A new cascade ring enlargement of isoxazolidines formed from 2-chloro-2-cyclopropylideneacetates

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2-Chloro-2-cyclopropylideneacetate 1 and spiropentane analog 2 cycloadd pyrroline *N*-oxide 3 to give spiro[cyclopropane-1,5′-isoxazolidine]s 4 and 5 in good yields; due to the presence of a chlorine substituent on the carbon α to the spirocyclopropane ring, which facilitates a cyclopropyl to cyclobutyl ring enlargement, these compounds undergo a cascade rearrangement to yield indolizinone derivatives 8 and 9 cleanly (70–73% yield), offering a new method for the synthesis of the indolizine skeleton.

The strain energy incorporated in a cyclopropane ring is an extremely useful handle for molecular transformations in organic synthesis.[1] The selectivity of such a transformation and the operational conditions strongly depend on the molecular surroundings of the cyclopropane ring in a given skeleton.

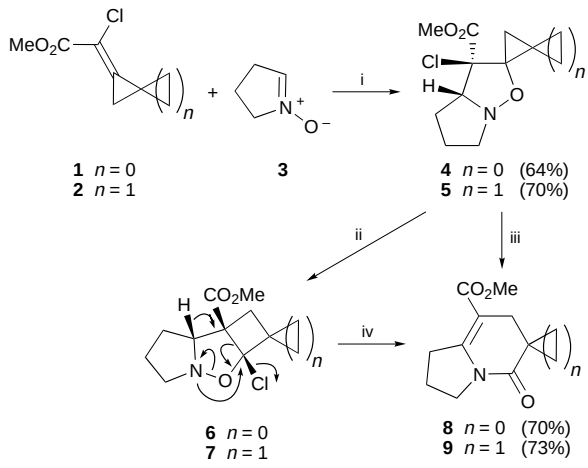
It has already been demonstrated that isoxazolidines or isoxazolines with a spirocyclopropane ring at the 5-position are capable of undergoing a selective rearrangement affording 2-substituted tetrahydro- or dihydro-4-pyridones, respectively.[2] This process has been applied to the synthesis of natural and non-natural heterocyclic compounds and it has proved particularly useful for the synthesis of heterocycles with nitrogen at the bridgehead.[3] We now report a new selective thermal cascade ring enlargement process of 4-chloro substituted spiro[cyclopropane-1,5′-isoxazolidine]s, obtained by nitrone cycloaddition to methyl 2-chloro-2-cyclopropylideneacetate **1**[4,5] and to methyl (*Z*)-2-chloro-2-spiropentanylideneacetate **2**[6] which further expands the synthetic utility of this class of compounds.

Compounds **1** and **2** smoothly react with pyrroline *N*-oxide **3** at room temperature to give cycloadducts **4** and **5**, respectively, as single regioisomers (Scheme 1).

The regioselectivity of these cycloadditions is in accord with the one previously observed for electron-acceptor substituted methylenecyclopropanes.[3b,7] Compounds **4** and **5** are obtained as single diastereoisomers, the configuration of which has tentatively been assigned on the basis of the known preference of the methoxycarbonyl group to be placed *endo* with respect to the nitrone in the cycloaddition process.[7,8]

When the isoxazolidines **4** and **5** were submitted to the usual conditions for thermal rearrangement (toluene, 110 °C),[2] a complex mixture of products was obtained. However, by replacing toluene with the more polar DMSO a clean reaction occurred at 100 °C to give the hexahydroindolizin-5-ones **8**[9] and **9** in 70 and 73% yield, respectively (Scheme 1). These compounds were present only in minute amounts in the heated toluene solution. Spectroscopic data were consistent with the proposed structures **8** and **9**. The regioselective formation of compound **9**, the structure of which was assigned on the basis of the long-range coupling (^5J = 1.8 Hz) between the two groups of allylic protons observed in the ^{1}H NMR spectrum, is quite remarkable. This unexpected result was finally confirmed by an X-ray crystal structure analysis of compound **8** (Fig. 1).§

The fact that a polar solvent is essential for the success of this rearrangement suggests that it occurs *via* a highly polar transition structure. The polar solvent would certainly favour the cyclopropyl to cyclobutyl ring enlargement leading from **4**/**5** to **6**/**7**.[10] This might occur as an intramolecular S_N2 displacement or *via* tight ion-pair intermediates. The further ring-enlargement could be initiated by abstraction of the bridgehead proton in **6**/**7**, followed by N–O bond cleavage and reclosure to the indolizidin-5-ones **8**/**9**.



