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Rapid and efficient synthesis of fused heterocyclic pyrimidines under ultrasonic irradiation

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ABSTRACT

Some fused heterocyclic pyrimidines have been synthesized in high yields using ultrasound irradiation in a one-pot, three-component and efficient process by condensation reaction of barbituric acids, aldehydes and a series of enamines in water. Prominent among the advantages of this new method are operational simplicity, good yields in short reaction times and easy work-up procedures employed.

1. Introduction

Recently published comprehensive books [1] and papers [2] indicate chemical applications of ultrasounds. "Sonochemistry", is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in high yields, short reaction times and mild conditions [1–3].

Heterocycles containing a pyrimidine moiety are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [4]. Furthermore, the pyrimidopyrimidines are an important class of annelated uracils with biological significance because of their connection with purine pteridine system [5]. Numerous reports delineate the antitumor [6], antiviral [7], and antioxidant [8] activity of these compounds. In addition, some pyrimidine fused heterocyclic systems like furo [9], pyrazolo [10], pyrrolo [11], pyridopyrazolo [12], and pyrazolotriazolo [13] pyrimidine have long been important to the pharmaceutical industry. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of amino-uracils or amino-pyrazoles. As result, a number of reports have appeared in literature, which usually requires forcing conditions, long reaction times, and complex synthetic pathway [14]. Thus new routes for the synthesis of pyrimidine fused heterocyclic systems have attracted considerable attention in search for a rapid entry to these heterocycles.

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules [15], reactions that provide maximum diversity are especially desirable. Here, expeditious domino [16], and multicomponent reactions (MCRs) [17] have emerged as powerful strategies. MCRs are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step.

Considering the above reports we wish to report a one-pot, three-component condensation reaction of barbituric acids **1a–c**, aldehydes **2a–f** and amino-uracils (**3a,b**) for the synthesis of some fused heterocyclic pyrimidines in water under ultrasonic irradiation (Scheme 1). In fact, as clearly stated by Sheldon, it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water" [18].

2. Experimental

2.1. Chemicals and apparatus

The chemical used in this work were obtained from Fluka and Merck, and amino-uracil was from Merck. 1,3-Diphenyl-1*H*-pyrazol-5-amine was prepared according to the literature procedure [19]. Melting points were measured on an Electrothermal 9200

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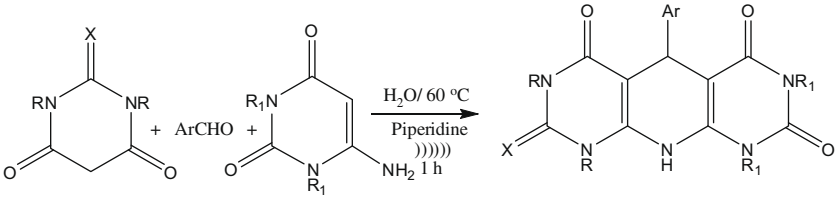


Scheme 1.

apparatus. IR spectra were recorded on a FT-IR 102 MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6 using TMS. Ultrasonication was performed in a EUROSONIC® 4D ultrasound cleaner with a frequency of 50 kHz and an output power of 350 W. The reactions were performed in open vessels.

2.2. General procedure

A mixture of barbituric acid (1 mmol), aromatic aldehyde (1 mmol), enamine (1 mmol), and piperidine (0.5 mmol) in water (5 mL) was sonicated at 60 °C for 1 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature. The solid was collected by filtration and washed with ethanol (10 mL) to afford the pure product.

2.2.1. 1,3-Dimethyl-5-phenyl-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4a**)

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3320, 1715, 1685; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.40 (3H, s, CH_3), 4.72 (1H, s, CH), 7.12–7.29 (5H, m, H–Ar), 8.90 (1H, s, NH), 10.09 (1H, s, NH), 10.81 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 28.0, 30.2, 34.8, 90.4, 90.9, 126.0, 128.2, 143.4, 146.8, 149.9, 150.7, 160.0, 162.6. MS (*m/z*): 353 (M^+). Anal. Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82%. Found: C, 57.85; H, 4.32; N, 19.75%.

