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Indium-mediated one-pot benzimidazole synthesis from 2-nitroanilines or 1,2-dinitroarenes with *ortho*esters

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ABSTRACT

One-pot reduction-triggered heterocyclizations from 2-nitroanilines or 1,2-dinitroarenes to benzimidazoles were investigated in this study. In the presence of indium/AcOH in ethyl acetate at reflux, reaction of 2-nitroanilines or 1,2-dinitroarenes with R–C(OMe)$_3$ (R=Me, Ph) produced excellent yields of the corresponding benzimidazoles within 30 min to 6 h depending on the substituents of the starting materials. Indium-mediated heterocyclization of 2-nitroanilines to benzimidazole was faster and had better yields than 1,2-dinitroarenes to benzimidazole under similar reaction conditions.

1. Introduction

Because of their pharmaceutical and biological significance, nitrogen-containing heterocyclic compounds have attracted considerable attention as an important class of organic molecules. In continuation of our studies searching for efficient synthetic methodologies for biologically important heterocyclic compounds, benzimidazoles were chosen as target molecules; benzimidazoles have several medicinal uses, such as antivirals, anticancers, antihypertensives, antihistamines, antiparasitics, and antiulcers.[1–3]

Diverse synthetic efforts for benzimidazoles have been reported,[4] with the most common method being the heterocyclization of *o*-diaminoarenes with carboxylic acids or their derivatives under acidic conditions.[5] More recently, cyclizations of *o*-diaminoarene with aldehydes under oxidative conditions,[6] with 2-nitroanilines under reductive conditions,[7] with transition metal-catalyzed amination followed by condensation,[8] with *o*-diaminoarene and *gem*-dibromoethylarenes,[9] and with several other conditions[10] have been reported for the synthesis of benzimidazoles.

Recently, we developed a simple and efficient indium-mediated one-pot reduction-triggered heterocyclization from 2-nitrophenol to benzoxazole and from 1-aryl-2-nitroethanone to oxazole.[11] We believe the same concept can be applied to the synthesis of benzimidazoles as the reaction path should be similar to the benzoxazole formation reaction. Herein we report the development of one-pot synthesis of indium-reduction-triggered intermolecular heterocyclization toward benzimidazole starting from 2-nitroaniline with *ortho*ester and include, in detail, mechanistic considerations. 1,2-Dinitroarenes were also examined as an alternative starting substrate for benzimidazole synthesis under similar reaction conditions.

2. Results and discussion

Initially, we examined the heterocyclization of 2-nitroaniline with trimethyl *ortho*benzoate using reaction conditions previously developed by our group for the synthesis of benzoxazoles; 2-nitrophenol (1 equiv)/*ortho*ester (4 equiv)/indium (4 equiv)/AcOH (10 equiv) in benzene at reflux.[11] Unfortunately, it produced a relatively lower yield compared to previous benzoxazole synthesis reactions (Table 1, entry 1). Therefore, a variety of reaction conditions were re-examined in order to determine the optimum reaction conditions for the reduction-initiated heterocyclization of 2-nitroanilines with trimethyl *ortho*benzoate using indium and appropriate acid additives. Trial experiments with acid additives other than AcOH, such as $InCl_3$, I_2, and HI, produced yields similar to the previous benzoxazole synthesis, and were therefore not successful in enhancing the yield. Because acid additive variation was not effective, we focused on varying the reaction medium. Several solvents were examined in the presence of indium/acetic acid (Table 1). The use of polar aprotic ethyl acetate (EA) solvent helped to improve the yield of the desired benzimidazole, while the other solvents including acetonitrile, THF, and methanol did not significantly affect the yield (Table 1). In addition, all of the reactions using 1 equiv of trimethyl *ortho*benzoate produced 3–33% of 1,2-diaminobenzene as a major by-product (entries 1–6), which indicated the need for more trimethyl *ortho*benzoate. 1,2-Diaminobenzene was not observed if more than 2 equiv of trimethyl *ortho*benzoate was applied (entries 7–12). After examining

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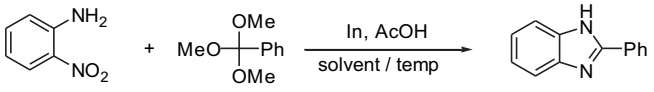
Table 1
Indium-mediated reductive heterocyclization of 2-nitroaniline (1 mmol) to trimethyl *ortho*benzoate under different reaction conditions



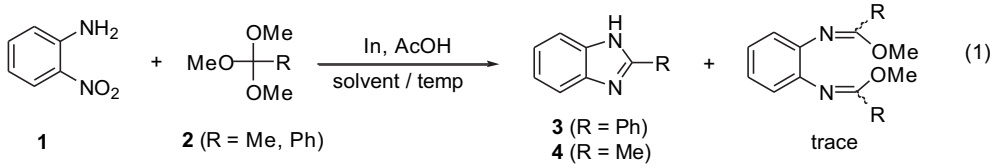
1 **2a** **3**

Entry	Molar equiv				Solvent (mL)/temp (°C)	Time (h)	Yield[a] (%)
	1	**2a**	In	AcOH			**3**
1	1	1	4	10	benzene (5)/reflux	1	62[b]
2	1	1	4	10	CH_3CN (5)/reflux	1	53[b]
3	1	1	4	10	THF (5)/reflux	1	68[c]
4	1	1	4	10	MeOH (5)/reflux	5	53[b]
5	1	1	4	10	EA (5)/reflux	1	72[b]
6	1	1	5	10	EA (5)/reflux	1	57[b]
7	1	2	4	10	EA (5)/reflux	1.5	79
8	1	3	4	10	EA (5)/reflux	1.5	79
9	1	2	3	10	EA (5)/reflux	2	81
10	1	2	5	5	EA (5)/reflux	1	80
11	1	2	5	10	EA (5)/50	4	62
12	1	2	5	10	EA (5)/reflux	1	95 (92)[d]

[a] GC yield with an internal standard (octane).
[b] 1,2-Diaminobenzene (3–19%) was observed.
[c] 1,2-Diaminobenzene (33%) was observed.
[d] Isolated yield.

the different reaction conditions, we selected 2-nitroaniline (1 equiv)/trimethyl *ortho*benzoate (2 equiv)/indium (5 equiv)/AcOH (10 equiv) in ethyl acetate at reflux (entry 12) as the most optimized condition, which produced a 92% isolated yield of 2-phenyl-1*H*-benzimidazole (**3**).

