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Synthesis and structure elucidation of new thiazolotriazepines

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Abstract

The reaction of 1,2,4-triazepine-3-thiones (**13**) with 2-haloketones afforded thiazolo[3,2-*b*][1,2,4]triazepines (**14**) selectively. The same bicycles were obtained by reaction of the chalcones **11** with 3-amino-2-imino-4-R-thiazolines. On the other hand, condensation of the chalcones **11** with 2-hydrazino-4-R-thiazoles led to the hydrazones **17** which upon treatment with acid underwent ring closure to yield the non-condensed bicyclic isomers of **14** *i.e.* the dihydropyrazolyl thiazoles **18**. The elucidation of structures and stereochemistry was achieved by comprehensive one- and two-dimensional NMR spectroscopy.

Keywords: bicyclic heterocyclic compounds; cyclisation; nitrogen heterocycles; sulfur heterocycles

Introduction

In a research program on new immunomodulating agents, we were interested in the synthesis of various sulfur and nitrogen containing condensed bicycles, including 5,7 bicycles and especially thiazolo[1,2,4]triazepines.

Till now only a few thiazolotriazepines are known. Such compounds were first prepared by Neidlein and Ober [1] from the triazepine **2** by condensation with ethyl bromoacetate (*cf.* Scheme 1). In principle, this reaction can lead to a thiazolo[3,2-*b*][1,2,4]triazepine **3** and/or the

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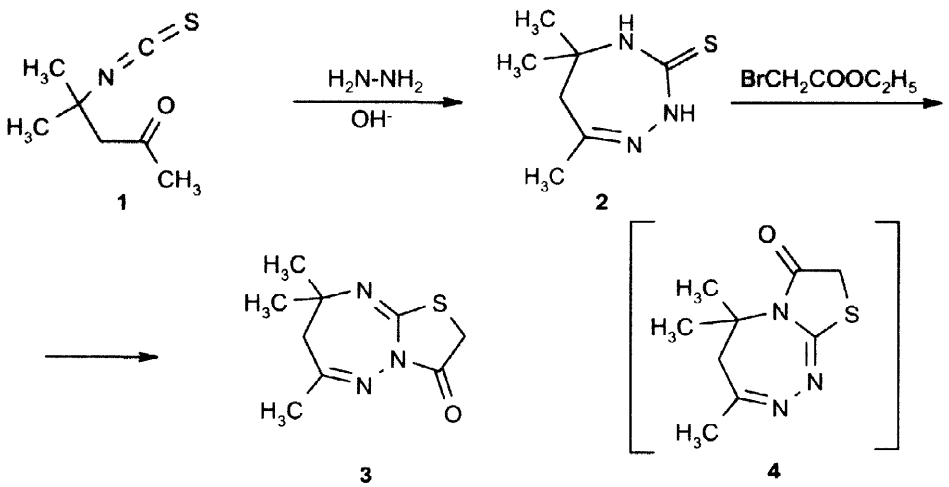
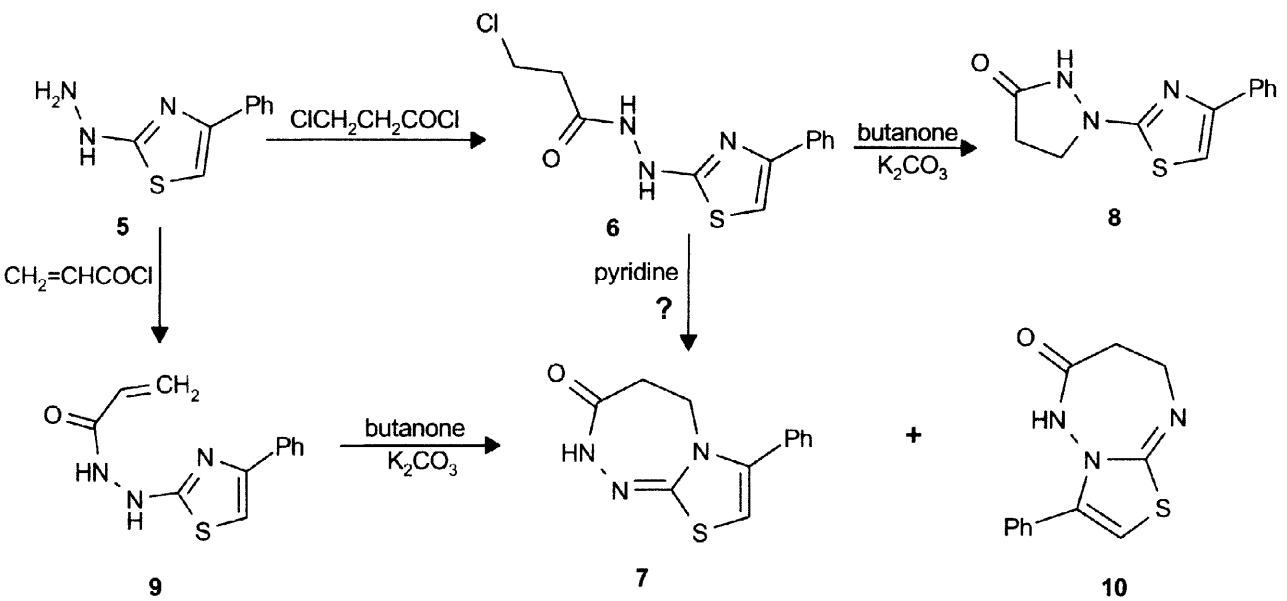
isomeric thiazolo[2,3-*c*][1,2,4]triazepine **4**. The above authors isolated one single product and proposed the thiazolo[3,2-*b*][1,2,4]triazepine structure **3** based on ^{1}H and ^{13}C NMR results.

