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Graphical Abstract

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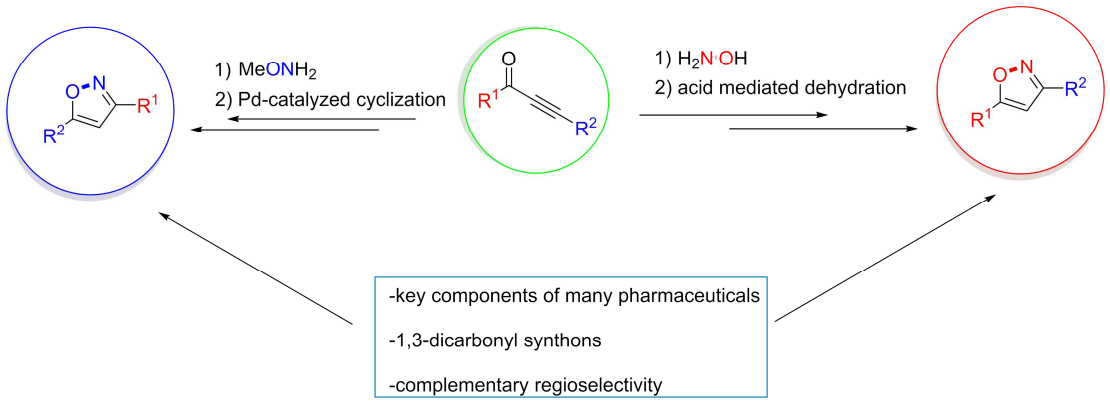

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ABSTRACT

Two regioselective synthetic routes towards 3,5-disubstituted isoxazoles from ynones are reported. One route takes place via first converting the ynones to ynone *O*-methyl oximes, followed by a palladium-catalyzed intramolecular cyclization. The other involves the formation of 5-hydroxy-4,5-dihydroisoxazoles by a cyclocondensation between ynones and hydroxylamine, and subsequent acid mediated dehydration. The two routes are not only both highly regioselective, but also complementary to each other as a pair of regioisomeric 3,5-disubstituted isoxazoles are readily prepared from one single ynone substrate. The efficiency of the two routes are further evaluated and demonstrated in the synthesis of three representative 3,5-disubstituted isoxazoles.

Introduction

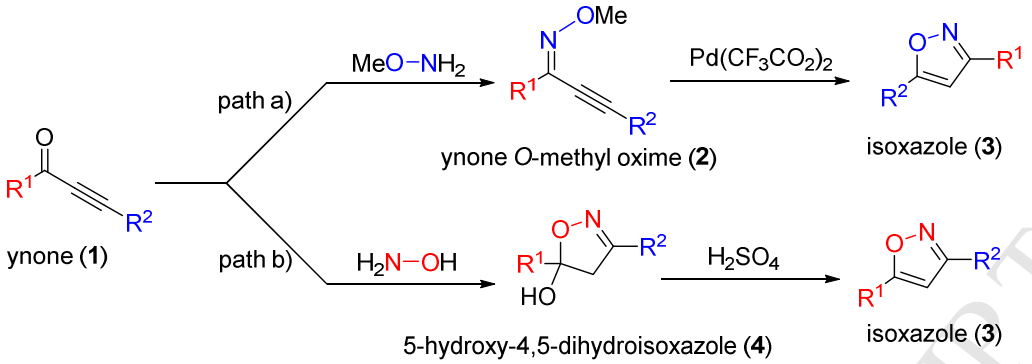
Isoxazoles are one of the most prominent classes of heterocycles. They are key components of many pharmaceuticals as well as biologically interesting compounds.[1] In addition, isoxazoles are known as masked 1,3-dicarbonyl synthons, and their relatively labile N-O bond can be readily cleaved, forming 1,3-dicarbonyl equivalents such as β-amino enones.[2] A variety of protocols have been developed for the synthesis of isoxazoles, including [3+2] cycloaddition reactions of alkenes/alkynes with nitrile oxides and cyclocondensation between α,β-unsaturated carbonyl compounds and hydroxylamine.[2,3] These synthetic methods all have their own advantages in terms of matters such as catalyst cost, substrate scope, regioselectivity and operational simplicity. Some of these methods are complementary to one another, providing more options to chemists if their synthetic target is restrained by the limitation of one particular method.

Our group has been interested in developing new synthetic methods towards isoxazoles[4] and employing isoxazoles as synthetic intermediates in construction of more complex heterocycles.[5] During the course of synthesizing trisubstituted isoxazoles by a palladium-catalyzed cascade reaction,[4] we noticed that we could selectively prepare either regioisomer of a pair of regioisomeric 3,5-disubstituted isoxazoles from a single ynone substrate when employing the following two complementary synthetic protocols: 1) converting the ynone (**1**) to ynone *O*-methyl oxime (**2**), followed by a palladium-catalyzed cyclization (Scheme 1, path a); 2) treating ynone (**1**) with hydroxylamine to form 5-hydroxy-4,5-dihydroisoxazole (**4**), followed by an acid mediated dehydration (Scheme 1, path b). We believe the current synthetic strategy is attractive, as examples of synthesis of regioisomeric isoxazoles from a single starting material via two mechanistically different synthetic routes are still scarce. We herein report the details of the work, including the synthetic protocol development, substrate scope investigation and comparison of the efficiency of the two routes.

Results and discussion

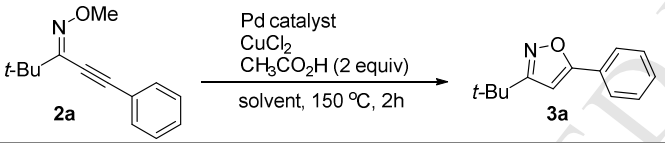
We first chose palladium-catalyzed cyclization of ynone-*O*-methyl oximes to construct isoxazole rings, based on the following reasons: 1) operational simplicity, especially because the starting material ynones were usually readily prepared by a simple Sonogashira coupling between an acid chloride and

Scheme 1. Regioselective Synthesis of 3,5-Disubstituted Isoxazoles from Ynones.



a terminal alkyne, and 2) the possibility of employing the direct cyclization product, an isoxazolylpalladium species, straight into a subsequent reaction step without terminating an on-going cascade process. The latter is particularly useful in preparing trisubstituted isoxazoles and more complex heterocycles. During the course of exploring new synthetic protocols for trisubstituted isoxazoles via palladium-catalyzed electrophilic cyclization of ynone *O*-methyl oximes,[4] we noticed that 3,5-disubstituted isoxazoles formed as the major product in the presence of proton sources such as a protic acid.

Table 1. Optimization of Reaction Conditions for the Cyclization of Ynone *O*-Methyl Oxime **2a**.[a]



Entry	Pd Catalyst (10 mol%)	$CuCl_2$	Solvent	Yield[b]
1	$PdCl_2$	2eq	DMF	65%
2	$Pd(O_2CCF_3)_2$	2eq	DMF	77%
3	$Pd(O_2CCF_3)_2$	2eq	DMSO	96%
4	$Pd(O_2CCF_3)_2$	1eq	DMSO	92%
5[c]	$Pd(O_2CCF_3)_2$	-	DMSO	49%
6[d]	-	1eq	DMSO	-

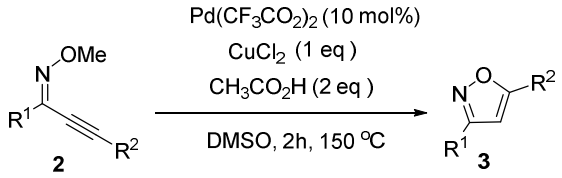
[a] General procedure: The palladium catalyst (10 mol%), $CuCl_2$, substrate **2a** (110.2 mg, 0.5 mmol), CH_3CO_2H (1.0 mmol, 2 equivalents), and solvent (4 mL) were added to a 20 mL glass vial sealed with a pressure relief cap. The reaction mixture was purged with argon, sealed, and stirred at 150 °C for 2 h. [b] Isolated yields after column chromatography. [c] Starting material **2a** was recovered in 50%. [d] Starting material **2a** was fully recovered.

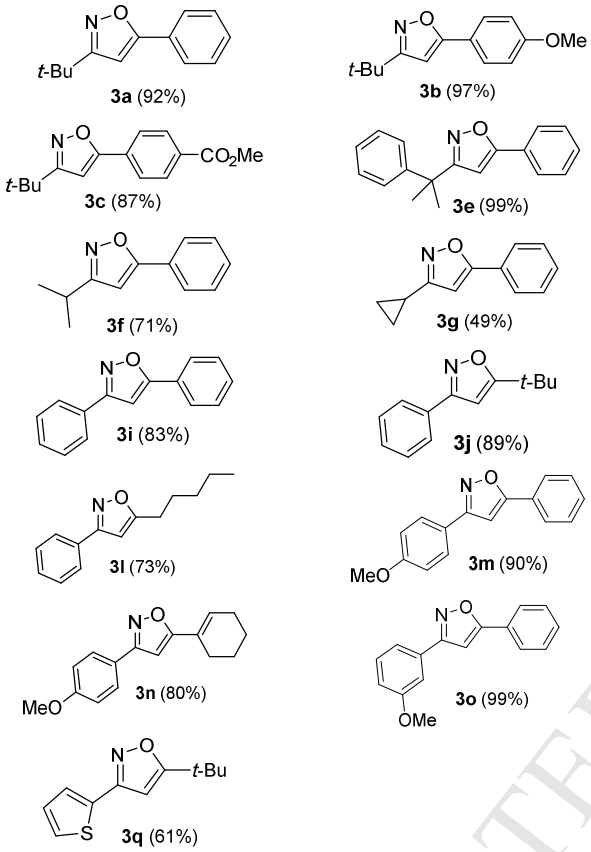
For example, in the presence of 10 mol% of $PdCl_2$, 2 equivalents of $CuCl_2$, and 2 equivalents of acetic acid, cyclization of ynone *O*-methyl oxime **2a** was completed in DMF at 150 °C within 2 hours, yielding isoxazole **3a** in 65% yield (Table 1, entry 1). The yield of **3a** was enhanced to 77%, when $PdCl_2$ was replaced by $Pd(O_2CCF_3)_2$ (Table 1, entry 2). A quick solvent screening showed that the chemical yield of the cyclized product was further increased to 96% in DMSO (Table 1, entry 3). A slight decrease of the yield to 92% was observed, when the amount of $CuCl_2$ was reduced to 1 equivalent (Table 1, entry 4). On the other hand, in the absence of $CuCl_2$, the chemical yield dropped dramatically to 49%, and the starting material **2a** was recovered in 50% (Table 1, entry 5). Further study showed that no **3a** was obtained in the absence of any palladium catalyst, and **2a** was fully recovered after 2 hours (Table 1, entry 6).

