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Note

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$ZnCl_2$-Catalyzed [3+2] Cycloaddition of Benzimidates and 2*H*-Azirines for the Synthesis of Imidazoles

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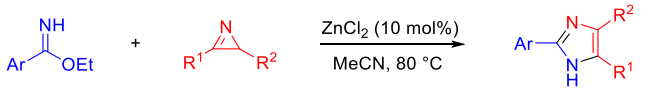
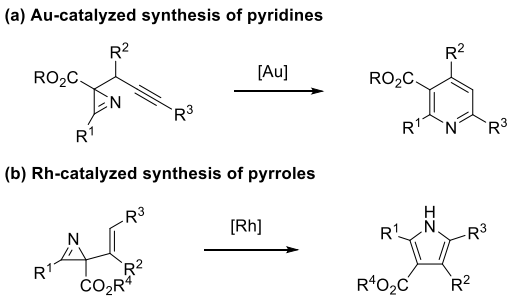
Supporting Information Placeholder



ABSTRACT: $ZnCl_2$-catalyed [3+2] cycloaddition reaction of benzimidates and 2*H*-azirines has been developed. This convenient method allowed the efficient construction of a serious of multi-substituted imidazoles in moderate to good yields under mild reaction conditions. This transformation exhibits good reactivity and high functional group tolerance.

2*H*-Azirine ring systems represent a highly important class of compounds found in natural products and biological active compounds.[1] Because of their high ring strain, 2*H*-azirines are also used as valuable building blocks in organic synthesis in the preparation of various N-heterocycles.[2,3] For example, the pyridines (**Scheme 1a**) synthesis via an Au-catalyzed ring-expansion of 2-propargyl 2*H*-azirine have been developed by Gagosz and co-workers.[4] The pyrroles (**Scheme 1b**)[5] and pyrazines (**Scheme 1c**)[6] synthesis from 2*H*-azirines catalyzed by Rh and Cu, respectively, have been reported by Park group. Synthesis of substituted imidazoles from 2*H*-azirine have also been investigated,[7] Leonard and co-worker reported the reaction of 2*H*-azirine and CH_3CN in the presence of $HClO_4$ to form imidazolium salt (**Scheme 1d**).[7a] Although much progress have been achieved in this area,[8-11] the development of new catalytic system for the construction of N-heterocycles using 2*H*-azirine as substrate under mild reaction conditions is still desirable. In this paper, we report a novel $ZnCl_2$-catalyzed [3+2] cycloaddition reaction between benzimidates[12] and 2*H*-azirines for the synthesis of substituted imidzoles (**Scheme 1e**).

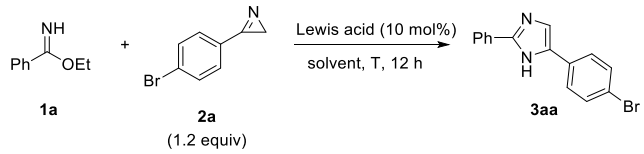
Scheme 1. Synthesis of N-Heterocycles from 2*H*-Azirines



We commenced our investigation with the optimization studies on the [3+2] cycloaddition of ethyl benzimidate **1a** and 3-(4-bromophenyl)-2*H*-azirine **2a** (**Table 1**). The reaction provided expected product **3aa** in 67% yield in the presence of 10 mol% $ZnCl_2$ in dichloromethane (DCE) at 80 °C (entry 1). Other Lewis acid such as $AlCl_3$, $CoBr_2$, $FeCl_2$ and $FeCl_3$ also promoted this reaction, but with lower yields (entries 2-5). The reaction did not take place without Lewis acid catalyst (entry 6). The slight lower yields were obtained when using toluene or tetrahydrofuran (THF) as solvents (entries 7-8), while the reaction did not occur at all when methanol was employed (entry 9). The product yield was further improved to 74% when CH_3CN[7a] was used instead of dichloromethane (entry 10). The use of lower temperature (60 °C or 25 °C) resulted in lower yields of **3aa** (entries 11-12), while higher temperature (100 °C) did not increase the product yield (entry 13). The reaction didn't occur

when HCl was used instead of $ZnCl_2$ (entry 14). The gram scale reaction was performed and the product was obtained in 78% yield (entry 15).

Table 1. Optimization of Reaction Conditions[a]

