Synthesis and Optical Resolution of 1-(4-Isopropylphenyl)-ethylamine

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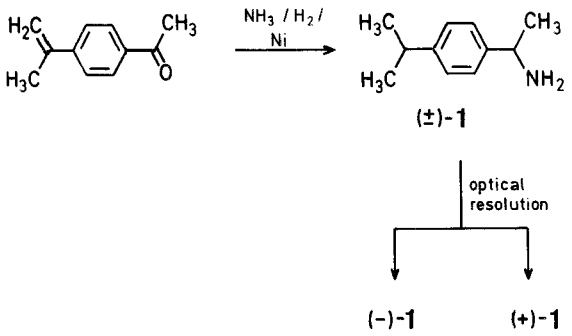
Among the many synthetic resolving agents, optically active 1-phenylethylamine is widely used for resolving chiral carboxylic acids[1]. In spite of the wide applicability of the amine, its contamination in the resolved products sometimes becomes troublesome because of its solubility in water, especially in the optical resolution of water-soluble carboxylic acids; thus, the development of a more hydrophobic agent is required.

Optically active 1-(4-isopropylphenyl)-ethylamine is expected to be as effective and more hydrophobic than 1-phenylethylamine. Concerning the optical resolution of 1-(4-isopropylphenyl)-ethylamine, no details have been reported, although its application to the optical resolution of 2-substituted propanoic acids was described in a patent[2].

(±)-1-(4-Isopropylphenyl)-ethylamine [(±)-**1**] was easily prepared in a good yield from 4-isopropenylacetophenone, which is commercially available in large quantities, by the catalytic hydrogenation of the isopropenyl group and the simultaneous reductive amination of the acetyl group in the presence of ammonia and hydrogen in a one pot reaction.

The salt, deposited from a 2-propanol solution of equimolar amounts of (±)-**1** and optically active mandelic acid [(−)-**2**], was recrystallized twice from 2-propanol to give optically pure (+)-**1** · (−)-**2** salt in 64% total yield. Treatment of the (−)-enriched **1**, recovered from the mother liquor, with (+)-**2** gave a 75% yield of the (−)-**1** · (+)-**2** salt in optically pure state without any recrystallizations.



To determine which conglomerate derivatives of **1** are resolvable by preferential crystallization, cinnamic acid was used in the first place as an achiral acidic derivatant since its salts with 1-phenylethylamine[3], 1-phenyl-2-(*p*-tolyl)-ethylamine[3], and *erythro*-2-amino-1,2-diphenylethanol[4], which have arylmethanamine parts as does **1**, have been found to be conglomerate. As expected, the **1** · cinnamic acid salt **(3)** satisfied the minimum requirements for being conglomerate, and alternate seeding of (+)- or (−)-**3** to a supersaturated solution of **3** was found to give (+)- or (−)-**3** in 68–95% optical purities. Recrystallization of the salts followed by liberation with an alkali solution gave almost optically pure (+)- or (−)-**1**.

Optically active **1** was applied to the optical resolution of (±)-malic acid **(4)**, a water-soluble carboxylic acid, and (+)- and (−)-**4** were obtained in high optical purities. No contamination of **1** in **4** after liberation was observed as expected.

(±)-1-(4-Isopropylphenyl)-ethylamine (1):
To 99% methanol (50 ml), saturated with ammonia by bubling at 0–5 °C, in a 200 ml autoclave is added 4-isopropenylacetophenone (16.0 g, 0.1 mol) and activated nickel catalyst (1.6 g, 10 wt%). After sealing the apparatus, the mixture is warmed to 110 °C over 25 min and kept at this temperature for 30 min with stirring. Then, hydrogen is introduced and the pressure is kept at 34 kg/cm^2 for 460 min at 110 °C. The mixture is then cooled and the catalyst filtered off through Celite. After concentration of the filtrate, the oily product which remains is treated with 4 normal hydrochloric acid (30 ml) and extracted with benzene (3 × 50 ml). The aqueous solution is basified with 50% sodium hydroxide solution (12 g) and extracted with benzene (3 × 50 ml). The extracts are dried with potassium carbonate and concentrated under reduced pressure. Distillation of the residual oil gives (±)-**1**; yield: 12.1 g (74%); b.p. 128 °C/3.87 kPa (Lit.[5], b.p. 111–113 °C/2.00 kPa).

Fractional Crystallization of 1-(4-Isopropylphenyl)-ethylamine · Mandelic Acid (1 · 2) Salt:
A mixture of (±)-**1** (24.50 g, 0.15 mol) and (−)-**2** (22.80 g, 0.15 mol) in 2-propanol (330 ml) is refluxed until the solution becomes clear. Then, the solution is cooled by standing at room temperature for 4 h and the precipitates deposited (21.73 g) are collected by filtration. Recrystallizations of the precipitates twice from 2-propanol (320 ml then 370 ml) gives the (+)-**1** · (−)-**2** salt; yield: 15.06 g (64%); m.p. 180–181 °C; $[\alpha]_D^{24}$: −41.4° (*c* 1.00, 99% CH_3OH).

The minus enriched **1** recovered from the mother liquor (12.9 g, 79 mmol) is similarly treated with (+)-**2** (12.00 g, 79 mmol) in 2-propanol (320 ml) to give the (−)-**1** · (+)-**2** salt; yield: 17.78 g (75%); m.p. 180.5–181.5 °C; $[\alpha]_D^{24}$: +41.5° (*c* 1.00, 99% CH_3OH).

