Regioselective Aziridine Ring Expansions

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1-Phenylmethyl-2-hydroxymethylaziridine (**1**) undergoes regioselective reactions with carbon disulfide to form thiazolidinethiones. Deuterium labeling experiments suggest that the reaction proceeds exclusively *via* aziridinium ring expansion. The regiospecificity appears to be electronically controlled.

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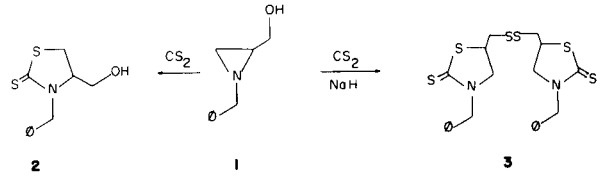
Our attempts to convert 1-phenylmethyl-2-hydroxymethylaziridine (**1**) to the corresponding xanthate under a variety of conditions resulted instead in the formation of high yields of thiazolidinethiones. Although similar ring expansions have been reported in the past at somewhat higher temperatures (1), we investigated these reactions because of the rather high regioselectivity observed as a function of reaction conditions.

Thus, refluxing **1** in a 1:1 mixture of tetrahydrofuran and carbon disulfide afforded after distillation an 89% yield of a 1:1 adduct identified as 4-hydroxymethyl-3-phenylmethyl-2-thiazolidinethione (**2**) on the basis of spectral data presented in the experimental. The hydroxymethyl substituent was assigned to the 4-position on the basis of the chemical shift observed for the substituted ring carbon in the ^{13}C nmr spectrum (δ 67.7).

When the reaction was run in the presence of excess sodium hydride the formation of **2** was not detected by nmr. Instead, when the reaction mixture was quenched with water and allowed to stand overnight in the presence of air, a solid precipitated (72%) which was identified as a 60:40 mixture of two diastereomers of 5,5'-dithiobis-(methylene)-bis-(3-phenylmethyl)-2-thiazolidinethione (**3**) (Scheme 1). The structure assignment was again based on spectral data presented in the experimental section. The methylene side chain was assigned to the 5-position on the basis of the chemical shift of the substituted ring carbon in the ^{13}C nmr spectrum (δ 41.86).

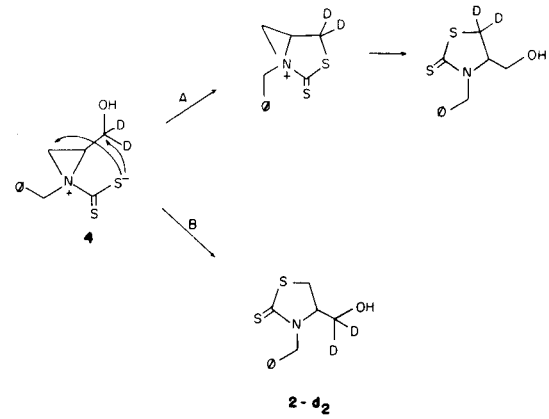
Scheme 1



2 **1** **3**

Two mechanisms for the formation of **2** were initially considered (Scheme 2). Both involved nucleophilic attack on carbon disulfide by the ring nitrogen to form a zwitterion (**4**) (2,3). This ion could then close on the exocyclic methylene (path A) to form a bicyclic ion which could be intercepted by water to form **2** (4). Alternatively, the zwitterion **4** could close on the aziridine ring at C_3 to form **2** directly (path B). It was noted that a clear distinction between these two paths could be made if the exocyclic methylene in **1** could be labeled. The labeled methylene would end up in the ring if path A were operative and would remain exocyclic if path B were involved. Deuterium was judged to be the label of choice for this experiment. Thus methyl 1-phenylmethyl-2-aziridinecarboxylate was reduced to the dideutero alcohol **1-d$_2$** with lithium aluminum deuteride. The nmr analysis indicated that all of the deuterium was attached to the exocyclic carbon. The reaction of this alcohol with carbon disulfide produced the thiazoldinethione **2-d$_2$** with all of the deuterium in the exocyclic position. The position of the deuterium in **2-d$_2$** was determined both by nmr and mass spectral analysis. This result effectively excludes path A from contention in the formation of **2**.

