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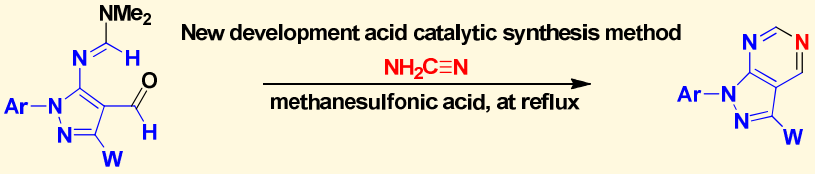

Efficient Acid Catalytic Synthesis of Pyrazolopyrimidines from 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidines with Cyanamide

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Key words: Pyrazolopyrimidines, Cyanamide, Formamidines, Heterocyclization

ABSTRACT: The efficient acid catalytic synthesis of pyrazolo[3,4-*d*]pyrimidine was developed by treating 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine with various aminating agents including *N*,*O*-bis(trimethylsilyl)hydroxylamine ($NHSiMe_3(OSiMe_3)$), cyanamide ($NH_2C{\equiv}N$), hydroxylamine (NH_2OH), methoxyamine (NH_2OMe), hydrazine (NH_2NH_2), and urea ($NH_2C(O)NH_2$) in acidic solution at reflux. Based on the experimental result, cyanamide ($NH_2C{\equiv}N$) and methanesulfonic acid were indicated the best aminating agent and acid mediated solvent. On the other hands, the reactivity tendency was involved the activity of original leaving species grafting on the aminating agents, such as –OH, –OMe, $–OSiMe_3$, $–NH_2$, $–OSiMe_3$, $–C(O)NH_2$, and –C≡N, in acid catalytic heterocyclic reaction.

INTRODUCTION

Pyrazolo[3,4-*d*]pyrimidines have attracted attention as potential drugs or molecular tools.[1-10] Some recently reported synthetic methods for this class of compounds are included functionalized barbituic acid,[11] 1-phenyl-5*H*,7*H*-pyrazolo[3,4-*d*]pyrimidine dithiones,[12] or pyrazolo[3,4-d]pyrimidin-4-ones,[13] and intramolecular heterocyclization of 5-amino-1-(2-hydroxy-2-phenylethyl)-1*H*-pyrazole carboxylic acid[14] or 5-amino-4-cyano-pyrazoles.[15] However, most of the methods are not straightforward and troublesome for preparation of starting materials. Therefore, we have previously also designed the convenient synthetic routes involved 5-aminopyrazoles with Vilsmeier reagents to construct pyrazolo[3,4-*d*]pyrimidine core structures via the directed intramolecular heterocyclization[16] or the sequential intermolecular heterocyclization with hexamethyldisilazane ($NH(SiMe_3)_2$) under neutralization/basic reaction condition (Figure 1).[17] Based on the above observations, we found most of approach were dangerous exothermic reaction. As a result, we planned to develop a efficient acid catalystic method for synthesis of pyrazolo[3,4-*d*]pyrimidines by treating 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines with aminating agent under the acidic solution (Figure 1).

At first, we estimated 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine with a series of aminating equivalent agents including *N*,*O*-bis(trimethylsilyl)hydroxylamine ($NHSiMe_3(OSiMe_3)$), cyanamide ($NH_2C{\equiv}N$), hydroxylamine (NH_2OH), methoxyamine (NH_2OMe), hydrazine (NH_2NH_2), and urea ($NH_2C(O)NH_2$) under the different acid mediated solution. Fortunately, we successfully found cyanamide ($NH_2C{\equiv}N$) and methanesulfonic acid were respectively indicated the best aminating agent and acid mediated solvent for synthesizing the desired

pyrazolo[3,4-*d*]pyrimidine products.

