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Synthesis and reactivity of non-activated 2-(chloromethyl)aziridines

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ABSTRACT

An efficient synthesis of non-activated 2-(chloromethyl)aziridines and 2-chloromethyl-2-methylaziridines as new representatives of the class of 2-(halomethyl)aziridines was developed. Furthermore, the reactivity of these azaheterocycles was assessed and compared to that of their brominated counterparts, pointing to a similar profile for 2-(chloromethyl)aziridines and 2-(bromomethyl)aziridines on the one hand, and a different behaviour of 2-chloromethyl-2-methylaziridines versus 2-bromomethyl-2-methylaziridines concerning their aptitude towards ring expansion to azetidines on the other hand.

Aziridines represent a valuable class of strained compounds in azaheterocyclic chemistry with diverse synthetic and biological applications.[1] The interest in aziridines as synthons in organic chemistry is due to the general influence of ring strain on chemical reactivity, making them important building blocks for the preparation of a large variety of ring-opened and ring-expanded amines.[2] It is known that the nucleofugality of the ring nitrogen and thus the reactivity of aziridines is dependent on the nature of the substituent at the nitrogen atom. For example, aziridines bearing an electron-withdrawing substituent at nitrogen (activated aziridines) are known to be reactive towards a large number of nucleophiles with respect to ring opening.[3] On the other hand, electron-donating groups at nitrogen render the aziridine more stable, and activation towards an aziridinium intermediate is, in most cases, required prior to nucleophilic ring opening.[4]

Within the class of 2-substituted, non-activated aziridines, the use of 2-(bromomethyl)aziridines as substrates for ring-opening reactions and nucleophilic substitutions has found great application in synthetic chemistry. In particular, 2-(bromomethyl)aziridines **4** have been shown to be suitable synthons for the preparation of, for example, cyclopropanes,[5] morpholines,[6] pyrrolizidines,[7] pyrrolidines,[7] 2-imino-1,3-thiazoli(di)nes[8] and piperidine derivatives.[9] In addition, the nucleophilic substitution of bromide in 2-(bromomethyl)aziridines with various heteroatom nucleophiles[6,8,10] and carbon nucleophiles[5,11] has provided a convenient access towards a variety of 2-substituted aziridines.

The synthesis of 2-(bromomethyl)aziridines **4** is well established and comprises cyclization of β,γ-dibromoamines **3** (R^2 = H), obtained through $NaBH_4$-mediated reduction of *N*-alkylidene-2,3-dibromopropylamines **1** (R^2 = H), in methanol under reflux (Scheme 1).[8,11b] Surprisingly, structurally similar β,γ-dibromoamines **3** bearing an additional methyl group (R^2 = Me), prepared via $NaBH_4$-reduction of both *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **1** (R^2 = Me) or *N*-(2,3-dibromo-2-methylpropylidene)amines **2** (R^2 = Me), have recently been shown to be easily convertible into 3-methoxy-3-methylazetidines **6** through rearrangement of 2-bromomethyl-2-methylaziridines **5** applying the same reaction conditions ($NaBH_4$, MeOH, Δ), pointing to a profound influence of the additional methyl group in amines **3** on the reaction outcome.[12] Next to aziridines, azetidines are also of interest due to their diverse applications from both a synthetic and a biological point of view.[13]

A detailed analysis of the latter transformation revealed the synthesis of azetidines **6** to proceed via the initial formation of 2-bromomethyl-2-methylaziridines **5**, obtained as the sole reaction products in the kinetically-controlled cyclization of amines **3** (R^2 = Me) using $NaBH_4$ in methanol at room temperature. Under thermodynamic conditions, 2-bromomethyl-2-methylaziridines **5** have been shown to completely rearrange into 3-methoxy-3-methylazetidines **6** upon treatment with sodium borohydride in methanol under reflux for 48 h.[12] In contrast to this clean aziridine (**5**) to azetidine (**6**) rearrangement, no reports on the transformation of 2-(bromomethyl)aziridines **4** (without an additional methyl group at the aziridine ring) into the corresponding azetidines are available in the literature. From these observations, it was clear that 2-bromomethyl-2-methylaziridines **5** exhibit a totally different reactivity as compared to 2-(bromomethyl)aziridines **4**.[12]

