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# Ring Opening of *cis*-2-Benzyl-3-phenyl-1-(phenylsulfonyl)aziridine by Alkoxide. The First Eliminative Fission of an Aziridine with Uncharged Nitrogen

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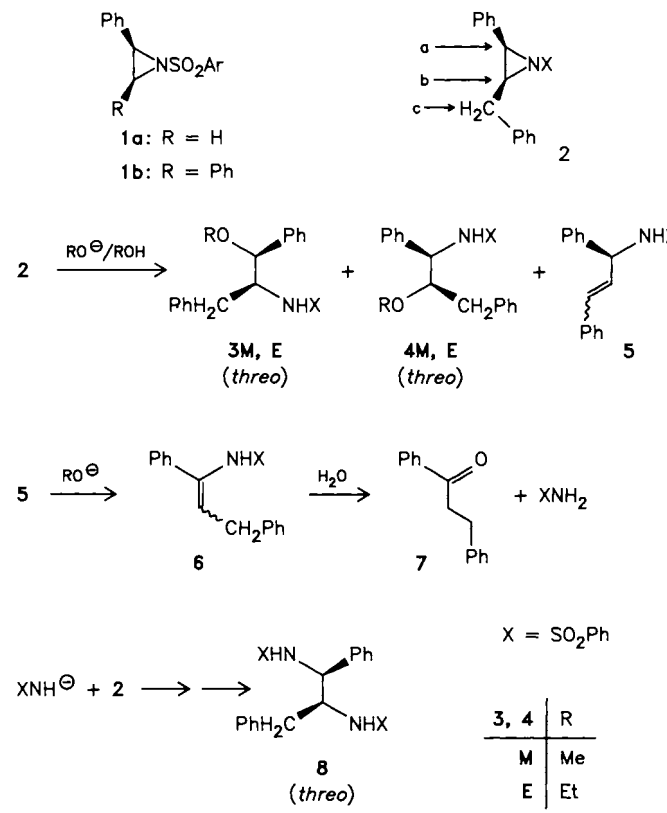
**The title compound 2 can be ring-opened in three ways by alcoholic sodium alkoxide: nucleophilic substitutive opening in (the benzylic) position 3 [attack (a)] and in position 2 [attack (b)] as well as the novel nucleophilic eliminative opening which is initiated by deprotonation of the benzylic substituent [attack (c)]. The primary cleavage product 5 of attack (c) is an allylic sulfonamide that slowly isomerizes to give the elusive enamide 6, the precursor of the isolated ketone 7. Attack (a) predominates with methoxide and less so with ethoxide. Attack (c) increases with size (and basicity?) of the alkoxide and is the only detected reaction with *tert*-butoxide.**

Scheme 1




Since a single electron transfer (SET) mechanism has been proposed to account for the extraordinary regioselectivity in nucleophilic ring opening of aziridines [2], efforts were made to mechanistically clarify the opening behaviour of activated aziridines. The following points were considered: regioselectivity [2–4], stereochemistry [2–5], steric hindrance of $S_N2$-like attack [2,4,6], kind of activation [2,4], steepness of the nitrogen pyramide and/or rate of nitrogen inversion [4,7], occurence of rearrangements [8], and competing reactions [4,9]. In the course of a regioselectivity study we now detect a competing reaction which is novel for uncharged aziridines and uncommon for the whole aziridine family.

Acid-catalyzed (double activation [4]) alcoholysis of **1a** [4] or **2** [3] proceeds exclusively at the benzylic carbon of the aziridine ring although with methanol a free (i.e. racemizing) carbenium ion is involved to about 8% only. Basic alcoholysis of **1a** (monoactivation by the sulfonyl group) prefers also attack on the benzylic position

