

# Enviro-economic, Ultrasound-assisted One-pot, Three-component Synthesis of Pyrido[2,3-*d*]pyrimidines in Aqueous Medium

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Tetra-*n*-butyl ammonium bromide (TBAB) was found to be an efficient phase-transfer catalyst for the synthesis of pyrido[2,3-*d*]pyrimidines by one-pot reaction of 6-aminouracils, aromatic aldehydes, and malononitrile or ethyl cyanoacetate in water under ultrasonic irradiation. The advantages of this method are the use of an inexpensive and readily available catalyst, short reaction time, easy work-up, improved yields, and the use of water as a solvent that is environmentally benign.

**Key words:** Ultrasound, Uracil, Pyrido[2,3-*d*]pyrimidine, Tetra-*n*-Butyl Ammonium Bromide

## Introduction

Multi-step reactions usually produce large amounts of waste, principally due to a series of complex isolation procedures which often involve toxic, hazardous and expensive solvents after each step. Thus, multi-component reactions (MCRs), in which multiple reactions are performed in one synthetic operation have been used extensively to form carbon-carbon bonds in synthetic chemistry [1,2]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. On the other hand, polyfunctionalized heterocycles play considerable roles in the drug discovery process, and analysis of drugs shows that most of them consists of polyfunctionalized heterocycles [3]. Therefore, research on the multi-components synthesis of polyfunctionalized heterocyclic compounds is an interesting challenge. Pyrido[2,3-*d*]pyrimidines are biologically interesting molecules that have established utility in the pharmaceutical and the agrochemical industries. Compounds with these ring systems have diverse pharmacological activity such as antitumor [4,5], cardioprotective [6,7], hepatoprotective [6], antihypertensive [6], antibronchitic [8], antifungal [9], antibacterial [10], and antifolate activity [11]. Therefore, these fused heterocycles have been extensively investigated, and their preparation is well documented [12,13]. As a result, a number of reports have appeared in the

literature, however, they usually require harsh conditions [14], long reaction times [15,16] and complex synthetic pathways [5]. So, new routes for the synthesis of these molecules have attracted considerable attention as a rapid entry for the formation of these heterocycles [17–19]. Ultrasonication, based on cavitation effects leading to mass transfer improvement, is an important technique that is widely used in organic synthesis and has a profound impact on the way chemists approach organic and parallel syntheses. Reduction in reaction times, improved yields and suppression of side products, relative to traditional thermal heating, are benefits of this technology [20,21].

As a consequence of our interest in the synthesis of *N*-heterocycles in aqueous medium [22,23], we investigated a three-component reaction of 6-aminouracils **1a, b**, aromatic aldehydes **2a–h**, and malononitrile (**3**) or ethyl cyanoacetate (**4**) in water under ultrasonic irradiation to afford a series of pyrido[2,3-*d*]pyrimidine derivatives (**5a–u**) instead of the corresponding 1,4-dihydropyrido[2,3-*d*]pyrimidine derivatives **6** via spontaneous aromatization (Scheme 1).

## Results and Discussion

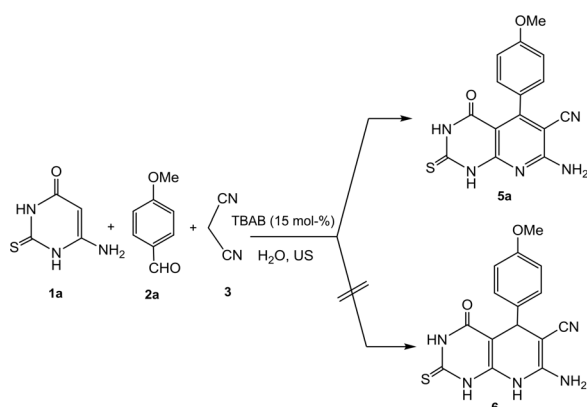
In our initial study, the evaluation of various additives was carried out for the synthesis of pyrido[2,3-*d*]pyrimidine derivatives in aqueous medium under ultrasonic irradiation. A mixture of 6-amino-2-thiouracil (**1a**), 4-methoxybenzaldehyde (**2a**) and malononitrile (**3**) as a simple model substrate in the pres-

Table 1. Optimization of the condition for the reaction depicted in Scheme 1<sup>a</sup>.

Entry	Additive <sup>b</sup>	Temp. (°C)	Time (min)	Yield (%) <sup>c</sup>
1	–	70	360	trace
2	K <sub>2</sub> CO <sub>3</sub>	70	240	30
3	PTSA	70	180	36
4	SDS	70	120	55
5	TEBA	70	90	72
6	TBAB	70	50	95
7	TBAB	r. t.	120	60
8	TBAB	40	90	70
9	TBAB	60	50	81
10	TBAB	80	50	95
11	TBAB	90	50	95

<sup>a</sup> The reaction was carried out with 6-amino-2-thiouracil (**1a**), 4-methoxybenzaldehyde (**2a**) and malononitrile (**3**) in water;

<sup>b</sup> the amount of each additive was 15 mol-%; <sup>c</sup> isolated yield of **5a**.

