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Synthesis of Trisubstituted Isoxazoles by Palladium(II)-Catalyzed Cascade Cyclization−Alkenylation of 2-Alkyn-1-one *O*-Methyl Oximes

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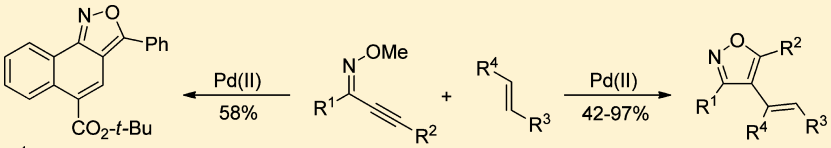
Supporting Information



R1 = 2-bromophenyl
R2 = phenyl
R3 = CO2-t-Bu
R4 = H

ABSTRACT: A palladium-catalyzed, cascade 5-*endo-dig* cyclization−alkenylation synthesis of isoxazoles has been developed. The addition of 1 equiv of *n*-Bu_4NBr significantly increases the yield of the desired 4-alkenyl-3,4,5-trisubstituted isoxazoles. A variety of trisubstituted isoxazoles are prepared in moderate to excellent yields. One example of the synthesis of a naphthoisoxazole is reported by a cascade cyclization−alkenylation-Heck reaction.

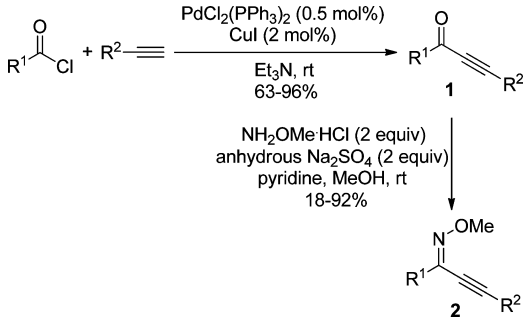
Isoxazoles exhibit a wide range of biological activities, including analgesic,[1] anti-inflammatory,[1] antinociceptive,[2] and anticancer[3] activity, and have been the focus of many biological studies in recent years.[4] A number of synthetic methods have been developed to construct the isoxazole core structure,[5] including the [3 + 2] cycloaddition of alkynes/alkenes and nitrile oxides,[6] intramolecular cyclization of α,β-unsaturated oximes,[7] and intermolecular cyclization of oximes with C−C double/triple bonds.[8] Alkenyl-substituted heteroaromatic moieties are found in numerous natural products and biologically active compounds.[9] Their synthesis has attracted a great degree of interest.[10]

Palladium-catalyzed cascade reactions have emerged as a valuable component in the synthesis of complex molecular scaffolds.[11] In the presence of catalytic amounts of palladium, sequential transformations can take place in one pot with the formation of multiple chemical bonds. Our interest in 4-(1-alkenyl)isoxazoles has prompted us to develop a convenient new synthesis of these isoxazoles by a palladium(II)-catalyzed cascade cyclization−alkenylation sequence from 2-alkyn-1-one *O*-methyl oximes and alkenes.

Ynones **1** were prepared by the Sonogashira coupling of an acid chloride and a terminal alkyne.[12] The *O*-methyl oximes **2** were prepared by the reaction of ynones with methoxylamine hydrochloride in the presence of pyridine and anhydrous Na_2SO_4 (Scheme 1).

Our initial study focused on the cyclization of *O*-methyl oxime **2a**, which afforded the 3,5-disubstituted isoxazole **3a** in a 67% yield in the presence of the $PdCl_2/CuCl_2$ catalyst system (Scheme 2).[13] However, when 2 equiv of *tert*-butyl acrylate were added to the reaction mixture under the same conditions,

Scheme 1. Preparation of 2-Alkyn-1-one *O*-Methyl Oximes



Scheme 2. Palladium-Catalyzed Cyclization of *O*-Methyl Oxime 2a

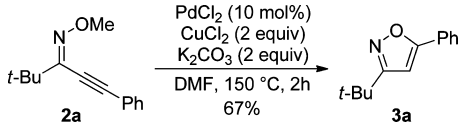


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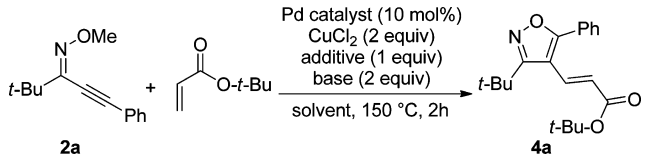
Table 1. Optimization of Reaction Conditions for the Palladium-Catalyzed Cascade Cyclization−Alkenylation[a]



