Synthesis and Conversions of 3-(4-Amino-5-methyl-4*H*-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline

Yoshihisa Kurasawa,* Yoshihisa Okamoto and Atsushi Takada

School of Pharmaceutical Sciences, Kitasato University,
Shirokane, Minato-ku, Tokyo 108, Japan

Received March 26, 1985

The reaction of the hydrazone **3a** with hydrazine hydrate in DBU/ethanol conveniently gave 3-(4-amino-5-methyl-4*H*-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline **6**. The reactions of **6** with an equimolar and 2-fold molar amount of nitrous acid afforded 3-(α-hydroxyimino-4-amino-5-methyl-4*H*-1,2,4-triazol-3-ylmethyl)-2-oxo-1,2-dihydroquinoxaline **9** and 3-(α-hydroxyimino-5-methyl-2*H*-1,2,4-triazol-3-ylmethyl)-2-oxo-1,2-dihydroquinoxaline **10**, respectively, which were converted into the 3-heteroarylisoxazolo[4,5-*b*]quinoxalines **13a,b** and **11**, respectively. Compound **9** was also cyclized into the 8-quinoxalinyl-1,2,4-triazolo-[3,4-*f*][1,2,4]triazines **14a,b**.

J. Heterocyclic Chem., **22**, 1715 (1985).

Recently, we have been interested in the various pharmacological activities of 1,3,4-oxadiazoles and 1,2,4-triazoles as bactericidal, fungicidal and herbicidal agents [2, 3], and we have synthesized a new type of oxazoles 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines **1** [2] and 3-(1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines **2** [3] *via* the hydrazones **3a,b** and thiosemicarbazides **4a,b**, respectively, from the hydrazide **5** (Chart 1). However, there was a limi-

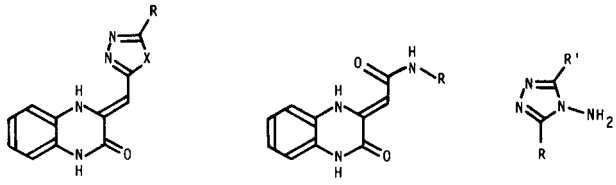
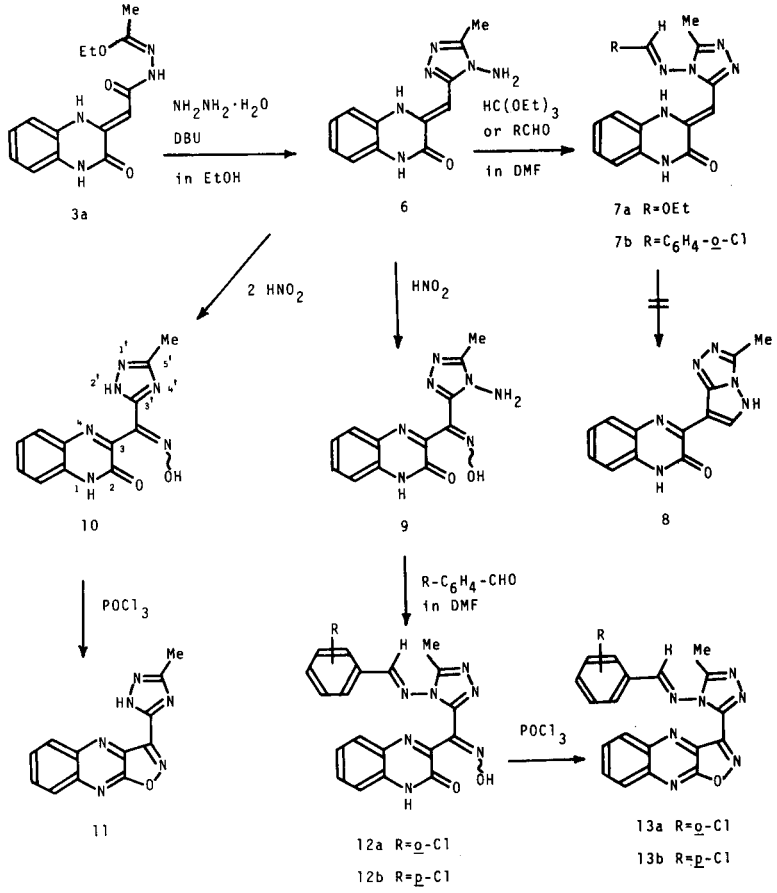


