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The Regioselectivity of Nitrone and Nitrile Oxide Cycloadditions to Alkylidenecyclopropanes

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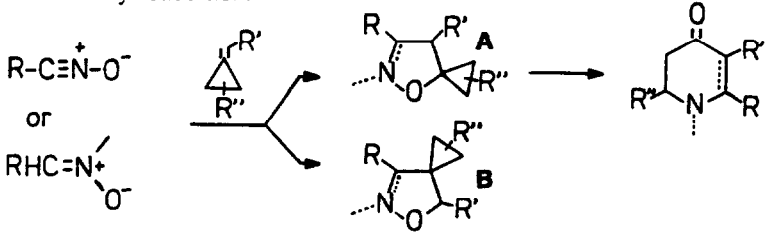
Abstract: *The 1,3-dipolar cycloaddition of nitrile oxides and a nitrone to alkylidencyclopropanes* **1-5**, *used as model for methylenecyclopropanes substituted with aryl group* (**1**), *electron-releasing groups* (**2** *and* **3**) *and electron-attracting groups* (**4** *and* **5**) *is reported. The cycloaddition to alkylidenecyclopropanes* **1-3** *gives prevalently or exclusively adducts bearing the cyclopropane ring on the C4 position of the isoxazoline (isoxazol idine) ring, whereas methoxycarbonyl substituted methylenecyclopropanes* **4** *and* **5** *give adducts with the opposite regiochemistry. The high regioselectivity observed in the case of dialkyl substituted methylenecyclopropanes raises the question of the role played by the cyclopropylidene ring in these cycloadditions. A FMO approach based both on semiempirical and ab initio calculations is unable to explain this "cyclopropylidene effect".*

The rearrangement of isoxazoline-[1] or isoxazolidine-[2,3]5-spirocyclopropanes has shown its potential as a new method for the synthesis of azaheterocycles. Particularly interesting appears to be the new access to N-bridgehead bicyclic structures widespread in natural alkaloids.[2,3]

The selectivity of the process in the presence of various substituents on the reagents is a goal for a wider application of the method. Since the overall process consists of two steps, a cycloaddition of a nitrile oxide or of a nitrone to a methylenecyclopropane derivative followed by a thermal rearrangement (Scheme 1), the substituents either on the 1,3-dipole or on the methylenecyclopropane may affect the process. In particular, the substitution on the cyclopropane ring (R", Scheme 1) is more likely to affect the rearrangement, whereas the substitution on the exocyclic double bond of the methylenecyclopropane (R', Scheme 1) affects the cycloaddition.

Scheme 1

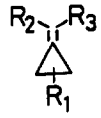


Unsubstituted or ring substituted methylenecyclopropanes have been shown[1,2] to react with nitrile oxides and nitrones to give mixtures of regioisomers **A** and **B**. The 4-spiro regioisomers **B** only account for roughly 5% of the reaction mixture from nitrile oxides but their formation can efficiently compete with that of the 5-spiro derivatives **A** in the reaction of nitrones; up to 37% (relative yield)[2] of the "anomalous"[4] 4-spiro derivative was isolated.

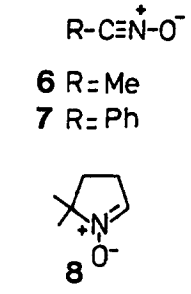
A substituent on the exocyclic double bond of methylenecyclopropanes should give rise to a significant change in the polarization of that bond. The study reported in this paper was carried out with the aim of establishing the influence of substituents on regioselectivity by using different alkylidenecyclopropanes. Moreover, these dipolarophiles lent themselves as appropriate substrates in order to confirm or to disprove the peculiar effect of the cyclopropylidene moiety on the regiochemical outcome.

RESULTS

Chart 1



1 $R_1=R_2=H$ $R_3=Ph$
2 $R_1=H$ $R_2=Me$ $R_3=Ph$
3 $R_1=R_2=H$ $R_3=$
4 $R_1=R_2=COOMe$ $R_3=H$
5 $R_1=R_2=H$ $R_3=COOMe$

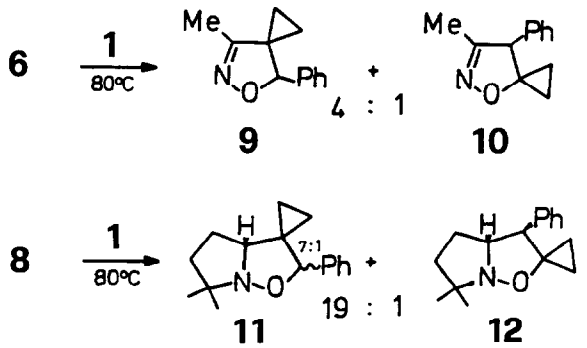


6 R = Me
7 R = Ph

8

Alkylidenecyclopropanes **1-5** were used as model for methylenecyclopropanes substituted with aryl groups (**1**), electron-releasing groups (**2** and **3**) and electron-attracting groups (**4** and **5**). Acetonitrile oxide (**6**) and 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole 1-oxide (DMPO, **8**) were taken as model 1,3-dipoles.[8]

Scheme 2

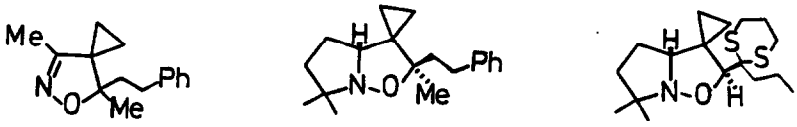


The cycloaddition of **1** with acetonitrile oxide (**6**), took place in refluxing benzene to give 50% of a mixture of regioisomeric isoxazolines, i.e. **9** and **10**, in 4:1 ratio (Scheme 2).[8a] A higher regioselectivity was observed in the reaction of nitrone **8** with **1** to give 61% of **11** and **12** (19:1)(Scheme 2).[8b]

The assignment of the regiochemistry in isoxazolines and isoxazolidines was unequivocally made on the basis of diagnostic ^1H and ^{13}C NMR data of isoxazoline ring 4 and 5 positions.

