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RESEARCH ARTICLE

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Microwave-Assisted, Divergent Solution-Phase Synthesis of 1,3,6-Trisubstituted Pyrazolo[3,4-*d*]pyrimidines

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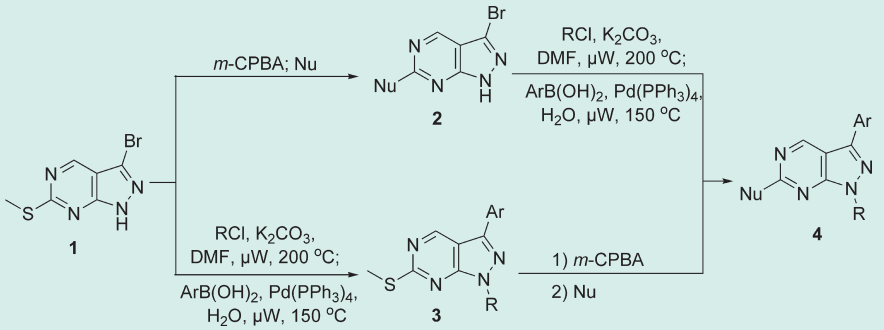
Supporting Information

ABSTRACT:



A concise and highly divergent synthetic route has been developed to rapidly access 1,3,6-trisubstituted pyrazolopyrimidines. The synthesis features a microwave assisted one-pot N1-alkylation/Suzuki−Miyaura reaction as the key step. The sequence of the synthetic scheme can be varied to selectively modify the N1, C3, or C6 position at a late synthetic stage, thereby providing a highly efficient approach to explore the structure−activity relationships of pyrazolopyrimidine derivatives. The scope of these reactions has also been explored.

KEYWORDS: pyrazolopyrimidine, microwave-assisted reaction, divergent synthesis, tandem reaction, Suzuki−Miyaura reaction, S_NAr displacement

INTRODUCTION

Pyrazolopyrimidines are popular synthetic pharmacophores with numerous reported biological activities partially because of their structural similarity to purines.[1] Purine-containing small molecules (such as ATP and GTP) are widely distributed in nature, and can be recognized by various proteins such as kinases and GTPases.[2] Consequently, pyrazolopyrimidines have been exploited as ATP competitive inhibitors of kinases (EGFR,[3] Btk,[4] PI3K,[5] mTOR,[6] CDK2,[7] Src,[8] and others[9]), cAMP phosphodiesterase,[10] and DNA polymerase.[11] The substitution patterns of the pyrazolopyrimidines play a critical role in determining their activity and selectivity toward different proteins. For example, A-**420983** acts as an orally active selective Lck inhibitor (IC_{50} = 37 nM)[12] while the pyrazolopyrimidine derivative **5** is a highly potent inhibitor for Ack1 (IC_{50} = 2 nM)[13] (Scheme 1). Therefore, significant efforts have been made to develop efficient routes to synthesize pyrazolopyrimidine analogues.

Among various synthetic strategies in the literature, most approaches start from highly substituted pyrimidines or pyrazoles (Scheme 2).[14] The cyclization of pyrimidines with hydrazines provides pyrazolopyrimidines via the construction of the pyrazole ring. Alternatively, pyrazolopyrimidines can also be synthesized through the construction of the pyrimidine ring from substituted pyrazoles.

These approaches, however, are not suitable for accessing diversified analogues due to the lack of appropriate advanced substrates and difficulty in modifying substituents at later stages. This is especially true for substituents R^2 (Scheme 2) at the N1 position of pyrazolopyrimidines. In general, R^2 is introduced before the pyrazolopyrimidine core is formed. Introduction of R^2 after the formation of the pyrazolopyrimidine core requires the N1-alkylation of pyrazolopyrimidines with alkyl halides under basic conditions and usually leads to low yields and poor selectivity (between the N1 and N2 position).[15] Alternatively, the Mitsunobu reaction has been used to selectively introduce R^2 at the N1 position.[16] However, this reaction employs highly toxic diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and it is often difficult to completely remove the triphenylphosphine oxide byproduct through chromatography. Clearly, a better strategy to efficiently and selectively modify different positions of pyrazolopyrimidines is needed.

