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An efficient one-pot construction of substituted pyrimidinones

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Abstract—A concise, scaleable synthesis of building block **10** for p38 kinase inhibitor **B** is described. The key step is the one-pot construction of 5-aryl-3-methyl-2-methylsulfanyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one **4** from arylacetic acid ethyl ester **1**. Subsequent hydrolysis of the thiomethyl group to the hydroxy group and chlorination provided the key intermediate, 2-chloro-3-methyl-6-pyridin-4-yl-5-aryl-3*H*-pyrimidin-4-one **10**. This class of reactive building blocks enabled the rapid evaluation of a variety of side chains at the 2-position of the pyrimidinone in SAR studies of inhibitors of p38 MAP kinase.

1. Introduction

Inhibition of p38 MAP kinase (p38α) has been proposed as a disease-modifying approach toward the treatment of inflammatory disorders.[1–8] The vicinal aryl/pyridinyl heterocycles **A** are the most widely studied early p38 inhibitors.[2,3] Drug discovery efforts at Amgen have identified a variety of aryl/pyridyl pyrimidinones **B** (Fig. 1) as potent and selective inhibitors of p38α kinase. They can be generated via nucleophilic displacement of a leaving group at the 2-position by amines (Scheme 1). In order to facilitate the exploration of a broad array of substituents at the 2-position of this heterocycle, a concise, scaleable process leading to a suitably reactive intermediate was desired. The resulting process was ultimately used to prepare large quantities of particular leads for preclinical studies.

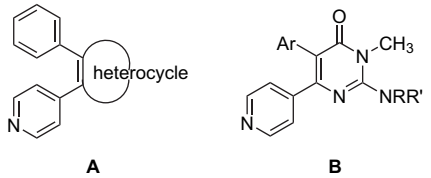
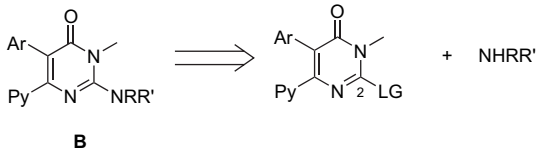


Figure 1.



Scheme 1.

Early exploratory efforts involving ring formation of 5,6-disubstituted-2-thiomethyl-pyrimidin-4-one **4** via condensation of a β-keto-ester and thiourea are summarized in Scheme 2. In this process, commercially available ethyl 2-(3-methylphenyl) acetate **1** was reacted with ethyl isonicotinate using NaH as a base to yield ethyl α-phenyl-β-oxo-4-pyridinepropanoate **2** after column chromatography.[9] When the β-ketoester **2** was treated with thiourea at 140 °C (melt) in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate, thiouracil **3** was isolated, but only in low yield (<20%). The crude product also required repeated recrystallization. Subsequent bis-methylation resulted in 2-thiomethyl-pyrimidin-4-one **4** along with a variety of by-products, including *S*-monomethyl and *O*,*S*-dimethyl derivatives, which were removed by column chromatography. Due

Keywords: Pyrimidinone; Methylisothiocyanate cyclization; Chlorination; Nucleophilic displacement; Inhibitors of p38 MAP kinase.
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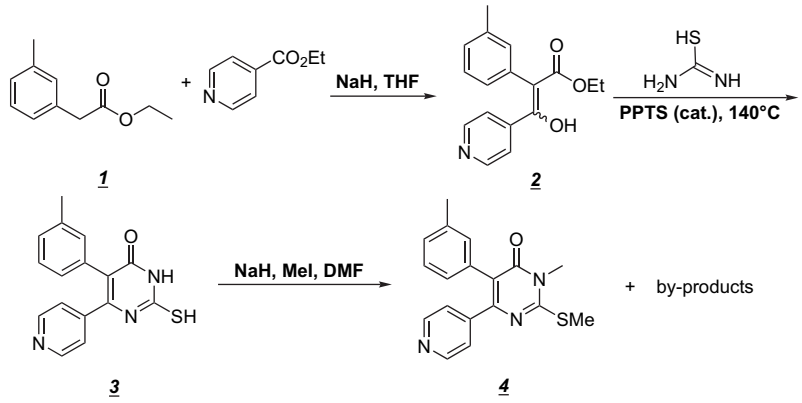
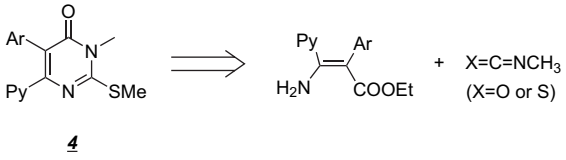


Scheme 2. Early route to 2-thiomethyl-pyrimidin-4-one.

to these issues, an alternative approach for construction of the pyrimidinethione ring was investigated.

The preparation of 4-pyrimidinethiones and related compounds from enamines and acryl/aryl isothiocyanates has been extensively investigated.[10–14] Of particular relevance to our target is the report of Hassan and co-workers[14] describing the synthesis of a 2-thiouracil from 2-amino-nicotinate and phenyl isothiocyanate. This encouraged us to utilize the reactivity of 3-amino-2-alkenoates toward methyl isothiocyanate (Scheme 3).



Scheme 3. Alternative approach to 2-thiomethyl-pyrimidin-4-one.

