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Synthesis of polysubstituted 5-aminopyrimidines from α-azidovinyl ketones and amidines

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ABSTRACT

A simple and direct synthesis of polysubstituted 5-aminopyrimidines from α-azidovinyl ketones and amidines in the present of base was developed. The reactions were performed under mild conditions in good to excellent yields. Additionally a possible mechanism of 1,4-Michael addition is proposed.

1. Introduction

Pyrimidines represent an important class of heterocycles[1] and their structural framework is a key constituent of numerous natural biologically active compounds.[2] These compounds have been shown to possess antitumor,[3] anti-inflammatory,[4] anti-viral,[5] antiproliferative activities,[6] as well as the potential to inactivate human DNA repair.[7] Furthermore, several pyrimidines are used in polymer and supramolecular chemistry.[8,9] 5-Aminopyrimidine derivatives, in particular, exhibit various important pharmacological activities, such as anti-anoxic and anti-lipid peroxidation activities to ameliorate brain ischemic damage.[10] In addition, the 5-aminopyrimidine substructures are useful for treating a disorder, disease or a condition of a subject, which is responsive to activation of K_v7 channels.[11]

Polysubstituted pyrimidines have been synthesized using various procedures based on classical condensation reactions between C–C–C and N–C–N[12] or cross-coupling reactions.[13] It is worthwhile to note that the direct syntheses of 5-aminopyrimidines are rare in literature. The most common method for the preparation of 5-aminopyrimidines employs the reduction from 5-nitropyrimidines with multiple steps.[14,15] In this regard, the development of synthetic methods, which enable a facile access to polysubstituted 5-aminopyrimidines is desirable.

Recently, by exploiting vinyl azides including α-azidovinyl ketones, novel synthetic approaches toward nitrogen-containing heterocycles have emerged from the literature.[16–18] Our attention was drawn to the potential chemical reactivity of α-azidovinyl ketones as a three-atom unit including one nitrogen to synthesize heterocycles.[17] Our previous work have developed a domino approach to synthesize pyrrolo[1,2-α]pyrazine from vinyl azides and 2-pyrrolecarbaldehyde.[19] Herein, we report a simple, straightforward and efficient methodology to prepare structurally diverse 5-aminopyrimidines from α-azidovinyl ketones and amidines.

2. Results and discussion

First, the coupling of (*Z*)-2-azido-3-(4-bromophenyl)-1-(4-chlorophenyl) prop-2-en-1-one with formamidine acetate was selected as the model reaction to optimize the reaction conditions (Table 1). Initially we found out that the use of a 1:1 ratio of formamidine acetate to base at 25 °C in DMF gave a very low conversion to the desired product. But when the ratio was 1:2, the conversion was much higher. As shown in Table 1, six bases were tested (entries **1**–**6**), and Cs_2CO_3 was first used as base source (entry 1). Increase of the basicity only led to trace amount of the target product (entry 4). When Na_2CO_3 or Et_3N was employed, decreased yields of 50% and 35% were obtained, respectively (entries 5 and 6). However, we were pleased to find that K_2CO_3 was the most effective base with a highly improved chemical yield of 96% (entry 2). The effect of solvents was also investigated (Table 1, entries **7**–**11**). The employment of polar solvents, such as EtOH,

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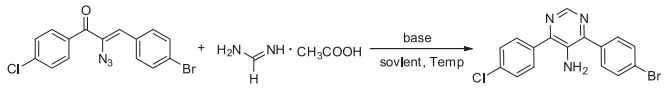
Table 1
Optimization of reaction conditions[a]



Entry	Base	Solvent	T (°C)	Yield[b] (%)
1	Cs_2CO_3	DMF	25	67
2	**K_2CO_3**	**DMF**	**25**	**96**
3	DBU	DMF	25	75
4	*t*-BuOK	DMF	25	Trace
5	Na_2CO_3	DMF	25	50
6	Et_3N	DMF	25	35
7	K_2CO_3	DCM	25	Trace
8	K_2CO_3	EtOH	25	36
9	K_2CO_3	Dioxane	25	43
10	K_2CO_3	CH_3CN	25	55
11	K_2CO_3	Toluene	25	n.r.
12	K_2CO_3	DMF	40	80

