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Synthesis and Characterization of New Indole Based Benzothiazole

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Research Article

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ABSTRACT

Indole based benzothiazole **3** was successfully synthesized from indole-3-carbazoldehyde and benzothiazole-2-amine via Schiff base synthesis strategy. The identities of targeted compound were confirmed by ^{1}H NMR, ^{13}C NMR, infrared (IR), and MALDI-TOF mass spectrometry. The final evidences of the compound **3** was further supported by the single X-ray crystal method.

1. Introduction

Design and synthesis of novel heterocyclic scaffolds containing nitrogen and sulfur atoms are found in the skeletal structure of various organic compounds and pharmacologically active molecules. Such cyclic compounds can display a wide range of biological activities depending on the type of pharmacophore group they contain. It is well known that the construction of novel scaffolds possesses two or more types of heterocycles could afford a novel entity with increased biological activities [1-3]. Among the heterocyclic units, indole and benzothiazole derivatives are of significant synthetic interest because of their diverse range of biological activity.

Indole and its derivatives, which are formed by the fusion of benzene and pyrrole rings, an important class of nitrogen-containing aromatic heterocyclic compounds, having attracted attention from researchers because of their valuable properties [4-5]. It is known that indole and its derivatives, which are at the forefront with their biological activities, are found in the structure of many drugs. For example; reserpine which is effective against the SARS-CoV-2 virus [6-9], brassini which has an anti-cancer effect [10-11], indomethacin which is used as a pain and fever reducer [12], sumatriptan used in migraine disease [13] and pindolol used as heart rhythm and the hypertension regulator [14].

Compounds with a benzene ring fused to a thiazole ring called benzothiazoles. They can be found in naturally occurring compounds and show variety of antimicrobial, analgesic, anti-inflammatory and antidiabetic activities. Many benzothiazole ingredient drugs such as riluzole serve as a glutamate antagonist and ethoxzolamide use in the treatment of duodenal ulcers have taken place on the shelves [15-16].

The imine functional group *(-N=CH-)* found frequently in organic compounds, are formed as a result of the condensation reaction between the aldehyde or ketone and the primer amines with the elimination of water. This class of compounds also known as Schiff base has a tendency to form metal complexes and show biological activity through the free electrons on the nitrogen atom [17-23]. The widespread applications of Schiff bases in medicinal chemistry are very significant.

From the synthetic point of view, indole undergoes electrophilic aromatic substitution reactions mainly at C3 position. Among the substitution reactions, 'Vilsmeier-Haack' method is the most commonly used strategy to introduce the substituent at C3 position. Vilsmeier-Haack reaction using $POCl_3$ and DMF as reagents has been employed for the formylation of aromatic compounds such as indole [23-25].

Considering the importance of indole and benzothiazole derivatives, we are interested in the preparation of novel indole Schiff base with 2-amino benzothiazole.

2. Material and Method

All reagents used in the reactions were purchased from Sigma-Aldrich and Merck companies and used without any purification. 1H-NMR and 13C-NMR data was measured in DMSO-d6 solvents using a Varian 500 MHz spectroscopy. Perkin Elmer Spectrum 100 FT-IR device was used to record IR measurements in the range of 650-4000 cm-1. X-ray data was obtained with Bruker APEX II QUAZAR three-circle diffractometer. The reaction was followed by thin layer

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chromatography consisting of silica gel coated on an aluminum layer of Merck GF254. Thin layer chromatography was followed by a UV lamp with wavelengths 254 nm and 365 nm.

3. Results and Discussion

The synthetic strategy of indole based benzothiazole 3 was begun with the formylation of 2-methyl indole under 'Vilsmeier-Haack' conditions. The formation of the chloro iminium cation from $POCl_3$ and DMF gives an electrophilic aromatic substitution reaction with indole 1 to synthesize the 2-methyl-indole-3-carbaldehyde 2 [25], (Scheme 1). The formylation of 2-methyl indole was completed with cooling and purified via flash column chromatography. Attention subsequently turned to the condensation of indole-3-carbaldehyde 2 with benzothiazole-2-amine. For the synthesis of 3; indole 2 was reacted with benzothiazole-2-amine in ethanol in the presence of catalytic amount of glacial acetic acid under reflux for 22 hours. The reaction generated the compound 3 in 72% yield.

