Synthesis and Pyrolytic Behaviour of Chiral Thiazolidine 1,1-Dioxides

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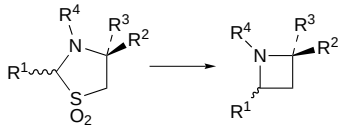
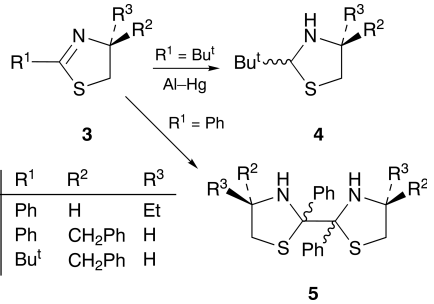
Five chiral thiazolidine 1,1-dioxides have been prepared and the pyrolytic behaviour of this class of compound has been examined for the first time.

In recent papers we have described the synthesis of chiral 4,5-dihydrothiazole 1,1-dioxides[1] and thiazolidin-2-one 1,1-dioxides[2] and their thermal behaviour upon flash vacuum pyrolysis (FVP). In a continuation of this study, it was of interest to examine the thermal decomposition of the thiazolidine 1,1-dioxides **1** which might be expected to produce chiral azetidines **2**. If this were successful, introduction of additional functionality by alkylation α- to the SO_2 group prior to pyrolysis could be envisaged, leading to versatile synthetic building blocks. We describe here the preparation of five thiazolidine 1,1-dioxides and their behaviour upon FVP.



1 **2**

We first considered preparing the required thiazolidines by reduction of the corresponding 4,5-dihydrothiazoles **3** which are readily available in enantiomerically pure form in a few steps from amino acids.[1] Use of Meyers' aluminium amalgam method,[3] which is effective for 4-unsubstituted thiazolidines, did produce the thiazolidine **4** in good yield but only for the 2-*tert*-butyl example **3c**. When this method was applied to the 2-phenyl compounds **3a,b** it resulted in reductive dimerisation to give the 2,2′-bi(thiazolidines) **5** in good to excellent yield. As far as we are aware, such reductive coupling of 4,5-dihydrothiazoles has not been observed before, although the corresponding reaction of 2-aryl-4,5-dihydrooxazolium salts using Zn–TMSCl or electrochemical reduction has been reported recently.[4] The stereochemistry of these reductions is of some interest. The thiazolidine **4** was obtained as a 75:25 mixture of diastereomers indicating a rather poor degree of stereocontrol at the newly formed centre. The situation with **5** is rather more complex since two new stereogenic centres are formed in addition to the two derived from **3**. Consideration of the symmetry of the four possible diastereomers of **5** gives a theoretical maximum of 36 ^{13}C NMR signals for **5a** and 48 for **5b**.

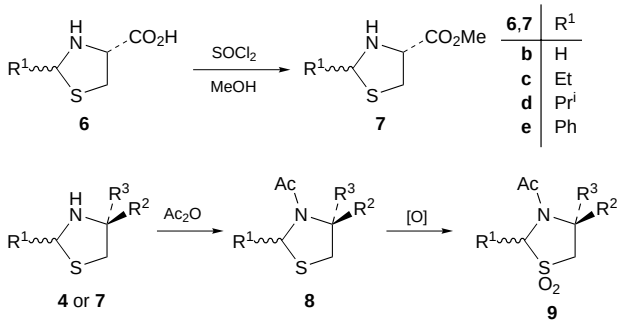


3 **4** **5**

3–5	R^1	R^2	R^3
a	Ph	H	Et
b	Ph	CH_2Ph	H
c	Bu^t	CH_2Ph	H

Although the complexity of the spectra in the aromatic CH region precluded full assignment, the appearance of sets of four approximately equal signals in each of the other regions including that for the atoms at the newly formed stereogenic centres (δ_C 90–95 ppm) clearly showed the coupling to have taken place without selectivity to give an almost equal mixture of all four possible diastereomers.

To obtain some further thiazolidines, we made use of the well known reaction of cysteine with aldehydes to obtain four examples of thiazolidines **6** and then converted these into the methyl esters **7**. In the cases **7c–e** where $R^1 \neq H$, these were obtained as approximately 2:1 mixtures of diastereomers at the newly formed stereocentre (Table 1). We have previously reviewed the oxidation of five-membered rings containing N and S,[7] and noted that almost all successful *S*-oxidations of thiazolidines have been on *N*-substituted examples while, in the absence of an *N*-substituent, ring-opened products are generally formed. The thiazolidines **4** and **7** were therefore *N*-acetylated using acetic anhydride to afford **8a–e**. For oxidation to the



