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Synthesis of Imidazo[4,5-c]pyrazoles via Copper-Catalyzed Amidine Cyclization

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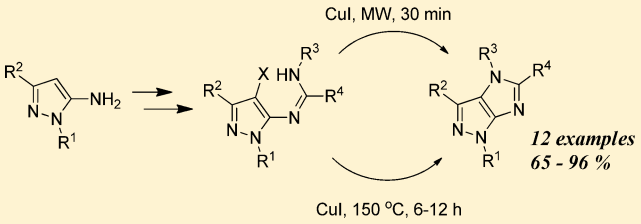
Supporting Information

ABSTRACT: A new synthetic approach to 4-substituted imidazo[4,5-c]pyrazoles is proposed on the basis of the *N*′-(4-halopyrazol-5-yl)amidine cyclization under the conditions of copper-catalyzed cross-coupling reactions. Using 5-amino-pyrazoles and copper catalysts as starting materials, the method is inexpensive and convenient and allows a wide range of substituents at all positions of the imidazo[4,5-c]pyrazole nucleus.



INTRODUCTION

Many bicyclic pyrazole derivatives are well recognized for their potent and diverse bioactivity, which can be exemplified by simple indazoles contained in the antiemetic Granisetron[1] or by pyrazolo[4,3-d]pyrimidine, a basic component of the urology drugs Sildenafil and Udenafil (Figure 1).[2] Much interest has

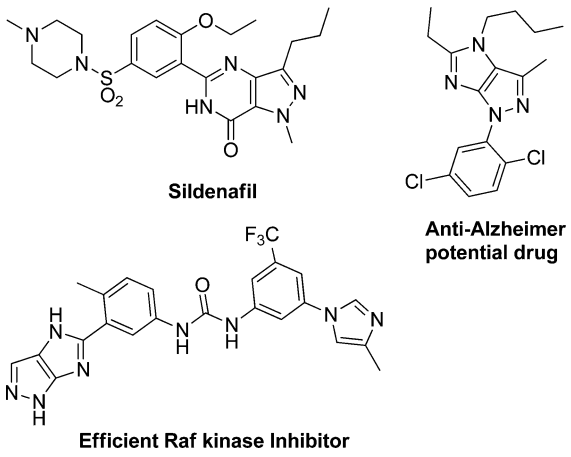


Figure 1. Biologically active imidazo[4,5-c]pyrazoles.

also been focused on pyrazolo[3,4-b]pyridine derivatives efficiently inhibiting p38α mitogen-activated protein kinase.[3] However, one of the simplest pyrazole-containing nuclei, imidazo[4,5-c]pyrazole, remains largely unexplored since reliable synthetic routes to this heterocyclic system have been lacking so far. At the same time, imidazo[4,5-c]pyrazole derivatives show promise as antineurodegenerative (e.g., anti-Alzheimer) drugs.[4] Moreover, recent in vitro studies suggest that 5-aryl substituted heterocycles of this class act as selective Raf kinase inhibitors.[5]

As a rule, imidazo[4,5-c]pyrazoles are synthesized by annelation of imidazole to the [c] edge of the pyrazole ring. An alternative pathway, construction of the pyrazole moiety at the imidazole ring, was reported only once in the literature and involved the addition of diazomethane to the CC bond of 5-nitroimidazoles.[6]

The use of 4,5-diaminopyrazoles in the synthesis of imidazo[4,5-c]pyrazole derivatives is restricted to condensations with aromatic carboxylic acids as well as with carbon disulfide or thiophosgene. The former reactions afford 5-aryl substituted imidazo[4,5-c]pyrazoles[5,7]and the latter 5-thiones,[8] which are desulfurized with Raney nickel to provide bare heterocycles.[9]

4,5-Diaminopyrazoles can be replaced by more easily accessible 4-carboxy-5-aminopyrazoles; they are converted via standard reactions to 4-isocyanato-5-aminopyrazoles, which are readily cyclizable to the corresponding imidazo[4,5-c]pyrazol-5-ones.[10]

The most general synthetic approach to imidazo[4,5-c]-pyrazoles is offered by the intramolecular cyclocondensation of 4-nitroso-5-alkylaminopyrazoles in which the nitroso group reacts with the α-methylene unit of the alkyl substituent, thus giving rise to the imidazole ring.[1,10] Both 5-aryl and 5-alkyl substituted derivatives can be obtained by this method. However, it cannot be considered as a convenient strategy since the procedure includes many steps with a low yield each, especially the inefficient cyclization (20−40%).

Preparation of 4- and/or 6-substituted imidazo[4,5-c]-pyrazoles presents a separate synthetic problem. These compounds were reported to be alkylated with alkyl halides at position 4 of the heterocyclic nucleus.[4b] However, the alkylation selectivity remains an open question, as does the possibility

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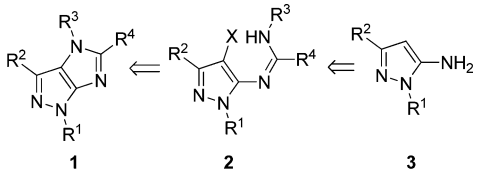
to obtain *N*-aryl substituted imidazo[4,5-c]pyrazoles by direct arylation.

As evident from the retrosynthesis of the imidazo[4,5-c]-pyrazole system (see Scheme 1), it is obtainable by the intramolecular

Scheme 1. Retrosynthesis of Imidazo[4,5-c]pyrazoles



cyclization of halopyrazolyl-substituted amidines **2**, which are derived from commercially available and inexpensive 5-aminopyrazoles **3**. The key step of the synthetic retroscheme is the CN bond formation resulting from the nucleophilic substitution of the halogen atom in the pyrazole nucleus. In the recent years, much insight has been gained into such *N*-arylation and heteroarylation reactions catalyzed by transition metals.[11] Palladium(0) compounds such as $Pd_2(dba)_3$[12] or $Pd(PPh_3)_4$[13] are now extensively used as catalysts in the synthesis of various heterocyclic systems including imidazole and benzimidazole derivatives. Over the past decade, considerable interest has been focused on the development of cheap and environmentally friendly nonpalladium catalysts. For instance, complexes of copper rather than of palladium are employed to catalyze *N*-arylation reactions. In particular, using the complexes of Cu(I)[14] and Cu(II)[15] formed in situ or under ligand-free conditions,[16] benzimidazole derivatives can be obtained by the mild and high-yield cyclization of *o*-halogenaryl substituted ureas, thioureas, and amidines.

