Cyclization of Isothiosemicarbazones. Part 8.[1] Formation and Structure of gem-Bis(3-alkylthio-1H-1,2,4-triazol-1-yl)alkanes and Related Compounds

Chiji Yamazaki,* Toshie Takahashi, and Kumiko Hata
Department of Chemistry, School of Hygienic Sciences, Kitasato University, Kitasato, Sagamihara, Kanagawa 228, Japan

Symmetrical gem-bis(3-alkylthio-1H-1,2,4-triazol-1-yl)alkanes (6) are directly obtained by the reaction of aliphatic ketone isothiosemicarbazones (1) with ethyl ethoxymethylenenitroacetate (2) as a methine donor in aqueous formic acid. Aldehyde isothiosemicarbazones indirectly give both symmetrical and unsymmetrical terminal gem-bis(triazolyl)alkanes, after conversion into the 4-[2,2-bis(ethoxycarbonyl)vinyl]-3-alkylisothiosemicarbazones (5) and exposure to aqueous acidic media, with the former being the major product. Electronic and steric factors in the starting isothiosemicarbazones exert a marked influence on the yield of bis(triazolyl)alkanes. Two unsymmetrical bis(azole)s are obtained through these reactions, one in which the two triazole rings are linked together by the different nitrogens, and the other, which carries a different substituent on each sulphur in two azole rings, the latter being obtained through the cross-reaction between differently substituted isothiosemicarbazones. The gem-bis(azole) formation may involve nucleophilic attack of 4-(substituted vinyl)isothiosemicarbazone (4) or (5) on an intermedially formed iminium cation (14) as the key step, followed by intramolecular cyclization of the resulting oxonium ion.

Bis(azolyl)alkanes have been prepared by connecting two azole rings at the nitrogen or carbon atom by a reaction with a bifunctional compound,[2] in some cases with appropriate modifications of the precursor to the final products.[3] They have also been obtained through simultaneous formation of two azole rings on an appropriately structured linear molecule.[4] A number of recent reports[5] dealing with the preparation of bis-(azole)s fall under these categories of synthetic route.

In the course of a study[1] on the preparation of N-alkenyl-1,2,4-triazoles (10), we found that a diester (5i), upon exposure to non-aqueous acidic media, yielded a mixture consisting of alkenyltriazole (10d) and bis(triazole) (6i) and that the latter compound was invariably a major component. In general, however, cyclization of diesters (5) in a non-aqueous acidic medium gave N-alkenyl-1,2,4-triazole derivatives as the major product and did not produce any bis(triazole) under such conditions. After attempts to direct the reaction of diesters (5) to the formation of bis(triazole)s with inhibition of the N-alkenylation reaction, it was found that an acidic medium containing an appropriate amount of water was effective in controlling alkenyltriazole formation and favourable to the bis(triazole) formation. However, when some of the simple diesters (5) were subjected to the cyclization conditions under which the bis(azole) formation was most favourable, the yields of the corresponding bis(azole)s (6) remained unacceptably low.

Recently, we reported that N-alkenyl-1,2,4-triazoles could be obtained in good yield by the direct cycloalkenylation[1] of N(4)-unsubstituted isothiosemicarbazones (1) with ethyl ethoxymethylenenitroacetate (ethyl β-ethoxy-α-nitroacrylate) (2). Our interest in the one-step formation of bis(triazole)s led us to investigate further the application of nitroacrylate (2) as a methine donor in order to realize an efficient, novel route to bis(1,2,4-triazole)s. Thus the present paper describes a one-step synthesis of the gem-bis(3-alkylthio-1H-1,2,4-triazol-1-yl)-alkanes (6) and related compounds from N(4)-unsubstituted isothiosemicarbazones (1) and presents a reaction mechanism for the bis(azole) formation.

Results and Discussion

The reaction of acetone S-methylisothiosemicarbazone (1a) with nitroacrylate (2) was performed by heating an equimolar

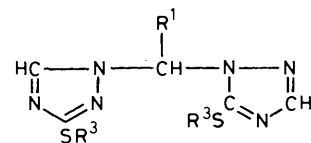|	R¹	R²	R³
a;	Me	Me	Me
b;	Me	Me	Et
c;	Me	Me	p-ClC₆H₄CH₂
d;	Me	Et	Me
e;	Me	Pr^i	Me
f;	Me	Bu^t	Me
g;	-[CH₂]₄-		Me
h;	-[CH₂]₅-		Me
i;	Me	H	Me
j;	Et	H	Me

Scheme 1.

mixture of these reactants in 50% v/v aqueous formic acid at 70 °C. After neutralization and extraction of the reaction mixture, a crude product consisting of bis(triazole) (6a), nitro-acetate (7a), and unchanged isothiosemicarbazone (1a) was obtained. The incomplete reaction of isothiosemicarbazone (1a) was ascribed to the instability of nitroacrylate (2) under these conditions which caused relatively quick decomposition of nitroacrylate (2) to nitroacetate (7a) and some unidentifiable products. Introduction of an additional amount of nitroacrylate (2) with appropriate intervals resulted in a slight improvement in the yield of bis(triazole) (6a) from 79.6% under the former conditions to 83.3%.* This procedure using an excess of nitro-acrylate (2) invariably gave better results than those obtained from the use of an equimolecular proportion of nitroacrylate (2), thereby representing the standard method of the one-step synthesis of bis(triazole)s (6) from isothiosemicarbazones (1).

The bis(triazolyl)alkane formation was highly susceptible to the steric effect of the substituents on the ketonic carbon of compounds (1) that became the bridging carbon in the final bis-(triazole). Thus significant reduction in the yield of bis(triazole) (6) was noted upon changing R^2 from Et (1d) (82%), though Pr^i (1e) (65%), to Bu^t (1f) (7%). A similar effect was observed from a comparison of the yields of bis(triazole)s (6a—c) in which R^3 was changed from Me, through Et, to p-chlorobenzyl. Un-expectedly, isothiosemicarbazones (1i) and (1j) which were derived from an aldehyde gave a highly complex mixture from which the desired bis(triazole) could not be separated. Ring size may present another factor that influences the yield of bis-(triazole) (6) when cycloalkanone isothiosemicarbazones (1g) and (1h) are used. The lower yield of bis(triazole) (6g) can be ascribed to its strong tendency to produce the corresponding N-alkenyltriazole derivative (11).

