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Intramolecular Cycloadditions and Thermal Rearrangement of Cyclopropylidene Nitrones. Straightforward Access to Bicyclic Tetrahydropyridones

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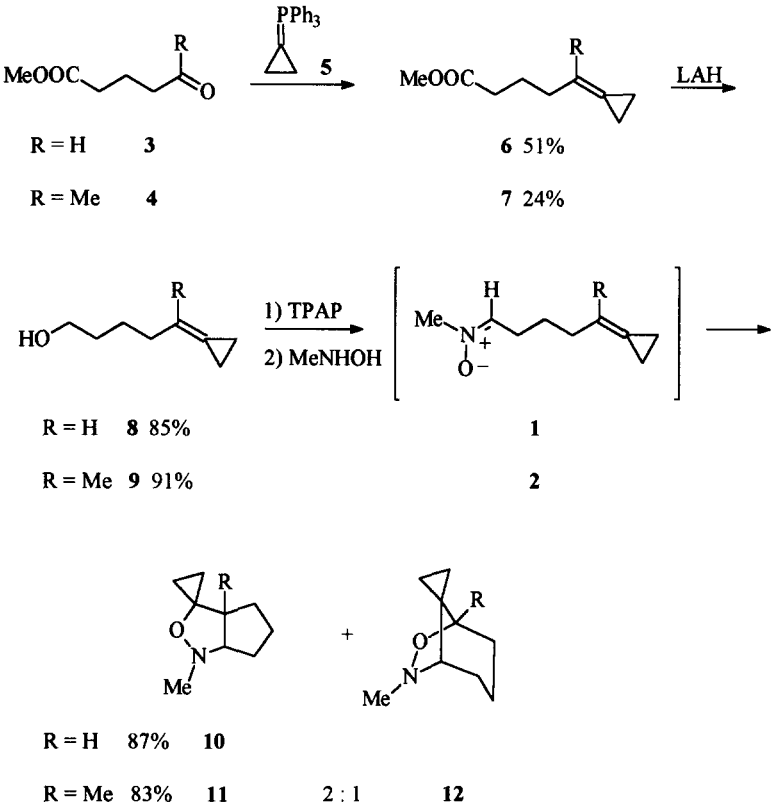
Abstract: *The intramolecular cycloaddition of cyclopropylidene nitrones (1 and 2) gives the "fused" adducts exclusively or predominantly over the "bridged" adduct (2:1). The "fused" adducts posses the cyclopropyloxy functionality which is prone to undergo a selective thermal rearrangement. The adducts* ***10*** *and* ***11*** *rearrange by heating in solution at 140°C and 160°C, respectively, to give the bicyclic tetrahydropyridones* ***13*** *and* ***14****.*

The strain release associated with the cleavage of a cyclopropane ring offers the possibility of many chemoselective manipulations of compounds containing this substructure.[1] The development of new reagents that incorporate a reactive cyclopropyl ring is therefore a goal for many useful synthetic applications. Recently, a new synthesis of nitrogen heterocycles with different ring skeletons using the thermal rearrangement of 5-spirocyclopropane isoxazolines or isoxazolidines has utilised this concept.[2] These substrates incorporating the cyclopropyl ring can be obtained by 1,3-dipolar cyloadditions of nitrile oxides and nitrones, respectively, to methylenecyclopropanes. Despite the general applicability of this methodology, a limitation is the use of alkylidenecyclopropanes as dipolarophiles to obtain 5-spirocyclopropane isoxazolines and isoxazolidines.[3] In these circumstances, only the thermally stable 4-spirocyclopropane adducts were obtained. This high regioselectivity of alkylidenecyclopropanes, unexpected if we compare them with tri- or tetrasubstituted olefins, suggested a "cyclopropylidene effect", that, however, could not be explained with an FMO approach based both on semiempirical and *ab initio* calculations.[3]

We now report on the synthesis of alkylidenecyclopropanes bearing a nitrone functionality on the side chain (**1** and **2**) which could enter the same cycloaddition-rearrangement protocol for the synthesis of azaheterocycles[2] through an intramolecular cycloaddition if a reversal of the regioselectivity occurs (Scheme 1).

