A NEW THERMAL DECOMPOSITION OF THE ISOXAZOLE RING[1]

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Abstract - The thermal decomposition of 5-methoxy-3-methyl-4-phenylazoisoxazole (1) was re-investigated. Cleavage in the presence of dipolarophiles gave methyl 5-methyl-2-phenyl-1,2,3-triazole-4-carboxylate (3), which derives from a known rearrangement, and N-phenylmethoxycarbonylnitrilimine, which was trapped. The mechanism of the thermal decomposition is discussed.

The thermolysis of the isoxazole ring, due to the easy cleavage of its N-O bond, is one of the best studied topics among the rearrangements of heterocyclic rings. The most usual thermal conversion of isoxazoles gives 2H-azirines[2] or oxazoles.[3] Recently Wentrup and co-workers[4] extensively studied the flash-vacuum-pyrolysis of several 3-methylisoxazol-5-ones. By loss of acetonitrile and carbon dioxide a carbenoid species, localized at the carbon atom in position 4, was generated.

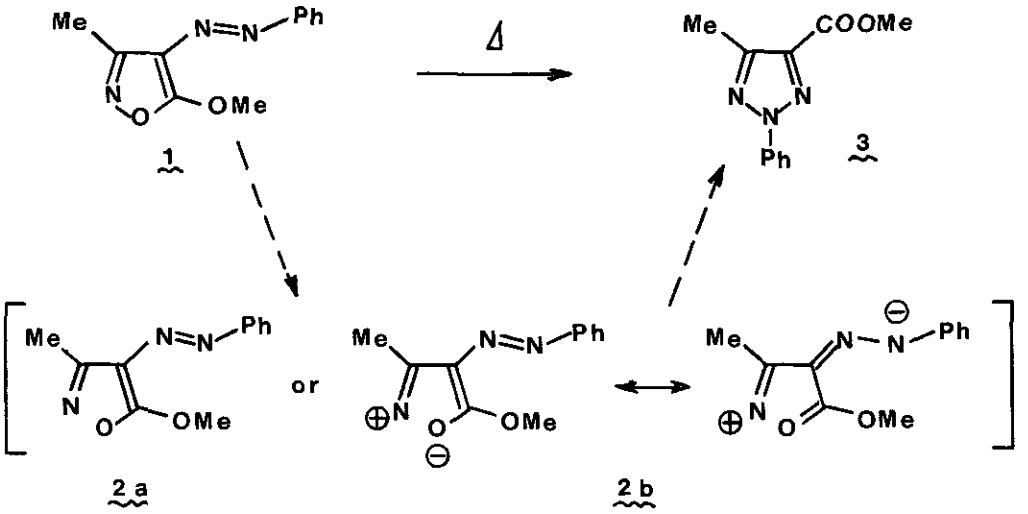
Pursuing our research on the thermal rearrangement of isoxazole derivatives,[5] we have reconsidered the behaviour of 5-methoxy-3-methyl-4-phenylazoisoxazole (1). This is known to rearrange to methyl 5-methyl-2-phenyl-1,2,3-triazole-4-carboxylate (3),[6] probably through an intermediate which can be written either in the form of a diradical (2a) or of a zwitterion (2b) (Scheme 1). This rearrangement was first discovered by Wittig for 3-methyl-5-phenyl-4-phenylazoisoxazole.[7]

Taking into account both the results of Wentrup[4] and the behaviour of dimethyl 3-(4-nitrophenyl)isoxazoline-4,5-dicarboxylate, which at 210°C gives 4-nitrobenzonitrile and tetramethyl 1,4-dioxanetetracarboxylate,[8] we planned to trap the hypothetical intermediate, generated by loss of acetonitrile, with a dipolarophile.

