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SYNTHESIS AND REACTIVITY OF NOVEL 5-IMINO-1,2-OXAZOLE

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Abstract – A convenient synthetic approach towards 5-imino-1,2-oxazoles beginning from *N*-substituted *C*-benzotriazolated nitrones and Reformatsky reaction reagent is developed. The conversion of trisubstituted 5-imino-1,2-oxazoles into the corresponding 5-functionalized 1,2-oxazoles by interactions with phenyl isocyanates and 20% HCl is provided. In addition, one-pot synthesis of 1,2-oxazole-5-ones is achieved with yield of 85-90%

INTRODUCTION

Development of simple methods for the synthesis of new analogs of bioactive heterocyclic compounds is of extreme importance in heterocyclic and medicinal chemistry. The yet unknown 5-imino-1,2-oxazoles (**I**) are analogs of 1,2-oxazol-5-ones (**II**) (Figure 1), a class of compounds which are useful synthetic intermediates for the preparation of heterocyclic compounds,[1-4] and has attracted considerable attention in medicinal chemistry due to their pharmacological activity,[5,6] as well as remarkable activity as anti-inflammatory agents,[5,7] and anti-cancer agents.[8,9] They are also used for the treatment of central nervous system disorder.[10,11]

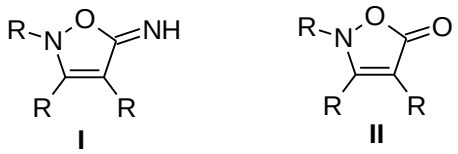
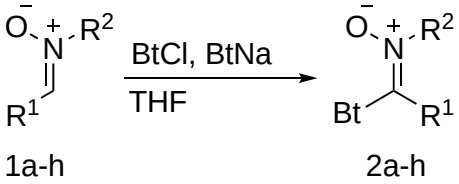


Figure 1. 5-Imino-1,2-oxazoles (**I**) and 1,2-oxazol-5-ones (**II**)

As part of our ongoing studies on applications of benzotriazole (BtH) in organic synthesis and on development of new protocols for the synthesis of heterocyclic compounds we investigated the applicability of *C*-benzotriazolated nitrones for the synthesis of 5-imino-1,2-oxazoles **I**.[12-15]

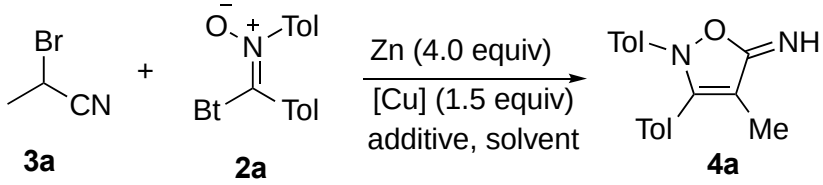
RESULTS AND DISCUSSION

Diaryl (heteroaryl) nitrones **1a-h** were prepared following literature procedures.[16-18] Treatment of **1a-h** with chlorobenzotriazole (BtCl) and sodium benzotriazolate (BtNa) in THF furnished exclusively **2a-h** in high overall yields according to an established procedure (Scheme 1).[15]



Scheme 1. Synthesis of *C*-benzotriazolated nitrones

Then, *N*-[(1*H*-benzotriazol-1-yl)-(4-methylphenyl)methylene]-4-methylbenzenamine oxide (**2a**) was used as the substrate to investigate the Reformatsky reaction of 2-bromopropionitrile (**3a**) to prepare 5-imino-4-methyl-2,3-di(4-methylphenyl)-2*H*-1,2-oxazole (**4a**) (Scheme 2).



