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Heterocyclic Amines. A Convenient Synthesis of 3,5-Diamino-1,2,4-Triazine Derivatives

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A facile synthesis of 3,5-diamino-1,2,4-triazines (I) via condensations in acidic media of acylnitriles with aminoguanidine and subsequent base-catalyzed cyclization of the resulting acylnitrile amidinohydrazones (IV) is described.

In connection with our efforts to develop agents capable of sexually sterilizing insects (1), it became necessary to prepare a number of 6-substituted-3,5-diamino-1,2,4-triazines (I).

In 1952, Hitchings and his co-workers (2-4) noted the structural similarities between I and certain effective folic acid inhibitors in the 1,3,5-triazine (II) and pyrimidine (III) series. They described preparation of several derivatives of I by amination of the corresponding 3-methylthio-5-chloro compounds. The latter were obtained by chlorination of 3-methylthio-5-hydroxy-1,2,4-triazines which, in turn, arose from condensation of *S*-methylthiosemicarbazide hydrochloride with derivatives of ethyl glyoxylate.

Grundmann, Schroeder and Rätz (5) found that cleavage of the triazine ring occurred before the second chlorine atom in 3,5-dichloro-1,2,4-triazine was displaced by ammonia (6). Thus, conversion of 3-hydroxy-1,2,4-triazines to their amino analogs is best accomplished by reaction with phosphorus pentasulfide to produce 3-mercapto intermediates, rather than by chlorination (4,7).

In what appears to be the only other reference to the synthesis of I, Beyer, Pyl and Wünsch (8) in 1960 described the cyclization, in 53% yield, of pyruvonitrile amidinohydrazone (IVa) nitrate to Ia nitrate. However, the transformation, which was accomplished by warming in cyclohexanol at 160°, reportedly failed with three similar hydrazones. The amidinohydrazone salts were prepared by reaction of corresponding acylnitriles with aminoguanidine nitrate in dilute nitric acid. Inasmuch as this latter approach, if it could be generalized, seemed to offer an attractive route to a variety of 3,5-diamino-1,2,4-triazine derivatives, the work of Beyer *et al.* was repeated and extended in the present study.

The described reaction of pyruvonitrile with aminoguanidine nitrate (8) was extended to water-insoluble acylnitriles by the use of dimethylsulfoxide as co-solvent. Apparently, these condensations must be carried out in a medium that is acidic enough to insure formation of a protonated carbonyl-addition intermediate (V) capable of preferential elimination of water rather than of cyanide ion (9). Thus, in the absence of added acid, the only product obtained from the reaction of benzonitrile with aminoguanidine nitrate was benzamidoguanidine (VI) (10).

The amidinohydrazones (Table I) were sometimes isolated as their nitrate derivatives by addition of ice-water to the reaction mixture, although a more common procedure was to add excess 20% aqueous sodium hydroxide, which caused precipitation of the hydrazone bases in slightly higher yield.

In contrast to the difficulty encountered by Beyer *et al.*, in attempting to cycloisomerize acylnitrile amidohydrazones prepared by them (8), all of the hydrazone bases in the present study were transformed almost quantitatively into the required 1,2,4-triazines (Table II) by warming for several minutes in methanolic potassium hydroxide.

IR and UV spectra, consistent with their structures, were recorded for all of the new compounds reported.

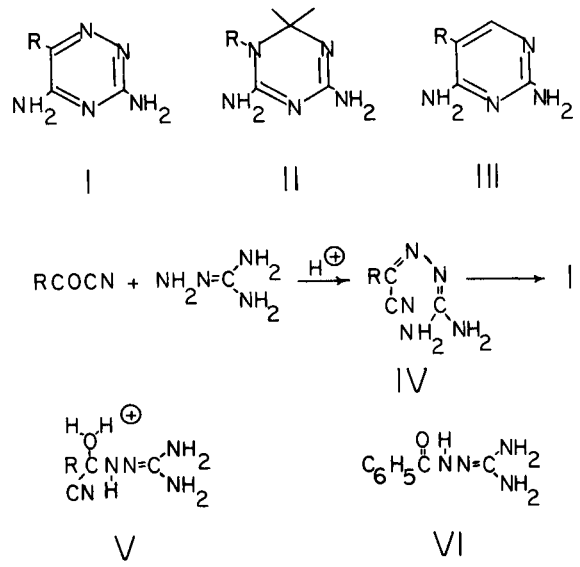

TABLE I

Compound Number	R	Yield %	M.p., °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
IVa	CH_3-	21(a)	135-136(b)	$C_4H_7N_5$	38.40	38.27	5.63	5.65	55.97	55.98
IVb	C_6H_5-	69	174-176	$C_9H_9N_5$	57.76	57.69	4.82	4.83	37.41	37.28
IVc	*p*-ClC_6H_4-	69	187-189	$C_9H_8ClN_5$	48.78	48.85	3.63	3.77	31.57	31.45
IVd	*p*-$CH_3OC_6H_4$-	79	184-186	$C_{10}H_{11}N_5O_3$	55.30	55.42	5.09	5.16	32.24	32.06
IVe	3,4,5-$(CH_3O)_3C_6H_2$-	42	295-297(c)	$C_{12}H_{15}N_5O_3$	52.02	51.95	5.45	5.64	25.25	25.08
IVf	C_4H_3O-(d)	74	201-203	$C_7H_7N_5O$	47.46	47.38	3.98	4.20	39.52	39.69

(a) When isolated as its nitrate derivative, the yield was 68%; conversion to the base was complicated by the marked tendency of this hydrazone to undergo cyclization. (b) Reported (8) m.p. 250°. In view of the facile cyclization of this hydrazone, these workers may have observed the melting point of the corresponding 1,2,4-triazine. (c) After slowly cyclizing above 230° to its 1,2,4-triazine isomer. (d) 2-Furyl.

