Synthesis of Nitrogen-Containing Heterocycles 6 [1]. Formation and Structures of Imidazolinones and Related Compounds through Cyclization of Diaminomethylenehydrazones with Dimethyl Acetylenedicarboxylate

Yoshiko Miyamoto* and Chiji Yamazaki

Department of Chemistry, School of Hygienic Sciences,
Kitasato University, Kitasato, Sagamihara, Kanagawa 228, Japan
Received June 28, 1993.

Diaminomethylenehydrazones **1** of aromatic and aliphatic carbonyl compounds react with dimethyl acetylenedicarboxylate (DMAD) at room temperature to give four types of heterocycles, (5-oxoimidazolin-4-ylidene) acetates **2**, **3** and **6**, (2-imino-5-oxoimidazolidin-4-ylidene) acetate **4** and 6-oxo-1,6-dihydropyrimidine-4-carboxylates **5** according to the substitution patterns of **1** in moderate to high yields. Amino (*N,N*-dimethylamino)methylenehydrazones of ketones give exclusively (5-oxoimidazolin-4-ylidene) acetates, both (*Z*)- and (*E*)-isomers **2** and **3** about the exocyclic alkenic linkage, with the (*Z*)-isomer **2** generally being predominant, while those of aldehydes give **5**. Diamino- and amino (*N*-methylamino)methylenehydrazones produce **5** and/or **6** and di (*N*-methylamino) methylenehydrazone gives (2-imino-5-oxoimidazolidin-4-ylidene) acetate **4** as the sole cyclized product.

J. Heterocyclic Chem., **31**, 1445 (1994).

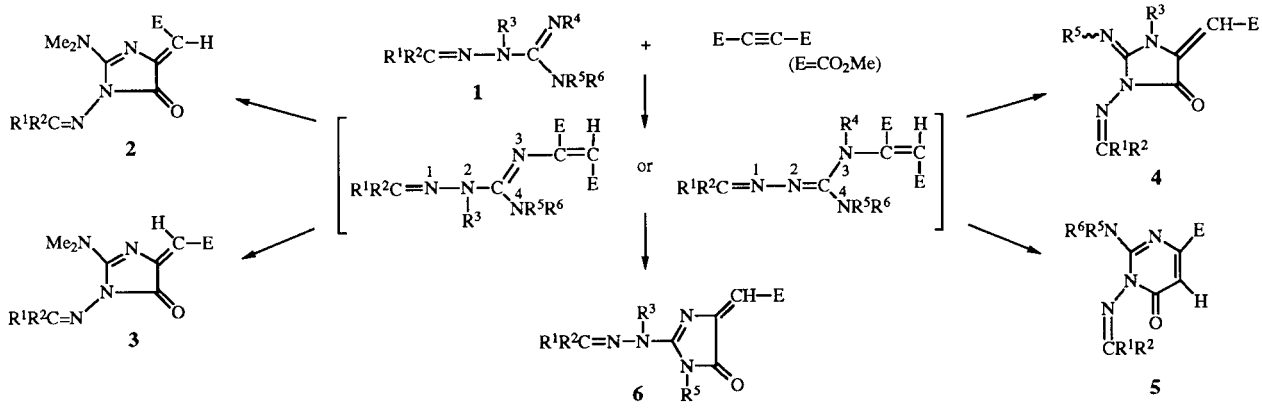
The reactions of acetylenic diesters with nitrogen nucleophiles, such as amidines, guanidines, and aminoguanidines [2] have long been known to be a good process for preparing nitrogen-containing heterocycles. The products are mainly classified into five-membered heterocycles, *e.g.*, imidazolines [3] or imidazolidines having an oxo and an alkoxycarbonylmethylene grouping on the ring, except for those from aminoguanidines [4]. We have recently reported [3b] that the cyclization of aromatic isothiosemicarbazones with acetylenedicarboxylate esters led to the formation of (*E*)- and/or (*Z*)-(1-arylmethyleneamino-2-alkylthio-5-oxo-2-imidazolin-4-ylidene) acetates [5] and that the *E/Z* ratios of the products could be controlled by appropriate selection of the reaction conditions. In the continuing study on the similar cyclization of the nitrogen analogue, *i.e.*, diaminomethylenehydrazones **1** of both aromatic and aliphatic carbonyl compounds, further complications were introduced according to the orientation dictated by the substitution patterns of **1**. Thus we have now obtained four types of polyfunctional cyclization products, (5-oxoimidazolin-4-ylidene) acetates **2**, **3** and **6**, (2-imino-5-oxoimidazolidin-4-ylidene) acetate **4** and 1,6-dihydro-6-oxopyrimidine-4-carboxylates **5** as represented in Scheme 1. The present report describes the formation and structural assignment of the cyclized products of differently substituted diaminomethylenehydrazones **1** with dimethyl acetylenedicarboxylate (DMAD). Also indicated are the characteristic behaviors of **1b** and **1h** to produce simultaneously isomeric pairs of five- and six-membered compounds in contrast to those of guanidines [3a] and isothiosemicarbazones [3b].