The preparation of compounds (6i) and (6j) could be accomplished by converting aldehyde isothiosemicarbazones (1i) and (1j) into the corresponding diesters (5) and exposing these diesters to an aqueous acid medium, with the overall yields calculated on the amount of the starting materials (1) initially used for preparation of diester (5) amounting to 26—31%. When this procedure was applied to isothiosemi-carbazones (1a—e), except for (1c), the overall yields similarly calculated from the amount of isothiosemicarbazone (1) of the corresponding compound (6) fell into a much lower range (29—35%) than the yields for the standard procedure (65—83%). The highly hindered product (6f) could not be obtained from diester (5f) by this method. The cyclization of diesters (5i) and (5j) to the corresponding bis(triazole)s (6) was invariably accompanied by the formation of unsymmetrical bis(triazole)s (8a) and (8b) as minor products (8—11% yields).

As was suggested in the previous paper,[1,6b] triazole ring formation through a 4-(substituted vinyl)isothiosemicarbazone (4) or (5) should involve an iminium cation (14) as a potential intermediate. Various interactions between the cation and any nucleophile or base available in the reaction mixture can produce different products, such as bis(triazole)s (6), (8), and (9), N-alkenyltriazoles (10),[6b] 3-alkylthio-1H-1,2,4-triazoles (12), and 2(3)-(3-alkylthio-1H-1,2,4-triazole-1-yl)alkan-2(3)-yl acylates (13).[1] In the standard procedure for preparation of compounds (6), the presence of water is essential to prevent the formation of N-alkenyltriazoles (10) which are produced through abstraction of the alpha-hydrogen from the iminium cation (14) by a base. Water should function to prevent the abstraction process by stabilizing the base through hydration but should not prevent the formation of the iminium cation (14), thereby successfully directing the reaction to formation of the bis(triazole). If a large excess of water is present, the interaction
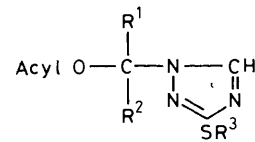

(8) a; $R^1 = R^3 = Me$

b; $R^1 = Et, R^3 = Me$
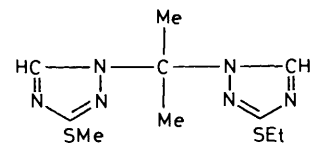
(9)
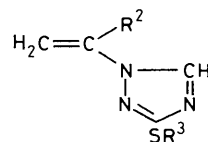
(10) a; $R^2 = R^3 = Me$

b; $R^2 = Me, R^3 = Et$

c; $R^2 = Bu^t, R^3 = Me$

d; $R^2 = H, R^3 = Me$
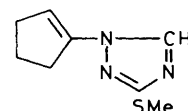
(11)
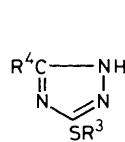
(12)

(13)

between the cation (14) and water molecule might predominate. When the cationic centre accepts a water molecule, an oxonium ion (19)† is produced and this can break down to triazole (12) and a ketone ($R^1R^2C=O$). Substitution of acetic for formic acid resulted in contamination of bis(triazole) (6) with compounds (13; Acyl = Ac).

Bis(triazole)s have a structure formally formed by nucleo-philic attack of 1H-triazole (12) on an alkenyltriazole (10) or an iminium ion (14), which are the possible species in the reaction mixture. When diester (5a) was subjected to the cyclization conditions in the presence of compound (12; $R^3 = Me$, $R^4 = Et$), no incorporation of the 5-ethyl structure originating from compound (12) into the bis(triazole) product was observed, with the triazole (12) remaining totally unchanged. Furthermore, unsymmetrical bis(triazole) (9) was obtained from a cross-reaction between two isothiosemicarbazones (1a) and (1b) under the standard reaction conditions but not from the reaction of isothiosemicarbazone (1b) in the presence of compound (12; $R^3 = Me$, $R^4 = H$). The same cross-reaction product could also be obtained by the reaction between two diesters (5a) and (5b) in an acidic medium. Thus, the probable

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† The oxonium ion produced from the cation (14) and a water molecule is represented by the formula
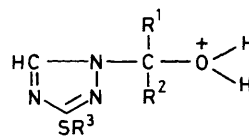
(19)

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* The yields reported in this paper refer to those of purified compounds after chromatography.

nucleophile that attacks the cation (14) may be compound (4)*
or (5). Consequently, the formation of bis(triazole) from N(4)-
unsubstituted isothiosemicarbazone (1) may be depicted as in
Schemes 1 and 3. The reaction may be initiated by nucleophilic
attack of N-1 of 4-(substituted vinyl)isothiosemicarbazone (4)
or (5) on the positive centre of iminium ion (14) to form a
cationic species (17). A water molecule reacts with the cationic
carbon of the newly formed iminium ion (17) to generate an
oxonium ion (18), which may then cyclize intramolecularly
through a sequential S_N2-like mechanism by the attack of N-1
on the methine carbon of the electron-deficient ethylenic linkage
bonded to the electron-withdrawing groups Y and CO_2Et. The
carbonyl component $R^1R^2C=O$ cleaved in the cyclization
step could be identified if it was non-volatile. Thus elimination
of a ketone and an ester (7) from an oxonium ion (18) produces
a bis(triazole) (6).

The steric or electronic effects of R^1 and/or R^2 on the
formation of bis(triazole) (6) can be explained by mechanistic
considerations. A bulky group on the alkylidene carbon of 4-
(substituted vinyl)isothiosemicarbazone (4) or (5) obviously
prevents nucleophilic attack of compound (4) or (5) on the
iminium cation (14) which is also hindered about the cationic
centre. An electron-withdrawing group on the alkylidene
carbon is also unfavourable to the same reaction due to a
decrease in the nucleophilicity of N-1 of compound (4) or (5).
Thus isothiosemicarbazones (1), in which R^1 was an electron-
withdrawing group, such as phenyl or trifluoromethyl, gave
no product (6). The ring size of cycloalkanone isothiosemi-
carbazones (1g) and (1h) offers another factor with regard to the
stereochemistry of the corresponding iminium cations (14g) and
(14h). The six-membered carbonium ion (14h) allows an easier
approach of the ester (4h) to the less hindered positive centre
where the two equatorial alpha-hydrogens and the cationic
carbon are coplanar than does the five-membered cation (14g)
where the four alpha-hydrogens are all axial. The abstraction of
the alpha-hydrogen in the cation (14g) may thus predominate
over the nucleophilic attack on the positive carbon, leading to
the major production of the N-cyclopentenyltriazole (11).