Table 1. Reactions of **2** with RONa in boiling alcohols ROH

| run | 2/RONa [mmol] | in ml ROH | time [days] | products, % yields from $^1$H-NMR analysis 3 | 4 | 5 | 7 | 8 | 2 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5/5 | 70 MeOH | 1.8 | 48 **3M** | 13 **4M** | 3 | | | 36[a] |
| 2 | 5/5 | 70 MeOH | 4 | 61 **3M** | 22 **4M** | 2 | 1 | | 13 |
| 3 | 2/4 | 40 MeOH | 6 | 76 **3M** | 22 **4M** | | trace[a] | | |
| 4 | 5/5 | 70 EtOH | 0.6 | 21 **3E** | 12 **4E** | 11 | | | 42[b] |
| 5 | 5/5 | 70 EtOH | 6 | 32 **3E** | 16 **4E** | 1 | 25 | 7 | 1 |
| 6 | 2/4 | 40 EtOH | 7 | 48 **3E** | 25 **4E** | | 19 | 1 | |
| 7 | 2/2.6 | 150 EtOH | 5 | 43 **3E** | 20 **4E** | 4 | 21 | trace[a] | 11 |
| 8 | 2/16 | 40 EtOH | 5 | 42 **3E** | 21 **4E** | | 7 | | |
| 9 | 1.75/0 | 30 EtOH | 8 | 19 **3E** | 6 **4E** | | | | 69 |
| 10 | 2/4 | 40 tBuOH | 0.056 | | | 10[b] | – | – | 87[b] |

[a] Detected by TLC. – [b] Isolated yields.

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but is not highly regioselective: the regioselectivity was 3.9:1 for methoxide. With **2** (Scheme 1, Table 1) we now find a ration of 3:1 (products **3** and **4**) for the attacks (a) and (b) by methoxide (runs 1–3) and of 2:1 by ethoxide (runs 4–8). Thus, the preference for nucleophilic attack at the benzylic carbon of the aziridine decreases with the steric demands of the nucleophile. None of the four ethers **3M**, **E** and **4M**, **E** showed any sign of diastereomers (cf. ref.[3]). In accordance with previous works[3,5,7] and with $S_N2$-like mechanism the *threo* configuration is assigned to **3** and **4**.

Considering the different reaction conditions, **2** seems to react with methoxide roughly as fast as **1b**[7] but definitely more slowly than **1a**[4]. This is assumed to be caused by steric hindrance and by an influence of the nitrogen conformation. Ring opening is assumed[4,7] to be the faster the flatter the nitrogen pyramide is. **1b** and **2** will exist in the steep *anti* conformation with a high inversional barrier. In most runs the slowness of the nucleophilic ring opening, i. e. of attacks (a) and (b), allowed a competing deprotonation of the benzyl group, i. e. attack (c), leading to **5** and hence to **7** via an isomerization **5** → **6** (cf. ref.[8]) followed by hydrolytic cleavage of **6**. The enamide **6** could not be detected. A simple thermal isomerization **2** → **5** is ruled out by run 9 since neither **5** nor **7** were formed in the absence of ethoxide. Thus, this is the first example of a nucleophilic eliminative ring fission[10] of an aziridine with uncharged nitrogen. Owing to the fast competing nucleophilic substitutive ring opening (Type **2** → **3**, **4**) there have been so far only two examples reported of a nucleophilic eliminative fission of an aziridine ring. Both examples had an aziridinium structure. Stirling's excellent review[10] gives one example only, namely Baldwin's 2-methylaziridine *N*-oxide[11] which is an intramolecular variant possessing no intermolecular competitor. Very recently[12], Lilloci reported on a 2:1 competition between substitutive and eliminative ring fission in the reaction of the hexamethylaziridinium ion with sodium methoxide. In the latter case, the substitutive opening requires an attack on a tertiary carbon making this opening slow. An influence of the steric demands of the alkoxide on the competition between substitutive and eliminative ring opening had not been reported by Lilloci. Our results, however, clearly show this influence. Calculated for a total of 100% the ratio {(a) + (b)}/(c) of substitutive (products **3** and **4**) to eliminative (products **5** and **7**) ring opening had a range from 95:5 to 100:0 for methoxide and a range from 72:28 to 87:13 for ethoxide. With *tert*-butoxide (run 10) this ratio was 0:100. As expected, with the short reaction time in run 10 it was possible to prevent secondary reactions of **5** and to isolate crystalline **5**. This material proved to be exclusively the *trans* isomer. In the other runs of Table 1 except for run 4 only the *trans* isomer was identified by $^1$H NMR under conditions, however, which do not exclude *cis*-**5** as minor isomer. Run 4 gave a 1:4 mixture of *cis* and *trans* isomer. *cis*-**5** was not separated from *trans*-**5**.

