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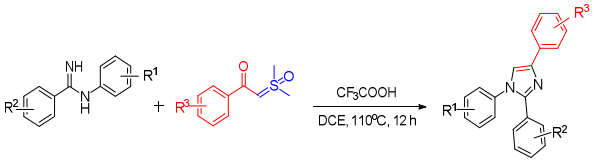


- metal-free
- environmentally friendly
- C-N bond formation
- broad substrates (31 examples, up to 91% yield)

Acid-catalysed synthesis of imidazole derivatives *via* *N*-phenylbenzimidamides and sulfoxonium ylides cyclization

[a] Yuan Tian, [a] Mingda Qin, [a] Xueying Yang, [a] Xueguo Zhang, [a] Yafeng Liu, Xin Guo[*a,b], Baohua Chen[*a,c]

[a.] *State Key Laboratory of Applied Organic Chemistry, Key laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, Gansu, China. E-mail: chbh@lzu.edu.cn*
[b.] *School of Chemistry and Chemical Engineering, North Minzu University, Yinchuan 750021, P.R.China.*
[c.] *Zhongwei High-Tech Institute of Lanzhou University, Zhongwei, Ningxia 755500, China*

ABSTRACT

A straightforward method to synthesize imidazole derivatives from amidines and sulfoxonium ylides catalyzed by acids is reported in this study. Specifically, catalysed by trifluoroacetic acid in DCE solvents can improve synthesis efficiency under metal-free conditions. A series of imidazole scaffolds were produced in good to excellent yields.

Keywords:

Amidines

Sulfoxonium ylides

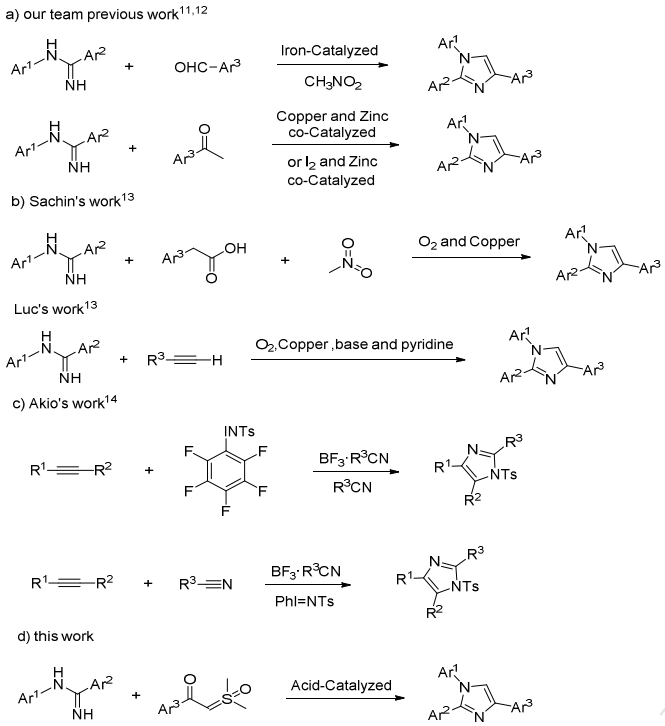
N-phenylbenzimidamides

Mild conditions Environment- friendly

1. Introduction

The imidazole ring represents an important class of heterocycles, which have been widely applied in natural products, biological fields and pharmaceutical industries.[1] As a privileged structural motif, imidazole derivatives possess many meaningful biological properties, such as anti-plasmodium,[2] anti-inflammatory,[3] antifungal,[4] antibacterial[5] and antitumoral[6] , among them, losartan (antihypertension), etomidate (hypnotic agent) and flumazenil (benzodiazepine antagonist) are a few examples of *N*-aylimidazoles-containing drugs[7a], which have been widely explored and utilized. Moreover, with the continuous advancement of the chemical industry, imidazole derivatives have been exploited as precursors of ligands in synthetic organic chemistry.[7b-c, 8] Traditionally, many chemists had used a wide variety of transition metal catalysed direct C-N formation reactions.[9] Although effective as they were, most of them needed complex reductants or suffered from some other disadvantages, such as a required use of non-ideal solvents and poor functional group tolerance.[10]

Previously, our team worked to synthesize multi-substituted imidazoles efficiently through metal-catalysed oxidation processes. For example, we formerly reported iron(III)-catalyzed synthesis of 1,2,4-trisubstituted imidazoles through the reactions of amidines, nitromethanes and aldehydes.[11] The latest synthetic multi-substituted imidazole methods have been published by our group in which amidines and ketones were used to synthesize multi-substituted imidazoles via a [3+2] cycloaddition reaction co-catalyzed by copper and zinc or I_2 and zinc.[12] For other synthetic methods of imidazoles using amidines, the Sachin's



Scheme 1. Strategies or the synthesis of imidazoles

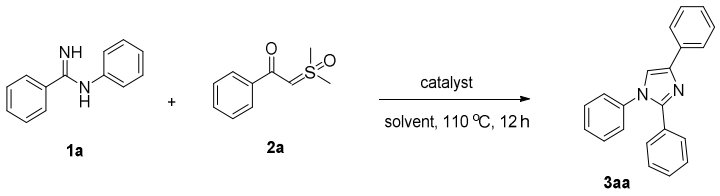
group reported copper and oxygen co-catalyzed simultaneous activation of C-H and N-H bonds: a three-component one-pot cascade synthesis of multisubstituted imidazoles. Also the Luc's group reported copper-catalyzed oxidative deamination of terminal alkynes by amidines: synthesis of 1,2,4-trisubstituted imidazoles[13]. Akio's group also reported a method of metal-free synthesis of imidazole some years ago. Such as development of imino□λ^3□iodanes with improved reactivity for metal□free [2+2+1] cycloaddition□type reactions[14]. These strategies were shown in Scheme 1. Although some achievements were made, the reactions required precious metals or metal sails and some other strict conditions. Moreover, the operations of these reactions were quite complicated. Encouraged by previous works, we have focused on a more direct method for synthesizing multi-substituted imidazoles in the absence of metals and ligands under mild conditions.

