Tetrahedron Vol. 34, pp. 2961–2966
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0040-4020/78/1001-2961/$02.00/0

REARRANGEMENT OF AZIDOXIMES TO TETRAZOLE DERIVATIVES†

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(*Received in UK 9 February 1978; Accepted for publication 27 April 1978*)

Abstract—Some new azidoximes and their O-substituted derivatives as well as 5-substituted-1-acyloxy- and 1-hydroxytetrazoles were prepared. O-Substitution of azidoximes followed by protonation were found to be the initial steps in their cyclisation to tetrazole derivatives. The mechanism of the cyclisation reaction was proposed and the structure of 5-substituted-1-hydroxytetrazoles discussed.

The reaction of hydroxamic acid chlorides (hydroxamoyl chlorides) with the azide ion has been known for almost 70 years. According to early structural assignments,[1,2] 1-hydroxytetrazole derivatives were considered as final products, and azidoximes, as unstable intermediates of this reaction. IR-spectroscopic investigations[3–5] of numerous known and new compounds prepared in this way revealed the presence of a strong N_3 stretching vibrations band, which gave evidence of the azidoxime structure. At the same time it was found[3] that azidoximes were stable only in the linear form and that they did not cyclise to the corresponding 1-hydroxytetrazoles though quite a number of closely related azidoazomethines were well known to exist in an equilibrium with tetrazoles:

Fig. 1.

To explain the stability of azidoximes, the electron withdrawing capacity of the OH group was considered[6] to prevent the π electron shift from the azomethine bond to the azide N atom and, therefore, preventing cyclisation.

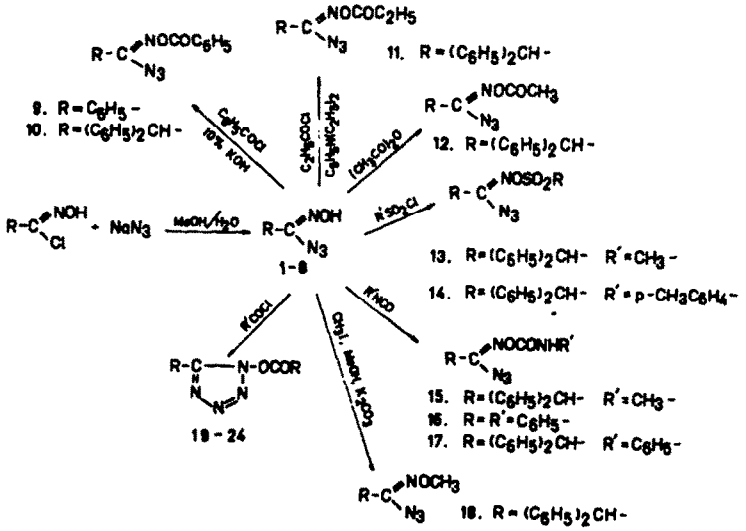
In an earlier communication,[7] I have reported on the cyclisation of azidoximes to tetrazoles which was effected by the action of acyl chlorides in inert solvents. In the present research an attempt was made to amplify the knowledge of the reaction by studying reactivity of particular azidoximes and investigating factors that control the cyclisation process.

RESULTS AND DISCUSSION

The azidoximes (1–8) were prepared by the reaction of sodium azide with the appropriate hyroxamic acid chloride. Yields of the reactions were in the 80–90% range. Properties of the synthesized azdoximes are collected in Table 1.

The characteristic IR frequencies presented in Table 1 are in agreement with the azidoxime structure of the compounds. The ^1H NMR spectra taken at room temperature for the saturated solutions in $(CD_3)_2CO$ revealed sharp signals of the OH protons in the $\delta = 9.70$–11.70 ppm region. Further transformations of the azidoximes are shown in Scheme 1.

Some of the azidoximes were benzoylated with benzoyl chloride. As judged by the m.p., compound **9** was



Scheme 1. Reactions of azidoximes.

†Preliminary results of this study were presented in a note (Ref. 7).

