

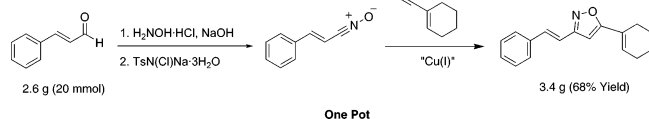
One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles

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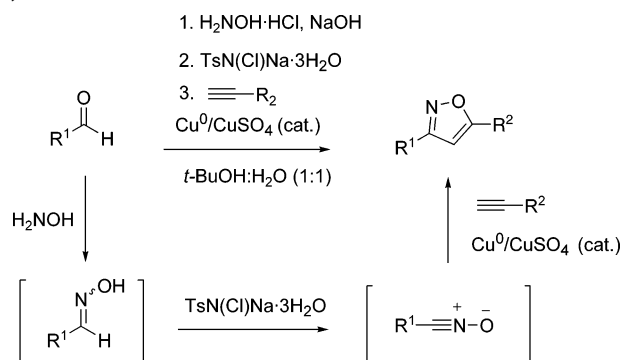
3,5-Disubstituted isoxazoles are obtained in good yields by a convenient one-pot, three-step procedure utilizing a regioselective copper(I)-catalyzed cycloaddition reaction between in situ generated nitrile oxides and terminal acetylenes. Most functional groups do not interfere with the reaction, which can be performed in aqueous solvents without protection from oxygen. Since all reagents are used in stoichiometric amounts, formation of byproducts is minimized.

Introduction

The copper(I)-catalyzed “fusion” of terminal acetylenes and organic azides to give exclusively 1,4-disubstituted 1,2,3-triazoles¹ is a quintessential example of a click reaction.² Owing to its efficiency and reliability, it has quickly found many applications in chemistry, biology, and materials science.³ In addition, this mode of reactivity of the in situ generated copper(I) acetylides is not limited to azides as dipoles, and nitrones, nitrile oxides, and azomethine imines have been shown to participate in similar catalytic transformations.⁴

Although the uncatalyzed 1,3-dipolar cycloaddition of nitrile oxides to acetylenes has been known for a long

SCHEME 1. One-Pot Synthesis of 3,5-Disubstituted Isoxazoles



time,⁵ its applications to the synthesis of isoxazoles are scarce. In the reported procedures, the yields of isoxazole products are often quite low, side reactions result in impurities, and both regioisomers are often obtained.⁶ Furthermore, nitrile oxides are not very stable themselves and dimerize readily, especially when electron-rich substituents are present.^{7c} Since isoxazoles are often encountered in molecules of medicinal interest,⁷ a simple and efficient procedure for their synthesis would be a welcome advance. Herein, we report an experimentally convenient, one-pot three-step process for the regioselective synthesis of 3,5-disubstituted isoxazoles from aldehydes and alkynes, whereupon nitrile oxide intermediates are generated in situ and further reacted without isolation.

An aldehyde is first converted to the corresponding aldoxime via reaction with hydroxylamine. Without isolation, the aldoxime is transformed to the corresponding nitrile oxide using 1.05 equiv of chloramine-T trihydrate, which acts as both a halogenating agent and a base.⁸ In the presence of a catalytic amount of copper(I), obtained from comproportionation of Cu metal and copper(II) sulfate, the in situ generated nitrile oxide undergoes a stepwise addition to a copper(I) acetylide^{4b} at ambient temperature, furnishing the 3,5-disubstituted isoxazole (Scheme 1).

Nitrile oxides generated from a range of aliphatic aldehydes readily participate in this transformation. The

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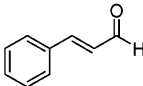
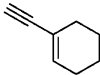
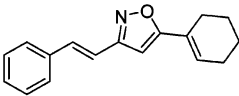

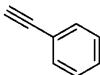
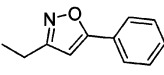
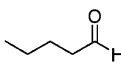
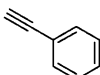
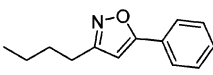
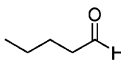
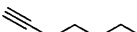
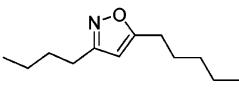
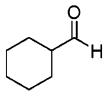
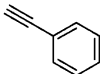
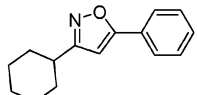