Benzylic protons in compounds **9** (δ 5.35 ppm) and **11a,b** (δ 5.10 and δ 4.96 ppm) (Scheme 2) were found sensibly downfield with respect to those of the minor isomers **10** (δ 4.00 ppm) and **12** (δ 3.46 ppm). This proton in **12** shows also a coupling constant (J = 3.7 Hz) with the 3-H (isoxazolidine numbering) proton further confirming the assigned regiochemistry.

Scheme 3

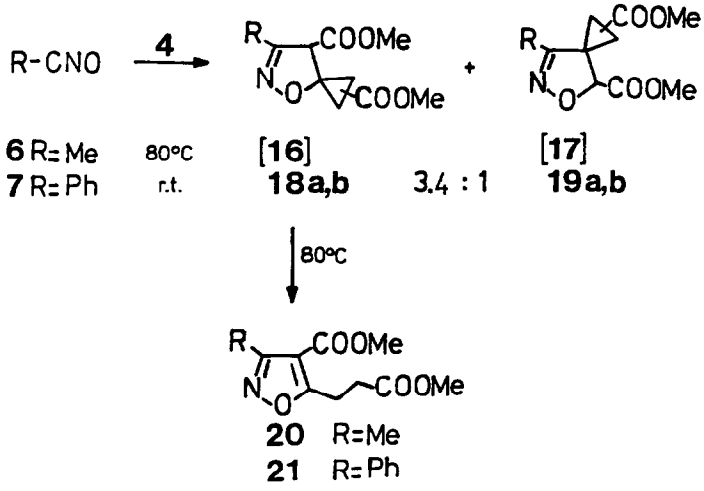


13 **14** **15**

The presence of electron-releasing alkyl substituents, as in **2** or **3**, led to a regiospecific formation of isoxazolidine-4-spirocyclopropanes **14** (90%) and **15** (38%), respectively, in the reaction with nitrone **8** (Scheme 3).[8b] Disappointingly, no adducts could be isolated from the reaction of the nitrile oxide **6** with **3** but 65% of isoxazoline-4-spirocyclopropane **13**, as the only detected product, were obtained from the reaction of **6** with **2** (Scheme 3).

The assignment of the regiochemistry in isoxazoline **13** and isoxazolidine **14** lacking diagnostic protons on the 5-C carbon (isoxazoline numbering), was made unambiguously by the observation of the ^{13}C NMR resonances in the two compounds. Their 5-C resonances lie at lower fields (δ 84.2 and 80.12 ppm for **13** and **14**, respectively) and are roughly 15 ppm higher than those of 5-spirocyclopropane compounds. On the other hand, 4-C resonances (δ 38.3 and 38.96 ppm for **13** and **14**, respectively) attest to the shielding effect of a spiro-fused cyclopropane ring.

Scheme 4

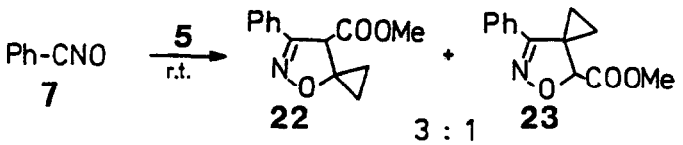


A reversal of regioselectivity was observed in the reactions of methoxycarbonyl substituted methylenecyclopropanes **4** and **5** with nitrile oxides **6** and **7** and nitrone **8**. The isoxazole **20** was the only isolated product from the reaction of acetonitrile oxide (**6**) with **4** (Scheme 4). The primary adduct **16** underwent a cyclopropane ring cleavage followed by a 1,4-hydrogen shift to give **20** (refluxing benzene, see Experimental). In fact, when benzonitrile oxide (**7**) was allowed to react at room temperature with

the same methylenecyclopropane **4** a mixture of the four possible isomeric isoxazolidines, i.e. **18a,b** and **19a,b**, was formed although in low yield (15%; **18**:**19** = 3.4) (Scheme 4). By running this latter reaction in refluxing benzene only the isoxazolines **18a,b** along with some isoxazole **21** (overall yield 48%) could be isolated. Prolonged heating of a solution of **18a,b** in benzene brought aboutcomplete rearrangement to **21**, thus unambiguously establishing the origin of **21** as well as, by analogy, that of **20**. Moreover, the absence of the regioisomers **19a,b** in the reaction at 80°C suggested that these compounds (as well as **17a,b**) enter a decomposition process which does not result in any characterizable product.

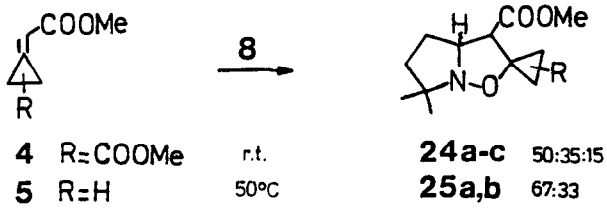
A very similar regioisomeric ratio in favour of the 4-methoxycarbonyl substituted isoxazoline was obtained in the cycloaddition of **7** with methylenecyclopropane **5** (Scheme 5). Both regioisomers **22** (40%) and **23** (13%) showed relatively high stability under thermal or basic conditions. The presence of an electron-withdrawing group on the cyclopropane ring is, therefore, assumed to promote rearrangements or decomposition showed by compounds **16-19**. Compounds **18, 19** and **22, 23** showed the same ^{1}H NMR trend for 4-H and 5-H protons that allowed the assignment of the regiochemistry. Signals for 5-spirocyclopropane regioisomers (δ 4.55 and 4.59 ppm for **18a,b**; δ 4.22 ppm for **22**) were sensibly more upfield than those of their regioisomer (δ 5.18 and 5.15 ppm for **19a,b**; δ 4.93 ppm for **23**)

Scheme 5



The nitrone **8** gave higher regioselective cycloadditions with the same methylenecyclopropanes **4** and **5**. Three of the four possible 5-spirocyclopropane adducts (**24a-c**, 50%) were the only isolated compounds from cycloaddition with **4** (Scheme 6). With methoxycarbonylmethylenecyclopropane **5**, nitrone **8** gave the two 5-spirocyclopropane isoxazolidines **25a** and **25b** in 2:1 ratio and 65% yield (Scheme 6).

