Regio- and stereospecific ring opening of 1,1-dialkyl-2-(aryloxymethyl)aziridinium salts by bromide†

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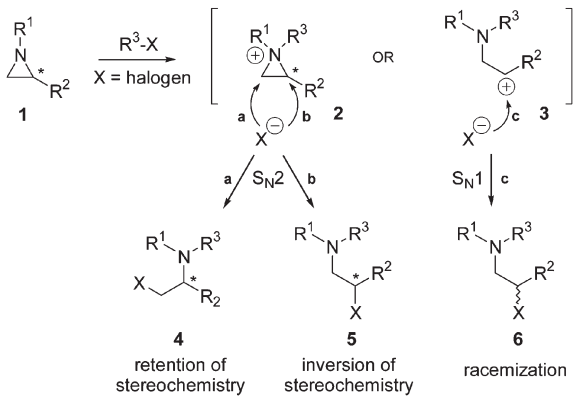
Enantiomerically pure 2-(aryloxymethyl)aziridines are efficiently transformed into chiral *N*-(2-bromo-3-aryloxypropyl) amines *via* a regio- and stereospecific ring opening of the intermediate aziridinium salts, and the experimental results are rationalized on the basis of some high level *ab initio* 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 towards a large variety of ring opened or ring expanded amines.[1] Moreover, regio- and stereocontrolled ring opening reactions of chiral aziridines constitute useful tools in asymmetric synthesis for the preparation of chiral nitrogen-containing target compounds.[2]

Unactivated aziridines, *i.e.* aziridines without an electron-withdrawing group at nitrogen, can easily be transformed into aziridinium salts upon treatment with alkyl halides, which are subsequently opened by a suitable nucleophile (usually the counter ion). As depicted in Scheme 1, the reaction of a chiral aziridine **1** with an alkyl halide may lead to three different amines **4–6** depending on the reaction mechanism. In this way, the initial chiral center at the substituted aziridine carbon atom can be retained (pathway **a**, amine **4**), inverted (pathway **b**, amine **5**) or racemized (pathway **c**, amine **6**). Consequently, the elucidation of the underlying reaction mechanism is of utmost importance when



Scheme 1

the design of asymmetric syntheses towards chiral amines is contemplated starting from chiral 2-substituted aziridines such as **1**. Although the ring opening of aziridinium salts by halides has been studied in the past,[3] only very few reports dealing with the stereochemistry of this type of reaction have been published,[4] in contrast with the study of the ring opening of activated aziridines.[1d] Up to now, only 2-(alkoxycarbonyl), 2-phenyl and 2-methyl monosubstituted aziridinium salts (besides some di- and trisubstituted aziridinium salts) have been studied in terms of stereochemistry in ring opening reactions with fluoride, chloride or iodide (but never bromide), affording the corresponding β-haloamines as a result of a regioselective C–N cleavage at the more hindered carbon atom or at the benzylic position. In this communication, the ring opening of a novel type of substrate, *i.e.* chiral 2-(aryloxymethyl)aziridinium salts, by bromide will be studied for the first time in terms of regio- and stereoselectivity, resulting in an efficient approach towards chiral *N*-(2-bromo-3-aryloxypropyl)amines with diverse applications. The experimental results are rationalized on the basis of some high level *ab initio* calculations on the transition states and reactants of the various routes as depicted in Scheme 1.

Enantiomerically pure 2-(hydroxymethyl)aziridines **7** and **10** were easily tosylated using 1.05 equivalents of tosyl chloride in CH_2Cl_2 in the presence of Et_3N and a catalytic amount of DMAP, affording the corresponding 2-(tosyloxymethyl)aziridines **8** and **11** in high yields after stirring for 4 hours at room temperature (Scheme 2). The latter aziridines **8** and **11** were subsequently transformed into 2-(aryloxymethyl)aziridines **9** and **12** upon treatment with 2.2 equivalents of 3-chlorophenol or 4-methoxyphenol in DMF–acetone (1 : 1) in the presence of K_2CO_3 and reflux for 20 hours (Scheme 2).[5] In the latter reaction, the tosylate is displaced by a phenolate ion *via* an S_N2 process at the tosylated carbon atom, without affecting the chirality of the aziridine carbon atom, in analogy with the previously reported substitution by methoxide.[6] 2-(Aryloxymethyl)aziridines **9** and **12** represent a novel class of compounds and are valuable substrates for the synthesis of a large variety of different aryloxypropylamines, the latter being of significant interest due to their diverse biological activities and their applicability in medicinal chemistry.[7]

Subsequently, aziridines **9** and **12** were exclusively converted into β-bromoamines **14** and **16** upon treatment with an aryl bromide in refluxing acetonitrile (Scheme 3) (see ESI†) as a useful elaboration of a formerly reported ring opening reaction of 2-(bromomethyl)aziridines towards *N*-(2,3-dibromopropyl) amines.[8] Only one analogous substrate has been reported in a ring opening reaction with iodide, although in this case the ring opening of the chiral 2-(hydroxymethyl)aziridinium salt took place

