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Studies of Heteroaromaticity. IV.[1] The Thermal 1, 3-Dipolar Cycloaddition of Fur- and 5-Nitro-2-furhydroxamoyl Chlorides with Olefinic and Acetylenic Compounds

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The corresponding isoxazolines and isoxazoles were prepared by 1, 3-dipolar cycloaddition with olefinic and acetylenic dipolarophiles by two methods, a) and b). Here, method a) means the routine method *via* nitrile oxide formation, while method b) means the new type of reaction named in the title. Method b) is concluded to be superior to method a) for the purpose of preparing isoxazoles and isoxazolines. The mechanism of the thermal 1, 3-dipolar cycloaddition is discussed.

In the preceding paper.[1] we have reported on the 1, 3-dipolar cycloaddition reaction of furonitrile oxide with olefins; by this reaction we could obtain the corresponding 3, 5-disubstituted isoxazolines in yields ranging from 5 to 95%, depending on the stability of the nitrile oxide. Recently, Minami and Matsumoto[2] have described the same type of reaction of 5-nitro-2-furonitrile oxide with various olefinic dipolarophiles, involving a series of enamines from aldehydes and ketones; their report has prompted us to report our findings on the 1, 3-dipolar cycloaddition reaction of 5-nitro-2-furonitrile oxide with several olefinic and acetylenic compounds.[3]

In the course of our studies of the reactivity of of fur- and 5-nitro-2-furhydroxamoyl chlorides,[4] we happened to discover that the same 1, 3-dipolar cycloaddition took place directly from the hydroxamoyl chlorides and dipolarophiles only when they were heated in such an inert solvent as toluene, not *via* a step of nitrile oxide formation; this produced the same 3, 5-disubstituted isoxazolines and isoxazoles as *via* the nitrile oxide from olefinic and acetylenic dipolarophiles respectively. Since this new thermal procedure b) is interesting in the preparative aspect, we tried to establish its advantages over the usual method a).

In this paper we will report the results of a comparison between these two methods. Tables 1 and 2 show the results when olefinic and acetylenic dipolarophiles were used respectively.

The structural elucidation and identification of those products were carried out by their microanalyses, by measurement of their IR, UV, and NMR spectra, and by comparison with a specimen prepared by another method, if neccessary.

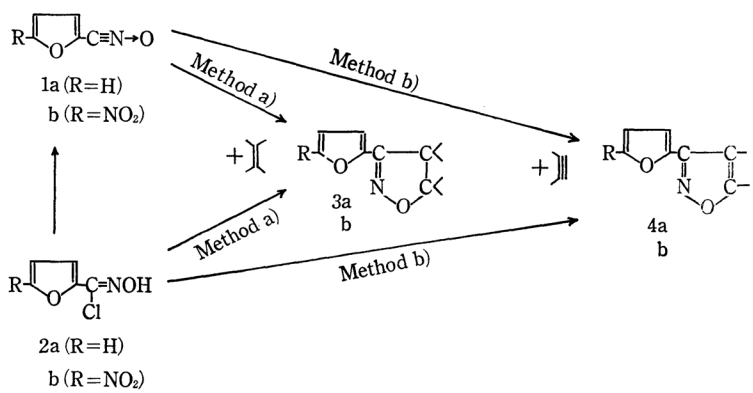


Chart 1

1) Part III: T. Sasaki and T. Yoshioka, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **88**, 1122 (1967).

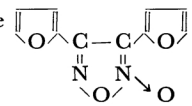
2) S. Minami and J. Matsumoto, *Chem. Pharm. Bull.*, **15**, 366 (1967).

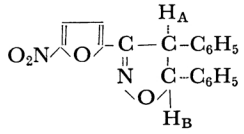
3) Presented at the 23rd Annual Meeting of the Japanese Pharmaceutical Association, Sendai, October, 1966.

4) T. Sasaki and T. Yoshioka, *J. Syn. Org. Chem. Japan*, **25**, 665 (1967).