Scheme 2. Synthesis of 5-imino-1,2-oxazole **4a**

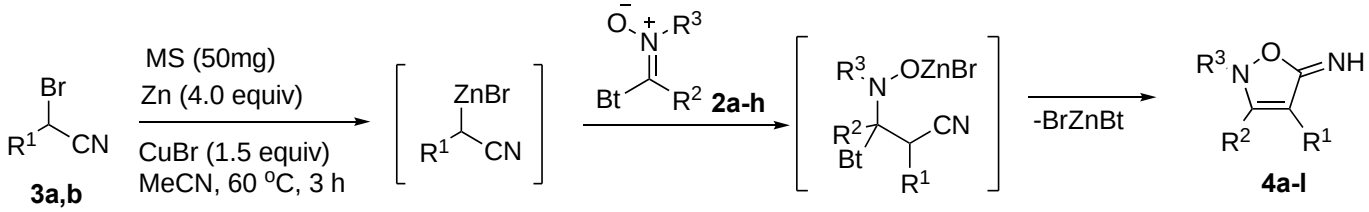
Table 1. Screening of reaction conditions for synthesis of 5-imino-1,2-oxazole **4a**

Entry	[Cu]	Additive	Solvent	Temperature, ^{o}C	Time, h	Yield, %
1	-	-	THF	rt	5	20
2	-	-	THF	60	5	35
3	-	-	MeCN	60	3	38
4	CuBr	-	MeCN	60	3	65
5	CuI	-	MeCN	60	3	57
6	CuBr	4 Å MS	MeCN	60	3	85
7	CuBr	4 Å MS	THF	60	3	82
8	CuBr	4 Å MS	CH_2Cl_2	40	3	15
9	CuBr	4 Å MS	PhMe	60	3	7

When the reaction was carried out with 4.0 equivalents of zinc powder in THF at room temperature, the desired product **4a** was obtained in 20% yield (Table1, entry 1). When the reaction was carried out at 60 ^{o}C in THF or MeCN, compound **4a** was still obtained in low yields of 35% and 38% respectively (Table 1,

entry 2 and 3). Next we used MeCN in the presence of various Cu(I) species; CuBr and CuI were found to improve the yields of **4a** to 65% and 57%, respectively (Table 1, entries 4 and 5). When molecular sieves (MS) were added to the reaction mixture, **4a** was obtained in 85% yield (Table 1, entry 6). Further examination of solvent effects revealed that THF, in the presence of molecular sieves, afforded a result similar to that noted when using MeCN as solvent (Table 1, entry 7). Very low yield was obtained when using CH_2Cl_2 or PhMe as solvents (Table 1, entries 8 and 9). Consequently, the optimal reaction conditions were assigned to include 4.0 equivalents of zinc and 1.5 equivalents of CuBr in the presence of molecular sieves in MeCN at 60 ^oC for 3 h.

Using the optimized conditions, the scope and generality of the method was examined. A number of benzotriazolated nitrones **2a-h** and 2-bromonitriles with aryl and heteroaryl groups were converted to the corresponding trisubstituted 5-imino-1,2-oxazoles **4a-i** in good to high yields (75-91%) in short time under mild conditions (Scheme 3, Table 2).

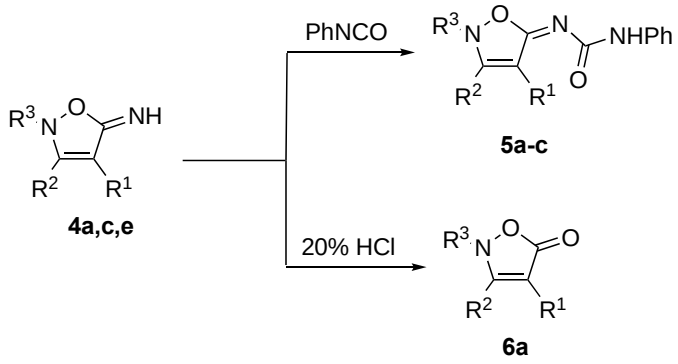


Scheme 3. Reformatsky reaction of 1-bromonitriles **3a,b** and *C*-benzotriazolated nitrones **2a-h**