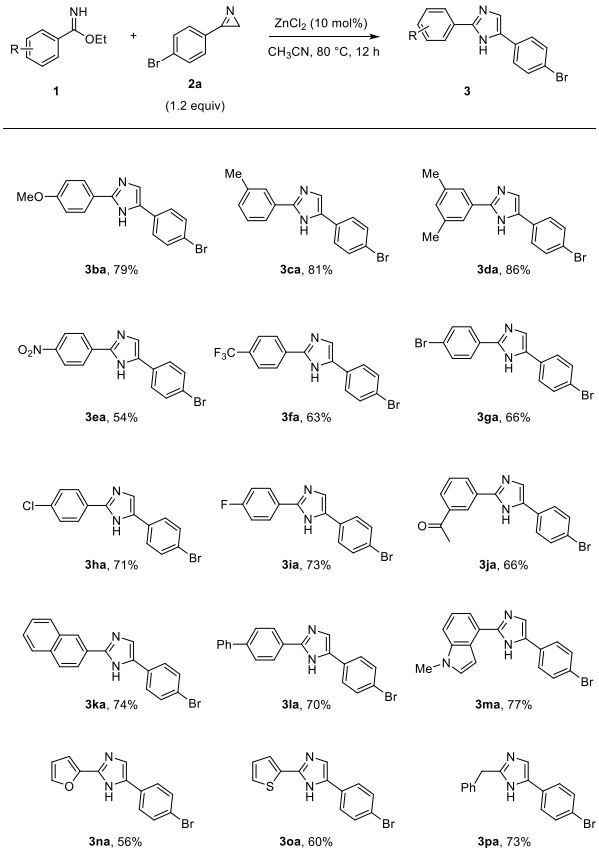


entry	Lewis acid	solvent	T (°C)	Yield[b] (%)
1	$ZnCl_2$	DCE	80	67
2	$AlCl_3$	DCE	80	26
3	$CoBr_2$	DCE	80	60
4	$FeCl_2$	DCE	80	46
5	$FeCl_3$	DCE	80	49
6	-	DCE	80	nr
7	$ZnCl_2$	toluene	80	66
8	$ZnCl_2$	THF	80	59
9	$ZnCl_2$	MeOH	80	nr
10	$ZnCl_2$	CH_3CN	80	74
11	$ZnCl_2$	CH_3CN	60	68
12	$ZnCl_2$	CH_3CN	25	49
13	$ZnCl_2$	CH_3CN	100	72
14	HCl	CH_3CN	80	nr
15	$ZnCl_2$	CH_3CN	80	78[c]

[a] Reactions were carried out under atmosphere on a 0.3 mmol scale in solvent (1.5 mL). [b] Isolated yields. nr = no reaction. [c] The reaction was performed in 5 mmol scale.

After screening the reaction conditions, we examined the substrate scope of benzimidates **1** (**Scheme 2**). Benzimidates bearing electron-donating groups such as methoxy, methyl groups participated in this reaction well, and provided the corresponding products in 79-86% yields (**3ba**, **3ca**, **3da**). The electron-withdrawing group nitro and CF_3 could be tolerated in the reaction conditions with moderate product yields (**3ea** and **3fa**). Halogen substituents such as bromo, chloro and fluoro are tolerated well in the reaction conditions, the desired products were obtained in good yields (**3ga**, **3ha**, **3ia**). The reaction proceeded well when an acetyl group at the *meta* position of benzimidate and gave the product **3ja** in 66% yield. The 2-naphthimidate substrate also underwent this reaction with good reactivity (**3ka**). A 4-phenyl substituted benzimidate underwent the cycloaddition reaction of **2a** as smoothly as model substrate and afforded the expected product in 70% yield (**3la**). The reaction also proceeded well when indole-4-carbimidate was used as substrate and provided imidazolyl substituted indole in good yield (**3ma**). Furan-2-carbimidate and thiophene-2-carbimidate underwent the reaction well and afforded the corresponding imidazole in moderate yields (**3na** and **3oa**). When the imidate with a benzyl substituent at 2-position, the reaction proceeded and gave the desired product **3pa** in73% yield.

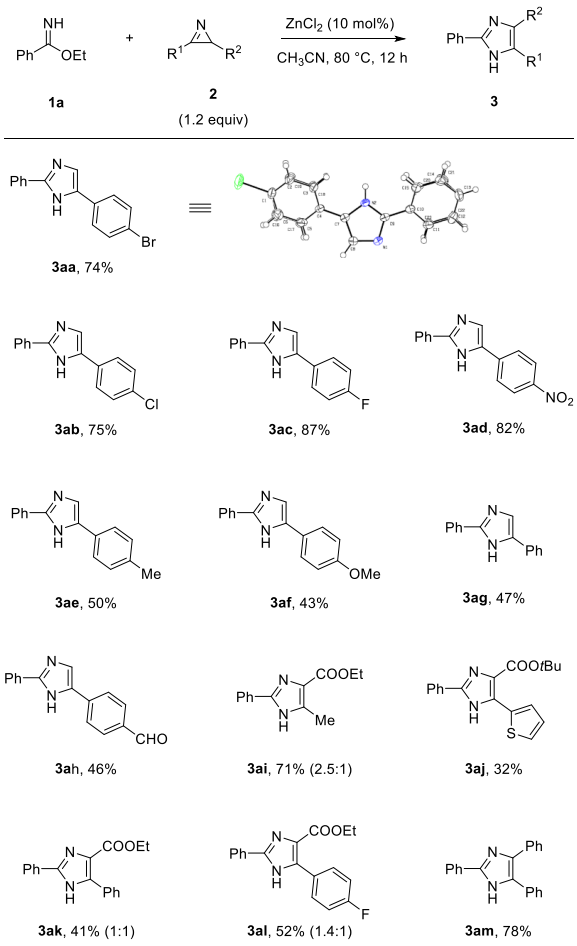
Scheme 2. Scope of benzimidates[a,b]



[a] Reactions were carried out under atmosphere on a 0.3 mmol scale in solvent (1.5 mL). [b] Isolated yields.

