The Darzens Condensation: Structure Determination through Spectral Analysis and Understanding Substrate Reactivity ɯ

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For many years, laboratory experiments served as illustrations of reactions described in the lecture portion of the undergraduate organic class. Recently, however, experiments have been devised that more accurately reflect chemical research, requiring students to "figure out" what has happened by applying the principles from the classroom and analyzing data from the experiment *(1).* Organic chemistry is replete with multiple step "name reactions" in which each step is covered individually in the undergraduate curriculum. Examples include the Ritter reaction *(2),* the Baylis–Hillman reaction *(3),* the Pechmann reaction *(4),* and the Biginelli synthesis *(5).* In each of these examples, the individual steps of the reaction are routinely discussed in the sophomore-level curriculum but the overall transformation—the name reaction—is not. The inclusion of such reactions in the teaching lab affords students the opportunity to engage in a process that more accurately reflects organic research *(6).* We wish to add our version of the Darzens condensation to this list of experiments.

The Darzens condensation *(7),* also known as the Darzens glycidic ester condensation, involves two steps: a base-mediated aldol reaction of an α-halocarbonyl compound with an aldehyde or ketone followed by an intramolecular nucleophilic substitution reaction to form an epoxide or oxirane (Scheme I). Sodium ethoxide is a common choice as a base and appears to have been Darzens' preference *(7).* But, in our efforts to find a suitable, easy-to-perform method for conducting this classic reaction in the sophomore-level organic lab, attempts to use sodium alkoxides have proven problematic. However, a recent article describes the use of KOH and a phase transfer catalyst to achieve diastereoselective Darzens condensations *(8)* and we have modified this method for use in our organic chemistry labs. Our experiment involves the condensation of *t*-butyl chloroacetate and *p*-tolualdehyde with KOH and benzyltriethylammonium chloride in THF (Scheme II). Although in the original study *(8)* the Darzens condensation reaction was allowed to stand overnight, our version produces the best results in 5–7 days. Thus, this experiment is set up at the end of one week's lab session and the product is isolated the following week.
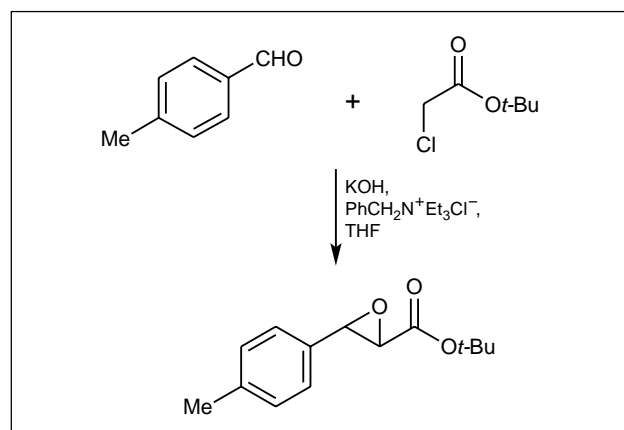
Experimental

A 10-mL round-bottomed flask containing a spin bar was charged with 120 mg (1.0 mmol) of *p*-tolualdehyde, 171 μL (1.2 mmol) of *t*-butyl chloroacetate, 22 mg (0.1 mmol) of benzyltriethylammonium chloride, 134 mg (2.4 mmol) of powdered KOH, and 5 mL of THF. The contents were stirred for several minutes. Then, the flask was removed from the magnetic stirrer, a screw cap was affixed, and the flask was placed in the student lab drawer until the following week's lab session. Upon return to lab, the reaction mixture was transferred to a separatory funnel and partitioned between 20 mL of diethyl ether and 20 mL of water. The layers were separated and the organic phase was dried with $MgSO_4$, filtered, and concentrated using the rotary evaporator. The resultant white solid product (194 mg, 83%) was sufficiently pure for NMR spectroscopy.

^{1}H NMR: (300 MHz, $CDCl_3$, δ) 7.22 (m, 4H), 4.18 (d, *J* = 4.7 Hz), 3.99 (d, *J* = 1.7 Hz, 1H), 3.69 (d, *J* = 4.7 Hz), 3.40 (d, *J* = 1.8 Hz, 1H), 2.34, 2.32 (s, 3H), 1.21 (s, 9H).

