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One-pot synthesis of novel *N,N*-bis(isoxazol-5-yl) methyl tertiary arylamines via sequential diprop-3-ynylation and 1,3-dipolar cycloaddition from primary amines

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Abstract

A simple and efficient one-pot multicomponent approach for the synthesis of tertiary arylamines bearing *N,N*-bis(isoxazol-5-yl)methyl groups is developed through reactions including sequential diprop-3-ynylation of primary amines with propargyl bromide in the presence of calcium hydride in *N,N*-dimethylformamide, and 1,3-dipolar cycloaddition with nitrile oxides generated in situ from hydroximyl chlorides in DMF-Et_3N. This protocol provides advantages such as high regioselectivity, easy operation, and moderate-to-good product yields with a wide substrate scope under mild conditions.

Keywords

1,3-dipolar cycloaddition, diprop-3-ynylation, nitrile oxides, *N,N*-bis(isoxazol-5-yl)methyl tertiary arylamines, one-pot procedure

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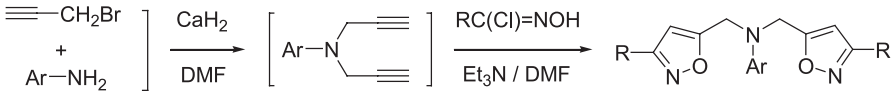
Copies of ^1H NMR and ^{13}C NMR spectra of all compounds



Introduction

Amines and isoxazoles are examples of nitrogen-containing compounds occupying a significant position in many fields such as organic chemistry, natural products, materials science, and pharmaceuticals. A secondary or tertiary amino group is often embedded as a structural motif in various biologically active compounds, which are important intermediates in the synthesis of pharmaceutically active substances, dyes, and fine chemicals.[1] The formation of C–N bonds between primary amines and organic halides has been applied as the major method to prepare secondary and tertiary amines.[2–4] Isoxazoles are important five-membered heteroaromatic molecules because of their wide applications in organic synthesis, pharmacy, chemistry, biologically active molecules, and advanced organic materials.[5,6] Among various synthetic methods for the synthesis of isoxazoles, the major routes typically involve 1,3-dipolar cycloadditions of alkenes/alkynes and nitrile oxides.[7–11] Introduction of the isoxazole scaffold into amine molecules represents a meaningful research area for the exploration of biologically active compounds and pharmaceutical agents. As far as we know, several synthetic methods have been developed for the construction of isoxazolyl-containing

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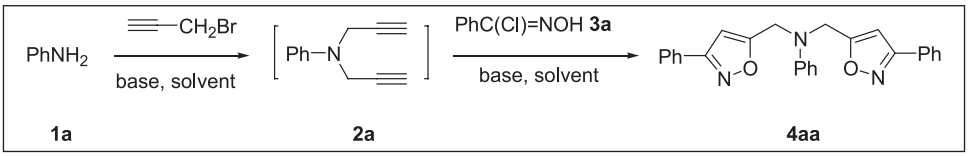


Scheme 1. Optimization of the one-pot reaction from aniline **1a**.

primary,[12–16] secondary, and tertiary amines.[17–21] However, there are very few reports on the synthesis of tertiary arylamines with isoxazolyl groups.[21] Therefore, the development of simple, efficient, and economical protocols for the synthesis of isoxazole-containing tertiary arylamines using readily accessible starting material will be of great use. It is well known that multicomponent reactions (MCRs) are very useful synthetic methods because they allow rapid and convergent construction of complex molecules without the isolation of intermediates.[22–24] Moreover, this process is especially useful when the reaction intermediates are unstable and difficult to isolate. Obviously, in order to construct isoxazole scaffolds, the generation of terminal alkynes in situ from suitable precursors, followed by reaction with nitrile oxides in a one-pot process, would avoid the difficulties associated with the volatile nature of terminal alkynes. Herein, we report a highly regioselective one-pot MCR protocol for the facile synthesis of *N,N*-bis(isoxazol-5-yl) methyl tertiary arylamines involving in situ generation of terminal alkynes, *N,N*-di(prop-2-yn-1-yl) arylamines via diprop-3-ynylation of primary amines with propargyl bromide and 1,3-dipolar cycloaddition with nitrile oxides under mild reaction conditions.

