Tetrahedron Letters Vol. 21, pp 1417 - 1420
©Pergamon Press Ltd. 1980. Printed in Great Britain
0040-4039/80/0408-1417$02.00/0

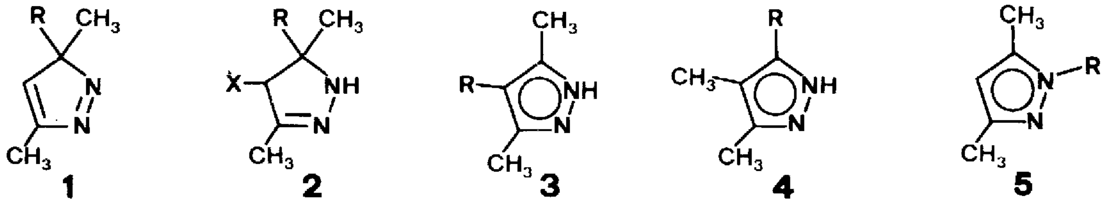
MIGRATION TENDENCIES OF FUNCTIONAL GROUPS TOWARD SIGMATROPIC REARRANGEMENT IN 3,3-DISUBSTITUTED 3H-PYRAZOLES

Peter Schiess* and Henri Stalder
Institut für Organische Chemie der Universität
St. Johanns-Ring 19, CH-4056 Basel, Switzerland

3,3-Disubstituted 3H-pyrazoles 1a - e aromatise through an intramolecular sigmatropic 1,5-(1,2-)shift of one of the quaternary groups. From a kinetic study of the uncatalysed and of the acid catalysed isomerisation reaction migration tendencies of functional groups in sigmatropic rearrangement toward neutral and toward cationic centers are obtained.

It is well established that not only hydrogen atoms but many carbon functional groups are able to participate in 1,5-sigmatropic shift reactions [1]. Several attemps have been reported in recent years at classifying functional groups according to their migration tendency [2] in sigmatropic reactions [3], [4]. These attempts have failed however to include less reactive functional groups due to the high temperature required to induce sigmatropic change [5]. In this communication we wish to show that 3,3-disubstituted 3H-pyrazoles because of their tendency for aromatisation are suitable model compounds to study the 1,5-(1,2-)sigmatropic shift reaction of a variety of unreactive functional groups at moderate temperature.

Scheme 1



a) R = CH_3 b) R = C_2H_5 c) R = C_6H_5 d) R = $CH_2C_6H_5$ e) R = $COOCH_3$

The four 3,5-dimethyl-3H-pyrazoles 1a - d [6] carrying a further hydrocarbon group at position 3 have been prepared from appropriately substituted pyrazolines 2 (X = H) through bromination-dehydrobromination. The ester 1e was obtained from 2e (X = OAc) through treatment with base as described in the preceding communication [7].

Uncatalised 1,5-(1,2-)migration toward neutral carbon

When heated neat or in solution at 50 - 200° all five model compounds give rearranged product in nearly quantitative yield. Migration of hydrocarbon groups in 1a - c occurs to the adjacent carbon atom exclusively leading to a single product of structure 3 in the case of 1a and 1c and to a mixture of 3b and 4b in the case of 1b. The benzyl group in 1d and the carbomethoxy group in 1e migrate both to carbon and to nitrogen, giving mixtures of 3 and 5 (see table 1).

Table 1 Uncatalised rearrangement of 1a - 1e at 120°.

	R	products, % 3	4	5	log A	E_a, kcal/mol	k_{obs}, s^{-1} a)	k^{rel}_{1-3} b)
1a	CH_3 c)	100		-	11.2 ± 0.5	30.8 ± 0.7	$1.15 \cdot 10^{-6}$	1 e)
1b	C_2H_5 c)	94	6	-	10.9 ± 0.4	28.4 ± 0.4	$1.42 \cdot 10^{-5}$	23
1c	C_6H_5 d)	100	-	-	11.5 ± 0.3	27.0 ± 0.4	$3.05 \cdot 10^{-4}$	530
1d	$CH_2C_6H_5$ d)	67	-	33	11.9 ± 0.4	28.4 ± 0.4	$1.35 \cdot 10^{-4}$	157
1e	$COOCH_3$ c)	31	-	69	11.5 ± 0.3	23.4 ± 0.4	$3.53 \cdot 10^{-2}$	19000

a) Overall first order rate constants for disappearance of 1. b) Relative rates (migration tendencies) for migration of R to neutral carbon (1 - 3). c) In t-butanol. d) In DMSO. e) Corrected for by a statistical factor of 2.

