Conventional and Microwave Irradiation Assisted Synthesis of New 1,2,4-Triazepine-3-thiones

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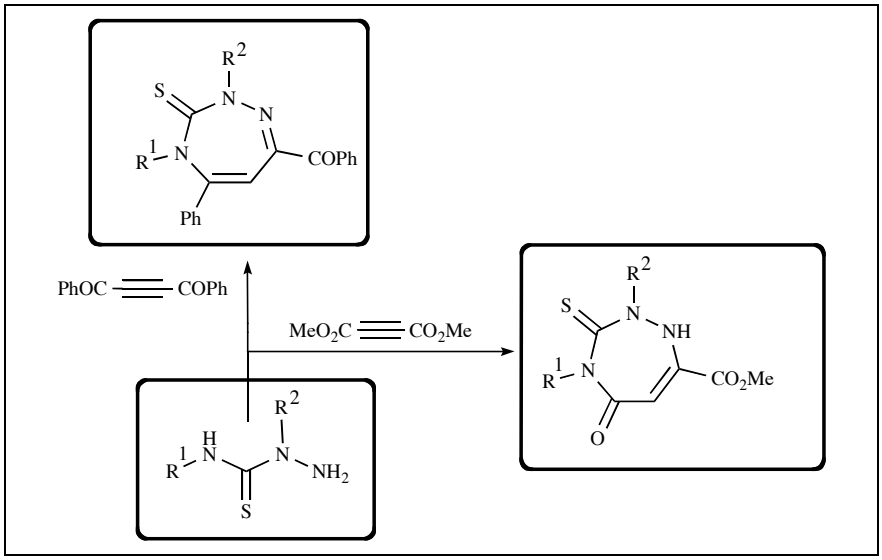

New 1,2,4-triazepine-3-thiones have been obtained during the respective reactions of *N*-substituted-hydrazino carbothioamides with dimethyl acetylenedicarboxylate and dibenzoyl acetylene under prolonged reflux in acetic acid and/or DMF. However, the reaction of the starting materials in DMF under microwave irradiation afforded the same products in higher yields within a few minutes.

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INTRODUCTION

Thiosemicarbazides are easily cyclized by the action of acids, bases or oxidants; therefore they are useful versatile building blocks for the preparation of heterocyclic ring systems. The heterocyclization of 1,4-disubstituted thiosemicarbazides - in basic or acidic media and under various reaction conditions - were investigated [1-3]. Four-, five-, six- and seven-membered heterocyclic compounds were prepared by the reaction of thiosemicarbazide derivatives with α- and β-haloketones [4-6]. The N^2 of the thiosemicarbazide group is a softer nucleophilic center than the harder and more powerful terminal nitrogen N^1. Thus, reagents susceptible to nucleophilic attack by N^1 may in a second step undergo cyclization to afford the aforesaid heterocycles in excellent yields, even under mild reaction conditions [4,5]. Microwave (MW) irradiation of thiosemicarbazides has been employed for rapid synthesis of a wide variety of heterocyclic compounds such as thiadiazoles, triazole-3-thiols, thioxoimidazoles and thiadiazepines [6-8]. The course of microwave assisted or conventional thermal intramolecular heterocyclization of thiosemicarbazides has been previously investigated [9,10]. Synthetic organic reactions performed under non-traditional conditions are gaining popularity, primarily to circumvent growing environmental concerns [11-13]. Microwave technology has become a powerful tool in organic synthesis, since by employing this technique it is generally possible to prepare organic compounds very fast, with high purity and better yields compared to conventional methods [14,15]. Some time ago, we synthesized many heterocyclic ring systems such as thiazoles, thiazines, thiadiazoles, thiadiazines, pyrazines and indazoles from the reactions of thiosemicarbazides with π-deficient compounds [16,17]. Besides, Aly *et al* reported on the synthesis of various thiazin-4-ones from the reactions of aroylthioureas (ArCONHCSNHR) with dimethyl acetylenedicarboxylates [18]. In addition, thiosemicarbazides show unusual reactivity towards 2,3-diphenylcyclopropenone, giving a variety of pyridazinethiones and 1,2,4-triazolo[4,3-*b*]pyridazinethiones [19]. Recently, we have utilized microwave irradiation to assist the synthesis of triazoloquinazolinones and benzimidazoquinazolinones

[20]. It was also reported [21] on the synthesis of 7-alkyl-5-aryl-1,2,4-triazepine-3-thiones using hydrazinediium dithiocyanate and α,β-unsaturated ketones as starting materials. Viallefont and his co-workers reported on the methods used to prepare various derivatives of 1,2,4-triazepines disubstituted by oxo, thioxo, methoxy or methylthio groups [22]. Interestingly, triazepines and their fused derivatives exhibit interesting biological properties [23]. Moreover, it was also demonstrated that those compounds might serve as black toning agents for laminated photographs or as starting materials for the synthesis of thiazolo[3,2-*b*][1,2,4]triazepines, which are supposed to have immunomodulating activities [24]. Yamamoto *et al* [25] patented triazepine derivatives as inhibitors of cytokine production. In this publication our goal is to synthesize new triazepine-3-thiones from the reaction of thiosemicarbazides with dimethyl acetylenedicarboxylate and dibenzoyl acetylene under conventional methods and/or microwave irradiation.

