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Straightforward microwave-assisted synthesis of 2-thiazolines using Lawesson's reagent under solvent-free conditions

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ABSTRACT

2-Thiazolines are synthesized from carboxylic acids and 1,2-aminoalcohols in the presence of Lawesson's reagent under solventless conditions. The developed method is valid for either substituted or unsubstituted aminoalcohols and a wide variety of aromatic, heteroaromatic and aliphatic carboxylic acids; thus it constitutes a general synthetic method for these kinds of compounds. The role of Lawesson's reagent is dual: to transform the 1,2-aminoalcohol into 1,2-aminothiol and to activate its reaction with the carboxylic acid leading to the formation of a thiazoline ring, all in one pot.

1. Introduction

Thiazoline rings are found in a large number of biologically active natural products. Thus, some thiazoline derivatives present interesting activities, such as: anti-HIV,[1] anti-cancer,[2–4] cell division inhibition,[5] pheromone activity,[6] metal binders,[7] antibiotic[8–10] and radioprotective.[11,12] Furthermore, a thiazoline ring is a good directing group for ruthenium catalyzed carbonylation of aromatic rings[13] and synthesis of chalcogenobenzenes.[14] General methodologies for the synthesis of thiazolines include the coupling of imidates or esters with aminothiols,[15–17] the cyclodehydration of hydroxy thioamides,[2,18–21] the condensation of nitriles with mercaptoalcohols.[22,23] They can also rely on the formation of an intermediate amide from carboxylic acid and aminoalcohols and its conversion into the corresponding thioamide (obtained by thionation using P_2S_5[11] or Lawesson's reagent[24,25]), followed by cyclization to thiazoline. There have also been some reports on the use of microwaves to prepare a thiazoline ring, i.e., the irradiation of 2-aminoethanethiol with *N*-acylbenzotriazoles followed by the addition of thionyl chloride and a new irradiation step,[26] or the preparation of 2-arylthiazolines from aryl keto nitriles and cysteamine.[27] The fact that microwave-assisted organic synthesis (MAOS) is seldom used for 2-thiazolines is surprising since the use of MAOS in heterocyclic chemistry[28] has proven to be a useful tool, specially when solventless reactions are sought.[29–34]

Recently, our group has demonstrated the usefulness of Lawesson's reagent (LR) for activating carboxylic acids in the synthesis of benzoxazoles and benzothiazoles by irradiation with microwaves under solvent-free conditions.[30] The effective action of LR in this coupling prompted us to explore its use in the synthesis of a thiazoline ring. Earlier, Nishio[25] had demonstrated the possibility of converting (1,2)-*N*-acylamino alcohols into thiazolines in the presence of LR using conventional heating in the presence of toluene; however, this procedure requires the previous formation of the amide bond, which is not always a straightforward step from aminoalcohol and carboxylic acid.

2. Results and discussion

Hence, in this paper the possibility of activating the formation of the amide bond between carboxylic acid and 1,2-aminoalcohol using LR under solventless conditions is studied. Furthermore, LR can act as a thionating agent and allows for the replacement of the hydroxyl by the thiol group, leading to a 2-thiazoline ring in a one-pot conversion.

As a model, the reaction of benzoic acid (**1a**) and 2-aminoethanol (**2**) was used to study the conditions necessary to carry out the transformation (Scheme 1). So, benzoic acid, aminoalcohol **2** and LR (molar ratio 1:1.5:0.5, respectively) were irradiated with microwaves at 190 °C for 4 min (the same conditions used for the synthesis of benzoazoles[30]). This yielded 2-thiazoline **5a** in 60%, as well as the presence of several by-products. In order to improve the yield, different times, temperatures and reagent ratios were studied. We found that the best conditions are: irradiation for 8 min of a mixture 1:1.5:0.75 of the above mentioned reagents, at 150 °C/300 W. This yields 80% of the 2-thiazoline **5a**. Lower temperatures lead to a considerable amount of unreacted starting materials.

