Asymmetric Synthesis of α,α-Dichlorosulphoxides from Substituted Thioacetates and Sodium Hypochlorite in β-Cyclodextrin Complexes

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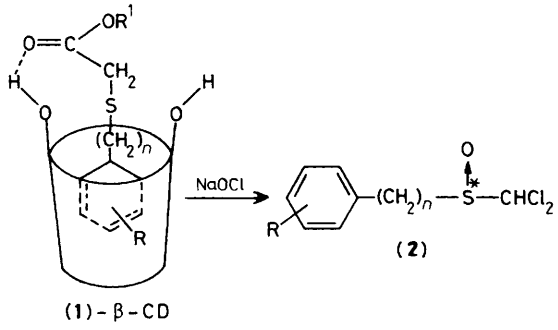
The reaction of β-cyclodextrin complexes of substituted thioacetates (**1**) with sodium hypochlorite in aqueous medium gives optically active α,α-dichlorosulphoxides (**2**) in good yields with an enantiomeric excess (e.e.) of up to 53%.

Cyclodextrins, with their chiral environment, have excited much interest as enzyme mimics owing to their ability to bind substrates selectively and catalyse reactions,[1–3] but so far their use in asymmetric synthesis has been limited.[4,5] Optically active α,α-dichlorosulphoxides are promising chiral auxiliaries in the transfer of chirality from sulphur to carbon in various asymmetric syntheses,[6–9] since they can be transformed to compounds with different functionalities, *e.g.* carbonyl-, imino-, and α-monochloro-sulphoxides. However, the asymmetric synthesis of such chiral sulphoxides has not hitherto been reported. Herein, we report the utility of a cyclodextrin as a tool in asymmetric induction in the simple synthesis of optically active α,α-dichlorosulphoxides (**2**) from arylthioacetates[10] (**1**) by complex formation with the chiral template β-cyclodextrin (β-CD), followed by reaction with sodium hypochlorite (Scheme 1).

The asymmetric oxidation of the arylthioacetates (**1a—h**) with sodium hypochlorite to give the sulphoxides (**2a—h**) has been studied (Table 1).

The inclusion complexes were prepared by adding the pure sulphides (**1**) (purified twice by flash chromatography) in ethanol to an aqueous solution of β-cyclodextrin at 60 °C; crystalline complexes were obtained on cooling. All sulphides formed 1:1 inclusion compounds with β-cyclodextrin as determined by ^{1}H n.m.r. spectroscopy[11] and from the amount



Scheme 1. R = H, *p*-Me, or p-Cl; *n* = 0 or 1; X = Et or Bu^t.

of sulphide extracted from a known amount of complex. These sulphides did not form stable complexes with α-cyclodextrin.

To the complexes in water (20 ml of doubly distilled water per g of complex), sodium hypochlorite was added (2 ml of 5% NaOCl per mmol of sulphide; excess of hypochlorite has no effect on product formation) at room temperature and the mixture stirred overnight. Extraction with chloroform and chromatography on silica gel gave the products. Sodium hypochlorite, in addition to oxidising the sulphide to sulphoxide, cleaves the carboxylate group with concomitant α-chlori-

Table 1. Oxidation of the sulphides (**1**).

Starting sulphide (**1**) R–S–CH_2CO_2X		Product (**2**)		
R	X	% Yield[a,b]	$[\alpha]_D^{20}$ (°)[c]	% E.e.[d,e]
(**1a**) Ph	Et	70	+ 2.2	3.7
(**1b**) Ph	Bu^t	75	+32.3	53.8
(**1c**) *p*-MeC_6H_4	Et	77	+ 2.2	5.4
(**1d**) *p*-MeC_6H_4	Bu^t	72	+14.0	36.7
(**1e**) *p*-ClC_6H_4	Et	78	+ 1.5	2.8
(**1f**) *p*-ClC_6H_4	Bu^t	75	+10.4	21.6
(**1g**) $PhCH_2$	Et	81	+ 3.3	6.7
(**1h**) $PhCH_2$	Bu^t	83	+20.4	35.6

[a] All products were characterised by high resolution mass spectrometry, ^{1}H n.m.r. spectroscopy, and elemental analyses. [b] Sulphones corresponding to product (**2**) were also obtained (8—10%). [c] In acetone (*c* 1.0). [d] Determined by ^{1}H n.m.r. (300 MHz) spectroscopy with $Eu(hfc)_3$ as chiral reagent. [e] Absolute configurations not known.

nation as observed earlier by Farrar[12] for racemic *S*-substituted mercaptoacetic acids.

The results (Table 1) for the sulphoxides (**2b**, **d**, **f**, and **h**) obtained from sulphides with a t-butyl substituent show enhanced enantioselectivity, whereas low stereoselectivity is seen for the sulphoxides (**2a**, **c**, **e**, and **g**) obtained from the ethyl acetates. The higher asymmetric bias observed for the t-butyl derivatives may be due to favourable control of geometry in the approach of the substrate to the 'active site.'

Since cyclodextrins are known to show enantioselectivity in complex formation of racemic compounds,[13] it is possible that the present results may be due to optical resolution of racemic sulphoxides formed in the reaction. To rule out this possibility, optical resolution was carried out with racemic aryl α,α-dichloromethyl sulphoxides [obtained by the direct reaction of arylthioacetates (**1a—h**) with sodium hypochlorite] by forming crystalline complexes with β-cyclodextrin. The enantiomeric excesses observed for the α,α-dichloromethyl sulphoxides obtained from this resolution of racemic mixture by β-cyclodextrin is negligible (<1%). This shows that the observed enantioselectivity in the present asymmetric synthesis is not due to optical resolution but due to kinetic selection in the reaction.

The occurrence of asymmetric oxidation only in the presence of sodium hypochlorite (whereas reagents like hydrogen peroxide and *m*-chloroperbenzoic acid failed to oxidise the sulphide–β-CD complexes) may be explained through the initial formation of β-cyclodextrin hypochlorite as reported by Breslow[14] in the chlorination of anisole.

Thus, the optically active α,α-dichlorosulphoxides (**2**) are now readily accessible as chiral auxiliaries for asymmetric syntheses.

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