Notes

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Reaction of Biguanides and Related Compounds. XV.[1] Cyclizations of Arylbiguanides and 2-Guanidinobenzimidazole with Bifunctional Unsaturated Dicarboxylates to *s*-Triazines and Imidazolines

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Arylbiguanide (**1**) and 2-guanidinobenzimidazole (**2**) were reacted with diethyl azodicarboxylate (**3**) to give dihydro-*s*-triazine (**6**) and dihydrobenzimidazo[1,2-*a*]-*s*-triazine (**9**), respectively. The reactions of **1** and **2** with dimethyl acetylenedicarboxylate (**4**) in alcohol provided the corresponding imidazolinylideneacetylguanidines (**10** and **12**), which were converted to alkyl imidazolidinylideneacetates (**11** and **13**) by alcoholysis. The compounds **10** and **12** underwent acid-catalyzed ring conversion to pyrimidine compounds (**15** and **16**).

Keywords——arylbiguanide; guanidinobenzimidazole; diethyl azodicarboxylate; dimethyl acetylenedicarboxylate; *s*-triazine; imidazoline; cyclization; ring conversion

In previous investigations on the reactions[2-4] of biguanides with dicarboxylates and α,β-unsaturated carboxylates, we have reported that cyclization to *s*-triazines or pyrimidines readily took place in the absence of any catalyst. We newly examined the behavior of arylbiguanides (**1**) and the related compound, 2-quanidinobenzimidazole (**2**), toward some other unsaturated dicarboxylates, diethyl azodicarboxylate (**3**) and dimethyl acetylenedicarboxylate (**4**).

Reactions of Arylbiguanides and 2-Guanidinobenzimidazole with Diethyl Azodicarboxylate

When **1** was treated with an excess of **3** in ethanol at room temperature, 1,2-dihydro-1-aryl-4,6-diamino-*s*-triazin-2-ones (**6**) were obtained in 40—70% yields, with vigorous evolution of nitrogen gas. In this reaction, the use of methanol instead of ethanol as the solvent resulted in considerable lowering of the yield of **6**. The infrared (IR), mass, and ultraviolet (UV) spectral data for **6** are summarized in Table I.

On the basis of the spectral and analytical data, the isomeric structure, 6-amino-4-arylamino-*s*-triazin-2-ol (**7**), is also possible for the product. The distinction between **6** and **7** can conveniently be made from the UV spectra, though it is extremely difficult to distinguish them by IR, nuclear magnetic resonance (NMR), and mass spectral data and analysis. Kurzer[5] reported that the UV spectra of 1-substituted hexahydro-4,6-diimino-*s*-triazin-2-ones feature a narrow absorption maximum in the 220—230 nm range, while 6-amino-4-anilino-*s*-triazin-2-ols show a broad high-intensity maximum at *ca.* 260 nm, which is absent in the former compound. These data suggest that the structure **6** is more likely for the product. In order to establish the assigned structure, **6a** (R = H)[5] and **7** (R = H)[6] were each prepared by alternative methods, and their IR and mass spectra were compared with those of the product. Consequently, the product was conclusively identified as **6**.

The reaction of **2**[7] with an excess of **3** was also successfully achieved by refluxing in

