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An improved process for eszopiclone: Anti-insomnia agent

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Abstract: Application of stable hydrochloride salt of 1-chlorocarbonyl-4-methylpiperzine **2** and tetrabutyl ammonium bromide (TBAB) as a phase transfer catalyst in an improved process of eszopiclone **1** is presented.

Keywords: Zopiclone; phase transfer tatalyst; resolution.

1. Introduction

Eszopiclone **1**, (*S*)-zopiclone enantiomer which is a non-benzodiazepine derivative that has application in the management of the insomnia disorder. The therapeutical effects of **1** is possibly due

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to interaction with the GABA receptor binding domains.[1] The racemate of **1**, zopiclone **8**, was found to be less effective and more toxic that led to the discovery of enantiomeric forms (**1**&**2**) as shown in Figure 1.

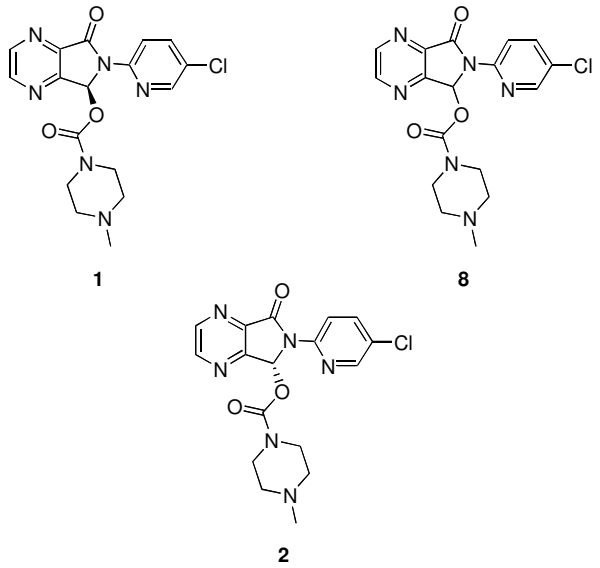
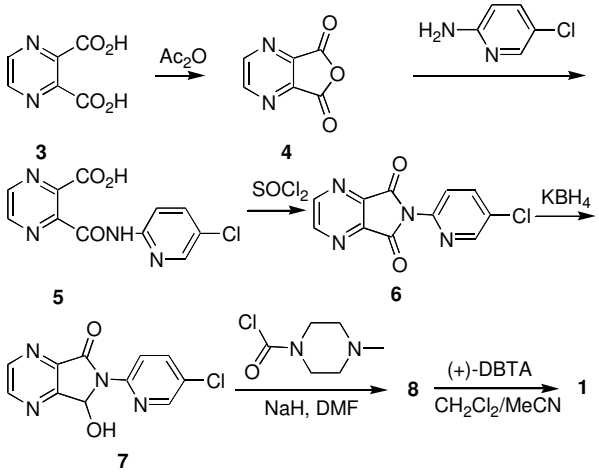


Figure 1. Structures of zopiclone and its enantiomers

The enantiomer having *S*-configuration, **1** was adjudged to possess two fold enhanced pharmacological activity than racemate (zopiclone) while its opposite enantiomer *R*-zopiclone appears to have almost zero activity and elevated toxicity. Nevertheless, the toxicity profile of eszopiclone **1** is not alarming.[2]

The precedented synthesis, as shown in Scheme 1, involves dehydration of pyrazine-2, 3-dicarboxylic acid **3** in presence of acetic anhydride in toluene that afforded pyrazine anhydride **4**.



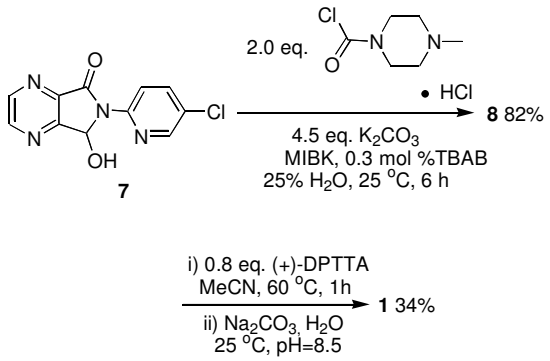
Scheme 1. KnownApproach

Condensation of **4** with 2-amino-5-chloro pyridine in acetonitrile at reflux temperature gave rise to **5**. Further transformation comprises acid chloride formation followed by intramolecular condensation to obtain **6**. Borohydride mediated reduction to afford **7** followed by condensation with 1-chlorocarbonyl-4-methylpiperzine (CCMP) afford **8** and finally resolution with (+)-dibenzoyl tartaric acid [(+)-DBTA] provided the desired enantiomer **1**.

