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# Chiral Sulfinyl Chlorides as Intermediates in Interconversion of 4-Oxoazetidine-2-sulfinic Acid Derivatives

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Stereochemically pure methylsulfinates **3** and benzylsulfinamides **4** are readily epimerized in the presence of hydrogen chloride and at the same time they can be transformed by sulfinate-sulfinamide interconversion. Formation of sulfinyl chlorides **2** as intermediates and their epimerization by rapid chloride anion exchange at sulfur atom is proposed. The equilibrated ratio between epimers **2a** and **2b** determines the enantioselectivity of these processes.

## INTRODUCTION

There are some reports in the literature on the preparation of 4-oxoazetidine-2-sulfinates[1–3] and sulfinamides,[4–6] the compounds of considerable importance in the synthesis of analogues of β-lactam antibiotics. The precursors in these reactions are sulfinyl chlorides prepared from the corresponding penicillanate sulfoxides in the presence of sulfuryl chloride or *N*-chlorosuccinimide[4,5] or by the action of thionyl chloride on the corresponding sulfinic acid.[1,2] The chlorine atom of sulfinyl chloride can be readily displaced by alcohols or amines as nucleophiles, producing a mixture of sulfinates or sulfinamides as a result of epimerization at sulfur.[7]

Generally, by comparison to sulfoxides, the epimerization and the stereochemical transformation of the optically active sulfinic acid derivatives has been very little investigated despite their importance in the organic sulfur stereochemistry as the main source of the optically active sulfoxides.[8,9]

As a continuation of our work on 4-oxoazetidine-2-sulfinic and sulfonic acid derivatives,[2,3,6] we should like to report a useful and simple procedure for preparation of sulfinic acid **1** and its derivatives **3** and **4** by acid-ester-amide interconversion in the presence of hydrogen chloride. We also wish to show that the equilibrated ratio between the two forms of sulfinyl chlorides **2a** and **2b** determines the enantioselectivity of these processes.

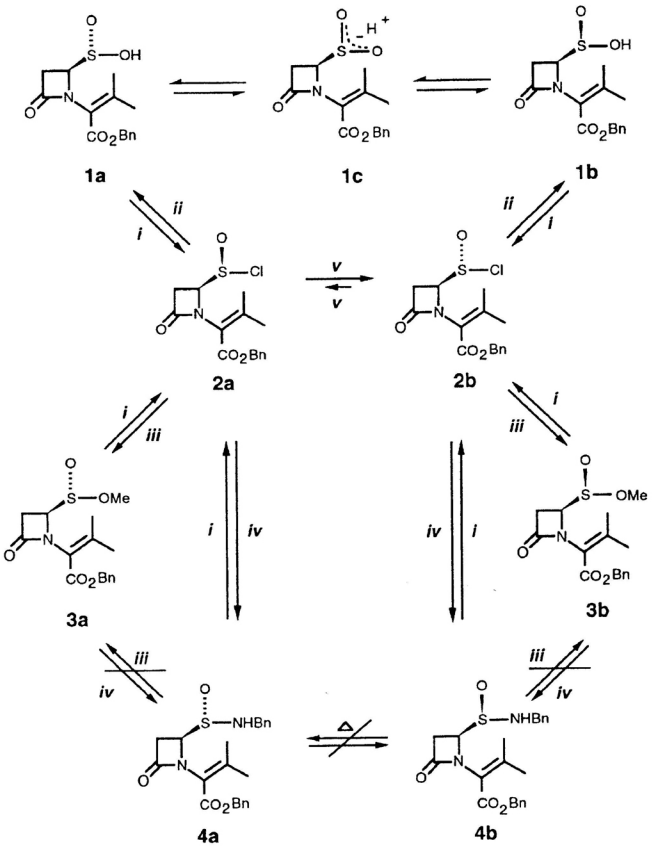
## RESULTS AND DISCUSSION

Enantiomerically pure methyl 4-oxoazetidine-2-sulfinate **3a**[7] was treated with anhydrous hydrogen chloride in dry dichloromethane. The nonvolatile residue, ob-

