Microwave-Assisted Solvent-Free Synthesis of Highly Functionalized Pyrimidine Derivatives

Shengjiao Yan, Yanfei Niu, Xuebing Chen, Yongjiang Liu, and Jun Lin*

Key Laboratory of Medicinal Chemistry for Natural Resources (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, People's Republic of China

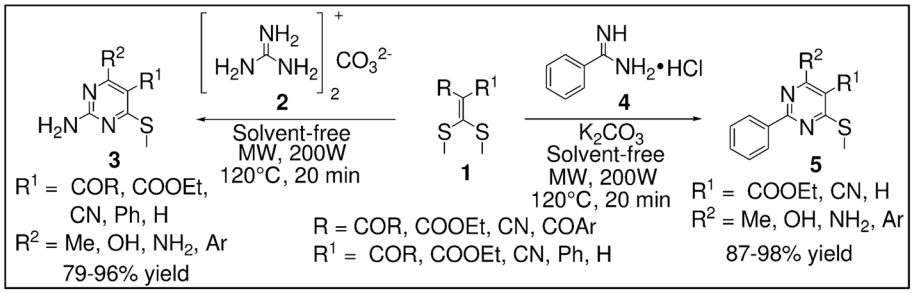
*E-mail: linjun@ynu.edu.cn

Shengjiao Yan and Yanfei Niu contributed equally to this work.

Received January 7, 2011

DOI 10.1002/jhet.891

View this article online at wileyonlinelibrary.com.



We here described an efficient method for the synthesis of a series of highly functionalized pyrimidines via the addition and condensation reaction of ketene dithioacetals with guanidine carbonate or amidine hydrochlorides by microwave irradiation under solvent-free conditions in the absence of a catalyst, giving the products with good yields (79–98%).

J. Heterocyclic Chem., **49**, 877 (2012).

INTRODUCTION

Demands for sustainable and ecologically friendly organic syntheses [1] are stimulating the search for alternates to using organic solvents in synthetic reactions. Performing reactions under solvent-free reaction conditions is an important and interesting alternate [2].

Pyrimidine derivatives including 2-amino-pyrimidines and 2-arylpyrimidines possess prominent biological activity and have widely served as HIV reverse-transcriptase inhibitors [3], dihydrofolate reductase inhibitors [4], the growth hormone secretagogue receptor inhibitors [5], adenosine receptor antagonists [6], STAT6 inhibitors [7], histamine H_4 receptor inhibitors [8], tryptophan hydroxylase inhibitors [9], vascular endothelial growth factor receptor inhibitors [10], antimalarial drugs [4b,11], antibacterial agents [12], analgesics [13], and so forth [14]. With this broad range of biological activities, pyrimidine derivatives have long received increasing interest, making the synthesis and biological activity of pyrimidines an important field.

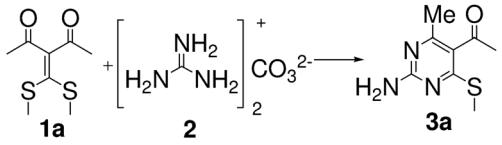
Numerous syntheses of pyrimidines have been described in the literature [15–17]. There are three main synthetic procedures. The first route is ketene dithioacetals, guanidine or amidine, which were treated with NaH or K_2CO_3 in solvents such as DMF or CH_3CN and refluxed for many hours to obtain the products in low to moderate yields [15]. The second procedure is multistep reactions approaches, which usually required complex experimental processes [16]. The third method is *S*-methylisothiourea and guanidine derivatives, which also react readily with alpha-oxoketene dithioacetals to form pyrimidines [17]. However, these methods all have some limitations such as lengthy reaction steps [16], the use of large amounts of solvents, longer reaction times, relatively poor yields and tedious workup and some can only obtain simply substituted pyrimidines [15]. So a general, concise, and environmentally friendly approach to this class of heterocycles that tolerates a wide variety of functional groups is highly desirable. We have paid attention to the environmentally friendly organic synthesis methods in recent years [18]. To continue our work, here we report on an efficient method for the synthesis of a series of diverse pyrimidine derivatives under solvent-free conditions.

RESULTS AND DISCUSSION

In our initial research, the reactions of ketene dithioacetal with guanidine carbonate proceeded efficiently under solvent-free conditions simply by heating the well-ground mixture of substrates at 120°C for 60 min. This afforded the corresponding 2-aminopyrimidine at an excellent yield of 83% (Scheme 1) (Table 1, entry 1).

