

## Solid-Phase Synthesis of $\Delta^2$ -Isoxazolines

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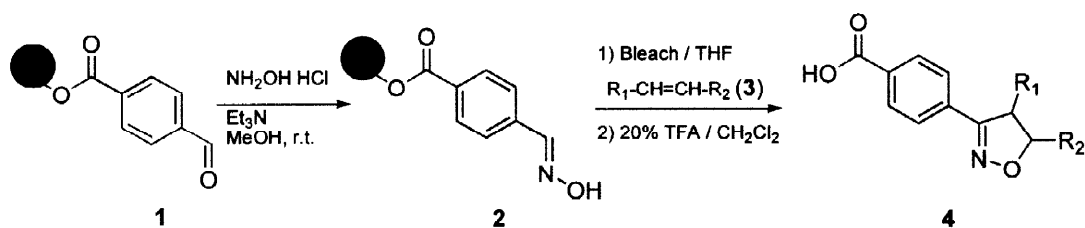
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**Abstract:** Solid-phase synthesis of  $\Delta^2$ -isoxazolines through a 1,3-dipolar cycloaddition of nitrile oxides is described. The aldoxime is oxidized with commercially available bleach to give the corresponding nitrile oxide, which reacts *in situ* with dipolarophiles to afford  $\Delta^2$ -isoxazolines in good yields.

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1,3-Dipolar cycloaddition of a nitrile oxide to alkenes is a useful procedure for the introduction of  $\Delta^2$ -isoxazolines, which are versatile intermediates for the synthesis of a wide variety of complex natural products<sup>1</sup> and are important pharmacophores in medicinal chemistry.  $\Delta^2$ -Isoxazolines are found in a number of pharmaceutical agents for example GPIIb/IIIa inhibitors<sup>2</sup> and human leukocyte elastase inhibitors.<sup>3</sup> Solid-phase 1,3-dipolar cycloaddition has been reported by Kurth's<sup>4</sup> and Pei's<sup>5</sup> groups for modification of the side chains of an oligomeric peptoid library and for the preparation of  $\Delta^2$ -isoxazolines. Most recently, Studer and Curran reported a preparation of a small  $\Delta^2$ -isoxazoline library by using "fluorous synthesis".<sup>6</sup> Nitrile oxides used in these solid-phase synthesis were prepared by either Mukaiyama's dehydration of a primary nitroalkane<sup>7</sup> or by Huisgen's method from the corresponding hydroximoyl chlorides.<sup>8</sup> In this account we would like to describe a facile solid-phase synthesis of this important class of compounds.

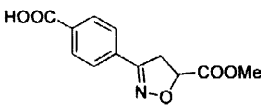
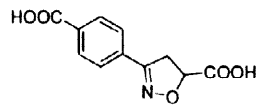
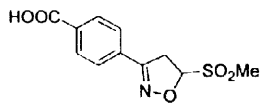
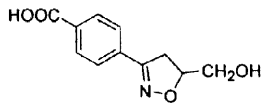
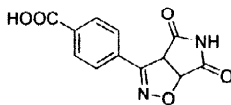
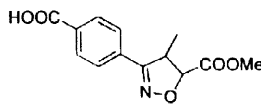
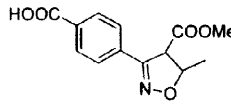
The starting point in our synthesis is the formation of a resin-bound aldoxime **2**. In order to prepare a resin-bound aldoxime, the 4-formyl benzoic acid is coupled to the benzyl alcohol of Wang's resin using a standard DIC/DMAP coupling procedure.<sup>9</sup> Reaction of aldehyde resin **1** with hydroxylamine in the presence of triethylamine in MeOH at room temperature affords the desired aldoxime resin **2**. The reaction goes to completion within several hours and gives a high yield of the corresponding aldoxime resin **2**.



Scheme 1

The resin-bound aldoxime **2** thus obtained is suspended in THF and treated with an excess of commercially available bleach<sup>10</sup> (Clorox, 10eq.) to form the nitrile oxide, which reacts *in situ* with alkenes **3** in one pot to furnish the corresponding resin-bound  $\Delta^2$ -isoxazolines. Cleavage of the product from the resin under standard condition (20% TFA in  $\text{CH}_2\text{Cl}_2$ ) gives the desired  $\Delta^2$ -isoxazolines in good yields (Table 1).

