ALKENYL-SUBSTITUTED *N,N'*-DIOXYGENATED PYRAZOLES BY NITROSATION OF DIENONE OXIMES

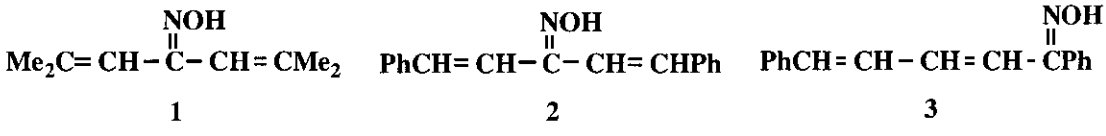
John F. Hansen* and Jinlin Wang

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA

Abstract - Nitrosation of 2,6-dimethyl-2,5-heptadien-4-one oxime gave 3,3-dimethyl-5-(2-methyl-1-propenyl)-3*H*-pyazole 1,2-dioxide, while 1,5-diphenyl-1,4-pentadien-3-one oxime gave 3(5)-phenyl-5(3)-styryl-1-hydroxypyrazole 2-oxide. The latter pyrazole could also be obtained in low yield by nitrosation of 1,5-diphenyl-2,4-pentadien-1-one oxime.

The nitrosation of α,β-unsaturated ketoximes is a versatile route to a variety of *N*-oxygenated pyrazoles, including 1-hydroxypyrazole 2-oxides[1,2] and 3*H*-pyrazole 1,2-dioxides.[3] To date no successful application of this strategy to the oxines of cross-conjugated or through-conjugated dienones has been reported, although an attempted nitrosation of dibenzalacetone oxime was mentioned by Harries and Tietz, who obtained amorphous or resinous material.[4] We wish to report our preliminary results in the nitrosation of the oximes of two cross-conjugated dienones and a through-conjugated dienone, and the characterization of the first alkenyl-substituted 3*H*-pyrazole 1,2-dioxide and 1-hydroxypyrazole 2-oxide derivatives produced in the reactions.

The oximes selected for our initial studies were the cross-conjugated dienone oximes, 2,6-dimethyl-2,5-heptadien-4-one oxime (phorone oxime) (**1**) and 1,5-diphenyl-1,4-pentadien-3-one oxime (dibenzalacetone oxime) (**2**), and the through-conjugated dienone oxime, 1,5-diphenyl-2,4-pentadien-1-one oxime (cinnamalacetophenone oxime) (**3**).



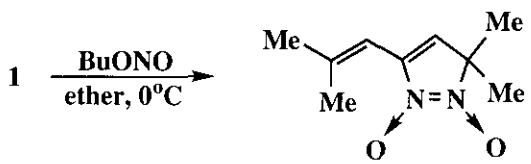
1 **2** **3**

Phorone oxime (**1**) is listed in at least two secondary references, with a melting point of 48°C.[5,6] This value appears to originate in the work of Nägeli,[7] who obtained a compound with this melting point from the reaction of phorone with hydroxylamine in aqueous ethanol. However, Harries and Lehmann reported that they were unable to obtain an oxime upon repeating Nägeli's work, finding instead, in low yield, a compound, mp 51°C, which they believed to be 1-hydroxy-2,2,6,6-tetramethyl-4-piperidone.[8] Subsequently Rice and Weiss identified this compound as 2,3,4,5,6,7-hexahydro-3,3,7,7-tetramethyl-1,2-oxazepin-5-one.[9] A more detailed investigation of the reaction of phorone with hydroxylamine under basic conditions by Verducci and coworkers resulted in the characterization of several cyclic and acyclic products resulting from conjugate addition,[10] but none of these later reports makes any mention of the formation of **1**. Phorone oxime is mentioned as one of ninety-four compounds studied as accelerators for photographic development,[11] but no information was provided regarding the origin or characterization of the compound used in that study. Thus, the previous preparation of **1**, if it has been achieved, appears to lack satisfactory documentation.

