Synthesis and Some Reactions of 2-Acyl-2-alkyl-1,3-dithiolane 1,1-Dioxides

by **M. Teresa Barros**[b]), **António S. Henriques**[a]), **Alcino J. Leitão**[a])[c]), and **Christopher D. Maycock***[a])[d])

[a]) Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Rua da Quinta Grande 6, P-2780 Oeiras

[b]) Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, P-2825 Monte da Caparica

[c]) Faculdade de Farmácia, Universidade de Coimbra, R. do Norte, P-3000 Coimbra

[d]) Faculdade de Ciências, Universidade de Lisboa, R. Ernesto de Vasconcelos, P-1700 Lisboa

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The selective formation of optically active 2-acyl-2-alkyl-1,3-dithiolane 1,1-dioxides from the corresponding 2-acyl-2-alkyl-1,3-dithiolane 1-oxides, by reaction with OsO_4 and NMO in acetone, is reported. These compounds underwent stereoselective reactions at the carbonyl group of the acyl group with organometallic reagents. These reactions were completely regioselective, and no attack at either of the S-atoms was observed, unlike similar reactions with the corresponding sulfoxides. The nature of the metal atom had a direct effect upon the configuration of the product alcohols.

Introduction. – 2-Acyl-2-alkyl-1,3-dithiolane 1-oxides [1–3] and 2-acyl-2-alkyl-1,3-dithiane 1-oxides [4–8] have been used in asymmetric synthesis, particularly in additions to their C=O groups by organometallic reagents and hydrides. It has been shown that 2-acyl-1,3-dithiolanes and dithianes afford good diastereoselectivity in these organometallic addition [3][4], reductions [1][5][6], enolate alkylations [7], aminations [8], *Mannich* reactions [9], cycloadditions [10], aldol reactions [11], and conjugate additions [12].

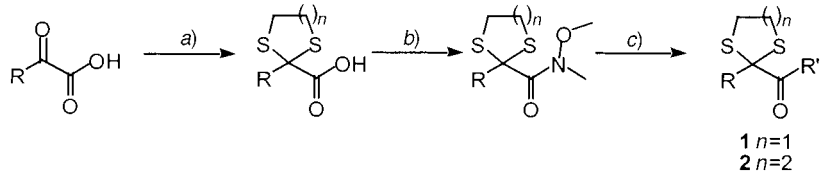
The main drawback to the use of dithiolane and dithiane monosulfoxides is their chemical instability towards nucleophiles and reducing agents, leading to moderate yields of the required product [3–6], and, in some cases, racemisation of the monosulfoxides due to acid-catalysed ring opening. Our main goal was to transform the chemically susceptable sulfoxides into the more stable sulfones through further selective oxidation of the sulfoxide, and to study the stereoselectivity of reactions of these compounds at the acyl C=O group.

Results and Discussion. – Previous reports of sulfur oxidations with OsO_4 include the direct oxidation of sulfides to sulfones [13], and a few reports of the dihydroxylation of olefins in the presence of sulfur. Using ferricyanide as the reoxidant afforded dihydroxylated products [14] and mixtures of various oxidised sulfur compounds [15]. Oxidation of cyclic dithioacetal sulfoxides with catalytic OsO_4 and ferricyanide did not afford significant quantities of the 1,1-dioxide, but the use of *N*-methylmorpholine *N*-oxide (NMO) as reoxidant resulted in the smooth formation of the corresponding sulfones. This difference of behaviour is difficult to explain since it is assumed that the

oxidation states of the Os during both processes is logically the same, both systems being used for the dihydroxylation of unsaturated systems. 2-Acyl-1,3-dithiolane 1,1-dioxides and 2-acyl-1,3-dithiane 1,1-dioxides were, thus, successfully obtained from the corresponding monosulfoxides, and have proven to be excellent substrates in reactions with organomagnesiums, organozincs, and hydrides, with almost total chemoselectivity.

2-Acyl-1,3-dithianes **2** are available by acylation of the dithiane anion, but the equivalent dithiolane anion is not stable. Symmetrical 2-acyl-1,3-dithiolanes (**1** R = R′) can be efficiently obtained from the corresponding 1,2-diketone [16]. Unsymmetrical 2-acyldithiolanes were obtained through the protection of α-keto acids with ethane-1,2-dithiol, followed by conversion to the *Weinreb* amide, and consequent reaction with an organolithium or organomagnesium reagent to afford the monodithioacetals of unsymmetrical diketones (*Scheme 1*).

