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Ultrasound-promoted synthesis of novel dihydropyrido[2,3-d:5,6-d`]dipyrimidine derivatives

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ABSTRACT

An efficient synthesis of dihydropyrido[2,3-d:5,6-*d*`]pyrimidine derivatives was developed via one-pot three-component reaction of 6-amino-2-(alkylthio)-pyrimidine-4(3*H*)one and aryl aldehydes in the mixed solvent of glacial acetic acid and DMF (1:1, v:v) under ultrasonic irradiation. In this protocol novel fused dihydropyrido[2,3-d]pyrimidines were synthesized in high yields (80-97%) and lower reaction times (5-25 min).

Keywords

6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one; pyrido[2,3-*d*]pyrimidine; ultrasonic irradiation; three-component reaction.

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INTRODUCTION

Pyridopyrimidines, their oxo and thioxo derivatives have been recognized as important organic materials in drug design, and showing interesting biological activities. For example they are known to be inhibitors of tyrosine kinase of the epidermal growth factor receptor family [1], antiviral [2], antioxidant [3] and antitumor [4]. Among them, pyrimido[4,5-d]pyrimidines and pyrimido[2,3-d]pyrimidines, have been known to display a wide range of pharmacological activities [5,6]. It is well known that many pyrido[2,3-*d*]pyrimidine derivatives possess interesting biological logical properties. It has been proven that they possess diuretic [7], antibacterial [8], analgesic, anti-inflammatory [9], antiviral [10], anticonvulsive [11,12], antipyretic [13], cardiotonic [14, 15], antitumoral [16], bactericidal [17], bronchiodilator [18], antihistaminic [19], and other activities [20]. As a result, compounds of this class present considerable interest for research. Considering the important biological properties of fused pyrimidines, a number of methods have been reported for the synthesis of these heterocycles [21-28]. Some of these methods, suffer from one or more disadvantages such as using costly reagents, toxic catalysts and solvents, low yielding of products, harsh reaction conditions, and require prolonged heating and tedious work. As a result, development of a simple and green protocol for the synthesis of pyrido[2,3-*d*]pyrimidines is highly required.

On the other hand green chemistry has become a major driving force for organic chemists to develop eco-friendly routes for the synthesis of organic compounds. For example, the possibility of performing reactions under ultrasound irradiations. ultrasonic reactions have been increasingly used as green, clean and environmentally benign routes for the preparation of organic compounds [29-34]. A large number of organic reactions can be carried out in higher yield, shorter reaction time and under milder conditions, by using ultrasonic irradiation [35-38].

These observations led us to attempt the synthesis of some novel pyridodipyrimidine derivatives using 6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one under ultrasonic irradiations.

RESULTS AND DISCUSSION

In continuation of our ongoing program aiming to develop efficient and eco-friendly methods for the synthesis of biologically important heterocyclic compounds [39-42], we carried out a simple one-pot three-component reaction reaction for the synthesis of dihydropyridopyrimidines under ultrasonic irradiation. In this protocol the reaction of 6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one and arylaldehydes was studied in the mixed solvent of glacial acetic acide and DMF (1:1, v:v) under ultrasonic irradiation (Scheme 1). The reaction furnished desired dihydropyridopyrimines in excellent yields (80-97%) and short reaction times (5-25 min) (Table 3).

Scheme 1: Synthesis of pyrido[2,3-*d*]pyrimidine derivatives (3a-v).

In the initial experiments, different solvents and catalysts screened for the synthesis of dihydropyridopyrimine derivatives (3a-v). To optimize the reaction conditions, preparation of 5-(4-chlorophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-d:5,6-d`]dipyrimidin-4,6(3H,7*H*)-dione) (3a) by the reaction of 6-amino-2-(ethylthio)pyrimidin-4(3*H*)-one (2 mmol) and 4-chlorobenzaldehyde (1 mmol) was selected as a model reaction. The results are summarized in Table 1. It is evident from the results that AcOH/DMF (1:1, v:v) is the most effective reaction medium among the solvents and catalysts selected, resulting in the highest yield (97 %) and the shortest reaction time (10 min) at 80 °C. For comparison the preparation of 3a was carried out under conventional heating at reflux temperature which furnished the product at lower yield and much higher reaction time (Table 1, entry 1).

Table 1. Effect of various catalysts and solvents in the synthesis of 3a.

