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PAPER

TEMPO-catalyzed Synthesis of 5-Substituted Isoxazoles from Propargylic Ketones and $TMSN_3$

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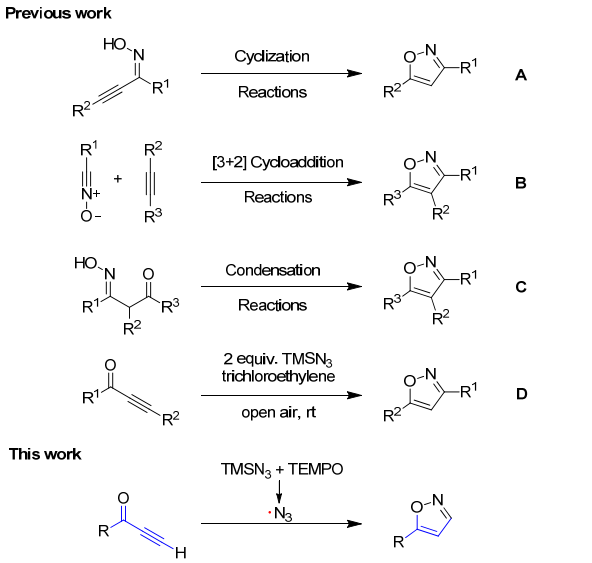
A novel and efficient TEMPO-catalyzed synthesis of 5-substituted isoxazoles from propargylic ketones and $TMSN_3$ via the radical mechanism process is described. This methodology provides an easy access to a variety of useful 5-substituted isoxazoles from simple and readily available propargylic ketones and $TMSN_3$ in good to excellent yields. A plausible reaction mechanism for this process is proposed.

Introduction

The isoxazole core, one of the important five-membered nitrogen heterocyclic, occupy an important place in organic chemistry[1] because of their wide applications in medicinal chemistry,[2] material science,[3] biologically active molecules,[4] and as intermediates in organic synthesis.[5] For this reason, considerable research efforts have been focused on the development of novel and efficient methods for the synthesis of isoxazoles. There are three main methodologies: the cyclization of ketoxime dianions or propargylic oximes (Scheme 1, A),[6] [3+2] cycloaddition reaction (Scheme 1, B),[7] and condensations with hydroxylamine (Scheme 1, C).[8] For example, in 2005, Larock and co-workers reported the isoxazole products obtained from cycloisomerizations of propargylic oximes with ICl, I_2, Br_2, or PhSeBr.[6a] Fokin group in 2008 reported that a Ru(II)-catalyzed [3+2] cycloaddition of alkynes with nitrile oxides to give 3,4-disubstituted isoxazoles.[7b] And In 2014, Liang reported the synthesis of disubsituted isoxazoles from homopropargylic alcohol, *t*-BuONO, and H_2O *via* condensation with hydroxylamine.[8c] Very recently, Reddy et al. reported the direct tandem azidation and denitrogenative cyclization of internal propargylic ketones with trimethylsilyl azide as an amino surrogate (Scheme 1, D).[9] However, they did not elaborate their methodology with unsubstituted propargylic ketones. Although, the poly-substituted isoxazoles could be get by these methods which are general, regioselective, and high yielding, only a limited number of methods for the synthesis of 5-substituted isoxazoles have been described.[10] Forthermore, some of these methods face the limitation of low atom efficiency, substrate specificity or forcing conditions. Therefore, the development of new methods for the regioselective synthesis of 5-substituted isoxazoles under mild reaction conditions is still highly desired.

Recently, organocatalysis has attracted considerable attention and has been significantly developed.[11] 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), a shelf-stable radical species, is the catalyst of choice in industry and has been widely used for the oxidation of alcohols to carbonyls.[12] Notably, TEMPO has been reported as a nonmetal catalyst in C=C double-bond cleavage to produce oxo nitriles.[13] Herein, we report a TEMPO catalyzed unsubstituted propargylic ketones to produce 5-substituted isoxazoles using a useful reagent $TMSN_3$ as the nitrogen source (Scheme 1).



