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Resolution of 1-cyclohexylethylamine via diastereomeric salt formation with enantiopure 2-phenylacetic acids

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Abstract—The resolution of 1-cyclohexylethylamine **1** with enantiopure 2-phenylacetic acids via diastereomeric salt formation was investigated. (*R*)-2-Methoxy-2-phenylacetic acid **3** and the (*S*)-2-phenylpropionic acid **5** were found to be efficient resolving agents for obtaining the single enantiomer (*S*)-**1** as the correspondingly less-soluble diastereomeric salt (resolution efficiency = 48% and 52%, respectively).

1. Introduction

To date, amongst the various new and attractive techniques for the preparation of enantiopure compounds, optical resolution via diastereomeric salt formation is still a useful technique on an industrial scale, since it is generally simple, clean, and easy to reproduce laboratory-scale data on an industrial scale.[1] In fact, it has been estimated that more than half of the chiral drugs on the pharmaceutical market are produced by the diastereomeric salt formation method using enantiopure resolving agents.[2]

It is well known that enantiopure 1-cyclohexylethylamine **1** is an important chiral intermediate for various pharmaceuticals,[3] functional materials for the stationary phase of chiral LC columns,[4] and an efficient resolving agent for chiral acids.[5] To obtain enantiopure **1**, several processes have been contrived, such as the direct hydrogenation of enantiopure 1-phenylethylamine[6] and resolution with *d*-camphoric acid.[7] However, both preparation methods are ineffective from an industrial point of view. The former cannot avoid partial racemization during the reduction reaction while the latter needs six successive crystallizations to obtain enantiopure **1**. No other resolving agent is currently known; hence, we tried to find a better resolving agent suitable for an industrial-scale resolution of racemic **1** and found two efficient new resolving agents for the resolution of (*RS*)-**1**.

2. Results and discussion

Commercially available acidic resolving agents of a series of 2-phenylacetic acids were tested in order to find a suitable resolving agent for (*RS*)-**1**. Actually, (*S*)-2-hydroxy-2-phenylacetic acid (mandelic acid) **2**, (*R*)-2-methoxy-2-phenylacetic acid **3**, (*S*)-2-acetoxy-2-phenylacetic acid **4**, and (*S*)-2-methyl-2-phenylacetic acid (2-phenylpropionic acid) **5** were examined using water as a solvent (Fig. 1).

An equimolar resolving agent was used with (*RS*)-**1** and the solvent volume determined by the solubility of the solid substances at 50 °C in each resolution experiment. Experimental results are summarized in Table 1. Although their chiral purities were high enough, all resolving agents **2**–**5** gave poor yields (1–11% yield, 60–96% de, $E = 1$–20%).[8] It is noteworthy that hemi-hydrated less-soluble diastereomeric salts were crystallized with (*S*)-**2**, whereas non-hydrated salts were crystallized with (*R*)-**3**, (*S*)-**4**, and (*S*)-**5**. These results indicate that water would be an essential component for the crystallization of (*R*)-**1**:(*S*)-**2**:1/2H_2O salt. The water molecule could play a distinctive role for chiral discrimination during salt crystallization, since the diastereomeric excess of the salt was quite high (91% de) despite the lower yield. On the other hand, it is interesting to note that the resolving agents **2** and **3** afforded heterochiral salts, whereas the resolving agents **4** and **5** afforded

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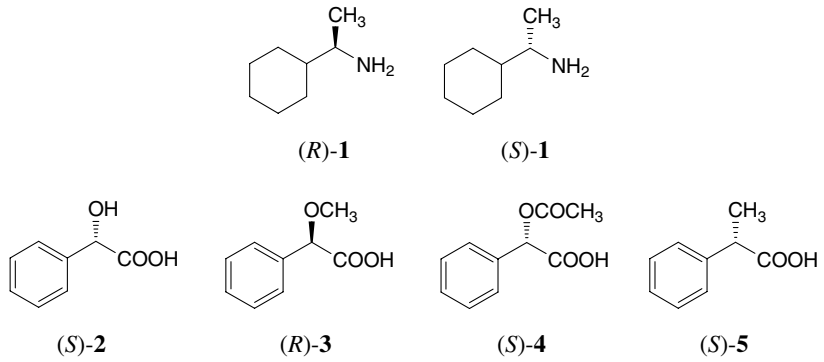

Figure 1.