Entry	Catalyst/Solvent	Conventional Method[a]		Sonochemical method[b]	
		Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	AcOH/DMF (1:1)	120	76	10	97
2	AcOH/DMF (1:2)	120	70	13	92
3	*P*-TSA/EtOH	180	72	15	85
4	AcOH	210	75	15	87
5	AcOH/EtOH (1:1)	220	72	20	80
6	Ethylene glycol	210	60	25	70

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7	EtOH	250	60	25	72

[a]Reflux conditions.

[b]At 80 ^{o}C.

[c]Isolated Yield.

To optimize the reaction condition under ultrasonic irradiations, we verified different temperature for the preparation of 3a and the best result was obtained at 80 ^{o}C (Table 2).

Table 2. Effect of various temperature in the synthesis of 3a.

Entry	Temperature (^{o}C) [a]	Time (min)	Yield (%)
1	25	40	60
2	60	15	83
3	80	10	97

[a]Ultrasonic irradiations.

The starting material 1 was synthesized by condensation of thiourea with ethylcyanoacetate in sodium ethoxide and followed by alkylation with alkyl iodide according to the known procedure [43]. By using the optimized reaction conditions several derivatives of dihydropyridopyrimines (3a-v) were prepared in high to excellent yields (80-97%) and lower reaction times (5-25 min) (Table 3). The structures of all the products were confirmed by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.

Table 3. Synthesis of 3a-v under optimized conditions.

Entry	Product	R	Ar	Sonochemical method	
				Time (min)	Yield [a] (%)
1	3a	SEt	4-ClC_6H_4	10 (120)[b]	97 (76)[b]
2	3b	SEt	3-HOC_6H_4	15 (120)[b]	95 (75)[b]
3	3c	SMe	2-ClC_6H_4	10	87
4	3d	SMe	2,4-$Cl_2C_6H_3$	8	92
5	3e	SMe	4-FC_6H_4	6	93
6	3f	SMe	4-MeOC_6H_4	15	85
7	3g	SMe	4-$O_2NC_6H_4$	10	90
8	3h	SMe	3-$O_2NC_6H_4$	10 (90)[b]	88 (78)[b]
9	3i	SMe	C_6H_5	9 (95)[b]	87 (75)[b]
10	3j	SMe	3-HOC_6H_4	5	95
11	3k	SMe	4-ClC_6H_4	6	97
12	3l	SEt	2,4-$Cl_2C_6H_3$	10 (120)[b]	92 (79)[b]
13	3m	SEt	4-$O_2NC_6H_4$	13 (125)[b]	90 (80)[b]
14	3n	SEt	4-BrC_6H_4	13 (125)[b]	88 (75)[b]
15	3o	SEt	2-ClC_6H_4	15 (130)[b]	85 (76)[b]
16	3p	SEt	4-$CF_3C_6H_4$	10 (120)	82 (79)
17	3q	SEt	2-FC_6H_4	15 (140)	85 (78)
18	3r	SEt	2-BrC_6H_4	15 (140)	85 (77)
19	3s	SEt	4-OMeC_6H_4	20 (160)	85 (75)
20	3t	SEt	4-CHOC_6H_5	14 (155)	83 (77)
21	3u	SEt	2-naphtyl	22	76
22	3v	SEt	C_6H_5	25	77

