[Chem. Pharm. Bull. 36(6)1963—1969(1988)]

Synthesis of Nitrogen-Containing Heterocycles. II.[1] Cyclization of Diaminomethylenehydrazones with Ethoxymethylene Compounds

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(Received October 30, 1987)

Condensation of diaminomethylenehydrazones (**1**) with ethyl ethoxymethylenecyanoacetate (**2**) gave amino(substituted vinylamino)methylenehydrazones (**3**) in high yields. Amino(monomethylamino)methylenehydrazones were more reactive than amino(dimethylamino)methylenehydrazones and, when the reaction temperature was raised, with or without addition of a base, directly produced 2,3-dihydro- or 2,3-dehydro[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylates, depending upon the carbonyl component of the diaminomethylenehydrazone. Ketone amino(dimethylamino)methylenehydrazone gave no cyclized product. Similar condensation of diaminomethylenehydrazones with diethyl ethoxymethylenemalonate gave the linear products (**7**) and, when R^2 was hydrogen, the intermediate cyclized to dihydro-4-oxopyrimidinecarboxylate by exclusive intramolecular attack of N(4) on the ethoxycarbonyl carbon.

Keywords——diaminomethylenehydrazone; ethyl ethoxymethylenecyanoacetate; diethyl ethoxymethylenemalonate; amino(substituted vinylamino)methylenehydrazone; [1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate; dihydro-4-oxopyrimidine

It has recently been reported[1] that the treatment of diaminomethylenehydrazones of both aromatic aldehydes and ketones with ethoxymethylenemalononitrile gave directly 2,3-dihydro[1,2,4]triazole[1,5-*c*]pyrimidine derivatives and that, in a few cases, the precursor 2,2-dicyanovinylamino(dimethylamino)methylenehydrazones could be isolated. In the present work, an attempt was made to extend this cyclization to the reaction of diaminomethylenehydrazones with ethyl ethoxymethylenecyanoacetate (**2**), to isolate the linear intermediates (**3**),[2] and to investigate the relationship between the structure of the linear compounds (**3**) and their reactivities under various conditions. We also studied the reaction between diamino methylenehydrazones and diethyl ethoxymethylenemalonate (**6**) in order to obtain new derivatives of dihydropyrimidines.

Results and Discussion

The reaction between **1** ($R^2=H$) and **2** was performed by allowing a solution of the reactants in benzene to stand at room temperature. The reaction smoothly proceeded and, when a slight excess of **2** was employed, high yields of the corresponding amino(substituted vinylamino)methylenehydrazones (**3**) could be obtained after isolation. In this reaction, however, when R^2 was methyl, the compounds **1c** and **1d** required a longer reaction time or higher temperature to obtain a comparable yield of the corresponding **3**. If the reaction of aldehyde diaminomethylenehydrazones ($R^2=H$) was carried out at the reflux temperature, the reaction mixture was found to contain both the triazolopyrimidine product (**5**) and the linear intermediate (**3**) in an approximately equimolar proportion. Prolonged heating caused an increase in the proportion of the cyclized product (**5**). The apparently direct cyclization to

