HETEROCYCLES FROM NITRILE OXIDES. PART IV[1]. 1,2,4,5-OXATRIAZINES[2]

Ahmad Q. Hussein*, Mustafa M. El-Abadelah, Hamdallah A. Hodali, Marwan R. Kamal, and Mohammed M. Aouf

Department of Chemistry, Faculty of Science, University of Jordan, Amman, Jordan

Abstract — The reaction of nitrile oxides with hydrazones is found to constitute a convenient synthetic route to the hitherto unknown 4,5-dihydro-6H-1,2,4,5-oxatriazines. Elemental analysis and spectral data conform with the present oxatriazine ring system and disprove the 1,2,4-triazole structure previously assigned for such reaction products.

INTRODUCTION

The oxatriazine ring system has received limited attention in the literature. To our knowledge, the only member of this class of heterocycles known so far is the 2H-1,3,4,5-oxatriazine system reported recently by Gainsford and Woolhouse[3]. This prompted us to develop a convenient synthetic route for the hitherto undescribed 1,2,4,5-oxatriazines. Our successful synthesis of oxadiazines from nitrile oxides (I) and selected aza-nucleophiles[4], led us to expect that oxatriazines could be accessible via interaction of I with suitably functionalized diaza-substrates. In the present work, we find that nitrile oxides (I) do react with hydrazones (II) to give directly the expected 6H-1,2,4,5-oxatriazine derivatives (IV) as quite stable crystalline solids (Scheme 1, Table 1).

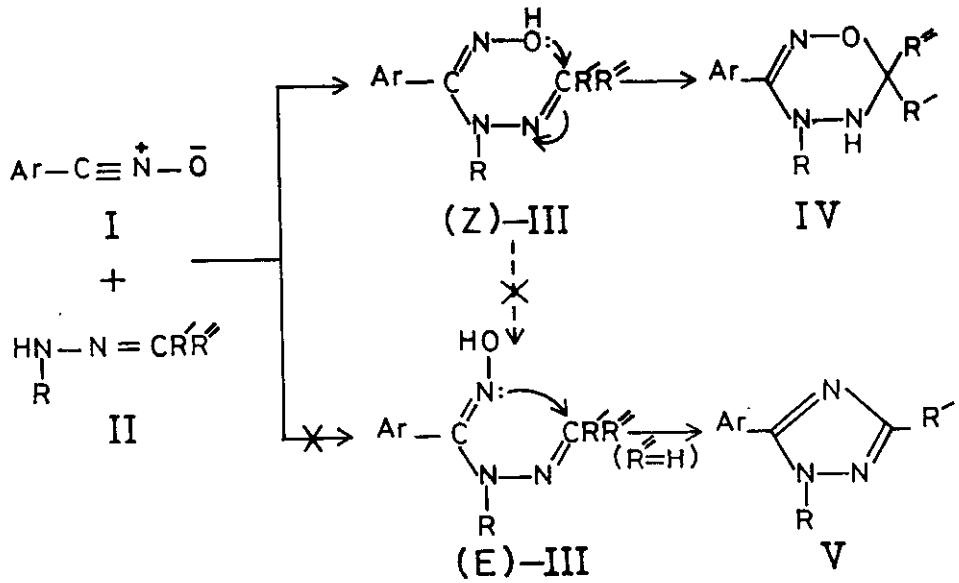
RESULTS AND DISCUSSION

A. Mechanism

The addition of nucleophiles to nitrile oxides (I) is well known to proceed in a stereospecific manner and results exclusively in the initial formation of the corresponding (Z)-adducts[5-7] in which the entering nucleophile and the forming lone pair at the nitrogen atom are mutually trans. Accordingly, the formation of compounds IV in the above reaction could also be assumed to involve a stereo-

specific syn-1,3-addition of II onto I which leads to the initial formation of the (Z)-hydrazoximes (III) as the kinetically controlled, nonisolable adducts. In these latter acyclic intermediates the reactive termini (the oximino oxygen and the azomethine carbon) are suitably located for intramolecular cyclization in an allowed "6-endo-trig" process[8] to yield the corresponding 1,2,4,5-oxatriazines (IV). Related intramolecular cyclizations, following the initial nucleophilic addition step, have been reported for the reaction of nitrile oxides (I) with nucleophilic substrates incorporating suitably located electrophilic centers[4,7]. The nucleophilic addition, displayed in Scheme 1, takes precedence over a 1,3-dipolar cycloaddition at the azomethine-linkage in compounds II. This is because the latter π-bond is normally unreactive dipolarophile, except for its activated types[9], towards nitrile oxides.

