Coupling of 1-alkyl-2-(bromomethyl)aziridines with heteroatom-centered nucleophiles towards 2-[(heteroatom)methyl]aziridines

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Dedicated to Prof. Oleg Kulinkovich on the occasion of his 60th birthday

Abstract

The reactivity of 1-alkyl-2-(bromomethyl)aziridines with respect to different types of oxygen-, nitrogen- and sulphur-centered nucleophiles has been evaluated, pointing to the conclusion that these substrates can be applied successfully as synthetic equivalents for the aziridinylmethyl cation synthon towards the corresponding 2-[(heteroatom)methyl]aziridines in good yields.

Keywords: 2-(Bromomethyl)aziridines, aziridinylmethyl cation synthon, 2-[(heteroatom)methyl]aziridines

Introduction

Aziridines have proven to be excellent building blocks for the synthesis of a large variety of ring opened and ring expanded amines due to the inherent reactivity of the constrained ring.[1] 2-(Halomethyl)aziridines comprise a remarkable class of aziridine derivatives with diverse synthetic applications. In former communications, we have demonstrated that activated 1-arenesulfonyl-2-(bromomethyl)aziridines **1** can be applied successfully as synthetic equivalents for the 2-aminopropane dication synthon **2** (Figure 1) towards α-branched *N*-tosylamides upon treatment with either carbon-centered[2] or heteroatom-centered[3] nucleophiles. Their non-activated counterparts, 1-alkyl-2-(bromomethyl)aziridines **3**,[4] comprise a mainly unexplored class of functionalized aziridine derivatives. Previously, we reported the successful coupling of 1-alkylaziridines **3** with carbon-centered nucleophiles (organocuprates) as a useful method for the synthesis of 1,2-dialkylaziridines, pointing to the observation that 1-alkyl-2-(bromomethyl)aziridines **3** are suitable equivalents for the aziridinylmethyl cation **4** (Figure 1).[5] Contrary to the above-mentioned *N*-activated 1-arenesulfonylaziridines, the focus lies on the absence of ring opening in order to develop a convenient method for aziridine synthesis. In the present report, the aziridinylmethyl cation equivalency of 1-alkyl-2-(bromomethyl)aziridines **3** will be further elaborated extensively utilizing different heteroatom-centered nucleophiles instead of carbon nucleophiles, affording a suitable approach towards 1-alkyl-2-[(heteroatom)methyl]aziridines as useful synthons in organic chemistry.

1 **2** **3** **4**

Figure 1

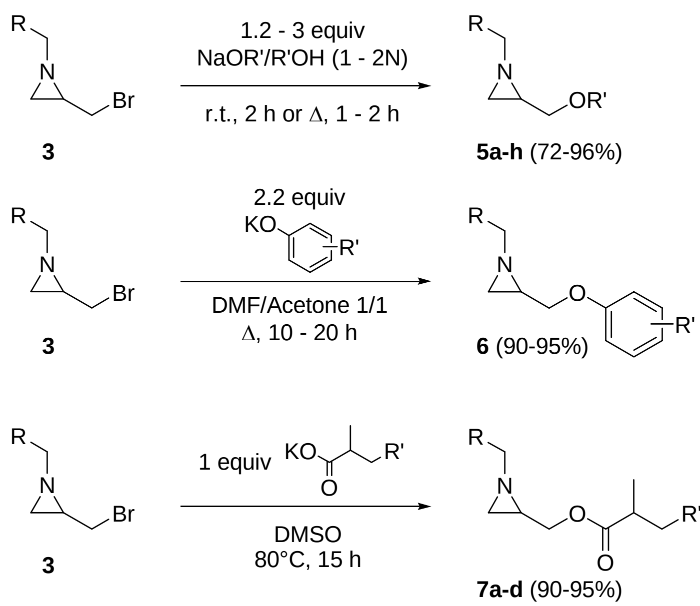
Results and Discussion

1-Alkyl-2-(bromomethyl)aziridines **3** can easily be prepared in a three-step procedure starting from the appropriate aldehydes.[4] Subsequently, these aziridines **3** were treated with a variety of oxygen, nitrogen and sulphur nucleophiles to afford the corresponding 2-[(heteroatom)methyl]aziridines. As demonstrated before, the substitution of the bromo atom in 1-alkyl-2-(bromomethyl)aziridines **3** by a nucleophile takes place *via* a direct attack at the halogenated carbon atom (instead of ring opening and subsequent ring closure which occurs when *N*-activated 2-(bromomethyl)aziridines **1** are used),[6] which is of significance whenever asymmetric synthesis towards chiral targets compounds is contemplated, e.g. starting from chiral substrates **3**.[7]

For the synthesis of 2-(oxymethyl)aziridines, three different types of oxygen-centered nucleophiles were evaluated successfully, i.e. alkoxides, aryloxides and carboxylates. 1-Alkyl-2-(bromomethyl)aziridines **3** can be easily transformed into the corresponding 2-(alkoxymethyl)aziridines **5** upon treatment with 1.2 – 3 equiv of sodium alkoxides in alcohol at room temperature or reflux for 1 to 2 hours (Scheme 1, Table 1). This has resulted in the synthesis of 2-(methoxymethyl)aziridines **5a**,**c**,**e**,**f**, 2-(ethoxymethyl)aziridine **5b**, 2-(isopropoxymethyl)aziridine **5d** and 2-(allyloxymethyl)aziridine **5g**. This methodology offers an easy and efficient alternative for the procedure developed by Deyrup, in which alcoholic sodium hydroxide (1N) was used for the treatment of 2-(tosyloxymethyl)aziridines upon a prolonged reaction time (2 days).[8] Several other 2-(allyloxymethyl)aziridines have been prepared and used previously for the diastereoselective synthesis of *cis*-3,5-disubstituted morpholine derivatives upon treatment with bromine in dichloromethane.[9] 2-(*tert*-Butoxymethyl)-1-neopentylaziridine **5h** was prepared in a different way, involving the treatment of 2-(bromomethyl)-1-neopentylaziridine with 2 equiv of KO*t*Bu in refluxing THF for 1 hour (Table 1, entry 8).