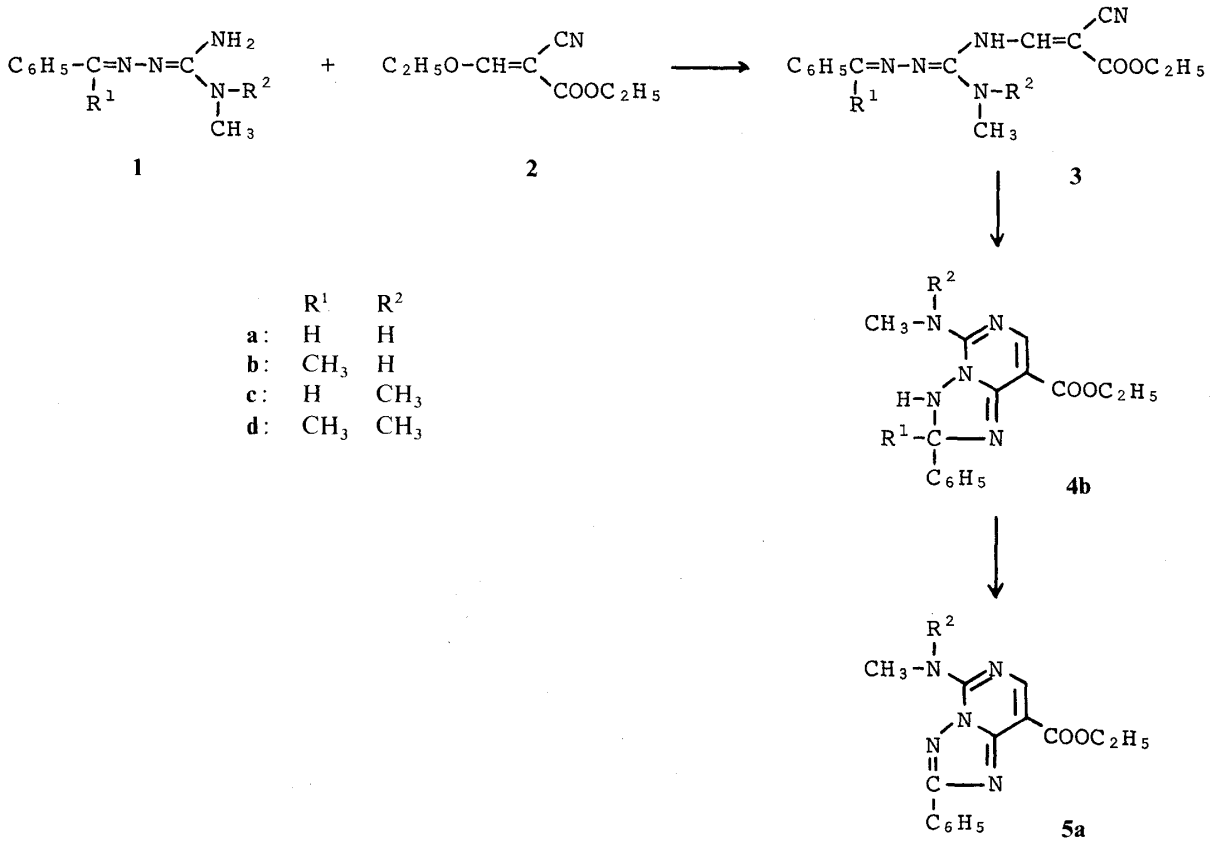


Chart 1

the dehydro compound (**5**) starting with **1** and **2** can be explained as a sequential stepwise process involving cyclization of the first condensation product (**3**) to **4**, followed by dehydrogenation of the initial cyclized product **4** ($R^1 = H$). The initial cyclized product **4a** from **1a** has not been isolated in this study. Further, the diaminomethylenehydrazones **1a** and **1b** were found to give readily the corresponding cyclized products **5a** and **4b**, respectively, with high purity, if the reaction was carried out in the presence of a small amount of a base such as triethylamine in hot benzene. The accelerating effect of the base on ring closure of the intermediate (**3**), however, was ineffective for the direct cyclization of **1c** and **1d** ($R^2 = Me$), and onyl the linear intermediate (**3**) was formed.

As discussed above, the product formed from the reaction between **1** and **2** is highly dependent upon the nature of the substituents (R^1 and R^2) on diaminomethylenehydrazones (**1**) as well as the reaction conditions. Thus, when R^2 is hydrogen, the amino(monomethylamino)methylenehydrazones (**1a** and **1b**) give the corresponding linear compounds (**3**) in high yields at room temperature in the reaction with **2**, whereas amino(dimethylamino)methylenehydrazones ($R^2 = Me$) (**1c** and **1d**) are less reactive under such conditions and give **3** in only low yield. When the reaction temperature is increased, diaminomethylenehydrazone (**1b**: $R^1 = Me$, $R^2 = H$) directly produces the cyclized product (**4b**), while **1a** ($R^1 = R^2 = H$) affords **5a** with spontaneous dehydrogenation of the potential precursor **4a**. The presence of a base in the reaction mixture appears to accelerate both cyclization of **3** and dehydrogenation of **4a**. When R^2 is methyl, the diaminomethylenehydrazone (**1c**) gives the corresponding linear compound (**3c**) in high yield in hot benzene containing an amine, but **3c** resists the further reaction of ring closure even under forcing conditions. Similarly, the ketone diaminomethylenehydrazone (**1d**) ($R^1 = R^2 = Me$) can undergo the initial condensation to form **3d**, but this product fails to cyclize. Consequently, in order to

obtain triazolopyrimidine derivatives through the reaction of diaminomethylenehydrazone with **2**, at least one hydrogen must be present on N (4) of **1**.