The present reaction was applicable to a variety of 2*H*-azirines **2**, as illustrated in **Scheme 3**. 3-Aryl-2*H*-azirine derivatives participated in this reaction and afforded the corresponding cycloaddition products **3aa**-**3ah** in moderate to good yields. The substrates bearing bromo and chloro groups gave the products **3aa** and **3ac**, respectively, in 74% and 75% yields. The structure of **3aa** was confirmed by X-ray crystal structure analysis.[13] The reaction proceeded well when the substrates bore electron-withdrawing groups such as fluoro and nitro groups afforded the products (**3ac** and **3ad**) in good yields (87% and 82%). On the other hand, the reaction became sluggish with methyl, methoxy group and provided the products (**3ae** and **3af**) in ca. 50% yield. Some functional groups such as formyl group could be tolerated in this reaction conditions and gave the annulation product **3ah** in 46% yield. The 2,3-di-substituted 2*H*-azirines also underwent cycloaddition reaction to generate tri-substituted imidazoles. When 2*H*-azirine **2i** was employed, the reaction proceeded well and afforded the imidazole products **3ai** and **3ai'** with 2.5:1 ratio in 71%. A thienyl-substituted 2*H*-azirine **2j** also underwent the reaction with modest reactivity (**3aj**). Ethyl 3-phenyl-2*H*-azirine-2-carboxylate **3k** reacted with benzimidate **1a** to provide products **3ak** and **3ak'** with 1:1 ratio in moderate yield. When a fluoro was introduced to para position of benzene ring of the 2*H*-azirine, the products ratio was 1.4:1 with 52% yield (**3al**). The symmetric 2,3-diphenyl-2*H*-azirine also participated in this annulation reaction and afforded the corresponding product **3am** in 78% yield.

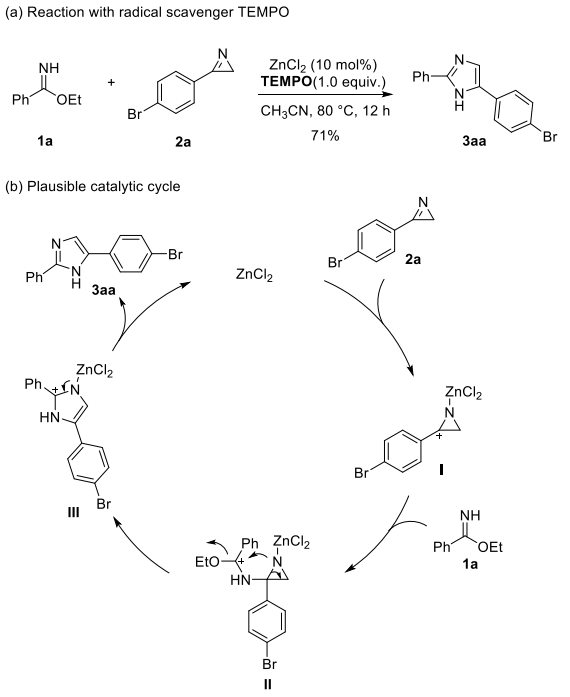
Scheme 3. Scope of 2*H*-Azirines[a,b]



[a] Reactions were carried out under atmosphere on a 0.3 mmol scale in solvent (1.5 mL). [b] Isolated yields.

We then performed the reaction with addition of 1 equivalent of 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) and product **3aa** was obtained in 71% (**Scheme 4a**). This experiment excluded the possibility of free radical reaction mechanism. Based on the previous reports and our data, we proposed the reaction mechanism of this transformation (**Scheme 4b**). First, in the presence of $ZnCl_2$, the cationic azirine complex **I** was formed. Then complex **I** undergoes nucleophilic attack by benzimidate **1a** to generate intermediate **II**. A subsequent ring opening and intramolecular nucleophilic attack of the N to the carbocation and OEt as a leaving group to form the five membered ring intermediate **III**. Finally, the elimination of $ZnCl_2$ catalyst to afford the imidazole product **3aa** and finish the catalytic cycle.

Scheme 4. Proposed Mechanism



In summary, we have developed a $ZnCl_2$-catalyzed [3+2] cycloaddition reaction of benzimidates and 2*H*-azirines for the synthesis of substituted imidazoles. The reaction exhibits excellent reactivity, good functional group tolerance and moderate to good yields. Ongoing effort in our laboratory will explore the cycloaddition reaction to construct other heterocycles catalyzed by Lewis acid.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. All reactions were performed by standard Schlenk techniques in oven-dried reaction vessels under air. Flash column chromatography was carried out using commercially available 300-400 mesh under pressure unless otherwise indicated. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-300 (300 MHz) NMR spectrometer. ^{1}H and ^{13}C{^{1}H } NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm), and DMSO-d6 (δ H = 2.50 ppm; δ C = 39.51 ppm), respectively. Infrared (IR) spectra were recorded using a thin film supported on KBr disks. High Resolution Mass measurement was performed on Agilent QTOF 6520 mass spectrometer with electron spray ionization (ESI) as the ion source. Anhydrous acetonitrile (MeCN) was distilled and stored over molecular sieves. Benzimidate derivatives **1** were prepared by following the same procedure as described in the literature.[14] 2H-azirines **2** were prepared by known procedure.[15]

