**Diastereoselective Darzens Condensations of α-haloamides: Influence of Aryl Substituents on Diastereoselectivity**

Michael North* and Francesca Pizzato

School of Chemistry and University Research centre in Catalysis and Intensified Processing, Bedson Building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK.

Email: Michael.north@ncl.ac.uk
Tel: +44 (0)191 2227128
Fax: +44 (0)870 1313783

**Abstract**

*N,N*-Diaryl α-haloamides undergo Darzens condensations with aldehydes induced by metal hydroxides. The diastereoselectivity of epoxide formation is strongly influenced by the electronic properties of the arylamide, which can be rationalised on the basis of the acidity of the substrate hydrogens and hence on reaction occurring under kinetic or thermodynamic control.

**Key Words**

Darzens condensation; metal hydroxide; aldehyde; proton-acidity; diastereoselectivity; epoxide

**Running Header**

Diastereoselective Darzens condensations
**Introduction**

The Darzens condensation [1] between an α-halocarbonyl compound and an aldehyde or ketone is a potentially useful way of synthesising epoxy-carbonyl compounds (Scheme 1). Although this reaction has been known since the 19th century, its use in synthesis has been limited due to lack of control in the stereoselectivity with which the two new stereocentres are created: leading to mixtures of enantiomers and diastereomers. We recently reported [2, 3] that N,N-diphenylamides (1a-c) undergo Darzens condensations under mild heterogeneous conditions in the presence of an aldehyde and solid metal hydroxide base. The diastereoselectivity of these reactions was determined by an interplay of the leaving group ability of the halide, the basicity of the metal hydroxide and the solvent polarity, allowing either the cis- or trans-epoxide to be obtained with high diastereoselectivity by choice of appropriate reaction conditions. Other workers have also reported the influence of base [4] and solvent [5, 6] on Darzens condensations.

![Scheme 1](image)

Our results could be rationalised on the basis of kinetic versus thermodynamic control in the aldol step of the reaction mechanism. Thus, the initially formed enolate 2a will have the Z-configuration for steric reasons (the large NPh₂ group is cis to the hydrogen) and also for electronic reasons since the metal can chelate to the halide (Scheme 2). A chelation controlled aldol reaction involving enolate 2a will place the halide in an axial position in the transition state, leading to the syn-aldol product and hence to the cis-epoxide. A good leaving group (bromide or iodide) and a polar solvent (acetonitrile or DMF) will increase the rate of epoxide formation (k₃) relative to the rate of the retro-aldol reaction (k₂) and so favour this pathway leading to predominant formation of the cis-epoxide. It is also possible that the cis-epoxide is formed by a non-chelated transition state or via a boat transition state to avoid the necessity for the halide to be in an axial position in the transition state. Both of these possibilities also lead to preferential formation of the cis-epoxide. In contrast, use of a poorer leaving group (chloride) in a less polar solvent (toluene or dichloromethane) decreases the rate of cyclisation so that k₂ is greater than k₃. This allows the initial aldol product to equilibrate with enolate 2a and also allows Z-enolate 2a to equilibrate with E-enolate 2b. The latter can also undergo a chelation controlled aldol reaction leading to the anti-aldol product and thus to the trans-epoxide. Since in this process, the chelated transition state has all of the substituents equatorial, it is thermodynamically preferred and hence the trans-epoxide will predominate whenever the rate of aldol equilibration is greater than the rate of cyclisation (k₂ and k₂' greater than k₃').
Based on this analysis, we reasoned that the electronic nature of the aryl rings in N,N-diarylamides could also have an influence on the diastereoselectivity of the Darzens condensations. Electron-donating substituents attached to the aromatic rings should reduce the acidity of the α-protons, thus destabilising formation of enolate 2 (reduce $k_1$ and $k_{-2}$) and encouraging the aldol reaction to occur under kinetically controlled conditions, leading to the cis-epoxide. On the other hand, electron-withdrawing substituents should increase the acidity of the α-protons, thus stabilising enolate 2 and facilitating the retro-aldol reaction (increase $k_{-2}$) so that the product is formed via the thermodynamically controlled chelated enolate, leading to the trans-epoxide. In this Letter we report the results of this investigation.
Results and Discussion

