Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 3691–3700
Tetrahedron
www.elsevier.com/locate/tet

Synthesis of 2,3,4,7-tetrahydro[1,4]thiazepines from thiazolidines and β-enaminonitriles

Luis A. Calvo, Alfonso González-Ortega*, Rocío Marcos, Mónica Pérez, M. Carmen Sañudo

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Dr. Mergelina s/n, 47011 Valladolid, Spain

Received 1 January 2008; received in revised form 7 February 2008; accepted 7 February 2008
Available online 12 February 2008

Abstract

A wide library of 2,3,4,7-tetrahydro[1,4]thiazepines have been prepared by simple heating of thiazolidine and β-enaminonitrile derivatives in acetonitrile. The procedure, whose yields depend on the nature and position of the substituents, gave good results if the substituents were not very bulky but it is less effective when starting from 2-substituted thiazolidines.

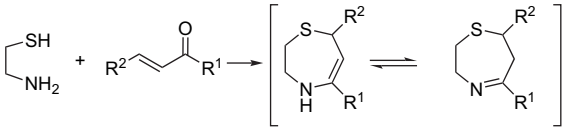
Keywords: β-Enaminonitrile; Tetrahydro[1,4]thiazepine; Thiazolidine

1. Introduction

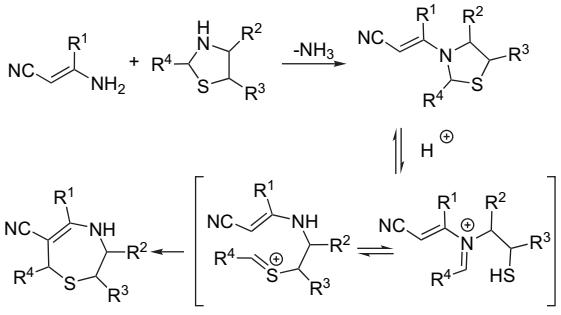
Thiazepinones, benzothiazepines and other thiazepine derivatives are moieties whose biological activity has received much attention.[1] However, 2,3,4,7-tetrahydro[1,4]thiazepines are relatively unknown heterocycles and may be due to the absence of adequate methods of synthesis no pharmacological tests have been published. Typically, they have been prepared from unsaturated α,β-carbonyls, leading to imines or enamines, which upon reduction gave hexahydro[1,4]thiazepines[2] (Scheme 1).

In a recent exploratory work, we have confirmed that they can be prepared with a higher degree of functionalisation by reaction of β-aminocrotonitrile with proline derivatives. Among the different mechanistic interpretations that we proposed, the rearrangement of the *N*-vinylthiazolidine cycle with ring enlargement to give 2,3,4,7-tetrahydro[1,4]thiazepines is probably the most feasible pathway (Scheme 2).[3]

In view of the singularity of the 2,3,4,7-tetrahydro[1,4]thiazepine cycle, in this paper we have carried out a systematic study of the former reaction with the aim of determining the scope and generality of this synthetic method. For this purpose several enamines and thiazolidines bearing different alkyl or aryl substituents have been tested (Scheme 3) and we have attempted to determine the scope and limitations derived from their nature and position. The results are accompanied by a brief study regarding the optimisation of the reaction conditions carried out with simple commercial substrates.



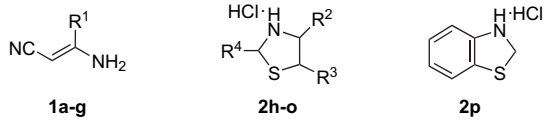
Scheme 1.



Scheme 2.

* Corresponding author.
E-mail address: algon@qo.uva.es (A. González-Ortega).

0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.02.027



1a-g **2h-o** **2p**

a R^1 = H
b R^1 = Me
c R^1 = Et
d R^1 = CH_2CH_2Ph
e R^1 = *i*-Pr
f R^1 = *t*-Bu
g R^1 = Ph

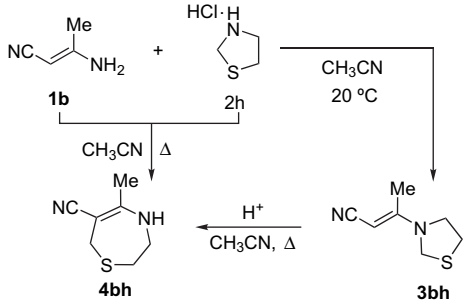
h R^2 = R^3 = R^4 = H
i R^2 = Et, R^3 = R^4 = H
j R^2 = *i*-Pr, R^3 = R^4 = H
k R^2 = Ph, R^3 = R^4 = H
l R^2 = R^4 = H,R^3 = Me
m R^2 = R^4 = H, R^3 = Ph
n R^2 = R^3 = H, R^4 = Me
o R^2 = R^3 = H, R^4 = Ph

Scheme 3.

2. Results and discussion

2.1. Optimization of the reaction conditions

Optimization of the reaction conditions has been carried out using β-aminocrotonitrile **1b** and thiazolidine **2h**. At room temperature, nitrogen exchange resulting from conjugate addition–elimination was observed leading to 3-(thiazolidine-3-yl)but-2-enenitrile **3bh** as the only product. Heating of the reaction was necessary to accomplish the formation of 2,3,4,7-tetrahydro[1,4]thiazepine **4bh** (Scheme 4). Among all the solvents tested (methanol, ethanol, acetonitrile and toluene) acetonitrile gave the best yields.



1b **2h** **4bh** **3bh**

Scheme 4.

It should be pointed out that the slightly acidic conditions provided by the thiazolidine hydrochloride were necessary (rate of enaminonitrile/thiazolidine 1:1.2) for the reaction to proceed. All attempts to carry out the reaction with the free amine were unsuccessful.

According to previous tests, refluxing acetonitrile was used in general as standard solvent. However, in those cases in which low yields were obtained, other conditions were also tested. Among these, multicomponent reactions (3-CR) from β-enaminonitrile, aldehyde and cysteamine derivatives were also examined.

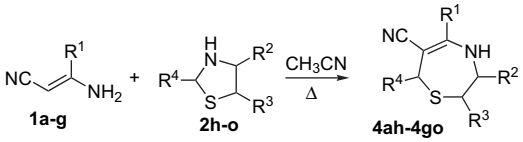
2.2. Scope and limitations

2.2.1. Effect of the R^1, R^2 and R^3 substituents

As observed in Table 1, the reaction of thiazolidine **2h** with β-alkylenaminonitriles **1b–f** (R^1=Me, Et, CH_2CH_2Ph, *i*-Pr, *t*-Bu) (entry 2, 10, 15, 20, and 25) led in all cases to the expected 2,3,4,7-tetrahydro[1,4]thiazepines. The reactivity diminishes considerably as the size of R^1 increases although longer reaction times balance partially the final outcome. The lowest yields were obtained using **1g** (entry 32) and **1a** (entry 1). In the first case phenyl conjugation reduces notably the reactivity of **1g**; on the contrary, **1a** reacts too fast giving complex mixtures. Compound **1a** was scarcely used (only in the synthesis of **4ah**) due to its difficult preparation and manipulation,[4] which lowers appreciably the yield.

A more general behaviour was observed when different C-4 substituted thiazolidines (**2i–k**) react with β-aminocrotonitrile

Table 1
Preparation of thiazepines **4ah–go** from **1** and **2**[a]