The compound 3 is new and its structure was confirmed with the help of spectroscopic data. The 1H NMR spectrum of the compound 3 demonstrated that the aldehyde the aldehyde proton of the starting compound was replaced by a singlet at 9.22 ppm which indicated the presence of the imine proton. The spectrum also demonstrates a singlet at 2.72 ppm corresponding to methyl group on the indole ring. Similarly, the 13C NMR spectrum illustrated the methyl carbon at 12.35 ppm. MALDI-TOF mass spectra revealed molecular ion at 291 (M), consistent with data of the compound 3. Additionally, the structure of the targeted indole based benzothiazole 3 was confirmed by X-ray crystallography (Figure 1).

3.1. 2-Methyl-indole (2)

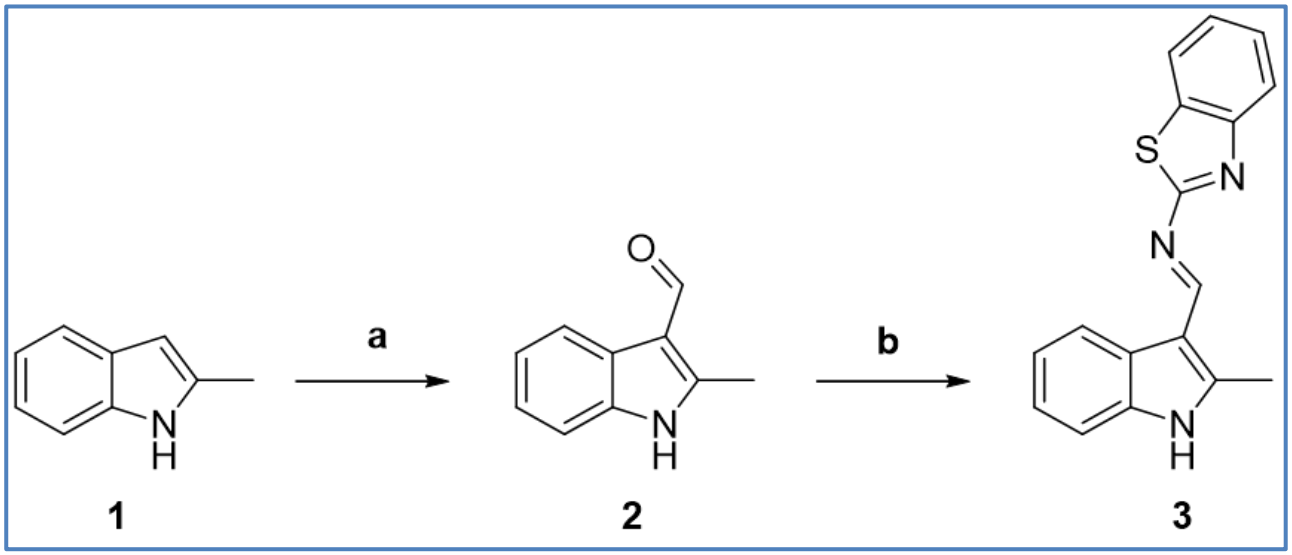
Phosphoryl chloride (10.3 mL, 111.5 mmol, 5 eq.) was added dropwise to an ice cooled anhydrous N,N-dimethylformamide (15 mL), and this cooled solution was added dropwise to a previpously cooled stirred solution of indole 1 (2.9178 g, 22.3 mmol) in anhydrous N,N-dimethylformamide (5 mL) at 0 °C. After the addition the reaction mixture was stirred with cooling for 3 h. The reaction was quenched with ice water followed by 10% sodium hydroxide solution to make the mixture strongly basic. The resulting precipitate was filtered, thoroughly washed with water to afford the 2-methyl indole 2 as a yellow solid (3.37 g, 95%). IR (KBr): υmax 3183, 3111, 1617, 1581, 1459, 1377, 1361, 1241, 1160, 744 cm-1. [M+H]+: requires 160.195; found 160.715.

