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Direct conversion of *tert*-butyl 2-hydroxyalkyl sulfides to 1,3-oxathiolanes

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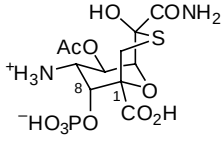
Abstract—*tert*-Butyl 2-hydroxyalkyl sulfides, prepared by reaction of epoxides with 2-methylpropane-2-thiol, are converted directly to 1,3-oxathiolanes upon treatment with pivalaldehyde and boron trifluoride diethyl etherate in the presence of thioanisole.

1. Introduction

As part of a research programme[1] targeted towards the synthesis of the RNA polymerase inhibitor tagetitoxin **1**,[2] we wished to synthesise the cis-disubstituted 1,3-oxathiolane ester **2-c** as a single enantiomer. It was hoped that subsequent deprotonation and reaction with an appropriate aldehyde would allow stereospecific construction of the C1–C8 bond of tagetitoxin.[3] Literature reports concerning the enolates of related sulfur-containing heterocycles left some doubt as to whether the proposed coupling would be feasible. Seebach et al. reported that the lithium enolate of thiazolidine **3** rapidly decomposed by a β-elimination process and could not be induced to react with electrophiles.[4] Conversely, Pattenden et al. were successful in alkylating the enolate of thiazolidine **4**, which differs from **3** only in the nature of the nitrogen protecting group.[5] It was thus unclear prior to this study whether the enolate of **2-c** would be sufficiently stable to allow reaction with an aldehyde to take place. While **2-c** had not previously been synthesised, it was anticipated that it should be readily prepared by acid-catalysed condensation of the corresponding β-hydroxythiol with pivalaldehyde.



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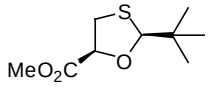
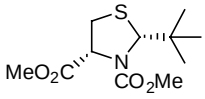


2-*c*



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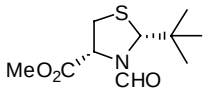

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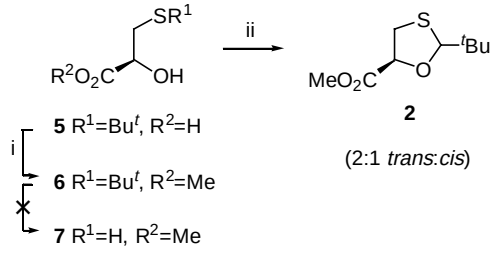
2. Results and discussion

L-Serine was converted via potassium (*R*)-glycidate to carboxylic acid **5** by literature procedures.[6] Esterification was accomplished with thionyl chloride/methanol to afford ester **6** (Scheme 1).[7]



Scheme 1. Reagents and conditions: (i) $SOCl_2$, MeOH, 45%; (ii) ^{t}BuCHO (1 equiv), $BF_3 \cdot OEt_2$ (2 equiv), PhSMe (1 equiv), CH_2Cl_2, 55%.

Keywords: Heterocycles; Sulfur; Protecting groups; *tert*-Butyl sulfides; Lewis acids.
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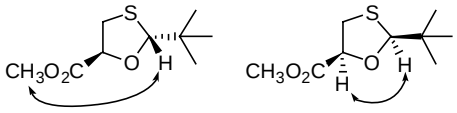
The next step, removal of the *tert*-butyl protecting group to generate a vicinal hydroxythiol **7**,[7] proved problematic. Treatment of **6** with a range of protic and Lewis acids (including $Hg(OAc)_2$/TFA followed by H_2S;[7b] TFA/Et_3-SiH,[7c] and HBF_4/TFA)[7d] failed to give efficient deprotection, and attempts to generate the corresponding disulfide by treatment with oxidising agents (I_2 or $PhI(OAc)_2$)[7e] were also unsuccessful. We were thus forced to develop a new method for removal of the *tert*-butyl group, and were gratified to discover that treatment of **6** with pivalaldehyde, $BF_3\cdot OEt_2$ and thioanisole in dichloromethane led directly to the formation of the desired 1,3-oxathiolane **2**, which was obtained as a 2:1 mixture of isomers. NOE experiments on this mixture (Fig. 1), together with analysis of ^1H–^1H coupling constants,[8] indicated that the major component was the trans-isomer **2-t**.



2-*t* (major) **2-*c*** (minor)

Figure 1. Selected nuclear Overhauser enhancements in **2-t** and **2-c**.