For this study, amides 3-7a,b were studied relative to N,N-diphenylamides 1a,b using benzaldehyde as the enolate acceptor and with a range of solid alkali metal hydroxides (NaOH, KOH, RbOH and CsOH) as bases in dichloromethane solvent at room temperature to give epoxides 8a-f and 9a-f as shown in Scheme 3 [7]. Compounds 4-6 were prepared by reaction of diaryl amines 11-13 with chloroacetyl chloride and bromoacetyl bromide in dichloromethane in the presence of triethylamine for 16 hours to give 4a-6a and 4b-6b respectively as shown in Scheme 4 [8]. For compounds 3a,b and 7a,b, this synthesis was modified by running the reaction in the absence of solvent and triethylamine in view of the low nucleophilicity of nitroamines 10 and 14. Amines 10-14 are known compounds [9-12] which were prepared by an amino acid promoted Ullmann reaction [13] involving 4-methoxyaniline (to form compounds 12-13) or an S_N_Ar reaction involving 4-nitrofluorobenzene (to form diamines 10, 11 and 14) [9].

![Scheme 3](image)

Table 1 compares the results obtained with chloroamides 3a-7a with those obtained using N,N-diphenyl chloroamide 1a. As expected, the most electron-rich substrate (6a) was also the least reactive with reaction times of 65 hours being required to produce high conversions. This is consistent with the low acidity of the hydrogens in 6a resulting in a low value for rate constant k1. Removal of one of the methoxy groups to give substrate 5a results in a significant increase in
reactivity (reaction times 16 hours), though this is still significantly less reactive than unsubstituted substrate 1a. It is also apparent from Table 1 that for any base, the percentage of trans epoxide 9a-e formed increases as the substrate becomes more electron-deficient. Indeed, the 4-nitrophenyl containing substrates (3a and 4a) give exclusively trans-epoxide 9d,e with sodium and potassium hydroxide as bases. However, the conversions obtained with substrate 3a which contains two 4-nitrophenyl groups are much higher than those obtained with substrate 4a (reaction time of 16 hours in each case to allow comparison). This is also consistent with the mechanism shown in Scheme 2 since both k1 and k-2 will increase as the substrate becomes more electron-deficient, resulting in higher chemical yields and a greater amount of reaction through the thermodynamically controlled aldol transition state, resulting in a greater proportion of trans-epoxide 9 being formed. For any of substrates 1a and 3a-7a, the highest percentage of trans-epoxide was formed using sodium hydroxide.

![Scheme 4](image)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>10: Y = Z = NO₂</td>
<td>a: X = Cl; b: X = Br</td>
</tr>
<tr>
<td>11: Y = H, Z = NO₂</td>
<td>3a,b: Y = Z = NO₂</td>
</tr>
<tr>
<td>12: Y = H, Z = OMe</td>
<td>4a,b: Y = H, Z = NO₂</td>
</tr>
<tr>
<td>13: Y = Z = OMe</td>
<td>5a,b: Y = H, Z = OMe</td>
</tr>
<tr>
<td>14: Y = OMe, Z = NO₂</td>
<td>6a,b: Y = Z = OMe</td>
</tr>
<tr>
<td>7a,b: Y = OMe, Z = NO₂</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 here

The diastereoselectivities obtained with substrate 7a which contains both a 4-nitro and a 4-methoxy substituted aromatic ring are comparable to those of substrate 5a which contains just the 4-methoxy substituent, indicating that the influence of the methoxy substituent is greater than that of the nitro group. The conversions achieved using substrate 7a with rubidium and caesium hydroxides were however much greater than those achieved using compound 5a which may reflect the acidifying influence of the nitro group on the protons adjacent to the carbonyl, thus increasing k1.

