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A NEW SYNTHETIC METHOD FOR SUBSTITUTED 2,4-DIHYDRO-3*H*-1,2,4-TRIAZOL-3-ONES AND 3-THIONES *VIA* 1,4-DIALKYL-5-PHENYLTHIO-1*H*-1,2,4-TRIAZOLIUM SALTS

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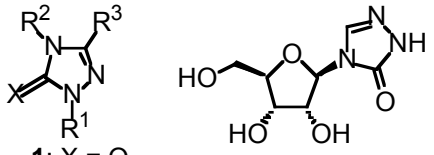
Abstract – Novel 2,4-di- and 2,4,5-trialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones and 2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones were prepared by the reaction of 1,4-dialkyl-5-phenylthio-1,2,4-triazolium salts with aqueous potassium carbonate or sodium sulfide in DMF, respectively.

2,4-Dihydro-3*H*-1,2,4-triazol-3-one derivatives (**1**) have been found as a basic skeleton of several biologically active compounds such as angiotensin II antagonists,[1] anticonvulsant agents[2] and a phytotoxic natural product (**3**), isolated from an *Actinomadura*,[3] and the 3-thione derivatives (**2**) have also been reported to have antidepressant activity[4] (Figure 1).



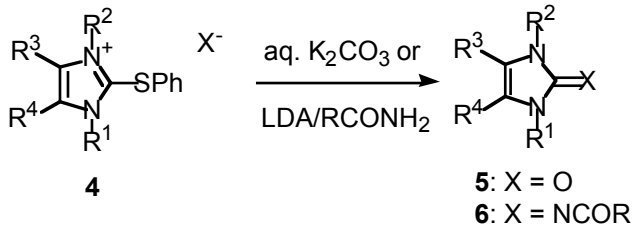
1: X = O
2: X = S

3

Figure 1

Hitherto, there have been several examples of synthetic methods based on cyclization for the functionalized 2,4-dihydro-3*H*-1,2,4-triazol-3-one and 3-thione derivatives,[1a, 2, 5] and a few examples of conversion of *N*-amino-1,2,4-triazole compounds into *N*-amino-1,2,4-triazolones and their thione derivatives through *N*-aminotriazolium salts,[6] however, transformation of polyalkylated triazoles into 2,4-dihydro-3*H*-1,2,4-triazol-3-ones and 3-thiones still remained unknown. We have developed several new synthetic methods of imidazole and triazole derivatives in view of the interest in the

biological properties of these compounds as well as the need for development of new preparation methods.[7] In the preceding papers, we reported a new synthetic method of 1,3-dialkyl-1,3-dihydroimidazol-2-ones (**5**) and 1,3-dialkyl-2,3-dihydro-2-imino-1*H*-imidazoles (**6**) by treatment of readily available 1,3-dialkyl-2-phenylthio-1*H*-imidazolium salts (**4**) with an aqueous potassium carbonate solution[8] and RCONHLi (R = Me, Ph or alkoxy group),[9] respectively (Scheme 1). At this time, we would like to report an application of similar reaction conditions to the preparation of novel 2,4-di- and 2,4,5-trialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**1a-n**) and 2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-thiones (**2a-f**) *via* the corresponding 1,2,4-triazolium salts (**8**).

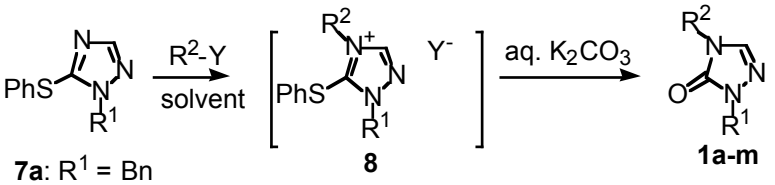


Scheme 1

1-Alkyl-5-phenylthio-1*H*-1,2,4-triazoles (**7a-c**) were easily prepared by treatment of 5-lithio-1-alkyl-1*H*-1,2,4-triazoles with phenyl disulfide according to the reported procedure.[10] Reactions of **7a-c** with various alkyl halides followed by treatment with an aqueous potassium carbonate solution were examined, and the results are summarized in Table 1 Heating a mixture of **7a** and iodomethane without a solvent for 2 h gave the crude triazolium iodide (**8a**) in quantitative yield, then, treatment of the triazolium salt with an aqueous potassium carbonate solution gave 2-benzyl-2,4-dihydro-4-methyl-3*H*-1,2,4-triazol-3-one (**1a**) in 88 % overall yield from **7a** (Entry 1). The sulfides (**7a-c**) reacted similarly with various alkylating agents as above-mentioned, followed by alkaline hydrolysis to give the corresponding triazolones (**1a-m**) in a variety of yields as shown in Table 1. The structure of **1a** was confirmed by HMBC experiment as shown in Figure 2. The regiochemistry of **1a** indicated that the quaternization of **7a** by reaction with iodomethane exclusively occurred at the 4-position in the 1*H*-1,2,4-triazole ring and not at the 2-position, and this regioselectivity was the same as that of quaternization of the 1-substituted 1*H*-1,2,4-triazoles with alkyl halides.[11] Use of methyl tosylate and dimethyl sulfate as methylating agent also gave **1a** in good yield (86 and 92 %, respectively) (Entries 2 and 3). 4-Benzyl- and 4-allyl-3*H*-1,2,4-triazol-3-ones (**1b**) and (**1c**) could be obtained by treatment of **7a** with benzyl bromide and allyl bromide in 75-87 % yields (Entries 4-6). 2-Methyl- and 2-ethyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**1h-m**) were also obtained in reasonable yields (37-73 %) by similar treatment starting from 1-methyl- and 1-ethyl-5-phenylthio-1*H*-1,2,4-triazoles (**7b**,**c**) (Entries 11-15). It is noteworthy that the present reactions could be carried out in one-pot without purification of the

intermediate imidazolium salts (**8**).

