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One-pot synthesis of novel ether-linked diisoxazole derivatives via sequential *O*-propargylation and 1,3-dipolar cycloaddition from 2-bromohomoallylic alcohols

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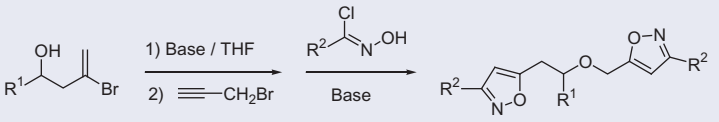
ABSTRACT

A simple and efficient, one-pot approach for the synthesis of ether-linked diisoxazole derivatives has been developed through sequential reactions, which includes *O*-propargylation of 2-bromohomoallylic alcohols with propargyl bromide in the presence of sodium hydride in THF, and 1,3-dipolar cycloaddition by the addition of hydroximinoyl chlorides and triethylamine. This protocol provides some advantages such as high regioselectivity, easy operation and good product yields with a wide scope of substrates under mild conditions.

GRAPHICAL ABSTRACT



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Ether-linked diisoxazole derivatives; O-propargylation reaction; 1,3-dipolar cycloaddition; 2-bromohomoallylic alcohols; hydroximinoyl chlorides; one-pot procedure

Introduction

Multicomponent reactions (MCRs) are special and useful organic synthesis reactions, in which three or more starting materials react to form a final product in a one-pot procedure.[1] Owing to their inherent advantages such as short reaction time, low manpower requirement, high atom economy and simple purification process, MCRs have been recognized as effective, economical, convenient and environmentally friendly methods, which are important synthetic strategy for the heterocycles.[2,3] Therefore, the development of new, versatile and efficient MCRs for the preparation of heterocyclic compounds is an important research area in organic and bio-organic chemistry. Compared with the single heterocycle, the fused or linked two heterocyclic scaffolds with two heteroatom-containing rings are expected to provide more binding opportunities and diversified expansion options. Isoxazoles are important five-membered heteroaromatic molecules with wide applications in organic synthesis, pharmacy chemistry, biologically active molecules, and advanced organic materials.[4] Generally, isoxazoles

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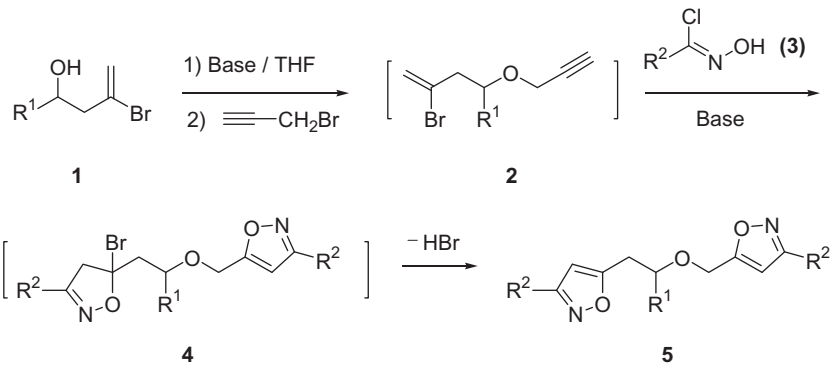
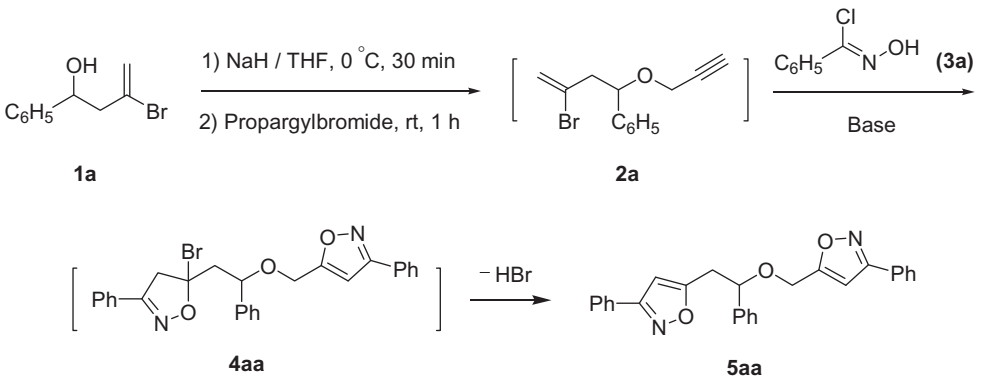