2.2.2. 1,3-Dimethyl-5-(4-chlorophenyl)-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4b**)

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3389, 3188, 1698; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 3.30 (3H, s, CH_3), 4.79 (1H, s, CH), 7.09–7.30 (4H, m, H–Ar), 8.90 (1H, s, NH), 10.10 (H, s, NH), 10.88 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 28.3, 30.9, 34.0, 91.0, 91.9, 127.5, 128.7, 142.6, 147.2, 148.8, 152.7, 161.4, 162.9. MS (*m/z*): 387 (M^+). Anal. Calcd. for $C_{17}H_{14}ClN_5O_4$: C, 52.65; H, 3.64; N, 18.06%. Found: C, 52.60; H, 3.60; N, 18.13%.

2.2.3. 1,3-Dimethyl-5-(4-nitrophenyl)-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4c**)

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3360, 1688; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.08 (3H, s, CH_3), 3.45 (3H, s, CH_3), 4.91 (1H, s, CH), 7.54 (2H, d, $^3J_{HH}$ = 9.0 Hz, H–Ar), 8.06 (2H, d, $^3J_{HH}$ = 8.9 Hz, H–Ar), 9.01 (1H, s, NH), 10.09 (1H, s, NH), 10.90 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 28.0, 30.0, 35.2, 88.5, 89.0, 123.1, 128.3, 129.4, 146.4, 149.4, 150.9, 153.8, 154.5, 160.9, 162.0. MS (*m/z*): 398 (M^+). Anal. Calcd. for $C_{17}H_{14}N_6O_6$: C, 51.26; H, 3.54; N, 21.10%. Found: C, 51.29; H, 3.50; N, 21.05%.

2.2.4. 1,3-Dimethyl-5-(4-methylphenyl)-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7. H)-tetraone (**4d**)

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3260, 3145, 1700, 1670; ^{1}H NMR (300 MHz, DMSO-d_6 δ_H (ppm) 2.31 (3H, s, CH_3), 3.05 (3H, s, CH_3), 3.40 (3H, s, CH_3), 4.72 (1H, s, CH), 6.69–7.09 (4H, m, H–Ar), 8.94 (1H, s, NH), 10.08 (1H, bs, NH), 10.93 (1H, s, NH) ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 21.1, 28.3, 29.8, 34.1, 90.1, 90.3, 114.4, 120.5, 129.0, 143.1, 146.2, 148.9, 151.0, 159.6, 161.0, 162.6. MS (*m/z*): 367. Anal. Calcd. for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06%. Found: C, 58.89; H, 4.60; N, 19.0%.

Solubility of the products **4e–j** is very low and we can not report the ^{13}C NMR data for these products.

2.2.5. 5-Phenyl-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4e**)

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3225, 3080, 1698, 1660. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.70 (1H, s, CH), 7.02–7.21 (5H, m, H–Ar), 9.97 (2H, s, 2NH), 10.90 (2H, s, 2NH). MS (*m/z*): 326 (M^++1). Anal. Calcd. for $C_{15}H_{11}N_5O_4$: C, 55.39; H, 3.41, N, 21.53%. Found: C, 55.44; H, 3.37; N, 21.46%.

2.2.6. 5-(4-Chlorophenyl)-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4f**)

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3261, 3200, 3012, 1711, 1700, 1685. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.60 (1H, s, CH), 7.23–7.30 (4H, m, H–Ar), 10.80 (2H, s, 2NH), 11.12 (2H, s, 2NH). MS (*m/z*): 360 (M^++1). Anal. Calcd. for $C_{15}H_{10}ClN_5O_4$: C, 50.08; H, 2.80; N, 19.47%. Found: C, 50.13; H, 2.74; N, 19.53%.

2.2.7. 5-(Thiophen-2-yl)-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4g**)

Brown powder; 168 °C dec.; IR (KBr) (ν_{max}, cm^{-1}): 3320, 3165, 3056,1732, 1676, 1655. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.91 (1H, s, CH), 7.50 (1H, m, thienyl), 7.98 (1H, d, $^3J_{HH}$ = 4.3 Hz, thienyl), 8.08 (1H, d, $^3J_{HH}$ = 4.1 Hz, thienyl), 9.99 (2H, s, 2NH), 10.95 (2H, s, 2NH). MS (*m/z*): 331 (M^+). Anal. Calcd. for $C_{13}H_9N_5O_4S$: C, 47.13; H, 2.74, N, 21.14%. Found: C, 47.19; H, 2.70; N, 21.08%.