The recent disclosure involves the conceptually similar preparation of zopiclone and its resolution to **1** as presented in scheme 1.[3,4] In addition to this, enzyme catalyzed synthesis is also precedented but it is not practically feasible with industrial settings.[5-7] Nevertheless, most of the reported syntheses particularly the strategy presented in scheme 1 has following disadvantages: a) usage of relatively more hazardous base, sodium hydride, (b) the solvent DMF used in the penultimate stage is irrecoverable, (c) requirement of cryogenic temperatures, (d) multiple crystallizations, (e) relatively low yielding transformation (23%) in a resolution step which makes this process less viable for commercial production. Herein we report an improved and robust process for Eszopiclone **1**.

2. Results and Discussion

Our improved process, as shown in Scheme 2, features the application of milder base (K_2CO_3), methyl isobutyl ketone (MIBK) solvent (90% recovery), 3% tetrabutylammonium bromide (TBAB) and 25% H_2O with respect to batch size exercised in the transformation of **7** to **8**.



Scheme 2. Improved process for **1**

Intermediate **7** was procured from external resources (Dongshong Sinochem. Ltd.). The reaction did not require lower temperatures in fact it did proceed well at ambient temperature in 85-90% yield. We observed that the condensation of **7** with CCMP HCl salt (stable and easy to handle) to afford **8** was found to be advantageous since the use of free base (CCMP) did not allow the reaction to completion possibly due to the degradation of CCMP. We also observed that this condensation event did not afford intermediate **8** in absence of TBAB and/or H_2O. It appears that water and the phase transfer moiety play a major role in the reaction. As per precedented approach, the reaction of **7** with CCMP (free base) by employing sodium hydride in anhydrous dimethyl formide at a cryogenic temperature, -10 °C yielded pyrazine intermediate **8** in 47%.[8,9] In our hand, use of K_2CO_3 and MIBK solvent combination afforded intermediate **8** in high yield.

Finally resolution of **8** with (+)-di-paratoluyl tartaric acid mono hydrate [D-(+) DPTTA][10,11] in acetonitrile followed by treatment with sodium carbonate afforded eszopiclone in 35% yield and 99.9% HPLC chiral purity. However, the resolution of **8** employing D-(+)-di-benzoyltartaric acid monohydrate in binary solvent (dichloromethane and acetonitrile) as per the precedented approach afforded **1** in relatively lower yield (23%).

As per patent route, sodium hydride was used to effect the transformation of **7** to **8**. Considering the cost factor and hazardous nature of employed base (NaH) in combination with DMF, we intended to screen non-toxic and inexpensive bases to effect the transformation in an efficient

manner. Among the screened bases (sodium carbonate, potassium hydroxide and potassium carbonate) potassium carbonate in combination with MIBK indicated the best result.

In our optimization efforts, the quantity of potassium carbonate was also ascertained. The optimal conversion of **7** to **8** was achieved with 4.5 eq. of base.

In order to quantify one of the substrates employed in the transformation of **7** to **8**, we performed an optimization for hydrochloride salt of CCMP. Our optimization studies revealed that 2.0 eq. of hydrochloride salt of CCMP is sufficient to afford the product in high yield and purity.

During the experiments to screen the bases for the transformation of **7** to **8** we observed that the maximum conversion took place in MIBK. In order to improve the yield we screened the other solvents (acetone, methanol, 2-butanol, toluene and MIBK) however, none of them shows any improvement in yield.

To find out the cumulative effect of base and solvent on transformation in terms of yield and efficiency, we optimized the volume of solvent in presence of 4.5 eq. of K_2CO_3. It turned out that the 2.6 L of MIBK is required for 1 mol of substrate **7** to yield the product **8**.

TBAB, as mentioned above, plays a pivotal role in the transformation. As per our observation, the 0.3 mol% of the TBAB was required to catalyze the conversion of **7** to **8**.

The quantity of water was also optimized. During our optimization studies it was found that the 66 mL of water, per mole of substrate **7**, was required to afford **8**.

Without altering the optimized quantities of bases, catalyst and water we also optimized the reaction conditions of temperature and time. It was observed that the reaction (**7** to **8**) proceeds smoothly in 6 h at 25-35 ^{o}C.

