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One-Pot Synthesis of 3,5-Disubstituted Isoxazoles from Propargylic Alcohols through Propargylic *N*-Hydroxylamines

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An efficient approach has been described for the synthesis of 3,5-disubstituted isoxazoles from propargylic alcohols. The strategy involves a one-pot *p*-TSA-catalyzed *N*-propargylation of protected hydroxylamines followed by a TBAF-mediated detosylative 5-*endo*-*dig* cyclization. The method was successfully used for the synthesis of various 3,5-disubstituted isoxazoles.

Introduction

The isoxazole core is one of the important five-membered nitrogen heterocyclic motifs embedded in several natural products and drugs (Figure 1).[1] Among this prolific family of heterocycles, 3,5-disubstituted isoxazoles attract great interest owing to their wide range of applications in medicinal chemistry.[2] Consequently, various strategies have been developed to synthesize these valuable compounds[3–7] and the majority of these methods are based on either a [3+2] cycloaddition between an alkyne and nitrile oxide[3] or a condensation reaction between a hydroxylamine and a 1,3-dicarbonyl compound/α,β-unsaturated carbonyl compound.[4,5] However, thermal nitrile oxide–alkyne cycloaddition reactions typically give relatively low yields, side-reactions and poor regioselectivity. Furthermore, most of these methods require expensive metal catalysts. Therefore, the regioselective synthesis of isoxazoles under mild reaction conditions is useful.

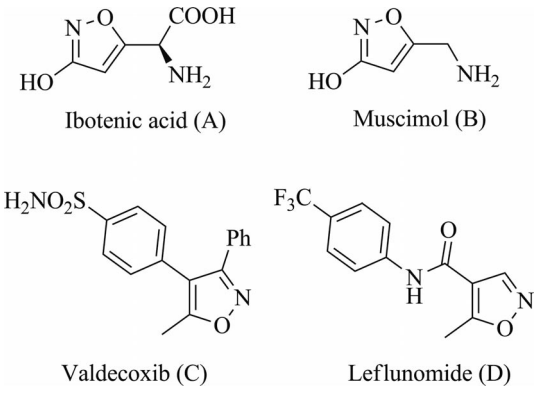

Figure 1. Representative examples of natural products and drugs containing an isoxazole skeleton.

Propargylic *N*-hydroxylamines represent a class of adaptable building blocks for the synthesis of various nitrogen-containing heterocycles such as dihydroisoxazoles (Δ4-isoxazolines), isoxazoles and acyl aziridines (Figure 2).[8] These compounds are encountered as key intermediates in the synthesis of several bioactive compounds.[9] Thus, these compounds are interesting synthetic targets for chemists. Usually, propargylic *N*-hydroxylamines are obtained through a nucleophilic addition reaction of acetylides with nitrones.[10] Recently, Campagne and co-workers developed a $FeCl_3$-catalyzed propargylic alcohol substitution reaction by using *N*-protected hydroxylamine to afford propargylic *N*-hydroxylamines, which were further converted into substituted isoxazoles or isoxazolines.[8b,8c,8e] Although, this is

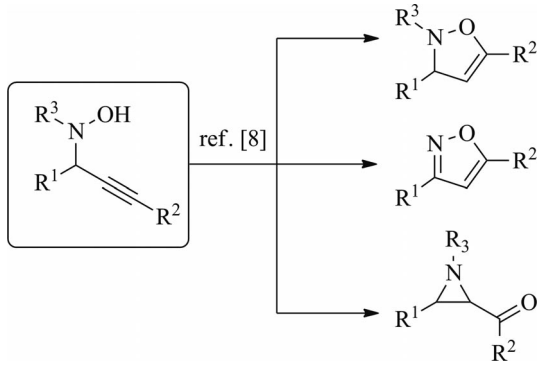

Figure 2. Synthesis of nitrogen-containing heterocycles from propargylic *N*-hydroxylamine.

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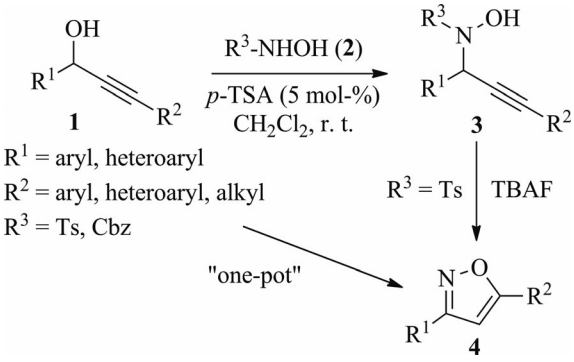
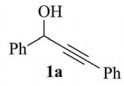
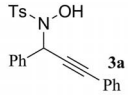
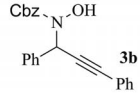
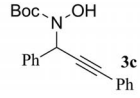
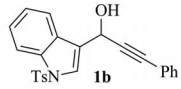
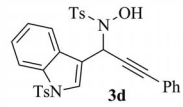
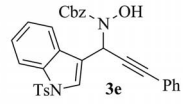
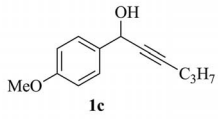
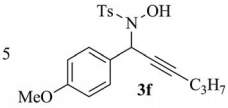
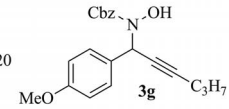
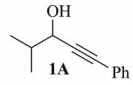
an attractive one-pot method, it requires a metal-catalyst for the nucleophilic substitution reaction (C–N bond formation) and reflux temperatures for both the substitution and the cyclization reactions. Meanwhile, we have developed an acid-catalyzed alkylation reaction using π-activated alcohols as the alkylating agents.[11] Recently, *O*-propargylation of hydroximides in the presence of an organic acid catalyst was accomplished,[12] which encouraged us to investigate the *N*-propargylation of protected hydroxylamines under similar reaction conditions. Sanz and co-workers have extensively studied *p*-TSA-catalyzed propargylic alcohol substitution reactions by using different carbon, oxygen, sulfur and nitrogen nucleophiles,[13] however there is no example that uses a hydroxylamine. In this paper we report the *p*-TSA-catalyzed *N*-propargylation of protected hydroxylamines to give propargylic *N*-hydroxylamines and application of this reaction as a one-pot synthesis for 3,5-disubstituted isoxazoles (Scheme 1).