Scheme 1



B. Spectral Data

Structure (IV) is elucidated from spectral data and elemental analysis. The ir spectra of compounds IVa-o exhibit a sharp N-H stretching band in the range 3240-3280 cm^{-1} and an absorption band around 1640 cm^{-1} attributed to $C_3 = N$ stretching. The ^{1}H-nmr data are also consistent with the assigned structure. Thus, in compounds IVb-g,j,n the N-H and the neighboring C_6- H protons are mutually coupled and appear as two doublets at about δ 4.3 and 5.4 (J = 5 Hz) respectively; upon addition of deuterium oxide, the N-H signal disappears, and the C_6-H doublet

Table 1. Physical and Analytical Data of Compounds IV.

No	Ar	R	R'	R''	Mp(°C)	Formula	Analyses Calcd. C	H	N	Found C	H	N
IVa	C_6H_5	CH_3	$-CH_2(CH_2)_3CH_2-$		76-77[a]	$C_{14}H_{19}N_3O$	68.54	7.81	17.13	68.88	7.45	17.40
IVd	C_6H_5	CH_3	p-$CH_3OC_6H_4$	H	136-137[a]	$C_{16}H_{17}N_3O_2$	67.83	6.05	14.83	67.66	6.06	14.80
IVc	C_6H_5	CH_3	o-HOC_6H_4	H	134-135[c]	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.60	66.70	5.69	15.30
IVd	p-ClC_6H_4	CH_3	C_6H_5	H	142-143[c]	$C_{15}H_{14}ClN_3O$	62.61	4.90	14.60	62.73	5.07	14.40
IVe	p-ClC_6H_4	CH_3	p-$CH_3OC_6H_4$	H	132-134[c]	$C_{16}H_{16}ClN_3O_2$	60.48	5.08	13.32	60.45	5.11	13.20
IVf	p-ClC_6H_4	CH_3	o-$CH_3OC_6H_4$	H	145-146[b]	$C_{16}H_{16}ClN_3O_2$	60.48	5.08	13.22	60.20	4.95	13.10
IVg	p-ClC_6H_4	CH_3	o-HOC_6H_4	H	149-150[c]	$C_{15}H_{14}ClN_3O_2$	59.31	4.65	13.83	59.53	4.65	13.80
IVh	p-ClC_6H_4	CH_3	$-CH_2(CH_2)_3CH_2-$		112-113[c]	$C_{14}H_{18}ClN_3O$	60.11	6.49	15.02	59.96	6.46	15.00
IVi	o-ClC_6H_4	H	C_6H_5	C_6H_5	168-169[b]	$C_{20}H_{16}ClN_3O$	68.67	4.61	12.01	68.64	4.67	11.90
IVj	o-ClC_6H_4	CH_3	o-$CH_3OC_6H_4$	H	172-173[b]	$C_{16}H_{16}ClN_3O_2$	60.48	5.08	13.22	59.98	5.20	13.00
IVk	o-ClC_6H_4	CH_3	$-CH_2(CH_2)_3CH_2-$		84-85[b]	$C_{14}H_{18}ClN_3O$	60.11	6.49	15.02	60.56	6.54	15.10
IVl	m-$NO_2C_6H_4$	H	C_6H_5	C_6H_5	158-159[b]	$C_{20}H_{16}N_4O_3$	66.66	4.48	15.55	66.19	4.49	15.30
IVm	m-$NO_2C_6H_4$	CH_3	$CH(CH_3)_2$	H	126-127[c]	$C_{12}H_{16}N_4O_3$	54.54	6.10	21.20	54.72	6.10	21.30
IVn	m-$NO_2C_6H_4$	CH_3	o-$CH_3OC_6H_4$	H	143-145[c]	$C_{16}H_{16}N_4O_4$	58.53	4.90	17.06	58.49	5.02	16.90
IVo	m-$NO_2C_6H_4$	CH_3	$-CH_2(CH_2)_3CH_2-$		133-134[c]	$C_{14}H_{18}N_4O_3$	57.92	6.25	19.30	57.82	6.28	19.20