[a] Reaction conditions: α-azidovinyl ketone(0.2 mmol), formamidine acetate (0.24 mmol), base(0.48 mmol), 2 mL solvent under N_2 atmosphere, 24 h, rt.
[b] Isolated yield. The most successful entry is highlighted in bold.

dioxane, and CH_3CN (entries 8, 9, and 10) led to dramatically decreased yields. Only trace of the desired product was observed when DCM was used (entry 7). Meanwhile, there was no reaction when the nonpolar solvent toluene was utilized (entry 11). The reaction was also accessed at a higher temperature (Table 1, entry 12), and it gave a reduced yield, probably due to the instability of α-azidovinyl ketones in the reaction conditions. Therefore, the optimal reactivity was obtained in DMF at 25 °C when K_2CO_3 was employed (96%, Table 1, entry **2**).

Based on the optimized reaction conditions, we next examined the reaction for a range of α-azidovinyl ketones with amidines. The α-azidovinyl ketones were readily prepared according to reports by Knittel,[20] Gilchrist,[21] and Patonay.[22]

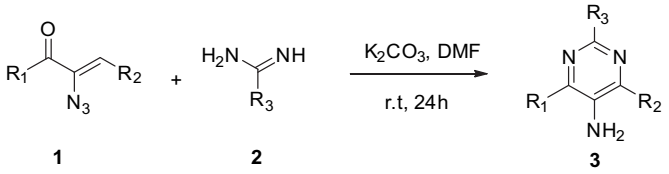
As shown in Table 2, analog compounds were synthesized when R_3 was either hydrogen or methyl, and the desired final product was achieved with relatively similar yields (for example, **3a** and **3b**, **3g** and **3h**). However, when R_3 was phenyl group, the final yields were generally lower than the other analogs (**3c** and **3a**, **3b**). R_1 with electrophilic groups on the aromatic ring were converted into the corresponding products with good efficiency (**3h** and **3d**). When R_1 was 4-methoxyphenyl group, the reactions were relatively sluggish, requiring a higher temperature (Table 2, entries 16–18). When R_2 was 4-methoxyphenyl group, the reactions (Table 2, entries 10–13) were not so compatible, probably due to their low activities. Higher yields were also achieved when the R_2 functionality was an aromatic ring containing an electron-withdrawing group (**3g** and **3j**, **3m** and **3o**, **3p**, **3q**, and **3r**). Especially, heteroaryl motifs such as thiophene (**3m**, **3n**, **3o**) were successfully incorporated. These results indicated that the nucleophilicity of the C-1 and C-3 of α-azidovinyl ketones played an important role in the entire process.

A possible reaction mechanism for the reaction process is proposed in Scheme 1. Our strategy relies on intermolecular Michael addition of amidine **2** to the α-azidovinyl ketone **1** in the presence of base. Consecutive elimination of dinitrogen of the active intermediate **I** affords **II**, followed by subsequent intramolecular nucleophilic attack to the carbonyl group. Dehydration of cyclized intermediate **III** and further rearrangement of **IV** provide the desired product **3**.

