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

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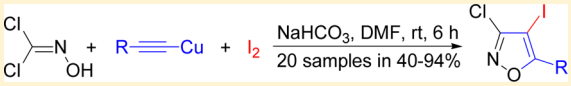
Supporting Information

ABSTRACT: A tandem synthesis for structurally novel 3-chloro-4-iodoisoxazoles 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 synthetic equivalent of 1-iodoalkyne without the need for tedious preparation, purification, and storage of 1-iodoalkyne.



Isoxazoles 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 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]

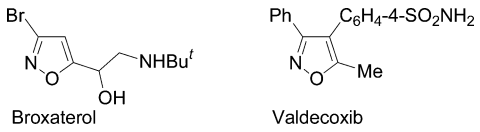


Figure 1. Structures of broxaterol and valdecoxib.

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 3-chloroisoxazoles 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-chloro-4-iodoisoxazoles (**1**) from 1-Cu(I) alkynes (**2**), dichloroformaldoxime ($Cl_2C{=}NOH$, **3**), and I_2 under extremely simple conditions.

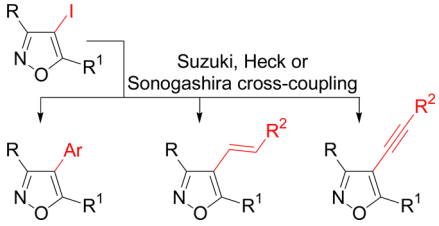
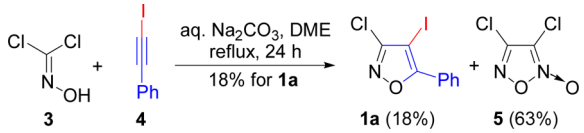


Figure 2. 4-Iodoisoxazoles as versatile substrates.

There are three types of methods for the synthesis of 4-iodoisoxazoles 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-alumino-alkynes) with nitrile oxides.[8] Since 1,3-dipolar cycloadditions of alkynes with chloronitrile oxide [Cl−C≡N→O, generated *in situ* by dehydrochlorination of $Cl_2C{=}NOH$ (**3**)] was the only practical method for introduction of a Cl-atom into the 3-position of isoxazole ring, the procedure reported by Browne[8c] was initially tested for our purpose. It is well-known that the 1,3-dipolar 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 Na_2CO_3 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.

Scheme 1



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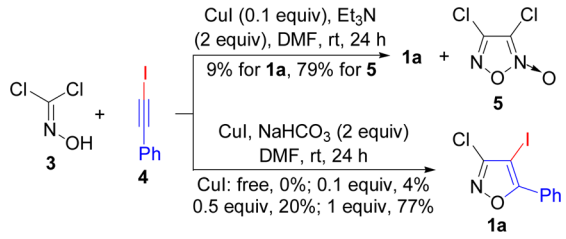
the mixture of **3** and **4** was treated with CuI/Et_3N (Scheme 2). The problem may be caused by the fact that Et_3N may function as

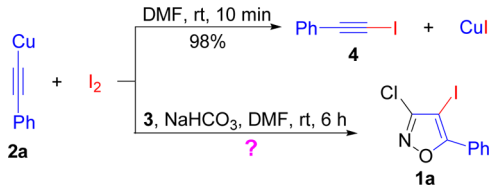
Scheme 2



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]

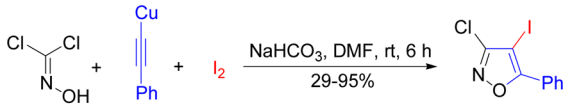
In further experiments, we found that the preparation of 1-iodoalkynes was the main obstacle to generalize this method. In the literature, many methods have been reported to convert terminal alkynes into the corresponding 1-iodoalkynes under mild conditions (without using strong bases or air sensitive reagents),[10i,12] but the special iodination reagents and tedious workup processes were essential to each of them. Since 1-iodoalkynes 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 $NaHCO_3$ into this reaction system.

Scheme 3



As shown in Table 1, the desired **1a** was obtained in 74% yield when **3**, **2a**, I_2, and $NaHCO_3$ 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 I_2 (entries 2 and 3), which may be caused by the oxidative property of I_2 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.