tained after removal of the solvent, was divided into equal parts and treated under different conditions. Thus, after aqueous work-up of the nonvolatile residue, the starting enantiomerically pure sulfinate **3a** and sulfinic acid **1** were isolated. On the other hand, the nonvolatile residue, after addition of methanol instead of water, gave a diastereoisomeric mixture of methylsulfinates **3a/3b** with predominant **3b** epimer, determined on the basis of $^1$H-NMR spectroscopic data. Both diastereoisomers of **b** configuration (**3b** and **4b**) as compared with diastereoisomers of **a** configuration (**3a** and **4a**), exhibit a downfield shift for the 3β-H atoms and an upfield for the methyl H atoms, which was in agreement with our earlier observation[7] (see Experimental).

Only traces of sulfinic acid **1** were obtained from combined aqueous layers.

Furthermore, the nonvolatile residue treated with benzylamine in addition to the starting methylsulfinate **3a**, gave the corresponding benzylsulfinamides **4a/4b**. Column chromatography on silica gel led to isolation of pure epimers **4a** and **4b** in the diastereoisomeric ratio 2:3. They were identical in all respects with the authentic samples whose structures were established earlier by X-ray crystallographic analysis.[10]




Scheme I. Reagents and conditions: (i) HCl(g)/$CH_2Cl_2$, r.t. 15 min; (ii) HOH/$CH_2Cl_2$, r.t. 1 hour; (iii) MeOH/$CH_2Cl_2$, r.t. 1 hour; (iv) $BnNH_2$/$CH_2Cl_2$, r.t. 30 min; (v) $Cl^-$/$CH_2Cl_2$, r.t. very fast.

Similar results were obtained by changing the starting stereoisomer. The nonvolatile residue prepared in the reaction of sulfinate **3b** and anhydrous hydrogen chloride, treated with methanol, gave the diastereoisomeric mixture of **3a/3b** with predominant **3b** epimer. On the other hand, by the treatment of the nonvolatile residue with water or benzylamine, methylsulfinate **3b** and sulfinic acid **1** or **3b** and the mixture of diastereoisomers **4a/4b** in the ratio 2:3 were isolated.

Finally, the nonvolatile residue prepared from sulfinic acid **1** and anhydrous hydrogen chloride subjected to methanol or benzylamine gave sulfinates **3a/3b** or sulfinamides **4a/4b** of the same diastereoisomeric ratio (2:3).

These results imply partial formation of sulfinyl chlorides **2a/2b** as the actual intermediates, in the equilibrated diastereoisomeric ratio 3:2.

It should be noted here that in every possible way some non-β-lactam products (15 – 20%) were isolated. To complete the chemical reaction, the starting sulfinates **3** and the sulfinic acid **1** were subjected to a longer treatment with dry hydrogen chloride. Unfortunately, the quantities of non-β-lactam products were increased.

We turned our attention to sulfinamides to test whether similar reactions could be used for their epimerization and their transformation to sulfinic acid and sulfinates. Thus, sulfinamides **4a** and **4b** reacted completely and the reaction proceeded smoothly, even under ice-cooling, when treated with anhydrous hydrogen chloride in dichloromethane solution to give crystalline benzylamine hydrochloride and the mixture of sulfinyl chlorides **2a/2b**.

Although the isolation and the characterization of these very reactive intermediates from the reaction mixture failed, their presence was confirmed by chemical transformations. Sulfinyl chlorides **2a/2b** could be easily converted with water to sulfinic acid **1**. After addition of methanol or benzylamine, they were transformed into the 2:3 diastereoisomeric mixture of sulfinates **3a/3b** or sulfinamides **4a/4b** in high yields.