Table 1 One-pot reactions for 2,4-dihydro-3*H*-1,2,4-triazol-3-one derivatives (**1a-m**).



7a: R^1 = Bn
7b: R^1 = Me
7c: R^1 = Et

Entry	R^1	R^2	Y	Solvent	Product	Yield (%)[a]
1	Bn	Me	I	-[b]	**1a**	88
2	Bn	Me	TsO	AcOEt	**1a**	86
3	Bn	Me	$MeOSO_3$	AcOEt	**1a**	92
4	Bn	Bn	Br	AcOEt	**1b**	84
5	Bn	Bn	Br	$CHCl_3$	**1b**	87
6	Bn	CH_2=$CHCH_2$	Br	-[c]	**1c**	75
7	Bn	$Ph(CH_2)_3$	TsO	-[b]	**1d**	28
8	Bn	$Ph(CH_2)_2$	Br	-[b]	**1e**	5
9	Bn	Bu	Br	-[b]	**1f**	11
10	Bn	Et	I	-[b]	**1g**	55
11	Me	Bn	Br	AcOEt	**1h**	73
12	Me	CH_2=$CHCH_2$	Br	-[c]	**1i**	62
13	Me	Bu	Br	-[b]	**1j**	37
14	Me	Et	I	-[b]	**1k**	59
15	Et	Me	I	-[b]	**1m**	53

[a] Overall yield from **7**. [b] Solvent was not used (**7**→**8**). [c] Reacted in a sealed tube without solvent (**7**→**8**).

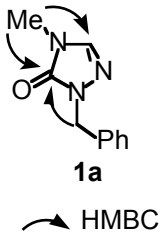
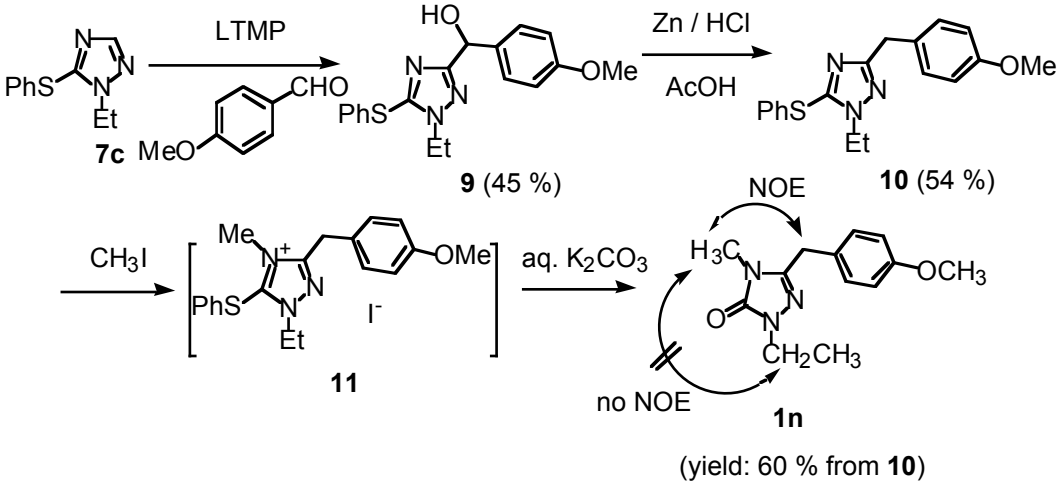


Figure 2 HMBC correlations of **1a**

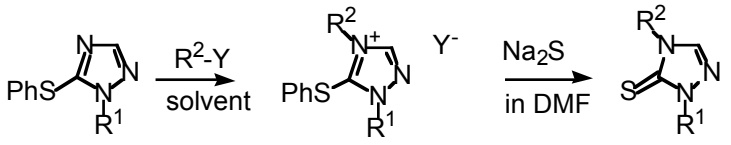
Next, the 5-substituted 2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one derivative (**1n**), all possible ring positions of which were fully substituted, was prepared through the corresponding triazolium salts by application of the present method as shown in Scheme 2. 1,3,5-Trisubstituted 1*H*-1,2,4-triazole (**9**) was prepared by reaction of **7c** with a combination of LTMP and *p*-anisaldehyde according to the reported procedure.[10] The benzylic hydroxy group of **9** was removed by reduction with a zinc powder – *conc*.-HCl system to give the sulfide (**10**) in 54 % yield. The triazolium iodide (**11**) was easily

prepared by treatment of **10** with an excess of iodomethane, then, the salt (**11**) was treated with an aqueous potassium carbonate to afford 2-ethyl-2,4-dihydro-5-(4-methoxybenzyl)-4-methyl-3*H*-1,2,4-triazol-3-one (**1n**) in 60 % yield from **10** in the one-pot manner. The structure of **1n** was confirmed by the NOE experiments as shown in Scheme 2. This method might be more advantageous in view of the regioselective synthesis for the 2,4,5-trialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones rather than the reported method based on the *N*-alkylation of 5-substituted 2-alkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones.[12]



Scheme 2

Table 2 Stepwise preparation of 2,4-dihydro-3*H*-1,2,4-triazol-3-thione derivatives (**2a-f**).



7a: R^1 = Bn
7b: R^1 = Me
7c: R^1 = Et

Entry	R^1	R^2	Y	Solvent	Yield of **8** (%)[a]	Yield of **2** (%)[b]
1	Bn	Me	I	-[c]	Quant. (**8a**)	64 (**2a**)
2	Bn	Bn	Br	AcOEt	Quant. (**8b**)	61 (**2b**)
3	Bn	CH_2=$CHCH_2$	Br	-[d]	75 (**8c**)	63 (**2c**)
4	Bn	Et	I	-[c]	73 (**8d**)	82 (**2d**)
5	Me	Me	I	-[c]	Quant. (**8e**)	28 (**2e**)
6	Me	Bn	Br	AcOEt	78 (**8f**)	40 (**2f**)

[a] The salts (**8a-f**) were used after purification for the next reaction (stepwise reaction). [b] Yield from **8**. [c] Solvent was not used (**7**→**8**). [d] Reacted in a sealed tube without solvent (**7**→**8**).

