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Isoxazoles from 1,1-Disubstituted Bromoalkenes

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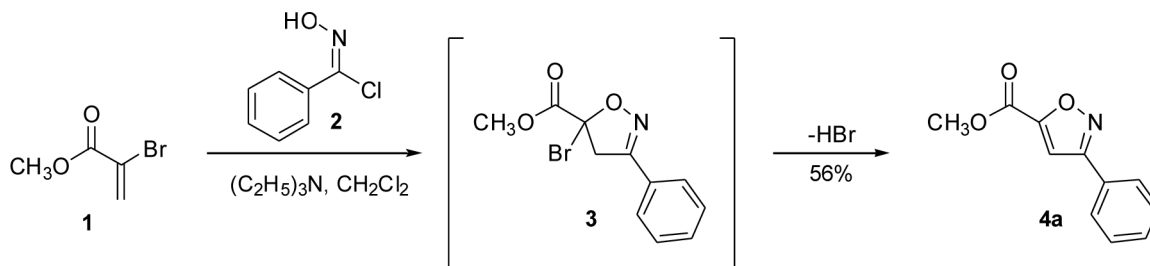
Abstract

The regioselective synthesis of 3,5-disubstituted isoxazoles was achieved through the 1,3-dipolar cycloaddition of nitrile oxides with 1,1-disubstituted bromoalkenes. The substituted bromoalkenes function as alkyne synthons which were used to construct 5,5-disubstituted bromoisoxazoline intermediates that aromatize to the analogous isoxazoles through the loss of HBr.

Keywords

Cycloaddition; Regioselectivity; Heterocycles; Alkyne Surrogate; Dehydrohalogenation

Since a number of isoxazoles display anti-inflammatory¹, antiviral,² as well as antitubulin³ activity, the synthesis of this family of heterocycles continues to be of interest. One of the most frequently used methods to synthesize isoxazoles is a 1,3-dipolar cycloaddition involving a nitrile oxide, and the usual dipolarophile for this process is an alkyne.⁴ Although some alkynes are commercially available, the synthesis of many functionalized alkynes can take two or more steps. Additionally, the 1,3-dipolar cycloaddition of alkynes, with a few exceptions,⁵ often lead to a mixture of regioisomeric products.^{4,6b} The use of alkyne synthons⁶ can serve to alleviate many of the alkyne preparatory and cycloaddition regioselectivity issues.⁷ These alkyne surrogates are usually alkenes that have a functional group that can be eliminated in situ during cycloaddition.⁶ Herein we report the application of 1,1-disubstituted bromoalkenes as alkyne equivalents for the regioselective synthesis of 3,5-disubstituted isoxazoles via 1,3-dipolar cycloaddition.



Scheme 1.

Isoxazole synthesis from 2-bromo-acrylic acid methyl ester through a 5-bromoisoxazoline intermediate.

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Supplementary Data.

The supplementary data is available online with the paper in ScienceDirect.

During our study of the synthesis of functionalized 5,5-disubstituted isoxazolines, we discovered that when 2-bromo-acrylic acid methyl ester (**1**) was used as the alkene, isoxazole (**4**) was isolated as the sole product instead of the bromoisoxazoline (**3**, Scheme 1).⁸ The most probable driving force for the formation of **4** is the creation of a stable aromatic system through the loss of HBr. Alternatively, since the reaction conditions are basic, it is quite possible for the bromoalkene, **1**, to decompose to the corresponding alkyne before reacting with the nitrile oxide. In order to rule out this reaction pathway, we exposed **1** to triethylamine for 24 hours, and no decomposition or formation of alkyne was observed. The experimental data point to the formation of **3** followed by its aromatization to **4**,⁶ and the regioselectivity is in accordance with both steric and frontier molecular orbital interactions of the 1,3-dipole and the alkene.⁹ The study of the 1,3-dipolar cycloaddition reaction of compound **1** and other bromoalkenes was undertaken in order to determine the general efficacy of these bromoalkenes as alkyne substitutes. The results of the cycloaddition of **1** and 3-bromo-but-3-en-2-one with three different nitrile oxides are shown in Table 1. All of these cycloadditions occurred with complete regiochemical integrity¹⁰ in reasonable to good isolated yields.