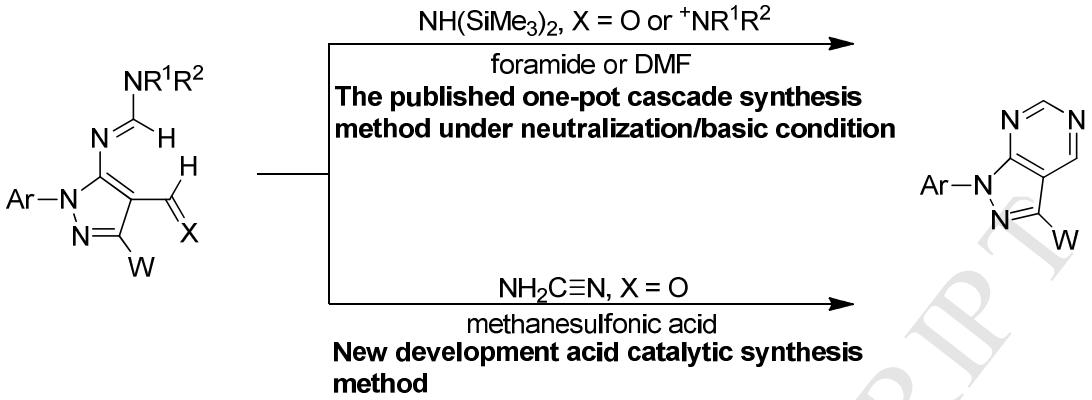


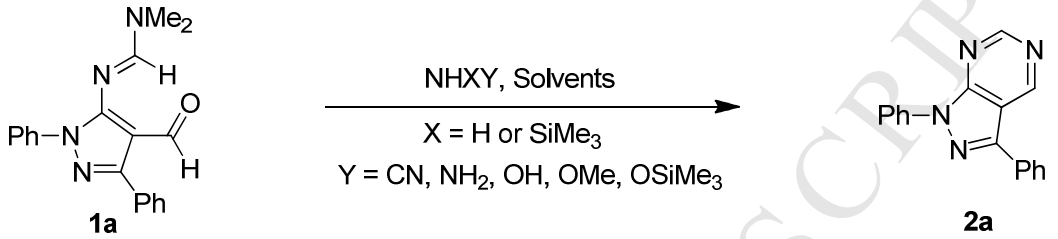
Figure 1. The published one-pot cascade reaction and acid catalytic synthesis of pyrazolo[3,4-*d*]pyrimidines.

RESULTS AND DISCUSSION

In view of our previous investigation experience of Vilsmeier-Haack reagent[16,17] we estimated 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines[18] were respectively important starting materials for the new designed synthesis. On the other hands, cyanamides ($NH_2C{\equiv}N$) were available versatile aminating intermediates or precursors for synthesis of widely heterocyclic compounds.[19-25] Therefore, we initiated our study to explore the possibility of the amination cyclization reaction between 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1a** and cyanamides ($NH_2C{\equiv}N$). Table 1 presents the typical amination cyclization study by reacting the model starting material 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidine **1a** with cyanamide ($NH_2C{\equiv}N$, 3.0 equiv) in presence of a series of acidic mediate solutions (2.0 mL), such as aqueous HCl solution (5%, 10%, and 35%), acetic acid (AcOH), trifluoroacetic acid (TFA), methanesulfonic acid, and *p*-toluenesulfonic acid at reflux for 3.0–5.0 h. The corresponding pyrazolo[3,4-*d*]pyrimidine product **2a** were afforded from ~32% to 82% yields (Table 1, entries 1–7). Based on the control experimental result, the promoted reactivity tendency of acid mediated solvents was methanesulfonic acid >

35% $HCl_{(aq)}$ > TFA > *p*-toluenesulfonic acid > 10% $HCl_{(aq)}$ > 5% $HCl_{(aq)}$ > AcOH. The result was also revealed the Brønsted-Lowry acid catalytic heterocyclization was favorable carried out in strong acid reaction condition.

Table 1. The amination study for synthesis of pyrazolopyrimidines in the different of acid mediated solvents



Entry	Solvent	Aminating Agents	Equiv.	Yields (%) of **2a**
1	5% $HCl_{(aq)}$	$NH_2C{\equiv}N$	3	32
2	10% $HCl_{(aq)}$	$NH_2C{\equiv}N$	3	43
3	35% $HCl_{(aq)}$	$NH_2C{\equiv}N$	3	62
4	AcOH	$NH_2C{\equiv}N$	3	6
5	TFA	$NH_2C{\equiv}N$	3	52
6	*p*-Toluenesulfonic acid	$NH_2C{\equiv}N$	3	46
7	Methanesulfonic acid	$NH_2C{\equiv}N$	3	83
8	Methanesulfonic acid	$NH_2C{\equiv}N$	4	81
9	Methanesulfonic acid	$NH_2C{\equiv}N$	2	61
10	Methanesulfonic acid	$NH_2C{\equiv}N$	1	27
11	Methanesulfonic acid	NH_2OH	3	26
12	Methanesulfonic acid	NH_2OMe	3	75
13	Methanesulfonic acid	NH_2NH_2	3	37
14	Methanesulfonic acid	$NH_2(C{=}O)NH_2$	3	-[a]
15	Methanesulfonic acid	$NHSiMe_3(OSiMe_3)$	3	73

[a]not-detectable.

