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An Investigation on Key Parameters That Influence the Resolution of Omeprazole Sodium†

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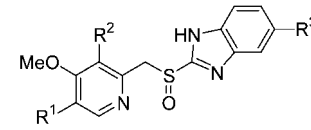
Abstract:

In this document are highlighted systematic studies on factors such as water content, temperature, solvent, and mole ratio of the resolving agents that influence the resolution of omeprazole sodium.

Introduction

Chiral sulfoxides are useful synthons for the construction of many chemically and pharmaceutically significant molecules.[1] The traditional approach to the preparation of optically active sulfoxides involves either optical resolution of racemates[2] or asymmetric oxidation of the prochiral sulfides.[3] Prazoles are a class of active pharmaceutical ingredients that contain a chiral sulfoxide group as an active component. Prazoles are known as proton pump inhibitors, which inhibit gastric acid secretion and are thus used as antiulcer agents.[4] Nexium, the magnesium salt of *S*-omeprazole, was one such prazole developed by AstraZeneca and used for the treatment of acid-related diseases.[5] Earlier we have reported a resolution process for the synthesis of the magnesium salt of *S*-omeprazole through a transition metal complex using a combination of D-(−)-diethyl tartrate, $Ti(O^iPr)_4$, and L-(+)-mandelic acid as resolving agents.[6] Herein we wish to report our systematic investigation on the significant role of water, temperature, and the mole ratio of the resolving agents in the resolution of omeprazole sodium. Though the influence of water and temperature in asymmetric sulfoxidation is well precedent in the literature,[7] the effect of these parameters on the resolution of sulfoxides is not yet explored.

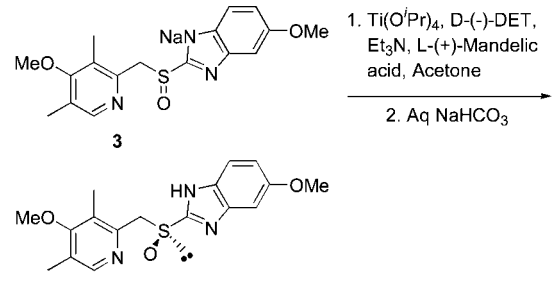


$R^1 = CH_3$, $R^2 = CH_3$, $R^3 = OCH_3$ Omeprazole **1**
$R^1 = H$, $R^2 = OCH_3$, $R^3 = OCHF_2$ Pantoprazole **2**

Results and Discussions

In one of our earlier experiments, we observed that no resolution occurred when racemic omeprazole **1** was exposed to a resolving agent such as a mixture of $Ti(O^iPr)_4$, D-(−)-diethyl tartrate, L-(+)-mandelic acid, and triethylamine. Later, this resolution process was optimized using the sodium salt of racemic omeprazole **3** (Scheme 1). Although this process gave *S*-omeprazole *S*-**1** in >99% ee, some inconsistency was observed as some of the batches failed in plant. This prompted us to investigate the influence of various factors that affect the resolution process, such as water content, temperature, and mole ratio of the resolving agents.

Scheme 1. **Resolution of omeprazole sodium 3**



>99% *ee*, 39% yield

To investigate the role of water in the resolution process, we examined the water content of the omeprazole sodium **3** in both failed and successful batches. This revealed that the water content of **3** in the failed batch was 0.5 mol (hemihydrate), whereas in the successful batch it was 1–2 mol. These

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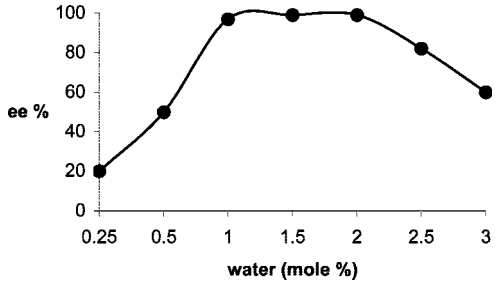


Figure 1. **Influence of water on resolution of 3.**

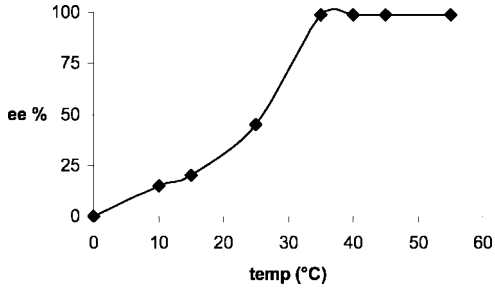


Figure 2. **Influence of temperature on resolution of 3.**

Table 1. **Influence of mole ratio of Ti(O^iPr)$_4$ and D-(−)-DET**

Ti (O^iPr)$_4$ (mol)	D-(−)-DET (mol)	ee (*S*)
0.25	0.5	25
0.5	0.5	28
0.5	**1.0**	**>99**
1.0	1.0	76
1.0	1.5	81
1.0	2.0	78

observations encouraged us to explore this resolution process further by altering the composition of water content present in the reaction.