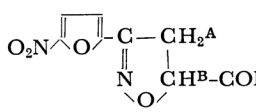
TABLE 1. REACTION WITH OLEFINES

Case No.	Di-polar	Olefins	Method	Reflux time hr	Yield %	Melting point °C	Microanalysis Found(Calcd) C	H	N	IR(KBr) cm^{-1}	UV λ_{max}^{EtOH} $m\mu(\varepsilon\times10^{-3})$
I	1a	$C_6H_5CH=CH_2$	a	*	95	91—92	72.64 (73.22	4.77 5.20	6.49 6.57)	$1610\nu_{C=N}$	274(21.8)
	2a		b	12	76.5						
II	1a	$C_6H_5CH=CH_2$	a	*	68	135—136	60.59 (60.49	3.97 3.90	11.03 10.85)	$1610\nu_{C=N}$	340(14.2) 252(9.1)
	2b		b	10	87.5						
III	1b	$CH_2=CHCONH_2$	a	*	61	225—227#2	52.94 (53.33	4.46 4.48	15.47 15.55)	$3400\nu_{NH}$ $1675\nu_{C=O}$	338(10.5) 250(5.3)
	2b		b	24	44.4						
IV	1b		a	*	**	145—146	55.67 (55.93	5.12 5.12	11.78 11.86)	$1595\nu_{C=N}$	342(13.7) 256(6.1)
	2b		b	12	92.5						
V	1a	$C_6H_5CH=CHC_6H_5$ (trans)	a	*	***	110—112	78.40 (78.87	5.09 5.23	4.88 4.84)	$1605\nu_{C=N}$	278(15.0)
	2a		b	12	32.2						
VI	1b	$C_6H_5CH=CHC_6H_5$ (trans)	a	*	**	158—160#1	68.07 (68.25	4.11 4.22	8.25 8.38)	$1607\nu_{C=N}$	344(12.9) 254(5.9)
	2b		b	11	57						
VII	1b	Cyclooctene	a	*	8	128—130	57.73 (57.13	6.20 6.39	10.56 11.11)	$1603\nu_{C=N}$	347(14.2) 258(7.4)
	2b		b	11	95						
VIII	1b	Dicyclopentadiene	a	*	82	130—131#3	62.97 (62.93	5.06 4.93	9.57 9.79)	$1600\nu_{C=N}$	350(14.9) 259(7.4)
	2b		b	8	93						

* 30 min ** Unidentified oil *** Furoxane  mp 115—116°C

#1 

NMR ($CDCl_3$)
H_A: 5.33 τ (doublet), J_{AB}, 6 cps
H_B: 4.30 τ (doublet), J_{BA}, 6 cps

#2 

NMR (DMSO-d_6)
H_A: 6.49 τ (2H. triplet), J, 9 cps
H_B: 4.80 τ (1H. triplet), J, 9 cps

#3 The structural elucidation by the NMR is under investigation.

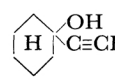
Results and Discussion

From Table 1 it can be seen that method b) is, generally speaking, superior to method a) with respect to the yields, although, in the cases of I and III, the thermal polymerization of styrene and acrylamide caused a lowering of the yields. In the cases of IV and VI, an expected isoxazoline was obtained by method b), while method a) afforded unidentified oily products. In the case of V, methods a) and b) gave different products; the former gave a furoxane, a dimer of the nitrile oxide, while the latter gave the isoxazoline. These results are interesting when compared with the finding that benzonitrile oxide did not react with cyclohexene.[5] The comparison between I & II and V & VI show that the presence of a nitro group in the furan ring has a good effect in method b) because of the ring stability towards acid.

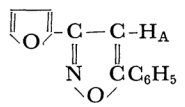
When acetylenic compounds were used as dipolarophiles, the difference between methods a) and b) becomes more remarkable, as is shown in Table 2. In the case of IX, the yield by method b) is about ten times as high as that by method a) and in the case of XIII, twice as high. In the cases of XII, XV and XVI, only method b) afforded the isoxazoles. In the case of X, method a) gave a furoxane, but method b) afforded the isoxazole in a 64% yield. Even in other cases,

5) A. Quilico, N. Barbulescu, P. Grünager and N. R. Langella, *Tetrahedron Letters*, **1961**, 89.

