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Efficient and library-friendly synthesis of furo- and thieno[2,3-*d*] pyrimidin-4-amine derivatives by microwave irradiation

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ABSTRACT

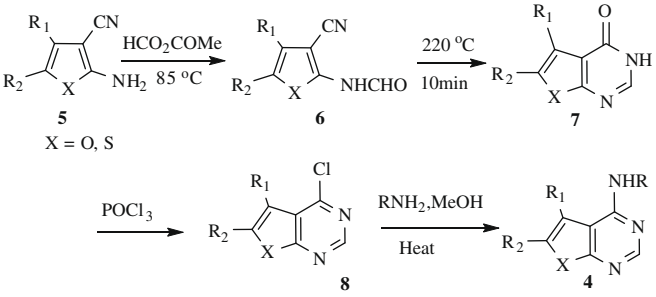
A new, divergent, efficient, and selective synthesis of furo- and thieno[2,3-*d*]pyrimidin-4-amine derivatives by microwave irradiation has been developed starting from readily available amines and substituted 2-aminofuran-3-carbonitrile or 2-aminothiophene-3-carbonitrile, which are converted into corresponding formamidines in DMF using benzenesulfonyl chloride.

Furo- and thieno[2,3-*d*]pyrimidin-4-amine derivatives have been the focus of great interest because of their remarkable biological properties in drug discovery (e.g., VEGFR2, GSK-3, DHFR, and TS).[1–14] In our efforts to pursue hit to lead and lead optimization, we have focused on developing expedient parallel synthetic methods for a straightforward library synthesis route to furo-, thieno-, and pyrrolo[2,3-*d*]pyrimidin-4-amine derivatives.

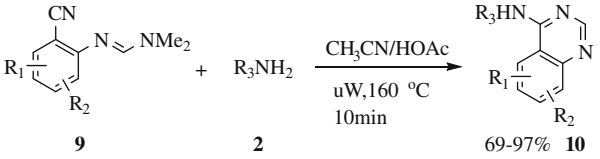
The traditional preparation of furo- and thieno[2,3-*d*]-pyrimidin-4-amine derivatives **4** involves the reaction of aminofurans or aminothiophenes **5** (Scheme 1) with in situ-generated acetic formic anhydride, which provides the *N*-formyl derivatives **6**.[10–15] Thermal cyclization, chlorination with phosphorus oxychloride, and finally displacement with an amine provide the target compounds. Overall, this four-step synthetic route is fairly labor intensive, requires several intermediate purifications, as well as a relatively high temperature reaction. In our view, access to the target compounds would require an alternate synthetic route to be effectively accessed via library synthesis.

Recently, a new methodology for the preparation of 4-aminoquinazolines **10** has been reported in high yields from reactions of amines **2** and the corresponding *N*′-(2-cyano-phenyl)-*N*,*N*-dimethylformamidine **9** via microwave irradiation (Scheme 2).[16] The procedure is very efficient and straightforward, providing both ring cyclization and incorporation of an anilino group at position 4 in a single step. We envisioned that this process could be extended to synthesize furo- and thieno [2.3-*d*]pyrimidin-4-amine derivatives **4** effectively.

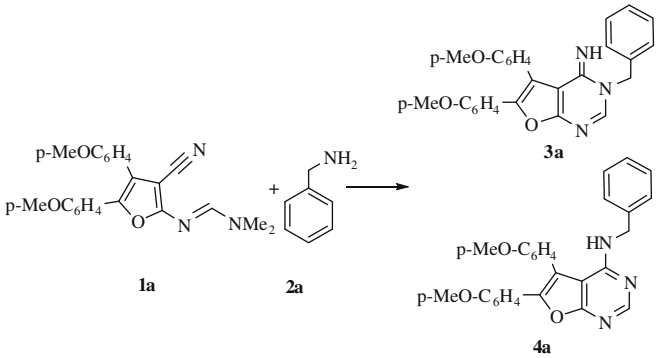
In an initial study (Scheme 3), we exposed formamidine **1a** to benzyl amine **2a** under the same conditions described previously (microwave, 160 °C, CH_3CN/HOAc = 1:3, 10 min).[16] Rather than isolating only the expected *N*-benzyl-5,6-bis(4-methoxy-



Scheme 1. Multi-step synthesis of compound **4**.



Scheme 2. Synthesis of 4-aminoquinazoline derivatives.[16]



Scheme 3. Synthesis of compounds **3a** and **4a**.

