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SPONTANEOUS TRANSPOSITIONS FROM PYRAZOLENINES INTO PYRAZOLES. COMPETITIVE [1,5] MIGRATIONS OF AN ACYL OR CARBALKOXY GROUP TO THE CARBON AND NITROGEN.

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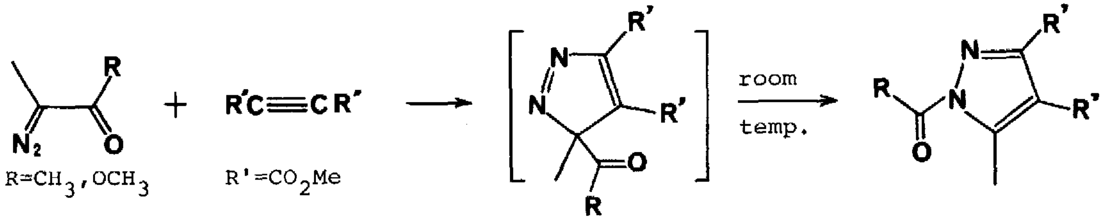
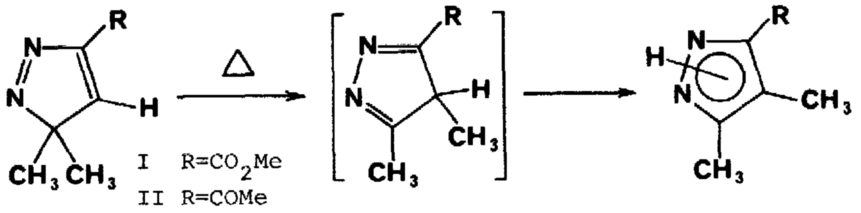
We have previously reported that the pyrazolenines resulting from the 1,3-dipolar cycloaddition of disubstituted diazoketones or diazoesters with dimethyl acetylendicarboxylate are unstable. Usually, under the conditions of the cycloaddition, these adducts undergo a transposition leading to N-substituted pyrazoles by a specific [1,5] migration of the acyl or carbalkoxy groups to the nitrogen (1) (A):



(A)

We (2), as well as others (3-5), have utilized these facile intramolecular acyl migrations in new syntheses of nitrogen containing heterobicycles via the ring expansion of starting diazocyclanones. The instability of these 3-acyl pyrazolenines contrasts sharply with the stability of the gem-dimethylpyrazolenines obtained by the reaction of 2-diazopropane with activated acetylenics (6). Thus the pyrazolenines I(R=CO_2Me) and II (R=COMe) are entirely converted to the products III and IV after heating at 180°C for 3 hours. The pyrazoles III and IV were separated from apparently polymeric material by chromatography over silica in 50 and 70% yield respectively. They apparently result from a methyl followed by hydrogen migration.



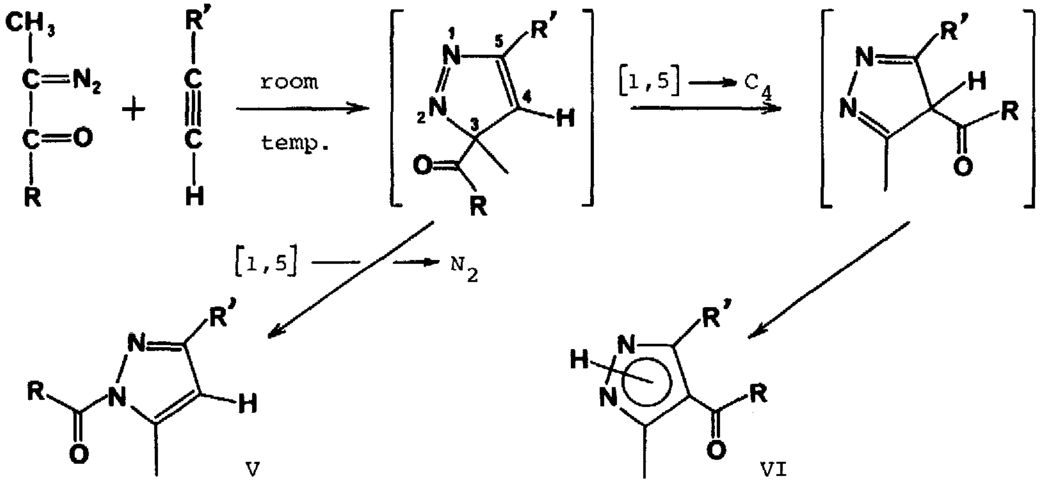
(B)

