

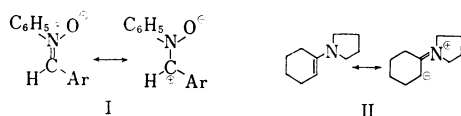
“Reverse-oriented” Cycloaddition of Nitron to Enamine

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In the preliminary communication¹⁾ we showed that the reaction between benzylidenaniline *N*-oxide (diphenylnitron) (Ia, Ar=C₆H₅) and 1-pyrrolidino-1-cyclohexene (II) gave the expected 5-pyrrolidinoisoxazolidine III.



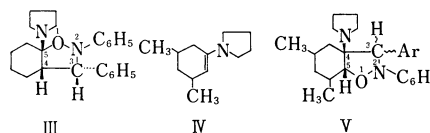
In the 1,3-dipolar cycloaddition between a nitron and a monosubstituted olefin, the oxygen atom of the former generally attacks the substituted carbon atom of the olefin to give a “normal” cycloadduct, 5-substituted isoxazolidine. Thus, from 1-hexene,²⁾ styrene,²⁾ acrylonitrile,³⁾ or ethyl acrylate,³⁾ the expected normal cycloadducts are formed. If the other end of the olefinic double bond is overcrowded to a similar extent, the electronic effect will then become important; from ethyl crotonate or α,β -dimethylcrotonate, the “reverse-oriented” cycloadduct 4-ethoxycarbonylisoxazolidines are formed.³⁾ In such cases the reaction is under “electronic” control.

In the case of the reaction between a nitron and an enamine, the normal cycloadduct formation is expected not only from the steric, but also from the electronic basis.

Here we report an unexpected “reverse-oriented” cycloaddition of nitrones to an enamine where no steric effect comparable to that in crotonates is involved. A dimethylformamide solution of Ib (Ar=*m*-NO₂C₆H₄) and 1-pyrrolidino-*cis*-3,5-dimethylcyclohexene (IV) was stirred at room temperature for 48 hr. After the removal of the solvent *in vacuo*, the residue was crystallized from ethanol to yield yellow crystals of 4-pyrrolidinoisoxazolidine Vb, mp 65–67°C, in 66% yield.

Found: C, 71.35; H, 7.60; N, 10.18%; mol wt (mass), 421. Calcd for C₂₅H₃₁N₃O₃: C, 71.23; H, 7.41; N, 9.97%; mol wt, 421.

The proton NMR spectrum (in CDCl₃) of Vb shows a sharp singlet at τ 5.60 (3-H) and a doublet at τ 6.33 (the angular 5-H, deshielded by the

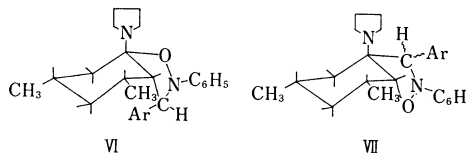


neighboring oxygen atom), in contrast with that of the normal cycloadduct III¹⁾ where benzylic-H (3-H) appears at τ 5.40 as a doublet (coupled with the angular 4-H, $J=ca.$ 10 Hz) and 4-H as a broad doublet centered at τ 7.35.

In a similar manner, from Ic (Ar=*p*-ClC₆H₄) and IV, 3-*p*-chlorophenyl-4-pyrrolidinoisoxazolidine Vc was obtained as colorless plates (from ethanol), mp 112–112.5°C, in 27% yield.

Found: C, 72.85; H, 7.50; N, 6.72%; mol wt (mass), 410. Calcd for C₂₅H₃₁ClN₂O: C, 73.01; H, 7.60; N, 6.82%; mol wt, 410.

It is well established that the electrophilic reagent attacking the β -carbon atom of cyclohexanone enamines can approach only from the direction to form the axial bond because of the large allyl strain (Johnson strain) in the enamine (or in its immonium structure).⁴⁾ Assuming that the reaction between a nitron and an enamine is one-step concerted type,⁵⁾ and that no ring inversion is involved during the cycloaddition as we confirmed,⁶⁾ the structure of the hypothetical normal cycloadduct between I and IV would be VI. Apparently there is in VI a severe non-bonded interaction between C-aryl and one of the methyl groups. Since this interaction should be even greater in the transition state, VI is kinetically as well as thermodynamically less favorable than the reverse-oriented VII (=V) which is free from this type of interaction.



This unexpected formation of reverse-oriented cycloadduct gives, in turn, a support for the stereochemistry of nitron-enamine reaction.⁶⁾

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4) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

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