Pergamon

Tetrahedron Letters, Vol. 38, No. 7, pp. 1245-1248, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00048-8

The Addition of Nitric Oxide to 2,5-Dimethyl-hexa-2,4-diene Gives Nitrogen Dioxide Adducts

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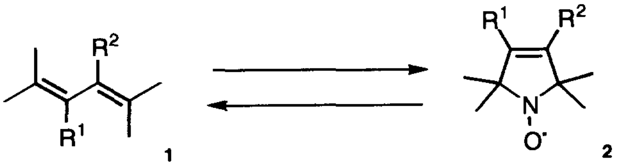
Abstract. The reaction of nitric oxide with 2,5-dimethyl-hexa-2,4-diene **1a** gives (*E*)-2,5-dimethyl-5-nitro-hexa-1,3-diene **3**, (*E*)-2,5-dimethyl-6-nitro-hexa-2,4-diene **4**, (*rac*)-2,5-dimethyl-4,5-dinitro-hexa-2-ene **5**, (*E*)-2,5-dimethyl-2,5-dinitro-hex-3-ene **6** and (*E*)-2,5-dimethyl-5-hydroxy-2-nitro-hexa-2-ene **8**. The tertiary nitrodiene **3** rearranges to the primary nitrodiene **4** *via* a unique 1,5-rearrangement.

Nitric oxide acts as a short range biological messenger in an extraordinary number of physiological processes[1]. Progress in the study of these processes is currently restrained by the lack of reliable analytical methods for the quantification of nitric oxide. Nitric oxide has an unpaired electron which can be detected by ESR spectroscopy, but its relatively high reactivity under physiological conditions causes rapid decay of the signal. Unstable free radicals are frequently identified as their adducts with diamagnetic trapping reagents, but nitric oxide reacts slowly with all common spin traps. Thus far, it has not been possible to develop a spin trap which is sufficiently reactive to trap nitric oxide and which can persist under physiological conditions[2].



	R^1	R^2
a	H	H
b	Ph	Ph
c	$CONH_2$	H

Scheme 1

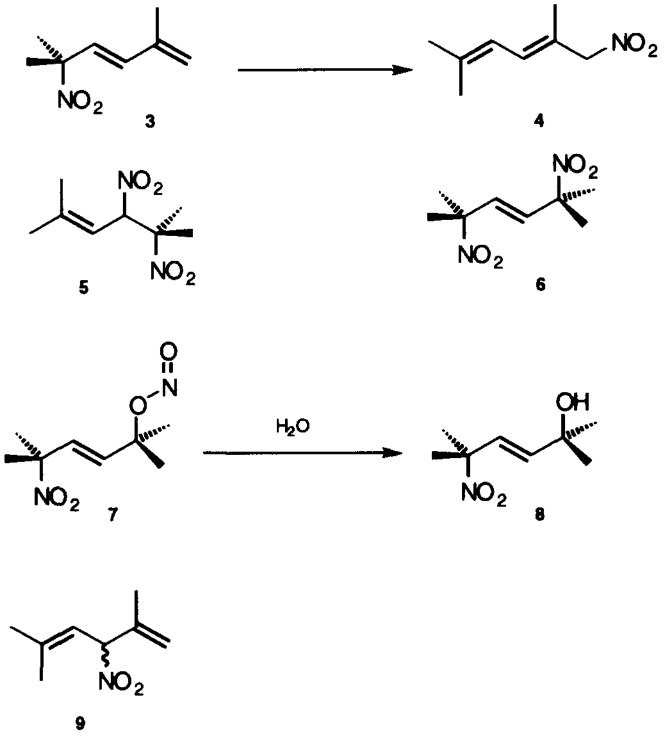
It has been claimed that 2,3-dimethylbutadiene and 2,5-dimethyl-hexa-2,4-diene **1a** act as chelotropic spin traps for nitric oxide[3] (Scheme 1). The interpretation of the ESR spectra obtained was challenged because the hydrogen hyperfine couplings observed were smaller than expected for the nitroxide radical **2a**[4], and the claim was withdrawn during the course of our investigations[5]. Similarly addition of nitric oxide to the diphenyldiene **1b** gave a species with a strong ESR signal, but "work-up gave only unreacted starting material as the major component of the reaction mixture"[6]. However the corresponding retro-reaction; the conversion of the nitroxide **2c** to the diene **1c** is induced by photolysis and presumably involves the elimination of nitric oxide, although no attempt was made to isolate or identify it[7].

We sought to resolve the conflicting data by isolating the spin adduct(s). Moreover if the addition of nitric oxide to dienes proved to give significant yields of nitroxide it would provide a novel and convenient way to spin label substrates such as unsaturated fatty acids[8].

