Original Article

Synthesis and Antifungal Activity of [1,2,4]Triazolo-[1,5-*c*]pyrimidine Derivatives

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Condensation of amidinohydrazones with ethoxymethylenemalononitrile gave 2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidines in moderate to high yields. Of the variously substituted amidinohydrazones, aldehyde 4-monosubstituted ones were most reactive in the condensation, regardless of the nature of the 4-substituent. The 2,3-dihydro compounds were oxidized with iron(III) chloride in aqueous acetic acid or with iodine in ethyl alcohol to give the corresponding [1,2,4]triazolo[1,5-*c*]pyrimidines. Thirty-eight compounds were subjected to fungicidal screening tests, which showed no or weak activity against test organisms.

INTRODUCTION

A number of triazolopyrimidines, in which triazole and pyrimidine rings fused with each other in 1,5-*a* or 4,3-*a* condensation, have been synthesized¹⁻³⁾ and tested for pesticidal activity. It has previously been reported that certain [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives possess potent pesticidal activity, particularly against fungi.⁴⁻⁶⁾ In the triazolopyrimidine chemistry, there have been only a few reports on the synthesis⁷⁾ and biological properties of [1,2,4]triazolo[1,5-*c*]pyrimidines, probably due to their unavailability. The author has now attempted to prepare [1,2,4]triazolo[1,5-*c*]pyrimidine derivatives by a new synthetic method, which essentially differs from the known step-wise procedures and gives the bicyclic structure in one step from an open-chain material. The new products thus obtained were evaluated for their protective activity against some plant diseases caused by *Pyricularia oryzae*, *Rhizoctonia solani*, *Xanthomonas oryzae*, *Sphaerotheca fuliginea*, *Pseudoperonospora cubensis*, *Botrytis cinerea* and *Erwinia carotovora*. None of these compounds showed potent activity in *in vivo* tests except such a few compounds as 8-cyano-2-(2,3-dichlorophenyl)-2,3-dihydro-5-dimethyl-

amino[1,2,4]triazolo[1,5-*c*]pyrimidine (**4f**), 8-cyano-5-dimethylamino-2-(*p*-methoxyphenyl)-[1,2,4]triazolo[1,5-*c*]pyrimidine (**5c**) and 8-cyano-2,3-dihydro-5-methylamino-2-phenyl [1,2,4]triazolo[1,5-*c*]pyrimidine (**8g**), which exhibited weak antifungal activity.

MATERIALS AND METHODS

1. Instrumental Analyses

Melting points were uncorrected. IR spectra were recorded on a Hitachi EPI-G2 or 260-30 spectrophotometer and ¹H NMR spectra with a Hitachi R-24 spectrometer at 60 MHz using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a JEOL JMS D100 mass spectrometer.

2. Preparation of Materials

2.1 Benzaldehyde 4,4-dimethylamidinohydrazone (**1a**)

A mixture of benzaldehyde (1.1 g, 0.01 mol), 4,4-dimethylaminoguanidine hydriodide (2.3 g, 0.01 mol) and 20 ml of methyl alcohol was acidified with 0.2 ml of concentrated hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 30 min, during which time crystallization of the desired amidinohydrazone hydriodide was completed.

The crystals were collected by filtration and converted to the free base in the usual manner to give a pale yellow needle (1.8 g, 98%), mp 146–148°C. Anal. Found: C, 63.27; H, 7.53; N, 29.39. Calcd. for $C_{10}H_{14}N_4$: C, 63.13; H, 7.42; N, 29.45%. ^1H NMR (in $CDCl_3$) δ ppm: 2.96 [6 H, s, $N(CH_3)_2$], 5.20 (2 H, s, NH_2), 7.30 (3 H, m, phenyl), 7.70 (2 H, m, phenyl), 8.20 (1 H, s, $CH=N$).

Other amidinohydrazones (**1b–j** and **6a–n**) were prepared similarly and gave appropriate spectral data and satisfactory elemental analyses.

2.2 Benzaldehyde 3-(2,2-dicyanovinyl)-4,4-dimethylamidinohydrazone (**3a**)

A mixture of **1a** (0.19 g, 1 mmol) and ethoxymethylenemalononitrile (**2**) (0.15 g, 1.2 mmol) was dissolved in 0.5 ml of acetonitrile and the reaction mixture was allowed to stand at room temperature. After 30 min, crystals gradually deposited from the solution were collected by filtration to give 0.1 g (38%) of analytically pure **3a** in pale yellow needle, mp 158–159°C. Anal. Found: C, 62.80; H, 5.20; N, 31.17. Calcd. for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.56%. IR ν_{max}^{KBr} cm^{-1} : 2200, 2210 (CN). ^1H NMR (in $DMSO-d_6$) δ ppm: 3.17 [6 H, s, $N(CH_3)_2$], 7.48 (5 H, m, phenyl), 8.08 (1 H, s, $C=CH$), 8.27 (1 H, s, $CH=N$), 11.25 (1 H, s, NH). MS m/z : 266 (M^+), 264 ($M^+ - 2H$), 189 ($M^+ - C_6H_5$), 103 (C_6H_5CN).

