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Resolution of 1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]indole via Diastereomeric Salt Formation with *N*-Tosyl-(*R*)-phenylglycine

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Enantiopure 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole, the starting material of indoline dyes, could be obtained from the diastereomeric salt with *N*-tosyl-(*R*)-phenylglycine in ethanol.

Dye-sensitized solar cells (DSCs) have been extensively investigated as potential candidates for renewable-energy systems.[1] A number of organic dyes such as coumarin,[2a] oligothiophene,[2b] porphyrin,[2c] ethyldioxythiophenethienothiophene,[2d] oligo(phenylenevinylene),[2e] phenoxazine,[2f] and indoline dyes have been proposed as highly efficient sensitizers. In particular, indoline dyes D149 and D205 shown in Figure 1 have attracted much attention as highly efficient sensitizers.[3a,3b]

Indoline dyes have been synthesized from 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole **1**. Since compound **1** is prepared as racemates, all the reported indoline dyes are racemates. Racemic dyes can easily aggregate to decrease conversion efficiency.[4] We believe that optically active indoline dyes can show improved performance compared to racemates. This strategy might enable us to investigate the inherent performance of these dyes, excluding the effects of additives such as chenodeoxycholic acid.[3b] However, no method for preparing enantiopure **1** has been reported so far.

We tried to accomplish the resolution via diastereomeric salt formation, because this is simple and useful for obtaining enantiopure compounds in large scale.

First, to find the most suitable resolving agent for racemic **1**, several acidic resolving agents such as L-tartaric acid, L-malic acid, (*R*)-mandelic acid, dibenzoyl-L-tartaric acid, *N*-tosyl-(*S*)-phenylalanine, and *N*-tosyl-(*R*)-phenylglycine ((*R*)-**2**) were examined using ethanol as a solvent.[5] The resolving agents except for (*R*)-**2** did not afford any crystals. Compound (*R*)-**2** gave the best results (38.7% yield, 56.4% de (diastereomeric excess), 43.7% resolution efficiency).[6]

Next, the resolution conditions of racemic **1** with (*R*)-**2** were optimized in various solvents by seeding pure (3a*R*,8b*R*)-**1**/(*R*)-**2** salt or (3a*S*,8b*S*)-**1**/(*R*)-**2** salt as shown in Figure 2.[7] A typical experimental procedure is as follows: To a 50 mL flask were added racemic **1** (0.8 g, 5.0 mmol), (*R*)-**2** (1.5 g, 5.0 mmol), and solvent (5 mL), and the mixture was heated to 50 °C to give a clear solution. Then the solution was cooled, seeded (0.5 mg) at 40 °C, and gradually cooled to 20 °C. After aging this solution at 20 °C for 24 h, the resulting crystals were filtered off to afford **1**/(*R*)-**2** diastereomeric salt. When crystallization was not observed, the solution was cooled to −20 °C, aged at −20 °C for 24 h and filtered to afford the salt. The results are summarized in Table 1.

We serendipitously found that the absolute configuration of **1** in the diastereomeric salt was controlled by the kind of seed. In most solvents, when (3a*S*,8b*S*)-**1**/(*R*)-**2** salt was seeded, (3a*S*,8b*S*)-**1**/(*R*)-**2** salt was obtained, and when (3a*R*,8b*R*)-**1**/(*R*)-**2** salt was seeded, (3a*R*,8b*R*)-**1**/(*R*)-**2** salt was obtained. The solubility of two types of diastereomeric salts in ethanol is similar {(3a*R*,8b*R*)-**1**/(*R*)-**2** salt: 11 g/100 g, (3a*S*,8b*S*)-**1**/(*R*)-**2** salt: 8 g/100 g at 18 °C}. Therefore both the diastereomers could be obtained from the same solution by seeding different kinds of diastereomeric crystals. Furthermore, the diastereomeric excess (de) of the salt depended on the dielectric constant of the solvent. When the dielectric constant was in the range of 21 to 24, the diastereomeric salt of (3a*S*,8b*S*)-**1** was obtained with good de (Entries 7 and 9). And the diastereomeric salt of (3a*R*,8b*R*)-**1** was obtained with good de when the dielectric constant was in the range of 24 to 29 (Entries 6 and 8). In the solvents of higher (>30) and lower (<20) dielectric constants, the diastereomeric salts with lower de were obtained (Entries 1, 2, 11, and 12). When the dielectric constant was larger than 28.5, the resolution efficiency of (3a*S*,8b*S*)-**1** salt was higher than that of (3a*R*,8b*R*)-**1** salt (Entries 1–4). When the dielectric constant was smaller than 28.5, the resolution efficiency of (3a*S*,8b*S*)-**1** was lower than that of (3a*R*,8b*R*)-**1** salt (Entries 7–12). Sakai et al. have reported that the dielectric constant of the solvent employed in the resolution

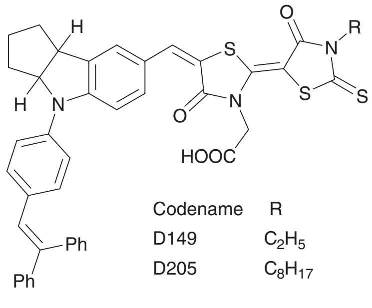

Figure 1. The structure of indoline dye.

