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Practical resolution of 3-aminopyrrolidine via diastereomeric salt formation with (*S*)-2-methoxy-2-phenylacetic acid

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ABSTRACT

The resolution of 3-aminopyrrolidine **1**, a versatile key intermediate for chiral pharmaceuticals, via diastereomeric salt formation was investigated. The resolution conditions were optimized focusing on an industrial-scale production to afford enantiopure (*R*)-**1**, while (*S*)-methoxy-2-phenylacetic acid **5** was found to be a suitable resolving agent. The less-soluble diastereomeric salt, 1:2 (*R*)-**1**:(*S*)-**5**, was obtained with high resolution efficiency (*E*) (yield 44%, 98% de, *E* 86%) under the best resolution conditions; (*RS*)-**1**/(*S*)-**5**/HCl molar ratio = 1.0/1.0/1.0 in water solvent in the presence of sodium chloride. The optimized resolution process was scaled up to a pilot-scale production using 50 kg of (*RS*)-**1** dihydrochloride as a starting racemate, and the resolution efficiency successfully reproduced the laboratory results.

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1. Introduction

It is well known that enantiopure 3-aminopyrrolidine **1** is a versatile key intermediate for chiral pharmaceuticals. Enantiopure **1** is widely used as an essential component of the antibacterial agents, Tosufloxacin,[1a] Clinafloxacin,[1b] and Ceftobiprole.[1c] Moreover, the basic skeleton of 3-aminopyrrolidine is also found in many promising medicines with various indications currently being developed, such as Ca-sensitive receptor agonist,[2] histamine H3 receptors antagonists,[3] adenosine A_{2A} receptor agonist,[4] allergic inflammatory,[5] and antitumor compounds.[6] Therefore, the establishment of a practical process for obtaining enantiopure **1** in high enantiomeric purity at a low cost is urgently required.

To obtain enantiopure **1**, the asymmetric synthesis and resolution of racemic 3-aminopyrrolidine derivatives have been reported. In the asymmetric synthesis, enantiopure 3-hydroxypyrrolidine is used as a starting material in which a 3-hydroxyl group is converted into an amino group by a nucleophilic displacement reaction.[7] However, this process requires five steps to obtain a precursor of **1**, 3-acetamidepyrrolidine, and the total yield is insufficient (46%). On the other hand, the resolution of (*RS*)-**1** using L-tartaric acid **2** as a resolving agent has been reported.[8a] Despite this, there are some critical issues, such as low resolution yield (28%) and difficulty in recovery of the resolving agent **2** from both the resulting less-soluble salt and resolution mother liquor because of high solubility of L-**2** in the water solvent. The resolution of *rac*-*N*-benzyl-3-aminopyrrolidine with various chiral acids is also widely known: using mandelic acid,[8a] tartaric acid[8b] and its derivative (dibenzoyl-tartaric acid),[8b,c] amino acid derivatives (*N*-acyl-, or *N*-sulfonyl amino acid),[8c] and 10-camphorsulfonic acid.[8d] To obtain enantiopure **1**, however, an additional step, the de-*N*-benzylation process, should follow the resolution step. As described above, a facile, simple, and effective process to obtain enantiopure **1** which is applicable for the industrial-scale production has not yet been found. We tried to establish an effective resolution process for producing enantiopure **1** via diastereomeric salt formation, since the resolution process is still a useful and simple tool for obtaining enantiopure compounds in industrial production, and because it is easy to reproduce laboratory-scale data in an industrial-scale operation. We found the best resolution conditions to obtain the less-soluble diastereomeric salt with high enantiomeric purity and sufficient industrial productivity.