Scheme 1 Synthesis of isoxazoles

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† Electronic Supplementary Information (ESI) available: [general experimental procedures, and spectral data, NMR spectra, high resolution mass spectra for all compounds, and X-ray crystallographic files (CIF) for **2g**]. See DOI: 10.1039/x0xx00000x

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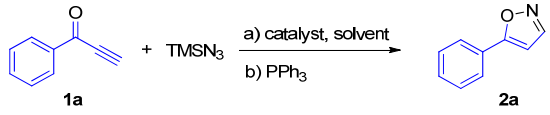
Results and discussion

At the outset of our studies, the reaction of propargylic ketone **1a** with $TMSN_3$ was attempted under different conditions (Table 1). When the reaction was catalyzed by TEMPO, no desired product was detected with most of propargylic ketone **1a** remained (Table 1, entry 1). Then, we were glad to find that propargylic ketone **1a** was converted into isoxazole **2a** when $Mn(OAc)_2{\cdot}2H_2O$ (15 mol %) was employed (Table 1, entry 2). We conjectured that the reaction were carried out in the presence of H_2O. Therefore, various catalyst were subsequently screened in this reaction, such as CuBr, MnO_2, $MnCl_2$, $MnBr_2$ and TEMPO (Table 1, entries 3-7). Among them, TEMPO was found to be the optimal one and afforded product **2a** in 76% yield (Table 1, entry 7). Subsequently, various solvents examined, DMSO, toluene, CH_2Cl_2, 1,4-dioxane and DMF turned out to give the product (Table 1, entries 8-12). To our delight, in CH_3OH without H_2O, TEMPO performed well with high effectivity delivering the product in good yield (78% isolated yield, Table 1, entry 13). CH_2Cl_2 and 1,4-dioxane without H_2O were tested, we can not get the desired product (Table 1, entries 14-15).

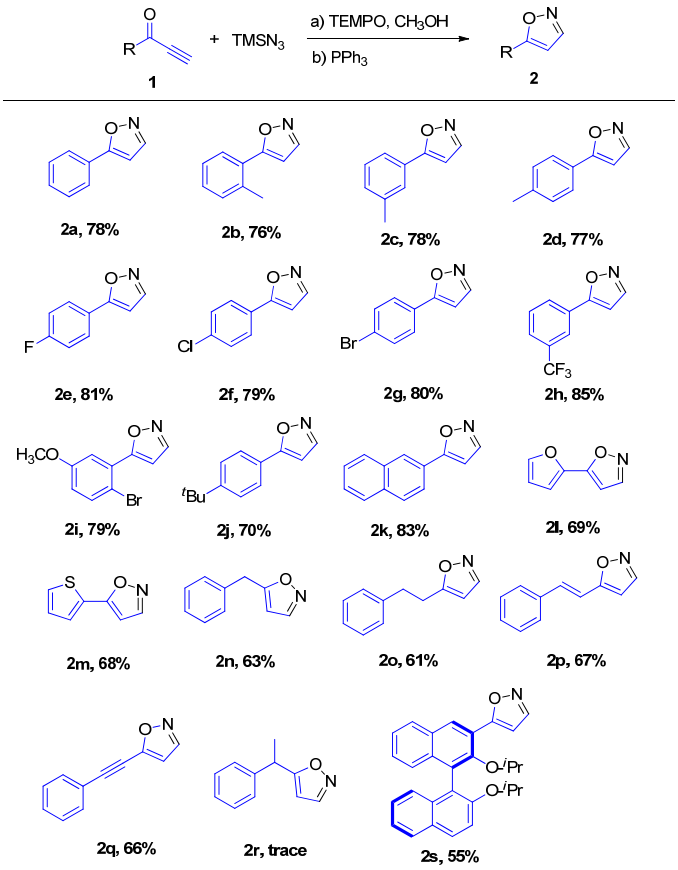
Table 1 Optimization of reaction conditions [a]