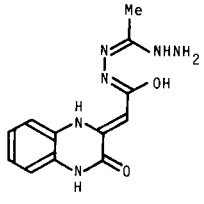
Chart 1



Scheme 1

tation on derivatization of the above compounds **1** and **2** in the azole nuclei, and hence the synthesis of the **1** and **2** type of 4-amino-4*H*-1,2,4-triazole **6** was undertaken because of its facile derivatization at the 4-amino group of the triazole ring. While there have been many reports on the 4-amino-4*H*-1,2,4-triazole synthesis [4a], we have found a convenient method for the synthesis of 3-(4-amino-5-methyl-4*H*-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline **6** from the above hydrazone **3a**. Moreover, **6** was converted into the oxime **9**, whose selective cyclizations furnished the isoxazolo[4,5-*b*]quinoxalines **13a,b** and 1,2,4-triazolo[3,4-*f*][1,2,4]triazines **14a,b**. This paper describes the synthesis of the 4-amino-4*H*-1,2,4-triazole **6** and its conversions into the various new compounds.

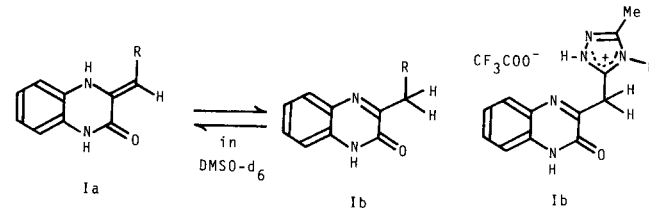
The reaction of **3a** with hydrazine hydrate in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) resulted in substitution and dehydrative cyclization [4a] to afford **6**, presumably *via* an intermediate **A** shown in Chart 2. Compound **6** reacted with triethyl orthoformate and with *o*-chlorobenzaldehyde to provide the substituted $N_{4'}$-amino



A

Chart 2

compounds **7a** and **7b**, respectively. Compound **7a** hardly cyclized into compound **8** on refluxing in *N,N*-dimethylformamide [2]. The reaction of **6** with an equimolar amount of nitrous acid resulted in hydroxyimination at the methylenic carbon [3] to furnish the oxime **9**, while an excess of nitrous acid effected deamination [4b] as well as hydroxyimination to give the oxime **10**. Refluxing of **10** in phosphoryl chloride resulted in dehydrative cyclization [5] to afford the isoxazolo[4,5-*b*]quinoxaline **11**. The reactions of **9** with *o*- and *p*-chlorobenzaldehydes provided the $N_{4'}$-benzylideneamino compounds **12a** and **12b**, respectively,



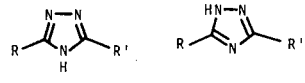
Ia Ib Ib

in trifluoroacetic acid

Scheme 2

whose refluxing in phosphoryl chloride also effected dehydrative cyclization to form the isoxazolo[4,5-*b*]quinoxalines **13a** and **13b**, respectively.