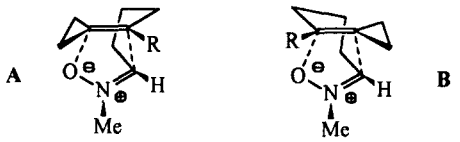
The cyclopropylidene esters **6**[4] and **7**[4] were obtained (Scheme 1) by a Wittig reaction with cyclopropylidenephosphorane **5**[5] and their reduction with lithium aluminum hydride gave the alcohols **8**[4] and **9**,[4] respectively. Oxidation of **8** and **9** to the respective aldehydes was carried out with PCC or TPAP,[6] but the second reagent gave the best results, particularly with the alcohol **9**. Both aldehydes proved to be very unstable, and were used without purification for the next reaction. Treatment of the aldehydes with methylhydroxylamine afforded solutions of the desired nitrones **1** and **2** that were used without purification for the cycloaddition reaction (Scheme 1).

Scheme 1



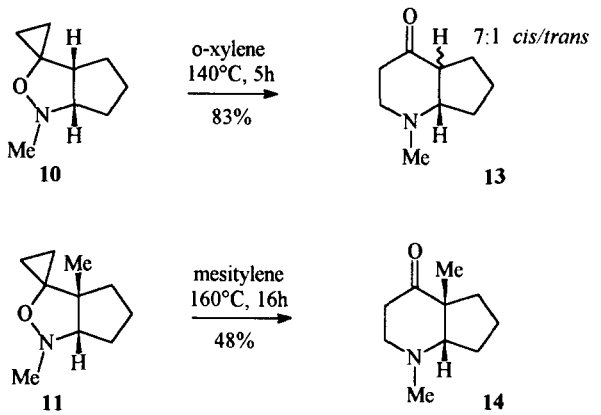
The nitrone **1** underwent intramolecular cycloaddition at room temperature, and the reaction was complete in one day affording only the "fused" cycloadduct **10**[4,7] in 89% overall yield for the three steps. The nitrone **2** underwent cycloaddition only at higher temperature. The reaction was completed after 2h in refluxing benzene and gave a mixture of the "fused" **11**[4,7] and "bridged" **12**[4,7] adducts (91%) in 2:1 ratio. The most diagnostic signals for the assignment of the structure to compounds **10**, **11** and **12** were the ^{13}C NMR resonances of quaternary carbons. Values of δ 65.7 ppm and δ 54.9 ppm for **10** and **11**, respectively, are in agreement for a shielded spiro C5 (isoxazolidine numbering) carbon. The corresponding C5 carbon (isoxazolidine numbering) in **12** resonates at δ 82.7 ppm.[7]

Scheme 2



The "fused" isomer appears to be the unique or the predominant isomer obtained in these intramolecular 1,3-dipolar cycloadditions, consistently with the literature.[8] In general, if compared with intermolecular cycloadditions, a reversal of regioselectivity is expected in intramolecular nitrone cyclodditions, because of the strain caused by the chain joining the reactive sites. In our case, this inversion of regioselectivity leads to the formation of 5-spirocyclopropane isoxazolidines, useful for further synthetic elaboration. The regioselectivity decreases on passing from nitrone **1** to **2** as expected.[8] This reduction has to be ascribed to steric effects, caused by the replacement of a proton with a methyl group on the dipolarophile moiety, which operates against "fused" product regiochemistry deriving from the transition state **A** (Scheme 2).[8b] Despite the methyl substituent (R = Me) the transition state **B** seems to be still disfavoured for the presence of the cyclopropyl ring. This allows the preferential formation of 5-spirocyclopropane isoxazolidines (2:1) also with substituted nitrone **2**, suggesting that the "cyclopropylidene effect"[3] does not exsist and only steric effects steer the regiochemistry of these inter- and intramolecular cycloadditions.

