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Silver-Assisted [3 + 2] Annulation of Nitrones with Isocyanides: Synthesis of 2,3,4-Trisubstituted 1,2,4-Oxadiazolidin-5-ones

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ABSTRACT: A silver-assisted method for [3 + 2] annulation of nitrones with isocyanides has been developed. The developed protocol allows access to a variety of 2,3,4-trisubstituted 1,2,4-oxadiazolidin-5-one derivatives as single diastereomers in good to excellent yields using silver oxide as the catalyst and molecular oxygen as the terminal oxidant. A plausible mechanism involving a nucleophilic addition/cyclization/protodeargentation/oxidation pathway is proposed on the basis of experimental results.

KEYWORDS: annulation; isocyanide; nitrone; oxadiazolidinone; silver

INTRODUCTION

Nitrones and isocyanides constitute multifaceted building blocks in organic synthesis and have been extensively implemented in the construction of nitrogen-based heterocyclic compounds.[1,2] Thus far, several remarkable reaction manifolds have been realized. Among these, the [3 + 2] dipolar cycloaddition reaction represents a powerful strategy to access five-membered heterocyclic compounds owing to its simplicity and atom efficiency.[3,4] In contrast, [3 + 1] and [3 + 1 + 1] cycloaddition reactions of nitrones with isocyanides to assemble heterocycles have rarely been utilized.[5,6,7,8]

Only a handful of reports detailing the cycloaddition manifolds of nitrones with isocyanides have been disclosed (Figure 1a). For example, the Zhu, Zeeh, and Lorke groups have demonstrated that nitrones can undergo [3 + 1] cycloaddition with isocyanides to afford four-membered 4-imino-1,2-oxazetidine motifs.[6] Furthermore, a proposed [3 + 3] cycloaddition process involving nitrones and α-metalated isocyanides to produce five-membered 2-imidazolidinones was recently reported.[8] Also, Xu and coworkers realized that isocyanoacetates could react with nitrones to produce polysubstituted pyrroles in the presence of commercially available copper salts through a [3 + 1 + 1] cycloaddition manifold.[7] Luzyanin and coworkers have also described a metal-mediated strategy in which nitrones react with palladium-bound isocyanides to provide carbene complexes (Figure 1b).[9] Despite the number of synthetic methodologies that have been realized[10] the development of new and efficient methods that rely on easily available starting materials are of great value. As a continuation of the recently witnessed reports on isocyanide-involving reaction manifolds,[11] we have explored silver-mediated manifolds involving isocyanides.[12] Here, we disclose a silver-assisted [3 + 2] annulation reaction of nitrones with isocyanides for the assembly of 1,2,4-

oxadiazolidin-5-ones and the subsequent decarboxylative process for accessing amidines, which are vital motifs in pharmaceuticals and natural products.[13] The developed methods display broad substrate scope and are conducted under mild reaction conditions (Figure 1c).

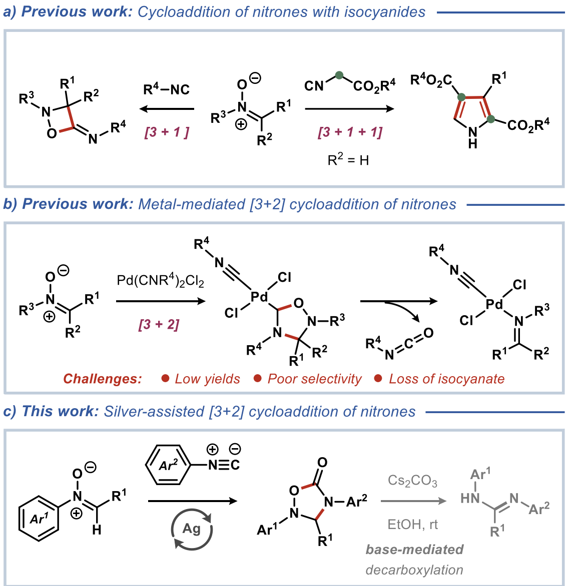
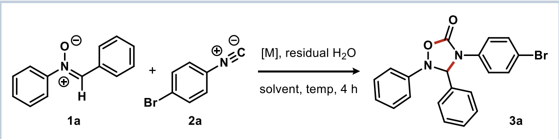


Figure 1. Annulation Reactions of Isocyanides with Nitrones.

RESULTS AND DISCUSSION

N-benzylideneaniline oxide (**1a**) and 1-bromo-4-isocyanobenzene (**2a**) were selected as model substrates for optimization of the [3 + 2] annulation reaction. To our delight, conducting the reaction in DMF at 80 °C in the presence of Ag_2O (10 mol%) afforded the desired product 4-(4-bromophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3a**) in 76% isolated yield after merely 4 h (Table 1, entry 1). Screening of other silver salts, including AgOAc, Ag_2CO_3, AgOTf, $AgBF_4$ and other metal precursors, such as CuI and $Pd(OAc)_2$, showed that Ag_2CO_3 and Ag_2O displayed the best reactivity while AgOAc proved to be less efficient and the other metal catalysts were inactive (Table 1, entries 2–7). Next, switching to 1,4-dioxane greatly increased the yield of annulation adduct **3a** to 91% (Table 1, entry 8). The use of aprotic or polar solvents, such as toluene and MeCN, had a negative effect on the reaction and delivered **3a** in diminished yields (Table 1, entries 9 and 10) while employing the protic solvent EtOH nearly inhibited the reaction (Table 1, entry 11). Decreasing the reaction temperature from 80 °C to 40 °C led to significantly diminished yield of the desired product (Table 1, entry 12). A control experiment established that the silver catalyst is required for the reaction to proceed (Table 1, entry 13). Furthermore, the annulation affords product **3a** as a single diastereomer as confirmed by single crystal X-ray diffraction analysis (CCDC 1915298, see Scheme 1).

