SIMPLE AND EFFICIENT PROCESS FOR THE LARGE-SCALE PREPARATION OF AGOMELATINE: AN ANTIDEPRESSANT DRUG

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GRAPHICAL ABSTRACT

Abstract A simple and efficient process for the large-scale preparation of agomelatine (1), an antidepressant drug is described. Agomelatine was prepared in a linear manner starting from readily available, inexpensive 2-naphthol. Key steps in the synthesis are Friedel–Crafts acylation of 2-naphthyl acetate with chloroacetyl chloride, reduction of keto intermediate, and nucleophilic displacement of chloro intermediate with sodium diformylamide. A systemic approach was described to streamline the process into a robust scalable process by controlling the impurities.

Keywords Agomelatine; chloro acetylchloride; Friedel–Crafts acylation; sodium diformylamide
INTRODUCTION

Agomelatine has been reported as an effective melatonergic antidepressant.\[1\] Agomelatine has a new pharmacological mechanism of action that combines its melatonin MT₁ and MT₂ agonist properties with a serotonin 5-HT₂C antagonist effect.

Agomelatine was first synthesized by Yous et al.\[2\] in a multistep synthetic route starting from (7-methoxy-1-naphthyl) acetic acid. Zlotos et al.\[3\] reported a four-step approach that involves use of pyrophoric reagents and ion exchange resins. Although many syntheses aiming at industrial scale have been published in the literature,\[4-6\] still it remains challenging to develop a simple process that makes use of readily available inexpensive raw materials, avoids the use of highly hazardous reagents, minimizes the steps, simplifies workup procedures, and precludes detrimental impurity issues. However, developing new synthetic approaches to agomelatine from a cheap starting material other than 7-methoxy-1-tetralone is still remains challenging. During the new synthesis of agomelatine,\[7\] it was synthesized from 8-aminonaphthalen-2-ol by diazotization, formylation, C-C bond formation, and hydrogenation of β-nitrovinylnaphthalene. In this synthesis, toxic reagents such as CuCN and pyrophoric reagents such as DIBAL and n-BuLi were used, as well as temperatures ranging from −78 °C to 100 °C. In continuation of our work on agomelatine\[8\] to reduce the length of the synthesis, herein we report a simple and improved process for the synthesis of agomelatine on a large scale.

RESULTS AND DISCUSSION

The synthesis involves acetylation of 2-naphthol in acetone to give 2-acetoxy-naphthalene, 3, which on Friedel–Crafts acylation in the presence of AlCl₃ using chloro acetylchloride affords acylated intermediate, 4. This Friedel–Crafts acylation is a regioselective reaction having 80% selectivity to provide the desired acylated product along with other regioisomers, 7 and 8. Recrystallization of crude 4 in methanol removed all the isomers and unreacted 2-acetoxy naphthalene.

Reduction of 5 using triethylsilane in presence of TiCl₄ followed by ester hydrolysis afforded the intermediate, 6.

Methyl protection of intermediate 7 followed by reaction with sodium diformylamide\[9\] in the presence of TBAI catalyst in DMSO\[10\] afforded 10 (a mixture of mono- and di- formylamides 10a and 10b).

Hydrolysis of amides 10a and 10b gave the amine hydrochloride 11, which was not isolated, and further amidation with acetic anhydride under basic conditions afforded 1 in 85% yield.
During initial experimentation, it was observed that significant amounts of impurities 13 and 14 were formed in the conversion of intermediate 9 to 10, which was due to high reaction temperatures, and also traces of sodium methoxide as sodium diformylamide was prepared in situ.

To minimize the formation of impurities 13 and 14, sodium diformylamide prepared and isolated in pure form was employed in the reaction.

The impurity 14 will transform to impurity 15 in the hydrolysis step, which is difficult to minimize in isolation because of similar solubility of 15 and 1.
Recrystallization of the intermediate 10 in toluene/hexane mixture reduced the impurity 14 from 3.0% to 0.2%.

After hydrolysis, the acidic reaction mixture was extracted with toluene to remove the organic impurities that are not forming the salts with aqueous HCl. This modification improved the quality and the yield of the agomelatine.

