

Diastereoselective Darzens condensations

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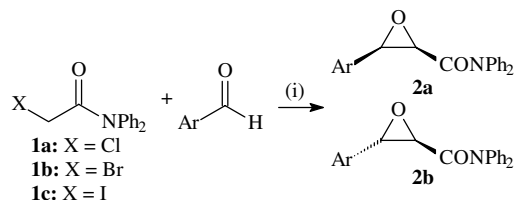
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Abstract—*N,N*-Diphenyl- α -haloacetamides undergo Darzens condensations with aldehydes under heterogeneous reaction conditions in the presence of a metal hydroxide base. By appropriate choice of solvent, base and halide, very high diastereoselectivities favouring formation of the *cis*- or *trans*-epoxide can be obtained.

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Epoxides are particularly versatile synthetic intermediates which can readily be converted into a wide range of polyfunctional compounds. A useful method for the synthesis of α,β -epoxy-carbonyl compounds and related compounds is the Darzens condensation between a carbonyl compound and an α -halo-carbonyl compound (or related species).¹ This reaction has been known for over 100 years, but only recently has progress been made in controlling the relative and absolute stereochemistry of the reaction. Thus, Arai et al. have reported that the diastereoselectivity obtained using *N,N*-diphenyl α -chloroacetamide **1a** and 4-*tert*-butylbenzaldehyde in the presence of tetrahexylammonium bromide was base dependent, giving largely *cis*-epoxide **2a** when potassium hydroxide was used as base, but exclusively the *trans*-epoxide **2b** when lithium hydroxide was used as base.²

As a prelude to a project aimed at developing metal(salen) complexes as asymmetric catalysts for the Darzens condensation, we investigated in more detail the factors that determine the diastereoselectivity of the Darzens condensation of substrates **1a–c** with carbonyl compounds (Scheme 1). Substrates **1a–c** were chosen^{3,4} due to the literature precedent for the use of substrate **1a** in diastereoselective Darzens condensations,² use of substrates **1a–b** in enantioselective Darzens condensations⁵ and the known versatility of epoxy amides which can readily be converted into other epoxy-carbonyl com-



Scheme 1. Reagents and conditions: (i) MOH (solid), solvent, 4–24 h, rt.

pounds and undergo regioselective ring-opening reactions.^{5,6} In this Letter, we show that the nature of the halide, base and solvent are all important factors and that by choice of appropriate conditions, either *cis*- or *trans*-epoxides can be obtained with high diastereoselectivity.

An initial study was carried out using benzaldehyde as the carbonyl compound and dichloromethane as solvent with no added phase transfer catalyst. The results of this study using substrates **1a–c** and powdered sodium, potassium or rubidium hydroxide as base are reported in Table 1. Other bases (lithium hydroxide, potassium bicarbonate, sodium acetate, potassium *tert*-butoxide) gave no significant reaction under these conditions.

α -Chloroamide **1a** underwent Darzens condensations in the presence of sodium or potassium hydroxide (Table 1, entries 1 and 2) to give selectively *trans*-epoxide **2b**, with sodium hydroxide giving a particularly good diastereoselectivity (Table 1, entry 1). Rubidium hydroxide

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Table 1. Darzens condensation between α -haloamides **1a–c** and benzaldehyde in dichloromethane

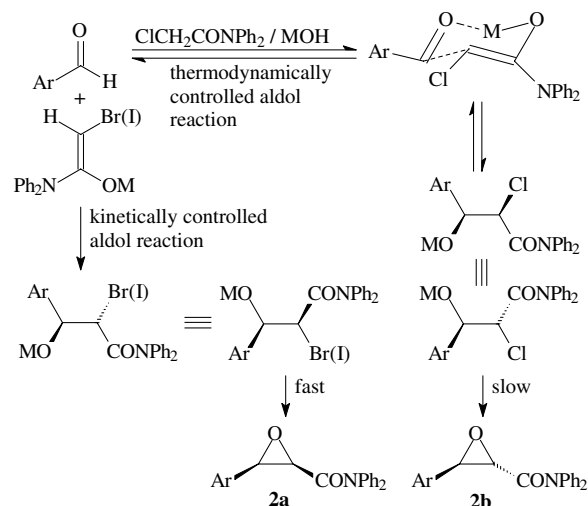
Entry	Haloamide	Base	Time (h)	<i>cis/trans</i> ratio ^a	Yield (%)
1	1a	NaOH	4	1:16.0	68
2	1a	KOH	4	1:1.8	73
3	1a	RbOH	4	1.4:1	71
4	1b	NaOH	24	1.5:1	73
5	1b	KOH	4	2.4:1	78
6	1b	RbOH	4	2.0:1	76
7	1c	NaOH	24	1.2:1	51
8	1c	KOH	24	2.3:1	62
9	1c	RbOH	24	2.2:1	80