These reaction conditions were applied to a variety of substitution patterns for the benzoic acids (electron-donating and

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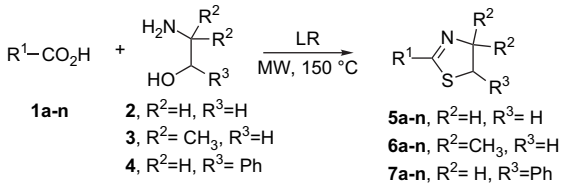


Scheme 1.

withdrawing groups in the aromatic ring) and for the amino-alcohols (**2**, **3** and **4**, Scheme 1). For 2-aminoethanol (**2**), the presence of an electron-donating group (methoxy or methyl substituents) in the ring of the acid gave similar yields as for unsubstituted benzoic acid (Table 1, entries 2 and 3). It is noteworthy that for acid **1d**, the 2-thiazoline obtained is mainly the 2-demethylated compound (53%), due to demethylation in the hindered *ortho*-position (Table 1, entry 4). Similar behaviour has been observed in previous reactions with LR.[30,35] Also the condensated aromatic acid 2-naphthoic acid gave 83% of 2-thiazoline **5e** (Table 1, entry 5). Meanwhile, the presence of halogen atoms slightly reduced the yields to 60 and 57%, respectively (Table 1, entries 6 and 7).

The reaction is also compatible with heteroaromatic acids, so pyridyl, furyl and thienyl derivatives gave 50–63% yields (Table 1, entries 8–10). Even this conversion is applicable to non-conjugated carboxylic acids such as phenylacetic acid, which yielded 72% of 2-thiazoline **5k** (Table 1, entry 11). Aliphatic acids like heptanoic and decanoic acids led to the corresponding 2-thiazolines in 86% yield (Table 1, entries 12 and 13). It is even possible to obtain a bis-thiazoline (**5n**) in 61% yield from a dicarboxylic acid like azelaic acid (Table 1, entry 14).

The positive results obtained with these reaction conditions were checked with substituted 1,2-aminoalcohols to verify its wide application, since most of previously described methods for the synthesis of 2-thiazolines reduce their examples to benzoic acids and unsubstituted aminoalcohol **2**. Thus, the reactivity of 2-amino-2-methyl-1-propanol (**3**) with the same carboxylic acids studied above gave similar results (Table 2), yet the reaction required a shorter time (4 min).[40] However, lower yields were obtained for halogenated benzoic acids (Table 2, entries 6 and 7).

The irradiation of carboxylic acids with LR in the presence of 2-amino-1-phenylethanol (**4**) led to 2-thiazolines **7a**–**n** in lower yields (Table 3). This is probably due to the presence of the phenyl group in 1,2-aminoalcohol, which induces the aromatization of the five-membered ring and gives thiazoles **8e**–**i** as by-products (Table 3, entries 5–9). These oxidation compounds were produced in small amounts, lower than 20%.

As for the reaction mechanism, it can proceed through the activation of the carboxylic acid by LR, as previously described,[45] to promote the formation of the amide. Then, after replacement of the hydroxyl by a thiol group it could cyclize to 2-thiazoline in the presence of LR as was suggested by Nishio.[25] A similar mechanism was postulated by Metzger in the formation of 2-thiazolines from hydroxyamides with P_4S_{10}.[46] However, we found that when a mixture of benzoic acid and LR was irradiated, and then amino-alcohol **3** was added and irradiated again, it led to a complex mixture of reaction products. On the contrary, the irradiation of aminoalcohol **3** together with LR for 1 min, followed by the addition of benzoic acid and irradiation at 150 °C for 4 min yielded 73% of 2-thiazoline **6a**. This suggests a first step where the LR acts as a thionating agent to exchange the hydroxyl for a thiol group (**9**). Then, an activated species must be formed, which favours the reaction with carboxylic acids, has been proposed in the synthesis of benzoxazoles and benzothiazoles from 2-aminophenol and 2-aminothiophenol, respectively.[30] In fact, when the aminoalcohol **3** was irradiated with LR an 1,3,2-thiazaphospholidine-2-methoxyphenyl-2-sulfide (**10**) was isolated and this was transformed, upon irradiation with benzoic acid, into a 2-thiazoline **6a** in good