Activation parameters have been determined for the uncatalised rearrangement of 1a-e *in dimethylsulfoxide or t-butanol solution (table 1).* Values for log A lie around 11.5 which is typical for intramolecular, cyclic processes [8]. Relative rates for the isomerisation 1 → 3 (k^{rel}_{1-3} in table 1) correspond to migration tendencies [2] of functional groups R in 1,5-(1,2-)sigmatropic rearrangement. Our results extend previously obtained reactivity sequences [3], [4] to groups of low migration tendency.

The reactivity sequence alkyl $<$ phenyl $<$ ester is not unexpected in the light of previous work [3]. It can be explained [4] through second order interaction of the empty π^*-orbital of the migrating group with an occupied molecular orbital of the stationary array of atoms in the heterocyclic ring. The importance of this interaction should decrease the higher the energy of the π^*-level in the migrating group, thus explaining the low reactivity of alkyl groups which lack such an orbital. The large reactivity difference between methyl, ethyl and benzyl, however, shows that there must be additional factors such as ground state strain or bond strength of the shifting σ-bond which affect the migration tendency of functional groups.

Acid catalised 1,5-(1,2-)migration toward cationic carbon

The rearrangement of 1a - e is strongly catalised by acid. All five compounds react instantaneously with mineral acid at room temperature and with moderate rate in acetic acid at 60°. The same rearrangement products are formed as in the uncatalised reaction, however, in somewhat different ratios (see table 2).

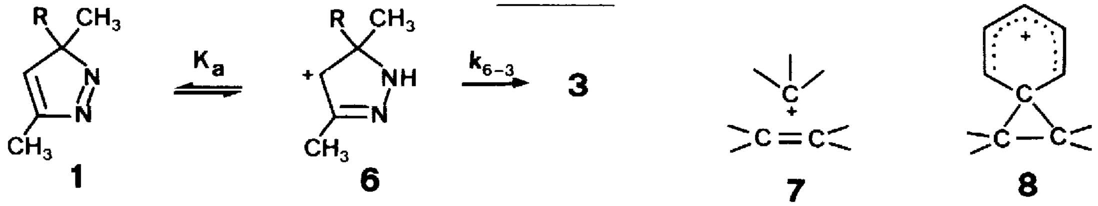
Table 2 Rearrangement of 1a - 1e in acetic acid at 60°.

	R	products, %			k_{obs}, s^{-1} a)	k^{rel}_{1-3} b)
		3	4	5		
1a	CH_3	100		-	$3.15\cdot10^{-5}$	1 c)
1b	C_2H_5	98	2	-	$8.80\cdot10^{-4}$	55
1c	C_6H_5	100	-	-	$1.39\cdot10^{-3}$	88
1d	$CH_2C_6H_5$	63	-	37	$7.07\cdot10^{-2}$ d)	2830
1e	$COOCH_3$	71	-	29	$2.11\cdot10^{-3}$	95

a) Overall first order rate constants for disappearance of 1. b) Relative rates for migration of R to carbon (1 → 3). c) Corrected for by a statistical factor of 2. d) Extrapolated from measurements at lower temperature.

A kinetic study of the rearrangement of 1a - e in acetic acid yields relative rates for the acid catalised carbon migration 1→3 (k^{rel}_{1-3} in table 2). Compound 1a (R = CH_3) is by far the least reactive, 1b, 1c and 1e (R = C_2H_5, C_6H_5, $COOCH_3$) yield higher and comparable values for k^{rel}_{1-3}, while 1d (R = $CH_2C_6H_5$) is the most reactive.

