

A simple and convenient one-pot method for the preparation of heteroaryl-2-imidazoles from nitriles

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Abstract

A simple, convenient and high-yielding one-pot method for the synthesis of 2-heterocycle-substituted imidazoles from the corresponding nitriles has been developed. The procedure is easily scaleable and the workup does not involve chromatography. This synthesis is also applicable to the preparation of imidazoles with electron-poor aryl substituents.

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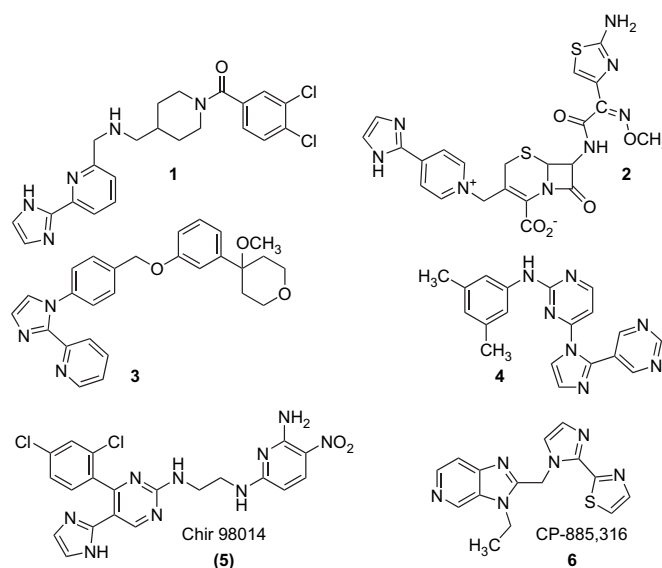
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1. Introduction

Many imidazoles with a single heterocyclic substituent in the 2-position serve as key intermediates in the synthesis of pharmacologically active compounds (Scheme 1). These targets include agonists of serotonin 1A receptors (**1**),^{1a} antimicrobials (**2**),^{1b} as well as 5-lipoxygenase (**3**),^{1c} kinase domain insert receptors (KDR, **4**),^{1d} and glycogen synthase kinase 3 (**5**)^{1e} inhibitors, as well as selective γ -aminobutyric acid A receptors ligands (**6**).^{1f,g} Additionally, pyridinyl-2-imidazoles have been shown to have dramatically decreased Cytochrome P450 binding as compared to imidazoles with other substitution patterns.² Due to its ability to complex metals, 2-pyridinyl-2-imidazole has also found the application as a ligand in palladium-catalyzed coupling reactions.³

As a part of recent research on KDR inhibitors, we required a short and potentially scaleable route to 2-heterocycle-substituted imidazoles, particularly pyridinyl-2-imidazoles. To our surprise, we were not able to find a satisfactory general procedure.⁴ For instance, a two-step route, beginning with the

corresponding aldehydes, via imidazole-4,5-dicarboxylic acids resulted in 26% yield of 4-pyridinyl-2-imidazole (**11a**) and 31% yield of 3-pyridinyl-2-imidazole (**11b**).^{5a} The classical

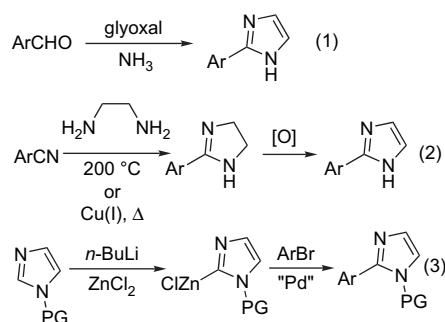


Scheme 1. Pharmacologically active 2-heterocycle-substituted imidazoles.