To facilitate the operational program, accelerate the reaction and improve the temperature accuracy, microwave

Scheme 1



(MW) irradiation was used to examine the practicality of the solvent-free synthetic route. A set of experiments were carried out using ketene dithioacetal **1a** and guanidine carbonate **2** as model substrates. The mixture composed of a 1:1.6 ratio of **1a** to **2** were subjected to MW in solvent-free conditions (Scheme 1) (Table 1, entries 2–10). This showed that the optimum reaction conditions to obtain the product **3a** were 120°C for 20 min with a maximum power of 200 W (Table 1, entry 6).

Then **1b–j** were reacted with guanidine carbonate at 120°C with a maximum power of 200 W of MW and allowed 20 min to finish. They also generated excellent yields (Scheme 2) (Table 2, entries 2–9). The structures of ketene dithioacetals had an obvious influence on the yields (Table 2, entries 1–9). Mono-substituted ketene dithioacetals provide higher yields than that of bis-substituted substrates (Table 2, entries 1–6 vs. 7–9). Among the bis-substituted ketene dithioacetals, the acetyl groups of substrate are more advantageous to cyclization and provide the desired products (Table 2, entries 1 and 5 vs. 2–4, 6). The cyano group of the substrate is the most disadvantageous to cyclization (Table 2, entries 3, 4, and 6). It is important that the bis-substituted ketene dithioacetal **1a–e** also obtain only one product. This indicates that the cyclization for the group of the substrate has very high selectivity, the cyclization order of the groups is CH_3CO > COOEt > CN (Table 2, entries 4 and 5).

Encouraged by this result, we explored the scope and limitations of the cyclocondensation reactions involving various ketene dithioacetals **1** with another substrate amidine hydrochloride **4** (Scheme 3). The results demonstrated that mono- and bis-substituted ketene dithioacetals were all good substrates for the cyclocondensation reaction (Table 3, entry 1–7). The substituents of the ketene dithioacetals **1** had slight influence on the reactivity and product yield. The yields of all substrates are all similar (Table 3, entries 1–7).

Table 1

Synthesis of 2-aminopyrimidine derivatives **3a** under solvent-free conditions.

Entry	Power	T(°C)	Time/min	Yield (%)[a]
1	Grinding	120	60	83
2	MW/180 W	110	20	71
3	MW/180 W	120	20	80
4	MW/180 W	130	20	81
5	MW/200 W	110	20	73
6	MW/200 W	120	20	84
7	MW/200 W	130	20	82
8	MW/220 W	110	20	74
9	MW/220 W	120	20	81
10	MW/220 W	130	20	79

[a] Isolated yield based on ketene dithioacetal **1a**.

EXPERIMENTAL

All novel compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), chemical shifts (δ) are expressed in ppm, *J* values are given in Hz and deuterated DMSO-d_6, $CDCl_3$ and CH_3OD were used as solvents. IR spectra were recorded on a FTIR Thermo Nicolet Avatar 360 using KBr pellets. The reactions were monitored by thin layer chromatography using the silica gel GF_{254}. The melting points were determined on a XT-4A melting point apparatus and are uncorrected. HRMs were performed on an Agllent LC/Msd TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh). The materials **1a–j** were synthesized according to the literature [19].

General procedure for the preparation of 2-aminopyrimidines 3. A dry mortar was charged with ketene dithioacetal **1** (1 mmol) and guanidine carbonate **2** (1.6 mmol). The mixture was vigorously ground using a pestle at room temperature for a few minutes (*ca.*1–2 min). A MW reactor (Discover) was charged with the mixture and irradiated, and control of power and temperature by infrared detection, at 120°C for 20 min (maximum power 200 W). After cooling, the reaction mixture was poured into 10 mL of water and filtered to obtain the crude product. Then the crude product was recrystallized from ethanol and gave the desired products **3**.

1-(2-Amino-4-methyl-6-(methylthio)pyrimidin-5-yl)ethanone (3a). The compound was obtained in 84% yield as a yellow solid. IR (KBr): 3395, 3185, 1653, 1535, 1305 cm^{-1}; ^{1}H NMR (500 MHz, CH_3OD): δ 2.30 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 2.54 (s, 3H, SCH_3), 3.33 (br, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.1, 21.9, 31.0, 122.7, 163.7, 169.3, 193.0, 202.9; HRMS (TOF

