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# A new and efficient method for the synthesis of 5-arylmethylene-pyrimidine-2,4,6-trione under solvent and catalyst free conditions

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A new and efficient method has been developed for the synthesis of 5-arylmethylene-pyrimidine-2,4,6-trione without any catalyst and solvent under microwave irradiation. A number of condensation products are prepared in very short reaction time with high yields.

**Keywords**: 5-Arylmethylene-pyrimidine-2,4,6-trione, aromatic aldehyde, barbituric acid, solvent-free, microwave irradiation

**IPC: Int.Cl.[8] C07D**

The derivatives of barbituric acid have a special place in pharmaceutical chemistry. Their biological activities range from classical applications in medical treatments as sedative, hypnotic, anticonvulsant, antispasmodic and local anaesthetic drugs[1,2] to the more recent reports indicating that they have applications in anti-tumour[3], anti-cancer[4], and anti-osteoporosis[5] treatments. Arylidene barbituric acids are useful as potential organic oxidizers[6] for the preparation of oxadeaza-flavines[7] and for the unsymmetrical synthesis of disulphides[8]. Some of them have been recently studied as non-linear optical materials[9].

Barbituric acid is a strong acid (*p*Ka = 4.01, in aqueous medium) with an active methylene group and can be involved in condensation reactions with aldehydes or ketones that do not contain an α-hydrogen. The general type of this reaction is usually called Knoevenagel condensation[10]. The reaction of barbituric acid with carbonyl compounds was studied as early as in 1864. The isolated products contain mono- as well as di-substituted products[11]. To achieve the formation of only one (mono) condensation product between aromatic aldehydes and barbituric acid, various acid and base catalysed reactions were used[12-18]. There are some other approaches to obtain high yield in this condensation. For instance, Villemin and Labiad microwaved a mixture of barbituric acid, aromatic aldehydes and clay (montmorillonite KSF) without solvent[14].

The product was obtained in high yield after the DMF extraction from the solid reaction mixture. Another approach also performs condensation in the solid state with another clay (Tonsil Actisil FF) and infrared irradiation[19, 20].

Jursic[21] performed Knoevenagel condensation using aromatic or α,β-conjugated aromatic aldehydes and barbituric acid in a large excess of methanol without any external acid or base catalyst and the reaction mixture was left to stir at room temperature for few hr to as long as five days. Benzaldehyde with extended conjugation or with electron-releasing substituents yielded the desired product in minutes with almost quantitative yields, while benzaldehydes with electron-attracting substituents or aliphatic aldehydes yielded very little or no product at all.

All of these methods, while offering some advantages, also suffer from disadvantages such as the use of expensive reagents (catalysts), requirement of excess solvent, longer reaction times (up to several days in some cases) and low yields. Accordingly the development of a new and efficient methodology for Knoevenagel condensation is desired.

The existing literature reveals that, either a catalyst (acid or base) or a solvent is a must to perform Knoevenagel condensation. An expeditious method for performing Knoevenagel condensation between barbituric acid and aromatic aldehydes (with electron-releasing and electron withdrawing substituents) and

heterocyclic aldehydes under non-catalytic and solvent-free conditions by microwave irradiation is reported. This method is extremely efficient and neat and all reactions are performed under solvent and catalyst free conditions, to afford good yields within a very short reaction time **(Scheme I).**

The procedure involves mixing of an aromatic aldehyde and barbituric acid (wetted with methanol) and irradiated with a domestic microwave oven. The reactions were usually completed within 30-60 sec, and resulted in the desired products in 84-97% yields. Separation of the product from traces of reactants involves the addition of water and simple filtration of the reaction mixture followed by washing with ether. Scope and generality of this condensation is illustrated with different aldehydes and the results are summarized in the **Table I.**

In addition to the benzaldehydes with electron-releasing substituents, benzaldehydes with electron-withdrawing substitutes (entry **h** and **i**) also underwent smooth condensation, under the reaction conditions, and yielded the products in excellent yields (92 and 96%). A new and efficient method for Knoevenagel condensation is developed. The advantages of this method are: (i) no catalyst, (ii) solvent-free, (iii) a simple experimental procedure applicable to both electron-releasing and electron-withdrawing aromatic aldehydes, (iv) excellent yields, and (v) very short reaction times.

