Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 6, pp. 909–912, 1997

Printed in Great Britain

PII: S0957-4166(97)00046-3

0957-4166/97 $17.00 + 0.00

An efficient resolution of (±)-*S*-methyl-*S*-phenylsulfoximine with (+)-10-camphorsulfonic acid by the method of half-quantities

Jochen Brandt and Hans-Joachim Gais *

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule Aachen, Professor-Pirlet-Straße 1, 52056 Aachen, Germany

Abstract: Racemic *S*-methyl-*S*-phenylsulfoximine (±)-**1** can be resolved with only 0.6 equivalents of (+)-camphorsulfonic acid by avoiding any recrystallization to give (+)-**1** of ≥99% ee in 80% yield and (−)-**1** of 97–99% ee in 74% yield. This procedure, which is based on the separation of the diastereomeric salt (+)-**1**/(+)-CSA and the sulfoximine (−)-**1**, should be suited for a large scale application. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Both enantiomers of *S*-methyl-*S*-phenylsulfoximine **1** (Scheme 1) are valuable reagents of increasing importance for asymmetric synthesis.[1,2] The optically active sulfoximines (+)-**1** and (−)-**1** are best prepared by resolution of (±)-**1** with (+)- and (−)-10-camphorsulfonic acid (CSA).[3–6] The original resolution procedure calls for the use of 1 equivalent of (+)-CSA and the isolation of the salt (+)-**1**/(+)-CSA by crystallization from hot acetone.[3,4] Two recrystallizations of (+)-**1**/(+)-CSA from acetonitrile are required to obtain, after base treatment, the sulfoximine (+)-**1** of ≥99% ee.[5] If the isolation of the enantiomer (−)-**1** is desired, than (−)-CSA has to be applied. Because of the crystallization and recrystallizations, which require large amounts of solvents, this procedure is not well suited for large scale application. It has been reported occasionally that the resolution of an acid proceeds more efficiently if only half an equivalent of the base is used (method of half-quantities).[7,8] Because of our need in large quantities of (+)-**1** and (−)-**1** for the total synthesis of carbacyclins and isocarbacyclins,[9,10] we were interested to see if the application of this method to the resolution of (±)-**1** would offer any advantage.

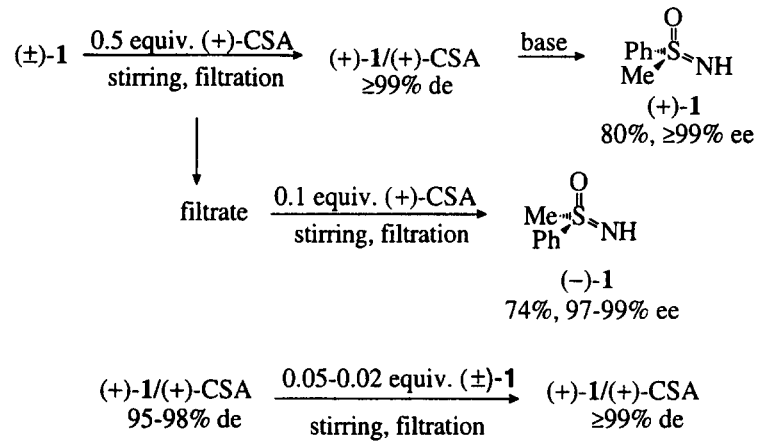
Results and discussion

Solutions of (±)-**1** and 0.5 equivalents of (+)-CSA in dry acetone were combined, and the resulting suspension was stirred at room temperature (Scheme 1). Filtration and thorough washing of the solid material with acetone afforded the salt (+)-**1**/(+)-CSA of ≥99% de in 84% yield. A base treatment of (+)-**1**/(+)-CSA[3–5] gave the sulfoximine (+)-**1** of ≥99% ee in 80% overall yield.