2. Results and discussion

2.1. Finding a suitable resolving agent for the resolution of (*RS*)-1

To find the most suitable resolving agent for (*RS*)-**1**, 8 kinds of commercially available acidic resolving agents were examined; tartaric acids [L-tartaric acid **2** (as a reference) and dibenzoyl-L-tartaric acid **3**], α-substituted phenylacetic acids [(*S*)-mandelic acid **4**, (*S*)-2-methoxy-2-phenylacetic acid **5**, and (*S*)-2-acetoxy-2-phenylacetic acid **6**], amino acid derivative [*N*-tosyl-(*S*)-phenylalanine **7**], and other monocarboxylic acids derived from (*R*)-1-methylbenzylamine with diacids [(*R*)-(+)-*N*-(α-methylbenzyl)phthalic acid monoamide **8** and (1*R*,3*R*)-1-(1-phenylethyl)-5-oxo-3-pyrrolidine

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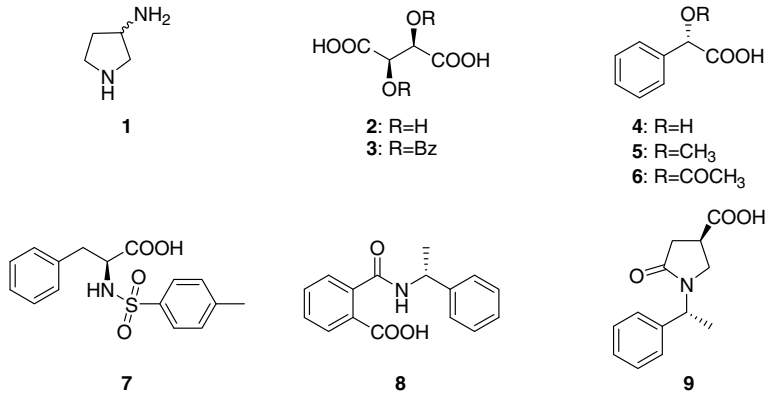

Figure 1.

carboxylic acid **9**] (Fig. 1). The resolution solvent in each resolution experiment was selected from water, alcohols (C_1–C_3), or their mixed solvent, and the solvent volume was determined after considering the solubility of the solutes at 50 °C. The less-soluble diastereomeric salts obtained from the resolution experiments were evaluated by ^{1}H NMR, chiral GC, and elemental analyses. The diastereomeric purity of the salt obtained in each resolution experiment was determined as de(diastereomeric excess)% based on enantiomeric purity of **1** in the salt.[9] The resolution efficiency (*E*, %) of the salt was calculated based on the yield and de%.[9] Resolution experiments were performed under neutral conditions using a stoichiometric quantity of resolving agent to (*RS*)-**1**, that is, since (*RS*)-**1** is a diacidic base with two amino groups (primary and secondary amines) in its molecule, dibasic acids **2** and **3** were used in a molar amount to (*RS*)-**1**, respectively. On the other hand, monobasic acids **4**, **5**, **6**, **7**, **8**, and **9** were used in 2.0 molar amounts to (*RS*)-**1**, respectively. The experimental results are summarized in Table 1.

At first, the reported resolution method using L-tartaric acid (*R*,*R*)-**2** as a resolving agent was examined according to the literature [(*RS*)-**1**/L-**2** molar ratio = 1.0/1.0 in 40% MeOH aqueous solution].[8a] To our surprise, the reported data could not be reproduced with no crystal forming, only an oil, as shown in Table 1 (entry 1). Moreover, no salt crystals were obtained from water solvent (entry 2). In contrast, only *O*,*O*′-dibenzoyl-L-tartaric acid **3** afforded diastereomeric salt crystals, (*R*)-**1**/L-**3**, from the ethanol–water mixed solvent (83% and 71% ethanol), whereas no crystals were obtained from pure ethanol, although their resolution efficiencies were poor: *E* 25% (yield 16%, 77% de) from 83% ethanol and *E* 12% (yield 62%, 10% de) from 71% ethanol (entries 3 and 4). On the other hand, no crystals were deposited with the other resolving agents (*S*)-**4**, (*S*)-**6**, (*R*)-**8**, and (1*R*,3*R*)-**9**, although the solutes of each resolution reaction finally dissolved at around 50 °C (entries 6, 7, 9, 11, and 12). In a case using (*S*)-**7**, the resolution reaction system was solidified at around ambient temperature, although the solutes of the resolution were completely dissolved at 50 °C and crystallization was observed upon cooling (entry 10). When using (*S*)-**5**, no sign of dissolution of the solutes was observed at all (entry 8). From these experimental results, we concluded that the partially resolved **1** can be obtained by using L-**3** as a resolving agent, but the resolution efficiencies were unsatisfactory (*E* 12–25%) for industrial-scale production. Since other resolving agents seemed to be unable to resolve (*RS*)-**1**, we promptly tested (*S*)-**5** or (*S*)-**7** as a resolving agent. We discovered that resolution conditions using resolving agent **5** or **7** may be improved upon by changing the resolution environments such as its molar ratio to (*RS*)-**1** and/or the solvent system because these resolving agents have the capacity to make a salt with molecule **1**. Thus, we attempted to optimize the resolution conditions using (*S*)-**5** or (*S*)-**7** as a resolving agent.