The unreactivity of **3c** and **3d** toward ring closure may in part be explained on the basis of their molecular geometry. The formation of **4** from **3** requires a planar arrangement of nine atoms in the transition state and may proceed in an electrocyclic manner by analogy with the reaction of isothiosemicarbazones.[3] In order to cyclize smoothly, the planar arrangement further requires all *E* configuration about the three double-bonds along the linear skeleton of **3**. The cyanoacrylate (**3**) may exist in six geometrical isomers. The carbonyl frequencies in the infrared (IR) spectra of **3** appear in the range of 1690—1675 cm^{-1}, which corresponds to the internally bonded bands of the bis(ethoxycarbonyl)vinyl compounds **7**. Thus the geometry about the CH=C bond of **3** should be *Z*. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the α-methylbenzylidene derivative (**3b**) showed a set of resonances arising from the MeNH–C(=)–NHCH= moiety [two methine-proton resonances at δ 8.52 and 8.30 (poorly resolved doublets), two NH proton resonances at δ 10.25 and 12.11 (disappeared on addition of deuterium oxide), and two methyl-proton resonance at δ 3.03 (d, J=5 Hz) and 2.98 (d, J=5 Hz)], suggesting the existence of two isomeric forms of **3b** in solution. Because the methyl-proton resonance on the benzylidene carbon appeared as a singlet at δ 2.43, the observed isomerism of **3b** should be about the central N(2)=C bond, and not about the α-methylbenzylideneamino double bond.[4]

The structural assignment of the two isomers could be made on the basis of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of compound **3b** in dimethyl-d_6 sulfoxide. Splitting of the NH–CH= carbon resonance into two doublets (δ 163.30 and 149.78 with respective coupling constants of 156.8 and 172.7 Hz) allows easy assignment of the resonances to the methine carbons.

Greant and Cheney[5] proposed that the chemical shift of a sterically perturbed carbon atom is generally found at higher magnetic field than those of similar carbons which are not spatially crowded. Thus, on the basis of the steric compression shift phenomenon, the upfield resonance (δ 149.78) of **3b** may be due to the sterically perturbed carbon atom, while the downfield resonance (δ 163.30) may arise from the carbon that is not spatially crowded. Spatial crowding about the methine carbon can occur by approach of the arylmethyleneamino grouping to that carbon, which should be possible only in the *Z* configuration[6] (Fig. 1). Thus, the downfield resonance (δ 163.30) can be assigned to the methine carbon in the *E* form. The *E*/*Z* ratio of **3b** was found to be about 4/1 under the conditions of spectroscopy and this was confirmed by the ^{1}H-NMR spectrum of **3b**.

The ^{1}H- and ^{13}C-NMR spectra of other cyanoacrylates (**3a**, **3c**, and **3d**) showed no signals of isomeric species. The methine-proton resonances appeared at δ 162.55, 152.19, and 152.08, respectively, each as a doublet. Although the assignment is not conclusive because comparison is impossible between two isomeric forms, these chemical shift values for **3a**, **3c**, and **3d** strongly suggest the configuration about the N(2)=C double bond to be *E*, *Z*, and *Z*, respectively.

