JOC The Journal of Organic Chemistry

Article

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Evaluation of Electrophilic Heteroaromatic Substitution: Synthesis of Heteroaromatic-Fused Pyrimidine Derivatives via Sequential Three-Component Heterocyclization

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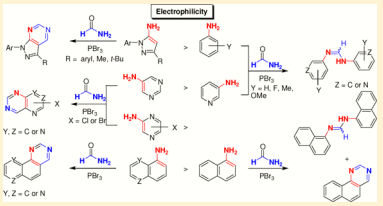
Supporting Information

ABSTRACT: A new sequential three-component heterocyclization was developed by reacting aromatic and heterocyclic substrates, including aminobenzenes, 1-aminonaphthalene, 2-aminopyrazines, 5-aminopyrazoles, 3-aminopyridine, 5-aminopyrimidine, 5-aminoquinoline, and 8-aminoquinoline, with formamide in the presence of PBr_3. The reaction gave the corresponding pyrazolo[3,4-*d*]pyrimidines in good yields (59−96%), except for aminobenzenes and 3-aminopyridine. A plausible reaction mechanism involving amidination, electrophilic substitution imination, and oxidative cyclization in three steps was proposed to account for the heterocyclization. The reactivity of the reaction was found proportional to the electrophilicity of the aromatic or heterocyclic substrate.



INTRODUCTION

Electrophilic aromatic substitution reactions are widely applied to the synthesis of various aromatic and heterocyclic compounds with potential pharmacological applications.[1,2] Most of the evaluations of aromatic or heterocyclic reactivity can be said to have begun with the results of electrophilic substitution processes.[2] Therefore, the reaction of heterocycles with electrophilic reagents is still extremely useful to construct the fused heterocyclic ring, particularly fused pyrimidine derivatives.[3−5]

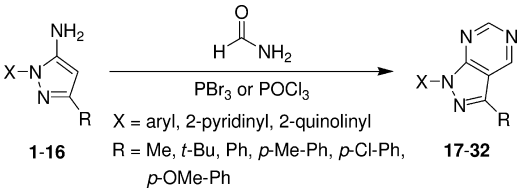
Fused pyrimidine derivatives are an important class of compounds with remarkable pharmaceutical applications, for example, antibacterial,[6] antifungal,[7,8] antioxidant,[9] antitumor,[10] herbicidal,[11] and antivirus,[12] and are effective inhibitors of inflammatory mediators in intact cells.[13] As a result, many synthetic methods were enthusiastically developed to prepare heteroaromatic-fused pyrimidine derivatives.[14,15] However, most of the methods are not straightforward and purification is troublesome.

Recently, one-pot multicomponent processes have attracted considerable academic, economic, and ecological interest, for they address very fundamental principles of synthetic efficiency and reaction-designed approach.[16] Herein, we have developed an efficient one-pot, three-component synthesis of heteroaromatic-fused pyrimidines by treating aminoaromatic or aminoheterocyclic substrates with formamide using PBr_3 as the coupling agent. The activity of electrophilic aromatic and heterocyclic substitution imination was also studied to determine the difference in electrophilicity between aromatic and heterocyclic substrates.

RESULTS AND DISCUSSION

Development of the Sequential Three-Component Synthesis of Pyrazolo[3,4-*d*]pyrimidine Derivatives 17−32 and Mechanism Study. Scheme 1 shows the typical

Scheme 1



reaction condition of the new sequential three-component heterocyclization for the synthesis of pyrazolo[3,4-*d*]-pyrimidines **17**−**32**. 5-Amino-1,3-disubstituted pyrazoles **1**−**16**, prepared by our previously developed method,[17] were used as the starting materials. To evaluate the reaction conditions, 5-amino-1,3-diphenylpyrazole (**1**) was used as the model case. Various coupling agents in different amounts were used to search for the best reaction conditions. These agents include benzoyl chloride (PhCOCl), oxalyl chloride (ClCOCOCl), phosphorus tribromide (PBr_3), phosphorus oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), and *p*-toluenesulfonic chloride (TsCl). Without the coupling agent, only the starting material **1** was recovered after the reaction proceeded for 48 h at 60 °C (see entry 1 in Table 1). When the compound **1** was allowed to react with different amounts of coupling agents, such as PBr_3 and $POCl_3$, the reaction gave the corresponding

Received: July 12, 2012
Published: September 5, 2012

Table 1. Study of Coupling Agents in the Sequential Three-Component Reaction

	coupling agent		
entry	agent	amt (equiv)[a]	yield of pyrazolo[3,4-*d*]pyrimidine **17** (%)
1	no base		*b*
2	PBr_3	1	76
3	PBr_3	3	97
4	PBr_3	5	95
5	$POCl_3$	1	73
6	$POCl_3$	3	96
7	$POCl_3$	5	97
8	$SOCl_2$	3	49
9	ClCOCOCl	3	68
10	PhCOCl	3	23
11	TsCl	3	28

[a]Based on the weight of 5-amino-1,3-diphenylpyrazole **17**. [b]The starting material **1** was recovered.

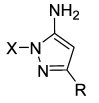
pyrazolo[3,4-*d*]pyrimidine product **17** in 73−97% yields (see entries 2−7 in Table 1).

On treatment with 3.0 equiv of PhCOCl, ClCOCOCl, $SOCl_2$, and TsCl, the reaction gave the corresponding pyrazolo[3,4-*d*]pyrimidine **17** in lower yields (49−68%; see entries 8−11 of Table 1). The unreactive starting material **1** was recovered by using these coupling agents. Following the experimental results, we found that the use of 3.0 equiv of the coupling agent PBr_3 provided the best yield of the desired pyrazolo[3,4-*d*]pyrimidine **17** (>96%; see entries 3 and 6 of Table 1). As a result, a reliable procedure for the new heterocyclization involved the treatment of 5-aminopyrazole **1** with 3.0 equiv of PBr_3 in formamide solution at 60 °C for 0.5−1.0 h. After aqueous workup and purification by column chromatography on silica gel, the corresponding pyrazolo[3,4-*d*]pyrimidine **17** was isolated in excellent yield (97%; see Scheme 1 and Table 1).

On application of the obtained reliable procedure to 5-aminopyrazoles **2**−**11** bearing various N-1-substituents, including *o*-MePh, *o*-ClPh, *m*-MePh, *m*-ClPh, *m*-NO_2Ph, *p*-ClPh, *p*-OMePh, 2-pyridinyl, and 2-quinolinyl, the one-pot heterocyclization also proceeded smoothly to give the corresponding pyrazolo[3,4-*d*]pyrimidines **18**−**27** in 87−97% yields (see Scheme 1 and Table 2). For further investigation of the substitution effect, the same reaction conditions were applied to 5-amino-1-phenyl-3-substituted pyrazoles **12**−**16**, which contained a methyl, *tert*-butyl, *p*-MePh, *p*-ClPh, or *p*-OMePh group at the C-3 position of the pyrazole ring. The reaction also gave the corresponding compounds **28**−**32** in 91−94% yields (see Scheme 1 and Table 2). All pyrazolo[3,4-*d*]pyrimidines **17**−**32** were fully characterized by spectroscopic methods. For example, compound **17** presented two singlet peaks at δ 9.02 and 9.31 ppm for the pyrimidine ring in ^{1}H NMR. In the ^{13}C NMR spectrum, compound **17** possessed characteristic absorptions at δ 155.0 ppm for the pyrimidine carbon N=^{13}CHN=C, at δ 34.4 ppm for −^{13}C(CH$_3$)$_3$, and at δ 30.0 ppm for −C(^{13}CH$_3$)$_3$.