Scheme 1. Synthesis of propargylic *N*-hydroxylamines (**3**) and isoxazoles (**4**).

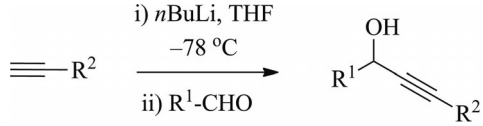
Table 1. *p*-TSA-catalyzed *N*-propargylation of protected hydroxylamines.[a]

Entry	Propargylic alcohol	*N*-Hydroxylamine	Time (min)	Product[b]	Yield (%)[c]
1	 **1a**	TsNHOH **2a**	20	 **3a**	88
2	**1a**	CbzNHOH **2b**	35	 **3b**	81
3	**1a**	BocNHOH **2c**	240	 **3c**	40
4	 **1b**	**2a**	15	 **3d**	82
5	**1b**	**2b**	20	 **3e**	71
6	 **1c**	**2a**	15	 **3f**	98
7	**1c**	**2b**	20	 **3g**	95
8	 **1A**	**2a**	600	–	–

[a] Conditions: alcohol (1 mmol), TsNHOH (1 mmol), *p*-TSA (5 mol-%), CH_2Cl_2. [b] All the products were characterized by ^1H, ^{13}C NMR, and mass spectrometry. [c] Isolated yields.

Results and Discussion

Initially, we attempted the *N*-propargylation of *N*-tosyl hydroxylamine (**2a**) with propargylic alcohol **1a**[14] in the presence of *p*-TSA (5 mol-%) in dichloromethane at room temperature. The starting material was consumed in 20 min and desired *N*-propargylic hydroxylamine **3a** was obtained in 88% yield (Table 1, Entry 1). The use of *N*-benzyloxycarbonyl hydroxylamine (**2b**) did not influence the efficiency of the propargylic hydroxy substitution reaction and *N*-propargylic hydroxylamine **3b** was isolated in 81% yield (Table 1, Entry 2). However, the use of *N*-*tert*-butyloxycarbonyl hydroxylamine (**2c**) gave a low yield of desired product **3c** (Table 1, Entry 3) possibly owing to the acid labile nature of the di-*tert*-butyl dicarbonate (Boc) group. To investigate the generality of the reaction, a diverse range of substituted propargylic alcohols were considered as alkylating agents for *N*-propargylation of TsNHOH (**2a**) and CbzNHOH (**2b**) under optimized conditions (Table 1). Consequently, propargylic alcohols **1b** and **1c** were prepared (Scheme 2) using a similar procedure for **1a** and explored for their efficacy in the present reaction. Propargylic alcohol **1b** successfully reacted to give the corresponding *N*-propargylated products **3d** and **3e** in good yields (Table 2, Entries 4 and 5). 1-(4-Methoxyphenyl)hex-2-yn-1-ol (**1c**) also reacted with both **2a** and **2b** under *p*-TSA-catalyzed conditions to give corresponding propargylic *N*-hydroxylamines **3f** and **3g** in 98 and 95% yields, respectively (Table 1, Entries 6 and 7). In contrast, reaction of propargylic alcohol **1A** with *N*-tosyl hydroxylamine failed to give the expected product even after 10 h at room temperature or at 40 °C (Table 1, Entry 8). These results clearly demonstrate that the *N*-propargylation of protected *N*-hydroxyl-

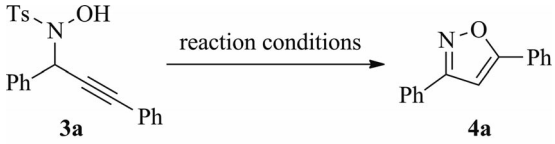


R^1 = aryl, heteroaryl
R^2 = Ph (**1b**); C_3H_7 (**1c**); C_6H_{13} (**1d**)
CH_2OBn (**1e**, **1f**); $CH_2OTBDPS$ (**1g** to **1j**)
4-$C_5H_{11}O$-Ph (**1k**)

Scheme 2. Synthesis of propargylic alcohols **1b** to **1k**.

amines is successful only with propargyl alcohols generated from aromatic aldehydes and not with those generated from aliphatic aldehydes.

Table 2. Conversion of *N*-propargylic hydroxylamine **3a** to isoxazole **4a**.



