A Facile Three-Components, One-Pot Synthesis of Pyrimido[4,5-*d*]pyrimidine-2,5-dione Derivatives under Microwave-Assisted Conditions

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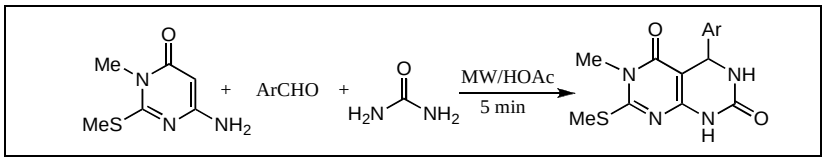

Pyrimido[4,5-*d*]pyrimidine-2,5-dione derivatives have been synthesized in high yields in a novel, one-pot, and efficient process by condensation of 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3*H*)-one, aldehydes and urea under microwave-assisted conditions.

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INTRODUCTION

The importance of fused pyrimidines, common source for the development of new potential therapeutic agents [1], is well known. Among them, the pyrimido[4,5-*d*]pyrimidines and pyrimido[2,3-*d*]pyrimidines are an important class of annelated uracils with biological significance because of their connection with purine pteridine system [2]. Numerous reports delineate the antitumor [3], antiviral [4], antioxidant [5], antifungal [6] and hepatoprotective [7] activity of these compounds. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As result, a number of reports have appeared in literature, which usually requires harsh conditions, long reaction times, and complex synthetic pathway [8]. Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

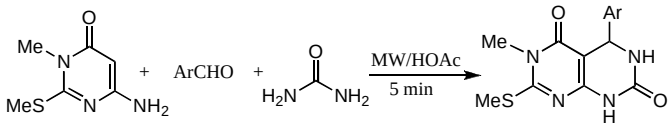
One-pot multi-component reactions (MCRs) by virtue of their convergence, productivity, facile execution, and generally high yield of products have attracted considerable attention from the point of view of ideal synthesis [9]. MCRs are perfectly suited for combinatorial library synthesis, thus are finding increasing use in the discovery process for new drugs and agrochemicals [10]. The potential application of microwave technology in organic synthesis is increasing rapidly because of reaction simplicity, less pollution and minimum reaction times providing rapid access to large libraries of diverse small molecules [11].

Considering the above reports and in continuation of our previous work on microwave-assisted synthesis of heterocyclic compounds [12], and pursuing our studies on multi-component reactions [13], herein, we wish to report a novel, efficient, one-pot and three-components method for the preparation of 3,4-dihydro-6-methyl-7-(methylthio)-4-arylpyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione derivatives under microwave-assisted conditions.

RESULTS AND DISCUSSION

To the best of our knowledge, there are no reports in the literature for the preparation of 3,4-dihydro-6-methyl-7-(methylthio)-4-arylpyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione derivatives **4** *via* condensation of 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3*H*)-one **1**, aldehyde **2** and urea.

After some preliminary experimentation, it was found that a mixture of 6-aminopyrimidine **1**, benzaldehyde **2a** and urea 3 in the presence of a catalytic amount of acetic acid (HOAc) afforded 3,4-dihydro-6-methyl-7-(methylthio)-4-phenylpyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione **4a** in 80% yield under microwave-assisted conditions for 5 min (Scheme 1).



In order to find the best catalyst for the synthesis of the pyrimido[4,5-*d*]pyrimidine-2,5-dione derivatives **4**, the reaction of 6-aminopyrimidine **1**, benzaldehyde **2a** and urea was performed in the absence of catalyst or in the presence of various protic acid or Lewis acids under similar conditions. As indicated in Table 1, the best yield was obtained when HOAc was used (Table 1).

Table 1

Catalyst Effect on the Reaction[a]

Entry	Catalyst	Yields %
1	CH_3COOH	80
2	CF_3COOH	43
3	4-Me-$C_6H_4SO_3H$	35
4	LiCl	-
5	$ZnCl_2$	-
6	$CuCl_2$	20<
7	Without Cat.	-

[a] Benzaldehyde **2a** (1 mmol), urea (1.5 mmol), 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3*H*)-one **1** (1 mmol) and Cat. (0.5 mmol).

To explore the scope and limitation of this reaction, we extended the procedure to various *para*-substituted benzaldehydes. The optimized results are summarized in Table 2. High yields were obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents.

