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Research Article

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A novel and efficient process for the preparation of zolpidem, an insomnia drug

Eswaraiah P.[a,b], Ravi Kumar Reddy N.[a] , Chakravarthy I. E.[b], Prasada Rao D. E.[a] and Rajendiran C.[a]*

[a]*Department of Research and development, Suven Life Sciences Ltd, IDA Jeedimetla, Hyderabad, Telangana, India*
[b]*Department of Chemistry, Rayalaseema University, Kurnool, Andhrapradesh, India*

ABSTRACT

Zolpidem, is an imidazopyridine group of non-benzodiazepine class drug, used for the treatment of insomnia. Here with presenting a new approach for the synthesis zolpidem without isolation of intermediates. The modified process is efficient, cost effective, simplified work up process and scalable synthesis of zolpidem with reducing cycle time.

Key words: Cyanomethylation; Imidazo[1,2-a]pyridine; Insomnia; Zolpidem

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INTRODUCTION

Imidazo[1,2-a]pyridines have significant importance in the pharmaceutical industry owing to the interesting biological activities [1] displayed over a broad range of therapeutic classes , exhibiting anti-inflammatory [2], antiulcer [3], antibacterial [4], selective cyclin-dependant kinase inhibitors [5] , GABA and benzodiazepine receptor agonists [6], cardiotonic [7], gastric anti secretory [8], hypnotic [9], and anti anxiety agents [10].

Zolpidem, chemically known as N,N,6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide (**1**), used for the short term treatment of insomnia [8]. Although zolpidem is chemically unrelated to the benzodiazepines, it interacts with benzodiazepine receptors located on the gamma-amino butyricacid (GABA) receptors [11]. The selective binding of zolpidem on the omega-1-receptor may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies. It shows high affinity and selectivity towards non-benzodiazepine –2-receptors, which mean an improved activity for the treatment of anxiety, sleep disorders and convulsion[12].

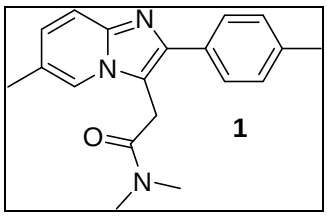


Figure 1: structure of Zolpidem

Literature studies revealed several different methods [13-20] for the preparation of zolpidem (**1**) and they differ mostly in the procedure for the introduction of acetamide chain at the 3-position from its basic skelton, 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine(**2**). Mannich aminomethylation, Vilsmeier-Heck formylation and using glyoxylic acid derivatives are reported for the introduction of acetamide functional group on **2**. Preparation of cyanomethyl derivative **6**, a key intermediate for the preparation of Zolpidem, is reported by the use of

dimethylaminomethylation and formylation processes. In formylation approach[9], compound **2** treated with oxalylchloride and dimethylformamide to get the formyl derivative of 3-Formyl-2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine (**3)**, which on reduction with sodium borohydride produce the corresponding alcohol derivative [6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-yl]methanol (**4**). This compound on treatment with p-toluenesulfonylchloride in pyridine to produce pyridinium tosylate salt **5**, which on further treatment with sodium cyanide to obtain the compound **6**. This converted to acid by base hydrolysis, further amidation by usinf carbonyldiimidazole (CDI) and gaseous dimethylamine (Figure 2). However this process involves the usage of toxic chemicals oxalyl chloride and sodium borohydride, more number of steps with lower yield is not suitable for large scale production.