In our efforts to employ pyrazolopyrimidines as selective kinase inhibitors, a concise and divergent method has been developed to synthesize 1,3,6-trisubstituted pyrazolo[3,4-*d*]pyrimidines from

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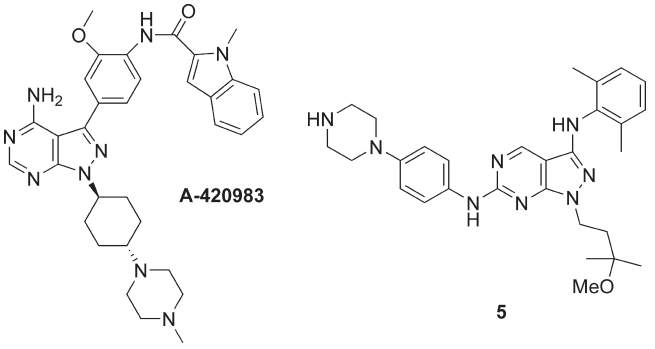
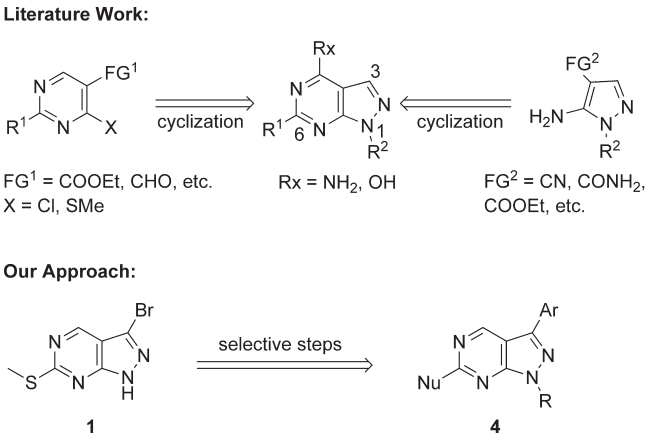
Scheme 1. Known Tyrosine Kinases Inhibitors



Scheme 2. Strategies for Synthesis of Pyrazolopyrimidine Derivatives

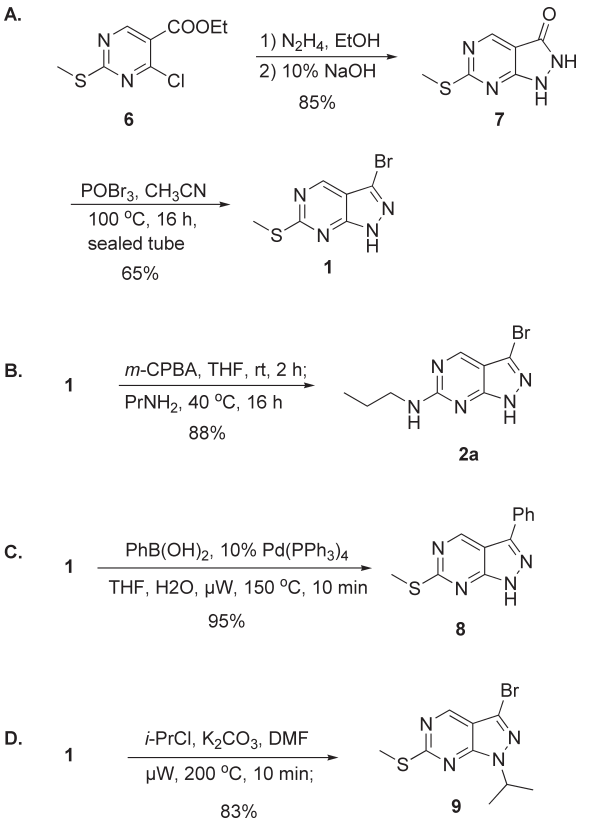


the key building block **1**. N1-Alkylation of **1** with alkyl chlorides in the presence of K_2CO_3 provided excellent yields and selectivity under microwave irradiation.[17] The resulting bromide can then be used to modify the C3 position through microwave-assisted Suzuki−Miyaura coupling while the C6 position can be substituted with different nucleophiles through a S_NAr displacement. More importantly, these three steps can be carried out in varying order, thereby making modification of the N1, C3, and C6 (Scheme 2) positions at late stages of analog synthesis possible. This is particularly critical for studying structure−activity relationships (SAR) for a given scaffold as hundreds of analogs may have to be synthesized.

