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Efficient resolution of (±)-*trans*-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid and enrichment of enantiomeric purity of non-racemic 2,3-diphenylpiperazine using different achiral acids

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Abstract. Enantiomerically pure (*R*,*R*)-(+)-2,3-diphenylpiperazine with 98% *ee* was obtained by resolution of the corresponding racemic mixture using (1*S*)-(+)-10-camphorsulfonic acid. The partially resolved enriched sample of (*S*,*S*)-(–)-2,3-diphenylpiperazine with 73% *ee* was purified to obtain samples of 97% *ee* using different achiral acids *via* the preparation of either homochiral or heterochiral hydrogen bonded aggregates.

Keywords. 2,3-Diphenylpiperazine; camphorsulfonic acid; resolution; homochiral aggregates; heterochiral aggregates.

1. Introduction

Though several new processes appeared in recent years for the asymmetric synthesis of enantiomerically pure compounds, most of the commercially important products are still manufactured via the processes of resolution of racemic mixtures. The most often used modern methods of resolution of racemates has recently been reviewed.[1] In recent years, new procedures for the resolution of a variety of diamines,[2] amino alcohols,[3] diols[4,5] and diacids[6] have been developed in this laboratory using a range of commercially available and less expensive chiral resolving agents such as L-(+)-tartaric acid, *O*,*O*-dibenzoyltartaric acid, BINOL/boric acid, L-proline and chiral amine/boric acid. Also, a conceptually novel method of achieving homogeneity of chirality by purification of partially resolved amino alcohols and a C_2-symmetric chiral diamine *via* the preparation of corresponding hydrogen bonded homochiral or heterochiral aggregates was reported from this laboratory.[7] Recently, we have reported a novel method for the resolution of (±)-2,3-diphenylpiperazine using L-(+)-tartaric acid.[8] Using this method, enantiomerically pure 2,3-diphenylpiperazine was obtained in two successive operations from racemic piperazine. It was of our interest to design a single step resolution process to access the enantiomerically pure compound of this skeleton which has biological importance.[9] In this study, we report a convenient procedure for the resolution of (±)-2,3-diphenylpiperazine.

2. Experimental

2.1 *Synthesis of (±)-2,3-diphenylpiperazine*

(±)-2,3-Diphenylpiperazine was synthesized using the previously reported procedure and employed in the resolution processes.[8]

2.2 *Resolution of (±)-2,3-diphenylpiperazine* ***1*** *using (1S)-(+)-10-camphorsulfonic acid* ***2***

The (1*S*)-(+)-10-camphorsulfonic acid (4·65 g, 20 mmol) and (±)-2,3-diphenylpiperazine **1** (2·4 g, 10 mmol) were taken in CH_2Cl_2 (100 mL) and the contents were stirred at 25°C for 24 h and filtered. The precipitate I was suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3. The solvent was evaporated to obtain (*R*,*R*)-**1**. The filtrate I was concentrated to reduce its volume by 50 mL and stirred for another 12 h and filtered. The precipitate II was separated and suspended in a mixture of CH_2Cl_2 and aq. Na_2CO_3 (2M) and stirred until dissolution oc-

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curred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain (*S,S*)-**1**. The filtrate was stirred with aq. Na_2CO_3 (2M) and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extract was washed with brine, dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain (*R,R*)-**1**.

Precipitate I
Yield: 0·60 g (25%), mp: 88–90°C, *ee*: 98% (*R,R*) from HPLC.
Precipitate II
Yield: 1·50 g (62%), *ee*: 73% (*S, S*) from HPLC.
Fitrate II
Yield: 0·24 g (10%), *ee*: 80% (*R,R*) from HPLC.

2.3 *Purificaton of non-racemic 2,3-diphenylpiperazine **1** using achiral acids **3**–**5***

The partially resolved (*S,S*)-(–)-2,3-diphenylpiperazine **1** (73% ee, 0·12 g, 0·5 mmol) was dissolved in THF (5 mL) and achiral acid (0·3 mmol) was added and the contents were stirred at 25°C for 2 h and filtered. The precipitate was suspended in a mixture of CH_2Cl_2 (10 mL) and 2M Na_2CO_3 (5 mL) and stirred until the precipitate is completely dissolved. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain (*S,S*)-(–)-**1**. The filtrate was evaporated and the residue was taken in CH_2Cl_2 (10 mL) and digested with 2M Na_2CO_3 (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 5 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous K_2CO_3 and the solvent was evaporated to obtain (*S,S*)-(–)-**1**.

