Highly unusual conversion of 1-alkyl-2-(bromomethyl)aziridines into 1-alkyl-2-(*N*-alkyl-*N*-ethylaminomethyl)aziridines using methyllithium

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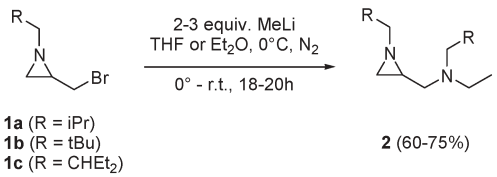
1-Alkyl-2-(bromomethyl)aziridines were transformed into 1-alkyl-2-(*N*-alkyl-*N*-ethylaminomethyl)aziridines upon treatment with 2–3 equiv. of methyllithium in THF or Et_2O; the peculiarity in this transformation comprises the presence of an *N*-ethyl group in the end-products as well as the total number of carbon atoms, resulting from a highly unusual reaction course with a novel S_N2'-type substitution at the aziridine moiety and liberation of acetylene from an intermediate vinylamine as the key reaction steps.

The uncommon combination of reactivity, synthetic flexibility and atom economy in aziridines has paved the way for their widespread use in organic synthesis.[1] The chemistry of non-activated 1-alkylaziridines still constitutes an underdeveloped area of research, and new insights in the reactivity of these constrained azaheterocycles contribute to the full elaboration of these valuable synthons in organic chemistry. 2-(Bromomethyl)aziridines form a peculiar and rather unknown class of constrained β-halo amines prone to ring opening reactions and ring transformations towards a variety of nitrogen containing compounds. When treated with nucleophiles, non-activated 1-alkyl-2-(bromomethyl)aziridines have proven to be suitable synthetic equivalents for the aziridinylmethyl cation, thus providing an easy access to the corresponding substituted aziridines,[2] whereas activated 1-arenesulfonyl-2-(bromomethyl)aziridines can be applied successfully as synthetic equivalents for the 2-aminopropane dication synthon towards 2-substituted 1-arenesulfonylaziridines on the one hand and ring opened *N*-tosylamides on the other hand, depending on the amount of reagent used.[3] Both carbon-centered nucleophiles (lithium dialkylcuprates, cyanide) and heteroatom-centered nucleophiles (alkoxides, thiolates, azides, phenoxides, carboxylates) have been evaluated in these studies, all pointing to the same above mentioned conclusions. Treatment of 1-tosyl-2-(bromomethyl) aziridines with alkyllithium reagents such as methyllithium and butyllithium, however, resulted in *N*-(allyl)tosylamide due to metal–halogen exchange and subsequent ring opening.[3a]

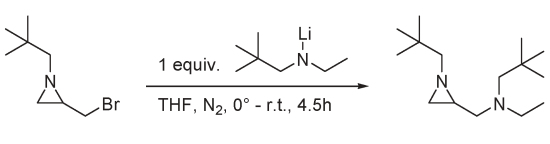
In order to have a complete overview of the reactivity of 1-alkyl-2-(bromomethyl)aziridines, their behaviour with regard to methyllithium was evaluated. 1-Alkyl-2-(bromomethyl)aziridines **1** are easily accessible substrates for further syntheses, prepared in a three-step procedure starting from the appropriate aldehydes.[4] When these aziridines **1** were treated with 2–3 equiv. of methyllithium in diethyl ether or THF, the reaction mixtures thus obtained contained 2-(aminomethyl)aziridines **2** as the major constituents (Scheme 1).[5] After isolation of these curious compounds by means of column chromatography, their peculiar molecular structure was confirmed by detailed spectroscopic analysis and independent synthesis. The formation of these compounds was totally unexpected, and the presence of an *N*-ethyl group as well as the total number of carbon atoms in compounds **2** indicated a highly unusual reaction course totally different from the known behaviour of 1-alkyl-2-(bromomethyl) aziridines **1** towards organocopper reagents and other nucleophiles. It should be remarked that the aziridines **2** contain one carbon atom less then double the number of carbon atoms in the starting material, which rules out a simple dimerisation-like process.



