Studies on Heteroaromaticity. XVI.[1] Further Studies on the Thermal 1,3-Dipolar Cycloaddition Reactions of Some Aromatic Hydroxamoyl Chlorides

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With a view of extending the synthetic utility of the thermal 1,3-dipolar cycloaddition reactions,[2] 5-nitro-2-furyl- (Ia), phenyl- (Ib), *p*-nitrophenyl- (Ic) and *m*-nitrophenylhydroxamoyl chloride (Id) were treated with i) triphenylphosphine, ii) benzonitrile or acetonitrile, iii) aromatic aldehydes, iv) quinones, v) anthranilate and vi) cyclic non-conjugated polyenes; each reaction proceeded smoothly with evolution of hydrogen chloride gas except when basic dipolarophiles were used. By this reaction, the yields of products were better than those *via* the routine nitrile oxide methods.

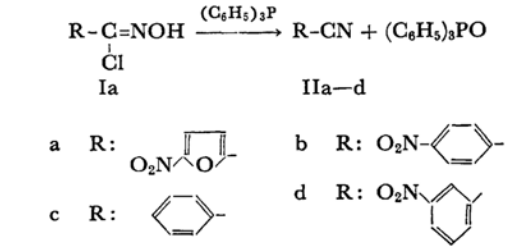
In the previous report,[2] the thermal 1,3-dipolar cycloaddition reactions of furyl- and 5-nitro-2-furylhydroxamoyl chloride with olefinic and acetylenic compounds was described and this paper deals with further experimental results carried out on several dipolarophiles with a view of extending the synthetic potentials of the thermal procedure. Reactions were carried out by using 5-nitro-2-furyl- (Ia), phenyl- (Ib), *p*-nitrophenyl- (Ic) and *m*-nitrophenylhydroxamoyl chloride (Id) and each reactivity was compared with those of the corresponding nitrile oxides, if possible.

Results and Discussion

Reaction with Triphenylphosphine. Stable aromatic nitrile oxides such as tri- and tetramethyl-substituted benzonitrile oxides are known to react with triphenylphosphine to afford the corresponding aromatic nitriles accompanied with the formation of triphenylphosphine oxide[3] but no description about the reaction of triphenylphosphine with benzonitrile oxide can be found. The corresponding nitrile oxides derived from Ia–d were treated with triphenylphosphine under the given reaction conditions[3] to afford the furoxane-type products instead of nitriles presumably because of strongly basic character of triphenylphosphine, but when Ia–d were directly heated in toluene with an equimolecular amount of triphenylphosphine for several hours, the corresponding nitriles, IIa–d, were obtained in good yields as shown in Table 1, also accompanied with the formation of triphenylphosphine oxide in almost quantitative yields. Such different yields might come from the different stability of each

Table 1. Nitriles (IIa—d)

Dipolar	Reflux hr	Yield %	Melting point, °C	IR (KBr) ν_{CN}, cm^{-1}
Ia	9	52	65—67[19]	2290
Ib	5	60	bp 190—192	2290
Ic	7	65	140—143[15]	2290
Id	9	71	119—118[16]	2290



1) Part XV of this series: T. Sasaki, S. Eguchi and K. Kojima, *J. Heterocyclic Chem.*, **5**, (1968) in press.

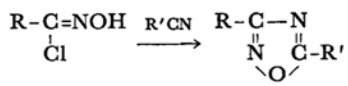
2) T. Sasaki and T. Yoshioka, This Bulletin, **40**, 2604 (1967).

3) C. Grundmann and H.-Q. Frommeld, *J. Org. Chem.*, **30**, 2077 (1965).

hydroxamoyl chloride, Ia—d, under the given creation conditions. It should be added that by this thermal procedure, no furoxane formation was observed as reported in the previous paper.[2]

Reaction with Benzonitrile or Acetonitrile. Benzonitrile oxide has been converted to oxadiazoles by the 1,3-dipolar cycloaddition reactions with both aromatic nitriles[4] and the nitriles activated by an electron-attracting substituent,[5] but the reaction with aliphatic nitriles was unsuccessful, though the catalytic action of boron trifluoride in the cycloaddition of benzonitrile oxide with nitriles and carbonyl compounds has been reported by Morrocchi, *et al.*[6]

