OXAZOLONES. PART VI.[1] REACTION OF 5(4*H*)-OXAZOLONES WITH NITRILE IMINES: SYNTHESIS OF 1*H*-1,2,4-TRIAZOLES THROUGH [3+2] CYCLOADDITION

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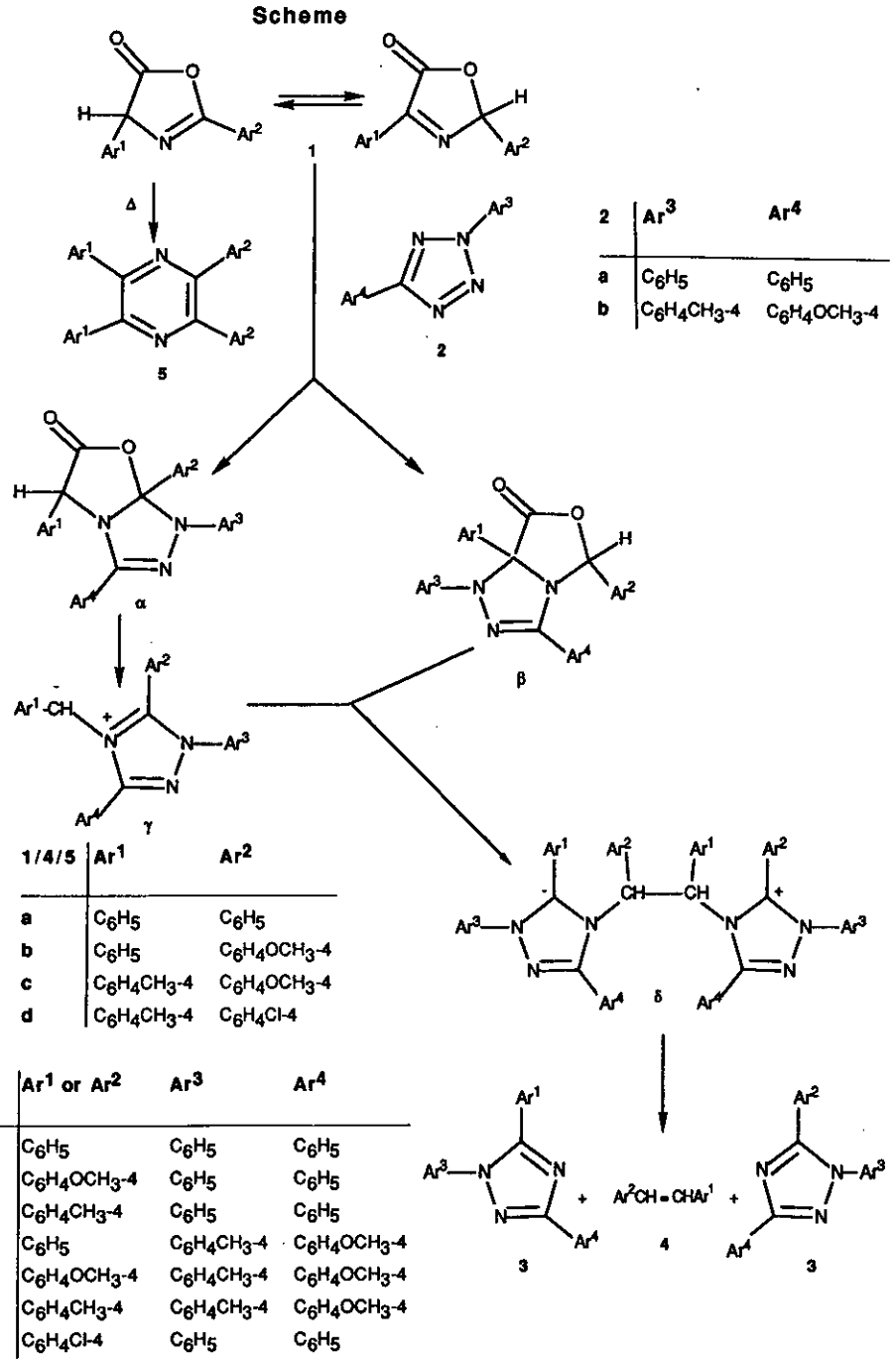
Abstract - 5(4*H*)-Oxazolones (**1**) react as dipolarophiles in [3+2] cycloadditions with nitrile imines generated from tetrazoles (**2**) in refluxing anisole affording two 1*H*-1,2,4-triazole derivatives (**3**) and diarylethylenes (**4**).