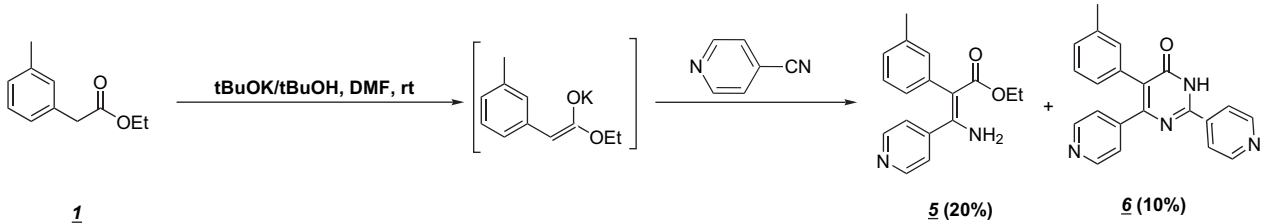
2. Results and discussion

2.1. Addition of alkanoate potassium enolates to nitriles

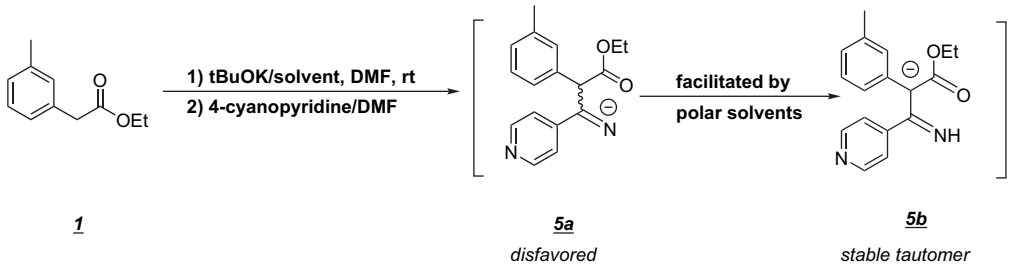
It has been reported that magnesium ester enolates can react with nitriles to provide (*Z*)-3-amino-2-alkenolates in moderate to good yields.[15] Although nitriles are usually considered to be inert to enolates, some pyridyl-derived analogs were found to be reactive. Our first attempt to generate the magnesium enolate of ethyl 2-(3-methylphenyl) acetate **1** with magnesium amide, as reported by Hiyama,[15] in the presence of 4-cyanopyridine was unsuccessful. Presumably, $Mg(NH_2)_2$ is not of sufficient basicity to deprotonate the α-position of **1**. In accordance with Hiyama's results,[15] the use of a lithium or sodium counterion also failed to provide any carbon–carbon bond formation. We envisaged that the use of a potassium counterion might render the enolate more reactive.[16] Indeed, it was found that the potassium enolate of *m*-tolyl-acetic acid ethyl ester **1**, prepared with potassium *tert*-butoxide, reacted with 4-cyanopyridine in DMF at room temperature to provide the corresponding 3-amino-2-alkenolate **5** along with a by-product, characterized as bis-pyridyl pyrimidinone **6** (Scheme 4). Although **6** was isolated in only 10% yield, this served to demonstrate the potential of this reaction sequence to construct the desired heterocyclic ring system in a stepwise, one-pot fashion.

Subsequent experiments produced some interesting observations: (i) the nitrile addition appeared to be faster and cleaner when *t*-BuOK in *t*-BuOH was used as opposed to *t*-BuOK in THF and (ii) use of KH in DMF or THF did not result in any of the desired alkenoate **5**, even though the dark purple color of the KH–ester mixture was indicative of enolate anion formation. It is likely that *t*-BuOH serves to either directly protonate the incipient, nitrogen-centered anion generated during attack of enolate **1** upon the nitrile substrate, or to facilitate subsequent tautomerization to the more stable **5b**. B3LYP/6-31G* calculations fail to locate a non-tautomerized minimum corresponding to **5a** in the gas phase; its existence in solution is likely to be disfavored as well. In the presence of protic solvents, formation of **5b** is facilitated, whereas in non-protic media, addition of **1** to the nitrile is disfavored (Scheme 5).

A loose correlation is observed between nitrile electrophilicity (as gauged by LUMO energy at the RHF/6-31G* level) and both the calculated exothermicity of the model enolate addition, as well as final yield of 'one pot' cyclization/quenching product **4** (Table 1).

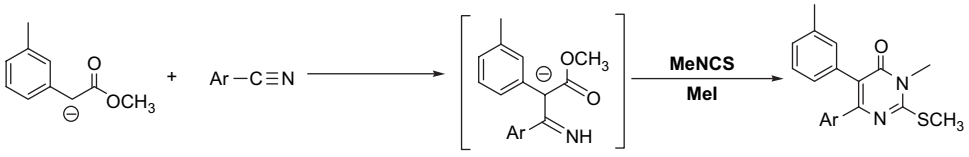


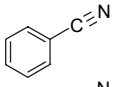
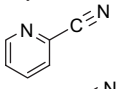
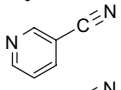
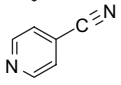
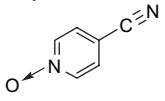
Scheme 4. Formation of 3-amino-2-alkenoate.



Scheme 5. Addition of potassium ester enolates to nitriles.

Table 1. Computed electrophilicities and relative reactivities of aryl nitrile substrates



2	E_{rxn} (**1**+**2**→**5**)[a,b]	E(LUMO), **2**[c]	% Yield, **4**[d]
	−9.9 (**0.0**)	+0.08353	0
	−11.8 (**−1.9**)	+0.06960	0
	−14.6 (**−4.7**)	+0.07126	30
	−16.6 (**−6.7**)	+0.05903	50−60
	−19.1 (**−9.2**)	+0.03844	40

[a] Absolute (relative in bold) energies of reaction (kcal/mol) at the B3LYP/6-31G*+ZPE level.
[b] All calculations performed with the Gaussian 98[17] program system.
[c] a.u., RHF/6-31G*//B3LYP/6-31G*.
[d] From Table 2.