The same reaction conditions used above were applied to the reaction of 2-nitroaniline with trimethyl *ortho*acetate, producing 83% of 2-methyl-1*H*-benzimidazole (**4**) without any major by-products. However, a trace amount of diimidate was observed upon GC–MS analysis (Eq. 1); diimidate is somehow an expected intermediate of benzimidazole formation based on our previous mechanistic study of benzoxazole formation.[11]



1 **2** (R = Me, Ph) **3** (R = Ph) **4** (R = Me) trace

To elucidate the reaction path more clearly, we attempted to carry out the heterocyclization reaction toward 2,5-dimethyl-1*H*-benzimidazole using 5-methyl-2-nitroaniline and trimethyl *ortho*acetate at 50 °C, a lower reaction temperature, to monitor the intermediates using GC and GC–MS analysis. By applying the lower reaction temperature, we were able to slow down the reaction, which made it possible for us to effectively follow the formation and changes in the distribution of intermediates. Data obtained from the control experiments are shown in Fig. 1.

Within 5 min of the reaction start, approximately half of the 5-methyl-2-nitroaniline was turned into monoimidate, and the amount of monoimidate increased for ~15 min and decreased thereafter (line A, Fig. 1). Diimidate started to form 5–10 min later as the reduction began (line B, Fig. 1). Interestingly, a potentially required monoimidate–amine intermediate (Scheme 1, **B**) was barely observed at any sampling points. Presumably, a coupling reaction between the amino group and trimethyl *ortho*acetate occurred simultaneously as soon as the amino group was formed by the

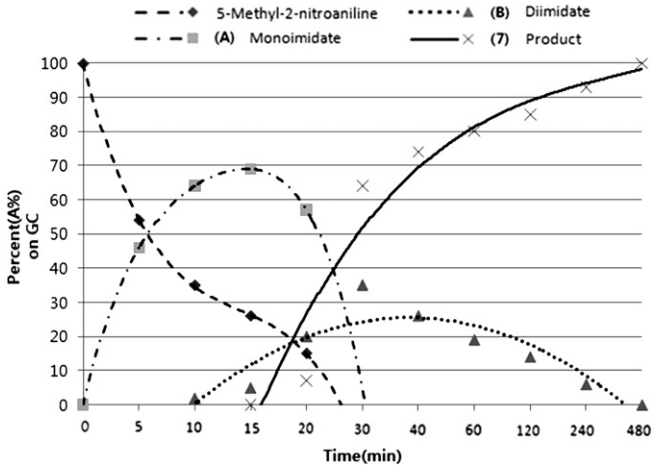
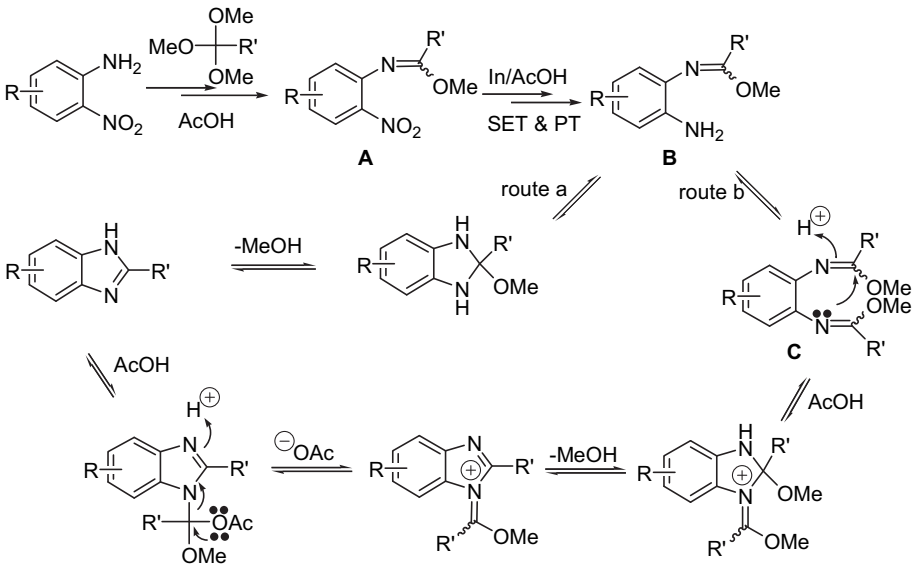


Fig. 1. Heterocyclization reaction toward 2,5-dimethyl-1*H*-benzimidazole using 5-methyl-2-nitroaniline and trimethyl *ortho*acetate at 50 °C monitored by GC and GC–MS.

reduction of the nitro group. After ~30 min, both 5-methyl-2-nitroaniline and monoimidate disappeared and only diimidate and 2,5-dimethyl-1*H*-benzimidazole were observed in the solution at a ~1:2 ratio. The diimidate intermediate was slowly converted to 2,5-dimethyl-1*H*-benzimidazole and the reaction was completed after 8 h. Our results clearly show that monoimidate and diimidate are intermediates in the benzimidazole formation reaction. Direct intramolecular cyclization from the monoimidate–amine intermediate (**B**) toward the benzimidazole product (Scheme 1, route a) may not be completely excluded because more than 50% of benzimidazole was formed, even when a lesser amount (1 equiv) of *ortho*ester was applied (Table 1, entry 6). However, as shown in Fig. 1, cyclization via the diimidate intermediate (route b) seemed to be the major reaction pathway when 2 equiv of *ortho*ester was applied.