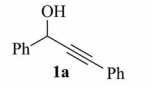
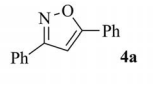
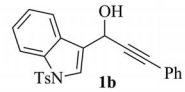
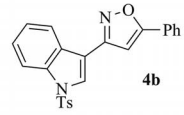
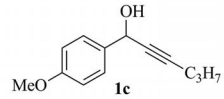
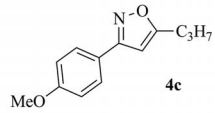
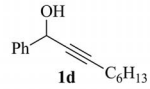
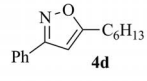
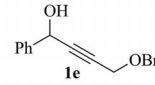
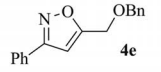
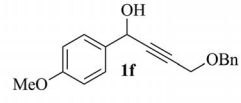
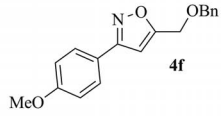
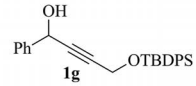
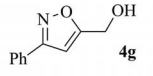
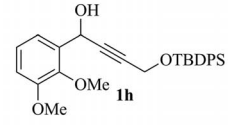
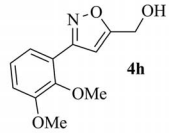
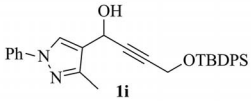
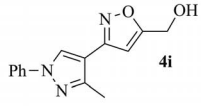
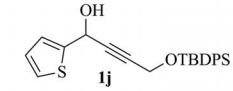
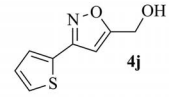
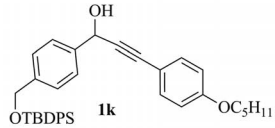
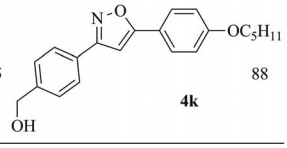
Entry	Base (3 equiv.)	Solvent	Time	Yield (%)[a]
1	K_2CO_3	CH_3CN/r.t.	20 h	58
2	CsF	CH_2Cl_2/r.t.	12 h	36
3	TBAF	CH_2Cl_2/r.t.	10 min	86

[a] Isolated yield after purification.

Next, our attention turned to the conversion of propargylic *N*-hydroxylamines (**3**) to isoxazoles (**4**) through detosylative 5-*endo*-*dig*-cyclization. To identify suitable reaction conditions, **3a** was treated with different bases to obtain corresponding isoxazole **4a** (Table 2). The reaction of **3a** with K_2CO_3 provided desired isoxazole **4a** in 58% yield in 20 h along with a mixture of unidentified products (Table 2, Entry 1), and treatment with CsF gave a similar result in 12 h providing **4a** in 36% yield (Table 2, Entry 2). Interestingly, tetrabutylammonium fluoride (TBAF) was more effective giving **4a** in 86% yield at room temperature (Table 2, Entry 3) and these conditions are mild relative to those described in a literature method (Et_3N, CH_2Cl_2, reflux).[8c] To the best of our knowledge, there is no literature precedence on TBAF-mediated cyclization reactions for the synthesis of substituted isoxazoles.

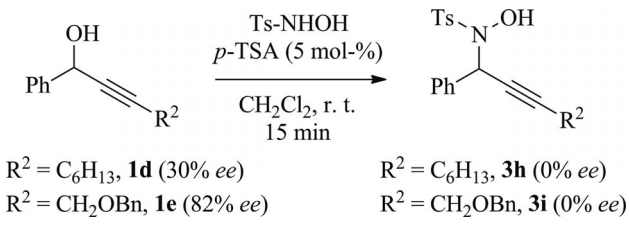
Having defined the mild reaction conditions for the synthesis of propargylic *N*-hydroxylamines and their conversion to 3,5-disubstituted isoxazoles, we were interested in developing a one-pot reaction. Reaction of propargylic alcohol **1a** with *N*-tosyl hydroxylamine (**2a**) in the presence of *p*-TSA (5 mol-%) in dichloromethane for 30 min, followed by the addition of TBAF resulted in the clean formation of 3,5-diphenyl isoxazole (**4a**) in 82% yield (Table 3, Entry 1). The above success encouraged us to extend this one-pot method to the synthesis of 3,5-disubstituted isoxazoles (Table 3) from diverse propargylic alcohols, which were prepared as shown in Scheme 2. Propargylic alcohol **1b** (bearing an aryl group on the alkyne), **1c** and **1d** (with alkyl substitution on the alkyne) afforded the corresponding 3,5-disubstituted isoxazoles **4b** to **4d**, respectively, under one-pot reaction conditions (Table 3, Entries 2–4).[15] Alcohols **1e** and **1f**, generated from benzyloxy prop-2-yne, were also suitable for this one-pot protocol and gave desired isoxazoles **4e** and **4f** (Table 3, Entries 5 and 6). Propargylic alcohols **1g** to **1j**, derived from *tert*-butyldiphenyl silyloxy prop-2-yne, reacted smoothly with TsNHOH in the presence of *p*-TSA (5 mol-%) followed by TBAF-mediated detosylative 5-*endo*-*dig* cyclization to afford corresponding isoxazoles **4g** to **4j** in good yields (Table 3, Entries 7–10). Likewise, propargylic alcohol **1k** (Scheme 2) afforded desilylated isoxazole **4k** in 88% yield (Table 3, Entry 11). During the TBAF-mediated cyclization step, deprotection of the *tert*-butyldiphenyl silyl group also occurred to furnish **4g**–**4k** with a free hydroxy group, which is a useful functionality for further derivatization of these isoxazoles.

Table 3. One-pot synthesis of isoxazoles from propargylic alcohols.[a]

Entry	Propargylic alcohol	Time (min) substitution/cyclization	Isoxazole[b]	Yield (%)[c]
1	 **1a**	20/10	 **4a**	82
2	 **1b**	15/30	 **4b**	80
3	 **1c**	15/30	 **4c**	83
4	 **1d**	15/30	 **4d**	78
5	 **1e**	20/30	 **4e**	85
6	 **1f**	10/40	 **4f**	51
7	 **1g**	15/30	 **4g**	85
8	 **1h**	15/15	 **4h**	82
9	 **1i**	15/15	 **4i**	82
10	 **1j**	10/15	 **4j**	68
11	 **1k**	20/25	 **4k**	88

[a] Conditions: alcohol (1 mmol), TsNHOH (1 mmol), *p*-TSA (5 mol-%), CH_2Cl_2 then TBAF (3 mmol). [b] All the products were characterized by ^1H, ^{13}C NMR, and mass spectra; isolated yields.

