Supporting Information

TEMPO-catalyzed Synthesis of 5-Substituted Isoxazoles from Propargylic Ketones and TMSN₃

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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 (\(\delta\) 7.26 ppm) for \(^1\)H NMR and (\(\delta\) 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 preparation of propargylic ketones substrates

The following synthesis procedure is the general procedure used to prepare all substrates.

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O
\[ \text{Ph} - \text{H} \xrightarrow{n-\text{BuLi}} \xrightarrow{\text{THF}} \xrightarrow{TMS} \xrightarrow{\text{K}_2\text{CO}_3} \xrightarrow{\text{MeOH}} \xrightarrow{\text{MnO}_2} \xrightarrow{\text{Ph}} \]
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Under an Ar atmosphere, to a solution of trimethylsilylacetylene (1.5 mL, 10.00 mmol) in THF (20.0 mL) were added dropwise n-BuLi (9.38 mL, 1.6 M in hexane) at −78 °C, and the mixture was stirred for 30 min at the same temperature. To the above reaction mixture was added benzaldehyde (1.02 mL, 10.00 mmol) at −78 °C, and the mixture was stirred with slowly warming to room temperature. After stirring for 2 h at the same temperature, the reaction was quenched with sat. NH₄Cl aq., and the mixture was extracted with CH₂Cl₂, dried over MgSO₄, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (CH₂Cl₂: hexane = 4:1) to afford 1-phenyl-3-trimethylsilanylprop-2-yn-1-ol (S1a) (2.01 g, 9.82 mmol) as colorless oil.

To a solution of S1a (2.01 g, 9.82 mmol) in MeOH (20.0 mL) were added K₂CO₃ (1.38 g, 10.00 mmol) at room temperature, and the mixture was stirred for 2 h at the same temperature, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄ and filtered. The solvent was removed under vacuum. The crude residue was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether = 1:20 to 1:10) to afford propargyl alcohols S2a (1.30 g, 9.8 mmol).

The crude alcohol was dissolved in dichloromethane and treated with MnO₂ (15 equiv.). After stirring at room temperature for 2 h, the reaction was complete as
determined by TLC. Excess MnO₂ was removed by filtration of the reaction mixture through a pad of celite. The filtrate was washed sequentially with water and brine and dried over MgSO₄. The solvent was removed under reduced pressure to afford a yellow residue that was purified by flash column chromatography. The crude residue was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether = 1:20 to 1:10) to afford propargylic ketones 1a (1.04 g, 8.00 mmol).

Propargylic ketones (1a) ¹H NMR (400 MHz, CD₃CN): δ 8.15–8.09 (m, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H), 3.02 (s, 1H).
Labeling experiments:

\[
\text{1a} + \text{TMSN}_3 \xrightarrow{1) \text{TEMPO, N}_2, \text{CH}_3^{18}\text{OH}} \text{16O-N} \xrightarrow{2) \text{PPh}_3} \text{none of } ^{18}\text{O-2a}
\]

Reaction conditions: 1a (0.3 mmol), TMSN\(_3\) (0.45 mmol), TEMPO (15 mol\%) in CH\(_3^{18}\)OH (2 mL) under argon atmosphere at room temperature. PPh\(_3\) (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The \(^{18}\text{O-2a}\) was determined by HRMS.

\[
\text{1a} + \text{TMSN}_3 \xrightarrow{1) \text{TEMPO, } ^{18}\text{O}_2, \text{CH}_3\text{OH (ultradry)}} \text{16O-N} \xrightarrow{2) \text{PPh}_3} \text{none of } ^{18}\text{O-2a}
\]

Reaction conditions: 1a (0.3 mmol), TMSN\(_3\) (0.45 mmol), TEMPO (15 mol\%) in CH\(_3\)OH (2 mL) under \(^{18}\text{O}_2\) atmosphere at room temperature. PPh\(_3\) (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The \(^{18}\text{O-2a}\) was determined by HRMS.

HRMS analysis of 2a
Reaction conditions: 1a (0.3 mmol), TMSN₃ (0.45 mmol), TEMPO (15 mol%) in CH₃OD (2 mL) under ¹⁸O₂ atmosphere at room temperature. PPh₃ (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The 2a-d was determined by ¹H NMR.

**Spectral data of 2a-d and 2a-d**

2a-d ¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.83–7.76 (m, 2H), 7.51–7.41 (m, 3H) ppm.
2a-d $^1$H NMR (400 MHz, CDCl3) δ 7.81 (dd, J = 7.9, 1.6 Hz, 2H), 7.47 (d, J = 7.7 Hz, 3H), 6.53 (s, 1H)
ESI/MS experiments:

1 (0.3 mmol), TMSN$_3$ (0.45 mmol), TEMPO (15 mol%) in CH$_3$OH (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 and 50 μL of the mixture was used for the ESI analysis in CH$_3$OH.

The species B in the reaction mixture was identified by HRMS.

The intermediate 8 in the reaction mixture was identified by HRMS.
$^1$H NMR and $^{13}$C NMR spectra for products