Synthesis of Nitrogen-Containing Heterocycles. 4. A Facile Route to New 1,2,4-Triazole Derivatives

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The reaction of amino-*N*(4),*N*(4)-dimethylaminomethylenehydrazones **1** of some aliphatic carbonyl compounds with ethyl ethoxymethylenecyanoacetate **2** gave directly symmetrical *gem*-bis(3-dimethylamino-1,2,4-triazol-1-yl)alkanes **4** and (3-dimethylamino-1,2,4-triazol-1-yl)alkenes **5** at room temperature, with the former being major product. On the other hand, the reaction of amino-*N*(4)-methylaminomethylenehydrazone homologue **1** of aliphatic ketone with **2** gave ethyl 2-alkyl-5-methylamino[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate **7** as the only product with elimination of alkane.

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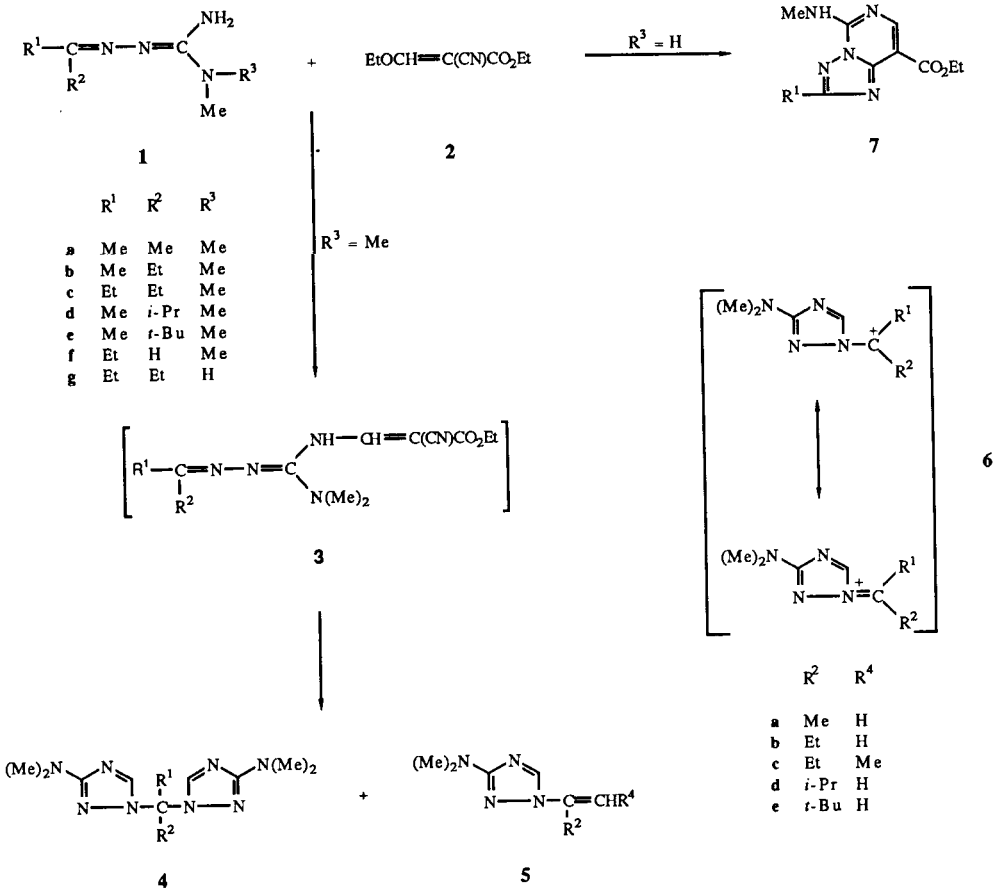
Introduction.

In a previous paper [1], we described the acidic cyclization of *N*(3)-[(2-cyano-2-ethoxycarbonyl)vinyl]amino-*N*(4),*N*(4)-dimethylaminomethylenehydrazones **3** (R^1 = aryl and R^2 = hydrogen or alkyl) of aromatic carbonyl compounds to symmetrical α,α-bis(3-dimethylamino-1,2,4-triazol-1-yl)toluenes and a *gem*-diaryl type of (3-dimethylamino-1,2,4-triazol-1-yl)alkenes. It was also suggested in the previous study that introduction of an *ortho*-substituent of electron-withdrawing character into the aryl group (R^1) completely prevented the formation of bistriazole and that in order to prepare bistriazoles by this process the aromatic carbonyl component of **3** should be aldehyde (R^2 = hydrogen). We are now interested in the use of aliphatic carbonyl component in place of the aromatic ones of **3**, because there might be expected easy

