



## 5-Bromomethyl-4,5-dihydroisoxazoles

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### ABSTRACT

The preparation of substituted 4,5-dihydroisoxazoles can be accomplished via the treatment of  $\beta,\gamma$ -unsaturated oximes with liquid bromine. The reaction provides a convenient route to the highly functionalized title compounds.

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4,5-Dihydroisoxazoles are often used as intermediates in the preparation of or protecting groups for a wide variety of difunctionalized compounds. For example, cleavage of the 4,5-dihydroisoxazole can give rise to  $\beta$ -hydroxyketones<sup>1</sup>,  $\alpha,\beta$ -unsaturated ketones<sup>2</sup>, and  $\gamma$ -aminoalcohols.<sup>3</sup> The dihydroisoxazole moiety is also found as the end product in many pharmaceutically active compounds.

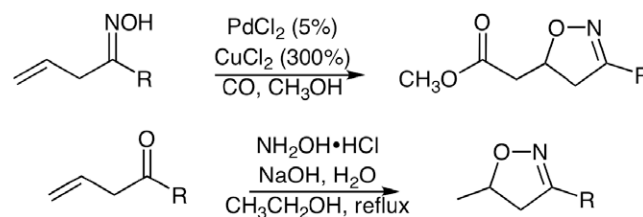
This ring system is typically prepared via an intramolecular 1,3-dipolar cycloaddition.<sup>4</sup> This reaction often involves the preparation of a substituted nitrile oxide in the presence of a dipolarophile, whether it is an intermolecular or intramolecular process. The regiochemical outcome of the reaction favors the formation of a 3,5-disubstituted-4,5-dihydroisoxazole in the intermolecular case, though in some cases 3,4-disubstituted products predominate. Control of the substitution in the product is due primarily to the electron density distribution of the dipolarophile.<sup>5</sup>

In our recent search for a regiochemically controlled route to the 4,5-dihydroisoxazole ring system, we noted that the palladium(II) catalyzed cyclization of a  $\beta,\gamma$ -unsaturated oxime gives rise to 3,5-disubstituted-4,5-dihydroisoxazoles in good yield.<sup>6</sup> In that study, we also noted that treatment of a  $\beta,\gamma$ -unsaturated ketone with hydroxylamine hydrochloride in excess aqueous base resulted in the direct formation of the dihydroisoxazole (Scheme 1).<sup>7</sup> Further study indicated that in the course of the reaction, the alkene moiety underwent isomerization to the conjugated system prior to internal addition of the oxygen nucleophile to form the

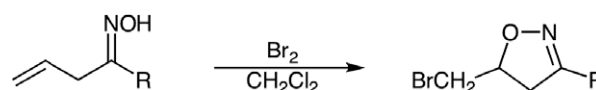
dihydroisoxazole.<sup>7</sup> Such information implies that strong electrophiles could be employed to affect the cyclization of the unsaturated oxime directly.

Herein, we wish to report that the cyclization of a series of  $\beta,\gamma$ -unsaturated oximes in the presence of bromine in dichloromethane affords the expected 5-bromomethyl-3-substituted-4,5-dihydroisoxazoles (Scheme 2). We have noted that the reaction is relatively rapid at room temperature, and, due to the color of the bromine reagent and the lack of color in the desired products, the reaction can be titrated to completion. However, in practice, we have noted that a 10% excess of bromine typically provides the best yield of the desired product.<sup>8</sup>

The product of the reaction, a primary bromide, was easily identifiable by proton NMR.<sup>9</sup> In fact, monitoring the reaction progress by TLC was often misleading due the presumed reaction of the



Scheme 1. Previous cyclizations of  $\beta,\gamma$ -unsaturated carbonyls.



Scheme 2. Electrophilic bromination yields the title compounds.

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**Table 1**  
Yield of title reaction outlined in Scheme 2

Entry	Compound (R=)	Spectroscopic yield <sup>a</sup> (%)	Isolated yield <sup>b</sup> (%)
1	<i>p</i> -CH <sub>3</sub> O-Ph-	>98%	79
2	<i>p</i> -CH <sub>3</sub> -Ph-	>97	65
3	2'-naphthyl	95	84
4	Ph-CH <sub>2</sub> -CH <sub>2</sub> -	>90	35 <sup>c</sup>
5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> -	>90	40 <sup>c</sup>

<sup>a</sup> Spectroscopic yields were determined by H NMR of an aliquot of the crude reaction mixture.

<sup>b</sup> Isolated yields express the yield of the product after workup and chromatographic separation.