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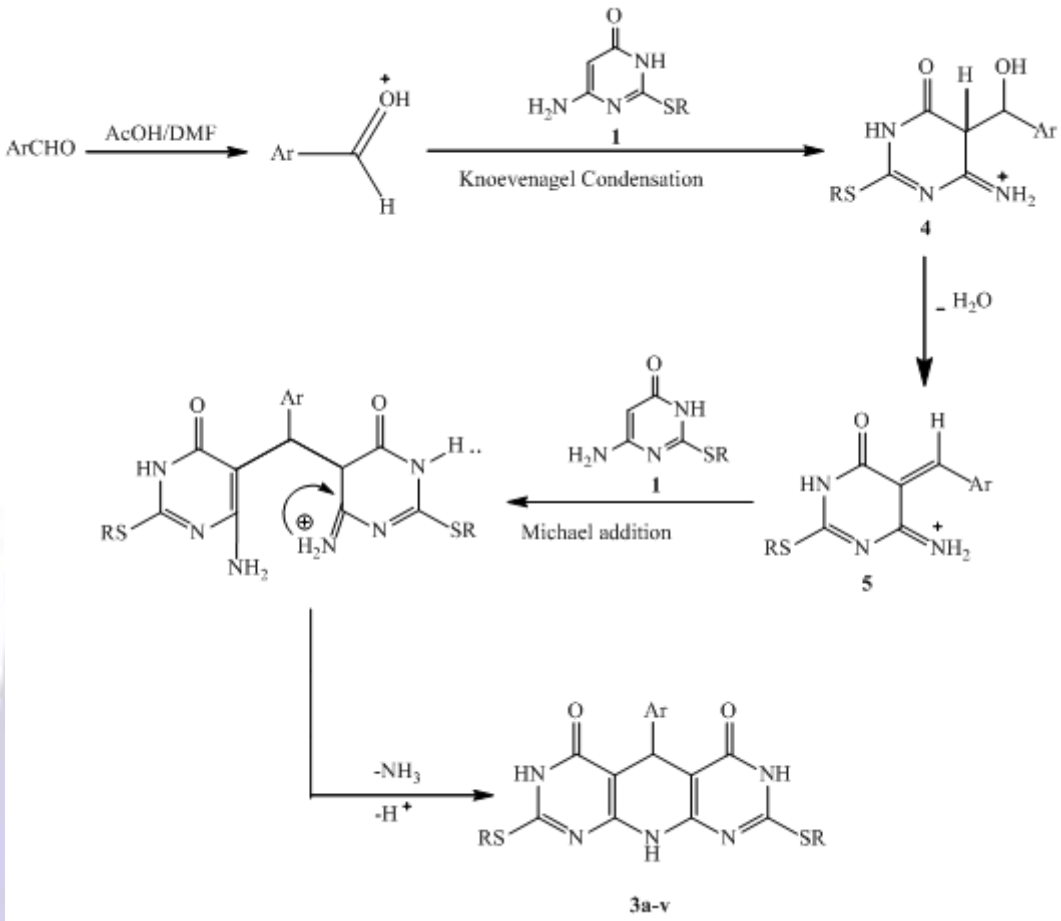
[a] Isolated Yield.

[b] Conventional heating in refluxing AcOH/DMF (1:1).

The plausible mechanism of the formation of 3a-v is outlined in Scheme 2. Due to the protonation of aldehyde by AcOH, aldehyde becomes a strong electrophile in reaction with 1. The high reactivity of enamine 1 allows the addition of this molecule to the protonated aldehyde through a Knoevenagel condensation and producing the arylidene intermediate 5 by loss of H_2O. Finally Michael addition of second molecule of enamine 1 to the intermediate 5 and loss of NH3 furnishes the desired dihydropyridodipyrimidines 4 (Scheme 2).



Scheme 2: Plausible mechanism for the synthesis of (3a-v).

EXPERIMENTAL

Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX-400 and DMSO-d_6 as solvent and TMS as an internal standard. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and agreed with the calculated values. Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures.

General procedure for preparation of (3a-v)

A mixture of 6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one (2 mmol) and aldehyde (1 mmol) in AcOH/DMF(1:1, v:v) (6 mL) was heated under reflux or by ultrasonic irradiations using Elmasonic S-40H ultrasonic cleaning unit at 80 ^{o}C (under silent condition). The progress of the reaction was monitored by TLC (EtOAc/hexane/methanol 8:3:1). After completion of the reaction, the mixture was poured into ice-water, the solid obtained was filtered off, washed by THF and recrystalyzed from DMF/ H_2O to furnish the desired pure products.

5-(4-Chlorophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3a). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3354; 3180; 3033; 2967; 2933; 2866; 1653; 1610; 1558; 1446; 1446; 1335; 1236; 1094; 831. ^{1}H NMR (DMSO-d_6), δ: 1.31 (t, *J* = 6.9 Hz, 6H, CH_3); 3.11 (q, 4H, CH_2, *J* = 6.9 Hz); 5.45 (s, 1H, CH); 6.82 (br. s, 1H, NH); 7.04 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.26 (d, 2H, Ar-H, *J* = 8.0 Hz); 11.98 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C:

15.2; 24.3; 33.5; 92.7; 128.0; 129.0; 129.8; 138.8; 158.3; 161.9; 163.8. Anal. Cald. for $C_{19}H_{18}ClN_5O_2S_2$ (447.96). Calculated (%): C, 50.94; H, 4.05; N, 15.63; Found (%): C, 50.86; H, 4.16; N, 15.79.