Table 1. Effect of the Ratios of 3, 2a, and I_2 on the Yield of 1a[a]

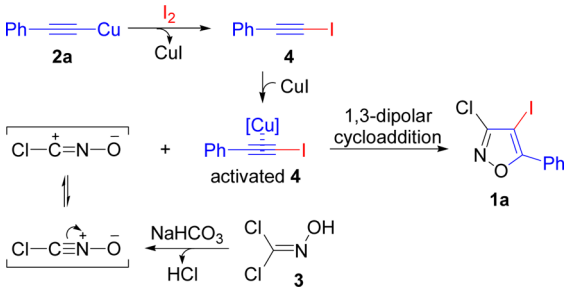


entry	3:2a:I_2 (mole ratio)	1a (%)[b]
1	1.0:1.0:1.0	74
2	1.0:1.0:**1.2**	60
3	1.0:1.0:**1.5**	29
4	**1.2**:1.0:1.0	60
5	**1.5**:1.0:1.0	63
6	1.0:**1.2**:1.0	94
7	1.0:**1.5**:1.0	95

[a]The mixture of **3**, **2a**, I_2, and $NaHCO_3$ (1 mmol, 2 equiv) in DMF (1 mL) was stirred in a stoppered glass tube. [b]The isolated yields.

As shown in Scheme 4, a tandem pathway was proposed for this novel method. First, **2a** reacts with I_2 to quantitatively

Scheme 4



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 I_2 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 cycloadditions 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.

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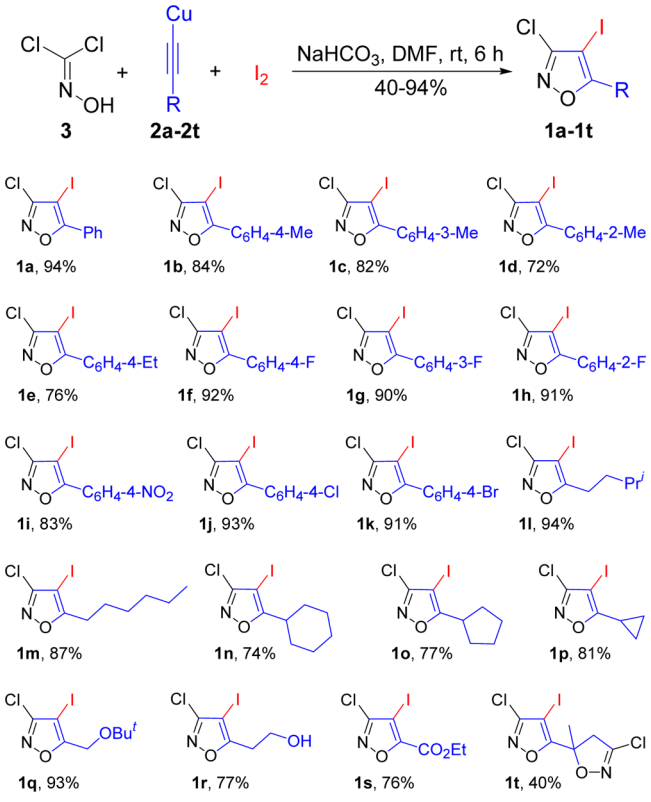
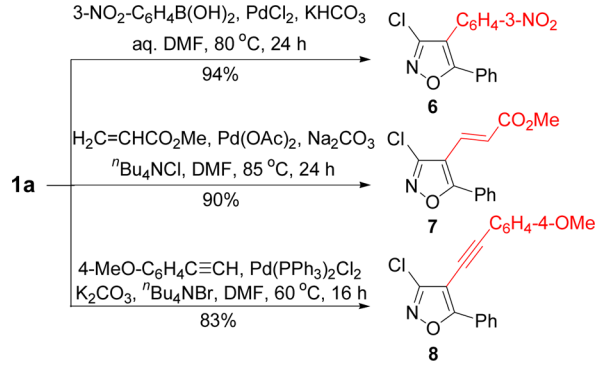
Scheme 5



