# Notizen

Reactions with Aziridines, 46[1]

## Ring Opening of Stilbene Imines by Thiophenolate

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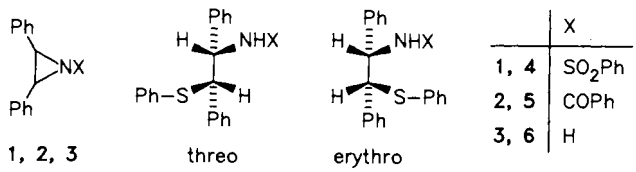
**Ring opening by thiophenolate of *cis-trans* pairs of stilbene imines proceeds stereospecifically irrespective of the kind of mono activation by the phenylsulfonyl group (1), by the benzoyl group (2), or by protonation of the aziridine base (3). In accordance with complete Walden inversion, the sole product from the *cis* isomer is always a diastereomer of the sole product from the *trans* isomer. The diastereomers obtained from 3 are correlated with the respective diastereomers obtained from 2.**

In our investigation (cf. ref.[1,2]) and preceding papers) of nucleophilic ring opening of aziridines we have a great interest in mechanistic aspects concerning the alternatives SET[3,4], $S_N2$, borderline behavior[5,6], and $S_N1$. This interest includes necessarily to some extent any kind of benzylic effect[5,7,2] as well as the stereochemistry of ring opening[5]. The stereoelectronic part of the benzylic effect, by far the largest possible component of the total benzylic effect, can by analogy be considered to be absent following the experimental evidence for styrene oxide[8]. This evidence was in accordance with the preferred conformation of styrene oxide as deduced from semiempirical calculations[9].

In a further contribution to this field we now report on ring opening of activated stilbene imines **1** and **2** (both *cis* and *trans* isomers) by thiophenolate ion in methanol. Except for the recently published[2] alcoholysis of **1**, this is the first investigation on ring opening of activated stilbene imines and on its stereochemical outcome, and it is the very first one that includes acyl activation. We are particularly interested in acyl activation since this activation induced a dramatic change in the regioselectivity[3,10] of ring opening of 2,2-dimethylaziridines. This change is considered to indicate a switch from $S_N2$ to SET that is triggered[3] by the poor nucleofugality of the carbonamide group and is made possible by the reducibility of the group. A reducible activation group is the necessary prequisite for SET ring opening.




**4, 5, 6**

Since aziridine bases, both without and with activation by an acid, are almost with certainty not capable of undergoing SET opening, reactions of **3** are included for comparison. The necessary acid was provided by an excess of free thiophenol. Ring opening of an aziridine base without acid catalysis (i.e. acid activation) is practically impossible with common nucleophiles under common conditions (see discussion and lit. cited in ref.[5]), because an aziridine nitrogen devoid of positive charge or electron withdrawing substituent is a very poor leaving atom.

Table 1. Reactions of **1**, **2**, and **3** with PhSNa in methanol at room temperature[a]

| | Run | Time | Products[b] |
|---|---|---|---|
| 1 | *cis*-**1** | 4.5 h | 100% *threo*-**4** |
| 2 | *trans*-**1** | 4.5 h | 95% *erythro*-**4** |
| 3 | *cis*-**2** | 50 h | 72% *threo*-**5**, 21% *cis*-**2** |
| 4 | *trans*-**2** | 3.5 h | 92% *erythro*-**5**, 8% *trans*-2,4,5-triphenyl-4,5-dihydrooxazole[c] |
| 5 | *cis*-**3** | 26 h | (75%) *threo*-**6**, (19%) *cis*-**3** |
| 6 | *trans*-**3** | 5.5 h | 53% *erythro*-**6**, 22% *trans*-**3** |

[a] 3 mmol of NaOMe, 10 mmol of PhSH, and 2 mmol of aziridine. — [b] Yields in parantheses from $^1$H-NMR analysis. — [c] This known[11] oxazoline arose probably from isomerization of *trans*-**2** either during the preparation of *trans*-**2** or, more likely, during workup of run 4.

Table 1 presents the results of our study. We always found one product only. Since the material balance was excellent and since for each *cis-trans* pair the *cis* isomer provided a diastereoisomer of the product obtained from the *trans* isomer, these ring openings are reasonably interpreted as pure $S_N2$ opening with complete Walden inversion. In this sense the *erythro* and *threo* configurations are assigned. This assignment has the highest degree of certainty with **6** (vide supra).