Similarly, dicyanovinyl amidinohydrazones **3g**, **7d** and **7h** were prepared.

2.3 8-Cyano-2,3-dihydro-5-dimethylamino-2-phenyl[1,2,4]triazolo[1,5-c]pyrimidine (**4a**): Procedure A

A mixture of **1a** (0.19 g, 1 mmol), **2** (0.15 g, 1.2 mmol), and 0.5 ml of acetonitrile containing 0.1 ml of triethylamine was heated under reflux for 5 min. The reaction mixture was evaporated to give a brown oil. The residual oil was crystallized from isopropyl alcohol and the crystals formed were collected by filtration to give 0.13 g (49%) of analytically pure **4a** as pale yellow needle, mp 165–173°C. IR ν_{max}^{KBr} cm^{-1} : 3170, 2920 (NH), 2200 (CN). ^1H NMR (in $CDCl_3$) δ ppm: 3.24 [6 H, s, $N(CH_3)_2$], 5.10 (1 H, d, $J=12.0$ Hz, NH), 6.00 (1 H, d, $J=12.0$ Hz, CH), 7.35 (5 H, m, phenyl), 7.62 (1 H, s, H-7). MS m/z : 266 (M^+), 264 ($M^+ - 2H$), 189 ($M^+ - C_6H_5$).

2.4 8-Cyano-2,3-dihydro-5-methylamino-2-phenyl[1,2,4]triazolo[1,5-c]pyrimidine (**8a**): Procedure B

A mixture of **6a** (0.18 g, 1 mmol) and **2** (0.15 g, 1.2 mmol) was dissolved in 0.5 ml of acetonitrile and the reaction mixture was allowed to stand at room temperature. After 1 hr, crystals gradually deposited were collected by filtration to give 0.12 g (48%) of analytically pure **8a** in pale yellow needle, mp 156–161°C. IR ν_{max}^{KBr} cm^{-1} : 3180, 3240 (NH), 2210 (CN). ^1H NMR (in $DMSO-d_6$) δ ppm: 2.32 (3 H, d, $J=4.0$ Hz, $NHCH_3$), 6.09 (1 H, d, $J=10.4$ Hz, H-3), 6.52 (1 H, d, $J=10.4$ Hz, H-2), 7.33 (5 H, s, phenyl), 7.88 (1 H, s, H-7). MS m/z : 252 (M^+), 175 ($M^+ - C_6H_5$), 103 (C_6H_5CN).

2.5 8-Cyano-5-dimethylamino-2-phenyl[1,2,4]triazolo[1,5-c]pyrimidine (**5a**): Procedure C

To a solution of **4a** (0.13 g, 0.5 mmol) in 1 ml of a mixture of acetonitrile, acetic acid and water in 2:1:1 by volume was added 1 mmol of iron (III) chloride in 1 ml of water, and the resulting cloudy solution was allowed to stand overnight at room temperature. The reaction mixture was diluted with sufficient water to completely precipitate the oxidized product, which was collected by filtration to give 0.09 g (34%) of an analytically pure colorless needle, mp 205–206°C. IR ν_{max}^{KBr} cm^{-1} : 2200 (CN). ^1H NMR (in CF_3COOD) δ ppm: 3.62 [6 H, s, $N(CH_3)_2$], 7.58 (3 H, m, phenyl), 8.19 (2 H, m, phenyl), 8.49 (1 H, s, H-7). MS m/z : 264 (M^+).

2.6 8-Cyano-5-methylamino-2-phenyl[1,2,4]triazolo[1,5-c]pyrimidine (**9a**): Procedure D

To a solution of **8a** (0.1 g, 0.4 mmol) in acetonitrile (1 ml) was added 3.5 ml of a solution containing 1 mmol/5 ml of iodine in ethyl alcohol (0.7 mmol), and the mixture was allowed to stand at room temperature with occasional agitation for 1 day. The reaction mixture was diluted with sufficient water to completely precipitate the oxidized product, which was collected by filtration to give 0.05 g (50%) of an analytically pure **9a** in pale yellow needle, mp 232–234°C. IR ν_{max}^{KBr} cm^{-1} : 3300 (NH), 2210 (CN). ^1H NMR (in CF_3COOD) δ ppm: 3.53 (3 H, s, CH_3), 7.72 (3 H, m, phenyl), 8.15 (2 H, m, phenyl), 8.90 (1 H, s, H-7). MS m/z : 250 (M^+), 249 ($M^+ - 1$), 147 ($M^+ - C_6H_5CN$).

