Practical Multi-Component Synthesis of *Di*- or *Tri*-Aryl (Heteraryl) Substituted 2-(Pyridin-2-yl)imidazoles from Simple Building Blocks

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A convenient and highly efficient multicomponent protocol has been developed for the synthesis of various *poly*-substituted 2-(pyridin-2-yl)imidazoles from 2-cyanopyridine, corresponding aromatic aldehydes, and NH_4OAc/primary amine. Notably, *tri*-substituted 2-(pyridin-2-yl)imidazoles were highly yielded when aromatic primary amines were used as substrates, but both *di*- and *tri*-substituted 2-(pyridin-2-yl)imidazoles were obtained in one pot when some aliphatic primary amines were used as substrates.

Introduction

Imidazoles with the heterocyclic substituent in 2-position, which are found in many natural products and drug cores, have exhibited extensive applications in organic synthesis.[1] 2-(Pyridin-2-yl)imidazoles are one of the key intermediates in the syntheses of pharmacologically active compounds, such as **I** and **II** (Scheme 1).[2] Moreover, 2-(pyridin-2-yl)imidazoles have also been used as excellent ligands in transition-metal-catalyzed coupling reactions.[3] Because of the extensive applicability of 2-(pyridin-2-yl)imidazoles, several strategies for the synthesis of the 2-(pyridin-2-yl)imidazole derivatives have been developed.[4] Although these methodologies have achieved remarkable success, the potential limitations including the demand of substrates which are not readily or commercially available and inefficiency of the transformations restrain the wider utilization. Therefore, to develop a concise and practical synthetic protocol for the preparation of 2-(pyridin-2-yl)imidazole derivatives is still currently an area of considerable interest. Recently, Tu et al. have developed a concise and efficient four-component approach to *di*-substituted 2-(pyridin-2-yl)imidazoles under the solvent-free and microwave-irradiation conditions.[4l] Compared with the traditional synthetic routes for imidazoles using complicated substrates such as 1,2-diketone, amino-acetaldehyde, or α-ketomonoxime,[5] they utilized more simple and readily available starting materials to construct a series of *di*-substituted 2-(pyridin-2-yl)imidazoles in good to excellent yields. As our continuing endeavors in developing novel multicomponent reactions to synthesize valuable heterocyclic compounds,[6] we made a systematic and deeper discussion to the novel approach based on the work of Tu et al. and explored a versatile, highly efficient multicomponent reaction to synthesize *di*- or *tri*-substituted 2-(pyridin-2-yl)imidazoles. As shown in Scheme 2, various *poly*-substituted 2-(pyridin-2-yl)imidazoles could be successfully synthesized from 2-cyanopyridine, corresponding aromatic aldehydes and NH_4OAc/primary amine in the solvent of acetic acid at 170 °C. Compared with Tu et al.'s work, not only more *di*-substituted 2-(pyridin-2-yl)imidazoles but also a variety of *tri*-substituted 2-(pyridin-2-yl)imidazoles could be efficiently synthesized in our protocol. Moreover, while some aliphatic primary amines were used as substrates, both *di*- and *tri*-substituted 2-(pyridin-2-yl)imidazoles were generated in one pot. Herein, we report these results.

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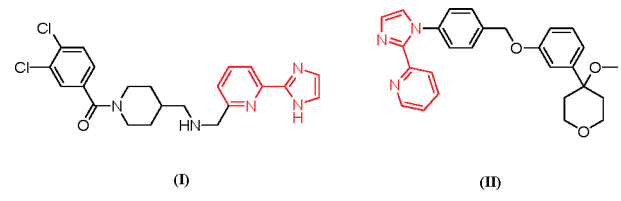
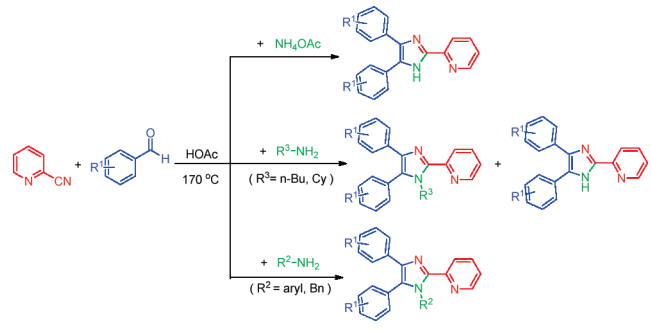
Results and Discussion