Table 1. Optimization of the Reaction Conditions.[a,b]

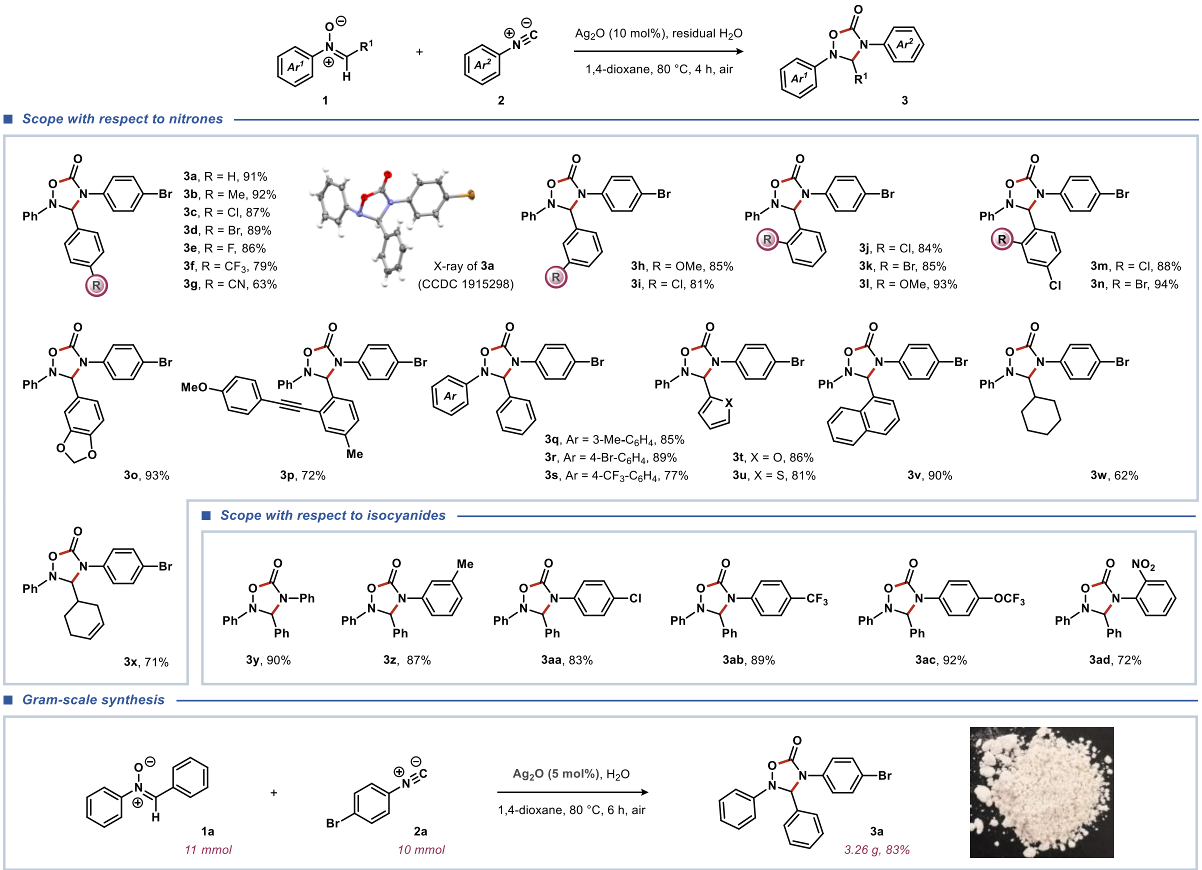


entry	[M]	solvent	temp (°C)	yield (%)[b]
1	Ag_2O	DMF	80	76
2	AgOAc	DMF	80	42
3	Ag_2CO_3	DMF	80	74
4	AgOTf	DMF	80	< 5[c]
5	$AgBF_4$	DMF	80	< 5[c]
6	CuI	DMF	80	< 5[c]
7	$Pd(OAc)_2$	DMF	80	< 5[c]
8	**Ag_2O**	**1,4-dioxane**	**80**	**91**
9	Ag_2O	toluene	80	76
10	Ag_2O	CH_3CN	80	53
11	Ag_2O	EtOH	80	< 10[c]
12	Ag_2O	1,4-dioxane	40	38
13	-	1,4-dioxane	80	< 5[c]

[a] Reaction conditions: All reactions were carried out with **1a** (0.55 mmol), **2a** (0.5 mmol), catalyst (10 mol%) in solvent (2.0 mL) under air for 4 h. [b] Yield are of isolated **3a** after purification by column chromatogrphy. [c] Yield determined by ^{1}H NMR analysis of the reaction mixture using CH_2Br_2 as internal standard.

