Tandem Synthesis of 3-Chloro-4-iodoisoxazoles from 1-Copper(I) Alkynes, Dichloroformaldoxime, and Molecular Iodine

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Supporting Information

ABSTRACT: A tandem synthesis for structurally novel 3-chloro-4iodoisoxazoles was developed by simply mixing 1-copper(I) alkynes, dichloroformaldoxime, and molecular iodine together. The combination of 1-copper(I) alkyne and molecular iodine was well used as a

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=N + R-== OH

synthetic equivalent of 1-iodoalkyne without the need for tedious preparation, purification, and storage of 1-iodoalkyne.

I soxazoles are important heterocycles found in numerous natural products and synthetic compounds.¹ Their novel biological properties have made them a focus of medicinal chemistry. As shown in Figure 1, broxaterol (as a β_2 -selective



Figure 1. Structures of broxaterol and valdecoxib.

agonist) was developed to be an orally active antiasthmatic drug.² Valdecoxib (as a selective inhibitor of COX-2) was a drug for the treatment of osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea.³

Possibly encouraged by the discovery of broxaterol, 3-haloisoxazoles have been popular synthetic targets over the years. Many methods have been developed for their synthesis to increase the diversity of structures and properties.^{4,5} Recently, 4-iodoisoxazoles have become attractive synthetic targets for their wide uses as versatile substrates. As shown in Figure 2, they can be smoothly converted into the corresponding 4-aryl, 4-alkenyl, or 4-alkynylisoxazoles by metal-catalyzed cross-couplings.^{6–8}

In our recent chemical biology project, a variety of 3chloroisoxazoles were required and 3-chloro-4-iodoisoxazoles (1) were assigned as key precursors. To our great surprise, such precursors represent a structurally new type of compound that, to the best of knowledge, has yet to appear in the literature. Herein, we would like to report a novel tandem synthesis of 3-



Figure 2. 4-Iodoisoxazoles as versatile substrates.

chloro-4-iodoisoxazoles (1) from 1-Cu(I) alkynes (2), dichloroformaldoxime (Cl₂C=NOH, 3), and I₂ under extremely simple conditions.

Cu + I₂ NaHCO₃, DMF, rt, 6 h 20 samples in 40-94%

There are three types of methods for the synthesis of 4iodoisoxazoles which can be categorized by the substrates employed: (a) direct iodination of 4-H-isoxazoles; 6 (b) electrophilic cyclization of α -alkynyl oximes;⁷ (c) 1,3-dipolar cycloadditions of special alkynes (such as 1-iodo- or 1-aluminoalkynes) with nitrile oxides.⁸ Since 1,3-dipolar cycloadditions of alkynes with chloronitrile oxide $[Cl-C \equiv N \rightarrow O, generated in$ situ by dehydrochlorination of Cl_2C =NOH (3)] was the only practical method for introduction of a Cl-atom into the 3position of isoxazole ring, the procedure reported by Browne^{8c} was initially tested for our purpose. It is well-known that the 1,3dipolar cycloadditions usually have two common drawbacks caused by the extremely high reactivity of nitrile oxide: poor regiocontrol of products and dimerization of nitrile oxide.^{1,5,9} These drawbacks were partially overcome in Browne's procedure by adding aqueous Na₂CO₃ with a syringe pump, by which the formation rate of nitrile oxide was controlled. As shown in Scheme 1, when we followed Browne's procedure to treat the



mixture of 3 and 1-iodo-2-phenylethyne (4) with aqueous Na_2CO_3 without using the syringe pump modification, the desired compound 1a was isolated in 18% yield from a mixture with dimer 5 as a major byproduct.