Table 1. Resolution of (*RS*)-**1** with (*S*)-2-phenylacetic acids from water

Entry	Resolving agent		Solvent	Yield (%)	de (%)	Absolute configuration	Salt chiral pair	*E* (%)
		R	Water w/w versus (*RS*)-**1**					
1	(*S*)-**2**	OH	12	7	91	*R*	Hetero	12
2	(*R*)-**3**	OCH_3	32	11	89	*S*	Hetero	20
3	(*S*)-**4**	$OCOCH_3$	21	1	60	*S*	Homo	1
4	(*S*)-**5**	CH_3	110	1	96	*S*	Homo	1

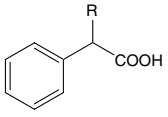

Table 2. Resolution of (*RS*)-**1** with (*S*)-2-phenylacetic acids from 2-PrOH

Entry	Resolving agent		Solvent	Yield (%)	de (%)	Absolute configuration	Salt chiral pair	*E* (%)
		R	2-PrOH w/w versus (*RS*)-**1**					
1	(*S*)-**2**	OH	7	3	24	*S*	Homo	2
2	(*R*)-**3**	OCH_3	44	27	88	*S*	Hetero	48
3	(*S*)-**4**	$OCOCH_3$	40	Not crystallized				0
4	(*S*)-**5**	CH_3	50	29	90	*S*	Homo	52

homochiral salts, although these were all crystallized from the same water solvent. Since only the structures of the α-substituents are different, the bulkiness of the α-substituent could play a distinctive role for chiral discrimination.

In order to improve resolution efficiency (*E*), less polar solvents, such as methanol, ethanol, 2-propanol, and their mixtures with water were tried as solvents. However, we could only obtain sufficient salt crystals only from 2-propanol. Experimental results are summarized in Table 2. As shown in Table 2, resolution efficiencies obtained by using (*R*)-**3** and (*S*)-**5** were extremely improved. However, the resolution efficiency for (*S*)-**2** was drastically decreased and (*S*)-**4** did not afford any salt crystals.

The diastereomeric excesses of these salts could be easily improved by a single recrystallization from 2-propanol to give >99% de. Therefore, it can be concluded that (*R*)-**3** and (*S*)-**5** are useful resolving agents for obtaining (*S*)-**1** when 2-propanol is used as a solvent. Resolving agent **2** afforded the homochiral salt from 2-propanol, whereas heterochiral salt was obtained from water.

3. Conclusion

(*R*)-2-Methoxy-2-phenylacetic acid **3** and (*S*)-2-methyl-2-phenylacetic acid **5** were found to serve as a new resolving agents for racemic **1** and are suited for the industrial production of the enantiopure **1**.

4. Experimental

4.1. General

(*RS*)-1-Cyclohexylethylamine **1**, (*S*)-mandelic acid **2** (>99.5% ee), (*R*)-methoxy-2-phenylacetic acid **3** (>99.5% ee), (*S*)-2-acetoxy-2-phenylacetic acid **4** (>99.5% ee), and (*S*)-phenylpropionic acid **5** (>99.5% ee) were made by Yamakawa Chemical (Tokyo).

^{1}H NMR spectra were recorded on a JEOL JNM-ECP400 spectrometer in DMSO-d_6 with Me_4Si as an internal reference. IR spectra were measured on a JASCO IR-700 spectrometer using KBr pellets. Optical rotations were

measured on a JASCO DIP-370 polarimeter with a circular temperature control unit. High-performance liquid chromatography was performed by a JASCO Intelligent HPLC system equipped with a 875-UV detector. Melting points were determined with a YAMATO MP-21 instrument and are uncorrected. Water contents in the salts were measured by the Karl Fischer method with a HIRANUMA Aquacounter AQV-5.

4.2. Determination of diastereomeric excess of 1

The enantiomeric purity of **1** presented in the salt was based on the enantiomeric excess of the amine liberated from the salt. The enantiomeric excess of **1** was directly determined by HPLC using a SUMICHIRAL OA-4600 column (ID 4.6 mm × 250 mm). Analytical conditions for the HPLC were as follows; eluent: *n*-hexane + ethanol (98/20), 1.0 mL/min, 40 °C, detected at 254 nm; injection sample 10 μL (10 mg/10 mL), retention times: the (*S*)-enantiomer 18.5 min, the (*R*)-enantiomer 17.1 min. The sample for chiral purity analysis by HPLC was treated with *p*-dinitrobenzoyl (DNB) chloride prior to injection.

4.3. Resolution procedure

A typical experimental procedure (e.g., preparation of the (*S*)-**1**:(*R*)-**3** salt) is as follows: To a 50 mL flask were added (*RS*)-**1** (1.0 g, 7.86 mmol), (*R*)-**3** (1.3 g, 7.88 mmol), and 2-propanol (44 g), and the mixture stirred and heated to about 49 °C to give a clear solution. The solution was then gradually cooled, kept for 1 h at 32–34 °C (corresponding to the crystallization temperature), and then cooled again to 20 °C. After leaving the suspension at that temperature for 1 h, the crystals were filtered off and washed twice with 2-propanol (2 mL in total) to afford the crude (*S*)-**1**:(*R*)-**3** salt (0.63 g, 2.15 mmol, 27% yield, 88% de, *E* 48%). Experimental results of the resolution of (*RS*)-**1** with enantiopure 2-phenylacetic acids from water and 2-propanol are summarized in Tables 1 and 2, respectively. Analytical data of the less-soluble diastereomeric salts obtained by the resolution are shown below. The following salts were obtained by recrystallization of the salt from the same solvent applied in the resolution.

