# An Improved Method for the Synthesis of 5-Arylidene Barbiturates using $BiCl_3$

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***Dedicated to Prof. Dr. M. Iqbal Choudhary on his 50th birthday***

**Summary**: An improved and eco-benign synthesis of arylidene barbiturates has been developed by using bismuth chloride ($BiCl_3$) in water. Execution is simple and products yields were very high. All the reactions were completed in 30 min time. The new methodology does not involve any solvent/solvent extraction while solid products were obtained in all cases which were filtered and washed.

## Introduction

Barbituric acids have attracted the attention of the pharmaceutical scientist for over 100 years due to their therapeutic value [1]. The first scientific data on barbiturates was published in 1903 [2].

5-Alkylidene or arylidene barbituric acid derivatives are important members of the pyrimidine family. The major importance of these compounds has been centered on their application as useful precursors in the preparation of new heterocyclic compounds [3] and as selective oxidizing agents [4-6]. Barbituric acid and its derivatives have exhibited biological activities such as antibacterial, hypotensive and tranquilizers [7]. The clinical use of barbiturates in neurological disorders also has been investigated [8]. Barbiturates may be synthesized by Knovenagel reaction of barbituric acid with different aldehydes [9]. Condensation of *N*-alkyl-*N*'-aryl carbodiimides and malonic acid monoesters leads to barbiturates in the presence of a base [10]. Optically active *N*-alkylated barbiturates were synthesized from disubstituted cyanoacetates [11] and 5-(cyclohexylmethyl)barbituric acid derivatives [12].

5-Arylidene barbiturates are generally prepared by condensation of barbituric/thioubarbituric acid with various aldehydes under aqueous reflux by using acetic acid as catalyst [13]. Villemein *et. al.* synthesized barbiturates in presence of montmorillonite KSF clay under microwave irradiation [14]. Dewan *et. al.* have reported various catalysts like $NH_4OAc$/AcOH, montmorillonite K-10, silica gel, basic alumina, NaCl, montmorillonite KSF, KSF/NaCl for the synthesis of 5-arylidene barbiturates [15]. A grinding method has also been employed for the synthesis of arylidene barbiturates [16].

Knovenagel condensations have either been reported in water only [17] or without solvents using $BiCl_3$ [18].

The eco-benign synthesis of organic reactions for preparation of biologically active compounds is well known [19]. At the dawn of new century, green chemistry approaches hold out noteworthy potential not only to diminish the byproducts, reduction in waste produced and lowering of energy costs but also in the advancement of new methodologies towards previously unattainable materials using existing technologies [20].

The need to replace toxic volatile solvents and organic catalyst in organic reactions is thus inevitable. In previous communication, Knoevenagel condensation has been achieved by employing $BiCl_3$ in stoichiometric amounts [18] under solvent free conditions at fairly high temperature, while the products were isolated by the use of organic solvents and yields ranged between 65-78 %.

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In this communication, we herein report an improved, rapid and convenient method for the synthesis of 5-arylidene barbiturates under eco-benign conditions *i.e.*, use of water as solvent and bismuth chloride ($BiCl_3$) as catalyst at room temperature. No use of organic solvents for isolation of products and the very high yields are the advantages of this improved methodology.

## Results and Discussion

During drug design and discovery program of our research group, we explored number of known classes of heterocyclic compounds to unveil their biological profiles for rendering better services to humanity using chemistry as a tool. We discovered number of lead molecules from different classes of these heterocycles [21]. For this purpose, we focused our attention simultaneously on the development of new and simple methods for the synthesis of these heterocyclic systems as well [22].

Bismuth salts have attracted attention due to their relatively non-toxicity, easy handling, low cost and good stability [23]. They have been reported as environmentally benign Lewis acids for many types of organic transformations [24]. With increasing environmental concerns and the need for green reagents, the interest in bismuth and its compounds have been increased enormously [25]. This potential in bismuth compounds lead us to utilize $BiCl_3$ in Knoevenagel condensation [26] between aldehydes and an active methylene compound *i.e.*, barbituric acid.

