A simple, efficient and scalable synthesis of hypnotic agent, zolpidem

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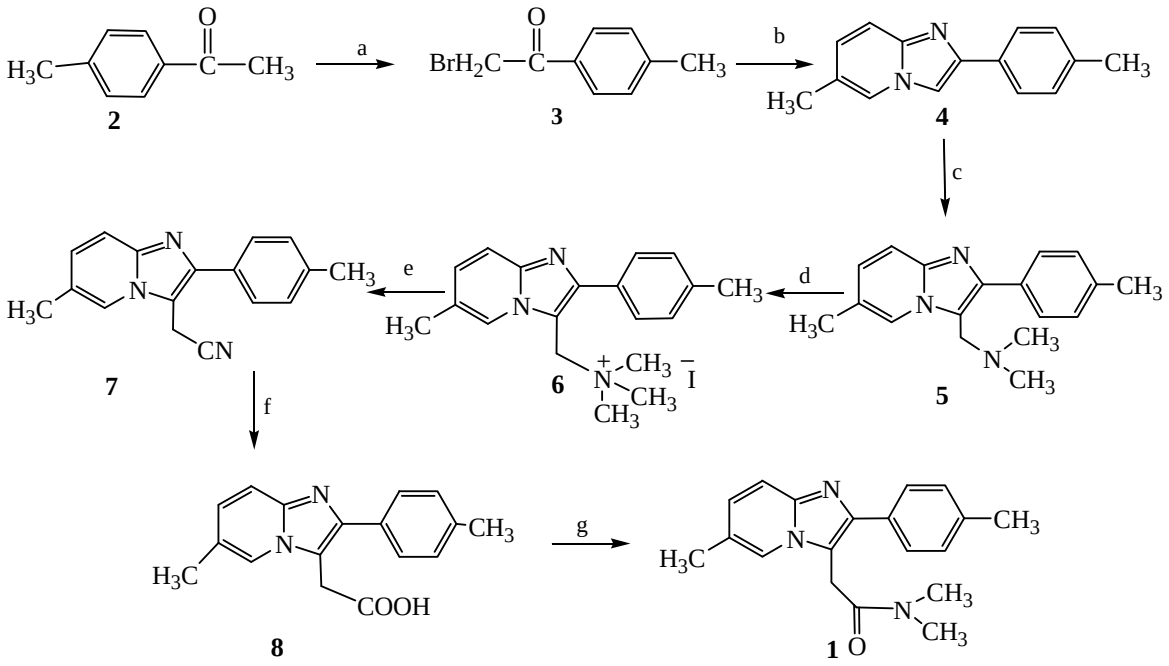
Abstract
A simple, efficient, scalable and cost effective synthesis of zolpidem is discussed. In the present article, the reported seven stage process modified in to four stages, overall yield was improved from 40% to 66% and more than 99.9% HPLC purity has been achieved with free of its process related impurities.

Keywords: Zolpidem, Hypnotic, Insomnia, Related substances

Introduction

Zolpidem (**1**) is a short acting nonbenzodiazepine imidazopyridine hypnotic drug, used for the treatment of insomnia and in the market it is available as its tartrate salt. It potentiates gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to benzodiazepine receptors located on the gamma-aminobutyric acid receptors[1]. Additionally zolpidem also possesses anxiolytic and anticonvulsant properties, thus useful for the treatment of anxiety, sleep disorders and other neurological and psychiatric complaints[2]. Our present work reports a scalable process for the preparation of N, N-dimethyl-2-(6-methyl-2-p-tolyl-imidazo[1,2-a]pyridin-3-yl)-acetamide (**1**), commonly known as zolpidem.

The reported synthesis (Scheme-1) of zolpidem involved the bromination of 4-methyl acetophenone (**2**) followed by condensation of resultant bromo derivative (**3**) with 2-amino 5-methyl pyridine[3] to give an imidazo pyridine intermediate compound **4**, which upon Mannich reaction[4] gave N, N-dimethyl amino imidazopyridine derivative **5**. Compound **5** was further converted into its cyano methyl imidazo pyridine derivative **7** through a methyl iodide quaternary salt **6**. The cyano compound **7** on alkaline hydrolysis yielded a pyridine acetic acid compound **8**[5]. Finally, the key intermediate **8** reacted with carbonyl diimidazole[6] and followed by amidation with anhydrous dimethyl amine yielded zolpidem (**1**).