Closer inspection of Table 1 reveals that low alcoholate concentrations seem to favor the eliminative fission. This may point to a difference between free and ion-paired alkoxide, the former favoring the eliminative process that requires a base rather than a nucleophile. Indeed, part of the above described increase in attack (c) may be ascribed to an increase in alkoxide basicity ($MeO^- < EtO^- < tBuO^-$) rather than to a steric deceleration of reactions (a) and (b).

The generation of ketone **7** from the enamide **6** may occur either during workup or prior to this by residual water. The latter is realized at least with EtONa/EtOH as the formation of the bissulfonamide **8** proves. **8** was indepedently obtained in 73% yield (along with 2% **3E** and 1% **4E**, 14% **2** recovered) from benzenesulfonamide and **2** in ethanolic sodium ethoxide solution. The isomerization **5** → **6** (both as amide anions) is unexpected for an allylic sulfonamide anion (cf. ref.[8a]) but a de- and re-protonation process will in this case profit from the stabilization of the intermediate allylic carbanion by the two phenyl groups (cf. ref.[13]).

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## Experimental

IR Spectra: Perkin-Elmer 283. – $^1$H NMR Spectra ($CDCl_3$): Bruker W 250. – Column chromatography: silica gel Merck 0.063–0.2 mm unless otherwise stated. Column dimensions (in cm) are given below. Thin layer chromatography (TLC): silica gel 60 $F_{254}$ Merck (aluminium sheets) and dichloromethane unless otherwise stated.

*General Method (Table 1):* Crystalline **2** was added to a solution of RONa in ROH. The solution was refluxed for the time given in Table 1 and then evaporated. The residue was taken up in dichloromethane and the solution washed with water until neutral. Evaporation provided a residue which was either analyzed by its $^1$H-NMR spectrum or chromatographed as stated below for each run. – *p*-Bromobenzaldehyde (CHO signal) was used as internal standard in $^1$H-NMR analysis when necessary.

*Run 1:* Chromatography (4 × 65, dichloromethane) provided in turn 634 mg (36%) of **2**, 447 mg of a mixture consisting ($^1$H NMR) of 401 mg of **3M** and 46 mg (3%) of **5**, 304 mg of **3M**, 295 mg of a mixture consisting ($^1$H NMR) of 221 mg of **3M** and 74 mg of **4M**, 177 mg of **4M**. Total yields were 926 mg (48%) of **3M**[3] and 251 mg (13%) of **4M**. For characterization of **5** see runs 4 and 10.

*threo-N-(1,3-Diphenyl-2-methoxypropyl)benzenesulfonamide* (**4M**): M. p. 77–78°C (petroleum ether 40–60°C). – IR (KBr): 3285 cm$^{-1}$ (NH), 1330 ($SO_2$), 1165 ($SO_2$), 1088 (C–O–C), 1064 (C–O–C). – $^1$H NMR: δ = 2.81 (dd, *J* = 13.9 Hz, *J* = 6.9 Hz, 1 benzylic H), 2.87 (dd, *J* = 13.9 Hz, *J* = 6.3 Hz, 1 benzylic H), 3.09 (s, OMe), 3.45 (ddd, *J* = 6.9 Hz, *J* = 6.3 Hz, *J* = 3.1 Hz, OCH), 4.36 (*dd*, *J* = 7.8 Hz, *J* = 3.1 Hz, NCH), 5.60 (d, *J* = 7.9 Hz, NH), 6.92–6.97 (m, 2 *o*-H of Ph), 7.02–7.41 (m, 11 aromatic H), 7.55–7.60 (m, 2 *o*-H of $PhSO_2$).