Ia was heated in toluene with benzonitrile for 11 hr giving the corresponding oxadiazole IIIa in only 8% yield; the similar procedure in the presence of boron trifluoride etherate as a catalyst gave the same product in a 36% yield, while the reaction of 5-nitro-2-furocarbonitrile oxide with benzonitrile only afforded intractable tars. Ib also afforded IIb in a 65% yield even without the catalyst and almost quantitatively with the catalyst. IIIb has been prepared by the 1,3-dipolar cycloaddition of benzonitrile oxide with benzonitrile without a catalyst in a 55% yield.[7] These results obviously indicate that the presence of boron trifluoride can improve the yields of the thermal 1,3-dipolar cycloaddition products. The reaction of Ia with acetonitrile did not occur even in the presence of the catalyst and Ia was recovered, though Ib afforded IVb in a 35% yield under the similar reaction conditions. IVb has been prepared by the reaction of benzonitrile oxide with acetonitrile in the presence of the catalyst in a 35% yield.[6]



Ia—d

IIIa—d (R′: C_6H_5), IVb (R′: CH_3)

These results are summarized in Table 2 except IVb.

Reaction with Aromatic Aldehydes. Similar 1,3-dipolar cycloaddition reactions of benzonitrile oxide with such carbonyl compounds as aromatic

Table 2. 1,2,4-Oxadiazoles (IIIa—d)

Dipolar	Reflux hr	Yield %	Melting point °C	Microanalysis Found (Calcd) C	H	N	UV λ_{max}^{EtOH} mμ (ε)
Ia	11	8	IIIa 206	56.10	2.73	16.13	313 (18600)
	11*	36		(56.03	2.74	16.34)	255 (22900)
Ib	16	65	IIIb 110[7]				244 (50500)
	10*	Quantitative					
Ic	10	<5	IIIc 210	62.74	3.05	15.48	275† (22200)
	10*	25		(62.92	3.39	15.73)	262 (28400)
Id	24	50	IIId 165	63.54	2.73	15.91	250† (31100)
	24*	80		(62.92	3.39	15.48)	232 (36000)

* In the presence of boron trifluoride etherate as a catalyst.
† Shoulder.

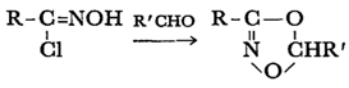
Table 3. Dioxazoles (Vb, VIb and VId)

Dipolar	Dipolarophile	Yield %	Product (Mp, °C)	Microanalysis Found (Calcd) C	H	N	UV λ_{max}^{EtOH} mμ (ε)	NMR ($CDCl_3$) C-5-H (τ)
Ib	p-NO_2-C_6H_4-CHO	55	Vb (133)	61.93 (62.22	3.37 3.73	10.52 10.37)	258 (23000)	3.00 (singlet)
Ib	5-NO_2-C_4H_2O-CHO	45	VIb (127)	54.99 (55.39	2.63 3.10	10.73 10.77)	288 (12200) 265 (11000)	3.02 (singlet)
Id	5-NO_2-C_4H_2O-CHO	10	VId (110)	47.51 (47.22	2.29 2.31	13.91 13.77)	290 (13900) 252 (18000)	

4) G. Leamdri and M. Palotti, *Ann. Chim.* (*Rome*), **47**, 376 (1957).
5) R. Huisgen, W. Mack and E. Anneser, *Tetrahedron Letters*, **1961**, 583.
6) S. Morrocchi, A. Ricca and L. Velo, *ibid.*, **1967**, 331.
7) F. Floy and R. Lenaers, *Helv. Chim. Acta*, **46**, 1067 (1961).

aldehydes, α-ketoesters and α-diketones have been reported to afford dioxazoles, but no reactions have been reported to occur with aliphatic aldehydes, acetophenone and aliphatic ketones in general.[5] Treatment of Ia with benzaldehyde, *p*-nitrobenzaldehyde and 5-nitro-2-furfural in the presence of the catalyst resulted in the formation of intractable tars, while Ib afforded with *p*-nitrobenzaldehyde and 5-nitro-2-furfural the corresponding dioxazoles, Vb, and VIb, respectively and similarly VId from Id and 5-nitro-2-furfural even in the absence of the catalyst. These results are summarized in Table 3.

