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# Synthesis and Biocidal Effects of Substituted β-Diketone Synthesized From 4-Bromophenol

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**ABSTRACT**
A new substituted β-diketone namely 1-(5-bromo-2-hydroxyphenyl)-3-(4-methoxyphenyl)-propane-1,3-dione was synthesized by the action of anisic acid on 5-bromo-2-hydroxyacetophenone in presence of $POCl_3$ followed by Baker-Venkataraman transformation with KOH in pyridine medium. The structure of newly synthesized substituted β-diketone was confirmed on the basis of chemical properties, elemental analysis and spectral studies and analyzed their biocidal activity against *S. aureus, E. coli* and *A. niger*.

**Keywords**: β-diketone, 4-Bromophenol, Biocidal activity.

## INTRODUCTION

The importance of β-diketones or 1, 3-diketones in synthetic organic chemistry is difficult to overestimate. Their accessibility, stability and often unique properties make them promising agent for their use in various fields of human activity. High reactivity of 1, 3-diketones opens wide prospects for the design of variety of organic compounds, including those structurally related to natural ones. They have gained lot of interest due to their importance as good ligands for chelation with various lanthanides and transition metals in material chemistry[1] and as key intermediates in the preparation of heterocyclic compounds[2-3] like pyrazoles, isoxazoles, imidazoles, benzimidazoles, diazepines and benzodiazepines, etc. They are also well known for their biological activities such as antibacterial, antioxidant, antiviral, systematic insecticidal, prophylactic antitumor and breast cancer chemo-preventive blocking agent. Now-a-days, β-diketones have been used in UV sunscreen cosmetics as an anti-sunscreen agent that filter ultraviolet rays to protect skin and recently it is observed that β-diketones in its keto-enol form are the important pharmacophores for the HIV-1 integrase inhibitors. As β-diketones are having such diverse biological applications and from literature survey it has been observed that synthesis of substituted β-diketone from 4-Bromophenol has not been so far reported. It was therefore thought interestingly to use 4-Bromophenol to synthesize new and novel substituted β-diketone. Hence, the present work deals with the synthesis of a new substituted β-diketone from 4-Bromophenol, its characterization by IR, PMR and Mass spectral data along with their biocidal effects against human pathogens.

## EXPERIMENTAL

The melting points was recorded on 'Precision' melting point apparatus and found uncorrected. The IR spectrum was recorded in KBr on Shimadzu (IRAffinity-1) FTIR spectrophotometer. The PMR spectra was recorded on Bruker Avance II 400 MHz NMR spectrometer using DMSO as solvent and TMS as an internal standard. The product was purified by recrystalization and their purity was checked by thin layer chromatography on silica-G layers.

**Synthesis of Substituted β-diketone**

The synthesis of β-diketone involves following preparatory steps:

**Preparation of 4-Bromophenyl acetate (I):**

Initially 4-Bromophenol (a) was refluxed with acetic anhydride in presence of anhydrous sodium acetate for 1 hour and cool for 15 min followed by decomposition in ice-cold water. Decant water and collect the lower organic layer which was purified by distillation to obtain 4-Bromophenyl acetate (I).

**Preparation of 5-Bromo-2-hydroxyacetophenone (II):**

5-Bromo-2-hydroxyacetophenone (II) was prepared by Fries rearrangement of 4-Bromophenyl acetate (I) in presence of anhydrous $AlCl_3$.

**Preparation of 2-(4-Methoxybenzoyloxy)-5-bromoacetophenone (III):**

5-Bromo-2-hydroxyacetophenone (II) (0.029 mol) and anisic acid (0.029 mol) were dissolved in pyridine and $POCl_3$ was added drop by drop with constant stirring till the viscous mass is obtained. Maintain the temperature below 10°C during the addition of $POCl_3$ to the reaction mixture. The reaction mixture was kept overnight at room temperature and then decomposed by 10% HCl. The product thus separated and was filtered, washed with water followed by 10% $NaHCO_3$ solution and then again with water. Finally it was crystallized from ethanol to obtain 2-(4-Methoxybenzoyloxy)-5-bromoacetophenone (III).

**Preparation of 1-(5-Bromo-2-hydroxyphenyl)-3-(4-methoxyphenyl)-propane-1,3-dione through Baker-Venkataraman transformation (IV):**

2-(4-Methoxybenzoyloxy)-5-bromoacetophenone (III) was dissolved in pyridine (40 ml). The solution was warmed up to 60°C and pulverized KOH was added slowly with constant stirring. After 4 hours the reaction mixture was acidified by ice-cold dil.HCl (1:1). The solid product thus separated was filtered, washed with 10% $NaHCO_3$ and finally several times with water. It was then recrystalized from ethanol to obtain 1-(5-Bromo-2-hydroxyphenyl)-3-(4-methoxyphenyl)-propane-1, 3-dione (IV). The reaction scheme for synthesis of substituted β-diketone from 4-Bromophenol is shown below in Figure-1.