Scheme 1. One-pot synthetic route to the ether linked diisoxazoles by O-propargylation and 1,3-dipolar cycloaddition in sequence

are constructed by [3 + 2] cycloadditions of alkenes/alkynes to nitrile oxides, which are generated in situ mainly from three routes, including oxidative dehydrogenation of aldoximes, dehydration of primary nitro compounds and base promoted dehydrodehalogenation of hydroximinoyl halides.[5] In recent years, many exciting advances in the synthesis and functionalization of isoxazoles have been reported.[6] Although a variety of diheterocyclic scaffolds containing isoxazole units such as triazoles, pyrroles, pyridines, furans and 1,2,4-oxadiazoles were developed,[7] there are relatively a few reports on the preparation of heterocycles with di, tri, tetra and polyisoxazole rings.[8] Consequently, the development of simple and efficient methods for the synthesis of diisoxazole-containing heterocyclic molecules using readily accessible substrates is still highly desirable. As a continuation of our ongoing research program on the design and synthesis of isoxazoles,[9] we here would like to report a facile one-pot synthesis of various ether linked diisoxazole compounds, *via* sequential *O*-propargylation reaction of 2-bromohomoallylic alcohols with propargyl bromide, and 1,3-dipolar cycloaddition reaction upon the addition of hydroximinoyl chlorides and base under mild reaction conditions, as shown in Scheme 1.

Initially, 1-phenyl-3-bromo-3-butenol (**1a**)[10] was used as the starting model substrate for evaluation to prepare the target molecule, 3-phenyl-5-{2-phenyl-2-[(3-phenylisoxazol-5-yl)methoxy]ethyl}isoxazole (**5aa**) (Scheme 2). 1-Phenyl-3-bromo-3-butenyl propargyl ether (**2a**) was synthesized by reaction of **1a** with 1.0 equivalent of propargyl bromide mediated with sodium hydride in THF using a similar method,[11] and was not further separated and purified. Indeed, to avoid deprotonation of the terminal alkyne, **1a** was added first to a suspension of sodium hydride (1.0 equiv) in THF. After alkoxide formation was complete (30 min at 0 °C), propargyl bromide was added. As mentioned earlier, the dehydrodehalogenation of hydroximinoyl halides promoted by base is one of three main routes to generation of nitrile oxides efficiently in situ. Additionally, some hydroxyimioyl chlorides are commercially available, and all hydroxyimioyl chlorides can be easily prepared from the corresponding aldehydes. So, in our studies, this method was used to generate nitrile oxides in situ.

Secondly, after the completion of the *O*-propargylation of **1a**, the subsequent [3 + 2] cycloaddition with phenyl nitrile oxide, generated in situ from *N*-hydroxybenzimidoyl chloride (**3a**) was further studied, and the optimization results were summarized in



Scheme 2. Optimization of one-pot reaction conditions for 5aa formation

Table 1. Optimization of one-pot reaction conditions to **5aa**[a].

Entry	**3a** (equiv.)	Additive (equiv.)	Temp. (°C)	Yield (%)[b]
1	3.0	–	r.t.	–
2	3.0	–	65	–
3	3.0	$NaHCO_3$ (3.0)	r.t.	55
4	3.0	AcONa (3.0)	r.t.	51
5	3.0	NaOH (3.0)	r.t.	68
6	3.0	Et_3N (3.0)	r.t.	85
7	3.0	Et_3N (3.0)	65	80
8	4.0	Et_3N (3.0)	r.t.	84
9	2.5	Et_3N (3.0)	r.t.	78
10	3.0	Et_3N (2.5)	r.t.	80
11	3.0	Et_3N (2.0)	r.t.	72

[a]All reaction was performed with **1a** (1.0 equiv.), propargyl bromide (1.0 equiv.) and THF (5 mL), and monitored by TLC, and **3a** and base were added after the *O*-propargylation of **1a** into propargyl ether **2a** was complete.
[b]Isolated yield based on **1a** after flash column chromatography.

