Abnormal Diels-Alder Reaction of 5-Alkoxythiazoles with Highly Reactive Dienophiles; 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione, Diethyl Azodicarboxylate, and Diethyl Oxomalonate

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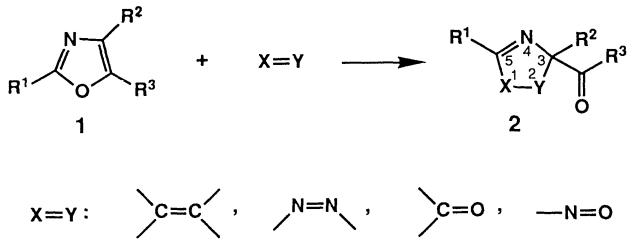
The reaction of 5-alkoxythiazoles with equimolar amount of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) in an acetonitrile solution at room temperature gave the corresponding *O*-alkyl 6,7-dihydro-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*] [1,2,4]triazole-1-carbothioate in high yields. The reaction was assumed to proceed through stepwise addition of PTAD toward thiazole accompanying thiazole ring opening. Diethyl azodicarboxylate also gave 2,3-dihydro-1*H*-1,2,4-triazole derivatives in moderate yields. High pressure improved the yields a little. On the other hand, the reaction of diethyl oxomalonate in the presence of tin tetrachloride with 4-unsubstituted thiazoles did not give an adduct of similar type but gave diethyl 2-hydroxy-2-(4-thiazolyl)malonate through the usual electrophilic substitution reaction of thiazole at C-4.

Although thiazole has an azadiene structure, its Diels–Alder reactivity is not so high.[1] Therefore, it is necessary to use high pressure[2] or catalyst[3] to promote the Diels–Alder reaction with usual dienophiles. In the previous papers of this series, we have reported the abnormal Diels–Alder reaction of oxazoles **1** with strong dienophiles, such as tetracyanoethylene (TCNE),[4] 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD),[5] diethyl oxomalonate,[6,7] and nitrosobenzene.[8] Similar reaction with diethyl azodicarboxylate (DEAD) was reported by Hassner and his co-worker.[7] In these reactions, the formal 1,3-dipolar cycloaddition of nitrile ylide with dienophiles was observed through the oxazole ring opening[9] to give nitrogen-containing heterocycles **2** with a carbonyl substituent on C-3.



Similar reaction of thiazole with strong dienophiles can be expected to give the corresponding 3-thiocarbonyl compounds. In order to expand the application of this reaction, we studied the reaction of thiazoles with PTAD, DEAD, and diethyl oxomalonate.

Results and Discussion

Reaction of 5-Alkoxythiazoles with PTAD. Reaction of 5-methoxy-2-(*p*-methoxyphenyl)-4-methylthiazole (**3a**) with equimolar amount of PTAD in an acetonitrile solution at room temperature resulted in disappearance of characteristic carmine red color of PTAD in half an hour. The usual treatment of the reaction mixture gave pale yellow prisms **5a** in high yield. The results of elemental analysis revealed that **5a** is a 1 : 1 adduct of the thiazole and PTAD.

A singlet signal of methyl group at 2.13 ppm in the ^{1}H NMR spectrum of **5a** indicates that this methyl group attaches not to sp^2-carbon but to sp^3-carbon.[5] A methoxyl signal at 4.17 ppm differs from the usual chemical shift of ester methyl or ether methyl group, and is assigned to a methoxyl group bonding to a thiocarbonyl group. Its ^{13}C NMR spectrum has signals of methyl carbon at 24.50 ppm, a quaternary carbon at 94.45 ppm, an sp^2-carbon at 152.80 ppm, and a thiocarbonyl carbon at 213.65 ppm. These spectroscopic data indicate that the adduct does not have a structure of the usual Diels–Alder adduct **6** but has a structure of *O*-methyl 6,7-dihydro-3-(*p*-methoxyphenyl)-1-methyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]-triazole-1-carbothioate (**5a**) which is the formal [3+2] cycloadduct of PTAD with the corresponding nitrile

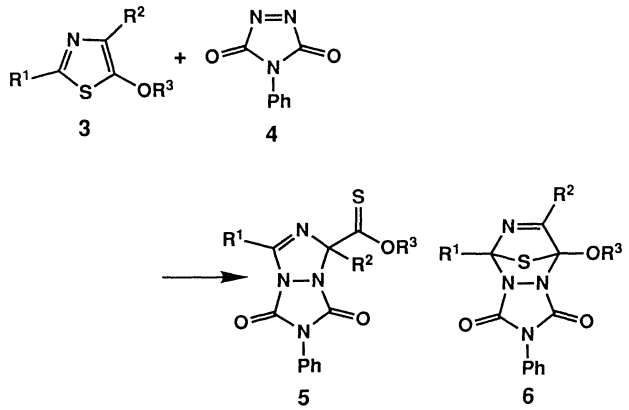


Table 1. Reactions of 5-Alkoxythiazoles **3** with PTAD **4**[a]

Run	Thiazole	R^1	R^2	OR^3	Reaction Conditions		Yield of **5**
					Temp/°C	Time/h	%
1	**3a**	*p*-$MeOC_6H_4$	Me	OMe	r.t.	0.5	97
2	**3b**	Me	Me	OMe	r.t.	5.0	72
3	**3c**	*n*-C_9H_{19}	Me	OMe	r.t.	0.5	89
4	**3d**	*c*-C_6H_{11}	Me	OMe	r.t.	0.5	93
5	**3e**	Me	H	OMe	r.t.	0.5	86
6	**3f**	*p*-$MeOC_6H_4$	H	OEt	80	1.0	38[b]

a) An equimolar amount of **3** was reacted with PTAD at atmospheric pressure in an acetonitrile solution. b) Three by-products **7f** (0—3%), **8f** (7—25%), and **9f** (2—6%) were obtained together with **5f** and recovered **3f** (7—18%) in different yields depending on the reaction conditions.

ylide derived by the opening of thiazole ring system. Other spectroscopic data of **5a** support this structure (see Experimental).