The pmr spectrum of **6** in deuteriodimethylsulfoxide exhibited the vinyl and methylene proton signals at δ 6.28 and 4.28 ppm due to two tautomers Ia and Ib (Ia:Ib = 5:1 at 30°, 3:1 at 80°), respectively, while the spectrum of **6** in trifluoroacetic acid represented the methylene proton signal at δ 4.93 ppm due to the tautomer Ib (Scheme 2) [2,3,6]. Compounds **7a** and **7b** were confirmed as the tautomer Ib, since their methylene proton signals were observed at δ 4.90 ppm. Moreover, the pmr spectrum of **9** in deuteriodimethylsulfoxide exhibited the paired $C_{5'}$-Me, N_1-H (or =N-OH) and $N_{4'}$-NH_2 proton signals, presumably due to the *syn* and *anti* oxime isomers (1:1 ratio) of **9**. On the other hand, **10** was assumed to be the 2*H*-1,2,4-triazole structure because of its favorable hydrogen bonding between the $N_{2'}$-proton and N_4-atom [7]. 4*H*-1,2,4-Triazole IIa is less stable than 1*H*- or 2*H*-1,2,4-triazole IIb (Chart 3) [77].



IIa IIb

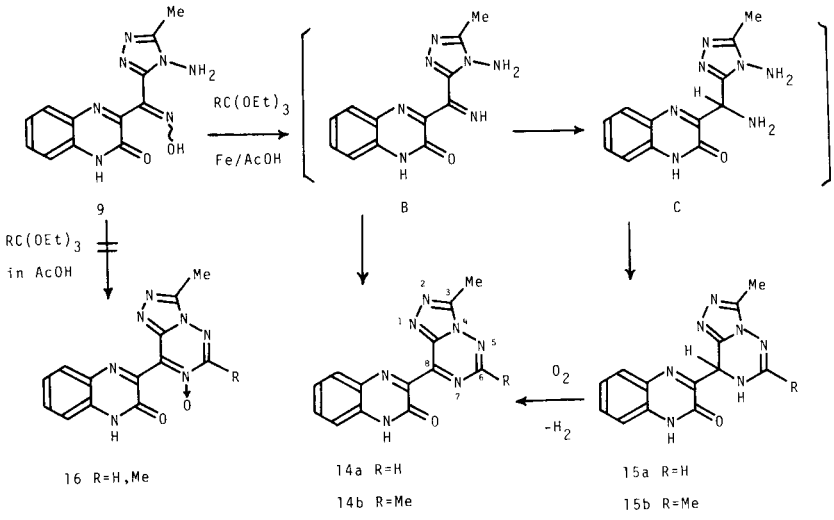
Chart 3

As described above, the oximes **9** and **10** were conveniently cyclized into the isoxazolo[4,5-*b*]quinoxalines **11**, **13a,b**. In continuation of these cyclizations, an additional type of annulation was further examined between the $N_{4'}$-amino and oxime groups of **9**. Namely, reduction of the

Table

Mass Spectral Data for **15a** and **15b**

Compound	m/z	Ion Species	Formula	Calcd.	Found	Relative intensity
15a	281	$[M]^{+\cdot}$	$C_{13}H_{11}N_7O$	281.103	281.103	100.0
	279	$[M-H_2]^{+\cdot}$	$C_{13}H_9N_7O$	279.087	279.085	16.0
	251	$[M-H_2-CO]^{+\cdot}$	$C_{12}H_9N_7$	251.092	251.089	8.5
15b	295	$[M]^{+\cdot}$	$C_{14}H_{13}N_7O$	295.118	295.118	100.0
	293	$[M-H_2]^{+\cdot}$	$C_{14}H_{11}N_7O$	293.103	293.103	40.3
	265	$[M-H_2-CO]^{+\cdot}$	$C_{13}H_{11}N_7$	265.108	265.108	42.6



Scheme 3

oxime into the amino or imino group [8] would produce the intermediary ambident diamine **B** or **C** (Scheme 3), which would easily incorporate one-carbon moieties to give the 1,2,4-triazolo[3,4-*f*][1,2,4]triazines **14** and **15**. In fact, this annulation method is successful and described below.

