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An improved synthesis of 2-mercapto-5-difluoromethoxy-*1H*-benzimidazole: An important medicinal intermediate

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ABSTRACT

*An improved, convergent and industrially useful process suitable for large-scale production of 2-mercapto-5-difluoromethoxy-1H-benzimidazole, required for synthesis of pantoprazole, has been described. Reaction of 4-hydroxy acetanilide with difluoromethylenechloride gave N-[4-(difluoromethoxy)phenyl]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: Pantoprazole, 4-hydroxy acetanilide, difluoromethylene chloride, spectral analysis.

INTRODUCTION

Compounds bearing benzimidazole moiety are reported to possess a number of interesting biological activities such as antitubercular[1], anticancer[2,3], anthelmintic[4], antiallergic[5,6], antioxidant[7,8,9], antihistaminic[10] and antimicrobial[11-17]. 2-mercaptobenzimidazole derivatives, one of the most important derivatives of benzimidazole also exhibited a wide variety of interesting biological activities such as antimicrobial[18], antihistamine[19] and neutropic[20] activities. The compound, 2-mercapto-5-difluoromethoxy-*1H*-benzimidazole, an important intermediate required for the synthesis of pentoprazole, is a new type of medicine intermediate. Pantoprazole is a substituted benzimidazole which markedly inhibits basal and stimulated gastric acid secretion. It is an irreversible inhibitor of the proton pump as it binds covalently to the enzyme H^+/K^+-ATPase, responsible for gastric acid production and is located in the secretary membranes of the parietal cell[21] and produces a long lasting effect in a single dose a day[22]. The proton pump inhibitors or the enzyme, H^+ / K^+ - ATPase, are found to be useful in the treatment of peptide ulceration, reflux esophatigilitis and Zollinger Ellison Syndrome (ZES). Since the demand for pentoprazole 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-difluoromethoxy-*1H*-benzimidazole. It is reported in literature[23,24] that it can be used to synthesize drugs which can prevent gastric juice from overmuch secreting.

MATERIALS AND METHODS

All the chemicals used in the synthesis were of analytical grade. All melting points were determined in HOOVER scientific melting point apparatus and are 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 GCMS-QP 1000EX SHIMADZU Gas Chromatography-MS apparatus. HPLC analyses were performed on SHIMADZU LC-10 (PDA, 254nm) using peerless C-18 column.

Synthetic Procedures:

Preparation of *N*-[4-(difluoromethoxy)phenyl]acetamide (1)

To isopropyl alcohol (150gm, 1.3mole), p-hydroxy acetanilide(22.6gm, 0.15mol) and NaOH(18gm, 0.0.45mole) were added and catalytic amount of PEG-600 was added then the reaction mass was heated to 50°C for 1 hr. Difluoromethylenechloride gas was purged and the temperature was maintained about 50-55°C. pH was checked intermittently after every 3-4 hrs. pH should always be greater than 9. If pH drops to 8, addition was stopped, NaOH was added and stirred for 1 hour at 50-55°C, then again purging was started same as above. Again pH was checked after every 2-3 hrs and NaOH was added if required & same procedure was followed till completion of the reaction. Sample was checked for TLC (Toluene:Ethyl acetate, 60:40) and HPLC after 70-75 hrs then the reaction mass was cooled to room temperature. It was filtered to remove the salt sludge and isopropyl alcohol was recovered from the reaction mass. Dichloromethane was added, the product was extracted in organic layer and the aqueous layer was separated. Aqueous layer was extracted by 30ml dichloromethane then organic layer and extract were combined.

Preparation of *N*-[4-(difluoromethoxy)-2-nitrophenyl] acetamide (3)

Organic layer containing intermediate **2** was taken and washed with water having pH=2 for 30 minutes, then organic layer was separated from aqueous layer. 1.5gm H_2SO_4(98%) was added, stirred at 30-35°C for 30min and then it was cooled to 20-25°C. Drop wise addition of fuming nitric acid(34.8g, 4.44 mole) at 20-25°C in 2-3 hrs was started. After HNO_3 addition, reaction mass was stirred at 20-25°C for 2 hrs. Reaction was monitored by TLC(Toluene:Ethyl acetate, 60:40) and HPLC. Layer was separated by adding 44ml water. Aqueous layer was extracted two times by 25ml dichloromethane. Extract and Organic layer were combined and neutralized by 20% NaOH solution. Now again layer was separated and organic layer was taken for next step.

Preparation of [4-(difluoromethoxy)-2-nitrophenyl]amine (4)

In a RBF, organic layer containing intermediate **3** was taken in 100ml methanol and 50% NaOH(16.0gm, 0.22mole) solution was added. Reaction mass was refluxed for 3 hrs. Progress of the reaction was monitored by TLC (Toluene,100) and HPLC. Reaction mass was allowed to cool at room temperature. Organic layer is directly taken for further process.

Preparation of 4-(difluoromethoxy)benzene-1,2-diamine (5)

Organic layer containing intermediate **4** was taken in a RBF. 50% NaOH solution was added till it became alkalescent. Raney Nickel catalyst (0.88gm) was added, slow addition of hydrazine hydrate was started by circulating chilling water in the condenser. Excess exothermicity was observed which rose the temperature to reflux. Cautiously addition of hydrazine hydrate was completed and the reaction mixture was slowly refluxed for 4 hrs. Reaction mass was cooled and

filtered to recover the catalyst. Progress of the reaction was monitored by TLC (Toluene:Ethyl acetate, 20:80) and HPLC. Organic layer was taken for preparation of final step.

