Tetrahedron: Asymmetry Vol. 1, No. 3, pp. 141-142, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

A General Method for the Enantiospecific Synthesis of Optically Active Aliphatic Sulfenyl Chlorides and Thiophthalimides

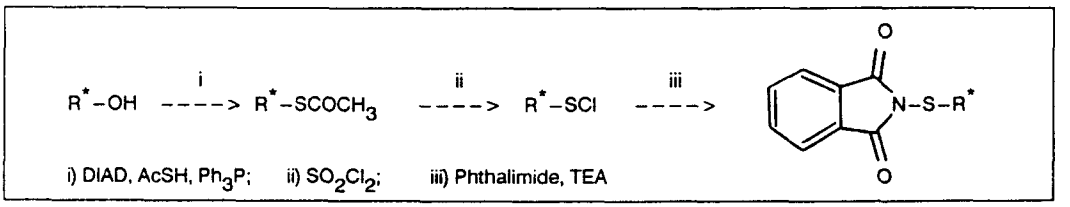
Giorgio Cevasco, Enrica Narisano, and Sergio Thea
Istituto di Chimica Organica dell'Università e C.N.R. Centro di Studio sui Diariloidi,
Corso Europa 26, I-16132, Genova (Italia)

(*Received* 22 *December* 1989)

Abstract: A simple and convenient method for the preparation of optically active sulfenyl chlorides and thiophthalimides starting from commercially available non-racemic alcohols is reported.

Sulfenyl chlorides are valuable intermediates in the synthesis of several sulfur derivatives, since they are converted easily into sulfenate esters, sulfenamides, sulfides, disulfides, sulfenyl carboxylates as well as β-keto sulfides and β-chloro sulfides.[1] Moreover, the general usefulness of sulfur compounds in organic synthesis is well established, and the widespread interest in asymmetric synthesis requires an increasingly larger number of new chiral starting compounds or intermediates. Nevertheless, perusal of the literature reveals that the reported syntheses of key chiral intermediates such as β-keto sulfides,[2] α-sulfenyl-β-hydroxy esters,[3] β-hydroxy sulfides,[4] and α-sulfenyl imides[5] do not make use, as starting materials, of chiral sulfenyl chlorides, of which, however, only a few, sparse examples have been reported in the literature so far[6]. The lack of a general approach to the latter compounds, coupled with our previous finding that thiolacetates react with sulfuryl chloride to afford sulfenyl chlorides cleanly and in excellent yields,[7] prompted us to apply such reaction to the preparation of optically active sulfenyl chlorides.

Herein we report our results on the enantiospecific conversion of some commercially available primary and secondary chiral alcohols into the corresponding sulfenyl chlorides and subsequently into *N*-(alkylthio)phthalimides:



Reactions were carried out as described previously,[7] and results are shown in the Table. Products were analysed by ^{1}H n.m.r. spectroscopy. Spectra were recorded with a 200 MHz instrument on the crude *N*-(alkylthio)phthalimides, obtained from optically active alcohols, in the presence of the chiral shift reagent Eu(hfc)$_3$ [hfc=3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]. Thiophthalimides obtained starting from racemic alcohols were employed as blanks to optimize the conditions of separation and integration of the peaks of the enantiomers.

N.m.r. data clearly indicated that no racemization occurs in the overall reaction: the enantiomeric excess (e.e.) was, making allowance for the uncertainty related to the analytical technique employed, always higher than 90%, since only one enantiomer was detectable in all cases. Since complete inversion of configuration occurs at the reaction centre (if chiral) in the first step of the above reaction sequence,[8] the absolute configuration of products can be established. It is likely that the enrichment in e.e. observed for the thiophthalimides obtained starting from alcohols of moderate optical

purity was due to enantiomeric resolution taking place during crystallization (crude thiophthalimides were recovered in quite satisfactory yields from the reaction mixture by precipitation upon addition of water).[9]

It is interesting that although sulfenimides are generally quite stable compounds,[10] still they may find application as sulfenylating agents.[2a,10,11]

We think that the availability of a straightforward method for the synthesis of optically active sulfenyl chlorides widens their range of application, disclosing new opportunities to workers involved in organosulfur chemistry.

TABLE

Alcohol (e.e.%)[a]	Sulfenyl chloride % yield[b]		abs. conf.	*N*-(alkylthio)phthalimide % yield[c]	e.e.%	$[\alpha]_D$[d]
2-methyl-1-butanol	93	(4)		70	–	
(*S*)-(−)-2-methyl-1-butanol (79)	95	(4)	*S*	76	90	+23.3
2-butanol	96	(2)		70	–	
(*S*)-(+)-2-butanol (99)	90	(2)	*R*	65	90	−6.0
2-octanol	95	(8)		79	–	
(*S*)-(+)-2-octanol (77)	80	(8)	*R*	81	90	−2.5
3β-cholestanol (99)	90	(0.5)[e]	3*R*	50	f	+15.2

[a]Estimated from the $[\alpha]_D$ values reported for the commercial specimens employed. [b]Based on the starting thiolacetates; CCl_4 was used as solvent; figures in brackets refer to reaction time (in hours). [c]Referred to crude products. Recrystallized samples gave excellent spectroscopic and elemental analyses. [d]c 1, $CHCl_3$. [e]Reaction carried out in the absence of solvent. [f]Not determined because of the unavailability of n.m.r. signals suitable for chiral L.I.S. analysis.

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