In the present study, fifteen (15) derivatives **1-15** have been synthesized from commercially available barbituric acid by condensing with different aldehydes in water using bismuth chloride ($BiCl_3$) as catalyst at room temperature. In all cases, solid products were formed which were filtered, washed with cold water and ether followed by drying under vacuum. Mechanism involves (Fig. 1) a net dehydration of alcoholic intermediate obtained by nucleophilic attack of active methylene to carbonyl of aldehyde. The acidic nature of bismuth chloride helps to dissociate barbituric acid to generate nucleophilic specie which is capable of attacking on electrophilic carbon of aldehydes. Therefore bismuth chloride acts as an enolization activator, a mildly acidic in aqueous media, which has not only reduced the reaction time but also reaction proceeded at room temperature. All the reactions were completed within 30 min yielding excellent quantities of the products (Scheme 1).

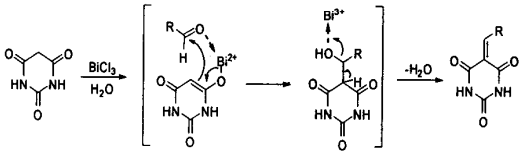
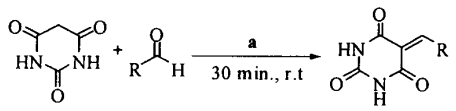


Fig. 1: Plausible mechanism of $BiCl_3$ mediated Knoevenagel condensation.

Conclusively, bismuth chloride ($BiCl_3$) is environmentally benign and its use in organic reactions with water makes it more compatible. Low cost is another advantage which makes the methodology extremely useful for the synthetic chemist for the synthesis of such an important class of compounds in very high yields. Products isolation is easy and clean, no solvent/solvent extraction is involved while products are obtained in pure forms exclusively. This improved methodology may directly be adopted by industry.



**a**: $BiCl_3$ (0.5 mol % to 1 mol %) **1-15**

**1**: R = 4-F-$C_6H_4$-
**2**: R = 4-$NO_2$-$C_6H_4$-
**3**: R = 3, 4-*di*-OH-$C_6H_3$-
**4**: R = 3-$NO_2$-$C_6H_4$-
**5**: R = 4-$CH_3S$-$C_6H_4$-
**6**: R = 4-Cl-$C_6H_4$-
**7**: R = 4-$NO_2$-$C_6H_4$-
**8**: R = 3-$C_2H_5O$, 5-OH-$C_6H_3$-
**9**: R = 2,3,4-*tri*-OH-$C_6H_2$-
**10**: R = 4-$C_6H_5$-$C_6H_4$-
**11**: R = 4-$(CH_3)_2N$-$C_6H_5$-
**12**: R = 3,4-*di*-$CH_3O$-$C_6H_3$-
**13**: R = 3-F-$C_6H_5$-
**14**: R = 3,4,5-*tri*-OH-$C_6H_2$-
**15**: R = 2-F-$C_6H_4$-

Scheme 1: Synthesis of arylidene barbiturates by $BiCl_3$.

## Experimental

EI mass spectra were measured with various MAT 711 (70 eV) spectrometers and data are tabulated as *m/z*. $^1$H-NMR spectra were recorded in DMSO-$d_6$ using Bruker AC400 (400 MHz) spectrophotometers, respectively. Splitting patterns were as follows; s, singlet; d, doublet; dd, double

doublets; t, triplet; m, multiplet. Chemical shifts are reported in δ (ppm) and coupling constants (*J*) are given in Hz. The progress of all reactions was monitored by TLC, which was performed on 2.0 X 5.0 cm aluminum sheets pre-coated with silica gel $60F_{254}$ to a thickness of 0.25 mm (Merck). The chromatograms were visualized under ultraviolet light (254-366 nm) or iodine vapors. Elemental analysis was performed on a Carlo Erba 1106 elemental analyzer. The title compounds were synthesized and characterized satisfactorily.

*General Procedure for the Synthesis of 5-arylidene Barbiturates 1-15*

In the newly developed methodology, $BiCl_3$ in 10 mL water was added to a stirred mixture of barbituric acid (0.2 g, 1.56 mmol) and corresponding aldehyde (1.56 mmol, 1 eq.). Reaction mixture was stirred at room temperature for 30 min as the TLC showed complete disappearance of aldehydes. In all cases, solid product was formed which was filtered and solid washed with cold water and ether followed by drying under vacuum.