(14) ⟶ (15) ⟶ (16)

Scheme 2.
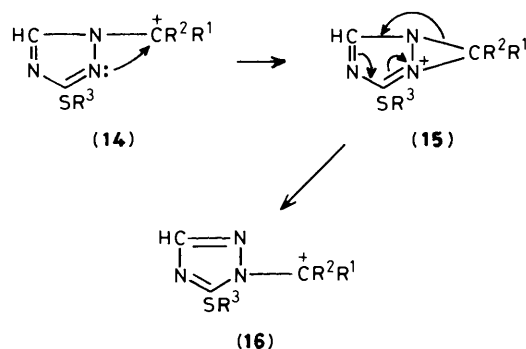
The formation of isomeric unsymmetrical bis(triazole)s (8a)
and (8b) may be explained as a result of the rearrangement of
the respective iminium ions (14i) and (14j) rather than the
tautomeric interconversion of compound (12), because the

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*Although the ester (4) has not been isolated in the present
work, benzaldehyde 4-[2-(ethoxycarbonyl)-2-nitrovinyl]-3-methyliso-
thiosemicarbazone (4; R^1 = Ph, R^2 = H, R^3 = Me) was isolated and
identified in previous work, and therefore, also by analogy with the
previous work,[6a] the initial product of the reaction between isothio-
semicarbazone (1) and nitroacrylate (2) should be compound (4)
(Scheme 1).

Scheme 3.
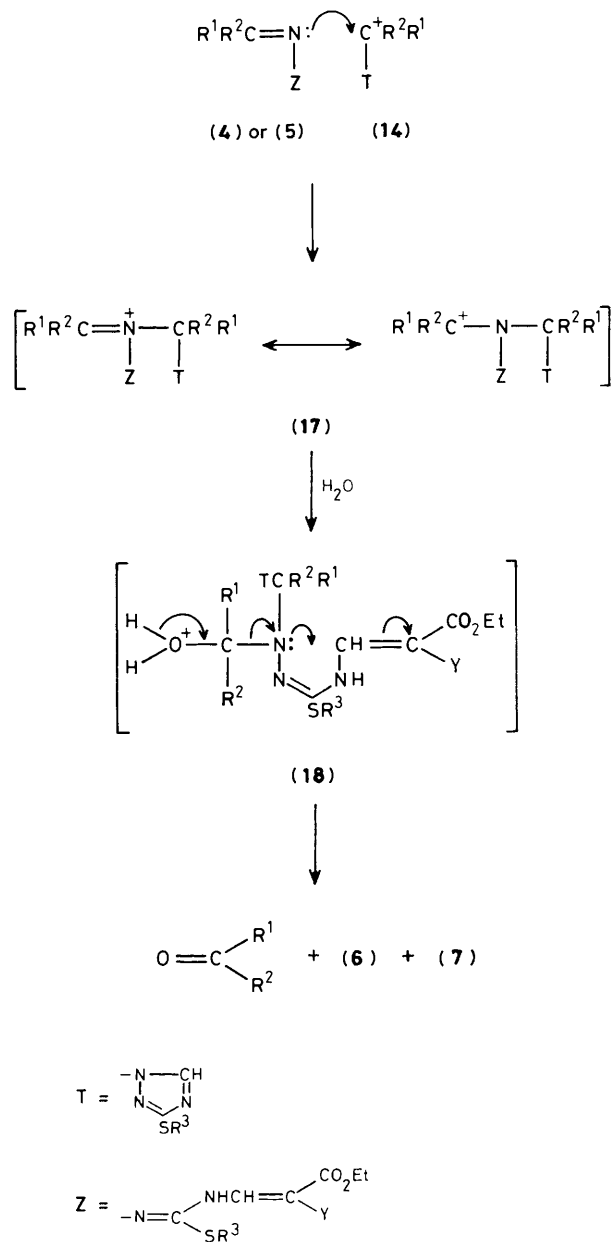
possibility that triazole (12) is a precursor to the bis(triazole)
can be ruled out. The iminium ions (14i) and (14j) are second-
ary carbocations and a better acceptor for electrons than those
which are generated from ketone isothiosemicarbazones and
should thus be tertiary cations. Thus the secondary cation may
partially rearrange to another ion (16) through a cyclic
structure (15) formed by acceptance of the lone electron pair on
N-2 (Scheme 2). If diester (5i) or (5j) attacks the rearranged
cation (16) as in Scheme 3, then the unsymmetrical bis(triazole)s
(8) result.

The symmetrical structure of bis(triazole)s (6) was sup-
ported by the presence of two equivalent triazole rings in a
molecule as evidenced by the ^{1}H and ^{13}C n.m.r. spectra. The
resonances of ring carbons C-3 and C-5 were observed with
appropriate multiplicity in the ranges δ_C 162—163 and 142—
144 p.p.m., respectively. The resonances from each respective
carbon of the two triazole rings completely overlapped to form a

single resonance and thus each set of carbons C-3 and C-5 should magnetically be equivalent. Furthermore, the resonances from ring protons 5-H (δ_H 8.15—8.41) and from SMe protons (δ_H 2.55—2.57) appeared as a sharp singlet corresponding to two-proton and six-proton intensities, respectively, also indicating the presence of two equivalent rings in compounds (6). The resonance of ring carbons C-5 appeared as a doublet with a large coupling constant ($^1J_{CH}$ 212 Hz). This n.m.r. spectroscopic behaviour indicates that the azolyl groups were bonded to the bridging carbon at position 1.[1] Further support on the bis(triazole) structure of compounds (6) was obtained from the mass spectra. The most important fragmentation of compounds (6) was the bond cleavage between N-1 of the triazole ring and the bridging carbon and produced an abundant fragment ion, an iminium-like ion, with relative intensities >85%.

The unsymmetrical bis(triazole)s (8a) and (8b) exhibited two sets of resonances arising from two non-equivalent triazole rings. The chemical-shift values of the ^1H and ^{13}C n.m.r. spectra for the one ring were consistent with the range characteristic of 3-methylthio-1H-1,2,4-triazol-1-yl structures. The proton-bearing carbon (C-5') on the triazol-1-yl group was coupled with a proton on the bridging carbon to split each component of the doublet ($^1J_{CH}$ 212 Hz) into a small doublet ($^3J_{CH}$ 2.7 Hz) and it thus appeared as a double doublet. This long-range coupling was observed in both symmetrical and unsymmetrical bis-(triazole)s and is believed to be characteristic of the triazol-1-yl structure as long as the bridging carbon carries a hydrogen atom [compounds (6i) and (6j), (8a) and (8b)]. On the other hand, the chemical-shift values for another triazole ring [δ_H 2.72 (SMe), 7.90 (ring proton); δ_C 152 and 154 p.p.m. (ring carbons)] evidently arise from different structure ('triazol-2-yl' or 'tri-azol-4-yl').* The proton-bearing carbon exhibited only one-bond coupling ($^1J_{CH}$ 209 Hz) to form a simple doublet. If the new ring in compounds (8a) and (8b) was that of the 3-methylthio-1,2,4-triazol-4-yl group, there would occur three-bond coupling to form a double doublet because the same circumstances as occur in the triazol-1-yl group would occur here. Consequently, the new triazole ring in the unsymmetrical bis(triazole)s should have a 5-methylthio-1,2,4-triazol-1-yl structure where the proton-bearing carbon (C-3") was separated from the proton on the bridging carbon via four or five bonds, thereby exhibiting much small coupling ($^4J_{CH}$ 0 Hz) than the $^3J_{CH}$ value.[7] Another differentiation between the two rings in compounds (8) comes from the unique long-range coupling that was observed only in the rearranged triazole ring and which splits the ring proton (3"-H) into a doublet ($^5J_{HH}$ 0.77 Hz). The decoupling technique confirmed that the spin–spin coupling occurred between the ring proton and the proton on the bridging carbon. The 5-methylthio group on the rearranged ring may stabilize the planar zig-zag conformation involving the coupled protons. The mass spectra of compounds (8) were identical with those of the corresponding symmetrical compounds (6) and therefore did not serve for differentiation.

