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## Graphical Abstract

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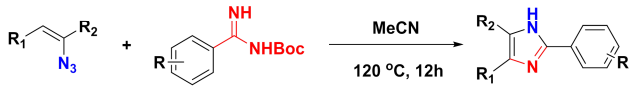


Vinyl azides NHBoc-amidines

$R_1$= aryl, alkyl;
$R_2$= COOEt

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# Synthesis of polyfunctional imidazoles from vinyl azides and amidine along with NHBoc as a leaving group

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ABSTRACT

An efficient method for the synthesis of polyfunctional imidazoles from vinyl azides and amidine has been developed. Starting from vinyl azide and amidine, this transformation proceeds without any additives and the obtained imidazoles can be decorated with ester functional group that is a promising site for further modification.



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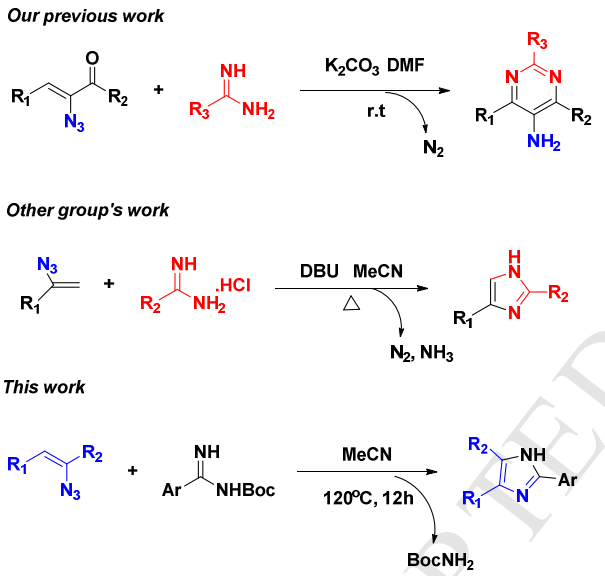
## 1. Introduction

Imidazoles are of highly importance in natural products and pharmaceuticals. Compounds with the imidazole core possess various biological activities, such as antitumor, [1a] antimicrobials[1b-1d] and antioxidants. [1e] And the substituents on the imidazole ring have a huge impact on the chemical and biological properties of the resultant molecules.[1f-1g] Therefore, some strategies have been developed for the synthesis of polyfunctional imidazoles, such as C−H amination of N-Alkyl enamines, [2a] $ZnCl_2$□catalyzed [3 + 2] cycloaddition of benzimidates and 2*H*-azirines, [2b] copper-mediated three-component reaction of ketones, aldehydes, and $Me_3SiN_3$[2c] and et al. Despite enormous attentions have been focused on effective construction of polyfunctional imidazoles, the universal biological activities make the pursue of new approaches from easily available reagents for the synthesis of imidazoles.

Vinyl azide is a well-developed three-atom synthon and plays a significant role in the construction of aza-heterocycles in recent years. Our group and others have developed a range of strategies for the aza-heterocycles synthesis including 4-aminopyridines, [3a] polyfunctional anilines, [3b] polyfunctional pyrazoles, [3c] pyrrolo [1, 2-α] pyrazine, [3d] thiazoles[3e] and others.[3f-3j]



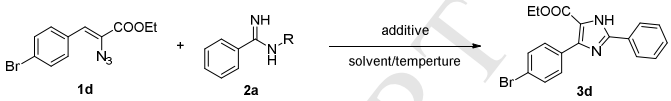

**Scheme 1.** The reactivity between vinyl azides and amidines

Previously, we have developed an approach for the synthesis of 5-aminopyrimidines from a-azidovinyl ketones and amidines.[4] In this work, the intramolecular Michael addition of amidine to the azidovinyl ketone occurred in the presence of $K_2CO_3$.The $N_3$ group was not involved in the formation of pyrimidine ring and transferred to amino group. Others also reported the synthesis of disubstituted imidazoles from vinyl azides and amidine with the addition of DBU.[5] The reaction undergoes cyclization by the loss of $N_2$ of vinyl azides and a subsequent elimination of ammonia giving the desired product. And the β-position substitution of vinyl azides did not tolerate in this reaction. For further understanding the promising chemical reactivity of vinyl azides, we study the possible reaction between vinyl azides (bearing with an ester group at the $R_2$ position) and amidine. Surprising, the reaction gave the formation of polyfunctional imidazoles as the major product and the $N_3$ group did involve in the formation of imidazole ring along with the leaving of NH-Boc. Moreover, the affording imidazoles possess the functional group ester that would be capable for further modification with diverse biological activities (**Scheme 1**). [1h]