The reaction of a ketone with hydroxylamine hydrochloride in pyridine is an alternative to other methods of oxime formation, sometimes succeeding when other methods are unsatisfactory. Accordingly, we treated phorone with hydroxylamine hydrochloride (25% excess) in pyridine at room temperature and, after three days, realized a yield of about 50% of the oxime, which was distilled (75-80°C and 0.1 torr) and recrystallized, mp 40-41°C (pet. ether). Elemental analysis and spectral data were fully consistent with the identification of this compound as phorone oxime.[12]

Dibenzalacetone oxime (**2**) could be prepared by a similar reaction of the parent ketone with hydroxylamine hydrochloride in pyridine. The literature contains several reliable reports of the preparation of this oxime, and the melting point of the product was in good agreement with values previously reported.[4,13] The preparation of cinnamalacetophenone oxime (**3**) was carried out by the method of Scholtz.[14]

Nitrosation of (**1**) was carried out by treatment with butyl nitrite (10% excess) in ether in the cold. After standing overnight, the product was collected by suction filtration and washed with cold ether. The product, mp 114-15.5°C, which was obtained in 80% yield, was identified as 3,3-dimethyl-5-(2-methyl-1-propenyl)-3*H*-pyrazole 1,2-dioxide (**4**), based upon satisfactory elemental analysis and IR and NMR spectral data.[12]



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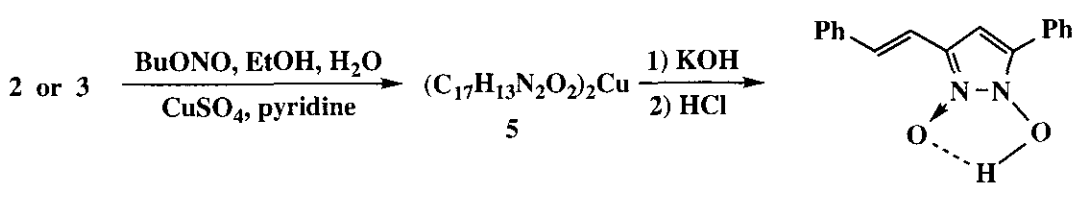
The earlier report by Harries and Tietz of amorphous or resinous material from the nitrosation of dibenzalacetone oxime (**2**) prompted us to adopt a strategy for its nitrosation which we have applied with success in the preparation of various 1-hydroxypyrazole 2-oxides when other nitrosation conditions have failed.[2] The oxime (**2**) in ethanol was treated at room temperature with an aqueous solution of copper(II) sulfate (1 molar equivalent), pyridine (2 moles) and butyl nitrite (1.5 moles). After stirring overnight, an insoluble copper complex (**5**), mp 213-14°C (decomp) was isolated by suction filtration in 80-90% yield. The 1-hydroxypyrazole 2-oxide (**6**), a colorless solid, mp 194-5°C (decomp), was liberated from the copper complex in greater than 90% yield by stirring at room temperature with aqueous ethanolic potassium hydroxide, filtration to remove inorganic solids, and acidification of the filtrate with hydrochloric acid. Compound (**6**) could be purified by dissolution in aqueous potassium hydroxide (5%) and reprecipitation



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by acidification of the basic solution with hydrochloric acid. The identification of **6** is based upon its acidity and ability to function as a bidentate ligand with copper(II), characteristic of other 1-hydroxy-

pyrazole 2-oxides, satisfactory elemental analysis for both **5** and **6**, and IR and NMR spectral properties consistent with the assigned structure.[12] In particular, the IR spectrum of **6** included a very distinctive pattern of strong, broad bands in the region of 1000-2000 cm^{-1}, which is a common feature of the IR spectra of 1-hydroxypyrazole 2-oxides.

