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Synthesis and Characterization of Some Novel Substituted Barbitones derived from Chalcones and Barbituric acid

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Abstract
Biologically active barbitones **(4a-e)** were synthesized by condensation of α-β unsaturated ketones (chalcones) and barbituric acid in acetic acid medium. Chalcones **(3a-e)** were first synthesized by treatment of aldehydes **(2a or 2b)** with different substituted acetophenones **(1a-d)** and 2-acetyl-3-methyl benzofuran **(1e)** by Claisen-Schmidt condensation. The structure of the newly synthesized compound **(4e)** was established on the basis of physical data and spectral methods such as IR, ^{1}H NMR and Mass spectra.

Keywords: Barbituric acid, acetophenones, benzofuran, chalcones, barbitones

Introduction

Nitrogen containing heterocyclic compounds such as barbital or barbitones, are the first commercially available barbiturate. The chemical names for barbitone are diethylmalonyl urea or diethylbarbituric acid. Barbituric acid derivatives recently have gained prominence because of their potential pharmaceutical values. There are more than forty synthetic drugs bearing barbituric acid. They possess diverse type of biological properties including hypnotic, sedatives, anticonvulsant, cardiovascular etc. The first member of hypnotic drugs series was barbital. Many barbituric acid derivatives play vital role in many physiological actions, they exert important action on the central nervous system and recently have been found totally new biomedical applications in fields such as cancer and AIDS therapy [1]. Most important is the effect of barbiturates on the central nervous system. Barbiturates are also used as anesthetics and sleeping agents, and are used for the treatment of anxiety, epilepsy and other psychiatric disorder, and possess effect on the motor and sensory functions [2]. Different methods are used for the synthesis of barbitones in literature [3-7]. Recent literature survey has indicated barbiturate derivatives has attracted considerable attention owing to their various biological effects such as immune modulators [8,9], anti-inflammatory, analgesic [10], molecular docking [11], cytotoxicity properties [12] and broad spectrum pharmacological properties including hypnotic [13] and sedative [14]. In continuation to our previous work and considering this background, some new barbituric acid derivatives were synthesised by the condensation of chalcones with barbituric acid in glacial acetic acid. The constitution of the synthesised products has been characterised using physical and spectral data such as IR, ^{1}H NMR and Mass spectroscopy.

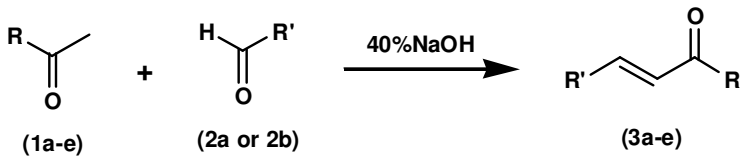
Material and Methods:

All AR grade chemicals of Merck and S.D. Fine were used for the synthesis without further purification. The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR spectrophotometer (KBr, v max in cm−1). 1H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane as an internal reference and DMSO-d6 as solvent. Chemical Shifts are given in parts per million (ppm). Positive-ion electro spray ionization mass spectra were obtained with a Waters Micromass Q-TOF micro, mass spectrophotometer. Elemental (CHN) analysis was done using thermo scientific (Flash-2000), the compounds were analyzed for carbon, hydrogen, and nitrogen and the results obtained are in good agreement with the calculated values. The reactions were monitored by E. Merck TLC aluminum sheet silica gel60F254 and visualizing the spot in UV cabinet and iodine chamber.

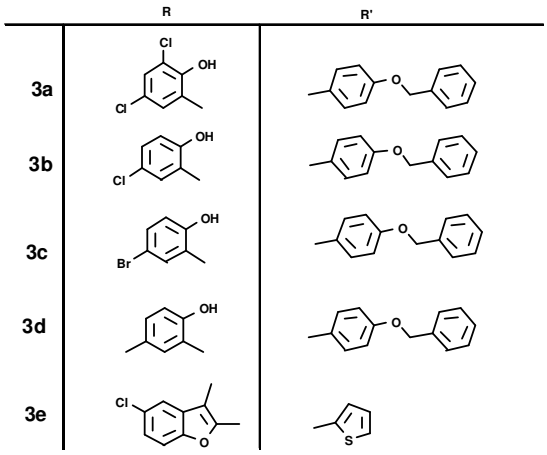
Experimental

Starting compounds such as 2-hydroxy substituted acetophenones **(1a-e),** benzyloxy benzaldehyde **(2a),** thiophene aldehyde **(2b)** and 3-[4-(benzyloxy)phenyl]-1-(5-substitiuted-2-hydroxyphenyl)prop-2-en-1-one **(3a-e)** were synthesised as per the below reaction scheme **1**, following the literature methods [15,16]. The synthesized compounds were confirmed from their melting points and spectral analysis.