Therefore, we came up with a simple and economical method of synthesizing multi-substituted imidazoles. We found a new substance called sulfoxonium ylide, which has a strong reactivity and can couple a partner to deliver a carbene.[15] Moreover, it was often used as a substrate, and would not require a critical condition. And we employed a Brønsted acid-catalysed strategy to construct the polycyclic heterocycles, among them, [3 + 2] cycloaddition proved to be one of the most efficient approaches, which could be used to construct five-membered heterocycles[16a]. This strategy was applied to our reaction and highlighted some advantages. The protocol is operationally simple, avoiding the use of toxic and scarce precious metal catalysts[16b]. And this method is economical and environmentally friendly, and thus represents a novel and efficient method for the construction of imidazoles.

2. Results and discussion

With reference to the previous works, our preliminary study began with 1 equiv of *N*-phenylbenzamidine (**1a**) and 2 equiv of sulfoxonium ylide (**2a**) as the model substrates in solvents at 110 ^{o}C for 12 h (**Table 1,**). In this reaction, the DCE was used as the best solvent among DMF, toluene, 1,4-dioxane and DCM. And our desired product called 1,2,4-triphenyl imidazole (**3aa**) was obtained in 32% yield (**Table 1, entry 5**). When

Table 1. Optimization of the Reaction Conditions [a]



Entry	Catalyst	Solvent	Yield of 3aa[b] %
1	-	DMF	nr[c]
2	-	Toluene	15
3	-	1,4-dioxane	21
4	-	DCM	trace
5	-	DCE	32
6[d]	-	DCE	23
7[e]	-	DCE	**34**
8	Na_2CO_3	DCE	trace
9	NaOAc	DCE	33
10	HOAc	DCE	41
11	HCOOH	DCE	57
12	PivOH	DCE	45
13	**CF_3COOH**	**DCE**	**83**
14	CF_3SO_3H	DCE	81
15	CCl_3COOH	DCE	53
16	PhCOOH	DCE	50
17[f]	CF_3COOH	DCE	78
18[g]	CF_3COOH	DCE	27

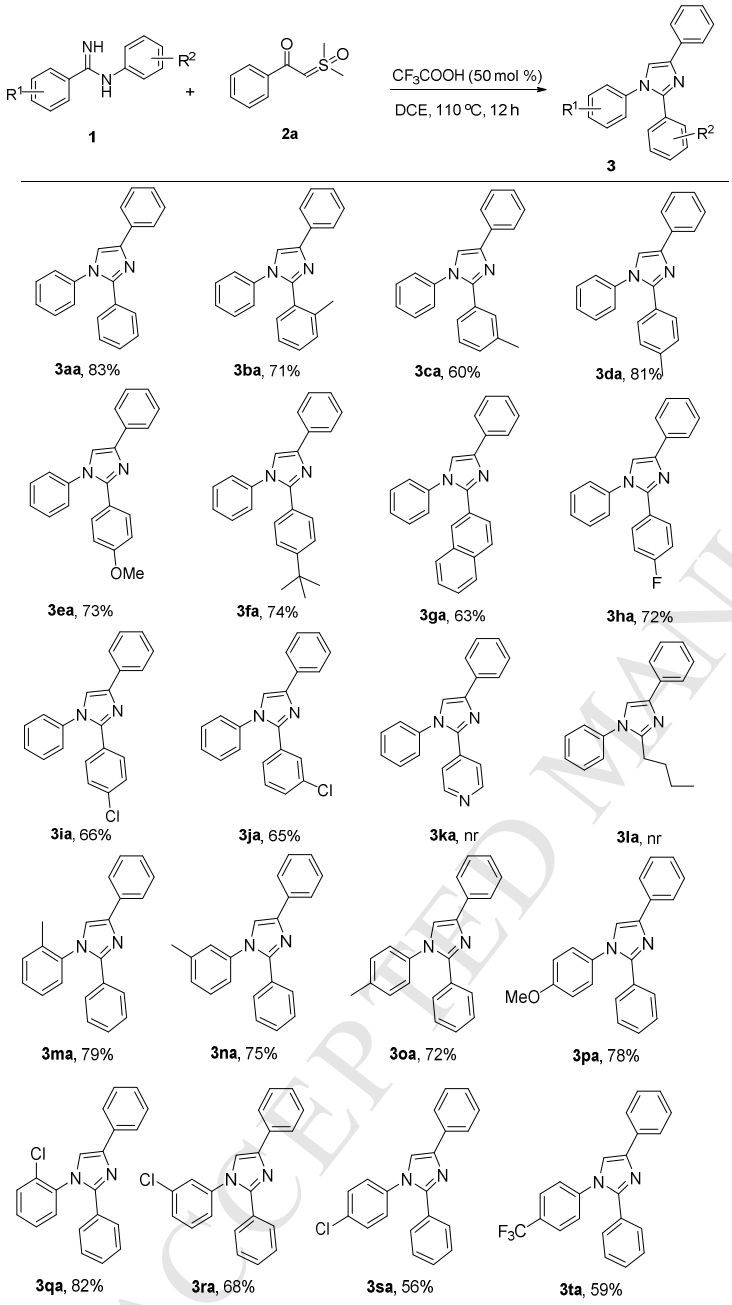
[a]Reaction conditions:**1a** (0.1 mmol)**, 2a** (0.2 mmol), catalyst (50 mol%) in solvent (2 mL) at heat for 12 h. [b] Isolated yield. [c] nr=no reaction. [d] 100 °C. [e] 120 °C. f catalyst (20 mol%）. [g] catalyst (100 mol%).