1a-g **2h-o** **4ah-4go**

Entry	Starting	R^1	R^2	R^3	R^4	Thiazepine (%)
1	**1a**+**2h**	H	H	H	H	**4ah** (25)
2	**1b**+**2h**	Me	H	H	H	**4bh** (75)
3	**1b**+**2i**	Me	Et	H	H	**4bi** (69)
4	**1b**+**2j**	Me	*i*-Pr	H	H	**4bj** (67)
5	**1b**+**2k**	Me	Ph	H	H	**4bk** (60)
6	**1b**+**2l**	Me	H	Me	H	**4bl** (62)
7	**1b**+**2m**	Me	H	Ph	H	**4bm** (47)
8	**1b**+**2n**	Me	H	H	Me	**4bn** (47)
9	**1b**+**2o**	Me	H	H	Ph	**4bo** (20)
10	**1c**+**2h**	Et	H	H	H	**4ch** (74)
11	**1c**+**2i**	Et	Et	H	H	**4ci** (64)
12	**1c**+**2j**	Et	*i*-Pr	H	H	**4cj** (41)
13	**1c**+**2k**	Et	Ph	H	H	**4ck** (51)
14	**1c**+**2l**	Et	H	Me	H	**4cl** (60)
15	**1d**+**2h**	CH_2CH_2Ph	H	H	H	**4dh** (61)
16	**1d**+**2i**	CH_2CH_2Ph	Et	H	H	**4di** (61)
17	**1d**+**2j**	CH_2CH_2Ph	*i*-Pr	H	H	**4dj** (41)
18	**1d**+**2k**	CH_2CH_2Ph	Ph	H	H	**4dk** (51)
19	**1d**+**2l**	CH_2CH_2Ph	H	Me	H	**4dl** (50)
20	**1e**+**2h**	*i*-Pr	H	H	H	**4eh** (62)[b]
21	**1e**+**2i**	*i*-Pr	Et	H	H	**4ei** (41)
22	**1e**+**2j**	*i*-Pr	*i*-Pr	H	H	**4ej** (<5)
23	**1e**+**2k**	*i*-Pr	Ph	H	H	—[c]
24	**1e**+**2l**	*i*-Pr	H	Me	H	**4el** (49)
25	**1f**+**2h**	*t*-Bu	H	H	H	**4fh** (61)[b]
26	**1f**+**2i**	*t*-Bu	Et	H	H	—[c]
27	**1f**+**2j**	*t*-Bu	*i*-Pr	H	H	—[c]
28	**1f**+**2k**	*t*-Bu	Ph	H	H	—[c]
29	**1f**+**2l**	*t*-Bu	H	Me	H	**4fl** (40)
30	**1f**+**2m**	*t*-Bu	H	Ph	H	**4fm** (<5)
31	**1f**+**2n**	*t*-Bu	H	H	Me	**4fn** (<5)
32	**1g**+**2h**	Ph	H	H	H	**4gh** (31)
33	**1g**+**2i**	Ph	Et	H	H	**4gi** (29)
34	**1g**+**2j**	Ph	*i*-Pr	H	H	—[c]
35	**1g**+**2k**	Ph	Ph	H	H	**4gk** (41)
36	**1g**+**2l**	Ph	H	Me	H	**4gl** (48)
37	**1g**+**2m**	Ph	H	Ph	H	**4gm** (43)
38	**1g**+**2n**	Ph	H	H	Me	**4gn** (17)

[a] Standard procedure: refluxing acetonitrile, 2 h; ratio of enaminonitrile/thiazolidine 1:1.2.
[b] Refluxing acetonitrile 6 h.
[c] The presence of thiazepine in the reaction mixture was not observed.

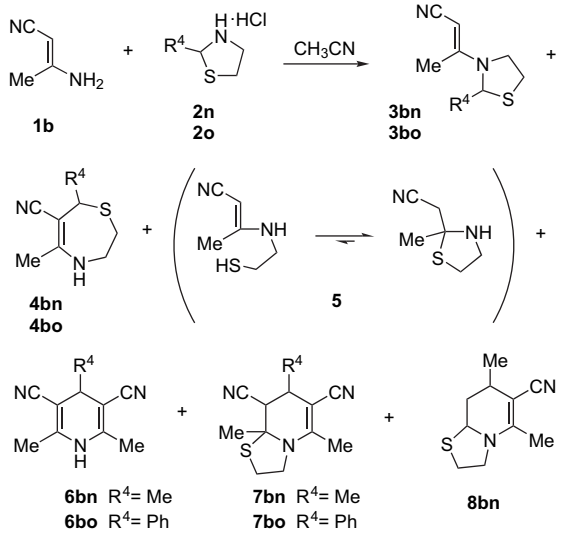
1b (Table 1, entry 2–5). The variation of yields can be explained in terms of the steric effect.

When the size of R^1 and R^2 was simultaneously increased, the decrease in the reactivity and yield could not always be compensated by increasing the reaction times or the temperature, because in many cases much degradation of the reagents was produced. For example, yields were less than 50% when R^1=*i*-Pr and $R^2 \neq H$ (entry 21–23), and null when R^1=*t*-Bu and $R^2 \neq H$ (entry 26–28). These observations were consistent with the mechanism depicted in Scheme 2, where the first step leading to nitrogen exchange should be highly affected by the steric hindrance of R^1 and R^2.

For the same reason, the size of R^3, which is placed far away from the nitrogen atom, has little influence on the reactivity. Thus, when R^1=*t*-Bu and R^2=Et (entry 26) nitrogen exchange did not take place and formation of **4fi** was not observed, whereas **4fl** (R^1=*t*-Bu and R^3=Me, entry 29) was obtained in moderate yield (40%).

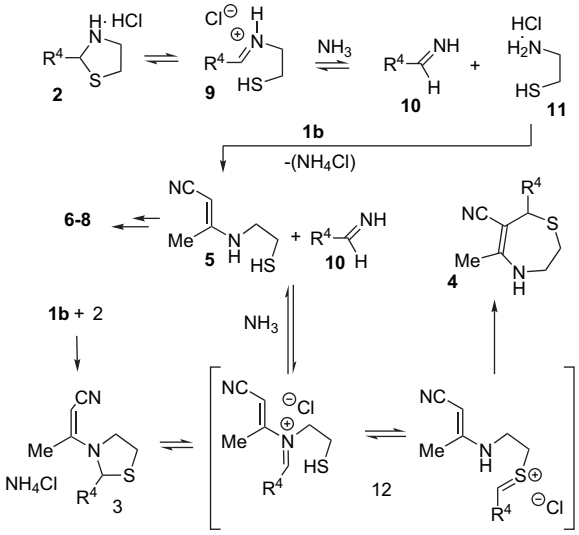
2.2.2. *Influence of the R^4 substituent*

The anomalous behaviour of **2n** (R^4=Me) and **2o** (R^4=Ph) with respect to the previous thiazolidines deserves some discussion on the influence of the substituents attached to C-2. Thus, the reaction of 2-methylthiazolidine hydrochloride **2n** with β-aminocrotonitrile **1b** at room temperature led to a complex mixture of products in which **3bn** (6%), **5** (15%), **6bn** (<5%), **7bn** (11%) and **8bn** (9%) (Scheme 5) could be identified. However, when the reaction of **1b** and **2n** was performed in refluxing acetonitrile, the intermediates **3** and **5** disappeared, the thiazepine **4bn** (25%) was isolated in low yield and the proportion of **6bn**–**8bn** increased. As expected, 2-phenylthiazolidine hydrochloride **2o** is less reactive than its regioisomers **2k** (R^2=Ph) and **2m** (R^3=Ph), and was proven to be inert at room temperature. By performing the reaction of **1b** and **2o** in refluxing acetonitrile, degradation of the β-aminocrotonitrile **1b** occurred in high extent, while formation of thiazepine **4bo** (20%) and dihydropyridine **6bo** (37%) was observed.



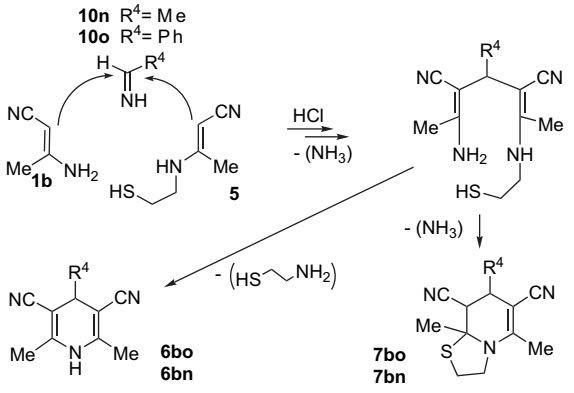
Scheme 5.

The equilibrium between thiazolidines **2**, their tautomers **9** and their precursors **10** and **11**[5] might explain the formation of compounds **6**–**8** (Scheme 6). In the same way we could formulate an equilibrium of the thiazolidine derivative **3** with **12**, **10** and **5**, and probably the influence of R^4 in the former equilibria causes the process to evolve towards **4** (when R^4=H) or **6**–**8** (when $R^4 \neq H$). Formation of **5** not only takes place from **12** by losing an imine molecule **10**, but also by reaction of cisteamine hydrochloride **11** with β-aminocrotonitrile **1b**.



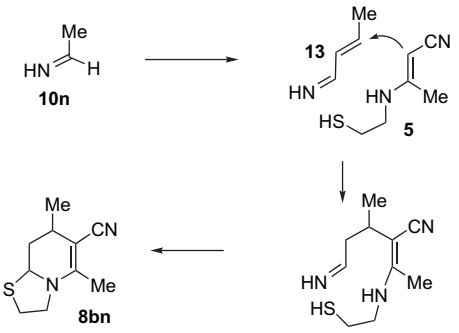
Scheme 6.

Further Hantzsch type reaction would afford **6bo**–**bn** or **7bo**–**bn** from **1b**, **5** and **10bo**–**bn** (Scheme 7). Similar explanations have been reported by other authors regarding the transformation of analogues to **5** into thiazolopyridines.[6] Moreover, we have observed that compounds **7bo**–**bn** can be prepared by heating a mixture of **5**,[7] acetaldehyde (or benzaldehyde) and cisteamine hydrochloride **11** without formation, in this particular case, of compounds **6bo**–**bn**.



Scheme 7.