2.2. Optimization of resolution conditions

First, resolution conditions were optimized using a half equivalent amount of monobasic acid (*S*)-**5** [1 molar to (*RS*)-**1** [compared with the former case [2 molar to (*RS*)-**1**; Table 1, entry 8] in water solvent. Experimental results are summarized in Table 2. Most surprisingly, the less-soluble salt 1:2 (*R*)-**1**:(*S*)-**5** (**1**/**5** molar ratio = 1/2) was crystallized with the highest diastereomeric purity although the resolution yield was low (Table 2, entry 1; >99% de, yield 11%, *E* 22%). This fact indicates that 2 mol of the resolving agent (*S*)-**5** are essential to form the less-soluble salt with (*R*)-**1**. Moreover, a reaction environment with 1 molar amount of resolving agent (*S*)-**5** in the

Table 1
Resolution of free (*RS*)-**1** with various resolving agents

Entry	Resolving agent	Molar ratio (equiv)	Solvent	Solvent volume versus (*RS*)-**1** (w/w)	Yield (%)	de (%)	Resolution efficiency (%)	Absolute configuration of **1**
1	L-**2**	1.0	40% MeOH	5	Oil out			
2		1.0	H_2O	5	Not crystallized			
3	L-**3**	1.0	EtOH	5	Oil out			
4		1.0	83% EtOH	6	16	77	25	(*R*)
5		1.0	71% EtOH	7	62	10	12	(*R*)
6	(*S*)-**4**	2.0	H_2O	5	Not crystallized			
7		2.0	83% IPA	6	Not crystallized			
8	(*S*)-**5**	2.0	H_2O	20	Not dissolved			
9	(*S*)-**6**	2.0	H_2O	10	Not crystallized			
10	(*S*)-**7**	2.0	H_2O	30	Solidified			
11	(*R*)-**8**	2.0	H_2O	10	Not crystallized			
12	(1*R*,3*R*)-**9**	2.0	EtOH	10	Not crystallized			

Table 2
Resolution of free (*RS*)-**1** with resolving agents (*S*)-**5** and (*S*)-**7**

Entry	Resolving agent	Molar ratio (equiv)	HCl (equiv)	Water volume versus (*RS*)-**1** (w/w)	Yield[a] (%)	de (%)	*E* (%)
1	(*S*)-**5**	1.0	None	8	11	>99	22
2		1.0	1.0	10	39	97	76
3		0.8	1.2	10	31	94	58
4	(*S*)-**7**	1.0	None	10	24	88	42
5		1.0	1.0	15	47	65	61

[a] The components of the salt are as follows: (*R*)-**1**/(*S*)-**5** = 1/2, (*R*)-**1**/(*S*)-**7**/H_2O = 1/2/2.

resolution reaction system favors the strict recognition of a particular stereoisomer (*R*)-**1**, whereas no particular chiral recognition was observed at **1**/**5** = 1/2, as shown in Table 1. In other words, chiral recognition of diamine **1** with (*S*)-**5** is sharpened under the less molar resolving agent, implying that molecule **1** is abundantly present.

