Thiocarbamate-based synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones

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A five-step synthesis of 5,7-diaryl-substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones starting from ethyl thiocarbamate was developed. The synthesis included a three-component condensation of ethyl thiocarbamate with aromatic aldehydes and *p*-toluenesulfinic acid to give *O*-ethyl[(aryl)(tosyl)methyl]thiocarbamates which were transformed into the corresponding *O*-ethyl (3-phenyl-3-oxopropyl) thiocarbamates by treatment with the sodium enolate of dibenzoylmethane followed by base-promoted retro-Claisen condensation. Reaction of the prepared thiocarbamates with hydrazine and subsequent acid-catalysed cyclisation of the derived 4-[(3-hydrazono-3-phenyl)prop-1-yl]semicarbazides gave the target triazepines.

Keywords: thiocarbamates, amidoalkylation, retro-Claisen reaction, thiosemicarbazides, 1,2,4-triazepine-3-thiones

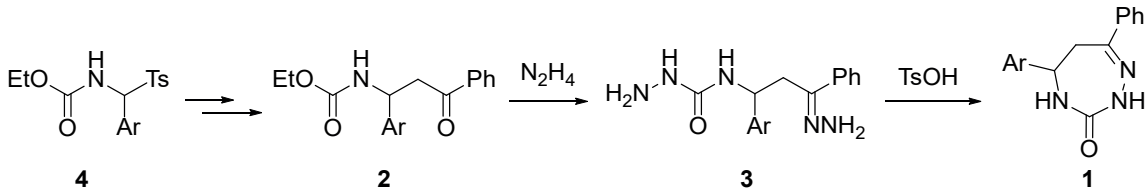
The development of new general approaches to rare heterocyclic scaffolds is one of the frontiers of contemporary chemistry. Non-annulated 1,2,4-triazepines (for reviews, see ref.[1–5]), particularly 1,2,4-triazepin-3-ones/thiones are typical representatives of such scaffolds. Only a restricted number of these compounds have been prepared by reaction of arylidene ketones with $N_2H_4 \cdot 2HNCS$,[6] addition of (thio)semicarbazides to α,β-unsaturated ketones or their synthetic equivalents,[7–9] reaction of hydrazines with β-isocyanatoketones[10,11] or β-isothiocyanatoketones,[12–16] condensation of 1,3-dicarbonyl compounds with (thio)semicarbazides,[17–24] CDI-mediated cyclisation of 3-hydrazino-substituted amines,[25–27] and reaction of thiosemicarbazides with dimethyl acetylenedicarboxylate and dibenzoylacetylene.[28,29] Recently, we have developed a new five-step approach to aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **1** starting from ethyl carbamate. The principal steps of this approach involved reaction of ethyl [(3-oxo-3-phenyl)prop-1-yl]carbamates **2** with hydrazine followed by acid-catalysed cyclisation of the prepared 4-[(3-hydrazono-3-phenyl)prop-1-yl]semicarbazides **3** into the target triazepinones **1** (Scheme 1).[30] Carbamates **2** were prepared in three steps *via* formation of the amidoalkylation reagents, ethyl *N*-(α-tosylbenzyl)carbamates **4**.

It was important to extend the above methodology to the preparation of 3-thioxo-analogues of compounds **1**. Herein, we report a five-step synthesis of aryl substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones starting from ethyl thiocarbamate.

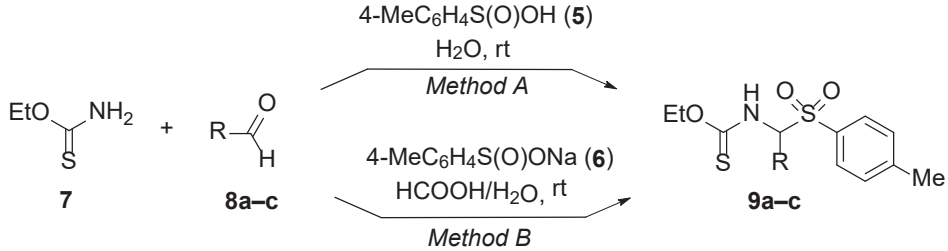
Results and discussion

The first step of the triazepinethione synthesis involved preparation of amidoalkylation reagents, the *O*-ethyl (α-tosylbenzyl)thiocarbamates **9a–c** (Scheme 2). Previously, these compounds were obtained by Engberts and coworkers *via* reaction of ethyl thiocarbamate with aromatic aldehydes and sodium *p*-toluenesulfinate in aqueous formic acid.[31] However, some important experimental details (*e.g.* reaction time) and relevant spectroscopic data of the compounds prepared were not provided in the paper. Therefore, it was necessary to develop suitable conditions for formation of thiocarbamates **9a–c**.

Compound **9a** was obtained by our convenient modification[30,32,33] of Engberts' method[31] using *p*-toluenesulfinic



Scheme 1 Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepin-3-ones **1**.



8–9a R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-$MeOC_6H_4$.

Scheme 2 Synthesis of amidoalkylation reagents **9a–c**.

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acid **5** instead of its sodium salt **6** in the presence of HCOOH. The three-component condensation of ethyl thiocarbamate **7** with equimolar amounts of benzaldehyde **8a** and sulfinic acid **5** proceeded in water at room temperature for 24 h to give sulfone **9a** (Scheme 2, Method A) which precipitated from the reaction mixture and was isolated by filtration in 86% yield.

Under similar conditions, reaction of *p*-tolualdehyde **8b** and *p*-anisaldehyde **8c** with ethyl thiocarbamate and sulfinic acid **5** gave condensation products as thick oils that could not be solidified in any way. The use of 80% aqueous HCOOH as a solvent afforded a positive result only in the case of aldehyde **8b**. However, the yield of the obtained sulfone **9b** did not exceed 54% and its purity was not good enough for further application. Our additional experimental studies showed that compounds **9b**,**c** could be prepared by reaction of aldehydes **8b** and **8c** with equimolar amounts of ethyl thiocarbamate **7** and sodium *p*-toluenesulfinate **6** in 16% aqueous HCOOH at room temperature for 48 h (Scheme 2, Method B). Sulfones **9b** and **9c** precipitated from the reaction mixtures were isolated by filtration in 70% and 65% yield, respectively.

Compounds **9a–c** were obtained as white solids with >95% purity according to ^{1}H NMR spectroscopic data of the crude products and used in the amidoalkylation step without additional purification.

It should be noted that both ^{1}H and ^{13}C NMR spectra of crude thiocarbamates **9a–c** in DMSO-d_6 at 25 °C, in contrast to their carbamate analogues,[30] showed the presence of two sets of signals in a ratio of 80:20, 80:20, and 79:21, respectively. These ratios did not change after recrystallisation of **9a–c** from ethanol. Therefore, it could be concluded that thiocarbamates **9a–c** were formed as equilibrium mixtures of two conformers that arise from a restricted rotation around the thioamide C–N bond. Indeed, the DFT calculations at the B3LYP/6-311++G(d,p) level of theory performed for two model compounds, ethyl isopropylcarbamate *i*-PrNHCOOEt (**10**) and *O*-ethyl isopropylthiocarbamate *i*-PrNHC(=S)OEt (**11**), in the gas phase and also in DMSO solution using the PCM solvation model showed that energy barriers of s-*cis*/s-*trans* (in respect to the C–N bond) conformer interconversion are distinctly higher for **11** than those for **10**. For example, the Gibbs free energy barriers of the s-*trans* to s-*cis* transformation for **10** and **11** in DMSO are 16.9 and 20.5 kcal mol^{-1}, respectively (298 K, 1 atm).

Reaction of sulfones **9a–c** with the sodium enolate of dibenzoylmethane, generated by treatment of dibenzoylmethane with NaH, proceeded readily in dry THF at room temperature for 8 h to afford the products of nucleophilic substitution of the tosyl group, the thiocarbamates **12a–c**, in 76–92% yields (Scheme 3). When MeCN was used instead of THF, the completion of the reaction between dibenzoylmethane and NaH was hampered by formation of a dense suspension of the enolate, reducing the yield and purity of the substitution products. Sulfone **9a** smoothly reacted with the sodium enolate of acetylacetone in dry MeCN (r.t., 8 h) to give thiocarbamate **13** in 91% yield.

O-Ethyl (3-oxo-3-phenylpropyl)thiocarbamates **14a–c** were prepared from **12a–c** by retro-Claisen reaction using solutions of KOH (5 equiv.) in 12–14% aqueous EtOH at room temperature for 19–27 h. It should be noted that under all conditions attempted, this reaction was accompanied by formation of significant amounts of the corresponding chalcones arising from base-catalysed eliminaton of ethyl thiocarbamate (**7**). As a result, isolated yields of **12a–c** were 35–48%. In contrast, retro-Claisen reaction of **13** proceeded readily by treatment with KOH (5.5 equiv.) in water at room temperature for 4 h to give thiocarbamate **15** in high yield (86%).