2.2. Quenching of the amino alkenoate anion by electrophiles

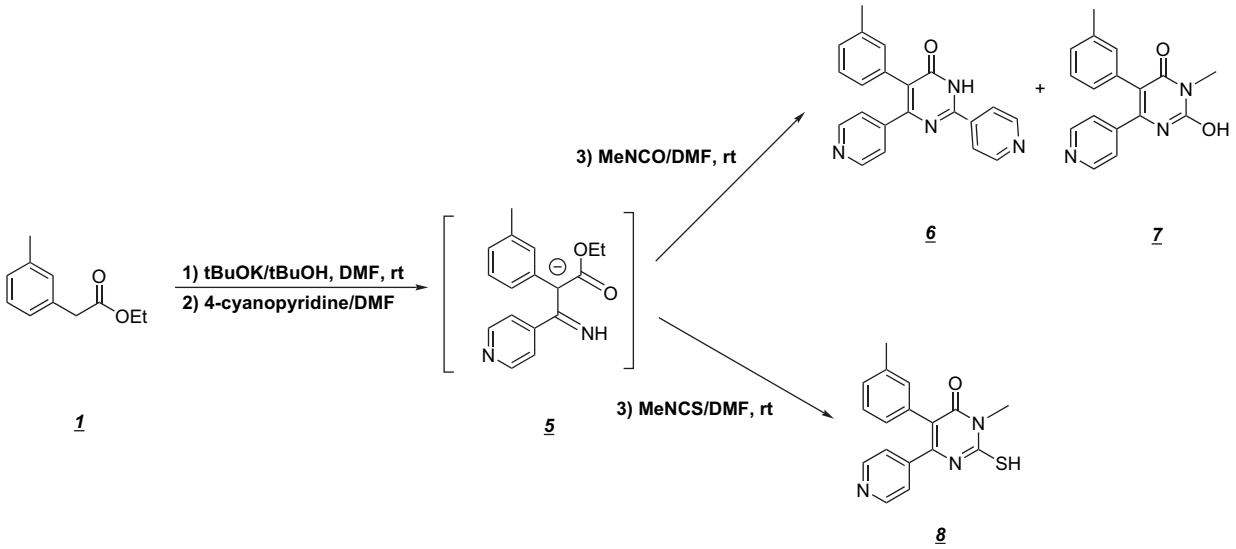
With the chemistry leading to amino alkenoate anion **5** established, efforts were undertaken to trap and cyclize this intermediate into the uracil- or thiouracil-like pyrimidinone in a single step. Early attempts to quench **5** with methyl isocyanate resulted in the formation of uracil **7** and bis-pyridyl pyrimidinone **6** as 1:1 mixture based on HPLC area ratio (Scheme 6).

In contrast, quenching **5** with methyl isothiocyanate in DMF at room temperature afforded the corresponding thiouracil **8** in good conversion (~95%) (Scheme 6). Furthermore, sequential addition of methyl isothiocyanate to **5**, followed by iodomethane, provided the desired 2-thiomethyl-pyrimidin-4-one **4** in 50% overall yield. Conveniently, the product **4** could be precipitated as an off-white solid by simple addition of an equal volume of water to the DMF and stirring at −5 to 0 °C for 48 h (Scheme 7).

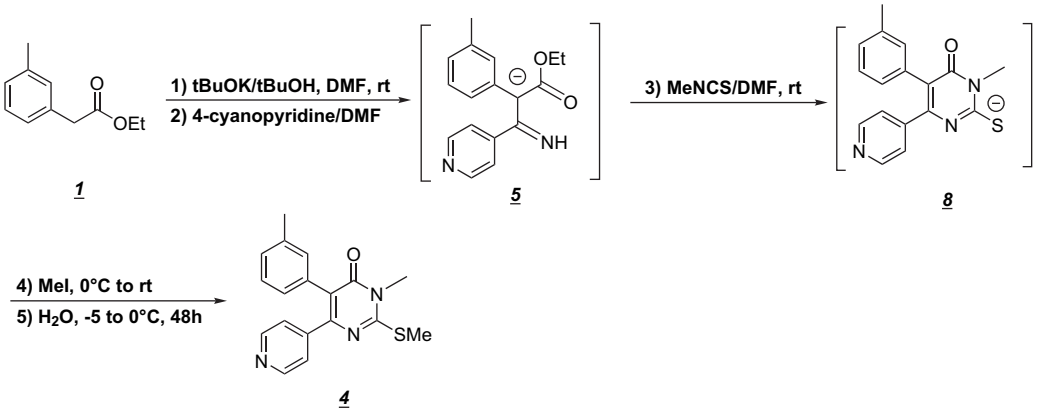
This one-pot process, consisting of enolate/nitrile addition, isothiocyanate addition/cyclization, and S-methylation, produced the desired 2-thiomethyl-pyrimidin-4-one **4**, for which an early medicinal chemistry route had required in three steps (Scheme 2). In addition to the simplification of the procedure, the overall yield increased by more than 10-fold. These conditions require only 1 equiv each of *t*-BuOK, the nitrile, methyl isothiocyanate, and iodomethane in relation to the starting ester. The convenient temperature range of this reaction (−5 to 25 °C) is another attractive feature, enabling successful scale-up to a multi-kilogram quantity.

2.3. The scope and limitation of the one-pot construction

When ethyl 2-(4-fluorophenyl) acetate was used as starting material, a complex mixture along with 4-cyanopyridine was obtained instead of the corresponding sulfide, possibly arising from defluorination of the aryl ring upon generation of the enolate. Therefore, the one-pot process was modified to avoid potential decomposition or self-condensation of the



Scheme 6. Quenching of 3-amino-2-alkenoate.