2.2.8. 5-(Furyl-2-yl)-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6,8(1H,3H,5H,7H)-tetraone (**4h**)

Red powder; 160 °C dec.; IR (KBr) (ν_{max}, cm^{-1}): 3332, 3175, 3076, 1728, 1698, 1659. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.98 (1H, s, CH), 7.53 (1H, m, furyl), 7.97 (1H, d, $^3J_{HH}$ = 4.1 Hz, furyl), 8.18 (1H, d, $^3J_{HH}$ = 4.2 Hz, furyl), 10.02 (2H, s, 2NH), 10.97 (2H, s, 2NH). MS (*m/z*): 315 (M^+). Anal. Calcd. for $C_{13}H_9N_5O_5$: C, 49.53; H, 2.88, N, 22.22%. Found: C, 49.45; H, 2.82; N, 22.31%.

2.2.9. 5-Phenyl-8-thioxo-9,10-dihydropyrido[2,3-d:6,5-d]dipyrimidine-2,4,6(1H,3H,5H,7H)-trione (**4i**)

Yellow powder; m.p. > 300 °C. IR (KBr) (ν_{max}, cm^{-1}): 3270, 3065, 1696, 1678. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 4.78 (1H, s, CH),

7.13–7.19 (5H, m, H–Ar), 9.06 (1H, s, NH), 9.72 (1H, s, NH), 10.78 (1H, s, NH), 12.40 (1H, s, NH). MS (*m/z*): 341 (M^+). Anal. Calcd. for $C_{15}H_{11}N_5O_3S$: C, 52.78; H, 3.25; N, 20.52%. Found: C, 52.82; H, 3.20; N, 20.59%.

*2.2.10. 5-(4-Chlorophenyl)-8-thioxo-9,10-dihydropyrido[2,3-d:6,5-d]-dipyrimidine-2,4,6(1H,3H,5H,7H)-trione (**4j**)*

Yellow powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3255, 3050, 1711, 1648. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 4.61 (1H, s, CH), 722–7.25 (4H, m, H–Ar), 9.01 (1H, s, NH), 9.73 (1H, s, NH), 10.72 (1H, s, NH), 11.70 (1H, s, NH). MS (*m/z*): 375 (M^+). Anal. Calcd. for $C_{15}H_{10}ClN_5O_3S$: C, 47.94; H, 2.68; N,18.64%. Found: C, 48.0; H, 2.71; N, 18.69%.

*2.2.11. 1,3-Dimethyl-5-phenyl-8-thioxo-9,10-dihydropyrido[2,3-d:6, 5-d]dipyrimidine-2,4,6(1H,3H,5H,7H)-trione (**4k**)*

Cream powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3234, 3178, 1698, 1689. ^1H NMR (300 MHz, DMSO-d_6): 3.07 (3H, s, CH_3), 3.40 (3H, s, CH_3), 4.67 (1H, s, CH), 7.10–7.28 (5H, m, H–Ar), 8.97 (1H, s, NH), 11.78 (1H, s, NH), 12.30 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.3, 30.0, 34.4, 89.7, 94.8, 125.8, 128.3, 128.7, 143.0, 144.6, 150.2, 160.1, 160.9, 172.6. MS (*m/z*): 369. Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96%. Found: C, 55.22; H, 4.05; N, 18.89%.

*2.2.12. 1,3-Dimethyl-5-(4-chlorophenyl)-8-thioxo-9,10-dihydro-pyrido[2,3-d:6,5-d]dipyrimidine-2,4,6(1H,3H, 5H,7H)-trione (**4l**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3240, 1697, 1662. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.08 (3H, s, CH_3), 3.41 (3H, s, CH_3), 4.76 (1H, s, CH), 7.20–7.27 (4H, m, H–Ar). 9.07 (1H, s, NH), 11.43 (1H, s, NH), 12.30 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.1, 30.4, 34.3, 89.9, 95.1, 125.9, 128.0, 128.6, 143.2, 144.5, 151.2, 162.1, 163.7, 172.8. MS (*m/z*): 404 (M^++1). Anal. Calcd. for $C_{17}H_{14}ClN_5O_3S$: C, 50.56; H, 3.49; N, 17.34%. Found: C, 50.50; H, 4.54; N, 17.26%.

