

Synthesis of barbituric acid derivatives using microwave irradiation method and *in vitro* evaluation of antimicrobial and cytotoxic activity

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ABSTRACT

The research work was involved in rapid and efficient procedure for the attachment of barbituric acid with arylidene acetophenone under microwave irradiation (MWI) and conventional heating. The result showed that the time was reduced from the conventional 24 hours to 5-10 minutes. In conventional heating, the yield of the compounds 2a-2e were very poor (75-81%), but in MW methods the yields were observed 96.48-98% which was comparatively too high. The structures of the compounds were characterized by FT-IR, ¹H-NMR spectral data. The antimicrobial and cytotoxic activities of the synthesized compounds were also investigated. *Staphylococcus aureus*, *Bacillus megaterium*, *Escherichia coli* and *Pseudomonas aeruginosa* revealed the zone of inhibition were 6-12 mm where sample concentration was 100 µg/disc. However, cytotoxic analysis, the mortality 47-95% were appeared when sample concentration were 0.78-25 (µg/ml) and more than 50 (µg/ml) concentration showed 100% mortality. The presence of a reactive and unsaturated ketone function in synthesized compounds was found to be responsible for their potential antimicrobial and cytotoxic activity.

INTRODUCTION

In general, Microwave-assisted synthesis is likely to have a large impact on synthetic organic chemistry, in particular the medicinal/combinatorial chemistry communities. Compared to traditional processing of organic synthesis, microwave-enhanced chemistry saves significant time and very often improves yields. The use of microwaves in organic synthesis has increased dramatically, receiving widespread acceptance (Thierney and Lidstrm, 2005). Microwave technology has become a powerful tool in organic synthesis, since by employing this technique it is generally possible to prepare organic compounds very fast, with high purity and better yields compared to other more conventional methods (Loupy, 2002; Hayes, 2002; Kappe and Stadler, 2005). Additionally, in the search for economic and environmentally friendly synthetic methods, one-pot syntheses could offer a significant step ahead.

Barbituric acid, chemically 2,4,6-trioxohexahydropyrimidine, a cyclic amide used as the parent compound to produce barbiturates that act as central nervous system depressants. Barbituric acid itself does not give sedative and hypnotic effects but the substituted derivatives with alkyl or aryl group at position 5 provide effects. The derivatives of barbituric acid have especial place in pharmaceutical chemistry. Their biological activities range from classical applications in medical treatments as sedative, hypnotic, anticonvulsant, antiplasmodic and local anaesthetic drugs (Tanka *et al.*, 1998; Sokmen *et al.*, 2013). It has also more recent reports indicated that they have applications in anti-tumor, anti-cancer and anti-osteoporosis treatments (Jones, 1967; Khajuria *et al.*, 1996).

A large number of reports are available on the reactions of barbituric acid and with carbonyl compounds-aldehydes, ketones and ester (Ahluwalia *et al.*, 1999; Ahmed *et al.*, 2006; Nasrin *et al.*, 2012). But it is observed that very little extent of work has been done on the reactions of barbituric acid with α,β -unsaturated carbonyl systems.

Although various routes for the synthesis of these compounds have been described, the majority of them involve a number of steps and the yields are poor (Nasrin *et al.*, 2012).

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Therefore, considering the necessity of efficient method development for the synthesis of barbituric acid derivatives, we synthesize the barbituric acid derivatives using MWI which is relatively in good yields and to find out the potential biological activities of these compounds.

MATERIALS AND METHODS

Apparatus

The microwave oven used for this study was classic white ProLine Micro Chef ST44 (720 W, 2450 MHz) which measures 38.2 cm (Height) × 52.6 cm (Width) × 34.5 cm (Depth), with nine power settings. Melting point was uncorrected and was measured with electric-melting point apparatus.