Next, the optimal reaction conditions were adopted on a variety of nitrones and aryl isocyanides to investigate the generality of the protocol (Scheme 1). A collection of diversely functionalized nitrones underwent annulation with aryl isocyanides to deliver the corresponding product **3** in good to excellent yield. For example, *para*-substituted arene motifs bearing electron-donating or electron-withdrawing moieties were tolerated in the annulation with 1-bromo-4-isocyanobenzene (**2a**) to produce the corresponding products (**3b**–**3g**) in high yields. Similarly, *ortho*-, *meta*, and disubstituted substrates were also well-tolerated, affording products **3h**–**3n** in good to high yields. Gratifyingly, common functional groups including alkyl, alkoxy, halogen, cyano and trifluoromethyl were all effective. A more elaborate substrate (**1p**) with a potentially sensitive alkyne moiety could also be successfully converted to product **3p** (72%), illustrating the compatibility of the developed method. Heteroaryl nitrones including 2-furyl and 2-thienyl were also evaluated, delivering the corresponding adducts **3t** and **3u** with high efficiency. Furthermore, subjecting the fused aromatic (**1v**) or alkyl (**1w** and **1x**) nitrones to isocyanide **2a**, afforded the desired products **3v**–**3x** in good to excellent yield. The protocol also tolerated a wide variation of substituents on the arene ring on the isocyanides (**2y**–**2ad**), efficiently delivering a set of diverse oxadiazolidinones (**3y**–**3ad**) in high yields. The applicability of the annulation protocol was highlighted through a gram-scale reaction of *N*-benzylideneaniline oxide (**1a**) and 1-bromo-4-isocyanobenzene (**2a**). The reaction was performed on a 10 mmol scale and proceeded smoothly to give product **3a** (3.26 g, 83%) even when decreasing the amount of the catalyst to 5 mol% (Scheme 1).

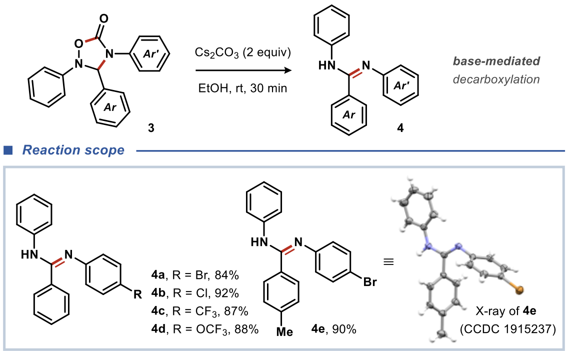
Scheme 1. Silver-Assisted Synthesis of Oxadiazolidinones.[a]



[a] All reactions were carried out with **1a** (0.55 mmol), **2a** (0.5 mmol) and Ag_2O (10 mol%) in 1,4-dioxane (2.0 mL) at 80 °C under air for 4 h. Yields are of isolated products after purification by column chromatogrphy. Products were isolated as single diastereomers.

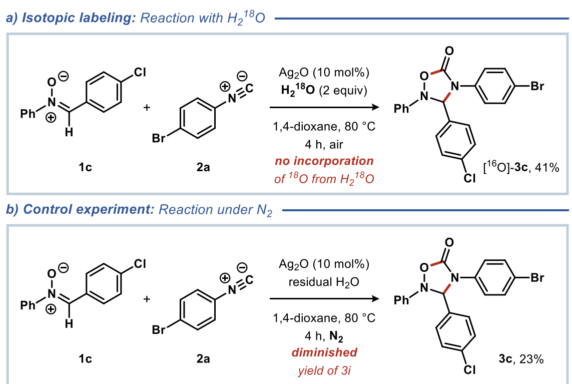
We further explored the application of the synthesized oxadiazolidinones. Intriguingly, subjecting **3a**, **3y**, **3z**, **3ab** and **3ac** to Cs_2CO_3 (2.0 equiv) triggered extrusion of CO_2 to give amidines **4a**–**4e** in up to 92% yield (Scheme 2). Compared to Anderson's reaction conditions,[10d] no reaction occurred using compound **3** even when extending the reaction time to 24 h. Therefore, the developed protocol undoubtedly represents a more general and practical methodology to amidines, complementing the existing ones.

Scheme 2. Application of Oxadiazolidinones to the Synthesis of Amidines through CO_2 Extrusion.



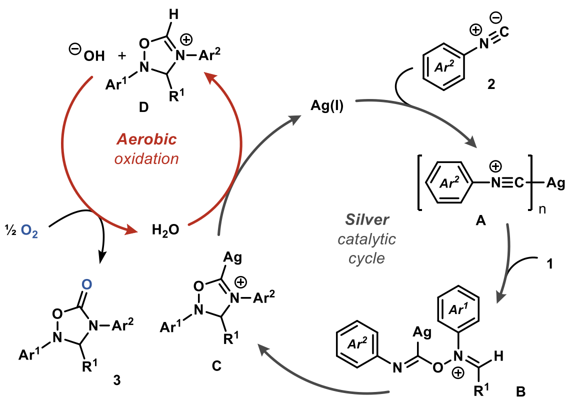
A series of mechanistic experiments was performed to gain insight into the reaction mechanism (Scheme 3). The key step is clearly to derive the source of the carbonyl oxygen that is incorporated in oxadiazolidinone **3**. Therefore, experiments were carried out with **1c** and **2a** under the optimized reactions conditions with addition of 2.0 equiv. of $H_2{}^{18}O$ (Scheme 3a). In the presence of $H_2{}^{18}O$, the reaction between **1c** and **2a** only provides [^{16}O]-**3c**; albeit with a decreased yield.[14] This implies that O_2 is the oxygen source in this reaction. Meanwhile, a decreased yield of product **3c** was obtained when carrying out the reaction under N_2, highlighting that O_2 is necessary for the reaction to proceed efficiently (Scheme 3b).