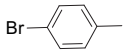
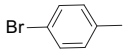
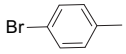
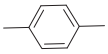
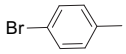
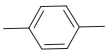
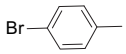
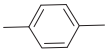
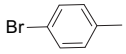
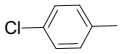
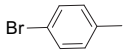
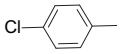
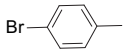
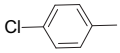
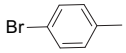
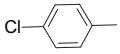
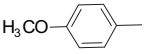
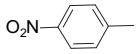
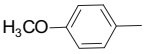
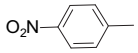
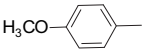
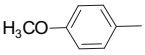
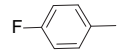
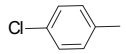
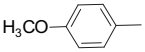
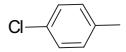
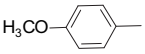
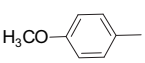
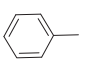
3. Conclusion

In conclusion, we have developed a simple, direct, and efficient method for the synthesis of polysubstituted 5-aminopyrimidines from readily available α-azidovinyl ketones and amidines in mild

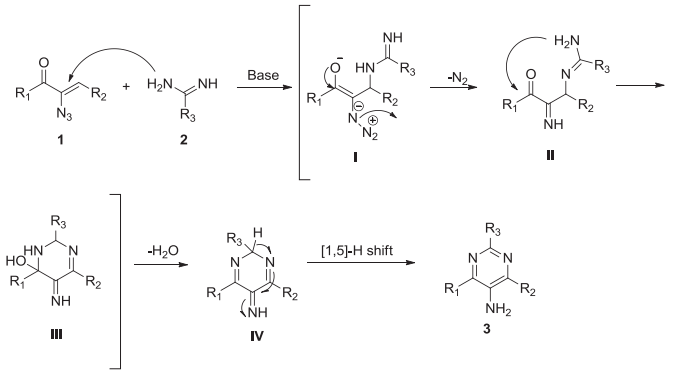
Table 2
Reactions of various α-azidovinyl ketones with amidines[a]



1 **2** **3**

Entry	R_1	R_2	R_3	Product **3**	Yield[b] (%)
1			H	**3a**	95
2			CH_3	**3b**	96
3[c]			Ph	**3c**	77
4			H	**3d**	74
5			CH_3	**3e**	81
6[c]			Ph	**3f**	73
7			H	**3g**	96
8			CH_3	**3h**	96
9[c]			Ph	**3i**	81
10			H	**3j**	70
11			CH_3	**3k**	77
12			Ph	**3l**	66
13			H	**3m**	56
14			CH_3	**3n**	82
15			H	**3o**	76
16[d]			H	**3p**	75
17[d]			H	**3q**	70
18[d]			H	**3r**	59

[a] Reactions were performed in anhydrous DMF with 1.2 equiv of amidine (**2**) and 2.4 equiv of K_2CO_3 under N_2 atmosphere at rt for 24 h unless mentioned otherwise.
[b] Isolated yield.
[c] The reaction was performed with 2 equiv of amidine (**2**) and 4 equiv of K_2CO_3.
[d] The reaction was performed at 50 °C for 24 h.



Scheme 1. Proposed mechanism of 5-aminopyrimidines formation.

conditions to obtain the corresponding products in good yields. The reaction may be realized by 1,4-Michael addition and subsequent rearrangement. Furthermore, it satisfies the green-chemistry features as only a molecule of nitrogen and water is lost in the whole process.

4. Experimental section

4.1. General

All solvents were purified according to standard methods prior to use. Reactions were under an atmosphere of nitrogen unless mentioned otherwise. Purification of reaction products were carried out by chromatography using silica gel (200–300 mesh). Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), and coupling constant(s) in hertz. For ^{13}C NMR, TMS (δ=0) or $CDCl_3$ (δ=77.26) was used as internal standard and spectra were obtained with complete proton decoupling. LC–MS and HRMS data was obtained using ESI ionization. The starting materials **1a**–**r** were prepared according to literature methods.

4.2. General procedure for the synthesis of polysubstituted 5-aminopyrimidines

A mixture of α-azidovinyl ketone **1** (1.0 mmol), amidine acid **2** (1.2 mmol), and K_2CO_3 (2.4 mmol) was stirred in anhydrous DMF (4 mL) at rt under nitrogen overnight. The reaction mixture was quenched with water (10 mL), and then extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by chromatography (silica gel, eluent PE/EA) to afford **3**.