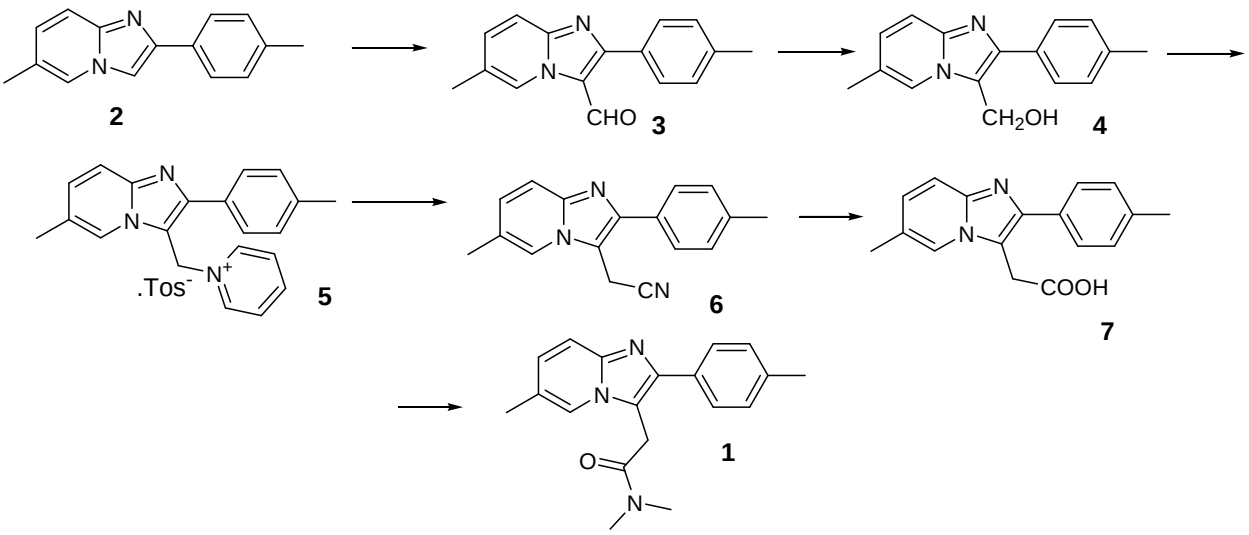


Figure 2: Reported synthesis of zolpidem by formylation process

Another reported procedure [8] for the preparation of **1,** as shown in Figure 3, involves the Mannich approach for the synthesis of acetonitrile intermediate compound **6**. Treatment of compound **2** with formalin and dimethylamine in the presence of acetic acid to obtain dimethylaminomethyl derivative, 3-(N,N-Dimethylaminomethyl)-2-(4-methylphenyl)-6-methylimidazo[1,2-a]pyridine (**8).** This compound on treatment with methyliodide to get the quaternary ammonium salt **9** followed by cyanation using Sodiumcyanide to attain **6** [21]. Hydrolysis of cyano derivative with alcoholic KOH provided the zolpidic acid (**7**). Amidation of **7** using carbonyldiimidazole (CDI) and anhydrous dimethylamine produced zolpidem **(1)** with an overall yield of 40%. The use of methyliodide, which is low boiling, toxic and highly expensive, is not viable for the commercial production. Using highly moisture sensitive and unstable CDI in the final step restricts the large scale industrial application.

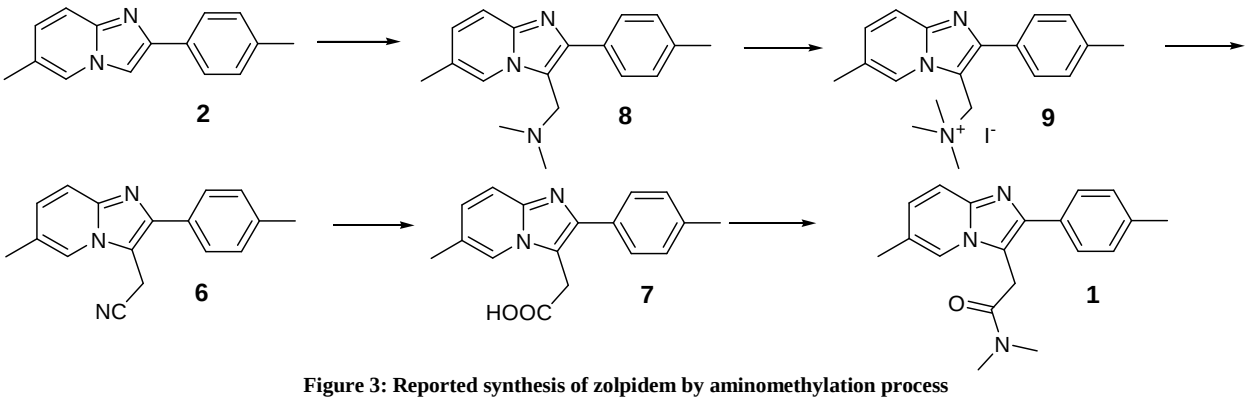


Figure 3: Reported synthesis of zolpidem by aminomethylation process

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. Progress of the reaction monitored by thin layer chromatography using silica gel – GF 254 (Merck) coated plates. The purity of all the compounds checked by HPLC. The IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer model-2000 instrument. ^{1}HNMR spectra were recorded on a Brucker 400 MHz instrument with TMS as internal standard (chemical shift in δ, ppm) and Mass spectra have been recorded on API 4000 model.