The structure of the cross-reaction product (9) was supported by the appropriate ^1H and ^{13}C n.m.r. spectra arising from two differently substituted triazole rings. This unsymmetrical bis-(triazole) (9) could be further characterized by the molecular ion peak (M^+, m/z 284) and two prominent fragment ions m/z 156 (100%) and m/z 170 (90%) formed by the cleavage of the C-N bonds between the bridging carbon and the ring nitrogens. The results of the mass spectrum and the elemental analysis of compound (9) present confirmation of the homogeneity of the compound by showing the product not to be an equimolar mixture of the symmetrical compounds (6a) and (6b).

* The numbering was tentatively based on the ring system of the symmetrical compounds.

Experimental

E,E-4-*Unsubstituted Isothiosemicarbazones.*—Isothiosemi-carbazones (1a—j) were obtained according to the literature method.[6b,c] New compounds are as follows.

(1f) (75.7%), *plates*, m.p. 59—60 °C (from hexane) (Found: C, 51.25; H, 9.1; N, 22.4. $C_8H_{17}N_3S$ requires C, 51.3; H, 9.15; N, 22.4%).

(1g) (86.3%), *prisms* (turned a light brown colour within one week at ambient temperature), m.p. 61.5—62.5 °C (from hexane) (Found: C, 49.0; H, 7.5; N, 24.7. $C_7H_{13}N_3S$ requires C, 49.1; H, 7.65; N, 24.55%).

4-[2,2-*Bis*(*ethoxycarbonyl*)*vinyl*]-3-*alkylisothiosemi-carbazones.*—Compounds (5a), (5b), (5i), and (5j) were obtained according to the literature procedure.[6b] New compounds are as follows.

(5a) (96%), *needles*, m.p. 63—64 °C (from hexane) (Found: C, 49.6; H, 6.8; N, 13.5. $C_{13}H_{21}N_3O_4S$ requires C, 49.5; H, 6.7; N, 13.3%); $\nu_{max.}$(CCl₄) 3 215 (NH), 1 727 (CO), and 1 704 cm⁻¹ (CO); δ_H 1.32 and 1.36 (each 3 H, t, J 7.3 Hz, together CH_2Me), 2.09 and 2.12 (each 3 H, s, together $=CMe_2$), 2.51 (3 H, s, SMe), 4.24 and 4.32 (each 2 H, q, J 7.3 Hz, together CH_2Me), 8.23 (1 H, d, J 13.6 Hz, NHCH=), and 11.76 (1 H, d, J 13.6 Hz, NHCH=).

(5b) (57%), *plates*, m.p. 45—48 °C (from hexane) (Found: C, 51.0; H, 7.0; N, 12.8. $C_{14}H_{23}N_3O_4S$ requires C, 51.05; H, 7.0; N, 12.8%); $\nu_{max.}$(CCl₄) 3 218 (NH), 1 727 (CO), and 1 704 cm⁻¹ (CO); δ_H 1.32 and 1.36 (each 3 H, t, J 7.3 Hz, together OCH₂Me), 1.39 (3 H, t, J 7.3 Hz, SCH₂Me), 2.08 and 2.12 (each 3 H, s, together $=CMe_2$), 3.13 (2 H, q, J 7.3 Hz, SCH_2Me), 4.23 and 4.31 (each 2 H, q, J 7.3 Hz, together OCH_2Me), 8.23 (1 H, d, J 13.8 Hz, NHCH=), and 11.75 (1 H, d, J 13.8 Hz, NHCH=).

(5j) (48%), *light yellow plates*, m.p. 59—61 °C (from hexane) (Found: C, 49.3; H, 6.7; N, 13.5. $C_{13}H_{21}N_3O_4S$ requires C, 49.5; H, 6.7; N, 13.3%); $\nu_{max.}$(CCl₄) 3 209 (NH), 1 725 (CO), and 1 700 cm⁻¹ (CO); δ_H 1.20 (3 H, t, J 7.6 Hz, =CHCH₂Me), 1.32 and 1.37 (each 3 H, t, J 7.3 Hz, together OCH₂Me), 2.47 (2 H, dq, J 5.0 and 7.0 Hz, =CHCH_2Me), 2.51 (3 H, s, SMe), 4.24 and 4.32 (each 2 H, q, J 7.3 Hz, together OCH_2Me), 7.87 (1 H, t, J 5.0 Hz, =CHCH₂), 8.22 (1 H, d, J 13.6 Hz, NHCH=), and 11.87 (1 H, d, J 13.6 Hz, NHCH=).

Preparation of 2,2-*Bis*(3-*methylthio*-1H-1,2,4-*triazol*-1-*yl*)-*propane* (6a).—*General procedure for cyclization of ketone isothiosemicarbazones* (1a—h). A mixture of compound (1a) (0.2 g, 1.38 mmol), nitroacrylate (2) (0.26 g, 1.38 mmol) (a 1:2 E/Z mixture, b.p. 163 °C/8 mmHg),[8] and aqueous formic acid (50% v/v) (0.2 ml) was heated at 70 °C. After 30 min, an additional amount of nitroacrylate (2) (0.26 g, 1.38 mmol) was added and the mixture was heated for a further 1 h. The reaction mixture was neutralized with aqueous sodium carbonate (20%) and extracted with chloroform (10 ml × 3). The combined extracts were washed with water, dried, and evaporated to give a solid residue (0.26 g) consisting of bis(triazole) (6a), starting material (1a), and compound (10a) in the molar proportions 5.75:1.03:1.00. Preparative h.p.l.c. on silica gel with chloroform