RESULTS AND DISCUSSION

The synthesis of 4-substituted 1-acetyl-7-oxy-3-thioxo-2,3,4,7-tetrahydro-1*H*-1,2,4-triazepine-5-carboxylic acid methyl esters **3a-c** was accomplished by refluxing equimolar amounts of *N*-aryl-hydrazino carbothioamides **1a-c** with dimethyl acetylenedicarboxylate (**2**) in acetic acid (Method **A**, Scheme 1). Unfortunately, on applying the same procedure using microwave irradiation in a small amount of DMF, the triazepines **3a**-**c** were not obtained. Instead, the reaction afforded, within a few minutes, the triazepine derivatives **4a**-**c** in 70-87% yields (Method **B**, Scheme 1). The structure of compounds **3a-c** and **4a-c** is in accord with their ir, ^{1}H nmr, ^{13}C nmr and mass spectral data in addition to elemental analyses. The ir and nmr spectra of compounds **3a**-**c** and **4a**-**c** showed that the structural difference between compounds **3a**-**c** and **4a**-**c** is related to the numbers of acetyl groups. The ir, nmr and mass spectra as well as the elemental analyses of **3a**-**c** and **4a**-**c** proved the presence of the substructures R^1-*N*-CS-HN-N(COCH$_3$) in **3a**-**c** and R^1-*N*-CS-HN-NH- in **4a**-**c** (Scheme 1). For example, the mass spectrum and elemental analysis proved the structural formula of **3a** as $C_{14}H_{13}N_3O_4S$. The ^{1}H nmr spectrum of **3a** (as an example) contained a broad singlet at δ 8.60, assignable to the hydrazine-proton. The ^{13}C nmr spectrum of **3a** contained three carbonyl carbon signals at δ 169.0, 170.3 and 175.0 assigned to *C*-5, *C*O-ester and *C*O-acetyl, respectively. Another deshielded carbon signal assigned to the thione group resonated at δ 181.6, and the ir spectrum of **3a** showed bands characteristic of vibration coupling of C=S and C-N groups at ν_{max} 1370-1350 and 988-1015 cm^{-1} [26,27]. Due to the appearance of the thione group, we have excluded the formation of compounds **5a**-**c** (Scheme 1). A singlet at δ 6.20 assigned to H-6 appeared in the ^{1}H nmr spectrum of **3a**, and CH-6 resonated in the ^{13}C nmr spectrum at δ 110.2. By contrast, in the ^{1}H nmr spectrum of compound **4a** (as an example), the presence of two hydrazine protons was indicated by two broad singlets at δ 7.30 and 7.60. Moreover the absence of the *C*O-acetyl carbon signal and the appearance of another hydrazine-NH proton (*N*^{1}) indicated that acetylation had not occurred at this nitrogen atom. Indeed, acetylation process had occurred with acetic acid under long refluxing time. In COSY C H studies of **3c** or **4c**, the allylic aliphatic CH_2 showed a correlation with the amide carbonyl, but *not* with the ester carbonyl. These data unambiguously exclude the formation of isomers **6a**-**c** (Scheme 1). Because the magnitude of the Nuclear Overhauser Effect (NOE) depends upon the internuclear distance as $1/r^6$, in practice, NOE's are rarely seen between pairs of protons that are separated by more than about 4.5 Å. [28] NOE's have been correlated with distance as follows: strong (1.8–2.9 Å), medium (1.8–3.7 Å) and weak (3.0–4.5 Å) [29]. Irradiation of the ester protons of the products gave a strong NOE in the hydrazine proton (*N*H^1), and a medium enhancement in the other one (*N*H^2), which agrees with structures **4a**-**c**, but is inconsistent with structures **6a-c**. The products were therefore assigned as 1-acetyl-1,2,4-triazepine-3-thiones **3a**-**c** and 1,2,4-triazepine-3-thiones **4a**-**c**, respectively (Scheme 1).

