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A New Approach to 2-Phenylthioalcohols in High Optical Purity

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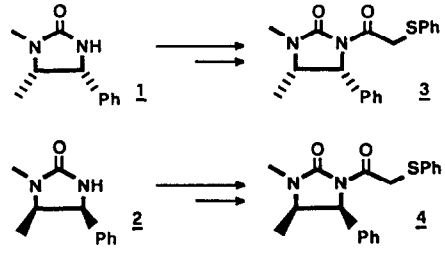
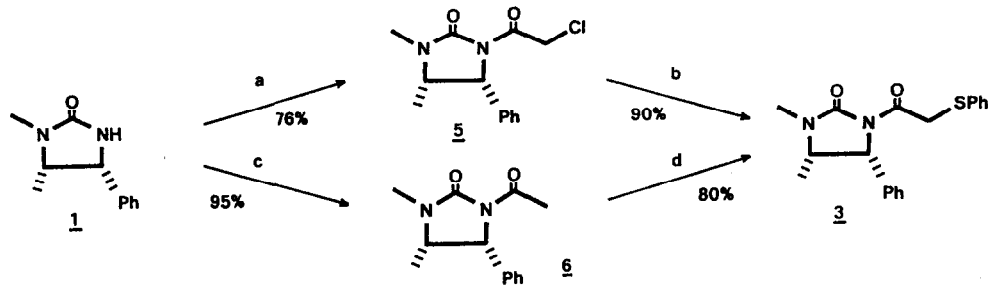
Key Words 2-Phenylthioalcohols, Diastereoselectivity, Chiral imidazolidin-2-ones, Alkylation, Sulphenylation

Abstract 2-Phenylthioalcohols are prepared in high optical purity by alkylation of chiral imides of 2-phenylthioacetic acid, obtained starting from chiral imidazolidin-2-ones.

In recent years extensive studies have been carried out on reactions employing enantiomerically pure enolates as reactants and the ones in which the chiral auxiliaries are covalently bonded to the reactants are of special synthetic utility. [1] Following this strategy, we report the synthesis of 2-phenylthioalcohols in high optical purity, that can be precursors of epoxides. [2-4] As the chiral auxiliaries we have employed the imidazolidin-2-ones **1** and **2**, [5] that we previously reported for the preparation of a number of compounds in high e.e. [6-9] The first step of this synthetic approach consists in the preparation of the imides of phenylthioacetic acid **3** and **4**.



Since direct preparation by reaction of phenylthioacetyl chloride and the anion of both **1** and **2** fails, two alternative routes to these imides have been devised. Thus by treating the anion of **1** with chloroacetyl chloride at -78°C in THF, the corresponding imide **5** is obtained in 76% yield, and subsequent reaction of this intermediate with PhS^-Na^+ in refluxing methanol leads to **3** in 90% yield. Conversely, the imide of the acetic acid **6** is treated in THF with LDA at -78°C and successive addition of diphenyl disulphide leads to the imide **3** in 80% yield. In analogy, starting from **2**, the imide **4** can be obtained in comparable yield.



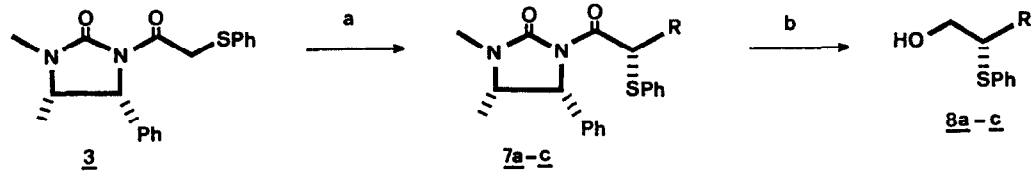
a. n-BuLi, THF, 0°C, then the mixture is added to chloroacetyl chloride at -78°C b. PhSNa, refluxing ethanol c. n-BuLi, THF, then acetyl chloride d. LDA, THF, - 78°C, then PhSSPh

In order to introduce a stereogenic centre at the C-2' position of the imides **3** or **4**, metalation is carried out by treatment with LHDMS at -78°C, followed by alkylation of the corresponding enolate anion at the same temperature. The reaction proceeds with high yields and diastereomeric ratio of the imides **3a-c** and **8** is ≥ 98:2, as determined on the basis of the ^{1}H NMR spectrum of the crude reaction mixture (Table 1). Moreover the temperature is determinant in order to obtain a high diastereoselectivity. In fact, carrying out the alkylation at 0°C, only a 60:40 d.r. is observed.

It is worth mentioning that also sulphenylation of the imides **11a-c** and **13**, obtained from both **1** and **2**, proceeds with very high asymmetric induction. [10] In fact the corresponding lithium enolates, obtained by treating with an equivalent of LHDMS in THF at -78°C, can be sulphenylated at C-2' at -78°C, and the sulphenylated products **12** and **14** are obtained in high yield. Phenylsulphenyl chloride, diphenyl disulphide and phenylthiosulphonate are employed as sulphenylating reagents, but very little differences have been observed in the reactivity. The reaction proceeds with high diastereoselectivity (≥98:2) and no trace of the other diastereomer appears in the ^{1}H NMR spectrum at 300 MHz (Table 2).