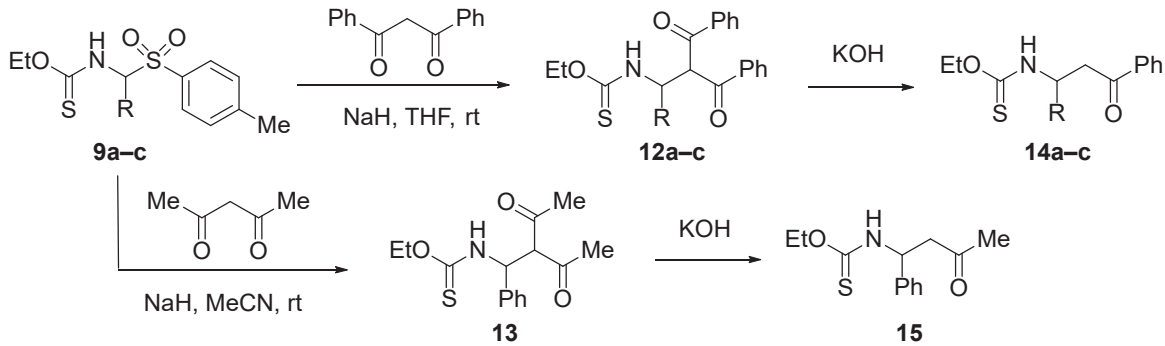
Therefore, three-step syntheses of compounds **13a–c** and **15**, which are the first representatives of previously unknown acyclic β-thiocarbamato ketones, have been developed.

Noteworthy, analogously to compounds **9a–c**, thiocarbamates **12a–c**, **13**, **14a–c**, and **15** were obtained as equilibrium mixtures of two conformers around the thioamide C–N bond in ratios of (62–71):(38–29) (NMR spectroscopic data for isolated crude materials). These ratios did not change after recrystallisation of these compounds.

Next, we studied reaction of thiocarbamates **14a–c** with excess hydrazine resulting in the corresponding thiosemicarbazide hydrazones **16a–c** (Scheme 4).

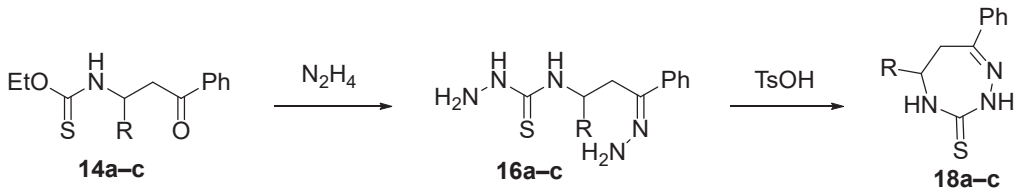
We used anhydrous hydrazine as reagent and solvent that was proved to be the best choice in the transformation of carbamates **2** into semicarbazides **3** (Scheme 1).[30] However, in contrast to carbamates **2**, which gave semicarbazides **3** upon refluxing in N_2H_4 for 20–24 h (28–46% yields), the reaction of thiocarbamates **14a–c** with hydrazine proceeded under significantly milder conditions, and in higher yields. Thus, treatment of **14a** with anhydrous N_2H_4 (80 equiv.) at room temperature for 2 h followed by evaporation of all the volatiles under reduced pressure and successive washing of the residue with diethyl ether and water afforded thiosemicarbazide hydrazone **16a** in 60% yield. The yield of **16a** was slightly increased (70%) when even milder reaction conditions were used (0 °C, 1 h). Under similar conditions (0 °C, 1 h), thiocarbamates **14b** and **14c** were transformed into thiosemicarbazides hydrazones **16b** and **16c** in 58% and 65% yield, respectively.

We also studied the reaction of thiocarbamate **15** with anhydrous hydrazine or hydrazine hydrate under various conditions. However, despite numerous attempts, we failed

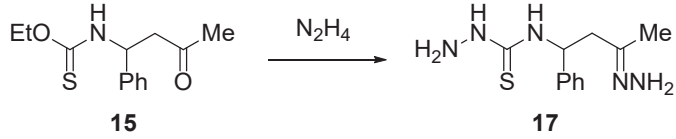


12,**14 a** R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-MeOC_6H_4.

Scheme 3 Synthesis of β-thiocarbamato ketones **14a–c** and **15**.



16,18 a R = Ph, **b** R = 4-MeC_6H_4, **c** R = 4-$MeOC_6H_4$.



Scheme 4 Synthesis of 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones **18a–c**.

to develop a preparative procedure for the synthesis of thiosemicarbazide hydrazone **17**. The reaction proceeded very fast, even at 0 °C, providing the target hydrazone **17** along with a complex mixture of unidentified products.

According to ^{1}H NMR spectroscopic data, thiosemicarbazides **16a–c** were formed as mixtures of two geometric isomers with significant predominance of the *E*-isomer (87–95%). The stereochemical assignments were based on ^{1}H and ^{13}C NMR spectroscopic data, ^{1}H,^{1}H NOESY experiment for **16a** in DMSO-d_6, and comparison of ^{1}H and ^{13}C NMR spectra of **16a–c** with those of structurally similar semicarbazides.[30] For the major isomer of **16a**, NOE was observed between the C=NNH_2 and CH_2 protons, and no NOE correlation was detected between the *ortho*-phenyl protons of the PhC=N fragment and the C=NNH_2 protons, thus confirming the *E*-configuration of the C=N double bond in this isomer.

Finally, we studied the heterocyclisation of **16a–c** in the presence of TsOH (1.05 equiv.). This reaction readily proceeded in refluxing EtOH for 0.5–1 h to give triazepines **18a–c** (Scheme 4) which were isolated in 46–57% yields using column chromatography on aluminium oxide or silica gel.

In summary, we have demonstrated that the acid-catalysed cyclisation of the hydrazones of 4-(1,3-diaryl-3-oxopropyl) thiosemicarbazides provides an efficient access to 5,7-diaryl-substituted 2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thiones. The starting thiosemicarbazides were readily prepared according to our original four-step approach involving amidoalkylation of the sodium enolate of dibenzoylmethane with *O*-ethyl[(aryl)(tosyl)methyl]thiocarbamates followed by base-promoted retro-Claisen reaction and treatment of the obtained *N*-(3-oxopropyl)thiocarbamates with hydrazine.

Experimental

All solvents were distilled before use. *p*-Toluenesulfinic acid **5** was synthesised by treatment of a saturated aqueous solution of sodium *p*-toluenesulfinate **6**[34] with hydrochloric acid at 0 °C, dried over P_2O_5, and stored at 0 °C. Sodium hydride (60% suspension in mineral oil) was thoroughly washed with dry hexane and dried under vacuum prior to use. Anhydrous hydrazine was obtained by refluxing with an equal weight of KOH pellets for 3 h under argon followed by distillation, and this operation was repeated twice. All other reagents and solvents were purchased from commercial sources and used without further treatment. FTIR spectra were recorded using a Bruker Vector 22 spectrophotometer in Nujol for solid samples. Band characteristics in the IR spectra are defined as very strong (vs), strong (s), medium (m), weak (w), shoulder (sh), and broad (br). ^{1}H NMR and proton-decoupled ^{13}C NMR spectra (solutions in DMSO-d_6) were acquired using a Bruker DPX 300 spectrometer at 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C). ^{1}H NMR chemical shifts are referenced to the residual proton signal in DMSO-d_6 (2.50 ppm). In ^{13}C NMR spectra, central signal of DMSO-d_6 (39.50 ppm) was used as a reference. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), and some combinations of these, multiplet (m). Selective ^{1}H–^{1}H decoupling and DEPT-135 experiments were used to aid in the assignment of ^{1}H and ^{13}C NMR signals. ^{1}H NMR signals for thiocarbamates **9**–**15** may be followed by the symbols: * indicates overlap with signals from the minor conformer, and § indicates overlap with signals from the major conformer. Elemental analyses (CHN) were performed by using a Thermo Finnigan Flash EA1112 apparatus. Thin-layer chromatography was carried out on Aldrich silica gel 60 F_{254} aluminum backed plates in $CHCl_3$ and $CHCl_3$/MeOH (9:1, v/v) as solvent systems. Spots were visualised with UV light or iodine vapours. Column chromatography was performed with Macherey–Nagel silica gel 60 (0.063–0.200 mm) or Macherey–Nagel aluminium oxide 90 neutral (activity 1). The DFT calculations were carried out at the B3LYP level of theory using Gaussian 09 suite[35] of quantum chemical programs. Pople's basis set, 6-311++G(d,p), was employed for geometry optimisation. The effect of continuum solvation was incorporated by using the polarisable continuum model (PCM). Enthalpies and Gibbs free energies were obtained by adding unscaled zero-point vibrational energy corrections (ZPVE) and thermal contributions to the energies. All yields refer to isolated, spectroscopically and TLC pure compounds. All products were colourless and obtained as white crystalline solids.