Scheme 1. Synthesis of **5a**.

ence of a catalytic amount of TBAB (15 mol-%) as phase transfer catalyst in water at 70 °C was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 1). The procedure was simple and easy to operate. It was reported [24, 25] that 1,4-dihydro-pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives were unstable in air and could easily be oxidized to the corresponding aromatization products.

We examined this reaction in the absence and presence of several other additives. When the reaction was carried out without any additives, only a trace amount of the product resulted (Table 1, entry 1). Bases or acids such as K<sub>2</sub>CO<sub>3</sub> or *p*-toluene sulfonic acid (PTSA) can push the reaction yield (Table 1, entries 2, 3). When surfactants, such as sodium dodecyl sulfate (SDS), triethyl benzyl ammonium chloride (TEBA) and *n*-tetrabutyl ammonium bromide (TBAB) were used in this reaction, the yields of the products were improved (Table 1, entries 4–6). The best result

Table 2. Solvent effects on the reaction of 6-amino-2-thiouracil (**1a**), 4-methoxybenzaldehyde (**2a**), and malononitrile (**3**) in the presence of TBAB (15 mol-%) at 70 °C.

Entry	Solvent <sup>a</sup>	Time (min)	Yield (%) <sup>b</sup>
1	CH <sub>3</sub> OH	180	78
2	C <sub>2</sub> H <sub>5</sub> OH	120	73
3	DMF	180	71
4	DMSO	180	65
5	THF	360	trace
6	CH <sub>3</sub> CN	360	trace
7	H <sub>2</sub> O	50	95

<sup>a</sup> 5 mL of solvent was used; <sup>b</sup> isolated yield of pure **5a**.

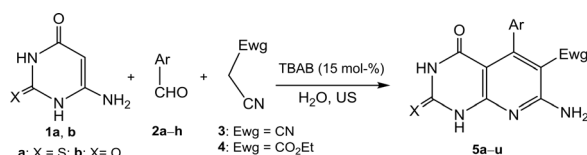
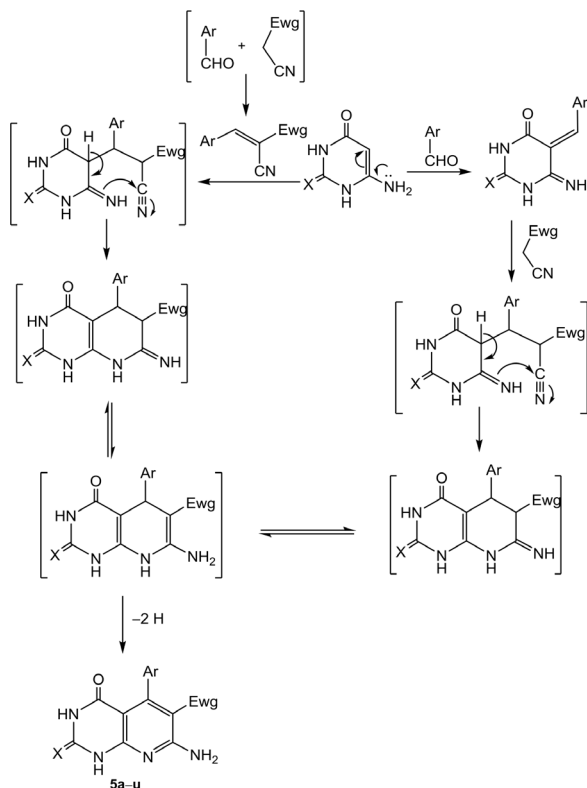
Table 3. Synthesis of pyrido[2,3-*d*]pyrimidines **5a–u** in aqueous medium under ultrasonic irradiation.

Entry	Product	X	Ar	Ewg	Time (min)	Yield (%)
1	<b>5a</b>	S	4-MeOC <sub>6</sub> H <sub>4</sub>	CN	50	95
2	<b>5b</b>	S	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	65	96
3	<b>5c</b>	S	4-ClC <sub>6</sub> H <sub>4</sub>	CN	60	94
4	<b>5d</b>	S	4-BrC <sub>6</sub> H <sub>4</sub>	CN	70	92
5	<b>5e</b>	S	4-HOC <sub>6</sub> H <sub>4</sub>	CN	60	93
6	<b>5f</b>	S	Ph	CN	75	90
7	<b>5g</b>	S	3-pyridyl	CN	75	95
8	<b>5h</b>	S	2-furyl	CN	80	91
9	<b>5i</b>	S	4-MeOC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	70	79
10	<b>5j</b>	S	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	95	85
11	<b>5k</b>	S	4-ClC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	90	84
12	<b>5l</b>	S	3-pyridyl	CO <sub>2</sub> Et	99	71
13	<b>5m</b>	O	4-MeOC <sub>6</sub> H <sub>4</sub>	CN	60	89
14	<b>5n</b>	O	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CN	80	86
15	<b>5o</b>	O	4-ClC <sub>6</sub> H <sub>4</sub>	CN	80	81
16	<b>5p</b>	O	3-pyridyl	CN	95	86
17	<b>5q</b>	O	2-furyl	CN	90	75
18	<b>5r</b>	O	4-MeOC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	80	89
19	<b>5s</b>	O	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	90	92
20	<b>5t</b>	O	4-ClC <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	95	81
21	<b>5u</b>	O	3-pyridyl	CO <sub>2</sub> Et	99	79

was obtained when TBAB was used which provided a yield of 95 %.