Then, we applied the present synthetic method to the preparation of 2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones by treatment of the intermediate (**8**) with sodium sulfide instead of the aqueous

potassium carbonate, and the results are shown in Table 2. For example, treatment of 1-benzyl-4-methyl-5-phenylthio-1*H*-1,2,4-triazolium iodide (**8a**) with sodium sulfide in DMF gave 2-benzyl-4-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**2a**) in 64 % yield (Entry 1). Various substituted 2,4-dihydro-3*H*-triazole-3-thiones (**2b**-**f**) could also be synthesized under similar reaction conditions as above-mentioned in 28-82 % yields from the corresponding triazolium salts (**8b**-**f**) (Entries 2-6).

In conclusion, we have developed a regioselective synthesis of the multi-substituted 2,4-dihydro-3*H*-1,2,4-triazol-3-ones and 3-thiones *via* 1,4-dialkyl-5-phenylthio-1*H*-1,2,4-triazolium salts. We are currently investigating the scope of this reaction and its application to preparation of biologically active compounds.

EXPERIMENTAL

All mps were measured with a Yanaco MP micro-melting-point apparatus and are uncorrected. IR spectra were taken with Shimadzu IR-435 spectrophotometer. NMR spectra were measured on Varian UNITY INOVA 400NB (^{1}H: 400 MHz, ^{13}C: 100 MHz) or JEOL EX-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer with tetramethylsilane as internal standard, and chemical shifts δ are reported in ppm. MS and HRMS spectra were measured on JEOL JMS-SX 102A QQ (FAB) or JEOL JMS BU-20 (EI) spectrometer, respectively. Silica gel (Merck Art. 7734) for column chromatography and Silica gel 60 PF_{254} (Nacalai Tesque Inc.) for preparative TLC (PTLC) were used.

1-Benzyl-5-phenylthio-1*H*-1,2,4-triazole (7a). *n*-BuLi (1.6 M in *n*-hexane; 22.5 mL, 36.0 mmol) was added to a stirred solution of 1-benzyl-1*H*-1,2,4-triazole[13] (4.776 g, 30.0 mmol) in THF (80 mL) under N_2 at -78 °C. After stirring for 30 min at the same temperature, diphenyl disulfide (7.860 g, 36.0 mmol) was added to the mixture and stirring was continued for 2 h at ambient temperature. Water (10 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The product was extracted with AcOEt (100 mL X 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified by column chromatography (AcOEt–*n*-hexane 1:1) on silica gel to give **7a** (6.983 g, 87 %) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.39 (s, 2H), 7.19-7.39 (m, 10H), 7.96 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 52.7, 127.7, 128.2, 128.4, 128.7, 129.4, 130.4, 131.3, 134.8, 149.4, 152.0. IR ($CHCl_3$) cm^{-1}: 3042, 1579, 1491, 1449, 1326, 1267, 1171, 1092. EI-HRMS *m/z* Calcd for $C_{15}H_{13}N_3S$: *M*, 267.0830. Found: M^+, 267.0835.

1-Ethyl-5-phenylthio-1*H*-1,2,4-triazole (7c). This was prepared in a similar manner as that used for preparation of **7a** except for use of 1-ethyl-1*H*-1,2,4-triazole[14] instead of 1-benzyl-1*H*-1,2,4-triazole. Yield; 5.050g (82 %). Colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, 3H, *J* = 7.3 Hz), 4.24 (q, 2H, *J* = 7.3 Hz), 7.27-7.41 (m, 5H), 7.94 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.8, 44.2, 128.2, 129.5,

130.8, 130.9, 148.2, 151.8. IR ($CHCl_3$) cm^{-1}: 2966, 1580, 1471, 1438, 1325, 1268, 1174, 1081. EI-HRMS *m/z* Calcd for $C_{10}H_{11}N_3S$: *M*, 205.0674. Found: M^+, 205.0668.

General procedure for synthesis of 1,4-dialkyl-5-phenylthio-1*H*-1,2,4-triazolium halides (8) and 2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (1); Synthesis of 2-Benzyl-2,4-dihydro-4-methyl-3*H*-1,2,4-triazol-3-one (1a) as an Example. A mixture of sulfide (**7a**) (134 mg, 0.5 mmol) and iodomethane (0.311 mL, 5.0 mmol) was refluxed under stirring for 2 h. The crude triazolium iodide was washed by decantation after addition of AcOEt (5 mL X 3). Then, the residue was dissolved in K_2CO_3 aqueous solution (1 M, 1.0 mL) and heated at 80 °C for 3 h. The product was extracted with AcOEt (30 mL X 3), and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified by PTLC (AcOEt) to give **1a** (83 mg, 88 %) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 3.31 (s, 3H, Me), 4.95 (s, 2H, PhC*H*$_2$), 7.26-7.37 (m, 6H, PhH and H-5). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 28.8 (Me), 49.2 (Ph*C*H_2), 127.8 (C-4'), 128.1 (C-2'), 128.6 (C-3'), 135.6 (C-5), 136.1 (C-1'), 153.4 (C=O). IR ($CHCl_3$) cm^{-1}: 2932, 1692, 1553, 1395, 1090. EI-HRMS *m/z* Calcd for $C_{10}H_{11}N_3O$: *M*, 189.0902. Found: M^+, 189.0898.

