1,3-DIPOLAR CYCLOADDITION REACTIONS INVOLVING CAPTODATIVE OLEFINS

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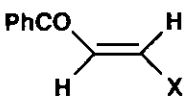
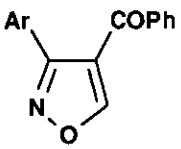
Abstract -A series of arylnitrile oxides (6a-e) were reacted with captodative olefins (4) to yield 5-acetyl-3-arylisoxazoles. No intermediate isoxazolines were formed, the olefins thus behaved as acetylene equivalents. A plausible explanation for the observed regioselectivity in the process is offered as well.

1,3-Dipolar cycloadditions of nitrile oxides to double or triple bonds are a general method for the construction of isoxazolines and isoxazoles.[1] The regiochemistry of the 1,3-dipolar cycloaddition process, particularly involving monosubstituted olefins has been rationalized and extensively reviewed.[2] In these cases the 5-regioisomers have been the predominant isolated isomers. However orientation of the cycloaddition reaction may be actually reversed in the presence of appropriate substituted olefins. Thus, cycloaddition of a series of arylnitrile oxides to olefins (1) and (2) exclusively formed the 4-acyl derivatives (3). It seems that introduction of sustituents with strong electron donating ability, such as methylthio or methoxy groups was responsible for the reversed orientation observed, which was properly explained in terms of the FMO theory.[3,4]

Since no reports in the literature were found related to the 1,3-dipolar cycloaddition reactions involving olefins bearing a donor and an acceptor group on the same carbon atom, such as **4** , the so called captodative olefins,[5] we became interested in the chemical behaviour that these might exhibit in such reactions. Particularly interesting is the fact that olefins (**4**) enjoy captodative stabilization besides carrying a different HOMO/LUMO distribution as compared to methyl vinyl ketone (MVK).[6]



1, X = SMe
2, X = OMe



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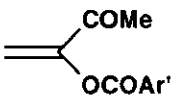
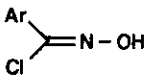


4a, Ar' = $C_6H_4NO_2$-*p*
4b, Ar' = C_6H_4Cl-*p*

In a first experiment, benzonitrile oxide (BNO) (**6a**) prepared <u>in situ</u> from benzohydroxyiminoyl chloride and triethylamine[7] was reacted with olefin (**4a**) or (**4b**) obtained from biacetyl and the corresponding acid chloride,[8] however none of the expected isomers (**7a,b**) were isolated from the reaction mixture, instead 3-phenyl-5-acetylisoxazole (**8a**) was obtained in good yield. Further proof of the isolated product structure came from a reaction of BNO with MVK,[9] followed by MnO_2/dioxane oxidation of intermediate oxazoline (**9**).
As expected, a crossed experiment showed that MVK reacts faster with BNO than olefin (**4**) does.



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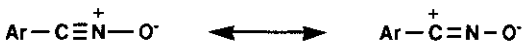

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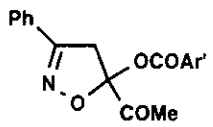
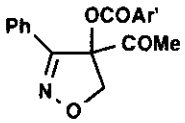
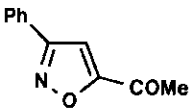
Ar = a, C_6H_5; b, 4-MeC_6H_4; c, 3,4-$(MeO)_2C_6H_3$; d, 3,4-(CH_2O)-C_6H_3; e, 4-$NO_2C_6H_4$



7a



7b



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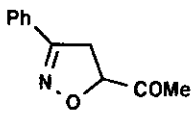

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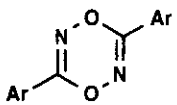


10, Ar = $C_6H_4NO_2$-*p*

Other arylnitrile oxides were then prepared. The requisite aryl-hydroxyminoyl chlorides (**5b-e**) were conveniently obtained through chlorination of the corresponding aldehyde oxime with N-chloro-succinimide in DMF as suggested by Liu.[10]

Treatment of intermediates (**5b-e**) with triethylamine in dried benzene followed by conventional work up gave the expected 5-acetyl-3-arylisoxazoles (**8**) in moderate to good yields as shown in Table 1. None of the 4-regioisomer was isolated.

p-Nitrophenylhydoxyiminoyl chloride (5e) was a difficult intermediate to work with. Attempts made to purify this product led only to its decomposition. Furthermore, although it was possible to generate arylnitrile oxide (6e), this dimerized to the oxadiazine (10) rather than perform the 1,3-dipolar cycloaddition reaction. Therefore isoxazole (8e) had to be prepared directly from the hydroxyminoyl chloride (5e) and olefin (4). This experiment suggests that the actual driving force for the isoxazoles (8) formation is probably the building of a more stable (aromatic) structure.