Table 1
Synthesis of 2-thiazolines from 2-aminoethanol (**2**)

Entry	Acid	R^1	Product	Yield %
1	**1a**	Ph	**5a**[36]	80
2	**1b**	3-MeC_6H_4	**5b**[27]	86
3	**1c**	4-$MeOC_6H_4$	**5c**[27]	79
4	**1d**	2,3-$(MeO)_2C_6H_3$	**5d** (R^1=2-HO-3-$MeOC_6H_3$)	53[a]
5	**1e**	2-Naphthyl	**5e**[37]	83
6	**1f**	4-ClC_6H_4	**5f**[38]	60
7	**1g**	4-BrC_6H_4	**5g**[11]	57
8	**1h**	3-Pyridyl	**5h**[23]	61
9	**1i**	2-Thienyl	**5i**[23]	63
10	**1j**	2-Furyl	**5j**[38]	50
11	**1k**	$C_6H_4CH_2$	**5k**[38]	72
12	**1l**	$CH_3(CH_2)_5$	**5l**	86
13	**1m**	$CH_3(CH_2)_8$	**5m**[39]	86
14	**1n**	$HOOC(CH_2)_7$	**5n** (Bis-thiazoline)[b]	61

Reactions were heated at 150 °C for 8 min, except for entry 8 (4 min). All yields are for isolated product with previous purification by flash chromatography.
[a] Non-demethylated compound in the hindered *ortho*-position was obtained in 8% yield.
[b] Reagents ratio: dicarboxylic acid/2-aminoethanol/LR is 1:3:1.5.

Table 2
Synthesis of 2-thiazolines from 2-amino-2-methyl-1-propanol (**3**)

Entry	Acid	R^1	Product	Yield %
1	**1a**	Ph	**6a**[41]	77
2	**1b**	3-MeC_6H_4	**6b**	71
3	**1c**	4-$MeOC_6H_4$	**6c**[42]	70
4	**1d**	2,3-$(MeO)_2C_6H_3$	**6d** (R^1=2-HO-3-$MeOC_6H_3$)	67[a]
5	**1e**	2-Naphthyl	**6e**	76
6	**1f**	4-ClC_6H_4	**6f**	22
7	**1g**	4-BrC_6H_4	**6g**	22
8	**1h**	3-Pyridyl	**6h**	77
9	**1i**	2-Thienyl	**6i**	72
10	**1j**	2-Furyl	**6j**	73
11	**1k**	$C_6H_4CH_2$	**6k**[43]	81
12	**1l**	$CH_3(CH_2)_5$	**6l**	82
13	**1m**	$CH_3(CH_2)_8$	**6m**	61
14	**1n**	$HOOC(CH_2)_7$	**6n** (Bis-thiazoline)[b]	40

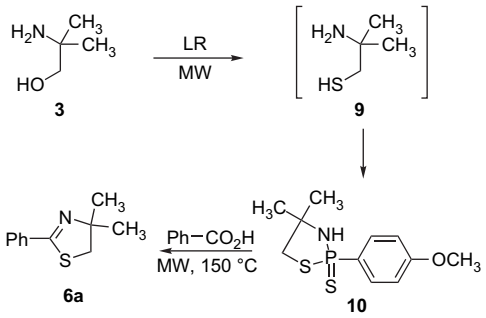
Reactions were heated at 150 °C for 4 min. All yields are for isolated product with previous purification by flash chromatography.
[a] Non-demethylated compound in the hindered *ortho*-position was obtained in 7% yield.
[b] Reagents ratio: dicarboxylic acid/2-amino-2-methyl-1-propanol/LR is 1:3:1.5.