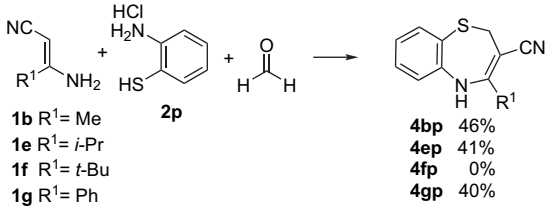
Formation of **8** should proceed by selfcondensation of the ethanimine **10n** to crotonimine **13** (Scheme 8), followed by conjugate addition of the enamine **5** and final cyclization to *N*/*S*-aminal. This



Scheme 8.

pathway has been proved by means of a multicomponent reaction from crotonaldehyde, β-aminocrotonitrile and cysteamine hydrochloride, leading to **8bn** (41%) with moderate yield.

The synthesis of thiazepines from β-enaminonitriles and 2-substituted thiazolidines ($R^4 \neq H$) is not useful for synthetic purposes, although such experiments were useful to get information about possible multicomponent reactions involving **7** and **8**. The former has been studied, along with the synthesis of thiazepines **4**, in different extension. Thus, the synthesis of thiazepines **4** from β-enaminonitriles, cysteamine hydrochloride and aldehydes gave worse results than the reaction between enaminonitriles and thiazolidine derivatives. The only yield that was improved corresponds to the preparation of benzothiazepines **4bp**, **4ep** and **4gp** from β-enaminonitriles, *o*-aminothiophenol and formaldehyde (Scheme 9). While work in progress shows that thiazolopyridines **8** can be obtained from 1,2-aminothiols, α,β-unsaturated aldehydes and β-enaminonitriles, their synthesis should be fully detailed in a future paper.



Scheme 9.

Finally, in order to establish that intermediate **5** might be a precursor of thiazolopyridines **7**, two experiments from cysteamine hydrochloride **11**, **5**[7] and acetaldehyde or benzaldehyde were performed, giving a mixture of diastereomers of **7** from which the major isomer could be isolated and its stereochemistry confirmed by X-ray analysis (Figs. 1 and 2).[8,9]

3. Experimental

3.1. General

Melting points were measured on a Reichert-Jung Thermo Galen and are uncorrected. IR spectra were obtained on a Perkin–Elmer 1720 X spectrometer. NMR spectra were recorded on a Bruker AC300 spectrometer, and chemical shifts are given

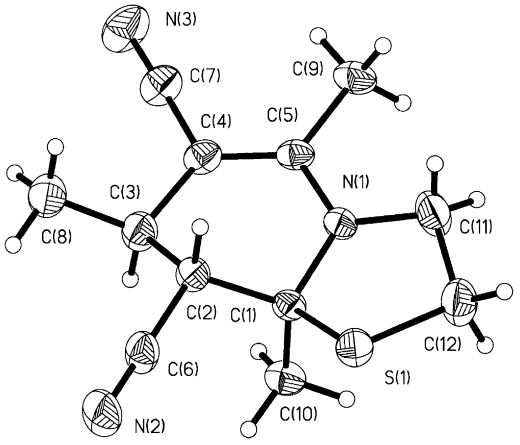


Figure 1. X-ray of **7bn**.

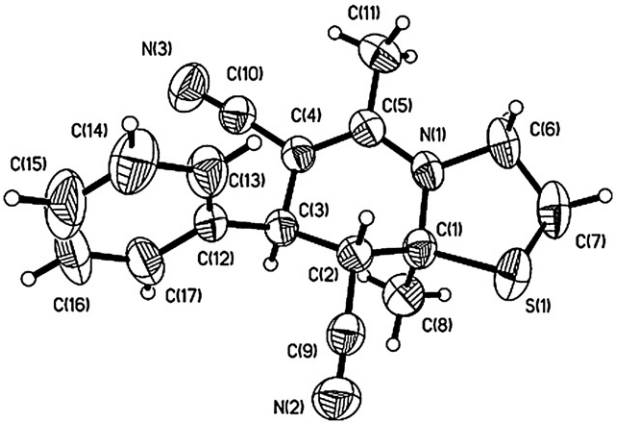


Figure 2. X-ray of **7bo**.

downfield from $SiMe_4$ as an internal standard; ^{13}C NMR spectra were carried out with complete ^1H decoupling and the assignments were made by additional DEPT experiments. Mass spectra were taken at an ionizing voltage of 70 eV on a Hewlett–Packard GC (5980)–MS (5988A) spectrometer.

The starting β-enaminonitriles were purchased from the usual suppliers (**1b**) or prepared by literature procedures (**1a**,[4] **1c–f**,[10] and **1g**[11]).

3.2. Preparation of thiazolidine hydrochlorides *2h–o*: general procedure

A mixture of aldehyde (44 mmol) and the corresponding 2-aminothiol hydrochloride[12] (44 mmol) in 15 cm^3 of dry ethanol was stirred at room temperature for 24 h. The solvent was removed and the concentrate was washed with dry THF. The solid residue thus obtained (**2h–o**) gave the sufficient purity (93–97%) for it to be used in subsequent stages.

3.3. Reaction of β-enaminonitriles *1* with thiazolidine hydrochlorides *2*. Preparation of *4* and *6–8*: general procedure

A solution of β-enaminonitriles **1** (7.8 mmol) and thiazolidine hydrochlorides **2** (9.4 mmol) in 5 cm^3 of dry acetonitrile

was refluxed for the time specified in Table 1. At the end of the reaction the solvent was removed and the residue was poured in 50 cm^3 of water and extracted with dichloromethane (3× 50 cm^3). The organic layer was dried over Na_2SO_4 and removed in vacuo. The product was chromatographed on silica gel (0.040–0.063 mm) using hexane/ethyl acetate (3:1) (**4bi–gi**, **4bk–ck**, **4cl–gl** and **4fn–gn**), hexane/ethyl acetate (5:2) (**4dk–gk** and **4bl**), dichloromethane/diethyl ether (20:1) (**4ah–bh**, **4bm** and **6bo–bn**), or dichloromethane (**4ch–gh**, **4bj–dj**, **4bn**, **4bo**, **4fm**, **4gm**, **7bo–bn** and **8bn**) as eluent.

3.3.1. 2,3,4,7-Tetrahydro[1,4]thiazepine-6-carbonitrile (*4ah*)

Yellow oil. R_f 0.35 (dichloromethane/diethyl ether (20:1)). IR (film): 3362, 2921, 2169, 1619, 1587, 1526, 1364, 1004 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.88–2.92 (m, 2H, S–CH_2), 3.43 (s, 2H, =C–CH_2), 3.65–3.70 (m, 2H, N–CH_2), 4.97 (br, 1H, NH), 6.78 (d, J=7.7 Hz, 1H, =CH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 29.3 (CH_2), 32.7 (CH_2), 47.4 (CH_2), 80.9 (C), 123.1 (C), 149.5 (CH). Anal. Calcd for $C_6H_8N_2S$: C, 51.40; H, 5.75; N, 19.98. Found: C, 51.55; H, 5.69; N, 20.05.

3.3.2. 5-Methyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4bh*)

Colourless solid. Mp 68–69 °C. IR (KBr): 3332, 2178, 1609, 1543, 1335, 1100, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, 3H, CH_3), 2.85 (dd, J=5.6 Hz, 2H, S–CH_2), 3.37 (s, 2H, S–CH_2–C=), 3.60 (q, J=5.6 Hz, 2H, N–CH_2), 5.03 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.7 (CH_3), 27.4 (CH_2), 31.2 (CH_2), 44.4 (CH_2), 76.6 (C), 123.3 (C), 159.8 (C). Anal. Calcd for $C_7H_{10}N_2S$: C, 54.51; H, 6.54; N, 18.16. Found: C, 54.35; H, 6.69; N, 18.05.

3.3.3. 5-Ethyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4ch*)

Yellow solid. Mp 79–80 °C. IR (KBr): 3334, 2970, 2933, 2172, 1598, 1527, 1466, 1109, 746 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J=7.6 Hz, 3H, CH_3), 2.31 (q, J=7.6 Hz, 2H, CH_2CH$_3$), 2.93 (m, 2H, S–CH_2), 3.46 (s, 2H, S–CH_2–C=), 3.67 (m, 2H, N–CH_2), 3.70 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.8 (CH_3), 28.3 (CH_2), 29.8 (CH_2), 31.8 (CH_2), 45.6 (CH_2), 77.5 (C), 122.9 (C), 165.4 (C). GC–MS (EI) m/z: 170 (5) [M^++2], 139 (100). Anal. Calcd for $C_8H_{12}N_2S$: C, 57.11; H, 7.19; N, 16.65. Found: C, 57.02; H, 7.24; N, 16.56.