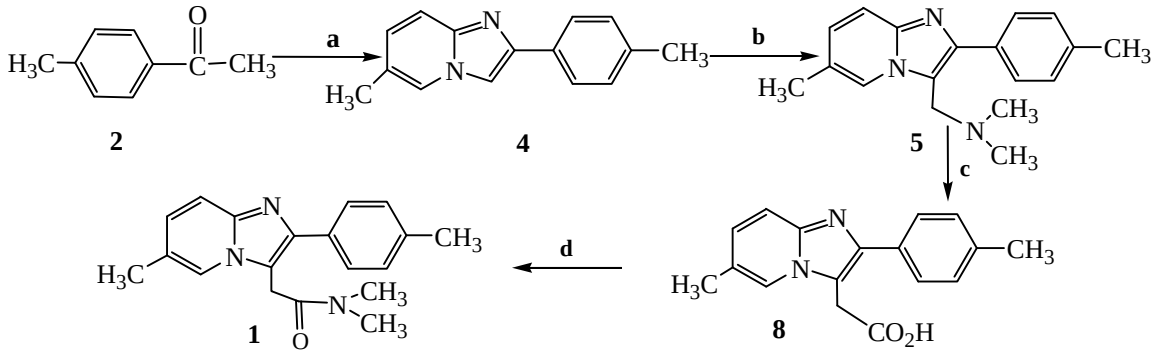
[a]Reagents and conditions: (a) Bromine/acetic acid/-5-0^{O}C. (b) 2-Amino5-methyl pyridine, ethanol/$NaHCO_3$/reflux. (c) Acetic acid/Aq. dimethylamine/formaline/RT. (d) Acetone, CH_3I/reflux. (e) NaCN, ethanol/reflux. (f) KOH/ethanol/reflux. (g) Carbonyldiimidazole, THF/Dimethyl amine/RT

Scheme 1. Reported synthetic scheme for zolpidem[a]

The reported seven stage process suffers from several disadvantages such as (a) It is very difficult to handle the lachrymatory bromo compound **3** at multi scale up level and requires more attention to avoid the exposure to the material, especially at the time of product filtration and drying,. (b) Multistep synthesis for compound **8** (3 steps from compound **5**). (c) Isolation (drying operations) of intermediates such as compounds **3, 6 &7** and their individual work up procedures led to increased life cycle time which in turn led to increase in the manufacturing cost. (d) Fifth stage work up procedure is hazardous and hence needs to be taken lot of safety measures with respect to handling of stage **5** solid material as it may contains residual cyanide. (e) Usage of carbonyl diimidazole (CDI) in the final stage may pose a big problem as it is a highly moisture sensitive reagent and some times, reactions are not proceeding for completion if the compound **8** contains even 0.5% of w/w moisture content, in addition to that larger amounts of imidazole is formed as a bye-product. (f) The overall yield of 40% from this process is also discouraging, which makes the process less viable for commercial production.

Results and Discussion

In our approach we had explored the original route, and we were clearly known about the disadvantages of the process with respect to scalability. Hence, to simplify the process from a commercial aspect and to further increase the yield as well as develop an economically and industrially scalable process, certain improvements were made in the above said reported process.



[a]Reagents and conditions: (a) Bromine/methanol/$AlCl_3$/-5-0^{O}C, 2-Amino5-methyl pyridine, water, /Na_2CO_3. (b) Acetic acid/Aq. dimethylamine/formaline/RT. (c) Acetone, CH_3I, NaCN, NaOH/reflux. (d) PCl_5, dichloromethane, dimethyl amine/RT.

Scheme 2. Modified synthetic scheme for zolpidem[a]

In our present work (Scheme 2), bromination of **2** was carried out in the presence of methanol as against reported acetic acid solvent, this reaction was very smooth and fast when the bromination reactions were conducted with catalytic amount of aluminium chloride. The lachrymatory compound **3** is not being isolated from the reaction mass and directly proceeded for condensation with 2-amino 5-methyl pyridine in the presence of aqueous sodium carbonate solution to yield imidazo pyridine derivative **4**. Several attempts were made for Mannich reaction and finally acetic acid as a solvent medium, formaline and aqueous dimethyl amine are the reagents chosen for the conversion of imidazo pyridine **4** to dimethyl amine derivative **5**.

