NH_4Cl Mediated New Protocol for the Synthesis of 5-Arylidene Barbiturates

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Abstract: Eco-benign method for synthesizing arylidene barbiturates has been developed by using ammonium chloride (NH_4Cl) in stoichiometric amount, as an enolization activator, in water. Execution of methodology is simple, products obtained in high yields and the reactions are completed within 30 min. The new methodology does not involve any solvent/solvent extraction while solid products were yielded in all cases which were filtered and washed.

Keywords: Barbituric acid, ammonium chloride, enolization activator, eco-friendly.

Dedicated to Professor Dr. Muhammad Iqbal Choudhary, Director, International Center for Chemical and Biological Sciences, University of Karachi, Pakistan, on the occasion of his 50th birthday.

INTRODUCTION

Medicinal chemists have paid attention towards barbituric acids and their analogs for over 100 years due to their therapeutic values [1]. The first scientific data on barbiturates were published in 1903 [2]. One of the important members of pyrimidine family is 5-arylidene barbiturates. The major importance of this class of compounds has been focusing on their application as useful precursors in the preparation of new heterocyclic compounds [3] and as selective oxidizing agents [4-6]. 5-Benzylidene barbiturate derivatives show inhibitory effects on mushroom tyrosinase and their antibacterial activities [7]. Medicinal use of barbiturates in neurological disorders has also been investigated [8]. Barbiturate may be synthesized by Knovenagel reaction of barbituric acid with different aldehydes [9]. We very recently reported an improved version of Knovenagel reaction of barbituric acid with different aldehydes in the presence of bismuth chloride [10]. Condensation between *N*-alkyl-*N′*-aryl carbodiimides and malonic acid monoesters leads to barbiturate in the presence of base [11]. Optically active *N*-alkylated barbiturates were synthesized from disubstituted cyanoacetates [12] and 5-(cyclohexylmethyl) barbituric acid derivatives [13].

5-Arylidene barbiturates are generally prepared by condensation of barbituric/thiobarbituric acid with various aldehydes on refluxing in water by using acetic acid as catalyst [14]. Villemein *et al.* reported the synthesis of barbiturates in the presence of montmorillonite KSF clay under microwave irradiation [15]. Dewan has reported various catalysts like NH_4OAc/AcOH, montmorillonite K-10, silica gel, basic alumina, NaCl, montmorillonite KSF, and KSF/NaCl for the synthesis of 5-arylidene barbiturates [16]. Grinding method has also been employed for the synthesis of arylidene barbiturates [17]. These condensation reactions have also been reported in water only or without solvents using $BiCl_3$ [18, 19].

Synthesis of eco-benign version of biologically active compounds is well known [20]. At the beginning of the 21st century, green chemistry approaches held out noteworthy potential not only to diminish the byproducts, a marked reduction in waste production and lowering of energy costs but also in the advancement of new methodologies towards previously unfeasible materials using existing technologies [21].

Previously reported methods using water without any catalyst were unfortunately not working in our hands, therefore we had used NH_4Cl as a catalyst [22, 23]. In any case this will be one of the new methods for synthesizing these types of compounds. In this communication, we wish to report a convenient method for the synthesis of 5-arylidene barbiturates in water using ammonium chloride (NH_4Cl) as catalyst.

RESULTS AND DISCUSSION

During the drug design and discovery program of our research group, we investigated a variety of heterocyclic compounds to disclose their biological potential [24]. In the present study, fifteen (15) arylidine barbiturates **1-15** have been synthesized from commercially available barbituric acid by condensing with different aldehydes using ammonium chloride (NH_4Cl) in stoichiometric amount, as an enolization activator, in water. In all cases, solid products were formed which were filtered, washed with cold water