The incorporation of an aryloxy moiety, which is often required for biological activity,[10] can be very efficiently established by means of a nucleophilic substitution of the bromo atom of the aziridines **3** using a phenolate anion as a nucleophile. As reported before, treatment of aziridines **3** with 2.2 equivalents of phenol or, alternatively, a substituted bromo- or chlorophenol, and 5 equivalents of K_2CO_3 in a mixture of DMF and acetone (1/1) afforded the corresponding 2-(aryloxymethyl)aziridines **6** in excellent yields and high purity after reflux for 10 to 20 hours (Scheme 1).[11] The latter aziridines have been used successfully for the synthesis of biologically relevant 2-amino-1-aryloxy-3-methoxypropanes.[11] Known methods for the synthesis of 2-(aryloxymethyl)aziridines are usually more cumbrous and start from the corresponding 2-(aryloxymethyl)oxiranes[12] or from acyclic β-amino alcohols,[13] or involve the addition of ethoxycarbonylnitrene and the ethoxycarbonylnitrenium ion to allylic ethers.[14]

Alternatively, the potassium salts of two different carboxylic acids were used as oxygen nucleophiles to accomplish the nucleophilic displacement of the bromo atom in aziridines **3**. Thus, 1-arylmethyl-2-(bromomethyl)aziridines **3** were converted into the corresponding 2-(alkanoyloxymethyl)aziridines **7** upon treatment with 1 equiv of potassium 2-methylpropanoate or potassium 2-methylbutyrate in DMSO in excellent yields after heating at 80°C for 15 hours (Scheme 1, Table 2). In the case of 2-methylbutyrate **7d**, the two diastereomers (ratio 53/47) appeared to be inseparable by chromatography (GC and flash).[15] For example, 2-(alkanoyloxymethyl)aziridines **7** can be used for the synthesis of functionalized β-fluoro amines,[15] which are of interest in medicinal chemistry.[16] 2-(Alkanoyloxymethyl)aziridines, mainly 2-(acetoxymethyl)aziridines, have been prepared in other (longer) ways, usually by (enzymatic) acetylation of 2-(hydroxymethyl)aziridines[17] or by ring closure of sulfonylated 1-acetoxy-2-amino-3-hydroxypropanes.[18]



Scheme 1

Table 1. Synthesis of 2-(alkoxymethyl)aziridines **5** from 2-(bromomethyl)aziridines **3** (Scheme 1)

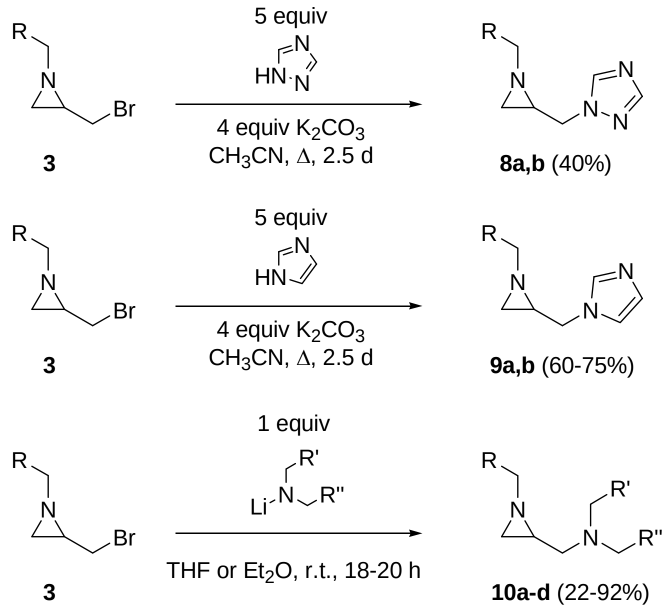
Entry	R	R'	Conditions	Compound **5** (Yield)
1	C_6H_5	Me	1.2 equiv NaOMe/MeOH (2N), r.t., 2 h	**5a** (93%)
2	C_6H_5	Et	1.2 equiv NaOEt/EtOH (2N), r.t., 2 h	**5b** (81%)
3	n-Pr	Me	1.2 equiv NaOMe/MeOH (2N), r.t., 2 h	**5c** (92%)
4	C_6H_5	*i*Pr	1.5 equiv NaO*i*Pr/*i*PrOH (1N), Δ, 1 h	**5d** (73%)
5	$C(Me)_2CH_2C_6H_5$	Me	1.5 equiv NaOMe/MeOH (2N), Δ, 1 h	**5e** (96%)
6	*t*Bu	Me	3 equiv NaOMe/MeOH (2N), Δ, 1.5 h	**5f** (72%)
7	4-ClC_6H_4	Allyl	2.1 equiv $NaOCH_2CH=CH_2$/allyl alcohol, Δ, 2 h	**5g** (95%)
8	*t*Bu	*t*Bu	2 equiv KO*t*Bu, THF, Δ, 1 h	**5h** (75%)

Table 2. Synthesis of 2-(alkanoyloxymethyl)aziridines **7** from 2-(bromomethyl)aziridines **3**[15] (Scheme 1)

Entry	R	R'	Compound **7** (Yield)
1	3-MeC_6H_4	H	**7a** (85%)
2	2-ClC_6H_4	H	**7b** (82%)
3	4-MeC_6H_4	H	**7c** (86%)
4	C_6H_5	Me	**7d** (77%)

Furthermore, also nitrogen-centered nucleophiles have been evaluated to broaden the aziridinylmethyl cation equivalency of 1-alkyl-2-(bromomethyl)aziridines **3**. 1*H*-[1,2,4]Triazole and 1*H*-imidazole were used in a large excess (5 equiv) in refluxing acetonitrile for 2.5 days in the presence of 4 equiv of potassium carbonate to afford the corresponding novel 2-[(1,2,4-triazol-1-yl)methyl]aziridines **8** and 2-[(imidazol-1-yl)methyl]aziridines **9** (Scheme 2, Table 3). An analogous substitution of 1-[(dialkoxyphosphoryl)methyl]-2-(bromomethyl)aziridines by cytosine, thymine, acetylguanine and adenine has been reported, affording 2-substituted aziridines as precursors for the corresponding nucleoside phosphonates as potential biologically active compounds.[19]

