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# One-Pot Resolution of *trans*-2-Iodo-cyclohexanol with *O*,*O*′-Dibenzoyl-(2*R*,3*R*)-tartaric Acid in Solid Phase

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**Abstract:** A one-pot, solid-state resolution of *racemic-trans*-2-iodo-cyclohexanol by *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid was performed. By mixing the solid racemate with half an equivalent resolving agent, the (1*R*,2*R*)-isomer of the alcohol remains uncomplexed and can be sublimated at lower temperature. By increasing the temperature, the complex decomposes and the (1*S*,2*S*)-isomer can be gained as a second fraction of the sublimation and the resolving agent remains back.

**Keywords:** Optical resolution, resolution by complex formation, solid-phase reactions

## INTRODUCTION

Optical resolution via diastereomer formation is a rather complicated process. An appropriate resolving agent and a solvent should be selected, the formed diastereomeric pair can be separated by fractional crystallization, and to regain the enantiomers and to win back the resolving agent there are two other steps.[1] There are only very few examples of one-pot resolutions.[2–4] They have mixed the solid resolving agent with a racemic liquid and separated the enantiomers by distillation.

In this article we present a one-pot resolution performed by reacting the resolving agent and the racemate in solid phase followed by separation of the enantiomers by sublimation.

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## RESULTS AND DISCUSSION

*O*,*O*′-Dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA) can be used as a complex forming resolving agent for the resolution of racemates having no basic groups, such as racemic alcohols. A number of racemic alcohols were resolved by the conventional method using hexane as solvent.[5]

The racemic *trans*-2-iodo-cyclohexanol (**1**) was selected as a model compound for the one-pot resolution because it is solid at room temperature (mp 43 °C) and sublimates well. DBTA monohydrate and *racemic*-**1** was mixed in a mortar (1:2 molar ratio) at room temperature, and after different reaction times the solid mixture was fractionally sublimated in vacuum. At lower temperature (50 °C) the sublimate enriches in the unreacted enantiomeric mixture of (1*R*,2*R*)-**1**. By increasing the temperature (up to 100 °C), the complex slowly decomposes, and the enantiomeric mixture of (1S,2S)-**1** that was complexed can be obtained as sublimate (Figure 1). The results are summarized in Table 1.

The reaction in the undisturbed solid mixture proceeds slowly. Although after 1 week substantial enantiomer separation had been achieved, the equilibrium was reached only after 3 weeks. When the solid reaction mixture was not simply left to stand but was rubbed intensively in a mortar for 1–2 h the same results as standing for 3–4 weeks could be achieved.