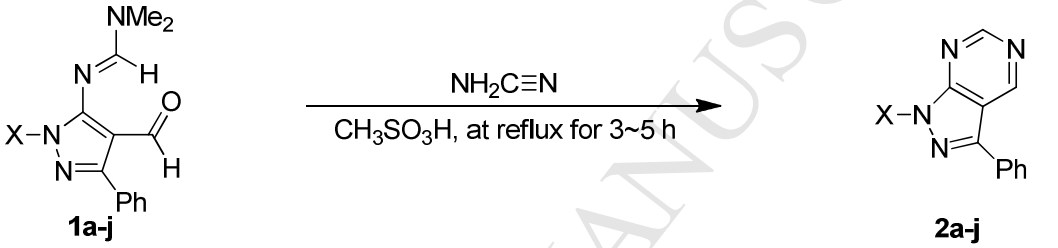
For the further optimization, we tried to use the different equivalent of cyanamide ($NH_2C{\equiv}N$) including 1.0, 2.0, 3.0, and 4.0 equivalent amounts. The corresponding isolated yields of pyrazolo[3,4-*d*]pyrimidine product **1a** were obtained in 27–83% yields, especially for 3.0 equivalents of $NH_2C{\equiv}N$ in 83% yield (Table 1, entries 7–10). Based on the experimental result, we believed the 3.0 equivalent of $NH_2C{\equiv}N$ is the suitable amount in our reaction condition.

Next, we investgated a range of aminating equivalent agents including *N*,*O*-bis(trimethylsilyl)hydroxylamine ($NHSiMe_3(OSiMe_3)$), cyanamide ($NH_2C{\equiv}N$), hydroxylamine (NH_2OH), methoxyamine (NH_2OMe), hydrazine (NH_2NH_2), and urea ($NH_2C(O)NH_2$) in the same reaction condition (Table 1, entries 7 and 11–15). Among of aminting agents be able to afford the corresponding pyrazolo[3,4-d]pyrimidine product **2a**,[25] except for urea. Note that cyanamide ($NH_2C{\equiv}N$) can provide the best result in 83% yield and the reactivity order was $NH_2C{\equiv}N$ > $NHSiMe_3(OSiMe_3)$ > NH_2OMe > NH_2NH_2 > NH_2OH >> $NH_2C(O)NH_2$ (Table 1, entries 7 and 11–15). As a result, the reactivity tendency was involved the activity of original leaving species grafting on the aminating agents in acid catalytic heterocyclization reaction. Several control experiments were conducted that the best reliable procedure for synthesis of pyrazolo[3,4-*d*]pyrimidines was involved the treatment of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1a** with 3.0 equivalent of $NH_2C{\equiv}N$ in methanesulfonic acid solution at reflux for 3.0–5.0 h. When the aminating cyclization reaction was completed, the resulting mixture was worked-up and purified by chromatography. The corresponding pyrazolo[3,4-*d*]pyrimidine product **2a** was obtained in 83% yield (Table 1).

Application of the reliable standard procedure to 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1b**–**j** bearing various *N*-1 substituents,

including *o*-, *m*-, *p*-Me-Ph, *o*-, *m*-, *p*-Cl-Ph, *p*-Br-Ph, *p*-OMe-Ph, and *p*-NO_2-Ph, the aminating cyclization proceeded smoothly to give the corresponding pyrazolo[3,4-d]pyrimidines **2b**–**j** in 63–83% yields (Table 2). All of pyrazolo[3,4-d]pyrimidines **2a**–**j** were characterized by spectroscopic methods, the physical properties and spectroscopic characteristics were consistent with our previously published data.[16]