Also lithium amides were employed, and treatment of 2-(bromomethyl)aziridines **3** with 1 equiv of a lithium amide in THF or Et_2O for 18 to 20 hours at room temperature under nitrogen atmosphere furnished the desired 2-(aminomethyl)aziridines **10** (Scheme 2, Table 4). Only very few examples of 2-(*N*-allylaminomethyl)aziridines can be found in the literature.[20,21] 2-(Aminomethyl)aziridines are valuable compounds in medicinal chemistry due to the known anti-tumor activity of platinum complexes of such type of compounds,[22] and they can be used as substrates for the synthesis of biologically relevant diaminopropane derivatives by ring opening reactions.[23]



Scheme 2

Table 3. Synthesis of 2-[(1,2,4-triazol-1-yl)methyl]aziridines **8** and 2-[(imidazol-1-yl)methyl] aziridines **9** from 2-(bromomethyl)aziridines **3** (Scheme 2)

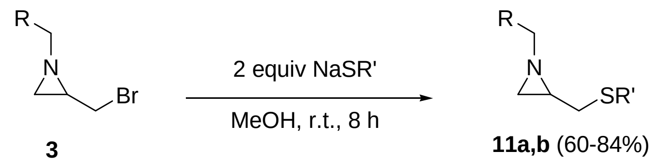
Entry	R	Compound **8** or **9** (Yield)
1	C_6H_5	**8a** (40%)
2	4-ClC_6H_4	**8b** (40%)
3	C_6H_5	**9a** (60%)
4	4-ClC_6H_4	**9b** (75%)

Table 4. Synthesis of 2-(aminomethyl)aziridines **10** from 2-(bromomethyl)aziridines **3** (Scheme 2)

Entry	R	R’	R’’	Compound **10** (Yield)
1	*i*Pr	*i*Pr	CH=CH_2	**10a** (40%)
2	*t*Bu	*t*Bu	CH=CH_2	**10b** (22%)
3	*i*Pr	Me	Me	**10c** (92%)
4	*t*Bu	*t*Bu	Me	**10d** (55%)

Finally, two different sulphur-centered nucleophiles were tested for the substitution of the bromo atom in 2-(bromomethyl)aziridines **3**. Sodium isopropylthiolate and sodium allylthiolate (2 equiv) were used successfully in methanol at room temperature to afford 2-[(alkylsulfanyl)methyl]aziridines **11** in an efficient approach (Scheme 3, Table 5). Chiral 2-[(alkylsulfanyl)methyl]aziridines, prepared from acyclic 3-alkylsulfanyl-2-aminopropan-1-ols, have been reported to be excellent catalysts for the enantioselective addition of diethylzinc to aldehydes[24] and for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-

propenyl acetate with the dimethymalonate anion.[25] Furthermore, a chiral 2-[(thiophenyl)methyl]-3-*tert*-butylaziridine has been prepared by cyclization of a 2-amino-3-(thiophenyl)propan-1-ol.[26]



Scheme 3

Table 5. Synthesis of 2-[(alkylsulfanyl)methyl]aziridines **11** from 2-(bromomethyl)aziridines **3** (Scheme 3)

Entry	R	R'	Compound **11** (Yield)
1	4-ClC_6H_4	*i*Pr	**11a** (84%)
2	4-ClC_6H_4	allyl	**11b** (60%)

Treatment of 2-(bromomethyl)aziridines **3** with 2 equivalents of the ambident nucleophile potassium thiocyanate has been reported previously to afford the corresponding 2-(thiocyanomethyl)aziridines in excellent yields after heating for 20 hours at 70°C in DMF.[27] The latter 2-(thiocyanomethyl)aziridines have been used for the synthesis of 2-iminothiazolidines via an intramolecular cyclisation reaction due to the presence of an electrophilic centre in δ-position with regard to the nucleophilic nitrogen atom.

In conclusion, 1-alkyl-2-(bromomethyl)aziridines are excellent synthetic equivalents for the aziridinylmethyl cation, providing an easy access to 1-alkyl-2-[(heteroatom)methyl]aziridines upon treatment with oxygen-, nitrogen- or sulphur-centered nucleophiles. As 1-alkyl-2-(bromomethyl)aziridines are considerably less reactive than the corresponding 1-(arenesulfonyl)aziridines, they are ideally suited for the synthesis of 2-substituted aziridine derivatives. In contrast with 1-arenesulfonyl-2-[(heteroatom)methyl]aziridines, the aziridine ring of 1-alkyl-2-[(heteroatom)methyl]aziridines is not susceptible to ring opening upon treatment with an excess of reagent.

Experimental Section

Synthesis of 2-(alkoxymethyl)aziridines 5. General procedure

2-(Bromomethyl)aziridine **3** (15 mmol) was dissolved in a solution of sodium alkoxide in the corresponding alcohol (1 - 2N, 1.2 - 3 equiv) and the mixture was stirred for 2 hours at room temperature or heated under reflux for 1 - 2 hours. Extraction with dichloromethane, drying

($MgSO_4$), filtration of the drying agent and removal of the solvent *in vacuo* afforded the corresponding 2-(alkoxymethyl)aziridine **5**, which can be purified by distillation.

