

One-Pot Two-Step Solvent-Free Rapid and Clean Synthesis of 2-(Substituted Amino)pyrimidines by Microwave Irradiation

Shyamaprosad Goswami,* Anita Hazra, and Subrata Jana†

Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah 711103, India

Received January 29, 2009; E-mail: spgoswamical@yahoo.com

A series of diversely 2-(substituted amino)pyrimidines (along with ring substitution) has been synthesized under solvent- and catalyst-free microwave conditions from substituted guanidines and β-diketones. The substituted guanidines are synthesized from (*S*)-methylisothiourea sulfate and different amines (various alkyl, aryl, or heterocyclic and also chiral amines) under microwave irradiation. These two-step reactions are performed in one-pot without isolating any intermediate. This protocol has been successfully applied for the synthesis of bisaminopyrimidines and 2-substituted aminopyrimidines containing chiral moiety where chirality remains undisturbed.

2-(Substituted amino)pyrimidines are of great interest due to their pharmacological importance.[1–4] Specifically 2-anilinopyrimidines are fungicides and bipyrimidines have antiamoebic activity.[5] Substituted pyrimidines are also important synthons for the synthesis of pterin and purine related compounds.[6,7] These different substituted aminopyrimidines are used as hosts for recognition as well as supramolecular studies with neutral molecules and metal ions.[8]

These types of compounds are synthesized either by direct condensation of substituted guanidines[9] with β-dicarbonyls, ethyl acetoacetate, and ethyl cyanoacetate or by nucleophilic aromatic substitution reactions of amines with halogenated pyrimidines.[10] The amino group of 2-aminopyrimidine is substituted by aryl- or alkylamines under acidic conditions for the synthesis of this type of compounds.[11] The other important type of synthesis is the condensation reaction between alkyl(aryl)amines with 2-methylthiopyrimidine under drastic conditions.[12] However all these reactions are carried out under drastic conditions following multi-step procedures. Here we have developed this new efficient, quick, and clean method for the synthesis of such pyrimidines.

Different organic synthesis has been exploited under microwave irradiation due to its immense environmental impact and short reaction time.[13] Currently this technique has been widely used for different organic transformations including the synthesis of a wide range of heterocyclic compounds.[14,15] Our continuing efforts for the successful implementation of microwave technique in solid-phase organic synthesis,[16] led us to attempt the one-pot synthesis of 2-(substituted amino)pyrimidines.

Results and Discussion

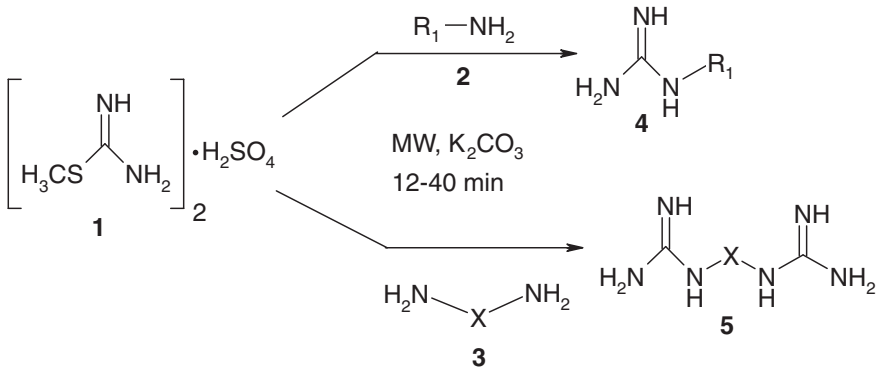
We have recently reported the synthesis of substituted 2-aminopyrimidines under microwave irradiation where substituents are varied only in the heterocyclic ring.[17] But as the secondary amino substitution in the pyrimidine ring is an important criteria for different pharmacological activities,[1–4] we report here a new one-pot synthesis of substituted aminopyrimidines where substituents in both ring and amine moiety may be varied simultaneously.

In conventional methods, substituted guanidines are prepared by the reaction of isothiourea (=aminoiminomethanethiol) salts[10d] and alkyl(aryl)amine in the presence of a strong base in ethanol for several hours under refluxing conditions. These substituted guanidines are condensed with β-diketones to produce 2-(substituted amino)pyrimidine under refluxing condition.[9] So both the steps require several hours along with drastic reaction conditions. But in our method, both the steps are performed in a single reaction vessel under microwave irradiation without using any solvent or catalyst.

Monosubstituted guanidines are obtained initially by the microwave reaction of (*S*)-methylisothiourea salt and corresponding amines in solid phase. In one representative case, benzyl-substituted guanidine is obtained from benzylamine (**2b**) (4 mmol), isothiourea salt (2 mmol), and potassium carbonate (2.5 mmol) by irradiation at 450 W for 18 min (Scheme 1). The unreacted benzylamine in the reaction mixture is removed by washing with chloroform and the solid residue is then dried well. This solid residue is again irradiated with acetylacetone (**7a**) at 300 W for 5 min to afford the 2-benzylamino-4,6-dimethylpyrimidine (**8d**) in an overall 78% yield. The required temperatures are 90–100 and 55–65 °C for the first step and second step of the reaction respectively, which have been measured by introducing a thermometer in the reaction mixture just at the end of the reactions.[18] We also followed the same reaction conditions in a conventional method in a preheated oil bath where the yields were very low. The synthesis of substituted guanidines from isothiourea salt and different amines is summarized in Table 1 whereas their condensation with β-diketones, ethyl acetoacetate, and ethyl cyanoacetate are shown in Table 2. Both the steps are carried out in solvent-free conditions and the final substituted aminopyrimidines are isolated by a simple workup.

