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[1] 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[2]; 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[3]: 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

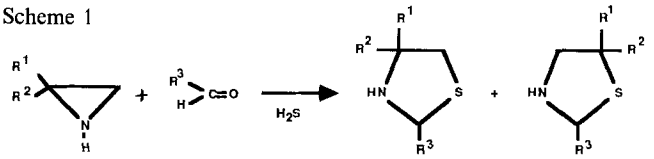


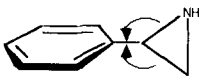
Table 1. Thiazolidines **1** and **2** from the reaction of 2-substituted aziridines with methanal or ethanal in the presence of H_2S

	R^1	R^2	R^3	Yield	%**1**	%**2**	B.p./Torr	Ref.
a	Me	H	H	71	100		65/13	3)
b	Me	Me	H	74	100		67/15	9)
c	tBu	H	H	47	100		94/12	
d	Ph	H	H	59	25	75	120/0.5	
e	Me	H	Me	64	100*		63/15	3)
f	Me	Me	Me	64	100		68/18	3)
g	tBu	H	Me	40	100*		90–94/12	
h	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 ^{1}H-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[4] is not consistent with our results since no 5-substituted thiazolidine is obtained with 2,2-dimethylaziridine. Calculations[5], ^{13}C-[6] and ^{15}N-[7] 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[8]. The easier cleavage of the C2–N bond hence explains the greater part of 5-phenylthiazolidine in the reaction mixtures.



Experimental

^{1}H-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°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**): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (s, 9H, *t*Bu), 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**): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 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**): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 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-

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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}H NMR (500 MHz, $CDCl_3$): more abundant: δ = 1.01 (s, 9H, *t*Bu), 1.03 (br, 1H, 3-H), 1.56 (d, 3H, 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, *t*Bu), 1.03 (br, 1H, 3-H), 1.44 (d, 3H, 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 (M^+), 102 (100%).

2-Methyl-4-phenylthiazolidine (**1h**) (Mixture of Diastereomers 71:29): ^{1}H NMR (250 MHz, $CDCl_3$): more abundant: δ = 1.62 (d, 3H, 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, 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 (M^+), 133 (100%).

2-Methyl-5-phenylthiazolidine (**2h**) (Mixture of Diastereomers 57:43): ^{1}H NMR (250 MHz, $CDCl_3$): more abundant: δ = 1.58 (d, 3H, 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, 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 (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 / H_2S: 7783-06-4 / HCHO: 50-00-0 / 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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