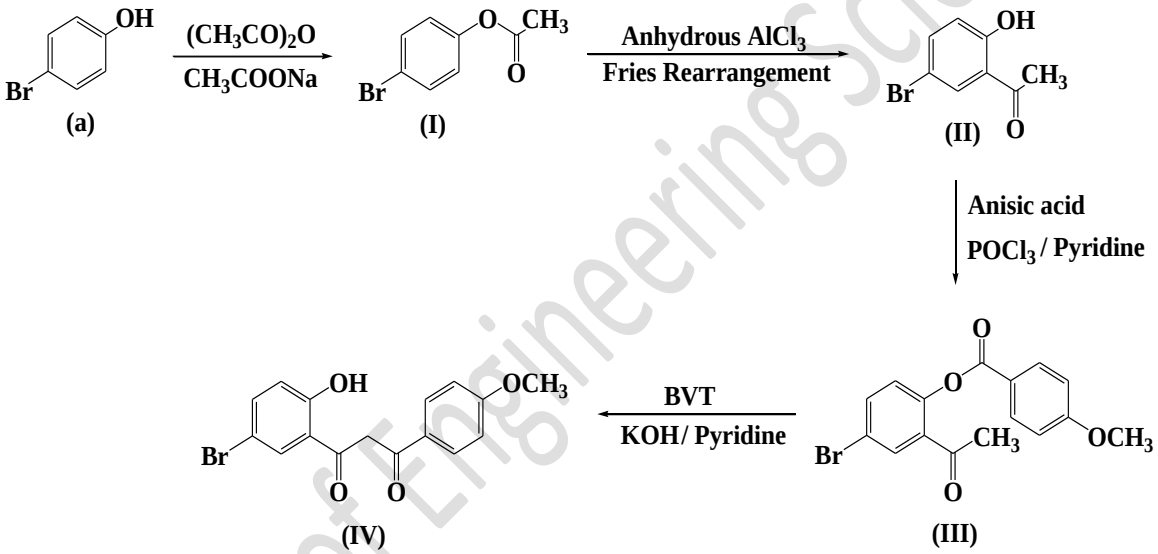



**Figure-1: Synthesis of substituted β-diketone (IV)**

**RESULTS AND DISCUSSION**

The physical and analytical data of synthesized substituted β-diketone (IV) is given in Table-1 and their IR, PMR and Mass spectral data are illustrated in Table-2, 3, 4 respectively.

**Table-1: Physical and analytical data of compound IV**

| Code | Mol. Formula | Mol.Wt. | M.P. (°C) | % Yield | Rf Value | Elements (%) | C | H | O |
|---|---|---|---|---|---|---|---|---|---|
| IV | $C_{16}H_{13}O_4Br$ | 350 | 144 | 70 | 0.13 | Observed | 54.90 | 3.69 | 18.26 |
| | | | | | | Calculated | 55.01 | 3.75 | 18.28 |

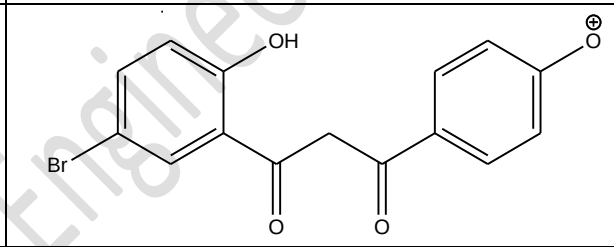
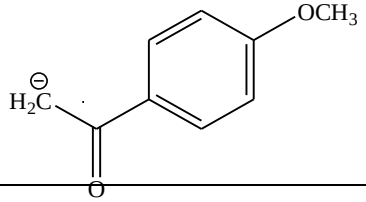
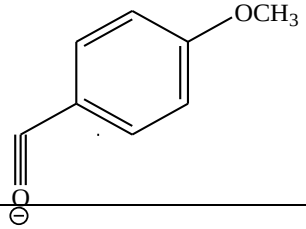
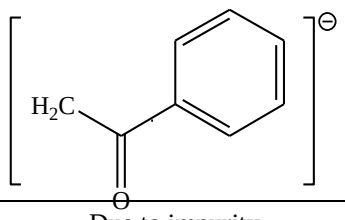
**Table-2: IR Spectral data of compound IV**

| Literature value $cm^{-1}$ | Frequency $cm^{-1}$ | Assignment |
|---|---|---|
| 3650-3600 | 3648 | Ar-OH stretching (free) |
| 3000-2850 | 2949 | C-H stretching (Aliphatic) |
| 1725-1675 | 1687 | C=O (Ketonic) |
| 1600-1500 | 1558 | C=C (Aromatic) |
| 1300-1000 | 1263 | C-O stretch |
| < 667 | 616 | C-Br stretch |