The reactions of **9** with orthoesters and iron powder in acetic acid gave the 1,2,4-triazolo[3,4-*f*][1,2,4]triazines **14a,b** and the 7,8-dihydro compounds **15a,b**, while the absence of iron powder did not afford the *N*-oxides **16a,b**, but recovered the starting material **9**. The 7,8-dihydro compounds **15a,b** were susceptible to oxidation, changing into **14a,b** during purification, and hence the formations of **15a,b** were checked by high resolution mass spectrometry. The molecular ion peaks of **15a,b** were observed as the base peaks as shown in the Table.

EXPERIMENTAL

All melting points were determined on a Ishii melting point apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The pmr spectra were recorded in deuteriodimethylsulfoxide (unless otherwise noted) with an EM 390 spectrometer at 90 MHz using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer.

3-(4-Amino-5-methyl-4*H*-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (**6**).

A suspension of the hydrazone **3a** (10 g) in hydrazine hydrate (10 ml)/DBU (2 ml)/ethanol (400 ml) was refluxed on a boiling water bath for 2 hours to precipitate yellow needles **6**, which were collected by suction filtration (4.80 g). Trituration of the yellow needles with hot ethanol gave an analytically pure sample, mp 333-334°. Evaporation of the above filtrate *in vacuo* afforded additional yellow needles of **6** (2.34 g) [total yield, 7.14 g (80%)]; ir: ν cm^{-1} 3340, 3175, 1680, 1630, 1610; ms: m/z 256 (M$^+$); pmr: 11.30 (s, 1H, NH), 11.03 (s, 1H, NH), 8.00-6.77 (m, 4H, aromatic), 6.28 (s, 1H, vinyl), 5.95 (s, 2H, $N_{4'}$-NH_2), 4.28 (s, methylene) [9], 3.28 (s, 3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.80. Found: C, 56.12; H, 4.68; N, 32.68.

3-(4-Ethoxycarbonylmethyleneamino-5-methyl-4*H*-1,2,4-triazol-3-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxaline (**7a**).

A solution of **6** (2 g) and triethyl orthoformate (10 ml) in *N,N*-dimethylformamide (40 ml) was refluxed in an oil bath for 2 hours, and removal of the solvent by evaporation *in vacuo* provided yellow crystals of **7a** (2.04 g, 84%). Recrystallization from ethanol gave yellow needles, mp 227-228°; ir: ν cm^{-1} 3220, 1680, 1640, 1610; ms: m/z 312 (M$^+$); pmr (trifluoroacetic acid): 8.80 (s, 1H, $N_{4'}$-N=C*H*OEt), 8.23-7.00 (m, 4H, aromatic), 4.90 (brs, 2H, methylene), 4.53 (q, J = 7 Hz, 2H, CH_2 of EtO), 2.83 (s, 3H, $C_{5'}$-Me), 1.47 (t, J = 7 Hz, Me of EtO). NH proton signals were not observed.

Anal. Calcd. for $C_{15}H_{16}N_6O_2$: C, 57.68; H, 5.16; N, 26.91. Found: C, 57.49; H, 5.16; N, 27.07.

3-[4-(*o*-Chlorobenzylideneamino)-5-methyl-4*H*-1,2,4-triazol-3-ylmethylene]-2-oxo-1,2,3,4-tetrahydroquinoxaline (**7b**).

A solution of **6** (2 g, 7.81 mmoles) and *o*-chlorobenzaldehyde (1.65 g, 11.72 mmoles) in *N,N*-dimethylformamide (50 ml) was refluxed in an oil bath for 3 hours, and removal of the solvent by evaporation *in vacuo* furnished yellow crystals of **7b** (1.31 g, 45%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 259-260°; ir: ν cm^{-1} 1680, 1630, 1610; ms: m/z 378 (M$^+$), 380 (M$^+$+2); pmr (trifluoroacetic acid): 9.44 (s, 1H, $N_{4'}$-N=C*H*C_6H_4Cl), 8.50-6.93 (m, 8H, aromatic), 4.90 (brs, 2H, methylene), 2.86 (s, 3H, $C_{5'}$-Me). NH proton signals were not observed.