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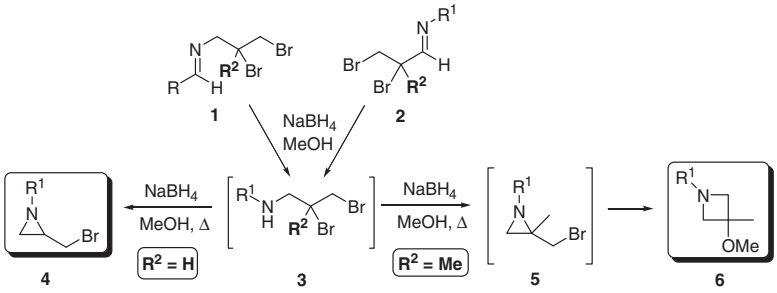


Scheme 1. Reactivity of β,γ-dibromoamines **3** (R^2 = H or Me) towards $NaBH_4$ Ref. 12.

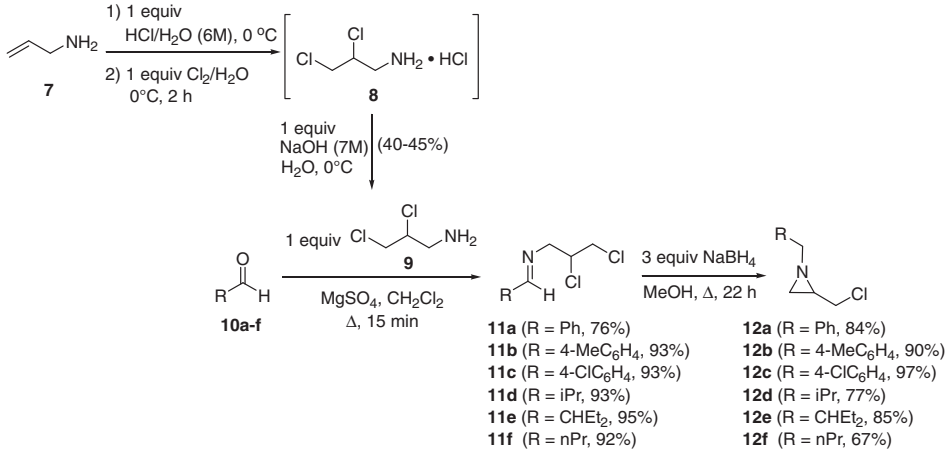
In contrast to the widely explored chemistry of 2-(bromomethyl)aziridines **4**, the synthesis of their chlorinated counterparts received only limited interest in the literature.[14,15] In these reports, the preparation of non-activated *N*-*t*-butyl-, *N*-isopropyl- and *N*-cyclohexyl-2-(chloromethyl)aziridine has been described through nucleophilic displacement of amines bearing a good leaving group in β-position,[14] or through reductive cyclization of α,α,β-trichlorinated *N*-alkylimines using lithium aluminium hydride.[15] The synthesis of 2-chloromethyl-2-methylaziridines, however, has not been reported in the literature so far.

In the present Letter, a new and efficient synthesis of non-activated 2-(chloromethyl)aziridines through reductive cyclization of *N*-alkylidene- and *N*-arylmethylidene-2,3-dichloropropylamines is described, as well as the synthesis of 2-chloromethyl-2-methylaziridines applying an analogous methodology, that is, the reductive cyclization of *N*-(2,3-dichloro-2-methylpropylidene)amines. Whereas 2-(chloromethyl)aziridines were shown to have a similar (and as expected slightly reduced) reactivity as compared to the corresponding 2-(bromomethyl)aziridines, the behaviour of 2-chloromethyl-2-methylaziridines was demonstrated to be intrinsically different than that of their brominated analogues.