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Table 1
Optimization of reaction condition—the ratio of **3a** and **4a** affected by temperature[a]

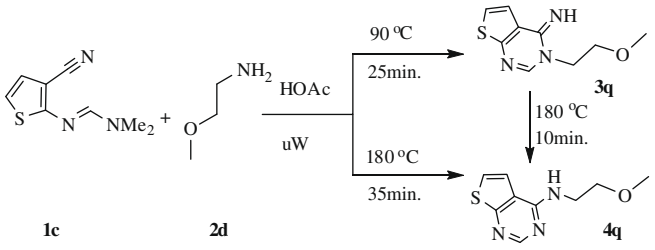
Entry	Temperature (°C)	Conversion of **1a** to products[b] (%)	Ratio (**3a**/**4a**)[c]	Yield (**3a** or **4a**)[d]
1	100	53	>99:1	45% (**3a**)
2	110	78	>99:1	69% (**3a**)
3	140	100	61/39	n/a
4	160	100	33/67	n/a
5	180	100	<1:99	88% (**4a**)

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), HOAc (0.8 mL) microwave irradiation at the power of 25–40 W at target temperature for 35 min.
[b] Determined by HPLC.
[c] Determined by HPLC.
[d] Isolated yields and characterized by ^{1}H NMR, ^{13}C NMR, LC–MS, and HRMS.

Table 2
Optimization of reaction condition—the ratio of **3a** and **4a** affected by concentration, equivalence of amine, and reaction times[a]

Entry	Eqs. of amine (**2a**) (equiv)	HOAc (mL)	Ratio (**3a**/**4a**)[b]
1	1	0.8	9/91 (2/98)[c]
2	1.5	0.8	3/97 (<1/99)[c]
3	1.5	1.2	11/89 (<1/99)[c]
4	2.0	0.8	1/99 (<1/99)[c]
5	3.0	0.8	0/100 (0/100)[c]

[a] All reactions were run at 180 °C for 25 min.
[b] Determined by HPLC.
[c] The data in parentheses are from additional 10-min runs to the same sample.



Scheme 4. Synthesis of thieno[2,3-*d*]pyrimidin-4-amine derivatives (**3q** and **4q**).

Table 3
Optimization of reaction condition—the ratio of **3q** and **4q** affected by temperature

Entry	Temperature (°C)	Conversion of **1c** to products[a] (%)	Ratio (**3q**/**4q**)[b]	Yield[c]
1	70	46[d]	>99/1	n/a
2	90	59[e]	>99/1	47% (**3q**)
3	120	100	35/65	n/a
4	140	100	17/83	n/a
5	160	100	2/98	n/a
6	180	100	<1:99	87% (**4q**)

[a,b] Determined by HPLC.
[c] Isolated yields characterized by ^{1}H NMR, ^{13}C NMR, LC–MS, and HRMS.
[d] 54% of **1c** remained.
[e] 41% of **1c** remained.

phenyl)furo[2,3-*d*]pyrimidin-4-amine **4a**, we observed a significant amount of the imine **3a**, presumably a kinetic product—known as Dimroth reaction.[17] Also, there were some unidentified impurities detected by LC–MS. Then we tested the same reaction in acetic acid only and found that the reaction was much cleaner. However, it still produced both **3a** and **4a** as a mixture.

By using acetic acid only, we were able to significantly alter the product ratios simply by altering the reaction temperature as shown in Table 1.

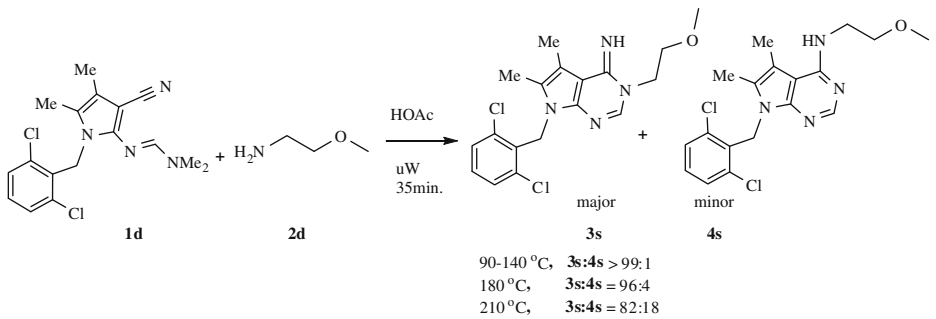
Further studies focused on the effects of reaction time and stoichiometric ratios of **1a** and **2a**, the results of which are summarized in Table 2. As the number of equivalents of **2a** was increased from 1.0 to 3.0 in 25-min runs, the ratio of **3a**/**4a** decreased from 9/91 to 0/100 (entries 1, 2, 4, and 5). Heating the same reaction for additional 10 min (35 min in total) showed a decrease in the ratio of **3a**/**4a** from 9/91 to 2/98 (entry 1) and 3/97 to <1/99 (entry 2). Furthermore, the reaction concentration was also important. As shown in entries 2 and 3, the ratio of **3a**/**4a** increased from 3/97 to 11/89, when the concentration was decreased from 0.2 mmol/0.8 mL to 0.2 mmol/1.2 mL in 25-min runs.