Results and discussion

Initially, the diprop-3-ynylation conditions, such as the base and solvent, for the reaction of aniline (**1a**) with propargyl bromide were investigated (Scheme 1). It was reported that *N,N*-di(prop-2-yn-1-yl)aniline (**2a**) could be obtained in 80% yield by reaction of **1a** with propargyl bromide in *N,N*-dimethylformamide (DMF) at room temperature in the presence of potassium carbonate.[25] Encouraged by this positive result, other polar solvents and bases were screened (Table 1, entries 2–8). Clearly, good yields of **2a** in the model reaction were obtained in DMF and dimethylsulfoxide (DMSO) in the presence of different bases such as potassium carbonate, *N,N*-diisopropylethylamine (DIPEA), and calcium hydride (CaH_2) (Table 1, entries 1, 2, 7, and 8). Among them, CaH_2 was shown to be a very effective base for the reaction (Table 1, entry 8). After a considerable number of experiments, **2a** was produced in 95% yield when the reaction was carried out in DMF at room temperature in the presence of CaH_2 (40 mol%) for 8 h (Table 1, entry 11).

Second, after completion of the diprop-3-ynylation, the excess propargyl bromide was removed by vacuum distillation. Without further isolation and purification of intermediate **2a**, the subsequent [3 + 2] cycloaddition reaction with phenyl nitrile oxide, generated in situ from *N*-hydroxybenzimidoyl chloride (**3a**), affording *N,N*-bis[(3-phenylisoxazol-5-yl)methyl]aniline (**4aa**) was investigated.

Table 1. Optimization of the diprop-2-ynylation conditions.[a]

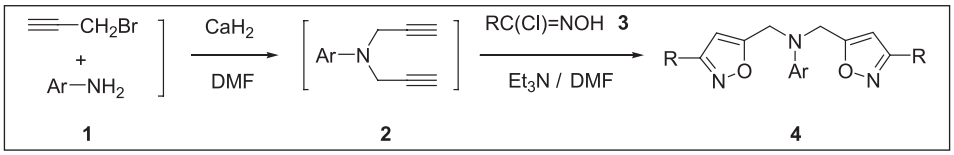
Entry	Solvent	Base (mol%)	Time (h)	Yield (%)[b]
1	DMF	K_2CO_3 (20)	6	80[c]
2	DMSO	K_2CO_3 (20)	6	78
3	Dioxane	K_2CO_3 (20)	6	65
4	MeCN	K_2CO_3 (20)	6	68
5	THF	K_2CO_3 (20)	6	60
6	DMF	Et_3N (20)	6	72
7	DMF	DIPEA (20)	6	82
8	DMF	CaH_2 (20)	6	85
9	DMF	CaH_2 (30)	6	90
10	DMF	CaH_2 (40)	6	92
11	DMF	CaH_2 (40)	8	95
12	DMF	CaH_2 (50)	8	96

DMF: *N,N*-dimethylformamide; DMSO: dimethylsulfoxide; THF: tetrahydrofuran; DIPEA: *N,N*-diisopropylethylamine.
[a]Unless otherwise noted, all reactions were performed with 1.0 mmol of aniline, 4.0 mmol of propargyl bromide, and 5 mL of solvent at room temperature.
[b]Isolated yield after column chromatography, based on aniline.
[c]Cited in Ji et al.[25]

In our initial attempt involving treatment of the reaction system with 2 equiv. of **3a** without adding another base for 6 h at room temperature resulted in **4aa** in only 35% isolated yield. A further attempt to run the [3 + 2] cycloaddition reaction at an elevated temperature did not work well. However, when 3 equiv. of Et_3N were added to the reaction system, the corresponding product **4aa** was isolated in 72% yield. Indeed, the use of 2.5 equiv. of **3a** was found to increase the yield to 76%. In addition, it was found that using additional Et_3N and **3a** did not increase the yield or shorten the reaction time. To our delight, when the reaction proceeded at 65 °C for 3 h, the desired product **4aa** was isolated in 82% yield as the exclusive product.