1-Benzyl-2-(methoxymethyl)aziridine (5a). Yield 93%. Colorless oil. ^{1}H NMR (60 MHz, CCl_4): δ 1.1-1.8 (3H, m, NCH_2CH); 3.1-3.6 (2H, m, OCH_2); 3.28 (3H, s, OCH_3); 3.29 and 3.51 (2H, 2×d, J=14 Hz, NCH_2Ar); 7.33 (5H, s, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.27 (N*C*H_2CH); 38.36 (NCH); 58.47 (OCH_3); 64.24 (NCH_2Ar); 74.48 (OCH_2); 126.96 (NCH_2HC_{para}); 128.01 and 128.24 ($NCH_2HC_{ortho}HC_{meta}$); 139.03 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν = 1498, 1456, 1347, 1164, 1109. MS (70 eV) m/z (%): 177 (M^+, 5); 147 (21); 146 (21); 91 (100); 86 (75); 65 (18); 56 (69), 45 (69). Purity (GC) > 97%. Anal. Calcd for $C_{11}H_{15}NO$: C 74.54, H 8.53, N 7.90. Found: C 74.71, H 8.68, N 7.77.

1-Benzyl-2-(ethoxymethyl)aziridine (5b). Yield 81%. Colorless oil. Bp. 45-48°C/0.04 mmHg. ^{1}H NMR (60 MHz, CCl_4): δ 1.1-1.9 (3H, m, NCH_2CH); 1.12 (3H, t, J=7.0 Hz, CH_3); 3.0-3.6 (6H, m, NCH_2Ar and CH_2OCH_2); 7.28 (5H, s, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.17 (CH_3); 31.71 (N*C*H_2CH); 38.61 (NCH); 64.37 (NCH_2Ar); 66.30 (O*C*H_2Me); 72.73 (O*C*H_2CHN); 127.02 (NCH_2HC_{para}); 128.05 and 128.31 ($NCH_2HC_{ortho}HC_{meta}$); 139.04 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν = 1496, 1456, 1338, 1163, 1110. MS (70 eV) m/z (%): 191 (M^+, 1); 147 (10); 146 (16); 91 (97); 72 (25); 65 (23); 56 (100). Anal. Calcd for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32. Found: C 75.47, H 9.13, N 7.54.

2-(Methoxymethyl)-1-propylaziridine (5c). Yield 92%. Colorless oil. ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.93 (3H, ~t, CH_3); 1.1-2.5 (9H, m, $(CH_2)_3NCH_2CH$); 3.3-3.6 (2H, m, CH_2O); 3.45 (3H, s, OCH_3). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.08 (CH_3); 20.54 (*C*H_2CH_3); 31.34 and 31.93 (N*C*H_2CH and NCH_2*C*H_2); 37.98 (NCH); 58.84 ($0CH_3$); 61.01 (NCH_2Pr); 74.92 (*C*H_2OCH_3). IR (NaCl, cm^{-1}): ν = 1460, 1347, 1168, 1114. MS (70 eV) m/z (%): 143 (M^+, 3); 100 (25); 98 (53); 86 (13); 70 (100); 58 (12); 57 (21); 58 (12); 57 (21); 56 (35); 55 (12); 45 (41). Purity (GC) > 97%. Anal. Calcd for $C_8H_{17}NO$: C 67.09, H 11.96, N 9.78. Found: C 67.22, H 12.11, N 9.88.

1-Benzyl-2-(isopropoxymethyl)aziridine (5d). Yield 73%. Colorless oil. Bp. 88-96°C/0.4 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.12 (6H, d, J=6.3 Hz, $(CH_3)_2CH$); 1.45 (1H, d, J=6.6 Hz, $N(H_{cis}CH)CH$); 1.70 (1H, d, J=3.6 Hz, $N(HCH_{trans})CH$); 1.72-1.80 (1H, m, NCH_2CH); 3.37-3.43 (2H, m, CH_2O); 3.45 (2H, s, NCH_2Ar); 3.53-3.62 (1H, m, CHO); 7.22-7.38 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.80 and 22.28 ((*C*$H_3)_2$CH); 31.86 (N*C*H_2CH); 39.01 (NCH); 64.33 (NCH_2Ar); 70.35 (OCH_2); 71.46 (CHO); 126.97 (NCH_2HC_{para}); 127.99 and 128.28 ($NCH_2HC_{ortho}HC_{meta}$); 139.08 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν = 2966, 1497, 1454, 1380, 1370, 1327, 1160, 1130, 1075, 1028. MS (70 eV) m/z (%): no M^+; 162 (M^+-43); 146 (22); 132 (11); 91 (100); 72 (25); 65 (13); 56 (33). Anal. Calcd for $C_{13}H_{19}NO$: C 76.06, H 9.33, N 6.82. Found: C 76.26, H 9.50, N 6.68.

1-(2,2-Dimethyl-3-phenylpropyl)-2-(methoxymethyl)aziridine (5e). Yield 96%. Colorless oil. ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.90 (6H, s, 2×CH_3); 1.1-1.7 (3H, m, NCH_2CH); 2.04 and 2.66 (2×2H, 2×s, $NCH_2C(Me)_2CH_2Ar$); 3.2-3.4 (2H, m, OCH_2); 3.36 (3H, s, OCH_3); 7.26 (5H, s, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.66 and 25.75 (2×CH_3); 32.11 (*C*H_2CHN); 36.41

(*C*(Me)$_2$); 38.35 (CHN); 46.61 (CH_2Ar); 58.62 (OCH_3); 71.60 (OCH_2); 75.04 (N*C*H_2C); 125.73 (HC_{para}); 127.56 and 130.67 (HC_{ortho} and HC_{meta}); 139.10 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{OMe} = 2820; ν_{az} = 3025. MS (70 eV) m/z (%): 233 (M^+, 14); 188 (8); 146 (6); 131 (9); 100 (56); 91 (28); 71 (12); 70 (40); 56 (8); 55 (8); 45 (16); 42 (100). Purity (GC) > 97%. Anal. Calcd for $C_{15}H_{23}NO$: C 77.21, H 9.93, N 6.00. Found: C 77.34, H 10.09, N 5.88.

