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SYNTHESIS OF MEXILETINE ANALOGUES FROM NON-ACTIVATED AZIRIDINES

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Abstract – A general method for the synthesis of mexiletine analogues by nucleophilic ring opening of non-activated racemic aziridines has been developed (Scheme 1). Structural variation is introduced by employing different nucleophiles or by altering the substitution on the aziridine ring.

INTRODUCTION

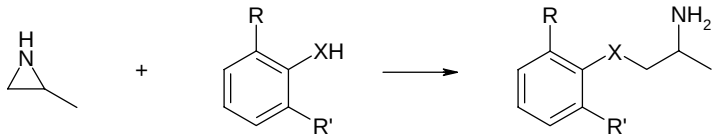
The lidocain analogue mexiletine, 1-(2,6-dimethylphenoxy)-2-aminopropane, **10**, is a sodium channel blocker that also possesses antiarrhythmic and anaesthetic properties in addition to being used in the therapy of different myotonic syndromes.[1] Recent results have revealed that structural modifications have a great influence on the properties of the drug.[2] In this respect it has been shown that lipophilicity is an important factor and introduction of large groups on the stereogenic carbon, substitution of oxygen by sulphur and chain elongation have been reported. General methods for the synthesis of this type of compound is thus of interest and aziridines should be excellent starting materials since they are easily accessible both in racemic and in enantiomerically pure form.[3]

In general, ring opening reactions on aziridines are performed on compounds in which the ring is activated by tosylation/acylation on the nitrogen atom[4] or Lewis acid catalysis is employed, e.g. ytterbium triflate.[5] The range of nucleophiles used in ring-opening reactions is vast and includes thiophenolates,[6] chloride ion,[7] azide[8] and organometallic reagents such as organocuprates[9] or Grignard reagents.[10] Non-ionic nucleophiles have been less commonly used since the nucleophile has to supply a proton to the aziridine in order to generate a good leaving group. However, thiophenols have been shown by Stamm and co-workers to be excellent nucleophiles in some reactions.[11] In our research we have focused on employing non-activated aziridines as substrates since no activating group has to be introduced or removed in the synthetic sequence and difficulties with side-reactions and work-up are avoided if no catalyst is employed.

RESULTS AND DISCUSSION

The project was initiated when it was discovered that mexiletine could be synthesised in one step from 2-methyl aziridine **1**, when reacted with 2,6-dimethylphenol. Interestingly only one of the two possible regioisomers was produced in the reaction and this encouraged us to further investigate the applicability of this reaction (Scheme 1).

Scheme 1. Ring opening of 2-methylaziridine.



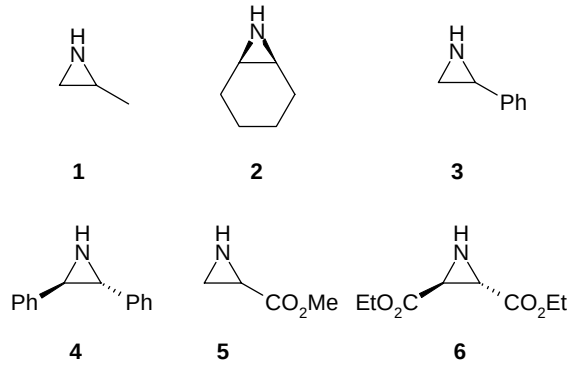
1

7a, X = O, R = R' = H
7b, X = O, R = R' = Me
7c, X = O, R = *t*-Bu, R' = H
8a, X = S, R = R' = H
8b, X = S, R = R' = Me
9 X = NH, R = R' = H

Traces
10 80 %
11 45 %
12 67 %
13 65 %
-

The study was therefore extended to include a series of racemic aziridines with different properties (Figure 1). Aziridines **1** and **2** contain alkyl groups which should make the aziridine more basic while aziridines **3** and **4** contain phenyl groups that should have a slightly electron withdrawing effect on the aziridine ring. In addition the carboxylic acid derivatives **5** and **6** were included in the study since these should have a large influence on the properties of the aziridine due to the large electron withdrawing effect but also because more complex target molecules may be synthesised by this route, e.g. α-amino acid derivatives.

