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Research Article

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A Simple and One Step Commercially Cost Effective Process for Eluxadoline Intermediates

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ABSTRACT

Methyl-5-formyl-2-methoxybenzoate (1) and (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine (2) are key intermediates in the synthesis of Eluxadoline drug. We described a new cost effective process for synthesis of Methyl-5-formyl-2-methoxybenzoate (1) with salicylic acid, Methanesulfonic acid, Hexamethylenetetramine and (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine (2), with boc-L-Alanine and 2-chloroacetophenone. All the synthetic results were confirmed by ESI-MS and NMR analysis.

Keywords: Eluxadoline**;** Duff reaction; Hexamethylenetetramine; Ammonium acetate; Cyclization

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INTRODUCTION

Methyl-5-formyl-2-methoxybenzoate (1) and (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine (2) are key intermediates for eluxadoline [1]. Eluxadoline is an orally-active drug approved for the treatment of diarrhea-predominant irritable bowel syndrome [2]. Eluxadoline also makes the nerves in intestines less sensitive to stimulation [3]. Methyl-5-formyl-2-methoxybenzoate can be synthesized in two routes staring from salicylic acid. One is formylation of salicylic acid and followed by methylation to get target (1). Second is methylation of salicylic acid and followed by formylation to get target (1). We found that Methyl-5-formyl-2-methoxybenzoate (1) was synthesized in more economical process usingsalicylic acid to form Methyl 2-methoxy benzoate with Dimethyl sulfate and potassium carbonate in the presence of acetone [4]. Preparation of Methyl 2-methoxy 5-formyl benzoate (1) with Methanesulfonic acid and Hexamethylenetetramine as Duff reaction. Duff reaction is the most important method in the synthesis of formylation on phenols [5]. We have tried Duff reaction in various acids like acetic acid, polyphosphoric acid, trifluoroacetic acid and methanesulphonic acid and Methanesulphonic acid is more suitable for this molecule. (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine (2) was synthesized using boc-L-Allanine condensed with 2-chloroacetophenonein the presence of Dimethylformamide and potassiumcarbonate to form (S)-2-tert-Butoxycarbonylamino-propionic acid-2-oxo-2-phenyl-ethyl ester [6]. The above phencylester cyclised with ammonium acetate [7] in the presence of toluene to form the (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine(2). The prior art process [8] teaches the oxalate salt formation to obtain the pure product. The process involves additional step and leads to more manufacturing cost. Here we have isolated the product in conventional process of purification and more of manufacturing feasibility.

EXPERIMENTAL SECTION

Chemicals were procured from AVRA synthesis and were used as such without furtherpurification. Melting points were determined using a calibrated thermometer by Polmon Melting Point apparatus MP96. They expressed in degrees centigrade (°C) and are uncorrected. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence lamp. ^{1}H NMR spectra were reported using Me_4Si (δ 0.0 ppm) as internal standard or residual $CHCl_3$peak (δ 7.26 ppm) and ESI mass spectra were recorded. Purity analysed by Agilent, 1200HPLC system having 1260UWD UV detector with EZ crome open lab soft ware.

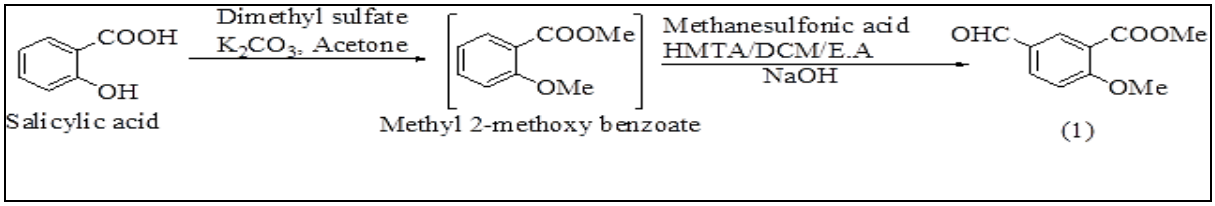
Synthesis of Methyl 5-formyl-2-methoxybenzoate (Scheme 1)

Part A:

Salicylic acid 200 g and potassium carbonate 415.6 g were charged in Acetone 1000 mL and Dimethyl sulfate 403 g was added slowly at 25-30°C. The reaction was maintained at 55-60°C for 3-4 hrs and reaction progress was monitored by TLC. The reaction mixture was cooled to 25-30°C and filtered remove salts. The resulting filtrate concentrated under vacuum to obtained 2-Methoxy-benzoic acid methyl ester.