Table 1. As seen from Table 1, the first attempt to employ **3a** in the absence of base failed to give the desired product (Table 1, entries 1–2). Then, the addition of bases such as $NaHCO_3$, AcONa, NaOH, and Et_3N (Table 1, entries 3–6) was investigated, Interestingly, it was found that **5aa** was isolated as the sole product, no bromoisoxazoline compound (**4aa**) was obtained. Obviously, the most probable driving force for **5aa** formation is the creation of stable aromatic systems by the loss of HBr in the presence of base.[12] Among them, Et_3N was the best, and the yield of **5aa** was 85% (Table 1, entry 6). However, an attempt of the [3 + 2] cycloaddition reaction at an elevated temperature was unsuccessful (Table 1, entry 7). Further optimization showed that the formation of **5aa** required 3.0 equivalents of **3a** and 3.0 equivalents of Et_3N. It should be pointed out that a mixture of allyl and propynyl intermediates might be formed in the presence of Et_3N before the addition reaction of **2a** with phenyl nitrile oxide in the conversion **2a–5aa**. But it did not affect the formation of target compounds.

The structure of **5aa** was characterized by NMR and mass spectroscopic data. In the ^1H NMR spectrum of **5aa**, there were two characteristic single signals at $\delta = 6.24$, 6.22 ppm, assignable to the isoxazolyl C4–*H* protons, respectively. And its 13C NMR spectrum has the $ArCH_2O$ and $ArCH_2$ carbon peaks, appearing at $\delta = 61.65$ and 35.80, *C*4 peaks of the triazole rings appearing at $\delta = 101.03$ and 100.74, and *C*5 peaks at $\delta = 170.22$ and 169.64, respectively, along with other carbon peaks.

Table 2. The yields of the ether-linked diisoxazole derivatives (**5**)[a].

Entry	R^1 (**1**)	R^2 (**3**)	Product (**5**)	Yield (%)[b]
1	C_6H_5 (**1a**)	C_6H_5 (**3a**)	**5aa**	85
2	C_6H_5 (**1a**)	3-$CH_3C_6H_4$ (**3b**)	**5ab**	82
3	C_6H_5 (**1a**)	2-$CH_3C_6H_4$ (**3c**)	**5ac**	78
4	C_6H_5 (**1a**)	3-$CH_3OC_6H_4$ (**3d**)	**5ad**	84
5	C_6H_5 (**1a**)	4-BrC_6H_4 (**3e**)	**5ae**	86
6	C_6H_5 (**1a**)	$CH_3CH_2CH_2$ (**3f**)	**5af**	65
7	4-BrC_6H_4 (**1b**)	C_6H_5 (**3a**)	**5ba**	85
8	4-BrC_6H_4 (**1b**)	3-$CH_3C_6H_4$ (**3b**)	**5bb**	83
9	4-BrC_6H_4 (**1b**)	2-$CH_3C_6H_4$ (**3c**)	**5bc**	80
10	4-BrC_6H_4 (**1b**)	3-$CH_3OC_6H_4$ (**3d**)	**5bd**	87
11	4-BrC_6H_4 (**1b**)	4-ClC_6H_4 (**3g**)	**5bg**	88
12	4-$CH_3C_6H_4$ (**1c**)	C_6H_5 (**3a**)	**5ca**	83
13	4-$CH_3C_6H_4$ (**1c**)	4-$NO_2C_6H_4$ (**3h**)	**5ch**	90
14	$CH_3CH_2CH_2$ (**1d**)	C_6H_5 (**3a**)	**5da**	81
15	C_6H_5 (**1a**)	4-HOC_6H_4 (**3i**)	**5ai**	0
16	C_6H_5 (**1a**)	4-$(Me_2N)C_6H_4$ (**3j**)	**5aj**	0

[a]All reaction was performed with **1a–1d** (1.0 equiv.), propargyl bromide (1.0 equiv.) and THF (5 mL), and monitored by TLC, and **3a–3j** (3.0 equiv.) and Et_3N (3.0 equiv.) were added after the *O*-propargylation of **1a–3d** into the corresponding propargyl ethers was complete.
[b]Isolated yield based on **1a–1d** after column chromatography.

Finally, to test the scope of this reaction, various 2-bromohomoallylic alcohols **1a**–**1d** and hydroximyl chlorides **3a**–**3j** were subjected to the above optimized reaction conditions (Table 2). As shown in Table 2, for most of the examined substrates, experiments were performed smoothly and the corresponding ether-linked diisoxazole derivatives were obtained. It is noteworthy that there is no significant difference in the reactivity of all examined 2-bromohomoallylic alcohols (Table 2, entries 1–14).