Table 1 5-Disubstituted amino 8-cyano-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidines.

Com- pound	R ¹	R ²	R ³	R ⁴	Yield (%)	mp (°C)	Formula	Analysis (%)		
								Calcd.	(Found)	
								C	H	N
4a	C ₆ H ₅	H	CH ₃	CH ₃	49	165-173 ^{a)}	C ₁₄ H ₁₄ N ₆	63.14 (62.57)	5.30 5.22	31.56 31.60)
4b	<i>o</i> -CH ₃ OC ₆ H ₄	H	CH ₃	CH ₃	63	175-176	C ₁₅ H ₁₄ N ₆ O	60.80 (60.60)	5.44 5.37	28.36 28.51)
4c	<i>p</i> -CH ₃ OC ₆ H ₄	H	CH ₃	CH ₃	44	136-148 ^{a)}	C ₁₅ H ₁₄ N ₆ O	60.80 (60.83)	5.44 5.45	28.36 28.14)
4d	<i>o</i> -ClC ₆ H ₄	H	CH ₃	CH ₃	63	156-157	C ₁₄ H ₁₃ ClN ₆	55.91 (55.48)	4.36 4.29	27.94 27.75)
4e	<i>p</i> -ClC ₆ H ₄	H	CH ₃	CH ₃	43	151-156	C ₁₄ H ₁₃ ClN ₆	55.91 (55.84)	4.36 4.26	27.94 28.15)
4f	2,6-Cl ₂ C ₆ H ₃	H	CH ₃	CH ₃	44	178-179	C ₁₄ H ₁₂ Cl ₂ N ₆	50.17 (50.12)	3.61 3.59	25.07 25.38)
4g	C ₆ H ₅	CH ₃	CH ₃	CH ₃	60	160-162	C ₁₅ H ₁₆ N ₆	64.27 (63.74)	5.57 5.52	29.98 30.02)
4h	<i>o</i> -ClC ₆ H ₄	CH ₃	CH ₃	CH ₃	43	176-177	C ₁₅ H ₁₅ ClN ₆	57.32 (57.10)	4.80 4.81	26.70 26.91)
4i	<i>p</i> -CH ₃ OC ₆ H ₄	H	(CH ₂) ₄		61	161-182 ^{a)}	C ₁₇ H ₁₈ N ₆ O	63.34 (63.17)	5.63 5.52	26.07 25.85)
4j	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	(CH ₂) ₄		54	248-250	C ₁₈ H ₂₀ N ₆ O	64.27 (64.31)	5.99 6.01	24.98 24.93)

^{a)} Partial oxidation during the course of melting point measurement is presumably responsible for the wide melting range.

2.7 5-Amino-8-cyano-2-phenyl[1,2,4]triazolo[1,5-*c*]pyrimidine (**9m**)

A mixture of **6m** (0.16 g, 1 mmol), **2** (0.15 g, 1.2 mmol) and 1 ml of acetonitrile containing 0.1 ml of triethylamine was allowed to stand at room temperature. After 3 days crystals gradually deposited were collected by filtration to give 0.16 g (68%) of the desired yellow crystals, mp 279-280°C. Recrystallization from ethyl alcohol gave pale yellow needle, mp 279-280°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3460 (NH), 2230 (CN). ¹H NMR (in CF₃COOD) δ ppm: 7.68 (3 H, m, phenyl), 8.20 (2 H, m, phenyl), 8.78 (1 H, s, H-7). MS m/z : 236 (M⁺), 235 (M⁺-1), 104 (C₆H₅CNH⁺).

2.8 Conversion of **3g** to **4g**

A mixture of **3g** (0.2 g) and triethylamine (0.1 ml) in a mixture (1 ml) of acetonitrile and methyl alcohol (1:1 by volume) was refluxed for 10 min and then evaporated. The residue

was crystallized from methyl alcohol to give **4g** of a pale yellow needle (0.15 g, 75%), mp 160-161°C, not depressed upon admixture with a product from direct cyclization of **1g** with **2**.

3. Evaluation of Activity

3.1 Test plants

The following plants were employed for the evaluation of compounds: rice (variety Nihonbare), cucumber (variety Sagamihanjiro), tomato (variety Fukuju No. 2), and Chinese cabbage (variety Kinsyo No. 2). They were cultivated in a green house and used; rice at the fourth-leaf stage, cucumber at the second-leaf stage, tomato at the third-node stage, and Chinese cabbage at the three-week-old stage.