5-(3-Hydroxyphenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dion (3b). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3441; 3340; 3155; 2968; 2926; 2862; 1647; 1616;1558; 1452;1452; 1367; 1230; 878; 812; 698. ^{1}H NMR (DMSO-d_6), δ: 1.31 (t, 6H, CH_3, *J* = 7.0 Hz); 3.11 (q, 4H, CH_2, *J* = 7.0 Hz); 5.41 (s, 1H, CH); 6.50 (m, 3H, Ar-H); 6.78 (br. s, 1H, NH); 6.98 (t, 1H, Ar-H, *J* = 7.6 Hz); 9.0 (s, 1H, OH); 11.93 (br. s, 2H, NH-C=O) . ^{13}C NMR (DMSO-d_6), δ_C: 15.2; 24.3; 33.8; 112.2; 112.3; 113.9; 114.0; 117.9; 128.9; 141.4; 157.3; 157.4; 157.8. Anal. Cald. for $C_{19}H_{19}N_5O_3S_2$ (429.52). Calculated (%): C, 53.13; H, 4.46; N, 16.31; Found (%): C, 53.00; H, 4.59; N, 16.18.

5-(2-Chlorophenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3c). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3427; 3209; 3112; 2923; 1649; 1608; 1537; 1431; 1344; 1238; 1033; 771; 739. ^{1}H NMR (DMSO-d_6), δ: 2.47 (s, 6H, CH_3); 5.42 (s, 1H, CH); 6.88 (br.s, 1H, NH); 7.27-7.13 (m, 4H, Ar-H); 11.94 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d6), δ_C: 12.9; 33.3; 110.8; 126.8; 127.4; 127.5; 129.3; 129.6; 133.1; 138.7; 158.6; 161.5. Anal. Cald. for $C_{17}H_{14}ClN_5O_2S_2$ (419.91). Calculated (%): C, 48.63; H, 3.36; N, 16.68; Found, %: C, 48.50; H, 3.16; N, 16.49.

5-(2,4-Dichlorophenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3d). White powder, m.p. > 300 °C. IR spectrum, v/cm^{-1}: 3360; 3200; 3009; 2926; 2813; 1658; 1607; 1577; 1539; 1437; 1437; 1340; 1236; 1099; 1043; 890; 808; 758. ^{1}H NMR (DMSO-d_6), δ: 2.47 (s, 6H, CH_3); 5.38 (s, 1H, CH); 6.94 (br. s, 1H, NH); 7.21 (d, 1H, Ar-H, *J* = 8.8 Hz); 7.32 (dd, 2.1 Hz, 1H, Ar-H, *J* = 8.6 Hz); 7.41 (d, 1H, Ar-H, *J* = 2.0 Hz); 12.00 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 33.0; 92.3; 127.0; 129.0; 130.6; 131.0; 133.9; 138.0; 158.9; 161.4, 161.5; 161.6; 163.2. Anal. Cald. for $C_{17}H_{13}Cl_2N_5O_2S_2$ (454.36). Calculated (%): C, 44.94; H, 2.88; N, 15.41; Found (%): C, 44.82; H, 2.97; N, 15.25.

5-(4-Fluorophenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3e). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3456; 3292; 3163; 3090; 2999; 2922; 1645; 1614; 1577; 1450; 1450; 1335; 1234; 1155; 846. ^{1}H NMR (DMSO-d_6), δ: 2.48 (s, 6H, CH_3); 5.44 (s, 1H, CH); 6.81 (br.s, 1H, NH); 7.05-6.98 (m, 4H, Ar-H); 12.01 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 33.3; 92.9; 114.6 (d, $^2J_{C\text{-}F}$ = 21.0 Hz); 128.7 (d, $^3J_{C\text{-}F}$ = 8.0 Hz); 135.5 (d, $^4J_{C\text{-}F}$ = 2.0 Hz); 158.8; 160.6 (d, $^1J_{C\text{-}F}$ = 239.0 Hz); 163.7. Anal. Cald. for $C_{17}H_{14}FN_5O_2S_2$ (403.45). Calculated (%): C, 50.61; H, 3.50; N, 17.36; Found (%): C, 50.48; H, 3.55; N, 17.47.

5-(4-Methoxyphenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dion (3f). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3400; 3312; 3180; 3080; 2995; 2926; 1633; 1610; 1577; 1541; 1512; 1442; 1442; 1338; 1240; 1034; 831. ^{1}H NMR (DMSO-d_6), δ: 2.48 (s, 6H, CH_3); 3.71 (s, 3H, OCH_3); 5.42 (s,1H, CH); 6.77 (d, 2H, Ar-H, *J* = 8.4 Hz); 6.92 (d, 2H, Ar-H, *J* = 8.4 Hz); 7.26 (br. s, 1H, NH); 11.96 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 33.2; 55.3; 93.3; 113.5;128.0; 131.3; 157.3; 158.6; 161.9; 163.7. Anal. Cald. for Calculated (%): C, 52.03; H, 4.12; N, 16.86; Found (%): C, 52.20; H, 4.02; N, 16.98. $C_{18}H_{17}N_5O_3S_2$ (415.49).