† Present address: Department of Chemistry, University of Victoria, Victoria, Canada

Published on the web September 9, 2009; doi:10.1246/bcsj.82.1175



Scheme 1. Synthesis of substituted guanidines (for R_1 and X see Table 1) from (*S*)-methylisothiourea salt **1**.

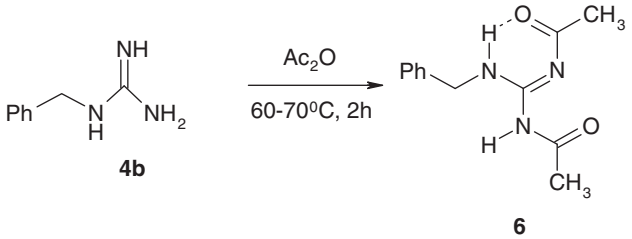
Table 1. Microwave-Assisted Synthesis of Substituted Guanidines from (*S*)-Methylisothiourea Salt **1** and Various Amines **2** and **3**

Entry	Mono/diamine (**2**/**3**)	MW conditions		Substituted guanidine (**4**/**5**)
		P/W	*t*/min	
a	$R_1 = –C_4H_9$	450	12	**4a**
b	$R_1 = –CH_2C_6H_5$	450	18	**4b**
c	$R_1 = –C_6H_5$	450	30	**4c**
d	$R_1 = 4\text{-MeO–}C_6H_4–$	450	27	**4d**
e	$R_1 =$ 1-Phenylethyl	450	12	**4e**
f	$R_1 =$ 2-Furfuryl	450	20	**4f**
g	$R_1 = 6\text{-}CH_3–C_5H_3N–$	450	40	**4g**
h	$X = –(CH_2)_6–$	450	18	**5h**
i	$X = 1,3\text{-}CH_2(–C_6H_4–)CH_2–$	450	25	**5i**
j	$R_1 = 3\text{-}NO_2–C_6H_4–$	450	40	no reaction
k	$R_1 =$ Diphenyl	450	45	no reaction

So the substituted guanidines are easily synthesized by nucleophilic replacement of a thiomethyl group by various amines including alkyl, aromatic, heteroaromatic, and chiral moieties (Scheme 1) under microwave irradiation. The important observation during the synthesis of substituted guanidines is that no substituted products of (*S*)-methylisothiourea salt with secondary amine like di-*n*-butylamine, diisopropylamine, or diphenylamine are formed. Similar results are also observed in the case of nitro-substituted aryl amines, which are very much less reactive toward nucleophilic displacement. So the substituted guanidines containing these groups are not obtained under microwave irradiation.

The formation of substituted guanidine in the first step (Scheme 1) under microwave irradiation is proven by the formation of the acetyl derivative of benzyl-substituted guanidine **4b**. The acetate derivative **6** is obtained by acetylation (Ac_2O, 60–70 °C, 2 h) of compound **4b** (Scheme 2).

The ^{1}H NMR spectrum of this benzylguanidine diacetate (**6**) shows the appearance of a secondary benzylamine proton at a very downfield position (δ 13.18) due to intramolecular hydrogen bonding with one of the amide carbonyl groups. The other amide proton appears at δ 9.33. The appearance of a doublet of two benzylic protons at δ 4.65 ($J = 5.7$ Hz) implies that benzyl-substituted N–H is not acetylated with acetic anhydride. So only the imino and primary amino groups of the

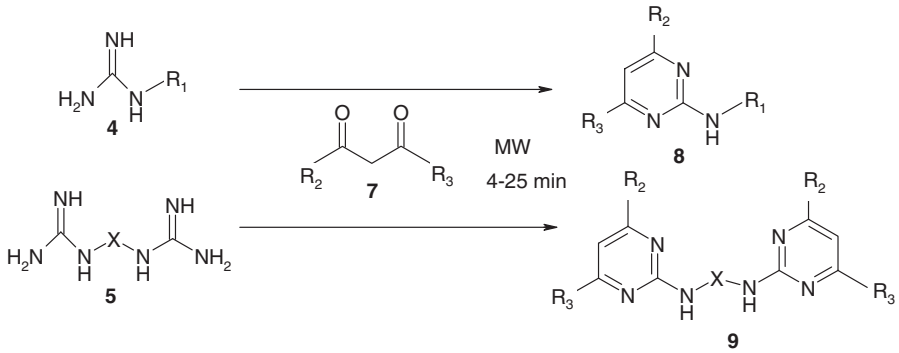


Scheme 2. Synthesis of the acetyl derivative of benzyl-guanidine.

benzyl-substituted guanidine moiety are converted to their acetyl derivatives. The molecular ion peak of compound **6** is observed at 234.4 (MH^+, 20%).

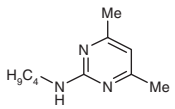
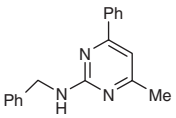
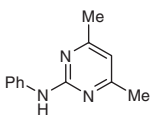
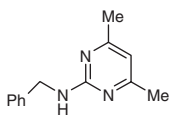
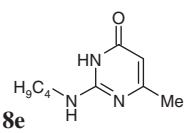
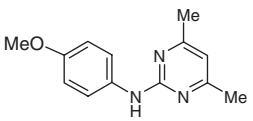
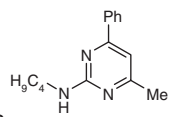
These substituted guanidines are used for the condensation in the next step. Upon condensation with β-diketones, ethyl acetoacetate, and ethyl cyanoacetate, diversely substituted 2-aminopyrimidines are synthesized. The subsequent condensation of these substituted guanidines with β-diketones (Scheme 3) affords the fully aromatized 2-(substituted amino)-pyrimidines (**8a–8p** and **9q–9r**, Table 2). The interesting observation in this study is that the substituted amino groups are always attached to "C2" of the substituted pyrimidine rings. So the ring formation always takes places through two unsubstituted amine and imine groups of the substituted guanidines with β-diketones. During the condensation reactions, no dihydropyrimidines were isolated which indicates that the substituted amine moiety of guanidines are not involved in the cyclization process.

