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Nitrosation of β′-hydroxylamino-α,β-unsaturated oximes: synthesis of 1,7-dioxa-2,6-diaza-spiro[4,4]nona-2,8-diene ring system

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Abstract—Nitrosation of bis arylidene acetone oximes with nitrous acid in glacial acetic acid gives 3-vinyl pyrazolone-*N*,*N*′-dioxides in 32–37% yield. Similar reactions of 2-arylidene-6-(hydroxylamino-aryl-methyl)-cyclohexanone oximes give tricyclic compounds with dioxa-2,6-diaza-spiro[4,4]nona-2,8-diene ring systems in 77–84% yield.

Nitrosation is a well-known reaction in organic chemistry,[1] particularly in the area of nitrogen containing compounds. α,β-Unsaturated ketoximes are given little attention in the nitrosation reaction probably because they are known to produce complex mixtures of products, which include 1-hydroxypyrazole-2-oxides, pyrazolone dioxides and their corresponding oximes.[2–4]

α-Substituted α,β-unsaturated oximes (**1**) are a particularly interesting class of compounds in these reactions. When treated with 1 equiv of HNO_2 in glacial acetic acid, these compounds give 1-hydroxypyrazole 2-oxides (**3**) in good to excellent yields[4] as shown in Figure 1.

The reaction appeared to involve an initial N-nitrosation followed by ring closure to a pyrazole *N*,*N*′-dioxide intermediate[3] (**2**). This intermediate undergoes a proton transfer to yield 1-hydroxypyrazole 2-oxide (**3**).

This mechanism is further supported by the fact that β,β-disubstituted-α,β-unsaturated oximes, also react similarly and the reaction stops at the cyclization step leading to a pyrazole *N*,*N*′-dioxide. Thus 4-methyl-pent-3-en-2-one oxime, a β,β-disubstituted-α,β-unsaturated oxime, was converted to 3,5,5-trimethylpyrazole-nine 1,2-dioxide.[4]

α-Position unsubstituted-α,β-unsaturated oximes (**4**), (Fig. 2) such as benzylidene acetone oxime, upon treatment with HNO_2 yielded complex mixtures of products, with two distinct major products, that can be identified in the mixture.[3]

These are pyrazolone *N*,*N*′-dioxides (**5**) and the corresponding oximes (**6**). When the reaction is carried out under an inert atmospheric conditions and excess HNO_2 is present, the pyrazolone dioxide oxime (**6**) is the major product. This is probably coming from a mechanism[3] similar to the case of β-substituted α,β-unsaturated oximes as shown in Figure 1. Further, in the presence of excess HNO_2, nitrosonium electrophile adds to the 4-position of the intermediate compound,

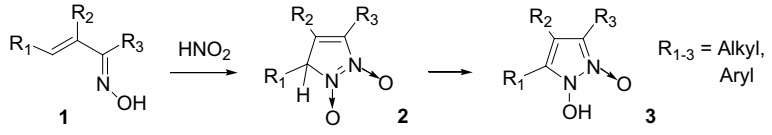

Figure 1.

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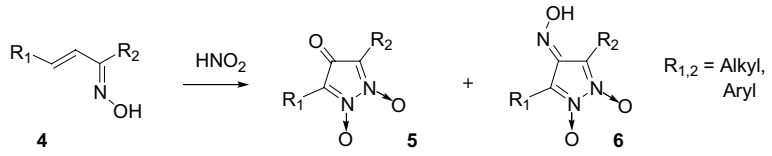

Figure 2.

which isomerizes to an oxime group, leading to compound **6**.

When this reaction is carried out open to atmospheric oxygen and only 1 equiv of HNO_2 is present, pyrazolone *N*,*N*′-dioxide (**5**) is formed as the major product. Interestingly, it is not possible to obtain the ketone product from the hydrolysis of the oxime **6** under mild acidic conditions employed during these reactions.[3] It is believed[3] that the pyrazolone type ketone product (**5**) is produced by a separate series of reactions, which may involve free radical intermediates.

Similar pyrazolone *N*,*N*′-dioxide type ketones can be obtained by oxidative nitrosation of the corresponding dialkyl ketones as well.[5]

These pyrazolone *N*,*N*′-dioxides are known to undergo 1,3-dipolar cycloadditions with verity of electron rich and poor dipolarophiles to produce pyrazolo[1,5-*b*]isoxazoles,[6] thus serve as important intermediates to prepare fused pyrazoles and isoxazoles.