Figure 1. Aziridines **1** – **6**.



1 **2** **3**

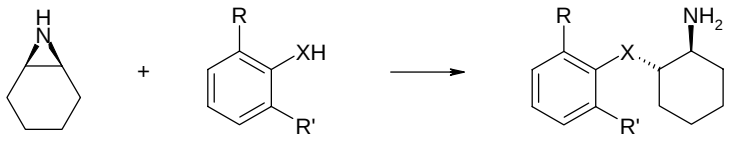
4 **5** **6**

ALKYL AZIRIDINES

Since the fairly sterically congested 2,6-dimethylphenol reacted, it was surprising that phenol itself did not react but was recovered together with polymeric material, while reaction between 2-*t*-butylphenol and 2-methylaziridine gave product although in lower yield (Scheme 1). Prolonged heating did not improve the yield but resulted in more polymeric material, thus making isolation of the product more difficult.

Since it seemed that results did not depend on steric factors, electronic factors had to have an influence on the reaction. By introducing electron-donating or withdrawing groups it was found that the p*K*a of the nucleophile was important; if the acidity of the substrate was too high the aziridine polymerised (a violent reaction occurred when 4-nitrophenol reacted) and if the acidity was too low (as for 4-methoxyphenol) no reaction took place. This is probably because the substrate is not able to protonate the aziridine thus creating a good leaving group. At this stage it was decided to investigate thiols as nucleophiles. All of the aromatic thiols gave the expected product even though the acidity is much higher than for the corresponding phenols. This is not surprising in view of sulfur being a much better nucleophile than oxygen. As with the phenols, in all cases it was only the less substituted carbon atom of the aziridine that was attacked, giving the mexiletine analogues. When *cis*-cyclohexylaziridine **2** was employed as substrate the nucleophiles that ring opened 2-methylairidine also worked well and in addition phenol also reacted as expected leading to racemic products **14** – **17** (Scheme 2).

Scheme 2. Ring opening of cyclohexylaziridine.



2

7a, X = O, R = R' = H
7b, X = O, R = R' = Me
7c, X = O, R = *t*-Bu, R' = H
8a, X = S, R = R' = H
8b, X = S, R = R' = Me

14 43 %
15 56 %
16 20 %
17 91 %
18 84 %

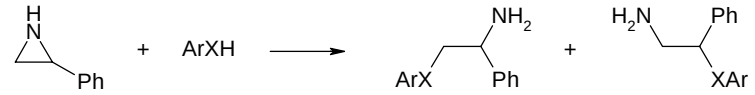
Since steric hindrance on the nucleophile did not seem to inflict any restrictions it may be that cyclohexylaziridine is more basic than 2-methylaziridine and therefore, is more readily ring-opened even though it is more sterically congested. This was considered as further evidence that the p*K*a of the nucleophile and that of the aziridine have to be matched in order to achieve the desired reactions.

Alkyl alcohols, amines and thiols were also tested as nucleophiles with 2-methylaziridine, but only with the thiols were traces of expected product detected. From literature it is known that anionic nucleophiles can be used as nucleophiles in aziridine ring opening reactions under certain conditions.[12] This, together with the indications that the p*K*a of the nucleophile is important for the reaction under the chosen conditions made us investigate 1,3-dicarbonyls as substrates. If substrates were not too acidic, causing polymerisation of the aziridine, reactions with the aziridine took place. However, all substrates resulted in complex mixtures of several products and since yields were low these reactions were not further pursued.

PHENYL-SUBSTITUTED AZIRIDINES

Investigating aziridines with phenyl groups attached was the next approach. The slight electron withdrawing effect of the phenyl ring should make the carbon(s) of the aziridine ring less electrophilic and nitrogen atom less basic. No rection at all was observed between 2-phenylaziridine and phenols while the thiophenols reacted readily. Additionally, a marked change in the regioselectivity was observed in that the benzylic carbon was more readily attacked than the less substituted carbon as was the case with 2-methylaziridine (Scheme 3).

Scheme 3. Ring opening of 2-phenylaziridine.