3.2. (*E*)-N-(Benzo[d]thiazol-2-yl)-1-(2-methyl-1H-indol-3-yl)methanimine (3)

To a stirred mixture of 2-methyl-indole-3-carbaldehyde 2 (0.10 g, 0.63 mmol), 2-aminobenzothiazole (0.10 g, 0.66 mmol) in ethanol (3 mL) at room temperature, two drops of glacial acetic acid was added and the reaction mixture was heated to reflux. After stirring for 22 h, the resulting reaction mixture was cooled to room temperature and then poured into ice-water. Once the precipitates were observed, they were filtered, washed with hexane (10 mL) and dried to give the target product 3 (0.13 g, 0.46 mmol) in 72% yield as red solid. Suitable single crystal of the compound 3 was obtained after crystallization in dichloromethane/hexane. 1H NMR (500 MHz, DMSO) δ 12.18 (s, 1H, NH), 9.22 (s, 1H, CH), 8.33 (s, 1H, Ar H), 7.97 (d, J = 7.5 Hz, 1H, Ar H), 7.85 (d, J = 7.7 Hz, 1H, Ar H), 7.45 (d, J = 7.7 Hz, 2H, Ar H), 7.34 (d, J = 6.9 Hz, 1H, Ar H), 7.24 (d, J = 2.6 Hz, 2H, Ar H), 2.72 (s, 3H, CH3) ppm. 13C NMR (126 MHz, DMSO) δ 174.19, 159.78, 152.23, 149.70, 136.54, 133.94, 126.65, 126.20, 124.52, 123.48, 122.42, 121.93, 120.39, 112.02, 111.19 (Aryl C), 12.35 (CH3) ppm. [M]+: requires 291,372; found 291.875.

4. Conclusion

In the current work, the successful synthesis of indole linked benzothiazole employing Schiff base method was described.



Scheme 1. Reagent and conditions: a) $POCl_3$, DMF; b) Benzothiazole-2-amine, acetic acid, ethanol.

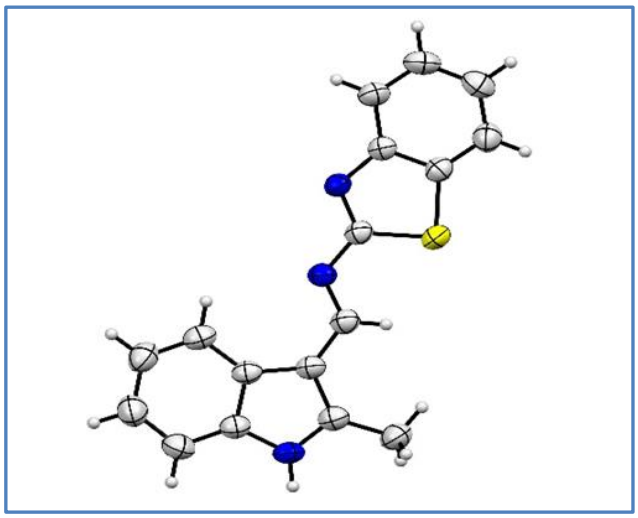


Fig. 1 X-ray crystal structure of compound 3.

Declaration

Author Contribution: Conceive– H. K.; Design– H. K., I. F.S.; Supervision- H.K., Experimental Performance, Data Collection and/or Processing– I.F.S., M. S.; Analysis and/or Interpretation- H. K., I. F.S.; Literature Review– E. T., M. T., N.Ş.O.; Writer– H. K., M. S.; Critical Review– H. K., I. F.S., M. S.

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