To prepare thieno[2,3-*d*]pyrimidin-4-amine derivatives, we next investigated the reaction of compound **1c** with compound **2d** (Scheme 4) applying our results from the studies of furo [2,3-*d*]pyrimidin-4-amine derivative. Not surprising, the regioselectivity was controlled by temperature. As demonstrated in Table 3, temperatures below or at 90 °C led to the formation of imine **3q** only, with significant unreacted starting material **1c**, while at 180 °C amine **4q** was the only product. Between 120 °C and 160 °C, a mixture of compounds 3**q** and **4q** was formed, with an increasing amount of **4q** as the temperature was increased. Compound **3q** was transformed to compound **4q** under microwaving at 180 °C for 10 min.

Interestingly, when pyrrole **1d** reacted with **2d** at 90–140 °C for 35 min by microwave irradiation, **3s** (86% isolated yield) was the only product (Scheme 5). Unlike **1a** and **1c**, microwave heating of **1d** and **2d** at 180 °C and 210 °C gave **3s** as the major product.

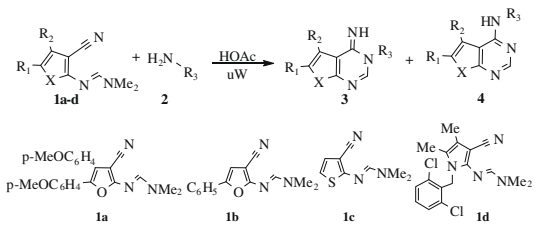
The microwave conditions depicted in Schemes 3–5 and Tables 1–3 were used to identify the preferred reaction conditions for the synthesis of structurally diverse furo- and thieno [2,3-*d*] pyrimidin-4-amine derivatives: 180 °C, 1 equiv of formamidine, and 1.5 equiv of amine in HOAc (0.8 mL) for 35 min. Optimum conditions were similarly identified for the preparation of furo-, thieno-, and pyrrolo[2,3-*d*]pyrimidin-4-imine derivatives: below 110 °C or at 140 °C, 1 equiv of formamidine and 1.5 equiv of amine, and 25–35 min. Table 4 summarizes library synthesis of a variety of compounds by these conditions. Benzylamines (**2a**, **2b**, **2e**, **2f**, and **2g**), an aliphatic amine (**2d**), and an electron-rich aniline (**2c**) were effective nucleophiles and offered good yields of desired products.[18,19]

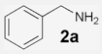
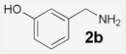
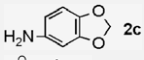
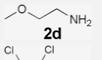
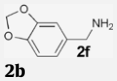
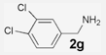
The proposed reaction mechanism via Dimroth rearrangement is shown in Scheme 6. First, the nitrogen of amine **2** attacked the carbon of formamidine to give species **11**. Then the intramolecular



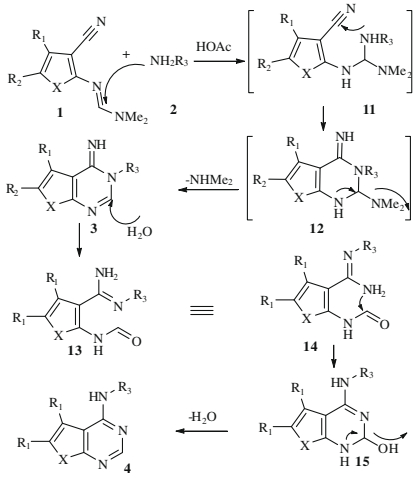
Scheme 5. Selective synthesis of 3*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-imine derivative (**3s**).