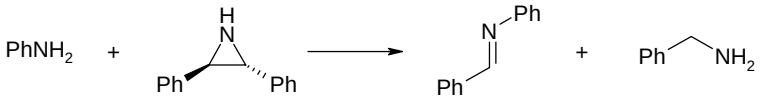


3 **8a** **8b** **9** **19a** 15 % **20a** 14 % **21a** 0 % **19b** 55 % **20b** 63 % **21b** 18 %

Since this results from sulfur attacking a more sterically demanding position the reason for this selectivity must be electronic. It may be that the mechanism is more S_N1 in character and that the benzylic position of the intermediate ring opened aziridine cation is stabilized by the phenyl ring, despite the electron withdrawing effect. An interesting observation was that aniline only reacts at the more substituted (benzylic) position giving the diamine in 18% yield, similar to the preferred reactivity of the thiols. It is not clear why this is, but substituted anilines and alkyl amines did not exhibit this reactivity.

Interestingly *trans*-2,3-diphenylaziridine also reacted with aniline resulting in a rearrangement similar to what was reported by Shimizu and Makino,[13] while reaction with other nucleophiles did not result in any product at all (Scheme 4).

Scheme 4. Ring opening of *trans*-2,3-diphenylaziridine.



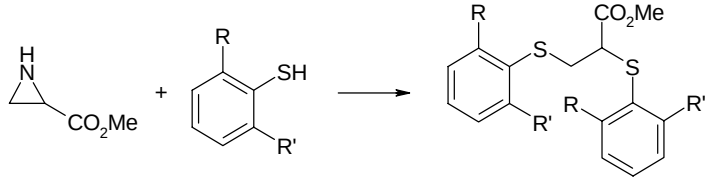
9 **4** **22** 24 % Not isolated

CARBOXYLATE AZIRIDINES

An interesting reaction took place when 2-aziridine carboxylic acid methyl ester was reacted with the sulfur nucleophiles. With thiophenol the *bis*-phenylsulfanyl propionic acid methyl ester was formed in 94% yield while the product from reaction with 2,6-dimethylthiophenol **8b** led to the isomeric product in 46% yield in a reaction possibly proceeding through an episulfonium ion intermediate (Scheme 5).[14] These results have been confirmed for other aromatic thiols, but no other nucleophiles tested reacted with this compound. Thiophenol **8a**, on the other hand, even reacted with the 2,3- aziridinedicarboxylic acid diethyl ester **6**, having two strongly electron withdrawing substituents, resulting in a mixture of

2-phenylsulfanyl fumaric acid diethyl ester, 2-phenylsulfanyl maleic acid diethyl ester and meso and racemic 2,3-bis-(phenylsulfanyl)-succinic acid diethyl ester.[14]

Scheme 5. Ring opening of aziridinecarboxylic acid ester.



5 **8a** **8b** **23**, R = R' = H 94% **24**, R = R' = Me 46%

CONCLUSIONS

A variety of mexiletine analogues can be synthesized by the the reaction of non-activated mono-substituted aziridines with aromatic sulfur nucleophiles under mild conditions without the aid of a catalyst. If the substituent is an ester the reaction gives disulfide propionic esters. In contrast, phenols only react with alkyl aziridines, even if these are disubstituted, if the p*K*a is suitable. This reaction thus adds to the number of mexiletine analogues that are available. Carbon nucleophiles seem promising in ring opening of alkylaziridines, but the results are not conclusive. Aniline only reacts with 2-phenylaziridine in a process that needs more investigation.

EXPERIMENTAL

General

Chemicals of minimum 98% purity were supplied by Fluka except for 2-*t*-butylphenol (Fluka, >97%), 2,6-dimethylthiophenol (Aldrich, 95%), 1-(2,6-dimethylphenoxy)-2-propanamine hydrochloride (Aldrich, 97%), aziridine-2-carboxylic acid methyl ester (TCI, > 95%) and 2-methylaziridine (TCI, >90%, stabilized with NaOH) and were used as delivered. 7-Azabicyclo[4.1.0]heptane **2**[15] and *trans*-2,3-diphenylaziridine **4**[16] were prepared by literature methods while the procedure for preparing 2-phenylaziridine **3**[17] was modified in that wet dimethoxy ethane was used as solvent in the final step. Spectral data for this compound corresponded in all respects with published data.[16, 18]