TABLE II

Compound Number	R	Dec. p. °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
Ia	CH_3-	254-255 (a)	$C_4H_7N_5$	38.40	38.50	5.63	5.40	55.97	56.47
Ib	C_6H_5-	218-219 (b)	$C_9H_9N_5$	57.76	57.82	4.82	4.79	37.41	37.38
Ic	*p*-ClC_6H_4-	219-222 (c)	$C_9H_8ClN_5$	48.78	48.76	3.63	3.60	31.57	31.60
Id	*p*-$CH_3OC_6H_4$-	219-219.5	$C_{10}H_{11}N_5O$	55.30	55.09	5.09	5.22	32.24	32.44
Ie	3,4,5-$(CH_3O)_3C_6H_2$-	295-297	$C_{12}H_{15}N_5O_3$	52.02	52.18	5.45	5.67	25.25	25.55
If	C_4H_3O- (d)	229-230	$C_7H_7N_5O$	47.46	47.60	3.98	4.20	39.52	39.63

(a) Reported m.ps. 250° (8) and 234-238° (4). (b) Reported m.p. 206° (3). (c) Reported m.p. 218-220° (3). (d) 2-Furyl.

TABLE III

Compound	Ultraviolet: 0.01 *M* HCl in 95% EtOH		Ultraviolet: 0.01 *M* NaOH in 95% EtOH		Infrared (KBr) μ
	τ max mμ	ε	τ max mμ	ε	
Ia	252	6,400	221	10,100	3.0, 3.17, 6.12, 6.42
			302	5,000	6.95, 12.78, 13.50
Ib	237(s)	13,000	249	9,100	3.1-3.2, 6.15, 6.50, 6.68,
	280(s)	5,900	315	6,900	6.98, 7.48, 8.10, 9.90
Ic	216(s)	15,300	243	12,500	3.25, 6.12, 6.84, 6.95,
	315	6,200	332	11,200	8.50, 12.18
Id	247	15,600	252	12,600	3.05, 6.18, 7.0, 8.0, 12.10
	309	5,800	326	8,800	
Ie	250	12,900	255	(a)	2.94, 3.04(w), 3.20, 6.10, 6.98,
	310	4,500	318	(a)	8.90, 10.18, 11.45, 12.0, 13.10
If	217	19,500	265	10,500	3.25, 6.10, 6.55, 7.0, 8.05,
	258	9,600	354	15,500	12.10(w), 14.05
	327	13,800			

(a) Concentration unknown; O.D. at 255mμ/O.D. at 287 mμ = 2.28. O.D. at 318 mμ/O.D. at 287 mμ = 1.66.

EXPERIMENTAL

Acylnitriles.

References to all of the acylnitriles utilized in the present study were found in the literature. Those that were not available commercially were prepared by the method of Oakwood and Weisgerber (12) and their physical constants checked by comparison with previously reported values.

Acylnitrile Amidinohydrazones Listed in Table I.

General Procedure.

A 50% solution of acylnitrile in dimethylsulfoxide was added dropwise with stirring and cooling (ice-water bath) to an equimolar amount of aminoguanidine dissolved in 2*N* nitric acid (0.5 g./ml.). The reaction mixture was allowed to stand for 10 hours at 0-5° before precipitating the amidinohydrazone by adding excess ice-cold 20% aqueous sodium hydroxide. The precipitate was collected by filtration and washed well with water. Specimens for analysis were recrystallized twice from ethanol. Acylnitrile amidinohydrazone structures for these bases were supported by bands at 2222-2240 cm^{-1} (C≡N) and and at 1620-1677 cm^{-1} (C=N) in their infrared spectra.

Pyruvonitrile Amidinohydrazone.

The nitrate and hydrochloride derivatives of this compound were prepared by the method of Beyer *et al.* (8). Attempted preparation of its base by the general method (above) or by the procedure described by Beyer led to isolation of 3,5-diamino-6-methyl-1,2,4-triazine in good yields. However, careful neutralization of concentrated aqueous solutions of its hydrochloride with ice-cold 40% aqueous sodium hydroxide produced a small amount of precipitate. After filtering and washing with a few drops of ice water and then petroleum ether, the colorless powder was identified as pyruvonitrile amidinohydrazone by its infrared spectrum as well as by elemental analyses performed on a sample recrystallized from ether-petroleum ether.

3,5-Diamino-1,2,4-triazines.

These compounds were prepared by warming the corresponding amidinohydrazones for 5 minutes in a 10% solution of potassium hydroxide in methanol. Filtration of the chilled reaction mixture produced almost quantitative yields of the desired triazines. With one exception, specimens were prepared for analysis by recrystallization from methanol. 3,5-Diamino-6-(3,4,5-trimethoxyphenyl)-1,2,4-triazine was too insoluble to recrystallize from any solvent tried. It was dissolved in warm, dilute hydrochloric acid, filtered, and reprecipitated by addition of aqueous sodium hydroxide to provide a sample for analysis.

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