Realizing many 1,3-dipolar cycloadditions using 1-iodoalkyne as a dipolarophile could be catalyzed by Cu(I)-catalysts,¹⁰ the catalytic system CuI/Et_3N^{10i} was tested in our reaction. Unfortunately, the lower yield of **1a** (9%) was obtained when

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the mixture of 3 and 4 was treated with CuI/Et_3N (Scheme 2). The problem may be caused by the fact that Et_3N may function as





both a ligand and a base, because a large amount of dimer 5 was separated. However, the same reaction gave a trace of 1a when Et_3N was replaced with powdered $NaHCO_3$. To our delight, the yield of 1a increased to 77% yield when a stoichiometric amount of CuI was employed. These results may arise from the fact that the catalytic cycle of Cu(I) may be inhibited in the absence of a ligand.^{10i,11}

In further experiments, we found that the preparation of 1iodoalkynes was the main obstacle to generalize this method. In the literature, many methods have been reported to convert terminal alkynes into the corresponding 1-iodoalkynes under mild conditions (without using strong bases or air sensitive reagents),^{10i,12} but the special iodination reagents and tedious workup processes were essential to each of them. Since 1iodoalkynes normally are sensitive to air and light, they tend to darken caused by decomposition during preparation, purification, and storage.¹³ In our recent work, 1-iodo-2-phenyethyne (4) was accidentally obtained in 98% yield by simply mixing 1-Cu(I) phenyethyne (2a) and NIS in CH_2Cl_2 within 10 min.¹⁴ Thus, we were encouraged to test the same conversion by using I_2 as a source of I^+ in DMF, and similarly excellent results were obtained (Scheme 3). Since this conversion clearly produces equimolar amounts of 4 and CuI only, the desired 1a may be synthesized by simply adding 3 and NaHCO₃ into this reaction system.





As shown in Table 1, the desired 1a was obtained in 74% yield when 3, 2a, I₂, and NaHCO₃ were mixed together in DMF for 6 h (entry 1), which matched well with the result obtained from the premade substrate 4. It was interesting to observe that this reaction was influenced significantly by the ratio of the reactants. The yield of 1a was decreased by increasing the ratio of I₂ (entries 2 and 3), which may be caused by the oxidative property of I₂ because the oxidative coupling product 1,4-diphenylbutadiyne was separated. Similarly, the yield of 1a was also decreased by using an excess of 3 (entries 4 and 5). To our delight, 1a was obtained in 94% yield when 1.2 equiv of 2a was used (entry 6). But, no significant improvement was observed by using a higher ratio of 2a (entry 7). Thus, entry 6 was assigned as our standard conditions.





As shown in Scheme 4, a tandem pathway was proposed for this novel method. First, $\mathbf{2a}$ reacts with I_2 to quantitatively





produce **4** and CuI. Then, the triple bond of **4** is activited by coordination with Cu(I).^{10a,b} Finally, the activated **4** as a dipolarophile undergoes a 1,3-dipolar cycloaddition with α -chloronitrile oxide to give the desired **1a**. Since 1-Cu(I) alkynes usually can be prepared as yellow crystals within 1 h^{15,6d,17a} and stored in air over one year without notable decomposition,^{15–17} the combination of 1-Cu(I) alkyne and I₂ could be well used as a synthetic equivalent of 1-iodoalkyne, but without the need for tedious separation, purification, and storage.

To generalize this method, the scope of substrates was tested. As shown in Scheme 5, all products (1a-1t) were obtained in good to excellent yields. The steric effects have significant influences on the arylethynes bearing electron-donating groups (see: 1b-1d), but almost no influences on those bearing electron-withdrawing groups (see: 1f-1h). The arylethynes usually gave the products in higher yields (see: 1a-1k) compared to the alkylethynes (see: 1l-1s). When 1-Cu(I)-2-isopropenylethyne (2t) was used as a substrate, both its triple and double bonds underwent the corresponding 1,3-dipolar cyclo-additions to give the expected product 1t containing both isoxazole and isoxazoline rings. The structure of 1a was further confirmed by its single crystal X-ray diffraction analysis (see Supporting Information (SI)).

As was expected, the iodine atom in **1a** was smoothly converted into the corresponding aryl, alkenyl, or alkynyl groups under Suzuki,^{7d} Heck,^{7d} or Sonogashira^{6f} cross-coupling conditions, while the chlorine atom stayed intact (Scheme 6). In practice, these structurally novel products could not be synthesized easily by other routine methods.