To confirm the assignment for **5**, we therefore correlated *erythro*-**5** with *erythro*-**6** and *threo*-**5** with *threo*-**6** by benzoylation of both **6**. Actually, we selected thiophenolate as nucleophile in this study because of this possibility that only could be realized with a good nucleophile (thiophenolate) whose conjugate acid (thiophenol) was able to protonate **3** in situ.

It has been supposed[5,2] that ring opening of aziridines possessing a tervalent (i.e. pyramidal) nitrogen proceeds most easily in the transition state of nitrogen inversion. Since a *trans* stilbene imine can be expected[2] to invert faster than its *cis* isomer, the nitrogen inversion hypothesis suggests a faster reaction of the *trans* isomer. This was experimentally observed with alkoxide attack on **1** in contrast to alkoxide attack on the stilbene oxide *cis-trans* pair[2]. Table 1 contains a similar finding. Both run 1 and 2 had gone to completion making a reactivity comparison impossible, but a comparison of run 3 with run 4 again reveals for **2** a faster reaction of the *trans* isomer. Unexpectedly, runs 5 and 6 seem to reveal that also in the case of a non-inverting stilbene imine with tetrahedral nitrogen (i.e. protonated **3**) the *trans* isomer reacts faster. However,

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here the observed difference is less pronounced and perhaps even questionable. If the oberserved effect reflects a real reactivity difference of protonated *cis*-**3** and *trans*-**3**, this may tentatively be explained as follows. The reason for the faster opening[2] of the *cis* isomer of the two stilbene oxides was not clear but a tentative explanation[2] considered a steric hindrance of attack on position 2 by the rotating phenyl ring in position 3 of *trans* stilbene oxide. This hindering rotation is impossible in the *cis* isomer. Actually in all *cis* isomers discussed here, both phenyl rings are held in a conformation close to that one that had been called perpendicular[9]. This conformation cannot change on protonation of *cis*-**3**. In contrast, for protonated *trans*-**3** in the preferred conformations of both phenyl rings, the plane of a phenyl ring will bisect (as calculated for the *cis* invertomer of stilbene imine[9]) the aziridine ring, while in *trans* stilbene oxide (as calculated for styrene oxide and imine[9,12]) the preferred conformations will deviate by 30° from the bisected ones. Steric hindrance of attack in position 2 will be smaller when the phenyl in position 3 prefers the bisected conformation. Generally, one would expect steric hindrance to play an important role in $S_N2$ ring opening of stilbene imines and oxides.

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## Experimental

IR spectrometer: Perkin-Elmer 283. – $^1$H-NMR spectrometer: Bruker W 250. – Column chromatography: Silica gel, Merck, 0.063–0.2 mm. Column dimensions (in cm) are given below.

*Starting Material: cis*-**1** and *trans*-**1** are decribed in ref.[2]. *cis*-**3** is described in ref.[13], *trans*-**3** in ref.[14], *cis*-**2** and *trans*-**3** were prepared from benzoyl chloride and *cis*-**3** or *trans*-**3**, respectively, according to a known method[15].

*cis-1-Benzoyl-2,3-diphenylaziridine* (*cis*-**2**): Recrystallized from petroleum ether (b.p. 50–70°C), yield 92%. – M.p. 141–142°C. – IR (KBr): 1675 cm$^{-1}$ (C=O). – $^1$H-NMR ($CDCl_3$): δ = 4.08 (s, NCH), 7.14–7.38 (m, N–C–Ph and *m*-H of benzoyl), 7.47–7.52 (m, *p*-H of benzoyl), 8.03–8.07 (*o*-H of benzoyl).

$C_{21}H_{17}NO$ (299.4) Calcd. C 84.25 H 5.73 N 4.68
Found C 84.19 H 5.70 N 4.45

*trans-1-Benzoyl-2,3-diphenylaziridine* (*trans*-**2**): Recrystallized from petroleum ether (b.p. 50–70%), yield 90%. – M.p. 98–99°C. – IR (KBr): 1651 cm$^{-1}$ (C=O). – $^1$H-NMR ($CDCl_3$): δ = 3.98 (s, NCHPh), 7.22–7.31 (m, N–C–Ph and *m*-H of benzoyl), 7.37–7.43 (m, *p*-H of benzoyl), 7.88–7.91 (m, *o*-H) of benzoyl).

$C_{21}H_{17}NO$ (299.4) Calcd. C 84.25 H 5.73 N 4.68
Found C 84.07 H 5.78 N 4.59

*General Method* (Table 1): The reactions were performed with continous stirring. 3 mmol of sodium was dissolved in 30 ml of methanol, 10 mmol of thiophenol, and then 2 mmol of the respective aziridine was added. After the time given in Table 1, the solvent was removed in a rotary evaporator (bath temperature 40–50°C). The residue was taken up in dichloromethane, washed with water, and evaporated. Further workup is given below.