Our initial attempts to explore the feasibility of the proposed process focused on heating the 0.5:1:5 mixtures of 2-cyanopyridine, 4-chlorobenzaldehyde, and NH_4OAc in the solvent of HOAc at 170 °C. Satisfyingly, the process

Scheme 1. Pharmacologically Active 2-Pyridiny-Substituted Imidazoles



Scheme 2. Novel Strategy to Synthesize *Poly*-Substituted 2-(Pyridin-2-yl)imidazoles



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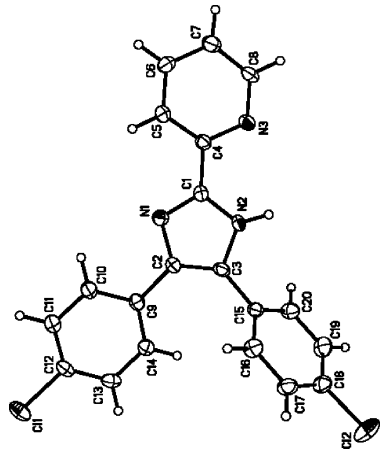
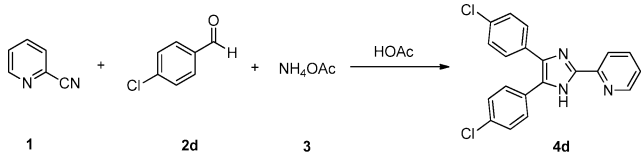


Figure 1. Crystal Structure of **4d**.

Table 1. Optimization of Reaction Conditions[a]



1 2d 3 4d

entry	substrate **1**:**2d**:**3**	temperature (°C)	time (h)	yield[b] (%)
1	0.5:1:5	170	10	52
2	1:1:5	170	10	62
3	1.5:1:5	170	10	70
4	2:1:5	170	10	79
5	2.5:1:5	170	10	93
6	3:1:5	170	10	89
7	2.5:1:3	170	10	77
8	2.5:1:1	170	10	74
9	2.5:1:5	150	10	77
10	2.5:1:5	130	10	69
11	2.5:1:5	170	6	87
12	2.5:1:5	170	4	74

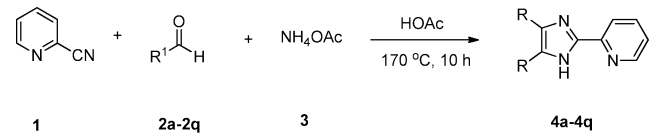
[a] Reactions run in 3.0 mL of HOAc with 1.0 mmol 4-chlorobenzaldehyde. [b] Isolated yield, calculated based on the amount of aldehyde.

was successfully accomplished and generated *di*-substituted 2-(pyridin-2-yl)imidazole **4d** in 52% yield. The definite structure of the final product was confirmed by the X-ray crystal structure (Figure 1).[7]

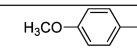
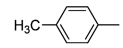
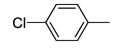
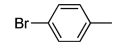
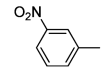
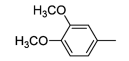
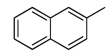
Subsequently, optimization of the reaction conditions was undertaken to increase the yield by employing various molar ratios of substrates at different temperatures for several hours. The results are summarized in Table 1. The yield was increased up to 93% under the optimized conditions with a molar ratio of 2.5:1:5 for 2-cyanopyridine/4-chlorobenzaldehyde/NH_4OAc in 3.0 mL solvent of HOAc at 170 °C for 10 h (entry 5).

According to the optimized conditions, we continued to examine 2-cyanopyridine, NH_4OAc, and a wide variety of aromatic aldehydes to establish the scope of the strategy. As shown in Table 2, aromatic adehydes bearing either electron-withdrawing or electron-donating groups perform equally well in the reactions (entries 1−6). However, aliphatic aldehydes (propionaldehyde) have no reaction activity in the novel method (entry 17). To study the steric influence of the approach, we also tested several aromatic aldehydes with substituent in different positions. To our delight, 3-substituted aromatic aldehydes were also very

Table 2. Substrate Scope for the Synthesis of 4, 5-Disubstitued 2-(pyridin-2-yl)imidazoles[a]