GC analyses were performed on a Varian 3300 gas chromatograph equipped with a CP-Sil-8 (25 m, 0.32 mm i.d.) column. IR spectra were recorded on a Perkin Elmer model 1600 FT-IR. NMR spectra were recorded on a Varian Mercury 400 plus (399.65 /100.54 MHz) spectrometer with $CDCl_3$ or CD_3OD as solvent. Mass spectral (MS) analyses were performed on a VG Analytical Tribid mass spectrometer connected to a Hewlett Packard 5890 gas chromatograph equipped with HP 5 (30 m, 0.25mm i.d.) column. Preparative reversed phase high performance liquid chromatography (RP-HPLC) was performed using a C_{18}-column (Delta-Pak™ C_{18}, 100 Å, 15 µm, 25 x 100 mm, Waters Corp., Milford, MA, USA)

with a mixture of water and MeCN (both containing 0.1% v/v CF_3CO_2H) as the mobile phase, a flow rate of 7.0 mL/min and UV-detection at 254 nm. A linear gradient varying from 30% to 50% MeCN in 30 min effected separation and fractions containing the pure compounds were pooled and the solvent was removed under reduced pressure. If the TFA-salt was not directly analyzed, the samples were diluted with a 10% aqueous $NaHCO_3$ solution and extracted into a Et_2O phase, dried over magnesium sulfate before solvent removal under reduced pressure.

Isolation of products

Method A

The reaction mixture was dissolved in ether, Dowex 50 Wx8 was added and the solution was stirred at rt for 2h. The contents were filtered through a Büchner funnel, and the resin was washed with Et_2O before being transferred to an Erlenmeyer flask and washed with 10 % NH_4OH and ether in a two phase system, in order to release the free amine from the resin. This procedure was repeated 3-5 times and the two-phase system was separated in a separatory funnel, the combined organic layer was dried with brine and $MgSO_4$(s), before solvent removal under vacuum.

Method B

The crude compound was chromatographed on silica using CH_2Cl_2:MeOH (95:5) and the solvent was removed under reduced pressure.

Isomer identification

Isomers were identified from MS data based on the fact that primary amines without branching at the α-carbon always show the loss of fragment with m/z 30 which was absent in all compounds being branched at the α-position. Comparing the mass spectra and NMR spectra of the two isomers of mexiletine to commercial material supports this fact.

Aziridine-2,3-dicarboxylic acid diethyl ester (6)

To a stirred solution of diethyl tartrate (10.25g, 47.9 mmol) at rt thionyl chloride (6.51 g , 54.75 mmol) was added over a periode of 10-15 min and stirring was continued overnight. The reaction mixture was extracted with Et_2O and the organic phase was treated with 1% aqueous $NaHCO_3$ before drying over magnesium sulfate. The solvent was removed under reduced pressure resulting in (11.04 g, 88 %) of the cyclic sulfite with spectroscopic data in accordance with earlier reported material.[19] The cyclic sulfite (1.34 g, 5.32 mmol) was reacted with NaN_3 (0.78 g, 12 mmol) in refluxing wet MeCN for 20h. The mixture was extracted with Et_2O and the organic layer was shaken with water and brine followed by

drying over magnesium sulfate yielding the azido alcohol (0.85 g, 69%).[19] The aziridine was synthezised according to published procedure,[20] and was isolated in 17 % yield with spectroscopic data in accordance with reported material.[21] ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.27 (4H, q, *J* = 6.8 Hz), 2.9 (2H, s), 1.8 (1H, bs), 1.34 (6H, t, *J* = 6.6 Hz)

1-(2,6-Dimethylphenoxy)-2-propanamine (10)

Phenol **7b** (0.15 g, 1.0 mmol) and aziridine **1** (50 μL, 0.7 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 130 °C for 12 h. Aziridine was added 4 more times and heating was continued as described. After work-up (Method A) the product was isolated as a slightly yellow oil (229 mg, 80%). All spectral data were in accordance with commercial material. ^{1}H NMR (CD_3OD) 6.99-6.83 (3H, m), 3.63-3.59 (1H, dd, *J* = 4.8, 9.2 Hz), 3.58-3.54 (1H, dd, *J* = 7.0, 9.2 Hz), 3.30-3.22 (1H, m, *J* = 4.8, 6.6, 7.0 Hz), 2.25 (6H, s), 1.17 (3H, d, *J*= 6.6 Hz).

