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Copper-Catalyzed Cascade Reaction of 4-Iodopyrazole Derivatives with Amidines for the Synthesis of Pyrazolo[4,3-*d*]pyrimidine Derivatives[‡]

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Keywords: Synthetic methods / Nitrogen heterocycles / Copper / C-N coupling

An efficient copper-catalyzed cascade reaction of 4-iodopyrazolecarbaldehydes and 4-iodopyrazolecarboxamides with substituted amidines for the preparation of substituted pyrazolo[4,3-*d*]pyrimidines and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones, respectively, is described.

Introduction

Research on pyrazole chemistry is currently in focus because of its potential application to a range of spheres including agricultural, pharmaceutical, polymers, food, cosmetics, and liquid crystals.[1] A recent review article by Fustero et al.[1a] vividly describes the diverse synthetic routes available to accomplish the synthesis of pyrazole and its derivatives. A noticeable feature in the compilation is that, although C–C coupling reactions at the 3, 4, or 5 positions in pyrazole are widely reported, no C–N cross-coupling reactions are known for these positions. Indeed, C–N coupling in pyrazoles is limited to Ullman type coupling involving the free NH of the pyrazole. An earlier review by Stanetty et al. also noted the C–N coupling reaction in pyrazole only at the nitrogen atom of the ring.[2] Intrigued by this observation, we initiated a project in which we focussed on probing approaches that enable C–N cross-coupling reactions at the 4-position by employing substituted 4-iodopyrazoles as the starting material. To this end, we have achieved considerable success. For example, we have demonstrated that amides derived from the Morita–Baylis–Hillman (MBH) adducts of 4-iodopyrazolecarbaldehyde undergo copper-catalyzed intramolecular Goldberg-type C–N coupling to afford substituted pyrazolo[4,3-*b*]pyridin-5-ones, whereas the allylamines obtained from the MBH adducts undergo Ullman-type C–N coupling to afford substituted pyrazolo[4,3-*b*]pyridines.[3,4] In addition, we successfully synthesized pyrazolo-fused benzodiazepines and benzoxazoazepines through copper-mediated C–N and C–O cross-coupling cascade reactions of 4-iodopyrazolecarbaldehydes with 1,2-phenylenediamines and 2-aminophenols, respectively.[5] However, interestingly, during the study we discovered that only intramolecular C–N and C–O couplings could be performed; the intermolecular version resulted in failure. Continuing with an exploration of other possibilities for C–N couplings, we reasoned that substituted amidines would also react with 4-iodopyrazolecarbaldehydes to afford substituted pyrazolo[4,3-*d*]pyrimidines

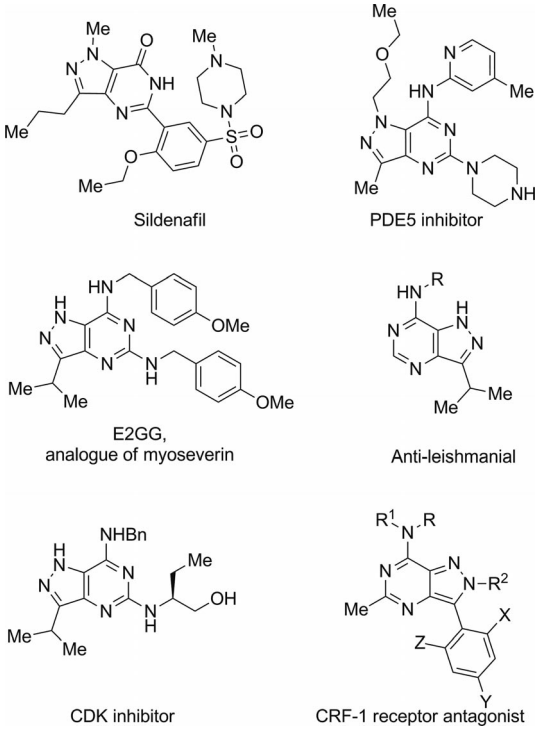

Figure 1. Some of the biologically active compounds incorporating the pyrazolo[4,3-*d*]pyrimidine core.