Chemicals

Aromatic aldehydes (benzaldehyde, 4-hydroxy benzaldehyde, 4-chlorobenzaldehyde and 4-methoxy benzaldehyde), acetophenones (acetophenone, 4-chloro acetophenone and 4-hydroxyacetophenone), barbituric acid was used for this experiment. 3M NaOH, 95% ethanol, rectified spirit and water were used as solvents. All chemicals were used of commercial grade (Mark, Germany) without further purification.

Product Analysis

FT-IR spectrum (KBr) was obtained on a Fourier transform spectrometer (FTIR-8300). The ¹H-NMR spectra was obtained at room temperature using chloroform-d (CDCl₃) with a JEOL EX 270 spectrophotometer at 270 MHz. The product was characterized by FT-IR, ¹H-NMR spectra and compared their melting point with the literature value.

Rate Enhancements

The rate enhancement for comparable microwave and conventionally heated reactions was calculated by using identical concentration of the following manner:

$$\text{Rate enhancement} = \frac{\text{conventional reaction time}}{\text{microwave reaction time}}$$

Where, for the reactions the conventional reaction time and microwave reaction time were taken to the same extent of completion. In the present work, the reactions were carried out by following a general procedure (Vogel, 1978; Veeriah and Sondu, 1996; Ahmed *et al.*, 2011).

Synthesis of Barbituric acid derivatives (2a-2e)

The reflux condition (conventional method)

A mixture of arylidene acetophenone (1a-1e) (0.005 mol) and barbituric acid (0.005 mol) were dissolved in rectified spirit (25 ml) and water (25 ml) in a 250 ml round-bottomed flask. The flask was equipped with a refluxing condenser placed in a paraffin oil bath on a magnetic stirrer.

The reaction mixture was refluxed for 18 hours and the course of the reaction was followed by TLC on silica gel plates (eluting solvent, Pet. ether: EtOAc; 5:1). The mixture was allowed

to cool and the solid separated out was dried in air and recrystallized from hot rectified spirit.

Microwave irradiation methods (MWI)

In a 250 ml conical flask an equimolar mixture of barbituric acid (2) (0.005 mol) and arylideneacetophenone (1a-1e) (0.005 mol) were dissolved in 25 ml rectified spirit and 25 ml water. The mixture was irradiated with microwave at different power level for several minutes and the progress of the reaction was followed by TLC on silica gel plate (eluting solvent, Pet. Ether: EtOAc; 5:1).

The reaction mixture was cooled and the solid was separated out by filtration and recrystallized from hot rectified spirit. The purity of the product was checked by TLC.

5,7-diphenyl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrano [2,3-d]pyrimidine (2a)

Powder solid, color: whitish; melting point: 290-292 °C; IR, ν : 3155, 3030, 1716, 1664, 1620, 1505, 1446, 1153, 1035, 862, 744 (KBr) cm⁻¹; ¹H NMR (CDCl₃) δ : 11.06 (m, 2H, NH), 7.56-7.25 (m, 10H, Ar-H), 5.35 (d, 1H, 6-H), 4.43 (d, 1H, 5-H).

5-(4-hydroxyphenyl)-7-phenyl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrano [2,3-d]pyrimidine (2b)

Powder solid, color: whitish; melting point: 190-192 °C; IR ν : 3600, 3155, 3100, 3030, 1710, 1680, 1620, 1494, 1450, 1100, 935, 862, 744 (KBr) cm⁻¹; ¹H NMR (CDCl₃) δ : 11.02 (m, 2H, NH), 7.72-6.93 (m, 9H, Ar-H), 5.34 (d, 1H, 6-H), 4.44 (d, 1H, 5-H), 4.98 (s, 1H, Ar-OH).