Table 3
Synthesis of 2-thiazolines from 2-amino-1-phenylethanol (**4**)

Entry	Acid	R^1	Product	Yield %[a]
1	**1a**	Ph	**7a**[44]	69
2	**1b**	3-MeC_6H_4	**7b**	71
3	**1c**	4-$MeOC_6H_4$	**7c**	66
4	**1d**	2,3-$(MeO)_2C_6H_3$	**7d** (R^1=2-HO-3-$MeOC_6H_3$)	47[b]
5	**1e**	2-Naphthyl	**7e** (+**8e**)	52 (14)
6	**1f**	4-ClC_6H_4	**7f** (+**8f**)	38 (7)
7	**1g**	4-BrC_6H_4	**7g** (+**8g**)	33 (13)
8	**1h**	3-Pyridyl	**7h** (+**8h**)	21 (20)
9	**1i**	2-Thienyl	**7i**[25] (+**8i**)	44 (13)
10	**1j**	2-Furyl	**7j**[25]	42
11	**1k**	$C_6H_4CH_2$	**7k**[25]	40
12	**1l**	$CH_3(CH_2)_5$	**7l**	62
13	**1m**	$CH_3(CH_2)_8$	**7m**	64
14	**1n**	$HOOC(CH_2)_7$	**7n** (Bis-thiazoline)[c]	28

Reactions were heated at 150 °C for 8 min. All yields are for isolated product with previous purification by flash chromatography.
[a] Yields in brackets correspond to by-products shown in column 4.
[b] Non-demethylated compound in the hindered *ortho*-position was obtained in 8% yield.
[c] Reagents ratio: dicarboxylic acid/2-amino-1-phenylethanol/LR is 1:3:1.5.

yield (Scheme 2). However, it is noticeable that in the previously described reaction of 1,2-aminoalcohols with LR heating under conventional conditions (reflux in xylene), no replacement of the hydroxyl group by a thiol takes place; this leads to 1,3,2-oxazaphospholidines-2-sulfides.[47]



Scheme 2.

3. Conclusion

In summary, a new, simple, fast, efficient and versatile method for the synthesis of 2-thiazolines from 1,2-aminoalcohols and carboxylic acid employing Lawesson's reagent is presented. In this solvent-free procedure, the LR has two roles, to transform the 1,2-aminoalcohol into the 1,2-aminothiol and, to bring about a reaction with the carboxylic acid leading to the formation of 2-thiazoline ring. All these transformations are carried out in a one-pot reaction. The method is competitive with previous ones, both with conventional or microwave heating, since it leads to good yields and requires shorter reaction times. Moreover, it has a wider range of examples than the previously described synthesis both for the kind of carboxylic acids (aromatic and aliphatic) and 1,2-aminoalcohols used. In fact, 42 2-thiazolines were synthesized of which 24 had not been previously prepared. The process can also be used for parallel-synthesis of 2-thiazolines since the reaction conditions (reaction time, power setting and temperature) for each kind of 1,2-aminoalcohol are similar.

4. Experimental

4.1. General methods

Melting points were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$. Mass spectra were recorded in a low-resolution spectrometer. Infrared spectra were measured on FTIR instrument (cm^{-1}). The reactions were irradiated in an open vessel with microwaves in a monomode oven Discover CEM.

4.2. General procedure

Synthesis of 4,4-dimethyl-2-phenyl-2-thiazoline (**6a**). A mixture of benzoic acid (**1a**) (122 mg, 1 mmol), 2-amino-2-methyl-1-propanol (**3**) (133 mg, 1.5 mmol) and Lawesson's reagent (303 mg, 0.75 mmol) was irradiated in an open vessel with microwaves in a monomode oven (Discover CEM, 300 W and temperature control set at 150 °C measured with an IR sensor) for 4 min. The crude was dissolved in dichloromethane (30 mL) and washed with 10% aq NaOH (3×15 mL), dried (Na_2SO_4) and evaporated to give 4,4-dimethyl-2-phenyl-2-thiazoline (**6a**) pure as per NMR, further purification by flash chromatography (AcOEt/hexane, 5:95) gave 147 mg (77%), as an oil.