Thus 0.5 mmoles of 1 were heated at 110°C (a lower temperature required a longer reaction time) in the presence of 3 equiv. of dimethyl acetylenedicarboxylate (DMAD) (4), dimethyl fumarate (5), dimethyl maleate (6), 1,1-diethoxyethene (7), ethoxyethyne (8) and 1-diethylaminopropyne (9). (See Table for conditions).

The starting product 1 disappeared and two products were always obtained, these be-

Scheme 1



ing easily separated by column chromatography. The first product eluted was always methyl 5-methyl-2-phenyl-1,2,3-triazole-4-carboxylate (3), followed by a product whose elemental analysis and NMR showed it was an adduct of dipolarophile and isoxazole 1, less acetonitrile.

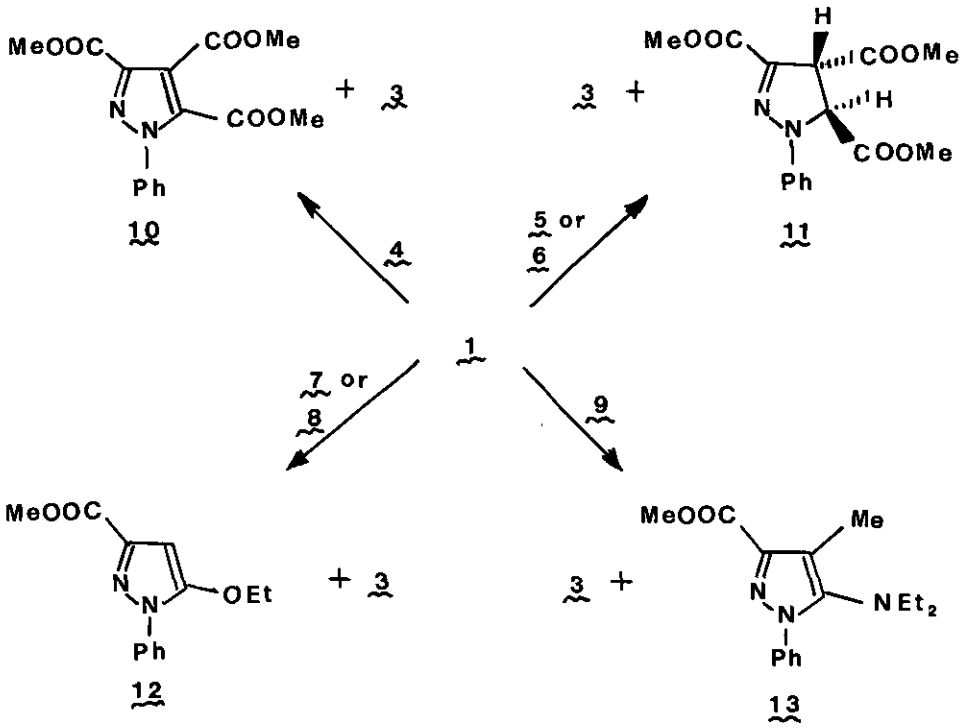
Adduct 10 from DMAD was found to be identical in every respect with a sample of trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate.[9]

Adduct 12 from 1,1-diethoxyethene showed a single ethoxy group in the NMR, hence it was methyl 5-ethoxy-1-phenylpyrazole-3-carboxylate, generated from methyl 5,5-diethoxy-1-phenyl-2-pyrazoline-3-carboxylate by loss of ethanol. This attribution was confirmed when 12 was obtained from 1 and ethoxyethyne[8] heated at 110°C in a Parr bomb for 30 min.

Furthermore 5 and 6 gave the same adduct 11, which was trimethyl trans-1-phenyl-2-pyrazoline-3,4,5-tricarboxylate, in accordance with the data of its NMR spectrum. Scheme 2 reports all these results.

