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Tunable Regioselective Synthesis of Pyrazolo[3,4-d]pyrimidine Derivatives via Aza-Wittig Cyclization and Dimroth-type rearrangement

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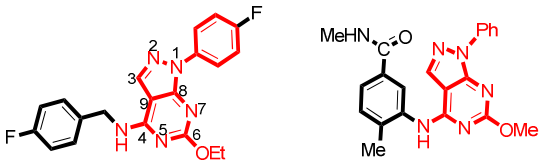
A novel tunable regioselective synthesis of pyrazolo[3,4-d]pyrimidine derivatives via aza-wittig/Ag(I) or base-promoted tandem reaction has been developed. This approach provides a simple and efficient way to construct Pyrazolo[3,4-d]-pyrimidine derivatives under mild condition.

Introduction

Pyrazolo[3,4-d]-pyrimidine and their partially saturated derivatives represent an important class of heterocycles, which are basic constituents in a myriad of natural products, biologically active alkaloids and pharmaceuticals.[1] In particular, functionalization at N-1 , C-4 and C-6 positions of these ring systems is extremely important from a drug discovery viewpoint, these key heterocyclic units have been found broad use in synthetic drugs, and drug candidates (Figure 1).[2] As a result, numerous synthetic methods have been developed for the construction and modification of the multisubstituted pyrazolo[3,4-d]-pyrimidine structure.[3] Although most of these methods suffer from low efficiency and selectivity, in addition, long reaction times , high temperatures and tedious workup procedure are often required in these reactions. Thus, the development of a straightforward and convenient route to multisubstituted pyrazolo[3,4-d]-pyrimidine derivatives under mild reaction conditions is highly attractive in synthetic methodology and pharmaceutical chemistry.

Recently, the aza-Wittig tandem reactions of iminophosphoranes have received much attention for the synthesis of substituted N-containing heterocycles.[4] Carbodiimides, which were efficiently formed in situ from aza-Wittig reaction of iminophosphoranes with isocyanates under mild neutral conditions, can be used directly as versatile synthetic intermediates. These active carbodiimides can be easily trapped by nucleophiles such as alcohols and amines to form carbamimidates and guanidines which react with ester or nitrile groups in an intramolecular manner to afford N-containing heterocycles. In past decades, a series of tandem processes had been designed based on this principle. Thus far, substituted diaminoimidazoles,[4a] dipyrimidinediones,[4d] isoquino-line,[4e] phen-anthridine,[4f] benzoxazole,[4f] oxadiazole,[4g] amino-oxindole[4h] and quinazolin[4i] had been prepared by using these tandem protocols. In addition, Dimroth-type rearrangement [5] is an important isomerization process which is assigned to the translocation of hetero atom on heterocycles such as purine, pyrimidine bases of nucleosides and nucleotides.[5d] In many cases, Dimroth rearrangement is reversible, so controlling variable reaction condition can remarkably improve the desired product. Here we report a protocol to synthesized two series pyrazolo[3,4-d]pyrimidine derivatives via aza-Wittig tandem process followed by controllable Dimroth-type rearrangement.

Figure 1. Examples of significant pyrazolo[3,4-d]-pyrimidines



HCV Entry Inhibitors p38α Inhibitors

Results and Discussion

Based on our continued interest on the aza-Wittig tandem protocol to construct heterocycles, we envisioned that the pyrazolo[3,4-d]-pyrimidine frameworks could also be obtained by above protocol. To our delight, the cyclization of carbodiimides

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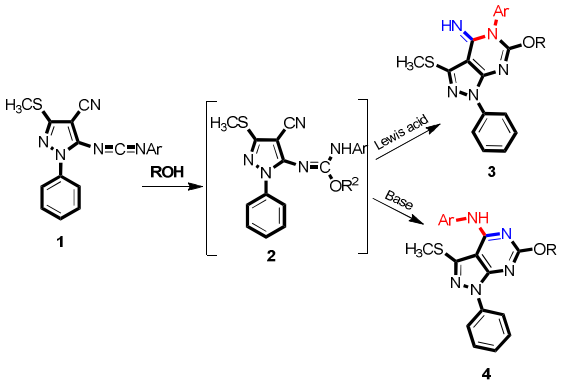
Electronic supplementary information (ESI) available: IR, ^{1}H and ^{13}C NMR of Compound 3 and 4 See DOI: 10.1039/x0xx00000x/

compounds **1** (generated from the reactions of iminophosphoranes **5** with isocyanates **6**, scheme 2) indeed proceed as we expected to afford pyrazolo[3,4-d] pyrimidine in the presence of alcohol and various Lewis acids, but not only that, simply changing Lewis acids to base in the reaction, a new product with the functionalization at N-1, C-4 and C-6 positions of pyrazolo[3,4-d]-pyrimidine structure was obtained in good selectivity (Scheme 2). This interesting tunable transformation to the pyrazolo[3,4-d]-pyrimidine heterocycles encouraged us to further examine the feasibility of this cyclization reaction.

Our initial efforts focused on the reaction of 5-((((4-chlorophenyl)imino)methylene)amino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-carbonitrile **1a** with various Lewis acids as the promoter. We found that in the presence of 10 mol% $AgNO_3$ in methanol at room temperature in one hour was the best reaction conditions for this cyclization reaction to afford the product **3a** (Table 1, entry 4). The reaction could also proceed in other Lewis acids, such as CuI, AgI, AgOAc, $Cu(NO_3)_2$ and $FeCl_3$, albeit in reduced yields (Table 1, entries 1–3 and 5–6). A lesser amount of $AgNO_3$ would reduce the reaction yield (Table 1, entries 7).