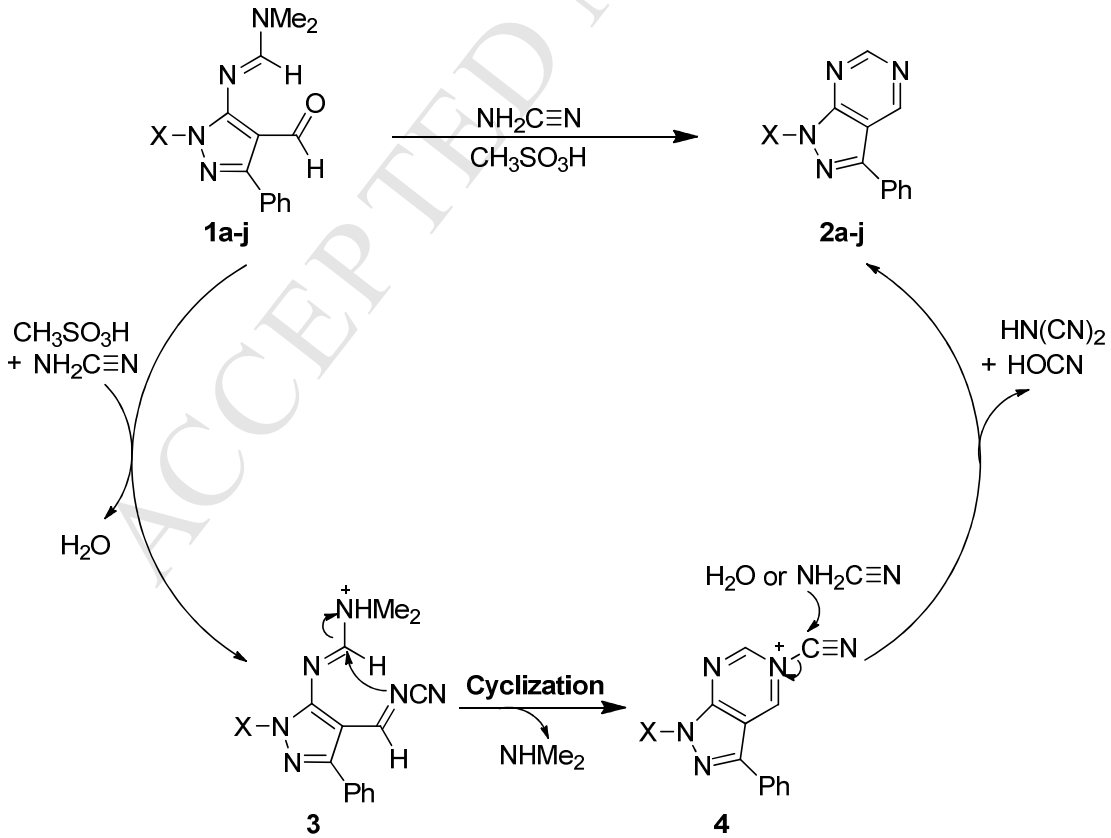
Table 2. The results of synthesis of pyrazolopyrimidines from 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines with cyanamide ($NH_2C{\equiv}N$)



S.M.	X	Products	Yields of **2a**–**j** (%)
1a	Ph	**2a**	83
1b	*o*-Me-Ph	**2b**	63
1c	*m*-Me-Ph	**2c**	73
1d	*p*-Me-Ph	**2d**	79
1e	*o*-Cl-Ph	**2e**	70
1f	*m*-Cl-Ph	**2f**	68
1g	*p*-Cl-Ph	**2g**	81
1h	*p*-Br-Ph	**2h**	71
1i	*p*-OMe-Ph	**2i**	78
1j	*p*-NO_2-Ph	**2j**	68

A plausible mechanism for synthesis of pyrazolo[3,4-*d*]pyrimidines was depicted in Scheme 1. Preliminarily, 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1a**–**j** was

effectively initiated by Brønsted-Lowry methanesulfonic acid to form the activate sulfonamide cation intermediate **3**. Subsequently, the aminating agent cyanamide ($NH_2C{\equiv}N$) was added to happen the nucleophilic attacking towards intermediate **3** affording an active cyanimino species **4**. Due to the strength driving force by the excellent leaving-group ability in quaternary ammonium cation moiety, the intramolecular cyclization was effectively occurred and the de-cyanating reaction took place by nucleophile (ex. Water or excess cyanamide) to give the corresponding pyrazolo[3,4-d]pyrimidine products **2a**–**j** were obtained from 63% to 83% yields. On the other hands, dicyanamide and cyanic acid could be formed as the side-products.[26] Notably, dicyanamide and urea were able be identified in aqueous layer by LC-MS analysis technique. Urea may come from the hydrolysis of excess cyanamide under acidic mediate.[19,27] Therefore, this result provided the specific proof for the proposed mechanism.