Scheme 2

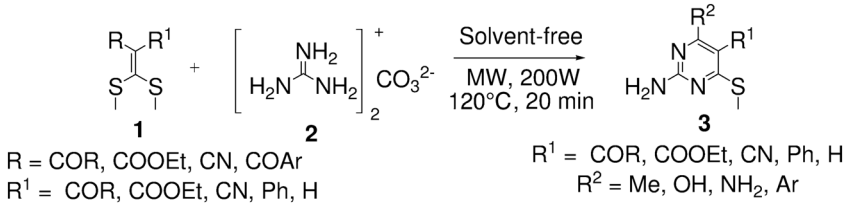
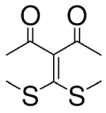
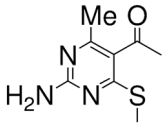
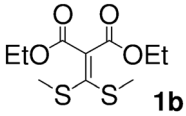
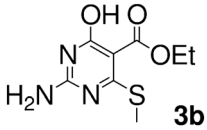
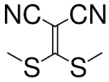
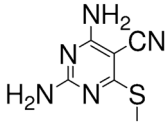
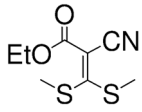
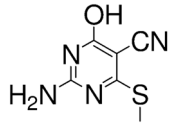
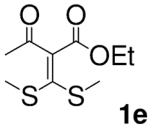
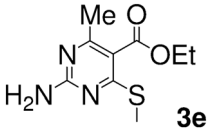
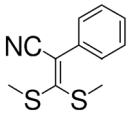
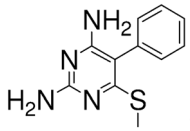
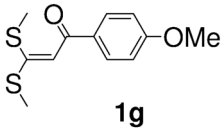
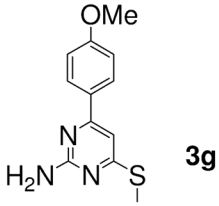
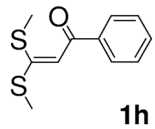
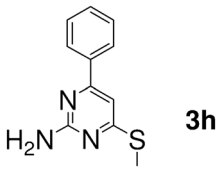
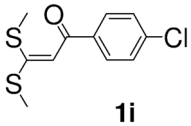
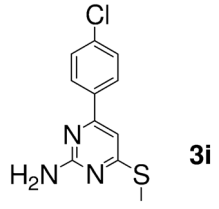


Table 2

Synthesis of 2-aminopyrimidine derivatives **3** under solvent-free conditions.

Entry	1	3	Yield (%)[a]
1	 **1a**	 **3a**	84
2	 **1b**	 **3b**	85
3	 **1c**	 **3c**	79
4	 **1d**	 **3d**	87
5	 **1e**	 **3e**	92
6	 **1f**	 **3f**	86
7	 **1g**	 **3g**	96
8	 **1h**	 **3h**	95
9	 **1i**	 **3i**	94

[a]Isolated yield.

ES$^+$): *m/z* calcd for $C_8H_{12}N_3OS$ [(M+H)$^+$], 198.0696; found, 198.0693 [20].

Ethyl 2-amino-4-hydroxy-6-(methylthio)pyri- midine-5-carboxylate (3b). The compound was obtained in 85% yield as a yellow solid, mp >250°C. IR (KBr): 3394, 3321, 3184, 1619, 1534, 1305, 1209 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.21 (t, J = 7.0 Hz, 3H, CH_3), 2.33 (s, 3H, SCH_3), 4.10-4.15 (t, J = 7.0 Hz, 2H, OCH_2), 10.93 (br, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.5, 15.2, 60.2, 101.7, 154.9, 159.6, 166.4, 175.2; HRMS (TOF ES$^+$): *m/z* calcd for $C_8H_{12}N_3NaO_3S$ [(M+Na)$^+$], 252.0413; found, 252.0415.

Scheme 3

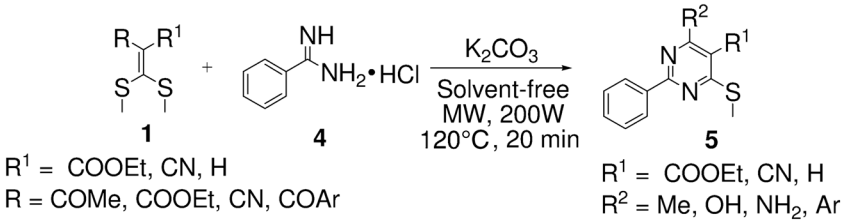
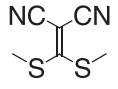
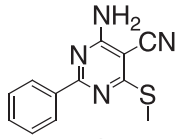
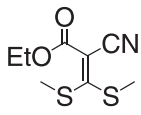
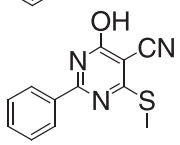
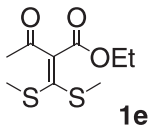
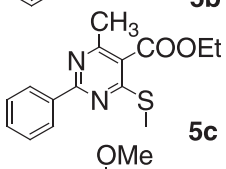
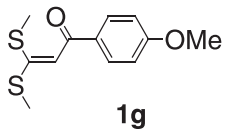
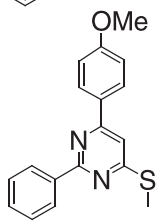
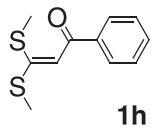
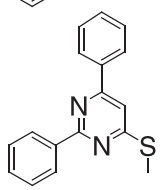
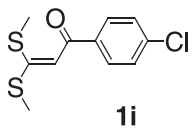
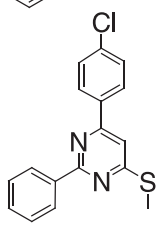
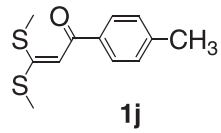
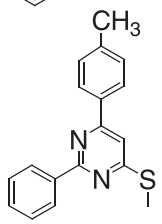


Table 3

Synthesis of 2-arylpyrimidine derivatives **5** under solvent-free conditions.