Entry	Catalyst	Solvent	Yield [b] (%)
1	TEMPO	CH_3CN	N.R.
2	$Mn(OAc)_2{\cdot}2H_2O$	CH_3CN	55%
3[c]	CuBr	CH_3CN/H_2O	N.R.
4[c]	MnO_2	CH_3CN/H_2O	N.R.
5[c]	$MnCl_2$	CH_3CN/H_2O	N.R.
6[c]	$MnBr_2$	CH_3CN/H_2O	63%
7[c]	TEMPO	CH_3CN/H_2O	76%
8[c]	TEMPO	$DMSO/H_2O$	40%
9[c]	TEMPO	$toluene/H_2O$	47%
10[c]	TEMPO	CH_2Cl_2/H_2O	71%
11[c]	TEMPO	$1,4\text{-dioxane}/H_2O$	74%
12	TEMPO	DMF/H_2O	69%
13	**TEMPO**	**CH_3OH**	**78%**
14	TEMPO	CH_2Cl_2	N.R.
15	TEMPO	1,4-dioxane	N.R.

[a] Reaction conditions: **1a** (0.3 mmol), $TMSN_3$ (0.45 mmol), catalyst (15 mol%) in solvent (2 mL) at room temperature for 12 h under air. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. [b] Isolated yield of pure product based on **1a**. [c] 0.2 mL H_2O was added.

Table 2 Substrate Scope for the reaction of propargylic ketones **1** and $TMSN_3$ [a, b]



[a] Reaction conditions: **1** (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (15 mol%) in CH_3OH (2 mL) under air at room temperature. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. [b] Isolated yield of pure product based on **1**.

With the optimized conditions in hand, the scope of substrates that could participate in the reaction was next investigated (Table 2). The acetylenic ketones **1a**-**1s** were either commercially available or prepared using a known procedure (see ESI). To our delight, aryl-alkynyl ketones bearing various substitutes participated well in the cyclization reaction, gave 5-substituted isoxazoles **2a-2j** in moderate to good yields (70-85%). And the substrate with an electron-withdrawing group on the aromatic ring gave better yield than that of an electron-donating group on the aromatic ring. The crystallization of compound **2g** from ethanol gave a single crystal suitable for X-ray analysis. Figure 1 illustrates the molecular structure of the 5-substituted isoxazole **2g**. When the aryl group was substituted in the 2-, 3-, and 4-positions by a CH_3 group, the corresponding isoxazole compound could be synthesized in 76%, 78%, and 77% yield, respectively. Gratifyingly, 5-(2-bromo-5-methoxyphenyl)isoxazole (**1i**) and 5-(4-(*tert*-butyl)phenyl)isoxazole (**1j**) were found to the reaction, providing the desired products **2i** and **2j** in 79% and 70% yield, respectively. Fortunately, propargylic ketones containing heteroaryl units or condensed rings were also tolerated (**2k**, **2l** and **2m**). It should be noted that the reactions with the alkyl acetylenic ketone, leading to moderate yields of products

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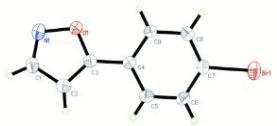
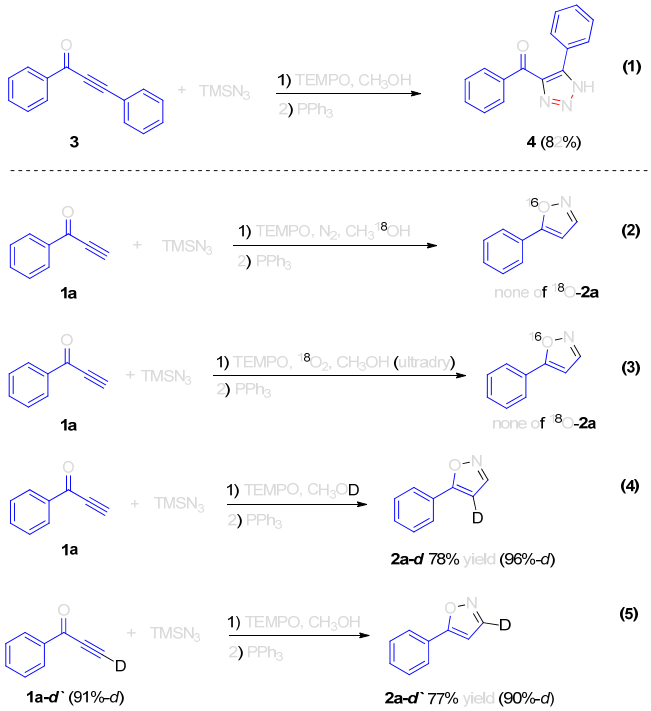