We then examined the substrate scope of the palladium-catalyzed cyclization reaction, using the conditions listed in Entry 4 in Table 1. Both aliphatic (alkyl and alkenyl) and aromatic (aryl and heteroaryl) substituents are well accommodated at either the proximal (R^1 group) or the distal (R^2 group) position to the ynone *O*-methyl oxime (**2**) carbon. In addition, both an electron-donating group such as methoxy (MeO) and an electron-withdrawing group such as methyl ester (CO_2Me) are tolerated in the reaction (Table 2, **3b** and **3c**). Steric effects, however, play a significant role in this cyclization reaction. While the cyclization products formed in high yields when a sterically hindered *tertiary* alkyl or phenyl group was present proximal to the oxime carbon (as the R^1 group) (**3a-c**, **3e**, Table 2), moderate yields were generally observed when a sterically less hindered secondary alkyl or thienyl group was present at the same position (**3f**, **3g**, and **3q**, Table 2). The lower chemical yields obtained in the latter cases resulted from the intrinsic nature of this electrophilic cyclization protocol. It only takes place on the oxime substrates where the *O*-methyl group is *cis* to the ynone triple bond[6] (these isomers are usually in the *Z* configuration[7] according to IUPAC nomenclature). We found that the configuration of the oximes that we prepared was dependent on the difference in steric bulk of the two groups flanking the ynone carbonyl, giving a preference for the oxime *O*-methyl group *anti* to the sterically bulkier substituent. For instance, both the *tertiary*-butyl and phenyl groups (as R^1) together with an alkynyl (as R^2) gave exclusive formation of the desired *Z* isomer. On the other hand, when sterically less hindered secondary alkyl groups and a thienyl group were present at the same position (as R^1) in ynone **1**, the stereoselectivity in the oxime formation step dramatically decreased, leading to the formation of a pair of inseparable *E/Z* isomers. The lower yields observed in the palladium-catalyzed cyclization products **3f**, **3g**,

and **3q** resulted from the contamination of the unreactive and inseparable *E*-isomers generated together with the desired *Z*-isomers in the oxime formation step.

Table 2. Palladium-Catalyzed Cyclization of Ynone *O*-Methyl Oximes.[a,b,c]





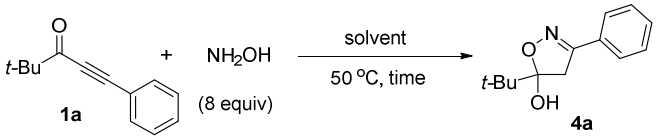
[a] An oven dried 20 mL glass vial was charged with ynone *O*-methyl oximes (0.50 mmol, 1.0 eq), $Pd(CF_3CO_2)_2$ (16.6 mg, 0.05 mmol, 10 mol%), $CuCl_2$ (67.2 mg, 0.50 mmol, 1.0 eq), acetic acid (60.1 mg, 1.00 mmol, 2.0 eq) and dimethyl sulfoxide (4 mL). The reaction mixture was stirred at 150 °C for 2 h. [b] The chemical yields in the parentheses are isolated yields after column chromatography. [c] The chemical yields of products **3f**, **3g**, and **3q** are calculated based on the weight of a mixture of the *E/Z* isomers of the corresponding ynone *O*-methyl oximes.

The disadvantage of the palladium-catalyzed ynone *O*-methyl oxime cyclization protocol prompted us to explore alternative synthetic methods for isoxazoles from ynone substrates. Previous work showed that direct treatment of ynones with hydroxylamine can lead to formation of 5-hydroxy-3,5-disubstituted-4,5-dihydroisxazoles,[8] which could be converted to isoxazoles upon dehydration. It is worth noting this cyclocondensation reaction can generate 3,5-disubstituted isoxazoles with the opposite regioselectivity to what is observed in our palladium-catalyzed cyclization protocol. Therefore, these two synthetic routes are excellent complements to each other, as a pair of regioisomeric 3,5-disubstituted isoxazoles can be readily prepared from one single ynone.

The cyclocondensation protocol towards 3,5-disubstituted isoxazoles was first reported by Linderman's group in the preparation of trifluoromethyl substituted isoxazoles.[8a] It was then employed by several other groups in syntheses of 3,5-disubstituted isoxazoles and 5-hydroxy-4,5-dihydroisoxazoles.[8b-f] The outcome of the cyclocondensation is often highly dependent on the substrates and reaction conditions employed. For example, Xie's group reported that when the R^1 group in ynone (**1**) is an alkyl a complex mixture was obtained in the cyclocondensation.[8c] Sydnes's group found the cyclocondensation products of 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones were very stable and resistant to dehydration to form isoxazoles even in acidic reaction medium.[8f] Trofimov's group observed an interesting cyclocondensation with regioselectivity opposite to what was reported by other groups.[8d]

Considering the aforementioned facts, we decided to investigate the cyclocondensation with the ynone substrates employed in our palladium-catalyzed cyclization protocol in order to determine if we could develop a new complementary synthetic route towards 3,5-disubstituted isoxazoles with the same batch of ynones. We first treated ynone (**1a**) with NH_2OH (8 equivalents, 50 wt% aqueous solution) in several common organic solvents such as DMSO, THF, CH_3CN, NMP, MeOH, and DMF (Table 3, Entries 1-6). The cyclocondensation took place smoothly in these solvents at 50 °C, and the desired 5-hydroxy-4,5-dihydroisoxazole **4a** was obtained in good to excellent yields. The highest yield was obtained in DMF (Table 3, Entry 6). When the reaction temperature was decreased to 25 °C, the reaction occurs at a slower rate with a slight decrease in yield (Table 3, Entry 7). When the amount of NH_2OH was reduced to 4 equivalents, the yield dropped to 85% (Table 3, Entry 8). We therefore chose the conditions listed in Entry 6 in Table 3 as our optimal condition.

Table 3. Optimization of Reaction Conditions for Cyclocondensation of Ynone (**1a**) and Hydroxylamine.[a]



Entry	Solvent	Time (h)	Isolated yield[b] (%)
1	DMSO	1 h	81
2	THF	2 h	86
3	CH_3CN	1 h	92
4	NMP	1.5 h	85
5	MeOH	2 h	93
6	DMF	1 h	98
7[c]	DMF	2 h	91
8[d]	DMF	1.5 h	85

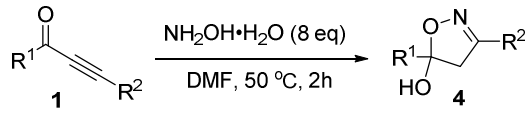
[a] General procedure: A 20 mL glass vial was charged with ynone (**1a**, 0.50 mmol), hydroxylamine (NH_2OH, 50 wt% aqueous

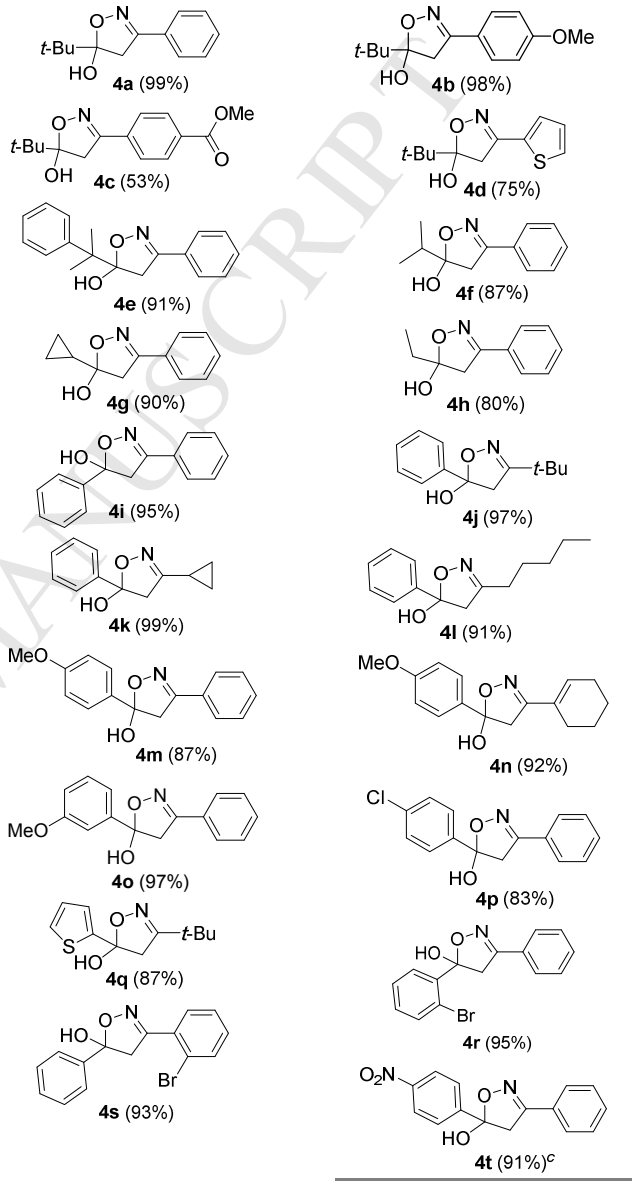
solution, 264.2 mg, 4.00 mmol), and solvent (4 mL). The reaction mixture was stirred at 50 °C until the starting material **1a** is fully consumed. [b] Isolated yields after column chromatography. [c] Reaction was carried out at 25 °C. [d] 4 equivalents of NH_2OH was added.