entry	catalyst	base	additive	solvent	**4a** yield (%)[b]
1	$PdCl_2$	K_2CO_3		DMF	52
2	$Pd(OAc)_2$	K_2CO_3		DMF	62
3	$Pd(O_2CCF_3)_2$	K_2CO_3		DMF	73
4	$Pd(O_2CCF_3)_2$	K_2CO_3		DMSO	60
5	$Pd(O_2CCF_3)_2$	K_2CO_3		DMAc	62
6	$Pd(O_2CCF_3)_2$	K_2CO_3		NMP	70
7	$Pd(O_2CCF_3)_2$	Cs_2CO_3		NMP	72
8	$Pd(O_2CCF_3)_2$	Na_2CO_3		NMP	73
9	$Pd(O_2CCF_3)_2$	Li_2CO_3		NMP	81
10	$Pd(O_2CCF_3)_2$	Li_2CO_3	*n*-Bu_4NCl	NMP	89
11	$Pd(O_2CCF_3)_2$	Li_2CO_3	*n*-Bu_4NBr	NMP	95
12[c]	$Pd(O_2CCF_3)_2$	Li_2CO_3	*n*-Bu_4NBr	NMP	80
13[d]	$Pd(O_2CCF_3)_2$	Li_2CO_3	*n*-Bu_4NBr	NMP	37
14[e]	$Pd(O_2CCF_3)_2$	Li_2CO_3	*n*-Bu_4NBr	NMP	86
15[f]	$Pd(O_2CCF_3)_2$	Li_2CO_3	*n*-Bu_4NBr	NMP	58
16		Li_2CO_3	*n*-Bu_4NBr	NMP	(3)[g]

[a]Representative procedure: the palladium catalyst (0.05 mmol), $CuCl_2$ (1.0 mmol), additive (0.5 mmol), base (1.0 mmol), *O*-methyl oxime (0.5 mmol), *t*-butyl acrylate (1.0 mmol), and solvent (3 mL) were mixed in a sealed 4-dram vial. The reaction was stirred at the indicated temperature for 2 h. [b]Isolated yields after column chromatography. [c]5 mol % of $Pd(O_2CCF_3)_2$ was added. [d]1 equiv of $CuCl_2$ was added. [e]The reaction was run at 120 °C. [f]The reaction was run at 180 °C. [g]The yield in parentheses was determined by ^1H NMR.

the desired 3,4,5-trisubstituted isoxazole **4a** was isolated in a 52% yield, alongside 10% of **3a** (Table 1, entry 1). A similar problem was encountered in the previously reported palladium-catalyzed cascade cyclization−alkenylation synthesis of indoles[10a] and isoquinolines,[10b] where the direct cyclization products were obtained together with the desired cyclization−alkenylation products.

The yield of **4a** was improved to 62 and 73%, respectively, when $Pd(OAc)_2$ and $Pd(O_2CCF_3)_2$ were used (Table 1, entries 2 and 3). The amount of **3a** was around 5% in both cases. Different solvents and bases were also screened in the reaction (Table 1, entries 4−9), and it was found that the combination of NMP and Li_2CO_3 afforded superior yields of **4a** (Table 1, entry 9). The beneficial effect of quaternary ammonium salts in the Heck reaction is known.[14] The presence of *n*-Bu_4NBr[15] or *n*-Bu_4NCl[16] can accelerate the reaction rate and increase the chemical yields of the Heck reaction. To our delight, the yield of **4a** was increased to 89% with the addition of 1 equiv of *n*-Bu_4NCl (Table 1, entry 10). The addition of 1 equiv of *n*-Bu_4NBr further increased the yield to 95% with no **3a** detected (Table 1, entry 11). The yield of **4a** dropped to 80% when $Pd(O_2CCF_3)_2$ was reduced to 5 mol % (Table 1, entry 12). A significant drop in yield was observed when the amount of $CuCl_2$ was decreased to 1 equiv (Table 1, entry 13). Inferior results were obtained when temperatures 30 degrees lower or higher than 150 °C were used (Table 1, entries 14 and 15). Only a trace amount of the desired product **4a** was obtained when the reaction was carried out in the absence of a palladium catalyst (Table 1, entry 16).

This one-pot cyclization−alkenylation cascade reaction protocol has proved to be a very general route to a variety of isoxazoles (Table 2). A wide variety of *O*-methyl oxime substrates have been studied in this cascade process, including those bearing aryl, alkyl, and alkenyl substituents. Both an electron-donating substituent, such as a methoxy group (Table 2, entries 6 and 8), and an electron-withdrawing substituent, such as a nitrile group (Table 2, entry 13), are compatible. A variety of alkenes have been employed in this cascade, including both electron-rich and electron-poor alkenes. Alkenes with an electron-withdrawing substituent afford good to excellent yields (Table 2, entries 1−8 and 13−14), while the electron-rich alkene, ethyl vinyl ether, only produces a moderate yield (Table 2, entry 11). When vinyl acetate is used, the acetate group on the alkene is eliminated instead of a β-hydrogen elimination, leading to the 4-ethenylisoxazole **4j** in a 52% yield (Table 2, entry 10). A 42% yield is obtained when the sterically more demanding (*E*)-methyl but-2-enoate is used (Table 2, entry 12). A wide variety of functional groups are tolerated under the current reaction conditions, including ester, aldehyde, ketone, amide, ether, nitrile, and chloro groups. High *trans*-selectivity is observed in the alkenylation step since only a single isomer with $^3J_{HH} > 15$ Hz for the two alkene hydrogen atoms was seen in all relevant cases (entries 1−9, 13, 14; see the Supporting Information).