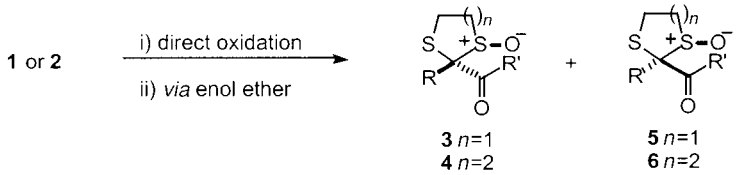
Scheme 1. *Approaches to Acyldithioacetals*



a) $(CH_2SH)_2$ (1 equiv.), $BF_3 \cdot OEt_2$ (2 equiv.), CH_2Cl_2. b) DCC (2 equiv.), MeNHOMe·HCl (2 equiv.), CH_2Cl_2. c) R′MX (1.2–2 equiv.), THF or Et_2O, −78 to 0°.

Optically active monosulfoxides were obtained by a method that gave high diastereo- and enantioselectivity [2]. This involved oxidation ((+)-DET/(i-PrO)$_4$Ti/TBHP 2:1:1.1, CH_2Cl_2, at −20°) of a (*Z*)-TBDMS-enol ether (TBDMS = (*t*-Bu)-Me_2Si) derived from the ketone (where enolization was possible), followed by hydrolysis of the TBDMS group with TBAF[1]). This afforded principally the *anti* (with respect to the acyl group) monosulfoxide with overall yields of *ca.* 70–80% and enantiomeric excesses (ee), in some cases, over 90% (*Scheme 2*, *Table 1*).

Scheme 2. Sharpless *Asymmetric Sulfoxidation*



For the synthesis of 2-acyl-1,3-dithiane 1-oxides, the addition of H_2O to the *Sharpless* reagent (*Orsay* protocol) [5][17] is reported to give good enantioselectivity, and this we have confirmed. However, supporting our previous results [1][2], we again

[1]) DET = Diethyl tartrate; TBHP = *tert*-butyl hydroperoxide; TBDMS = (*tert*-butyl)dimethylsilyl; TBAF = tetrabutylammoniumfluoride.

found that strictly anydrous conditions give the best results in the asymmetric oxidation of 2-acyl-1,3-dithiolanes and their enolates.

The *anti* 2-acyl-1,3-dithiolane 1-oxides **3** and **4** were converted to the corresponding sulfones **7** and **8**, respectively, in good-to-quantitative yields with OsO_4 (1–2 mol-%) and NMO (1.2 equiv.) as reoxidant [13] (*Scheme 3*). The *syn*-sulfoxides **5** and **6** similarly afforded the enantiomeric sulfones **9** and **10**, respectively.

An undesirable aspect of this oxidation was that optical purity was lost during the conversion, but this depended heavily upon the substrate used. On the other hand, it was observed that, during the oxidation of mixtures of *anti*- and *syn*-sulfoxides, the *anti*-sulfoxide was converted to sulfone much more rapidly than the *syn*-isomer. This constituted a useful method for the separation of these isomers and, hence, retention of the optical purity of the major isomer. This selectivity could be explained by coordination of the carbonyl O-atom with an OsO_4/NMO or NMM complex, which delivers the O-atom to the S-atom lone pair on the most-hindered side of the dithiolane ring, whereas the *syn*-sulfoxide could not undergo the same rapid intramolecular oxidation (*Scheme 4*). The sulfide S-atom was never oxidised in anything but trace quantities, and the tri- or tetraoxide were, thus, not isolated.

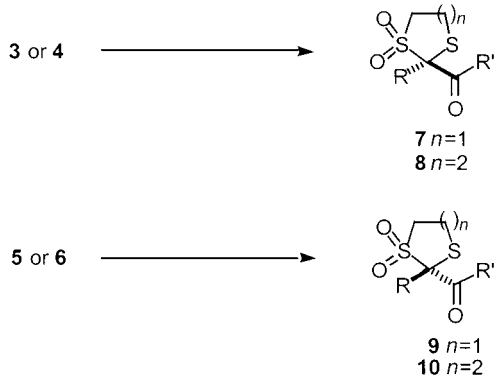
In *Table 1*, we present our results in the formation of these sulfones[2]) from the corresponding 2-acyl-2-alkyl-1,3-dithiolane 1-oxides, and also of the *tert*-butyl esters of 2-alkyl-1,3-dithiolane-2-carboxylic acids, formed *via* direct *Sharpless* asymmetric oxidation.