Scheme 7. The one-pot reaction.

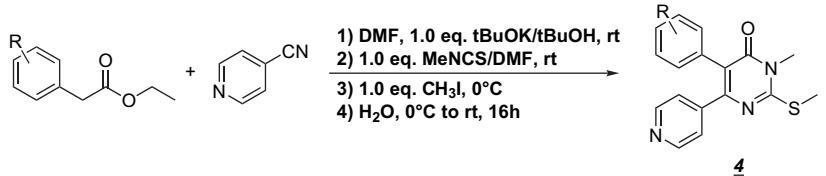
alkenoate anion. In the improved procedure, *t*-BuOK/*t*-BuOH was added to the premixed DMF solution of the ester and 4-cyanopyridine, allowing for immediate addition with the nitrile substrate upon enolate generation. The rest of reaction sequence remains same (Scheme 8).

This one-pot reaction has been used to generate the 2-thiomethyl-pyrimidin-4-ones **4** as reported in Table 2.

Contrary to when generated in situ, aminoalkenoate **5**, isolated after work-up, reacted poorly with alkyl nitriles in the presence of base or acid over a wide temperature range (rt–120 °C).[18] Neutral enamine **5** could potentially exist as either (*E*) or (*Z*)-isomers; B3LYP/6-31G* calculations predict (*Z*)-**5** (Fig. 2) to be 6.1 kcal/mol lower in energy than (*E*)-**5** due in part to intramolecular hydrogen bonding and π-stacking of the aromatic rings and 7.5 kcal/mol lower in energy than its imine tautomer. The prediction of (*Z*)-**5** as the exclusive neutral species present upon protonation of the anion of **5** was subsequently confirmed on the basis of NOE experiments (see Section 3.6).

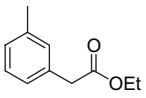
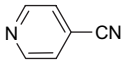
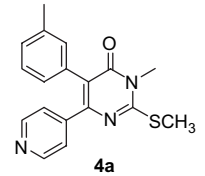
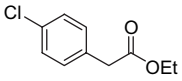
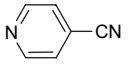
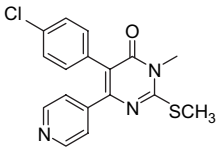
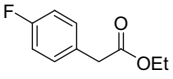
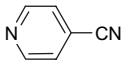
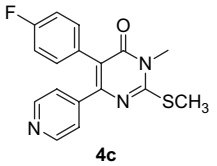
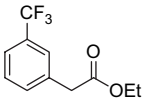
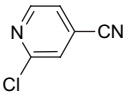
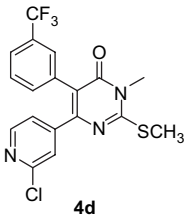
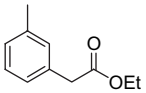
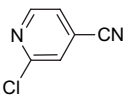
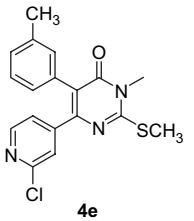
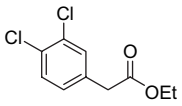
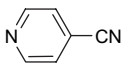
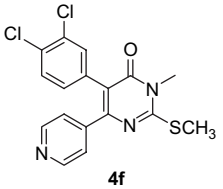
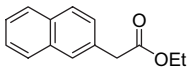
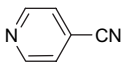
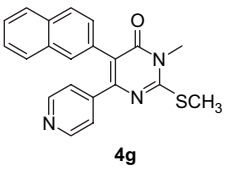
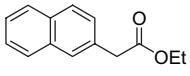
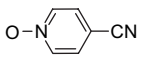
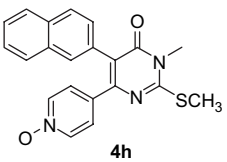
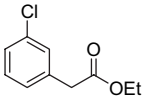
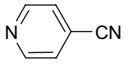
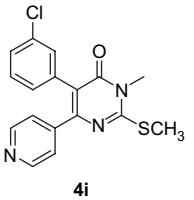
2.4. Conversion of the sulfide-pyrimidinones to the more reactive chloro-pyrimidinones

The thiomethyl moiety could, in principle, be used as a leaving group to introduce amines at the 2-position. However, we found that this displacement required harsh conditions (neat, high temperature, and sealed vessel), which were not practical for scale-up. As the displacement of



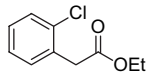
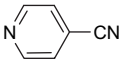
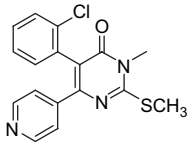
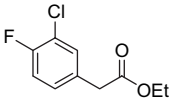
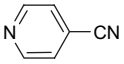
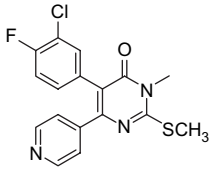
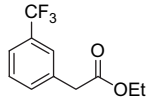
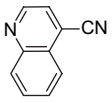
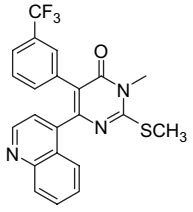
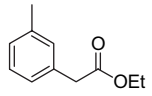
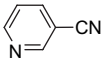
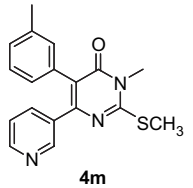
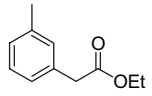
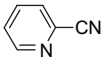
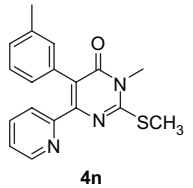
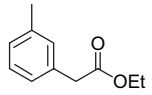
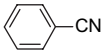
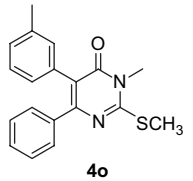
Scheme 8. The modified one-pot process.