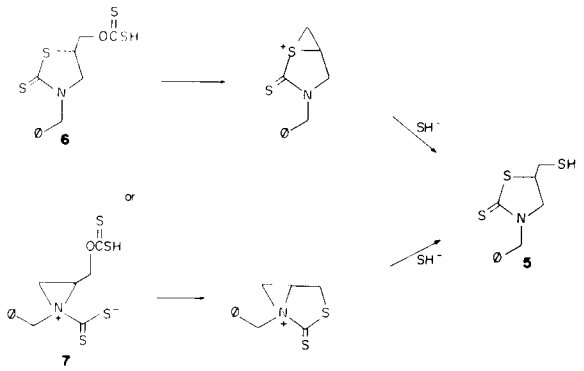
Scheme 2



4 **2-d$_2$**

The regiospecificity observed for the above reaction (*i.e.*, closure of the zwitterion occurring at C_3 only) is consistent with reports by Leonard and co-workers that the regiospecificity of ring opening of aziridinium ions is con-

Scheme 3



trolled by ion stability (5), *i.e.*, nucleophilic attack predominates at the ring carbon better able to accommodate positive charge. In this case that would be the ring carbon furthest removed from the inductively electron withdrawing hydroxy group. It is also in accord with the regiospecificity observed in reactions of alkyl substituted aziridines with carbon disulfide where steric effects may be the predominant factor (2,3).

Although the regiospecificity of the ring expansion forming **3** in the presence of sodium hydride is different, the mechanism of the reaction appears to be quite similar. When **1-d$_2$** was subjected to carbon disulfide in the presence of sodium hydride, the product, **3-d$_2$**, was shown by nmr and mass spectral analysis to have deuterium again exclusively in the exocyclic position. This suggests that if an ion such as **4** is involved, closure of the zwitterion is occurring at the more substituted position. Under the strongly basic conditions used this would likely be the position better able to accommodate partial positive charge in the aziridinium ion, *i.e.*, the position closer to the site of the anion. Thus, formation of the 5-substituted thisazolidinethione under basic conditions is also consistent with the expected electonic control of the regioselectivity of the ring opening of aziridinium ions. More perplexing is the transformation of the alcohol to the disulfide **3**. The disulfide is presumably formed by air oxidation of the thiol **5** which could be isolated in crude form but was unstable and thus not characterized. The formation of the thiol is less clear. Participation by the aziridine ring nitrogen to form an azabicyclobutonium ion (6-9) which could be intercepted by sulfide ion is not in accord with the deuterium labeling study. The azabicyclobutonium ion is symmetrical and would effectively scramble the position of the deuterium, a result not experimentally observed. Additionally, because neither benzyl alcohol nor 1-butanol can be converted to their corresponding thiols under these reaction conditions, it is unlikely that a simple Sn1 or Sn2 type reaction with either an alcohol or a xanthate before or after ring expansion accounts for the formation of **5**.

It may be speculated that participation by sulfur occurs from a 5-substituted thiazolidinethione (**6**) or that participation by sulfur occurs from a zwitterion such as **7** (Scheme 3). We have been unable to verify or exclude either of these explanations experimentally.

EXPERIMENTAL

The ir spectra were run on a Beckman IR-8 Infrared Spectrophotometer. The mass spectra were recorded on a Hitachi-Perkin Elmer Model RMU-6H Mass Spectrometer. The proton nmr spectra were recorded on a Perkin Elmer R 24A Spectrophotometer. The ^{13}C nmr spectra were recorded on a Varian FT 80 Spectrophotometer. All nmr spectra were measured in deuteriochloroform and are reported relative to tetramethylsilane. Melting points are uncorrected.

4-(Hydroxymethyl)-3-(phenylmethyl)-2-thiazolidinethione (**2**).

A solution of **1** (1.0 g, 6.0 mmoles) prepared by the procedure of Capellar *et al.* (9), in 55 ml of carbon disulfide was added dropwise to 55 ml of dry tetrahydrofuran and the resulting solution was refluxed for 6 hours. The solvents were evaporated *in vacuo* and the residual yellow oil was distilled (0.5 mm, 216-219°) to give 1.28 g **2** (89%); ir (liquid film): 3400, 3040 and 2950 cm^{-1}; ^{1}H nmr: δ 2.5 (s, 1), 2.9 (m, 2), 4.9 (d, 1) and 7.4 (s, 5); ^{13}C nmr: δ 30.0, 51.0, 60.5, 67.7, 127.9, 128.2, 129.0, 135.3 and 198.5; ms: m/e 239 (61), 208 (34), 192 (32), 148 (100) and 91 (27).