Scheme 1. The plausible mechanism for the newly developed acid catalytic synthesis

of pyrazolo[3,4-*d*]pyrimidines.

CONCLUSIONS

We have successfully developed new Brønsted-Lowry acid catalytic synthesis of pyrazolo[3,4-*d*]pyrimidines, involving the subsequent imination, heterocyclization, and aromation three steps. Based on the control experimental results, cyanamide ($NH_2C{\equiv}N$) was the best aminating agent. Furthermore, the key heterocyclic reaction was catalyzed by methanesulfonic acid to yield the corresponding pyrazolo[3,4-*d*]pyrimidine products in moderate yields.

EXPERIMENTAL SECTION

General Procedure: All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography purification of compounds was carried out by gradient elution using hexanes in ethyl acetate (EA) unless otherwise stated. ^{1}H NMR were recorded at 400 or 500 MHz and ^{13}C NMR recorded at 100 or 125 MHz, respectively, in $CDCl_3$, CD_3OD, and DMSO-d_6 as solvent. The standard abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constant (*J*), whenever discernible, have been reported in Hz. Infrared spectra (IR) were recorded as neat solutions or solids; and mass spectra were recorded using electron impact or electrospray ionization techniques. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. High-resolution mass spectra were obtained by means of a JEOL JMS-HX110 mass spectrometer.

Standard Procedure for Synthesis of Pyrazolo[3,4-*d*]pyrimidines (2a–j). The reliable procedure involved the treatment of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines (**1a**–**j**, 1.0 equiv) with 3.0 equivalent of

various aminating agents including *N*,*O*-bis(trimethylsilyl)hydroxylamine ($NHSiMe_3(OSiMe_3)$), cyanamide ($NH_2C{\equiv}N$), hydroxylamine (NH_2OH_2), methoxyamine (NH_2OMe), hydrazine (NH_2NH_2), or urea ($NH_2C(O)NH_2$) in methanesulfonic acid solution (2 mL) at reflux for 3–5 h. When the reaction was completed (monitored by TLC), the resulting mixture was added to water (15 mL) and extracted with dichloromethane (15 mL × 2). The organic extracts were washed with saturate sodium bicarbonate (15 mL × 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography (EtOAc/*n*-hexane as eluent) on silica gel to give the corresponding pyrazolo[3,4-*d*]pyrimidines products (**2a**–**j**) in 63–83% yields.

1,3-Diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2a).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine 1a (159mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2a** in 83% yield (111 mg). Light-yellow solid; mp 157–158°C (hexane–EtOAc) ;^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37–7.40 (1H, m, Ar*H*), 7.49–7.52(1H, m, ArH), 7.55–7.58(4H, m, Ar*H*), 8.05 (2H, d, *J* = 7.5 Hz, Ar*H*), 8.27–8.29 (2H, m, ArH), 9.15 (1H, s), 9.58 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.0, 121.5 (2 × C), 127.2, 127.4 (2 × C), 129.3 (4 × C), 129.9, 131.0, 138.2, 145.6, 151.6, 153.0, 154.1; IR (KBr): 1577, 1558, 1501, 1418, 1364, 1219, 1090 cm^{-1}. EIMS m/z: 272 (M^+, 100), 273 (19), 271 (32), 142 (12), 77 (30), 51 (10).

1-(2-Methylphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2b).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1b** (116 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was

purified by chromatography on silica gel to give pure **2b** in 63% yield (90.2 mg). Light-yellow solid; mp 140–141°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.49 (3H, s, C*H*$_3$), 7.42–7.51(1H, m, Ar*H*), 7.48–7.46(1H, m, Ar*H*), 7.55–7.58 (3H, m, Ar*H*), 8.06–8.11 (4H, m, Ar*H*), 9.13 (1H, s), 9.51 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.63, 114.19, 118.77, 122.18, 127.42 (2 × C), 127.78, 129.24 (2 × C), 129.62, 131.56, 138.39, 139.33, 144.92, 152.80, 153.33, 155.61. IR (KBr): 1634, 1609, 1585, 1557, 1493, 1364, 1229, 1098, 1085 cm^{-1}. EIMS m/z: 286 (M^+, 100), 287 (20), 285 (25), 272 (17), 271 (10), 156 (10),91 (12), 77 (30), 65 (12).