Table 1. Yields and properties of azidoximes

No.	R	m.p. °C	Yield %	Calculated %			Found %			ν_{OH} cm^{-1}	$\nu_{C=N}$ cm^{-1}	ν_{N_3} cm^{-1}
				C	H	N	C	H	N			
1	C_6H_5	123-4*	87							3200	1635	2200 2155 2110
2	$p\text{-}CH_3C_6H_4$	108.5-110	88	54.54	4.55	31.82	54.44	4.77	31.61	3250	1625	2200 2138 2093
3	$p\text{-}NO_2C_6H_4$	142-4	99	40.58	2.42	33.83	40.78	2.56	34.01	3240	1632	2230 2160 2112
4	$(C_6H_5)_2CH$	146-7	94	66.66	4.80	22.22	66.67	4.91	22.36	3275	1655	2160 2137
5	C_6H_5, $p\text{-}CH_3C_6H_4$, CH	122-4	92	67.66	5.26	21.05	67.89	5.34	21.12	3270	1660	2130
6	$(p\text{-}CH_3C_6H_4)_2CH$	133-5	93	68.54	5.76	19.99	68.61	5.75	20.07	3260	1660	2135
7	C_6H_5, $p\text{-}ClC_6H_4$, CH	113.5-114.5	69	58.63	3.83	19.54	58.59	3.82	19.47	3270	1655	2175 2125
8	C_6H_5, $2,6\text{-}Cl_2C_6H_3$, CH	132-3	92	52.33	3.11	17.45	52.07	3.07	17.42	3250	1660	2180 2152 2130

* Lit.[1] m.p. 124°

identical with that prepared by Forster.[1] The azidoxime structure of compounds **9** and **10** was confirmed by the presence of strong ν_{N_3} bands in the 2160–2115 cm^{-1} region. Acylation of diphenylacetazidoxime (**4**) with propionyl chloride in cyclohexane in presence of an excess of N,N-diethylaniline gave also a linear product, namely O-propionyldiphenylacetazidoxime (**11**).

Diphenylacetazidoxime (**4**) treated at room temperature with an excess of acetic anhydride, yielded O-acetyldiphenylacetazidoxime (**12**). When the reaction was carried out under reflux, **12** was accompanied by small amounts of 1-acetoxy-5-benzhydryltetrazole (**19**) and diphenylacetonitrile.

Treatment of **4** at room temp. with methanesulphonyl or tosyl chlorides in cyclohexane resulted in decomposition of the starting material and the formation of diphenylacetonitrile as the sole product. The same reaction effected in pyridine gave the appropriate O-sulphenyl derivatives **13** and **14**, together with small quantities of diphenylacetonitrile.

Azidoximes reacted at room temp with organic isocyanates in an inert solvent, e.g. benzene gave the appropriate O-carbamoyl derivatives **15–17**. All the reactions gave high yields of fairly stable products. The azidoxime structure of the compounds was established on the basis of their IR spectra.

The reaction of **4** with methyl iodide in methanol solution in presence of potassium carbonate yielded O-methyldiphenylacetazidoxime (**18**).

Treatment of azidoximes with carboxylic acid chlorides or bromides in an inert solvent or without any solvent led to the appropriate 1-acyloxytetrazoles.[7] In the case of acetyl, chloroacetyl, and propionyl chlorides, very high yields of the reaction were secured by simply mixing the reagents in a cyclohexane, benzene or acetonitrile solution at room temperature, and then stirring for a few hours. The benzoyl derivative was obtained with neat benzoyl chloride at 75–80°. A similar reaction of **4** with pivaloyl chloride yielded 60% of 1-hydroxy-5-benzhydryltetrazole **28** and 30% of diphenylacetonitrile. Some data of the synthesised 1-acyloxytetrazoles (**19–24**) are summarised in Table 2.