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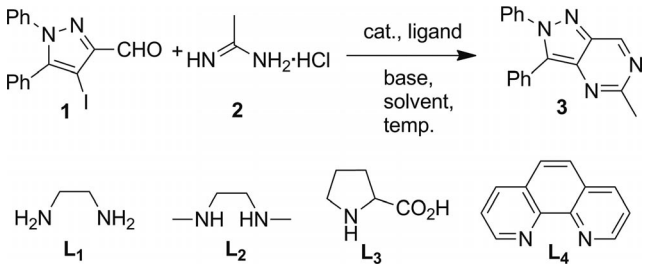
through a cascade reaction involving initial Schiff base formation followed by intramolecular Ullman type C–N coupling reaction. It may be noted that Huang et al.[6] have reported analogous coupling reactions with 2-halobenzaldehydes. Substituted pyrazolo[4,3-*d*]pyrimidines are of significant pharmaceutical importance because they display a variety of bioactivities including anticancer, PDE5 inhibition, antileishmanial, adenosine A_3 receptor antagonist, corticotropin-releasing factor (CRF-1) antagonist and cannabinoid receptor ligand binding (Figure 1).[7] For these reasons, several elegant methods for the preparation of substituted pyrazolo[4,3-*d*]pyrimidines have been reported in the literature, but, to the best of our knowledge, no route involving copper-mediated cross-coupling reaction has been developed. Towards this end, we have successfully accomplished the synthesis of substituted pyrazolo[4,3-*d*]pyrimidines from 4-iodopyrazole derivatives in a single step in excellent yields. We present herein the results of this study.

Results and Discussion

The starting materials for the study were generated by following reported procedures.[3–5] 4-Iodo-1,5-diphenyl-1*H*-pyrazole-3-carbaldehyde and acetamidine hydrochloride were selected as model substrates to optimize the reaction conditions, including optimization of the copper source, ligands, base, and solvents under a nitrogen atmosphere. As delineated in Table 1, four ligands were investigated at 90 °C using 10 mol-% CuI as catalyst and 300 mol-% Cs_2CO_3 as base in dimethyl sulfoxide (DMSO) (Table 1, entries 2–5); it was found that L-proline (20 mol-%) displayed the best activity.[8] No product was formed in the absence of ligand (Table 1, entry 1). Other copper catalysts including Cu_2O, CuCl, CuBr showed weaker activity compared with CuI (Table 1, entries 10–12). The effect of solvent was also investigated (Table 1, entries 4, 6, and 7), and DMSO was established as the best choice (entry 4); the reaction failed in toluene (Table 1, entry 7). Of the three bases evaluated, Cs_2CO_3 proved to be the most effective (Table 1, entries 4, 8, and 9).

After successful optimization of the reaction conditions, the reaction between several 4-iodopyrazolecarbaldehydes and substituted amidine hydrochlorides were carried out in the presence of 10 mol-% CuI, 20 mol-% L-proline, and 300 mol-% Cs_2CO_3 in DMSO at 90 °C under a nitrogen atmosphere. As shown in Table 2, all the substrates examined afford the required product in good yields. It was observed that changes in the substitution at the pyrazole ring did not have any deleterious effect on the outcome. Of the three amidines investigated, it was observed that acetamidine gave the products with relatively better yields, whereas the (pyridine-4-yl)acetamidine generated the desired products with slightly lower yields. Nevertheless, from the study it may be inferred that the protocol is general and works efficiently with a wide range of substrates. As demonstrated previously,[5] we assume that, here too, the condensation reaction between the formyl and the amino group is the initial step, which is followed by cross coupling in the cascade cycle (Scheme 1).

Table 1. Optimizing the reaction of 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carbaldehyde with acetamidine hydrochloride.[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield [%][b]
1	CuI	–	Cs_2CO_3	DMSO	0
2	CuI	L_1	Cs_2CO_3	DMSO	62
3	CuI	L_2	Cs_2CO_3	DMSO	65
4	CuI	L_3	Cs_2CO_3	DMSO	78
5	CuI	L_4	Cs_2CO_3	DMSO	46
6	CuI	L_3	Cs_2CO_3	DMF	68
7	CuI	L_3	Cs_2CO_3	toluene	0
8	CuI	L_3	K_2CO_3	DMSO	54
9	CuI	L_3	K_3PO_4	DMSO	56
10	Cu_2O	L_3	Cs_2CO_3	DMSO	58
11	CuCl	L_3	Cs_2CO_3	DMSO	42
12	CuBr	L_3	Cs_2CO_3	DMSO	46

[a] Reagents and conditions: 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carbaldehyde (1.0 mmol), acetamidine hydrochloride (1.2 mmol), Cu-salt (0.1 mmol), ligand (0.2 mmol), base (3.0 mmol), solvent (1.0 mL), 90 °C, 12 h. [b] Isolated yield after column chromatography.