O-*Ethyl [(phenyl)(tosyl)methyl]thiocarbamate* (**9a**)

p-Toluenesulfinic acid (**5**) (17.83 g, 110 mmol) and H_2O (50 mL) were added to a stirred emulsion of benzaldehyde (**8a**) (12.11 g, 110 mmol) in H_2O (50 mL) and the resulting mixture was stirred for 30 min at room temperature. Ethyl thiocarbamate (**7**) (12.01 g, 110 mmol) and H_2O (40 mL) were added to the formed suspension and the mixture was stirred for 24 h at room temperature, cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give thiocarbamate **9a** (34.22 g, 86%) as a mixture of two conformers in a ratio of 80:20. This product was used in the next step without additional purification. An analytically pure sample (a 80:20 conformer mixture) was obtained after crystallisation from EtOH. M.p. 154–155.5 °C (decomp., EtOH) (lit.[31] 145.5–147 °C); IR (Nujol) ν_{max}/cm^{-1}: 3296 (vs) (NH), 3086 (w), 3060 (w), 3040 (w), 3030 (w) (CH_{arom}), 1593 (m) (CC_{arom}), 1506 (s) (thioamide-II), 1494 (m) (CC_{arom}), 1316 (s), 1303 (s) (SO_2), 1219 (s) (C–O), 1146 (s) (SO_2), 809 (s), 703 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 10.71 (1H, d, ^3J = 10.6 Hz, NH), 7.38–7.79* (9H, m, ArH), 6.82 (1H, d, ^3J = 10.6 Hz, CHN), 4.19–4.38 (2H, m, OCH_2), 2.40 (3H, s, CH_3 in Ts), 1.15 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 10.44 (1H, d, ^3J = 10.5 Hz, NH), 7.38–7.79§ (9H, m, ArH), 6.35 (1H, d, ^3J = 10.5 Hz, CHN), 4.05–4.16 (1H, m, H_A in OCH_2), 3.80–3.91 (1H, m, H_B in OCH_2), 2.41 (3H, s, CH_3 in Ts), 0.97 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 191.50 (C=S), 144.90 (C), 133.70 (C),

129.81 (C), 129.73 (2CH), 129.63 (2CH), 129.58 (CH), 129.23 (2CH), 128.37 (2CH), 78.04 (CHN), 66.60 (OCH_2), 21.17 (CH_3 in Ts), 14.03 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 187.87 (C=S), 144.97 (C), 134.07 (C), 130.03 (2CH), 129.69 (2CH), 129.13 (2CH), 128.23 (2CH), 74.78 (CHN), 66.80 (OCH_2), 21.11 (CH_3 in Ts), 13.40 (CH_3 in OEt), signals of two carbons are not resolved in the aromatic region. Anal. calcd for $C_{17}H_{19}NO_3S_2$: C, 58.43; H, 5.48; N, 4.01; found: C, 58.72; H, 5.60; N, 4.06%.

O-*Ethyl [(4-methylphenyl)(tosyl)methyl]thiocarbamate* (**9b**)

9.775 g of sodium *p*-toluenesulfinate hydrate (**6**) (86.2 wt%; 8.426 g, 47.28 mmol) was added to a stirred solution of *p*-tolyl aldehyde (**8b**) (6.248 g, 52.0 mmol) in 81% aqueous HCOOH (11.8 mL). Ethyl thiocarbamate (**7**) (4.973 g, 47.29 mmol) and H_2O (47.5 mL) were then added to the formed solution . An emulsion resulted, which gradually turned into a suspension. The reaction mixture was stirred for 48 h at room temperature and cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give thiocarbamate **9b** (12.015 g, 70%) as a mixture of two conformers in a ratio of 80:20. This product was used in the next step without additional purification. An analytically pure sample (a 80:20 conformer mixture) was obtained after crystallisation from EtOH. M.p.136–138 °C (decomp., EtOH) (lit.[31] 138–139 °C); IR (Nujol) ν_{max}/cm^{-1}: 3337 (br s) (NH), 3062 (w), 3033 (m) (CH_{arom}), 1597 (m) (CC_{arom}), 1506 (s) (thioamide-II), 1303 (s) (SO_2), 1211 (s), 1188 (s) (C-O), 1144 (s) (SO_2), 816 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 10.64 (1H, d, ^3J = 10.6 Hz, NH), 7.19–7.77* (8H, m, ArH), 6.76 (1H, d, ^3J = 10.6 Hz, CHN), 4.19–4.37 (2H, m, OCH_2), 2.40 (3H, s, CH_3 in Ts), 2.32 (3H, s, CH_3 in $CH_3C_6H_4$), 1.14 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 10.37 (1H, d, ^3J = 10.4 Hz, NH), 7.19–7.77[§] (8H, m, ArH), 6.29 (1H, d, ^3J = 10.4 Hz, CHN), 4.05–4.15 (1H, m, H_A in OCH_2), 3.79–3.89 (1H, m, H_B in OCH_2), 2.41 (3H, s, CH_3 in Ts), 2.32 (3H, s, CH_3 in $CH_3C_6H_4$), 0.97 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 191.42 (C=S), 144.79 (C), 139.15 (C), 133.81 (C), 129.60 (4CH), 129.19 (2CH), 128.90 (2CH), 126.74 (C), 77.86 (CHN), 66.52 (OCH_2), 21.14 (CH_3 in Ts), 20.81 (CH_3 in $CH_3C_6H_4$), 14.01 (CH_3 in OEt). Anal. calcd for $C_{18}H_{21}NO_3S_2$: C, 59.48; H, 5.82; N, 3.85; found: C, 59.48; H, 5.93; N, 3.92%.

O-*Ethyl [(4-methoxylphenyl)(tosyl)methyl]thiocarbamate* (**9c**)

9.874 g of sodium *p*-toluenesulfinate hydrate (**6**) (86.2 wt%; 8.511 g, 47.76 mmol) was added to a stirred solution of *p*-anisaldehyde (**8c**) (7.153 g, 52.54 mmol) in 81% aqueous HCOOH (12 mL). Ethyl thiocarbamate (**7**) (5.023 g, 47.77 mmol) and H_2O (48 mL) were then added to the formed solution. An emulsion resulted, which gradually turned into a suspension. The reaction mixture was stirred for 48 h at room temperature and cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give thiocarbamate **9c** (11.850 g, 65%) as a mixture of two conformers in a ratio of 79:21. This product was used in the next step without additional purification. An analytically pure sample (a 79:21 conformer mixture) was obtained after crystallisation from EtOH. M.p.130.5–132 °C (decomp., EtOH) (lit.[31] 133–134.5 °C); IR (Nujol) ν_{max}/cm^{-1}: 3361 (sh), 3325 (br s) (NH), 3099 (w), 3081 (w), 3063 (w), 3045 (w), 3033 (w), 3011 (w) (CH_{arom}), 1611 (s), 1596 (s), 1586 (m) (CC_{arom}), 1513 (s), 1505 (s) (thioamide-II), 1303 (s) (SO_2), 1254 (s), 1208 (s), 1183 (s) (C–O), 1144 (SO_2), 838 (s), 817 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 10.62 (1H, d, ^3J = 10.6 Hz, NH), 7.38–7.76* (6H, m, ArH), 6.94–7.00* (2H, m, ArH), 6.74 (1H, d, ^3J = 10.6 Hz, CHN), 4.19–4.37 (2H, m, OCH_2), 3.77 (3H, s, OCH_3), 2.39 (3H, s, CH_3 in Ts), 1.14 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 10.36 (1H, d, ^3J = 10.4 Hz, NH), 7.38–7.76[§] (6H, m, ArH), 6.94–7.00[§] (2H, m, ArH), 6.28 (1H, d, ^3J = 10.4 Hz, CHN), 4.05–4.15 (1H, m, H_A in OCH_2), 3.79–3.89 (1H, m, H_B in OCH_2), 3.78 (3H, s, OCH_3), 2.41 (3H, s, CH_3 in Ts), 0.97 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 191.36 (C=S), 160.21 (C), 144.73 (C), 133.85 (C), 131.11 (2CH), 129.58 (2CH), 129.18 (2CH), 121.50 (C), 113.80 (2CH), 77.64 (CHN), 66.50 (OCH_2), 55.23 (OCH_3), 21.14 (CH_3 in Ts), 14.02 (CH_3 in OEt). Anal. calcd for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69; found: C, 57.16; H, 5.72; N, 3.76%.