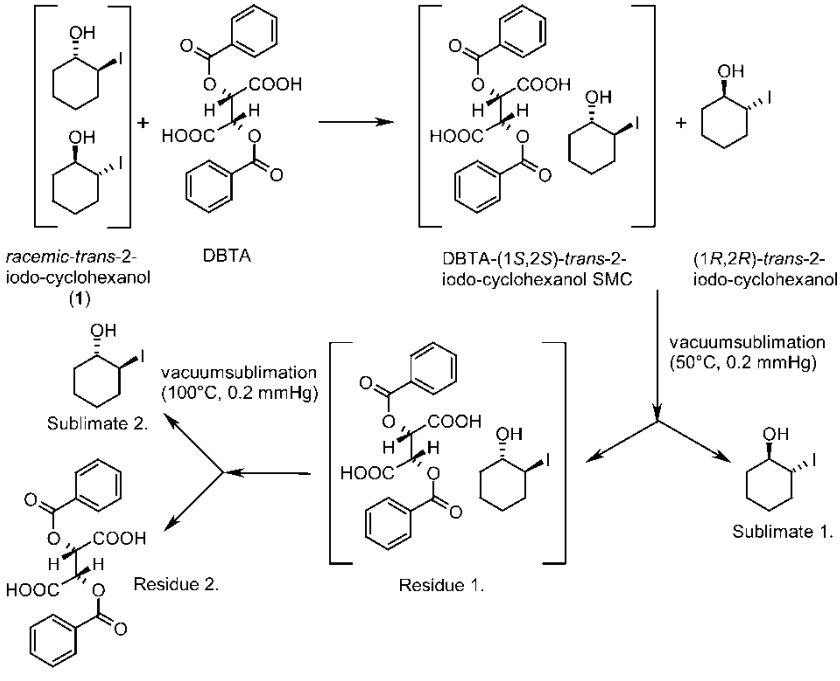


***Figure 1.*** One-pot solid-phase resolution of *racemic*-**1** with DBTA.

***Table 1.*** Summary of the results of solid-phase resolution of *racemic*-**1** with DBTA monohydrate

| Reaction time (weeks) | Molar ratio | Sublimation temperature (°C) | Sublimate fraction No. | Yield (%)[a] | Results of sublimates | | |
|---|---|---|---|---|---|---|---|
| | | | | | Absolute config. | *E.e.* (%) | S |
| 1 | 1:2 | 50 | 1 | 30 | (1*R*,2*R*)-(−) | 68.0 | 0.20 |
| | | 50 | 2 | 58 | (1*R*,2*R*)-(−) | 86.0 | 0.50 |
| | | 100 | 3 | 53 | (1*S*,2*S*)-(+) | 80.0 | 0.42 |
| 2 | 1:2 | 50 | 1 | 56 | (1*R*,2*R*)-(−) | 75.6 | 0.42 |
| | | 50 | 2 | 37 | (1*R*,2*R*)-(−) | 55.1 | 0.20 |
| | | 100 | 3 | 53 | (1*S*,2*S*)-(+) | 46.2 | 0.25 |
| 3 | 1:2 | 50 | 1 | 10 | (1*R*,2*R*)-(−) | 76.2 | 0.08 |
| | | 50 | 2 | 77 | (1*R*,2*R*)-(−) | 78.7 | 0.61 |
| | | 100 | 3 | 18 | (1*S*,2*S*)-(+) | 72.0 | 0.13 |
| 4 | 1:2 | 50 | 1 | 15 | (1*R*,2*R*)-(−) | 76.8 | 0.12 |
| | | 50 | 2 | 77 | (1*R*,2*R*)-(−) | 78.9 | 0.61 |
| | | 100 | 3 | 26 | (1*S*,2*S*)-(+) | 58.1 | 0.15 |
| 4 | 1:4 | 50 | 1 | 34 | (1*R*,2*R*)-(−) | 40.1 | 0.14 |
| | | 50 | 2 | 28 | (1*R*,2*R*)-(−) | 23.2 | 0.07 |
| | | 100 | 3 | 18 | (1*S*,2*S*)-(+) | 92.2 | 0.17 |

[a]Yield refers to the half of the *racemic*-**1** mass; S = e.e.×Y (Fogassy parameter, efficiency of the resolution).

By using 1:4 molar ratio (resolving agent–racemate) the highest e.e. value can be attained, but because of the insufficient amounts of resolving agent, there is no chance for a good efficiency of resolution (Table 1, row 5).

We consider this resolution one of the simplest one ever made.

## EXPERIMENTAL

DBTA monohydrate was purchased from Fluka. *Racemic*-**1** was prepared from 1,2-epoxy-cyclohexanol.[5]

### One-Pot Solid-Phase Resolution of *Racemic*-1 with DBTA Monohydrate

*Racemic*-**1**, (4 × 1.00 g, 4 × 4.4 mmol) and 4 × 0.83 g (4 × 2.2 mmol) DBTA monohydrate were mixed in a mortar for 2 min. The solid mixture was collected and closed in a specie jar. After standing 7, 14, 21, and 28 days at room temperature, the mixture was fractionally sublimated in a vacuum (0.2 mmHg) at 50 °C, 70 °C, and 100 °C for 1 h. Mass, e.e., and optical rotation of the sublimates were measured.

After experimenting with 1:4 molar ratio, only 0.42 g (1.1 mmol) DBTA monohydrate was used.

A Hewlett Packard HP 5890/II instrument with flame ionization detector (FID) detector was used for GC analysis. The column used was a 12 m × 0.100 mm i.d. fused silica open tubular column coated with Chirasil-Dex chiral stationary phase at 0.15-μm film thickness.[6] The stationary phase was a methylsilicone polymer substituted with permethylated β-cyclodextrin via spacer. $H_2$ was used as carrier gas with 1 mL/min$^{-1}$ speed. The injection mode was split (1:160). Compound **1** was analyzed as an acetyl derivative at 100 °C.[7]

Optical rotation was measured with a Perkin Elmer 241 polarimeter. The absolute configuration of **1** sublimate was determined from the sign of the optical rotation. (1*S*,2*S*)-*trans*-2-Iodo-cyclohexanol (**1**), $[\alpha]_D^{23} = +33.1$ ($c = 2.5$; $CHCl_3$).[8]

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