Scheme 6

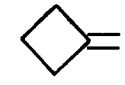


The major isomer **25a** in Scheme 6 showed a doublet at δ 3.21 ppm (J = 4 Hz) for the 4-H proton (isoxazolidine numbering) and the minor **25b** a doublet at 3.74 δ with a coupling constant of 7.5 Hz. As J_{cis} between 3-H and 4-H protons in isoxazolidines are, as a rule, larger than J_{trans} the observed coupling constants strongly suggest that the transition state leading to the major compound **25a** features an *exo* approach of the reactants.

DISCUSSION

The experimental findings reported above as well as earlier data quoted in the introduction clearly disclose a peculiar effect of a cyclopropylidene system both on reaction rates and regioselectivity. Actually, the parent methylenecyclopropane (**26**) as well as its derivatives, **1-5**, exhibit a high reactivity in 1,3-dipolar cycloadditions with nitrones and nitrile oxides. In contrast the related open chain isobutene and its derivatives are well known to enter 1,3-dipolar cycloadditions sluggishly.[5,6,7] For example there is no hope to obtain a cycloadduct from **8** and an open chain trialkyl and tetraalkylethylene as was obtained in the reaction of **8** with **2** and **3**.

26



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As for the regioselectivity of the reaction of **26** and its alkyl or aryl derivatives with nitrones, a tendency of the three-membered ring to end up at the 4 position of the final isoxazolidine ring clearly emerges from the new and previous experimental findings. Thus, for example, the "anomalous" isoxazolidine-4-spirocyclopropane accounts for 30%, 35% and 37% of the regioisomeric mixtures from the reaction of C-phenyl-N-methylnitrone,[2] **8**[2], and 6,7-dimethoxy-3,4-dihydroisoquinoline-N-oxide,[2] respectively, with **26**. This result is particularly noteworthy if compared to regiospecific formation of the 5,5-disubstituted isoxazolidines in the reactions of nitrones not only with open chain 1,1-disubstituted ethylenes but also with methylenecylobutane (**27**).[6,9] Moreover, regiospecificity of the reaction of **8** with **2** and **3** (Scheme 3), respectively, with formation of a 4-spirocyclopropane derivative clearly reflects the different effect of the three-membered ring moiety as compared to open chain alkyl substituents. To avoid an improper bias in this discussion it must be added that steric effects play a role in promoting regiospecificity, in particular in the case of **2**. A cyclopropylidene moiety certainly exhibits a lower steric requirement than an isopropylidene system; consequently, compound **14** is sterically less congested than its regioisomer and it is quite reasonable to assume that also the transition state leading to it is less crowded than the one leading to its regioisomer. However, the whole of regiochemical data of the reactions of nitrones with **26** and its alkyl and aryl derivatives seems to suggest that there is an inherent "electronic" effect in methylenecyclopropanes which promotes formation of the 4-spiro regioisomer. This tendency is somewhat tempered in the reaction of nitrile oxides as shown by the reactions of **6** with **1** (Scheme 2) and of **6** and **7** with **26** ($\leq$ 5% of the 4-spiro regioisomer are obtained).[1] However, it should be stressed that mono and 1,1-dialkylethylenes as well as **27** react with nitrile oxides to give only the 5-substituted isoxazoline and a trisubstituted olefin gives rise to a 4,5,5-trisubstituted isoxazoline.[7,9]

The regiochemical data of the reactions of nitrone **8** and nitrile oxides **6** and **7** with methoxycarbonyl derivatives **4** and **5** (Schemes 4, 5 and 6) are less clear-cut. In fact, while the $\approx$ 25% relative yield of 4-spirocyclopropane regioisomers **19** and **23** seem to testify that the "cyclopropylidene effect" is at work also in these dipolarophiles, this effect seems to disappear in the reactions of nitrone **8** with **4** and **5** (Scheme 6). The observed regiochemistry in this latter reaction is the same as that observed in the reactions of the related methyl 3,3-dimethylacrylate with nitrones[10] (and nitrile oxides),[7] that is

regiospecific formation of the 4-methoxycarbonyl adduct. This was unexpected since nitrone **8** reacts with methyl acrylate to give less than 5% of the 4-methoxycarbonyl isoxazolidine[11] (far less than the 35% 4-spiro regioisomer obtained in the reaction with methylenecyclopropane). Thus, when methoxycarbonyl and cyclopropylidene groups compete with each other on the same double bond the regiochemical outcome cannot be predicted on the basis of the sum of their effects when they act independently on a double bond.

Is it possible to adequately explain the behaviour of methylenecyclopropane and its derivatives in the context of the most simple PMO approach, i.e. the FMO approach?[12,13] It is well known that angle strain in a dipolarophile can affect its reactivity[14] and that this effect is not properly accounted for by PMO approach.[13] It has been observed that a decrease in angle strain on going from educts to adducts induces an increase in reaction rate.[14] Consequently, the higher reactivity of methylenecyclopropane compared with 1,1-dialkylethylenes may well simply reflect a decrease in angle strain of the cyclopropylidene system along the reaction coordinate and there is no cogent need to look for additional effects. However, the effect of angle strain on regioselectivity is not a common observation, at least as far as we know.

Consequently we carried out MO calculations both at the semiempirical (C-INDO[15] and MNDO[16]) and *ab initio* level (STO-3G)[17] in order to investigate whether or not there is some characteristic feature of the MOs of methylenecyclopropane which could open the way to an explanation of the regiochemistry of the reactions of this dipolarophile and its derivatives.