RESULTS AND DISCUSSION

Synthesis and Transformation of Building Block 1. Preparation of the key building block **1** began with commercially available pyrimidine **6** (Scheme 3A). Following a known two-step protocol, pure pyrazolopyrimidinone **7** was obtained in 85% yield after crystallization.[18] Bromination of **7** with phosphoryl tribromide ($POBr_3$) in a sealed tube provided the key building block **1** in 65% yield. Best results were obtained when the mixture was sonicated for 20 min before the reaction because of the poor solubility of **6** in CH_3CN. We next demonstrated that each position (N1, C3, or C6) of **1** could be independently modified. For example, the methyl thiol (CH_3S) group at the C6 position

Scheme 3. Synthesis and Transformation of the Key Building Block 1



can be substituted with nucleophiles through an oxidation/S_NAr reaction sequence. Oxidation of **1** with 1.5 equivalent of *m*-CPBA at ambient temperature afforded a mixture of sulfone and sulfoxide without any N-oxidation of the heterocyclic core (Scheme 3B).[19] After the complete consumption of substrate **1**, the reaction mixture was added to a THF solution of propyl amine (5.0 equivalents) at 0 °C. The resulting reaction mixture was heated at 40 °C for 2 h to afford **2a** in 88% yield over two steps after concentration and trituration with methanol.[19]

The order of the steps could also be modified by beginning with the Suzuki−Miyaura reaction. For example, the reaction of **1** with $PhB(OH)_2$ proceeded well to provide compound **8** (Scheme 3C). Other boronic acids including 4-fluorophenylboronic acid and 4-methoxyphenylboronic acid also worked under the same reaction condition.

The N1-alkylation of **1** with isopropyl chloride was optimized by screening different bases (NaH, KO*t*-Bu, NaHMDS, NaOH, KOH, and K_2CO_3) and solvents (THF, DME, Dioxanes, DMF, and DMSO). Quantitative conversion and excellent selectivity (N1/N2 > 20:1 possibly because of the steric effect of the 3-bromo substitution) was obtained under microwave irradiation (200 °C, 10 min) when K_2CO_3 was used as the base and DMF or DMSO as the solvent (Scheme 3D).

Microwave-Assisted One-Pot N1-Alkylation/Suzuki−Miyaura Coupling Reaction. Furthermore, sequential reactions with **1** proceed in high yield. For example, the crude alkylation reaction mixture (Scheme 3D) can be used directly for a subsequent Suzuki−Miyaura coupling reaction to modify the C3 position. Thus, after the N1-alkylation of **1** (Scheme 4), the reaction mixture was cooled to ambient temperature and phenyl boronic

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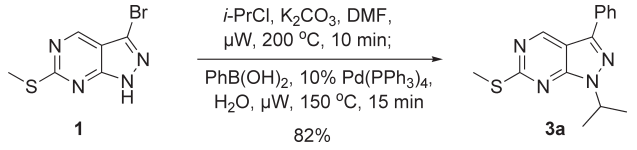
Scheme 4. One-Pot Reaction of N1-Alkylation/Suzuki−Miyaura Coupling of 1



acid (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), and H_2O (DMF/H_2O = 2:1) were added sequentially. After microwave irradiation at 150 °C for another 15 min, the desired Suzuki−Miyaura coupling product **3a** was obtained.

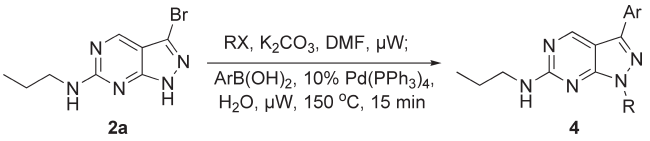
The scope of this new one-pot N1-alkylation/Suzuki−Miyaura coupling reaction was further explored with compound **2a** through solution-phase parallel synthesis using a microwave reactor with autosampler (Table 1).

