



## Unprecedented formation of $\Delta^2$ -isoxazoline and/or 1-nitroso-pyrazoline from $\alpha$ -bromoketone oximes and diazo compounds

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### ABSTRACT

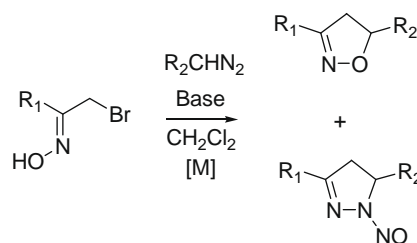
Reaction of  $\alpha$ -bromoketone oximes with diazo compounds in the presence of a metal catalyst and base led to the unprecedented formation of two types of rings:  $\Delta^2$ -isoxazolines and 1-nitrosopyrazolines.

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Nitrosoalkenes are usually generated through 1,4-elimination of a  $\alpha$ -haloketone oxime or  $\alpha$ -haloaldoxime with an organic or inorganic base such as sodium carbonate.<sup>1</sup> It is isolated occasionally as a relatively stable compound, but in general, it is unstable and was most often characterized through in situ trapping with certain reagents. For instance, reaction of a nitrosoalkene with a variety of electron-rich dienophiles such as silyl enol ethers,<sup>2</sup> silylated olefins,<sup>3</sup> and alkoxyallens<sup>4</sup> provides a hetero Diels–Alder product,<sup>5</sup> which could be further modified to produce 1,4-hydroxylamine derivatives. The flexibility and versatility of this hetero Diels–Alder reaction have attracted much attention in the past decade, and its scope and limitations were extensively investigated.<sup>1c</sup> Trapping nitrosoalkene with a one-carbon unit represents a novel and attractive strategy to construct five-member ring systems. However, only a few such [4+1] annulation reactions were reported to date,<sup>6</sup> one example being the reaction of nitrosoalkene with an isocyanide to provide 2-aminoisoxazole products in moderate yields.<sup>6a</sup>

Diazo compounds have been widely used as a carbene source in organic synthesis.<sup>7</sup> Transition metal-catalyzed decomposition of diazoalkanes followed by cycloadditions has been extensively studied.<sup>8</sup> Highly stereoselective cyclopropanation catalyzed by chiral metal complexes using diazo compounds as carbene sources has been achieved.<sup>9</sup> There are also some reports on copper-catalyzed [4+1] cycloaddition of  $\alpha,\beta$ -unsaturated ketones with diazo compounds.<sup>10</sup> However, a [4+1] cycloaddition of diazo compounds with nitrosoalkene has never been reported.

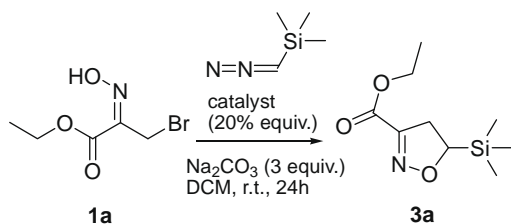
We report here our efforts to extend nitrosoalkene reaction with a diazo compound, which gives  $\Delta^2$ -isoxazoline and 1-nitroso-4,5-dihydropyrazole derivatives (Scheme 1). Neither of these formations is known in the literature.  $\Delta^2$ -Isoxazolines are versatile intermediates for the synthesis of a wide variety of complex natural products or pharmaceutical agents.<sup>11</sup> The ring system itself has been incorporated into a number of pharmaceutically important compounds or drug candidates.<sup>12</sup> They were typically prepared through a 1,3-dipolar cycloaddition of a nitrile oxide, which could be generated from a hydroxamic acid chloride<sup>13</sup> or primary nitroalkanes,<sup>14</sup> with a dipolarophile in either solution phase or on solid support.<sup>15,16</sup> Although [3+2] dipolar cycloaddition in general gave rise to the desired  $\Delta^2$ -isoxazoline products efficiently and in good yields, one of the common limitations was the difficulty in controlling the stereoselectivity.<sup>17</sup> On the other hand, 1-nitrosopyrazolines could be prepared from pyrazoline under nitrite oxidation condition.<sup>18</sup> It can be converted into the corresponding dihydropyrazoles or pyrazoles which are found frequently in pharmaceutical agents.



**Scheme 1.** Reaction of a nitrosoalkene and a diazo compound.

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**Scheme 2.** Formation of  $\Delta^2$ -isoxazoline.

We started to test the reaction of nitrosoalkenes and diazo compounds with 3-bromo-2-hydroxyimino-propionic acid ester (**1a**) and trimethylsilyldiazomethane (Scheme 2). Dichloromethane was chosen as solvent based on previous reports on the unstable nature of nitrosoalkene.<sup>1,6a</sup> **1a** was treated with freshly ground sodium carbonate in dichloromethane at room temperature under nitrogen to generate nitrosoalkene. Trimethylsilyldiazomethane was added dropwise in the presence of metal catalyst at room temperature. Isoxazoline **3a** was formed, and many metal catalysts are effective in catalyzing this reaction. However, copper-based catalysts turned to be slightly more effective (Scheme 2, Table 1).

