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N-Halogen Compounds of Cyanamide Derivatives. VII.[1] The Preparation and Amidination of 5-Ethoxy-Δ^4-1,2,4-thiadiazolines

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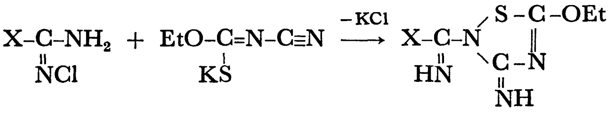
2-Methoxycarbonimidoyl and 2-amidino-3-imino-5-ethoxy-Δ^4-1,2,4-thiadiazolines (I and II) were prepared by the reaction of potassium ethoxythiocarbonylcyanamide (III) with *N*-chloro compounds of *O*-methylisourea and guanidine. Δ^4-1,2,4-Thiadiazoline, I reacted with aliphatic amine to give 2-amidino-Δ^4-1,2,4-thiadiazolines and 1,3,5-triazines in the presence of both the free amines and amine hydrochlorides. The ring opening of Δ^4-1,2,4-thiadiazoline, which finally results in the formation of 1,3,5-triazine, was found to be catalyzed mainly by a base and also by an acid.

Our previous papers[2–4] described that 2-imidoyl-3-imino-5-methylthio and 5-alkoxy-Δ^4-1,2,4-thiadiazolines were prepared in good yields by the reaction of *N*-chloroamidino compounds; we also described their reactivities for sodium hydroxide, amine, hydrogen chloride, and hydrogen sulfide.

In this paper, we wish to report on the preparation of two new Δ^4-1,2,4-thiadiazolines (TDZ), I and IIa, from III[4] and *N*-chloro compounds of *O*-methylisourea and guanidine, and on the amidination of I, together with the ring opening of TDZ, catalyzed by the amine, to give 1,3,5-triazine (IV).

Results and Discussion

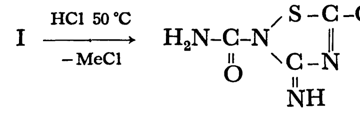
Preparation of 5-Ethoxy-TDZ (I and II). *N*-Chloro compounds of *O*-methylisourea and guanidine readily reacted with III in acetonitrile to form I and IIa. The structures of I and IIa were confirmed by means of elemental analysis and by a study of the IR spectrum.



(III)

X	Yield (%)
MeO	I (80)
H_2N	IIa (60)

Amidination of I. Since compound I can be regarded as *N,N*-disubstituted *O*-alkylisourea with a reactive imidate group, the amidination of I was examined using various kinds of amines. The amidination of I proceeded under reflux in ethanol in the presence of both amine and its hydrochloride to give 2-amidino-TDZ and 1,3,5-triazine (IV). 1,3,5-Triazine, IV has a composition in which sulfur can be excepted from TDZ. In the case of methylamine, desulfurization occurred almost completely, so IV and an unidentified product were obtained instead of 2-amidino-TDZ. In the case of benzylamine, when the amount of free amine was reduced by half, desulfurization was considerably inhibited. Therefore, free amine seemed to participate in the conversion of 2-amidino-TDZ to IV. In the case of a weak base such as aniline, neither the amidination nor ring opening of TDZ occurred, and 2-carbamoyl-TDZ (V) was obtained. Compound V was also obtained quantitatively by the treatment of I with excess dry hydrogen chloride in methanol.

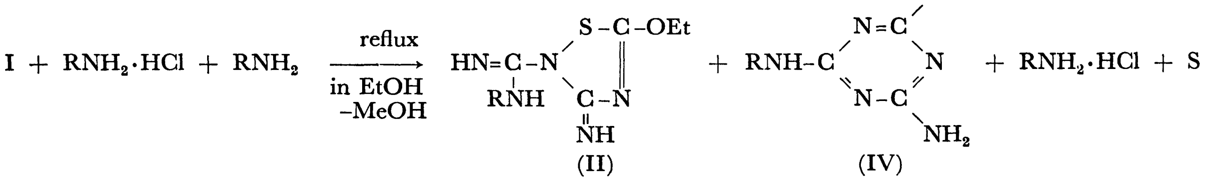


(V)

As is shown in Table 1, the ethoxyl group of I was found not to be reactive.

The physical properties and analytical data of TDZ are summarized in Table 2.