*2.2.13. 8,8-Dimethyl-5-phenyl-7,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,5H)-trione (**6a**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3336, 1708, 1665. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.94 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.47 (2H, s, CH_2), 2.56 (2H, s, CH), 4.86 (1H, s, CH), 7.20–7.24 (5H, m, H–Ar). 8.91 (1H, s, NH), 10.08 (1H, s, NH), 10.82 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.6, 28.8, 32.3, 33.5, 39.9, 50.2, 96.3, 118.3, 125.5, 127.4, 129.3, 146.7, 148.4, 154.1, 160.2, 162.3, 192.7. MS (*m/z*): 337 (M^+). Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46%. Found: C, 67.69; H, 5.64; N, 12.40%.

*2.2.14. 5-(4-Chlorophenyl)-8,8-dimethyl-7,8,9,10-tetrahydro-pyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione (**6b**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3345, 1708, 1673. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.94 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.47 (2H, s, CH_2), 2.57 (2H, s, CH), 4.92 (1H, s, CH), 7.22–7.26 (4H, m, H–Ar). 8.93 (1H, s, NH), 10.07 (1H, s, NH), 10.84 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.7, 28.7, 32.4, 33.6, 39.8, 50.5, 96.4, 118.6, 127.5, 129.4, 130.3, 145.7, 148.4, 154.5, 160.3, 162.8, 192.7. MS (*m/z*): 371 (M^+). Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.38; H, 4.88; N, 11.30%. Found: C, 61.42; H, 4.92; N, 11.25%.

*2.2.15. 8,8-Dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]-quinoline-2,4,6(1H,3H,5H)-trione (**6c**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3340, 1699, 1670. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.44 (2H, s, CH_2), 2.56 (2H, s, CH), 4.87 (1H, s, CH), 7.22–7.25 (4H, m, H–Ar). 8.90 (1H, s, NH), 10.06 (1H, s, NH), 10.83 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.3, 26.4, 28.8, 32.3, 33.8, 39.4, 50.2, 96.7, 118.2, 125.1, 127.0, 129.1, 145.9, 148.5, 154.0, 160.0, 162.1, 192.1. MS (*m/z*): 351 (M^+). Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96%. Found: C, 68.30; H, 5.97; N, 11.89%.

*2.2.16. 1,3,8,8-Tetramethyl-5-phenyl-7,8,9,10-tetrahydro-pyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione (**6d**)*

White powder; m.p. 268 °C (dec.); IR (KBr) (ν_{max}, cm^{-1}): 3222, 1700, 1673, 1679. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.0 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.45 (2H, s, CH_2), 2.56 (2H, s, CH), 3.03 (3H, s, CH_3), 3.41 (3H, s, CH_3), 4.91 (1H, s, CH), 7.21–7.26 (5H, m, H–Ar). 8.93 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.6, 28.4, 28.8, 31.3, 32.2, 33.3, 39.7, 50.4, 96.0, 119.0, 125.2, 127.4, 129.0, 146.4, 148.0, 154.3, 160.1, 162.0, 192.5. MS (*m/z*): 365 (M^+). Anal. Calcd. for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50%. Found: C, 69.06; H, 6.29; N, 11.56%.

*2.2.17. 5-(4-Chlorophenyl)-1,3,8,8-tetramethyl-7,8,9,10-tetrahydro-pyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H)-trione (**6e**)*

White powder; m.p. 291 °C (dec.) (lit., [20] m.p. 292 °C); IR (KBr) (ν_{max}, cm^{-1}): 3330, 1703, 1691, 1688. ^1H NMR (300 MHz, DMSO-d_6): δ_H 1.03 (6H, s, $2CH_3$), 2.42 (2H, s, CH_2), 2.50 (2H, s, CH), 3.02 (3H, s, CH_3), 3.41 (3H, s, CH_3), 4.89 (1H, s, CH), 7.24–7.26 (4H, m, H–Ar). 8.98 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.4, 28.7, 28.9, 31.5, 32.1, 33.4, 39.9, 50.9, 96.9, 119.6, 127.4, 128.9, 129.1, 146.4, 148.2, 154.7, 160.2, 162.5, 192.2. MS (*m/z*): 399 (M^+). Anal. Calcd. for $C_{21}H_{22}ClN_3O_3$: C, 63.08; H, 5.55; N, 10.51%. Found: C, 63.02; H, 5.59; N, 10.59%.