O-*Ethyl [(2-benzoyl-3-oxo-1,3-diphenyl)prop-1-yl]thiocarbamate* (**12a**)

Dry THF (8 mL) was added to a mixture of dibenzoylmethane (0.605 g, 2.70 mmol) and NaH (0.065 g, 2.70 mmol). The mixture was stirred in an ice-cold bath for 30 min, and to the resulting solution were added sulfone **9a** (0.940 g, 2.69 mmol) and THF (4 mL). The suspension was stirred at room temperature for 8 h, and solvent was removed in a vacuum. Saturated aqueous $NaHCO_3$ (4 mL) and petroleum ether (4 mL) was added to a solid residue and the obtained mixture was triturated until complete crystallisation and the resulting suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold water and petroleum ether, and dried to give **12a** (1.039 g, 92%) as a mixture of two conformers in a ratio of 63:37. An analytically pure sample (a 63:37 conformer mixture) was obtained after crystallisation from EtOH. M.p. 109–111 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3302 (br vs) (NH), 3104 (w), 3060 (m), 3028 (w) (CH_{arom}), 1687 (vs), 1658 (m) (C=O), 1594 (s), 1578 (m) (CC_{arom}), 1520 (s) (thioamide-II), 1495 (m) (CC_{arom}), 1282 (s), 1188 (s) (C–O), 770 (m), 699 (s), 688 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.68 (1H, d, ^3J = 8.5 Hz, NH), 7.94–8.01* (2H, m, ArH), 7.70–7.77* (2H, m, ArH), 7.45–7.65* (4H, m, ArH), 7.31–7.43* (4H, m, ArH), 7.03–7.22* (3H, m, ArH), 6.46 (1H, d, ^3J = 10.3 Hz, CHC=O), 6.15 (1H, dd, ^3J = 10.3, ^3J = 8.5 Hz, CHN), 4.16–4.39* (2H, m, OCH_2), 1.15 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.74 (1H, d, ^3J = 8.3 Hz, NH), 7.94–8.01[§] (2H, m, ArH), 7.70–7.77[§] (2H, m, ArH), 7.45–7.65[§] (4H, m, ArH), 7.31–7.43[§] (4H, m, ArH), 7.03–7.22[§] (3H, m, ArH), 6.50 (1H, d, ^3J = 10.4 Hz, CHC=O), 5.80 (1H, dd, ^3J = 10.4, ^3J = 8.3 Hz, CHN), 4.16–4.39[§] (2H, m, OCH_2), 1.14 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 193.21 (C=O in Bz), 192.39 (C=O in Bz), 189.17 (C=S), 138.99 (C), 136.11 (C), 135.49 (C), 133.98 (CH), 133.88 (CH), 128.95 (2CH), 128.85 (2CH), 128.56 (2CH), 128.39 (2CH), 128.04 (4CH), 127.39 (CH), 65.46 (OCH_2), 59.68 (*C*HBz$_2$), 58.61 (CHN), 14.05 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 193.23 (C=O in Bz), 192.28 (C=O in Bz), 187.64 (C=S), 138.77 (C), 136.01 (C), 135.38 (C), 133.89 (CH), 128.98 (2CH), 128.86 (2CH), 128.53 (2CH), 128.46 (2CH), 128.24 (2CH), 127.68 (2CH), 127.61 (CH), 66.44 (OCH_2), 59.30 (*C*HBz$_2$), 56.71 (CHN), 13.92 (CH_3 in OEt), a signal of one aromatic carbon (CH) could not be detected. Anal. calcd for $C_{25}H_{23}NO_3S$: C, 71.92; H, 5.55; N, 3.36; found: C, 71.89; H, 5.66; N, 3.50%.

O-*Ethyl {[2-benzoyl-1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}thiocarbamate* (**12b**)

Compound **12b** (0.459 g, 76%) as a mixture of two conformers in a ratio of 63:37 was prepared from dibenzoylmethane (0.316 g, 1.41 mmol), NaH (0.033 g, 1.38 mmol) and sulfone **9b** (0.505 g, 1.39 mmol) in dry THF (8 mL) (r.t., 8 h) as described for **12a**. An analytically pure sample (a 63:37 conformer mixture) was obtained after crystallisation from EtOH. M.p. 118.5–120 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3350 (s), 3316 (s) (NH), 3103 (w), 3056 (m), 3034 (w), 3027 (w) (CH_{arom}), 1685 (vs), 1659 (m) (C=O), 1595 (s), 1578 (m) (CC_{arom}), 1517 (s) (thioamide-II), 1282 (s), 1189 (s) (C–O), 826 (m), 767 (m), 707 (s), 683 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.61 (1H, d, ^3J = 8.6 Hz, NH), 7.95–8.02* (2H, m, ArH), 7.71–7.78* (2H, m, ArH), 7.37–7.65* (6H, m, ArH), 7.22–7.29* (2H, m, ArH), 6.95–7.02* (2H, m, ArH), 6.44 (1H, d, ^3J = 10.3 Hz, CHC=O), 6.14 (1H, dd, ^3J = 10.3, ^3J = 8.6 Hz, CHN), 4.15–4.38* (2H, m, OCH_2), 2.121 (3H, s, CH_3 in $CH_3C_6H_4$), 1.14 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.67 (1H, d, ^3J = 8.4 Hz, NH), 7.95–8.02[§] (2H, m, ArH), 7.71–7.78[§] (2H, m, ArH), 7.37–7.65[§] (6H, m, ArH), 7.22–7.29[§] (2H, m, ArH), 6.95–7.02[§] (2H, m, ArH), 6.49 (1H, d, ^3J = 10.5 Hz, CHC=O), 5.79 (1H, dd, ^3J = 10.5,

^3J = 8.4 Hz, CHN), 4.15–4.38§ (2H, m, OCH_2), 2.115 (3H, s, CH_3 in $CH_3C_6H_4$), 1.16 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 193.10 (C=O in Bz), 192.52 (C=O in Bz), 189.07 (C=S), 136.50 (C), 136.14 (C), 136.06 (C), 135.59 (C), 133.88 (CH), 133.83 (CH), 128.92 (2CH), 128.87 (2CH), 128.61 (2CH), 128.57 (2CH), 128.40 (2CH), 127.97 (2CH), 65.39 (OCH_2), 59.83 (*C*HBz_2), 58.36 (CHN), 20.57 (CH_3 in $CH_3C_6H_4$), 14.05 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 193.13 (C=O in Bz), 192.39 (C=O in Bz), 187.55 (C=S), 136.74 (C), 136.04 (C), 135.84 (C), 135.49 (C), 133.96 (CH), 133.93 (CH), 128.95 (2CH), 128.88 (2CH), 128.79 (2CH), 128.57 (2CH), 128.47 (2CH), 127.63 (2CH), 66.42 (OCH_2), 59.45 (*C*HBz_2), 56.46 (CHN), 20.56 (CH_3 in $CH_3C_6H_4$), 13.95 (CH_3 in OEt). Anal. calcd for $C_{26}H_{25}NO_3S$: C, 72.36; H, 5.84; N, 3.25; found: C, 72.29; H, 5.90; N, 3.32%.