Scheme 5



Scheme 6



In summary, a tandem synthesis of 3-chloro-4-iodo-isoxazoles was developed from 1-Cu(I) alkynes, dichloroformaldoxime, and I₂. The final results of this method appeared to involve a Cu(I)-catalyzed 1,3-dipolar cycloaddition by using 1-iodoalkynes as a dipolarophile. However, it not only avoided the tedious preparation, purification, and storage of 1-iodoalkyne but also avoided use of a syringe pump in the experimental operations. Since the method proceeded under extremely convenient conditions and the products have entirely new structures, they may have wide applications in organic synthesis and drug discovery.

EXPERIMENTAL SECTION

All spectra of ¹H and ¹³C NMR were recorded in $CDCl_3$, and TMS was used as an internal reference. 1-Copper(I) alkynes (2a–2t) were prepared by reported procedures in literature.^{15,16d,17a}

A Typical Procedure for the Synthesis of 3-Chloro-4-iodo-5-phenylisoxazole (1a). To a suspension of 1-copper(I)-2-phenyl-ethyne (2a, 99 mg, 0.6 mmol), NaHCO₃ (84 mg, 1.0 mmol), and I₂ (127

mg, 0.5 mmol) in DMF (1 mL) was added dichloroformaldoxime (**3**, 57 mg, 0.5 mmol) at room temperature. After the resultant suspension was stirred for 10 min, a red homogeneous solution was formed. The reaction system was converted into a deep red-brown solution at the end point [6 h, monitored by TLC, the *in situ* generated 1-iodo-2-phenylethyne (4) was exhausted]. The reaction mixture was allowed to directly pass through a column [silica gel, 2% EtOAc in petroleum ether (60–90 °C)] to give 143 mg (94%) of product **1a** as a white solid, mp 91–92 °C. IR ν 2922, 1555, 1434, 1330 cm⁻¹; ¹H NMR (400 MHz) δ 8.04–8.03 (m, 2H), 7.53–7.51 (m, 3H); ¹³C NMR (100 MHz) δ 169.8, 158.5, 131.3, 128.9 (2C), 127.2 (2C), 126.4, 57.7; HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₅CIINO, [M + H]⁺ 305.9177; found 305.9182. Anal. Calcd for C₉H₅CIINO: C, 35.38; H, 1.65; N, 4.58. Found: C, 35.43; H, 1.69; N, 4.49.

The products 1b-1t were prepared by the similar method.

3-Chloro-4-iodo-5-(4-tolyl) isoxazole (1b). White solid (134 mg, 84%), mp 80–81 °C. IR ν 2923, 1496, 1333 cm⁻¹; ¹H NMR (400 MHz) δ 7.93 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 2.43 (s, 3H); ¹³C NMR (75 MHz) δ 170.0, 158.4, 141.9, 129.6 (2C), 127.2 (2C), 123.7, 57.0, 21.6; HRMS (ESI-TOF) (m/z): calcd for C₁₀H₇ClINO, [M + H]⁺ 319.9334; found 319.9331.

3-Chloro-4-iodo-5-(3-tolyl)isoxazole (1c). White solid (131 mg, 82%), mp 62–63 °C. IR ν 2920, 1545, 1437, 1322 cm⁻¹; ¹H NMR (400 MHz) δ 7.86–7.84 (m, 2H), 7.43–7.34 (m, 2H), 2.45 (s, 3H); ¹³C NMR (100 MHz) δ 170.0, 158.5, 138.8, 132.1, 128.8, 127.7, 126.4, 124.4, 57.6, 21.4; HRMS (ESI-TOF) (*m*/*z*): calcd for C₁₀H₇ClINO, [M + H]⁺ 319.9334; found 319.9335.

3-Chloro-4-iodo-5-(2-tolyl)isoxazole (1d). White solid (115 mg, 72%), mp 61–62 °C. IR ν 2926, 1547, 1445, 1329 cm⁻¹; ¹H NMR (400 MHz) δ 7.47–7.42 (m, 2H), 7.35–7.30 (m, 2H), 2.36 (s, 3H); ¹³C NMR (75 MHz) δ 173.5, 157.8, 138.0, 131.3, 131.0, 130.1, 126.1, 125.9, 61.7, 20.2; HRMS (ESI-TOF) (*m*/*z*): calcd for C₁₀H₇ClINO, [M + H]⁺ 319.9334; found 319.9333.