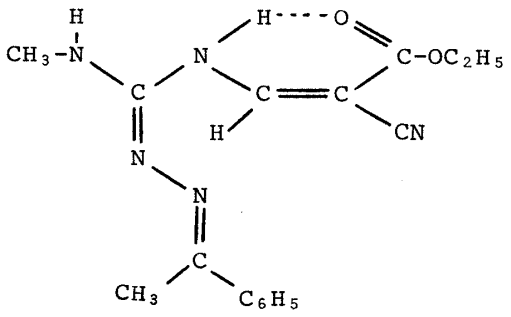


Fig. 1

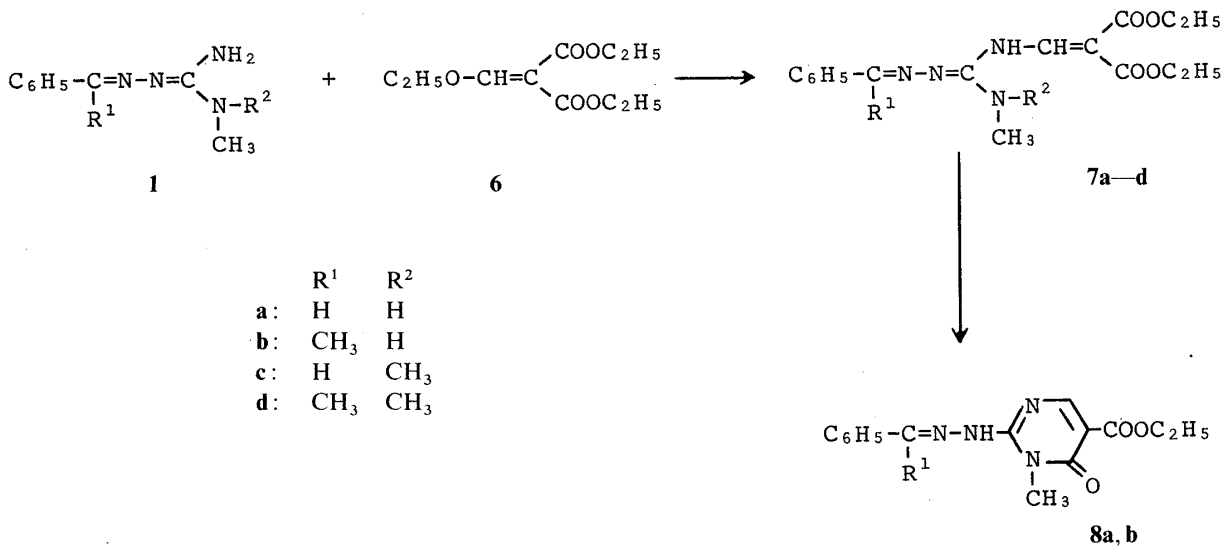
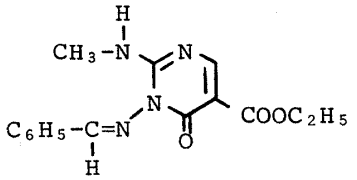


Chart 2

The cyanoacrylates **3a** and **3b** can produce the corresponding triazolopyrimidine derivatives (**5a** and **4b**) in moderate yields, probably through isomerization of the terminal double bond (CH=C) under the reaction conditions. However, the additional unfavorable factor of *Z* configuration about the N(2)=C bond for **3c** and **3d** may prevent cyclization of these cyanoacrylates to triazolopyrimidines.

The use of diethyl ethoxymethylenemalonate (**6**), in which the cyano group in **2** was replaced by an ethoxycarbonyl group, as a carbon source gave another type of heterocycle in the reaction with diaminomethylenehydrazones (**1**). As was expected, the initial condensation produced an open-chain compound (**7**). When R^2 was hydrogen, **1** gave the corresponding **7a** and **7b** in high yields under conditions similar to those of the reaction with **2**. When R^2 was methyl, however, the reaction required elevated temperature and the presence of triethylamine to obtain the corresponding **7**. Attempts to cyclize **7** in hot media resulted in the exclusive formation of **8**, indicating that it is N(4), but not N(2) that attacks one of the ethoxycarbonyl carbons. The dihydropyrimidone (**8**) was also obtained directly by heating a mixture of **1** and **6** in benzene in the presence of triethylamine. Although all the diaminomethylenehydrazones (**1a**—**d**) gave **7** by reaction with **6**, only two compounds (**7a** and **7b**) in which R^2 was hydrogen could produce dihydropyrimidone (**8**).

Again, the selective ring closure to **8** can be explained by the molecular geometry of **7** that may hinder the approach of an ethoxycarbonyl group to N(2). Bis(ethoxycarbonyl)vinyl compounds (**7**) may exist in four geometrical isomers. The ^{1}H-NMR spectrum of the benzylidene derivative (**7a**) showed a set of resonances of protons in the MeNH–C(=)–NHCH= moiety [two methine-proton resonances at δ 8.90 (d, J = 11.2 Hz) and 8.15 (d, J = 14.0 Hz), two NH proton resonances at δ 10.95 (d, J = 11.2 Hz) and 12.02 (d, J = 14.0 Hz), and two methyl-proton resonances at δ 3.00 (d, J = 5.2 Hz) and 2.96 (d, J = 5.2 Hz)], suggesting the existence of two isomeric forms of **7a** in solution. Because the benzylidene proton resonance appeared as a singlet at δ 8.28, the same discussion as in the case of the cyanoacrylates **3** may be applied to the isomerism of **7a**. On the basis of the chemical shift values of the two methine-proton resonances (δ 146.36 and 149.40 with respective coupling constants of 169.9 and 177.7 Hz), as well as the relative intensity, **7a** was found to exist as an *E* and *Z* mixture in a *E*/*Z* ratio of 4/1. Similarly, **7b** had an *E*/*Z* ratio of about 3/1. However, the 4-dimethylamino compounds **7c** and **7d** were found to exist as only a single isomeric form, probably with *E* configuration, in view of their chemical shift values of the methine carbon



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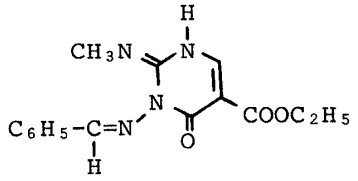

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Fig. 2

(δ 151.40 and 151.38). The preferential formation of the dihydropyrimidone (**8**) may thus be explained by the predominant existence of the *E* form, in which the ethoxycarbonyl group can not approach N(2).