Scheme 6



In summary, a tandem synthesis of 3-chloro-4-iodo-isoxazoles was developed from 1-Cu(I) alkynes, dichloroformaldoxime, and I_2. 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 ^{1}H and ^{13}C 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-phenylethyne (**2a**, 99 mg, 0.6 mmol), $NaHCO_3$ (84 mg, 1.0 mmol), and I_2 (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}; ^{1}H NMR (400 MHz) δ 8.04−8.03 (m, 2H), 7.53−7.51 (m, 3H); ^{13}C 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 C_9H_5ClINO, $[M + H]^+$ 305.9177; found 305.9182. Anal. Calcd for C_9H_5ClINO: 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}; ^{1}H NMR (400 MHz) δ 7.93 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 2.43 (s, 3H); ^{13}C 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 $C_{10}H_7ClINO$, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 7.86−7.84 (m, 2H), 7.43−7.34 (m, 2H), 2.45 (s, 3H); ^{13}C 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 $C_{10}H_7ClINO$, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 7.47−7.42 (m, 2H), 7.35−7.30 (m, 2H), 2.36 (s, 3H); ^{13}C 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 $C_{10}H_7ClINO$, $[M + H]^+$ 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}; ^{1}H 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); ^{13}C 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 $C_{11}H_9ClINO$, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 8.07−8.04 (m, 2H), 7.26−7.20 (m, 2H); ^{13}C 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 $C_9H_4ClFINO$, $[M - H]^-$ 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}; ^{1}H NMR (400 MHz) δ 7.87−7.75 (m, 2H), 7.54−7.48 (m, 1H), 7.26−7.22 (m, 1H); ^{13}C 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 $C_9H_4ClFINO$, $[M - H]^-$ 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}; ^{1}H NMR (300 MHz) δ 7.69−7.64 (m, 1H), 7.60−7.52 (m, 1H), 7.34−7.22 (m, 2H); ^{13}C 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 $C_9H_4ClFINO$, $[M - H]^-$ 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}; ^{1}H NMR (400 MHz) δ 8.40 (d, J = 9.2 Hz, 2H), 8.28 (d, J = 8.7 Hz, 2H); ^{13}C 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 $C_9H_4ClIN_2O_3$, $[M - H]^-$ 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}; ^{1}H

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NMR (400 MHz) δ 7.98 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H); ^{13}C 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 $C_9H_4Cl_2INO$, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 7.92 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H); ^{13}C 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 $C_9H_4BrClINO$, $[M - H]^-$ 381.8137; found 381.8123.

3-Chloro-4-iodo-5-isopentyl-isoxazole (1l). Colorless oil (141 mg, 94%). IR ν 2959, 2871, 1578, 1462, 1345 cm^{-1}; ^{1}H 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); ^{13}C 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 $C_8H_{11}ClINO$, $[M + H]^+$ 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}; ^{1}H 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); ^{13}C 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 $C_9H_{13}ClINO$, $[M + H]^+$ 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}; ^{1}H 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); ^{13}C 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 $C_9H_{11}ClINO$, $[M + H]^+$ 311.9647; found 311.9652.