1-(2-*tert*-Butyl-phenoxy)-2-propanamine (11)

Phenol **7c** (0.12 g, 1.1 mmol) and aziridine **1** (50 μL, 0.7 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 130 °C for 12 h. Aziridine was added twice more and heating was continued as described. After work-up (Method A) the product was isolated as a slightly yellow oil (93 mg, 45%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.30-7.26 (1H, m), 7.19-7.13 (1H, m), 6.92-6.85 (2H, m), 3.88 (1H, dd, *J* = 4.4, 8.9 Hz), 3.77 (1H, dd, *J* = 7.3, 8.8 Hz), 3. 47 -3. 39 (1H, m), 1.39 (9H, s), δ 1.22 (3H, d, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ 157.6, 137.9, 127.1, 126.77, 120.5, 112.0, 74.57, 46.7, 34.9, 30.0, 20.2. MS m/z 208 (2, M+1), 207 (7, M^+), 192 (0.6), 164 (8), 149 (8), 135 (10), 133 (9), 121 (6), 119 (6), 115 (15), 107 (14), 105 (18), 103 (7), 91 (29), 77 (10), 65 (7), 58 (94), 57 (15), 44 (100). IR (film) ν_{max} (cm^{-1}) 3282, 3056, 2959, 1670, 1596, 1579, 1488,1442.

1-Phenylsulfanyl-2-propanamine (12)

Thiol **8a** (0.12 g, 1.1 mmol) and aziridine **1** (50 μL, 0.7 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 60 °C for 12 h. After work-up (Method A) the product was isolated as a colorless oil (78 mg, 67%). Spectra in accordance with earlier reported material.[22] ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.49-7.25 (5H, m), 3.36-3.25 (1H, m), 3.21-3.09 (2H, m), 1.36 (3H, d, *J* = 6.6 Hz) ^{13}C NMR (100 MHz, CD_3OD) 136.1, 129.4, 128.70, 126.0, 45.7, 42.6, 20.8.

1-(2,6-Dimethylphenylsulfanyl)-2-propanamine (13)

Thiol **8b** (0.12 g, 1.09 mmol) and aziridine **1** (50 μL, 0.7 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 60 °C for 12 h. After work-up (Method A) the

product was isolated as a slightly yellow oil (89 mg, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.10-7.08 (3H, m), 2.88-2.79 (1H, m), 2.66 (1H, dd, *J* = 5.5, 12.8 Hz), 2.58 (1H, dd, *J* = 7.3, 12.8 Hz), 2.55 (6H, s), 1.12 (3H, d, *J* = 6.2 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ 142.6, 133.3, 128.1, 128.0, 46.7, 44.5, 21.0, 20.9. MS m/z 195 (M^+, 0.7), 153 (3), 152 (32), 151 (1), 138 (1), 137 (6), 135 (3), 105 (6), 91 (7), 77 (7), 44 (100). IR (film) ν_{max} (cm^{-1}) 3310, 3051, 2954, 2865, 1567, 1473, 1055.

trans-2-Phenoxycyclohexylamine (14)

Phenol **7a** (0.12 g, 1.3 mmol) and aziridine **2** (0.11 g, 1.13 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 160 °C for 12 h. After work-up (Method B) the product was isolated as a slightly yellow oil (94 mg, 43%). ^{1}H NMR correspond to earlier reported compound.[23]

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.31-7.27 (2H, m), 6.99-6.94 (3H, m), 3.92-3.84 (1H, m), 2.95-2.88 (1H, m), 2.40 (2H, bs), 2.20-2.14 (1H, m), 2.03-1.98 (1H, m), 1.80-1.71 (2H, m), 1.40-1.20 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$), δ 158.14, 129.52, 120.95, 116.24, 82.98, 54.95, 33.31, 29.89, 24.60, 24.36. MS m/z 191 (7), 99 (8), 98 (100), 97 (15), 96 (4), 94 (11), 91 (5), 82 (3), 81 (14), 79 (7), 77 (19), 69 (6), 68 (3), 66 (5), 65 (11), 57 (3), 56 (46), 55 (5), 54 (4), 53 (4), 51 (10), 43 (15), 42 (6), 41 (8).