A plausible mechanism based on our control experiments and previous work[11] is proposed in Scheme 1. Initially, 2-nitroaniline couples with the *ortho*ester immediately to form the monoimidate (**A**). The consequent single electron transfers (SET) and proton transfers (PT) result in the transformation of **A** into the monoimidate–amine intermediate (**B**). As soon as the amino group is formed, a coupling reaction occurs between the amino group and *ortho*ester to form the diimidate intermediate (**C**), which might be transformed gradually into the benzimidazole as shown in Scheme 1. Direct intramolecular cyclization of the monoimidate–amine intermediate (**B**) toward benzimidazole product seems to be another possible competing pathway for benzimidazole formation if insufficient *ortho*ester is supplied to the reaction batch.

Heterocyclizations of differently substituted 2-nitroanilines with *ortho*esters were examined using the optimized reaction conditions. Trimethyl *ortho*benzoate (**2a**)- and trimethyl *ortho*acetate (**2b**)-substituted 2-nitroanilines with *ortho*esters were tested to verify the synthetic utilization. These *ortho*esters produce 2-phenyl or 2-methyl substituted benzimidazoles, respectively. In most cases, the heterocyclization for benzimidazole formation was successful. Most reactions of the substituted 2-nitroanilines with *ortho*esters were completed within 30 min to 6 h and produced

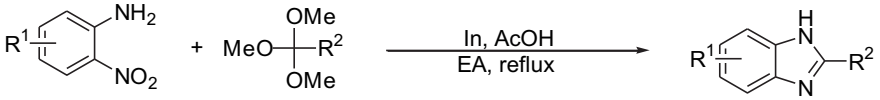


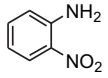
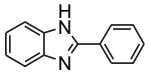
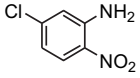
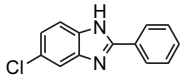
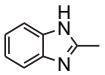
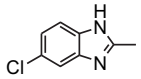
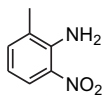
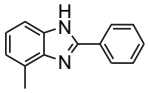
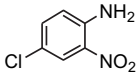
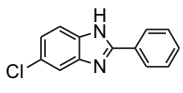
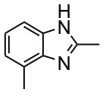
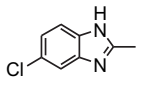
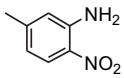
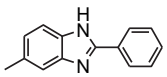
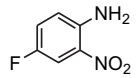
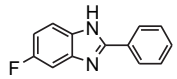
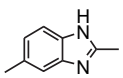
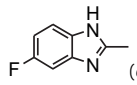
Scheme 1.

reasonable yields (62–96%) of the corresponding benzimidazoles (Table 2). Reactions of 2-nitroanilines with trimethyl *ortho*benzoate (**2a**) proceeded faster than the reactions of 2-nitroanilines with trimethyl *ortho*acetate (**2b**), probably because of enhanced thermodynamic stability due to the additional conjugative effect of the 2-phenyl substituent on the benzimidazole ring. In general, the reaction completion time of 2-nitroanilines with **2a** was approximately one half that of 2-nitroanilines with **2b** using the same substrate. In addition, reactions of electron-withdrawing group-substituted 2-nitroanilines such as halo, trifluoromethyl, or cyano groups proceeded slowly compared to those of methyl- or methoxy-substituted 2-nitroaniline substrates.

Our newly developed one-pot reaction of indium-reduction-triggered intermolecular heterocyclizations of 2-nitroanilines toward benzimidazoles with rapid diimidate intermediate formation demonstrated that not only 2-nitroanilines but also 1,2-dinitroarenes could be used if the proper reduction conditions are applied. Thus we attempted to carry out reactions of 1,2-dinitrobenzene with *ortho*esters **2a** or **2b** using similar reaction conditions. Heterocyclization of 1,2-nitrobenzene (1 equiv) with

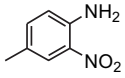
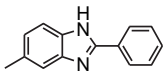
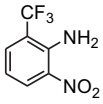
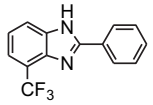
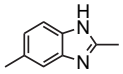
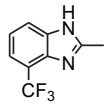
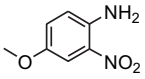
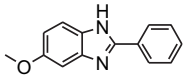
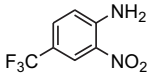
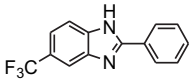
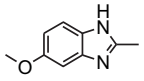
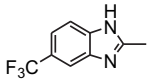
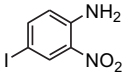
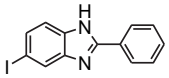
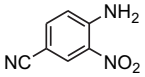
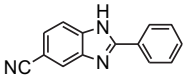
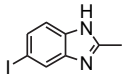
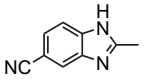
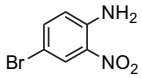
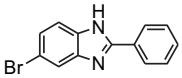
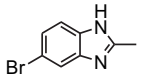
Table 2
Indium-acetic acid-mediated reductive heterocyclization of 2-nitroanilines (1 mmol) with trimethyl *ortho*ester (2 equiv) in the presence of indium (5 equiv) and acetic acid (10 equiv) in ethyl acetate (5 mL) at reflux