3-Chloro-4-iodo-5-cyclopentyl-isoxazole (1o). Yellowish oil (115 mg, 77%). IR (KBr) ν 2960, 2872, 1571, 1344 cm^{-1}; ^{1}H 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); ^{13}C 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 C_8H_9ClINO, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 2.10−2.03 (m, 1H), 1.21−1.11 (m, 4H); ^{13}C NMR (100 MHz) δ 176.0, 157.2, 58.2, 9.4, 8.7 (2C). HRMS (ESI-TOF) (m/z): calcd for C_6H_5ClINO, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 4.53 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz) δ 172.3, 157.4, 75.1, 61.1, 55.9, 27.3 (3C); HRMS (ESI-TOF) (m/z): calcd for $C_8H_{11}ClINO_2$, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 3.99 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 6.4 Hz, 2H), 1.96 (s, 1H); ^{13}C NMR (100 MHz) δ 173.6, 157.4, 61.2, 59.5, 31.1; HRMS (ESI-TOF) (m/z): calcd for $C_5H_5ClINO_2$, $[M + H]^+$ 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}; ^{1}H NMR (400 MHz) δ 4.48 (q, J = 7.4 Hz, 2H), 1.45 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz) δ 160.9, 159.4, 155.5, 68.2, 63.0, 14.0; HRMS (ESI-TOF) (m/z): calcd for $C_6H_5ClINO_3$, $[M + H]^+$ 301.9075; found 301.9072. Anal. Calcd for $C_6H_5ClINO_3$: 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}; ^{1}H NMR (400 MHz) δ 3.72 (d, J = 17.9 Hz, 1H), 3.28 (d, J = 17.4 Hz, 1H), 1.92 (s, 3H); ^{13}C 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 $C_7H_5Cl_2IN_2O_2$, $[M + H]^+$ 346.8846; found 346.8857. Anal. Calcd for $C_7H_5Cl_2IN_2O_2$: 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).[7d] After the mixture of **1a** (153 mg, 0.5 mmol), 3-nitrophenylboronic acid (117 mg, 0.7 mmol), $KHCO_3$ (70 mg, 0.7 mmol), and $PdCl_2$ (5 mg, 0.025 mmol) in DMF−H_2O (4:1, 3 mL) in a Schlenk tube was degassed, it was stirred for 24 h at 80 °C under N_2. Then the resultant mixture was poured into H_2O (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 Na_2SO_4. 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}; ^{1}H 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); ^{13}C 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 $C_{15}H_9ClN_2O_3$, $[M + H]^+$ 301.0374; found 301.0376. Anal. Calcd for $C_{15}H_9ClN_2O_3$: 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*-Bu_4NCl (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 mL) and was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. 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}; ^{1}H 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 $C_{13}H_{10}ClNO_3$, $[M - H]^-$ 262.0276; found 262.0272. Anal. Calcd for $C_{13}H_{10}ClNO_3$: 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*-Bu_4NBr (161 mg, 0.5 mmol), K_2CO_3 (166 mg, 1.2 mmol), and $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) in DMF (2 mL) in a Schlenk tube was degassed, it was stirred for 16 h at 60 °C under N_2. Then the resultant mixture was poured into H_2O (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 Na_2SO_4. 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}H 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); ^{13}C 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 $C_{18}H_{12}ClNO_2$, $[M + H]^+$ 310.0629; found 310.0631. Anal. Calcd for $C_{18}H_{12}ClNO_2$: C, 69.80; H, 3.90; N, 4.52. Found: C, 69.51; H, 3.91; N, 4.59.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C 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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REFERENCES

(1) For reviews, see: (a) Kumar, K. A.; Jayaroopa, P. *Int. J. Pharm. Chem. Biol. Sci.* **2013**, *3*, 294−304. (b) Giomi, D.; Cordero, F. M.; Machetti, F. Isoxazoles. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. *4*, pp 365−486. (c) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925−958. (d) Grunanger, P.; Vita Finzi, P. Isoxazole. Part I; In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Weissberger, A., Eds.; Wiley: New York, 1990; pp 183−209.

(2) De Amici, M.; De Micheli, C.; Carrea, G.; Spezia, S. *J. Org. Chem.* **1989**, *54*, 2646−2650.

(3) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643−9647.

(4) For selected references: (a) Liu, Y.; Cui, Z.; Liu, B.; Cai, B.; Li, Y.; Wang, Q. *J. Agric. Food Chem.* **2010**, *58*, 2685−2689. (b) Dallanoce, C.; Frigerio, F.; De Amici, M.; Dorsch, S.; Klotz, K.-N.; De Micheli, C. *Bioorg. Med. Chem.* **2007**, *15*, 2533−2543. (c) Cha, J. H.; Cho, Y. S.; Pae, A. N.; Koh, H. Y.; Jeong, D.; Kong, J. Y.; Lee, E.; Choi, K. I. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2855−2857. (d) Kim, D. J.; Seo, K. J.; Lee, K. S.; Shin, K. J.; Yoo, K. H.; Kim, D. C.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2799−2802. (e) Chiarino, D.; Grancini, G.; Frigeni, V.; Biasini, I.; Carenzi, A. *J. Med. Chem.* **1991**, *34*, 600−605. (f) Wigerinck, P.; Snoeck, R.; Claes, P.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1991**, *34*, 1767−1772. (g) Franke, A.; Frickel, F.-F.; Gries, J.; Lenke, D.; Schlecker, R.; Thieme, P. D. *J. Med. Chem.* **1981**, *24*, 1460−1464. (h) Carr, J. B.; Durham, H. G.; Hass, D. K. *J. Med. Chem.* **1977**, *20*, 934−939.