Because of particular susceptibility to hydrolysis, I was not able to obtain analytical samples of 1-acyloxytetrazoles prepared from arylazidoximes **1–3** and acetyl and propionyl chlorides and from *p,p'*-dimethyldiphenylacetazidoxime **6** and propionyl chloride. In such cases products were converted into the corresponding 1-hydroxytetrazoles by directly dissolving them in hot ethanol. Other 1-hydroxytetrazoles were obtained analogously. Yields and properties of 1-hydroxytetrazoles synthesised (**25–31**) are summarised in Table 3.

All the compounds presented in Table 3 are stable at room temp. and can be easily isolated pure. 5-[2.6-Dichloro-diphenylaceto]-1-hydroxytetrazole (**31**) crystallised with one molecule of ethanol. M.ps of all the 1-hydroxytetrazoles are considerably higher than those of the corresponding azidoximes. In the IR spectra of the tetrazoles taken as KBr pellets, there is no absorption in the 4000–3080 cm^{-1} region; a strong and very broad band between 2800 and 2000 cm^{-1}, with a maximum at approximately 2450 cm^{-1}, and a strong band in the 1245–1210 cm^{-1} range are characteristic of the compounds. The latter may be assigned to the N^+–O^- bond valence vibrations.[8]

In the ^1H NMR spectra of the 5-aryl substituted compounds (**25–27**) taken as $(CD_3)_2CO$ solutions

Table 2. Yields and properties of 1-acyloxytetrazoles

No.	R	R'	m.p. °C	Yield %	Calculated %				Found %				$\nu_{C=O}$ cm^{-1}
					C	H	N	O	C	H	N	O	
19	$(C_6H_5)_2CH$	CH_3	138.5–139.5	64	65.31	4.78	19.05	10.86	65.26	4.79	19.11	10.84	1838
20	$(C_6H_5)_2CH$	CH_2Cl	135–6	87	58.45	3.98	17.05	20.52	58.08	4.09	17.51	20.32	1858
21	$(C_6H_5)_2CH$	C_2H_5	121–3	96	66.23	5.10	18.18	10.46	66.46	5.19	18.08	10.28	1853
22	$(C_6H_5)_2CH$	C_6H_5	131–3	87	70.78	4.81	15.73	8.68	70.90	4.81	15.98	8.31	1810
23	$p\text{-}CH_3OC_6H_4\text{-}CH$ (with C_6H_5)	C_2H_5	83–4	58	67.06	5.62	17.37	9.95	67.51	5.84	17.31	9.34	1830
24	2.6-$Cl_2C_6H_3\text{-}CH$ (with C_6H_5)	C_2H_5	123–5	86	54.11	3.71	14.85	17.03	53.99	3.72	14.84	17.44	1840

Table 3. Yields and properties of 1-hydroxytetrazoles

No.	R	m.p. °C	Yield %	Calculated %			Found %		
				C	H	N	C	H	N
25	C_6H_5	151–2	82	51.85	3.70	34.57	51.98	3.78	34.48
26	$p\text{-}CH_3C_6H_4$	196–6	88	54.54	4.55	31.82	54.27	4.66	32.07
27	$p\text{-}NO_2C_6H_4$	178.5–180	85	40.58	2.41	33.81	40.29	2.71	33.62
28	$(C_6H_5)_2CH$	196.5–197	92	66.66	4.76	22.22	66.44	4.76	22.16
29	$p\text{-}CH_3C_6H_4(C_6H_5)CH$	147–8	87	67.66	5.26	21.05	67.95	5.36	21.18
30	$(p\text{-}CH_3C_6H_4)_2CH$	149.5–150.5	85	68.54	5.76	19.99	68.89	5.86	20.13
31	$2,6\text{-}Cl_2C_6H_3(C_6H_5)CH$	202–3	87	52.32	4.36	15.26	51.93	4.32	14.99

saturated at room temp. unlike those of the 5-benzhydryl derivatives (28–31), there is a distinct though very broad (approx. 50 Hz) one-proton signal in the $\delta = 6.40$–9.50 ppm region. Similar spectra taken in deuteriated pyridine for 5-phenyl-1-hydroxytetrazole (25), and 5-benzhydryl-1-hydroxytetrazole (28) showed a quite sharp one-proton signal at $\delta = 13.55$ and 15.92 ppm respectively. Such a significant downfield shift can be explained by assuming an H-bond to the pyridine N with the H atom in the pyridine ring plane. The results referred to do not deny the possible existence of the tautomeric form according to the following equilibrium:

Fig. 2.