1-Neopentyl-2-(methoxymethyl)aziridine (5f). Yield 72%. Colorless oil. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 0.97 (9H, s, $(CH_3)_3C$); 1.2-1.7 (3H, m, CH_2CHN); 1.98 and 2.14 (2H, 2×d, J=11.0 Hz, N(*H*C*H*)*t*Bu); 3.38 (3H, s, OCH_3); 3.2-3.4 (2H, m, OCH_2). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 25.59 ((*C*H_3)$_3$C); 29.17 (*C*H_2CHN); 30.02 ((CH_3)$_3$*C*); 35.88 (CHN); 56.08 (CH_3O); 71.10 (CH_2O); 72.41 (N*C*H_2*t*Bu). IR (NaCl, cm^{-1}): ν_{OMe} = 2820; ν_{az} = 3040. MS (70 eV) m/z (%): 157 (M^+, 1); 112 (7); 100 (21); 71 (7); 70 (22); 57 (6); 56 (7); 55 (6); 45 (21); 43 (15); 42 (100); 41 (21). Purity (GC) > 97%. Anal. Calcd for $C_9H_{19}NO$: C 68.74, H 12.18, N 8.91. Found: C 68.91, H 12.37, N 8.78.

1-[(4-Chlorophenyl)methyl]-2-[(propenyloxy)methyl]aziridine (5g). Yield 95%. Light-yellow oil. Filtration through a pad of silica (Hexane/EtOAc 5/4). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.45 (1H, d, J=6.2 Hz, N(H_{cis}CH)CH); 1.73 (1H, d, J=3.6 Hz, N(HCH_{trans})CH); 1.77-1.85 (1H, m, NCH); 3.35 and 3.50 (2H, 2×d×d, J=10.6, 6.6, 4.3 Hz, NCH(*H*C*H*)O); 3.43-3.44 (2H, m, NCH_2Ar); 3.96 (2H, d, J=4.9 Hz, OC*H*$_2$CH=CH_2); 5.15-5.28 (2H, m, CH=C*H*$_2$); 5.81-5.96 (1H, m, C*H*=CH_2); 7.30 (4H, s, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.23 (N*C*H_2CH); 38.56 (NCH); 63.27 (NCH_2Ar); 71.63 (O*C*H_2CH=CH_2); 72.18 (NCHCH_2O); 116.62 (CH=*C*H_2); 128.25 and 129.20 (NCH_2HC_{ortho}HC_{meta}); 132.45 (CCl); 134.64 (*C*H=CH_2); 137.63 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{max} = 1646, 1598, 1492, 1466, 1088, 807. MS (70 eV): m/z (%): 237/9 (M^+, 2); 180/2 (43);167 (24); 147 (35); 126 (14); 125/7 (100); 91 (56); 89 (22); 71 (10). Anal. Calcd for $C_{13}H_{16}ClNO$: C 65.68, H 6.78, N 5.89. Found: C 65.89, H 6.92, N 5.69.

2-(*tert*-Butoxymethyl)-1-neopentylaziridine (5h). Yield 75%. Colorless oil. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 0.97 (9H, s, (C*H*$_3$)$_3$CCH_2); 1.18 (9H, s, $(CH_3)_3CO$); 1.2-1.7 (3H, m, CH_2CHN); 2.02 and 2.31 (2H, 2×d, J=11.5 Hz, N(*H*C*H*)*t*Bu); 3.0-3.7 (2H, m, OCH_2). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 27.58 and 28.24 (2×(*C*H_3)$_3$C); 31.81 (*C*H_2CHN); 32.61 ((CH_3)$_3$*C*CH_2); 40.10 (CHN); 64.70 (CH_2O); 72.50 ((CH_3)$_3$*C*O); 73.67 (N*C*H_2*t*Bu). IR (NaCl, cm^{-1}): ν_{az} = 3040. MS (70 eV) m/z (%): 199 (M^+, 1); 142 (7); 112 (26); 86 (100); 57 (59). Purity (GC) > 97%. Anal. Calcd for $C_{12}H_{25}NO$: C 72.31, H 12.64, N 7.03. Found: C 72.44, H 12.80, N 6.90.

Synthesis of 2-(alkanoyloxymethyl)aziridines 7. General procedure

To a solution of carboxylic acid (0.01 mol) in DMSO (15 mL) was added K_2CO_3 (2 equiv), and the resulting suspension was stirred for 30’ at room temperature. Subsequently, 2-(bromomethyl)aziridine **3** (0.01 mol) was added, and the mixture was heated at 80°C for 15 hours. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3×15 mL). The combined organic extracts were washed with water (2×15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded the corresponding

2-(alkanoyloxymethyl)aziridine **7**, which was purified by filtration through silica gel (hexane/EtOAc 5/3).
The spectral data of 1-(3-methylbenzyl)aziridin-2-ylmethyl 2-methylpropanoate **7a** have been reported elsewhere.[15]

1-(2-Chlorobenzyl)aziridin-2-ylmethyl 2-methylpropanoate (7b). Yield 82%. Light-yellow oil. Filtration through silica gel (hexane/EtOAc 5/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 and 1.15 (6H, 2×d, J=6.9 Hz, $(CH_3)_2$CH); 1.57 (1H, d, J=6.3 Hz, (H_{cis}CH)N); 1.85 (1H, d, J=3.6 Hz, (HCH_{trans})N); 1.88-1.95 (1H, m, NCH); 2.52 (1H, sept, J=7.0 Hz, $(CH_3)_2$)C*H*); 3.44 and 3.69 (2H, 2×d, J=15.1 Hz, N(HCH)Ar); 3.85 and 4.27 (2H, 2×d×d, J=11.7, 7.6, 4.3 Hz, (HCH)O); 7.17-7.35 and 7.67-7.69 (3H and 1H, 2×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.90 and 18.95 ((*C*H_3)$_2$)CH); 31.64 (N*C*H_2CH); 33.90 ((CH_3)$_2$*C*H); 37.47 (CHN); 60.92 (NCH_2Ar); 66.46 (CH_2O); 126.79, 128.08, 129.03 and 129.23 (HC_{arom}); 132.88 (CCl); 136.71 ($NCH_2C_{arom,quat}$); 176.84 (CO). IR (NaCl): $\nu_{C=O}$ = 1735 cm^{-1}. MS (70 eV): m/z (%): 268/70 (M^++1, 100). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C 62.80, H 6.78, N 5.23. Found: C 62.97, H 6.98, N 5.11.