The overall yields at Table 2 are directly influenced by the nucleophilicity order of the alkyl, aryl, and heterocyclic amines. The yields of the 2-(substituted amino)pyrimidine containing alkyl group (**8a**, **8e**, **8g**, **8i**, and **9q**) are higher as alkyl groups enhance nucleophilicity of the guanidinium moiety. But the isolated yield of pyrimidines containing heteroaryl moiety (**8p**) is lower than the pyrimidines containing aryl moiety (**8c** and **8f**) as both aryls and heteroaryls reduce the nucleophilic reactivity of the guanidine moiety. In the case of 2-(substituted amino)pyrimidines containing benzylic substituents (**8b**, **8d**, **8h**, **8m**, **8n**, **8o**, and **9r**), the yields are in the intermediate range of both alkyl and aryl/heteroaryl 2-(substituted amino)pyrimidines. The other significant observation is that the chirality of the amine **2e**



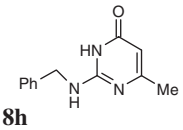
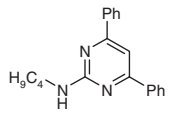
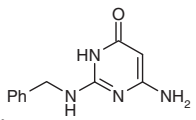
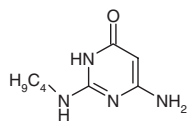
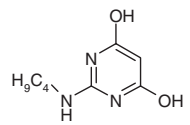
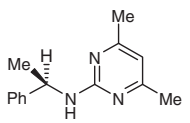
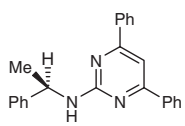
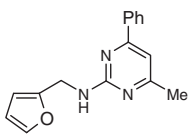
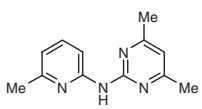
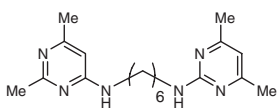
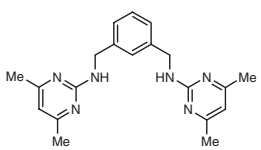
Scheme 3. Synthesis of 2-(substituted amino)pyrimidine from monosubstituted guanidines or diguanidino compound and β-diketones (for R_1, R_2, R_3, and X, see Table 2).

Table 2. Microwave-Supported Synthesis of 2-(Substituted Amino)pyrimidines from Monosubstituted Guanidines and Diguanidino Compounds with β-Diketones

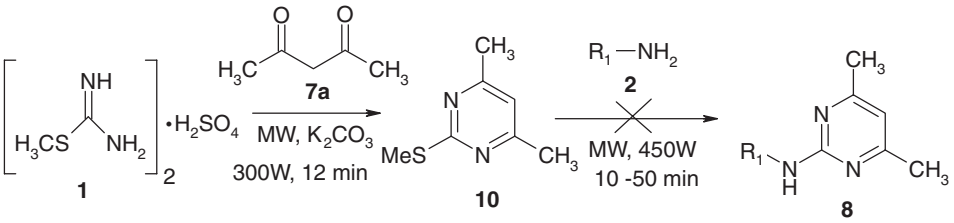
Entry	Mono/bis substituted guanidine **4**/**5**	β-Diketone **7**	MW conditions		Product **8**/**9**	Yield[a]/%	Mp[19a,19b] (lit)/°C
			P/W	t/min			
a	**4a**	**7a**: $R_2 = R_3 = Me$	300	4	 **8a**	80	Dense liquid
b	**4b**	**7b**: $R_2 = Ph$, $R_3 = Me$	300	5	 **8b**	74	112–114
c	**4c**	**7a**: $R_2 = R_3 = Me$	300	9	 **8c**	65	84–86 (96–97)
d	**4b**	**7a**: $R_2 = R_3 = Me$	300	5	 **8d**	78	110–112 (111–112)
e	**4a**	**7c**: $R_2 = OEt$, $R_3 = Me$	300	8	 **8e**	68	68–70 (91)
f	**4d**	**7a**: $R_2 = R_3 = Me$	300	8	 **8f**	67	80–82 (88–89)
g	**4a**	**7b**: $R_2 = Ph$, $R_3 = Me$	300	5	 **8g**	75	55–56

Continued on next page.

Continued.

Entry	Mono/bis substituted guanidine **4**/**5**	β-Diketone **7**	MW conditions		Product **8**/**9**	Yield[a]/%	Mp[19a,19b] (lit)/°C
			P/W	t/min			
h	**4b**	**7c**: $R_2 = OEt$, $R_3 = Me$	300	7	 **8h**	65	62–63
i	**4a**	**7d**: $R_2 = R_3 = Ph$	300	6	 **8i**	72	65–66
j	**4b**	**7e**: 	300	20	 **8j**	56	116–118
k	**4a**	**7e**: 	300	18	 **8k**	58	146–148
l	**4a**	**7f**: $R_2 = OEt$, $R_3 = OEt$	300	25	 **8l**	25	76–78
m	**4e**	**7a**: $R_2 = R_3 = Me$	300	6	 **8m**	75	Dense liquid
n	**4e**	**7d**: $R_2 = R_3 = Ph$	300	7	 **8n**	69	74–76
o	**4f**	**7b**: $R_2 = Ph$, $R_3 = Me$	300	6	 **8o**	70	120–122
p	**4g**	**7a**: $R_2 = R_3 = Me$	300	9	 **8p**	55	88–90
q	**5h**	**7a**: $R_2 = R_3 = Me$	300	7	 **9q**	64	122–124 (135)
r	**5i**	**7a**: $R_2 = R_3 = Me$	300	8	 **9r**	60	162–164

a) Isolated yields are of chromatographically obtained pure material.