To investigate the mechanism of the substitution reaction, an enantio-enriched propargylic alcohol **1d** (30% *ee*)[16a] was treated with TsNHOH and *p*-TSA (5 mol-%) in CH_2Cl_2 and product **3h** was obtained in 82% yield in racemic form. Similarly, reaction of alcohol **1e** (82% *ee*)[16b] also provided racemic *N*-hydroxylamine **3i** (Scheme 3). These results strongly suggest that the nucleophilic substitution reaction proceeds through a S_N1 mechanism.



$R^2 = C_6H_{13}$, **1d** (30% *ee*) $R^2 = C_6H_{13}$, **3h** (0% *ee*)
$R^2 = CH_2OBn$, **1e** (82% *ee*) $R^2 = CH_2OBn$, **3i** (0% *ee*)

Scheme 3. *N*-Propargylation with enantio-enriched alcohols **1d** and **1e**.

Conclusions

In conclusion, we have developed a *p*-TSA-catalyzed reaction (C–N bond formation) between propargylic alcohols and *N*-protected hydroxylamines to give propargylic *N*-hydroxylamines, which are useful precursors for various nitrogen-containing heterocycles. This method was extended to a one-pot synthesis of isoxazoles through a TBAF-mediated detosylative 5-*endo-dig* cyclization. The present method is short (a total of 2 steps) and flexible because it starts from three simple components (an aromatic aldehyde, an alkyne and tosylhydroxylamine). This mild and metal-free reaction makes it practical as an organic synthetic method to obtain 3,5-disubstituted isoxazoles.

Experimental Section

General: NMR spectra were recorded in $CDCl_3$ with 300, 400 and 500 MHz spectrometers at ambient temperature. The chemical shifts (δ) are reported relative to TMS as the internal standard and by using the signal patterns indicated as follows: s, singlet; d, doublet; dd, doublet of doublets; td, triplet of doublets; t, triplet; m, multiplet; br. s, broad singlet. All the reagents and solvents were reagent grade and were used without further purification. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring. Propargylic alcohol **1a** was prepared as described.[14] TsNHOH was prepared using the literature procedure.[17]

General Procedure for the Synthesis of 1b to 1k: The starting alkyne (1.1 mmol) was dissolved in dry THF (5 mL) and *n*-BuLi (1 mmol) was added slowly at –78 °C. After 40 min the appropriate aromatic aldehyde (1 mmol) in THF (5 mL) was added to the reaction mixture at –78 °C. The reaction mixture was stirred at –78 °C until the aldehyde had been consumed, then quenched by adding aq. saturated NH_4Cl solution and was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography (silica gel) to afford pure propargylic alcohols **1b** to **1k**.

The spectroscopic data of **1b** to **1f** were in full agreement with the literature data.[18]

4-(*tert*-Butyldiphenylsilyloxy)-1-phenylbut-2-yn-1-ol (1g): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3379, 2931, 1428, 1371, 1111, 1081, 739, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 4 H, Ar), 7.49–7.30 (m, 11 H, Ar), 5.38 (br. s, 1 H, CH–OH), 4.44–4.41 (m, 2 H, CH_2–OTBDPS), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 135.6, 133.0, 129.7, 128.4, 128.1, 127.6, 126.5, 84.9, 84.8, 64.4, 52.6, 26.6, 19.0 ppm. HRMS (ESI): calcd. for $C_{26}H_{28}NaO_2Si$ $[M + Na]^+$ 423.1751; found 423.1730.

4-(*tert*-Butyldiphenylsilyloxy)-1-(2,3-dimethoxyphenyl)but-2-yn-1-ol (1h): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3443, 2937, 1589, 1480, 1271, 1076, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.66 (m, 4 H, Ar), 7.43–7.31 (m, 6 H, Ar), 7.08–6.98 (m, 2 H, Ar), 6.91 (dd, *J* = 2.2, 7.5 Hz, 1 H, Ar), 5.55 (br. s, 1 H, CH–OH), 4.38 (d, *J* = 1.5 Hz, 2 H, CH_2–OTBDPS), 3.90 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3) 2.96–2.90 (br. s, 1 H, OH), 1.03 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 146.5, 135.5, 129.7, 127.6, 124.1, 119.5, 112.6, 85.2, 84.1, 61.2, 61.0, 55.8, 52.7, 26.6, 19.0 ppm. HRMS (ESI): calcd. for $C_{28}H_{32}NaO_4Si$ $[M + Na]^+$ 483.1962; found 483.1965.

4-(*tert*-Butyldiphenylsilyloxy)-1-(3-methyl-1-phenyl-1*H*-pyrazol-4-yl)but-2-yn-1-ol (1i): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3343, 2957, 2858, 1597, 1503, 1112, 1000, 757, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (s, 1 H, =CH–N), 7.75–7.69 (m, 5 H, Ar), 7.59 (d, *J* = 8.3 Hz, 2 H, Ar), 7.43–7.35 (m, 8 H, Ar), 5.39 (br. s, 1 H, CH–OH), 4.44 (d, *J* = 1.5 Hz, 2 H, CH_2–OTBDPS), 2.37 (s, 3 H, CH_3), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 139.8, 135.5, 133.0, 129.8, 129.2, 127.6, 126.3, 126.0, 121.8, 119.5, 118.7, 84.5, 83.4, 56.3, 52.6, 26.6, 19.1, 12.1 ppm. HRMS (ESI): calcd. for $C_{31}H_{33}O_3Si$ $[M + H]^+$ 481.2193; found 481.2220.

