

# Nucleophile-dependent regioselective ring opening of 2-substituted *N,N*-dibenzylaziridinium ions: bromide *versus* hydride†

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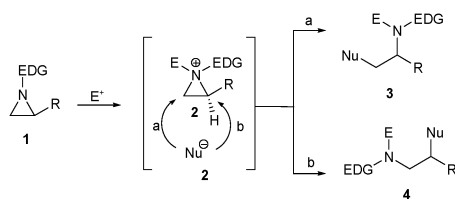
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The ring opening of 2-substituted *N,N*-dibenzylaziridinium ions by bromide exclusively occurs at the substituted aziridine carbon atom in a stereospecific way, whereas the opposite regioselectivity was observed for hydride-induced ring opening at the unsubstituted position; furthermore, this unprecedented hydride-promoted reactivity was validated by means of Density Functional Theory (DFT) calculations.

The aziridine moiety represents one of the most valuable three-membered ring systems in organic chemistry due to its widely recognized versatility as a building block for the preparation of a large variety of ring opened and ring expanded amines.<sup>1,2</sup> Moreover, regio- and stereo-controlled ring opening reactions of chiral aziridines constitute useful tools for the preparation of chiral nitrogen-containing targets.<sup>3</sup> Compared with cyclopropanes and oxiranes, the chemistry of aziridines depends on the characteristics of the substituent at the ring nitrogen as well as on the ring carbons.<sup>1,2</sup> Aziridines bearing an electron-withdrawing substituent at the ring nitrogen are less stable and more reactive towards nucleophiles with respect to ring opening.<sup>2</sup>

However, electron-donating groups (EDG) render the aziridine **1** more stable and activation towards an aziridinium intermediate **2** is required prior to nucleophilic ring opening. In this case, nucleophilic attack takes place either at the less substituted position C3 (pathway a, Scheme 1) or at the (electronically activated) position C2 (pathway b, Scheme 1) to yield amines **3** or **4**, respectively.<sup>4,5</sup> The study of the

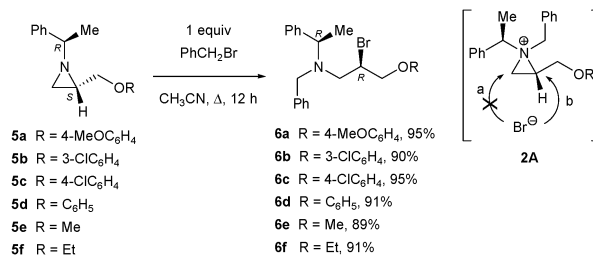


Scheme 1

regioselectivity of ring opening reactions of aziridinium salts **2** comprises a challenging topic for fundamental research, as it is known to be dependent on several factors such as the substrate, the type of nucleophile and the solvent. Whereas ring opening reactions of 2-substituted *N,N*-dialkylaziridinium salts by nucleophiles have been reported before,<sup>6</sup> no examples can be found in the literature in which two different nucleophiles induce a completely regioselective but contrasting ring opening of the same type of *N,N*-dialkylaziridinium ions.

Recently, treatment of optically pure (2*S*)-2-aryloxymethyl-1-( $\alpha$ -methylbenzyl)aziridines **5a–d** with benzyl bromide was reported to yield chiral 3-amino-2-bromo-1-aryloxypropanes **6a–d** as the unexpected ring opening products in a stereospecific way without any detectable amount of the counter regioisomer (Scheme 2).<sup>7</sup> Similar reaction conditions applied to 2-alkoxymethyl-1-( $\alpha$ -methylbenzyl)aziridines **5e–f** resulted in novel chiral  $\beta$ -bromoamines **6e–f** in good yields (Scheme 2). Aminopropanes **6** are a result of the regioselective ring opening of *N,N*-dialkylaziridinium ions **2A** by bromide attack at C2, with concomitant cleavage of the C2–N bond (pathway b, Scheme 2).

Up to now, hydride-induced ring opening reactions of 2-substituted aziridinium salts derived from non-activated aziridines have not been reported in the literature. Thus, ring opening of the aziridinium intermediate obtained from (2*R*)-3-amino-2-bromo-1-(4-methoxyphenoxy)propane **6a** was further studied using 3 molar equivalents of NaBH<sub>4</sub> in THF under reflux. Unexpectedly, (2*S*)-2-amino-1-(4-methoxyphenoxy)propane **7a** was obtained as a single isomer in high yield and purity (Scheme 3). This remarkable hydride-induced ring opening of 2-substituted aziridinium salts appeared not to be limited to the use of sodium borohydride, as the same reactivity profile was observed using different borohydride reagents including LiEt<sub>3</sub>BH, NaCNBH<sub>3</sub> and LiBH<sub>4</sub> in THF under reflux, affording 2-aminopropane **7a** in 81, 83 and 79% yield, respectively (Scheme 3).