5-phenyl-7-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrano [2,3-d]pyrimidine (2c)

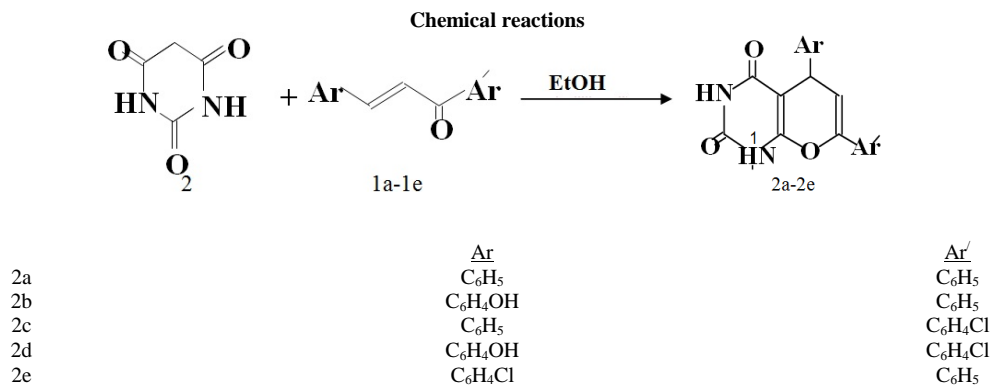
Powder solid, color: whitish; melting point: 285-287 °C; IR ν : 3155, 3030, 1718, 1680, 1620, 1505, 1446, 1103, 813, 786, 746, 617 (KBr) cm⁻¹; ¹H NMR (CDCl₃) δ : 10.96 (m, 2H, NH), 7.64-7.25 (m, 9H, Ar-H), 5.95 (d, 1H, 6-H), 4.43 (d, 1H, 5-H).

5-(4-hydroxyphenyl)-7-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrano [2,3-d]pyrimidine (2d)

Powder solid, color: whitish; melting point: 275-276 °C; IR ν : 3600, 3150, 3030, 1718, 1662, 1602, 1508, 1446, 1103, 977, 786, 750, 688 (KBr) cm⁻¹; ¹H NMR (CDCl₃) δ : 10.96 (m, 2H, NH), 7.71-6.93 (m, 8H, Ar-H), 5.64 (d, 1H, 6-H), 4.41 (d, 1H, 5-H), 4.63 (s, 1H, Ar-OH).

5-(4-chlorophenyl)-7-phenyl-1,2,3,4-tetrahydro-2,4-dioxo-5H-pyrano [2,3-d]pyrimidine (2e)

Powder solid, color: whitish; melting point: 284-286 °C; IR ν : 3155, 3030, 1710, 1680, 1565, 1505, 1450, 1100, 813, 786, 746, 680 (KBr) cm⁻¹; ¹H NMR (CDCl₃) δ : 10.96 (m, 2H, NH), 7.71-6.93 (m, 9H, Ar-H), 5.97 (d, 1H, 6-H), 4.40 (d, 1H, 5-H).



Scheme. 1: Synthesis of barbituric acid derivatives (2a-2e).

Bioassay of synthesized compounds

Antimicrobial activities

Microorganisms

The microorganisms used for the experiment were collected as pure culture from the instituted of Food Science and Technology, BCSIR, Dhaka, Bangladesh. *Aspergillus niger* and *Aspergillus flavus* were taken for the anti-fungal activity test. Cultures of each fungal species were maintained on potato-dextrose agar (PDA) slants and stored at 4°C and performed by disc diffusion method (Siddiqui *et al.*, 2013). On the other hand, the organisms *Staphylococcus aureus*, *Bacillus megaterium*, *Escherichia coli* and *Pseudomonas aeruginosa* were used for anti-bacterial activity test. Active cultures for experimental use were prepared by transferring a loopful of cells from stock cultures to flasks and inoculated in Luria-Bertani (LB) broth medium at 37°C for 24 hours. Cultures of each bacterial strain were maintained on LB agar medium at 4°C (Rahman *et al.*, 2013).