When the *O*-methyl oxime **2i** was subjected to the current reaction conditions, a cascade cyclization−alkenylation−Heck reaction took place to afford naphthoisoxazole **5** in a 58% yield (Scheme 3). Naphthoisoxazoles are known as estrogen receptor agonist and antagonist compounds, useful in preventing or treating estrogen receptor-mediated disorders such as osteoporosis and breast cancer.[17]

This cyclization−alkenylation reaction presumably takes place by Pd(II)-catalyzed 5-*endo-dig* cyclization to form the heteroaryl palladium intermediate **6**, which forms intermediate **7** after the loss of a methyl group. A Heck coupling then takes place between **7** and the alkene to afford the trisubstituted isoxazole **4** (Scheme 4). In the case of isoxazole **4o**, where an *ortho*-bromo group is present on the 3-aryl substituent, an

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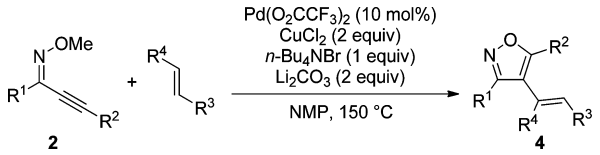
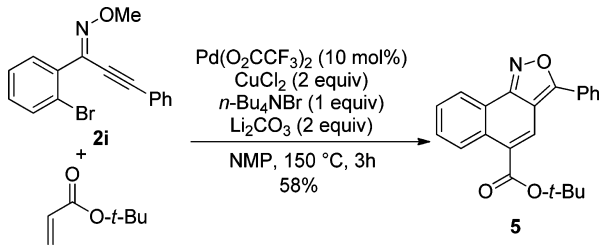
Table 2. Preparation of 3,4,5-Trisubstituted Isoxazoles by a Palladium-Catalyzed Cascade Reaction[a]



entry	2	R^1	R^2	R^3	R^4	t (h)	4	% yield[b]
1	**2a**	*t*-Bu	Ph	CO_2-*t*-Bu	H	2	**4a**	95
2	**2a**	*t*-Bu	Ph	CO_2Et	H	2	**4b**	86
3	**2a**	*t*-Bu	Ph	CHO	H	2	**4c**	72
4	**2b**	Ph	$(CH_2)_{12}CH_3$	C(O)Me	H	2	**4d**	81
5	**2c**		Ph	CHO	H	2	**4e**	80
6	**2d**	*t*-Bu		CO_2Me	H	2	**4f**	97
7	**2e**			C(O)Me	H	2	**4g**	86
8	**2f**		Ph	C(O)Me	H	2	**4h**	77
9	**2a**	*t*-Bu	Ph	Ph	H	2	**4i**	72
10[c]	**2g**	Ph	Ph	H	OAc	2	**4j'**	-
11	**2g**	Ph	Ph	H	OEt	2	**4k**	43
12	**2a**	*t*-Bu	Ph	CO_2Me	Me	3	**4l**	42
13	**2h**		Ph	$C(O)NMe_2$	H	5	**4m**	90
14	**2g**	Ph	Ph		H	3	**4n**	81

[a]Representative procedure: the $Pd(O_2CCF_3)_2$ (0.05 mmol), $CuCl_2$ (1.0 mmol), *n*-Bu_4NBr (0.5 mmol), Li_2CO_3 (1.0 mmol), *O*-methyl oxime (0.5 mmol), alkene (1.0 mmol), and NMP (3 mL) were mixed in a sealed 4-dram vial. The reaction mixture was stirred at 150 °C for the indicated time. [b]Isolated yields after column chromatography. [c]The major product 3,5-diphenyl-4-vinylisoxazole (**4j**) was obtained in a 52% yield.

Scheme 3. Synthesis of Naphtho[1,2-*c*]isoxazole by a Palladium-Catalyzed Cyclization−Alkenylation−Heck Reaction



intramolecular Heck coupling takes place subsequently to afford naphthoisoxazole **5**.

It is worth noting that although the majority of the studied intramolecular Heck reactions proceed in the *exo-trig* mode,[14] the intramolecular Heck coupling of **4o** gives the 6-membered ring exclusively via an *endo-trig* mode, rather than the 5-membered ring that would have resulted from the *exo-trig* reaction. Steric effects obviously play a significant role in the high regioselectivity observed for the current 6-*endo-trig* intramolecular Heck reaction, though the 6-*endo-trig* Heck reaction is electronically disfavored. The regioselectivity was unequivocally established by X-ray diffraction analysis of a single crystal of compound **5** (see the Supporting Information).

In conclusion, we have developed a palladium-catalyzed cascade cyclization−alkenylation for the synthesis of 3,4,5-trisubstituted isoxazoles. The yields of the undesired direct cyclization products, 3,5-disubstituted isoxazoles, are diminished by the addition of 1 equiv of *n*-Bu_4NBr. A wide variety of 2-alkyn-1-one *O*-methyl oximes and olefins have been successfully employed in this synthetic protocol. A number of functional groups, including ester, amide, aldehyde, ether, nitrile, and ketone groups, are compatible with the reaction conditions. One example of the synthesis of a polycyclic naphtho[1,2-*c*]isoxazole has been demonstrated by a palladium-catalyzed cyclization−alkenylation−Heck cascade. Preparation of the polycyclic naphtho[1,2-*c*]isoxazole derivatives using the current protocol is underway.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in sealed 4-dram oven-dried vials unless otherwise noted. All commercially available chemicals were used as received without further purification unless otherwise indicated. *N*-Methyl-2-pyrrolidone was dried by 4 Å molecular sieves before use. All ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, using $CDCl_3$ as a solvent. The chemical shifts of all ^1H and ^{13}C NMR spectra are referenced to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^1H NMR spectra and δ 77.23 ppm for the ^{13}C NMR spectra). The high resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using electrospray ionization. The melting points are uncorrected.

