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Graphical Abstract

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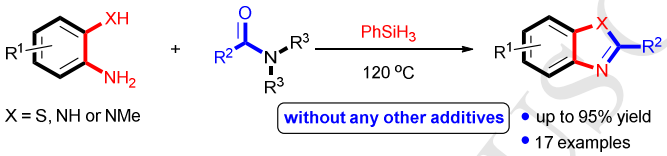

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ABSTRACT

A simple approach to preparation of benzimidazoles from *o*-phenylenediamines and DMF derivatives, only employing $PhSiH_3$ as promoter without any other additives, was reported. This route provided moderate to high yields with a broad substrate scope. A plausible mechanism for the reaction is proposed based on the spectroscopic characterization (e.g., HRMS and ^{1}H NMR) of the reaction mixture.

1. Introduction

Benzimidazoles are ubiquitous motifs, which have found practical applications in a number of fields such as synthesis of natural products and biologically active molecules.[1] Also, benzimidazoles are important intermediates in the synthesis of pharmaceutical compounds such as antimicrobial compounds, anthelmintic and antipsychotic drugs, antiulcer and anticancer agents (Fig. 1).[2-9] Many synthetic procedures for the synthesis of benzimidazoles from *o*-phenylenediamines were reported. For example, a condensation reaction between *o*-phenylenediamine and carboxylic acid or their derivatives to form benzimidazoles is the most popular method.[10] Many kinds of aldehydes, alcohols or orthoesters are utilized to generate benzimidazoles in the presence of various catalysts in oxidative conditions.[11] Using CO_2 as C_1 block for the synthesis of organic compouds is still a long-standing goal, and many cyclization of *o*-phenylenediamines by CO_2 to construct benzimidazoles was reported.[12] *N*,*N*-dimethylformamide (DMF) can be easily synthesized from CO_2 with dimethylamine in the presence of H_2 and suitable catalyst.[13] Also, DMF or its derivatives are efficient reagents for the synthesis of benzimidazoles with 1,2-diaminobenzene (Scheme 1, a).[14] The synthesis of benzimidazoles from DMF and *o*-phenylenediamines attracted our attention because using DMF as C_1 source could be considered as the indirect utilizing of CO_2.

As one of the most effective polar solvents for various chemical reactions, *N*,*N*-dimethylformamide has been employed as a widely utilized reactant in organic transformations such as formylation, amination, and cyanation reactions.[15] A few approaches have been reported to form benzimidazole from DMF

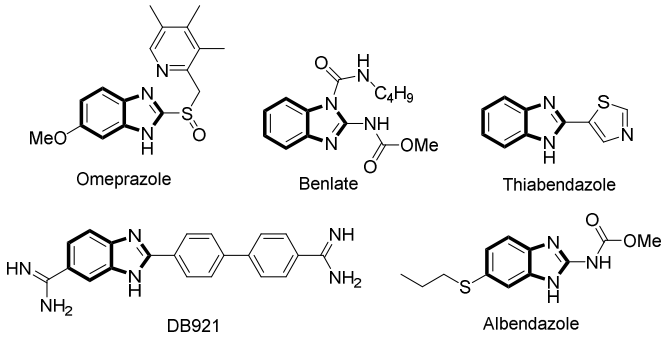

Fig. 1. Biologically active molecules containing benzimidazole moiety.

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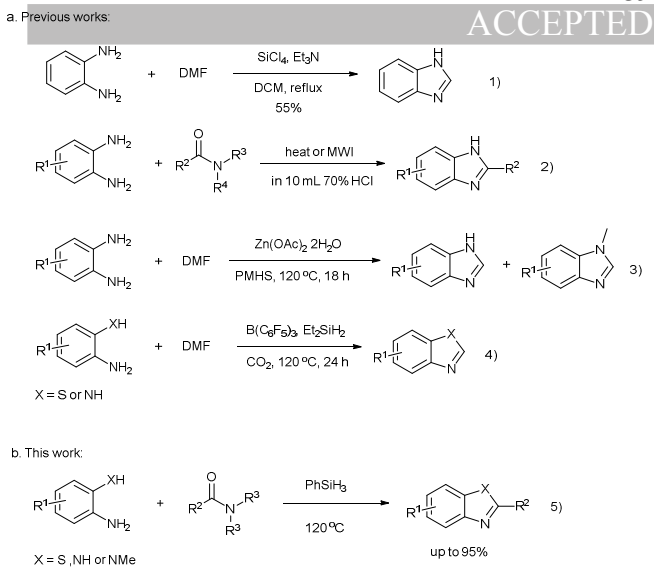
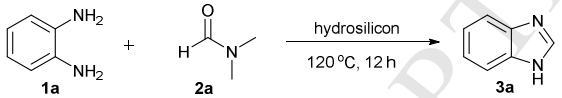