We are currently concerned with heterocyclic syntheses starting from amino derivatives of electron-rich heterocycles, e.g., 5-amino substituted pyrazoles, isoxazoles, and imidazoles, 2-aminothiophenes, etc.[17] In view of our ongoing synthetic efforts in this field and abundant literature on transition-metal-catalyzed *N*-arylation and heteroarylation reactions, here we report a novel approach to 4-substituted imidazo[4,5-c]-pyrazoles based on the cyclization of *N*-halopyrazolylamidines **2** under conditions of copper catalysis.

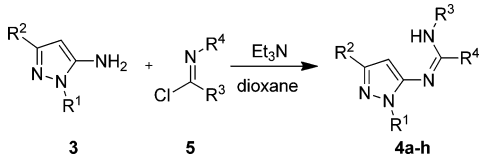
RESULTS AND DISCUSSION

First, we attempted the preparation of desired pyrazoles **2** by the reaction of 4-bromo-1-phenyl-3-methyl-5-aminopyrazole **8** with imidoyl chlorides. However, compound **8** proved unreactive toward imidoyl chlorides even on long boiling in dry dioxane. To circumvent this limitation, we chose to synthesize C(4)-unsubstituted pyrazolylamidines **4**, followed by C(4)-halogenation. Compounds **4** were obtained via two pathways: (A) the reaction of 5-aminopyrazoles **3** with imidoyl chlorides[18] and (B) the reaction of imino esters **6** with amines.

C(4)-Unsubstituted 5-aminopyrazoles **3** react with imidoyl chlorides **5** in dry 1,4-dioxane already at room temperature to give products **4** in high yields (see Table 1, entries 1−7). A lower yield of acetamidine derivative **4h** is probably due to the lability of the starting imidoyl chloride (see Table 1, entry 8).

N-Aryl substituted amidines **4i−l** were prepared in yields of 54−87% by the reaction of imino esters[19] **6** with anilines **7** (Table 2). Imino ester **6b** synthesized from *N*-phenyl-5-aminopyrazole and triethyl orthoacetate does not react with

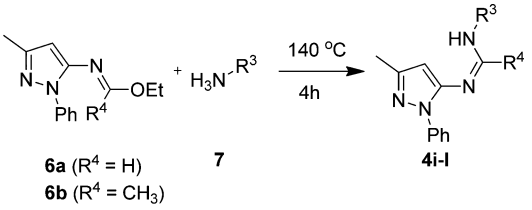
Table 1. Synthesis of *N*-Pyrazolylamidines from 5-Aminopyrazoles and Imidoyl Chlorides[a]



entry	amidine	R^1	R^2	R^3	R^4	yield, %
1	**4a**	Ph	Me	Me	Ph	82
2	**4b**	Ph	Me	Et	Ph	79
3	**4c**	Ph	Me	Me	4-MeO-phenyl	84
4	**4d**	Ph	Me	Me	3-Cl-phenyl	89
5	**4e**	Me	Me	Me	Ph	86
6	**4f**	Me	Me	Me	4-Me-phenyl	91
7	**4g**	Ph	H	Me	Ph	87
8	**4h**	Ph	Me	Ph	Me	53

[a]Reaction conditions: 1.0 mol of **3**, 1 mol of **5**, 2.0 mol of Et_3N, dry 1,4-dioxane, rt, 24 h.

Table 2. Synthesis of *N*-Pyrazolylamidines from Imino Esters and Amines[a]



entry	amidine	R^3	R^4	yield, %
1	**4i**	Ph	H	76
2	**4j**	4-Cl-phenyl	H	54
3	**4k**	4-Me-phenyl	H	81
4	**4l**	4-MeO-phenyl	H	62

[a]Reaction conditions: 1.0 mol of **6**, 1 mol of **7**, 140 °C, 4 h.

aniline and its derivatives even on temperature elevation from 140 to 220 °C.

Bromination of amidines **4a−g,i,j** with NBS in boiling acetonitrile occurs at the C(4) atom of the pyrazole ring to give compounds **2** (see Table 3). The procedure used, though simple and affording high yields of the final products, has, however, some limitations. As an example, treatment of compound **4h** with NBS gives rise to a complex product mixture, which is likely to result from additional bromination of the methyl group in acetamidine. Moreover, attempted bromination of *N*-arylamidines **4k,l** bearing electron-donor substituents on the benzene ring caused resinification. In these cases, *N*′-halopyrazolyl derivatives **2** of amidines **4** were obtained under milder conditions; namely, halogenation with elementary iodine was carried out in the presence of KOH at room temperature. Iodopyrazolyl-substituted amidines **2h,k,l** were thus prepared in yields of 65−85%, with the reaction being complete within 48−96 h.

Reaction conditions for intramolecular cross-coupling were designed using a microwave-assisted reaction with model compound **2a**; as a result, the experiment time was reduced to 15 min. Experiments were performed at 150 °C in all solvents. The reaction products were not isolated, and the conversion degree was determined by LC−MS analysis of the reaction mixture. The study of the model compound provided an insight into the effect caused by the solvent, ligand, and base

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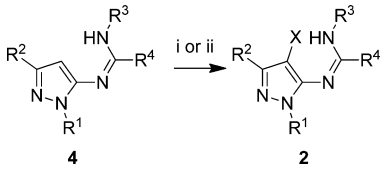
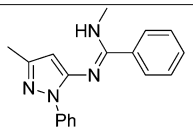
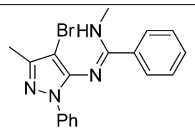
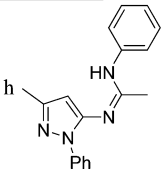
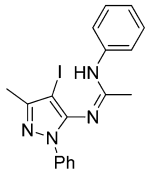
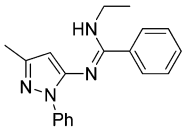
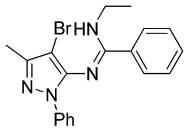
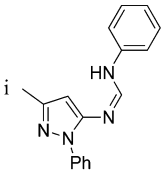
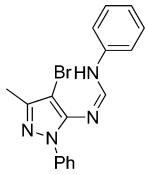
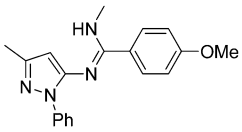
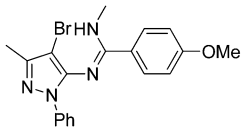
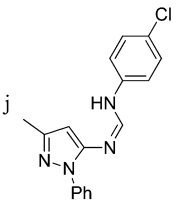
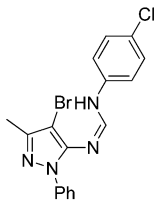
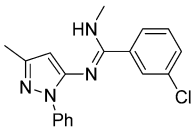
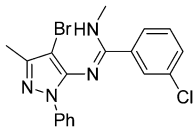
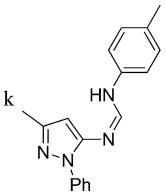
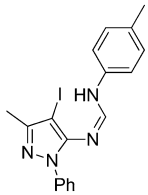
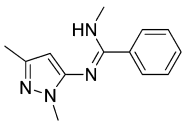
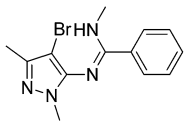
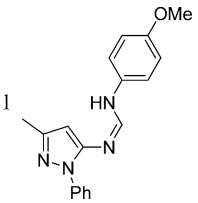
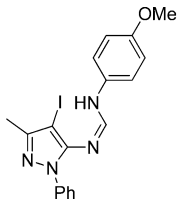
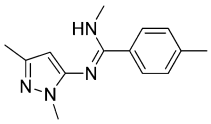
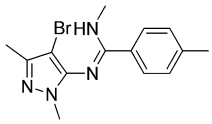
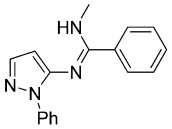
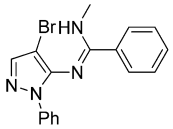
Table 3. Synthesis of *N*′-(4-Halopyrazol-5-yl)amidines[a]