General Procedure for the Preparation of Ynones (1). These compounds were prepared according to a literature procedure.[7d,12a] To a 50 mL round-bottom flask were added CuI (19 mg, 0.1 mmol),

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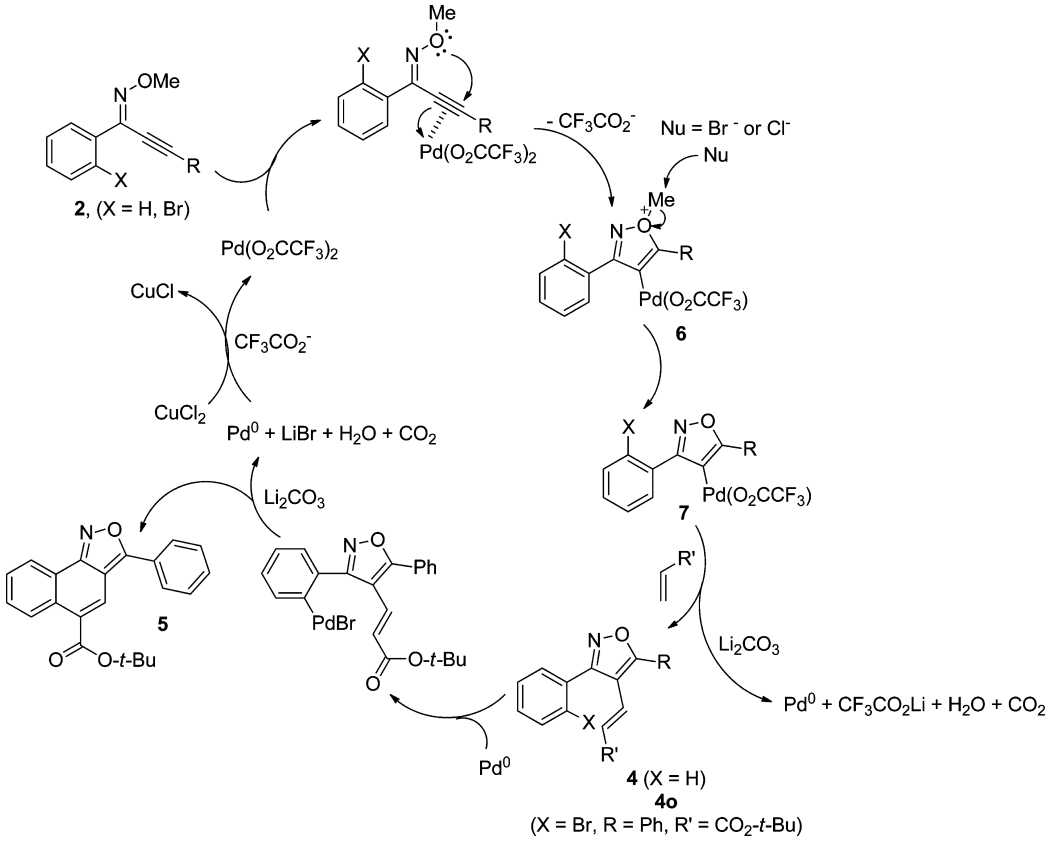
Scheme 4. Plausible Mechanism for the One-Pot Synthesis of Trisubstituted Isoxazoles (4) and Naphtho[1,2-*c*]isoxazole (5)



$PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and triethylamine (10 mL). The flask was flushed with nitrogen, and the terminal acetylene (5.0 mmol) was added to the stirred suspension, followed by immediate dropwise addition of acyl chloride (6.5 mmol). If the acyl chloride was a solid, it was added as a THF solution. The resulting mixture was allowed to stir at room temperature overnight. Water (10 mL) was added to the reaction mixture. The resulting solution was extracted with diethyl ether (3 × 20 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under a vacuum, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

4,4-Dimethyl-1-phenylpent-1-yn-3-one (1a). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a yellow oil in an 81% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.58 (m, 2H), 7.43−7.46 (m, 1H), 7.36−7.40 (m, 2H), 1.28 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[12b]

1-Phenylhexadec-2-yn-1-one (1b). Purification by flash column chromatography (20:1 hexanes/EtOAc). This compound was obtained as a light yellow oil in an 83% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−8.14 (m, 2H), 7.57−7.61 (m, 1H), 7.45−7.48 (m, 2H), 2.49 (t, J = 7.1 Hz, 2 H), 1.64−1.68 (m, 2 H), 1.45−1.48 (m, 2H), 1.22−1.34 (m, 18 H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 137.1, 134.1, 129.7, 128.7, 97.2, 79.8, 32.1, 29.9, 29.83, 29.78, 29.7, 29.5, 29.24, 29.16, 28.0, 22.9, 19.4, 14.3; HRMS (EI) calcd for $C_{22}H_{32}O$, 312.2453, found 312.2459.