Scheme 1

The molecular structure of the aziridine **2b** was unequivocally determined by an independent synthesis of this compound (Scheme 2). Reduction of the imine derived from pivaldehyde and ethylamine with sodium borohydride in methanol afforded *N*-ethyl-*N*-neopentylamine in 87% yield after reflux for 2 h. The corresponding lithium amide of the latter amine, generated upon treatment with 1 equiv. of *n*-BuLi in THF (0 °C, N_2, 1 h), was used to accomplish a nucleophilic substitution resulting in the desired 1-neopentyl-2-(*N*-ethyl-*N*-neopentylaminomethyl)aziridine **2b** in THF in 55% yield. The spectral data of compound **2b** obtained *via* both approaches (Scheme 1 and Scheme 2) appeared to be completely identical.

A plausible explanation for this highly unusual transformation is depicted in Scheme 3, in which the substrate **1** undergoes an S_N2'-type substitution, followed by conversion of the resulting enamine **3** into lithium amide **4**, furnishing 2-(aminomethyl)aziridines **2** upon nucleophilic substitution at the halogenated carbon atom of an unreacted aziridine **1**.



Scheme 2

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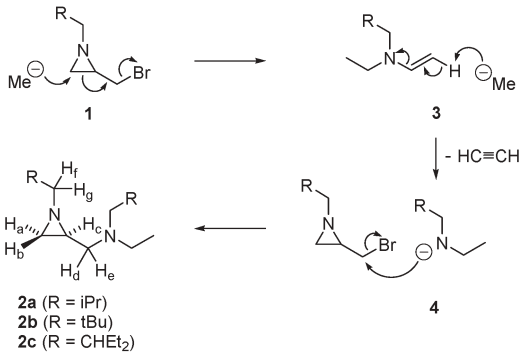
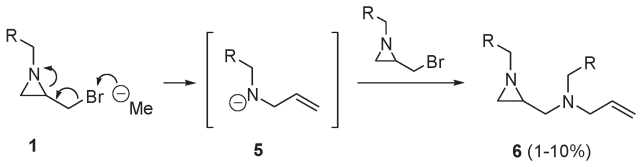


Scheme 3

The peculiarity in this transformation comprises the presence of an *N*-ethyl group in the end-products **2**, and the most plausible way for the introduction of this moiety involves a nucleophilic attack of a methyl carbanion at the unsubstituted aziridine carbon atom of aziridines **1** towards *N*-alkyl-*N*-ethylvinylamines **3** *via* an unprecedented S_N2'-type reaction. This is not unlikely, since constrained three-membered ring systems behave in some respects like double-bond compounds due to the so called bent bonds, which are intermediate in character between σ and π.[6] Unsubstituted enamines such as *N*-ethyl-*N*-butyl-, *N*,*N*-dimethyl- and *N*,*N*-diethylvinylamines are reported in the literature as being highly unstable,[7] and the thus quite labile enamines **3** can undergo deprotonation by the excess of methyllithium with expulsion of acetylene, resulting in *N*-ethyl lithium amides **4**. Only one literature precedent was found, in which *N*,*N*-dimethyl-*N*-(1,2-diphenylvinyl)amine underwent an elimination reaction triggered by sodium amide in ammonia with the formation of 1,2-diphenylacetylene.[8] Finally, substitution at the bromomethyl unit of an unreacted aziridine **1** affords the 2-(aminomethyl)aziridines **2**, which can easily be purified by column chromatography on silica gel. The presence of small amounts of *N*-ethyl-*N*-neopentylamine in the reaction mixtures (3–5%, GC-MS) is a good indication for the intervention of the lithium amides **4** in this reaction. Several unsuccessful attempts were made to identify the acetylene produced during the reaction, either by using bromine to induce an electrophilic addition across the triple bond or by adding benzaldehyde in order to trap lithium acetylide. However, the liberation of acetylene during this reaction was unambiguously demonstrated by means of gas chromatographic headspace analysis. To exclude a possible role of water during workup, *e.g.* the hydrolysis of enamines **3** by adventitious water with release of acetaldehyde, the reaction mixture of one experiment was directly analysed by GC-MS without prior contact with water. The results were similar to those obtained in all other experiments, indicating that water did not take part in this transformation. No traces of vinylamines **3** were found in the reaction mixtures (all attempts to identify them by GC-MS failed), contrary to the detection of *N*-ethylamines derived from anion **4**.