5-(4-Nitrophenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3g). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3447; 3300; 3188; 2928; 2851; 1642; 1610; 1533; 1515; 1438; 1515; 1342; 1438; 1342; 1236; 844. ^{1}H NMR (DMSO-d_6), δ: 2.49 (s, 6H, CH_3); 5.54 (s, 1H, CH); 6.91 (br. s, 1H, NH); 7.29 (d, 2H, Ar-H, *J* = 8.8 Hz); 8.10 (d, 2H, Ar-H, *J* = 8.8 Hz); 12.08 (s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 34.4; 92.4; 123.4; 128.4; 145.7; 149.0; 159.2; 163.0. Anal. Cald. for $C_{17}H_{14}N_6O_4S_2$ (430.46). Calculated (%): C, 47.43; H, 3.28; N, 19.52; Found (%): C, 47.58; H, 3.12; N, 19.41.

5-(3-Nitrophenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3h). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3355; 3198; 2923; 2850; 1658; 1606; 1528; 1434; 1523; 1342; 1342; 1238; 831. ^{1}H NMR (DMSO-d_6), δ: 2.50 (s, 6H, CH_3); 5.56 (s, 1H, CH); 6.94 (br. s, 1H, NH); 7.55-7.47 (m, 2H, Ar-H); 7.80 (dd, 1H, Ar-H, J_1 = 3.2 Hz, J_2 = 2.0 Hz); 8.03-8.00 (m, 1H, Ar-H); 12.11 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 33.9; 92.4; 120.8; 121.7; 129.6; 134.3; 142.5; 148.2; 159.2; 163.0. $C_{17}H_{14}N_6O_4S_2$ (430.46). Anal. Cald. for Calculated (%): C, 47.43; H, 3.28; N, 19.52; Found (%): C, 47.31; H, 3.39; N, 19.32.

5-(Phenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3i). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3448; 3290; 3159; 3084; 2997; 2916; 2878; 1641; 1610; 1578; 1531; 1450; 1450; 1326; 1236; 771; 692. ^{1}H NMR (DMSO-d_6), δ: 2.48 (s, 6H, CH_3); 5.47 (s, 1H, CH); 6.08 (br. s, 1H, NH); 7.02 (d, 2H, Ar-H, *J* = 8.4 Hz); 7.1 (dt, 1H, Ar-H, J_1 = 7.3, J_2 = 1.0 Hz); 7.20 (t, 2H, Ar-H, *J* = 7.4 Hz);11.98 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 33.9; 93.0; 125.3; 127.0; 128.1; 139.7; 158.1; 161.2; 163.0. Anal. Cald. for $C_{17}H_{15}N_5O_2S_2$ (385.46). Calculated (%): C, 52.97; H, 3.92; N, 18.17; Found (%): C, 52.81; H, 3.98; N, 18.05.

5-(3-Hydroxyphenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3j). White powder, m.p. > 300 °C. IR, v/cm^{-1}: 3446; 3294; 3178; 3088; 2995; 2920; 2891; 1641; 1606; 1577; 1448; 1448; 1336; 1234; 820; 783; 690. ^{1}H NMR (DMSO-d_6), δ: 2.43 (s, 6H, CH_3); 5.37 (s, 1H, CH); 6.43(m, 3H, Ar-H); 6.73 (br. s, 1H, NH); 6.93 (t, 1H, Ar-H, *J* = 7.58 Hz); 8.92 (br. s, 1H, OH); 11.90 (br. s, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 12.9; 33.8; 112.2; 113.8; 113.9; 117.9; 128.9; 141.4; 157.3; 157.4; 158.6; 162.8. Anal. Cald. for $C_{17}H_{15}N_5O_3S_2$ (401.46). Calculated (%): C, 50.86; H, 3.77; N, 17.44; Found (%): C, 50.60; H, 3.64; N, 17.35.