Entry	Substrate	R	Time (h)	Product		Yield[a] (%)	Entry	Substrate	R	Time (h)	Product		Yield[a] (%)
1		Ph	1		**(3)**	92	15		Ph	1.5		**(15)**	87
2		Me	1.5		**(4)**	83	16		Me	4		**(16)**	92
3		Ph	1		**(5)**	96	17		Ph	2		**(15)**	85
4		Me	2.5		**(6)**	70	18		Me	4		**(16)**	85
5		Ph	0.5		**(7)**	90	19		Ph	1.5		**(17)**	85
6		Me	1.5		**(8)**	85	20		Me	4		**(18)**	80

(*continued on next page*)

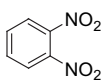
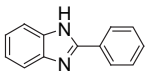
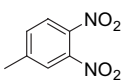
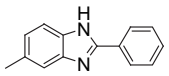
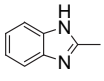
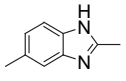
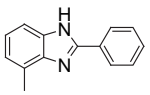
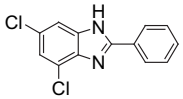
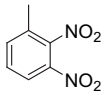
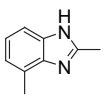
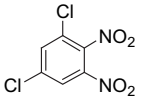
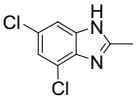
Table 2 (*continued*)

Entry	Substrate	R	Time (h)	Product		Yield[a] (%)	Entry	Substrate	R	Time (h)	Product		Yield[a] (%)
7		Ph	0.5		**(7)**	92	21		Ph	2.5		**(19)**	82
8		Me	1.5		**(8)**	81	22		Me	4		**(20)**	62
9		Ph	0.5		**(9)**	95	23		Ph	3		**(21)**	62
10		Me	2		**(10)**	74	24		Me	5		**(22)**	83
11		Ph	3		**(11)**	71[b]	25		Ph	3		**(23)**	70
12		Me	5		**(12)**	74[b]	26		Me	6		**(24)**	74
13		Ph	1.5		**(13)**	80[b]							
14		Me	4		**(14)**	90							

[a] Isolated yield.
[b] A dehalogenated product was observed.

trimethyl *ortho*benzoate (2 equiv)/indium (5 equiv)/AcOH (10 equiv) in ethyl acetate at reflux for 2 h produced the desired benzimidazole, **3**, with a 62% yield, which was lower than expected. As the reaction conditions for the 2-nitroanilines seemed inappropriate for the 1,2-dinitroarene reaction, several additional control experiments were performed in ethyl acetate solvent. Based on these control experiments, we determined that the reaction conditions with 1,2-dinitrobenzene (1 equiv)/trimethyl *ortho*benzoate (2 equiv)/indium (8 equiv)/AcOH (10 equiv) in ethyl acetate at reflux were the optimum conditions, producing 80% of the benzimidazole, **3**. Using these newly optimized reaction conditions, we examined the possibility of using 1,2-dinitroarenes for indium-reduction-triggered intermolecular heterocyclizations, and the results are summarized in Table 3. Compared to the 2-nitroaniline

Table 3
Indium-acetic acid-mediated reductive heterocyclization of 1,2-dinitroarenes (1 mmol) with trimethyl *ortho*ester (2 equiv) in the presence of indium (8 equiv) and acetic acid (10 equiv) in ethyl acetate (10 mL) at reflux

Entry	Substrate	R	Time (h)	Product		Yield[a] (%)	Entry	Substrate	R	Time (h)	Product		Yield[a] (%)
1		Ph	2.5		**(3)**	80	5		Ph	4		**(7)**	58
2		Me	5.5		**(4)**	52	6		Me	4.5		**(8)**	53
3		Ph	5		**(5)**	61	7		Ph	5.5		**(25)**	52
4		Me	6		**(6)**	50	8		Me	24		**(26)**	38

[a] Isolated yield.

reactions, yields were relatively poor in most cases, even though neither the starting substrate nor other isolable organic products were observed.

3. Conclusions

In conclusion, we have described a simple and efficient method for a one-pot reduction-triggered heterocyclization toward benzimidazole. In the presence of indium/AcOH in ethyl acetate at reflux, 2-nitroanilines and *ortho*ester, R–C(OMe)$_3$ (R=Me, Ph), produced the corresponding benzimidazole within 0.5–6 h with excellent yield. Similarly, the reaction of 1,2-dinitroarenes with *ortho*ester, R–C(OMe)$_3$ (R=Me, Ph), in the presence of indium/AcOH in ethyl acetate afforded the corresponding benzimidazole with reasonable yield. However, these yields were not as good as those seen with 2-nitroanilines.

4. Experimental section

4.1. General considerations

Most of the chemical reagents were purchased from Aldrich and, in most cases, were used without further purification. Solvents were purchased and dried using standard methods. ^{1}H NMR spectra were recorded on a 400 MHz Jeol instrument, and ^{13}C NMR spectra were recorded on a 100 MHz Jeol instrument. Chemical shifts were reported in parts per million relative to the residual solvent as an internal standard. HRMS spectra were recorded on a JEOL JMS-DX 303 mass spectrometer, and GC–MS spectra were recorded on an Agilent 6890N GC connected to an Agilent 5975 mass selective detector. Infrared (IR) spectra were recorded using an MB104 FTIR (ABB Bomem Inc.). Melting points were determined on an electrothermal apparatus and were uncorrected. All the major products were isolated by flash column chromatography on silica gel (230–400 mesh ATSM, purchased from Merck) with mixed solvent eluents (ethyl acetate/hexane or methanol/dichloromethane).