Attempts were made to answer this question by taking a broadband ^{14}N-decoupled ^{1}H NMR spectrum for a solution of 25 in pyridine-d_5. There was no change in the shape of the $\delta = 13.55$ ppm signal this being in agreement with the hydroxyimine structure concept. Also attempts at the reduction of the supposed N-oxide group with PCl_3 and sodium borohydride as well as the Katritzky's test[9] for N-oxides gave negative results supplying further evidence of the hydroxyimine structure.

Treatment of 12 solutions in moist benzene with acetyl chloride or bromide yielded 19. With concentrated hydrochloric acid used instead of the acyl halide 28 was obtained. The cyclisation was also effected with trifluoroacetic acid used as the protonating agent, it was, however, much slower (100% cyclisation in 2 hr with acetyl halide or hydrochloric acid and in 3 days with CF_3COOH). This effect is opposite to that observed previously[10] for various azidoazomethines in which protonation stabilised the azide form. The discrepancy may be attributed to different protonation sites. A comparison of the cyclisation rates showed that in benzene solutions and in presence of acetyl chloride 12 cyclised to 19 approximately eight times faster than 18 to 1-methoxy-5-benzhydryltetrazole[11] (2 and 16 hr, respectively, for complete cyclisation†).

The results presented above support the suggestion that cyclisation of O-acylazidoximes to tetrazoles can be initiated by protonation of the C-bonded azide N atom which bears the highest negative charge. Further steps may proceed according to the alternative paths as shown in Scheme 2.

In path I the lone pair of the azomethine N atom can form a dative bond with the positively charged terminal azide N atom. In path II, π-electrons of the azomethine double bond can be shifted towards the protonated N atom, and the lone pair of the terminal N atom can form a new bond with the azomethine N atom.[12] Of course, the formation of such a bond is possible only when we assume a considerable distortion of bond angles between N atoms in the azide group.[6] The difference observed in the cyclisation rate as between 12 and 18 may be considered to favour the path II. The electron-withdrawing CO group acts to diminish electron density on the azomethine N atom, and thus assists in the cyclisation. On the other hand, the electron donating Me group has an opposite effect.

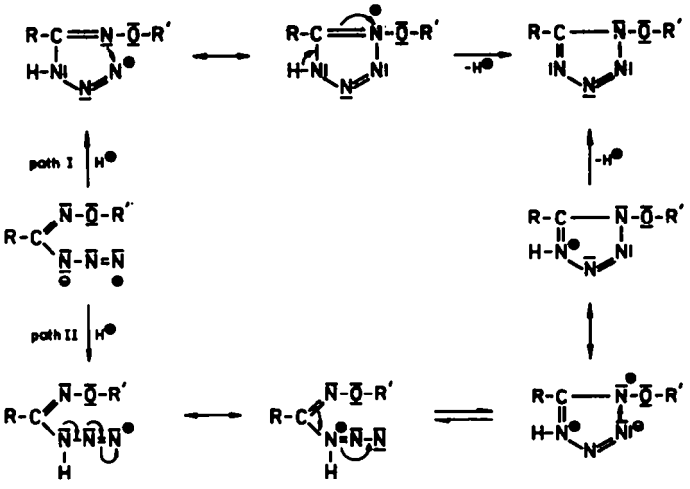
EXPERIMENTAL

M.ps are given uncorrected as measured in a Franz Küstner melting point apparatus. C, H and N analyses were performed on a Perkin–Elmer 240CHN Analyser. IR spectra were recorded with a Carl Zeiss UR-10 Spectrophotometer. NMR spectra were taken on a Jeol JNM-MN-100 Spectrometer.

