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REARRANGEMENT OF NITRONE CYCLOADDUCTS TO METHYLENE CYCLOPROPANE. SYNTHESIS OF INDOLIZIDINE AND QUINOLIZIDINE DERIVATIVES.

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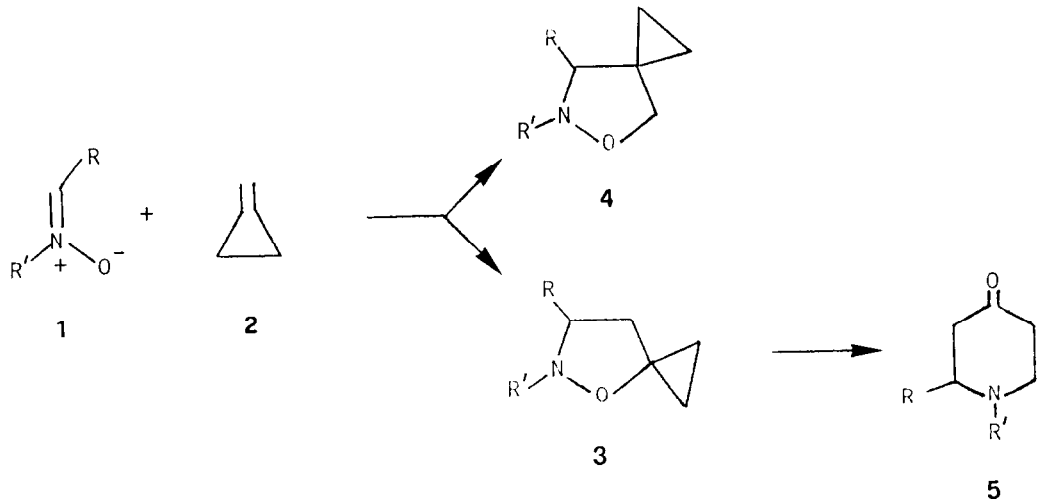
Summary: Isoxazolidines 3, obtained by cycloaddition of nitrones with methylene cyclopropane, undergo thermal rearrangement to piperidin-4-one derivatives. Indolizidine and quinolizidine derivatives are obtained from cyclic nitrones.

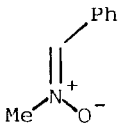
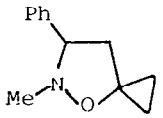
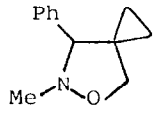
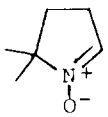
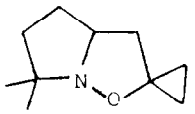
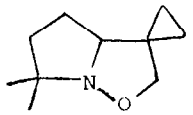
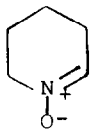
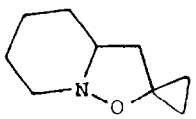
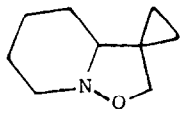
We reported recently on the novel rearrangement of 3-substituted-5-spirocyclopropylisoxazolines, as a new entry into the dihydropyridin-4-one system.[1] We also demonstrated [2] that, with a suitably functionalised side chain adjacent to nitrogen, the same rearrangement is followed by further ring-closure, thus affording indolizine or quinolizine derivatives, useful intermediates in the synthesis of N-bridgehead alkaloids.[3]

With the aim of expanding the synthetic utility of this new reaction, we expected that, in principle, isoxazolidines 3 could undergo, even more easily, the same rearrangement giving the piperidin-4-ones 5. The utility of such compounds in organic synthesis, prompted us to test this assumption.



By 1,3-dipolar cycloaddition of nitrones 1 [4] and methylene cyclopropane (2),[5] the isoxazolidines 3 are conveniently obtained as mixtures with the regioisomers 4, with predominance of the regioisomer 3 (Table 1). The formation of appreciable amounts of 4-spirocyclopropyl-regioisomers 4 requires a FMO treatment, in order to be fully rationalized,[8] and this is now in progress.