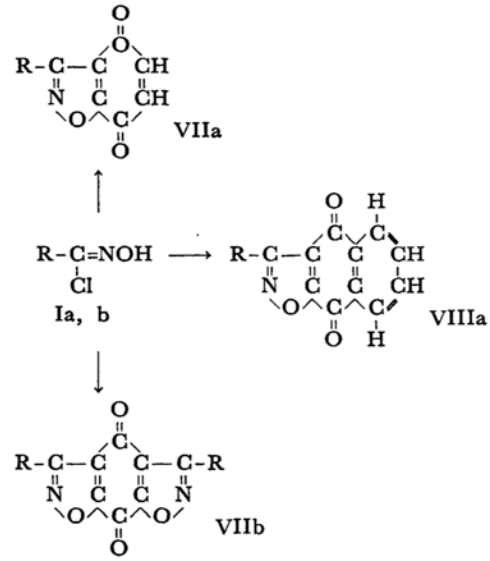
A role of such electrophilic catalyst as a Lewis acid in the thermal 1,3-dipolar cycloaddition reactions is uncertain at the present stage, but it could be said that the presence of boron trifluoride etherate might accelerate the removal of hydrogen chloride from hydroxamoyl chlorides and increase the polarization of a carbonyl group of dipolarophiles as predicted by Morrocchi, *et al.*[6]



Vb (R′: O_2N-C$_6$H$_4$-) VIb (R′: O_2N-furyl) VId (R′: O_2N-furyl)

Reaction with Quinones. Benzonitrile oxide is also known to react with 1,4-benzoquinone and 1,4-naphthoquinone giving the corresponding 1 : 1 adducts, with subsequent oxidation to quinones having condensed benzene-isoxazole and naphthalene-isoxazole nuclei respectively.[8]

Ia was heated with 1,4-benzoquinone for 9 hr to afford VIa in a 31% yield: the structure was confirmed by the NMR spectrum in DMSO-d_6, showing a chemical shift at 2.90 τ (singlet, 2 H) attributable to two equivalent aromatic protons of benzoqinone. Similar treatment of Ia with 1,4-naphthoquinone afforded VIIa in a 25% yield and similarly, VIIb from Ib and 1,4-benzoquinone in a 36% yield. The structure of VIIa was confirmed from the elemental analysis and the NMR spectrum and furthermore, from the mass spectrum as described in Experimental, and the structure of VIIb was characterized as a 1 : 2 adduct from the elemental analysis and the NMR spectrum in DMSO-d_6, showing no aromatic proton originated from benzoquinone. It is noteworthy that the thermal procedure always afforded the products possessing an isoxazole structure instead of the simple adducts with an isoxazoline structure without any side-formation of furoxanes.[2]



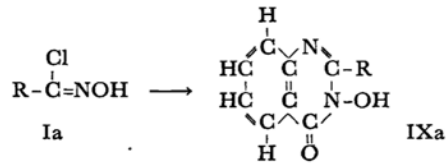
VIIa

Ia, b

VIIIa

VIIb

Reaction with Anthranilate. Dornow and Fischer[9] have reported the formation of a quinazoline-type product from Ib and two equivalent amounts of methyl anthranilate on keeping the reaction mixture at room temperature. Similar treatment of Ia with methyl anthranilate also afforded IXa in a 60% yield; the structure was consistent with 3-hydroxy-4-oxo-2-(5′-nitro-2′-furyl)-3,4-dihydroquinazoline on the basis of the elemental analysis and the spectral data. The infrared spectrum (KBr disc) exhibited a strong absorption of ν_{CO} at 1695 and that of intramolecular hydrogen bonding at 2500 cm^{-1}, supporting its *N*-hydroxyl structure rather than its *N*-oxide.[10] In the ultraviolet spectrum in ethanol, the absorption maxima at 374 mμ (ε = 16700) and at 268 (18200) resembled to those of the known product IXb.[9]