3-Chloro-4-iodo-5-(4-ethylphenyl)isoxazole (1e). White solid (127 mg, 76%), mp 50–52 °C. IR ν 2926, 1611, 1443, 1331 cm⁻¹; ¹H NMR (400 MHz) δ 7.95 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 2.72 (q, J = 7.8 Hz, 2H), 1.28 (t, J = 7.8 Hz, 3H); ¹³C NMR (100 MHz) δ 170.0, 158.4, 148.1, 128.4 (2C), 127.2 (2C), 123.9, 57.0, 28.9, 15.2; HRMS (ESI-TOF) (m/z): calcd for C₁₁H₉ClINO, [M + H]⁺ 333.9490; found 333.9490.

3-Chloro-4-iodo-5-(4-fluorophenyl)isoxazole (1f). White solid (149 mg, 92%), mp 87–88 °C. IR ν 2924, 1598, 1498, 1329 cm⁻¹; ¹H NMR (400 MHz) δ 8.07–8.04 (m, 2H), 7.26–7.20 (m, 2H); ¹³C NMR (100 MHz) δ 169.0, 164.3 (d, *J* = 252.7 Hz), 158.6, 129.5 (d, *J* = 8.6 Hz, 2C), 122.7 (d, *J* = 3.8 Hz), 116.2 (d, *J* = 21.9 Hz, 2C), 57.6. HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₄ClFINO, [M – H]⁻ 321.8937; found 321.8941.

3-Chloro-4-iodo-5-(3-fluorophenyl)isoxazole (1g). White solid (146 mg, 90%), mp 106–107 °C. IR (KBr) ν 3078, 1553, 1444, 1329 cm⁻¹; ¹H NMR (400 MHz) δ 7.87–7.75 (m, 2H), 7.54–7.48 (m, 1H), 7.26–7.22 (m, 1H); ¹³C NMR (100 MHz) δ 168.4, 162.6 (d, *J* = 246.0 Hz), 158.7, 130.7 (d, *J* = 8.6 Hz), 128.2 (d, *J* = 8.6 Hz), 122.9 (d, *J* = 2.9 Hz), 118.4 (d, *J* = 21.0 Hz), 114.2 (d, *J* = 23.8 Hz), 58.7. HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₄ClFINO, [M – H]⁻ 321.8937; found 321.8939.

3-Chloro-4-iodo-5-(2-fluorophenyl)isoxazole (1h). White solid (147 mg, 91%), mp 94–96 °C. IR ν 2921, 1617, 1468, 1331 cm⁻¹; ¹H NMR (300 MHz) δ 7.69–7.64 (m, 1H), 7.60–7.52 (m, 1H), 7.34–7.22 (m, 2H); ¹³C NMR (75 MHz) δ 168.4, 159.4 (d, *J* = 253.8 Hz), 158.3, 133.4 (d, *J* = 7.9 Hz), 130.6, 124.5 (d, *J* = 3.6 Hz), 116.8 (d, *J* = 20.8 Hz), 114.9 (d, *J* = 13.6 Hz), 62.4. HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₄ClFINO, [M – H]⁻ 321.8937; found 321.8935.

3-Chloro-4-iodo-5-(4-nitrophenyl)isoxazole (1i). Yellowish solid (145 mg, 83%), mp 156–158 °C. IR ν 3119, 1515, 1340 cm⁻¹; ¹H NMR (400 MHz) δ 8.40 (d, *J* = 9.2 Hz, 2H), 8.28 (d, *J* = 8.7 Hz, 2H); ¹³C NMR (100 MHz) δ 167.3, 159.1, 149.0, 131.8, 128.0 (2C), 124.2 (2C), 60.8; HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₄ClIN₂O₃, [M – H]⁻ 348.8882; found 348.8877.

