N-Halogen Compounds of Cyanamide Derivatives. VIII.[1] A Convenient Method of Preparing 1,2,4-Oxadiazoles from *N*-Haloamidino Compounds

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A new, efficient method for the preparation of 1,2,4-oxadiazoles from *N*-benzoylamidino compounds by treatment with *t*-butyl hypochlorite and sodium hydroxide has been devised. It was supposed that the ring formation proceeds *via* a nitrene intermediate.

1,2,4-Oxadiazoles have usually been prepared by the acylation of amidoximes[2] or by the Beckmann rearrangement of glyoximes.[3] In both cases, the cyclization involves dehydration and needs vigorous reaction conditions, and these procedures have not always given satisfactory results.

In this paper, we will describe a new, convenient method of synthesizing 1,2,4-oxadiazoles from *N*-chloro-*N'*-benzoylamidino compounds (amidines, *O*-alkylisoureas, and guanidine), together with the mechanism of the ring formation.

Results and Discussion

N-Benzoyl Derivatives of Amidino Compounds (I, II, and III). *N*-Benzoylamidines (I) are usually available by the reactions of amidines with benzoic anhydride.[4] We have found that I were prepared in good yields by the reaction of amidine hydrochlorides with benzoyl chloride in the presence of two equivalents of sodium hydroxide. *N*-Benzoyl-*O*-alkylisoureas (II) and *N*-benzoyl-*N',N'*-pentamethyleneguanidine (III) were prepared by a similar method. Isoureas, II, which were solids with low melting points, could be isolated from an aqueous reaction mixture by extraction with ether.

Table 1 summarizes the results of the preparation of I, II, and III.

Preparation of 1,2,4-Oxadiazoles (IV, V, and VI). 1,2,4-Oxadiazoles were easily obtained from I, II, and III in excellent yields under mild conditions. The following procedure is a typical one. An ethanolic suspension of an amidino compound was treated with *t*-butyl hypochlorite to form *N*-chloro compound, which was then warmed with aqueous sodium hydroxide. The structures of these heterocyclic compounds were confirmed by means of elemental analysis and by studies of the IR and mass spectra.

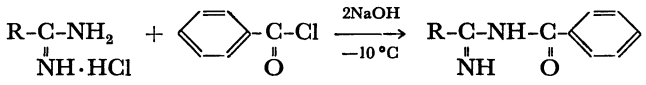
Table 2 shows the results of the preparation of IV, V, and VI.

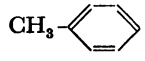
As is shown in Table 2, *N*-benzoylbenzamidine (Ia) was transformed to 1,2,4-oxadiazole (IVa) in a good yield. However, in the case of *N*-benzoyl-*p*-toluamidine (Ib), the yield of IVb decreased because of the formation of a by-product, *p*-tolylurea, which was due to the migration of the *p*-tolyl group to a nitrogen atom. Thus, the *p*-methyl group was found to cause the rearrangement, but the reason has not yet been clarified. Studies of the relationship between various substituents and the reactivities of *N*-chloro compounds of I are in progress.

In the case of II, 1,2,4-oxadiazoles (Va—d) were prepared in excellent yields without exception.

This new method of synthesizing 1,2,4-oxadiazoles

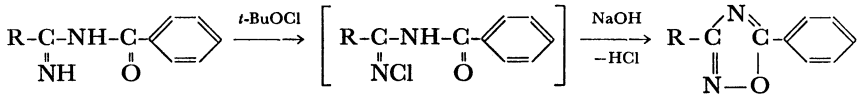
TABLE 1. PREPARATION OF *N*-BENZOYLAMIDINO COMPOUNDS (I, II, and III)

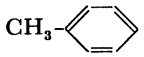


Amidino compd No.	R	Reaction time (h)	Yield (%)	Mp (°C)	Recrystn solvent	Found (calcd %) C	H	N
Ia		1.0	74	98 (98)[8]	aq MeOH	—	—	—
Ib	CH_3- 	0.5	82	129—130	aq MeOH	75.79 (75.61)	5.97 (5.92)	11.67 (11.76)
IIa	CH_3O	1.0	74	77 (76.5)[9]	aq MeOH	60.83 (60.63)	5.66 (5.66)	15.60 (15.72)
IIb	EtO	1.0	77	76 (74—75)[10]	aq MeOH	62.28 (62.49)	6.50 (6.29)	14.54 (14.57)
IIc	*i*-PrO	1.0	85[a]	153—155[b]	H_2O	46.77 (46.90)[c]	4.02 (3.94)[c]	16.12 (16.09)[c]
IId	*n*-BuO	1.0	75	40.5	Ligroin	65.14 (65.43)	7.59 (7.32)	12.73 (12.72)
III		1.0	81	149—150	MeOH	67.35 (67.51)	7.62 (7.41)	17.73 (18.13)

