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Synthesis and Spectral Studies of 2-mercapto-5-methoxy-1*H*-benzimidazole: An Imperative Medicinal Intermediate

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ABSTRACT

An improved, convergent and industrially useful process suitable for large-scale production of 2-mercapto-5-methoxy-1H-benzimidazole, required for synthesis of omeprazole, has been described. It is a proton pump inhibitor. In present work, reaction of 4-methoxy aniline with acetic anhydride gave N-(4-methoxyphenyl)acetamide ***(2)****, which on further processes like nitration followed by hydrolysis, reduction and cyclization gave title compound* ***(6)****. Structure of the synthesized compound was established on the basis of spectral analyses like IR, NMR and MASS.*

Keywords: omeprazole, proton pump inhibitor, 4-methoxy aniline, spectral analyses.

INTRODUCTION

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications[1–6]. 2-mercaptobenzimidazole derivatives, one of the most important derivatives of benzimidazole also exhibited a wide variety of interesting biological activities such as antimicrobial[7], antihistamine[8], neutropic[9] and anticonvulsant[10] activities. The incorporation of benzimidazole nucleus, a biologically accepted pharmacophore in medicinal compounds, has made it a versatile heterocyclic moiety possessing wide spectrum of biological activities. Moreover, pharmacological evaluations[11,12] of benzimidazole have always been studied by many researchers and several reviews[13] have also been reported describing biological properties of benzimidazole. Benzimidazole derivatives are structural isosters of naturally occurring nucleotides, which allow them to interact easily with the biopolymers of the living system which is responsible for their numerous biological activities and functions. The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux-oesophagitis and nonsteroidal anti-inflammatory drug-induced lesions[14]**.** Inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle in the treatment of gastric and doudenal ulcer disease[15]. Recently, 2-[(2-pyridylmethyl)sulfinyl] benzimidazoles (PSBs) such as omeprazole, lansoprazole, and pantoprazole have been found to have superior properties for complete suppression of gastric acid secretion[16]. Their antisecretory activity has been ascribed to a highly specific inhibitory action on the gastric proton pump, the H+/K+-ATPase, which is responsible for the transport of gastric acid into lumen of the stomach[17]. Acid secretion is therefore blocked at the final step of its production, independent of the different kinds of its stimulation[18]. Since the demand for omeprazole is increasing, there exists a tremendous scope for the development of its synthetic routes. This necessitates an easy availability of the intermediate, 2-mercapto-5-methoxy-1*H*-benzimidazole.

MATERIALS AND METHODS

All the chemicals used in the synthesis were of analytical grade. Melting point was determined in HOOVER scientific melting point apparatus and is uncorrected. The completion of reaction was monitored by thin-layer chromatography (TLC) using silica gel-G coated Al-plates (0.5mm thickness, Merck) and spots were visualized under UV radiation. Infrared spectra were determined in KBr on a Perkin Elmer Model-137 Infracord. The ^{1}H-NMR spectra were recorded on BRUKER (400MHz) spectrometer in DMSO-d_6 using TMS as internal standard. The mass

spectra were recorded on a LC-MSD, AGILENT Liquid Chromatography-MS apparatus. HPLC analyses were performed on SHIMADZU LC-10 (PDA, 254nm) using C-18 peerless column.

Synthetic Procedures

Preparation of *N*-(4-methoxyphenyl)acetamide (2)

To a well stirred solution of 4-methoxy aniline **(1)** (1.23gm, 0.01mole) in methylene dichloride (9.34gm, 0.11mole), acetic anhydride(1.02gm, 0.01mole) was added dropwise at room temperature in a period of 30 minutes. The reaction mass was further stirred at room temperature for 2 hrs. Reaction conversion was monitored by thin layer chromatography (TLC) using mobile phase (60:40, Ethyl acetate:Toluene). Water was added to the reaction mass and layer was separated. Organic layer was then extracted and subjected to nitration process for the preparation of next step.

Preparation of *N*-(4-methoxy-2-nitrophenyl)acetamide (3)

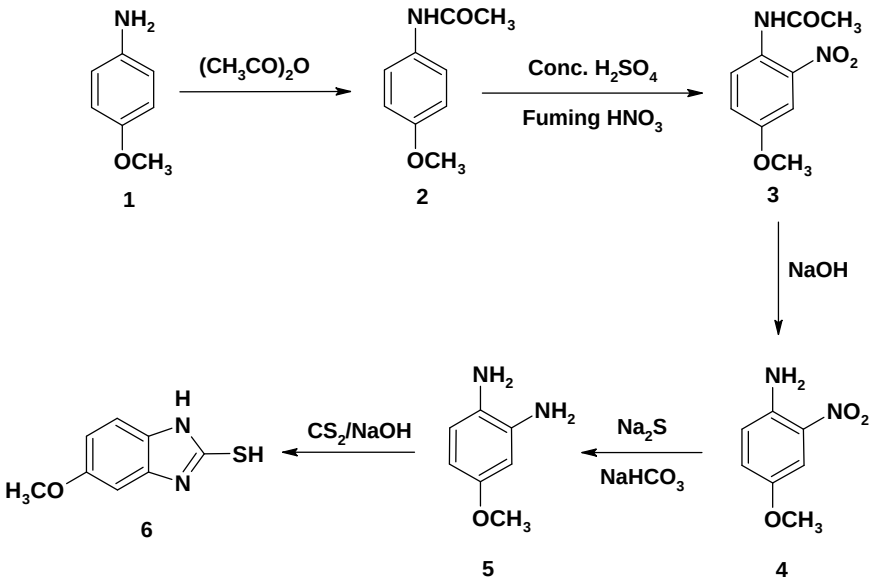
Organic layer (1.65gm, 0.01mole) containing **(2)** was taken in a round bottom flask and cooled to 20-25^{0}C. To this cooled solution, conc. sulphuric acid (1.47gm, 0.015mole) was added followed by the addition of fuming nitric acid (1.26gm, 0.02mole) at 20-25^{0}C in a period of 2 hrs. Reaction mass was maintained at that temperature for another 3 hours. Reaction conversion was monitored by TLC using mobile phase (60:40, Ethyl acetate:Toluene. Organic layer was neutralized by 10% NaOH solution. Solvent was recovered and crude obtained was used directly for the preparation of next step.