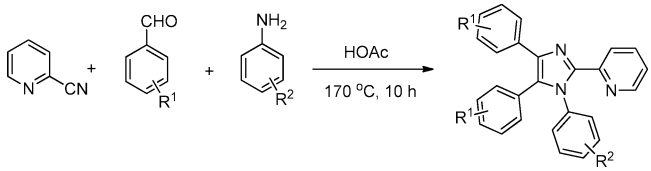
1 2a-2q 3 4a-4q

Entry	R^1	Product	Yield[b] (%)
1	 (**2a**)	**4a**[c]	92
2	 (**2b**)	**4b**[c]	88
3	 (**2c**)	**4c**[c]	81
4	 (**2d**)	**4d**[c]	93
5	 (**2e**)	**4e**[c]	85
6	 (**2f**)	**4f**	80
7	 (**2g**)	**4g**	88
8	 (**2h**)	**4h**	88
9	 (**2i**)	**4i**	84
10	 (**2j**)	**4j**[c]	50
11	 (**2k**)	**4k**	41
12	 (**2l**)	**4l**	62
13	 (**2m**)	**4m**	95
14	 (**2n**)	**4n**[c]	80
15	 (**2o**)	**4o**[c]	65
16	 (**2p**)	**4p**	78
17	 (**2q**)	**4q**	N.R

[a] Reaction conditions: 1 (2.5 mmol), 2 (1.0 mmol), 3 (5.0 mmol), 3.0 mL of HOAc at 170 °C for 10 h. [b] Isolated yield, calculated based on the amount of aldehydes. [c] These products have been reported in reference 4l.

reactive (entries 7−9). However, aromatic aldehydes with electron-withdrawing groups at *ortho*-position just provided modest yields of the corresponding 2-(pyridin-2-yl)imidazoles (entries 10, 11). We supposed that it was contributed to the strong steric and electron-withdrawing influence. Notably, the activity of 1-naphthaldehyde was much worse than 2-naphthaldehyde in this transformation (entries 12, 13). In addition, several heteroaromatic aldehydes also delivered the corresponding 2-(pyridin-2-yl)imidazoles in satisfactory yields (entries 14−16). All these examples illustrated the excellent generality of this approach for a wide variety of aromatic aldehydes.

Table 3. Substrate Scope Study for the Synthesis of 1,4,5-Trisubstituted 2-(pyridin-2-yl)imidazoles[a]



entry	substrate R^1	substrate R^2	product	yield[b] (%)
1	4-OCH_3 (**2a**)	4-OCH_3 (**5a**)	**6a**	92
2	4-OCH_3 (**2a**)	4-CH_3 (**5b**)	**6b**	89
3	4-OCH_3 (**2a**)	4-H (**5c**)	**6c**	83
4	4-OCH_3 (**2a**)	4-Cl (**5d**)	**6d**	87
5	4-OCH_3 (**2a**)	3-Cl (**5e**)	**6e**	82
6	4-Cl (**2d**)	4-OCH_3 (**5f**)	**6f**	97
7	4-Cl (**2d**)	4-CH_3 (**5g**)	**6g**	95
8	4-Cl (**2d**)	4-H (**5h**)	**6h**	85
9	4-Cl (**2d**)	4-Cl (**5i**)	**6i**	92
10	4-Cl (**2d**)	4-Br (**5j**)	**6j**	90
11	4-Cl (**2d**)	3-Cl (**5k**)	**6k**	90

[a] Reaction conditions: 1 (2.5 mmol), 2 (1.0 mmol), 5 (5.0 mmol), 3.0 mL of HOAc at 170 °C for 10 h. [b] Isolated yield, calculated based on the amount of aldehyde.

