The Halogen–Lithium Exchange Reaction of 3,3-Dichloro-2-azetidinones: Application to the Synthesis of cis-4-Aryl-3-chloro-2-azetidinones

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Abstract: A straightforward synthesis of new cis-4-aryl-3-chloro-2-azetidinones was developed, using a halogen–lithium exchange reaction on 4-aryl-3,3-dichloro-2-azetidinones. This methodology was further extended to the use of alkyl halides as electrophiles, while more complex electrophiles could not be introduced.

Key words: lactams, lithiation, stereoselectivity, alkylations, azetidinones

Previously, we have reported on the synthesis of 2-aryl-3,3-dichloroazetidines and their ring transformation towards functionalized aziridines. The scope of the reactivity of the former strained compounds was further investigated and it was found that reaction of 2-aryl-3,3-dichloroazetidines with lithium aluminum hydride in diethyl ether led to the isolation of a mixture of trans-2-aryl-3-chloroazetidines and cis-2-aryl-3-chloroazetidines (Scheme 1). A similar reaction on 3,3-dichloroazetidinones has been described earlier, i.e. treatment of cis-3,3-dichloro-2-methoxy-2,4-diphenylazetidine with lithium aluminum hydride in diethyl ether afforded the corresponding cis-3-chloro-2,4-diphenylazetidine in 28% yield.

Scheme 1

In order to characterize unequivocally the new compounds 2 and 3 obtained, their syntheses were performed independently. While this was straightforward for the trans-2-aryl-3-chloroazetidines 2 (synthesis of trans-4-aryl-3-chloro-2-azetidinones and subsequent reduction with chloroalanes), the synthesis of cis-2-aryl-3-chloroazetidines 3 proved to be more difficult. The straightforward synthesis of 4-aryl-3-chloro-2-azetidinones by [2+2] cycloaddition between chloroketene and the appropriate imine is known to give exclusively trans-stereoselectivity, or mainly trans-stereoselectivity when different substituents are present on the aromatic substituent.

Thus, another method to obtain the desired cis-derivatives was required. Although some methods are known that give mainly cis-stereoselectivity by in situ generation of the ketene from the corresponding acid and an activating compound, these methods were not elaborated for α-halogenated acids. Even more so, the stereoselectivity sometimes depends on the α-substituent of the acid and cannot be predicted. Therefore, the use of halogen–metal exchange reactions on 3,3-dichloroazetidin-2-ones to accomplish the aforementioned goal was investigated. The latter method has already been applied in the chemistry of β-lactams, mainly to 3-bromo or 3,3-dibromo derivatives by means of alkylmagnesium bromide, alkyllithium or diisobutylzinc reagents. In most of these cases, the introduction of the 3-(1-hydroxyethyl) side chain in thienamycin or thienamycin-like β-lactams was the purpose of the study.

Here, we wish to report our results on the application of this halogen–metal exchange reaction on 4-aryl-3,3-dichloroazetidin-2-ones en route to stereodefined cis-4-aryl-3-chloro-2-azetidinones.

4-Aryl-3,3-dichloro-2-azetidinones 4 were easily obtained by [2+2] cycloaddition between dichloroketene, derived from dichloroacetyl chloride and a base, and the appropriate imine, derived from dichloroacetyl chloride and a base, and the appropriate imine. The compounds thus obtained were used as substrates in the subsequent halogen–lithium exchange strategy (Scheme 2). 4-Aryl-3,3-dichloro-2-azetidinones 4, dissolved in tetrahydrofuran at –78 °C, were treated with n-butyllithium. The formation of the enolate 5 can be seen by the appearance of a deep red color after the addition of n-butyllithium. This mixture was kept at –78 °C for a given time to allow a complete reaction to occur. Finally, quenching of the intermediate 5 took place by the addition of a suitable electrophile. The results obtained by this sequence are summarized in Table 1. The optimum reaction conditions were determined to be as follows: addition of 1.0–1.5 equivalents of n-butyllithium at –78 °C and subsequent stirring at the same temperature for thirty minutes, followed by the addition of 2–5 equivalents of the electrophile and subsequent stirring at room temperature for 3–20 hours.