Anal. Calcd. for $C_{19}H_{15}ClN_6O$: C, 60.24; H, 3.99; N, 22.18. Found: C, 59.98; H, 4.15; N, 22.40.

3-(α-Hydroxyimino-4-amino-5-methyl-4*H*-1,2,4-triazol-3-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (**9**) and 3-(α-Hydroxyimino-5-methyl-2*H*-1,2,4-triazol-3-ylmethyl)-2-oxo-1,2-dihydroquinoxaline (**10**).

A solution of sodium nitrite (1.69 g, 1.25 equivalents) in water (50 ml) was added to a suspension of **6** (5 g, 19.5 mmoles) in water (50 ml)/acetic acid (150 ml) with stirring in an ice-water bath. After stirring for 30 minutes, the reaction mixture was heated on a boiling water bath for 1 hour to provide a clear solution. Evaporation of the solvent *in vacuo* gave colorless crystals of **9**, which were triturated with hot water. After cooling, the colorless crystals of **9** were collected by suction filtration (4.42 g, 79%).

Colorless crystals of **10** (5.52 g, 97%) were obtained by a similar procedure to the above, using 2.5 equivalents of sodium nitrite (3.37 g).

Compound **9**.

Recrystallization from *N,N*-dimethylformamide/ethanol afforded colorless needles, mp 310-311°; ir: ν cm^{-1} 3340, 1665, 1600; ms: m/z 285 (M$^+$); pmr: 13.86 (s, ½H, NH or =N-OH), 13.54 (s, 1H, NH or =N-OH), 12.13 (s, ½H, NH or =N-OH), 8.00-7.17 (m, 4H, aromatic), 6.10 (s) and 5.6 (s) (2H, $N_{4'}$-NH_2), 2.36 (s) and 2.33 (s) (3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{12}H_{11}N_7O_2$: C, 50.53; H, 3.89; N, 33.37. Found:

C, 50.37; H, 3.95; N, 33.61.

Compound **10**.

Recrystallization from *N,N*-dimethylformamide/ethanol provided colorless needles as monohydrate, mp 285-286°; ms: m/z 270 (M^+); ir: ν cm^{-1} 3440, 3160, 1650, 1605; pmr: 13.70 (brs, 1H, NH or =N-OH), 12.53 (brs, 1H, NH or =N-OH), 11.66 (brs, 1H, NH or =N-OH), 8.00-7.20 (m, 4H, aromatic), 3.33 (s, water), 2.33 (s, $C_{5'}$-Me).

Anal. Calcd. for $C_{12}H_{12}N_6O_3$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.27; H, 3.95; N, 29.40.

3-(5-Methyl-2*H*-1,2,4-triazol-3-yl)isoxazolo[4,5-*b*]quinoxaline (**11**).

A solution of **10** (1 g) in phosphoryl chloride (5 ml)/dioxane (5 ml) was refluxed in an oil bath for 1 hour, and the solution was poured onto crushed ice to precipitate crystals **11**, which were collected by suction filtration (0.82 g, 88%). Recrystallization from *N,N*-dimethylformamide/-ethanol gave colorless needles, mp 319-320°; ir: ν cm^{-1} 3100, 2980, 2890, 2800, 1580, 1560, 1545, 1500; ms: m/z 252 (M^+); pmr: 14.37 (brs, 1H, NH), 8.57-7.83 (m, 4H, aromatic), 2.53 (s, 3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{12}H_8N_6O$: C, 57.14; H, 3.20; N, 33.20. Found: C, 57.41; H, 3.15; N, 33.48.

3-[α-Hydroxyimino-4-(*o*-chlorobenzylideneamino)-5-methyl-4*H*-1,2,4-triazol-3-ylmethyl]-2-oxo-1,2-dihydroquinoxaline (**12a**) and 3-[α-Hydroxyimino-4-(*p*-chlorobenzylideneamino)-5-methyl-4*H*-1,2,4-triazol-3-ylmethyl]-2-oxo-1,2-dihydroquinoxaline (**12b**).