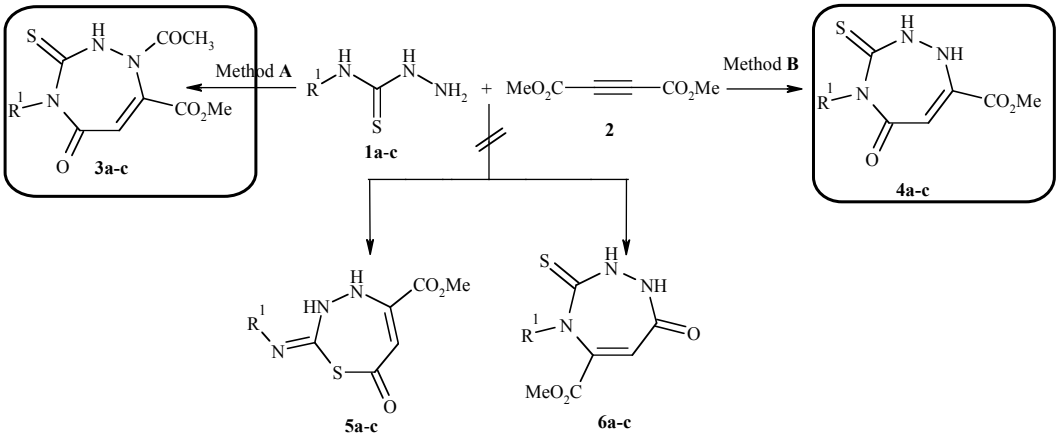
To establish the scope of the phenomena, we treated thiosemicarbazides **1d**-**g** with **2** in refluxing DMF or methanol (Method **A**, Scheme 2). The reaction produced the corresponding 2-aryl-triazepine-4-substituted-2-thiones **7a**-**d** in good yields (Scheme 2). However, the reaction of **1d**-**g** with **2** under microwave irradiation in a small amount of DMF produced **7a**-**d** (Method **B**, Scheme 2) in better yields and in a shorter time than the conventional method (Method **A**). In order to explore another mode of synthesis of triazepines, compounds **1a**-**c** reacted with dibenzoyl acetylene (**8**) in acetic acid, but the reaction failed. The reaction of **1a**-**c** with **8** in DMF afforded, after 24-48 hours of reflux, the triazepines **9a**-**c** (Method **A**, Scheme 3). Compounds **9a**-**c**, could also be obtained from the reaction of **1a**-**c** with **8** under microwave irradiation in a small amount of DMF (Method **B**, Scheme 3) for 10-20 minutes. The vibration coupling of C=S and C-N groups could be assigned in the ir spectra of the products **9a**-**c**, whilst the ^{13}C nmr spectra showed the thione carbon signals at their expected chemical shifts. The ^{1}H NMR spectrum of **9a** showed a singlet for H-6 at δ 6.10, and the corresponding CH-6 resonated in the ^{13}C nmr spectrum at δ 109.0. Additionally, the hydrazine-proton of *N*^{2} appeared in the ^{1}H nmr spectrum at δ 7.50. In **9b**, the ^{1}H nmr spectrum revealed three singlets at δ 5.30, 6.20 and 7.40 assigned to CH_2-Ph, H-6 and hydrazine-*N*H, respectively. COSY C H of **9a** indicated a correlation

between H-6 and both *C*-7 (δ 160.0) and C-5 (δ 156.0). In **9b**, COSY C H experiment showed correlation between *C*-5 (δ 156.4) and the CH_2-Ph protons. The ^1H nmr spectra of compounds **9a-c** revealed the *ortho*-benzoyl protons as the most deshielded aromatic protons. Irradiation of the *ortho*-benzoyl protons in **9c** (δ ~ 7.80) had no effect on the allylic protons. These results indicated the presence of compounds **9a-c** and excluded their isomeric products **10a-c** (Scheme 3). The products obtained under irradiation (Method **B**) have the same spectral data as those obtained from the conventional refluxing method (Method **A**).

EXPERIMENTAL

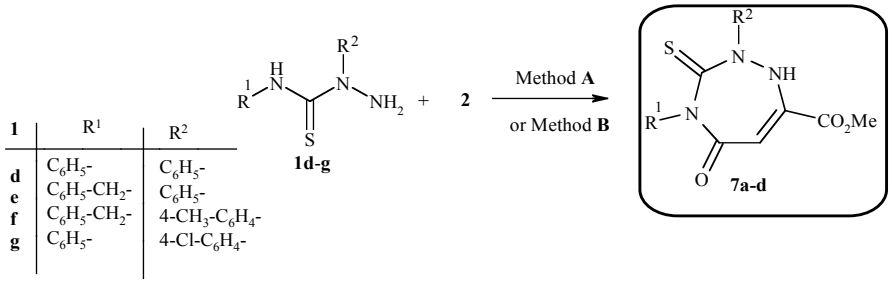
General. Melting points are uncorrected. ^1H- and ^{13}C-nmr spectra were recorded in chloroform-d and measured on a Bruker AM 400 (400.134 MHz and 100.60 MHz) instrument. The chemical shifts (δ's) were measured versus the internal standard TMS. Elemental analyses were performed by the Microanalysis Center of the Institut für Anorganische Chemie, Technische Universität Braunschweig, Germany. Mass spectra were obtained on a Finnigan MAT 8430 spectrometer at 70 eV. The ir spectra were obtained on a Nicolet 320 FT-ir using KBr pellets.

Starting Materials. 4-Phenyl- and allylthiosemicarbazide (**1a**,**c**) [30,31], and 4-benzylthiosemicarbazide (**1b**) [32] were



		Method **A** AcOH, reflux 10-18 h		Method **B** DMF, MW 5-10 min	
1, **3-6**	R^1	Time (h)	Yield of **3** (%)	Time (min)	Yield of **4** (%)
a	C_6H_5-	14	56	5	75
b	C_6H_5-CH_2-	10	60	7	87
c	CH_2=CH-CH_2-	18	54	10	70