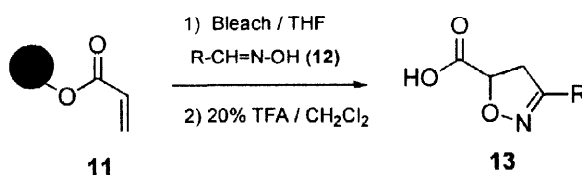
Table 1.  $\Delta^2$ -Isoxazoline synthesis from resin bound aldoximes

Entry	Dipolarophile	$\Delta^2$ -Isoxazolines	Yield(%)
a	Methyl acrylate	 5	94
b	Acrylic acid	 6	90
c	Methyl vinylsulfonate	 7	66
d	Allyl alcohol	 8	92
e	Maleic imide	 9	60
f	Methyl crotonate	 10 a	45
		 10b	40

Using the described procedure, a variety of  $\Delta^2$ -isoxazolines may be synthesized.<sup>11</sup> Nitrile oxide cycloadditions to terminal alkenes proceed regioselectively to give 5-substituted  $\Delta^2$ -isoxazolines as single products (entry a-d, **Table 1**). On the other hand, reactions with 1,2-disubstituted internal alkenes (e.g. entry f,

**Table 1)** lead to a mixture of regioisomers in approximately a 1:1 ratio. These results are in agreement with those reported for solution phase synthesis of  $\Delta^2$ -isoxazoline synthesis.<sup>1</sup> In almost all cases, the product after TFA cleavage is pure enough for primary biological screening and post cleavage purification is unnecessary.

The above-mentioned reaction conditions are also applicable to the reaction of resin-bound dipolarophile with aldoximes.<sup>11</sup> Thus, the acrylate resin **11** reacts with aldoximes **12** in the presence of bleach (10 eq) in THF to give the desired  $\Delta^2$ -isoxazolines in good yields (**Table 2**). Similarly, products **13** obtained in this fashion are quite pure and only single regioisomers are isolated in these reactions.



**Scheme 2**

**Table 2.  $\Delta^2$ -Isoxazoline synthesis from resin bound dipolarophiles**

Entry	Aldoxime	$\Delta^2$ -Isoxazoline	Yield(%)
a		 <b>14</b>	98
b		 <b>15</b>	95
c		 <b>16</b>	95
d		 <b>17</b>	90

In summary, a general and facile method for the solid-phase synthesis of  $\Delta^2$ -isoxazolines starting from either resin-bound aldoximes or dipolarophiles has been developed. The reaction can be conveniently carried

out under mild conditions and does not require preparation of hydroximoyl chloride from aldoximes or using strong dehydrating reagents. Both reactions have been successfully incorporated into the synthesis of  $\Delta^2$ -isoxazoline-containing libraries.

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## References and notes

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10. Sodium hypochlorite ( $\text{NaOCl}$ ) has been used in solution phase for preparation of nitrile oxides from aldoximes. See e.g. Confalone, P. N.; Ko, S. S. *Tetrahedron Lett.* **1984**, *25*, 947. (b) Kozikowski, A. P.; Scripko, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 253. In their paper (*cf.* Reference 5), Pei and Moos reported two examples that used benzaldehyde oxime and resin-bound acetylene derivatives to make isoxazoles.
11. All compounds give satisfactory high resolution  $^1\text{H}$  NMR spectra as well as ESI mass spectra. A typical procedure for cycloaddition of resin bound aldoxime or dipolarophile with dipolarophiles or aldoximes: The aldoxime resin **2** (0.2 g, 0.72 mmol/g) or dipolarophile resin **11** (0.2 g, 1.0 mmol/g) is suspended in THF (4 mL). The alkene **3** (5 eq) or aldoxime **12** (5 eq) is added in one portion followed by commercially available Clorox (0.7 M, 10 eq). The suspension is gently stirred for 4 h. The resin is filtered off and washed with MeOH,  $\text{H}_2\text{O}$  and MeOH and  $\text{CH}_2\text{Cl}_2$  repeatedly and dried *in vacuo*. The dried resin is then cleaved with 20% TFA in  $\text{CH}_2\text{Cl}_2$  (twice, 5 mL and 20 min each time) to give the desired isoxazoline. The product is purified with preparative TLC if necessary. Compound **7**:  $^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ):  $\delta$  12.5 (1H, b), 7.96 (2H, d, 8 Hz), 7.82 (2H, d, 8 Hz), 5.94 (1H, dd, 4.4 and 11.2 Hz), 3.92 (2H, ABX, 4.4 and 11.2 Hz), 3.03 (3H, s); ESIMS(-)  $m/z$  268 ( $\text{C}_{11}\text{H}_{11}\text{NO}_5\text{S}$ ,  $\text{M}^+$  269). Compound **14**:  $^1\text{H}$ NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  7.72 (4H, bs), 5.30 (1H, dd, 6.9 and 11.4 Hz), 3.72 (2H, ABX, 6.9 & 11.4 Hz); ESIMS(-):  $m/z$  269, 267 ( $\text{C}_{10}\text{H}_8\text{BrNO}_3$ ,  $\text{M}^+$  270, 268).