Scheme 1



	R^1	R^2	R^3
a	Me	Me	Me
b	Me	Et	Me
c	Et	Et	Me
d	Me	*i*-Pr	Me
e	Me	*t*-Bu	Me
f	Et	H	Me
g	Et	Et	H

	R^2	R^4
a	Me	H
b	Et	H
c	Et	Me
d	*i*-Pr	H
e	*t*-Bu	H

Table 1

% Yields [a] of Triazole Derivatives

Compound	4	5
a	25	27
b	30	6
c	54	2
d	26	22
f	46	-

[a] The yields reported in this paper refer to those purified compounds by chromatography.

formation of bistriazoles in view of the electron-donating character of alkyl groups (R^1 and/or R^2) on the alkylidene carbon as well as their reduced steric hindrance relative to the aryl group. It was found that treatment of aliphatic diaminomethylenehydrazones **1** (R^3 = Me) with ethyl ethoxymethylenecyanoacetate (**2**) gave directly the expected bistriazoles **4** in moderate yields without any acidic medium that was required to promote the intramolecular Michael-type addition through protonation [2]. In contrast to the reaction of **1**, the similarly structured aliphatic isothiosemicarbazones did require acidic media for the formation of bistriazoles [3]. Furthermore, one-step formation of bistriazoles from isothiosemicarbazones was possible only when the latter was treated with ethyl ethoxymethylenenitroacetate as a methine donor [3]. Accordingly, the behavior of the aliphatic diaminomethylenehydrazones **1** to produce directly bistriazoles **4** at room temperature by bringing together with **2** in benzene seems to be a characteristic feature of the aliphatic diaminomethylenehydrazone series. Thus the present paper describes a facile synthetic route to symmetrical *gem*-bis(3-dimethylamino-1,2,4-triazol-1-yl)alkanes **4** starting with some diaminomethylenehydrazones **1** of aliphatic carbonyl compounds. This paper also describes other unexpected cyclization of **1** that carries only a single methyl group on *N*(4) to 2-alkyl-5-methylamino[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate **7** upon similar treatment with **2**.

Results and Discussion.

The bistriazole formation was accomplished by allowing to stand a solution of **1** and a slight excess of **2** in benzene at room temperature for 24 hours. Preparative high performance liquid chromatography (hplc) on silica gel gave **4** in 25-54% yield as a major product, along with (3-dimethylamino-1,2,4-triazol-1-yl)alkenes **5** (Scheme 1). The bistriazoles **4**, except for **4f**, were invariably accompanied by the triazolylalkenes **5** which were formed in 2-27% yield, the increased yields of **4** being obtained with correspondingly decreased formation of **5** (Table 1). All the triazolylalkenes formed in this reaction, except for **5c**, were found to be the less substituted terminal alkenes, even though the internal alkenes would be thermodynamically more favorable. The same discussion as in the formation of *N*-alkenyl-3-alkylthio-1,2,4-triazoles with anti-Saytzeff orientation [4] may be applied to the present reaction of **1** with **2**. Highly hindered **1e** did not produce any cyclized product but yielded the precursor *N*(3)-[(2-cyano-2-ethoxycarbonyl)vinyl]amino-*N*(4),*N*(4)-dimethylaminomethylenehydrazone (**3e**) which, on brief exposure to hot acetic acid, gave **5e** in 80% yield based on the amount of **3e** used. No other *N*(3)-substituted vinylamino compounds

Table 2

Physical, Analytical and Spectroscopic Data for *gem*-Bis(3-dimethylamino-1,2,4-triazol-1-yl)alkanes **4**

Compound	Mp, °C	Formula (MW)	Elemental Analysis Calcd./(Found) C	H	N	M^+ [a]
4a	128-129	$C_{11}H_{20}N_8$ (264)	49.98 (50.02)	7.63 (7.66)	52.39 (42.15)	264 (11)
4b	68-70	$C_{12}H_{22}N_8$ (278)	51.78 (51.59)	7.97 (7.92)	40.25 (40.08)	278 (12)
4c	91-93	$C_{13}H_{24}N_8$ (292)	53.40 (53.55)	8.27 (8.35)	38.32 (38.39)	292 (7)
4d	oil	$C_{13}H_{24}N_8$ (292)	53.42 (53.51)	8.28 (8.31)	38.34 (38.25)	292 (16)
4f	88-90	$C_{11}H_{20}N_8$ (264)	49.98 (49.79)	7.63 (7.60)	42.39 (42.25)	264 (16)

[a] Relative intensities were reported in parentheses. All the base peaks correspond to ions M^+-111($C_4H_7N_4$).

that were believed to be potential intermediate to **4** and/or **5** could be detected in the reaction mixture under the reaction conditions indicated above. Thus the initial condensation product **3** should rapidly cyclize to the triazole derivatives **4** and/or **5** unless the substituents about the alkylidene carbon of **1** was significantly crowded. Aldehyde diaminomethylenehydrazone **1f** gave only **4** and this was similar tendency experienced in the aliphatic aldehyde isothiosemicarbazone [2].