2,4-Dibenzyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1b). This was similarly prepared using benzyl bromide (0.119 mL, 1.0 mmol) and $CHCl_3$ (0.3 mL) instead of iodomethane and the reaction mixture was refluxed at 80 °C for 4 h. The product was purified by PTLC (AcOEt–*n*-hexane 1:1) and recrystallized from AcOEt–*n*-hexane to give **1b** as colorless needles, mp 90-91 °C (lit.,[15] mp 91-93 °C). Yield: 116 mg (87 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 4.80 (s, 2H), 4.98 (s, 2H), 7.26-7.40 (m, 11H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 46.2, 49.3, 127.8, 128.0, 128.1, 128.3, 128.6, 129.0, 135.01, 135.04, 136.1, 153.1. IR ($CHCl_3$) cm^{-1}: 1698, 1547, 1403, 1164, 1091, 693.

2-Benzyl-2,4-dihydro-4-(2-propenyl)-3*H*-1,2,4-triazol-3-one (1c). This was similarly prepared using allyl bromide (0.216 mL, 2.5 mmol) and the reaction mixture was heated in a sealed tube at 80 °C for 13 h. The product was purified by PTLC (AcOEt–*n*-hexane 1:1) to give **1c** as a yellow oil. Yield: 81 mg (75 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 4.26 (dt, 2H, *J* = 6.1, 1.5 Hz), 4.96 (s, 2H), 5.23-5.32 (m, 2H), 5.89 (ddt, 1H, *J* = 17.0, 10.3, 5.9 Hz), 7.27-7.37 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 44.7, 49.2, 119.4, 127.9, 128.2, 128.6, 131.4, 135.0, 136.1, 152.9. IR ($CHCl_3$) cm^{-1}: 2977, 1696, 1548, 1402, 1331, 935, 697. EI-HRMS *m/z* Calcd for $C_{12}H_{13}N_3O$: *M*, 215.1058. Found: M^+, 215.1062.

2-Benzyl-2,4-dihydro-4-(3-phenylpropyl)-3*H*-1,2,4-triazol-3-one (1d). This was similarly prepared using 3-phenyl-1-propyl tosylate (726 mg, 2.5 mmol) instead of iodomethane and the reaction mixture was heated at 80 °C for 13 h. The product was purified by PTLC (AcOEt–*n*-hexane 1:1) and recrystallized from AcOEt–*n*-hexane to give **1d** as colorless needles, mp 48-49°C. Yield: 41 mg (28 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 2.02-2.09 (m, 2H), 2.66 (t, 2H, *J* = 7.6 Hz), 3.66 (t, 2H, *J* = 7.3 Hz), 4.95 (s, 2H), 7.16-7.36 (m, 11H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 30.5, 32.6, 42.1, 49.2, 126.2, 127.8, 128.1, 128.3, 128.5, 128.6, 135.2, 136.2, 140.2, 153.1. IR ($CHCl_3$) cm^{-1}: 1690, 1205, 1040, 923. EI-HRMS *m/z*

Calcd for $C_{18}H_{19}N_3O$: *M*, 293.1528. Found: M^+, 293.1518. *Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.40; H, 6.51; N, 14.51.

2-Benzyl-2,4-dihydro-4-(2-phenylethyl)-3*H*-1,2,4-triazol-3-one (1e). This was similarly prepared using phenethyl bromide (0.341 mL, 2.5 mmol) instead of iodomethane and the reaction mixture was heated at 90 °C for 12 h. The product was purified by PTLC (AcOEt) to give **1e** as a colorless oil. Yield: 7 mg (5 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 3.00 (t, 2H, *J* = 7.0 Hz), 3.89 (t, 2H, *J* = 7.0 Hz), 4.94 (s, 2H), 6.91-7.36 (m, 11H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 35.2, 44.1, 49.1, 127.0, 127.8, 128.1, 128.6, 128.7, 128.8, 135.4, 136.2, 137.2, 153.0. IR ($CHCl_3$) cm^{-1}: 1688, 1548, 1468, 1404, 1162, 1092, 694. EI-HRMS *m/z* Calcd for $C_{17}H_{17}N_3O$: *M*, 279.1371. Found: M^+, 279.1372.

2-Benzyl-4-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1f). This was similarly prepared using *n*-butyl bromide (0.537 mL, 5 mmol) instead of iodomethane and the reaction mixture was heated at 110 °C for 8 h. The product was purified by PTLC (AcOEt–*n*-hexane 1:1) to give **1f** as a yellow oil. Yield: 13 mg (11 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 0.95 (t, 3H, *J* = 7.3 Hz), 1.32-1.41 (m, 2H), 1.65-1.73 (m, 2H), 3.64 (t, 2H, *J* = 7.3 Hz), 4.95 (s, 2H), 7.26-7.37 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 13.5, 19.7, 31.2, 42.3, 49.2, 127.8, 128.1, 128.6, 135.2, 136.2, 153.2. IR ($CHCl_3$) cm^{-1}: 3009, 1696, 1548, 1404, 1228, 1096, 821, 694. EI-HRMS *m/z* Calcd for $C_{13}H_{17}N_3O$: *M*, 231.1371. Found: M^+, 231.1367.

2-Benzyl-4-ethyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (1g). This was similarly prepared using iodoethane (0.80 mL, 10 mmol) instead of iodomethane and the reaction mixture was refluxed for 12 h. The product was purified by PTLC (AcOEt–*n*-hexane 1:1) to give **1g** as a colorless oil. Yield: 56 mg (55 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 1.08 (t, 3H, *J* = 7.3 Hz), 3.66 (q, 2H, *J* = 7.3 Hz), 5.02 (s, 2H), 7.22-7.40 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 14.0, 37.5, 49.4, 127.9, 128.1, 128.2, 128.7, 129.6, 129.7. IR ($CHCl_3$) cm^{-1}: 2924, 1687, 1549, 1491, 1381, 1228, 1080, 954, 824, 693. EI-HRMS *m/z* Calcd for $C_{11}H_{13}N_3O$: *M*, 203.1058. Found: M^+, 203.1068.

