Tetrahedron Letters 55 (2014) 2308–2311

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An environmentally benign synthesis of isoxazolines and isoxazoles mediated by potassium chloride in water

Liuquan Han [a], Bijun Zhang [a], Min Zhu [b], Jie Yan [a,*]

[a] College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310032, Zhejiang, PR China
[b] College of Biological and Environmental Sciences, Zhejiang Shuren University, Hangzhou 310015, PR China

ARTICLE INFO

Article history:
Received 14 December 2013
Revised 24 February 2014
Accepted 27 February 2014
Available online 6 March 2014

Keywords:
Cycloaddition
Isoxazoline
Isoxazole
Potassium chloride

ABSTRACT

An effective and environmentally benign procedure for the synthesis of isoxazolines and isoxazoles has been developed by a cycloaddition of nitrile oxides with alkenes or alkynes in water. In this approach, potassium chloride is first oxidized into chlorine in water by the environmentally friendly oxidant Oxone®, then aldoximes are oxidized into nitrile oxides by the in situ generated hypochlorous acid, finally a 1,3-dipolar cycloaddition between nitrile oxides and alkenes or alkynes occurs to provide the corresponding isoxazolines and isoxazoles in good yields.

Introduction

Isoxazolines and isoxazoles are two major classes of five-membered nitrogen containing heterocycles, which are found in a large number of natural products and biologically active compounds.[1] A variety of synthetic methods has been developed for preparation of isoxazolines and isoxazoles, of which the most convenient and attractive route is probably the 1,3-dipolar cycloaddition of nitrile oxides to alkenes or alkynes.[2] Nitrile oxides are commonly generated from aldoximes via oxidations using different oxidants. Organic hypervalent iodine reagents, due to their low toxicity, ready availability, easy handling, and reactivity similar to that of heavy metal reagents, have been recently used as effective oxidants for the above purpose.[3] Other oxidants, such as NBS, NCS, NaOCl, *t*-BuOCl, and *t*-BuOI also have been used in the cycloaddition.[4] Due to most of the 1, 3-dipolar cycloadditions of nitrile oxides to alkenes or alkynes usually occurring in organic solvents or mixed solvent systems, utilization of water as a medium, an environmentally benign system, is less common. Hailes and Bala have investigated an intramolecular 1,3-dipolar cycloaddition in water albeit longer time is required to get good yield.[5] Rohloff et al. have reported a one-pot 1,3-dipolar cycloaddition in water but only tolerating water-soluble olefins and acetylenes as substrates.[6] Sarma group have developed a one-pot high-throughput synthesis of isoxazolines in bleach with moderate or low yield.[7] Therefore, from both environmental and economic viewpoints, to develop an efficient synthesis of isoxazolines and isoxazoles using water as the sole solvent is still desired.

Potassium hydrogen persulfate ($KHSO_5$), or Oxone® ($2KHSO_5$–$KHSO_4$–K_2SO_4), is an effective oxidant. Due to its good stability, water-solubility, ease of transport, nontoxic 'green' nature, nonpolluting byproducts, and cost-effectiveness, this solid reagent has become a popular reagent for oxidative transformations.[8] Recently, Zhdankin and co-workers have developed a novel cycloaddition of nitrile oxides with alkenes using KI as the catalyst and Oxone® as the terminal oxidant, which occurred in MeOH–H_2O (20:1) and provided isoxazolines in good yields.[9] However, this protocol is not suitable to prepare isoxazoles since alkynes were not active in the reaction when they were used in place of alkenes. In order to improve the application of Oxone® and develop a new process for the synthesis of isoxazolines and isoxazoles, we have investigated the reaction of nitrile oxides with alkenes or alkynes in the presence of potassium chloride (KCl) and Oxone® in water. Herein, an environmentally benign synthesis of isoxazolines and isoxazoles has been developed.

