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Studies of Heteroaromaticity. XXXII.[1] New Synthesis of 1,2,4-Oxadiazoles, Benzoxazoles, Benzothiazoles and Benzimidazole from Aromatic Hydroxamoyl Chlorides

Tadashi SASAKI, Toshiyuki YOSHIOKA and Yasuyuki SUZUKI

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya

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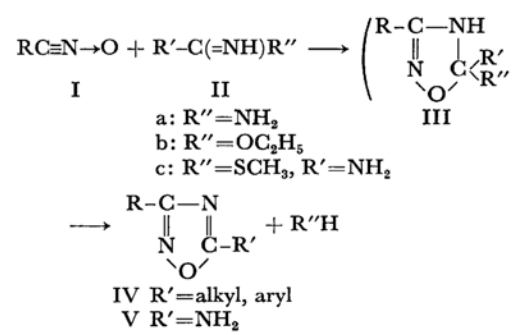
There are many papers concerning the synthesis of five-membered heterocycles by the 1,3-dipolar cycloaddition reactions of nitrile oxides, which afforded, with double bonded dipolarophiles, dihydro-heteroaromatic compounds in general.[2] It is also known that similar reactions with dipolarophiles having hetero-multiple bond generally proceed with some difficulty, except for their activated types.[3] This note deals with a new synthesis of 1,2,4-oxadiazoles, benzoxazoles, benzothiazoles and a benzimidazole from aromatic hydroxamoyl chlorides, the precursors of nitrile oxides. It is reported that aromatic nitrile oxides do not undergo the 1,3-dipolar cycloaddition reactions with an imino heteromultiple bond, when it is a part of a simple azomethine linkage. This note is based on our finding that aromatic hydroxamoyl chlorides can react with the imino group, if it is incorporated in amidines IIa, iminoethers IIb and *S*-methylthiourea IIc, leading to the formation of 1,2,4-oxadiazoles after hetero-aromatization of the intermediated oxadiazolines III by elimination of R″H.



1) Part XXXI of this series: T. Sasaki and T. Yoshioka, This Bulletin, **42**, 3008 (1969).

2) For a recent review, see R. Huisgen, R. Grashey and J. Sauer, "Cycloaddition Reactions of Alkenes," in "The Chemistry of Alkenes," ed. S. Patai, Interscience Publisher, New York, N. Y. (1964), pp. 806—987.

3) For a recent review, see T. Sasaki, *Kagaku no Ryoiki*, **23**, 220, 320 (1969).

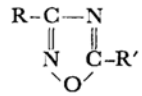
The general preparative method for 1,2,4-oxadiazales by the 1,3-dipolar cycloaddition of aromatic nitrile oxides with nitriles has been reported originally by Huisgen.[4] It is also reported, however, that the reactions with aliphatic nitriles hardly take place.[5,6] Musante[7] and Elory[8] reported independently the preparation of 1,2,4-oxadiazoles from nitrile oxide and benzamidine and benziminoether respectively. In order to investigate the applicability of these methods to aliphatic amidines and iminoethers, we investigated similar reactions using several aromatic nitrile oxides such as *p*- (Ia), *m*-nitrobenzonitrile oxide (Ib), 2-(5-nitrofuro)nitrile oxide (Ic), benzonitrile oxide (Id) and furonitrile oxide (Ie), all derived readily from the corresponding hydroxamoyl chlorides I'a—e in the presence of base. The results are summarized in Table 1. As indicated in this table, the method using amidines is found to be superior to that using iminoethers for the preparation of 5-aryl- and 5-alkyl-3-aryl-1,2,4-oxadiazoles (IV).

Elory[9] reported the preparation of 3-phenyl-5-amino-1,2,4-oxadiazole from benzonitrile oxide and guanidine. This method could not be applied to Ia—c, so we investigated similar reactions using thiourea instead of guanidine, but no reaction occurred. However, we found that *S*-methylthiourea reacted with Ia—c, affording the corresponding 5-amino-1,2,4-oxadiazoles (Va—c) after elimination of methylmercaptane even in such basic media as given in the reaction conditions, indicating that the presence of a suitable leaving group under the basic reaction conditions is an essential factor for the hetero-aromatization of the intermediated III. The results are summarized in Table 2.