as eluant yielded *bis(triazole)* (**6a**) (0.155 g, 83.3%) as prisms, m.p. 151—152 °C (from EtOH–Pr^{i}OH, 1:1, v/v) (Found: C, 39.9; H, 5.2; N, 31.1. $C_9H_{14}N_6S_2$ requires C, 40.0; H, 5.2; N, 31.1%); $\lambda_{max.}$ 205 and 241 nm (ε 13 100 and 7 900); δ_H 2.28 (6 H, s, CMe$_2$), 2.55 (6 H, s, 2 × SMe), and 8.19 (2 H, s, 5-H of two triazoles); δ_C 26.99 [q, $^1J_{CH}$ 130.9 Hz (each component split into a quartet, $^3J_{CH}$ 3.9 Hz), C*Me*$_2$], 75.33 (dq, $^2J_{CH}$ = $^3J_{CH}$ = 4.4 Hz, *C*Me$_2$), 142.29 (d, $^1J_{CH}$ 211.7 Hz, C-5 of two triazoles), and 162.67 (dq, $^3J_{CH}$ 4.4 and 13.2 Hz, C-3 of two triazoles); *m/z* 270 (M^+, 22%) and 156 (M^+ − 114, 100), A small amount (14 mg, 6.5%) of compound (**10a**) was isolated and characterized according to the literature method.[1] Compound (**6a**) was also obtained from ester (**5a**), according to the general procedure for the preparation of compound (**6i**) (*vide infra*), in 37% yield based on the amount of (**5a**) used. The following new bis-(triazolyl)alkanes were similarly prepared.

(**6b**) (75.8%), *large prisms*, m.p. 118—119 °C (from EtOH) (Found: C, 44.25; H, 6.1; N, 28.3. $C_{11}H_{18}N_6S_2$ requires C, 44.3; H, 6.1; N, 28.2%); $\lambda_{max.}$ 205 and 242 nm (ε 13 200 and 8 300); δ_H 1.36 (6 H, t, *J* 7.3 Hz, 2 × SCH$_2$Me), 2.29 (6 H, s, CMe$_2$), 3.10 (4 H, q, *J* 7.3 Hz, 2 × SCH$_2$), and 8.18 (2 H, s, 5-H of two triazoles); δ_C 26.94 [q, each component split into a quartet, $^1J_{CH}$ 130.9, $^3J_{CH}$ 4.4 Hz, C*Me*$_2$], 75.28 (dq, $^2J_{CH}$ = $^3J_{CH}$ = 4.4 Hz, *C*Me$_2$), 142.22 (d, $^1J_{CH}$ 211.7 Hz, C-5 of two triazoles), and 161.87 (dt, $^3J_{CH}$ 4.9 and 13.7 Hz, C-3 of two triazoles); *m/z* 298 (M^+, 12%) and 170 (M^+ − 114, 100). Compound (**6b**) was also obtained from ester (**5b**), in the same manner as in the preparation of compound (**6i**), in 60% yield based on amount of (**5b**) used.

(**6c**) (4.3%), *prisms*, m.p. 115—116 °C (from EtOH) (Found: C, 51.3; H, 4.1; N, 17.1. $C_{21}H_{20}Cl_2N_6S_2$ requires C, 51.3; H, 4.1; N, 17.1%); $\lambda_{max.}$ 202, 223, and 245sh nm (ε 36 300, 30 200, and 8 000); δ_H 2.24 (6 H, s, CMe$_2$), 4.23 (4 H, s, 2 × SCH$_2$), 7.23 (8 H, s, 2 × *p*-ClC$_6$H$_4$), and 8.15 (2 H, s, 5-H of two triazoles); δ_C 26.89 (q, $^1J_{CH}$ 131 Hz, C*Me*$_2$),* 35.58 (t, $^1J_{CH}$ 142 Hz, 2 × SCH$_2$), 75.54 (*C*Me$_2$), 142.24 (d, $^1J_{CH}$ 211.7 Hz, C-5 of two triazoles), and 161.18 (m, C-3 of two triazoles); *m/z* 490 (M^+, 3.7%), 266 (M^+ − C$_2$HN$_3$SCH$_2$C$_6$H$_4$Cl, 90), and 125 (C$_7$H$_6$Cl, 100).

(**6d**) (82.4%), *needles*, m.p. 106—107 °C (from EtOH–Pr^{i}OH, 2:1, v/v) (Found: C, 42.3; H, 5.7; N, 29.4. $C_{10}H_{16}N_6S_2$ requires C, 42.25; H, 5.7; N, 29.6%); $\lambda_{max.}$ 205 and 242 nm (ε 15 100 and 8 600); δ_H 0.94 (3 H, t, *J* 7.5 Hz, CH$_2$Me), 2.24 (3 H, s, EtC*Me*), 2.55 (6 H, s, 2 × SMe), 2.66 (2 H, q, *J* 7.5 Hz, C*H*$_2$Me), and 8.21 (2 H, s, 5-H of two triazoles); δ_C 78.55 (*C*MeEt),† 142.63 (d, $^1J_{CH}$ 211.7 Hz. C-5 of two triazoles), and 162.50 (dq, $^3J_{CH}$ 4.9 and 13.2 Hz, C-3 of two triazoles); *m/z* 284 (M^+, 15%) and 170 (M^+ − 114, 100). This compound was also obtained when a solution of the ester (**5d**) in 93% v/v aqueous acetic acid was heated at 70 °C for 2 h. Similar work-up to the standard procedure gave the bis-(triazole) (**6d**) in 30% yield based on (**5d**) used. When the ester (**5d**) (0.2 g) was heated in 62.5% v/v acetic acid (0.8 ml) at the same temperature and, after evaporation, the residue was washed with hexane to remove diethyl malonate (**7b**), 3-methyl-thio-1*H*-1,2,4-triazole (**12**; R^4 = H) crystallized (0.063 g, 90%), m.p. 101–102 °C (from CCl$_4$), not depressed on admixture with the authentic compound.[9]

(**6e**) (65.0%), *needles*, m.p. 118—119 °C (from Pr^{i}OH) (Found: C, 44.2; H, 6.1; N, 28.3. $C_{11}H_{18}N_6S_2$ requires C, 44.3; H, 6.1; N. 28.2%); $\lambda_{max.}$ 206 and 243 nm (ε 12 000 and 8 100); δ_H 0.88 (6 H, d, *J* 6.8 Hz, CHMe$_2$), 2.21 (3 H, s, Pr^{i}C*Me*), 2.56 (6 H, s, 2 × SMe), 3.32 (1 H, quin., *J* 6.8 Hz, C*H*Me$_2$), and 8.36

(2 H, s, 5-H of two triazoles); δ_C 14.37 (q, $^1J_{CH}$ 141.3 Hz, SMe), 16.59 (q, each component split into a multiplet, $^1J_{CH}$ *ca.* 131 Hz, Pr^{i}C*Me*), 16.79 (q, each component split into a multiplet, $^1J_{CH}$ *ca.* 131 Hz, CH*Me*$_2$), 36.48 (d, $^1J_{CH}$ 130 Hz, C*H*Me$_2$), 81.41 (m, Pr^i*C*Me), 143.05 (d, $^1J_{CH}$ 211.7 Hz, C-5 of two triazoles), and 161.96 (dq, $^3J_{CH}$ 4.9 and 13.2 Hz, C-3 of two triazoles); *m/z* 298 (M^+, 23%) and 184 (M^+ − 114, 100). Compound (**6e**) was also obtained from ester (**5e**), in the same manner as in the preparation of compound (**6i**), using 86% aqueous acetic acid in 33% yield ‡ based on the ester (**5e**) used.