*2.2.18. 8,8-Dimethyl-5-phenyl-2-thioxo-2,3,7,8,9,10-hexahydro-pyrimido[4,5-b]quinoline-4,6(1H,5H)-dione (**6f**)*

Cream powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3311, 3109, 1703, 1669. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (3H, s, CH_3), 1.04 (3H, s, CH_3), 2.46 (2H, s, CH_2), 2.56 (2H, s, CH), 4.89 (1H, s, CH), 7.24–7.28 (5H, m, H–Ar). 8.99 (1H, s, NH), 10.06 (1H, s, NH), 12.46 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.5, 28.7, 32.4, 33.6, 39.8, 50.7, 89.4, 119.0, 125.6, 127.6, 129.0, 146.6, 148.9, 154.3, 161.2, 169.8, 192.7. MS (*m/z*): 353 (M^+). Anal. Calcd. for $C_{19}H_{19}N_3O_2S$: C, 64.57; H, 5.42; N, 11.89%. Found: C, 64.51; H, 5.47; N, 11.80%.

*2.2.19. 5-(4-Chlorophenyl)-8,8-dimethyl-2-thioxo-2,3,7,8,9,10-hexa-hydropyrimido[4,5-b]quinoline-4,6(1H,5H)-dione (**6g**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3331, 3114, 1711, 1673, 1645. ^1H NMR (300 MHz, DMSO-d_6): δ_H 0.98 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.47 (2H, s, CH_2), 2.52 (2H, s, CH), 4.91 (1H, s, CH), 7.26–7.29 (4H, m, H–Ar). 8.98 (1H, s, NH), 10.09 (1H, s, NH), 12.53 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 26.6, 28.4, 32.8, 33.6, 39.7, 50.5, 89.1, 119.3, 126.6, 127.9, 129.4, 146.0, 148.7, 154.6, 161.5, 171.0, 192.8. MS (*m/z*): 387 (M^+). Anal. Calcd. for $C_{19}H_{18}ClN_3O_2S$: C, 58.83; H, 4.68; N, 10.83%. Found: C, 58.88; H, 4.64; N, 10.90%.

*2.2.20. 1,3,4-Triphenyl-4,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2, 3-d]pyrimidine-5,7(6H,8H)-dione (**8a**)*

White powder; m.p. 295 °C (dec.); IR (KBr) (ν_{max}, cm^{-1}): 3223, 3089, 1698, 1667^1H NMR (300 MHz, DMSO-d_6): δ_H 5.30 (1H, s, CH), 7.07–7.46 (15H, m, H–Ar), 9.11 (1H, s, NH), 10.01 (1H, s, NH), 10.78 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 35.1, 90.1, 102.3, 123.5, 126.0, 127.2, 128.6, 128.2, 130.1, 133.4, 136.9, 138.6, 145.5, 146.0, 147.9, 150.7, 163.8. MS (*m/z*): 433 (M^+). Anal. Calcd for $C_{26}H_{19}N_5O_2$: C, 72.04; H, 4.42; N, 16.16%. Found: C, 72.00; H, 4.36; N, 16.22%.

*2.2.21. 4-(4-Chlorophenyl)-1,3-diphenyl-4,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7. (6H,8H)-dione (**8b**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3234, 3089, 1704, 1639. ^1H NMR (300 MHz, DMSO-d_6): δ_H 5.31 (1H, s, CH), 7.14–7.67 (14H, m, H–Ar), 9.11 (1H, s, NH), 10.05 (1H, s, NH), 10.72 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 35.8, 89.7, 101.0, 123.1, 127.5, 128.1, 128.8, 128.2, 130.5, 131.4, 133.1, 137.4, 137.9, 145.2, 145.0, 147.2, 150.4, 163.7. MS (*m/z*): 467 (M^+). Anal. Calcd for $C_{26}H_{18}ClN_5O_2$: C, 66.74; H, 3.88; N, 14.97%. Found: C, 66.66; H, 3.84; N, 15.03%.

*2.2.22. 4-(4-Methylphenyl)-1,3-diphenyl-4,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7. (6H,8H)-dione (**8c**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3226, 3032, 1718, 1643. ^1H NMR (300 MHz, DMSO-d_6): δ_H 2.11 (3H, s, CH3), 5.30 (1H, s, CH), 704–7.70 (14H, m, H–Ar), 9.03 (1H, s, NH), 9.99 (1H, s, NH), 10.70 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.2, 35.6, 89.7, 102.0, 123.1, 127.4, 128.0, 128.1, 128.4, 128.7, 130.1, 133.7, 135.0, 137.8, 138.5, 143.2, 145.5, 147.4, 150.5, 163.1. MS (*m/z*): 447 (M^+). Anal. Calcd for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.73; N, 15.65%. Found: C, 72.52; H, 4.68; N, 15.60%.