TABLE 2. REACTION WITH ACETYLENS

Case No.	Di-polar	Acetylenes	Method	Reflux time hr	Yield %	Melting point °C	Microanalysis Found (Calcd) C	H	N	IR(KBr) cm^{-1}	UV λ_{max}^{EtOH} $m\mu$ ($\varepsilon \times 10^{-3}$)
IX	1b	$C_6H_5C{\equiv}CH$	a	*	7.8	209—210	60.65 (60.94	2.96 3.15	10.79 10.93)	$1610\nu_{C=C}$	318(16.8) 253(17.2)
	2b		b	10	64					$1580\nu_{C=N}$	
X	1a	$C_6H_5C{\equiv}CH$	a	*	**	98—100#	73.73 (73.92	4.12 4.30	6.73 6.63)	$1620\nu_{C=C}$	266(22.0)
	2a		b	10	64						
XI	1a	$CH{\equiv}CCH_2Br$	a	*	51	78—79	41.93 (42.14	3.43 2.65	5.90 6.14)	$1620\nu_{C=C}$	262(12.7)
	2a		b	12	62					$1600\nu_{C=N}$	
XII	1b	$CH{\equiv}CCH_2Br$	a	*	***	105—106	35.72 (35.19	1.95 1.84	10.20 10.26)	$1603\nu_{C=C}$	316(14.8)
	2b		b	23	27					$1600\nu_{C=N}$	
XIII	1b	$CH{\equiv}CCH_2OH$	a	*	15	145—147	45.95 (45.72	2.88 2.88	13.43 13.33)	$3380\nu_{OH}$	318(14.8)
	2b		b	13	30##					$1615\nu_{C=C}$ $1590\nu_{C=N}$	
XVI	1b	$CCOOCH_3$ ‖ $CCOOCH_3$	a	*	***	86—88	44.46 (44.60	2.45 2.72	9.27 9.46)	$1730\nu_{C=O}$	310(7.8)
	2b		b	18	28					$1610\nu_{C=C}$	
XV	1b	$C_6H_5C{\equiv}CC_6H_5$	a	*	***	193—195	68.50 (68.67	3.69 3.64	8.53 8.34)	$1625\nu_{C=C}$	318(13.2) 258(9.7)
	2b		b	12	28.2					$1600\nu_{C=N}$	
XVI	1b		a	*	***	135	55.73 (56.11	5.10 5.07	10.07 10.07)	$3300\nu_{OH}$	322(15.8)
	2b		b	19	77.5					$1610\nu_{C=C}$	
XVII	1b	$HC{\equiv}C\text{-}COOCH_3$	a	*	10	175—176	45.05 (45.39	2.55 2.54	11.62 11.76)	$1720\nu_{C=O}$	316(12.0)
	2b		b	25	29					$1610\nu_{C=C}$	

* 30 min ** Furoxane, mp 115—116°C *** Unidentified oil.

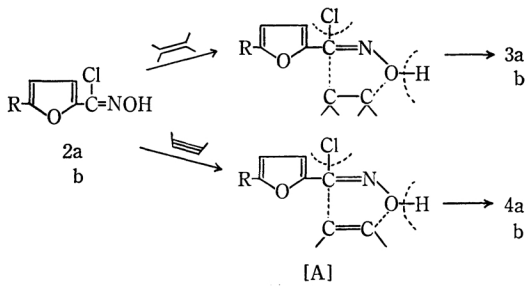
\#  NMR ($CDCl_3$) H_A: 3.23 τ (singlet)

21% of the starting material was recovered.

when the same isoxazole was obtained by both methods, the yields by method b) were always higher than those by method a). The reason why the yields in the cases of XIV, XV and V were rather low (around 30%) might be the steric hinderance of the bulky disubstituted acetylenic and olefinic dipolarophiles.

In conclusion, it can be said that method b) is superior to method a) for the preparation of isoxazolines and isoxazoles, especially for the former when cyclic olefins such as cyclohexene and cyclooctene, or dicyclopentadiene are used as dipolarophiles, and that, furthermore, method b) has the advantage of giving no furoxane, but the main product exclusively, so far as the thermal polymerization of dipolarophiles could be avoided, which is thought to be a main cause of lowering the yields.