Scheme 1. Tunable regioselective synthesis of pyrazolo[3,4-d]pyrimidine derivatives

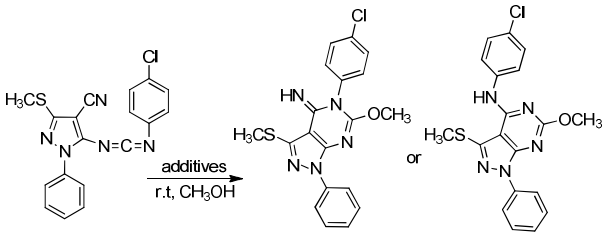


Scheme 2. Synthesis of 1

It also turned out to be ineffective to shorten the reaction time to half an hour (Table 1, entries 8). Interestingly, we observed that the product **4a** was formed with high selectivity when this reaction was carried out under alkaline reaction conditions. The reaction could proceed in either organic base or inorganic base. Generally, inorganic base offered better results than organic base (Table 1, entries 9–12). In the presence of 1.0 equiv. NaOH in methanol at room temperature was found to be the best reaction condition (Table 1, entries 13). A lesser amount of NaOH would reduce the reaction yield (Table 1, entries 16), but 2.0 equiv. of NaOH did not observably improve the yield (Table 1, entries 17). Albeit stronger base than NaOH, $NaOCH_3$ is not a better promoter, formation of water may be important to the transformation process (Table 1, entry 12). [5d] No improvement of the yield was found while further extending the reaction time (Table 1, entry 15). In addition, the employment with additional $AgNO_3$ did not improve the yield (Table 1, entry 18).

With the optimized conditions in hand, various carbodiimides compounds **1** were found to be the suitable reaction partners with methanol or ethanol to provide the corresponding products **3** or **4** in moderate to excellent yield (Table 2 and 3). This transformation showed good functional group tolerance when used the $AgNO_3$ as the catalyst to afford product **3**. Either electron-withdrawing and electron-donating substituted groups or halogen groups at the aromatic ring

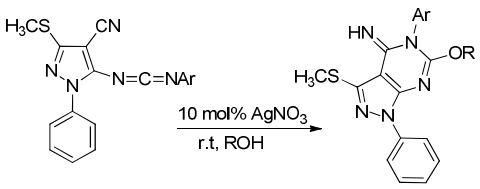
Table 1. Optimization of the reaction conditions.[a]



Entry	addtives	time (h)	Yield (%)[b]	
			3a	**4a**
1	0.1eq. CuI	1	58	-
2	0.1eq. AgI	1	51	-
3	0.1eq. AgOAc	1	56	-
4	**0.1eq. $AgNO_3$**	**1**	**73**	**-**
5	0.1eq.$Cu(NO_3)_2$	1	5	-
6	0.1eq.$FeCl_3$	1	trace	-
7	0.01eq. $AgNO_3$	1	11	-
8	0.1eq. $AgNO_3$	0.5	44	-
9	1.0 eq. Et_3N	21	-	14
10	1.0 eq. DABCO	21	-	trace
11	1.0 eq. Na_2CO_3	21	-	48
12	1.0 eq. CH_3ONa	21	-	43
13	**1.0 eq. NaOH**	**21**	**-**	**78**
14	1.0 eq. NaOH	12	-	59
15	1.0 eq. NaOH	48	-	70
16	0.1 eq. eq. NaOH	15	-	21
17	2.0 eq. NaOH	24	-	74
18[c]	1.0 eq. NaOH	21	-	72

[a] The reaction was carried out on the scale of mmol of **1a** in the presence of additives in 3 mL CH_3OH at 25 ºC. [b] isolated yield. [c] with additional 10 mol% $AgNO_3$.

Table 2. Substrate Scope [a]



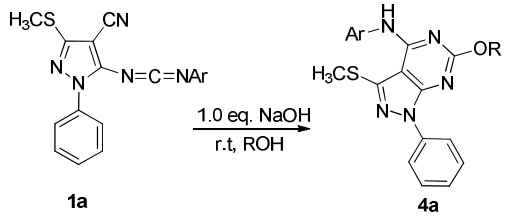
1 3

Product	Ar	R	yield[%] [b]
3a	p-Cl-Phenyl	CH_3	85
3b	p-F-Phenyl	CH_3	83
3c	Phenyl	CH_3	91
3d	p-CH_3-Phenyl	CH_3	64
3e	3,4-diCl-Phenyl	CH_3	66
3f	p-C_2H_5O-Phenyl	CH_3	98
3g	p-CH_3O-Phenyl	CH_3	90
3h	o-CH_3-Phenyl	CH_3	85
3i	m-CH_3-Phenyl	CH_3	73
3j	m-CH_3-Phenyl	CH_3CH_2	83
3k	o-CH_3-Phenyl	CH_3CH_2	94
3l	p-C_2H_5O-Phenyl	CH_3CH_2	89
3m	p-CH_3O-Phenyl	CH_3CH_2	74
3n	p-CH_3-Phenyl	CH_3CH_2	97

[a] The reactions were carried out with **1** (0.5 mmol), $AgNO_3$ (10 mol%), ROH (3mL), 25 °C, 1 h. [b] isolated yield.