Scheme 3. Mechanistic Investigations.



Based on the results from the described experiments and related literature precedents,[2,15] a plausible mechanism was proposed (Scheme 4). Initially, isocyanide **2** coordinates to the silver center, generating silver intermediate **A**.[16] Then, it is believed that nitrone **1** attacks complex **A**, producing intermediate **B**. This species presumably undergoes rapid intramolecular cyclization to generate the five-membered cyclized cationic intermediate **C**.[17] Subsequent protodeargentation of intermediate **C** produces **D**, which is oxidized by O_2,[18] delivering product **3** with the regeneration of water and completing the catalytic cycle. Thus, the protodeargentation step can be initiated by residual water present in the solvent or air (*cf*. Scheme 1).

Scheme 4. Proposed Reaction Mechanism for Formation of Oxadiazolidinone 3.



CONCLUSIONS

In summary, we have developed a silver-assisted protocol for [3 + 2] annulation between isocyanides and nitrones, providing a convenient approach for the construction of 2,3,4-trisubstituted 1,2,4-oxadiazolidin-5-ones in good to excellent yields. The reaction mechanism is proposed to proceed through a nucleophilic addition/cyclization/protodeargentation/oxidation pathway. Finally, base-promoted decarboxylation of the prepared oxadiazolidinones at ambient temperature is also described, providing a convenient protocol for the direct assembly of amidine compounds.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial suppliers and used without treatment, unless otherwise indicated. The products were purified by column chromatography on silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian NMR spectrometer at 400 MHz and 101 MHz, respectively. NMR spectra for compounds **3a**–**3ad** were recorded in $CDCl_3$, while compounds **4a**–**4e** displayed spectra containing signals from multiple tautomeric forms and geometrical isomers; however, good quality NMR spectra for these compounds were obtained in $CDCl_3$ upon addition of a small amount of D_2SO_4. Mass spectra were recorded on BRUKER AutoflexIII Smartbeam MS-spectrometer. High-resolution mass spectra (HRMS) were recorded on Bruker microTOF using APCI or ESI ionization methods.

General Procedure for Synthesis of 1,2,4-Oxadiazolidin-5-ones (with 3a as an Example). A 10 mL schlenk flask equipped with a magnetic stir bar was charged with a mixture of **1a** (108 mg, 0.55 mmol), **2a** (90 mg, 0.5 mmol) and 1,4-dioxane (2.0 mL). Then, Ag_2O (12 mg, 10 mol%) was added and the mixture was stirred at 80 °C in an oil bath until substrate **2a** was consumed as indicated by TLC (about 4 h). The resulting mixture was concentrated and the residue was taken up in CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography (silica gel; petroleum ether/ethyl acetate 10:1) afforded **3a** as a white solid (179 mg, 91%).

General Procedure for Synthesis of Amidines (with 4a as an Example). A 10 mL schlenk flask equipped with a magnetic stir bar was charged with a mixture of **3a** (197 mg, 0.5 mmol) and Cs_2CO_3 (325 mg, 1 mmol, 2.0 equiv). Then, EtOH (2.0 mL) was added and the mixture was stirred at room temperature until substrate **3a** was consumed as indicated by TLC (about 30 min). The resulting mixture was concentrated and the residue was taken up in CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography (silica gel; petroleum ether/ethyl acetate 10:3) afforded **4a** as a white solid (147 mg, 84%).

4-(4-Bromophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3a**). Yield: 91% (179 mg). White solid; mp 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.45–7.43 (m, 3H), 7.41–7.36 (m, 4H), 7.24–7.19 (m, 5H), 6.11 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.0, 149.1, 135.2, 134.7, 132.2, 130.2, 129.5, 129.4, 127.1, 125.9, 122.4, 118.8, 117.4, 86.3; HRMS (APCI) *m/z* calculated for $C_{20}H_{16}BrN_2O_2$ $[M + H]^+$: 395.0390, found: 395.0370.

4-(4-Bromophenyl)-2-phenyl-3-(p-tolyl)-1,2,4-oxadiazolidin-5-one (**3b**). Yield: 92% (187 mg). White solid; mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 6H), 7.25–7.19 (m, 7H), 6.07 (s, 1H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.0, 149.1, 140.4, 134.7, 132.2, 132.15, 130.0, 129.4, 127.1, 125.8, 122.5, 118.7, 117.4, 86.3, 21.3; HRMS (APCI) *m/z* calculated for $C_{21}H_{18}BrN_2O_2$ $[M + H]^+$: 409.0552, found: 409.0531.

4-(4-Bromophenyl)-3-(4-chlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3c**). Yield: 87% (186 mg). White solid; mp 160–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 8H), 7.26–7.16 (m, 5H), 6.08 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.8, 148.8, 136.3, 134.4, 133.7, 132.4, 129.6, 129.5, 128.6, 126.2, 122.6, 119.1, 117.5, 85.6; HRMS (APCI) *m/z* calculated for $C_{20}H_{15}BrClN_2O_2$ $[M + H]^+$: 429.0005, found: 429.0017.