a) Yield of crude IIc. b) Mp of the picrate; a substance free of IIc, which has a low melting point, could not be recrystallized. c) Calcd for $C_{17}H_{17}N_5O_9$.

Table 2. Preparation of 1,2,4-oxadiazoles from *N*-benzoylamidino compounds



Oxadiazole No.	R	Reaction temp (°C)	Reaction time (min)	Yield (%)	Mp (bp) (°C)	Recrystn solvent	Found (calcd %) C	H	N
IVa		≈70	5	80 (74)[a]	108 (108)[11]	aq EtOH	75.74 (75.66)	4.56 (4.54)	12.67 (12.60)
IVb		75—79	5	46 (44)[a]	103—104 (103)[12]	EtOH	76.26 (76.25)	5.02 (5.12)	11·92 (11.86)
Va	CH_3O	Room temp	60	91	57 (58—59)[13]	aq MeOH	61.33 (61.36)	4.52 (4.58)	15.94 (15.90)
Vb	EtO	Room temp	60	88	51 (49—55)[13]	aq MeOH	63.05 (63.15)	5.32 (5.30)	14.57 (14.73)
Vc	*i*-PrO	Room temp	60	96[b] (71)[c]	128—132/ 6 Torr	—	64.56 (64.70)	6.03 (5.92)	13.68 (13.72)
Vd	*n*-BuO	Room temp	60	93	36—37	MeOH	65.84 (66.04)	6.63 (6.46)	12.95 (12.83)
VI		≈15	30	58	169—170	aq EtOH	67.80 (68.10)	6.73 (6.59)	17.99 (18.33)

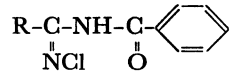
a) *N*-Chloro intermediate was isolated, and then 2 M sodium hydroxide was added. The yield was calculated based on the starting material, I. b) Yield of crude Vc. c) Yield of the distillate of Vc.

Table 3. Spectral data of 1,2,4-oxadiazoles

Compd No.	UV Absorption[a] λ_{max}, nm	NMR Spectra[b] δ ppm	
Vc	255 (13900)	$(CH_3)_2C$	1.46 (d, 6H)
		CH	5.00 (h, 1H)
		Ar-H (*o*-, *p*-)	7.55 (m, 3H)
		Ar-H (*m*-)	8.10 (m, 2H)
Vd	255 (15200)	CH_3	0.98 (t, 3H)
		CH_2CH_2	1.20—2.00 (m, 4H)
		CH_2O	4.38 (t, 2H)
		Ar-H (*o*-, *p*-)	7.55 (m, 3H)
		Ar-H (*m*-)	8.10 (m, 2H)
VI	234 (9700) 278 (16400)	—	— —

a) In CH_3OH. b) In $CDCl_3$. d-doublet, t-triplet, h-heptet, m-multiplet.

Table 4. Physical properties of *N*-chloro compounds



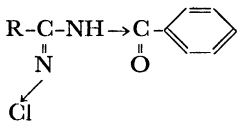
R	Mp (°C)	Appearance	Recrystn solvent	Cl Found[a] (calcd %)	Formula
	98	Needles	Acetone-P. ether	13.45 (13.70)	$C_{14}H_{11}N_2OCl$
	129—130	Needles	Acetone-P. ether	13.30 (13.30)	$C_{15}H_{13}N_2OCl$
CH_3O	—	Colorless oil	—	16.40 (16.67)	$C_9H_9N_2O_2Cl$
EtO	56—57	Needles	EtOH-Ether	15.40 (15.64)	$C_{10}H_{11}N_2O_2Cl$
i-PrO	62	Needles	EtOH-Ether	14.31 (14.73)	$C_{11}H_{13}N_2O_2Cl$
n-BuO	—	Colorless oil	—	13.58 (13.92)	$C_{12}H_{15}N_2O_2Cl$
	124—125	Granular form	Acetone-P. ether	13.26 (13.34)	$C_{13}H_{16}N_3OCl$

a) The active chlorine contents were iodometrically determined.

