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ASYMMETRIC OXIDATION OF 1,3-DITHIOLANES. A ROUTE TO THE OPTICAL RESOLUTION OF CARBONYL COMPOUNDS

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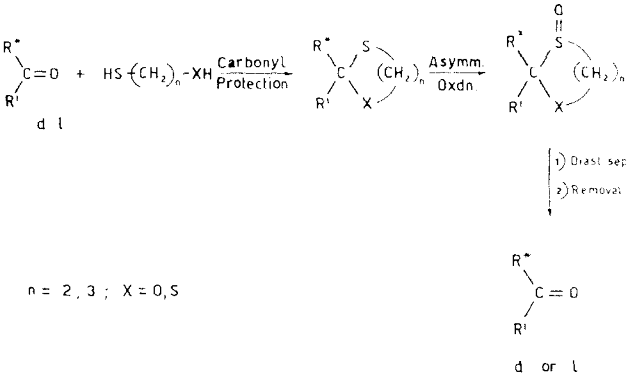
Abstract : The asymmetric oxidation ($\underline{t}$-BuO$_2$H, Ti(OPr-$\underline{i}$)$_4$, DET) of a series of 1,3-dithiolanes was carried out to produce the corresponding S-oxides with high chemical and optical yields. By contrast, the oxidation of 1,3-dithianes and 1,3-oxathiolane prepared from the same carbonyl compounds gave much lower optical yields. The optical resolution of the model ketone, dl-menthone, *via* a) 1,3-dithiolane formation b) asymmetric S-oxidation c) chromatographic diasteromeric separation d) regeneration of the carbonyl group, (93% optical yield), is described.

In 1984 two methods for the efficient asymmetric oxidation of sulfides (ee up to 90%) have been independently developed by Kagan's group[1] and by ourselves.[2] Both procedures involve a modification of the Sharpless reagent for the epoxidation of allylic alcohols.[3] Whereas the standard Sharpless reagent leads to almost racemic sulfoxides,[1] either the addition of 1 mol equiv. of water[1] or an increase of the DET/Ti(OR)$_4$ ratio[2] allow the production of sulfoxides with ee values often in the range of 80-90%.

These procedures might become an alternative to the Andersen method of synthesis of optically active sulfoxides.[4] However, in sulfides oxidation, much more than in allylic alcohols epoxidation, it is very difficult to predict the success of the asymmetric reaction since the nature of the substrate appears to play a dominant role. While alkyl aryl sulfides usually give high ee values, dialkyl sulfides, ß-hydroxy sulfides and cyclic sulfides provide rather modest optical yields.[5]

Of current interest in our laboratory is the application of the asymmetric oxidation of sulfides to the optical resolution of carbonyl compounds via the series of simple reaction shown in the scheme:

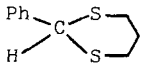
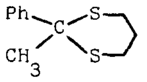
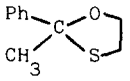
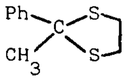
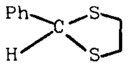
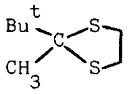
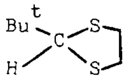


Taking into account that large variations of optical yields depending on the nature of the sulfide are expected, we have carried out a preliminary investigation on a series of model compounds in order to ascertain the structural requirements for high optical yields. The results of this study are presented in the Table. Inspection of the data reported in the Table reveals that the best results are obtained in the oxidation of 1,3-dithiolanes. Moreover, the optical yields, ranging from 70 to 80%, are not significantly affected by the nature of R and R'. Synthetically relevant are also the very large diasteromeric ratios observed. The pattern of the results reported in the Table does not allow an easy interpretation. 1,3-dithianes provide good diasteromeric ratios but low ee values. Curiously, the 1,3-oxathiolane gives the poorest results. It is likely that a rationale of these observations may be offered when more information concerning the mechanism of the asymmetric oxidation will be available. At any rate, the experiments reported above establish that 1,3-dithiolanes are suitable substrates, consistently providing fairly high ee values.

Thus, the optical resolution of a model ketone, dl-menthone, whose 1,3-dithiolane is easily obtainable from reaction with 1,2 ethanedithiol in the presence of BF_3 Et_2O,[6] has been attempted.

The oxidation reaction has been carried out by mixing $Ti(OPr\text{-}i)_4$ (1 mL, 3.4 mmol) dissolved in 15 mL of DCE and (R,R) DET (2.3 mL, 13.4 mmol) in 15 mL of DCE at 25°C, under stirring. To the solution, kept at -20°C, TBHP (0.66 mL, 6.7 mmol) and the menthone 1,3 dithiolane (17.5 mmol), are subsequently added. The reaction mixture is kept at -20°C until the oxidant is totally consumed (14 hours). Introduction of 1 mL of water to this cooled solution produces a gel which is stirred 1 h and warmed to 25°C. The reaction mixture is filtered and the organic layer is washed with 5% $Na_2S_2O_5$ (3 x 50 mL), 5% NaOH (3 x 50 mL) and

TABLE. Asymmetric oxidations of 1,3-dithiolanes and 1,3-dithianes by tert-butyl hydroperoxide and Ti(iPrO)$_4$ in DCE containing (+)diethyltartrate at -20°C.

Substrate	t, h	Yield, %[a]	Diast. ratio[b]	ee%[c]	ee% (after cryst.)
	15	88.2	90:10	14[d]	-
	15	86.8	85:15	39[e]	-
	16	48	78:22	3[f]	-
	15	66	97:3	83[g]	98[m]
	15	76	94:6	76[h]	99[n]
	14	61	99:1	68[i]	70[o]
	8	82	99:1	70[l]	[p]

a. Based on the oxidant. b. Obtained by ^{1}H-NMR after removal of the excess of the substrate by column chromatography (silica gel). c. Obtained by ^{1}H-NMR of the separated diastereoisomers in the presence of Eu(tfc)$_3$ in CDCl$_3$. The values always refer to the major diasteroisomer. d. Splitting of the methine proton at δ=4.6 (s); e. Splitting of the methyl signal at δ= 1.9 (s) f. Splitting of the methylene signal at δ=4.7 (m); g. Splitting of the methylene signal at δ=3.8 (m). h. Splitting of the methine proton at δ=5.3 (s). i. Splitting of the methyl signal at δ=1.7 (s). l. Splitting of the methine proton at δ=4.0 (s). m. From petroleum ether-ethyl ether 80-20 m.p. 71-72°C. n. From water-ethanol 95-5 m.p. 95-96°C. o. From petroleum ether m.p. 44-46°C. p. Liquid.

water, dried over $MgSO_4$ and concentrated. Only two diasteroisomers out of the four theoretically possible are obtained (87:13 ratio). No attempt to establish the absolute stereochemistry of the two menthone 1,3-dithiolane S-oxides diasteroisomers has been made. Their separation is attained by low-pressure liquid chromatography on silica gel (Et_2O).

The e.e. value of the minor isomer is determined by NMR in the presence of $Eu(tfc)_3$; (e.e. 83%). The e.e. of the major diasteroisomer is obtained by polarimetric measurement after removal of the 1,3-dithiolane S-oxide function by means of deoxygenation with $Ph_3P/I_2/NaI$[7] followed by regeneration of the menthone with $(MeS)_2SCH_3^+SbCl_6^-/Na_2CO_3$[8]. $[\alpha]_D^{25}=-27.4$ ($C=6$ $CHCl_3$) e.e. 93%.[9]

The use of 1,3-dithiolanes in the optical resolution of other synthetically significant carbonyl compounds as well as in other useful transformations is under investigation.

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