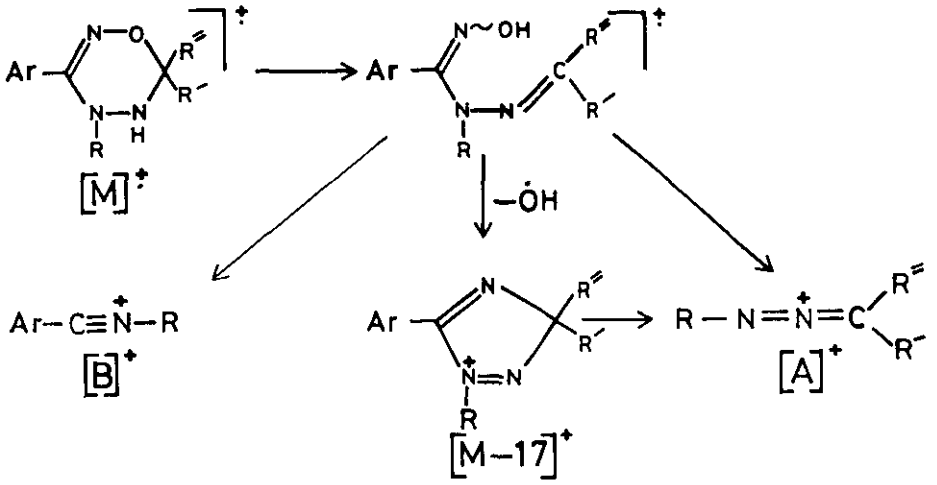
[a]Crystallized from petroleum ether (40-60°C). [b]From dichloromethane/petroleum ether. [c]From diethyl ether/petroleum ether.

collapses to a sharp singlet. The cyclohexyl methylene protons in IVa,h,k,o appear as one broadened signal centered at δ1.7 (10 H); in contrast, these protons appear in the acyclic form (E)-IIIh (vide infra) as two distinct signals at δ 2.2 (4 H) and 1.6 (6 H) of which the low-field signal belongs to the α-methylene protons as influenced by the anisotropic effect of the neighbouring azomethine π-system. The isopropyl methyl protons in IVm appear as two distinct doublets indicating them to be diastereotopic; this pattern conforms with the cyclic structure (IV), but not with the acyclic form (E)-IIIm (vide infra) in which the isopropyl methyls appear as one doublet at δ1.4. Furthermore, the C_6-H proton in IVm appears as two doublets at δ4.18 and 3.92 due to coupling with the vicinal NH (J = 5 Hz) and CH(J = 7 Hz). This signal collapses to one doublet upon addition of deuterium oxide.

^{13}C-Nmr spectra of compounds IV exhibit two signals characteristic of the C_6- and C_3- carbons of the oxatriazine ring. The signal in the range δ 80-90 is assigned to the sp^3-hybridized C_6-carbon; this assignment is in good agreement with reported data for an sp^3-carbon flanked by two electronegative atoms (nitrogen and oxygen) in related heterocycles[10]. The lowest field signal at 153-157 ppm is assigned to the sp^2-hybridized C_3-carbon, by analogy with several related azomethine systems[11]. The observed chemical shift of either signal conforms with structure IV, but not with the acyclic form (E)-III. The latter compounds exhibit two azomethine signals in the range δ 146-157, but lack the ^{13}C-signal at δ 80-90.