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To synthesize the compounds, which were under focus, namely cis-4-aryl-3-chloro-2-azetidinones 6–9, different proton sources were evaluated, i.e. water, p-toluene-
sulfonic acid, glacial acetic acid, pivalic acid and salicylic acid. Glacial acetic acid was prepared by distillation of commercial acetic acid (99+%) in the presence of acetic anhydride.9 As can be seen from Table 1 (entries 1 to 8), the use of all proton sources allowed to synthesize 4-aryl-3-chloro-2-azetidinones 6, however, the stereochemical outcome of each reaction was somewhat different. Using 4-aryl-3,3-dichloro-2-azetidinone 4a with monohydrated p-toluenesulfonic acid or glacial acetic acid, mainly cis-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (6a) was isolated, with the best results for glacial acetic acid (cis:trans ratio 1:0.06), while using water, a mixture of the cis- and trans-azetidinones 6a and 6b was obtained. The distinction between both stereoisomeric compounds was easily made by means of the coupling constants between the C3 and C4 proton (cis: J = 5–6 Hz, trans: J = 0–2 Hz).10

These results were rationalized as follows. The double bond in enolate 5 forms a planar part in the molecule with a sterically hindering aryl group at the allylic position. To

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Table 1  Results of the Halogen–Lithium Exchange Reactions Performed on 4-Aryl-3,3-dichloroazetidin-2-ones 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Reaction Conditionsa</th>
<th>R3</th>
<th>Yieldb (cis + trans)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr</td>
<td>H</td>
<td>H2O (5 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>6a + 6b (1:1.6) 60%</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>H</td>
<td>p-TsOH (5 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>6a + 6b (1:0.11) 59%</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>Me</td>
<td>p-TsOH (5 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>7a + 7b (1:0.08) 53%</td>
</tr>
<tr>
<td>4</td>
<td>c-Hex</td>
<td>H</td>
<td>p-TsOH (5 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>8a + 8b (1:0.09) 65%</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>H</td>
<td>p-TsOH (2 equiv), –78 °C to r.t., 3 h</td>
<td>H</td>
<td>9a + 9b (1:0.14) 63%</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>H</td>
<td>AcOH (2 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>9a (only cis) 61%</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>H</td>
<td>pivalic acid (5 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>9a + 9b (1:0.22) 61%</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>H</td>
<td>salicylic acid (2 equiv), –78 °C to r.t., 20 h</td>
<td>H</td>
<td>9a + 9b (1:0.19) 57%</td>
</tr>
<tr>
<td>9</td>
<td>i-Pr</td>
<td>H</td>
<td>AcOH (2 equiv), –78 °C to r.t., 3 h</td>
<td>H</td>
<td>6a + 6b (1:0.06) 65%</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr</td>
<td>H</td>
<td>MeI (5 equiv), –78 °C to r.t., 20 h</td>
<td>Me</td>
<td>10 (only cis) 57%</td>
</tr>
<tr>
<td>11</td>
<td>i-Pr</td>
<td>H</td>
<td>EtBr (5 equiv), –78 °C to r.t., 20 h</td>
<td>Et</td>
<td>11 (only cis) 40%</td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>H</td>
<td>PrBr (5 equiv), –78 °C to r.t., 20 h</td>
<td>Pr</td>
<td>12 (only cis) 23%</td>
</tr>
<tr>
<td>13</td>
<td>i-Pr</td>
<td>H</td>
<td>Br(CH2)2OSiMe3 (5 equiv), –78 °C to r.t., 20 h</td>
<td>(CH2)2OSiMe3</td>
<td>–d</td>
</tr>
<tr>
<td>14</td>
<td>i-Pr</td>
<td>H</td>
<td>CICO2Me (5 equiv), –78 °C to r.t., 20 h</td>
<td>CO2Me</td>
<td>–d</td>
</tr>
<tr>
<td>15</td>
<td>i-Pr</td>
<td>H</td>
<td>MeOCCO2Me (5 equiv), –78 °C to r.t., 20 h</td>
<td>CO2Me</td>
<td>–d</td>
</tr>
<tr>
<td>16</td>
<td>Bn</td>
<td>H</td>
<td>NCCO2Me (5 equiv), –78 °C to r.t., 20 h</td>
<td>CO2Me</td>
<td>–d</td>
</tr>
</tbody>
</table>