The final substitution reaction by the lithium amides **4** is limited by the size of the alkyl substituent R. Indeed, when the bulky 1-(2,2-dimethyl-3-phenylpropyl)-2-(bromomethyl)aziridine **1** [R = $C(Me)_2CH_2Ph$] was treated with 3 equiv. of MeLi in Et_2O, only the corresponding *N*-ethyl-*N*-(2,2-dimethyl-3-phenylpropyl)amine was isolated in 95% yield and no 2-(aminomethyl)aziridine was formed due to steric hindrance.



Scheme 4

Some of these experiments were conducted in the presence of an internal standard (1 equiv. of *n*-$C_{16}H_{34}$), pointing to a conversion of 60%, since in these experiments 30% of 2-(aminomethyl)aziridine **2a** was present with respect to the internal standard (100%) and 2 equiv. of starting material are consumed to form one equivalent of aziridine **2a**.

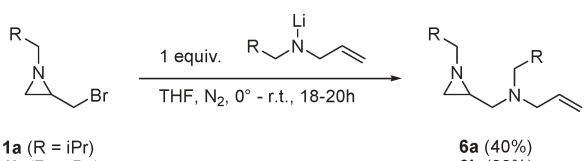
When at least two equivalents of MeLi were used, all the starting material **1** was consumed and 2-(aminomethyl)aziridines **2** were formed as the main compounds besides other constituents in minor quantities (<10%), such as 1-alkyl-2-(*N*-allyl-*N*-alkylaminomethyl)aziridines **6** due to a debromination by methyllithium (halophilic reaction) followed by ring opening to generate the *N*-allyl amide anion **5** and a subsequent nucleophilic substitution (Scheme 4).

To prove the presence of the minor constituents **6**, the lithium amides prepared from *N*-allyl-*N*-neopentylamine and *N*-allyl-*N*-isobutylamine with 1 equiv. of *n*-BuLi in THF were treated with the corresponding 2-(bromomethyl)aziridines **1a** and **1b** in THF for 18 to 20 h at room temperature under nitrogen atmosphere, furnishing the desired 2-(*N*-allylaminomethyl) aziridines **6a** and **6b**, which were purified by means of column chromatography yielding 40% of **6a** and 22% of **6b** (Scheme 5).

Comparison of retention times and mass spectra confirmed the presence of the aforementioned 2-(*N*-allylaminomethyl)aziridines **6** in the reaction mixtures obtained after treatment of aziridines **1** with MeLi. *N*-Allyl-*N*-neopentylamine and *N*-allyl-*N*-isobutylamine were prepared by imination of the appropriate aldehydes with allylamine and magnesium sulfate in CH_2Cl_2 (96–98%), followed by a reduction with $NaBH_4$ in methanol (90–92%). Only one example of a 2-(*N*-allylaminomethyl)aziridine could be found in the literature.[9]

Besides the peculiarity of this transformation, the 2-(aminomethyl)aziridines thus obtained are valuable compounds in medicinal chemistry due to the known anti-tumor activity of platinum complexes of such type of compounds.[10] Furthermore, the constrained aziridine ring allows a plethora of ring opening reactions and ring transformations towards a variety of biologically relevant 1,2- or 1,3-diamino compounds such as *e.g.* aziridinomitosene derivatives.[11]

In conclusion, a highly unusual and very selective new approach towards 2-(aminomethyl)aziridines, starting from 1-alkyl-2-(bromomethyl)aziridines, is disclosed. This one-step reaction proceeds



Scheme 5

in good yields and offers an efficient alternative towards the synthesis of biologically relevant targets with a diaminopropane moiety incorporated. The obtained results clearly broaden the scope of non-activated aziridine chemistry and contribute to the further elaboration of this field of research.