$C_{22}H_{23}NO_3S$ (381.5) Calcd. C 69.27 H 6.08 N 3.67
Found C 68.99 H 6.03 N 3.47

*Run 2:* Chromatography (3.5 × 45, dichloromethane) provided 110 mg of a mixture consisting ($^1$H NMR) of 95 mg of **2** and 15 mg (1%) of **7**, 140 mg of **2**, 480 mg of a mixture consisting ($^1$H NMR) of 44 mg of **3M** and 37 mg (2%) of **5**, 480 mg of **3M**, 670 mg of a mixture consisting ($^1$H NMR) of 251 mg of **3M** and 419 mg (22%) of **4M**.

*Run 3:* The residue consisted ($^1$H NMR) of 583 mg (76%) of **3M** and 167 (22%) of **4M**. TLC revealed a trace of **7**.

*Run 4:* Chromatography (4 × 50, dichloromethane) provided 734 mg (42%) **2**, 880 mg of a mixture and 126 mg (6%) **4E**. The mixture provided on chromatography (3 × 70, alumina Woelm activity I, methanol) 406 mg of a mixture consisting ($^1$H NMR) of 338 mg **3E**[3] and 68 mg of **4E**, 135 mg of mixture (a) and 185 mg of mixture (b). The composition ($^1$H NMR) of the mixtures was a follows: (a) 49 mg of **3E**, 30 mg of **4E** and 56 mg of **5**; (b) 34 mg of **3E**, 19 mg of **4E** and 132 mg of **5**. The total yields were 421 mg (21%) of **3E**, 243 mg (12%) of **4E** and 188 mg (11%) of **5**. 60 mg of mixture (b) on preparative TLC (neutral alumina 60 $F_{254}$ Merck;

dichloromethane/petroleum ether, 1:1) provided 30 mg of pure **5** as 1:4 mixture of *cis/trans* isomers. For pure *trans*-**5** see run 10.

*threo-N-(1,3-Diphenyl-2-methoxypropyl)benzenesulfonamide* (**4E**): M. p. 131–133 °C (chloroform). – IR (KBr): 3285 $cm^{-1}$, 1344 ($SO_2$), 1327 ($SO_2$), 1165 ($SO_2$), 1087 (C–O–C), 1065 (C–O–C). – $^1H$ NMR: δ = 0.95 (t, *J* = 7.0 Hz, Me), 2.84 (d, *J* = 6.7 Hz, $OCCH_2$), 3.02 (dq, *J* = 14.0 Hz, *J* = 7.0, 1H of $OCH_2$), 3.25 (dq, *J* = 14.0 Hz, *J* = 7.0 Hz, 1H of $OCH_2$), 3.50 ($m_c$, OCH), 4.37 (dd, *J* = 8.2 Hz, *J* = 2.7 Hz, NCH), 5.67 (d, *J* = 8.1 Hz, NH), 6.92–6.98 (m, 2 *o*-H of Ph), 7.04–7.09 (m, 3 aromatic H), 7.13–7.41 (m, 8 aromatic H), 7.57–7.62 (m, 2 *o*-H of $PhSO_2$).

$C_{23}H_{25}NO_3S$ (395.5) Calcd. C 69.84 H 6.37 N 3.54
Found C 69.75 H 6.39 N 3.40

*cis-N-(1,3-Diphenylallyl)benzenesulfonamide* (*cis*-**5** as 1:4 mixture with *trans*-**5**): Highly viscous material. – IR (film): 3300 $cm^{-1}$, 1335 ($SO_2$), 1165 ($SO_2$), 1156 ($SO_2$). – *cis*-**5**: $^1H$ NMR: δ = 5.42 (ddd, *J* = 9.7 Hz, *J* = 6.7 Hz, *J* = 0.6 Hz, NCH) (NH signal hidden under NCH signal of the *trans* isomer), 5.65 (dd, *J* = 11.4 Hz, *J* = 9.7 Hz, =CH–C–N), 6.47 (dd, *J* = 11.4 Hz, *J* = 0.6 Hz, HC=C–C–N), 7.04–7.09 (m, 2 *o*-H of Ph), 7.15–7.48 (m, 11 aromatic H hidden under aromatic H of *trans*-**5**), 7.56–7.61 (2 *o*-H of $PhSO_2$).

