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A Method for the Racemization of 2-Methylpyrrolidine: A Histamine H_3 Receptor Pharmacophore

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ABSTRACT: This paper describes a method for the racemization of unwanted (*S*)-**1** isomer arising from the resolution of (±)-**1**. The process of racemization involves thiyl radical-mediated reversible hydrogen abstraction at the chiral center, in the presence of AIBN in water. The racemized isomer was subsequently resolved by L-(+)-tartaric acid to get (*R*)-**1**, a histamine H_3 receptor pharmacophore. We foresee that such an approach of racemization will be industrially useful for recycling waste (*S*)-**1** enantiomer.

INTRODUCTION

Discovered by Pasteur in 1853, the separation of enantiomers from a racemic mixture with the help of chiral resolving agents is called the "classical method of resolution".[1] In the context of large-scale enantiomer separations, crystallization techniques are often straightforward and more economical than any other method. Hence, classical resolution is still an essential tool in the preparation of a majority of substances required in enantiopure form in the synthesis of pharmaceuticals and agrochemicals. To cite but a few examples, (*S*)-pregabalin,[2] (*S*)-naproxen,[3] D-phenylglycine, and D-4-hydroxyphenylglycine are produced by separation of diastereoisomeric salts.[4]

Histamine, a biogenic amine, acts as neurotransmitter and exerts its biological action by combining with four distinct cellular histamine G-protein-coupled receptors (H_1–H_4).[5] These presynaptic histamine H_3 receptor antagonists have found application as treatment in a variety of CNS disorders, such as cognitive disorders,[6] and attention-deficit hyperactivity disorder (ADHD).[7] The imidazole-based histamine H_3 receptor antagonist was discovered to have low clinical acceptability due to the potential to give rise to drug–drug interactions by inhibiting hepatic CYP (cytochrome P450) enzymes and poor CNS permeability. For these reasons the researchers are now emphasizing the development of non-imidazole-based histamine H_3 receptor antagonists. Figure 1 summarizes these H_3 receptor antagonists which have (*R*)-**1** as a common pharmacophore.[8]

Even though various multistep asymmetric routes for the preparation of (*R*)-**1** are reported,[9] classical resolution of the inexpensive racemic (±)-**1** with L-(+)-tartaric acid remains the route of choice for making (*R*)-**1** due to its commercial scalability (Scheme 1).[10] This route is also safe and does not require isolation of multiple intermediates. The disadvantage of this route is that the unwanted (*S*)-**1** isomer is lost in the mother liquor during the resolution step, hampering overall yield of the process. Thus, to increase the overall yield we report an approach which leads to successful racemization and recycling of the unwanted (*S*)-**1** isomer.

RESULTS AND DISCUSSION

In order to improve the overall throughput of the resolution process we devoted our efforts toward racemization and recycling of the unwanted (*S*)-**1** isomer. We were faced with a challenge of racemizing the antipodal (*S*)-**1** isomer which is not equipped with functionality that is susceptible for racemization. A literature search revealed that there are reports on the racemization of inactivated amines, such as thiyl radical-mediated racemization of nonactivated amines.[11] We hypothesized that our substrate, unwanted (*S*)-**1** isomer, will racemize under thiyl radical-mediated racemization in a similar manner.

To test this approach we required a reliable analytical method for the determination of the chiral purity of 2-methylpyrrolidine. Although reversed-phase HPLC for the determination of diastereomer formed between 2-methylpyrrolidine and Cbz-valine anhydride is reported in the literature,[12] we, however, adopted a GC method for the determination of the chiral purity of 2-methylpyrrolidine directly to avoid the additional step of derivatization. With a GC method in hand we focused our attention towards the racemization and recycling of unwanted (*S*)-**1**.

In our laboratory, resolution of (±)-**1** to (*R*)-**1** with L-(+)-tartaric acid was achieved after five crystallizations in 28% yield with >98% ee.[13] Solvents from the mother liquor obtained after the resolution step were distilled to obtain the tartaric acid salt of **1** enriched with (*S*)-isomer. This salt was treated with aqueous NaOH to liberate free amine, and analysis showed typically around 70–75% of the unwanted (*S*)-**1** enantiomer along with 30–25% of the (*R*)-**1** enantiomer. In order to make this process economically viable, the racemization of **1** enriched with (*S*)-**1** recovered from the mother liquor was a necessity. Table 1 summarizes our efforts for the racemization of this amine. Initially we screened different solvents, keeping the quantity of octanethiol (1.2 equiv) constant; smooth racemization was observed in all the conditions tested (entries 1–3). With toluene being a preferred commercial solvent, further reduction of the octanethiol quantity was tried successfully, and 10 mol % of octanethiol was found to be adequate (entry 4).