Scheme 1 *Reagents and conditions*: i, CH_2Cl_2, room temp., 5 d; ii, Al_2O_3, CH_2Cl_2, room temp.; iii, DMSO, 100 °C, 3 h; iv, DMSO, 100 °C

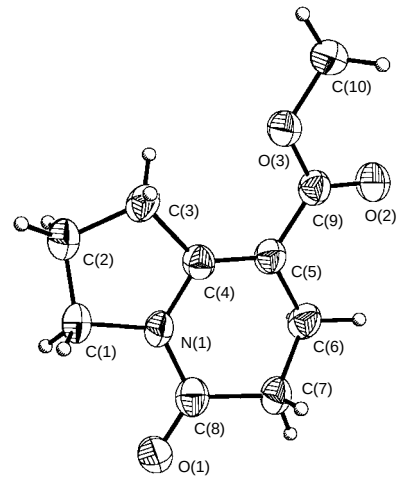


Fig. 1 Structure of 8-methoxycarbonyl-5-oxo-2,3,6,7-tetrahydro-1*H*-indolizine **8** in the crystal.

The intermediacy of the cyclobutyl derivatives **6**/**7** is probable, since these compounds could actually be isolated after stirring the isoxazolidines **4** and **5** in CH_2Cl_2 in the presence of Al_2O_3 at room temperature. Isoxazolidine **5** rearranged completely to **7** in 4 h, whereas **4** under the same conditions remained as a 6 : 1 mixture of **6** and **4** after 3 days.

The structural assignment of **6** and **7** was based on the presence of chlorine as proved by the mass spectrum, and the observation of diagnostic signals for the cyclobutane ring in the ^{13}C NMR spectrum (δ_C 102.1, 72.9, 27.7 and 25.8 in **6**; 107.5, 70.5, 28.5 and 25.5 in **7**). The *cis* relationship of the methoxycarbonyl group and the chlorine in **6**/**7** was tentatively assigned on the assumption that the displacement of chloride in **4** and **5** occurs *via* an S_N2 process, which fixes the relative configuration of the bridgehead proton and the CO_2Me group in any potential intermediate *en route* to **6**/**7**. The chloride then can enter only from the convex face of the molecule. When heated to 100 °C in DMSO, compounds **6** and **7** gave the same indolizidinones **8** and **9** as obtained directly from **4** and **5**.

In conclusion, a new domino rearrangement of spiro[cyclopropane-1,5′-isoxazolidine]s has been discovered. This process is made possible by the presence of a chlorine substituent on the carbon α to the spirocyclopropane ring, which facilitates a cyclopropyl to cyclobutyl ring enlargement mediated by a polar solvent. At higher temperature a further ring enlargement ensues with elimination of hydrogen chloride to produce hexahydroindolizidin-5-ones.

The generalization of this new process and its synthetic application are now being studied in our laboratories.

This work was supported on the Italian side by research funds from the University of Florence and, in part, CSCEA (CNR). On the German side this work was supported by the Deutsche Forschungsgemeinschaft (SFB 416, Project A) and the Fonds der Chemischen Industrie; generous gifts of chemicals by the BASF, Bayer, Hoechst, Degussa AG, and Hüls companies are gratefully acknowledged. C. Z. is grateful for financial support for the period in Göttingen by the ERASMUS Exchange Program.

Notes and References

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§ *Crystal data* for **8**: $C_{10}H_{13}NO_3$; crystal size 0.6 × 0.3 × 0.1 mm, monoclinic, $P2_1/c$, a = 13.787(11), b = 8.296(6), c = 8.264(5) Å, β = 91.582(19), γ = 90°, V = 944.9(12) Å^3, Z = 4, D_c = 1.372 Mg m^{-3}, 2.87 < θ < 23.16°, Mo-Kα radiation, λ = 0.71073, T = 133(2) K; 8957 measured reflections, 1328 independent reflections, empirical absorption correction, structure solution with direct methods with SHELXLS-86, refinement with SHELXL-93, 129 free parameters, R_1 = 0.0772 [$I > 2\sigma(I)$], wR_2 = 0.1999, refinement *via* full-matrix least-squares on F^2, largest diff. peak and hole 0.508 and −0.341 e Å^{-3}. CCDC 182/802.

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Received in Cambridge, UK, 10th February 1998; 8/01168K