Reaction Scheme : 1



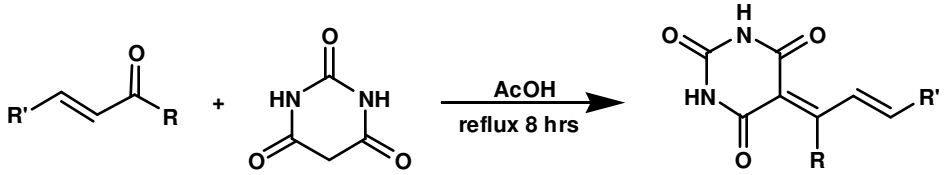
(1a-e) (2a or 2b) (3a-e)



Synthesis of Barbitones or Pyrimidine-2,4,6(1H,3H,5H)-triones:

Procedure for the synthesis of 5-(3-(4-(benzyloxy)phenyl)-1-(substituted phenyl)allylidene)pyrimidine-2,4,6(1H,3H,5H)-trione (4a-e): A mixture of **3a** (0.01 mol) and barbituric acid (0.01 mol) in glacial acetic acid (5mL) was refluxed on oil bath for 8h. The contents were poured into ice and product was isolated, crystallised from suitable solvent to afford **4a** (Scheme **2**). Similarly, **4b-e** were synthesised from **3b-e** by extending the same procedure followed for **4a**.

Reaction Scheme : 2



(3a-e) (4a-e)

5-(3-(4-(benzyloxy)phenyl)-1-(3,5-dichloro-2-hydroxyphenyl)allylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione (4a): Brown coloured crystals; mp: 130-132°C yield 71.0%; M. F. $C_{26}H_{18}Cl_2N_2O_5$; Recrystallizing solvent: Diluted DMF.

5-(3-(4-(benzyloxy)phenyl)-1-(5-chloro-2-hydroxyphenyl)allylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione (4b): Brown coloured crystals; mp: 170-172°C; yield 63.0%; M. F. $C_{26}H_{19}ClN_2O_5$; Recrystallizing solvent: Diluted DMF.

5-(3-(4-(benzyloxy)phenyl)-1-(5-bromo-2-hydroxyphenyl)allylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione (4c): Brown coloured crystals; mp: 220-222°C; yield 98.0%; M. F. $C_{26}H_{19}BrN_2O_5$; Recrystallizing solvent: Diluted DMF.

5-(3-(4-(benzyloxy)phenyl)-1-(2-hydroxy-5-methylphenyl)allylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione (4d): Brown coloured crystals; mp: 195-197°C; yield 87.0%; M. F. $C_{27}H_{22}N_2O_5$; Recrystallizing solvent: Diluted DMF.

5-(1-(5-chloro-3-methylbenzofuran-2-yl)-3-(thiophen-2-yl)allylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione (4e): Brown coloured crystals; mp 185-187°C; yield 82.0%; M. F. $C_{20}H_{13}ClN_2O_4S$; Recrystallizing solvent: Diluted DMF; IR(KBr, ν_{max}): 3200 (N-H), 3040 (ArH), 2917, 2842 (CH_3), 1746 (C=O), 1645, 1545 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): 11.32 (s, 1H, -NH), 11.28 (s, 1H, -NH), 7.30-8.56 (m, 8H, ArH, -CH=CH-), 2.56 (s, 3H, -CH_3) ppm; MS: *m/z* 413 $[M]^+$, 414 $[M+H]^+$, Calculated: C, 58.18; H, 3.17; N, 6.79; Found: C, 57.95; H, 3.04; N, 6.75.

Result and Discussions

The synthesis of the novel compounds **1a-e** to **4a-e** is described in the above reaction schemes. The identities of the newly synthesized compounds have been established on the basis of their spectral data such as IR, ^{1}H NMR and Mass Spectra.

The reaction of substituted 2-hydroxy acetophenones **(1a-d)** with benzyloxybenzaldehyde **(2a)** and 2-acetyl-3-methyl benzofuran **(1e)** with thiophene aldehyde **(2b)** in presence of 40% NaOH afforded substituted chalcones (**3a-e)** by Claisen-Schimidt condensation. The IR spectra of **3c** [16] showed stretching bands at 1574 and 1468 cm^{-1} due to the disappearance of –CH_3 group and appearance of –CH=CH- and bands at 1639 cm^{-1} due to presence of C=O group, similarly the ^{1}H NMR spectrum showed multiplet in the range of δ 7.00-8.31 ppm due to thirteen protons including CH=CH confirms the formation of **3b**. $FeCl_3$ test gave violet colouration showing the presence of phenolic –OH.