Scheme 2

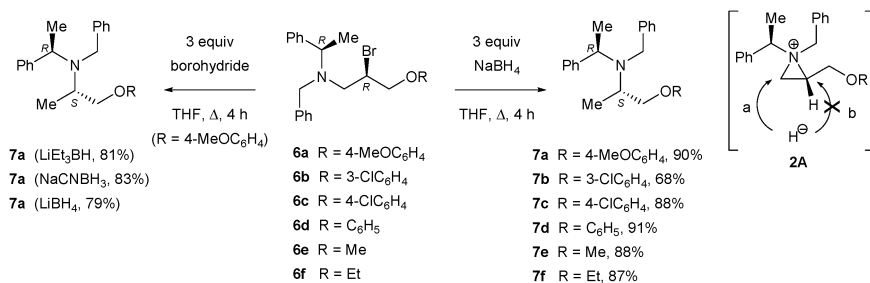
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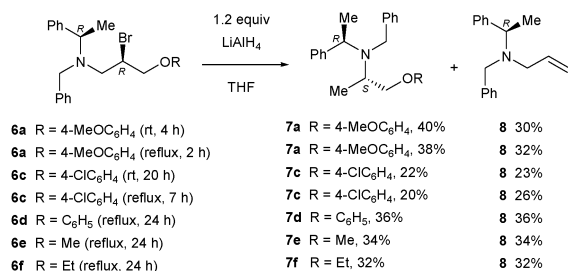
Scheme 3

Applying the same reductive reaction conditions, *i.e.* 3 molar equivalents of NaBH<sub>4</sub> in THF at reflux, to β-bromoamines **6b–d** resulted in the corresponding chiral 2-aminopropanes **7b–d** in 68–91% yield (Scheme 3). Furthermore, replacement of the aryloxy group by an alkoxy substituent in the aziridine side chain did not affect the reaction pathway, as treatment of 3-amino-2-bromo-1-methoxypropane **6e** and 3-amino-2-bromo-1-ethoxypropane **6f** with 3 equivalents of NaBH<sub>4</sub> in THF at reflux yielded 2-amino-3-alkoxypropanes **7e,f** in 87–88% yield.

The isolation of 2-aminopropanes **7** can be rationalized considering the formation of intermediate aziridinium salts **2A** (Scheme 3), followed by regioselective ring opening by hydride at the unsubstituted aziridine carbon atom (pathway a, Scheme 3).

Besides complex borohydrides, complex aluminium hydride reagents were also evaluated. The reaction of (2*R*)-3-amino-2-bromo-1-(4-methoxyphenoxy)propane **6a** with 1.2 equivalents of LiAlH<sub>4</sub> at room temperature furnished a mixture of the anticipated (2*S*)-2-amino-1-(4-methoxyphenoxy)propane **7a** and *N*-allyl-*N*-benzyl-*N*-(1-phenylethyl)amine **8** (Scheme 4). Both products (**7** and **8**) were shown to give similar yields under different reaction temperatures (40% and 30% yield at room temperature for 4 hours and 38% and 32% yield under reflux for 2 hours).

Similarly, chiral 2-aminopropane **7c** and allylamine **8** were obtained starting from 3-amino-2-bromo-1-(4-chlorophenoxy)propane **6c** in 22% and 23% yield at room temperature for 20 hours and in 20% and 26% yield under reflux for 7 hours, respectively. Analogous observations were made upon treatment of 3-amino-2-bromo-1-phenyloxypropane **6d** with LiAlH<sub>4</sub>, affording (2*S*)-2-amino-1-phenyloxypropane **7d** and 3-aminopropene **8**, both in 36% yield. Replacing the aryloxy group with an alkoxy substituent did not affect the reaction outcome, as treatment of 3-amino-2-bromo-1-methoxypropane **6e** and 3-amino-2-bromo-1-ethoxypropane **6f** with LiAlH<sub>4</sub> in THF afforded the same mixture containing chiral



Scheme 4

2-amino-1-alkoxypropanes (**7e** and **7f**) and 3-aminopropene **8** in 68% and 64% yield with the same ratio. The unprecedented formation of 3-aminopropene **8** from 3-aryloxy and 3-alkoxy-2-bromo-1-aminopropanes **6** upon reaction with LiAlH<sub>4</sub> seems to be promoted by the Lewis acidic character of the aluminium atom.