2.4 *HPLC analysis of the trifluoroacetamide derivatives of 2,3-diphenylpiperazine*

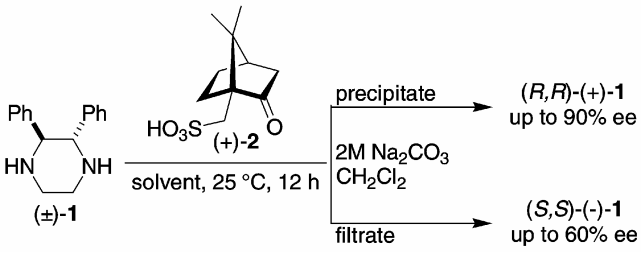
The (±)-2,3-diphenylpiperazine **1** (0·5 mmol) in CH_2Cl_2 (10 mL) was stirred overnight with excess trifluoroacetic anhydride (TFAA). The solution was concentrated under reduced pressure to remove the solvent and excess TFAA. The residue was purified by flash column chromatography (silicagel 230–400 mesh, 5% EtOAc/hexanes v/v) or re-crystallized from hexane/CH_2Cl_2 (99 : 1) mixture. The trifluoroacetamide derivative was dissolved in isopropanol (~10 mg/mL) and HPLC analyses were performed using a Chiralcel OD-H column supplied by Daicel Chemical Industries, Ltd with a binary gradient method using hexanes:isopropanol (98 : 2) in the flow rate 0·5 mL/min. Retention times for the trifluoroacetamide derivatives of 2,3-diphenylpiperazine are 10·5 min for the (*R,R*)-**1** and 12·3 min for the (*S,S*)-**1**.

2.5 *HPLC analysis of (±)-2,3-diphenylpiperazine **1***

The (±)-2,3-diphenylpiperazine **1** was dissolved in isopropanol (~10 mg/mL) and HPLC analyses were performed using a Chiralcel OD-H column supplied by Daicel Chemical Industries, Ltd with a binary gradient method using hexanes:isopropanol (90 : 10) in the flow rate 0·5 mL/min. Retention times for the enantiomers of (±)-2,3-diphenylpiperazine are 11·8 min for the (*S,S*)-**1** and 14·7 min for the (*R,R*)-**1**.

3. Results and discussion

In the initial studies, effect of the quantity of solvent and chiral resolving agent on the outcome of the resolution was studied (scheme 1, table 1). When the resolution was carried out in THF solvent using 2·25 mmol of (1*S*)-(+)-10-camphorsulfonic acid (for 1·5 mmol of (±)-2,3-diphenylpiperazine), 58% *ee* was obtained from the filtrate fraction (table 1, entry **1**). Employing 2 equivalents (3·0 mmol for 1·5 mmol of (±)-**1** of (1*S*)-(+)-10-camphorsulfonic acid, the enantiopurity was increased to 80% *ee*, albeit in 20% yield (table 1, entry **2**). When CH_2Cl_2 was used as the solvent, (*R,R*)-**1**, with 90% *ee* was obtained from the precipitate fraction and a sample of (*S,S*)-(**1**) with 60% *ee* was obtained from filtrate fraction (table 1, entry **3**).

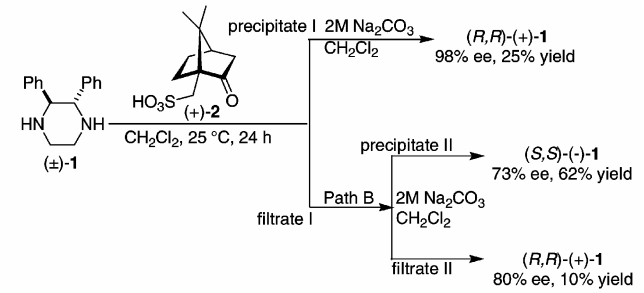


Scheme 1.