Scheme 4. Synthesis of substituted 2-methylthiopyrimidine.

remains undisturbed during the whole course of the reactions leading to the synthesis of chiral 2-(substituted amino)-pyrimidines **8m** and **8n** in good yields. The yield of substituted pyrimidinamines also depends on β-diketones or related compounds. In the case of acetyl acetone, the yield is higher whereas the reactivity gradually decreases when ethyl acetoacetate (**7c**), ethyl cyanoacetate (**7e**), and diethyl malonate (**7f**) are used for the condensation with substituted guanidines. The yield is low (25%) in the case of diethyl malonate.

To establish the effectiveness of the reaction, we attempt to study the reaction in a different pathway. Initially, the condensation of β-diketones with (*S*)-methylisothiourea salt is carried out under microwave irradiation to produce 2-methylthiopyrimidines. Then 2-methylthiopyrimidines are used for the synthesis of 2-(substituted amino)pyrimidines by the substitution of methylthio group of 2-methylthiopyrimidines with various amines under microwave irradiation. But the substitution of 2-methylthio by amine failed to produce the desired product under these conditions, though through conventional means,[10a] substitution of methylthio group was performed by primary amine with poor yield under refluxing conditions for several hours.

So from this alternate attempt for the synthesis of 2-(substituted amino)pyrimidines it is found that substitution of methylthio group in the pyrimidine ring by substituted amines is unfavorable under the present microwave conditions (Scheme 4). Though this reaction pathway should be advantageous regarding the synthesis of a series of 2-(substituted amino)pyrimidines from a single intermediate in one step but unfortunately this has not happened in our case. Therefore our reaction schemes (Schemes 1 and 3) are an effective alternate for the synthesis of 2-(substituted amino)pyrimidines under solvent-free microwave conditions.

Conclusion

We have thus developed a clean, rapid, and convenient solvent-free synthesis of various 2-(substituted amino)pyrimidines (alkyl, aryl, heteroaryl, and chiral amino moieties along with the alkyl or aryl substituents in the pyrimidine ring). All the reactions afford moderate to high yield of the desired products under microwave conditions. The significant advantage of this reaction is the flexibility of the substituents of the pyrimidine ring including amino moiety, which may be selected according to the requirement for the synthesis of various analogs for pharmacological study. Besides these, bis[2-(substituted amino)pyrimidine]s have also been synthesized by this procedure which may be used for both supramolecular and metal coordination chemistry.

Experimental

General Procedure for the Synthesis of Substituted Guanidine and 2-(Substituted Amino)pyrimidines. A mixture of (*S*)-methylisothiourea sulfate (**1**) (pseudourea) (556 mg, 2.0 mmol) and potassium carbonate (345 mg, 2.5 mmol) was thoroughly ground together. Then benzylamine (**2b**) (428 mg, 4.0 mmol) was added and mixed thoroughly, placed in an open mouth conical flask and then irradiated at 450 W (or at 90–100 °C) for 18 min (the time period varied from 12 to 40 min depending on amines) (Scheme 1 and Table 1) in a microwave oven. The reaction was carried out in a well-ventilated hood. The solid mass was washed with $CHCl_3$ to remove the unreacted amine and then dried. The solid mass (benzylguanidine) was mixed with acetylacetone (**7a**) (400 mg, 4.0 mmol) and again irradiated at 300 W (or at 55–65 °C) for 5 min (in the case of various β-diketones the time period varied from 4 to 25 min) (Scheme 3 and Table 2). The residue was dissolved in water and then extracted with $CHCl_3$. The organic layer was evaporated under reduced pressure. The crude product was then purified by column chromatography (silica gel, 100–200 mesh) to afford pure 2-benzylamino-4,6-dimethylpyrimidine (**8d**) using ethyl acetate–petroleum ether (1:10) as eluent. Representative spectral data for 2-(substituted amino)pyrimidines are as follows.

2-Butylamino-4,6-dimethylpyrimidine (8a): Yield: 80%; Dense liquid; R_f (15% ethyl acetate/petroleum ether) = 0.42; IR: 3282, 2961, 2927, 1570, 1552, 1357, 1338, 1213, 1142 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.28 (s, 1H), 4.89 (br s, 1H), 3.41 (q, 2H, J = 12.5 Hz), 2.27 (s, 6H), 1.57 (m, 2H), 1.41 (m, 2H), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δc 167.3, 162.4, 109.3, 40.9, 31.8, 23.8, 20.0, 13.8; HRMS (ES^+) Calcd for $C_{10}H_{18}N_3$ ($M + H^+$): 180.1500. Found: 180.1482.

2-Benzylamino-4-methyl-6-phenylpyrimidine (8b): Yield: 74%; White solid; R_f (12% ethyl acetate/petroleum ether) = 0.42; Mp 112–114 °C; IR: 3272, 3065, 2920, 1594, 1553, 1346, 1135, 1030, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (m, 2H), 7.43 (m, 3H), 7.39 (d, 2H, J = 7.4 Hz), 7.32 (t, 2H, J = 7.4 Hz), 7.27 (t, 1H, J = 7.2 Hz), 6.89 (s, 1H), 5.44 (br s, 1H), 4.75 (d, 2H, J = 5.9 Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 168.4, 164.6, 162.6, 139.7, 137.7, 130.2, 128.6, 128.5, 127.6, 127.0, 106.4, 45.5, 24.3; HRMS (ES^+): Calcd for $C_{18}H_{18}N_3$ ($M + H^+$): 276.1484. Found: 276.1493.