In a previous paper,[10] we reported the reaction of 2-(5-nitrofuro)hydroxamoyl chloride (I'd) with two equivalents of ethanolamine to afford *N*-(*β*-hydroxyethyl)-2-(5-nitrofuryl)amidoxime. When I'c was treated with *o*-aminophenol instead of ethanolamine under similar reaction conditions, the product was proved to be benzoxazole (VIc) which might be produced by the hetero-aromatization of the intermediated VIIa or VIIb after elimination of hydroxylamine moiety. From our previous report[11] concerning the similar hydroxylamine-elimination in the reactions of aromatic hydroxamoyl chlorides with methyl dithiocarbazinate, VIIa seems to be more plausible than VIIb. Table 3 shows the results obtained by use of several hydroxamoyl chlorides.

Similar treatment of hydroxamoyl chlorides with two equivalents of *o*-aminothiophenol afforded the corresponding benzothiazoles (VIII) as given in

Table 1. Oxadiazoles from amidines and iminoethers

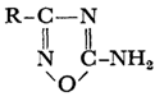


R	R'	Product	Mp °C	Yield (%)* a	b	c	d	Found (Calcd) C%	H%	N%	UV (EtOH) λmμ (ε)
p-NO_2-C_6H_4-	C_6H_5-	IVa-1	212—213	90		65	100				262 (24840)[6]
	CH_3-	IVa-2	139—141	80	60			52.91 (52.68	3.02 3.44	20.34 20.48)	276 (10500)
m-NO_2-C_6H_4-	C_6H_5-	IVb-1	165—166	80		50	80				244 (50500)[6]
	CH_3-	IVb-2	107—110	60	60			52.84 (52.68	3.57 3.44	20.40 20.48)	224 (21500)
2-(5-NO_2-C_4H_2O)-	C_6H_5-	IVc-1	206—208	75		8	36				313 (18600) 255 (22900)[6]
	CH_3-	IVc-2	104—105	45	55			43.17 (43.08	2.61 2.58	21.85 21.54)	304 (9280)
C_6H_5-	C_6H_5-	IVd-1	105—107	75							258 (35400)
	CH_3-	IVd-2	41	65		35					
C_4H_3O-	C_6H_5-	IVe-1	114—117	75				68.28 (67.92	3.58 3.80	13.46 13.20)	

* a: from amidines, b: from iminoethers, c: by the thermal 1,3-dipolar cycloaddition reactions previously reported by us,[6] d: in the presence of a catalyst in method c.

4) R. Huisgen, *Proc. Chem. Soc. (London)*, **1961**, 961.
5) S. Morrocchi, A. Ricca and L. Velo, *Tetrahedron Letters*, **1967**, 331
6) T. Sasaki and T. Yoshioka, This Bulletin, **41**, 2206 (1968).
7) C. Musante, *Gazz. Chim. Ital.*, **68**, 331 (1938); *Chem. Abstr.*, **32**, 9064 (1938).
8) F. Elory and R. Lenaers, *Bull. Soc. Chim. Belges*, **72**, 719 (1963).
9) F. Elory and R. Lenaers, *Helv. Chim. Acta*, **49**, 1430 (1966).
10) T. Sasaki and T. Yoshioka, *Yuki Gosei Kagaku Kyokai-shi (J. Synth. Org. Chem. Japan)*, **25**, 665 (1967).
11) T. Sasaki and T. Yoshioka, This Bulletin, **41**, 2211 (1968).