could be introduced into the desired product under the standard reaction conditions without any difficulties (Table 2, **3a**–**3n**). It was worth noting that the steric effect had no significant effect to the yields, regardless of the substitution pattern of the aryl ring (ortho, meta, or para) of the aryl isocyanates used in the reaction, the corresponding products (**3d**, **3h** and **3i**) were obtained in good yields. The reaction between iminophosphoranes and variety of isocyanates to afford product **4** in the presence of NaOH were also carried out to explore the scope of this transformation (Table 3). In most cases, the corresponding product **4** could be obtained in moderate to excellent yields. The steric and electronic properties of the substituents on the phenyl rings had little effect on the yield (Table 3, **4a**–**3r**). Such as the methyl, methoxyl, ethoxyl，fluorine and chlorine at the aromatic ring of aryl isocyanates all reacted smoothly affording the desired products in good to excellent yields. In addition, the structures of compounds **3b** and **4j** were unambiguously assigned by X-ray crystallography analysis (Figure 2). [6]

Table 3. Substrate Scope [a]

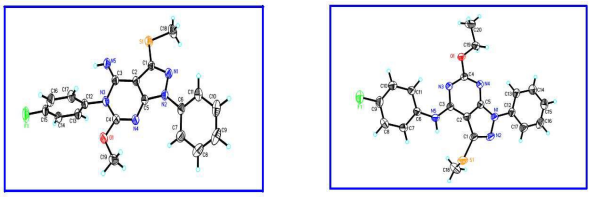


1a 4a

Product	Ar	R	yield[b]%
4a	p-Cl-Phenyl	CH_3	78
4b	p-F-Phenyl	CH_3	75
4c	Phenyl	CH_3	89
4d	p-CH_3-Phenyl	CH_3	60
4e	3,4-diCl-Phenyl	CH_3	57
4f	p-C_2H_5O-Phenyl	CH_3	56
4g	p-CH_3O-Phenyl	CH_3	56
4h	m-CH_3-Phenyl	CH_3	71
4i	o-CH_3-Phenyl	CH_3	64
4j	p-F-Phenyl	CH_3CH_2	59
4k	p-Cl-Phenyl	CH_3CH_2	78
4l	3,4-diCl-Phenyl	CH_3CH_2	81
4m	p-CH_3-Phenyl	CH_3CH_2	69
4n	o-CH_3-Phenyl	CH_3CH_2	65
4o	Phenyl	CH_3CH_2	65
4p	p-C_2H_5O-Phenyl	CH_3CH_2	85
4q	p-CH_3O-Phenyl	CH_3CH_2	51
4r	m-CH_3-Phenyl	CH_3CH_2	52

[a] The reactions were carried out with 1 (0.5 mmol), NaOH (1.0 eq.), ROH (3mL), 25 °C, 21h. [b] Isolated yield.

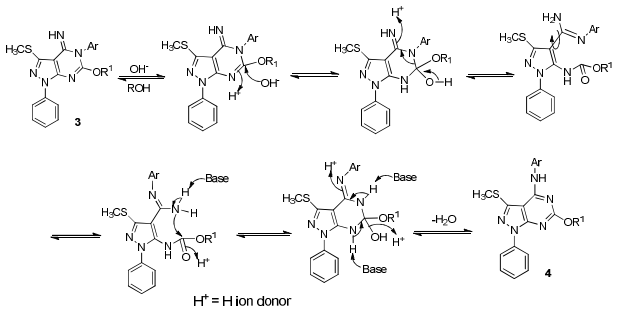
Figure 2. ORTEP diagram of 3b and 4j.



3b 4j

In order to understand the relationship between the two different products, the product **3a** was treated with 1 equiv. NaOH for 24 hours (Scheme 3), we found that the product **3a** could further equivalently converted to the product **4a.** Based on experiment and literature, [5] the proposed mechanism was outlined in scheme 3. The transformation process probably underwent a Dimroth-type rearrangement, and aromatized to thermodynamic stable compound **4a** in the presence of base and alcohol as solvent.[5d, 5e]

Scheme 3. Dimroth-type Rearrangement



Conclusions

In summary, we have developed an efficient tunable regioselective synthesis of pyrazolo[3,4-d]pyrimidine derivatives via aza-wittig/Ag(I) or base-promoted tandem reaction. The regioselectivity of this reaction can be easily controlled by using different reaction conditions. This methodology avoided the using of harsh reaction conditions and had been successfully used for the synthesis various different substituted pyrazolo[3,4-d] pyrimidine derivatives. Further mechanistic studies are still on going in our laboratory and will be reported in due course.

Experiments

General Experimental Methods:

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. FT-IR was recorded on Perkin Elmer-Spectrum One FTIR spectrometer; Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane (TMS) on the δ scale. ^{1}H NMR spectra, ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in chloroform-d[3]. All signals are reported in ppm with the internal TMS signal at 0 ppm as a standard. The data is being reported as (s = singlet, d = doublet, t = triplet, m =multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). High resolution mass spectrometry (HRMS) spectra were obtained on a micro-TOF II Instrument.

General procedure for compound 3 : To the solution of iminophos-phorane **1** (0.5 mmol) in dry CH_2Cl_2 (3 mL), ArNCO (0.6 mmol) was added under N_2. The mixture was stirred at 25 ^{o}C for 12-24h, then the solvent was removed under vacuum. The residue was dissolved into ROH (3 mL) and $AgNO_3$ (0.05 mmol, 10 mol%) was added and the solution was stirred at 25 ^{0}C for 0.5-1 h. After the solvent was removed, product **3** was obtained by flash chromatography (PE: EtOAc = 2:1).

