Pergamon

Tetrahedron Letters, Vol. 38, No. 28, pp. 5047-5050, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01101-5

Enhanced Diastereo and Enantioselectivity in the Formation of Acyldithiolane Sulphoxides by the Asymmetric Oxidation of their Enolsilyl Ethers.

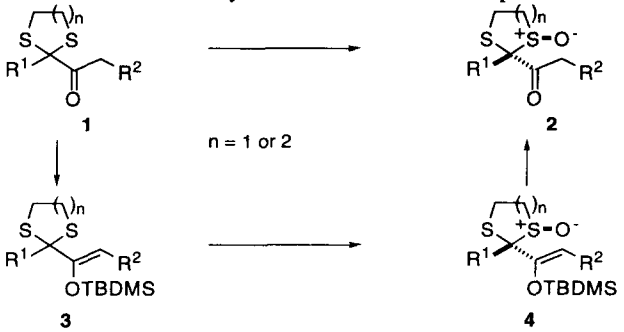
M. Teresa Barros[a,b], Alcino J. Leitão[b] and Christopher D. Maycock[b,c*]

[a]Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química, 2825 Monte da Caparica.
[b]Instituto de Tecnologia Química e Biológica, Rua da Quinta Grande 6, Apartado 127, 2780 Oeiras,
[c]Faculdade de Ciências da Universidade de Lisboa, Departamento de Química, Rua Ernesto de Vasconcelos, 1700 Lisboa, PORTUGAL.

Abstract: The sulphoxidation of the enol ethers of some acyldithiolanes using the Sharpless epoxidation reagents followed by fluorolysis results in better overall stereoselectivity than direct oxidation of the acyldithiolane thus providing a highly stereoselective route to acyldithiolane sulphoxides. Fluorolysis under acid conditions of non terminal enol ethers results in complete racemisation of the product. © 1997 Published by Elsevier Science Ltd.

2-Acyl dithioacetals **1** have been shown to be some of the best substrates for the enantioselective formation of their monosulfoxides by direct oxidation using variations of the Sharpless epoxidation reagent.[1,2] The use of the sulphoxides of acylated cyclic dithioacetals **1** in stereoselective synthesis[3] has been demonstrated by various groups. The acyl group of these compounds provides a useful functionality for further elaboration. For example, they undergo diastereoselective reduction at the carbonyl[2,4] such that removal of the dithioacetal group furnishes α-hydroxyketones or other alcohols of high optical purity.

Some of the advantages of the use of anhydrous conditions, or not, during the oxidation process have been discussed[5] and we have found[2] that for acyldithianes rigorously anhydrous conditions give marginally better diastereo and enantioselectivities. For acyldithiolanes this is not so clear cut[2] but the rigorous exclusion of moisture is necessary for the obtention of consistently good diastereo- and enantioselectivities. Even then, enantiomeric excesses of the order of 80-90% are the best obtainable in most cases (table 1). The diastereoselectivity and to some extent the enantioselectivity of the oxidation of acyl dithiolanes, using the above mentioned reagents, is dependent to a large degree upon the substituents present. Thus greater differences in size between the groups linked to the 2-position of the cyclic dithioacetal seemed to increase diastereoselectivity. Diastereoselectivity in these molecules is produced by preferencial attack to one side of the dithioacetal ring (the enantiomers are formed by attack at one of the two sulphur atoms from the same side).

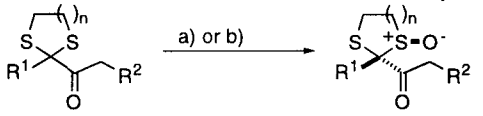


1 **2** **3** **4**

Scheme 1

The separation of mixtures of stereoisomers of **2** is not always easily carried out since crystallisation or chromatography is not applicable in many cases. The most efficient way of forming stereochemically homogeneous products was to increase the stereoselectivity of the oxidation process. We considered that an increase in the size of the group on the acyl side of the ring should at least increase the diastereoselectivity of the oxidation. A relatively easy way of doing this, in a reversible manner, was to produce an enolsilyl ether **3**. This would retain a π-system at the α-carbon and would also introduce a reactive handle into the molecule from which we hoped to elaborate more sophisticated systems using Mukaiyama technology. We knew at this stage that the formation of enolsilyl ethers from the preformed dithiolane sulphoxide was not possible. It has been shown that the oxidation of saturated alkyl substituted dithiolanes[6] does not give good enantioselectivities and we wondered if the C-C double bond of the silyl enol ether would induce the same degree of selectivity as a carbonyl group.

Table 1 Comparison of Stereoselectivities for the Two Routes to Acyldithiolane Sulphoxides.

