

Synthesis and spectral characterization of process-related substances to the hypnotic agent zolpidem

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Abstract

During the process development of the hypnotic drug zolpidem, five process-related substances present as impurities in the final crude material were initially identified by LC-MS. All five related compounds were subsequently synthesized and characterized by IR, MS and NMR spectral data. Three of the five related substances are known {(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-methanol, (6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetic acid methyl ester and *N*-methyl-2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetamide} whilst *bis*(6-methyl-2-*p*-tolyl-imidazo [1,2-*a*]pyridine) methane and 2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-1-*p*-tolyl-ethanone are new compounds reported for the first time in our process.

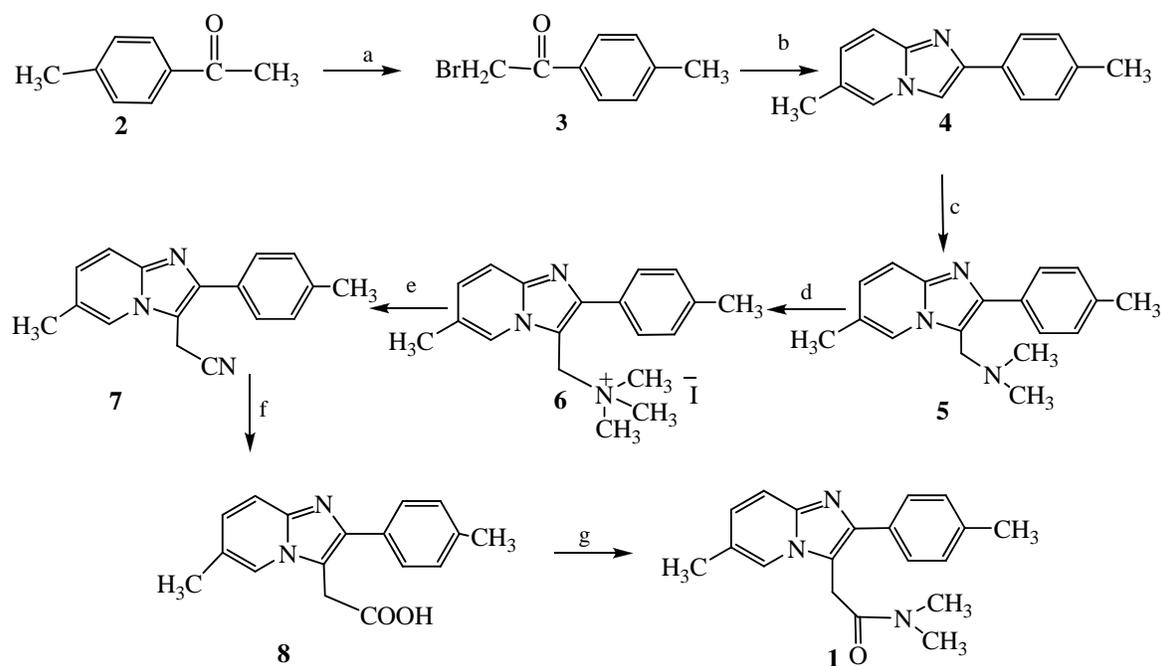
Keywords: Zolpidem, hypnotic, insomnia

Introduction

N,N-Dimethyl-2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetamide, commonly known as zolpidem, (**1**) is a short acting nonbenzodiazepine imidazopyridine hypnotic drug used for the treatment of insomnia and is commercially available as the tartrate salt.¹

Zolpidem (**1**) also possesses anxiolytic and anticonvulsant properties and is thus useful for the treatment of anxiety, sleep disorders and other neurological and psychiatric complaints.²

As zolpidem (**1**) is an important drug substance and to obtain information on product profile, we have undertaken a comprehensive study on the impurities generated during the production of zolpidem (**1**) (Scheme 1).³⁻⁶ The quality of a drug preparation is a critical hurdle to the commercialization of the product and it must be free of impurities to at least a level in excess of 99% pure. In this context, the present article describes the identification, synthesis and spectral characterization of five process-related compounds of zolpidem.



Reagents and conditions: a) bromine/acetic acid/ -5 to 0 °C. b) 2-amino-5-methyl pyridine, ethanol/ NaHCO_3 /reflux. c) acetic acid/aq. dimethylamine/formalin/RT. d) acetone, CH_3I /reflux, methanol. e) NaCN , ethanol/reflux. f) KOH /ethanol/reflux. g) carbonyldiimidazole, THF/dimethyl amine/RT.