5-(4-chlorophenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3a): white solid (yield 85%); mp：198-199 ^{o}C; IR (KBr, υ/ cm^{-1}): 3127, 2954, 1664, 1598, 1518, 1490, 1456, 1381, 1352, 1319, 1280, 1240, 1202, 838, 718; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.68 (s, 3H), 3.93 (s, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.45-7.51 (m, 4H), 8.08 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 56.1, 101.0, 121.0, 126.1, 128.9, 130.0, 130.2, 133.7, 135.0, 138.9, 145.0, 148.4, 153.9, 156.1. HRMS (ESI) calcd for $C_{19}H_{17}N_5OSCl$ $[M+H]^+$: 398.0842, found: 398.0846.

5-(4-fluorophenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3b): white solid (yield 83%); mp: 176-177 ^{o}C; IR (KBr, υ/ cm^{-1}): 3325, 3118, 2953, 1667, 1601, 1525, 1506, 1455, 1378, 1346, 1279, 1244, 1220, 1201, 829, 717; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.67 (s, 3H), 3.91 (s, 3H), 7.21 (d, *J* = 6.4 Hz, 4H), 7.28-7.29 (m, 1H), 7.46 (t, *J* = 8.0Hz,, 2H), 8.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 56.1, 101.0, 116.9 (d, *J* = 23 Hz), 120.9, 126.1, 128.9, 128.9, 130.6 (d, *J* = 9 Hz), 130.8 (d, *J* = 3 Hz), 138.9, 145.0, 148.5, 153.8, 156.2, 162.6 (d, *J* = 248 Hz). HRMS (ESI) calcd for $C_{19}H_{17}N_5OFS$ $[M+H]^+$: 382.1138, found: 382.1135.

6-methoxy-3-(methylthio)-1,5-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3c): white solid (yield 91%); mp: 204-205 ^{o}C; IR (KBr, υ/ cm^{-1}): 2956, 1668, 1598, 1523, 1496, 1423, 1350, 1282, 1240, 760; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.68 (s, 3H), 3.92 (s, 3H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.45-7.50 (m, 3H), 7.55 (t, *J* = 7.6 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 56.0, 101.1, 120.9, 126.0, 128.9, 128.9, 129.1, 129.9, 135.0, 139.0, 145.2, 148.7, 156.3. HRMS (ESI) calcd for $C_{19}H_{18}N_5OS$ $[M+H]^+$: 364.1232, found:364.1240

6-methoxy-3-(methylthio)-1-phenyl-5-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3d): white solid (yield 64%); mp: 190-191 ^{o}C; (KBr, υ/ cm^{-1}): 2924, 2853, 1712, 1671, 1508, 1344, 858, 765; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.43 (s, 3H), 2.67 (s, 3H), 3.92 (s, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 21.2, 55.9, 101.1, 120.9, 125.9, 128.5, 128.8, 130.5, 132.1, 139.1, 139.1, 145.2, 148.8, 153.4, 156.4. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1385

5-(3,4-dichlorophenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3e): white solid (yield 66%); mp: 202-203 ^{o}C; IR (KBr, υ/cm^{-1}): 2920, 1597, 1521, 1469, 1385, 1351, 1257, 1233, 860, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.68 (s, 3H), 3.94 (s, 3H), 7.12 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 56.3, 100.8, 121.0, 126.3, 128.4, 128.9, 131.0, 131.3, 133.4, 133.6, 134.8, 138.8, 144.9, 148.2, 154.2, 155.8. HRMS (ESI) calcd for $C_{19}H_{16}N_5OSCl_2$ $[M+H]^+$: 432.0453, found: 432.0448.

5-(4-ethoxyphenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3f): white solid (yield 98%); mp: 199-200 ^{o}C; IR (KBr, υ/ cm^{-1}): 3133, 1676, 1613, 1591, 1513, 1475, 1383, 1349, 1301, 1260, 862, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.38-1.46 (m, 3H), 2.67 (s, 3H), 3.91 (s, 3H), 4.05-4.10 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.6 Hz,1H), 7.46 (t, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 14.7, 56.0, 63.7, 101.1, 115.6, 120.9, 125.9, 126.8, 128.8, 129.8, 139.0, 145.2, 148.8, 153.4, 156.5, 159.3. HRMS (ESI) calcd for $C_{21}H_{22}N_5O_2S$ $[M+H]^+$: 408.1494, found: 408.1490.

6-methoxy-5-(4-methoxyphenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3g) : white solid (yield 92%); mp: 182-183 ^{o}C; IR (KBr, υ/ cm^{-1}): 1672, 1614, 1598, 1510, 1457, 1381, 1343, 1307, 1263, 1230, 1189, 824, 759; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.67 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 5.34 (br, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.25-7.30 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 55.5, 56.1, 101.0, 115.2, 120.8, 126.0, 127.0, 128.9, 129.9, 139.0, 145.2, 148.8, 153.5, 156.5, 159.9. HRMS (ESI) calcd for $C_{20}H_{20}N_5O_2S$ $[M+H]^+$: 394.1338, found: 394.1337.