## 2. Results and discussion

Initially, vinyl azide **1d** and benzamidine **2a** were selected to optimize the reaction conditions (Table 1). It was found that the desired imidazole **3d** was obtained with the yield of 49% in MeCN at 80 °C (Table 1, entry 1). However, additives ($Et_3N$ and $K_2CO_3$) were not favour for this transformation (Table 1, entries 2-3). Only a trace of the **3d** was obtained in the presence of $Et_3N$ and the reaction failed to proceed when $K_2CO_3$ was used as the additive. This is much different from our previous work.[3a]

**Table 1**. Optimization of the reaction conditions [a]




| Entry | Additive | R | Solvent | T (°C) | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 | — | Boc | MeCN | 80 | 49 |
| 2 | $Et_3N$ | Boc | MeCN | 80 | trace |
| 3 | $K_2CO_3$ | Boc | MeCN | 80 | n.r |
| 4 | — | Boc | MeCN | 100 | 62 |
| 5 | — | Boc | MeCN | 120 | 81 |
| 6 | — | Boc | MeCN | 60 | 21 |
| 7 | — | Boc | MeCN | 25 | n.r |
| 8 | — | Boc | EtOH | 80 | n.r |
| 9 | — | Boc | DMF | 80 | 21 |
| 10 | — | Boc | Toluene | 80 | 19 |
| 11 | — | Boc | 1,4-Dioxane | 80 | 53 |
| 12 | — | Boc | DCE | 80 | 71 |
| 13 | — | CBz | MeCN | 120 | 68 |
| 14 | — | Ts | MeCN | 120 | 10 |
| 15 | — | H | MeCN | 120 | n.r |

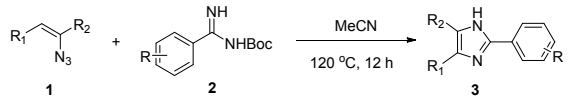
[a] Unless otherwise noted, the reactions were carried out with vinyl azide **1a** (0.3 mmol) and amidine **2** (0.3 mmol) heating in solvent (1.0 mL) in the presence or absence of the additive (0.1 mmol) for 12 h (sealed tubes). [b] Isolated yields.

And the reaction temperature is another important factor for this reaction. The reaction yields would be increased to 81% when the reaction was performed in a seal tube at 120 °C (Table 1, entry 5), while the reaction did not proceeded well when the reaction temperature lowered to 60 °C and 25 °C (Table 1, entries 6-7). Furthermore, the reaction solvents including EtOH, DMF, toluene, 1, 4-dioxane and DCE were screened (Table 1, entries 8-12). And MeCN shows the best one with the highest yield of 81%. As the proposed mechanism, we also tested the leaving capability of other substitutions, including NHCBz and NHTs (Table 1, entries 13-14). The reaction could be proceed although with a lower reaction yield, 68% and 10% respectively. The reaction failed to proceed when benzamidine was used as substrate, thus indicating the importance of $NH_2$ protection (Table 1, entry 15). In all, we have obtained the optimized reaction conditions in MeCN at 120 °C without any additives.