We also attempted the cascade cyclization with ethyl 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carboxylate and acetamidine hydrochloride for the synthesis of 5-methyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-one under similar standard reaction conditions.[6] However, initial attempts did not yield the desired results. Ding et al. reported the formation of quinazoline-4(3*H*)-ones under mild conditions by reaction of 2-haloarylcarboxamides with amidines.[9] Taking a cue from the report, we transformed 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carboxylate into 4-iodo-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide, which was then reacted with acetamidine under the standardized conditions. The reaction was complete in the stipulated time and, after purification, a solid product was isolated in 85% yields. Unlike their observation, in our hands, the reaction failed under ligand-free conditions. Spectroscopic analysis of the product led us to establish its structure as **5** (Table 3). This result contrasts with the outcome reported by Ding et al. who isolated the product carrying the *N*-phenyl group in major yields. The scope of the protocol was tested by including a *p*-methylphenyl-substituted substrate, which also reacted with acetamidine hydrochloride to afford the required product in 84% yield (Table 3, entry 2). We did not observe the formation of any other product during the reaction.

Table 2. Scope of reaction with substituted pyrazoles.[a]

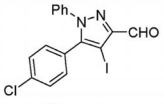
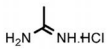
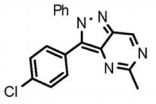
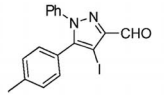
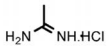
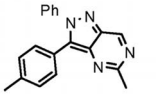
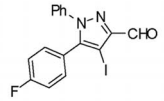
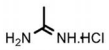
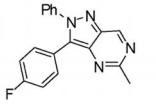
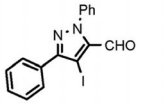
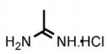
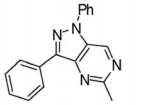
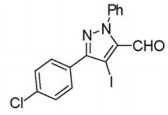
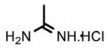
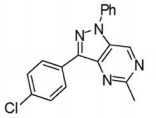
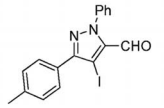
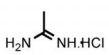
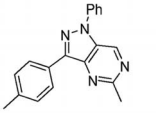
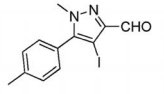
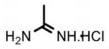
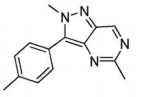
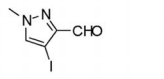
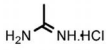
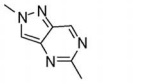
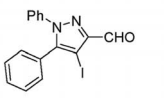
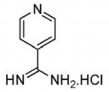
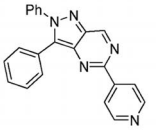
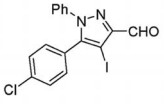
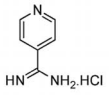
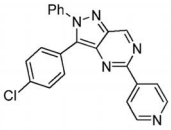
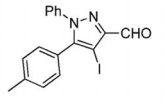
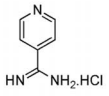
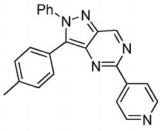
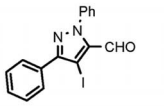
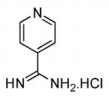
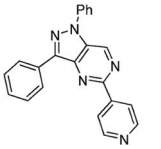
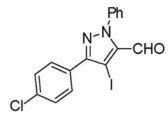
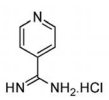
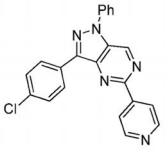
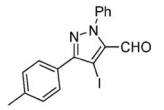
Entry	Pyrazole **1**	Amidine **2**	Product **3**	Yield [%][b]
1				76
2				77
3				74
4				79
5				78
6				79
7				70
8				78
9				68
10				65
11				66
12				69
13				67
14				68

Table 2. *(continued)*

Entry	Pyrazole **1**	Amidine **2**	Product **3**	Yield [%][b]
15				64
16				71
17				70
18				72

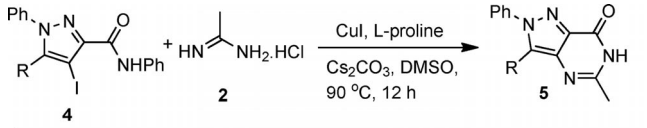
[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.2 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (3.0 mmol), DMSO (1.0 mL), 90 °C, 12 h. [b] Isolated yield after column chromatography.

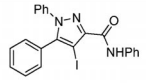
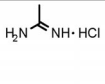
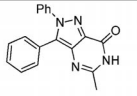
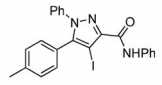
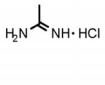
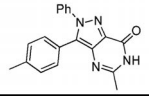
Scheme 1. Plausible mechanism for the synthesis of substituted pyrazolo[4,3-*d*]pyrimidines.

Finally, we examined a similar reaction between 4-iodopyrazolecarbaldehyde and guanidine instead of amidines. Accordingly, 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carbaldehyde was treated with guanidine hydrochloride under the optimized reaction conditions (Scheme 2). Unfortunately, under these conditions, the reaction resulted in a mixture of products that could not be purified or characterized.

Scheme 2. Attempted reaction of 4-iodoprazolecarbaldehyde with guanidine hydrochloride.