To study the effect of the amount of the catalyst, the reactions were carried out with different amounts of TBAB ranging from 10 to 20 mol-%. It was found that when increasing the amount of TBAB from 10 to 15, and 20 mol-%, the yields increased from 81 to 95 and 88 %, respectively. Thus 15 mol-% TBAB in water is sufficient to push this reaction forward. Larger amounts of TBAB did not improve the yields.

To optimize the reaction temperature, the reactions were carried out at different temperatures ranging from r. t. to 90 °C. It was found that the yield was improved and the reaction time was shortened when the temperature was increased to 70 °C. No significant change in yield was observed when the temperature was further increased to 80 and 90 °C (Table 1, entries 6–11).

Scheme 2. Synthesis of pyrido[2,3-*d*]pyrimidines **5a–u**.Scheme 3. Possible mechanism for the formation of pyrido[2,3-*d*]pyrimidines.

Furthermore, different solvents were screened in the model reaction. It was found that the reaction in water led to high yields after 50 min (Table 2).

Under the optimized reaction conditions, a series of pyrido[2,3-*d*]pyrimidine derivatives (**5a–u**) were synthesized (Scheme 2, Table 3).

As shown in Table 3, it was found that this method is successful with a variety of substrates. 6-Aminouracils (**1a, b**) and different aromatic aldehydes (**2a–h**) were used in this protocol, and also the reaction with malononitrile (**3**) or ethyl cyanoacetate (**4**) led to the desired products.

The structure of the obtained compounds was ascertained by spectroscopic data and elemental analysis. Taking **5b** as the example, sharp absorption bands

at 3310, 3220 cm<sup>−1</sup> for NH<sub>2</sub> and 2210 cm<sup>−1</sup> for CN were observed in the IR spectrum. The <sup>1</sup>H NMR spectrum showed the absence of the methine proton of the uracil and the presence of a singlet signal at  $\delta$  = 6.36 ppm for the NH<sub>2</sub> group and two singlet signals at  $\delta$  = 12.49, 13.10 ppm for two NH protons.

According to the structure of **5a–u** a sequential Knoevenagel condensation, Michael addition, and intramolecular cyclization followed by the aromatization may take place during the formation of the products. A possible mechanism is shown in Scheme 3.

In conclusion, an enviro-economic, ultrasound-assisted one-pot, and efficient three-component synthesis of pyrido[2,3-*d*]pyrimidines in aqueous medium has been developed. Prominent among the advantages of this new method are operational simplicity, good yields in short reaction times and easy work-up procedures.

## Experimental Section

The time required for the completion of each reaction was monitored by TLC. All melting points are uncorrected and were measured on a Gallenkamp apparatus. The IR spectra were recorded on a Shimadzu 470 IR spectrometer (KBr). The <sup>1</sup>H NMR spectra were measured on a Varian EM-390 (90 MHz). The <sup>13</sup>C NMR spectra were obtained on a Varian EM-200 (100 MHz) spectrometer with TMS as internal standard and [D<sub>6</sub>]DMSO as solvent. Mass spectra were determined on a Jeol JMS-600 spectrometer. Elemental analyses (C, H, N, and S) were performed on an elemental analysis system Vario EL V<sub>2.3</sub>. The results were found to be in good agreement with the calculated values. Ultrasonication was performed in an Elma<sup>®</sup> D-7700 (Singen, Germany) ultrasound cleaner with a frequency of 35 kHz. The reaction flasks were immersed in the cleaner in such a way that the surface of the reactants was slightly lower than the water in the cleaner, and the temperature of the water bath was controlled by an electronic temperature control system.

Compounds **1a, b** were prepared according to the method described in the literature [26]. Compounds **2a–h**, **3** and **4** are commercially available.

### *Amino-1,2,3,4-tetrahydro-5-(4-methoxyphenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5a)*

A mixture of 6-amino-2-thiouracil (**1a**) (0.143 g, 1 mmol), 4-methoxybenzaldehyde (**2a**) (0.136 g, 1 mmol), malononitrile (**3**) (0.066 g, 1 mmol), and TBAB (0.048 g, 15 mol-%) in water (5 mL) was sonicated at 70 °C for 50 min (TLC). After completion of the reaction, the reaction mixture was filtered and the precipitate washed with water and ethanol to afford the pure product **5a**.

Yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410 (NH), 3300, 3200 (NH<sub>2</sub>), 2200 (CN), 1680 (C=O), 1630 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 3.91 (s, 3H, CH<sub>3</sub>), 6.43 (s, 2H, NH<sub>2</sub>), 7.20 (d, 2H, H-Ar), 8.00 (d, 2H, H-Ar), 11.52 (s, 1H, NH), 11.59 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 325.40 (9) [M]<sup>+</sup>. – C<sub>15</sub>H<sub>11</sub>N<sub>5</sub>O<sub>2</sub>S (325.35): calcd. C 55.38, H 3.41, N 21.53, S 9.86; found C 55.16, H 3.25, N 21.38, S 9.61.

*7-Amino-1,2,3,4-tetrahydro-5-(4-nitrophenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5b)*

From **1a**, **2b** and **3**.

Yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410 (NH), 3310, 3220 (NH<sub>2</sub>), 2210 (CN), 1680 (C=O), 1635 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.36 (s, 2H, NH<sub>2</sub>), 8.15 (d, 2H, H-Ar), 8.40 (d, 2H, H-Ar), 12.49 (s, 1H, NH), 13.10 (s, 1H, NH). – <sup>13</sup>C NMR:  $\delta$  = 90.2, 108.2, 114.2, 115.1, 116.6, 122.8, 129.1, 133.3, 152.2, 154.4, 160.5, 161.7, 163.9, 174.6. – MS ((+)-FAB):  $m/z$  (%) = 342.00 (16) [M]<sup>+</sup>. – C<sub>14</sub>H<sub>8</sub>N<sub>6</sub>O<sub>3</sub>S (340.33): calcd. C 49.41, H 2.37, N 24.69, S 9.42; found C 49.30, H 2.15, N 24.51, S 9.25.

*7-Amino-1,2,3,4-tetrahydro-5-(4-chlorophenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5c)*

From **1a**, **2c** and **3**.

Pale-yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410 (NH), 3300, 3195 (NH<sub>2</sub>), 2210 (CN), 1685 (C=O), 1640 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.45 (s, 2H, NH<sub>2</sub>), 7.73 (d, 2H, H-Ar), 8.00 (d, 2H, H-Ar), 11.54 (s, 1H, NH), 11.62 (s, 1H, NH). – <sup>13</sup>C NMR:  $\delta$  = 88.8, 114.1, 115.1, 116.7, 123.1, 129.6, 133.8, 144.5, 152.2, 154.8, 161.1, 161.9, 164.3, 174.7. – MS ((+)-FAB):  $m/z$  (%) = 329.88 (19) [M]<sup>+</sup>. – C<sub>14</sub>H<sub>8</sub>ClN<sub>5</sub>OS (329.76): calcd. C 50.99, H 2.45, N 21.24, S 9.72, Cl 10.75; found C 50.84, H 2.33, N 21.09, S 9.62, Cl 10.60.

*7-Amino-1,2,3,4-tetrahydro-5-(4-bromophenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5d)*

From **1a**, **2d** and **3**.

Pale-yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410 (NH), 3300, 3200 (NH<sub>2</sub>), 2205 (CN), 1680 (C=O), 1630 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.31 (s, 2H, NH<sub>2</sub>), 7.49 (d, 2H, H-Ar), 7.78 (d, 2H, H-Ar), 11.60 (s, 1H, NH), 11.70 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 376.22 (10) [M+2]<sup>+</sup>, 374.91 (11) [M]<sup>+</sup>. – C<sub>14</sub>H<sub>8</sub>BrN<sub>5</sub>OS (374.22): calcd. C 44.93, H 2.15, N 18.71, S 8.57, Br 21.35; found C 44.75, H 2.11, N 18.57, S 8.46, Br 21.20.

*7-Amino-1,2,3,4-tetrahydro-5-(4-hydroxyphenyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5e)*

From **1a**, **2e** and **3**.

Pale-yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410 (NH), 3350, 3200 (NH<sub>2</sub>), 3100 (OH), 2210 (CN), 1690 (C=O), 1640 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.37 (s, 2H, NH<sub>2</sub>), 6.91 (d, 2H, H-Ar), 7.90 (d, 2H, H-Ar), 8.21 (s, 1H, OH), 11.67 (s, 1H, NH), 11.91 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 311.57 (8) [M]<sup>+</sup>. – C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O<sub>2</sub>S (311.32): calcd. C 54.01, H 2.91, N 22.50, S 10.3; found C 53.88, H 2.75, N 22.31, S 10.18.

*7-Amino-1,2,3,4-tetrahydro-5-phenyl-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5f)*

From **1a**, **2f** and **3**.

Pale-yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3400 (NH), 3300, 3200 (NH<sub>2</sub>), 2200 (CN), 1680 (C=O), 1630 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.30 (s, 2H, NH<sub>2</sub>), 7.55 (m, 3H, H-Ar), 7.85 (m, 2H, H-Ar), 11.75 (s, 1H, NH), 11.85 (s, 1H, NH). – <sup>13</sup>C NMR:  $\delta$  = 59.7, 84.3, 117.1, 125.2, 126.4, 127.1, 128.3, 128.9, 144.3, 151.3, 152.1, 164.8, 165.3, 178.8. – MS ((+)-FAB):  $m/z$  (%) = 295.05 (16) [M]<sup>+</sup>. – C<sub>14</sub>H<sub>9</sub>N<sub>5</sub>OS (295.33): calcd. C 56.94, H 3.07, N 23.71, S 10.86; found C 56.88, H 3.00, N 23.51, S 10.69.