General Procedure for $ZnCl_2$-Catalyzed [3+2] Cycloaddition Reaction of Benzimidate and 2*H*-azirines. An oven-dried Schlenk tube equipped with a magnetic stir bar was charged with $ZnCl_2$ (4.1 mg, 0.03 mmol, 10 mol %), benzimidate **1** (0.3 mmol, 1.0 equiv.), 2*H*-azirine **2** (0.36 mmol, 1.2 equiv). 1.5 mL CH_3CN were successively added and then stirred at 80 °C for 12 h. The reaction mixture was allowed to

cool down to room temperature and quenched with H_2O (2 mL × 1) and extracted with ethyl acetate (5 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash column chromatography (ethyl acetate/hexane) on silica gel and afforded corresponding imidazole **3**.

5-(4-Bromophenyl)-2-phenyl-1*H*-imidazole (3aa): A white solid; m.p. 169-171°C; Yield: 67 mg, 74%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.76 (s, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 3H), 7.63 – 7.53 (m, 2H), 7.52 – 7.43 (m, 2H), 7.41 – 7.32 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 146.6, 140.4, 134.4, 131.8, 130.9, 129.2, 128.7, 126.8, 125.5, 119.4, 115.4; IR (KBr) νmax = 3421, 3168, 2926, 2843, 1658, 1485, 1458, 1301, 1140, 1069, 1051, 1025, 1007, 941, 830, 775, 694, 510 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{12}BrN_2$: 299.0184, Found: 299.0180.

5-(4-Bromophenyl)-2-(4-methoxyphenyl)-1*H*-imidazole (3ba): A white solid; m.p. 197-198°C; Yield: 78 mg, 79%; ^{1}H NMR (300 MHz, DMSO-d6) δ 7.97 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.75 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 159.9, 146.9, 131.8, 127.0, 126.8, 123.7, 119.3, 114.6, 55.7; IR (KBr) νmax = 3434, 2922, 2850, 2357, 1649, 1611, 1542, 1492, 1402, 1256, 1174, 1114, 1028, 1007, 938, 836, 774, 736, 617, 567, 505 cm^{-1};HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{16}H_{14}BrN_2O$: 329.0290, Found: 329.0285.

5-(4-Bromophenyl)-2-(*m*-tolyl)-1*H*-imidazole (3ca): A white solid; Yield: 78 mg, 81%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.70 (s, 1H), 7.99 – 7.71 (m, 5H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.40 – 7.32 (m, 1H), 7.19 (d, *J* = 6.8 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 146.9, 138.4, 131.9, 130.9, 129.4, 129.1, 126.8, 126.1, 122.7, 119.4, 21.6; IR (KBr) νmax = 3426, 3154, 2921, 2852, 1660, 1612, 1483, 1401, 1324, 1138, 1069, 1008, 943, 830, 791, 726, 690, 503 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{16}H_{14}BrN_2$: 313.0340, Found: 313.0339.

5-(4-Bromophenyl)-2-(3,5-dimethylphenyl)-1*H*-imidazole (3da): A white solid; m.p. 197-199°C; Yield: 86 mg, 86%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.65 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.77 (s, 1H), 7.66 (s, 2H), 7.57 (d, *J* = 7.4 Hz, 2H), 6.99 (s, 1H), 2.34 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, DMSOd6) δ 147.0, 138.2, 131.8, 130.8, 130.2, 127.5, 127.0, 126.8, 126.2, 123.3, 119.4, 21.5; IR (KBr) νmax = 3447, 3197, 2920, 2843, 1654, 1605, 1478, 1402, 1025, 1007, 852, 827, 766, 732, 688, 507 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{17}H_{16}BrN_2$: 327.0497, Found: 327.0498.

5-(4-Bromophenyl)-2-(4-nitrophenyl)-1*H*-imidazole (3ea): A yellow solid; m.p. 206-207°C; Yield: 56 mg, 54%; ^{1}H NMR (300 MHz, DMSO-d6) δ 13.18 (s, 1H), 8.33 (d, *J* = 8.9 Hz, 2H), 8.27 – 8.18 (m, 2H), 7.99 (s, 1H), 7.89 – 7.80 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 147.1, 144.6, 141.7, 136.7, 134.0, 132.0, 127.1, 126.1, 124.8, 120.0, 117.4; IR (KBr) νmax = 3401, 3178, 2923, 2852, 1646, 1603, 1508, 1482, 1402, 1339, 1152, 1109, 1069, 1008, 854, 833, 767, 717, 501 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{11}BrN_3O_2$: 344.0035, Found:. 344.0034.