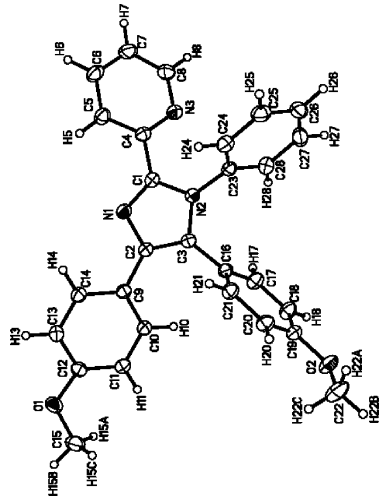
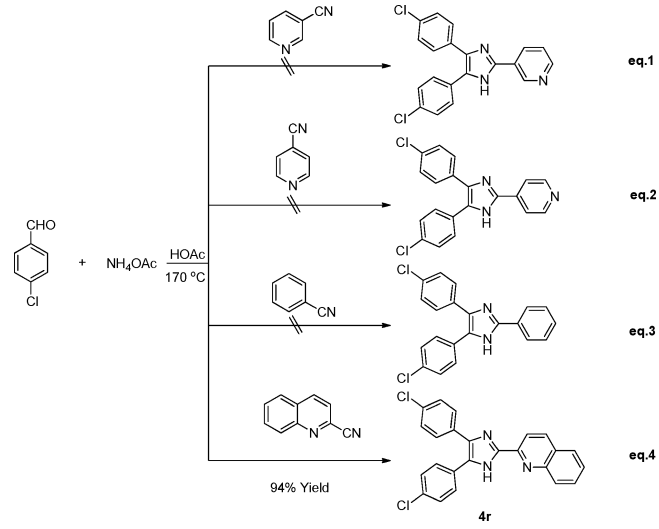


Figure 2. Crystal Structure of **6c**.

So far, the novel approach was found highly efficient for the syntheses of *di*-substituted 2-(pyridin-2-yl)imidazoles. Next, we were interested in the formation of *tri*-substituted 2-(pyridin-2-yl)imidazoles using this strategy. Although intensive efforts have been made to form highly substituted imidazoles, to our best knowledge, only a handful of general methods exist for the construction of *tetra*-substituted imidazoles.[8] Herein, we try our approach to construct *tri*-substituted 2-(pyridin-2-yl)imidazoles using the multicomponent condensation simply by changing NH_4OAc to primary amine. First, the same reaction conditions were applied for the synthesis of the product **6c** via the condensation of 2-cyanopyridine, 4-methoxybenzaldehyde, and aniline. To our pleasure, the 1,4,5-trisubstituted 2-(pyridin-2-yl)imidazole **6c** was obtained in a high yield (83%, Table 3, entry 3). The definite structure of **6c** was confirmed by the X-ray crystal structure (Figure 2).[9] Subsequently, the substrate scope of the reaction was evaluated using a variety of structurally diverse aldehydes and primary aromatic amines (Table 3). Both aromatic aldehydes and primary amines with either electron-deficient or electron-rich groups could be subjected successfully to this protocol. Moreover, the strategy is highly efficient to the sterically hindered systems as well.

Scheme 3

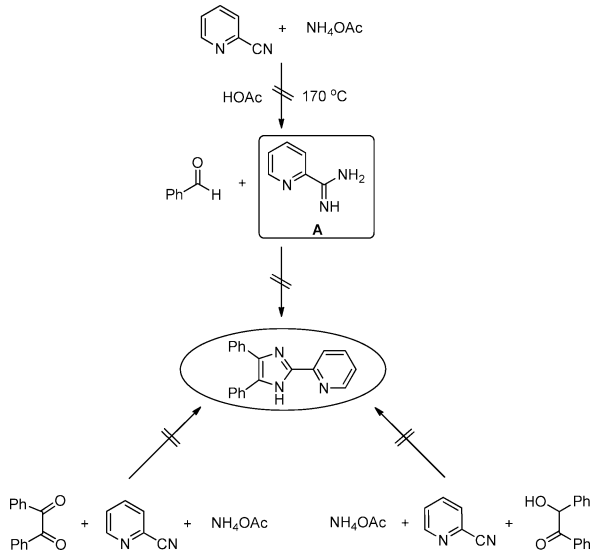


Furthermore, 3- or 4-cyanopyridine were used as substrates to extend the generality of this approach to synthesize 3- or 4-(pyrid-2-yl)imidazoles. As shown in Scheme 3, no product was obtained from either reaction as shown in the eqs 1 and 2 in Scheme 3. Additionally, the reaction also did not occur when benzonitrile was taken as substrate (Scheme 3, eq. 3). All these results indicated that 2-position cyanopyridine played a key role in the reaction. We thought that it might be due to the special electron influence of the 2-substituted pyridine. To confirm our assumption, 2-cyanoquinoline, the analogue of 2-cyanopyridine, was selected as the substrate to realize the transformation. As expected, the similar product **4r** was obtained in 94% yield (Scheme 3, eq. 4). Consequently, all these results lead us to pay attention to the insight into the mechanism of the reaction.