Typically, it was found that the isolated, enriched (*S*)-**1** obtained from distillation of the neutralized mother liquor of the resolution step was contaminated with ∼10% water. We

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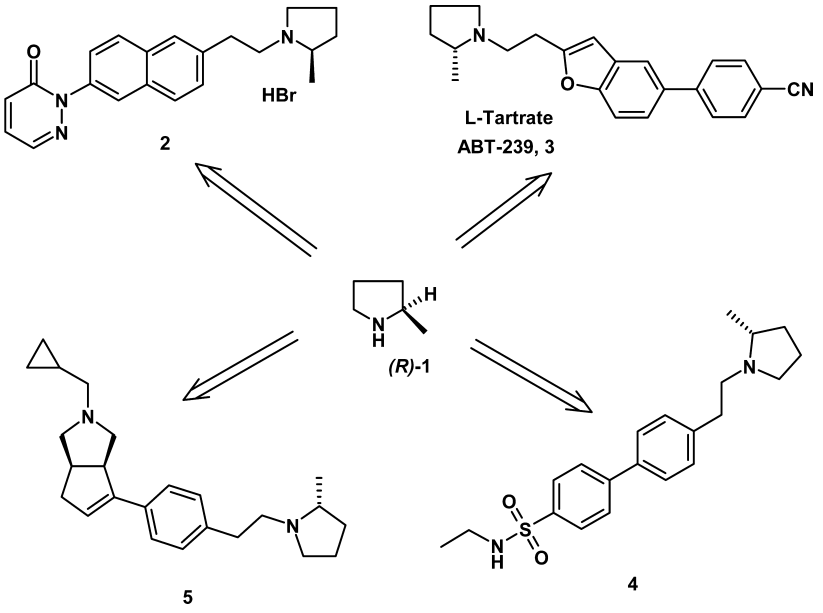

Figure 1. (*R*)-2-Methylpyrrolidine: a histamine H_3 receptor pharmacophore.

Scheme 1. Chiral separation of (±)-1 into (*R*)-1 using diasteromeric salt formation between (*R*)-1 and L-(+)-tartaric acid

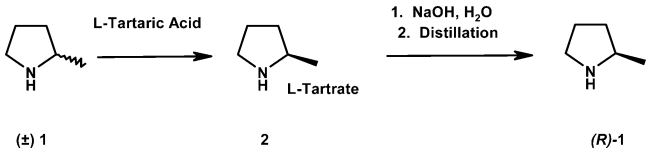

Table 1. Racemization of 2-methylpyrrolidine

entry[a]	octanethiol (equiv)	solvent[b]	chiral purity by GC[c] *S*	*R*
1	1.2	dichloromethane	49.68	50.32
2	1.2	chloroform	49.88	50.12
3	1.2	toluene	49.92	50.08
4	0.1	toluene	50.10	49.90
5	0.1	water	50.05	49.95
6	0.05	water	50.10	49.90
7	0.025	water	59.19	40.81

[a]All the reactions were done on 5 g scale using 2.0 volumes of solvent; 2 mol % AIBN was added in one lot. [b]All the reactions were maintained at reflux for 1 h. [c]Racemized product was not isolated.

experimentally found out that removal of the remaining water from enriched (*S*)-**1** was not a trivial job, and loss (4−6%) of enriched (*S*)-**1** was observed during the drying and distillation steps. Therefore, it was decided to check the feasibility of the racemization reaction in water so that the additional drying step can be avoided. To our delight complete racemization of enriched (*S*)-**1** was observed in water with 10 mol % of octanethiol (entry 5). The possibility of further reduction of octanethiol was attempted, and it was observed that even 5 mol % of octanethiol was adequate to racemize enriched (*S*)-**1** in 1 h (entry 6); however, using 2.5 mol % of octanethiol was not efficient (entry 7).