1-(4-Methylbenzyl)aziridin-2-ylmethyl 2-methylpropanoate (7c). Yield 86%. Light-yellow oil. Filtration through silica gel (hexane/EtOAc 5/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 and 1.11 (6H, 2×d, J=7.0 Hz, (CH_3)$_2$CH); 1.51 (1H, d, J=6.3 Hz, (H_{cis}CH)N); 1.77 (1H, d, J=3.6 Hz, (HCH_{trans})N); 1.81-1.89 (1H, m, NCH); 2.33 (3H, s, CH_3Ar); 2.46 (1H, sept, J=7.1 Hz, (CH_3)$_2$)C*H*); 3.26 and 3.56 (2H, 2×d, J=13.2 Hz, N(HCH)Ar); 3.80 and 4.19 (2H, 2×d×d, J=11.6, 7.4, 4.7 Hz, (HCH)O); 7.12-7.30 (4H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.87 ((*C*H_3)$_2$)CH); 21.07 (CH_3Ar); 31.65 (N*C*H_2CH); 33.85 ((CH_3)$_2$*C*H); 37.12 (CHN); 64.03 (NCH_2Ar); 66.51 (CH_2O); 128.07 and 129.02 (HC_{arom}); 135.76 and 136.62 (2×$C_{arom,quat}$); 177.02 (CO). IR (NaCl): $\nu_{C=O}$ = 1735 cm^{-1}. MS (70 eV): m/z (%): 248 (M^++1, 100). Anal. Calcd for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66. Found: C 72.97, H 8.71, N 5.59.

1-Benzylaziridin-2-ylmethyl 2-methylbutyrate (7d). Mixture of diastereomers, ratio 53/47. Yield 77%. Light-yellow oil. Filtration through silica gel (hexane/EtOAc 5/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, t, J=7.4 Hz, C$H_3$$CH_2$); 0.88 (3H, t, J=7.3 Hz, C$H_3$$CH_2$); 1.08 and 1.09 (2×3H, 2×d, J=6.9 Hz, 2×CH_3CH); 1.37-1.49 (2H, m, 2×(*H*CH)CH_3); 1.52 (2H, d, J=6.6 Hz, 2×(H_{cis}CH)N); 1.57-1.74 (2H, m, 2×(HC*H*)CH_3); 1.79 (2H, d, J=3.3 Hz, 2×(HCH_{trans})N); 1.83-1.90 (2H, m, 2×NCH); 2.25-2.44 (2H, m, 2×C*H*CH_3); 3.32 and 3.58, 3.34 and 3.60 (2×2H, 2×(2×d), J=13.5 Hz, 2×N(HCH)Ar); 3.83 (1H, d×d, J=11.6, 7.4 Hz, (*H*CH)O); 3.83 (1H, d×d, J=11.7, 7.3 Hz, (*H*CH)O); 4.11-4.31 (2H, m, 2×(HC*H*)O); 7.23-7.40 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.59 (2×*C*$H_3$$CH_2$); 16.46 (2×*C*$H_3$CH); 26.69 (2×$CH_3$*C*$H_2$); 31.65 (2×N*C*$H_2$CH); 37.28 and 37.33 (2×CHN); 40.92 (2×*C*HCH_3); 64.29 (2×NCH_2Ar); 66.45 (2×CH_2O); 127.09 (2×NCH_2HC_{para}); 128.05 and 128.33 (2×$NCH_2HC_{ortho}HC_{meta}$); 138.94 (2×$C_{arom,quat}$); 176.38 (2×CO). IR (NaCl): $\nu_{C=O}$ = 1736 cm^{-1}. MS (70 eV): m/z (%): 247 (M^+, 3); 219 (3); 146 (37); 91 (100); 85 (26); 72 (13); 57 (80). Anal. Calcd for $C_{15}H_{21}NO_2$: C 72.84, H 8.56, N 5.66. Found: C 73.03, H 8.76, N 5.58.

Synthesis of 2-[(1,2,4-triazol-1-yl)methyl]aziridines 8 and 2-[(imidazol-1-yl)methyl] aziridines 9. General procedure

To a solution of 2-(bromomethyl)aziridine **3** (4.5 mmol) in acetonitrile (50 mL) was added 1,2,4-triazole (5 equiv) and potassium carbonate (4 equiv). The resulting mixture was heated under reflux for 2.5 days, filtered and the solvent was removed in vacuo. A solution of sodium hydroxide (75 mL, 1N) was added to the residue, followed by extraction with diethyl ether (3×40 mL). Drying (K_2CO_3), filtration of the drying agent and evaporation of the solvent afforded the corresponding 2-[(1,2,4-triazol-1-yl)methyl]aziridine **8**, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH).

1-Benzyl-2-[(1,2,4-triazol-1-yl)methyl]aziridine (8a). Yield 40%. Colorless oil. R_f = 0.13 ($CHCl_3$/MeOH 95/5). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.63 (1H, d, J=6.3 Hz, N(H_{cis}CH)CH); 1.84 (1H, d, J=3.3 Hz, N(HCH_{trans})CH); 2.01-2.09 (1H, m, CHN); 3.25 and 3.53 (2H, 2×d, J=12.9 Hz, N(HCH)Ar); 3.93 and 4.32 (2H, 2×d×d, J=14.2, 7.6, 4.3 Hz, NCH(*H*C*H*)N); 7.18-7.36 (5H, m, C_6H_5); 7.85 and 7.92 (2×1H, 2×s, 2×N=CH). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 32.61 (CH_2N); 37.65 (NCH); 52.60 (NCH*C*H_2N); 64.10 (NCH_2Ar); 126.84 (NCH_2HC_{para}); 128.03 and 128.48 (NCH_2HC_{ortho}HC_{meta}); 138.18 ($C_{arom,quat}$); 143.07 and 151.61 (2×N=CH). IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1658. MS (70 eV) m/z (%): no M^+; 205 (20); 159 (15); 158 (19); 157 (11); 144 (19); 118 (35); 106 (19); 105 (14); 91 (63); 89 (10); 80 (10); 79 (100); 78 (13); 77 (62); 71 (10); 65 (18); 53 (15); 52 (10); 51 (32); 50 (15). Anal. Calcd for $C_{12}H_{14}N_4$: C 67.27, H 6.59, N 26.15. Found: C 67.41, H 6.83, N 26.03.