Table 3

^{1}H and ^{13}C NMR Data for Products 4

Compound	^{1}H NMR (J in Hz)	^{13}C NMR ($^1J_{CH}$ in Hz) NMe$_2$	Bridging C	C-5	C-3
4 a	2.12 [s, 6H, C(CH$_3$)$_2$], 2.90 [s, 12H, N(CH$_3$)$_2$ x 2], 7.88 (s, 2H, H-5 of two triazoles)	38.46 q (136)	74.19	140.61 d (208)	166.72
4 b	0.79 (t, 3H, 7, CH$_2$C*H*$_3$), 2.02 (s, 3H, EtCC*H*$_3$), 2.49 (q, 2H, 7, C*H*$_2$CH$_3$), 2.91 [q, 12H, N(CH$_3$)$_2$ x 2], 7.89 (s, 2H, H-5 of two triazoles)	38.46 q (136)	77.41	140.95 d (208)	166.57
4 c	0.86 [t, 6H, 7, C(CH$_2$C*H*$_3$)$_2$], 2.54 [q, 4H, 7, C(C*H*$_2$CH$_3$)$_2$], 2.92 [s, 12H, N(CH$_3$)$_2$ x 2], 7.90 (s, 2H, H-5 of two triazoles]	38.43 q (136)	72.84	141.29 d (208)	161.43
4 d	0.79 [d, 6H, 7, CH(C*H*$_3$)$_2$], 2.10 (s, 3H, *i*-PrCC*H*$_3$), 2.98 [s, 12H, N(CH$_3$)$_2$ x 2], 3.20 [quin, 1H, 7, C*H*(CH$_3$)$_2$], 8.06 (s, 2H, H-5 of two triazoles)	38.46 q (136)	80.04	141.34 d (208)	166.14
4 f	0.95 (t, 3H, 7, CH$_2$C*H*$_3$), 2.49 (quin, 2H, 7, C*H*$_2$CH$_3$), 2.93 [s, 12H, N(CH$_3$)$_2$ x 2], 5.94 (t, 1H, 7.5, EtC*H*), 8.00 (s, 2H, H-5 of two triazoles)	38.41 q (137)	72.96	142.02 d (208)	166.92

Table 4

Analytical and Spectroscopic Data for (3-Dimethylamino-1,2,4-triazol-1-yl)alkenes 5

Compound [a]	Formula	Elemental Analysis Calcd./(Found) C	H	N	^{1}H NMR (J in Hz)	^{13}C NMR ($^1J_{CH}$ in Hz) =CHR^4	C-5	C-3
5 a	$C_7H_{12}N_4$	55.24 (55.35)	7.95 (7.90)	36.82 (36.75)	2.20 (dd, 3H, 1.3 and 0.5, =CCH$_3$), 3.02 [s, 6H, N(CH$_3$)$_2$], 4.66 and 5.44 (m, each 1H, =CH$_2$), 7.90 (s, 1H, H-5 of triazole)	100.49 (t, 161)	139.73 (d, 207)	166.96
5 b	$C_8H_{14}N_4$	57.80 (57.68)	8.49 (8.45)	33.71 (33.83)	1.20 (t, 3H, 7, CH$_2$C*H*$_3$), 2.55 (q, 2H, 7, C*H*$_2$-CH$_3$), 3.02 [s, 6H, N(CH$_3$)$_2$], 4.71 and 5.41 (m, each 1H, =CH$_2$), 7.91 (s, 1H, H-5 of triazole)	99.47 (t, 161)	139.68 (d, 207)	166.86
5 c	$C_9H_{16}N_4$	59.97 (59.81)	8.95 (8.91)	31.09 (31.15)	1.04 (t, 3H, 7, CH$_2$C*H*$_3$), 1.76 (d, 3H, 7, =CH-C*H*$_3$), 2.58 (q, 2H, 7, C*H*$_2$CH$_3$), 3.00 [s, 6H, N(CH$_3$)$_2$], 5.84 (q, 1H, =C*H*CH$_3$), 7.82 (s, 1H, H-5 of triazole)	99.47 (t, 161)	139.68 (d, 208)	166.86
5 d	$C_9H_{16}N_4$	59.97 (59.90)	8.95 (8.93)	31.09 (31.24)	1.17 [d, 6H, 7, CH(C*H*$_3$)$_2$], 2.92 (quin, 1H, 7, C*H*Me$_2$), 3.01 [s, 6H, N(CH$_3$)$_2$], 4.76 and 5.36 (m, each 1H, =CH$_2$), 7.91 (s, 1H, H-5 of triazole)	99.71 (t, 161)	140.27 (d, 207)	166.96
5 e	$C_{10}H_{18}N_4$	61.82 (61.73)	9.34 (9.29)	29.84 (28.93)	1.22 [s, 9H, C(CH$_3$)$_2$], 3.00 [s, 6H, N(CH$_3$)$_2$], 5.09 and 5.12 (m, each, 1H, =CH$_2$), 7.74 (s, 1H, H-5 of triazole)	108.10 (t, 161)	146.68 (d, 209)	153.47