Table 2 here
Table 2 gives the same comparison for bromoamide substrates 1b and 3b-7b. In this case, the trends are less pronounced. The conversions are extremely variable and one reason for this may be the competing \( S_N2 \) reaction between hydroxide and the bromo-substrates. A bromo-substituent is less electron-withdrawing than a chloro-substituent, which may explain why the conversions are generally lower in the bromo series (compare Table 1 with Table 2) since \( k_1 \) will be smaller in the former case. In general, the nature of the substrate has a much greater influence on the diastereoselectivity of the Darzens condensation than the nature of the base counterion. For reactions involving methoxy-substituted amides (6b and 5b), the reactions all give predominantly \( cis \)-epoxide 8, though there is no significant change in diastereoselectivity compared to the results obtained with unsubstituted bromoamide 1b. Thus it seems that the methoxy-substituents do not decrease the value of \( k_2 \) below the value observed for bromoamide 1b. Substrates 4b and 3b which contain electron-withdrawing nitro groups still give predominantly \( trans \)-epoxide 9, though the percentage of \( trans \)-epoxide is (with the exception of substrate 3b and sodium hydroxide) always lower than that obtained from the corresponding chloroamides (4a and 3a). It is notable that the most electron-deficient substrate 3b when treated with sodium hydroxide gives exclusively the \( trans \)-epoxide product 9b in high yield, suggesting that in this case, even the good leaving group does not result in \( k_3 \) being large enough to prevent equilibration of enolates 2a,b. The results obtained with substrate 7b which contains both a 4-nitro and a 4-methoxy substituted aromatic ring are again roughly comparable with those obtained using substrate 5b which contains just the methoxy substituent, indicating that the influence of the methoxy substituent is again greater than that of the nitro group.

To investigate the need for two aromatic rings within the Darzens condensation substrates, known \( N\)-phenyl-\( N\)-alkyl haloamides 15-20 [14-18] and \( N,N\)-dialkyl haloamides 21-26 [19-23] were prepared and used as substrates for Darzens condensations to give epoxides 27a-f and 28a-f [24-27] (Scheme 5) with the results being tabulated in Table 3. Substrates 15-20 showed no variation in diastereoselectivity between the substrates with bromide and chloride leaving groups. In most cases an almost 1:1 ratio of \( cis \)- and \( trans \)-epoxides was formed, though in every case the amount of \( trans \)-epoxide 28a-c formed decreases slightly as the size of the base counterion increases. The chemical yields of epoxides 27d-f and 28d-f were significantly lower than those obtained from \( N \)-aryl haloamides which reflects the lower acidity of the hydrogens in substrates 21-26 since the lone pair of electrons on the nitrogen atom no longer has an aromatic ring to delocalise into and so is more delocalised into the carbonyl bond. The low yields are particularly apparent for bromoamide substrates 22, 24 and 26 and in these cases an \( S_N2 \) reaction of hydroxide on the alkyl bromide may compete with the desired deprotonation due to the low acidity of the hydrogens. The Darzens
reactions of substrates 21-25 show little or no diastereoselectivity and no discernable trends as the nature of the base counterion is varied.

\[
X \quad \xrightarrow{\text{PhCHO / MOH}} \quad \text{R}^1 \quad \xrightarrow{\text{CH}_2\text{Cl}_2, \text{RT, 16 h}} \quad \text{Ph}
\]

15: \( X = \text{Cl}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me} \)
16: \( X = \text{Br}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me} \)
17: \( X = \text{Cl}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Et} \)
18: \( X = \text{Br}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Et} \)
19: \( X = \text{Cl}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{iPr} \)
20: \( X = \text{Br}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{iPr} \)
21: \( X = \text{Cl}, \text{R}^1 = \text{R}^2 = \text{Me} \)
22: \( X = \text{Br}, \text{R}^1 = \text{R}^2 = \text{Me} \)
23: \( X = \text{Cl}, \text{R}^1 = \text{R}^2 = \text{Et} \)
24: \( X = \text{Br}, \text{R}^1 = \text{R}^2 = \text{Et} \)
25: \( X = \text{Cl}, \text{R}^1 = \text{R}^2 = \text{iPr} \)
26: \( X = \text{Br}, \text{R}^1 = \text{R}^2 = \text{iPr} \)