Preparation of discs

The antimicrobial activity was performed as the methods described previously (Bauer *et al.*, 1960). Three types of discs were used for anti-bacterial and anti-fungal screening. Measured amount of each test sample was dissolved in specific volume of solvent to obtain the desired concentrations in an aseptic condition. Then discs were soaked with solutions of test samples and dried. Standard discs were used as positive control to ensure the activity of standard antibiotic against the test organisms as well as for comparison of the response produced by the known anti-bacterial and anti-fungal agent with that of produced by the test sample. In this investigation, kanamycin (30 µg/disc) and ketoconazole (30 µg/disc) were used as standard reference disc for anti-bacterial and anti-fungal test, respectively. Blank discs were used as negative control which ensures that the residual solvents (left over the discs even after air-drying) and the filter papers were not active themselves.

Diffusion and Incubation

The sample discs, the standard antibiotic discs and the control discs were placed gently on the previously marked zones in

the agar plates pre-inoculated with test bacteria and fungi. The plates were then kept in a refrigerator at 4°C for about 24 hours to allow sufficient diffusion of the materials from the discs to the surrounding agar medium. The plates were then inverted and kept in an incubator at 37°C for 24 hours for bacteria and at 28 ± 2°C for 48 hours for fungi. After incubation, the antimicrobial activities of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with transparent scale.

Cytotoxicity bioassay

The cytotoxic activity was performed as described previously (Meyer *et al.*, 1982). The test samples were dissolved in dimethyl sulfoxide (DMSO) and serial dilution were made as 100, 50, 25, 12.5, 6.25, 3.125, 1.563, 0.781 µg/ml. Then each of these test solutions was added to test tubes containing 10 shrimps in simulated brine water (5 ml) and incubated at room temperature for 24 hours. After 24 hours, the mortality percentages of the shrimps were calculated.

RESULTS AND DISCUSSION

The final products 2a-2e were obtained by the condensation reactions between the primary product (1a-1e) and barbituric acid (2) under conventional heating and were completed in 18 hours with moderate yield, whereas the same reactions under MWI method gave excellent yield within few minutes of irradiation. The structural assignment of 2a-2e was based on spectroscopic data.

The FT- IR data of the compounds 2a-2e showed sharp as well as broad bands in the range (ν_{max}) 3155-3100 cm^{-1} indicating the presence of N-H group. The absorption bands at 1710-1680 cm^{-1} indicating the presence of C=O group. The bands at 1620-1505 cm^{-1} were assigned to C=C of aromatic rings and C=N of the conjugated form of barbituric acid part. 1460-1400 cm^{-1} were assigned to C-C stretching. The bands at 3700-3500 cm^{-1} indicating the presence of Ar-OH group, 800-600 cm^{-1} were assigned to aromatic C-Cl group and 1265-1240 cm^{-1} indicates Ar-CH₃O group. The ¹H-NMR spectrum of the synthesized

compounds showed the N-H protons were strongly deshielded at δ 11.06-10.96 (d). The proton at position 6 appeared as δ 5.97-5.32 (d), the 5-H proton appeared as δ 4.49-4.39 (d). Ar-H group at δ 7.80-6.93 (m), Ar-OH group at δ 4.98-4.63 (s) and Ar-CH₃O group at δ 3.97-3.34 (s). All the FT-IR, ¹HNMR signals are identical to the known compound barbituric acid derivatives (Habibi and Tarameshloo, 2011; Hedayati and Pesyan 2014).

The impact of microwave irradiation and conventional heating for the synthesis of compound 2a-2e has been compared. Moreover, the % yield and time on the reaction were also studied and the results summarized in (Table 1).

Table 1: Comparative study for the synthesis of barbituric acid derivatives.

