Reaction of Biguanides and Related Compounds. XVI. Synthesis of *s*-Triazinones and Fused *s*-Triazinones by Carbonylation of Biguanides and Related Compounds with Diethyl Azodicarboxylate

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Biguanides and the related compounds, in which a moiety of biguanide is involved in the structure as a part of the ring, were allowed to react with diethyl azodicarboxylate to afford triazinones and fused heterocycles including a triazinone ring, respectively. The mechanism of the reaction was elucidated to proceed through the initial formation of the amide intermediate, followed by cyclization to triazinone ring systems with elimination of nitrogen.

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Biguanides are highly useful versatile materials in the preparation of heterocyclic compounds. Reactions with a variety of carboxylic esters are known to provide pyrimidines and *s*-triazines [1-6]. Condensations with diethyl oxalate [5] and with α-diketones accompanying a benzilic acid rearrangement lead to the synthesis of imidazolidines [7]. Acid catalyzed condensations with ketones result in the cyclization to dihydro-*s*-triazines [8-10].

We have previously reported that the reaction of arylbiguanides with diethyl azodicarboxylate (DAD) provides 1-aryl-4,6-diamino-1,2-dihydro-*s*-triazin-2-ones [11] in moderate yields. In this reaction, the carbonyl group of DAD was consequently inserted between the terminal amino and imino groups to form *s*-triazinones. DAD has been shown to be highly useful as reagents in the preparations of heterocyclic ring systems by Diels-Alder reactions [12], 1,3-dipolar cycloadditions [13], additions with pyrimidines [14], and oxydative cyclizations [15]. However, any effective behavior of DAD as a carbonylation reagent for the preparation of heterocyclic ring systems had not hitherto been reported.

As an extension of our study, we newly examined the reactions of DAD **1** with *N,N*-disubstituted biguanides **2**, amidinoamidine **3**, and the related several 2-guanidino heterocycles **4-6**, in which structural moieties similar to biguanides are involved. When *N,N*-disubstituted biguanides **2** were treated with an excess of DAD in ethanol at ambient temperature, 4-amino-6-disubstituted amino-1,2-dihydro-*s*-triazin-2-ones **7** were obtained in moderate yields with the vigorous evolution of nitrogen. The structural assignment of **7** was based primarily upon the spectral data. The ir spectra of **7** exhibited the absorptions assignable to C=O and NH at 1660-1680 cm^{-1} and near 3400 and 3150 cm^{-1}, respectively. In the ^1H-nmr spectra, the NH signals were shown near δ 10.0 and 6.8, which disappeared by deuterium oxide exchange. The mass spectra indicated the molecular ion peak and the fragment ion peak corresponding to the elimination of isocyanic acid. The ^{13}C-nmr spectrum of **7a** exhibited the carbonyl signal at 164.7 ppm and the two imino signals in the triazine ring at 158.8 and 156.3 ppm. In order to verify the structural assignment, **7a** was prepared by an alternate procedure. Heating 1-(3′-oxapentamethylene)biguanide **2a** with ethylenecarbonate **8** in *N,N*-dimethylformamide at ambient temperature for a few days gave successfully **7a** in 47% yield.

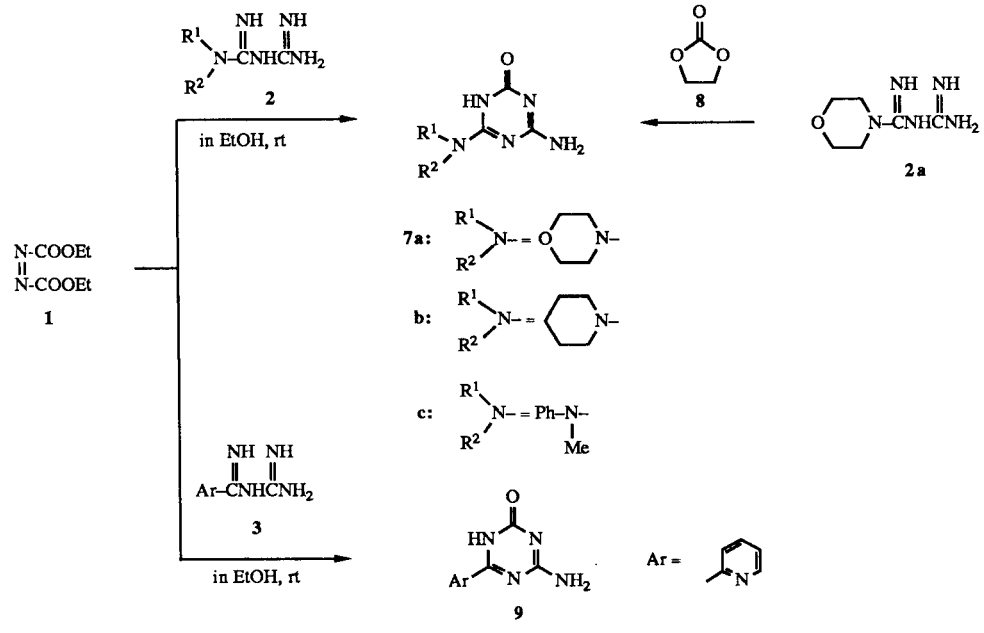
Amidinoamidine **3** [17] also reacted similarly with DAD under the same conditions to provide 6-substituted 4-amino-1,2-dihydro-*s*-triazin-2-one **9** in comparatively good yield (Scheme 1). Yields, mp and spectral data of **7** and **9** are shown in Table I.