1-[4-(Chlorophenyl)methyl]-2-[(1,2,4-triazol-1-yl)methyl]aziridine (8b). Yield 40%. Colorless oil. R_f = 0.15 ($CHCl_3$/MeOH 97/3). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.61 (1H, d, J=6.3 Hz, N(H_{cis}CH)CH); 1.85 (1H, d, J=3.3 Hz, N(HCH_{trans})CH); 2.02-2.10 (1H, m, CHN); 3.27 and 3.44 (2H, 2×d, J=13.2 Hz, N(HCH)Ar); 3.95 and 4.32 (2H, 2×d×d, J=14.4, 7.6, 4.0 Hz, NCH(*H*C*H*)N); 7.13 and 7.26 (2×2H, 2×d, J=8.4 Hz, 4×CH_{arom}); 7.88 and 7.90 (2×1H, 2×s, 2×N=CH). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 33.23 (CH_2N); 38.15 (NCH); 52.94 (NCH*C*H_2N); 63.74 (NCH_2Ar); 128.97 and 129.67 (2×HC_{arom}); 133.51 (CCl); 137.18 ($NCH_2$$C_{arom,quat}$); 143.54 and 152.22 (2×N=CH). IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1635. MS (70 eV) m/z (%): no M^+; 180 (17); 179 (19); 178 (19); 166/8 (37); 125/7 (100); 111 (13); 110 (12); 91 (10); 89 (24); 70 (12); 63 (10); 55 (22), 54 (99). Anal. Calcd for $C_{12}H_{13}ClN_4$: C 57.95, H 5.27, N 22.53. Found: C 58.12, H 5.36, N 22.38.

1-Benzyl-2-[(imidazol-1-yl)methyl]aziridine (9a). Yield 60%. Colorless oil. R_f = 0.26 ($CHCl_3$/MeOH 97/3). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.56 (1H, d, J=6.3 Hz, N(H_{cis}CH)CH); 1.79 (1H, d, J=3.3 Hz, N(HCH_{trans})CH); 1.82-1.90 (1H, m, CHN); 3.40 and 3.45 (2H, 2×d, J=12.9 Hz, N(HCH)Ar); 3.78 and 4.04 (2H, 2×d×d, J=14.4, 7.3, 4.1 Hz, NCH(*H*C*H*)N); 6.88 and 7.01 (2×1H, 2×s, NCH=CH); 7.26-7.32 (5H, m, C_6H_5); 7.46 (1H, s, NHC=N). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 31.22 (CH_2N); 37.81 (NCH); 48.84 (NCH*C*H_2N); 63.11 (NCH_2Ar); 118.19 (H*C*=CH); 126.38 and 128.21 (NCH_2HC_{para} and HC=*C*H); 127.19 and 127.57 (NCH_2HC_{ortho}HC_{meta}); 136.08 (HC=N); 137.66 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1666. MS (70 eV) m/z (%): no M^+; 213 (19); 146 (10); 132 (63); 122 (17); 109 (17); 108 (10); 105 (26); 95

(15); 91 (100); 65 (14). Anal. Calcd for $C_{13}H_{15}N_3$: C 73.21, H 7.09, N 19.70. Found: C 73.37, H 7.25, N 19.58.

1-[4-(Chlorophenyl)methyl]-2-[(imidazol-1-yl)methyl]aziridine (9b). Yield 75%. Colorless oil. R_f = 0.15 ($CHCl_3$/MeOH 95/5). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.54 (1H, d, J=6.3 Hz, N(H_{cis}CH)CH); 1.79 (1H, d, J=3.3 Hz, N(HCH_{trans})CH); 1.79-1.89 (1H, m, CHN); 3.33 and 3.42 (2H, 2×d, J=13.4 Hz, N(HCH)Ar); 3.77 and 4.06 (2H, 2×d×d, J=14.4, 7.3, 4.1 Hz, NCH(*H*C*H*)N); 6.88 and 7.01 (2×1H, 2×s, NCH=CH); 7.19 and 7.28 (2×2H, 2×d, J=8.6 Hz, 4×CH_{arom}); 7.48 (1H, s, NHC=N). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 31.72 (CH_2N); 38.33 (NCH); 49.17 (NCH*C*H_2N); 62.66 (NCH_2Ar); 118.51 (H*C*=CH); 127.96 and 128.84 (NCH_2HC_{ortho}HC_{meta}); 128.57 (HC=*C*H); 132.29 (CCl); 136.53 (HC=N); 136.69 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1630. MS (70 eV) m/z (%): 247/9 (M^+, 14); 148 (11); 125/7 (73); 109 (17); 108 (15); 107 (13); 95 (16); 87 (11); 85 (67); 83 (100); 81 (10); 48 (12); 47 (27). Anal. Calcd for $C_{13}H_{14}ClN_3$: C 63.03, H 5.70, N 16.96. Found: C 63.20, H 5.88, N 16.89.

Synthesis of 2-(aminomethyl)aziridines 10. General procedure

To an ice-cooled solution of a secondary amine (5 mmol) in dry diethyl ether or THF (5 mL) was added dropwise *n*-BuLi (2 mL, 1 equiv, 2.5M in hexane) via a syringe under nitrogen atmosphere. After stirring for 1 hour at 0°C, a solution of 2-(bromomethyl)aziridine **3** (1 equiv) in Et_2O or THF (5 mL) was added via a syringe at 0°C. The resulting solution was further stirred at room temperature for 18-20 hours under nitrogen atmosphere. Workup was carried out by pouring the reaction mixture in an aqueous sodium hydroxide solution (10 mL, 0.5M), followed by extraction with diethyl 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*, affording the desired 2-(aminomethyl)aziridine **10**.