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

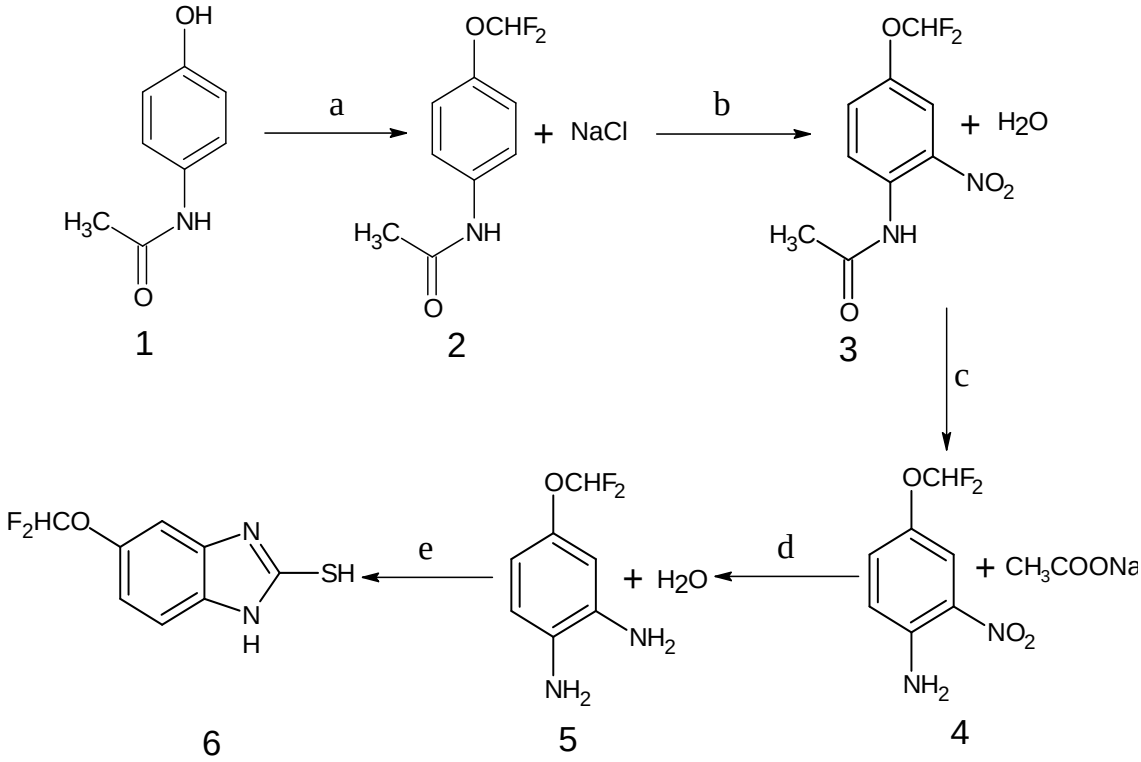
Filtrate containing **5** was taken in RBF, 3.0ml 50% NaOH solution and 0.122mole CS_2 were added and the reaction mass was slowly refluxed for 4 hrs. Solvent was recovered from the reaction mass at low temperature. Water (150ml) was added in the brown slurry like reaction mass and p^H of reaction mass adjusted to 2-3. The light brown solid was filtered and washed with water till it became free from salts, then it was dried to get 21gms crude product. The dried product was purified by charcoaling it in methanol, precipitated by water, filtered and dried to get off white powder.

Yield 52.59%, 17g, m.p. 249-251^{o}C (In literature[23] m.p. 250-252).

2-mercapto-5-difluoromethoxy-1H-benzimidazole (6):

IR (KBr) ν_{max} in cm^{-1}: 3094 (N-H), 2449 (S-H), 1634, 1526, 1495 (Ar-H), 1256, 1029 (Ar-OC), 1146, 1119 (C-F_2), 614 (C-S). ^{1}H NMR (DMSO-d_6), δ in ppm: 12.67(1H, NH), 7.19(1H, SH), 7.15(1H, OCHF_2), 6.95, 6.97, 7.0 (3H, Ar-H). MASS, m/z(%): 216(M, 100)

SCHEME-1



Reagents and conditions:

(a)PEG-600, difluoromethylenchloride, 50-55^{0}C, 70-74h. (b)HNO_3, H_2SO_4, 20-25^{0}C, 2h. (c)CH_3OH, Reflux, 3h. (d)Raney-Nickel, hydrazine hydrate, reflux, 4h. (e)CS_2, reflux, 4h.

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, fluorination of 4-hydroxyacetanilide yielded the intermediate *N*-[4-(difluoromethoxy)phenyl]acetamide **2**. Subsequent reactions like nitration

followed by hydrolysis, reduction and cyclization of intermediate **2** gave the title compound, 2-mercapto-5-difluoromethoxy-*1H*-benzimidazole **6**. In summary, an improved and convergent approach to the synthesis of 2-mercapto-5-difluoromethoxy-*1H*-benzimidazole has been developed by employing *in situ* process of intermediate **2** providing a yield of 52.59%. 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-difluoromethoxy-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 NH band (3094cm^{-1}) and NH proton signal (12.67ppm) in IR and ^{1}H NMR spectrum respectively of the synthesized compound confirmed the formation of imidazole ring. The presence of ArOC stretching (1256, 1029 cm^{-1}), CF_2 stretching (1146, 1119 cm^{-1}) in IR and proton signal at 7.15ppm in NMR confirmed the formation of fluoroalkoxy group. Weak stretching at 2449cm^{-1} and proton signals at 7.19ppm in IR and ^{1}H NMR spectrum respectively exhibited the presence of mercapto group.

CONCLUSION

As outlined in scheme1, an important medicinal intermediate, 2-mercapto-5-difluoromethoxy-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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