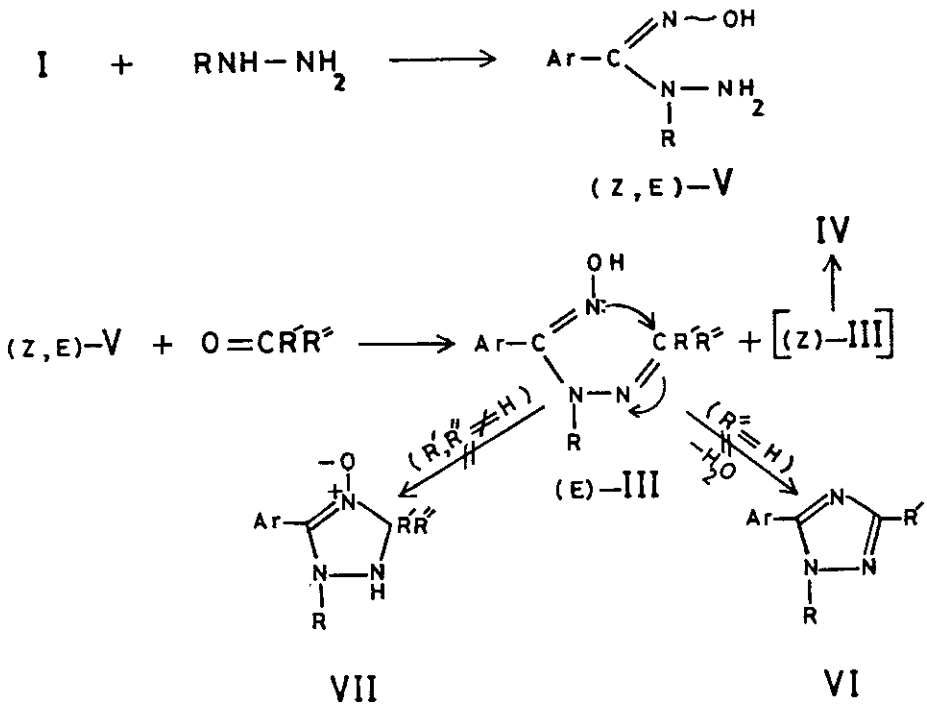
In addition to the molecular ion peaks $[M]^+$, the mass spectra of compounds IV are dominated by intense peaks corresponding to $[M-17]^+$ fragment ions for which a stable triazole structure is suggested (Scheme 2). Two other significant fragments $[A]^+$ and $[B]^+$ are also observed in all cases. Ion $[A]^+$ is probably formed either by expulsion of ArCN from $[M-17]^+$, or alternatively, via elimination of ArCNO and H• form $[M]^+$ in a retro 1,3-dipolar addition process. Ion $[B]^+$ originates from $[M]^+$ by ring-opening, via bond rupture at C_6-O, followed by elimination of R'R"C=NH and N=O.

Scheme 2



In the present work, compounds IV were also obtained, though in low yields, by condensation of hydrazidoximes (V), accessible from the reaction of nitrile oxides (I) and methylhydrazine[12], with the appropriate carbonyl compounds (Scheme 3). The major products isolated from this condensation were the isomeric acyclic adducts (E)-III. By analogy to literature reports[6,7] on the stereochemistry of the closely related amidoximes, the starting hydrazidoximes (V) are expected to exist as mixtures of both (Z)- and (E)-forms, in which the latter form predominates, being thermodynamically more stable. The stereochemistry of V is retained in the hydrazoximes (III) derived thereof. This explains the formation of both IV (produced by spontaneous cyclization of (Z)-III) and (E)-III from the condensation of hydrazidoximes (V) with carbonyl compounds. Compounds (E)-IIIh,m are quite stable and are recovered unchanged after prolonged reflux (24 h) in ether or ethanol. This behaviour lends support to the (E)-configuration assigned for these compounds. Cyclization of these acyclic adducts to the corresponding triazole derivatives VI,VII is unlikely (Scheme 3), as such step would involve a disfavoured "*5-endo-trig*." process[8].

Scheme 3



C. Conclusion

Our present findings are contrary to the results reported by Risitano and coworkers[13] who identified the reaction products, they obtained from the interaction of benzonitrile oxide with methylhydrazones, as 1,2,4-triazoles (VI). Reinvestigation of the reaction mixture revealed, in all cases, that the only by-products formed in the present study were furoxans (dimerization products of the nitrile oxides). Under the experimental conditions employed in the present study, triazoles were neither isolated nor detected.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer model 577 spectrophotometer, using potassium bromide pellets. A Varian T-60 A spectrometer was used for obtaining ^{1}H-nmr spectra in $CDCl_3$ with TMS as internal reference. ^{13}C-Nmr spectra (FT-mode) were recorded on a Bruker WM-250 spectrometer at 26.97 MHz using $CDCl_3$ as the solvent and TMS as internal reference. Mass spectra were determined on a Finnigan MAT 112 spectrometer using the direct inlet

technique (70 eV). Microanalysis was performed at the Mikroanalytisches Labor-Pascher (Bonn).