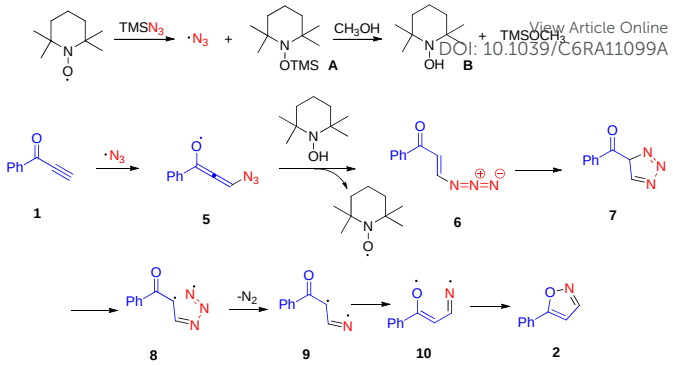
Figure 1 X-ray Crystal Structure of 5-substituted isoxazole **2g** (CCDC: 1449503)

(**2n**, **2o**). Similarly, propargylic ketones having a vinylic substituent (**1p**) and an acetylenic substituent (**1q**) gave the corresponding isoxazoles **2p** and **2q** in 67% and 66% yield, respectively. In addition, 4-phenylpent-1-yn-3-one (**1r**) was not an appropriate starting material under these reaction conditions. When the optically active acetylenic ketone (R)-1-(2,2'-diisopropoxy-[1,1'-binaphthalen]-3-yl)prop-2-yn-1-one was examined as a substrate, to our delight, (R)-5-(2,2'-diisopropoxy-[1,1'-binaphthalen]-3-yl)isoxazole **2s** was formed in 55% yield.

To our disappointment, internal propargylic ketones could not provide the desired product using the current catalytic system. Internal propargylic ketone **3** was tested under the standard conditions, providing the 4,5-disubstituted 1,2,3-triazole **4** in 82% yield (eq 1).

Some control experiments were carried out in order to explore the possible reaction pathway. $CH_3{}^{18}OH$ and $^{18}O_2$ isotopic labeling experiments were investigated. As expected, the oxygen atom of **2a** originated from propargylic ketone **1a** (eqs 2 and 3, the results were determined by HRMS, see SI). Furthermore, CH_3OD was investigated to the reaction and produced the deuterated product **2a-*d*** in 78% yield (eq 4). And the deuterated substrate **1a-*d*`** was subjected to the reaction and produced the product 5-phenylisoxazole **2a-*d*`** in 77% yield (eq 5).





Scheme 2 A plausible reaction mechanism

On the basis of the preliminary results, a plausible pathway is proposed for this cascade reaction (Scheme 2). Initially, $TMSN_3$ generates azido free radical associated with the formation of intermediate **A**. The TEMPO-TMS species **A** reacts with CH_3OH to form TEMPOH **B** and CH_3O-TMS. The azido free radical subsequently attacks the alkyne to form radical intermediate **5**.Subsequently, the radical **5** reacts directly with the TEMPOH species **B**, yields the intermediate **6** which is detected by HRMS (see SI), with the regeneration of the catalyst. The intramolecular azide-alkene cycloaddition was performed to afford triazole species **7**. This triazole **7** undergoes homolytic cleavage to give radical intermediate **8**, which release N_2 to give the imine **9**. Then, one-electron shift, followed by a subsequently intramolecular radical coupling to afford the product **2a**. The intermolecular [3+2] cycloaddition reaction of Internal propargylic ketone with $TMSN_3$ were occurred during the standard conditions because of the effect of steric hindrance.