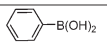
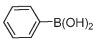
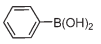
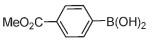
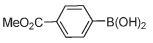
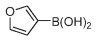
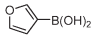
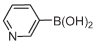
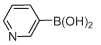
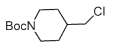
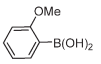
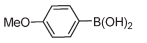
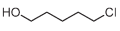
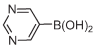
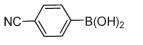
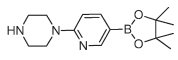
Chlorides were chosen as electrophiles mainly because of their commercial availability, low price, and better stability although alkyl bromides generally showed similar reactivity (Table 1, entry 1 vs entry 3). As expected, primary and benzyl chlorides were more reactive than secondary chlorides. While compound **2a** was converted to the corresponding N1-alkylation products by treatment with 1.5 equivalent of the primary or benzyl chlorides after microwave irradiation at 150 °C for 10 min (entries 10−14), secondary chlorides required higher stoichiometry (3.0 equiv), higher temperature (200 °C), and longer reaction time (10 to 30 min) (entries 1−9). The N1/N2 selectivity for all substrates was outstanding (>95%), and no N-alkylation at the nitrogen of the 6-alkylamino group was observed. A free secondary amine, 2-ethylpyrrolidine (entry 11), or free hydroxyl group (entry 12) was also compatible with these conditions. Interestingly, 4-picolyl chloride, which is prone to thermal polymerization, also gave quantitative N1-alkylation despite the elevated temperature (entry 14).

Water was required for the Suzuki−Miyaura coupling step. In the absence of water, the reaction progressed significantly slower (entries 2, 5, 7, 9), with lower yield (entries 5, 9), and increased reduction of aryl bromide **2a** was observed. It is possible that water participates in the decomposition of the excess alkyl halide from the previous alkylation step. Alkyl halides may affect the activity of palladium catalysts by oxidative addition and reductive elimination sequences. Electron donating (entry 10) and electron withdrawing (entry 13) groups on the aryl boronic acid had no effect on the reactivity of the boronic acid. A boronic acid pinacol ester also provided the desired product in high yield (entry 14). In addition, cyano, methyl ether, free hydroxyl, and free amino groups were tolerated under the Suzuki coupling condition (entries 10−14). A methyl ester was not compatible with the Suzuki−Miyaura conditions in the presence of water, resulting in the hydrolysis of the methyl ester. After irradiation at 150 °C for 30 min, the corresponding acid was obtained in 71% yield (entry 4). In the absence of water, the methyl ester product was obtained in 51% yield (entry 5).

In addition, this one-pot N1-alkylation/Suzuki−Miyaura coupling reaction (Scheme 4) was also successful under conventional heating conditions but with a longer reaction time (6 h for N1-alkylation and 2 h for Suzuki−Miyaura coupling). The selectivity of the N1-alkylation under both conventional heating conditions (93%) and microwave irradiation (97%) were comparable. The overall yields after purification were very similar as well (82% vs 80%). While microwave irradiation was much more efficient and suitable for analog synthesis, conventional thermal heating conditions were preferable for larger scale synthesis.

Table 1. One-Pot N1-Alkylation/Suzuki−Miyaura Coupling Reaction

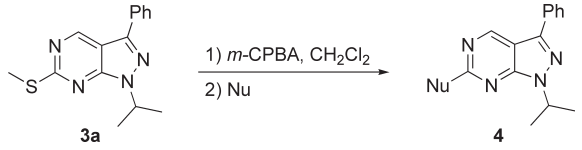


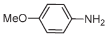
Entry	RX	$ArB(OH)_2$	Product	Yield (%)[f]
1			**4a**	67[a]
2			**4a**	65[a,b]
3			**4a**	60[a]
4			**4b**	71[a,c]
5			**4b'**	51[a,b]
6			**4c**	67[a]
7			**4c**	61[a,b]
8			**4d**	86[d]
9			**4d**	64[b,d]
10			**4e**	82[e]
11			**4f**	85[e]
12			**4g**	92[e]
13			**4h**	84[e]
14			**4i**	93[e]

[a] 3 equiv RCl, 200 °C, 30 min for N-alkylation. [b] Without H_2O for Suzuki coupling. [c] 30 min for Suzuki coupling; acid product obtained from hydrolysis of methyl ester. [d] 3 equiv RCl, 200 °C, 10 min for N-alkylation. [e] 1.5 equiv RCl, 150 °C, 10 min for N-alkylation. [f] The average of duplicate runs.