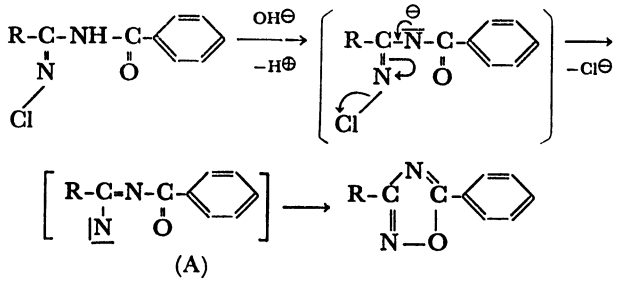
seems to be very convenient, that is, all operations are simple and the products can be obtained directly in an adequate purity.

N-Chloro compounds of I, II, and III are relatively stable; their physical properties are shown in Table 4.

Reaction Mechanism. The hydrogen atom of the NH group of a *N*-chloro compound seems to be acidic as a result of the electron-attracting effect of the chlorine atom and the benzoyl group.



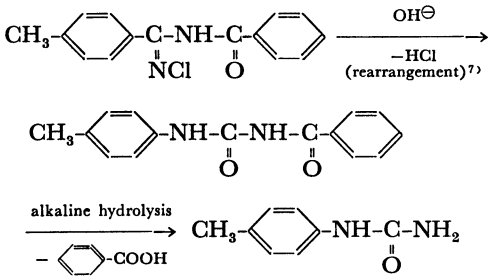
In fact, *N*-chloro compounds of I, II, and III are soluble in an alkaline solution, and the disapearance of the active chlorine takes only a short time. Therefore, this cyclization may be initiated by the removal of a proton from the NH group with a hydroxide ion. The loss of a chloride ion from the resulting anion may form a nitrene intermediate (A). The nitrene thus formed probably attacks the oxygen of the carbonyl group to give 1,2,4-oxadiazole. Such a



Scheme 1.

nitrene intermediate has previously been proposed by us[5] in the thermolysis of acyl derivatives of *N*-benzimidoyl-*S*,*S*-dimethylsulfilimine, giving 1,2,4-oxadiazoles, and by Miorana[6] in the photolysis of *β*-azidovinyl ketones, giving isoxazoles.

The by-product, *p*-tolylurea, may be formed by a mechanism similar to that mentioned in the rearrangement of *N*-alkyl-*N'*-chloroamidines.[7]



Experimental

The melting points are uncorrected. The NMR spectra were recorded at 60 MHz in $CDCl_3$, with TMS as the internal standard, using a Hitachi R-24A spectrometer. The mass spectra were taken with a JEOL JMS-D100 mass spectrometer. The UV spectra were taken with a Hitachi 624 spectrometer.

N-*Benzoylbenzamidine (Ia).* Benzamidine hydrochloride (3.85 g, 20 mmol) was dissolved in a solution of 2 M sodium hydroxide (25 ml) and acetone (5 ml) below 5 °C, and then benzoyl chloride (2.3 ml, 20 mmol) was gradually stirred in. After about 1 h of continued stirring below 10 °C, the white precipitate was filtered off and washed with water. The crude product melted at 90—92 °C; yield, 4.20 g (94%). Recrystallization from 80% aqueous methanol gave pure Ia; mp 98 °C.

N-*Benzoyl*-p-*toluamidine (Ib).* Using the same procedure, the crude product was obtained; yield, 3.50 g (82%). Recrystallization from aqueous methanol gave pure Ib; mp 129—130 °C.

N-*Benzoyl*-O-*methylisourea (IIa).* *O*-Methylisourea (5.53 g, 50 mmol) was dissolved in 70 ml of 2 M sodium hydroxide below 5 °C, and then benzoyl chloride (5.8 ml, 50 mmol) was gradually stirred in. After the addition, the reaction mixture was stirred below 10 °C for 1 h. The resulting oily material was extracted once with a 30-ml portion and twice with 10-ml portions of ether. After the combined ethereal extracts had been dried (Na_2SO_4), filtered, and concentrated under reduced pressure, colorless, needle-like crystals of *N*-benzoyl-*O*-methylisourea were obtained; yield, 6.60 g (74%); mp 76 °C. Recrystallization from aqueous methanol gave pure IIa; mp 77 °C.