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5 As a representative example, the synthesis of 1-isobutyl-2-(*N*-ethyl-*N*-isobutylamino)methylaziridine **2a** is described here. To an ice-cooled (0 °C) solution of 1-isobutyl-2-(bromomethyl)aziridine **1a** (0.19 g, 1 mmol) in dry THF (5 mL) was added slowly and under nitrogen atmosphere methyllithium (1.88 mL, 3.0 equiv., 1.6 M in diethyl ether) *via* a syringe. The reaction mixture was further stirred for 20 h at room temperature under nitrogen atmosphere. Workup was carried out by pouring the reaction mixture in 10 mL of a 0.5 M sodium hydroxide solution, followed by extraction with ether (2 × 10 mL, 1 × 5 mL). After drying of the organic phase with K_2CO_3 and filtration of the drying agent, the solvent was removed *in vacuo*. Isolation of the main reaction product was performed by means of column chromatography on silica gel (R_f 0.42, CH_2Cl_2/MeOH/Et_3N 90/10/1). Spectroscopic data of 1-isobutyl-2-(*N*-ethyl-*N*-isobutylaminomethyl)aziridine **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 0.90, 0.93 and 0.96 (12H, 2 × d, J = 6.60 Hz, $(CH_3)_2CH(H_fCH_g)$ and 1 × d, J = 6.60 Hz, $(CH_3)_2CH$); 1.01 (3H, t, J = 7.15 Hz, CH_3CH_2); 1.25 (1H, d, J = 6.33 Hz, CH_aN); 1.40–1.49 (1H, m, CH_cN); 1.56 (1H, d, J = 3.58 Hz, CH_bN); 1.68–1.91 (2H, m, 2 × $(CH_3)_2CH$); 1.98–2.24 (4H, m, 2 × iPrCH_2N); 2.37 and 2.57 (2H, 2 × d × d, J = 5.78, 6.19, 13.14 Hz, (H_dCH_e)N); 2.60 (2H, q, J = 7.15 Hz, CH_2CH_3). ^{13}C NMR (68 MHz, $CDCl_3$): δ(ppm) 11.87 (CH_3CH_2); 21.01 (2 × $(CH_3)_2CH$); 26.78 and 29.24 (2 × $(CH_3)_2CH$); 33.36 (H_aCH_b); 37.96 (CH_c); 48.60 (CH_2CH_3); 57.64 (H_dCH_e); 62.71 ($CH_3CH_2NCH_2$iPr); 69.69 (NCH_2iPr). IR (NaCl, cm^{-1}): ν = 3035; 1468; 1384; 1363; 1200; 1177; 1082. MS (70 eV) *m*/*z* (%): 212 (M^+, 1); 169 (100); 140 (15); 114 (81); 112 (49); 100 (51); 98 (24); 84 (77); 70 (61); 58 (28); 57 (27); 56 (40). Anal. Calcd for $C_{13}H_{28}N_2$: C 73.52%; H 13.29%; N 13.19%. Found: C 73.39%; H 13.41%; N 13.29%. Colorless liquid, TLC *R*f 0.42 (CH_2Cl_2/MeOH/Et_3N 90/10/1). Spectroscopic data of 1-neopentyl-2-(*N*-ethyl-*N*-neopentylaminomethyl)aziridine **2b**: ^{1}H NMR (270 MHz, $CDCl_3$): δ(ppm) 