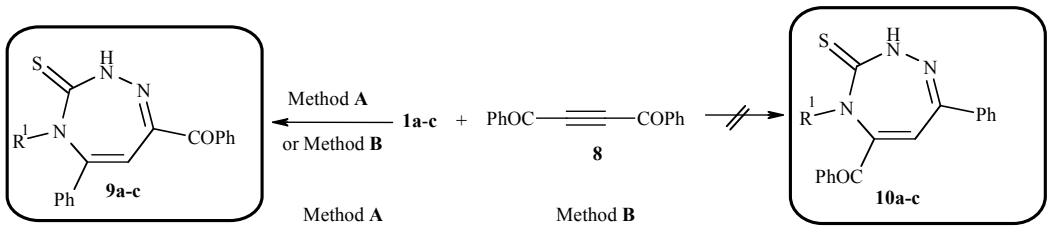
Scheme 1. Synthesis of 4-substituted-1,2,4-triazepine-3-thiones **3a-c** and **4a-c**



1	R^1	R^2
d	C_6H_5-	C_6H_5-
e	C_6H_5-CH_2-	C_6H_5-
f	C_6H_5-CH_2-	4-CH_3-C_6H_4-
g	C_6H_5-	4-Cl-C_6H_4-

			Method **A** MeOH or DMF reflux 15-36 h		Method **B** DMF, MW 10-20 min	
7	R^1	R^2	Time (h)	Yield of **7** (%)	Time (min)	Yield of **7** (%)
a	C_6H_5-	C_6H_5-	20	64	15	84
b	C_6H_5-CH_2-	C_6H_5-	15	68	10	92
c	C_6H_5-CH_2-	4-CH_3-C_6H_4-	24	77	12	96
d	C_6H_5-	4-Cl-C_6H_4-	36	60	20	76

Scheme 2. Synthesis of 2,4-disubstituted-1,2,4-triazepine-3-thiones **7a-d**



1, 9 and 10	R^1	Method A DMF, reflux 24-48 h Time (h)	Yield of 9 (%)	Method B DMF, MW 10-20 min Time (min)	Yield of 9 (%)
a	C_6H_5-	36	82	10	98
b	C_6H_5-CH_2-	24	72	12	82
c	CH_2=CH-CH_2-	48	76	20	92

Scheme 3. Synthesis of 7-benzoyl-5-phenyl-2*H*-3-substituted-1,2,4-triazepine-3-thiones **9a-c**

prepared according to literature procedures. 1,2-Dimethyl acetylenedicarboxylate (**2**) was bought from Fluka, whereas dibenzoyl acetylene (**8**) was prepared according to literature [33].

Method A

Synthesis of 3a-c. A mixture of **1a-c** (1 mmol) and **2** (1 mmol, 142 mg) in glacial acetic acid (50 ml) was heated under reflux for 10-18 h (the reaction was followed by TLC analysis). The solvent was evaporated under vacuum to half of its volume and the product obtained was recrystallized from the stated solvents.

1-Acetyl-5-oxo-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (3a). Yellow crystals of **3a** (0.18 g, 56%), m.p. 175° C (ethanol); ^{1}H nmr (chloroform-d): δ 2.30 (s, 3 H, CH_3CO), 3.82 (s, 3 H, CH_3-ester), 6.20 (s, 1 H, H-6), 6.60-6.78 (m, 3 H, Ph-H), 7.20-7.74 (m, 2 H, Ph-H), 8.60 (br, s, 1 H, *N*H^2) ppm; ^{13}C nmr (chloroform-d): δ 22.0 (*C*H$_3$CO), 51.0 (*C*H$_3$-ester), 110.2 (*C*H-6), 127.6 (*p*-Ph-*C*H), 128.2 (2 *m*-Ph-*C*H), 128.8 (2 *o*-Ph-*C*H), 133.5 (Ph-*C*), 150.0 (*C*-7), 169.0 (*C*-5), 170.3 (*C*O-ester), 175.0 (*C*O-acetyl), 181.6 (*C*-3) ppm; ir (potassium bromide): 3410 (NH), 3030-3000 (Ar-CH), 1735-1695 (C=O), 1592 (C=C), 1370, 988 (C=S, C-N), 1265-1256 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 319 [M$^+$] (62), 277 (100), 262 (14), 245 (12), 220 (16), 160 (14), 142 (32), 77 (72), 59 (20), 51 (36), 44 (44); *Anal*. Calcd. for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16. Found: C, 52.80; H, 4.15; N, 13.05.

1-Acetyl-4-benzyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (3b). Yellow crystals of **3b** (0.20 g, 60%), m.p. 142° C (ethanol); ^{1}H nmr (chloroform-d): δ 2.26 (s, 3 H, CH_3CO), 3.90 (s, 3 H, CH_3-ester), 5.20 (s, 2 H, CH_2-Ph), 6.28 (s, 1 H, H-6), 6.56-6.62 (m, 2 H, Ph-H), 7.16-7.30 (m, 3 H, Ph-H), 8.62 (br, s, 1 H, *N*H^2) ppm; ^{13}C nmr (chloroform-d): δ 22.4 (*C*H$_3$CO), 51.4 (*C*H$_3$-ester), 58.0 (*C*H$_2$-Ph), 111.0 (*C*H-6), 126.2 (*p*-Ph-*C*H), 127.0 (2 *m*-Ph-*C*H), 128.2 (2 *o*-Ph-*C*H), 134.6 (Ph-*C*), 150.8 (*C*-7), 169.6 (*C*-5), 170.8 (*C*O-ester), 175.4 (*C*O-acetyl), 182.0 (*C*-3) ppm; ir (potassium bromide): 3415 (NH), 3040-3008 (Ar-CH), 2990-2890 (Aliph-CH), 1732-1690 (C=O), 1594 (C=C), 1360, 1000 (C=S, C-N), 1265-1256 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 333 [M$^+$] (68), 290 (100), 200 (64), 160 (24), 142 (30), 91 (46), 77 (70), 59 (18), 51 (32), 44 (40). *Anal*. Calcd. for $C_{15}H_{15}N_3O_4S$: C, 54.04; H, 4.54; N, 12.60 Found: C, 54.20; H, 4.48; N, 12.50.