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a The halogen–metal exchange was performed by the addition of 1–1.5 equivalents of n-BuLi in hexane to a solution of dichloroazetidinone 4 in THF, stirring for 30 min and subsequent addition of the electrophile.
b Yields after purification (flash chromatography or recrystallization).
c cis:trans Ratio determined by signal integration in the 1H NMR spectrum of the crude product.
d No reaction product isolated (intractable mixtures).
avoid steric interactions, the incoming electrophile preferentially approaches the intermediate 5 from the opposite face of the space in which the aryl substituent resides. This reasoning satisfactorily explains the formation of cis-4-aryl-3-chloro-2-azetidinones 6a–9a. For the formation of substantial amounts of trans-4-aryl-3-chloro-2-azetidinones in the case of water (without acid) (Table 1, entry 1), the same mechanism can be proposed, but the base lithium hydroxide is formed, which is able to deprotonate the 3-position of cis-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (6a). In this way, the cis-compound 6a isomerizes to the thermodynamically more stable trans-derivative 6b.

Two experiments were conducted to confirm these assumptions. The first one was the workup of the reaction mixture (from 4a, R1 = i-Pr, R2 = H) immediately after addition of water, so as to leave little time for the isomerization to take place, and mainly the cis-derivative should be isolated. To conduct this experiment, the same procedure was followed as in the previous cases. After the addition of water to the enolate, the reaction mixture was stirred during only one minute and subsequently poured into 10% citric acid to neutralize lithium hydroxide. This procedure confirmed the above mentioned hypothesis and almost only the cis-derivative was observed in the crude reaction mixture (cis:trans 1:0.06) (Scheme 3).

The second experiment checked the potential of lithium hydroxide to isomerize the cis-isomer 6a to the trans-isomer 6b. Thus, the isolated cis-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (6a) was reacted with lithium hydroxide in a tetrahydrofuran–water mixture (THF–H2O, 4:1). After a reaction time of 40 hours, cis- and trans-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (6a and 6b) were isolated (cis:trans = 1:2.63). These two experiments are in agreement with the proposed course of the reaction, implying at first only the formation of cis-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (6a), which, in the presence of a base, isomerizes to the thermodynamically more stable trans-derivative 6b (Scheme 3).

This was also confirmed when alkyl halides were used as electrophiles (Table 1, entries 10–12 and Scheme 4). In these cases, only the formation of the cis-3-alkyl-3-chloro-4-phenylazetidin-2-ones 10a–12a was detected. This relative cis-stereochemistry was checked and confirmed by NOE experiments between the 3-alkyl substituent and the C4-proton of compounds 10 and 11 (Figure 1).

From these results, also the influence of steric hindrance during the reaction could be derived. The bulkier the introduced electrophile, the lower the yield of the compound obtained.

Further attempts to extend this reaction to the use of other electrophiles failed. The introduction of a methoxycarbonyl functionality by the use of methyl chloroformate, dimethyl carbonate or methyl cyanoformate did not succeed (entries 14–16). Very complex reaction mixtures were ob-
tained from which only trace amounts of cis- and trans-3-chloro-1-isopropyl-4-phenyl-2-azetidinones were isolated. Also more sterically and electronically demanding electrophiles, like trimethylsilyl 2-bromoethyl ether (entry 13), did not give an alkylation product. The expected product from this reaction could possibly lead towards the synthesis of spiro-β-lactams. Possibly, the previously observed influence of steric hindrance plays a major role in this negative result.

In conclusion, a straightforward method for the synthesis of new cis-4-aryl-3-chloro-2-azetidinones 6a–9a was developed. This methodology was further extended to the use of alkyl halides as electrophiles, while more complex electrophiles could not be introduced.