6-methoxy-3-(methylthio)-1-phenyl-5-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3h): white solid (yield 85%); mp:154-155 ^{o}C; IR (KBr, υ/ cm^{-1}): 3131, 1667, 1519, 1420, 1345, 1261, 761; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.95 (s, 3H), 2.60 (s, 3H), 3.84 (s, 3H), 5.04 (br, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.07-7.21 (m, 1H), 7.26 (m, 3H), 7.29-7.40 (m, 2H), 8.03 (d, *J* = 8.0 Hz 2H,); ^{13}C NMR

(100 MHz, $CDCl_3$): 14.1, 17.2, 56.1, 100.9, 120.9, 126.1, 127.5, 128.9, 129.5, 131.4, 133.6, 136.4, 139.0, 145.3, 149.0, 152.4, 156.1. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1395.

6-methoxy-3-(methylthio)-1-phenyl-5-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3i): white solid (yield 73%); mp: 192-193 ^oC; IR (KBr, υ/ cm^{-1}): 2981, 2850, 1709, 1673, 1598, 1552, 1520, 1494, 1457, 1376, 1350, 1314, 1289, 1277, 821, 743; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.41 (s, 3H), 2.68 (s, 3H), 3.92 (s, 3H), 7.03 (d, *J* = 6.8 Hz, 2H), 7.28 (t, *J* = 9.2 Hz, 2H), 7.42-7.48 (m, 3H), 8.10 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 21.3, 56.0, 101.1, 120.9, 125.8, 126.0, 128.8, 129.3, 129.6, 130.0, 134.7, 139.0, 140.0, 145.2, 148.8, 153.3, 156.3. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1382.

6-ethoxy-3-(methylthio)-1-phenyl-5-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3j): white solid (yield 83%); mp: 148-149 ^oC; IR (KBr, υ/ cm^{-1}): 1559, 1552, 1516, 1404, 1378, 1335, 1258, 862, 753; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.22-1.25 (t, *J* = 7.2 Hz, 3H), 2.40 (s, 3H), 2.67 (s, 3H), 4.36-4.42 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 6.4 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 14.1, 21.3, 65.2, 101.0, 120.9, 125.8, 125.9, 128.8, 129.3, 129.6, 129.9, 134.7, 139.0, 139.9, 145.2, 149.0, 153.4, 155.7. HRMS (ESI) calcd for $C_{21}H_{22}N_5OS$ $[M+H]^+$: 392.1545, found: 392.1541.

6-ethoxy-3-(methylthio)-1-phenyl-5-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3k): white solid (yield 93%); mp: 120-121 ^oC; IR (KBr, υ/ cm^{-1}): 2959, 1668, 1520, 1495, 1429, 1397, 1381, 1328, 1278, 1241, 762, 741; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.12-1.17 (m, 3H), 2.05 (s, 3H), 2.59 (s, 3H), 4.23-4.37 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.22-7.31 (m,3H), 7.37 (t, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 14.1, 17.2, 65.1, 101.0, 120.9, 125.9, 127.4, 128.8, 129.3, 131.3, 133.9, 136.4, 139.1, 145.2, 149.2, 152.4, 155.5. HRMS (ESI) calcd for $C_{21}H_{22}N_5OS$ $[M+H]^+$: 392.1545, found: 392.1552.

6-ethoxy-5-(4-ethoxyphenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3l): white solid (yield 89%); mp: 200-201 ^oC; IR (KBr, υ/ cm^{-1}): 1664, 1507, 1475, 1402, 1378, 1331, 1300, 1250, 820, 763; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.21-1.25 (t, *J* = 7.2 Hz, 3H), 1.43-1.46 (t, *J* = 7.2 Hz, 3H), 2.67 (s, 3H), 4.05-4.10 (m, 2H), 4.36-4.41 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 8.4 Hz, 2H), 8.09 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 14.0, 14.7, 63.7, 65.1, 101.0, 115.5, 120.8, 125.9, 126.9, 128.8, 129.8, 139.1, 145.2, 149.0, 153.4, 155.9, 159.2. HRMS (ESI) calcd for $C_{22}H_{24}N_5O_2S$ $[M+H]^+$: 422.1651, found: 422.1647.

6-ethoxy-5-(4-methoxyphenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3m)： white solid (yield 74%); mp: 175-176 ^oC; IR (KBr, υ/ cm^{-1}): 1671, 1611, 1510, 1430, 1398, 1381, 1327, 1303, 1281, 1263, 864, 795; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.22-1.25 (t, *J* = 7.2 Hz, 3H), 2.67 (s, 3H), 3.86 (s, 3H), 4.36-4.41 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 7.6 Hz,1H), 7.45 (t, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 14.1, 55.4, 65.2, 101.0, 115.0, 120.8, 125.9, 127.2, 128.8, 129.8, 139.0, 145.2, 149.0, 153.5, 155.9, 159.7. HRMS (ESI) calcd for $C_{21}H_{22}N_5O_2S$ $[M+H]^+$: 408.1494, found: 408.1488.

6-ethoxy-3-(methylthio)-1-phenyl-5-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-imine(3n): white solid (yield 96%); mp: 204-205 ^oC; IR (KBr, υ/ cm^{-1}): 1672, 1508, 1472, 1396, 1381, 1324, 1278, 1238, 793, 761; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.22-1.25 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 2.67 (s, 3H), 4.38-4.40 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.27 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 14.1, 21.3, 65.1, 101.0, 120.9, 125.9, 128.5, 128.8, 130.5, 132.2, 139.0, 139.1, 145.1, 149.0, 153.4, 155.8. HRMS (ESI) calcd for $C_{21}H_{22}N_5OS$ $[M+H]^+$: 392.1545, found: 392.1538.