Entry	1	5	Yield (%)[a]
1	 **1c**	 **5a**	87
2	 **1d**	 **5b**	92
3	 **1e**	 **5c**	89
4	 **1g**	 **5d**	95
5	 **1h**	 **5e**	98
6	 **1i**	 **5f**	93
7	 **1j**	 **5g**	91

[a]Isolated yield.

2,4-Diamino-6-(methylthio)pyrimidine-5-carbonitrile (3c). The compound was obtained in 79% yield as a yellow solid. IR (KBr): 3523, 3420, 3380, 2204, 1668, 1624, 1548, 1065 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.42 (s, 3H, SCH_3), 7.01 (br, 4H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.4, 75.4, 117.2, 162.6, 164.5, 173.1; HRMS (TOF ES^+): *m/z* calcd for $C_6H_8N_5S$ [$(M+H)^+$], 182.0495; found, 182.0492 [21].

2-Amino-4-hydroxy-6-(methylthio)pyrimidine-5-carbonitrile (3d). The compound was obtained in 87% yield as a yellow solid, mp >250°C. IR (KBr): 3388, 3340, 3210, 2222, 1663, 1598, 1501, 1055 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.09 (s, 3H, SCH_3), 6.92 (br, 1H, NH_2), 8.24 (br, 1H, NH_2), 11.44 (br, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.2, 82.6, 116.7, 156.0, 160.7, 176.9; HRMS (TOF ES^+): *m/z* calcd for $C_6H_7N_4OS$ [$(M+H)^+$], 183.0335; found, 183.0340.

Ethyl 2-amino-4-methyl-6-(methylthio)pyri- midine-5-carboxylate (3e). The compound was obtained in 92% yield as a yellow solid, mp >250°C. IR (KBr): 3400, 3316, 3173, 1676, 1644, 1532, 1310 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.27–1.3 (m, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.37 (s, 3H, SCH_3), 4.24–4.26 (m, 2H, OCH_2), 7.15 (br, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.4, 14.4, 60.8, 111.4, 161.4, 166.3, 167.5, 171.5; HRMS (TOF ES^+): *m/z* calcd for $C_9H_{14}N_3O_2S$ [$(M+H)^+$], 228.0801; found, 228.0803.

2,4-Diamino-6-(methylthio)-5-phenylpyrimidine (3f). The compound was obtained in 86% yield as a yellow solid, mp >250°C. IR (KBr): 3415, 3333, 3193, 3139, 1635, 1552, 1432 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.28 (s, 3H, SCH_3), 5.64 (br, 1H, NH_2), 6.06–6.10 (m, 3H, NH_2), 7.20–7.43 (m, 5H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.5, 104.9, 128.0, 129.3, 131.3, 134.9, 160.8, 161.5, 167.7; HRMS (TOF ES^+): *m/z* calcd for $C_{11}H_{13}N_4S$ [$(M+H)^+$], 233.0855; found, 233.0854.

2-Amino-4-(4-methoxyphenyl)-6-(methylthio)pyrimidine (3g). The compound was obtained in 96% yield as a yellow solid, mp 148–149°C. IR (KBr): 3459, 3295, 3176, 1622, 1537, 803, 440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 3.77 (s, 3H, OCH_3), 5.02 (s, 1H, ArH), 6.79 (br, 2H, NH_2), 6.87 (d, *J* = 8.7 Hz, 2H, ArH), 7.84 (d, *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8, 55.8, 104.4, 114.4, 128.9, 130.1, 162.0, 162.9, 163.4, 171.8; HRMS (TOF ES^+): *m/z* calcd for $C_{12}H_{14}N_3OS$ [$(M+H)^+$], 248.0852; found, 248.0852 [17a].

2-Amino-4-(methylthio)-6-phenylpyrimidine (3h). The compound was obtained in 95% yield as a yellow solid, mp 116–117°C. IR (KBr): 3449, 2975, 2928, 1576, 1468, 793 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 4.98 (br, 2H, NH_2), 6.85 (s, 1H, ArH), 7.35–7.38 (m, 3H, ArH), 7.84–7.87 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8, 105.4, 127.4, 129.1, 130.7, 162.9, 163.9, 172.1; HRMS (TOF ES^+): *m/z* calcd for $C_{11}H_{12}N_3S$ [$(M+H)^+$], 218.0746; found, 218.0747 [17a].