To overcome the loss of amine 11 in the aqueous layer after the hydrolysis step, we proceeded to the acetylation step in the same vessel by adding an ethyl acetate K₂CO₃ solution and acetic anhydride. After the reaction, the organic layer was separated, concentrated, and isolated in toluene to afford 1 in 85% yield.

Impurity 16 forms by the demethylation of 11 in the hydrolysis step when followed by acetylation. To control the formation of 16, the hydrolysis reaction was terminated after 4 h of reaction at 60 °C by monitoring with thin-layer chromatography (TLC).
EXPERIMENTAL

Solvents and reagents were obtained from commercial sources and used without further purification. $^1$H NMR spectra were recorded in CDCl$_3$ or dimethylsulfoxide (DMSO-$d_6$) at room temperature on a Varian Mercury Plus instrument at 400 MHz using tetramethylsiloxide (TMS) as an internal standard. $^{13}$C NMR spectra were obtained from a Varian Mercury Plus 400-MHz spectrometer in DMSO-$d_6$ at room temperature. IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer 1650 FT IR spectrometer. The mass spectrum (70 eV) was recorded on an HP 5989 A LC-MS spectrometer. TLC analyses were performed on Merck silica-gel 60 F254 plates.

1-(N,N-Diformylaminoethyl)-7-methoxynaphthalene and N-[2-(7-Methoxy-1-naphthyl)ethyl]formamide (10)

K$_2$CO$_3$ (61 g, 0.44 mol) was added to a solution of methanol (175 mL) and 1-(2-chloroethyl)-7-hydroxynaphthalene 6 (35 g, 0.17 mol), and the reaction mixture was cooled to 15 °C. Dimethyl sulfate (40 mL, 0.42 mol) was added to the reaction mixture and stirred for 2 h at 25 °C. The reaction was monitored by TLC, diluted with water (420 mL), and extracted with ethyl acetate (175 mL). The organic layer was washed with 10% NaCl solution (175 mL) and concentrated under reduced pressure to get an oily residue (9). The oily residue was dissolved in DMSO (105 mL), and then sodium diformylamide (64.4 g, 0.68 mol) and TBAI (0.7 g) were added. The resulting mixture was heated to 85 °C and stirred for 2–3 h. The reaction was monitored by TLC, cooled to 20 °C, diluted with water (350 mL), and then extracted with ethyl acetate (175 mL). The organic layer was separated then washed with 10% NaCl solution (175 mL). The organic layer was distilled under reduced pressure to get the crude product. The crude was dissolved in toluene (105 mL) at 60 °C and n-hexane (263 mL) was added slowly at 30 °C. The reaction mixture was further cooled to 0 °C and stirred for 2 h. The solid was filtered and dried at 45 °C under vacuum to afford the mixture of 10a and 10b (32 g, 77.7%).
Compound 10a. ESI-MS: m/z = 228 (M-H); calcd. for C_{14}H_{15}NO_{2}: 229.27; ¹H NMR (400 MHz, DMSO-d₆) δ = 3.13 (t, J = 8.24 Hz, 2H, CH₂CH₂N), 3.46 (m, 2H, CH₂CH₂N), 3.95 (s, 3H, OCH₃), 7.18 (dd, J = 2.5, 8.92 Hz, 1H, Ar-H), 7.24–7.32 (m, 2H, Ar-H), 7.56 (s, 1H, Ar-H), 7.72 (d, J = 7.8 Hz, 1H, Ar-H), 7.83 (d, J = 8.9 Hz, 1H, Ar-H), 8.99 (s, 2H, NCO₂H); ¹³C NMR (400 MHz, DMSO-d₆) δ = 31.3, 38.3, 39.0, 39.2, 39.4, 39.8, 40.0, 40.2, 55.6, 102.7, 118.6, 123.7, 127.5, 127.9, 129.3, 130.7, 131.3, 133.2, 158.1, 166.9; IR v_{max} cm⁻¹ 3264, 2941, 1652, 1627, 1509, 1258, 1215, 1030. Anal. calcd. for C_{14}H_{15}NO_{2}: C, 73.34; H, 6.59; N, 6.11; O, 13.96. Found: C, 73.36; H, 6.57; N, 6.13; O, 13.94.