27a-f

28a-f

\[ \text{Ph} \quad \xrightarrow{+} \quad \text{R}^1 \quad \xrightarrow{\text{N}} \quad \text{R}^2 \]
a: \( \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me} \)
b: \( \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Et} \)
c: \( \text{R}^1 = \text{Ph}, \text{R}^2 = \text{iPr} \)
d: \( \text{R}^1 = \text{R}^2 = \text{Me} \)
e: \( \text{R}^1 = \text{R}^2 = \text{Et} \)
f: \( \text{R}^1 = \text{R}^2 = \text{iPr} \)

Scheme 5

Table 3 here

Conclusions

The electronic nature of the aromatic rings in \( N,N \)-diaryl \( \alpha \)-haloamides have a pronounced influence on the diastereoselectivity of Darzens condensations. Electron-withdrawing nitro substituents favour formation of the \( \text{trans} \)-epoxide through a chelated, thermodynamically controlled aldol reaction, whilst electron-donating methoxy substituents enhance the formation of \( \text{cis} \)-epoxide, especially from \( \alpha \)-bromo substrates. When both 4-nitro and 4-methoxy substituents are present in the amide, the methoxy group has a greater influence on the diastereoselectivity than the nitro group.

If one of the \( N \)-aryl groups is changed to an alkyl group, then the influence of the halide on the diastereoselectivity of the Darzens condensation disappears and the reactions show no diastereoselectivity or a small preference for formation of \( \text{cis} \)-epoxides. \( N,N \)-Dialkyl haloamides are poor substrates for Darzens condensations with solid metal hydroxides as bases, giving low yields and little or no diastereoselectivity.
Acknowledgement

Mass spectra were recorded by the EPSRC national mass spectrometry service at the University of Wales, Swansea.

References

[7] To a stirring mixture of a haloacetamide (0.7 mmol) and a metal hydroxide base (1.14 mmol) in CH₂Cl₂ (4 mL) was added benzaldehyde (64 mg, 0.6 mmol). After being stirred for the appropriate time, the reaction was quenched with 1 N HCl (1 mL) and the aqueous layer was extracted with EtOAc (3×2 mL), washed with brine (6 mL) and dried (Na₂SO₄). The solvent was removed in vacuo and the crude product analysed by ¹H NMR spectroscopy to determine the diastereomeric ratio. Purification by flash column chromatography (hexane / EtOAc) then gave the cis- and trans-epoxides.
[8] Of compounds 3a,b to 7a,b, only compound 4a has been reported before: Wadia, M.S.; Patil, D.V. Synth. Commun. 2003, 33, 2725.