With an optimized condition in hand, we decided to run this process on preparative scale. The block-flow diagram explains our approach for the resolution, racemization, and recovery of (*R*)-**1** (Figure 2)

The (±)-**1** was resolved by forming a diastereomeric salt with L-(+)-tartaric acid. Solvents were distilled off from the mother liquor, and residual salt was basified by addition of aqueous NaOH. The enriched (*S*)-**1** was distilled and racemized using optimized conditions. The (±)-**1** obtained in this way was subjected to the next cycle of the resolution to realize 28% yield of (*R*)-**1** having >98% ee. The process executed in this fashion shows increased overall yield of the resolution step up to 43.3%.[14]

■ CONCLUSION

We have described a process for the recycling of the unwanted isomer from the mother liquor of the preparation of (*R*)-**1** by using thiyl radical-mediated racemization. Most significantly the racemization could be achieved in water, a green solvent. The racemized compound was subsequently resolved by L-(+)-tartaric acid to get (*R*)-**1** with the same efficiency as that of the original resolution. Recycling of the unwanted isomer not only helps to minimize the waste generated during the classical resolution process but also decreases the production cost and increases the overall throughput of the product.

■ EXPERIMENTAL SECTION

General. Reagents and materials were obtained from commercial suppliers and used without additional purification. All reactions were performed under nitrogen atmosphere. Chiral GC analysis was done on Agilent 7890A GC system with FID detector. Diluents: trifluoroacetic anhydride + MDC Column: Chiraldex-G-TA (30 mm × 0.25 mm × 0.12 μ), Conditions: 150 °C (110 °C/12) 250 °C. Flow rate 1.1 mL/min (helium), injection volume 1.0 μL split 1:250. R_t = 9.93 min (*S*) isomer, R_t = 9.29 min (*R*) isomer. Chemical purity was determined by GC analysis on Agilent 7890A GC system with FID detector. Diluents: acetonitrile, Column: HP-5 (30 mm × 0.32 mmID × 0.25 μ), Conditions 230 °C (50 °C/10 °C/min/250 °C/0) 280 °C. Flow rate 1.0 mL/min (N_2), Injection volume 1.0 μL split 1:20.

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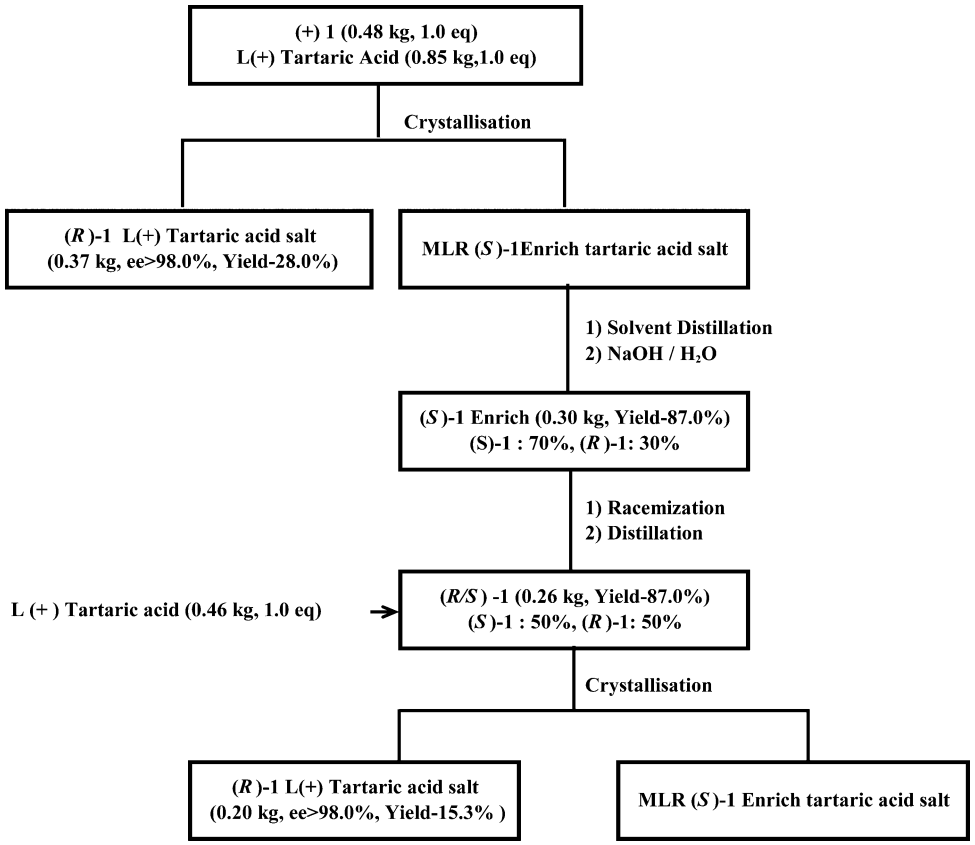

Figure 2. Resolutions and racemization of (±)-**1**.