Table 2

Reaction of 6-aminopyrimdine **1**, aldehydes **2** and urea under MW irradiation [a]

Products **4**	Ar	Yields %	Mp (°C)
a	C_6H_5	80	272-274
b	4-Me-C_6H_4	85	164 dec.
c	4-MeO-C_6H_4	76	289-291
d	4-Cl-C_6H_4	83	269-271
e	4-F-C_6H_4	79	245 dec.
f	4-Br-C_6H_4	85	303-305

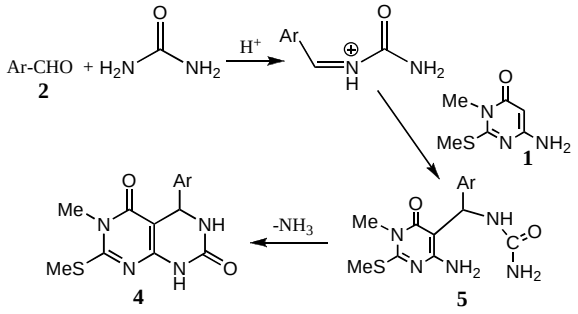
[a] With power of 900 W.

Under the same conditions, this reaction almost could not be observed when the aliphatic aldehydes were used as a starting material.

According to the results, and as in numerous classical multi-component reaction classic [14], the reaction can be mechanistically considered to proceed through the acylimine intermediate formed *in situ* by condensation reaction of the aldehyde with urea. The subsequent addition of the 6-aminopyrimdine **1** to the acylimine, followed by cyclization of the intermediate **5** afforded the corresponding products **4a-f** and ammonia (Scheme 2).

The structures of the products **4a-f** were characterized by ir, ^{1}H nmr, ^{13}C nmr and ms spectra. Finally the structure of **4a** was confirmed by a single-crystal X-ray analysis (Figure 1) [15].

Scheme 2



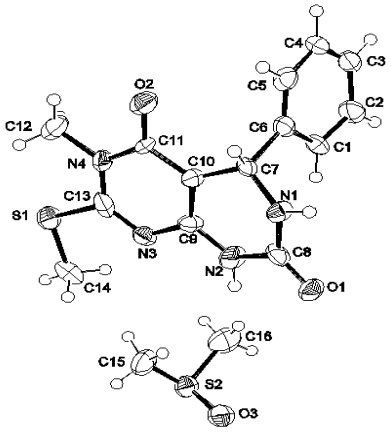


Figure 1. ORTEP diagram of **4a**

In summary, we have described a novel, efficient one-pot and green synthesis for the preparation of pyrimido-[4,5-*d*]pyrimidine-2,5-dione derivatives **4** in three-component cyclo-condensation reaction of 6-amino-3-methyl-2-(methylthio)pyrimidin-4(3*H*)-one **1**, aromatic aldehydes and urea under microwave irradiation. The novelty and synthetic usefulness of these methodologies was demonstrated in the efficient synthesis of uracil derivatives.

EXPERIMENTAL

Melting points were measured on an Elecrtothermal 9100 apparatus and are uncorrected. 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, respectively. IR spectra were recorded using an FTIR apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. The microwave oven was a domestic National model NN-6653 with select power levels. The reflections for X-ray diffraction analysis were collected on a STOE IPDSII two-circle diffractometer.

General procedure for preparation of 3,4-dihydro-6-methyl-7-(methylthio)-4-arylpyrimido[4,5-*d*]pyrimidine 2,5(1*H*,6*H*) dione (4a-f). A mixture of 6-aminopyrimidine 1 (1

mmol), aldehyde 2 (1 mmol), urea (1.5 mmol) and acetic acid (0.5 mmol) were finely mixed together. The reaction mixture was placed in a Pyrex test tube and irradiated for 5 min with a power of 900 W. After cooling, product was collected by filtration, washed with water, and then recrystallized from EtOH/H_2O to afford the pure product **4a-f** (Table 2).

3,4-Dihydro-6-methyl-7-(methylthio)-4-phenylpyrimido-[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)dione (4a). White powder, yield 80%, mp 272-274°; ir: 3416, 3330, 1688, 1639 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.25 (s, 1H, CH), 7.29 (m, 5H, arom), 7.76 (s, 1H, NH), 9.81 (s, 1H, NH).; ^{13}C nmr (DMSO-d_6): δ 14.8, 30.1, 52.3, 93.5, 126.6, 127.8, 128.8, 144.52, 151.9, 153.2, 159.4, 163.3; ms: m/z 302 (M^+, 12), 225 (100), 177 (23), 88 (35), 51 (30). *Anal*. Calcd. For $C_{14}H_{14}N_4O_2S$: C, 55.61; H, 4.67; N, 18.53. Found: C, 55.62; H, 4.68; N, 18.55.

3,4-Dihydro-6-methyl-7-(methylthio)-4-(4-methylphenyl)-pyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4b). White powder, yield 85%, mp 164° dec.; ir: 3448, 3229, 1697, 1661 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.29 (s, 3H, CH3), 5.21 (s, 1H, CH), 7.10-7.16 (m, 4H, arom), 7.67 (s, 1H, NH), 9.73 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.3, 20.5, 29.5, 51.5, 93.1, 126.1, 128.7, 136.4, 141.1, 151.4, 152.6, 158.8, 162.6; ms: m/z 316 (M^+, 89), 241 (13), 225 (100), 177 (33), 88 (55), 65 (30). *Anal*. Calcd. for $C_{15}H_{16}N_4O_2S$: C, 56.94; H, 5.10; N, 17.71. Found: C, 56.95; H, 5.12; N, 17.80.