S_NAr Displacement of 3a by Nucleophiles (Nu). As demonstrated in Scheme 3B, the C6 position in **1** can be modified before the highly efficient one-pot N1-alkylation/Suzuki−Miyaura

Table 2. S_NAr Displacement of 3a by Nucleophiles (Nu)



Entry	Nu	Solvent	Temp (°C)	t(h)	Product	Yield (%)
1		THF	50	2	**4j**	77
2		THF	50	4	**4k**	82
3		THF	50	24	**4l**	86[a]
4		THF	50	12	**4m**	80
5		DMSO	150	12	**4n**	73
6		DMSO	150	12	**4o**	82
7		DMSO	150	12	**4p**	79
8		THF	0 to rt	2	**4q**	68[b]
9		THF	0 to rt	2	**4r**	71[b]
10		THF	0 to rt	2	**4s**	73[b]
11		THF	0 to rt	2	**4t**	78[b]
12	MeMgBr	THF	-78 to rt	2	**4u**	74
13	*i*-PrMgBr	THF	-78 to rt	2	**4v**	79
14	BnMgBr	THF	-78 to rt	2	**4w**	60
15	PhMgBr	THF	-78 to rt	2	**4x**	66

[a] 10 equiv *N*,*N*-diisopropylethylamine was added. [b] NaH was used as a base.

coupling reaction which diversifies substituents at the N1 and C3 position. The C6 position can also be efficiently diversified after the alkylation/Suzuki−Miyaura reaction sequence. After oxidation of the intermediate **3a** by *m*-CPBA, the resulting mixture of sulfone and sulfoxide was substituted by various nucleophiles to yield 1,3,6-trisubstituted pyrazolopyrimidines (Table 2).

Since *m*-CPBA oxidation provided a common intermediate for the following S_NAr displacement, this reaction was purified by washing with diluted NaOH aqueous solution. The crude mixture of sulfone and sulfoxide was used directly for the S_NAr reaction. Alkyl amines generally provided the desired product in high yields (entries 1−4). Dimethylamine hydrochloride functioned well in the presence of Hünig's base, although the reaction proceeded more slowly (entry 3). Less nucleophilic anilines required higher reaction temperature (150 °C) (entry 5−7).[20] Alkoxides and phenoxides were also suitable substrates (entry 8−11).[21] In addition, Grignard reagents provided competent carbon nucleophiles for the S_NAr displacement, with alkyl Grignard reagents (entries 12 and 13) providing better yields than benzyl (entry 14) and phenyl (entry 15) Grignard reagents.[22] These features further demonstrate the versatility of the methodology we developed in synthesizing diverse pyrazolopyrimidine derivatives.

CONCLUSION

In summary, we have developed an efficient route to obtain 1,3,6-trisubstituted pyrazolopyrimidines from the common intermediate **1**. Our strategy features a novel one-pot microwave-assisted N1-alkylation/Suzuki−Miyaura coupling sequence. Furthermore, the methyl thiol group at the C6 position can be replaced with nucleophiles before or after the tandem alkylation/Suzuki−Miyaura coupling reaction, thus making derivatizing N1, C3, or C6 at various stages of synthesis highly divergent and efficient. The reactions occur rapidly with high yields and have broad substrate scopes. The versatility of **1** can easily be applied to library synthesis. The features of this chemistry are highly desirable when large numbers of 1,3,6-trisubstituented pyrazolopyrimidine analogues are needed in high yields and purity for SAR development via biological evaluation.

EXPERIMENTAL PROCEDURES

General Experimental Details. Microwave reaction was carried out using a Discover-S reactor with a vertically focused IR external temperature sensor and an Explorer 72 autosampler. The dynamic mode was used to set up the desired temperature and hold time with the following fixed parameters: PreStirring, 1 min; Pressure, 200 psi; Power, 200 W; PowerMax, off; Stirring, high. Flash chromatography was carried out on prepacked silica gel disposable columns. Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254}, 0.25 mm precoated TLC plates. TLC plates were visualized using UV_{254} or phosphomolybdic acid with charring. All ^1H NMR spectra were obtained with a 400 MHz spectrometer and ^{13}C NMR spectra were obtained with a 100 MHz spectrometer. Preparative HPLC was performed with the UV detection at 220 or 254 nm. LC-MS was performed with the UV detection at 220 nm, 254 nm, and 280 nm, and a single quadrupole mass spectrometer using electrospray ionization (ESI) source. High-resolution (positive ion) mass spectra (HRMS) were acquired using a LCMS-TOF mass spectrometer.