A side reaction was observed when this procedure was applied to sulfoxide **3** (R = Me, R′ = Bn), where, besides the normal sulfone, diketone **7** (R = Me, R′ = PhCO) was also produced through oxidation at the benzylic position. Sulfoxide **6** was also converted into the required sulfone in low yield, because dihydroxylation of the conjugated double bond occurred, even though NMO/OsO_4 is not the ideal system for this transformation [13][18]. For sulfoxides where the reaction times were much longer, the rate of oxidation was in competition with racemisation, resulting in a dramatic lowering of the ee. During the oxidation of sulfoxides where R = Ph, racemization was rapid probably due to the formation of a stable benzylic carbocation that accelerated the ring-opening racemization process. Sulfoxide **3** (R = R′ = Me) seemed to be more susceptible to racemisation even though the reaction time was shorter. Furthermore, changing the reoxidant to triethylamine *N*-oxide led to complete racemisation. We have no explanation for this behavior.

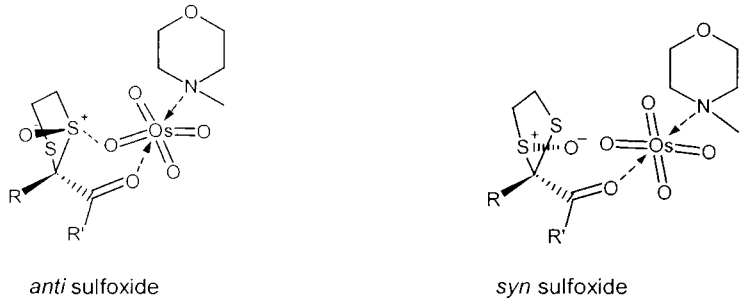
---

[2]) *Typical Procedure:* To a stirred soln. of (1*R*,2*R*)-*tert*-butyl 2-methyl-1,3-dithiolane-2-carboxylate 1-oxide (**3**, R = Me, R′ = *t*-BuO) (305 mg, 1.29 mmol) in acetone (20 ml) and 1.1 equiv. of NMO at room temperature was added 1 mol-% soln. of OsO_4 in MeCN. After 1 h, all starting material was consumed, and the reaction was stopped by adding a 5% soln. of $Na_2S_2O_3$ (20 ml) and stirring for another 0.5 h. The mixture was extracted three times with CH_2Cl_2 (20 ml), dried ($MgSO_4$), and, after evaporation of the solvent, the residue was purified by flash chromatography, affording white crystals of the desired (2*R*)-*tert*-butyl 2-methyl-1,3-dithiolane-2-carboxylate 1,1-dioxide (282 mg, 1.12 mmol, 87%). M.p. 106°. $[\alpha]_D^{20} = -97.42$ ($c = 1.63$, CH_2Cl_2). IR (ν_{max}, KBr): 1732, 1317. ^{1}H-NMR (300 Hz, $CDCl_3$): 1.53 (*s*, 9 H); 1.79 (*s*, 3 H); 3.12–3.20 (*m*, 1 H); 3.34–3.51 (*m*, 2 H); 3.69–3.78 (*m*, 1 H). ^{13}C-NMR (75 Hz, $CDCl_3$): 16.6; 21.9; 27.6; 50.3; 68.0; 84.6; 166.6. MS: 252.7. Anal. calc. for $C_9H_{16}O_4S_2$: C 42.84, H 6.39, S 25.41; found: C 42.93, H 6.36, S 25.56.

Scheme 3. *Oxidation of 2-Acyl-1,3-dithiolanes with OsO_4/NMO.* Reagents: OsO_4 (1–2 mol-%), NMO (1.2 equiv.), acetone.



Scheme 4. *Complexation Models for 2-Acyl-1,3-dithiolane 1-Oxides with OsO_4/NMM*



A difference in the reaction rates between the *anti*- and *syn*-sulfoxides is well-demonstrated in the conversion of *tert*-butyl-ester sulfoxides **3** and **5** (R = Me, Et, Ph; R′ = *t*-BuO) into sulfones. The *syn*-sulfoxides were converted more slowly into sulfones, with some loss of enantiomer purity and in lower yields.

The 2-acyl-2-alkyl-1,3-dithiolane 1,1-dioxides were then transformed into secondary and tertiary alcohols by addition of DIBAL-H and organometallic reagents, respectively (*Tables 2* and *3*, *Scheme 5*).

From *Table 2*, the excellent chemoselectivity of these new sulfones towards DIBAL-H is evident, affording the desired secondary alcohols with moderate-to-excellent diastereoselectivity. The use of complexing agents, such as $ZnCl_2$, prior to the addition of DIBAL-H gave generally poor diastereoselectivity.