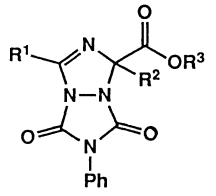
Other 5-alkoxythiazoles **3b**—**3e** also gave the same type of 1 : 1 adducts in high yields except 5-ethoxy-2-(*p*-methoxyphenyl)-thiazole (**3f**) as shown in Table 1. Aliphatic and aromatic substituents on C-2 of thiazole ring shows no effect on the yield of **5**. 4-Unsubstituted thiazole **3e** also afforded the corresponding adduct **5e** in high yield. However, 5-ethoxy-2-(*p*-methoxyphenyl)-thiazole (**3f**) gave an adduct **5f** in moderate yield recovering thiazole **3f**. Detail inspection of the reaction mixture by use of the medium pressure column chromatography revealed the formation of **8f** (7%) and **9f** (6%) besides **5f** (37%) and **3f** (18%).

The ^{13}C NMR spectrum of **8f** has two signals of sp^2-carbon at 157.79 ppm (C-5) and 159.10 ppm (C-3), and a signal of thiocarbonyl carbon at 198.42 ppm. A quartet ^1H NMR signal of O-CH_2 at 4.68 ppm indicates the presence of thiocarboxylic ester. Other ^{13}C NMR signals also support the structure **8f**. However, these spectroscopic data can not eliminate the possibility of its tautomer **8'f**.

Adduct **9f** has an N–H band at 3435 cm^{-1} in its IR spectrum, and shows signals of ethoxyl group at the usual position of ethereal ethyl group (4.20 (q) and 1.41 (t) ppm) in its ^1H NMR spectrum. The ^{13}C NMR spectrum of **9f** indicated the presence of thiazole ring system; at 153.87 (C-2), 127.29 (C-4), and 154.79 (C-5) ppm. Other spectroscopic data agreed with the structure **9f**.

In order to accelerate the reaction of **3f**, zinc chloride was used as a catalyst. However, reaction of **3f** with PTAD in an acetonitrile solution in the presence of equimolar amount of zinc chloride at −15 °C increased the yield of **9f** to 45% decreasing the yield of **5f** to zero. The desulfurization product **7f** was also obtained in 2% yield. The ^{13}C NMR spectrum of **7f** has signals of quaternary carbon at 82.32 ppm (C-1), sp^2-carbon at 155.36 ppm (C-3), and ester carbonyl carbon at 165.84 ppm. This indicates that **7f** has a triazoline structure with a carboxylic ester group not a carbothioic ester group. A signal of O-CH_2 of ethoxyl group at 4.30—4.40 (m) ppm in its ^1H NMR spectrum is not assigned to a carbothioic ester but to a carboxylic ester. Other ^{13}C NMR signals of this compound are consistent with the structure **7f**.

The zinc chloride-catalyzed reaction of **3e** with PTAD increased the yield of **7e** (8%) and **8e** (8%) accompanying the decrease of the yield of **5e** (13%) without affording **9e**. Control experiment showed that **7e** and **8e** are formed by heating of **5e** in a wet acetonitrile solution. The ^{13}C NMR spectrum of **8e** at room temperature gave broad signals. However, measurement at −40 °C gave signals shown in the experimental section. This indicates that there exists an equilibrium between **8e** and **8'e** at room temperature.



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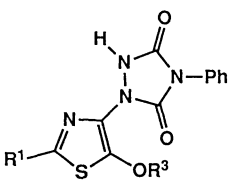

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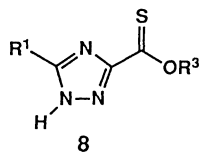

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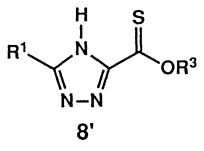

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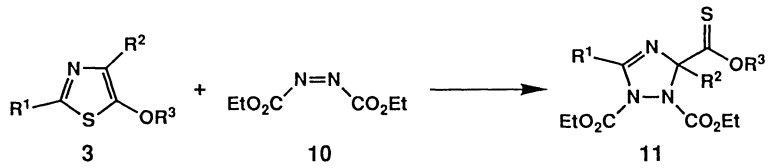
Reaction of 5-Alkoxythiazoles with DEAD. Reactivity of diethyl azodicarboxylate (DEAD) is lower than that of PTAD in the usual Diels–Alder reaction.[10] Reaction of **3a** with DEAD gave only 31% of adduct **11a** together with a recovered **3a** (21%), even under the forced conditions at 80 °C for 500 h. High pressure of 0.85 GPa increased the yield of **11a** up to 45%. The structure of **11a** was supported by the following spectroscopic properties. A singlet methyl signal at 2.02 ppm of its ^1H NMR spectrum indicates that this methyl group is bonding to an sp^3-carbon not to an sp^2-carbon. A methoxyl signal at 4.10 ppm shows that this is not the usual methoxyl group of ester but of thioester. The ^{13}C NMR data also support the 2,3-dihydro-1*H*-1,2,4-

triazole structure **11a** as described above; 24.45 (3-CH_3), 93.87 (C-3), 158.09 (C-5), and 215.68 ppm (C=S of thioester). The high pressure reaction of 5-methoxy-2,4-dimethylthiazole (**3b**) with DEAD also gave the corresponding adduct **11b** in good yield. However, the reaction of 5-methoxy-4-methyl-2-nonylthiazole (**3c**) under 0.85 GPa gave a mixture of **11c** (22%) and diethyl 2,3-dihydro-3-methyl-3-(methylthio)carbonyl-5-nonyl-1*H*-1,2,4-triazole-1,2-dicarboxylate (**12c**, 12%). Because the separation of **11c** and **12c** by medium pressure chromatography was difficult, product ratio was determined by HPLC analysis. The structure of **12c** was assigned on the basis of spectroscopic data (see Experimental).