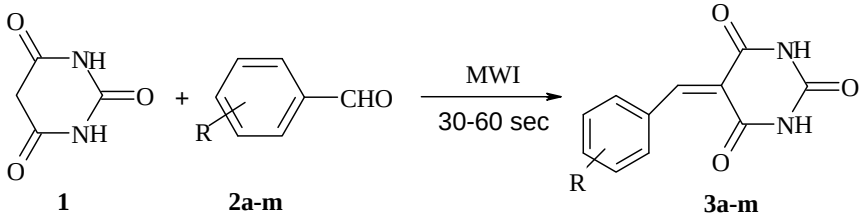
## Experimental Section

The reactions were monitored by TLC (EtOAc / hexane) performed on precoated aluminium sheet. Melting points were uncorrected and were determined in open glass capillaries on Fisher-Johns apparatus. IR spectra (KBr) were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer. NMR spectra were obtained on a Varion Gemini (200 MHz) spectrometer and TMS was used as an internal standard and DMSO-$d_6$ as the solvent. Mass spectra were recorded on a VG-Micromass 7070H mass spectrometer operating at 70 eV. For the microwave irradiation, a conventional household microwave oven was used (LG Electronics India Private Limited). All the aromatic aldehydes (Analar grade) are commercially available and were employed without further purification. The barbituric acid was prepared as per the literature procedure [11].

**General procedure for the synthesis of 5-arylmethylene-pyrimidine-2,4,6-trione**. A mixture of barbituric acid (0.01 mole) and aromatic aldehyde (0.01 mole) was taken in a glass tube and then wetted with methanol (1 drop) and placed the tube at the center of an alumina-bath which was made by using a 250 mL glass beaker (height: 9.5 cm; diameter: 7.5 cm) filled with three quarter alumina. The alumina-bath was kept inside a microwave oven and the mixture was irradiated (**Table I**) at 160 W microwave powers. After cooling, the product was stirred in cold water and the solid was filtered, washed with cold water and ether (3 × 10 mL). After drying, the crude product was recrystallized from EtOAc/hexane to get the pure product.

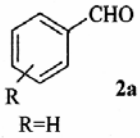
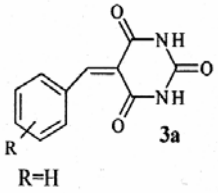
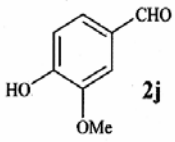
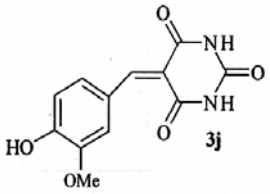
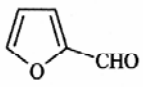
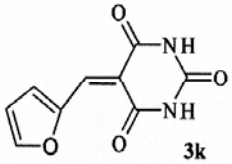
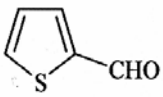
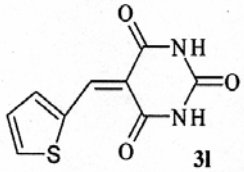
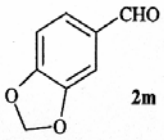
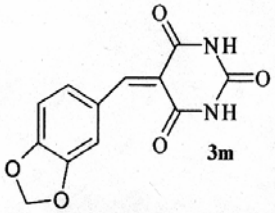
**5-(4-Hydroxy-benzylidene)-pyrimidine-2,4,6-trione 3c**. Yellow solid, Yield 97%; m.p. 297-99°C; IR (KBr) 3520-3480, 3090-3080, 1708, 1670, 1650, 1540, 1210 $cm^{-1}$; $^1H$ NMR: δ 11.30 (s, 1H, NH), 11.15 (s, 1H, NH), 8.39 (s, 1H, H*C*=*C*), 6.20 (1H, S, -OH), 7.31-7.03 (4H, Aro-$H_{2,3,5,6}$); $^{13}C$ NMR: δ 164.1 (C=O), 163.7 (C=O), 162.0 ($C_4$), 155.1 (H*C*=*C*), 136.3 ($C_{2,6}$), 150.1 (NHCONH), 125.0 ($C_1$), 117.8 (H*C*=*C*), 114.7 ($C_{3,5}$); MS (70 eV): 232 ($M^+$, 100), 227 (57), 213 (7), 205 (22), 183 (14), 168 (7), 161 (19), 149 (19), 121 (12), 115 (5).