3.3.4. 5-Phenethyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4dh*)

Colourless solid. Mp 105–106 °C. IR (KBr): 3333, 2925, 2175, 1600, 1537, 1459, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (t, J=6.5 Hz, 2H, CH_2–CH_2Ph), 2.90 (m, 2H, S–CH_2), 2.95 (m, 2H, CH_2–Ph), 3.54 (s, 2H, S–CH_2–C=), 3.55 (m, 2H, N–CH_2), 4.15 (br, 1H, NH), 7.40 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.3 (CH_2), 31.6 (CH_2), 34.6 (CH_2), 38.7 (CH_2), 45.6 (CH_2), 79.0 (C), 122.6 (C), 126.5 (CH), 128.4 (2CH), 128.6 (2CH), 139.9 (C), 163.0 (C). GC–MS (EI) m/z: 246 (5) [M^++2], 183 (100). Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.90; H, 6.51; N, 11.34.

3.3.5. 5-(iso-Propyl)-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4eh*)

Yellow solid. Mp 104–105 °C. IR (KBr): 3367, 2969, 2923, 2176, 1584, 1522, 1122, 744 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (d, J=7.0 Hz, 6H, CH(CH_3)$_2$), 2.91 (m, 2H, S–CH_2), 3.05 (m, 1H, CH), 3.50 (s, 2H, S–CH_2–C=), 3.72 (m, 2H, N–CH_2), 4.35 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.3 (2CH_3), 28.9 (CH_2), 31.8 (CH_2), 33.9 (CH), 45.9 (CH_2), 77.7 (C), 122.7 (C), 168.5 (C). GC–MS (EI) m/z: 184 (5) [M^++2], 139 (100). Anal. Calcd for $C_9H_{14}N_2S$: C, 59.30; H, 7.74; N, 15.37. Found: C, 59.12; H, 7.85; N, 15.25.

3.3.6. 5-(tert-Butyl)-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4fh*)

Yellow solid. Mp 122–123 °C. IR (KBr): 3389, 2959, 2906, 2163, 1560, 1509, 1482, 1218, 979 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 9H, C(CH_3)$_3$), 2.91 (m, 2H, S–CH_2), 3.55 (s, 2H, S–CH_2–C=), 3.65 (m, 2H, N–CH_2), 4.51 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.5 (3CH_3), 31.2 (CH_2), 31.9 (CH_2), 37.6 (C), 47.2 (CH_2), 76.9 (C), 123.7 (C), 171.2 (C). GC–MS (EI) m/z: 198 (5) [M^++2], 139 (100). Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.21; N, 14.27. Found: C, 61.05; H, 8.15; N, 14.35.

3.3.7. 5-Phenyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4gh*)

Yellow solid. Mp 105–106 °C. IR (KBr): 3316, 2964, 2178, 1589, 1523, 1465, 1335, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (m, 2H, S–CH_2), 3.71 (s, 2H, S–CH_2–C=), 3.85 (m, 2H, N–CH_2), 4.54 (br, 1H, NH), 7.51 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 30.4 (CH_2), 32.1 (CH_2), 47.3 (CH_2), 81.1 (C), 122.8 (C), 128.8 (3CH), 130.8 (2CH), 136.8 (C), 161.9 (C). GC–MS (EI) m/z: 218 (5) [M^++2], 216 (100). Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59; N, 12.95. Found: C, 66.78; H, 5.42; N, 12.81.

3.3.8. 3-Ethyl-5-methyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (*4bi*)

Colourless solid. Mp 120–121 °C. IR (KBr): 3331, 2963, 2924, 2177, 1603, 1527, 1328, 1060, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, J=7.5 Hz, 3H, CH_2CH_3), 1.61 (m, 2H, CH_2CH$_3$), 2.09 (s, 3H, CH_3), 2.69 (dd, J=12.9, 10.9 Hz, 1H, S–CHH), 2.91 (d, J=16.2 Hz, 1H, S–CHH–C=), 3.03 (dd, J=12.9, 2.9 Hz, 1H, S–CHH), 3.82 (m, 1H, N–CH–Et), 3.86 (m, 2H, NH), 4.04 (d, J= 16.2 Hz, 1H, S–CHH–C=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 10.7 (CH_3), 22.8 (CH_3), 28.4 (CH_2), 29.0 (CH_2), 36.2 (CH_2), 57.9 (CH), 78.5 (C), 122.9 (C), 158.5 (C). Anal. Calcd for $C_9H_{14}N_2S$: C, 59.30; H, 7.74; N, 15.37. Found: C, 59.18; H, 7.62; N, 15.52.

*3.3.9. 3,5-Diethyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4ci**)*

Yellow oil. R_f 0.35 (hexane/ethyl acetate (3:1)). IR (film): 3319, 2969, 2928, 2181, 1596, 1532, 1460, 1378, 1339, 1242, 1078 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, J=7.5 Hz, 3H, CH_3), 1.14 (t, J=7.6 Hz, 3H, =C−CH_2CH_3), 1.55 (m, 2H, CH_2CH_3), 2.30 (q, J=7.6 Hz, 2H, =C−CH_2CH_3), 2.63 (dd, J=12.9, 10.9 Hz, 1H, S−CHH), 2.84 (d, J=16.2 Hz, 1H, S−CHH−C=), 2.95 (dd, J=12.9, 2.8 Hz, 1H, S−CHH), 3.78 (m, 1H, J=10.9, 2.8 Hz, N−CH), 3.97 (d, J=16.2 Hz, 1H, S−CHH−C=), 4.15 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 10.6 (CH_3), 12.8 (CH_3), 28.3 (CH_2), 28.7 (CH_2), 29.7 (CH_2), 36.0 (CH_2), 53.4 (C), 57.7 (CH), 122.7 (C), 164.4 (C). GC−MS (EI) *m/z*: 198 (5) [M^++2], 121 (100). Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.21; N, 14.27. Found: C, 61.31; H, 8.17; N, 14.19.

*3.3.10. 3-Ethyl-5-phenethyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4di**)*

Yellow solid. Mp 78–79 °C. IR (KBr): 3314, 2967, 2929, 2174, 1594, 1531, 1455, 1068, 752, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, J=7.4 Hz, 3H, CH_3), 1.30 (m, 2H, CH_2CH_3), 2.48–2.69 (m, 3H, S−CHH, CH_2CH_2Ph), 2.85–3.15 (m, 4H, S−CHH−C=, S−CHH, CH_2Ph), 3.67 (m, 1H, N−CH), 3.85 (br, 1H, NH), 4.01 (d, J=16.3 Hz, 1H, S−CHH−C=), 7.24 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 10.5 (CH_3), 28.4 (CH_3), 28.9 (CH_2), 34.7 (CH_2), 35.8 (CH_2), 38.7 (CH_2), 57.7 (CH), 122.8 (C), 128.7 (CH), 126.5 (CH), 128.4 (2CH), 128.6 (2CH), 140.0 (C), 162.3 (C). GC−MS (EI) *m/z*: 274 (5) [M^++2], 91 (100). Anal. Calcd for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28. Found: C, 70.68; H, 7.29; N, 10.21.

*3.3.11. 3-Ethyl-5-(iso-propyl)-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4ei**)*

Yellow solid. Mp 77–78 °C. IR (KBr): 3362, 3321, 2964, 2928, 2182, 2163, 1592, 1538, 1518, 1094, 801 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, J=7.5 Hz, 3H, CH_3), 1.12 (d, J=6.8 Hz, 3H, CH(CH_3)CH_3), 1.14 (d, J=6.8 Hz, 3H, CH(CH_3)CH_3), 1.61 (m, 2H, CH_2CH_3), 2.64 (dd, J=12.9, 10.8 Hz, 1H, S=CHH), 2.96 (d, J=16.2 Hz, 1H, S−CHH−C=), 2.97 (dd, J=12.9, 2.9 Hz, 1H, S−CHH), 3.12 (m, 1H, $CHCH_3$), 3.72 (m, 1H, N−CH), 3.83 (br, 1H, NH), 3.96 (d, J=16.2 Hz, 1H, S−CHH−C=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 10.6 (CH_3), 20.3 (CH_3), 21.0 (CH_3), 29.1 (CH_2), 29.3 (CH_2), 33.9 (CH), 36.3 (CH_2), 58.2 (CH), 77.6 (C), 122.4 (C), 167.2 (C). Anal. Calcd for $C_{11}H_{18}N_2S$: C, 62.81; H, 8.63; N, 13.32. Found: C, 62.68; H, 8.54; N, 13.45.

*3.3.12. 3-Ethyl-5-phenyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4gi**)*

Yellow solid. Mp 114–115 °C. IR (KBr): 3307, 2962, 2878, 2180, 1589, 1532, 1076, 768, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J=7.3 Hz, 3H, CH_3), 1.67 (m, 2H, CH_2CH_3), 2.70 (dd, J=13.1, 10.75 Hz, 1H, S−CHH), 3.05 (dd, J=10.7, 2.7 Hz, 1H, S−CHH), 3.15 (d, J=16.2 Hz, 1H, S−CHH−C=), 3.88 (m, 1H, N−CH), 4.05 (br, 1H, NH), 4.07 (d, J=16.2 Hz, 1H, S−CHH−C=), 7.44 (m, 3H, 3×HPh), 7.52 (m, 2H, 2×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 10.9 (CH_3), 29.3 (CH_2), 30.1 (CH_2), 36.3 (CH_2), 59.1 (CH), 79.6 (C), 122.9 (C), 128.7 (2CH), 128.9 (2CH), 130.7 (CH), 137.1 (C), 160.9 (C). GC−MS (EI) *m/z*: 246 (5) [M^++2], 169 (100). Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.94; H, 6.45; N, 11.34.