^{13}C NMR: (300 MHz, $CDCl_3$, δ) 165.9, 137.9, 130.2, 128.5, 126.6, 82.2, 57.1, 56.0, 27.7, and 21.2.
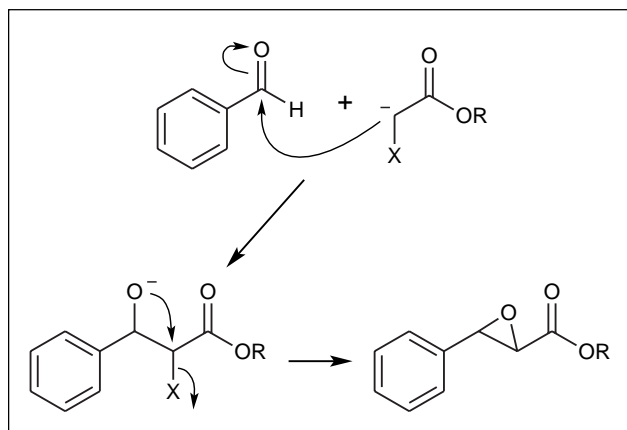
Scheme I. Generalized Darzens condensation.

Scheme II. Specific Darzens condensation used in this experiment.

Student yields ranged from 17 to 96% with an average yield of 65%. Many of the NMR spectra indicated the presence of some residual tolualdehyde as evidenced by the singlet near 9.9 ppm.

Hazards

All of the compounds used in this experiment are considered irritants and physical contact should be avoided. THF is flammable and KOH is caustic. Since *t*-butyl chloroacetate is toxic and a lachrymator, it should be dispensed under a hood and the reaction flask capped before returning to the lab bench. Chloroform-*d* is highly toxic and a cancer suspect agent.

Discussion

Most students will recognize that, in the presence of a base such as KOH, an aldol reaction is likely for an ester and an aldehyde. Students are asked to reconcile their spectral data with such a predicted result. The infrared spectrum of the product, however, shows no signs of an OH band as expected for an aldol reaction and the NMR spectrum shows no indication of alkene formation as expected in an aldol condensation. So, students are asked to consider what else may have occurred. An alkoxide is recognized as a possible nucleophile and Cl⁻ as a good leaving group. Some students, though, are reluctant to suggest an intramolecular nucleophilic substitution ($S_N i$). But, when they apply this second step of the mechanism, the NMR spectrum is consistent with the formation of an α,β-epoxy ester as the product.

The NMR spectrum is relatively simple. However, a closer look at the proposed product reveals two chiral centers and thus two possible products in the NMR. Although the original publication of this method indicates that only the cis isomer forms, expanding the region between 3.30 and 4.30 ppm reveals evidence of two stereoisomers. Integration reveals that the doublets at 3.40 and 3.99 ppm are produced by a minor diastereomer and another set of doublets at 3.69 and 4.18 ppm is produced by the major diastereomer. A comparison of the integrals of the two diastereomers yields a product ratio. Students determined product ratios to range from 15:1 to 2.5:1 (major:minor).

Coupling constants of the doublets produced by each diastereomer can be compared to determine which product, cis or trans, is formed in greater abundance. Cis-hydrogens on an epoxide typically produce coupling constants of 3.9–4.9 Hz while those produced by trans-hydrogens are about 1.5–2.0 Hz *(8, 9)*. In our example, the major product generated doublets with $J = 4.7$ Hz, indicating the major product was the cis diastereomer, while the coupling constants for the minor products were between 1.7 and 2.2 Hz, consistent with a trans product. Thus, after arriving at the epoxide structure of the product, students can determine that the cis isomer is preferentially formed. It is important to note that the instrument used in our labs is a 300 MHz NMR. Although less sensitive instruments may allow students to determine that one isomer is formed in greater abundance, elucidating which product is predominant may be difficult as coupling constants may not be discernible.

Conclusion

This experiment is easy to perform but the product is not easily predicted. Students are required to apply their understanding of the chemical behavior of the reactants and their analysis of the ¹H NMR spectrum to arrive at the product's structure. Then, integration and coupling constants can be used to determine the product ratio and the identity of the major and minor products.

ᵂSupplemental Material

Instructions for the students, notes for the instructor, and sample ¹H NMR spectra of the product are available in this issue of *JCE Online*.

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