General procedure for compound 4: To the solution of iminophosphorane **1** (0.5 mmol) in dry CH_2Cl_2 (3 mL), ArNCO (0.6 mmol) was added under N_2. The mixture was stirred at 25 ^0C for 12-24 h, then the solvent was removed under vacuum. The residue was dissolved in ROH(4 mL) and NaOH (0.5 mmol, 1.0equiv) was added and the mixture was stirred at 25 ^0C for 21 h. After the solvent was removed, product **4** was obtained by flash chromatography (PE : EtOAc = 2:1).

N-(4-chlorophenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4a): white solid (yield 78%); mp 174-175 ^oC; IR (KBr, υ/ cm^{-1}): 3129, 2956, 2925, 1624, 1505, 1489, 1446, 1382, 1335, 1327, 1306, 1253, 828, 751; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.76 (s, 3H), 4.06 (s, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 8.0 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): 17.1, 55.1, 99.0, 120.5, 121.9, 126.0, 129.0, 129.0, 129.1, 136.5, 138.8, 139.5, 155.56, 156.0, 165.1. HRMS (ESI) calcd for $C_{19}H_{17}N_5OSCl$ $[M+H]^+$: 398.0842, found: 398.0838.

N-(4-fluorophenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4b)： white solid (yield 75%); mp 177-179 ^oC; IR (KBr, υ/ cm^{-1}): 3130, 1629, 1591, 1505, 1468, 1410, 1384, 1336, 1307, 1255, 830, 751; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.74 (s, 3H), 4.03 (s, 3H), 7.08 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.68-7.71 (m, 2H), 7.93 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.1, 55.0, 98.9, 115.7 (d, *J* = 22 Hz), 120.6, 122.8, 126.0, 128.5 (d, *J* = 13 Hz), 129.0, 132.1 (d, *J* = 10 Hz), 133.8, 138.9, 139.6, 155.8, 156.2, 159.4 (d, *J* = 243 Hz), 165.2. HRMS (ESI) calcd for $C_{19}H_{17}N_5OSF$ $[M+H]^+$: 382.1138, found: 382.1135.

6-methoxy-3-(methylthio)-N,1-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4c): white solid (yield 89%); mp: 140-141 ^oC; IR (KBr, υ/ cm^{-1}): 3005, 2925, 2852, 1626, 1595, 1498, 1479, 1447, 1397, 1378, 1326, 1259, 1235, 752; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.75 (s, 3H), 4.06 (s, 3H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.2 Hz，1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 8.05 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.1, 55.1, 99.0, 120.5, 120.7, 124.1, 125.9, 128.9, 129.0, 137.8, 138.5, 139.5, 155.7, 156.1, 165.2. HRMS (ESI) calcd for $C_{19}H_{18}N_5OS$ $[M+H]^+$: 364.1232, found: 364.1228.

6-methoxy-3-(methylthio)-1-phenyl-N-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4d)： white solid，(yield 60%); mp 169-170 ^oC; IR (KBr, υ/ cm^{-1}): 3130, 2957, 1626, 1570, 1504, 1473, 1441, 1385, 1337, 1326, 1309, 1254, 862, 753; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.35 (s, 3H), 2.74 (s, 3H), 4.05 (s, 3H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.27 (m, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.98 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.0, 20.8, 55.0, 99.0, 120.7, 121.0, 125.9, 128.9, 129.5, 133.9, 135.3, 139.0, 139.6, 155.9, 156.3, 165.3. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1395.

N-(3,4-dichlorophenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4e): white solid (yield 57%); mp 202-203 ^oC; IR (KBr, υ/ cm^{-1}): 3125, 2919, 2850, 1623, 1590, 1504, 1475, 1450, 1380, 1329, 1308, 1262, 1248, 804, 753; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.68 (s, 3H), 3.99 (s, 3H), 7.19 (t, *J* = 12 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.50-7.51 (m,

1H), 7.92 (t, J = 8.0 Hz, 2H), 8.1 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.2, 55.2, 99.1, 120.0, 120.0, 122.3, 126.2, 127.3, 129.0, 130.5, 132.7, 137.4, 138.8, 139.4, 155.4, 156.0, 165.1. HRMS (ESI) calcd for $C_{19}H_{16}N_5OSCl_2$ $[M+H]^+$: 432.0453, found:432.0459.

N-(4-ethoxyphenyl)-6-methoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4f): white solid (yield 56%); mp 149-150 °C; IR (KBr, υ/ cm^{-1}): 3124, 1628, 1598, 1579, 1505, 1468, 1454, 1380, 1340, 1329, 1307, 1248, 816, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.42 (t, J = 7.2 Hz, 3H), 2.74 (s, 3H), 4.02-4.06 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H),7.27-7.28(m, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 8.21 (d, J = 8.0 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): 14.8, 17.0, 54.9, 63.7, 98.9, 114.9, 120.6, 122.9, 125.9, 128.9, 130.7, 139.1, 139.7, 156.0, 156.0, 156.3, 165.4. HRMS (ESI) calcd for $C_{21}H_{22}N_5O_2S$ $[M+H]^+$: 408.1494, found:408.1491.

6-methoxy-N-(4-methoxyphenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4g)：

white solid (yield 56%); mp 165-166 °C; IR (KBr, υ/ cm^{-1}): 3129, 1617, 1595, 1506, 1480, 1451, 1378, 1242, 1324, 1302, 827; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.74 (s, 3H), 3.82 (s, 3H), 4.02 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 8.21 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.0, 54.9, 55.5, 98.9, 114.3, 120.6, 123.0, 125.9, 128.9, 130.8, 139.0, 139.7, 156.0, 156.3, 156.6, 165.4 HRMS (ESI) calcd for $C_{20}H_{20}N_5O_2S$ $[M+H]^+$: 394.1338 found: 394.1335.

