Pergamon

Tetrahedron Letters, Vol. 37, No. 5, pp. 707-710, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02248-1

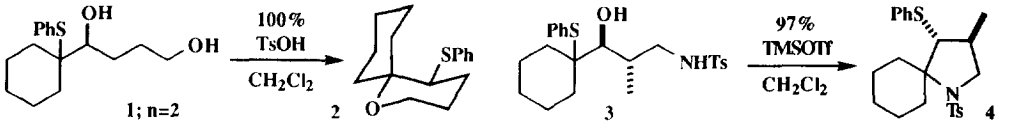
Synthesis of Cyclic Sulfides Using Phenylthio Migration

Jason Eames,[a] Ray V. H. Jones,[b] and Stuart Warren[a]*

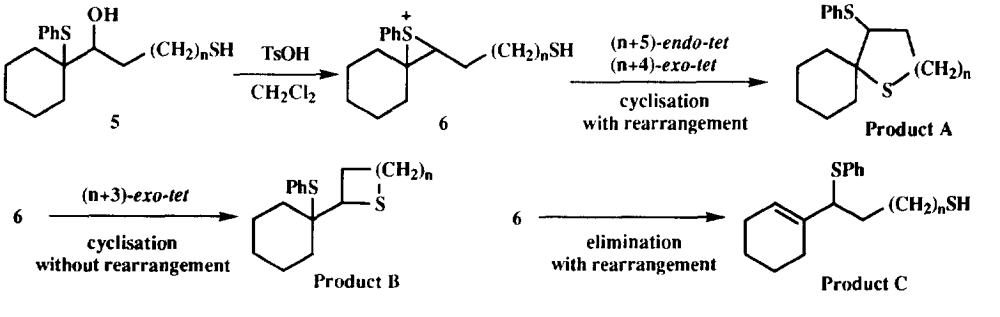
[a]University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW England
[b]Process Technology Department, ZENECA Grangemouth Works, Earls Road, Grangemouth FK3 8XG, Scotland

Abstract: New routes to cyclic and spirocyclic sulfides involve aldol reactions of dithioesters or chemoselective Mitsunobu reactions on diols to give 2-hydroxyalkyl sulfides with a terminal SH group. Treatment with acid gives cyclic sulfides, or by rearrangement with PhS migration, spirocyclic sulfides or allylic sulfides in good yield.

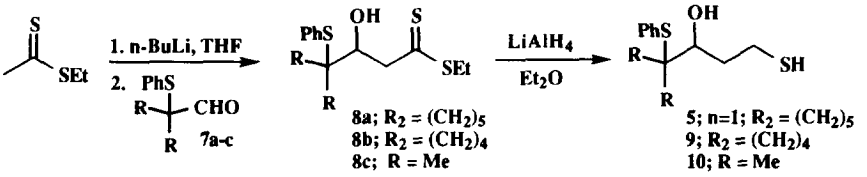
We have previously shown[1,2] that either oxygen or nitrogen atoms can capture an episulfonium ion with complete stereochemical control to form substitued lactones, cyclic ethers **2** and amines **3**. We now report an extension to this methodology: the capture of a episulfonium ion **6** by a second sulfur atom to give cyclic sulfides. We comment on the effects of different chain length (n in **6**) on the mode of cyclisation and on a surprising difference in the behaviour of OH and SH as nucleophiles towards episulfonium ions.



The three possible products from the rearrangement of thiol **5** are the spirocyclic sulfide of type **A** formed with PhS migration by the hybrid (n+5)-*endo*- and (n+4)-*exo-tet* cyclisation disfavoured by Baldwin's rules, the unrearranged cyclic sulfide of type **B** from the (n+3)-*exo-tet* cyclisation, and the allylic sulfide of type **C** formed by [1,2] PhS shift and elimination without cyclisation.[1-3]



We synthesised **5**; n=1 and two related thiols **9** and **10** by aldol reactions with dithioester enolates. Formation of the colourless lithium enolate[4] of yellow ethyl dithioacetate (Fluka 43795) by treatment with n-BuLi at –78 °C and reaction with aldehydes **7a-c** gave the corresponding yellow ethyl dithioesters **8a-c** in good yield (Table 1). The thiol **3**; n=1, and the related thiols **9** and **10** were prepared by reduction of the dithioesters **8a-c** with $LiAlH_4$ under carefully controlled conditions[5] to prevent reverse aldol reactions.