This letter describes the attempts to produce novel cyclic nitrone compounds by oxidative nitrosation process of some unsaturated oximes. During these studies, it was found that nitrosation of dibenzylidene acetone oxime (**7a**) in glacial acetic acid at 0 °C by the addition of 1 equiv of sodium nitrite gives a deep red solid in 37% yield after chromatography (Fig. 3).

^{1}H NMR spectrum[7] of this compound shows a pair of doublets at δ 6.83 and 8.01 with coupling constant of 16.5 Hz indicative of a *trans* double bond, and rest of the signals in the proton spectrum are consistent with two phenyl groups. Further, ^{13}C NMR spectrum of this compound shows a signal at δ 184.8, indicating a carbonyl carbon in a pyrazolone system.

UV–vis spectrum of this compound[7] shows three absorption maximas at 269 (42,000), 309 (4500), 477 (2100) nm. This pattern is similar to the spectrum of the known 3,5-diphenylpyrazolone *N*,*N*′-dioxide,[3] which shows peaks at 256 (39,100), 330 (4180), 452 (1700) nm. Based on this spectral data and elemental analysis results, structure **8a** is proposed for the product.

Reaction carried out under inert atmospheric conditions, and 2 equiv of HNO_2 also gave the same product, **8a** with lower yield. 1,3-Di(4-methylbenzylidene)propan-2-one oxime (**7b**) also gave the corresponding product **8b** in 32% yield. Most likely, these 3-vinyl pyrazolone products are produced from a mechanism involving radicals as suggested by Freeman et al.[3] as in the case of 3,5-diphenyl-pyrazolone *N*,*N*′-dioxide.

In an attempt to prepare 2,6-dibenzylidenecyclohexanone oxime by reacting 2,6-dibenzylidenecyclohexanone[8] (**9a**) with 1 equiv of hydroxylamine hydrochloride and sodium acetate in refluxing aqueous ethanol failed to yield any product and the unreacted starting compound could be isolated. The reaction was possible with 4 equiv of hydroxylamine hydrochloride and 4 equiv of sodium acetate in refluxing aqueous ethanol and the product isolated was the 2-benzylidene-6-(α-hydroxylamino-α-phenylmethyl)cyclohexanone oxime (**10a**) (Fig. 4). In fact this type conjugate additions of hydroxylamine to the α,β-unsaturated ketone or ketoximes are known in the literature.[9] These β-hydroxylamino oximes are an interesting class of compounds and as far as I am aware there are no reports of nitrosation of this class of oximes.

Nitrosation of 2-benzylidene-6-(α-hydroxylamino-α-arylmethyl)cyclohexanone oxime (**10a**) with 1 equiv of HNO_2 in glacial acetic acid, in an open container at 0 °C, yielded a pale yellow product, which upon recrystallization from methanol gave pale yellow crystals in 84% yield (Fig. 4). This product is stable and no significant change was observed in the sample left at room temperature for 3 months.

The same product could be isolated in low yield when the reaction is carried out in an inert atmosphere and the use of excess HNO_2 had no effect on the yield of the product.

^{1}H NMR of this product[10] showed seven protons in the high-field region, six in sets of two each, which appeared as three complex multiplets and the seventh proton at δ 4.21 as a doublet of a doublet with J = 4.0 and 7.0 Hz. The remaining 10 protons in the ^{1}H NMR spectrum were found in the aromatic region, indicating the two

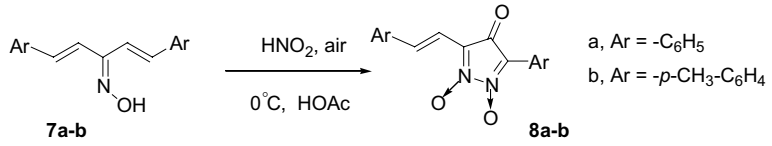

Figure 3.

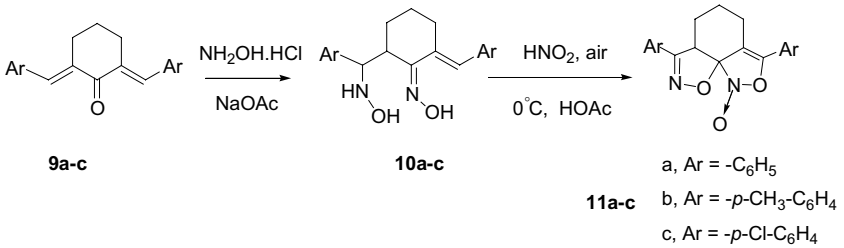

Figure 4.