5-(4-Chlorophenyl)-2,8-bis(methylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3k). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3445; 3391; 3306; 3173; 3091; 2923; 1635; 1608; 1577; 1539; 1442; 1442; 1336; 1240; 1091; 829. ^{1}H NMR (DMSO-d$_6$), δ: 2.43 (s, 6H, CH$_3$); 5.40 (s, 1H, CH); 6.76 (br. s, 1H, NH); 6.99 (d, 2H, Ar-H, *J* = 8.32 Hz); 7.22 (d, 2H, Ar-H, *J* = 8.32 Hz); 11.96 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 12.9; 33.6; 92.7; 128.0; 129.0; 129.8; 138.9; 159.0; 162.3; 163.8. Anal. Cald. for $C_{17}H_{14}ClN_5O_2S_2$ (419.91). Calculated (%): C, 48.63; H, 3.36; N, 16.68; Found (%): C, 48.68; H, 3.25; N, 16.52.

5-(2,4-Dichlorophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3l). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3360; 3205; 2963; 2924; 2880; 1655; 1605; 1558; 1441; 1441; 1370; 1240; 1133; 1043; 874; 690. ^{1}H NMR (DMSO-d$_6$), δ: 1.30 (t, 6H, CH$_3$, *J* = 7.4 Hz); 3.10 (q, 4H, CH$_2$, *J* = 7.4 Hz); 5.39 (s, 1H, CH); 6.89 (br. s, 1H, NH); 7.22 (d, 1H, Ar-H, *J* = 8.4 Hz); 7.35 (dd, 1H, Ar-H, *J*$_1$ = 8.4 Hz, *J*$_2$ = 2.4 Hz); 7.42 (d, 1H, Ar-H, *J* = 2.4 Hz); 11.88 (br. s, 1H, NH-C=O); 12.07 (br. s, 1H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.1; 24.3; 33.0; 127.0; 129.0; 130.6; 131.0; 133.9; 138.0; 158.2; 161.5. Anal. Cald. for $C_{19}H_{17}Cl_2N_5O_2S_2$ (482.41). Calculated (%): C, 47.31; H, 3.55; N, 14.52; Found (%): C, 47.20; H, 3.64; N, 14.60.

5-(4-Nitrophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3m). Cream powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3352; 3182; 2962; 2926; 2870; 1653; 1606; 1518; 1445; 1518; 1342; 1342; 1236; 845. ^{1}H NMR (DMSO-d$_6$), δ: 1.31 (t, 6H, CH$_3$, *J* = 7.4 Hz); 3.12 (m, 4H, CH$_2$); 5.55 (s, 1H, CH); 6.92 (br. s, 1H, NH); 7.30 (d, 2H, Ar-H, *J* = 8.6 Hz); 8.11 (d, 2H, Ar-H, *J* = 8.6 Hz); 12.07 (s, 2H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.2; 24.3; 34.5; 92.4; 123.4; 128.4; 145.7; 149.0; 158.6; 162.0; 163.9. Anal. Cald. for $C_{19}H_{18}N_6O_4S_2$ (458.51). Calculated (%): C, 49.77; H, 3.96; N, 18.33; Found (%): C, 49.65; H, 3.84; N, 18.48.

5-(4-Bromophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dion (3n). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3348; 3182; 2966; 2926; 2862; 1657; 1607; 1564; 1539; 1443; 1443; 1335; 1236; 1066; 827. ^{13}C NMR (DMSO-d$_6$), δ: 15.2; 24.3; 33.6; 92.6; 118.3; 129.5; 130.9; 139.4; 158.3; 162.1; 163.8. $C_{19}H_{18}BrN_5O_2S_2$ (492.41). Anal. Cald. for Calculated (%): C, 46.34; H, 3.68; N, 14.22; Found (%): C, 46.39; H, 3.52; N, 14.10.

5-(2-Chlorophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3o). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3350; 3196; 2965; 2933; 1653; 1605; 1558; 1439; 1439; 1358; 1234; 1126; 1038, 779. ^{1}H NMR (DMSO-d$_6$), δ: 1.30 (t, 6H, CH$_3$, *J* = 7.2 Hz); 3.11 (q, 4H, CH$_2$, *J* = 7.2 Hz); 5.43 (s, 1H, CH); 7.24-7.17 (m, 3H, Ar-H); 7.29 (d, 1H, Ar-H, *J* = 7.6 Hz); 11.96 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.1; 24.3; 33.3; 92.6; 126.9; 127.5; 129.3; 129.6; 133.1; 138.7; 158.0; 161.6; 161.7. Anal. Cald. for $C_{19}H_{18}ClN_5O_2S_2$ (447.96). Calculated (%): C, 50.94; H, 4.05; N, 15.63; Found (%): C, 50.76; H, 4.16; N, 15.44.