Table 2. Syntheses of 2-thiomethyl-pyrimidin-4-ones **4** via Scheme 8

Entry	Ester	Nitrile	Product	Yield (%)
1			 **4a**	51
2			 **4b**	51
3			 **4c**	50
4			 **4d**	50
5			 **4e**	50
6			 **4f**	65
7			 **4g**	63
8			 **4h**	40
9			 **4i**	60

(*continued*)

Table 2. (*continued*)

Entry	Ester	Nitrile	Product	Yield (%)
10			 **4j**	60
11			 **4k**	66
12			 **4l**	25
13			 **4m**	30
14			 **4n**	0
15			 **4o**	0

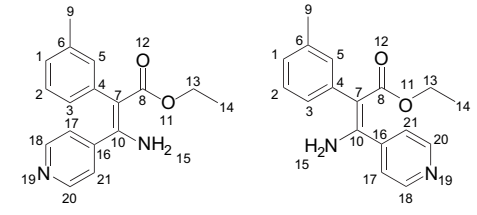
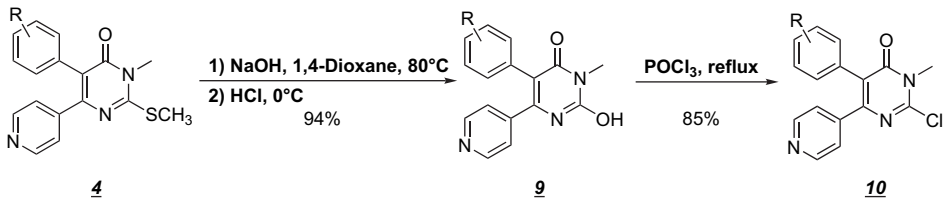


Figure 2.

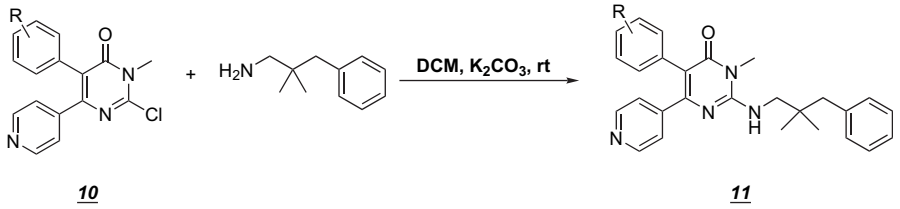
chloro-pyrimidines with amino nucleophiles has been reported to proceed under mild conditions,[19] the 2-thiomethyl moiety was converted to the more reactive corresponding 2-chloro derivative. First, hydrolysis of the sulfide was readily accomplished with aqueous sodium hydroxide in an organic solvent system (e.g., dioxane or THF/MeOH). Adjustment of the pH of the reaction solution to 6–7 precipitated the desired hydroxypyrimidinones **9** (Scheme 9).

Standard procedures were applied for the conversion of uracil **9** into the chloropyrimidinone **10**, utilizing either PCl_5, $SOCl_2$, or $POCl_3$.[20] The use of neat $POCl_3$ as solvent under reflux conditions afforded the best results (Scheme 9). After chromatographic purification, the chloride **10** was used as a reactive intermediate to introduce a variety of amines via nucleophilic displacement under mild conditions. An example is shown in Scheme 10.

In summary, a concise, scaleable synthesis of **10**, a building block for p38 kinase inhibitors, has been realized. This new route represents a significant improvement over the initial medicinal chemistry route. The key step is the one-pot construction of 5-aryl-3-methyl-2-methylsulfanyl-6-pyridin-4-



Scheme 9. Conversion of the sulfide-pyrimidinone **4** to chloro-pyrimidinone **10**.



Scheme 10. Nucleophilic displacement of chloro-pyrimidinone **10** with amine.

yl-3*H*-pyrimidin-4-one **4** from aryl acetic acid ethyl ester **1** and 4-cyanopyridine via enolate/nitrile nucleophilic condensation, isothiocyanate additon/cyclization, and subsequent S-methylation using equimolar amounts of all reactants. The convenient temperature range of this process (−5 °C to rt) and ease of isolation offer additional advantages. Subsequent hydrolysis of the thiomethyl group to the hydroxyl group, followed by chlorination provided the key intermediate, 2-chloro-3-methyl-6-pyridin-4-yl-5-aryl-3*H*-pyrimidin-4-one **10**. This class of reactive building blocks enabled the exploration of a variety of side chains at the 2-position of the pyrimidinone in an effort to optimize potency and in vivo efficacy.

3. Experimental

3.1. General

Solvents and reagents were obtained from commercial sources and used as received. Proton and carbon NMR spectra were obtained using a Bruker Avance II 400 MHz spectrometer. The signals are reported in parts per million relative to TMS using $CDCl_3$ as a solvent (unless otherwise indicated). The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in Hertz (Hz) using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. High-resolution mass spectra (HRMS) were acquired on a 7 Tesla Bruker Apex IV Fourier-Transform Mass Spectrometer (FTMS) using ESI ionization modes. FTIR spectra were obtained using a Nicolet 410 FT-IR spectrophotometer. Mercaptan safety studies were performed by the Wisconsin Occupational Health Lab of Madison, Wisconsin. Column chromatography was performed using silica gel 60-200 from EM Science. High-pressure liquid chromatography (HPLC) was performed with an Agilent 1100 series.