General method of preparation of azidoximes 1–8. To a stirred soln of the appropriate hydroxamic acid chloride (0.01 m) in 30 ml MeOH, a soln of sodium azide (0.71 g, 0.011 m) in 10 ml H_2O was added in small portions. Stirring was continued for 6–7 hr. The resulting ppt was filtered off and recrystallised from EtOH. The azidoximes readily soluble in dilute MeOH were isolated from the mixture by evaporation of the solvent and extraction with benzene and purified by recrystallisation from cyclohexane.

O-Benzoyldiphenylacetazidoxime 10 was obtained by the Schotten–Baumann method from diphenylacetazidoxime in the

†These investigations made use of tlc and IR spectroscopy decreasing intensity of the azide band. The cyclisation products were isolated and compared with reference samples.



Scheme 2. Proposed ways of cyclisation of azidoximes to tetrazoles.

yield of 96%, m.p. 110–111° after recrystallisation from n-hexane. $IR_{(KBr)}$: ν_{N_3} 2145; $\nu_{C=O}$ 1748 cm^{-1}. (Found: C, 70.65; H, 4.46; N, 15.58. Calc. for $C_{21}H_{16}N_4O_2$: C, 70.78; H, 4.49; N, 15.73%).

O-Propionyldiphenylacetazidoxime **11**. To a stirred suspension of diphenylacetazidoxime (2.52 g, 0.01 m) in 50 ml cyclohexane and 2.65 g, (0.022 m) N,N-diethylaniline, propionyl chloride (1.6 g, 0.017 m) was added dropwise. Stirring was continued over 24 hr at room temp. The ppt of N,N-diethylaniline hydrochloride was filtered off and filtrate was evaporated to dryness, yield: 2.6 g (84%), m.p. 59–59.5° after recrystallisation from n-hexane. $IR_{(KBr)}$: ν_{N_3} 2185, 2158; $\nu_{C=O}$ 1776 cm^{-1}. (Found: C, 66.35; H, 5.19; N, 18.19. Calc. for $C_{17}H_{16}N_4O_2$: C, 66.23; H, 5.19; N, 18.18%).

O-Acetyldiphenylacetazidoxime **12**. Diphenylacetazidoxime (2.52 g, 0.01 m) was added to 10 ml freshly distilled Ac_2O. The suspension was left for 16 hr at room temp. After evaporation of the excess Ac_2O under reduced pressure, the residue was treated with 15 ml water and extracted with benzene. The organic layer was washed with water, $NaHCO_3$ aq, again with water and dried over $MgSO_4$. After evaporation of the solvent, 2.5 g (85%) of **12** was obtained, m.p. 65–6° after recrystallisation from cyclohexane. $IR_{(KBr)}$: ν_{N_3} 2167, $\nu_{C=O}$ 1745 cm^{-1}. (Found: C, 65.52; H, 4.79; N, 18.98. Calc. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.76; N, 19.04%).

O-Methylsulphonyldiphenylacetazidoxime **13**. A soln of 2.52 g (0.01 m) of diphenylacetazidoxime in 10 ml pyridine was cooled to 0° and 1.25 g (0.011 m) methanosulphonyl chloride was added dropwise. Stirring was continued for 1 hr, the mixture allowed to warm up to room temp. and finally poured into 100 ml water. The resulting ppt was filtered off and recrystallised from benzene, yield: 2.7 g (82%), m.p. 118–9° with dec. $IR_{(KBr)}$: ν_{N_3} 2165 cm^{-1}. (Found: C, 54.56; H, 4.30; N, 17.25. Calc. for $C_{15}H_{14}N_4O_3S$: C, 54.54; H, 4.24; N, 16.97%).

O-Tolylsulphonyldiphenylacetazidoxime **14** was obtained in a similar manner, yield 78%, m.p. 114–5° after recrystallisation from benzene. $IR_{(KBr)}$: ν_{N_3} 2165 cm^{-1}, 2137 cm^{-1}. (Found: C, 61.99; H, 4.86; N, 13.51. Calc. for $C_{21}H_{18}N_4O_3S$: C, 62.54; H, 4.46; N, 13.79%).