In a previous paper we reported on the reactions of 5(4*H*)-oxazolones with hydrazonoyl halides.[2] The reactions were performed in the presence of bases and a complicate reaction pattern was observed. Three main reaction products were obtained, i.e. the derivatives of pyrazolone, oxazole and bis-imidazolone rings. Particularly, the formation of the third compounds was explained by a cycloaddition reaction of the nitrile imine intermediate formed by elimination of hydrogen chloride from the hydrazonoyl halide. However, an ionic stepwise mechanism could not be ruled out unequivocally. In any case, it appeard worth trying to get further information on possible cycloaddition reactions to the 5(4*H*)-oxazolone nucleus. Indeed, though an ample literature is available on the reactivity of oxazolones as 1,3-dipolar reactants (azomethine ylides),[3] to the best of our knowledge no reactions have been reported in which said heterocycles can act as dipolarophiles in [3+2] cycloaddition processes. This possibility is evidenced in this paper.

The thermal decomposition of tetrazoles is a classical method to generate unstable nitrile imine 1,3-dipoles under neutral conditions.[4] Oxazolones (**1a-d**) reacted with the nitrile imines from tetrazoles (**2**) in refluxing anisole. The reaction was continued until disappearance of **1** (tlc, 4-5 h). *Chromatographic separation of the reaction mixture allowed to isolate the main products indicated*

Scheme



2	Ar^3	Ar^4
a	C_6H_5	C_6H_5
b	$C_6H_4CH_3$-4	$C_6H_4OCH_3$-4

1/4/5	Ar^1	Ar^2
a	C_6H_5	C_6H_5
b	C_6H_5	$C_6H_4OCH_3$-4
c	$C_6H_4CH_3$-4	$C_6H_4OCH_3$-4
d	$C_6H_4CH_3$-4	C_6H_4Cl-4

3	Ar^1 or Ar^2	Ar^3	Ar^4
a	C_6H_5	C_6H_5	C_6H_5
b	$C_6H_4OCH_3$-4	C_6H_5	C_6H_5
c	$C_6H_4CH_3$-4	C_6H_5	C_6H_5
d	C_6H_5	$C_6H_4CH_3$-4	$C_6H_4OCH_3$-4
e	$C_6H_4OCH_3$-4	$C_6H_4CH_3$-4	$C_6H_4OCH_3$-4
f	$C_6H_4CH_3$-4	$C_6H_4CH_3$-4	$C_6H_4OCH_3$-4
g	C_6H_4Cl-4	C_6H_5	C_6H_5

in the Scheme and Table 1, i.e. the two 1*H*-1,2,4-triazole derivatives (**3**) (obviously only one triazole when $Ar^1 = Ar^2$) clearly deriving from the nitrile imine produced by the thermolysis of **2** and one of two tautomeric Ar-C=N moieties present in the starting oxazolone. Besides triazoles (**3**), the diarylethylene (**4**) bearing the same aryl groups of the oxazolone (**1**) was formed. Moreover, as a by-product, the 2,3,5,6,-tetraarylpyrazine corresponding to the oxazolone reactant was always found in the reaction mixture. Since it has been reported that 5(4*H*)-oxazolones afford tetraarylpyrazines when heated at high temperature,[5] this by-product was expected and not further investigated. However, the formation of this by-product accounted for the fact that an amount of tetrazole (**2**) was recovered unaltered. No other reaction products were detected, but some tarry material was always present, likely associated with the high reaction temperature.

Triazoles (**3**) are in part new compounds (**3a-c,g**) and could be easily identified on the basis of analytical and spectroscopic evidence and comparison with independently synthesized[6] compounds (in the case of **3b,d**). Products (**4**) were easily identified by analytical and spectroscopic evidence.

Table 1.

Substrates		Product (yield, %)[a]				Recovered (yield, %)[b]
1a	**2a**	**3a** (28)	-	**4a** (24)	**5a** (12)	**2a** (52)
1b	**2a**	**3a** (46)	**3b** (40)	**4b** (30)	**5b** (31)	**2a** (33)
1c	**2a**	**3b** (48)	**3c** (42)	**4c** (66)	**5c** (10)	**2a** (35)
1b	**2b**	**3d** (65)	**3e** (67)	**4b** (61)	**5b** (31)	**2b** (26)
1b	**2b**	**3e** (30)	**3f** (31)	**4c** (49)	**5c** (17)	**2b** (23)
1d	**2a**	**3c** (45)	**3g** (29)	**4d** (33)	**5d** (12)	**2a** (28)

a) Yield is given on **1**. b) Yield is given on **2**.