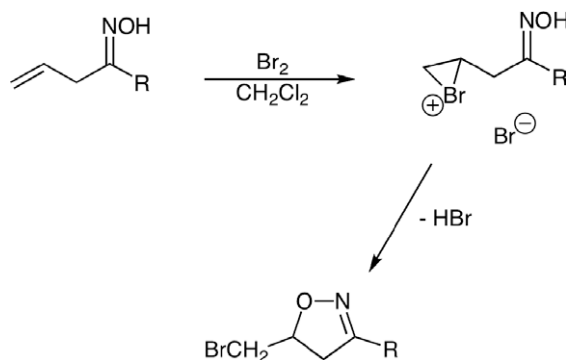
<sup>c</sup> Isolated products spectroscopically agreed with the literature values. See Ref. 13.

primary bromide with the TLC stationary phase. Instead, reaction progress was monitored by withdrawing aliquots from the reaction mixture and obtaining proton NMR data on the crude reaction mixture. In all cases examined, the reaction appeared to be complete (the presence of the starting material was not detected) after 30 min stirring at room temperature. Isolation of the desired products was, in some cases, significantly lower than the NMR yield. Again, this was mostly likely due to the ease of reaction of the primary bromide with the chromatographic stationary phase.

Based on the data given in Table 1, the reaction appears to be compatible with both aryl and alkyl substitutions. While the isolated yield of the 4,5-dihydroisoxazole does appear to reflect the geometry of the starting oxime (*syn* or *anti*) mixture as determined by proton NMR, that geometry was judged to not play a role in the reaction due to the spectroscopically determined yield prior to isolation. In fact, the aryl substituted  $\beta,\gamma$ -unsaturated oximes were very well behaved in the reaction, and the isolation of the aryl-dihydroisoxazoles from the reaction mixture was relatively easy. The alkyl substituted compounds were less well behaved and difficult to isolate—as evidenced by extensive streaking on TLC plates.

We postulate that the mechanism of this reaction (Scheme 3) involves the initial addition of bromine to the alkene to form the well-defined cyclic bromonium ion.<sup>10</sup> Formation of this intermediate activates the molecule for attack by the internal hydroxyl nucleophile. Subsequent ring opening gives the expected 4,5-dihydroisoxazole with a C5-bromomethyl group. The 4,5-dihydroisoxazole formed in this regiochemically controlled fashion is racemic at C5. This mechanism stands in contrast to the isomerization observed in the base-catalyzed cyclization of  $\beta,\gamma$ -unsaturated oximes<sup>7</sup>—where the thermodynamically more stable  $\alpha,\beta$ -unsaturated oxime forms rapidly under the reaction conditions.

Evidence that the alkene moiety does not migrate into conjugation is illustrated by the fact that the product of such a migration—



**Scheme 3.** Proposed mechanism of electrophilic bromination.

a 3-substituted-4-bromo-5-methyl-4,5-dihydroisoxazole—is not observed in the reaction mixture. We postulate, however, that a tri-substituted 4,5-dihydroisoxazole could be produced if the starting oxime was conjugated. Efforts are currently underway to explore such a possibility.

In summary, treatment of substituted  $\beta,\gamma$ -unsaturated oximes with bromine provides the expected 3-substituted-5-bromo-methyl-4,5-dihydroisoxazoles. Isolated yields were consistently better for the aryl substituted dihydroisoxazoles, but even the alkyl substituted oximes provided the desired products in acceptable yield. The products, primary bromides, provide a functional group handle that should be able to be further modified by nucleophilic substitution.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.106.

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- General procedure for the preparation of the title compounds*: to a 250 mL round-bottomed flask containing a stir bar and wrapped in aluminum foil were added 80 mL anhydrous CH<sub>2</sub>Cl<sub>2</sub> (freshly distilled from calcium hydride) and the respective oxime (6.0 mmol).<sup>11</sup> The solution was vigorously stirred at room temperature while a CH<sub>2</sub>Cl<sub>2</sub> solution of Br<sub>2</sub> (approximately 0.10 M, 6.6 mmol) was added dropwise by glass syringe. The red solution was stirred for 30 min in the dark. Then 25 mL distilled water was added and stirring was continued for an additional 5 min. The contents of the reaction vessel were then transferred to a separatory funnel and the organic phase was washed with water (80 mL  $\times$  1), sodium bisulfite solution (80 mL  $\times$  1), water (80 mL  $\times$  1), sodium bicarbonate solution (5%, 80 mL  $\times$  1), and brine (80 mL). The yellow organic phase was then dried over sodium sulfate, filtered, and evaporated to dryness on the rotary evaporator to give a crude yellow-red mixture. Flash chromatography<sup>12</sup> of the crude product on silica gel (8:2 hexane/ethyl acetate) gave the desired product as an off-white solid.
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