The structures of **4** and **5** have been established on the basis of spectral measurements and elemental analyses in the same manner as in the structural assignment of the 8-cyano analogues reported previously.[1)]

The 6-oxo dihydropyrimidinecarboxylates (**8**) showed appropriate spectral behavior. In particular, the IR spectra of **8** showed two carbonyl bands, an ester carbonyl at 1725—1720 cm^{-1} and a 6-oxo group at 1660 cm^{-1}. The 1-methyl proton resonance appeared at δ 3.45—3.50 as a singlet. This provides strong evidence differentiating **8** from the alternative structure **9**. If the product from the cyclization of **7** had the structure **9**, a doublet due to the methylamino protons ($R^1=R^2=H$) would appear at higher magnetic field, probably near δ 3.00, by analogy with the resonances of **4** or **6**. Further, if the alternative form **9** had a prototropic structure (**10**), another doublet would appear due to the ring proton (H-4) much further downfield (near that of H-4 in **8**).

Experimental

Melting points were taken in open glass capillaries and are uncorrected. IR spectra were recorded on a Hitachi EPI-G2 or 260—30 spectrophotometer and calibrated by comparision with that of a standard polystyrene film sample. ^{1}H-NMR spectra were obtained with a Hitachi R-24 spectrometer at 60 MHz. ^{13}C-NMR spectra were obtained with a JNM-FX90Q spectrometer operating at 22.50 MHz. Unless otherwise stated, chemical shifts are reported in parts per million (δ scale) downfield from internal tetramethylsilane (TMS). The solvents used were chloroform-*d* ($CDCl_3$) or dimethyl-d_6 sulfoxide (DMSO-d_6). The mass spectrum (MS) (75 eV) were recorded on a JEOL JMS D100 mass spectrometer.

Amino(substituted amino)methylenehydrazones (1)——Amino(substituted amino)methylenehydrazones (**1a—d**) were prepared by the method reported.[1)]

Benzaldehyde 2-Cyano-2-ethoxycarbonylvinylamino(methylamino)methylenehydrazone (3a) (*E*-Isomer)——A mixture of **1a** (0.35 g, 2 mmol) and **2** (0.4 g, 2.4 mmol) was suspended in 2 ml of benzene and the reaction mixture was allowed to stand at room temperature. After 1 h, crystals gradually deposited from the solution and were collected by filtration to give 0.46 g (77%) of analytically pure **3a** as pale yellow needles with mp 146—147 °C. *Anal.* Calcd for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 60.20; H, 5.69; N, 23.38. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O), 2200 (CN). ^{1}H-NMR (DMSO-d_6) δ: 3.05 (3H, d, J=4.6 Hz, NHC$\underline{H}_3$), 8.25 (1H, s, CH=N), 8.55 (1H, br s, HNC$\underline{H}$), 11.50 (1H, br s, CHN$\underline{H}$). ^{13}C-NMR (DMSO-d_6) δ: 79.85 (s, CH=$\underline{C}$), 146.61 (d, J=163.6 Hz, HC=N), 157.20 (s, N=$\underline{C}$–NH), 162.55 (d, NHCH=). MS *m/z*: 299 (M^+ 50%), 255 (M^+-74, 100%).

Acetophenone 2-Cyano-2-ethoxycarbonylvinylamine(methylamino)methylenehydrazone (3b) (*E*/*Z* Mixture)——Compound **3b** was prepared in the same manner as **3a** in 58% yield. Pale yellow needles, mp 157—158 °C. *Anal.* Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.46; H, 6.10; N, 22.19. MS *m/z*: 313 (M^+ 56%), 242 (M^+-71, 100%). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 2220 (CN).