A rationalisation of the course of this reaction is given in the Scheme. It is well known that 5(4*H*)-oxazolones are also reactive in the tautomeric form of 5(2*H*)-oxazolones. To the C=N bond of both tautomers a cycloaddition reaction of the nitrile imine dipole produced from the tetrazole (**2**) is postulated, by which intermediates (α) and (β) are formed, respectively. The structure of the final products (**3**) confirms the regiochemical course of the cycloaddition, in fair agreement with the literature data[6] on the addition of nitrile imines to C=N bonds. Ylide (γ) is produced from α by carbon dioxide elimination. Intermediate (β) is probably less disposed to lose carbon dioxide (an ylide devoid of the stabilizing effect of the triazolium moiety would be primarily produced) and can react with γ by a nucleophilic attack to C-2 followed by carbon dioxide elimination. The dipolar intermediate (δ) is thus produced from which products (**3**) and (**4**) arise by an elimination sequence.

EXPERIMENTAL SECTION

Melting points were recorded on a Buchi 510 (capillary) apparatus and are uncorrected. Ir spectra were taken with a PYE UNICAM SP3-200S Philips spectrophotometer. ^{1}H Nmr experiments are performed on Bruker AC 200 and EM-390 Varian instruments. Oxazolones (**1a**,[7] **1b**,[8] **1d**,[9]) and tetrazole (**2a**)[4] are known. **2b** was obtained according to the method described for **2a**[4]: mp 110°C (MeOH) (lit.,[10] 111-112°C); yield: 40%.

2-(4-Methoxyphenyl)-4-(4-methylphenyl)-5(4*H*)-oxazolone (1c) --- *N*-(4-Methoxybenzoyl)-2-(4-methylphenyl)glycine was prepared by Schotten-Baumann reaction from 2-(4-methylphenyl)glycine and 4-methoxybenzoyl chloride: yield 72%; mp 164 °C. Ir (nujol) ν_{max}: 3370 (NH) cm^{-1}; 3000-2500 (COOH); 1720, 1680 (CO). ^{1}H Nmr (DMSO-d$_6$) δ: 13.2-12.0 (br s, 1H, COOH), 8.8 (d, J = 7.7 Hz, 1H, NH), 8.0-6.9 (m, 8H, H$_{arom}$), 5.5 (d, J = 7.7 Hz, 1H, C*H*NH), 3.9 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C 68.21; H 5.78; N 4.68. Found: C 68.20; H 5.59; N 4.53.

The benzoylated glycine (10.5 g, 35 mmol) was suspended in Ac_2O (20 ml, 215 mmol) under nitrogen and stirred at room temperature for 6 h. The yellow solid was filtered and washed with *n*-

pentane yielding pure **1c** (6.2 g, 63%); mp 125-128 °C. Ir (nujol) ν_{max}: 1820 (CO) cm^{-1}; 1640 (CN). ^1H Nmr ($CDCl_3$) δ: 2.3 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 5.4 (s, 1H, H-4), 6.9-8.0 (m, 8H, H_{arom}). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C 72.58; H 5.37; N 4.98. Found: C 72.35; H 5.32; N 4.83.

Table 2.

Compd No.	mp (°C) (Cryst. Solvent)	Molecular Formula	^1H nmr ($CDCl_3$/TMS) δ (ppm) H_{arom}	OCH_3	CH_3	Analysis Calcd (Found) C	H	N
3d	109-110	$C_{22}H_{19}N_3O$	8.2-6.9	3.8	2.3	77.39	5.61	12.31
	(*n*-C_6H_{14}/*i*-Pr_2O)					(77.01)	(5.52)	(12.37)
3e	134-135	$C_{23}H_{21}N_3O_2$	8.2-6.7	3.8	2.4	74.35	5.70	11.31
	(*n*-C_6H_{14}/CH_2Cl_2)					(74.28)	(5.53)	(10.98)
3f	173-174	$C_{23}H_{21}N_3O$	8.3-6.9	3.8	2.3	77.72	5.95	11.82
	(*i*-Pr_2O/CH_2Cl_2)					(77.59)	(5.82)	(12.02)
5c	263-265	$C_{32}H_{28}N_2O_2$	7.8-6.8	3.8	2.4	81.32	5.97	5.93
	(*i*-Pr_2O)					(81.28)	(6.01)	(5.87)
5d	267-270	$C_{30}H_{22}Cl_2N_2$	7.6-6.8	-	2.3	74.84	4.60	5.82
	(*i*-Pr_2O)					(74.87)	(4.75)	(5.81)