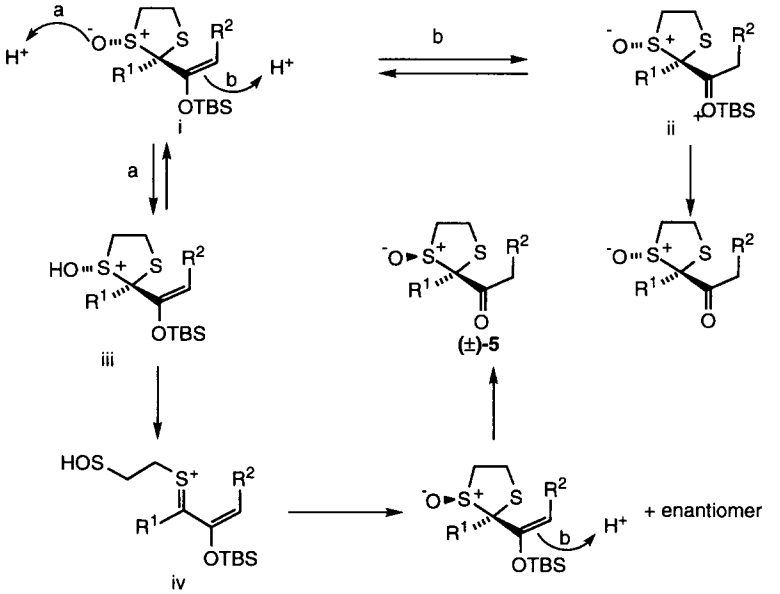


Reagent/Product			Direct Oxidation			Oxidation via the silyl enol ether		
R^1	R^2	n	Yield %	d.r.	e.e. %[a]	Yield %[b]	d.r.	e.e. %[c]
Me	H	1	85	8:1	80	80	1:0	98
Me	Me	1	80	>25:1	84	62	1:0	90
Me	Et	1	88	1:0	86	74	1:0	88
Et	H	1	75	2:1	73	64	1:0	92
Et	Me	1	62	-	-	72	20:1	90
Pr	H	1	80	2.5:1	-	77	1:0	99
Ph	H	1	72	1:1	-	74	2:1	-
Me	H	2	92	1.6:1	86	73	20:1	85
Et	Me	2	66	10:1	84	53	3.2:1	20[d]

[a] Data is missing where peak overlap made accurate determinations impossible. [b] Overall yield for steps i), ii) and iii). [c]Determined on the ketone. [d]enantiomer of direct oxidation product.
a) (+)-DET/TBHP/$Ti(OiPr)_4$ (2:1.5:1 respectively), -20°C, 3d. b) i) TBDMSOTf/Et_3N,
ii) (+)-DET/TBHP/$Ti(OiPr)_4$ (2:1.5:1 respectively), -20°C, 3d. iii) TBAF/H_2O. The rate of oxidation of the enol ethers was higher than that for the corresponding ketone. Reaction times were not optimised

A series of enolsilyl ethers **3** was produced in good yield by the reaction of acyldithiolanes with TBDMS triflate (TBDMSOTf) in the presence of triethylamine. Analysis of spectroscopic data indicated that, where possible, only one of the two geometric isomers was formed and that these enol ethers probably had the *Z*-configuration. These were submitted to anhydrous Sharpless oxidation to produce good yields of monosulphoxides **4** (see table 1) contaminated with very little overoxidation products. Analysis of the isomer

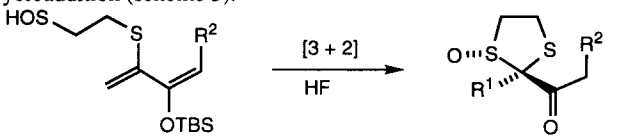
content of the products was carried out using 300MHz ^{1}H NMR and chiral HPLC using a Chiralcel® OD-H column. The results are shown in table 1 where they are compared with those from the direct oxidation of the corresponding ketone. Although the overall yields for the three step process via the enol ether is lower than for the direct method, the diastereoselectivity and enantioselectivity is greatly improved in all of the dithiolane (n=1) cases studied. This technique was not generally applicable to the dithianes (n=2) for reasons we do not yet understand.