1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-one (1c). Purification by flash column chromatography (20:1 hexanes/EtOAc). The product was obtained as a colorless oil in a 65% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 1H), 7.69(t, J = 7.6 Hz, 3H), 7.49 (t, J = 7.6 Hz, 1H), 7.41−7.44 (m, 3H), 7.18 (dd, J = 2.4 Hz, 1H), 3.88 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[18]

1-(4-Methoxyphenyl)-4,4-dimethylpent-1-yn-3-one (1d). Purification by flash column chromatography (10:1 hexanes/EtOAc). The product was obtained as a yellow oil in a 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.54 (m, 2H), 6.87−6.90 (m, 2H), 3.83 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 161.7, 135.2, 114.5, 112.2, 93.5, 86.0, 55.6, 44.9, 26.4; HRMS (EI) calcd for $C_{14}H_{16}O_2$, 216.1150, found 216.1151.

1-(4-Chlorophenyl)-3-(cyclohex-1-en-1-yl)prop-2-yn-1-one (1e). Purification by flash column chromatography (5:1 hexanes/EtOAc). This compound was obtained as a light yellow solid in a 68% yield: mp 83−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06−8.09 (m, 2H), 7.44−7.47 (m, 2H), 6.59−6.61 (m, 1H), 2.26−2.30 (m, 2H), 2.20−2.24 (m, 2H), 1.70−1.74 (m, 2H), 1.63−1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 143.4, 140.6, 135.6, 131.0, 129.1, 119.2, 96.5, 85.1, 28.5, 26.4, 22.1, 21.3; HRMS (EI) calcd for $C_{15}H_{13}ClO$, 244.0655, found 244.0657.

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (1f). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a light yellow oil in a 90% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19−8.22 (m, 2H), 7.67−7.69 (m, 2H), 7.46−7.50 (m, 1H), 7.40−7.44 (m, 2 H), 6.98−7.01 (m, 2H), 3.91(s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[12b]

1,3-Diphenylprop-2-yn-1-one (1g). Purification by flash column chromatography (40:1 hexanes/EtOAc). This compound was obtained as a yellow oil in a 96% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23−8.24 (m, 2H), 7.69−7.71 (m, 2H), 7.63−7.66 (m, 1H), 7.48−7.55 (m, 3H), 7.42−7.45 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[18]

4-(3-Phenylpropioloyl)benzonitrile (1h). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a yellow solid in a 92% yield: mp 51−52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31−8.32 (m, 2H), 7.82−7.84 (m, 2H), 7.69−7.71 (m, 2H), 7.52−7.55 (m, 1H), 7.44−7.47 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[18]

1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one (1i). Purification by flash column chromatography (10:1 hexanes/EtOAc). This

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compound was obtained as a light yellow oil in a 63% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.7, 1.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 7.7 Hz, 2H), 7.44−7.50 (m, 2H), 7.37−7.43 (m, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

General Procedure for the Preparation of Ynone *O*-Methyl Oximes (2). These compounds were prepared according to a literature procedure.[7d] To a 50 mL round-bottom flask were added the alkynone (3.5 mmol), methoxylamine hydrochloride (7.0 mmol, 579 mg), anhydrous Na_2SO_4 (7.0 mmol, 994 mg), pyridine (1 mL), and anhydrous methanol (10 mL). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed under a vacuum, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

(*Z*)-4,4-Dimethyl-1-phenylpent-1-yn-3-one *O*-Methyl Oxime (2a). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a yellow oil in an 82% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.55 (m, 2H), 7.32−7.37 (m, 3H), 3.97 (s, 3H), 1.26 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[7c]

(*Z*)-1-Phenylhexadec-2-yn-1-one *O*-Methyl Oxime (2b). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a light yellow oil in a 74% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.86 (m, 2H), 7.37−7.39 (m, 3H), 4.09 (s, 3H), 2.55 (t, J = 7.1 Hz, 2H), 1.65−1.70 (m, 2H), 1.45−1.49 (m, 2H), 1.22−1.35 (m, 18H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 134.1, 129.7, 128.5, 126.7, 104.2, 71.6, 63.1, 32.1, 29.88, 29.86, 29.8, 29.7, 29.6, 29.3, 29.1, 28.5, 22.9, 20.0, 14.3; HRMS (EI) calcd for $C_{23}H_{35}NO$, 341.2719, found 341.2721.

(*Z*)-1-(3-Methoxyphenyl)-3-phenylprop-2-yn-1-one *O*-Methyl Oxime (2c). Purification by flash column chromatography (10:1 hexanes/EtOAc). The product was obtained as a colorless oil in a 66% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61−7.63 (m, 2H), 7.52 (d, J = 7.7 Hz, 1H), 7.47−7.48 (m, 1H), 7.36−7.41 (m, 3H), 7.32 (t, J = 7.9 Hz, 1H), 6.95 (dd, J = 8.4, 2.4 Hz, 1H), 4.15 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 140.0, 135.1, 132.4, 129.8, 129.6, 128.7, 121.9, 119.4, 115.9, 111.6, 101.3, 79.6, 63.4, 55.5; HRMS (EI) calcd for $C_{17}H_{15}NO_2$, 265.1103, found 265.1105.