[a] All the compounds were obtained as a colorless to light yellow oil.

As has been described in the previous papers [1-3], the formation of 1,2,4-triazole derivatives **4** and **5** from *N*(3)-substituted vinylamino compounds **3** proceeds through intramolecular nucleophilic attack of *N*(1) on the electron-deficient ethylenic linkage with loss of a cyanoacetate or malonate ester, followed by an attack with either available nucleophiles or a base on the intermedially generated cation **6**. Protonation of **3**, probably on *N*(2), was the essential step to activate the ethylenic linkage on *N*(3) toward the Michael-type addition.

In contrast, the diaminomethylenehydrazones of aliphatic carbonyl compounds **1** employed in the present work gave the 1,2,4-triazole derivatives **4** and **5** apparently in one-step upon treatment with **2**. Neither acidic media nor heating were needed. Although extensive attempts to improve the yield of both products have not yet been made, the present reaction provides a facile route to bistriazoles and a further example of cycloalkenylation [4]. The easy cyclization with loss of ethyl cyanoacetate can be ascribed to the greater nucleophilicity of *N*(1) than that of diaminomethylenehydrazones of aromatic carbonyl compounds. Thus the ethylenic carbon on *N*(3) should have sufficient electrophilicity by virtue of the two electron-withdrawing groups to be attacked by *N*(1) without need to activate through protonation.

In contrast to the behavior of **1a-1f**, an *N*(4)-monomethyl homologue **1g** of **1c** produced a 2-ethyl[1,2,4]triazolo[1,5-*c*]pyrimidine derivative **7** (R^1 = Et) by similar treatment with **2** (Scheme 1). The apparently direct cyclization to **7** starting with **1g** and **2** can be explained as a sequential stepwise process involving cyclization of the initial open-chain product like **3** in which the dimethylamino group is replaced by a methylamino group to ethyl 2,2-diethyl-5-methylamino-2,3-dihydro[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate, followed by elimination of R^2H from the precursor. The 2,3-dihydrotriazolopyrimidine precursor could only be identified spectroscopically and was easily converted to **7** upon exposure to heat as encountered in the recrystallization to purify it. No triazole formation was observed in this case.

The structural assignments of the new heterocycles **4**, **5** and **7** were accomplished on the basis of the appropriate spectral data and the elemental analyses (Tables 2-4) according to the procedure reported previously [1,3,4].

Tables 2-4

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The ^1H and ^{13}C nmr spectra were determined in deuteriochloroform solution on a JNM-FX90Q spectrometer operating at 89.55 and 22.50 MHz, respectively. The chemical shift values are reported in parts per million on the δ scale with tetramethylsilane as the internal reference. The mass spectra (75 eV) were recorded on a JEOl JMS D100 mass spectrometer. 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.

N(4),*N*(4)-Dimethyldiaminomethylenehydrazones **1a-1f** and *N*(4)-monomethyldiaminomethylenehydrazone **1g** were prepared according to the literature method [5] and found to exist as an isomeric mixture [6], with one component usually predominating. All the products were obtained as a light yellow oil in 66-95% yield and employed without separation of the major component. The chemical shifts of ^1H nmr of the major component were reported in Table 5.