4-Benzyl-2,4-dihydro-2-methyl-3*H*-1,2,4-triazol-3-one (1h). This was similarly prepared using **7b**[10] instead of **7a** and benzyl bromide (0.12 mL, 1.0 mmol) and AcOEt (0.3 mL) were used instead of iodomethane, and the reaction mixture was refluxed at 80 °C for 20 h. The product was purified by PTLC (AcOEt) and recrystallized from AcOEt–*n*-hexane to give **1h** as colorless needles, mp 72-73 °C. Yield: 69 mg (73 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 3.48 (s, 3H), 4.79 (s, 2H), 7.28-7.37 (m, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 32.5, 46.1, 127.9, 128.3, 129.0, 134.5, 135.1, 153.2. IR ($CHCl_3$) cm^{-1}: 2977, 1698, 1548, 1421, 988, 694. EI-HRMS *m/z* Calcd for $C_{10}H_{11}N_3O$: *M*, 189.0902. Found: M^+, 189.0905. *Anal.* Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.30; H, 5.66; N, 22.21.

2,4-Dihydro-2-methyl-4-(2-propenyl)-3*H*-1,2,4-triazol-3-one (1i). This was similarly prepared using **7b**[10] instead of **7a** and allyl bromide (0.22 mL, 2.5 mmol) was used instead of iodomethane, and the reaction mixture was heated in a sealed tube at 80 °C for 11 h. The product was purified by PTLC (AcOEt) to give **1i** as a yellow oil. Yield: 43 mg (62 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 3.48 (s, 3H),

4.25 (dt, 2H, *J* = 5.9, 1.5 Hz), 5.24-5.33 (m, 2H,), 5.89 (ddt, 1H, *J* = 17.0, 10.3, 5.9 Hz), 7.39 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 32.4, 44.5, 119.1, 131.4, 134.5, 153.0. IR ($CHCl_3$) cm^{-1}: 3056, 1694, 1547, 1417, 1329, 1231, 988, 934, 565. EI-HRMS *m/z* Calcd for $C_6H_9N_3O$: *M*, 139.0745. Found: M^+, 139.0742.

4-Butyl-2,4-dihydro-2-methyl-3*H*-1,2,4-triazol-3-one (1j). This was similarly prepared using **7b**[10] instead of **7a** and *n*-butyl bromide (0.537 mL, 5.0 mmol) was used instead of iodomethane, and the reaction mixture was heated at 110 °C for 5 h. The product was purified by PTLC (AcOEt) to give **1j** as a yellow oil. Yield: 29 mg (37 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 0.90 (t, 3H, *J* = 7.3 Hz), 1.26-1.36 (m, 2H), 1.60-1.67 (m, 2H), 3.40 (s, 3H), 3.58 (t, 2H, *J* = 7.3 Hz), 7.36 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 13.4, 19.6, 31.2, 32.4, 42.3, 134.7, 153.3. IR ($CHCl_3$) cm^{-1}: 2974, 1686, 1547, 1421, 1098, 987, 657. EI-HRMS *m/z* Calcd for $C_7H_{13}N_3O$: *M*, 155.1058. Found: M^+, 155.1062.

4-Ethyl-2,4-dihydro-2-methyl-3*H*-1,2,4-triazol-3-one (1k). This was similarly prepared using **7b**[10] instead of **7a** and iodoethane (0.80 mL, 10.0 mmol) was used instead of iodomethane, and the reaction mixture was refluxed for 12 h. The product was purified by PTLC (AcOEt) to give **1k** as a colorless oil. Yield: 38 mg (59 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 1.36 (t, 3H, *J* = 7.3 Hz), 3.47 (s, 3H), 3.70 (q, 2H, *J* = 7.3 Hz), 7.41 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 14.5, 32.3, 37.4, 134.2, 153.1. IR ($CHCl_3$) cm^{-1}: 2971, 1697, 1547, 1421, 1225, 1081, 954, 816, 625. EI-HRMS *m/z* Calcd for $C_5H_9N_3O$: *M*, 127.0745. Found: M^+, 127.0748.

2-Ethyl-2,4-dihydro-4-methyl-3*H*-1,2,4-triazol-3-one (1m). This was similarly prepared using **7c** instead of **7a** and the reaction mixture was refluxed for 8 h. The product was purified by PTLC (AcOEt) to give **1m** as a yellow oil. Yield: 34 mg (53 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 1.25 (t, 3H, *J* = 7.3 Hz), 3.23 (s, 3H), 3.77 (q, 2H, *J* = 7.3 Hz), 7.32 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 13.8, 28.7, 40.4, 135.4, 153.1. IR ($CHCl_3$) cm^{-1}: 2969, 1696, 1550, 1399, 1229, 1052, 1014, 952. EI-HRMS *m/z* Calcd for $C_5H_9N_3O$: *M*, 127.0745. Found: M^+, 127.0739.