Disappointingly, MO calculations (at least at this level of theory) fail to differentiate the effect of a cyclopropylidene system from that of alkyl substituents, and therefore, to rationalize the experimental results.[18] In fact, all these calculations show that polarization of HOMO and LUMO in methylenecyclopropane is very similar to that in methylenecyclobutane and isobutylene. Moreover, alkylidenecyclopropanes exhibit a substantially unpolarized double bond in striking contrast with experimental data.[19]

EXPERIMENTAL

All the reactions were carried out under inert atmosphere (N_2) and the solvents were appropriately dried before the use. The R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}) obtained using the same eluant as in the column chromatographies. Melting points of **11a**, **14** and **22** were observed with a microscope RCH Kofler apparatus; all other compounds were oils. NMR spectra ($CDCl_3$ as solvent) were recorded on a Perkin Elmer R-32 (^1H, 90 MHz) and on a Varian Gemini (^1H, 200 MHz), and Varian FT-80A (^{13}C, 20 MHz) spectrometers. Chemical shift values are reported in ppm from tetramethylsilane: notation s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. The coupling constants J are given in Hz. IR spectra (in CCl_4 solution, unless otherwise stated) were recorded on Perkin-Elmer 283 or Perkin-Elmer 881 spectrophotometer. Mass spectra were recorded at 70 eV by GC inlet on a 5790A-5970A Hewlett-Packard instrument. Combustion analyses were carried out with a Perkin-Elmer 240 C elemental analyzer.

(3-Cyclopropylidenebutyl)benzene (**2**) [MS: m/e (rel intensity) 157 ($M^{\cdot+}$-15, 14), 143 (15), 130 (13), 129 (21), 104 (13), 91 (100), 65 (21), 51 (10). ^1H NMR: δ 7.40- 7.10 (m, 5H), 2.90-2.63 (m, 2H), 2.53-2.23

(m, 2H), 1.87-1.70 (m, 3H), 0.93-0.77 (m, 4H)] and 2-cyclopropylidenemethyl-2-propyl-1,3-dithiane (**3**) [MS: m/e (rel intensity) 214 ($M^{\cdot+}$, 15), 185 (22), 172 (17), 171 (63), 153 (14), 140 (39), 139 (100), 125 (27), 111 (85), 106 (44), 97 (76), 77 (43). ^{1}H NMR: δ 6.10-5.91 (m, 1H), 3.10-2.85 (m, 4H), 2.36-0.76 (m, 14H)] were synthesized according to reference 20 from 4-phenylbutan-2-one and 2-formyl-2-propyl-1,3-dithiane respectively. 1-Cyclopropylidenemethyl-benzene (**1**),[20] methoxycarbonylmethylene-2-methoxycarbonylcyclopropane (**4**),[21] and methoxycarbonylmethylenecyclopropane (**5**),[22] were prepared according to the literature.

Cycloaddition of Nitrile oxide **6** *to Methylenecyclopropane* **1**

A solution of nitroethane (337 mg, 4.5 mmol) and NEt_3 (7 mg, 10mL) in 2 mL of anhydrous benzene was added in small portions (0.2 mL) during 6 h to a refluxing solution of PhNCO (1.013 g, 8.5 mmol) and 1-cyclopropylidenemethyl-benzene (**1**) (390 mg, 3 mmol) in 20 mL of anhydrous benzene. After further refluxing for 2 h the reaction mixture was diluted with diethyl ether, filtered and concentrated. Monitoring of the crude mixture by GC-MS showed the presence of two isomers in 4:1 ratio. Purification of the oily residue by flash chromatography (eluant petroleum ether-ethyl acetate 4:1) gave two fractions. The first, Rf = 0.41, contained compound **9** (215 mg, 38%); the second, Rf = 0.17, contained compound **10** (69 mg, 12%).

4-Methyl-7-phenyl-6-oxa-5-azaspiro[2.4]hept-4-ene (**9**): Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48%. Found: C, 76.59;H, 6.89; N, 7.72%. MS: m/e (rel intensity) 187 ($M^{\cdot+}$, 12), 159 (100), 130 (35), 128 (31), 115 (24), 105 (82), 91 (18), 90 (14), 77 (50). ^{1}H NMR: δ 7.56-7.07 (m, 5H), 5.35 (s, 1H), 1.81 (s, 3H), 1.36-0.57 (m, 4H). ^{13}C NMR: δ 158.58 (s), 138.39 (s), 128.35 (d, 2C), 128.17 (d, 2C), 126.70 (d), 86.01 (d), 37.34 (d), 10.37 (t), 9.60 (t), 8.65 (q). IR: 3090, 3070, 3050, 3010, 2960, 2940, 2870, 1620, 1600, 1525, 1500, 1445, 1395, 1225, 1180, 1020 cm^{-1}.

6-Methyl-7-phenyl-4-oxa-5-azaspiro[2.4]hept-5-ene (**10**): MS: m/e (rel intensity) 186 ($M^{\cdot+}$-1, 1), 159 (8), 130 (14), 118 (100), 91 (12), 90 (75), 89 (37), 63 (14). ^{1}H NMR: δ 7.76-7.13 (m, 5H), 4.00 (s, 1H), 1.82 (s, 3H), 1.43-0.67 (m, 4H).

Cycloaddition of DMPO (**8**) *to Methylenecyclopropane* **1**

A solution of DMPO (**8**) (850 mg, 7.5 mmol) and **1** (815 mg, 6.3 mmol) in 10 mL of benzene was heated at reflux 15 h. The crude mixture was separated by flash chromatography (eluant petroleum ether-ethyl acetate 70:30) giving a fraction at Rf = 0.39 with compounds **11a** and **11b** (7:1 ratio, 887 mg, 58%) and a second fraction, Rf = 0.16, with compound **12** (48 mg, 3%).