*5-(4-Fluorobenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **1**

Yield: 1.15 g (98%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.39 (s, 1H, N-H), 11.25 (s, 1H, N-H), 8.25 (s, 1H, *vin.* H), 8.2 (dd, 2H, *J* = 8.8, 5.9 Hz, Ar-H), 7.31 (br. t, 2H, *J* = 8.8 Hz, Ar-H); EIMS *m/z* (% rel. abund.): 234 ($M^+$, 70), 233 (100), 215 (3.2), 190 (63.47), 162 (2.5), 147 (42), 120 (85.9), 95 (7.2). Anal. calcd. for $C_{11}H_7FN_2O_3$: C, 56.42; H, 3.01; N, 11.96; Found: C, 56.39; H, 3.08; N, 11.98.

*5-(4-Nitrobenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **2**

Yield: 0.95 g (91%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.48 (s, 1H, N-H), 11.31 (s, 1H, N-H), 8.31 (s, 1H, *vin.* H), 8.14 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.01 (d, 2H, *J* = 8.7 Hz, Ar-H); EIMS *m/z* (% rel. abund.): 261 ($M^+$, 92), 260 (40), 244 (93), 214 (70), 172 (25.7), 132 (12), 101 (51.4), 89 (100). Anal. calcd. for $C_{11}H_7N_3O_5$: C, 50.58; H, 2.70; N, 16.09; Found: C, 50.61; H, 2.67; N, 16.1.

*5-(3,4-Dihydroxybenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **3**

Yield: 1.5 g (94%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.19 (s, 1H, N-H), 11.06 (s, 1H, N-H), 10.36 (br. s, 1H, -OH), 9.44 (br. s, 1H, -OH), 8.17 (d, 1H, *J* = 2.1 Hz, Ar. H), 8.1 (s, 1H, *vin.* H), 7.6 (dd, 1H, *J* = 8.6, 2.1 Hz, Ar-H), 6.84 (d, 1H, *J* = 8.6 Hz, Ar-H); EIMS *m/z* (% rel. abund.): 248 ($M^+$, 100), 247 (40), 231 (11.8), 203 (31), 187 (14.3), 134 (21), 109 (5.5). Anal. calcd. for $C_{11}H_8N_2O_5$: C, 53.23; H, 3.25; N, 11.29; Found: C, 53.212; H, 3.26; N, 11.28.

*5-(3-Nitrobenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **4**

Yield: 1.3 g (96%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.47 (s, 1H, N-H), 11.33 (s, 1H, N-H), 8.9 (br. s, 1H, Ar. H), 8.52 (dd, 1H, *J* = 8.1, 2.3 Hz, Ar. H), 8.32 (s, 1H, *vin.* H), 7.9 (t, 2H, *J* = 8.0 Hz, Ar-H); EIMS *m/z* (% rel. abund.): 261 ($M^+$, 48.7), 260 (37.7), 216 (16.8), 214 (63.3), 172 (30.1), 116 (53), 101 (59.8), 89 (83.6) Anal. calcd. for $C_{11}H_7N_3O_5$. C, 50.58; H, 2.70; N, 16.09; Found: C, 50.57; H, 2.71; N, 16.08.

*5-[4-(Methylsulfanyl)benzylidene]-2,4,6(1H,3H,5H)-pyrimidinetrione* **5**

Yield: 0.93 g (89%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.32 (s, 1H, N-H), 11.2 (s, 1H, N-H), 8.21 (s, 1H, *vin.* H), 8.18 (d, 2H, *J* = 8.6, Ar. H), 7.33 (d, 2H, *J* = 8.6, Ar. H), 2.3 (s, 3H, -$SCH_3$); EIMS *m/z* (% rel. abund.): 262 ($M^+$, 100), 261 (21.3), 215 (8.6), 172 (38), 148 (14.2), 133 (21.13), 89 (46.7). Anal. calcd. for $C_{12}H_{10}N_2O_3S$. C, 54.95; H, 3.84; N, 10.68; Found: C, 54.96; H, 3.83; N, 10.67.

*5-(4-Chlorobenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **6**

Yield: 1.3 g (85%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.38 (s, 1H, N-H), 11.23 (s, 1H, N-H), 8.23 (s, 1H, *vin.* H), 8.06 (d, 2H, *J* = 8.6, Ar. H), 7.52 (d, 2H, *J* = 8.6, Ar. H); EIMS *m/z* (% rel. abund.): 250 ($M^+$, 70.8), 249 (100), 206 (58.6), 172 (35.2), 136 (52.5), 101 (38.7), 75 (42.7). Anal. calcd. for $C_{11}H_7ClN_2O_3$. C, 52.71; H, 2.82; N, 11.18; Found: C, 52.72; H, 2.83; N, 11.17.

