Three-Component Reactions of Alkynone α-Methyloximes, Element Selenium, and Boronic Acids Leading to 4-Organoselenylisoxazoles

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ABSTRACT: We report an Ag-catalyzed one-pot three-component reaction of alkynone α-methyloxime, element selenium, and boronic acid, providing a facile route to selenated isoxazole product. This protocol features high efficiency, wide substrate scope, and the use of selenium powder as the selenium source.

1. INTRODUCTION

Isoxazoles represent an important class of heterocycles, as their derivatives are shown to exhibit a wide range of promising pharmaceutical properties including anti-inflammatory, antimicrobial, anticancer, COX-2 inhibitory, and antinociceptive activity. On the other hand, selenium is also a useful element in biologically active molecules, functional materials, synthetic intermediates, and organic catalysts. Incorporation of the selenium atom into a heterocyclic skeleton can pose a certain degree of influence on physicochemical and biological properties as well as the reactivity. For example, the presence of the selenium atom results in an increased native biological activity in a potentially bioactive molecule. In this context, the installation of a selenium moiety into the isoxazoles skeleton provides a useful way to modulate their properties and reactivity. Additionally, the selenated isoxazoles can serve as a convenient precursor for the synthesis of isoxazole derivatives. Therefore, the development of the method for the synthesis of selenated isoxazoles is desirable.

Despite a large number of existing synthetic approaches to functionalized isoxazole derivatives, the methods to access selenated isoxazoles have been less reported. The pioneering work for the construction of 4-organoselenylisoxazoles through the reaction of 2-alkyn-1-one α-methyloximes and phenylselanyl bromide was developed by Larock and co-workers, although only two substrates were used (Scheme 1a). Alternatively, the electrophilic cyclization of hydroxylamine derivative using phenylselanyl chloride as an electrophilic element selenium as a selenium source, we disclose a one-pot three-component reaction of alkynone α-methyloxime, Se powder, and organoboronic acid, providing a facile and efficient route to 4-organoselenylisoxazoles (Scheme 1d).

2. RESULTS AND DISCUSSION

Our investigations began with the model reaction of 1,3-diphenylprop-2-yn-1-one α-methyloxime (1a), Se powder, and phenylboronic acid (2a) (Table 1). Interestingly, we found that the three-component model reaction could deliver the desired product (3aa) in 84% isolated yield using AgNO3 as a catalyst at 120 °C (entry 1). The examination of other silver sources including AgNO3, AgOTf, CH3COOAg, and Ag2SO4 (entries 2–5) demonstrated that the employment of AgNO3 was the best choice (entry 2). The inferior yield was observed when a lower catalyst loading was used (entry 6). Inspired by our previous work on selenylation of olefin, the mixture of 1a, Se powder, and phenylboronic acid was submitted into the catalytic system containing CuBr2/tricyclohexylphosphonium tetrafluoroborate, giving a lower yield of 3aa (entry 7).

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dioxane, toluene, or C$_2$H$_5$OH as the solvent led to no formation of the desired product (entries 10–12). Raising the reaction temperature to 130 °C did not improve the reaction efficiency but resulted in an inferior yield (entry 13). Decreasing the reaction temperature led to an increased amount of raw material being recovered (entries 14 and 15). Worse reaction efficiency was observed when the model reaction was performed under an air atmosphere (entry 16). The replacement of O$_2$ with a N$_2$ atmosphere led to no observed isoxazoles product (entry 17), which indicates that O$_2$ is indispensable in this reaction. The optimal reaction involved the use of AgNO$_2$ as a catalyst DMSO as the solvent at 120 °C under the O$_2$ atmosphere (entry 2).

Under optimal conditions, the scope with respect to organoboronic acids and alkynone o-methyloximes was explored (Table 2). Arylboronic acids with a para electron-rich group or a para electron-withdrawing group were found to be effective substrates and furnished the corresponding products in 50–93% yields (3ab–3ag). Both ortho- and meta-substituents on the aryl ring were well tolerated, providing the selenated isoxazoles products with good yields (3ah–3ak). Of particular interest is that either alkylboronic acid (2l) or heterocyclic boronic acid (2m) proved to be a suitable substrate. A subsequent survey of alkynone o-methyloximes revealed that a variety of functional groups could be tolerated in the optimal conditions. Substrates in which R$_1$ carried various substituents such as methyl, trifluoromethyl, chloro, and ester groups reacted well to give the desired products in 40–93% yields (3ba–3ea, 3ga, 3ha). The presence of the methoxy group resulted in no formation of the desired product (3fa). Furthermore, R$_1$ could also be a fused ring (1i), an alkene moiety (1j), or an alkyl group (1k). On the other hand, R$_2$ could be a substituted phenyl moiety (1l–1q) or an alkyl group (1r and 1s).

To investigate the mechanism of this three-component reaction, we performed several control reactions (Scheme 2). It was found that the presence of 3 equiv of TEMPO shut down this reaction of 1a, Se powder, and 2a, implying that the three-component reaction proceeded in a radical way (Scheme 2a). In the absence of 1a, the reaction between Se powder and

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**Scheme 1. Strategies to Synthesize 4-Organoselenylisoxazoles**

**Previous work:**

![Previous reaction scheme](image)

**This work:**

![This reaction scheme](image)
2a delivered diphenyldiselenide (4) in 87% yield but failed to afford diphenyldiselenide in the presence of 3 equiv of TEMPO (Scheme 2b). Furthermore, 1a could react with diphenyldiselenide to provide the desired product in 95% yield (Scheme 2c). [1,1′-Biphenyl]-4-ol (6) and alcohol (8) could be isolated when substrate 5 or 7 was subjected to the standard conditions (Scheme 2d,e).