In order to practically improve the resolution yield, the Pope and Peachey method,[10] which is known as the 'half equivalent method of resolution', was examined. In doing so, we expected a drastic improvement of the resolution efficiency. In the resolution experiments according to this method, the total acid molar ratio to diamine **1** was adjusted to be equivalent on the basis of an acid–base equilibrium, that is, if one mole of monobasic acid (*S*)-**5** is used, the residual base is neutralized with one mole of another inorganic acid such as HCl. As intended, the 1:2 (*R*)-**1**:(*S*)-**5** salt was successfully crystallized as the less-soluble salt with a higher resolution efficiency under the molar ratios of (*RS*)-**1**/(*S*)-**5**/HCl = 1.0/1.0/1.0 in water solvent (Table 2, entry 2; yield 39%, 97% de, *E* 76%). Meanwhile, we found that increasing HCl content [(*RS*)-**1**/(*S*)-**5**/HCl = 1.0/0.8/1.2] decreased the resolution efficiency (Table 2, entry 3; yield 31%, 94% de, *E* 58%). These results revealed that the Pope and Peachey method using (*R*)-**5** as a resolving agent and HCl as a supplemented acid is extremely effective for the resolution of (*RS*)-**1**. The same process was applied to the resolution with (*S*)-**7**. However, the resolution efficiency did not improve relative to the use of (*S*)-**5** (Table 2, entry 4 vs entry 5). Therefore, further optimization of resolution of (*RS*)-**1** was achieved using (*S*)-**5**, and not (*S*)-**7**, as a resolving agent.

To optimize the resolution conditions when taking into account the industrial-resolution process, the effect of sodium chloride was examined since (*RS*)-**1** is sold on the market as a dihydrochloride. Sodium chloride is also a by-product of the recovery–recycling process of the resolving agent. In the resolution experiments, diamine **1** dihydrochloride was freed in the resolution solvent with sodium hydroxide prior to adding resolving agent (*S*)-**5** and supplementing with HCl acid. Experimental results are summarized in Table 3. As shown in Table 3, the resolution efficiency was improved upon, as intended, while maintaining a high diastereomeric purity (Table 3, entry 1; yield 44%, 98% de, *E* 86%). Meanwhile, an increase in the molar ratio of (*S*)-**5** from 1.0 to 1.5 negatively affected the diastereomeric purity, whereas resolution efficiencies (*E*) remained at a higher range, that is, between 86% and 89% (Table 3, entries 2 and 3). These results indicate that coexisting sodium chloride in the resolution system played a great role in improving the yield without influencing the diastereomeric purity of the salt.

From the experimental results obtained in the resolution of (*RS*)-**1** with (*S*)-**5** in water solvent containing 2 mol of sodium chloride and one mole of HCl to diamine **1**, we conclude that the best molar ratios of **1**/**5**/HCl are 1.0/1.0/1.0. We applied this optimized process in practice to a pilot production using 50 kg scale (*RS*)-**1** dihydrochloride [free (*RS*)-**1** 27 kg]. The experimental result obtained in the laboratory could be successfully reproduced and scaled-up to obtained the salt (*R*)-**1**:2(*S*)-**5** (53.8 kg, yield 44%, 98% de, *E* 86%).

Table 3
Resolution of (*RS*)-**1** dihydrochloride with resolving agent (*S*)-**5**

Entry	Molar ratio (equiv)	HCl (equiv)	Water volume versus (*RS*)-**1** (w/w)	Yield[a] (%)	de (%)	*E* (%)
1	1.0	1.0	8	44	98	86
2	1.2	0.8	8	48	93	89
3	1.5	0.5	8	52	85	88

[a] The component of the salt is as follows: (*R*)-**1**/(*S*)-**5** = 1/2.

3. Conclusion

A new resolution process for (*RS*)-3-aminopyrrolidine **1** based on the Pope and Peachey method has been established. (*S*)-2-Methoxy-2-phenylacetic acid **5**, HCl, and water were found to be a suitable resolving agent, supplemented acid, and solvent, respectively. The less-soluble salt, 1:2 (*R*)-**1**:(*S*)-**5**, was obtained in 44% yield with 98% de (*E* 86%) under the optimal conditions: (*RS*)-**1**/(*S*)-**5**/HCl molar ratios = 1.0/1.0/1.0. The optimized process has been successfully demonstrated in a pilot-scale production using 50 kg of (*RS*)-**1** dihydrochloride to give 53.8 kg of the less-soluble diastereomeric salt with 98% de.