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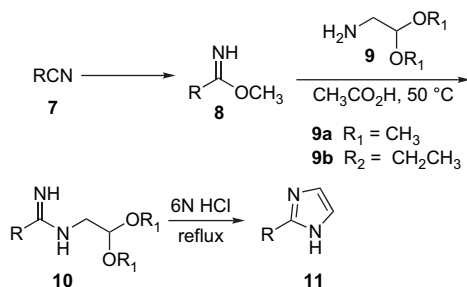
imidazole preparation (Scheme 2, Eq. 1) from the corresponding aldehydes, glyoxal, and ammonia afforded only 55% of 2-pyridinyl-2-imidazole (**11c**)^{5b} and 20% of **11a**.^{5c} Due to the lack of imidazoles with 2-heterocyclic substituent in the literature we turned to the methods of the synthesis of aryl-2-imidazoles. These compounds are generally prepared through the conversion of the corresponding nitrile into the imidazoline followed by oxidation to the desired imidazole (Scheme 2, Eq. 2).^{1a–c,h,6–8} The first step requires either heating to high temperature, usually over 200 °C,^{6a,b} or the use of equimolar amount of transition metal salts.^{6c} Metal salts serving as oxidants are also often employed in the second step.^{1a,b,7,8} High temperatures, the need for the subsequent separation of inorganic byproducts, and low to moderate overall yield have made this approach unattractive to us.



Scheme 2. Literature syntheses of aryl-2-imidazoles.

Recently, several examples of the transition metal catalyzed 2-arylation of imidazoles under Negishi or Stille conditions have appeared in the literature (Scheme 2, Eq. 3).^{1f,9} The downside of this approach is the necessity of protecting and then deprotecting the NH-group of imidazole, as well as the use of *n*-butyllithium and of strict water- and air-free conditions. Direct arylation of imidazole in the presence of copper(I) and palladium salts has been advanced by Bellina and Rossi,¹⁰ and appears to be a promising method for the synthesis of aryl-2-imidazoles. However, this method requires high temperature (140 °C) and 2 equiv of both copper(I) iodide and aryl iodide. In addition, this reaction has no precedent with heterocycles.

At the same time, a rarely used method, which consists of the nucleophilic substitution of an imidate with the acetal-protected aminoacetaldehyde followed by deprotection-cyclization, attracted our attention (Scheme 3).¹¹ Earlier attempts to



Scheme 3. Synthesis of aryl and heteroaryl-2-imidazoles from nitriles.

prepare heterocyclic imidazoles **11**, following this route, included tedious isolation of intermediates **8** or **10** and afforded low to moderate overall yield of **11**,^{12,13,19} discouraging further research in this direction. However, it occurred to us that, if imidate **8** could be formed cleanly from the corresponding nitrile (for example, under alkaline catalysis), reaction of **8** in situ with aminoacetaldehyde derivative **9** would bring about a one-pot preparation of 2-substituted imidazoles **11** from nitriles (Scheme 3).

2. Results and discussion

To our delight, the very first application of the above approach to the preparation of 4-pyridinyl-2-imidazole (**11a**) was successful. Treatment of a methanolic solution of 4-cyanopyridine (**7a**) with sodium methoxide (0.1 equiv) at rt for 1 h resulted in complete conversion to imidate **8a**. The reaction mixture was acidified with acetic acid, and the subsequent addition of aminoacetal **9a** produced **10a**. Deprotection and concomitant cyclization to **11a** were achieved by treating **10a** with hydrochloric acid and then bringing the reaction to reflux. The entire sequence was run in the same pot, and the intermediates were not isolated. Over three steps, a remarkable 82% yield of pure imidazole **11a** was obtained (Table 1, entry 1). Alternatively, it was found that catalytic cesium carbonate (10 mol %) could be used as a base in place of sodium methoxide affording 72% yield of **11a**.

The above procedure was then successfully applied to other heterocyclic nitriles (Table 1, entries 2–13). Pyridinyl-2-imidazoles **11b–f** (Table 1, entries 2–6), including functionalized compounds **11e,f**, were prepared in good to excellent yield. The method is applicable to other six-membered cyano-heterocycles, affording moderate to good yield of pyrazinyl and pyrimidinyl-substituted imidazoles **11g–i** (Table 1, entries 7–9). Novel imidazolyl quinoline **11j** and isoquinoline **11k** as well as imidazoles substituted with five-membered heterocycles thiophene (**11l**) and thiazole (**11m**) were easily obtained in moderate to good yield (Table 1, entries 10–13).

The procedure is robust and easily scaleable: for example, the preparation of **11a** was performed several times on 20–150-g scale, without any significant changes, affording 74–82% yield of **11a**. Similarly, **11b** was synthesized on a 100-g scale in 56% yield.