4.3. Data of previously unreported compounds

*4.3.1. 2-(2-Hydroxy-3-methoxyphenyl)-2-thiazoline (**5d**)*

Mp 74–74.5 °C (hexane). ^{1}H NMR δ 3.32 (t, 2H, J=8.4 Hz, CH_2S), 3.88 (s, 3H, OCH_3), 4.45 (t, 2H, J=8.4 Hz, CH_2N), 6.78 (t, 1H, J=7.9 Hz, ArH), 6.93 (dd, 1H, J=8.2, 1.6 Hz, ArH), 7.03 (dd, 1H, J=7.9, 1.3 Hz, Ar–H). ^{13}C NMR δ 32.1 (SCH_2), 56.5 (OCH_3), 63.5 (NCH_2), 114.9, 116.7, 118.3, 122.5 (C_{Ar}), 148.7 (C–OH), 149.8 (*C*–OCH_3), 172.8 (C=N). IR (KBr, film): 2949, 2843, 1599 (C=N), 1468, 1257, 1013, 781, 731 cm^{-1}. MS (EI): *m*/*z* (%) 210 (M^++1, 40), 209 (M^+, 100), 181 (49), 180 (32), 166 (38), 153 (85), 149 (47), 148 (41), 131 (49), 121 (29), 106 (33), 61 (52). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.43; H, 5.57; N, 6.47; S, 14.89.

*4.3.2. 2-Hexyl-2-thiazoline (**5l**)*

Oil. ^{1}H NMR δ 0.87 (t, 3H, J=6.6 Hz, CH_3), 1.23–1.40 (m, 6H, 3×CH_2), 1.63 (quint, 6H, J=4.8 Hz, CH_2), 250 (tt, 2H, J=7.9 and 1.8 Hz, CH_2C=N), 3.26 (t, 2H, J=8.4 Hz, CH_2S), 4.20 (t, 2H, J=8.4 Hz, CH_2N). ^{13}C NMR δ 14.2 (CH_3), 22.7, 27.7, 29.0, 31.7, 33.9, 34.6 (CH_2), 64.7 (NCH_2), 172.2 (*C*=N). MS (EI): *m*/*z* (%) 171 (M^+, 5), 129 (13), 114 (24), 101 (100), 61 (20), 60 (64), 59 (22), 55 (14). IR (KBr, film): 2925, 2855, 1629 (C=N), 1455, 1194, 1150, 973, 674 cm^{-1}. Anal. Calcd for $C_9H_{17}NS$: C, 63.10; H, 10.00; N, 8.18; S, 18.72. Found: C, 63.24; H, 10.04; N, 7.99; S, 18.76.

*4.3.3. 1,7-Bis(4,5-dihydrothiazol-2-yl)heptane (**5n**)*

Oil. ^{1}H NMR δ 1.21–1.36 (m, 6H, 3×CH_2), 1.58 (quint, 4H, J=7.4 Hz, 2×CH_2), 2.45 (tt, 4H, J=7.9, 1.3 Hz, 2×CH_2C=N), 3.23 (t, 4H, J=8.4 Hz, 2×CH_2S), 4.20 (tt, 4H, J=8.4, 1.3 Hz, 2×CH_2N). ^{13}C NMR δ 27.6, 29.11, 29.13, 33.9, 34.5 (CH_2), 64.7 (NCH_2), 171.9 (C=N). IR (KBr, film): 3300, 2928, 2854, 1639 (C=N), 1547, 1439, 1196, 984 cm^{-1}. MS (EI): *m*/*z* (%) 271 (M^++1, 30), 270 (M^+, 21), 269 (M^+−1, 58), 237 (44), 211 (50), 209 (52), 172 (50), 170 (64), 114 (75), 101 (100), 61 (50), 60 (64). Anal. Calcd for $C_{13}H_{22}N_2S_2$: C, 57.73; H, 8.20; N, 10.36; S, 23.71. Found: C, 57.93; H, 8.50; N, 10.51; S, 23.73.