Table 4
Synthesis of substituted furo, thieno[2,3-*d*] pyrimidin-4-amines, and substituted 3*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-imine derivatives by microwave irradiation[a]



Entry	1	2	Product (yield)[b]
1	**1a**	 **2a**	**4a** (88%)
2	**1a**	**2a**	**3a** (69%)[c]
3	**1a**	 **2b**	**4b** (87%)
4	**1a**	 **2c**	**4c** (53%)
5	**1a**	 **2d**	**4d** (91%)
6	**1a**	 **2e**	**4e** (62%)
7	**1b**	**2a**	**4f** (72%)
8	**1b**	**2b**	**4g** (60%)
9	**1b**	**2c**	**4h** (51%)
10	**1b**	**2e**	**4i** (80%)
11	**1b**	 **2f**	**4j** (68%)
12	**1c**	**2b**	**4k** (86%)
13	**1c**	**2f**	**4l** (68%)
14	**1c**	**2e**	**4m** (77%)
15	**1c**	 **2g**	**4n** (81%)
16	**1d**	**2a**	**3t** (79%)[d]
17	**1d**	**2b**	**3u** (81%)[d]
18	**1d**	**2c**	**3v** (69%)[d]
19	**1d**	**2f**	**3w** (54%)[d]

[a] Reaction conditions: 0.2 mmol of formamidine, 0.3 mmol of amine in HOAc (0.8 mL) at 180 °C for 35 min with Biotage Initiator, and **1a**–**d** were prepared from the corresponding 2-amino-3-carbonitrile starting materials in DMF in the presence of benzenesulfonyl chloride.
[b] Isolated yields and all products were characterized by ^{1}H NMR, ^{13}C NMR, HPLC, and HRMS.
[c] Reaction was run at 110 °C.
[d] Reactions were run at 140 °C.



Scheme 6. Proposed mechanism of the Dimroth rearrangement to **3** and **4**.

reaction of **11** and ring closing took place to form species **12** followed by eliminating $HNMe_2$, to yield product **3** (imino-product **3** is a kinetic product). Second, water as a nucleophile attacked the pyrimidine ring, and opened the ring to afford a ring-opened species **13**, which could undergo a 180° turn to its tautomeric form **14**. Third, a subsequent electrocyclization to **15** and elimination of water yielded the thermodynamic stable product **4** (favored at high temperature). Even when pyrrole **1d** was used as starting material this tendency was also observed (Scheme 5).

For comparison, entry 5 in Table 1 was conducted using an oil bath under otherwise identical conditions (concentration, reaction vessel, and temperature). After capping tightly, the microwave vial was immersed in an oil bath at 180 °C for 35 min. The reaction was then cooled to room temperature. LC–MS analysis gave the ratio of 20/80 of **3a**/**4a** in 100% conversion versus <1/99 in 100% conversion with microwave conditions. It is demonstrated that microwave irradiation conditions are superior.

In summary, we have developed library friendly and highly selective methods for the synthesis of furo- and thieno [2,3-*d*] pyrimidin-4-amine derivatives. Also, we provided a method for the preparation of furo-, thieno-, and pyrrolo-[2,3-*d*]pyrimidin-4-imine derivatives. The advantages of our methods are: (1) a short synthetic route; (2) a high selectivity for amine and imine derivatives by simply changing the reaction temperature; and (3) a protocol suitable for library synthesis. Further studies and applications of this new methodology will be reported in due course.

Acknowledgments

We thank Drs. Louis Chupak and Tao Wang for discussion of this chemistry.

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18. *Typical procedure for the preparation of* **1a**–**d**: (*E*)-*N*′-(3-cyano-4,5-bis(4-methoxyphenyl)furan-2-yl)-*N*,*N*-dimethylformamidine **1a**: To a 100 mL flask equipped with a magnetic stir bar were added DMF (20 mL) and

benzenesulfonyl chloride (2.1 g, 12 mmol). The solution was stirred for 20 min and the color of the solution turned to light yellow. Then 2-amino-4,5-bis(4-methoxyphenyl)furan-3-carbonitrile (2 g, 6.2 mmol) was added as solid and the mixture was stirred for 30 min at room temperature. A solid was formed and diethyl ether (70 mL) was added. After filtration, the solid was neutralized with 2 N NaOH, extracted with ethyl acetate, washed with water and brine, and dried with Na_2SO_4. After removal of the solvents, the pure product was obtained as a colorless solid, 2.2 g, 94% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.05 (s, 3H), 3.18 (s, 3H), 3.74 (s, 3H), 3.81 (s, 3H), 6.88 (d, J = 8.55 Hz, 2H), 7.03 (d, J = 8.55 Hz, 2H), 7.31 (d, J = 8.55 Hz, 2H), 7.34 (d, J = 8.85 Hz, 2H), 8.45 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 34.27, 55.08,80.55, 114.01, 114.37, 115.57, 119.84, 122.12, 123.16, 126.47, 130.05, 139.83, 155.05, 158.53, 158.98, 162.94; HRMS calcd for $C_{22}H_{21}N_3O_3$: 375.1583, found 375.1571.