When benzaldehyde diaminomethylenehydrazone **1a** was allowed to react with an equimolar proportion of DMAD in methanol at room temperature, 2-benzylidenehydrazinoimidazoline **6a** was crystallized out of the reaction mixture in 72% yield. Although **1a** which carries no substituent on the terminal nitrogens could produce all of the five types of cyclized products **2-6**, the reaction was unexpectedly selective and gave exclusively **6a**, indicating that **1a** behaves essentially in the same manner as

Table 1

Compounds	R^1	R^2	R^3	R^5	R^6	Mp (°C)	Yield (%)	Formula	Analysis Calcd./Found C	H	N
2d	Ph	Me	H	Me	Me	158-160	64	$C_{16}H_{18}N_4O_3$	61.14	5.77	17.82
									60.95	5.88	17.58
2e	Ph	Et	H	Me	Me	141-142	46	$C_{17}H_{20}N_4O_3$	62.18	6.14	17.06
									62.15	6.16	17.26
2f	Ph	Pr	H	Me	Me	139-140	67	$C_{18}H_{22}N_4O_3$	63.14	6.48	16.36
									63.10	6.44	16.22
6i	Et	H	H	Me	H	oil	59	$C_{10}H_{14}N_4O_3$	50.42	5.92	23.52
									50.60	5.90	23.68
6k	Ph	H	Me	H	H	258	42	$C_{14}H_{14}N_4O_3$	58.74	4.93	19.57
									58.54	4.90	19.49

Scheme 1



	R^1	R^2	R^3	R^4	R^5	R^6
a	Ph	H	H	H	H	H
b	Ph	H	H	H	Me	H
c	Ph	H	H	H	Me	Me
d	Ph	Me	H	H	Me	Me
e	Ph	Et	H	H	Me	Me
f	Ph	Pr	H	H	Me	Me
g	Et	Et	H	H	Me	Me
h	Et	H	H	H	Me	Me
i	Et	H	H	H	Me	H
j	Ph	H	H	Me	Me	H
k	Ph	H	Me	H	H	H

Table 2

Compounds	^{1}H NMR spectra	IR (CCl_4) ν CO	MS M$^+$(%)
2d	2.40 (s, 3H), 3.26 (s, 6H), 3.43 (s, 3H), 6.00 (s, 1H), 7.43 (m, 3 Ar-H), 7.85 (m, 2 Ar-H)	1710 1670	314 (13)
2e	1.15 (t, 3H), 2.89 (q, 2H), 3.30 (s, 6H), 3.46 (s, 3H), 6.00 (s, 1H), 7.52 (m, 3 Ar-H), 7.90 (m, 2 Ar-H)	1710 1670	328 (19)
2f	0.95 (t, 3H), 1.50 (quin, 2H), 2.75 (t, 2H), 3.31 (s, 6H), 3.47 (s, 3H), 6.00 (s, 1H), 7.55 (m, 3 Ar-H), 7.90 (m, 2 Ar-H)	1710 1680	342 (14)
6i	1.20 (t, 3H), 2.51 (q, 2H), 3.21 (s, 3H), 3.70 (s, 3H), 5.82 (s, 1H), 7.65 (t, 1H)	1760 1690	238 (20)
6k	3.73 (s, 3H), 3.84 (s, 3H), 5.99 (s, 1H), 7.48 (m, 3 Ar-H), 7.76 (m, 2 Ar-H), 7.94 (s, 1H)	1740 1690	286 (26)