Scheme 1. Reported synthetic scheme for zolpidem.

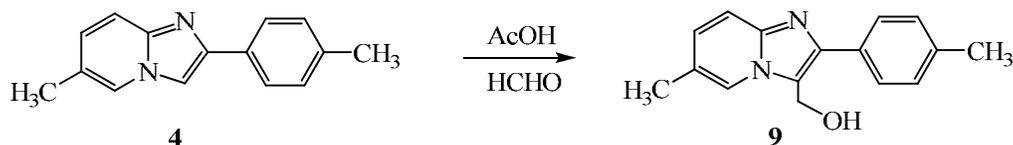
Results and Discussion

During the process development of zolpidem (**1**), HPLC analysis of crude zolpidem (**1**) revealed five impurities ranging from 0.01-0.15%. According to ICH (International Chemical Harmonium) guidelines, the amount of acceptable level for known and unknown compounds in a final drug candidate must be less than 0.15% and 0.10%, respectively. In order to meet the stringent regulatory requirements, the impurities needed to be identified and characterized. Hence, samples of zolpidem (**1**) were initially analyzed by LCMS to provide parent ions of m/z 253, 457, 354, 294 and 295 for the five impurities and thus provide a basis for initial identification. To confirm their proposed structures and complete their characterization, all five substances were individually synthesized and characterized by their respective IR, NMR and MS spectral data. The structure of these related substances were assigned as (6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-methanol (**9**), bis(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridine)-methane (**10**), 2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-1-*p*-tolyl-ethanone (**11**), (6-

methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetic acid methyl ester (**12**) and *N*-methyl-2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetamide (**13**).

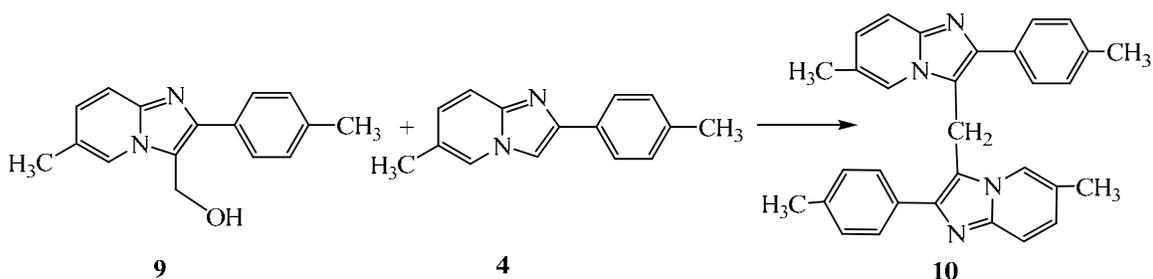
Formation of related compounds

In the course of the Mannich reaction of imidazo pyridine compound **4** with formaldehyde and dimethyl amine, initially formaldehyde and dimethyl amine react together to form the Mannich base which in turn reacts with compound **4** to yield **5**. However, a competing reaction occurs between imidazo pyridine **4** and formaldehyde to yield compound **9**, which consequently shows up in the HPLC. Compound **9** was synthesized by simply treating the imidazo pyridine compound **4** with formaldehyde and acetic acid (Scheme 2). The ESI-MS spectrum of **9** displayed a protonated molecular ion at m/z 253 whilst in the IR spectrum a broad OH signal appeared at 3085 cm^{-1} . The ^1H NMR spectrum also contained a singlet at δ 5.00 ppm corresponding to a two-proton hydroxy methylene group and this spectral data is consistent with the structure of (6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-methanol (**9**).



