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1,3-DIPOLAR CYCLOREVERSIONS OF ISOXAZOLIDINES AND PYRAZOLIDINES

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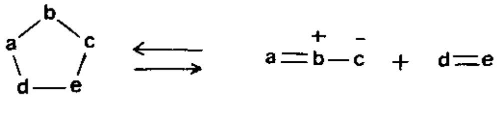
1,3-Dipolar cycloreversion reactions of the adducts of 3,4-dihydroisoquinoline-N-oxide and of 3,4-dihydroisoquinoline-N-phenylimine with cyclic α,β-unsaturated ketones and their ethylene ketals were investigated. The easier fragmentation of the adducts with α,β-unsaturated ketones compared with that of the corresponding ketals can be explained on the basis of conjugation gain in the cycloreversion transition state of the former compounds.

This paper is intended to stimulate interest on 1,3-dipolar cycloreversions, a 5→3+2 process according to Huisgen's classifications (1), which has been overlooked in comparison to the much more studied 3 + 2 → 5 cycloadditions (2).



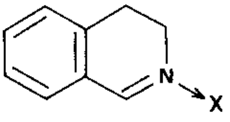
Fragmentation of pentaatomic heterocycles which produces 1,3-dipolar systems and dipolarophiles is induced either by heat or light or on electron impact (3). Despite the relatively large number of examples reported of such reaction only in few cases experiments have been carried out in order to obtain data useful to define the factors affecting the 5→3+2 processes (3).

The present paper reports on the cycloreversion of isoxazolidines and pyrazolidines **2** - **5**.

3,4-Dihydroisoquinoline-N-oxide (1a) reacted smoothly and regiospecifically in benzene at room temperature with a two-fold excess of cyclopent-2-enone (6h) and cyclohept-2-enone (70h) to give 2a and 2b respectively. In similar reaction conditions 1a was reacted with large excess of tricarbonyltroponeiron (4) and tricarbonyl-8-p-chlorophenyl-8-azaheptafulveneiron (5) to yield the corresponding adducts 5a and 5b. The reaction took place in 15 days. Ethylene ketals of cyclopent-2-enone and cyclohept-2-enone required more drastic conditions in their reactions with 1a. With the former dipolarophile (two-fold excess in benzene) 1a yielded 3a in eight hours at 80°C while with the latter a mixture of 3b and 4b in a 0.50 ratio was obtained in seven days at the same temperature. Acidic hydrolysis of 3a-c and 4b led to 2a-c and 4a respectively.

3,4-Dihydroisoquinoline-N-phenylimine (1b) generated "in situ" by heating the dimer in benzene at 80°C (2) adds to cyclopentenone, its ketal and cycloheptenone in a regiospecific manner to give adducts 2c, 3c and 2d respectively.

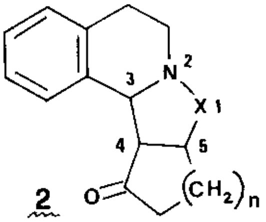
Adducts structure was based on ^{1}Hnmr data. Multiplicity of proton at position 5 of the heterocyclic moiety of the molecule permitted to choose between the two possible regioisomers, since the corresponding signal is a multiplet in 2 and 3 whereas it appears as a doublet in 4 and a double doublet in 5.[1] Nmr could not define the *cis* or *trans* relation-



1

a : X = O

b : X = N-Ph



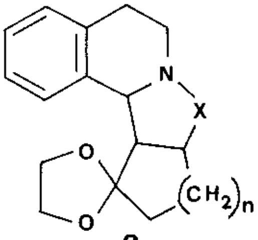
2

a : X = O, n = 1

b : X = O, n = 3

c : X = N-Ph, n=1

d : X = N-Ph, n=3



3

a : X = O, n = 1

b : X = O, n = 3

c : X = N-Ph, n=1

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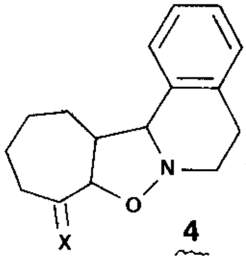
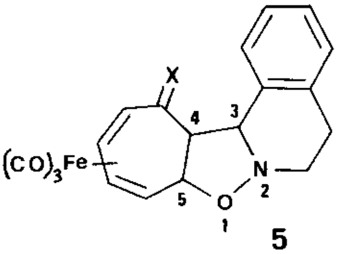
[1] Compound 5a : $J_{4,5}$ = 8.3 Hz, $J_{5,HC}$=4.0 Hz and $J_{3,4}$ = 9.0 Hz.



