethyl α -chlorocinnamate. In that case the yield of aldol in the product could not be calculated from its chlorine content. However, in the case of ethyl α -chloropropionate, no cinnamic-type of product could be formed, and the assumption seems to be justified that the main product is the aldol, which is contaminated with small amounts of glycidic ester, whose boiling point is so near to that of the aldol that separation by distillation is difficult. The product also has a faint but characteristic smell of phenylglycidic ester, whereas the pure aldol isolated from it is odorless. Darzens and Lévy, in their preparation of the aldol ester, apparently obtained the compound as a yellowish liquid, and their

* The conclusion that the chlorine containing material is this ester is, according to Claisen, drawn from the fact that α -chlorocinnamic acid, m.p. 137°, neutr. equiv. 183.1 (calc. 182.63) is obtained after saponification, acidification and steam-distillation, by which latter process the glycidic acid is decarboxylated into phenylacetaldehyde; the chlorocinnamic acid crystallizes from the residue.

product may also have been contaminated with glycidic ester. During the present investigation this procedure was repeated. The product was a yellow oil which, according to its chlorine content, contained about 85 % aldol; the pure aldol did, however, after long standing, crystallize also from this product. The aldol was, furthermore, prepared in a second independent way, *viz.* by esterification of α -chloro- β -hydroxy- β -phenylpropionic acid, and was found to be identical with the aldol obtained in the condensation process and with that obtained according to the Darzens-Lévy procedure.

α -Chloro- β -hydroxy- β -phenylpropionic acid was prepared according to Rassow and Burmeister¹³ by the addition of hypochlorous acid to cinnamic acid. The yield was 20 % (18 g). The esterification was effected by dissolving the crystalline acid in absolute ethanol and refluxing for ten hours while passing dry hydrogen chloride through the solution. On pouring into ice-water a viscous oil, which soon crystallized partially, was obtained. The product was distilled *in vacuo*, b.p. 180–190° at 15 mm. After recrystallization from ligroin (b.p. 60–100°) the melting point was 72° (uncorr.). The yield was 50 % (10 g).

$C_{11}H_{13}O_3Cl$ (228.69)	Calc.	C 57.77	H 5.72	Cl 15.51
	Found	» 57.68	» 5.82	» 15.48

Mixed melting points with the products obtained by the condensation and by the Darzens-Lévy procedure showed no depression.

The analogous preparation of the aldol ester corresponding to ethyl α -chloropropionate was attempted. However, α -chloro- α -methyl- β -hydroxy- β -phenylpropionic acid is a liquid, which apparently dissolves some unchanged α -methylcinnamic acid, and by the subsequent esterification, the ester becomes contaminated with ethyl α -methylcinnamate. The chlorine content of the product (b.p. 115–117° at 0.5 mm, $n_D^{25} = 1.5145$) was therefore too low (13.2 %; calc. Cl = 14.61).

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