Name of the Compounds	Conventional method		Microwave method		
	Time (hr)	Yield (%)	Time (min)	Power (W)	Yield (%)
2a	18	80.00	8	320	98.00
2b	18	79.00	8	320	97.00
2c	18	75.00	8	320	97.50
2d	18	81.00	8	320	98.00
2e	18	81.00	8	160	96.48

Comparative analysis of percentage yields and total reaction time for all synthesised barbituric acid derivatives by both conventional method and microwave-assisted method was carried out to find out if microwave-assisted synthesis of barbituric acid derivatives adds any advantage or not. It was found that there is improvement in percentage yields of barbituric acid derivatives and also drastic reduction in total reaction time. By using microwave irradiation, reaction is possible within few minutes; and it also improves the yield. This would be highly advantageous for drug discovery in laboratories where small amounts of different analogues have to be synthesised in short periods of time. This is very useful for combinatorial synthesis of new libraries of compounds. Microwave-assisted synthesis is quicker, high yielding, environment friendly and shows cleaner chemistry.

The synthesised arylidene acetophenone (1a-1e), barbituric acid derivatives (2a-2e) were screened for their antibacterial activity against both Gram positive and Gram negative organisms by disc diffusion method using Kanamycin and Ketoconazole as the standard and methanol as the vehicle. *Staphylococcus aureus*, *Bacillus megaterium*, *Escherichia coli* and *Pseudomonas aeruginosa* are used as the organisms. Screenings for the newly synthesized compounds were done at concentrations 100 μ g/disc. *Staphylococcus aureus* and *Bacillus megaterium* were found to be resistant to all the compounds. The values zone of inhibition were 6-12 mm. However, The two Gram negative organism namely *Escherichia coli* and *Pseudomonas aeruginosa* were showed zone of inhibition 6-10 mm resistant to most of the compounds tested (Table 2) (Mathew *et al.*, 2013; Jain *et al.*, 2014).

All the synthesized compounds were also screened for antifungal activity against *Aspergillus niger* and *Aspergillus flavus* by disc diffusion method using ketoconazole (30 μ g/disc) as

the standard and methanol as the vehicle. As shown in Table 2 both the fungal strains were found to be moderately sensitive to all the tested compounds (Shaker and Ishak, 2011; Soayed *et al.*, 2014).

Table 2: Antimicrobial activities of the synthesized compounds.

Tested Sample	Name of Bacteria			Name of Fungi		
	<i>S. aureus</i>	<i>B. megaterium</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>A. niger</i>	<i>A. flavus</i>
Diameter of Zone of Inhibition (mm)						
2a	12	12	9	7	17	16
2b	12	11	10	10	13	17
2c	11	8	6	-	12	17
2d	7	6	-	-	14	16
2e	8	8	7	6	14	17
Ketoconazole	-	-	-	-	22	26
Kanamycin	28	29	28	27	-	-

The cytotoxic activities of the synthesized compounds were determined by using brine shrimp lethality bioassay. The mortality percentages for all the tested samples were found to be very high. Some compounds showed 100% mortality at very low concentration as shown in Table 3. Sample concentration 0.78-25 (μ g/ml) showed the mortality of 47-95%, whereas 50-100 (μ g/ml) concentration showed 100% mortality. From this study, it is evident that all the test samples were lethal to brine shrimp nauplii. These positive results suggested that they may contain antitumor or pesticidal activity (Copper, 2013; Dhorajiya *et al.*, 2014).

Table 3: Cytotoxic activities of the synthesized compounds.

Tested Sample	Sample Concentration (μ g/ml)							
	0.78	1.56	3.125	6.25	12.5	25	50	100
Mortality (%)								
2a	68	74	85	89	89	95	100	100
2b	49	78	89	89	89	95	100	100
2c	47	62	62	89	89	93	100	100
2d	57	79	89	89	90	90	100	100
2e	56	83	83	89	89	93	100	100

CONCLUSION

The preparation procedure followed in this work for the synthesis of schiff base offers reduction in reaction time, excellent yields without formation of undesirable side products, operation simplicity, cleaner reaction and easy work-up in Microwave-assisted syntheses. These synthesis apart from reducing the use of organic solvents from work up step, also gave improved yield as compared to the conventional heating with reaction time reduced from hours to minutes. Low amount of chemicals were used making the method of synthesis environmental friendly. In other words, as a modest work of green chemistry, it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals.

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