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REGIOSELECTIVITY IN THE 1,3-DIPOLAR CYCLOADDITION OF NITRILE OXIDES TO ALKYLIDENECYCLOPROPANES.

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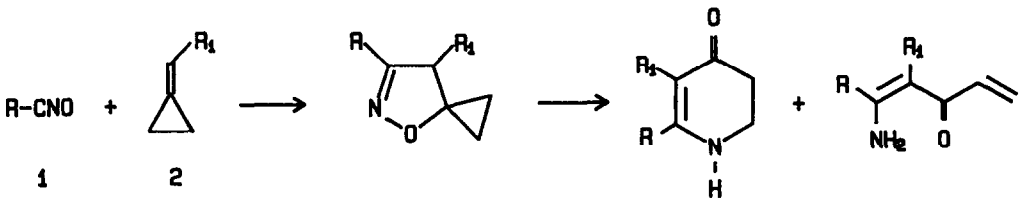
Summary- The 1,3-dipolar cycloaddition of nitrile oxides to methylenecyclopropanes substituted on the exocyclic double bond gives prevalently or exclusively 4-spirocyclopropane isoxazolines when the substituent is arylic or alkylic group, 5-spirocyclopropane isoxazolines when the substituent is an electron-withdrawing group. Adducts **16** and **17** selectively rearrange photochemically to the enaminoenone **19**.

Recently a new method for the synthesis of 5,6-dihydro-pyrid-4-ones **4a** and enaminoenones **5a** has been reported,[1,2] consisting of a thermal or photochemical rearrangement of 5-spirocyclopropane isoxazolines. The isoxazolines **3a** (R_1 = H) can be obtained quite generally and regioselectively by 1,3-dipolar cycloaddition of nitrile oxides **1** to methylenecyclopropane **2a**.[1,2]

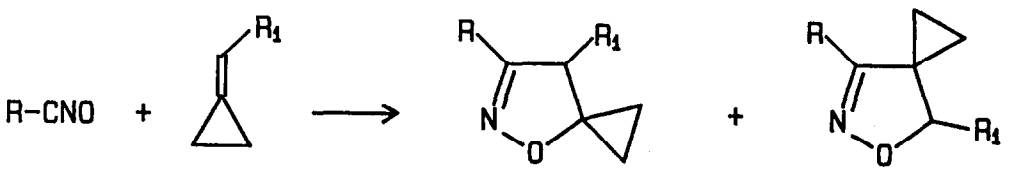


1 2 3 4 5 eq.1

a: R_1 = H

b: R_1 ≠ H

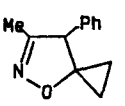
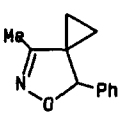
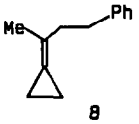
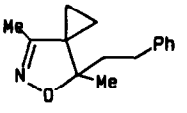
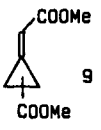
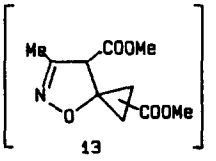
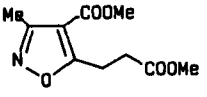
The possible extension of this new method to the synthesis of more complex molecules is based upon the flexibility of the technique in introducing different substituents. Our attention was driven to consider the same sequence of eq.1 with R_1 other than hydrogen. The success of this procedure depends, however, on the regioselectivity of the cycloaddition of nitrile



1 2b 3b 6

oxides to alkylidenecyclopropanes **2b** towards the 5-spirocyclopropane isoxazolines **3b**. The presence of a substituent on the exocyclic double bond affects the dipole/dipolarophile interaction depending on the character of the substituent, resulting in different Frontier Orbital control.[3,4] The lack of any report on 1,3-dipolar cycloadditions with such compounds did not allow any prediction on the regioselectivity obtained in the cycloaddition. We briefly tested, then, the cycloaddition of acetonitrile oxide **1** to the alkylidenecyclopropanes **7**[5], **8**[5] and **9**[6], chosen as models of substituted methylenecyclopropanes with aryl, alkyl and electron-withdrawing groups[7] (Table I).

Table I

entry	alkylidene-cyclopropanes	reaction conditions[a] Yield	Adducts		
a	 7	Benzene, 1h 62 %	 10	1 : 4	 11
b	 8	Toluene, 1h 65 %	—		 12
c	 9	Benzene, 1h 45 %	 13		 14