Scheme 1 Synthesis of benzimidazoles from *o*-phenylenediamines and DMF.

and 1,2-dimethylamine. Treatment of *o*-phenylenediamine with DMF and 2.5 equivalents of $SiCl_4$ in refluxing CH_2Cl_2 to provide benzimidazole was reported by Bourguignon, but there was only one example in moderate yield (Scheme 1, eq. 1).[14c] Kamble and co-workers reported an flexible method to form benzimidazole from *o*-phenylenediamine and DMF, but a large amount of concentrated hydrochloric acid (70%) was used in this process (Scheme 1, eq. 2).[14b] Recently, Bhanage and Liu also reported the preparation of benzimidazole derivatives from DMF and *o*-phenylenediamines in the presence of hydrosilicon, but in their report, metal catalyst $Zn(OAc)_2$•$2H_2O$ or additive $B(C_6F_5)_3$ and CO_2 were necessary, respectively (Scheme 1, eq. 3 and 4).[14a,16] In a continuation of our ongoing research on the synthesis of valuable benzimidazole compounds,[12e] we fortunately found an efficient protocol for the synthesis of benzimidazoles from *o*-phenylenediamines and DMF derivatives employing $PhSiH_3$ as the only promoter without any other catalysts or additives under metal-free conditions (Scheme 1, b).

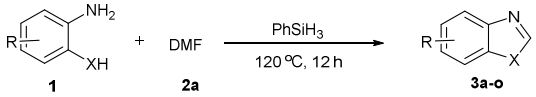
Table 1 Optimization of reaction conditions.[a]



entry	hydrosilicon	equiv	T (^oC)	time (h)	yield(%)[b]
1	$PhSiH_3$	4	120	12	95
2	Ph_2SiH_2	4	120	12	12
3	Ph_3SiH	4	120	12	trace
4	$(CH_3)_2PhSiH$	4	120	12	trace
5	$(CH_3CH_2O)_3SiH$	4	120	12	NR[c]
6	PMHS[d]	4	120	12	trace
7	$PhSiH_3$	3	120	12	85
8	$PhSiH_3$	0	120	12	NR[c]
9	$PhSiH_3$	4	100	12	21
10	$PhSiH_3$	4	120	10	81

[a] The reactions were carried out in a heavy wall pressure tube with **1a** (0.4 mmol) and hydrosilicon in 1 mL DMF.
[b] Isolated yields. [c] NR = No reaction. [d] PMHS = Polymethylhydrosiloxane.

Table 2 Scope of cyclization of *o*-phenylenediamines with DMF.[a]

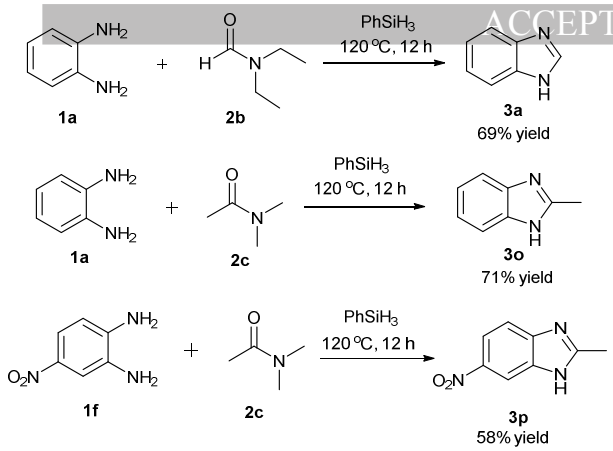


entry	substrate	product	yield (%)[b]
1	**1a**	**3a**	95
2	**1b**	**3b**	82
3	**1c**	**3c**	80
4	**1d**	**3d**	58
5	**1e**	**3e**	72
6	**1f**	**3f**	89
7	**1g**	**3g**	88
8	**1h**	**3h**	73
9	**1i**	**3i**	61
10	**1j**	**3j**	50
11	**1k**	**3k**	41
12	**1l**	**3l**	31
13	**1m**	**3m**	46
14	**1n**	**3n**	83

[a] The reactions were carried out in a heavy wall pressure tube with **1a** (0.4 mmol) and $PhSiH_3$ (1.6 mmol) in 1 mL DMF at 120 ^oC for 12 h.
[b] Isolated yields.