We proposed a plausible mechanism for the sequential three-component heterocyclization reaction as shown in Scheme 2. Formamide first reacted with the coupling agent PBr_3 or $POCl_3$ to form the Vilsmeier reactive species **33** in situ.[18] In the model case, 5-amino-1,3-diphenylpyrazole (**1**) with the reactive species **33** underwent an amidination reaction to give the intermediate **34** (see Scheme 2). Under strongly acidic conditions, amidination intermediate **34** simultaneously reacted with the second equivalent of **33** to perform the electrophilic heteroaromatic substitution and generate imination intermediate **35**. Intramolecular heterocyclization of intermediate **35** consequently took place to generate **36**, which then gave the final product **17** by elimination of the amino group.

Table 2. Results of the One-Pot Synthesis of Pyrazolo[3,4-*d*]pyrimidines from 5-Aminopyrazoles, Formamide, and PBr_3



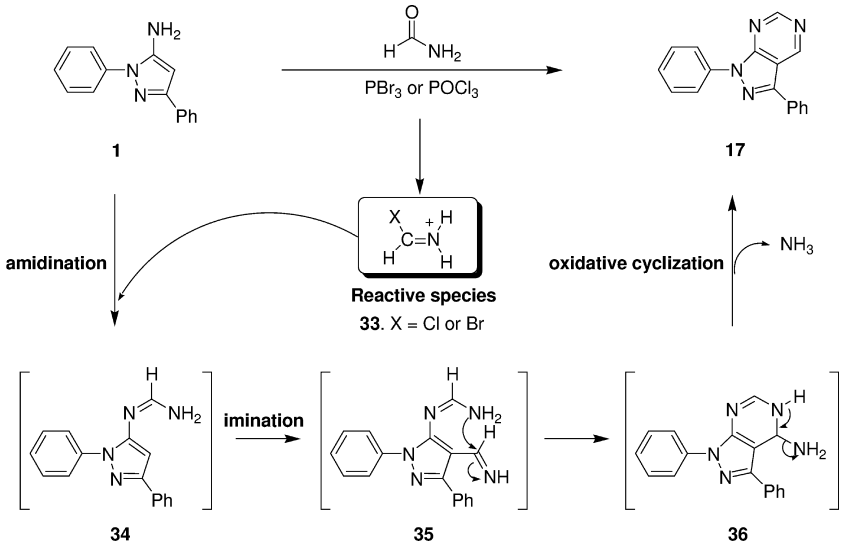
			Pyrazolo[3,4-*d*]pyrimidine (**17**–**32**)	
Substrates	X	R	No.	Yields (%)
1	Ph	Ph	**17**	96
2	*o*-Me-Ph	Ph	**18**	93
3	*o*-Cl-Ph	Ph	**19**	91
4	*m*-Me-Ph	Ph	**20**	92
5	*m*-Cl-Ph	Ph	**21**	96
6	*m*-NO_2-Ph	Ph	**22**	87
7	*p*-Cl-Ph	Ph	**23**	91
8	*p*-Br-Ph	Ph	**24**	95
9	*p*-OMe-Ph	Ph	**25**	89
10	2-Pyridinyl	Ph	**26**	88
11	2-Quinolinyl	Ph	**27**	91
12	Ph	Me	**28**	93
13	Ph	*t*-Bu	**29**	91
14	Ph	*p*-Me-Ph	**30**	93
15	Ph	*p*-Cl-Ph	**31**	91
16	Ph	*p*-OMe-Ph	**32**	94

For further investigation of the reaction mechanism, we prepared the series of pyrazolylimidoformamides **37**−**41**[19] to react with reactive species **33** generated from the reaction of HCHO and PBr_3. The reaction proceeds by an amidination reaction to give the intermediate **42**, which is expected as the chemical synthetic equivalent to **35** (see Scheme 3). We also obtained the corresponding pyrazolo[3,4-*d*]pyrimidines **28**−**32** in 91−97% yields (see Scheme 3 and Table 3). A similar heterocyclization has been reported by Jachak et al., and the spectroscopic data of compound **39** were consistent with those reported by Jachak.[20] As a result, *N*′-[4-(iminomethyl)-1*H*-pyrazol-5-yl]formamidine **35** could be presumed as a important key intermediate in this newly developed heterocyclization reaction.

Investigation of the Electrophilic Aromatic and Heterocyclic Substitution Reactivity. For a further investigation of the electrophilic substitution reactivity in aminobenzene substrates, we applied the same reaction conditions to compounds **43**−**49** with various substituents, including H, *o*-Me, *o*-OMe, *p*-OMe, *o*-F, *m*-F, and *p*-F.

dx.doi.org/10.1021/jo301463m | J. Org. Chem. 2012, 77, 8492−8500

Scheme 2



Scheme 3

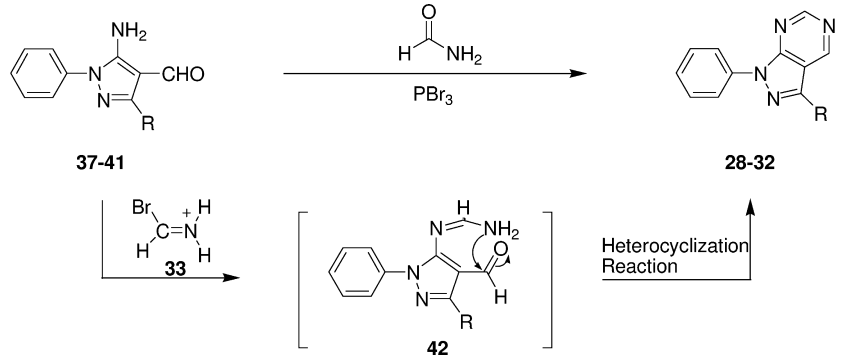
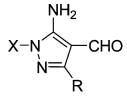


Table 3. Mechanistic Study of the Cyclization of 5-Amino-4-formylpyrazoles 37−41 with Formamide and PBr_3 for Synthesis of Pyrazolo[3,4-*d*]pyrimidines 28−32

Entry				Pyrazolo[3,4-*d*]pyrimidines **28–32**	
	Substrates	X	R	Products	Yields (%)
1	**37**	Ph	Me	**28**	96
2	**38**	Ph	*t*-Bu	**29**	91
3	**39**	Ph	*p*-Me-Ph	**30**	95
4	**40**	Ph	*p*-Cl-Ph	**31**	92
5	**41**	Ph	*p*-OMe-Ph	**32**	97

However, the reaction did not give the desired quinazoline products **60** (see Scheme 5); only *N*,*N*′-bisphenylformamidines **50−56** were obtained in 91−97% yields (see Scheme 4 and Table 4). The spectroscopic data of **50−56** were also consistent with the data reported in the literature.[21] For example, compound **50** presented a singlet peak at δ 8.24 ppm for formamidine in ^{1}H NMR. In the ^{13}C NMR spectrum, compound **50** possessed a characterization absorption at δ 149.5 ppm for the formamidine carbon PhN=^{13}CHNHPh.