6-methoxy-3-(methylthio)-1-phenyl-N-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4h): white solid (yield 71%); mp 126-127 °C; IR (KBr, υ/ cm^{-1}): 3129, 2956, 1631, 1570, 1507, 1492, 1480, 1455, 1380, 1337, 1306, 1254, 787, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.39 (s, 3H), 2.75 (s, 3H), 4.06 (s, 3H), 6.96 (d, J = 7.6 Hz, 1H), 7.25-7.30 (m, 2H), 7.45-7.51 (m, 3H), 7.64 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 8.21 (t, J = 7.6 Hz 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.1, 21.5, 55.0, 99.1, 118.1, 121.4, 125.0, 126.0, 126.8, 128.9, 137.9, 138.9, 139.0, 139.6, 155.8, 156.3, 165.3. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1396.

6-methoxy-3-(methylthio)-1-phenyl-N-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4i): white solid (yield 64%); mp 141-142 °C; IR (KBr, υ/ cm^{-1}): 1619, 1592, 1507, 1479, 1455, 1376, 1336, 1318, 1308, 1216, 757; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 2.43 (s, 3H), 2.76 (s, 3H), 4.02 (s, 3H), 7.10-7.12 (m, 1H), 7.24-7.29 (m, 3H), 7.48 (t, J = 8.0 Hz, 2H), 7.89 (s, 1H), 8.21-8.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.0, 18.3, 55.0, 99.3, 120.6, 122.9, 124.7, 126.0, 126.8, 128.8, 129.0, 130.6, 136.2, 139.0, 139.7, 156.1, 156.4, 165.3. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1393.

6-ethoxy-N-(4-fluorophenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4j)： white solid (yield 59 %); mp 157-158 °C; IR (KBr, υ/ cm^{-1}): 3129, 1625, 1591, 1575, 1503, 1475, 1445, 1417, 1381, 1357, 1307, 1256, 1209, 862, 748; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.44-1.48 (m, 3H), 2.75(s, 3H), 4.46-4.49 (m, 2H), 7.09 (t, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.68-7.71 (m, 2H), 7.94 (s, 1H), 8.20 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 17.1, 63.7, 98.9, 115.7 (d, J = 22 Hz), 120.6, 122.8 (d, J = 8 Hz), 126.0, 128.9, 133.9, 139.0, 139.5, 155.8, 156.3, 159.6 (d, J = 242 Hz), 164.8. HRMS (ESI) calcd for $C_{20}H_{19}N_5FOS$ $[M+H]^+$: 396.1294, found: 396.1288.

N-(4-chlorophenyl)-6-ethoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4k)： white solid (yield 78%); mp 169-170 °C; IR (KBr, υ/ cm^{-1}): 3132, 1624, 1602, 1503, 1490, 1475, 1456, 1444, 1414, 1381, 1357, 1311, 1290, 1255, 1240, 843, 747; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.47 (t, J = 8.0 Hz, 3H), 2.75(s, 3H), 4.47-4.50 (m, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 8.0 Hz, 2H), 7.71 (d, J =8.0 Hz, 2H), 7.99 (s, 1H), 8.19 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 16.1, 62.8, 97.9, 119.5, 120.9, 124.9, 127.9, 127.9, 128.0, 135.5, 137.8, 138.4, 154.5, 155.1, 163.6. HRMS (ESI) calcd for $C_{20}H_{19}N_5OSCl$ $[M+H]^+$: 412.0999, found: 412.1005.

N-(3,4-dichlorophenyl)-6-ethoxy-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4l): white solid (yield 81%); mp: 157-158 °C; IR (KBr, υ/ cm^{-1}): 3127, 2957, 2917, 2849, 1633, 1599, 1504, 1473, 1453, 1416, 1382, 1325, 1310, 1260, 862, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.49 (t, J =8.0, 3H), 2.75 (s, 3H), 4.48-4.50 (m, 2H), 7.28 (d, J = 8.0 Hz, 1H), 7.41-7.49 (m, 3H), 7.57 (dd, J = 2.0, 8.0 Hz, 1H), 7.99 (s, 1H), 8.03 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 8.0Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 17.2, 64.0, 99.0, 119.8, 120.6, 122.2, 126.1, 127.1, 129.0, 130.5, 132.7, 137.2, 138.8, 139.4, 155.3, 156.2, 164.6. HRMS (ESI) calcd for $C_{20}H_{18}N_5OSCl_2$ $[M+H]^+$: 446.0609, found: 446.0616.

6-ethoxy-3-(methylthio)-1-phenyl-N-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4m)： white solid (yield 69%); mp 141-142 °C; IR (KBr, υ/ cm^{-1}): 3130, 2976, 1623, 1599, 1503, 1473, 1453, 1375, 1361, 1332, 1325, 1305, 1291, 1249, 820, 765; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.46 (t, J =8.0, 3H), 2.34 (s, 3H), 2.73 (s, 3H), 4.45-4.50 (m, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.27 (m, 1H), 7.47 (t, J =8.0 Hz, 2H), 7.62 (d, J =8.0 Hz, 2H), 7.96 (s, 1H), 8.20 (d, J = 8.0Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 16.1, 19.8, 62.7, 97.9, 119.6, 119.8, 124.8, 127.9, 128.4, 132.8, 134.2, 137.9, 138.5, 154.7, 155.2, 163.8. HRMS (ESI) calcd for $C_{21}H_{22}N_5OS$ $[M+H]^+$: 392.1545, found: 392.1539.