5-(4-Bromophenyl)-2-(4-(trifluoromethyl)phenyl)-1*H*-imidazole (3fa): A white solid; m.p. 190-191°C; Yield: 69 mg, 63%; ^{1}H NMR (300 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 2H), 7.90 (s, 1H), 7.84 (d, *J* = 8.5 Hz, 4H), 7.58 (d, *J* = 8.4 Hz, 2H); 13C{^{1}H} NMR (75 MHz, DMSO-d6) δ 145.2, 134.5, 131.9, 128.6 (q, $^2J_{C-H}$= 31.8 Hz), 128.0, 126.9, 126.5, 126.3, 126.2, 125.9, 122.9, 119.8; IR (KBr) νmax = 3421, 3193, 2924, 2849, 1620, 1442, 1327, 1167, 1124, 1065, 1026, 1009, 849, 823, 504 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{16}H_{11}BrF_3N_2$: 367.0058, Found: 367.0047.

2,5-Bis(4-bromophenyl)-1*H*-imidazole (3ga): A white solid; m.p. 203-205°C; Yield: 64 mg, 66%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.83 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.90 – 7.75 (m, 3H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 145.6, 132.1, 131.8, 130.0, 127.3, 126.8, 121.8, 119.7; IR (KBr) νmax = 3449, 3231, 2922, 2850, 1647, 1482, 1431, 1291, 1152, 1072, 1009, 943, 829, 780, 725, 503 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{11}Br_2N_2$: 376.9289, Found: 376.9288.

5-(4-Bromophenyl)-2-(4-chlorophenyl)-1*H*-imidazole (3ha): A yellow solid; m.p. 198-200°C; Yield: 71 mg, 71%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.83 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.91 – 7.78 (m, 3H), 7.63 – 7.47 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 133.3, 131.9, 129.7, 129.4, 128.8, 127.4, 127.2, 127.0, 126.8; IR (KBr) νmax = 3434, 3178, 2922, 2851, 2353, 1655, 1596, 1483, 1399, 1271, 1092, 1069, 1009, 944, 833, 762, 731, 501 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{11}BrClN_2$: 332.9794, Found: 332.9794.

5-(4-Bromophenyl)-2-(4-fluorophenyl)-1*H*-imidazole (3ia): A yellow solid; Yield: 69 mg, 73%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.75 (s, 1H), 8.20 – 7.98 (m, 2H), 7.96 – 7.73 (m, 3H), 7.68 –7.50 (m, 2H), 7.43 – 7.23 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 162.6 (d, $^1J_{C-F}$= 245.4 Hz), 145.8, 140.4, 134.4, 131.8, 127.6 (d, $^3J_{C-F}$= 3.4 Hz), 126.8, 119.4, 116.2 (d, $^2J_{C-F}$= 21.9 Hz), 115.4; IR (KBr) νmax = 3421, 2921, 2851, 1612, 1503, 1444, 1400, 1247, 1147, 1072, 1008, 964, 833, 769, 739, 615, 532 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{11}BrFN_2$: 317.0090, Found: 317.0088.

1-(3-(5-(4-Bromophenyl)-1*H*-imidazol-2-yl)phenyl)ethanone (3ja): A white solid; m.p. 223-224°C; Yield: 68 mg, 66%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.94 (s, 1H), 8.59 (s, 1H), 8.27 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.81 (dd, *J* = 24.7, 8.2 Hz, 3H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 2.66 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 198.3, 137.8, 131.9, 131.3, 129.8, 129.7, 128.4, 126.9, 124.9, 27.3; IR (KBr) νmax = 3428, 3202, 2919, 2851, 1663, 1473, 1445, 1404, 1260, 1139, 1024, 1007, 943, 834, 754, 727, 683, 595 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{17}H_{13}BrN_2O$: 341.0290, Found: 341.0285.

5-(4-Bromophenyl)-2-(naphthalen-2-yl)-1*H*-imidazole (3ka): A gray solid; m.p. 206-207°C; Yield: 78 mg, 74%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.93 (s, 1H), 8.55 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.05 – 7.86 (m, 6H), 7.64 – 7.50 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 133.5, 133.2, 131.9, 128.8, 128.6, 128.4, 128.2, 127.2, 126.9, 124.0, 123.8; IR (KBr) νmax = 3533, 3229, 3193, 2920, 2850, 2616, 2360, 1657, 1598, 1478, 1410, 1292, 1149, 1132, 1070, 1006, 950, 864, 825, 751, 489 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{19}H_{14}BrN_2$: 349.0340, Found: 349.0338.

2-([1,1'-Biphenyl]-4-yl)-5-(4-bromophenyl)-1*H*-imidazole (3la): A yellow solid; m.p. 251-253°C; Yield: 80 mg, 70%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.83 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 3H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 7.3 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.38 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 133.5, 133.2, 131.9, 128.8, 128.6, 128.4, 128.2, 127.2, 126.9, 126.8, 124.0, 123.8; IR (KBr) νmax = 3414, 2921, 2851, 1646, 1483, 1422, 1401, 1128, 1107, 1079, 1067, 1007, 942, 837, 767, 732, 690, 561, 504 cm^{-1};HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{21}H_{16}BrN_2$: 375.0497, Found: 375.0498.