$C_{21}H_{19}NO_2S$ (349.5) Calcd. C 72.18 H 5.48 N 4.01
(*cis/trans* mixture): Found C 71.68 H 5.60 N 4.03

*Run 5:* Chromatography (3.5 × 45, dichloromethane) provided 250 mg of **7**, 30 mg of a mixture consisting ($^1H$ NMR) of 21 mg (1%) of **2** and 9 mg of **7**, 160 mg of a mixture consisting ($^1H$ NMR) of 150 mg of **3E** and 10 mg (1%) of **5**, 560 mg of a mixture consisting ($^1H$ NMR) of 490 mg of **3E** and 70 mg of **4E** and finally 240 mg of pure **4E**. Subsequent elution with ethyl acetate yielded 210 mg of a mixture containing ($^1H$ NMR) 175 mg (7%) of **8**. Trituration of this mixture with acetonitrile left 30 mg of pure **8** undissolved. The total yields were 640 mg (32%) of **3E**, 310 mg (16%) of **4E**, and 259 mg (25%) of **7**.

*threo-N,N'-(1-Benzyl-2-phenyl-1,2-ethanediyl)bis(benzenesulfonamide)* (**8**): M. p. 172–174 °C. – IR (KBr): 3385 $cm^{-1}$ (NH), 3300 (NH), 1334, 1171, 1164 (all $SO_2$). – $^1H$ NMR: δ = 2.21 (dd, *J* = 13.9 Hz, *J* = 8.3 Hz, 1 benzylic H), 2.95 (dd, *J* = 13.7 Hz, *J* = 5.0 Hz, 1 benzylic H), 3.81 ($m_c$, NC*H*CHPh), 4.42 ($m_c$, NC*H*Ph), 4.64 (d, *J* = 8.0 Hz, PhCCN*H*), 5.51 (d, *J* = 6.4 Hz, PhCN*H*), 6.80–6.85 (m, 2 *o*-H of Ph), 6.97–7.40 (m, 12 aromatic H), 7.43–7.52 (m, 2 aromatic H), 7.54–7.58 (m, 2 *o*-H of $PhSO_2$), 7.68–7.73 (m, 2 *o*-H of $PhSO_2$).

$C_{27}H_{26}N_2O_4S_2$ (506.6) Calcd. C 64.01 H 5.17 N 5.53
Found C 64.13 H 5.34 N 5.72

*Run 6:* Chromatography and $^1H$-NMR analyses similar to run 5. 80 mg (19%) of pure **7** were isolated. Total yields were 378 mg (48%) of **3E** and 198 mg (25%) of **4E**, and 7 mg (1%) of **8**.

*Run 7:* The residue consisted ($^1H$ NMR) of 337 mg (43%) of **3E**, 161 mg (20%) of **4E**, 30 mg (4%) of **5**, 89 mg (21%) of **7**, and 178 mg (11%) of **2**.

*Run 8:* The residue consisted ($^1H$ NMR) of 332 mg (42%) of **3E**, 165 mg (21%) of **4E**, and 29 mg (7%) of **7**.

*Run 9:* The residue consisted ($^1H$ NMR) of 130 mg (19%) of **3E**, 43 mg (6%) of **4E**, and 420 mg (69%) of **2**.

*Run 10:* Chromatography (3 × 15, dichloromethane) yielded 605 mg (87%) of **2** and 70 mg (10%) of *trans*-**5**.