*5-(3-Chlorobenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **7**

Yield: 1.37 g (95%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.41 (s, 1H, N-H), 11.25 (s, 1H, N-H), 8.22 (s, 1H, *vin.* H), 8.16 (br. s, 1H, Ar. H), 7.84 (d, 1H, *J* = 7.7 Hz, Ar. H), 7.55 (d, 1H, *J* = 8.3 Hz, Ar. H), 7.47 (br. t, 1H, *J* = 8.0 Hz, Ar. H); EIMS *m/z* (%

rel. abund.): 250 ($M^+$, 99.7), 249 (100), 206 (67.6), 172 (60.2), 136 (70.7), 101 (61.7), 75 (77.2) Anal. calcd. for $C_{11}H_7ClN_2O_3$. C, 52.71; H, 2.82; N, 11.18; Found: C, 52.73; H, 2.84; N, 11.19.

*5-(3-Hydroxy-5-methoxybenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **8**

Yield: 1.1 g (92%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.21 (s, 1H, N-H), 11.1 (s, 1H, N-H), 8.47 (br. s, 1H, Ar. H), 8.22 (s, 1H, *vin.* H), 7.74 (d, 1H, J = 1.9 Hz, Ar. H), 7.72 (d, 1H, *J* = 1.9 Hz, Ar. H), 4.07 (q, 2H, *J* = 14.0, 6.9 Hz, -$OCH_2CH_3$), 1.35 (t, 3H, *J* = 6.9 Hz, -$OCH_2CH_3$); EIMS *m/z* (% rel. abund.): 276 ($M^+$, 100), 275 (2.5), 247 (67.1), 204 (25.6), 188 (18.6), 161 (15.6), 134 (21.3), 105 (17). Anal. calcd. for $C_{12}H_{10}N_2O_5$. C, 54.97; H, 3.84; N, 10.68; Found: C, 54.98; H, 3.83; N, 10.68.

*5-(2,3,4-Trimethoxybenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **9**

Yield: 1.15 g (95%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.29 (s, 1H, N-H), 11.13 (s, 1H, N-H), 8.47 (s, 1H, *vin.* H), 8.3 (d, 1H, *J* = 9.1 Hz, Ar. H), 6.91 (d, 1H, *J* = 9.1 Hz, Ar. H), 3.89 (s, 3H, -$OCH_3$), 3.87 (s, 3H, -$OCH_3$), 3.75 (s, 3H, -$OCH_3$); EIMS *m/z* (% rel. abund.): 306 ($M^+$, 20.4), 275 (100), 232 (47.5), 189 (3), 162 (8.5), 134 (9.3), 106 (6.1). Anal. calcd. for $C_{14}H_{14}N_2O_6$. C, 54.90; H, 4.61; N, 9.15 Found: C, 54.91; H, 4.61; N, 9.16.

*5-([1,1'-Biphenyl]-4-ylmethylene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **10**

Yield: 0.95 g (85%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.39 (s, 1H, N-H), 11.25 (s, 1H, N-H), 8.31 (s, 1H, *vin.* H), 8.23 (d, 2H, *J* = 8.5 Hz, Ar. H), 7.8 (d, 2H, *J* = 8.5 Hz, Ar. H), 7.7 (d, 2H, *J* = 7.2 Hz, Ar. H), 7.5 (br. t, 1H, *J* = 7.2 Hz, Ar. H), 7.43 (d, 2H, *J* = 7.2 Hz, Ar. H); EIMS *m/z* (% rel. abund.): 292 ($M^+$, 100), 291 (53.2), 248 (48.5), 215 (40.8), 165 (30), 139 (8.3), 102 (10.7), 76 (28.5). Anal. calcd. for $C_{17}H_{12}N_2O_3$. C, 69.86; H, 4.14; N, 9.58;Found: C, 69.87; H, 4.15; N, 9.59.