The spectral data of 2-(aminomethyl)aziridines **10a,b,d** have been reported elsewhere.[20,4d]

1-(2-Methylpropyl)-2-(*N*,*N*-diethylaminomethyl)aziridine (10c). Yield 92%. Light-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 and 0.93 (6H, 2×d, J=6.7 Hz, CH(CH_3)$_2$); 1.05 (6H, t, J=7.2 Hz, 2×CH_2CH_3); 1.25 (1H, d, J=6.3 Hz, N(H_{cis}CH)CH); 1.48 (1H, m, CHN); 1.55 (1H, d, J=3.4 Hz, N(HCH_{trans})CH); 1.80 (1H, sept, J=6.7 Hz, C*H*(CH_3)$_2$); 1.95 and 2.15 (2H, 2×d×d, J=11.6, 7.3, 6.3 Hz, N(*H*C*H*)$CHMe_2$); 2.42 and 2.58 (2H, 2×d×d, J=13.3, 5.8, 5.7 Hz, NCH(*H*C*H*)N); 2.60-2.70 (4H, m, 2×C$H_2$$CH_3$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.7 (2×CH_2CH_3); 20.9 and 21.0 (CH(CH_3)$_2$); 29.2 (*C*H(CH_3)$_2$); 33.5 (N*C*H_2CH$CH_2$$NEt_2$); 37.8 ($NCH_2$*C*H$CH_2$$NEt_2$); 47.3 (2×*C*$H_2$$CH_3$); 56.4 (*C*$H_2$$NEt_2$); 69.6 (N*C*$H_2$$CHMe_2$). IR (NaCl, cm^{-1}): ν = 3035, 1469, 1383, 1070. MS (70 eV) m/z (%): 184 (M^+, 5); 169 (2); 155 (2); 141 (2); 113 (16); 112 (39); 86 (100); 72 (39); 70 (70); 58 (16); 56 (23). Anal. Calcd for $C_{11}H_{24}N_2$: C 71.68, H 13.12, N 15.20. Found: C 71.84, H 13.29, N 15.11.

Synthesis of 2-[(alkylsulfanyl)methyl]aziridines 11. General procedure

To a solution of sodium methoxide (2 equiv) in methanol (0.25N) was added an alkanethiol (3 equiv) at room temperature. After stirring for 30 minutes, aziridine **3** (2 mmol) was added, and the resulting mixture was further stirred for 8 hours at room temperature. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with water (2×15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded the corresponding 2-[(alkylsulfanyl)methyl]aziridines **11**, which were purified by column chromatography on silica gel (Hexane/EtOAc 4/1).

1-[(4-Chlorophenyl)methyl]-2-[(isopropylsulfanyl)methyl]aziridine (11a). Yield 84%. Colorless oil. R_f = 0.25 (Hexane/EtOAc 4/1). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.22 and 1.24 (6H, 2×d, J=6.5 Hz, 2×CH_3); 1.47 (1H, d, J=5.9 Hz, N(H_{cis}CH)CH); 1.72-1.74 (2H, m, CHN and N(HCH_{trans})CH); 2.52 and 2.65 (2H, 2×d×d, J=13.4, 5.9, 5.6 Hz, (HCH)S); 2.92 (1H, sept, J=6.5 Hz, C*H*Me_2); 3.38 and 3.44 (2H, 2×d, J=13.5 Hz, N(HCH)Ar); 7.30 (4H, s, CH_{arom}). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 23.32 and 23.41 (2×CH_3); 33.60 (CH_2S); 34.09 (N*C*H_2CH); 34.64 (*C*HMe_2); 39.71 (NCH); 63.74 (NCH_2Ar); 128.41 and 129.43 (NCH_2HC_{ortho}HC_{meta}); 132.76 (CCl); 137.45 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{max} = 1597, 1491, 1462, 1240, 805. MS (70 eV) m/z (%): 255/7 (M^+, 1); 181 (49); 180/2 (75); 166 (19); 146 (18); 125/7 (100); 99/101 (8): 89 (25); 56 (20). Anal. Calcd for $C_{13}H_{18}ClNS$: C 61.04, H 7.09, N 5.48. Found: C 61.18, H 7.25, N 5.32.

2-[(Allylsulfanyl)methyl]-1-[(4-chlorophenyl)methyl]aziridine (11b). Yield 60%. Colorless oil. R_f = 0.33 (Hexane/EtOAc 4/1). ^{1}H NMR ($CDCl_3$, 270 MHz): δ 1.46 (1H, d, J=6.2 Hz, N(H_{cis}CH)CH); 1.72-1.73 (2H, m, CHN and N(HCH_{trans})CH); 2.46 and 2.57 (2H, 2×d×d, J=13.5, 5.6, 5.6 Hz, NCH(*H*C*H*)S); 3.12 (2H, d, J=7.2 Hz, SCH_2CH=CH_2); 3.38 and 3.43 (2H, 2×d, J=13.3 Hz, N(HCH)Ar); 5.03-5.08 (2H, m, CH=CH_2); 5.68-5.81 (1H, m, C*H*=CH_2); 7.30 (4H, s, CH_{arom}). ^{13}C NMR ($CDCl_3$, 68 MHz): δ 33.55 (NCH*C*H_2S); 34.03 (N*C*H_2CH); 34.72 (S*C*H_2CH=CH_2); 39.35 (NCH); 63.74 (NCH_2Ar); 117.16 (CH=*C*H_2); 128.44 and 129.43 (NCH_2HC_{ortho}HC_{meta}); 132.79 (CCl); 134.19 (*C*H=CH_2); 137.41 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{max} = 1634, 1597, 1491, 1464, 805. MS (70 eV) m/z (%): 253/5 (M^+, 3); 183 (34); 181 (61); 180/2 (85); 166 (38); 154 (27); 146 (34); 125/7 (100); 99/101 (24); 89 (38); 56 (28). Anal. Calcd for $C_{13}H_{18}ClNS$: C 61.04, H 7.09, N 5.48. Found: C 61.18, H 7.25, N 5.32.

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