4.2. General procedure for the indium-mediated reductive reaction of 2-nitroanilines or 1,2-dinitroarenes with trimethyl *ortho*esters to benzimidazoles

2-Nitroaniline derivative (1 mmol) was added to a mixture of indium powder (574 mg, 5.0 mmol for 2-nitroaniline, 918 mg 8.0 mmol for 1,2-dinitroarene), and acetic acid (0.572 mL, 10 mmol) in ethyl acetate (2 mL), followed by the addition of trimethyl *ortho*ester (2.0 mmol) in ethyl acetate (3 mL for 2-nitroaniline; 8 mL for 1,2-dinitroarene). The reaction mixture was stirred at reflux under a nitrogen atmosphere. After the reaction was completed, the reaction mixture was diluted with ethyl acetate (30 mL), filtered through Celite, poured into 10% $NaHCO_3$ (30 mL), and then extracted with ethyl acetate (30 mL×3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v=10/90) for 2-phenylbenzimidazole derivatives or methanol/dichloromethane (v/v=1/99) for 2-methylbenzimidazole derivatives through a silica gel column to give the corresponding benzimidazoles. The structures of the benzimidazoles were characterized by ^{1}H NMR, ^{13}C NMR, FTIR, and GC–MS, and were mostly known compounds. HRMS data were reported in addition for unknown compounds.

*4.2.1. 2-Phenyl-1H-benzimidazole (**3**)*[6c,7d,h]. Yield 92%. Pale yellow solid, mp 295–297 °C (lit.[7d] mp 289–290 °C). TLC (50% ethyl acetate/hexane) R_f 0.42; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 8.20 (d, 2H, J=7.3 Hz), 7.61–7.46 (m, 5H), 7.23–7.19 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 151.0, 139.2, 130.2, 129.3, 128.4, 126.1, 121.8, 114.7; IR (KBr) 3445, 3049, 1463, 1444 cm^{-1}; GC–MS m/z (rel intensity) 194 (M$^+$, 100), 166 (5), 104 (4), 90 (4), 77(4).

*4.2.2. 2-Methyl-1H-benzimidazole (**4**)*[7f,10d,e]. Yield 83%. Pale yellow solid, mp 180–181 °C (lit.[10d] mp 175–176 °C). TLC (10% methanol/dichloromethane) R_f 0.36; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 7.45 (dd, 2H, J=5.6, 3.4 Hz), 7.11–7.09 (m, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 138.7, 122.1, 114.4, 14.9; IR (KBr) 3246, 3178, 3064, 2991, 1450, 1417 cm^{-1}; GC–MS m/z (rel intensity) 132 (M$^+$, 100), 104 (10), 90 (7), 77 (4), 63 (10).

*4.2.3. 4-Methyl-2-phenyl-1H-benzimidazole (**5**)*[10a]. Mixture of tautomers. Yield 96%. White solid, mp 250–252 °C (lit.[10a] mp 246–247 °C). TLC (50% ethyl acetate/hexane) R_f 0.30; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (br s, 0.55H), 12.61 (br s, 0.45H), 8.24 (s, 2H), 7.54–7.37 (m, 4H), 7.10 (t, 1H, J=6.5 Hz), 6.99 (d, 1H, J=6.5 Hz), 2.59 (br s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.1, 150.4, 143.5, 143.2, 134.6, 130.4, 129.7, 128.9, 128.4, 126.5, 123.1, 122.4, 121.9, 121.4, 116.3, 108.8, 17.1, 16.8; IR (KBr) 3163, 3056, 2975, 1459, 1419 cm^{-1}; GC–MS m/z (rel intensity) 208 (M$^+$, 100), 104 (24), 77 (14), 51 (4).

*4.2.4. 2,4-Dimethyl-1H-benzimidazole (**6**)*[10c]. Yield 70%. Yellow solid, mp 173–174 °C. TLC (10% methanol/dichloromethane) R_f 0.37; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.26 (br s, 1H), 7.27 (d, 1H, J=7.7 Hz), 6.98 (t, 1H, J=7.7 Hz), 6.88 (d, 1H, J=7.6 Hz), 2.49 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 138.6, 138.0124.8, 122.6, 122.1, 111.6, 17.1, 14.8; IR (KBr) 3378, 3171, 3059, 2993, 2914, 1424 cm^{-1}; GC–MS m/z (rel intensity) 146 (M$^+$, 100), 131 (13), 104 (15), 77 (12), 51 (5).

*4.2.5. 5-Methyl-2-phenyl-1H-benzimidazole (**7**)*[10a,b]. Yield 92%. White solid, mp 244–246 °C (lit.[10b] mp 243–244 °C). TLC (50% ethyl acetate/hexane) R_f 0.42; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (br s, 1H), 8.18 (d, 2H, J=6.6 Hz), 7.52–7.47 (m, 5H), 7.02 (d, 1H, J=6.6 Hz), 2.42 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.1, 140.4, 139.4, 132.7, 131.6, 130.4, 129.7, 127.3, 124.6, 116.1, 115.3, 21.7; IR (KBr) 3416, 3046, 3019, 2965, 2918, 1463, 1401 cm^{-1}; GC–MS m/z (rel intensity) 208 (M$^+$, 100), 104 (32), 77 (21), 51 (7).

*4.2.6. 2,5-Dimethyl-1H-benzimidazole (**8**)*[10c,d,e]. Yield 81%. White solid, mp 203–204 °C (lit.[10d] mp 203–204 °C). TLC (10% methanol/dichloromethane) R_f 0.36; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 7.30 (d, 1H, J=7.8 Hz), 7.21 (s, 1H), 6.90 (d, 1H, J=7.8 Hz), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 138.6, 137.2, 131.8, 123.4, 114.3, 114.0, 21.5, 14.8; IR (KBr) 3045, 2914, 2758, 1450, 1400 cm^{-1}; GC–MS m/z (rel intensity) 146 (M$^+$, 100), 131 (9), 104 (13), 77 (12), 51 (5).