1-Ethyl-3-{(1-hydroxy)-[1-(4-methoxyphenyl)methyl]}-5-phenylthio-1*H*-1,2,4-triazole (9). *n*-BuLi (1.6 M in *n*-hexane; 0.69 mL, 1.1 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.203 mL, 1.2 mmol) and *N,N,N,N*-tetramethylethylenediamine (0.196 mL, 1.3 mmol) in THF (4 mL) under N_2 at -78 °C. After stirring for 10 min at the same temperature, a solution of **7c** (205 mg, 1.0 mmol) in THF (1.0 mL) was added and the whole was stirred for 1 h at -78 °C. Then, *p*-anisaldehyde (0.146 mL, 1.2 mmol) was added to the mixture and stirring was continued for 3 h at ambient temperature. Water (5 mL) was added to it and the solvent was removed under reduced pressure. The product was extracted with AcOEt (30 mL X 3) and the organic layers were dried over anhydrous sodium sulfate. The solvent was evaporated and the product was purified by PTLC (AcOEt–*n*-Hexane 1:1) to give **9** (154 mg, 45 %) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) □: 1.31(t, 3H, *J* = 7.3 Hz), 3.12 (br, 1H), 3.79 (s, 3H), 4.19 (q, 2H, *J* = 7.3 Hz), 5.83 (s, 1H), 6.87 (d, 2H, *J* = 8.4 Hz), 7.26-7.42 (m,

7H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.8, 44.3, 55.2, 70.3, 113.8, 127.9, 128.0, 129.4, 130.1, 133.7, 136.1, 147.9, 159.2, 165.7. IR ($CHCl_3$) cm^{-1}: 3384, 2969, 1698, 1606, 1574, 1506, 1437, 1243, 1054. EI-HRMS *m/z* Calcd for $C_{18}H_{19}N_3O_2S$: *M*, 341.1198. Found: M^+, 341.1189.

1-Ethyl-3-[(4-methoxyphenyl)methyl]-5-phenylthio-1*H*-1,2,4-triazole (10). Zn powder (240 mg) was added to a mixture of **9** (52 mg, 0.15 mmol) in *conc*.-HCl (0.24 mL) and AcOH (0.81 mL), and the whole was stirred at 80 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated, diluted with water (5 mL) and basified by addition of K_2CO_3 powder. The product was extracted with AcOEt (20 mL X 4), and the organic phase was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified by PTLC (AcOEt–*n*-Hexane 1:1) to give **10** (27 mg, 55 %) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.30 (t, 3H, *J* = 7.1 Hz), 3.77 (s, 3H), 4.01 (s, 2H), 4.16 (q, 2H, *J* = 7.1 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 7.25-7.30 (m, 7H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.9, 34.0, 44.1, 55.2, 113.8, 127.7, 129.4, 129.77, 129.79, 130.0, 131.9, 147.3, 158.2, 163.9. IR ($CHCl_3$) cm^{-1}: 3013, 1580, 1506, 1475, 1239, 1050. EI-HRMS *m/z* Calcd for $C_{18}H_{19}N_3OS$: *M*, 325.1249. Found: M^+, 325.1247.

2-Ethyl-2,4-dihydro-5-[(4-methoxyphenyl)methyl]-4-methyl-3*H*-1,2,4-triazol-3-one (1n). A mixture of **10** (21 mg, 0.06 mmol) and iodomethane (0.039 mL, 0.62 mmol) was refluxed under stirring for 5 h. The crude triazolium iodide was washed by decantation after addition of AcOEt (3 mL X 3). Then, the residue was dissolved in K_2CO_3 aqueous solution (1 M, 1.0 mL) and heated at 80 °C for 5 h. The mixture was extracted with AcOEt (30 mL X 3), and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified by PTLC (AcOEt) to give **1n** (9 mg, 60 %) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.35 (t, 3H, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 3.03 (s, 3H, NCH$_3$), 3.80 (s, 3H, OCH$_3$), 3.85 (q, 2H, *J* = 7.1 Hz, CH$_3$C*H*$_2$), 3.84 (s, 2H, ArC*H*$_2$), 6.86 (d, 2H, *J* = 8.8 Hz, H-3' and H-5'), 7.11 (d, 2H, *J* = 8.8 Hz, H-2' and H-6'). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.0, 27.5, 31.8, 40.2, 55.3, 114.3, 126.1, 129.3, 145.1, 153.8, 158.8. IR ($CHCl_3$) cm^{-1}: 2970, 1685, 1506, 1242, 1031. EI-HRMS *m/z* Calcd for $C_{13}H_{17}N_3O_2$: *M*, 247.1321. Found: M^+, 247.1314.

1-Benzyl-4-methyl-5-phenylthio-1*H*-1,2,4-triazolium iodide (8a). The crude triazolium iodide (**8a**) was obtained in the same manner as that used for preparation of **1a**. After washing the crude **8a** by decantation after addition of AcOEt, the residue was dried at 50 °C for 24 h under reduced pressure (2 mmHg) to give pure **8a** (205 mg, 100 %) as colorless amorphous. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 4.00 (s, 3H)**,** 5.67 (s, 2H), 7.16 (m, 10H), 9.72 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 35.7, 56.4, 125.7, 128.5, 128.9, 129.1, 130.1, 130.5, 131.4, 131.5, 146.2, 148.9. IR ($CHCl_3$) cm^{-1}: 3005, 1491, 1349, 1224, 1066, 657. FAB-HRMS *m/z* Calcd for $C_{16}H_{16}N_3S$: *M*-I, 282.1065. Found: $(M\text{-}I)^+$, 282.1062. *Anal.* Calcd for $C_{16}H_{16}N_3IS$: C, 46.95; H, 3.94; N, 10.27. Found: C, 47.21; H, 4.05; N, 9.99.

1,4-Dibenzyl-5-phenylthio-1*H*-1,2,4-triazolium bromide (8b). The crude triazolium bromide (**8b**) was obtained in the same manner as that used for preparation of **1b**. After washing the crude **8b** by

decantation after addition of AcOEt, the residue was recrystallized from $CHCl_3$–AcOEt to give pure **8b** as colorless needles, mp 173-175 °C. Yield: 219 mg (100 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 5.59 (s, 2H), 5.77 (s, 2H), 6.91-7.46 (m, 15H), 9.74 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 52.3, 56.2, 127.0, 128.7, 129.0, 129.2, 129.27, 129.31, 129.4, 129.8, 130.4, 130.7, 131.3, 131.6, 145.8, 148.7. IR ($CHCl_3$) cm^{-1}: 2922, 1492, 1072, 657. FAB-HRMS *m/z* Calcd for $C_{22}H_{20}N_3S$: *M*-Br, 358.1378. Found: $(M\text{-}Br)^+$, 358.1373. *Anal.* Calcd for $C_{22}H_{20}N_3BrS$: C, 60.27; H, 4.60; N, 9.59. Found: C, 60.26; H, 4.61; N, 9.34.