Hexahydro-6',6'-dimethyl-2-phenyl- spiro[cyclopropane-1,3'-pyrrolo[1,2-b]isoxazole] (**11a,b**): Anal. of the mixture of isomers **11a,b**, Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76%. Found: C, 78.58; H, 8.46; N, 5.52%. MS: m/e (rel intensity) 243 ($M^{\cdot+}$, 15), 228 (37), 157 (64), 152 (37), 141 (22), 138 (23), 129 (100), 128 (51), 115 (62), 114 (73), 91 (54), 77 (61). IR: 3080, 3040, 3000, 2980, 2960, 2880, 1500, 1470, 1430, 1390, 1370, 1035, 1020 cm-1. **11a**: m.p. = 57-59 °C; ^{1}H NMR: δ 7.50-7.20 (m, 5H), 5.10 (s, 1H), 3.70-3.47 (m, 1H), 2.30-1.60 (m, 4H), 1.43 (s, 3H), 1.10 (s, 3H), 0.80-0.30 (m, 4H). ^{13}C NMR: δ 137.12 (s), 127.81 (d, 2C), 127.55 (d), 126.96 (d, 2C), 82.12 (d), 72.38 (d), 69.57 (s), 36.56 (s), 36.39 (t), 30.40 (t), 26.69 (q), 23.79 (q), 11.01 (t), 2.48 (t). **11b**: ^{1}H NMR: δ 7.50- 7.20 (m, 5H), 4.96 (s, 1H), 3.70-3.47 (m, 1H), 2.30-1.60 (m, 4H), 1.43 (s, 3H), 1.10 (s, 3H), 0.80-0.30 (m, 4H). ^{13}C NMR: δ 137.85 (s), 128.04 (d, 2C), 127.69 (d), 127.13 (d, 2C), 84.17 (d), 72.17 (d), 68.32 (s), 36.82 (s), 35.49 (t), 30.40 (t), 26.69 (q), 23.79 (q), 11.22 (t), 8.95 (t).

Hexahydro-6',6'-dimethyl-3-phenylspiro[cyclopropane-1,2'-pyrrolo[1,2-b]isoxazole] (**12**): MS: m/e (rel intensity) 243 ($M^{\cdot+}$, 16), 228 (25), 186 (21), 172 (56), 157 (41), 146 (12), 129 (100), 118 (71), 115

(41), 104 (56), 96 (45), 91 (61), 77 (23), 55 (58). ^{1}H NMR: δ 7.70-7.10 (m, 5H), 4.16-4.03 (m, 1H), 3.46 (d, J = 3.7 Hz, 1H), 2.37-1.52 (m, 4H), 1.36 (s, 3H), 1.11 (s, 3H), 1.11-0.71 (m, 2H), 0.62-0.52 (m, 1H), 0.30-0.20 (m, 1H). ^{13}C NMR: δ 140.00 (s), 128.35 (d, 2C), 128.30 (d, 2C), 126.78 (d), 73.50 (d), 68.29 (s), 67.26 (s), 60.67 (d), 35.74 (t), 32.42 (t), 26.27 (q), 23.87 (q), 9.34 (t), 8.36 (t).

Cycloaddition of Nitrile oxide **6** *to Methylenecyclopropane* **2**

A solution of nitroethane (671 mg, 9 mmol) and NEt_3 (22 mg, 30 mL) in 2 mL of anhydrous toluene was added in small portions (0.2 mL) during 6 h to a refluxing solution of PhNCO (1.388 g, 13.5 mmol) and **2** (345 mg, 3.7 mmol) in 10 mL of anhydrous toluene. After further refluxing for 2 h the reaction mixture was cooled, added of 10 mL of NH_4Cl (1 M) and stirred for 10 min. The mixture was partitioned between diethyl ether and water and organic layer washed and concentrated. The residue, purified by chromatography (eluant petroleum ether-ethyl acetate 75:25), afforded compound **13** (551 mg, 65%).

4,7-Dimethyl-7-(2-phenylethyl)-6-oxa-5-azaspiro[2.4]hept-4-ene (**13**): Anal. Calcd for $C_{15}H_{19}NO$: C, 78.53; H, 8.35; N, 6.11%. Found: C, 78.21; H, 8.37; N, 6.51%. MS: m/e (rel intensity) 229 ($M^{\cdot+}$, 2), 214 (3), 186 (8), 124 (100), 110 (20), 105 (13), 91 (25), 82 (30), 77 (9). ^{1}H NMR: δ 7.35-7.05 (m, 5H), 2.90-2.63 (m, 2H), 1.85-1.55 (m, 5H), 1.36-1.15 (m, 3H), 0.97-0.80 (m, 4H). ^{13}C NMR: δ 158.7 (s), 142.0 (s), 128.1 (d, 4C), 125.5 (d), 84.2 (s), 40.9 (t), 38.3 (s), 29.6 (t), 23.3 (q), 8.8 (q), 7.5 (t), 7.1 (t). IR (CDCl3): 3100, 2980, 2940, 2875, 1495, 1455, 1440, 1390, 1380, 1350, 1150, 1120 cm^{-1}.

Cycloaddition of DMPO (**8**) *to Methylenecyclopropane* **2**

A solution of DMPO (**8**) (280 mg, 2.5 mmol) and **1** (344 mg, 2 mmol) in 5 mL of toluene was heated at reflux 13 h. The crude mixture was separated by flash chromatography (eluant petroleum ether-ethyl acetate 80:20) to give the compound **14** (Rf = 0.36, 514 mg, 90%).