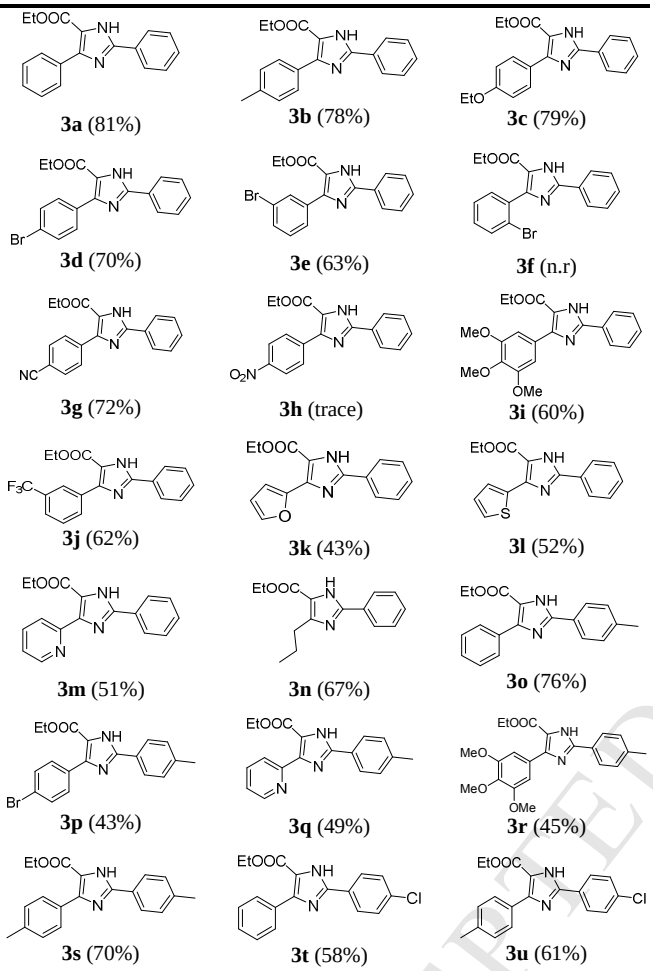
Next, the generality of the synthesis of polyfunctional imidazoles was explored using a series of vinyl azides **1** and

NHBoc-amidines **2**. As shown in table 2, various substituted vinyl azides worked well to provide the corresponding imidazoles in moderate to excellent yields. The steric and electronegativity effects were also investigated.

**Table 2**. Substrate scope of vinyl azides and NHBoc-amidine [a]



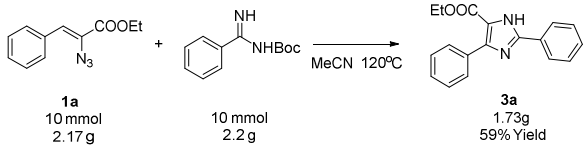

1 2 3




[a] Reaction conditions: vinyl azides **1** (1.0 mmol), NHBoc-amidine **2** (1.0 mmol) in MeCN (2 mL) heated in a sealed tube (120 °C, 12 h). Yields shown are those of the isolated products.

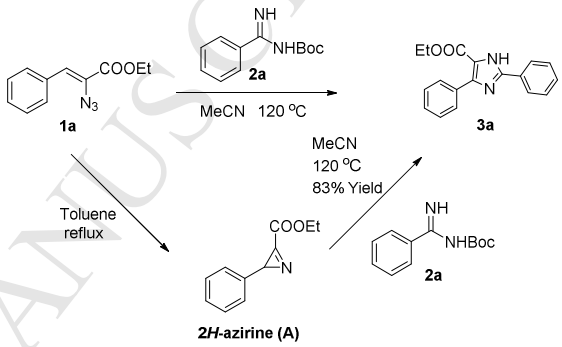
Vinyl azides with either aryl or alkyl substituents could work well in the reaction conditions in moderate to good yields. And electron-donating groups (Me and OEt) and electron-withdrawing groups (Br, CN and $CF_3$) on aryl ring of $R_1$ are well tolerated in the transformation. It seems that strong electron-withdrawing group such as $NO_2$ may have detrimental effect on the formation of unstable intermediate (**3h**). The heterocyclic substitutions on $R_1$ were also tolerated in the reaction though with lower yields. For example, furyl (**3k**), thienyl (**3l**) and pyridyl (**3m**) substitutions affords the desired imidazoles with the yields of 43%, 52% and 51%, respectively. Moreover, the scopes of NHBoc-amidine **2** were also investigated. It was found that either electron-donating (Me) or electron-withdrawing (Cl) group on aryl ring of R, is compatible. The desired products were obtained as expected (**3o**-**3u**) with isolated yields of 43-76%.

To validate the process for scale-up studies, we performed the reaction of **1a** with **2a** under optimal conditions and obtained the corresponding product **3a** in 59% yield (Scheme 2). This study indicates the feasibility of the method for industrial production.