3,4-Bis(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3d**). Yield: 89% (209 mg). White solid; mp 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.42–7.35 (m, 6H), 7.25–7.16 (m, 5H), 6.07 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 148.8, 134.4, 134.2, 132.6, 132.4, 129.5, 128.9, 126.2, 124.6, 122.6, 119.2, 117.5, 85.7; HRMS (APCI) *m/z* calculated for $C_{20}H_{15}Br_2N_2O_2$ $[M + H]^+$: 472.9500, found: 472.9471.

4-(4-Bromophenyl)-3-(4-fluorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3e**). Yield: 86% (177 mg). White solid; mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H), 7.41–7.37 (m, 4H), 7.24–7.18 (m, 4H), 7.16–7.10 (m, 3H), 6.10 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 85.7, 116.5 (d, $J_{(F-C)}$ = 21.9 Hz), 117.5, 119.1, 122.7, 126.1, 129.2 (d, $J_{(F-C)}$ = 8.5 Hz), 129.5, 131.1 (d, $J_{(F-C)}$ = 3.2 Hz), 132.3, 134.4, 148.8, 153.8, 163.6 (d, $J_{(F-C)}$ = 248.9 Hz); HRMS (APCI) *m/z* calculated for $C_{20}H_{15}BrFN_2O_2$ $[M + H]^+$: 413.0301, found: 413.0300.

4-(4-Bromophenyl)-2-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazolidin-5-one (**3f**). Yield: 79% (182 mg). White solid; mp 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.44–7.41 (m, 4H), 7.27–7.23 (m, 3H), 7.20–7.18 (m, 2H), 6.18 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 148.9, 139.2, 134.4, 132.5, 132.2, 129.7, 127.6, 126.4, 124.9, 122.4, 122.2, 119.2, 117.5, 85.5; HRMS (APCI) *m/z* calculated for $C_{21}H_{15}BrF_3N_2O_2$ $[M + H]^+$: 463.0269, found: 463.0276.

4-(4-(4-Bromophenyl)-5-oxo-2-phenyl-1,2,4-oxadiazolidin-3-yl)benzonitrile (**3g**). Yield: 63% (132 mg). White solid; mp 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.44–7.40 (m, 4H), 7.28–7.22 (m, 3H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.6, 148.7, 140.2, 134.2, 133.1, 132.6, 129.7, 127.9, 126.5, 122.4, 119.4, 117.8, 117.5, 114.3, 85.2; HRMS (APCI) *m/z* calculated for $C_{21}H_{15}BrN_3O_2$ $[M + H]^+$: 420.0348, found: 420.0353.

4-(4-Bromophenyl)-3-(3-methoxyphenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3h**). Yield: 85% (180 mg). White solid; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 5H), 7.25–7.19 (m, 5H), 7.05–7.03 (m, 2H), 6.97–6.95 (m, 1H), 6.07 (s, 1H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.3, 153.9, 149.1, 136.7, 134.6, 132.2, 130.5, 129.4, 125.9, 122.4, 119.3, 118.8, 117.3, 115.5, 112.7, 86.2, 55.4; HRMS (APCI) *m/z* calculated for $C_{21}H_{18}BrN_2O_3$ $[M + H]^+$: 425.0501, found: 425.0509.

4-(4-Bromophenyl)-3-(3-chlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3i**). Yield: 81% (173 mg). White solid; mp 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.43–7.39 (m, 5H), 7.38–7.33 (m, 2H), 7.25–7.18 (m, 5H), 6.08 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 148.9, 137.4, 135.4, 134.4, 132.4, 130.7, 130.5, 129.6, 127.3, 126.2, 125.2, 122.4, 119.1, 117.4, 85.5; HRMS (APCI) *m/z* calculated for $C_{20}H_{15}BrClN_2O_2$ $[M + H]^+$: 429.0005, found: 429.0011.

4-(4-Bromophenyl)-3-(2-chlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3j**). Yield: 84% (179 mg). White solid; mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 2H), 7.44–7.33 (m, 8H), 7.24–7.21 (m, 3H), 6.70 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.4, 149.3, 134.5, 133.3, 132.4, 132.3, 131.5, 130.5, 129.5, 128.1, 127.9, 126.1, 121.3, 118.6, 117.5, 81.9; HRMS (APCI) *m/z* calculated for $C_{20}H_{15}BrClN_2O_2$ $[M + H]^+$: 429.0005, found: 429.0008.

3-(2-Bromophenyl)-4-(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3k**). Yield: 85% (200 mg). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.42–7.39 (m, 7H), 7.33–7.29 (m, 1H), 7.25–7.21 (m, 3H), 6.69 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.4, 149.1, 134.4, 133.9, 133.8, 132.3, 131.7, 129.5, 128.8, 128.3, 126.2, 123.2, 121.6, 118.7, 117.9, 84.0; HRMS (APCI) *m/z* calculated for $C_{20}H_{15}Br_2N_2O_2$ $[M + H]^+$: 472.9500, found: 472.9504.

4-(4-Bromophenyl)-3-(2-methoxyphenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3l**). Yield: 93% (197 mg). White solid; mp 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 7H), 7.30–7.28 (m, 1H), 7.26–7.24 (m, 2H), 7.20–7.16 (m, 1H), 7.03–6.97 (m, 2H), 6.66 (s, 1H), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR (101

MHz, $CDCl_3$) δ 157.1, 154.6, 150.2, 135.1, 132.1, 131.4, 129.3, 126.8, 125.3, 122.8, 121.3, 120.8, 117.9, 116.6, 111.3, 80.7, 55.7; HRMS (APCI) *m/z* calculated for $C_{21}H_{18}BrN_2O_3$ $[M + H]^+$: 425.0501, found: 425.0470.