4. Experimental

4.1. General

Reagents used in laboratory experiments, free diamine (*RS*)-3-aminopyrrolidine **1**, L-tartaric acid **3**, and dibenzoyl-L-tartaric acid **4** were purchased from Tokyo Chemical Industry Co., Ltd. (*S*)-Mandelic acid **4** (>99.5% ee), (*S*)-2-methoxy-2-phenylacetic acid **5** (>99.5% ee), (*S*)-2-acetoxy-2-phenylacetic acid **6** (>99.5% ee), *N*-tosyl-(*S*)-phenylalanine **7** (>99.5% ee), (*R*)-(+)-*N*-(α-methylbenzyl)phthalic acid monoamide **8** (>99.5% ee), and (1*R*,3*R*)-1-(1-phenylethyl)-5-oxo-3-pyrrolidine carboxylic acid **9** (>99.5% ee) were made in Yamakawa Chemical Industry Co., Ltd (Tokyo). ^1H NMR spectra were recorded on a JEOL JNM-ECP400 spectrometer in D_2O. 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. Gas chromatography was performed by a SHIMAZU GC-17A system. Melting points were determined with a YAMATO MP-21 instrument and are uncorrected.

4.2. Determination of diastereomeric excess of 1 in the salt

The diastereomeric excess (de%) of the salt was determined based upon the enantiomeric excess of the diamine **1** liberated from the salt. A sample preparation for the enantiomeric purity by GC analysis is as follows: 1:2 (*R*)-**1**:(*S*)-**5** 49 mg (0.117 mmol, containing (*R*)-**1** 10 mg) was placed in a vial to which 2 mL water and 2–3 drops 30% NaOH aq were added. The mixture was dis-

solved followed by extraction of amine **1** with CH_2Cl_2 (3 mL). The extract (1.5 mL) was transferred to a vial with a pipette for GC analysis. Next 3–5 drops of trifluoroacetic anhydride were added to the solution, and *N*-acylation immediately proceeded to yield *N*-acyl **1**, after which 4 μL of this solution was injected into the GC. The diastereomeric purity of the salt was indicated in % de. Analytical conditions for the GC were as follows: Column: CHIRALDEX B-TA ID 0.25 mm × 30 m, detection: FID, detection temp: 250 °C, injection temp: 200 °C, column temp: 160 °C, carrier gas: He, pressure: 300 kPa, split: 1/10. Retention times: the (*S*)-enantiomer 14.2 min, the (*R*)-enantiomer 15.3 min.

4.3. Resolution procedure

4.3.1. Resolution of free diamine (*RS*)-1 with (*S*)-5

A typical experimental procedure [e.g., preparation of the 1:2 (*R*)-**1**:(*S*)-**5** salt] is as follows (Table 2, entry 2): To a 50 mL flask, free diamine (*RS*)-**1** (2.0 g, 23.2 mmol) and water (16 g) were added. The mixture was stirred, and then (*S*)-**5** (3.9 g, 23.5 mmol) was added to the mixture at room temperature, and heated up to about 70 °C to give a clear solution. Next 35% HCl (2.4 g, 23.0 mmol) was added dropwise to the solution at this temperature, upon which crystallization began immediately. The suspension was maintained for 1 h at 70 °C (corresponding to the crystallization temperature), and then gradually cooled to 20 °C for about 3 h. After aging the suspension at this temperature for 1 h, crystals were filtered off and washed twice with water (8 mL in total) to yield wet salt crystals, which were dried at 60 °C for 3 h to afford crude 1:2 (*R*)-**1**:(*S*)-**5** salt (3.8 g, 9.3 mmol, yield 39%, 97% de, *E* 76%).