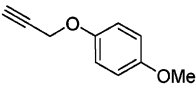
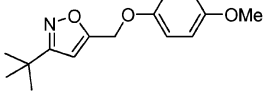
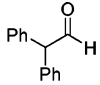
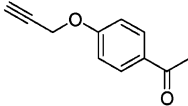
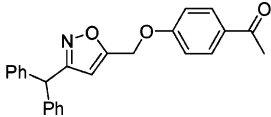
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TABLE 1. Isoxazoles Prepared from Aliphatic Aldehydes and Terminal Alkynes

entry	aldehyde	acetylene	isoxazole	yield, (%)
1				68
2				73
3				70
4				69
5 ^a				73
6 ^b				57
7				61

^a At 80 °C without copper catalyst, a mixture of 3,5- and 3,4-disubstituted isoxazoles (5:1) was isolated in 55% combined yield. ^b At 80 °C without copper catalyst, a mixture of 3,5- and 3,4-disubstituted isoxazoles (10:1) was isolated in 50% combined yield.

3,5-disubstituted isoxazole products are obtained in moderate to good yields after a simple filtration or aqueous workup. Trace amounts of toluenesulfonamide and unreacted acetylene are easily removed by recrystallization or by passing the product through a short plug of silica.

The same sequence can be applied to aromatic aldehydes, affording the products in 60–76% yields. The yields obtained in this one-pot procedure compare favorably to other reported syntheses of isoxazoles, especially in cases with alkenyl or activated aryl or heteroaryl group, such as *p*-anisyl or α -furyl, respectively.^{7a}

The scope of this substitution is demonstrated by the wide range of substituents tolerated in both the aldehyde/nitrile oxide and acetylene components. For example, propyolic acid, after neutralization with sodium bicarbonate, undergoes cycloaddition reaction with nitrile oxide derived from *p*-anisaldehyde to afford the isoxazole **16** in 61% yield (Table 2, entry 9). Likewise, ketone



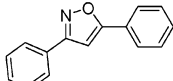

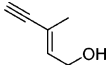
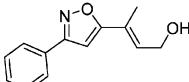
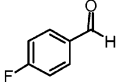
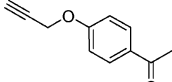
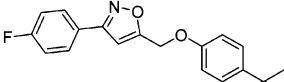


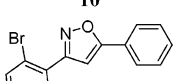
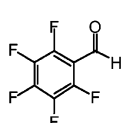

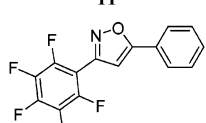
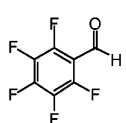

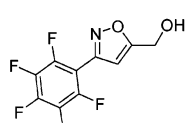
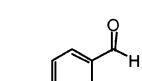
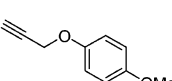
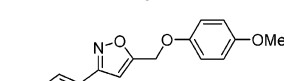
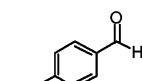
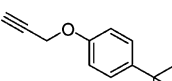
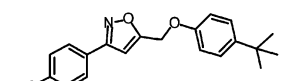
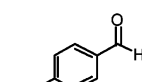

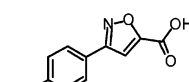
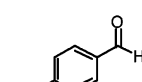

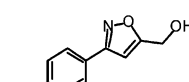
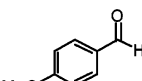
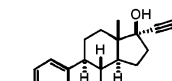
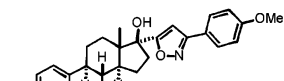

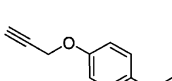
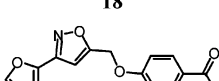
functionality is not affected under the conditions of the reaction (Table 1, entry 7; Table 2, entries 3 and 12).