Compound 10b. ESI-MS: m/z = 258 (M+H); calcd. for C_{15}H_{15}NO₃: 257.28; ¹H NMR (400 MHz, DMSO-d₆) δ = 3.20 (t, J = 6.16 Hz 2H, CH₂CH₂NH), 3.43–3.48 (m, 2H, CH₂CH₂NH), 3.73 (s, 3H, OCH₃), 7.19 (dd, J = 2.5, 8.9 Hz, 1H, Ar-H), 7.55 (d, J = 2.44 Hz 1H, Ar-H), 8.09 (s, 1H, NHCHO), 8.26 (br s, 1H, NHCO); ¹³C NMR (400 MHz, DMSO-d₆) δ = 33.1, 34.7, 38.6, 39.0, 39.4, 39.6, 39.8, 40.0, 40.2, 42.1, 55.7, 102.9, 118.4, 123.7, 127.1, 127.5, 129.3, 130.6, 133.2, 134.2, 157.9, 162.2, 165.1; IR v_{max} cm⁻¹ 3389, 1753, 1675, 1650, 1134, 1025. Anal. calcd. for C_{14}H_{15}NO₃: C, 70.02; H, 5.88; N, 5.44; O, 18.66. Found: C, 70.06; H, 5.84; N, 5.42; O, 18.68.

N-[2-(7-Methoxy-1-naphthylen-1-yl)ethyl] Acetamide (1)
A mixture of N-[2-(7-methoxy-1-naphthyl)ethyl]formamide 10a, N-formyl-N-[2-(7-methoxy-1-naphthyl)ethyl]formamide 10b) (50 g, 0.21 mol), and HCl (42 g, 0.41 mol) was added to a solution of methanol (250 mL) and intermediate 9. Then the reaction mixture was heated to 60 °C and stirred for 4 h. The reaction mixture was concentrated under reduced pressure followed by co-distillation with toluene (100 L) to obtain a suspension, which was dissolved in water (600 mL) and washed with toluene (2 × 100 mL). The aqueous layer was treated with carbon (5 g) and filtered through Hyflow. Ethyl acetate (375 mL) was added to the filtrate and then K₂CO₃ solution (71 g, 0.51 mol of K₂CO₃ in 36 L water) was added slowly. Then acetic anhydride (23 mL, 0.25 mol) was added slowly below 30 °C, and stirring continued for 30 min. The reaction was monitored by TLC; organic layer was separated, washed with 2% NaCl solution (250 mL), and concentrated under reduced pressure to obtain the crude product. Toluene (150 mL) was added and codistilled. Toluene (150 mL) was added again and heated to 65 °C. The reaction mixture was cooled to 10 °C and stirred for 2 h. The solid product was filtered, washed with toluene (50 mL), and then dried at 60 °C under vacuum to give 1 (42.5 g, 85%) with HPLC purity of 99.9%.

ESI-MS: m/z = 244.2 (M+H); calcd. for C_{15}H_{17}NO₂: 243.0; ¹H NMR (400 MHz, DMSO-d₆) δ = 1.84 (s, 3H, OCH₃), 3.13 (t, J = 7.2 Hz, 2H, CH₂CH₂ NHAc), 3.34 (m, 2H, CH₂CH₂NHAc), 3.95 (s, 3H, OCH₃), 7.17 (dd, J = 2.5, 8.9 Hz, 1H, Ar-H), 7.25–7.29 (m, 1H, Ar-H), 7.32–7.34 (dd, J = 1.23, 6.96 Hz, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.71 (d, J = 7.8 Hz, 1H, Ar-H), 7.83 (d, J = 8.9 Hz, 1H, Ar-H), 8.13 (br s, 1H, NHCO); ¹³C NMR (400 MHz, DMSO-d₆) δ = 23.1, 33.5, 40.6, 55.7, 103.1, 118.5, 123.6, 127.0, 127.4, 129.3, 130.5, 133.4, 134.6, 157.9, 170.0; IR v_{max} cm⁻¹ 1639, 1626, 1509, 1251, 1031.
CONCLUSION

In conclusion, a simple and scalable process for the high-yielding synthesis of agomelatine has been discussed. The important features of this procedure are control of the impurities in Friedel–Crafts acylation, minimization of impurities in the hydrolysis step, and in situ acetylation leading to isolation of agomelatine in good yields.

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SUPPLEMENTAL MATERIAL

Detailed experimental procedures and spectral characterization data for this article can be accessed on the publisher’s website.

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