trans-2-(2,6-Dimethylphenoxy)cyclohexylamine (15)

Phenol **7b** (0.12 g, 1.0 mmol) and aziridine **2** (0.10 g, 1.03 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 160 °C for 12 h. After work-up (Method B) the product was isolated as white crystals (120 mg, 56%). mp 77.5-78.5 ºC (from CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.04-6.90 (3H, m), 3.77-3.67 (1H, m), 3.06-2.97 (1H, m), 2.33 (6H, s), 2.06-1.88 (3H, m), 1.80-1.66 (3H, m), 1.40-1.08 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$), δ 153.44, 131.42, 128.93, 123.32, 85.26, 56.02, 33.68, 30.14, 24.69, 24.61, 17.59. MS m/z 219 (3), 122 (7), 121 (4), 107 (5), 105 (5), 103 (5), 99 (11), 98 (100), 96 (3), 91 (9), 81 (18), 79 (8), 78 (3), 77 (10), 69 (3), 56 (15), 43 (3). IR (film)ν_{max} 3308, 3183, 2933, 2858, 1670, 1469, 1381, 1199, 1022, 909, 733.

trans-2-(2-*tert*-Butylphenoxy)cyclohexylamine (16)

Phenol **7a** (0.15 g, 1.0 mmol) and aziridine **2** (0.11 g, 1.13 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 160 °C for 12 h. After work-up (Method B) the product was isolated as a yellow oil (50 mg, 20%) which for analytical purposes was purified by RP-HPLC. ^{1}H NMR (of TFA-salt), (400 MHz, $CDCl_3$), δ 7.95 (2H, bs), 7.33-7.28 (1H, m), 7.19-7.12 (1H, m), 7.00-6.89 (2H, m), 4.64-4.54 (1H, m), 3.45-3.34 (1H, m), 2.30-2.18 (2H, m), 1.84-1.60 (3H, m), 1.45-1.23 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 154.1, 139.1, 127.5, 127.2, 121.8, 113.7, 75.6, 55.8,

34.8, 30.4, 29.0, 28.6, 23.8, 23.3; MS m/z 247 (4), 135 (7), 115 (6), 107 (8), 99 (16), 98 (100), 97 (11), 96 (5), 91 (18), 81 (31), 56 (9); IR (film)ν_{max} 3373, 3283, 3057, 2996, 2933, 2880, 1595, 1486, 1444, 1358, 1290, 1229, 1092, 1030, 748.

***trans*-2-Phenylsulfanylcyclohexylamine (17)**

Thiol **8a** (0.13 g, 1.18 mmol) and aziridine **2** (0.10 g, 1.03 mmol) were mixed in a tube that was flushed with argon, sealed and stirred at rt for 12 h. After work-up (Method B) the product was isolated as a colorless oil (193 mg, 91%). Spectra correspond with earlier reported material.[23, 24] ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.50-7.47 (2H, m), 7.35-7.28 (3H, m), 2.74-2.62 (1H, m), 2.61-2.57 (1H, dt, *J* = 4.0, 10.0 Hz), 2.12-2.07 (1H, m), 2.04-2.00 (1H, m), 1.76-1.71 (4H, m), 1.41-1.18 (4H, m).

***trans*-2-(2,6-Dimethylphenylsulfanyl)cyclohexylamine (18)**

Thiol **8b** (0.17 g, 1.30 mmol) and aziridine **2** (0.10 g, 1.03 mmol) were mixed in a tube that was flushed with argon, sealed and stirred at rt for 12 h. After work-up (Method B) the product was isolated as a colorless viscous oil (203 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.14-7.09 (3H, m), 2.82-2.71 (1H, m), 2.68-2.62 (1H, m), 2.56 (6H, s), 2.35 (2H, bs), 2.05-1.98 (1H, m), 1.80-1.59 (3H, m), 1.45-1.04 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$), δ 143.5, 132.4, 130.8, 128.2, 56.5, 55.3, 35.8, 33.0, 26.1, 24.9, 22.6. MS m/z 219 (7), 202 (3), 122 (16), 121 (9), 107 (11), 105 (8), 103 (8), 99 (22), 98 (100), 96 (5), 82 (8), 81 (56), 79 (19), 77 (23), 69 (11), 65 (6), 56 (51), 55 (8), 53 (8), 43 (12). IR (film)ν_{max} 3356, 2928, 2854, 1457.