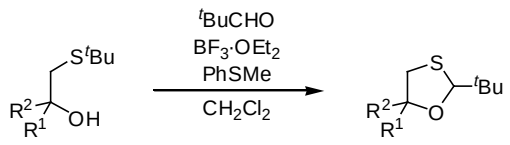
Attempts to improve the yield of the reaction by use of other Lewis or Brønsted acids ($ZnCl_2$, $InCl_3$, $ZrCl_4$, Dowex-50) were unsuccessful, with only boron trifluoride, of the acids investigated, giving the desired product. Replacement of pivalaldehyde with other aldehydes or ketones also proved unsuccessful, while omission of the thioanisole gave a much slower reaction, with appreciable quantities of starting material still present after 40 h.

Our attention next turned to the scope of this transformation. A range of racemic or achiral *tert*-butyl 2-hydroxyalkyl sulfides was prepared by opening of the corresponding mono- or 1,1-disubstituted epoxides with 2-methylpropane-2-thiol under basic conditions.[9] These compounds were subjected to the deprotection–cyclisation conditions developed for compound **6**: the results are summarised in Table 1.

Sulfides derived from monosubstituted epoxides (**8a**–**8g**) were converted to the corresponding 1,3-oxathiolanes **9a**–**9g** as mixtures of diastereomers, which were in general not separable by column chromatography. In the case of **9a**, as for **2**, the trans-isomer was the major one; in all other cases, the cis-isomer predominated. Achiral sulfide **8h**, which incorporates a tertiary alcohol, could also be converted to the corresponding 1,3-oxathiolane in high yield under the same conditions.

Given the ready interconversion of 1,3-oxathiolane stereoisomers in the presence of $BF_3\cdot OEt_2$,[8] the product ratios observed may reflect the relative thermodynamic stability of the two diastereomers. Indeed, previous equilibration studies have indicated that the cis-isomer of 2,5-dialkyl-1,3-oxathiolanes is the more stable.[8] By contrast, Brønsted acid-catalysed condensation of methyl 3-mercapto-2-hydroxypropanoate with acetaldehyde was reported to give the trans-isomer, analogous to **2-t**, as the major isolated product.[10]

Table 1. Conversion of *tert*-butyl sulfides to 1,3-oxathiolanes



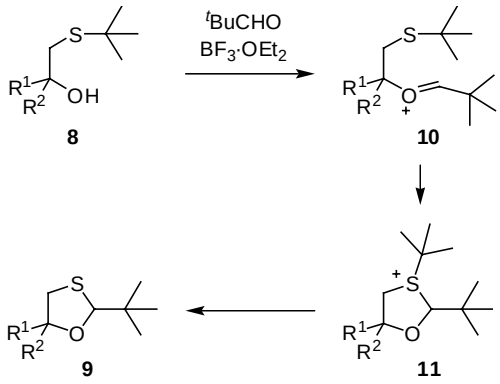
8a-8h **9a-9h**

Sulfide	R^1	R^2	Time (h)	Yield (%) (trans:cis)[a]
8a	CO_2Et	H	4	67 (2.2:1)
8b	*n*-C_3H_7	H	4	15 (1:2.5)[b]
8c	CH_2Ph	H	22	47 (1:3.8)
8d	CH_2OPh	H	5	74 (1:3.1)
8e	CH_2OBn	H	24	82 (1:3.0)
8f	$CH_2OCH_2CH{=}CH_2$	H	25	36 (1:2.9)
8g	$(CH_2)_6CH{=}CH_2$	H	5	12 (1:3.7)
8h	CH_2OPh	CH_2OPh	23	91

[a] Isolated yields of mixtures of diastereomers. The figures in parentheses represent the trans:cis isomeric ratio in the crude reaction mixture, as determined by ^1H NMR spectroscopy.
[b] Isolated yield of cis-isomer.

Yields of oxathiolanes were moderate to good, with the exceptions of **9b**, whose volatility made isolation troublesome, and of **9g**, where isolation of a pure product was hampered by problems in separating the oxathiolane product from non-polar impurities.

The mechanism for this combined deprotection–cyclisation transformation is presumed to be that outlined in Scheme 2. Condensation of the alcohol functionality of **8** with pivalaldehyde, catalysed by the Lewis acid, gives cation **10**, which is attacked in an intramolecular fashion by the sulfur atom to afford **11**. Loss of a *tert*-butyl cation, which is scavenged by thioanisole, leads to the observed product **9**.



Scheme 2. Proposed mechanism for deprotection–cyclisation.

An alternative mechanism in which acid-catalysed removal of the *tert*-butyl group to yield a hydroxythiol is followed by condensation with pivalaldehyde was ruled out by a control experiment carried out in the absence of pivalaldehyde; in this case, no reaction occurred and the starting material was recovered unchanged.