(5) (a) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707−6714. (b) Stevens, J. L.; Welton, T. D.; Deville, J. P.; Behar, V. *Tetrahedron Lett.* **2003**, *44*, 8901−8903. (c) Ruano, J. L. G.; Fraile, A.; Martin, M. R. *Tetrahedron* **1999**, *55*, 14491−14500. (d) Chiarino, D.; Napoletano, M.; Sala, A. *J. Heterocycl. Chem.* **1987**, *24*, 43−46.

(6) (a) Choi, M. J.; No, E. S.; Thorat, D. A.; Jang, J. W.; Yang, H.; Lee, J.; Choo, H.; Kim, S. J.; Lee, C. S.; Ko, S. Y.; Lee, J.; Nam, G.; Pae, A. N. *J. Med. Chem.* **2013**, *56*, 9008−9018. (b) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J. Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326−10329. (c) Iglesias, M.; Schuster, O.; Albrecht, M. *Tetrahedron Lett.* **2010**, *51*, 5423−5425. (d) Brough, P. A.; Aherne, W.; Barril, X.; Borgognoni, J.; Boxall, K.; Cansfield, J. E.; Cheung, K.-M. J.; Collins, I.; Davies, N. G. M.; Drysdale, M. J.; Dymock, B.; Jordan, A. M.; Lockie, A.; Martins, V.; Massey, A.; Matthews, T.; McDonald, E.; Northfield, C. J.; Pearl, L. H.; Prodromou, C.; Ray, S.; Raynaud, F. I.; Roughley, S. D.; Sharp, S. Y.; Surgenor, A.; Walmsley, D. L.; Webb, P.; Wood, M.; Workman, P.; Wright, L. *J. Med. Chem.* **2008**, *51*, 196−218. (e) Day, R. A.; Blake, J. A.; Stephens, C. E. *Synthesis* **2003**, 1586−1590. (f) Kromann, H.; Sløk, F. A.; Johansen, T. N.; Krogsgaard-Larsen, P. *Tetrahedron* **2001**, *57*, 2195−2201.

(7) (a) kalin, J. H.; Zhang, H.; Gaudrel-Grosay, S.; Vistoli, G.; Kozikowski, A. P. *ChemMedChem* **2012**, *7*, 425−439. (b) Okitsu, T.; Sato, K.; Potewar, T. M.; Wada, A. *J. Org. Chem.* **2011**, *76*, 3438−3449. (c) Debleds, O.; Gayon, E.; Ostaszuk, E.; Vrancken, E.; Campagne, J.-M. *Chem.—Eur. J.* **2010**, *16*, 12207−12213. (d) Waldo, J. P.; Mehta, S.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 658−663. (e) Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 9643−9647. (f) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203−5205.

(8) (a) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chem.—Eur. J.* **2014**, *20*, 11101−11110. (b) Jackowshi, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664−5667. (c) Crossley, J. A.; Browne, D. L. *J. Org. Chem.* **2010**, *75*, 5414−5416.

(9) Grundmann, C. *Synthesis* **1970**, 344−359.

(10) (a) Lal, S.; Rzepa, H. S.; Díez-González, S. *ACS Catal.* **2014**, *4*, 2274−2287. (b) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457−460. (c) Fu, D.; Zhang, J.; Cao, S. *J. Fluorine Chem.* **2013**, *156*, 170−176. (d) Brotherton, W. S.; Clark, R. J.; Zhu, L. *J. Org. Chem.* **2012**, *77*, 6443−6455. (e) García-Álverez, J.; Díez, J.; Gimeno, J.; Suárez, F. J.; Vincent, C. E. *J. Inorg. Chem.* **2012**, 5854−5863. (f) Juríček, M.; Stout, K.; Kouwer, P. H.; Rowan, A. E. *Org. Lett.* **2011**, *13*, 3494−3497. (g) Recsei, C.; McErlean, C. S. P. *Tetrahedron: Asymmetry* **2010**, *21*, 149−152. (h) García-Álverez, J.; Díez, J.; Gimeno, J. *Green Chem.* **2010**, *12*, 2127−2130. (i) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8018−8021.

