

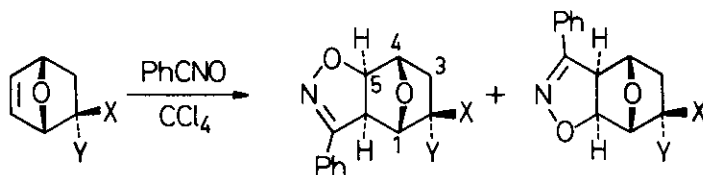
REGIOSELECTIVITY OF 1,3-DIPOLAR CYCLOADDITIONS
 CONTROLLED BY REMOTE SUBSTITUTION AND LEWIS ACID CATALYSTS

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Abstract- In the presence of ZnI_2 , benzonitrile oxide adds to the C=C double bond of 2-endo-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-exo-carbonitrile with interesting regioselectivity.

Electrophilic additions of bicyclo[2.2.1]hept-5-enes are highly exo-face selective; their regioselectivity can be controlled by the substituents at C(2)¹. The possibility of introducing directly two substituents at C(5) and C(6) of the 7-oxanorbornenes 1-3 in a stereoselective fashion makes these systems valuable synthetic intermediates,² even more so since they are readily obtained optically pure³. The Diels-Alder addition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene to enone 2 was moderately regioselective because of the homoconjugated carbonyl group⁴. The 1,3-dipolar cycloaddition⁵ of benzonitrile oxide to 1-3 would be a valuable method for introducing an oxygen and a carbon substituent at C(5) and C(6) of these molecules⁶ if the reaction could be made stereo- and regioselective. We disclose preliminary results which demonstrate that possibility.



		25°C	25°C, AlCl ₃	25°C, ZnI ₂
X = CN; Y = OAc	<u>1</u>	<u>4</u> / <u>5</u>	60:40	85:15
X, Y : =O	<u>2</u>	<u>6</u> / <u>7</u>	65:35	65:35
X, Y : OCH ₂ CH ₂ O	<u>3</u>	<u>8</u> / <u>9</u>	53:47	65:35

When equimolar amounts of (chlorophenylmethylidene)azanol (the precursor of PhCNO), Et₃N and olefins 1, 2 and 3 were allowed to react in CCl₄ (3-4·10⁻²M) at 25°C for 5 h, the adduct mixtures 4+5, 6+7 and 8+9, respectively, were obtained in 95-98% yield. Dimerization of benzonitrile N-oxide was a slow process under these conditions⁷. 360 MHz ¹H-NMR spectra of the crude reaction mixture allowed one to determine the ratio (± 5%) of the regioisomers (see above). No trace of adducts resulting from the endo-face attack of the C-C double bond in 1-3 could be detected. The results showed that the oxygen atom of PhCNO attacked preferentially centre C(5) of 1-3. Adducts 4-9 could be isolated by column chromatography on silica gel and their structure was established by their elemental analyses and spectral data⁸.

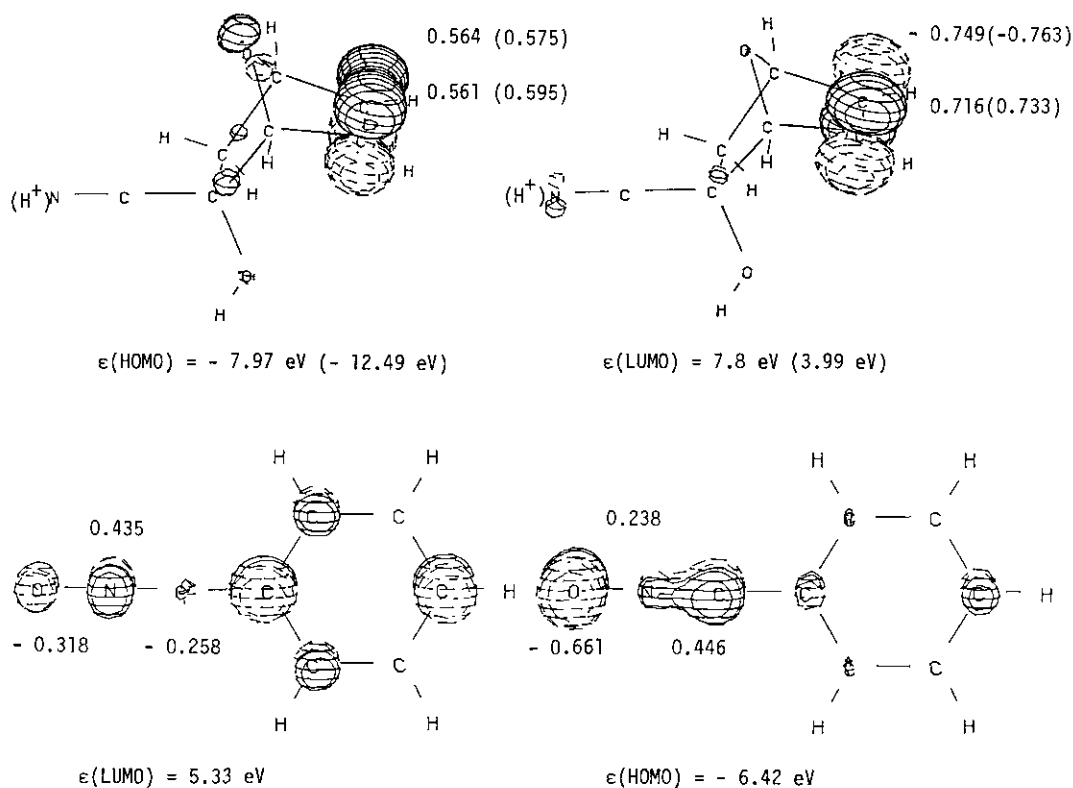


Figure 1. Frontier orbitals of 2-endo-hydroxy-7-oxabicyclo[2.2.1]heptane-2-exo-carbonitrile (10) and of benzonitrile oxide⁹. In parenthesis, the characteristics of the frontier orbitals of 10 protonated on the CN group are shown (ab initio STO 3G on MNDO optimized geometries)