Table 3

Compounds	^{13}C NMR Spectra
2d	40.9 (q, NMe_2), 51.7 (q, OMe), 99.2 (d, =CH), 140.2 (s, C-4), 164.7 (s, N=C), 168.3 (s, C-2), 173.8 (s, C-5), 180.3 (s, C=O)
2e	41.1 (q, NMe_2), 51.7 (q, OMe), 98.4 (d, =CH), 139.6 (s, C-4), 164.7 (s, N=C), 167.4 (s, C-2), 173.3 (s, C-5), 183.5 (s, C=O)
2f	41.1 (q, NMe_2), 51.7 (q, OMe), 98.1 (d, =CH), 139.6 (s, C-4), 164.7 (s, N=C), 167.2 (s, C-2), 173.3 (s, C-5), 182.4 (s, C=O)
6i	26.1 (q, NMe), 51.7 (q, OMe), 93.5 (d, CH=N), 134.4 (s, C-4), 150.9 (s, C-2), 161.8 (d, CH=N), 165.0 (s, C-5), 173.0 (s, C=O)
6k	32.2 (q, NMe), 51.9 (q, OMe), 94.2 (d, CH=N), 133.1 (s, C-4), 143.8 (s, C-2), 146.7 (d, CH=N), 167.2 (s, C-5), 174.7 (s, C=O)

guanidine [3a]. When a methyl group, however, was introduced onto the terminal nitrogen (**1b**), the selectivity was diminished and another type of cyclization to produce **5b**, in which the substituted nitrogen resided out of the ring, competed with the main reaction to form **6b**.

The *N,N*-dimethylaminomethylenehydrazones **1c-1h** can cyclize such that the two nitrogens, N-2 and N-3, are incorporated into the ring to form both five- and six-membered compounds **2**, **3** and **5**. There was observed, however, a distinctive preference as to the ring size being formed, *i.e.*, with one exception, when R^2 was alkyl the five-membered heterocycles **2** and **3** were predominant, whereas when R^2 was hydrogen the six-membered heterocycle **5** was the major product. Thus, for example, when **1c** was reacted with DMAD under the same conditions as described for the reaction of **1a**, **5c** was obtained in 73%

yield. The α-methyl homologue **1d**, however, gave **2d** and **3d** as an isomeric pair in which the *Z*-isomer **2** predominated and no formation of the corresponding six-membered isomer was observed. The orientation of cyclization to the five-membered compounds **2** and **3** may be interpreted as the result of steric repulsion between the benzylidene or alkylidene and methoxycarbonylmethylene groupings in the transition state.

The structures of the compounds **2-6** were confirmed on the basis of the analytical and spectral data (Tables 1-3) as well as according to the discussion reported previously for the 5-oxoimidazoline derivatives [3b].

EXPERIMENTAL

Melting points were determined in open glass capillary tubes and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform solution on JNM-FX90Q (90 MHz) and EX400 (400 MHz) spectrometers. The chemical shift values are reported in parts per million (ppm) on the δ scale with tetramethylsilane as the internal reference. The ir and mass spectra were recorded on a Perkin-Elmer 983 and a JEOL JMS-D100 instruments, respectively. Microanalyses were performed with a Perkin-Elmer 240D elemental analyser at the Microanalytical Laboratory of Kitasato University. Preparative high-performance liquid chromatography (hplc) was carried out on a Kusano Kagaku KHLC-201 instrument with a 300 x 22 or a 300 x 15 mm glass column packed with silica gel.

All the *N*-substituted and unsubstituted diaminomethylenehydrazones **1a-1k** employed in this study were known compounds and prepared according to the literature methods [1, 6, 7].

Reaction of Benzaldehyde Diaminomethylenehydrazone (**1a**) with DMAD.

A solution of **1a** (0.16 g, 1 mmole) and DMAD (0.14 g, 1 mmole) in methanol (1 ml) was allowed to stand at room temperature with occasional agitation. Crystals gradually deposited from the solution and, after 30 minutes, were collected by filtration to give 0.195 g (72%) of **6a** as pale yellow needles, mp 183-187°. Recrystallization from methanol gave pale yellow needles, mp 197-198°; ir (potassium bromide): 1750 (ester), 1660 cm^{-1} (5-oxo); ^1H nmr (DMSO-d_6): δ 3.50 (s, 3H, OCH_3), 5.80 (s, 1H, =CHCO), 8.20 (s, 1H, CH=N); ^{13}C nmr (DMSO-d_6): δ 96.8 (d, =*C*HCO), 136.3 (s, C-4), 161.2 (d, CH=N), 164.5 (s, C-2), 167.4 (s, C-5), 173.5 (s, ester C=O); ms: m/z 272 (M^+, 19%), 77 (M^+-195, 100%).

Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.50; N, 4.41; N, 20.68.

Similarly, other hydrazinoimidazoline derivatives **6i** and **6k** were obtained (Tables 1-3).

Reaction of Benzaldehyde Amino (*N*-methylamino) methylenehydrazone (**1b**) with DMAD.

A solution of **1b** (0.18 g, 1 mmole) and DMAD (0.14 g, 1 mmole) in acetonitrile (1 ml) was heated under reflux for 1 hour and evaporated under reduced pressure to give an oil mainly consisting of two components. Preparative hplc on silica gel with chloroform gave two fractions from which **6b** (0.12 g, 42%) and the lower-Rf isomer **5b** (0.06 g, 21%) were isolated.

Compound **6b** was obtained as pale yellow needles, mp 95-97°; ir (potassium bromide): 1760 (ester), 1680 cm^{-1} (5-oxo); ^1H nmr (deuteriochloroform): δ 3.24 (s, 3H, NCH_3), 3.61 (s, 3H, OCH_3), 5.96 (s, 1H, =CHCO), 8.23 (s, 1H, CH=N); ^{13}C nmr (deuteriochloroform): δ 96.0 (d, =*C*HCO), 133.8 (s, C-4), 150.6 (s, C-2), 161.4 (d, CH=N), 161.4 (s, C-5), 165.1 (s, C=O); ms: m/z 286 (M^+, 15%), 152 (M^+-134, 100%).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.74; H, 4.93; N, 19.57. Found: C, 58.46; H, 4.89; N, 19.69.

Compound **5b** had mp 174°; ^1H nmr (deuteriochloroform): δ 3.21 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 6.02 (s, 1H, H-5), 8.40 (s, 1H, CH=N); ^{13}C nmr (deuteriochloroform): δ 29.7 (q, NCH_3), 52.7 (q, OCH_3), 102.1 (d, C-5), 127.9 (d, phenyl), 129.1 (d, phenyl), 132.0 (d, phenyl), 132.5 (s, phenyl), 136.0 (s, C-4), 153.9 (d, N=CH), 165.4 (s, C-2), 165.6 (s, C-6), 171.3 (s, ester C=O). Because the yield of **5b** considerably diminished in the course of crystallization, the other spectral and analytical data were not available.

Reaction of Benzaldehyde *N,N*-Dimethylaminomethylenehydrazone (**1c**) with DMAD.

A mixture of **1c** (0.19 g, 1 mmole) and DMAD (0.14 g, 1 mmole) in methanol (1 ml) was allowed to stand at room temperature. After 1 hour, crystals gradually deposited from the mixture and were collected by filtration to give 0.22 g (73%) of **5c** in an analytically pure, pale yellow crystalline form, mp 168-169°; ir (potassium bromide): 1720 (ester), 1670 cm^{-1} (6-oxo); ^1H nmr (deuteriochloroform): δ 3.50 (s, 6H, $N(CH_3)_2$), 3.68 (s, 3H, OCH_3), 6.38 (s, 1H, H-5), 7.90 (s, 1H, N=CH); ^{13}C nmr (deuteriochloroform): δ 103.5 (d, C-5), 138.0 (s, C-4), 154.4 (d, N=CH), 164.8 (s, C-2), 169.7 (s, C-6), 173.8 (s, ester C=O); ms: m/z 300 (M^+, 10%), 70 (M^+-230, 100%).

Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 60.22; H, 5.40; N, 18.78.

Reaction of 3-Pentanone *N,N*-Dimethylaminomethylenehydrazone (**1g**) with DMAD.

A mixture of **1g** (0.17 g, 1 mmole) and DMAD (0.14 g, 1 mmole) in methanol was allowed to stand at room temperature. After 1 hour, the reaction mixture was evaporated to give the crude product as an oil. The oil, after being dissolved in chloroform, was subjected to preparative hplc on silica gel with chloroform as the eluent to give two fractions, I and II in the eluting order. Fraction I gave spectroscopically pure **3g** (0.1 g, 36%) as pale yellow needles, mp 67-70°; ir (carbon tetrachloride): 1710 (ester), 1670 cm^{-1} (5-oxo); ^1H nmr (deuteriochloroform): δ 1.14 (t, 3H, J = 6.6 Hz, CCH_3), 1.24 (t, 3H, J = 6.6 Hz, CCH_3), 2.37 (q, 2H, J = 6.6 Hz, CH_2), 2.57 (q, 2H, J = 6.6 Hz, CH_2), 3.30 (s, 6H, $N(CH_3)_2$), 3.82 (s, 3H, OCH_3), 5.79 (s, 1H, =CH); ^{13}C nmr (deuteriochloroform): δ 100.2 (d, =CH), 148.5 (s, C-4), 162.2 (s, N=C), 166.2 (s, C-2 and C-5), 183.7 (s, C=O); ms: m/z 280 (M^+, 54%), 56 (M^+-224, 100%).

