# HIGH REGIO- AND STEREOSELECTIVE CYCLOADDITION OF A NITRONE TO ALKYLIDENECYCLOPROPANES

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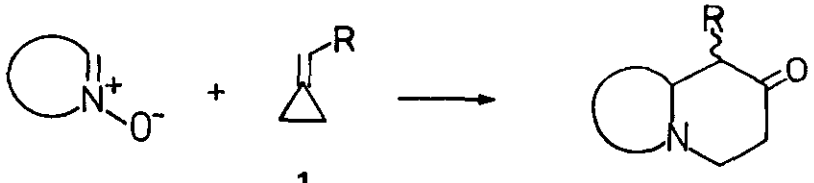
Abstract- The 1,3-dipolar cycloaddition of 5,5-dimethylpyrroline-N-oxide (DMPO) **3** to methylenecyclopropanes substituted on the exocyclic double bond gives exclusively 4-spirocyclopropane isoxazolines when the substituent is aryl or alkyl group, 5-spirocyclopropane isoxazolines when the substituent is an electron-withdrawing group. This cyclic nitrone gives cycloadducts with high diastereoselectivity.

The recently reported method for the synthesis of octahydro-indolizin-7-ones and octahydro-quinolizin-2-ones[1] by thermal rearrangement of the cycloadducts of a cyclic nitrone with methylenecyclopropane, prompted us to study its wider applicability to the synthesis of natural compounds.
The incorporation of substituents in either the nitrone or the methylenecyclopropane should allow the synthesis of selectively substituted octahydro-indolizinones or quinolizinones. We first considered, then, the substitution on the exocyclic double bond of the methylenecyclopropane (**1**). This would afford, eventually, bicyclic bases **2** substituted in the 3 position of the piperidone ring. Except our




**1** **2**

previous work,[2] the lack of literature reports on 1,3-dipolar cycloaddition to alkylidenecyclopropanes induced us to carry out a study on the regiochemistry of nitrone cycloaddition to this system. 5,5-Dimethyl-1-pyrroline-N-oxide (**3**) (DMPO) was chosen as a model nitrone, and alkylidenecyclopropanes **4**,[2] **5**,[3] **6**,[2] **7**[2] and **8**[4] as models for aryl, electron-donating and electron-withdrawing substituted methylenecyclopropanes. The results of this study are reported in Table I.
The cycloaddition of DMPO to **4** (entry a) gives prevalently the regioisomer **10** as an epimeric mixture at C-2 (7:1). Structure assignment rests on the chemical shift of the benzylic protons at 5.10 and 4.96 $\delta$ in major **10a** and minor **10b** isomer respectively. The regioisomer **9** (only one of the two possible epimers is detected) shows a benzylic resonance at 3.46 $\delta$ with J=3.7 Hz in agreement with a trans

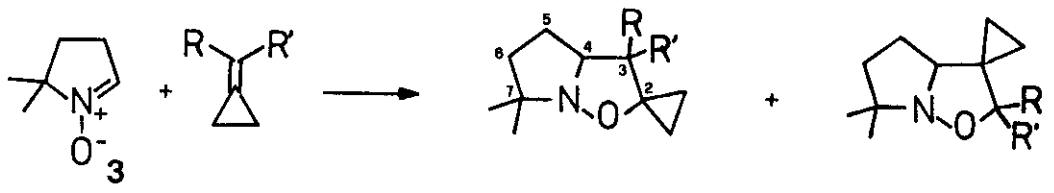
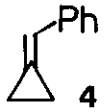
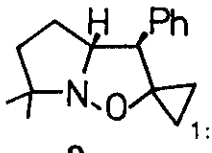
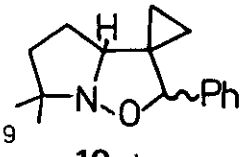
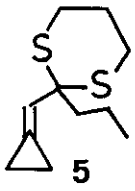
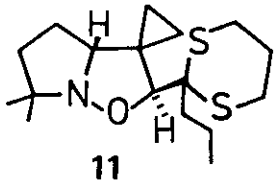
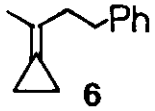
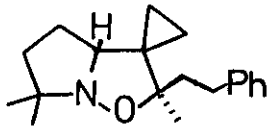
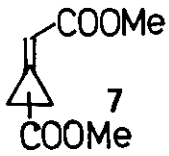
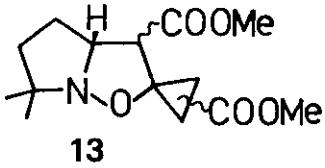
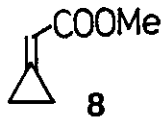
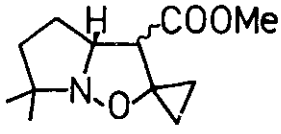


Table I

| entry | alkylidene cyclopropanes | reaction conditions (°C) yield % | adducts[5] |
|---|---|---|---|
| a |  **4** | Benzene, 11, 15h 60 |  **9** 1:19  **10a,b** |
| b |  **5** | Toluene, 11, 45h 38 | —  **11** |
| c |  **6** | Toluene, 11, 13h 90 | —  **12** |
| d |  **7** | neat, r.t., 90h 50 |  **13** — |
| e |  **8** | neat, 50°C, 40h 63 |  **14a,b** — |

coupling with the bridgehead hydrogen in C-4. The lack of correlation between the benzylic hydrogen on C-2 and the bridgehead proton in a 2D-NOESY spectrum of **10a**, indicates a *trans* relationship. The favored "*exo*" transition state[6] of the cycloaddition explains the stereochemistry of the main products **9** and **10a**. Steric repulsion should disfavour the "*endo*" transition states, without significant secondary interactions, between nitrones like **3** and dipolarophiles.[7]