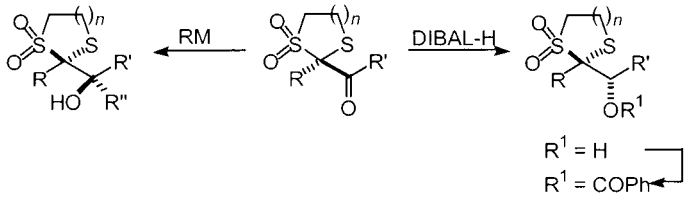
Addition of organometallics to the acyl sulfones (*Table 3*) was also accomplished in good-to-excellent yields. Addition of MeMgI gave good yields and diastereoselectivity, while EtMgI gave some secondary alcohol due to the hydride originating from the organometallic reagent. Homoallylic alcohols were obtained in excellent yields and with good-to-total diastereoselectivity by using allylmetal halides. Allylzinc bromide

Table 1. *Formation of the Sulfones* **7**–**10** via Sharpless *Oxidation*

Sulfoxide			*n*	Initial ee	*t*	Yield	ee	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)
	R	R′		[%]		[%]	[%]	
3	Me	Me	1	92	20 min	94	60	−41.13 (1.94)
4	Me	Me	2	73	5 h	89	71[a])	+82.65 (1.06)
3	Me	Bu	1	89	20 min	75	85	−53.66 (1.03)
3	Me	Ph	1	81	1.5 h	94	72[a])	−22.07 (0.82)
3	Me	Bn	1	75	1 h	21[b])	[c])	−34.69 (0.64)
3	Me	(*E*)-prop-1-enyl	1	[c])	1 h	38	[c])	−67.00 (0.10)
3	Me	Et	1	81	0.5 h	84	71[a])	−47.39 (1.94)
3	Et	Me	1	86	1 d	91	2[a])	−1.20 (3.26)
3	Et	Bu	1	86	4 h	79	79	−24.49 (1.03)
3	Ph	Me	1	[d])	1 d	85	1[a])	+0.63 (0.96)
3	Me	*t*-BuO	1	95	1 h	87	94	−97.42 (1.63)
5	Me	*t*-BuO[e])	1	63	2 d	30[f])	63	+66.36 (0.33)
3	Et	*t*-BuO	1	*ca.* 99	1 d	97	88	−60.50 (1.63)
5	Et	*t*-BuO[e])	1	93	5 d	39	88	+60.84 (1.08)
5	Ph	*t*-BuO[e])	1	97	5 d	43[g])	6	+5.57 (1.55)

[a]) Determined by HPLC analysis of the corresponding benzoate of the secondary alcohol produced by reduction with DIBAL-H. [b]) Together with 15% of diketone **3** (R = Me, R′ = PhCO) and 16% of starting material. [c]) Compound not eluted from HPLC column. [d]) Nonseparable mixture of enantiomers. [e]) *syn*-Sulfoxide. [f]) 8% of starting material recovered. [g]) 37% of starting material recovered with 96% ee.

Scheme 5



seemed to be the reagent of choice, when compared with the corresponding organomagnesium reagent, affording higher diastereoselectivities and, in some cases, the diastereoisomer opposite to that obtained with the corresponding organomagnesium (*Table 3*).

Optically active sulfones were obtained in high yields from optically active *anti*-sulfoxides with some loss of optical purity, depending upon the substitution, in most cases. *syn*-Sulfoxides were transformed into sulfones but with much longer reaction times and dramatic loss of optical purity. Coordination between the C=O group and the OsO_4 could explain the different rates of reaction of the much less-hindered *syn*-sulfoxide in comparison with the *anti*-isomer. Acyl sulfones reacted with a series of reducing agents and nucleophiles without the problems of chemoselectivity observed with the corresponding sulfoxides, providing a method for the synthesis of secondary and tertiary alcohols.

Table 2. *Conversion of Sulfones* **7** *and* **8** *to Secondary Alcohols by Addition of DIBAL-H*

Sulfone			*n*	Yield of alcohol [%]	dr	Yield of benzoate [%]
	R	R′				
7	Me	Me	1	92	3.1 : 1	93
	Me	Me	1	84	1.6 : 1[a])	–
8	Me	Me	2	91	1 : 0	91
	Me	Me	2	92	1 : 1[a])	–
7	Me	Bu	1	90	1 : 4.8	88
	Me	Bu	1	98	6.7 : 1[a])	62
7	Me	Ph	1	98	1 : 0	9
	Me	Ph	1	78	1.1 : 1[a])	78
7	Me	Et	1	95	8.2 : 1	77
	Me	Et	1	99	1 : 1[a])	36[b])
7	Ph	Me	1	93	1.5 : 1	96
	Ph	Me	1	99	1 : 1.5[a])	74
7	Et	Me	1	64	1 : 6	94