*3.3.13. 5-Methyl-3-(iso-propyl)-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4bj**)*

Yellow solid. Mp 124–125 °C. IR (KBr): 3331, 2961, 2187, 1602, 1430, 1321, 1027, 806 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J=5.9 Hz, 3H, CH(CH_3)CH_3), 1.03 (d, J=5.9 Hz, 3H, CH(CH_3)CH_3), 1.71 (m, 1H, $CH(CH_3)_2$), 2.06 (s, 3H, =C−CH_3), 2.66 (dd, J=12.8, 11.1 Hz, 1H, S−CHH), 2.88 (d, J=16.3 Hz, 1H, S−CHH−C=), 3.11 (dd, J=12.8, 2.8 Hz, 1H, S−CHH), 3.86 (m, 2H, NH, N−CH), 4.04 (d, J=16.3 Hz, 1H, S−CHH−C=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.0 (CH_3), 18.1 (CH_3), 18.3 (CH_3), 28.7 (CH_2), 30.1 (CH_2), 33.3 (CH), 62.0 (CH), 77.2 (C), 122.3 (C), 164.5 (C). Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.21; N, 14.27. Found: C, 61.04; H, 8.29; N, 14.41.

*3.3.14. 5-Ethyl-3-(iso-propyl)-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4cj**)*

Yellow solid. Mp 78–79 °C. IR (KBr): 3319, 2963, 2928, 2187, 1623, 1594, 1461, 1412, 1080, 1038, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (d, J=5.9 Hz, 3H, CH(CH_3)CH_3), 1.01 (d, J=5.9 Hz, 3H, CH(CH_3)CH_3), 1.18 (t, J=7.6 Hz, 3H, CH_2CH_3), 1.83 (m, 1H, $CH(CH_3)_2$), 2.35 (q, J=7.6 Hz, 2H, CH_2CH_3), 2.72 (dd, J=12.8, 11.1 Hz, 1H, S−CHH), 2.90 (d, J=16.3 Hz, 1H, S−CHH−C=), 2.96 (dd, J=12.8, 2.8 Hz, 1H, S−CHH), 3.71 (m, 1H, N−CH), 3.91 (br, 1H, NH), 4.01 (d, J=16.3 Hz, 1H, S−CHH−C=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.0 (CH_3), 18.5 (CH_3), 18.8 (CH_3), 28.4 (CH_2), 30.0 (CH_2), 33.3 (CH), 33.6 (CH_2), 61.7 (CH), 76.9 (C), 122.7 (C), 164.3 (C). GC−MS (EI) *m/z*: 212 (5) [M^++2], 121 (100). Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.21; N, 14.27. Found: C, 61.35; H, 8.32; N, 14.04.

*3.3.15. 5-Phenethyl-3-(iso-propyl)-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4dj**)*

Colourless solid. Mp 97–98 °C. IR (KBr): 3324, 2961, 2923, 2171, 1597, 1522, 1456, 1372, 1072, 736, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (d, J=7.0 Hz, 3H, CH(CH_3)CH_3), 0.87 (d, J=7.0 Hz, 3H, CH(CH_3)CH_3), 1.62 (m, 1H, $CH(CH_3)_2$), 2.62–2.68 (m, 3H, S−CHH, CH_2CH_2Ph), 2.86–2.95 (m, 4H, S−CHH−C=, S−CHH, CH_2Ph), 3.61 (m, 2H, N−CH, NH), 4.03 (d, J=16.2 Hz, 1H, S−CHH−C=), 7.27 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.1 (CH_3), 18.6 (CH_3), 28.4 (CH_2), 33.0 (CH), 33.1 (CH_2), 34.8 (CH_2), 38.7 (CH_2), 61.4 (CH), 77.1 (C), 123.0 (C), 126.5 (CH), 128.5 (2CH), 128.6 (2CH), 140.0 (C), 162.5 (C). GC−MS (EI) *m/z*: 288 (5) [M^++2], 91 (100). Anal. Calcd for $C_{17}H_{22}N_2S$: C, 71.28; H, 7.74; N, 9.78. Found: C, 71.12; H, 7.59; N, 9.89.

*3.3.16. 5-Methyl-3-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4bk**)*

Colourless solid. Mp 132–133 °C. IR (KBr): 3312, 2917, 2176, 1599, 1518, 1398, 1316, 727, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 3.06 (m, 2H, S–CH_2), 3.08 (d, J=16.0 Hz, 1H, S–C*H*H–C═), 4.02 (d, J=16.0 Hz, 1H, S–CH*H*–C═), 4.06 (br, 1H, NH), 4.80 (m, 1H, N–CH), 7.33–7.42 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 23.4 (CH_3), 29.4 (CH_2), 38.3 (CH_2), 62.5 (CH), 81.3 (C), 122.4 (C), 126.3 (2CH), 128.9 (CH), 129.4 (2CH), 141.3 (C), 158.5 (C). GC–MS (EI) *m/z*: 232 (5) [M^++2], 184 (100). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.65; H, 6.19; N, 12.29.

*3.3.17. 5-Ethyl-3-phenyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4ck**)*

Yellow solid. Mp 73–74 °C. IR (KBr): 3302, 3030, 2969, 2926, 2180, 1600, 1532, 1112, 1085, 1051, 731, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J=7.6 Hz, 3H, CH_3), 2.37 (q, J=7.6 Hz, 2H, CH_2CH_3), 3.01 (dd, J=13.5, 10.9 Hz, 1H, S–C*H*H), 3.09 (d, J=16.0 Hz, 1H, S–C*H*H–C═), 3.12 (dd, J=13.5, 2.9 Hz, 1H, S–CH*H*), 3.96 (d, J=16.0 Hz, 1H, S–CH*H*–C═), 4.07 (br, 1H, NH), 4.75 (m, 1H, N–CH), 7.35 (m, 3H, 3×HPh), 7.40 (m, 2H, 2×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.7 (CH_3), 29.6 (CH_2), 30.3 (CH_2), 38.1 (CH_2), 62.6 (CH), 80.6 (C), 122.0 (C), 126.3 (2CH), 128.8 (CH), 129.3 (2CH), 141.3 (C), 164.2 (C). GC–MS (EI) *m/z*: 246 (5) [M^++2], 198 (100). Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.92; H, 6.54; N, 11.35.

*3.3.18. 5-Phenethyl-3-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4dk**)*

Yellow solid. Mp 98–99 °C. IR (KBr): 3297, 3026, 2910, 2182, 1599, 1526, 1495, 1450, 1170, 1073, 1023, 715, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.68 (m, 2H, S–CH_2), 2.89–2.98 (m, 4H, CH_2CH_2Ph), 3.07 (d, J=16.1 Hz, 1H, S–C*H*H–C═), 3.90 (br, 1H, NH), 4.0 (d, J=16.1 Hz, 1H, S–CH*H*–C═), 4.62 (m, 1H, N–CH), 7.10 (m, 2H, 2×HPh), 7.20 (m, 5H, 5×HPh), 7.35 (m, 3H, 3×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 29.6 (CH_2), 34.5 (CH_2), 38.3 (CH_2), 39.0 (CH_2), 62.3 (CH), 81.0 (C), 122.2 (C), 126.1 (2CH), 126.5 (CH), 128.4 (2CH), 128.6 (3CH), 129.3 (2CH), 139.7 (C), 141.6 (C), 161.9 (C). GC–MS (EI) *m/z*: 322 (5) [M^++2], 183 (100). Anal. Calcd for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74. Found: C, 74.82; H, 6.24; N, 8.86.

*3.3.19. 3,5-Diphenyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4gk**)*

Colourless solid. Mp 187–188 °C. IR (KBr): 3338, 2923, 2181, 1586, 1559, 1514, 1445, 1333, 1272, 1255, 750, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.04–3.19 (dd, J=10.1, 2.8 Hz, 2H, S–CH_2), 3.37 (d, J=15.8 Hz, 1H, S–C*H*H–C═), 4.04 (d, J=15.8 Hz, 1H, S–CH*H*–C═), 4.27 (br, 1H, NH), 4.76 (m, 1H, N–CH), 7.48–7.54 (m, 10H, 2Ph). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 31.6 (CH_2), 38.4 (CH_2), 64.0 (CH), 83.3 (C), 122.5 (C), 126.3 (2CH), 128.8 (2CH), 128.9 (3CH), 129.5 (2CH), 130.9 (CH), 136.8 (C), 141.6 (C), 161.1 (C). GC–MS (EI) *m/z*: 294 (5) [M^++2], 246 (100). Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58. Found: C, 73.82; H, 5.59; N, 9.67.