the temperature was raised to 120 °C, there was only a small increase in yield (**Table 1, entry 7**). So we finally chose 110 °C as the best reaction temperature. Later we used bases and acids (50 mol%) as catalysts respectively, and found that the catalytic performance of the base was worse than that of the acid in this reaction. After employing trifluoracetic acid as the catalyst, we found that the yield could be satisfactorily increase to 83% (**Table 1, entry 13**). Also trifluoromethanesulfonic acid was employed and could improve the yield to 81% (**Table 1, entry 14**). However, under other acids, such as HOAc, HCOOH, PivOH, CCl_3COOH and PhCOOH, there seemed to appear less remarkable changes in the yields. Furthermore, we tested the amount of acid separately with 20 mol% and 100 mol%, but still found that 50 mol% acids were the best choice. Up to now, we have completed the qualification: **1a** (1 equiv), **2a** (2 equiv) and CF_3COOH (50 mol%) in DCE (2 ml) at 110 °C for 12 h.

Under the optimal condition, the substrates scope of amidine (**1**) and sulfoxonium ylide (**2a**) were examined to establish the limitation of the reaction and the results are showed in **Scheme 2.** A variety of 1,2,4-trisubstituted imidazoles (**3ba-3ja**, **3ma-3ta**) could be obtained by employing various amidines (**1b-1t**) and sulfoxonium ylides (**2a**) , giving good yields ranging from 47% to 82%. Generally, compared to the

electron-withdrawing groups (**3ha-3ja,3qa-3ta**), the electron-donating groups such as methyl-, methoxy-, *tert*-butyl- could produce the corresponding products in better yields (**3ba-3fa,3ma-3pa**), which might be

Scheme 2. Substrate scope of amidine [a]



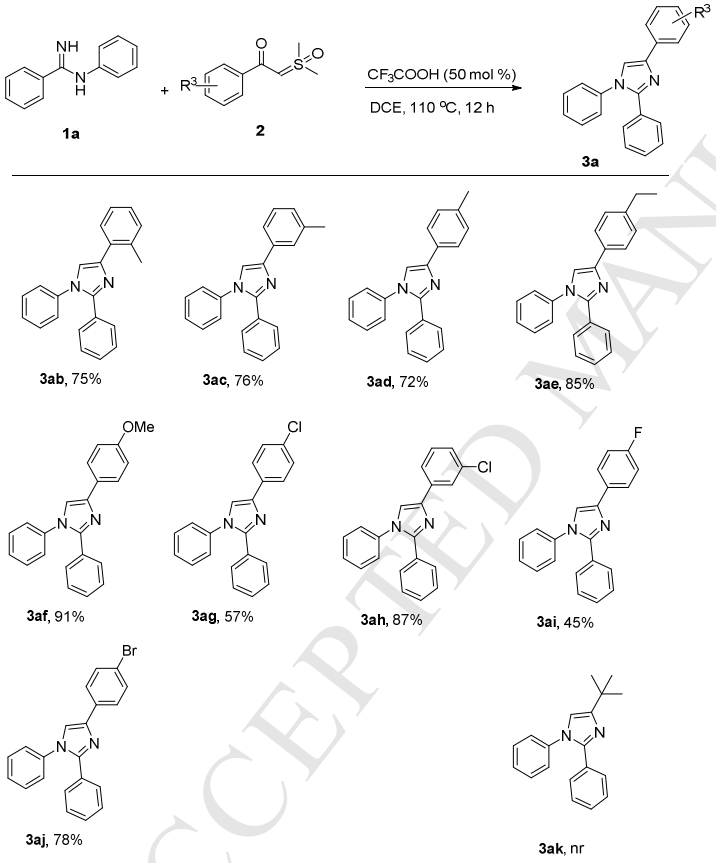
[a] Reaction conditions:**1a** (0.1 mmol), **2a** (0.2 mmol), CF_3COOH (50 mol%), DCE (2 mL), 110 °C, 12 h. [b] Isolated yields. [c] nr=no reaction.

attributed to the electronic effects. More precisely, the electron-donating groups were able to increase the activity of the amidines, which would be more conducive to the reaction. Specially, some substrates with the *meta* substituent in *N*-phenylbenzimidamide (**3ca**) came up with low yields. Probably, due to the fact that the electron-donating groups were detrimental to *meta*-activation. To our surprise, a substrate with an *ortro*-chlorine (**R^2=2-Cl, 3qa**) had an excellent yield up to 82%. Nevertheless, once the benzene ring was replaced by a naphthalene ring, the yield would drop to 63% (**3ga**). We suspected that this might be due to the steric hindrance effect of the naphthalene ring. To our disappointment, we failed to find the target products when we changed benzene ring to pyridine ring (**3ka**) and *n-butyl* **(3la)** group. As to these

phenomena, we suspected that the pyridine ring had a strong blunt effect not conducive to the reaction. We also speculate that compared with the aliphatic substrate, the aromatic ring had conjugating effect beneficial to the reaction.