4-(4-Bromophenyl)-3-(2,4-dichlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3m**). Yield: 88% (195 mg). White solid; mp 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.51 (m, 1H), 7.46–7.40 (m, 5H), 7.37–7.33 (m, 3H), 7.24–7.19 (m, 3H), 6.64 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.2, 149.0, 137.0, 134.2, 134.0, 132.5, 131.1, 130.4, 129.6, 129.0, 128.6, 126.3, 121.5, 118.9, 117.6, 81.5; HRMS (APCI) *m/z* calculated for $C_{20}H_{14}BrCl_2N_2O_2$ $[M + H]^+$: 462.9616, found: 462.9622.

3-(2-Bromo-4-chlorophenyl)-4-(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3n**). Yield: 94% (229 mg). White solid; mp 108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.6 Hz, 1H), 7.48–7.37 (m, 8H), 7.27–7.23 (m, 1H), 7.21–7.19 (m, 2H), 6.64 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.2, 148.7, 137.0, 134.1, 133.4, 132.5, 132.4, 129.5, 129.2, 129.1, 126.4, 123.6, 121.7, 118.9, 117.9, 83.5; HRMS (APCI) *m/z* calculated for $C_{20}H_{14}Br_2ClN_2O_2$ $[M + H]^+$: 506.9105, found: 506.9122.

3-(Benzo[d][1,3]dioxol-5-yl)-4-(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3o**). Yield: 93% (203 mg). White solid; mp 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 4H), 7.23–7.18 (m, 5H), 7.00 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.01–6.005 (m, 2H), 5.99 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.8, 149.3, 148.8, 134.6, 132.3, 129.4, 128.9, 126.0, 122.9, 121.7, 119.0, 117.6, 108.6, 107.2, 101.7, 86.3, 29.7; HRMS (APCI) *m/z* calculated for $C_{21}H_{16}BrN_2O_4$ $[M + H]^+$: 439.0293, found: 439.0297.

4-(4-Bromophenyl)-3-(2-((4-methoxyphenyl)ethynyl)-4-methylphenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3p**). Yield: 72% (193 mg). White solid; mp 168–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.43–7.41 (m, 5H), 7.38–7.35 (m, 2H), 7.33–7.29 (m, 4H), 7.20–7.14 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 1H), 3.85 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2, 154.2, 149.6, 140.2, 134.8, 133.5, 133.1, 133.06, 132.2, 130.3, 129.3, 126.3, 125.6, 122.9, 121.3, 118.2, 117.3, 114.2, 96.0, 85.2, 83.3, 55.4, 21.1; HRMS (APCI) *m/z* calculated for $C_{30}H_{24}BrN_2O_3$ $[M + H]^+$: 539.0965, found: 539.0973.

4-(4-Bromophenyl)-3-phenyl-2-(m-tolyl)-1,2,4-oxadiazolidin-5-one (**3q**). Yield: 85% (173 mg). White solid; mp 164–165 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.43 (m, 5H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.29–7.25 (m, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 7.03–7.01 (m, 2H), 6.11 (s, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.1, 149.3, 139.6, 135.3, 134.8, 132.2, 130.2, 129.3, 129.26, 127.1, 126.7, 122.3, 118.7, 117.9, 114.3, 86.3, 21.6; HRMS (APCI) *m/z* calculated for $C_{21}H_{18}BrN_2O_2$ $[M + H]^+$: 409.0552, found: 409.0563.

2,4-Bis(4-bromophenyl)-3-phenyl-1,2,4-oxadiazolidin-5-one (**3r**). Yield: 89% (209 mg). White solid; mp 153–154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2H), 7.47–7.43 (m, 5H), 7.40–7.38 (m, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.05 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.6, 148.0, 134.7, 134.4, 132.5, 132.3, 130.5, 129.4, 127.2, 122.7, 119.1, 119.0, 86.3; HRMS (APCI) *m/z* calculated for $C_{20}H_{15}Br_2N_2O_2$ $[M + H]^+$: 472.9500, found: 472.9513.

4-(4-Bromophenyl)-3-phenyl-2-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazolidin-5-one (**3s**). Yield: 77% (178 mg). White solid; mp 134–135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.51–7.46 (m, 5H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.15 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.2, 151.8, 134.7, 134.2, 132.4, 130.6, 129.5, 127.2, 126.8, 126.7, 122.9, 119.4, 116.6, 86.1; HRMS (APCI) *m/z* calculated for $C_{21}H_{15}BrF_3N_2O_2$ $[M + H]^+$: 463.0269, found: 463.0271.

4-(4-Bromophenyl)-3-(furan-2-yl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3t**). Yield: 86% (165 mg), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.44–7.39 (m, 4H), 7.28–7.20 (m, 5H), 6.54–6.53 (m, 1H), 6.42–6.41 (m, 1H), 6.21 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.7, 149.0, 147.9, 144.3, 134.6, 132.3, 129.5, 125.9, 121.9, 118.9, 117.1, 111.0, 110.6, 79.9; HRMS (APCI) *m/z* calculated for $C_{18}H_{14}BrN_2O_3$ [M + H]$^+$: 385.0188, found: 385.0197.