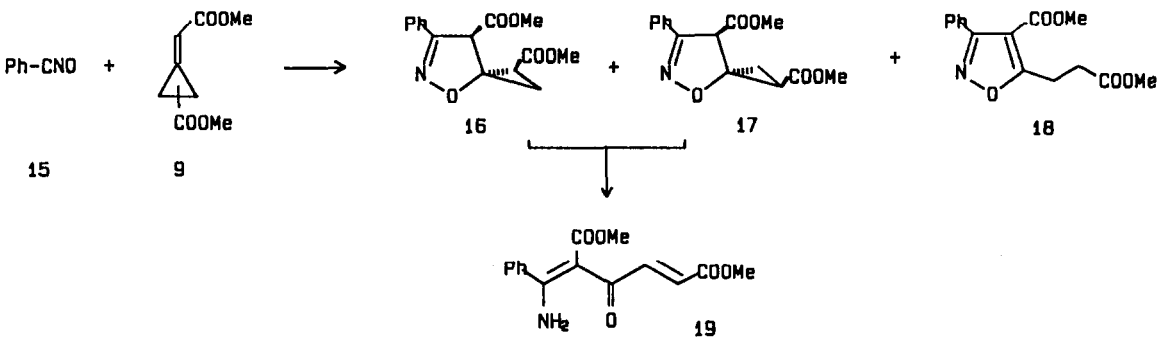
The cycloaddition to **7** (entry a) gives a couple of regioisomers in ratio 4:1. The assignment of the major isomer as 5-phenyl-4-spirocyclopropaneisoxazoline (**11**) is based on the chemical shifts of the benzylic CH (^{1}H: 5.35 δ; ^{13}C: 86.01 δ), downfield with respect to those of the minor isomer **10** (^{1}H: 4.00 δ; ^{13}C: 60.33 δ), and of the adjacent spiro-C (^{13}C 70.94 δ in **10**, 37.34 δ in **11**).

The cycloaddition to **8** (entry b) gives with good yield only one regioisomer (**12**) assigned as the 4-spirocyclopropane derivative on the basis of the chemical shifts of C-4 and C-5, at δ 38.3 and 84.2 respectively, indicating a strong shielding influence of the spirocyclopropane ring on the 4 po-

sition of the isoxazoline, together with the expected value for the C-5.

From the cycloaddition reaction of **9**[6] only the isoxazole **14** has been obtained. Its formation can be rationalised assuming the intermediate formation of the cycloaddition product **13** that rearranges in the reaction conditions. The propionate chain in position 5 of the isoxazolidine is evidenced by the multiplicity of the ^{13}C signals of C-4 and C-5 in the H-coupled spectra. The C-4 signal (108.26 ppm) appears as a quadruplet with J_3= 2 Hz, and the C-5 (171.65 ppm) as a complex multiplet arising from the long range couplings with two different methylenes.

The acidity of the proton α to the ester group on C-4 seems to be responsible for the observed rearrangement, if we consider the presence of triethylamine required for the preparation of the nitrile oxide **1** *in situ*. In fact, when we add the isolated nitrile oxide **15**[9] to the solution of **12** in refluxing benzene (3 h), the two expected[6] isomers **16** and **17** are obtained, besides the isoxazole **18** in 2:1:1 molar ratios respectively and 47% overall



yield. The structural assignment to the cycloadducts is based on the ^{13}C-NMR spectra. The chemical shift of the methylene carbon in the cyclopropane ring is δ 14.75 in **17** and δ 21.49 in **16**, because of the deshielding effect of the carbomethoxy group.

The presence of the rearranged product besides the minor cycloadduct in equal amount, since **9** was 1:1,[6] suggested that the isoxazole originated from **17** by selective opening of the cyclopropane ring, followed by hydrogen shift. Subjected to heating for a further 4h, the same mixture gave a clean mixture of the cycloadduct **16** and the isoxazole **18** in 1:1 ratio. The steric hindrance experienced by the isomer **17**, having the two ester groups close each other, is probably the driving force for the easy thermal opening of the strained ring. Only prolonged heating at higher temperature (48 h in refluxing mesit-

ylene, 163°C) causes the more stable isomer **16** to rearrange to **18**.

The cycloaddition of nitrile oxides to alkylidenecyclopropanes shows a high regioselectivity whith the aryl substituent (entry a) and regiospecificity with dialkyl (entry b) and electron-withdrawing (entry c) substituted methylenecyclopropanes. The results are in fair accord with those reported in the literature for substituted olefins.[10] However, it is worth to be noted the high reactivity and the unexpected high degree of selectivity observed in the case of the alkylidenecyclopropane **11**, with respect to a simple tetraalkylsubstituted olefin, that can be ascribed to the effect of the cyclopropane ring, not yet elucidated.

In view of the previously described rearrangement,[1,2] isoxazoline-5-spirocyclopropanes carrying a substituent at the isoxazoline position 4 are accessible if this substituent is an electron-withdrawing one (products **13**, **16** and **17**). Thus, the mixture of the adducts **16** and **17** rearranges photochemically to the highly substituted enaminoenone **19** in 42% isolated yield. The second carbomethoxy group on the cyclopropane ring stabilizes, in this case, the open chain product of the rearrangement.[1,2]

The proof that eq. 1 applies when R_1 is an electronwithdrawing substituent represents a valuable extension of the general method. The selective synthesis of 4-spirocyclopropane isoxazolines, moreover, represents a new route to selectively substituted cyclopropane systems.

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5. K. Utimoto, M. Tamura, K. Sisido, *Tetrahedron* 1973, **29**, 1169. The alkylidenecyclopropane **8** is prepared from 3-oxobutylbenzene in 64% yield.
6. Prepared from commercially available Feist's acid (Aldrich) in accord to E.F. Ullman, *J. Am. Chem. Soc.* 1959, **81**, 5386; the diester **9** is obtained as an unseparable 1:1 mixture of cis and trans isomers.
7. All new compounds were fully characterised by spectroscopical means and/or combustion analyses.
8. Acetonitrile oxide is prepared accordingly to Mukaiyama's procedure. A mixture of Nitroethane and catalytic NEt_3 is added in small portions to the refluxing reaction mixture containing alkylidenecyclopropanes and PhNCO.
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