*4.3.4. 4,4-Dimethyl-2-(3-methylphenyl)-2-thiazoline (**6b**)*

Oil. ^{1}H NMR δ 1.47 (s, 6H, 2×CH_3), 2.38 (s, 3H, Ar–*C*H_3), 3.20 (s, 2H, CH_2S), 7.25–7.30 (m, 2H, ArH), 7.60 (dt, 1H, J=7.0, 1.3 Hz, ArH), 7.67 (d, 1H, J=0.9 Hz, ArH). ^{13}C NMR δ 21.5 ($ArCH_3$), 27.8 (2×CH_3), 45.2 (SCH_2), 79.0 (*C*–$(CH_3)_2$), 125.9, 128.5, 128.9, 132.0, 133.7, 138.4 (C_{Ar}), 164.6 (C=N). IR (KBr, film): 2966, 2923, 1596 (C=N), 1582, 1460, 1359, 1274, 1160, 955, 893, 787, 693 cm^{-1}. MS (EI): *m*/*z* (%) 206 (M^++1, 34), 205 (M^+, 49), 190 (M^+−CH_3, 100), 159 (36), 118 (66), 88 (95, $SCH_2CH(CH_3)_2^+$), 84 (57), 55 (47), 51 (49). Anal. Calcd for $C_{12}H_{15}NOS$: C, 70.20; H, 7.36; N, 6.82; S, 15.62. Found: C, 70.49; H, 7.02; N, 6.50; S, 15.42.

*4.3.5. 2-(2-Hydroxy-3-methoxyphenyl)-4,4-dimethyl-2-thiazoline (**6d**)*

Mp 106–108 °C (hexane). ^{1}H NMR δ 1.46 (s, 6H, 2×CH_3), 3.13 (s, 2H, CH_2S), 3.87 (s, 3H, OCH_3), 6.77 (t, 1H, J=7.9 Hz, ArH), 6.93 (dd, 1H, J=7.9, 1.3 Hz, ArH), 7.00 (dd, 1H, J=7.9, 1.8 Hz, ArH). ^{13}C NMR δ 27.9 (2×CH_3), 43.5 (SCH_2), 56.5 (OCH_3), 78.0 (*C*–$(CH_3)_2$), 115.0, 116.7, 118.3, 122.1 (C_{Ar}), 148.7 (C–OH), 150.0 (*C*–OCH_3), 168.6 (C=N). IR (KBr, film): 2964, 2928, 1593 (C=N), 1566, 1462, 1256, 1173, 999, 735 cm^{-1}. MS (EI): *m*/*z* (%) 238 (M^++1, 26), 237 (M^+, 93), 181 (37), 165 (49), 153 (62), 150 (44), 149 (100), 88 (28), 71 (49), 57 (60), 55 (75). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 61.04; H, 6.60; N, 5.83; S, 13.88.

*4.3.6. 4,4-Dimethyl-2-naphthyl-2-thiazoline (**6e**)*

Mp 51–53 °C. ^{1}H NMR δ 1.52 (s, 6H, 2×CH_3), 3.27 (s, 2H, CH_2S), 7.48–7.55 (m, 2H, ArH), 7.83–7.92 (m, 3H, ArH), 7.99 (dd, 1H, J=8.4, 1.8 Hz, ArH), 8.26 (d, 1H, J=1.3 Hz, ArH). ^{13}C NMR δ 27.8 (2×CH_3), 45.3 (SCH_2), 79.2 (*C*–$(CH_3)_2$), 125.2, 126.7, 127.5, 127.9, 128.3, 129.0,

129.1, 131.3, 133.1, 134.9 (C_{Ar}), 164.3 (C=N). IR (KBr, film): 2968, 2928, 1607, 1277, 1169, 928, 822, 748 cm^{-1}. MS (EI): *m*/*z* (%) 242 (M^++1, 5), 241 (M^+, 29), 226 (M^+-CH_3, 23), 154 (35), 153 (100), 127 (21), 126 (17), 88 (40, $SCH_2CH(CH_3)_2^+$), 73 (15), 55 (28). Anal. Calcd for $C_{15}H_{15}NS$: C, 74.65; H, 6.26; N, 5.80; S, 13.29. Found: C, 74.41; H, 6.69; N, 5.67; S, 13.21.