O-Methylcarbamoyldiphenylacetazidoxime **15**. Methyl isocyanate (0.65 g, 0.011 m) was added to a stirred suspension of 2.52 g (0.011 m) diphenylacetazidoxime in 30 ml benzene. Stirring was continued for 20 hr. The ppt was filtered off, yield: 2.5 g (81%), m.p. 63–8°, m.p. 71–2° after repeated recrystallisation from n-hexane. $IR_{(KBr)}$: ν_{NH} 3320; ν_{N_3} 2195, 2178, 2134; $\nu_{C=O}$ 1737 cm^{-1}. (Found: C, 62.30; H, 4.86; N, 22.80. Calc. for $C_{16}H_{15}N_5O_2$: C, 62.14; H, 4.85; N, 22.65%).

O-Phenylcarbamoylbenzazidoxime **16** was obtained analogously in the yield of 78%, m.p. 85–6° after recrystallisation from cyclohexane. $IR_{(KBr)}$: ν_{NH} 3360; ν_{N_3} 2170, 2130; $\nu_{C=O}$ 1749 cm^{-1}. (Found: C, 60.06; H, 4.03; N, 24.64. Calc. for $C_{14}H_{11}N_5O_2$: C, 59.79; H, 3.91; N, 24.91%).

O-Phenylcarbamoyldiphenylacetazidoxime **17** was prepared in a similar manner, yield 94%, m.p. 136–7° after recrystallisation from 96% EtOH. $IR_{(KBr)}$: ν_{NH} 3384; ν_{N_3} 2173, 2135; $\nu_{C=O}$ 1763 cm^{-1}. (Found: C, 68.15; H, 4.69; N, 18.89. Calc. for $C_{21}H_{17}N_5O_2$: C, 67.96; H, 4.60; N, 18.86%).

O-Methyldiphenylacetazidoxime **18**. To the suspension of 2.52 g (0.01 m) diphenylacetazidoxime and 3 g K_2CO_3 in 25 ml MeOH, 4.26 g (0.03 m) MeI was added. The mixture was stirred for 12 hr at room temp., and next 8 hr at 40–50°. Inorganic salts were filtered off, and filtrate was evaporated to dryness and purified on chromatography column (benzene/n-hexane 1.5:2 by vol.), yield 1.9 g (71%) of oily substance. $IR_{(film)}$: ν_{N_3} 2145, 2180 cm^{-1}. (Found: C, 67.81; H, 5.21; N, 20.63. Calc. for $C_{15}H_{14}N_4O$: C, 67.67; H, 5.26; N, 21.05%).

General method of preparation of 1-acyloxytetrazoles **19–24** *and 1-hydroxytetrazoles* **25–31**. The appropriate acid chloride (0.02 m) was added dropwise with stirring to a suspension or soln of 0.01 m azidoxime in a neutral solvent. Stirring was continued at room temp. for 12 hr. 1-Acyloxytetrazole was filtered off, or isolated by evaporation of the solvent. Crude product was recrystallised from benzene or cyclohexane.

1-Hydroxytetrazoles were obtained by recrystallisation of the appropriate 1-acyloxy derivatives from 96% EtOH.

General method of cyclisation of O-substituted azidoximes to corresponding tetrazole derivatives. The appropriate azidoxime derivative (0.3 g) was dissolved in 5 ml benzene and 0.5 ml of a protonating agent was added. The soln was left at room temp. and the reaction course was checked on tlc plates (benzene/chloroform 1:2). After evaporation of the solvent the residue was recrystallised.

Acknowledgements—I wish to thank Prof. Walter Lwowski, New Mexico State University, Las Cruces, for taking ^{14}N-decoupled ^1H NMR spectra and helpful discussion. I would also thank Prof. M. Makosza for discussing the results of the work prior to publication.

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