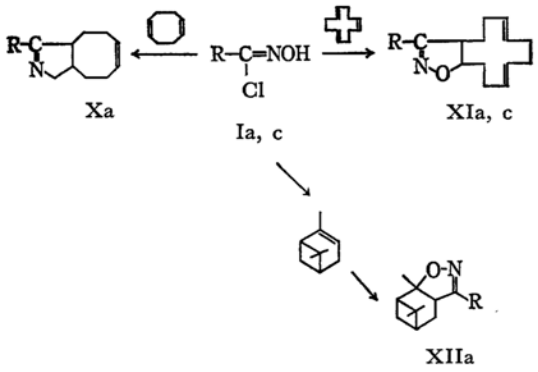
Ia IXa

Reaction with Olefins. In addition to the previous report,[2] Ia was treated with non-conjugated cyclic polyenes like 1,5-cyclooctadiene and 1,5,9-cyclodecatriene to afford 1 : 1 adducts, Xa and XIa, in 55 and 70% yields, respectively. Ic also afforded a 1 : 1 adduct Xc in a 55% yield. However, the reactions of Ia with conjugated polyenes like 1,3-cyclooctadiene, myrcene and butadiene did not occur at all and the starting materials were

8) A. Quilico, C. Stagno and D'Alcontres, *Gazz. Chim. Ital.*, **80**, 140 (1950); *Chem. Abstr.*, **45**, 606c (1951). The yields of the products are very low and diphenylfuroxane and benzonitrile are always accompanied as the by-products.

9) A. Dornow and K. Fischer, *Chem. Ber.*, **99**, 72 (1966).

10) Similar phenomena have been observed in 2-hydroxypyridine *N*-oxide (E. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949)) and 2-hydroxyquinoline *N*-oxide (K. G. Cunningham, G. T. Newbold, F. S. Spring and J. Sharp, *J. Chem. Soc.*, **1949**, 2091).



recovered, though benzonitrile oxide is known to react with conjugated dienes[11] or myrcene.[12]

As is pointed out in the previous paper,[2] cyclic monoolefins like cyclohexene, cyclooctene give good yields in the thermal 1,3-dipolar cycloaddition reactions; similarly, α-pinene underwent the same reaction with Ia giving a 1 : 1 adduct XIIa in a 90% yield.

As a conclusion, the thermal 1,3-dipolar cycloaddition reactions using hydroxamoyl chloride can be said to have more versatile applicability than those using the corresponding nitrile oxides; the reaction proceeds with evolution of hydrogen chloride gas which is a very convenient clue for determining the end-point of the reaction except when basic dipolarophiles are used. In the latter case, two equivalent amounts of bases are used and care should be paid to control the reaction temperature as low as possible enough to proceed the reaction. This is the case when basic dipolarophiles are readily decomposed by hydrogen chloride evolved, as is observed in the formation of IXa.

Experimental

The melting points were measured on a microhot stage and are not corrected. The microanalyses were carried out with a Yanagimoto C. H. N. Corder, Model MT-1 type. The infrared spectra were measured on a Nippon-Bunko IR-S type spectrophotometer and the ultraviolet spectra, on a Nippon-Bunko optical rotary dispersion recorder, Model ORD/UV-5. The NMR spectra were determined on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard and the peak positions are expressed by τ-values. The mass spectrum was obtained with a Hitachi RMU-6D mass spectrometer with an energy of 70 eV.

Hydroxamoyl Chlorides. Ia,[12] Ib,[13] Ic[14] and Id[15] were prepared by the known procedures.

Reaction of Ia—d with Triphenylphosphine. A solution of 1.0 g (5 mmol) of Id and 1.3 g (5 mmol) of triphenylphosphine in 30 m*l* of dry toluene was refluxed at 140—150°C for 9 hr until evolution of hydrogen chloride gas had completely ceased. The solvent and surplus triphenylphosphine were removed under reduced pressue and the residue was dissolved in chloroform and chromatographed on a silica-gel (Mallinckrodt, 100 mesh) column, using chloroform as an eluent. From the first fraction, 0.57 g of *m*-nitrobenzonitrile was obtained. This was identified by the comparison with an authentic sample[16] spectroscopically (IR). From the second fraction, 1.4 g (96%) of triphenylphosphine oxide, mp 166°C (lit.,[17] mp 166°C) was obtained. Similar treatment of Ia—c with triphenylphosphine afforded the corresponding nitriles as shown in Table 1.