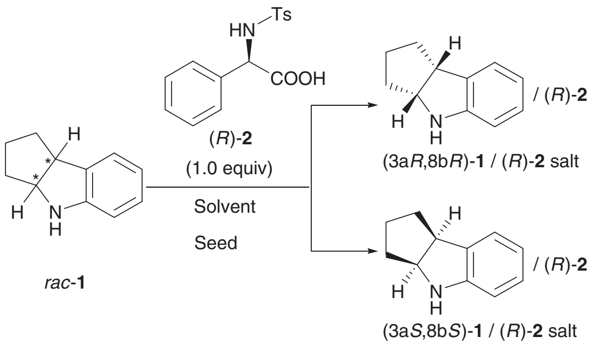

Figure 2. Resolution of racemic **1** with (*R*)-**2**.

Table 1. Resolution of racemic **1** with (*R*)-**2** in various solvents with seeding

Entry	Solvent	Dielectric constant[a]	Seed type[b]	Filtration temperature /°C[c]	Yield /%[d]	de /%[e]	Resolution efficiency /%[f]	Absolute configuration[g]
1	MeOH	33.1	*S*	−20	43.0	36.6	31.5	(3a*S*,8b*S*)
2	MeOH	33.1	*R*	−20	53.4	9.0	9.6	(3a*R*,8b*R*)
3	MeOH/acetone = 9/1	31.9	*S*	−20	40.5	53.2	43.1	(3a*S*,8b*S*)
4	MeOH/acetone = 9/1	31.9	*R*	−20	42.6	26.3	22.4	(3a*R*,8b*R*)
5	MeOH/EtOH = 1/1	28.5	*S*	−20	33.5	50.3	33.7	(3a*S*,8b*S*)
6	MeOH/EtOH = 1/1	28.5	*R*	20	18.5	95.1	35.2	(3a*R*,8b*R*)
7	EtOH	23.8	*S*	20	20.6	85.5	35.2	(3a*S*,8b*S*)
8	EtOH	23.8	*R*	20	34.8	74.6	51.9	(3a*R*,8b*R*)
9	Acetone	20.7	*S*	−20	14.6	84.4	24.6	(3a*S*,8b*S*)
10	Acetone	20.7	*R*	−20	22.3	59.7	26.6	(3a*R*,8b*R*)
11	*i*-PrOH	18.0	*S*	20	47.7	13.4	12.8	(3a*R*,8b*R*)
12	*i*-PrOH	18.0	*R*	20	52.5	14.3	15.0	(3a*R*,8b*R*)

[a] Dielectric constant for a mixed solvent is the weighted average value calculated from those of pure solvents. [b] Seed types are as follows: *S* = (3a*S*,8b*S*)-**1**/(*R*)-**2** salt, *R* = (3a*R*,8b*R*)-**1**/(*R*)-**2** salt. [c] These temperatures were almost corresponded to the crystallization temperature. [d] Yield was calculated based on racemic **1**. [e] Diastereomeric excess was determined by chiral HPLC using a CHIRALPAK AD-H column. [f] Resolution efficiency = yield (%) × de (%) × 0.02. [g] Absolute configuration of the major enantiomer of **1** in a diastereomeric salt.

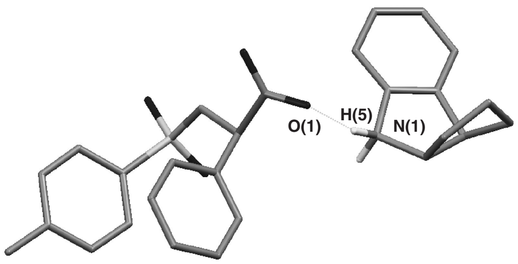

Figure 3. Structure of (3a*R*,8b*R*)-**1**/(*R*)-**2** salt (All hydrogen atoms except that attached to nitrogen are omitted for clarity). Selected bond distances and angles: O(1)···N(1) 2.705 Å.

significantly affects the molecular discrimination process by controlling the molecular interactions involving the solvent molecules such as water.[8] However, in our case, (3a*R*,8b*R*)-**1** and (3a*S*,8b*S*)-**1** salts do not include any solvent molecules judging from elemental analysis.[6] It is suspected that the added seed could determine the kind of produced diastereomeric salt.