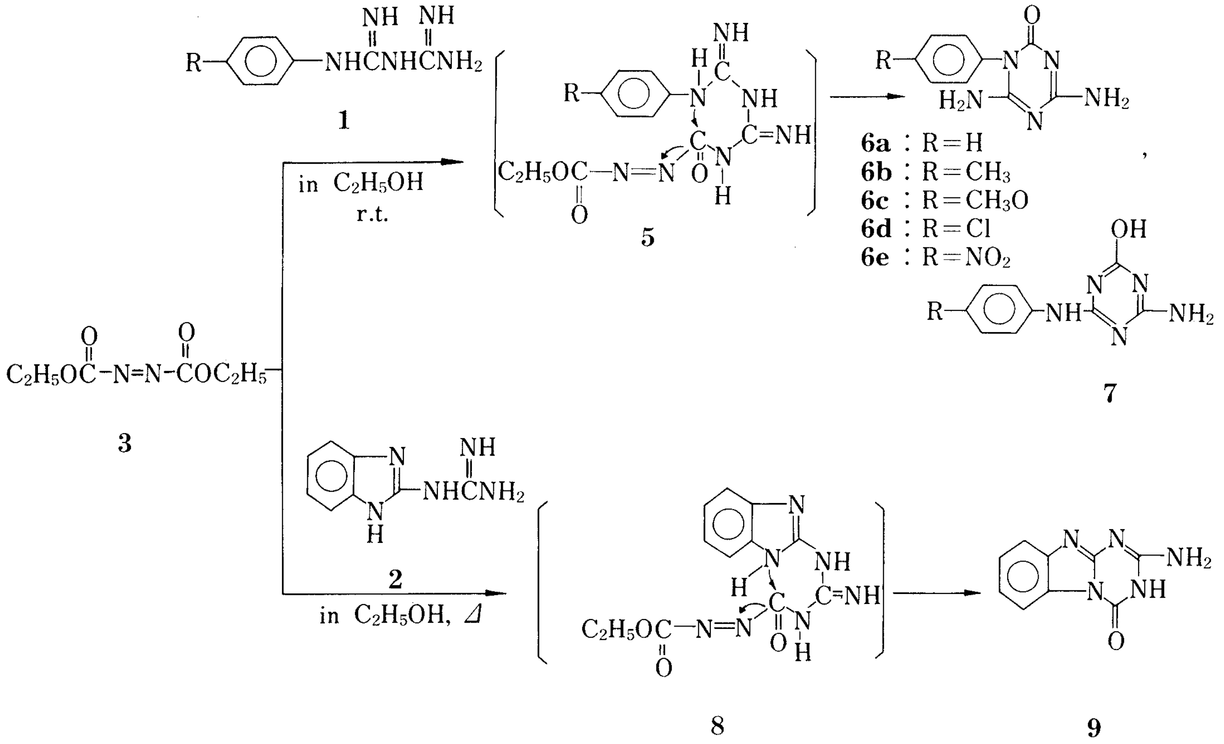

Chart 1

Table I. IR, UV, and Mass Spectral Data for Dihydro-1-aryl-4,6-diamino-*s*-triazin-2-ones (**6**)

Compd. No.	R	MS m/e (M^+)	IR ν_{max}^{KBr} cm^{-1} NH and =NH	IR ν_{max}^{KBr} cm^{-1} C=O	UV[a] Solvent	UV[a] λ_{max} nm ($\varepsilon \times 10^3$)
6a	H	203	3460, 3250	1680	H_2O	232 (15.1)
			(br)		1 N HCl	241 (14.6)
6b	CH_3	217	3460, 3260	1680	H_2O	232 (12.6)
			(br)		1 N HCl	233 (20.6)
6c	CH_3O	233	3400, 3250	1680	H_2O	230 (24.6)
			(br)		1 N HCl	232 (25.6)
6d	Cl	236	3460, 3280	1700	H_2O	222 (19.8)
			(br)		1 N HCl	233 (23.5)
6e	NO_2	248	3390, 3250	1720	—	—
			(br)		1 N HCl	232 (13.6)

a) For the measurement of the UV spectra, the hydrochlorides of **6** were used at a concentration of 5×10^{-5} mol/l.

ethanol to give 2-amino-4-oxo-3,4-dihydrobenzimidazo[1,2-*a*]-*s*-triazine (**9**) in 62% yield with evolution of nitrogen gas. The structure of **9** was assigned on the basis of the spectral data, and confirmed by direct comparison with an authentic sample[8)] of **9** prepared from **2** and benzoyl isocyanate.

The reactions of **3** with **1** and **2** are presumed to proceed through the initial formation of the acyl intermediates (**5** and **8**) followed by cyclization with elimination of nitrogen gas and ethyl formate. As a result, the carbonyl group arising from diethyl azodicarboxylate was introduced between the terminal amino group and the amino group adjacent to the benzene