DAD serves as two different electrophiles. It is known that aromatic amines combine with the N=N nitrogen to afford triazenes, while aliphatic amines react with the ester carbonyl to give amides [16]. Based on these facts, the reaction mechanism is presumed as follow: The hard terminal amino group of **2** should selectively attack the hard ester carbonyl rather than the soft nitrogen of DAD, followed by cyclization due to the intramolecular nucleophilic attack of the imino group on the amide carbonyl

Table I
Preparation of 6-Substituted 4-Amino-1,2-dihydro-*s*-triazin-2-ones **7,9**

No.	R^1R^2N or Ar	Yield (%)	mp (°C)	IR (KBr) cm^{-1}	HR-MS (m/z) (M^+) Calcd./Found
7a	morpholino	72	>300	3460 (NH_2) 3220 (NH) 1690 (C=O)	197.0913 197.0948
7b	piperidino	53	>300	3380 (NH_2) 3100 (NH) 1680 (C=O)	195.1120 195.1154
7c	*N*-methyl-anilino	51	296-297	3290 (NH_2) 3124 (NH) 1660 (C=O)	217.0964 217.0953
9	*m*-pyridyl	93	>300	3368 (NH_2) 3194 (NH) 1698 (C=O)	189.0651 189.0641

Scheme 1



Scheme 2

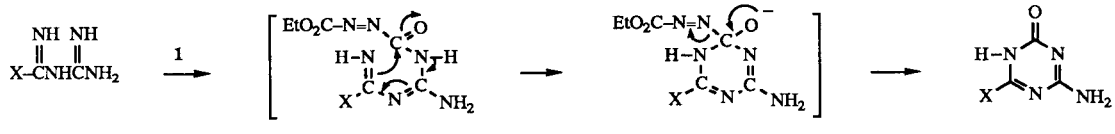


Table I (Continued)

No.	R^1R^2N or Ar	^{1}H-NMR (DMSO-d_6), δ
7a	morpholino	3.38-3.88 (8H, m, CH_2 x 4), 6.93 (2H, s, NH_2), 10.21 (1H, br, NH)
7b	piperidino	1.20-1.86 (6H, m, CH_2 x 3), 3.40-4.00 (4H, m, CH_2 x 2), 6.76 (2H, s, NH_2), 9.78 (1H, s, NH)
7c	*N*-methylanilino	3.35 (3H, s, CH_3), 6.89 (2H, s, NH_2), 7.06-7.50 (5H, m, ArH), 10.20 (1H, s, NH)
9	*m*-pyridiyl	7.20-8.20 (3H, m, ArH and NH_2), 8.45-8.69 (2H, m, ArH), 9.12-9.48 (1H, m, ArH), 11.47 (1H , s, NH)

Table I (Continued)

No.	R^1R^2N or Ar	Formula	Analysis (%) Calcd. (Found) C	H	N
7a	morpholino	$C_7H_{11}N_5O_2 \cdot 1/2H_2O$	40.77 (40.68)	5.78 (6.18)	33.69 (33.56)
7b	piperidino	$C_8H_{13}N_5O$	49.22 (49.10)	6.71 (6.59)	35.87 (35.36)
7c	*N*-methyl-anilino	$C_{10}H_{11}N_5O \cdot 1/3EtOH$ [a]	55.08 (55.09)	5.63 (5.48)	30.11 (30.58)
9	*m*-pyridyl	$C_8H_7N_5O \cdot 2/3H_2O$	47.72 (47.79)	4.14 (4.01)	34.79 (34.53)

[a] The ^{1}H-nmr spectrum of the compound **7c** shows the ethanol signals with a third intensity.

group of the intermediate product with elimination of nitrogen to form triazines (Scheme 2).