4-(*tert*-Butyldiphenylsilyloxy)-1-(thiophen-2-yl)but-2-yn-1-ol (1j): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3447, 2930, 2858, 1428, 1369, 1111, 703 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75–7.70 (m, 4 H, Ar), 7.46–7.35 (m, 6 H, Ar), 7.28 (d, *J* = 4.4 Hz 1 H, Ar), 7.08 (s, 1 H, Ar), 6.97–6.94 (m, 1 H, Ar), 5.59 (s, 1 H, CH–C), 4.44 (s, 2 H, CH_2–OTBDPS), 2.13 (br. s, 1 H, OH), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 135.5, 132.8, 129.8, 127.7, 127.0, 126.6, 126.3, 126.2, 86.1, 81.8, 64.8, 52.7, 26.6, 19.1 ppm.

1-{4-[(*tert*-Butyldiphenylsilyloxy)methyl]phenyl}-3-[4-(pentyloxy)-phenyl]prop-2-yn-1-ol (1k): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3409, 2933, 2192, 1604, 1509, 1288, 1248, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.67 (m, 5 H, Ar), 7.59 (d, *J* = 8.1 Hz, 2 H, Ar), 7.44–7.36 (m, 9 H, Ar), 6.86–6.81 (m, 2 H, Ar), 5.68 (s, 1 H, CH–OH), 4.79 (s, 2 H, CH_2–OTBDPS), 3.95 (t, *J* = 6.6 Hz, 2 H, Ar–OCH_2), 1.83–1.74 (m, 2 H, CH_2), 1.49–1.33 (m, 4 H, CH_2–CH_2), 1.10 (s, 9 H, *t*Bu), 0.93 (t, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 141.2, 139.4, 135.4, 135.1, 133.1, 129.8, 129.6, 129.5, 127.7, 127.6, 126.6, 126.1, 125.7, 114.8, 114.3, 87.3, 86.6, 67.9, 65.1, 64.9, 28.8, 28.0, 26.7, 22.3, 19.2, 13.9 ppm. HRMS (ESI): calcd. for $C_{37}H_{42}NaO_3Si$ $[M + Na]^+$ 585.2795; found 585.2801.

General Procedure for the Preparation of Propargylic *N*-Hydroxylamines: *p*-TSA (5 mol-%) was added to a mixture of propargylic alcohols **1a**–**1c** (1.0 mmol) and *N*-protected hydroxylamine **2a**–**2c** (1.0 mmol) in dichloromethane (5 mL) at room temperature and stirred (for times, see: Table 1). The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The combined or-

ganic layers were dried with anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography to afford *N*-propargylated hydroxylamines **3a** to **3g**.

***N*-(1,3-Diphenylprop-2-ynyl)-*N*-hydroxy-4-methylbenzenesulfonamide (3a):** White solid; m.p. 126–129 °C. IR (KBr): $\tilde{\nu}$ = 3369, 3032, 2228, 1491, 1452, 1166, 1089, 758, 670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.3 Hz, 2 H, Ar), 7.63 (d, J = 6.4 Hz, 2 H, Ar), 7.41–7.15 (m, 8 H, Ar), 7.05 (d, J = 6.4 Hz, 2 H, Ar), 5.99 (s, 1 H, CH–N), 2.22 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 136.0, 131.6, 129.8, 129.2, 128.5, 128.4, 127.9, 122.0, 88.8, 81.3, 57.1, 21.4 ppm. HRMS (ESI): calcd. for $C_{22}H_{19}NNaO_3S$ $[M + Na]^+$ 400.0978; found 400.0996.

Benzyl 1,3-Diphenylprop-2-ynyl(hydroxy)carbamate (3b): White solid; m.p. 116–118 °C. IR (KBr): $\tilde{\nu}$ = 3301, 3034, 2222, 1705, 1491, 1450, 1408, 756, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, J = 6.4 Hz, 2 H, Ar), 7.50–7.42 (m, 2 H, Ar), 7.39–7.25 (s, 11 H, Ar), 6.30 (s, 1 H, CH–N), 5.23 (s, 2 H, $PhCH_2$), 4.10 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 135.8, 135.5, 131.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 122.2, 86.4, 84.0, 68.4, 56.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{20}NO_3$ $[M + H]^+$ 358.1438; found 358.1453.

***tert*-Butyl 1,3-Diphenylprop-2-ynyl(hydroxy)carbamate (3c):** White solid; m.p. 120–123 °C. IR (KBr): $\tilde{\nu}$ = 3357, 3031, 2227, 1650, 1490, 1425, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 6.6 Hz, 2 H, Ar), 7.54–7.48 (m, 2 H, Ar), 7.44–7.30 (m, 6 H, Ar), 6.24 (s, 1 H, OH), 5.89 (s, 1 H, CH–N), 1.54 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 136.1, 131.8, 128.5, 128.4, 128.2, 127.9, 122.3, 86.1, 84.2, 83.0, 56.3, 28.2 ppm. HRMS (ESI): calcd. For $C_{20}H_{21}NNaO_3$ $[M + Na]^+$ 346.1414; found 346.1415.