Notably, the yield of heterocyclic imidazoles obtained by our one-pot method was almost uniformly higher than the overall yield achieved via various two and three-step procedures in the literature (see Table 1, entries 1–4, 7, 12 and 13). One exception is the synthesis of **11c** via Negishi reaction in 87% overall yield; however, it involved three steps, including *n*-butyllithium metalation at –70 °C, and required strict air-free and water-free conditions.^{9a} Interestingly, 2-cyanothiophene (**7m**) was converted into a key intermediate in the synthesis of CP-885,316 imidazole **11m** in 93% yield, while in the literature **11m** was obtained via a lithiation procedure in 60% yield.^{1g}

Encouraged by these results, we applied the one-pot procedure to the synthesis of aryl-2-imidazoles from the

corresponding nitriles (Table 1, entries 14–17). Somewhat lower yields than for the heterocyclic derivatives were obtained. Nevertheless, in some cases, for example, for imidazoles **11n** (Table 1, entry 14) and **11p** (Table 1, entry 16) our procedure is preferable to the earlier reported methods.

It should be noted that, when necessary, imidazoles **11** could be easily separated from the side products and unreacted nitriles **7** by a simple acid–base workup. This allowed us to isolate analytically pure imidazoles **11** without resorting to chromatography in all examples with the exception of **11j** (Table 1, entry 10). When conversion of **7** to **8** was incomplete, the potentially re-usable nitrile **7** could be recovered cleanly from the organic extract. This also increased the effective yield, which is calculated in the parentheses in Table 1 (entries 10, 11, 14–16).

During our efforts to expand the scope of the synthesis, we found that the overall yield in the reaction sequence depends mostly on the degree of conversion of nitrile **7** to imidate ester **8**. It has long been known that this transformation under basic conditions is reversible,¹⁴ reaching equilibrium within several hours at rt. The behavior of the equilibrium constant can be described by the Hammett equation and shows good correlation with the σ -constant.^{15a} The equilibrium is shifted in favor of the imidate **8** in the case of nitriles **7** substituted with electron-withdrawing groups. It should be noted that for more electron-rich or *ortho*-substituted nitriles the equilibrium is shifted in favor of the nitrile **7**.^{14,15} Our results are consistent with this observation. For example, thiophene (**11l**) and benzoate (**11p**) substituted imidazoles were obtained in a lower yield than pyridine (**11a–f**) or nitrobenzene (**11n,o**) substituted imidazoles. At the same time, *ortho*-substituted nitriles, such as *o*-nitrobenzonitrile (**7r**), 1-cyanoisoquinoline, and *o*-chlorobenzonitrile as well as more electron-rich unsubstituted benzonitrile (**7s**) and 5- and 7-cyanoindoles gave little or no desired imidazole (not shown in Table 1; 7% of **11r** and 6% of **11s**; no reaction in other cases).

3. Conclusion

An efficient one-pot synthesis of imidazoles with a single heterocyclic substituent in 2-position from the corresponding nitriles is described. The synthesis affords high yields of imidazoles substituted by electron-poor heterocycle. This method also works well if applied to benzonitriles with strong electron-withdrawing groups. The yield decreases with either *ortho*-substitution or increase electron density in the aromatic or heteroaromatic ring.

4. Experimental

4.1. General

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton and carbon nuclear magnetic resonance spectra were obtained on a Bruker AVANCE 300 spectrometer at 300 MHz for proton and 75 MHz for carbon, or on a Bruker AVANCE 500

spectrometer at 500 MHz for proton and 125 MHz for carbon. NMR chemical shifts (δ) are reported in parts per million and coupling constants (J) are reported in hertz. Tetramethylsilane was used as an internal standard for proton and carbon NMR spectra. Mass spectra were obtained on a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer or a PESCiex API 150EX mass spectrometer using atmospheric chemical ionization (APCI). High resolution mass spectra were obtained on a TOF mass spectrometer using electrospray ionization at the Center for Functional Genomics, University at Albany (Albany, NY). Melting points were determined on an Electrothermal Mel-Temp apparatus and are uncorrected. Ethyl 4-cyanopicolinate (**7f**) and thiazole-2-carbonitrile (**7m**) were prepared according to the literature.²⁰ All isolated compounds had purity greater than 95% (area percent) as judged by HPLC analysis.