The structure of **4aa** was characterized by nuclear magnetic resonance (NMR) spectroscopic data. In the ^{1}H NMR spectrum of **4aa**, a characteristic singlet appeared at 6.95 ppm due to the isoxazolyl C5–*H* proton and a singlet at 4.61 ppm for ArNCH_2 along with other protons. In the ^{13}C NMR spectrum of **4aa**, the ArN*C*H_2 carbon appeared at 48.23 ppm, carbons of *C*4 and *C*5 of the triazole ring appeared at 102.34 and 169.85 ppm, respectively, along with other carbons at expected chemical shifts.

Finally, the optimized reaction conditions were extended to a variety of primary aromatic amines and hydroximyl chlorides with different substituents (Scheme 2), and the corresponding results were summarized in Table 2. As observed in Table 2, for most of the examined substrates, the reactions were performed smoothly and the corresponding tertiary arylamines containing *N,N*-bis(isoxazol-5-yl)methyl groups were obtained. It is noteworthy that no significant



Scheme 2. Access to *N,N*-bis(isoxazol-5-yl)methyl tertiary arylamines **4** by a diprop-3-ynylation and 1,3-dipolar cycloaddition sequence.

Table 2. Sequential transformation of various arylamines and chlorooximes into *N,N*-bis(isoxazol-5-yl)methyl tertiary arylamines **4**.[a]

Entry	Ar (**1**)	R (**3**)	Product (**4**)	Yield (%)[b]
1	C_6H_5 (**1a**)	C_6H_5 (**3a**)	**4aa**	82
2	C_6H_5 (**1a**)	2-$CH_3C_6H_4$ (**3b**)	**4ab**	70
3	C_6H_5 (**1a**)	3-$CH_3C_6H_4$ (**3c**)	**4ac**	76
4	C_6H_5 (**1a**)	3-$CH_3OC_6H_4$ (**3d**)	**4ad**	71
5	3-$CH_3C_6H_4$ (**1b**)	C_6H_5 (**3a**)	**4ba**	81
6	3-$CH_3C_6H_4$ (**1b**)	2-$CH_3C_6H_4$ (**3b**)	**4bb**	72
7	3-$CH_3C_6H_4$ (**1b**)	3-$CH_3C_6H_4$ (**3c**)	**4bc**	75
8	2-$CH_3C_6H_4$ (**1c**)	C_6H_5 (**3a**)	**4ca**	80
9	2-$CH_3C_6H_4$ (**1c**)	3-$CH_3C_6H_4$ (**3c**)	**4cc**	78
10	2-$CH_3C_6H_4$ (**1c**)	3-$CH_3OC_6H_4$ (**3d**)	**4cd**	72
11	2-$CH_3C_6H_4$ (**1c**)	4-ClC_6H_4 (**3e**)	**4ce**	86
12	2-$CH_3C_6H_4$ (**1c**)	4-BrC_6H_4 (**3f**)	**4cf**	84
13	2-$CH_3C_6H_4$ (**1c**)	4-$NO_2C_6H_4$ (**3g**)	**4cg**	88
14	4-ClC_6H_4 (**1d**)	$C_6H_5CH_2$ (**3h**)	**4dh**	62
15	4-ClC_6H_4 (**1d**)	$CH_3CH_2CH_2$ (**3i**)	**4di**	45
16	C_6H_5 (**1a**)	4-HOC_6H_4 (**3j**)	**4aj**	0
17	C_6H_5 (**1a**)	4-$(Me_2N)C_6H_4$ (**3k**)	**4ak**	0

[a]All reactions were performed in 5 mL of DMF with 1.0 mmol of primary aromatic amine, 4.0 mmol of propargyl bromide, and 3.0 mmol of the chlorooxime.
[b]Isolated yield based on the primary aromatic amine after column chromatography.

