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# A Solvent Free Green Protocol for Synthesis of 5-Arylidine Barbituric Acid Derivatives

**Uttam BM***

Department of Chemistry, Sadguru Gadage Maharaj College, Karad, India

***Corresponding author:** Uttam BM, Department of Chemistry, Sadguru Gadage Maharaj College, Karad, India, E-mail: uttambmore@rediffmail.com

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## Abstract

**A green approach to the condensation reaction of aromatic aldehydes and barbituric acid has been described using sodium acetate as a catalyst with grinding at room temperature without using solvent. Short reaction time, higher yields and clean reaction makes this protocol an attractive alternative to the existing methods.**

***Keywords:*** ***Grinding; Barbituric acid; 5-arylidine barbituric acid***

## Introduction

Barbituric acid is a strong acid in aqueous medium with an active methylene group and can be involved in Knoevenagel type condensation reaction. Barbituric acid is 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 special place in pharmaceutical chemistry. They have broad biological spectrum ranging from classical applications in medical treatments as anticonvulsant, sedative, antiplasmodic, hypnotic and local anesthetic drugs [1,2]. They have been also found useful in anti-osteoporosis, anti-tumor and anti-cancer treatments [3,4].

Different synthetic routes have been reported for the synthesis of 5-arylidine barbituric acid derivatives by using $NH_2SO_3H$ [5], infra-red promoted [6], microwave irradiation [7], ionic liquid mediated condensation [8], and uses variety of catalysts such as $ZnCl_2$ [9], $CdI_2$ [10], Ni-$SiO_2$[11], KF–$Al_2O_3$ [12], natural phosphate [(NP)/KF or NP/$NaNO_3$] [13] and synthetic phosphate ($Na_2CaP_2O_7$) [14], $K_2NiP_2O_7$ [15], dry condensation with acidic clay catalysts [16], Ni nanoparticles [17], microwave irradiation [18] etc. However, these methods are suffering by limitation of longer reaction time, effluent pollution, bis-addition and self-condensation, lower yields etc.

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Solvent free organic reaction have drawn great interest, particularly from the viewpoint of green chemistry as organic solvent are toxic and flammable. Solid state reactions are simple to handle, reduce pollution and comparatively cheaper to operate.

Organic synthesis employs large amounts of hazardous and toxic solvents. The choice of pursuing aqueous reactions is becoming more and more important due to its environmental impact and cost of chemicals. Organic reactions under aqueous conditions have increasingly attracted chemist's interests particularly from the view point of green chemistry. Organic solvents are conventionally used in organic synthesis and in industrial processes on a large scale. These solvents are often problematic owing to their toxicity and flammability. There is now a realization that more benign chemical synthesis is required, as an integral part of developing sustainable technologies. Eliminating the use of organic solvents can reduce the generation of waste, which is a requirement of one of the principles of green chemistry.

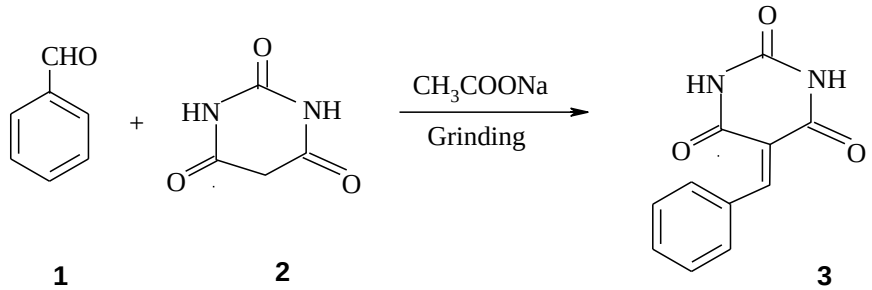
The grinding method is used more and more frequently in organic synthesis. In comparison with traditional methods, this method is more convenient and easily controlled. A number of organic reactions can be carried out in higher yields, shorter times or milder conditions by the grinding method. The synthesis of fused isoxazole derivatives has been achieved by grinding method [19]. It can even set off some reactions that cannot be carried out under traditional conditions. All of these results prompted us to study the possibility of Knoevenagel condensation of aromatic aldehydes with barbituric acid catalyzed by sodium acetate under grinding without solvent.