TABLE 1

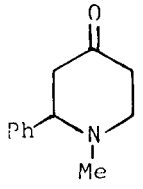
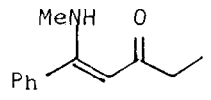
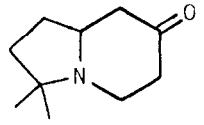
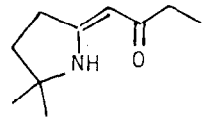
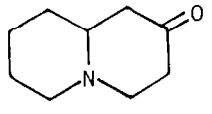
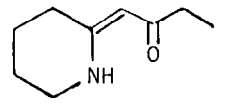
nitrones	reaction time	isoxazolidines	yield %[6]
 **1a**	5 d	 **3a** :  **4a** 70 : 30	83
 **1b**	2 d	 **3b** :  **4b** 65 : 35	86
 **1c**	2 d	 **3c** :  **4c** 90 : 10	69[7]

Attempted separation of the two regioisomers by distillation or by flash column chromatography failed and was found to be unnecessary for our purposes. In fact, as we already established for a similar case,[1] 4-spirocyclopropylisoxazolidines 4 are thermally more stable than the corresponding

regioisomers: this is ascribed to the lack, in the isomers 4, of the cyclopropyloxy system [9] which supplies the driving force of the observed rearrangement. Thus, when the mixtures of the two regioisomers 3 and 4 are subjected to FVT (400°C, 0.2 mmHg), the isoxazolidines 4 are collected unchanged together with the products of rearrangement of the isoxazolidines 3. The separation of the products can then be carried out by flash chromatography without problems.

The enaminones 6 are always produced along with the piperidin-4-one derivatives 5 (Table 2). Their formation can be assumed to involve a common intermediate,[1] from which the open chain isomer is produced by H-shift from the carbon in α to the nitrogen atom.

TABLE 2

entry	isoxazolidines	rearrangement products	yields %[10]	
			5	6
I	3a	 5a	46	14
		 6a		
II	3b	 5b	54	17
		 6b		
III	3c	 5c	32	19
		 6c		

The reported process demonstrates its efficiency in the production of indolizidine and quinolizidine systems (entries II and III),[3] and appears to be competitive with the analogous procedure reported by Tufariello,[11] since it consists of a "one-pot" reaction. In fact the same rearrangement products 5b and 6b can be obtained by direct heating of a mixture of reagents 1b and 2 in a sealed tube at 100°C for 24 h.

Synthetic applications of this new method are the object of further studies in our group.

Acknowledgments

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References and notes

1. A. Guarna, A. Brandi, A. Goti, and F. De Sarlo, *J.C.S. Chem. Commun.*, 1985, 1518.

2. A. Brandi, A. Goti, A. Guarna, and F. De Sarlo, *J.C.S. Chem. Commun.*, in the press.

3. a) J. A. Lamberton, *Alkaloids* (London), 13, 82 (1983); b) M. F. Grundon, *ibid.*, 13, 87 (1983); see also preceding volumes.

4. a) J. Hamer and A. Macaluso, *Chem. Rev.*, 64, 473 (1964); b) D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 1975, 205.

5. Reaction conditions: a mixture of neat nitrone and methylene cyclopropane (2 eq.) was heated in a sealed tube at 60°C.

6. Overall yield of the regioisomers, purified by passing the crude reaction mixture through a short pad of silica gel and concentrating. The new cycloadducts 3a-c and 4a-c gave satisfactory GC-MS, NMR (^1H and ^{13}C) and IR analyses; compounds 4a and 4b were isolated after rearrangement of the regioisomers (see the text).

7. Based on the nitrone 1c precursor, *i.e.* N-hydroxypiperidine.

8. R. Huisgen, H. Seidl, and I. Brüning, *Chem. Ber.*, 102, 1102 (1969).

9. a) B. M. Trost, *Chem. Soc. Rev.*, 11, 141 (1982); b) B. M. Trost, *Gazz. Chim. Ital.*, 114, 139 (1984).

10. Compounds isolated by flash chromatography (eluant CH_2Cl_2-MeOH, 10:1). The reported structures 5a-c and 6a-c are supported by spectral data (MS, ^1H and ^{13}C NMR, IR); these agree with the available values reported for the previously known compounds 5a [K. Hohenlohe-Oehringen, *Monatsh.*, 94, 1222 (1963)] and 5c [S. F. Mason, K. Schofield, and R. J. Wells, *J. Chem. Soc.* (C), 1967, 626].

11. J. J. Tufariello, *Acc. Chem. Res.*, 12, 396 (1979).

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