The crude salt was recrystallized from water solvent. To a 100 mL flask, 1:2 (*R*)-**1**:(*S*)-**5** salt (3.9 g, 9.3 mmol) and water (60.9 g) were added. The suspension was stirred, then heated up to about 96 °C to give a clear solution. The solution was then gradually cooled, seeded (2 mg) at 90 °C, kept for 1 h at 87 °C (corresponding to the crystallization temperature), and then cooled again to 20 °C. After aging the suspension at this temperature for 1 h, the crystals were filtered off and washed twice with water (8 mL in total) to give wet salt crystals, which were dried at 60 °C for 3 h to afford pure 1:2 (*R*)-**1**:(*S*)-**5** salt (2.4 g, 5.8 mmol, yield 62%, >99% de). Analytical data of the less-soluble diastereomeric salts obtained by the resolution are shown below. 1:2 (*R*)-**1**:(*S*)-**5**: $[\alpha]_D^{20} = +91.8$ (*c* 0.5, H_2O); 99.5% de; mp 222.0–223.0 °C; IR (KBr) cm^{-1}: 3446, 2997, 2931, 2875, 2823, 2499, 2208, 1639, 1571, 1450, 1400, 1338, 1198, 1099, 1072, 1030, 993, 957, 783, 731; ^1H NMR (D_2O, 400 MHz): δ 7.27–7.20 (10H, m), 4.47 (2H, s), 3.94 (1H, tt, J = 8.0, 6.0 Hz), 3.58 (1H, dd, J = 13.2, 8.0 Hz), 3.37 (1H, ddd, J = 12.4, 7.6, 6.8 Hz), 3.28–3.20 (2H, m), 3.19 (6H, s), 2.39–2.29 (1H, m), 2.01–1.92 (1H, m); Anal. Calcd for $C_{22}H_{30}N_2O_6$ (FW 418.48): C, 63.14; H, 7.23; N, 6.69. Found C, 62.89; H, 7.06; N, 6.65.

4.3.2. Resolution of (*RS*)-1 dihydrochloride with (*S*)-5 in pilot run

Resolution of (*RS*)-**1** dihydrochloride in a pilot run is described as follows: To a 500 L glass-lined reactor (*RS*)-**1**·2HCl (50.0 kg, CP 93%, 292 mol), water (203 L), and 30% NaOH aqueous solution (85 kg, 638 mol) were added. The mixture was stirred, and then (*S*)-**5** (47.8 kg, 288 mol) was added at room temperature, and heated up to about 60 °C to give a clear solution. To this solution, 35% HCl aq (36.3 kg, 348 mol) was added dropwise at the same temperature, following which crystallization immediately started. The slurry solution was adjusted to a final pH of 5.0 after the addition of 35% HCl. The slurry was gradually cooled to 20 °C over 3 h, and kept for 1 h at this temperature. The salt crystals were collected by a centrifuge and washed twice with water for each centrifugation (18 L in total; centrifugation 3 times) to afford the crude salt (wet 61.8 kg, net weight 53.8 kg, 129 mol, yield 44%, 98% de, *E* 86%).

To a 500 L glass-lined reactor, the crude salt (wet 61.8 kg, dry-basis 53.8 kg), water (261 kg), and 30% NaOH aq (34.3 kg) were added. The mixture was stirred, and heated up to about 60 °C to give a clear solution. To this solution, 35% HCl aq (26.8 kg, 257 mol) was added dropwise at this temperature, after which crystallization started immediately. The slurry was gradually cooled to 20 °C, and kept for 1 h at this temperature. The salt crystals were collected by a centrifuge and washed twice with water for each centrifugation (18 L in total; centrifugation 3 times) to give the pure salt (wet 47.1 kg), and dried at 60 °C for 3 h to afford the dry 1:2 (*R*)-**1**:(*S*)-**5** salt (43.6 kg, 104 mol, yield 81%, >99% de).

Analytical data of the less-soluble diastereomeric salts obtained by the recrystallization were identical to those of the recrystallized salt obtained in the laboratory run: 1:2 (*R*)-**1**:(*S*)-**5**: $[\alpha]_D^{20} = +91.8$ (*c* 0.5, H_2O); 99.5% de; mp 222.0–223.0 °C.

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