In a similar reaction, 4-unsubstituted thiazoles **3e** and **3f** were unreactive and gave no product at all. High pressure (0.85 GPa) accelerated the reaction of **3f** with DEAD to give **11f** in 7% yield. However, the reaction of **3e** with DEAD at 0.85 GPa gave a Friedel–Crafts type of electrophilic substitution product[11] **14e** on C-4 of thiazole in 25% yield without affording the expected adduct **11e**.

Reaction of **3c** with DEAD in the presence of zinc chloride gave only **13c** (5% yield), of which structure was tentatively assigned to desulfurization product on the basis of ^{1}H NMR spectrum; 3.71 ppm (OCH_3).



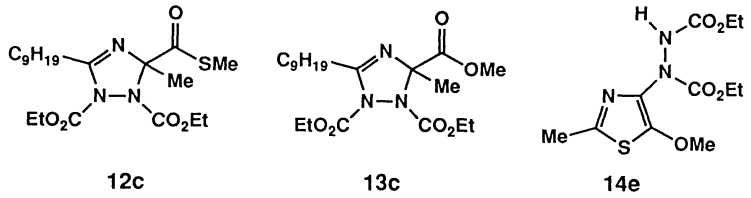
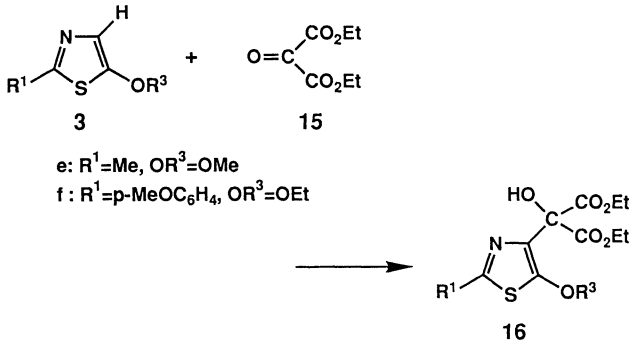


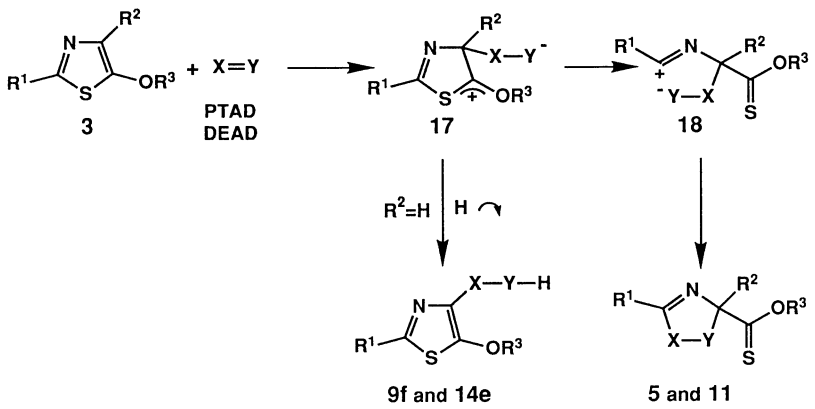
Table 2. Reactions of 5-Alkoxythiazoles **3** with DEAD **10**[a]

Run	Thiazole	R^1	R^2	OR^3	Reaction Conditions				Yield of **11**
					3:**10**	Temp	Time	Pres.	
						°C	h	GPa	%
1	**3a**	*p*-$MeOC_6H_4$	Me	OMe	1:2	Reflux	500	10^{-4}	31
2	**3a**	*p*-$MeOC_6H_4$	Me	OMe	1:2	60	100	0.85	33
3	**3a**	*p*-$MeOC_6H_4$	Me	OMe	1:1	50	70	0.85	31
4	**3a**	*p*-$MeOC_6H_4$	Me	OMe	1:2	50	215	0.85	45
5	**3b**	Me	Me	OMe	1:2	50	70	0.8	66
6	**3c**	*n*-C_9H_{19}	Me	OMe	1:1	Reflux	500	10^{-4}	38
7	**3c**	*n*-C_9H_{19}	Me	OMe	1:1	50	168	0.85	22[b]
8	**3e**	Me	H	OMe	1:2	Reflux	76	10^{-4}	0[c]
9	**3e**	Me	H	OMe	1:2	50	168	0.85	0[d]
10	**3f**	*p*-$MeOC_6H_4$	H	OEt	1:2	50	168	0.85	7

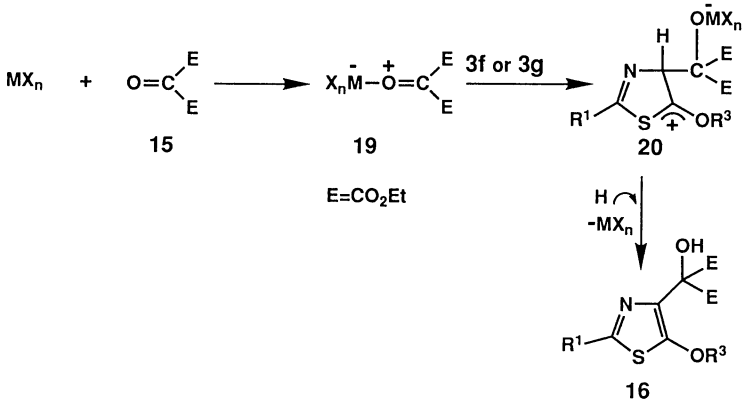
a) Reactions were carried out in an acetonitrile solution under the described reaction conditions. b) Obtained as a mixture with **12c** (12%). The yields were determined by HPLC analysis. c) Only recovered **3e** was obtained. d) **14e** was obtained in 25% yield.