***(R)*-2-Methylpyrrolidine L-Tartrate.** Absolute ethanol (7.15 L, 5.64 kg), methanol (2.04 L, 1.65 kg), and L-tartaric acid (0.85 kg, 5.63 mol) were charged to a 30-L all glass reactor. Racemic 2-methylpyrrolidine **1** (0.48 kg, 5.63 mol) was charged to the above reaction mixture. The mixture was heated to 72 °C to ensure a homogeneous solution and was maintained for 30 min. The solution was then cooled to 25 °C at approximately 10 °C/h. The solution was stirred at 25 °C for 8 h. The slurry was cooled to −5 °C, held for 1.0 h, filtered, and dried at 60 °C under vacuum with a nitrogen bleed overnight to yield 1.02 kg (ee >20%, Yield 77%) of the partially resolved tartrate. The enantiomeric purity of the tartrate could be improved to >99% by repeated recrystallizations from ethanol/methanol (78:22) (16.24 L/kg of solid) as described above. After five recrystallizations, 0.37 kg (ee 99.0%, Yield 28%) of the desired product was isolated.

Racemization of 2-Methylpyrrolidine. To a 10-L four neck RB flask equipped with overhead stirrer, condenser, addition funnel and thermometer pocket was charged mother liquor obtained from all the five crystallizations, and the reaction mass was heated to distill ethanol and methanol. The oily residue of 2-methypyrrolidine tartrate salt (0.95 kg, 4.04 mol) obtained was cooled to 10 °C. Sodium hydroxide solution (3.20 kg, 40.04 mol) was added to the reaction mass, maintaining the reaction temperature below 10 °C. The reaction mass was stirred for 30 min at 30 °C. The temperature was slowly raised to 100 °C for distilling 2-methypyrrolidine. (Oil bath temperature is 100 °C, solution temperature is 95 °C and vapor temperature is 68−80 °C.) 2-Methypyrrolidine which weighs 0.36 kg (contains 12% moisture) was obtained. Recovered (*S*)-enriched **1**; 0.34 kg (purity based 0.30 kg) was dissolved in 0.56 L of water. To this clear solution was charged 25.25 g (0.05 equiv) of octanethiol and 11.58 g of AIBN (0.02 equiv). The reaction mass was heated to reflux and maintained at reflux for 1 h. The reaction mass was submitted for chiral GC analysis (compound was found to be fully racemized). Reaction mass was cooled to 25 °C, 0.36 kg of NaOH was charged to the reaction, and then the product was recovered by distillation to get (±) **1** which was contaminated with 15% water. This product was dried over KOH pellets to get 0.26 kg of (±) **1**; yield 87%.

^{1}H NMR [$CDCl_3$]: 1.21 (d, J = 8.0 Hz, 3H), 1.74 (m, 2H), 1.84 (m, 2H), 2.81 (m, 1H), 3.07 (m, 2H).

^{13}C NMR [$CDCl_3$]: 21.0, 25.5, 33.5, 46.5, 54.4.

GC Purity: 97.55%, Chiral Purity (GC): 0.2% ee.

(*R*)-2-Methylpyrrolidine L-Tartrate. Absolute ethanol (3.89 L, 3.06 kg) and methanol (1.11 L, 0.87 kg) were charged to a 10-L glass reactor. To this were charged racemic 2-methylpyrrolidine **1** (0.26 kg, 3.06 mol), and L-tartaric acid (0.46 kg, 3.06 mol), and following the above resolution method, after five recrystallizations, 0.20 kg (ee > 98.0%, 15.3% based on initial 0.48 kg of (±)-**1**) of the desired product was isolated.

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Notes

The authors declare no competing financial interest.

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(12) (a) For determination of chiral purity of (*R*)-**1** and (*S*)-**1** by chiral HPLC derivitization with Cbz-valine, see ref 9c.
(13) L-(+)-Tartaric acid diasteromeric salt of (*R*)-**1** was used as such without converting it into free amine (*R*)-**1**; please see reference 10c.
(14) Resolution of (±)-**1** with L-(+)-tartaric acid, after five crystallisations gave 28% yield of L-(+)-tartaric acid diastereomeric salt of (*R*)-**1**, while an additional 15.3% was obtained after the first cycle of racemization and diastereomeric crystallization, taking the overall yield to 43.3%.