^a Determined by ¹H NMR analysis of the crude mixture of epoxides **2a** and **2b**.

also induced the Darzens condensation of substrate **1a**, but gave *cis*-epoxide **2a** as the major product, though with low diastereoselectivity (Table 1, entry 3). All of these reactions were complete in 4 h. In contrast, substrates **1b** and **1c** gave *cis*-epoxide **2a** as the major product with all three bases (Table 1, entries 4–9). The best diastereoselectivity with substrate **1b** was 2.4:1, obtained using potassium hydroxide as base (Table 1, entry 5). Almost identical diastereoselectivities could be obtained using α -iodoamide **1c** and either potassium or rubidium hydroxide as base (Table 1, entries 8 and 9). In the latter case, a control experiment showed that the diastereoselectivity was not time dependent as a 2.3:1 ratio of **2a:2b** was observed after a reaction time of 4 h.

The above results suggested that under these reaction conditions, the initial deprotonation of α -haloamide **1a–c** was the rate limiting step of the reaction. Thus, as the acidity of the substrate decreased from **1a** to **1b** to **1c**, the chemical yield decreased and/or the reaction time increased; whilst increasing the strength of the base from lithium through sodium and potassium to rubidium hydroxide generally increased the chemical yield and/or reduced the reaction time.

The inversion of diastereoselectivity observed with sodium or potassium hydroxide on changing the leaving group from chloride to bromide or iodide (Table 1, compare entries 1 and 2 with entries 4, 5, 7 and 8) appears to be unprecedented in previous work on the Darzens condensation. The results are however consistent with the established mechanism for the Darzens condensation, which involves an aldol reaction followed by an intramolecular substitution reaction.¹ Depending upon the substrate and reaction conditions, the initial aldol reaction may be reversible or irreversible. For reactions involving α -bromoamide **1b** and α -iodoamide **1c**, the results are consistent with a kinetically controlled, irreversible aldol reaction which occurs through a non-chelated transition state to give the *anti*-aldol intermediate which undergoes a rapid intramolecular cyclization to produce the *cis*-epoxide as shown in Scheme 2. In contrast, for reactions involving α -chloroamide **1a**, the intramolecular cyclization step is slower than the retro-aldol reaction and this allows the aldol reaction to equilibrate prior to cyclization. The thermodynamically

**Scheme 2.**

controlled aldol reaction then occurs through a chelated transition state to give the *syn*-aldol product which on cyclization forms the *trans*-epoxide as shown in Scheme 2. The effect of the metal counter-ion is also explained on this basis. Thus, for reactions involving α -chloroamide **1a**, a sodium ion will give a tighter chelated transition state, resulting in a higher diastereoselectivity. In contrast, for reactions involving α -bromoamide **1b** or α -iodoamide **1c**, the greater degree of ionic character in the potassium or rubidium oxygen bond will increase the tendency for the enolate to be electrostatically repelled by the polarized aldehyde bond, thus favouring the kinetic aldol product which leads to the *cis*-epoxide.

On the basis of the results shown in Table 1 and the mechanistic analysis shown in Scheme 2, the use of sodium hydroxide with α -chloroamide **1a** was optimal for the synthesis of *trans*-epoxide **2b** (Table 1, entry 1) whilst the use of potassium hydroxide with α -bromoamide **1b** was optimal for the synthesis of *cis*-epoxide **2a** (Table 1, entry 5). These combinations thus provided the starting point for a subsequent study to determine the most appropriate solvent for the reaction. The results of this investigation are presented in Table 2.

Reactions carried out in non-polar solvents such as toluene, ether or THF⁷ usually failed to go to completion and gave a mixture of the desired epoxides **2a,b** and the intermediate aldol products (Table 2, entries 1–6). These reactions also tended to exhibit low diastereoselectivities, though the use of α -chloroamide **1a** with sodium hydroxide in toluene was exceptional in this respect (Table 2, entry 1). Methanol was a satisfactory solvent for reactions involving α -chloroamide **1a**, but not for those using α -bromoamide **1b**, due to a competing methanolysis of the bromide (Table 2, entries 7 and 8).