Scheme 1



On the other hand Mahajan, Sondhi and Ralhan [2] reported on the preparation of a thiazolo[2,3-*c*][1,2,4]triazepine **7** by reacting 2-hydrazino-4-phenylthiazole **5** with 3-chloropropionyl chloride followed by ring closure in pyridine (*cf.* Scheme 2).

Scheme 2



Later Mahajan *et al.* and others [3,4] repeated this reaction using acetylacetone, dibenzoylmethane and ethyl acetoacetate, respectively, instead of 3-chloropropionyl chloride, and reported on the isolation of analogous thiazolo[2,3-*c*][1,2,4]triazepine **7** derivatives.

In contrast with the above results, Peet *et al.* [5,6] concluded that the thiazolo[2,3-*c*][1,2,4]-triazepine ring system cannot be prepared by the above method. They found that cyclisation of **6** under basic conditions leads to the tetrahydropyrazolyl thiazole **8** rather than to the thiazolotriazepinone **7**. On the other hand, the same authors prepared the thiazolotriazepine ring system by cyclization of the unsaturated precursor **9** (*cf.* Scheme 2) yielding an isomeric mixture of **7** and **10**. This mixture was separated by column chromatography. Compounds **7** and **10** have very similar UV and NMR spectra and even their mass spectra exhibit only minor differences which were utilised for the above structure assignment. Although it is difficult to explain the formation of isomer **10** from the precursor **9**, Peet *et al.* suggested a partial Dimroth type rearrangement.

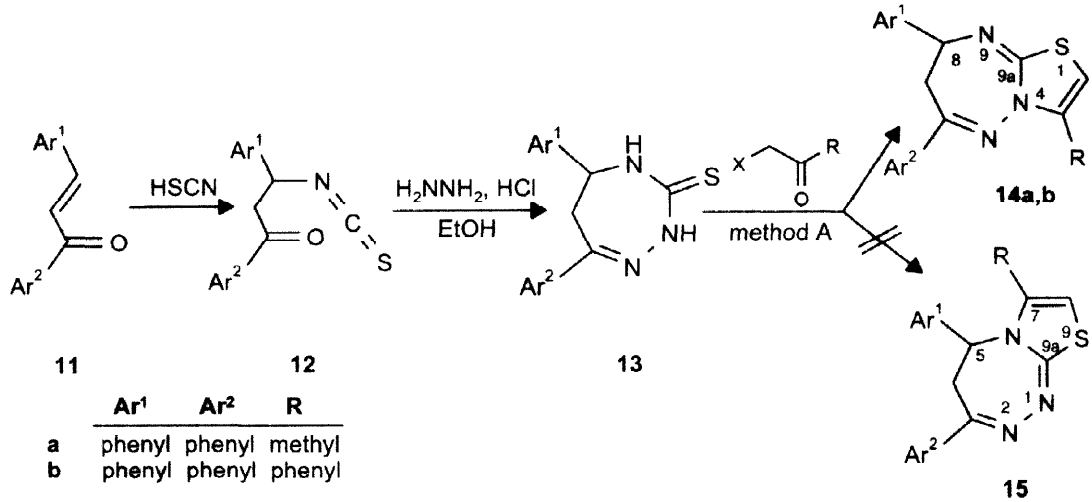
The above literature data suggest that the conventional tools of spectroscopy are not effective enough for an unambiguous structure assignment. For a safe differentiation both isomers are to be prepared and the formation of the tetrahydropyrazolyl thiazole is also to be considered.

Results and discussion

The aim of the present work was to synthesize diaryl-thiazolotriazepines with potential biological activity where the aryl groups (phenyl, 4-fluorophenyl and 4-pyridyl) were chosen on the basis of pharmacological considerations. We intended to prepare the target compounds by reaction of the 1,2,4-triazepine-3-thiones (**13**) with 2-haloketones (*cf.* Scheme 3). The starting thiones were obtained by the addition of thiocyanic acid to the chalcones **11** according to the known method [1] followed by reaction of the intermediate **12** with hydrazine.

In the spectrum of **13** recorded in DMSO-d_6 H-N(4) and H-5 are coupled (4.9 Hz) and NOESY cross peaks were measured between H-N(4) (9.08d) and H-5 as well as between H-N(4) and the ortho protons of Ar^1. Additional proofs were obtained from the HMBC cross peaks H-N(4)/C-5, H-N(4)/C-6, H-N(2)/C-3 and H-N(2)/C-7, respectively.