3-Chloro-4-iodo-5-(4-chlorophenyl)isoxazole (1j). White solid (158 mg, 93%), mp 103–105 °C. IR ν 2922, 1586, 1474, 1327 cm⁻¹; ¹H

NMR (400 MHz) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H); ¹³C NMR (75 MHz) δ 168.6, 158.6, 137.5, 129.2 (2C), 128.3 (2C), 124.7, 58.1; HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₄Cl₂INO, [M + H]⁺ 339.8787; found 339.8783.

3-Chloro-4-iodo-5-(4-bromophenyl)isoxazole (1k). White solid (175 mg, 91%), mp 101–103 °C. IR ν 3086, 1584, 1479, 1327 cm⁻¹; ¹H NMR (400 MHz) δ 7.92 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H); ¹³C NMR (100 MHz) δ 168.8, 158.7, 132.3 (2C), 128.6 (2C), 126.0, 125.3, 58.2; HRMS (ESI-TOF) (m/z): calcd for C₉H₄BrClINO, [M – H]⁻ 381.8137; found 381.8123.

3-Chloro-4-iodo-5-isopentyl-isoxazole (11). Colorless oil (141 mg, 94%). IR ν 2959, 2871, 1578, 1462, 1345 cm⁻¹; ¹H NMR (400 MHz) δ 2.80 (t, *J* = 7.4 Hz, 2H), 1.62–1.58 (m, 3H), 0.95 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (100 MHz) δ 176.4, 157.1, 59.4, 35.6, 27.5, 25.5, 22.1 (2C). HRMS (ESI-TOF) (*m*/*z*): calcd for C₈H₁₁ClINO, [M + H]⁺ 299.9647; found 299.9633.

3-Chloro-4-iodo-5-heptyl-isoxazole (1m). Colorless oil (136 mg, 87%). IR ν 2928, 1578, 1460, 1346 cm⁻¹; ¹H NMR (400 MHz) δ 2.80 (t, J = 7.8 Hz, 2H), 1.74–1.67 (m, 2H), 1.38–1.26 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz) δ 176.3, 157.1, 59.6, 31.2, 28.6, 27.5, 26.9, 22.4, 14.0. HRMS (ESI-TOF) (m/z): calcd for C₉H₁₃ClINO, [M + H]⁺ 313.9803; found 313.9805.

3-Chloro-4-iodo-5-cyclohexyl-isoxazole (1n). Colorless oil (115 mg, 74%). IR ν 2933, 1570, 1445, 1340 cm⁻¹; ¹H NMR (400 MHz) δ 2.88–2.81 (m, 1H), 1.90–1.85 (m, 3H), 1.76–1.73 (m, 1H), 1.68–1.58 (m, 2H), 1.43–1.26 (m, 4H); ¹³C NMR (100 MHz) δ 178.9, 157.0, 57.9, 37.9, 29.8 (2C), 25.8 (2C), 25.5; HRMS (ESI-TOF) (*m*/*z*): calcd for C₉H₁₁ClINO, [M + H]⁺ 311.9647; found 311.9652.

3-Chloro-4-iodo-5-cyclopentyl-isoxazole (10). Yellowish oil (115 mg, 77%). IR (KBr) ν 2960, 2872, 1571, 1344 cm⁻¹; ¹H NMR (400 MHz) δ 3.30–3.22 (m, 1H), 2.06–2.02 (m, 2H), 1.86–1.79 (m, 4H), 1.71–1.70 (m, 2H); ¹³C NMR (100 MHz) δ 178.8, 157.1, 58.6, 38.3, 31.0 (2C), 25.7 (2C). HRMS (ESI-TOF) (*m*/*z*): calcd for C₈H₉ClINO, [M + H]⁺ 297.9490; found 297.9489.

3-Chloro-4-iodo-5-cyclopropyl-isoxazole (1p). Colorless oil (109 mg, 81%). IR (KBr) ν 2925, 1581, 1340 cm⁻¹; ¹H NMR (400 MHz) δ 2.10–2.03 (m, 1H), 1.21–1.11 (m, 4H); ¹³C NMR (100 MHz) δ 176.0, 157.2, 58.2, 9.4, 8.7 (2C). HRMS (ESI-TOF) (*m*/*z*): calcd for C₆H₅ClINO, [M + H]⁺ 269.9177; found 269.9181.