CuO was chosen as the catalyst for reactions with different oximes and diazo compounds (Table 2).<sup>19,20</sup> For reaction of oxime **1a** with *t*-butyl diazoacetate, isoxazoline **3a'** was obtained similarly. But products with an unusual 1-nitroso-4,5-dihydropyrazole ring were obtained when oximes **1b** and **1c** were used. Formation of isoxazoline in these reactions is either trace amount or undetectable. Without adding metal catalyst, reaction of **1b** with *t*-butyl diazoacetate generated **4b** in 36% yield, but no isoxazoline at all. In these reactions, the products are formed with other uncharacterized materials. Yields of the separated products from these reactions varied from 10% to 48%. The structure of compound **4c'**, one

**Table 1**

Influence of metal catalyst on the reaction yield

Catalyst	Yield <sup>a</sup> ( <b>3a</b> , %)
(Ph <sub>2</sub> PC <sub>5</sub> H <sub>4</sub> ) <sub>2</sub> Fe	31
Ag(CF <sub>3</sub> CO <sub>2</sub> )	34
AgO	47
AgOAc	52
Cu(acac) <sub>2</sub>	13
Cu(OAc) <sub>2</sub>	37
Cu(OTf) C <sub>6</sub> H <sub>6</sub>	9
Cu(OTf) <sub>2</sub>	30
Cu <sub>2</sub> O	54
CuBr	22
CuBr <sub>2</sub>	28
CuCl	7
CuI	37
CuO	57
FeCl <sub>3</sub>	0
MgCl <sub>2</sub>	29
MgO	22
Pd(OAc) <sub>2</sub>	19
Rh <sub>2</sub> (OAc) <sub>2</sub>	27
Sc(OTf) <sub>3</sub>	6
ZnCl <sub>2</sub>	4

<sup>a</sup> Yields by HPLC.

of the 1-nitroso-4,5-dihydropyrazole compounds, was solved by X-ray crystallographic study (Fig. 1).<sup>21</sup>

Based on these results, we propose a possible mechanism for the formation of these products (Scheme 3).  $\alpha$ -Bromoketone oxime reacts with base to generate nitrosoalkene **A**. Diazo compound was decomposed by metal catalyst (CuO or catalysts listed in Table 1) to form metal carbene complex **B**. A concert [4+1] cycloaddition between nitrosoalkene **A** and metal carbene **B** produces  $\Delta^2$ -isoxazoline **3**. Nitrosoalkene **A** could also undergo a [3+2] reaction with

**Table 2**  
The reactions between oximes and diazomethane

Entry	Reactant 1	Reactant 2	Isoxazoline (yield)	Nitrosopyrazoline (yield)
1		TMSCHN <sub>2</sub>	 <b>3a</b> (48%)	
2		N <sub>2</sub> CHCOO <i>t</i> -Bu	 <b>3a'</b> (16%)	
3		N <sub>2</sub> CHCOO <i>t</i> -Bu		 <b>4b</b> (45%, 36%*)
4		TMSCHN <sub>2</sub>	 <b>3c</b> (10%)	 <b>4c</b> (23%)
5		N <sub>2</sub> CHCOO <i>t</i> -Bu		 <b>4c'</b> (25%)

Reaction without CuO. All yields are separated yields.

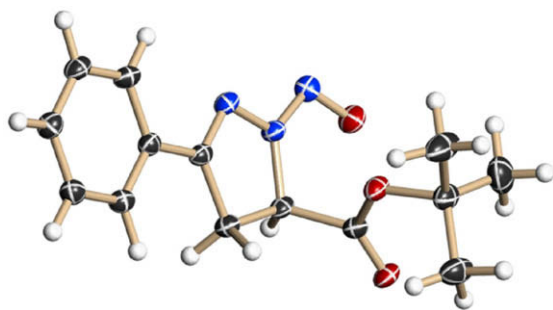
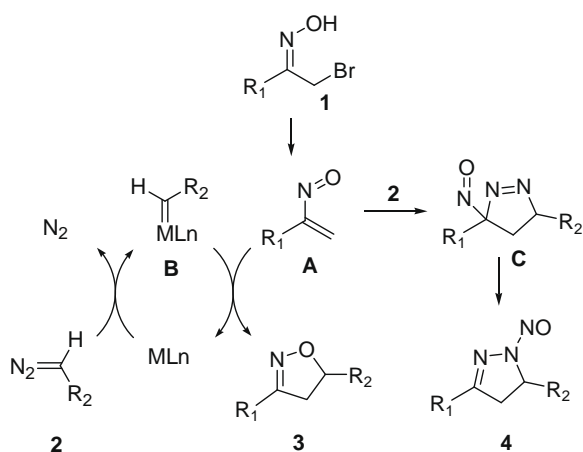


Figure 1. ORTEP of compound 4c.



Scheme 3. Proposed reaction mechanisms.

diazo compound to provide the nitrosopyrrolidine intermediate **C**, which could form *N*-nitrosopyrrolizine product **4** through 1,3-nitroso migration.<sup>22</sup> In reactions using trimethylsilyldiazo methane, the trimethylsilyl group ( $R_2$ ) in product **4** seems to easily fall off and is replaced by a proton. In reactions with base and metal catalyst, electron-deficient nitrosoalkene **A** reacts with metal carbene complex exclusively, while electron-rich nitrosoalkene favors cycloaddition with diazo compounds directly. In reactions without metal catalysts, there is no metal carbene complex thus no  $\Delta^2$ -isoxazoline formation, and nitrosopyrrolizine product formed through the cycloaddition between nitrosoalkene and diazo compounds.

In summary, reaction of nitrosoalkene with a diazo compound can proceed smoothly in the presence of an inorganic base and/or metal catalyst to provide unique products,  $\Delta^2$ -isoxazoline and 1-nitroso-4,5-dihydropyrazole derivatives, in modest yields. The reaction may be useful for developing metal-catalyzed asymmetric synthesis of  $\Delta^2$ -isoxazolines.

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## Supplementary data

Synthetic, spectroscopic, and X-ray diffraction details (PDF, CIF). This material is available free of charge via the Internet. Crystallographic data (excluding structure factors) for the structure in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-

336033 or e-mail: deposit@ccdc.cam.ac.uk) Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2008.12.032.

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