Conclusions

In summary, we have demonstrated a facile transformation of propargylic ketones into 5-substituted isoxazoles catalyzed by TEMPO. The reaction has been delineated to proceed by a radical mechanism. Readily available, cheap starting substrates, an inexpensive catalyst, metal-free mild reaction conditions, a simple experimental procedure, and good yields, are some of the attractive attributes of the present protocol. Further work concerning synthetic applications and biological assessment of these isoxazoles is underway and the results shall be reported in due course.

Experimental

General remarks

Melting points were measured with a SGW X-4 melting point instrument (uncorrected). Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 400 MHz and 100 MHz, respectively, using $CDCl_3$ as reference standard (δ 7.26 ppm) for ^{1}H NMR and (δ 77 ppm) for ^{13}C NMR. HRMS (ion trap) were recorded using ESI. Precoated silica gel plates GF-254 were used for thin-layer analytical

chromatography. Column chromatography was performed on silica gel (300-400 mesh). Starting materials azidomethyl aromatics were readily prepared according to literature procedures. Unless otherwise noted, all reagents were obtained commercially and used without further purification.

General procedure for the synthesis of 5-Substituted Isoxazoles

To the mixture of propargylic ketones (1.0 equiv, 0.3 mmol) and azides (1.5 equiv., 0.45 mmol), TEMPO (15 mol%), and 2.0 mL CH_3OH at 25 °C for 12 h in the air. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The progress of the reaction was monitored by thin-layer chromatography. Upon completion, the mixture was evaporated under reduced pressure, and the residue was separated by column chromatography (ethyl acetate/petroleum ether = 1:40 to 1:20) to give the pure product.

5-phenylisoxazole (2a): colorless solid; m.p. 79-81°C (lit.[14] 80-81 °C);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.78 (d, *J* = 7.1 Hz, 2H), 7.48–7.39 (m, 3H), 6.50 (s, 1H) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 169.24, 150.73, 130.07, 128.88, 127.15, 125.73, 98.57 ppm; HRMS (*m/z*) (ESI): calcd for C_9H_7NO 146.06059 [M+H$^+$]; found 146.05994.

5-(*o*-tolyl)isoxazole (2b): white oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 1.8 Hz, 1H), 7.72 (dd, *J* = 5.6, 3.5 Hz, 1H), 7.38–7.33 (m, 1H), 7.33–7.28 (m, 2H), 6.43 (d, *J* = 1.8 Hz, 1H), 2.51 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.39, 150.44, 136.16, 131.30, 129.97, 128.51, 126.84, 126.19, 101.73, 21.39 ppm; HRMS (*m/z*) (APCI*)*: calcd for $C_{10}H_9NO$ 160.07624 [M+H$^+$]; found 160.07557.

5-(*m*-tolyl)isoxazole (2c): light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.59 (d, J = 11.3 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 6.49 (s, 1H), 2.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45, 150.69, 138.66, 130.88, 128.79, 127.08, 126.34, 122.92, 98.46, 21.26 ppm; HRMS (*m/z*) (APCI): calcd for $C_{10}H_9NO$ 160.07624 [M+H$^+$]; found 160.07556.

5-(*p*-tolyl)isoxazole (2d): colorless solid; m.p. 55-57 °C (lit.[15] 60-61 °C);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 1.8 Hz, 1H), 2.42 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.53, 150.74, 140.44, 129.64, 125.78, 124.58, 98.00, 21.41 ppm; HRMS (*m/z*) (APCI): calcd for $C_{10}H_9NO$ 160.07624 [M+H$^+$]; found 160.07550.