1-(3-Methylphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2c).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1c** (116 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2c** in 73% yield (104 mg). Yellow solid; mp 81–82°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.47 (3H, s, C*H*$_3$), 7.15 (1H, d, *J* = 6.8 Hz, Ar*H*), 7.39–7.48 (2H, m, Ar*H*), 7.51–7.55 (2H, m, Ar*H*), 8.02–8.09 (4H, m, Ar*H*), 9.10 (1H, s) , 9.46 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.56, 114.07, 118.57, 121.96, 127.29 (2 × C), 127.62, 128.95, 129.11 (2 × C), 129.49, 131.44, 138.31, 139.19, 144.73, 152.67, 153.18, 155.46; IR (KBr): 1662, 1611, 1584, 1558, 1493, 1477, 1364, 1315, 1229, 1194, 1096 cm^{-1}. EIMS m/z: 286 (M^+, 100), 287 (20), 285 (24), 77 (16).

1-(4-Methylphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2d).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1d** (116 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2d** in 79% yield (113mg). Yellow solid; mp 133–135°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41

(3H, s, C*H*$_3$), 7.34 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.46 –7.50 (3H, m, Ar*H*), 8.04 (2H, d, *J* = 8.4 Hz, Ar*H*), 8.13 (2H, d, *J* = 8.4 Hz, Ar*H*), 9.09 (1H, s), 9.46 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.11, 114.09, 121.51 (2 × C), 127.38 (2 × C), 129.21 (2 × C), 129.56, 129.80 (2 × C), 131.60, 136.05, 136.83, 144.74, 152.76, 153.15, 155.53; IR (KBr): 1589, 1557, 1513, 1474, 1364, 1265, 1221, 1088 cm^{-1}. EIMS m/z: 286 (M^+, 100), 287 (21), 285 (28), 77 (14).

1-(2-Chlorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2e).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1e** (176 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2e** in 70% yield (107 mg). Yellow solid; mp 136–138°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44–7.49 (3H, m, Ar*H*), 7.52–7.55 (2H, m, Ar*H*), 7.60–7.63 (2H, m, Ar*H*), 8.03–8.05 (2H, m, Ar*H*), 9.07 (1H, s), 9.53 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 112.9, 127.3 (2 × C), 127.6, 129.1 (2 × C), 129.6 (2 × C), 131.0 (2 × C), 131.3, 132.1, 134.6, 145.6, 152.8, 154.4, 155.8; IR (KBr): 1582, 1557, 1495, 1362, 1223, 1161, 1086 cm^{-1}. EIMS m/z: 306 (M^+, 74), 308 (M^+ + 2, 25), 307 (16), 272 (20), 271 (100), 195 (19), 194 (12), 111 (17), 90 (14), 77 (79), 75 (21), 63 (12), 51 (26).

1-(3-Chlorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2f).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1f** (176 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2f** in 68% yield (104 mg). White solid; mp 180–182°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.45–7.58 (4H, m, Ar*H*), 8.04 (2H, d, *J* = 7.6 Hz, Ar*H*), 8.32–8.43 (2H, m, Ar*H*), 9.14 (1H, s), 9.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ

114.46, 118.82, 121.10, 126.63, 127.42 (2 × C), 129.26 (2 × C), 129.86, 130.22, 134.96, 139.59, 145.39, 152.90, 153.60, 155.75; IR (KBr): 1585, 1489, 1404, 1368, 1213, 1132, 1092 cm^{-1}. EIMS m/z: 306 (M^+, 100), 308 (M^+ + 2, 34), 307 (28), 305 (25), 77 (26).