Scheme 4

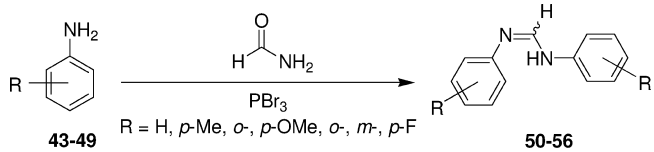
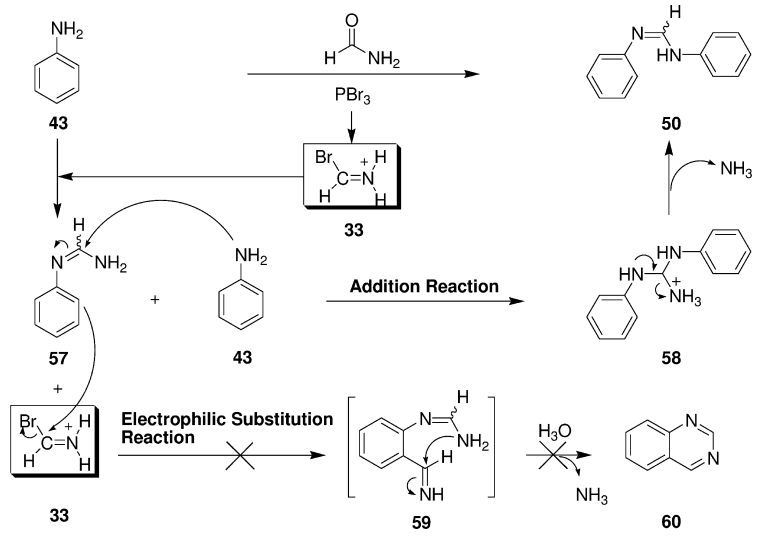


Table 4. Results of the Reactions of Aromatic Amines with Formamide and PBr_3

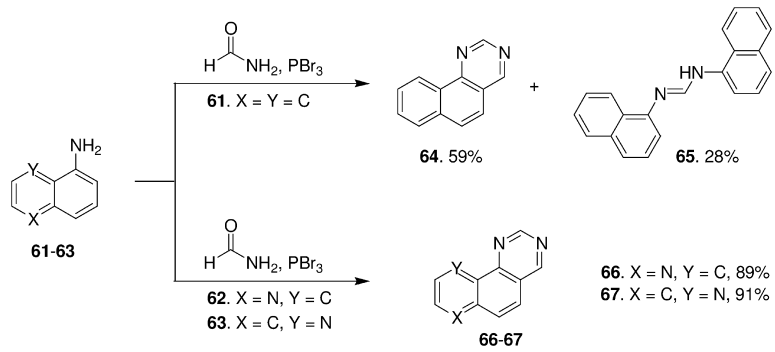
Entry			*N*,*N*′-Bisphenylformamidines **49–55**	
	Substrates	R	Products	Yields (%)
1	**43**	H	**50**	96
2	**44**	*p*-Me	**51**	91
3	**45**	*o*-OMe-Ph	**52**	95
4	**46**	*p*-OMe-Ph	**53**	92
5	**47**	*o*-F-Ph	**54**	91
6	**48**	*m*-F-Ph	**55**	93
7	**49**	*p*-F-Ph	**56**	97

dx.doi.org/10.1021/jo301463m | *J. Org. Chem.* 2012, 77, 8492−8500

Scheme 5



Scheme 6



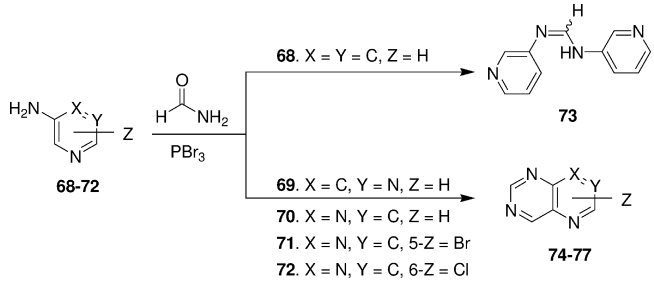
Following the above experimental results, we also proposed a plausible reaction mechanism as shown in Scheme 5 to account for the different reactivities between aminobenzenes and 5-aminopyrazoles. At first, the reaction of formamide with PBr_3 generates the reactive species bromomethyleniminium salts **33** in situ (see Scheme 5).[18] In the model study, aniline **43** was preliminarily reacted with the reactive iminium species **33** to afford the amidination intermediate **57** (see Scheme 5). The addition reaction of amidine intermediate **57** with the second equivalent of aniline **43** then took place to provide the *N*,*N*′-diphenylformamidine product **58**. After workup, the reaction gave the formamidine product **50**. However, the conversion of *N*,*N*′-diphenylformamidine **50** is straightforward without carrying out the electrophilic aromatic substitution reaction (**57** → **59** → **60**).

The difference results between 5-aminopyrazoles **1**−**16** and aminobenzenes **42**−**48** might come from the pyrazole's π-excessive properties which thus make the pyrazole derivatives more reactive than benzene rings toward the electrophilic aromatic substitution reaction.[22] As a result, the expected pyrazolo[3,4-*d*]pyrimidine products were produced. However, benzene is more stable; further electrophilic substitution and oxidative cyclization did not take place to give the expected product quinazoline **60** (see Scheme 5).

Consequently, we applied the reaction conditions to bicyclic aromatic amines such as 1-aminonaphthalene (**61**), 5-aminoquinoline (**62**), and 8-aminoquinoline (**63**) (see Scheme 6). For **62** and **63** as the reactants, only the corresponding heterocyclization pyridoquinazoline products **66** and **67** were obtained in 89% and 91% yields, respectively (see Scheme 6). When 1-aminonaphthalene **61** was used as the substrate under the same conditions, the reaction gave the cyclized benzoquinazoline **64** in 59% yield with the unexpected formamidine product **65** in 28% yield (see Scheme 6). Following the above experimental results, quinolinamines **62** and **63** were more electrophilic than naphthalen-1-amine **61**. Furthermore, the bicyclic aromatic amines **61**−**63** were also found to be more active than aminobenzene in performing the new sequential heterocyclization reaction.