1-Acetyl-4-allyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (3c). Pale yellow crystals of **3c** (0.15 g, 54%), m.p. 155° C (ethyl acetate); ^{1}H nmr (chloroform-d): δ 2.30 (s, 3 H, CH_3CO), 3.92 (s, 3 H, CH_3-ester), 4.50-4.56 (m, 2 H, allyl-CH_2), 5.18-5.26 (m, 2 H, allyl-CH_2=), 5.76-5.80 (m, 1 H, allyl-CH=), 6.14 (s, 1 H, H-6), 8.70 (br, s, 1 H, *N*H^2) ppm; ^{13}C nmr (chloroform-d): δ 22.4 (*C*H$_3$CO), 45.0 (allyl-*C*H$_2$-N), 52.0 (*C*H$_3$-ester), 112.0 (*C*H-6), 116.0 (allyl-CH$_2$=), 131.0 (ally-*C*H=), 151.0 (*C*-7), 170.0 (*C*-5), 172.0 (*C*O-ester), 176.8 (*C*O-acetyl), 182.4 (*C*-3); ir (potassium bromide): 3420 (NH), 2992-2894 (Aliph-CH), 1732-1694 (CO), 1596 (C=C), 1365, 1015 (C=S, C-N), 1260 (st C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 283 [M$^+$] (48), 243 (100), 200 (58), 130 (34), 91 (46), 59 (18), 51 (32), 32 (36). *Anal*. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.64; H, 4.63; N, 14.83. Found: C, 46.50; H, 4.60; N, 14.80.

Method B

Synthesis of 4a-c by MW. Equimolar amounts of **1a-c** (1 mmol) and **2** (1 mmol, 142 mg) were well-mixed in DMF (5-8 ml). The mixture was irradiated in a microwave oven for 5-10 min (100 °C). On cooling to room temperature, the precipitated products **4a-c** were collected by filtration and recrystallized from the stated solvents.

5-Oxo-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (4a). Pale yellow crystals of **4a** (0.23 g, 75%), m.p. 240° C (acetonitrile); ^{1}H nmr (chloroform-d): δ 3.90 (s, 3 H, CH_3-ester), 6.34 (s, 1 H, H-6), 6.56-6.70 (m, 3 H, Ph-H), 7.20-7.24 (m, 2 H, Ph-H), 7.30 (br, s, 1 H, *N*H^1), 7.60 (br, s, 1 H, *N*H^2) ppm; ^{13}C nmr (chloroform-d): δ 51.8 (*C*H$_3$-ester), 100.2 (*C*H-6), 127.4 (*p*-Ph-*C*H), 128.2 (2 *m*-Ph-*C*H), 128.6 (2 *o*-Ph-*C*H), 134.0 (Ph-*C*), 152.0 (*C*-7), 166.0 (*C*-5), 168.0 (*C*O-ester), 183.0 (*C*-3) ppm; ir (potassium bromide): 3420-3180 (NH), 3045-3010 (Ar-CH), 1720-1700 (CO), 1596 (C=C), 1350, 988 (C=S, C-N), 1220 (C=S) cm^{-1}; ms (electron impact, 70 eV): 277 [M$^+$] (100), 262 (20), 246 (24), 218 (40), 194 (64), 165 (32), 88 (22), 77 (40), 74 (26), 51 (36), 44 (40). *Anal.* Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 4.00; N, 15.15. Found: C, 52.20; H, 4.00; N, 15.05.

4-Benzyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (4b). Pale yellow crystals of **4b** (0.25 g, 87%), m.p. 190° C (methanol); ^{1}H nmr (chloroform-d): δ 3.94 (s, 3 H, CH_3-ester), 5.40 (s, 2 H, CH_2-Ph), 6.30 (s, 1 H, H-6), 6.70-6.76 (m, 2 H, Ph-H), 7.18-7.30 (m, 3 H, Ph-H), 7.34 (br, s, 1 H, *N*H^1), 7.66 (br, s, 1 H, *N*H^2) ppm; ^{13}C nmr (chloroform-d): δ 48.60 (*C*H_2-Ph), 50.9 (*C*H_3-ester), 100.4 (*C*H-6), 127.0 (*p*-Ph-*C*H), 127.6 (2 *m*-Ph-*C*H), 128.4 (2 *o*-Ph-*C*H), 133.8 (Ph-*C*), 153.2 (*C*-7), 165.0 (*C*-5), 168.8 (*C*O-ester), 182.2 (*C*-3) ppm; ir (potassium bromide): 3400-3190 (NH), 3030-3000 (Ar-CH), 2980-2967 (Aliph-CH), 1718-1700 (CO), 1592 (C=C), 1360, 990 (C=S, C-N), 1230 (C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 291 [M$^+$] (100), 276 (18), 260 (26), 232 (20), 200 (50), 116 (34), 88 (26), 91 (38), 77 (30), 60 (30), 44 (30). *Anal.* Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42. Found: C, 53.40; H, 4.40; N, 14.50.