The other *N*-benzoylisoureas (IIb—d) were prepared by the same procedure.

N-*Benzoyl*-N',N'-*pentamethyleneguanidine (III).* Using the same procedure but without acetone, the crude product was obtained; yield, 5.60 g (81%); mp 133—135 °C. Recrystallization from methanol gave pure III; mp 149—150 °C.

3,5-Diphenyl-1,2,4-oxadiazole (IVa). To a stirred suspension of Ia (1.12 g, 5 mmol) in ethanol (8 ml), we gradually added, drop by drop, an ethanolic solution (2 ml) of *t*-butyl hypochlorite (0.60 g, 5.5 mmol) at 0—5 °C. After the mixture had been stirred at the same temperature for 30 min, a 4-ml portion of 2 M sodium hydroxide was added. After the mixture had then been warmed at 70 °C, white needle-like crystals began to appear. After 5 min, the mixture was cooled, and then the precipitate was separated by filtration; IVa, 0.77 g; mp 108 °C. Further IVa was obtained by the addition of water (10 ml) to the filtrate; 0.11 g; mp 105—106 °C. The total yield was 80%. Recrystallization from aqueous ethanol gave a pure product; mp 108 °C; *m/e* 222 (M^+).

3-p-*Tolyl*-*5*-*phenyl*-*1,2,4*-*oxadiazole (IVb) and* p-*Tolylurea.* To a stirred suspension of Ib (1.36 g, 5 mmol) in ethanol (8 ml), we gradually added, drop by drop, an ethanolic solution (2 ml) of *t*-butyl hypochlorite (0.60 g, 5.5 mmol) at 0—5 °C. After the mixture had been stirred at the same temperature for 30 min, 4 ml of 2 M sodium hydroxide was added. The reaction mixture was subsequently warmed at 70—75 °C for 5 min and then cooled. The resulting needle-like precipitate was separated by filtration; IVb; yield, 0.54 g (46%). Recrystallization from aqueous ethanol gave pure IVb; mp 103—104 °C; *m/e* 236 (M^+). When the filtrate was evaporated to remove the ethanol, the precipitate, *p*-tolylurea, was filtered off and washed with a small amount of benzene. The yield was 0.16 g (21%). Recrystallization from dioxane-benzene gave a pure product; mp 176—177 °C.

3-Methoxy-5-phenyl-1,2,4-oxadiazole (Va). By the same procedure, but using ether as a solvent, a mixture of *N*-chloro compound of IIa (0.89 g, 5 mmol) and 3 ml of 2 M sodium hydroxide was stirred at room temperature for 60 min. When the reaction mixture was then evaporated under reduced pressure to remove the ether, an oily material was separated. The oily material was crystallized by rubbing with spatera and filtered off; mp 57 °C; yield 0.80 g (91%). Recrystalli-

zation from aqueous methanol gave pure Va; mp 57 °C; *m/e* 176 (M^+).

3-Ethoxy and *3-n*-butoxy-*5*-phenyl-*1,2,4*-oxadiazoles (Vb, d) were obtained by a similar method.

3-Isopropoxy-5-phenyl-1,2,4-oxadiazole (Vc). After working up the reaction mixture (10 mmol) as has been described above, the upper oily material was extracted once with a 10-ml portion and twice with 5-ml portions of dichloromethane. After the combined extracts had then been dried (Na_2SO_4), filtered, and concentrated under reduced pressure, the oily material Vc was obtained (1.95 g, 96%). Distillation under reduced pressure gave a fraction; bp 128—132 °C/6 Torr; 1.50 g (71%); *m/e* 204 (M^+).

3-Piperidino-5-phenyl-1,2,4-oxadiazole (VI). By the same procedure, 4 ml of 2 M sodium hydroxide was added to a solution of a *N*-chloro compound of III (1.16 g, 5 mmol). The mixture, which soon turned reddish yellow, was stirred below 15 °C for 30 min. An orange-yellow precipitate was then filtered off and washed with water; dp 173 °C; yield, 0.67 g (58%). Recrystallization from aqueous ethanol gave a pure product melting at 175 °C (with decomposition); *m/e* 229 (M^+).

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