Scheme 3

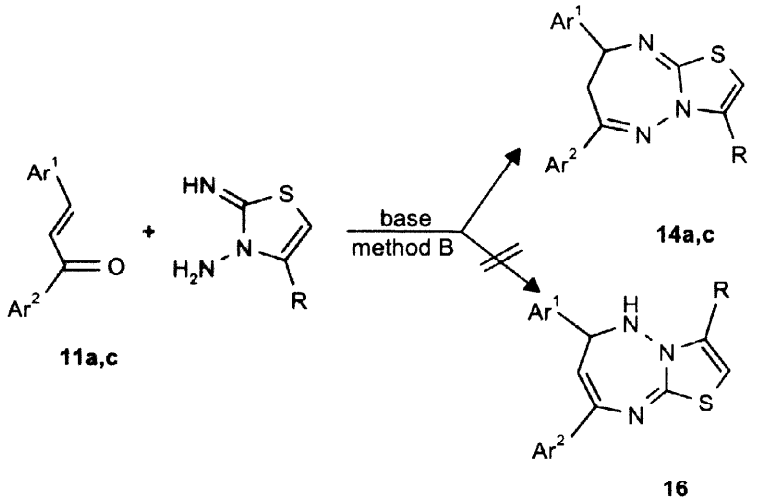


	Ar^1	Ar^2	R
a	phenyl	phenyl	methyl
b	phenyl	phenyl	phenyl

The reaction of the thiones **13** with 2-haloketones (method A) afforded in each case a single product but on the basis of the usual IR and mass spectra as well as ^1H and ^{13}C NMR chemical shifts it could not be determined which of the isomers **14** and **15** was obtained. Therefore various other NMR techniques were used as described below. For the differentiation of the structural isomers it was considered that the methine proton of the triazepine ring in **15** should exhibit a vicinal J(C,H) coupling with both quaternary carbons in the thiazoline ring, whereas in **14** only the C-9a carbon of isothiourea type is coupled with the above methine proton. The appearance of the cross peak H-8/C-9a in the two-dimensional HMBC experiment, allowing the identification of carbon-proton couplings over two or three bonds, proved the structure of type **14**. Further evidence for this structure was obtained from the phase sensitive NOESY measurement, which is known to identify hydrogen atoms in proximity. The NOESY cross peak detected between the methyl group on the thiazole ring and the ortho protons of the aromatic ring attached to the triazepine C=N afforded unambiguous evidence for **14**.

Next, an attempt was made to prepare isomers **14** and **15** by other routes, *i.e.* starting with the appropriate thiazole derivatives. Addition and condensation of chalcones **11** with 3-amino-2-imino-4-R-thiazolines (*cf.* Scheme 4) can lead to **14** or to the inversely oriented **16**. Under basic conditions (method B) a single product was isolated which was identical with the compound obtained in the reaction of 1,2,4-triazepine-3-thiones (**13**) with 2-haloketones (*cf.* Scheme 3). Structure **16** could be ruled out by the ^1H and ^{13}C NMR signals proving the presence of a CH_2 group in the triazepine ring (δ_C 42, δ_H 3.15-3.53).

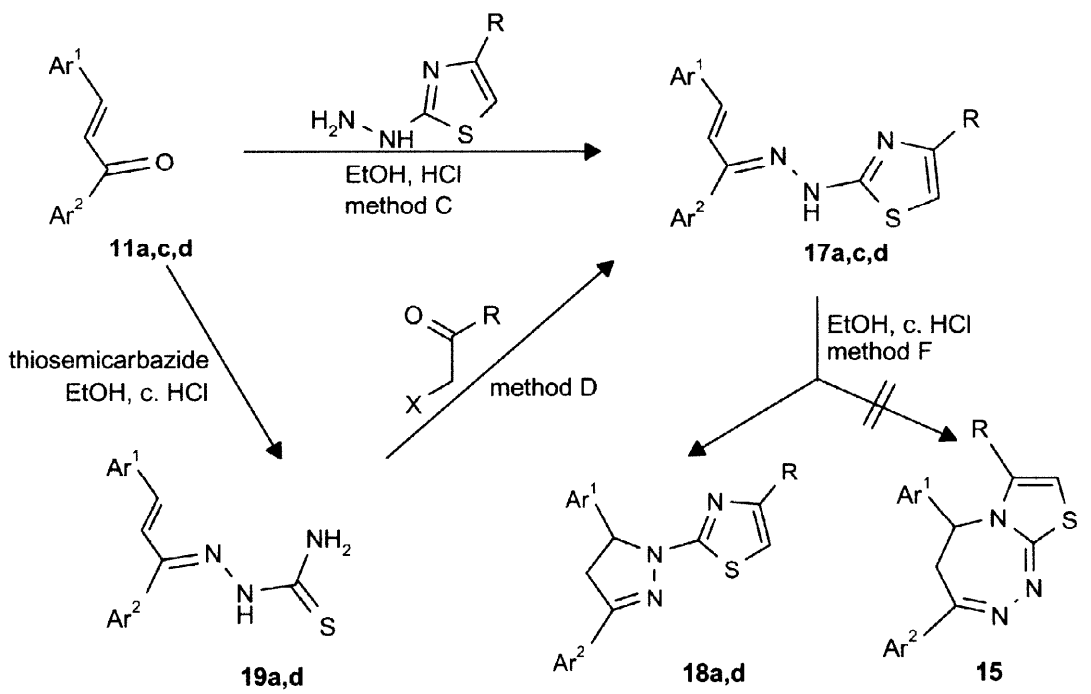
Scheme 4



	Ar¹	Ar²	R
a	phenyl	phenyl	methyl
c	4-FC_6H_4	4-FC_6H_4	methyl

For the preparation of isomer **15** the ring closure of the hydrazone **17** (*cf.* Scheme 5) was considered, similarly to the cyclization of **9** by Peet [5] (*cf.* Scheme 2). This hydrazone could be prepared on one hand directly by condensation of **11** with the 2-hydrazino-4-R-thiazoles (method C).