4-(5-(4-Bromophenyl)-1*H*-imidazol-2-yl)-1-methyl-1*H*-indole (3ma): A yellow solid; Yield: 82 mg, 77%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.64 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.83 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.49 – 7.42 (m, 3H), 7.29 – 7.22 (m, 1H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 147.5, 137.7, 131.9, 130.6, 126.8, 125.4, 122.5, 121.3, 119.3, 116.9, 110.5, 102.7, 33.1; IR (KBr) νmax = 3398, 3132, 2922, 2849, 2360, 1901, 1723, 1657, 1598, 1512, 1485, 1449, 1417, 1333, 1286, 1119, 1065, 1018, 1006, 943, 831, 752, 509 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{18}H_{15}BrN_3$: 352.0449, Found: 352.0450.

5-(4-Bromophenyl)-2-(furan-2-yl)-1*H*-imidazole (3na): A yellow solid; m.p. 209-210°C; Yeild: 49mg, 56%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.77 (s, 1H), 7.78 (d, *J* = 6.6 Hz, 4H), 7.55 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 3.2 Hz, 1H), 6.68-6.58 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 145.8, 142.9, 131.4, 126.3, 119.0, 111.8, 107.0; IR (KBr) νmax = 3414, 3229, 2923, 2852, 1637, 1618, 1521, 1483, 1475, 1400, 1289, 1173, 1150, 1108, 1070, 1019, 1006, 983, 890, 813, 765, 731, 640, 596, 501 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{13}H_{10}BrN_2O$: 288.9977, Found: 288.9973.

5-(4-Bromophenyl)-2-(thiophen-2-yl)-1*H*-imidazole (3oa): A white solide; m.p. 212-213°C; Yeild: 55mg, 60%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.74 (s, 1H), 7.77 (d, *J* = 6.9 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.17 – 7.09 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 142.6, 140.1, 134.5, 134.1, 131.8, 128.3, 126.8, 126.6, 124.4, 119.4, 114.9; IR (KBr) νmax = 3552, 3475, 3414, 3110, 2921, 1640, 1617, 1496, 1476, 1419, 1227, 1139, 1084, 1064, 1008, 947, 930, 847, 830, 781, 726, 698, 624, 502, 481 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{13}H_{10}BrN_2S$: 304.9748, Found: 304.9746.

2-Benzyl-5-(4-bromophenyl)-1*H*-imidazole (3pa): A yellow oil; Yeild: 69mg, 73%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.05 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.33 – 7.15 (m, 5H), 4.00 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 147.7, 138.9, 131.7, 128.9, 128.8, 126.7, 126.5, 118.9, 34.7; IR (KBr) νmax = 3413, 3137, 2923, 2853, 2360, 2342, 1637, 1617, 1535, 1493, 1477, 1454, 1399, 1135, 1069, 1008, 952, 829, 772, 726, 693, 506 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{16}H_{14}BrN_2$: 313.0340, Found: 313.0336.

5-(4-Chlorophenyl)-2-phenyl-1*H*-imidazole (3ab): A green solid; m.p. 156-158°C; Yield: 58 mg, 75%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.75 (s, 1H), 8.03 (d, *J* = 7.5 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.84 (s, 1H), 7.54 – 7.41 (m, 4H), 7.40 – 7.34 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 146.6, 140.4, 134.1, 130.9, 129.2, 128.9, 128.7, 126.5, 125.4, 115.4; IR (KBr) νmax = 3428, 3138, 2920, 2843, 1648, 1486, 1458, 1410, 1295, 1091, 1026, 1011, 941, 827, 781, 709, 695, 582, 514, 501 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{12}ClN_2$: 255.0689, Found: 255.0688.

5-(4-Fluorophenyl)-2-phenyl-1*H*-imidazole (3ac): A green solid; m.p. 169-170°C; Yield: 63 mg, 87%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.69 (s, 1H), 8.02 (d, *J* = 7.4 Hz, 2H), 7.90 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.75 (s, 1H), 7.53 – 7.43 (m, 2H), 7.41 – 7.32 (m, 1H), 7.23 (t, *J* = 8.8 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 161.4 (d, $^1J_{C\text{-}F}$ = 242.4 Hz), 146.4, 131.0, 129.2, 128.6, 126.7 (d, $^3J_{C\text{-}F}$ = 7.9 Hz), 125.4, 115.8 (d, $^2J_{C\text{-}F}$ = 21.7 Hz); IR (KBr) νmax = 3445, 3144, 2923, 2843, 2360, 1658, 1607, 1566, 1497, 1462, 1459, 1402, 1232, 1156, 1025, 838, 774, 693, 602, 513 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{12}FN_2$: 239.0985, Found: 239.0982.

5-(4-Nitrophenyl)-2-phenyl-1*H*-imidazole (3ad): A yellow solid; m.p. 178-179°C; Yield: 66 mg, 82%; ^{1}H NMR (300 MHz, DMSO-d6) δ 13.00 (s, 1H), 8.25 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 3H), 8.05 (d, *J* = 7.5 Hz, 2H), 7.54 – 7.45 (m, 2H), 7.43 – 7.35 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 147.5, 145.7, 141.8, 139.6, 130.5, 129.3, 129.1, 125.6, 125.2, 124.6, 118.5; IR (KBr) νmax = 3519, 3108, 2923, 2852, 2363, 1655, 1600, 1511, 1330, 1182, 1143, 1111, 858, 788, 752, 713, 689, 486 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{15}H_{12}N_3O_2$: 266.0930, Found: 266.0928.