After screening various monocyclic heteroaromatic amines, we selected 3-aminopyridine **68**, 5-aminopyrimidine **69**, and 2-aminopyrazines **70**−**72** as the substrates to study the reaction (see Scheme 7). For the 3-aminopyridine substrate **68**, only the

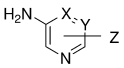
Scheme 7



dx.doi.org/10.1021/jo301463m | *J. Org. Chem.* 2012, 77, 8492−8500

N,*N*′-dipyridinylformamidine product **73** was detected, without the formation of the corresponding cyclization product. Although the electron density of 3-aminopyridine was proved to be superior to that of the benzene ring,[22,23] the heterocyclization did not smoothly take place to give the expected fused pyrimidine product. Treatment of 5-aminopyrimidine **69** and 2-aminopyrazines **71** and **72** with the Vilsmeier reagent **33** successfully afforded the fused pyrimidine products **74**−**77** in good yields (82−89%; see Table 5). Finally,

Table 5. Results of the Reactions of Heterocyclic Amines with Formamide and PBr_3

Entry			*N*,*N*′-Bispyridinylformamidine **73** or the Heteroaromatic-fused Pyrimidine **74**–**77**	
	Substrates	Heterocyclic Amines	Products	Yields (%)
1	**68**	3-Aminopyridine	**73**	88
2	**69**	5-Aminopyrimidine	**74**	86
3	**70**	2-Aminopyrazine	**75**	82
4	**71**	5-Bromo-2-aminopyrazine	**76**	89
5	**72**	6-Chloro-2-aminopyrazine	**77**	87

we found tha tthe phenyl and pyridinyl substrates cannot undergo the new sequential heterocyclization reaction because they possess poor electrophilicity and stable resonance ability.

CONCLUSIONS

We have successfully developed a one-pot multicomponent reaction to prepare pyrazolo[3,4-*d*]pyrimidines or heterocyclic fused pyrimidines by treating 5-aminopyrazoles, 5-aminopyrimidine, 2-aminopyrazines, 5-aminoquinoline, and 8-aminoquinoline with formamide in the presence of PBr_3 as a coupling agent. On the basis of the mechanistic study, *N*′-[4-(iminomethyl)-1*H*-pyrazol-5-yl]formamidine (**59**) was demonstrated to be a key intermediate in this one-pot heterocyclization reaction. When further applying the same reaction conditions to phenyl- and pyridinylamines, we only obtained the unexpected *N*,*N*′-diphenylformamidine products. This was attributed to the fact that benzene and pyridine are more stable and less reactive resonance rings. On the basis of experimental results, the order of electrophilicity was 5-aminopyrazole ≥ 5-aminopyrimidine and 2-aminopyrazines ≥ 5-aminoquinoline and 8-aminoquinoline > 1-aminonaphthalene > 3-aminopyridine > aminobenzenes.

EXPERIMENTAL SECTION

General Procedure. All chemicals were reagent grade and were used as purchased. All reactions were carried out under a nitrogen atmosphere and monitored by TLC analysis. Commercially available reagents were used without further purification unless otherwise noted. ^{1}H NMR spectra were recorded at 200, 400, or 500 MHz, and ^{13}C NMR spectra were recorded at 50, 100, or 125 MHz, respectively, in $CDCl_3$, CH_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 constants (*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. Flash column chromatography purification of compounds was carried out by gradient elution using hexanes in ethyl acetate (EA) unless otherwise stated.

Standard Procedure for Synthesis of Pyrazolo[3,4-*d*]-pyrimidines (17−32, 65, 66, and 73−76). The reliable procedure involved the treatment of 5-aminopyrazoles (**1**−**16**; 1.0 equiv), 5-amino-4-formylpyrazoles (**37**−**41**; 1.0 equiv), 5-aminoquinoline (**61**; 1.0 equiv), 8-aminoquinoline (**62**; 1.0 equiv), 5-aminopyrimidine (**68**; 1.0 equiv), or 2-aminopyrazines (**69**−**71**; 1.0 equiv) with PBr_3 (∼3 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1 h. When the reaction was complete, the reaction mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding aromatic or heterocyclic fused pyrimidine products (**17**−**32**, **65**, **66**, and **73**−**76**) in 82−96% yields.

1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidine (17).[24] The standard procedure involved the treatment of 5-amino-1,3-diphenyl-1*H*-pyrazole (**1**; 100 mg, 0.37 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.1 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **17**: 96% yield (96 mg), light yellow solid; mp 157−158 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29−7.36 (1H, m), 7.41−7.48 (1 h, m), 7.48−7.56 4H, m), 7.97−8.07 (2H, m), 8.25−8.35 (2H, m), 9.09 (1H, s), 9.45 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.1, 121.2 (2 × C), 126.7, 127.2 (2 × C), 129.0 (2 × C), 129.1 (2 × C), 129.5, 131.4, 138.5, 144.8, 152.7, 153.2, 155.5. IR (KBr): 2364, 2331, 1589, 1498, 1417, 1369, 1219, 1093 cm^{-1}. EIMS *m*/*z* (rel int): 272 (100, M^+). Anal. Calcd for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.96; H, 4.45; N, 20.61.

1-(2-Methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (18). The standard procedure involved the treatment of 5-amino-1-(2-methylphenyl)-3-phenyl-1*H*-pyrazole (**2**; 101 mg, 0.35 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.1 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **18**: 93% yield (93 mg), light yellow solid; mp 142−143 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.21 (3H, s), 7.33−7.43 (3H, m), 7.44−7.50 (2H, m), 7.51−7.57 (2H, m), 8.02−8.08 (2H, m), 9.05 (1H, s), 9.53 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.2, 112.8, 126.7, 127.2 (2 × C), 127.6, 129.2 (2 × C), 129.5 (2 × C), 131.4, 131.7, 135.5, 136, 144.9, 152.8, 154.1, 155.8. IR (KBr): 3053, 2922, 2360, 2339, 1579, 1556, 1498, 1222, 1085 cm^{-1}. EIMS *m*/*z* (rel int): 286 (100, M^+). Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.53; H, 4.92; N, 19.58.

1-(2-Chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (19). The standard procedure involved the treatment of 5-amino-1-(2-chlorophenyl)-3-phenyl-1*H*-pyrazole (**3**; 99 mg, 0.32 mmol, 1.0 equiv) with PBr_3 (0.09 mL, 0.97 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **19**: 91% yield (89 mg), yellow solid; mp 142−143 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43−7.49 (3H, m), 7.50−7.56 (2H, m), 7.57−7.65 (2H, m), 8.02−8.08 (2H, m), 9.07 (1H, s), 9.52 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 122.9, 127.3 (2 × C), 127.6, 129.2 (2 × C), 129.6 (2 × C), 130.7 (2 × C), 131.4, 132.1, 134.7, 145.6, 152.8, 154.5, 155.9. IR (KBr): 3061, 2924, 2370, 2349, 1581, 1557, 1516, 1497, 1304, 1223, 1088 cm^{-1}. EIMS *m*/*z* (rel int): 306 (89, M^+). Anal. Calcd for $C_{17}H_{11}ClN_4$: C, 66.56; H, 3.61; N, 18.26. Found: C, 66.59; H, 3.58; N, 18.22.