2-Anilino-4,6-dimethylpyrimidine (8c): Yield: 65%; R_f (15% ethyl acetate/petroleum ether) = 0.40; Mp 84–86 °C (lit.[19] 96–97 °C); IR: 3269, 3060, 1600, 1563, 1531, 1496, 1439, 1340, 1247, 824 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, 2H, J = 8.6 Hz), 7.31 (t, 2H, J = 8.0 Hz), 7.04 (br s, 1H), 7.01 (m, 1H), 6.49 (s, 1H), 2.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 167.9, 160.2, 140.4, 129.2, 122.4, 119.2, 112.1, 24.3; HRMS (ES^+): Calcd for $C_{12}H_{14}N_3$ ($M + H^+$): 200.1187. Found: 200.1181.

2-Benzylamino-4,6-dimethylpyrimidine (8d): Yield: 78%; White crystalline solid; R_f (15% ethyl acetate/petroleum ether) = 0.45; Mp 110–112 °C (lit.[19] 111–112 °C); IR: 3276, 3045, 2926,

1542, 1484, 1362, 1024, 832 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (d, 2H, $J = 6.9$ Hz), 7.31 (t, 2H, $J = 7.4$ Hz), 7.25 (m, 1H), 6.33 (s, 1H), 5.25 (br s, 1H), 4.65 (d, 2H, $J = 5.9$ Hz), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 167.9, 162.7, 140.1, 128.9, 127.9, 127.4, 110.3, 45.8, 24.3; HRMS (ES^+): Calcd for $C_{13}H_{16}N_3$ ($M + H^+$): 214.1344. Found: 214.1339.

2-Butylamino-6-methyl-3*H*-pyrimidin-4-one (8e): Yield: 68%; Off-white solid; R_f (25% ethyl acetate/petroleum ether) = 0.40; Mp 68–70 °C (lit.[19] 91 °C); IR: 3255, 2958, 2872, 1656, 1608, 1518, 1451, 1331, 1220, 967 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.70 (br s, 1H), 5.89 (br s, 1H), 5.57 (s, 1H), 3.37 (m, 2H), 2.16 (s, 3H), 1.57 (m, 2H), 1.37 (m, 2H), 0.94 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 164.2, 163.1, 154.7, 108.2, 102.7, 41.7, 31.8, 20.4, 14.1; HRMS (ES^+): Calcd for $C_9H_{16}N_3O$ ($M + H^+$): 182.1250. Found: 182.1283.

2-(4-Methoxyanilino)-4,6-dimethylpyrimidine (8f): Yield: 67%; R_f (15% ethyl acetate/petroleum ether) = 0.45; Mp 80–82 °C (lit.[19] 88–89 °C); IR: 3260, 2933, 1588, 1562, 1508, 1458, 1339, 1034, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, 2H, $J =$ 6.8 Hz), 6.93 (br s, 1H), 6.87 (d, 2H, $J = 9.0$ Hz), 6.44 (s, 1H), 3.79 (s, 3H), 2.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δc 167.4, 159.9, 154.9, 133.1, 120.9, 113.9, 110.9, 55.4, 23.7; HRMS (ES^+): Calcd for $C_{13}H_{16}N_3O$ ($M + H^+$): 230.1293. Found: 230.1302.

2-Butylamino-4-methyl-6-phenylpyrimidine (8g): Yield: 75%; R_f (15% ethyl acetate/petroleum ether) = 0.45; Mp 55–56 °C; IR: 3278, 2926, 2856, 1557, 1462, 1376, 1230, 1028, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.02 (m, 2H), 7.45 (m, 3H), 6.85 (s, 1H), 5.06 (br s, 1H), 3.52 (q, 2H, $J = 12.9$ Hz), 2.39 (s, 3H), 1.63 (m, 2H), 1.45 (m, 2H), 0.97 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δc 168.2, 164.5, 162.7, 137.8, 130.1, 128.5, 126.9, 105.8, 41.1, 31.9, 24.2, 20.1, 13.8; HRMS (ES^+): Calcd for $C_{15}H_{20}N_3$ ($M + H^+$): 242.1641. Found: 242.1653.

2-Benzylamino-6-methyl-3*H*-pyrimidin-4-one (8h): Yield: 65%; R_f (25% ethyl acetate/petroleum ether) = 0.43; Mp 62–63 °C; IR: 3279, 3030, 2925, 1656, 1602, 1515, 1326, 967 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.52 (br s, 1H), 7.33 (m, 5H), 6.62 (s, 1H), 5.31 (s, 1H), 4.56 (s, 2H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δc 164.3, 153.9, 138.1, 129.3, 128.5, 127.3, 126.5, 100.5, 44.8, 23.5; HRMS (ES^+): Calcd for $C_{12}H_{14}N_3O$ ($M + H^+$): 216.1094. Found: 216.1134.

2-Butylamino-4,6-diphenylpyrimidine (8i): Yield: 72%; R_f (12% ethyl acetate/petroleum ether) = 0.45; Mp 65–66 °C; IR: 3248, 2968, 2846, 1558, 1548, 1480, 1208, 856 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.09 (d, 4H, $J = 5.1$ Hz), 7.49 (m, 6H), 7.39 (s, 1H), 5.26 (t, 1H, $J = 5.3$ Hz), 3.59 (q, 2H, $J = 13.3$ Hz), 1.67 (m, 2H), 1.48 (m, 2H), 0.98 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 166.1, 163.6, 138.6, 130.7, 129.1, 127.5, 103.1, 41.8, 32.4, 20.7, 14.4; HRMS (ES^+): Calcd for $C_{20}H_{22}N_3$ ($M + H^+$): 304.1813. Found: 304.1807.