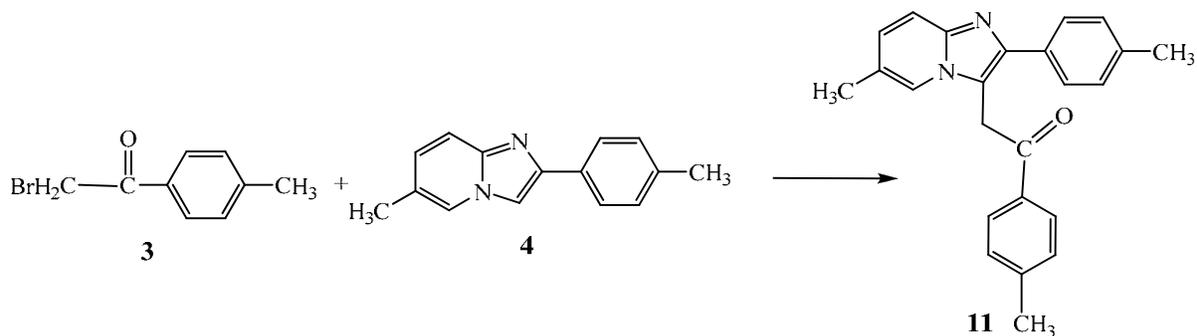
Scheme 2

The related compound **9** formed during the Mannich reaction also reacts with the starting material of this step of the synthetic sequence, the imidazo pyridine compound **4**, yielding the related compound **10**, which is a new compound (Scheme 3) and reported for the first time. The related compound **10** was synthesized by the reaction of **9** with **4** in presence of acetic acid. The mass spectrum displayed a protonated molecular ion at m/z 457. The proton NMR spectrum was similar to that of compound **4**, but lacking one aromatic proton and with the presence of a two-proton singlet at δ 4.95 ppm. Based on this spectral data, the structure of this impurity is assigned as *bis*(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridine) methane (**10**)⁷.



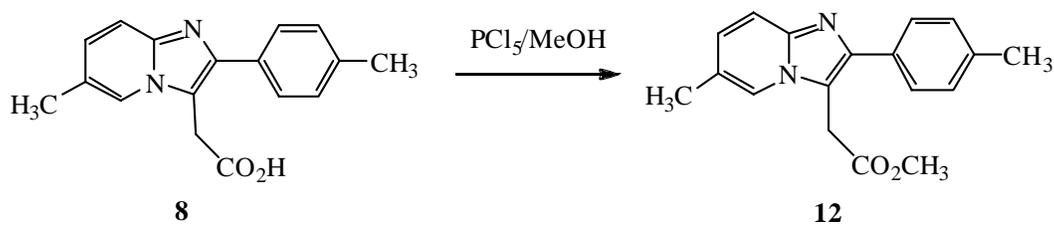
Scheme 3

Another competing reaction in the second step of the synthetic sequence is that of the product of this step, imidazo pyridine **4**, with the starting material in this step, bromo derivative **3**, to yield the related compound **11**, which is also a new compound (Scheme 4) and reported for the first time. Compound **11** was synthesized from **4** by reacting it with bromo derivative **3**. The ESI-MS spectrum of **11** displayed an $M + 1$ ion at m/z 354 and in the IR spectrum, a band at 1689 cm^{-1} corresponding to $\text{C}=\text{O}$ stretching was observed. In the ^1H NMR spectrum, a singlet at δ 6.20 ppm with a two-proton integration and three sharp singlets corresponding to three aromatic methyl groups were observed at δ 2.30, 2.45 and 2.55 ppm. Based on the spectral data, the structure was confirmed as 6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-1-*p*-tolyl-ethanone (**11**).



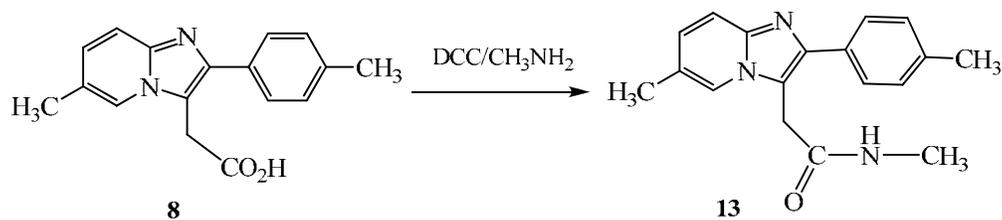
Scheme 4

Two impurities arise in the final step of the reaction sequence from the presence of undesired reactants. The first of these reactants is residual methanol carried over from previous steps and which yields related compound **12** by its reaction with compound **8**. Compound **12** was quantitatively synthesized (Scheme 5) by treating the acid chloride of **8** with methanol. The ESI-MS spectrum of **12** displayed a protonated molecular ion at m/z 295 whilst in the IR spectrum a sharp band appeared at 1745 cm^{-1} corresponding to an ester carbonyl. The ^1H NMR spectrum displayed a singlet at δ 3.90 ppm corresponding to a three-proton methyl ester group and this spectral data is consistent with the structure of (6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetic acid methyl ester (**12**)⁷.