difference in reactivity was observed for the examined arylamines substituted with 3-Me, 2-Me, and 4-Cl groups on the benzene rings (Table 2, entries 5–15). In general, aromatic nitrile oxides bearing electron-withdrawing groups such as chloro, bromo, and nitro (**3e**–**g**), as well as electron-donating groups such as methyl and methoxy (**3b**–**d**), and even *N*-hydroxy-2-methylbenzimidoyl chloride **3b** bearing a hindered methyl substituent afforded the desired products in moderate to good yields (Table 2, entries 2–4, 6, 7, and 9–13). It was also observed that electron-deficient aromatic nitrile oxides were preferred over electron-rich nitrile oxides in this MCR. However, other electron-rich benzonitrile oxides such as 4-hydroxy-benzonitrile oxide and 4-(*N,N*-dimethylamino)benzonitrile oxide did not participate in this reaction (Table 2, entries 16 and 17). In addition, phenylacetonitrile oxide produced the corresponding product in moderate yield (Table 2, entry 14), while the aliphatic nitrile oxide *n*-butyl-nitrile oxide gave a low yield of the product **4di** (Table 2, entry 15).

Conclusion

In summary, a facile and efficient, one-pot method for the preparation of *N,N*-bis(isoxazol-5-yl)methyl tertiary arylamines from primary amines, propargyl bromide, and hydroximyl chlorides has been developed. The procedure does not require isolation of the *N,N*-dipropargylated arylamine intermediates, and has considerable advantages in terms of its use of easily available substrates, its mild reaction conditions, its simple operation, and the moderate to good yields obtained.

Experimental

Melting points were measured with a Beijing-Taike X-4 apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance-Bruker 400 MHz NMR spectrometer, operating at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to TMS or the deuterated solvent as the internal reference. Fourier transform infrared (FTIR) analyses were performed with a PerkinElmer SP One FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer. Hydroximyl chlorides **3a**−**k** are known compounds and were prepared from the corresponding readily available aldehydes via the reported method.[26] Other reagents and solvents were purchased from commercial suppliers and were used as received without further purification. All experiments were carried out in air. Analytical thin-layer chromatography (TLC) was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminum plates, and the products were visualized

by UV detection. Column chromatography was performed on Merck silica gel 60 (250–400 mesh).

Preparation of N,N-*bis(isoxazol-5-yl) methyl tertiary arylamines* **4aa–di**; *general procedure*

To a stirred solution of primary aromatic amine **1** (1.0 mmol) in DMF (5 mL) was added CaH_2 (20 mg, 0.4 mmol) and propargyl bromide (480 mg, 4.0 mmol). The resulting mixture was stirred at room temperature until complete conversion of the amine into the *N,N*-di(prop-2-yn-1-yl) arylamine **2** had occurred (as monitored by TLC). The excess of propargyl bromide was then removed under reduced pressure. Next, hydroximyl chloride **3** (2.5 mmol) and Et_3N (3.0 mmol) were added to the reaction mixture, which was warmed to 65 °C and stirred until completion of the reaction (as monitored by TLC). The resulting solution was filtered through a short pad of Celite 545 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10:1) to afford the target compound **4**.

N,N-*Bis[(3-phenylisoxazol-5-yl)methyl]aniline* (**4aa**). Yellow solid, m.p. = 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.82 (m, 5H), 7.50–7.48 (m, 8H), 7.33 (s, 2H), 6.95 (s, 2H), 4.61 (s, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.85, 162.17, 144.93, 132.19, 130.67, 129.32, 128.90, 128.17, 127.05, 126.08, 102.34, 48.23. IR (KBr): ν 3050, 2965, 1607, 1466, 1368, 1269, 1136, 1065, 742 cm^{-1}. Anal. calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31; found: C, 76.72; H, 5.29; N, 10.35%.