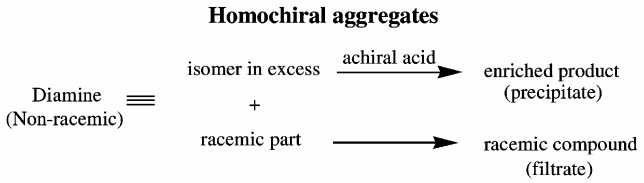
Table 1. Resolution of (±)-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid.[a]

			Piperazine **1** obtained from			
			Precipitate fraction		Filtrate fraction	
Entry	Piperazine **1** (mmol)	CSA **2** (mmol)	% *ee*[b]/conf	Yield (%)[c]	% *ee*[b]/conf	Yield (%)[c]
1[d]	1.5	2.25	50 (*R,R*)	42	58(*S,S*)	52
2[d]	1.5	3.0	3 (*R,R*)	75	80(*S,S*)	20
3[e]	1.5	3.0	90 (*R,R*)	32	60(*S,S*)	59
4[e,f]	10.0	20.0	98 (*R,R*)	25	73 (*S,S*)	62

[a]All the reactions were carried out using racemic piperazine **1** and CSA **2** in solvent (10 mL per mmol of piperazine) for 12 h. [b]All *ee* values reported here are based on HPLC analysis. [c]The yields are of the isolated products, based on the total amount of the piperazine **1** used. [d]THF was used as solvent. [e]CH_2Cl_2 was used as solvent. [f]The resolution was carried out as outlined in scheme **2**

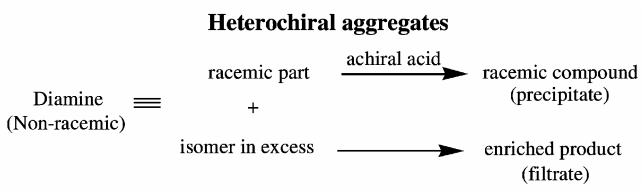


Scheme 2.



Scheme 3.

When the resolution was carried out in 10 mmol scale in CH_2Cl_2 solvent, (*R,R*)-**1** with 98% *ee* was obtained from the precipitate fraction (scheme 2, table 1, entry **4**). In this process, 10 mmol of (±)-2,3-diphenylpiperazine **1** and 20 mmol of (1*S*)-(+)-10-camphorsulfonic acid **2** were taken in CH_2Cl_2 (100 mL) and stirred for 24 h. (*R,R*)-(+)-2,3-Diphenylpiperazine **1**, with 98% *ee* was obtained from precipitate fraction I. The filtrate was concentrated to approximately 50 mL in volume, stirred for another 12 h. The precipitate thus formed was separated. From the precipitate fraction II, (*S,S*)-(–)-2,3-diphenylpiperazine **1**, with 73% *ee* was obtained in 62% yield. (*R,R*)-(+)-2,3-diphenylpiperazine **1**, with 80% *ee* was obtained from filtrate fraction II in 10% yield.



Scheme 4.

Recently, a conceptually new method of purification of non-racemic samples via the preparation of homochiral/heterochiral aggregates was developed in our laboratory.[7,8] This concept is based on the formation of homochiral and heterochiral aggregates which can be visualized as outlined in the scheme 4 and scheme 5. Homochiral aggregates are considered to be aggregates of single enantiomer of chiral amine and the achiral acids. The heterochiral salt aggregates are formed through the aggregation of both isomers of amine and the achiral acids. The non-racemic sample can be considered as a combination of racemic sample and single isomer present in excess. In homochiral salt aggregates, the isomer present in excess in the non-racemic diamine forms aggregates with achiral acid and precipitates out, leaving the racemic part in the filtrate fraction (scheme 3, table 2, entries **1**, **2**).

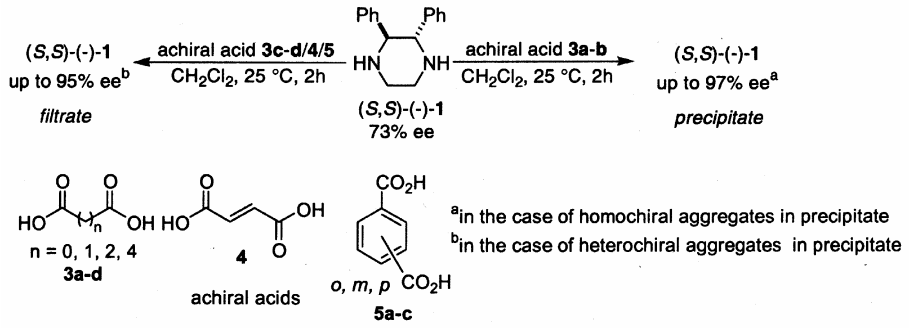
In the formation of heterochiral salt aggregates, the racemic part in the non-racemic sample forms aggregates with achiral acid and precipitates out. The isomer present in excess will be left out in the filtrate fraction, giving enantiomerically enriched product in the filtrate fraction (scheme 4, table 2, entries **3–8**).