2-Amino-4-(4-chlorophenyl)-6-(methylthio)pyrimidine (3i). The compound was obtained in 94% yield as a yellow solid, mp 140–141°C. IR (KBr): 3470, 3312, 3190, 1637, 1535, 1093, 807 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ 2.53 (s, 3H, SCH_3), 5.29 (br, 2H, NH_2), 6.87 (s, 1H, ArH), 7.41 (d, *J* = 8.0 Hz, 2H, ArH), 7.88 (d, *J* = 8.0 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8, 105.1, 128.8, 129.3, 136.1, 136.9, 162.5, 162.9, 172.4; HRMS (TOF ES^+): *m/z* calcd for $C_{11}H_{11}ClN_3S$ [$(M+H)^+$], 252.0357; found, 252.0358.

General procedure for the preparation of 2-arylpyrimidines 5. A dry mortar was charged with ketene dithioacetal **1** (1 mmol), amidine hydrochlorides **4** (1.5 mmol) and potassium carbonate (2.0 mmol). The mixture was vigorously ground using a pestle at room temperature for a few minutes (*ca*. 1–2 min). Then the mixture was charged with the MW tube and irradiated in a MW reactor (Discover), and control of power and temperature by infrared detection, at 120°C for 20 min (maximum power 200 W). After cooling, the reaction mixture was poured into 10 mL of water and filtered to obtain the crude product. Then the crude product was recrystallized from ethanol and gave the desired products **5**.

4-Amino-6-(methylthio)-2-phenylpyrimidine-5-carbonitrile (5a). The compound was obtained in 87% yield as a yellow solid, mp 170–180°C. IR (KBr): 3330, 3225, 2922, 2856, 2214, 1627, 1530, 1384, 980 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.58 (s, 3H, SCH_3), 7.41–7.47 (m, 3H, ArH), 8.25–8.29 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.5, 82.8, 115.1, 128.9, 128.9, 132.1, 136.6, 163.1, 163.1, 173.1; HRMS (TOF ES^+): *m/z* calcd for $C_{12}H_{11}N_4S$ [$(M+H)^+$], 243.0699; found, 243.0703 [22].

4-Hydroxy-6-(methylthio)-2-phenylpyrimidine-5-carbonitrile (5b). The compound was obtained in 92% yield as a yellow solid, mp > 250°C. IR (KBr): 3443, 2206, 1539, 1480, 1385 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.58 (s, 3H, SCH_3), 7.42–7.46 (m, 3H, ArH), 8.29–8.34 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.2, 89.3, 119.2, 128.4, 128.5, 130.6, 139.0, 163.4, 170.7, 171.7; HRMS (TOF ES^+): *m/z* calcd for $C_{12}H_{10}N_3OS$ [$(M+H)^+$], 244.0539; found, 244.0549 [23].

Ethyl 4-methyl-6-(methylthio)-2-phenylpyr-imidine-5-carboxylate (5c). The compound was obtained in 89% yield as a white solid, mp 48–50°C. IR (KBr): 2987, 2927, 1703, 1522, 1260, 1079 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.1 Hz, 3H, CH_3), 2.59 (s, 3H, $ArCH_3$), 2.60 (s, 3H, SCH_3), 4.39 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.41–7.46 (m, 3H, ArH), 8.42–8.46 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 14.6, 24.3, 62.2, 121.3, 128.9, 129.1, 131.7, 137.3, 162.7, 165.3, 166.8, 170.6; HRMS (TOF ES^+): *m/z* calcd for $C_{15}H_{17}N_2O_2S$ [$(M+H)^+$], 289.1005; found, 289.1001 [24].

4-(4-Methoxyphenyl)-6-(methylthio)-2-phenylpyrimidine (5d). The compound was obtained in 95% yield as a white solid, mp 112–113.5°C. IR (KBr): 2927, 1556, 1511, 1256, 1167, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.67 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 6.96 (d, *J* = 8.7 Hz, 2H, ArH), 7.34 (s, 1H, ArH), 7.45–7.50 (m, 3H, ArH), 8.09 (d, *J* = 8.7 Hz, 2H, ArH), 8.55–8.59 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5, 55.3, 110.8, 114.1, 128.3, 128.3, 128.6, 129.2, 130.6, 137.9, 161.1, 161.8, 163.2, 170.3; HRMS (TOF ES^+): *m/z* calcd for $C_{18}H_{17}N_2OS$ [$(M+H)^+$], 309.1056; found, 309.1061.