O-*Ethyl {[2-benzoyl-1-(4-methoxyphenyl)-3-oxo-3-phenyl]prop-1-yl} thiocarbamate* (**12c**)

Compound **12c** (4.367 g, 85%) as a mixture of two conformers in a ratio of 62:38 was prepared from dibenzoylmethane (2.573 g, 11.47 mmol), NaH (0.275 g, 11.46 mmol) and sulfone **9c** (4.350 g, 11.46 mmol) in dry THF (22 mL) (r.t., 8 h) as described for **12a**. An analytically pure sample (a 62:38 conformer mixture) was obtained after crystallisation from EtOH. M.p. 125–127 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3276 (br vs) (NH), 3057 (m), 3009 (w) (CH_{arom}), 1685 (vs), 1659 (m) (C=O), 1610 (m), 1593 (s), 1577 (m) (CC_{arom}), 1517 (s) (thioamide-II), 1493 (w) (CC_{arom}), 1280 (s), 1183 (s) (C–O), 834 (s), 768 (s), 707 (s), 688 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.60 (1H, d, ^3J = 8.6 Hz, NH), 7.95–8.01* (2H, m, ArH), 7.72–7.78* (2H, m, ArH), 7.37–7.65* (6H, m, ArH), 7.24–7.33* (2H, m, ArH), 6.70–6.77* (2H, m, ArH), 6.43 (1H, d, ^3J = 10.3 Hz, CHC=O), 6.11 (1H, dd, ^3J = 10.3, ^3J = 8.6 Hz, CHN), 4.16–4.40* (2H, m, OCH_2), 3.611 (3H, s, OCH_3), 1.15 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.64 (1H, d, ^3J = 8.4 Hz, NH), 7.95–8.01§ (2H, m, ArH), 7.72–7.78§ (2H, m, ArH), 7.37–7.65§ (6H, m, ArH), 7.24–7.33§ (2H, m, ArH), 6.70–6.77§ (2H, m, ArH), 6.47 (1H, d, ^3J = 10.5 Hz, CHC=O), 5.78 (1H, dd, ^3J = 10.5, ^3J = 8.4 Hz, CHN), 4.16–4.40§ (2H, m, OCH_2), 3.606 (3H, s, OCH_3), 1.17 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 193.13 (C=O in Bz), 192.49 (C=O in Bz), 188.99 (C=S), 158.34 (C), 136.16 (C), 135.61 (C), 133.83 (CH), 133.81 (CH), 130.97 (C), 129.23 (2CH), 128.90 (2CH), 128.84 (2CH), 128.55 (2CH), 128.38 (2CH), 113.39 (2CH), 65.34 (OCH_2), 59.93 (*C*HBz_2), 58.07 (CHN), 54.92 (OCH_3), 14.03 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 193.18 (C=O in Bz), 192.39 (C=O in Bz), 187.51 (C=S), 158.44 (C), 136.06 (C), 135.50 (C), 133.91 (CH), 133.90 (CH), 130.76 (C), 128.93 (2CH), 128.90 (2CH), 128.86 (2CH), 128.52 (2CH), 128.44 (2CH), 113.57 (2CH), 66.39 (OCH_2), 59.55 (*C*HBz_2), 56.14 (CHN), 54.92 (OCH_3), 13.95 (CH_3 in OEt). Anal. calcd for $C_{26}H_{25}NO_4S$: C, 69.78; H, 5.63; N, 3.13; found: C, 69.69; H, 5.83; N, 3.06%.

O-*Ethyl [(2-acetyl-3-oxo-1-phenyl)but-1-yl]thiocarbamate* (**13**)

A solution of acetylacetone (0.887 g, 8.86 mmol) in MeCN (10 mL) was added to an ice-cooled stirred suspension of NaH (0.211 g, 8.79 mmol) in dry MeCN (10 mL) and the resulting mixture was stirred for 25 min. The ice-bath was removed, and sulfone **9a** (2.932 g, 8.39 mmol) and MeCN (10 mL) were added to the obtained suspension. The mixture was stirred at room temperature for 8 h, and the solvent was removed *in vacuo*. The oily residue was triturated with petroleum ether (3 × 10 mL), petroleum ether was decanted, and saturated aqueous $NaHCO_3$ (10 mL) and petroleum ether (10 mL) were added. The obtained mixture was triturated until crystallisation was complete, left overnight at room temperature and cooled to 0 °C. The precipitate was filtered, washed with ice-cold H_2O and petroleum ether, and dried to give compound **13** (2.237 g, 91%) as a mixture of two conformers in a ratio of 70:30. An analytically pure sample (a 71:29 conformer mixture) was obtained after crystallisation from ethanol/water mixture (v/v = 7:5). M.p. 80.5–82.5 °C (EtOH-H_2O); IR (Nujol) ν_{max}/cm^{-1}: 3310 (s), 3257 (br s) (NH), 3086 (w), 3060 (w), 3029 (m) (CH_{arom}), 1726 (s), 1701 (s) (C=O), 1584 (w) (CC_{arom}), 1533 (m), 1521 (s) (thioamide-II), 1495 (m) (CC_{arom}), 1262 (s), 1194 (s) (C–O), 769 (s), 702 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.72 (1H, d, ^3J = 8.9 Hz, NH), 7.21–7.3* (5H, m, ArH), 5.83 (1H, dd, ^3J = 11.4, ^3J = 8.9 Hz, CHN), 4.57 (1H, d, ^3J = 11.4 Hz, CHC=O), 4.20–4.37* (2H, m, OCH_2), 2.23 (3H, s, CH_3 in Ac), 1.874 (3H, s, CH_3 in Ac), 1.20 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.67 (1H, d, ^3J = 8.3 Hz, NH), 7.21–7.39§ (5H, m, ArH), 5.36 (1H, dd, ^3J = 11.4, ^3J = 8.3 Hz, CHN), 4.67 (1H, d, ^3J = 11.4 Hz, CHC=O), 4.20–4.37§ (2H, m, OCH_2), 2.26 (3H, s, CH_3 in Ac), 1.868 (3H, s, CH_3 in Ac), 1.17 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 201.09 (C=O in Ac), 200.95 (C=O in Ac), 189.26 (C=S), 139.07 (C), 128.33 (2CH), 127.82 (2CH), 127.70 (CH), 71.64 (*C*HAc_2), 65.63 (OCH_2), 57.56 (CHN), 31.03 (CH_3 in Ac), 29.62 (CH_3 in Ac), 14.09 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 200.82 (C=O in Ac), 200.58 (C=O in Ac), 187.49 (C=S), 139.06 (C), 128.51 (2CH), 127.82 (CH), 127.51 (2CH), 70.51 (*C*HAc_2), 66.36 (OCH_2), 55.56 (CHN), 31.07 (CH_3 in Ac), 30.56 (CH_3 in Ac), 13.93 (CH_3 in OEt). Anal. calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77; found: C, 61.43; H, 6.71; N, 4.82%.

O-*Ethyl [(3-oxo-1,3-diphenyl)prop-1-yl]thiocarbamate* (**14a**)

Thiocarbamate **12a** (3.556 g, 8.52 mmol) and EtOH (4.2 mL) were added to a stirred solution of KOH (2.374 g, 42.31 mmol) in H_2O (30 mL) at room temperature. A gummy substance resulted which gradually solidified (in about 3.5 h). Then, the obtained solid was triturated until complete crystallisation, and the resulting suspension was stirred at room temperature. After 27 h 20 min from the beginning of the reaction, the suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold water (4 × 5 mL), then washed thoroughly with petroleum ether to remove chalcone, and dried to give compound **14a** (1.285 g, 48%) as a mixture of two conformers in a ratio of 67:33. An analytically pure sample (a 67:33 conformer mixture) was obtained after crystallisation from ethanol/water mixture (v/v = 8:3). M.p. 94–95 °C (EtOH–H_2O); IR (Nujol) ν_{max}/cm^{-1}: 3301 (br s), 3268 (sh) (NH), 3083 (w), 3056 (m), 3031 (m) (CH_{arom}), 1690 (s) (C=O), 1595 (m), 1580 (w) (CC_{arom}), 1537 (s) (thioamide-II), 1496 (m) (CC_{arom}), 1227 (s), 1202 (s), 1175 (s) (C–O), 766 (s), 696 (s), 689 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.64 (1H, d, ^3J = 8.1 Hz, NH), 7.91–7.98* (2H, m, ArH), 7.60–7.68* (1H, m, ArH), 7.48–7.57* (2H, m, ArH), 7.19–7.39* (5H, m, ArH), 5.74 (1H, ddd, ^3J = 8.9, ^3J = 8.1, ^3J = 5.4 Hz, CHN), 4.23–4.39* (2H, m, OCH_2), 3.70 (1H, dd, ^2J = 17.4, ^3J = 8.9 Hz, H_A in CH_2C=O), 3.42 (1H, dd, ^2J = 17.4, ^3J = 5.4 Hz, H_B in CH_2C=O), 1.22 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.63 (1H, d, ^3J = 7.5 Hz, NH), 7.91–7.98§ (2H, m, ArH), 7.60–7.68§ (1H, m, ArH), 7.48–7.57§ (2H, m, ArH), 7.19–7.39§ (5H, m, ArH), 5.42 (1H, ddd, ^3J = 9.8, ^3J = 7.5, ^3J = 4.2 Hz, CHN), 4.23–4.39§ (2H, m, OCH_2), 3.79 (1H, dd, ^2J = 17.8, ^3J = 9.9 Hz, H_A in CH_2C=O), 3.30 (1H, dd, ^2J = 17.8, ^3J = 4.2 Hz, H_B in CH_2C=O), 1.12 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 196.70 (C=O), 189.04 (C=S), 141.94 (C), 136.48 (C), 133.33 (CH), 128.75 (2CH), 128.26 (2CH), 128.02 (2CH), 127.03 (CH), 126.92 (2CH), 65.26 (OCH_2), 54.56 (CHN), 44.22 (*C*H_2C=O), 14.21 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 196.64 (C=O), 142.21 (C), 128.75 (2CH), 128.42 (2CH), 128.02 (2CH), 127.17 (CH), 126.58 (2CH), 66.11 (OCH_2), 52.32 (CHN), 43.85 (*C*H_2C=O), 13.99 (CH_3 in OEt), a signal of C=S carbon and two aromatic carbon (C, CH) could not be detected. Anal. calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47; found: C, 68.70; H, 6.44; N, 4.60%.

