Tetrahedron Letters Vol. 21, pp 1413 - 1416
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0040-4039/80/0408-1413$02.00/0

AROMATISATION OF 3-CARBOMETHOXY-3-METHYL-3H-PYRAZOL
SOLVENT EFFECT AND CATALYSIS THROUGH ACID

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At 60° the title compound isomerises quantitatively to aromatic products 3 and 4. A kinetic study reveals the influence of solvent polarity and of acid on the rate and direction of this reaction.

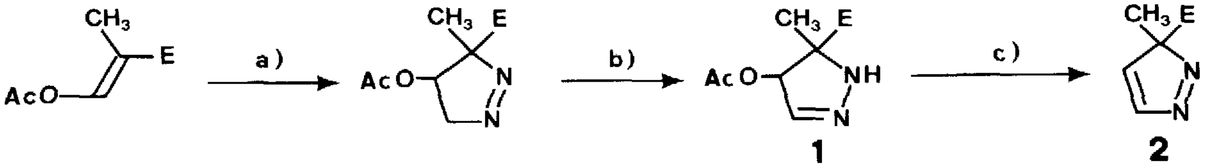
The rearrangement of 3,3-disubstituted 3H-pyrazoles under the influence of heat or acid to aromatic products, first described by Van Alphen [1] and by Hüttel [2], is documented by many examples in the recent literature. This reaction can be considered as proceeding through a sigmatropic 1,5-(1,2-)shift of a functional group to the adjacent carbon or nitrogen atom [3].

In this communication we describe the synthesis and rearrangement of 3-carbomethoxy-3-methyl-3H-pyrazol (2). This compound serves as a model for the study of the influence of solvent polarity and acid on the rate and direction of sigmatropic carbomethoxy-migration, a reaction which we have observed in an other system [4].

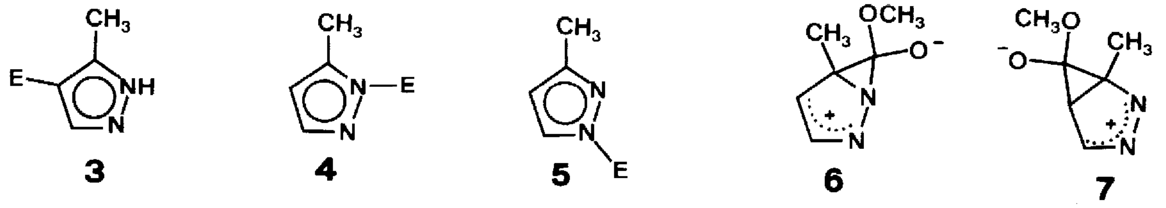
The title compound 2, a colourless oil of bp. 42 - 47°/0.1 Torr [5], has been prepared by the sequence of reaction steps indicated in scheme 1. Elimination of acetic acid from pyrazolin 1 (mp. 58 - 59° [5]) occurs at 100° or with 1N HCl at room temperature yielding 3 (60 - 90%) and 4/5 (10 - 40 %). From this we conclude that 2 is an intermediate and that it rearranges faster than it is formed from 1. Base catalysed elimination with potassium hexamethyldisilylamide in THF at -70° gives 5 and a small amount of 3-methylpyrazol. It is likely that 2 is actually formed under these conditions but is converted to 5 through the catalytic action of the 3-methylpyrazol anion. This led us to carry out the reaction in the presence of chloromethylformate as a scavenger for this anion. In this way compound 2 was obtained as the major reaction product from 1 and could be isolated in a yield of 52 %.

Scheme 1

E = $COOCH_3$



a) CH_2N_2/ether/20° b) 0.6N HCl/ether/0° c) $((CH_3)_3Si)_2NK/ClCOOCH_3$/THF/ −70°



As other 3-acyl-3H-pyrazoles [6] compound 2 is labile. At 60° it rearranges quantitatively to a mixture of 3 and 4 through a shift of the carbomethoxy group. The formation of 4 at the exclusion of its more stable isomer 5 [7] is evidence for an intramolecular, pericyclic mechanism for the rearrangement. Such a reaction course for both isomerisation pathways of 2 is further confirmed by the independence of product composition from reactant concentration.

The first order rate constants for the formation 3/4 from 2 [8] show a significant but small solvent effect (see table). This leads us to exclude zwitterionic structures such as 6 or 7 as distinct reaction intermediates [9]. However, it indicates some polar character in the transition state of the sigmatropic shift reaction. Unexpectedly the charge separation seems to be more pronounced for carbomethoxy-migration toward carbon (2 → 3) than for migration toward nitrogen (2 → 4).