Though a mechanism had been proposed by Tu el al.,[41] it was demonstrated in the basic reaction condition. We thought that the mechanism was not suitable to our acidic reaction condition; we needed to explore a more reasonable mechanism. According to the literature,[6] two common mechanistic hypotheses might be possible: One path involved the cyclocondensation of 1, 2-diketone or α-hydroxyketone, 2-cyanoarene, and NH_4OAc. To explore the possibility, our initial attempt was taken by employing benzil or benzoin as substrate, but none of the reactions occurred (Scheme 4). Subsequently, we attempted to explore another possibility for the involvement of the cyclocondensation of amidine **A** and benzaldehyde. Unfortunately, no product was observed. Either, the amidine **A** could not be synthesized from 2-cyanopyridine and NH_4OAc in the acid condition (Scheme 4). All these results indicated that our approach could not be achieved on this mechanism.

Fortunately, while 1-phenylethanamine **5l** served as substrate, the unexpected products gave us some clue to the mechanism. In this reaction, no 4,5-bis(4-chlorophenyl)-2-(pyridin-2-yl)-1-benzyl-imidazole was obtained, as expected. However, some unexpected products were observed (Scheme 5): one confirmed product, which was characterized by the

Scheme 4



X-ray crystal structure (Figure 3),[10] was an unexpected *tri*-substituted 2-(pyridin-2-yl)imidazole **6l**. Other products were the *di*-substituted 2-(pyridin-2-yl)imidazole **4d** and styrene. According to the literature,[11] we thought that they were formed from the route as shown in Scheme 5. To confirm our assumption, we chose imine as a substrate to achieve the reaction. However, no product was formed and the phenomenon of the cleavage of imine was observed. The known cleavage products were well observed in the TLC. This result also supported our hypothetic synthetic route to the product **6l**.

On the basis of all above observations and the literature, the mechanism is thought to include the following steps (Scheme 6). First, the imine was obtained from aromatic aldehyde and amine. Second the swift nucleophilic attack occurred between imine, 2-cyanopyridine, and another molecule of aromatic aldehyde in the acidic condition. The

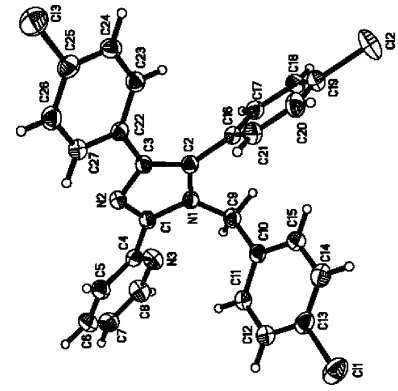
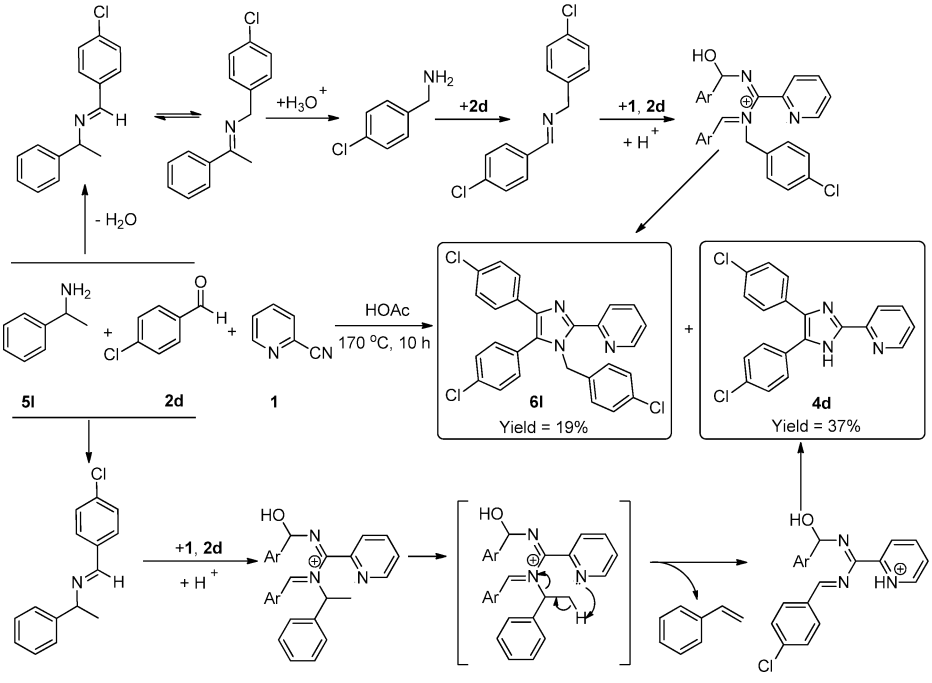