On the other hand, the scope of sulfoxonium ylide was investigated as shown in **Scheme 3**. Generally, benzoyl-substituted sulfoxonium ylides bear both electron-donating (**3ab**-**3af**) and a part of -withdrawing groups (**3ah,3ai,3ak**), which all work well to deliver the desired products in moderate to good yields, such as methyl-, ethyl-, methoxy-, ortro- or meta-chloro- and bromo-. But for para-chlorine (**2g**) and -fluorine (**2j**) substrates of sulfoxonium ylides, the yield of the obtained products was only 57% and 45%. We suspected that they might be caused by a strong electron withdrawing effect of fluorine and chlorine in the para position. But for aliphatic substrates, they were still not conducive to the reaction, which was likely due to aliphatic substrates of N- phenylbenzimidamide.

Scheme 3. Substrate scope of sulfoxonium ylide.

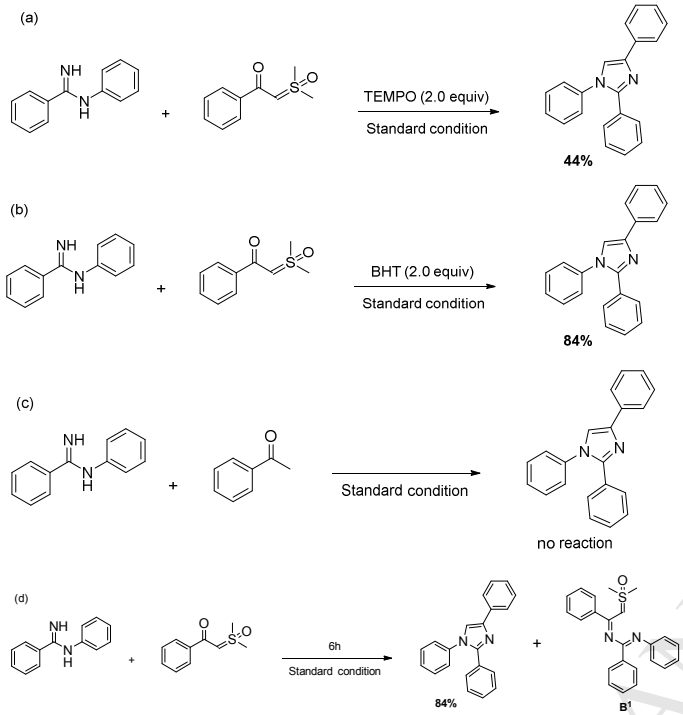


[a] Reaction conditions:**1a** (0.1 mmol), **2a** (0.2 mmol), CF_3COOH (50 mol%), DCE (2 mL), 110 °C, 12 h. [b] Isolated yields. [c] nr=no reaction

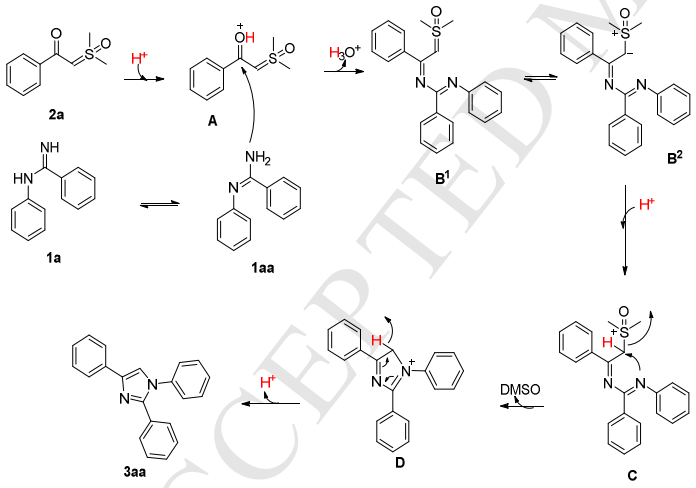
To gain a further insight into the reaction, 2,2,6,6- tetramethyl- 1-piperidinyloxy (TEMPO, 2.0 equiv) was added to the system, but the reaction provided merely a yield of 44% (**Scheme 4, a**). Then, we replaced the TEMPO with 2,6-di-tert-butyl-4-methyl- phenol (BHT) in this system and to our surprise, the reaction still provided a yield of 84% (**Scheme 4, b**). However, we discovered through experiments that TEMPO did not capture any free radical intermediate. So we suggested that the reaction yield might have been reduced due to the oxidative nature of TEMPO. So we rule out the possibility of a free radical reaction process. Later, we replaced sulfoxonium ylide with acetophenone under the optimized condition and did not get any target products (**Scheme 4, c**). Fortunately, the intermediate (E)-N-((Z)-2-(dimethyl(oxo)-l6-sulfanylidene) -1-

phenylethylidene)-N'-phenylbenzimidamide **B1** was detected by GC-MS analysis (m/ z = 374) after 6 h of reaction.