In order to expand this cyclization to the preparation of fused heterocyclic ring systems, several 2-guanidino heterocycles **4-6** were allowed to react with DAD. When 2-guanidinobenzimidazoles **4** [18], 2-guanidinobenzothiazole **5** [19], and 2-guanidinobenzoxazole **6** [20] were respectively treated with DAD in boiling ethanol, the fused heterocyclic compounds **10-12** involving a triazinone ring were, as anticipated, formed in good yields. Only in the case of **5**, the amide intermediate **13** was successfully isolated in 46% yield under more mild conditions by stirring in ether at ambient temperature. The intermediate **13** was readily converted to **11** by cyclization in dioxane under boiling in 48% yield (Scheme 3). The results are summarized in Table II.

Although the EI-mass spectrum of **13** exhibited the almost same spectral pattern as that of **11**, both ir and ^{1}H-nmr spectra showed entirely different spectral pat-

Scheme 3

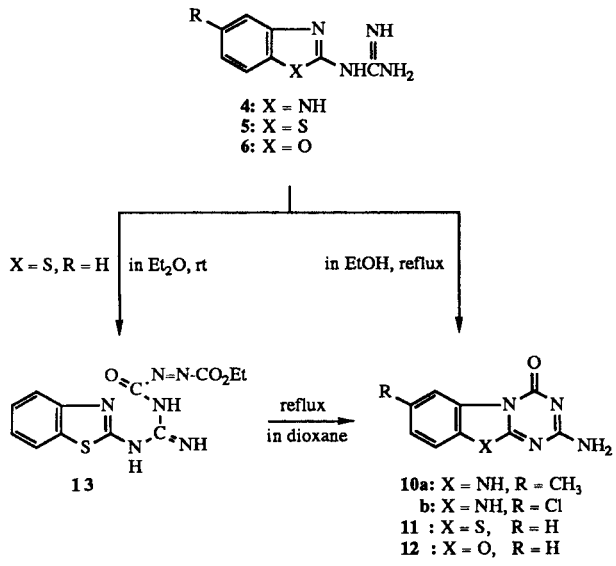


Table II

Preparation of Triazinones **10, 11, 12**

No.	X	R	Yield (%)	mp (°C)	IR (KBr), cm^{-1} Calcd./Found	HR-MS (m/z) (M^+)
10a	NH	CH_3	97	>300	3250 (NH_2)	215.0807
					3100 (NH)	215.0790
					1700 (C=O)	
10b	NH	Cl	89	>300	3250 (NH_2)	235.0261
					3100 (NH)	235.0253
					1700 (C=O)	
11	S	H	26	>300	3270 (NH_2)	218.0262
					1700 (C=O)	218.0256
12	O	H	37	>300	3350 (NH_2)	202.0491
					1700 (C=O)	202.0474

Table II (Continued)

No.	X	R	^{1}H-NMR (DMSO-d_6), δ
10a	NH	CH_3	2.34 (3H, s, CH_3), 3.00-3.80 (1H, br, NH), 6.30-7.50 (4H, m, ArH and NH_2), 7.55-8.20 (1H, m, ArH)
10b	NH	Cl	3.40 (1H, br, NH), 6.61-7.47 (4H, m, ArH and NH_2), 7.75-8.06 (1H, m, ArH)
11	S	H	7.40-7.85 (4H, m ArH and NH_2), 7.90-8.35 (1H, m, ArH), 8.55-8.80 (1H, m, ArH)
12	O	H	7.08-8.14 (6H, m, ArH and NH_2)

Table II (Continued)

No.	X	R	Formula	Analysis (%) Calcd. (Found) C	H	N
10a	NH	CH_3	$C_{10}H_9N_5O$	55.81	4.22	32.54
				(56.20)	(4.38)	(32.04)
10b	NH	Cl	$C_9H_6N_5OCl$	45.88	2.57	29.72
				(46.01)	(2.78)	(29.38)
11	S	H	$C_9H_6N_4OS$	49.53	2.77	25.67
				(49.88)	(2.96)	(25.19)
12	O	H	$C_9H_6N_4O_2$	53.47	2.99	27.71
				(53.65)	(3.04)	(27.54)

terns, respectively. In the ir spectrum, the absorption assignable to the ester carbonyl group appeared at 1735 cm^{-1}, which is not, of course, observed in that of **11**. The ^{1}H-nmr spectrum indicated the characteristic signals due to the ethoxy methylene and methyl protons at δ 3.95 and 1.10. The elemental analysis was entirely consistent with the assigned intermediate structure. The agreement of the mass spectra of **13** and **11** may be due to the rapid cyclization of **13** to **11** by heating in measurement of the mass spectrum. The FAB-mass spectrum showed the molecular ion corresponding to **13**.

On the bases of these results, it is evident that the cyclization with DAD to triazinones proceed through the initial formation of the amide intermediate.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ir spectra were recorded with a JASCO IR-1 grating infrared spectrometer. The ^{1}H-nmr spectra were recorded on a JEOL 60 MHz high-resolution nmr instrument. Mass spectra were obtained on a JEOL 01SG mass spectrometer.