Under the optimized reaction condition, a variety of ynone substrates were employed in the cyclocondensation (Table 3). A broad range of substituents are compatible on the ynone (**1**) substrates, including primary, secondary, and *tertiary*-alkyl, alkenyl, aryl and heteroaryl groups. Both electron-donating and electron-withdrawing groups are tolerated, though a lower yield was observed in the presence of an electron-withdrawing methyl ester group (CO_2Me) (Table 4, **4c**). We paid special attention to those ynone substrates with a sterically less hindered *primary*-, *secondary*-alkyl on the proximal side of the ynone carbonyl group, as these substrates generally are considered challenging since they form the *E/Z* isomers in the ynone *O*-methyl oxime formation step. It turned out steric hindrance does not affect the chemical yields and reaction rate, as both the sterically hindered *tertiary*-alkyl (Table 4, **4a-e**) and *o*-Br-phenyl (Table 4, **4r**) groups and sterically less hindered *primary*-, *secondary*-alkyl (Table 4, **4f-h**) and thienyl groups (Table 4, **4q**) are all well accommodated at the proximal position to the ynone carbonyl, affording high yields of the cyclized products.

The regioselectivity outcome of the cyclocondensation has been shown to depend on the acidity of the reaction medium. In general, in either basic or neutral medium, 3,5-disubstituted 4,5-dihydroisoxazoles form with the opposite regioselectivity to what is observed in our palladium-catalyzed cyclization route. We observed the same regioselectivity pattern in the cyclocondensation as Linderman's, Xie's and Sydnes's groups.[8a,c,f] Our results showed the cyclocondensation between ynones (**1**) and hydroxylamine is an excellent complementary protocol to our palladium-catalyzed cyclization of ynone *O*-methyl oximes (**2**) for the 3,5-disubstituted isoxazole synthesis.

Table 4. Preparation of 5-Hydroxy-4,5-dihydroisoxazoles (**4**) from Ynones (**1**) and Hydroxylamine.[a,b]



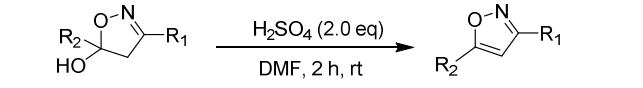


[a] A 20 mL glass vial was charged with ynone (**1**, 0.50 mmol), hydroxylamine (NH_2OH, 50 wt% aq. Soln., 264.2 mg, 4.00 mmol), and DMF (4 mL). The reaction mixture was stirred at 50 °C for 2 h. [b] The chemical yields in parentheses are isolated yields after column chromatography. [c] The reaction was carried out at 100 °C for two hours.

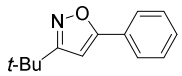
Taking Sydnes's results into account, we further examined the dehydration reaction of our 5-hydroxy-4,5-dihydroisoxazoles. In order to assess the efficiency of the two synthetic routes, we selected to dehydrate the 4,5-dihydroisoxazoles **4j**, **4k**, and **4d**, as dehydration of these compounds will lead to the same isoxazole products **3a**, **3g**, and **3q** (listed in Table 2) synthesized by the

palladium-catalyzed cyclization protocol. In addition, dehydration of 4,5-dihydroisoxazoles **4f**, **4h**, **4r**, **4s** and **4t** were also carried out, as these substrates contain the representative substituents such as *primary*- and *secondary*-alkyls, the sterically hindered *o*-bromophenyl group, and an electron-deficient *p*-nitrophenyl group. In the presence of 2 equivalents of H_2SO_4, dehydration of the selected 5-hydroxy-4,5-dihydroisoxazoles all took place smoothly at room temperature and afforded the desired isoxazoles in moderate to excellent yields within 2 h,[9] except **4t**. No reaction occurred on **4t** at room temperature, and the dehydration product **3u** was obtained only after **4t** was heated at 50 °C overnight.

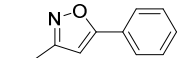
Table 5. Preparation of 3,5-Disubstituted Isoxazoles (**3**) by Acid Mediated Dehydration of 3,5-Disubstituted 5-Hydroxy-4,5-dihydroisoxazoles (**4**).[a,b]



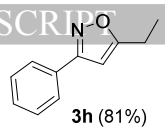
4j, 4k, 4h, 4d, 4r, 4s, 4f, 4t → **3a, 3g, 3h, 3q, 3r, 3s, 3t, 3u**



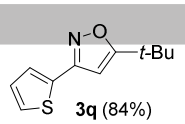
3a (95%)



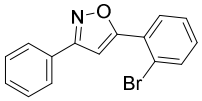
3g (96%)



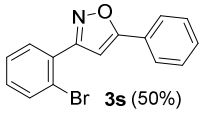
3h (81%)



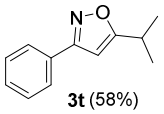
3q (84%)



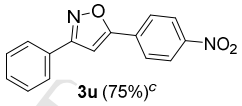
3r (61%)



3s (50%)



3t (58%)

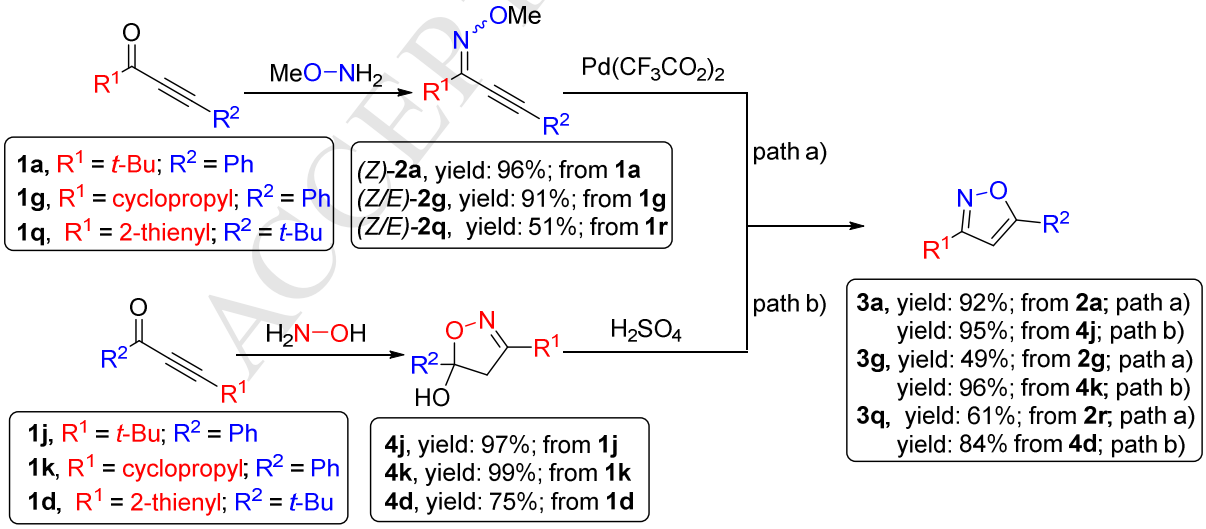


3u (75%)[c]

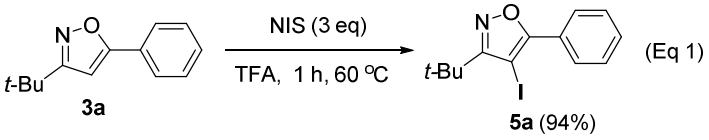
[a] A 20 mL glass vial was charged with 5-hydroxy-4,5-dihydroisoxazoles (**4**, 0.50 mmol), H_2SO_4 (98.0 mg, 1.00 mmol), and DMF (4 mL). The reaction mixture was stirred at room temperature for 2 h. [b] Isolated yields after column chromatography. [c] The reaction was heated at 50 °C for 15 hours.

The efficiency of the two synthetic routes were briefly evaluated based on the chemical yields obtained for isoxazoles **3a**, **3g**, and **3q** via the two routes respectively (path a and path b, Scheme 2). While **3a** was prepared in similar overall chemical yields via the two routes, isoxazoles **3g** and **3q** were synthesized in much higher overall yields via the cyclocondensation-dehydration route (path b, Scheme 2). The difference between the two routes displayed in the synthesis of **3g** and **3q** mainly resulted from the low stereoselectivity obtained for the ynone *O*-methyl oximes **2g** and **2q** in the palladium-catalyzed cyclization protocol.

Scheme 2. Efficiency Assessment of the Two Routes Based on the Synthesis of Isoxazoles **3a**, **3g**, and **3q**.

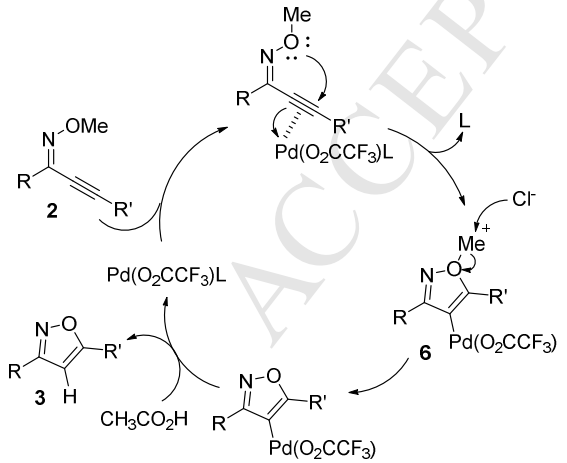


One selected isoxazole **3a** was successfully converted to 4-iodoisoxazole **5a** in 94% yield in the presence of NIS and trifluoroacetic acid (Eq 1).[10] Since the iodo group readily participates in transition metal catalyzed coupling reactions, the success of iodination of 3,5-disubstituted isoxazoles will enhance the possibility of further functionalizing the isoxazole framework and enrich the chemistry.



The palladium-catalyzed protocol presumably takes place from a *5-endo-dig* cyclization of ynone oxime (**2**) to form the isoxazolylpalladium intermediate **6**, which forms isoxazole (**3**) upon subsequent demethylation and depalladation-protonation (Scheme 3). While $CuCl_2$ does not directly participate in the Pd-mediated catalytic cycle, it helps to maintain the concentration of palladium (II) catalyst in the reaction mixture by oxidizing Pd(0) species back to Pd(II) species upon any reduction occurring. In the absence of $CuCl_2$, the cyclization of ynone *O*-methyl oximes stops after about 50% of substrate conversion, with a precipitate of palladium black particles.