## Experimental

All the reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer BX serried FTIR spectrometer using KBr pellet. NMR spectra were recorded on 300 MHz spectrometer.

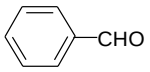
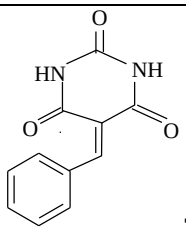
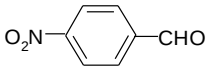
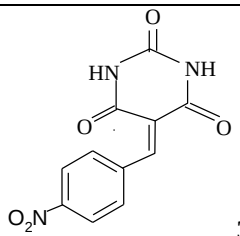
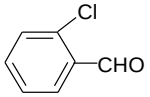
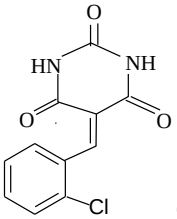
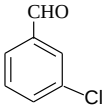
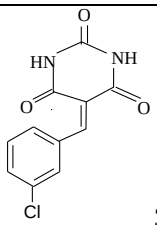
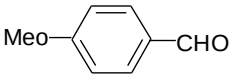
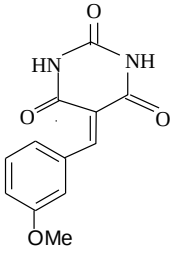
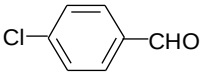
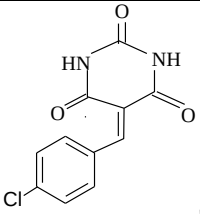
### General Procedure for the Synthesis of 5-Arylidene Barbituric Acids

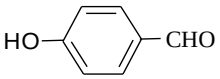
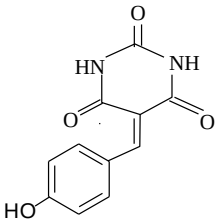
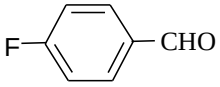
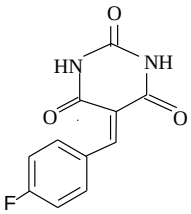
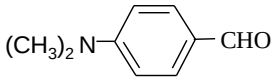
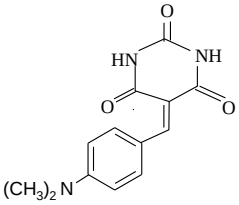
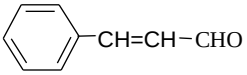
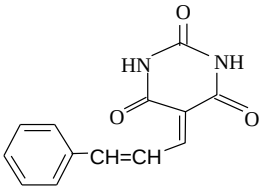
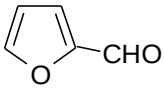
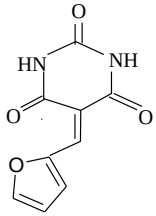
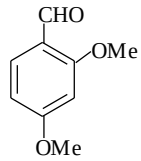
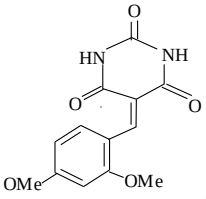
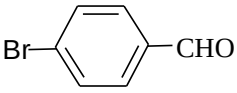
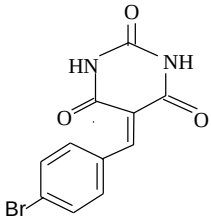
A mixture of aromatic aldehyde (10 mmol), barbituric acid (10 mmol) and sodium acetate (10 mmol) was grinded at room temperature till the completion of reaction. The reaction was monitored by TLC (hexane and ethyl acetate). After completion of reaction solid product was washed with distilled water, filtered and recrystallized using suitable solvent (SCHEME 1 and TABLE 1).