N,N-*Bis[(3-(*o*-tolyl)isoxazol-5-yl)methyl]aniline* (**4ab**). Yellow solid, m.p. = 53–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.34 (m, 4H), 7.26–7.13 (m, 7H), 7.06 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.23 (s, 2H), 4.44 (s, 4H), 2.33 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.29, 163.05, 144.29, 136.87, 131.28, 131.13, 130.61, 129.42, 128.49, 127.72, 126.04, 125.14, 104.26, 48.46, 21.10. IR (KBr): ν 3035, 2972, 2869, 1602, 1488, 1384, 1291, 1125, 751 cm^{-1}. Anal. calcd for $C_{28}H_{25}N_3O_2$: C, 77.25; H, 5.75; N, 9.65; found: C, 77.32; H, 5.89; N, 9.73%.

N,N-*Bis[(3-(*m*-tolyl)isoxazol-5-yl)methyl]aniline* (**4ac**). Yellow solid, m.p. = 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.51 (m, 4H), 7.30–7.20 (m, 6H), 6.87–6.82 (m, 3H), 6.43 (s, 2H), 4.72 (s, 4H), 2.35 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.86, 162.68, 147.13, 138.68, 130.90, 129.60, 128.84, 128.68, 127.47, 124.00, 119.09, 113.59, 100.79, 47.48, 21.37. IR (KBr): ν 3033, 2975, 2872, 1605, 1490, 1386, 1290, 1127, 757, 698 cm^{-1}. Anal. calcd for $C_{28}H_{25}N_3O_2$: C, 77.25; H, 5.75; N, 9.65; found: C, 77.38; H, 5.90; N, 9.71%.

N,N-*Bis{[3-(3-methoxyphenyl)isoxazol-5-yl]methyl}aniline* (**4ad**). Yellow solid, m.p. = 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.04 (m, 8H), 6.83–6.73 (m, 5H), 6.55 (s, 2H), 4.69 (s, 4 H), 3.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.19, 161.21, 158.34, 147.18, 131.19, 129.53, 128.86, 124.16, 119.25, 117.54, 115.30, 113.84, 104.10, 55.68, 47.50. IR (KBr): ν 3430, 3045, 2927, 2848, 1605, 1508, 1248, 1178, 1030, 897, 752, 694 cm^{-1}. Anal. calcd for $C_{28}H_{25}N_3O_4$: C, 71.96; H, 5.35; N, 8.99; found: C, 71.85; H, 5.46; N, 8.92%.

N,N-*Bis[(3-phenylisoxazol-5-yl)methyl]-3-methylaniline* (**4ba**). Yellow solid, m.p. = 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.75 (m, 5H), 7.44–7.43 (m, 9H), 6.47 (s, 2H), 4.50 (s, 4H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.43, 162.42, 146.23, 135.69, 133.91, 130.83, 130.11, 128.90, 127.59, 126.83, 125.88, 122.05, 101.53, 48.52, 19.21. IR (KBr): ν 3031, 2972, 2870, 1604, 1495, 1385, 1288, 1125, 862, 765, 700 cm^{-1}. Anal. calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97; found: C, 76.82; H, 5.64; N, 9.91%.

N,N-*Bis{[(3-(*o*-tolyl)isoxazol-5-yl)]methyl}-3-methylaniline* (**4bb**). Yellow solid, m.p. = 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.32–7.20 (m, 8H), 6.78 (s, 2H), 6.33 (s, 2H), 4.66 (s, 4H), 2.44 (s, 6H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.04, 163.12, 146.21, 136.80, 133.47, 131.10, 130.93, 129.53, 129.42, 128.86, 126.00, 125.05, 117.12, 113.57, 103.51, 47.65, 20.56, 19.21. IR (KBr): ν 3040, 2978, 2875, 1603, 1489, 1385, 1287, 1122, 857, 768 cm^{-1}. Anal. calcd for $C_{29}H_{27}N_3O_2$: C, 77.48; H, 6.05; N, 9.35; found: C, 77.58; H, 6.16; N, 9.43%.

