Tetrahedron Letters,Vol.27,No.43,pp 5271-5274,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

NEW SYNTHESIS OF AZEPIN-4-ONES BY FLASH VACUUM THERMOLYSIS OF DIHYDRO AND TETRAHYDROISOXAZOLE-5-SPIROCYCLOBUTANE DERIVATIVES

Andrea Goti, Alberto Brandi,* Francesco De Sarlo and Antonio Guarna

Centro di studio sulla chimica e la struttura dei composti eterociclici e loro applicazioni, CNR. Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, via G. Capponi 9, 50121 Firenze, Italy.

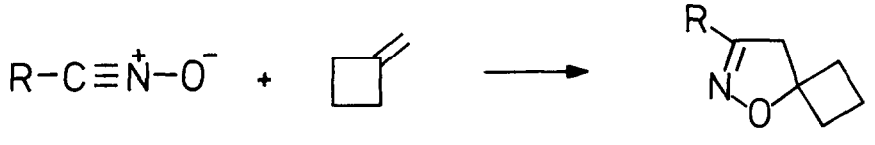
Summary: Azepin-4-ones (4) and (10) are synthesized by Flash Vacuum Thermolysis of the isoxazolines (3) and of the isoxazolidine (9) obtained by 1,3-dipolar cycloadditions to methylenecyclobutane.

We have reported recently on the synthesis and the thermal rearrangement of 4,5-dihydroisoxazole-5-spirocyclopropanes[1] as an useful synthetic route to 5,6-dihydro-4-pyridones. In addition, α,β-unsaturated enaminoketones were obtained as by-products. This novel rearrangement is made possible by a combination of the easy opening of an isoxazole ring[2] with the strain of a cyclopropane ring[3] that delivers the cyclopropyloxy systems undergoing ring closure on the nitrogen atom.

As a cyclobutyloxy system could, in principle, work in the same way, because of the considerable strain of a cyclobutane ring,[4] the attractive view of a facile synthesis of azepinones has prompted us to test this possibility.

The 1,3-dipolar cycloaddition of benzonitrile oxide (1a) with methylenecyclobutane (2) has been reported to give quantitatively 3-phenyl-4,5-dihy-

Scheme 1



1 2 3

a: R=Ph 100 %[5]

b: R=Me 72 %

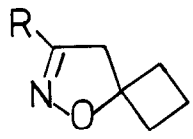
droisoxazole-5-spirocyclobutane (3a),[5] which, however, was not submitted to thermolysis. We synthesized, then, the isoxazoline 3a in accord to the reported procedure[5] (scheme 1) in order to ascertain if these products undergo a thermal rearrangement analogous to that observed on the lower homologues.

Any attempt to obtain the rearrangement in the same experimental conditions used for 4,5-dihydroisoxazole-5-spirocyclopropanes (heating at 200°C in solution or FVT at 400°C) failed: the starting material was always recovered unchanged. The direct heating of neat 3a in a sealed tube afforded a complex reaction mixture with predominance of deep decomposition products. However, when FVT is carried out in more severe conditions (700°C, 0.1 mmHg) a much cleaner mixture is obtained (scheme 2), in which the starting material has disappeared and the expected 2-phenyl-1,5,6,7-tetrahydro(4H)azepin-4-one (4a) is the major product (37% yield by flash column chromatography, CH_2Cl_2-MeOH 10:1).[6,7] Besides the azepinone an isomer is isolated in 28% yield, identified as 1-benzoyl-2-methylenetetrahydropyrrole (5a) on the basis of its spectroscopic data.[6,7] The mechanism of the rearrangement leading to compounds 5 is far yet to be elucidated. Compounds of type 6 or 7, which could be expected by analogy with the thermolysis of the homologue spirocyclopropane,[1] are not detected. The same result is obtained in the FVT of 3-methyl-4,5-dihydroisoxazole-5-spirocyclobutane (3b), obtained by cycloaddition of methylene cyclobutane (2) and acetonitrile oxide (1b), generated *in situ* from nitroethane by Mukaiyama's method.[8,6] FVT, in the same conditions, affords 2-methyl-1,5,6,7-tetrahydro(4H)azepin-4-one (4b) and 1-acetyl-2-methylenetetrahydropyrrole (5b) in 30% and 17% yield respectively.[6,7,9]

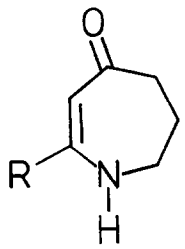
Since the above reaction sequence has been successfully extended, in the case of methylene cyclopropane, to some nitrone cycloadducts,[10] we tested the analogous rearrangement in isoxazolidine derivatives.