Reaction of Ia—d with Benzonitrile. A solution 0.75 g (5 mmol) of Ib and 0.55 g (5 mmol) of benzonitrile in 20 m*l* of dry toluene was refluxed at 140—150°C for 16 hr until evolution of hydrogen chloride gas had completely ceased. After removing toluene and surplus benzonitrile under reduced pressure, ethanol was added to the residue and the precipitated colorless needles were collected and recrystallized from ethanol-benzene to give 0.6 g of 3,5-diphenyl-1,2,4-oxadiazole, mp 110°C (lit.,[7] mp 109°C, no depression by the mixed melting point). Similar treatment of Ia—d with benzonitrile afforded the corresponding oxadiazoles as indicated in Table 2.

Reaction of Ib with Acetonitrile. A solution of 0.74 g (5 mmol) of Ib and 0.25 g (5 mmol) of acetonitrile in 25 m*l* of dry toluene was refluxed for 32 hr in the presence of a catalytic amount of boron trifluoride etherate. After the removal of distillable parts from the reaction mixture under reduced pressure, the residue was purified according to the procedure given by Tieman and Krueger[18] to afford 3-phenyl-5-methy-1,2,4-oxadiazole, mp 41°C (lit.,[18] mp 41°C) in a 35% yield.

Reaction with Aromatic Aldehydes. A solution of 0.72 g (5 mmol) of Ib and 0.73 g (5 mmol) of *p*-nitrobenzaldehyde in 20 m*l* of dry toluene was refluxed for 21 hr. After toluene was removed under reduced pressure, the residue was dissolved in chloroform and chromatographed on a silica-gel column, using chloroform as an eluent. The first fraction afforded 0.7 g of 3-phenyl-5-(*p*-nitrophenyl)-1,2,4-dioxazole (Vb). Similarly, 3-phenyl-5-(5′-nitro-2′-furyl)- (VIb) and 3-(*m*-nitrophenyl)-(5′-nitro-2′-furyl)-1,2,4-dioxazole (VId) were prepared from the corresponding components after 11 and 24 hrs' refluxing, respectively. These results are summarized in Table 3.

Reaction of Ia—b with Quinones. A solution of 0.9 g (5 mmol) of Ia and 1.0 g (10 mmol) of 1,4-benzoquinone in 30 m*l* of dry toluene was refluxed for 9 hr. The reaction mixture was filtered while hot and the filtrate was allowed to stand. The resulting precipitates were collected and recrystallized from ethanol-benzene to give 0.4 g of VIIa, mp 200—202°C. IR (KBr) cm^{-1}: 1690, 1670 (CO). UV λ_{max}^{EtOH} mμ (ε): 314 (13800), 246 (11600).

Found: C, 50.65; H, 1.40; N, 10.48%. Calcd for $C_{11}H_4O_6N_2$: C, 50.78; H, 1.54; N, 10.77%.

Similar treatment of Ib with 1,4-benzoquinone afforded VIIb, mp 264°C, after 22 hrs' refluxing.

11) A. Quilico, P. Grünanger and R. Mazzini, *Gazz. Chim. Ital.*, **82**, 349 (1952).
12) T. Sasaki, S. Eguchi and T. Ishii, in preparation.
13) M. H. Benn, *Can. J. Chem.*, **42**, 2393 (1964).
14) H. R. Rheinboldt, *Liebigs Ann.*, **451**, 166 (1927).
15) M. T. Bogert and L. Kohnstamm, *J. Am. Chem. Soc.*, **25**, 478 (1903).
16) M. T. Bogert and H. T. Beans, *ibid.*, **26**, 464 (1904).
17) V. F. Kucherov, *Zhur. Obshch. Khim.*, **19**, 126 (1949); *Chem. Abstr.*, **43**, 6178 (1949).
18) Tieman and Krueger, *Ber.*, **17**, 1685 (1884).