3-Chloro-4-iodo-5-(*tert***-butoxymethyl)isoxazole (1q).** Colorless oil (147 mg, 93%). IR ν 2976, 1584, 1339 cm⁻¹; ¹H NMR (400 MHz) δ 4.53 (s, 2H), 1.29 (s, 9H); ¹³C NMR (100 MHz) δ 172.3, 157.4, 75.1, 61.1, 55.9, 27.3 (3C); HRMS (ESI-TOF) (m/z): calcd for C₈H₁₁ClINO₂, [M + H]⁺ 315.9596; found 315.9588.

2-(3-Chloro-4-iodo-isoxazol-5-yl)-ethan-1-ol (1r). Yellowish oil (105 mg, 77%). IR ν 3416, 2889, 1579, 1433, 1345 cm⁻¹; ¹H NMR (400 MHz) δ 3.99 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 6.4 Hz, 2H), 1.96 (s, 1H); ¹³C NMR (100 MHz) δ 173.6, 157.4, 61.2, 59.5, 31.1; HRMS (ESI-TOF) (m/z): calcd for C₃H₃ClINO₂, [M + H]⁺ 273.9126; found 273.9124.

Ethyl 3-Chloro-4-iodoisoxazole-5-carboxylate (1s). White solid (115 mg, 76%), mp 109–110 °C. IR ν 2992, 1724, 1442, 1258 cm⁻¹; ¹H NMR (400 MHz) δ 4.48 (q, *J* = 7.4 Hz, 2H), 1.45 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz) δ 160.9, 159.4, 155.5, 68.2, 63.0, 14.0; HRMS (ESI-TOF) (*m*/*z*): calcd for C₆H₅CIINO₃, [M + H]⁺ 301.9075; found 301.9072. Anal. Calcd for C₆H₅CIINO₃: C, 23.90; H, 1.67; N, 4.65. Found: C, 23.89; H, 1.76; N, 4.71.

3,3'-Dichloro-4'-iodo-5-methyl-4,5-dihydro-5,5'-biisoxazole (**1t**). Yellowish oil (69 mg, 40%). IR ν 2988, 1569, 1432, 1330, 1131 cm⁻¹; ¹H NMR (400 MHz) δ 3.72 (d, *J* = 17.9 Hz, 1H), 3.28 (d, *J* = 17.4 Hz, 1H), 1.92 (s, 3H); ¹³C NMR (100 MHz) δ 171.7, 159.0, 148.1, 84.4, 59.1, 49.2, 24.6; HRMS (ESI-TOF) (*m*/*z*): calcd for C₇H₅Cl₂IN₂O₂, [M + H]⁺ 346.8846; found 346.8857. Anal. Calcd for C₇H₅Cl₂IN₂O₂: C, 24.23; H, 1.45; N, 8.07. Found: C, 24.10; H, 1.53; N, 8.19.

Synthesis of 3-Chloro-4-(3-nitrophenyl)-5-phenyl-isoxazole (6).rd After the mixture of 1a (153 mg, 0.5 mmol), 3-nitrophenylboronic acid (117 mg, 0.7 mmol), KHCO₃ (70 mg, 0.7 mmol), and PdCl₂ (5 mg, 0.025 mmol) in DMF-H₂O (4:1, 3 mL) in a Schlenk tube was degassed, it was stirred for 24 h at 80 °C under N₂. Then the resultant mixture was poured into H₂O (15 mL) and was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na₂SO₄. The solvent was removed on a rotavapor, and the residue was purified by flash chromatography [silica gel, 4% EtOAc in petroleum ether (60–90 °C)] to give 142 mg (94%) of **6** as a white solid, mp 118–119 °C. IR (KBr) ν 3070, 1632, 1529, 1391 cm⁻¹; ¹H NMR (400 MHz) δ 8.32–8.27 (m, 2H), 7.72–7.64 (m, 2H), 7.52–7.50 (m, 2H), 7.48–7.45 (m, 1H), 7.41–7.37 (m, 2H); ¹³C NMR (100 MHz) δ 167.6, 153.5, 148.7, 136.0, 131.2, 130.2, 129.9, 129.1 (2C), 127.0 (2C), 126.2, 124.9, 123.7, 113.0. HRMS (ESI-TOF) (*m/z*): calcd for C₁₅H₉ClN₂O₃, [M + H]⁺ 301.0374; found 301.0376. Anal. Calcd for C₁₅H₉ClN₂O₃: C, 59.91; H, 3.02; N, 9.32. Found: C, 59.80; H, 3.13; N, 9.47.