1-Benzyl-5-phenylthio-4-(2-propenyl)-1*H*-1,2,4-triazolium bromide (8c). The crude triazolium bromide (**8c**) was obtained in the same manner as that used for preparation of **1c**. After washing the crude **8c** by decantation after addition of AcOEt, the residue was recrystallized from $CHCl_3$–AcOEt to give pure **8c** as colorless needles, mp 140-141 °C. Yield: 146 mg (75 %). ^{1}H-NMR ($CDCl_3$, 300 MHz) □: 4.26 (d, 2H, *J* = 6.2 Hz), 5.33 (d, 1H, *J* = 16.9 Hz), 5.42 (d, 1H, *J* = 10.3 Hz), 5.68 (s, 2H), 5.89 (ddt, 1H, *J* = 16.9, 10.3, 6.4 Hz), 7.13 (d, 2H, *J* = 7.3 Hz), 7.27-7.39 (m, 8H), 9.79 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) □: 50.8, 56.4, 123.1, 126.7, 128.5, 128.7, 129.1, 129.3, 130.1, 130.6, 131.2, 131.7, 146.0, 148.5. IR ($CHCl_3$) cm^{-1}: 2922, 1474, 1438, 1234, 1070, 657. FAB-HRMS *m/z* Calcd for $C_{18}H_{18}N_3S$: *M*-Br, 308.1221. Found: $(M\text{-}Br)^+$, 308.1214. *Anal.* Calcd for $C_{18}H_{18}N_3BrS$: C, 55.67; H, 4.67; N, 10.82. Found: C, 55.51; H, 4.70; N, 10.63.

1-Benzyl-4-ethyl-5-phenylthio-1*H*-1,2,4-triazolium iodide (8d). The crude triazolium iodide (**8d**) was obtained in the same manner as that used for preparation of **1g**. After washing the crude **8d** by decantation after addition of AcOEt, the residue was recrystallized from $CHCl_3$–AcOEt to give pure **8d** as colorless needles, mp 149-150 °C. Yield: 155 mg (73 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 1.46 (t, 3H, *J* = 7.3 Hz), 4.44 (q, 2H, *J* = 7.3 Hz), 5.70 (s, 2H), 7.08-7.37 (m, 10H), 9.74 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 14.8, 44.6, 56.9, 126.7, 128.9, 129.1, 129.4, 130.1, 130.7, 131.1, 131.7, 145.5, 148.4. IR ($CHCl_3$) cm^{-1}: 2924, 1491, 1445, 1228, 657. FAB-HRMS *m/z* Calcd for $C_{17}H_{18}N_3S$: *M*-I, 296.1221. Found: $(M\text{-}I)^+$, 296.1219. *Anal.* Calcd for $C_{17}H_{18}N_3IS$: C, 48.23; H, 4.29; N, 9.93. Found: C, 48.30; H, 4.46; N, 9.83.

1,4-Dimethyl-5-phenylthio-1*H*-1,2,4-triazolium iodide (8e). The crude triazolium iodide (**8e**) was obtained in the similar manner as that used for preparation of **1a** except for use of **7b**[10] instead of **7a**. After washing the crude **8e** by decantation after addition of AcOEt, the residue was dried at 50 °C for 8 h under reduced pressure (2 mmHg) to give pure **8a** as a yellow oil. Yield: 167 mg (100 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 4.07 (s, 3H), 4.12 (s, 3H), 7.35-7.91 (m, 5H), 9.56 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 35.9, 39.9, 126.0, 130.5, 130.9, 132.0, 145.9, 149.7. IR ($CHCl_3$) cm^{-1}: 3012, 1473, 1430, 1230, 1065, 657. FAB-HRMS *m/z* Calcd for $C_{10}H_{12}N_3S$: *M*-I, 206.0752. Found: $(M\text{-}I)^+$, 206.0757. *Anal.* Calcd for $C_{10}H_{12}N_3IS$: C, 36.05; H, 3.63; N, 12.61. Found: C, 36.33; H, 3.93; N, 12.35.

4-Benzyl-1-methyl-5-phenylthio-1*H*-1,2,4-triazolium bromide (8f). The crude triazolium bromide (**8f**) was obtained in the same manner as that used for preparation of **1h**. After washing the crude **8f** by

decantation after addition of AcOEt, the residue was recrystallized from $CHCl_3$–AcOEt to give pure **8f** as colorless plates, mp 84-86 °C. Yield: 141 mg (78 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 3.99 (s, 3H), 5.85 (s, 2H,), 7.15-7.50 (m, 10H), 9.69 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 39.5, 52.4, 126.3, 129.25, 129.31, 129.4, 130.2, 130.6, 131.5, 132.0, 145.4, 149.1. IR ($CHCl_3$) cm^{-1}: 3006, 1495, 1439, 1231, 1069, 657. FAB-HRMS *m/z* Calcd for $C_{16}H_{16}N_3S$: *M*-Br, 282.1065. Found: $(M-Br)^+$, 282.1070. *Anal*. Calcd for $C_{16}H_{16}N_3BrS{\cdot}H_2O$: C, 50.53; H, 4.77; N, 11.05. Found: C, 50.94; H, 4.66; N, 10.78.