Anal. Calcd. for $C_{13}H_{20}N_4O_3$: C, 55.70; H, 7.19; N, 19.99. Found: C, 55.59; H, 7.15; N, 20.05.

Fraction II gave pure **2g** (0.05 g, 18%) as pale yellow needles, mp 93-96°; ir (carbon tetrachloride): 1710 (ester), 1660 cm^{-1} (5-oxo); ^1H nmr (deuteriochloroform): δ 1.14 (t, 3H, J = 6.6 Hz, CCH_3), 1.24 (t, 3H, J = 6.6 Hz, CCH_3), 2.37 (q, 2H, J = 6.6 Hz, CH_2), 2.57 (q, 2H, J = 6.6 Hz, CH_2), 3.27(s, 6H, $N(CH_3)_2$), 3.63

(s, 3H, OCH_3), 5.90 (s, =CH); ^{13}C nmr (deuteriochloroform): δ 97.7 (d, =CH), 140.2 (s, C-4), 164.6 (s, N=C), 167.4 (s, C-2), 173.5 (s, C-5), 189.9 (s, ester C=O); ms: m/z 280 (M^+, 34%), 56 (M^+-224, 100%).

Anal. Calcd. for $C_{13}H_{20}N_4O_3$: C, 55.70; H, 7.19; N, 19.99. Found: C, 55.61; H, 7.20; N, 19.95.

Compound **1d** gave a similar pair of **2d** and **3d**, but the yield of the latter isomer was very poor (6%) and thus the only data on ^1H and ^{13}C nmr spectra were available: ^1H nmr (deuteriochloroform): δ 2.38 (s, 3H, CCH_3), 3.30 (s, 6H, $N(CH_3)_2$), 3.80 (s, 3H, OCH_3), 5.85 (s, 1H, =CH), 7.42 (m, 3H, Ar-H), 7.89 (m, 2H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 39.5 [q, $N(CH_3)_2$], 51.4 (q, OCH_3), 100.8 (d, =CH), 148.2 (s, C-4), 162.1 (s, N=C), 166.1 (s, C-2); 166.4 (s, 5-oxo), 171.6 (s, C=O).

Other compounds **2** similarly prepared were reported in Table 1, but the minor isomers **3e** (9%) and **3f** (10%) gave only incomplete spectral and analytical data, *i.e.*, **3e** had ^1H nmr (deuteriochloroform): δ 1.14 (t, 3H, CCH_3), 2.85 (q, 2H, CH_2), 3.30 (s, 6H, $N(CH_3)_2$), 3.82 (s, 3H, OCH_3), 5.85 (s, 1H, =CH), 7.70 (m 3H, Ar-H), 7.80 (m, 2H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 10.5 (q, CCH_3), 26.4 (t, CH_2), 39.4 (q, $N(CH_3)_2$), 51.4 (q, OCH_3), 100.5 (d, =CH), 148.3 (s, C-4), 162.2 (s, N=C), 166.2 (s, C-2), 166.3 (s, C-5), 177.8 (s, C=O); **3f** had ^1H nmr (deuteriochloroform): δ 0.94 (t, 3H, CCH_3), 1.53 (quin, 2H, CH_2CH_3), 2.71 (t, 3H, $=CCH_2$), 3.30 (s, 6H, $N(CH_3)_2$), 3.79 (s, 3H, OCH_3), 5.82 (s, 1H, =CH), 7.50 (m, 3H, Ar-H), 7.80 (m, 2H, Ar-H); ^{13}C nmr (deuteriochloroform): δ 14.3 (q, CCH_3), 20.4 (t, CH_2CH_3), 33.4 (t, $=CCH_2$), 39.5 (q, $N(CH_3)_2$), 51.4 (q, OCH_3), 100.5 (d, =CH), 148.3 (s, C-4), 162.1 (s, N =C), 166.2 (s, C-2), 166.4 (s, C-5), 176.8 (s, C=O).