3.2. General procedure for the preparation of 5-aryl-3-methyl-2-methylsulfanyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (4)

To a solution of the ester (6.9 mol) and 4-cyanopyridine (7.0 mol) in DMF (15 L) was slowly added *t*-BuOK (1.0 M in *t*-BuOH, 7 L, 7.0 mol). The resultant dark-red solution was stirred at room temperature for 1.5 h. A DMF solution of methyl isothiocyanate (8.4 mol dissolved in 614 mL DMF) was added to the dark-red solution at such a rate that the internal temperature was maintained below 25 °C. After the addition was complete, the mixture was stirred at room temperature for 1 h. The solution was cooled to 0 °C, and methyl iodide (7.0 mol) was added at such a rate that temperature remained below 5 °C. The reaction mixture was stirred for 1 h at room temperature, and then cooled to 0 °C. Deionized water (21.5 L) was added at such a rate that internal temperature was maintained below 10 °C. The resulting suspension was stirred at room temperature for 16 h. The solid was filtered off via an Aurora filter. The wet cake was washed with water (3×3 L) and dried in an oven under vacuum at 70 °C to provide the desired pyrimidinones.

4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.66 (s, 3H), 3.61 (s, 3H), 6.9 (d, J=7.5 Hz, 1H), 7.03 (s, 1H), 7.08 (d, J=7.5 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.23 (d, J=6 Hz, 2H), 8.46 (d, J=6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 21.3, 30.8, 120.8, 123.8, 127.7, 128.2, 128.7, 131.1, 133.1, 137.8, 145.9, 149.4, 154.0, 161.0, 162.3. FTIR (KBr) ν_{max} 1659, 1596, 1571, 1540, 1525, 1409, 1367, 1347, 1310, 1188, 1165, 1099, 1088, and 1068 cm^{-1}. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{17}N_3OS$ 323.1092, found 323.1079.

4b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 7.12 (d, J=5.33 Hz, 2H), 7.22 (d, J=3.82 Hz, 2H), 7.26 (d, J=5.33 Hz, 2H), 8.50 (d, J=3.82 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.9, 119.4, 123.9, 128.6, 131.8, 132.2, 134.0, 145.7, 149.7, 154.6, 161.8, 162.1. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}ClN_3OS$ 344.0624, found 344.0618.

4c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 6.98 (d, J=8.61 Hz, 2H), 7.15 (d, J=8.61 Hz, 2H), 7.22 (d, J=5.87 Hz, 2H), 8.49 (d, J=5.87 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 30.9, 115.6, 119.6, 123.9, 129.2, 132.6, 145.8, 149.6, 154.5, 161.2, 162.3, 163.6. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}FN_3OS$ 328.09144, found 328.09166.

4d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.63 (s, 3H), 6.96 (dd, J=5.28, 1.37 Hz, 1H), 7.33 (d, J=8.22 Hz, 1H), 7.35 (s, 1H), 7.43 (t, J=8.22 Hz, 1H), 7.49 (s, 1H), 7.57 (d, J=7.63 Hz, 1H), 8.21 (d, J=5.28 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 31.0, 119.5, 122.5, 124.5, 125.2, 127.7, 129.0, 130.8, 131.1, 133.8, 134.2, 148.5, 149.3, 151.7, 153.7, 161.7, 162.7. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{13}ClF_3N_3OS$ 412.01927, found 412.04932.

4e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.66 (s, 3H), 3.61 (s, 3H), 6.90 (d, J=7.43 Hz, 1H), 7.01 (m, 2H), 7.12 (d, J=7.63 Hz, 1H), 7.19 (t, J=7.63 Hz, 1H), 7.41 (s, 1H), 8.18 (d, J=5.09 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.4, 29.9, 120.3, 121.8, 123.5, 126.7, 127.5, 128.1, 130.1, 131.7, 137.2, 148.0, 148.1, 150.4, 151.7, 160.5, 161.2. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{16}ClN_3OS$ 358.0781, found 358.0785.

4f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 6.95 (dd, J=5.2, 1.24 Hz, 1H), 7.23 (dd, J=6.06, 1.57 Hz, 2H), 7.33 (d, J=8.41 Hz, 1H), 7.37 (d, J=1.76 Hz, 1H), 8.54 (dd, J=6.26, 1.57 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 31.0, 118.2, 123.8, 130.2, 130.3, 132.2, 132.5, 132.7, 133.4, 145.3, 149.8, 155.0, 161.8, 162.4. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{13}Cl_2N_3OS$ 378.02291, found 378.02324.

4g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.67 (s, 3H), 7.25 (m, 3H), 7.48 (m, 2H), 7.77 (m, 4H), 8.45 (d, J=7.24 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 31.4, 120.9, 124.4, 126.5, 126.8, 127.9, 128.1, 128.2, 128.3, 128.6, 128.8, 130.6, 131.2, 133.2, 133.6, 146.4, 149.9, 154.9, 161.8, 162.8. HRMS (ESI) *m/e* (M+H) calcd for $C_{21}H_{17}N_3OS$ 360.11651, found 360.11635.

4h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.64 (s, 3H), 7.25 (m, 5H), 7.48 (m, 2H), 7.75 (m, 2H), 7.83 (m, 2H), 7.93 (d, J=7.24 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 31.0, 120.1, 126.4, 126.7, 126.8, 127.7, 128.0, 128.2, 128.5, 130.1, 130.6, 132.9, 133.3, 135.7, 138.6, 152.1, 161.6, 162.3. HRMS (ESI) *m/e* (M+H) calcd for $C_{21}H_{17}N_3O_2S$ 376.1119, found 376.1116.