Table 3. Scope of reaction with 4-iodopyrazolecarboxamides and amidine hydrochloride.



Entry	Carboxamide **4**	Amidine **2**	Product **5**	Yield [%][b]
1				85
2				84

[a] Reagents and conditions: **4** (1.0 mmol), **2** (1.2 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (3.0 mmol), DMSO (1.0 mL), 90 °C, 12 h. [b] Isolated yield after column chromatography.

Conclusions

We have described a copper-mediated cascade protocol for the facile syntheses of substituted pyrazolo[4,3-*d*]pyrimidines and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones from 4-iodopyrazolecarbaldehydes and 4-iodopyrazolecarboxamides. The strategy is simple and efficient, and works with a range of substrates. This study adds to the repertoire of annulated-pyrazoles that can be generated through C–N cross-coupling reactions of 4-iodopyrazole derivatives.

Experimental Section

General: Melting points are uncorrected and were determined in capillary tubes with a Precision melting point apparatus containing silicon oil. IR spectra were recorded with a Perkin–Elmer RX I FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded either with a Bruker DPX-200, a Bruker Avance DRX-300 or a Bruker-400 MHz FT spectrometer, using TMS as internal standard (chemical shifts: δ values). The MS (EI) were recorded with a MICROMASS Quadro-II LCMS system. HRMS (EI) spectra were recorded with an Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer.

Typical Procedure; Synthesis of 5-Methyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: To a solution of 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carbaldehyde (250 mg, 0.67 mmol) and acetamidine hydrochloride (75 mg, 0.80 mmol) in DMSO (4 mL), Cs_2CO_3 (652 mg, 2.00 mmol), CuI (13 mg, 0.067 mmol), and L-proline (15 mg, 0.134 mmol) were added and the reaction mixture was heated at 90 °C for 12 h under a nitrogen atmosphere. Thereafter, water (50 mL) and ethyl acetate (25 mL) were added and the reaction mass was pass through a Celite bed and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 20 mL) and the collected organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated under vacuum. Column chromatography (ethyl acetate/hexanes, 1:5) of the crude product over silica gel furnished pure 5-methyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine as a white solid (149 mg, 78%).

5-Methyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 1; m.p. 155–156 °C; R_f = 0.26 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (s, 3 H, CH_3), 7.38–7.50 (m, 10 H, ArH), 9.45 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5, 124.9, 126.1, 127.9, 128.7, 129.0, 129.1, 129.5, 129.9, 130.4, 135.4, 138.7, 139.5, 140.3, 152.3, 162.1 ppm. MS (ESI+): *m*/*z* = 287.2 [M$^+$ + 1]. HRMS (ESI+): calcd. for $C_{18}H_{15}N_4$ [MH]$^+$ 287.1297; found 287.1294.

3-(4-Chlorophenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 1; yield 76%; white solid (149 mg from 250 mg); m.p. 154–155 °C; R_f = 0.17 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.87 (s, 3 H, CH_3), 7.38 (d, *J* = 8.5 Hz, 2 H, ArH), 7.45–7.49 (m, 7 H, ArH), 9.45 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5, 126.1, 126.3, 129.3, 129.7, 129.8, 131.1, 134.2, 135.3, 138.7, 140.0, 152.4, 162.3 ppm. MS (ESI+): *m*/*z* = 321.2 [M$^+$ + 1]. HRMS (ESI+): calcd. for $C_{18}H_{14}ClN_4$ [MH]$^+$ 321.0907; found 321.0911.

5-Methyl-3-(4-methylphenyl)-2-phenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 2; yield 77%; white solid (149 mg from 250 mg); m.p. 174–175 °C; R_f = 0.17 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 2.86 (s, 3 H, CH_3), 7.20 (d, *J* = 7.9 Hz, 2 H, ArH), 7.40 (d, *J* = 8.0 Hz, 2 H, ArH), 7.46 (s, 5 H, ArH), 9.43 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 26.6, 124.9, 126.1, 129.5, 129.7, 129.8, 135.6, 138.7, 139.2, 139.5, 140.4, 152.3, 161.9 ppm. MS (ESI+): *m*/*z* = 301.3 [M$^+$ + 1]; HRMS (DART): calcd. for $C_{19}H_{17}N_4$ [MH]$^+$ 301.1453; found 301.1435.

3-(4-Fluorophenyl)-5-methyl-2-phenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 3; yield 74%; yellow solid (143 mg from 250 mg); m.p. 164–165 °C; R_f = 0.21 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (s, 3 H, CH_3), 7.10 (t, *J* = 8.5 Hz, 2 H, ArH), 7.46–7.52 (m, 7 H, ArH), 9.45 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5, 116.1, 116.4, 124.0, 126.1, 129.6, 129.7, 131.8, 131.9, 134.4, 138.7, 139.4, 140.1, 152.4, 161.9, 162.2 ppm. MS (ESI+): *m*/*z* = 305.0 [M$^+$ + 1]. HRMS (ESI+): calcd. for $C_{18}H_{14}FN_4$ [MH]$^+$ 305.1202; found 305.1196.