3-Bromo-6-(methylthio)-1*H*-pyrazolo[3,4-*d*] pyrimidine (1). To a suspension of 6-(methylthio)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one **7** (2.0 g, 11 mmol) in CH_3CN (180 mL) in a pressure vessel was added a CH_3CN solution of $POBr_3$ (6.3 g, 22 mmol). The mixture was sonicated for 30 min before heating at 100 °C for 16 h. After cooling to 0 °C, H_2O and aqueous ammonium hydroxide were added. The aqueous layer was extracted with EtOAc (10×) and the layers were separated. The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by an ISCO silica gel column to afford the title compound **1** (1.75 g, 65%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 14.21 (bs, 1H), 8.98 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 155.0, 151.9, 120.5, 110.8, 13.8; HRMS (TOF, ESI+) *m*/*z*: $[M+H]^+$ calculated for $C_6H_6BrN_4S$, 244.9496; found 244.9499.

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3-Bromo-*N*-propyl-1*H*-pyrazolo[3,4-*d*] pyrimidin-6-amine (2a). To a mixture of 3-bromo-6-(methylthio)-1*H*-pyrazolo[3,4-*d*] pyrimidine **1** (0.49 g, 2.0 mmol) in THF (5.0 mL) was added *meta*-chloroperoxybenzoic acid (0.52 g, 99%, 3.0 mmol) at room temperature. The white mixture was stirred for 2.0 h and transferred into a THF (5.0 mL) solution of *n*-propylamine (0.82 mL, 10 mmol) at 0 °C. The resulting solution was heated at 40 °C for 2.0 h. After removal of the solvent under reduced pressure, MeOH was added and the mixture was filtered. The white solid was washed with MeOH (3×) and dried to provide the title compound **2a** (0.45 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (bs, 1H), 8.63 (s, 1H), 7.69 (bs, 1H), 3.29−3.17 (m, 2H), 1.54 (qt, J = 14.4, 7.2 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 157.0, 152.7, 120.1, 106.7, 42.7, 21.7, 11.5; HRMS (TOF, ESI+) m/z: $[M + H]^+$ calculated for $C_8H_{11}BrN_5$, 256.0198; found 256.0195.

1-Isopropyl-6-(methylthio)-3-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine (3a) (Procedure A). A 10 mL microwave tube was charged with **2a** (0.052 g, 0.20 mmol), K_2CO_3 (0.14 g, 1.0 mmol), DMF (2.0 mL), and isopropyl chloride (0.047 g, 0.60 mmol). The resulting mixture was heated at 200 °C for 10 min under microwave irradiation. After the reaction was cooled to room temperature, phenylboronic acid (0.037 g, 0.30 mmol), $Pd(PPh_3)_4$ (0.023 g, 0.020 mmol), and H_2O (1.0 mL) were added sequentially. The mixture was stirred at ambient temperature for 3.0 min and then heated at 150 °C for 15 min. After cooling to ambient temperature, the mixture was partitioned in H_2O and Et_2O. The aqueous phase was extracted with diethyl ether (3×). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by an ISCO silica gel column to provide the title compound **3a** (0.047 g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.42 (tt, J = 7.6, 2.0 Hz, 1H), 5.19 (septet, J = 6.7 Hz, 1H), 2.66 (s, 3H), 1.63 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 153.6, 152.2, 143.7, 132.5, 129.1, 129.0, 127.1, 109.8, 49.3, 22.0, 14.4; HRMS (TOF, ESI+) m/z: $[M + H]^+$ calcd 285.1174 for $C_{15}H_{17}N_4S$; found 285.1179.

