Pergamon

Tetrahedron Letters 39 (1998) 4851–4852

TETRAHEDRON LETTERS

Improved Generation Method for Functionalized Nitrile Oxide

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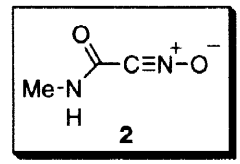
Received 6 April 1998; revised 27 April 1998; accepted 1 May 1998

Abstract

Gentle generation of nitrile oxide bearing a carbamoyl group was performed. 4-Nitro-3-isoxazolin-5-one was treated with dipolarophiles in the mixed solvent (MeCN / H_2O) at room temperature to afford cycloadducts in good yields.

Keywords: Nitrile oxides; Isoxazolines; Nitro compounds; Water

Functionalized nitrile oxides are useful for syntheses of polyfunctionalized compounds, but only several preparative methods are known [1-7]. We have previously revealed that 2-methyl-4-nitro-3-isoxazolin-5-one (**1**) [8,9] behaves as the precursor of nitrile oxide **2** bearing a carbamoyl group [10]. This reaction, however, did not satisfy us because of the requiring somewhat severe conditions which prevented the facile application of it to organic syntheses.



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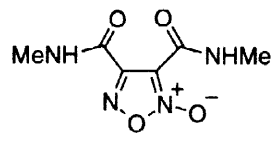

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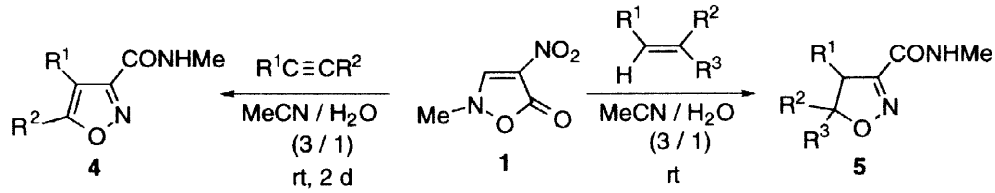
Isoxazolone **1** remained intact even though it was heated under reflux in MeCN, but furoxan **3**, the dimer of **2**, was isolated from the aqueous solution of **1** in 80 % yield at room temperature. These facts prompted us to design a convenient method for generation of nitrile oxide **2** initiated by H_2O under milder conditions.



0040-4039/98/$19.00
PII: S0040-4039(98)00919-8

To a solution of isoxazolone (**1**, 144 mg, 1 mmol) in MeCN (7.5 mL), phenylacetylene (202 mg, 2 mmol) and H_2O (2.5 mL) were added. The reaction mixture was stirred at room temperature with monitoring by the thin layer chromatography. The solution gradually turned to yellow, and the reaction almost finished after 1 day. The solvent was evaporated under reduced pressure, and the residue was recrystallized from PhH to afford 3-carbamoyl-5-phenylisoxazole (**4a**, 171 mg, 85 %).

Table 1

R^1	R^2	**4**	Yield / %
H	Ph	**a**	85
H	CH_2OH	**b**	94
H	CH_2Br	**c**	61
COOEt	COOEt	**d**	29

Table 2

R^1	R^2	R^3	**5**	Time / d	Yield / %
Me	H	Et	**a**	3	50 [a)]
H	CH_2OH	H	**b**	2	74
H	OEt	H	**c**	4	86
—$(CH_2)_3$—		H	**d**	2	86
—$(CH_2)_2O$—		H	**e**	4	96
H	Me	COOEt	**f**	2	88
COOMe	COOMe	H	**g**	2	81

a) a mixture of regioisomers

Propargyl derivatives and diethyl acetylenedicarboxylate were similarly transformed to isoxazole **4b-d** (Table 1). Versatile alkenes were investigated. Isoxazolone **1** effectively reacted with both electron-rich and electron-deficient alkenes to furnish corresponding isoxazoline derivatives **5a-g** in good yields (Table 2).

Commonly used procedures for preparation of nitrile oxides need particular conditions or reagents such as halogenating agents, dehydrating ones and strong bases [5-7]. As compared with these conventional methods, only the presence of H_2O is necessary for our method. The very simple experimental procedure in cooperation with readily available **1** offers an excellent method for preparing functionalized nitrile oxide **2** although the definitive mechanism has not been evident. Since this reaction proceeds under mild conditions and **2** is formed gently, it also may be possible to control the regioselectivity or the stereoselectivity in the cycloaddition of nitrile oxides more easily.

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