4-(Methylthio)-2,6-diphenylpyrimidine (5e). The compound was obtained in 98% yield as a yellow solid, mp 73–75°C. IR (KBr): 2923, 1551, 1510, 1368, 1322 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.69 (s, 3H, SCH_3), 7.42 (s, 1H, ArH), 7.43–7.51 (m, 6H, ArH), 8.14 (d, *J* = 4.4 Hz, 2H, ArH), 8.60 (d, *J* = 4.0 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 112.4, 127.7, 128.9, 128.9, 129.3, 131.1, 131.2, 137.4, 138.3, 162.1, 163.9, 171.2; HRMS (TOF ES^+): *m/z* calcd for $C_{17}H_{15}N_2S$ [$(M+H)^+$], 279.0950; found, 279.0953 [25].

4-(4-Chlorophenyl)-6-(methylthio)-2-phenylpyrimidine (5f). The compound was obtained in 93% yield as a yellow solid, mp 129–130°C. IR (KBr): 3062, 2923, 1554, 1516, 1373, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.65 (s, 3H, SCH_3), 7.29 (s, 1H, ArH), 7.39 (d, *J* = 8.1 Hz, 2H, ArH), 7.45–7.50 (m, 3H, ArH), 8.00 (d, *J* = 8.1 Hz, 2H, ArH), 8.51–8.54 (m, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.01, 112.0, 128.8, 128.8, 129.4, 129.4, 131.3,

135.7, 137.2, 138.0, 160.7, 163.9, 171.4; HRMS (TOF ES$^+$): *m/z* calcd for $C_{17}H_{14}ClN_2S$ [(M+H)$^+$], 313.0561; found, 313.0568.

4-(Methylthio)-2-phenyl-6-p-tolylpyrimidine (5g). The compound was obtained in 91% yield as a yellow solid, mp 104–106°C. IR (KBr): 3032, 2920, 1556, 1517, 1373, 1321, 812 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H, $ArCH_3$), 2.69 (s, 3H, SCH_3), 7.28 (d, *J* = 7.8 Hz, 2H, ArH), 7.40 (s, 1H, ArH), 7.47–7.50 (m, 3H, ArH), 8.04 (d, *J* = 7.8 Hz, 2H, ArH), 8.59 (d, *J* = 5.2 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 21.9, 112.0, 127.6, 128.9, 128.9, 130.0, 131.2, 134.4, 138.3, 141.5, 162.0, 163.8, 171.1; HRMS (TOF ES$^+$): *m/z* calcd for $C_{18}H_{17}N_2S$ [(M+H)$^+$], 293.1107; found, 293.1112.

CONCLUSIONS

In summary, an efficient and environmentally friendly procedure for the synthesis of highly functionalized pyrimidines via the addition and condensation reaction of ketene dithioacetals with guanidine carbonate or amidine hydrochlorides under solvent-free conditions was constructed. By using different types of ketene dithioacetals, guanidine carbonate, or amidine hydrochlorides, we obtained the library of pyrimidine with molecular diverse features that make the method suitable for combinatorial and parallel synthesis in drug discovery.

Acknowledgments. We gratefully acknowledge the financial support from the Natural Science Foundation of China (grant Nos 30860342 and 20762013) and the Natural Science Foundation of Yunnan Province (2009CC017, 2008CD063).

REFERENCES AND NOTES

[1] (a) Clark, J.; Macquarrie, D. Handbook of Green Chemistry and Technology; Blackwell Science: Oxford,2002; (b) Adams, D. J.; Dyson, P. J.; Tavener, S. J. Chemistry in alternative reaction media; Wiley:Chichester, UK, 2004.

[2] Loupy, A. Top Curr Chem 1999, 206, 153; (b) Tanaka, K.; Toda, F. Chem Rev 2000, 100, 1025.

[3] (a) Das, K.; Clark, A. D., Jr.; Lewi, P. J.; Heeres, J.; de Jonge, M. R.; Koymans, L. M. H.; Vinkers, H. M.; Daeyaert, F.; Ludovici, D. W.; Kukla, M. J.; De Corte, B.; Kavash, R. W.; Ho, C. Y.; Ye, H.; Lichtenstein, M. A.; Andries, K.; Pauwels, R.; de Béthune, M. P.; Boyer, P. L.; Clark, P.; Hughes, S. H.; Janssen, P. A. J.; Arnold, E. J Med Chem 2004, 47, 2550; (b) Tian, X. T.; Qin, B. J.; Lu, H.; Lai, W. H.; Jiang, S. B.; Lee, K. H.; Chen, C. H.; Xie, L. Bioorg Med Chem Lett 2009, 19, 5482; (c) Pauwels, R. Curr Opin Pharmacol 2004, 4, 437.