Moreover the configuration of the stereogenic centre introduced by either alkylation or sulphenylation can be easily assigned on the basis of both the reaction mechanism and the configuration of the chiral auxiliary. Thus, simply changing the chiral auxiliary **1** with **2**, as it appears for either **7a** and **9** and **12c** and **14**, the configuration at C-2' results inverted.

The conversion of the chiral imides **7a-c** and **9** into the corresponding 2-phenylthioalcohols **8a-c** and **10** can be accomplished by reductive cleavage with $LiEt_3BH$ in THF. The reaction is carried out at 20°C for 6 h and the 2-phenylthioalcohols are obtained in good yield and high optical purity, together with the unchanged chiral auxiliary.



a. LHDMS, THF, -78°C, then RX b. $LiEt_3BH$, THF, r.t.

A useful extension of the reductive cleavage of the imides has been exploited by treating at 0°C with 2 eq of a Grignard reagent. In fact the corresponding tertiary phenylthioalcohol is obtained in good yield, which is a key intermediate to geminal 1,1-disubstituted epoxides.

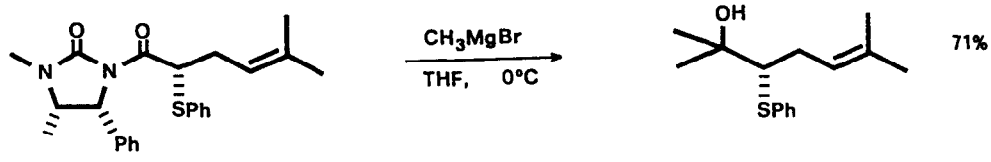
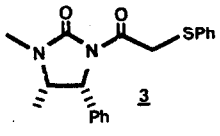
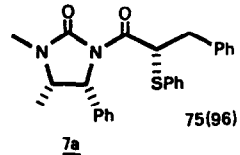
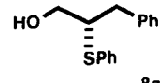
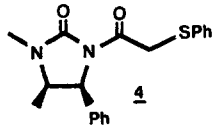
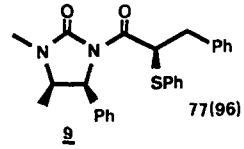
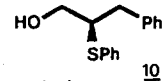
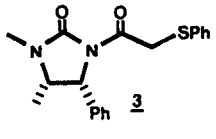
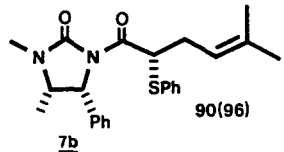
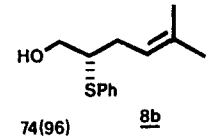
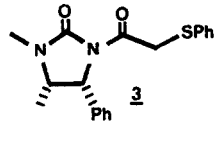
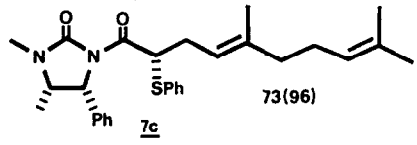
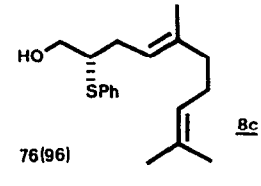
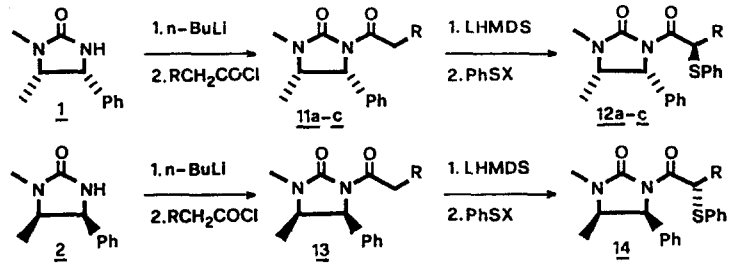


Table 1. Preparation of 2-Phenylthioalcohols in High Optical Purity via Chiral Imides

Substrate	Alkylation product[a] yield% (d.e.)[b]	Reductive cleavage[a] product yield% (e.e.)[c]
 3	 7a 75(96)	 8a 74(96)
 4	 9 77(96)	 10 77(96)
 3	 7b 90(96)	 8b 74(96)
 3	 7c 73(96)	 8c 76(96)

[a] All new compounds were well characterized by spectroscopic analysis [b] Determined by ^{1}H NMR spectroscopy [c] Determined by ^{1}H NMR spectra of MTPA esters.

Table 2. Diastereoselective Sulphenylation of Chiral Imides



Substrate	R	PhS-X	Yield %[a]	d.r.[b]
11a	CH_3	X= Cl	86	≥98:2
		SPh	93	≥98:2
		SO_2Ph	92	≥98:2
11b	$(CH_3)_2CH$	Cl	82	≥98:2
		SPh	86	≥98:2
		SO_2Ph	88	≥98:2
11c	$C_6H_5CH_2$	SPh	92	≥98:2
		SO_2Ph	97	≥98:2
13	$C_6H_5CH_2$	SPh	90	≥98:2
		SO_2Ph	93	≥98:2

[a] All compounds were well characterized by spectroscopic analysis [b] Determined by ^1H NMR spectroscopy

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