

SYNTHESIS OF BENZOFURAN DERIVATIVES AND THEIR PHOTOCHEMICAL STUDY

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Abstract: The plan of the present work is to synthesize, characterize and study the photochemical reaction of clinically important and active heterocyclic benzofuran derivatives. In general, the synthesis of heterocyclic compounds can be accomplished by thermal reactions. But in the present study, the synthesis of 1-(3-methyl benzofuran-2-yl)-carbohydrazide-3-chloro-4-phenyl azetidine-2-one was prepared using o-hydroxy acetophenone as starting material. The structures of all the synthesized and target compounds were made clear by ¹H-NMR, IR and ESI-MS.

Keywords: Benzofurans, Fused heterocycles, Photochemical reaction

Introduction: Heterocyclic compounds containing benzofuran ring in their structures exhibit an array of pharmacological properties [1, 2, 3]. Benzofuran core is a highly flexible, presents in many important natural products and natural drugs. Benzofuran is the colourless liquid and heterocyclic compound consisting of fused benzene and furan rings. Many benzofuran containing synthetic drugs and clinical candidates have been derived from natural products. It is extracted from coal tar and is the parent of many intermediated compounds with more complex structures. The production of benzofuran derivatives has received significant attention due to their presence in large number of natural and synthetic products [4, 5]. It can be obtained by dehydrogenation of 2-ethylphenol [6]. It can be synthesized by various methods in laboratory. Because of their varied actions, much interest has been paid to synthetic approaches to access these systems, and a number of methods have been widened [7, 8]. (This provoked us to continued synthesizing benzofuran derivatives through photochemical approach.

Materials and Methodology: All chemicals were pure and of LR grade. Melting points were determined in an open capillary method and are uncorrected. TLC was employed on microscopic slides (2x7.5 cm) to check the purity of the compounds on silica gel and spots were visualized under resembling iodine. The IR spectra were recorded on a Nicolet Impact 410 FT-IR Spectrophotometer, using KBr pellets. ¹H NMR spectra were recorded on a Bruker-400 MHz spectrometer in CDCl₃ or DMSO using TMS as an internal standard. High-resolution mass spectra (HRMS-ESI) were obtained on a MicroTM Q-TOF Mass Spectrometer.

Synthesis of 1-(3-methyl benzofuran-2-yl)-carbohydrazide-3-chloro-4-phenyl azetidin-2-one
It involves following steps: The entire procedure for preparation of compounds is summarized in Scheme 1 and 2.

Step1: Preparation of 3-methyl-2-ethoxy carbonyl benzofuran: In the first step, 3ml of o-hydroxy

acetophenone was taken in a flask and 10ml of acetone and 3gm of K₂CO₃ crystals were added. The reaction mixture was blended for 5 minutes in ice-bath and 2.8 ml of ethyl bromo acetate was added drop by drop to this reaction mixture. Thereafter, whole reaction mixture was allowed for 20 minutes with catalytic amount of potassium iodide. The resultant was filtered and recrystallized from ethanol to produce 3-methyl-2-ethoxy carbonyl benzofuran.