[4] Otzen, T.; Wempe, E. G.; Kunz, B.; Bartels, R.; Lehwark-Yvetot, G.; Hänsel, W.; Schaper, K. J.; Seydel, J. K. J Med Chem 2004, 47, 240.

[5] Xin, Z. L.; Serby, M. D.; Zhao, H. Y.; Kosogof, C.; Szczepankiewicz, B. G.; Liu, M.; Liu, B.; Hutchins, C. W.; Sarris, K. A.; Hoff, E. D.; Falls, H. D.; Lin, C. W.; Ogiela, C. A.; Collins, C. A.; Brune, M. E.; Bush, E. N.; Droz, B. A.; Fey, T. A.; Knourek-Segel, V. E. Shapiro;, R.Jacobson, P. B.; Beno, D. W. A.; Turner, T. M.; Sham, H. L.; Liu, G. J Med Chem 2006, 49, 4459.

[6] Lanier, M. C.; Moorjani, M.; Luo, Z. Y. Chen;, Y. S.Lin, E.; Tellew, J. E.; Zhang, X. H.; Williams, J. P.; Gross, R. S.; Lechner, S. M.; Markison, S.; Joswig, T.; Kargo, W.; Piercey, J.; Santos, M.; Malany, S.; Zhao, M.; Petroski, R.; Crespo, M. I.; Díaz, J. L.; Saunders, J.; Wen, J.; O'Brien, Z.; Jalali, K.; Madan, A.; Slee, D. H. J Med Chem 2009, 52, 709.

[7] Nagashima, S.; Nagata, H.; Iwata, M.; Yokota, M.; Moritomo, H.; Orita, M.; Kuromitsu, S.; Koakutsu, A.; Ohga, K.; Takeuchi, M.; Ohta, M.; Tsukamoto, S. I. Bioorg Med Chem 2008, 16, 6509.

[8] Altenbach, R. J.; Adair, R. M.; Bettencourt, B. M.; Black, L. A.; Fix-Stenzel, S. R.; Gopalakrishnan, S. M.; Hsieh, G. C.; Liu, H. Q.; Marsh, K. C.; McPherson, M. J.; Milicic, I.; Miller, T. R.; Vortherms, T. A.; Warrior, U.; Wetter, J. M.; Wishart, N.; Witte, D. G.; Honore, P.; Esbenshade, T. A.; Hancock, A. A.; Brioni, J. D.; Cowart, M. D. J Med Chem 2008, 51, 6571.

[9] Shi, Z. C.; Devasagavarai, A.; Gu, K. J.; Jin, H. H; Marinelli, B.; Samala, L.; Sheldon, S.; Stouch, T.; Tunoori, A.; Wang, Y.; Zang, Y.; Zhang, C. M.; Kimball, S. D.; Main, A. J.; Sun, W. M.; Yang, Q.; Nouraldeen, A.; Yu, X. Q.; Buxton, E.; Patel, S.; Nguyen, N.; Swaffield, J.; Powell, D. R.; Wilson, A.; Liu, Q. Y. J Med Chem 2008, 51, 3684.

[10] Harris, P. A.; Boloor, A.; Cheung, M.; Kumar, R.; Crosby, R. M.; Davis-Ward, R.; Epperly, A. H.; Hinkle, K. W.; Hunter, R. N.; Johnson, J. H.; Knick, V. B.; Laudeman, C. P.; Luttrell, D. K.; Mook, R. A.; Nolte, R. T.; Rudolph, S. K.; Szewczyk, J. R.Truesdale;, A. T.Veal, J. M.; Wang, L. P.; Stafford, J. A. J Med Chem 2008, 51, 4632.

[11] (a) Grimberg, B. T.; Jaworska, M. M.; Hough, L. B.; Zimmerman, P. A.; Phillips, J. G. Bioorg Med Chem Lett 2009, 19, 5452; (b) Sirichaiwat, C.; Intaraudom, C.; Kamchonwongpaisan, S.; Vanichtanankul, J.; Thebtaranonth, Y.; Yuthavong, Y. J Med Chem 2004, 47, 345.

[12] Ali, A.; Aster, S. D.; Graham, D. W.; Patel, G. F.; Taylor, G. E.; Tolman, R. L.; Painter, R. E.; Silver, L. L.; Young, K.; Ellsworth, K.; Geissler, W.; Harris, G. S. Bioorg Med Chem Lett 2001, 11, 2185.

[13] Carte, D. S.; Alam, M.; Cai, H. Y.; Dillon, M. P.; Ford, A. P. D. W.; Gever, J. R.; Jahangir, A.; Lin, C.; Moore, A. G.; Wagner, P. J.; Zhai, Y. S. Bioorg Med Chem Lett 2009, 19, 1628.