(*E*)-Isomer: ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s, CH_3C=N), 3.03 (3H, d, J=4.8 Hz, NHC$\underline{H}_3$), 8.52 (1H, br d, NHC$\underline{H}$), 10.25 (1H, br s, N$\underline{H}$CH). ^{13}C-NMR (DMSO-d_6) δ: 79.07 (s, CH=$\underline{C}$), 149.93 (s, Me$\underline{C}$=N), 158.52 (s, N=$\underline{C}$–NH), 163.30 (d, J=156.8 Hz, NHCH=).

(*Z*)-Isomer: ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s, CH_3C=N), 2.98 (3H, d, J=5.2 Hz, NHC$\underline{H}_3$), 8.30 (1H, d, J=14.0 Hz, NHC$\underline{H}$), 12.11 (1H, d, J=14.0 Hz, N$\underline{H}$CH). ^{13}C-NMR (DMSO-d_6) δ:79.07 (s, CH=$\underline{C}$), 149.78 (dq, J=

172.7 Hz, NHCH$_3$), 149.93 (s, MeC=N), 158.52 (s, N=C(N)–NH).

Benzaldehyde 2-Cyano-2-ethoxycarbonylvinylamino(dimethylamino)methylenehydrazone (3c) (*Z*-Isomer)——A mixture of **1c** (0.36 g, 2 mmol) and **2** (0.4 g, 2.4 mmol) was suspended in 2 ml of benzene and the reaction mixture was refluxed for 1 h, and then allowed to cool. Crystals gradually deposited from the solution and were collected by filtration to give 0.55 g (88%) of the desired product (**3c**) as a colorless crystalline powder with mp 136—140 °C. Recrystallization from ethyl alcohol gave a colorless crystalline powder, mp 139—140 °C. *Anal.* Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.46; H, 6.10; N, 22.19. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1690 (C=O), 2200 (CN). ^{1}H-NMR ($CDCl_3$) δ: 3.17 (6H, s, N(CH$_3$)$_2$), 7.63 (1H, d, J=13.0 Hz, NHCH), 8.30 (1H, s, HC=N), 11.32 (1H, d, J=13.0 Hz, NHCH). ^{13}C-NMR ($CDCl_3$) δ: 79.21 (s, CH=C), 152.19 (d, J=174.6 Hz, NHCH=), 155.57 (s, C=N), 155.57 (s, N=C(N)–NH). MS *m/z*: 313 (M^+, 89%), 242 (M^+-71, 100%).

Acetophenone 2-Cyano-2-ethoxycarbonylvinylamino(dimethylamino)methylenehydrazone (3d) (*Z*-Isomer)——Compound **3d** was prepared in the same manner as **3c** in 88% yield. Colorless crystalline powder, mp 104—105 °C. *Anal.* Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39. Found: C, 62.52; H, 6.49; N, 21.20. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1690 (C=O), 2200 (CN). ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s, CH$_3$C=N), 3.15 [6H, s, N(CH$_3$)$_2$], 7.65 (1H, d, J=14.0 Hz, NHCH), 11.40 (1H, d, J=14.0 Hz, NHCH). ^{13}C-NMR ($CDCl_3$) δ: 78.94 (s, CH=C), 152.08 (d, J=174.0 Hz, NHCH=), 153.52 (s, MeC=N), 160.86 (s, N=C(N)–NH). MS *m/z*: 327 (M^+, 51%), 215 (M^+-112, 100%).

Ethyl 2,3-Dihydro-2-methyl-5-methylamino-2-phenyl-[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate (4b)——A mixture of **1b** (0.19 g, 1 mmol), **2** (0.17 g, 1 mmol), and 1 ml of benzene containing 0.1 ml of triethylamine was heated under reflux for 1 h. The reaction mixture was evaporated to give a crude product. The residual oil was crystallized from isopropyl alcohol and the crystals formed were collected by filtration to give 0.15 g (48%) of **4b** as pale yellow crystals with mp 161—162 °C. Recrystallization from acetonitrile gave pale yellow needles, mp 165—166 °C. *Anal.* Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.14; H, 6.01; N, 22.13. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.86 (3H, d, J=4.4 Hz, NHCH$_3$), 6.09 (1H, s, H-3), 8.02 (1H, s, H-7). MS *m/z*: 313 (M^+, 8%), 252 (M^+-61, 100%).

