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Enantioselective Oxidation of Thioethers[1]: Synthesis of *trans*-2-*N*,*N*-Dialkylacetamide-1,3-dithiolanes-*S*-oxide and Their Use in Asymmetric Aldol-Type Reactions

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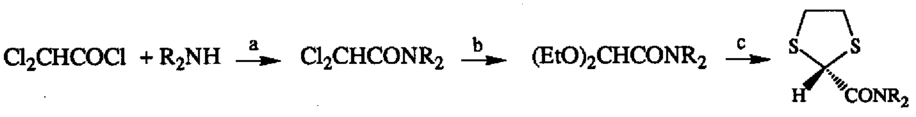
Abstract: (-)-*trans*-2-*N*,*N*-dialkylacetamide-1,3-dithiolanes-*S*-oxide **2** have been obtained in high d.e. (>99:1) and e.e. (up to 94%, >98% after crystallization) by enantioselective oxidation [Ti(*i*-PrO)$_4$, (+)-DET, *t*-BuOOH]. The aldol-type addition of the magnesium enolate of the N,N-diethyl derivative (-)-**2b** to *iso*-butyraldehyde afforded good chemical yields of a single diastereomer.

The aldol-type addition of optically active α-sulfinyl enolates[2,3] to carbonyl compounds usually affords the corresponding adducts in high enantiomeric excess(up to 98%) and good chemical yields.

We have investigated the scope of our direct enantioselective oxidation procedure based on a modified Sharpless reagent (Ti(IV)/(+)-DET/t-BuOOH=1:4:2)[4] in the synthesis of chiral-non racemic precursors of α-sulfinyl enolates. Here we report on the preparation and reactivity of 2-acyl-1,3-dithiolanes-*S*-oxide, and, in particular, of 2-*N*,*N*-dialkylacetamides. These compounds were selected owing to the previously observed ability of variously substituted 1,3-dithiolanes to provide the corresponding sulfoxides with rather good enantioselections.[5] Moreover, such compounds are known to give stable enolates which can react with electrophilic species *e.g.* α,β-insaturated esters[6], vinyl chlorides[6] and aldehydes.[7]

Three different derivatives, the *N*,*N*-dimethyl **1a**, *N*,*N*-diethyl **1b** and *N*-pyrrolidyl-1,3-dithiolane **1c**, were synthesized.



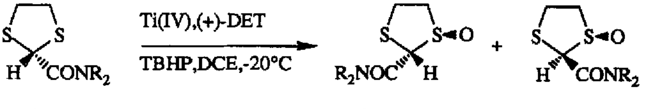
1

a. Et_3N/CH_2Cl_2; b. EtONa/EtOH, reflux; c. $HSCH_2CH_2SH/BF_3{\cdot}OEt_2$, $CHCl_3$, reflux

The results of the enantioselective oxidation of substrates **1** are reported in table 1.

The asymmetric oxidation proceeds in all three cases with high enantioselection and it is also characterized by a total diastereoselectivity. The enantiomeric excess of the *N*,*N*-diethyl derivative (-)-**2b** (e.e.= 94%[8], $[\alpha]_D^{25}$=-24.9, (c=1.0, chloroform)) was increased by crystallization (chloroform/pentane) to afford the enantiomerically pure product, e.e. >98% [mp 117-118°C, $[\alpha]_D^{25}$=-26.3 (c=1.0, chloroform)]. The relative stereochemistry of (-)-**2b** was unequivocally determined to be 1R, 2R by diffractometric analysis, by assigning the R configuration to the sulfinyl stereocenter.[9,10]

Table 1.



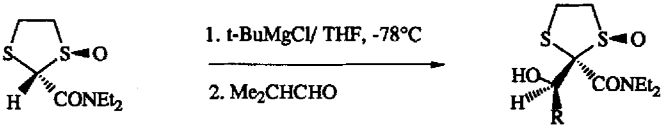
1 **2** (*trans*) (*cis*)

#	R	Yield, %	Diast. Ratio *trans*:*cis*	e.e., %[8] *trans*
1a	Me	70	>99:1	63^a
1b	Et	79	>99:1	80^a ($>98^c$)
1b	Et	87	>99:1	94^b ($>98^c$)
1c	$(CH_2)_4$	62	>99:1	77^a

a. non optimized procedure; b. optimized procedure; c. After crystallization (chloroform/pentane).

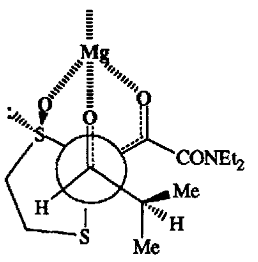
The reaction of the magnesium enolate of (-)-**2b**, obtained by reaction with *t*-BuMgCl in THF, -78°C, with *iso*-butyraldehyde afforded a single diastereomer (-)-**3** [mp 94-96°C, $[\alpha]_D^{25}$= -13.3 (c=1.0, chloroform)] in 82% yield.

(-)-2b



(-)-3

The relative stereochemistry of (-)-**3**, determined to be 1R, 2R, 1'R *via* diffractometric analysis[9,10], likely originates from a rigid transition state where the oxygen atoms of the enolate and of the aldehyde are coordinated to the magnesium atom.



Both the easy synthesis of (-)-**2b** and the total diastereoselection, accompanied by the good chemical yields, obtained in the reaction of its magnesium enolate with the model electrophile *iso*-butyraldehyde makes (-)-**2b** an interesting chiral synthon. Work is now in progress to establish its general applicability in asymmetric aldol-type reactions with different classes of electrophiles.

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10. All sulfoxides obtained so far by direct asymmetric oxidation with our system, whose absolute configuration was already known, have R absolute configuration.

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