	Amidine	Reagent	Product	Yield, %		Amidine	Reagent	Product	Yield, %
a		NBS 3h		93	h		I_2/ KOH 96h		65
b		NBS 3h		91	i		NBS 1h		81
c		NBS 3h		89	j		NBS 1h		76
d		NBS 3h		96	k		I_2/ KOH 72h		86
e		NBS 3h		87	l		I_2/ KOH 48h		84
f		NBS 3h		94					
g		NBS 3h		90					

[a]Reaction conditions: (i) 1 mol of **7**, 1.05 mol of NBS, CH_3CN, heating, 2−5 h; (ii) 1 mol of **7**, 1 mol of I_2, 2 mol of KOH, DMF, rt, 48−96 h.

on the course of copper-catalyzed intramolecular arylation (see Table 4). The nature of the solvent proves to be the most significant parameter controlling the reaction efficiency; in all cases, using DMSO or DMF instead of acetonitrile or toluene leads to a drastically increased yield of the target product. Another major factor of reaction optimization is an appropriate choice of ligands; as seen from entries 9, 10, 15, and 16 of Table 4, DMEDA and L-Pro appear most advantageous among the compounds conventionally used in such syntheses (cf. with phenanthroline and 8-hydroxyquinoline). Though cesium carbonate used as a base affords the highest conversion degree, potassium carbonate, causing only a slight yield reduction, offers a cheaper and competitive alternative to it, whereas potassium phosphate turns out to be quite inefficient (cf. Table 4, entries 9−11 and 15−16).

For reliability, some selected experiments were repeated without microwave assistance so that the cyclization was run in suitable boiling solvents for 6 h. As shown, the reaction of intramolecular cross-coupling does not proceed without a catalyst (see Table 4, entry 21). On the other hand, DMF−DMEDA−K_2CO_3 appears to be the optimum system both with and without microwave irradiation (see Table 4, entries 9 and 19).

N′-halopyrazolylamidines **2a−g** were cyclized to the corresponding 4-alkyl substituted imidazo[4,5-c]pyrazoles **1a−g** using 0.05 mol of CuI, 0.1 mol of DMEDA, and an excess of K_2CO_3 under microwave irradiation (method A) and conventional heating in boiling DMF (method B) or CH_3CN (method C); see Table 5. The procedures with and without microwave assistance furnished much the same yields of the desired products (83−95%). At the same time, cyclization of *N*′-(4-bromopyrazolyl) and *N*′-(4-iodopyrazolyl) derivatives **2h−l** of *N*-aryl substituted amidines both by methods A and B was accompanied by complete decomposition of starting

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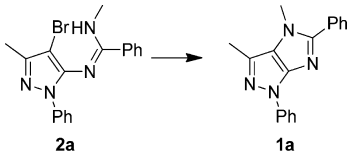
Table 4. Condition Optimization for the Cu-Catalyzed Cyclization



entry	solvent	ligand	base	conversion,[c] %
		Microwave Assisted[a]		
1	toluene	DMEDA	K_2CO_3	0
2	toluene	DMEDA	Cs_2CO_3	4
3	toluene	8-Oxy	K_2CO_3	2
4	toluene	8-Oxy	Cs_2CO_3	0
5	toluene	Phen	K_2CO_3	18
6	toluene	Phen	Cs_2CO_3	16
7	CH_3CN	DMEDA	K_2CO_3	4
8	CH_3CN	Phen	K_2CO_3	5
9	DMF	DMEDA	K_2CO_3	92
10	DMF	DMEDA	Cs_2CO_3	97
11	DMF	DMEDA	K_3PO_4	29
13	DMF	8-Oxy	K_2CO_3	15
14	DMF	Phen	K_2CO_3	54
15	DMSO	L-Pro	K_2CO_3	76
16	DMSO	L-Pro	Cs_2CO_3	81
		Not Assisted[b]		
17	CH_3CN	DMEDA	K_2CO_3	0
18	CH_3CN	DMEDA	Cs_2CO_3	15
19	DMF	DMEDA	K_2CO_3	93
20	DMSO	L-Pro	Cs_2CO_3	76
21	DMF	no ligand and CuI	K_2CO_3	0

[a]Conditions: 1 mol of amidine, 2 mol of base, 0.05 mol of CuI, 0.1 mol of ligand, 3 mL of solvent, vial tube, microvawe irradiation, stirring, 15 min, 150 °C. [b]Conditions: 1 mol of amidine, 2 mol of base, 0.05 mol of CuI, 0.1 mol of ligand, 5 mL of solvent, stirring, 6 h, and heating at solvent boiling point. [c]The conversion value given as the average of three independent experiments.

compounds to form a mixture of unidentifiable products. However, the reaction conducted under milder conditions by method C afforded 4-aryl substituted imidazo[4,5-c]pyrazoles **1h–l** in yields of 90–95% (see Table 5, entries h–l). A higher reactivity of *N*′-halopyrazolylamidines **2h–l** in copper-catalyzed intramolecular cross-coupling reactions may be attributable to the aromatic ring at one of the amidine nitrogens, which increases the NH-acidity of these compounds compared to **2a–g**. A similar effect was described previously for the cyclization of *o*-haloaryl amidines and guanidines to the corresponding benzimidazole derivatives,[14a,15] thus suggesting that not amidines themselves but their conjugate anions coordinate with the copper–ligand system in the reactions concerned. Going from bromine to iodine evidently has a much weaker effect on the reaction course since both bromo derivative **2j** and iodo derivatives **2h–l** readily cyclize under mild conditions to the corresponding imidazo[4,5-c]pyrazoles.