*2.2.23. 5,8-Dimethyl-1,3,4-triphenyl-4,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7(6H,8H)-dione (**8d**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3210, 1714, 1632. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.01 (3H, s, CH3), 3.43 (3H, s, CH3), 5.31 (1H, s, CH), 7.11–7.77 (15H, m, H–Ar), 9.01 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.6, 31.4, 35.5, 90.5, 102.5, 123.6, 127.2, 128.0, 128.1, 128.9, 129.7, 130.6, 133.6, 135.2, 137.6, 138.0, 143.4, 145.1, 147.7, 150.3, 163.4. MS (*m/z*): 461 (M^+). Anal. Calcd. for $C_{28}H_{23}N_5O_2$: C, 72.87; H, 5.02; N, 15.17%. Found: C, 72.81; H, 5.06; N, 15.10%.

*2.2.24. 4-(4-Chlorophenyl)-5,8-dimethyl-1,3-diphenyl-4,9-dihydro-1H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-5,7(6H,8H)-dione (**8e**)*

White powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3231, 1721, 1631. ^1H NMR (300 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH3), 3.40 (3H, s, CH3), 5.34 (1H, s, CH), 7.16–7.79 (14H, m, H–Ar), 9.11 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 28.7, 31.4, 35.7, 90.0, 102.6, 123.9, 127.6, 128.3, 128.6, 128.9, 129.6, 130.5, 133.8, 135.0, 137.5, 138.1, 143.3, 145.4, 147.9, 150.8, 163.9. MS (*m/z*): 495 (M^+). Anal. Calcd. for $C_{28}H_{22}ClN_5O_2$: C, 67.81; H, 4.47; N, 14.12%. Found: C, 67.76; H, 4.51; N, 14.17%.

*2.2.25. 1,3,4-Triphenyl-5-thioxo-1,4,5,6,8,9-hexahydro-7H-pyrazolo-[4′,3′:5,6]pyrido[2,3-d]pyrimidine-7-dione (**8f**)*

Cream powder; m.p. 258 °C (dec.); IR (KBr) (ν_{max}, cm^{-1}): 3256, 3180, 1709, 1677. ^1H NMR (300 MHz, DMSO-d_6): δ_H 5.39 (1H, s, CH), 7.07–7.70 (15H, m, H–Ar), 9.21 (1H, s, NH), 10.17 (1H, s, NH), 10.77 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 35.9, 90.5, 102.7, 123.4, 127.2, 128.4, 128.6, 129.9, 130.2, 131.6, 133.8, 135.0, 137.2, 138.0, 143.1, 145.6, 147.7, 150.6, 163.3. MS (*m/z*): 449 (M^+). Anal. Calcd. for $C_{26}H_{19}N_5OS$: C, 69.47; H, 4.26; N, 15.58%. Found: C, 69.40; H, 4.33; N, 15.50%.

*2.2.26. 4-(4-Chlorophenyl)-1,3-diphenyl-5-thioxo-1,4,5,6,8,9-hexahydro-7H-pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-7-dione (**8g**)*

Cream powder; m.p. > 300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3250, 3171, 1700, 1667. ^1H NMR (300 MHz, DMSO-d_6): δ_H 5.34 (1H, s, CH), 7.16–7.76 (14H, m, H–Ar), 9.25 (1H, s, NH), 10.21 (1H, s, NH), 10.81 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 35.8, 91.0, 102.3, 123.8, 127.5, 128.3, 128.7, 129.3, 130.0, 131.9, 132.9, 135.2, 137.0, 138.4, 143.5, 145.9, 147.4, 150.1, 163.6. MS (*m/z*): 483 (M^+). Anal. Calcd. for $C_{26}H_{18}ClN_5OS$: C, 64.52; H, 3.75; N, 14.47%. Found: C, 64.56; H, 3.70; N, 14.53%.