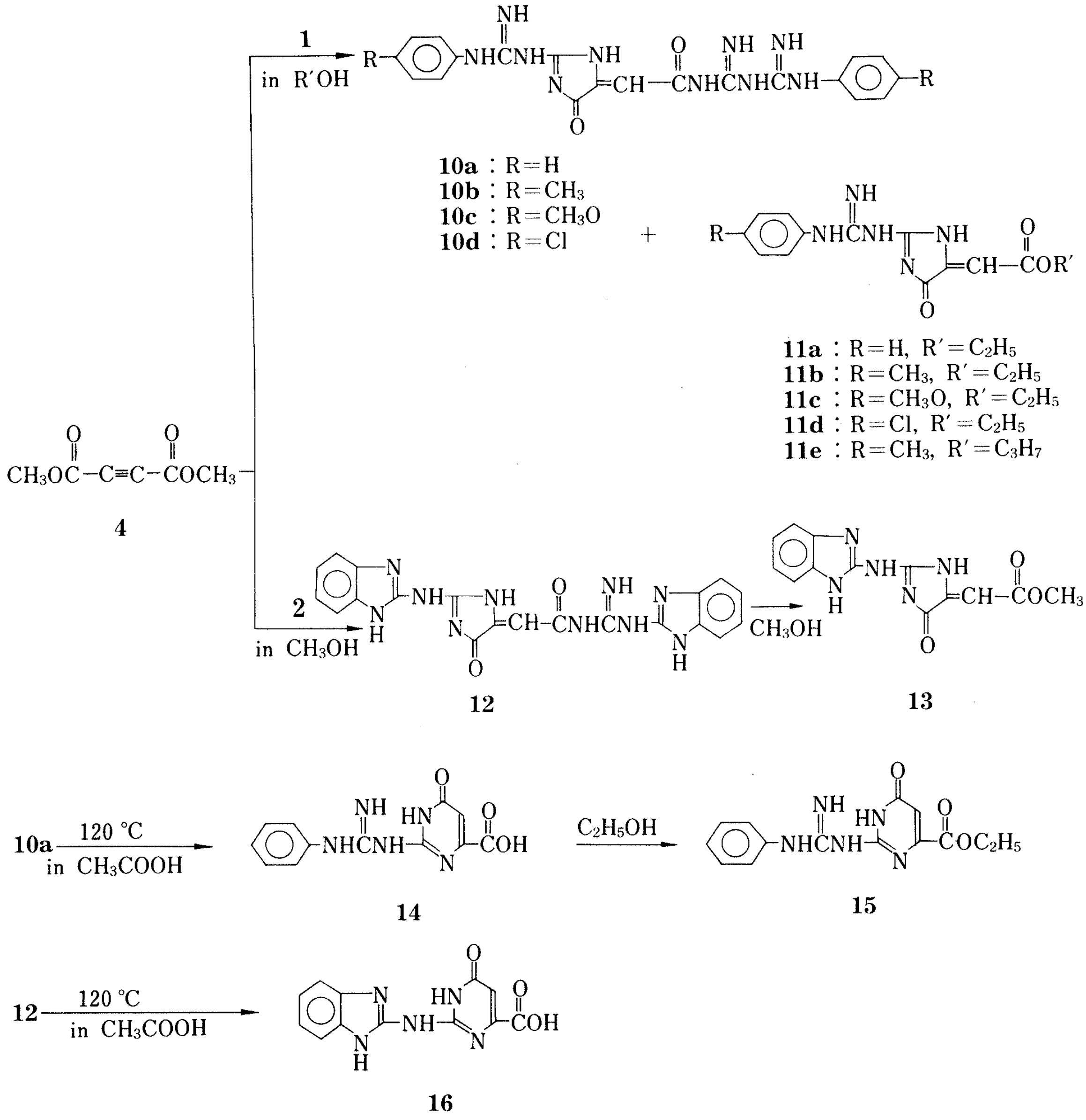

Chart 2

nucleus in **1** and **2** to form *s*-triazinones. It is noteworthy that diethyl azodicarboxylate serves as a carbon source.

Reactions of Arylbiguanides and 2-Guanidinobenzimidazole with Dimethyl Acetylenedicarboxylate

The reaction of **4** with guanidines is known to give imidazolines.[9,10] We examined the condensation of **4** with **1**, in which a moiety similar to guanidine is involved in the molecule. The reaction readily proceeded at room temperature in alcohol to give 1-[2-(3-arylguanidino)-4-oxo-2-imidazolin-5-ylideneacetyl]-5-aryl-biguanides (**10**) and alkyl 2-(3-arylguanidino)-4-oxo-2-imidazolin-5-ylideneacetates (**11**). The formation of **11** is presumed to be due to the alcoholysis of **10**. In fact, **10** was readily converted to **11** by heating in alcohol.