(**6f**) (7.2%), *prisms*, m.p. 91—92 °C (from Pr^{i}OH) (Found: C, 46.15; H, 6.4; N, 27.0. $C_{12}H_{20}N_6S_2$ requires C, 46.1; H, 6.45; N, 26.9%); $\lambda_{max.}$ 204 and 241 nm (ε 16 500 and 9 700); δ_H 1.06 (9 H, s, CMe$_3$), 2.31 (3 H, s, Bu^t C*Me*), 2.62 (6 H, s, 2 × SMe), and 8.41 (2 H, s, 5-H of two triazoles); δ_C 14.45 (q, $^1J_{CH}$ 141.3 Hz, SMe), 22.60 (q, $^1J_{CH}$ 130.8 Hz, Bu^{t}C*Me*), 26.40 (q, each component split into a multiplet, $^1J_{CH}$ 127.0 Hz, C*Me*$_3$) 41.46 (m, *C*Me$_3$), 85.07 (m, Bu^t*C*Me), 144.63 (d, $^1J_{CH}$ 213.9 Hz, C-5 of two triazoles), and 162.06 (dq, $^3J_{CH}$ 4.9 and 13.2 Hz, C-3 of two triazoles); *m/z* 312 (M^+, 8%), 198 (M^+ − 114, 30), 116 (100), and 83 (50).

(**6g**) (21.7%), *prisms*, m.p. 173—174 °C (from EtOH–Pr^{i}OH, 1:1, v/v) (Found: C, 44.65; H, 5.5; N, 28.3. $C_{11}H_{16}N_6S_2$ requires C, 44.6; H, 5.4; N, 28.4%); $\lambda_{max.}$ 205 and 242 nm (ε 14 000 and 8 700); δ_H 1.90 [4 H, m, (CH$_2$)$_2$], 2.55 (6 H, s, 2 × SMe), 2.89 [4 H, m, C(CH$_2$)$_2$], and 8.25 (2 H, s, 5-H of two triazoles); δ_C 84.31 [m, *C*(CH$_2$)$_4$], 143.10 (d, $^1J_{CH}$ 211.1 Hz, C-5 of two triazoles), and 162.65 (dq, $^3J_{CH}$ 4.4 and 13.2 Hz, C-3 of two triazoles); *m/z* 296 (M^+, 12%), 182 (M^+ − 114, 100), and 82 (38).

(**6h**) (49%), *prisms*, m.p. 161—161.5 °C (from Pr^{i}OH) (Found: C, 46.4; H, 5.85; N, 27.2. $C_{12}H_{18}N_6S_2$ requires C, 46.4; H, 5.85; N, 27.1%); $\lambda_{max.}$ 204 and 242 nm (ε 15 300 and 8 700); δ_H 1.60 [6 H, m, (CH$_2$)$_3$], 2.55 (6 H, s, 2 × SMe), 2.77 [4 H, m, C(CH$_2$)$_2$], and 8.24 (2 H, s, 5-H of two triazoles); δ_C 77.16 [m,‡ *C*(CH$_2$)$_5$], 142.56 (d, $^1J_{CH}$ 211.7 Hz, C-5 of two triazoles), and 162.43 (dq, $^3J_{CH}$ 4.9 and 13.2 Hz, C-3 of two triazoles); *m/z* 310 (M^+, 12%) and 196 (M^+ − 114, 100).

Preparation of 1,1-Bis(3-methylthio-1H-1,2,4-triazol-1-yl)-ethane (**6i**).—*General procedure for cyclization of 4-[2,2-bis-(ethoxycarbonyl)vinyl]-3-alkylisothiosemicarbazones* (**5**). A solution of diester (**5i**) (1.0 g, 3.3 mmol) in aqueous acetic acid (62.5% v/v, 4.0 ml) was heated at 70 °C for 2 h. The mixture was partitioned between 20% aqueous sodium carbonate (25 ml) and chloroform (10 ml). The organic layer was washed with water, dried, and evaporated to dryness. Preparative h.p.l.c. (silica gel; chloroform) of the residue (0.31 g) yielded the product (**6i**) (0.20 g, 47%) as *prisms*, m.p. 70—71 °C (from hexane) (Found: C, 37.7; H, 4.8; N, 32.6. $C_8H_{12}N_6S_2$ requires C, 37.5; H, 4.7; N, 32.8%); $\lambda_{max.}$ 204 and 242 nm (ε 13 800 and 8 500); δ_H 2.21 (3 H, d, *J* 6.9 Hz, CHMe), 2.57 (6 H, s, 2 × SMe), 6.53 (1 H, q, *J* 6.9 Hz, C*H*Me), and 8.26 (2 H, s, 5-H of two triazoles); δ_C 14.35 (q, $^1J_{CH}$ 141.8 Hz, SMe), 19.08 (dq, $^1J_{CH}$ 131.4, $^2J_{CH}$ 3.8 Hz, CH*Me*), 67.94 (dq, $^1J_{CH}$ 155.6, $^3J_{CH}$ 4.4 Hz, *C*HMe), 143.30 (dd, $^1J_{CH}$ 211.7, $^3J_{CH}$ 2.7 Hz, C-5 of two triazoles), and 163.18 (dq, $^3J_{CH}$ 4.4 and 13.2 Hz, C-3 of two triazoles); *m/z* 256 (M^+, 21%) and 142 (M^+ − 114, 100).

Separation of 1-(3'-Methylthio-1'H-1',2',4'-triazol-1'-yl)-1-(5''-methylthio-1''H-1'',2'',4''-triazol-1''-yl)ethane (**8a**).—This

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* Further information as to the multiplicity could not be obtained due to low concentration as a result of the poor yield of the material.
† The multiplicity could not be determined due to overlap with the solvent resonance.