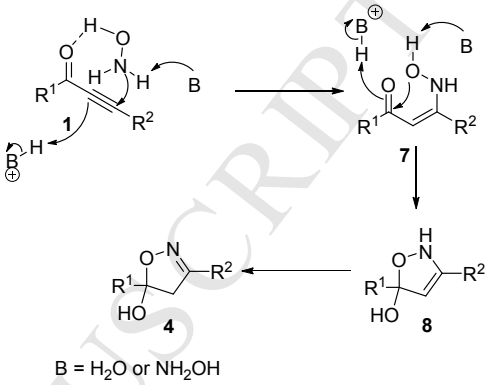
Scheme 3. Proposed Mechanism for Pd-catalyzed Cyclization of Ynone *O*-Methyl Oximes.



$CuCl_2$ oxidizes Pd(0) back to Pd(II) upon its reduction in the reaction mixture.

The cyclocondensation between ynones and hydroxylamine probably takes place from the conjugate addition of hydroxylamine to ynone (**1**) forming β-hydroxyamino enone **7**. Hydrogen bonding between the ynone carbonyl oxygen and the hydroxyl group of $HONH_2$ presumably plays a significant role in this step, so that the nucleophilic attack of $HONH_2$ to the ynone triple bond results in the formation of alkenes (**7**) with the carbonyl and the hydroxyamino groups residing on the *cis* position. An intramolecular cyclization of β-hydroxyamino enone **7** leads to 2,5-dihydroisoxazole **8**. Isomerization of **8** then gives 2,5-dihydroisoxazole **4** (Scheme 4).

Scheme 4. Proposed Mechanism of Cyclocondensation between Ynones and Hydroxylamine



Conclusion

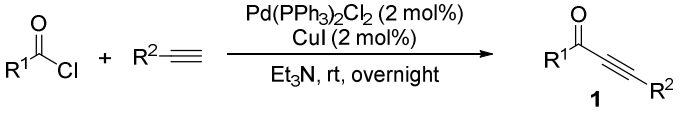
Synthesis of 3,5-disubstituted isoxazoles from simple ynones by two complementary highly regioselective routes is reported. The efficiency of the two synthetic routes has been assessed in the course of preparing three 3,5-disubstituted isoxazoles. While the palladium-catalyzed cyclization protocol is more advantageous in the sophisticated cascade synthesis of complex molecules, the cyclocondensation-dehydration protocol proves to be more competitive in the synthesis of simple 3,5-disubstituted isoxazoles. The two routes provide synthetic chemists with convenient options towards 3,5-disubstituted isoxazoles from one single ynone substrate. Upon the availability of starting materials and the special needs for the target isoxazole products, synthetic chemists can choose either protocol to prepare their desired isoxazoles. The success of iodination at the 4-position of a sample 3,5-disubstituted isoxazole shows further extension and potential application of the current methodology is promising. Further research on employing the isoxazole synthon in cascade synthesis is currently underway in our group and will be reported in due course.

Experimental section

General Information: All reactions were carried out in sealed 20 mL glass reaction vials with pressure relief caps, unless otherwise indicated. All commercially available chemicals were used as received without further purification, unless otherwise noted. Triethylamine, tetrahydrofuran (THF) and methanol were dried by 4Å molecular sieves over 48 hours before use. Molecular sieves (4Å) were activated at 200 °C at 0.5 mmHg for a week before use. All ^{1}H and ^{13}C NMR spectra were recorded at 400 or 500 MHz and 100 or 125 MHz, respectively, using $CDCl_3$ or acetone-d_6 as solvent. The chemical shifts of all ^{1}H and ^{13}C NMR spectra are referenced to the residual signal of $CDCl_3$ (δ 7.26 ppm for the ^{1}H NMR spectra and δ 77.16 ppm for the ^{13}C NMR spectra) or acetone-d_6 (δ 2.09 ppm for the ^{1}H NMR spectra

and δ 30.60 ppm for the ^{13}C NMR spectra). The high-resolution mass analysis was carried out on high resolution mass spectrometers using electrospray ionization (ESI) or heated electrospray ionization (HESI) method. Samples were dissolved in methylene chloride and methanol and analyzed via flow injection into the mass spectrometer at a flow rate of 200 µL/min. The mobile phase was 90:10 methanol:water, with 0.1% formic acid. The melting points of the solid compounds are uncorrected.

Preparation of Ynones (1).



General Procedure:[11] An oven dried 20 mL glass vial was charged with $PdCl_2(PPh_3)_2$ (28.1 mg, 0.04 mmol), CuI (7.6 mg, 0.04 mmol), acid chloride (2.60 mmol), terminal alkyne (2.00 mmol) and anhydrous triethylamine (10 mL). The vial was flushed with nitrogen and sealed with a pressure relief cap. The reaction mixture was stirred at room temperature, overnight, until the disappearance of starting material was observed, as monitored by thin layer chromatography. The reaction mixture was diluted with diethyl ether (40 mL) and washed with brine (40 mL). The aqueous phase was then extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The resulting residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate).

4,4-dimethyl-1-phenylpent-1-yn-3-one (1a)

This compound was obtained as a yellow oil (350.2 mg, 94% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 1.28 (s, 9H). The ^1H NMR spectral data are in good agreement with the literature data.[12]

1-(4-methoxyphenyl)-4,4-dimethylpent-1-yn-3-one (1b)

This compound was obtained as a yellow oil (276.5 mg, 64% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 1.27 (s, 9H). The ^1H NMR spectral data are in good agreement with the literature data.[4]

methyl 4-(4,4-dimethyl-3-oxopent-1-yn-1-yl)benzoate (1c)

Note: Only one equivalent of triethylamine (relative to the terminal alkyne) was used and the reaction was carried out in anhydrous THF (10 mL). This compound was obtained as a white solid (288.3 mg, 59% yield): m.p. 68.9-70.7 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 3.94 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 166.2, 132.8, 131.2, 129.7, 124.8, 90.5, 87.8, 52.6, 45.1, 26.1; HRMS (ESI) calcd for $(C_{15}H_{16}O_3+H)^+$ $[M+H]^+$ 245.1172, found 245.1178.

4,4-dimethyl-1-(thiophen-3-yl)pent-1-yn-3-one (1d)

This compound was obtained as a brown oil (200.0 mg, 52% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (t, *J* = 4.4 Hz, 2H), 7.07 (t, *J* = 4.4 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 136.5, 131.5, 127.8, 120.1, 90.8, 86.3, 44.9, 26.3; HRMS (ESI) calcd for $(C_{11}H_{12}OS+H)^+$ $[M+H]^+$ 193.0682, found 193.0685.

4-methyl-1,4-diphenylpent-1-yn-3-one (1e)

This compound was obtained as a brown oil (480.3 mg, 97% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 5H), 7.35-7.28 (m, 5H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 143.3, 133.1, 130.6, 128.7, 128.6, 127.2, 126.7, 120.2, 93.5, 86.7, 52.9, 25.1; HRMS (ESI) calcd for $(C_{18}H_{16}O+H)^+$ $[M+H]^+$ 249.1274, found 249.1279.

4-methyl-1-phenylpent-1-yn-3-one (1f)

This compound was obtained as a brown oil (289.3 mg, 84% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 6.9 Hz, 2H), 2.70-2.82 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 6H). The ^1H NMR spectral data are in good agreement with the literature data.[13]

1-cyclopropyl-3-phenylprop-2-yn-1-one (1g)

This compound was obtained as a yellow oil (275.4 mg, 81% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 2H), 2.12-2.21 (m, 1H), 1.29-1.36 (m, 2H), 1.06-1.13 (m, 2H). The ^1H NMR spectral data are in good agreement with the literature data.[14]

1,3-diphenylprop-2-yn-1-one (1i)

This compound was obtained as a yellow oil (396.0 mg, 96% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.7 Hz, 2H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.55-7.48 (m, 3H), 7.43 (t, *J* = 7.5 Hz, 2H). The ^1H NMR spectral data are in good agreement with the literature data.[15]

4,4-dimethyl-1-phenylpent-2-yn-1-one (1j)

This compound was obtained as a yellow oil (349.9 mg, 94% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.9 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 1.39 (s, 9H). The ^1H NMR spectral data are in good agreement with the literature data.[16]

3-cyclopropyl-1-phenylprop-2-yn-1-one (1k)

This compound was obtained as a yellow oil (333.6 mg, 98% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.62–7.56 (m, 1H), 7.46 (dd, *J* = 10.5, 4.8 Hz, 2H), 1.58-1.49 (m, 1H), 1.09-0.99 (m, 4H). The ^1H NMR spectral data are in good agreement with the literature data.[17]

1-phenyloct-2-yn-1-one (1l)

This compound was obtained as a red oil (394.0 mg, 99% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.64-1.73 (m, 2H), 1.41-1.51 (m, 2H), 1.32-1.41 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). The ^1H NMR spectral data are in good agreement with the literature data.[18]

1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (1m)

This compound was obtained as an orange solid (472.5 mg, 99% yield): m.p. 85.6-86.6 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H). The ^1H NMR spectral data are in good agreement with the literature data.[15]

3-(cyclohex-1-en-1-yl)-1-(4-methoxyphenyl)prop-2-yn-1-one (1n)

This compound was obtained as a brown oil (297.7 mg, 62% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.52-6.57 (m, 1H), 3.88 (s, 3H), 2.23-2.30 (m, 2H), 2.16-2.23 (m, 2H), 1.60-1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 164.4, 142.2, 132.0, 130.6, 119.4,

113.9, 95.1, 85.3, 55.7, 28.6, 26.3, 22.1, 21.3; HRMS (ESI) calcd for $(C_{16}H_{16}O_2+H)^+$ $[M+H]^+$ 241.1223, found 241.1228.

1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-one (1o)

This compound was obtained as a yellow solid (462.1 mg, 98% yield): m.p. 51.0-51.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.66-7.72 (m, 3H), 7.39-7.53 (m, 4H), 7.17 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.89 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (1p)

This compound was obtained as a brown solid (481.4 mg, 99% yield): m.p. 98.6-99.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 3H), 7.42 (t, *J* = 7.3 Hz, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[19]

4,4-dimethyl-1-(thiophen-2-yl)pent-2-yn-1-one (1q)

This compound was obtained as a brown solid (379.2 mg, 99% yield): m.p. 53.4-54.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.8 Hz, 1H), 7.66 (d, *J* = 4.9 Hz, 1H), 7.13 (t, *J* = 4.1 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 145.2, 134.9, 128.3, 102.7, 77.9, 30.2, 28.1 (fewer ^{13}C signals were observed due to signal overlapping); HRMS (ESI) calcd for $(C_{11}H_{12}OS+H)^+$ $[M+H]^+$193.0682, found 193.0686.