*4.2.7. 5-Methoxy-2-phenyl-1H-benzimidazole (**9**)*[6c,10a,b]. Yield 95%. White solid, mp 147–148 °C (lit.[10b] mp 149–150 °C). TLC (50% ethyl acetate/hexane) R_f 0.41; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 8.15 (d, 2H, J=7.3 Hz), 7.54–7.43 (m, 4H), 7.09 (br s, 1H), 6.84 (dd, 1H, J=8.8, 2.0 Hz), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 152.1, 139.5, 134.2, 130.0, 129.8, 129.0, 126.7, 116.2, 112.5, 97.5, 55.7; IR (KBr) 3404, 3062, 2960, 2934, 1456, 1435, 1160, 1029 cm^{-1}; GC–MS m/z (rel intensity) 224 (M$^+$, 100), 209 (91), 181 (23), 154 (8), 127 (4), 112 (4), 104 (5), 77 (7), 51 (4).

*4.2.8. 5-Methoxy-2-methyl-1H-benzimidazole (**10**)*[7f]. Yield 74%. Pale yellow solid, mp 134–135 °C. TLC (10% methanol/dichloromethane) R_f 0.36; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 7.32 (d, 1H, J=8.4 Hz), 6.96 (br s, 1H), 6.72 (dd, 1H, J=8.4, 2.1 Hz), 3.74 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 151.1, 138.9, 133.7, 115.2, 111.2, 97.6, 55.8, 14.9; IR (KBr) 3051, 3007, 2959, 2908, 1488,

1253, 1163, 1036 cm^{-1}; GC–MS *m*/*z* (rel intensity) 162 (M^+, 100), 147 (95), 119 (36), 78 (5), 63 (4), 52 (5).

*4.2.9. 5-Iodo-2-phenyl-1H-benzimidazole (**11**).* Yield 71%. Yellow solid, mp 198–201 °C. TLC (50% ethyl acetate/hexane) R_f 0.54; ^1H NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H) 8.15 (d, 2H, *J*=7.3 Hz), 7.94 (br s, 1H), 7.57–7.42 (m, 5H); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.2, 142.7, 139.9, 131.8, 131.0, 130.7, 129.7, 127.5, 125.0, 117.8, 85.8; IR (KBr) 3062, 1463, 1395 cm^{-1}; GC–MS *m*/*z* (rel intensity) 320 (M^+, 100), 193 (16), 166 (13), 104 (4), 90 (6), 77 (4), 63 (6); HRMS (EI) calcd for $C_{13}H_9IN_2$ 319.9810, found 319.9807.

*4.2.10. 5-Iodo-2-methyl-1H-benzimidazole (**12**)*[12]. Yield 74%. White solid, mp 240–241 °C (lit.[12] mp 219–221 °C). TLC (10% methanol/dichloromethane) R_f 0.45; ^1H NMR (400 MHz, DMSO-d_6) δ 12.36 (br s, 1H), 7.81 (s, 1H), 7.38 (d, 1H, *J*=8.0 Hz), 7.29 (d, 1H, *J*=8.0 Hz), 2.48 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6, 40 °C) δ 153.3, 142.7, 139.3, 131.0, 124.6, 117.5, 84.7, 14.9; IR (KBr) 3398, 3092, 2964, 2893, 1437, 1394, 1275 cm^{-1}; GC–MS *m*/*z* (rel intensity) 258 (M^+, 100), 131 (37), 104 (13), 90 (11), 77 (3), 63 (11).

*4.2.11. 5-Bromo-2-phenyl-1H-benzimidazole (**13**)*[6c]. Yield 80%. Yellow solid, mp 204–207 °C. TLC (50% ethyl acetate/hexane) R_f 0.47; ^1H NMR (400 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 8.17 (d, 2H, *J*=7.1 Hz), 7.79 (br s, 1H), 7.56–7.47 (m, 4H), 7.33 (dd, 1H, *J*=8.4, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 139.8, 138.3, 130.6, 129.3, 129.2, 126.7, 126.2, 117.9, 116.4, 116.0; IR (KBr) 3421, 3097, 3049, 1444, 1397 cm^{-1}; GC–MS *m*/*z* (rel intensity) 274 (M^++2, 95), 272 (M^+, 100), 192 (14), 166 (14), 137 (5), 104 (5), 90 (8), 77 (6), 63 (10).

*4.2.12. 5-Bromo-2-methyl-1H-benzimidazole (**14**)*[10e,12]. Yield 90%. White solid, mp 223–224 °C (lit.[12] mp 214–215 °C, lit.[10e] mp 232–233 °C). TLC (10% methanol/dichloromethane) R_f 0.45; ^1H NMR (400 MHz, DMSO-d_6) δ 12.41 (br s, 1H), 7.64 (s, 1H), 7.40 (d, 1H, *J*=7.9 Hz), 7.23 (d, 1H, *J*=7.9 Hz), 2.47 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.6, 142.0, 139.2, 125.0, 118.3, 116.4, 114.6, 14.8; IR (KBr) 3412, 3082, 3011, 2957, 2897, 1454, 1397, 1274 cm^{-1}; GC–MS *m*/*z* (rel intensity) 212 (M^++2, 98), 210 (M^+, 100), 131 (23), 104 (10), 90 (8), 76 (5), 63 (12), 52 (4).