It is well known that nitric oxide is easily oxidised to nitrogen dioxide and higher oxides of nitrogen[9], accordingly careful precautions were taken to exclude oxygen. Carefully purified nitric oxide[10] was passed through a solution of 2,5-dimethyl-hexa-2,4-diene **1a** in hexane. During 30 minutes the reaction slowly turned blue and after 2 hours the flow of nitric oxide was terminated. The crude reaction mixture was blue/green and gave ESR spectra identical to those previously reported[3], but a ^{1}H NMR spectrum indicated that the predominant constituent (>95%) was the starting material **1a**. Evaporation of the starting material and flash column chromatography over silica gel (eluent petrol: diethyl ether), yielded four fractions. The least polar fraction consisted of a circa 50:50 mixture of the nitrodienes **3**, **4** (Scheme 2). Repeated chromatography gave a small sample of the tertiary nitrodiene **3** and mixtures **3**, **4**. The mixture was stable in the freezer (-20°) for 6 months. However upon standing at room temperature for two weeks isomerisation yielded a 20:80 mixture (**3**:**4**) plus polymeric material from which it was possible to separate the primary nitrodiene **4** by repeated column chromatography. Several 1,3-rearrangements of allylic nitrocompounds have been reported[11], however we are unaware of a report of a 1,5 rearrangement. No evidence could be adduced for the presence of the regioisomer **9**.

The remaining fractions were repurified by repeated column chromatography (petrol:diethyl ether and petrol:benzene) to give (in order of elution) the 1,2-dinitro- **5** and the 1,4-dinitro- **6** adducts plus the 1,4-nitroalcohol **8**. The last of these undoubtedly results from hydrolysis of the nitrite **7**. Satisfactory analytical data were obtained for all compounds, but mass spectrometry measurements were confounded by facile loss of NO_2 to give ions at *m/z* 109 or 110. NMR assignments were greatly aided by ^{1}H-^{13}C TOCSY experiments and well resolved $^4J_{H,H}$ allylic couplings (circa 1.5Hz) which mitigated the paucity of reference chemical shift data[12]. The structure of the 1,4-dinitroadduct **6** was confirmed by a X-ray crystallography study which will be reported elsewhere. Analysis of the crude reaction mixture by GC-MS confirmed that all the major components of the mixture had been isolated, although there was also a plethora of minor components.

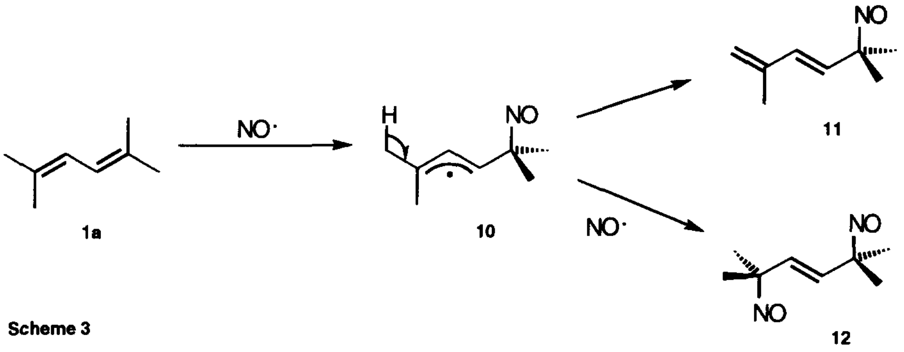
A chemical abstracts search for the 1,4-dinitro-adduct **6** revealed that an essentially identical reaction, (with benzene as the solvent) had been reported by Brindley and Nicholson[13]. They also took considerable pains to avoid contamination by nitrogen dioxide, but also isolated the dinitro-adduct **6**.



Scheme 2

Given that we successfully prevented the formation of nitrogen dioxide, the products can be rationalised as follows. The diene **1a** exists predominantly in the *s-trans* conformation and hence a single step chelotropic addition of nitric oxide is impossible. Nitric oxide addition occurs to give an allylic nitroso radical **10** which undergoes elimination of hydrogen or addition of nitric oxide (Scheme 3). The *trans*-allylic nitroso radical **10** has a significant barrier to rotation; this will disfavour cyclisation which requires the *cis*-conformation. The means by which the nitroso adducts **11**, **12** etc are then oxidised to the corresponding nitrocompounds is currently unclear, but oxidation by nitric oxide is a possibility[14].

In summary we have found no evidence for the formation of the nitroxide **2a** by chelotropic addition of nitric oxide. The products isolated are consistent with stepwise addition and/or elimination



Scheme 3

References and Notes

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10. Blanchard, A. A. *Inorg. Synth.* **1946**, *2*, 126-128; Nitric oxide (3 equiv.) was generated according to the method of Blanchard or obtained from a cylinder (Matheson, 99%+) and passed through a NaOH solution (6M) to remove impurities, NaOH pellets to dry it and finally through an acetone/cardice trap to remove NO_2 (mp. -11.2°C, bp. 21.15°C). The purified gas was bubbled through a previously degassed, stirred solution of 2,5-dimethyl-2,4-hexadiene **1a** in hexane and the apparatus was maintained under a positive pressure of argon. No yields are reported because the amounts of material isolated are solely a consequence of the difficulty of purification. In one run; diene **1a** (1.65g) was reacted with nitric oxide (3 equiv. based on sodium nitrite) in hexane (150mls). The reaction was partially evaporated to give an oily residue which deposited crystals of **6** (59mg, 2%). The remaining oil consisted of a mixture of **6** (approx. 50%) and a mixture of the other components **3**, **4**, **5**, **8** plus polymeric materials as judged by ^{1}H NMR.
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(*Received in UK* 4 *November* 1996; *revised* 23 *December* 1996; *accepted* 10 *January* 1997)