*4.2.1. 4-(4-Bromophenyl)-6-phenylpyrimidin-5-amine (**3a**).* Pale yellow solid (309 mg, 95%); mp: 142.0–144.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (s, 2H), 7.47 (t, *J*=7.0, 7.5 Hz, 1H), 7.52 (t, *J*=7.0, 8.0 Hz, 2H), 7.64 (d, *J*=8.5 Hz, 2H), 7.70 (d, *J*=8.5 Hz, 2H), 7.76 (d, *J*=7.5 Hz, 2H), 8.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.88, 128.40, 129.08, 129.67, 130.15, 132.22, 135.38, 135.43, 136.31, 149.29, 150.09, 151.91; LC–MS (ESI): *m*/*z* $[M+H]^+$: 326.2; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{12}N_3Br$ $(M)^+$: 325.0215. Found: 325.0219.

*4.2.2. 4-(4-Bromophenyl)-2-methyl-6-phenylpyrimidin-5-amine (**3b**).* Pale yellow solid (326 mg, 96%); mp: 127.5–128.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (S, 3H), 3.85 (s, 2H), 7.46 (t, *J*=7.0, 7.5 Hz, 1H), 7.51 (t, *J*=7.0, 8.0 Hz, 2H), 7.64 (d, *J*=8.5 Hz, 2H), 7.68 (d, *J*=8.5 Hz, 2H), 7.74 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.16, 123.67, 128.46, 129.07, 129.47, 130.24, 132.19, 132.60, 135.73, 136.60, 150.55, 152.43, 157.99; LC–MS (ESI): *m*/*z* [M+H]+: 340.2; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_3Br$ (M)+: 339.0371. Found: 339.0371.

*4.2.3. 4-(4-Bromophenyl)-6-(p-tolyl)pyrimidin-5-amine (**3d**).* Pale yellow solid (251 mg, 74%); mp: 195.0–197.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3H), 4.05 (s, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.63–7.70 (m, 6H), 8.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.43, 123.85, 128.32, 129.74, 130.18, 132.20, 133.34, 135.37, 135.46, 149.26, 152.08; LC–MS (ESI): *m*/*z* $[M+H]^+$: 340.2; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_3Br$ $(M)^+$: 339.0371. Found: 339.0368.

*4.2.4. 4-(4-Bromophenyl)-2-methyl-6-(p-tolyl)pyrimidin-5-amine (**3e**).* Pale yellow solid (286 mg, 81%); mp: 188.0–190.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (S, 3H), 2.68 (s, 3H), 3.85 (s, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 7.62–7.68 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.64, 25.36, 123.84, 128.61, 129.94, 130.50, 132.38, 132.84, 133.89, 136.02, 139.79, 150.59, 152.81, 158.16; LC–MS (ESI): *m*/*z* $[M+H]^+$: 354.3; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}N_3Br$ $(M)^+$: 353.0528. Found: 353.0536.

*4.2.5. 4-(4-Bromophenyl)-6-(4-chlorophenyl)pyrimidin-5-amine (**3g**).* Pale yellow solid (346 mg, 96%); mp: 203.0–205.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (s, 2H), 7.50 (d, *J*=8.5 Hz, 2H), 7.65–7.70 (m, *J*=8.5, 8.5 Hz, 4H), 7.75 (d, *J*=8.5 Hz, 2H), 8.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.09, 129.33, 129.90, 130.14, 132.30, 134.67, 135.15, 135.33, 135.80, 149.35, 150.56, 150.59; LC–MS (ESI): *m*/*z* $[M+H]^+$: 360.1; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{11}N_3ClBr$ $(M)^+$: 358.9825. Found: 358.9820.

