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The Darzens condensation of α,β-unsaturated aldehydes and ketones

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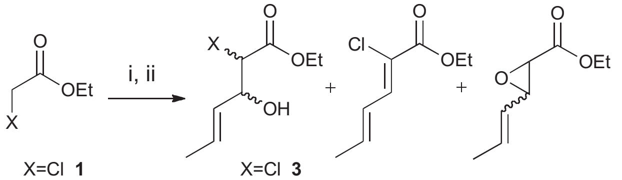
ABSTRACT

The one-pot Darzens condensation of α,β-unsaturated aldehydes and ketones with enolates of an α-bromo ester or ketone is described.

The reaction of α-halo esters with aldehydes and ketones under basic conditions to generate α,β-epoxy esters was first demonstrated in 1892 by Erlenmeyer.[1] However, it was the extensive study of the reaction by Darzens in the 1900's that resulted in the christening of the reaction.[2] The procedure is extremely useful for the preparation of functionalized molecules and as such, the transformation has found application in a number of syntheses. The reaction was fundamental to Schwartz's synthesis of the calcium channel blocker Diltiazem® and its analogues,[3] while Steel's synthesis of Epiasarinin also featured the aforementioned reaction as a key step.[4] More recently research has focused on improved asymmetric induction[5] and expansion of the reaction scope to encompass aziridine synthesis via the aza-Darzens reaction.[6] In the course of our studies we chose to utilize the Darzens reaction *en route* to a synthetic target.

On studying the literature it became evident that a number of aromatic and aliphatic aldehydes and ketones have been employed in the reaction, however, the use of unsaturated substrates is limited. Examples do exist, which involve the use of crotonaldehyde[7] and cinamaldehyde,[8] however, both are two-step procedures that pass through the isolated aldol product before further reaction with base at elevated temperatures to induce epoxide formation. Herein, we present examples of the successful application of α,β-unsaturated substrates in the one-pot Darzens condensation and provide further evidence regarding the mechanism involved in these transformations.

In terms of substrate scope both α-chloro and α-bromo esters are primarily used. Literature procedures currently employ strong bases for enolate generation such as LDA,[9] LiHMDS[10] and KHMDS,[9] with pre-formation of the α-halo ester enolate generally affording a more efficient reaction. As a consequence we initially attempted the reaction with ethyl chloroacetate and ethyl bromoacetate with enolate generation through low temperature treatment with LiHMDS[10] followed by reaction with crotonaldehyde. The reaction appeared capricious and depending on the reaction conditions employed, a range of products was observed (Eq. 1). In addition to the desired epoxide **6**, the aldol products **3** or **4**, the condensation product **5** and starting materials **1** or **2** were all obtained. A number of reactions were performed to identify the optimum conditions to achieve the desired transformation (Table 1). At reduced temperatures (Table 1, entries 1 and 2) reaction of ethyl chloroacetate resulted, in addition to the starting ester, in the formation of only the aldol product; no epoxide formation was observed. This is likely due to the poor leaving group ability of the chloride anion. This was further demonstrated when carrying out the reaction at 25 °C (Table 1, entry 3) where the increased temperature favored elimination of the hydroxyl group to form the condensation product **5** over epoxide



X=Cl **1**
X=Br **2**

X=Cl **3**
X=Br **4**

5

6

(1)

i) LiHMDS (1.0 equiv.), THF, -78 °C, 15 min.
ii) Crotonaldehyde (1.0 equiv.), T °C, 2 h.

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Table 1
Optimization of reaction conditions (Eq. (1))

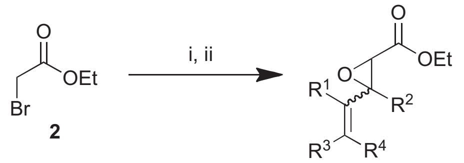
Entry	Ester	*T* (°C)	Product distribution[a]				Epoxide **6** *Cis*:*trans*[a]
			1/2	**3/4**	**5**	**6**	
1	**1**	−78	1	3.2	—	—	—
2	**1**	−25	1	8.1	—	—	—
3	**1**	25	1	1.9	1.1	0.3	0:100
4	**2**	−78	1	3.2	—	—	—
5	**2**	−25	1	0.7	—	1	41:59
6	**2**	25	1	—	—	2.9	43:57

[a] Determined from the ^{1}H NMR spectrum of the crude reaction mixture.

formation. The β-elimination of hydroxide to form the enone has been observed as a side reaction in previous studies, and is particularly prevalent in the case of chloride as the leaving group.[11,12] Although only minimal epoxide formation was observed, complete selectivity for the thermodynamically more stable *trans*-isomer was obtained.