*7-Amino-1,2,3,4-tetrahydro-5-(3-pyridyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5g)*

From **1a**, **2g** and **3**.

Yellow-crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3400 (NH), 3310, 3220 (NH<sub>2</sub>), 2210 (CN), 1685 (C=O), 1635 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.40 (s, 2H, NH<sub>2</sub>), 7.50–7.80 (m, 4H, H-Ar), 11.82 (s, 1H, NH), 11.86 (s, 1H, NH). – <sup>13</sup>C NMR:  $\delta$  = 91.3, 105.2, 117.3, 130.4, 131.1, 134.5, 141.1, 144.3, 152.1, 156.2, 161.1, 164.8, 173.8. – MS ((+)-FAB):  $m/z$  (%) = 296.02 (20) [M]<sup>+</sup>. – C<sub>13</sub>H<sub>8</sub>N<sub>6</sub>OS (296.31): calcd. C 52.70, H 2.72, N 28.36, S 10.82; found C 52.60, H 2.55, N 28.15, S 10.69.

*7-Amino-1,2,3,4-tetrahydro-5-(2-furyl)-4-oxo-2-thioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5h)*

From **1a**, **2h** and **3**.

Pale-brown crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3400 (NH), 3300, 3200 (NH<sub>2</sub>), 2220 (CN), 1685 (C=O), 1630 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 6.42 (s, 2H, NH<sub>2</sub>), 6.90–7.85 (m, 3H, H-Ar), 11.82 (s, 1H, NH), 11.90 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 285.05 (11) [M]<sup>+</sup>. – C<sub>12</sub>H<sub>7</sub>N<sub>5</sub>O<sub>2</sub>S (285.28): calcd. C 50.52, H 2.47, N 24.55, S 11.24; found C 50.33, H 2.35, N 24.40, S 11.12.

*Ethyl 7-amino-1,2,3,4-tetrahydro-4-oxo-5-(4-methoxyphenyl)-2-thioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (5i)*

From **1a**, **2a** and **4**.

Pale-yellow crystals; m.p. 201–202 °C. – IR (KBr):  $\nu$  = 3422, 3315 (NH<sub>2</sub>), 3200 (NH), 1720 (C=O),

1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 1.35 (t, 3H,  $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{CH}_3$ ), 4.33 (q, 2H,  $\text{CH}_2$ ), 6.44 (s, 2H,  $\text{NH}_2$ ), 7.00 (d, 2H, H-Ar), 8.00 (d, 2H, H-Ar), 11.91 (s, 1H, NH), 12.15 (s, 1H, NH). –  $^{13}\text{C}$  NMR:  $\delta$  = 14.6, 50.3, 62.8, 91.9, 107.2, 115.5, 123.7, 124.8, 127.2, 132.1, 137.1, 149.6, 152.5, 154.2, 161.6, 170.4, 174.5. – MS ((+)-FAB):  $m/z$  (%) = 372.21 (10)  $[\text{M}]^+$ . –  $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_4\text{S}$  (372.40): calcd. C 54.83, H 4.33, N 15.04, S 8.61; found C 54.65, H 4.21, N 14.89, S 8.48.

*Ethyl 7-amino-1,2,3,4-tetrahydro-4-oxo-5-(4-nitrophenyl)-2-thioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (5j)*

From **1a**, **2b** and **4**.

Bright-yellow crystals; m.p. 226–228 °C. – IR (KBr):  $\nu$  = 3330, 3290 ( $\text{NH}_2$ ), 3100 (NH), 1715 (C=O), 1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 1.40 (t, 3H,  $\text{CH}_3$ ), 4.45 (q, 2H,  $\text{CH}_2$ ), 6.45 (s, 2H,  $\text{NH}_2$ ), 7.70 (d, 2H, H-Ar), 8.40 (d, 2H, H-Ar), 11.69 (s, 1H, NH), 12.04 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 387.10 (13)  $[\text{M}]^+$ . –  $\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_5\text{S}$  (387.37): calcd. C 49.61, H 3.38, N 18.08, S 8.28; found C 49.50, H 3.10, N 17.91, S 8.20.

*Ethyl 7-amino-1,2,3,4-tetrahydro-4-oxo-5-(4-chlorophenyl)-2-thioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (5k)*

From **1a**, **2c** and **4**.