4.2. General procedure used for the water-soluble imidazoles (Method A, Table 1, entries 1–3, 5–6, 8, 9, and 12)

To 250-mL flask containing **7** (50 mmol) and MeOH (20 mL) a 30% solution of NaOMe in MeOH (0.94 mL, 5 mmol) was added. The reaction mixture was stirred for the time period needed for equilibrium to be reached between **7** and **8** (see Table 1). Compound **9a** (0.6–1.0 equiv; see Table 1) followed by AcOH (5.5 mL, 96 mmol) was added dropwise. The reaction mixture was then heated to reflux for 30 min. After cooling to rt, MeOH (30 mL) and 6 N HCl in H₂O (25 mL) were added, and the mixture was heated to reflux for 3–12 h (see Table 1). Once the cyclization was complete, the solution was evaporated to dryness on a rotary evaporator (15 mmHg, 50 °C). A freshly prepared warm solution of K₂CO₃ (27.5 g) in H₂O (27.5 g) was added carefully, bringing pH to 10. The resulting suspension was allowed to cool to rt and filtered or extracted affording **11**, which was purified by recrystallization.

4.3. General procedure used for other imidazoles (Method B, Table 1, entries 4, 7, 10–12, 14–17)

A 100-mL flask was charged with **7** (10 mmol), MeOH (10 mL), and a 30% solution of NaOMe in MeOH (0.38 mL, 1 mmol). The reaction mixture was stirred for the time period needed for equilibrium to be reached between **7** and **8** (see Table 1). Compound **9a** or **9b** (0.78–2 equiv; see Table 1) was added to the reaction mixture followed by AcOH (1.2 mL, 20 mmol). The reaction mixture was heated to 50 °C for 1 h and then cooled to rt. MeOH (20 mL) and 6 N HCl in H₂O (5 mL) were added, and the reaction mixture was heated to reflux for 5 h. Once the cyclization was complete, the solution was removed on a rotary evaporator, and the residue was taken up in a 1:1 mixture of H₂O and Et₂O (30 mL). The layers were separated. (Note: To recover starting material **7**, the aqueous phase was further extracted with Et₂O (2×10 mL) and the combined ethereal extracts were washed with brine (10 mL), dried over MgSO₄, and evaporated to dryness under reduced pressure.) The pH of the aqueous layer was adjusted to pH