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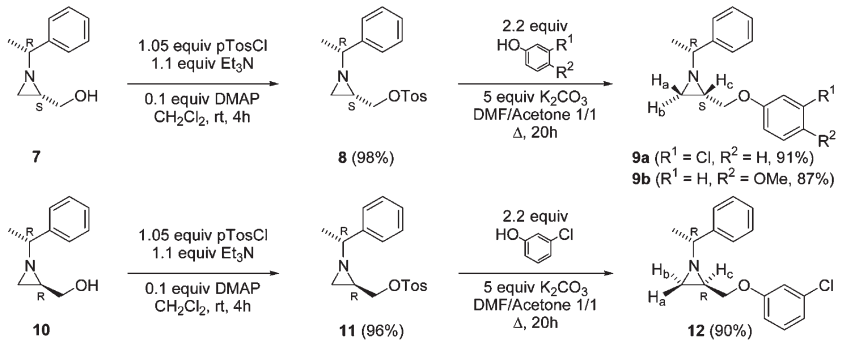
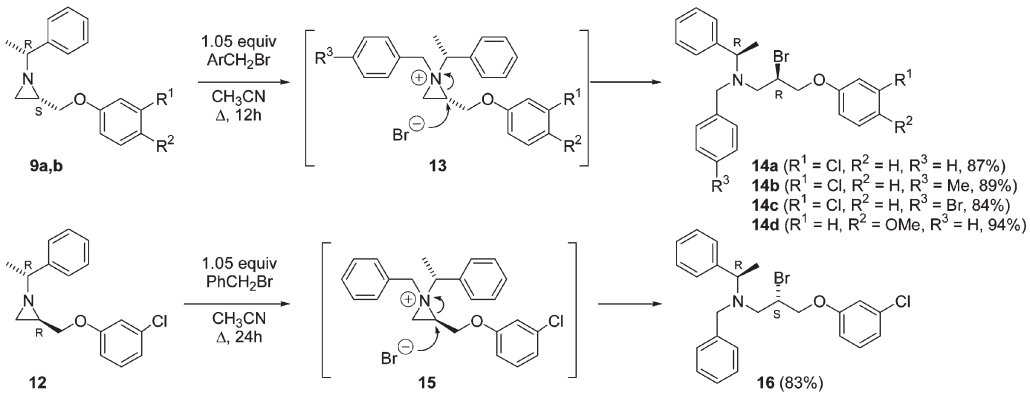
† Electronic supplementary information (ESI) available: Spectral data of compounds **9a**, **12**, **14a** and **16**. See DOI: 10.1039/b518298k



Scheme 2



Scheme 3

at the unsubstituted carbon instead of at the more hindered position.[9] The observed regiospecificity can be explained considering a nucleophilic attack of bromide at the more hindered carbon atom of the aziridinium intermediates **13** and **15**, giving rise to 2-bromopropylamines **14** and **16**. As depicted in Scheme 1, the formation of β-bromoamines **5** and **6** can be the result of an S_N2 reaction (pathway **b**) or an S_N1 process (pathway **c**), resulting in inversion or racemization of the chiral center, respectively. However, in all cases one single isomer was isolated, based on NMR spectroscopy, pointing to the conclusion that this transformation can only be described by an S_N2 process (Scheme 1, pathway **b**). If an initial ring opening of the intermediate aziridinium salt had taken place (Scheme 1, pathway **c**), neutralization by bromide of the planar carbocation thus formed would result in the formation of the two diastereomers in the same reaction mixture. Based on detailed spectroscopic analysis, no traces of β-bromoamine **16** could be detected after reaction of aziridine **9a** with benzyl bromide, and *vice versa*. Apparently, these reactions proceed through the formation of a transition state TSb (Fig. 1), affording the corresponding β-bromoamines **18** in a regio- and stereospecific way by attack of bromide at the more hindered aziridine carbon atom C_2 of