*3.3.20. 2,5-Dimethyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4bl**)*

Yellow solid. Mp 92–93 °C. IR (KBr): 3314, 2178, 1605, 1542, 1463, 1378, 1330, 644 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, J=6.5 Hz, 3H, CH–CH_3), 2.03 (s, 3H, ═C–CH_3), 3.32–3.49 (m, 2H, N–CH_2), 3.38 (d, J=16.8 Hz, 1H, S–C*H*H–C═), 3.55 (d, J=16.8 Hz, 1H, S–CH*H*–C═), 3.65 (m, 1H, S–C*H*–CH_3), 4.52 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.7 (CH_3), 22.0 (CH_3), 26.6 (CH_2), 39.4 (CH), 50.8 (CH_2), 76.3 (C), 123.5 (C), 159.5 (C). GC–MS (EI) *m/z*: 170 (5) [M^++2], 107 (100). Anal. Calcd for $C_8H_{12}N_2S$: C, 57.11; H, 7.19; N, 16.65. Found: C, 57.28; H, 7.25; N, 16.49.

*3.3.21. 5-Ethyl-2-methyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4cl**)*

Yellow solid. Mp 131–132 °C. IR (KBr): 3290, 3065, 2969, 2935, 2186, 1630, 1595, 1453, 1215, 1021 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J=7.6 Hz, 3H, CH_2CH_3), 2.33 (q, J=7.6 Hz, 2H, CH_2CH_3), 3.32–3.49 (m, 2H, N–CH_2), 3.38 (d, J=16.7 Hz, 1H, S–C*H*H–C═), 3.56 (d, J=16.7 Hz, 1H, S–CH*H*–C═), 3.67 (m, 1H, S–CH), 4.44 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 12.8 (CH_3), 20.6 (CH_3), 26.8 (CH_2), 29.6 (CH_2), 39.5 (CH), 51.4 (CH_2), 76.6 (C), 122.8 (C), 164.7 (C). Anal. Calcd for $C_9H_{14}N_2S$: C, 59.30; H, 7.74; N, 15.37. Found: C, 59.21; H, 7.79; N, 15.46.

*3.3.22. 2-Methyl-5-phenethyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4dl**)*

Yellow solid. Mp 151–152 °C. IR (KBr): 3306, 3064, 2925, 2175, 1601, 1594, 1464, 1172, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, J=6.2 Hz, 3H, CH_3), 2.57 (m, 2H, CH_2CH_2Ph), 2.90 (t, J=7.5 Hz, 2H, CH_2Ph), 3.27 (m, 2H, N–CH_2), 3.39 (m, 1H, S–C*H*H–C═), 3.44 (m, 1H, S–CH), 3.54 (d, J=16.7 Hz, 1H, S–CH*H*–C═), 4.19 (br, 1H, NH), 7.18–7.34 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.5 (CH_3), 26.7 (CH_2), 34.7 (CH_2), 38.5 (CH_2), 39.3 (CH), 51.3 (CH_2), 77.4 (C), 122.7 (C), 126.5 (CH), 128.5 (2CH), 128.6 (2CH), 140.0 (C), 162.7 (C). GC–MS (EI) *m/z*: 260 (5) [M^++2], 91 (100). Anal. Calcd for $C_{15}H_{18}N_2S$: C, 69.73; H, 7.02; N, 10.84. Found: C, 69.63; H, 6.95; N, 10.95.

*3.3.23. 2-Methyl-5-(iso-propyl)-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4el**)*

Yellow solid. Mp 113–114 °C. R_f 0.29 (CH_2Cl_2). IR (KBr): 3362, 2168, 1586, 1525, 1460, 1377, 1360, 1147, 1127, 1004 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, J=7.0 Hz, 6H, $CH(CH_3)_2$), 1.28 (d, J=6.6 Hz, 3H, S–CH–CH_3), 3.06 (m, 1H, C$H(CH_3)_2$), 3.28–3.45 (m, 2H, N–CH_2), 3.37 (d, J=16.8 Hz, 1H, S–C*H*H), 3.57 (d,

J=16.8 Hz, 1H, S−CH*H*), 3.62−3.70 (m, 1H, S−C*H*−CH_3), 4.44 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.4 (CH_3), 20.5 (CH_3), 20.5 (CH_3), 27.3 (CH_2), 33.6 (CH_2), 39.6 (CH), 51.6 (CH_2), 76.7 (C), 122.6 (C), 167.8 (C). Anal. Calcd for $C_{10}H_{16}N_2S$: C, 61.18; H, 8.21; N, 14.27. Found: C, 61.35; H, 8.26; N, 14.15.

*3.3.24. 5-(tert-Butyl)-2-methyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4fl**)*

Colourless solid. Mp 116−117 °C. IR (KBr): 3400, 2955, 2916, 2163, 1556, 1515, 1484, 1465, 1363, 1220, 1028, 978 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, J=6.7 Hz, 3H, CH_3), 1.35 (s, 9H, C(C*H*$_3$)$_3$), 3.18−3.28 (m, 1H, N−C*H*H), 3.31−3.38 (m, 1H, N−CH*H*), 3.37 (d, J=16.4 Hz, 1H, S−C*H*H), 3.57−3.65 (m, 1H, S−C*H*−CH_3), 3.67 (d, J=16.4 Hz, 1H, S−CH*H*), 4.56 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.1 (CH_3), 28.5 (3CH_3), 30.0 (CH_2), 37.5 (C), 39.0 (CH), 53.0 (CH_2), 75.7 (C), 123.8 (C), 170.6 (C). Anal. Calcd for $C_{11}H_{18}N_2S$: C, 62.81; H, 8.63; N, 13.32. Found: C, 62.72; H, 8.57; N, 13.41.

*3.3.25. 2-Methyl-5-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4gl**)*

Yellow solid. Mp 67−68 °C. IR (KBr): 3325, 2924, 2181, 1590, 1570, 1445, 1029, 772, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (d, J=6.7 Hz, 3H, CH_3), 3.35 (m, 1H, N−C*H*H), 3.52 (d, J=16.7 Hz, 1H, S−C*H*H−C═), 3.68 (dd, J=14.7, 7.02 Hz, 1H, N−CH*H*), 3.56 (d, J=16.7 Hz, 1H, S−CH*H*−C═), 3.81 (m, 1H, S−C*H*−CH_3), 4.57 (br, 1H, NH), 7.50 (m, 5H, Ph). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.3 (CH_3), 28.1 (CH_2), 39.6 (CH), 52.5 (CH_2), 78.7 (C), 122.1 (C), 127.4 (CH), 128.7 (CH), 129.2 (CH), 130.7 (CH), 131.3 (CH), 136.6 (C), 161.4 (C). GC−MS (EI) *m*/*z*: 232 (5) [M^++2], 169 (100). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.89; H, 6.08; N, 12.25.

*3.3.26. 5-Methyl-2-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4bm**)*

Colourless solid. Mp 130−131 °C. R_f 0.45 (CH_2Cl_2/petroleum ether (10:1)). IR (KBr): 3396, 2178, 1603, 1490, 1449, 1081, 908, 753, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 3H, CH_3), 3.48 (d, J=16.7 Hz, 1H, S−C*H*H), 3.76 (d, J=16.7 Hz, 1H, S−CH*H*), 3.83 (t, J=5.8 Hz, 2H, N−CH_2), 4.42 (t, J=5.7 Hz, 1H, S−CH), 4.82 (t, J=5.5 Hz, 1H, NH), 7.25−7.42 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.2 (CH_3), 28.1 (CH_2), 49.0 (CH), 51.2 (CH_2), 77.4 (C), 123.1 (C), 127.3 (2CH), 127.9 (CH), 128.7 (2CH), 140.9 (C), 159.1 (C). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.62; H, 6.08; N, 12.28.

*3.3.27. 5-(tert-Butyl)-2-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4fm**)*

Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 9H, C(C*H*$_3$)$_3$), 3.62−3.71 (m, 1H, N−C*H*H), 3.60 (d, J=16.5 Hz, 1H, S−C*H*H), 3.78 (d, J=16.5 Hz, 1H, S−CH*H*), 3.87−3.96 (m, 1H, N−CH*H*), 4.28 (q, J=3.8 Hz, 1H, CH−Ph), 4.58 (br, 1H, NH), 7.28−7.41 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.9 (3CH_3), 31.7 (CH_2), 37.6 (C), 48.8 (CH), 53.0 (CH_2), 77.2 (C), 123.4 (C), 127.4 (2CH), 127.9 (CH), 140.5 (C), 170.3 (C). Anal. Calcd for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28. Found: C, 70.42; H, 7.34; N, 10.37.