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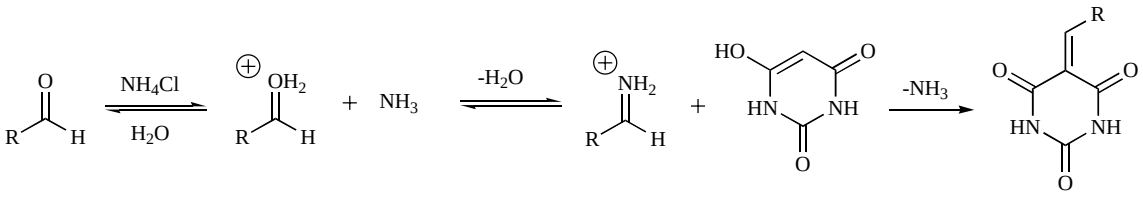
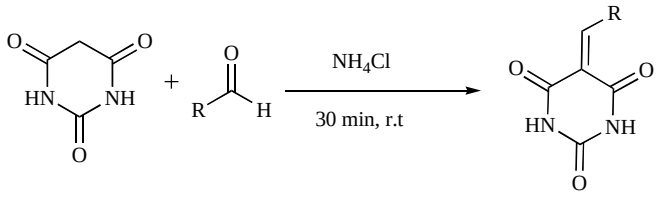
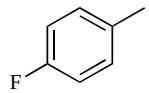
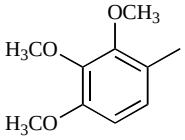
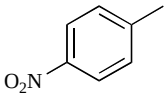
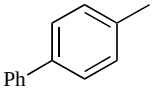
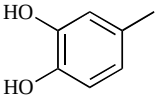
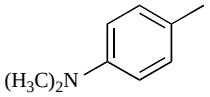
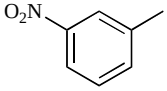
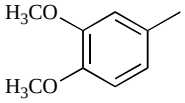
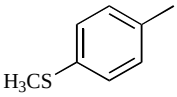
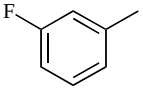
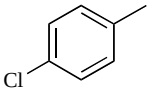
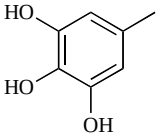
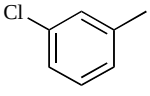
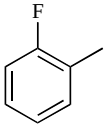
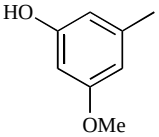


Fig. (1). Proposed mechanism of arylidene barbiturates *via* iminium ion formation.

and ether followed by drying under vacuum. Mechanism involved a net dehydration *via* aldol intermediate obtained by nucleophilic attack of active methylene at aldehyde carbonyl. The acidic nature of ammonium chloride helps to dissociate barbituric acid to generate nucleophilic specie which is capable of attacking on electrophilic carbon of aldehydes. Therefore, ammonium chloride (NH_4Cl), a mildly acidic in aqueous media acts as an enolization activator,



1-15

S. No.	R-	Yield (%)	S. No.	R-	Yield (%)
1		98	9		95
2		91	10		85
3		94	11		82
4		96	12		81
5		89	13		89
6		85	14		93
7		95	15		94
8		92	-	-	-

Scheme 1. Synthesis of arylidene barbiturates **1-15** by using NH_4Cl.

which not only speeds up the reaction but also the reaction proceeded at room temperature. There is another plausible mechanism which may be predicted by assuming the formation of iminium ion through the reaction of aldehyde and ammonia (Fig. **1**). In the next step, the intermediate iminium ion is attacked by enol barbituric acid to form transitory aldol specie, which is later on converted to final adduct by dehydration. All the reactions were completed within 30 min in excellent yields (Scheme **1**).

To generalize our method, we have used a variety of aldehydes with different functional groups for this condensation and found that the method is valid for all types of species and obtained high yields. The immiscibility of aldehydes in water does not affect the progress of reaction and yields of products in all cases.

Hence, ammonium chloride (NH_4Cl) is environmentally benign and its use in organic reactions with water enhances its compatibility. 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 excellent yields. Product isolation is easy and clean, no solvent/solvent extraction is required while products are obtained in pure forms.

EXPERIMENTAL GENERAL

EI mass spectra were recorded 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 Avance AC400 (400 MHz) spectrometer, 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 are given in Hz. Elemental analysis was performed on a Carlo Erba 1106 elemental analyzer. 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 by iodine vapors. The compounds **1-15** were synthesized and characterized satisfactorily.

General Procedure for the Synthesis of 5-Arylidene Barbiturates 1-15

Ammonium chloride (1.56 mmol, 1 eq) was dissolved in cold distilled water (10 mL) followed by the addition of barbituric acid (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 starting aldehyde. In all cases, solid product was formed which was filtered and solid was 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, NH), 11.25 (s, 1H, NH), 8.25 (s, 1H, Vin.-H), 8.2 (dd, 2H, *J* = 8.8, 5.8 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 $C_{11}H_7FN_2O_3$ (234.18): C, 56.42; H, 3.01; F, 8.11; N, 11.96; O, 20.50; Found: C, 56.35; H, 3.06; N, 11.89.