Scheme 5



	Ar¹	Ar²	R
a	phenyl	phenyl	methyl
c	4-FC_6H_4	4-FC_6H_4	methyl
d	4-FC_6H_4	4-pyridyl	methyl

On the other hand, under acidic conditions the reaction of chalcones **11** with thiosemicarbazide afforded the thiosemicarbazones **19,** which could also be transformed into the hydrazones **17** using 2-haloketones (method D).

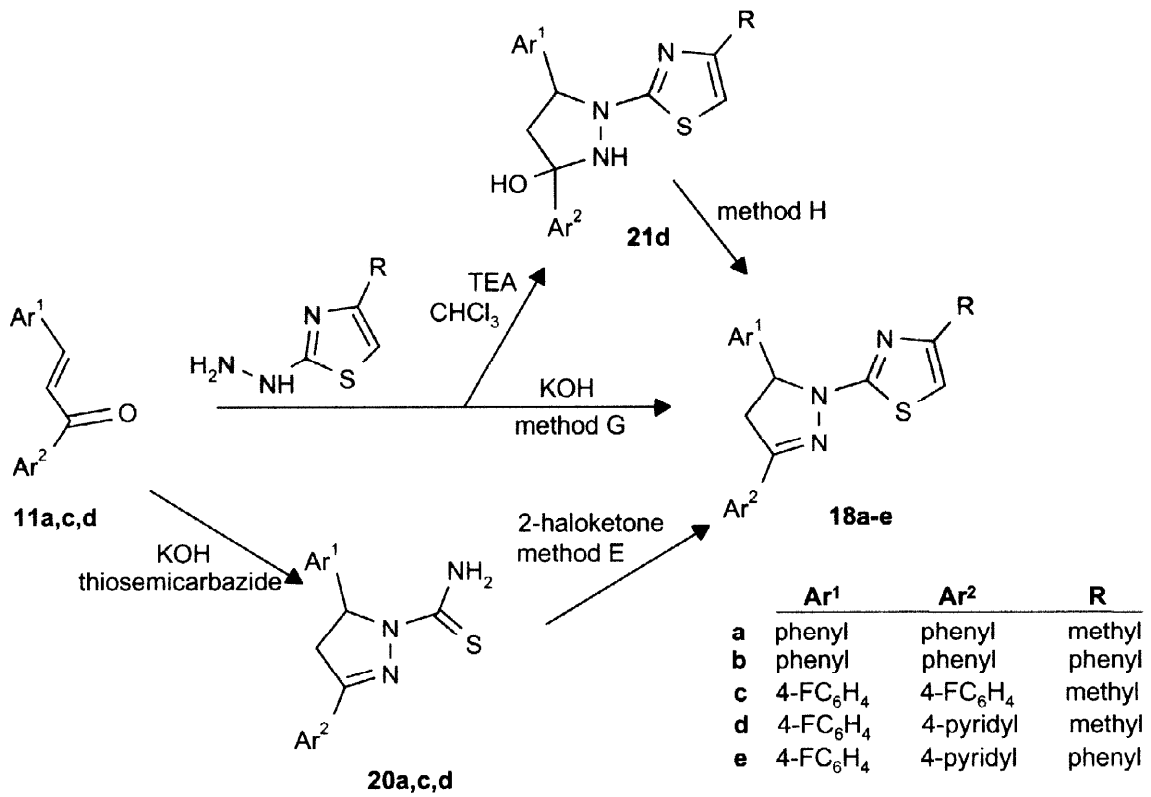
In compounds **17** and **19** the appearance of *Z/E* isomers of the C=N bond was observed. Upon standing in dimethyl sulfoxide or chloroform solutions for one week the products isolated as pure *E* isomers underwent transformation into *Z/E* mixtures (90/10). Similar *E*→*Z* isomerizations were reported by Dimmock *et al.* [7]. Assignment of the stereochemistry was based upon the consideration that in the *E* isomer, the NH group and the =CH (δ_C ~117) attached to C=N are in proximity, resulting in an upfield shift compared to the chemical shift of the *Z* isomer (δ_C ~128), this shift being due to the known γ-steric effect [8]. The presence of the diaryl substituted vinyl group with *E* configuration in **19** obtained from **11** with thiosemicarbazide under acidic conditions follows from the ^{1}H doublet signals δ 7.74 and 6.83 (^3J 16 Hz) and from the corresponding ^{13}C signals δ_C 138.4 and 117.7.

Our attempts to cyclize **17** under basic conditions similar to those applied by Peet [5,6] failed. Upon heating **17** in HCl (method F) a new product, **18** was obtained. This exhibited ^{1}H and ^{13}C NMR data characteristic for the thiazole and pyrazoline moieties [9,10]. In accordance with the structure of type **18,** no NOE was observed between the hydrogens of the methyl group (R) and those of the Ar^1 moiety. The ^{15}N NMR study of these compounds delivered further support for their structure [11].

To find synthetic evidence for the structure of **18** the potential precursor pyrazoline-1-thioamide **20** was prepared (*cf.* Scheme 6). Thus the reaction of **11** with thiosemicarbazide under basic conditions led to **20**. In this case the formation of the triazepine **13** (*cf.* Scheme 3) had also to be considered.

Deuteration experiments and a comparison of the NMR data of compound **20** with those of its isomers, *i.e.* the thiosemicarbazone **19** and the triazepinethione **13** (see above), proved the structure of **20**. Exchange on the NH group in **13** resulted in a characteristic isotopic shift on the C-5 signal while treatment of the isomeric **20** pyrazoline with a 1:1 mixture of H_2O and D_2O afforded an isotopic shift only on the C=S signal, resulting in the appearance of a characteristic virtual triplet (1:2:1 ratio). This experiment proved the presence of a primary amino group in **20**.