2. Results and discussion

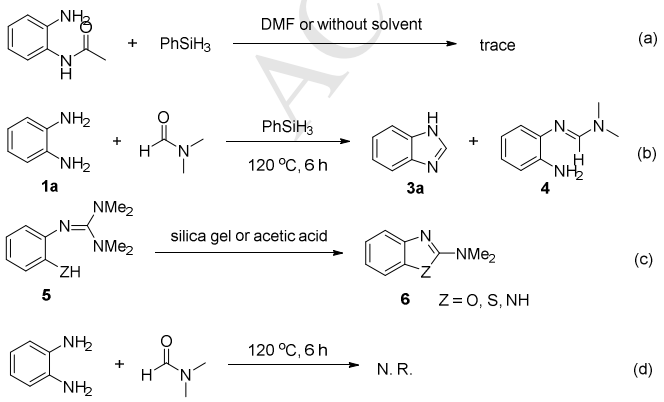
Initially, we began our studies by investigating the condensation reaction of commercially available *o*-phenylenediamines **1a** with DMF **2a**. To our delight, when $PhSiH_3$ was employed, the reaction afforded the desired benzimidazole **3a** in 95% yield at 120 °C after 12 h (Table 1, entry 1). With this preliminary and intriguing result in hand, we turned to extensively screen a series of hydrosilicons. Various hydrosilicons were tested under the same conditions such as Ph_2SiH_2, Ph_3SiH, $(CH_3)_2PhSiH$, $(CH_3CH_2O)_3SiH$ and PMHS (Table 1, entries 2−6). The results showed that when the reaction



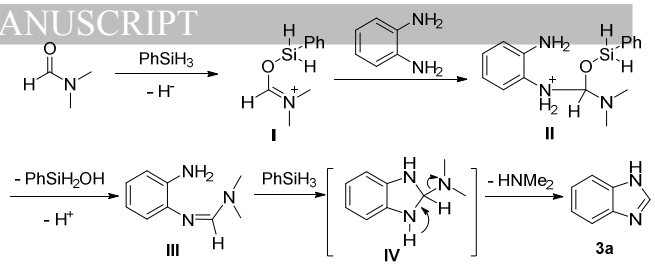
Scheme 2 The reaction with DMF derivatives.

was promoted by Ph_2SiH_2, it afforded the desired product in a lower yield along with most of the starting materials recovered after 12 h (Table 1, entry 2), while Ph_3SiH, $(CH_3)_2PhSiH$, $(CH_3CH_2O)_3SiH$ and PMHS were ineffective in promoting the reaction (Table 1, entries 3−6). Further optimization showed that reducing the amount of $PhSiH_3$ decreased the yield of compound **3a** (Table 1, entry 7). The reaction did not occur at all in the absence of $PhSiH_3$ (Table 1, entry 8). Lowering reaction temperature or shortening reaction time led to the decrease in the yield of benzimidazole **3a** (Table 1, entries 9 and 10).

Under the optimized conditions, we proceeded to explore the scope of *o*-phenylenediamines, and the results are shown in Table 2. The *o*-phenylenediamines bearing electron-donating and -withdrawing groups were tolerated well under the reaction conditions, affording the desired benzimidazoles in moderate to good yields (Table 2, entries 1−11). It was noteworthy that the electron properties and steric hindrance of the substituent groups on the phenyl ring played an important role in the reaction. *o*-Phenylenediamines containing electron-withdrawing groups provided the desired benzimidazoles in better yields than those of electron-donating groups (Table 2, entries 2, 3, 6 and 7 vs entries 8 and 11). The 4,5-disubstituted-1,2-diamine showed less reactivity in comparison with that of 4-monosubstituted-1,2-dimine and gave corresponding products in relative low yields (Table 2, entries 4 and 10 vs entries 2 and 8). *N*-substituted-*o*-phenylenediamine could also generate the corresponding product **3l**, although inferior yield was obtained probably owing to its steric hindrance (Table 2, entry 12). In addition, the heterocyclic compound **1m** could tolerate and afford the corresponding product **3m** in 46% yield (Table 2, entry 13). 2-Aminobenzenethiol was also compatible, efficiently providing **3n** in 83% yield (Table 2, entry 14). Then, we turned to investigate



Scheme 3 Control experiment.