4i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.61 (s, 3H), 7.00 (d, J=8.02 Hz, 1H), 7.17–7.19 (m, 1H), 7.22 (dd, J=6.26, 1.57 Hz, 2H), 7.25–7.27 (m, 2H), 8.50 (d, J=6.06 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.9, 119.3, 123.8, 129.1, 130.8, 134.2, 135.2, 145.5, 149.7, 154.8, 161.9, 162.0. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}ClN_3OS$ 344.0624, found 344.0622.

4j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3H), 3.63 (s, 3H), 7.08 (dd, J=7.63, 1.57 Hz, 1H), 7.17–7.29 (m, 4H), 7.41 (d, J=7.24 Hz, 1H), 8.48 (d, J=5.87 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 30.9, 118.8, 123.1, 127.1, 129.7, 129.8, 132.2, 133.0, 134.7, 145.5, 149.6, 155.3, 161.4, 162.4. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{14}ClN_3OS$ 344.0624, found 344.0615.

4k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.62 (s, 3H), 6.95 (m, 1H), 7.03 (t, J=8.60 Hz, 1H), 7.23 (dd, J=6.06, 1.57 Hz, 2H), 7.32 (dd, J=7.04, 2.15 Hz, 1H), 8.53 (d, J=6.06 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 31.0, 116.7, 118.4, 121.2, 123.8, 130.4, 130.8, 133.0, 145.5, 149.8, 154.9, 156.5, 159.0, 162.2. HRMS (ESI) *m/e* (M+H) calcd for $C_{17}H_{13}ClFN_3OS$ 362.0530, found 362.0522.

4l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.62 (s, 3H), 6.95 (dd, J=5.2, 1.24 Hz, 1H), 7.23 (dd, J=3.8, 1.88 Hz, 2H), 7.33 (d, J=5.17 Hz, 1H), 7.37 (d, J=1.22 Hz, 1H), 8.53 (d, J=3.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 31.0, 120.7, 121.4, 122.4, 124.4, 125.4, 126.9, 127.3, 128.3, 130.0, 130.4, 133.4, 133.9, 144.2, 148.4, 149.6, 154.9, 156.5, 161.7, 162.2. HRMS (ESI) *m/e* (M+H) calcd for $C_{22}H_{16}F_3N_3OS$ 428.1044, found 428.1047.

4m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.66 (s, 3H), 3.61 (s, 3H), 6.9 (d, J=7.5 Hz, 2H), 6.92 (d, J=4.70 Hz, 1H), 7.06–7.15 (m, 4H), 7.55 (t, J=4.70 Hz, 1H), 8.45 (d, J=3 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 21.4, 30.8, 120.4, 122.4, 127.9, 128.3, 128.7, 131.4, 133.5, 134.1, 137.0, 138.0, 149.4, 150.8, 154.0, 161.0, 162.4. HRMS (ESI) *m/e* (M+H) calcd for $C_{18}H_{17}N_3OS$ 324.1170, found 324.1171.

3.3. General procedure for the preparation of 5-aryl-2-hydroxy-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (9)

To a solution of the sulfide (1.32 mol) in 1,4-dioxane (1.05 L) was added 2 N NaOH (6.6 mol, 5 equiv). The solution was heated to 80 °C and allowed to stir overnight under N_2. Upon complete conversion, the reaction mixture was cooled to 0 °C. HCl 1 N (6.1 L) was added slowly until the pH reached 7. The product was then collected on a fritted glass funnel, and washed three times with copious amount of water. The solid was then dried at 80 °C in vacuo to provide the product as a white solid (94%). This product is of suitable purity to be taken directly to the next step; however, a cleaner reaction profile was obtained if the crude product was further dried via azeotropic distillation with toluene.

9a (R=*m*-CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.23 (s, 3H), 6.76 (d, J=7.5 Hz, 1H), 6.9 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 7.04 (t, J=7.5 Hz, 1H), 7.2 (d, J=6.0 Hz, 2H), 8.48 (d, J=6.0 Hz, 2H), 11.5 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 27.2, 111.8, 120.7, 123.7, 127.6, 128.5, 132.0, 132.7, 136.6, 140.3, 146.0, 149.5, 150.8, 162.8. FTIR (KBr) ν_{max} 3056, 3041, 2917, 2776, 1720, 1652, 1602, 1450, 1420, 1297, 1228, 1072, and 1004 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.50; H, 5.18; N, 14.45.

3.4. General procedure for the preparation of 5-aryl-2-chloro-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (10)

A three-necked, 2-L round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, temperature probe, and gas inlet/exit was charged with the hydroxide (2 mol) and then $POCl_3$ (70 mol, 35 equiv). The suspension was heated to reflux and a solution was obtained within 10 min. The reaction was allowed to proceed for 16 h at reflux, and the excess $POCl_3$ was distilled under low pressure. The resulting dark residue was allowed to cool to −5 to 0 °C

and a mixture of dichloromethane/ice water was added. Saturated aqueous $NaHCO_3$ was added dropwise into the cooled DCM/water solution with aggressive agitation. The basic quenching was completed once the pH reached 6–7. The phases were separated and the organic layer was washed with a 10% aq solution of $NaHCO_3$ followed by water, and allowed to dry over Na_2SO_4. The crude chloride was isolated after removal of solvent and purified by chromatography with ethyl acetate/hexanes to give the pure chloride (85%).