N,N-*Bis{[(3-(*m*-tolyl)isoxazol-5-yl)methyl]-3-methylaniline* (**4bc**). Yellow solid, m.p. = 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.45 (m, 5H), 7.25–7.07 (m, 6H), 6.86–6.78 (m, 1H), 6.37 (s, 2H), 4.38 (s, 4H), 2.43 (s, 3H), 2.30 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.27, 162.52, 144.55, 138.67, 136.07, 131.43, 130.86, 128.81, 128.70, 127.58, 127.41, 126.23, 123.98, 122.07, 101.60, 48.49, 21.37. IR (KBr): ν 3037, 2974, 2883, 1606, 1491, 1382, 1285, 1126, 865, 772, 765 cm^{-1}. Anal. calcd for $C_{29}H_{27}N_3O_2$: C, 77.48; H, 6.05; N, 9.35; found: C, 77.60; H, 6.14; N, 9.44%.

N,N-*Bis[(3-phenylisoxazol-5-yl)methyl]-2-methylaniline* (**4ca**). Yellow solid; m.p. = 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.53 (m, 4H), 7.52–7.51 (m, 1H), 7.43–7.42 (m, 6H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.38 (s, 2H), 4.33 (s, 4H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.42, 162.37, 146.34, 136.42, 131.27, 130.94, 130.41, 130.09, 128.90, 126.81, 126.60, 123.87, 101.55, 49.03, 17.96. IR (KBr): ν 3033, 2977, 2886, 1604, 1500, 1384, 1285, 1127, 745 cm^{-1}. Anal. calcd for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97; found: C, 76.85; H, 5.62; N, 8.90%.

N,N-*Bis{[3-(*m*-tolyl)isoxazol-5-yl]methyl}-2-methylaniline* (**4cc**). Yellow solid, m.p. = 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.55–7.52 (m, 3H),

7.32 (t, J = 7.6 Hz, 2H), 7.23 (dd, J = 9.9, 4.9 Hz, 3H), 7.08 (dd, J = 8.5, 2.4 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.37 (s, 2H), 4.33 (s, 4H), 2.41 (s, 3H), 2.39 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.27, 162.47, 146.39, 138.67, 131.38, 131.25, 130.68, 129.23, 128.95, 128.86, 128.82, 127.39, 126.59, 123.95, 101.60, 49.02, 21.37, 19.20. IR (KBr): ν 3033, 2975, 2887, 1604, 1490, 1384, 1282, 1122, 862, 770, 745 cm^{-1}. Anal. calcd for $C_{29}H_{27}N_3O_2$: C, 77.48; H, 6.05; N, 9.35; found: C, 77.61; H, 6.16; N, 9.47%.

N,N-*Bis{[3-(3-methoxyphenyl)isoxazol-5-yl]methyl}-2-methylaniline* (**4cd**). Yellow solid, m.p. = 65–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, J = 8.9 Hz, 3H), 7.23–7.21 (m, 4H), 7.11 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.1 Hz, 2H), 6.89 (dd, J = 8.9, 3.1 Hz, 2H), 6.56 (s, 2H), 4.39 (s, 4H), 3.78 (s, 6H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.17, 160.98, 158.33, 147.74, 134.46, 131.30, 130.94, 128.82, 126.62, 125.27, 124.17, 122.69, 117.44, 115.23, 104.78, 55.66, 49.14, 18.03. IR (KBr): ν 3028, 2951, 1602, 1467, 1238, 1031, 823, 647 cm^{-1}. Anal. calcd for $C_{29}H_{27}N_3O_4$: C, 72.33; H, 5.65; N, 8.73; found: C, 72.16; H, 5.77; N, 8.85%.