1-Phenyl-2-phenylsulfanylethylamine (19a)

Thiol **8a** (0.14 g, 1.27 mmol) and aziridine **3** (0.17 g, 1.42 mmol) were mixed in a tube that was flushed with argon, sealed and stirred at rt for 12 h. After work-up (Method B) the product was isolated as a colorless oil (51 mg, 18%) that corresponded to earlier reported material.[22] ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.44-7-24 (10H, m), 4.13 (1H, dd, *J* = 3.8, 9.8 Hz), 3.34 (1H, dd, *J* =3.8, 13.4 Hz), 3.05 (1H, dd, *J* = 9.6, 13.2 Hz), 1.90 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$), δ 144.3, 135.8, 129.8, 129.1, 128.7, 127.6, 126.43, 126.38, 54.6, 43.9.

2-Phenyl-2-phenylsulfanylethylamine (19b)

Isolated as a colorless oil (159 mg, 55 %). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.36-7.24 (10H, m), 4.20 (1H, t, *J* = 7.0 Hz), 3.16 (2H, d, *J* = 6.8 Hz), 1.38 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$), δ 140.1, 134.5, 132.4, 128.9, 128.7, 128.1, 127.6, 127.3, 57.1, 47.3. MS m/z 229 (11), 202 (7), 201 (18), 200 (100), 199 (97), 198 (5), 197 (33), 184 (8), 167 (5), 166 (18), 165 (29), 122 (5), 121 (26), 120 (52), 119 (10), 118 (18),

117 (6), 110 (11), 109 (19), 106 (7), 104 (8), 103 (26), 92 (6), 91 (53), 89 (8), 78 (8), 77 (27), 65 (13), 51 (14). IR (film)ν_{max} 3371, 3300, 3055, 3025, 2926, 2855, 1581, 1478, 1449, 1087, 1072, 837, 745, 696.

2-(2,6-Dimethylphenylsulfanyl)-1-phenylethylamine (20a)

Thiol **8b** (0.15 g, 1.09 mmol) and aziridine **3** (0.15 g, 1.34 mmol) were mixed in a tube that was flushed with argon, sealed and stirred at rt for 12 h. After work-up (Method B) the product was isolated as a colorless oil (38 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.37-7.27 (5H, m), 7.18-7-10 (3H, m), 4.01 (1H, dd, *J* = 3.8, 9.8 Hz), 3.01 (1H, dd, *J* = 3.6, 13.0 Hz), 2.86 (1H, dd, *J* = 9.6, 12.8 Hz), 2.58 (6H, s), 1.84 (2H, bs). ^{13}C NMR (100 MHz, $CDCl_3$), δ 144.4, 142.9, 133.5, 128.6, 128.26, 128.24, 127.5, 126.4, 55.7, 45.3, 22.2. MS m/z 257 (M^+, 1), 240 (3), 152 (6), 107 (13), 106 (100). IR (film)ν_{max} 3372, 3304, 3055, 3026, 2952, 2917, 2851, 1597, 1581, 1490, 1459, 1375, 1056, 1028, 889, 769, 699.

2-(2,6-Dimethylphenylsulfanyl)-2-phenylethylamine (20b)

Isolated as a colorless oil (176 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$), δ 7.34-7.21 (5H, m), 7.16-7.07 (3H, m), 3.85 (1H, dd, *J* = 6.0, 8.4 Hz), 3.24 (1H, dd, *J* = 8.4, 13.2 Hz), 3.12 (1H, dd, *J* = 6.0, 13.2 Hz), 2.45 (6H, s), 1.31 (2H, bs). ^{13}C NMR (100 MHz, $CDCl_3$), δ 143.6, 140.3, 132.4, 128.6, 128.5, 128.2, 127.9, 127.5, 56.8, 47.0, 22.1. MS m/z 257 (8), 240 (4), 229 (21), 228 (87), 227 (100), 225 (8), 194 (6), 193 (12), 179 (8), 178 (5), 135 (6), 134 (6), 121 (11), 120 (46), 118 (6), 105 (7), 103 (14), 92 (6), 91 (55), 77 (11), 45 (8). IR (film)ν_{max} 3373, 3302, 3054, 3025, 2921, 2854, 1598, 1580, 1490, 1456, 1375, 1072, 1029, 842, 767, 699.