1-Cyclohexyl-3-phenyl-*N*-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine (4a) (Procedure B). A 10 mL microwave tube was charged with **2a** (0.052 g, 0.20 mmol), K_2CO_3 (0.14 g, 1.0 mmol), DMF (2.0 mL), and cyclohexyl chloride (0.072 g, 0.60 mmol). The resulting mixture was heated at 200 °C for 30 min under microwave irradiation. After the reaction was cooled to room temperature, phenylboronic acid (0.037 g, 0.30 mmol), $Pd(PPh_3)_4$ (0.023 g, 0.020 mmol), and H_2O (1.0 mL) were added sequentially. The mixture was stirred at ambient temperature for 3.0 min and then heated at 150 °C for 15 min. After cooling to ambient temperature, the mixture was partitioned in H_2O and Et_2O. The aqueous phase was extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by an ISCO silica gel column to provide the title compound **4a** (0.045 g, 67%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 6.0 Hz, 2H), 7.38 (t, J = 6.0 Hz, 1H), 5.42 (bs, 1H), 4.60 (tt, J = 11.6, 4.1 Hz, 1H), 3.48 (dt, J = 13.1, 6.8 Hz, 2H), 2.13 (ddd, J = 24.6, 12.5, 3.4 Hz, 2H), 2.04−2.00 (m, 2H), 1.95−1.92 (m, 2H), 1.77−1.74 (m, 1H), 1.69 (qt, J = 14.6, 7.4 Hz, 2H), 1.50 (qt, J = 13.06, 3.12 Hz, 2H), 1.35 (tt, J = 12.8, 6.3 Hz, 1H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.4, 153.5, 143.7, 133.3, 129.1, 128.6, 127.1, 106.9, 56.1, 43.7, 32.2, 25.9, 25.6, 23.0, 11.8; HRMS (TOF, ESI+) m/z: $[M + H]^+$ calculated for $C_{20}H_{26}N_5$, 336.2188; found 336.2180.

***tert*-Butyl 4-((3-(2-methoxyphenyl)-6-(propylamino)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl) methyl) piperidine-1-carboxylate (4e) (Procedure C).** A 10 mL microwave tube was charged with **2a** (0.052 g, 0.20 mmol), K_2CO_3 (0.11 g, 0.80 mmol), DMF (2.0 mL), and *tert*-butyl 4-(chloromethyl)piperidine-1-carboxylate (0.070 g, 0.30 mmol). The resulting mixture was heated at 150 °C for 10 min under microwave irradiation. After the reaction was cooled to room temperature, 2-methoxyphenyl boronic acid (0.046 g, 0.30 mmol), $Pd(PPh_3)_4$ (0.023 g, 0.020 mmol), and H_2O (1.0 mL) were added sequentially. The mixture was stirred at ambient temperature for 3.0 min and then heated at 150 °C for 15 min. After cooling to ambient temperature, the mixture was partitioned in H_2O and Et_2O. The aqueous phase was extracted with ether (3×). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by an ISCO silica gel column to provide the title compound **4e** (0.079 g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.75 (dd, J = 7.6, 1.6 Hz, 1H), 7.41−7.34 (m, 1H), 7.08−6.99 (m, 2H), 5.55 (bs, 1H), 4.20 (d, J = 7.1 Hz, 2H), 4.14−3.99 (m, 2H), 3.87 (s, 3H), 3.48−3.40 (m, 2H), 2.68 (t, J = 11.9 Hz, 2H), 2.28−2.16 (m, 1H), 1.72−1.57 (m, 4H), 1.43 (s, 9H), 1.34−1.22 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 156.8, 156.1, 154.9, 153.8, 143.1, 130.6, 130.5, 121.8, 121.3, 111.4, 107.4, 79.5, 55.6, 51.5, 43.6, 36.7, 29.9, 28.6, 22.7, 11.7; HRMS (TOF, ESI+) m/z: $[M+H]^+$ calculated for $C_{26}H_{37}N_6O_3$, 481.2927; found 481.2936.