Table 1
Preparation of 2-substituted imidazoles **11** from nitriles **7**

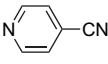
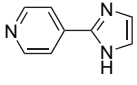
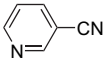
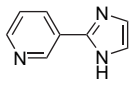
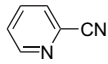
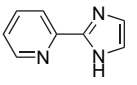
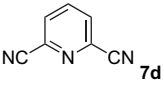
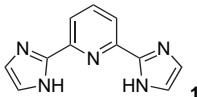
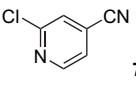
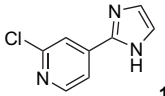
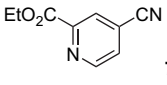
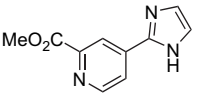
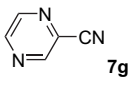
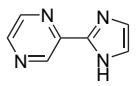
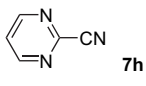
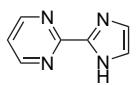
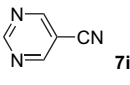
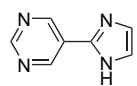
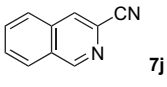
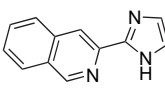
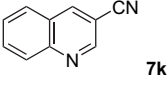
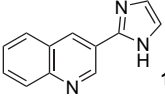
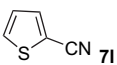
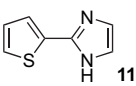
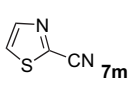
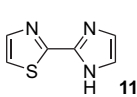
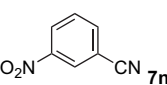
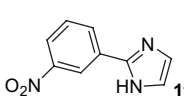
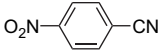
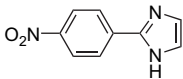
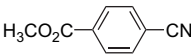
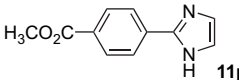
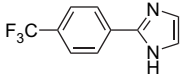
Entry	Nitrile	7 → 8 Time (h), temperature	9 (equiv)	10 → 11 Time (h)	Imidazole	Yield ^a (%)	Lit. yield (%) (method: Scheme 2 , Eq. #) ^{Ref.}
1	 7a	1, rt	9a (1.0)	3	 11a	82	20 (1); ^{5c} 26 (NA); ^{5a} 25 (NA) ^{12a}
2	 7b	1, 35 °C	9a (1.0)	8	 11b	99	31 (NA) ^{5a}
3	 7c	1, 40 °C	9a (1.0)	4.5	 11c	75	55 (1); ^{5b} 42 (1); ^{3b} 62 (Scheme 3 , ^b); ^{12b} 87 (3) ^{9a}
4	 7d	2, rt	9b (2.0)	5	 11d	85	50 (3) ^{9b}
5	 7e	1, 40 °C	9a (1.0)	8	 11e	74	
6	 7f	0.5, rt	9a (1.0)	6	 11f	82	
7	 7g	0.33, rt	9b (1.0)	5	 11g	69	45 (Scheme 3 , ^b) ^{12b}
8	 7h	1.5, rt	9a (0.6)	5	 11h	40	No yield (Scheme 3 , ^b) ¹⁹
9	 7i	1, rt	9a (1.0)	5	 11i	62	No yield (1) ¹⁷
10	 7j	4, rt	9b (1.0)	5	 11j	77 (85)	
11	 7k	15, rt	9b (1.0)	5	 11k	51 (67)	
12	 7l	16, rt	9a (0.8)	5	 11l	49	31 (2) ¹⁶
13	 7m	1, rt	9a (1.0)	12	 11m	93	60 (NA); ^{1g} 26 (3) ¹⁹
14	 7n	16, rt	9b (1.0)	5	 11n	68 (79)	40 (NA) ¹⁸

Table 1 (continued)

Entry	Nitrile	7→8 Time (h), temperature	9 (equiv)	10→11 Time (h)	Imidazole	Yield ^a (%)	Lit. yield (%) (method: Scheme 2, Eq. #) ^{Ref.}
15	 7o	4, rt	9b (1.0)	5	 11o	64 (83)	72 (2) ⁸
16	 7p	6, rt	9b (1.0)	5	 11p	31 (57)	For the corresponding ethyl ester: 28 (2) ^{1c,h}
17	 7q	2, rt	9b (1.0)	5	 11q	58	44 (Scheme 3 ^b); ^{11b} 84(NA) ¹⁰

^a Isolated yield, based on the total amount of **7** used in the reaction. Yield corrected for the recovered starting material **7** is in parenthesis.

^b Prepared in the literature by a version of the procedure depicted in Scheme 3.

8–9 with 2 N aqueous NaOH, and aqueous mixture was stirred for 30 min to allow complete precipitation of the product. The solid was collected by filtration and dried under vacuum to provide pure **11**.

4.4. Examples

4.4.1. 4-(Imidazol-2-yl)pyridine (**11a**)

The crude reaction product obtained as a filter cake according to Method A was recrystallized from boiling water (40 mL) to give **11a** as an off-white solid (5.95 g, 82%): mp 210–211 °C (lit.^{5a} 206–208 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.90 (br s, 1H), 8.64 (dd, 2H, *J*=4.5, 1.5 Hz), 7.88 (dd, 2H, *J*=4.5, 1.5 Hz), 7.28 (br s, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 150.1, 143.1, 137.3, 130–120 (br s), 118.7; (ESI) *m/z* 146 (M+H). The ¹H NMR spectrum of this product was consistent with the literature data.^{5a}

4.4.2. 3-(Imidazol-2-yl)pyridine (**11b**)