Part B:

Hexamethylenetetramine 243 g was added slowly below 70°C in to 1800 g methane sulfonic acid. The resulting mixture maintain for 2 hrs at 75-80°C and cool the mass below 50°C. Part A was added slowly to the mixture. The reaction mixture was maintain at 70-80°C for 1-3 hrs and the reaction progress was monitored by TLC. The mixture was into water (1250 mL) and dichloromethane (1250 mL) mixture at below 10°C. The mixture pH was adjusted between 1-2 with 48% NaOH solution. The aqueous and organic layers were separated and the organic layer was concentrated under vacuum. The resulting residue was crystallized from ethyl acetate gave the product (1). Yield: 130 g purity by HPLC NLT 98% and any individual impurity less than 0.1%.



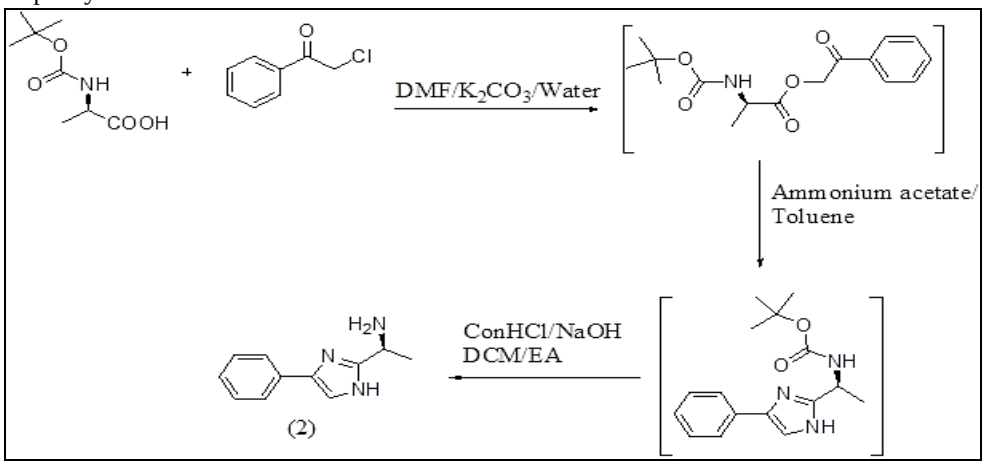
Scheme 1: Synthesis of Methyl 5-formyl-2-methoxybenzoate

Melting range: 82-85°C

NMR ($CDCl_3$-d_6), 3.92 (s, OCH_3), 4.00 (s, OCH_3), 7.13 (d, J=8.6 Hz, 1H, ar), 8.04 (d, J=8.5 Hz, 1H, ar), 8.33 (s, 1H, ar), 9.92 (s, CHO),; Mass spectra (m/z): 195 (M^++H)

(S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine (Scheme 2)

100 g of boc-L-Alanine and 51.1 g of potassium carbonate charged into 250 mL of dimethyl- formamide at 25-35°C and stirred the mass for 10-15 min. 77.5 g of 2-chloroacetophenone was added slowly below 35°C. The reaction mixture was maintain at 25-35°C for 14-16 hrs and the reaction progress was monitored by TLC. The reaction mixture diluted with 750 mL of water below 30°C. (S)-2-tert-Butoxycarbonylamino-propionic acid 2-oxo-2-phenyl-ethyl ester was isolated. The wet material and 155 g of ammonium acetate were charged into 600 mL of toluene and refluxed at105-110°C and reaction was monitored by TLC. 120 mL of CpHCl added to reaction mixture and maintained for 2 hrs at 45-50°C. The de-protection was monitored by TLC. Aqueous and Organic layers were separated. The aqueous layer pH was adjusted to 10.5-12 with sodium hydroxide solution and the product extracted with 1000 mL of Dichloromethane. Organic layer was concentrate under vacuum and crystallized in ethyl acetate 150 mL gave pure product (2). Yield: 55 g purity by HPLC NLT 98%, any individual impurity is less than 0.1%



Scheme 2: (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine

NMR ($CDCl_3$-d_6), 1.48 (d, J=8.2 Hz CH_3), 4.3 (m, CH, NH_2,NH), 7.21 (m, 2H, ar), 7.32 (m, 2H, ar), 7.64 (m, 2H, ar);Mass spectra (m/z): 188 (M^++H)

CONCLUSION

In conclusion, we have developed a short, cost effective and efficient process for the synthesis of Methyl-5-formyl-2-methoxybenzoate (1) and (S)-alpha-Methyl-4-phenyl-1H-imidazole-2-methanamine (2) which was key intermediate in the eluxadoline drug.

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