3. Results and discussion

To achieve suitable conditions for the synthesis of fused heterocyclic pyrimidines, we investigated the reaction of barbituric acid **1a**, benzaldehyde **2a** and 6-amino-uracil **3a** in different conditions. In refluxing various solvent or under solvent-free conditions, the reaction was very slow and the yield of product was very low. We found that the best results were obtained in the presence of piperidine under ultrasound irradiation at 60 °C in water (Table 1). As indicated in Table 1, ultrasonic irradiation (Table 1, entry 6) relative to refluxing water (Table 1, entry 4) induces acceleration for reaction, the reaction time decreases from 6 h to 1 h. Also, under ultrasonic irradiation the yield of product is higher. In absence of piperidine under ultrasonic irradiation at 60 °C yield was found to be low even after 3 h (Table 1, entry 7). Table 1 demonstrates that water was the best choice of solvent and the use of ultrasound radiation in water improves the rate of the reaction and also the yield of the product. To study the effect of temperature on this synthesis, we also performed three experiments in 40, 50, and 60 °C under sonication (Table 1). It was observed that a lower reaction temperature leads to a lower yield.

To explore the scope and limitation of this reaction, we have extended the reaction of barbituric acids (**1a–c**) with a range of aromatic or heteroaromatic aldehydes (**2a–f**) and uracils (**3a,b**) under

Table 1
Conditions effect on reaction[a].

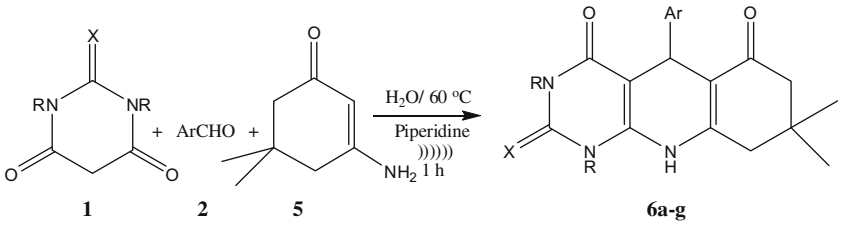
Entry	Conditions	Catalyst	Time (h)	Yields (%)
1	CH_3CN (Reflux)	Piperidine	12	<40
2	EtOH (Reflux)	Piperidine	12	<40
3	DMF (Reflux)	Piperidine	12	54
4	H_2O (Reflux)	Piperidine	6	71
5	Solvent-free/100 °C	Piperidine	12	50
6	H_2O/60 °C/Ultrasound	Piperidine	1	87
7	H_2O/60 °C/Ultrasound	–[b]	3	56
8	H_2O/50 oC/Ultrasound	Piperidine	1	71
9	H_2O/40 °C/Ultrasound	Piperidine	1	55
10	H_2O/60 °C/Ultrasound	Et_3N	1	77
11	H_2O/60 °C/Ultrasound	Na_2CO_3	1	65
12	H_2O/60 °C/Ultrasound	K_2CO_3	1	69
13	H_2O/60 °C/Ultrasound	KOH	1	<40
14	EtOH/60 °C/Ultrasound	Piperidine	1	75
15	CH_3CN/60 °C/Ultrasound	Piperidine	1	56

[a] Barbituric acids (1 mmol), benzaldehyde (1 mmol), 6-amino-uracil (1 mmol), Cat. (0.5 mmol).
[b] In the absence of catalyst.

Table 2
Preparation of pyrido[2,3-*d*:6,5-*d*]dipyrimidines.

Product **4**	R	R_1	Ar	X	Yield (%)[a]
a	H	Me	C_6H_5	O	85
b	H	Me	4-Cl–C_6H_4	O	87
c	H	Me	4-NO_2–C_6H_4	O	85
d	H	Me	4-Me–C_6H_4	O	81
a	Me	H	C_6H_5	O	86
b	Me	H	4-Cl–C_6H_4	O	89
c	Me	H	4-NO_2–C_6H_4	O	90
d	Me	H	4-Me–C_6H_4	O	91
e	H	H	C_6H_5	O	87
f	H	H	4-Cl–C_6H_4	O	88
g	H	H	Thiophen-2-yl	O	81
h	H	H	Furan-2-yl	O	78
i	H	H	C_6H_5	S	91
j	H	H	4-Cl–C_6H_4	S	88
k	H	Me	C_6H_5	S	90
l	H	H	4-Cl–C_6H_4	S	87

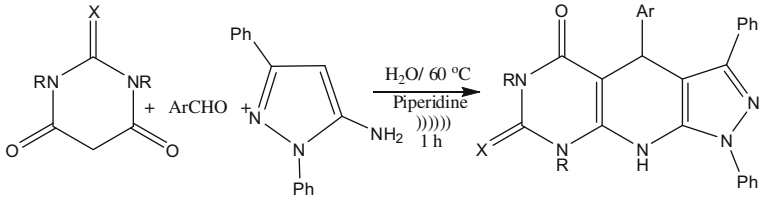
[a] Isolated yields.