5-(4-(Trifluoromethyl)phenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dion (3p). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3348; 3184; 2960; 2940; 2867; 1653; 1610; 1541; 1448; 1448; 1327; 1163; 1119; 1238; 841. ^{1}H NMR (DMSO-d$_6$), δ: 1.31 (t, 6H, CH$_3$, *J* = 7.4 Hz); 3.12 (m, 4H, CH$_2$); 5.53 (s, 1H, CH); 6.86 (br. s, , 1H, NH); 7.24 (d, 2H, Ar-H, *J* = 8.2 Hz); 7.57 (d, 2H, Ar-H, *J* = 8.2 Hz); 12.03 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.2; 24.3; 34.1; 92.6; 124.1 (d, $^{1}J_{C\text{-}F}$ = 270.0 Hz, CF$_3$); 125.0 (q, $^{3}J_{C\text{-}F}$ = 3.0 Hz); 126.1 (q, $^{2}J_{C\text{-}F}$ = 31.0 Hz, C-CF$_3$); 127.8; 145.1; 158.5; 162.2; 163.9. Anal. Cald. for $C_{20}H_{18}F_3N_5O_2S_2$ (481.51). Calculated (%): C, 49.89; H, 3.77; N, 14.54; Found (%): C, 49.75; H, 3.62; N, 14.39.

5-(2-Fluorophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3q). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3362; 3198; 2963; 2923; 2873; 1653; 1608; 1533; 1510; 1439; 1439; 1343; 1228; 758. ^{1}H NMR (DMSO-d$_6$), δ: 1.30 (t, 6H, CH$_3$, *J* = 7.2 Hz); 3.09 (q, 4H, CH$_2$, *J* = 7.2 Hz); 5.48 (s, 1H, CH); 6.8 (br. s, 1H, NH); 6.98 (dd, 1H, Ar-H, *J*$_1$ = 11.2 Hz, *J*$_2$ = 8.4 Hz); 7.07-7.05 (m, 2H, Ar-H); 7.19-7.17 (m, 1H, Ar-H), 11.95 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.2; 24.3; 29.8; 92.6; 115.0 (d, $^{2}J_{C\text{-}F}$ = 23.0 Hz); 124.0 (d, $^{4}J_{C\text{-}F}$ = 2.0 Hz); 127.5 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz); 127.6 (d, $^{2}J_{C\text{-}F}$ = 16.8 Hz); 128.9 (d, $^{3}J_{C\text{-}F}$ = 4.0 Hz); 158.0; 161.4; 161.5 (d, $^{1}J_{C\text{-}F}$ = 244.0 Hz); 163.6. $C_{19}H_{18}FN_5O_2S_2$ (431.51). Anal. Cald. for Calculated (%): C, 52.89; H, 4.20; N, 16.23; Found (%): C, 52.73; H, 4.08; N, 16.21.

5-(2-Bromophenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3r). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}:3362; 3198; 2960; 2920; 2860; 1649; 1608; 1531; 1450; 1450; 1232; 800. ^{1}H NMR (DMSO-d$_6$), δ: 1.30 (t, *J* = 7.2 Hz, 6H, CH$_3$); 3.11 (br.s, 4H, CH$_2$); 5.35 (s, 1H, CH); 6.88 (s, br,1H, NH); 7.09-7.06 (m, 1H, Ar-H); 7.27-7.25 (m, 2H, Ar-H); 7.47 (d, 1H, Ar-H, *J* = 8.0 Hz); 11.78 (s, br, 1H, NH-C=O); 12.05 (br. s, 1H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.1; 24.3; 35.5; 123.6; 127.4; 127.8; 129.5; 133.1; 140.4; 158.0; 158.1; 161.82; 161.84. $C_{19}H_{18}BrN_5O_2S_2$ (492.41). Anal. Cald. for Calculated (%): C, 46.34; H, 3.68; N, 14.22; Found (%): C, 46.25; H, 3.58; N, 14.31.

5-(4-Methoxyphenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dion (3s). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3350; 3178; 2959; 2946; 1649; 1606; 1578; 1539; 1512; 1441; 1441; 1335; 1240; 1034; 833. ^{1}H NMR (DMSO-d$_6$), δ: 1.30 (t, 6H, CH$_3$, *J* = 7.2 Hz); 3.10 (q, 4H, CH$_2$, *J* = 7.2 Hz); 5.42 (s, 1H, CH); 3.71 (s, 3H, OCH$_3$); 6.65 (br. s, 1H, NH); 6.77 (d, 2H, Ar-H, *J* = 8.6 Hz); 6.92 (d, 2H, Ar-H, *J* = 8.6 Hz); 11.93 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d$_6$), δ$_C$: 15.2; 24.3; 33.2; 55.3; 93.4; 113.5; 128.0; 131.4; 157.2; 158.0; 162.2; 163.8. Anal. Cald. for $C_{20}H_{21}N_5O_3S_2$ (443.54). Calculated (%): C, 54.16; H, 4.77; N, 15.79; Found (%): C, 54.03; H, 4.68; N, 15.70.