Hexahydro-2'(2-phenylethyl)-2',6',6'-trimethyl-spiro[cyclopropane-1,3'-pyrrolo [1,2-b]isoxazole] (**14**): m.p. = 62-63 °C (EtOH-H_2O); Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91%. Found: C, 80.32; H, 9.45; N, 5.00%. MS: m/e (rel intensity) 285 ($M^{\cdot+}$, 9), 270 (10), 180 (5), 166 (11), 138 (10), 114 (100), 105 (11), 91 (59), 77 (4), 65 (11), 55 (16). ^{1}H NMR: δ 7.40-7.16 (m, 5H), 3.42-3.20 (m, 1H), 2.88-2.60 (m, 2H), 2.10-1.46 (m, 6H), 1.41 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H), 0.81-0.60 (m, 4H). ^{13}C NMR: δ 142.88 (s), 128.21 (d, 2C), 128.17 (d, 2C), 125.51 (d), 80.12 (s), 73.36 (d), 68.48 (s), 41.22 (t), 38.96 (s), 35.46 (t), 30.08 (t), 29.56 (t), 26.52 (q), 24.90 (q), 23.96 (q), 11.79 (t), 7.94 (t). IR ($CDCl_3$): 3080, 3030, 2970, 2940, 2770, 1600, 1490, 1450, 1370, 1185, 1125 cm^{-1}.

Cycloaddition of DMPO (**8**) *to Methylenecyclopropane* **3**

A solution of DMPO (**8**) (147 mg, 1.3 mmol) and **3** (214 mg, 1 mmol) in 5 mL of toluene was heated at reflux 45 h. The crude mixture was separated by flash chromatography (eluant petroleum ether-ethyl acetate 75:25) to give **15** (Rf = 0.50, 125 mg, 38%).

Hexahydro- 6',6'-dimethyl-2' (2-propyl-1,3-dithian-2-yl)-spiro [cyclopropane- 1,3'-pyrrolo [1,2-b]isoxazole] (**15**): Anal. Calcd for $C_{17}H_{29}NOS_2$: C, 62.34; H, 8.92; N, 4.28%. Found: C, 62.38; H, 8.87; N, 4.46%. ^{1}H NMR: δ 4.50 (s, 1H), 3.56-3.40 (m, 1H), 3.20-2.98 (m, 2H), 2.90-2.70 (m, 2H), 2.20-1.50 (m, 10H), 1.38 (s, 3H), 1.10 (s, 3H), 0.97 (t, 3H), 0.95-0.65 (m, 4H). ^{13}C NMR: δ 82.82 (d), 73.42 (d), 68.50 (s), 55.88 (s), 38.10 (t), 35.89 (t), 32.25 (s), 28.62 (t), 27.38 (q), 26.54 (t), 26.25 (t), 24.68 (t), 23.93 (q), 17.87 (t), 14.37 (q), 12.23 (t), 8.25 (t). IR ($CDCl_3$): 2970, 2940, 2880, 1565, 1450, 1380, 1275 cm^{-1}.

Cycloaddition of Nitrile oxide **6** *to Methylenecyclopropane* **4**

A solution of nitroethane (810 mg, 10.8 mmol) and NEt_3 (7mg, 10 mL) in 1.5 mL of anhydrous benzene

was added in small portions (0.2 mL) during 6 h to a refluxing solution of PhNCO (1.925 g, 16.2 mmol) and **4** (923 mg, 5.4 mmol) in 10 mL of anhydrous benzene. After further refluxing for 2 h the reaction mixture was diluted with diethyl ether, filtered and concentrated. Purification of the oily residue by flash chromatography (eluant petroleum ether-ethyl acetate 3:1) afforded compound **20** (557 mg, 45%).

5-(2-Methoxycarbonylethyl)-4-methoxycarbonyl-3-methylisoxazole (**20**): Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16%. Found: C, 53.20; H, 6.06; N, 6.16%. MS: m/e (rel intensity) 227 ($M^{\cdot+}$, 3), 196 (21), 195 (27), 168 (17), 167 (100), 136 (56), 115 (11), 82 (16), 81 (11), 59 (36), 55 (66). ^{1}H NMR: δ 3.92 (s, 3H), 3.75 (s, 3H), 3.43 (t, J = 7.5 Hz, 2H), 2.80 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR: δ 176.13 (s), 171.65 (s), 162.19 (s), 159.60 (s), 108.26 (s, $^3J_{CH}$ = 2Hz), 51.57 (q), 51.23 (q), 30.32 (t), 22.54 (t), 11.34 (t). IR ($CDCl_3$): 3000, 2940, 1730 vs broad, 1610, 1460, 1437, 1420, 1377, 1365, 1290, 1190, 1100 cm^{-1}.

Cycloaddition of Benzonitrile oxide (**7**) *to Methylenecyclopropane* **4**

A solution of methylenecyclopropane **4** (880 mg, 5.1 mmol) in 1 mL of benzene was added to a benzene solution (5 mL) of benzonitrile oxide (**7**) [prepared according to ref. 23 from 2.3 g (15 mmol) of benzohydroximoyl chloride]. The resulting mixture was stirred at room temperature for 24 h. Purification of the mixture by flash column chromatography afforded a mixture of two diastereomeric 5-spirocyclopropane regioisomers **18** in 12% yield and two diastereomeric 4-spirocyclopropane regioisomers **19** in 3.5% yield.

1,7-Dimethoxycarbonyl-6-phenyl-4-oxa-5-azaspiro[2.4]hept-5-ene (**18**). MS: m/e (rel intensity) 289 ($M^{\cdot+}$, 1.5), 257 (30), 229 (40), 202 (16), 198 (57), 188 (13), 170 (29), 144 (100), 130 (24), 103 (27), 77 (64). **18a**: ^{1}H NMR: δ 7.95- 7.75 (m, 2H), 7.60-7.30 (m, 3H), 4.55 (s, 1H), 3.67 (s, 3H), 3.58 (s, 3H), 2.60 (dd, J = 7, 12 Hz, 1H), 1.90-1.15 (m, 2H); ^{13}C NMR: δ 171.39 (s), 167.76 (s), 154.76 (s), 130.53 (d), 128.60 (d, 2C), 127.87 (d, 2C), 126.53 (s), 73.55 (s), 55.16 (d), 52.32 (q), 51.87 (q), 22.45 (d), 21.53 (t). **18b**: ^{1}H NMR: δ 7.75-7.30 (m, 5H), 4.59 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.35 (dd, J = 7, 12 Hz, 1H), 1.90-1.15 (m, 2H). ^{13}C NMR: δ 170.34 (s), 168.12 (s), 155.48 (s), 130.51 (d), 128.64 (d, 2C), 126.69 (d, 2C), 126.32 (s), 74.63 (s), 55.11 (d), 52.53 (q), 51.78 (q), 26.27 (d), 14.75 (t).