1,3,5-Triaryl-1*H*-1,2,4-triazoles (3a-g), 1,2-Diarylethylenes (4a-d), and 2,3,5,6-tetraarylpyrazines (5a-d); General Procedure: --- Oxazolone (**1**) (11 mmol) and tetrazole (**2**) (10 mmol) were dissolved in anisole (50 ml) and refluxed for 5 h. The solvent was evaporated under reduced pressure. The crude mixture was chromatographed on a silica gel column: petroleum ether (40-60°C) was used as eluent which was gradually mixed with CH_2Cl_2. The separated fractions were crystallized: yields of unchanged tetrazole (**2**) and of reaction products (**3**, **4**, and **5**) are given in Table 1. **3a**: mp 103-104 °C (MeOH) (lit.,[11] mp 104 °C); **3b**: mp 106-107 °C (*n*-C_6H_{14}/*i*-Pr_2O) (lit.,[11] mp 107-108 °C); **3c**: 110 °C (*i*-PrOH) (lit.,[6] mp 100 °C); **3g**: mp 137-140 °C (*i*-PrOH) (lit.,[6] mp 138-140 °C); **4a**: mp 122-124 °C (EtOH) (lit.,[12] mp 121-124 °C); **4b**: mp 134-

135 °C (EtOH) (lit.,[13] mp 136 °C); **4c**: mp 165 °C (*n*-C_6H_{14}/*i*-Pr_2O) (lit.,[14] mp 166-167 °C); **4d**: mp 203-204 °C (*n*-C_6H_{14}/CH_2Cl_2) (lit.,[15] mp 203-204 °C); **5a**: mp 254-255 °C (*i*-Pr_2O) (lit.,[16] mp 255-256 °C); **5b**: mp 235-236 °C (*i*-Pr_2O) (lit.,[16] 236 °C). Crystallization solvent, analytical and spectroscopic data for new compounds (**3d-f**) and (**5c,d**) are listed in Table 2.

REFERENCES

1. Part V. F. Clerici, E. Folpini, M. L. Gelmi, and D. Pocar, *Tetrahedron*, 1991, **47**, 8907.
2. F. Clerici, R. Destro, E. Erba, M. L. Gelmi, and D. Pocar, *Heterocycles*, 1988, **27**, 1411.
3. J. W. Lown, '1,3-Dipolar Cycloaddition Chemistry: Azomethine ylides.' Vol. 11, ed. A. Padwa, Wiley Interscience, New York, 1984, pp. 653-732.
4. R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, 1961, **94**, 2503.
5. N. Gakis, M. Marky, H. Hansen, H. Heimgartner, H. Schmid, and W. E. Oberhansli, *Helv. Chim. Acta*, 1976, **59**, 2149.
6. R. Huisgen, R. Grashey, M. Seidel, G. Wallbillich, N. Knupfer, and R. Schmid, *Liebigs Ann. Chem.*, 1962, **653**, 105.
7. R. Huisgen, M. O. Bayer, and H. Gotthard, *Chem. Ber.*, 1970, **103**, 2356.
8. H. O. Bayer, M. Gotthard, and R. Huisgen, *J. Am. Chem. Soc.*, 1970, **92**, 4340.
9. E. Erba, M. L. Gelmi, and D. Pocar, *Chem. Ber.*, 1988, **121**, 1519.
10. S. Ito, Y. Tanaka, A. Kakehi, and K. Kondo, *Bull. Chem. Soc. Japan*, 1976, **49**, 1920.
11. R. Huisgen, R. Grashey, E. Aufderhaar, and R. Kunz, *Chem. Ber.*, 1965, **98**, 642.
12. F. Bergmann, J. Weizman, and D. Schapiro, *J. Org. Chem.*, 1944, **9**, 408.
13. C. Hell, *Ber.*, 1904, **37**, 453.
14 D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, 1956, **78**, 4064.
15. M. Kirilov and J. Petrova, *Chem. Ber.*, 1970, **103**, 1047.
16. N. Vinot and J. Pinson, *Bull. Soc. Chim. Fr.*, 1968, **12**, 4970.

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