5-Methyl-1,3-diphenyl-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 4; yield 79%; white solid (151 mg from 250 mg); m.p. 142–143 °C; R_f = 0.47 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (s, 3 H, CH_3), 7.41–7.45 (m, 2 H, ArH), 7.54 (t, *J* = 7.5 Hz, 2 H, ArH), 7.60 (t, *J* = 7.6 Hz, 2 H, ArH), 7.80 (d, *J* = 7.9 Hz, 2 H, ArH), 8.59 (d, *J* = 7.8 Hz, 2 H, ArH), 9.30 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 121.9, 127.47, 127.52, 128.9, 129.1, 129.8, 130.1, 131.4, 139.5, 141.9, 144.3, 145.5, 162.0 ppm. MS (ESI+): *m*/*z* = 287.3 [M$^+$ + 1]. HRMS (DART): calcd. for $C_{18}H_{15}N_4$ [MH]$^+$ 287.1297; found 287.1295.

3-(4-Chlorophenyl)-5-methyl-1-phenyl-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 5; yield 78%; white solid (153 mg from 250 mg); m.p. 198–188 °C; R_f = 0.46 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (s, 3 H, CH_3), 7.44 (t, *J* = 7.2 Hz, 1 H, ArH), 7.50 (d, *J* = 8.5 Hz, 2 H, ArH), 7.61 (t, *J* = 7.8 Hz, 2 H, ArH), 7.79 (d, *J* = 7.9 Hz, 2 H, ArH), 8.57 (d, *J* = 8.5 Hz, 2 H, ArH), 9.31 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 121.9, 127.7, 128.7, 129.2, 129.9, 130.2, 135.0, 139.4, 142.1, 145.3, 147.2, 162.2 ppm. MS (ESI+): *m*/*z* = 321.2 [M$^+$ + 1]. HRMS (DART): calcd. for $C_{18}H_{14}ClN_4$ [MH]$^+$ 321.0907; found 321.0864.

5-Methyl-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 6; yield 79%; white solid (153 mg from 250 mg); m.p. 144–145 °C; R_f = 0.48 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.95 (s, 3 H, CH_3), 7.35 (d, *J* = 7.9 Hz, 2 H, ArH), 7.42 (t, *J* = 7.4 Hz, 1 H,

ArH), 7.60 (t, J = 7.8 Hz, 2 H, ArH), 7.80 (d, J = 7.9 Hz, 2 H, ArH), 8.48 (d, J = 8.0 Hz, 2 H, ArH), 9.30 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 26.1, 121.8, 127.4, 128.5, 129.7, 129.8, 130.1, 139.1, 139.6, 141.8, 144.5, 145.5, 161.9 ppm. MS (ESI+): m/z = 301.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{19}H_{17}N_4$ [MH]$^+$ 301.1453; found 301.1430.

2,5-Dimethyl-3-(4-methylphenyl)-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 7; yield 70%; yellow solid (128 mg from 250 mg); m.p. 164–165 °C; R_f = 0.12 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 2.81 (s, 3 H, CH_3), 4.26 (s, 3 H, NCH_3), 7.38 (d, J = 7.8 Hz, 2 H, ArH), 7.56 (d, J = 7.8 Hz, 2 H, ArH), 9.32 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 26.4, 40.1, 124.8, 129.8, 130.0, 136.0, 137.7, 139.5, 139.7, 151.1, 161.5 ppm. MS (ESI+): m/z = 239.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{14}H_{15}N_4$ [MH]$^+$ 239.1297; found 239.1300.

2,5-Dimethyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 8; yield 78%; yellow oil (122 mg from 250 mg); R_f = 0.21 (hexanes/EtOAc, 50:50, v/v). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, CH_3), 4.19 (s, 3 H, NCH_3), 7.99 (s, 1 H, ArH), 9.19 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 40.9, 124.1, 136.9, 139.9, 150.4, 159.7 ppm. MS (ESI+): m/z = 149.2 [M^+ + 1]. HRMS (ESI): calcd. for $C_7H_9N_4$ [MH]$^+$ 149.0827; found 149.0830.