Reaction of 5-Alkoxythiazole with Diethyl Oxomalonate. Although diethyl oxomalonate (**15**) has high Diels–Alder reactivity, in usual carbonyl compounds,[12] the reaction with thiazoles could not be expected to give an adduct under the ordinary reaction conditions. Therefore, tin chloride-catalyzed reaction of **3f** with **15** was carried out in an acetonitrile solution at room temperature. A hydroxyalkylation product[13] **16f** was obtained in 52% yield by Friedel–Crafts type electrophilic substitution reaction on C-4.[11] Similar result was observed in the reaction of **3e** with **15** affording the





Scheme 1.



Scheme 2.

corresponding substituted thiazole **16e** in the yield up to 53%. IR spectrum of **16e** have a broad band of OH group at 3478 cm^{-1} and ester carbonyl band at 1746 cm^{-1}. The ^{13}C NMR spectrum of **16e** has a signal of sp^3-carbon connected to hydroxyl group at 77.28 ppm besides the signals of ethoxycarbonyl and thiazole ring system (see Experimental).

Mechanism of the Reaction of Thiazole with Dienophiles. In the abnormal Diels–Alder reaction of oxazoles, we have proposed a stepwise mechanism initiated by the electrophilic attack of dienophile on C-2 or C-4 of oxazole.[4,5] Similar reaction mechanism is possible for the abnormal reactions of thiazoles with PTAD, DEAD, and diethyl oxomalonate in the absence of Lewis acid catalyst (Scheme 1). However, formation of **9f** by the reaction of **3f** with PTAD, and formation of **14e** under high pressure prefer the attack on C-4 rather than on C-2. The electrophilic attack of dienophile X=Y on C-4 of thiazole gives zwitterionic intermediate **17**, which gives final products **5** or **11** through intermediate **18** formed by the ring opening of thiazole. When R^2 is hydrogen, proton migration from C-4 to Y of **17** competes with ring opening, and gave substitution products **9f** and **14e**.

Formation of **16** in the Lewis acid-catalyzed reaction of **3** with **15** is explained by the attack of zwitterion **19** on C-4 of thiazole followed by the proton migration accompanying elimination of Lewis acid (Scheme 2).

Experimental

Melting points were measured with a Yanagimoto Melting Point Apparatus and were not corrected. IR spectra were recorded on a Perkin-Elmer model 983. NMR spectra were recorded on a Varian EM-390 (90 MHz) for proton, and on a JEOL GX-500 for proton (500 MHz) and ^{13}C NMR (125.65 MHz) in $CDCl_3$ using TMS as an internal standard.

Materials. All 5-alkoxythiazoles were prepared by the treatment of the corresponding *N*-acylamino esters with P_2S_5 in $CHCl_3$ solution according to the literature procedure.[14]

PTAD was prepared by the method described in a literature.[15]

Acetonitrile was purified by distillation from P_2O_5 and then from CaH_2, and kept over molecular sieves type 4A.

General Procedure for the Reaction of 5-Alkoxythiazole 3 with PTAD. A solution of **3** (1.0 mmol) and PTAD (1.0 mmol) dissolved in 10 ml of acetonitrile was kept under magnetic stirring at room temperature under nitrogen atmosphere until carmine red color of PTAD disappeared. After about half an hour, solvent was removed under reduced pressure. The residue was separated by medium pressure column chromatography on silica gel using a mixed eluent of

hexane–ethyl acetate. Products were characterized by elemental analysis and IR, ^{1}H NMR, and ^{13}C NMR spectra after recrystallization from proper solvent.

General Procedure for the Reaction of 5-Alkoxythiazole with DEAD at Atmospheric Pressure. A solution of **3** (1.0 mmol) and DEAD (1.0 mmol) in dry acetonitrile (5 ml) was kept under magnetic stirring at room temperature monitoring **3** by TLC. Usual treatment of the reaction mixture for separation and purification gave products as shown in Table 2.

General Procedure for the Reaction of 5-Alkoxythiazole with DEAD at High Pressure. A solution of **3** (1.0 mmol) and DEAD (1.0 mmol) in dry acetonitrile (5 ml) was kept in a teflon capsule and pressurized hydraulically using Hikari Kouatsu High Pressure reaction apparatus at 0.85 GPa and room temperature.[16] The reaction mixture was treated by the usual method for separation and purification of the products.

General Procedure for the Reaction of 5-Alkoxythiazole with PTAD or DEAD in the Presence of Lewis Acids. A solution of thiazole **3** (1.0 mmol) and DEAD (2.0 mmol) and $ZnCl_2$ (1.04 mmol) in 10.0 ml of dry acetonitrile was refluxed for 40 h under N_2 atmosphere, and treated as usual. Similar procedure was used for the reaction of **3** (1.0 mmol) with PTAD (1.0 mmol) in the presence of $ZnCl_2$ (1.0 mmol) at 25 °C.

