

# On the Selectivity of the Cleavage of 2-Substituted Aziridines in the Synthesis of Thiazolidines

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2-Alkylaziridines react with carbonyl compounds in the presence of hydrogen sulfide to give regioselectively 4-alkylthiazolidines **1**. With 2-phenylaziridine 4-phenyl- (**1d**) and 5-phenylthiazolidine (**2d**) are obtained, the latter in larger amounts. This result is rationalized on the basis of pseudoconjugation between the phenyl and aziridine ring.

A recent paper<sup>1)</sup> on the reactivity of activated 2-phenylaziridines prompts us to report our results on the ring opening of *N*-unsubstituted aziridines. Cleavage of these compounds by carbonyl compounds plus hydrogen sulfide is a well-known process of synthesis of thiazolidines<sup>2)</sup>; with *N*-unsubstituted aziridines, the reaction may involve ring-opening of the aziridine-carbonyl adduct and (or) formation of the corresponding 2-aminoethanethiol followed by cyclisation with the carbonyl compound<sup>3)</sup>; the former mechanism seems to be preponderant with reactive carbonyl compounds as methanal or ethanal. This reaction is regioselective with 2-monoalkylaziridine and leads to 4-alkylthiazolidine by nucleophilic attack ( $S_N2$ -like mechanism) on the unsubstituted carbon of the heterocycle (Table 1).

Scheme 1

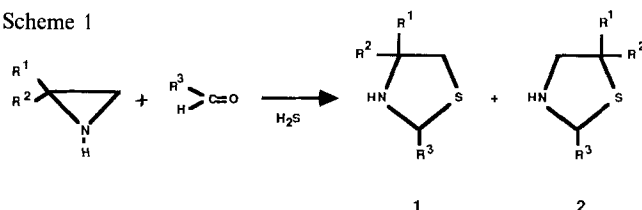


Table 1. Thiazolidines **1** and **2** from the reaction of 2-substituted aziridines with methanal or ethanal in the presence of  $H_2S$

|          | R <sup>1</sup> | R <sup>2</sup> | R <sup>3</sup> | Yield | %1   | %2  | B.p./Torr | Ref. |
|----------|----------------|----------------|----------------|-------|------|-----|-----------|------|
| <b>a</b> | Me             | H              | H              | 71    | 100  |     | 65/13     | 3)   |
| <b>b</b> | Me             | Me             | H              | 74    | 100  |     | 67/15     | 9)   |
| <b>c</b> | tBu            | H              | H              | 47    | 100  |     | 94/12     |      |
| <b>d</b> | Ph             | H              | H              | 59    | 25   | 75  | 120/0.5   |      |
| <b>e</b> | Me             | H              | Me             | 64    | 100* |     | 63/15     | 3)   |
| <b>f</b> | Me             | Me             | Me             | 64    | 100  |     | 68/18     | 3)   |
| <b>g</b> | tBu            | H              | Me             | 40    | 100* |     | 90–94/12  |      |
| <b>h</b> | Ph             | H              | Me             | 55    | 21*  | 79* | 100/0.5   |      |

\* Mixture of diastereomers.

Reaction of 2-phenylaziridine with methanal or ethanal plus hydrogen sulfide is not selective any more. Mixtures of 4-phenyl- and 5-phenylthiazolidine (**1d** and **2d**) are obtained the latter being the more abundant. This mixture of isomers is analysed by  $^1H$ -NMR spectroscopy: the geminal coupling constant of each 4-H, 5-H part

of the spectrum allows the identification of the compounds. For 5-substituted compounds, the value of  $^2J_{4,4'}$  is close to  $-12.5$  Hz; for 4-substituted compounds, the value of  $^2J_{5,5'}$  is reduced to the  $-10.0$  and  $-10.5$  Hz range.