Based on these results and previous references, the proposed mechanism for the three-component reaction of 1a, element selenium, and PhB(OH)2 is presented in Scheme 3. In the beginning, the reaction of PhB(OH)2 with O2 in the presence of Ag catalyst to generate phenyl radical (A), which is further captured by element selenium to form selenium-centered radical intermediate (B). The intermediate B can undergo reversible radical coupling to produce diphenyldiselenide. Alternatively, the intermediate B can be further oxidized into PhSe cation (C), which then reacts with 1a to generate intermediate D. Finally, D undergoes hydrolysis to form the desired product 3aa along with methanol.

### 3. CONCLUSIONS

We have developed a facile method for the synthesis of 4-organoselenylisoxazoles via Ag-catalyzed three-component reaction of alkynone O-methyloximes, element selenium, and boronic acids. This reaction displays high efficiency towards a wide range of boronic acids and alkynone O-methyloximes alkynone O-methyloximes. In addition, an attractive strategy for the incorporation of the selenium atom into a heterocyclic skeleton using selenium powder as a selenium source has been highlighted. Further developments of this strategy in the construction of other selenated heterocycles are reported.

## 4. EXPERIMENTAL SECTION

### 4.1. General Experimental Procedures for the Synthesis of 4-Organoselenylisoxazoles.

A 10 mL Schlenk tube equipped with a stir bar was charged with 2-alkyn-1-one O-methyloximes (0.2 mmol), arylboronic acid (0.4 mmol), AgNO2 (0.04 mmol), DMSO (2.0 mL), under O2 atmosphere. The tube was fitted with a rubber septum and then the septum was replaced by a Teflon screwcap. The reaction mixture was stirred at 120 °C for 12 h. After cooling down, the reaction mixture was diluted with 2 mL of ethyl ether, filtered through a pad of silica gel, followed by washing the pad of the silica gel with the same solvent (20 mL), and concentrated under reduced pressure. The residue
Scheme 2. Some Control Experiments

\[ \text{Scheme 2. Some Control Experiments}^{\text{a}} \]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{O} \\
\text{NOMe} & \quad + \quad \text{Se} \\
1a \ (0.2 \text{ mmol}) & \quad 0.4 \text{ mmol} \\
\text{Ph} & \quad \text{Ph} \\
\text{PhB(OH)}_2 & \quad \text{standard conditions} \\
2a \ (0.4 \text{ mmol}) & \quad \text{TEMPO} \ (3 \text{ equiv}) \\
\text{3aa, 0\% yield} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Se} + \text{PhB(OH)}_2 & \quad \text{standard conditions} \\
0.2 \text{ mmol} & \quad 2a \ (0.2 \text{ mmol}) \\
4 & \quad 87\% \text{ yield} \\
\text{with TEMPO} \ (3 \text{ equiv}) & \quad 4, \ 0\% \text{ yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{O} \\
\text{NOMe} & \quad + \quad \text{PhSeSePh} \\
1a \ (0.2 \text{ mmol}) & \quad 0.4 \text{ mmol} \\
\text{Ph} & \quad \text{Ph} \\
\text{PhSeSePh} & \quad \text{standard conditions} \\
4 & \quad \text{3aa, 95\% yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
5 & \quad \text{Se, PhB(OH)}_2 \\
\text{standard conditions} & \quad \text{PhSeSePh} \\
\text{3aa, trace} & \quad \text{6, 46\% yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
7 & \quad \text{Se, PhB(OH)}_2 \\
\text{standard conditions} & \quad \text{PhSeSePh} \\
\text{3aa, 51\% yield} & \quad \text{8, 33\% yield} \\
\end{align*}
\]

\[^{\text{a}}\text{Standard conditions: AgNO}_2 \ (20 \text{ mol \%}), \text{DMSO} \ (2.0 \text{ mL}), \text{under O}_2, 120 ^\circ \text{C}, 12 \text{ h}, \text{and isolated yields.} \]

Scheme 3. Proposed Mechanism

\[\frac{O_2}{\text{O}}\]

\[\frac{\text{PhB(OH)}_2}{\text{2a}} \quad \frac{\text{Ag}^{2+}}{\text{Ag}^+} \quad \text{Ph}^+ \quad \text{Se} \quad \text{PhSe}^+ \quad \text{PhSeSePh} \]

\[\frac{\text{PhSeSePh}}{\text{3aa}} \quad \text{CH}_3\text{OH} \quad \text{1a} \quad \frac{\text{Ag}^{2+}}{\text{Ag}^+} \quad \text{O}_2 \quad \text{PhSe}^+ \]

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was then purified by flash chromatography on silica gel to provide the corresponding product.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c03254.

General information on the instruments and $^1$H NMR and $^{13}$C NMR spectra of the products (PDF)

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**ASSOCIATED CONTENT**

Notes

The authors declare no competing financial interest.

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