CONCLUSIONS

We have found a new synthetic access to 4-substituted imidazo[4,5-c]pyrazole derivatives based on the cyclization of *N*′-(4-halopyrazol-5-yl)amidines under the conditions of copper-catalyzed cross-coupling reactions. The facile and inexpensive method using 5-aminopyrazoles and copper catalysts allows a variety of substituents to be introduced at all positions of the imidazo[4,5-c]pyrazole nucleus; because of high intermediate yields, the desired products can be obtained in multigram amounts.

EXPERIMENTAL PROCEDURES

Condensation of Aminopyrazoles with Orthoesters. Aminopyrazole (6.0 mmol) was boiled with 30 mmol of triethyl ortoformate for **6a** or triethyl orthoacetate for **6b** for 6 h. The mixture was evaporated (boiling water bath, 12 Torr), and after that, the crude product was dissolved in minimum amount of EtOAc and applied to the SiO_2. The silica was washed by hexane (about 100 mL) to remove the residues of triethyl ortoformate/acetate. Then, the product was eluated by the mixture EtOAc/hexane (1:1).

Ethyl *N*-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)methanimidoate (6a). Yield: 0.65 g (71%); reddish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (1H, s), 7.67 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.29–7.19 (m, 1H), 5.82–5.75 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 1.31 (dt, J = 1.3 Hz, 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 148.9, 147.0, 139.6, 128.5, 126.1, 123.5, 93.6, 63.2, 14.11, 14.09. Anal. Calcd for $C_{13}H_{15}N_3O$: C 68.10; H 6.59; N 18.33. Found C 68.08; H 6.60; N 18.31.

Ethyl *N*-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)ethanimidoate (6b). Yield: 0.91 g (93%); mp 45–46 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0 Hz, 2H), 7.36 (t, J = 9.5 Hz, 2H), 7.23 (t, J = 9.0 Hz, 1H), 5.61 (s, 1H), 4.18 (q, J = 8.5 Hz, 2H), 2.29 (s, 3H), 2.02 (s, 3H), 1.26 (t, J = 8.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 148.8, 146.5, 139.7, 128.4, 125.9, 123.5, 96.6, 62.3, 17.5, 14.2, 14.1. Anal. Calcd for $C_{14}H_{17}N_3O$: C 69.11; H 7.04; N 17.27. Found C 69.13; H 7.02; N 17.25.

Acylation of Aminopyrazoles with Imidoyl Chlorides. To a stirred solution of 6.0 mmol of aminopyrazole in 50 mL of dry 1,4-dioxane with 12.0 mmol of Et_3N was added 6.0 mmol of imidoyl chloride at room temperature. After stirring for 12 h, the suspension was evaporated under a vacuum, diluted with 50 mL of water, and extracted with 100 mL of dichloromethane. The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The crude product was purified by crystallization from the mixture EtOAc/hexane.

***N*-Methyl-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-benzimidamide (4a).** Yield: 1.43 g (82%); mp 207–208 °C (Lit.[18] 203–204 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, J = 7.3 Hz, 2H), 7.62–7.45 (m, 1H), 7.45–7.33 (m, 5H), 7.24–7.14 (m, 3H), 4.69 (br, 1H), 2.88 (d, J = 4.6 Hz, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.1, 150.4, 147.5, 140.8, 135.3, 129.9, 128.80, 128.78, 128.1, 125.3, 122.6, 96.1, 28.9, 14.4; IR (KBr) ν_{max} 3061, 2964, 1588, 1497, 1468, 1381. Anal. Calcd for $C_{18}H_{18}N_4$: C 74.46; H 6.25; N 19.30. Found C 74.58; H 6.11; N 19.31.

***N*-Ethyl-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-benzimidamide (4b).** Yield: 1.44 g (79%); mp 158–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.1 Hz, 3H), 7.34–7.28 (m, 2H), 7.24–7.18 (m, 1H), 7.18–7.10 (m, 2H), 4.89 (s, 1H), 4.81 (br, 1H), 3.60–3.35 (m, 2H), 2.10 (s, 3H), 1.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 149.5, 148.5, 140.3, 135.0, 129.8, 128.5, 128.3, 127.5, 125.2, 123.2, 96.3, 36.7, 14.7, 14.1; IR (KBr) ν_{max} 3060, 2972, 1497, 1464, 1381. Anal. Calcd for $C_{19}H_{20}N_4$: C 74.97; H 6.62; N 18.41. Found C 74.90; H 6.67; N 18.43.

4-Methoxy-*N*-methyl-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzimidamide (4c). Yield: 1.61 g (84%); mp 127–128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 7.8 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.15–7.00 (m, 2H), 6.80 (d, J = 8.1 Hz, 2H), 4.97 (s, 1H), 4.85 (s, 1H), 3.82 (s, 3H), 3.02 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 160.4, 148.5, 140.3, 129.0, 128.,3 127.0, 125.2, 123.1, 113.8, 96.3, 55.3, 28.9, 14.1; IR (KBr) ν_{max} 2964, 1597, 1563, 1501, 1460, 1380, 1246, 1038. Anal. Calcd for $C_{19}H_{20}N_4O$: C 71.23; H 6.29; N 17.49. Found C 71.38; H 6.20; N 17.57.

3-Chloro-*N*-methyl-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-benzimidamide (4d). Yield: 1.73 g (89%); mp 182–183 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, J = 7.6 Hz, 2H), 7.69 (s, 1H), 7.54–7.32 (m, 4H), 7.32–7.15 (m, 2H), 7.11 (d, J = 6.1 Hz, 1H), 4.83

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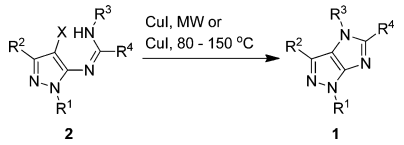
Table 5. Synthesis of 4-Substituted Imidazo[4,5-c]pyrazoles[a]



2 1

Product	Method	Product	Yield, %	Product	Method	Product	Yield, %
a	A		96	h	C		90
	B		93				
b	A		93	i	C		90
	B		87				
c	A		88				
	B		92				
d	A		94	j	C		93
	B		90				
e	A		89	k	C		95
	B		91				
f	A		91				
	B		83				
g	A		95	l	C		91
	B		92				

[a]Reaction conditions. Method A: vial tube, 1 mol of **2**, 2 mol of K_2CO_3, 0.05 mol of CuI, 0.1 mol of DMEDA, DMF, microvawe irridation, 30 min, 150 °C. Method B: 1 mol of **2**, 2 mol of K_2CO_3, 0.05 mol of CuI, 0.1 mol of DMEDA, DMF, 8 h, heating. Method C: 1 mol of **2**, 2 mol of K_2CO_3, 0.05 mol of CuI, 0.1 mol of DMEDA, CH_3CN, 12 h, heating.