3.2 Test organisms

Pyricularia oryzae, *Rhizoctonia solani*, *Xan-*

Table 2 5-Monosubstituted amino 8-cyano-2,3-dihydro[1,2,4]triazolo[1,5-c]pyrimidines.

Compound	R ¹	R ²	R ⁴	Yield (%)	mp (°C)	Formula	Analysis (%)		
							Calcd.	(Found)	
							C	H	N
8a	C ₆ H ₅	H	CH ₃	48	156–161 ^{a)}	C ₁₃ H ₁₂ N ₆	61.89 (61.73)	4.79 4.72	33.31 33.56
8b	<i>o</i> -CH ₃ OC ₆ H ₄	H	CH ₃	64	186–189	C ₁₄ H ₁₄ N ₆ O	59.56 (59.32)	5.00 4.91	29.77 29.90
8c	<i>p</i> -CH ₃ OC ₆ H ₄	H	CH ₃	67	185–200 ^{a)}	C ₁₄ H ₁₄ N ₆ O	59.56 (59.71)	5.00 4.97	29.77 29.79
8e	<i>p</i> -ClC ₆ H ₄	H	CH ₃	63	170–179 ^{a)}	C ₁₃ H ₁₁ ClN ₆	54.46 (54.36)	3.87 3.81	29.31 29.14
8f	2,6-Cl ₂ C ₆ H ₃	H	CH ₃	63	186–187	C ₁₃ H ₁₀ Cl ₂ N ₆	48.62 (48.31)	3.14 2.97	26.17 26.39
8g	C ₆ H ₅	CH ₃	CH ₃	53	221–224	C ₁₄ H ₁₄ N ₆	63.14 (63.26)	5.30 5.28	31.56 31.40
8h	<i>o</i> -ClC ₆ H ₄	CH ₃	CH ₃	20	162–164 ^{b)}	C ₁₄ H ₁₃ ClN ₆	55.91 (55.81)	4.36 4.29	27.94 28.24
8i	C ₆ H ₅	H	C(CH ₃) ₃	65	201–202	C ₁₆ H ₁₈ N ₆	65.29 (64.78)	6.16 6.03	28.55 28.58
8j	<i>o</i> -ClC ₆ H ₄	H	C(CH ₃) ₃	49	171–182 ^{a)}	C ₁₆ H ₁₇ ClN ₆	58.45 (58.55)	5.21 5.19	25.56 25.79
8l	C ₆ H ₅	CH ₃	C ₆ H ₅	35	116–117 ^{b)}	C ₁₉ H ₁₆ N ₆ · ½ C ₂ H ₅ OH	68.36 (68.48)	5.45 5.43	23.91 24.09
8m	C ₆ H ₅	H	H	50	185–187	C ₁₂ H ₁₀ N ₆	60.50 (60.23)	4.23 3.89	35.27 35.30
8n	C ₆ H ₅	CH ₃	H	60	255–256	C ₁₃ H ₁₂ N ₆	61.89 (61.73)	4.79 4.72	33.31 33.56

^{a)} Partial oxidation during the course of melting point measurement is presumably responsible for the wide melting range.

^{b)} Refluxed in acetonitrile for 3 hr.

thomonas oryzae, *Sphaerotheca fuliginea*, *Pseudoperonospora cubensis*, *Botrytis cinerea*, and *Erwinia carotovora* were employed as test organisms.

3.2.1 Preventive activity against rice blast (Foliar application)

An aqueous suspension of a test compound was prepared at a concentration of 500 ppm. The suspension was sprayed onto the rice plants cultivated in a pot, 9 cm in diameter, filled with 20 ml of soil per pot. The next day a spore suspension of *P. oryzae* was sprayed onto the plants and the plants were maintained at a temperature of 25°C and a relative humidity higher than 95% for 24 hr. The treated plants were then transferred to a green

house and the controlling effect against the disease was examined 7 days after inoculation.

3.2.2 Preventive activity against rice blast (Soil drench application)

The rice plants grown in soil covered with water to simulate a paddy field in a beaker-pot, 8 cm in diameter, were treated with an aqueous suspension of a test compound at 500 ppm by giving the suspension dropwise to the water surface at a rate of 10 ml/pot. Seven days after application, a spore suspension of *P. oryzae* was sprayed onto the plants, which were then maintained at 25°C under a relative humidity higher than 95% for 24 hr. The treated plants were then transferred to a green house and the controlling effect was examined

Table 3 5-Disubstituted amino 8-cyano[1,2,4]triazolo[1,5-c]pyrimidines.