5-(4-fluorophenyl)isoxazole (2e): colorless solid; m.p. 46-52 °C (lit.[16] 51-53 °C);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.8 Hz, 1H), 7.81–7.74 (m, 2H), 7.19–7.12 (m, 2H), 6.47 (d, *J* = 1.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.43, 165.00, 162.51, 150.89, 127.99, 127.91, 123.69, 123.66, 116.34, 116.12, 98.46 ppm; HRMS (*m/z*) (APCI): calcd for C_9H_6FNO 164.05117 [M+H$^+$]; found 164.05047.

5-(4-chlorophenyl)isoxazole (2f): colorless solid; m.p. 79-83 °C (lit.[16] 84-85 °C);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.50 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.20, 150.84, 136.20, 129.27, 127.07, 125.68, 98.94 ppm; HRMS (*m/z*) (APCI): calcd for C_9H_6ClNO 180.02162 [M+H$^+$]; found 180.02066.

5-(4-bromophenyl)isoxazole (2g): colorless solid; m.p. 114-115 °C (lit.[16] 114-116 °C);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.9 Hz, 1H), 7.66–7.63 (m, 2H), 7.60–7.57 (m, 2H), 6.51 (d, *J* = 1.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.26, 150.81, 132.24, 127.28, 126.14, 124.51, 99.00 ppm; HRMS (*m/z*) (APCI): calcd for C_9H_6BrNO 223.97110 [M+H$^+$]; found 223.97028.

5-(3-(trifluoromethyl)phenyl)isoxazole (2h): white oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 1.7 Hz, 1H), 8.03 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.72, 150.91, 132.10, 131.77, 131.44, 131.12, 129.65, 128.92, 128.91, 127.94, 126.72, 126.68, 126.65, 126.61, 124.97, 122.73, 122.69, 122.65, 122.61, 122.27, 99.68; ppm; HRMS (*m/z*) (APCI): calcd for $C_{10}H_6F_3NO$ 214.04797 [M+H$^+$]; found 214.04721.

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5-(2-bromo-5-methoxyphenyl)isoxazole (2i): colorless solid; m.p. 62-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 3.1 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 6.84 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.80, 158.88, 150.49, 134.85, 128.58, 117.71, 114.66, 111.38, 103.41, 55.58 ppm; HRMS (*m/z*) (APCI): calcd for $C_{10}H_8BrNO_2$ 253.98167 [M+H$^+$]; found 253.98083.

5-(4-(tert-butyl)phenyl)isoxazole (2j): white oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 6.47 (s, 1H), 1.35 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.43, 153.53, 150.70, 125.86, 125.60, 124.49, 98.07, 34.80, 31.07 ppm; HRMS (*m/z*) (APCI): calcd for $C_{13}H_{15}NO$ 202.12319 [M+H$^+$]; found 202.12237.

5-(naphthalen-2-yl)isoxazole (2k): colorless solid; m.p. 92-94 °C (lit.[17] 93-95 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 10.5 Hz, 2H), 7.92–7.88 (m, 2H), 7.86–7.80 (m, 2H), 7.56–7.52 (m, 2H), 6.61 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.35, 150.96, 133.80, 132.96, 128.77, 128.56, 127.74, 127.23, 126.83, 125.51, 124.39, 122.83, 98.99 ppm; HRMS (*m/z*) (APCI): calcd for $C_{13}H_9NO$ 196.07624 [M+H$^+$]; found 196.07550.

5-(furan-2-yl)isoxazole (2l): light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.7 Hz, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 3.4 Hz, 1H), 6.54 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.45 (d, *J* = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.05, 150.39, 144.05, 143.21, 111.91, 110.45, 98.25 ppm; HRMS (*m/z*) (APCI): calcd for $C_7H_5NO_2$ 136.03985 [M+H$^+$]; found 136.03930.

5-(thiophen-2-yl)isoxazole (2m): yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.44 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.38 (d, *J* = 1.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.25, 150.59, 128.98, 127.93, 127.87, 126.91, 98.28 ppm; HRMS (*m/z*) (ESI): calcd for C_7H_5NOS 152.01701 [M+H$^+$]; found 152.01649.