*4.2.6. 4-(4-Bromophenyl)-6-(4-chlorophenyl)-2-methylpyrimidin-5-amine (**3h**).* Pale yellow solid (359 mg, 96%); mp: 188.5–191.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (s, 3H), 3.83 (s, 3H), 7.49 (d, *J*=8.5 Hz, 2H), 7.63–7.67 (m, *J*=8.5, 8.5 Hz, 4H), 7.73 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.10, 123.83, 129.28, 129.97, 130.22, 132.24, 132.57, 135.00, 135.49, 135.56, 151.00, 151.23, 158.13; LC–MS (ESI): *m*/*z* [M+H]+: 374.2; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}N_3ClBr$ $(M)^+$: 372.9981. Found: 372.9985.

*4.2.7. 4-(4-Chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-5-amine (**3j**).* Yellow solid (218 mg, 70%); mp: 165.0–167.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.04 (s, 2H), 7.03 (d, *J*=8.0 Hz, 2H), 7.48 (d, *J*=7.5 Hz, 2H), 7.76 (d, *J*=7.5 Hz, 4H), 8.71 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.63, 114.63, 128.85, 129.45, 130.18, 135.30, 135.53, 135.74, 149.55, 150.10, 160.90; LC–MS (ESI): *m*/*z* $[M+H]^+$: 312.2; HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_3OCl$ $(M)^+$: 311.0825. Found: 311.0825.

*4.2.8. 4-(4-Methoxyphenyl)-2-methyl-6-(4-nitrophenyl)pyrimidin-5-amine (**3k**).* Red solid (259 mg, 77%); mp: 180.0–182.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (s, 3H), 3.87 (s, 3H), 3.91 (s, 2H), 7.05 (d, *J*=8.5 Hz, 2H), 7.75 (d, *J*=9.0 Hz, 2H), 8.02 (d, *J*=8.5 Hz, 2H), 7.86 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.35, 55.68, 114.74, 124.37, 128.71, 130.03, 130.23, 133.00, 143.62, 148.27, 148.78, 153.45, 158.41, 160.97; LC–MS (ESI): *m*/*z* $[M+H]^+$: 337.2; HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}N_4O_3$ $(M)^+$: 336.1222. Found: 336.1216.

*4.2.9. 4-(4-Methoxyphenyl)-6-(thiophen-2-yl)pyrimidin-5-amine (**3m**).* Yellow solid (159 mg, 56%); mp: 158.0–160.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 1H), 4.29 (s, 2H), 7.05 (d, *J*=9.0 Hz, 2H), 7.19–7.21 (m, 1H), 7.54 (d, *J*=5 Hz, 1H), 7.75–7.79 (m, 3H), 8.70 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.42, 114.44, 127.63, 128.09, 128.55, 128.96, 130.09, 134.15, 141.37, 144.76, 149.15, 152.57, 160.72;

LC–MS (ESI): *m/z* $[M+H]^+$: 284.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_3OS$ $(M)^+$: 283.0779. Found: 283.0773.

*4.2.10. 4-(4-Fluorophenyl)-2-methyl-6-(thiophen-2-yl)pyrimidin-5-amine (**3n**).* Yellow solid (234 mg, 82%); mp: 158.0–161.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.66 (s, 3H), 4.05 (s, 2H), 7.16–7.20 (m, 3H), 7.50–7.52 (m, 1H), 7.71–7.74 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.01, 115.60 (d, *J*=22 Hz), 116.08 (d, *J*=22 Hz), 127.74, 128.02, 128.85 (d, *J*=221 Hz), 128.92, 130.67 (d, *J*=8 Hz), 130.91 (d, *J*=8 Hz), 131.51, 132.50 (d, *J*=3 Hz), 141.21, 145.46, 152.10, 157.83, 162.33, 164.31; *m/z* $[M+H]^+$: 286.2; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N_3SF$ $(M)^+$: 285.0736. Found: 285.0724.