TABLE 4. REACTIONS WITH CYCLIC POLYENES

Dipolar	Olefin	Product (Mp, °C)	Microanalysis Found (Calcd) C	H	N	UV λ_{max}^{EtOH}, mμ (ε)
Ia	A*	Xa (117)	59.47 (59.53	5.17 5.38	10.85 10.68)	348 (15800), 258 (8200), 235 (8000)
Ic	A*	Xc (110)	65.86 (66.16	5.68 5.92	9.97 10.29)	311 (16200), 225 (11000)
Ia	B*	XIa (164)	64.26 (64.54	6.53 6.37	9.08 8.86)	350 (14900), 260 (7600), 236 (7400)

A*: 1,5-Cyclooctadiene B*: 1,5,9-Cyclododecatriene

Found: C, 70.54; H, 2.53; N, 7.82%. Calcd for $C_{20}H_{10}O_4N_2$ for 1:2 adduct: C, 70.17; H, 2.94; N, 8.18%. Calcd for $C_{13}H_7O_3N$ for 1:1 adduct: C, 69.33; H, 3.13; N, 6.22%.

Similarly, VIIIa was obtained from Ia and 1,4-naphthoquinone after 30 hrs' refluxing. IR (KBr) cm^{-1}: 1685 (CO). UV λ_{max}^{EtOH} mμ (ε): 325 (16900). NMR (DMSO-d_6) τ: 1.90 (multiplet, 4 H, phenyl protons). Mass: M^+ 314 (Calcd 314).

Found: C, 58.18; H, 1.94; N, 9.25%. Calcd for $C_{15}H_6O_6N_2$: 58.07; H, 1.95; N. 9.03%.

Reaction of Ia with Methyl Anthranilate. A solution of 0.95 g (5 mmol) of Ia and 1.5 g (10 mmol) of methyl anthranilate in 30 m*l* of dry ether was kept standing at room temperature for 6 months. Solidified crystals were collected, washed with water and recrystallized from ethanol to give 1.1 g of IXa, mp 223°C (decomp).

Found: C, 52.95; H, 2.59; N, 15.09%. Calcd for $C_{12}H_7O_5N_3$: C, 52.75; H, 2.58; N, 15.38%.

Reaction with Olefins. A solution of 0.95 g (5 mmol) of Ia and 1 m*l* of 1,5-cyclooctadiene in 20 m*l* of dry toluene was refluxed for 9 hr. After toluene and surplus 1,5-cyclooctadiene were removed under reduced pressure, the residual oil was dissolved in chloroform and chromatographed on a silica-gel column, using chloroform as an eluent. 0.73 g of Xa, mp 116°C, was obtained from the first fraction. Analytical values are shown in Table 4 with those of other products.

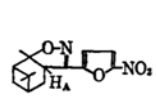
Similar treatment of Ia with α-pinene afforded XIIa, mp 197°C, after 24 hrs' refluxing and purifying the crude product by means of column chromatography. UV λ_{max}^{EtOH} mμ (ε): 350 (14600), 255 (8500). NMR ($CDCl_3$) τ: 6.55 (1 H, quartet, J=4.0 and 10.0 cps, H_A*).

Found: C, 61.60; H, 6.25; N, 9.65%. Calcd for $C_{15}H_{20}O_4N_2$*: C, 62.05; H, 6.25; N, 9.65%.

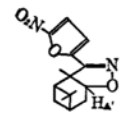
The authors wish to express their gratitude to Mr. Akiho Ishihara of their laboratories for microanalyses and to the Dainippon Pharmaceutical Co. for measuring NMR spectra.

19) T. Sasaki and T. Yoshioka, *Yukigosei Kagaku Kyokaishi* (*J. Synth. Org. Chem. Japan*), **25**, 665 (1967).

* Two possible structures, XII and XIIa′, are



XIIa



XII′a

presumable for this formula. If XIIa′ is assumed to be a correct structure, H_A' should be appeared in more lower magnetic field than the observed value, 6.55 τ, by the presence of a neighboring oxygen atom.