III F=134°
IV F=108°

IR : ν(NH) near 3410 cm^{-1}
NMR : δ(CH_3) : two singlets both close to 2,20 ppm
δ(NH) : broad signal between 9 and 12 ppm.

This second type of transposition (B) in which the initial step involves a [1,5] migration ending on the carbon atom instead on the nitrogen, recalls the acid catalyzed transpositions in the 3,3-diphenyl series described by van Alphen in 1943 (7). More recently several studies have shown that this type of transposition can also often occur without the help of an acid catalyst (4,8). Thus, our methyl migrations and the migrations observed by van Alphen are probably both examples of thermal [1,5] migrations. However, in the pyrazole series the migrations can apparently be of two different types depending on the nature of the migrating group : specific migration to N(2) at room temperature if the motile group is acyl or carbalkoxy, or migration to C(4) by a phenyl or methyl group at higher temperature. The latter transposition becomes particularly facile if the substituent in position 4 is a hydrogen.

In order to check if this dichotomy of pathways was general and if two mechanisms were necessary (4), we re-examined the behaviour of the cycloadducts between diazoketones or diazoesters and monosubstituted activated acetylenics. In all cases studied, both types of [1,5] migrations were observed. Even at room temperature the acyl or carbalkoxy group migrated competitively to the carbon and to the nitrogen as shown in the following reaction scheme :



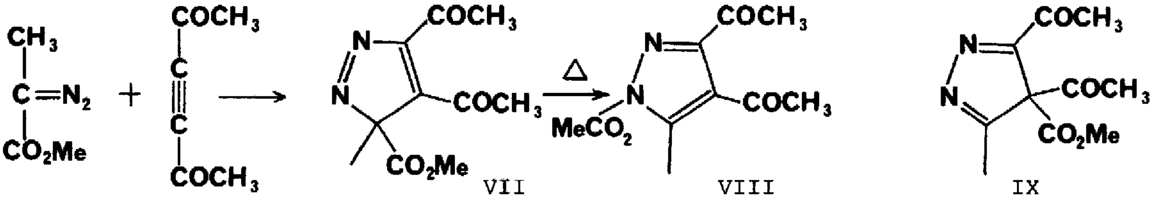
The N-substituted pyrazoles show in the NMR a sharp signal near 6,60 ppm for the vinyl proton, whereas these of the other pyrazoles show a broad NH signal in the region 9-12 ppm. In the IR the amide or urethane carbonyl absorb between 1735 and 1770 cm^{-1} whereas the carbonyl of keto and ester groups which have moved to the carbon C(4) absorb respectively near 1675 cm^{-1} and 1720 cm^{-1}.

The material balance shows that the reactions are quantitative ; the yields of the isolated products depend only on the work-up procedure, usually chromatography over silica (30-70%).