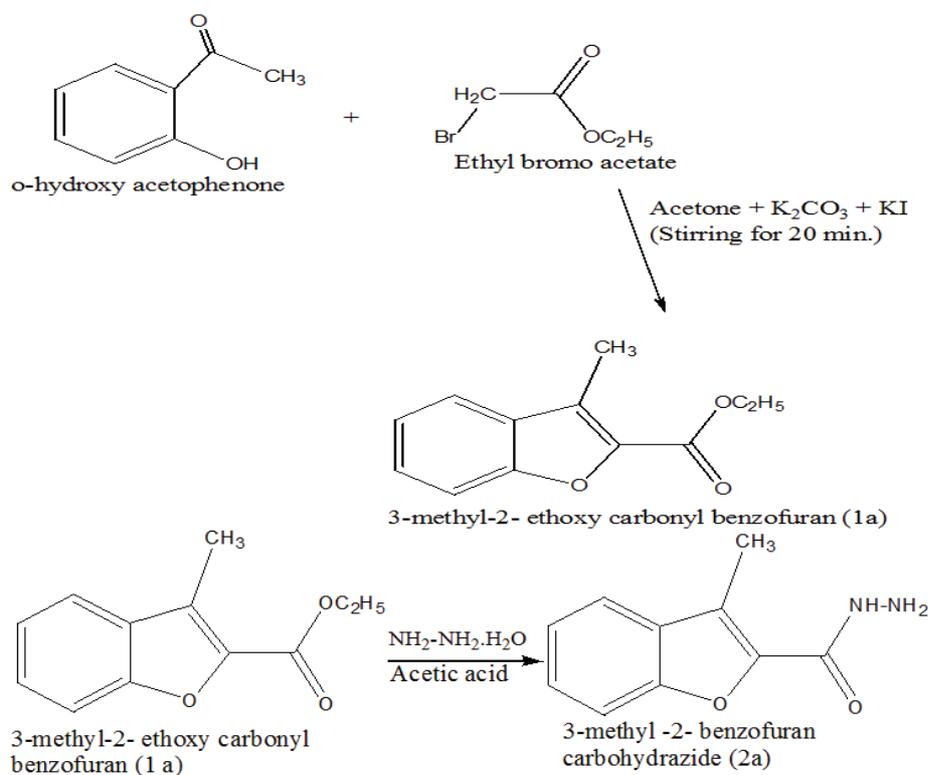
Step 2: Preparation of 3-methyl-2-benzofurancarbohydrazide: In this step, 3gm of 3-methyl-2-ethoxy carbonyl benzofuran (Compound 1a) was dissolved in 25ml ethanol and catalytic amount of acetic acid. To this, 1ml hydrazine hydrate was added. The reaction mixture was stirred carefully at room temperature for about 2 hours and confirmation study was performed by thin layer chromatography using 1:1: Benzene: Hexane solvent system. The reaction mixture was cooled and transferred into crushed ice, the solid obtained of 1-(3-methyl benzofuran-2-yl) - carbohydrazide -3-chloro -4-phenyl azetidine-2-one was recrystallized from ethanol. It yielded 3gm of 3-methyl-2-benzofuran carbohydrazide with melting Point of 95°C.

Step 3: Preparation of 3-methyl -N'-(phenylmethylene) benzofuran-2-carbohydrazide: In this step, 1.9gm of 3-methyl-2-benzofurancarbohydrazide was treated with 1 ml benzaldehyde in ethanol, in the presence of acetic acid (catalytic amount). As a result, 3-methyl -N'-(phenylmethylene) benzofuran-2- carbohydrazide was produced.

Step.4. Synthesis of 1-(3-methyl benzofuran-2-yl)-carbohydrazide-3-chloro-4-phenyl azetidine-2-one
: In the final step, 2.5gm of the 3-methyl -N'-(phenylmethylene) benzofuran-2- carbohydrazide (Compound 3a) was dissolved in 25ml of Dioxane in presence of 0.2ml of triethylamine (0.2ml). The reaction mixture was altered with 2ml of Chloroacetyl chloride for 4-5 hours. After the completion of the reaction a confirmation study was performed by thin layer chromatography using 1:1: Benzene: Hexane solvent system. The reaction mixture was cooled and

transferred into crushed ice. The reaction mixture was cooled and transferred into crushed ice, the solid obtained of 1-(3-methyl benzofuran-2-yl) -carbohydrazide -3-chloro -4-phenyl azitidine-2-one

was recrystallized from ethanol. It yielded 3gm of 3-methyl-2-benzofurancarbohydrazide (Compound 2a) with melting Point of 95°C.



Spectral Study of 3-methyl-2-benzofurancarbohydrazide: The IR spectra (KBr) of the compound shows absorption at 1647.10 cm^{-1} , 1070.42 cm^{-1} , 3346.27 cm^{-1} , 3128.32 cm^{-1} , 2856.38 cm^{-1} , 582.46 cm^{-1} due to $>\text{C}=\text{O}$, $<\text{C}-\text{O}-\text{C}$, $-\text{NH}$, aromatic $>\text{CH}$, $-\text{CH}_3$, $>\text{C}-\text{Cl}$ stretch respectively. The ^1H NMR in CDCl_3 shows in the region 8.30 δ (1H) due to NH, 1.75 δ (3H) due to furan- CH_3 , 7.28-7.60 δ (4H) due to aromatic proton, 2.89 δ (1H) due to $\text{CH}-\text{Cl}$ and 2.32 δ (5H) due to C_6H_5 . The Mass spectrum shows molecular ion peak at m/z 352 (Molecular formula- $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_3\text{Cl}$).