Table 2. The yields of trisubstituted 5-imino-1,2-oxazoles **4a-l**

Product	R^1	R^2	R^3	Yield, %
4a	Me	4-MeC_6H_4	4-MeC_6H_4	85
4b	Me	Ph	Ph	88
4c	Me	furan-2-yl	Ph	91
4d	Me	thiophen-2-yl	Ph	89
4e	Me	pyridin-3-yl	Ph	82
4f	Me	4-$MeOC_6H_4$	Ph	84
4g	Me	4-$MeOC_6H_4$	4-ClC_6H_4	75
4h	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	79
4i	Ph	4-MeC_6H_4	4-MeC_6H_4	78
4j	Ph	furan-2-yl	Ph	82
4k	Ph	thiophen-2-yl	Ph	80
4l	Ph	pyridin-3-yl	Ph	75

Next, we investigated the synthetic potential of 5-imino-1,2-oxazoles **4a,c,e** as precursors in the preparation of 5-functionalized 1,2-oxazole derivatives. Reactions of 5-imino-1,2-oxazoles **4a,c,e** with phenyl isocyanate afforded the corresponding urea derivatives **5a-c** in high yields (85-92%). Acidic hydrolysis of 5-imino-1,2-oxazole **4a** with 20% HCl afforded the 1,2-oxazol-5-one **6a** in high yield (95%) (Scheme 4, Table 3).



Scheme 4. Reactions of 5-imino-1,2-oxazoles **4a,c,e** with phenylisocyanates and 20% HCl

Table 3. The yields of 5-functionalized 1,2-oxazoles

Starting material	Product	R^1	R^2	R^3	Yield, %
4a	**5a**	Me	4-MeC_6H_4	4-MeC_6H_4	92
4c	**5b**	Me	furan-2-yl	Ph	88
4e	**5c**	Me	pyridin-3-yl	Ph	85
4a	**6a**	Me	4-MeC_6H_4	4-MeC_6H_4	95

The smooth conversion of 5-imino-1,2-oxazole **4a** into 1,2-oxazol-5-one **6a** promoted us to develop the one-pot protocol for the synthesis of 1,2-oxazol-5-ones **6a-c**. Treatment of 2-bromopropoinitrile (**3a**) with compounds **2a,c,d** in THF afforded 5-imino-1,2-oxazoles **4a,c,d** as intermediates, which upon treatment with 20% HCl at room temperature for 3 h underwent hydrolysis to give 1,2-oxazol-5-ones **6a-c** in high yields (85-90%) (Scheme 5, Table 4). The overall yield of 1,2-oxazol-5-one **6a** is comparable in one-pot and multistep procedures.

Table 4. One-pot synthesis of 1,2-oxazol-5-ones **6**

Product	R^1	R^2	R^3	Yield, %
6a	Me	4-MeC_6H_4	4-MeC_6H_4	85
6b	Me	thiophen-2-yl	Ph	88
6c	Me	furan-2-yl	Ph	90

The structures of all synthesized compounds (**4-6**) were all elucidated by IR ^{1}H, ^{13}C NMR, MS spectroscopy and elemental analysis.

In conclusion, we have synthesized a variety of novel 5-imino-1,2-oxazole derivatives, furthermore, we have developed a new and operationally simple one-pot protocol for the synthesis of 1,2-oxazol-5-ones.

EXPERIMENTAL

Melting points were determined on a Reichert hot-stage microscope and are uncorrected; The NMR spectra were recorded eith a Varian 300 MHz instrument (300 MHz for ^{1}H and 75 MHz for ^{13}C) in DMSO-d_6 using TMS as an internal standard. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. MS spectra were measured by a JEOL JMS AX505 HA spectrometer. Column chromatography was performed on silica gel 200-245 mesh. *C*-Benzotriazolated nitrones **2a-h** were prepared according to previously published procedures.[16]

Synthesis of 5-imino-1,2-oxazoles 4a-l (general method): 1-Bromonitrile **3a,b** (1.0 mmol) and molecular sieves (4 Å, 50 mg) was added to a suspension of zinc (4.0 mmol) and CuBr (1.5 mmol) in MeCN (3.0 mL) and the mixture was stirred for 1 h at room temperature followed by addition of *C*-benzotriazolated nitrones **2a-h** (1.0 mmol) dissolved in MeCN (1 mL). The reaction mixture was heated to 60 ^{o}C for 3 h and cooled to room temperature. The mixture was filtered, concentrated under reduced pressure and the residue subjected to column chromatography on silica gel using EtOAc-hexane, 9:1 as eluent.