1*N*,1-Diphenylethane-1,2-diamine (21b)

Aniline **9** (0.09 g, 0.97 mmol) and aziridine **3** (0.10 g, 0.839 mmol) were mixed in a tube that was flushed with argon, sealed and heated in an oil bath kept at 90 °C for 3 h. After work-up (Method B) the product was isolated as a colorless viscous oil (32 mg, 18%). Spectra correspond to reported material.[25] ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.42-7.22 (5H, m), 7.10 (2H, dd, *J* =7.4, 8.6 Hz), 6.67 (1H, t, *J* = 7.4 Hz), 6.59 (2H, d, *J* = 7.6 Hz), 4.90 (1H, bs), 4.44 (1H, dd, *J* = 5.0, 6.9 Hz), 3.15 (1H, dd, *J* = 4.6, 12.6 Hz), 3.03 (1H, dd, *J* = 7.2, 12.4 Hz), 1.3 (2H, s).

***N*-Benzylideneaniline (22)**

Reaction was run in a sealed tube for 12h at 160 °C with 2,3-diphenyl aziridine **4** (0.17 g, 0.872 mmol) and aniline 9 (0.11 g, 1.18 mmol). The product was isolated after flash chromatography heptane:EtOAc (85:15) as white crystals (37.8 mg, 24%) in accordance with commercial material. mp 49.5-50.1 ºC (from EtOAc)

2,3-Bis-phenylsulfanylpropionic acid methyl ester (23)

Thiol **8a** (0.31 g, 2.83 mmol) and aziridine **5** (0.112 g, 1.1 mmol) were mixed in a tube that was flushed with argon, sealed and stirred at rt for 12 h. Isolated after chromatography on silica with heptane:Et_2O (97:3) as a colorless oil in (320 mg, 94 %) in accordance with earlier reported material.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44-7.32 (10H, m), 3.80-3.75 (1H, dd, *J* = 4.8, 10.4 Hz), 3.72 (3H, s), 3.38-3.24 (2H, m, *J* = 4.6, 10.2, 13.6 Hz).

2,3-Bis-(2,6-dimethylphenylsulfanyl)propionic acid methyl ester (24)

Thiol **8b** (0.30 g, 2.17 mmol) and aziridine **5** (0.112 g, 1.1 mmol) were mixed in a tube that was flushed with argon, sealed and stirred at rt for 12 h. Isolated after chromatography on silica with heptane:Et_2O (97:3) as white crystals (180 mg, 46%). Mp 76.5-78ºC (from Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.05 (6H, m), 3.56 (3H, s), 3.44 (1H, dd, *J* = 3.6, 11.2 Hz), 3.29 (1H, dd, *J* = 11.4, 13.4 Hz), 2.96 (1H, dd, *J* = 3.4, 13.0 Hz), 2.46 (6H, s), 2.39 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 143.6, 143.0, 131.8, 130.9, 129.2, 128.5, 128.28, 128.26, 52.2, 49.5, 35.8, 21.9, 21.8. MS m/z 360 (4), 225 (5), 224 (10), 223 (77), 163 (7), 151 (9), 149 (9), 139 (8), 138 (18), 137 (100), 136 (6), 135 (12), 134 (6), 121 (7), 105 (17), 103 (9), 93 (9), 91 (22), 78 (5), 77 (12), 65 (5), 59 (6), 55 (8), 45 (27). IR (film)ν_{max} 3052, 2955, 2363, 2338, 1733, 1458. Anal. Calcd for $C_{20}H_{24}O_2S_2$ C, 66.63; H, 6.71; S, 17.79. Found C, 66.4; H, 6.5; S, 18.2.

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