(*Z*)-1-(4-Methoxyphenyl)-4,4-dimethylpent-1-yn-3-one *O*-Methyl Oxime (2d). Purification by flash column chromatography (10:1 hexanes/EtOAc). The product was obtained as a light yellow oil in a 75% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.48 (m, 2H), 6.84−6.87 (m, 2H), 3.96 (s, 3H), 3.80 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 149.5, 133.8, 114.2, 114.1, 100.9, 78.5, 62.4, 55.4, 37.1, 28.4; HRMS (EI) calcd for $C_{15}H_{19}NO_2$, 245.1416, found 245.1414.

(*Z*)-1-(4-Chlorophenyl)-3-(cyclohex-1-en-1-yl)prop-2-yn-1-one *O*-Methyl Oxime (2e). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a beige solid in a 37% yield: mp 47−48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76−7.79 (m, 2H), 7.32−7.35 (m, 2H), 6.39−6.41 (m, 1H), 4.09 (s, 3H), 2.25−2.28 (m, 2H), 2.16−2.19 (m, 2H), 1.67−1.72 (m, 2H), 1.60−1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 139.1, 135.6, 132.5, 128.7, 127.9, 120.0, 104.0, 76.9, 63.3, 29.0, 26.1, 22.3, 21.5; HRMS (EI) calcd for $C_{16}H_{16}ClNO$, 273.0920, found 273.0920.

(*Z*)-1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one *O*-Methyl Oxime (2f). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a light yellow solid in a 50% yield: mp 63−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88−7.91 (m, 2H), 7.63−7.66 (m, 2H), 7.37−7.43 (m, 3H), 6.93−6.96 (m, 2H), 4.14 (s, 3H), 3.84 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[20]

(*Z*)-1,3-Diphenylprop-2-yn-1-one *O*-Methyl Oxime (2g). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a colorless oil in a 67% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.93 (m, 2H), 7.63(d, J = 7.6 Hz, 2H), 7.38−7.42 (m, 6H), 4.15 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[7c]

(*Z*)-4-(1-(Methoxyimino)-3-phenylprop-2-yn-1-yl)-benzonitrile (2h). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a white solid in a 42% yield: mp 55−56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01−8.03 (m, 2H), 7.67−7.69 (m, 2H), 7.61−7.63 (m, 2H), 7.38−7.45 (m, 3H), 4.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.9, 132.4, 132.3, 130.1, 128.7, 127.1, 121.4, 118.8, 113.1, 102.5, 78.6, 63.8; HRMS (EI) calcd for $C_{17}H_{12}N_2O$, 260.0950, found 260.0950.

(*E*)-1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one *O*-Methyl Oxime (2i). Purification by flash column chromatography (10:1 hexanes/EtOAc). The product was obtained as a light yellow oil in an 18% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63−7.67 (m, 1H), 7.50−7.59 (m, 3H), 7.34−7.40 (m, 5H), 4.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 135.1, 133.7, 132.2, 131.2, 130.8, 129.7, 128.5, 127.6, 122.6, 121.8, 102.3, 80.1, 63.4; HRMS (EI) calcd for $C_{16}H_{12}BrNO$, 313.0102, found 313.0101.

General Procedure for the Preparation of 3,4,5-Trisubstituted Isoxazoles (4) and Naphtho[1,2-*c*]isoxazole (5). To an oven-dried 4-dram vial were added $Pd(O_2CCF_3)_2$ (16.6 mg, 0.05 mmol), $CuCl_2$ (134.5 mg, 1.0 mmol), Li_2CO_3 (74 mg, 1.0 mmol), *n*-Bu_4NBr (161.2 mg, 0.5 mmol), *O*-methyl oxime (0.5 mmol), alkene (1.0 mmol), and NMP (3 mL). The reaction mixture was stirred at 150 °C for the desired time. The reaction mixture was cooled to room temperature and diluted with 5 mL of diethyl ether. The mixture was then washed with 10 mL of a saturated NH_4Cl aqueous solution. The aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

(*E*)-*tert*-Butyl 3-(3-(*tert*-Butyl)-5-phenylisoxazol-4-yl)acrylate (4a). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a white solid in a 95% yield: mp 81−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62−7.66 (m, 3H), 7.43−7.45 (m, 3H), 5.98 (d, J = 16.1 Hz, 1H), 1.47 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 167.8, 165.8, 133.1, 130.5, 129.1, 128.03, 128.00, 125.2, 110.2, 81.0, 33.4, 29.1, 28.3; HRMS (EI) calcd for $C_{20}H_{25}NO_3$, 327.1834, found 327.1836.

(*E*)-Ethyl 3-(3-(*tert*-Butyl)-5-phenylisoxazol-4-yl)acrylate (4b). Purification by flash column chromatography (10:1 hexanes/EtOAc). The product was obtained as a light yellow oil in an 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 16.1 Hz, 1H), 7.63−7.65 (m, 2H), 7.42−7.45 (m, 3H), 6.04 (d, J = 16.1 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.42 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 168.0, 166.4, 134.2, 130.5, 129.1, 128.0, 127.9, 123.6, 110.1, 60.8, 33.4, 29.1, 14.3; HRMS (EI) calcd for $C_{18}H_{21}NO_3$, 299.1521, found 299.1523.