5-(4-Formylphenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dion (3t). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3367; 3184; 2966; 2924; 1695; 1642; 1608; 1570; 1435; 1435; 1335; 1227, 831. ^{1}H NMR (DMSO-d$_6$), δ: 1.31 (t, *J* = 7.2 Hz, 6H, CH$_3$); 3.13-3.10 (m, 4H, CH$_2$); 5.53 (s, 1H, CH); 6.86 (br.s, 1H, NH); 7.25 (d,

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2H, Ar-H, *J* = 8.0 Hz); 7.77 (d, 2H, Ar-H, *J* = 8.0 Hz); 9.94 (s, 1H, CHO); 12.02 (br.s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 15.2; 24.3; 34.5; 92.6; 123.5; 127.8; 129.6; 134.2; 193.1; 164.7; 158.5; 147.9. Anal. Cald. For $C_{20}H_{19}N_5O_3S_2$ (441.53).Calculated (%): C, 54.41; H, 4.34; N, 15.86; Found (%): C, 54.58; H, 4.25; N, 15.71.

5-(Naphthalen-2-yl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3u). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3350; 3184; 2950; 2926; 2858; 1653; 1608; 1533; 1443; 1443; 1329; 1238; 814; 739; 708. ^{1}H NMR (DMSO-d_6), δ: 1.33 (t, *J* = 7.4 Hz, 6H, CH_3); 3.14-3.12 (m, 4H, CH_2); 5.63 (s, 1H, CH); 6.83 (br.s, 1H, NH); 7.25 (d, 1H, Ar-H, *J* = 8.6 Hz); 7.43-7.41 (m, 2H, Ar-H); 7.46 (s, 1H, Ar-H); 7.74 (d, 1H, Ar-H, *J* = 8.6 Hz); 7.84-7.77 (m, 2H, Ar-H); 11.99 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 15.2; 24.3; 34.2; 89.0; 124.0; 125.3; 126.0; 127.0; 127.4; 127.6; 127.9; 128.8; 131.8; 133.5; 137.7; 139.0; 158.5. Anal. Cald. for $C_{23}H_{21}N_5O_2S_2$ (463.58). Calculated (%): C, 59.59; H, 4.57; N, 15.11; Found (%): C, 59.67; H, 4.62; N, 15.01.

5-(Phenyl)-2,8-bis(ethylthio)-5,10-dihydropyrido[2,3-*d*:5,6-*d*`]dipyrimidin-4,6(3*H*,7*H*)-dione (3v). White powder, m.p. > 300 ^{o}C. IR, v/cm^{-1}: 3360; 3302; 3194; 2972; 2924; 2862; 1610; 1568; 1539; 1443; 1443; 1373; 1238; 773; 694 . ^{1}H NMR (DMSO-d_6), δ: 1.31 (t, 6H, CH_3, *J* = 7.0 Hz); 3.10 (q, 4H, CH_2, *J* = 7.0 Hz); 5.48 (s, 1H, CH); 6.77 (br. s, 1H, NH); 7.03 (d, 2H, Ar-H, *J* = 7.6 Hz); 7.1 (t, 1H, Ar-H, *J* = 7.0 Hz); 7.20 (t, 2H, Ar-H, *J* = 7.4 Hz); 11.82 (br. s, 2H, NH-C=O). ^{13}C NMR (DMSO-d_6), δ_C: 15.2; 24.3; 33.9; 93.0; 125.3; 127.0; 139.8; 128.0; 158.1; 161.2; 162.8. Anal. Cald. for $C_{19}H_{19}N_5O_2S_2$ (413.52). Calculated (%): C, 55.19; H, 4.63; N, 16.94; Found (%): C, 55.10; H, 4.78; N, 16.75.

CONCLUSION

In summary, we have developed a simple and efficient protocol for the synthesis of new derivatives of dihydropyridodipyrimidines in the mixed solvent of glacial acetic acid and DMF (1:1, v:v) under ultrasonic irradiation. The reaction induced by ultrasound offered better yields and much lower reaction times than the conventional heating. The easy work of the products, mild reaction condition and cleaner reaction are the notable features of this protocol.

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