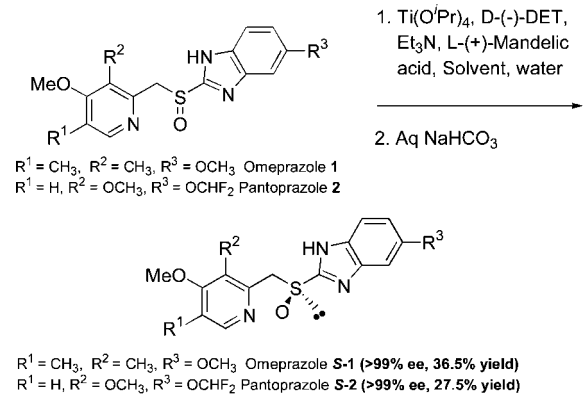
A systematic investigation on the influence of water in the resolution of **3** at 35–40 °C showed an interesting phenomenon for the combination of Ti(O^iPr)$_4$/D-(−)-DET/L-(+)-mandelic acid/Et_3N/H_2O (mole ratio 0.5:1:1:3:*x*) where *x* ranged from 0 to 6. The maximum separation of enantiomers (99% ee of *S*-**1**)[8] was achieved when *x* ranged from 1 to 2. No resolution observed when $x = 0$ and $x = 6$. When $x = 6$, some precipitation occurred (presumably TiO_2). Figure 1 shows the effect of water on the resolution of omeprazole sodium **3**.

The reaction temperature also played a key role in chiral discrimination. No resolution was observed at 0 °C, and the best selectivity (>99% ee) was obtained at 35–40 °C. Some product degradation occurred above 40 °C, which led to the formation of many impurities. Interestingly, an increase in temperature above 40 °C did not affect the enantiometic excess of the product. Figure 2 explains the influence of temperature in the resolution of omeprazole sodium **3** (with water content 1–2 mol).

We also extended our studies toward the effect of mole ratio of the resolving agents, base, and solvents. Table 1 illustrates how the resolution of **3** (with water content 1–2 mol) was

(8) HPLC data: Chiral pack AD 50 mm × 4.6 mm or equivalent, flow rate 0.5 mL/min with a UV detector at 280 nm, load 20 μL, runtime 30 min at 25–30 °C.

Scheme 2. **Resolution of omeprazole 1 and pantoprazole 2**



influenced by altering the ratio of Ti(O^iPr)$_4$ and D-(−)-DET. The optimal mol ratio of Ti(O^iPr)$_4$ and D-(−)-DET was found to be 0.5:1.

Although the mole ratio of triethylamine had minimal influence on the resolution, satisfactory results were obtained by using 3 mol of triethylamine with respect to **3**. Solvents such as ethyl acetate, methanol, acetonitrile, and acetone were screened for this process, and it was found that the resolution occurred only when acetone was used as a solvent. Resolution in other solvents led to racemic omeprazole.

Another interesting observation is that the order of addition of the reagents also played a significant role in resolution. The best results were obtained by adding D-(−)-DET first followed by Ti(O^iPr)$_4$, triethylamine, and finally L-(+)-mandelic acid. If Ti(O^iPr)$_4$ was added before D-(−)-DET, precipitation (presumably TiO_2) occurred. If triethylamine was added before D-(−)-DET and Ti(O^iPr)$_4$, no resolution observed. Since *S*-omeprazole *S*-**1** is sensitive towards acids, L-(+)-mandelic acid should be added after the addition of triethyl amine.

We also executed these standard conditions to resolve omeprazole base **1** and pantoprazole **2** by adding 1.5 mol of water to the reaction mixture. Surprisingly, both (**1** and **2**[9]) were resolved with >99% ee using acetone and EtOAc as solvents respectively (Scheme 2). No resolution was observed without the addition of water in each case (**1** and **2**). In the case of omeprazole, the yield of the product *S*-**1** was inferior (36.5% on the basis of racemate) when compared to the Nexium process,[5b] which involves asymmetric sulfoxidation, but the enantiomeric excess of the product in our resolution technique was excellent (>99% ee) and the process appears to be robust. Strategies towards converting unwanted *R*-**1** isomer to racemic **1** are currently under investigation.