TABLE 1. AMIDINATION OF I

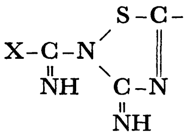


(II) (IV)

Amine			Reaction time (h)	Products (Yield %)			
R	Free base[a)]	Salt[a)]		TDZ(II)	1,3,5-Triazine(IV)	S	Others
Me	2	1	3.0	0	10(IVd)	94	+[b)]
n-Pr	2	1	2.5	20(IIb)	39(IVb)	55	—
Bzl	2	1	3.0	50(IIc)	19(IVc)	25	—
Bzl	1	1	3.0	40(IIc)	Trace(IVc)	6	I
Ph	2	1	3.0	0	0	0	86[c)]

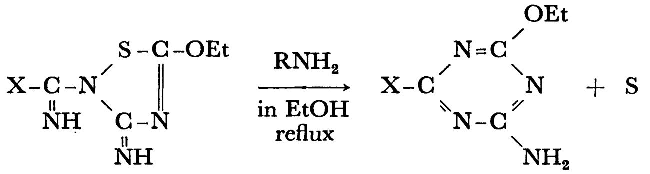
a) Molar ratio. b) The structure could not be determined. c) Yield of IV.

Table 2. Physical properties and analytical data of Δ^4-1,2,4-thiadiazolines



Compound		Mp (°C)	UV Spectra λ_{max}^{MeOH} ($\varepsilon \times 10^{-4}$)	Found (Calcd) %		
No	X			C	H	N
I	MeO	143	263 (1.0)	34.66 (35.63)	4.99 (4.98)	27.40 (27.70)
IIa	H_2N	177—180	242 (0.7)	32.12 (32.08)	4.99 (4.85)	37.31 (37.41)
IIb	*n*-PrNH	161—162	272 (1.1)	41.72 (41.91)	6.29 (6.59)	30.24 (30.54)
IIc	BzlNH	143—145	267 (1.0)	52.21 (51.97)	5.53 (5.45)	25.30 (25.25)
V	HO	300	272 (1.3)	31.54 (31.91)	3.98 (4.28)	29.45 (29.77)

Table 3. Conversion of TDZ to 1,3,5-triazines



X	Amine				Reaction time (h)	1,3,5-Triazine (IV)		
	R	R′	Free base[a)]	Salt[a)]		Yield (%)	Mp (°C)	
MeO	Ph	H	4	0	3	0		
MeO	H	H	4	0	3	54 (46)[b)]		(IVe)
MeO	Me	H	1	0	3	83	102—103	
MeO	Et	Et	1	0	3	Trace		
MeO	Et	Et	4	0	3	Quant.		
MeO	[c)]		4	0	2	0		
H_2N	Et	H	4	0	3	Quant.	182 (182)[5)]	(IVa)
BzlNH	zBl	H	3	0	4	0		
BzlNH	Bzl	H	2	1	3	Quant.	181—183	(IVc)

a) Molar ratio. b) Yield of recovered TDZ. c) Triethylamine.

Conversion of TDZ into 1,3,5-Triazine. Since the above results suggest that free amine participates in the ring opening of TDZ, the conversion of TDZ into 1,3,5-triazine was examined using various kinds of TDZ and amines. Methylamine reacted with I under reflux in ethanol to give IV, as expected, in a good yield. In the case of a bulky amine such as diethylamine, traces of IV were obtained in the presence of an equivalent of the base, and, finally, four equivalents of the base were needed for the quantitative conversion. In the case of triethylamine, no ring opening occurred, and the starting TDZ was recovered. The result may be due to the steric hindrance of triethylamine. Ammonium chloride reacted also with I to give V in about a 50% yield. In the reaction with a weak base such as aniline, no reaction occurred. TDZ (IIc) did not react with free benzylamine, while in the presence of the hydrochloride the reaction occurred to give IVc quantitatively. Amine was found to act as a catalyzer, because the amine used as a neucleophile is not included in IV. The above results showed that the conversion of TDZ to IV depends on the bulkiness and basicity of the amine and on the presence of acid.

The conversion may be initiated by the attack of the free amine on the 5-carbon. The cleavage of the C–S bond, the loss of sulfur from the resulting intermediate, and the recyclization take place to give IV. In the presence of acid, protonation may occur at the imino group. The electron density at the 5-carbon may be

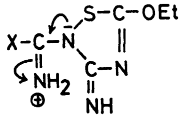
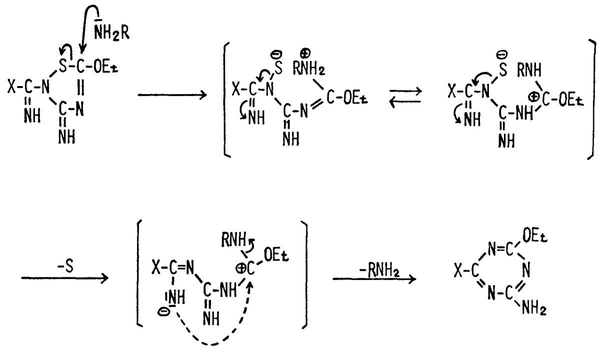


Fig. 1.



Scheme 1. Conversion of TDZ to 1,3,5-triazine.

reduced by the effect of the protonated imino group, and so the attack of the amine may be easier (Fig. 1).

