

# One-Pot Synthesis of 3-Substituted Isoxazoles from Phenyl Vinylic Selenide

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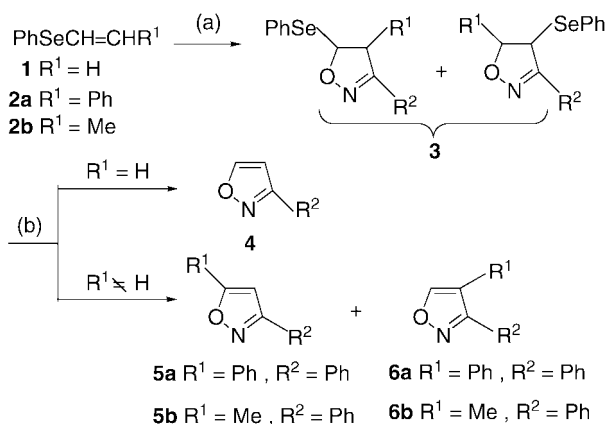
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**Abstract:** Phenyl vinylic selenide was adopted for 1,3-dipolar cycloaddition to nitrile oxides and subsequent oxidation-elimination furnished 3-substituted isoxazoles with good yields in a one-pot, two-step transformation.

**Key words:** isoxazoles, phenyl vinylic selenide, 1,3-dipolar cycloaddition, oxidation-elimination

1,3-Dipolar cycloaddition of nitrile oxides with acetylenes is a useful procedure for the introduction of isoxazoles, which are important class of heterocycles used as intermediates for natural product synthesis and building blocks for construction of new molecular systems.<sup>1</sup> Although methods for the synthesis of isoxazoles are well documented,<sup>2</sup> efforts are continuing for the development of more efficient methods with experimental simplicity. To the best of our knowledge, all previous related reports for the synthesis of isoxazoles have paid no attention to the use of phenyl vinylic selenides as dipolarophiles. Phenyl vinyl selenide as a synthetically useful anionophile was used in the preparation of heterocyclic compounds such as isoxazolidines<sup>3</sup> and pyrrolidines.<sup>4</sup> It is well known that phenylseleno group is readily converted to a leaving group giving access to carbon-carbon double bond via oxidation followed by  $\beta$ -elimination.<sup>5</sup> Herein, we wish to report a one-pot, two-step preparation of isoxazoles from phenyl vinylic selenide by treatment with nitrile oxides followed by 30% hydrogen peroxide (Scheme 1). The present method has advantages such as mild reaction condition, convenient manipulation and good yields.

Reaction of phenylselenenyl bromide with ethene followed by dehydrobromination or by Wittig reaction of phenylselenoalkylidene phosphoranes with aldehydes provided phenyl vinylic selenides **1**,<sup>6</sup> **2a** or **2b**<sup>7</sup> in good yields, respectively. Treatment of phenyl vinylic selenide with nitrile oxides generated in situ from aldoximes and *N*-chlorosuccinimide (NCS) in the presence of Et<sub>3</sub>N afforded the phenyl isoxazoline selenides **3**. Although selenated intermediates **3** can be isolated and purified by chromatography, we have found it most convenient to carry out the oxidation of these materials in one-pot. To the stirred solution of the selenide at 0 °C was added 30% H<sub>2</sub>O<sub>2</sub> slowly resulting in a facile oxidation of the selenide to the corresponding selenoxide. When R<sup>1</sup> was hydrogen, a *syn*-elimination of the selenoxide effected the release of



**Scheme 1** Reagents and conditions: (a) R<sup>2</sup>CH=NOH, NCS, Et<sub>3</sub>N, CHCl<sub>3</sub>, r.t. 12 h; (b) 30% H<sub>2</sub>O<sub>2</sub>, 0 °C r.t., 30 min.

3-substituted isoxazoles **4** in good yield (Table 1). However, it should be noted that, when R<sup>1</sup> was other than hydrogen (R<sup>1</sup> = Ph, CH<sub>3</sub>), a mixture of regioisomers **5a** and **6a**, **5b** and **6b** in the ratio of 60:40, 55:45, respectively, were obtained under the same reaction conditions. The re-

**Table 1** Synthesis of Isoxazoles

Entry	R <sup>1</sup>	R <sup>2</sup>	Products	Yield (%) <sup>a</sup>
1	H	C <sub>6</sub> H <sub>5</sub>	<b>4a</b>	85
2	H	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>4b</b>	86
3	H	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	<b>4c</b>	86
4	H	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>4d</b>	78
5	H	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>4e</b>	82
6	H	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	<b>4f</b>	83
7	H	2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>4g</b>	80
8	H	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	<b>4h</b>	82
9	H	2-furyl	<b>4i</b>	83
10	H	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	<b>4j</b>	81
11	H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>4k</b>	78
12	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	<b>5a</b> + <b>6a</b>	50 (30 + 20)
13	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	<b>5b</b> + <b>6b</b>	54 (30 + 24)

<sup>a</sup> Isolated yields based on phenyl vinylic selenide.

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ported ratio was based on the integration of the proton signal on the isoxazole ring in **5a** and **5b**, **6a** and **6b** appearing at  $\delta_{\text{H}} = 6.65\text{--}6.70$  ppm,  $8.36\text{--}8.40$  ppm, respectively. Attempts to improve the yields of them by replacing solvents such as THF and  $\text{CH}_2\text{Cl}_2$ , changing reaction temperature or prolonging reaction time were unsuccessful (Table 1, entries 12 and 13).