phenyl groups. Four signals at δ 21.0, 24.6, 25.7 and 55.1 were observed in the high-field region of the ^{13}C NMR spectrum and can be assigned to three methylene carbons and one C–H carbon. ^{13}C signal at δ 118.8 could be assigned to a sp^3 carbon attached to two heteroatoms. The colour and the UV–vis spectrum of this compound are very different from the pyrazolone *N*,*N*′-dioxides obtained in the case of nitrosation of diarylidene acetone oximes, and the NMR data clearly indicated that both the alkene function and hydroxylamine group have participated in this reaction. Elemental analysis showed the formula of the compound as $C_{20}H_{17}N_2O_3$. As NMR and other spectroscopic methods are not providing sufficient information on the structure, I have obtained a single crystal X-ray analysis[11] of this compound, which showed an unusual tricyclic structure (**11a**) for this compound (Fig. 5). This is a novel structural class with a fused spiro dihydroisoxazole system. As far as I am aware this is the first report of the 1,7-dioxa-2,6-diaza-spiro[4,4]nona-2,8-diene ring system. Further this is the first synthesis of a tricyclic ring system with a fused cyclohexane containing two spiro dihydroisoxazole rings.

X-ray data[11] of **11a** shows one dihydroisoxazole ring with N-oxide function and a nitrogen in +4 oxidation state. The N → O bond distance in this unusual dihydroisoxazole N-oxide is 1.240 Å, which indicates the partial double bond character in this N → O bond. This N → O bond distance is comparable with the N → O bond distance in 3,5-dimethyl-pyrazolone *N*,*N*′-dioxide,[12] which is 1.226 Å.

Nitrosation of β′-hydroxylamino-α,β-unsaturated oximes **10b** and **10c** with nitrous acid under similar conditions gave the corresponding tricyclic compound **11b** and **11c** in 80% and 77% yields, respectively, showing the generality of this reaction.

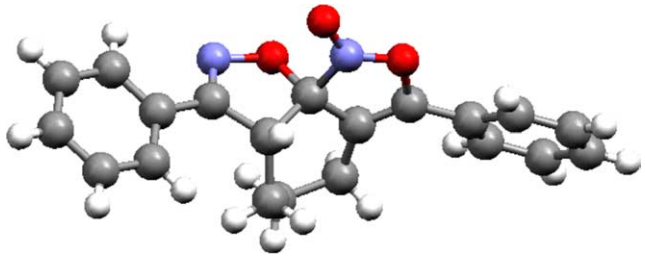

Figure 5. X-ray structure of compound **11a**.

In conclusion, the nitrosations of β′-hydroxylamino-α,β-unsaturated oximes produces a novel class of stable tricyclic compounds with 1,7-dioxa-2,6-diaza-spiro[4,4]-nona-2,8-diene ring system in high yield.

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7. Data for **8a**: mp 191–3 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 6.83 (1H, d, J = 16.5 Hz); 7.38–7.43 (3H, m); 7.51–7.57 (3H, m); 7.61 (2H, d, J = 8.0 Hz); 8.01 (1H, d, J = 16.5 Hz); 8.37 (2H, d, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 105.8, 107.0, 108.4, 121.9, 127.4, 127.7, 129.1, 129.2, 130.2, 131.1, 135.8, 139.8, 184.8. UV 269 (42,000), 309 (4500), 477 (2100) cm^{-1}. Calculated for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.67; H, 4.24; N, 9.47.
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10. Data for **11a**: mp 176–7 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.71–1.75 (2H, m); 1.82–1.88 (2H, m); 2.88 (2H, m); 4.21 (1H, dd, J = 4.0, 7.0 Hz); 7.43–7.51 (6H, m); 7.71 (2H, dd, J = 1.5, 8.0 Hz); 7.75 (2H, dd, J = 1.5, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 24.6, 25.7, 55.1, 113.4, 118.8, 126.8, 127.8, 128.2, 128.9, 129.3, 129.9, 130.3, 131.3, 145.3, 161.1. UV 202 (17,500), 256 (17,100), 355 (1300) cm^{-1}. Calculated for $C_{20}H_{17}N_2O_3$: C, 72.06; H, 5.14; N, 8.40. Found: C, 72.11; H, 5.20; N 8.25.
11. Compound **11a**: $C_{20}H_{17}N_2O_3$, M = 333.36, shape: rod, space group: $P2_1/c$, a = 14.267(3), b = 11.190(2), c = 10.576(2) (Å), volume = 1669.9(6) $Å^3$, Z = 4. Density (calcd) = 1.326 g/cm^3.The data were collected in a Bruker CCD 1000 Diffractometer with Mo Kα (0.71073 Å) radiation.

Crystallographic data for **11a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 253212. Copies of the data can be obtained, free of charge, on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK (fax: +440 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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