1-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2g).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1g** (176 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2g** in 81% yield (124 mg). Yellow solid; mp 149–151°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48–7.51 (3H, m, Ar*H*), 7.54–7.57 (2H, m, Ar*H*), 8.03 (2H, d, *J* = 8.0 Hz, Ar*H*), 8.32 (2H, d, *J* = 9.0 Hz, Ar*H*), 9.12 (1H, s), 9.49 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ114.3, 122.2 (2 × C), 127.4 (2 × C), 129.2 (2 × C), 129.3 (2 × C), 129.8, 131.2, 132.1, 137.1, 145.2, 152.9, 153.3, 155.6; IR (KBr): 1587, 1555, 1499, 1406, 1265, 1219, 1084 cm^{-1}. EIMS m/z: 306 (M^+, 100), 308 (M^+ + 2, 31), 307 (24), 305 (20), 296 (14), 294 (31), 159 (11), 91 (28), 77 (26).

1-(4-Bromophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2h).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1h** (199 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2h** in 71% yield (125 mg). White solid; mp 177–178°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49–7.2 (1H, m, Ar*H*), 7.55–7.58 (2H, m, Ar*H*), 7.65–7.67 (2H, dd, *J* = 1.5, 1.5 Hz,Ar*H*), 8.04–8.05 (2H, dd, *J* = 1, 1 Hz , Ar*H*), 8.27–8.29 (2H, dd, *J* = 1, 1 Hz, Ar*H*), 9.13 (1H, s), 9.49 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.4, 120.0, 122.5 (2 × C), 127.4 (2 × C), 129.3 (2 × C), 129.8, 131.2, 132.3 (2 × C), 137.7, 145.3, 152.9, 153.4,

155.7; IR (KBr): 3030, 2920, 1572, 1551, 1488, 1403, 1216, 1072 cm^{-1}. EIMS m/z: 350 (M^+, 5), 352 (M^+ + 2, 5), 319 (22), 318 (100), 317 (36), 303 (17), 275 (15), 274 (20), 262 (11), 248 (10), 246 (10), 186 (18), 143 (10), 116 (10), 104 (10), 84 (12), 83 (15), 77 (60), 51 (13).

1-(4-Methoxylphenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2i).[16] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1i** (174 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2i** in 78% yield (118 mg). Brown solid; mp 167–168°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.87 (1H, s, OCH_3), 7.05 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.34 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.54 (2H, t, *J* = 8.0, Ar*H*), 7.98 (2H, d, *J* = 8.0, Ar*H*), 8.28 (2H, d, *J* = 8.0, Ar*H*), 9.09 (1H, s), 9.44 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.35, 114.57 (2 × C), 121.26 (2 × C), 123.99, 126.61, 126.78, 128.61 (2 × C), 129.14 (2 × C), 129.39, 138.49, 144.74, 152.66, 155.42, 160.71. IR (KBr): 1643, 1587, 1555, 1497, 1402, 1368, 1215, 1130, 1074. EIMS m/z: 302 (M^+ , 100), 303 (21), 301 (17), 287 (18), 258 (11), 77 (47), 51 (12).

1-(4-Nitrophenyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (2j). A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1i** (182 mg, 0.50 mmol, 1.0 equiv), and cyanamide (63.1 mg 1.5 mmol, 3.0 equiv) was stirred in methanesulfonic acid (2.0mL) at reflux for 3–5 h. The reaction mixture was then worked-up, and the residue was purified by chromatography on silica gel to give pure **2i** in 68% yield (108 mg). Brown solid; mp 182–184°C (hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55–7.61 (3H, m, Ar*H*), 8.06 (2H, d, Ar*H*, *J* = 7.2 Hz, Ar*H*), 8.41 (2H, d, *J* = 8.4 Hz, Ar*H*), 8.74 (2H, dd, *J* = 8.4 Hz, *J* = 2 Hz Ar*H*), 9.19 (1H, s), 9.54 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.06, 120.42 (2 × C), 124.99 (2 × C), 127.53 (2 × C), 129.38

(2 × C), 130.31, 130.71, 143.58, 145.26, 146.59, 153.08, 154.39, 156.00; IR (KBr): 1596, 1561, 1516, 1503, 1408, 1335, 1213, 1110, 1081 cm^{-1}. EIMS m/z: 317 (M^+, 100), 318 (20), 287 (10), 168 (10), 77 (24); HRMS Calcd. for $C_{17}H_{11}N_5O_2$: 317.0913; Found: 317.0909.

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Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra for products **2a–j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Efficient Acid Catalytic Synthesis of Pyrazolopyrimidines from 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidines with Cyanamide

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