The crystal structure of (3a*R*,8b*R*)-**1**/(*R*)-**2** salt is shown in Figure 3. The protonated amino moiety of (3a*R*,8b*R*)-**1** forms the salt with the carboxylate anion of (*R*)-**2**.[9]

Pure diastereomeric salts were easily obtained by recrystallizing the salts from ethanol. Then, the target enantiopure **1** was obtained by neutralizing the pure diastereomeric salts in 80–90% yield.

In conclusion, we have established a convenient and efficient preparation of enantiopure 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole, the starting material of optically active indoline dyes. The diastereomeric salts with *N*-tosyl-(*R*)-phenylglycine were resolved in ethanol. The absolute configuration of the diastereomeric salts were controlled by changing the chirality of seed.

References and Notes

1 B. O'Regan, M. Grätzel, *Nature* **1991**, *353*, 737; M. Grätzel, *Nature* **2001**, *414*, 338; F. Gao, Y. Wang, J. Zhang, D. Shi, M. Wang, R. Humphry-Baker, P. Wang, S. M. Zakeeruddin, M. Grätzel, *Chem. Commun.* **2008**, 2635.

2 a) Z.-S. Wang, Y. Cui, Y. Dan-oh, C. Kasada, A. Shinpo, K. Hara, *J. Phys. Chem. C* **2007**, *111*, 7224. b) N. Koumura, Z.-S. Wang, S. Mori, M. Miyashita, E. Suzuki, K. Hara, *J. Am. Chem. Soc.* **2006**, *128*, 14256; Z.-S. Wang, N. Koumura, Y. Cui, M. Takahashi, H. Sekiguchi, A. Mori, T. Kubo, A. Furube, K. Hara, *Chem. Mater.* **2008**, *20*, 3993. c) W. M. Campbell, K. W. Jolley, P. Wagner, K. Wagner, P. J. Walsh, K. C. Gordon, L. Schmidt-Mende, M. K. Nazeeruddin, Q. Wang, M. Grätzel, D. L. Officer, *J. Phys. Chem. C* **2007**, *111*, 11760; H.-P. Lu, C.-L. Mai, C.-Y. Tsia, S.-J. Hsu, C.-P. Hsieh, C.-L. Chiu, C.-Y. Yeh, E. W. Diau, *Phys. Chem. Chem. Phys.* **2009**, *11*, 10270. d) G. Zhang, H. Bala, Y. Cheng, D. Shi, X. Lv, Q. Yu, P. Wang, *Chem. Commun.* **2009**, 2198. e) H. Im, S. Kim, C. Park, S.-H. Jang, C.-J. Kim, K. Kim, N.-G. Park, C. Kim, *Chem. Commun.* **2010**, *46*, 1335. f) H. Tian, X. Yang, J. Cong, R. Chen, J. Liu, Y. Hao, A. Hagfeldt, L. Sun, *Chem. Commun.* **2009**, 6288.

3 a) S. Ito, S. M. Zakeeruddin, R. Humphry-Baker, P. Liska, R. Charvet, P. Comte, M. K. Nazeeruddin, P. Péchy, M. Takata, H. Miura, S. Uchida, M. Grätzel, *Adv. Mater.* **2006**, *18*, 1202. b) S. Ito, H. Miura, S. Uchida, M. Takata, K. Sumioka, P. Liska, P. Comte, P. Péchy, M. Grätzel, *Chem. Commun.* **2008**, 5194.

4 M. Matsui, T. Fujita, Y. Kubota, K. Funabiki, H. Miura, M. Shiro, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 709.

5 Synthesis of racemic **1**: a) J. Shimizu, S. Murakami, T. Oishi, Y. Ban, *Chem. Pharm. Bull.* **1971**, *19*, 2561. Synthesis of (*R*)-**2**: b) H. Murakami, S. Satoh, T. Tobiyama, K. Sakai, H. Nihira, Eur. Pat. Appl. EP 710,652, **1996**.

6 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

7 The absolute configuration of resolved **1** was assigned by comparing the retention time of (3a*R*,8b*R*)-**1**/(*R*)-**2** salt whose absolute configuration was determined by X-ray analysis.

8 K. Sakai, R. Sakurai, N. Hirayama, *Tetrahedron: Asymmetry* **2004**, *15*, 1073; K. Sakai, R. Sakurai, A. Yuzawa, N. Hirayama, *Tetrahedron: Asymmetry* **2003**, *14*, 3713.

9 A single crystal of (3a*R*,8b*R*)-**1**/(*R*)-**2** salt was recrystallized from EtOH. Crystal data. $C_{26}H_{28}N_2O_4S$, $M_r = 464.56$, orthorhombic, $a = 5.413(3)$, $b = 13.686(6)$, $c = 31.066(16)$ Å, $U = 2301(2)$ Å^3, $T = 123$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, 5222 reflections measured, 4640 unique ($R_{\text{int}} = 0.063$) which were used in all calculation. The final wR_2 was 0.132 (all data). Crytstallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-776684.