**5-(2-Hydroxy-benzylidene)-pyrimidine-2,4,6-trione 3d**. Orange solid, yield 91%; m.p. 249-51°C; IR (KBr) 3270-3400, 3090-3080, 1715, 1660, 1590, 1550 $cm^{-1}$; $^1H$ NMR: δ 11.40 (s, 1H, NH), 11.21 (s, 1H, NH), 8.58 (s, 1H, H*C*=*C*), 4.7 (s, 1H, -OH), 7.13 (1H, Aro-$H_3$), 7.10 (1H, Aro-$H_4$), 7.36 (1H, Aro-$H_5$), 7.52 (1H, Aro-$H_6$); $^{13}C$ NMR: δ 163.2 (C=O), 161.1 (C=O), 158.6 ($C_2$), 151.0 (NHCONH), 139.5 (H*C*=*C*), 134.8 ($C_6$), 133.0 ($C_{4,5}$), 122.4 ($C_1$), 119.2 (H*C*=*C*), 111.5 ($C_3$); MS (70 eV): 232 ($M^+$ 100), 225




**Scheme I**

**Table I**—Microwave promoted synthesis of 5-arylmethylene-pyrimidine-2,4,6-trione

| Entry | Aldehyde | | Time (sec) | Product | | Yield (%) | m.p. °C obs./(lit) |
|---|---|---|---|---|---|---|---|
| 1 |  R=H | 2a | 30 |  R=H | 3a | 93 | 270-71/(273)(Ref.13) |
| 2 | 4-Me | 2b | 30 | 4-Me | 3b | 92 | 297-98 |
| 3 | 4-OH | 2c | 30 | 4-OH | 3c | 97 | 297-99 |
| 4 | 2-OH | 2d | 40 | 2-OH | 3d | 91 | 249-51 |
| 5 | 4-Cl | 2e | 40 | 4-Cl | 3e | 84 | 279-81/(271)(Ref.13) |
| 6 | 3-Cl | 2f | 40 | 3-Cl | 3f | 86 | 252-54/(264) (Ref.23) |
| 7 | 4-N(Me)$_2$ | 2g | 30 | 4-N(Me)$_2$ | 3g | 97 | 262-63 |
| 8 | 4-NO$_2$ | 2h | 30 | 4-NO$_2$ | 3h | 92 | 272-74 |
| 9 | 3-NO$_2$ | 2i | 60 | 3-NO$_2$ | 3i | 96 | 231-33 |
| 10 |  | 2j | 30 |  | 3j | 90 | 289-91 |
| 11 |  | 2k | 30 |  | 3k | 92 | 263-64/ (264)(Ref.14) |
| 12 |  | 2l | 30 |  | 3l | 93 | 270-71/ (271)(Ref.24) |
| 13 |  | 2m | 30 |  | 3m | 94 | 268-69/(265) (Ref.14) |

(16), 119 (5), 181 (3), 171 (2), 141 (24).

**5-(3-Chloro-benbzylidene)-pyrimidine-2,4,6-trione 3f**. Yellow solid, yield 86%; m.p. 252-54°C; IR (KBr) 3100-3080, 3520-3460, 1730, 1680, 1650, 1565 cm$^{-1}$; $^1$H NMR: δ 11.45 (s, 1H, NH), 11.25 (s, 1H, NH), 8.35 (s, 1H, HC=*C*), 7.8-7.1 (4H, Aro-H$_{2,4,5,6}$); $^{13}$C NMR: δ 163.8 (C=O), 162 (C=O), 143.5 (HC=*C*), 119.2 (HC=*C*), 150.5 (HNCONH), 137.0 (C$_1$), 134.7 (C$_2$), 139.1 (C$_3$), 134.9 (C$_4$), 131.0 (C$_5$), 130.2 (C$_6$); MS (70 eV): 250 (M$^+$ 41), 234 (7), 226 (3), 215 (65), 208 (100), 190 (58), 157 (2), 140 (20).