General Procedure for the Reaction of 5-Alkoxythiazole with Diethyl Oxomalonate in the Presence of Lewis Acid. A solution of **3** (1.0 mmol) with diethyl oxomalonate (1.0 mmol) and $SnCl_4$ (1.0 mmol) at −40—−35 °C. Similar treatment of the reaction mixture gave the substitution product.

***O*-Methyl 6,7-Dihydro-3-(*p*-methoxyphenyl)-1-methyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothioate (5a):** Pale yellow crystals; mp 155—155.5 °C; IR (KBr) 1787, 1730, 1608, 1511, 1404, 1334, 1271, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.13 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 4.17 (3H, s, $CSOCH_3$), 6.93 (2H, d, J=9.0 Hz, arom-H), 7.45 (5H, s, Ph), 8.03 (2H, d, J=9.0 Hz, arom-H); ^{13}C NMR ($CDCl_3$) δ=24.50 (1-Me), 55.53 (OCH_3), 60.41 (OCH_3), 94.45 (1-C), 113.89, 117.57, 132.44 (1-, 2-, 3-, 5-, 6-C of Ar), 126.03, 128.77, 129.23 (*o*-, *m*-, *p*-C of Ph), 131.09 (1-C of Ph), 147.83 (C=O), 152.73 (C=O), 152.80 (3-C), 163.73 (4-C of Ar), 213.65 (C=S). Found: C, 58.81; H, 4.53; N, 13.48%. Calcd for $C_{20}H_{18}N_4O_4S$: C, 58.53; H, 4.42; N, 13.65%.

***O*-Methyl 6,7-Dihydro-1,3-dimethyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothioate (5b):** Yellow viscous oil; IR (neat) 3051, 2995, 2943, 1786, 1735 (C=O), 1647 (C=N), 1597, 1499, 1450, 1382, 1289, 1136, 1086, 894, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.04 (3H, s, 1-Me), 2.45 (3H, s, 3-Me), 4.17 (3H, s, OMe), 7.38—7.49 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$) δ=14.36 (1-Me), 23.95 (3-Me), 60.50 (OMe), 94.92 (1-C), 125.94, 128.82, 129.31 (*o*-, *m*-, *p*-C of Ph), 130.90 (1-C of Ph), 147.47, 151.60 (C=O), 151.83 (3-C), 213.06 (C=S).

***O*-Methyl 6,7-Dihydro-1-methyl-3-nonyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothioate (5c):** Yellow oil; IR (neat) 2927, 2854 (CH_2), 1787, 1734 (C=O), 1641 (C=N), 1501, 1449, 1397, 1282, 1137, 1086, 757, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (3H, t, J=7.0 Hz, CH_3), 1.27—1.43 (12H, m, $-(\underline{CH_2})_6CH_3$) 1.79 (2H, quint, J=7.6 Hz, $\underline{CH_2}$-Hept), 2.04 (3H, s, CH_3), 2.77 (2H, t, J=7.6 Hz, $\underline{CH_2}$-Oct), 4.16 (3H, s, OCH_3), 7.37—7.49 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.07, 22.66, 25.74, 28.00, 28.92, 29.11, 29.22, 29.41, 31.86 (Nonyl), 23.95 (q, 1-CH_3) 60.45 (q, OCH_3), 94.76 (1-C), 125.95, 128.76, 129.28 (*o*-, *m*-, and *p*-C of Ph), 130.98 (1-C of Ph), 147.14, 151.71 (C=O), 155.48 (3-C), 213.22 (C=S). Found: C, 60.95; H, 6.97; N, 13.07%. Calcd for $C_{22}H_{30}N_4O_3S$: C, 61.37; H, 7.02; N, 13.01%.

***O*-Methyl 3-Cyclohexyl-6,7-dihydro-1-methyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothioate (5d):** Yellow oil; IR (neat) 2934, 2854 (CH_2), 1785, 1734 (C=O), 1630 (C=N), 1598, 1499, 1449, 1401, 1335, 1274, 1227, 1137, 1086, 1027, 904, 756, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ=1.25—1.84 (10H, m, *c*-Hex), 2.03 (3H, s, CH_3), 2.93 (1H, tt, J=11.3 Hz, 3.6 Hz, H-Hex), 4.16 (3H, s, OCH_3), 7.37—7.48 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=23.85 (1-Me), 25.30, 25.61, 25.69, 28.92, 30.20, 36.85 (C-Hex), 60.46 (OMe), 94.59 (1-C), 125.95, 128.72, 129.24 (*o*-, *m*-, *p*-C of Ph), 131.03 (1-C of Ph), 146.84, 151.75 (C=O), 158.73 (3-C), 213.52 (C=S).

***O*-Methyl 6,7-Dihydro-3-methyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothioate (5e):** Pale yellow prisms; mp 111—114 °C; IR (KBr) 1793, 1736 (C=O), 1645 (C=N), 1451, 1405, 1339, 1295, 1200 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ=2.46 (3H, d, J=1.2 Hz, 3-CH_3), 4.20 (3H, s, OCH_3), 6.26 (1H, q, J=1.2 Hz, 1-H), 7.4—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.35 (3-Me), 60.11 (OMe), 87.90 (1-C), 125.82, 128.99, 129.39 (*o*-, *m*-, *p*-C of Ph), 130.58 (1-C of Ph), 149.28, 153.33 (each C=O), 154.44 (3-C), 210.88 (C=S). Found: C, 51.38; H, 3.97; N, 18.30%. Calcd for $C_{13}H_{12}O_3N_4S$: C, 51.31; H, 3.97; N, 18.41%.