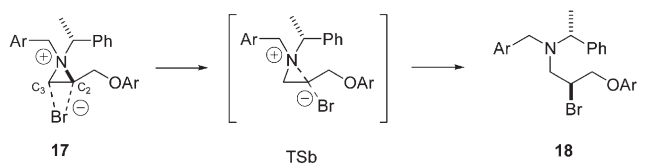


Fig. 1

intermediate **17** *via* an S_N2 pathway. This hypothesis was further validated by performing *ab initio* calculations on the aziridinium intermediate **13** and the transition states for the proposed reaction routes in Scheme 1. The optimization was performed at the MPW1B95/6-31 + g(d) level of theory, which is known to give reliable estimates of the geometries.[10] The reaction barriers were furthermore obtained at the MPWB1K/6-31 + g(d) level which is parametrized to give reliable reaction barriers.[10] Moreover we have tested a variety of other electronic levels and the selected methods have been found most suitable. Also the effect of solvent is taken into account, explicitly by surrounding the reactive center of the complexes with two acetonitrile molecules and implicitly by embedding all structures in a polarizable medium characterized by a fixed dielectric constant which is typical for acetonitrile (*i.e.* $\varepsilon = 36.64$). The calculations were performed in Gaussian 03.[11] Approaching the aziridinium cation with the bromide ion leads to a stable intermediate (**17** in Fig. 1) on the potential energy surface. The C–N bond lengths of the aziridinium cation are substantially different, the one involving the substituted carbon atom being longer (C_2–N = 1.50 Å; C_3–N = 1.48 Å, *cf.* Fig. 1). The weakening of the C_2–N bond upon substitution gives a preliminary indication that nucleophilic attack could be favourable at the substituted center. The aziridinium cation keeps almost exactly its isolated geometry by approaching it with a bromide anion. Moreover, the stabilization energy of the two approaching species is substantial (405 kJ mol^{-1}, *cf.* SE in Fig. 2). Both arguments make any suggestion of an S_N1 substitution reaction very doubtful. Furthermore, the coordination of the intermediate by solvent molecules is highly exothermic as the coordination solvation energy (CSE in Fig. 2) amounts to 93 kJ mol^{-1} for two acetonitrile

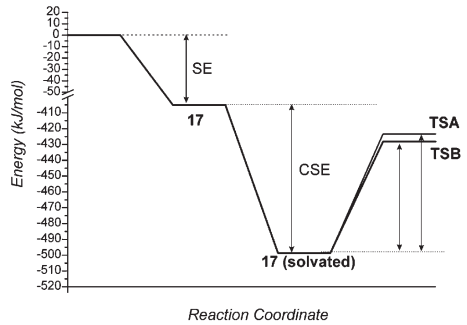


Fig. 2 Energy profile for reaction route a and b with SE the stabilization energy and CSE the coordination solvation energy as defined in the text. The energies are relative to the isolated species.

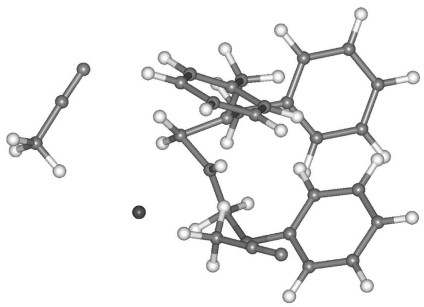


Fig. 3 Transition state for route b as depicted in Scheme 1.

molecules. More details about the effects of solvation can be found in the literature.[12]

At second instance the transition states for both S_N2 reaction routes were calculated (pathway a and b in Scheme 1). Both transition states are consistent with an S_N2 mechanism (C_3–N = 1.77 Å and C_3–Br = 2.73 Å for **b**; C_2–N = 1.70 Å and C_2–Br = 2.68 Å for **a**). The reaction barriers for pathway **a** and **b** amount to 76 and 70 kJ mol^{-1}, respectively (*cf.* Fig. 2). The transition state for route **b** is shown in Fig. 3. Our theoretical calculations thus confirm the experimental results that an S_N2 reaction at the most substituted carbon atom is preferred by approximately 6 kJ mol^{-1}. Furthermore, these calculations have pointed out an important result of taking into account solvent effects. Without inclusion of bulk solvent effects, no reaction preference was found for route **b**. Only when all species were properly embedded in a continuous dielectric medium was the correct reaction preference found. This theoretical finding is a preliminary indication for further experimental work of aziridinium salts in a variety of solvents as the reaction preference might be altered depending on the molecular environment used, which is currently under investigation. A previous theoretical study on the hydrolysis of 2-methyl and 2,2-dimethyl substituted aziridinium salts found that the correct reaction preference, *i.e.* attack at the less or most substituted carbon atom, was already correctly described by gas phase calculations.[13] These systems dealt however with neutral nucleophiles for which the polar effects might be expected to be less important.

N-(2-Halo-3-aryloxypropyl)amines have been reported to exhibit a variety of biological activities, resulting in the application of analogous compounds as *e.g.* antidepressants, antimicrobial and antifungal agents.[14] Due to the presence of such a biologically relevant moiety in amines **14** and **16**, their preparation might be of importance as target compounds or as substrates for further elaboration. The versatility of these compounds as substrates in organic synthesis is currently under investigation, and will be communicated in due course.

In conclusion, it has been demonstrated that 2-(aryloxymethyl) aziridinium salts can be opened in a regio- and stereospecific way by bromide to give *N*-(2-bromo-3-aryloxypropyl)amines, in accordance with an S_N2 type reaction mechanism. This methodology constitutes a novel protocol for the design of chiral syntheses towards substituted aminopropane derivatives as biologically relevant targets in medicinal chemistry.

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