Nitrone and Nitrile Oxide Cycloadditions to Bicyclopropylidene. Rearrangement of the Isoxazolidine Adducts to 3-Spirocyclopropane-4-pyridone Derivatives

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The two-step nitrone or nitrile oxide cycloaddition–rearrangement thermal process applied to bicyclopropylidene gives 4-pyridone, 7-indolizinone, and 2-quinolizinone derivatives containing a spirocyclopropane linkage α to a carbonyl group.

The synthetic methodology based on nitrone or nitrile oxide cycloaddition to alkylidenecyclopropanes followed by thermal rearrangement of the resulting adducts has demonstrated its utility and versatility for the construction of structurally differentiated azaheterocycles,¹ including a number of alkaloids in racemic and non-racemic form.²

The choice of the methylenecyclopropane dipolarophile is strategic for the synthetic application of this methodology. In this connection, bicyclopropylidene 1 represents an excellent candidate for this reaction, as it should open up new useful synthetic pathways for the methodology.

Bicyclopropylidene 1³ is a strained tetra-substituted alkene, which has been demonstrated to possess a unique reactivity towards a wide range of electrophiles and cyclophiles.^{3e,4} It has, however, received only scarce attention as a dipolarophile in 1,3-dipolar cycloadditions,[†] probably because of the low reactivity ordinarily associated with tetra-substitution.⁵ Its high lying HOMO,⁶ however, should enable it to react with 1,3-dipoles and its symmetrical structure permits it to overcome all the problems of regiocontrol in the cycloaddition step, which are particularly severe in this methodology, especially with nitrones.^{1,2,7} Moreover, the additional cyclopropane ring as compared with methylenecyclopropane might serve as a powerful reactive site suitable for further elaboration on the final heterocycle.

We now report preliminary results on the cycloaddition reactions of three nitrones (including endocyclic derivatives) and two nitrile oxides to 1, and the thermal rearrangement of the adducts.

Nitrones 2 react thermally with bicyclopropylidene 1 to give high yields of the bis(spirocyclopropane)isoxazolidines 3 (Scheme 1), which contain two spirofused cyclopropane rings, at C-4 and C-5 of the isoxazolidine heterocycle. The reactivity of 1, in comparison with the methylenecyclopropane counterparts, is generally lower than expected (nitrone 2a reacts with 1 in 30 vs. 2 d).^{2a}



Scheme 1 Reagents and conditions: a: R = Ph, R' = Me i, benzene, 60 °C, 30 d; ii, toluene, 110 °C, 5 d b: $R-R' = -(CH_2)_2CMe_2-i$, benzene, r.t., 7 d; ii, benzene, 80 °C, 7 d c: $R-R' = -(CH_2)_4-i$, benzene, 60 °C, 7 d; ii, xylene, 120 °C, 7 d

The two spirocyclopropane rings on C-4 and C-5 (isoxazolidine numberings) behave differently upon heating, as observed for 5- and 4-spirocyclopropane isoxazolidines,^{1,2a} only the cyclopropane in the 5 position being involved in the following rearrangement, since it is adjacent to the labile N–O bond.

Prolonged heating of 1 mol dm⁻³ solutions of isoxazolidines 3 under the appropriate conditions (Scheme 1) led to a clean rearrangement of the adducts. In every instance, only the 3-spirocyclopropane pyridones 4 were obtained in good yields after simple chromatographic separations. The structural assignment follows straightforwardly from the observation of a characteristically shaped signal of the methine proton α to the spirocyclopropane ring in the ¹H NMR spectrum.

It is remarkable that in this case no open-chain isomers, which are invariably found as side-products in the rearrangement of 3-monosubstituted 5-spirocyclopropane isoxazolidines, 1,2a-c were formed. This result might be ascribed to a conformational constraint caused by the spirocyclopropane ring which favours the diradical coupling.

Isoxazolidine **3b**, upon heating under reduced pressure (10^{-2} Torr) at 40 °C (a temperature not adequate to give the rearrangement), undergoes a retrocycloaddition process, which is probably due to the nature of the five-membered cyclic nitrone, known in the literature to undergo similar processes.⁸ In order to improve the method, and to avoid retrocycloaddition processes (albeit limited to five-membered cyclic nitrones), both steps are more conveniently accomplished in a 'one-pot' procedure by directly heating the mixture of the starting materials at the temperature at which the rearrangement occurs for the appropriate time (Scheme 1). The cyclic nitrones **2b** and **2c** in this way give direct access to valuable 8-spirocyclopropane-7-indolizidinone **4b** and 1-spirocyclopropane-2-quinolizidinone **4c**, respectively.

The cycloadditions of nitrile oxides 5 to 1 give much poorer yields of cycloadducts 6 (Scheme 2), as expected. Benzonitrile oxide 5a, slowly generated *in situ* from the corresponding hydroximoyl chloride, was treated, in refluxing methanol, with 1 to give 24% of crystalline 6a. Acetonitrile oxide 5b, generated at room temp. from nitroethane according to Mukaiyama's method,⁹ gave the isoxazoline 6b in only 10% yield. The scarce reactivity of bicyclopropylidene, which requires higher temperatures or longer reaction times, unfavourably matches with the instability of nitrile oxides. On the other hand, it is yet remarkable that 1 as a tetrasubstituted olefin⁵ gave cycloadducts with nitrile oxides at all, albeit in poor yields.





2186

The thermal rearrangement of a 5-spirocyclopropane isoxazoline always required higher temperatures than the isoxazolidine counterparts.¹ In fact, isoxazoline **6a** was stable below 140 °C in solution. At this temperature a reaction occurred that, however, led to none of the expected products. In these conditions also the second cyclopropyl ring was cleaved to give not yet identified products.

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Footnote

[†] The only reported 1,3-dipolar cycloaddition, to our knowledge, is the addition of ozone [see ref. 4(a)].

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J. CHEM. SOC., CHEM. COMMUN., 1994

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