***O*-Ethyl 6,7-Dihydro-3-(*p*-methoxyphenyl)-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothioate (5f):** Yellow crystals; mp 131.8—136.8 °C; IR (KBr) 3512, 3441, 2979, 2935, 1792, 1736 (C=O), 1607, 1569, 1508, 1456, 1400, 1375, 1328, 1261, 1177, 1142, 1026, 844, 772, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.46 (3H, t, J=7.1 Hz, CH_3), 3.85 (3H, s, OCH_3), 4.58—4.68 (2H, m, OCH_2), 6.35 (1H, s, CH), 6.97 (2H, d, J=8.9 Hz, arom-H), 7.36—7.47 (5H, m, Ph), 8.07 (2H d, J=8.9 Hz, arom-H); ^{13}C NMR ($CDCl_3$) δ=13.47 ($OCH_2\underline{CH_3}$) , 55.53 (OCH_3), 69.94 ($O\underline{CH_2}CH_3$), 88.20 (1-C), 113.88, 125.90 (*o*-, *m*-C of Ar), 117.43 (1-C of Ar), 128.86, 130.89 (1-, 4-C of Ph), 129.25, 132.48 (*o*-, *m*-C of Ph), 149.12, 153.60, 154.72 (3-C, C=O), 163.75 (4-C of Ar), 210.84 (C=S). Found: C, 58.50; H, 4.47; N, 13.60%. Calcd for $C_{20}H_{18}N_4O_4S$: C, 58.53; H, 4.42; N, 13.65%.

***O*-Ethyl 6,7-Dihydro-3-(*p*-methoxyphenyl)-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carboxylate (7f):** ^{1}H NMR ($CDCl_3$) δ=1.36 (3H, t, J=7.3 Hz, CH_3), 3.87 (3H, s, OCH_3), 4.30—4.40 (2H, m, OCH_2), 6.19 (1H, s, CH), 6.98 (2H, d, J=8.9 Hz, arom-H), 7.40—7.48 (5H, m, Ph), 8.07 (2H, d, J=8.9 Hz, arom-H); ^{13}C NMR ($CDCl_3$) δ=14.05 (q, CH_3), 55.54 (q, OCH_3), 63.14 (t, OCH_2), 82.32 (d, 1-C), 113.82, 132.50 (each d, *o*- and *m*-C of Ar), 117.05 (t, ^2J=7.3 Hz, 1-C of Ar), 125.89 (d, *p*-C of Ph), 128.98, 129.31 (each d, *o*-C and *m*-C of Ph), 130.64 (s, 1-C of Ph), 149.59 (s, C=O), 154.30 (s, C=O), 155.36 (s, 3-C), 163.75 (s, *p*-C of Ar), 165.84 (d, ^2J=3.1 Hz, C=O of ester). Found: M$^+$+1, 395.1362. Calcd for $C_{20}H_{18}N_4O_5$: M+1, 395.1355.

***O*-Ethyl 5-(*p*-Methoxyphenyl)-1*H*-1,2,4-triazole-3-carbothioate (8f):** Yellow needles; mp 181.0—184.6 °C; IR (KBr) 3428, 1613 (C=N), 1502, 1457, 1256, 1180, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ=1.37 (3H, t, J=7.1 Hz, CH_3), 3.80 (3H, s, OCH_3), 4.68 (2H, q, J=7.1 Hz, OCH_2), 6.87 (2H, d, J=8.9 Hz, arom-H), 7.98 (2H, d, J=8.9 Hz, arom-H); ^{13}C NMR ($CDCl_3$) δ=13.45 (q, CH_3), 55.35 (q, OCH_3), 68.82 (t, CH_2), 114.35, 128.48 (d, 2-, 3-, 5-, 6-C of Ar), 120.22 (s, 1-C of Ar), 157.79 (s,

5-C), 159.10 (s, 3-C), 161.47 (s, 4-C of Ar), 198.42 (s, C=S).

1-[5-Ethoxy-2-(*p*-methoxyphenyl)-4-thiazolyl]-4-phenyl-1,2,4-triazolidine-3,5-dione (9f): Colorless prisms; mp 183—186 °C; IR (KBr) 3435 (br, NH), 1779, 1717 (C=O), 1605 (C=C), 1568, 1418, 1254, 1176, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=1.41 (3H, t, J=7.0 Hz, CH_3), 3.81 (3H, s, OCH_3), 4.20 (2H, q, J=7.0 Hz, OCH_2), 6.89 (2H, dt, J=8.9, 2.5 Hz, arom-H), 7.34-7.56 (5H, m, Ph), 7.69 (2H, dt, J=8.9, 2.5 Hz, arom-H); ^{13}C NMR ($CDCl_3$) δ=14.98 (q, CH_3), 55.43 (q, OCH_3), 73.98 (t, OCH_2), 114.42, 127.29 (each d, *o*- and *m*-C of Ar), 125.87 (d, *p*-C of Ph), 126.15 (t, ^2J=7.8 Hz, 1-C of Ar), 127.29 (s, 4-C), 128.30 (dt, ^2J=7.4 Hz, *m*-C of Ph), 129.14 (dd, ^2J=7.4 Hz, *o*-C of Ph), 131.40 (t, ^2J=9.8 Hz, 1-C of Ph), 151.04, 153.51 (each s, C=O), 153.87, 154.79 (each t, ^3J=4.8 Hz, ^3J=3.2 Hz, 2-C, 5-C), 161.33 (s, 4-C of Ar). Found: C, 58.28; H, 4.55; N, 13.69%. Calcd for $C_{20}H_{18}N_4O_4S$: C, 58.53; H, 4.42; N, 13.65%.