The cycloaddition of 5,5-dimethylpyrroline N-oxide to methylenecyclobutane (scheme 3) is accomplished by heating a mixture of the nitrone 8 and 1.5 equivalents of methylenecyclobutane (2) in a sealed tube at 100°C over four days.[11] The sole 5-spirocyclobutane regioisomer 9 is isolated by distillation (50°, 0.1 mmHg), in very good yield (90%).[6] The remarkable regioselectivity observed is in contrast with the lower selectivity exhibited by the same nitrone 8 with methylenecyclopropane, where a 65:35 ratio was obtained for 5 and 4-spirocyclopropyl regioisomers.[10] This different behaviour will be the object of a theoretical FMO approach. The cycloadduct 9 is unaffected by

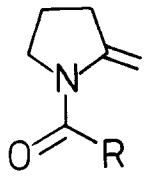
Scheme 2



3

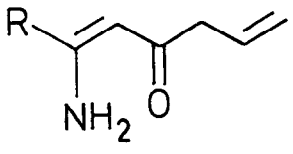


4

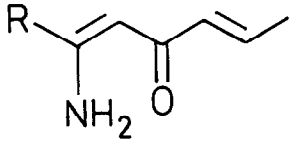


5

a:	37%	28%
b:	30%	17%

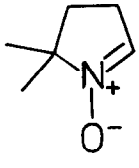


6



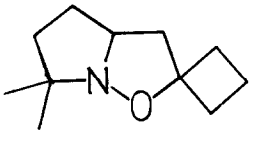
7

Scheme 3



8

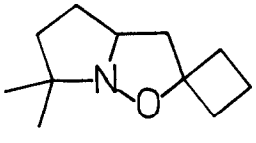
2



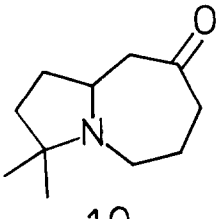
9

90%

Scheme 4

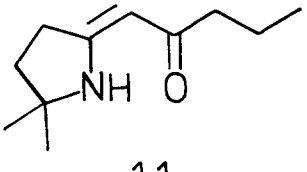


9



10

25%



11

30%

heating at 200°C in a toluene 0.2 M solution and is only slightly converted into 10 and 11 by FVT at 400°C. FVT at 600°C leads to a clean reaction mixture (GC-MS analysis), from which 3,3-dimethyloctahydro-1H-pyrrolo[1,2-a]azepin-8-one (10) and 5,5-dimethyl-2(2'-oxo)pentylidenetetrahydropyrrole (11) are obtained in 25% and 30% yield respectively by flash column chromatography (scheme 4). Despite the low selectivity of the rearrangement that gives the open-chain enaminone 11 as the major product, the reaction affords the valuable pyrrolo-azepine derivative 10 in a straightforward process and fair non optimized yield.

The wider applicability of this novel rearrangement of the cyclobutyloxy system will be object of further studies in our group.

References and notes

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

2. a) C. Kashima, *Heterocycles*, 1979, 12, 1343; b) A.A. Akrem, F.A. Lakhvich, and V.A. Khripach, *Khim. Geterotsikl. Soedin.*, 1981, 17, 1155.

3. B.M. Trost, *Top. Curr. Chem.*, 1986, 133, 5-82, and references cited therein.

4. H.N.C. Wong, K.-L. Lau, and K.-F. Tam, *ibid.*, 1986, 133, 85-157 and references cited therein.

5. N. Barbulescu and I. Sebe, *Revista de Chimie*(Bucharest), 1974, 25, 695.

6. All new compounds gave satisfactory GC-MS, NMR (^{1}H and ^{13}C) and IR analyses.

7. 4a ^{1}H-NMR:δ 7.80-7.30 (m,5H), 5.90 (broad,1H), 5.31 (s,1H), 3.68 (dt, J=5, 5 Hz, 2H), 2.74 (t, J=7 Hz, 2H), 2.30-1.90 (m,2H); ^{13}C-NMR:δ 199.51, 157.77, 139.37, 129.90, 128.46, 126.72, 101.34, 47.13, 42.46, 24.22.

   4b ^{1}H-NMR: δ 6.53 (broad,1H), 4.95 (s,1H), 3.46 (dt, J=4.5, 4.5 Hz, 2H), 2.66 (t, J=6 Hz, 2H), 2.16-1.80 (m,2H), 2.00 (s,3H); ^{13}C-NMR: δ 198.67, 156.14, 100.35, 46.54, 42.48, 24.50, 22.71.

   5a ^{1}H-NMR:δ 7.45 (m,5H), 5.43 (s,1H), 5.35 (s,1H), 3.57 (t, J=6 Hz,2H), 2.80-2.40 (m,2H), 2.30-1.80 (m,2H); ^{13}C-NMR: δ 174.44, 143.41, 136.06, 128.55, 128.26, 126.19, 109.14 t, 49.37, 31.73, 18.36.

   5b ^{1}H-NMR: δ 4.53 (s,1H), 4.43 (m,1H), 3.62 (t, J=7 Hz, 2H), 2.65-2.35 (m,2H), 2.24 (s,3H), 2.20-1.90 (m,2H); ^{13}C-NMR: δ 174.72, 141.92, 98.83, 48.58, 32.69, 20.72, 17.56.

8. Obtained as the sole regioisomer in 72% yield after distillation (50°C, 0.1 mmHg).

9. The azepinone 4b on standing in $CDCl_3$ solution (five days at room temperature) completely isomerizes to the azadienol tautomer showing the following signals: ^{1}H-NMR δ 9.80 (broad,1H), 5.17 (s,1H), 3.66 (t, J=7 Hz,2H), 2.60 (t, J = 8 Hz, 2H), 2.13-1.75 (m,2H), 2.08 (s,3H); ^{13}C-NMR δ 194.79 s, 167.36 s, 89.64 d, 47.29 t, 32.10 t, 28.39 q, 21.13 t.

10. A. Brandi, A. Guarna, A. Goti and F. De Sarlo, *Tetrahedron Lett.*, 1986, 27, 1727.

(Received in UK 18 July 1986)