This investigation showed without any doubt that 4-oxoazetidine-2-sulfinic acid **1** and its sulfinates **3** and sulfinamides **4** could be easily transformed into each other in the presence of anhydrous hydrogen chloride. The formation of the diastereoisomeric mixture of sulfinyl chlorides **2a/2b** as intermediate, prepared from sulfinic acid **1**, or sulfinates **3a** and **3b** or sulfinamides **4a** and **4b**, can be either a straightforward result of chloride ion attack on the sulfinyl sulfur in the earlier epimerized starting compound, or it can accrue by later epimerization of sulfinyl chloride. The sulfinic acid can be epimerized by fast proton exchange between the **1a** and **1b** forms *via* the achiral sulfinic acid anion **1c**. Formation of methylsulfone in a short time reaction of methyl iodide with sodium salt of sulfinic acid indicated such a possibility.[11] The sulfinates and sulfinamides could not be epimerized in this way.

The starting stereochemically pure sulfinates **3a** or **3b**, regenerated in the process sulfinate → sulfinic acid or sulfinate → sulfinamide and diastereisomeric ratios (2:3) of isolated compounds **3a/3b** and **4a/4b** in the interconversion sulfinate ↔ sulfinamide, (regardless of the starting diastereoisomer) suggested that the mechanism included the formation of sulfinyl chlorides **2** as an intermediate and the epimerization was a result of rapid chloride anion exchange at sulfur between the two epimers **2a** and **2b**. The conclusion was supported by the observation that each isolated epimer of sulfinates **3** or sulfinamides **4** subjected to thermal treatment did not give an appropriate epimeric mixture. Similarly, action of methanol on sulfinamides **4** or benzylamine on sulfinates **3** did not result in their interconversion without the presence of hydrogen chloride. These results are in agreement with the previous obser-

vation that some of the acid-catalyzed hydrolyses of sulfinic acid derivatives were accelerated by addition of halide ions.[12,13]

Finally, according to some of the published information, the racemization of the sulfinates[14] and sulfoxides[15] in the presence of hydrogen chloride formulate the equilibrated mixture of sulfinyl chlorides as intermediate.

## EXPERIMENTAL

IR spectra were recorded using a Perkin-Elmer Model 257 G spectrometer. $^1$H-NMR spectra were determined for solutions in deuterochloroform with a Jeol FX 90Q spectrometer. Chemical shifts $\delta_H$ are in ppm downfield from $Me_4Si$ and $J$ values are given in Hz. Thin layer chromatography was run on Merck Kieselgel HF254 plates and was visualized under UV light or $I_2$ vapour adsorption. Column chromatography was performed on Merck Kieselgel 60 (70–230 mesh ATM) activated at 105 °C. Solvent were used either as purchased or dried and purified by standard methods. The starting stereochemically pure methylsulfinates **3a** and **3b** and benzylsulfinamides **4a** and **4b** were prepared from the appropriate sulfinic acid **1**[11] *via* sulfinyl chlorides **2a/2b** and separated in part by column chromatography according to our previously published methods.[2,3]

All products were known compounds, identified by comparison of the TLC and spectra (IR and $^1$H-NMR) with those of authentic samples.

### *Transformation of Methylsulfinate (3a)*

Hydrogen chloride was bubbled through a stirred solution of stereochemically pure methylsulfinate **3a** (5 mmol) in dry dichloromethane (70 mL) at room temperature for 15 minutes. The reaction mixture was then stirred for further 15 minutes and dichloromethane was removed by evaporation under reduced pressure to give the nonvolatile residue, which was divided into three equal parts and treated under different conditions.

Method A.

A solution of the nonvolatile residue in dichloromethane (30 mL) and water (30 mL) was stirred at room tmeperature for 1 hour and then aqueous sodium hydrogen carbonate was added until the pH was adjusted to 7.5. The layers were separated and the aqueous layer was again extracted with dichloromethane (10 mL). The combined organic layers were washed and dried over $Na_2SO_4$. After solvent evaporation under reduced pressure and purification of the residue by silica gel column chromatography with dichloromethane-ethyl acetate, the starting stereoisomer **3a** (35%) was regenerated.