4-(4-Bromophenyl)-2-phenyl-3-(thiophen-2-yl)-1,2,4-oxadiazolidin-5-one (**3u**). Yield: 81% (162 mg). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.38 (m, 5H), 7.25–7.21 (m, 5H), 7.15–7.14 (m, 1H), 7.01–6.99 (m, 1H), 6.38 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.4, 148.5, 138.6, 134.3, 132.4, 129.5, 128.3, 127.9, 127.1, 126.1, 123.2, 119.4, 117.5, 82.4; HRMS (APCI) *m/z* calculated for $C_{18}H_{14}BrN_2O_2S$ [M + H]$^+$: 400.9959, found: 400.9967.

4-(4-Bromophenyl)-3-(naphthalen-1-yl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3v**). Yield: 90% (200 mg). White solid; mp 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 1H), 7.97–7.93 (m, 2H), 7.65–7.55 (m, 3H), 7.49–7.45 (m, 1H), 7.42–7.38 (m, 2H), 7.34–7.24 (m, 5H), 7.20–7.16 (m, 2H), 6.88 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.5, 148.7, 134.8, 134.3, 132.2, 131.1, 130.6, 129.6, 129.5, 129.2, 127.3, 126.7, 126.3, 126.2, 125.3, 122.2, 122.1, 119.0, 118.7, 82.9; HRMS (APCI) *m/z* calculated for $C_{24}H_{18}BrN_2O_2$ [M + H]$^+$: 445.0546, found: 445.0558.

4-(4-Bromophenyl)-3-cyclohexyl-2-phenyl-1,2,4-oxadiazolidin-5-one (**3w**). Yield: 62% (124 mg). White solid; mp 185–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.40–7.36 (m, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.19–7.15 (m, 3H), 5.16 (d, *J* = 3.2 Hz, 1H), 1.85–1.82 (m, 4H), 1.76–1.70 (m, 2H), 1.54–1.39 (m, 2H), 1.33–1.22 (m, 2H), 1.19–1.16 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.3, 151.0, 135.0, 132.5, 129.4, 125.2, 122.3, 118.5, 116.3, 88.9, 40.6, 28.9, 26.0, 25.5; HRMS (APCI) *m/z* calculated for $C_{20}H_{22}BrN_2O_2$ [M + H]$^+$: 401.0859, found: 401.0866.

4-(4-Bromophenyl)-3-(cyclohex-3-en-1-yl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3x**). Yield: 71% (141 mg). White solid; mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.41–7.37 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.21–7.17 (m, 3H), 5.70–5.69 (m, 2H), 5.28–5.25 (m, 1H), 2.37–1.93 (m, 6H), 1.81–1.62 (m, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.3, 150.8, 134.9, 132.5, 129.5, 127.4, 126.5, 125.3, 125.1, 122.6, 116.4, 88.6, 37.1, 27.3, 24.7, 22.0; HRMS (APCI) *m/z* calculated for $C_{20}H_{20}BrN_2O_2$ $[M + H]^+$: 399.0703, found: 399.0709.

2,3,4-Triphenyl-1,2,4-oxadiazolidin-5-one (**3y**). Yield: 90% (142 mg). White solid; mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.08 (m, 15H), 6.21 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.3, 149.5, 135.8, 135.7, 130.1, 129.5, 129.31, 129.3, 127.2, 125.8, 125.7, 121.1, 117.3, 86.5; HRMS (APCI) *m/z* calculated for $C_{20}H_{17}N_2O_2$ $[M + H]^+$: 317.1285, found: 317.1293.

2,3-Diphenyl-4-(m-tolyl)-1,2,4-oxadiazolidin-5-one (**3z**). Yield: 87% (143 mg). White solid; mp 108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2H), 7.45–7.37 (m, 5H), 7.27–7.25 (m, 2H), 7.22–7.18 (m, 2H), 7.16–7.12 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.14 (s, 1H), 2.27 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.3, 149.5, 139.3, 135.9, 135.5, 130.0, 129.4, 129.2, 129.0, 127.1, 126.5, 125.7, 121.7, 118.0, 117.2, 86.5, 21.4; HRMS (APCI) *m/z* calculated for $C_{21}H_{19}N_2O_2$ $[M + H]^+$: 331.1441, found: 331.1449.

4-(4-Chlorophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3aa**). Yield: 83% (145 mg). White solid; mp 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.46–7.43 (m, 3H), 7.42–7.38 (m, 2H), 7.25–7.23 (m, 5H), 7.22–7.20 (m, 2H), 6.11 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.0, 149.2, 135.2, 134.1, 131.1, 130.3, 129.5, 129.4, 129.3, 127.2, 125.9, 122.3, 117.4, 86.4; HRMS (APCI) *m/z* calculated for $C_{20}H_{16}ClN_2O_2$ $[M + H]^+$: 351.0895, found: 351.0899.

2,3-Diphenyl-4-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazolidin-5-one (**3ab**). Yield: 89% (171 mg). White solid; mp 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.44 (m, 9H), 7.43–7.38 (m, 2H), 7.27–

7.26 (m, 1H), 7.25–7.20 (m, 2H), 6.20 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.0, 149.1, 138.84, 138.8, 134.9, 130.3, 129.53, 129.5, 127.0, 126.4, 126.36, 126.1, 119.8, 117.4, 86.0; HRMS (APCI) *m/z* calculated for $C_{21}H_{16}F_3N_2O_2$ $[M + H]^+$: 385.1158, found: 385.1161.