3,4-Dihydro-6-methyl-7-(methylthio)-4-(4-methoxyphenyl)-pyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4c). White powder, yield 76%, mp 289-291°, ir: 3342, 3100, 1695, 1658 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 5.19 (s, 1H, CH), 6.84-7.18 (m, 4H, arom), 7.69 (s, 1H, NH), 9.77 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.8, 30.1, 51.7, 55.5, 93.7, 114.1, 127.7, 136.7, 151.7, 153.1, 159.0, 159.3, 163.11; ms: m/z 332 (M^+, 33), 301 (39), 225 (100), 177 (23), 88 (55), 42 (30). *Anal*. Calcd. for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86. Found: C, 54.22; H, 4.86; N, 16.88.

3,4-Dihydro-6-methyl-7-(methylthio)-4-(4-chlorophenyl)-pyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4d). White powder, yield 83%, mp 269-271°; ir: 3421, 1706, 1656 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.26 (s, 1H, CH), 7.31-7.36 (m, 4H, arom), 7.77 (s, 1H, NH), 9.84 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.8, 30.1, 51.8, 93.0, 128.5, 128.7, 132.3, 143.4, 151.9, 152.9, 159.3, 163.5.; ms: m/z 336 (M^+, 14), 301 (10), 225 (100), 138 (23), 75 (35), 43 (30). *Anal.calcd*. for $C_{14}H_{13}ClN_4O_2S$: C, 49.93; H, 3.89; N, 16.64. Found: C, 49.94; H, 3.90; N, 16.66.

3,4-Dihydro-6-methyl-7-(methylthio)-4-(4-flourophenyl)-pyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4e). White powder, yield 79%, mp 245° dec.; ir: 3320, 1692, 1659 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.26 (s, 1H, CH), 7.10-7.33 (m, 4H, arom), 7.77 (s, 1H, NH), 9.84 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.8, 30.1, 51.7, 93.3, 115.3, 115.6, 128.5, 128.7, 140.7, 151.9, 153.0, 161.5; ms: m/z 320 (M^+, 45), 245 (27), 225 (100), 177 (46), 88 (28). *Anal*. Calcd. for $C_{14}H_{13}FN_4O_2S$: C, 52.49; H, 4.09; N, 17.49. Found: C, 52.48; H, 4.11; N, 17.50.

3,4-Dihydro-6-methyl-7-(methylthio)-4-(4-bromophenyl)-pyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4f). White powder, yield 85%, mp 303-305°; ir: 3420, 3100, 1692, 1654 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 5.24 (s, 1H, CH), 7.23-7.49 (m, 4H, arom), 7.77 (s, 1H, NH), 9.84 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.8, 30.1, 51.9, 92.9, 120.8, 128.9, 131.6, 143.8, 151.9, 152.9, 159.3, 163.5; ms: m/z 381 (M^+, 39), 338 (17), 225 (100), 177 (34), 88 (30). *Anal*. Calcd. for $C_{14}H_{13}BrN_4O_2S$: C, 44.11; H, 3.44; N, 14.70. Found: C, 44.13; H, 3.45; N, 14.71.

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[15] Crystal data analyses: Stoe IPDS-II two-circle diffractometer, MoKα radiation (λ = 0.71073); T =293(2) K; Graphite monochromator; numerical absorption correction. Structure solution by direct methods using SHELXS and refinement by full-matrix least-squares on F^2 using SHELXL of the X-STEP32 suite of programs [16] all non-hydrogen atoms were refined anisotropically. Crystal data for **4a**: $C_{14}H_{14}N_4O_2S$ (DMSO), M = 380.50 $gmol^{-1}$; crystal dimensions 0.20 x 0.10 x 0.05 mm^3; Triclinic, space group P1, Z=2; a = 8.661(4), b = 10.132(4), c = 11.185(4) Å, α = 77.11(3)°, β = 67.16(3)°, γ = 86.52(3)°; V = 881.3(6) $Å^3$; Z = 2; F(000) = 400, ρcalc = 1.434 g cm^{-3}; 2.02°< θ<29.30°; section of the reciprocal lattice: -11 ≤ h ≤ 10, -13 ≤ k ≤ 13, -13 ≤ l ≤ 14; of 8552 measured reflections, 7279 were independent (R_{int}=0.1081) and 5583 with I > 2 σ(I); absorption coefficient 0.326 mm^{-1}; R1 = 0.0684 for I > 2 σ(I), wR2 = 0.2296 (all data) and S = 1.119; largest peak (0.298 $eÅ^{-3}$) and hole (-0.360 $eÅ^{-3}$).

[16] X-STEP32 Version 1.07b, X-ray structure evaluation package, 2000, Stoe & Cie, Darm-stadt, Germany.