Interestingly, the major isolated cycloadduct from the reaction of nitrile oxides with phenyl sulfone containing alkynes is the 4-substituted isoxazole⁴ which is contrary to the observed regioselectivity with carbonyl alkynes.^{6b} To test this influence on the regioselectivity of the sulfone, a phenyl sulfone containing bromoalkene was subjected to the 1,3-dipolar cycloaddition reaction with three different 1,3-dipoles. As shown in table 2, the exclusive isolated regioisomer is the isoxazole with the phenyl sulfone in the 5-position. Under certain reaction conditions, phenyl sulfoxides can serve as leaving groups.¹¹ Therefore, a phenyl sulfoxide bromoalkene was reacted with three different nitrile oxides in order to determine if the phenyl sulfoxide would compete with the bromide ion as a leaving group. The cycloaddition occurred with complete regioselectivity, and the 5-benzenesulfinyl isoxazole was isolated with no evidence of the 5-bromoisoxazole as shown in table 2.^{10,12}

In summary, this study shows the application of 1,1-disubstituted bromoalkenes as alkyne synthons that allow for direct and regioselective synthesis of isoxazoles through 1,3-dipolar cycloaddition. Future investigations designed to extend this methodology towards isoxazole synthesis from a mono substituted alkene and an α -chlorobenzaldoxime in one reaction vessel are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References and Notes

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12. General Procedure: A solution of the bromoalkene (0.25 mmol) and the hydroximinoyl chloride (0.25 mmol) in 5 mL dry dichloromethane was treated with triethylamine (28 mg, 0.275 mmol). The reaction mixture was stirred at rt until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete, a minimum amount of silica gel was added, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography over silica gel using hexanes-ethyl acetate (4:1) as an eluent system

Table 1

Isoxazoles formed from the 1,3-dipolar cycloaddition reactions using carbonyl containing bromoalkenes as the dipolarophile.

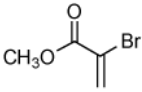
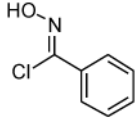
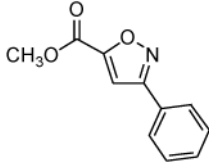
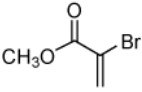
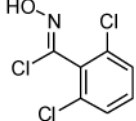
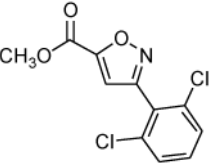
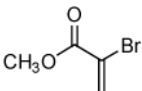
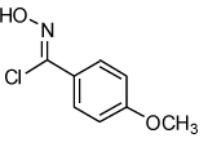
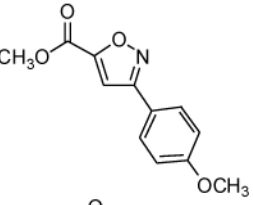
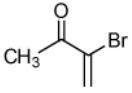
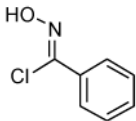
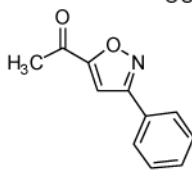
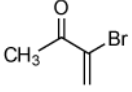
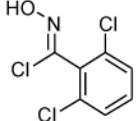
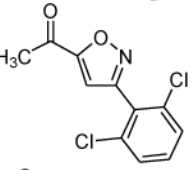
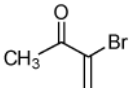
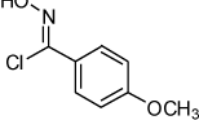
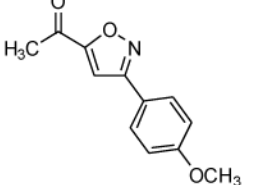
Entry	Alkene	α -Chloro oxime	Product	% Yield
1				79
2				68
3				64
4				75
5				80
6				80

Table 2

Isoxazoles formed from the 1,3-dipolar cycloaddition reactions using sulfone and sulfoxide containing bromoalkenes as the dipolarophile.

Entry	Alkene	α -Chloro oxime	Product	% Yield
7				91
8				85
9				81
10				91
11				69
12				71