2,3-Diphenyl-5-(pyridin-4-yl)-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 9); yield 68%; white solid (159 mg from 250 mg); m.p. 203–204 °C; R_f = 0.13 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.48 (m, 3 H, ArH), 7.51–7.52 (m, 5 H, ArH), 7.61–7.63 (m, 2 H, ArH), 8.41 (d, J = 5.1 Hz, 2 H, ArH), 8.77 (d, J = 4.6 Hz, 2 H, ArH), 9.62 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.4, 126.2, 129.0, 129.4, 129.7, 129.9, 130.0, 140.2, 145.7, 147.7, 150.6, 152.6, 158.2 ppm. MS (ESI+): m/z = 350.2 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{22}H_{16}N_5$ [MH]$^+$ 350.1406; found 350.1428.

3-(4-Chlorophenyl)-2-phenyl-5-(pyridin-4-yl)-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 10; yield 65%; white solid (152 mg from 250 mg); m.p. 167–168 °C; R_f = 0.14 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.5 Hz, 2 H, ArH), 7.52 (s, 5 H, ArH), 7.57 (d, J = 8.5 Hz, 2 H, ArH), 8.40 (d, J = 5.5 Hz, 2 H, ArH), 8.78 (d, J = 4.0 Hz, 2 H, ArH), 9.62 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.4, 126.1, 128.0, 129.4, 129.9, 130.1, 131.1, 135.7, 139.4, 140.0, 145.6, 147.3, 150.5, 152.7, 156.9 ppm. MS (ESI+): m/z = 384.2 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{22}H_{15}ClN_5$ [MH]$^+$ 384.1016; found 384.1033.

3-(4-Methylphenyl)-2-phenyl-5-(pyridin-4-yl)-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 11; yield 66%; white solid (154 mg from 250 mg); m.p. 200–201 °C; R_f = 0.14 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.26 (d, J = 7.8 Hz, 2 H, ArH), 7.51–7.54 (m, 7 H, ArH), 8.40 (d, J = 5.4 Hz, 2 H, ArH), 8.76 (d, J = 3.8 Hz, 2 H, ArH), 9.60 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 122.3, 124.7, 126.1, 129.6, 129.7, 129.8, 139.4, 140.3, 145.7, 150.5, 152.5, 156.5 ppm. MS (ESI+): m/z = 364.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{23}H_{18}N_5$ [MH]$^+$ 364.1562; found 364.1561.

1,3-Diphenyl-5-(pyridin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 12; yield 69%; white solid (161 mg from 250 mg); m.p. 186–187 °C; R_f = 0.25 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.49 (m, 2 H, ArH), 7.57–7.63 (m, 4 H, ArH), 7.84 (d, J = 7.0 Hz, 2 H, ArH), 8.46 (s, 2 H, ArH), 8.68 (d, J = 6.8 Hz, 2 H, ArH), 8.81 (s, 2 H, ArH), 9.46 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.0, 122.3, 127.6, 128.0, 129.0, 129.5, 130.2, 130.4, 131.0, 139.3, 142.3, 145.2, 150.7, 156.8 ppm. MS (ESI+): m/z = 350.3 [M^+ + 1]. HRMS (DART): calcd. for $C_{22}H_{16}N_5$ [MH]$^+$ 350.1406; found 350.1408.

3-(4-Chlorophenyl)-1-phenyl-5-(pyridin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 13; yield 67%; white solid (157 mg from 250 mg); m.p. 239–240 °C; R_f = 0.26 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.56 (m, 3 H, ArH), 7.64 (s, 2 H, ArH), 7.82 (s, 2 H, ArH), 8.43 (s, 2 H, ArH), 8.63 (d, J = 6.6 Hz, 2 H, ArH), 8.82 (s, 2 H, ArH), 9.47 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.1, 122.3, 128.1, 128.7, 129.3, 129.6, 130.3, 130.5, 135.5, 142.4, 145.1, 150.7, 157.0 ppm. MS (ESI+): m/z = 384.1 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{22}H_{15}ClN_5$ [MH]$^+$ 384.1016; found 384.1019.

3-(4-Methylphenyl)-1-phenyl-5-(pyridin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 14; yield 68%; white solid (159 mg from 250 mg); m.p. 220–221 °C; R_f = 0.24 (hexanes/EtOAc, 70:30, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 7.40 (d, J = 7.7 Hz, 2 H, ArH), 7.47 (t, J = 7.4 Hz, 1 H, ArH), 7.63 (t, J = 7.6 Hz, 2 H, ArH), 7.85 (d, J = 7.8 Hz, 2 H, ArH), 8.46 (d, J = 4.6 Hz, 2 H, ArH), 8.57 (d, J = 7.8 Hz, 2 H, ArH), 8.82 (s, 2 H, ArH), 9.47 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 122.0, 122.3, 127.5, 127.9, 128.2, 129.8, 130.2, 130.4, 139.3, 139.6, 142.2, 145.4, 145.7, 150.7, 156.7 ppm. MS (ESI+): m/z = 364.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{23}H_{18}N_5$ [MH]$^+$ 364.1562; found 364.1561.