Compound	R ¹	R ³	R ⁴	Yield (%)	mp (°C)	Procedure	Formula	Analysis (%)		
								Calcd.	(Found)	
								C	H	N
5a	C ₆ H ₅	CH ₃	CH ₃	34	204–206	C	C ₁₄ H ₁₂ N ₆	63.63 (63.40)	4.58 (4.58)	31.80 (31.73)
5b	<i>o</i> -CH ₃ OC ₆ H ₄	CH ₃	CH ₃	31	218–224	C	C ₁₅ H ₁₄ N ₆ O	61.22 (61.10)	4.79 (4.69)	28.55 (28.72)
5c	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₃	CH ₃	68	180–190	C	C ₁₅ H ₁₄ N ₆ O	61.22 (61.19)	4.58 (4.77)	28.55 (28.37)
5d	<i>o</i> -ClC ₆ H ₄	CH ₃	CH ₃	64	205–209	C	C ₁₄ H ₁₁ ClN ₆	56.29 (56.04)	3.71 (3.50)	28.13 (28.33)
5e	<i>p</i> -ClC ₆ H ₄	CH ₃	CH ₃	56	239–249	C	C ₁₄ H ₁₁ ClN ₆	56.36 (56.36)	3.71 (3.57)	28.13 (28.38)
5h	<i>p</i> -CH ₃ OC ₆ H ₄	(CH ₂) ₄		40	250–252	a)	C ₁₇ H ₁₆ N ₆ O	63.74 (63.52)	5.03 (5.02)	26.23 (26.22)
9a	C ₆ H ₅	H	CH ₃	67	232–234	D	C ₁₃ H ₁₀ N ₆	62.39 (62.29)	4.03 (3.99)	33.58 (33.27)
9b	<i>o</i> -CH ₃ OC ₆ H ₄	H	CH ₃	42	200–201	D	C ₁₄ H ₁₂ N ₆ O	59.99 (59.85)	4.31 (4.13)	29.98 (30.02)
9c	<i>p</i> -CH ₃ OC ₆ H ₄	H	CH ₃	64	263–266	D	C ₁₄ H ₁₂ N ₆ O	59.99 (59.88)	4.31 (4.26)	29.98 (29.82)
9d	<i>o</i> -ClC ₆ H ₄	H	CH ₃	28	180–181	D	C ₁₃ H ₉ ClN ₆	54.84 (54.58)	3.19 (3.00)	29.52 (29.34)
9e	<i>p</i> -ClC ₆ H ₄	H	CH ₃	28	234–235	D	C ₁₃ H ₉ ClN ₆	54.84 (54.73)	3.19 (3.09)	29.52 (29.65)
9f	2,6-Cl ₂ C ₆ H ₃	H	CH ₃	29	243–245	D	C ₁₃ H ₈ Cl ₂ N ₆	48.92 (48.67)	2.53 (2.37)	26.33 (26.05)
9i	C ₆ H ₅	H	C(CH ₃) ₃	48	215–216	D	C ₁₆ H ₁₆ N ₆	65.74 (65.78)	5.52 (5.46)	28.75 (28.60)
9j	<i>p</i> -CH ₃ OC ₆ H ₄	H	C(CH ₃) ₃	26	218–222	a)	C ₁₇ H ₁₈ N ₆ O	63.34 (63.28)	5.63 (5.57)	26.07 (25.93)
9k	C ₆ H ₅	H	C ₆ H ₅	20	225–226	a)	C ₁₈ H ₁₂ N ₆	69.22 (69.11)	3.87 (3.71)	26.91 (26.77)
9m	C ₆ H ₅	H	H	68	279–280	a)	C ₁₂ H ₈ N ₆	61.01 (60.79)	3.41 (3.26)	35.57 (35.29)

a) A mixture of **6** and **2** in acetonitrile containing triethylamine was allowed to stand at room temperature for 3 days.

7 days after inoculation.

3.2.3 Preventive activity against sheath blight (Foliar application)

The cultivation of rice plants and their treatment with test compounds were the same as 3.2.1. On the day following the application, the treated plants were inoculated with *R. solani*, which had previously been grown on a branculture for 5 days, by placing the culture medium containing the organism in contact with shoot of the plants at a rate of

10 g/pot. The plants were maintained at a temperature of 27–30°C and a relative humidity higher than 95%, and the controlling effect was examined 6 days after inoculation.