*Run 1:* 393 mg of *threo*-**4** was sucked off from the reaction mixture and washed with petroleum ether (b.p. 50–70°C) prior to workup. The residue obtained after workup was chromatographed (17 × 3). Elution with toluene removed thiophenol, elution with ethyl acetate yielded 499 mg of *threo*-**4** summing up to a total yield of 892 mg (100%).

*threo-N-(1,2-Diphenyl-2-phenylthioethyl)benzenesulfonamide* (*threo*-**4**): M.p. 146–148°C. – IR (KBr): 3240 cm$^{-1}$ (NH), 1333 ($SO_2$), 1155 ($SO_2$). – $^1$H NMR ($CDCl_3$): δ = 4.42 (d, *J* = 8.0 Hz, SCH), 4.71 (dd, *J* = 8.0 Hz, *J* = 5.9 Hz, NCH), 5.80 (d, *J* = 5.8 Hz, NH), 6.75–6.79 (m, 2H, *o*-H of 1 Ph), 6.90–7.26 (m, 10H, 1 Ph, *m*-H and *p*-H of 1 Ph, *m*-H of $SO_2$Ph), 7.34–7.40 (m, *p*-H of $SO_2$Ph), 7.53–7.56 (m, *o*-H of $SO_2$Ph).

$C_{26}H_{23}NO_2S_2$ (445.6) Calcd. C 70.08 H 5.20 N 3.14
Found C 70.09 H 5.34 N 3.39

*Run 2:* Chromatography (20 × 3) with toluene removed thiophenol, subsequent elution with ethyl acetate yielded 842 mg (95%) of *erythro*-**4**.

*erythro-N-(1,2-Diphenyl-1-phenylthioethyl)benzenesulfonamide* (*erythro*-**4**) M.p. 120–121°C. – IR (KBr): 3290 cm$^{-1}$ (NH), 1330 ($SO_2$), 1167 ($SO_2$). – $^1$H NMR ($CDCl_3$): δ = 4.39 (d, *J* = 5.5 Hz, SCH), 4.80 (dd, *J* = 5.6 Hz, *J* = 7.9 Hz, NCH), 5.47 (d, *J* = 7.9 Hz, NH), 6.75–6.79 (m, 2H, *o*-H of 1 Ph), 6.98–7.28 (m, 10H, 1 Ph, *m*-H and *p*-H of 1 Ph, *m*-H of $SO_2$Ph), 7.34–7.41 (m, *p*-H of $SO_2$Ph) 7.54–7.58 (m, *o*-H of $SO_2$Ph).

$C_{26}H_{23}NO_2S_2$ (445.6) Calcd. C 70.08 H 5.20 N 3.14
Found C 70.14 H 5.16 N 3.22

*Run 3:* Chromatography (18 × 3) with dichloromethane gave thiophenol and then 127 mg (21%) of *cis*-**2**. Elution with dichloromethane/ethyl acetate (1:1) yielded 589 mg (72%) of *threo*-**5**.

*threo-N-(1,2-Diphenyl-2-phenylthioethyl)benzamide* (*threo*-**5**): M.p. 158–160°C. – IR (KBr): 3290 cm$^{-1}$ (NH), 1635 (amide I), 1540 (amide II). – $^1$H NMR ($CDCl_3$): δ = 4.76 (d, *J* = 7.0 Hz, SCH), 5.65 (dd, *J* = 7.8 Hz, *J* = 7.7 Hz on decoupling, NCH), 6.92 (d, *J* = 7.6 Hz, NH), 7.08–7.32 (m, 2 Ph), 7.39–7.55 (m, *m*-H and *p*-H) of benzoyl), 7.74–7.81 (m, *o*-H of benzoyl).

$C_{27}H_{23}NOS$ (409.6) Calcd. C 79.18 H 5.66 N 3.42
Found C 79.43 H 5.84 N 3.64

*Run 4:* 579 mg of *erythro*-**5** was sucked off from the reaction mixture and washed with petroleum ether (b.p. 50–70°C) prior to workup. The residue obtained by workup was chromatographed (20 × 3). Elution with toluene removed thiophenol, elution with ethyl acetate yielded 50 mg (8%) of *trans*-2,4,5-triphenyloxazoline and then 169 mg of *erythro*-**5**, amounting to a total yield of 748 mg (92%).