1-(3-Methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (20). The standard procedure involved the treatment of 5-amino-1-(3-methylphenyl)-3-phenyl-1*H*-pyrazole (**4**; 103 mg, 0.36 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.1 mmol, 3 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **20**: 92% yield (94 mg), light yellow solid; mp 75−76 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.47 (3H, s), 7.12−7.18 (1H, m), 7.38−7.42 (1H, m), 7.43−7.49 (1H, m), 7.50−

dx.doi.org/10.1021/jo301463m | J. Org. Chem. 2012, 77, 8492−8500

7.56 (2H, m), 8.00−8.06 (2H, m), 8.07−8.11 (2H, m), 9.10 (1H, s), 9.46 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 114.1, 118.6, 122.0, 127.3 (2 × C), 127.6 (2 × C), 129.0, 129. (2 × C), 129.5, 131.5, 138.3, 139.2, 144.7, 152.7, 153.2, 155.5. IR (KBr): 3053, 2920, 1611, 1582, 1557, 1495, 1386, 1229, 1094 cm^{-1}. EIMS m/z (rel int): 286 (100, M$^+$). Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.54; H, 4.96; N, 19.53.

1-(3-Chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**21**). The standard procedure involved the treatment of 5-amino-1-(3-chlorophenyl)-3-phenyl-1*H*-pyrazole (**5**; 101 mg, 0.33 mmol, 1.0 equiv) with PBr_3 (0.09 mL, 0.99 mmol, 3 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **21**: 96% yield (97 mg), yellow solid; mp 188−189 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27−7.33 (1H, m), 7.43−7.48 (1H, m), 7.48−7.52 (1H, m), 7.53−7.59 (2H, m), 8.01−8.07 (2H, m), 8.32−8.36 (1H, m), 8.42−8.44 (1H, m), 9.14 (1H, s), 9.50 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.5, 118.9, 121.1, 126.6, 127.4 (2 × C), 129.3 (2 × C), 129.9, 130.2, 131.2, 135.0, 139.6, 145.4, 152.9, 153.6, 155.8. IR (KBr): 3099, 3062, 2922, 2851, 1585, 1491, 1406, 1215 cm^{-1}. EIMS m/z (rel int): 306 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}ClN_4$: C, 66.56; H, 3.61; N, 18.26. Found: C, 66.58; H, 3.62; N, 18.29.

1-(3-Nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**22**). The standard procedure involved the treatment of 5-amino-1-(3-nitrophenyl)-3-phenyl-1*H*-pyrazole (**6**; 98 mg, 0.31 mmol, 1.0 equiv) with PBr_3 (0.09 mL, 0.92 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **22**: 93% yield (93 mg), brown solid; mp 183−184 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50−7.61 (3H, m), 7.67−7.73 (1H, m), 8.02−8.10 (2H, m), 8.14−8.20 (1H, m), 8.81−8.87 (1H, m), 9.18 (1H, s), 9.31−9.35 (1H, m), 9.52 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.7, 115.6, 120.8, 126.0, 127.5 (2 × C), 129.3 (2 × C), 130.1, 130.1, 130.8, 139.6, 146.0, 148.8, 153.1, 154.0, 156.0. IR (KBr): 2924, 2348, 1531, 1431, 1416, 1343, 1215, 1092 cm^{-1}. EIMS m/z (rel int): 317 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}N_5O_2$: C, 64.35; H, 3.49; N, 22.07. Found: C, 64.37; H, 3.51; N, 22.03.

1-(4-Chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**23**). The standard procedure involved the treatment of 5-amino-1-(4-chlorophenyl)-3-phenyl-1*H*-pyrazole (**7**; 106 mg, 0.35 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.0 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **23**: 91% yield (97 mg), yellow solid; mp 144−145 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46−7.52 (3H, m), 7.52−7.58 (2H, m), 8.00−8.06 (2H, m), 8.29−8.35 (2H, m), 9.12 (1H, s), 9.49 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.3, 122.2 (2 × C), 127.4 (2 × C), 129.2 (2 × C), 129.3 (2 × C), 129.8, 131.3, 132.1, 137.2, 145.2, 152.9, 153.4, 155.7. IR (KBr): 3051, 2922, 2851, 2384, 2349, 1589, 1554, 1406, 1367, 1215 cm^{-1}. EIMS m/z (rel int): 306 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}ClN_4$: C, 66.56; H, 3.61; N, 18.26. Found: C, 66.53; H, 3.58; N, 18.23.

1-(4-Bromophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**24**). The standard procedure involved the treatment of 5-amino-1-(4-bromophenyl)-3-phenyl-1*H*-pyrazole (**8**; 102 mg, 0.29 mmol, 1.0 equiv) with PBr_3 (80 μL, 0.87 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **24**: 95% yield (96 mg), yellow solid; mp 176−177 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45−7.57 (3H, m), 7.60−7.66 (2H, m), 7.98−8.06 (2H, m), 8.21−8.29 (2H, m), 9.10 (1H, s), 9.47 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.3, 120.0, 122.4 (2 × C), 127.3 (2 × C), 129.2 (2 × C), 130.0, 131.2, 132.2 (2 × C), 137.6, 145.2, 152.8, 153.4, 155.6. IR (KBr): 2374, 2347, 1585, 1495, 1398, 1389, 1215, 1072 cm^{-1}. EIMS m/z (rel int): 350 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}BrN_4$: C, 58.14; H, 3.16; N, 15.95. Found: C, 58.16; H, 3.18; N, 15.91.

1-(4-Methoxylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**25**). The standard procedure involved the treatment of 5-amino-1-(4-methoxylphenyl)-3-phenyl-1*H*-pyrazole (**9**; 104 mg, 0.34 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.0 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **25**: 89% yield (91 mg), yellow solid; mp 149−150 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.84 (3H, s), 7.00−7.06 (2H, m), 7.42−7.48 (1H, m), 7.50−7.54 (2H, m), 7.99−8.05 (2H, m), 8.09−8.13 (2H, m), 9.10 (1H, s), 9.45 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5, 113.8, 114.3 (2 × C), 123.1 (2 × C), 127.2 (2 × C), 129.1 (2 × C), 129.4, 131.5, 131.6, 144.5, 152.7, 152.8, 155.4, 158.4. IR (KBr): 3053, 2836, 2347, 1580, 1555, 1514, 1416, 1366, 1250, 1219, 1177, 1088, 1034 cm^{-1}. EIMS m/z (rel int): 302 (100, M$^+$). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.49; H, 4.71; N, 18.51.

3-Phenyl-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**26**). The standard procedure involved the treatment of 5-amino-3-phenyl-1-(pyridin-2-yl)-1*H*-pyrazole (**10**; 97 mg, 0.36 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.1 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **26**: 88% yield (84 mg), yellow solid; mp 206−207 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30−7.22 (1H, m), 7.55−7.41 (3H, m), 7.91−7.83 (1H, m), 8.05−7.99 (2H, m), 8.26−8.20 (1H, m), 8.70−8.66 (1H, m), 9.19 (1H, s), 9.47 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114, 116, 122, 128 (2 × C), 129 (2 × C), 130, 131, 139, 146, 149, 151, 153, 154, 156. IR (KBr): 3049, 2920, 2851, 2380, 2349, 1593, 1481, 1452, 1368, 1265, 1219, 1080 cm^{-1}. EIMS m/z (rel int): 273 (100, M$^+$). Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.32; H, 4.06; N, 25.63. Found: C,70.28; H, 4.09; N, 25.66.