$C_{19}H_{25}NO_3$ (315.4)				
calc.	C 72.35	H 7.99	N 4.44	
found	72.30	7.91	4.49	for (+)-**1** · (−)-**2** salt
	72.41	8.27	4.22	for (−)-**1** · (+)-**2** salt

The (+)-**1** · (−)-**2** salt (9.75 g, 31 mmol) is treated with 1 normal sodium hydroxide solution (38 ml) and extracted with benzene (3 × 50 ml). The extracts are dried with potassium carbonate and concentrated under reduced pressure. Distillation of the residual oil gives (−)-**1**; yield: 4.81 g (95%); b.p. 123 °C/3.20 kPa; $[\alpha]_D^{22}$: +23.9° (*c* 2.19, 99% CH_3OH).

Liberation of the (−)-**1** · (+)-**2** salt (12.00 g, 38 mmol) in a similar manner gives (−)-**1**; yield: 5.72 g (92%); b.p. 122 °C/3.07 kPa; $[\alpha]_D^{22}$: −23.9° (*c* 2.32, 99% CH_3OH).

The optical purities of these amines were confirmed to be over 99% by H.P.L.C. analysis of the diastereodiamides with optically active *anti*-head-to-head coumarin dimer[6].

Preparation of Seeds for the Preferential Crystallization:
Seeds for the preferential crystallization are prepared from optically active **1**, obtained as above, and cinnamic acid, followed by recrystallization from 2-propanol: m.p. 148–149 °C; $[\alpha]_D^{23}$: + or −7.6° (*c* 1.00, 99% CH_3OH).

$C_{20}H_{25}NO_2$ (311.4)				
calc.	C 77.14	H 8.09	N 4.50	
found	77.11	7.81	4.29	for (+)-salt
	77.17	7.96	4.54	for (−)-salt

Preferential Crystallization of 1-(4-Isopropylphenyl)-ethylamine · Cinnamic Acid Salt (3):
A refluxed clear solution of (±)-**3** (4.93 g) and (±)-**1** · acetic acid salt (13.40 g) is cooled at about 24 °C, seeded with (+)-**3** (15 mg), and stirred gently at 3 °C for 200 min. The precipitates deposited are collected by filtration to give 0.93 g of (+)-**3** (91% optical purity). To the mother liquor is added (±)-**3** (1.25 g), and the solution is similarly refluxed, cooled, and seeded with (−)-**3** to give 1.74 g of (−)-**3** (68% optical purity). The process is repeated in a similar manner supplying 2.5–3.0 g of (±)-**3** in each run to give optically active **3** in 72–95% optical purity. The initial four runs are shown in the Table. The crystals having the same sign of optical rotation are combined and recrystallized from 2-propanol to yield almost optically pure (+)- and (−)-**3**, respectively. For example, recrystallization of plus enriched salt (2.99 g, 93% optical purity) from 2-propanol (30 ml) gives 1.95 g of (+)-**3**; $[\alpha]_D^{18}$: +7.5° (*c* 1.00, 99% CH_3OH); 99% optical purity.

Similarly recrystallization of minus enriched salt (3.45 g, 71% optical purity) from 2-propanol (30 ml) affords 2.23 g of (−)-**3**; $[\alpha]_D^{18}$: −7.4° (*c* 1.00, 99% CH_3OH); 97% optical purity. Treatment of these salts with 1 normal sodium hydroxide solution followed by extraction and distillation gives 90–92% of (+)- and (−)-**1** ($[\alpha]_D^{18}$: +23.5° and −23.4°; 98% optical purity), respectively.

Table. Preferential Crystallization of **3**

Run[a]	(±)-**3** [g]	Seed	Cooling Time [min]	Yield [g]	O.P. [%][b]
1	–	(+)-**3**	200	0.93	91
2	1.25	(−)-**3**	160	1.74	68
3	2.12	(+)-**3**	120	2.45	95
4	2.18	(−)-**3**	160	2.95	72

[a] The initial composition of the mother liquor: (±)-**3** (4.93g) and (±)-**1** · acetic acid salt (13.40g) in 2-propanol (65 ml).
[b] The optical purities (O.P.) were calculated based on the specific rotations of seeds; $[\alpha]_D^{23}$: + and −7.6° (*c* 1.00, 99% CH_3OH).

Resolution of Malic Acid (4):
The salt prepared from equimolar amounts of (±)-**4** and (+)-**1** is recrystallized from water three times to give 39% of the (−)-**4** · (+)-**1** salt; $[\alpha]_D^{18}$: +7.2° (*c* 1.00, 99% CH_3OH). The filtrates from the recrystallizations are combined and treated with 2 normal sodium hydroxide solution followed by Amberlite IR 120B resin to give plus enriched **4**. The acid is allowed to form the salt with an equimolar amount of (−)-**1**, and the salt is recrystallized from water twice to afford the (+)-**4** · (−)-**1** salt in 56% yield; $[\alpha]_D^{18}$: −7.0° (*c* 1.00, 99% CH_3OH).

The alkali solutions, obtained from both diastereomeric salts by treatment with 2 normal sodium hydroxide solution followed by

extraction of **1** with benzene, are treated with Amberlite 120B resin to give (−)- and (+)-**4** on concentration, respectively; (−)-**1**: m.p. 98–99 °C (Lit.[7], m.p. 99–100 °C); $[\alpha]_D^{15}$: −5.9° (*c* 5.00, acetone); 95% optical purity[8]; (+)-**1**: m.p. 98–99 °C (Lit.[7], m.p. 99–100 °C); $[\alpha]_D^{17}$: +6.0° (*c* 5.00, acetone); 97% optical purity[8].

Received: September 7, 1984

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[8] Based on $[\alpha]_D^{15}$: −6.2° (*c* 5.00, acetone), which is larger than the specific rotation value of commercial malic acid but the highest one we obtained previously.