Scheme 6



	Ar¹	Ar²	R
a	phenyl	phenyl	methyl
b	phenyl	phenyl	phenyl
c	4-FC_6H_4	4-FC_6H_4	methyl
d	4-FC_6H_4	4-pyridyl	methyl
e	4-FC_6H_4	4-pyridyl	phenyl

Reaction of **20** with 2-haloketones yielded **18** as expected.

When the chalcones **11** were allowed to react with 2-hydrazino-4-R-thiazoles under basic conditions (method G), again the dihydropyrazolyl thiazoles **18** were obtained. By a proper choice of the solvent, the hydroxy containing intermediate **21** could also be isolated as a single diastereomer; this was transformed into **18** upon heating (method H). The NOE experiment proved the *cis* arrangement of the methine proton (H-5) and the 3-OH.

Conclusion

We conclude that starting with the chalcones **11** the thiazolo[3,2-*b*]triazepine derivatives **14** could be obtained *via* the triazepinethiones **13** while the isomeric thiazolo-[2,3-*c*]triazepines **15** were not formed. The same thiazolo[3,2-*b*]triazepine derivatives **14** could be isolated when the chalcones **11** were allowed to react directly with 3-amino-2-imino-4-R-thiazolines. On the other hand, cyclization of the hydrazone derivatives **17** did not furnish the

expected thiazolo[2,3-*c*]triazepines **15** but the isomeric non-condensed dihydropyrazolyl thiazoles **18**.

Experimental

The starting materials **11a, 11c, 11d** and **12** were synthesized according to published procedures [12-15]. Melting points are uncorrected. All yields refer to isolated products. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solutions on a Bruker DRX-500 spectrometer at room temperature. The chemical shifts are given on the δ scale with TMS as internal standard. For the 2D experiments (H,H-COSY, HMQC, HMBC and phase sensitive NOESY) the standard Bruker software package was applied.

5,7-Diphenyl-3,4,5,6-tetrahydro-2H-1,2,4-triazepine-3-thione (**13**)

Hydrazine hydrate (2 ml, 98%) was added to the stirred mixture of 3-isothiocyanato-1,3-diphenylpropan-1-one **12** (0.46 g, 1.8 mmol) and 10% ethanolic HCl solution (10 ml) while the temperature was maintained below 15 °C. After 2 h under cooling stirring was continued for 2 days at RT, then the precipitate was filtered off, washed with water, 5% $NaHCO_3$ solution and acetone. Yield 32%, m.p. 166-168 °C. Anal. Calcd for $C_{16}H_{15}N_3S$: C 68.30 H 5.37 N 14.93; found: C 68.53 H 5.29 N 15.12. ^{1}H NMR (DMSO-d_6) δ 10.89 (s, 1H, N(2)-H), 9.08 (d, *J* 4.9 Hz, 1H, N(4)-H), 4.97 (m, 1H, 5-H), 7.38 (d, 2H, ortho-H of Ph at C-5). ^{13}C NMR (DMSO-d_6) δ 177.2 (C-3), 59.2 (C-5), 37.0 (C-6), 158.2 (C-7).

3-Methyl-6,8-diphenyl-7,8-dihydrothiazolo[3,2-b][1,2,4]triazepine (**14a**)

Method A:

Triazepine-3-thione **13** (0.5 g, 1.8 mmol) was dissolved in 10 ml of ethanol. To this solution chloroacetone (0.5 ml, 6.25 mmol) was added at room temperature. After refluxing for 2 h the reaction mixture was cooled, the precipitate was filtered off and washed with ethanol. The solids were mixed with 5% $NaHCO_3$ solution and extracted with ether. The organic layer was dried and concentrated under reduced pressure to afford the free base of 3-methyl-6,8-diphenyl-7,8-dihydrothiazolo[3,2-*b*][1,2,4]triazepine (**14a**). Yield 68%, m.p. 135-137 °C. Anal. Calcd for $C_{19}H_{17}N_3S$: C 71.44 H 5.36 N 13.15, found: C 71.47 H 5.27 N 13.10. ^{1}H NMR ($CDCl_3$) δ 5.71 (s, 1H, 2-H), 2.21 (s, 3H, Me), 3.19 (dd, 1H, 7-H_{trans}), 3.48 (dd, 1H, 7-H_{cis}), 5.02

(dd, 1H, 8-H), 7.59 (dm, 2H, ortho-H of aryl at C-6). ^{13}C NMR ($CDCl_3$) δ 95.5 (C-2), 42.5 (C-7), 63.4 (C-8), 154.4 (C-9a).

Method B:

A mixture of 1,3-diphenyl-1-propen-3-one **11a** (1.04 g, 5 mmol), 2-imino-3-amino-4-methyl-thiazole.HCl (1.65 g, 10 mmol) [16] and K_2CO_3 (1.0 g) in dimethylformamide (10 ml) was stirred at RT. After 24 h, the mixture was diluted with 50 ml of water and extracted with ether. The organic layer was dried and concentrated under reduced pressure. The residue was refluxed in the mixture of ethanol (10 ml) and cc. HCl (1.0 ml) for 3 h. After standing overnight in the refrigerator, the precipitate was filtered off and washed with ethanol. The filtrate was mixed with 5% $NaHCO_3$ solution and extracted with ether. The ethereal extract was dried and concentrated under reduced pressure to afford the free base of 3-methyl-6,8-diphenyl-7,8-dihydrothiazolo[3,2-*b*][1,2,4]triazepine. Yield 29%, m.p. 139-141 °C.