1-Isopropyl-3-phenyl-*N*-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine (4j) (Procedure D). To a 0.15 M THF stock solution of sulfone and sulfoxide (2.0 mL, 0.30 mmol) was added propylamine (0.12 mL, 1.5 mmol) at ambient temperature. The solution was then heated at 50 °C for 2.0 h. After evaporation of the solvent, the residue was purified by an ISCO silica gel column to provide the title compound **4j** (0.068 g, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.92 (d, J = 7.1 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 5.46 (s, 1H), 5.03 (septet, J = 6.7 Hz, 1H), 3.47 (dt, J = 13.2, 6.7 Hz, 2H), 1.69 (qt, J = 14.4, 7.3 Hz, 2H), 1.59 (d, J = 6.7 Hz, 6H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.3, 153.4, 143.7, 133.2, 129.0, 128.6, 127.0, 106.8, 48.5, 43.6, 22.9, 21.9, 11.7; HRMS (TOF, ESI+) m/z: $[M + H]^+$ calculated for $C_{17}H_{22}N_5$, 296.1875; found 296.1870.

1-Isopropyl-*N*,3-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-amine (4n) (Procedure E). To a 0.15 M DMSO stock solution of sulfone and sulfoxide (2.0 mL, 0.30 mmol) was added aniline (0.093 g, 1.0 mmol) at ambient temperature. The solution was then heated at 150 °C for 12 h. After cooling to ambient temperature, the reaction was diluted with CH_2Cl_2 and washed with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3×). The organic extracts were combined and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by an ISCO silica gel column to provide the title compound **4n** (0.048 g, 73%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 7.8 Hz, 2H), 7.51 (t, 2H), 7.46−7.34 (m, 4H), 7.08 (t, J = 7.4 Hz, 1H), 5.12 (septet, J = 6.7 Hz, 1H), 1.65 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 154.4, 153.7, 143.9, 139.7, 132.9, 129.1, 129.1, 128.8, 127.1, 122.7, 119.1, 108.0, 49.1, 22.0.

6-(3-Chloropropoxy)-1-isopropyl-3-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine (4q) (Procedure F). To a suspension of NaH (0.020 g, 60% in mineral oil, 0.50 mmol) in THF (2.0 mL) was added 3-chloro-1-propanol (0.057 g, 0.60 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature over 1.0 h.

After cooling to 0 °C, a 0.15 M THF stock solution of sulfone and sulfoxide (2.0 mL, 0.30 mmol) was added. The reaction was warmed to ambient temperature over 2.0 h and quenched by saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by an ISCO silica gel column to provide the title compound **4q** (0.045 g, 68%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.95 (dt, J = 5.2, 3.4 Hz, 2H), 7.51 (tt, J = 10.3, 4.7 Hz, 2H), 7.43 (tt, J = 7.4, 1.1 Hz, 1H), 5.14 (septet, J = 6.7 Hz, 1H), 4.63 (t, J = 6.0 Hz, 2H), 3.80 (t, J = 6.4 Hz, 2H), 2.34 (pent, J = 6.2 Hz, 2H), 1.62 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 154.9, 154.6, 143.9, 132.6, 129.2, 129.1, 127.1, 109.6, 64.6, 49.1, 41.7, 32.1, 22.0.

1-Isopropyl-6-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (4u) (Procedure G). To a 0.15 M THF stock solution of sulfone and sulfoxide (2.0 mL, 0.30 mmol) was slowly added Grignard reagent MeMgBr (0.10 mL, 3.0 M in diethyl ether, 0.30 mmol) at −78 °C. The resulting mixture was allowed to warm to ambient temperature over 2.0 h, at which time it was quenched with aqueous saturated NH_4Cl. The mixture was extracted with EtOAc (3×). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified with an ISCO silica gel column to provide the title compound **4u** (0.037 g, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.98 (dt, J = 7.1, 1.4 Hz, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.43 (tt, J = 7.3, 1.0 Hz, 1H), 5.26 (septet, J = 6.7 Hz, 1H), 2.84 (s, 3H), 1.62 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 153.6, 152.3, 143.4, 132.7, 129.2, 129.0, 127.2, 110.7, 48.8, 26.4, 22.2.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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J.L. and X.W. conceived and designed the experiments, J.L. performed the experiments, and J.L. and X.W. wrote the manuscript and Supporting Information.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper published May 10, 2011 with a reference citation error in the Results & Discussion section, as well as errors to author names in references 15 and 17. The correct version published June 3, 2011.