Pale-yellow crystals; m.p. 211–212 °C. – IR (KBr):  $\nu$  = 3350, 3250 ( $\text{NH}_2$ ), 3100 (NH), 1715 (C=O), 1635  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 1.32 (t, 3H,  $\text{CH}_3$ ), 4.31 (q, 2H,  $\text{CH}_2$ ), 6.40 (s, 2H,  $\text{NH}_2$ ), 7.60 (d, 2H, H-Ar), 8.01 (d, 2H, H-Ar), 12.45 (s, 1H, NH), 12.61 (s, 1H, NH). –  $^{13}\text{C}$  NMR:  $\delta$  = 13.7, 65.7, 93.1, 106.6, 114.7, 123.2, 124.1, 126.3, 130.6, 137.2, 149.7, 150.1, 152.0, 161.6, 170.4, 174.6. – FAB MS:  $m/z$  (%) = 376.58 (19)  $[\text{M}]^+$ . –  $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{O}_3\text{S}$  (376.82): calcd. C 51.00, H 3.48, N 14.87, S 8.51, Cl 9.41; found C 50.89, H 3.30, N 14.70, S 8.40, Cl 9.22.

*Ethyl 7-amino-1,2,3,4-tetrahydro-4-oxo-5-(3-pyridyl)-2-thioxopyrido[2,3-*d*]pyrimidine-6-carboxylate (5l)*

From **1a**, **2g** and **4**.

Yellow crystals; m.p. 215–216 °C. – IR (KBr):  $\nu$  = 3400, 3300 ( $\text{NH}_2$ ), 3150 (NH), 1720 (C=O), 1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 1.20 (t, 3H,  $\text{CH}_3$ ), 4.51 (q, 2H,  $\text{CH}_2$ ), 6.30 (s, 2H,  $\text{NH}_2$ ), 7.30–7.85 (m, 4H, H-Ar), 9.82 (s, 1H, NH), 9.95 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 343.05 (16)  $[\text{M}]^+$ . –  $\text{C}_{15}\text{H}_{15}\text{N}_5\text{O}_3\text{S}$  (343.36): calcd. C 52.47, H 3.82, N 20.40, S 9.34; found C 52.30, H 3.75, N 20.25, S 9.22.

*7-Amino-1,2,3,4-tetrahydro-5-(4-methoxyphenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5m)*

From **1b**, **2a** and **3**.

Pale-yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410, 3400 ( $\text{NH}_2$ ), 3190 (NH), 2205 (CN), 1700 (C=O),

1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 3.95 (s, 3H,  $\text{CH}_3$ ), 6.24 (s, 2H,  $\text{NH}_2$ ), 7.18 (d, 2H, H-Ar), 8.00 (d, 2H, H-Ar), 10.10 (s, 1H, NH), 10.20 (s, 1H, NH). –  $^{13}\text{C}$  NMR:  $\delta$  = 54.6, 115.1, 115.6, 116.2, 124.2, 132.4, 133.5, 134.5, 134.6, 149.1, 153.6, 159.0, 160.5, 164.4, 165.1. – MS ((+)-FAB):  $m/z$  (%) = 309.96 (7)  $[\text{M}]^+$ . –  $\text{C}_{15}\text{H}_{11}\text{N}_5\text{O}_3$  (309.28): calcd. C 58.25, H 3.58, N 22.64; found C 58.10, H 3.42, N 22.45.

*7-Amino-1,2,3,4-tetrahydro-5-(4-nitrophenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5n)*

From **1b**, **2b** and **3**.

Yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3410 (NH), 3300, 3200 ( $\text{NH}_2$ ), 2205 (CN), 1705 (C=O), 1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 6.90 (s, 2H,  $\text{NH}_2$ ), 7.87 (d, 2H, H-Ar), 8.32 (d, 2H, H-Ar), 10.60 (s, 1H, NH), 10.75 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 324.00 (10)  $[\text{M}]^+$ . –  $\text{C}_{14}\text{H}_{10}\text{N}_6\text{O}_4$  (324.25): calcd. C 51.86, H 2.49, N 25.92; found C 51.76, H 2.29, N 25.75.

*7-Amino-1,2,3,4-tetrahydro-5-(4-chlorophenyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5o)*

From **1b**, **2c** and **3**.

Pale-yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3400, 3310 ( $\text{NH}_2$ ), 3200 (NH), 2205 (CN), 1705 (C=O), 1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 6.15 (s, 2H,  $\text{NH}_2$ ), 7.50 (d, 2H, H-Ar), 7.86 (d, 2H, H-Ar), 10.44 (s, 1H, NH), 10.70 (s, 1H, NH). –  $^{13}\text{C}$  NMR:  $\delta$  = 80.5, 114.1, 115.1, 116.7, 123.3, 129.9, 133.7, 136.2, 154.8, 157.1, 161.1, 161.9, 163.9, 165.1. – MS ((+)-FAB):  $m/z$  (%) = 313.25 (12)  $[\text{M}]^+$ . –  $\text{C}_{14}\text{H}_8\text{ClN}_5\text{O}_2$  (313.70): calcd. C 53.60, H 2.57, N 22.33, Cl 11.30; found C 53.42, H 2.49, N 22.20, Cl 11.20.

*7-Amino-1,2,3,4-tetrahydro-5-(3-pyridyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5p)*

From **1b**, **2g** and **3**.

Yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3400, 3300 ( $\text{NH}_2$ ), 3200 ( $\text{NH}_2$ ), 2205 (CN), 1700 (C=O), 1630  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 6.20 (s, 2H,  $\text{NH}_2$ ), 7.20–8.00 (m, 4H, H-Ar), 10.45 (s, 1H, NH), 10.52 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 280.00 (10)  $[\text{M}]^+$ . –  $\text{C}_{13}\text{H}_8\text{N}_6\text{O}_2$  (280.24): calcd. C 55.72, H 2.88, N 29.99; found C 55.53, H 2.80, N 29.70.

*7-Amino-1,2,3,4-tetrahydro-5-(2-furyl)-2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5q)*

From **1b**, **2h** and **3**.

Yellow crystals; m.p. > 300 °C. – IR (KBr):  $\nu$  = 3350 (NH), 3200, 3150 ( $\text{NH}_2$ ), 2210 (CN), 1705 (C=O), 1640  $\text{cm}^{-1}$  (C=N). –  $^1\text{H}$  NMR:  $\delta$  = 6.30 (s, 2H,  $\text{NH}_2$ ), 6.66–7.50 (m, 3H, H-Ar), 10.24 (s, 1H, NH), 10.60 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 269.05 (11)  $[\text{M}]^+$ . –  $\text{C}_{12}\text{H}_7\text{N}_5\text{O}_3$

(269.22): calcd. C 53.54, H 2.62, N 26.01; found C 53.40, H 2.50, N 25.90.

*Ethyl 7-amino-1,2,3,4-tetrahydro-5-(4-methoxyphenyl)-2,4-dioxypyrido[2,3-*d*]pyrimidine-6-carboxylate (5r)*

From **1b**, **2a** and **4**.

Pale-yellow crystals; m. p. 196–198 °C. – IR (KBr):  $\nu$  = 3400, 3300 (NH<sub>2</sub>), 3200 (NH), 1715 (C=O), 1640 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 1.34 (t, 3H, CH<sub>3</sub>), 3.85 (s, 3H, CH<sub>3</sub>), 4.30 (q, 2H, CH<sub>2</sub>), 6.77 (s, 2H, NH<sub>2</sub>), 7.00 (d, 2H, H-Ar), 8.10 (d, 2H, H-Ar), 10.70 (s, 1H, NH), 10.85 (s, 1H, NH). – <sup>13</sup>C NMR:  $\delta$  = 14.2, 50.4, 63.1, 92.2, 107.6, 115.6, 123.8, 124.5, 127.2, 132.1, 137.3, 149.7, 152.5, 155.2, 161.6, 163.3, 164.8. – MS ((+)-FAB):  $m/z$  (%) = 356.00 (10) [M]<sup>+</sup>. – C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub> (356.33): calcd. C 57.30, H 4.53, N 15.72; found C 57.15, H 4.45, N 15.60.

*Ethyl 7-amino-1,2,3,4-tetrahydro-5-(4-nitrophenyl)-2,4-dioxypyrido[2,3-*d*]pyrimidine-6-carboxylate (5s)*

From **1b**, **2b** and **4**.

Yellow crystals; m. p. 220–221 °C. – IR (KBr):  $\nu$  = 3350, 3250 (NH<sub>2</sub>), 3100 (NH), 1715 (C=O), 1640 (C=N). – <sup>1</sup>H NMR:  $\delta$  = 1.32 (t, 3H, CH<sub>3</sub>), 4.35 (q, 2H, CH<sub>2</sub>), 6.76 (s, 2H, NH<sub>2</sub>), 7.39 (d, 2H, H-Ar), 8.30 (d, 2H, H-Ar), 10.71 (s, 1H, NH), 10.90 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 371.00 (12) [M]<sup>+</sup>. – C<sub>16</sub>H<sub>13</sub>N<sub>5</sub>O<sub>6</sub> (371.30): calcd. C 51.76, H 3.53, N 18.86; Found C 51.65, H 3.39, N 18.75.

*Ethyl 7-amino-1,2,3,4-tetrahydro-5-(4-chlorophenyl)-2,4-dioxypyrido[2,3-*d*]pyrimidine-6-carboxylate (5t)*

From **1b**, **2c** and **4**.

Pale-yellow crystals; m. p. 205–207 °C. – IR (KBr):  $\nu$  = 3350, 3200 (NH<sub>2</sub>), 3100 (NH), 1715 (C=O), 1630 cm<sup>-1</sup> (C=N). – <sup>1</sup>H NMR:  $\delta$  = 1.30 (t, 3H, CH<sub>3</sub>), 4.30 (q, 2H, CH<sub>2</sub>), 6.65 (s, 2H, NH<sub>2</sub>), 7.12 (d, 2H, H-Ar), 8.00 (d, 2H, H-Ar), 10.35 (s, 1H, NH), 10.60 (s, 1H, NH). – <sup>13</sup>C NMR:  $\delta$  = 14.1, 65.5, 93.2, 106.5, 114.9, 122.6, 124.1, 126.3, 130.6, 137.2, 149.7, 152.0, 156.4, 161.3, 163.4, 165.2. – MS ((+)-FAB):  $m/z$  (%) = 360.95 (6) [M]<sup>+</sup>. – C<sub>16</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>4</sub> (360.75): calcd. C 53.27, H 3.63, N 15.53, Cl 9.83; found C 53.19, H 3.45, N 15.40, Cl 9.70.