19. *Typical procedure for the preparation of* **4**: *N*-benzyl-5,6-bis(4-methoxyphenyl) furo-[2,3-*d*]pyrimidin-4-amine **4a**: To a 0.5–2 mL Biotage microwave vial equipped with a magnetic stir bar were added acetic acid (0.8 mL), formimidamide **1a** (0.2 mmol), and benzylamine **2a** (0.3 mmol). The vial was capped and heated in a Biotage Initiator at 180 °C for 35 min. The solution was transferred into a 16 × 100 mm culture tube and dried with nitrogen in a TurboVap evaporator at 40 °C overnight. Then the crude product was dissolved in DMF (1.6 mL) and purified by HPLC. (**4a**, 88% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (s, 1H), 7.44 (d, J = 8.55 Hz, 2H), 7.38 (d, J = 8.85 Hz, 2H), 7.30 (t, J = 7.32 Hz, 2H), 7.24 (d, J = 7.02 Hz, 1H), 7.20 (d, J = 7.02 Hz, 2H), 7.08 (d, J = 8.55 Hz, 2H), 6.94 (d, J = 8.85 Hz, 2H), 5.58 (t, J = 5.65 Hz, 1H), 4.62 (d, J = 5.49 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 146.27, 159.40, 156.90, 153.35, 146.04, 138.83, 130.89, 128.25, 127.39, 126.72, 121.69, 115.03, 114.27, 113.16, 55.17, 55.1, 43.78; HRMS calcd for $C_{27}H_{23}N_3O_3$: 437.1739, found 437.1729.

3-Benzyl-5,6-bis(4-methoxyphenyl)furo[2,3-d]pyrimidin-4(3H)-imine **3a** (69% yield): The procedure for the preparation of **3a** is similar to that for **4a** while the reaction temperature was 110 °C. Compound **3a** was obtained as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.33 (s, 1H), 7.23–7.47 (m, 9H), 7.09 (d, J = 8.55 Hz, 2H), 6.90 (d, J = 8.85 Hz, 2H), 5.17 (s, 2H), 3.83 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 171.79, 159.30, 159.11, 157.96, 154.05, 149.33, 145.63, 137.02, 130.84, 128.32, 127.60, 127.28, 126.84, 123.10, 121.77, 116.59, 114.76, 114.23, 105.29, 55.14, 48.72, 20.93. HRMS calcd for $C_{27}H_{23}N_3O_3$: 437.1739, found 437.1720.

N-(2-Methoxyethyl)thieno[2,3-d]pyrimidin-4-amine (**4q**, 87% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.32 (s, 1H), 3.54 (t, J = 5.65 Hz, 2H), 3.67 (q, J = 5.60 Hz, 2H), 7.55 (d, J = 6.10 Hz, 1H), 7.64 (d, J = 5.80 Hz, 1H), 8.06 (t, J = 5.04 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 40.14, 57.91, 70.27, 116.08, 119.31, 122.4, 153.59, 156.92, 165.47; HRMS calcd for $C_9H_{11}N_3OS$: 209.0623, found 209.0616.

3-(2-Methoxyethyl)thieno[2,3-d]-pyrimidin-4(3H)-imine **3q** (47% yield): The preparation of **3q** was similar to that of **4q** while the reaction temperature was 90 °C, 25 min. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 3.26 (s, 4H), 3.61 (t, J = 5.04 Hz, 3H), 4.14 (t, J = 5.04 Hz, 2H) 7.42 (d, J = 5.80 Hz, 1H), 7.60 (d, J = 5.80 Hz, 1H), 7.92 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 46.00, 58.04, 68.22, 122.18, 122.53, 148.41, 152.24, 157.37, 171.89; HRMS calcd for $C_9H_{11}N_3OS$: 209.0623, found 209.0621.

7-(2,6-Dichlorobenzyl)-3-(2-methoxyethyl)-5,6-dimethyl-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-imine (**3s**, 86% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.72 (s, 1H), 7.44–7.51 (m, 2H), 7.30–7.41 (m, 1H), 5.48 (s, 2H), 4.13 (t, J = 5.19 Hz, 2H), 3.59 (t, J = 5.19 Hz, 2H), 3.24 (s, 3H) 2.24 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 172.06, 154.14, 145.32, 142.72, 135.36, 131.85, 130.27, 128.92, 127.02–127.40, 108.46, 102.85, 68.74, 58.03, 45.89, 41.76, 21.45, 10.29, 9.16; HRMS calcd for $C_{18}H_{20}Cl_2N_4O$: 378.1014 found 378.1006.