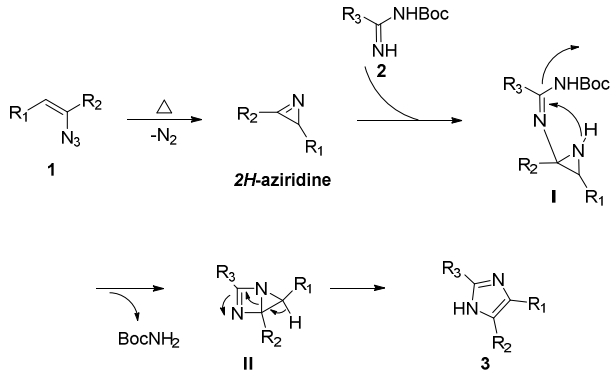

**Scheme 2.** Gram scale preparation

To gain insight into the reaction mechanism for the formation of **3a**, we conducted the control experiments using 2*H*-aziridine in the replacement of vinyl azide **1a** (**Scheme** 3). The formation of 2*H*-aziridines from thermolysis of vinyl azides has been reported before.[6] As expected, the reaction of 2*H*-aziridine and **2a** went smoothly to give the desired product **3a** with 83% yield.




**Scheme 3.** Control reaction[9]

Based on these observations, a possible mechanism for the formation of **3** is proposed in **Scheme** 4. Under thermal conditions, vinyl azides was first transformed into the corresponding 2*H*-aziridines by an elimination of $N_2$. The imino carbon of 2*H*-aziridine undergoes nucleophilic attack by NHBoc-amidine **2** to generate intermediate **I**. A subsequent intramolecular nucleophilic attack occurred by the loss of $BocNH_2$. Finally, the strained three-membered ring of intermediate **II** is opened to obtain the imidazole **3**.




**Scheme 4**. A possible reaction mechanism

## Conclusions

In conclusion, we have demonstrated an efficient method for the synthesis of 2, 4, 5-trisubstituted imidazoles from vinyl azides and NHBoc-amidines without any additives. This transformation involved a thermolysis formation of aziridine from vinyl azides and a leaving of NHBoc group. Moreover, the method could easily construct an imidazole scaffold bearing the

functional ester group that would be capable for further modification.

## 4. Experiment sections

### 4.1 General Information:

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without any purification. All solvents were purified according to standard methods prior to use. Purifications of reaction products were carried out by chromatography using silica gel (200-300 mesh). Melting points were recorded on a melting point apparatus. NMR spectra were recorded for $^1$H NMR at 500 MHz and for $^{13}$C NMR at 125 MHz. For $^1$H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant(s) in Hz. For $^{13}$C NMR, TMS (δ=0) or $CDCl_3$ (δ=77.26) was used as internal standard and spectra were obtained with complete proton decoupling. HPLC analysis and the HRMS of all biologically evaluated compounds was confirmed on a Agilent 1290 HPLC-6224 Time of Fight Mass Spectrometer using PhenomenexLuna 5μ C18, 100 Å, 150 × 4.60 mm 5 micron column at a flow rate of 0.5 mL/min using liner gradients buffer B in A (B: $CH_3OH$ containing 0.1 % formic acid, A: $H_2O$ containing 0.1% formic acid). Mobile phase B was increased linearly from 5% to 95% over 7 min and 95% over the next 2 min, after which the column was equilibrated to 5% for 1 min. The starting material **1** and **2** were prepared according to literature methods.[7, 8]

### 4.2 General Procedure for the Synthesis of **3**

A mixture of vinyl azide **1** (1.0 mmol) and NHBoc-amidine **2** (1.0 mmol, 1.0 equiv.) was stirred in MeCN (2 mL) in a sealed tube at 120 $^o$C (the temperature of oil bath) for 12.0 h. The reaction mixture was quenched with water (25 mL), and then extracted three times with EtOAc. The combined organic layer was collected and washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography using PE / EtOAc to afford **3a**-**3u**.

#### 4.2.1. *Ethyl 2, 4-diphenyl-1H-imidazole-5-carboxylate (**3a**)*

White solid, 237 mg, yield: 81%. m.p.: 156.2-159.1 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.97 (s, 4H), 7.56 – 7.32 (m, 6H), 4.34 (q, *J* = 7.0 Hz, 2H), 1.32 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.5, 148.6, 133.6, 130.2, 129.7, 129.2, 128.7, 128.0, 126.3, 118.8, 61.4, 14.5. HRMS (ESI): m/z calcd for $(C_{18}H_{16}N_2O_2+H)^+$:293.1290; found: 293.1291.