Scheme 5

The second undesirable reagent, methylamine, was present as an impurity in dimethyl amine and this also reacts with **8** to yield the related compound **13** (Scheme 6). Compound **13** was synthesized by the reaction of DCC-treated **8** with methyl amine (CH_3NH_2). The mass spectrum of **13** displayed a protonated molecular ion at m/z 294 and a sharp band at 1659 cm^{-1} was observed in the IR spectrum which was attributed to amide $\text{C}=\text{O}$ stretching. In the ^1H NMR spectrum, two singlet signals at δ 4.05 ppm and 6.05 ppm were observed and are characteristic for amide methyl and amide NH, respectively. This spectral data is consistent with the structure of *N*-methyl-2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetamide (**13**).



Scheme 6

Conclusions

In conclusion, we have identified, synthesized and characterized five potential process-related impurities (**9–13**) of zolpidem (**1**).

Experimental Section

General Procedures. The ^1H NMR spectra were recorded on a Gemini 200 MHz FT NMR spectrometer with chemical shifts reported in ppm relative to TMS. The IR spectra were recorded in the solid state as KBr discs using a Perkin Elmer FT-IR spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP8000 and AB-4000 Q-trap LC-MS/MS instruments. Elemental analysis for CHN were performed on a Perkin Elmer model 2400 CHNS/O analyzer at Dr. Reddy's Laboratories Ltd., Hyderabad.

(6-Methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-methanol (9**).** To a mixture of **4** (40.0 g, 0.180 mol) and acetic acid (60.0 mL), 36% formalin (37.5 g, 0.45 mol) was added under stirring. The reaction was stirred at 25–35 °C till completion. The reaction mass was cooled to 0–5 °C and to it a solution of sodium hydroxide (48% w/w, 60.0 mL) in water (160.0 mL) was added and stirred for 2 hours at 25–35 °C. The precipitated compound was filtered, washed with water methanol mixture (50.0 mL 1:1) and dried at 85 °C to yield **9** (35 g, % yield: 77.0, purity by HPLC: 99.2%); IR (cm^{-1}): 3085 (OH); ^1H NMR (DMSO- d_6 , δ ppm): 2.45 (s, 6H, CH_3), 5.00 (s,

2H, CH₂), 7.25–7.45 (m, 4H, Ar-H), 7.75 (d, 2H, Ar-H), 8.25 (s, 1H, Ar-H); MS: *m/z* 253 (M + H⁺). Analysis Calcd. for C₁₆H₁₆N₂O: C, 76.16; H, 6.39; N, 11.10; Found: C, 76.24; H, 6.55; N, 11.19.

Bis(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridine)-methane (10). Mixture of **9** (40.0 g, 0.15 mol), **4** (35.3 g, 0.15 mol) and acetic acid (50.0 mL) were heated to 80 °C. To it 36% formalin (37.5 g, 0.45 mol) was added slowly under stirring. The reaction mass was stirred at 75–80 °C till the reaction completion. Water (160.0 mL) was added and the reaction mass, pH adjusted to 7 with sodium hydroxide and stirred for solid isolation. The isolated solid was filtered, washed with water (50.0 mL) and finally the wet compound was recrystallized from acetone to yield **10** (63 g, yield: 86.0%; purity by HPLC 99 %). IR (cm⁻¹): 1536 (C=N); ¹H NMR (DMSO-d₆, δ ppm): 2.25 (s, 6H, CH₃), 2.40 (s, 6H, CH₃), 4.95 (s, 2H, CH₂), 7.05 (d, 2H, Ar-H), 7.15 (s, 2H, Ar-H), 7.55 (m, 6H, Ar-H), 7.95 (m, 4H, Ar-H); ¹³C NMR (DMSO-d₆, ppm): 151.05, 137.92, 136.67, 134.69, 133.03, 135.23, 134.28, 133.42, 132.01, 131.25, 128.14, 127.23, 123.83, 22.34, 20.78, 14.21; MS: *m/z* 457 (M + H⁺); Analysis Calcd. for C₃₁H₂₈N₄: C, 81.55; H, 6.18; N, 12.27. Found: C, 81.74; H, 6.15; N, 12.29.