The IR spectra of **11** exhibited absorptions assignable to the carbonyl groups at 1660 and 1695 cm^{-1}. Such a shift of the absorption of the ester carbonyl group to lower frequency is probably due to the formation of the chelate between the ester carbonyl and the ring amino groups, and it provides support for the assigned structures of **10** and **11**. In the ^{1}H-NMR spectra of **11**, the double bond characteristic methine proton was observed near δ 5.5 as a singlet.

The reaction of **4** with **2** was also successfully carried out in methanol at room temperature to afford 1-[2-(2-benzimidazolylamino)-4-oxo-2-imidazolin-5-ylideneacetyl-3-(2-benzimidazolyl)guanidine (**12**) in almost quantitative yield. Compound **12** underwent easy methanolysis by heating in methanol and gave methyl 2-(2-benzimidazolylamino)-4-oxo-2-imidazolin-5-ylideneacetate (**13**) and **2** in 85% and 75% yields. Compound **13** was also obtained by the treatment of **4** with **2** in boiling methanol. As with **11**, the carbonyl absorption of the ester in **13** showed a considerable shift to lower frequency, 1660 cm^{-1}. The MS of **13** showed the molecular ion peak at *m/e* 285 (M$^+$).

Attempts to hydrolyze **10** and **12** with boiling water unfortunately resulted in failure. Under more drastic acidic conditions, however, these imidazoline compounds (**10** and **12**) were found to undergo ring conversion to pyrimidines. When **10a** was heated in acetic acid under reflux and the resulting precipitate was treated with boiling ethanol, ethyl 2-(3-phenylguanidino)-6-(1*H*)-oxo-4-pyrimidinecarboxylate (**15**) was obtained in good yield. Compound **10a** would probably be converted to the pyrimidinecarboxylic acid (**14**) through hydrolysis, followed by esterification to **15**. In contrast to **11**, the IR spectrum of **15** exhibited the absorption assignable to the ester group at ordinary frequency, 1720 cm^{-1}. The ^{1}H-NMR spectrum showed the hydrogen of the 5-position in pyrimidine ring as a singlet at δ 6.47. Similarly, **12** was converted to 2-(2-benzimidazolylamino)-6-(1*H*)-oxo-4-pyrimidinecarboxylic acid (**16**) by heating in acetic acid at 120 °C or in 1 N hydrochloric acid under reflux in good yield. Compound **16** was also obtained by heating of **13** in acetic acid at 120 °C in almost quantitative yield. The IR spectrum of **16** showed the absorption of the carboxylic acid at 1700 cm^{-1}. The MS exhibited the molecular ion peak at *m/e* 271 (M$^+$). Although such ring conversions of imidazolines to pyrimidines under basic conditions are known in a few instances,[10-12] it is of interest that this type of ring conversion also occurs under acidic conditions.

Experimental

All the melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected.

TABLE II. Dihydro-1-aryl-4,6-diamino-*s*-triazin-2-ones (**6**)

Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
6a	H	73	>300	$C_9H_9N_5O$	53.19 (53.49)	4.46 (4.44)	34.47 (34.43)
6b	CH_3	72	>300	$C_{10}H_{11}N_5O$	55.29 (55.05)	5.10 (5.05)	32.24 (32.19)
6c	CH_3O	65	>300	$C_{10}H_{11}N_5O_2$	51.49 (51.14)	4.75 (4.65)	30.03 (29.96)
6d	Cl	50	>300	$C_9H_8ClN_5O$	45.48 (45.97)	3.34 (3.39)	29.47 (29.86)
6e	NO_2	40	>300	$C_9H_8N_6O_3$	43.55 (43.45)	3.25 (2.97)	33.86 (33.88)

TABLE III. Alkyl 2-(3-Arylguanidino)-4-oxo-2-imidazolin-5-ylideneacetates (**11**)