(*S*)-**1**:(*S*)-**2**: $[\alpha]_D^{20} = +49.3$ (*c* 1.02, MeOH); 98.5% de; Mp 146.5–147.5 °C; IR (KBr) cm^{-1}: 3400, 2924, 2850, 1617, 1578, 1556, 1533, 1449, 1420, 1347, 1261, 1243, 1186, 1097, 1064, 781, 757, 728, 697, 624; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.38 (2H, d, $J = 7.2$ Hz), 7.21 (2H, t, $J = 7.2$ Hz), 7.13 (1H, t, $J = 7.2$ Hz), 4.54 (1H, s), 2.88 (1H, qui, $J = 6.8$ Hz), 1.60–1.72 (5H, m), 1.33–1.42 (1H, m), 1.07 (3H, d, $J = 6.8$ Hz), 1.04–1.22 (3H, m), 0.91–1.00 (2H, m); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.61, 143.82, 127.32, 126.26, 126.00, 73.49, 50.85, 40.76, 28.56, 26.99, 25.70, 25.54, 25.43, 15.45. Anal. Calcd for $C_{16}H_{25}NO_3$ (FW 279.37): C, 68.79; H, 9.02; N, 5.01. Found C, 68.63; H, 8.92; N, 4.98.

(*R*)-**1**:(*S*)-**2**:1/2H_2O: $[\alpha]_D^{20} = +53.3$ (*c* 1.02, MeOH); 99.5% de; Mp 139.5–141.0 °C; IR (KBr) cm^{-1}: 3408, 3158, 2924, 2856, 1667, 1615, 1580, 1565, 1538, 1446, 1410, 1367, 1318, 1248, 1181, 1096, 1063, 731, 696, 510; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.38 (2H, d, $J = 7.2$ Hz), 7.21 (2H, t, $J = 7.2$ Hz), 7.13 (1H, t, $J = 7.2$ Hz), 4.54 (1H, s), 2.88 (1H, qui, $J = 6.8$ Hz), 1.59–1.72 (5H, m), 1.33–1.42 (1H, m), 1.07 (3H, d, $J = 6.8$ Hz), 1.04–1.24 (3H, m), 0.91–1.00 (2H, m); water content (KF): calcd for 1/2H_2O 3.12%. Found 3.36%. Anal. Calcd for $C_{16}H_{25}NO_3$:1/2 H_2O (FW 288.38): C, 66.64; H, 9.09; N, 4.86. Found C, 66.51; H, 8.97; N, 4.82.

(*S*)-**1**:(*R*)-**3**: $[\alpha]_D^{20} = -56.6$ (*c* 1.01, MeOH); 99.4% de; Mp 178.5–180.0 °C; IR (KBr) cm^{-1}: 2994, 2920, 2850, 2754, 2692, 2590, 2542, 2148, 1637, 1577, 1492, 1449, 1394, 1336, 1305, 1235, 1199, 1152, 1104, 1074, 1026, 997, 954, 889, 781, 727, 699, 616; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.38 (2H, d, $J = 7.6$ Hz), 7.25 (2H, t, $J = 7.6$ Hz), 7.19 (1H, t, $J = 7.6$ Hz), 4.46 (1H, s), 3.27 (3H, s), 2.81 (1H, qui, $J = 6.4$ Hz), 1.60–1.70 (5H, m), 1.30–1.37 (1H, m), 1.07–1.22 (3H, m), 1.04 (3H, d, $J = 6.4$ Hz), 0.91–0.99 (2H, m). Anal. Calcd for $C_{17}H_{27}NO_3$ (FW 293.40): C, 69.59; H, 9.09; N, 4.86. Found C, 69.50; H, 9.19; N, 4.77.

(*S*)-**1**:(*S*)-**5**: $[\alpha]_D^{20} = +1.8$ (*c* 1.01, MeOH); 99.7% de; Mp 177.5–179.0 °C; IR (KBr) cm^{-1}: 2924, 2852, 2678, 2584, 2526, 2360, 2204, 1621, 1556, 1534, 1449, 1388, 1342, 1304, 1284, 1246, 1189, 1156, 1062, 1033, 1006, 877, 829, 770, 733, 699, 682, 583; ^1H NMR (DMSO-d_6, 400 MHz): δ 7.23–7.29 (4H, m), 7.14–7.18 (1H, m), 3.54 (1H, q, $J = 7.2$ Hz), 2.68 (1H, qui, $J = 6.4$ Hz), 1.60–1.71 (5H, m), 1.33 (3H, d, $J = 7.2$ Hz), 1.07–1.22 (4H, m), 0.98 (3H, d, $J = 6.4$ Hz), 0.90–0.99 (2H, m). Anal. Calcd for $C_{17}H_{27}NO_2$ (FW 277.40): C, 73.61; H, 9.81; N, 5.05. Found. C, 73.50; H, 9.81; N, 5.04.

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8. De % is based on the enantiomeric excess (ee) of amine **1** liberated from the less-soluble salt. The yield is calculated based on (*RS*)-**1**. Resolution efficiency (*E*, %) = Yield (%) × De (%) × 2/100.