***N*-Hydroxy-4-methyl-*N*-[3-phenyl-1-(1-tosyl-1*H*-indol-3-yl)prop-2-ynyl]benzenesulfonamide (3d):** White solid; m.p. 155–158 °C. IR (KBr): $\tilde{\nu}$ = 2912, 1593, 1446, 1164, 1098, 770, 673 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 7.96 (d, J = 8.1 Hz, 1 H, Ar), 7.87 (d, J = 8.1 Hz, 3 H, Ar), 7.75 (d, J = 8.1 Hz, 3 H, Ar), 7.40–7.16 (m, 10 H, Ar, & CH=C), 7.08 (d, J = 6.4 Hz, 1 H, Ar), 6.21 (s, 1 H, CH–N), 2.33 (s, 3 H, CH_3–N), 2.24 (s, 3 H, CH_3–*N*–Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO): δ = 144.7, 144.3, 134.8, 134.7, 131.7, 131.3, 129.7, 129.5, 128.8, 128.4, 128.0, 127.6, 126.6, 126.3, 124.6, 123.0, 121.7, 120.3, 118.4, 113.1, 86.4, 81.1, 50.2, 21.2, 21.1 ppm. HRMS (ESI): calcd. for $C_{31}H_{26}N_2NaO_5S_2$ $[M + Na]^+$ 593.1175; found 593.1199.

Benzyl Hydroxy[3-phenyl-1-(1-tosyl-1*H*-indol-3-yl)prop-2-ynyl]-carbamate (3e): Colorless liquid. IR (KBr): $\tilde{\nu}$ = 2923, 2197, 1705, 1596, 1490, 1446, 1174, 754, 675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.3 Hz, 1 H, Ar), 7.85 (s, 1 H, CH=C), 7.77 (d, J = 8.3 Hz, 2 H, Ar), 7.61 (d, J = 7.4 Hz, 1 H, Ar), 7.50 (d, J = 6.5 Hz, 2 H, Ar), 7.42–7.28 (m, 9 H, Ar), 7.21 (d, J = 8.3 Hz, 3 H, Ar), 6.51 (s, 1 H, CH–N), 6.05–5.95 (m, 1 H, OH), 5.25 (s, 2 H, Ph–CH_2), 2.32 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 144.9, 135.3, 135.1, 134.8, 131.8, 129.7, 128.6, 128.4, 128.1, 128.0, 126.7, 126.5, 124.8, 123.2, 121.9, 120.0, 117.9, 113.4, 85.2, 83.3, 68.3, 48.9, 21.3 ppm. HRMS (ESI): calcd. for $C_{32}H_{26}N_2NaO_5S$ $[M + Na]^+$ 573.1455; found 573.1471.

***N*-Hydroxy-*N*-[1-(4-methoxyphenyl)hex-2-ynyl]-4-methylbenzenesulfonamide (3f):** White solid; m.p. 103–105 °C. IR (KBr): $\tilde{\nu}$ = 3339, 2962, 1743, 1604, 1458, 809, 668 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.3 Hz, 2 H, Ar), 7.46 (d, J = 9.0 Hz, 2 H, Ar), 7.34 (d, J = 7.5 Hz, 2 H, Ar), 6.85 (d, J = 8.3 Hz, 2 H, Ar), 5.77 (t, J = 2.2 Hz, 1 H, CH–N), 3.79 (s, 3 H, OCH_3), 2.45 (s, 3 H, Ts–CH_3), 1.84 (td, J = 2.2, 6.7 Hz, 2 H, C–CH_2), 1.36–1.23 (m, 2 H, CH_3CH_2), 0.85 (t, J = 7.5 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 144.4, 132.1, 129.9, 129.5, 129.0, 128.6, 113.6, 89.6, 72.3, 56.2, 55.3, 21.6, 21.5, 20.5, 13.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}NNaO_4S$ $[M + Na]^+$ 396.124; found 396.122.

Benzyl Hydroxy[1-(4-methoxyphenyl)hex-2-ynyl]carbamate (3g): Colorless liquid. IR (KBr): $\tilde{\nu}$ = 3308, 3034, 2218, 1704, 1457, 754, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.3 Hz, 2 H, Ar), 7.40–7.32 (m, 5 H, Ar), 6.85 (d, J = 8.3 Hz, 2 H, Ar), 6.07 (t, J = 1.5 Hz, 1 H, CH–N), 5.23 (d, J = 2.2 Hz, 2 H, $PhCH_2$), 3.79 (s, 3 H, OCH_3), 2.25 (td, J = 2.2, 7.5 Hz, 2 H, C–CH_2), 1.61–1.53 (m, 2 H, CH_3CH_2), 1.00 (t, J = 7.5 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 157.0, 135.6, 129.2, 128.8, 128.5, 128.4, 128.2, 128.0, 113.5, 86.8, 75.2, 68.1, 55.1, 55.0, 21.9, 20.6, 13.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}NNaO_4S$ $[M + Na]^+$ 376.0978; found 376.0909.

***N*-Hydroxy-4-methyl-*N*-(1-phenylnon-2-ynyl)benzenesulfonamide (3h):** Colorless liquid. IR (KBr): $\tilde{\nu}$ = 2925, 2855, 1689, 1454, 1376, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.87 (d, 2 H, Ar), 7.58–7.53 (m, 2 H, Ar), 7.37–7.28 (m, 5 H, Ar), 5.79 (t, J = 2.2 Hz, 1 H, CH–N), 2.45 (s, 3 H, CH_3–SO_2), 1.86–1.80 (m, 2 H, OCH_2), 1.31–1.19 (m, 8 H, aliphatic), 0.88 (t, J = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.4, 136.4, 132.0, 129.9, 129.0, 128.3, 128.2, 90.9, 71.9, 56.7, 31.2, 28.5, 28.1, 22.4, 21.6, 18.5, 13.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{27}NO_3SNa$ 408.1609 $[M + Na]^+$; found 408.1610; HPLC (Chiral pack IC 250 × 4.6 mm, 5 μ, 4% 2-propanol in hexanes, flow rate = 1 mL min^{-1}): tR = 15.25 (50.08%), 20.57 (49.91%) min.