Rearrangement of these thiols with toluene-*p*-sulphonic acid (TsOH) or with TMSOTf both in CH_2Cl_2 gave the type **A** spirocyclic sulfides **11**, **12**, and **13** in near quantitative yield (Table 1) *via* the hybrid 5-*exo-tet*- and 6-*endo-tet*- cyclisation. The ^{1}H NMR spectra of these compounds include a double doublet for H^a with surprisingly dissimilar coupling constants (Table 3). In the mass spectra the only fragmentation observed is between the ring and PhS group. Acid catalysed rearrangement of the intermediate dithioester **8a** gave another type **A** product, the spirocyclic dithiolactone **15** in 85 % yield *via* **14**. Spirocyclic sulfides are not well known. One other 1-thiaspiro[4.4]nonane (like **12**) has been made by alkyl migration in a pinacol rearrangement[6] but that route gives the 1-thiaspiro[4.5] system (like **11**) in only low yield.

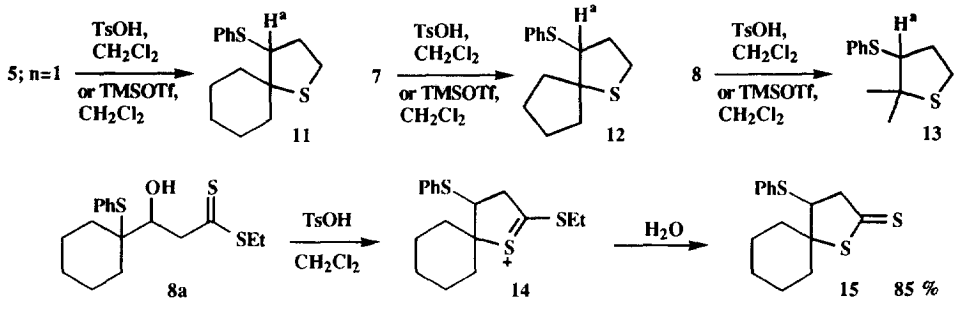
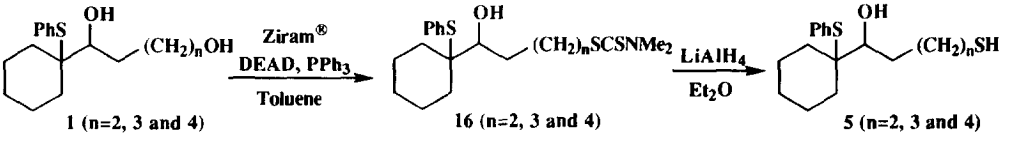


Table 1: Yields in the Synthesis and Rearrangement of the Thiols **5**; n=1, **9** and **10**.

	Reaction ⟶		aldol	$LiAlH_4$	TsOH	TMSOTf
Entry	aldehyde 7	R R	dithioesters	thiols	spirocyclic sulfides	
1	**7a**	—$(CH_2)_5$—	**8a** (93 %)	**5**; n=1 (99 %)	**11** (99 %)	(99 %)
2	**7b**	—$(CH_2)_4$—	**8b** (82 %)	**9** (83 %)	**12** (99 %)	(99 %)
3	**7c**	CH_3 CH_3	**8c** (78 %)	**10** (79 %)	**13** (98 %)	(99 %)

The longer chain thiols **5**; n=2, 3 and 4 were made from the diols[7] **1**; n=2, 3 and 4 by chemoselective Mitsunobu displacement[8] of the primary alcohol with Ziram® (zinc dimethyldithiocarbamate, Fluka 96480) to give the dithiocarbamates **16**; n=2, 3 and 4. Reduction ($LiAlH_4$) gave the thiols **5**; n=2, 3 and 4 and the results of the rearrangement of these thiols are presented in Table 2.