4-Allyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (4c). Pale yellow crystals of **4c** (0.17 g, 70%), m.p. 212° C (ethanol); ^{1}H nmr (chloroform-d): δ 3.96 (s, 3 H, CH_3-ester), 4.28-4.34 (m, 2 H, allyl-CH_2), 5.20-5.30 (m, 2 H, allyl-CH_2=), 5.70-5.76 (m, 1 H, allyl-CH=), 6.28 (s, 1 H, H-6), 7.30 (br, s, 1 H, *N*H^1), 7.60 (br, s, 1 H, *N*H^2); ^{13}C nmr (chloroform-d_3): δ 45.8 (allyl-*C*H_2-N), 50.8 (*C*H_3-ester), 112.6 (*C*H-6), 116.0 (allyl-CH_2=), 131.4 (allyl-*C*H=), 153.0 (*C*-7), 165.6 (*C*-5), 169.2 (*C*O-ester), 182.0 (*C*-3) ppm; ir (potassium bromide): 3400-3180 (NH), 2986-2960 (Aliph-CH), 1722-1700 (CO), 1596 (C=C), 1370, 988 (C=S, C-N), 1220 (C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 241 [M$^+$] (100), 200 (50), 185 (22), 169 (24), 141 (18), 116 (34), 88 (36), 74 (30), 44 (38). *Anal.* Calcd. For $C_9H_{11}N_3O_3S$: C, 44.80; H, 4.60; N, 17.42. Found: C, 44.90; H, 4.50; N, 17.52.

Method A

Synthesis of 7a-d. A mixture of **1d**-**g** (1 mmol) and **2** (1 mmol, 142 mg) in absolute methanol (100 ml) or DMF (30 ml) was heated under reflux for 15-36 h (the reaction was followed by TLC analysis). The solvent was evaporated under vacuum to half its volume to give compounds **7a**-**d**. These compounds were recrystallized from the stated solvents.

2,4-Diphenyl-5-oxo-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (7a). Pale red crystals **7a** (0.23 g, 64%), m.p. 282° C (ethanol); ^{1}H nmr (chloroform-d): δ 3.95 (s, 3 H, CH_3-ester), 6.50 (s, 1 H, H-6), 6.60-6.90 (m, 5 H, Ph-H), 7.20-7.30 (m, 3 H, Ph-H), 7.50 (br, s, 1 H, *N*H^1), 7.70-7.78 (m, 2 H, Ph-H) ppm; ^{13}C nmr: (chloroform-d): δ 52.2 (*C*H_3-ester), 105.0 (*C*H-6), 127.0, 127.6 (*p*-Ph-*C*H), 128.0, 128.6 (2 *m*-Ph-*C*H), 129.4, 130.0 (2 *o*-Ph-*C*H), 132.8, 134.2 (Ph-*C*), 154.0 (*C*-5), 168.0 (*C*-7), 168.8 (*C*O-ester), 182.4 (*C*-3) ppm; ir (potassium bromide): 3422 (NH), 3060-3020 (Ar-CH), 1725-1708 (CO), 1592 (C=C), 1360, 988 (C=S, C-N), 1260-1255 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 353 [M$^+$] (40), 276 (30), 208 (40), 200 (50), 194 (64), 135 (42), 91 (100), 77 (40), 51 (34). *Anal.* Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 61.30; H, 4.20; N, 12.05.

4-Benzyl-5-oxo-2-phenyl-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (7b). Red crystals of **7b** (0.25 g, 68%), m.p. 258° C (methanol); ^{1}H nmr (chloroform-d): δ 3.96 (s, 3 H, CH_3-ester), 5.30 (s, 2 H, CH_2-Ph), 6.50 (s, 1 H, H-6), 6.60-6.80 (m, 5 H, Ph-H), 7.20-7.50 (m, 5 H, Ph-H), 7.70 (br, s, 1 H, *N*H^1) ppm; ^{13}C nmr (chloroform-d): δ 48.8 (*C*H_2-Ph), 52.0 (*C*H_3-ester), 106.4 (*C*H-6), 126.8, 127.4 (*p*-Ph-*C*H), 128.2, 128.8 (2 *m*-Ph-*C*H), 129.2, 129.6 (2 *o*-Ph-*C*H), 130.5, 130.8 (Ph-*C*), 153.0 (*C*-5), 165.4 (*C*-7), 170.0 (*C*O-ester), 182.0 (*C*-3) ppm; ir (potassium bromide): 3400 (NH), 3060-3008 (Ar-CH), 2990-2960 (Aliph-CH), 1722-1700 (CO), 1592 (C=C), 1350, 988 (C=S, C-N), 1262-1257 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 367 [M$^+$] (100), 352 (18), 336 (16), 290 (22), 276 (24), 207 (46), 232 (20), 167 (30), 116 (34), 88 (26), 105 (80), 91 (60), 77 (48). *Anal.* Calcd. for $C_{19}H_{17}N_3O_3S$: C, 62.11; H, 4.66; N, 11.44. Found: C, 62.30; H, 4.60; N, 11.40.