Scheme 2



However, k^{rel}_{1-3} values are not equal to migration tendencies of functional groups R in migration toward cationic carbon since the five model compounds cannot be expected to show equal basicity [9]. As discussed in the preceding communication [3] cation 6 is the likely precursor of the C-migration product 3. Therefore relative rates for the conversion 6 → 3 (k^{rel}_{6-3}) would correspond to cationic migration tendencies. At constant acid strength (in acetic acid) the following expression holds for the conversion of experimental rate values to migration tendencies: $k^{rel}_{6-3} = k^{rel}_{1-3} \cdot 10^{-\Delta pK_a}$ where ΔpK_a is the difference in pK_a of the compound in question relative to 1a. Unfortunately pK_a measurements with compounds

1a - e were precluded because of their high reactivity with acid. Therefore pK_a for 1a - e was estimated from pK_a values of R-substituted model compounds [10]. As detailed in footnote [11] approximate ΔpK_a values of +0.1, -1,0, -0.5 and -2.0 for 1b, 1c, 1d and 1e respectively are assumed. By applying these pK_a corrections to k^{rel}_{1-3} we obtain the following estimates for the migration tendencies of functional groups R in cationic rearrangement (k^{rel}_{6-3} values): $CH_3 : C_2H_5 : C_6H_5 : CH_2C_6H_5 : COOCH_3 = 1 : 44 : 880 : 9000 : 9500$.

No matter how crude the applied pK_a corrections are, our results clearly show that migration tendencies in cationic sigmatropic rearrangement differ appreciably from those in neutral systems. Significantly, benzyl and carbomethoxy are the most reactive of the groups tested. As in the uncatalised rearrangement different qualities of functional groups R must be evoked to explain their different migration tendencies. From the sequence $CH_3 < C_2H_5 < CH_2C_6H_5 \sim COOCH_3$ we conclude that there is substantial charge transfer in the transition state according to formula 7. The high reactivity of C_6H_5 indicates that for this group participation according to 8 is important. Further experiments will have to be performed to test these hypotheses.

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

[1] C.W. Spangler, Chem. Rev. 76, 187 (1976).

[2] For a definition of the term "migration tendency" see: M. Stiles & R.P. Mayer, J. Amer. Chem. Soc. 81, 1497 (1959).

[3] P. Schiess & P. Fünfschilling, Tetrahedron Letters 1972, 5195.

[4] D.J. Fields, D.W. Jones & G. Kneen, Chem. Commun. 1975, 754; 1976, 873; J. chem. Soc. Perkin I 1978, 1050; R.W. Bushby & D.W. Jones, Chem. Commun. 1979, 688.

[5] P. Schiess & R. Dinkel, Tetrahedron Letters 1975, 2503.

[6] All new compounds gave satisfactory elemental analyses and spectral data in accord with their structure.

[7] P. Schiess & H. Stalder, preceding communication.

[8] H.E. O'Neal & S.W. Benson, J. phys. Chemistry 71, 2903 (1967).

[9] This has been assumed in a recent study of cationic migrations by J.N. Marx, J.C. Argyle & L.R. Norman, J. Amer. chem. Soc. 96, 2121 (1974).

[10] C.A. Grob & M. Schlageter, Helv. chim. Acta 59, 264 (1976).

[11] In 4-substituted quinuclidines the following ΔpK_a values relative to CH_3 were found [10]: C_2H_5 + 0.08; C_6H_5 -0.83; $COOCH_3$ -1.59. There are four bonds in these model compounds between R and the site of protonation, whereas in 1 there are only two. It is reasonable therefore to assume slightly larger ΔpK_a values of +0.1, -1.0 and -2.0 respectively for 1b, 1c and 1e. For 1d with three intervening bonds between the phenyl group and the nitrogen a ΔpK_a value of -0.5 is estimated.

(Received in Germany 4 February 1980)