The crude reaction product obtained as a filter cake according to Method A was recrystallized from boiling water (40 mL) to give **11b** as an off-white solid (7.17 g, 99%): mp 208–209 °C (lit.^{5a} 206–207 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.87 (br s, 1H), 9.17 (d, 1H, *J*=1.5 Hz), 8.53 (dd, 1H, *J*=4.8, 1.5 Hz), 8.30 (dt, 1H, *J*=8.0, 1.8 Hz), 7.47 (dd, 1H, *J*=8.0, 4.8 Hz), 7.21 (br s, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 148.6, 146.0, 142.9, 131.8, 131–127 (br s), 126.6, 123.7, 120–117 (br s); MS (ESI) *m/z* 146 (M+H). The ¹H NMR spectrum of this product was consistent with the literature data.^{5a}

4.4.3. 2-(Imidazol-2-yl)pyridine (**11c**)

The product was extracted with CH₂Cl₂ (50 mL) from the crude filter cake obtained according to Method A and, after evaporating the extract, recrystallized from boiling EtOAc (25 mL) to afford **11c** (5.43 g, 75%) as an off-white solid: mp 137–138 °C (lit.^{12b} 134–135 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.79 (br s, 1H), 8.59 (d, 1H, *J*=4.4 Hz), 8.05 (d, 1H, *J*=7.9 Hz), 7.88 (td, 1H, *J*=7.9, 1.5 Hz), 7.35 (m, 1H), 7.23 (br s, 1H), 7.08 (br s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 148.9 (C2-Py), 148.8 (C6-Py), 145.5 (C2-imid), 137.1 (C4-Py), 129.4 (br s, C5-imid), 122.8 (C3-Py), 119.3 (C5-Py),

118.6 (br s, C4-imid); MS (ESI) *m/z* 146 (M+H). The ¹H and ¹³C NMR spectra of this product were consistent with the literature data.^{3b,12b}

4.4.4. 2,6-Di(imidazol-2-yl)pyridine (**11d**)

Compound **11d** (1.79 g, 85%) was obtained as a white solid following Method B: mp 272–276 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, 2H, *J*=7.9 Hz), 7.84 (dd, 1H, *J*=8.0, 7.8 Hz), 7.22 (s, 4H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 145.4, 144.0, 136.2, 122.9, 119.5; MS (ESI) *m/z* 212 (M+H). The ¹H NMR spectrum of this product was consistent with the literature data.^{9b}

4.4.5. 2-Chloro-4-(imidazol-2-yl)pyridine (**11e**)

The crude reaction product obtained as a filter cake according to Method A was heated to reflux with water (65 mL) to give, after cooling to rt and filtration, **11e** as a light brown solid (6.62 g, 74%): mp 186–188 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.04 (br s, 1H), 8.46 (d, 1H, *J*=5.2 Hz), 7.96 (d, 1H, *J*=0.6 Hz), 7.89 (dd, 1H, *J*=5.2, 1.2 Hz), 7.25 (br s, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 150.0, 149.5, 140.9, 139.7, 130–118 (br s), 117.6, 117.1; HRMS Calcd for (C₈H₆ClN₃+H⁺): 180.0328. Found: 180.0329.

4.4.6. Methyl 4-(imidazol-2-yl)pyridine-2-carboxylate (**11f**)

Pure **11f** (8.32 g, 82%) was obtained as a white solid after extracting the basic reaction mixture with EtOAc (5×65 mL) following by drying and evaporating the extract: mp 92–95 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.68 (dd, 1H, *J*=5.2, 0.6 Hz), 8.63 (m, 1H), 8.04 (dd, 1H, *J*=5.1, 1.8 Hz), 7.31 (s, 2H), 3.93 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 150.7, 148.7, 143.7, 139.5, 122.9, 121.26, 53.3; HRMS Calcd for (C₁₀H₉N₃O₂+H⁺): 204.0773. Found: 204.0774.