In order to investigate the mechanism of this thermal cyclization, in other words, to determine whether or not it proceeds *via* an intermediate of the nitrile oxide formation, we heated 5-nitro-2-furhydroxamoyl chloride with ethanol in toluene as long as 18 hr, since aromatic nitrile oxide is known to react with ethanol[6]; however, no evolution of hydrogen chloride was observed, and the starting material was completely recovered. Considering the facts that no furoxane was formed by method



[A]

Chart 2

6) C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **31**, 157 (1966).

b) and that a drastic evolution of hydrogen chloride was always observed when the reaction proceeded smoothly, this reaction might proceed *via* a multicentered transition state like (A) instead of the nitrile oxide; this adduct is assumed to have a structure favoring simultaneous dehydrochlorination to give the same product as that *via* nitrile oxide, as is shown below:

Experimental

The melting point were measured on a micro hot stage and are not corrected. Microanalyses were carried out with a Yanagimoto C. H. N. Corder, MT-1 type. The IR spectra were measured on a Nippon-Bunko IR-S-type spectrophotometer and the UV spectra, on a Nippon-Bunko optical rotary dispersion recorder, Model ORD/UV-5.

Furhydroxamoyl Chloride.[7]

5-Nitro-2-furhydroxamoyl Chloride.[8]

Method a). The general procedure has already been described.[1,2]

Method b). General procedure: The hydroxamoyl chloride and an equimolecular amount of a dipolarophile were dissolved in about ten times as much toluene; the resulting mixture was heated on an oil bath of 140—160°C until the evolution of hydrogen chloride had ceased. After the toluene had been removed under reduced pressure, the residue was purified either by direct recrystallization when it was solid, or by column chromatography[9] and then recrystallization when it was oily. The yields, melting points, microanalyses and IR and UV spectra of the products are summarized in Tables 1 and 2.

Examples of Method a). Reaction of 5-Nitro-2-furonitrile Oxide with Phenylacetylene. To an ethereal solution of 5-nitro-2-furonitrile oxide, prepared *in situ* from 1.96 g of 5-nitro-2-furhydroxamoyl chloride and 1.5 m*l* of triethylamine in ether, 1.79 g of phenylacetylene were added; the mixture was then gently refluxed on a water bath for 2 hr. The mixture was washed with 10% HCl, 5% Na_2CO_3, and finally with water until the washing water became neutral. The ether layer was dried over anhydrous Na_2SO_4. After the removal of the ether, the residual yellow oil was recrystallized from a benzene - petroleum ether mixture (1 : 1) to give 0.21 g of yellow crystals (mp 209—210°C; lit.,[2] 203—204°C), which were identified as 3-(5-nitro-2-furyl)-5-phenylisoxazole by comparison with a specimen prepared by another method.[2]

Example of Method b). Reaction of 5-Nitro-2-furhydroxamoyl Chloride with Dimethyl Acetylenedicarboxylate. 5-Nitro-2-furhydroxamoyl chloride (1.16 g) and dimethyl acetylenedicarboxylate (1 g) were dissolved in 20 m*l* of toluene, after which the mixture was heated at 150—160°C for 18 hr under refluxing. After any toluene had been removed under reduced pressure, the residual red oil was dissolved in chloroform and chromatographed through a silica-gel column by using chloroform as an eluent. The first fraction gave an unidentified red oil, while from the second fraction, 0.5 g of purple crystals (mp 86—88°C) was obtained after recrystallization from ethanol; the yield was 28%.

The authors wish to express their gratitude to Mr. Akiho Ishihara of their laboratories for his microanalyses and to the Ueno Pharmaceutical company for kindly supplying some of the starting materials.

7) H. Rheinholdt, *Liebigs Ann.*, **451**, 166 (1927).
8) R. Renaers and F. Eloy, *Helv. Chim. Acta*, **46**, 1067 (1963).
9) By using a silica-gel (100 mesh, Wako) column and chloroform as an eluent.