Table

Substituents		Ratio of the pyrazoles obtained (NMR)		
R	R'	V	/	VI
CH_3	$COCH_3$	1	:	4
CH_3	CO_2CH_3	1	:	1,4
CH_3	CN	1	:	1,2
OCH_3	CN	1	:	3
OCH_3	CO_2CH_3	1	:	20
OCH_3	$COCH_3$	1	:	5

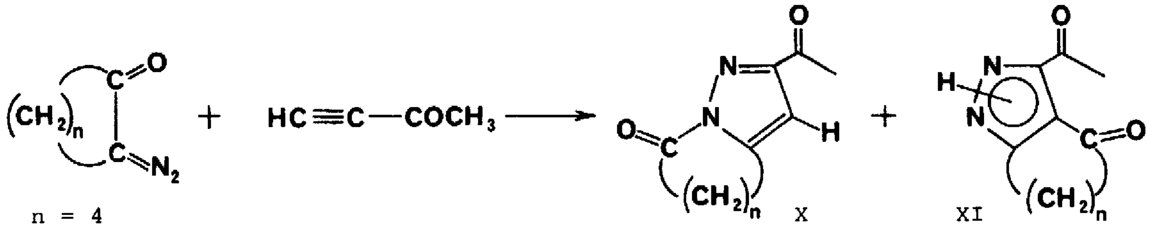
These results indicate that there is probably no essential difference between the two observed migrations, both being probably concerted [1,5] sigmatropic shifts, similar to those observed for the same groups in the homocarbonated series (9). In order to see if the migrations to nitrogen are direct or the result of successive [1,5] migrations starting on C(4), we have studied the reaction between bis-acetylacetylene and 2-diazomethylpropionate :



VII VIII IX

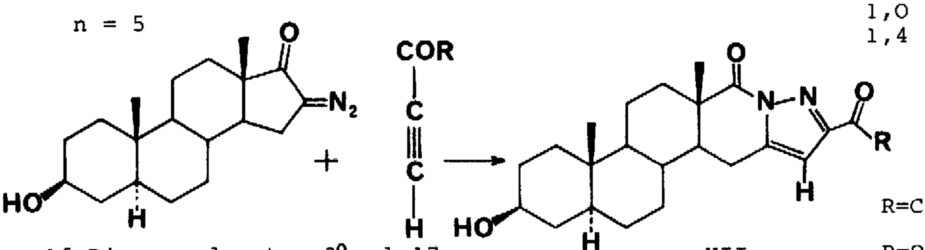
The pyrazole VIII was obtained without any detectable amount of the N-acetyl derivative (10) by warming (60°) the pyrazolenine VII ; VIII results from the exclusive migration of the carbomethoxy group to nitrogen. Since an acetyl group is known to be a better migrating group than a carbalkoxy (11) an intermediate structure like IX can be excluded and the observed migration takes place directly to the nitrogen. A similar result was obtained with hexafluorobutyne. Only with monosubstituted acetylenics have we observed the concurrent migration to carbon, and, indeed in those cases, this is the predominant mode of transposition (see table). Our results suggest that -all other substituents being the same- a carbalkoxy group migrates more easily to carbon than does an acyl group, the pyrazolenines bearing a carbalkoxy in the 3 position being more stable than those with an acyl group in the same position (12). In addition, an acyl group in position 5 seems to make this migration more facile than do carbalkoxy or cyano substituents. [1,5] Phosphoryl group migrations have been recently described in the pyrazole series but all of these occur specifically to the nitrogen even if the 4 substituent is a hydrogen (13). Since it has also been shown that the phosphoryl group is a better migratory function than benzoyl, a general trend in the pyrazole series may be that the greater the migratory aptitude of a group, or at least the more unstable the pyrazolenine, the more pronounced the tendency for migration to nitrogen.

With α-diazocyclanones, the acyl migration to carbon still takes place, giving an expansion of the carbocyclic ring as illustrated by the following examples (pyrazoles of type X and XI). However the only assay done with a steroidal diazoketone gave only migration to the nitrogen, most likely for steric reasons (pyrazoles of type XII).



n = 4
n = 5

1,0 : 1,2
1,4 : 1,0



16-Diazo-androstan-3β-ol-17-one

R=CH_3	70%	F=217°
R=OCH_3	50%	F=172°

Analogous [1,5] migrations in the pyrazole series have recently been described starting however from differently substitued diazocyclopentadienes (14) or showing the reverse migration from nitrogen to carbon (15).

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