4-Methyl-2,3-di(*p*-tolyl)isoxazol-5(2*H*)-imine (4a): Yield 237 mg (85%), colorless crystals, mp 192-194 ^{o}C; IR (KBr): ν 1660 cm^{-1} (C=N). ^{1}H NMR δ 2.02 (s, 3H), 2.22 (s, 3H), 2.30 (s, 3H), 6.93 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 20.7, 21.3, 21.4, 118.3, 128.1, 128.7, 129.1, 129.3, 132.0, 132.6, 137.4, 139.8, 147.4, 165.1; MS *m/z*: 278. Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.52; H, 6.40; N, 10.10.

4-Methyl-2,3-diphenylisoxazol-5(2*H*)-imine (4b): Yield 220 mg (88%), colorless crystals, mp 186-188 ^{o}C; IR (KBr): ν 1665 cm^{-1} (C=N). ^{1}H NMR δ 1.93 (s, 3H), 6.66 (d, *J* = 8.1 Hz, 2), 7.26-7.46 (m, 6H), 7.58-7.64 (m, 2H); ^{13}C NMR δ 18.0, 116.6, 124.8, 126.7, 128.6, 128.7, 128.9, 129.3, 131.8, 137.4, 147.3, 162.2; MS *m/z*: 250. Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.82; H, 5.72; N, 11.08.

3-Furan-2-yl-4-methyl-2-phenylisoxazol-5(2*H*)-imine (4c): Yield 219 mg (91%), colorless crystals, mp 162-164 ^{o}C; IR (KBr): ν 1670 cm^{-1} (C=N). ^{1}H NMR δ 1.89 (s, 3H), 6.39 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 3.4, 0.8 Hz, 1H), 7.35-7.63 (m, 3H), 7.74 (dd, *J* = 1.8, 0.8 Hz, 1H); ^{13}C NMR δ 18.1, 109.7, 110.8, 116.7, 124.8, 128.7, 129.2, 137.5, 143.1, 145.4, 147.4, 162.3; MS *m/z*: 240. Anal. Calcd. for $C_{14}H_{12}N_2O_2$: %: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.06; H, 5.10; N, 11.55.

4-Methyl-2-phenyl-3-thiophen-2-ylisoxazol-5(2*H*)-imine (4d): Yield 228 mg (89%), colorless crystals, mp 159-161 ºC; IR (KBr): ν 1666 cm^{-1} (C=N). ^{1}H NMR δ 1.94 (s, 3H), 6.67 (d, *J* = 8.1 Hz, 2H), 7.13 (dd, *J* = 7.1, 4.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.53 (dd, *J* = 4.5, 1.3 Hz, 1H), 7.60-7.68 (3H, m); ^{13}C NMR δ 18.0, 116.7, 124.8, 126.1, 126.3, 127.4, 128.7, 129.2, 133.6, 137.5, 147.4, 162.3; MS *m/z*: 256. Anal. Cacld. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.51; H, 4.81; N, 11.01.

4-Methyl-2-phenyl-3-pyridin-3-ylisoxazol-5(2*H*)-imine (4e): Yield 206 mg (82%), colorless crystals, mp 201-203 ºC; IR (KBr): ν 1670 cm^{-1} (C=N). ^{1}H NMR δ 1.90 (s, 3H), 6.67 (d, *J* = 8.1 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.46-7.75 (m, 4H), 8.55 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.92 (dd, *J* = 1.9, 1.6 Hz, 1H). ^{13}C NMR δ 18.0, 116.7, 123.9, 124.7, 128.6, 128.7, 129.2, 131.3, 137.5, 145.0, 147.4, 149.8, 162.3; MS *m/z*: 251. Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.60; H, 5.11; N, 16.56.