*3.3.28. 2,5-Diphenyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4gm**)*

Yellow solid. Mp 186−187 °C. R_f 0.31 (CH_2Cl_2). IR (KBr): 3390, 2167, 1588, 1571, 1513, 1491, 778, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (d, J=16.7 Hz, 1H, C*H*H−C−CN), 3.84 (d, J=16.7 Hz, 1H, CH*H*−C−CN), 3.82−3.92 (m, 1H, N−C*H*H), 4.02−4.12 (m, 1H, N−CH*H*), 4.41 (q, J=3.7 Hz, 1H, S−CH−Ph), 4.65 (t, J=5.7 Hz, 1H, NH), 7.27−7.56 (m, 10H, 2Ph). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 29.6 (CH_2), 49.2 (CH), 52.4 (CH_2), 79.0 (C), 122.9 (C), 127.4 (2CH), 127.9 (CH), 128.7 (4CH), 128.8 (2CH), 130.8 (CH), 136.5 (C), 140.5 (C), 161.3 (C). Anal. Calcd for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58. Found: C, 73.80; H, 5.48; N, 9.67.

*3.3.29. 5,7-Dimethyl-2,3,4,7-tetrahydro[1,4]thiazepine-6-carbonitrile (**4bn**)*

Colourless solid. Mp 119−120 °C. IR (KBr): 3319, 2168, 1593, 1542, 1376, 628 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (d, J=7.3 Hz, 3H, CH−C*H*$_3$), 2.08 (s, 3H, ═C−CH_3), 2.87−2.92 (m, 1H, S−C*H*H), 3.04−3.13 (m, 1H, S−CH*H*), 3.39−3.43 (m, 1H, N−C*H*H), 3.95−4.06 (m, 1H, N−CH*H*), 4.25 (q, J=7.3 Hz, 1H, C*H*−CH_3), 4.24 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.3 (CH_3), 22.7 (CH_3), 30.5 (CH_2), 34.3 (CH), 45.7 (CH_2), 84.6 (C), 121.1 (C), 158.6 (C). GC−MS (EI) *m*/*z*: 170 (5) [M^{+2}], 168 (100). Anal. Calcd for $C_8H_{12}N_2S$: C, 57.11; H, 7.19; N, 16.65. Found: C, 57.32; H, 7.15; N, 16.57.

*3.3.30. 5-(tert-Butyl)-7-methyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4fn**)*

Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H, C(C*H*$_3$)$_3$), 2.74−2.82 (m, 1H, S−C*H*H), 2.97−3.06 (m, 1H, S−CH*H*), 3.27−3.37 (m, 1H, N−C*H*H), 3.95−4.03 (m, 1H, N−CH*H*), 4.16 (q, J=7.1 Hz, 1H, C*H*−CH_3), 4.26 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.1 (CH_3), 28.5 (3CH_3), 29.7 (CH_2), 37.8 (CH), 48.2 (CH_2), 76.6 (C), 120.1 (C), 172.3 (C). Anal. Calcd for $C_{11}H_{18}N_2S$: C, 62.81; H, 8.63; N, 13.32. Found: C, 62.70; H, 8.58; N, 13.47.

*3.3.31. 7-Methyl-5-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4gn**)*

Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (t, J=7.3 Hz, 3H, CH_3), 2.87−2.95 (m, 1H, SC*H*H), 3.12−3.20 (m, 1H, SCH*H*), 3.47−3.61 (m, 1H, NC*H*H), 4.05−4.15 (m, 1H, NCH*H*), 4.24 (q, J=7.3 Hz, 1H, C*H*−CH_3), 4.93 (br, 1H, NH), 7.37−7.60 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.6 (CH_3), 30.9 (CH_2), 36.8 (CH), 47.7 (CH_2), 85.7 (C), 118.9 (C), 129.0 (2CH), 130.8 (CH), 132.5 (2CH), 137.0 (C), 160.7 (C). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.70; H, 6.10; N, 12.24.

*3.3.32. 5-Methyl-7-phenyl-2,3,4,7-tetrahydro[1,4]-thiazepine-6-carbonitrile (**4bo**)*

Colourless solid. Mp 138–139 °C. IR (KBr): 3357, 2164, 1601, 1523, 1366, 762, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.79–2.75 (m, 2H, S–CH_2), 3.35–3.41 (m, 2H, N–CH_2), 4.71 (br, 1H, NH), 4.79 (s, 1H, Ph–C*H*), 7.26–7.61 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 23.3 (CH_3), 29.9 (CH_2), 45.7 (CH_2), 45.8 (CH), 80.5 (C), 122.9 (C), 127.2 (CH), 127.8 (CH), 128.6 (CH), 141.7 (C), 151.8 (C). GC–MS (EI) *m/z*: 232 (5) [M^++2], 230 (100). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.57; H, 6.27; N, 12.31.

*3.3.33. 2,4,6-Trimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (**6bn**)*

Colourless solid. Mp 193–194 °C. IR (KBr): 3291, 3243, 3125, 2973, 2199, 1659, 1516, 1385, 1291, 617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, J=6.6 Hz, 3H, CH–CH_3), 2.03 (s, 6H, 2CH_3), 3.30 (q, J=6.6 Hz, 1H, C*H*–CH_3), 7.26 (br, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.2 (CH_3), 22.9 (CH_3), 30.5 (CH_3), 85.2 (C), 119.0 (C), 146.0 (C). Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.41; H, 6.47; N, 24.13.

*3.3.34. 2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile (**6bo**)*

Colourless solid. Mp 218–219 °C. IR (KBr): 3313, 3258, 2193, 1669, 1503, 1278, 739, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 6H, 2CH_3), 4.33 (s, 1H, CH), 6.78 (s, 1H, NH), 7.24–7.41 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.2 (CH_3), 42.0 (CH), 84.7 (C), 118.8 (C), 127.6 (CH), 128.1 (CH), 129.0 (CH), 142.5 (C), 145.6 (C). Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.70; H, 5.51; N, 17.75.

*3.3.35. 5,7,8a-Trimethyl-3,7,8,8a-tetrahydro-2H-thiazolo-[3,2-a] pyridine-6,8-dicarbonitrile (**7bn**)*

Colourless solid. Mp 131–132 °C. IR (KBr): 3449, 2977, 2879, 2238, 2187, 1585, 1404, 1367, 1266, 1135, 986, 857 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, J=6.3 Hz, 3H, CH–CH_3), 1.60 (s, 3H, =C–CH_3), 2.21 (d, J=1.3 Hz, 3H, CH_3–C–(N,S)), 2.50–2.64 (m, 2H, 2CH), 3.05–3.19 (m, 2H, S–CH_2), 3.86–3.91 (m, 2H, N–CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 18.4 (CH_3), 20.5 (CH_3), 24.6 (CH_3), 28.5 (CH_2), 30.9 (CH), 45.5 (CH), 52.5 (CH_2), 69.4 (C), 79.7 (C), 118.6 (C), 120.4 (C), 150.1 (C). Anal. Calcd for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48; N, 18.01. Found: C, 61.70; H, 6.42; N, 18.15.

*3.3.36. 5,8a-Dimethyl-7-phenyl-3,7,8,8a-tetrahydro-2H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (**7bo**)*

Colourless solid. Mp 142–143 °C. IR (KBr): 3449, 2977, 2879, 2238, 2187, 1585, 1404, 1367, 1266, 1135, 986, 857 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.74 (s, 3H, =C–CH_3), 2.31 (d, J=1.4 Hz, 3H, CH_3), 2.92 (d, J=11.9 Hz, 1H, CH–CN), 3.13–3.23 (m, 2H, S–CH_2), 3.68 (dd, J=11.9, 1.4 Hz, 1H, C*H*–Ph), 3.95 (m, 2H, N–CH_2), 7.27–7.44 (m, 5H, 5×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.6 (CH_3), 24.4 (CH_3), 28.6 (CH_2), 43.5 (CH), 47.0 (CH), 52.5 (CH_2), 69.8 (C), 79.3 (C), 118.0 (C), 120.3 (C), 128.1 (2C), 128.6 (C), 129.1 (2C), 137.4 (C), 151.1 (C). Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.23; H, 5.76; N, 14.17.