4.4.7. 2-(Imidazol-2-yl)pyrazine (**11g**)

Compound **11g** (1.01 g, 69%) was obtained as a white solid following Method B: mp 199–201 °C (lit.^{12b} 202–203 °C); ¹H NMR (300 MHz, CDCl₃) δ 13.10 (br s, 1H), 9.29 (d, 1H, *J*=1.5 Hz), 8.67 (m, 1H), 8.62 (d, 1H, *J*=2.6 Hz), 7.37 (br s, 1H), 7.22 (br s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 144.8, 144.1, 143.8, 143.6, 141.7, 130.5, 120.1; HRMS Calcd for

($\text{C}_7\text{H}_6\text{N}_4+\text{H}^+$): 147.0670. Found: 147.0669. The ^1H NMR and ^{13}C spectra of this product were consistent with the literature data.^{12b}

4.4.8. 2-(Imidazol-2-yl)pyrimidine (**11h**)

The crude reaction product obtained as a filter cake according to Method A was washed with ice-cold water (2×5 mL) (40 mL) to give pure **11h** as a white solid (2.91 g, 40%): mp 196–197 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.98 (br s, 1H), 8.87 (d, 2H, $J=4.8$ Hz), 7.44 (t, 1H, $J=4.8$ Hz), 7.24 (s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 157.5, 156.8, 144.3, 124.9 (br s), 119.8; MS (ESI) m/z 147 ($\text{M}+\text{H}$). The ^1H NMR spectrum of this product was consistent with the literature data.¹⁹

4.4.9. 5-(Imidazol-2-yl)pyrimidine (**11i**)

The product was extracted with EtOAc (5×500 mL) from the basic solution obtained according to Method A. After evaporating the extract, **11i** (4.54 g, 62%) was obtained as a brown solid: mp 188–189 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.88 (br s, 1H), 9.27 (s, 2H), 9.15 (s, 1H), 7.29 (br s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 157.2, 152.8, 140.1, 124.8; MS (ESI) m/z 147 ($\text{M}+\text{H}$). The ^1H NMR spectrum of this product was consistent with the literature data.¹⁷

4.4.10. 3-(Imidazol-2-yl)isoquinoline (**11j**)

The solid obtained according to Method B was purified by flash chromatography on silica gel (60–200 μm) eluting with 2% methanol in chloroform (0.2% concentrated ammonium hydroxide) to afford **11j** (1.50 g, 77%) as a white solid: mp 141–143 °C; ^1H NMR (300 MHz, CDCl_3) δ 11.13 (br s, 1H), 9.17 (s, 1H), 8.57 (s, 1H), 7.95 (d, 1H, $J=8.3$ Hz), 7.89 (d, 1H, $J=8.2$ Hz), 7.69 (dt, 1H, $J=7.0$, 1.2 Hz), 7.58 (dt, 1H, $J=7.0$, 1.1 Hz), 7.28 (br s, 1H), 7.17 (br s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 152.2, 147.2, 142.8, 137.0, 131.5, 130.9, 128.7, 128.1, 127.9, 127.6, 117.2, 116.7. HRMS Calcd for ($\text{C}_{12}\text{H}_9\text{N}_3+\text{H}^+$): 196.0874. Found: 196.0870.

4.4.11. 3-(Imidazol-2-yl)quinoline (**11k**)

Compound **11k** (0.99 g, 51%) was obtained as a white solid following Method B: mp 257–260 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.91 (s, 1H), 9.50 (d, 1H, $J=2.2$ Hz), 8.78 (d, 1H, $J=2.1$ Hz), 8.03 (t, 2H, $J=8.0$ Hz), 7.77 (dt, 1H, $J=6.9$, 1.5 Hz), 7.67 (dt, 1H, $J=7.0$, 1.2 Hz), 7.27 (br s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 148.4, 147.3, 143.6, 130.8, 129.9, 129.2, 128.7, 127.7, 127.6, 124.3, 124.2. HRMS Calcd for ($\text{C}_{12}\text{H}_9\text{N}_3+\text{H}^+$): 196.0874. Found: 196.0871.

