A Mild Copper-Catalyzed Route to Substituted Isoxazoles

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Abstract

A mild, copper-catalyzed cycloaddition between terminal alkynes and in-situ-generated nitrile oxides gives 3,5-disubstituted isoxazoles in good to excellent yield under ambient conditions. The reaction tolerates a broad range of functional groups and avoids the strongly basic conditions required by classical isoxazole syntheses.

Keywords

copper catalysis; cycloaddition; heterocycles; isoxazole synthesis

Introduction

Isoxazoles are privileged heterocycles in medicinal chemistry, appearing in numerous approved drugs. Classical routes to 3,5-disubstituted isoxazoles rely on strongly basic conditions that are incompatible with acid- or base-sensitive substrates [1].

Results and Discussion

Treatment of a terminal alkyne with hydroxylamine hydrochloride and sodium hypochlorite in the presence of catalytic $CuSO_4$ and sodium ascorbate gave the corresponding isoxazole in 87% isolated yield (Table 1). The reaction proceeds via in-situ generation of a nitrile oxide, which undergoes 1,3-dipolar cycloaddition with the alkyne [2].

Table 1: Substrate scope for the copper-catalyzed isoxazole synthesis.

[htb]

Substituent	Time (h)	Yield (%)
Phenyl	4	87
4-Methoxyphenyl	5	91
4-Nitrophenyl	6	74

Conclusion

This copper-catalyzed method offers a mild, functional-group-tolerant alternative to classical isoxazole synthesis, and is readily scaled to gram quantities without loss of yield.

Experimental

General procedure

To a solution of the terminal alkyne (1.0 mmol) in a 1:1 mixture of *tert*-butanol and water was added hydroxylamine hydrochloride (1.2 mmol), sodium hypochlorite (1.2 mmol), copper(II) sulfate pentahydrate (5 mol%) and sodium ascorbate (10 mol%). The mixture was stirred at room temperature until TLC indicated complete consumption of the starting alkyne, then extracted with ethyl acetate and purified by column chromatography.

References

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