6-Amino-2-benzylamino-3*H*-pyrimidin-4-one (8j): Yield: 56%; R_f (3% MeOH/$CHCl_3$) = 0.44; Mp 116–118 °C; IR: 3330, 2926, 1614, 1467, 1275, 1104, 792 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 12.70 (br s, 1H), 7.24 (m, 5H), 6.66 (br s, 1H), 4.59 (s, 1H), 4.52 (s, 2H), 4.49 (d, 2H, $J = 5.3$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 165.8, 154.8, 138.9, 128.9, 127.9, 127.6, 124.0, 78.6, 44.7; HRMS (ESI-TOF): Calcd for $C_{11}H_{13}N_4O$ ($M + H^+$), 217.1084. Found: 217.1160.

6-Amino-2-butylamino-3*H*-pyrimidin-4-one (8k): Yield: 58%; R_f (3% MeOH/$CHCl_3$) = 0.43; Mp 146–148 °C; IR: 3340, 2931, 1615, 1478, 1428, 1281 cm^{-1}; ^1H NMR (DMSO-d_6 in $CDCl_3$, 400 MHz): δ 10.03 (br s, 1H), 5.66 (br s, 1H), 4.76 (s, 1H), 4.49 (br s, 2H), 3.22 (q, 2H, $J = 12.3$ Hz), 1.46 (m, 2H), 1.31 (m, 2H), 0.86 (t, 3H, $J = 7.28$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 165.9, 154.9, 124.6, 78.4, 40.7, 31.8, 20.4, 14.1; HRMS (ES^+): Calcd for $C_8H_{15}N_4O$ ($M + H^+$) 183.1242. Found: 183.1418.

2-Butylaminopyrimidine-4,6-diol (8l): Yield: 25%; R_f (4% MeOH/$CHCl_3$) = 0.43; Mp 76–78 °C; IR: 3420, 3181, 2929, 1709, 1626, 1526, 1250, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.19 (s, 1H), 5.10 (s, 1H), 4.97 (s, 1H), 3.48 (s, 1H), 3.28 (m, 2H), 1.50 (m, 2H), 1.34 (m, 2H), 1.26 (t, 3H, $J = 7.28$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δc 169.2, 167.7, 166.0, 40.4, 29.6, 19.9, 13.7; MS (FIA): m/z (%): 182.0 [$(M - H)^+$, 5], 208.0 [$(M + 2H + Na)^+$, 50]; HRMS (ES^+): Found: 182.1368 $(M - H)^+$.

4,6-Dimethyl-2-(1-phenylethylamino)pyrimidine (8m): Yield: 75%; R_f (10% ethyl acetate/petroleum ether) = 0.43; Liquid; $[\alpha]_D^{25}$ +95.4 (c 0.074, $CHCl_3$); IR: 3425, 2975, 2930, 1644, 1567, 1367, 1224 cm^{-1}, ^1H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, 2H, $J = 7.0$ Hz), 7.40 (t, 2H, $J = 7.6$ Hz), 7.31 (t, 1H, $J = 7.3$ Hz), 6.37 (s, 1H), 5.35 (br s, 1H), 5.32 (m, 1H), 2.34 (s, 6H), 1.63 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 167.8, 161.9, 145.3, 128.8, 127.2, 126.6, 110.2, 50.6, 24.3, 23.3; HRMS (ES^+): Calcd for $C_{14}H_{18}N_3$ ($M + H^+$): 228.1500. Found: 228.1489.

4,6-Diphenyl-2-(1-phenylethylamino)pyrimidine (8n): Yield: 69%; R_f (8% ethyl acetate/petroleum ether) = 0.43; Mp 74–76 °C; $[\alpha]_D^{25}$ +46.58 (c 0.068, $CHCl_3$); IR: 3066, 2919, 2849, 1568, 1543, 1491, 1214, 1028; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.02 (m, 5H), 7.49 (m, 7H), 7.39 (s, 1H), 7.34 (t, 2H, $J = 6.8$ Hz), 7.23 (m, 1H), 5.58 (d, 1H, $J = 7.1$ Hz), 5.37 (m, 1H), 1.67 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 166.1, 162.5, 145.6, 138.4, 130.7, 129.1, 128.9, 127.5, 127.3, 126.6, 103.5, 51.5, 23.4; HRMS (ESI-TOF): Calcd for $C_{24}H_{22}N_3$ ($M + H^+$): 352.1808. Found: 352.1813.

2-Furfurylamino-4-methyl-6-phenylpyrimidine (8o): Yield: 70%; R_f (6% ethyl acetate/petroleum ether) = 0.39; Mp 120–122 °C; IR: 3247, 3066, 2926, 1600, 1555, 1439, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (s, 2H), 7.44 (m, 3H), 7.35 (s, 1H), 6.90 (s, 1H), 6.30 (s, 1H), 6.26 (s, 1H), 5.38 (br s, 1H), 4.73 (d, 2H, $J = 5.7$ Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 168.9, 164.8, 162.6, 151.3, 142.9, 130.7, 129.0, 128.6, 127.4, 110.8, 107.8, 107.1, 40.6, 24.7; HRMS (ES^+): Calcd for $C_{16}H_{16}N_3O$ ($M + H^+$) 266.1287. Found: 266.1255 ($M + H^+$).

4,6-Dimethyl-2-(6-methyl-2-pyridylamino)pyrimidine (8p): Yield: 55%; R_f (20% ethyl acetate/petroleum ether) = 0.42; Mp 88–90 °C; IR: 3245, 2927, 2885, 2410, 1623, 1595, 1250, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.28 (d, 1H, $J = 8.3$ Hz), 7.80 (br s, 1H), 7.55 (t, 1H, $J = 7.9$ Hz), 6.76 (d, 1H, $J = 7.4$ Hz), 6.53 (s, 1H), 2.44 (s, 3H), 2.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 167.4, 158.9, 156.6, 152.4, 137.9, 116.6, 112.2, 109.2, 24.1, 23.9; HRMS (ES^+): Calcd for $C_{12}H_{15}N_4$ ($M + H^+$): 215.1328. Found: 215.1293.