Reaction of ethyl bromoacetate at −78 °C (Table 1, entry 4) provided an identical result to that of the chloride (Table 1, entry 1). However, the superior leaving group ability of the bromide resulted in epoxide formation at −25 °C albeit with little selectivity in geometry (Table 1, entry 5). Increasing the reaction temperature further to 25 °C (Table 1, entry 6) enhanced epoxide formation but with no discernible effect on the geometrical ratio. This was judged to be the optimum temperature as higher temperatures resulted in a large amount of decomposition. Extension of the reaction times resulted in the formation of additional by-products affording the epoxide in reduced quantities but with increased *trans* selectivity. This changing ratio is most likely due to the preferential decomposition of the less stable *cis*-epoxide than selective formation of the *trans*-form. Employing more dilute conditions was also found to be detrimental, leading to a more complex reaction mixture. Finally we examined the effect of altering the ratio of bromoacetate to crotonaldehyde on the yield. However, neither an excess of bromoacetate or crotonaldehyde lead to an improvement in the extent of conversion to the epoxide. It should also be noted that no 1,4-addition products were observed under any of the reaction conditions examined.

The optimal reaction conditions (Table 1, entry 6) were applied to a range of α,β-unsaturated aldehydes and ketones with varying substitution patterns (Table 2, Eq. 2) to test the generality of the procedure.[13] It was hoped that any observed differences arising from altering the alkene substituents would provide insight into the mechanistic intricacies of the transformation.

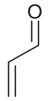
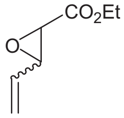
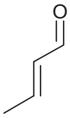
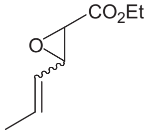
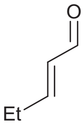
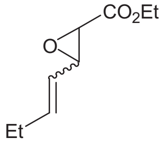
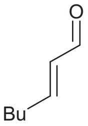
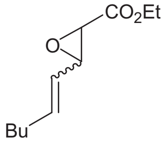
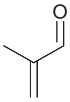
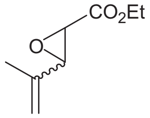
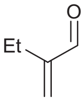
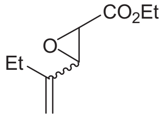
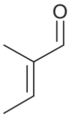
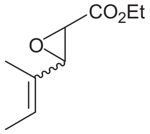
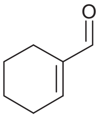
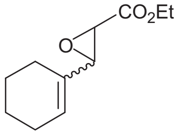
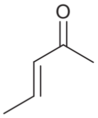
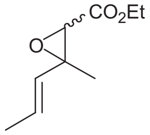
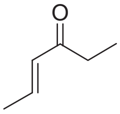
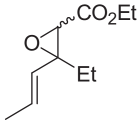
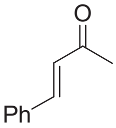
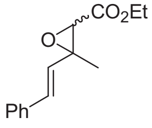


(2)

i) LiHMDS (1.0 equiv.), THF, -78 °C, 15 min.
ii) Electrophile (1.0 equiv.), 25 °C, 2 h.

The aldehydes possessed different substituents at the enone β-position (Table 2, entries 1–4), enone α-position (Table 2, entries 5 and 6) and both enone α- and β-positions (Table 2, entries 7 and 8). In all of these cases the optimized conditions afforded the desired epoxides in good yields with limited variation. In most cases the remainder of the mass balance was largely unreacted starting material. There appears a slight tendency for higher yields with an increase in the molecular weight of the epoxide, suggesting product volatility may be the cause. In terms of epoxide geometry there was surprisingly little selectivity through the variety of substrates tried, a 2:3 ratio of *cis*:*trans* was generally observed. Several α,β-unsaturated ketones were also examined (Table 2, entries 9–11). The reactions proceeded in a similar fashion to those of the aldehydes with comparable yields. There was still very little selectivity between the *cis* and *trans*-epoxide isomers except with an ethyl ketone (entry 10) where a 4:1 ratio favoring the cis isomer was obtained.

Table 2
Reaction scope (Eq. 2)

Entry	Electrophile	Epoxide	Yield[a] (%)	*Cis*:*trans*[b]
1			57	43:57
2			62	43:57
3			60	45:55
4			72	40:60
5			58	38:62
6			64	41:59
7			69	35:65
8			70	34:66
9			63	50:50
10			57	81:19[c]
11			44	50:50

[a] Isolated yield after purification by SiO_2 column chromatography.
[b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Determined by ^{1}H NMR NOE spectroscopy.