However, the use of polar aprotic solvents gave more positive outcomes. In both acetonitrile⁸ and DMF, all of the reactions favoured the formation of *cis*-epoxide **2a** (Table 2, entries 9–26). Thus, whereas the combina-

Table 2. Darzens condensation between α -haloamides **1a,b** and benzaldehyde in various solvents

Entry	Haloamide	Base	Solvent	<i>cis/trans</i> ratio ^a	Conversion ^b (%)
1	1a	NaOH	Toluene	Only <i>trans</i>	71 ^c
2	1b	KOH	Toluene	1.6:1	97
3	1a	NaOH	Et ₂ O	1:2.1	81 ^c
4	1b	KOH	Et ₂ O	1.4:1	100
5	1a	NaOH	THF		0 ^c
6	1b	KOH	THF	1:6.4	92 ^c
7	1a	NaOH	MeOH	2:1	98
8	1b	KOH	MeOH		0
9	1a	NaOH	MeCN	6.0:1	100
10	1b	NaOH	MeCN	7.3:1	100
11	1c	NaOH	MeCN	8.8:1	100
12	1a	KOH	MeCN	3.2:1	100
13	1b	KOH	MeCN	22.8:1	100
14	1c	KOH	MeCN	5.0:1	100
15	1a	RbOH	MeCN	5.2:1	100
16	1b	RbOH	MeCN	6.3:1	100
17	1c	RbOH	MeCN	Only <i>cis</i>	98
18	1a	NaOH	DMF	Only <i>cis</i>	100
19	1b	NaOH	DMF	2.6:1	100
20	1c	NaOH	DMF	1.8:1	83
21	1a	KOH	DMF	3.7:1	100
22	1b	KOH	DMF	Only <i>cis</i>	100
23	1c	KOH	DMF	Only <i>cis</i>	69
24	1a	RbOH	DMF	3.5:1	100
25	1b	RbOH	DMF	16.6:1	100
26	1c	RbOH	DMF	4.4:1	61

^a Determined by ¹H NMR analysis of the crude mixture of epoxides **2a** and **2b**.

^b Reactions involving NaOH took 24 h at room temperature, reactions involving KOH or RbOH were complete after 4 h at room temperature except for entry 26 which required 24 h.

^c The intermediate aldol product was also detected in these reactions.

tion of substrate **1a** and sodium hydroxide had given a *cis/trans* ratio of 1:16 in dichloromethane (Table 1, entry 1), the same combination in acetonitrile gave a *cis/trans*

ratio of 6:1 (Table 2, entry 9) and in DMF, exclusively *cis*-epoxide **2a** was obtained (Table 2, entry 18). Use of other bases with substrate **1a** in acetonitrile or DMF also resulted in the selective formation of *cis*-epoxide **2a**, though with lower diastereoselectivity (Table 2, entries 12, 15, 21 and 24). With substrate **1b**, all three bases showed enhanced diastereoselectivity for the formation of *cis*-epoxide **2a** in both acetonitrile and DMF compared to reactions carried out in dichloromethane (compare Table 1, entries 4–6 with Table 2, entries 10, 13, 16, 19, 22 and 25). However, the use of potassium hydroxide in either acetonitrile or DMF gave exceptional diastereoselectivities in favour of *cis*-epoxide **2a** (Table 2, entries 13 and 22). Reactions involving α -iodoamide **1c** were also *cis*-selective in acetonitrile and DMF (Table 2, entries 11, 14, 17, 20, 23 and 26) and gave exclusively *cis*-epoxide **2a** when rubidium hydroxide was used as base in acetonitrile (Table 2, entry 17) or potassium hydroxide was used as base in DMF (Table 2, entry 23).

In polar aprotic solvents, it is likely that the initial aldol reaction always occurs through a non-chelated transition state which accounts for the *cis*-selectivity that is observed in all of these reactions as shown in Scheme 2. In many cases, the diastereoselectivity increased from substrate **1a** through **1b** to **1c** (Table 2, entries 9–11, 15–17 and 21–23), consistent with the better leaving group increasing the rate of the intramolecular substitution reaction and hence decreasing the reversibility of the aldol reaction. However, there are also exceptions to this rule where specific combinations of base and substrate gave high diastereoselectivities.

On the basis of these results, it can be concluded that highly diastereoselective syntheses of *cis*-epoxide **2a** can be achieved with each of substrates **1a–c** by choice of appropriate base and solvent. However, the use of substrate **1b** and potassium hydroxide in acetonitrile (Table 2, entry 13) was particularly experimentally

Table 3. Darzens condensation between α -haloamides **1a,b** and various carbonyl compounds

Entry	Haloamide	Aldehyde	Base	<i>cis/trans</i> ratio ^a	Yield ^b (%)
1	1a	2-MeC ₆ H ₄ CHO	NaOH	1:28.9	81
2	1b	2-MeC ₆ H ₄ CHO	KOH	12.5:1	100
3	1a	3-MeC ₆ H ₄ CHO	NaOH	1:1.4	84
4	1b	3-MeC ₆ H ₄ CHO	KOH	2.7:1	100
5	1a	4-MeC ₆ H ₄ CHO	NaOH	1:3.0	72
6	1b	4-MeC ₆ H ₄ CHO	KOH	21.1:1	100
7	1a	4-MeOC ₆ H ₄ CHO	NaOH	1:5.4	66
8	1b	4-MeOC ₆ H ₄ CHO	KOH	Only <i>cis</i>	93
9	1a	4-O ₂ NC ₆ H ₄ CHO	NaOH	1:4.8	78
10	1b	4-O ₂ NC ₆ H ₄ CHO	KOH	1:1	100
11 ^c	1b	4-O ₂ NC ₆ H ₄ CHO	KOH	1.7:1	72
12	1a	Me ₃ CCHO	NaOH	Only <i>trans</i>	99 ^d
13	1b	Me ₃ CCHO	KOH	4.9:1	99 ^d
14	1a	PhCOMe	NaOH	1:2.7	93 ^d
15	1b	PhCOMe	KOH		0 ^d

^a Determined by ¹H NMR analysis of the crude mixture of epoxides **2a** and **2b**.