**Table-3: PMR Spectral data of compound IV**

| Peak observed | Muliplicity | No. of Proton | Assignment |
|---|---|---|---|
| 2.5 | Singlet | 3H | $OCH_3$ |
| 3.7-3.9 | Singlet | 2H | $CH_2$ |
| 4.7 | Singlet | 1H | Phenolic -OH |
| 6.9-8.1 | Multiplet | 7H | Aromatic-H |

**Table-4: Mass Spectral data of compound IV**

| m/e value | Probable fragments |
|---|---|
| 355 ($M^+$) | $[C_{16}H_{12}O_4Br]^+$ |
| 333 |  |
| 152 |  |
| 135 |  |
| 117 |  |
| 415 | Due to impurity |

**Biocidal Activity of Synthesized β-diketone**

**Antibacterial analysis:**

The newly synthesized β-diketone (IV) was analyzed for their antibacterial activity against *Staphylococcus aureus* (Gram+ve), *Escherichia coli* (Gram-ve) at the concentrations ranging from 25-1000 µg/ml by agar diffusion method[4-5]. Ethanol was used as solvent to prepare the solutions of compound and nutrient agar was used as media. Ciprofloxacin was used as standard antibiotic for reference. Initially the stock cultures of bacteria were revived by inoculating in broth media and grown at 37ºC for 18 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 hrs old cultures (100 µl, $10^{-4}$ CFU) and spread evenly on the plate. After 20 minutes, the wells were filled with of compound at different volumes. All the plates were incubated at 37ºC for 24 hrs and diameter of inhibition zone were noted. The resulting data are presented in the following tables as diameter of inhibition zones in mm.

**Table-5: Antibacterial analysis against *S.aureus***

| Samples | 25 µg | 50 µg | 100 µg | 250 µg | 500µg | 1000 µg | MIC µg |
|---|---|---|---|---|---|---|---|
| Ethanol | 0 | 0 | 0 | 6 | 5 | 9 | 250 |
| IV | 3 | 3 | 3 | 4 | 7 | 9 | 25 |

**Table-6: Antibacterial analysis against *E.coli***

| Samples | 25 µg | 50 µg | 100 µg | 250 µg | 500µg | 1000 µg | MIC µg |
|---|---|---|---|---|---|---|---|
| Ethanol | 0 | 0 | 0 | 3 | 9 | 10 | 250 |
| IV | 3 | 5 | 6 | 8 | 9 | 10 | 25 |

Note- The sample zone of inhibition is in comparison with ethanol taken for reference.

**Table-7: Standard antibiotic Ciprofloxacin against organisms**

| Organism | 25 µg | 50 µg | 100 µg | 200 µg | 400µg | 800 µg | MIC µg |
|---|---|---|---|---|---|---|---|
| *S.aureus* | 13 | 18 | 21 | 25 | 27 | 34 | 25 |
| *E.coli* | 18 | 20 | 23 | 26 | 28 | 31 | 25 |

**Anti-fungal analysis**

The antifungal activity of newly synthesized β-diketone (IV) was also investigated against *Aspergillus niger* at the concentrations ranging from 25-1000 µg/ml by agar diffusion method[4-5]. Ethanol was used as solvent to prepare the solutions of compound and Czapek-Dox agar was used as media. Amphotericin was used as standard antibiotic for reference. Initially the stock culture was revived by inoculating in broth media and grown at 27ºC for 48 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 48 hrs old culture (100 µl, $10^4$ CFU) and spread evenly on the plate. After 20 minutes, the wells were filled with different concentrations of sample and antibiotic. All the plates were incubated at 27ºC for 96 hrs and diameter of inhibition zones were noted. The resulting data of antifungal analysis are presented in following table as diameter of inhibition zones in mm.

**Table-8: Standard Amphotericin against organisms**

| Organism | 25 µg | 50 µg | 100 µg | 200 µg | 400µg | 800 µg | MIC µg |
|---|---|---|---|---|---|---|---|
| *A.niger* | 0 | 0 | 0 | 0 | 7 | 10 | 400 |

## CONCLUSION

The substituted β-diketone compound (IV) containing 4-Bromophenolic moiety was successfully synthesized and screened for biocidal effects against human pathogens. From the result of screening, it was observed that, the growth of *S.aureus* and *E.coli* were stop by this newly synthesized β-diketone and was found to be moderately active against *S.aureus* and *E.coli* bacteria but in case of fungi *A.niger*, it was found to be inactive. It has also been found that the antibacterial activity of the test compound increases with structure complexity. Hence, this newly synthesized β-diketone can be easily used for the treatment of diseases caused by tested bacteria only when they do not have any toxic and other side effects and could be examined further for obtaining more convincing results which shall be encouraging there for to incorporate therapeutic value of this compound in future.

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