Amine intermediate **5** reacted with precooled methyl iodide (to avoid the loss during the scale up) in the presence of acetone to yield the iodide quaternary salt. The resulted wet quaternary salt reacted with sodium cyanide in the presence of water medium and after cyanation reaction, the same reaction mass further subjected for alkaline hydrolysis under reflux conditions to convert the cyano derivative to pyridine acetic acid derivative **8**. By this insitu synthesis of **8** from **5** in a single step with 80% yield, the cycle time for total synthesis was reduced drastically. With that multistep isolation of intermediates and handling of hazardous work up procedures were eliminated from the process.

In the last stage, during the amide bond formation from **8** to **1**, costly and highly moisture sensitive reagent of carbonyl diimidazole (CDI) was replaced with dicyclohexyl carbodiimide (DCC). This reaction was carried out in the presence of cheaper solvent dichloromethane as against tetrahydrofuran. Though this reaction was simple and very good with respect to quality and yield, but a larger amount of DCC urea by-product formation was observed hence, this process was not considered for scale up.

Further trials were made for amide bond formation through acid chloride, for this phosphorous pentachloride (PCl_5) and thionyl chloride ($SOCl_2$) reagents were tried. Of the two reagents, PCl_5 gave better yield and quality of the product and in case of $SOCl_2$ the traces of un reacted reagent must be removed from acid chloride reaction mass, otherwise it is affecting the quality of the product. Acid chloride preparations were carried out with various solvents like toluene, ethyl acetate and dichloromethane and the resulted acid chloride reaction mass as such directly proceeded for dimethyl amine (anhydrous gas in cylinders for scale up) condensation to get the required zolpidem (**1**). The reaction of **8** to **1** via acid chloride was very neat and smooth in presence of dichloromethane solvent and at scale up level, the required quantity of solid PCl_5 was added to the reaction medium under nitrogen atmosphere and refluxed for reaction completion. Incase of toluene, product **1** is not soluble, heterogeneous reaction mass was obtained and this requires lengthy work up procedure to isolate the product. Where as ethyl acetate (EA) solvent producing inconsistency yields and that to, it is very difficult to recover the EA solvent for reuse purpose and in case of dichloromethane, it was recovered and reused in the same stage.

Finally, after condensation of acid chloride with dimethyl amine, the reaction mass was washed with aqueous sodium hydroxide to remove the traces of acid impurities and isolated the crude zolpidem. An in-situ recrystallization procedure was incorporated for wet material to get the pure (99.95% purity by HPLC) zolpidem (**1**) with free of its process related compounds as well as organic volatile impurities like methanol, dichloromethane and acetic acid. The overall yield was improved from 40 % to 66% with the modified 4 stage process.

Conclusion

In conclusion, we have provided a cost effective and industrially scalable process for the preparation of zolpidem as per the regulatory requirement.

Experimental Section

General Procedures. The ^{1}H NMR spectra were recorded on a Gemini 200 MHz FT NMR spectrometer; the chemical shifts were reported on δ ppm relative to TMS. The IR spectra were recorded in the solid state as KBR dispersion using Perkin Elmer FT-IR spectrophotometer. The

mass spectra were recorded on Shimadzu LCMS-QP8000, LC-MS and AB-4000 Q-trap LC-MS/MS. Elemental analysis for CHN were performed on Perkin Elmer model 2400 CHNS/O analyzer at Dr. Reddy's Laboratories Ltd. Hyderabad.

6-Methyl-2-p-tolyl-imidazo[1,2-a]pyridine (4). To a pre cooled solution of methanol (45.0 L) and 4-methyl acetophenone (**2**, 15.0 kg, 111 mol), aluminium chloride (0.75 kg, 5.6 mol) was added under stirring at 0-5 ^{0}C. To this reaction mixture bromine (19.16 kg, 112 mol) was added slowly at 0-5 ^{0}C and stirred for 30 minutes. To the reaction mass, water (300.0 L), sodium carbonate (15.0 kg, 12 mol) and 2-amino 5-methyl pyridine solution (12.7 kg, 118 mol in 30.0 L) were added at 25-35 ^{0}C and stirred for reaction completion. The isolated solid was filtered, washed with water (120.0 L). Wet crude product was crystallized from acetone and dried at 60^{0}C to yield the desired pale yellow solid of **4** (23.5 kg, yield: 95.0%, purity by HPLC: 99.5%). IR (cm^{-1}): 1640 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.20-2.40 (s, 6H, CH_3), 7.25-7.55 (d, 4H, Ar-H), 7.80-8.00 (d, 2H, Ar-H), 8.20-8.35 (s, 1H, Ar-H); MS: *m/z* 223 (M^{+1}); Analysis Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.17; H, 6.45; N, 12.72.