[a]) In the presence of 2 equiv. of $ZnCl_2$. [b]) One of the diastereoisomers did not react totally with PhCOCl

Table 3. *Conversion of Sulfones* **7** *and* **8** *to Tertiary Alcohols by Addition of Organometallic Reagents*

Sulfone			*n*	R″MX	Yield of alcohol [%]	dr[a])
	R	R′				
7	Me	Me	1	(allyl)ZnBr	96	14 : 1
8	Me	Me	2	(allyl)MgBr	95[b])	1.1 : 1
	Me	Me	2	(allyl)ZnBr	84	1 : 4.1[c])
7	Me	Bu	1	MeMgI	78	1 : 0
	Me	Bu	1	(allyl)MgBr	84[b])	1.4 : 1
	Me	Bu	1	(allyl)ZnBr	91	1 : 0
7	Me	Ph	1	EtMgI	65[d])	1.3 : 1
	Me	Ph	1	MeMgI	50[e])	15 : 1
	Me	Ph	1	(allyl)ZnBr	98	6 : 1
7	Me	Et	1	MeMgI	76	10 : 1
	Me	Et	1	(allyl)ZnBr	94	1 : 0
7	Et	Me	1	(allyl)MgBr	75[b])	2.3 : 1
	Et	Me	1	(allyl)ZnBr	75	1 : 20[c])

[a]) Determined by NMR. [b]) Addition at 0°. [c]) In these cases, the major isomer has the opposite diastereoselectivity to that obtained with the corresponding Mg reagent. [d]) Formation of secondary alcohol. [e]) 15% of the starting material recovered.

We thank the *Fundação para a Ciência e Tecnologia* for financial support and a grant to *A. S. H.*

REFERENCES

[1] M. T. Barros, A. J. Leitão, C. D. Maycock, *Tetrahedron Lett.* **1995**, *36*, 6537.
[2] M. T. Barros, A. J. Leitão, C. D. Maycock, *Tetrahedron Lett.* **1997**, *38*, 5047.
[3] A. J. Leitão, unpublished results.
[4] P. C. B. Page, D. Westwood, J. C. Prodger, *Tetrahedron* **1993**, *49*, 10355.
[5] P. C. B. Page, M. Purdle, D. Lathbury, *Tetrahedron Lett.* **1996**, *37*, 8929.
[6] P. C. B. Page, J. C. Prodger, *Synlett* **1990**, 460.

[7] P. C. B. Page, M. J. McKenzie, S. M. Allin, S. S. Klair, *Tetrahedron* **1997**, *53*, 13149.
[8] P. C. B. Page, S. M. Allin, E. W. Collington, R. A. Carr, *Tetrahedron Lett.* **1994**, *35*, 2427.
[9] P. C. B. Page, S. M. Allin, E. W. Collington, R. A. Carr, *J. Org. Chem.* **1993**, *58*, 6902.
[10] P. C. B. Page, J. C. Prodger, *Synlett* **1991**, 84.
[11] J. L. G. Ruano, D. Barros, M. C. Maestro, A. M. Z. Slawin, P. C. B. Page, *J. Org. Chem.* **2000**, *65*, 6027.
[12] P. C. B. Page, J. C. Prodger, M. Hursthouse, M. Mazid, *J. Chem. Soc., Perkin Trans. 1* **1990**, 167.
[13] S. Kaldor, M. Hammond, *Tetrahedron Lett.* **1991**, *32*, 5043.
[14] P. J. Walsh, P. T. Ho, S. B. King, K. B. Sharpless, *Tetrahedron Lett.* **1994**, *35*, 5129.
[15] T. Sammakia, T. B. Hurley, D. M. Sammond, R. S. Smith, S. B. Sobolov, T. R. Oeschger, *Tetrahedron Lett.* **1996**, *37*, 4427.
[16] C. A. Afonso, M. T. Barros, L. S. Godinho, C. D. Maycock, *Synthesis* **1991**, 575.
[17] P. C. B. Page, R. D. Wilkes, E. S. Namwindwa, M. Witty, *Tetrahedron* **1995**, *51*, 2125.
[18] P. C. B. Page, M. J. McKenzie, D. R. Buckle, *Tetrahedron* **1998**, *54*, 14581.

Received August 6, 2002