4.4.12. 2-(Thiophen-2-yl)imidazole (**11l**)

Compound **11l** (0.73 g, 49%) was obtained as a white solid following Method B: mp 194–195 °C (lit.¹⁶ 197–198 °C); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.53 (br s, 1H), 7.49 (m, 2H), 7.10 (dd, 1H, $J=5.1$, 3.6 Hz), 7.07 (br s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 141.4, 134.5, 127.6, 125.5, 123.2;

MS (ESI) m/z 151 ($\text{M}+\text{H}$). The ^1H and ^{13}C NMR spectra of this product were consistent with the literature data.²²

4.4.13. 2-(Imidazol-2-yl)thiazole (**11m**)

Compound **11m** (7.02 g, 93%) was obtained as a light yellow solid following Method A and the workup procedure described for **11i**: mp 174–175 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.09 (br s, 1H), 7.90 (d, 1H, $J=3.1$ Hz), 7.73 (d, 1H, $J=3.1$ Hz), 7.28 (br s, 1H), 7.07 (br s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 158.9, 143.1, 140.9, 129.5, 120.1, 118.9; MS (ESI) m/z 152 ($\text{M}+\text{H}$). The ^1H and ^{13}C NMR spectra of this product were consistent with the literature data.¹⁸

4.4.14. 2-(3-Nitrophenyl)imidazole (**11n**)

Compound **11n** (1.29 g, 68%) was obtained as a light yellow solid following Method B: mp 190–191 °C (lit.¹⁸ 193–194 °C); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.92 (br s, 1H), 8.80 (s, 1H), 8.39 (d, 1H, $J=7.8$ Hz), 8.18 (dd, 1H, $J=8.2$, 1.5 Hz), 7.75 (t, 1H, $J=8.0$ Hz), 7.37 (br s, 1H), 7.13 (br s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 148.7, 143.9, 132.7, 131.1, 130.7, 130.0, 122.6, 119.4, 119.1; HRMS Calcd for ($\text{C}_9\text{H}_7\text{N}_3\text{O}_2+\text{H}^+$): 190.0616. Found: 190.0614. The ^1H NMR spectrum of this product was consistent with the literature data.²¹

4.4.15. 2-(4-Nitrophenyl)imidazole (**11o**)

Compound **11o** (0.62 g, 64%) was obtained as a yellow solid following Method B: mp 304 °C (dec) (lit.²² 309–311 °C); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.99 (br s, 1H), 8.33 (d, 1H, $J=9.0$ Hz), 8.18 (d, 1H, $J=9.0$ Hz), 7.30 (br s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 146.8, 144.0, 137.0, 125.7, 124.6; HRMS Calcd for ($\text{C}_9\text{H}_7\text{N}_3\text{O}_2+\text{H}^+$): 190.0616. Found: 190.0619. The ^1H NMR spectrum of this product was consistent with the literature data.²²

4.4.16. Methyl 4-(imidazol-2-yl)benzoate (**11p**)

Compound **11p** (1.20 g, 31%) was obtained as a white solid following Method B: mp 227–230 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.80 (br s, 1H), 8.09 (d, 1H, $J=8.6$ Hz), 8.03 (d, 1H, $J=8.6$ Hz), 7.24 (s, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 166.3, 144.8, 135.3, 130.0, 128.9, 125.1, 52.5; HRMS Calcd for ($\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2+\text{H}^+$): 203.0820. Found: 203.0817. The ^1H NMR spectrum of this product was consistent with the literature data.²³

4.4.17. 2-(4-(Trifluoromethyl)phenyl)imidazole (**11q**)

Compound **11q** (1.23 g, 58%) was obtained as a white solid following Method B: mp 233–235 °C (lit.^{10b} 219–221 °C); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.82 (br s, 1H), 8.16 (d, 2H, $J=8.2$ Hz), 7.82 (d, 2H, $J=8.2$ Hz), 7.12 (br s, 1H), 7.09 (br s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 144.1, 134.4, 129.7, 127.8 (q, $J_{\text{C-F}}=31.9$ Hz), 125.7 (q, $J_{\text{C-F}}=3.8$ Hz), 125.1, 124.3 (q, $J_{\text{C-F}}=247.1$ Hz), 118.7; HRMS Calcd for ($\text{C}_9\text{H}_7\text{N}_3\text{O}_2+\text{H}^+$): 213.0639. Found: 213.0646. The ^1H and ^{13}C NMR spectra of this product were consistent with the literature data.^{10b}

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