3-(*p*-Methoxyphenyl)-4-methyl-2-phenylisoxazol-5(2*H*)-imine (4f): Yield 235 mg (84%), colorless crystals, mp 182-184 ºC; IR (KBr): ν 1665 cm^{-1} (C=N). ^{1}H NMR δ 2.22 (s, 3H), 3.73 (s, 3H), 6.65 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.35-7.53 (m, 3H), 7.64 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR δ 18.0, 55.5, 114.2, 116.7, 124.7, 128.7, 129.1, 129.2, 131.9, 137.5, 147.4, 160.4, 162.3; MS *m/z*: 280. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.68; H, 5.88; N, 10.07.

2-(*p*-Chlorophenyl)-3-(*p*-methoxyphenyl)-4-methylisoxazol-5(2*H*)-imine (4g): Yield 236 mg (75%), colorless crystals, mp: 210-212 ºC; IR (KBr): ν 1672 cm^{-1} (C=N). ^{1}H NMR δ 2.24 (s, 3H), 3.77 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.50-7.60 (m, 6H). ^{13}C NMR δ 18.0, 55.5, 114.2, 124.9, 127.8, 129.1, 129.2, 129.4, 131.9, 137.5, 147.4, 160.4, 162.3; MS *m/z*: 314. Anal. Calcd. For $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.92; H, 4.72; N, 8.73.

2,3-di-(*p*-Methoxyphenyl)-4-methylisoxazol-5(2*H*)-imine (4h): Yield 245 mg (79%), colorless crystals, mp 204-206 ºC; IR (KBr): ν 1677 cm^{-1} (C=N). ^{1}H NMR δ 2.24 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 18.0, 55.4, 55.5, 114.2, 115.1, 117.3, 129.1, 129.3, 131.9, 137.5, 147.4, 156.9, 160.4, 162.3; MS *m/z*: 310. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.73; H, 5.93; N, 8.94.

4-Phenyl-2,3-di-(*p*-tolyl)isoxazol-5(2*H*)-imine (4i): Yield 266 mg (78%), colorless crystals, mp 198-200 ºC; IR (KBr): ν 1660 cm^{-1} (C=N). ^{1}H NMR δ 2.22 (s, 3H), 2.31 (s, 3H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.26-7.38 (m, 7H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR δ 21.2, 21.3, 118.2, 127.5, 128.3, 128.6, 128.9, 129.0, 129.2, 129.3, 131.8, 132.4, 132.7, 137.5, 139.7, 147.4, 162.3; MS *m/z*: 340. Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.34; H, 6.01; N, 8.12.

3-Furan-2-yl-2,4-diphenylisoxazol-5(2*H*)-imine (4j): Yield 248 mg (82%), pale yellow crystals, mp 170-172 ºC; IR (KBr): ν 1672 cm^{-1} (C=N). ^{1}H NMR δ 6.56 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.24-7.44 (m, 7H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.81 (dd, *J* = 1.8, 0.8 Hz, 1H); ^{13}C NMR δ 109.7, 110.8,

116.7, 124.7, 127.5, 128.6, 128.7, 128.9, 129.2, 132.7, 137.5, 143.0, 145.4, 147.4, 162.3; MS *m/z*: 302. Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.56; H, 4.78; N, 9.14.

2,4-Diphenyl-3-thiophen-2-ylisoxazol-5(2*H*)-imine (4k): Yield 255 mg (80%), pale yellow crystals, mp 168-170 ºC; IR (KBr): ν 1665 cm^{-1} (C=N). ^1H NMR δ 7.05 (d, *J* = 8.2 Hz, 2H), 7.19 (dd, *J* = 7.3, 5.2 Hz, 1H), 7.27-7.31 (m, 2H), 7.42-7.55 (m, 5H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.78 (dd, *J* = 7.3, 1.3 Hz, 1H); ^{13}C NMR δ 116.7, 124.7, 126.1, 126.3, 127.4, 127.5, 128.6, 128.7, 128.9, 129.2, 132.7, 133.6, 137.5, 147.4, 162.3; MS *m/z*: 318. Anal. Calcd. for $C_{19}H_{14}N_2OS$: C, 71.67; H, 4.43; N, 8.80. Found: C, 71.56; H, 4.51; N, 8.95.