Every uncertainty concerning the structure of these products was eliminated when 10-13 were obtained from N-phenylmethoxycarbonylnitrilimine 15 generated from methyl 2-chloro-2-hydrazonoacetate 14 in the presence of dipolarophiles 4-9. Adduct 11 was obtained, again, either from dimethyl fumarate or from dimethyl maleate, and conversion of the cis to the more stable trans-adduct probably occurred by epimerization of the proton in position 4. This behaviour was also observed by Huisgen and co-workers[10] in the reaction of the same dipolarophiles with diphenylnitrilimine, which was generated either thermally from 2,5-diphenyltetrazole or by dehydrochlo-

Scheme 2



rination of benzophenylhydrazonoyl chloride.

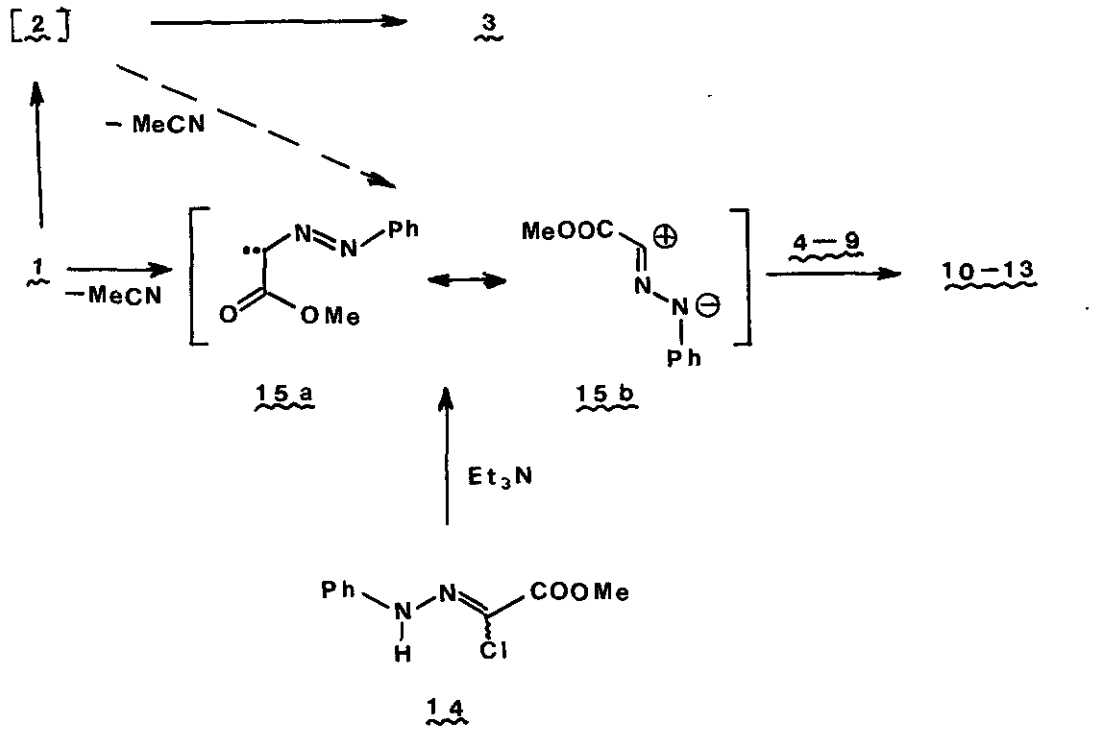
There are two possible routes to rationalize the formation of 10-13 from the thermolysis of 1.

As a first possibility the intermediate 2 could either rearrange to 3, or, with its negative charge delocalized on the nitrogen atom, attack 4-9. Thus a new zwitterion could be obtained and its intramolecular cyclization would give 10-13 by loss of acetonitrile.

We prefer to propose a second mechanism involving a new type of fragmentation of the isoxazole ring. The loss of acetonitrile generates ketocarbene 15a, which is more reactive in its resonance structure of N-phenylmethoxycarbonylnitrilimine 15b. This is the same 1,3-dipole that we obtained from 14, and should react in the same way with dipolarophiles 4-9 in accordance with a 1,3-dipolar cycloaddition (Scheme 3).