Table 1: Comparison of chloroamides 1a and 3a-7a in the Darzens condensation with benzaldehyde.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>NaOH</th>
<th>KOH</th>
<th>RbOH</th>
<th>CsOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a\textsuperscript{b}</td>
<td>100 (55% trans)</td>
<td>64 (55% trans)</td>
<td>80 (40% trans)</td>
<td>28 (38% trans)</td>
</tr>
<tr>
<td>5a\textsuperscript{c}</td>
<td>96 (71% trans)</td>
<td>81 (52% trans)</td>
<td>0</td>
<td>18 (33% trans)</td>
</tr>
<tr>
<td>1a\textsuperscript{a}</td>
<td>68 (94% trans)</td>
<td>73 (64% trans)</td>
<td>71 (42% trans)</td>
<td>87 (38% trans)</td>
</tr>
<tr>
<td>4a\textsuperscript{c}</td>
<td>49 (100% trans)</td>
<td>48 (100% trans)</td>
<td>70 (91% trans)</td>
<td>17 (79% trans)</td>
</tr>
<tr>
<td>3a\textsuperscript{c}</td>
<td>95 (100% trans)</td>
<td>90 (100% trans)</td>
<td>82 (100% trans)</td>
<td>35 (100% trans)</td>
</tr>
<tr>
<td>7a\textsuperscript{c}</td>
<td>54 (77% trans)</td>
<td>65 (48% trans)</td>
<td>44 (50% trans)</td>
<td>62 (31% trans)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} In each cell, the conversion is given first followed in brackets by the percentage of trans-epoxide in the cis / trans mixture prior to purification as determined by \textsuperscript{1}H NMR spectroscopy. b) Reaction time 65 hours. c) Reaction time 16 hours. d) Reaction time 4 hours.
Table 2: Comparison of bromoamides 1b and 3b-7b in the Darzens condensation with benzaldehyde.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>NaOH</th>
<th>KOH</th>
<th>RbOH</th>
<th>CsOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>6b\textsuperscript{b}</td>
<td>100 (48% trans)</td>
<td>49 (28% trans)</td>
<td>34 (33% trans)</td>
<td>39 (33% trans)</td>
</tr>
<tr>
<td>5b\textsuperscript{c}</td>
<td>79 (55% trans)</td>
<td>58 (45% trans)</td>
<td>57 (43% trans)</td>
<td>90 (30% trans)</td>
</tr>
<tr>
<td>1b</td>
<td>73\textsuperscript{d} (40% trans)</td>
<td>78\textsuperscript{d} (29% trans)</td>
<td>76 (33% trans)</td>
<td>79 (29% trans)</td>
</tr>
<tr>
<td>4b\textsuperscript{c}</td>
<td>35 (74% trans)</td>
<td>45 (74% trans)</td>
<td>39 (56% trans)</td>
<td>60 (89% trans)</td>
</tr>
<tr>
<td>3b\textsuperscript{c}</td>
<td>89 (100% trans)</td>
<td>73 (60% trans)</td>
<td>84 (71% trans)</td>
<td>59 (60% trans)</td>
</tr>
<tr>
<td>7b\textsuperscript{c}</td>
<td>27 (64% trans)</td>
<td>53 (40% trans)</td>
<td>73 (50% trans)</td>
<td>50 (42% trans)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} In each cell, the conversions is given first followed in brackets by the percentage of trans-epoxide 9 in the cis / trans mixture prior to purification as determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{b} Reaction time 65 hours. \textsuperscript{c} Reaction time 16 hours. \textsuperscript{d} Reaction time 4 hours.
Table 3: Comparison of haloamides 15-26 in the Darzens condensation with benzaldehyde.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Substrate</th>
<th>NaOH</th>
<th>KOH</th>
<th>RbOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>100 (50% trans)</td>
<td>97 (50% trans)</td>
<td>92 (48% trans)</td>
</tr>
<tr>
<td>16</td>
<td>89 (50% trans)</td>
<td>85 (50% trans)</td>
<td>78 (45% trans)</td>
</tr>
<tr>
<td>17</td>
<td>89 (50% trans)</td>
<td>95 (40% trans)</td>
<td>87 (37% trans)</td>
</tr>
<tr>
<td>18</td>
<td>88 (48% trans)</td>
<td>89 (40% trans)</td>
<td>77 (40% trans)</td>
</tr>
<tr>
<td>19</td>
<td>84 (48% trans)</td>
<td>96 (40% trans)</td>
<td>95 (34% trans)</td>
</tr>
<tr>
<td>20</td>
<td>87 (48% trans)</td>
<td>82 (40% trans)</td>
<td>87 (40% trans)</td>
</tr>
<tr>
<td>21</td>
<td>43 (50% trans)</td>
<td>71 (50% trans)</td>
<td>64 (50% trans)</td>
</tr>
<tr>
<td>22</td>
<td>26 (58% trans)</td>
<td>36 (55% trans)</td>
<td>8 (67% trans)</td>
</tr>
<tr>
<td>23</td>
<td>21 (50% trans)</td>
<td>28 (45% trans)</td>
<td>41 (43% trans)</td>
</tr>
<tr>
<td>24</td>
<td>16 (43% trans)</td>
<td>17 (48% trans)</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>11 (45% trans)</td>
<td>31 (43% trans)</td>
<td>68 (38% trans)</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} In each cell, the conversions is given first followed in brackets by the percentage of \textit{trans}-epoxide 28 in the \textit{cis} / \textit{trans} mixture prior to purification as determined by \textsuperscript{1}H NMR spectroscopy. In each case the reaction time was 16 hours.