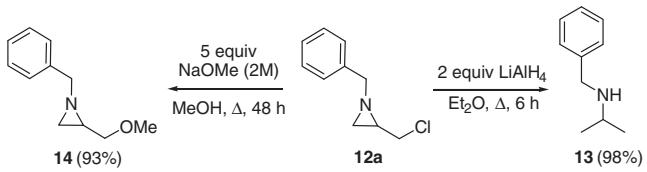
In the first part of this work, the synthesis and reductive cyclization of *N*-alkylidene- and *N*-arylmethylidene-2,3-dichloropropylamines into 2-(chloromethyl)aziridines was evaluated. After unsuccessful attempts towards the chlorination of *N*-(phenylmethylidene)allylamine[16] in dichloromethane or carbon tetrachloride using 1 equiv of chlorine gas, an alternative approach to access *N*-alkylidene- and *N*-arylmethylidene-2,3-dichloropropylamines **11** en route to aziridines **12** was applied.

Thus, the synthesis of 2-(chloromethyl)aziridines **12** commenced with the chlorination of allylamine **7** in water by introducing 1 equiv of chlorine gas at 0 °C for 2 h after initial treatment with 1 equiv of HCl in water (6 M) at 0 °C (Scheme 2). Since attempted crystallization of 2,3-dichloropropylamine hydrochloride **8** failed, the crude product was then treated with one equiv of sodium hydroxide in water (2 M) with the intention to isolate the free amine **9**, but only small amounts of this amine **9** were obtained in this way (10–15%). Finally, using a more concentrated solution of sodium hydroxide in water (7 M), 2,3-dichloropropylamine **9** was obtained in acceptable yields (40–45%) (Scheme 2). After nucleophilic addition of the latter amine **9** across aldehydes **10a–f** in dichloromethane under reflux in the presence of $MgSO_4$, the corresponding novel *N*-arylmethylidene- and *N*-alkylidene-2,3-dichloropropylamines **11a–f** were formed in good yields and used as such in the next step due to their lability (Scheme 2). Subsequently, novel 2-(chloromethyl)aziridines **12a–f** were obtained in high yields and purity as a result of $NaBH_4$-mediated reduction of imines **11** in methanol after 22 h under reflux.[17] It should be noted that the reductive cyclization of *N*-arylmethylidene- and *N*-alkylidene-2,3-dichloropropylamines **11a–f** required a prolonged reaction time (22 h) as compared to the cyclization of the corresponding *N*-arylmethylidene-2,3-dibromopropylamines (2 h),[18] which can be rationalized considering the weaker leaving group capacity of chloride as compared to bromide.

With regard to their reactivity, it was shown that 2-(chloromethyl)aziridines **12** display the same reactivity towards $LiAlH_4$ and NaOMe as their brominated counterparts.[19,20] Indeed, *N*-benzyl-*N*-isopropylamine **13** was obtained upon treatment of aziridine **12a** with 2 equiv of $LiAlH_4$ in diethyl ether after 6 h under reflux (Scheme 3), and 2-(methoxymethyl)aziridine **14** was formed through nucleophilic substitution of chloride by methoxide after treatment of aziridine **12a** with 5 equiv of NaOMe (2 M) in methanol under reflux for 48 h (Scheme 3). As compared to the reactivity of 2-(bromomethyl)aziridines **4**, more drastic reaction conditions, such as prolonged reaction times and heating under reflux, were required in order to drive these reactions to completion. The above-described results show that 2-(chloromethyl)aziridines **12** can be prepared in an efficient and straightforward way and point



Scheme 2. Synthesis of 2-(chloromethyl)aziridines **12**.



Scheme 3. Reactivity of 2-(chloromethyl)aziridine **12a** towards NaOMe and $LiAlH_4$.

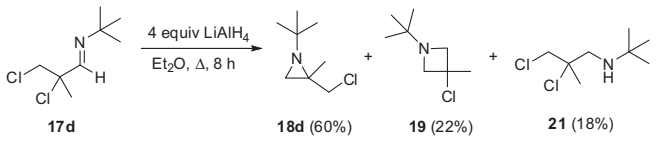
to a similar and—as expected—reduced reactivity profile of these azaheterocycles as compared to the analogous 2-(bromomethyl)aziridines **4**.