^b All reactions involving substrate **1a** were carried out in dichloromethane, whilst reactions involving substrate **1b** were conducted in acetonitrile. Reaction time 24 h when NaOH was used as base and 4 h when KOH was used as base except where stated. All reactions were carried out at room temperature.

^c Reaction carried out in dichloromethane.

^d Reaction time 3 days.

convenient. In contrast, the optimal yield and diastereoselectivity in the synthesis of *trans*-epoxide **2b** (1:16.0) was obtained using chloroamide **1a** in dichloromethane (Table 1, entry 1). These two sets of conditions were then utilized with a range of carbonyl compounds to demonstrate the generality of the process (Table 3).

The Darzens condensation of chloroamide **1a** with various aromatic aldehydes induced by sodium hydroxide was always found to be diastereoselective in favour of *trans*-epoxide **2b** (Table 3, entries 1, 3, 5, 7 and 9). 2-Methylbenzaldehyde was a particularly good substrate for this reaction (Table 3, entry 1), giving a 1:28.9 ratio of epoxides **2a** and **2b** in high yield. The high diastereoselectivity observed in this case is probably due to steric effects as 3-methylbenzaldehyde exhibited very little diastereoselectivity (Table 3, entry 3) and 4-methylbenzaldehyde gave epoxides **2a** and **2b** in only a 1:3 ratio (Table 3, entry 5). Both the electron rich 4-methoxybenzaldehyde (Table 3, entry 7) and the electron deficient 4-nitrobenzaldehyde (Table 3, entry 9) gave around a 1:5 ratio of epoxides **2a** and **2b** suggesting that the electronic nature of the aldehyde had little influence in this case. These results confirm that a diastereoselective synthesis of *trans*-epoxides **2b** can be achieved by use of solid sodium hydroxide in dichloromethane.

For Darzens reactions involving α -bromoamide **1b**, the use of potassium hydroxide as base generally resulted in preferential formation of *cis*-amide **2a** (Table 3, entries 2, 4, 6, 8, 10 and 11). Both 2-methyl and 4-methylbenzaldehydes gave epoxide **2a** with excellent diastereoselectivity (Table 3, entries 2 and 6), whilst the 3-methyl isomer reacted with much lower diastereoselectivity (Table 3, entry 4). 3-Methylbenzaldehyde was also the least diastereoselective substrate with chloroamide **1a** (Table 3, entry 3). Unlike the corresponding reactions with chloroamide **1a**, electronic effects had a pronounced influence on reactions involving bromoamide **1b**. Thus, 4-methoxybenzaldehyde reacted with **1b** to give only *cis*-epoxide **2a** (Table 3, entry 8), whilst under the same conditions, 4-nitrobenzaldehyde gave a 1:1 mixture of epoxides **2a** and **2b** (Table 3, entry 10). Some diastereoselectivity in favour of epoxide **2a** could be restored in this case by changing the solvent from acetonitrile to dichloromethane (Table 3, entry 11).

Aliphatic aldehydes were also investigated as substrates. Pivaldehyde was a good substrate (Table 3, entries 12 and 13), giving exclusively *trans*-epoxide with α -chloroamide **1a**, and a good selectivity in favour of *cis*-epoxide with α -bromoamide **1b**. However, aliphatic aldehydes with α -protons (cyclohexane carboxaldehyde and nonanal) failed to give any epoxide-containing products, presumably due to competing aldol reactions. Finally, acetophenone reacted with substrate **1a** and sodium hydroxide as expected to give predominantly *trans*-epoxide **2b** (Table 3, entry 14), but failed to react with substrate **1b** (Table 3, entry 15), possibly due to competing hydrolysis of the alkyl bromide.

In conclusion, we have shown that the diastereoselectivity of the Darzens condensation between α -haloamides **1a–c** and aldehydes is significantly influenced by both the base and the solvent. Reactions involving α -chloroamide **1a** and sodium hydroxide in dichloromethane usually exhibit good to excellent *trans*-selectivity, whilst use of α -bromoamide **1b** and potassium hydroxide in acetonitrile gives high *cis*-selectivity.

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