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Diastereoselective Oxidation of Substituted 1,2-Dithiolan-3-ones

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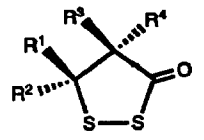
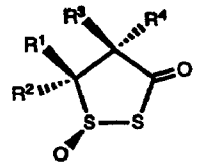
Abstract: Oxidation of 1,2-dithiolan-3-ones **1** with one equivalent of dimethyldioxirane in dichloromethane at -78°C produces the corresponding 1,2-dithiolan-3-one 1-oxides **2** in high yield and with diastereoselectivities as high as 18:1. The major diastereomer formed is the trans isomer. An X-ray crystallographic structure study of the major diastereomer **2c** obtained by oxidation of **1g** is reported.

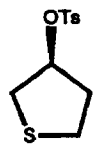
Although substituted 1,2-dithiolan-3-one 1-oxide[1] **2** and 1,2-oxathiolan-5-one 2-oxides[2] are known, they have been little studied. However, there is renewed interest in 1,2-dithiolan-3-one 1-oxides because the recently isolated potent antitumor antibiotic leinamycin[3] not only contains this moiety but it is essential for its activity.[4] Synthetic studies[5] as well as a total synthesis[6] of leinamycin have been reported. Oxidation of substituted 1,2-dithiolan-3-ones **1** with MCPBA or dimethyldioxirane is known[5] to afford the corresponding 1,2-dithiolan-3-one 1-oxides **2** as a mixture of diastereomers with little or no stereoselectivity. This paper reports diastereoselective oxidation of substituted 1,2-dithiolan-3-ones with up to 18:1 diastereoselectivity.



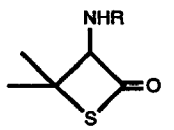
1 a, R^1 = Me, R^2 = R^3 = R^4 = H
b, R^1 = R^2 = Me, R^3 = NHAc, R^4 = H
c, R^1 = R^2 = Me, R^3 = NHCbz, R^4 = H
d, R^1 = R^2 = Me, R^3 = NHBz, R^4 = H
e, R^1 = R^2 = Me, R^4 = H
R^3 = $NHCOC_6H_3$-3,5-$(NO_2)_2$
f, R^1 = R^2 = Me, R^3 = NHTs, R^4 = H
g, R^1 = R^2 = Me, R^4 = H
R^3 = $NHSO_2C_6H_4$-*p*-Br
h, R^1 = R^2 = Me, R^3 = $NH_3^+Br^-$, R^4 = H



2 a, R^1 = Me, R^2 = R^3 = R^4 = H
b, R^2 = Me, R^1 = R^2 = R^4 = H
c, R^1 = R^2 = Me, R^3 = H
R^4 = $NHSO_2C_6H_4$-*p*-Br



3



4 a, R = Cbz
b, R = Ac
c, R = Bz

Oxidation of the known[7] 5-methyl-1,2-dithiolan-3-one **1a** with one equivalent of dimethyldioxirane[8] in dichloromethane at -78°C gave the corresponding 1-oxide as a 2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopic analysis. Chromatography on silica gel led to preferential decomposition of the minor diastereomer leading to material enriched in the major isomer. The stereochemistry of these diastereomers was determined by Eu(fod)$_3$ induced shifts and aromatic solvent induced shifts in the ^{1}H NMR spectra of these isomers. Thus the change in the chemical shift with added Eu(fod)$_3$ of H(5) was greater than that for the methyl group in the major diastereomer and this was reversed for the minor diastereomer. Consequently, the major diastereomer is trans **2b** and the minor diastereomer is cis **2a**. Analysis of the aromatic solvent induced shifts further supported this conclusion.

Oxidation of the known[5b] 1,2-dithiolan-3-one **1b** derived from N-acetylpenicillamine with one equivalent of dimethyldioxirane in dichloromethane at 0°C afforded the corresponding 1-oxide as a 1.6:1

mixture of diastereomers. However, such oxidation at -78°C yielded the corresponding 1-oxide as an 8:1 mixture of diastereomers. Recrystallization of this mixture from $CHCl_3$- hexanes produced the pure major diastereomer in 53% yield. Encouraged by the diastereoselectivity of the reaction at low temperatures such oxidation of analogues of **1b**, in which the acetyl group was replaced by other groups with the aim of increasing the diastereoselectivity of the reaction, was studied. These compounds were synthesized as follows. Known β-thiolactone **4a**[9] was converted to 1,2-dithiolan-3-one **1c** adopting the procedure used for transforming **4b** into **1b**.[7,10] The Cbz group was cleaved with HBr in acetic acid, following the procedure used for cleaving the Cbz group in **4a**,[9] to yield ammonium salt **1h**. Treatment of ammonium salt **1h** with the appropriate acyl or sulfonyl chloride in pyridine afforded 1,2-dithiolan-3-ones **1d-g**. The known[11] benzamido derivative **1d** prepared in this way was identical with that prepared from β-thiolactone **4c** using the procedure reported[7,10] for converting **4b** into **1b**. All of the oxidations gave the corresponding 1-oxides in high yield with the ratio of diastereomers determined by ^1H NMR spectroscopy in parenthesis: **1c** (8:1), **1d** (2:1), **1e** (5:1), **1f** (15:1), **1g** (18:1). Comparison of the chemical shifts of the major and minor isomers of each diastereomeric mixture suggests that the major diastereomer has the same stereochemistry in each case. The structure of the major diastereomer obtained by oxidation of **1g** was unequivocally shown to be trans **2c** by X-ray crystallographic analysis.[12] An ORTEP drawing of this diastereomer is shown in Figure 1. Steric effects apparently mediate these diastereoselective oxidations. It should be noted that highly diastereoselective oxidation of thiolane **3** to the trans S-oxide was achieved with potassium peroxymonosulfate.[13] Although the dimethyldioxirane used in the experiments reported above was obtained from the reaction of potassium peroxymonosulfate with acetone, dimethyldioxirane *not* potassium peroxymonosulfate was the oxidizing agent because distilled reagent was used.

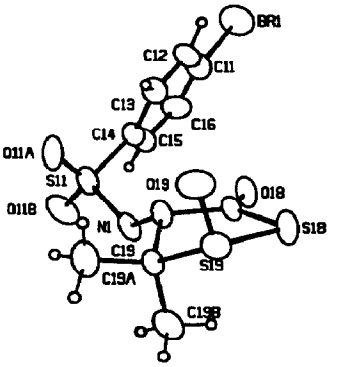


Fig. 1 ORTEP Drawing of **2c**

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