#### 4.2.2. *Ethyl 2-phenyl-4-(p-tolyl)-1H-imidazole-5-carboxylate (**3b**)*

White solid, 239 mg, yield: 78%. m.p.: 229.2-230.4 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.96 (s, 2H), 7.87 (s, 2H), 7.44 (s, 3H), 7.22 (d, *J* = 7.5 Hz, 2H), 4.34 (q, *J* = 7.0 Hz, 2H), 2.39 (s, 3H), 1.33 (t, *J* = 6.5 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.7, 147.9, 138.7, 130.0, 129.5, 129.3, 129.2, 128.8, 126.2, 61.2, 21.6, 14.5. HRMS (ESI): m/z calcd for $(C_{19}H_{18}N_2O_2+H)^+$: 307.1447; found: 307.1447.

#### 4.2.3. *Ethyl 4-(4-ethoxyphenyl)-2-phenyl-1H-imidazole-5-carboxylate (**3c**)*

White solid, 299 mg, yield: 89%. m.p.: 176.3-177.2 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.95 (d, *J* = 5.4 Hz, 4H), 7.43 (s, 3H), 6.92 (s, 2H), 4.33 (dd, *J* = 8.2, 3.4 Hz, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 6.9 Hz, 3H), 1.32 (t, *J* = 6.7 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ159.6, 147.7, 130.9, 130.0, 129.3, 129.1, 126.2, 114.2, 63.7, 61.1, 15.1, 14.5. HRMS (ESI): m/z calcd for $(C_{20}H_{20}N_2O_3+H)^+$: 337.1552; found: 337.1552.

#### 4.2.4. *Ethyl 4-(4-bromophenyl)-2-phenyl-1H-imidazole-5-carboxylate (**3d**)*

White solid, 259 mg, yield: 70%. m.p.: 158.0-159.3 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.97 (d, *J* = 6.3 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.43 (m, 3H), 4.35 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.5, 148.2, 147.3, 132.5, 131.3, 131.2, 130.3, 129.2, 128.9, 126.3, 122.9, 118.9, 61.6, 14.50. HRMS (ESI): m/z calcd for $(C_{18}H_{15}BrN_2O_2+H)^+$: 371.0395; found: 371.0398.

#### 4.2.5. *Ethyl 4-(3-bromophenyl)-2-phenyl-1H-imidazole-5-carboxylate (**3e**)*

White solid, 233 mg, yield: 63%. m.p.: 140.7-142.6 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.16 (t, *J* = 1.7 Hz, 1H), 7.99 (d, *J* = 1.8 Hz, 1H), 7.98 (d, *J* = 1.3 Hz, 1H), 7.95-7.92 (m, 1H), 7.52 – 7.45 (m, 4H), 7.30 (t, *J* = 7.9 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.6, 148.3, 146.7, 135.6, 132.7, 131.6, 130.3, 129.6, 129.3, 128.9, 128.3, 126.3, 122.0, 119.3, 61.7, 14.4. HRMS (ESI): m/z calcd for $(C_{18}H_{15}BrN_2O_2+H)^+$: 371.0395; found: 371.0398.

#### 4.2.6. *Ethyl 4-(4-cyanophenyl)-2-phenyl-1H-imidazole-5-carboxylate (**3g**)*

White solid, 228mg, yield: 72%. m.p.: 148.2-146.9 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 2H), 8.05 – 7.95 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.53-7.43 (m, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.1, 148.4, 146.2, 138.1, 131.9, 130.6, 130.2, 129.3, 128.7, 126.3, 119.8, 119.3, 111.9, 61.8, 14.5. HRMS (ESI): m/z calcd for $(C_{19}H_{15}N_3O_2+H)^+$: 318.1243; found: 318.1247.

#### 4.2.7. *Ethyl 2-phenyl-4-(3, 4, 5-trimethoxyphenyl)-1H-imidazole-5-carboxylate (**3i**)*

White solid, 229 mg, yield: 60%. m.p.: 203.2-204.8 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.98 (d, *J* = 7.0 Hz, 2H), 7.56 – 7.44 (m, 3H), 7.38 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 6H), 3.89 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.2, 152.9, 148.4, 147.6, 138.7, 130.3, 129.2, 129.0, 127.7, 126.2, 118.5, 106.9, 61.3, 61.2, 56.4. 14.7. HRMS (ESI): m/z calcd for $(C_{21}H_{22}N_2O_5+H)^+$: 383.1607; found: 383.1606.