1,7-Dimethoxycarbonyl-4-phenyl-6-oxa-5-azaspiro[2.4]hept-5-ene (**19**). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84%. Found: C, 62.17; H, 5.38; N, 5.32%. **19a**: MS: m/e (rel intensity) 289 ($M^{\cdot+}$, 2), 258 (13), 230 (18), 188 (100), 170 (23), 134 (10), 128 (11), 77 (39). ^{1}H NMR: δ 7.42 (m, 5H), 5.18 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.60- 2.40 (m, 1H), 2.15-1.30 (m, 2H). ^{13}C NMR: d 169.99 (s), 169.08 (s), 158.06 (s), 130.23 (d), 128.76 (d, 2C), 127.91 (d, 2C), 127.64 (s), 78.92 (d), 52.24 (q, 2C), 42.71 (s), 24.15 (d), 13.82 (t). **19b**: MS: m/e (rel intensity) 289 ($M^{\cdot+}$, 3), 257 (13), 230 (86), 202 (59), 198 (26), 188 (20), 170 (100), 144 (36), 128 (30), 77 (87). ^{1}H NMR: δ 7.42 (m, 5H), 5.15 (s, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.60-2.40 (m, 1H), 2.15-1.30 (m, 2H). ^{13}C NMR: δ 171.42 (s), 168.39 (s), 159.34 (s), 130.18 (d), 128.76 (d, 2C), 127.91 (d, 2C), 127.64 (s), 82.51 (d), 52.47 (q, 2C), 40.33 (s), 23.04 (d), 18.80 (t).

A solution of methylenecyclopropane **4** (306 mg, 1.8 mmol) in 1 mL of benzene was added to a benzene solution (5 mL) of benzonitrile oxide (**7**) [prepared according to ref. 23 from 930 mg (6 mmol) of benzhydroximoyl chloride]. The resulting mixture was stirred at room temperature for 1 h than at reflux for 3 h. Purification of the crude mixture by flash column chromatography afforded a mixture of isomers **18a**, **18b** and isoxazole **21** in 2:1:1 ratio respectively with an overall yield of 37% which raises to 48% considering the recovery of methylenecyclopropane **4** (70 mg). Prolonged heating (4 h) of the mixture of isomers in benzene results in the complete rearrangement of the isomer **18b** to isoxazole **21**. For the

same rearrangement of isomer **18a** higher temperature are required (48 h in refluxing mesitylene, 163 °C).

5-(2-Methoxycarbonyl)-ethyl-4-methoxycarbonyl-3-phenylisoxazole (**21**): Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84%. Found: C, 61.95; H, 5.55; N, 5.03%. MS: m/e (rel intensity) 289 ($M^{\cdot+}$, 12), 257 (61), 229 (66), 202 (55), 198 (31), 171 (15), 143 (62), 115 (77), 103 (12), 77 (68), 55 (100). ^{1}H NMR: δ 7.50 (m, 5H), 3.83 (s, 3H), 3.77 (s, 3H), 3.52 (t, J = 7.6 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H). ^{13}C NMR: d 176.88 (s), 171.79 (s), 162.44 (s), 161.96 (s), 129.66 (d), 129.13 (d, 2C), 127.05 (d, 2C), 126.74 (s), 108.07 (s), 52.78 (q), 51.51 (q), 30.54 (t), 22.90 (t).

Cycloaddition of Benzonitrile oxide (**7**) *to Methylenecyclopropane* **5**

Triethylamine (253 mg, 2.5 mmol) was added during 4.5 h to a solution of benzohydroximoyl chloride (387 mg, 2.5 mmol) and methylenecyclopropane **5** (224 mg, 2 mmol) in 5 mL of dichloromethane and the resulting mixture stirred at room temperature for 17 h. The mixture was then washed with H_2O, dried and concentrated to give an oil that contained the two regioisomers **22** and **23** in 3:1 ratio (^{1}H NMR monitoring). Purification of the mixture by flash chromatography (eluant *n*-hexane-ethyl acetate 70:30) gave a fraction at $R_f = 0.38$ containing compound **22** (184 mg, 40%) and a second fraction at $R_f = 0.25$ with compound **23** (59 mg, 13%).

7-Methoxycarbonyl-6-phenyl-4-oxa-5-azaspiro[2.4]hept-5-ene (**22**): m.p. = 103-104 °C (dichloromethane-*n*- hexane). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06%. Found: C, 67.07; H, 5.62; N, 5.78%. MS: m/e (rel intensity) 231 ($M^{\cdot+}$, 5), 202 (14), 200 (22), 172 (69), 144 (100), 130 (63) 103 (44), 77 (81), 69 (60). ^{1}H NMR: δ 7.71-7.63 (m, 2H), 7.44-7.35 (m, 3H), 4.22 (s, 1H), 3.70 (s, 3H), 1.41-1.19 (m, 2H), 1.12-1.02 (m, 1H), 0.89-0.77 (m, 1H). ^{13}C NMR: δ 168.9 (s), 154.7 (s), 130.3 (d), 128.6 (s), 128.8 (d, 2C), 126.4 (d, 2C), 69.6 (s), 56.7 (d), 52.7 (q), 15.3 (t), 7.4 (t). IR ($CDCl_3$): 3068, 3033, 3008, 2957, 1739, 1593, 1564, 1498, 1446, 1436, 1353, 1278, 1244 cm^{-1}.