N,N-*Bis{[3-(4-chlorophenyl)isoxazol-5-yl]methyl}-2-methylaniline* (**4ce**). Yellow solid, m.p. = 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.71 (m, 2H), 7.66 (d, J = 8.8 Hz, 4 H), 7.43–7.40 (m, 2H), 7.38 (d, J = 8.4 Hz, 4H), 6.34 (s, 2H), 4.36 (s, 4H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.18, 161.37, 147.90, 136.05, 131.54, 130.93, 129.14, 128.85, 128.04, 126.68, 125.33, 122.32, 101.25, 49.28, 19.20. IR (KBr): ν 3036, 2956, 2788, 1604, 1495, 1386, 1235, 1028, 905, 834, 760, 705 cm^{-1}. Anal. calcd for $C_{27}H_{21}N_3Cl_2O_2$: C, 66.13; H, 4.32; N, 8.57; found: C, 66.25; H, 4.41; N, 8.49%.

N,N-*Bis{[3-(4-bromophenyl)isoxazol-5-yl]methyl}-2-methylaniline* (**4cf**). Yellow solid, m.p. = 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.60–7.50 (m, 8H), 7.05 (dd, J = 8.0, 19.6 Hz, 2H), 6.34 (s, 2H), 4.35 (s, 4H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.21, 161.43, 147.90, 132.20, 131.54, 130.92, 128.56, 127.81, 126.68, 125.34, 124.32, 122.32, 101.21, 49.29, 19.20. IR (KBr): ν 3036, 2956, 2788, 1604, 1495, 1382, 1233, 1073, 905, 832, 757, 695 cm^{-1}. Anal. calcd for $C_{27}H_{21}N_3Br_2O_2$: C, 55.98; H, 3.65; N, 7.25; found: C, 55.85; H, 3.76; N, 7.16%.

N,N-*Bis{[3-(4-nitrophenyl)isoxazol-5-yl]methyl}-2-methylaniline* (**4cg**). Yellow solid, m.p. = 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.8 Hz, 4H), 7.73–7.68 (m, 4H), 7.43 (d, J = 8.8 Hz, 4H), 6.45 (s, 2H), 4.37 (s, 4H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.23, 162.33, 148.34, 147.93, 134.45, 131.58, 130.96, 128.85, 128.04, 126.69, 124.33, 122.35, 101.28, 49.31, 19.29. IR (KBr): ν 3072, 2935, 2855, 1604, 1510, 1495, 1445, 1382, 1345, 1135, 1108, 925, 850 cm^{-1}. Anal. calcd for $C_{27}H_{21}N_5O_6$: C, 63.40; H, 4.14; N, 13.69; found: C, 63.25; H, 4.26; N, 13.57%.

*4-Chloro-*N,N-*bis[(3-benzylisoxazol-5-yl)methyl]aniline* (**4dh**). Yellow solid, m.p. = 97–99 °C. δ 7.35–7.33 (m, 6H), 7.19–7.16 (m, 4H), 7.08 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 6.30 (s, 2H), 4.63 (s, 4H), 4.29 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.27, 161.52, 147.96, 134.66, 131.15, 129.12, 128.73, 127.88, 123.00, 115.17, 101.22, 47.22, 32.42. IR (KBr): ν 3034, 2970, 2785, 1603, 1490, 1235, 1026, 906, 835, 760, 699 cm^{-1}. Anal. calcd for $C_{28}H_{24}ClN_3O_2$: C, 71.56; H, 5.15; N, 8.94; found: C, 71.42; H, 5.24; N, 8.86%.

*4-Chloro-*N,N-*bis[(3-propylisoxazol-5-yl)methyl]aniline* (**4di**). Yellow liquid. δ 7.56 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.26 (s, 2H), 4.38 (s, 4H), 2.37 (t, J = 7.2 Hz, 4H), 1.68–1.67 (m, 4H), 1.11 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.67, 160.92, 146.80, 132.46, 128.94, 115.22, 100.76, 47.02, 30.07, 19.78, 13.89. IR (film): ν 3034, 2962, 2932, 1608, 1455, 1016, 760, 698 cm^{-1}. Anal. calcd for $C_{18}H_{24}ClN_3O_2$: C, 61.79; H, 6.91; N, 12.01; found: C, 61.93; H, 6.80; N, 12.11%.

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Supplemental material

Supplemental material for this article is available online.

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