*3-Phenyl-6,8-diphenyl-7,8-dihydrothiazolo[3,2-b][1,2,4]triazepine (***14b***)*

Method A was followed, using 2-bromoacetophenone instead of chloroacetone, yield 30%, m.p. 116-118 °C. Anal. Calcd for $C_{24}H_{19}N_3S$: C 75.56 H 5.02 N 11.01, found: C 75.21 H 4.92 N 10.92. ^{1}H NMR ($CDCl_3$) δ 6.12 (s, 1H, 2-H), 3.36 (dd, 1H, 7-H_{trans}), 3.53 (dd, 1H, 7-H_{cis}), 5.12 (dd, 1H, 8-H). ^{13}C NMR ($CDCl_3$) δ 99.0 (C-2), 41.0 (C-7), 62.3 (C-8), 154.7 (C-9a).

*3-Methyl-6,8-di(4-fluorophenyl)-7,8-dihydrothiazolo[3,2-b][1,2,4]triazepine (***14c***)*

Method B was followed, starting with 1,3-di(4-fluorophenyl)-1-propen-3-one (**11c**). Yield 29%, m.p. 152-153 °C. Anal. Calcd for $C_{19}H_{15}F_2N_3S$: C 64.21 H 4.25 N 11.82 found: C 64.12 H 4.53 N 11.42. ^{1}H NMR ($CDCl_3$) δ 5.71 (s, 1H, 2-H), 2.14 (s, 3H, Me), 3.15 (dd, 1H, 7-H_{trans}), 3.40 (dd, 1H, 7-H_{cis}), 5.02 (dd, 1H, 8-H), 7.55 (dm, 2H, ortho-H of aryl at C-6). ^{13}C NMR ($CDCl_3$) δ 97.8 (C-2), 42.1 (C-7), 61.9 (C-8), 154.4 (C-9a).

*2-[N^2-(1,3-Diphenyl-2-propen-1-ylidene)hydrazino]-4-methylthiazole (***17a***)*

Method C

A mixture of 1,3-diphenyl-1-propen-3-one **11a** (1.04 g, 5 mmol), 2-hydrazino-4-methyl-thiazole.HCl (1.65 g, 10 mmol) [17] and c. HCl (1.0 ml) in ethanol (10 ml) was refluxed for

1 h, diluted with water (80 ml) and neutralized with 25 % (w/v) NH_4OH. The precipitate was filtered off, washed with water and petroleum ether. Yield 89%, m.p. 130-132 °C. Anal. Calcd for $C_{19}H_{17}N_3S$: C 71.44 H 5.36 N 13.15, found: C 71.06 H 5.34 N 13.14. ^1H NMR ($CDCl_3$) *E*-isomer: δ 7.12 (d, *J* 17 Hz, 1H, 1-H), 6.84 (d, *J* 17 Hz, 1H, 2-H), 2.18 (s, 3H, Me). *Z*-isomer: δ 7.22 (d, *J* 17 Hz, 1H, 1-H), 6.30 (d, *J* 17 Hz, 1H, 2-H), 2.21 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) *E*-isomer: δ 117.8 (C-2), 16.8 (Me), *Z*-isomer: δ 128.3 (C-2), 17.2 (Me).

2-{N^2-[1,3-Di(4-fluorophenyl)-2-propen-1-ylidene]hydrazino}-4-methylthiazole (**17c**)

Method C was followed, starting with 1,3-di(4-fluorophenyl)-1-propen-3-one (**11c**). Yield 47%, m.p. 83-85 °C. Anal. Calcd for $C_{19}H_{15}F_2N_3S$: C 64.21 H 4.25 N 11.82, found: C 63.92 H 4.23 N 10.52. ^1H NMR ($CDCl_3$) *E*-isomer: δ 6.95 (d, *J* 17 Hz, 1H, 1-H), 6.63 (d, *J* 17 Hz, 1H, 2-H), 2.13 (s, 3H, Me), *Z*-isomer: δ 7.01 (d, *J* 17 Hz, 1H, 1-H), 6.15 (d, *J* 17 Hz, 1H, 2-H), 2.14 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) *E*-isomer: δ 117.8 (C-2), 16.6 (Me), *Z*-isomer: δ 128.0 (C-2), 17.2 (Me).

2-{N^2-[3-(4-Fluorophenyl)-1-(4-pyridyl)-2-propen-1-ylidene]hydrazino}-4-methylthiazole hydrochloride (**17d**)

Method C was followed, starting with 1-(4-fluorophenyl)-3-(4-pyridyl)-1-propen-3-one (**11d**). After refluxing for 1 h, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 66%, m.p. 157-160 °C (HCl salt). Anal. Calcd for $C_{18}H_{15}FN_4S.2HCl.0.5EtOH$: C 52.54 H 4.64 N 12.90 Cl 16.32 found: C 52.48 H 4.65 N 12.87 Cl 16.21. ^1H NMR (DMSO-d_6) δ 7.67 (d, *J* 17 Hz, 1H, 1-H), 7.20 (d, *J* 17 Hz, 1H, 2-H), 2.23 (s, 3H, Me), ^{13}C NMR (DMSO-d_6) δ 117.8 (C-2), 15.1 (Me).