Scheme 4 A plausible mechanism for the formation of benzimidazole from o-phenylenediamine and DMF.

the reaction of different *N*-substituted formamides including *N*,*N*-diethylformamide and *N*,*N*-dimethylacetamide. To our delight, both of them could serve as good cyclization partners to readily access the benzimidazole or 2-methyl-benzimidazole in high yields (Scheme 2).

After an exploration of the substrate scope, we focused on elucidating the mechanism of the synthesis of benzimidazoles from *o*-phenylenediamines and DMF derivatives, and some control experiments were conducted (Scheme 3). At first, we thought that the reaction should generate acylated intermediate, and the acylated intermediate dehydrated to form benzimidazoles. So we performed the reaction of N-(2-aminophenyl)acetamide with $PhSiH_3$ to test our thought, but whether in DMF or without solvent, the reaction did not occur (Scheme 3, a). Then we tried to shorten the reaction time to 6 h on the standard condition in order to find out what has been formed during the reaction, and we tested the mixture on ^1H NMR and HRMS as soon as the reaction was finished. To our delight, substrate (*o*-phenylenediamine), product benzimidazole and the intermediate **4** were found in the mixture (Scheme 3, b, Fig S1 and S2, Supporting Information). To our knowledge, the similar compound **5** could cyclize in the presence of silica gel or acetic acid to form the benzimidazole derivatives **6** (Scheme 3, c),[17] so we consider that compound **4** might go through a similar route to transfer into benzimidazole in the presence of $PhSiH_3$. At last, *o*-phenylenediamine and DMF were heated at 120 °C for 6 h without $PhSiH_3$ to test whether the intermediate **4** could be formed without $PhSiH_3$, and no reaction took place. This observation indicated that $PhSiH_3$ is necessary for construction of intermediate **4**.

On the basis of this finding, a plausible mechanism for the formation of benzimidazole from *o*-phenylenediamine and DMF is depicted in Scheme 4. Firstly, DMF was activated by $PhSiH_3$ to afford **I** and a Si-O bond was formed.[18] Next, the intermediate **I** cooperated with 1,2-diaminobenzene to form the compound **II**, one silanol left and the compound **III** was formed,[18, 19] which could be detected by HRMS and ^1H NMR. Afterwards, the intermediate **IV** was formed by intermolecular cyclization of the compound **III** in the present of $PhSiH_3$, and one molecule of $HNMe_2$ was removed and the product benzimidazole **3a** was afforded.[17]

3. Conclusions

In summary, a simple method for the synthesis of benzimidazoles from *o*-phenylenediamines and DMF using $PhSiH_3$ as the only promotor is reported. Azabenzimidazole, benzothiazoles and 2-substituted benzimidazoles are also performed in good yields. This work presents a simple system to synthesize benzimidazoles under mild condition. This method has wide substrate scope, providing moderate to high yields. Besides, NMR characterization and HRMS also gave some hints for proposed mechanism. Future studies are underway to fully

acquire the role of $PhSiH_3$ and to build new systems for synthesizing heterocyclic compounds.

4. Experimental

4.1. General information

All reagents and reactants were obtained from commercial sources and used without further purification. Anhydrous solvents were stored in the desiccator. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash column chromatography was carried out by using 200-300 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AvanceIII NMR spectrometer (400 MHz) in $CDCl_3$ or DMSO-d_6 internally referenced to tetramethylsilane (TMS) or $CDCl_3$ (DMSO-d_6) signals. Chemical shifts are reported in ppm and coupling constants (*J*) in Hz. All substrates are known compounds and prepared according to the literature.