General Procedure for the Preparation of 6-Substituted 4-Amino-1,2-dihydro-*s*-triazin-2-ones (**7a-c** and **9**).

A solution of DAD (5.1 ml, 30 mmoles) in ethanol (10 ml) was added with stirring into a suspension of *N,N*-disubstituted biguanide (10 mmoles) or amidinoamidine (10 mmoles) in ethanol (40 ml). After being stirred for 3 hours, the deposited precipitates were collected, washed with cold ethanol, and recrystallized from water or ethanol. The results are summarized in Table I.

4-Amino-6-morpholino-1,2-dihydro-*s*-triazin-2-one (**6a**) from Morpholinoamidinoamidine (**2**, R^1R^2N- = morpholino) and Ethylene Carbonate.

A solution of morpholinoamidinoamidine (1.38 g, 8 mmoles) and ethylene carbonate (0.7 g, 8 mmoles) in *N,N*-dimethylformamide (20 ml) was stirred at room temperature for 3-4 days. Resulting precipitates were collected and recrystallized from water to give **a** in 47% yield.

7-Substituted 2-Aminobenzimidazo[3,2-*a*]-*s*-triazin-4-ones (**10a,b**).

A mixture of 5-substituted 2-guanidinobenzimidazole (8 mmoles), DAD (2.8 ml, 16 mmoles) and ethanol (15 ml) was heated for 3 hours under reflux. Resulting precipitates were collected and washed with ethanol. The data are shown in Table I.

2-Aminobenzothiazo[3,2-*a*]-*s*-triazin-4-one (**11**) and 2-Aminobenzoxazo[3,2-*a*]-*s*-triazin-4-one (**12**).

A mixture of 2-guanidinobenzothiazole (1.9 g, 10 mmoles) of 2-guanidinobenzoxazole (1.8 g, 10 mmoles), DAD (5.1 ml, 30 mmoles) and dioxane (20 ml) was heated for 12 hours under reflux. Resulting precipitates were collected and washed with eth-

anol. The data are exhibited in Table I.

N^1-2-Benzothiazolyl-N^2-ethoxycarbonylazocarbonylguanidine (**13**).

DAD (3.5 ml, 20 mmoles) was added dropwise with stirring into a solution of 2-guanidinobenzothiazole (1.0 g, 5 mmoles) in ether (80 ml), and then stirring was continued for 12 hours at room temperature. The resulting precipitates were collected, washed with ether, and recrystallized from *N,N*-dimethylformamide-water to give **13** (0.74 g, 46%), mp 164-165°; ir: 3270, 3190 cm^{-1} (NH), 1735, 1660 cm^{-1} (C=O); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 1.10 (3H, t, CH_3, J = 6.0 Hz), 3.95 (2H, q, CH_2, J = 6.0 Hz), 7.20-8.26 (4H, m, ArH), 8.65 (2H, br, NH x 2), 10.56 (1H, br, NH); EI-ms: 264 (M^+-CN_2O), 218 (M^+-$C_3H_6N_2O_2$); FAB-ms: 321 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{12}N_6O_3S$: C, 45.00; H, 3.78; N, 26.24. Found: C, 45.34; H, 3.79; N, 25.91.

2-Aminobenzothiazo[3,2-*a*]-*s*-triazin-4-one (**11**) from N^1-2-Benzothiazolyl-N^2-ethoxycarbonylazocarbonylguanidine (**13**).

A solution of **13** (3.0 g, 10 mmoles) in dioxane (40 ml) was heated for 12 hours under reflux. Resulting precipitates were collected, washed with ethanol, and recrystallized from *N,N*-dimethylformamide to give **11** (1.05 g) in 48% yield.

2-Aminopyrrolidino[1,2-**a**]-*s*-triazin-4-one (**7b**).

DAD (5.1 ml, 30 mmoles) was added dropwise with stirring into a solution of 2-guanidino-1-pyrroline (1.26 g, 10 mmoles) in ethanol (10 ml), and the solution was stirred for 3 hours at room temperature. Resulting precipitates were collected and recrystallized from methanol to give **7b** (1.27 g) in 84% yield, mp >300°; ir: 3300 cm^{-1} (NH), 1688 cm^{-1} (C=O); ^{1}H-nmr (deuteriodimethyl sulfoxide): δ 1.86-2.27 (2H, ddd, CH_2, J = 7.2 Hz), 2.89 (2H, t, CH_2, J = 7.2 Hz), 3.80 (2H, t, CH_2, J = 7.2 Hz), 7.20 (2H, br, NH_2); ms: 151 (M^+).

Anal. Calcd. $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.82. Found: C, 47.11; H, 5.55; N, 36.84.

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