Scheme 4. Control experiments



Scheme 5. Proposed mechanism



On the basis of the aforementioned information[17] and our preliminary mechanistic results, a plausible mechanism of coupling of **1a** with **2a** was proposed in **Scheme 5**. Initially, under acidic conditions, hydrogen ions attacked the carbonyl oxygen atoms of the sulfoxonium ylide **2a**, causing the carbonyl group to have a positive charge to form intermediates **A**. At the same time, amidines are subjected to resonance transformation to form intermediates **1aa**. Then, the amino nitrogen atoms attacked the carbonyl carbon atoms and then removed the hydronium ions to form intermediates **B1**. At the same time, intermediates **B1** resonated to form intermediates **B2**. Next, the negatively charged carbon atoms of intermediate **B2** were combined with protons again to form intermediate **C**. In the intermediate **C** molecule, the nitrogen atom which attached to the benzene ring attacked the same carbon atom, and the DMSO molecule was removed to form intermediate **D**. Finally, the proton was removed from intermediate **D** *via* electron transferring inside the intermediate **D** molecule to form the target product **3aa**.

3. Conclusion

In summary, an efficient acid-catalyzed method to synthesize multi-substituted imidazoles from the amidines and sulfoxonium ylides was carried out. We used CF_3COOH as the catalyst in the DCE, which served as thesolvent in this reaction. The reaction tolerates a wide range of aromatic functional groups such as alkyl-, methoxy-, fluoro-, chloro-, trifluoromethyl- and naphthalene rings, which afforded the imidazole skeletons in good yields with high regioselectivity. Moreover, the reaction is economical, easy-to-operate and environmentally friendly.

4.Experimental section

4.1 General

All reagents were commercially available and used as is without further purification. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using TMS as the internal standard. Melting points were determined on a microscopic apparatus..HRMS was performed using an FT-ICRMS mass instrument and measured with electrospray ionization (ESI). Products were purified by flash chromatography on 200-300 mesh silica gel. Unless otherwise noted, commercially reagents were used without further purification.

4.2 General procedure for the synthesis of 1,2,4- triphenylimidazole (3a)

All the reactions were carried out in a reaction vessel (10 mL), *N*-phenylbenzamidine (**1a**, 0.1 mmol), sulfoxonium ylides (**2a**,0.2 mmol), trifluoroacetate (50 mol%) and DCE (2 ml) were successfully mixed in the flask using a magnetic stir bar and reacted at 110 ^{o}C for 12 h in the presence of air. Then the mixture was removed from the oil bath and cooled to room temperature. The mixture was filtered and washed with ethyl acetate (3×50 mL) and the crude product was obtained by concentrating under reduced pressure. Finally, product **3a** was isolated as a yellow oil by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 as the eluent).The remaining substituted imidazoles were prepared in a similar manner.

4.3Compound data of products 3aa

*4.3.1. 1,2,4-triphenyl-1H-imidazole（**3aa**）*

Compound **3aa** was isolated as yellow oil (83% yield, 24.6 mg) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 7.3 Hz, 2H), 6.80 (d, J= 17.3 Hz, 7H), 6.69 – 6.55 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.86 (s), 141.55 (s), 138.33 (s), 133.68 (s), 129.36(s),129.11(s),128.08 (s), 127.71 (s),128.08 (s), 126.88 (s), 125.70 (s) 124.92(s), 118.40 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.2. 2,4-diphenyl-1-(o-tolyl)-1H-imidazole (**3ba**)*

Compound **3ba** was isolated as yellow oil (71% yield, 22.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.3 Hz, 2H), 7.41– 7.26 (m, 5H), 7.24 – 7.13 (m, 8H), 1.90 (s, 3H).^{13}C NMR (75MHz, CDCl3) δ 147.18 (s), 141.54 (s), 137.73 (s), 134.97 (s),133.88 (s), 131.22 (s), 130.41 (s), 129.08 (s), 128.52 (s), 128.17(s), 127.64 (s), 127.01 (s),124.91 (s), 118.45 (s), 17.46 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.3. 2,4-diphenyl-1-(m-tolyl)-1H-imidazole (**3ca**)*

Compound **3ca** was isolated as yellow oil (60% yield, 18.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.5 Hz, 2H), 7.45–7.29 (m, 6H), 7.22 – 7.11 (m, 6H), 7.04 (s, 1H), 2.28 (s, 3H).^{13}C NMR (75MHz, CDCl3) δ 141.63 (s), 139.70 (s), 138.49 (s),133.97 (s), 130.43 (s), 129.26 (s), 129.00 (s), 128.81 (s), 128.65(s), 128.45 (s), 128.21 (s),127.90 (s), 127.01 (s), 126.36 (s),125.09 (s), 123.10 (s), 118.67 (s), 21.36 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.4. 2,4-diphenyl-1-(p-tolyl)-1H-imidazole (**3da**)*

Compound **3da** was isolated as yellow oil (80% yield, 24.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.79 (m,2H), 7.42 –7.37 (m, 2H), 7.35 – 7.29 (m, 3H), 7.22 – 7.16 (m, 4H), 7.15 –7.04 (m, 4H), 2.32 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 146.94(s), 141.50 (s), 138.15 (s), 135.94 (s), 133.89 (s), 130.01 (s), 128.75 (s), 128.56 (s), 128.33 (s), 128.14 (s)，126.91 (s), 125.59 (s), 124.99 (s), 118.63 (s), 21.12 (s). This spectrum is in agreement with previously reported spectral data.[12]