The reason for this choice lies in the types of dipolarophile we found to be reactive. These were either electrophilic (4-6) or nucleophilic (7-9) olefins and acetylenes. Other types were found to be significantly less reactive.[11] This could hardly be rationalized if 2 was the reacting species, but it is consistent with a 1,3-dipo-

Scheme 3



lar intermediate 15 whose HOMO and LUMO energy levels are both involved in its reactivity,[13] the former favouring reactivity with electrophiles, the latter with nucleophiles.

Nitrilimine 15 could hypothetically be generated either by 1,3-dipolar cycloreversion of 1 or by a stepwise pathway through 2 (Scheme 3). Further research is being undertaken on these lines.

EXPERIMENTAL

Melting points were determined by the capillary method on a Tottoli apparatus (Büchi). Elemental analyses were carried out with a C.Erba mod.1106 CHN analyzer. IR spectra (*Nujol mulls*) were recorded on a Perkin-Elmer 983 spectrophotometer and ^{1}H-NMR spectra on a Bruker WP80SY spectrometer ($CDCl_3$ was the solvent).

5-Methoxy-3-methyl-4-phenylazoisoxazole (1). - To an ice-cooled ethereal solution of diazomethane (large excess) 3-methyl-4-phenylazoisoxazol-5-one (4.0 g) was added. The mixture was stirred overnight, the solvent evaporated ($T \leqslant 35°C$) and the residue chromatographed over silica gel (70-230 mesh, Merck). Elution with cyclo-

hexane-ethyl acetate (90:10) gave first 1 (2.2 g, 52% yield; solvent to be evaporated below 35°C!) followed by 3-methyl-4-(2-methyl-2-phenylhydrazono)isoxazol-5-one (2.0 g, 47% yield, mp 105°C, lit.[14] 106.5°C). Following this method, yields of 1 were significantly higher than those reported in the literature[14,15] and no trace of 3 was obtained.

Thermal Decomposition of 1 in the Presence of Dipolarophiles. - General procedure. A mixture of 1 (0.5 mmoles) and the suitable dipolarophile was heated under the conditions reported in Table. The excess dipolarophile, when possible, was evaporated under reduced pressure and the residue was chromatographed over silica gel (70-230 mesh, Merck). Elution with cyclohexane-ethyl acetate (85:15) gave first methyl 5-methyl-2-phenyl-1,2,3-triazole-4-carboxylate (3) (mp 55-56°C, lit.[14,16] 54-56°C) followed by the pyrazole derivatives 10-13 whose analytical and spectral data are reported below.

Trimethyl 1-Phenylpyrazole-3,4,5-tricarboxylate (10): light yellow crystals, mp 89°C (lit.[9] 89°C).

Trimethyl trans-1-Phenyl-2-pyrazoline-3,4,5-tricarboxylate (11): light yellow crystals mp 101-102°C (EtOH). IR ν_{CO}: 1753, 1727 and 1690 cm^{-1}. NMR δ: 3.75 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 4.40 (H_4, d, J=5.5 Hz, 1H), 5.20 (H_5, d, J=5.5 Hz, 1H), 7.0-7.5 (m, 5H). Anal: Calcd. for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.48; H, 5.17; N, 8.97.

Methyl 5-Ethoxy-1-phenylpyrazole-3-carboxylate (12): light yellow crystals mp 104-105°C (MeOH). IR ν_{CO}: 1725 cm^{-1}. NMR δ: 1.40 (t, 3H), 4.30 (q, 2H), 3.88 (s, 3H), 6.25 (s, 1H), 7.4-7.8 (m, 5H). Anal: Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.23; H, 5.88; N, 11.45.