*4.2.11. 4-(4-Chlorophenyl)-6-(thiophen-2-yl)pyrimidin-5-amine (**3o**).* Yellow solid (218 mg, 76%); mp: 139.0–140.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.27 (s, 2H), 7.18–7.20 (m, 1H), 7.48–7.53 (m, 2H), 7.53–7.54 (m, 1H), 7.72–7.73 (m, 2H), 7.74–7.76 (m, 1H), 8.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.01, 128.41, 129.48, 129.55, 130.24, 134.44, 134.93, 136.03, 141.26, 145.54, 149.37, 151.50; LC–MS (ESI): *m/z* $[M+H]^+$: 288.1; HRMS (ESI): *m/z* calcd for $C_{14}H_{10}N_3SCl$ $(M)^+$: 287.0284. Found: 287.0282.

4.3. General procedure for the synthesis of 3c, 3f, 3i, 3l

A mixture of α-azidovinyl ketone **1** (1.0 mmol), amidine acid **2** (2.0 mmol), and K_2CO_3 (4.0 mmol) was stirred in anhydrous DMF (4 mL) at rt under nitrogen overnight. The reaction mixture was quenched with water (10 mL), and then extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by chromatography (silica gel, eluent PE/EA) to afford **3**.

*4.3.1. 4-(4-Bromophenyl)-2,6-diphenylpyrimidin-5-amine (**3c**).* Pale yellow solid (309 mg, 77%); mp: 192.0–194.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (s, 2H), 7.38 (t, *J*=7.0, 7.5 Hz, 1H), 7.43 (t, *J*=7.5, 7.5 Hz, 2H), 7.49 (t, *J*=7.0, 7.5 Hz, 2H), 7.54 (t, *J*=7.5, 7.5 Hz), 7.81 (d, *J*=8.5 Hz, 2H), 7.88 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.78, 127.28, 128.33, 128.74, 129.00, 130.47, 132.14, 133.51, 136.02, 136.89, 138.04, 150.38, 152.18, 155.38; LC–MS (ESI): *m/z* $[M+H]^+$: 402.3; HRMS (ESI): *m/z* calcd for $C_{22}H_{16}N_3Br$ $(M)^+$: 401.0528. Found: 401.0523.

*4.3.2. 4-(4-Bromophenyl)-2-phenyl-6-(p-tolyl)pyrimidin-5-amine (**3f**).* Pale yellow solid (304 mg, 73%); mp: 223.0–225.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.03 (s, 2H), 7.33 (d, *J*=7.5 Hz, 2H), 7.38 (d, *J*=7.0 Hz, 1H), 7.42 (t, *J*=7.0, 7.5 Hz, 2H), 7.65 (d, *J*=8.5 Hz, 2H), 7.77–7.80 (m, *J*=8.0, 8.5 Hz, 4H), 8.43 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.70, 123.94, 127.52, 128.54, 128.89, 129.41, 129.89, 130.73, 132.33, 133.74, 134.24, 136.33, 138.35, 139.92, 150.40, 152.55, 155.55; LC–MS (ESI): *m/z* $[M+H]+$: 416.2; HRMS (ESI): *m/z* calcd for $C_{23}H_{18}N_3Br$ $(M)+$: 415.0684. Found: 415.0688.

*4.3.3. 4-(4-Bromophenyl)-6-(4-chlorophenyl)-2-phenylpyrimidin-5-amine (**3i**).* Pale yellow solid (353 mg, 81%); mp: 240.0–242.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 2H), 7.38–7.44 (m, 3H), 7.52 (d, *J*=8.0 Hz, 2H), 7.68 (d, *J*=8.0 Hz, 2H), 7.80 (d, *J*=8.5 Hz, 2H), 7.86 (d, *J*=8.0 Hz, 2H), 8.42 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.94, 127.25, 128.37, 129.23, 129.37. 130.19, 130.44, 132.19, 133.43, 135.30, 135.65, 135.78, 137.83, 150.83, 155.48; LC–MS (ESI): *m/z* $[M+H]^+$: 436.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{15}N_3ClBr$ $(M)^+$: 435.0138. Found: 435.0136.