O-*Ethyl {[1-(4-methylphenyl)-3-oxo-3-phenyl]prop-1-yl}thiocarbamate* (**14b**)

Compound **14b** (0.056 g, 35%) as a mixture of two conformers in a ratio of 67:33 was prepared by treatment of thiocarbamate **12b** (0.213 g, 0.50 mmol) with KOH (0.138 g, 2.46 mmol) in EtOH (0.2 mL) and H_2O (1.7 mL) (r.t., 19 h) as described for **14a**. An analytically pure sample (a 67:33 conformer mixture) was obtained after crystallisation

from EtOH. M.p. 73–74 °C (EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3267 (br s) (NH), 3081 (w), 3060 (m), 3026 (m) (CH_{arom}), 1691 (s) (C=O), 1594 (m), 1580 (w) (CC_{arom}), 1538 (s), 1516 (m) (thioamide-II), 1491 (w) (CC_{arom}), 1229 (s), 1204 (s), 1178 (s) (C–O), 817 (m), 761 (s), 686 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.58 (1H, d, ^3J = 8.0 Hz, NH), 7.89–7.97* (2H, m, ArH), 7.59–7.68* (1H, m, ArH), 7.48–7.56* (2H, m, ArH), 7.21–7.28* (2H, m, ArH), 7.08–7.17* (2H, m, ArH), 5.71 (1H, ddd, ^3J = 8.6, ^3J = 8.0, ^3J = 5.7 Hz, CHN), 4.23–4.39* (2H, m, OCH_2), 3.67 (1H, dd, ^2J = 17.3, ^3J = 8.6 Hz, H_A in CH_2C=O), 3.41 (1H, dd, ^2J = 17.3, ^3J = 5.7 Hz, H_B in CH_2C=O), 2.26 (3H, s, CH_3 in $CH_3C_6H_4$), 1.22 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.57 (1H, d, ^3J = 7.6 Hz, NH), 7.89–7.97§ (2H, m, ArH), 7.59–7.68§ (1H, m, ArH), 7.48–7.56§ (2H, m, ArH), 7.21–7.28§ (2H, m, ArH), 7.08–7.17§ (2H, m, ArH), 5.39 (1H, ddd, ^3J = 9.6, ^3J = 7.6, ^3J = 4.4 Hz, CHN), 4.23–4.39§ (2H, m, OCH_2), 3.76 (1H, dd, ^2J = 17.7, ^3J = 9.6 Hz, H_A in CH_2C=O), 3.28 (1H, dd, ^2J = 17.7, ^3J = 4.4 Hz, H_B in CH_2C=O), 2.27 (3H, s, CH_3 in $CH_3C_6H_4$), 1.14 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 196.73 (C=O), 188.90 (C=S), 138.83 (C), 136.49 (C), 136.08 (C), 133.24 (CH), 128.73 (2CH), 128.70 (2CH), 127.95 (2CH), 126.81 (2CH), 65.15 (OCH_2), 54.31 (CHN), 44.15 (CH_2C=O), 20.62 (CH_3 in $CH_3C_6H_4$), 14.17 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 196.66 (C=O), 187.41 (C=S), 139.14 (C), 136.49 (C), 136.23 (C), 133.26 (CH), 128.89 (2CH), 128.70 (2CH), 127.94 (2CH), 126.47 (2CH), 65.05 (OCH_2), 52.04 (CHN), 43.81 (CH_2C=O), 20.63 (CH_3 in $CH_3C_6H_4$), 13.97 (CH_3 in OEt). Anal. calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28; found: C, 69.61; H, 6.73; N, 4.38%.

O-*Ethyl {[1-(4-methoxyphenyl)-3-oxo-3-phenyl]prop-1-yl}thiocarbamate* (**14c**)

Compound **14c** (0.726 g, 35%) as a mixture of two conformers in a ratio of 67:33 was prepared by treatment of thiocarbamate **12c** (2.693 g, 6.02 mmol) with KOH (1.680 g, 29.94 mmol) in EtOH (3 mL) and H_2O (21 mL) (r.t., 22 h) as described for **14a**. An analytically pure sample (a 67:33 conformer mixture) was obtained after crystallisation from EtOH. M.p. 88–89 °C (EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3366 (br s) (NH), 3082 (w), 3060 (m), 3035 (w), 3025 (w), 3016 (w) (CH_{arom}), 1688 (s) (C=O), 1611 (m), 1596 (m), 1585 (m) (CC_{arom}), 1526 (s), 1514 (s) (thioamide-II), 1491 (w) (CC_{arom}), 1229 (s), 1204 (s), 1178 (s) (C–O), 821 (s), 756 (s), 686 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.57 (1H, d, ^3J = 8.1 Hz, NH), 7.90–7.9* (2H, m, ArH), 7.60–7.68* (1H, m, ArH), 7.48–7.57* (2H, m, ArH), 7.25–7.32* (2H, m, ArH), 6.84–6.93* (2H, m, ArH), 5.70 (1H, ddd, ^3J = 8.4, ^3J = 8.1, ^3J = 5.9 Hz, CHN), 4.23–4.39* (2H, m, OCH_2), 3.72 (3H, s, OCH_3), 3.67 (1H, dd, ^2J = 17.2, ^3J = 8.4 Hz, H_A in CH_2C=O), 3.41 (1H, dd, ^2J = 17.2, ^3J = 5.9 Hz, H_B in CH_2C=O), 1.21 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.55 (1H, d, ^3J = 7.6 Hz, NH), 7.90–7.97§ (2H, m, ArH), 7.60–7.68§ (1H, m, ArH), 7.48–7.57§ (2H, m, ArH), 7.25–7.32§ (2H, m, ArH), 6.84–6.93§ (2H, m, ArH), 5.38 (1H, ddd, ^3J = 9.5, ^3J = 7.6, ^3J = 4.6 Hz, CHN), 4.23–4.39§ (2H, m, OCH_2), 3.73 (3H, s, OCH_3), 3.76 (1H, dd, ^2J = 17.7, ^3J = 9.5 Hz, H_A in CH_2C=O), 3.29 (1H, dd, ^2J = 17.7, ^3J = 4.6 Hz, H_B in CH_2C=O), 1.16 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 196.80 (C=O), 188.80 (C=S), 158.26 (C), 136.51 (C), 133.76 (C), 133.25 (CH), 128.71 (2CH), 128.11 (2CH), 127.96 (2CH), 113.56 (2CH), 65.15 (OCH_2), 55.01 (OCH_3), 54.05 (CHN), 44.17 (CH_2C=O), 14.19 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 196.73 (C=O), 187.33 (C=S), 158.31 (C), 136.51 (C), 134.10 (C), 133.27 (CH), 128.71 (2CH), 127.95 (2CH), 127.77 (2CH), 113.71 (2CH), 66.06 (OCH_2), 55.04 (OCH_3), 51.75 (CHN), 43.85 (CH_2C=O), 14.00 (CH_3 in OEt). Anal. calcd for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; found: C, 66.48; H, 6.21; N, 4.11%.