2,4-Diphenyl-3-pyridin-3-ylisoxazol-5(2*H*)-imine (4l): Yield 235 mg (75%), colorless crystals, mp 218-220 ºC; IR (KBr): ν 1666 cm^{-1} (C=N). ^1H NMR δ 7.05 (d, *J* = 8.2 Hz, 2H), 7.27-7.52 (m, 7H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.99 (ddd, *J* = 8.2, 1.9, 1.7 Hz, 1H), 8.59 (ddd, *J* = 4.8, 1.9, 1.9 Hz, 1H), 8.93 (ddd, *J* = 1.9, 1.7, 0.5 Hz, 1H); ^{13}C NMR δ 116.7, 123.9, 124.7, 127.5, 128.5, 128.6, 128.7, 128.9, 129.2, 131.3, 132.7, 137.5, 145.0, 147.4, 149.7, 162.3; MS *m/z*: 313. Anal. Calcd. for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.82; H, 4.90; N, 13.29.

Synthesis of compounds 5a-c (general method): Phenyl isocyanate (1.0 mmol) was added to a solution of **4a-c** (1.0 mmol) in anhydrous THF (5.0 mL) under ice cooling, and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the remaining mixture was purified by column chromatography on silica gel with EtOAc-hexane, 8:2 as an eluent. Crystallization from EtOAc-hexane afforded compounds **5a-c** as white powder.

1-(4-Methyl-2,3-di(*p*-tolyl)isoxazol-5(2*H*)-ylidene)-3-phenylurea (5a): Yield 366 mg (92%), colorless crystals, mp 207-209 ºC; IR (KBr): ν 1695, 1720 cm^{-1} (C=N, C=O). ^1H NMR δ 2.22 (s, 3H), 2.25 (s, 3H), 2.34 (s, 3H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.21-7.37 (m, 8H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 18.0, 21.2, 21.3, 118.2, 118.9, 124.7, 128.3, 128.9, 129.1, 129.2, 129.3, 131.8, 132.4, 135.5, 137.5, 139.7, 147.4, 158.2, 162.3; MS *m/z*: 397. Anal. Calcd. for $C_{25}H_{23}N_3O_2$: C, 75.55; H, 5.83; N, 10.57. Found: C, 75.61; H, 5.72; N, 10.69.

1-(3-Furan-2-yl-4-Methyl-2-phenylisoxazol-5(2*H*)-ylidene)-3-phenylurea (5b): Yield 316 mg (88%), colorless crystals, mp 201-203 ºC; IR (KBr): ν 1690, 1725 cm^{-1} (C=N, C=O). ^1H NMR δ 2.24 (s, 3H), 6.57 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.27-7.44 (m, 6H), 7.63-7.77 (m, 4H), 7.90 (dd, *J* = 1.8, 0.8 Hz, 1H); ^{13}C NMR δ 18.0, 109.7, 110.8, 116.7, 118.9, 124.7, 125.0, 128.7, 129.1, 129.2, 135.5, 137.5, 143.0, 145.4, 147.4, 158.2, 162.3; MS *m/z*: 359. Anal. Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.01; H, 4.59; N, 11.78.