1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (1r)

This compound was obtained as a yellow oil (467.6 mg, 82% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.71 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.64-7.66 (m, 2H), 7.37-7.50 (m, 5H). The ^{1}H NMR spectral data are in good agreement with the literature data.[4]

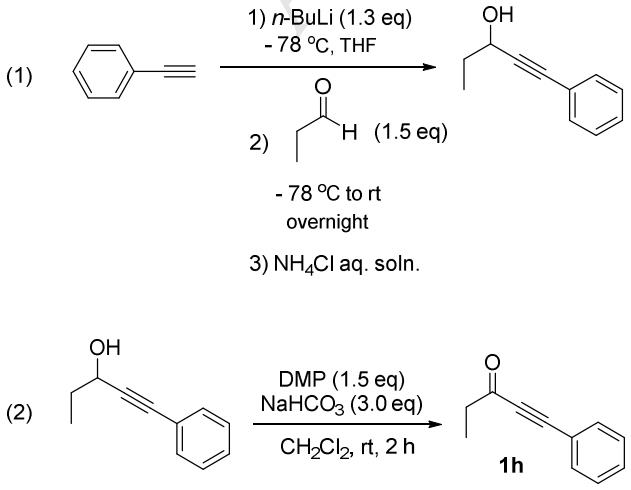
3-(2-bromophenyl)-1-phenylprop-2-yn-1-one (1s)

This compound was obtained a yellow solid (490.4 mg, 86% yield): mp 86.0-88.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.34 (m, 2H), 7.72 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.63-7.66 (m, 1H), 7.51-7.55 (m, 2H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H), 7.34 (td, *J* = 7.7, 2.0 Hz, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[5]

1-(4-nitrophenyl)-3-phenylprop-2-yn-1-one (1t)

This compound was obtained as a yellow solid (196.0 mg, 39% yield): m.p. 155.2-156.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 4H), 7.72 (d, *J* = 6.9 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7Hz, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[20]

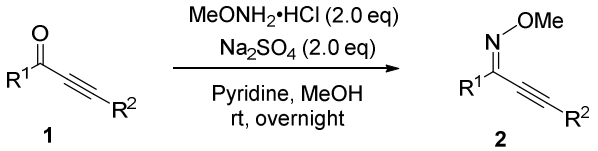
Preparation of 1-phenylpent-1-yn-3-one (1h)[21]



To a 100-mL round-bottomed flask was added phenylacetylene (1326.0 mg, 13.00 mmol) and anhydrous THF (30 mL). The solution was cooled to −78 °C. *n*-Butyllithium (1.6 M in hexanes, 10.6 mL, 16.90 mmol, 1.3 equivalents) was added dropwise to the stirred solution over 20 minutes. After the addition, the mixture was stirred at −78 °C for another 30 min. A solution of propionaldehyde (1160.0 mg, 20.00 mmol, 1.5 equivalents) in THF (5 mL) was added dropwise at −78 °C. After the addition, the reaction mixture was stirred and gradually warmed to room temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with diethyl ether (3 × 50 mL). The organic phases were combined and dried over anhydrous Mg_2SO_4, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford 1-phenylpent-1-yn-3-ol in 71% yield (1476.8 mg). The product was obtained as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.32-7.30 (m, 3H), 4.55 (d, *J* = 6.02 Hz, 1H), 1.93 (d, *J* = 5.63 Hz, 1H), 1.87-1.79 (m, 2H), 1.08 (t, *J* = 7.58 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[22]

To a stirred solution of 1-phenylpent-1-yn-3-ol (640.0 mg, 4.00 mmol) in DCM (10 mL) was added Dess–Martin periodinane (DMP) (2544.0 mg, 6.00 mmol) and $NaHCO_3$ (1008.0 mg, 12.00 mmol). The reaction mixture was stirred at room temperature for 2 h, then quenched by saturated aqueous $Na_2S_2O_3$ solution (15 mL), and extracted with DCM (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Mg_2SO_4, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate). The product 1-phenylpent-1-yn-3-one was obtained as a yellow oil (625.0 mg, 99% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (m, 2H), 7.47-7.43 (m, 1H), 7.40-7.36 (m, 2H), 2.70 (q, *J* = 8.0 Hz, 2H), 1.21 (t, *J* = 8.0 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[23]

Preparation of Ynone *O*-Methyl Oximes (2).



General Procedure:[24] An oven-dried 20 mL glass vial was charged with *O*-methylhydroxylamine hydrochloride (167.0 mg, 2.00 mmol), anhydrous Na_2SO_4 (284.0 mg, 2.00 mmol), pyridine (0.5 mL), alkynone (**1**, 1.00 mmol), and anhydrous methanol (5 mL). The reaction vial was sealed with a pressure relief cap and the mixture was stirred at room temperature overnight. Methanol was removed by using a rotary evaporator under reduced pressure (20 mmHg). The residue was diluted with diethyl ether (30 mL) and washed with brine (30 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The residue was then purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate).

(Z)-4,4-dimethyl-1-phenylpent-1-yn-3-one *O*-methyl oxime (2a)

This compound was obtained as a yellow oil (206.7 mg, 96% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.55 (m, 2H), 7.31-7.38 (m, 3H), 3.97 (s, 3H), 1.26 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[25]

(Z)-1-(4-methoxyphenyl)-4,4-dimethylpent-1-yn-3-one *O*-methyl oxime (2b)

This compound was obtained as a colorless oil (191.3 mg, 78% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 1.25 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[4]

methyl (Z)-4-(3-(methoxyimino)-4,4-dimethylpent-1-yn-1-yl)benzoate (2c)

This compound was obtained as a yellow oil (262.4 mg, 96% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 148.9, 132.1, 130.5, 129.6, 126.8, 99.3, 82.0, 62.6, 52.5, 37.1, 28.3; HRMS (ESI) calcd for $(C_{16}H_{19}NO_3+H)^+$ $[M+H]^+$ 274.1438, found 274.1440.

(E)-4-methyl-1,4-diphenylpent-1-yn-3-one *O*-methyl oxime (2e)

This compound was obtained as a brown oil (116.5 mg, 42% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.5, 1.5 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.32-7.24 (m, 6H), 4.07 (s, 3H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 146.3, 132.1, 129.3, 128.3, 128.3, 126.5, 126.4, 122.0, 100.8, 80.1, 62.7, 44.8, 27.5; HRMS (ESI) calcd for $(C_{19}H_{19}NO+H)^+$ $[M+H]^+$ 278.1539, found 278.1545.

4-methyl-1-phenylpent-1-yn-3-one *O*-methyl oxime (2f)

The compounds were obtained as a yellow oil (173.1 mg, 86% yield), ratio of two isomers (Z:E = 3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 [m, 2H (Z) and m, 2H (E)], 7.38-7.28 [m, 3H (Z); and m, 3H (E)], 3.97 [s, 3H (Z); and s, 3H (E)], 3.45-3.35 [m, 1H (E)], 2.77-2.70 [m, 1H (Z)], 1.23 [d, J = 6.9 Hz, 6H (Z)], 1.16 [d, J = 6.9 Hz, 6H (E)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7 (E), 147.0 (Z), 132.2 (Z), 132.0 (E), 129.4 (Z), 129.0 (E), 128.4 (Z/E), 122.2 (E), 122.0 (Z), 100.3 (Z), 92.2 (E), 82.6 (E),79.0 (Z), 62.5 (E), 62.3 (Z), 33.5 (Z), 27.0 (E), 20.6 (Z), 19.6 (E); HRMS (ESI) calcd for $(C_{13}H_{15}NO+H)^+$ $[M+H]^+$ 202.1226, found 202.1231.

1-cyclopropyl-3-phenylprop-2-yn-1-one *O*-methyl oxime (2g)

The compounds were obtained as a yellow oil (181.3 mg, 91% yield), ratio of two isomers (Z:E = 2:1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 [m, 2H, (Z); and 2H, (E)], 7.48-7.44 (m, 1H, (Z); and 1H, (E)], 7.39-7.29 [m, 2H, (Z); and 2H, (E)], 4.00 [s, 3H, (E)], 3.97 [s, 3H, (Z)], 2.42 (s, 1H, (E)], 1.86 [ddd, J = 8.3, 4.9, 3.3 Hz, 1H, (Z)], 1.04-0.97 [m, 2H, (E)], 0.96-0.87 [m, 2H, (E); and 2H, (Z)], 0.89-0.80 [m, 2H, (Z)]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.73 (E), 144.57(Z), 132.30(Z), 132.11(E), 129.64(Z), 129.27(E), 128.54(Z), 121.84(E), 121.62(Z), 99.63(Z), 91.06(E), 80.85(E), 62.64(E), 62.51, 31.12(E), 14.27(Z), 9.35(E), 6.83(Z), 5.75(Z and E); HRMS (ESI) calcd for $(C_{13}H_{13}NO+H)^+$ $[M+H]^+$200.1070, found 200.1075.

(Z)-1,3-diphenylprop-2-yn-1-one *O*-methyl oxime (2i)

This compound was obtained as a white solid (157.6 mg, 67% yield): m.p. 43.1-44.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.87 (m, 2H), 7.65-7.58 (m, 2H), 7.40 (dd, J = 7.3, 5.0 Hz, 6H), 4.15 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[25]

(Z)-4,4-dimethyl-1-phenylpent-2-yn-1-one *O*-methyl oxime (2j)

This compound was obtained as a colorless oil (204.5 mg, 95% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.86 (m, 2H), 7.35-7.39 (m, 3H), 4.08 (s, 3H), 1.39 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[25]

(Z)-1-phenyloct-2-yn-1-one *O*-methyl oxime (2l)

This compound was obtained as a yellow oil (110.1 mg, 48% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.87 (m, 2H), 7.34-7.40 (m, 3H), 4.09 (s, 3H), 2.53 (t, J = 7.2 Hz, 2H), 1.64-1.72 (m, 2H), 1.42-1.50 (m, 2H), 1.33-1.42 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 134.0, 129.6, 128.4, 126.6, 104.2, 71.6, 63.1, 31.2, 28.1, 22.3, 19.9, 14.1; HRMS (ESI) calcd for $(C_{15}H_{19}NO+H)^+$ $[M+H]^+$ 230.1539, found 230.1544.