(*E*)-3-(3-(*tert*-Butyl)-5-phenylisoxazol-4-yl)acrylaldehyde (4c). Purification by flash column chromatography (10:1 hexanes/EtOAc). The product was obtained as a light yellow oil in a 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, J = 7.6 Hz, 1H), 7.60−7.62 (m, 2H), 7.53 (d, J = 16.1 Hz, 1H), 7.47−7.49 (m, 3H), 6.36 (dd, J = 16.1, 7.6 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 169.4, 169.3, 142.1, 132.5, 131.0, 129.3, 128.3, 127.6, 110.1, 33.4, 29.2; HRMS (EI) calcd for $C_{16}H_{17}NO_2$, 255.1259, found 255.1255.

(*E*)-4-(3-Phenyl-5-tridecylisoxazol-4-yl)but-3-en-2-one (4d). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a yellow oil in an 81% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.55 (m, 2H), 7.47−7.50 (m, 3H), 7.31 (d, J = 16.4 Hz, 1H), 6.29 (d, J = 16.4 Hz, 1H), 2.91 (t, J = 7.7 Hz, 2H), 2.24 (s, 3H), 1.76−1.82 (m, 2H), 1.37−1.42 (m, 2H), 1.32−1.36 (m, 2H), 1.25−1.30 (m, 16H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 173.9, 162.1, 131.4, 130.2, 129.1, 128.9, 128.7, 128.6, 110.4, 32.1, 29.83, 29.80, 29.76, 29.6, 29.5, 29.44, 29.39, 28.0, 27.4, 26.9, 22.9, 14.3; HRMS (EI) calcd for $C_{26}H_{37}NO_2$, 395.2824, found 395.2826.

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(*E*)-3-(3-(3-Methoxyphenyl)-5-phenylisoxazol-4-yl)-acrylaldehyde (4e). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a beige solid in an 80% yield: mp 108−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, J = 7.7 Hz, 1H), 7.72−7.74 (m, 2H), 7.56−7.58 (m, 3H), 7.40−7.47 (m, 2H), 7.09−7.13 (m, 2H), 7.05−7.07 (m, 1H), 6.28 (q, J = 16.3, 7.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 170.3, 162.4, 160.0, 140.4, 131.5, 131.2, 130.4, 129.49, 129.46, 128.4, 126.9, 121.2, 116.2, 114.4, 110.7, 55.5; HRMS (EI) calcd for $C_{19}H_{15}NO_3$, 305.1052, found 305.1053.

(*E*)-Methyl 3-(3-(*tert*-Butyl)-5-(4-methoxyphenyl)isoxazol-4-yl)acrylate (4f). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a light yellow oil in a 97% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 16.1 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.07 (d, J = 16.3 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 168.3, 167.0, 161.3, 134.8, 129.6, 122.5, 120.1, 114.5, 109.1, 55.5, 51.9, 33.3, 29.1; HRMS (EI) calcd for $C_{18}H_{21}NO_4$, 315.1471, found 315.1473.

(*E*)-4-(3-(4-Chlorophenyl)-5-(cyclohex-1-en-1-yl)isoxazol-4-yl)but-3-en-2-one (4g). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a light yellow oil in an 86% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.48 (m, 4H), 7.44 (d, J = 16.4 Hz, 1H), 6.36−6.38 (m, 1H), 6.15 (d, J = 16.4 Hz, 1H), 2.46−2.49 (m, 2H), 2.29−2.33 (m, 2H), 2.21 (s, 3H), 1.78−1.83 (m, 2H), 1.70−1.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 172.3, 161.0, 136.4, 136.2, 131.4, 130.4, 129.4, 129.2, 127.5, 126.7, 109.4, 28.5, 26.13, 26.12, 22.2, 21.6; HRMS (EI) calcd for $C_{19}H_{18}ClNO_2$, 327.1026, found 327.1029.

(*E*)-4-(3-(4-Methoxyphenyl)-5-phenylisoxazol-4-yl)but-3-en-2-one (4h). Purification by flash column chromatography (5:1 hexanes/EtOAc). This compound was obtained as a light yellow solid in a 77% yield: mp 120−121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.71 (m, 2H), 7.49−7.53 (m, 6H), 6.99−7.02 (m, 2H), 6.32 (d, J = 16.4 Hz, 1H), 3.85 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 169.6, 162.2, 161.1, 131.2, 131.0, 130.3, 129.9, 129.3, 128.2, 127.3, 120.7, 114.5, 110.5, 55.5, 28.2; HRMS (EI) calcd for $C_{20}H_{17}NO_3$, 319.1208, found 319.1210.