Method D

A mixture of **19d** (0.6 g, 2 mmol) and chloroacetone (0.2 ml, 2.5 mmol) in ethanol (10 ml) was refluxed for 1 h. Further chloroacetone (0.2 ml, 2.5 mmol) was added and the reflux was continued for another h. The precipitate was filtered off, washed with ethanol. Yield 93%, m.p. 154-157 °C (HCl salt). Anal. Calcd for $C_{18}H_{15}FN_4S.HCl$: C 57.67 H 4.30 N 14.95 Cl 9.46 found: C 57.56 H 4.53 N 14.66 Cl 9.35.

*2-(3,5-Diphenyl-4,5-dihydropyrazol-1-yl)-4-methylthiazole (**18a**)*

Method E

A mixture of **20a** (0.56 g, 2 mmol) and chloroacetone (0.2 ml, 2.5 mmol) in ethanol (5 ml) was refluxed for 1 h, diluted with water (20 ml), and neutralized with 5% $NaHCO_3$ solution. The precipitate was filtered off, washed with water and ether. Yield 75%, m.p. 128-130 °C. Anal. Calcd for $C_{19}H_{17}N_3S$: C 71.44 H 5.36 N 13.15, found: C 71.53 H 5.33 N 13.10: ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, Me-4), 6.13 (s, 1H, 5-H), 3.21 (dd, 1H, 4'-H_{trans}), 3.83 (dd, 1H, 4'-H_{cis}), 5.61 (dd, 1H, 5'-H). ^{13}C NMR ($CDCl_3$) δ 164.9 (C-2), 17.5 (Me-4), 103.3 (C-5), 43.5 (C-4'), 64.0 (C-5').

Method F

A mixture of **17a** (1.46 g, 5 mmol) and c. HCl (1.0 ml) in ethanol (10 ml) was refluxed for 15 h. The precipitate was filtered off, mixed with 5% $NaHCO_3$ solution and extracted with ether. The organic layer was dried and concentrated under reduced pressure. The residue was treated with water, filtered off and washed with water and ether. Yield 21%, m.p. 127-130 °C.

*2-(3,5-Diphenyl-4,5-dihydropyrazol-1-yl)-4-phenylthiazole (**18b**)*

Method E was followed, starting with **20a** and 2-bromoacetophenone. Yield 97%, m.p. 214-215 °C. Anal. Calcd for $C_{24}H_{19}N_3S$: C 75.56 H 5.02 N 11.01, found: C 75.33 H 4.95 N 10.95. ^{1}H NMR (DMSO-d_6) δ 7.23 (s, 1H, 5-H), 3.35 (dd, 1H, 4'-H_{trans}), 4.07 (dd, 1H, 4'-H_{cis}), 5.69 (dd, 1H, 5'-H). ^{13}C NMR (DMSO-d_6) δ 164.4 (C-2), 104.8 (C-5), 43.0 (C-4'), 64.3 (C-5').

*2-[3,5-Di(4-fluorophenyl)-4,5-dihydropyrazol-1-yl]-4-methylthiazole (**18c**)*

Method E was followed, starting with **20c**. Yield 95%, m.p. 191-193 °C. Anal. Calcd for $C_{19}H_{15}F_2N_3S$: C 64.21 H 4.25 N 11.82, found: C 64.03 H 4.12 N 11.73. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, Me-4), 6.15 (s, 1H, 5-H), 3.17 (dd, 1H, 4'-H_{trans}), 3.83 (dd, 1H, 4'-H_{cis}), 5.63 (dd, 1H, 5'-H). ^{13}C NMR ($CDCl_3$) δ 165.0 (C-2), 17.2 (Me-4), 103.5 (C-5), 43.6 (C-4'), 63.4 (C-5').

*2-[5-(4-Fluorophenyl)-3-(4-pyridyl)-4,5-dihydropyrazol-1-yl]-4-methylthiazole (**18d**)*

Method E was followed, starting with **20d**.Yield 56%, m.p. 201-202 °C. Anal. Calcd for $C_{18}H_{15}FN_4S$: C 63.89 H 4.47 N 16.56 S 9.47, found: C 63.90 H 4.32 N 16.38 S 9.58. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H, Me-4), 6.20 (s, 1H, 5-H), 3.18 (dd, 1H, 4'-H_{trans}), 3.83 (dd, 1H, 4'-H_{cis}), 5.67 (dd, 1H, 5'-H). ^{13}C NMR ($CDCl_3$) δ 164.4 (C-2), 17.6 (Me-4), 104.9 (C-5), 42.8 (C-4'), 64.0 (C-5'). This compound was also prepared by method F, starting with **17d**. Yield 59%, m.p. 198-199 °C.

Method G

A mixture of chalcone **11d** (1.14 g, 5 mmol), 2-hydrazino-4-methylthiazole.HCl (0.83 g, 5 mmol) and KOH (0.78g, 1.4 mmol) in ethanol (10 ml) was stirred for 1 h at RT, then diluted with water. The precipitate was filtered off, washed with water and ethanol. Yield 58%, m.p. 196-198 °C.

Method H

A solution of **21d** (0.36 g, 1 mmol) in ethanol (6 ml) was refluxed for 1.5 h. After cooling, the precipitate was filtered off and washed with ethanol. Yield 77%, m.p. 201-202 °C.