The aqueous layer was acidified with 10% hydrochloric acid, the product was extracted with ethyl acetate and the organic layer was washed with saturated NaCl solution. After evaporation under reduced pressure of dried ($Na_2SO_4$) organic extract, sulfinic acid **1** (40%) was obtained.

Method B.

To a cooled solution (10 °C) of the nonvolatile residue in dry dichloromethane (30 mL), methanol (10 mL) was gradually added. The reaction mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and water (30 mL) and worked up according to the method A procedure. After purification of the residue by silica gel column chromatography with dichloromethane-ethyl acetate, the epimeric mixture of sulfinates **3a/3b** (70%) was obtained with predominant **3b** epimer, determined on the basis of $^1$H-NMR spectroscopic data. The representative $^1$H-NMR data for compound **3a**: $\delta$ 2.00 and 2.24 (each 3 H, s, $CMe_2$), 3.09 (1 H, dd, $J$ 5.0 and 15.6, 3α-H), 3.43 (1H, dd, $J$ 2.6 and 15.6, 3β-H), 3.70 (3 H, s, OMe), 4.69 (1H, dd, $J$ 2.6 and 5.0, 2-H), 5.28 and 5.30 (each 1 H, d, $J$ 16, $CH_2Ph$), 7.35 (5 H, s, $C_6H_5$); and for compound **3b**: 2.07 and 2.24 (each 3 H, s, $CMe_2$), 3.10 (2 H, d, $J$ 4.4, 3-$H_2$), 3.71 (3 H, s, OMe), 4.74 (1 H, t, $J$ 4.4, 2-H), 5.12 and 5.30 (each 1 H, d, $J$ 12.3 C$H_2$Ph), 7.36 (5 H, s, $C_6H_5$)

Only traces of sulfinic acid **1** were obtained from combined aqueous layers.

Method C

To a cooled solution (10 °C) of the nonvolatile residue in dichloromethane (30 mL), benzylamine was added dropwise until the pH was adjusted to 7.5. The resulting mixture was allowed to gradually warm to room temperature. After being stirred for 30 minutes, the layers were separated and the organic phase was washed successively with water, 5% hydrochloric acid, water, aqueous sodium hydrogen carbonate and again with water. After the solvent evaporation under reduced pressure and purification of the residue by silica gel column chromatography with dichloromethane-ethyl acetate (gradient eluation), the starting stereoisomer **3a** (28%) and the mixtures of sulfinamides **4a/4b** in the diastereoisomeric ratio 2:3 were obtained, determined on the basis of $^1$H-NMR spectroscopic data. The representative $^1$H-NMR data for compound **4a**: $\delta$ 1.94 and 2.24 (each 3 H, s, $CMe_2$), 3.14 (1 H, dd, $J$ 5.0 and 15.3, 3α-H), 3.36 (1 H, dd, $J$ 2.6 and 15.3, 3β-H), 4.00–4.30 (3H, m, $NHCH_2$), 4.77 (1 H, dd, $J$ 2.6 and 5.0, 2-H), 5.09 and 5.25 (each 1 H, d, $J$ 12.0, $OCH_2Ph$), 7.32 (10 H, s, 2 $C_6H_5$), and for compound **4b**: $\delta$ 2.08 and 2.21 (each 3 H, s, $CMe_2$), 2.94 (1 H, dd, $J$ 3.2 and 15.4, 3β-H), 3.16 (1 H, dd, $J$ 4.7 and 15.4, 3α-H), 4.19 (3 H, br, $NHCH_2$), 4.77 (1 H, dd, $J$ 3.2 and 4.7, 2-H), 5.06 and 5.28 (each 1 H, d, $J$ 12.3, $OCH_2Ph$), 7.32 (10 H, s, 2 $C_6H_5$).