(*E*)-3-(*tert*-Butyl)-5-phenyl-4-styrylisoxazole (4i). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a white solid in a 72% yield: mp 125−127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81−7.83 (m, 2H), 7.36−7.43 (m, 7H), 7.29−7.33 (m, 1H), 6.99 (d, J = 16.4 Hz, 1H), 6.67 (d, J = 16.4 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 165.5, 136.9, 135.8, 129.8, 129.0, 128.9, 128.7, 128.3, 127.6, 126.5, 117.7, 112.4, 33.5, 29.2; HRMS (EI) calcd for $C_{21}H_{21}NO$, 303.1623; found 303.1625.

3,5-Diphenyl-4-vinylisoxazole (4j). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a white solid in a 52% yield: mp 66−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80−7.82 (m, 2H), 7.67−7.69 (m, 2H), 7.45−7.52 (m, 6H), 6.65 (dd, J = 17.8, 6.5 Hz, 1H), 5.36 (dd, J = 7.8, 1.4 Hz, 1H), 5.33 (dd, J = 14.2, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 162.4, 130.2, 129.7, 129.5, 129.01, 129.00, 128.8, 128.2, 127.7, 124.8, 120.6, 112.8; HRMS (EI) calcd for $C_{17}H_{13}NO$, 247.0997, found 247.0998.

4-(1-Ethoxyvinyl)-3,5-diphenylisoxazole (4k). Purification by flash column chromatography (20:1 hexanes/EtOAc). This product was obtained as a white solid in a 43% yield: mp 61−62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88−7.90 (m, 2H), 7.77−7.79 (m, 2H), 7.43−7.48 (m, 6H), 4.46 (d, J = 2.4 Hz, 1H), 4.28 (d, J = 2.4 Hz, 1H), 3.92 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 162.3, 151.9, 130.3, 129.8, 129.3, 128.8, 128.6, 128.3, 127.8, 127.2, 112.4, 90.3, 63.8, 14.5; HRMS (EI) calcd for $C_{19}H_{17}NO_2$, 291.1259, found 291.1264.

(*E*)-Methyl 3-(3-(tert-Butyl)-5-phenylisoxazol-4-yl)but-2-enoate (4l). Purification by flash column chromatography (10:1 hexanes/EtOAc). This product was obtained as a white solid in a 42% yield: mp 78−79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.69 (m, 2H), 7.39−7.43 (m, 3H), 6.06 (q, J = 1.4 Hz, 1H), 3.77 (s, 3H), 2.42 (d, J = 1.5 Hz, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 166.3, 164.3, 149.4, 130.1, 129.1, 127.8, 126.5, 124.3, 117.0, 51.6, 33.9, 29.7, 21.6; HRMS (EI) calcd for $C_{18}H_{21}NO_3$, 299.1521, found 299.1526.

(*E*)-3-(3-(4-Cyanophenyl)-5-phenylisoxazol-4-yl)-*N*,*N*-dimethylacrylamide (4m). Purification by flash column chromatography (10:1 hexanes/EtOAc). This product was obtained as a yellow solid in a 90% yield: mp 146−148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.81 (m, 6H), 7.66 (d, J = 15.4 Hz, 1H), 7.52−7.53 (m, 3H), 6.37 (d, J = 15.4 Hz, 1H), 2.99 (s, 3H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 165.7, 160.9, 133.9, 132.8, 131.2, 129.9, 129.44, 129.39, 128.1, 127.1, 122.7, 118.3, 113.9, 111.1, 37.1, 36.0; HRMS (EI) calcd for $C_{21}H_{17}N_3O_2$, 343.1321, found 343.1323.

(*E*)-3-(3,5-Diphenylisoxazol-4-yl)-1-morpholinoprop-2-en-1-one (4n). Purification by flash column chromatography (10:1 hexanes/EtOAc). This compound was obtained as a yellow solid in an 81% yield: mp 135−136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77−7.79 (m, 2H), 7.71 (d, J = 15.6 Hz, 1H), 7.60−7.62 (m, 2H), 7.50−7.54 (m, 6H), 6.28 (d, J = 15.6 Hz, 1H), 3.64−3.66 (m, 4H), 3.45−3.52 (m, 2H), 3.03−3.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 164.7, 162.4, 130.9, 130.5, 129.9, 129.3, 129.2, 129.1, 129.0, 128.1, 127.3, 120.7, 111.2, 66.8, 66.6, 45.8, 42.5; HRMS (EI) calcd for $C_{22}H_{20}N_2O_3$, 360.1474, found 360.1480.

***tert*-Butyl 3-Phenylnaphtho[1,2-*c*]isoxazole-5-carboxylate (5).** Purification by flash column chromatography (10:1 hexanes/EtOAc). This product was obtained as a yellow solid in a 58% yield: mp 110−112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J = 7.9 Hz, 1H), 8.59 (d, J = 7.9 Hz, 1H), 8.27 (s, 1H), 8.04 (d, J = 7.6 Hz, 2H), 7.69−7.72 (m, 1H), 7.59−7.66 (m, 3H), 7.53−7.56 (m, 1H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.2, 157.1, 131.0, 130.9, 130.2, 129.62, 129.59, 128.2, 128.0, 127.4, 127.2, 124.4, 123.1, 122.7, 110.9, 82.5, 28.5; HRMS (EI) calcd for $C_{22}H_{19}NO_3$, 345.1365, found 345.1365.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, ORTEP drawing of **5**, and X-ray data for **5**. 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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