Figure 3. Crystal Structure of **6l**.

next step, which might be the key step, involved the intramolecular nucleophilic attack to finally construct the imidazole core. We consider that this step may be the result of the special electron influence of the 2-substituted pyridine, which has been confirmed in some reported researches.[12] This hypothesis is also supported by the fact that only 2-substituted pyridine and its analogue can achieve the transformation (Scheme 4).

According to our proposed mechanism, the structure of quaternary ammonium cation may emerge in the transformation. Considering the thermalytic cleavage mechanism of quaternary ammonium, we predicted that *di*- or *tri*-substituted 2-(pyridin-2-yl)imidazoles might be synthesized in a one-pot manner using our protocol. Therefore, we selected butan-1-amine **5m** (aliphatic amine) as the ammonia source to achieve our prediction. As expected, both products (**6m** and **4d**) were obtained (Table 4, entry 1). The structure of *tri*-substituted 2-(pyridin-2-yl)imidazole **6m** was also confirmed by the X-ray crystal structure (Figure 4).[13] The possible synthetic route was also shown in Scheme 7. Furthermore, the same situation also happened in the syntheses of **6n** and **4d** with cyclohexylamine **5n** as a substrate (Table 4, entry

Scheme 5. Routes to the Synthesis of **6l** and **4d**



Scheme 6. Possible Mechanism for the Formation of *poly*-Substituted 2-(Pyridin-2-yl)imidazole

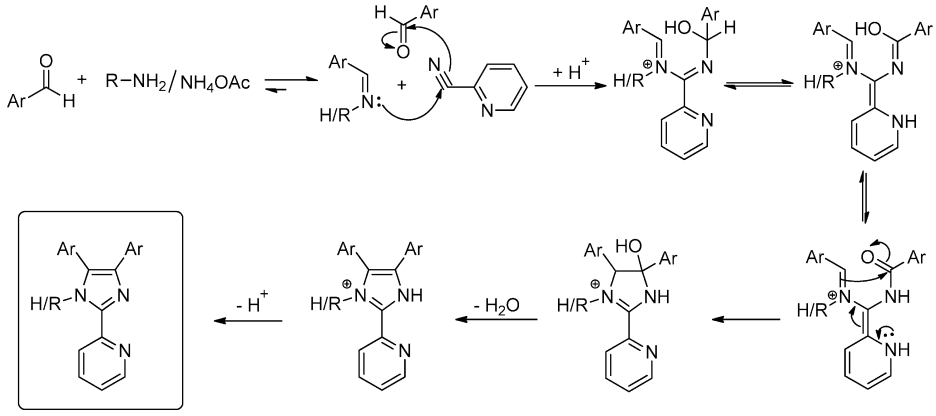
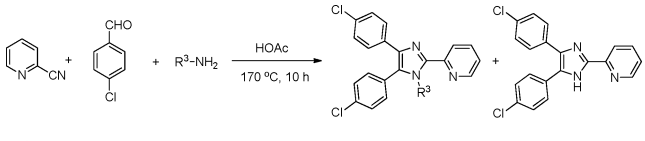


Table 4. Substrate Scope Study for the Synthesis of Both *Di*- and *Tri*-substituted 2-(pyridin-2-yl)imidazoles[a]



1 2d 5m-5n 6m-6n 4d

entry	R^3	yield[b] (%)	yield[b] (%)
1	R^3 = *n*-Bu (**5m**)	69 (**6m**)	28 (**4d**)
2	R^3 = CyHex (**5n**)	31 (**6n**)	62 (**4d**)

[a] Reaction conditions: **1** (2.5 mmol), **2d** (1.0 mmol), **5** (5.0 mmol), 3.0 mL of HOAc at 170 °C for 10 h. [b] Isolated yield, calculated based on the amount of aldehyde.