Preparation of (4-methoxy-2-nitrophenyl)amine (4)

Methanol (6.72gm, 0.21mole) was added to crude **(3)** (1.89gm, 0.009mole) and the resulting yellow solution was stirred. 50% NaOH solution (2.16gm, 0.027mole) was slowly added to it and refluxed. Reaction mass was allowed to stirred at room temperature for another 3 hours. Reaction conversion was monitored by TLC using mobile phase (60:40, Ethyl acetate:Toluene). This organic layer was directly subjected to reduction process for preparation of **(5)**.

Preparation of 4-methoxybenzene-1,2-diamine (5)

Organic layer containing **(4)** (1.34gm, 0.008mole) was reduced by adding $Na_2S.9H_20$ (3.84gm, 0.016mole) and $NaHCO_3$ (1.18gm, 0.014mole) and water (5.4gm, 0.3mole). The reaction mixture was refluxed for 5 hours. Reaction conversion was measured by TLC using mobile phase (60:40, Ethyl acetate:Toluene). Organic layer is directly used for the preparation of next step.



Scheme 1

Preparation of 2-mercapto-5-methoxy-1*H*-benzimidazole (6)

Organic layer containing **(5)** (1.0gm, 0.0072mole) was cooled at 30^{0}C. To this NaOH (1.08gm, 0.027mole) was added and stirred at room temperature. CS_2 (1.21gm, 0.016 mole) was added slowly in 1 hr at temperature below 30^{0}C and then stirred at room temperature for one hour. Reaction mass was slowly heated to reflux for 6 hours. Reaction conversion was monitored by TLC using mobile phase (60:40, Ethyl acetate:Toluene). Solvent was evaporated under reduced pressure and reaction mass was acidified to pH=2 by adding 33% conc. hydrochloric acid

(4.0gm, 0.036mole) to obtain brown coloured crude product **(6)**. This crude product was filtered, dried and purified by recrystallized from methanol to get pure light brown coloured product **(6).** Yield: 72%, m.p. 254-255^{0}C.

2-mercapto-5-methoxy-1*H*-benzimidazole (6):
IR (KBr) ν_{max} in cm^{-1}: 2565 (S-H str.), 3294 (N-H str.), 618 (C-S), 1268 (O-C aryl str), 1180, 1030 (O-C, alkyl str.). ^{1}H NMR (DMSO-d_6), δ in ppm: 12.41(s, 1H, NH), 3.72(s, 1H, SH), 3.72(s, 3H, OCH_3), 6.5(d, 1H, Ar-H), 6.7(d, 1H, Ar-H), 6.8(s, 1H, Ar-H). MASS, m/z(%): 180(M, 100)

RESULTS AND DISCUSSION

In our attempt to synthesize the title compound **(6)**, we have developed an improved *in situ*, linear multistep process (Scheme 1). In this process, acetylation of 4-methoxy aniline yielded the intermediate *N*-(4-methoxyphenyl)acetamide**(2)**. Subsequent reactions like nitration followed by hydrolysis, reduction and cyclization of intermediate **(2)** gave the title compound, 2-mercapto-5-methoxy-1*H*-benzimidazole **(6)**. In summary, an improved and convergent approach to the synthesis of title compound has been developed by employing *in situ* process of intermediate **(2)** providing a yield of 70%. After the foregoing improvements (Scheme-1), there are advantages like operation is simplified, cost is reduced, yield and quality are good, the whole technical condition is mild and period is short and it is more applicable to industrial production. Thus, scheme 1 was found to be more economical route for the synthesis of 2-mercapto-5-methoxy-1*H*-benzimidazole. The title compound was characterized by spectral analyses like IR, ^{1}H NMR and MASS and purity of all synthesized steps has also been observed by HPLC. The spectral data obtained were found to be promising and were in correlation with literature value[19].

CONCLUSION

As outlined in Scheme 1, an imperative medicinal intermediate, 2-mercapto-5-methoxy-1*H*-benzimidazole has been synthesized. The results so far obtained with the compound are found to be promising. In present investigation, the title compound has been synthesized by *in situ* process in which synthesized intermediates were collected in organic layer and were directly subjected to further treatment with appropriate reagents, which in turn resulted in improved yield of compound.

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