TABLE 2. 5-AMINO-1,2,4-OXADIAZOLES



R	Product	Mp °C	Yield %	Found (Calcd) C%	H%	N%	UV (EtOH) mμ (ε)		IR (KBr) ν_{NH} cm^{-1}	
p-NO_2-C_6H_4–	Va	>300	80	46.67 (46.60	2.68 2.93	27.06 27.18)	298 (7860)	261 (14500)	3190	3450
m-NO_2-C_6H_4–	Vb	234—236	30	46.37 (46.60	2.92 2.93	26.98 27.18)	253 (10300)		3120	3320
2-(5-NO_2-C_4H_2O)–	Vc	239—241	60	36.54 (36.74	1.91 2.06	28.16 28.57)	317 (11500) 254 (7780)	285 (9250)	3280	3440
C_6H_5–	Vd	158—160[9]	90				254 (3390)		3100	3320

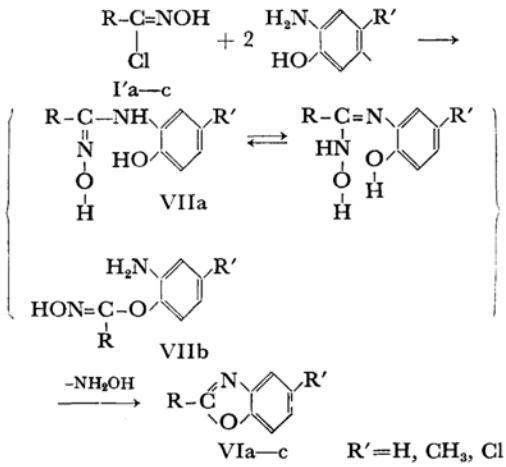
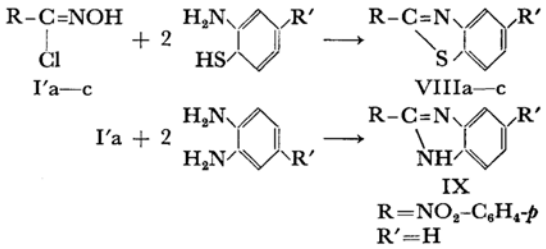


Table 4 and the reaction of *p*-nitrobenzhydroxamoyl chloride (I'a) with *o*-phenylenediamine afforded 2-(*p*-nitrophenyl)benzimidazole IX.



Experimental

The melting points were measured on a micro hot stage and are not corrected. The microanalyses were carried out with a Yanagimoto C. H. N. Corder, Model MT-1 type. The ultraviolet spectra were obtained 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.

TABLE 3. BENZOXAZOLES (VI)

R	R'	Mp °C	Yield %	Micoranalysis Found (Calcd) C	H	N	UV λ_{max}^{EtOH} mμ (ε)
p-NO_2-C_6H_4–	H	276—277	70	65.33 (65.00	3.08 3.36	11.74 11.66)	326 (23300) 230 (14000)
	CH_3	220—221	75	66.26 (66.13	3.58 3.96	11.10 11.02)	334 (24800) 232 (15200)
	Cl	248—250	80	57.38 (56.85	2.37 2.57	10.24 10.20)	330 (16900) 232 (8200)
m-NO_2-C_6H_4–	H	221—223	80	64.98 (65.00	3.10 3.36	11.64 11.66)	295 (23000) 263 (20300)
	CH_3	181—183	90	66.08 (66.13	3.80 3.96	10.61 11.02)	304 (14800) 264 (13000)
	Cl	192—193	60	57.44 (56.85	2.54 2.57	10.29 10.20)	307 (20200) 263 (21600)
2-(5-NO_2-C_4H_2O)–	H	233—235	50	57.74 (57.40	2.40 2.63	12.31 12.17)	349 (27600) 265 (14100) 230 (12600)
	CH_3	190—192	90	58.88 (59.02	3.22 3.30	11.51 11.47)	356 (25000) 269 (12900) 230 (11200)
	Cl	201—203	70	50.48 (49.92	1.92 1.90	10.69 10.58)	352 (22800) 269 (10600) 233 (9600)

Table 4. Benzothiazoles (VIII)

R	Mp °C	Yield %	Microanalysis Found (Calcd) C%	H%	N%	UV λ_{max}^{EtOH} mμ (ε)
p-NO_2-C_6H_4-	236—238	40	61.16 (60.94	3.19 3.15	11.07 10.93)	342 (13100) 305 (3200)
m-NO_2-C_6H_4-	188—189	70	60.43 (60.94	2.88 3.15	10.87 10.93)	294 (11400) 271 (11000)
2-(5-NO_2-C_4H_2O)-	248—250	40	53.60 (53.67	2.17 2.46	11.24 11.38)	364 (24000) 280 (7100)

Aromatic Hydroxamoyl Chlorides.