*4.3.4. 4-(4-Methoxyphenyl)-6-(4-nitrophenyl)-2-phenylpyrimidin-5-amine (**3l**).* Red solid (263 mg, 66%); mp: >250 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.11 (s, 2H), 7.08 (d, *J*=9.0 Hz, 2H), 7.41–7.47 (m, 3H), 7.89 (d, *J*=8.5 Hz, 2H), 8.16 (d, *J*=9.0 Hz, 2H), 8.39 (d, *J*=9.0 Hz, 2H), 8.44 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.68, 114.68, 124.29, 127.49, 128.60, 129.10, 129.64, 130.15, 133.85, 138.05, 143.88, 148.36, 148.65, 153.24, 155.75, 161.10; LC–MS (ESI): *m/z* $[M+H]^+$: 399.3; HRMS (ESI): *m/z* calcd for $C_{23}H_{18}N_4O_3$ $(M)^+$: 398.1379. Found: 398.1372.

4.4. General procedure for the synthesis of 3p, 3q, 3r

A mixture of α-azidovinyl ketone **1** (1.0 mmol), amidine acid **2** (1.2 mmol), and K_2CO_3 (2.4 mmol) was stirred in anhydrous DMF (4 mL) at 50 °C for 24 h under nitrogen. The reaction mixture was quenched with water (10 mL), and then extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification of the crude product by chromatography (silica gel, eluent PE/EA) to afford **3**.

*4.4.1. 4-(4-Chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-5-amine (**3p**).* Yellow solid (233 mg, 75%); mp: 177.5–180.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.05 (s, 2H), 7.03 (d, *J*=8.5 Hz, 2H), 7.48 (d, *J*=8.5 Hz, 2H), 7.76 (d, *J*=8.5 Hz, 4H), 8.71(s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.64, 114.62, 128.84, 129.45, 130.18, 135.29, 135.55, 135.74, 149.55, 150.09, 152.00, 160.88; LC–MS (ESI): *m/z* $[M+H]^+$: 312.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{14}N_3OCl$ $(M)^+$: 311.0825. Found: 311.0826.

*4.4.2. 4-(2-Bromophenyl)-6-(4-methoxyphenyl)pyrimidin-5-amine (**3q**).* Yellow-brown solid (248 mg, 70%); mp: 190.0–193.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 5H), 6.94 (d, *J*=9.0 Hz, 2H), 7.19–7.24 (m, 1H), 7.33–7.38 (m, 2H), 7.62 (d, *J*=8.0 Hz, 1H), 7.69 (d, *J*=8.5 Hz, 2H), 8.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.40, 114.41, 122.15, 128.25, 128.52, 129.82, 130.75, 130.79, 133.40, 135.64, 137.08, 148.60, 151.12, 151.26, 160.65; LC–MS (ESI): *m/z* $[M+H]^+$: 356.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{14}N_3OBr$ $(M)^+$: 355.0320. Found: 355.0327.

*4.4.3. 4-(4-Methoxyphenyl)-6-phenylpyrimidin-5-amine (**3r**).* Yellow solid (163 mg, 59%); mp: 128.0–130.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.07 (s, 2H), 7.05 (d, *J*=9.0 Hz, 2H), 7.47 (t, *J*=7.0, 7.5 Hz, 1H), 7.53 (t, *J*=7.0, 7.5 Hz, 2H), 7.78–7.80 (m, 4H), 8.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.41, 114.39, 128.47, 128.87, 129.03, 129.49, 129.96, 135.32, 136.65, 149.34, 151.28, 151.40, 160.58; LC–MS (ESI): *m/z* $[M+H]^+$: 278.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_3O$ $(M)^+$: 277.1215. Found: 277.1208.

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Supplementary data

Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.01.062. These data include MOL files and InChiKeys of the most important compounds described in this article.

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