#### 4.2.8. *Ethyl 2-phenyl-4-(3-(trifluoromethyl) phenyl)-1H-imidazole-5-carboxylate (**3j**)*

White solid, 223 mg, yield: 62%. m.p.: 189.3-191.4 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.26 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.09 – 7.95 (m, 2H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.52-7.39 (m, 3H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).$^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.7, 148.5, 146.7, 132.9, 130.4, 129.2, 128.9, 128.6, 126.7, 126.7, 126.4, 125.3, 125.3, 119.4, 61.8, 14.3. HRMS (ESI): m/z calcd for $(C_{19}H_{15}F_3N_2O_2+H)^+$: 361.1164; found: 361.1168.

#### 4.2.9. *Ethyl 4-(furan-2-yl)-2-phenyl-1H-imidazole-5-carboxylate (**3k**)*

Pale yellow solid, 121 mg, yield: 43%. m.p.: 221.7-224.9 $^o$C. $^1$H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 7.58 (s, 1H), 7.50 – 7.35 (m, 4H), 6.54 (s, 1H), 4.49 – 4.37 (m, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz,

$CDCl_3$) δ 159.8, 143.1, 142.6, 130.3, 129.8, 129.1, 126.3, 125.9, 113.2, 112.8, 112.1, 111.7, 61.4, 14.6. HRMS (ESI): m/z calcd for $(C_{16}H_{14}N_2O_3+H)^+$: 283.1083; found: 283.1083.

4.2.10. *Ethyl 2-phenyl-4-(thiophen-2-yl)-1H-imidazole-5-carboxylate (**3l**)*

White solid, 156 mg, yield: 52%. m.p.: 148.6-149.7 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.10 (s, 1H), 7.97 (d, *J* = 6.6 Hz, 2H), 7.50-7.38 (m, 3H), 7.39 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).$^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.4, 147.9, 142.6, 136.6, 130.3, 129.2, 128.8, 128.5, 127.7, 127.2, 126.4, 117.3, 61.5, 14.7. HRMS (ESI): m/z calcd for $(C_{16}H_{14}N_2O_2S+H)^+$:299.0854; found: 299.0855.

4.2.11. *Ethyl 2-phenyl-4-(pyridin-2-yl)-1H-imidazole-5-carboxylate (**3m**)*

White solid, 149 mg, yield: 51%. m.p.: 204.4-205.2 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 11.51 (s, 1H), 8.86 (d, *J* = 7.6 Hz, 1H), 8.53 (s, 1H), 7.96 (d, *J* = 6.8 Hz, 2H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.26 – 7.17 (m, 1H), 4.48 (d, *J* = 6.8 Hz, 2H), 1.46 (t, *J* = 6.5 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 164.1, 148.8, 147.2, 146.5, 137.4, 136.5, 130.6, 129.9, 129.1, 126.2, 124.5, 123.6, 61.4, 14.6. HRMS (ESI): m/z calcd for $(C_{17}H_{15}N_3O_2+H)^+$: 294.1243; found: 294.1245.

4.2.12. *Ethyl 2-phenyl-4-propyl-1H-imidazole-5-carboxylate (**3n**)*

White solid, 173 mg, yield: 67%. m.p.: 167.5-169.1 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 5.9 Hz, 2H), 7.36 (s, 3H), 4.51 – 4.21 (m, 2H), 2.89 (t, *J* = 7.0 Hz, 2H), 1.48 – 1.12 (m, 5H), 1.00 – 0.79 (m, 4H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 164.9, 147.2, 129.6, 129.5, 129.0, 126.1, 61.4, 60.8, 29.9, 23.2, 14.6, 14.1. HRMS (ESI): m/z calcd for $(C_{15}H_{18}N_2O_2+H)^+$:259.1447; found: 259.1444.

4.2.13. *Ethyl 4-phenyl-2-(p-tolyl)-1H-imidazole-5-carboxylate (**3o**)*

White solid, 233 mg, yield: 76%. m.p.: 203.2-203.9 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.96 (s, 2H), 7.85 (s, 2H), 7.39 (m, 3H), 7.26 (s, 2H), 4.34 (q, *J* =7.0 Hz, 2H), 2.40 (s, 3H), 1.32 (t, *J* = 6.7 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.7, 148.3, 140.3, 129.9, 129.6, 128.7, 128.1, 126.4, 126.1, 61.2, 21.7, 14.5. HRMS (ESI): m/z calcd for $(C_{19}H_{18}N_2O_2+H)^+$: 307.1447; found: 307.1446.