(Z)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (2m)

Benzene (1 mL) was added as a co-solvent. This compound was obtained as a yellow solid (138.0 mg, 52% yield): m.p. 57.7-58.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.9 Hz, 2H), 7.56-7.66 (m, 2H), 7.34-7.44 (m, 3H), 6.92 (d, J = 8.9, 2H), 4.12 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 139.7, 132.3, 129.6, 128.6, 128.0, 126.4, 121.9, 113.9, 101.0, 79.7, 63.1, 55.5; HRMS (ESI) calcd for $(C_{17}H_{15}NO_2+H)^+$ $[M+H]^+$ 267.1208, found 267.1212.

(Z)-3-(cyclohex-1-en-1-yl)-1-(4-methoxyphenyl) prop-2-yn-1-one *O*-methyl oxime (2n)

This compound was obtained as a colorless oil (169.7 mg, 63% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 6.37-6.40 (m, 1H), 4.07 (s, 3H), 3.82 (s, 3H), 2.25-2.30 (m, 2H), 2.19-2.14 (m, 2H), 1.72-1.66 (m, 2H), 1.66-1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 139.9, 138.6, 128.0, 126.5, 120.0, 113.8, 103.2, 77.3, 63.0, 55.4, 28.9, 26.0, 22.2, 21.4; HRMS (ESI) calcd for $(C_{17}H_{19}NO_2+H)^+$ $[M+H]^+$ 270.1494, found 270.1494.

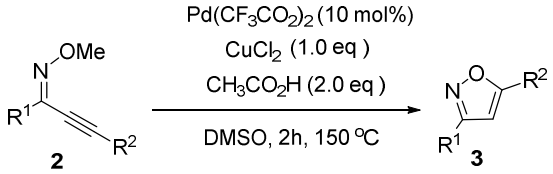
(Z)-1-(3-methoxyphenyl)-3-phenylprop-2-yn-1-one *O*-methyl oxime (2o)

This compound was obtained as a colorless oil (148.6 mg, 56% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.5, 1.5 Hz, 2H), 7.52 (d, J = 7.3 Hz, 1H), 7.47 (t, J = 2.2 Hz, 1H), 7.35-7.44 (m, 3H), 7.31 (t, J = 8.0 Hz, 1H), 6.95 (dd, J = 8.2, 2.2 Hz, 1H), 4.15 (s, 3H), 3.86 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[4]

4,4-dimethyl-1-(thiophen-2-yl)pent-2-yn-1-one *O*-methyl oxime (2q)

This compound was obtained as an orange oil (225.5 mg, 51% yield), ratio of two isomers (E:Z = 2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 [dd, J = 3.8, 1.1 Hz, 1H (Z)], 7.53 [dd, J = 5.1, 1.1 Hz, 1H (Z)], 7.41 [dd, J = 3.6, 1.1 Hz, 1H (E)], 7.28 [dd, J = 5.1, 1.0 Hz, 1H (E)], 7.11 [dd, J = 5.0, 3.9 Hz, 1H (Z)], 7.03 [dd, J = 5.0, 3.7 Hz, 1H (E)], 4.14 [s, 3H (Z)], 4.05 [s, 3H (E)], 1.39 [s, 9H (E/Z)]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 (E), 136.7 (Z), 136.1 (E), 134.9 (Z), 132.7 (Z), 132.2 (Z), 131.0 (E), 128.3 (E), 128.1 (Z), 127.03 (E), 127.01 (E), 125.8 (Z), 110.2 (E) , 100.4 (Z), 69.5 (Z), 63.0 (E), 30.7 (Z), 30.6 (E), 30.2 (E), 28.5 (Z); HRMS (ESI) calcd for $(C_{12}H_{15}NOS+H)^+$ $[M+H]^+$ 222.0947, found 222.0952.

Preparation of 3,5-Disubstituted Isoxazoles (3) by Palladium-Catalyzed Cyclization of Ynone *O*-Methyl Oximes (2)



General Procedure: An oven dried 20 mL glass vial was charged with ynone *O*-methyl oximes (0.50 mmol), $Pd(CF_3CO_2)_2$ (16.6 mg, 0.05 mmol, 0.1 eq), $CuCl_2$ (67.2 mg, 0.50 mmol, 1.0 eq), acetic acid (60.1 mg, 1.00 mmol, 2.0 eq) and dimethyl sulfoxide (4 mL). The reaction vial was sealed with a pressure relief cap and the mixture was stirred at 150 °C for 2 h. The reaction mixture was diluted with 20 mL of diethyl ether and washed with brine (20 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The subsequent residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding cyclization product.

3-(*tert*-butyl)-5-phenylisoxazole (3a)

This compound was obtained as a yellow oil (92.6 mg, 92% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.81 (m 2H), 7.43-7.45 (m, 3H), 6.25 (s, 1H), 1.40 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[26]

3-(*tert*-butyl)-5-(4-methoxyphenyl) isoxazole (3b)

This compound was obtained as a yellow solid (112.2 mg, 97% yield): m.p. 60.3-61.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.30 (s, 1H), 3.84 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 169.4, 160.9, 127.4, 120.7, 114.4, 96.2, 55.5, 32.2, 29.7; HRMS (ESI) calcd for $(C_{14}H_{17}NO_2+H)^+$ $[M+H]^+$ 232.1332, found 232.1333.

methyl 4-(3-(*tert*-butyl) isoxazol-5-yl) benzoate (3c)

This compound was obtained as a yellow solid (112.8 mg, 87% yield): m.p. 113.4-114.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07(d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 6.52 (s, 1H), 3.90 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 168.3, 166.5, 131.6, 131.2, 130.3, 125.7, 99.1, 52.4, 32.3, 29.7; HRMS (ESI) calcd for $(C_{15}H_{17}NO_3+H)^+$ $[M+H]^+$ 260.1281, found 260.1287.

5-phenyl-3-(2-phenylpropan-2-yl) isoxazole (3e)

This compound was obtained as a yellow solid (131.7 mg, 99% yield): m.p. 107.6-109.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.38-7.48 (m, 3H), 7.28-7.38 (m, 4H), 7.21-7.26 (m, 1H), 6.18 (s, 1H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.6, 147.2, 130.1, 129.0, 128.5, 127.7, 126.6, 126.2, 125.9, 98.8, 39.9, 28.8; HRMS (ESI) calcd for $(C_{18}H_{17}NO+H)^+$ $[M+H]^+$ 264.1383, found 264.1385.

3-isopropyl-5-phenylisoxazole (3f)

This compound was obtained as a yellow oil (66.5 mg, 71% yield, from starting material **2f** [Z:E = 3:1]): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.39-7.47 (m, 3H), 6.40 (s, 1H), 3.06-3.17 (m, 1H), 1.33 (d, *J* = 7.0, 6H). The ^{1}H NMR spectral data are in good agreement with the literature data.[26]

3-cyclopropyl-5-phenylisoxazole (3g)

This compound was obtained as an orange solid (45.4 mg, 49% yield, from starting material **2g** [Z/E=2:1]): m.p. 60.9-61.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.74 (m, 2H), 7.38-7.45 (m, 3H), 6.17 (s, 1H), 2.01-2.06 (m, 1H), 1.03-1.08 (m, 2H), 0.85-0.89 (m, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[27]

3,5-diphenylisoxazole (3i)

This compound was obtained as a white solid (91.8 mg, 83% yield): m.p. 102.0-103.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (ddd, *J* = 9.8, 6.9, 1.9 Hz, 4H), 7.54-7.40 (m, 6H), 6.84 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[28]

5-(*tert*-butyl)-3-phenylisoxazole (3j)

This compound was obtained as a colorless oil (89.6 mg, 89% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.82 (m, 2H), 7.39-7.48 (m, 3H), 6.25 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 162.3, 129.9, 129.6, 129.0, 126.9, 96.6, 33.0, 29.0; HRMS (ESI) calcd for $(C_{13}H_{15}NO+H)^+$ $[M+H]^+$ 202.1226, found 202.1228.

5-pentyl-3-phenylisoxazole (3l)

This compound was obtained as a yellow oil (78.6 mg, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.73 (m, 2H), 7.52-7.37 (m, 3H), 6.29 (s, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.75 (dd, *J* = 9.9, 5.0 Hz, 2H), 1.45-1.29 (m, 4H), 0.97-0.85 (m, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[29]

3-(4-methoxyphenyl)-5-phenylisoxazole (3m)

This compound was obtained as a white solid (113.1mg, 90% yield): m.p. 172.4-173.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.74 (m, 4H), 7.56-7.39 (m, 3H), 7.07-6.94 (m, 2H), 6.78 (s, 1H), 3.86 (d, *J* = 9.1 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[30]

5-(cyclohex-1-en-1-yl)-3-(4-methoxyphenyl) isoxazole (3n)

This compound was obtained as a brown oil (102.1 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.61-6.66 (m, 1H), 6.32 (s, 1H), 3.85 (s, 3H), 2.34-2.41 (m, 2H), 2.21-2.29 (m, 2H), 1.73-1.82 (m, 2H), 1.64-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 162.1, 161.0, 130.2, 128.2, 125.5, 122.1, 114.4, 96.1, 55.5, 25.5, 25.3, 22.2, 21.9; HRMS (ESI) calcd for $(C_{16}H_{17}NO_2+H)^+$ $[M+H]^+$ 256.1332, found 256.1333.

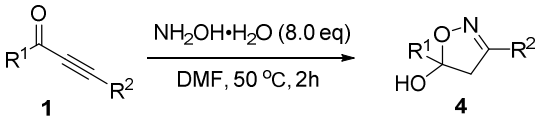
3-(3-methoxyphenyl)-5-phenylisoxazole (3o)

This compound was obtained as a yellow oil (125.6 mg, 99% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.56-7.35 (m, 6H), 7.07-6.96 (m, 1H), 6.82 (s, 1H), 3.89 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[31]

5-(*tert*-butyl)-3-(thiophen-2-yl)isoxazole (3q)

This compound was obtained as a yellow solid (63.2 mg, 61% yield, from starting material **2q** [Z/E=1:2]): m.p. 49.4-50.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 3.6, 0.7 Hz, 1H), 7.39 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.18 (s, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 157.4, 131.5, 127.7, 127.4, 127.1, 96.7, 33.0, 29.0; HRMS (ESI) calcd for $(C_{11}H_{13}NOS+H)^+$ $[M+H]^+$ 208.0791, found 208.0796.