Compd. No.	R	R′	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)			IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}		^{1}H-NMR (DMSO-d_6) δ, ppm		
						C	H	N	NH	C=O	–$CH_2C\underline{H}_3$	–CH_2CH_3	=$C\underline{H}$–
11a	H	C_2H_5	32	223—224	$C_{14}H_{15}N_5O_3$	55.80 (55.93)	5.02 (5.01)	23.25 (23.39)	3350, 3300, 3080	1660, 1695	0.85 (3H, t)	3.48 (2H, q)	5.57 (1H, s)
11b	CH_3	C_2H_5	41	231—232	$C_{15}H_{17}N_5O_3$	57.13 (57.29)	5.43 (5.44)	22.21 (22.14)	3350, 3300, 3100	1660, 1695	0.85 (3H, t)	3.52 (2H, q)	5.55 (1H, s)
11c	CH_3O	C_2H_5	38	214—215	$C_{15}H_{17}N_5O_4$	54.37 (54.52)	5.17 (5.12)	21.14 (21.26)	3350, 3270, 3070	1660, 1695	0.92 (3H, t)	3.57 (2H, q)	5.55 (1H, s)
11d	Cl	C_2H_5	36	229—230	$C_{14}H_{14}ClN_5O_3$	50.00 (49.79)	4.17 (4.08)	20.86 (20.83)	3300, 3100	1660, 1695	0.93 (3H, t)	3.63 (2H, q)	5.57 (1H, s)
11e	CH_3	C_3H_7	43	208—209	$C_{16}H_{19}N_5O_3$	58.35 (58.16)	5.82 (5.59)	21.29 (21.43)	3360, 3300, 3200	1660, 1695	0.73 (3H, t) 3.45 (2H, q, –O–$C\underline{H}_2$–)	1.23 (2H, m)	5.60 (1H, s)

TABLE IV. 1-[2-(3-Arylguanidino)-4-oxo-2-imidazolin-5-ylideneacetyl]-5-aryl-biguanides (**10**)

Compd. No.	R	React. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)			IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}	
						C	H	N	NH	C=O
10a	H	EtOH MeOH	14 37	183—184	$C_{20}H_{20}N_{10}O_2$	55.56 (55.12)	4.63 (4.85)	32.41 (32.07)	3470, 3300, 3150	1660, 1630
10b	CH_3	EtOH MeOH	9 50	203—204	$C_{22}H_{24}N_{10}O_2$	57.14 (57.11)	5.52 (5.51)	30.30 (29.48)	3470, 3290, 3150	1655, 1630
10c	CH_3O	EtOH MeOH	16 43	205—206	$C_{22}H_{24}N_{10}O_4$	53.66 (53.60)	4.88 (4.69)	28.46 (28.35)	3470, 3300, 3140	1660, 1625
10d	Cl	EtOH MeOH	4 26	209—210	$C_{20}H_{18}Cl_2N_{10}O_2$	47.90 (47.51)	3.59 (3.77)	27.94 (26.97)	3470, 3310, 3130	1660, 1625

IR spectra were recorded with a JASCO IRA-1 grating infrared spectrometer. ^{1}H-NMR spectra were determined with a JEOL 60H high resolution NMR instrument. MS were measured with a JEOL 01SG mass spectrometer. UV spectra were recorded on a Hitachi 124 spectrometer.

General Procedure for Reaction of Arylbiguanides (1) with Diethyl Azodicarboxylate (3)——A solution of **3** (5.22 g, 30 mmol) in EtOH (10 ml) was added to a stirred solution of **1** (10 mmol) in EtOH (40 ml). The mixture was stirred for 1 h, and the resulting precipitate was collected by filtration, washed with H_2O and EtOH, and dried under reduced pressure to give the corresponding dihydro-1-aryl-4,6-diamino-*s*-triazin-2-one (**6**) in a comparatively pure state. The yields, melting points, and elementary analyses are summarized in Table II.

2-Amino-4-oxo-3,4-dihydrobenzimidazo[1,2-*a*]-*s*-triazine (9)——Compound **3** (6.96 g, 40 mmol) was added dropwise with stirring to a solution of 2-guanidinobenzimidazole (**2**) (3.50 g, 20 mmol) in EtOH (30 ml), and the mixture was heated for 2 h under reflux. The resulting precipitate was collected by filtration under cooling and recrystallized from *N*,*N*-dimethylformamide (DMF) to give **9** (2.50 g, 62%). The IR spectrum of **9** agreed with that of an authentic sample[8] prepared by the reaction of **2** with benzoyl isocyanate. mp >300 °C. *Anal.* Calcd for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.95; H, 3.44; N, 34.80. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3400, 3120 (NH and NH_2), 1720 (C=O). MS *m*/*e*: 201 (M^+), 158 ($M^+ - HNC{=}O$).