The ee-value of **1** could be determined without prior derivatization[5] directly by capillary GC on a per-*O*-methylated β-cyclodextrin column.

In order to obtain also the sulfoximine (−)-**1**, the above filtrate from the isolation of the salt (+)-**1**/(+)-CSA, which contained mainly (−)-**1** of 79% ee, was treated with 0.1 equivalents of solid (+)-CSA based on the initial amount of (±)-**1** used for the resolution. The solvent was evaporated and the residue dissolved in acetone. The addition of toluene to the solution caused the formation of a fine suspension. After stirring the suspension at room temperature for one day, it was kept for an additional day at 2°C. Removal of the salt (−)-**1**/(+)-CSA (45% de) and work-up of the filtrate gave the sulfoximine (−)-**1** of 97–99% ee in 74% yield.

* Corresponding author. Email: gais@RWTH-Aachen.de



Scheme 1.

If (−)-**1** of ≥99% ee is required, then (−)-CSA has to be applied for the enhancement of the ee-. Thus, the above filtrate from the isolation of the salt (+)-**1**/(+)-CSA was treated with base to give the sulfoximine (−)-**1** of 79% ee in 97% yield. Solutions of the sulfoximine (−)-**1** (79% ee) and of 0.9 equivalents (−)-CSA in dry acetone were combined, and the resulting suspension was stirred at room temperature. Filtration and washing of the solid material with acetone gave the salt (−)-**1**/(−)-CSA of ≥99% de in 82% yield. A base treatment of the salt (−)-**1**/(−)-CSA afforded the sulfoximine (−)-**1** of ≥99% ee in 78% overall yield.

Eventually, we also found a very simple way for the diastereomeric enrichment of the salt (+)-**1**/(+)-CSA without recrystallization. The salt (+)-**1**/(+)-CSA of 95–98% de was suspended in dry acetone and 2 equivalents of the racemic sulfoximine (±)-**1**, based on the amount of (−)-**1**/(+)-CSA present, were added. After stirring the suspension at room temperature for twelve hours, the salt (+)-**1**/(+)-CSA with a de-value of ≥99% de was isolated in 95–98% yield (Scheme 1). This kind of enrichment works also in case the de-value of the salt (+)-**1**/(+)-CSA is lower than 95%.

The (+)-10-camphorsulfonic acid was recovered in 97% yield by passing the basic solution of its salt through an acidic cation exchanger followed by a recrystallization of the acid from ethyl acetate.

Conclusion

Racemic *S*-methyl-*S*-phenylsulfoximine (±)-**1** can be efficiently resolved with 0.6 equivalents of (+)-camphorsulfonic acid. Thereby both sulfoximines (+)-**1** and (−)-**1** are obtained enantiomerically highly enriched in good yields without the necessity of recrystallization. This resolution is based on the separation of the diastereomeric salt (+)-**1**/(+)-CSA and the sulfoximine (−)-**1** rather than on the separation of the two diastereomeric salts (+)-**1**/(+)-CSA and (−)-**1**/(+)-CSA present in equal quantities in the case of the use of 1 equivalent of (+)-CSA.[3–5] Although resolutions by the method of half-quantities have been known for a long time the present example is a particularly efficient one.[7,8]

Experimental section

Melting points were determined on a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at room temperature (23°C) and are recorded in units of deg cm^{-3} g^{-1} dm^{-1} (*c* in g 10^{-2} cm^{-3}). The ee-values were determined by GC on a Carlo-Erba HRGS 5300 Mega-Series instrument by using a commercially available, chemically bound glass capillary column filled with per-*O*-methylated β-cyclodextrin (25 m × 0.25 mm ID, 0.25 μm film; 130°C isotherm; carrier gas dihydrogen at 100 kPa; R_t((+)-**1**)=13.0 min, R_t((−)-**1**)=14.0 min; analysis

of (±)-**1** gave (+)-**1** and (−)-**1** in a ratio of 50.1:49.9). The injector temperature was 250°C, and the detector temperature was 275°C. Acetone was dried with phosphorous pentoxide and distilled. Toluene was distilled from potassium/benzophenone. Racemic *S*-methyl-*S*-phenylsulfoximine was prepared from racemic *S*-methyl-*S*-phenylsulfoxide and sodium azide/sulfuric acid.[3–5] The optically active camphorsulfonic acids were purchased from Aldrich and used as such.