*4.2.13. 5-Chloro-2-phenyl-1H-benzimidazole (**15**)*[6c,10b]. Yield 85%. White solid, mp 212–214 °C (lit.[10b] mp 212–213 °C). TLC (50% ethyl acetate/hexane) R_f 0.49; ^1H NMR (400 MHz, DMSO-d_6) δ 13.09 (br s, 1H), 8.18 (d, 2H, *J*=7.1 Hz), 7.65–7.47 (m, 5H), 7.21 (dd, 1H, *J*=8.5, 2.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 153.8, 141.5, 139.1, 130.9, 130.8, 129.7, 128.1, 127.5, 123.4, 116.9, 115.8; IR (KBr) 3418, 3069, 3049, 1463, 1440, 1399 cm^{-1}; GC–MS *m*/*z* (rel intensity) 230 (M^++2, 35), 228 (M^+, 100), 192 (13), 166 (7), 114 (6), 104 (4), 90 (6), 77 (6), 63 (7).

*4.2.14. 5-Chloro-2-methyl-1H-benzimidazole (**16**)*[10d]. Yield 85%. White solid, mp 209–210 °C (lit.[10d] mp 200–201 °C). TLC (10% methanol/dichloromethane) R_f 0.44; ^1H NMR (400 MHz, DMSO-d_6) δ 12.36 (br s, 1H), 7.51 (d, 1H, *J*=2.0 Hz), 7.45 (d, 1H, *J*=8.5 Hz), 7.13 (dd, 1H, *J*=8.5, 2.0 Hz), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 139.4, 137.3, 127.9, 122.8, 115.2, 114.4, 15.0; IR (KBr) 3425, 3020, 2970, 2903, 1464, 1399 cm^{-1}; GC–MS *m*/*z* (rel intensity) 168 (M^++2, 34), 166 (M^+, 100), 131 (25), 104 (5), 90 (6), 76 (3), 63 (9), 52 (3).

*4.2.15. 5-Fluoro-2-phenyl-1H-benzimidazole (**17**)*[10b]. Yield 85%. White solid, mp 245–246 °C (lit.[10b] mp 242–243 °C). TLC (50% ethyl acetate/hexane) R_f 0.46; ^1H NMR (400 MHz, DMSO-d_6) δ 13.05 (br s, 1H), 8.19–8.17 (m, 2H), 7.61–7.47 (m, 4H), 7.41 (dd, 1H, *J*=9.4, 1.8 Hz), 7.09–7.04 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.3 (d, *J*=234.6 Hz), 153.7, 140.7, 137.3, 131.2, 130.8, 129.8, 127.4, 116.6, 111.1 (d, *J*=25.5 Hz), 101.9; IR (KBr) 3049, 1466, 1409 cm^{-1}; GC–MS *m*/*z* (rel intensity) 212 (M^+, 100), 184 (8), 106 (7), 82 (8), 77 (6).

*4.2.16. 5-Fluoro-2-methyl-1H-benzimidazole (**18**)*[13]. Yield 80%. Pale yellow solid, mp 177–179 °C. TLC (10% methanol/dichloromethane) R_f 0.41; ^1H NMR (400 MHz, DMSO-d_6) δ 12.30 (br s, 1H), 7.41 (dd, 1H, *J*=8.7, 5.0 Hz), 7.24 (dd, 1H, *J*=9.5, 2.4 Hz), 6.93 (ddd, 1H, *J*=10.5, 8.1, 1.2 Hz), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, *J*=237.5 Hz), 152.3, 138.9, 135.1, 114.9, 110.3 (d, *J*=25.2 Hz), 100.8, 15.0; IR (KBr) 3119, 3051, 2924, 1437, 1412 cm^{-1}; GC–MS *m*/*z* (rel intensity) 150 (M^+, 100), 122 (12), 108 (9), 95 (4), 82 (9), 63 (3).

*4.2.17. 4-Trifluoromethyl-2-phenyl-1H-benzimidazole (**19**).* Yield 82%. Pale yellow solid, mp 175–178 °C. TLC (50% ethyl acetate/hexane) R_f 0.50; ^1H NMR (400 MHz, DMSO-d_6) δ 13.19 (br s, 1H), 8.23 (d, 2H, *J*=7.1 Hz), 7.85 (d, 1H, *J*=7.8 Hz), 7.59–7.52 (m, 4H), 7.36 (t, 1H, *J*=7.7 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 151.2, 139.6 (br), 139.2 (br), 131.3, 130.7, 129.8, 127.9, 125.3 (q, *J*=270.0 Hz), 122.7, 120.1 (q, *J*=4.8 Hz), 119.3 (br), 118.3 (br); IR (KBr) 3180, 3066, 1461, 1424 cm^{-1}; GC–MS *m*/*z* (rel intensity) 262 (M^+, 100), 242 (4), 223 (22), 192 (6), 139 (13), 121 (7), 103 (6), 77 (6); HRMS (EI) calcd for $C_{14}H_9F_3N_2$ 262.0718, found 262.0714.

*4.2.18. 4-Trifluoromethyl-2-methyl-1H-benzimidazole (**20**)*[7g]. Yield 62%. Pale yellow solid, mp 176–177 °C. TLC (10% methanol/dichloromethane) R_f 0.48; ^1H NMR (400 MHz, DMSO-d_6) δ 12.68 (br s, 1H), 7.73 (d, 1H, *J*=7.8 Hz), 7.42 (d, 1H, *J*=7.8 Hz), 7.24 (t, 1H, *J*=7.8 Hz), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 141.6 (br), 133.3 (br), 124.2 (d, *J*=270.2 Hz), 121.6, 119.5, 116.0, 14.7; IR (KBr) 3470, 3177, 3107, 1431, 1333 cm^{-1}; GC–MS *m*/*z* (rel intensity) 200 (M^+, 100), 180 (70), 161 (10), 153 (10), 139 (13), 126 (4), 100 (5), 88 (3), 75 (3), 63 (4).