1 2 5 6a-g

Product **6**	R	Ar	X	Yield (%)
a	H	C_6H_5	O	82
b	H	4-Cl-C_6H_4	O	83
c	H	4-Me-C_6H_4	O	81
d	Me	C_6H_5	O	83
e	Me	4-Cl-C_6H_4	O	84
f	H	C_6H_5	S	78
g	H	4-Cl-C_6H_4	S	80

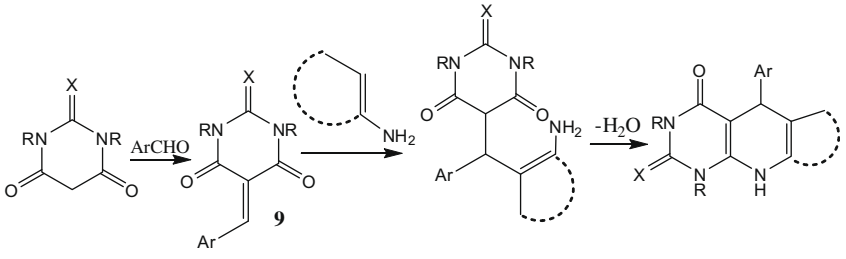
Scheme 2.



1 2 7 8a-g

Product **8**	R	Ar	X	Yield (%)	M.P. (°C)	
					Found	Reported
a	H	C_6H_5	O	86	295 (dec.)	297 (dec.)[21]
b	H	4-Cl-C_6H_4	O	85	>300	320 (dec.)[21]
c	H	4-Me-C_6H_4	O	87	>300	314 (dec.)[21]
d	Me	C_6H_5	O	83	>300	-
e	Me	4-Cl-C_6H_4	O	86	>300	-
f	H	C_6H_5	S	81	258 (dec.)	-
g	H	4-Cl-C_6H_4	S	83	>300	-

Scheme 3.



Scheme 4.

similar conditions (H_2O/60 °C/Ultrasound/piperidine), furnishing the respective pyrido[2,3-*d*:6,5-*d*]dipyrimidines (**4a–l**) in good yields (Scheme 1). The optimized results are summarized in Table 2. The results were excellent in terms of yields and product purity using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents. Under the same conditions, with aliphatic aldehydes the yields of the reaction notably decreased (i.e., 20%, with butanal or hexanal), probably due to the possible aldol condensation side reaction.

As expected, when the uracils (**3**) was replaced by 3-amino-5,5-dimethylcyclohex-2-enone (**5**), another series of fused heterocyclic pyrimidines, tetrahydropyrimido[4,5-*b*]quinolines (**6**), were obtained in good yields under the same reaction conditions (Scheme 2).

Recently, Bazgir et al. reported the synthesis of pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine-diones (**8**) under solvent-free conditions at 100 °C for 4 h [21]. Therefore, when 1,3-diphenyl-1*H*-pyrazol-5-amine (**7**) was selected as enamine, the pyrazolo[4′,3′:5,6]pyrido[2,3-d]pyrimidine-dione derivatives **8** produced in good yields for 1 h under ultrasound irradiation (Scheme 3).

The formation of pyrimidine derivatives (**4**), (**6**) and (**8**), can be explained by the tentative mechanism presented in Scheme 4. The Knoevenagel condensation product (**9**) reacted with enamine to give the corresponding product.

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m/z* values. Compounds (**4**), (**6**) and (**8**), are stable solids whose structures are fully supported by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis.

4. Conclusion

In conclusion, we have developed a simple, efficient and green protocol for the synthesis of pyrimidine derivatives by a one-pot and three-component reaction under ultrasound irradiation in water. The simple work-up in isolation of the products in good yields with high purity, mild reaction conditions, high atom economy of the reaction are features of this new procedure.

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