1H and 13C NMR spectra were recorded at 270 and 68 MHz, respectively. The type of carbon and hydrogen was determined by DEPT 135. 1H and 13C NMR spectra were recorded at 270 and 68 MHz, respectively. 2-Aryl-3,3-dichloroazetidinones were isolated from which only trace amounts of cis- and trans-3-chloro-1-isopropyl-4-phenyl-2-azetidinones were isolated. Also more sterically and electronically demanding electrophiles, like trimethylsilyl 2-bromoethyl ether (entry 13), did not give an alkylation product. The expected product from this reaction could possibly lead towards the synthesis of spiro-β-lactams. Possibly, the previously observed influence of steric hindrance plays a major role in this negative result.

In conclusion, a straightforward method for the synthesis of new cis-4-aryl-3-chloro-2-azetidinones 6a–9a was developed. This methodology was further extended to the use of alkyl halides as electrophiles, while more complex electrophiles could not be introduced.

Halogen–Lithium Exchange Reactions of 4-Aryl-3,3-dichloroazetidinones 4; cis-3-Chloro-1-isopropyl-4-phenyl-2-azetidinone (6a); Typical Procedure

A solution of 3,3-dichloro-1-isopropyl-4-phenyl-2-azetidinone (4a; R1 = i-Pr, R2 = H) (1.00 g, 3.9 mmol) in THF (10 mL) was placed under N2 and kept at –78 °C. With a syringe, a 2.5 M solution of t-BuLi in hexanes (1.90 mL, 4.7 mmol) was added through the septum. t-BuLi and THF were freshly distilled from sodium wire and sodium benzophenone ketyl, respectively. Petroleum ether used had bp 40–60 °C. Melting points were measured with a Büchi 535 or Büchi 540 apparatus and are uncorrected. 2-Aryl-3,3-dichloroazetidinones were synthesized by cyclodehydration of dichloroketones, generated in situ from dichloroacetyl chloride, and an appropriate arenylamine.

Flash chromatography: petroleum ether–EtOAc (6:4), Rf 0.53. Flash chromatography: petroleum ether–EtOAc (6:4), Rf 0.53. Flash chromatography: petroleum ether–EtOAc (6:4), Rf 0.53. Flash chromatography: petroleum ether–EtOAc (6:4), Rf 0.53.
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Synthesis of cis-4-Aryl-3-chloro-2-azetidinones

MS: m/z (%) = M+ (not detected), 157 (3), 147 (2), 145 (2), 139/141 (100), 132 (3), 104 (19), 101 (3), 83 (3), 77 (7), 67 (1), 57 (4), 55 (6), 51 (3).

Anal. Calcd for C13H16ClNO: C, 65.70; H, 6.74; N, 5.90. Found: C, 65.80; H, 6.94; N, 5.86.

cis-3-Chloro-1-ethyl-1-isopropyl-4-phenyl-2-azetidine (11)

Yield: 40%; mp 70.9–71.1 °C (MeOH).

IR (KBr): 1748 cm–1 (C=O).

Flash chromatography: petroleum ether–EtOAc (8:2), Rf 0.36.

1H NMR (CDCl3): δ = 1.13 and 1.36 (2 × 3 H, 2 d, J = 6.6 Hz, CH(CH3)2), 1.17 (3 H, t, J = 7.26 Hz, CH(CH3)2), 2.14 (2 H, m, CH(CH3)2), 3.76 (1 H, septet, J = 6.93 Hz, CHMe2), 4.67 (1 H, s, NC(=O)H), 7.30–7.44 (5 H, m, C6H5).

13C NMR (CDCl3): δ = 90.7 (CH(CH3)2), 20.31 and 21.06 (CH(CH3)2), 50.64 (CH2CH3), 45.59 (CHMe2), 65.91 (NCH2CH3), 77.43 (C1(C=O)CH2CH3), 128.10 and 128.26 (C6H5). C2, C3, 128.82 (C2), 135.40 (C6), 166.95 (C=O).