After optimizing quantities of substrates involved in the conversion of **7** to **8** and reaction conditions we also conducted the experiments to screen the resolving agents [CSA, mandelic acid, tartaric acid, NAGA (*N*-acetyl gulatamic acid) and DPTTA (D-(+)-di-paratoluoyl tartaric acid)] to afford **1**. In our studies we found that the DPTTA is a resolving reagent of choice. The quantity of resolving agent was optimized. We found that the 0.8 eq. of DPTTA is sufficient to afford best chiral purity of the product.

Hydrophilic or hydrophobic nature of solvents plays a pivotal role in the resolution. We examined the effect of different solvents on the resolution event. Among the tested solvents (methanol, acetone, ethyl acetate, THF, water, 1, 4-dioxane, acetonitrile), acetonitrile was found to be solvent of choice that allows transformation at optimal level.

Quantity of solvent, one of the factors to determine the yield, was also optimized. In order to achieve best yield and chiral purity of the DPTTA salt of **1** we found that the 65 mL of acetonitrile per 0.013 mol of substrate **8** is required.

It is well established fact that the temperature and time both play crucial roles in resolution. By keeping other factors constant we optimized the temperature and time. It was found that the optimal resolution of desired enantiomer can be achieved at 50-60 ^{0}C in 1 h.

3. Conclusion

In conclusion, we have employed stable hydrochloride salt of 1-chlorocarbonyl-4-methylpiperzine **2**, a milder base and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in order to achieve an improved process of Eszopiclone **1**.

4. Experimental

The ^{1}H spectra was recorded in $CDCl_3$ using 400 MHz, on a Varian Gemini NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The mass spectrum (70 eV) was recorded on HP-5989a LC-MS spectrometer. The solvents and reagents were used without any purification.

6-(5-Chloropyrid-2-yl)-5-(4-methyl piperazine-1-yl)-carbonyloxy-7-oxo-5, 6-dihydropyrrolo [3,4-b] pyrazine, zopiclone 8

To a stirred solution of 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5, 6-dihydropyrrolo [3,4-b] pyrazine **7** (100 g, 0.38 mol), 1-chlorocarbonyl-4-methylpiperazine hydrochloride (151 g, 0.76 mol), potassium carbonate (240 g, 1.7 mol), tetrabutylammonium bromide (3.0 g, 0.01 mol) and methyl isobutyl ketone (700 mL) was slowly added water (25 mL) at below 35 °C. After stirring for 6-8 h, water (1 L) was added and after stirring for more 1 h the reaction mass was filtered. Finally, the precipitate was thoroughly washed with water (200 mL) and subsequent re-crystallization employing ethyl acetate (1.5 L) to obtain zopiclone **8** (120 g) in 82% yield. The structure was confirmed by ^{1}HNMR and mass spectroscopy and found to be in complete agreement with the reported values.[6]

Resolution to 1

To a solution of **8** (100 g, 0.26 mol) in acetonitrile (1.2 L) was added D-(+)-di-paratoluoyl tartaric acid mono hydrate (84 g, 0.21 mol) at 50-60 °C. After stirring for 1 h, reaction mixture was cooled to 35-45 °C and the product thus obtained was separated by filtration. The filtered solid was washed with acetonitrile (100 mL), the wet solid was directly dissolved in water (100 mL) and the pH of the resulting solution was adjusted to 7.5-8.0 with 10% sodium carbonate solution and the stirring of the reaction mass was continued for ½ h to precipitate Eszopiclone as a crystalline solid. The crystalline solid obtained was filtered, washed thoroughly with water (100 mL) and the wet solid was re-crystallized with ethyl acetate (1.4 L) and dried at 70-75 °C for 4-5 h under vacuum to obtain eszopiclone **1** as a white crystalline solid (34 g) in 34% yield and 99.9% HPLC chiral purity.[12] The structure confirmed by ^{1}H and other spectroscopic techniques which was found to be in complete agreement with the reported values.[6] ^{1}H NMR ($CDCl_3$) δ 8.89 (d, 1H, *J* = 2.40 Hz), 8.86 (d, 1H, *J* = 2.40 Hz), 8.52 (d, 1H, *J* = 8.80 Hz), 8.40 (s, 1H), 8.00 (s, 1H), 7.80 (dd, 1H, *J* = 2.50, 8.85 Hz), 3.72-3.43 (m, 2H), 3.30-3.18 (m, 2H), 2.45-2.24 (m, 2H), 2.23 (s, 3H), 2.13-1.97 (m, 2H).

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