6,7	R^1
b	H
c	Et
d	Pr^i
e	Ph

6 **7** **4 or 7** **8** **9**

1,1-dioxides **9** the use of potassium permanganate and benzoic acid under phase-transfer conditions[1] generally gave excellent results (Table 1). The sulfones **9** were all obtained as crystalline solids. In the case of **9c,d** the diastereomer ratio was preserved from **7** while significant enrichment occurred at the stage of the acetylation in the cases of **7a,e** to give **9a** in particular as essentially a single diastereomer. This phenomenon, which involves epimerisation at C-2 by means of a ring-opened intermediate, has been described in detail before by Györgydeák and co-workers.[8] The ^{33}S NMR spectrum of **9d** was readily obtained at natural abundance and showed a relatively sharp signal at δ_S 18.7 ($w_{1/2}$ 400 Hz) which is in the expected range for cyclic sulfones, although this is the first thiazolidine 1,1-dioxide to be observed. For both **8a** and **9a**, the NMR spectra were complex at room temperature owing to restricted rotation about the *N*-acetyl group and this was quantified by means of a variable temperature study of both the ^1H and ^{13}C NMR spectra over the range −40 to +50 °C. Calculations based on the observed coalescence temperatures for several signals for each compound gave average energy barriers to rotation of $\Delta G^{\ddagger}$ 61.7 kJ mol^{-1} for **8a** and 60.9 kJ mol^{-1} for **9a** and differences in energy between the two forms of ΔG 0.79 kJ mol^{-1} for **8a** and 0.39 kJ mol^{-1} for **9a**.

Although thermal extrusion of SO_2 from a wide variety of cyclic sulfones has been examined,[10] no example of a

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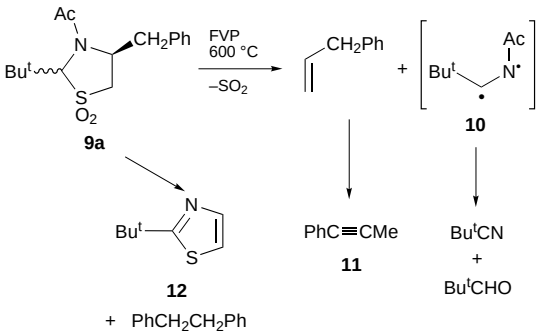
Table 1 Formation of thiazolidine 1,1-dioxides **9**

				4 or **7**		**8**		**9**	
	R^1	R^2	R^3	% Yield from **3** or **6**	d.r.	% Yield from **4** or **7**	d.r.	% Yield from **8**	d.r.
a	Bu^t	CH_2Ph	H	80	75:25	81	96:4	90	> 99:1
b	H	H	CO_2Me	79	–	96	–	50	–
c	Et	H	CO_2Me	58	67:33	89	63:37	90	66:34
d	Pr^i	H	CO_2Me	66	69:31	97	64:36	95	59:41
e	Ph	H	CO_2Me	39	62:38	*98	88:12	95	85:15

Table 3 Products from FVP of thiazolidine 1,1-dioxides **9** (%)

	T/ °C	$R^2R^3C{=}CH_2$	R^1CN	R^1CHO	AcOH	$AcNH_2$	MeOH
a	600	43	9	7	–	–	–[a]
b	700	22	–	–	11	11	11
c	600	17	–	–	47	–	33
d	700	28	–	–	60	0.5	30
e	700	47	18	17	73	–	41

[a]Additional products: **11** (5%), **12** (6%), $PhCH_2CH_2Ph$ (7%).



Scheme 2

thiazolidine 1,1-dioxide has apparently been studied before. The compounds **9a–e** were found to react under FVP conditions in the range 600–700 °C and the results are summarised in Table 3. For **9a** the major product was allylbenzene, indicating that loss of SO_2 has been accompanied by complete fragmentation of the ring. As shown in Scheme 2, this produces the diradical **10** which apparently fragments to give trimethylacetonitrile and, perhaps by hydrolysis of the corresponding imine upon isolation, trimethylacetaldehyde. No non-gaseous product derived from the *N*-acetyl group was isolated. The formation of 1-phenylpropyne **11** presumably involves a secondary dehydrogenation of the allylbenzene in an excited state, since the latter was recovered unchanged upon repyrolysis at the same temperature. The unexpected formation of 2-*tert*-butylthiazole **12** together with bibenzyl most likely results from loss of benzyl radical from **9a** followed by aromatisation with loss of the elements of acetaldehyde. For **9b–e** methyl acrylate was produced in each case together with methanol and acetic acid. Only for **9e** were benzonitrile and benzaldehyde produced, corresponding to the fragmentation of the diradical corresponding to **10** for **9a**. For **9b** and **e** only, acetamide was also obtained.

We have thus established that, although chiral thiazolidine 1,1-dioxides can be prepared in good yield, the conditions required to bring about extrusion of SO_2 are such that only alkenes and other products resulting from complete fragmentation of the ring are obtained.

Techniques used: ^1H, ^{13}C and ^{33}S NMR, IR, MS, GC–MS, flash vacuum pyrolysis

References: 16

Tables: 3 (yields, ^{13}C NMR data and pyrolysis products for thiazolidine dioxides)

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