The alkyl substituted methylenecyclopropanes **5** and **6** give selectively only one diastereoisomer **11** and **12** respectively (entries b and c). The $^{13}$C-nmr values for C-2, C-3 and C-4 (**11**: 82.92, 32.25, 73.42; **12** 80.12, 38.96, 73.36 ppm) clearly indicate the regiochemistry of the two cycloadducts. The proton signal at $\delta$4.50 in **11** doesn't correlate with the bridgehead proton in C-4 at 3.48 $\delta$, nor the methyl at C-2 in **12** with the proton at C-4. These analyses allowed us to assign the given stereochemistry.

When neat DMPO is mixed with **7** at room temperature, after 90h an unseparable mixture of three isomers (3.3:2.3:1 by GLC) is obtained (entry d). $^{1}$H-Nmr spectra are too complex to be interpreted, although the lack of signals above 4.00 ppm indicates that 4-spirocyclopropane regioisomers are not present. $^{13}$C resonances of the three isomers inequivocally assign them as 5-spirocyclopropane isoxazolidines.[8]

The cycloaddition to cyclopropylidene methylacetate **8** gives a simpler mixture of only two diastereoisomers **14a** and **14b** in 2:1 ratio (entry e). These isomers are 5-spirocyclopropane isoxazolidines as shown by the $^{1}$H-nmr spectra, which display characteristic doublets at 3.26 $\delta$ (J=3.5 Hz) for the major isomer **14a** and at 3.80 $\delta$ (J = 7.5 Hz) for **14b**. The $^{13}$C spectrum confirms the assignment (**14a** C-2: 67.22; C-3: 58.72; C-4: 67.81; **14b** C-2: 67.58; C-3: 53.98; C-4: 67.70). The H(C3)-H(C4) couplings allow the assignment of the "*exo*" stereochemistry to the major isomer. The lower value of the coupling constant is related to a *trans* relationship of two hydrogen atoms in a five membered ring.[9]

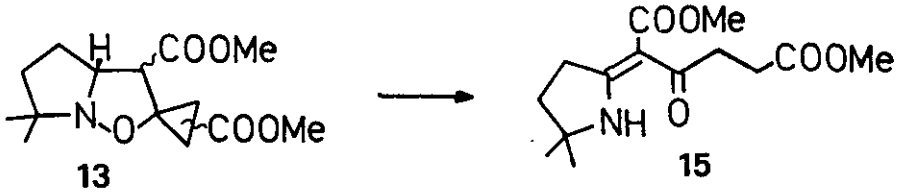
The regiochemical outcome of the cycloaddition of the nitrone **3** to alkylidenecyclopropanes closely resembles that one observed in the cycloaddition of nitrile oxides to dipolarophiles **4**, **6** and **7**.[2] The higher selectivity towards the 4-spirocyclopropane derivative obtained for the benzylidenecyclopropane (entry a) and towards 5-spirocyclopropanes for alkylidenecyclopropanes **7** and **8** (entries d and e), agrees with previous data.[10] However, the high selectivity observed in the reactions b or c is unexpected, as both regioisomers are claimed in the cycloaddition of nitrones to alkyl disubstituted olefins.[11] This control of the regioselectivity by the cyclopropane ring will be the object of a theoretical study.

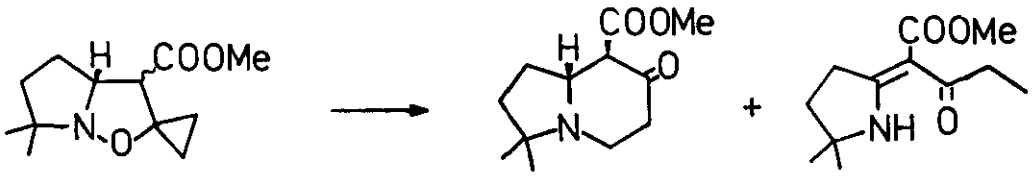
The nitrone cycloaddition also displays high diastereoselectivity, since the "*exo*" product is always preferred or the only one observed.

The results described above demonstrate that nitrone **3** cycloadds to alkylidenecyclopropanes with high regio- and stereoselectivity. The product composition depends upon the substituent on the exocyclic double bond, only electron-withdrawing substituents giving the 5-spirocyclopropaneisoxazolidines able to thermally rearrange.

When compounds **13** were subjected to heating in refluxing mesitylene for 4h only the enaminone **15** was obtained in 60% yield. The presence of a carbomethoxy group on the cyclopropane ring stabilizes the diradical form disfavouring the annu-

lation.




When the mixture of **14** is heated in the same conditions, the indolizidinone **16** is obtained besides the isomer **17** (overall yield 70%) in 4.5:1 ratio. Only one diastereoisomer of **16** is obtained, with the depicted stereochemistry, assigned on the observation of a coupling (J=11 Hz) of the proton at 3.34 δ, in α to COOMe, with the adjacent bridgehead proton.

The application of this process to the synthesis of natural products is the object of further studies in our group.

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