3-Phenyl-1-(quinolin-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (**27**). The standard procedure involved the treatment of 5-amino-3-phenyl-1-(quinolin-2-yl)-1*H*-pyrazole (**11**; 101 mg, 0.31 mmol, 1.0 equiv) with PBr_3 (90 μL, 0.94 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **27**: 93% yield (91 mg), yellow solid; mp 194−195 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59−7.49 (4H, m), 7.79−7.75 (1H, m), 7.87−7.89 (1H, m), 8.13−8.11 (2H, m), 8.37−8.39 (1H, m), 8.47−8.49 (1H, m), 9.26 (1H, s), 9.55 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.9, 115.6, 126.8, 127.2, 127.5, 127.8 (2 × C), 129.2 (2 × C), 129.5, 130.4, 131.2, 139.0, 146.6, 147.0, 149.8, 153.0, 154.4, 156.4. IR (KBr): 3055, 2376, 2347, 1582, 1557, 1502, 1477, 1409, 1368, 1325, 1219, 1090 cm^{-1}. EIMS m/z (rel int): 323 (100, M$^+$). Anal. Calcd for $C_{20}H_{13}N_5$: C, 74.29; H, 4.05; N, 21.66. Found: C, 74.33; H, 3.98; N, 21.61.

3-Methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**28**).[24] The standard procedure involved the treatment of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole (**12**; 103 mg, 0.49 mmol, 1.0 equiv) with PBr_3 (0.14 mL, 1.5 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **28**: 93% yield (96 mg), light yellow solid; mp 79−80 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.63 (3H, s), 7.23−7.29 (1H, m), 7.42−7.50 (2H, m), 8.13−8.19 (2H, m), 9.02 (1H, s), 9.10 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4, 115.6, 120.8 (2 × C), 126.3, 129.1 (2 × C), 138.4, 143.2, 151.6, 152.6, 155.5. IR (KBr): 3051, 2922, 2852, 1593, 1562, 1508, 1440, 1355, 1211, 1066 cm^{-1}. EIMS m/z (rel int): 210 (100, M$^+$). Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.58; H, 4.76; N, 26.61.

3-tert-Butyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**29**). The standard procedure involved the treatment of 5-amino-3-*tert*-butyl-1-phenyl-1*H*-pyrazole (**13**; 108 mg, 0.43 mmol, 1.0 equiv) with PBr_3 (0.12 mL, 1.3 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **29**: 91% yield (99 mg), light yellow solid; mp 48−49 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.55 (9H, s), 7.23−7.29 (1H, m), 7.44−7.52 (2H, m), 8.19−8.12 (2H, m), 9.02 (1H, s), 9.31

dx.doi.org/10.1021/jo301463m | J. Org. Chem. 2012, 77, 8492−8500

(1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.3 (3 × C), 34.4, 114.0, 121.0 (2 × C), 126.2, 129.0 (2 × C), 138.6, 152.8, 153.1, 154.8, 155.0. IR (KBr): 3049, 2968, 2666, 1599, 1578, 1555, 1508, 1427, 1366, 1261, 1098 cm^{-1}. EIMS m/z (rel int): 252 (44, M$^+$). Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.43; H, 6.35; N, 22.17.

*3-(4-Methylphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**30**).* The standard procedure involved the treatment of 5-amino-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazole (**14**; 102 mg, 0.36 mmol, 1.0 equiv) with PBr_3 (0.10 mL, 1.1 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **30**: 93% yield (96 mg), light yellow solid; mp 139−140 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (3H, s), 7.32−7.42 (3H, m), 7.51−7.61 (2H, m), 7.86−8.02 (2H, m), 8.24−8.38 (2H, m), 9.11 (1H, s), 9.47 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 114.2, 121.3 (2 × C), 126.7, 127.2 (2 × C), 128.7, 129.2 (2 × C), 129.9 (2 × C), 138.5, 139.8, 145.0, 152.8, 153.3, 155.5. IR (KBr): 3030, 2920, 2374, 2349, 2313, 1584, 1503, 1430, 1368, 1220 cm^{-1}. EIMS m/z (rel int): 286 (100, M$^+$). Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.49; H, 4.91; N, 19.55.

*3-(4-Chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**31**).*[25] The standard procedure involved the treatment of 5-amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole (**15**; 99 mg, 0.32 mmol, 1.0 equiv) with PBr_3 (90 μL, 0.97 mmol, 3 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **31**: 91% yield (89 mg), light yellow solid; mp 196−197 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34−7.38 (1H, m), 7.48−7.58 (m, 4 H, ArH), 7.96−8.02 (2H, m), 8.24−8.30 (2H, m), 9.12 (1H, s), 9.46 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 114.0, 121.5 (2 × C), 127.0, 128.5 (2 × C), 129.3 (2 × C), 129.5 (2 × C), 130.0, 135.7, 138.4, 143.8, 152.6, 153.3, 155.7. IR (KBr): 3043, 2926, 2848, 1585, 1368, 1219, 1093 cm^{-1}. EIMS m/z (rel int): 306 (100, M$^+$). Anal. Calcd for $C_{17}H_{11}ClN_4$: C, 66.56; H, 3.61; N, 18.26. Found: C, 66.53; H, 3.62; N, 18.29.

*3-(4-Methoxylphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**32**).* The standard procedure involved the treatment of 5-amino-3-(4-methoxylphenyl)-1-phenyl-1*H*-pyrazole (**16**; 101 mg, 0.33 mmol, 1.0 equiv) with PBr_3 (90 μL, 1.0 mmol, 3 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **32**: 94% yield (94 mg), yellow solid; mp 175−176 °C (hexane−EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (3H, s), 7.08−7.84 (2H, m), 7.32−7.36 (1H, m), 7.50−7.56 (2H, m), 7.95−8.01 (2H, m), 8.28−8.32 (2H, m), 9.10 (1H, s), 9.45 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.4 (CH_3), 114.2, 114.6 (2 × C), 121.3 (2 × C), 124.1, 126.7, 128.7 (2 × C), 129.2 (2 × C), 138.6, 144.8, 152.8, 153.2, 155.5, 160.8. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 302 (100, M$^+$). Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.48; H, 4.68; N, 18.50.

*Pyrido[2,3-h]quinazoline (**66**).*[26] The standard procedure involved the treatment of 5-aminoquinoline (**62**; 101 mg, 0.85 mmol, 1.0 equiv) with PBr_3 (0.24 mL, 2.5 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **66**: 59% yield (91 mg), light yellow solid; mp 125−126 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.23−7.29 (1H, m), 7.57−7.61 (1H, m), 7.82−7.86 (1H, m), 7.98−8.02 (1H, m), 8.79−8.83 (1H, m), 9.13 (1H, s), 9.18 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 119.8, 123.2, 125.9 (2 × C), 126.6, 131.1, 134.4, 148.2 (2 × C), 153.8, 155.2. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 181 (100, M$^+$). Anal. Calcd for $C_{11}H_7N_3$: C, 72.92; H, 3.89; N, 23.19. Found: C, 72.89; H, 3.92; N, 23.16.