In general, aromatic hydroximyl chlorides bearing strong electron-withdrawing groups like nitro (**3h**), moderate electron-withdrawing groups such as bromo (**3e**) and chloro (**3g**), as well as electron-donating groups such as methyl (**3b** and **3c**) and methoxy (**3d**), and even *N*-hydroxy-2-methylbenzimidoyl chloride **(3c)** with methyl at the *ortho* position of the benzene ring could afford the desired products in good yields (Table 2, entries 2–5, entries 8–11, and entry 13). It was also observed that electron-deficient aromatic hydroximyl chlorides were preferred over electron-rich ones in the one-pot multicomponent reactions. Among them, electron-rich aromatic hydroximyl chloride containing 4-methoxy substituent could produce the desired products (**5ad** and **5bd**) in good yields. When other electron-rich hydroximyl chlorides such as *N*-hydroxy-4-hydroxybenzimidoyl chloride **(3i)** and *N*-hydroxy-4-(*N*,*N*-dimethylamino)benzimidoyl chloride **(3j)** were used, the formation of **2a** and the corresponding nitrile oxides were observed, but the corresponding products **(5ai** and **5aj)** were not obtained in this reaction (Table 2, entries 15 and 16), indicating the cycloaddition reaction was limited. Besides, aliphatic hydroximyl chlorides, such as *N*-hydroxybutylimidoyl chloride **(3f)** produced the corresponding compound **5af** in moderate yield (Table 2, entry 14).

In summary, a facile and efficient, one-pot strategy was developed to obtain a wide variety of ether-linked diisoxazole derivatives from 2-bromohomoallylic alcohols, propargyl bromide and hydroximyl chlorides. The procedure does not require the isolation of the propargyl ether intermediates, and has considerable advantages in terms of high regioselectivity, easy available substrate, mild reaction condition, simple operation and good yield.

Experimental

All reactions, unless otherwise described, were carried out under an inert atmosphere of dry nitrogen. Analytical TLC was performed on Merck 0.2-mm silica gel 60 F254 analytical aluminum plates, and the products were visualized by UV detection. Column chromatography was performed on Merck silica gel 60 (250–400 mesh). Melting points were measured with a Beijing-Taike X-4 apparatus without corrected. ^{1}H NMR and 13C NMR spectra were recorded on an Avance-Bruker 400 MHz NMR spectrometer, operating at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm relative to TMS or the deuterated solvent as internal reference. FTIR analyses were recorded with a Perkin-Elmer SP One FTIR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 Elemental Analyzer. Mass spectra were recorded on a Thermofisher scientific LCQ FLEET mass spectrometer. 2-Bromohomoallylic alcohols (**1a**−**1d**) are known compounds and prepared by indium-mediated 2-bromoallylation of the corresponding readily aldehydes with 2,3-dibromopropene according to the reported method.[10] All hydroximyl chlorides (**3a**−**3k**) were prepared from the corresponding readily available aldehydes through the reported method.[13] Tetrahydrofuran was distilled from sodium/benzophenone immediately prior to use. Triethylamine was distilled from calcium hydride and stored over KOH. The other reagents and solvents were purchased from commercial suppliers and were used as received without further purification.

General procedure for the preparation of ether-linked diisoxazole derivatives

A flame-dried 25-mL round-bottomed flask was charged with 2-bromohomoallylic alcohol (**1**) (1.0 mmol) and sodium hydride (1.0 mmol) in THF (5 mL). The resulting suspension was cooled to 0 °C and stirred for 30 min under an atmosphere of nitrogen. Propargyl bromide (80% in toluene, 120 mg, 1.0 mmol) was then added slowly, and the reaction was warmed to room temperature and stirred for 1 h or until the complete conversion of **1** to the corresponding propargyl ether (**2**), as judged by TLC. After this, hydroximyl chloride **3** (3.0 equiv.) and triethylamine (0.42 mL, 3.0 equiv.) dissolved in dried THF (0.5 mL) was added to the reaction mixture, which was stirred continuously until the completion of the reaction (by TLC). The resulting mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic phase was washed with brine (2 mL), dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether–EtOAc as eluent) to afford the target compounds **5aa**–**5da**, with the following physicochemical properties.

Characterization data of all target compounds, copies of ^{1}H NMR and 13C NMR spectra of all compounds. This material can be found via the "Supplementary Content".

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