Previous experimental data have revealed that nucleophile identity plays a key role in the regio- and stereoselective ring opening of aziridinium salts.<sup>7</sup> Theoretical calculations were performed to further rationalize the unprecedented ring opening of 2-substituted aziridinium salts by hydride at the less hindered aziridine carbon atom. Thus hydride attacks at the substituted (C2) and unsubstituted (C3) positions of the aziridinium ring (**2A**) were modeled (Scheme 3, pathways a and b, respectively) at the MPW1B95<sup>8</sup> and B3LYP<sup>9</sup> level of theory with a 6-31++G\*\* basis set, where diffuse functions were added to hydrogen atoms to account for hydride character. Full geometry optimizations of transition states and their corresponding minima were performed with the Gaussian 03 program package.<sup>10</sup>

The transition state structure for hydride attack through pathway a (**TS-a**) depicts ring opening as BH<sub>4</sub><sup>-</sup> approaches the aziridinium ring—from the least hindered side—in an S<sub>N</sub>2 fashion (Fig. 1), similar to nucleophilic substitution reactions of aziridines.<sup>12</sup> Both transition states have a reactant-like structure, which is consistent with the highly exothermic nature of the reaction as seen in Fig. 2. Relative free energies of activation (Δ*G*<sup>‡</sup>) clearly indicate a preference for hydride attack at the unsubstituted aziridinium carbon atom (pathway a, Scheme 3) for both methods (ΔΔ*G*<sup>‡</sup><sub>B3LYP</sub> = 10.3 kJ/mol; ΔΔ*G*<sup>‡</sup><sub>MPW1B95</sub> = 15.5 kJ/mol), affording the thermodynamically more stable product, hence confirming the experimentally observed regioselectivity of the hydride attack on the aziridinium ring. Furthermore, NPA<sup>13</sup> and CHELPG<sup>14</sup>

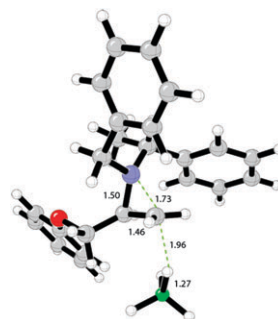
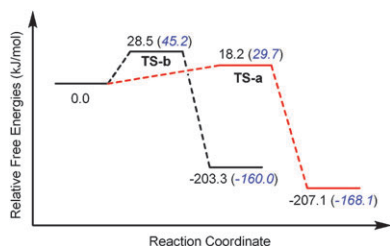


Fig. 1 B3LYP/6-31++G\*\* optimized transition state structure (TS-a).<sup>11</sup> Distances given in Å.



**Fig. 2** Free energy profile (B3LYP/6-31++G\*\*) for hydride attack on **2A** (Scheme 3) through pathways a and b. MPWB95/6-31++G\*\* energies given in parenthesis. Energy values for gas phase optimizations include thermal free energy corrections at 298 K and 1 atm.

charges indicate that C3 (NPA = 0.215; CHELPG = 0.145) is considerably more positive than C2 (NPA = 0.076; CHELPG = 0.047) at the B3LYP/6-31++G\*\* level of theory, also consistent with the experimentally observed preference.

The difference in activation barriers for pathways a and b is closely linked to the structural difference between the transition states, where the extent of elongation along the N–C bond (N–C3 = 1.73 Å and N–C2 = 1.50 Å, respectively) varies significantly, indicating a difference in progression along the reaction coordinate for the two pathways. This has been further verified by the activation strain model of chemical reactivity<sup>15</sup>,  $\Delta E^\ddagger = \Delta E_{\text{str}}^\ddagger + \Delta E_{\text{int}}^\ddagger$ , which dissects the activation energy ( $\Delta E^\ddagger$ ) into activation strain ( $\Delta E_{\text{str}}^\ddagger$ ), (also known as deformation energy<sup>16</sup> or distortion energy<sup>17</sup>) and interaction energy ( $\Delta E_{\text{int}}^\ddagger$ ) between distorted fragments. Single point energy calculations (B3LYP/6-31++G\*\*) on the **2A** fragment, in the geometry of both transition states, reveal that the difference in activation energies ( $\Delta\Delta E^\ddagger = 13.1$  kJ/mol, where  $E$  is electronic energy) is mainly caused by the difference in activation strain ( $\Delta\Delta E_{\text{str}}^\ddagger = 16.3$  kJ/mol), in line with the aforementioned structural differences in transition state geometries.

In conclusion, the stereospecific ring opening of 2-substituted *N,N*-dibenzylaziridinium ions by hydride at the unsubstituted aziridine carbon atom towards the corresponding 2-aminopropanes has been described for the first time and stands in contrast with the previously reported ring opening of the same aziridinium salts by bromide at the substituted position. The observed regioselectivity was rationalized by means of DFT calculations. Future theoretical work will focus on analyzing the main factors causing the difference in regioselectivity for bromide and hydride attack on the aziridinium rings, as well as elucidating the mechanism for the formation of the *N*-allyl-*N*-benzyl-*N*-(1-phenylethyl)amine upon reaction with LiAlH<sub>4</sub>.

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