Highly Selective Tandem Nitrone Formation/1,3-Dipolar Cycloaddition Catalyzed by Ruthenium Porphyrin

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INTRODUCTION

1,3-Dipolar cycloaddition of nitrones with alkenes is a powerful method for the synthesis of isoxazolidines which are frequently present in bioactive molecules and are versatile building blocks used in organic synthesis.[1] Conventional approaches to nitrones usually require the addition of oxidant, acid or the use of harsh reaction conditions and thus have limited substrate scope. In addition, the issue of low diastereo-control is often encountered in 1,3-dipolar cycloaddition reaction of acyclic nitrones.[2] Thus, there has been a continuing interest in developing new methods for selective nitrone formation/1,3-dipolar cycloaddition cascade under mild reaction conditions.

RESULTS AND DISCUSSION

At the outset, we examined the cycloaddition of ethyl α-diazo acetate (EDA), nitrosobenzene and N-phenylmaleimide using [Ru(TTP)(CO)] (H_2TTP = *meso*-tetrakis(4-tolyl)porphyrin) as catalyst. Slow addition of a CH_2Cl_2 solution of EDA to a mixture of nitrosobenzene, N-phenylmaleimide and [Ru(TTP)(CO)] in CH_2Cl_2 via syringe pump afforded cycloadduct **4a** in 91% yield (Figure 1).

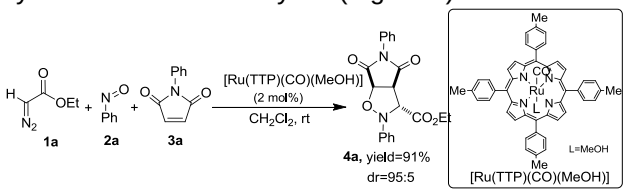
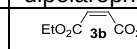
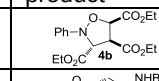
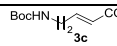
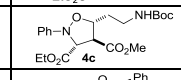
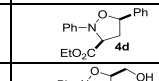
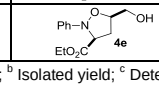


Figure 1. 1,3-Dipolar Cycloaddition of diazo compounds, nitrosoarenes and alkenes.

With the optimal conditions, we have examined several types of alkenes. As shown in Table 1, a broad array of alkenes including electron-deficient, electron-rich and electron-neutral ones are reactive dipolarophiles to undergo the cycloaddition reaction with high regio- and diastereoselectivity. Moreover we have not found any side products which were reported in other catalytic methods such as cyclopropanation, O-H insertion or deprotection of functional groups.

The effect of substituent of nitrosoarenes on the cycloaddition was also investigated.

Table 1. 1,3 Dipolar Cycloaddition with Various Dipolarophiles[a]

entry	dipolarophile	product	Yield(%)[b]	dr[c]
1	 3b	 4b	95	95:5
2[d]	 3c	 4c	55	98:2
3	 3d	 4d	75	86:14
4	 3e	 4e	94	95:5

[a] **1a**:**2a**:**3**:[Ru(TTP)(CO)]=1:2:2:0.01; [b] Isolated yield; [c] Determined by ^{1}H NMR; [d] 40° C.

It is noteworthy that the Ru-catalyzed 1,3-dipolar cycloaddition is compatible with a variety of functional groups including ester, hydroxyl, halo, nitro and Cbz as well as acid-sensitive functionalities such as Boc, TBDMS and *t*-butyl ester.

CONCLUSION

We have developed an efficient ruthenium porphyrin-catalyzed tandem nitrone formation/1,3-dipolar cycloaddition reaction of diazo compounds with nitrosoarenes and alkenes to synthesize isoxazolidines. This method is applicable to a broad substrate scope of alkenes with excellent compatibility of various functionalities, with high chemo-, regio-, and diastereo-selectivity and neutral reaction conditions, all these features being particularly valuable in organic synthesis. Our *in silico* analysis and *in vitro* biochemical experiments illustrate that isoxazolidines are better leukotriene A4 hydrolase inhibitor.

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