4.3.5. *1-(4-methoxyphenyl)-2,4-diphenyl-1H-imidazole (**3ea**)*

Compound **3ea** was isolated as yellow oil (73% yield, 23.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.4 Hz, 2H), 7.43–7.28 (m, 5H), 7.19 (dd, J = 6.2, 2.5 Hz, 4H), 7.11 (d, J = 8.8 Hz,2H), 6.83 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.50 (s), 141.61 (s), 134.09 (s), 128.95 (s), 128.81 (s), 128.58 (s), 128.40 (s), 127.30 (s), 127.17 (s), 125.25 (s), 122.56 (s), 119.08 (s), 114.80 (s), 114.64 (s), 55.76 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.6.1-(4-(tert-butyl)phenyl)-2,4-diphenyl-1H-imidazole (**3fa**)*

Compound **3fa** was isolated as yellow oil (74% yield, 26.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dt, J = 8.2, 1.7 Hz, 2H), 7.40– 7.36 (m, 2H), 7.34 – 7.28 (m, 5H), 7.21 – 7.14 (m, 4H), 7.11 –7.06 (m, 2H), 1.26 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 151.30(s), 146.86 (s), 141.38 (s), 135.71 (s), 133.78 (s), 130.26 (s), 128.68 (s), 128.46 (s), 128.23 (s), 128.03 (s),126.81 (s), 126.21 (s), 126.03 (s),125.19 (s), 124.92 (s), 118.56 (s), 34.61 (s), 31.19 (s), 29.58 (s). HRMS (ESI) calcd for $C_{25}H_{24}N_2$ $(M+H)^+$ 353.2012, found 353.2013.

*4.3.7. 1-(naphthalen-2-yl)-2,4-diphenyl-1H-imidazole (**3ga**)*

Compound **3ga** was isolated as a white solid (63% yield, 21.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 – 7.81 (m, 6H), 7.59 – 7.53 (m, 3H), 7.51 – 7.48 (m, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.31– 7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.33 (s), 142.01 (s), 136.19 (s), 134.06 (s), 133.53 (s), 132.71 (s), 130.53 (s), 129.71 (s),129.04 (s), 128.85 (s), 128.72 (s), 128.49 (s), 128.25(s), 128.12 (s), 127.39 (s), 127.27 (s), 127.13 (s),125.30 (s), 124.37 (s), 124.04 (s), 119.03 (s). HRMS (ESI) calcd for $C_{25}H_{18}N_2$ $(M+H)^+$ 347.1543, found 347.1544.

*4.3.8. 1-(4-fluorophenyl)-2,4-diphenyl-1H-imidazole (**3ha**)*

Compound **3ha** was isolated as yellow oil (72% yield, 22.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.2, 0.8 Hz, 2H), 7.36 (ddd, J = 11.4, 8.0, 6.0 Hz, 5H), 7.26 – 7.15 (m, 6H), 7.04 (t, J = 8.2 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 147.11 (s), 141.80 (s), 133.68 (s), 130.88 - 130.06 (d, J = 61.5 Hz), 128.77 (s), 128.60 (s), 128.57 (s), 128.28 (s), 127.67-127.56 (d, J = 8.3 Hz), 127.55 (s),127.08 (s), 125.04 (s), 118.48 (s), 116.61 -116.31 (d, J=22.5 Hz). HRMS (ESI) calcd for $C_{21}H_{15}N_2F$ (M+H)+ 315.1292, found 315.1294.

*4.3.9. 1-(4-chlorophenyl)-2,4-diphenyl-1H-imidazole (**3ia**)*

Compound **3ia** was isolated as yellow oil (66% yield, 21.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.40 – 7.27 (m, 7H), 7.25 – 7.16 (m, 4H), 7.15 – 7.08 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 146.80 (s), 141.76 (s), 136.71 (s), 133.78 (s), 133.36 (s), 129.74 (s), 129.47 (s), 128.61 (s), 128.40 (s), 128.12 (s), 126.93 (s), 126.78 (s),124.84 (s), 117.97 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.10. 1-(2-chlorophenyl)-2,4-diphenyl-1H-imidazole (**3ja**)*

Compound **3ja** was isolated as a light yellow solid (65% yield, 21.4 mg). ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.88 – 7.82 (m, 2H),7.45 (dd, J = 4.8, 4.0 Hz, 1H), 7.35 (ddt, J = 7.8, 6.3, 2.8 Hz, 6H), 7.28 – 7.14 (m, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 147.24 (s), 135.87 (s), 133.29 (s), 131.31 (s), 130.22 (s), 129.75 (s), 128.95 (s),128.13 (s), 127.78 (s), 127.60 (s), 127.35 (s), 126.58 (s), 124.63 (s), 118.03 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.11. 1,4-diphenyl-2-(o-tolyl)-1H-imidazole (**3ma**)*

Compound **3ma** was isolated as yellow oil (79% yield, 24.5 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.50 (s, 1H), 7.38 (t, J = 7.7 Hz, 2H), 7.31 – 7.19 (m, 6H), 7.15 – 7.06 (m, 4H), 2.10 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 146.87 (s), 141.30 (s), 137.76 (s), 133.74 (s), 130.84 (s), 130.36 (s), 130.16 (s), 129.08 (s), 128.47 (s), 127.35 (s), 126.82 (s), 125.44 (s), 124.85 (s), 124.39 (s), 116.29 (s),19.84 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.12. 1,4-diphenyl-2-(m-tolyl)-1H-imidazole (**3na**)*