An explanation in terms of the SET mechanism<sup>4)</sup> is not consistent with our results since no 5-substituted thiazolidine is obtained with 2,2-dimethylaziridine. Calculations<sup>5)</sup>,  $^{13}C$ -<sup>6)</sup> and  $^{15}N$ -<sup>7)</sup> NMR spectroscopy suggest that conjugation is operative in 2-phenylaziridine: the overlap of the bonding orbitals of aziridine (Walsh orbitals) with the antibonding orbitals of the aromatic ring involve the sterically less favored bisected conformation of 2-phenylaziridine; a weakening of the C2–N and C2–C3 adjacent bonds and a reinforcement of the C3–N opposite bond result from these interactions<sup>8)</sup>. The easier cleavage of the C2–N bond hence explains the greater part of 5-phenylthiazolidine in the reaction mixtures.



## Experimental

$^1H$ -NMR spectra: Bruker WM 250 or AM 500. MS: Ribermag 10-10.

### Synthesis of Thiazolidines **1** and **2**

**Reaction with Methanal:** 30 ml of an aqueous solution of methanal (7.5 g, 0.25 mol) is added dropwise at  $0^\circ C$  to 60 ml of an ethanolic solution of the corresponding aziridine (0.25 mol). The mixture is then saturated with hydrogen sulfide during 2 h. 50 ml of benzene is added and a ternary mixture, benzene/ethanol/water, is distilled first to eliminate the water and then the binary mixture benzene/ethanol followed by the thiazolidines.

**4-tert-Butylthiazolidine (1c):**  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta$  = 1.03 (s, 9H, tBu), 1.65 (br, 1H, 3-H), 2.51 (m, 1H, 5-H,  $^2J$  =  $-10.1$ ,  $^3J$  = 9.7 Hz), 2.77 (m, 1H, 5-H,  $^3J$  = 6.0 Hz), 2.95 (m, 1H, 4-H), 4.06 and 4.32 (m, 2H, 2-H,  $^2J$  =  $-9.4$  Hz). – MS:  $m/z$  = 145 ( $M^+$ ), 88 (100%).

**4-Phenylthiazolidine (1d):**  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta$  = 2.15 (br, 1H, 3-H), 2.83 (m, 1H, 5-H,  $^2J$  =  $-10.3$ ,  $^3J$  = 8.9 Hz), 3.35 (m, 1H, 5-H,  $^3J$  = 6.2 Hz), 4.21 (m, 1H, 4-H), 4.4 (m, 2H, 2-H), 7.1–7.56 (m, 5H, aromatic H). – MS:  $m/z$  = 165 ( $M^+$ ), 118 (100%).

**5-Phenylthiazolidine (2d):**  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta$  = 2.15 (br, 1H, 3-H), 3.01 (m, 1H, 4-H,  $^2J$  =  $-12.5$ ,  $^3J$  = 6.2 Hz), 3.51 (m, 1H, 4-H,  $^3J$  = 6.4 Hz), 4.53 (m, 1H, 5-H), 4.33 and 4.48 (m, 2H, 2-H,  $^2J$  =  $-9.4$  Hz), 7.1–7.55 (m, 5H, aromatic H). – MS:  $m/z$  = 165 ( $M^+$ ), 43 (100%).

**Reaction with Ethanal:** 20 ml of a solution of ethanal (11 g, 0.25 mol) in pentane is added dropwise to 40 ml of a solution of the cor-

responding aziridine (0.25 mol) in pentane. The mixture is then saturated with hydrogen sulfide during 2 h, dried with magnesium sulfate, and distilled.

**4-tert-Butyl-2-methylthiazolidine (1g)** (Mixture of Diastereomers 86:14):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ): more abundant:  $\delta = 1.01$  (s, 9H, tBu), 1.03 (br, 1H, 3-H), 1.56 (d, 3H,  $\text{CH}_3$ ,  $J = 6.1$  Hz), 2.70 (m, 1H, 5-H,  $^2J = -10.0$ ,  $^3J = 9.8$  Hz), 2.91 (m, 1H, 5-H,  $^3J = 6.1$  Hz), 2.98 (m, 1H, 4-H), 4.56 (q, 1H, 2-H); less abundant: 0.99 (s, 9H, tBu), 1.03 (br, 1H, 3-H), 1.44 (d, 3H,  $\text{CH}_3$ ,  $J = 6.5$  Hz), 2.63 (m, 1H, 5-H,  $^2J = -10.5$ ,  $^3J = 9.7$  Hz), 3.02 (m, 1H, 5-H,  $^3J = 6.1$  Hz), 3.08 (m, 1H, 4-H), 4.72 (q, 1H, 2-H). — MS:  $m/z = 159$  ( $\text{M}^+$ ), 102 (100%).