*4.2. General procedure for the synthesis of benzimidazoles (**3a-3p**) from dimethylamine (**1a-1n**) and DMF **2a** (**2b-2c**).*

A mixture of **1a** (**1b-1n**, 0.4 mmol) and $PhSiH_3$ (98 μL, 1.6 mmol) in *N*,*N*-dimethylformamide **2a** (**2b-2c**, 1 mL) was stirred at 120 ^{o}C for 12 h. When the reaction was completed, the resulting mixture was extracted with ethyl acetate three times. The combined organic layer was washed by NaCl aqueous solution and dried over anhydrous Na_2SO_4, after which the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with petroleum ether and ethyl acetate (6:1-1:2) to give the corresponding product **3a** (**3b**-**3p**).

*4.3. 1H-benzo[d]imidazole (**3a**)*[14a]

Yellow solid (44.8 mg, 95%); Spectral data of **3a**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 8.14 (s, 1H), 7.68 (t, *J* = 2.8 Hz, 2H), 7.31 (t, *J* = 3.2 Hz, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.6, 137.6, 123.2, 115.7. HRMS (ESI) calcd for $C_7H_7N_2$ $[M+H]^+$ 119.0604, found: 119.0603.

*4.4. 6-Fluoro-1H-benzo[d]imidazole (**3b**)*[14a]

Yellow solid (44.6 mg, 82%); Spectral data of **3b**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 8.16 (s, 1H), 7.58 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.32 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.05 (td, *J* = 8.8, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 159.9 (d, *J* = 237.6 Hz), 141.9, 137.7 (d, *J* = 13.6 Hz), 134.5, 116.4 (d, *J* = 10.3 Hz), 111.6 (d, *J* = 25.5 Hz), 101.6 (d, *J* = 25.8 Hz). HRMS (ESI) calcd for $C_7H_6FN_2$ $[M+H]^+$ 137.0510, found: 137.0509.

*4.5. 6-Bromo-1H-benzo[d]imidazole (**3c**)*[14a]

Yellow solid (63.1 mg, 80%); Spectral data of **3c**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 8.15 (s, 1H), 7.82 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 141.7, 139.0, 136.7, 126.4, 118.6, 116.8, 116.2. HRMS (ESI) calcd for $C_7H_6BrN_2$ $[M+H]^+$ 196.9709, found: 196.9714.

*4.6. 5,6-Difluoro-1H-benzo[d]imidazole (**3d**)*[14a]

Yellow solid (34.5 mg, 56%); Spectral data of **3d**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.67 (s, 1H), 8.29 (s, 1H), 7.65 (t, *J* = 8.4 Hz, 2H), ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.9 (d, *J* = 16.7 Hz), 145.5 (d, *J* = 16.6 Hz), 144.1, 103.0. HRMS (ESI) calcd for $C_7H_5F_2N_2$ $[M+H]^+$ 155.0415, found: 155.0421.

*4.7. 5,6-Dichloro-1H-benzo[d]imidazole (**3e**)*[14a]

Yellow solid (53.8 mg, 72%); Spectral data of **3e**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (s, 1H), 8.34 (s, 1H), 7.87 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.8, 124.3. HRMS (ESI) calcd for $C_7H_5Cl_2N_2$ $[M+H]^+$ 186.9824, found: 186.9829.

*4.8. 6-Nitro-1H-benzo[d]imidazole (**3f**)*[14a]

Yellow solid (58.0 mg, 89%); Spectral data of **3f**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.58 (s, 1H), 8.53 (s, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.8, 142.9, 142.6, 117.6, 115.6, 111.6. HRMS (ESI) calcd for $C_7H_6N_3O_2$ $[M+H]^+$ 164.0455, found: 164.0457.

*4.9. 1H-benzo[d]imidazole-6-carbonitrile (**3g**)*[20]

White solid (50.4 mg, 88%); Spectral data of **3g**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.3, 125.4, 120.1, 103.8. HRMS (ESI) calcd for $C_8H_6N_3$ $[M+H]^+$ 144.0556, found: 144.0562.

*4.10. 6-Methyl-1H-benzo[d]imidazole (**3h**)*[14a]

Yellow solid (38.5 mg, 73%); Spectral data of **3h**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.39 (s, 1H), 8.09 (s, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.11 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.6, 137.6, 136.4, 132.9, 124.5, 115.6, 114.9, 21.8. HRMS (ESI) calcd for $C_8H_9N_2$ $[M+H]^+$ 133.0760, found: 133.0760.