2-Methyl-3-(4-methylphenyl)-5-(pyridin-4-yl)-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 15; yield 64%; white solid (148 mg from 250 mg); m.p. 200–201 °C; R_f = 0.13 (hexanes/EtOAc, 60:40, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 4.36 (s, 3 H, NCH_3), 7.45 (d, J = 8.0 Hz, 2 H, ArH), 7.69 (d, J = 8.1 Hz, 2 H, ArH), 8.36 (dd, J_1 = 1.4, J_2 = 4.6 Hz, 2 H, ArH), 8.73 (d, J = 6.0 Hz, 2 H, ArH), 9.50 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 25.9, 40.5, 122.3, 129.8, 130.1, 140.0, 140.5, 142.7, 147.9, 150.4, 163.0 ppm. MS (ESI+): m/z = 302.2 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{18}H_{16}N_5$ [MH]$^+$ 302.1406; found 302.1407.

5-Cyclopropyl-2,3-diphenyl-2*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 16; yield 71%; white solid (148 mg from 250 mg); m.p. 160–161 °C; R_f = 0.48 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.09 (m, 2 H, CH_2), 1.11–1.15 (m, 2 H, CH_2), 2.35–2.42 (m, 1 H, CH), 7.27–7.34 (m, 4 H, ArH), 7.36–7.40 (m, 4 H, ArH), 7.51–7.54 (m, 2 H, ArH), 9.38 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3, 12.0, 18.9, 126.1, 128.7, 128.9, 129.5, 129.9, 130.8, 134.8, 139.3, 152.4, 166.0 ppm. MS (ESI+): m/z = 313.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{20}H_{17}N_4$ [MH]$^+$ 313.1453; found 313.1464.

3-(4-Chlorophenyl)-5-cyclopropyl-1-phenyl-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 17; yield 70%; white solid (148 mg from 250 mg); m.p. 155–156 °C; R_f = 0.63 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.17 (m, 2 H, CH_2), 1.24–1.28 (m, 2 H, CH_2), 2.46–2.53 (m, 1 H, CH), 7.42 (t, J = 7.4 Hz, 1 H, ArH), 7.49 (d, J = 8.6 Hz, 2 H, ArH), 7.59 (t, J = 7.9 Hz, 2 H, ArH), 7.78 (d, J = 7.7 Hz, 2 H, ArH), 8.56 (d, J = 8.6 Hz, 2 H, ArH), 9.24 (s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 18.5, 121.8, 127.6, 128.6, 129.1, 130.1, 134.9, 139.5, 142.1, 142.9, 145.3, 166.4 ppm. MS (ESI+): m/z = 347.2 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{20}H_{16}ClN_4$ [MH]$^+$ 347.1063; found 347.1150.

5-Cyclopropyl-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[4,3-*d*]pyrimidine: See Table 2, entry 18; yield 72%; white solid (151 mg from 250 mg); m.p. 160–161 °C; R_f = 0.65 (hexanes/EtOAc, 80:20, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.16 (m, 2 H, CH_2), 1.25–1.28 (m, 2 H, CH_2), 2.44 (s, 3 H, CH_3), 2.48–2.53 (m, 1 H, CH), 7.34 (d, J = 7.9 Hz, 2 H, ArH), 7.40 (t, J = 7.3 Hz, 1 H, ArH), 7.58 (t, J = 7.7 Hz, 2 H, ArH), 7.79 (d, J = 8.2 Hz, 2 H, ArH), 8.49 (d, J = 7.9 Hz, 2 H, ArH), 9.23 (s, 1 H, ArH) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 11.0, 18.4, 21.7, 121.7, 127.3, 128.7, 129.6, 130.0, 139.0, 139.7, 141.8, 144.2, 145.6, 166.1 ppm. MS (ESI+): *m*/*z* = 327.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{21}H_{19}N_4$ [MH]$^+$ 327.1610; found 327.1634.

Synthesis of 4-Iodo-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide (Typical Procedure): To a stirred solution of 4-iodo-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid (250 mg, 0.64 mmol) and aniline (0.07 mL, 0.77 mmol) in anhydrous CH_2Cl_2 (10 mL) was added *N*-methylmorpholine (NMM; 0.084 mL, 0.77 mmol) and the mixture was cooled to –10 °C in an ice/salt bath. Thereafter *N*-ethyl-*N*′-[3-(dimethylamino)propyl]carbodiimide (EDC; 148 mg, 0.77 mmol) was added to the reaction mixture over 10 min, which was stirred for another 2 h. Upon completion, the reaction mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography of the crude product over silica gel (ethyl acetate/hexanes, 1:20) furnished 4-iodo-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide as a white solid (247 mg, 83%).