(br, 1H), 2.88 (d, J = 3.7 Hz, 3H), 1.98 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.3, 149.9, 147.6, 140.6, 137.2, 133.5, 130.6, 129.9, 127.9, 126.8, 125.4, 122.6, 96.3, 28.8, 14.4; IR (KBr) ν_{max} 3064, 1602, 1580, 1496, 1467, 1381. Anal. Calcd for $C_{18}H_{17}ClN_4$: C 66.56; H 5.28; N 17.25. Found C 66.68; H 5.11; N 17.13.

***N*′-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-*N*-methylbenzimidamide (4e).** Yield: 1.18 g (86%); mp 136−137 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47−7.37 (m, 4H), 7.25−7.15 (m, 1H), 4.32 (s, 1H), 3.53 (s, 3H), 3.36 (s, 3H), 2.89 (s, 3H).1.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.6, 149.3, 144.7, 135.8, 129.8, 128.8, 128.1, 93.3, 34.1, 28.6, 14.3; IR (KBr) ν_{max} 3030, 1381, 1347. Anal. Calcd for $C_{13}H_{16}N_4$: C 68.39; H 7.06; N 24.54. Found C 68.51; H 7.00; N 24.49.

***N*′-(1,3-Dimethyl-1*H*-pyrazol-5-yl)-*N*,4-dimethylbimidamide (4f).** Yield: 1.32 g (91%); mp 167−169 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33 (s, 1H), 7.19 (d, J = 7.7 Hz, 2H), 7.12 (d, J = 7.5 Hz, 2H), 4.40 (br, 1H), 3.51 (s, 3H), 2.87 (d, J = 4.2 Hz, 3H), 2.33 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.6, 149.4, 144.7, 139.4, 132.3, 129.3, 128.1, 93.3, 34.1, 28.6, 21.4, 14.3; IR (KBr) ν_{max} 3030, 1596, 1487, 767, 728. Anal. Calcd for $C_{14}H_{18}N_4$: C 69.39; H 7.49; N 23.12. Found C 68.97; H 7.65; N 23.38.

***N*-Methyl-*N*′-(1-methyl-1*H*-pyrazol-5-yl)benzimidamide (4g).** Yield: 1.12 g (87%); mp 146−147 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60−7.45 (m, 1H), 7.45−7.35 (m, 3H), 7.30−7.15 (m, 2H), 4.50 (br, 1H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.1, 150.4, 147.5, 140.8, 135.3, 129.9, 128.80, 128.78, 128.1, 125.3, 122.6, 96.1, 28.9; IR (KBr) ν_{max} 2963, 1596, 1469, 1392. Anal. Calcd for $C_{12}H_{14}N_4$: C 67.27; H 6.59; N 26.15. Found C 67.25; H 6.63; N 26.13.

***N*′-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-phenyletanimidamide (4h).** Yield: 922 mg (53%); mp 169−171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 5.1 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.8 Hz, 3H), 7.06 (t, J = 7.1 Hz, 1H), 6.69 (br, 1H), 5.64 (s, 1H), 2.33 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.1, 147.9, 147.3, 139.1, 138.5, 127.8, 127.5, 124.9, 122.8, 122.6 M 119.7, 95.6, 17.7, 12.6; IR (KBr) ν_{max} 1602, 1588, 1497, 1377. Anal. Calcd for $C_{18}H_{18}N_4$: C 74.46; H 6.25; N 19.30. Found C 74.51; H 6.18; N 19.31.

Condensation of Imino Esters of Aminopyrazoles with Anilines. A round-bottom flask with a magnetic stirrer was charged with 6.0 mmol of 5-aminopyrazole, 6.0 mmol of aniline, and 5 mL of MeOH. The mixture was stirred until all reagents dissolved. Then the

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mixture was heated at 140 °C without stirring for 6 h. The crude product was purified by flash chromatography.

***N*-(Phenyl-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-mehtanimidamide (4i).** Yield: 1.25 g (76%); mp 169−171 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 5.1 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.25 (t, J = 7.8 Hz, 3H), 7.06 (t, J = 7.1 Hz, 1H), 6.81−6.49 (br, 1H), 5.64 (s, 1H), 2.33 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.8, 150.9, 148.3, 140.3, 129.5, 128.9, 125.9, 123.5, 123.0, 119.3, 116.8, 93.0, 14.6; IR (KBr) ν_{max} 3042, 1497, 1381. Anal. Calcd for $C_{17}H_{14}N_4$: C 74.46; H 6.25; N 19.30. Found C 74.51; H 6.18; N 19.31.

***N*-(4-Chlorophenyl)-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-mehtanimidamide (4j).** Yield: 1.01 g (54%); mp 178−179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.70 (t, J = 7.8 Hz, 2H), 7.40 (t, J = 8.1 Hz, 2H), 7.30−7.20 (m, 3H), 7.20−6.75 (m, 2H), 5.87 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 149.2, 139.5, 137.7, 129.4, 128.5, 126.3, 123.9, 117.7, 92.5, 14.2; IR (KBr) ν_{max} 1495, 1380. Anal. Calcd for $C_{17}H_{15}ClN_4$: C 65.70; H 4.86; N 18.03. Found C 65.73; H 4.80; N 18.05.

***N*-(4-Methylphenyl)-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-imidoformamide (4k).** Yield: 1.41 g (81%); mp 159−160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37−8.10 (br, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.63−7.40 (m, 1H), 7.38 (t, J = 7.7 Hz, 2H), 7.25−7.20 (m, 1H), 7.09 (d, J = 8.1 Hz, 2), 7.00−6.20 (m, 1H), 5.83 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 139.5, 136.5, 133.2, 130.0, 128.5, 126.1, 123.9, 116.9, 92.3, 20.7, 14.2; IR (KBr) ν_{max} 3031, 1601, 1505. Anal. Calcd for $C_{18}H_{18}N_4$: C 74.46; H 6.25; N 19.29. Found C 74.51; H 6.23; N 19.26.