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl)aceticacid (7) without isolation of intermediates starting from 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine (2)

To the cooled solution of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine (**2**) (100 grams, 0.45 mmol) in acetic acid (500 mL) added 40% dimethylamine (76 grams) slowly, followed by paraformaldehyde (17.7 grams). Stirred at 50 - 55 ^{o}C for 3 hours and removed acetic acid under reduced pressure. pH adjusted to 8.0 by dilute sodium hydroxide solution, extracted with dichloromethane (3x300 mL). Organic layer washed with water, brine solution, dried with anhydrous sodium sulfate, filtered and distill off the solvent until the volume reaches to around 300 mL. This solution contains 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-N,N-dimethylmethylamine (**8**), purity by HPLC is around 90%, and used further as it is.

Above organic solution cooled to 0 - 5 ^{o}C and treated with ethylchloroformate (58.3 grams, 0.54 mmol) slowly over a period of 30 minutes. Stirred for one hour and distilled off the solvent under reduced pressure to obtain carbamate salt as bright yellow colored solid. Dissolved in water (300 mL), adjusted pH 7.5 - 8.0 using 10% sodium hydroxide and added sodium cyanide (26.5 grams, 0.54 mmol). Stirred at 50 - 55 ^{o}C for 3 hours, cooled, filtered and washed the solid with water (500 mL). This crude solid contains 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetonitrile (**6**), purity by HPLC around 85% and used further without any purification.

The above crude solid was dissolved in 50% sulfuric acid (600 mL), stirred at 110 ^{o}C for 4 hours. Cooled and added to ice cold water (2.5 L). Adjusted the pH 9.0 by adding Sodium hydroxid and washed with dichloromethane (2 x 300 mL). Aqueous layer treated with charcoal, adjusted pH 5.5 with acetic acid. Filtered the solid, washed with water (500 mL) and dried to obtain 96.8 grams of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-aceticacid (**7**) as off-white solid. Purity: 99.5%; Mp: 234.0 - 235.2 ^{o}C; IR (cm^{-1}): 3427, 2919, 1701, 1508, 1183, 827, 805; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H), 2.34 (s, 3H), 4.08 (s, 2H), 7.17 (dd, J= 9.1 Hz, J= 1.5 Hz, 1H), 7.28 (d, J= 8.0 Hz, 2H), 7.51 (d, J= 9.1 Hz, 1H), 7.61 (d, J= 8.0 Hz, 2H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 17.57, 20.93, 29.16, 111.36, 116.75, 123.69, 124.88, 127.11(2C), 128.23(2C), 130.08, 133.22, 135.82, 137.93, 140.33,169.83; Mass (m/z): 281.2 $(M+H)^{+}$.

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-N,N-dimethylacetamide (1)

To the suspension of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetic acid (**7**) (20g, 71.4mmol) in dichloromethane (500mL) was added triethylamine (10g, 99 mmol) maintaining the temperature at 0 - 5^{o}C. Then pivaloyl chloride (11.2g, 93.3mmol) was added to the above reaction mass and stirred for 30 minutes. After completion, 40% aqueous solution of dimethylamine (18 mL, 160mmol) was added in one lot at 0 - 5^{o}C and the reaction mass stirred for 30 minutes. Later 5% aqueous sodium hydroxide solution (150 mL) was added and the reaction mass stirred for 10 minutes, the organic layer was separated, washed with water (100mL), brine solution (100mL), dried with anhydrous sodium sulfate and filtered. The solvent was distilled under reduced pressure, n-hexane (100mL) was added to the residue and stirred for a period of 15 minutes. The solid was filtered and washed with n-hexane (20 mL), and dried in the oven to obtain 6-methyl-2-(4-methylphenyl) imidazo[1,2-a]pyridine-3-N,N-dimethylacetamide (**1**) as white solid (20.8g, 90% yield and 99.8% purity); IR (cm^{-1}) 1635 (C=O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.40 (s, 3H), 2.88 (s, 3H), 2.94 (s, 3H), 4.09 (s, 2H), 7.04 (dd, *J* = 9.15 Hz, J= 1.58 Hz, 1H), 7.26 (d, *J* = 7.87 Hz, 2H), 7.55-7.52 (m, 3H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.03, 142.79, 142.40, 136.48, 131.93, 129.12, 127.58, 127.04, 122.35, 120.64, 115.79, 115.22, 36.94, 35.29, 28.88, 20.79, 17.76; ESI MS: 308.5 (M+1);