Preparation of 3,5-Disubstituted Isoxazolines (4) from Ynones (1) and Hydroxylamine



General Procedure: A 20 mL glass vial was charged with ynone (**1**, 0.50 mmol), hydroxylamine (NH_2OH, 50 wt% aq. Soln., 264.2 mg, 4.00 mmol, 8.0 eq), and dimethylformamide (4 mL). The reaction vial was sealed with a pressure relief cap and the mixture was stirred at 50 °C for 2 h, then diluted with 20 mL of diethyl ether and washed with brine (20 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The subsequent residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding cyclization product.

5-(*tert*-butyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (4a)

This compound was obtained as a yellow solid (109.6 mg, 99% yield): m.p. 141.8-142.7 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.74 (dd, J = 6.5, 3.1 Hz, 2H), 7.47 (dd, J = 5.0, 1.8 Hz, 3H), 5.56 (s, 1H), 3.65, 3.15 (ABq, J_{AB} = 18.1 Hz, 2H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.7, 132.3, 131.2, 130.2, 128.0, 114.4, 43.2, 39.0, 26.2; HRMS (ESI) calcd for $(C_{13}H_{17}NO_2+H)^+$ $[M+H]^+$ 220.1332, found 220.1336.

5-(*tert*-butyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-ol (4b)

This compound was obtained as a white solid (122.2 mg, 98% yield): m.p. 123.4-123.7 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.70-7.64 (m, 2H), 7.04-6.99 (m, 2H), 5.45 (s, 1H), 3.87 (s, 3H), 3.61, 3.11 (ABq, J_{AB} = 18.0 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.6, 157.2, 129.5, 124.7, 115.6, 114.0, 56.4, 43.5, 38.9, 26.2; HRMS (ESI) calcd for $(C_{14}H_{19}NO_3+H)^+$ $[M+H]^+$ 250.1438, found 250.1439.

methyl 4-(5-(*tert*-butyl)-5-hydroxy-4,5-dihydroisoxazol-3-yl) benzoate (4c)

This compound was obtained as a white solid (73.5 mg, 53% yield): m.p. 146.0-146.9 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.09 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 5.64 (s, 1H), 3.94 (s, 3H), 3.71, 3.20 (ABq, J_{AB} = 17.9 Hz, 2H), 1.14 (s, 9H); ^{13}C NMR (100MHz, acetone-d_6) δ 167.5, 157.3, 136.5, 132.6, 131.2, 128.0, 115.2, 53.3, 42.9, 39.0, 26.1; HRMS (ESI) calcd for $(C_{15}H_{19}NO_4+H)^+$ $[M+H]^+$ 278.1387, found 278.1390.

5-(*tert*-butyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazol-5-ol (4d)

This compound was obtained as a yellow solid (84.5 mg, 75% yield): m.p. 126.3-127.6 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.59 (d, J = 4.7 Hz, 1H), 7.36 (d, J = 2.9 Hz, 1H), 7.15 (dd, J = 4.7, 3.9 Hz, 1H), 5.65 (s, 1H), 3.66, 3.16 (ABq, J_{AB} = 18.1 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 153.8, 134.5, 130.3, 129.3, 129.0, 114.6, 43.9, 38.9, 26.2; HRMS (ESI) calcd for $(C_{11}H_{15}NO_2S+Na)^+$ $[M+Na]^+$ 248.0716, found 248.0719.

3-phenyl-5-(2-phenylpropan-2-yl)-4,5-dihydroisoxazol-5-ol (4e)

This compound was obtained as a yellow solid (128.0 mg, 91% yield): m.p. 101.4-102.4 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.75-7.67 (m, 2H), 7.65 (dd, J = 6.7, 3.0 Hz, 2H), 7.42 (dd, J = 4.2, 2.4 Hz, 3H), 7.33 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 5.61 (s, 1H), 3.49, 3.05 (ABq, J_{AB} = 18.1 Hz, 2H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 157.9, 146.9, 132.0, 131.3, 130.2, 129.7, 129.2, 127.9, 127.8, 113.9, 46.2, 44.3, 25.8, 25.3; HRMS (ESI) calcd for $(C_{18}H_{19}NO_2+H)^+$ $[M+H]^+$ 282.1489, found 282.1493.

5-isopropyl-3-phenyl-4,5-dihydroisoxazol-5-ol (4f)

This compound was obtained as a yellow solid (89.3 mg, 87% yield): m.p. 96.3-96.8 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.79-7.69 (m, 2H), 7.53-7.42 (m, 3H), 5.61 (s, 1H), 3.45, 3.16 (ABq, J_{AB} = 18.1 Hz, 2H), 2.27-2.13 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.7, 132.3, 131.2, 130.2, 127.9, 113.1, 43.2, 37.2, 19.0, 18.5; HRMS (ESI) calcd for $(C_{12}H_{15}NO_2+H)^+$ $[M+H]^+$ 207.1208, found 207.1212.

5-cyclopropyl-3-phenyl-4,5-dihydroisoxazol-5-ol (4g)

This compound was obtained as a yellow solid (91.5 mg, 90% yield): m.p. 96.7-97.7 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.75-7.68 (m, 2H), 7.51-7.42 (m, 3H), 5.72 (s, 1H), 3.46, 3.32 (ABq, J_{AB} = 17.7 Hz, 2H), 1.48-1.39 (m, 1H), 0.69-0.59 (m, 2H), 0.59-0.49 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.2, 132.1, 131.3, 130.2, 127.9, 109.5, 46.8, 19.2, 2.9, 2.6; HRMS (ESI) calcd for $(C_{12}H_{13}NO_2+H)^+$ $[M+H]^+$ 204.1019, found 204.1024.

5-ethyl-3-phenyl-4,5-dihydroisoxazol-5-ol (4h)

This compound was obtained as a yellow oil (76.5 mg, 80% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2H), 7.41-7.38 (m, 3H), 3.27 (s, 2H), 2.90 (s, 1H), 2.07-1.96 (m, 2H), 1.09 (t, J = 7.53 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data[29]

3,5-diphenyl-4,5-dihydroisoxazol-5-ol (4i)

This compound was obtained as a white solid (113.7 mg, 95% yield): m.p. 97.8-99.9 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.79 (dd, J = 6.5, 2.9 Hz, 2H), 7.71 (d, J = 7.3 Hz, 2H), 7.51-7.47 (m, 3H), 7.45 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.2 Hz, 1H), 6.43 (s, 1H), 3.70, 3.64 (ABq, J_{AB} = 17.5 Hz, 2H). The ^{1}H NMR spectral data are in good agreement with the literature data.[32]

3-(*tert*-butyl)-5-phenyl-4,5-dihydroisoxazol-5-ol (4j)

This compound was obtained as a white solid (106.4 mg, 97% yield): m.p. 76.3-77.0 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.61 (dd, J = 7.0, 1.4 Hz, 2H), 7.41 (dd, J = 8.0, 6.5 Hz, 2H), 7.36 (d, J = 6.9 Hz, 1H), 6.01 (s, 1H), 3.30, 3.18 (ABq, J_{AB} = 18.1 Hz, 2H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.1, 144.3, 129.6, 129.5, 127.3, 108.3, 50.1, 34.5, 29.1; HRMS (ESI) calcd for $(C_{13}H_{17}NO_2+H)^+$ $[M+H]^+$ 220.1332, found 220.1335.

3-cyclopropyl-5-phenyl-4,5-dihydroisoxazol-5-ol (4k)

This compound was obtained as a light yellow oil (100.5 mg, 99% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.95, 1.49 Hz, 2H), 7.38-7.34 (m, 3H), 3.03, 2.96 (ABq, J_{AB} = 17.1 Hz, 2H), 2.49 (s, 1H), 1.86-1.81 (m, 1H), 0.98-0.89 (m, 2H), 0.85-0.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 140.9, 128.9, 128.6, 125.7, 106.7, 49.2, 9.3, 6.9, 6.1; HRMS (HESI) calcd for $(C_{12}H_{13}NO_2+H)^+$ $[M+H]^+$ 204.1019, found 204.1018.

3-pentyl-5-phenyl-4,5-dihydroisoxazol-5-ol (4l)

This compound was obtained as a yellow oil (106.2 mg, 91% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 7.63-7.59 (m, 2H), 7.41 (ddd, J = 8.0, 5.0, 3.7 Hz, 2H), 7.38-7.34 (m, 1H), 6.04 (s, 1H), 3.20, 3.19 (ABq, J_{AB} = 20.0 Hz, 2H), 2.42 (t, J = 7.6 Hz, 2H),

1.70-1.56 (m, 2H), 1.43-1.32 (m, 4H), 1.00-0.89 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.4, 144.2, 129.6, 129.5, 127.4, 108.0, 52.6, 32.8, 29.1, 27.4, 23.7, 15.0; HRMS (ESI) calcd for $(C_{14}H_{19}NO_2+H)^+$ $[M+H]^+$ 234.1489, found 234.1489.

5-(4-methoxyphenyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (4m)

This compound was obtained as a yellow solid (116.6 mg, 87% yield): m.p. 142.1-142.6 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.78 (dd, J = 6.7, 3.0 Hz, 2H), 7.65-7.57 (m, 2H), 7.53-7.44 (m, 3H), 7.05-6.93 (m, 2H), 6.29 (s, 1H), 3.86 (s, 3H), 3.64, 3.62 (ABq, J_{AB} = 18.0 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.4, 158.2, 135.7, 132.0, 131.5, 130.3, 128.8, 128.2, 114.9, 109.4, 56.3, 50.3; HRMS (ESI) calcd for $(C_{16}H_{15}NO_3+H)^+$ $[M+H]^+$ 270.1125, found 270.1129.