Photochemical study: In this experiment 0.5 gm of 1-(3-methylbenzofuran-2-yl) carbohydrazide-3-chloro-4-phenylazitidine-2-one was dissolved in a minute level of dry benzene and then made up to 500 ml of benzene. To this, 0.01 gm of benzophenone was added as sensitizer. The reaction mixture was illuminated with a low pressure mercury lamp. Progress of the reaction mixture was followed by TLC analysis (1:1: Benzene: Hexane solvent system). Starting material was almost completely consumed in 10 hrs. Solvent was removed under reduced pressure and residue was chromatographed over silica gel. Elution of the column with a mixture (8:2) of benzene and hexane gave a 0.3 gm of a new product which was

identified as the 1-(3-methylbenzofuran-2-yl) carbohydrazide -2-chloro-3-phenyl aziridine. (Melting Point: -121-123°C).

3. Results and Discussion:

Characterization Data of the Synthesized Compound: 1-(3-methyl-6 hydroxy benzofuran-2-yl)-carbohydrazide-3-chloro-4-phenyl azetidine-2-one: The IR spectra (KBr) of the compound shows absorption at 3217.04 cm^{-1} , 3028.03 cm^{-1} , 1076.21 cm^{-1} , 1645.17 cm^{-1} , 594.03 cm^{-1} , 3338.55 cm^{-1} due to aromatic-OH, aromatic $>\text{CH}$, $<\text{C}-\text{O}-\text{C}$, $>\text{C}=\text{O}$, $>\text{C}-\text{Cl}$, $-\text{NH}$ stretch respectively.

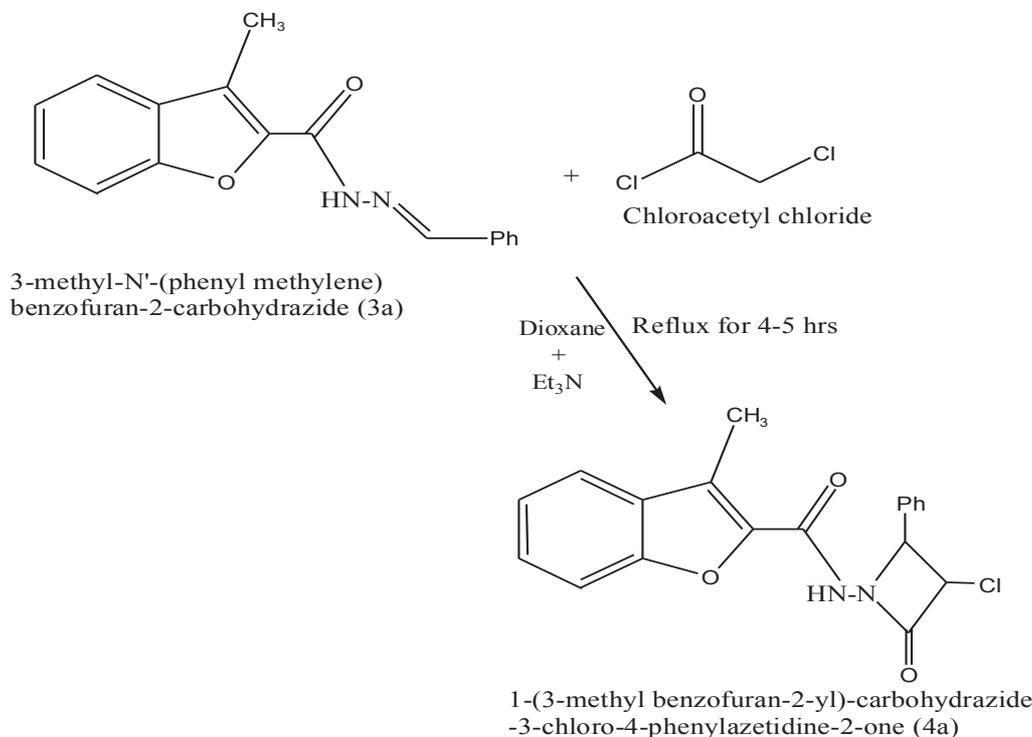
The ^1H NMR in CDCl_3 shows in the region 5.05 δ (1H) due to aromatic-OH, 7.11 δ (3H) due to aromatic-H, 1.77 δ (3H) due to furan- CH_3 , 2.90 δ (1H) due to $\text{CH}-\text{Cl}$, 8.29 δ (1H) due to NH and 2.30 δ (5H) due to C_6H_5 . The Mass spectrum shows molecular ion peak at m/z 368 (Molecular formula- $\text{C}_{19}\text{H}_{13}\text{N}_2\text{O}_4\text{Cl}$).