The thiol **5**; n=2 rearranged to the type **B** product, thiolane **17** (99%) exclusively, *via* a 5-*exo-tet* cyclisation. The ^{1}H NMR spectrum of **17** includes (Table 3) a triplet (J=6.9 Hz) for H^a which is typical for a

five-membered ring, as $J_{gem}=J_{syn}=J_{anti}$. Coupling constants in the spirocyclic thiolanes are not like this. In the mass spectrum, fragmentation between the ring and the $C_6H_{10}SPh$ group is observed (Table 3).

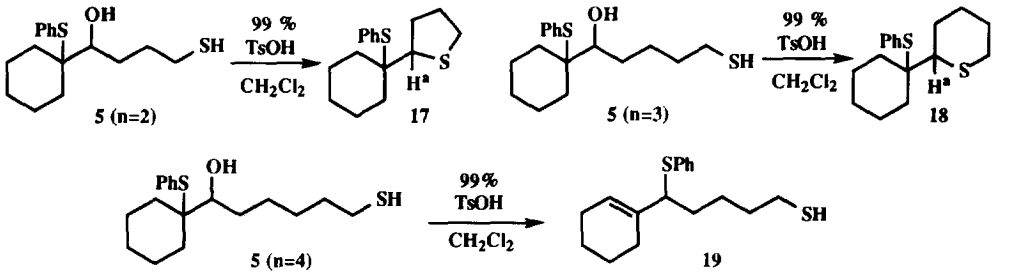


Table 2: Yields in the Synthesis and Rearrangement of the Thiols **5** ; n=2,3 and 4.

	Reaction⟶	Mitsunobu	$LiAlH_4$	TsOH	
Entry	Diols	dithiocarbamate	thiols	sulfides	
1	**1**; n=2	**16**; n=2 (85 %)	**5**; n=2 (76 %)	**17**	(99 %)
2	**1**; n=3	**16**; n=3 (83 %)	**5**; n=3 (75 %)	**18**	(99 %)
3	**1**; n=4	**16**; n=4 (90 %)	**5**; n=4 (69 %)	**19**	(98 %)

With **5**, n=3 the acid catalysed rearrangement gave the thiane **18** (99 %), again a type **B** product, *via* a 6-*exo*-*tet* cyclisation. The thiane **18** (Table 3), by contrast to both **11** and **17**, has a double doublet for H^a with axial/axial (12 Hz) and an axial/equatorial (2.7 Hz) coupling constants typical of a six-membered ring. In the mass spectrum, both fragments from cleavage between the ring and the $C_6H_{10}SPh$ group are observed. When the chain is longer **5** (n=3), the acid catalysed reaction forms only the type **C** product, the allylic sulphide **19** (98 %), as the alternative would have been the unfavourable thiepine.

Table 3: Identification of Thiolanes and Thiane by ^1H NMR and Mass Spectra

δ (ppm) or *J* (Hz)	Thiolanes				Thiane
or Mass Spectrum	**11**	**12**	**13**	**17**	**18**
δ H^a	3.33 (dd)	3.64 (dd)	3.4 (dd)	3.6 (t)	2.59 (dd)
J_{syn} H^a	5.4	5.2	5.7	6.9	2.7
J_{anti} H^a	10.8	8.3	11.6	6.9	12.0
191.1 ($PhSC_6H_{10}$)	0%	-	-	90%	100%
M - 191.5	0%	-	-	80%	60%
M - PhS	100%	100%	100%	100%	70%

The alternative products of type **C**, the allylic sulfides **21** (n=2, 3 and 4), were synthesised from the same starting materials **16** by reversing the order of the reduction and the rearrangement. Acid catalysed rearrangement of the dithiocarbamates **16**; n=2, 3 and 4 gave the allylic sulfides **20**; n=2, 3 and 4 by a simple [1,2] PhS shift without cyclisation (Table 4) . Participation by the C=S group would require a medium ring intermediate so it is not surprising that the dithiocarbamate cyclises less effectively than the dithioester in **8**. Consequently the dithiocarbamate functionality serves as a protection against cyclisation. Reduction of the allylic dithiocarbamate **20**; n=2, 3 and 4 gave the type **C** products **21**; n=2, 3, 4. Allylic sulfides of this type have potential in [2,3] sigmatropic rearrangements of the corresponding sulfoxides or sulfonium salts.[9]

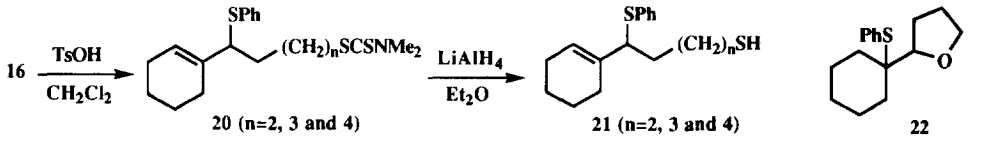


Table 4: Yields in the Synthesis of Allylic Sulfides **20**.