This concept was applied for the enrichment of partially resolved non-racemic 2,3-diphenylpipera-

Table 2. Purification of non-racemic 2,3-diphenylpiperazine (*S,*S)-**1** (73% *ee*) using achiral acids.[a]

		2,3-Diphenylpiperazine **1** obtained from			
		Precipitate fraction		Filtrate fraction	
Entry	Achiral acid	% *ee*[b]/conf	Yield (%)[c]	% *ee*[b]/conf	Yield (%)[c]
1	Oxalic acid	97 (*S,S*)	62	21 (*S,S*)	31
2	Malonic acid	94 (*S,S*)	65	35 (*S,S*)	33
3	Fumaric acid	48 (*S,S*)	58	94 (*S,S*)	34
4	Succinic acid	58 (*S,S*)	50	95 (*S,S*)	35
5	Adipic acid	46 (*S,S*)	51	90 (*S,S*)	42
6	Phthalic acid	61 (*S,S*)	60	82 (*S,S*)	35
7	Isophthalic acid	57 (*S,S*)	58	80 (*S,S*)	38
8	Terephthalic acid	63 (*S,S*)	51	81 (*S,S*)	40

[a]All the reactions were carried out using non-racemic piperazine (*S,*S)-**1** (73% *ee*, 0·5 mmol) and achiral acid (0·3 mmol) in THF (2 mL) for 2 h. [b]All *ee* values reported here are based on HPLC analysis. [c]The yields are of the isolated products, based on the total amount of the starting non-racemic piperazine used



Scheme 5.

zine (*S,S*)-**1** of 73% *ee* obtained in the resolution (scheme 2) using different achiral dicarboxylic acids (scheme 5, table 2). Among the achiral acids used, oxalic acid **3a** and malonic acid **3b** gave enantiomerically enriched (*S,S*)-**1** up to 95% *ee* in the precipitate fraction; in accordance with the predominant formation of homochiral salt aggregates in the precipitate fraction (table 2, entries **1**, **2**). By using other dicarboxylic acids such as fumaric acid **4**, succinic acid **3c**, adipic acid **3d**, phthalic acid **5a**, isophthalic acid **5b** and terephthalic acid **5c**, enantiomerically enriched samples of **1** were obtained in the filtrate fraction. In these cases, presumably, heterochiral aggregates are formed predominantly in the precipitate fraction, leaving the enantiomerically enriched product in the filtrate fraction (table 2, entries **3**–**8**).

In order to accomplish the maximum enrichment of **1**, through the homochiral aggregate enrichment process, the amount of achiral acid employed in the process should be equivalent to the amount of one of the isomers present in excess excluding the racemic compound, or less than that. In the case of enrichment of the product through the heterochiral aggregates formation, the amount of achiral acid should be equivalent to the racemic part present in the non-racemic sample or slightly more than that. In this case, if the amount of achiral acid is less than that is required, the racemic part also will be left out in the filtrate fraction, leading to lower enantiomeric purity in the filtrate fraction.

4. Conclusions

In summary, enantiomerically pure (*R,R*)-(+)-2,3-diphenylpiperazine was obtained in 98% *ee* in a single-step operation from the resolution of (±)-2,3-diphenylpiperazine using (1*S*)-(+)-10-camphorsulfonic acid. Partially resolved (*S,S*)-(–)-2,3-diphenylpipera-

zine (73% *ee*) obtained from the filtrate fraction in the resolution was enriched up to 97% *ee* using different achiral dicarboxylic acids *via* the formation of homochiral or heterochiral salt aggregates. This method of purification of partially resolved samples has significant potential for further exploitation in large scale chiral processes.

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