Hydroxamoyl Chlorides (Precursors of Nitrile Oxides I). Benzhydroxamoyl chloride, p-chlorobenzhydroxamoyl chloride, o-chlorobenzhydroxamoyl chloride and m-nitrobenzhydroxamoyl chloride, used in this study, were prepared by direct chlorination of the respective aldoximes following previously published procedures[14].

Monomethylhydrazones (II). Methylhydrazones employed in this work, were obtained by direct interaction between monomethylhydrazine and the corresponding carbonyl compound following literature procedures[15].

Isobutyraldehyde Methylhydrazone. This compound was obtained in 80% yield, bp 148-150°C/680 mmHg. Anal. Calcd. for $C_5H_{12}N_2$: C,59.95; H,12.00; N,27.97. Found: C,59.78; H,11.95; N,27.70.

General Procedure for the Preparation of 6H-1,2,4,5-Oxatriazines (IVa-o). A solution of the appropriate hydroxamoyl chloride (0.01 mol) in chloroform (10 ml) was added dropwise to a stirred solution of the respective hydrazone II (0.01 mol) and triethylamine (0.03 mol) in chloroform (40 ml) at -20°C. The temperature of the reaction mixture was then allowed to rise slowly to room temperature following the addition, and stirring was continued for 1 h. The solvent was finally removed in vacuo, and the residue washed with water (2 x 20 ml), dried and treated with absolute ethanol (20 ml). The insoluble furoxan by-product was removed by filtration and the alcoholic filtrate was evaporated in vacuo. The remaining solid product was recrystallized from the appropriate solvent. Yields were in the range of 45-65%.

Hydrazidoximes (V). These compounds were prepared from the reaction of hydrazine hydrate or methylhydrazine (0.1 mol) with the appropriate hydroxamoyl chloride (0.1 mol) in chloroform, in the presence of triethylamine at zero to -5°C.

p-Chlorophenyl-N-methylhydrazidoxime (Vh). This compound was obtained in 40% yield, mp 98-100°C (decomp.), recrystallized from ether/petroleum ether

(bp 40-60°C). Anal. Calcd. for $C_8H_{10}ClN_3O$: C,48.13; H,5.05; N,21.05. Found: C,48.15; H,5.19; N,20.90.

m-Nitrophenyl-N-methylhydrazidoxime (Vm). This compound was obtained in 45% yield, mp 113-115°C (decomp.), recrystallized from dichloromethane/petroleum ether. Anal. Calcd. for $C_8H_{10}N_4O_3$: C,45.70; H,4.80; N,26.66. Found: C,45.77; H,4.88; N,26.50.

Condensation of Hydrazidoximes (V) with Carbonyl Compounds. Cyclohexanone (0.01 mol) and the hydrazidoxime (Vh, 0.01 mol) were refluxed in absolute ether (100 ml) for 1 h. The solvent was then evaporated leaving a solid residue composed of compounds IVh and IIIh. Separation of this mixture on preparative silica gel plates (using chloroform as the developing solvent) gave compounds IVh (20%) and (E)-IIIh (75%). Compound (E)-IIIh: mp 125-126°C, crystallized from ether/petroleum ether. Anal. Calcd. for $C_{14}H_{18}ClN_3O$: C,60.11; H,6.49; N,15.02. Found: C,59.94; H,6.41; N,15.03. Compounds IVm (12%) and (E)-IIIm (80%) were similarly obtained from the reaction between isobutyraldehyde (0.01) and the hydrazidoxime (Vm) (0.01 mol). Compound (E)-IIIm: mp 136-138°C, crystallized from ether/petroleum ether. Anal. Calcd. for $C_{12}H_{16}N_4O_3$: C,54.54; H,6.10; N,21.20. Found: C,54.48; H,6.08; N,21.14.

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