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DISPLACEMENT OF NITRITE ION FROM A 1,3-DINITROALKANE IN THE FORMATION OF AN ISOXAZOLINE-2-OXIDE

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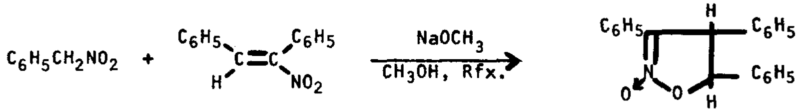
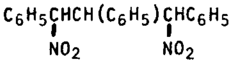
The base-catalyzed formation of 3,4,5-triphenylisoxazoline-2-oxide (III) from phenylnitromethane (I) and cis-α-nitrostilbene (II) is an important route to cyclic nitronic esters.[2]



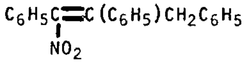
I II III

The reaction has been reasonably considered by many[2-7] to involve the Michael adduct, 1,3-dinitro-1,2,3-triphenylpropane (IV) (isolated in small yield by Heim[8] by a condensation of benzaldehyde with phenylnitromethane in which III was not isolated; from this reaction Heim also isolated a very small amount of a compound which he believed to be 1-nitro-1,2,3-triphenylpropene, V). Neither IV nor V has since been prepared or characterized, or shown to be an intermediate leading to III. Based largely on work of Heim, the generally accepted mechanism leading to III is said to involve an intramolecular cyclization of V nitronate anion (Eqn. 1).[2-7]



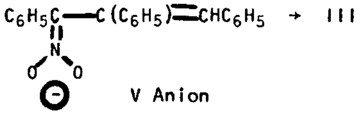
$$\underset{NO_2}{C_6H_5CH}CH(C_6H_5)\underset{NO_2}{CHC_6H_5}$$

IV



$$C_6H_5\underset{NO_2}{C}{=}C(C_6H_5)CH_2C_6H_5$$

V



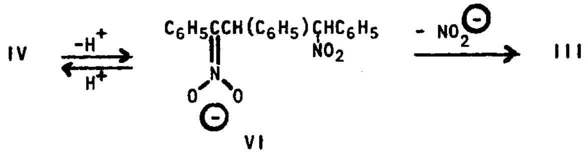
$$C_6H_5\underset{\overset{\|}{N}(O)O^{\ominus}}{C}{-}C(C_6H_5){=}CHC_6H_5 \rightarrow III \qquad (1)$$

V Anion

Our present results disprove this mechanism and establish that a nitrite displacement occurs in a reaction which does not involve a nitroolefin intermediate.

Nitronate anion ($>C{=}NO_2^{\ominus} \leftrightarrow {\ominus}{>}CNO_2$) is an ambident nucleophile which can attack at either carbon or oxygen. The mechanism represented by equation 1 would be the only known example of nitronate anion oxygen adding to a double bond. Ordinarily, when involved in an addition reaction, nitronate reacts by carbon attack (Michael addition,[9] Henry reaction[10]), whereas in most nucleophilic displacement reactions it reacts by oxygen attack leading to nitronic esters or their decomposition products.[11]

A displacement mechanism leading to III would involve formation of intermediate nitro-nitronate anion VI, followed by an intramolecular displacement of nitrite ion (Eqn. 2). The mechanism of Michael addition suggests that VI is a precursor of IV when formed from I and II by base catalysis.[9]



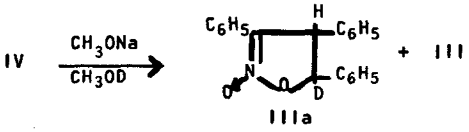
$$\mathrm{IV} \underset{H^+}{\overset{-H^+}{\rightleftarrows}} C_6H_5\underset{\underset{O^{\ominus}\ \ O}{\overset{\|}{N}}}{C}CH(C_6H_5)\underset{NO_2}{C}HC_6H_5 \xrightarrow{-NO_2^{\ominus}} \mathrm{III} \qquad (2)$$

VI

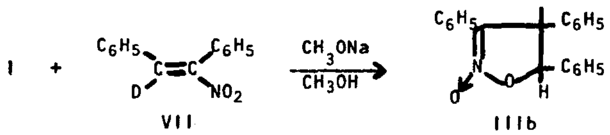
In refluxing methanolic sodium methoxide the reaction of I with II gave an 82% yield of III and no isolable intermediate products. When the reaction of I with II is conducted in benzene with diethylamine catalyst IV is isolated in 60% yield; m.p. 175-176°; lit.[8] m.p. 177°. Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73; mol wt 362. Found: C, 69.70; H, 4.93; N, 7.61; mol wt 355. In methanolic sodium methoxide IV is converted quantitatively into III.

The rate of conversion of IV to III was examined spectroscopically. A 5×10^{-5} M solution of IV in 1×10^{-4} M ethanolic sodium hydroxide revealed essentially no initial ultraviolet absorption between 230 and 400 mμ. After 53 minutes at 25° the reaction was complete and the characteristic absorption of pure III was obtained; λ_{max} 285 mμ (ϵ_{max} 17,700). No other absorption maxima were noted at any time during the reaction. In particular, no long wavelength band near 350 mμ or 300 mμ, characteristic of phenylalkene- or phenylalkane-nitronate anions, was noted. These observations indicate: (1) no accumulation of an olefin nitronate intermediate, and (2) a slow, rate-limiting proton abstraction from IV leading directly, in a fast step, to III.

The formation of III in CH_3OD with participation of an olefin nitronate intermediate (V) (Eqn. 1) would require incorporation of deuterium at C-4 of the product in the final step. The direct displacement mechanism (Eqn. 2), on the other hand, would not involve the central proton in IV, and incorporation of deuterium at C-4 should not occur. Reaction of IV in CH_3OD showed no deuterium incorporation at C-4 in the product IIIa as evidenced by its nmr spectrum. The characteristic C-4 doublet at τ 5.10 ($CDCl_3$, TMS internal standard) in the hydrogen compound (III) collapsed, in part, to a singlet (τ 5.10), with reduction in intensity of the C-5 doublet signal at τ 4.55, showing ca. 85% deuterium incorporation at C-5 to form IIIa. This result is due to deuterium incorporation into the 1- and 3-positions of IV by C-deuteration which occurs at a sufficiently rapid rate relative to cyclization.



Further support of the displacement mechanism and establishment of the proton nmr signal assignments was obtained by synthesis of the C-4 deuterio derivative IIIb. α-Deuterio-α'-nitrostilbene (VII) was prepared from deuteriobenzaldehyde and phenylnitromethane.[12,13] Formation of IIIb from VII and phenylnitromethane in methanolic sodium methoxide led to 100% deuterium incorporation at C-4. In IIIb, the C-4 proton doublet is absent and the C-5 proton signal collapsed to a singlet at τ 5.10.



The mechanism proposed (Eqn. 2) would appear to be the first example of nitrite displacement by nitronate anion. The first examples of displacement of a nitro group from a tertiary carbon atom (by thiophenoxide and malonate anions) have only recently been reported.[14] Formation of 3,5-dicarbethoxy-5-arylisoxazoline-2-oxides by reaction of the sodium salt of ethyl α-nitroacetate with the Schiff base of an aromatic aldehyde is believed to involve a similar cyclization mechanism.[4]

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