Compound **3na** was isolated as yellow oil (75% yield, 23.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.3, 1.2 Hz, 2H), 7.47 – 7.35 (m, 7H), 7.26 (ddd, J = 7.1, 5.2, 1.7 Hz, 3H), 7.12 –7.04 (m, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.13 (s), 141.56 (s), 138.45 (s), 137.97 (s), 133.80 (s), 130.05 (s),129.57 (s), 129.37 (s), 129.20 (s), 128.55 (s), 128.07 (s), 127.85 (s), 126.92 (s), 125.77 (s), 125.01 (s), 118.37 (s),21.31 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.13. 1,4-diphenyl-2-(p-tolyl)-1H-imidazole (**3oa**)*

Compound **3oa** was isolated as yellow oil (72% yield, 22.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.3 Hz, 2H), 7.31 (ddd, J = 17.0, 10.8, 6.6 Hz, 8H), 7.19 (dt, J = 5.8, 2.7 Hz, 3H), 7.00 (d, J = 8.0 Hz, 2H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.44 (s), 138.47 (s), 138.29 (s),133.78 (s), 129.34 (s), 128.80 (s), 128.60 (s), 128.48 (s), 128.00 (s), 127.28 (s), 126.84 (s), 125.76 (s), 124.95 (s), 118.23 (s), 21.19 (s).

This spectrum is in agreement with previously reported spectral data.[13]

*4.3.14. 2-(4-methoxyphenyl)-1,4-diphenyl-1H-imidazole (**3pa**)*

Compound **3pa** was isolated as yellow oil (78% yield, 25.4 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.38 – 7.26 (m, 7H), 7.23 – 7.15 (m, 4H), 6.75 – 6.68 (m, 2H), 3.70 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 159.99 (s), 147.22 (s), 141.68 (s), 138.84 (s), 134.16 (s), 130.43 (s), 129.68 (s),128.80 (s), 128.30 (s), 127.14 (s), 126.10 (s), 125.25 (s), 123.11 (s), 118.35 (s), 113.88 (s),55.45 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.15. 2-(2-chlorophenyl)-1,4-diphenyl-1H-imidazole (**3qa**)*

Compound **3qa** was isolated as yellow oil (82% yield, 27.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 2H), 7.51 – 7.46 (m, 2H), 7.37 – 7.29 (m, 2H), 7.28 – 7.17 (m, 7H), 7.12 –7.07 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 144.94 (s), 142.03 (s), 138.07 (s), 134.68 (s), 133.92 (s), 132.96 (s),130.87 (s), 130.72 (s), 129.90 (s), 129.42 (s), 128.85 (s), 127.96 (s), 127.29 (s), 126.98 (s), 125.29 (s), 124.80 (s), 117.19 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.16. 2-(3-chlorophenyl)-1,4-diphenyl-1H-imidazole (**3ra**)*

Compound **3ra** was isolated as yellow oil (58% yield, 19.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.4 Hz, 2H), 7.51 (s, 1H), 7.42 – 7.31 (m, 6H), 7.25 – 7.17 (m, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 141.98 (s), 138.16 (s), 134.27 (s), 133.62 (s), 132.01 (s), 129.65 (s), 129.34 (s), 128.83 (s), 128.65 (s), 128.54 (s), 128.49 (s), 127.17 (s), 126.66 (s), 125.87 (s), 125.06 (s), 118.91 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.17. 2-(4-chlorophenyl)-1,4-diphenyl-1H-imidazole (**3sa**)*

Compound **3sa** was isolated as yellow oil (65% yield, 20.5 mg). ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.4 Hz, 2H), 7.47–7.38 (m, 7H), 7.32 – 7.22 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.85 (s), 138.29 (s), 134.53 (s), 129.98 (s), 129.65 (s), 128.83 (s), 128.65 (s),128.49 (s), 127.14 (s), 125.88 (s), 125.06 (s), 118.79 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.18. 1,4-diphenyl-2-(4-(trifluoromethyl)phenyl)-1H-imidazole (**3ta**)*

Compound **3ta** was isolated as yellow oil (47% yield, 17.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.2, 1.0 Hz, 2H), 7.48 (dd, J = 20.8, 8.5 Hz, 4H), 7.41 – 7.30 (m, 6H), 7.25 – 7.17 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.58 - 164.10 (d, J = 261.0 Hz), 145.24 (s), 142.08 (s), 138.01 (s), 130.77 (s), 129.64-128.68 (d, J = 72.0 Hz), 128.71 (s),127.15 (s), 125.77 (s), 125.11–124.95 (q, J = 12.0 Hz), 119.19 (s), 112.78 (s).This spectrum is in agreement with previously reported spectral data.[12]

*4.3.19. 1,2-diphenyl-4-(o-tolyl)-1H-imidazole (**3ab**)*

Compound **3ab** was isolated as yellow oil (75% yield, 23.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 7.1 Hz, 1H), 7.42-7.28 (m, 5H), 7.18 (ddd, J = 9.0, 6.3, 3.5 Hz, 9H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.99 (s), 140.99 (s), 138.49 (s), 134.97 (s), 133.12 (s), 130.71 (s), 130.26 (s), 129.45 (s), 128.76 (s), 128.63 (s), 128.35 (s), 128.13 (s), 126.93 (s), 125.95 (s), 125.87 (s), 120.99 (s), 21.87 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.20. 1,2-diphenyl-4-(m-tolyl)-1H-imidazole (**3ac**)*