4-Benzyl-5-oxo-2-(4'-methylphenyl)-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (7c). Pale yellow crystals of **7c** (0.29 g, 77%), m.p. 225° C (methanol); ^{1}H nmr (chloroform-d): δ 2.38 (s, 3 H, CH_3-tolyl), 3.98 (s, 3 H, CH_3-ester), 5.20 (s, 2 H, CH_2-Ph), 6.60 (s, 1 H, H-6), 6.70-6.90 (m, 5 H, Ph-H), 7.30-7.56 (m, 4 H, Ph-H), 7.76 (br, s, 1 H, *N*H^1) ppm; ^{13}C nmr (chloroform-d): δ 32.8 (*C*H_3Ph), 50.2 (*C*H_2-Ph), 52.4 (*C*H_3-ester), 107.0 (*C*H-6), 127.8 (*p*-Ph-*C*H), 128.4, 128.8 (2 *m*-Ph-*C*H), 129.2, 132.6 (2 *o*-Ph-*C*H), 130.8, 133.2 (Ph-*C*), 134.8 (CH_3-Ph-*C*), 153.8 (*C*-7), 166.8 (*C*-5), 172.0 (*C*O-ester), 181.0 (*C*-3) ppm; ir (potassium bromide): 3420 (NH), 3060-3008 (Ar-CH), 2980-2960 (Aliph-CH), 1725-1700 (CO), 1598 (C=C), 1340, 1000 (C=S, C-N), 1260 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 381 [M$^+$] (100), 366 (18), 288 (64), 198 (30), 169 (30), 92 (84), 77 (60). *Anal.* Calcd. for $C_{20}H_{19}N_3O_3S$: C, 62.98; H, 5.20; N, 11.02. Found: C, 63.10; H, 5.10; N, 11.12.

2-(4'-Chlorophenyl)-5-oxo-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,2,4-triazepine-7-carboxylic acid methyl ester (7d). Pale red crystals of **7d** (0.23 g, 60%), m.p. 170° C (ethanol); ^{1}H nmr (chloroform-d): δ 3.92 (s, 3 H, CH_3-ester), 6.30 (s, 1 H, H-6), 6.50-6.66 (m, 4 H, Ph-H), 7.20-7.36 (m, 5 H, Ph-H), 7.70 (br, s, 1 H, *N*H^1) ppm; ^{13}C nmr (chloroform-d): 52.4 (*C*H_3-ester), 107.0 (*C*H-6), 127.8 (*p*-Ph-*C*H), 128.4, 128.8 (2 *m*-Ph-*C*H), 129.2, 132.6 (2 *o*-Ph-*C*H), 130.8, 133.2 (Ph-*C*), 134.8 (CH_3-Ph-*C*), 153.8 (*C*-5), 166.8 (*C*-7), 172.0 (*C*O-ester), 181.0 (*C*-3) ppm; ir (potassium bromide): 3430 (NH), 3050-3012 (Ar-CH), 1725-1700 (CO), 1596 (C=C), 1350, 1000 (C=S, C-N), 1250 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 389 [M+2] (34), 387 [M$^+$] (100), 386 (32), 372 (18), 356 (42), 352 (46), 366 (18), 277 (34), 275 (36), 190 (30), 112 (24), 98 (20), 77 (50). *Anal.* Calcd. for $C_{18}H_{14}ClN_3O_3S$: C, 55.74; H, 3.64; Cl, 9.14; N, 10.83. Found: C, 55.60; H, 3.60; Cl, 9.00; N, 10.70.

Method B

Synthesis of 7a-d by MW. As stated above, the mixture of **1a**-**g** and **2** was well-mixed in DMF (10 ml). The mixture was irradiated in a microwave oven for 10-20 min (100 °C). On cooling to room temperature, the precipitated products **7a**-**d** were collected by filtration and recrystallized from the stated solvents.

Method A

Synthesis of triazepines 9a-c. A mixture of **1a**-**c** (1 mmol) and **8** (1 mmol, 234 mg) in DMF (20 ml) was gently heated at 80 °C for 24-48 h (the reaction was followed by TLC analysis). The solvent was evaporated under vacuum to half of its volume and the obtained products **9a**-**c** were recrystallized from the stated solvents.