The isomerisation of 2 is subject to acid catalysis. In acetic acid the rate is faster than would be expected from the increased solvent polarity. In dioxane a strong rate enhancement is observed upon addition of trifluoroacetic acid (TFA). Furthermore, the 3/4 product ratio changes from 22:78 in the uncatalysed reaction (dioxane) to 90:10 with acid.

We interpret the formation of 3 and 4 in the acid catalysed process as occurring from the two isomeric cations 8 and 9 according to scheme 2, the product ratio being determined by the value of the equilibrium constant K between 8 and 9 and by the ratio k_{8-3}/k_{9-4} of the two rate constants for reaction from 8 and from 9. Protonation on oxygen, which has been proposed in other acid catalysed ester migrations [12], cannot rigorously be excluded. However, it seems unlikely in view of the known basicity of the cis-azo group [13].

Table Isomerisation of 2 to 3 & 4 at 64.8°.

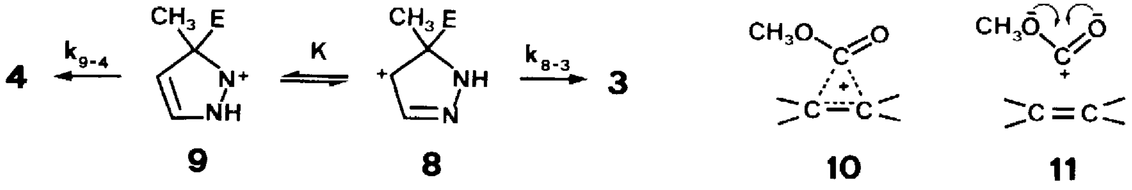
solvent	E_T a)	$k_{obs} \cdot 10^4$ s^{-1}	products	partial rate constants, s^{-1}	
			3 : 4	$k_{2-3} \cdot 10^4$	$k_{2-4} \cdot 10^4$
CCl_4	32.5	1.09	20 : 80	0.22	0.87
dioxane	36.0	1.36	22 : 78	0.30	1.06
C_6H_5Cl	37.5	1.70	28 : 72	0.48	1.22
C_6H_5CN	42.0	2.57	39 : 61	1.00	1.57
t-butanol	43.9	3.19	44 : 56	1.40	1.79
DMSO	45.0	3.09	46 : 54	1.42	1.67
acetic acid	51.2	47.8	90 : 10	43.0	4.8
0.1N TFA/dioxane		2.1	39 : 61	0.8	1.3
1N TFA/dioxane		16.9	81 : 19	13.7	3.2
5N TFA/dioxane		4800 b)	90 : 10	4320	480

a) Solvent polarity parameter: Ch. Reichardt, Angew. Chem. 91, 119 (1979).

b) Extrapolated from rate measurements at lower temperature.

The participation of the carbomethoxy group in cationic 1,2-shifts is known from pinacol type rearrangements in aliphatic systems [14]. It implies a transfer of positive charge to the carbonyl carbon in the transition state 10 and its stabilisation according to formula 11 through the oxygen free electron pairs.

Scheme 2



This work shows that 3H-pyrazoles are suitable model compounds for the study of sigmatropic 1,5- (1,2-)shift reactions involving functional groups at moderate temperature. Further results along this line are reported in the accompanying communication [15].

We wish to thank the Swiss National Science Foundation (project Nr. 2.943.0.77) and Ciba-Geigy Co. for their generous support.

Notes and References

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[7] Compound 4 is slowly converted to 5 at 100°. Acylation of 3-methylpyrazol with chloromethylformate gave 5, the product of thermodynamic control only.

[8] Activation parameters for the conversion of 2 to 3/4 in chlorobenzene: $E_a = 24.0 \pm 0.4$ kcal/mol; $\log A = 11.8 \pm 0.4$.

[9] The solvent sensitivity R_E ($R_E = \Delta \log k/\Delta E_T$ [10]) for migration toward carbon ($2 \rightarrow 3$) is 0.070 and for migration toward nitrogen ($2 \rightarrow 4$) 0.024. Comparable R_E-values are found for other reactions with slightly polar transition states, such as e.g.: Cycloaddition of diphenylketene to dihydropyrane [10] ($R_E = 0.110$); racemisation of 1,2-di-t-butyl-cyclopropanone [11] ($R_E = 0.069$).

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[15] See following communication.

(Received in Germany 4 February 1980)