Similar reaction of propanal *N,N*-dimethylaminomethylenehydrazone **1h** with DMAD gave the corresponding **5h** as the major product, pale yellow needles from hexane: diisopropyl ether (2:1), mp 115-116°; 0.10 g (40%); ir (carbon tetrachloride): 1720 (ester), 1660 cm^{-1} (5-oxo); ^1H nmr (deuteriochloroform): δ 3.37 (s, 6H, $N(CH_3)_2$), 3.71 (s, 3H, OCH_3), 6.26 (s, 1H, H-5), 7.37 (t, 1H, N=CH); ^{13}C nmr (deuteriochloroform): δ 102.2 (d, C-5), 139.3 (s, C-4), 163.5 (d, N=CH), 164.8 (s, C-2), 170.1 (s, C-6), 174.0 (s, ester C=O); ms: m/z 252 (M^+, 19%), 70 (M^+-182, 100%).

Anal. Calcd. for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21. Found: C, 52.26; H, 6.44; N, 22.20.

The reaction simultaneously gave **3h** as the minor product as an oil (10 mg, 4%); ^1H nmr (deuteriochloroform): δ 1.20 (t, 3H, J = 6.6 Hz, CCH_3), 2.54 (quin, 2H, J = 6.6 Hz, CH_2), 3.25 (s, 6H, $N(CH_3)_2$), 3.80 (s, 3H, OCH_3), 5.50 (s, 1H, =CH), 7.98 (t, 1H, J = 6.6 Hz, N=CH); ^{13}C nmr (deuteriochloroform): δ 9.8 (q, CCH_3), 26.6 (t , CH_2), 40.9 (q, NCH_3), 52.5 (q, OCH_3), 101.4 (d, =CH), 140.7 (s, C-4), 165.6 (s, N=C), 167.4 (s, C-2), 167.4 (s, C-5), 170.1 (s, ester C=O). The yield (4%) of **3h** was too poor to obtain the other spectral and analytical data.

Reaction of Benzaldehyde Di(*N*-methylamino)methylenehydrazone (**1j**) with DMAD.

A mixture of **1j** (0.19 g, 1 mmole) and DMAD (0.14 g, 1 mmole) in acetonitrile (1 ml) was stirred at room temperature for 1 hour. The solid gradually dissolved and yellow needles were deposited within 5 minutes. The crystals were filtered off (0.14 g, 47%) and recrystallized from methanol to give the 5-oxoimidazolidine (**4**), mp 135-139°; ir (potassiom bromide): 1720 (ester), 1690 cm^{-1} (5-oxo); ^1H nmr (deuteriochloroform): δ 2.20 (s, 3H, $=NCH_3$), 3.50 (s, 3H, NCH_3), 3.58 (s, 3H, OCH_3), 5.96 (s, 1H, C=CH), 7.50 (s, 1H, N =CH); ^{13}C nmr (deuteriochloroform): δ 96.0 (d, C=*C*H), 135.5 (s, C-4), 139.8 (s, C-2), 159.9 (d, N=CH), 161.8 (s, C-5); ms: m/z 300 (M^+ 23%), 104 (M^+-196, 100%).

Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.76; H, 5.46; N, 18.61.

REFERENCES AND NOTES

[1] Part 5: Y. Miyamoto, C. Yamazaki and M. Matzui, *J. Heterocyclic Chem.*, **27**, 1553 (1990).

[2] M. V. George, S. K. Khetan and R. K. Gupta, *Adv. Heterocyclic Chem.*, **19**, 279 (1976).

[3] [a] A. S. Katner and E. A. Ziege, *J. Chem. Soc., Chem. Commun.*, 865 (1971); [b] C. Yamazaki, Y. Miyamoto and N. Tzukada, *J. Chem. Res. (S)*, 188 (1992).

[4] H. Sasaki, H. Sakata and Y. Iwanami, *J. Chem. Soc. Japan*, **85**, 704 (1964).

[5] The designations of *E* and *Z* refer to the configuration about the exocyclic double bond at the 4-position throughout in this paper.

[6] Y. Miyamoto, *Chem. Pharm. Bull.*, **33**, 2678 (1985).

[7] Y. Miyamoto and C. Yamazaki, *J. Heterocyclic Chem.*, **26**, 763 (1989).