5-benzylisoxazole (2n): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.31 (t, *J* = 7.1 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 3H), 5.89 (s, 1H), 4.08 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.46, 150.34, 135.88, 128.77, 127.12, 101.03, 33.01 ppm; HRMS (*m/z*) (APCI): calcd for $C_{10}H_9NO$ 160.07624 [M+H$^+$]; found 160.07562.

5-phenethylisoxazole (2o): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 5.93 (s, 1H), 3.11 (dd, *J* = 11.6, 4.7 Hz, 2H), 3.02 (dd, *J* = 11.5, 4.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.71, 150.20, 139.95, 128.51, 128.24, 126.41, 100.37, 33.56, 28.29 ppm; HRMS (*m/z*) (APCI): calcd for $C_{11}H_{11}NO$ 174.09189 [M+H$^+$]; found 174.09128.

(E)-5-styrylisoxazole (2p): colorless solid; m.p. 41-43 °C (lit.[18] 42-43 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 1.7 Hz, 1H), 7.48–7.43 (m, 2H), 7.36–7.24 (m, 4H), 6.93 (d, J = 16.4 Hz, 1H), 6.20 (d, J = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.86, 150.62, 135.49,

134.95, 129.17, 128.87, 127.10, 112.85, 100.67 ppm; HRMS (*m/z*) (APCI): calcd for $C_{11}H_9NO$ 172.07624 [M+H$^+$]; found 172.07556.

5-(phenylethynyl)isoxazole (2q): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 1.7 Hz, 1H), 7.58 (dd, J = 7.9, 1.6 Hz, 2H), 7.44–7.37 (m, 3H), 6.50 (d, J = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.08, 150.34, 131.86, 129.89, 128.56, 120.82, 107.02, 98.65, 75.29 ppm; HRMS (*m/z*) (APCI): calcd for $C_{11}H_7NO$ 170.06059 [M+H$^+$]; found 170.05984.

5-(1-phenylethyl)isoxazole(2r): yellow oil; HRMS (*m/z*) (ESI): calcd for $C_{11}H_{11}NO$ 173.08406 [M-H$^+$]; found 172.07597.

(R)-5-(2,2'-diisopropoxy-[1,1'-binaphthalen]-3-yl)isoxazole (2s): light yellow oil; $[\alpha]_D^{20}$ = +62 (*c* 0.22, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.34 (t, J = 3.8 Hz, 1H), 7.96 (dd, J = 8.4, 5.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.34–7.30 (m, 1H), 7.24 (dd, J = 12.9, 6.3 Hz, 3H), 7.18 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 1.2 Hz, 1H), 4.55 (dt, J = 11.9, 5.9 Hz, 1H), 3.87–3.78 (m, 1H), 1.15 (d, J = 5.9 Hz, 3H), 1.02 (d, J = 6.0 Hz, 3H), 0.81 (d, J = 6.1 Hz, 3H), 0.69 (d, J = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.17, 152.78, 150.33, 150.09, 133.91, 133.07, 129.16, 129.02, 128.07, 127.92, 127.36, 127.11, 126.27, 125.85, 125.61, 124.95, 124.44, 124.30, 122.77, 121.40, 119.13, 114.60, 102.89, 75.13, 69.92, 21.55, 21.50, 21.39 ppm; HRMS (*m/z*) (ESI): calcd for $C_{29}H_{28}NO_3$ 438.20692 [M+H$^+$]; found 438.20599.

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Graphic abstract

TEMPO-catalyzed Synthesis of 5-Substituted Isoxazoles from Propargylic Ketones and $TMSN_3$

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A novel and efficient TEMPO-catalyzed synthesis of 5-substituted isoxazoles from propargylic ketones and $TMSN_3$ *via* the radical mechanism process is described. This methodology provides an easy access to a variety of useful 5-substituted isoxazoles from simple and readily available propargylic ketones and $TMSN_3$ in good to excellent yields. A plausible reaction mechanism for this process is proposed.