Methyl 5-Diethylamino-4-methyl-1-phenylpyrazole-3-carboxylate (13): colourless crystals, mp 65-66°C (light petroleum ether). IR ν_{CO}: 1710 cm^{-1}. NMR δ: 0.96 (t, 6H), 2.33 (s, 3H), 3.01 (q, 4H), 3.93 (s, 3H), 7.2-7.7 (m, 5H). Anal: Calcd. for $C_{16}H_{21}N_3O_3$: C, 66.87; H, 7.37; N, 14.62. Found: C, 66.96; H, 7.24; N, 14.42.

Reaction of N-Phenylmethoxycarbonylnitrilimine (15) with Dipolarophiles 4-9. - General procedure. To a stirred solution of methyl 2-chloro-2-phenylhydrazonoacetate (14)[17] (0.3 mmoles) in benzene (3 ml), triethylamine (1.0 mmoles) and the dipolarophile (0.6 mmoles) were added. After stirring at room temperature for 24 h, the solution was washed with water, the solvent evaporated and the residue chromatographed over silica gel (70-230 mesh, Merck). Elution with cyclohexane-ethyl acetate (85:15) (93:7 for 13) gave variable amounts (from 15% of 12 to 47% of 11) of adducts 10-13 identical in every respect with the samples obtained by thermal decomposition of 1. Yields were not optimized.

Table - Thermal decomposition of 1

Entry	Dipolarophile[a]	Time at 110°C (min)	Triazole 3 % [b]	Pyrazole derivatives Adduct	% [b]
1	4	30	70	10	19
2	5	30	46	11	46
3	6	30	45	11	47
4	7	30	70	12	23
5	8	30	50	12	22
6	9	12	40	13	21

[a] 3 equiv. of dipolarophile [b] Yields of crystallized material

REFERENCES AND NOTES

1. This research was assisted financially by grants of C.N.R. (Rome) and M.P.I.
2. T.Nishiwaki, Synthesis, 20 (1975) and references therein.
3. A.Padwa, E.Chen, and K.Ku, J.Am.Chem.Soc., 97, 6484 (1975).
4. H.Briehl, A.Lukosch, and C.Wentrup, J.Org.Chem., 49, 2772 (1984) and references therein.
5. A.Corsico Coda, G.Desimoni, and A.Coda, Heterocycles, 23, 1893 (1985).
6. L.A.Summers, P.F.H.Freeman, and D.J.Shields, J.Chem.Soc., 3312 (1965).
7. G.Wittig, F.Baugert, and H.Kleiner, Chem.Ber., 61, 1140 (1928).
8. G.Westphal and K.Karge, Zh.Chem., 22, 217 (1982).
9. M.K.Saxena, M.N.Gudi, and M.V.George, Tetrahedron, 29, 101 (1973).
10. R.Huisgen, M.Seidel, G.Wallbillich, and H.Knupfer, Tetrahedron, 17, 3 (1962).
11. E.g. trans-stilbene at 110°C gave 64% of 3 and 5% yield of methyl trans-1,4,5-triphenyl-2-pyrazoline-3-carboxylate, colourless crystals, mp 120-121°C (from cyclohexane-petroleum ether) with consistent IR, NMR and elemental analysis. Cis-stilbene[12] at 70°C gave 85% yield of 3 and a trace of pyrazoline adducts.
12. R.E.Buckles and N.G.Wheeler, Org.Synth., Coll. IV, 857 (1963).
13. K.N.Houk, J.Sims, C.R.Watts, and L.J.Luskus, J.Am.Chem.Soc., 95, 7301 (1973).
14. G.Cum, G.Lo Vecchio, and M.C.Aversa, Gazz.Chim.Ital., 95, 583 (1965).
15. L.A.Summers, P.F.H.Freeman, and D.J.Shields, J.Chem.Soc., 3312 (1965).
16. L.A.Summers, Experientia, 22, 499 (1966).
17. R.Fusco and G.Romani, Gazz.Chim.Ital., 76, 435 (1946).

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