***N*-(4-Methoxyphenyl)-*N*′-(3-methyl-1-phenyl-1*H*-pyrazol-5yl)imidoformamide (4l).** Yield: 1.14 g (62%); mp 63−64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45−7.70 (m, 2H), 7.70−7.50 (m, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.00−6.60 (m, 2H), 6.79 (d, J = 6.2 Hz, 2H), 5.80 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 153.2, 150.7, 148.3, 139.6, 131.9, 128.9, 128.6, 126.5, 123.5, 118.9, 114.9, 55.6, 14.9; IR (KBr) ν_{max} 2992, 2951, 1178, 1128, 1031. Anal. Calcd for $C_{18}H_{18}N_4O$: C 70.57; H 5.92; N 18.29. Found C 70.46; H 5.98; N 18.15.

Bromination of Amidines with NBS. To a suspension of 4.0 mmol of amidine in 25 mL of dry acetonitrile was added 4.1 mmol of NBS at room temperature. The mixture was refluxed and monitored by TLC. Then the solution was evaporated, diluted with 100 mL of dichloromethane, and washed twice with 25 mL of water. The organic layer was dried over Na_2SO_4 and evaporated.

***N*′-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-methyl-benzimidamide (2a).** Yield: 1.37 g (93%); mp 106−107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 6.8 Hz, 2H), 7.34 (t, J = 7.1 Hz, 2H), 7.30 (t, J = 7.8 Hz, 1H), 7.26−7.11 (m, 3H), 7.10−6.75 (m, 2H), 5.23−5.06 (br, 1H), 3.72−3.66 (m, 2H), 3.09 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 147.2, 134.8, 129.9, 128.6, 128.3, 127.1, 125.7, 122.5, 86.0, 29.2, 12.9; IR (KBr) ν_{max} 1497, 1381. Anal. Calcd for $C_{18}H_{17}BrN_4$: C 58.55; H 4.64; N 15.17. Found C 58.60; H 4.60; N 15.26.

***N*′-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-ethyl-benzimidamide (2b).** Brown solid. Yield: 1.39 g (91%); mp 162−163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.31−7.25 (m, 1H), 7.25−7.09 (m, 3H), 7.09−6.75 (m, 2H), 5.15 (s, 1H), 3.70−3.41 (m, 2H), 2.13 (s, 3H), 1.40−1.12 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 147.2, 140.0, 135.0, 129.9, 128.6, 128.2, 127.1, 125.7, 122.4, 86.0, 37.0, 14.6, 12.9; IR (KBr) ν_{max} 1594, 1378. Anal. Calcd for $C_{19}H_{19}BrN_4$: C 59.54; H 5.00; N 14.62. Found C 59.49; H 5.05; N 14.53.

***N*′-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-4-methoxy-*N*-methybenzimidamide (2c).** Yield: 1.42 g (89%); mp 105−106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.03−6.80 (m, 2H), 6.68 (d, J = 8.0 Hz, 2H), 5.05 (s, 1H), 3.76 (s, 3H), 3.09 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 160.7, 147.4, 147.2, 140.1, 128.7, 128.6, 127.2, 125.7, 122.4, 113.7, 85.9, 55.3, 29.2, 12.9; IR (KBr) ν_{max} 1598. Anal. Calcd for $C_{19}H_{19}BrN_4O$: C 57.15; H 4.80; N 14.03. Found C 57.10; H 4.92; N 14.15.

***N*′-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-3-chloro-*N*-methyl-benzimidamide (2d).** Yield: 1.55 g (96%); mp 124−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.1 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.31−7.15 (m, 2H), 7.15−6.98 (m, 1H), 6.98−6.52 (br, 2H), 5.47−5.19 (br, 1H), 3.02 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 147.3, 146.7, 139.7, 136.4, 134.2, 131.2, 130.1, 129.5, 128.7, 127.3, 126.0, 125.2, 123.9, 122.7, 86.2, 29.1, 12.8; IR (KBr) ν_{max} 1590, 1499, 1363. Anal. Calcd for $C_{18}H_{16}BrClN_4$: C 53.55; H 3.99; N 13.88. Found C 53.50; H 3.90; N 13.82.

***N*′-(4-Bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*-methylbenz-imidamide (2e).** Yield: 1.07 g (87%); mp 120−122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.18 (m, 5H), 5.28−5.12 (br, 1H), 3.57 (s, 3H), 3.10 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 147.1, 145.3, 135.0, 130.2, 129.1, 128.4, 127.3, 83.3, 35.1, 29.1, 12.7; IR (KBr) ν_{max} 1377. Anal. Calcd for $C_{13}H_{15}BrN_4$: C 50.83; H 4.92; N 18.24. Found C 50.76; H 4.87; N 18.34.

***N*′-(4-Bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*,4-dimethyl-benzimidamide (2f).** Yield: 1.21 g (94%); mp 159−160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.01 (m, 4H), 5.32−4.99 (br, 1H), 3.54 (s, 3H), 3.07 (s, 3H), 2.31 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 145.3, 140.4, 132.0, 129.2, 127.2, 83.4, 35.2, 29.2, 21.4, 12.7; IR (KBr) ν_{max} 2964, 1602. Anal. Calcd for $C_{14}H_{17}BrN_4$: C 52.35; H 5.33; N 17.44. Found C 52.47; H 5.40; N 17.37.

***N*′-(4-Bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-methylbenzimi-damide (2g).** Yield: 1.05 g (90%); mp 164−165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86−7.69 (br, 1H), 7.46−7.26 (m, 3H), 7.26−7.15 (m, 2H), 7.09 (s, 1H), 3.52 (s, 3H), 2.91 (d, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.6, 147.6, 137.5, 130.3, 128.6, 127.9, 81.2, 35.8, 29.9. ; IR (KBr) ν_{max} 1596. Anal. Calcd for $C_{12}H_{13}BrN_4$: C 49.16; H 4.47; N 19.11. Found C 49.15; H 4.45; N 19.13.

***N*′-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-phenyli-midoformamide (2i).** Yield: 1.19 g (81%); mp 112−113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92−8.55 (br, 1H), 8.37−7.93 (br, 1H), 7.62 (d, J = 7.1 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.32−7.16 (m, 3H), 7.06 (t, J = 7.3 Hz, 1H), 6.98−6.55 (br, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 147.8, 145.3, 139.6, 138.7, 129.7, 128.6, 126.6, 123.9, 123.7, 116.8, 13.0; IR (KBr) ν_{max} 3033, 1594, 1496, 1383. Anal. Calcd for $C_{17}H_{15}BrN_4$: C 57.48; H 4.26; N 15.77. Found C 57.00; H 4.39; N 15.67.