Characterization Data of the Synthesized Compound: 1-(3-methyl-6-hydroxy benzofuran-2-yl) carbohydrazide -2-chloro-3-phenyl aziridine: The IR spectra (KBr) of the compound shows absorption at 3228.62 cm^{-1} , 3039.60 cm^{-1} , 1062.70 cm^{-1} , 584.39 cm^{-1} , 3361.69 cm^{-1} and 1244.00 cm^{-1} due to aromatic-OH, aromatic $>\text{CH}$, $<\text{C}-\text{O}-\text{C}$, $>\text{C}-\text{Cl}$, $-\text{NH}$ and $>\text{C}-\text{N}$ stretch respectively.

The ^1H NMR in CDCl_3 shows in the region 5.10 δ (1H) due to aromatic-OH, 7.13 δ (3H) due to aromatic- H, 1.69 δ (3H) due to furan- CH_3 , 8.31 δ (1H) due to -NH, 2.33 δ (5H) due to C_6H_5 . The Mass spectrum of 1-(3-methyl-6-hydroxybenzofuran-2-yl)-carbohydrazide-3-phenyl-2-chloro aziridine exhibits the molecular

ion peak at m/z 342, which is the molecular weight of the compound and other fragments at m/z 307, 230, 190, 147, 132, 115.

The fragmentation pattern is shown in Fig.1 Molecular formula- $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$



Scheme 2. Method of preparation of compounds

Conclusions: The present work provides an alternate and simple method for clinically important and active benzofuran derivatives. But clinical and pharmaceutical significance of newly synthesized benzofuran derivatives is yet to be tested. Experiments are in progress in our microbiology laboratory to test the antimicrobial and antifungal activities of these derivatives.

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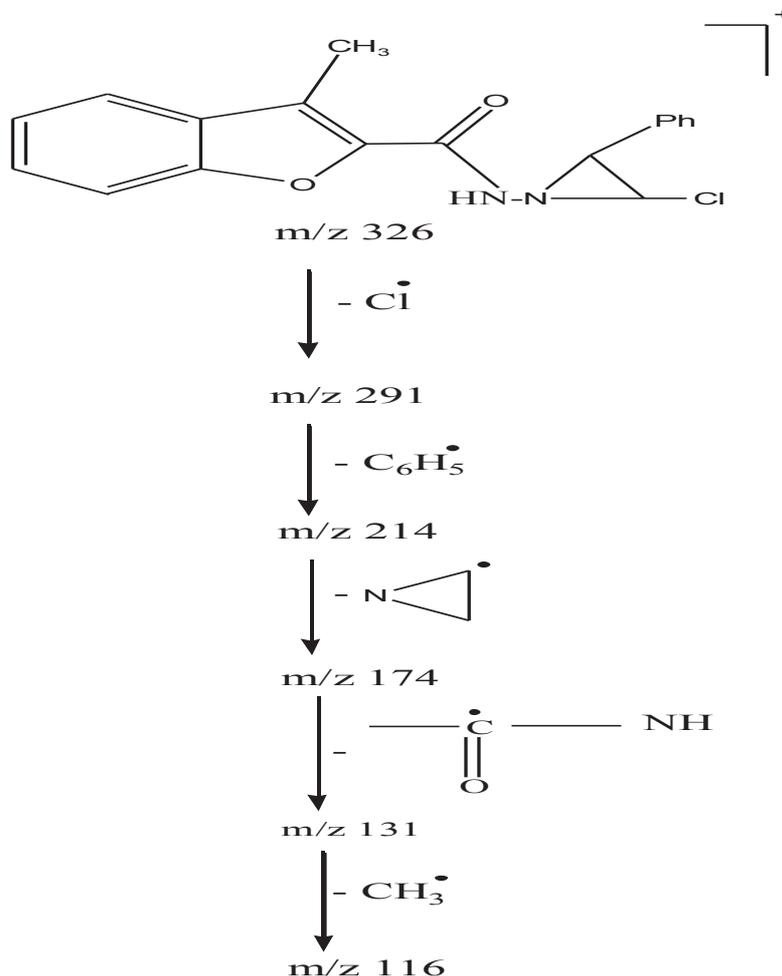


Fig.1 The fragmentation pattern of 1-(3-methylbenzofuran-2-yl)carbohydrazide-2-chloro-3-phenyl aziridine

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