*5-[4-(dimethylamino)benzylidene]-2,4,6(1H,3H,5H)-pyrimidinetrione* **11**

Yield: 0.97 g (82%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.04 (s, 1H, N-H), 10.9 (s, 1H, N-H), 8.42 (d, 2H, *J* = 9.2 Hz, Ar. H), 8.14 (s, 1H, *vin.* H), 6.78 (d, 2H, *J* = 9.2 Hz, Ar. H), 3.11 (s, 6H, -$N(CH_3)_2$); EIMS *m/z* (% rel. abund.): 259 ($M^+$, 100), 258 (57), 215 (15), 172 (13.2), 144 (23), 101 (8.6), 77 (6.5). Anal. calcd. for $C_{13}H_{13}N_3O_3$. C, 60.22; H, 5.05; N, 16.21 Found: C, 60.23; H, 5.07; N, 16.22.

*5-(3,4-dimethoxybenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **12**

Yield: 0.85 g (81%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.3 (s, 1H, N-H), 11.2 (s, 1H, N-H), 8.39 (d, 1H, J = 1.9 Hz, Ar. H), 8.24 (s, 1H, *vin.* H), 7.89 (dd, 1H, *J* = 8.6, 1.9 Hz, Ar. H), 7.1 (d, 1H, *J* = 8.6 Hz, Ar. H), 3.87 (s, 3H, -$OCH_3$), 3.79 (s, 3H, -$OCH_3$); EIMS *m/z* (% rel. abund.): 276 ($M^+$, 100), 275 (13.2), 232 (6.1), 190 (23.2), 147 (13.2), 119 (23.5), 76 (38). Anal. calcd. for $C_{13}H_{12}N_2O_5$. : C, 56.52; H, 4.38; N, 10.14;Found: C, 56.53; H, 4.39; N, 10.16.

*5-(3-Fluorobenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **13**

Yield: 0.91 g (89%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.43 (s, 1H, N-H), 11.28 (s, 1H, N-H), 8.23 (s, 1H, *vin.* H), 8.16 (br. s, 1H, Ar. H), 7.84 (d, 1H, *J* = 7.7 Hz, Ar. H), 7.55 (d, 1H, *J* = 8.2 Hz, Ar. H), 7.47 (br. t, 1H, *J* = 8.1 Hz, Ar. H); EIMS *m/z* (% rel. abund.): 234 ($M^+$, 90.8), 233 (99.1), 215 (8.6), 190 (69), 147 (44), 120 (100), 94 (30.7). Anal. calcd. for $C_{11}H_7FN_2O_3$: C, 56.42; H, 3.01; N, 11.96; Found: C, 56.40; H, 3.04; N, 11.99.

*5-(3,4,5-Trihydroxybenzylidene)-2,4,6(1H,3H,5H)-pyrimidinetrione* **14**

Yield: 0.91 g (93%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.19 (s, 1H, N-H), 11.06 (s, 1H, N-H), 10.36 (br. s, 1H, -OH), 9.44 (br. s, 1H, -OH), 9.35 (br. s, 1H, -OH), 8.17 (d, 1H, *J* = 2.1 Hz, Ar. H), 8.1 (s, 1H, *vin.* H), 7.91 (d, 1H, *J* = 2.1 Hz, Ar-H); EIMS *m/z* (% rel. abund.): 265 ($M^+$, 100), 264 (40), 248 (11.8), 220 (31), 187 (14.3), 134 (21), 109 (5.5). Anal. calcd. for $C_{14}H_{14}N_2O_6$. C, 54.90; H, 4.61; N, 9.15 Found: C, 54.91; H, 4.62; N, 9.15.

*5-(2-Fluorobenzylidene)-2,4,6(1H.3H,5H)-pyrimidinetrione* **15**

Yield: 1.15 g (94%); $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 11.39 (s, 1H, N-H), 11.25 (s, 1H, N-H), 8.25 (s, 1H, *vin.* H), 8.2 (dd, 2H, *J* = 8.8, 5.9 Hz, Ar-

H), 7.31 (br. t, 2H, $J$ = 8.8 Hz, Ar-H); EIMS *m/z* (% rel. abund.): 234 ($M^+$, 70), 233 (100), 215 (3.2), 190 (63.47), 162 (2.5), 147 (42), 120 (85.9), 95 (7.2). Anal. calcd. for $C_{11}H_7FN_2O_3$: C, 56.42; H, 3.01; N, 11.96; Found: C, 56.38; H, 3.02; N, 11.95.

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