Ethyl 5-Methylamino-2-phenyl-[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate (5a)——A mixture of **1a** (0.18 g, 1 mmol), **2** (0.17 g, 1 mmol), and 1 ml of benzene containing 0.1 ml of triethylamine was heated under reflux for 1 h. The reaction mixture was evaporated to give a crude product as a brown oil. The oil, after being dissolved in $CHCl_3$, was charged onto a silica gel column which was then eluted with the same solvent to give a homogeneous fraction from which the desired product was obtained as crystals. Recrystallization from acetonitrile gave pale yellow needles, 0.21 g (39%), mp 179—180 °C. *Anal.* Calcd for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.55. Found: C, 60.52; H, 4.97; N, 23.50. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 3.40 (3H, d, NHCH$_3$), 8.56 (1H, s, H-7). MS *m/z*: 297 (M^+, 48%), 225 (M^+-72, 100%).

Benzaldehyde 2,2-Bis(ethoxycarbonyl)vinylamino(methylamino)methylenehydrazone (7a) (*E*/*Z* Mixture)——A mixture of **1a** (0.18 g, 1 mmol) and **6** (0.22 g, 1 mmol) was suspended in 2 ml of benzene and the reaction mixture was allowed to stand at room temperature for 1 d. The solvent was evaporated off under reduced pressure to give an oily residue. The residue, after being dissolved in $CHCl_3$, was charged onto a silica gel column which was then eluted with the same solvent to give the product as crystals. Recrystallization of the solid from isopropyl alcohol gave colorless needles (**7a**) (*E*/*Z* mixture), mp 126—127 °C (60%). *Anal.* Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 59.13; H, 6.42; N, 16.24. MS *m/z*: 346 (M^+, 68%), 152 (M^+-194, 100%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1700, 1730 (C=O).

(*E*)-Isomer: ^{1}H-NMR ($CDCl_3$) δ:3.00 (3H, d, J=5.2 Hz, NHCH$_3$), 8.28 (1H, s, CH=N), 8.90 (1H, d, J=11.2 Hz, NHCH), 10.95 (1H, d, J=11.2 Hz, NHCH). ^{13}C-NMR ($CDCl_3$) δ: 98.36 (s, CH=C), 149.40 (d, J=177.7 Hz, NHCH), 152.32 (d, J=161.7 Hz, CH=N), 153.16 (s, N=C(N)–NH).

(*Z*)-Isomer: ^{1}H-NMR ($CDCl_3$) δ: 2.96 (3H, d, J=5.2 Hz, NHCH$_3$), 8.15 (1H, d, J=14.0 Hz, NHCH), 8.28 (1H, s, CH=N), 12.02 (1H, d, J=14.0 Hz, NHCH). ^{13}C-NMR ($CDCl_3$) δ: 98.36 (s, CH=C), 146.36 (d, J=169.89 Hz, NHCH), 152.32 (d, J=161.7 Hz, CH=N), 153.16 (s, N=C(N)–NH).

Acetophenone 2,2-Bis(ethoxycarbonyl)vinylamino(methylamino)methylenehydrazone (7b) (*E*/*Z* Mixture)——Compound **7b** was prepared similarly as colorless needles, mp 104—105 °C (89%). *Anal.* Calcd for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.86; H, 6.64; N, 15.56. MS *m/z*: 360 (M^+, 44%), 299 (M^+-61, 100%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1695, 1720 (C=O).

(*E*)-Isomer: ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s, CH$_3$C=N), 3.04 (3H, d, J=5.2 Hz, NHCH$_3$), 9.00 (1H, d, J=12.4 Hz, NHCH), 10.85 (1H, d, J=12.4 Hz, NHCH). ^{13}C-NMR ($CDCl_3$) δ: 97.36 (s, CH=C), 149.98 (d, J=177.7 Hz, NH-CH), 152.05 (s, C=N), 158.23 (s, N=C(N)–NH).

(*Z*)-Isomer: ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s, $CH_3C=N$), 2.99 (3H, d, $J=5.2$ Hz, $NHC\underline{H}_3$), 8.10 (1H, d, $J=14.0$ Hz, NHC$\underline{H}$), 11.94 (1H, d, $J=14.0$ Hz, N$\underline{H}$CH). ^{13}C-NMR ($CDCl_3$) δ: 97.36 (s, CH=$\underline{C}$), 146.39 (d, $J=169.1$ Hz, NH-$\underline{C}$H), 152.05 (s, Me$\underline{C}$=N), 158.23 (s, N=$\underline{C}$–NH).