2,3-Diphenyl-4-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazolidin-5-one (**3ac**). Yield: 92% (186 mg). White solid; mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.47–7.44 (m, 3H), 7.42–7.38 (m, 2H), 7.35–7.33 (m, 2H), 7.25–7.20 (m, 3H), 7.13–7.11 (m, 2H), 6.13 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 154.1, 149.1, 146.3, 146.2, 135.2, 134.2, 130.3, 129.5, 129.4, 127.1, 125.9, 122.1, 121.8, 117.3, 86.5; HRMS (APCI) *m/z* calculated for $C_{21}H_{16}F_3N_2O_3$ $[M + H]^+$: 401.1108, found: 401.1112.

4-(2-Nitrophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3ad**). Yield: 72% (129 mg). Yellow solid; mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.97 (m, 1H), 7.57–7.51 (m, 2H), 7.48–7.29 (m, 7H), 7.23–7.12 (m, 3H), 7.91–6.86 (m, 1H), 6.09 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.6, 147.5, 145.9, 134.4, 133.8, 130.7, 130.4, 129.18, 129.17, 129.1, 128.8, 128.1, 126.2, 125.9, 118.6, 87.4; HRMS (APCI) *m/z* calculated for $C_{20}H_{16}N_3O_4$ $[M + H]^+$: 362.1135, found: 362.1139.

N'-(4-Bromophenyl)-N-phenylbenzimidamide (**4a**). Yield: 84% (147 mg). White solid; mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3 + D_2SO_4$) δ 7.40–7.33 (m, 1H), 7.26–7.18 (m, 3H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.09–7.03 (m, 4H), 6.98–6.89 (m, 3H), 6.87–6.77 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3 + D_2SO_4$) δ 135.56, 134.96, 132.44, 132.08, 130.47, 129.20, 129.03, 127.10, 126.81, 125.29, 120.60; HRMS (ESI-TOF) *m/z* calculated for $C_{19}H_{16}BrN_2$ $[M + H]^+$: 351.0491, found: 351.0507.

N'-(4-Chlorophenyl)-N-phenylbenzimidamide (**4b**). Yield: 92% (140 mg). White solid; mp 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3 + D_2SO_4$) δ 14.16 (br s, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.13–7.01 (m, 5H), 6.90 (d, *J* = 6.8 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H); $^{13}C\{^{1}H\}$

NMR (101 MHz, $CDCl_3$ + D_2SO_4) δ 162.02, 136.41, 135.32, 132.17, 131.83, 130.11, 129.27, 128.92, 128.83, 126.42, 126.32, 126.03, 124.95; HRMS (ESI-TOF)) *m/z* calculated for $C_{19}H_{16}ClN_2$ $[M + H]^+$: 307.0997, found: 307.1003.

N-Phenyl-N'-(4-(trifluoromethyl)phenyl)benzimidamide (**4c**). Yield: 87% (147 mg). White solid; mp 110–111 °C; ^1H NMR (400 MHz, $CDCl_3$ + D_2SO_4) δ 14.28 (br s, 1H), 7.52–7.45 (m, 1H), 7.40–7.30 (m, 5H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.18–7.09 (m, 3H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.98–6.92 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ + D_2SO_4) δ 162.24, 139.94, 136.24, 132.50, 130.12, 129.45, 128.93, 128.08, 127.76, 126.68, 126.14, 126.00, 125.97, 125.00, 124.59, 122.36; HRMS (ESI-TOF) *m/z* calculated for $C_{20}H_{16}F_3N_2$ $[M + H]^+$: 341.1260, found: 341.1277.

N-Phenyl-N'-(4-(trifluoromethoxy)phenyl)benzimidamide (**4d**). Yield: 88% (157 mg). White solid; mp 82–84 °C; ^1H NMR (400 MHz, $CDCl_3$ + D_2SO_4) δ 7.45 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.16–7.03 (m, 3H), 7.01–6.85 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ + D_2SO_4) δ 162.05, 146.90, 136.44, 135.39, 132.26, 130.08, 129.32, 128.86, 126.44, 126.33, 126.04, 124.92, 121.56, 121.31, 119.00; HRMS (ESI-TOF) *m/z* calculated for $C_{20}H_{16}F_3N_2O$ $[M + H]^+$: 357.1209, found: 357.1217.

N'-(4-Bromophenyl)-4-methyl-N-phenylbenzimidamide (**4e**). Yield: 90% (163 mg). White solid; mp 121–122 °C; ^1H NMR (400 MHz, $CDCl_3$ + D_2SO_4) δ 7.27 (d, *J* = 8.6 Hz, 1H), 7.23–7.14 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.05–6.94 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ + D_2SO_4) δ 163.51, 144.00, 132.34, 130.60, 130.11, 129.27, 127.41, 126.67, 126.63, 125.16, 125.12, 121.58, 120.98, 21.73; HRMS (ESI-TOF) *m/z* calculated for $C_{20}H_{18}BrN_2$ $[M + H]^+$: 365.0648, found: 365.0657.

ASSOCIATED CONTENT

Supporting Information

NMR spectra of compounds **3** and **4**, and X-ray crystallographic data for compounds **3a** and **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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