2-Phenyl-5-(*p*-tolyl)-1*H*-imidazole (3ae): A white solid; m.p. 168-170°C; Yield: 35 mg, 50%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.61 (s, 1H), 8.03 (d, *J* = 7.4 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.66 (s, 1H), 7.52 – 7.43 (m, 2H), 7.40 – 7.32 (m, 1H), 7.23 – 7.16 (m, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 146.3, 135.9, 131.1, 129.6, 129.2, 128.5, 125.4, 124.8, 21.3; IR (KBr) νmax = 3424, 3162, 2921, 2849, 2259, 1655, 1607, 1499, 1459, 1405, 1298, 1179, 1143, 1045, 1025, 1006, 822, 774, 693, 507 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{16}H_{15}N_2$: 235.1235, Found: 235.1230.

5-(4-Methoxyphenyl)-2-phenyl-1*H*-imidazole (3af): A yellow solid. Yield: 33 mg, 43%; ^{1}H NMR (300 MHz, DMSO-d6) δ 8.01 (d, *J* = 7.4 Hz, 2H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.59 (s, 1H), 7.51 – 7.43 (m, 2H), 7.40 – 7.31 (m, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 158.5, 146.2, 131.1, 129.2, 128.5, 126.2, 125.3, 114.4, 55.5; IR (KBr) νmax = 3392, 3162, 2921, 2843, 1604, 1499, 1460, 1247, 1178, 1027, 833, 774, 708, 693, 610, 524 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{16}H_{15}N_2O$: 251.1184, Found: 251.1184.

2,5-Diphenyl-1*H*-imidazole (3ag): A white solid; Yield: 31 mg, 47%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.67 (s, 1H), 8.03 (d, *J* = 7.3 Hz, 2H), 7.87 (d, *J* = 7.3 Hz, 2H), 7.73 (s, 1H), 7.53 – 7.44 (m, 2H), 7.43 – 7.34 (m, 3H), 7.27 – 7.19 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 146.5, 131.1, 129.2, 129.0, 128.6, 128.4, 126.8, 125.4, 125.1, 125.0, 124.9; IR (KBr) νmax = 3463, 3144, 2923, 2852, 1646, 1606, 1488, 1459, 1401, 1143, 1072, 1024, 1006, 822, 773, 757, 692, 501 cm^{-1}; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{13}N_2$: 221.1079, Found: 221.1077.

4-(2-Phenyl-1*H*-imidazol-5-yl)benzaldehyde (3ah): A yellow solid, m.p. 168-169°C; Yield: 35 mg, 46%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.93 (s, 1H), 9.98 (s, 1H), 8.18 – 7.99 (m, 5H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.56 – 7.44 (m, 2H), 7.44 – 7.35 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 192.7, 147.1, 141.1, 140.4, 134.5, 130.7, 130.6, 129.3, 128.9, 125.6, 125.1, 117.6; IR (KBr) νmax = 3455, 3324, 3287, 2921, 2850, 1683,

1601, 1458, 1424, 1395, 1303, 1215, 1165, 1127, 1026, 943, 834, 775, 698, 649, 507 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{13}N_2O$: 249.1028, Found: 249.1025.

Ethyl 5-methyl-2-phenyl-1*H*-imidazole-4-carboxylate (3ai): Obtained as a 2.5:1 mixture with its regioisomer ethyl 4-methyl-2-phenyl-1*H*-imidazole-5-carboxylate (**3ai'**); A white solid; m.p. 197-198°C; Yield: 50 mg, 71%; ^{1}H NMR (400 MHz, DMSO-d6) δ 12.99 (s, 1H, **3ai'**), 12.85 (s, 1H, **3ai**), 8.12 (d, *J* = 6.6 Hz, 2H, **3ai'**), 7.93 (d, *J* = 7.5 Hz, 2H, **3ai**), 7.50 – 7.36 (m, 3H, **3ai** and **3ai'**), 4.30 – 4.21 (m, 2H, **3ai** and **3ai'**) 2.51 (s, 3H, **3ai**), 2.42 (s, 3H, **3ai'**), 1.31 – 1.27 (m, 3H, **3ai** and **3ai'**); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d6) δ 163.8, 160.8, 147.8, 146.6, 144.8, 137.1, 130.3, 129.6, 129.3, 129.1, 128.9, 126.6, 125.5, 60.4, 59.9, 59.7, 15.1, 14.9, 11.6; IR (KBr) νmax = 3466, 2978, 2345, 1707, 1597, 1535, 1491, 1458, 1400, 1320, 1213, 1112, 1100, 1024, 972, 783, 708, 618, 465 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{15}N_2O_2$: 231.1134, Found: 231.1131.