*erythro-N-(1,2-Diphenyl-2-phenylthioethyl)benzamide* (*erythro*-**5**): M.p. 176–177°C. – IR (KBr): 3410 cm$^{-1}$ (NH), 1643 (amide I), 1516 (amide II). – $^1$H NMR ($CDCl_3$): δ = 4.77 (d, *J* = 5.1 Hz, SCH), 5.70 (dd, *J* = 5.1 Hz, *J* = 8.7 Hz, NCH), 6.90 (d, *J* = 8.7 Hz, NH). 7.04–7.07 (m, *o*-H of 1 Ph), 7.14–7.52 (m, 1 Ph, *m*-H and *p*-H of 1 Ph and of benzoyl), 7.66–7.70 (m, *o*-H of benzoyl).

$C_{27}H_{23}NOS$ (409.6) Calcd. C 79.18 H 5.66 N 3.42
Found C 78.84 H 5.72 N 3.40

*trans-2,4,5-Triphenyl-4,5-dihydrooxazole:* Oil[11]. – $^1$H NMR ($CDCl_3$): δ = 5.23 (d, *J* = 7.5 Hz, NCH), 5.42 (d, *J* = 7.5 Hz, OCH), 7.31–7.49 (m, Ph except for *o*-H of 2-Ph), 8.12–8.15 (m, *o*-H of 2-Ph); ref.[11] (90 MHz): 5.3 (d, *J* = 9 Hz, both NCH and OCH!), 6.9–8.4 (m, Ph).

*Run 5:* Chromatography (18 × 3) with dichloromethane removed thiophenol. Elution with dichloromethane/ethyl acetate (1:1) provided 528 mg of a mixture consisting ($^1$H-NMR analysis) of 73 mg (19%) of *cis*-**3** and 455 mg (75%) of *threo*-**6**. 393 mg of this mixture was separated by preparative TLC (silica gel 60 F 254, Merck, thickness 2 mm, 20 cm × 20 cm, dichloromethane/ethyl acetate, 100:1) into 81 mg of *cis*-**3** (upper zone) and 273 mg of *threo*-

**6**. The latter provided a benzoyl derivative that was identical (m.p., IR, $^1$H NMR) with *threo*-**5**.

*threo-1,2-Diphenyl-2-(phenylthio)ethylamine* (*threo*-**6**): Oil. – IR (KBr): 3380 $cm^{-1}$ (NH), 3340 (NH). – $^1$H NMR ($CDCl_3$): δ = 1.97 (s, $NH_2$), 4.34 (s, S–CHCH–N), 7.07–7.23 (m, Ph).

$C_{20}H_{19}NS$ (305.5) Calcd. C 78.65 H 6.27 N 4.59
Found C 78.49 H 6.43 N 5.00

*Run 6:* Chromatography (17 × 3) with dichloromethane removed thiophenol and then 84 mg (22%) of *trans*-**3**. Elution with dichloromethane/ethyl acetate (10:1) yielded 325 mg (53%) of *erythro*-**6** whose benzoyl derivative was identical (m.p., IR, $^1$H NMR) with *erythro*-**5**.

*erythro-1,2-Diphenyl-2-(phenylthio)ethylamine* (*erythro*-**6**): M.p. 83–84°C. – IR (KBr): 3480 $cm^{-1}$ (NH) 3360 (NH). – $^1$H NMR ($CDCl_3$): δ = 1.67 (s, $NH_2$), 4.37 (d, *J* = 7.0 Hz, NCH), 4.41 (d, *J* = 7.0 Hz, SCH), 7.10–7.28 (m, Ph).

$C_{20}H_{19}NS$ (305.5) Calcd. C 78.65 H 6.27 N 4.59
Found C 78.76 H 6.41 N 4.91

CAS Registry Numbers

*cis*-**1**: 110143-77-6 / *trans*-**1**: 110143-78-7 / *cis*-**2**: 13866-14-3 / *trans*-**2**: 79102-23-1 / *cis*-**3**: 1605-06-7 / *trans*-**3**: 25125-72-8 / *threo*-**4**: 113747-51-6 / *erythro*-**4**: 113726-12-8 / *threo*-**5**: 113726-13-9 / *erythro*-**5**: 113726-14-0 / *threo*-**6**: 113747-52-7 / *erythro*-**6**: 113726-15-1 / *trans*-2,4,5-triphenyl-4,5-dihydrooxazole: 71027-98-0 / thiophenol: 108-98-5


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