Given the recently reported successful and efficient synthesis of 2-bromomethyl-2-methylaziridines **5**,[12] the same synthetic methodology was applied for the preparation of novel 2-chloromethyl-2-methylaziridines. The chlorination of methacrolein **15** with chlorine gas (neat) furnished 2,3-dichloro-2-methylpropanal **16** in nearly quantitative yield after 1.5 h. Treatment of the latter aldehyde **16** with 1.1 equiv of a primary amine in dichloromethane in the presence of $MgSO_4$ afforded α,β-dichloroimines **17a–d**. Subsequently, the reaction of aldimines **17a–c** with 1.1 equiv of $NaBH_4$ in methanol under reflux for 4 h provided new 2-chloromethyl-2-methylaziridines **18a–c** in high yields (Scheme 4).[21]

Interestingly, in contrast to the preparation of 2-bromomethyl-2-methylaziridines **5**, the synthesis of aziridines **18a–c** required heating under reflux in order to achieve reductive cyclization of α,β-dichloroimines **17**. In addition, when aziridine **18b** was treated with $NaBH_4$ in methanol for 62 h under reflux, no traces of the corresponding 3-methoxyazetidine were found, pointing to a high stability of these aziridines towards ring expansion. It should be stressed that 2-bromomethyl-2-methylaziridines **5** have been shown to rearrange smoothly into 3-methoxy-3-methylazetidines **6** applying the same reaction conditions ($NaBH_4$, MeOH, Δ).[12]

In contrast to the synthesis of 2-chloromethyl-2-methylaziridines **18a–c**, *N*-(2,3-dichloro-2-methylpropylidene)-*t*-butylamine **17d** was transformed into a rather complex mixture upon treatment with $NaBH_4$ in methanol for 26 h under reflux (Scheme 4), consisting of 3-chloroazetidine **19** (36%), 3-methoxyazetidine **20** (44%), β,γ-dichloroamine **21** (12%) and small amounts of *N*-*t*-butyl-2,3-dichloro-2-methylpropionamide (<8%), formed by reaction of 2,3-dichloro-2-methylpropionyl chloride (obtained during the chlorination of methacrolein) with *t*-butylamine.

Furthermore, when the same imine **17d** was treated with an excess (4 equiv) of $LiAlH_4$ in Et_2O for 8 h under reflux, a complex mixture was obtained in which the presence of aziridine **18d** (60%), azetidine **19** (22%) and β,γ-dichloroamine **21** (18%) was observed by means of NMR and GC analysis (Scheme 5). Apparently, the presence of the sterically hindered *t*-butyl group at nitrogen has a strong influence on the outcome in these reactions.



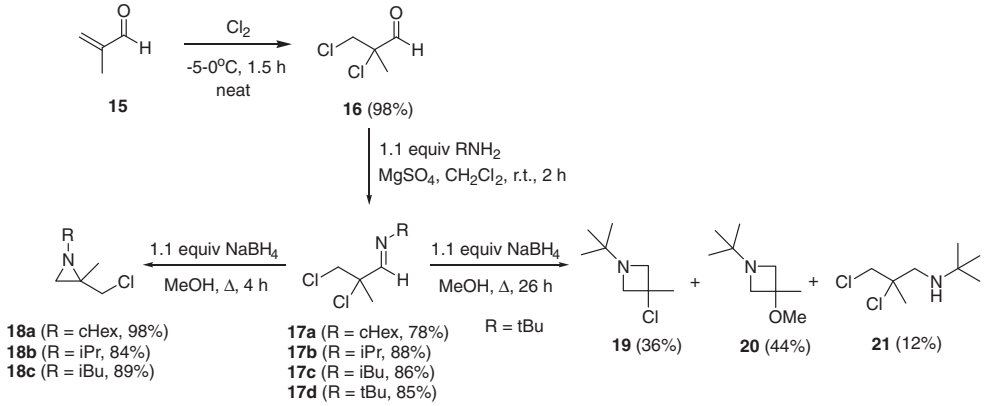
Scheme 5. Reactivity of imine **17d** towards $LiAlH_4$.