***N*-[4-(Benzyloxy)-1-phenylbut-2-ynyl]-*N*-hydroxy-4-methylbenzenesulfonamide (3i):** Colorless liquid. IR (KBr): $\tilde{\nu}$ = 3238, 1452, 1343, 1165, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.7 Hz, 1 H, Ar), 7.84 (d, J = 7.7 Hz, 2 H, Ar), 7.59–7.53 (m, 2 H, Ar), 7.40–7.26 (m, 10 H, Ar), 6.72 (s, 1 H, OH), 6.30 (s, 1 H, CH–N), 4.64–4.59 (m, 1 H, Ph–CH_2), 4.45–4.39 (m, 1 H, Ph–CH_2), 4.27 (s, 1 H, O–CH_2), 3.83 (s, 1 H, O–CH_2), 2.46 (s, 3 H, SO_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 143.2, 136.1, 133.9, 129.3, 128.7, 128.4, 128.1, 128.0, 127.8, 127.5, 127.4, 127.2, 126.1, 83.9, 79.1, 70.6, 56.4, 56.2, 21.0 ppm. MS (ESI): *m*/*z* = 444 $[M + Na]^+$. HPLC (Chiral pack IC 250 × 4.6 mm, 5 μ, 10% 2-propanol in hexanes, flow rate = 1 mL min^{-1}): tR = 9.63 (50.48%), 10.42 (49.52%) min.

Synthesis of Isoxazole 4a from 3a: TBAF (1 M in THF, 3.0 mmol) was added to a solution of *N*-propargylated hydroxylamine (**3a**, 1.0 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 min. The mixture was quenched by adding saturated NH_4Cl solution and was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography (silica gel) to afford pure **4a**.

3,5-Diphenylisoxazole (4a):[8c] White solid; m.p. 135–138 °C. IR (KBr): $\tilde{\nu}$ = 3110, 3044, 2924, 1612, 1568, 1485, 1453, 1259, 1073, 762, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.82 (m, 4 H, Ar), 7.54–7.44 (m, 6 H, Ar), 6.84 (s, 1 H, CH=C) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 162.9, 130.2, 129.9, 129.1, 129.0, 128.9, 127.4, 126.8, 125.8, 97.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{12}NO$ $[M + H]^+$ 222.0913; found 222.0919.

General Procedure for One-Pot Synthesis of Isoxazoles 4a to 4k from Propargylic Alcohols: *p*-TSA (5 mol-%) was added to a mixture of propargylic alcohol **1a**–**h** (1.0 mmol) and tosyl hydroxylamine **2a** (1.0 mmol) in dichloromethane (5 mL) at room temperature, and stirred (for times, see Table 1). Next, TBAF (1 M in THF, 3.0 mmol) was added at 0 °C and stirred at room temperature until

complete consumption of the starting material (for times, see Table 2). The mixture was quenched by adding saturated NH_4Cl solution and was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography (silica gel) to afford the 3,5-disubstituted isoxazoles **4a**–**h**.

5-Phenyl-3-(1-tosyl-1*H*-indol-3-yl)isoxazole (4b): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3119, 1619, 1490, 1439, 1133, 762, 657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.28–8.23 (m, 1 H, Ar), 8.06–8.00 (m, 2 H, Ar), 7.89–7.80 (m, 4 H, Ar), 7.55–7.33 (m, 5 H, Ar), 7.29–7.22 (m, 2 H, Ar), 6.84 (s, 1 H, CH=C–Ph), 2.37 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 157.3, 145.4, 135.2, 134.8, 130.3, 130.0, 129.0, 127.7, 127.2, 126.9, 125.8, 125.7, 125.5, 124.1, 122.6, 113.4, 112.4, 97.7, 21.5 ppm. HRMS (ESI): calcd. for $C_{24}H_{19}N_2O_3S$ $[M + H]^+$ 415.1111; found 415.1076.

3-(4-Methoxyphenyl)-5-propylisoxazole (4c): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 2963, 1610, 1577, 1528, 1461, 1178, 793 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.9 Hz, 2 H, Ar), 6.94 (d, J = 8.9 Hz, 2 H, Ar), 6.20 (s, 1 H, CH=C–O), 3.85 (s, 3 H, OCH_3), 2.76 (t, J = 7.9 Hz, 2 H, =C–CH_2), 1.84–1.75 (m, 2 H, CH_3–CH_2), 1.04 (t, J = 7.9 Hz, 3 H, CH_3–CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 161.8, 160.7, 128.0, 121.9, 114.1, 98.5, 55.2, 28.6, 20.8, 13.6 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176; found 218.1174.

5-Hexyl-3-phenylisoxazole (4d): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3109, 1614, 1563, 1456, 1169, 774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.75 (m, 2 H), 7.49–7.39 (m, 3 H), 6.28 (s, 1 H), 2.78 (t, J = 7.4 Hz, 2 H), 1.80–1.62 (m, 2 H), 1.46–1.25 (m, 6 H), 0.9 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 162.2, 129.7, 128.8, 126.7, 98.7, 31.4, 28.7, 27.5, 26.8, 22.5, 14.0 ppm.