SCHEME 1: **Synthesis of 5-Arylidene Barbituric Acids.**

TABLE 1. **Condensation of barbituric acid with aromatic aldehydes catalyzed by sodium acetate using grinding method.**

| Entry | Aldehyde | Product | Time (min) | Yield (%) | m. p. (°C) | |
|---|---|---|---|---|---|---|
| | | | | | Found | Reported [20,21] |
| 1 |  |  **3a** | 07 | 86 | 265-266 | 263-265 |
| 2 |  |  **3b** | 15 | 81 | 268-270 | 272-274 |
| 3 |  |  **3c** | 07 | 90 | 248-250 | 252-254 |
| 4 |  |  **3d** | 15 | 85 | 276-278 | 274-278 |
| 5 |  |  **3e** | 10 | 87 | 295-297 | 296-298 |
| 6 |  |  **3f** | 10 | 91 | 296-798 | 301-302 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 |  |  **3g** | 15 | 83 | >300 | >320 |
| 8 |  |  **3h** | 20 | 77 | >300 | 309-310 |
| 9 |  |  **3i** | 15 | 82 | 274-276 | 277-279 |
| 10 |  |  **3j** | 10 | 84 | 268-270 | 270 |
| 11 |  |  **3k** | 15 | 76 | 260-262 | 264 |
| 12 |  |  **3l** | 10 | 84 | 285-287 | 288-290 |
| 13 |  |  **3m** | 20 | 77 | 288-290 | 292-293 |

**Spectral data of some compounds**

**3c:** IR (KBr) υ $cm^{-1}$: 3450, 3126, 2978, 1728, 1562, 1450, 1073; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 7.30 (t, 1H Ar-H), 7.41 (t, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 7.68 (d, 1H, Ar- H), 8.21 (s, 1H, HC=C), 11.15 (s, 1H, NH), 11.41(s, 1H, NH).

**3d:** IR (KBr) υ $cm^{-1}$: 3255, 3210, 2970, 1730, 1570, 1440, 1078; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 7.51-7.01 (m, 2H Ar-H), 7.78 (d, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 8.26 (s, 1H, CH=), 11.16 (s, 1H, NH), 11.22 (s, 1H, NH).

**3e:** IR (KBr) υ $cm^{-1}$: 3210, 3052, 2965, 1728, 1692, 1650, 1552; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 3.80 (s, 3H, MeO), 7.01 (d, 2H Ar-H), 7.86 (t, 1H, Ar-H), 8.16 (s, 1H, CH=), 8.30 (s, 1H, Ar- H), 11.10 (s, 1H, NH), 11.16 (s, 1H, NH).

**3f:** IR (KBr) υ $cm^{-1}$: 3414, 3210, 2965, 1745, 1700, 1564; $^1$H NMR: (300 MHz, DMSO-$d_6$): δ: 7.45 (d, 2H, Ar-H), 8.18 (2d, 2H, Ar-H), 8.16 (s, 1H, HC=), 11.18 (s, H, NH), 11.44 (S, 1H, NH).

**3g:** IR (KBr) υ $cm^{-1}$: 3412, 3214, 2968, 1732, 1706, 1572; $^1$H NMR: (300 MHz, DMSO-$d_6$): δ: 6.80 (d, 2H, Ar-H), 8.28 (2d, 2H, Ar-H), 8.20 (s, 1H, HC=), 10.63 (S, 1H, OH), 1.10 (s, H, NH), 11.19 (S, 1H, NH).

**3j:** IR (KBr) υ $cm^{-1}$: 3220, 3068, 2966, 2866, 1601, 1726, 1510, 1418, 1370, 1292; $^1$H NMR: (300 MHz, DMSO-$d_6$) δ: 7.40-7.62 (m, 5H Ar-H), 7.61 (d, 1H, HC=), 7.12 (d, 1H, HC=), 11.12 (s, 1H, NH), 11.23 (s, 1H, NH).

## Results and Discussion

We have described mild, easy and green protocol for the synthesis of 5-arylidine barbituric acid derivatives using sodium acetate at room temperature under grinding condition. Short reaction times, appropriate yields and clean reactions make this procedure an attractive alternative to the existing methods. Furthermore, this method is of interest in the perspective of environmentally greener and safer method.

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