2-(6-Methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-1-*p*-tolyl-ethanone (11). To a mixture of **4** (40.0 g, 0.180 mol) and acetic acid (80.0 mL), 4-methyl-phenacyl bromide **3** (37.5 g, 0.17 mol) was added under stirring. The reaction mass was stirred at 25–35 °C for 6 hours and water (200.0 mL) was added, stirred for 2 hours for solid separation. The precipitated compound was filtered, washed with 5% aqueous sodium hydroxide solution (50.0 mL), water (100.0 mL), dried 65 °C and finally purified by column chromatography to yield **11** (41 g, yield: 65.0%, purity by HPLC: 99.2%). IR (cm⁻¹): 1689 (C=O); ¹H NMR (DMSO-d₆, δ ppm): 2.30 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 2.55 (s, 3H, CH₃), 6.20 (s, 2H, CH₂), 7.45 (m, 6H, Ar-H), 7.95 (m, 3H, Ar-H), 8.25 (s, 2H, Ar-H); ¹³C NMR (DMSO-d₆, ppm): 184.21, 153.28, 143.87, 139.27, 138.28, 132.04, 129.93, 129.59, 129.00, 128.84, 128.14, 127.89, 127.32, 126.71, 126.94, 126.78, 126.71, 126.04, 125.93, 124.83, 124.33, 22.37, 20.64, 20.24; MS: *m/z* 354 (M + H⁺); Analysis Calcd. for C₂₄H₂₂N₂O: C, 81.33; H, 6.26; N, 7.90; Found: C, 81.34; H, 6.45; N, 7.79.

(6-Methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetic acid methyl ester (12). To a cold mixture of dichloromethane (250.0 mL) and phosphorous pentachloride (15.6 g, 0.074 mol), **8** (20.0 g, 0.07 mol) was added and refluxed for reaction completion. The reaction mass was cooled and to it methanol (11.0 mL) was added slowly and maintained at 20 °C for reaction completion. Water (200.0 mL) was added to the reaction mixture and the separated organic layer was concentrated under reduced pressure. The residual mass triturated with cyclohexane (200.0 mL), filtered and dried at 80 °C to yield **12** (20 g, yield: 95.0%, purity by HPLC: 99.8 %). IR (cm⁻¹): 1745 (C=O); ¹H NMR (CDCl₃, δ ppm): 2.45 (s, 3H, CH₃), 2.65 (s, 3H, CH₃), 3.90 (s, 3H, O-CH₃), 4.35 (s, 2H, CH₂), 7.35 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.25 (s, 1H, Ar-H); MS: *m/z* 295 (M + H⁺); Analysis Calcd. for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.60; H, 6.24; N, 9.67.

***N*-Methyl-2-(6-methyl-2-*p*-tolyl-imidazo[1,2-*a*]pyridin-3-yl)-acetamide (13).** To a cold mixture of **8** (25.0 g, 0.089 mol), dicyclohexylcarbodiimide (18.3 g, 0.089 mol), 1-hydroxy

benzotriazole (12.0 g, 0.089 mol) and dichloromethane (250.0 mL), mono methyl amine gas was purged till the reaction completion. The dicyclohexyl urea was filtered off, filtrate was washed with saturated sodium bicarbonate solution and dichloromethane was removed under reduced pressure. To the residue, water (200.0 mL) was added, stirred for 1 hour, filtered and dried at 80 °C to yield **13** (25 g, yield: 97.0%, purity by HPLC: 99.8 %). IR (cm⁻¹): 3233 (N-H), 1659 (C=O); ¹H NMR (CDCl₃ δ ppm): 2.45 (s, 3H, CH₃), 2.55 (s, 3H, NCH₃), 2.85 (s, 3H, CH₃), 4.05 (s, 2H, CH₂), 6.05 (s, 1H, N-H), 7.05 (d, 1H, Ar-H), 7.25 (m, 2H, Ar-H), 7.55 (d, 1H, Ar-H), 7.75 (d, 2H, Ar-H), 7.85 (d, 1H, Ar-H); MS: *m/z* 294 (M + H⁺); Analysis Calcd. for C₁₈H₁₉N₃O: C, 73.69; H, 6.53; N, 14.32; Found: C, 73.80; H, 6.74; N, 14.47.

Acknowledgments

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