(11) For example, the mixture of 1-iodoalkyne, azide, and CuI failed to give a cycloaddition product; see: Kuijpers, B. H. M.; Dijkmans, G. C. T.; Groothuys, S.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Synlett* **2005**, 3059−3062. Yet the same mixture gave excellent yields of 5-iodo-1,2,3-triazoles in the presence of a ligand; see ref 10i.

(12) (a) Nouzarian, M.; Hosseinzadeh, R.; Golchoubian, H. *Synth. Commun.* **2013**, *43*, 2913−2925. (b) Starkov, P.; Rota, F.; D'Oyley, J. M.; Sheppard, T. D. *Adv. Synth. Catal.* **2012**, *354*, 3217−3224. (c) Reddy, K. R.; Venkateshwar, M.; Maheswari, C. U.; Kumar, P. S. *Tetrahedron Lett.* **2010**, *51*, 2170−2173. (d) Yan, J.; Li, J.; Cheng, D. *Synlett* **2007**, 2442−2444. (e) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2004**, *45*, 1417−1419. (f) Homsi, F.; Rousseau, G. *Tetrahedron Lett.* **1999**, *40*, 1495−1498. (g) Monenschein, H.; Soukourni-Argirusi, G.; Schubothe, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett.* **1999**, *1*, 2101−2104. (h) Naskar, D.; Roy, S. *J. Org. Chem.* **1999**, *64*, 6896−6897. (i) Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1995**, *36*, 2619−2622. (j) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1988**, 909−910.

(13) Pelletier, G.; Lie, S.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2012**, *14*, 5464−5467. In this article, the decomposition of 1-iodoalkynes was studied and a special note was given in the SI (pp S12−S13): "**Note:** The synthesized 1-iodoalkynes were found usually unstable to light exposure and trace of iodine is observed when the product is solubilized or purified by flash chromatography (a pink color gradually appears when flashed or stored on the bench at room temperature). They should be kept under argon in the freezer (−20 °C) or use directly in a further reaction."

(14) Wang, B.; Zhang, J.; Wang, X.; Liu, N.; Chen, W.; Hu, Y. *J. Org. Chem.* **2013**, *78*, 10519−10523.

(15) (a) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 4829−4837. (b) Owsley, D. C.; Castro, C. E. *Org. Synth.* **1972**, *52*, 128−130. (c) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Moje, S. *J. Am. Chem. Soc.* **1969**, *91*, 6464−6470. (d) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313−3315.

(16) Recent works on 1-Cu(I) alkynes: (a) Jouvin, K.; Veillard, R.; Theunissen, C.; Alayrac, C.; Gaumont, A.-C.; Evano, G. *Org. Lett.* **2013**, *15*, 4592−4595. (b) Verna, F.; Guissart, C.; Pous, J.; Evano, G. *Monatsh. Chem.* **2013**, *144*, 523−529. (c) Laouiti, A.; Jouvin, K.; Bourdreux, F.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Synthesis* **2012**, *44*, 1491−1500. (d) Jouvin, K.; Heimburger, J.; Evano, G. *Chem. Sci.* **2012**, *3*, 756−760. (e) Buckley, B. R.; Dann, S. E.; Heaney, H.; Stubbs, E. C. *Eur. J. Org. Chem.* **2011**, 770−776.

(17) For our recent works on 1-Cu(I) alkynes, see: Reference 14 and (a) Chen, W.; Wang, B.; Liu, N.; Huang, D.; Wang, X.; Hu, Y. *Org. Lett.* **2014**, *16*, 6140−6143. (b) Wang, B.; Liu, N.; Chen, W.; Huang, D.; Wang, X.; Hu, Y. *Adv. Synth. Catal.* **2014**, *356*, ASAP (DOI: 10.1002/adsc.201400471). (c) Wang, B.; Ahmed, M. N.; Zhang, J.; Chen, W.; Wang, X.; Hu, Y. *Tetrahedron Lett.* **2013**, *54*, 6097−6100. (d) Wang, B.; Liu, N.; Shao, C.; Zhang, Q.; Wang, X.; Hu, Y. *Adv. Synth. Catal.* **2013**, *355*, 2564−2568.

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