Synthesis of Methyl (E)-3-(3-Chloro-5-phenyl-isoxazol-4-yl)acrylate (7).^{7d} After the mixture of 1a (153 mg, 0.5 mmol), Na_2CO_3 (133 mg, 1.25 mmol), n-Bu₄NCl (139 mg, 0.5 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), and methyl acrylate (172 mg, 2.0 mmol) in DMF (2 mL) in a Schlenk tube was degassed, it was stirred for 24 h at 85 °C under N_2 . Then the resultant mixture was poured into $H_2O(15 \text{ mL})$ and was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na₂SO₄. The solvent was removed on a rotavapor, and the residue was purified by flash chromatography [silica gel, 4% EtOAc in petroleum ether (60–90 °C)] to give 118 mg (90%) of 7 as white solid, mp 80–81 °C. IR ν 2953, 1644, 1445, 1274 cm⁻¹; ¹H NMR (400 MHz) δ 7.70-7.67 (m, 2H), 7.62-7.54 (m, 4H), 6.78–6.74 (m, 1H), 3.81 (s, 3H); 13 C NMR (100 MHz) δ 170.5, 166.7, 152.7, 131.5, 130.1, 129.3 (2C), 127.9 (2C), 126.2, 121.5, 109.8, 51.9; HRMS (ESI-TOF) (m/z): calcd for C₁₃H₁₀ClNO₃, [M – H]⁻ 262.0276; found 262.0272. Anal. Calcd for C₁₃H₁₀ClNO₃: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.04; H, 3.94; N, 5.50.

Synthesis of 3-Chloro-4-[(4-methoxyphenyl)ethynyl]-5-phenylisoxazole (8).^{6f} After the mixture of 1a (153 mg, 0.5 mmol), 1-ethynyl-4-methoxybenzene (132 mg, 1 mmol), n-Bu₄NBr (161 mg, 0.5 mmol), K₂CO₃ (166 mg, 1.2 mmol), and Pd(PPh₃)₂Cl₂ (7 mg, 0.01 mmol) in DMF (2 mL) in a Schlenk tube was degassed, it was stirred for 16 h at 60 $^{\circ}$ C under N₂. Then the resultant mixture was poured into H₂O (15 mL) and was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na₂SO₄. The solvent was removed on a rotavapor, and the residue was purified by flash chromatography [silica gel, 5% EtOAc in petroleum ether (60-90 °C)] to give 128 mg (83%) of 8 as a white solid, mp 103–105 °C. IR ν 2973, 2221, 1603, 1510, 1403, 1276, 1249 cm $^{-1};\,^{1}\!\mathrm{H}\,\mathrm{NMR}$ (400 MHz) δ 8.17-8.15 (m, 2H), 7.52-7.51 (m, 5H), 6.92 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H); ¹³C NMR (100 MHz) δ 169.5, 160.3, 155.3, 133.2 (2C), 131.3, 129.0 (2C), 126.6, 126.1 (2C), 114.2 (2C), 114.1, 99.6, 97.7, 74.9, 55.3; HRMS (ESI-TOF) (m/z): calcd for C₁₈H₁₂ClNO₂, [M + H]⁺ 310.0629; found 310.0631. Anal. Calcd for C18H12ClNO2: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.51; H, 3.91; N, 4.59.

ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra for products **1a–1t**, as well as a CIF file for the single crystal X-ray diffraction analysis of **1a**. 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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