Scheme 2

Hydrolysis of the enolsilyl ethers **4** to the corresponding ketone using an aqueous HF/acetonitrile solution of the sulphoxides, produced a result which was at the time unexpected. When the enol ether was derived from an acetyl group **4** (R^2=H), that is the double bond was terminal, the product was the expected one and that is the sulphoxide **2** (R^2=H). Its optical activity reflected its previously determined e.e. Similar hydrolysis of a non-terminal double bond enol silyl ether **4** ($R^2 \neq H$) produced almost exclusively the diastereoisomer of the expected product which was devoid of any optical activity. Thus a reaction had occurred in which the molecule had been isomerised presumably to give the most stable sulphoxide. Simultaneous racemisation can only be explained by the cleavage and reformation of an acetal C-S bond and since it had also occurred at the sulphoxide we assume that the C-S(O) bond had been broken[7] to form a symmetric species. The five membered ring was subsequently reformed. The racemisation process (scheme 2) is probably initiated by protonation of the sulphoxide oxygen (iii) followed by ring opening to form the symmetric intermediate sulphonium species (iv), having a sulphenic acid appendage. Recyclisation in a diastereoselective manner affords the observed product. Why does this not occur with the terminal enol silyl ether? It also does not occur when any of the ketones is treated under the same conditions with HF. Thus we conclude that the terminal compound (i, R^2=H) is C-protonated and hydrolysed very rapidly to give the ketone which is then completely stable under the reaction conditions. The non-terminal compounds must undergo hydrolysis much more slowly and complete racemisation occurs in the meantime via the ring opening mechanism.

The formation of a sulphonium adjacent to a carbonyl group or in species (ii) would not be expected as would the formation of a species derived from the protonation of the enol system of (iv). Recyclisation appears to be occurring on intermediate (iv) since the alternative (v) should reform the original diastereoisomer by an intramolecular [3 + 2] cycloaddition (scheme 3).

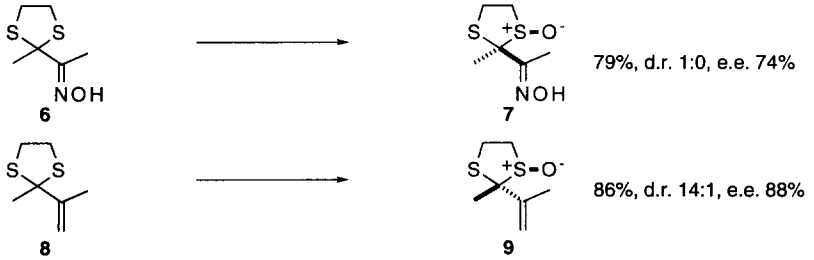


v

Scheme 3

Fluorolysis using aqueous TBAF afforded the desired products in all cases with no isomerisation as verified by nmr and HPLC. Thus we had a useful method for the regeneration of the carbonyl group from the enolsilyl ether. The HF fluorolysis provided us with selective methods for the synthesis of both diastereoisomers of some of these compounds, albeit in racemic form.

We have also studied the asymmetric oxidation of two other dithiolanes containing π-systems. For example the oxime **6** was subjected to the oxidation process and a good yield of monosulphoxide **7** was afforded with high stereoselectivity. The stereochemistry of the product was determined by an independent synthesis from the known sulphoxide **2** (R^1=Me, R^2=H). The olefine **8** was also subjected to asymmetric sulphoxidation. Good diastereo- and enantioselectivity was achieved.



We are able to produce acyl dithiolanes with high stereoselectivity via oxidation of the enol silyl ether. Other substituted dithiolanes having π-systems are also substrates for this oxidation process. Our studies are continuing with similar systems in an attempt to create molecules with possible anti HIV activity.

References.

1. Page, P.C.B.; Namwindwa, E.S.; Klair, S.S.; Westwood, D. *Synlett*, **1990**, 457.
2. Barros, M.T.; Leitão, A.J.; Maycock, C.D. *Tetrahedron Letters*, **1995**, *36*, 6537. Traces of water can cause dramatic lowering of the diastereo- and enantioselectivities. See also reference 3.b).
3. a)Page, P.C.B.; Allihn, S.M.; Collingwood, E.W.; Carr, R.A.E. *Tetrahedron Letters*, **1994**, *35*, 2607. and references therein. b) Aggarwal, V.K.; Evans, G.; Moya, E.; Dowden, J. *J. Org. Chem.*, **1992**, *57*, 6390. The formation of the *trans*-dioxides of acyl dithiolanes is best carried out by periodate oxidation of the monosulphoxide and is completely diastereoselective.
4. Page, P.C.B.; Prodger, J.C. *Synlett*, **1990**, 460.
5. Page, P.C.B.; Purdle, M.; Lathbury, D. *Tetrahedron Letters*, **1996**, *37*, 8929.
6. Di Furia, F.; Licini, G.; Modena, G. *Gazz. Chim. Italiana*, **1990**, *120*, 165.
7. For a related reaction see, Chen, C.H.; Donatelli, B.A. *J. Org. Chem.*, **1976**, *41*, 3053.

(*Received in UK* 24 *March* 1997; *revised* 4 *June* 1997; *accepted* 6 *June* 1997)