0.87 and 0.96 (18H, 2 × s, 2 × tBu); 0.99 (3H, t, J = 7.07 Hz, CH_3CH_2); 1.21 (1H, d, J = 6.27 Hz, CH_aN); 1.38–1.56 (1H, m, CH_cN); 1.57 (1H, d, J = 3.30 Hz, CH_bN); 1.93 and 2.12 (2H, 2 × d, J = 11.72 Hz, (H_fCH_g)N); 2.18 (2H, s, *t*-BuCH_2N); 2.33 and 2.73 (2H, 2 × d × d, J = 4.95, 6.43, 13.45 Hz, (H_dCH_e)N); 2.60 (2H, q, J = 7.07 Hz, CH_2CH_3). ^{13}C NMR (68 MHz, $CDCl_3$): δ(ppm) 12.08 (CH_3CH_2); 28.10 and 28.18 (2 × $(CH_3)_3C$); 32.58 and 33.01 (2 × Me_3C); 33.84 (H_aCH_b); 38.60 (CH_c); 50.35 (CH_2CH_3); 59.19 (H_dCH_e); 66.88 (*t*-BuCH_2N); 73.89 (H_fCH_g). IR (NaCl, cm^{-1}): ν = 2952; 2905; 2866; 2816; 1479; 1465; 1361. MS (70 eV) *m*/*z* (%): 240 (M^+, 0.5); 183 (100); 128 (13); 126 (21); 84 (45); 71 (10); 70 (11); 56 (19). Anal. Calcd for $C_{15}H_{32}N_2$: C 74.93%; H 13.42%; N 11.65%. Found: C 74.80%; H 13.59%; N 11.78%. Colorless liquid, TLC *R*f 0.60 (CH_2Cl_2/MeOH/Et_3N 90/10/1). Spectroscopic data of 1-(2-ethylbutyl)-2-(*N*-ethyl-*N*-(2-ethylbutyl)aminomethyl)aziridine **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 0.86 and 0.87 (12H, 2 × t, J = 7.15 Hz, 2 × $(CH_3CH_2)_2CH$); 1.00 (3H, t, J = 7.15 Hz, CH_3CH_2N); 1.20 (1H, d, J = 6.33 Hz, CH_aN); 1.17–1.50 (11H, m, CH_cN and 2 × $(CH_3CH_2)_2CH$); 1.52 (1H, d, J = 3.58 Hz, CH_bN); 2.09 and 2.20 (2H, 2 × d × d, J = 5.09, 5.64, 11.97 Hz, (H_fCH_g)N); 2.24–2.28 (2H, m, Et_2CHCH_2N); 2.35 and 2.51 (2H, 2 × d × d, J = 5.64, 6.19, 13.62 Hz, (H_dCH_e)N); 2.57 (2H, q, J = 7.15 Hz, NCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) 10.81, 10.89 and 10.98 (2 × $(CH_3CH_2)_2CH$); 11.68 (CH_3CH_2N); 23.94, 24.00 and 24.09 (2 × $(CH_3CH_2)_2CH$); 33.36 (H_aCH_b); 37.97, 38.81 and 41.70 (3 × CH); 48.45 (NCH_2CH_3); 57.47 (H_dCH_e); 57.77 (Et_2CHCH_2N); 64.61 (H_fCH_g). IR (NaCl, cm^{-1}): ν = 2962; 2875; 2812; 1460; 1379. MS (70 eV) *m*/*z* (%): 268 (M^+, 0.5); 253 (1); 239 (1); 197 (100); 168 (10); 142 (22); 140 (14); 128 (38); 112 (10); 98 (15); 84 (45); 70 (50); 58 (10); 56 (16); 43 (25). Anal. Calcd for $C_{17}H_{36}N_2$: C 76.05%; H 13.52%; N 10.43%. Found: C 75.91%; H 13.43%; N 10.54%. Light yellow liquid, TLC *R*f 0.25 (Hexane/EtOAc 1/3).

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