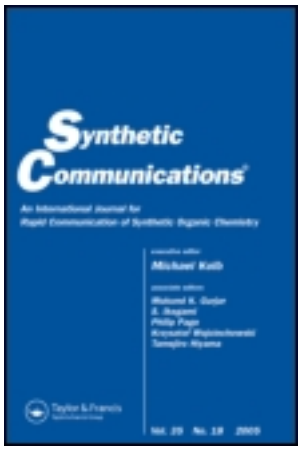

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

EFFICIENT RESOLUTION OF (±)-1-(9-ANTHRYL)ETHYLAMINE

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Published online: 22 May 2009.

To cite this article: Marin Roje , Zdenko Hameršak & Vitomir Šunjić (2002) EFFICIENT RESOLUTION OF (±)-1-(9-ANTHRYL)ETHYLAMINE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:22, 3413-3417, DOI: 10.1081/SCC-120014769

To link to this article: http://dx.doi.org/10.1081/SCC-120014769

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SYNTHETIC COMMUNICATIONS
Vol. 32, No. 22, pp. 3413–3417, 2002

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ABSTRACT

Conditions for efficient resolution of (±)-1-(9-anthryl)ethylamine ((±)-**1**) by fractional crystallization of its salts with (*S*)-(+)-mandelic acid (**2**) are reported. When crystallization was performed by fast addition of chloroform solution of an equivalent of (±)-**1** to the hot chloroform solution of (+)-**2**, crystals of mandelate of (+)-1-(9-anthryl)ethylamine ((*R*,*S*)-**3**) are collected in 56% yield. (*R*)-(+)-**1** (98.6% e.e.) is isolated by extraction from bicarbonate solution of mandelate salt. Ulterior collection of four crops afforded (*R*,*S*)-**3** with 71.5% cumulative yield and >98% e.e. of (+)-**1** in a any single crop. With only 0.5 equivalents of (+)-**2** crystallization afforded (*R*,*S*)-**3** in 47.4% yield and (+)-**1** with 98.1% e.e.

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DOI: 10.1081/SCC-120014769
0039-7911 (Print); 1532-2432 (Online)

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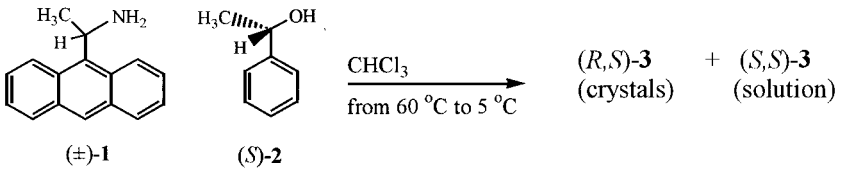
Enantiomerically pure 1-arylethylamines emerge as important chiral auxiliaries in stoichiometric and catalytic asymmetric reactions,[1,2] and for enantiorecognition.[3] Whereas both enantiomers of phenylethylamine are nowadays biotechnologically produced in multiton quantities,[4] and have found application on an industrial scale,[5] enantiomerically pure 1-(1-naphthyl)ethylamine still represents an expensive laboratory reagent.[6] A number of 1-arylethylamines are nowadays available in the enantiomerically pure form following "family approach" to the resolution of their racemates.[7] Neither racemic nor enantiomerically pure 1-(9-anthryl)ethylamine (**1**) is commercially available, however. Its use as chiral auxiliary is described in a few papers, where the authors have reported resolution of racemate to (−)-**1** via (−)-mandelic acid salt. This enantiomer was obtained in a very low (8%) yield (>99% e.e.) only after repeated crystallizations of its mandelate salt from ethanol.[8,9] Absolute (*R*) configuration of (+)-**1** has been assigned on the bases of the NMR spectra of its camphanic acid amide,[10] and more recently confirmed by the analysis of the experimental and calculated CD spectra of its *s*-triazine derivative.[9b]

We have recently attempted resolution of racemic **1**, via enantioselective acetylation (kinetic resolution) by lipases in organic solvents.[11] Best results ($E>200$) were obtained only at low conversions (<30%) with *Candida antarctica* A lipase, which were also difficult to reproduce on a larger scale. Prompted by this result, and inefficient resolutions reported previously,[8,9] we have focused our attention on resolution of the racemic **1** by crystallisation, Sch. 1.