General procedure for synthesis of 2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (2); Synthesis of 2-Benzyl-2,4-dihydro-4-methyl-3*H*-1,2,4-triazole-3-thione (2a) as an Example. A solution of sodium sulfide nonahydrate (480 mg, 2.0 mmol) in DMF (0.5 mL) was added to the triazolium iodide (**8a**) (409 mg, 1.0 mmol) under N_2, and the mixture was heated at 80 °C under stirring for 4 h. Water (5 mL) was added to the reaction mixture and the product was extracted with Et_2O (30 mL X 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give an oily residue, which was purified by PTLC (AcOEt–*n*-Hexane 1:1) and recrystallized from AcOEt–*n*-hexane to give **2a** (131 mg, 64 %) as colorless needles, mp 118-119 °C (lit.,[16] mp 116-118 °C). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 3.58 (s, 3H), 5.38 (s, 2H), 7.32-7.45 (m, 5H), 7.76 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 32.8, 52.7, 128.2, 128.55, 128.60, 135.0, 140.0, 166.8. IR ($CHCl_3$) cm^{-1}: 2947, 1694, 1541, 1437, 1413, 1351.

2,4-Dibenzyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (2b). This was similarly prepared using triazolium bromide (**8b**) instead of **8a**. The product was purified by PTLC (AcOEt) and recrystallized from AcOEt–*n*-hexane to give **2b** as colorless needles, mp 99-100 °C. Yield: 172 mg (61 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 5.16 (s, 2H), 5.41 (s, 2H), 7.25-7.46 (m, 10H), 7.55 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 49.8, 52.7, 128.2, 128.5, 128.6, 128.7, 128.8, 129.2, 134.1, 135.1, 138.9, 166.6. IR ($CHCl_3$) cm^{-1}: 2948, 1533, 1492, 1439, 1416, 1347, 1228, 1090, 1035. EI-HRMS *m/z* Calcd for $C_{16}H_{15}N_3S$: *M*, 281.0987. Found: M^+, 281.0983. *Anal*. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.50; H, 5.50; N, 14.75.

2-Benzyl-2,4-dihydro-4-(2-propenyl)-3*H*-1,2,4-triazole-3-thione (2c). This was similarly prepared using triazolium bromide (**8c**) instead of **8a**. The product was purified by PTLC (AcOEt) to give **2c** as a yellow oil. Yield**:** 146 mg (63 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) □: 4.63 (d, 2H, *J* = 6.0 Hz), 5.32 (br d, 1H, *J* = 17.2 Hz), 5.38 (br d, 1H, *J* = 10.1 Hz), 5.41 (s, 2H), 5.95 (ddt, 1H, *J* = 16.7, 10.3, 6.0 Hz), 7.26-7.46 (m, 5H), 7.73 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) □: 48.4, 52.7, 120.7, 128.2, 128.6, 128.7, 130.4, 135.1, 138.8, 166.3. IR ($CHCl_3$) cm^{-1}: 2954, 1532, 1490, 1438, 1414, 1354, 1226, 938. EI-HRMS *m/z* Calcd for $C_{12}H_{13}N_3S$: *M*, 231.0830. Found: M^+, 231.0832.

2-Benzyl-4-ethyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (2d). This was similarly prepared using triazolium bromide (**8d**) instead of **8a**. The product was purified by PTLC (AcOEt), and recrystallization from AcOEt–*n*-hexane gave **2d** as colorless plates, mp 122-124 °C. Yield: 180 mg (82 %). ^{1}H-NMR

($CDCl_3$, 400 MHz) δ: 1.42 (t, 3H, *J* = 7.3 Hz), 4.04 (q, 2H, *J* = 7.3 Hz), 5.39 (s, 2H), 7.19-7.45 (m, 5H), 7.75 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 13.9, 41.2, 52.4, 128.1, 128.51, 128.54, 135.1, 138.5, 165.9. IR ($CHCl_3$) cm^{-1}: 2953, 1532, 1490, 1439, 1417, 1363, 1246. EI-HRMS *m/z* Calcd for $C_{11}H_{13}N_3S$: *M*, 219.0830. Found: M^+, 219.0833. *Anal.* Calcd for $C_{11}H_{13}N_3S$: C, 60.24; H, 5.97; N, 19.16. Found: C, 60.17; H, 6.22; N, 18.99.

2,4-Dihydro-2,4-dimethyl-3*H*-1,2,4-triazole-3-thione (2e). This was similarly prepared using triazolium bromide (**8e**) instead of **8a**. The product was purified by PTLC (AcOEt), and recrystallization from AcOEt–*n*-hexane gave **2e** as colorless needles, mp 92-93 °C (lit.,[17] mp 94-95 °C). Yield: 36 mg (28 %). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.60 (s, 3H), 3.64 (s, 3H), 7.75 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 32.8, 36.6, 139.1, 166.5. IR ($CHCl_3$) cm^{-1}: 2946, 1539, 1474, 1389, 1358, 1220, 1170, 1022, 977.

4-Benzyl-2,4-dihydro-2-methyl-3*H*-1,2,4-triazole-3-thione (2f). This was similarly prepared using triazolium bromide (**8f**) instead of **8a**. The product was purified by PTLC (AcOEt), and recrystallization from AcOEt–*n*-hexane gave **2f** as colorless needles, mp 79-81 °C. Yield: 82 mg (40 %). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.83 (s, 3H), 5.17 (s, 2H), 7.32-7.41 (m, 5H), 7.58 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 36.7, 49.7, 128.4, 128.8, 129.2, 134.2, 138.4, 166.4. IR ($CHCl_3$) cm^{-1}: 2948, 1529, 1460, 1396, 1352, 1177, 975, 697. EI-HRMS *m/z* Calcd for $C_{10}H_{11}N_3S$: *M*, 205.0674. Found: M^+, 205.0684. *Anal.* Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47. Found: C, 58.43; H, 5.59; N, 20.19.

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