4,7-Diphenyl-3-thioxo-3,4-dihydro-2*H*-(1,2,4-triazepin-5-yl)-phenyl methanone (9a). Yellow crystals of **9a** (0.31 g, 82%), m.p. 210-2° C (ethanol); ^{1}H nmr (chloroform-d): δ 6.10 (s, 1 H, H-6), 6.62-6.80 (m, 5 H, Ph-H), 7.10-7.30 (m, 8 H, Ph-H),

7.50 (br, s, 1 H, *N*H^2), 7.60-7.64 (m, 2 H, Ph-H) ppm; ^{13}C nmr (chloroform-d$_3$): δ 109.0 (*C*H-6), 126.0, 127.7, 128.2 (*p*-Ph-*C*H), 128.6, 129.0, 129.4, 130.2, 130.6, 131.0 (2 Ph-*C*H), 132.0, 132.6, 134.0 (Ph-*C*), 156.0 (*C*-5), 160.0 (*C*-7), 175.0 (*C*OPh), 182.2 (*C*-3) ppm; ir (potassium bromide): 3400 (NH), 3070-3020 (Ar-CH), 1695 (CO), 1590 (C=C), 1350, 988 (C=S, C-N), 1270-1254 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 383 [M$^+$] (54), 322 (10), 280 (24), 223 (10), 191 (24), 147 (10), 105 (100), 77 (76). *Anal.* Calcd. for $C_{23}H_{17}N_3OS$: C, 72.04; H, 4.47; N, 10.96. Found: C, 72.20; H, 4.55; N, 11.06.

4-Benzyl-7-phenyl-3-thioxo-3,4-dihydro-2*H*-(1,2,4-triazepin-5-yl)-phenyl methanone (9b). Yellow crystals of **9b** (0.29 g, 72%), m.p. 200-2° C (methanol); ^{1}H nmr (chloroform-d): δ 5.30 (s, 2 H, CH_2-Ph), 6.20 (s, 1 H, H-6), 6.70-6.84 (m, 5 H, Ph-H), 7.00-7.30 (m, 8 H, Ph-H), 7.40 (br, s, 1 H, *N*H^2), 7.70-7.74 (m, 2 H, Ph-H) ppm; ^{13}C nmr (chloroform-d): δ 48.6 (*C*H$_2$Ph), 110.8 (*C*H-6), 126.4, 127.2, 128.0 (*p*-Ph-*C*H), 128.8, 130.0 130.4, 130.6, 130.8, 131.4 (2 Ph-*C*H), 132.4, 133.0, 133.8 (Ph-*C*), 156.4 (*C*-5), 158.8 (*C*-7), 176.0 (*C*OPh), 182.0 (*C*-3) ppm; ir (potassium bromide): 3380 (NH), 3080-3026 (Ar-CH), 2980-2890 (Aliph-CH), 1700 (CO), 1594 (C=C), 1350, 988 (C=S), 1256 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 397 [M$^+$] (60), 320 (20), 306 (30), 292 (48), 280 (20), 223 (10), 191 (24), 147 (10), 84 (34), 91 (100), 77 (36). *Anal.* Calcd. for $C_{24}H_{19}N_3OS$: C, 72.52; H, 4.82; N, 10.57. Found: C, 72.70; H, 4.78; N, 10.68.

4-Allyl-7-phenyl-3-thioxo-3,4-dihydro-2*H*-(1,2,4-triazepin-5-yl)-phenyl methanone (9c). Yellow crystals of **9c** (0.26 g, 76%), m.p. 125 °C (ethanol); ^{1}H nmr (chloroform-d): δ 4.40 (m, 2 H, allyl-CH_2), 5.20-5.34 (m, 2 H, allyl-CH_2=), 5.80-5.85 (m, 1 H, allyl-CH=), 6.04 (s, 1 H, H-6), 7.06-7.26 (m, 8 H, Ph-H), 7.38 (br, s, 1 H, *N*H^2), 7.80-7.84 (m, 2 H, Ph-H) ppm; ^{13}C nmr (chloroform-d): δ 46.0 (allyl-*C*H$_2$-N), 116.2 (allyl-CH$_2$=), 112.0 (*C*H-6), 127.0, 127.8 (*p*-Ph-*C*H), 138.4, 128.6, 130.0, 130.4 (2 Ph-*C*H), 131.8 (ally-*C*H=), 132.4, 133.0 (Ph-*C*), 156.2 (*C*-5), 158.4 (*C*-7), 176.2 (*C*OPh), 182.4 (*C*-3) ppm; ir (potassium bromide): 3360 (NH), 3090-3010 (Ar-CH), 2986-2880 (Aliph-CH), 1706 (C=O), 1590 (C=C), 1360, 988 (C=S), 1254 (st. C=S) cm^{-1}; ms (electron impact, 70 eV): m/z (%) 347 [M$^+$] (40), 306 (30), 242 (34), 223 (10), 202 (26), 191 (24), 126 (40), 105 (100), 77 (34). *Anal.* Calcd. for $C_{20}H_{17}N_3OS$: Found: C, 69.14; H, 4.93; N, 12.09. Found: C, 69.30; H, 4.90; N, 11.98.

Method B

As described above, **1a**-**c** (1 mmol) and **8** (1 mmol, 234 mg) were well mixed in DMF (5 ml). The mixture was irradiated in a microwave oven for 10-20 min (100 °C). On cooling to room temperature, the precipitated products **9a**-**c** were collected by filtration and recrystallized from the stated solvents. The spectral data were in good agreements with those given before.

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