*4.2.19. 5-Trifluoromethyl-2-phenyl-1H-benzimidazole (**21**)*[7e]. Yield 62%. White solid, mp 196–197 °C. TLC (50% ethyl acetate/hexane) R_f 0.57; ^1H NMR (400 MHz, DMSO-d_6) δ 13.34 (br s, 1H), 8.21 (d, 2H, *J*=7.6 Hz), 7.95 (s, 1H), 7.77 (d, 1H, *J*=8.3 Hz), 7.58–7.50 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.0, 142.2, 141.1, 131.3, 130.7, 129.8, 127.7, 126.1 (q, *J*=269.6 Hz), 124.7 (q, *J*=31.7 Hz), 119.9 (q, *J*=3.6 Hz), 116.0, 114.2; IR (KBr) 3468, 3109, 3059, 1332 cm^{-1}; GC–MS *m*/*z* (rel intensity) 262 (M^+, 100), 243 (12), 212 (5), 192 (5), 131 (5), 77 (4).

*4.2.20. 5-Trifluoromethyl-2-methyl-1H-benzimidazole (**22**)*[7f]. Yield 83%. White solid, mp 194–195 °C. TLC (10% methanol/dichloromethane) R_f 0.47; ^1H NMR (400 MHz, DMSO-d_6) δ 12.66 (br s, 1H), 7.81 (s, 1H), 7.62 (d, 1H, *J*=8.3 Hz), 7.41 (d, 1H, *J*=8.3 Hz), 2.53 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.2, 141.9, 140.5, 126.2 (q, *J*=269.2 Hz), 124.1 (q, *J*=31.2 Hz), 119.1 (q, *J*=3.7 Hz), 115.3, 113.3, 14.9; IR (KBr) 3468, 3072, 1421, 1333 cm^{-1}; GC–MS *m*/*z* (rel intensity) 200 (M^+, 100), 181 (18), 172 (8), 140 (5), 131 (20), 113 (3), 100 (5), 75 (3), 63(5).

*4.2.21. 2-Phenyl-1H-benzimidazole-5-carbonitrile (**23**)*[14]. Yield 70%. White solid, mp 201–202 °C. TLC (50% ethyl acetate/hexane) R_f 0.34; ^1H NMR (400 MHz, DMSO-d_6) δ 13.34 (br s, 1H), 8.20 (d, 2H, *J*=6.3 Hz), 8.13 (s, 1H), 7.74 (d, 1H, *J*=8.3 Hz), 7.60–7.54 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.4, 142.9, 140.9, 131.6, 130.4, 129.9, 127.8, 126.6, 121.3, 120.4, 116.7, 106.0; IR (KBr) 3528, 3257, 3066, 2224, 1451 cm^{-1}; GC–MS *m*/*z* (rel intensity) 219 (M^+, 100), 191 (5), 109 (4), 90 (4), 77 (6).

*4.2.22. 2-Methyl-1H-benzimidazole-5-carbonitrile (**24**)*[7f]. Yield 74%. White solid, mp 242–243 °C. TLC (10% methanol/dichloromethane) R_f 0.54; ^1H NMR (400 MHz, DMSO-d_6) δ 12.76 (br s, 1H), 7.97 (br s, 1H), 7.58 (d, 1H, *J*=8.3 Hz), 7.47 (dd, 1H, *J*=8.3, 1.2 Hz), 2.51 (s, 3H);

^{13}C NMR (100 MHz, acetone-d_6) δ 155.7, 142.8, 134.5, 125.8, 120.6, 120.3, 115.8, 105.1, 14.9; IR (KBr) 3339, 3063, 2222, 1414, 1302 cm^{-1}; GC–MS *m*/*z* (rel intensity) 157 (M^+, 100), 129 (8), 115 (4), 103 (4), 90 (5), 76 (3), 62 (4).

*4.2.23. 4,6-Dichloro-2-phenyl-1H-benzimidazole (**25**).* Yield 52%. White solid, mp 200–201 °C. TLC (50% ethyl acetate/hexane) R_f 0.59; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (br s, 1H), 8.17 (d, 2H, *J*=6.6 Hz), 7.56–7.51 (m, 4H), 7.35 (d, 1H, *J*=1.5 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 154.4, 140.1, 138.9, 131.4, 130.4, 129.8, 128.3, 127.8, 122.8, 120.8, 113.2; IR (KBr) 3535, 3088, 3057, 1451, 1401 cm^{-1}; GC–MS *m*/*z* (rel intensity) 264 (M^++2, 62), 262 (M^+, 100), 226(5), 192(9), 131(7), 124 (7), 104 (5), 97 (7), 88 (7), 77 (10), 62 (4), 51 (4); HRMS (EI) calcd for $C_{13}H_7Cl_2N_2$ 262.0065, found 262.0064.

*4.2.24. 4,6-Dichloro-2-methyl-1H-benzimidazole (**26**)*[7f]. Yield 38%. Pale yellow solid, mp 222–223 °C. TLC (10% methanol/dichloromethane) R_f 0.46; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.72 (br s, 1H), 7.47 (d, 1H, *J*=1.7 Hz), 7.23 (d, 1H, *J*=1.7 Hz), 2.49 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 154.7, 140.4, 137.9, 127.4, 121.9, 121.3, 113.2, 14.8; IR (KBr) 3094, 3024, 1399 cm^{-1}; GC–MS *m*/*z* (rel intensity) 202 (M^++2, 64), 200 (M^+, 100), 165 (22), 137 (6), 124 (10), 97 (11), 88 (10), 75 (5), 62 (6).

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