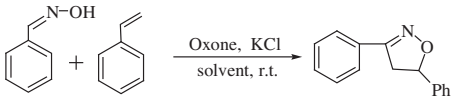
Discussion and results

At first, an inexpensive and readily available KCl was attempted to mediate the cycloaddition of nitrile oxides and alkenes, and a mixture of benzaldoxime (1.0 equiv), styrene (2.0 equiv), Oxone® (2.0 equiv) and KCl (1.0 equiv) in methanol was stirred at room temperature for 12 h, the desired cycloaddition product 3,5-diphenylisoxazoline was observed with only a trace amount (Table 1, entry 1). With the observation of the bad solubility of KCl and Oxone®

* Corresponding author. Tel.: +86 13805734975; fax: +86 (571)88320238.
E-mail address: jieyan87@zjut.edu.cn (J. Yan).

http://dx.doi.org/10.1016/j.tetlet.2014.02.118
0040-4039/

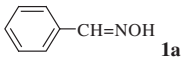
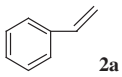
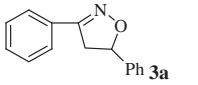
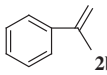
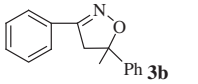
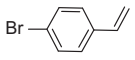
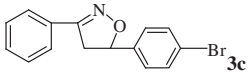
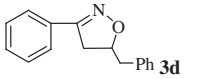
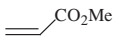
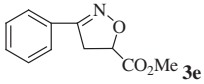
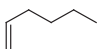
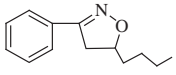
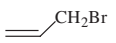
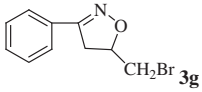
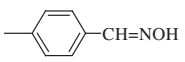
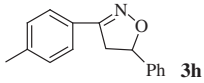
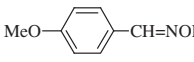
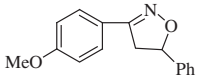
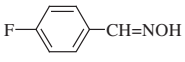
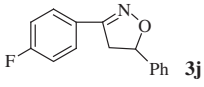
Table 1
Optimization of the cycloaddition of nitrile oxide from benzaldoxime with styrene mediated by KCl



Entry	Oxone® (equiv)	KCl (equiv)	PhCH=CH$_2$ (equiv)	Solvent	Time (h)	Yield[a] (%)
1	2.0	1.0	2.0	CH_3OH	12	Trace
2	2.0	1.0	2.0	MeOH–H_2O (4:1)	12	21
3	2.0	1.0	2.0	MeOH–H_2O (3:1)	12	33
4	2.0	1.0	2.0	MeOH–H_2O (2:1)	12	36
5	2.0	1.0	2.0	MeOH-H_2O (1:1)	12	71
6	2.0	1.0	2.0	H_2O	2	85
7	2.0	0	2.0	H_2O	24	Trace
8	2.0	0.2	2.0	H_2O	4	68
9	2.0	0.5	2.0	H_2O	4	72
10	2.0	1.0	2.0	H_2O	4	86
11	2.0	1.5	2.0	H_2O	4	32
12	2.0	NaCl (1.0)	2.0	H_2O	4	80
13	2.0	NH_4Cl (1.0)	2.0	H_2O	4	84
14	2.0	1.0	1.0	H_2O	4	56
15	2.0	1.0	1.2	H_2O	4	52
16	2.0	1.0	1.5	H_2O	4	64
17	2.0	1.0	2.5	H_2O	4	98
18	2.0	1.0	3.0	H_2O	4	96
19	1.2	1.0	2.5	H_2O	4	78
20	1.5	1.0	2.5	H_2O	4	96
21	2.5	1.0	2.5	H_2O	4	94
22	1.5	1.0	2.5	H_2O	2	94
23	1.5	1.0	2.5	H_2O	3	98
24	1.5	1.0	2.5	H_2O	5	97

[a] Isolated yield.

Table 2
The result of cycloaddition of nitrile oxides from aldoximes to alkenes or alkynes

Entry	Aldoxime **1**	Alkene/alkyne **2**	Isoxazoline/isoxazole **3**	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	98
2	**1a**	 **2b**	 **3b**	81
3	**1a**	 **2c**	 **3c**	85
4	**1a**	 **2d**	 **3d**	79
5	**1a**	 **2e**	 **3e**	88
6	**1a**	 **2f**	 **3f**	73
7	**1a**	 **2g**	 **3g**	92
8	 **1b**	**2a**	 **3h**	92
9	 **1c**	**2a**	 **3i**	83
10	 **1d**	**2a**	 **3j**	89

(*continued on next page*)