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Sulfenylation of chiral Schiff bases

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Summary. The purpose of this study was to examine the conditions of sulfenylation reactions of chiral α-amino esters Schiff bases to protect the chirality in the α-position.

Keywords: Amino acids – Schiff bases – 2-Hydroxypinan-3-one – Sulfenylation – Desulfenylation

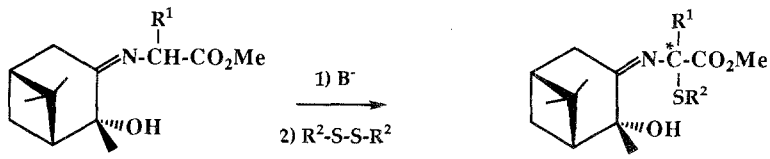
Introduction

Previously (El Marini et al., 1989) we have shown that substitution reactions of cuprates with serine derivatives, in particular β-iodoalanine, are difficult and the elimination product is obtained preferentially. Temporary replacement of the α-hydrogen by a labile group could suppress the elimination reaction, but the chirality of the α-center would have to be maintained during the reaction. Here we investigate the introduction of an easily removable thioether group introduced via a sulfenylation reaction with a disulfide such as R-S-S-R.

Results

Sulfenylation reactions

The Schiff bases were prepared from 2-hydroxypinan-3-one (Schmidt, 1960; Oguri et al., 1978) and α-amino esters. The conditions of the sulfenylation reactions are the same as those we have used previously for alkylation reactions (El Achqar et al., 1988; Tabcheh et al., 1991) the sulfenylating agent being dimethyldisulfide (CH_3–S–S–CH_3).



Scheme 1. Sulfenylation reaction

Of the two bases tried, potassium terbutoxide and lithium diisopropylamide (t-BuOK and L.D.A), t-BuOK is better and gives good chemical yields and excellent diastereomeric excesses (d.e) as shown in Table 1.

The dianion was formed by stirring a solution of the α-amino ester Schiff base in tetrahydrofuran (T.H.F) in the presence of t-BuOK for 15 min at −80 °C, followed by the slow addition of dimethyldisulfide. The d.e. were established from ^{1}H NMR data (250 MHz) using the methoxy group. The diastereoselectivity is very high except in the case of the Schiff base of alanine methyl ester (d.e. = 80%). However after sulfenylation the major diastereomer was obtained pure following two recrystallisations. For the Schiff base of phenylalanine methyl ester, sulfenylation reactions were performed starting from each diastereomer R*, R (R* being the absolute configuration of the three chiral atoms of 2-hydroxypinan-3-one, and R the absolute configuration of the amino ester) (or S*, S) and R*, S (or S*, R).

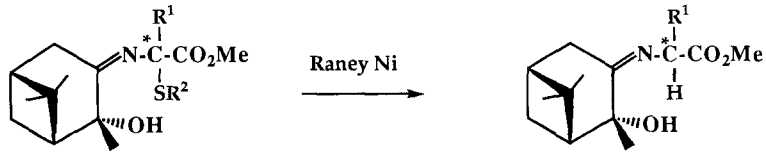
After work-up and purification, we have always obtained the mixture of the sulfenylated Schiff base (with the d.e. indicated in the table) and the starting product having the configuration R*, S (if we start from R*, R or R*, S Schiff bases) or S*, R (if we start from S*, S or S*, R). The isomers R*, R or S*, R have never been recovered. Moreover, starting from the R*, R or R*, S isomers the same sulfenylated product is obtained; S*, S or S*, R Schiff bases afforded after sulfenylation reactions only one product, this being the enantiomer of the preceding one. ^{1}H NMR spectra are identical in different solvents ($CDCl_3$, or C_6D_6).The specific rotation has the same absolute value, but is of opposite sign.

The stereochemistry will be assigned by X-ray diffraction.

Desulfenylation reactions

Following introduction of the S-R group as a protective group, it is important to have a good method to remove this group after stereospecific reactions. The method generally used in the literature consists of treatment by Raney Nickel in methanol at room temperature (Newman, 1950). However very little is known about the stereochemistry of this reaction.

The sulfenylated derivative of R*, S or R*, R phenylalanine methyl ester Schiff base gives after treatment with Raney Nickel a single diastereomer with the R*, S configuration. The reaction of desulfenylation starting from the mixture of diastereomers [obtained by sulfenylation of alanine methyl ester Schiff base (d.e = 85%)] gives alanine methyl ester Schiff base with the same d.e.. On the other hand, sulfenylation of S* glycine methyl ester Schiff base led to a single



Scheme 2. Desulfenylation reaction

diastereomer which can be crystallized allowing the determination of the configuration (S*, R) by X-ray diffraction. Thus starting from (S*) 2-hydroxypinan-3-one, we obtained (S*, R) sulfenylated Schiff base. If this result can be extended to alanine and phenylalanine methyl ester Schiff bases, starting from (R*) 2-hydroxypinan-3-one, after sulfenylation (R*, S) compounds will be obtained. However desulfenylation gave Schiff bases with (R*, S) configuration, so desulfenylation took place with inversion of configuration. This result is in contradiction with some results in the literature. It is reported (Horner et al., 1978) that desulfenylation was accomplished with retention of configuration. Much work will be needed to confirm our results.

Materials and methods

Reagents and solvents were purified in the usual way. Spectra were recorded with the following instruments: ^{1}H NMR: Varian EM 360 and Brucker 250, Mass Spectra: Jeol JMS DX 100 and DX 300. Optical rotations were determined with a Perkin Elmer 141 polarimeter.

Sulfenylation reactions

To two equivalents of base (t-BuOK or LDA) dissolved in anhydrous THF at $-78\,^\circ$C and under N_2 was added one equivalent of amino acid methyl ester Schiff base. After 15 min (for potassium enolates) or 30 min (for lithium enolates) methyl disulfide (one equivalent) dissolved in THF was added. The mixture was stirred under N_2 for 10 h, the temperature raised to 30 °C. The reaction was followed by T.L.C. After addition of a saturated solution of NH_4Cl, the organic layer was decanted and the aqueous layer extracted twice with ether. The organic layers were dried ($MgSO_4$), filtered and concentrated and the crude product was chromatographed on silica column (eluant: ether/hexane). For chemical yields and d.e. see Table 1.

Table 1. Results of sulfenylation reactions

	R′	HP	Base	Yd%	e.d%
1	H	S,S,S	tBuOK	55	>98
2	CH_3	R,R,R	tBuOK	70	85
	CH_3	R,R,R	LDA	50	80
	CH_3	S,S,S	tBuOK	68	80
3	CH_2Ph	R,R,R	tBuOK	76	>98
	CH_2Ph	S,S,S	tBuOK	72	>92
	CH_2Ph	S,S,S	LDA	20	>98
4	Ph	S,S,S	tBuOK	68	>98

1 m.p. = 83 °C (hexane), ^{1}H NMR ($CDCl_3$) δ ppm (SCH_3) = 2.4; **2** m.p. = 60 °C (hexane), ^{1}H NMR ($CDCl_3$) δ ppm (SCH_3) = 2.19; **3** oil, ^{1}H NMR ($CDCl_3$) δ ppm (SCH_3) = 2.14; **4** oil, ^{1}H NMR ($CDCl_3$) δ ppm (SCH_3) = 2,30.

Desulfenylation reactions

To the sulfenylated Schiff base (0.64 mole) dissolved in methanol, Raney Nickel (2g) was added at room temperature. The mixture was filtered off and the solvent evaporated under vacuum. The raw product was chromatographed on a silica column (eluant: ether/hexane).

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