Typical Example for the Preparation of Bis(3-dimethylamino-1,2,4-triazol-1-yl)alkanes **4** and (3-Dimethylamino-1,2,4-triazol-1-yl)alkenes **5**.

A solution of **1a** (0.28 g, 2 mmoles) and **2** (0.41 g, 2.4 mmoles) in benzene (2 ml) was allowed to stand at room temperature for 24 hours. The reaction mixture was evaporated under reduced pressure to give a light yellow oil. The oil was subjected to preparative hplc on silica gel with chloroform as an eluent to give two major fractions [7]. The higher Rf fraction gave spectroscopically pure **5a** (0.08 g, 27%) and lower Rf one gave pure **4a** (0.13 g, 25%). Analytical and spectroscopic data for these products and other compounds similarly obtained were shown in Tables 2-4.

Ethyl 2-Ethyl-5-methylamino[1,2,4]triazolo[1,5-*c*]pyrimidine-8-carboxylate (**7**).

A mixture of **1g** (0.31 g, 2 mmoles) and **2** (0.41 g, 2.4 mmoles) in benzene (2 ml) was allowed to stand at room temperature for 20

Table 5

^1H NMR Data for Diaminomethylenehydrazones **1**

Compound	^1H NMR (J in Hz)
1a	1.96 and 2.03 [s, each 3H, $=C(CH_3)_2$], 2.95 [s, 6H, $N(CH_3)_2$], 4.86 (bs, 2H, NH_2)
1b	1.08 (t, 3H, 7, CH_2CH_3), 2.00 (s, 3H, $=CCH_3$), 2.24 (q, 2H, 7, CH_2CH_3), 2.90 [s, 6H, $N(CH_3)_2$], 4.92 (bs, 2H, NH_2)
1c	1.06 and 1.09 (t, each 3H, 7, CH_2CH_3 x 2), 2.23 and 2.50 (q, each 2H, 7, CH_2CH_3 x 2), 2.91 [s, 6H, $N(CH_3)_2$], 4.90 (bs, 2H, NH_2)
1d	1.07 [d, 6H, 7, $CH(CH_3)_2$], 1.93 (s, 3H, $=CCH_3$), 2.47 [quin, 1H, 7, $CH(CH_3)_2$], 2.88 [s, 6H, $N(CH_3)_2$], 4.98 (bs, 2H, NH_2)
1e	1.12 [s, 9H, $C(CH_3)_3$], 1.98 (s, 3H, $=CCH_3$), 2.89 [s, 6H, $N(CH_3)_2$], 5.00 (bs, 2H, NH_2)
1f	1.07 (t, 3H, 7, CH_2CH_3), 2.28 (m, 2H, CH_2CH_3), 2.93 [s, 6H, $N(CH_3)_2$], 5.00 (bs, 2H, NH_2), 7.70 (t, 1H, 5, EtCH)
1g	1.05 and 1.18 (t, each 3H, 7, CH_2CH_3 x 2), 2.22 and 2.48 (q, each 2H, 7, CH_2CH_3 x 2), 2.80 (s, 3H, NCH_3), 4.35 (bs, 3H, $HNCNH_2$)

hours and then evaporated under reduced pressure. The residual solid, after being washed with a hexane-2-propanol mixture (1:1 v/v), was recrystallized from the same solvent mixture to give yellow needles, mp 185-187°, 0.34 g (68%). Further recrystallization from 2-propanol gave light yellow needles, mp 187-188°; ir (potassium bromide): 3350 (NH), 1712 (C=O) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide, TMS): δ 1.30 and 1.32 (t, each 3H, J = 7 Hz, CH_2CH_3 x 2), 2.85 (q, 2H, J = 7 Hz, CCH_2CH_3), 3.04 (d, 3H, J = 6 Hz, $NHCH_3$), 4.28 (q, 2H, J = 7 Hz, OCH_2), 8.51 (s, 1H, H-7), 8.72 (poorly resolved bq, 1H, J = *ca.* 6 Hz, $NHCH_3$); ms: m/e (relative intensity) 249 (39) M^+, 177 (100) M^+-$CO_2C_2H_4$.

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10 (MW 249). Found: C, 52.87; H, 6.06; N, 27.95.

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[6] The configuration of *N*(1)=C and *N*(2)=C bonds was determined on the basis of steric compression shift phenomenone of the appropriate alkyl carbons about these bonds: see F. W. Wehrli and T. Wirthlin, "Interpretation of Carbon-13 NMR Spectra", Heyden & Son Inc., London, 1978, p 187.

[7] Ethyl cyanoacetate was always recovered as a minor fraction.