3-(cyclohex-1-en-1-yl)-5-(4-methoxyphenyl)-4,5-dihydroisoxazol-5-ol (4n)

This compound was obtained as a yellow solid (125.7 mg, 92% yield): m.p. 116.7-117.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.57-7.51 (m, 2H), 6.99-6.93 (m, 2H), 6.10-6.12 (m, 1H), 6.06 (s, 1H), 3.84 (s, 3H), 3.36, 3.23 (ABq, J_{AB} = 17.2 Hz, 2H), 2.41 (td, J = 6.1, 1.8 Hz, 2H), 2.26-2.18 (m, 2H), 1.69 (ddt, J = 10.8, 5.3, 4.2 Hz, 4H); ^{13}C NMR (125 MHz, acetone-d_6) δ 161.2, 160.0, 136.0, 133.8, 131.4, 128.7, 114.8, 108.7, 56.3, 49.9, 27.1, 25.9, 23.6, 23.5; HRMS (ESI) calcd for $(C_{16}H_{19}NO_3+H)^+$ $[M+H]^+$ 274.1438, found 274.1438.

5-(3-methoxyphenyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (4o)

This compound was obtained as a white solid (130.6 mg, 97% yield): m.p. 120.9-121.2 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.82-7.75 (m, 2H), 7.50 (dd, J = 4.1, 2.3 Hz, 3H), 7.36 (t, J = 8.1 Hz, 1H), 7.29-7.24 (m, 2H), 7.00-6.93 (m, 1H), 6.36 (s, 1H), 3.86 (s, 3H), 3.68, 3.65 (ABq, J_{AB} = 18.0 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.3, 158.2, 145.2, 131.9, 131.6, 130.8, 130.3, 128.2, 119.7, 115.3, 113.2, 109.3, 56.3, 50.5; HRMS (ESI) calcd for $(C_{16}H_{15}NO_3+H)^+$ $[M+H]^+$ 270.1125, found 270.1129.

5-(4-chlorophenyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (4p)

This compound was obtained as a white solid (113.6 mg, 83% yield): m.p. 193.0-193.3 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.81-7.76 (m, 2H), 7.75-7.69 (m, 2H), 7.52-7.45 (m, 5H), 6.53 (s, 1H), 3.71, 3.67 (ABq, J_{AB} = 16.0 Hz, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 158.3, 142.7, 135.3, 131.69, 131.65, 130.4, 129.8, 129.4, 128.2, 108.9, 50.4; HRMS (ESI) calcd for $(C_{15}H_{12}ClNO_2+H)^+$ $[M+H]^+$ 274.0629, found 274.0635.

3-(*tert*-butyl)-5-(thiophen-2-yl)-4,5-dihydroisoxazol-5-ol (4q)

This compound was obtained as a white solid (98.0 mg, 87% yield): m.p. 93.2-93.7 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 7.20 (dd, J = 3.6, 1.2 Hz, 1H), 7.03 (dd, J = 5.1, 3.6 Hz, 1H), 6.37 (s, 1H), 3.36, 3.30 (ABq, J_{AB} = 15.0 Hz, 2H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.5, 147.4, 128.2, 127.3, 126.5, 106.8, 50.3, 34.5, 29.0; HRMS (ESI) calcd for $(C_{11}H_{15}NO_2S+H)^+$ $[M+H]^+$ 226.0896, found 226.0901.

5-(2-bromophenyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (4r)

This compound was obtained as a yellow solid (151.1 mg, 95% yield): m.p. 122.4-123.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.72-7.74 (m, 2H), 7.68 (dd, J = 8.0, 1.1 Hz, 1H), 7.43 (d, J = 2.3 Hz, 2H), 7.42 (d, J = 1.7 Hz, 1H), 7.37 (td, J = 7.5, 1.1 Hz, 1H), 7.22-7.25 (m, 1H), 3.91, 3.76 (ABq, J_{AB} = 17.9 Hz, 2H), 3.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 139.4, 134.8, 130.7, 130.6, 129.2, 128.9, 128.2, 127.6, 127.0, 121.5, 107.1, 47.6; HRMS (HESI) calcd for $(C_{15}H_{12}BrNO_2+H)^+$ $[M+H]^+$ 318.0124, found 318.0123.

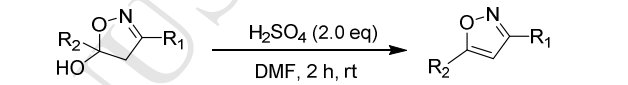
3-(2-bromophenyl)-5-phenyl-4,5-dihydroisoxazol-5-ol (4s)

This compound was obtained as a yellow oil (147.9 mg, 93% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.69 (m, 4H), 7.36-7.48 (m, 4H), 7.29 (td, J = 7.8, 1.9 Hz, 1H), 3.77, 3.72 (ABq, J_{AB} = 17.4 Hz, 2H), 3.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 140.5, 133.9, 131.4, 131.2, 131.0, 129.2, 128.8, 127.7, 125.8, 122.0, 108.2, 51.4; HRMS (HESI) calcd for $(C_{15}H_{12}BrNO_2+H)^+$ $[M+H]^+$ 318.0124, found 318.0126.

5-(4-nitrophenyl)-3-phenyl-4,5-dihydroisoxazol-5-ol (4t)

This compound was obtained as a yellow solid (129.0 mg, 91% yield): m.p. 151.0-152.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, J = 9.4 Hz, 2H), 7.90 (s, 1H), 7.84 (d, J = 9.4 Hz, 2H), 7.72-7.74 (m, 2H), 7.47-7.48 (m, 3H), 3.67(ABq J = 15.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.9, 148.9, 147.4, 130.4, 129.4, 128.9, 127.5, 126.7, 123.4, 106.9, 48.6. The HRMS data are in good agreement with the literature data.[32]

Preparation of 3,5-Disubstituted Isoxazoles (3) by Acid Mediated Dehydration of 3,5-Disubstituted 4,5-dihydroisoxazoles (4) [9]



4j, 4k, 4h, 4d, 4r, 4s, 4f, 4t **3a, 3g, 3h, 3q, 3r, 3s, 3t, 3u**

General Procedure: A 20 mL glass vial was charged with 3,5-disubstituted 4,5-dihydroisoxazoles (**4**, 0.50 mmol), H_2SO_4 (98.0 mg, 1.00 mmol), and dimethylformamide (4.0 mL). The reaction vial was sealed with a pressure relief cap and the mixture was stirred at room temperature for 2 h, then diluted with 20 mL of diethyl ether and washed with brine (20 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The subsequent residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding dehydration product.

3-(*tert*-butyl)-5-phenylisoxazole (3a)

This compound was prepared from **4j** and obtained as a yellow oil (95.0 mg, 95% yield).

3-cyclopropyl-5-phenylisoxazole (3g)

This compound was prepared from **4k** and obtained as an orange solid (89.0 mg, 96 % yield).

5-ethyl-3-phenylisoxazole (3h)

This compound was prepared from **4h** and obtained as a yellow oil (70.2 mg, 81% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.81 (m, 2H), 7.41-7.46 (m, 3H), 6.29 (s, 1H), 2.82 (q, J = 7.86 Hz, 2H), 1.35 (t, J = 7.47 Hz, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[29]

5-(*tert*-butyl)-3-(thiophen-2-yl)isoxazole (3q)

This compound was prepared from **4d** and obtained as a yellow solid (87.1 mg, 84% yield).

5-(2-bromophenyl)-3-phenylisoxazole (3r)

This compound was obtained as a yellow solid (91.5 mg, 61% yield): m.p. 54.6-55.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.91 (m, 3H), 7.70 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42-7.47 (m, 4H), 7.23-7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 162.8, 134.3, 131.2, 130.23, 130.20, 129.2, 129.1, 128.5, 127.9, 127.0, 121.2, 102.4; HRMS (HESI) calcd for $(C_{15}H_{10}BrNO+H)^+$ $[M+H]^+$ 300.0019, found 300.0018.

3-(2-bromophenyl)-5-phenylisoxazole (3s)

This compound was obtained as a yellow solid (75.0 mg, 50% yield): m.p. 43.8-44.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.87 (m, 2H), 7.69-7-73 (m, 2H), 7.41-7.52 (m, 4H), 7.33 (td, *J* = 7.8, 2.1 Hz, 1H), 6.96(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 163.1, 133.8, 131.5, 131.2, 130.7, 130.4, 129.2, 127.8, 127.6, 126.0, 122.4, 101.0; HRMS (HESI) calcd for $(C_{15}H_{10}BrNO+H)^+$ $[M+H]^+$ 300.0019, found 300.0018.

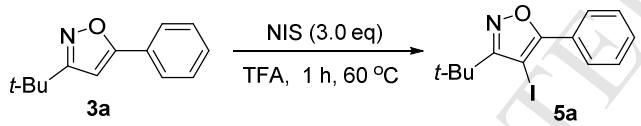
5-isopropyl-3-phenylisoxazole (3t)

This compound was obtained as a yellow oil (54.3 mg, 58% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.81 (m, 2H), 7.42-7.46 (m, 3H), 6.27 (s, 1H), 3.12 (sep, 1H). 1.36 (d, 6H). The ^{1}H NMR spectral data are in good agreement with the literature data.[33]

5-(4-nitrophenyl)-3-phenylisoxazole (3u)

The reaction was carried out at 50 °C for 15 hours. This compound was obtained as a yellow solid (100.0 mg, 75% yield): m.p. 226.0-227.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 9.6 Hz, 2H), 7.86-7.89 (m, 2H), 7.50-7.52 (m, 3H), 7.02 (s, 1H). The ^{1}H NMR spectral data are in good agreement with the literature data.[34]

Preparation of 3-(*tert*-Butyl)-4-iodo-5-phenylisoxazole (5a) from 3-(*tert*-Butyl)-5-phenylisoxazole (3a)[10]



An oven dried 20 mL glass vial was charged with 3,5-disubstituted isoxazoles (**3a**, 100.5 mg, 0.50 mmol), *N*-iodosuccinimide (337.0 mg, 1.50 mmol, 3 equivalents), and trifluoroacetic acid (TFA, 2.0 mL). The reaction vial was sealed with a pressure relief cap and the mixture was stirred at 60 °C for 1 h. Saturated aq. $NaHCO_3$ solution (15 mL) was added at room temperature. The mixture was extracted by diethyl ether (3 × 20 mL). The combined organic phases were washed with 10% aq. $Na_2S_2O_3$ solution (20 mL) and brine (20 mL), respectively, then dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator under reduced pressure (20 mmHg). The subsequent residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the corresponding cyclization product. The product was obtained as a white solid (154.0 mg, 94% yield): m.p. 80.0-82.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.92 (m, 2H), 7.50-7.48 (m, 3H), 1.53 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[25]

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