3.2.4 Preventive activity against bacterial leaf blight of rice (Foliar application)

The cultivation of rice plants and their treatment were the same as 3.2.1. On the day following the application, the leaves were drilled at the center and inoculated with *X. oryzae* by penetrating the bacteria suspension

into the drilled point. The inoculated plants were maintained at 25°C under a relative humidity higher than 95% for 24 hr. The treated plants were then transferred to a green house and the controlling effect was examined 20 days after inoculation.

3.2.5 Preventive activity against powdery mildew of cucumber (Foliar application)

Cucumber plants were grown in a pot, 9 cm in diameter, filled with soil. The treatment with test compounds was the same as 3.2.1. After placed overnight on a green house, the plants were inoculated with *S. fuliginea* by spraying a spore suspension of the organism. The inoculated plants were kept in the green house continuously. The controlling effect was examined 10 days after inoculation.

3.2.6 Preventive activity against downy mildew of cucumber (Foliar application)

Cucumber plants were grown as described in 3.2.5. The treatment with test compounds and the subsequent inoculation with *P. cubensis* were similarly performed as in 3.2.5. The controlling effect was examined 7 days after inoculation.

3.2.7 Preventive activity against tomato gray mold (Foliar application)

Tomato plants were grown as in 3.2.5. The screening test was repeated in a similar manner to the one for the cucumber plants. The controlling effect was examined 5 days after inoculation with *B. cinerea*.

3.2.8 Preventive activity against Chinese cabbage soft rot (Foliar application)

Chinese cabbage plants were grown as in 3.2.5. The next day of application the leaves drilled at the center were inoculated with *E. carotovora* by penetrating the bacteria suspension into the drilled point. The inoculated plants were maintained at 27°C under a relative humidity higher than 95%. The controlling effect was examined 5 days after inoculation.

3.3 Protective value

The protective value was calculated from the following equation:

Protective value (%) =

$$\left[1 - \frac{\text{Infestation degree (treated)}}{\text{Infestation degree (untreated)}} \right] \times 100$$

Infestation degree; 0: no infestation, 5: severe

infestation.

3.4 Evaluation of activity

The preventive activity was expressed by a score from 0 through 2.

0: below 70, 1: 71–99 and 2: 100%.

RESULTS AND DISCUSSION

1. Syntheses

The best result was obtained by allowing a solution of 4,4-disubstituted amidinohydrazones (**1**) and ethoxymethylenemalononitrile (**2**) at a molar ratio of 1:1.2 in acetonitrile containing triethylamine to heat to the reflux temperature (Procedure A), giving 43–72% yields of **4** after isolation. In the absence of the amine, the yields diminished to 27–36% and, if R² is methyl group, *i.e.*, the starting amidinohydrazone is of ketone, the reaction did not proceed over the initial condensation stage. When the reaction mixture was left to stand at room temperature (Procedure B), **3** was the only product whether the amidinohydrazone was of aldehyde or ketone. The intermedially formed product could be converted to the corresponding **4** by being isolated and heated under the conditions of Procedure A.

N,N-Polymethyleneamidinohydrazones (**1i**, **1g**), which fall into category of 4,4-disubstituted amidinohydrazones, similarly reacted with **2**. When the reaction was carried out by Procedure A, however, the cyclization occurred only on aldehyde amidinohydrazones.

Generally, 4-monosubstituted amidinohydrazones were more reactive than 4,4-disubstituted amidinohydrazones and the reaction proceeded so rapidly that the linear intermediate **7** could not be isolated even under the mild conditions (Procedure B). Amidinohydrazones, having either methyl, *t*-butyl, or phenyl group on N(4), were compared with one another for their reactivity toward **2** by Procedure B. The result showed that the 4-monomethylamidinohydrazone was most reactive, readily giving **8a–8h** of high purity. Compounds **6i–6j**, in spite of the presence of a sterically bulky group on N(4), reacted smoothly with **2** to give the corresponding **8i–8j**, indicating no steric hindrance to the cyclization. 4-Phenylamidinohydrazones (**6k**, **6l**) similarly reacted with **2** to give a mixture of 2,3-dihydro compound **8k** and dehydrogenated

product **9k**, with the latter being a major component. Thus the phenyl substituent on N(4) did not prevent the cyclization but accelerated the dehydrogenation of the initially

formed dihydro compound **8** to **9**.

Under the conditions of Procedure B, **6m** cyclized directly to **9m** by Procedure A. The 2,3-dihydro compound **8m** could be obtained

only by the method in which **6m** was heated with **2** at reflux temperature in acetonitrile.

The dehydrogenation of 2,3-dihydrotriazolo-pyrimidines could be achieved with iron(III) chloride in aqueous acetic acid (Procedure C) or with iodine in ethyl alcohol at room temperature (Procedure D), with the yields varying over a wide range.