10a (R=*m*-CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.76 (s, 3H), 6.91 (d, J=7.5 Hz, 1H), 7.02 (s, 1H), 7.16 (m, 4H), 8.48 (d, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 33.9, 123.5, 124.4, 127.4, 128.4, 129.2, 129.3, 130.8, 132.1, 138.1, 144.4, 147.8, 149.6, 154.6, 162.3. FTIR (KBr) ν_{max} 1662, 1582, 1551, 1532, 1414, 1350, 1167, and 1094 cm^{-1}. Anal. Calcd for $C_{17}H_{14}Cl\ N_3O_2$: C, 65.49; H, 4.53; N, 13.45. Found: C, 65.41; H, 4.54; N, 13.26.

3.5. General procedure for the preparation of 2-alkylamino-5-aryl-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (11)

A three-necked, 2-L round-bottomed flask equipped with a mechanical stirrer, reflux condenser, temperature probe, and gas inlet/exit were charged with 5-aryl-2-chloro-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one (0.15 mol), the alkylamine (0.165 mol), dichloromethane (1 L, 0.15 M), and potassium carbonate (0.165 mol). The reaction mixture was stirred for 16 h at ambient temperature under nitrogen. Water was then added into the reaction solution. The phases were separated, and the organic layer was washed with a 10% aq solution of $NaHCO_3$, followed by water, and allowed to dry over Na_2SO_4. The crude product was isolated after removal of solvent and purified by chromatography with ethyl acetate/hexanes to give the pure product (90%).

11 (R=*o*-F): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 6H), 2.67 (s, 2H), 3.11 (s, 3H), 3.56 (d, J=5.7 Hz, 2H), 5.30 (s, 1H), 6.90–6.94 (m, 2H), 7.05–7.09 (m, 2H), 7.12–7.14 (m, 2H), 7.23–7.25 (m, 2H), 7.29–7.36 (m, 3H), 8.40 (d, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.8, 36.1, 47.8, 51.4, 113.5, 115.1, 115.3, 124.0, 126.8, 128.6, 130.3, 132.8, 138.7, 146.9, 149.4, 152.5, 156.5, 162.6, 163.6. HRMS (ESI) *m/e* (M+H) calcd for $C_{27}H_{27}FN_4O$ 443.2242, found 443.2246.

3.6. Structural elucidation of 5

^{1}H and ^{13}C NMR spectra were recorded in 0.15 mL DMSO-d_6 at 30 °C (303 K) in 3 mm NMR tube (3 mm Bruker DCH Dual CryoProbe) and run at 600.13 and 150.92 MHz on a Bruker Avance 600 MHz spectrometer. Chemical shifts are reported in parts per million by assigning the residual solvent peak to 2.50 and 39.51 ppm for DMSO for ^{1}H and ^{13}C, respectively. The nuclear overhauser effect (NOE) experiments were determined with an 800 ms mixing time for the one-dimensional (1D) selective NOE and the two-dimensional (2D) nuclear overhauser effect spectroscopy (NOESY). Both the ^{1}H–^{13}C heteronuclear single quantum correlation (HSQC) and the ^{1}H–^{13}C heteronuclear multiple bond correlation (HMBC) spectra were determined using gradient pulses for coherence selection. The HSQC spectrum was determined with decoupling during acquisition. Delays corresponding to one bond ^{13}C–^{1}H coupling (ca. 145 Hz) for the low-pass filter and the 2–3 bond ^{13}C–^{1}H long-range coupling (7.7 Hz) were used for the HMBC.

3.6.1. (*Z*)-3-Amino-3-pyridin-4-yl-2-*m*-tolyl-acrylic acid ethyl ester ((*Z*)-5). ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.09 (t, J=7.1 Hz, 3H, H-14), 2.09 (s, 3H, H-9), 4.04 (q, J=7.1 Hz, 2H, H-13), 6.71 (d, J=7.6 Hz, 1H, H-3), 6.74 (s, 1H, H-5), 6.79 (d, J=7.6 Hz, 1H, H-1), 6.91 (t, J=7.6 Hz, 1H, H-2), 7.07 (d, J=6.1 Hz, 2H, H-17, 21), 7.77 (d, J=6.1 Hz, 1H, H-15), 8.38 (d, J=6.1 Hz, 2H, H-18, 20), 8.71 (d, J=6.1 Hz, 1H, H-15); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.5 (C-14), 20.9 (C-9), 58.7 (C-13), 97.1 (C-7), 123.5 (C-17, 21), 126.2 (C-1), 127.0 (C-2), 129.8 (C-3), 133.4 (C-5), 135.9 (C-4), 137.0 (C-6), 145.5 (C-16), 149.1 (C-18, 20), 150.3 (C-10), 169.0 (C-8).

1D ^{1}H NOE experiments using selective excitation with a shaped pulse (gradient version) were used to determine the stereochemistry of **5** (Fig. 2). Irradiation of the aromatic protons at C-17, 21 elicited NOE signals from H-3 (weak), H-5 (weak), and H-18, 20 (strong), confirming further that the disposition of tolyl and the pyridine rings are such as those for the (*Z*) isomer and suggestive of a stacking interaction. Irradiation of the methyl protons at C-9 elicited NOE signals from H-1 (weak), H-3 (strong), H-5 (strong), H-13 (weak), H-14 (weak), H-17, 21 (weak), and H-18, 20 (weak), indicating once again that compound **5** exists as the (*Z*) isomer, with evidence of stacking of the aromatic rings and a disposition of the ethyl group *syn* to the tolyl ring. The distinct proton chemical shifts corresponding to the primary amino group (δ, 7.77 and 8.71 ppm) suggest restricted rotation about the C–N bond.

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