‡ The alternative method for preparation of bis(triazole)s (**6**) starting with esters (**5**) gave the compounds (**6a**—**e**) in 31—60% yield based on the amount of the corresponding esters (**5a**—**e**) initially used, which were in turn obtained from isothiosemicarbazones (**1a**—**e**) in 57—95% yield. Thus the overall yields of compounds (**6a**—**e**) based on the isothiosemicarbazones (**1**) amounted to 29—35% as described in the Discussion section.

compound was obtained from a fraction preceding that of the symmetrical compound (6i); work-up gave the *title compound* as an oil (33 mg, 7.8%) (Found: C, 37.6; H, 4.7; N, 32.6. $C_8H_{12}N_6S_2$ requires C, 37.5; H, 4.7; N, 32.8%); $\lambda_{max.}$ 207 and 238 nm (ε 19 800 and 15 800); δ_H 2.17 (3 H, d, J 6.8 Hz, CH*Me*), 2.57 (3 H, s, 3'-SMe), 2.71 (3 H, s, 5''-SMe), 6.59 (1 H, q, J 6.8 Hz, C*H*Me), 7.88 (1 H, d, J 0.77 Hz, 3''-H), and 8.22 (1 H, s, 5'-H); δ_C 14.37 (q, $^1J_{CH}$ 141.8 Hz, 3'-SMe), 15.79 (q, $^1J_{CH}$ 142.9 Hz, 5''-SMe), 19.45 (dq, $^1J_{CH}$ 131.4, $^2J_{CH}$ 3.8 Hz, CH*Me*), 66.62 (dq, $^1J_{CH}$ 153.4, $^3J_{CH}$ 4.4 Hz, Me*C*H), 142.63 (dd, $^1J_{CH}$ 211.7, $^3J_{CH}$ 2.7 Hz, C-5'), 152.05 (d, $^1J_{CH}$ 208.9 Hz, C-3''), 153.95 (m,† C-5''), and 162.69 (m,† C-3'); m/z 256 (M^+, 30) and 142 ($M^+ - 114$, 100). Similarly, compounds (6j) and (8b) were obtained from the corresponding ester (5j).

(6j) (53.8%), *needles*, m.p. 92—93 °C (from Pr^i_2O–Pr^iOH, 4:1, v/v) (Found: C, 40.0; H, 5.3; N, 31.0. $C_9H_{14}N_6S_2$ requires C, 40.0; H, 5.2; N, 31.1%); $\lambda_{max.}$ 205 and 241 nm (ε 13 700 and 8 600); δ_H 0.98 (3 H, t, J 7.3 Hz, CH_2Me), 2.57 (6 H, s, 2 × SMe), 2.59 (2 H, quin., J *ca.* 7.5 Hz, CH_2), 6.23 (1 H, t, J 7.6 Hz, Et*CH*), and 8.27 (2 H, s, 5-H of two triazoles); δ_C 9.66 (q, $^1J_{CH}$ 127.6 Hz, CH_2Me), 14.35 (q, $^1J_{CH}$ 141.3 Hz, SMe), 26.53 (tq, $^1J_{CH}$ 130.9, $^2J_{CH}$ 3.8 Hz, CH_2Me), 73.23 (dsex, $^1J_{CH}$ 153.9, $^2J_{CH} = {}^3J_{CH} = $ 6.6 Hz, H*C*Et), 143.83 (dd, $^1J_{CH}$ 211.7, $^3J_{CH}$ 2.7 Hz, C-5 of two triazoles), and 162.98 (dq, $^3J_{CH}$ 4.9 and 13.2 Hz, C-3 of two triazoles); m/z 270 (M^+, 20%) and 156 ($M^+ - 114$, 100).

(8b) (10.9%), *oil* (Found: C, 40.3; H, 5.3; N, 31.2. $C_9H_{14}N_6S_2$ requires C, 40.0; H, 5.2; N, 31.1%); δ_H 0.95 (3 H, t, J 7.3 Hz, CH_2Me), 2.57 (3 H, s, 3'-SMe), 2.62 (2 H, m,* CH_2Me), 2.72 (3 H, s, 5''-SMe), 6.39 (1 H, t, J 7.4 Hz, Et*CH*), 7.89 (1 H, d, J 0.77 Hz, 3''-H), and 8.26 (1 H, s, 5'-H); δ_C 9.64 (q, $^1J_{CH}$ 128.1 Hz, CH_2Me), 14.40 (q, $^1J_{CH}$ 141.3 Hz, 3'-SMe), 15.76 (q, $^1J_{CH}$ 143.5 Hz, 5''-SMe), 26.99 (tquin., $^1J_{CH}$ 130.9, $^2J_{CH}$ 3.8 Hz, CH_2Me), 71.77 (d, each component split into a multiplet, $^1J_{CH}$ 151.7 Hz, Et*CH*), 142.95 (dd, $^1J_{CH}$ 211.1, $^3J_{CH}$ 2.7 Hz, C-5'), 152.22 (d, $^1J_{CH}$ 208.9 Hz, C-3''), 154.47 (m,† C-5''), and 162.37 (m,† C-3'); m/z 270 (M^+, 21%) and 156 ($M^+ - 114$, 100).

Preparation of 2-(3-*Ethylthio*-1H-1,2,4-*triazol*-1-*yl*)-2-(3-*methylthio*-1H-1,2,4-*triazol*-1-*yl*)*propane* (9).—A mixture of diester (5a) (1.0 g, 3.17 mmol), diester (5b) (1.0 g, 3.04 mmol), and aqueous acetic acid (93% v/v, 7.5 ml) was heated at 70 °C for 2 h. The reaction mixture was partitioned between 20% aqueous sodium carbonate (50 ml) and chloroform (20 ml). The organic layer was washed with water, dried, and evaporated. The residue (0.59 g) was subjected to preparative h.p.l.c. on silica gel with chloroform–dichloromethane (1:1 v/v) as eluant to yield a high R_F fraction (0.16 g) consisting of alkenes (10a) and (10b) in a 1:1.3 molar ratio, and a second fraction (0.40 g) consisting of bis(azole)s (6a), (6b), and the cross-compound (9). Further fractionation of the second fraction on the same chromatographic system gave compounds (6a) (0.1 g, 23.3%), (6b) (0.1 g, 22.1%), and impure cross-compound (9) (0.18 g, 20.8%), from which analytically pure product (9) (0.12 g, 13.9%) could be obtained after repeated h.p.l.c. on silica gel with chloroform as eluant; *needles*, m.p. 109—110 °C (from Pr^iOH) (Found: C, 42.2; H, 5.7; N, 29.3. $C_{10}H_{16}N_6S_2$ requires C, 42.25; H, 5.7; N, 29.6%); $\lambda_{max.}$ 205 and 241 nm (ε 14 500 and 8 900); δ_H 1.36 (3 H, t, J 7.4 Hz, CH_2Me), 2.28 (6 H, s, CMe_2), 2.55 (3 H, s, SMe), 3.10 (2 H, q, J 7.4 Hz, SCH_2), and 8.18 (2 H, s, 5-H of two triazoles); δ_C 14.35 (q, $^1J_{CH}$ 141.8 Hz, SMe), 14.89 (qt, $^1J_{CH}$ 128.1, $^2J_{CH}$ 3.3 Hz, CH_2Me), 26.18 (tq, $^1J_{CH}$ 141.3, $^2J_{CH}$ 4.3 Hz, SCH_2), 26.92 (qq, $^1J_{CH}$ 130.9, $^3J_{CH}$ 3.8 Hz, C*Me*$_2$), 75.28 (dq, $^2J_{CH} = {}^3J_{CH} = $ 4.4 Hz, *C*Me$_2$), 142.24 and 142.34 (d, $^1J_{CH}$ 211.7