In view of these results, and in light of a recently established aziridine to azetidine rearrangement,[12] the formation of 3-chloro-3-methylazetidine **19** in both the above-mentioned reactions might be the result of the ring expansion of the initially formed 2-chloromethyl-2-methylaziridine **18d** under thermodynamic conditions through chloride-induced ring opening of bicyclic aziridinium intermediate **22** (Scheme 6). It should be mentioned that the formation of intermediate **22** from aziridine **18d** is more difficult than from 2-bromomethyl-2-methylaziridines **5** because of the less pronounced leaving group capacity of chloride as compared to bromide. Furthermore, the presence of azetidine **20** (Scheme 4) can be explained by nucleophilic attack of methanol at the more hindered carbon atom of the same intermediate bicyclic aziridinium salt **22**. The comparable nucleophilicity of chloride and methanol can account for the competing pathways yielding a mixture of azetidines **19** and **20** (Scheme 6).

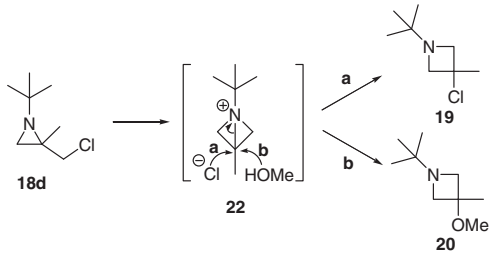
The different reactivity of 1-*t*-butylaziridine **18d** as compared to 1-alkylaziridines **18a–c** (R = *c*Hex, *i*Pr, *i*Bu) might be attributed to the slightly increased electron density of the nitrogen atom in the former due to the higher electron-donating capacity of the *t*-butyl group, rendering the aziridine nitrogen atom in aziridine **18d** more reactive in terms of nucleophilicity.

The influence of an additional methyl group in aziridines **18** as compared to 2-(chloromethyl)aziridines **12** was demonstrated by the reactions of aziridine **18b** with NaOMe and $LiAlH_4$. Treatment of aziridine **18b** with 2 equiv of $LiAlH_4$ in Et_2O or THF at both room temperature and under reflux gave only the starting compound, and the nucleophilic substitution of aziridine **18b** with 5 equiv of NaOMe in methanol (2 M) also resulted in the full recovery of the starting material, even after heating for 62 h under reflux. Treatment of 2-bromomethyl-2-methylaziridines **5** with NaOMe in methanol under reflux, however, has previously been shown to furnish 3-methoxyazetidines.[12]

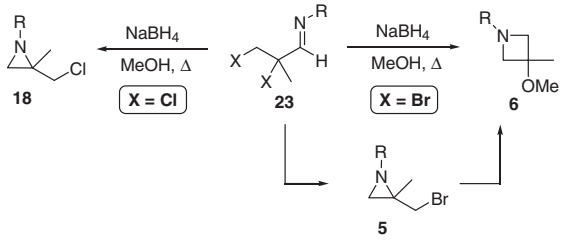
In conclusion, the present Letter provides efficient syntheses of 2-(chloromethyl)aziridines and 2-chloromethyl-2-methylaziridines as new representatives of the class of 2-(halomethyl)aziridines. It was elucidated that 2-(chloromethyl)aziridines **12** show a similar (and as expected a slightly reduced) reactivity profile as compared to the corresponding 2-(bromomethyl)aziridines **4**, reflected in the nucleophilic substitution using NaOMe and the ring



Scheme 4. Synthesis of 2-chloromethyl-2-methylaziridines **18**.



Scheme 6. Formation of azetidines **19** and **20** from **18d**.