*Pyrido[3,2-h]quinazoline (**67**).*[27] The standard procedure involved the treatment of 8-aminoquinoline (**63**; 97 mg, 0.81 mmol, 1.0 equiv) with PBr_3 (0.23 mL, 2.4 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **67**: 91% yield (133 mg), light yellow solid; mp 171−172 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.13−7.19 (1H, m), 7.46−7.51 (1H, m), 7.72−7.76 (1H, m), 7.82−7.86 (1H, m), 8.69−8.73 (1H, m), 9.12 (1H, s), 9.17 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 119.3, 124.8, 126.6 (2 × C), 127.1, 133.8, 148.4, 152.3, 154.7. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 181 (100, M$^+$). Anal. Calcd for $C_{11}H_7N_3$: C, 72.92; H, 3.89; N, 23.19. Found: C, 72.88; H, 3.86; N, 23.22.

*Pyrimido[5,4-d]pyrimidine (**74**).*[28] The standard procedure involved the treatment of 5-aminopyrimidine (**69**; 51 mg, 0.65 mmol, 1.0 equiv) with PBr_3 (0.18 mL, 2.0 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **74**: 86% yield (74 mg), light yellow solid; mp 126−127 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.53 (1H, s), 8.61 (1H, s), 9.12 (1H, s), 9.18 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.7 (2 × C), 156.2, 156.6, 158.7, 159.1. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 132 (100, M$^+$). Anal. Calcd for $C_6H_4N_4$: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.51; H, 3.02; N, 42.37.

*Pyrazino[2,3-d]pyrimidine (**75**).*[29] The standard procedure involved the treatment of 2-aminopyrazine (**70**; 53 mg, 0.56 mmol, 1.0 equiv) with PBr_3 (0.16 mL, 1.7 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **75**: 82% yield (61 mg), light yellow solid; mp 136−137 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.47 (2H, m), 8.73 (1H, s, ArH), 9.14 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.7, 142.5 (2 × C), 149.8, 155.9, 158.2. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 132 (100, M$^+$). Anal. Calcd for $C_6H_4N_4$: C, 54.54; H, 3.05; N, 42.41. Found: C, 54.53; H, 3.06; N, 42.43.

*6-Bromopteridine (**76**).* The standard procedure involved the treatment of 5-bromo-2-aminopyrazine (**71**; 48 mg, 0.51 mmol, 1.0 equiv) with PBr_3 (0.14 mL, 1.5 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **76**: 89% yield (95 mg), yellow solid; mp 102−103 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.96 (1H, s, ArH), 9.98 (1H, s, ArH), 10.17 (1H, s, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.3, 146.2, 148.1, 155.3, 160.1, 164.6. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 209 (98, M$^+$). Anal. Calcd for $C_6H_3BrN_4$: C, 34.15; H, 1.43; N, 26.55. Found: C, 34.17; H, 1.41; N, 26.58.

*7-Chloropteridine (**77**).*[30] The standard procedure involved the treatment of 6-chloro-2-aminopyrazine (**72**; 48 mg, 0.53 mmol, 1.0 equiv) with PBr_3 (0.15 mL, 1.6 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **77**: 87% yield (77 mg), light yellow solid; mp 96−97 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.96 (1H, s), 9.98 (1H, s), 10.17 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.3, 146.2, 148.1, 155.3, 160.1, 164.6. IR (KBr): 3047, 2924, 1612, 1582, 1503, 1431, 1356, 1254, 1219, 1092 cm^{-1}. EIMS m/z (rel int): 166 (100, M$^+$). Anal. Calcd for $C_6H_3C1N_4$: C, 43.26; H, 1.82; N, 33.64. Found: C, 43.28; H, 1.81; N, 33.61.

Standard Procedure for Synthesis of *N,N′*-Diarylformamidines (50−56 and 73). The reliable procedure involved the treatment of arylamines (**43−49**; 1.0 equiv) or 3-aminopyridine (**68**; 1.0 equiv) with PBr_3 (~3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. When the reaction was complete, the crude solid was triturated in cold *n*-pentane and filtered through a glass frit with suction. Then the solid was washed with *n*-pentane and dried in vacuo to give the crude formamidines (**50−56** and **73**). The crude products were recrystallized from the mixture of acetone and diisopropyl ether to give the corresponding *N,N′*-diarylformamidine products (**50−56** and **73**) in 88−97% yields as white to light yellow solids.

*N,N′-Diphenylformamidine (**50**)*..[20,31] The standard procedure involved the treatment of aniline (**43**; 51 mg, 0.55 mmol, 1.0 equiv) with PBr_3 (0.16 mL, 1.7 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **50**: 96% yield (103 mg), light yellow solid; mp 138−139 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09−7.42 (10H, m), 8.24 (1H, s), 8.86 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 119.1, 123.3, 129.3, 145.2, 149.5. IR (KBr): 3048, 2965, 1671, 1659, 1598, 1572, 1493, 1439, 1320, 1205, 1169 cm^{-1}. EIMS *m*/*z* (rel int): 196 (100, M$^+$). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.59; H, 6.13; N, 14.22.

*N,N′-Bis(4-methylphenyl)formamidine (**51**)*.[32] The standard procedure involved the treatment of 4-toluidine (**44**; 47 mg, 0.44 mmol, 1.0 equiv) with PBr_3 (0.12 mL, 1.3 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **51**: 91% yield (90 mg), light yellow solid; mp 140−141 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.28 (3H, s), 2.30 (3H, s), 6.99−6.93 (2H, m), 7.14−7.06 (4H, m), 7.43−7.37 (2H, m), 8.29 (1H, s), 8.91 (1H, m) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7, 20.8, 119.0 (2 × C), 120.0 (2 × C), 129.4 (2 × C), 130.0 (2 × C), 134.2, 134.3, 135.0, 159.3, 163.1. IR (KBr): 3106, 2953, 2835, 1653, 1583, 1495, 1459, 1296, 1243, 1200, 1175, 1113, 1026, 996, 743 cm^{-1}. EIMS *m*/*z* (rel int): 256 (31, M$^+$). Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.29; H, 7.16; N, 12.51.

*N,N′-Bis(2-methoxyphenyl)formamidine (**52**)*..[20,33] The standard procedure involved the treatment of 2-anisidine (**45**; 51 mg, 0.41 mmol, 1.0 equiv) with PBr_3 (0.12 mL, 1.2 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **52**: 95% yield (100 mg), yellow solid; mp 82−84 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.67 (6H, s), 7.04−6.86 (8H, m), 7.95 (1H, s), 8.22 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.6, 56.2, 110.9, 117.1 (2 × C), 121.0 (2 × C), 123.3 (2 × C), 134.5 (2 × C), 147.2, 150.1, 159.6, 162.7. IR (KBr): 3315, 3126, 3037, 2987, 2889, 2813, 1664, 1591, 1459, 1300, 1236, 1021 cm^{-1}. EIMS *m*/*z* (rel int): 256 (31, M$^+$). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.33; H, 6.31; N, 10.96.

*N,N′-Bis(4-methoxyphenyl)formamidine (**53**)*.[34] The standard procedure involved the treatment of 4-anisidine (**46**; 49 mg, 0.40 mmol, 1.0 equiv) with PBr_3 (0.11 mL, 1.2 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **53**: 92% yield (94 mg), yellow solid; mp 118−119 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.66 (6H, s), 6.54−7.26, (8H, m), 7.89 (1H, s), 8.07 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.9, 57.8, 114.9, 115.2, 118.3 (2 × C), 124.3 (2 × C), 135.2 (2 × C), 139.8 (2 × C), 149.5, 160.1, 163.7. IR (KBr): 3313, 3136, 3022, 2991, 2886, 2804, 1675, 1577, 1465, 1301, 1247, 1036 cm^{-1}. EIMS *m*/*z* (rel int): 256 (51, M$^+$). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.26; H, 6.32; N, 10.91.