**2-Methyl-4-phenylthiazolidine (1h)** (Mixture of Diastereomers 71:29):  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): more abundant:  $\delta = 1.62$  (d, 3H,  $\text{CH}_3$ ,  $J = 6.1$  Hz), 2.06 (br, 1H, 3-H), 2.95 (m, 1H, 5-H,  $^2J = -10.1$ ,  $^3J = 10.0$  Hz), 3.43 (m, 1H, 5-H,  $^3J = 6.2$  Hz), 4.24 (m, 1H, 4-H), 7.15–7.4 (m, 5H, aromatic H), 2-H hidden by other lines; less abundant: 1.55 (d, 3H,  $\text{CH}_3$ ,  $J = 6.4$  Hz), 2.06 (br, 1H, 3-H), 3.06 (m, 1H, 5-H,  $^2J = -10.6$ ,  $^3J = 6.8$  Hz), 3.4 (m, 1H, 5-H,  $^3J = 6.3$  Hz), 7.15–7.4 (m, 5H, aromatic H), 2-H and 4-H hidden by other lines. — MS:  $m/z = 179$  ( $\text{M}^+$ ), 133 (100%).

**2-Methyl-5-phenylthiazolidine (2h)** (Mixture of Diastereomers 57:43):  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ): more abundant:  $\delta = 1.58$  (d, 3H,  $\text{CH}_3$ ,  $J = 6.1$  Hz), 2.06 (br, 1H, 3-H), 2.90 (m, 1H, 4-H,  $^2J = -12.7$ ,  $^3J = 8.7$  Hz), 3.72 (m, 1H, 4-H,  $^3J = 6.3$  Hz), 4.61 (m, 1H, 5-H), 4.91 (q, 1H, 2-H), 7.15–7.4 (m, 5H, aromatic H); less abundant: 1.68 (d, 3H,  $\text{CH}_3$ ,  $J = 6.2$  Hz), 2.06 (br, 1H, 3-H), 3.27 (m,

1H, 4-H,  $^2J = -12.5$ ,  $^3J = 3.2$  Hz), 3.33 (m, 1H, 4-H,  $^3J = 6.4$  Hz), 4.67 (m, 1H, 5-H), 4.72 (q, 1H, 2-H), 7.15–7.4 (m, 5H, aromatic H). — MS:  $m/z = 179$  ( $\text{M}^+$ ), 57 (100%).

#### CAS Registry Numbers

**1a:** 33174-83-3 / **1b:** 56400-70-5 / **1c:** 107326-17-0 / **1d:** 107326-18-1 / **(cis)-1e:** 72760-75-9 / **(trans)-1e:** 72760-76-0 / **1f:** 16862-60-5 / **(cis)-1g:** 107326-20-5 / **(trans)-1g:** 107326-23-8 / **(cis)-1h:** 107326-21-6 / **(trans)-1h:** 107326-24-9 / **2d:** 107326-19-2 / **(cis)-2h:** 107326-22-7 / **(trans)-2h:** 107326-25-0 /  $\text{H}_2\text{S}$ : 7783-06-4 /  $\text{HCHO}$ : 50-00-0 /  $\text{MeCHO}$ : 75-07-0 / 2-methylaziridine: 75-55-8 / 2,2-dimethylaziridine: 2658-24-4 / 2-*t*-butylaziridine: 13639-44-6 / 2-phenylaziridine: 1499-00-9

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