Scheme 7. Different reactivity of imines **23** with respect to $NaBH_4$ depending on the substituent X (X = Cl or Br).

opening by means of $LiAlH_4$. On the other hand, the behaviour of 2-chloromethyl-2-methylaziridines **18** was shown to be intrinsically different than that of their brominated analogues **5**. While 2-bromomethyl-2-methylaziridines **5** have previously been shown to be the kinetic products in the formation of 3-methoxy-3-methylazetidines **6** upon treatment of α,β-dibrominated imines **23** (X = Br) with $NaBH_4$ in methanol under reflux, α,β-dichloroaldimines **23** (X = Cl) were converted into 2-chloromethyl-2-methylaziridines **18** applying the same reaction conditions (with the exception of the *t*-butyl derivative), pointing to the relative stability of these aziridines **18** towards ring expansion as a result of the less pronounced leaving group capacity of chloride as compared to bromide (Scheme 7).

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17. As a representative example, the synthesis of 1-(4-chlorobenzyl)-2-(chloromethyl)aziridine **12c** is described here. *N*-(4-Chlorobenzylidene)-2,3-dichloropropylamine **11c** (2.51 g, 10 mmol) was dissolved in methanol (30 ml), after which $NaBH_4$ (1.13 g, 3 mol equiv) was added in small portions at 0 °C, and the mixture was stirred for 22 h under reflux. The reaction mixture was poured into water (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were washed with H_2O (2 × 15 ml) and brine (20 ml). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(4-chlorobenzyl)-2-(chloromethyl)aziridine **12c** (2.10 g, 97%), which was purified by distillation (Bp = 86–92 °C/0.09 mmHg) in order to obtain an analytically pure sample. 1-(4-Chlorobenzyl)-2-(chloromethyl) aziridine **12c**: B_p = 86–92 °C/0.09 mmHg; Yield 97%; ^1H NMR (60 MHz, CCl_4) δ 1.30–2.00 (3H, m), 2.90–3.80 (4H, m), 7.28 (4H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.0, 40.2, 46.8, 63.5, 128.5, 129.4, 133.0, 137.1. IR (NaCl, cm^{-1}) ν_{max} = 1597, 1492, 1408, 1354, 1268, 1088, 1018. MS *m*/*z* (%) 215/7/9 (M^+, 6), 180/2 (40), 126/8 (9), 125/7 (100), 98 (5), 92 (17), 90 (56), 89 (16), 75 (5), 63 (7), 55 (8).
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21. As a representative example, the synthesis of 2-chloromethyl-1-cyclohexyl-2-methylaziridine **18a** is described here. *N*-(2,3-Dichloro-2-methylpropylidene) cyclohexylamine **17a** (2.22 g, 10 mmol) was dissolved in methanol (30 ml), after which $NaBH_4$ (0.42 g, 1.1 mol equiv) was added in small portions at 0 °C, and the mixture was stirred for 4 h under reflux. The reaction mixture was poured into a 0.5 M solution of NaOH in H_2O (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were washed with H_2O (2 × 15 ml) and brine (20 ml). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-chloromethyl-1-cyclohexyl-2-methylaziridine **18a** (1.84 g, 98%), which was purified by distillation (Bp = 120–134 °C/19 mmHg) in order to obtain an analytically pure sample. 2-Chloromethyl-1-cyclohexyl-2-methylaziridine **18a**: B_p = 120–134 °C/19 mmHg; Yield 98%; ^1H NMR (60 MHz, $CDCl_3$) δ 0.9–2.4 (13H, m), 1.33 (3H, s), 3.1–3.8 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 24.6, 24.9, 26.2, 32.8, 33.9, 38.2, 40.0, 54.7, 60.3. IR (NaCl, cm^{-1}) ν_{max} = 2922, 2850, 1450, 1383, 1259. MS *m*/*z* (%) 187/9 (M^+, 5), 152 (100), 144/6 (6), 108 (6), 106 (13), 104 (17), 96 (6), 83 (10), 82 (8), 81 (8), 77 (99), 70 (98), 69 (13), 68 (10), 67 (8), 56 (26), 55 (51), 54 (11), 53 (9), 49 (11).