Scheme 3



The tricyclic isoxazolidines **10** and **11**, having the reactive cyclopropyloxy system frozen in the tricyclic structure, are able to undergo a thermal rearrangement upon cleavage of the N-O bond. The two compounds are relatively stable at prolonged heating in toluene, compared with other 2,3-disubstituted-5-spirocyclopropane isoxazolidines. By heating in xylenes at 140°C for 5h, a clean rearrangement of **10** occurs to afford the ketone **13**[4,9] in 83% yield (Scheme 3). Isoxazolidine **11** requires somewhat higher temperature and longer reaction time (160°C, 16h) to rearrange to ketone **14**[4,9] in 48% yield. Ketone **13** is isolated as a mixture of *cis* and *trans* fused isomers in 7:1 ratio. The

formation of the *trans* isomer is rationalised by the increased acidity of the 7a-H α to a carbonyl group in **13**. When a methyl group replaces the proton, like in **14**, only one isomer should be obtained, as, in fact, was observed. Assignment to the major isomer of the *cis* fusion cannot be made on the basis of the ^{1}H NMR spectrum, but follows considerations on the ring fusion of the starting isoxazolidine and the higher thermodynamic stability of a *cis*-fused 5-azahydrindan-8-one structure compared with a *trans*, as measured by molecular mechanics calculations.

We have, then, demonstrated that the process of cycloaddition to methylenecyclopropanes and thermal rearrangement of spirocyclopropane isoxazolidines can be utilised also in an intramolecular fashion, and can lead to interesting bicyclic tetrahydropyridones with high selectivity and atom economy. Further studies are in progress in our laboratory to apply this sequence to the synthesis of more complex structures.

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7. **10:** ^{1}H NMR: δ 3.51-3.41 (m, 1 H), 2.97-2.88 (m, 1 H), 2.73 (s, 3 H), 1.78-1.39 (m, 6 H), 1.03-0.55 (m, 4 H). ^{13}C NMR: δ 75.5 d, 65.7 s, 50.3 d, 45.47 q, 32.7 t, 30.2 t, 25.3 t, 11.9 t, 6.2 t. **11:** ^{1}H NMR: δ 2.90 (m, 1 H), 2.70 (s, 3 H), 1.92-1.40 (m, 6 H), 1.25-0.55 (m, 4 H), 1.13 (s, 3 H). ^{13}C NMR: δ 82.9 d, 54.9 s, 45.1 q, 38.1 s, 32.3 t, 32.2 t, 25.1 q, 23.4 t, 2.6 t, 1.3 t. **12:** ^{1}H NMR: δ 2.78 (s, 3 H), 2.66 (d, J = 3.7 Hz, 1 H), 1.85-1.31 (m, 6 H), 0.95-0.77 (m, 1 H), 0.92 (s, 3 H), 0.59 (m, 2 H), 0.24 (dt, J = 9.7; 2.4 Hz, 1 H). ^{13}C NMR: δ 82.7 s, 70.6 d, 47.4 q, 36.9 t, 33.4 s, 29.6 t, 19.7 q, 18.9 t, 11.1 t, 1.5 t.
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9. **13:** ^{1}H NMR: major isomer, δ 2.99-2.82 (m, 2H), 2.75-2.52 (m, 3H), 2.49-2.28 (m, 1H), 2.34 (s, 3H), 2.14-1.42 (m, 6 H); minor isomer (only discerned signals), δ 3.30-3.12 (m, 1H), 2.35 (s, 3H). ^{13}C NMR: major isomer, δ 211.7 s, 68.7 d, 53.3 t, 52.1 d, 43.4 q, 39.2 t, 30.5 t, 26.8 t, 22.9 t; minor isomer (C=O resonance not detected), δ 72.4 d, 57.8 t, 56.0 d, 42.7 q, 41.6 t, 31.0 t, 20.7 t, 19.5 t. **14:** ^{1}H NMR: δ 3.01-2.86 (m, 1H), 2.73-2.46 (m, 4H), 2.32 (s, 3H), 2.30-2.12 (m, 1H), 1.91-1.32 (m, 5H), 1.61 (s, 3H). ^{13}C NMR: δ 213.7 s, 75.3 d, 54.7 s, 52.7 t, 43.7 q, 37.9 t, 35.2 t, 28.5 t, 23.2 q, 21.4 t.

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