Reaction of substituted chalcones **(3a-e)** with barbituric acid in presence of glacial acetic acid yielded corresponding barbitones **(4a-e)**. The structure of **4e** was confirmed from its spectral data [17]. The ^{1}H NMR spectra in **4e** showed multiplet for eight protons due to ArH and =CH, a singlet at δ 2.56 ppm for three protons of –CH_3, one singlet at 11.28 ppm and another singlet at 11.32 ppm for one proton of two –NH of pyrimidine trione ring, also confirms its formation. Similarly, its mass spectrum with a molecular ion peak at m/z 413 $[M]^+$ and 414 $[M+H]^+$ is in agreement with the molecular formula $C_{20}H_{13}ClN_2O_4S$ which confirms that the barbitones has been formed (Scheme **2**). Fig.**1-2**

Spectra of 4e: 5-(1-(5-chloro-3-methylbenzofuran-2-yl)-3-(thiophen-2-yl)allylidene)pyrimidine-2,4,6 (1H,3H,5H)-trione

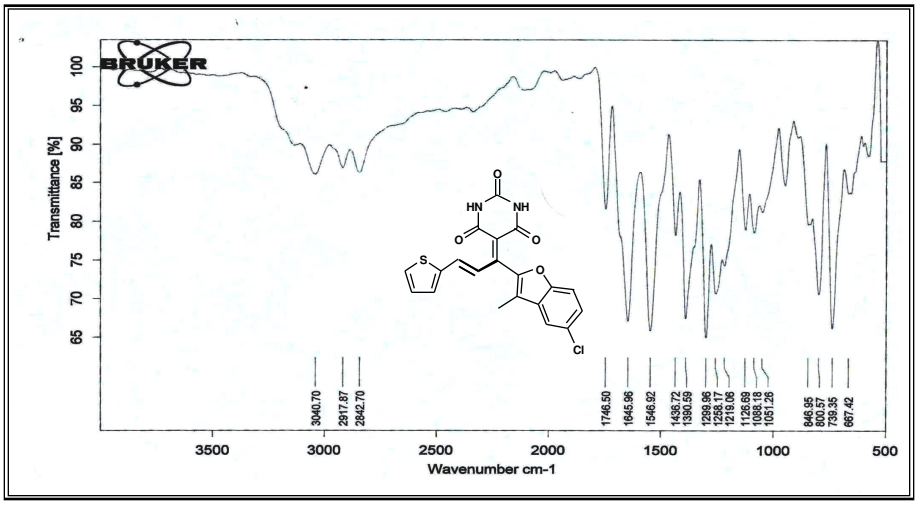


Figure 1: IR Spectra

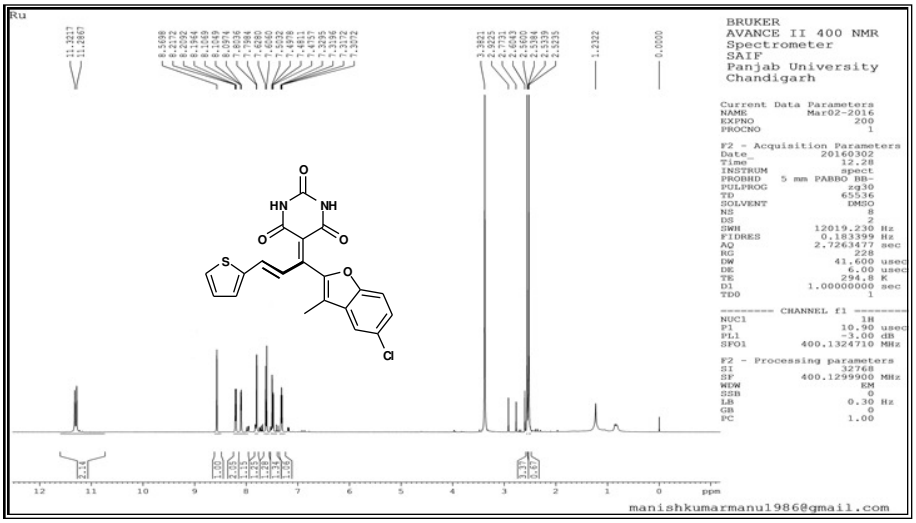


Figure 2: ^{1}H NMR Spectra

Conclusion

In conclusion, starting from substituted acetophenones (**1a-d),** and 2-acetyl-3-methyl benzofuran (**1e),** we have synthesized in a very simple, readily available, and convenient procedure, substituted barbitones (**4a-e)** by condensation of chalcones (**3a-e)** in presence of glacial acetic acid in good yields. Their purity, formation and structures were confirmed from their melting point and spectral data.

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