On screening, chloroform turned out as the solvent of choice, while formerly used ethanol proved inconvenient.[8] We also observed that the traditional crystallisation procedure, mixing of equimolar quantities of the solid racemate and optically pure acid in the selected solvent and then heating, inevitably led to partial crystallisation of optically impure (*R*,*S*)-**3**. Examination of the solubility of the samples of pure diastereomeric salts revealed very low (0.9 mg/mL) solubility of (*S*)-(+)-mandelate salt of (+)-**1** ((*R*,*S*)-**3**) in chloroform, and surprisingly, complete miscibility of the oily mandelate of (−)-enantiomer ((*S*,*S*)-**3**), with this solvent. We also



Scheme 1.

observed that solubility of (+)-mandelic acid ((*S*)-(+)-**2**) rises from 15 mg/mL at 20°C to 45 mg/mL at 60°C. Having these data at hand, we completed fractional crystallisation by fast addition of the saturated solution of (±)-**1** in chloroform to hot, saturated solution of (+)-**2** in the same solvent. On slow crystallisation (*R*,*S*)-**3** was obtained in 56% yield, and (*R*)-(+)-**1** was isolated with 98.6% e.e. On repeated partial evaporation and crystallisation additional crops of (*R*,*S*)-**3** were collected; 71.5% overall yield was achieved and the isolate (+)-**1** regularly exhibited >98% e.e.

In view of the large difference in solubility of the two diastereomeric salts, in the set of experiments an attempt was made to "titrate" racemic amine by less than equimolar quantity of acid (+)-**2**, expecting selective recovery of (*R*)-(+)-**1** in the less soluble salt (*R*,*S*)-**3**. Quite promising results were obtained; e.g., with 0.5 mol equivalent of (+)-**1** 47.8% yield and 98.1% e.e. of the salt (*R*,*S*)-**3**, obtained in two crops. This yield is ca 10% lower than obtained at the same concentration of (±)-**3** with equimolar quantity of acid (+)-**2**, while the e.e. is only slightly lower.

Finally, it is interesting that using various ratios of (±)-**1**/(+)-**2** a much higher quantity of (*R*,*S*)-**3** salt remained in solution then expected from its very low solubility, indicating certain "salting in" effect of the second diastereomeric salt.

In conclusion, efficient resoluton of (±)-**1** is completed in two different modes, by crystallization of its salt with (+)-mandellic acid in chloroform, which substantially improve former results and is amenable to the large-scale preparation of (+)-**1** with high enantiomeric purity.

EXPERIMENTAL

A typical experimental procedure of the resolution of (±)-**1** is as follows: to the hot, ca 60°C, solution of (+)-**2** (880 mg, 5.8 mmol) in $CHCl_3$ (30 mL) amine (±)-**1** (1280 mg, 5.8 mmol) in $CHCl_3$ (5.0 mL) was added in one shot. This solution was seeded, while hot, with crystals of mandelate salt (*R*,*S*)-**3**, then slowly cooled to room temperature and kept at 5°C overnight. Precipitate was collected on filter and washed with cold $CHCl_3$ (2×5.0 mL), to obtain diastereomeric salt (*R*,*S*)-**3**, colourless to slightly yellow crystals (610 mg, 56%), m.p. 193–194°C, $[\alpha]_D^{25} + 9.0$ ($c = 1.0$, EtOH). Anal. calcd. for $C_{24}H_{23}NO_3$ (373.46): C 77.19%, H 6.21%, N 3.75%. Found: C 77.42%, H 6.46%, N 3.91%.

This salt was suspended in CH_2Cl_2 (20 mL) and satd. aqueous $NaHCO_3$ solution was added dropwise to the stirred suspension. Stirring was continued for 45 min at r.t., and the resulting mixture extracted with CH_2Cl_2 (3×15 mL). Organic extracts were dried, filtered and evaporated

affording pure (*R*)-(+)-**1** (355 mg, quantitative) pale yellow crystals, m.p. 110–113°C, e.e. 98.6% $[\alpha]_D + 18.0$ ($c = 1.0$, $CHCl_3$).

The HPLC conditions for enantioseparation of (±)-**1** were as follows: Chiralcel OD-R column (250 × 4.6 mm), MeCN/0.5 M $NaClO_4$ pH 2.5 ($HClO_4$) (7 : 3) as mobile phase, flow 0.5 mL/min, UV detector at 254 nm.

Note: The solubility of mandelic acid in $CHCl_3$ was determined gravimetrically, the solubility of the diastereomeric salt (*R*,*S*)-**3** was determined spectrophotometrically at 366 nm, both for samples from satd. thermostated solutions.

ACKNOWLEDGMENT

This work was supported by the Ministry of Science and Technology, Republic of Croatia, grant No. 980701.

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Received in the Netherlands November 11, 2001

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