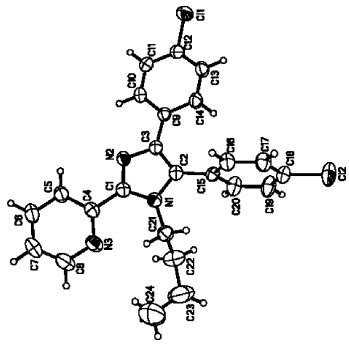


Figure 4. Crystal Structures of **6m**.

2). Moreover, in the presence of benzyl amine **5o** as a substrate, only *tri*-substituted 2-(pyridin-2-yl)imidazole **6o** was obtained in 92% yield, without observing the formation of **4d** (Scheme 8). We thought that this was due to the absence of the active β-hydrogen in the structure of benzyl amine **5o** to accomplish the thermalytic cleavage.

Therefore, all these results of aliphatic amine substrates demonstrated that the synthetic processes of both *di*- and *tri*-substituted 2-(pyridin-2-yl)imidazoles could be achieved in one-pot using this approach. Moreover, these results also supported our hypothetic mechanism to some extent.

Conclusion

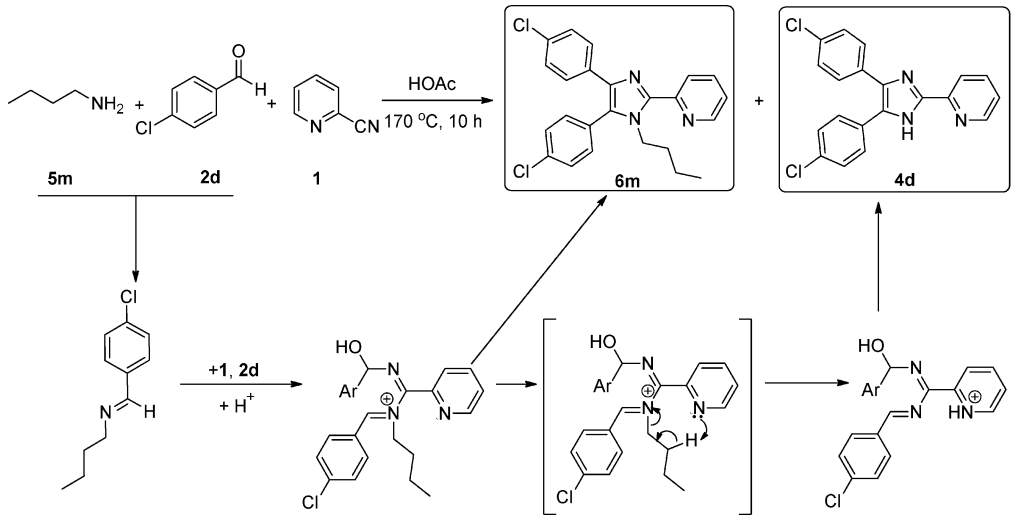
In summary, we have developed a novel and highly efficient method for the synthesis of various *di*- or *tri*-aryl (heteraryl) substituted 2-(pyridin-2-yl)imidazoles from simple and readily available starting materials. Moreover, while aliphatic primary amines with *beta*-hydrogen were used as substrates, both *di*- and *tri*-substituted 2-(pyridin-2-yl)imidazoles could be synthesized in one pot.

Experimental Section

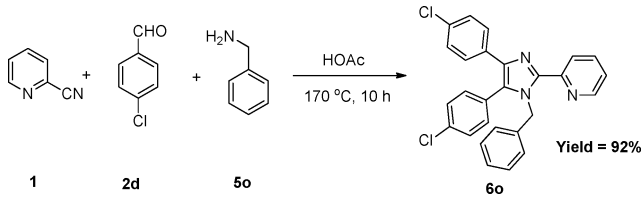
General Experimental Methods. All reagents were purchased form Aldrich or Alfa. Analytical thin-layer chromatography was performed using glass plates precoated with 200−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Melting points were recorded on an electrothermal digital melting point apparatus. IR spectra were recorded on a Varian FT-1000 spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (300 MHz for ^{1}H NMR and 100 or 75 MHz for ^{13}C NMR) with TMS as an internal reference. High resolution mass spectra were obtained using Microma GCT-TOF instrument. X-ray diffraction data were recorded on a Rigaku Mercury CCD area detector with graphite monochromated MoKα radiation.