Compound **3ac** was isolated as yellow oil (76% yield, 23.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.39 – 7.32 (m, 3H), 7.29 (dd, J = 5.3, 1.7 Hz, 3H), 7.20-7.12 (m, 6H), 6.99 (d, J = 7.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.88 (s), 141.76 (s), 138.44 (s), 138.15 (s), 133.68 (s), 130.30 (s), 129.42 (s), 128.79 (s), 128.45 (s), 128.39 (s), 128.16 (s), 128.10 (s), 127.77 (s), 125.78 (s), 125.74 (s), 122.09 (s), 118.47 (s), 21.48 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.21. 1,2-diphenyl-4-(p-tolyl)-1H-imidazole (**3ad**)*

Compound **3ad** was isolated as yellow oil (72% yield, 22.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 2H), 7.40-7.27 (m, 6H), 7.22 – 7.09 (m, 7H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.75 (s), 141.72 (s), 138.45 (s), 136.56 (s), 130.96 (s), 130.30 (s), 129.38 (s), 129.23 (s), 128.74 (s), 128.31 (s), 128.11 (s), 128.02 (s), 125.75 (s), 124.88 (s), 118.03 (s), 21.21 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.22. 4-(4-ethylphenyl)-1,2-diphenyl-1H-imidazole (**3ae**)*

Compound **3ae** was isolated as yellow oil (85% yield, 27.5 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.46-7.34 (m, 6H), 7.28 – 7.19 (m, 7H), 2.66 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 147.07 (s), 143.32 (s), 142.07 (s), 138.75 (s), 131.51 (s), 130.59 (s), 129.69 (s),

129.07 (s), 128.64 (s), 128.43 (s), 128.35 (s), 126.06 (s), 125.30 (s), 118.37 (s), 28.91 (s), 15.84 (s). HRMS (ESI) calcd for $C_{23}H_{20}N_2$ $(M+H)^+$ 325.1699, found 325.1698.

*4.3.23. 4-(4-methoxyphenyl)-1,2-diphenyl-1H-imidazole (**3af**)*

Compound **3af** was isolated as yellow oil (91% yield, 29.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.47 – 7.32 (m, 6H), 7.27 – 7.19 (m, 5H), 6.97 – 6.89 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.08 (s), 146.99 (s), 141.81 (s), 138.76 (s), 129.69 (s), 129.03 (s),128.61 (s), 128.43 (s), 128.32 (s), 126.93 (s), 126.54 (s), 126.05 (s), 117.80 (s), 114.27 (s), 55.53 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.24. 4-(4-chlorophenyl)-1,2-diphenyl-1H-imidazole (**3ag**)*

Compound **3ag** was isolated as yellow oil (57% yield,18.8 mg). ^{1}H NMR (300 MHz, CDCl) δ 7.83 (d, J = 8.5 Hz, 2H), 7.47-7.34 (m, 8H), 7.31 – 7.22 (m, 5H).^{13}C NMR (75 MHz, $CDCl_3$) δ 146.83 (s), 140.76 (s), 138.44 (s), 132.68 (s), 131.06 (s), 129.68 (s), 128.92 (s), 128.74 (s), 128.45 (s), 128.39 (s), 126.41 (s), 125.94 (s), 118.81 (s). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.25. 4-(3-chlorophenyl)-1,2-diphenyl-1H-imidazole (**3ah**)*

Compound **3ah** was isolated as yellow oil (87% yield,28.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (t, J = 1.8 Hz, 1H), 7.72 (d, J= 7.7 Hz, 1H), 7.40 (ddd, J = 7.0, 6.2, 2.0 Hz, 6H), 7.29 – 7.19 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.57 (s), 138.46 (s), 135.89 (s), 134.80 (s), 131.11 (s),130.21 (s), 130.05 (s), 129.73 (s), 128.98 (s), 128.82 (s), 128.54 (s), 128.45 (s), 127.11 (s), 126.00 (s), 125.28 (s), 123.24 (s). This spectrum is in agreement with previously reported spectral data.[13]

*4.3.26. 4-(4-fluorophenyl)-1,2-diphenyl-1H-imidazole (**3ai**)*

Compound **3ai** was isolated as yellow oil (45% yield,14.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.47 – 7.37 (m, 6H), 7.26 (ddd, J = 6.9, 3.4, 1.2 Hz,5H), 7.09 (t, J = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.80 - 160.55 (d, J=243.8 Hz), 147.09 (s), 140.90 (s), 138.42 (s), 130.18 (s), 130.12 -130.08 (d, J=3.0 Hz), 129.56(s), 128.83 (s), 128.29 (s), 126.75-126.65 (d, J = 7.5 Hz), 125.87 (s), 118.21 (s), 115.67 - 115.39 (d, J = 21.0 Hz). This spectrum is in agreement with previously reported spectral data.[12]

*4.3.27. 4-(4-bromophenyl)-1,2-diphenyl-1H-imidazole (**3aj**)*

Compound **3aj** was isolated as yellow oil (78% yield, 29.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.72 (m, 2H), 7.52 – 7.47 (m, 2H), 7.45 – 7.35 (m, 6H), 7.29 – 7.18 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.54 (s), 140.95 (s), 138.62 (s), 133.20 (s), 132.03 (s), 130.39 (s), 129.89 (s),129.13 (s), 128.96 (s), 128.67 (s), 128.60 (s), 126.95 (s), 126.14 (s), 121.01 (s), 119.08 (s). This spectrum is in agreement with previously reported spectral data.[12]

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