The structures of the 2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidines and [1,2,4]triazolo[1,5-*c*]pyrimidines have been established on the basis of spectral measurements and elemental analyses.

In the ^1H NMR spectra, the 2,3-dihydro structure of 5-(substituted and unsubstituted amino)[1,2,4] triazolo [1,5-*c*] pyrimidines were confirmed by the observation of spin-coupling between H-2 and H-3 protons and the disappearance of H-3 on exchanging with deuterium

by simultaneous conversion of H-2 resonance from a doublet to a singlet.

The spectrum of 2-deuterated **4a-d₁** ($\text{R}^2=\text{D}$), which was obtained by using benzaldehyde- d_1 ($\text{C}_6\text{H}_5\text{CDO}$) 4,4-dimethylamidino-hydrazone (**1a-d₁**) following Procedure A, exhibited the H-3 proton as a singlet. The ring proton at 7-position resonated near $\delta 7.62\text{--}7.76$ (CDCl_3), whose value was not substantially influenced by any structural changes in the remainder of molecule. The resonance of methyl protons at 2-position showed an upfield shift by about 0.5 ppm relative to the starting amidino-hydrazones, reflecting the change in hybridization of C-2 from sp^2 to sp^3 .

In mass spectrometry, molecular ions were obtained for all 2,3-dihydro compounds with the intensity (5–41%) depending upon the steric crowding at C-2. Abundant ions M^+-R^1

Table 4 Spectral data on 8-cyano-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidines.

Compound	IR (KBr) cm^{-1}	^1H NMR spectra δ/ppm (from TMS in DMSO-d_6)			Mass spectra, m/z (rel int.)		
		H-2(<i>J</i>)	H-3(<i>J</i>)	H-7	M^+	M^+-R^1	M^+-R^2
4a	2200	6.00 (12.0)	5.10 (12.0)	7.63 ^{a)}	266 (19)	189 (34)	265 (17)
4a-d₁	2200	—	5.10	7.64	267 (23)	190 (42)	265 (15)
4b	2200	6.68 (11.0)	6.18 (11.0)	7.85	296 (16)	189 (23)	295 (24)
4c	2200	5.93 (12.0)	5.08 (12.0)	7.63 ^{a)}	296 (22)	189 (14)	295 (17)
4d	2200	6.95 (11.0)	6.26 (11.0)	7.92	300 (30)	189 (16)	299 (29)
4e	2200	6.01 (12.0)	5.40 (12.0)	7.62 ^{a)}	300 (29)	189 (23)	299 (19)
4f	2200	7.46 (12.0)	5.40 (12.0)	7.63	334 (21)	189(100)	333 (5)
4g	2200	1.71 ^{b)}	4.67	7.63 ^{a)}	280 (14)	203 (19)	265(100)
4h	2200	1.89 ^{b)}	4.67	7.76 ^{a)}	314 (5)	203 (24)	293(100)
4i	2200	5.55 (11.0)	5.86 (11.0)	7.80	322 (9)	216 (6)	321 (18)
4j	2200	1.57 ^{b)}	6.41	7.80	336 (5)	229 (7)	321 (86)
8a	2210	6.52 (10.4)	6.09 (10.4)	7.88	252 (26)	175(100)	251 (34)
8a-d₁	2200	—	6.09	7.89	253 (22)	176(100)	251 (10)
8b	2200	6.55 (10.4)	6.32 (10.4)	7.90	282 (20)	175(100)	281 (20)
8c	2200	6.42 (10.4)	6.05 (10.4)	7.90	282 (39)	175 (61)	281 (73)
8e	2200	6.68 (10.4)	6.18 (10.4)	7.92	286 (39)	175 (81)	285 (36)
8f	2200	7.45 (8.8)	7.13 (8.8)	7.98	320 (6)	175 (1)	319 (1)
8g	2200	1.67 ^{b)}	6.30	7.89	266 (13)	189 (50)	251(100)
8h	2200	1.80 ^{b)}	6.50	7.90	300 (5)	189 (35)	285(100)
8i	2200	6.42 (11.0)	6.02 (11.0)	7.86	294 (29)	217 (20)	293 (9)
8j	2200	6.32 (11.0)	6.00 (11.0)	7.90	328 (15)	217 (11)	327 (1)
8k	2200	1.70 ^{b)}	4.75	7.75	328 (11)	251 (26)	313(100)
8l	2200	1.70 ^{b)}	4.75	7.75	328 (11)	251 (26)	313(100)
8m	2200	6.60 (10.4)	6.10 (10.4)	7.79	238 (41)	161 (41)	237 (50)
8n	2210	1.65 ^{b)}	6.30	7.78	252 (11)	175 (20)	237(100)

^{a)} in CDCl_3 .