***O*-Methyl 6,7-Dihydro-3-methyl-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carboxylate (7e):** Colorless needles; mp 182—183 °C; IR (KBr) 1793, 1755, 1743 (C=O), 1645 (C=N), 1408, 1390, 1297, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=2.46 (3H, d, J=1.1 Hz, 3-CH_3), 3.87 (3H, s, OCH_3), 6.07 (1H, q, J=1.1 Hz, CH), 7.4—7.5 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=14.30 (q, 3-Me), 53.54 (q, OMe), 81.98 (d, 1-C), 125.80, 129.06, 129.42 (each d, *o*-, *m*-, *p*-C of Ph), 130.53 (s, 1-C of Ph), 149.68 (s, C=O), 153.98 (s, C=O), 155.25 (s, 3-C), 165.99 (s, COOMe). Found: C, 54.27; H, 4.27; N, 19.28%. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44%.

***O*-Methyl 5-Methyl-1*H*-1,2,4-triazole-3-carbothioate (8e):** Yellow prisms; mp 188—193 °C; IR (KBr) 3127 (NH), 3052, 3005, 2941, 2907, 2839, 2716, 1560 (C=N), 1464, 1446, 1402, 1248, 1193 (C=S), 1116, 1064, 1014 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.56 (3H, s, CH_3), 4.32 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$, −40 °C) δ=12.64 (Me), 59.52 (OMe), 155.01—155.28, 159.71—160.01. Found: C, 38.62; H, 4.48; N, 26.31%. Calcd for $C_5H_7N_3OS$: C, 38.21; H, 4.49; N, 26.73%.

Diethyl 2,3-Dihydro-5-(*p*-methoxyphenyl)-3-methoxy-(thiocarbonyl)-3-methyl-1*H*-1,2,4-triazole-1,2-dicarboxylate (11a): Yellow oil; IR (KBr) 1746 (C=O), 1626 (C=N), 1608, 1512, 1373, 1305, 1258 (C=S), 1173, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=1.14 (3H, t, J=7.1 Hz, CH_3), 1.28 (3H, t, J=7.1 Hz, CH_3), 2.02 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 4.13—4.29 (4H, m, OCH_2CH_3) 6.91 (2H, d, J=8.9 Hz, arom-H), 7.82 (2H, d, J=8.9 Hz, arom-H); ^{13}C NMR ($CDCl_3$) δ=14.00, 14.40 (q, CH_3), 24.45 (q, 5-Me), 55.44 (q, OCH_3), 59.94 (q, OMe), 62.44 (t, OCH_2CH_3), 63.68 (t, OCH_2CH_3), 93.87 (3-C), 113.30, 121.13, 131.85 (1-, 2-, 3-, 5-, 6-C of Ar), 153.20 (COOEt), 153.79 (COOEt), 158.09 (5-C), 162.60 (4-C of Ar), 215.68 (C=S). Found: M^++1, 410.1391. Calcd for $C_{18}H_{23}N_3O_6S$: M+1, 410.1386.

Diethyl 2,3-Dihydro-3-methoxy(thiocarbonyl)-3,5-dimethyl-1*H*-1,2,4-triazole-1,2-dicarboxylate (11b): Yellow oil; IR (neat) 2984, 2941, 1737 (C=O), 1650 (C=N), 1445, 1371, 1274, 1192, 1141, 1111, 1085, 905, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=1.24, 1.34 (each 3H, t, J=7.1 Hz, Me of Et), 1.91 (3H, s, 3-Me), 2.41 (3H, s, 5-Me), 4.10 (3H, s, OMe), 4.09—4.35 (4H, m, CH_2 of Et); ^{13}C NMR ($CDCl_3$) δ=14.23, 14.27 (each Me of Et), 17.07 (5-Me), 25.37 (3-Me), 59.93 (OMe), 62.53, 63.74 (each CH_2 of OEt), 94.58 (3-C), 151.52, 154.36 (each CO_2Et), 155.86 (5-C), 215.89 (C=S). Found: C, 45.10; H, 5.92; N, 13.02%. Calcd for $C_{12}H_{19}N_3O_5S$: C, 45.42; H, 6.03; N, 13.42%.

Diethyl 2,3-Dihydro-3-methoxy(thiocarbonyl)-3-methyl-5-nonyl-1*H*-1,2,4-triazole-1,2-dicarboxylate (11c): Yellow oil; IR (neat) 2925, 2855 (CH_2), 1740 (C=O), 1646 (C=N), 1371, 1273, 1138, 1110, 1083, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=0.88 (3H, t, J=7.0 Hz, CH_3), 1.21—1.37, 1.68—1.75 (14H, m, $-(CH_2)_6CH_3$; 6H, m, OCH_2CH_3), 1.90 (3H, s, CH_3), 2.67 (1H, dt, J=15.4, 7.7 Hz, CH_2-Oct), 2.80 (1H, dt, J=15.4, 7.7 Hz, CH_2-Oct), 4.09 (3H, s, OCH_3), 4.07—4.35 (4H, m, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ=14.08, 22.67, 25.20, 26.41, 29.05, 29.25, 29.51, 30.13, 31.89 (Nonyl, 3-CH_3), 14.23, 14.29 (OCH_2CH_3), 59.81 (OCH_3), 62.40, 63.64 (OCH_2CH_3), 94.46 (3-C), 151.64, 154.33 (C=O), 159.46 (5-C), 216.11 (C=S). Found: C, 55.72; H, 8.02; N, 10.03%. Calcd for $C_{20}H_{35}N_3O_5S$: C, 55.92; H, 8.21; N, 9.78%.