	Reaction ⟶	TsOH		$LiAlH_4$	
Entry	dithiocarbamate	allylic sulfides/ dithiocarbamates		allylic sulfides/ thiols **20**	
1	**16**; n=2	**20**; n=2	(95 %)	**21**; n=2	(82 %)
2	**16**; n=3	**20**; n=3	(97 %)	**21**; n=3	(76 %)
3	**16**; n=4	**20**; n=4	(96 %)	**21**; n=4	(69 %)

Most of the oxygen analogues of **5**, i.e. **1**, give similar heterocycles in acid. One example is quite different: the diol **1**; n=2 gave the tetrahydropyran **2** (100%) of type **A** by attack at the more substituted carbon atom of the episulfonium ion.[1] The type **B** tetrahydrofuran **22** can be prepared by other means[7] (TsCl/pyridine) and rearranges to the tetrahydropyran **2** under the conditions of acid catalysed rearrangement ($TsOH/CH_2Cl_2$). The oxygen heterocycle is the thermodynamic product. The less basic thiolane **17** does not rearrange into the thiane in acid and is the kinetic product. In the kinetically controlled cyclisation with SH as nucleophile, Baldwin's rules are more important, and 5-*exo-tet* cyclisation is preferred. Diol **1**; n=3 gave a mixture[7] of the type **B** (59%) and type **C** (13%) products while **5**; n =3 gave only the type **B** thiane.

In conclusion, the shortest chain thiols **5**; n=1 cyclise to the spirocyclic sulfides **11** of type **A**, intermediate chain lengths (n=2 and 3) give unrearranged type **B** heterocycles **17** and **18**, and the longest chains (n>4) give type **C** allylic sulfides **19**. Dithiocarbamates **16**; n=2 and 3 give allylic sulfides **21** without cyclisation. All the reactions go in near quantitative yield.

Acknowledgements: We thank EPSRC for a grant (to J. E.).

References and Notes

1. Sansbury, F. H.; Warren, S. *Tetrahedron Lett.*, **1991**, *28*, 3425-3428.
2. Coldham, I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1637-1656.
3. Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 451-460.
4. Meyers, A. I.; Walkup, R. D. *Tetrahedron*, **1985**, *41*, 5089-5106.
5. Procedure for the $LiAlH_4$ reduction of dithioesters **8a-c** to avoid retro-aldol reaction.—A solution of the dithiocarboxylic ester **8** (1 mmol) in ether was added dropwise to a solution of $LiAlH_4$ (3 mmol) in ether at 0 °C at a rate to cause immediate decolourisation of the dithioester. The solution was stirred for 1 hour and then poured onto ice. NaOH (3 molar, 2 cm^3) and saturated sodium potassium tartrate solutions (5 cm^3) were added. The solution was extracted with ether (3 x 10 cm^3). The combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography of the residue on silica eluting with light petroleum, b.p. 40-60 °C/ether (1:1) gave the product as an oil.
6. Paquette, L. A.; Dullweber, U.; Branan, B. M. *Heterocycles*, **1994**, *37*, 189-191.
7. Djakovitch, L.; Eames, J.; Jones, R. V. H.; McIntyre, S.; Warren, S. *Tetrahedron Lett.*, **1995**, *36*, 1723-1726.
8. Rollin, P. *Tetrahedron Lett.*, **1986**, *27*, 4169-4172; *Synth. Commun.*, **1986**, *16*, 611-616.
9. Hartley, R. C.; Warren, S.; Richards, I. C. *Tetrahedron Lett.*, **1992**, *33*, 8155-8158.

(*Received in UK* 30 *October* 1995; *revised* 23 *November* 1995; *accepted* 24 *November* 1995)