General Procedure.

A solution of **9** (4 g, 14.0 mmoles) and *o*- or *p*-benzaldehyde (2.96 g, 21.04 mmoles) in *N,N*-dimethylformamide (100 ml) was refluxed in an oil bath for 3 hours. Removal of the solvent by evaporation *in vacuo* provided colorless crystals of **12a** or **12b**, respectively, which were collected by suction filtration.

Compound **12a**.

This compound was obtained in 76% yield (4.33 g). Recrystallization from *N,N*-dimethylformamide/ethanol afforded colorless prismic needles, mp 276-277°; ir: ν cm^{-1} 3160, 3100, 2960, 2880, 2820, 2760, 1650, 1605, 1590; ms: m/z 407 (M^+), 409 ($M^+ + 2$); pmr: 13.00 (brs, 2H, NH and =N-OH), 9.43 (s, 1H, $N_{4'}$-N=CH_6H_4Cl), 8.33-7.23 (m, 8H, aromatic), 2.55 (s, 3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{19}H_{14}ClN_7O_2$: C, 55.56; H, 3.46; N, 24.04. Found: C, 55.78; H, 3.45; N, 24.29.

Compound **12b**.

This compound was obtained in 41% yield (2.36 g). Recrystallization from *N,N*-dimethylformamide/ethanol afforded colorless needles, mp 281-282°; ir: ν cm^{-1} 3235, 3190, 3140, 3060, 3030, 2820, 2770, 1660, 1610, 1595; ms: m/z 407 (M^+), 409 ($M^+ + 2$); pmr: 12.83 (brs, 2H, NH and =N-OH), 9.00 (s, 1H, $N_{4'}$-N=CH_6H_4Cl), 8.00-7.33 (m, 8H, aromatic), 2.50 (s, 3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{19}H_{14}ClN_7O_2$: C, 55.56; H, 3.46; N, 24.04. Found: C, 55.80; H, 3.36; N, 24.13.

3-[4-(*o*-Chlorobenzylideneamino)-5-methyl-4*H*-1,2,4-triazol-3-yl]isoxazolo[4,5-*b*]quinoxaline (**13a**) and 3-[4-(*p*-Chlorobenzylideneamino)-5-methyl-4*H*-1,2,4-triazol-3-yl]isoxazolo[4,5-*b*]quinoxaline (**13b**).

General Procedure.

A solution of **12a** or **12b** (1 g) in phosphoryl chloride (5 ml)/dioxane (5 ml) was refluxed in an oil bath for 1 hour, and the solution was poured onto crushed ice to precipitate colorless crystals of **13a** or **13b**, respectively, which were collected by suction filtration.

Compound **13a**.

This compound was obtained in 76% yield (0.73 g). Recrystallization from ethanol gave colorless needles, mp 238-239°; ir: ν cm^{-1} 3060, 1600, 1580, 1555, 1510, 1495; ms: m/z 390 (M^+), 392 ($M^+ + 2$); pmr: 9.39 (s, 1H, $N_{4'}$-N=CH_6H_4Cl), 8.43-7.27 (m, 8H, aromatic), 2.63 (s, 3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{19}H_{12}ClN_7O$: C, 58.54; H, 3.10; N, 25.15. Found: C, 58.58; H, 3.05; N, 25.35.

Compound **13b**.

This compound was obtained in 91% yield (0.87 g). Recrystallization from ethanol provided colorless needles, mp 235-236°; ir: ν cm^{-1} 3060, 1605, 1590, 1575, 1545, 1510, 1495; ms: m/z 390 (M^+), 392 ($M^+ + 2$); pmr: 9.12 (s, 1H, $N_{4'}$-N=CH_6H_4Cl), 8.53-7.53 (m, 8H, aromatic), 2.60 (s, 3H, $C_{5'}$-Me).