Typical Experimental Procedure for the Synthesis of 2,4,5-Trisubstituted Imidazole (4a). 2-Cyanopyridine (260 mg, 2.5 mmol), 4-methoxy-benzaldehyde (136 mg, 1.0 mmol), and NH_4OAc (385 mg, 5.0 mmol) were combined and heated in 3 mL of acetic acid at 170 °C for 10 h in a Teflon-lined stainless steel autoclave(25 mL of the volume). After that, the mixture was added to by the freshly prepared saturated solution of $NaHCO_3$, brought pH to 7, and extracted with ethyl acetate; then the organic phase was dried by anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography ($V_{ethyl\ acetate}/V_{petroleum\ ether}$ = 1:8) to afford the pure product (164 mg). Mp**:** 189−191 °C (lit.mp:190−191 °C).[4m] IR(KBr) ν: 3412, 3060, 2948, 1612, 1597, 1568, 1516, 1458, 1422 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 6H, $2OCH_3$), 6.85−6.89 (m, 4H, ArH), 7.18 (t, J = 6.2 Hz, 1H, ArH), 7.37 (d, J = 8.4 Hz, 2H, ArH), 7.60 (d, J = 8.4 Hz, 2H, ArH), 7.76 (t, J = 7.8 Hz, 1H, ArH), 8.27 (d, J = 8.0 Hz, 1H, ArH), 8.44 (d, J = 4.2 Hz, 1H, ArH), 10.82 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.06, 148.86, 145.35, 137.50, 129.66, 129.39, 123.32, 120.45, 114.56, 114.22, 55.70 ppm. HRMS M^+: calcd for $C_{22}H_{19}N_3O_2$: 357.1477, found: 357.1478.

Scheme 7. Approach to Synthesis of **4d** and **6m**



Scheme 8. Approach to Synthesis of **6o**



Typical Experimental Procedure for the Synthesis of 1,2,4,5-Tetrasubstituted Imidazole (6a). 2-Cyanopyridine (260 mg, 2.5 mmol), 4-methoxy-benzaldehyde (136 mg, 1.0 mmol), and 4-methoxyaniline (616 mg, 5.0 mmol) were combined and heated in 3 mL of acetic acid at 170 °C for 10 h in a Teflon-lined stainless steel autoclave (25 mL of the volume). After that the mixture was added to by the freshly prepared saturated solution of $NaHCO_3$, brought pH to 7, and extracted with ethyl acetate; then the organic phase was dried by anhydrous $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography ($V_{ethyl\ acetate}/V_{petroleum\ ether} = 1:8$) to afford the pure product (213 mg). Mp: 197−198 °C. IR(KBr) ν: 2956, 2833, 1615, 1587, 1515, 1488, 1383 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.77-3.78$ (m, 9H, $3OCH_3$), 6.72−6.81 (m, 6H, ArH), 6.98−7.13 (m, 5H, ArH), 7,54 (d, $J = 8.4$ Hz, 2H, ArH), 7.63 (t, $J = 7.4$ Hz, 1H, ArH), 7.80 (d, $J = 7.8$ Hz, 1H, ArH), 8.38 (d, $J = 3.0$ Hz, 1H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.58$, 159.18, 158.80, 150.30, 149.35, 145.91, 138.48, 136.50, 132.84, 131.55, 131.01, 129.80, 128.94, 127.71, 124.23, 123.31, 122.85, 114.27, 114.08, 113.96, 55.74, 55.60, 55.55 ppm. HRMS M^+: calcd for $C_{29}H_{25}N_3O_3$: 463.1896, found: 463.1899.

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Supporting Information Available. Characterization data including Mp, IR, MS, ^1H and ^{13}C NMR spectra for compounds **4a**-**4r**, **6a**−**6o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Crystallographic data for the crystal structure of **6l** has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication with No. CCDC 749494. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (E-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; fax: +44 01223 336033). Structural parameters for **6l**: data collection: Rigaku Mercury CCD area detector; crystal size: 0.45 × 0.22 × 0.20 mm^3; $C_{27}H_{18}N_3Cl_3$, Mr = 490.79, Triclinic, space group $P\bar{1}$, a = 9.6681(6) Å, b = 10.5590(8) Å, c = 12.4197(10) Å, α = 78.349(8)°, β = 75.715(8) °, γ = 71.087(7)°, V = 1152.00(15) Å^3, Z = 2, D_{calcd} = 1.415 mg /cm^{-3}, $R[I > 2\sigma(I)]$ = 0.0472, $wR[I > 2\sigma(I)]$ = 0.1106.

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