^{b)} Methyl proton.

Table 5 Spectral data on 8-cyano[1,2,4]triazolo[1,5-*c*]pyrimidines.

Compound	IR (KBr) cm ⁻¹	¹ H NMR (CF ₃ COOD) ^δ	Mass spectra, <i>m/z</i> (rel int.)		
	CN	H-7	M ⁺	R ¹ CN	R ¹ CNH ⁺
5a	2210	8.49	264 (100)	103 (10)	104 (12)
5b	2220	8.78	294 (9)	133 (24)	134 (60)
5c	2220	8.05	294 (100)	133 (13)	134 (13)
5d	2220	8.75	298 (100)	137 (11)	138 (10)
5e	2210	8.81	298 (100)	137 (14)	138 (10)
5h	2200	8.20	320 (60)	133 (8)	—
9a	2210	8.90	250 (100)	103 (9)	104 (23)
9b	2220	8.92	280 (58)	133 (21)	134 (15)
9c	2230	8.90	280 (100)	133 (25)	134 (19)
9d	2230	8.56 ^{a)}	284 (100)	137 (7)	138 (11)
9e	2220	8.94	284 (100)	137 (10)	138 (12)
9f	2230	8.90	315 (55)	171 (1)	172 (1)
9i	2200	8.40	292 (23)	103 (7)	104 (14)
9j	2200	8.52 ^{a)}	322 (17)	133 (7)	134 (9)
9k	2210	8.75	312 (100)	103 (5)	104 (8)
9m	2230	8.78	236 (100)	103 (7)	104 (17)

^{a)} in DMSO-*d*₆.

and M⁺-R² observed in the spectra of 2,3-dihydrotriazolopyrimidines further characterized the 2,3-dihydro structure. The fragmentation pathways were confirmed by the mass spectra of deuterated compounds, **4a-d**₁ and **8a-d**₁, in which R² was D. The peaks (100%) of molecular ions of dehydrogenated compounds were intenser than those (5–30%) of the corresponding 2,3-dihydro compounds. The fragment ion R¹CN (5–38%) observed in the spectra of dehydrogenated compounds is characteristic of the triazolopyrimidine structure, which provides a means to distinguish dehydrogenated compounds from the corresponding 2,3-dihydro structure. All of these spectral data support the proposed arrangements of 2,3-dihydro- and dehydrogenated triazolopyrimidines.

2. Biological Activity

As the results of the fungicidal screening test showed, all the compounds **4a–g**, **5a–f**, **8a–n**, **9a–f**, **9i–k** and **9m** exhibited no activity against the test organisms (score 0). Extensive modifications of both substituents on the benzene ring at 2-position and the nitrogen at 5-position of the [1,2,4]triazolo[1,5-*c*]pyrimidine skeleton resulted in no effect on the develop-

ment of biocidal potency. It seems that the presently offered structure of the [1,2,4]triazolo[1,5-*c*]pyrimidine has inherent inertness on any kind of organisms employed in this investigation. Thus, some substituents possessing intensive influence on the molecular geometry or rigidity, the state of electronic distribution, and the like, of the [1,2,4]triazolo[1,5-*c*]pyrimidine need to be introduced.

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要 約

[1, 2, 4]トリアゾロ [1, 5-*c*] ピリミジン誘導体の合成とその抗菌活性

宮本美子

[1, 2, 4]トリアゾロ [1, 5-*a*] ピリミジン誘導体には抗菌活性、殺虫活性および除草活性を有するものが報告されている。これらのトリアゾロピリミジンは合成容易であるが、しかし、[1, 2, 4]トリアゾロ [1, 5-*c*]ピリミジンは報告例の非常に少ない合成困難な化合物である。したがっ

て、それらの生物活性に対する報告例はほとんどない。本研究は [1, 5-*c*] 骨格をもつトリアゾロピリミジンの新しい合成経路の開発である。この合成法は、入手容易な鎖状アミジノヒドラゾン (AH) とエトキシメチレンマロノニトリルとから温和な条件下で純粋な [1, 2, 4]トリアゾロ [1, 5-*c*] ピリミジンを好収率で得る一段階合成である。この反応における AH の反応性は窒素原子上の置換様式に大きく影響され、芳香族環上の置換基の位置は多少の影響を及ぼすが、置換基の種類はほとんど影響しない。そして、アルデヒドとケトン部分を比較すると前者のほうが反応性に富んでいる。このようにして合成したトリアゾロピリミジン誘導体の抗菌活性試験を行なったところ、強い活性を見い出すことはできなかった。