Anal. Calcd. for $C_{11}H_{13}NOS_2$: C, 55.20; H, 5.47; N, 5.85. Found: C, 55.66; H, 5.55; N, 5.92.

5,5'-Dithiobis-(methylene)-bis-(3-phenylmethyl)-2-thiazolidenethione (**3**).

A solution of **2** dissolved in 25 ml of carbon disulfide was added dropwise to a slurry of sodium hydride (288 mg, 3.0 mmoles) and 25 ml of dry tetrahydrofuran. The resulting mixture was refluxed overnight. Water (50 ml) was added and the resulting mixture was washed with ether. The aqueous layer was left standing overnight during which time a solid separated. This was isolated by filtration and recrystallized from alcohol affording 1.09 g (72%) of **3** mp 138.5-139°; ir (potassium bromide): 3040 and 2980 and 1490 cm^{-1}; ^{1}H nmr: δ 2.9 (m, 4), 3.9 (m, 6), 4.85 (d, 2), 5.25 (d, 2) and 7.4 (s, 10); ^{13}C nmr: δ 41.86, 42.11, 42.44, 42.66, 52.64, 59.05, 59.17, 128.3, 128.4, 129.1, 134.9 and 195.4; ms: m/e 508 (4), 287 (4), 255 (15), 208 (8), 148 (31) and 91 (100).

Anal. Calcd. for $C_{22}H_{24}N_2S_6$: C, 51.93; H, 4.76; N, 5.51. Found: C, 52.17; H, 4.84; N, 5.66.

1-Phenylmethyl-2-hydroxy-dideuteromethylaziridine (**1-d$_2$**).

A solution of 1-phenylmethyl-2-carbomethoxyaziridine (10) (4.8 g, 25 mmoles) in 100 ml ether was added dropwise to a slurry of lithium aluminum deuteride (1.4 g, 0.038 mole) in 100 ml ether. The resulting mixture was stirred overnight. The reaction was then quenched with 10 ml portions of water, 15% sodium hydroxide, and water respectively. Solids were removed by filtration and the filtrate was concentrated *in vacuo* to an oil which on distillation (112°, 1.0 mm) afforded 1.8 g (43%) of **1-d$_2$**, mp 65-70°; ^{1}H nmr: δ 1.35 (m, 1), 1.6 (m, 2), 3.2 (d, 1), 3.5 (d, 1) and 3.5 (broad s, exchanges with deuterium oxide, 1).

Anal. Calcd. for $C_{10}H_{11}D_2NO$: C, 72.69; N, 8.48. Found: C, 72.30; N, 8.31.

4-Hydroxydideuteromethyl-3-phenylmethyl-2-thiazolidinethione (**2-d$_2$**).

A solution of **1-d$_2$** (500 mg, 3.0 mmoles) in 25 ml carbon disulfide was added dropwise to 25 ml tetrahydrofuran and refluxed for 5 hours. The resulting solution was concentrated *in vacuo* to an oil which on kogelrohr distillation (223°, 0.7 mm) yielded 260 mg (36%) of **2-d$_2$**; ir (liquid film): 3400, 2220 and 2120 cm^{-1}; nmr: δ 2.5 (s, 1), 3.2 (m, 3), 4.9 (d, 1), 5.8 (d, 1) and 7.4 (s, 5); ms: m/e 241 (95), 208 (209), 148 (100) and 91 (100).

Anal. Calcd. for $C_{11}H_{11}D_2NOS_2$: C, 54.78; N, 5.80. Found: C, 55.00; N, 5.81.

5,5'-Dithiobis-(dideuteromethylene)-3-(phenylmethyl)-2-thiazolidinethione (**3-d$_2$**).

A solution of **1-d$_2$** (500 mg, 0.003 mole) in 25 ml of carbon disulfide was added dropwise to a slurry of sodium hydride (0.3 g, 3.0 mmoles) in 30 ml tetrahydrofuran. The mixture was stirred at reflux for 5 hours. Water was added and the resulting mixture was left exposed to the air overnight. The solids which precipitated were removed by filtration and recrystallized from ethanol affording 87.4 mg (18%) of **3-d$_2$**, mp 138-139°; ^{1}H nmr: δ 3.0 (m, 6), 5.0 (q, 4) and 7.4 (s, 10); ms: m/e 512 (5), 289 (6), 257 (25), 208 (10), 148 (40) and 91 (100).

Anal. Calcd. for $C_{22}H_{20}D_4N_2S_6$: C, 51.53; N, 5.46. Found: C, 51.54; N, 5.62.

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