MS: m/z (%) = 251/253 (M+ - 1), 216 (M+ - Cl, 2), 166/168 (100), 151 (6), 131 (41), 115 (10), 91 (6).

Anal. Calcd for C13H16ClNO: C, 66.81; H, 7.16; N, 5.57. Found: C, 66.95; H, 7.32; N, 5.52.

cis-1-Benzyl-3-chloro-4-phenyl-3-propyl-2-azetidine (12)

Flash chromatography: petroleum ether–EtOAc (8:2); Rf: 0.36.

Yield: 23%.

IR (neat): 1781 cm–1 (C=O).

1H NMR (CDCl3): δ = 0.95 (3 H, t, J = 7.6 Hz, CH3), 1.41–1.72 (2 H, m, CH2CH3), 1.89–2.17 (2 H, m, CH2CH3), 3.86 (1 H, d, J = 14.5 Hz, NCH(CH3)), 4.41 (1 H, d, J = 14.5 Hz, NCH(CH3)), 7.10–7.45 (10 H, m, C6H5).

13C NMR (CDCl3): δ = 13.93 (CH2CH3), 17.99 (CH3CH2), 39.21 (CH2CH3), 44.49 (NCH2), 66.38 (NCH2CH3), 77.99 (C3), 127.57, 127.99, 128.10, 128.34, 124.46 and 126.87 (2 C6H5, C2, C3, 128.10 and 128.26 (C6H5)). C2, C3, 133.82 and 134.63 (2 C6H5), 166.88 (C=O).

MS: m/z (%) = 278 (M+ - Cl, 2), 145 (13), 103 (7), 91 (100), 77 (11), 65 (10), 51 (3).

Anal. Calcd for C19H20ClNO: C, 72.74; H, 6.38; N, 4.47. Found: C, 72.94; H, 6.68; N, 4.45.

Halogen–Lithium Exchange Experiments Confirming the Proposed Reaction Mechanism

The first experiment (vide supra) conducted to confirm some mechanistic aspects of the results obtained from the previously described halogen–lithium exchange reactions, was concerned with the isomerization of cis-3-chloro-1-isopropyl-4-phenyl-2-azetidinone (6a) to the corresponding trans-derivative 6b. cis-3-Chloro-1-isopropyl-4-phenyl-2-azetidinone (6a; 0.10 g, 0.4 mmol) was dissolved in a H2O–THF solvent mixture (1:4, 2 mL). Subsequently, LiOH·H2O (0.06 g, 0.5 mmol) was added and the resulting mixture was stirred during 40 h. Afterwards, H2O was added and the aqueous layer was extracted with EtO. Drying (MgSO4), filtration and evaporation of the solvent yielded the crude reaction product, i.e. a mixture of cis- and trans-3-chloro-1-isopropyl-4-phenyl-2-azetidinones (6a and 6b), which was used to determine the ratio of both products by 1H NMR spectroscopy. The cis/trans ratio obtained turned out to be 1:2.63.

In a second experiment, the conventional procedure was followed. A solution of 3,3-dichloro-1-isopropyl-4-phenyl-2-azetidinone (4a; R1 = i-Pr, R2 = H; 1.00 g, 3.9 mmol) in THF (10 mL) was placed under N2 and kept at –78 °C. With a syringe, a 2.5 M solution of n-BuLi in hexanes (1.90 mL, 4.7 mmol) was added through the septum. The mixture was kept at –78 °C for 1 h. Afterwards, H2O (0.14 g, 7.8 mmol) in THF (10 mL) was added. The reaction mixture was stirred for only 1 min and subsequently poured into 10% citric acid.
to neutralize LiOH. The aqueous layer was extracted with Et₂O. Drying (MgSO₄), filtration and evaporation of the solvent yielded the crude reaction product, i.e. a mixture of cis- and trans-3-chloro-1-isopropyl-4-phenyl-2-azetidinones (6a and 6b), which was used to determine the ratio of both products by ¹H NMR spectroscopy. The cis:trans ratio obtained turned out to be 1:0.06.

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