6-ethoxy-3-(methylthio)-1-phenyl-N-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4n): white solid (yield 65%); mp 134-135 °C; IR (KBr, υ/ cm^{-1}): 2928, 1619, 1574, 1505, 1478, 1441, 1379, 1357, 1308, 1259, 1235, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.44 (t, J =7.2, 3H), 2.43 (s, 3H), 2.75 (s, 3H), 4.43-4.49 (m, 2H), 7.09 (t, J = 7.2 Hz, 1H), 7.24-7.30 (m, 3H), 7.47 (t, J = 8.4 Hz, 2H), 7.88 (s, 1H), 8.21 (t, J = 8.0 Hz, 2H), 8.26 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 17.1, 18.3, 63.7, 99.3, 120.7, 122.9, 124.7, 125.9, 126.7, 128.8, 129.0, 130.6, 136.2, 139.0, 139.7, 156.1, 156.5, 164.9. HRMS (ESI) calcd for $C_{21}H_{22}N_5OS$ $[M+H]^+$: 392.1545, found: 392.1552.

6-ethoxy-3-(methylthio)-N,1-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4o): white solid (yield 65%); mp 147-148 °C; IR (KBr, υ/ cm^{-1}): 3131, 1638, 1618. 1573, 1496, 1477, 1455, 1437, 1412, 1381, 1358, 13210, 1257, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.48 (t, J =8.0, 3H), 2.75 (s, 3H), 4.49-4.53 (m, 2H), 7.15 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H), 7.48 (t, J =8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 8.06 (s, 1H), 8.21 (d, J = 8.0Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.4, 16.1, 62.7, 97.9, 119.6, 119.7, 123.0, 124.8, 127.9, 128.0, 136.9, 137.9, 138.5, 154.6, 155.2, 163.7. HRMS (ESI) calcd for $C_{20}H_{20}N_5OS$ $[M+H]^+$: 378.1389, found: 378.1382.

6-ethoxy-N-(4-ethoxyphenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4p)： white solid (yield 85%); mp 120-121 °C; IR (KBr, υ/ cm^{-1}): 3131, 2958, 1629, 1571, 1504, 1476, 1418, 1384, 1359, 1327, 1305, 1257, 1243, 817, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.40-1.46 (m, 6H), 2.73(s, 3H), 4.04-4.05 (m, 2H), 4.46-4.48 (m, 2H), 6.93 (t, J = 6.8 Hz, 2H), 7.27 (d, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.60 (d, J =8.8 Hz, 2H), 7.98 (s, 1H), 8.19 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.5, 13.8, 16.0, 62.6, 62.8, 97.9, 113.9, 119.7, 121.9, 124.9, 127.9, 129.8, 138.1, 138.6, 154.9, 155.0, 155.4, 163.9. HRMS (ESI) calcd for $C_{22}H_{24}N_5O_2S$ $[M+H]^+$: 422.1651, found: 422.1644.

6-ethoxy-N-(4-methoxyphenyl)-3-(methylthio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4q) : white solid (yield 51%); mp 133-134 ^{o}C; IR (KBr, υ/ cm^{-1}): 3132, 2931, 1622, 1506, 1446, 1382, 1356, 1327, 1314, 1260, 1246, 818, 755; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.44 (t, *J* =6.8, 3H), 2.74 (s, 3H), 3.82 (s, 3H), 4.45-4.49 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.88 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.7, 15.2, 53.7, 61.8, 97.1, 112.5, 114.4, 118.9, 121.2, 124.1, 127.1, 129.1, 137.3, 137.8, 154.2, 154.8, 163.1. HRMS (ESI) calcd for $C_{21}H_{22}N_5O_2S$ $[M+H]^+$: 408.1494, found: 408.1487.

6-ethoxy-3-(methylthio)-1-phenyl-N-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine(4r): white solid (yield 52%); mp 126-127 ^{o}C; IR (KBr, υ/ cm^{-1}): 2958, 2927, 2873, 1629, 1589, 1569, 1503, 1382, 1337, 1306, 1254, 789, 751 ; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.63 (t, *J* =6.4, 3H), 2.32 (s, 3H), 2.67 (s, 3H), 4.41-4.43 (m, 2H), 6.89 (d, *J* = 6.8 Hz, 1H),7.20 (t, *J* = 7.2 Hz, 2H), 7.38-7.44 (m, 3H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.95 (br, 1H), 8.12 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 17.2, 21.5, 63.8, 99.0, 118.0, 120.7, 121.4, 125.0, 126.0, 128.9, 129.0, 137.9, 138.9, 139.0, 139.6, 155.7, 156.3, 164.8. HRMS (ESI) calcd for $C_{21}H_{22}N_5OS$ $[M+H]^+$: 392.1545, found: 392.1552.

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Notes and References

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[6] **CCDC** 850784 (**3b**) and 850785 (**4j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk]

Tunable Regioselective Synthesis of Pyrazolo[3,4-d]pyrimidine Derivatives via Aza-Wittig Cyclization and Dimroth-type rearrangement

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A novel tunable regioselective synthesis of pyrazolo[3,4-d]pyrimidine derivatives via aza-wittig/Ag(I) or base-promoted tandem reaction has been developed. This approach provides a simple and efficient way to construct Pyrazolo[3,4-d]-pyrimidine derivatives under mild condition.