*4.11. 7-Methyl-1H-benzo[d]imidazole (**3i**)*[14a]

Yellow solid (32.2 mg, 61%); Spectral data of **3i**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.69 (s, 1H), 8.13 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.4, 137.8, 137.0, 126.0, 123.4, 123.1, 112.7, 17.3. HRMS (ESI) calcd for $C_8H_9N_2$ $[M+H]^+$ 133.0760, found: 133.0758.

*4.12. 5,6-Dimethyl-1H-benzo[d]imidazole (**3j**)*[14a]

Yellow solid (29.2 mg, 50%); Spectral data of **3j**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 8.02 (s, 1H), 7.44 (s, 2H), 2.36 (s, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*). δ 140.0, 136.2, 132.1, 115.6, 20.5. HRMS (ESI) calcd for $C_9H_{11}N_2$ $[M+H]^+$ 147.0917, found: 147.0919.

*4.13. 6-Methoxy-1H-benzo[d]imidazole (**3k**)*[14a]

Yellow solid (24.3 mg, 41%); Spectral data of **3k**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.38 (s, 1H), 8.05 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 6.93 (dd, *J* =8.8, 1.6 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 157.0, 140.2, 137.3, 132.3, 116.5, 113.3, 97.6, 56.0. HRMS (ESI) calcd for $C_8H_9N_2O$ $[M+H]^+$ 149.0709, found: 149.0711.

*4.14. 1-Methyl-1H-benzo[d]imidazole (**3l**)*[14a]

Yellow solid (16.4 mg, 31%); Spectral data of **3l**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.39 (s, 1H), 8.09 (s, 1H), 7.56 (s, 1H), 7.45 (s, 1H), 7.11 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.6, 137.6, 136.4, 132.9, 124.5, 115.6, 114.9, 21.8. HRMS (ESI) calcd for $C_8H_9N_2$ $[M+H]^+$ 133.0760, found: 133.0761.

*4.15. 3H-imidazo[4,5-c]pyridine (**3m**)*[14a]

Yellow solid (21.9 mg, 46%); Spectral data of **3m**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.39 (s, 1H), 8.30 (s, 1H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.3, 141.2,

139.8, 109.4. HRMS (ESI) calcd for $C_6H_6N_3$ $[M+H]^+$ 120.0556, found: 120.0555.

*4.16. Benzo[d]thiazole (**3n**)[14a]*

Light yellow liquid (44.8 mg, 83%); Spectral data of **3n**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.99 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.52 (t, J = 6.8 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 154.0, 153.3, 133.8, 126.3, 125.6, 123.7, 122.0. HRMS (ESI) calcd for C_7H_6NS $[M+H]^+$ 136.0215, found: 136.0221.

*4.17. 2-Methyl-1H-benzo[d]imidazole (**3o**)[21]*

Yellow solid (37.5 mg, 71%); Spectral data of **3o**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.56 (s, 2H), 7.23 (s, 2H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 151.4, 138.4, 122.4, 114.6, 15.0. HRMS (ESI) calcd for $C_8H_9N_2$ $[M+H]^+$ 133.0760, found: 133.0766.

*4.18. 2-Methyl-6-nitro-1H-benzo[d]imidazole (**3p**)[22]*

Yellow solid (41.1 mg, 58%); Spectral data of **3p**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.8, 2.4, Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 156.7, 142.1, 117.2, 113.8, 111.3, 14.9. HRMS (ESI) calcd for $C_8H_8N_3O_2$ $[M+H]^+$ 178.0611, found: 178.0612.

*4.19. Spectral data of the intermediate **4***

Spectral data of **4**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 7.44 (d, J = 6.8 Hz, 1H), 7.36 (t, J = 7.2 Hz, 2H), 6.86 (t, J = 7.2 Hz, 2H), 4.79 (NH_2, s, 2H), 3.01 (NCH_3, s, 6H). ^{13}C NMR (100 MHz, Chloroform-d) δ 152.9, 140.5, 134.7, 128.0, 123.5, 118.9, 118.1, 77.4. HRMS (ESI) calcd for $C_9H_{14}N_3$ $[M+H]^+$ 164.1182, found: 164.1177.

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