***N*′-(4-Bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-(4-chlorophenyl)imidoformamide (2j).** Yield: 1.18 g (76%); mp 182−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85−8.50 (br, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.37 (t, J = 10.0 Hz, 2H), 7.32−7.13 (m, 2H), 7.11−6.60 (br, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 147.9, 144.9, 139.3, 137.4, 129.6, 129.0, 128.6, 123.6, 117.9, 83.9, 13.0; IR (KBr) ν_{max} 3031, 1377. Anal. Calcd for $C_{17}H_{14}BrClN_4$: C 52.40; H 3.62; N 14.38. Found C 52.38; H 3.63; N 14.37.

Iodination of Amidines with Iodine. To 4.0 mmol of amidine dissolved in 3 mL of dry DMF at room temperature were added 4.0 mmol of iodine and 8.0 mmol of KOH under stirring. The reaction mixture was stirred for 2 h at room temperature and then left to stand under TLC monitoring until the reaction was complete. Then the mixture was poured into 100 mL of water and the precipitate was filtered off. The crude product was used in the next step without purification.

(1*E*)-*N*′-(4-Iodo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-phenylethanimidamide (2h). Yield: 1.08 g (65%); mp 141−142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.69−9.55 (m, 1H), 7.69 (d, J = 6.8 Hz, 2H), 7.58 (t, J = 7.7 Hz, 2H), 7.46 (d, J = 8.1 Hz, 1H), 7.40 (t, J = 6.8 Hz, 2H), 7.26 (m, 2H), 7.02 (t, J = 6.6 Hz, 1H), 2.19 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.73, 146.8, 140.3, 140.0, 131.9, 129.3, 129.0, 126.6, 123.5, 114.9, 85.3, 20.2, 13.2; IR (KBr) ν_{max} 1594, 1362. Anal. Calcd for $C_{18}H_{17}IN_4$: C 51.94; H 4.12; N 13.46. Found C 51.90; H 4.10; N 13.56.

***N*′-(4-Iodo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-(4-methylphenyl)imidoformamide (2k).** Yield: 1.46 g (88%); dark brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (m, 1H), 7.30 (d, J = 6.1 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.0 Hz, 1H), 6.84 (m, 1H), 6.83 (d, J = 8.1 Hz, 2H), 5.83 (s, 1H), 3.79 (s, 3H), 2.33 (s, 3H);

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^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 150.5, 149.0, 139.7, 139.6, 132.2, 128.4, 126.1, 123.8, 119.0, 114.8, 92.2, 55.6, 14.2; IR (KBr) ν_{max} 1602, 1502, 1456. Anal. Calcd for $C_{18}H_{17}IN_4$: C 51.94; H 4.12; N 13.46. Found C 51.90; H 4.11; N 13.47.

***N′*-(4-Iodo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N*-(4-methoxyphenyl)imidoformamide (2l).** Yield: 1.45 g (84%); mp 64−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56−8.35 (m, 2H), 7.75−7.57 (m, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 6.93−6.72 (m, 3H), 3.79 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 153.2, 150.7, 148.4, 139.6, 131.9, 128.6, 126.5, 123.5, 118.9, 114.9, 55.6, 14.9; IR (KBr) ν_{max} 1601, 1452. Anal. Calcd for $C_{18}H_{17}IN_4O$: C 50.02; H 3.96; N 12.96. Found C 50.10; H 3.94; N 12.93.

Cyclization of *N′*-(Halopyrazolyl)amidines to Imidazo[4,5-*c*]pyrazoles under Microwave Irridation (Method A). A vial was charged with 0.84 mmol of *N′*-halopyrazolylamidine **2**, 1.68 mol of Cs_2CO_3, 0.084 mol of DMEDA, 3 mL of dry DMF, and 0.042 mol of powdered CuI under Ar. The stirred mixture was heated for 30 min at 150 °C under microwave irridation, evaporated, diluted with 100 mL of dichloromethane, and filtered. The organic layer was washed twice with 50 mL of water, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (EtOAc/hexane).

Cyclization of *N′*-(Halopyrazolyl)amidines to Imidazo[4,5-*c*]pyrazoles without Microwave Irridation (Methods B and C). A round-bottom flask was charged with 0.84 mmol of *N′*-halopyrazolylamidine **2**, 1.68 mol of Cs_2CO_3, 0.084 mol of DMEDA, and 3 mL of dry DMF (method B) or 10 mL of dry MeCN (method C). To the stirred mixture was then added 0.042 mol of powdered CuI under Ar. The stirred mixture was heated under Ar and monitored by TLC, evaporated, diluted with 100 mL of dichloromethane, and filtered. The organic layer was washed twice with 50 mL of water, dried over Na_2SO_4, and evaporated. The crude product was purified by flash chromatography (EtOAc/hexane).

3,4-Dimethyl-1,5-diphenyl-1,4-dihydroimidazo[4,5-*c*]pyrazole (1a). Method A. Yield: 232 mg (96%). Method B. Yield: 225 mg (93%); mp 155−156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 7.6 Hz, 2H), 7.60−7.48 (m, 3H), 7.45 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 8.1 Hz, 1H), 3.87 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 150.5, 139.9, 130.3, 130.1, 129.6, 129.4, 129.1, 128.7, 125.3, 124.0, 117.1, 33.1, 12.5; IR (KBr) ν_{max} 3027, 1597, 1501, 1379. Anal. Calcd for $C_{18}H_{16}N_4$: C 74.98; H 5.59; N 19.43. Found C 74.92; H 5.63; N 19.45.

4-Ethyl-3-methyl-1,5-diphenyl-1,4-dihydroimidazo[4,5-*c*]pyrazole (1b). Method A. Yield: 236 mg (93%). Method B. Yield: 220 mg (87%); mp 153−155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20−8.17 (m, 1H), 8.17−8.14 (m, 1H), 7.70 (m, 2H), 7.53 (m, 3H), 7.45 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.52 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 150.9, 139.9, 130.6, 129.9, 129.6, 129.4, 129.2, 128.7, 124.0, 123.9, 117.2, 40.9, 29.7, 17.0, 13.2; IR ($CHCl_3$) ν_{max} 1383. Anal. Calcd for $C_{19}H_{18}N_4$: C 75.47; H 6.00; N 18.53. Found C 75.48; H 6.02; N 18.50.

5-(4-Methoxyphenyl)-3,4-dimethyl-1-phenyl-1,4-dihydroimidazo[4,5-*c*]-pyrazole (1c). Method A. Yield: 235 mg (88%). Method B. Yield: 246 mg (92%); mp 96−97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 8.3 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 153.6, 149.4, 138.9, 129.7, 129.0, 128.1, 124.0, 122.9, 121.7, 116.0, 113.2, 54.4, 32.0, 11.5; IR (KBr) ν_{max} 1597, 1504, 1251, 1177. Anal. Calcd for $C_{19}H_{18}N_4O$: C 71.68; H 5.70; N 17.60. Found C 71.63; H 5.72; N 17.59.