O-*Ethyl [(3-oxo-1-phenyl)but-1-yl]thiocarbamate* (**15**)

Thiocarbamate **13** (2.233 g, 7.61 mmol) was added to a stirred solution of KOH (2.341 g, 41.73 mmol) in H_2O (36.5 mL) at room temperature. A homogeneous solution formed for several minutes, from which solid immediately started to precipitate. After 4 h from the beginning of the reaction, the suspension was cooled to 0 °C. The precipitate was filtered, washed with ice-cold water (4 × 4 mL), then washed thoroughly with petroleum ether, and dried to give compound **15** (1.642 g, 86%) as a mixture of two conformers in a ratio of 70:30. An analytically pure sample (a 70:30 conformer mixture) was obtained after crystallisation from ethanol/water mixture (v/v = 3:2). M.p. 76.5–77.5 °C (EtOH–H_2O); IR (Nujol) ν_{max}/cm^{-1}: 3219 (br s), 3056 (s) (NH), 3032 (m) (CH_{arom}), 1719 (s) (C=O), 1604 (w) (CC_{arom}), 1556 (s) (thioamide-II), 1494 (m) (CC_{arom}), 1243 (s), 1196 (s) (C–O), 749 (s), 699 (s) (CH_{arom}); ^{1}H NMR of the major conformer (300.13 MHz, DMSO-d_6) δ: 9.59 (1H, d, ^3J = 8.3 Hz, NH), 7.18–7.36* (5H, m, ArH), 5.58 (1H, ddd, ^3J = 8.8, ^3J = 8.3, ^3J = 5.8 Hz, CHN), 4.24–4.40* (2H, m, OCH_2), 3.00 (1H, dd, ^2J = 16.8, ^3J = 8.8 Hz, H_A in CH_2C=O), 2.89 (1H, dd, ^2J = 16.8, ^3J = 5.8 Hz, H_B in CH_2C=O), 2.08 (3H, s, CH_3 in Ac), 1.23 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{1}H NMR of the minor conformer (300.13 MHz, DMSO-d_6) δ: 9.56 (1H, d, ^3J = 7.5 Hz, NH), 7.18–7.36§ (5H, m, ArH), 5.18 (1H, ddd, ^3J = 9.5, ^3J = 7.5, ^3J = 4.8 Hz, CHN), 4.24–4.40§ (2H, m, OCH_2), 3.10 (1H, dd, ^2J = 17.5, ^3J = 9.5 Hz, H_A in CH_2C=O), 2.77 (1H, dd, ^2J = 17.5, ^3J = 4.8 Hz, H_B in CH_2C=O), 2.07 (3H, s, CH_3 in Ac), 1.10 (3H, t, ^3J = 7.1 Hz, CH_3 in OEt); ^{13}C NMR of the major conformer (75.48 MHz, DMSO-d_6) δ: 205.40 (C=O), 189.07 (C=S), 141.76 (C), 128.23 (2CH), 127.01 (CH), 126.71 (2CH), 65.29 (OCH_2), 54.35 (CHN), 48.87 (CH_2C=O), 29.96 (CH_3 in Ac), 14.19 (CH_3 in OEt); ^{13}C NMR of the minor conformer (75.48 MHz, DMSO-d_6) δ: 205.20 (C=O), 187.49 (C=S), 142.12 (C), 128.36 (2CH), 127.09 (CH), 126.37 (2CH), 66.06 (OCH_2), 52.13 (CHN), 48.29 (CH_2C=O), 30.04 (CH_3 in Ac), 13.91 (CH_3 in OEt). Anal. calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57; found: C, 61.95; H, 6.98; N, 5.65%.

4-{[(3-Hydrazono-1,3-diphenyl)prop-1-yl]}thiosemicarbazide (**16a**)

Method A: An ice bath cooled solution of thiocarbamate **14a** (0.917 g, 2.93 mmol) in anhydrous N_2H_4 (7.8 mL) was stirred for 1 h, then N_2H_4 was removed *in vacuo* at about 60 °C (bath temperature), the oily residue was co-evaporated 5–7 times with toluene until a white solid was formed. The obtained solid was triturated with cold Et_2O (5 mL) and the resulting suspension was cooled (–18 °C). The precipitate was filtered, washed with cold Et_2O (4 × 5 mL) and dried on the filter by sucking air through the filter. The powder product was washed on the filter with ice-cold water (4 × 5 mL), petroleum ether, and dried to give **16a** (0.645 g, 70%) as a mixture of (*E*)- and (*Z*)-isomers in a ratio of 95:5.

Method B: Compound **16a** (0.614 g, 60%) as a 92:8 mixture of (*E*)- and (*Z*)-isomers was synthesised by treatment of thiocarbamate **14a** (1.032 g, 3.29 mmol) with anhydrous N_2H_4 (8.3 mL) at room temperature for 2 h as described in Method A. An analytically pure sample (a 99:1 isomeric ratio) was obtained after crystallisation from EtOH. M.p. 172.5–173 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3432 (m), 3416 (m), 3309 (s), 3259 (sh), 3225 (s), 3191 (br s) (ν NH), 3107 (w), 3085 (w), 3065 (w), 3053 (w), 3027 (w) (ν CH_{arom}), 1629 (s) (ν C=N, δ NH_2), 1588 (m) (ν CC_{arom}), 1529 (br s) (thioamide-II), 1493 (s) (ν CC_{arom}), 756 (s), 695 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.79 (1H, br s, N*H*NH_2), 8.30 (1H, br d, ^3J = 7.9 Hz, N*H*CH), 7.49–7.55 (2H, m, ArH), 7.12–7.38 (8H, m, ArH), 6.69 (2H, br s, NH_2N=C), 5.71 (1H, ddd, ^3J = 8.0, ^3J = 7.9, ^3J = 7.7 Hz, CHN), 4.50 (2H, br s, NH_2NH), 3.29 (1H, dd, ^2J = 14.3, ^3J = 7.7 Hz, H_A in CH_2), 3.11 (1H, dd, ^2J = 14.3, ^3J = 8.0 Hz, H_B in CH_2); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.57 (C=S), 142.19 (C), 141.67 (C=N), 138.99 (C), 128.11 (2CH), 127.83 (2CH), 127.01 (CH), 126.79 (2CH), 126.69 (CH), 125.01 (2CH), 54.02 (CHN), 31.50 (CH_2). Anal. calcd for $C_{16}H_{19}N_5S$: C, 61.32; H, 6.11; N, 22.35; found: C, 61.37; H, 6.30; N, 22.39%.

4-{[3-Hydrazono-1-(4-methylphenyl)-3-phenyl]prop-1-yl}semicarbazide (**16b**)

Compound **16b** (1.407 g, 58%) as a 90:10 mixture of (*E*)- and (*Z*)-isomers was prepared by treatment of thiocarbamate **14b** (2.426 g, 7.41 mmol) with anhydrous N_2H_4 (19 mL) (0 °C, 1 h) as described for **16a** in Method A. An analytically pure sample (a 93:7 isomeric ratio) was obtained after crystallisation from EtOH. M.p. 148.5–150 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3432 (m), 3419 (sh), 3379 (w), 3312 (s),

3233 (br s), 3192 (br s) (ν NH), 3103 (w), 3051 (w), 3021 (w) (ν CH_{arom}), 1626 (s) (ν C=N, δ NH_2), 1590 (m) (ν CC_{arom}), 1530 (br s) (thioamide-II), 1492 (s) (ν CC_{arom}), 802 (s), 765 (s), 697 (s) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.73 (1H, br s, N*H*NH_2), 8.21 (1H, br d, ^3J = 8.5 Hz, N*H*CH), 7.49–7.57 (2H, m, ArH), 7.00–7.28 (7H, m, ArH), 6.64 (2H, br s, NH_2N=C), 5.66 (1H, ddd, ^3J = 8.5, ^3J = 8.2, ^3J = 7.6 Hz, CHN), 4.47 (2H, br s, NH_2NH), 3.26 (1H, dd, ^2J = 14.3, ^3J = 7.6 Hz, H_A in CH_2), 3.09 (1H, dd, ^2J = 14.3, ^3J = 8.2 Hz, H_B in CH_2), 2.23 (3H, s, CH_3); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.50 (C=S), 141.72 (C=N), 139.06 (C), 138.99 (C), 136.02 (C), 128.62 (2CH), 127.78 (2CH), 126.65 (3CH), 125.01 (2CH), 53.77 (CHN), 31.48 (CH_2), 20.62 (CH_3). Anal. calcd for $C_{17}H_{21}N_5S$: C, 62.36; H, 6.46; N, 21.39; found: C, 62.03; H, 6.73; N, 21.51%.