4.2.14. *Ethyl 4-(4-bromophenyl)-2-(p-tolyl)-1H-imidazole-5-carboxylate (**3p**)*

White solid, 165 mg, yield: 43%. m.p.: 181.2-182.4 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 4H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.28 (s, 1H), 7.26 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 161.4, 148.2, 147.4, 140.6, 131.3, 131.2, 129.9, 126.2, 126.1, 122.9, 61.4, 21.7, 14.5. HRMS (ESI): m/z calcd for $(C_{19}H_{17}BrN_2O_2+H)^+$:385.0555; found: 385.0552.

4.2.15. *Ethyl 4-(pyridin-2-yl)-2-(p-tolyl)-1H-imidazole-5-carboxylate (**3q**)*

White solid, 150 mg, yield: 49%. m.p.:175.3-177.3 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 11.45 (s, 1H), 8.84 (s, 1H), 8.53 (s, 1H), 7.85 (d, *J* = 7.9 Hz, 2H), 7.80-7.77 (m, 1H), 7.22 (t, *J* = 6.4 Hz, 3H), 4.46 (d, *J* = 5.4 Hz, 2H), 2.36 (s, 3H), 1.44 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 164.1, 148.8, 147.4, 146.7, 140.0, 137.3, 129.7, 126.3, 126.1, 124.5, 123.5, 61.4, 21.6, 14.6. HRMS (ESI): m/z calcd for $(C_{18}H_{17}N_3O_2+H)^+$: 308.1399; found: 308.1396.

4.2.16. *Ethyl 2-(p-tolyl)-4-(3, 4, 5-trimethoxyphenyl)-1H-imidazole-5-carboxylate (**3r**)*

White solid, 178 mg, yield: 45%. m.p.: 220.3-221.4 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.34 (s, 2H), 7.27 (s, 1H), 7.26 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 6H), 3.88 (s, 3H), 2.40 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.5, 152.9, 148.3, 147.9, 140.5, 138.6, 129.9, 129.7, 129.0, 126.2, 118.2, 106.9, 61.3, 61.1, 56.4, 21.7, 14.7. HRMS (ESI): m/z calcd for $(C_{22}H_{24}N_2O_5+H)^+$: 397.1763; found: 397.1763.

4.2.17. *Ethyl 2, 4-di-p-tolyl-1H-imidazole-5-carboxylate (**3s**)*

White solid, 224 mg, yield: 70%. m.p.: 228.8-230.4 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.84 (d, *J* = 7.1 Hz, 4H), 7.26 – 7.09 (m, 4H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 2.39 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.5, 148.3, 140.2, 138.6, 129.8, 129.5, 128.8, 126.4, 126.1, 61.2, 21.7, 21.6, 14.50. HRMS (ESI): m/z calcd for $(C_{20}H_{20}N_2O_2+H)^+$: 321.1603; found: 321.1600.

4.2.18. *Ethyl 2-(4-chlorophenyl)-4-phenyl-1H-imidazole-5-carboxylate (**3t**)*

White solid, 189 mg, yield: 58%. m.p.: 182.9-184.0 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.92 (s, 3H), 7.79 – 7.25 (m, 6H), 4.32 (d, *J* = 6.0 Hz, 2H), 1.30 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.8, 148.7, 147.1, 136.2, 133.4, 129.7, 129.4, 128.8, 128.1, 127.6, 119.0, 61.5, 14.3. HRMS (ESI): m/z calcd for $(C_{18}H_{15}ClN_2O_2+H)^+$: 327.0900; found: 327.0903.

4.2.19. *Ethyl 2-(4-chlorophenyl)-4-(p-tolyl)-1H-imidazole-5-carboxylate (**3u**)*

White solid, 208 mg, yield: 61%. m.p.: 190.5-191.3 °C. $^1H$ NMR (500 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.90 (s, 2H), 7.81 (s, 2H), 7.40 (s, 2H), 7.20 (s, 2H), 4.30 (s, 2H), 2.38 (s, 3H), 1.30 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 161.1, 147.0, 138.6, 136.0, 130.9, 129.8, 129.4, 129.3, 128.8, 128.2, 127.7, 127.5, 126.1, 61.3, 21.6, 14.4. HRMS (ESI): m/z calcd for $(C_{19}H_{17}ClN_2O_2+H)^+$:341.1057; found: 341.1056.

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**Supporting Information**

Supplementary data (characterization data, and copies of $^1H$ and $^{13}C$ NMR spectra for all products) associated with this article can be found in the online version, at http://dx.doi.org/

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