Dimethyl-(6-methyl-2-p-tolyl-imidazo[1,2-a] pyridin-3-yl-methyl)-amine (5). To a mixture of **4** (10.0 kg, 45 mol) in acetic acid (15.0 L), aqueous dimethyl amine solution (6.33 kg, 56 mol) and ~36 % formaline solution (4.7 kg, 56 mol) were added slowly and stirred at 25-35 ^{0}C for reaction completion. The reaction mass was cooled to 0-10 ^{0}C and pH was adjusted to 8-9 using 20% aqueous sodium hydroxide (60.0 L). The isolated solid was filtered, washed with water (10.0 L), dried at 80-90 ^{0}C and crystallized from acetone to give yellow solid of **5** (11.0 kg, yield: 88.0%, purity by HPLC: 99.2%). IR (cm^{-1}): 1640 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.25-2.45 (s, 12H, CH_3), 3.80-4.05 (s, 2H, CH_3), 7.25-7.45 (m, 4H, Ar-H), 7.45-7.60 (d, 2H, Ar-H), 8.15-8.25 (s, 1H, Ar-H); .MS: *m/z* 280 (M^{+1}); Analysis Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.19; H, 7.64; N, 15.14.

(6-Methyl-2-p-tolyl-imidazo[1, 2-a]pyridin-3-yl)-acetic acid (8). To a mixture of **5** (70.0 kg, 250 mol) and acetone (700.0 L), precooled methyl iodide (33.8 kg, 238 mol) was added under stirring. The reaction mass was stirred at 20-30 ^{0}C for 8 hours and filtered. The wet compound, sodium cyanide (12.3 kg, 251mol) were added to water (525.0 L) and stirred at 80-85 ^{0}C for reaction completion. Later caustic lye (48%w/w, 157.0 L) and water (350.0 L) were added to the reaction mixture and refluxed for reaction completion. The reaction mass was cooled to room temperature and washed with toluene (350.0 L). The aqueous layer pH was adjusted to 5.0 to 6.0 with acetic acid. The precipitated compound was filtered, washed, dried at 85 ^{0}C and recrystallized from methanol to yield an off-white solid of **8** (58 kg, yield: 83%, purity by HPLC: 99.2%); IR (cm^{-1}): 1700 (C=O), 3415 (OH); ^{1}H NMR (CD_3OD + DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.35-7.45 (d, 2H, Ar-H), 7.55-7.75 (m, 4H, Ar-H), 8.25 (s, 1H, Ar-H); .MS: *m/z* 281 (M^{+1}); Analysis Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.74; N, 9.99. Found: C, 72.74; H, 5.85; N, 9.79.

N, N-Dimethyl-2-(6-methyl-2-p-tolyl-imidazo[1, 2-a]pyridin-3-yl)-acetamide (1). A mixture of pyridine acetic acid **8** (50.0 kg, 178 mol), dichloromethane (600.0 L) and phosphorous penta

chloride (38.0 kg, 190 mol) was refluxed for reaction completion. The reaction mass was cooled to 0-10 ^{0}C and to it dimethyl amine gas was purged till the reaction completion. 80-90 % of the solvent was removed under reduced pressure and water (400.0 L) was added to the residue, heated to 85-90 ^{0}C to remove traces of dichloromethane. The reaction mass was cooled to room temperature, pH was adjusted to 9-10 using caustic lye and stirred for solid isolation. The isolated solid was filtered, washed with water (50.0 L) and dried at 80-90 ^{0}C. Finally recrystallisation using acetone yielded an off white solid of **1** (52 kg, yield: 95.0%, purity by HPLC: 99.8 %); IR (cm^{-1}): 1635 (C=O); ^{1}H NMR ($CDCl_3$ δ ppm): 2.25 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3), 2.85 (s, 3H, N-CH_3), 2.95 (s, 3H, N-CH_3), 4.15 (s, 2H, CO-CH_2), 7.05 (d, 2H, Ar-H), 7.45-7.65 (m, 4H, Ar-H), 8.10 (s, 1H, Ar-H); .MS: *m/z* 308 (M^{+1}); Analysis Calcd. for $C_{19}H_{21}N_3O$: C, 74.25; H, 6.88; N, 13.67; Found: C, 74.09; H, 6.74; N, 13.77.

Acknowledgments

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