***tert*-Butyl-2-phenyl-5-(thiophen-2-yl)-1*H*-imidazole-4-carboxylate (3aj):** A yellow solid; Yield: 32 mg, 32%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.97 (s, 1H), 8.16 (d, *J* = 6.6 Hz, 2H), 8.04 – 7.99 (m, 1H), 7.60 – 7.56 (m, 1H), 7.54 – 7.46 (m, 3H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 1.61 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 159.8, 147.9, 140.8, 137.3, 130.1, 129.4, 129.1, 127.9, 127.9, 127.3, 127.0, 119.3, 82.3, 28.5; IR (KBr) νmax = 3439, 3071, 2977, 2926, 2851, 1700, 1563, 1506, 1480, 1453, 1433, 1393, 1367, 1300, 1170, 1111, 1047, 1021, 847, 780, 694 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{19}N_2O_2S$: 327.1167, Found: 327.1167.

Ethyl-2,5-diphenyl-1*H*-imidazole-4-carboxylate (3ak): Obtained as a 1:1 mixture with its regioisomer Ethyl-2,4-diphenyl-1*H*-imidazole-5-carboxylate (**3ak'**); A yellow solid; m.p. 167-169°C; Yield: 37 mg, 41%; ^{1}H NMR (300 MHz, DMSO-d6) δ 13.23 (s, 1H, **3ak**), 13.09 (s, 1H, **3ak'**), 8.21 (d, *J* = 6.5 Hz, 1H, **3ak** and **3ak'**), 8.08 (d, *J* = 6.8 Hz, 1H, **3ak** and **3ak'**), 7.91 (d, *J* = 6.4 Hz, 1H, **3ak** and **3ak'**), 7.73 – 7.66 (m, 1H, **3ak** and **3ak'**), 7.54 – 7.36 (m, 6H, **3ak** and **3ak'**), 4.34 – 4.15 (m, 2H, **3ak** and **3ak'**), 1.31 – 1.15 (m, 3H, **3ak** and **3ak'**); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 165.71, 163.34, 160.41, 148.31, 147.45, 146.3, 130.1, 129.7, 129.2, 129.0, 128.3, 128.1, 126.9, 126.1, 119.3, 60.8, 60.0, 14.6; IR (KBr) νmax = 3428, 2921, 2850, 2357, 1712, 1531, 1487, 1474, 1381, 1311, 1258, 1265, 1235, 1129, 1023, 997, 966, 780, 762, 717, 693 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{17}N_2O_2$: 293.1290, Found: 293.1290.

Ethyl-5-(4-fluorophenyl)-2-phenyl-1*H*-imidazole-4-carboxylate (3al): Obtained as a 1.4:1 mixture with its regioisomer Ethyl-4-(4-fluorophenyl)-2-phenyl-1*H*-imidazole-5-carboxylate (**3al'**); A white solid; m.p. 206-207°C; Yield: 49 mg, 52%; ^{1}H NMR (300 MHz, DMSO-d6) δ 13.23 (s, 1H, **3al**), 13.09 (s, 1H, **3al'**), 8.20 (d, *J* = 6.6 Hz, 2H, **3al**), 8.07 (d, *J* = 7.3 Hz, 2H, **3al'**), 7.97 (dd, *J* = 8.7, 5.8 Hz, 2H, **3al**), 7.75 (dd, *J* = 8.6, 5.6 Hz, 2H, **3al'**), 7.55 – 7.40 (m, 5H, **3al**), 7.41 – 7.22 (m, 5H, **3al'**), 4.30 (q, *J* = 7.1 Hz, 2H, **3al**), 4.20 (q, *J* = 7.1 Hz, 2H, **3al'**), 1.28 (t, *J* = 7.1 Hz, 3H, **3al**), 1.21 (t, *J* = 7.0 Hz, 3H, **3al'**); 13C{^{1}H} NMR (75 MHz, DMSO-d6) δ 164.2 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 163.3, 161.0 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 160.0, 148.3, 146.4, 146.3, 137.7, 132.4 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 131.7 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 130.7 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 130.1, 130.0, 129.7, 129.4, 129.23, 129.15, 128.9, 126.9, 126.4 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 126.1, 119.3, 115.4, 115.1, 115.0, 114.8, 60.9, 60.0, 14.61, 14.56. IR (KBr) νmax = 3452, 3074, 2922, 2851, 1710, 1607, 1533, 1503, 1485, 1474, 1381, 1316, 1230, 1158, 1130, 1023, 965, 842, 789, 715, 703 cm^{-1}; HRMS (ESI) m/z$[M+H]^+$: Calcd for $C_{18}H_{16}FN_2O_2$: 311.1196, Found: 311.1188.

2,4,5-Triphenyl-1*H*-imidazole(3am): A white solid; m.p. 274-275°C; Yield: 70 mg, 78%; ^{1}H NMR (300 MHz, DMSO-d6) δ 12.74 (s, 1H), 8.13 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 4H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.44 – 7.23 (m, 7H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d6) δ 146.0, 130.8, 129.2, 128.9, 128.7, 128.6-127.1(m), 125.7; IR (KBr) νmax = 3434, 3037, 2963, 2920, 2851, 2363, 1600, 1488, 1460, 1460, 1396, 1127, 1070, 1027, 965, 915, 840, 765, 736, 697, 495 cm^{-1}; HRMS (ESI) m/z$[M+H]^+$: Calcd for $C_{21}H_{17}N_2$: 297.1392, Found: 297.1383.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra for all the products (PDF)

X-ray crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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