***N*-(2,6-Dimethylpyrimidin-4-yl)-*N*′-(4,6-dimethylpyrimidin-2-yl)-1,6-hexanediamine (9q):** Yield: 64%; R_f (10% ethyl acetate/petroleum ether) = 0.42; Mp 122–124 °C (lit[19] 135 °C); IR: 3270, 2925, 2854, 1599, 1574, 1468, 1357, 1142 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.28 (s, 2H), 4.94 (br s, 2H), 3.39 (q, 4H, $J = 13.4$ Hz), 2.27 (s, 12H), 1.58 (m, 4H), 1.43 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δc 167.2, 162.3, 109.3, 41.2, 29.6, 26.5, 23.7; HRMS (ES^+): Calcd for $C_{18}H_{29}N_6$ ($M + H^+$): 329.2422. Found: 329.2441.

Compound 9r: Yield: 60%; R_f (8% ethyl acetate/petroleum ether) = 0.44; Mp 162–164 °C; IR: 3264, 2928, 2824, 1636, 1565, 1468, 1332, 832 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (s, 1H), 7.25 (s, 1H), 7.24 (s, 2H), 6.32 (s, 2H), 5.26 (br s, 2H), 4.63 (d, 4H, $J = 5.9$ Hz), 2.28 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz):

δc 167.8, 162.6, 140.3, 128.8, 127.1, 126.7, 110.3, 45.7, 24.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{25}N_6$ ($M + H^+$): 349.2135. Found: 349.2147.

1,2-Diacetyl-3-benzylguanidine (6): Acetate derivative **6** of the benzylguanidine **4b** is obtained by acylation (Ac_2O at 60–70 °C, 2 h), which was initially synthesized from benzylamine and isothiourea salt under microwave irradiation (450 W, 18 min). R_f (3% MeOH/$CHCl_3$) = 0.47; Mp 126–27 °C; IR (KBr): 3432, 2469, 2118, 1686, 1637, 1586, 1445, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 13.18 (br s, 1H), 9.33 (br s, 1H), 7.34 (m, 5H), 4.65 (d, 2H, $J = 5.7$ Hz), 2.18 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δc 186.2, 172.5, 155.4, 137.2, 128.6, 127.7, 127.6, 44.6, 28.6, 24.9; MS (FIA-MS): m/z (%): 234.4 [$(M + H)^+$, 20], 192.3 (100), 150.3; HRMS (ES^+): m/z (%): 192.1100 [$(M + 2H - CH_3CO)^+$, 27], 150.0999 [$(M + 3H - CH_3CO)^+$, 100].

4,6-Dimethyl-2-methylthiopyrimidine (10): Acetylacetone (200 mg, 2.0 mmol) was added to a mixture of (*S*)-methylisothiourea sulfate (278 mg, 1.0 mmol) and potassium carbonate (172 mg, 1.5 mmol), and irradiated at 300 W (or at 55 °C) for 12 min (Scheme 4). The residue was dissolved in water and extracted with $CHCl_3$. The organic layer was evaporated under reduced pressure. The crude product was then purified by column chromatography (silica gel, 100–200 mesh) to afford pure 4,6-dimethyl-2-methylthiopyrimidine (**10**) using ethyl acetate–petroleum ether (1:20) as eluent. Yield: 70%; Liquid; R_f (5% ethyl acetate/petroleum ether) = 0.49; IR: 3252, 2924, 1624, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.67 (s, 1H), 2.54 (s, 3H), 2.39 (s, 6H); MS (FIA-MS): m/z (%): 155.1 [$(M + H)^+$, 50], 149.1 (40).

We thank the DST [SR/S1/OC-13/2005] and CSIR [01(1913)/04/EMR-II], Government of India for financial support. A.H. thanks the CSIR, Government of India for a research fellowship.

Supporting Information

Supporting Information for general procedure and spectral data are available free of charge on the web at http://www.csj.jp/journals/bcsj/.

References

1 a) F. H. S. Curd, M. I. Davis, F. L. Rose, *J. Chem. Soc.* **1946**, 351. b) R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, A. R. Todd, *J. Chem. Soc.* **1946**, 357. c) F. H. S. Curd, F. L. Rose, *J. Chem. Soc.* **1946**, 362. d) F. H. S. Curd, C. G. Raison, F. L. Rose, *J. Chem. Soc.* **1946**, 366. e) F. H. S. Curd, M. I. D. Vis, E. C. Owen, F. L. Rose, G. A. P. Tuey, *J. Chem. Soc.* **1946**, 370. f) F. H. S. Curd, D. N. Richardson, F. L. Rose, *J. Chem. Soc.* **1946**, 378.

2 F. X. Tavares, J. A. Boucheron, S. H. Dickerson, R. J. Griffin, F. Preugschat, S. A. Thomson, T. Y. Wang, H.-Q. Zhou, *J. Med. Chem.* **2004**, *47*, 4716.

3 R. J. Chorvat, R. Bakthavatchalam, J. P. Beck, P. J. Gilligan, R. G. Wilde, A. J. Cocuzza, F. W. Hobbs, R. S. Cheeseman, M. Curry, J. P. Rescinito, P. Krenitsky, D. Chidester, J. A. Yarem, J. D. Klaczkiewicz, C. N. Hodge, P. E. Aldrich, Z. R. Wasserman, C. H. Fernandez, R. Zaczek, L. W. Fitzgerald, S.-M. Huang, H. L. Shen, Y. N. Wong, B. M. Chien, C. Y. Quon, A. Arvanitis, *J. Med. Chem.* **1999**, *42*, 833.