4-Iodo-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide: M.p. 187–188 °C; R_f = 0.28 (hexanes/EtOAc, 80:20, v/v); IR (KBr): $\tilde{\nu}_{max}$ = 1683 (CONH), 3381 (NH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 7.1 Hz, 1 H, ArH), 7.26–7.29 (m, 4 H, ArH), 7.34–7.40 (m, 8 H, ArH), 7.74 (d, *J* = 8.2 Hz, 2 H, ArH), 8.86 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.2, 120.0, 124.4, 125.3, 128.8, 129.2, 129.7, 130.7, 138.0, 139.5, 144.9, 147.4, 159.1 ppm. MS (ESI+): *m*/*z* = 466.0 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{22}H_{17}IN_3O$ [MH]$^+$ 466.0416; found 466.0430.

4-Iodo-5-(4-methylphenyl)-*N*,1-diphenyl-1*H*-pyrazole-3-carboxamide: Yield 82%; white solid (243 mg from 250 mg); m.p. 214–215 °C; R_f = 0.26 (hexanes/EtOAc, 80:20, v/v). IR (KBr): $\tilde{\nu}_{max}$ = 1667 (CONH), 3435 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 7.10–7.18 (m, 5 H, ArH), 7.24–7.27 (m, 2 H, ArH), 7.34–7.38 (m, 5 H, ArH), 7.73 (d, *J* = 7.7 Hz, 2 H, ArH), 8.85 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 63.1, 120.0, 124.4, 125.3, 128.6, 129.2, 129.5, 130.6, 138.0, 139.6, 139.8, 147.5, 159.1 ppm. MS (ESI+): *m*/*z* = 480.1 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{23}H_{19}IN_3O$ [MH]$^+$ 480.0573; found 480.0570.

Synthesis of 5-Methyl-2,3-diphenyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (Typical Procedure): To a solution of 4-iodo-*N*,1,5-triphenyl-1*H*-pyrazole-3-carboxamide (250 mg, 0.54 mmol) and acetamidine hydrochloride (61 mg, 0.65 mmol) in DMSO (4 mL), Cs_2CO_3 (527 mg, 1.62 mmol), CuI (10 mg, 0.054 mmol), and L-proline (12 mg, 0.108 mmol) were added and the reaction mixture was heated at 90 °C for 12 h under a nitrogen atmosphere. Thereafter, water (50 mL) and ethyl acetate (25 mL) were added and the reaction mass was pass through a Celite bed. The layers were separated and the aqueous layer was further extracted with ethyl acetate (2 × 20 mL). The collected organic layer was washed with brine, dried with anhydrous Na_2SO_4 and concentrated under vacuum. Column chromatography of the crude product over silica gel (ethyl acetate/hexanes, 1:1) furnished pure 5-methyl-2,3-diphenyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one as a white solid (138 mg, 85%).

5-Methyl-2,3-diphenyl-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one: See Table 3, entry 1); m.p. >250 °C; R_f = 0.25 (hexanes/EtOAc, 50:50, v/v); IR (KBr): $\tilde{\nu}_{max}$ = 1687 (CONH), 3374 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 7.35–7.41 (m, 10 H, ArH), 11.72 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 126.0, 128.0, 128.8, 129.0, 129.2, 129.9, 135.7, 136.1, 137.0, 139.9, 152.7, 159.9 ppm. MS (ESI+): *m*/*z* = 303.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{18}H_{15}N_4O$ [MH]$^+$ 303.1246; found 303.1248.

5-Methyl-3-(4-methylphenyl)-2-phenyl-2,6-dihydro-7*H*-pyrazolo-[4,3-*d*]pyrimidin-7-one: See Table 3, entry 2; yield 84%; white solid (139 mg from 250 mg); m.p. >250 °C; R_f = 0.27 (hexanes/EtOAc, 50:50, v/v); IR (KBr): $\tilde{\nu}_{max}$ = 1689 (CONH), 3400 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 2.57 (s, 3 H, NCH_3), 7.18 (d, *J* = 7.9 Hz, 2 H, ArH), 7.32 (d, *J* = 8.0 Hz, 2 H, ArH), 7.40–7.45 (m, 5 H, ArH), 11.65 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 22.2, 125.1, 126.0, 128.9, 129.2, 129.6, 129.8, 132.1, 135.7, 136.3, 137.1, 139.1, 140.1, 152.4, 160.1 ppm. MS (ESI+): *m*/*z* = 317.3 [M^+ + 1]. HRMS (ESI+): calcd. for $C_{19}H_{17}N_4O$ [MH]$^+$ 317.1402; found 317.1406.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all compounds.

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