Anal. Calcd. for $C_{19}H_{12}ClN_7O$: C, 58.54; H, 3.10; N, 25.15. Found: C, 58.36; H, 2.87; N, 24.85.

8-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3-methyl-1,2,4-triazolo[3,4-*f*][1,2,4]-triazine (**14a**) and 8-(3-Oxo-3,4-dihydroquinoxalin-2-yl)-3,6-dimethyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazine (**14b**).

A solution of **9** (2 g), the appropriate orthoester (20 ml) and iron powder (2 g) in acetic acid (200 ml) was refluxed in an oil bath for 2 hours to precipitate yellow crystals **15**, which were collected by suction filtration while hot [10]. A solution of the whole crystals **15** in *N,N*-dimethylformamide (100 ml) was refluxed in an oil bath for 30 minutes and then the solution was filtered. Removal of the solvent by evaporation *in vacuo* afforded yellow crystals **14**, which were recrystallized from *N,N*-dimethylformamide/ethanol/*n*-hexane to provide yellow needles [**14a** (360 mg), **14b** (330 mg)].

Evaporation of the above filtrate (acetic acid solution) *in vacuo* gave yellow crystals, which were collected by suction filtration. Recrystallization from the same solvent system as the above afforded yellow needles **14** [**14a** (650 mg), **14b** (630 mg)], total yield, **14a** (56%) **14b** (47%).

Compound **14a** had mp 313-314° dec; ms: m/z 279 (M^+); ir: ν cm^{-1} 1665, 1605; pmr: 13.07 (brs, 1H, NH), 9.34 (s, 1H, C_6-H), 8.00-7.30 (m, 4H, aromatic), 2.80 (s, 3H, C_3-Me).

Anal. Calcd. for $C_{13}H_9N_7O$: C, 55.91; H, 3.25; N, 35.11. Found: C, 55.66; H, 3.23; N, 34.93.

Compound **14b** had mp 311-312° dec; ms: m/z 293 (M^+); ir: ν cm^{-1} 1665, 1605; pmr: 13.00 (brs, 1H, NH), 8.00-7.30 (m, 4H, aromatic), 2.77 (s, 6H, C_3- and C_6-Me).

Anal. Calcd. for $C_{14}H_{11}N_7O$: C, 57.33; H, 3.78; N, 33.43. Found: C, 57.16; H, 3.96; N, 33.26.

REFERENCES AND NOTES

[1] Preliminary reports: Y. Kurasawa, M. Ichikawa, I. Kamata, Y. Okamoto and A. Takada, *Heterocycles*, **23**, 281 (1985); Y. Kurasawa, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **22**, 935 (1985).

[2] Y. Kurasawa, Y. Moritaki and A. Takada, *Synthesis*, 238 (1983); Y. Kurasawa, Y. Moritaki, T. Ebukuro and A. Takada, *Chem. Pharm. Bull.*, **31**, 3897 (1983).

[3] Y. Kurasawa, K. Suzuki, S. Nakamura, K. Moriyama and A. Takada, *Heterocycles*, **22**, 695 (1984); *Idem., Chem. Pharm. Bull.*, **32**, 4752 (1984).

[4] C. Temple, Jr., "The Chemistry of Heterocyclic Compounds, Triazoles 1.2.4", J. A. Montgomery, ed, John Wiley and Sons, New York, Chichester, Brisbane, Toronto, 1981, Vol 37, (a) pp 155-162; (b) p 314, and references cited therein.

[5] D. D. Chapman, *J. Org. Chem.*, **37**, 2498 (1972).

[6] R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).

[7] J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "Advances in Heterocyclic Chemistry, Suppl. 1, The Tautomerism of Heterocycles", A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, San Francisco, London, 1976, p 287.

[8] Y. Kurasawa, Y. Okamoto and A. Takada, *Heterocycles*, **22**, 1391 (1984).

[9] This signal appears due to the tautomerism shown in Scheme 2.

[10] The crystals **15** were collected together with a trace amount of iron powder.