4-{[3-Hydrazono-1-(4-methoxyphenyl)-3-phenyl]prop-1-yl} semicarbazide (**16c**)

Compound **16c** (0.332 g, 65%) as a 87:13 mixture of (*E*)- and (*Z*)-isomers was prepared by treatment of thiocarbamate **14c** (0.510 g, 1.49 mmol) with anhydrous N_2H_4 (3.8 mL) (0 °C, 1 h) as described for **16a** in Method A. An analytically pure sample (a 98:2 isomeric ratio) was obtained after crystallisation from EtOH. M.p. 77–79 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3305 (m), 3262 (m), 3195 (br s) (ν NH), 3052 (w), 3033 (w) (ν CH_{arom}), 1650 (m) (ν C=N, δ NH_2), 1612 (m), 1585 (m) (ν CC_{arom}), 1536 (br s) (thioamide-II), 1514 (s), 1500 (sh) (ν CC_{arom}), 1252 (s), 1033 (m) (ν C–O), 827 (m), 766 (m), 700 (m) (δ CH_{arom}); ^{1}H NMR of the major isomer (300.13 MHz, DMSO-d_6) δ: 8.74 (1H, br s, N*H*NH_2), 8.18 (1H, br d, ^3J = 7.9 Hz, N*H*CH), 7.49–7.55 (2H, m, ArH), 7.12–7.29 (5H, m, ArH), 6.77–6.83 (2H, m, ArH), 6.65 (2H, br s, NH_2N=C), 5.64 (1H, ddd, ^3J = 8.4, ^3J = 7.9, ^3J = 7.3 Hz, CHN), 4.47 (2H, br s, NH_2NH), 3.69 (3H, s, OCH_3), 3.25 (1H, dd, ^2J = 14.2, ^3J = 7.3 Hz, H_A in CH_2), 3.10 (1H, dd, ^2J = 14.2, ^3J = 8.4 Hz, H_B in CH_2); ^{13}C NMR of the major isomer (75.48 MHz, DMSO-d_6) δ: 180.36 (C=S), 158.26 (C), 141.71 (C=N), 139.02 (C), 134.02 (C), 127.99 (2CH), 127.82 (2CH), 126.67 (CH), 125.03 (2CH), 113.48 (2CH), 55.02 (OCH_3), 53.47 (CHN), 31.53 (CH_2). Anal. calcd for $C_{17}H_{21}N_5OS$: C, 59.45; H, 6.16; N, 20.39; found: C, 59.53; H, 6.35; N, 20.20%.

*5,7-Diphenyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione* (**18a**)

A solution of hydrazone **16a** (0.641 g, 2.05 mmol) and TsOH·H_2O (0.411 g, 2.16 mmol) in EtOH (5 mL) was stirred under reflux for 35 min, and the solvent was removed in vacuum. The residue was triturated with saturated aqueous $NaHCO_3$ (4 mL) upon cooling until crystallisation was completed, and the obtained suspension was cooled. The precipitate was filtered, washed with ice-cold H_2O (4 × 4 mL), petroleum ether (4 × 4 mL), and dried. The crude product was purified using column chromatography on silica gel (22 g) eluting with petroleum ether-$CHCl_3$ (1:1) to give triazepine **18a** (0.274 g, 48%) (*note*: purification of the crude product was also performed using aluminium oxide column chromatography eluting with petroleum ether-$CHCl_3$, 3:1). An analytically pure sample was obtained by crystallisation from EtOH. M.p. 168–170 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3361 (s), 3129 (br s), 1619 (m) (ν C=N), 1577 (m), 1549 (s) (thioamide-II), 1187 (s) (δ NH + ν CN), 764 (s), 690 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.92 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}$H), 9.10 (1H, br dd, ^3J = 4.9, ^4J = 2.0 Hz, $N_{(4)}$H), 7.34–7.39 (2H, m, ArH), 7.12–7.32 (8H, m, ArH), 4.96 (1H, ddd, ^3J = 6.2, ^3J = 4.9, ^3J = 2.7 Hz, H-5), 3.54 (1H, ddd, ^2J = 14.7, ^3J = 6.2, ^4J = 1.0 Hz, H_A-6), 3.24 (1H, dd, ^2J = 14.7, ^3J = 2.7 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.00 (C-3), 158.35 (C-7), 142.03 (C), 137.22 (C), 129.32 (CH), 128.20 (2CH), 128.13 (2CH), 127.27 (CH), 125.91 (4CH), 59.04 (C-5), 36.84 (C-6). Anal. calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93; found: C, 67.95; H, 5.62; N, 15.18%.

*5-(4-Methylphenyl)-7-phenyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione* (**18b**)

Compound **18b** (0.207 g, 46%) was obtained from hydrazone **16b** (0.502 g, 1.53 mmol) and TsOH·H_2O (0.306 g, 1.61 mmol) in EtOH (15 mL) (reflux, 1 h) as described for **18a**. The crude product was purified using column chromatography on silica gel (13 g) eluting with petroleum ether-$CHCl_3$ (from 3:1 to 1:1) (*note*: purification of the crude product was also performed using aluminium oxide column chromatography eluting with petroleum ether-$CHCl_3$ [from 3:1 to 1:1]). An analytically pure sample was obtained by crystallisation from EtOH. M.p. 198.5–200 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3190 (br vs), 3104 (m) (ν NH), 1619 (m) (ν C=N), 1572 (m) (ν CC_{arom}), 1548 (s) (thioamide-II), 1513 (m) (ν CC_{arom}), 1177 (s) (δ NH + ν CN), 815 (m), 767 (s), 702 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.87 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}$H), 9.06 (1H, br dd, ^3J = 5.0, ^4J = 2.0 Hz, $N_{(4)}$H), 7.37–7.44 (2H, m, ArH), 7.22–7.34 (3H, m, ArH), 7.03–7.13 (4H, m, ArH), 4.90 (1H, ddd, ^3J = 6.2, ^3J = 5.0, ^3J = 2.6 Hz, H-5), 3.53 (1H, ddd, ^2J = 14.8, ^3J = 6.2, ^4J = 0.9 Hz, H_A-6), 3.20 (1H, dd, ^2J = 14.8, ^3J = 2.6 Hz, H_B-6), 2.19 (3H, s, CH_3); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 177.00 (C-3), 157.98 (C-7), 139.10 (C), 137.31 (C), 136.31 (C), 129.28 (CH), 128.72 (2CH), 128.14 (2CH), 125.92 (2CH), 125.81 (2CH), 58.68 (C-5), 36.88 (C-6), 20.55 (CH_3). Anal. calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22; found: C, 69.08; H, 6.00; N, 14.42%.

*5-(4-Methoxyphenyl)-7-phenyl-2,4,5,6-tetrahydro-3*H*-1,2,4-triazepine-3-thione* (**18c**)

Compound **18c** (0.262 g, 57%) was obtained from hydrazone **16c** (0.508 g, 1.48 mmol) and TsOH·H_2O (0.296 g, 1.56 mmol) in EtOH (15 mL) (reflux, 30 min) as described for **18a**. The crude product was purified using column chromatography on silica gel (13.5 g) eluting with petroleum ether-$CHCl_3$ (from 3:1 to 1:1) (*note*: purification of the crude product was also performed using aluminium oxide column chromatography eluting with petroleum ether-$CHCl_3$ [from 3:1 to 1:1]). An analytically pure sample was obtained by crystallisation from EtOH. M.p. 163.5–165.5 °C (decomp., EtOH); IR (Nujol) ν_{max}/cm^{-1}: 3181 (br vs), 3097 (m) (ν NH), 1612 (m) (ν C=N), 1579 (s), 1566 (m) (thioamide-II), 1512 (s), 1486 (m) (ν CC_{arom}), 1251 (s) (ν C–O), 1174 (s) (δ NH + ν CN), 1037 (s) (ν C–O), 832 (m), 769 (s), 698 (s) (δ CH_{arom}); ^{1}H NMR (300.13 MHz, DMSO-d_6) δ: 10.88 (1H, br d, ^4J = 2.0 Hz, $N_{(2)}$H), 9.04 (1H, br dd, ^3J = 5.0, ^4J = 2.0 Hz, $N_{(4)}$H), 7.38–7.44 (2H, m, ArH), 7.22–7.34 (3H, m, ArH), 7.10–7.16 (2H, m, ArH), 6.78–6.85 (2H, m, ArH), 4.89 (1H, ddd, ^3J = 6.3, ^3J = 5.0, ^3J = 2.6 Hz, H-5), 3.66 (3H, s, OCH_3), 3.50 (1H, ddd, ^2J = 14.7, ^3J = 6.3, ^4J = 0.9 Hz, H_A-6), 3.20 (1H, dd, ^2J = 14.7, ^3J = 2.6 Hz, H_B-6); ^{13}C NMR (75.48 MHz, DMSO-d_6) δ: 176.90 (C-3), 158.36 (C-7), 158.23 (C), 137.29 (C), 134.17 (C), 129.33 (CH), 128.18 (2CH), 127.12 (2CH), 125.96 (2CH), 113.57 (2CH), 58.49 (C-5), 55.05 (OCH_3), 37.00 (C-6). Anal. calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49; found: C, 65.57; H, 5.73; N, 13.36%.

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Electronic supplementary information

The ESI (copies of IR, ^{1}H and ^{13}C NMR spectra of all the synthesised compounds) is available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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