(+)-(S)-S-Methyl-S-phenylsulfoximine (+)-1

A solution of (+)-(*S*)-10-camphorsulfonic acid ((+)-CSA) (87.3 g, 376 mmol) in dry acetone (550 mL) was added gradually at room temperature under stirring to a solution of racemic *S*-methyl-*S*-phenylsulfoximine ((±)-**1**) (116.6 g, 751 mmol) in dry acetone (430 mL). After the addition of about one-third of the solution of (+)-CSA, fine white crystals of the salt (+)-**1**/(+)-CSA began to precipitate. The resulting suspension was stirred at room temperature for 12 h. The crystals were filtered with the aid of a glass filter, washed thoroughly with dry acetone (4 × 100 mL) and dried in vacuum to give the salt (+)-**1**/(+)-CSA (123.0 g, 84%) of ≥99% de as colorless crystals: mp 178°C; $[\alpha]_D$ +43.9 (*c* 1.20, acetone). Base treatment of the salt (+)-**1**/(+)-CSA[5,6] and distillation (89°C, 0.1 Torr) gave the sulfoximine (+)-**1** (47.3 g, 96%) of ≥99% ee as a colorless oil, which solidified in the freezer: $[\alpha]_D$ +36.2 (*c* 1.10, acetone); $[\alpha]_D$ +20.0 (*c* 1.12, MeOH).

(−)-(R)-S-Methyl-S-phenylsulfoximine (−)-1

(a) With (+)-(S)-camphorsulfonic acid

The filtrate remaining from the above isolation of (+)-**1**/(+)-CSA, which contained the sulfoximine (−)-**1** (79% ee), was treated with solid (+)-CSA (17.5 g, 75.4 mmol). After the concentration of the solution in vacuum (40°C, Torr), the resulting oil was treated under stirring with dry acetone (2 mL) and dry toluene (800 mL) whereby a fine suspension was formed. The suspension was stirred at room temperature for 1 d and kept at 2°C for 1 d. Filtration and drying of the solid material in vacuum gave the salt (−)-**1**/(+)-CSA (5.6 g) of 45% de. Concentration of the filtrate and distillation gave the sulfoximine (−)-**1** (43 g, 74%) of 97–99% ee.

(b) With (−)-(R)-camphorsulfonic acid

The filtrate remaining from the above isolation of (+)-**1**/(+)-CSA was evaporated to give an oil which was dissolved in $CHCl_3$ (400 mL). The solution was washed with 10% NaOH (100 mL), the organic layer separated and the water layer extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with water (50 mL). The aqueous layer was separated and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuum. Distillation of the residue (89°C, 0.1 Torr) gave the sulfoximine (−)-**1** (65.3 g, 97%) of 79% ee as a colorless oil. A solution of (−)-(*R*)-10-camphorsulfonic acid ((−)-CSA) (87.3 g, 376 mmol) in dry acetone (550 mL) was added gradually under stirring to a solution of (−)-**1** (65.2 g, 420 mmol) (79% ee) in dry acetone (430 mL). After the addition of about one-third of the solution, fine white crystals of the camphorsulfonate salt began to precipitate. The resulting suspension was stirred at room temperature for 12 h. The crystals were filtered, washed thoroughly with dry acetone (4 × 100 mL) and dried in vacuum to give the salt (−)-**1**/(−)-CSA (119.4 g, 82%) of ≥99% de as colorless crystals: mp 179°C; $[\alpha]_D$ −43.9 (*c* 1.20, acetone). Base treatment of the salt (−)-**1**/(−)-CSA and distillation gave the sulfoximine (−)-**1** (45.5 g, 96%) of ≥99% ee: $[\alpha]_D$ −36.2 (*c* 1.06, acetone); $[\alpha]_D$ −20.0 (*c* 1.11, MeOH).