General Procedure for Reaction of Arylbiguanides (1) with Dimethyl Acetylenedicarboxylate (4)——A solution of **4** (1.42 g, 10 mmol) in alcohol (10 ml) was added to a stirred solution of **1** (10 mmol) in alcohol (40 ml) at room temperature, and stirring was continued for an additional 12 h. The mixture was then concentrated to one-third of its original volume. The precipitate deposited on standing overnight was collected by filtration and recrystallized from MeOH to give 1-[2-(3-arylguanidino)-4-oxo-2-imidazolin-5-ylideneacetyl]-5-aryl-biguanide (**10**). The filtrate was concentrated to dryness, and the residue was recrystallized from EtOH to give alkyl 2-(3-arylguanidino)-4-oxo-2-imidazolin-5-ylidene acetate (**11**). The yields, melting points, elementary analyses, and spectral data of **10** and **11** are summarized in Tables III and IV.

2-(2-Benzimidazolylamino)-4-oxo-2-imidazolin-5-ylideneacetyl-3-(2-benzimidazolyl)guanidine (12)——A solution of **4** (1.42 g, 10 mmol) in MeOH (10 ml) was added with stirring to a solution of **2** (3.50 g, 10 mmol) in MeOH (40 ml) at room temperature, and the mixture was stirred for 12 h. The resulting yellow precipitate was collected by filtration under cooling and washed with cold MeOH to give **12** in comparatively pure form in almost quantitative yield. mp 218 °C. *Anal.* Calcd for $C_{20}H_{16}N_{10}O_2$: C, 56.07; H, 3.73; N, 32.71. Found: C, 55.57; H, 3.64; N, 32.48. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360, 3245, 3050 (NH and =NH), 1700 (C=O).

Methyl 2-(2-Benzimidazolylamino)-4-oxo-2-imidazolin-5-ylideneacetate (13)——A solution of 2-(2-benzimidazolylamino-4-oxo-2-imidazolin-5-ylideneacetyl-3-(2-benzimidazolyl)guanidine (**12**) (1.28 g, 3 mmol) in MeOH (100 ml) was heated for 40 h under reflux. The resulting precipitate was collected by filtration and washed with MeOH to give **13** (0.73 g, 85%). mp 235 °C. *Anal.* Calcd for $C_{13}H_{11}N_5O_3$: C, 54.73; H, 3.85; N, 24.00. Found: C, 54.64; H, 3.88; N, 24.00. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3340, 3190 (NH), 1660, 1627 (C=O). ^{1}H-NMR (CF_3COOH) δ: 4.48 (3H, s, CH_3), 7.75 (4H, s, aromatic), 8.50—8.85 (2H, br, NH). MS *m*/*e*: 285 (M^+).

Ethyl 2-(3-Phenylguanidino)-6-(1*H*)-oxo-4-pyrimidinecarboxylate (15)——A solution of **10a** (1.30 g, 3 mmol) in acetic acid (30 ml) was heated at 120—130 °C for 30 min. The resulting precipitate was collected by filtration and heated in EtOH (30 ml) under reflux for 30 min. After removal of the solvent by distillation, the residue was recrystallized from EtOH. Yield: 0.72 g (80%). mp 225—226 °C. *Anal.* Calcd for $C_{14}H_{15}N_5O_3$: C, 55.77; H, 5.01; N, 23.24. Found: C, 55.40; H, 5.16; N, 22.85. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280, 3100 (NH), 1720 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.07 (3H, t, CH_3), 3.45 (2H, q, $\underline{CH_2}$–CH_3), 6.47 (1H, s, pyrimidine), 7.50 and 7.63 (5H, s, phenyl).

2-(2-Benzimidazolylamino)-6-(1*H*)-oxo-4-pyrimidinecarboxylic Acid (16)——A solution of **12** (1.28 g, 3 mmol) in AcOH (30 ml) was heated at 120—130 °C for 30 min. The resulting precipitate was collected by filtration under cooling, washed with AcOH and H_2O, and dried to give **16** (0.69 g, 85%). mp >300 °C. *Anal.* Calcd for $C_{12}H_9N_5O_3$: C, 53.13; H, 3.32; N, 25.49. Found: C, 53.31; H, 3.32; N, 25.83. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360, 3290, 3210 (NH), 1705 (COOH). MS *m*/*e*: 271 (M^+). The filtrate was concentrated to dryness under reduced pressure, and the residue was treated with 5% NaOH solution to give **2** in good yield. Compound **16** was also obtained from **13** (0.51 g, 18 mmol) by heating in AcOH (30 ml) in almost quantitative yield.

References and Notes

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