4

a : X = O

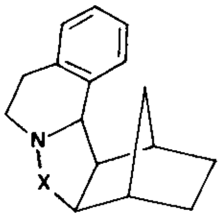
b : X = O-CH_2-CH_2-O



5

a : X = O

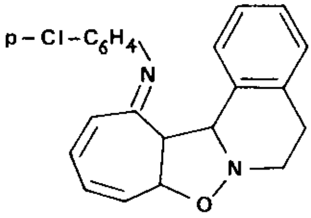
b : X = N-C_6H_4-p-Cl



6

a : X = O

b : X = N-Ph



7

Table

Comp.	Yield (%)	Mp (°C)	Reaction conditions[a] Time (h)	 Temperature (°C)	Yield (%) of 6[b]
2a	74	110-113	9[c]	80	92
2b	64	93-95	60[c]	110	90
2c	64	194-196	100	140	52
2d	44	203-205	100	140	d
3a	68	97-99	100	110	10
3b	16	81-83	100	110	d
3c	79	152-154	100	140	d
4a	-	127-128	70[c]	110	85
4b	31	124-125	100	110	d
5a	70	117-118	4[c]	80	88
5b	63	125-128	4[c]	80	80

[a] In benzene (80°C), in toluene (110°C) and in xylene (140°C). [b] Isolated by column chromatography; compound 6a, mp 69-71°C (lit.(8) 69-70°C); compound 6b, mp 141-143°C. [c] After this time tlc analysis showed the complete disappearance of the adduct. [d] No reaction. Starting material recovered unchanged.

ship of H-3 and H-4 protons.[2] However we advance as the most probable the *trans* relationship, at least in the case of 2-4, considering an *exo* approach of the reactants sterically favoured over the *endo*.

The experiments of retrocycloaddition (see Table) have been set up heating the pure cycloadducts with a large excess of norbornene in benzene, toluene or xylene as solvents. The 1,3-dipole scavenger norbornene gave adducts of the type 6 which have been tested to be stable in the experiment conditions. Adducts 5 have been proved to be particularly unstable, cycloreversion taking place already at room temperature in benzene. In this latter case the equilibrium adducts $\rightleftarrows$ addends was detected already by tlc; if norbornene was added, cycloreversion was completed in ≃ one month.

From the data reported in the Table the determinant effect of the nature of the emerging dipolarophile on the 1,3-dipolar cycloreversion is apparent. A comparison of the behaviour of the adducts 2 - 5 suggests that the driving force is mostly due to the conjugation of the forming dipolarophile. The data found indicate also a role of the 1,3-dipole on cycloreversions studied. A comparison between 1a, a stable 1,3-dipole, with 1b indicates that the former is more effective in promoting cycloreversion.

The higher reactivity of adducts 2a, 3a and 2c compared with that of 2b, 3b and 2d is probably due to the two following factors: the higher steric strain relief for the former group of adducts, and the complexity and difficulty to achieve conformational reorganization for the latter group of compounds to reach the transition state.

Our results provide another piece of evidence that the 1,3-dipolar cycloaddition-cycloreversion process is characterized by a transition state in which the addends largely retain their electronic properties (e.g. conjugation). On this basis the higher reactivity of

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[2] $J_{3,4}$ range from 5.3 Hz for 2a to 9.3 Hz for 4a.

α,β-unsaturated ketones compared with that of their ketal derivatives in 1,3-dipolar cycloaddition finds a rationale: in the case of ketones, in fact, the stabilization gained by a strong frontier orbital interaction of addends provides the requisite driving force necessary to compensate the small loss in conjugation stabilization of dipolarophile.

Furthermore the results found for adducts **5** explain the lack of reactivity found for **1a** towards tropone and 8-aryl-8-azaheptafulvenes (5). We suggest that in both cases the reaction reach an equilibrium where the pericyclic addends are largely favourite over the adducts. That this is the case was proved by the failure of our efforts of preparation of **7** from **5b** *via* trimethylamine-N-oxide decomplexation in acetone. Tlc monitoring of the reaction progress revealed, after some time (2-3 h), the formation of substantial amount of 8-p-chlorophenyl-8-azaheptafulvene which must be necessarily produced in the 1,3-dipolar cycloreversion of the transient **7**.

To our knowledge only one example of cycloreversion of pyrazolidines leading to an azomethine imine system and a C=C dipolarophile has been already reported (6), while more numerous are the cases of such reaction for isoxazolidines (3). For the latter class, however, only the adducts made up of C-benzoyl-N-phenyl nitrone and α,β-unsaturated esters undergo cycloreversion at room temperature (7).

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