*2-[5-(4-Fluorophenyl)-3-(4-pyridyl)-4,5-dihydropyrazol-1-yl]-4-phenylthiazole (**18e**)*

Method E was followed, starting with **20c** and 2-bromoacetophenone. Yield 56%, m.p. 204-205 °C. Anal. Calcd for $C_{23}H_{17}FN_4S$: C 68.98 H 4.28 N 13.99, found: C 69.25 H 4.12 N 13.65. ^{1}H NMR ($CDCl_3$) δ 6.84. (s, 1H, 5-H), 3.24 (dd, 1H, 4'-H_{trans}), 3.82 (dd, 1H, 4'-H_{cis}), 5.68 (dd, 1H, 5'-H). ^{13}C NMR ($CDCl_3$) δ 164.0 (C-2), 104.1 (C-5), 42.5 (C-4'), 64.4 (C-5').

*N^1-(1,3-Diphenyl-2-propen-1-ylidene)thiosemicarbazide (**19a**)*

Prepared as described in the literature [7]. Yield 64%, m.p. 128-129 °C (lit. m.p. 135-137 °C).

*N^1-[3-(4-Fluorophenyl)-1-(4-pyridyl)-2-propen-1-ylidene]thiosemicarbazide (**19d**)*

Prepared by analogy of **19a**. Yield 60%, m.p. 212-215 °C. Anal. Calcd for $C_{15}H_{13}FN_4S$: C 59.98 H 4.36 N 18.65, found: C 60.27 H 4.48 N 18.45. ^{1}H NMR (DMSO-d_6) δ *E*-isomer: 7.74 (d, *J* 16 Hz, 1H, 1-H), 6.83 (d, *J* 16 Hz, 1H, 2-H). ^{13}C NMR (DMSO-d_6) δ 117.7 (C-2), 179.4 (C=S).

*2-(3,5-Diphenyl-4,5-dihydropyrazol-1-yl)thiocarboxamide (**20a**)*

Method I

A mixture of 1,3-diphenyl-1-propen-3-one **11a** (2.08 g, 10 mmol), thiosemicarbazide (0.91 g, 10 mmol) and KOH (1.0g, 1.8 mmol) in ethanol (30 ml) was refluxed for 2 h. After cooling the precipitate was filtered off, washed with ethanol and ether. Yield 66%, m.p. 204-206 °C. Anal. Calcd for $C_{16}H_{15}N_3S$: C 68.30 H 5.37 N 14.93, found: C 68.12 H 5.27 N 14.79. ^{1}H NMR (DMSO-d_6) δ 3.12 (dd, 1H, 4-H_{trans}), 3.90 (dd, 1H, 4-H_{cis}), 6.05 (dd, 1H, 5-H), 7.96 (br, 1H, NH), 8.11 (br, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 42.6 (C-4), 63.0 (C-5), 176.3 (C=S).

*2-[3,5-Di(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)thiocarboxamide(**20c**)*

Method I was followed, starting with chalcone **11c**. Yield 55%, m.p. 261-262 °C. Anal. Calcd for $C_{16}H_{13}F_2N_3S.H_2O$: C 57.30 H 4.51 N 12.53, found C 57.28 H 4.39 N 12.40. ^{1}H NMR (DMSO-d_6) δ 3.20 (dd, 1H, 4-H_{trans}), 3.93 (dd, 1H, 4-H_{cis}), 5.95 (dd, 1H, 5-H), 8.00 (br, 1H, NH), 8.12 (br, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 42.6 (C-4), 62.3 (C-5), 176.3 (C=S).

*2-[3-(4-Pyridyl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)thiocarboxamide(**20d**)*

Method I was followed, starting with chalcone **11d**. Yield 22%, m.p. 227-228 °C. Anal. Calcd for $C_{15}H_{13}FN_4S$: C 59.98 H 4.36 N 18.65, found C 60.16 H 4.39 N 18.40. ^{1}H NMR (DMSO-d_6) δ 3.15 (dd, 1H, 4-H_{trans}), 3.88 (dd, 1H, 4-H_{cis}), 5.97 (dd, 1H, 5-H), 8.15 (br, 1H, NH), 8.30 (br, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 42.0 (C-4), 62.9 (C-5), 176.9 (C=S).

*2-[5-(4-Fluorophenyl)-3-hydroxy-3-(4-pyridyl)-2,3,4,5-tetrahydropyrazol-1-yl]-4-methylthiazole (**21d**)*

A mixture of chalcone **11d** (1.14 g, 5 mmol), 2-hydrazino-4-methylthiazole.HCl (0.83 g, 5 mmol) and TEA (0.7 ml, 0.5 mmol) in chloroform (10 ml) was stirred for 3 h at RT. The

precipitate was filtered off, washed with water and ether. Yield 67%, m.p. 160-162 °C. Anal. Calcd for $C_{18}H_{17}FN_4OS$: C 60.66 H 4.81 N 15.72, found C 60.34 H 4.52 N 15.38. ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H, Me-4), 6.36 (s, 1H, 5-H), 5.99 (s, 1H, HO-3), 2.16 (dd, 1H, 4'-H_{trans}), 3.01 (dd, 1H, 4'-H_{cis}), 5.25 (dd, 1H, 5'-H). ^{13}C NMR (DMSO-d_6) δ 176.6 (C-2), 17.9 (Me-4), 104.5 (C-5), 91.5 (C-3'), 52.2 (C-4'), 66.5 (C-5').

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