[14] (a) Naganuma, K.; Omura, A.; Maekawara, N.; Saitoh, M.; Ohkawa, N.; Kubota, T.; Nagumo, H.; Kodama, T.; Takemura, M.; Ohtsuka, Y.; Nakamura, J.; Tsujita, R.; Kawasaki, K.; Yokoi, H.; Kawanishi, M. Bioorg Med Chem Lett 2009, 19, 3174; (b) Sirisoma, N.; Pervin, A.; Nguyen, B.; Crogan-Grundy, C.; Kasibgatla, S.; Tseng, B.; Drewe, J.; Cai, S. X. Bioorg Med Chem Lett 2009, 19, 2305; (c) Orjales, A.; Mosquera, R.; López, B.; Olivera, R.; Labeaga, L.; Núñez, M. T. Bioorg Med Chem 2008, 16, 2183; (d) Van Veldhoven, J. P. D.; Chang, L. C. W.;von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Struensee-Link, R.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. Bioorg Med Chem 2008, 16, 2741.

[15] (a)Chauhan, S. M. S.; Junjappa, H. Synthesis 1974, 12, 880; (b) Mathews, A.; Asokan, C. V. Tetrahedron 2007, 63, 7845; (c) Kumar, S.; Ila, H.; Junjappa, H. Tetrahedron 2007, 63, 10067; (d) Panda, K.; Venkatesh, C.; Ila, H.; Junjappa, H. Eur J Org Chem 2005, 2045; (e) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G. J Org Chem 1983, 48, 4841.

[16] (a) Chunjian Liu, C. J.; Wrobleski, S. T.; Lin, J.; Ahmed, G.; Metzger, A.; Wityak, J.; Gillooly, K. M.; Shuster, D. J.; McIntyre, K. W.; Pitt, S.; Shen, D. R.; Zhang, R. F.; Zhang, H. J.; Doweyko, A. M.; Diller, D.; Henderson, I.; Barrish, J. C.; Dodd, J. H.; Schieven, G. L.; Leftheris, K. J Med Chem 2005, 48, 6261; (b) Arvanitis, E. A.; Chadha, N.; Pottorf, R. S.; Player, M. R. J Comb Chem 2004, 6, 414; (c) Altmann, E.; Aichholz, R.; Betschart, C.; Buhl, T.; Green, J.; Irie, O.; Teno, N.; Lattmann, R.; Tintelnot-Blomley, M.; Missbach, M. J Med Chem 2007, 50, 591; (d) Asadi, A.; Patrick, B. O.; Perrin, D. M. J Org Chem 2007, 72, 466; (e) Fabrice, G.; Patrick, R.; Heinz, M.; Peter, K.; Mark, B. Chem Eur J 1999, 5, 3450.

[17] (a) Masquelint, T.; Sprenger, D.; Baer, R.; Gerber, F.; Mercadal, Y. Helv Chim Acta 1998, 81, 646; (b) Chauhan, S. M. S.; Junjappa, H. Tetrahedron 1976, 32, 1911; (c) Rudorf, W. D.; Schierhom, A.; Augustin, M. Tetrahedron 1979, 35, 551.

[18] (a) Yan, S. J.; Huang, C.; Su, C. X.; Ni, Y. F.; Lin, J. J Comb Chem 2010, 12, 91; (b) Yan, S. J.; Huang, C.; Zheng, X. H.; Huang, R.; Lin, J. Bioorg Med Chem Lett 2010, 20, 48; (c) Yan, S. J.; Lin, J. Chin J Org Chem 2010, 30, 465.

[19] (a) Sommen, G. L.; Comel, A.; Kirsch, G. Synth Commun 2005, 35, 693; (b) Huang, Z. T.; Liu, Z. R. Synth Commun 1989, 19, 943; (c) Huang, Z. T.; Shi, X. Chem Ber 1990, 123, 541.

[20] Dorokhov, V. A.; Komkov, A. V.; Bogdanov, V. S. Russ Chem Bull 1997, 46, 1969.

[21] Hirose, M.; Hagimori, M.; Shigemitsu, Y.; Mizuyama, N.; Wang, B. C.; Tominaga, Y. Heterocycles 2009, 78, 899.

[22] Middleton, W. J.; Engelhardt, V. A. J Am Chem Soc 1958, 80, 2829.

[23] Bagli, J.; Bogri, T.; Palameta, B.; Rakhit, S.; Peseckis, S.; McQuillan, J.; Lee, D. K. H. J Med Chem 1988, 31, 814.

[24] Goerdeler, J.; Wieland, D. Chem Ber 1967, 100, 47.

[25] Spitzner, R.; Lesinski, M.; Richter, M.; Schroth, W. Monat Chem 1987, 118, 485.