Cycloaddition of nitrile oxides to olefins resulting in isoxazolines is well precedented.^{7a} Nevertheless, in the presence of a copper(I) catalyst, this side reaction was not observed. Thus, nitrile oxide obtained from *trans*-cinnamaldehyde reacted only with the terminal acetylene of 1-ethynylcyclohexene (Table 1, entry 1).

The reaction exhibits excellent regioselectivity. By comparison with previously reported data and by NMR studies, the products were determined to be 3,5-disubstituted regioisomers.⁹ Furthermore, LC-MS and ¹H NMR analyses of the crude reaction mixtures confirmed that in all cases no 3,4-regioisomers were formed, even though the uncatalyzed reactions may proceed with

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TABLE 2. Isoxazoles Prepared from Aromatic Aldehydes and Terminal Acetylenes

entry	aldehyde	acetylene	isoxazole	yield, (%)
1 ^a			 8	72
2			 9	76
3			 10	66
4			 11	72
5			 12	68
6			 13	64
7			 14	69
8			 15	74
9			 16	61
10			 17	68
11			 18	66
12			 19	68

^a At 80 °C without copper(I), 3,5- and 3,4-disubstituted isoxazoles (3:1) were isolated in 51% combined yield.

appreciable rate. This is also in agreement with the proposed mechanism of the catalytic cycloaddition reported in a recent article.^{4b}

In conclusion, a regioselective, experimentally convenient one-pot copper(I)-catalyzed procedure for rapid preparation of isoxazoles has been developed. The isolation and handling of potentially harmful and unstable¹⁰ hydroximoyl chlorides is avoided, as nitrile oxides are obtained directly from oximes. All reagents are used in stoichiometric quantities, thus further simplifying purification of products. The sequence exhibits wide scope, is tolerant of most functional groups, and performs well in aqueous solvents without the need for protection from oxygen. It is equally reliable for both small-scale discovery and preparative scale synthetic applications (cf. Experimental Section).

Experimental Section

General Procedure for Preparation of 3,5-Disubstituted Isoxazoles. Typical experimental procedure for synthesis of 3,5-disubstituted isoxazoles, as exemplified for 5-cyclohex-1-enyl-3-styrylisoxazole (**1**). *trans*-Cinnamaldehyde (2.6 g, 20 mmol) was added to the solution of hydroxylamine hydrochloride (1.46 g, 21 mmol) in 80 mL of 1:1 *t*-BuOH:H₂O. To this was added NaOH (0.84 g, 21 mmol), and after being stirred for 30 min at ambient temperature, TLC analysis indicated that oxime formation was

(10) It has been reported that some hydroximoyl chlorides are strong skin irritants and may cause allergic reactions; see ref 5a, p 365.

complete. Chloramine-T trihydrate (5.9 g, 21 mmol) was added in small portions over 5 min, followed by CuSO₄·5H₂O (0.15 g, 0.6 mmol) and copper turnings (ca. 50 mg). 1-Ethynylcyclohexene (2.23 g, 21 mmol) was added, pH was adjusted to ca. 6 by addition of a few drops of 1 M NaOH, and stirring was continued for another 6 h. The reaction mixture was poured into ice/water (150 mL), and 10 mL of dilute NH₄OH was added to remove all copper salts. The product was collected by filtration, redissolved, and passed through a short plug of silica gel (ethyl acetate/hexanes 1:6, *R_f* = 0.6) affording 3.4 g (68%) of 5-cyclohex-1-enyl-3-styrylisoxazole as an off-white solid, mp 138–139 °C. ¹H NMR (CDCl₃, 600 MHz): δ = 7.52 (d, *J* = 7.4 Hz, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 7.14 (d, *J* = 6.2 Hz, 2H), 6.64 (m, 1H), 6.31 (s, 1H), 2.36 (m, 2H), 2.25 (m, 2H), 1.78 (m, 2H), 1.69 (m, 2H). ¹³C NMR (CDCl₃, 150 MHz): δ = 170.9, 161.7, 135.9, 135.4, 130.2, 128.8, 128.76, 126.9, 125.2, 116.5, 95.1, 25.4, 25.2, 22.1, 21.7. HRMS calcd. for (MH⁺): 252.1383, found: 252.1381.

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Supporting Information Available: Spectral characterization of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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