*N,N′-Bis(2-fluorohenyl)formamidine (**54**)*.[35] The standard procedure involved the treatment of 2-fluoroaniline (**47**; 51 mg, 0.53 mmol, 1.0 equiv) with PBr_3 (0.15 mL, 1.6 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **54**: 91% yield (112 mg), yellow oil (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.42−6.46 (1H, m), 6.57−6.61 (1H, m), 6.70−6.76 (2H, m), 7.08−7.12 (2H, m), 7.21−7.25 (2H, m), 7.61 (1H, s), 7.92 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 114.3, 116.3, 118.4, 125.5, 124.4 (2 × C), 127.9 (2 × C), 128.1, 137.5, 153.9, 156.1, 162.8. IR (KBr): 3127, 2951, 2847, 1637, 1561, 1494, 1456, 1277, 1232, 1207, 1175, 1121, 1038 cm^{-1}. EIMS *m*/*z* (rel int): 232 (100, M$^+$). Anal. Calcd for $C_{13}H_{10}F_2N_2$: C, 67.24; H, 4.32; N, 12.06. Found: C, 67.22; H, 4.31; N, 12.01.

*N,N′-Bis(3-fluorophenyl)formamidine (**55**)*.[35] The standard procedure involved the treatment of 3-fluoroaniline (**48**; 50 mg, 0.52 mmol, 1.0 equiv) with PBr_3 (0.15 mL, 1.6 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **55**: 93% yield (108 mg), yellow oil (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.22−6.28 (2H, m), 6.32−6.36 (1H, m), 7.14−7.18 (4H, m), 7.25−7.29 (1H, m), 7.48 (1H, s), 8.01 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 103.6, 106.5, 109.1, 111.8, 113.9, 118.6, 130.8 (2 × C), 143.6, 150.8, 163.0, 164.8, 165.2. IR (KBr): 3132, 2968, 2827, 1655, 1574, 1481, 1466, 1280, 1257, 1214, 1169, 1109, 1017 cm^{-1}. EIMS *m*/*z* (rel int): 232 (100, M$^+$). Anal. Calcd for $C_{13}H_{10}F_2N_2$: C, 67.24; H, 4.32; N, 12.06. Found: C, 67.20; H, 4.36; N, 12.02.

*N,N′-Bis(4-fluorophenyl)formamidine (**56**)*.[35] The standard procedure involved the treatment of 4-fluoroaniline (**49**; 49 mg, 0.51 mmol, 1.0 equiv) with PBr_3 (0.14 mL, 1.5 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **56**: 97% yield (115 mg), yellow solid; mp 142−144 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09−6.96 (8H, m), 8.02 (1H, s), 9.61 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.8, 1573.0, 150.2, 141.2, 120.5, 120.4, 116.2, 115.8. IR (KBr): 3428, 2928, 2862, 1671, 1603, 1502, 1380, 1313, 1202 cm^{-1}. EIMS *m*/*z* (rel int): 236 (100, M$^+$). Anal. Calcd for $C_{13}H_{10}F_2N_2$: C, 67.24; H, 4.32; N, 12.06. Found: C, 67.23; H, 4.34; N, 12.07.

*Pyrido[3,4-d]pyrimidine (**73**)*. The standard procedure involved the treatment of 3-aminopyridine (**68**; 52 mg, 0.55 mmol, 1.0 equiv) with PBr_3 (0.16 mL, 1.7 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **73**: 88% yield (96 mg), yellow solid; mp 130−131 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.24−7.28 (1H, m), 8.47−8.53 2H, m), 8.69 (1H, s), 9.12 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 115.3, 120.6, 139.7, 147.9, 148.2, 155.3, 156.4. IR (KBr): 3106, 2953, 2835, 1653, 1583, 1495, 1459, 1296, 1243, 1200, 1175, 1113, 1026 cm^{-1}. EIMS *m*/*z* (rel int): 198 (100, M$^+$). Anal. Calcd for $C_{11}H_{10}N_4$: C, 66.65; H, 5.08; N, 28.26. Found: C, 66.63; H, 5.04; N, 28.27.

Standard Procedure for Synthesis of Benzo[*h*]quinazoline (64) and *N,N′*-Dinaphthalenylformamidine (65). The reliable procedure involved the treatment of 1-aminonaphthalene (**61**; 1.0 equiv) with PBr_3 (∼3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. When the reaction was complete, the reaction mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding benzo[*h*]quinazoline as the major product (**64**) in 59% yield and *N,N′*-dinaphthalenylformamidine (**65**) as the minor product in 28% yield.

*Benzo[h]quinazoline (**64**)*.[37] The standard procedure involved the treatment of 1-naphthylamine (**61**; 99 mg, 0.79 mmol, 1.0 equiv) with PBr_3 (0.22 mL, 2.4 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **64**: 59% yield (84 mg), light yellow solid; mp 101−102 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.48 (1H, s), 9.31 (1H, s), 9.23 (1H, m), 7.84 (1H, m), 7.76 (1H, m), 7.71 − D;7.68 (2H, m), 7.59 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.8, 153.2, 148.5, 135.3, 133.0, 128.1, 127.9 (2 × C), 127.3 (2 × C), 125.9, 125.9. EIMS *m*/*z* (rel int): 180 (100, M$^+$). Anal. Calcd for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.55. Found: C, 79.93; H, 4.43; N, 15.57.

*N,N′-Dinaphthalenylformamidine (**65**)*.[31] The standard procedure involved the treatment of 1-naphthylamine (**61**; 99 mg, 0.79 mmol, 1.0 equiv) with PBr_3 (0.22 mL, 2.4 mmol, 3.0 equiv) in formamide solution (2 mL) at 50−60 °C over 0.5−1.0 h. The reaction mixture was then worked up, and the residue was purified by chromatography on silica gel to give pure **65**: 28% yield (65 mg), light yellow solid; mp 202−203 °C (CH_2Cl_2−methanol). ^{1}H NMR ($CDCl_3$, 200 MHz): δ

dx.doi.org/10.1021/jo301463m | J. Org. Chem. 2012, 77, 8492−8500

7.19−7.06 (6H, m), 7.41−7.30 (4H, m), 8.30 (1H, s), 9.97 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 121.0, 123.3, 132.5, 147.2, 150.0. IR (KBr): 3241, 1659, 1578, 1391, 1296, 1210 cm^{-1}. EIMS m/z (rel int): 296 (31, M^+). Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.13; H, 5.46; N, 9.47.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR and ^{13}C NMR spectra for products **17**−**32**, **54**, **55**, **66**, **73**, and **77**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Council of Republic of China for financial support (NSC-99-2320-B-039-014-MY3). This study was also supported in part by the Taiwan Department of Health Clinical Trial and Research Center of Excellence (DOH100-TD-B-111-004).

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