4 D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis*, John Wiley & Sons, New York, **1977**, Vols. 1, 2, 3, and 4.

5 a) A. B. Sen, S. K. Gupta, *J. Indian Chem. Soc.* **1962**, *39*, 129. b) M. Botta, F. D. Angelis, G. Finizia, A. Gambacorta, R. Nicoletti, *Synth. Commun.* **1985**, *15*, 27.

6 a) D. J. Brown, *Fused Pyrimidines: Pteridines* in *The Chemistry of Heterocyclic Compounds*, John Wiley & Sons, New York, **1988**, Vol. 24, p. 3. b) D. J. Brown, *The Pyrimidines* in *The Chemistry of Heterocyclic Compounds*, Wiley, New York, **1962**, Vol. 16; D. J. Brown, *The Pyrimidines* in *The Chemistry of Heterocyclic Compounds*, Wiley, New York, **1970**, Vol. 16, Suppl. 1; D. J. Brown, *The Pyrimidines* in *The Chemistry of Heterocyclic Compounds*, Wiley, New York, **1985**, Vol. 16, Suppl. 2.

7 C. J. Suckling, J. K. Huggan, C. L. Gibson, in *Bicyclic 6–6 System: Pteridines* in *Comprehensive Heterocyclic Chemistry III*, ed. by A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, R. J. K. Taylor, Elsevier, Oxford, **2008**, Vol. 10, p. 915.

8 a) M. C. Etter, *Acc. Chem. Res.* **1990**, *23*, 120. b) S. Goswami, S. Jana, N. K. Das, H.-K. Fun, S. Chantraproma, *J. Mol. Struct.* **2008**, *876*, 313. c) S. Goswami, S. Jana, A. Hazra, H.-K. Fun, S. Chantrapromma, *Supramol. Chem.* **2008**, *20*, 495, and references cited therein. d) Y.-H. Wang, K.-L. Chu, H.-C. Chen, C.-W. Yeh, Z.-K. Chan, M.-C. Suen, J.-D. Chen, J.-C. Wang, *CrystEngComm* **2006**, *8*, 84. e) Y.-N. Chi, K.-L. Huang, F.-Y. Cui, Y.-Q. Xu, C.-W. Hu, *Inorg. Chem.* **2006**, *45*, 10605.

9 a) E. Brand, F. C. Brand, *Org. Synth., Coll. Vol.* **1955**, *3*, 440.

10 a) F. H. S. Curd, F. L. Rose, *J. Chem. Soc.* **1946**, 343. b) Y. Ma, L. Margarida, J. Brookes, G. M. Makara, S. C. Berk, *J. Comb. Chem.* **2004**, *6*, 426. c) G. Luo, L. Chen, G. S. Poindexter, *Tetrahedron Lett.* **2002**, *43*, 5739. d) P. R. Shildneck, W. Windus, *Org. Synth., Coll. Vol.* **1976**, *2*, 411.

11 a) D. J. Brown, B. T. England, J. M. Lyall, *J. Chem. Soc. C* **1966**, 226. b) C. W. Whitehead, J. J. Traverso, *J. Am. Chem. Soc.* **1960**, *82*, 3971.

12 H. Eck, G. Fisher, F. Mueller, S. Wihrheim, E. Swen, *Chem. Abstr.* **1974**, *81*, 63670m; H. Eck, G. Fisher, F. Mueller, S. Wihrheim, E. Swen, Ger. Off. 2,256,289, June, **1974**.

13 For recent book and reviews on microwave-assisted organic reactions: a) B. L. Hayes, *Mircowave Synthesis: Chemistry at the Speed of Light,* CEM Publishing, Mattaws, NC 28105, **2002**. b) B. Wathey, J. Tierney, P. Lidström, J. Westman, *Drug Discov. Today* **2002**, *7*, 373. c) C. O. Kappe, *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. d) B. A. Roberts, C. R. Strauss, *Acc. Chem. Res.* **2005**, *38*, 653.

14 a) D. Dallinger, C. O. Kappe, *Chem. Rev.* **2007**, *107*, 2563. b) For a recent review on the synthesis of heterocyclic compounds under microwave irradiation; see: Y. Xu, Q.-X. Guo, *Heterocycles* **2004**, *63*, 903.

15 H. Sandin, M.-L. Swanstein, E. Wellner, *J. Org. Chem.* **2004**, *69*, 1571.

16 a) S. Goswami, A. K. Adak, *Tetrahedron Lett.* **2002**, *43*, 8371. b) S. Goswami, A. K. Adak, *Synth. Commun.* **2003**, *33*, 475. c) S. Goswami, S. Dey, S. Jana, A. K. Adak, *Chem. Lett.* **2004**, *33*, 916. d) S. Goswami, S. Jana, A. Hazra, A. K. Adak, *J. Heterocycl. Chem.* **2007**, *44*, 1191.

17 S. Goswami, S. Jana, S. Dey, A. K. Adak, *Aust. J. Chem.* **2007**, *60*, 120, and references therein.

18 a) M. Raghavendra, H. S. Bhojya Naik, B. S. Sherigara, *Can. J. Chem.* **2007**, *85*, 1041. b) C.-S. Jia, Z. Zhang, S.-J. Tu, G.-W. Wang, *Org. Biomol. Chem.* **2006**, *4*, 104.

19 a) G. Menichi, M. Hubert-Habart, *J. Heterocycl. Chem.* **1984**, *21*, 209. b) A. R. Katrizky, *J. Chem. Soc., Parkin Trans. 1* **1982**, 153.