In summary, we have developed a mild and efficient method for the synthesis of 3-substituted isoxazoles by 1,3-dipolar cycloaddition of phenyl vinyl selenide with nitrile oxides and subsequent oxidation-elimination in a one-pot, two-step transformation.

Melting points were uncorrected.  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using  $\text{CDCl}_3$  as the solvent and TMS as internal standard. Mass spectra (EI, 70 eV) were recorded on a HP5989B mass spectrometer. IR spectra were recorded on a Bruker Vector 22 spectrometer. Microanalyses were performed with a Carlo-Erba 1106 elemental analyzer.  $\text{CHCl}_3$  was dried by distillation from  $\text{P}_2\text{O}_5$  prior to use. Phenyl vinylic selenides **1**<sup>6</sup> and **2**<sup>7</sup> were prepared according to the literature procedures. Aldoximes were synthesized based on the procedure described in the literature.<sup>8</sup> All reactions were monitored by TLC.

#### Preparation of Isoxazoles; General Procedure

To a stirred solution of *N*-chlorosuccinimide (NCS, 2.0 mmol) in anhydrous  $\text{CHCl}_3$  (5 mL) was added aldoxime (2 mmol) under a  $\text{N}_2$  atmosphere at r.t. in one portion. Phenyl vinylic selenide **1** or **2** (2 mmol) was added after 20 min, and the  $\text{Et}_3\text{N}$  (2.1 mmol in 2 mL of  $\text{CHCl}_3$ ) was added dropwise over ca. 30 min. The mixture was stirred at r.t. for 12 h, then cooled to  $0^\circ\text{C}$  and 30%  $\text{H}_2\text{O}_2$  (0.5 mL) was added over 10 min. After an additional stirring for 20 min at r.t.,  $\text{H}_2\text{O}$  (5 mL) was added and the  $\text{CHCl}_3$  layer was separated and washed with sat.  $\text{NaHCO}_3$  solution (5 mL). After being dried over  $\text{MgSO}_4$ , the solution was filtered and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography (10–15% EtOAc in hexane) to give pure product.

Structures of compounds **4a**,<sup>2c</sup> **4b**,<sup>9</sup> **4c**,<sup>2d</sup> **4d**,<sup>2c</sup> **4e**,<sup>2d</sup> **4f**,<sup>2c</sup> **4g**,<sup>2c</sup> **4j**,<sup>10</sup> **4k**,<sup>10</sup> **5**,<sup>11</sup> **6**<sup>12</sup> have been already described, our spectral data were in accordance with those in the literatures.

#### 3-(*p*-Fluorophenyl)isoxazole (**4h**)

The crude product was purified by silica gel column chromatography (hexane–EtOAc, 9:1) affording 267 mg (1.64 mmol) of **4h** as a white solid; mp  $35\text{--}36^\circ\text{C}$ .

IR (KBr): 3030, 2929, 1607, 1557, 1520, 1494, 1434, 1379, 1236, 1159, 1125, 1098, 885, 842, 777  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR:  $\delta = 8.38$  (d,  $J = 1.6$  Hz, 1 H), 7.77 (d,  $J = 8.1$  Hz, 2 H), 7.12 (d,  $J = 8.0$  Hz, 2 H), 6.66 (d,  $J = 1.6$  Hz, 1 H).

$^{13}\text{C}$  NMR:  $\delta = 166.1, 162.2, 134.1, 128.3, 121.0, 114.7, 102.2$ .

EIMS:  $m/z$  (%) = 163 (100) [ $\text{M}^+$ ], 108 (48.3), 107 (61.7), 95 (80.7), 75 (52.1), 57 (49.9), 43 (41.8).

Anal. Calcd for  $\text{C}_9\text{H}_6\text{FNO}$ : C, 66.26; H, 3.71; N, 8.59. Found: C, 66.22; H, 3.65; N, 8.53.

#### 3-(2-Furyl)isoxazole (**4i**)

The crude product was purified by silica gel column chromatography (hexane–EtOAc, 9:1) affording 222 mg (1.64 mmol) of **4i** as colorless oil.

IR (neat): 3128, 2958, 2927, 1616, 1556, 1514, 1459, 1438, 1387, 1365, 1125, 1014, 872, 780  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR:  $\delta = 8.43$  (d,  $J = 1.6$  Hz, 1 H), 7.57 (dd,  $J = 1.8, 0.8$  Hz, 1 H), 7.28 (dd,  $J = 3.5, 0.8$  Hz, 1 H), 6.62 (d,  $J = 1.6$  Hz, 1 H), 6.54 (dd,  $J = 3.5, 1.8$  Hz, 1 H).

$^{13}\text{C}$  NMR:  $\delta = 160.9, 146.9, 146.6, 135.0, 128.3, 125.5, 102.2$ .

EIMS:  $m/z$  (%) = 135 (49.2) [ $\text{M}^+$ ], 86 (59.7), 84 (100), 78 (52.1), 52 (53.9), 51 (50.1), 43 (40.8).

Anal. Calcd for  $\text{C}_7\text{H}_6\text{NO}_2$ : C, 66.22; H, 3.73; N, 10.37. Found: C, 66.16; H, 3.70; N, 10.32.

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