4-Phenyl-7-methoxycarbonyl-6-oxa-5-azaspiro[2.4]hept-4-ene (**23**): MS: m/e (rel intensity) 231 ($M^{\cdot+}$, 11), 172 (100), 144 (16), 77 (44), 59 (10), 51 (20). ^{1}H NMR: δ 7.38 (m, 5H), 4.93 (s, 1H), 3.80 (s, 3H), 1.36-1.08 (m, 4H). ^{13}C NMR: δ 169.5 (s), 160.1 (s), 130.0 (d), 128.7 (d, 2C), 127.6 (d, 2C), 126.9 (s), 83.0 (d), 52.4 (q), 34.8 (s), 13.8 (t), 8.8 (t). IR ($CDCl_3$): 3065, 3011, 2956, 1735, 1643, 1444, 1438, 1291, 1202 cm^{-1}.

Cycloaddition of DMPO (**8**) *to Methylenecyclopropane* **4**

A solution of DMPO (**8**) (283 mg, 2.5 mmol) and **4** (425 mg, 2.5 mmol) in 5 mL of benzene was kept at room temperature for 90 h. GC-MS analysis of the crude mixture showed the presence of three isomers in 50:35:15 ratio. The crude mixture was purified without separation by elution on a short pad of silica gel (eluant diethyl ether) to give 351 mg (50% yield) of the three isomers **24a-c** as waxy solid.

Hexahydro-2,3'-dimethoxycarbonyl-6',6'-dimethylspiro[cyclopropane-1,2'-pyrrolo[1,2-b]isoxazole] (**24a,b,c**): Anal. of the mixture of three isomers. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94%. Found: C, 58.18; H, 7.58; N, 4.92%. MS m/e (rel intensity): (isomer a) 283 ($M^{\cdot+}$, 2), 268 (4), 224 (13), 196 (13), 154 (28), 122 (37), 110 (100), 96 (89); (isomer b) 283 ($M^{\cdot+}$, 3), 268 (8), 224 (23), 196 (22), 154 (33), 122 (47), 110 (100), 96 (87); (isomer c) 283 ($M^{\cdot+}$, 11), 268 (40), 224 (59), 196 (40), 164 (22), 154 (37), 122 (63), 110 (100), 96 (86). ^{1}H NMR (mixture of the three isomers): δ 3.98-3.61 (m, 6H), 3.60-3.20 (m, 2H), 3.34-3.26 (m, 4H), 2.54- 1.16 (m, 7H), 1.15- 1.03 (m, 2H). ^{13}C NMR: δ (isomer a) 171.95 (s), 170.92 (s), 69.92 (s), 68.89 (d), 68.43 (s), 56.54 (d), 51.80 (q), 51.63 (q), 36.22 (t) 31.06 (t), 26.30 (q), 24.09 (q), 21.53 (d), 19.16 (t); (isomer b) 172.26 (s), 171.00 (s), 70.57 (s), 69.55 (s), 67.54 (d), 53.88 (d), 52.01 (q), 51.63 (q), 36.33 (t) 30.64 (t), 26.10 (d), 25.96 (q), 23.99 (q), 15.09 (t); (isomer c) 171.80 (s),

171.12 (s), 70.97 (s), 68.17 (s), 67.15 (d), 53.88 (d), 52.19 (q), 51.54 (q), 35.86 (t) 30.10 (t), 27.19 (q), 23.32 (q), 21.97 (d), 21.85 (t). IR ($CDCl_3$) (mixture of the three isomers): 2980, 2950, 2840, 1740, 1620, 1440, 1380, 1370, 1260, 1250, 1230, 1200, 1167 cm^{-1}.

Cycloaddition of DMPO **(8)** *to Methylenecyclopropane* **5**

A solution of DMPO **(8)** (320 mg, 2.8 mmol) and **5** (250 mg, 2.2 mmol) in 3 mL of benzene was heated at 50 °C for 40 h. Analysis of the crude mixture by ^1H NMR showed the presence of two diastereoisomers in 2:1 ratio. Purification of the mixture by flash chromatography (eluant petroleum ether-ethyl acetate 70:30) gave fractions only enriched of the single diastereoisomers **25a** and **25b** (overall 310 mg, 63%).

Hexahydro-3'-methoxycarbonyl-6',6'-dimethylspiro[cyclopropane-1,2'-pyrrolo[1,2-b]isoxazole] **(25a)**: Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22%. Found: C, 63.64; H, 8.57; N, 6.07%. ^1H NMR: δ 4.33 (dt, J = 9.4, 4 Hz, 1H), 3.67 (s, 3H), 3.21 (d, J = 4 Hz, 1H), 2.36-2.13 (m, 1H), 2.03-1.85 (m, 1H), 1.78-1.50 (m, 2H), 1.27 (s, 3H), 1.06 (s, 3H), 1.10-0.55 (m, 4H). ^{13}C NMR: δ 171.79 (s), 68.42 (d), 68.37 (s), 63.79 (s), 59.34 (d), 52.36 (q), 35.94 (t), 32.36 (t), 26.50 (q), 24.12 (q), 10.40 (t), 8.56 (t). IR ($CDCl_3$): 2973, 2955, 2877, 1735, 1449, 1437, 1366, 1277, 1195, 1173 cm^{-1}. **25b**: Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22%. Found: C, 63.60; H, 8.50; N, 5.99%. ^1H NMR: δ 4.40-4.07 (m, 1H), 3.74 (d, J = 7.5 Hz, 1H), 3.66 (s, 3H), 2.08-1.65 (m, 4H), 1.26 (s, 3H), 1.06 (s, 3H), 1.10-0.85 (m, 3H) 0.75-0.57 (m, 1H). ^{13}C NMR: δ 170.91 (s), 67.51 (d), 68.23 (s), 62.48 (s), 54.28 (d), 51.57 (q), 35.99 (t), 27.63 (t), 26.60 (q), 23.91 (q), 10.84 (t), 8.23 (t). IR ($CDCl_3$): 2974, 2954, 2874, 1736, 1449, 1436, 1366, 1260, 1194, 1169 cm^{-1}.

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