**5-(4-Nitro-benzylidene)-pyrimidine-2,4,6-trione 3h**. White solid, yield 92%; m.p. 272-74°C; IR (KBr) 3510-3450, 1720, 1670, 1600, 1650, 1352 cm$^{-1}$; $^1$H

NMR: δ 11.3 (s, 1H, NH), 11.17 (s, 1H, NH), 8.42 (s, 1H, CH=), 8.6 (d, 2H, Aro-$H_{3,5}$), 8.0 (d, 2H, $H_{2,6}$); $^{13}C$ NMR: 165.3 (C=O), 162.2 (C=O), 157.0 ($C_4$), 136.3 (H*C*=*C*), 136.1 ($C_{2,6}$), 150. (HNCONH), 135.3 ($C_1$), 118.4 (H*C*=*C*), 134.1 ($C_{3,5}$); MS (70 eV): 261 (M, 41), 245 (12), 237 (3), 219 (100), 207 (5), 189 (2), 151 (5), 129 (32).

**5-(3-Nitro-benzylidene)-pyrimidine-2,4,6-trione 3i**. Light pink solid, yield 96%; m.p. 231-33°C; IR (KBr) 3510-3450, 1725, 1670, 1600, 1650, 1352 $cm^{-1}$; $^1H$ NMR: δ 11.3 (s, 1H, NH), 11.15 (s, 1H, NH), 8.40 (s, 1H, CH=), 7.9-8.6 (4H, Aro-$H_{2,4,5,6}$); $^{13}C$ NMR: δ 165.1 (C=O), 162.2 (C=O), 152.0 ($C_3$), 145.1 (H*C*=*C*), 132.1 ($C_2$), 150.0 (HNCONH), 135.2 ($C_1$), 133.2 ($C_4$), 118.4 (H*C*=*C*), 131.0 ($C_5$), 150.3 ($C_6$); MS (70eV); 261 ($M^+$, 100), 249 (4), 227 (4), 204 (3), 166 (13), 107 (2).

**5-(4-Hydroxy-3-methoxy-benzylidene)-pyrimidine-2,4,6-trione 3j**. Dark orange solid, yield 90%; m.p. 289-91°C; IR (KBr) 3520-3480, 3100-3080, 1708, 1670, 1650, 1550 $cm^{-1}$; $^1H$ NMR: δ 11.58 (s, 1H, NH), 11.53 (s, 1H, NH), 5.7 (1H, -OH), 8.42 (s, 1H, H*C*=*C*), 3.90 (s, 3H, $CH_3O$), 7.3 (s, 1H, Aro-$H_2$), 7.18 (d, 1H, Aro-$H_6$), 7.12 (d, 1H, Aro-$H_5$); $^{13}C$ NMR: δ 163.1 (C=O), 162.5 (C=O), 143.2 (H*C*=*C*), 150.0 (HNCONH), 115.6 (H*C*=*C*), 129.8 ($C_1$), 112.0 ($C_2$), 155.1 ($C_3$), 149.0 ($C_4$), 117.1 ($C_5$), 123.1 ($C_6$), 59.6 ($CH_3$), MS (70 eV): 262 ($M^+$, 55), 225 (7), 151 (100), 136 (13).

**5-Thiophen-2-yl-methylene-pyrimidine-2,4,6-trione 3l**. Yellow-brown solid, yield 93%; m.p. 270°C, (lit[24] 271°C); IR (KBr) 3520-3460, 1735, 1690, 1650, 1540 $cm^{-1}$; $^1H$ NMR: δ 11.40 (s, 1H, NH), 11.35 (s, 1H, NH), 8.50 (s, 1H, CH=), 7.20-7.30 (3H, Aro-$H_{3,4,5}$); $^{13}C$ NMR: δ 158.1 (C=O), 157.5 (C=O), 150.0 (*CH*=*C*), 148.0 (HNCONH), 112.0 (H*C*=*C*), 127.4 ($C_5$), 139.7 ($C_2$), 121.0 ($C_4$), 130.1 ($C_3$); MS (70 eV): 222 ($M^+$, 100).

The spectral and analytical data of the known products **3a, 3b** and **3e** (ref. 20), **3g** (ref. 20, 21), **3k** (ref. 21), **3m** (ref. 20) were found to be identical with their reported data.

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