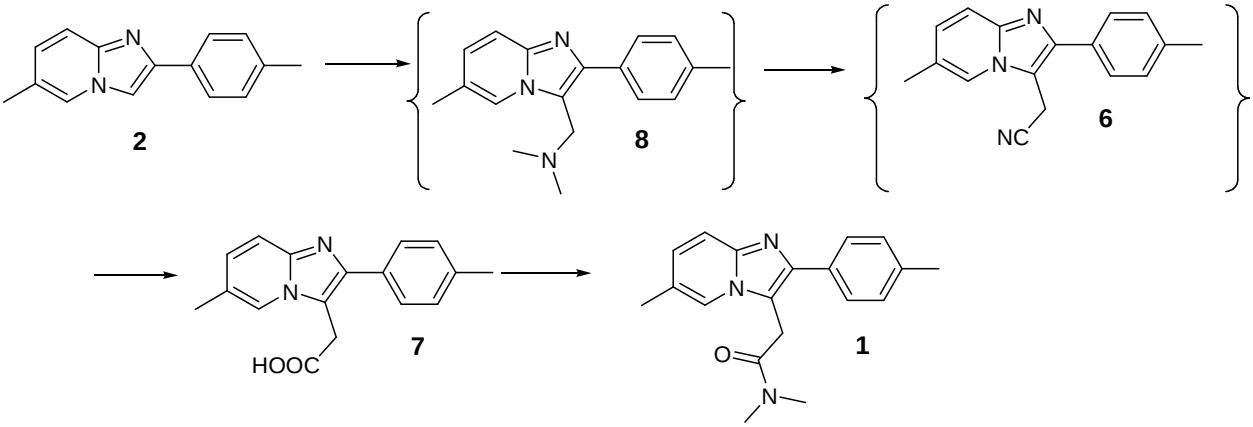
RESULTS AND DISCUSSION

In view of the above drawbacks, we focused our attention to circumvent the use of volatile, low boiling and expensive methyliodide and make the process simple and scalable for industrial application. Inexpensive, stable ethylchloroformate used as the reagent for the formation of quaternary salt and without isolation dissolved in slightly basic aqueous solution and treated with sodium cyanide to produce the key nitrile intermediate **6** in good yield and purity. We applied this method for the preparation of various imidazo[1,2-a]pyridine-3-acetonitrile derivatives [22].

For the conversion of cyano derivative, so far, all the reports used alkaline hydrolysis for conversion of **6** in to zolpidic acid (**7**), but it took long hours at higher temperatures. Our attempts to use conc. Hydrochloric acid in aqueous medium and acetic acid medium did not give desired yield and quality. When used 10% and 20% aqueous Sulfuric acid solutions, reaction proceeding but take longer hours to complete the reaction. Finally, reaction in 50% Sulfuric acid solution completed within two hours and produced good results.

After successful cyanation and hydrolysis, our focus shifted to eliminate the use of CDI in the amidation step. Thionylchloride and phosphorous pentachloride [23] were tried for the formation of acidchloride and passing

dimethylamine gas produce the required product. But passing anhydrous dimethylamine gas to the reaction mass is cumbersome and results were not to our satisfactory. We discovered that acid **7** on treatment with pivaloyl chloride in the presence of triethylamine produce mixed anhydride, which by adding aqueous 40% dimethylamine solution produce zolpidem in good yield and quality [24].



Scheme 1: Modified process for the synthesis of zolpidem

Having the new approach in hand, we attempted for the simplification of the process by avoiding the isolation of intermediates (Scheme 1). After completion of the mannich reaction, the crude product extracted in to dichloromethane and used for the next stage. The dichloromethane solution, which contains compound **8**, treated with ethylchloroformate to produce quaternary carbamate salt. After completion of the reaction, solvent distilled off and obtained crude salt treated with sodium cyanide in alkaline aqueous medium to get the cyano derivative **6** by filtration. This crude product without any purification treated with sulfuric acid solution and after work up obtained zolpidic acid **7** in good yield and purity. All this intermediates used as it is they obtained without any purification. This acid reacted with pivaloyl chloride to get mixed anhydride, which on treatment with aqueous dimethylamine produced the zolpidem with >99% purity by HPLC and overall yield of 70%.

CONCLUSION

In conclusion, we developed a simple method for the synthesis of zolpidem, by avoiding the isolation of intermediates. The *insitu* approach for the synthesis of zolpidem is efficient, cost effective by avoiding expensive and unstable reagents methyliodide and CDI, reduces cycle time with increased yield and purity.

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