### *Transformation of Methylsulfinate (**3b**)*

The same treatment of stereochemically pure methylsulfinate **3b** (5 mmol) with dry hydrogen chloride as previously reported for **3a** afforded the nonvolatile residue, which was divided into three equal parts and treated under different coditions: The treatment with water according to method A gave the starting sulfinate **3b** (32%) and sulfinic acid **1** (35%); The treatment with methanol according to method B gave the epimeric mixture of sulfinates **3a/3b** (68%) with predominant **3b** epimer; and the treatment with benzylamine according to method C gave the starting stereoisomer **3a** (30%) and the mixture of sulfinamides **4a/4b** (56%) in the diastereisomeric ratio 2:3.

### *Transformation of Sulfinic Acid (**1**)*

Hydrogen chloride was bubbled through a stirred solution of sulfinic acid **1** (7.5 mmol) in dry dichloromethane (70 mL) at room temperature for 15 minutes. The reaction mixture was then stirred for further 15 minutes and dichloromethane was removed by evaporation under reduced pressure to give the nonvolatile residue, which was divided into two equal parts and treated under different conditions. The treatment with methanol according to method B gave the mixture of sulfinates **3a/3b** (45%) and the treatment with benzylamine according to method C gave the mixture of sulfinamides **4a/4b** (48%), in the diastereoisomeric ratio 2:3 in both cases.

### *Transformation of Benzylsulfinamides (**4a**)*

Hydrogen chloride was bubbled through an ice-cooled solution of stereochemically pure benzylsulfinamides **4a** (4.5 mmol) in dry dichloromethane (40 mL) for 15 minutes. The reaction mixture was stirred at the same temperature. TLC analysis after 15 minutes showed that the starting sulfinamide was not present in the reaction mixture. The white precipitate of benzylamine hydrochloride was filtered off. The filtrate was concentrated under reduced pressure to give a nonvolatile residue, which was divided into three equal parts and treated under different conditions.

A solution of the nonvolatille residue in dichloromethane (30 mL) was worked up with water according to method A, and sulfinic acid **1** (60%) was obtained.

A solution of the nonvolatile residue in methanol (30 mL) was stirred at room temperature for 1 hour and the reaction mixture was evaporated under reduced pressure. The residue was worked up according to method B. The mixture of sulfinates **3a** and **3b** (72%) in the diastereoisomeric ratio 2:3 was obtained.

A solution of the nonvolatile residue in dichloromethane (30 mL) was treated with benzylamine according to method C, and the stereoisomers **4a** and **4b** (76%) in the diastereoisomeric ratio 2:3 were isolated.

*Transformation of Benzylsulfinamides (**4b**)*

The same treatment of stereochemically pure benzylsulfinamides **4b** (4.5 mmol) with hydrogen chloride as previously reported for **4a** afforded the nonvolatile residue, which was divided into three equal parts and treated under different conditions: The treatment with water according to method A gave sulfinic acid **1** (58%); The treatment with methanol according to method B gave the mixture of sulfinates **3a/3b** (68%) and, after the treatment with benzylamine according to method C, gave the mixture of sulfinamides **4a/4b** with the diastereoisomeric ratio 2:3 in both cases.

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## SAŽETAK

### Kiralni sulfinil-kloridi kao intermedijari u pretvorbi derivata 4-oksoazetidin-2-sulfinskih kiselina

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Stereokemijski čisti metilsulfinati **3** i benzilsulfinamidi **4** lagano se epimeriziraju u prisutnosti vodikova klorida i pritom se mogu prevesti jedan u drugi. Predloženo je stvaranje intermedijara sulfinil-klorida **2** i njihova epimerizacija kao posljedica brze izmjene kloridnih iona na sumporovu atomu. Uravnoteženi odnos između epimera **2a** i **2b** određuje enantioselektivnost tih procesa.