They were prepared according to the methods described in previous papers.[6,10,11]

Preparation of 1,2,4-Oxadiazoles. *Method a (Table 1).* From Amidines. To a solution of *p*-nitrobenzhydroxamoyl chloride (I'a) (1.0 g, 5 mmol) in 50 m*l* of ether was added a solution of acetamidine hydrochloride (1 g, 10 mmol) in 20 m*l* of water. A 5% aqueous sodium carbonate (1.3 g, 12 mmol) was added dropwise to the above reaction mixture under ice-cooling. After stirring for 1 hr at this temperature (*ca.* 5°C), the reaction mixture was further stirred at room temperature for 3 hr. The water layer was washed with ether (20 m*l*×3). The ether washing were combined with the original ether layer and dried over sodium sulfate. The residue obtained after removal of ether was recrystallized from ethanol to afford 3-(*p*-nitrophenyl)-5-methyl-1,2,4-oxadiazole (IVa-2) as white needles. The physical constants, yield and microanalysis are given in Table 1.

Method b (Table 1). From iminoethers. A similar procedure as above, except that acetiminoethyl ether hydrochloride (1.85 g, 15 mmol) was used instead of acetamidine hydrochloride, afforded the same product. This result is given in Table 1.

Reactions with S-Methylthiourea. A similar procedure as above except that *S*-methylthiourea sulfate (1.4 g, 5 mmol) was used instead of imioether hydrochloride afforded the corresponding 5-amino-1,2,4-oxadiazole (Va), which precipitated in the reaction mixture. The yield and analysis are given in Table 2.

Preparation of Benzoxazoles. To a stirred solution of I'a (1 g, 5 mmol) in 50 m*l* of ether was added dropwise a solution of *o*-aminophenol (1.1 g, 10 mmol) in 50 m*l* of benzene-ether (1 : 1) at room temperauter. Stirring was continued for 1 week. The resulting precipitates were filtered and recrystallized from ethanol-benzene to afford 2-(*p*-nitrophenyl)benzoxazole (VIa-1), which was identical with a specimen prepared from *p*-nitrobenzaldehyde and *o*-aminophenol in the presence of lead tetraacetate in acetic acid.[12] This result is given in Table 3. When I'a (1 g, 5 mmol) and *o*-aminophenol (1.1 g, 10 mmol) were refluxed in 50 m*l* of ethanol for 5 hr, VIa-1 precipitated in the cooling reaction mixture; the yield was almost the same as that described above.

Preparation of Benzothiazoles. Similar treatment as in the preparation of benzoxazoles was applied to *o*-aminothiophenol instead of *o*-aminophenol and the results are summarized in Table 4.

Preparation of Benzimidazole. A solution of I'a (1 g, 5 mmol) and *o*-phenylenediamine (1.1 g, 10 mmol) in 100 m*l* of ether was stirred at room temperature for 2 days and the resulting precipitates were filtered. The filtrate was condensed to give a crystalline residue, which was recrystallized from acetone to give an 80% yield of dark colored crystals, mp >300°C. ν_{max}^{KBr} 3000—2600, 1608, 1520, 1450, 1400, 1340, 1230 and 1100 cm^{-1}. Found: C, 65.42; H, 3.82; N, 17.83%. Calcd for $C_{13}H_9O_2N_3$: C, 65.26; H, 3.79; N, 17.57%.

12) F. F. Stephenes and J. D. Bower, *J. Chem. Soc.*, **1949**, 665.