*3.3.37. 5,7-Dimethyl-3,7,8,8a-tetrahydro-2H-thiazolo[3,2-a]-pyridine-6-carbonitrile (**8bn**)*

Yellow oil. R_f 0.33 (CH_2Cl_2). IR (film): 3516, 2956, 2927, 2174, 1589, 1424, 1374, 1326, 1259, 1190, 1033, 980, 718, 635 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, J=7.0 Hz, 3H, CH_3–CH), 1.74 (ddd, J=12.9, 10.7, 5.7 Hz, 1H, C*H*H–CH), 1.97 (ddd, J=12.9, 3.2, 2.5 Hz, 1H, CH*H*–CH), 2.18 (s, 3H, CH_3–C=), 2.60–2.55 (m, 1H, C*H*–CH_3), 3.08–2.94 (m, 2H, CH_2–S), 3.66–3.59 (m, 1H, C*H*H–N), 3.85–3.77 (m, 1H, CH*H*–N), 4.52 (dd, J=10.7, 3.2 Hz, 1H, S–CH–N). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 19.7 (CH_3), 21.8 (CH_3), 28.6 (CH), 29.0 (CH_2), 33.7 (CH_2), 51.2 (CH_2), 58.5 (CH), 81.0 (C), 122.9 (C), 150.9 (C). Anal. Calcd for $C_{10}H_{14}N_2S$: C, 61.82; H, 7.26; N, 14.42. Found: C, 61.71; H, 7.19; N, 14.51.

*3.4. Preparation of 2,5-dihydrobenzo[b][1,4]thiazepine-3-carbonitriles **4bp**, **4ep** and **4gp** from 2-aminothiophenol, formaldehyde and β-enaminonitriles **1**: general procedure*

A mixture of 2-aminothiophenol (1.95 g, 15.6 mmol), paraformaldehyde (1.00 g, 11.0 mmol) and β-enaminonitriles **1** (7.8 mmol) in 5 cm^3 of dry acetonitrile was refluxed for 2 h. At the end of the reaction the procedure was continued as in the previous case. The product was chromatographed on silica gel (0.040–0.063 mm) using hexane/ethyl acetate (3:1) (**4bp** and **4gp**) or hexane/ethyl acetate (4:1) (**4ep**) as eluent.

*3.4.1. 4-Methyl-2,5-dihydrobenzo[b][1,4]thiazepine-3-carbonitrile (**4bp**)*

Yellow oil. R_f 0.31 (hexane/ethyl acetate (3:1)). IR (film): 3336, 2921, 2188, 1606, 1585, 1471, 1309, 1121, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.55 (s, 2H, S–CH_2), 6.40 (br, 1H, NH), 6.90 (dd, J=8.1, 1.1 Hz, 1H, =CH), 7.00 (ddd, J=7.8, 7.5, 1.2 Hz, 1H, =CH), 7.20 (ddd, J=8.1, 7.5, 1.1 Hz, 1H, =CH), 7.40 (dd, J=7.8, 1.2 Hz, 1H, =CH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 26.5 (CH_3), 36.2 (CH_2), 83.3 (C), 121.8 (C), 122.0 (CH), 123.5 (CH), 127.8 (C), 128.5 (CH), 133.9 (CH), 142.6 (C), 150.1 (C). GC–MS (EI) *m/z*: 204 (5) [M^++2], 150 (100). Anal. Calcd for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85. Found: C, 65.24; H, 4.84; N, 13.94.

*3.4.2. 4-(iso-Propyl)-2,5-dihydrobenzo[b][1,4]thiazepine-3-carbonitrile (**4ep**)*

Yellow oil. R_f 0.45 (hexane/ethyl acetate (3:1)). IR (film): 3447, 3291, 3206, 3076, 2193, 1633, 1594, 1584, 1543, 1477, 1350, 772, 751, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (d, J=6.9 Hz, 6H, CH(CH_3)$_2$), 3.41 (m, 1H, C*H*(CH_3)$_2$), 3.58 (s, 2H, S–CH_2–C=), 6.30 (br, 1H, NH),

6.91 (dd, J=8.1, 1.1 Hz, 1H, =CH), 7.02 (ddd, J=7.8, 7.5, 1.2 Hz, 1H, =CH), 7.21 (ddd, J=8.1, 7.5, 1.1 Hz, 1H, =CH), 7.41 (dd, J=7.8, 1.2 Hz, 1H, =CH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 19.8 ($2CH_3$), 35.5 (CH), 36.6 (CH_2), 79.6 (C), 121.9 (C), 123.2 (CH), 123.7 (CH), 128.1 (CH), 128.1 (C), 133.0 (CH), 143.2 (C), 160.1 (C). GC–MS (EI) *m/z*: 232 (5) [M^++2], 187 (100). Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.89; H, 6.19; N, 12.05.

*3.4.3. 4-Phenyl-2,5-dihydrobenzo[b][1,4]thiazepine-3-carbonitrile (**4gp**)*

Yellow solid. Mp 133–134 °C. IR (KBr): 3447, 3291, 3206, 3077, 2193, 1634, 1594, 1584, 1543, 1477, 1350, 772, 751, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 2H, S–CH_2), 6.60 (br, 1H, NH), 6.88 (dd, J=8.1, 1.1 Hz, 1H, =CH), 7.02 (ddd, J=7.8, 7.5, 1.2 Hz, 1H, =CH), 7.22 (ddd, J=8.1, 7.5, 1.1 Hz, 1H, =CH), 7.42 (dd, J=7.8, 1.2 Hz, 1H, =CH), 7.50 (m, 3H, 3×HPh), 7.59 (m, 2H, 2×HPh). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 36.8 (CH_2), 84.9 (C), 121.9 (C), 122.0 (CH), 123.5 (CH), 127.6 (C), 128.3 (2CH), 128.5 (CH), 129.0 (2CH), 130.4 (CH), 133.9 (CH), 138.0 (C), 142.56 (C), 153.8 (C). GC–MS (EI) *m/z*: 266 (5) [M^++2], 212 (100). Anal. Calcd for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.84; H, 4.62; N, 10.50.

References and notes

1. (a) Strzelczyk, M.; Matyjewska, H.; Strozynski, H. *Pol. J. Pharmacol. Pharm.* **1990**, *42*, 377; (b) Ueyama, N.; Wakabayashi, S.; Tomiyama, T. *Yakugaku Zasshi* **1996**, *116*, 106; (c) Lee, C. L.; Lam, Y.; Lee, S. Y. *Tetrahedron Lett.* **2001**, *42*, 109; (d) Upreti, M.; Seema, S.; Dandia, A.; Pant. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *36B*, 1181; (e) Dandia, A.; Sehgal, V.; Upreti, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *105*, 93; (f) Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 1017.
2. (a) Mushkalo, L. K.; Lanovaya, Z. I. *Ukr. Khim. Zh.* **1955**, *21*, 631; (b) Mushkalo, L. K.; Shokol, Z. I. *Zh. Obshch. Khim.* **1960**, *30*, 1023; (c) Hankovszky, O. H.; Hideg, K.; Lloyd, D. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1619.
3. Calvo, L.; González-Ortega, A.; Pérez, M.; Sañudo, M. C. *Synlett* **2005**, 239.
4. Xiang, Y. B.; Drenkard, S.; Baumann, K.; Hickey, D.; Eschenmoser, A. *Helv. Chim. Acta* **1994**, *77*, 2209.
5. (a) Fülop, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 6545; (b) Lambert, J. B.; Majchrzak, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3588; (c) Lázar, L.; Fülop, F. *Eur. J. Org. Chem.* **2003**, 3025; (d) Fernández, X.; Duñach, E. *Tetrahedron: Asymmetry* **2001**, 1279.
6. Caballero, E.; Puebla, P.; Medarde, M.; Honores, Z.; San Feliciano, A. *Tetrahedron* **1999**, *55*, 7915 and references there in.
7. Compound **5** was prepared in situ by reaction of **1b** and **11** (ratio 1:1.5) in refluxing methanol for 2 h. The ^{1}H NMR spectrum showed a technical yield of 90% and a shift of the equilibrium towards the cyclic tautomer. IR (film): 3313, 2193, 1603 cm^{-1}. ^{1}H RMN (300 MHz, $CDCl_3$): δ 1.68 (s, 3H, CH_3), 2.09 (s, 1H, NH), 2.69 (d, J=16.7 Hz, 1H, CH*H*–CN), 2.74 (d, J=17.6 Hz, 1H, C*H*H–CN), 3.00–3.20 (m, 3H, S–C*H*$_2$, N–C*H*H), 3.45 (m, 1H, N–CH*H*), 7.40 (dd, J=7.8, 1.3 Hz, 1H, =CH). ^{13}C RMN (75.4 MHz, $CDCl_3$): δ 28.4 (CH_3), 32.8 (CH_2), 37.7 (CH_2), 51.2 (CH_2), 75.0 (C), 117.1 (C).
8. Deposition number CCDC 670615.
9. Deposition number CCDC 668565.
10. Hackler, R. E.; Burow, K. W.; Kaster, S. V.; Wickiser, D. I. *J. Heterocycl. Chem.* **1989**, *26*, 1575.
11. Ridge, D. N.; Hanifin, J. W.; Harten, L. A.; Johnson, B. D.; Menschik, J.; Nicolau, G.; Sloboda, A. E.; Watts, D. E. *J. Med. Chem.* **1979**, *22*, 1385.
12. Larice, J. L.; Roggero, J.; Metzger, J. *Bull. Soc. Chim. Fr.* **1967**, 3637.