Hz, C-5 of two triazoles), and 161.79 and 162.52 (m, C-3 of two triazoles); m/z 284 (M^+, 36%), 170 ($M^+ - 114$, 90), and 156 ($M^+ - 128$, 100).

The cross-reaction product (9) was also prepared when an equimolar mixture of the required starting materials (1a), (1b), and (2) (1.38 mmol each) in aqueous formic acid (50% v/v, 0.4 ml) was heated at 70 °C for 0.5 h and then an additional amount (1.38 mmol) of nitroacrylate (2) was added and the mixture was held at the same temperature for 1 h. After separation by preparative h.p.l.c. (silica gel; $CHCl_3$), bis(triazole)s were obtained in the molar proportions (6a):(6b):(9) = 1:1.12:1.09, with the yield of the cross-product (9) being 22.7%.

Separation of 3-*Ethylthio*-1-*isopropenyl*-1H-1,2,4-*triazole* (10b).—This compound was obtained from a fraction preceding to that of compound (6b) on h.p.l.c.; work-up gave an oil (15 mg, 7.1%) (Found: C, 49.9; H, 6.5; N, 24.5. $C_7H_{11}N_3S$ requires C, 49.7; H, 6.55; N, 24.8%); $v_{max.}(CCl_4)$ 1 660 cm^{-1} (C=C); δ_H 1.41 (3 H, t, J 7.3 Hz, SCH_2Me), 2.26 (3 H, dd, $^4J_{HH}$ 0.5 and 1.3 Hz, =CMe), 3.16 (2 H, q, J 7.3 Hz, SCH_2), 4.81 and 5.51 (each 1 H, m, together =CH_2), and 8.19 (1 H, s, 5-H of triazole); δ_C 15.01 (qt, $^1J_{CH}$ 127.6, $^3J_{CH}$ 3.3 Hz, CH_2Me), 18.81 (q, each component split into two doublets, $^1J_{CH}$ 129.2 Hz, =C*Me*), 26.31 (tq, $^1J_{CH}$ 141.8, $^2J_{CH}$ 3.8 Hz, SCH_2), 102.71 (tq, $^1J_{CH}$ 161.1, $^3J_{CH}$ 4.9 Hz, =CH_2), 137.80 (m, =*C*Me), 141.22 (d, $^1J_{CH}$ 210.6 Hz, C-5 of triazole), and 161.96 (dt, $^3J_{CH}$ 4.9 and 13.7 Hz, C-3 of triazole); m/z 169 (M^+, 92%), 136 (100), 114 (20), 96 (59), and 41 (64).

The following compounds were similarly obtained from the fraction preceding that of the corresponding bis(azole)s (6).

(10c) (13.3%), *oil* (Found: C, 54.5; H, 7.4; N, 21.1. $C_9H_{15}N_3S$ requires C, 54.8; H, 7.7; N, 21.3%); $v_{max.}(CCl_4)$ 1 633 cm^{-1} (C=C); δ_H 1.21 (9 H, s, CMe_3), 2.61 (3 H, s, SMe), 5.14 and 5.25 (each 1 H, d, $^2J_{HH}$ 0.9 Hz, together =CH_2), and 8.04 (1 H, s, 5-H of triazole); δ_C 14.52 (q, $^1J_{CH}$ 141.3 Hz, SMe), 28.82 (q, each component split into a multiplet, $^1J_{CH}$ 127.0 Hz, C*Me*$_3$), 36.21 (m, *C*Me$_3$), 109.96 (t, $^1J_{CH}$ 160 Hz, =CH_2), 144.49 (d, $^1J_{CH}$ 210.6 Hz, C-5 of triazole), 153.20 (m, *C*=CH$_2$), and 161.96 (m, C-3 of triazole); m/z 197 (M^+, 38%), 155 (32), 124 (37), 115 (28), and 41 (100).

(11) (59.1%), *needles*, m.p. 68—69 °C (from hexane) (Found: C, 53.3; H, 6.1; N, 23.1. $C_8H_{11}N_3S$ requires C, 53.0; H, 6.1; N, 23.2%); $v_{max.}(CCl_4)$ 1 666 cm^{-1} (C=C); δ_H 2.12 (2 H, q, J 6.8 Hz, =CHCH_2), 2.52 (2 H, m, $CH_2CH_2CH_2$), 2.60 (3 H, s, SMe), 2.78 (2 H, m, CH=CCH_2), 6.00 (1 H, m, C=CH), and 8.11 (1 H, s, 5-H of triazole); δ_C 14.45 (q, $^1J_{CH}$ 141.85 Hz, SMe), 22.13 [t, each component split into a multiplet, $^1J_{CH}$ 130 Hz, $CH_2(CH_2)_2$], 30.58 and 30.97 [each t, each split into a multiplet, $^1J_{CH}$ 130 Hz, $CH_2(CH_2)_2$], 116.21 (d, each component split into a multiplet, $^1J_{CH}$ 166.6 Hz, C=*C*H), 136.60 (m, =CH*C*), 141.78 (d, $^1J_{CH}$ 210.6 Hz, C-5 of triazole), and 162.72 (dq, $^3J_{CH}$ 4.4 and 13.2 Hz, C-3 of triazole); m/z 181 (M^+, 100%), 115 (6), and 67 (27).

5-*Ethyl*-3-*methylthio*-1H-1,2,4-*triazole* (12; R^3 = Me, R^4 = Et).—This compound was obtained when isothiosemicarbazone (1j) was oxidized with iron(III) chloride according to the known method,[10] and crystallized as white crystals, m.p. 81—82 °C (from hexane containing a small amount of benzene) [lit.,[9] 80 °C (from hexane)].

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