Diethyl 3-Ethoxy(thiocarbonyl)-2,3-dihydro-5-(*p*-methoxyphenyl)-1*H*-1,2,4-triazole-1,2-dicarboxylate (11f): Yellow oil; IR (KBr) 3313, 2980, 1730 (C=O), 1662, 1606, 1499, 1375, 1305, 1257, 1176, 1061, 1025, 847, 767 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.11—1.47 (9H, m, CH_3), 3.85 (3H, s, OCH_3), 4.05—4.65 (6H, m, OCH_2), 6.37 (1H, s, CH), 6.91 (2H, d, J=9.0 Hz, arom-H), 7.84 (2H, d, J=9.0 Hz, arom-H).

Diethyl 2,3-Dihydro-3-methyl-3-(methylthio)carbonyl-5-nonyl-1*H*-1,2,4-triazole-1,2-dicarboxylate (12c): Yellow oil; IR (KBr) 2928, 2853 (CH_2), 1734 (C=O), 1690, 1642 (C=N), 1465, 1371, 1297, 1140, 1093, 996, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (3H, t, J=7.0 Hz, CH_3), 1.21—1.39, 1.70—1.76 (20H, m, OCH_2CH_3, and $CH_2(CH_2)_7CH_3$), 1.82 (3H, s, CH_3), 2.29 (3H, s, SCH_3), 2.69—2.88 (2H, m, CH_2-Oct), 4.16—4.34 (4H, m, OCH_2); ^{13}C NMR δ=11.95 (q, SCH_3), 14.08 (q, $(CH_2)_8CH_3$), 14.21 (q, $COOCH_2CH_3$), 22.68 (q, 3-CH_3), 22.61, 26.28, 29.14, 29.23, 29.25, 29.47, 30.15, 31.89 (t, $(CH_2)_8CH_3$), 62.89 (tq, ^2J=4.6 Hz, $COOCH_2CH_3$), 63.69 (tq, ^2J=4.6 Hz, $COOCH_2CH_3$), 93.86 (q, ^2J=5.1 Hz, 3-C), 151.13 (t, ^2J=3.2 Hz, COOEt), 154.61 (t, ^2J=3.2 Hz, COOEt), 160.13 (s, 5-C), 197.63 (s, $COSCH_3$).

Diethyl 2,3-Dihydro-3-methoxycarbonyl-3-methyl-5-nonyl-1*H*-1,2,4-triazole-1,2-dicarboxylate (13c): ^1H NMR ($CDCl_3$) δ=0.87 (3H, t, J=6.9 Hz, CH_3), 1.06—1.91 (20H, m, OCH_2CH_3, and $(CH_2)_7CH_3$), 1.71 (3H, s, CH_3), 2.56—2.93 (2H, m, CH_2Oct), 3.71 (3H, s, OCH_3), 4.03—4.43 (4H, m, OCH_2). Found: M^++1, 414.2631. Calcd for $C_{20}H_{35}N_3O_6$: M+1, 414.2604.

Diethyl *N*-(5-Methoxy-2-methyl-4-thiazolyl)bicarbamate (14e): IR (KBr) 3185 (NH), 2999, 1745 (C=O), 1582 (N-H), 1532, 1458, 1371, 1335, 1246, 1187, 1061 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24 (3H, t, J=7.3 Hz, CH_3), 1.26 (3H, t, J=7.3 Hz, CH_3), 2.85 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 4.22 (4H, q, J=7.3 Hz, OCH_2).

Diethyl 2-(5-Methoxy-2-methyl-4-thiazolyl)-2-hydroxymalonate (16e): Yellow oil; IR (neat) 3478 (OH), 2985, 2933, 1746 (C=O), 1561, 1448, 1368, 1239, 1221, 1035, 862 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.32 (6H, t, J=7.3 Hz, CH_3), 2.54 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 4.34 (2H, q, J=7.3 Hz, OCH_2), 4.35 (2H, q, J=7.3 Hz, OCH_2); ^{13}C NMR ($CDCl_3$) δ=13.99 (qt, ^2J=2.4 Hz, CH_3), 19.94 (q, 2-CH_3), 62.94 (tq, ^2J=4.3 Hz, OCH_2), 64.36 (q, OCH_3), 77.28 (s, C-OH), 132.61 (s, 4-C), 153.19 (q, ^2J=7.9 Hz, 2-C), 158.04 (q, ^3J=5.5 Hz, 5-C), 168.83 (t, ^3J=3.7 Hz, C=O). Found: M^+, 303.0793. Calcd for $C_{12}H_{17}NO_6S$: M, 303.0777.

Diethyl 2-[5-Ethoxy-2-(*p*-methoxyphenyl)-4-thiazolyl]-2-hydroxymalonate (16f): Colorless crystals; mp 106.2—109.1 °C; ^1H NMR ($CDCl_3$) δ=1.34 (6H, t, J=7.3 Hz, CH_3), 1.40 (3H, t J=7.3 Hz, CH_3), 3.83 (3H, s, OCH_3), 4.13 (2H, q,

J=7.3 Hz, OCH_2), 4.37 (4H, q, J=7.3 Hz, OCH_2), 6.89 (2H, d, J=8.9 Hz, arom-H), 7.69 (2H, d, J=8.9 Hz arom-H); ^{13}C NMR ($CDCl_3$) δ=14.07, 14.25, 14.86 (q, CH_3), 55.36 (q, OCH_3), 62.86 (t, OCH_2), 73.76 (t, OCH_2), 77.48 (d, C–OH), 114.14, 127.11 (d, *o*- and *m*-C of Ar), 126.75 (s, 1-C of Ar), 134.59 (4-C), 154.52 (2-C), 156.92 (5-C), 160.81 (s, 4-C of Ar), 168.87 (s, C=O). Found: C, 55.61; H, 5.58; N, 3.44%. Calcd for $C_{19}H_{23}NO_7S$: C, 55.73; H, 5.66; N, 3.42%.

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