*Ethyl 7-amino-1,2,3,4-tetrahydro-5-(3-pyridyl)-2,4-dioxypyrido[2,3-*d*]pyrimidine-6-carboxylate (5u)*

From **1b**, **2g** and **4**.

Yellow crystals; m. p. 210–211 °C. – IR (KBr):  $\nu$  = 3400, 3300 (NH<sub>2</sub>), 3150 (NH), 1715 (C=O), 1640 (C=N). – <sup>1</sup>H NMR:  $\delta$  = 1.25 (t, 3H, CH<sub>3</sub>), 4.59 (q, 2H, CH<sub>2</sub>), 7.49 (s, 2H, NH<sub>2</sub>), 7.50–8.00 (m, 4H, H-Ar), 11.10 (s, 1H, NH), 11.21 (s, 1H, NH). – MS ((+)-FAB):  $m/z$  (%) = 327.00 (7) [M]<sup>+</sup>. – C<sub>15</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub> (327.29): calcd. C 55.05, H 4.00, N 21.40; found C 54.85, H 3.81, N 21.29.

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- [1] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3168–3210.
- [2] I. Ugi, A. Dömling, *Endeavour* **1994**, *18*, 115–123.
- [3] A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.
- [4] A. Gangjee, O. Aldair, S. F. Queener, *J. Med. Chem.* **1999**, *42*, 2447–2455.
- [5] E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch, C. A. Nichol, *J. Med. Chem.* **1980**, *23*, 327–329.
- [6] S. Furuya, T. Ohtaki, Eur. Pat. 608565.
- [7] D. Heber, C. Heers, U. Ravens, *Pharmazie* **1993**, *48*, 537–541.
- [8] Y. Sakuma, M. Hasegawa, K. Kataoka, K. Hoshina, N. Yamazaki, T. Kadota, H. Yamaguchi, *PCT Int.* 91 05,785.
- [9] G. Singh, G. Singh, A. K. Yadav, K. Mishraa, *Indian. J. Chem.* **2002**, *41*, 430–432.
- [10] A. V. Zakharov, M. Y. Gavrilov, L. M. Demina, G. N. Novoselova, N. A. Gornova, M. Y. Konshin, *Kim. Farm. Zh.* **1994**, *28*, 24–26.
- [11] J. I. DeGraw, P. H. Christie, W. T. Clowell, F. M. Sirot-nak, *J. Med. Chem.* **1992**, *35*, 320–324.
- [12] G. Tamura, T. Sakaguchi, T. Kawasaki, Y. Kita, *Heterocycles* **1975**, *3*, 183–186.
- [13] J. Quiroga, A. Hormaza, B. Insuasty, M. Nogueras, A. Sánchez, N. Hanold, H. Meier, *J. Heterocycl. Chem.* **1997**, *34*, 521–524.
- [14] K. Hirota, H. Kuki, Y. Maki, *Heterocycles* **1994**, *37*, 563–570.
- [15] P. Srivastava, A. S. Saxena, V. J. Ram, *Synthesis* **2000**, 541–544.
- [16] A. D. Broom, J. L. Shim, G. L. Anderson, *J. Org. Chem.* **1976**, *41*, 1095–1099.
- [17] I. Devi, B. S. D. Kumar, P. J. Bhuyan, *Tetrahedron Lett.* **2003**, *44*, 8307–8310.
- [18] J. Quiroga, H. Insuasty, B. Insuasty, R. Abonia,

- J. Cobo, A. Sánchez, M. Nogueras, *Tetrahedron* **2002**, 58, 4873–4877.
- [19] S. Samai, G. C. Nandi, S. Chowdhury, M. S. Singh, *Tetrahedron* **2011**, 67, 5935–5941.
- [20] G. Cravotto, P. Cintas, *Chem. Soc. Rev.* **2006**, 35, 180–196.
- [21] T.J. Mason, J.P. Lorimer, *Applied Sonochemistry*, Wiley-VCH, Weinheim **2002**.
- [22] E.M. Hussein, A.M. El-Khawaga, *J. Heterocycl. Chem.* **2011**, in press.
- [23] E.M. Hussein, *Heterocycl. Lett.* **2012**, 2, 19–26.
- [24] R. A. Subba, R. B. Mitra, *Indian J. Chem.* **1981**, 20B, 159–160.
- [25] S. Wawzonek, *J. Org. Chem.*, **1976**, 41, 3149–3151.
- [26] Sh. Youssif, S. El-Bahaie, E. Nabih, *Bull. Korean Chem. Soc.* **2003**, 24, 1429–1432.