Cinnamalacetophenone oxime (**3**) was investigated as an alternative to **2** as a precursor of **6**. Nitrosation of **3** was carried out using the same procedure as had been applied for **2**. A copper complex (**5**) was obtained from the nitrosation of **3** which was identical with that formed from the nitrosation of **2**, but in lower yield. Nitrosation of **3** gave less than 35% of **5**, compared with a yield greater than 80% from **2**. After liberation from the copper complex, *vida supra*, the overall yields of **6** were about 75% from **2** and 30% from **3**.

The reason for the low yield of **5** in the nitrosation of **3** has not been fully elucidated and is under continuing investigation. However, in previous reports we have shown a strong correlation between oxime geometry and the rate and yield of pyrazole formation in the nitrosation of α,β-unsaturated ketoximes.[2d-e, 3b] If the carbon-nitrogen double bond in **3** exists mainly in the (*E*) configuration (hydroxyl group *syn* with respect to the carbon-carbon double bond), a low yield of the pyrazole would, in fact, be expected on the basis of analogy with our earlier observations. Oxime geometry is not a factor in the nitrosation of the cross-conjugated ketoximes (**1**) or (**2**), since in those cases one of the carbon-carbon double bonds will always be favorably oriented relative to the oxime for efficient pyrazole formation.

Our observations to date show that the nitrosation of α,β-unsaturated ketoximes can be extended to include cross-conjugated or through-conjugated dienone oximes, providing, for the first time, a route to alkenyl-substituted derivatives of the 1-hydroxypyrazole 2-oxide and 3*H*-pyrazole 1,2-dioxide families. We are investigating the extension of this methodology to other dienone oximes, including unsymmetrical cross-conjugated dienone oximes and to the isomeric (*E*) and (*Z*) oximes of through-conjugated dienones. We are also examining the chemical behavior of the novel alkenylpyrazole derivatives.

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12. Elemental analysis and spectral data:

1. IR (Nujol): 3240 cm^{-1}, 1643, 1597, 981; ^1H NMR ($CDCl_3$): 9.25 ppm (1 H, br s), 6.01 (1 H, m), 5.72 (1 H, m), 1.79 (3 H, d, J = 0.9 Hz), 1.77 (3H, d, J = 0.9 Hz), 1.74 (3 H, d, J = 1.2 Hz), 1.70 (3 H, d, J = 0.6 Hz); ^{13}C NMR ($CDCl_3$): 155.0 ppm, 142.1, 140.8, 121.3, 117.3, 26.8, 26.5, 20.5, 20.1. Anal. Calcd for $C_9H_{15}NO$: C, 70.54; H, 9.87; N, 9.14. Found: C, 70.46; H, 9.73; N, 9.23.

4. IR (Nujol): 3130 cm^{-1}, 1652 (w), 1478; ^1H NMR ($CDCl_3$): 6.48 (1 H, s), 6.22 (1 H, m), 2.03 (3 H, br s), 1.99 (3 H, br s), 1.62 (6 H, s); ^{13}C NMR ($CDCl_3$): 147.9 ppm, 139.6, 121.9, 109.3, 72.4, 27.5, 23.9, 21.1. Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.48; H, 7.43; N, 15.45.

5. IR (Nujol): 1602 cm^{-1} (w), 782, 754, 692. Anal. Calcd for $(C_{17}H_{13}N_2O_2)_2Cu$: C, 66.06; H, 4.24; N, 9.06. Found: C, 66.03; H, 4.01; N, 8.99.

6. IR (Nujol): 776 cm^{-1}, 750, 688 (also includes envelop of strong, broad bands 1000-2000 cm^{-1}); ^1H NMR (pyridine-d_5): 8.39 ppm (2H, d, J = 7.5 Hz), 7.70 (1H, d, J = 16.5 Hz), 7.60 (2H, d, J = 7.0 Hz), 7.44-7.53 (3H, m), 7.30-7.38 (3 H, m), 7.26 (1H, t, J = 7.5 Hz), 6.84 (1H, s); Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.56; H, 4.81; N, 10.07.

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