According to the PMO theory⁹, the regioselectivity of the dipolar cycloadditions of benzonitrile oxide can be predicted by analysis of the shape of the frontier orbitals of PhCNO and of the

reacting alkenes. MO calculations^{9,10} suggested that the oxygen terminus of PhCNO is the most nucleophilic site (the centre with the greater negative charge and the highest HOMO coefficient). Using MNDO¹¹ optimized geometries, we have calculated the ab initio STO 3G¹² MO's of 2-endo-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2-exo-carbonitrile (10). This molecule can be considered as a reasonable model for 1 (see Figure 1).

The LUMO(dipole)-HOMO(dipolarophile) interaction would not induce a regioselective cycloaddition $\underline{1} + \text{PhCNO} \rightarrow \underline{4} + \underline{5}$ as the coefficients of the HOMO at C(5) and C(6) of 10 were calculated to be nearly the same. In contrast, the coefficients at C(5) and C(6) of the LUMO of 10 were found to be slightly different and might lead, because of the HOMO(dipole)-LUMO(dipolarophile) interaction, to a preference for the regioisomer 4. Our calculations suggested that centre C(5) in 10 (and 1) is more electrophilic than centre C(6). This was expected for an olefin perturbed by homoconjugated electron-withdrawing groups. Thus, the PMO theory predictions are in accord with the experimental results reported for the cycloaddition of PhCNO to 1. Similarly, the shape of the frontier orbitals of 2 and 3¹³ suggested that C(5) in these alkenes is slightly more electrophilic than centre C(6), in agreement with our experiments.

The orientation of the 1,3-dipole and olefins 1-3 could also be governed by dipole-dipole interactions. Nevertheless, it is not clear to us why there is no improvement of the regioselectivity of the cycloadditions in the presence of strong Lewis acids such as AlCl₃ and BF₃·Et₂O. Coordination of the oxygen atom of PhCNO and of the X and Y groups of 1-3 should increase the dipole moments of these molecules and lead to enhanced regioselectivity. This was not observed for reactions involving 1 to 2 equivalents of AlCl₃ or BF₃·Et₂O (CCl₄, 25°C). However, in the presence of ZnI₂, an interesting regioselectivity of 85:15 (4/5) was observed for 1 + PhCNO. ZnI₂ had a smaller effect on the regioselectivity of the cycloadditions of 2 and 3 (see above). This can be attributed to the high affinity of ZnI₂ for carbonitrile groups. Thus upon coordination of the CN function, 1 becomes more electrophilic at centre C(5) and makes its reaction with PhCNO more regioselective. On protonation of the carbonitrile group in 10 no significant change was calculated for the coefficients at C(5) and C(6) of the HOMO and the LUMO of this olefin (see Figure 1). Further work is required before these explanations can be considered as definitive. Our results demonstrate, however, the possibility to control the regioselectivity of 1,3-dipolar cycloadditions of 7-oxanorborn-5-enes by the substituents at C(2) and with the help of a Lewis acid¹⁴.

REFERENCES AND FOOTNOTES

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8. E.g.: ¹H-NMR (360 MHz, CDCl₃) of 4: δ 7.67 & 7.45 (5H_{arom}), 5.33 (s, H-C(1)), 4.91 (d, 8.2 Hz, H-C(6)), 4.6 (d, 5.6 Hz, H-C(4)), 4.12 (d, 8.2 Hz, H-C(5)), 2.78 (dd, 15.0, 5.6 Hz, Hexo-C(3)), 2.30 (s, AcO), 1.97 (d, 15 Hz, Hendo-C(3)); of 5: δ 7.67 & 7.45 (5H), 5.33 (s, H-C(1)), 5.12 (d, 8.2 Hz, H-C(6)), 4.86 (d, 5.6 Hz, H-C(4)), 4.02 (d, 8.2 Hz, H-C(5)), 2.83 (dd, 15.0; 5.6 Hz, Hexo-C(3)), 2.22 (s, 3H), 2.10 (d, 15 Hz, Hendo-C(3)). Signal attributions were confirmed by NOE measurements.
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13. Shape of the frontier orbitals of 2: LUMO (ε = 7.28 eV): coefficients at C(5): 0.57, at C(6): -0.50; HOMO (ε = -7.65 eV): at C(5): 0.42, at C(6): 0.39. Shape of the frontier orbitals of 3: LUMO (ε = 8.09 eV): coefficients at C(5): 0.78; at C(6): -0.77; HOMO (ε = -7.37 eV): at C(5): 0.41, at C(6): 0.38.
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