5-(Benzyloxymethyl)-3-phenylisoxazole (4e): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3032, 1607, 1577, 1445, 1169, 771 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, J = 5.8 Hz, 2 H, Ar), 7.46 (d, J = 5.8 Hz, 3 H, Ar), 7.41–7.33 (m, 5 H, Ar), 6.59 (s, 1 H, CH=C–O), 4.68 (s, 2 H, CH_2–OBn), 4.66 (s, 2 H, OCH_2Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 162.3, 137.0, 129.9, 128.8, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.4, 126.7, 100.9, 72.9, 62.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1176; found 266.1153.

5-(Benzyloxymethyl)-3-(4-methoxyphenyl)isoxazole (4f): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 2923, 1611, 1528, 1456, 1177, 740, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.7 Hz, 2 H, Ar), 7.39–7.30 (m, 5 H, Ar), 6.97 (d, J = 8.7 Hz, 2 H, Ar), 6.52 (s, 1 H, CH=C–O), 4.65 (s, 2 H, =C–CH_2), 4.64 (s, 2 H, OCH_2Ph), 3.85 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 161.9, 160.9, 137.1, 130.2, 128.5, 128.1, 128.0, 127.9, 121.4, 114.2, 100.8, 72.9, 62.8, 55.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}NO_3$ $[M + H]^+$ 296.1281; found 296.1249.

(3-Phenylisoxazol-5-yl)methanol (4g):[19] Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3368, 2924, 1607, 1445, 1406, 1168, 1037, 768, 693 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.77 (m, 2 H, Ar), 7.48–7.43 (m, 3 H, Ar), 6.57 (s, 1 H, CH=C–O), 4.82 (s, 2 H, CH_2–OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 162.3, 130.0, 128.8,128.6, 126.7, 99.9, 56.2 ppm.

5-(Benzyloxymethyl)-3-(2,3-dimethoxyphenyl)isoxazole (4h): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3393, 2934, 1604, 1579, 1483, 1453, 1103, 789 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (dd, J = 1.3, 7.9 Hz, 1 H, Ar), 7.13 (t, J = 8.1 Hz, 1 H, Ar), 7.00 (dd, J = 1.1, 8.1 Hz, 1 H, Ar), 6.75 (s, 1 H, CH=C–O), 4.81 (s, 2 H, CH_2OH), 3.90 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 159.8, 153.1, 147.3, 124.4, 123.0, 120.7, 113.7, 102.9, 60.8, 56.3, 55.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{14}NO_4$ $[M + H]^+$ 236.0917; found 236.0909.

[3-(3-Methyl-1-phenyl-1*H*-pyrazol-4-yl)isoxazol-5-yl]methanol (4i): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3359, 2923, 1513, 1458, 1368, 1161, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, =CH–NPh), 7.66 (d, J = 7.5 Hz, 2 H, Ar), 7.44 (t, J = 7.5 Hz, 2 H, Ar), 7.29 (t, J = 7.5 Hz, 1 H, Ar), 6.41 (s, 1 H, CH=C–O), 4.78 (s, 2 H, CH_2OH), 2.54 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 156.0, 149.0, 139.4, 129.4, 126.7, 119.0, 111.3, 100.5, 56.4, 13.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}N_3O_2$ $[M + H]^+$ 256.1081; found 256.1059.

[3-(Thiophen-2-yl)isoxazol-5-yl]methanol (4j): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3375, 2925, 1604, 1551, 1464, 1156, 709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 2 H, Ar), 7.11 (q, J = 3.7 Hz, 1 H, Ar), 6.49 (s, 1 H, CH=C–O), 4.79 (s, 2 H, CH_2OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 157.6, 130.4, 127.7, 127.6, 127.5, 100.0, 56.4 ppm.

(4-{5-[4-(Pentyloxy)phenyl]isoxazol-3-yl}phenyl)methanol (4k): Viscous liquid. IR (KBr): $\tilde{\nu}$ = 3402, 2932, 1601, 1508, 1256, 1171, 1020, 808 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.9 Hz, 2 H, Ar), 7.76 (d, J = 8.9 Hz, 2 H, Ar), 7.48 (d, J = 7.9 Hz, 2 H, Ar), 6.98 (d, J = 8.9 Hz, 2 H, Ar), 6.69 (s, 1 H, CH–C–O), 4.77 (s, 2 H, CH_2–OH), 4.02 (t, J = 6.9 Hz, 2 H, Ar–OCH_2), 1.85–1.79 (m, 2 H, CH_2), 1.49–1.38 (m, 4 H, CH_2–CH_2), 0.95 (t, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 160.7, 142.6, 135.5, 127.3, 127.2, 126.9, 114.8, 95.9, 68.1, 64.9, 28.8, 28.1, 22.4, 14.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ $[M + H]^+$ 338.1751; found 338.1740.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds.

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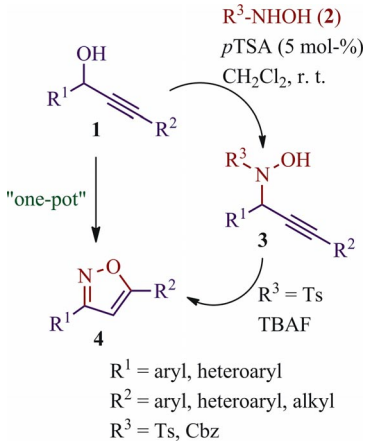
Nucleophilic Substitution

A mild and efficient synthesis of propargylic *N*-hydroxylamines from propargylic alcohols used as alkylating agents is described. The method was successfully extended to a one-pot synthesis of 3,5-disubstituted isoxazoles through a detosylative 5-*endo*-*dig* cyclization.



Keywords: Synthetic methods / Nitrogen heterocycles / Alkylation / Propargylic alcohol / Isoxazole