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, NH), 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 $C_{11}H_7N_3O_5$ (261.19): C, 50.58; H, 2.70; N, 16.09; O, 30.63; Found: C, 50.51; H, 2.78; N, 16.14.

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, NH), 11.06 (s, 1H, NH), 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 $C_{11}H_8N_2O_5$ (248.19): C, 53.23; H, 3.25; N, 11.29; O, 32.23; Found: C, 53.30; H, 3.18; N, 11.24.

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, NH), 11.33 (s, 1H, NH), 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 $C_{11}H_7N_3O_5$ (261.19): C, 50.58; H, 2.70; N, 16.09; O, 30.63; Found: C, 50.65; H, 2.63; N, 16.04.

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, NH), 11.2 (s, 1H, NH), 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 $C_{12}H_{10}N_2O_3S$ (262.28): C, 54.95; H, 3.84; N, 10.68; O, 18.30; S, 12.23; Found: C, 54.85; H, 3.89; N, 10.72.

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, NH), 11.23 (s, 1H, NH), 8.23 (s, 1H, Vin.-H), 8.06 (d, 2H, *J* = 8.55, Ar-H), 7.52 (d, 2H, *J* = 8.55, 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 $C_{11}H_7ClN_2O_3$ (250.64): C, 52.71; H, 2.82; Cl, 14.15; N, 11.18; O, 19.15; Found: C, 52.64; H, 2.91; N, 11.19.

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, NH), 11.25 (s, 1H, NH), 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* = 8.27 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 $C_{11}H_7ClN_2O_3$ (250.64): C, 52.71; H, 2.82; Cl, 14.15; N, 11.18; O, 19.15; Found: C, 52.73; H, 2.80; N, 11.16.

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, NH), 11.1 (s, 1H, NH), 8.47 (br. s, 1H, Ar-H), 8.22 (s, 1H, Vin.-H), 7.74 (d, 1H, *J* = 1.8 Hz, Ar-H), 7.72 (d, 1H, *J* = 1.8 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 $C_{12}H_{10}N_2O_5$ (262.22): C, 54.97; H, 3.84; N, 10.68; O, 30.51; Found: C, 54.95; H, 3.86; N, 10.63.

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, NH), 11.13 (s, 1H, NH), 8.47 (s, 1H, Vin.-H), 8.3 (d, 1H, *J* = 9.1 Hz, Ar-H), 6.91 (d, 1H, *J* = 9.2 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 $C_{14}H_{14}N_2O_6$ (306.27): C, 54.90; H, 4.61; N, 9.15; O, 31.34; Found: C, 54.88; H, 4.63; N, 9.13.

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, NH), 11.25 (s, 1H, NH), 8.31 (s, 1H, Vin.-H), 8.23 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.8 (d, 2H, *J* = 8.4 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 $C_{17}H_{12}N_2O_3$ (292.29): C, 69.86; H, 4.14; N, 9.58; O, 16.42; Found: C, 69.83; H, 4.17; N, 9.55.

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, NH), 10.9 (s, 1H, NH), 8.42 (d, 2H, *J* = 9.24 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 $C_{13}H_{13}N_3O_3$ (259.26): C, 60.22; H, 5.05; N, 16.21; O, 18.51; Found: C, 60.23; H, 5.09; N, 16.17.

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, NH), 11.2 (s, 1H, NH), 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 $C_{13}H_{12}N_2O_5$ (276.24): C, 56.52; H, 4.38; N, 10.14; O, 28.96; Found: C, 56.49; H, 4.40; N, 10.11.

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, NH), 11.28 (s, 1H, NH), 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* = 8.14 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 $C_{11}H_7FN_2O_3$ (234.18): C, 56.42; H, 3.01; F, 8.11; N, 11.96; O, 20.50; Found: C, 56.39; H, 2.99; N, 11.98.

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, NH), 11.06 (s, 1H, NH), 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 $C_{11}H_8N_2O_6$ (264.19): C, 50.01; H, 3.05; N, 10.60; O, 36.34; Found: C, 49.97; H, 2.98; N, 10.65.

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, NH), 8.25 (s, 1H, Vin.-H), 8.2 (dd, 2H, *J* = 8.8, 5.85 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 $C_{11}H_7FN_2O_3$ (234.18): C, 56.42; H, 3.01; F, 8.11; N, 11.96; O, 20.50; Found: C, 56.43; H, 2.99; N, 11.97.

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