Benzaldehyde 2,2-Bis(ethoxycarbonyl)vinylamino(dimethylamino)methylenehydrazone (7c)——A solution of **1c** (0.19 g, 1 mmol) and **6** (0.22 g, 1 mmol) in benzene (2 ml) was refluxed for 3 h and the solvent was removed under reduced pressure. Recrystallization of the crystalline residue from 50% ethyl alcohol gave **7c** as pale yellow needles (0.22 g, 61%), mp 70—71 °C. *Anal.* Calcd for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71; N, 15.56. Found: C, 60.11; H, 6.73; N, 15.62. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1700, 1720 (C=O). ^{1}H-NMR ($CDCl_3$)δ: 2.93 (6H, s, $N(CH_3)_2$), 8.20 (1H, d, $J=14.0$ Hz, NHC$\underline{H}$), 8.39 (1H, s, CH=N), 11.21 (1H, d, $J=14.0$ Hz, N$\underline{H}$CH). ^{13}C-NMR ($CDCl_3$) δ: 97.50 (s, $\underline{C}$H=C), 151.40 (d, $J=174.0$ Hz, NHCH=), 154.58 (d, $J=161.1$ Hz, CH=N), 156.58 (s, N=$\underline{C}$–NH). MS *m/z*: 360 (M^+, 59%), 165 (M^+-195, 100%).

Acetophenone 2,2-Bis(ethoxycarbonyl)vinylamino(dimethylamino)methylenehydrazone (7d)——Compound **7d** was prepared in the same manner as **7c** in 80% yield. Pale yellow oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1700, 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (1H, s, $CH_3C=N$), 2.90 [6H, s, $N(CH_3)_2$], 8.19 (1H, d, $J=13.6$ Hz, NHC$\underline{H}$), 11.20 (1H, d, $J=13.6$ Hz, N$\underline{H}$CH). ^{13}C-NMR ($CDCl_3$) δ: 97.17 (s, CH=$\underline{C}$), 151.38 (d, $J=173.9$ Hz, NHCH=), 154.60 (s, Me$\underline{C}$=N), 159.61 (s, N=$\underline{C}$–NH).

Ethyl 2-Benzylidenehydrazino-3-methyl-4-(3*H*)-oxopyrimidine-5-carboxylate (8a)——A mixture of **1a** (0.18 g, 1 mmol), **6** (0.22 g, 1 mmol) and 1 ml of benzene containing 0.1 ml of triethylamine was heated under reflux for 1 h. The reaction mixture was evaporated to give a crude product as a brown oil. The oil was crystallized from isopropyl alcohol and the crystals formed were collected by filtration to give 0.24 g (80%) of **8a** as pale yellow crystals with mp 196—197 °C. Recrystallization from acetonitrile gave the pure product as pale yellow needles, mp 200—201 °C. *Anal.* calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.78; H, 5.27; N, 18.59. IR ν_{max}^{KBr} cm^{-1}: 1660, 1725 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 3.26 (3H, s, NCH_3), 8.10 (1H, s, H-4 of dihydro pyrimidine). MS *m/z*: 300 (M^+, 100%).

Ethyl 2-(α-Methylbenzylidenehydrazino)-3-methyl-4(3*H*)-oxopyrimidine-5-carboxylate (8b)——Compound **8b** was prepared in the same manner as **8a** in 81% yield. Pale yellow needles, mp 200—201 °C. *Anal.* Calcd for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found: C, 61.04; H, 5.71; N, 18.05. IR ν_{max}^{KBr} cm^{-1}: 1660, 1720 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.41 (3H, s, $CH_3C=N$), 3.22 (3H, s, NCH_3), 8.03 (1H, s, H-4 of dihydropyrimidine). MS *m/z*: 314 (M^+, 48%), 299 (M^+-15, 100%).

References and Notes

1) Y. Miyamoto, *Chem. Pharm. Bull.*, **33**, 2678 (1985); the previous paper will be designated as part I in this series.
2) In the reaction of isothiosemicarbazones with ethoxymethylene compounds, 4-[2-cyano-2-(ethoxycarbonyl)-vinyl]-3-methylisothiosemicarbazones were prepared in good yields when ethyl(ethoxymethylene)cyano-acetate was substituted for ethoxymethylenemalononitrile.[3]
3) C. Yamazaki, *J. Org. Chem.*, **46**, 3956 (1981).
4) The configuration about the benzylideneamino double bond of hydrazones has been reported as *E* by many investigators and so that of the present compounds is believed to be *E*.
5) D. M. Greant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
6) Unless otherwise stated, the symbols *E* and *Z*, as used in the Discussion and Experimental sections, refer to the configuration about the N(2)=C bond.