1-(4-Methyl-2-phenyl-3-pyridin-3-ylisoxazol-5(2*H*)-ylidene)-3-phenylurea (5c): Yield 315 mg (85%), colorless crystals, mp 240-242 ºC; IR (KBr): ν 1695, 1722 cm^{-1} (C=N, C=O). ^1H NMR δ 2.22 (s, 3H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.27-7.50 (m, 6H), 7.60-7.70 (m, 4H), 7.98 (ddd, *J* = 8.2, 1.9, 1.6 Hz, 1H), 8.65

(ddd, *J* = 4.7, 1.9, 1.8 Hz, 1H), 9.19 (ddd, *J* = 1.9, 1.6, 0.5 Hz, 1H); ^{13}C NMR δ 18.0, 116.7, 118.9, 123.9, 124.7, 125.0, 128.6, 128.7, 129.1, 129.2, 131.3, 135.5, 137.5, 145.0, 147.4, 149.8, 158.2, 162.3; MS *m/z*: 370. Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13. Found: C, 71.22; H, 5.03; N, 14.96.

Synthesis of 1,2-oxazol-5-one 6a from 4-methyl-5-phenylcarbamoylimino-2,3-di(*p*-tolyl)-2*H*-1,2-oxazole (6a):

Aqueous HCl (5.0 mL, 20%) was added to a solution of **4** (1.0 mmol) in THF (3.0 mL) and the mixture was stirred at room temperature for 3 h. The mixture was extracted with CH_2Cl_2 (3 x 5.0 mL), the combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was chromatographed using EtOAc-hexane, 8:2.

One-pot synthesis of 1,2-oxazol-5-ones 6a-c (general method):

1-Bromonitrile (1.0 mmol) and molecular sieves (4 Å, 50 mg) were added to a suspension of zinc (1.0 mmol) and CuBr (0.25 mmol) in THF (3.0 mL) and the mixture was stirred for 1 h at room temperature followed by addition of **2** (1.0 mmol) dissolved in THF (1.0 mL). The reaction mixture was heated to 60 ^{o}C for 3 h and cooled to room temperature. Aqueous HCl (5.0 mL, 20%) was added to the mixture and stirred at room temperature for 3 h. The mixture was extracted with CH_2Cl_2 (3 x 7.0 mL), the combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was chromatographed using EtOAc-hexane 8:2.

4-Methyl-2,3-di-(*p*-tolyl)isoxazol-5(2*H*)-one (6a): Yield 224 mg (85%), colorless crystals, mp 172-174 ^{o}C; IR (KBr): ν 1730 cm^{-1} (C=O). ^{1}H NMR δ 1.91 (s, 3H), 2.22 (s, 3H), 2.29 (s, 3H), 6.99 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR δ 18.0, 21.2, 21.3, 118.2, 128.3, 128.9, 129.2, 129.3, 131.8, 132.5, 137.5, 139.8, 147.4, 169.1; MS *m/z*: 263. Anal. Calcd. for $C_{18}H_{17}NO$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.53; H, 6.27; N, 4.92.

4-Methyl-2-phenyl-3-thiophen-2-ylisoxazol-5(2*H*)-one (6b): Yield 226 mg (88%), colorless crystals, mp 142-144 ^{o}C; IR (KBr): ν 1735 cm^{-1} (C=O). ^{1}H NMR δ 1.91 (s, 3H), 6.95 (m, 2H), 7.13 (dd, *J* = 7.0, 4.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.64-7.70 (m, 3H), 7.75 (dd, *J* = 7.0, 1.3 Hz, 1H); ^{13}C NMR δ 18.0, 116.7, 124.7, 126.1, 126.3, 127.4, 128.7, 129.2, 133.6, 137.5, 147.4, 169.1; MS *m/z*: 257. Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.46; H, 4.44; N, 5.29.

3-Furan-2-yl-4-methyl-2-phenylisoxazol-5(2*H*)-one (6c): Yield 217 mg (90%), colorless crystals, mp 138-140 ^{o}C; IR (KBr): ν 1730 cm^{-1} (C=O). ^{1}H NMR δ 1.90 (s, 3H), 6.55 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.25 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.28-7.64 (m, 5H), 7.79 (dd, *J* = 1.8, 0.8 Hz, 1H); ^{13}C NMR δ 18.0, 109.7, 110.8, 116.7, 124.7, 128.7, 129.2, 137.5, 143.0, 145.4, 147.4, 169.1; MS *m/z*: 241. Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.82; H, 4.48; N, 5.93.

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