*trans-N-(1,3-Diphenylallyl)benzenesulfonamide* (*trans*-**5**): M. p. 111–114 °C. – IR (KBr): 3305 $cm^{-1}$ (NH), 1333, 1157, 1166 (all $SO_2$). – $^1H$ NMR: δ = 5.14 (ddd, *J* = 7.4 Hz, *J* = 6.6 Hz, *J* = 1.2 Hz, =CH–C–N), 5.30 (d, *J* = 7.3 Hz, NH), 6.10 (dd, *J* = 15.5 Hz, *J* = 6.5 Hz, =CH–C–N), 6.38 (dd, *J* = 15.7 Hz, *J* = 1.1 Hz, HC=C–C–N), 7.13–7.30 (m, 10 aromatic H), 7.31–7.39 (m, 2 *o*-H of Ph), 7.42–7.50 (m, 1 *o*-H of Ph), 7.74–7.81 (m, 2 *o*-H of $PhSO_2$).

$C_{21}H_{19}NO_2S$ (349.5) Calcd. C 72.18 H 5.48 N 4.01
Found C 72.19 H 5.59 N 4.02

*Synthesis of* **8** *from Benzenesulfonamide and* **2**: A solution of 0.23 g (10 mmol) of sodium, 2.36 g (15 mmol) of benzenesulfonamide, and 1.747 g (5 mmol) of **2** in 100 ml of ethanol was refluxed for 52 h. After workup (see General Method), chromatography (3.5 × 45, dichloromethane) provided 189 mg of a mixture consisting ($^1H$ NMR) of 155 mg of **2** and 34 mg of **3E** and then 102 mg of a mixture consisting ($^1H$ NMR) of 93 mg of **2**, 3 mg of **3E**, and 6 mg (1%) of **4E**. Elution with ethyl acetate yielded 1.86 g (73%) of **8**. Total yields were 37 mg (2%) of **3E** and 248 mg (14%) of **2**.

CAS Registry Numbers

**2**: 121838-18-4 / **3M**: 121838-20-8 / **3E**: 121846-96-6 / **4M**: 121846-92-2 / **4E**: 121846-97-7 / *cis*-**5**: 121846-93-3 / *trans*-**5**: 121846-94-4 / **7**: 1083-30-3 / **8**: 121846-95-5 / Benzenesulfonamide sodium salt: 18522-93-5

[1] Part 50: J. Werry, H. Stamm, P.-Y. Lin, R. Falkenstein, *Tetrahedron*, in the press.
[2] H. Stamm, P. Assithianakis, B. Buchholz, R. Weiß, *Tetrahedron Lett.* **23** (1982) 5021.
[3] H. Stamm, D. Speth, *Arch. Pharm. (Weinheim, Ger.)* **322** (1989) 277.
[4] B. Buchholz, H. Stamm, *Isr. J. Chem.* **27** (1986) 17.
[5] T. Mall, H. Stamm, *Chem. Ber.* **121** (1988) 1353.
[6] B. Buchholz, H. Stamm, *Chem. Ber.* **120** (1987) 1239.
[7] T. Mall, H. Stamm, *J. Org. Chem.* **1987**, 4812.
[8] A. Onistschenko, B. Buchholz, H. Stamm, *Tetrahedron* **43** (1987) 565; H. Stamm, A. Onistschenko, B. Buchholz, T. Mall, *J. Org. Chem.* **54** (1989) 193.
[9] H. Stamm, W. Wiesert, *Chem. Ber.* **111** (1978) 2665.
[10] C. J. M. Stirling, *Chem. Rev.* **78** (1978) 517.
[11] J. E. Baldwin, A. K. Bhatnagar, Se Chun Choi, T. Shortridge, *J. Am. Chem. Soc.* **93** (1971) 4082.
[12] C. Lilloci, *J. Org. Chem.* **53** (1988) 1733.
[13] The related 1,1,3-triphenylpropene has the remarkably low $pK_a$ value of about 26.5: A. Streitwieser Jr., J. H. Hammons, E. Ciuffarin, J. I. Brauman, *J. Am. Chem. Soc.* **89** (1967) 59; A. Streitwieser Jr., E. Ciuffarin, J. H. Hammons, *ibid.* **89** (1967) 63.

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