Experimental

2-Methoxycarbonimidoyl-3-imino-5-ethoxy-Δ^4-1,2,4-thiadiazoline (I). To a stirred mixture of III[4] (6.27 g, 40 mmol) and acetonitrile (40 ml), we added a solution of *N*-chloro-*O*-methylisourea (4.34 g, 40 mmol) in acetonitrile (20 ml). The temperature was maintained below 5 °C during the reaction. After 1.75 h of continued stirring, the reaction mixture was evaporated to dryness under reduced pressure. The title compound was obtained by washing the residue with water 6.45 g; 80%; mp 138—143 °C. Recrystallization from ethanol gave a pure product; mp 143 °C. Picrate: mp 137 °C (from water). Found: C, 33.32; H, 2.97; N, 22.78%. Calcd for $C_{12}H_{13}N_7SO_9$: C, 33.42; H, 3.04; N, 22.73%.

2-Amidino-3-imino-5-ethoxy-Δ^4-1,2,4-thiadiazoline (IIa). The title compound was prepared according to approximately the same procedure as that described previously.[3] Recrystallization from methanol-water gave pure IIa; mp 177—180 °C. Picrate: mp 288 °C (from water). Found: C, 31.77; H, 2.93; N, 26.80%. Calcd for $C_{11}H_{12}N_8SO_8$: C, 31.74; H, 2.91; N, 26.92%.

Amidination of I. *Amidination of I with Benzylamine*: A solution of I (2.02 g, 10 mmol), benzylamine (2.14 g, 20 mmol), and benzylamine hydrochloride (1.44 g, 10 mmol) in ethanol (25 ml) was refluxed for 3 h. After the reaction mixture had been evaporated to dryness under reduced pressure, the residue was washed with ether (10 ml). TDZ, IIc containing sulfur was obtained by washing the residue with water: 1.39 g; 50%; mp 137—140 °C (from MeOH). The addition of petroleum ether to the ethereal washings afforded 2-amino-4-benzylamino-6-ethoxy-1,3,5-triazine (IVc) (0.47 g; 19%; mp 181—183 °C (from DMF). Found: C, 58.61; H, 6.26; N, 28.45%. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55%. Picrate: mp 174—175 °C (from EtOH). Found: C, 45.45; H, 3.83; N, 23.51%. Calcd for $C_{18}H_{18}N_8O_8$: C 45.57; H, 3.82; N, 23.62%.

Amidination of I with n*-Propylamine*: Using the same procedure as above (20 mmol scale), after the sulfur had been removed, the filtrate was concentrated. The residual oily material was crystallized from water (20 ml), subsequent recrystallization from ethanol (15 ml) afforded two kinds of products. IIb: 0.92 g; 20%; mp 162—163 °C (from EtOH). 2-Amino-4-ethoxy-6-*n*-propylamino-1,3,5-triazine (IVb): 1.53 g; 39%; mp 132—134 °C (from aq MeOH). Found: C, 48.59; H, 7.45; N, 35.31%. Calcd for $C_8H_{15}N_5O$: C, 48.72; H, 7.67; N, 35.51%.

2-Amino-4-ethoxy-6-methylamino-1,3,5-triazine (IVd) was obtained in a similar manner by the reaction of I with methylamine: 10%; mp 171—172 °C (170—171 °C)[6] (from water). Picrate: dp 202—203 °C (from water). Found: C, 36.26; H, 3.74; N, 27.70%. Calcd for $C_{12}H_{14}N_8O_8$: C, 36.19; H, 3.54; N, 28.13%.

2-Carbamoyl-3-imino-5-ethoxy-Δ^4-1,2,4-thiadiazoline (V). A slow stream of dry hydrogen chloride was passed through a solution of I (2.02 g, 10 mmol) in methanol (30 ml) at 50 °C for 40 min. A small amount of a brown precipitate was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The title compound was obtained by washing the residue with ether; 1.84 g, 98%; dp> 300 °C (from DMF-EtOH).

Reaction of TDZ with Free Amines. *Reaction of I with Aqueous Ammonia*: A solution of I (1.01 g, 5 mmol) and 5% ammonium hydroxide (8 ml, 20 mmol) in ethanol (15 ml) was refluxed for 3 h. After the precipitated sulfur had been filtered off, the filtrate was cooled and I was precipitated; 0.46 g, 46%. After the filtration of I, the concentration of the filtrate afforded 2-amino-4-ethoxy-6-methoxy-1,3,5-triazine (IVe): 0.46 g, 54%; mp 102—103 °C. Found: C, 41.92; H, 6.03; N, 32.62%. Calcd for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.92%.

Reaction of IIc with Benzylamine: A mixture of IIb (0.55 g 2 mmol), benzylamine (0.72 g, 4 mmol), and benzylamine hydrochloride (0.29 g, 2 mmol) was refluxed in ethanol (6 ml) for 3 h. After the reaction mixture had been concentrated, the residue was washed with ether and water; 1,3,5-triazine (IVc) was thus obtained; 0.49 g; quant.

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