(+)-(S)-S-Methyl-S-phenylsulfoximine (+)-1 through diastereomeric enrichment

The salt (+)-**1**/(+)-CSA (30 g, 77.4 mmol) of 97% de was suspended in dry acetone (100 mL) and (±)-**1** (0.50 g, 3.22 mmol) was added to the suspension. After stirring the suspension at room temperature for 18 h, it was filtered. The residue was washed thoroughly with dry acetone (3 × 75 mL) and dried in vacuum to give the salt (+)-**1**/(+)-CSA (29.1 g, 97%) of ≥99% de as a colorless powder: $[\alpha]_D$ +43.9 (*c* 1.20, acetone). Base treatment of the salt (+)-**1**/(+)-CSA and distillation gave

the sulfoximine (+)-**1** (11.2 g, 96%) of ≥99% ee: $[\alpha]_D$ +36.2 (*c* 1.10, acetone); $[\alpha]_D$ +20.0 (*c* 1.12, MeOH).

Recovery of (+)-10-camphorsulfonic acid

The basic aqueous solution, which remained from the base treatment of the salt (+)-**1**/(+)-CSA and extraction of the sulfoximine (+)-**1**, was passed through a column containing an acidic cation exchanger (Lewatit S100). Concentration of the thus obtained solution in vacuum and recrystallization of the residue from ethyl acetate gave (+)-CSA in 97% yield: mp 193°C; $[\alpha]_D$ +19.8 (*c* 2.0, H_2O).

Acknowledgements

We gratefully acknowledge the financial support of this work by the Deutsche Forschungsgemeinschaft (SFB 380) and the Fonds der Chemischen Industrie. We thank Dipl.-Chem. Manfred Jungen for valuable suggestions.

References

1. For reviews, see: (a) Johnson, C. R. In *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 1, p 223. (b) Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3. (c) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D.; Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, p. 227. (d) Pyne, S. G. *Sulfur Reports* **1992**, *12*, 57.
2. For most recent examples, see: (a) Bolm, C.; Kaufmann, D.; Zehnder, M.; Neuburger, M. *Tetrahedron Lett.* **1996**, *37*, 3985. (b) Hainz, R.; Gais, H.-J.; Raabe, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2505. (c) Jackson, R. F. W.; Briggs, A. D.; Brown, P. A.; Clegg, W.; Frampton, C. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1673. (d) Pyne, S. G.; Dong, Z. *J. Org. Chem.* **1996**, *61*, 5517.
3. Fusco, R.; Tericoni, F. *Chim. Ind. (Milan)* **1965**, *47*, 61.
4. Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418.
5. Shiner, C. S.; Berks, A. H. *J. Org. Chem.* **1988**, *53*, 5542.
6. Sulfoximines (+)-**1** and (−)-**1** can also be prepared by imination of the corresponding optically sulfoxides (Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458) which are accessible by catalytic asymmetric oxidation of methyl phenyl sulfide (Brunel, J.-M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 8086). Large scale synthesis of the sulfoximines by this route is hampered, however, by the necessity to use the hazardous reagent *O*-mesitylsulfonylhydroxylamine for the imination.
7. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger: Malabar, 1991 and references cited therein.
8. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994 and references cited therein.
9. Erdelmeier, I.; Gais, H.-J. *J. Am. Chem. Soc.* **1989**, *111*, 1125.
10. Bund, J.; Gais, H.-J.; Erdelmeier, I. *J. Am. Chem. Soc.* **1991**, *113*, 1442.

(Received in UK 9 January 1997)