Conclusion

We have extensively examined the effects of various factors that influence the resolution of omeprazole sodium **3**. The optimized resolution conditions were successfully extended to omeprazole base **1** and other prazoles such as pantoprazole **2**. Further optimization to make this resolution process a common platform applicable to all prazoles is currently under progress.

(9) HPLC data: HI-CHROM TBB, flow rate 1.0 ml/min with a UV detector at 280 nm, load 22 μL, runtime 50 min at 25–30 °C.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on 400 MHz Varian Gemini FT NMR spectrometer. Optical rotations were recorded on Perkin-Elmer model 341 polarimeter. The solvents and reagents were used without further purification.

Resolution of Omeprazole Sodium (3). To a suspension of omeprazole sodium **3** (50.0 kg, 136.2 mol) [with 7.2% water content (200.0 mol)] in acetone (600 L) was added D-(−)-diethyl tartrate (28.1 kg, 136.2 mol) followed by titanium(IV) isopropoxide (19.4 kg, 68.1 mol) and triethylamine (41.3 kg, 408.7 mol) at 35–40 °C. The reaction was maintained at the same temperature till it became homogeneous. L-(+)-Mandelic acid (20.7 kg, 136.2 mol) was added to the reaction mixture, and stirring was continued for additional 2 h. The separated solid was filtered and washed with acetone (350 L). It was suspended in CH_2Cl_2 (200 L) and treated with 5% sodium bicarbonate solution (200 L) for 30 min The organic phase was separated, dried over anhydrous sodium sulfate, and subjected to distillation under reduced pressure to afford *S*-omeprazole *S*-**1**[10] as an oily residue. Yield 18.3.kg (78% with respect to the single isomer); 99.92% ee (by HPLC);[8] $[\alpha]^{25}_D = -157.0$ (*c* 0.5 in $CHCl_3$) {lit.[10] $[\alpha]^{20}_D = -155.0$ (*c* 0.5 in $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.21 (s, 3H), 3.61 (s, 3H), 3.83 (s, 3H), 4.74 (s, 2H), 6.93 (d, $J = 8.9$ Hz, 1H), 6.94 (d, $J = 9.1$ Hz, 1H), 7.52 (bs, 1H), 8.20 (s, 1H), 12.11 (bs, 1H).[10]

Resolution of Omeprazole (1). To a suspension of omeprazole **1** (1.0 kg, 2.9 mol) in acetone (12 L) were added water (78.2 mL, 4.3 mol) and D-(−)-diethyl tartrate (597.6 g, 2.9 mol) followed by titanium(IV) isopropoxide (412.1 g, 1.5 mol) and triethyl amine (878.1 g, 8.7 mol) at 35–40 °C. The reaction was maintained at same temperature till it became homogeneous. L-(+)-Mandelic acid (441.1 g, 2.9 mol) was added to the reaction mixture, and stirring was continued for additional 2 h. The separated solid was filtered and washed with acetone (7 L). It was suspended in CH_2Cl_2 (4 L) and treated with 5% sodium bicarbonate solution (4 L) for 30 min The organic phase was separated, dried over anhydrous sodium sulfate, and subjected to distillation under reduced pressure to afford *S*-omeprazole *S*-**1** as an oily residue. Yield 365.0 g (73% with respect to the single isomer); 99.76% ee (by HPLC).[8]

Resolution of Pantoprazole (2). To a suspension of pantoprazole **2** (20.0 g, 0.052 mol) in ethyl acetate (200 mL) were added water (1.4 mL, 0.078 mol) and D-(−)-diethyl tartrate (10.72 g, 0.052 mol) followed by titanium(IV) isopropoxide (7.39 g, 0.026 mol) and triethylamine (15.75 g, 0.156 mol) at 40–45 °C. The reaction was maintained at same temperature till it became homogeneous. L-(+)-Mandelic acid (7.91 g, 0.052 mol) was added to the reaction mixture, and stirring was continued for additional 2 h. The separated solid was filtered and washed with ethyl acetate (140 mL). It was suspended in EtOAc(80 mL) and treated with 5% sodium bicarbonate solution (80 mL) for 30 min. The organic phase was separated, dried over anhydrous sodium sulfate, and subjected to distillation under reduced pressure to afford *S*-pantoprazole *S*-**2** as an oily residue. Yield 5.51 g (55% with respect to the single isomer); 99.99% ee (by HPLC);[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.89 (s, 3H), 4.72 and 4.80 (AB q, $J = 13.1$ Hz, 2H), 6.57 (t, $J_{H\text{-}F} = 74.3$ Hz, 1H), 6.82 (d, $J = 5.6$ Hz, 1H), 7.08 (d, $J = 8.8$ Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 1H), 7.40 (bs, 1H), 7.62 (bd, $J = 8.0$ Hz, 1H).

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