Table 1. Preparation of 3-Aryl-5-acetylisoxazoles (8)

Isoxazole 8	Reaction time (h)	Solvent	mp (°C)[a]	Yield (%)
a	4.0	Benzene	103-104	90
b	3.5	Benzene	92-93	90
c	1.5	Benzene	142-143	96
d	3.0	Benzene	141-142	81
e	15.0[b]	Xylene	158-159	66

[a] They have not been corrected.

[b] Starting material was p-nitrophenylhydroxyiminoyl chloride.

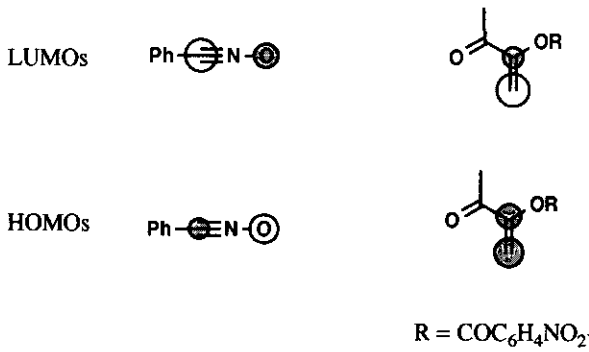
In the ^{1}Hnmr spectrum isolated isoxales (8a-e) gave singlets for the methyl of the acetyl and for the H-4 proton at δ 2.6-2.7 and 7.2-7.3 respectively. Compound (8e) showed H-4 singlet at δ 7.6. The aromatic protons displayed multiplets in the range 6.8-7.2 ppm, whereas compound (8e) showed these at δ 8.1-8.6.

In addition, the methyl group in **8b** showed as a singlet at δ 2.4, the methoxy sustituents in **8c** appeared as two singlets at δ 3.85, 3.90 and the methylene protons of **8d** gave a singlet at δ 6.1. Isoxazole (**8a**) had a similar mp as that reported in the literature.[11]

The observed process regiochemistry cannot be accounted for in terms of the FMO theory. Recently, the MINDO/3 eigenvectors of the FMO's of several captodative olefins, including **4a** were calculated.[12] The HOMO energy of these olefins was higher than that of a single olefin substituted by an electron withdrawing group, like MVK, whilst the LUMO's had an energy content either similar or smaller than MVK. In contrast , ab initio STO-3G calculations showed a LUMO's energies trend to be slightly higher than that of MVK.[6] This could be explained by the electron donor contribution to perturbational interactions on the captodative system.[13,14]

Considering semiempirical and experimental FMO energies of BNO,[15] it is possible to figure out an FMO interaction diagram for the 1,3-dipolar addition with the olefin (**4a**) . The energy gap HOMO-dipole/LUMO-dipolarophile (ΔE = 8.64 eV) is smaller than that of LUMO-dipole/HOMO-dipolarophile (ΔE = 9.9 eV) in nearly 1.26 eV. Regioselectivity could then be estimated on the basis of maximimum overlap between the energetically more favourable dipole and dipolarophile FMO interaction.[13] However captodative substitution of olefin (**4a**) results in a polarization of the HOMO/LUMO's alkene on the unsubstituted carbon double bond. Besides , BNO-HOMO shows a polarization towards the oxygen atom, whilst the LUMO shows a higher coefficient on the carbon atom (Figure 1). Hence the transition state leading to the observed regioisomer (**8**) will be the less stabilized as well (LUMO-dipole/HOMO-dipolarophile).

Figure 1

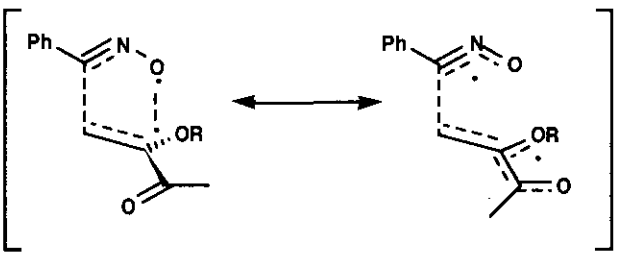


$R = COC_6H_4NO_2\text{-}p$

From this analysis , it seems that the FMO treatment is unsuccesful to rationalize the 1,3-dipolar cycloaddition of BNO to olefin (4). Maybe further improved calculations must be made to asses the observed regiochemistry by the FMO approach.

However, the qualitative perturbational treatment might provide an alternative explanation by regarding substituent effects upon a biradical character transition state.[16] Thus, major regioisomer (8), could be favoured by an stabilized interaction by both allylic conjugation and the so called, captodative effect.[5] (**Figure 2**)

Figure 2



In conclusion captodative olefins behave like acetylene equivalents in a 1,3-dipolar cycloaddition reaction with aryl nitrile oxides giving isoxazoles directly. At present stage the regiochemistry of the process could only be qualitatively explained in terms of a radicaloid transition state. The study is now being further extended to other captodative olefins and 1,3-dipoles.

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