5-(3-Chlorophenyl)-3,4-dimethyl-1-phenyl-1,4-dihydroimidazo[4,5-*c*]pyrazole (1d). Method A. Yield: 254 mg (94%). Method B. Yield: 244 mg (90%); mp 148−149 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 2H), 7.57 (s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.50−7.40 (m, 4H), 7.17 (t, J = 7.6 Hz, 1H), 3.85 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 150.3, 139.8, 134.8, 131.9, 130.1, 129.9, 129.6, 129.4, 129.2, 127.3, 125.4, 124.1, 117.0, 33.2, 12.5; IR (KBr) ν_{max} 1600, 1499, 1379. Anal. Calcd for $C_{18}H_{15}ClN_4$: C 66.98; H 4.68; N 17.36. Found C 66.93; H 4.65; N 17.35.

1,3,4-Trimethyl-5-phenyl-1,4-dihydroimidazo[4,5-*c*]pyrazole (1e). Method A. Yield: 169 mg (89%). Method B. Yield: 173 mg (91%); mp 127−128 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72−7.62 (m, 2H), 7.55−7.43 (m, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 151.2, 130.3, 129.4, 129.2, 128.6, 127.2, 123.5, 35.0, 33.2, 12.3; IR ($CHCl_3$) ν_{max} 1459, 1382. Anal. Calcd for $C_{13}H_{14}N_4$: C 69.00; H 6.24; N 24.76. Found C 69.02; H 6.20; N 24.78.

1,3,4-Trimethyl-5-(4-methylphenyl)-1,4-dihydroimidazo-[4,5-*c*]pyrazole (1f). Method A. Yield: 184 mg (91%). Method B. Yield: 168 mg (83%); mp 75−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 3.94 (s, 3H), 3.83 (s, 3H), 2.50 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 151.8, 139.6, 129.3, 129.1, 127.4, 127.2, 123.4, 34.8, 33.1, 21.4, 12.2; IR (KBr) ν_{max} 1500, 1376. Anal. Calcd for $C_{14}H_{16}N_4$: C 69.67; H 6.71; N 23.32. Found C 69.68; H 6.70; N 23.32.

1,4-Dimethyl-5-phenyl-1,4-dihydroimidazo[4,5-*c*]pyrazole (1g). Method A. Yield: 169 mg (95%). Method B. Yield: 164 mg (92%); mp 113−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 6.5 Hz, 2H), 7.55−7.44 (m, 3H), 7.35 (s, 3H), 4.02 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 151.1, 130.2, 129.6, 129.2, 128.7, 125.6, 117.6, 35.5, 33.8; IR (KBr) ν_{max} 1595, 1458, 1365, 768, 732, 700. Anal. Calcd for $C_{12}H_{12}N_4$: C 67.90; H 5.70; N 26.40. Found C 67.89; H 5.71; N 26.40.

3,5-Dimethyl-1,4-diphenyl-1,4-dihydroimidazo[4,5-*c*]-pyrazole (1h). Method C. Yield: 217 mg (90%); mp 124−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 1.0 Hz, 8.4 Hz, 2H), 7.60−7.51 (m, 2H), 7.51−7.42 (m, 3H), 7.42−7.31 (m, 2H), 7.14 (t, J = 7.5 Hz, 1H), 2.50 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 150.0, 139.8, 136.3, 129.9, 129.6, 129.2, 128.5, 126.1, 124.2, 117.2, 14.9, 12.6; IR (KBr) ν_{max} 1594, 1460, 1384. Anal. Calcd for $C_{18}H_{16}N_4$: C 74.98; H 5.59; N 19.43. Found C 74.97; H 5.58; N 19.45.

4-Phenyl-1,4-dihydro-3-methyl-1-phenylimidazo[4,5-*c*]-pyrazole (1i). Method C. Yield: 207 mg (90%); mp 132−133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 7.7 Hz, 2H), 7.81 (s, 1H), 7.55−7.41 (m, 8H), 7.17 (t, J = 7.3 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 139.5, 136.5, 130.1, 130.0, 129.3, 127.8, 124.6, 122.4, 122.0, 117.3, 13.7; IR (KBr) ν_{max} 1600, 1505, 1464, 1382. Anal. Calcd for $C_{17}H_{14}N_4$: C 74.43; H 5.14; N 20.42. Found C 74.42; H 5.15; N 20.42.

4-(4-Chlorophenyl)-1,4-dihydro-3-methyl-1-phenylimidazo-[4,5-*c*]pyrazole (1j). Method C. Yield: 240 mg (93%); mp 146−147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 2H), 7.79 (s, 1H), 7.53 (d., J = 8.6 Hz, 2H), 7.51−7.39 (m, 4H), 7.20 (t, J = 7.1 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 140.8, 138.5, 134.1, 132.5, 129.2, 128.8, 128.3, 123.6, 122.5, 120.7, 116.3, 12.1; IR (KBr) ν_{max} 1595, 1500, 1383. Anal. Calcd for $C_{17}H_{13}ClN_4$: C 66.13; H 4.24; 18.14. Found C 66.20; H 4.30; N 29.50.

3-Methyl-4-(4-methylphenyl)-1-phenyl-1,4-dihydroimidazo-[4,5-*c*]pyrazole (1k). Method C. Yield: 230 mg (95%); mp 113−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 2H), 7.77 (s, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.40−7.27 (m, 4H), 7.17 (t, J = 7.5 Hz, 1H), 2.46 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 141.9, 139.6, 137.8, 134.0, 130.5, 130.0, 129.2, 124.4, 122.4, 122.1, 117.2, 21.0, 13.6; IR (KBr) ν_{max} 1596, 1460, 1380. Anal. Calcd for $C_{18}H_{16}N_4$: C 74.98; H 5.59; N 19.43. Found C 74.91; H 5.61; N 19.48.

4-(4-Methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydroimidazo-[4,5-*c*]pyrazole (1l). Method C. Yield: 232 mg (91%); mp 167−168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 2H), 7.76 (s, 1H), 7.48 (t, J = 8.1 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 3.91 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 161.6, 142.1, 139.7, 130.0, 129.6, 129.2, 124.4, 124.1, 122.5, 117.2, 115.1, 55.7, 13.4; IR (KBr) ν_{max} 1597, 1460, 1383, 1158, 1028. Anal. Calcd for $C_{18}H_{16}N_4O$: C 71.04; H 5.30; N 18.41. Found C 71.04; H 5.30; N 18.39.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. 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.

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