*4.3.7. 2-(4-Chlorophenyl)-4,4-dimethyl-2-thiazoline (**6f**)*

^1H NMR δ 1.46 (s, 6H, 2×CH_3), 3.22 (s, 2H, CH_2S), 7.36 (d, 2H, *J*=8.4 Hz, ArH), 7.74 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR δ 27.7 (2×CH_3), 45.5 (SCH_2), 79.2 (*C*–$(CH_3)_2$), 128.8, 129.8, 132.3, 137.3 (C_{Ar}), 163.3 (C=N). IR (KBr, film): 2967, 2923, 1604 (C=N), 1488, 1399, 1264, 1169, 1088, 945, 832, 610 cm^{-1}. MS (EI): *m*/*z* (%) 227 ($^{37}Cl-M^+$, 26), 226 (13), 225 ($^{35}Cl-M^+$, 64), 210 (83), 179 (52), 138 (59), 88 (100, $SCH_2CH(CH_3)_2^+$), 73 (51), 55 (60), 54 (53). Anal. Calcd for $C_{11}H_{12}ClNS$: C, 58.53; H, 5.36; N, 6.20; S, 14.20. Found: C, 58.87; H, 5.12; N, 6.49; S, 14.19.

*4.3.8. 2-(4-Bromophenyl)-4,4-dimethyl-2-thiazoline (**6g**)*

Oil. ^1H NMR δ 1.46 (s, 6H, 2×CH_3), 3.22 (s, 2H, CH_2S), 7.52 (d, 2H, *J*=8.8 Hz, ArH), 7.68 (d, 2H, *J*=8.4 Hz, ArH). ^{13}C NMR δ 27.7 (2×CH_3), 45.4 (SCH_2), 79.2 (*C*–$(CH_3)_2$), 125.7, 130.0, 131.8, 133.6 (C_{Ar}), 161.6 (C=N). MS (EI): *m*/*z* (%) 271 ($^{81}Br-M^+$, 30), 270 (12), 269 ($^{79}Br-M^+$, 38), 256 (47), 254 (54), 225 (22), 223 (24), 184 (23), 182 (28), 102 (46), 88 (100, $SCH_2CH(CH_3)_2^+$), 73 (30), 55 (54), 54 (45). IR (KBr, film): 2955, 2924, 2854, 1736, 1605 (C=N), 1589, 1462, 1263, 1070, 1013, 949 cm^{-1}. Anal. Calcd for $C_{11}H_{12}BrNS$: C, 48.90; H, 4.48; N, 5.18; S, 11.87. Found: C, 49.12; H, 4.35; N, 5.18; S, 12.01.

*4.3.9. 4,4-Dimethyl-2-(3-pyridyl)-2-thiazoline (**6h**)*

Oil. ^1H NMR δ 1.42 (s, 6H, 2×CH_3), 3.19 (s, 2H, CH_2S), 7.27 (ddd, 1H, *J*=7.9, 4.8, 0.9 Hz, ArH), 8.03 (ddd, 1H, *J*=7.9, 2.2, 1.8 Hz, ArH), 8.60 (dd, 1H, *J*=4.8, 1.3 Hz, ArH), 8.96 (d, 1H, *J*=1.8 Hz, ArH). ^{13}C NMR δ 27.6 (2×CH_3), 45.4 (SCH_2), 79.2 (*C*–$(CH_3)_2$), 123.4, 129.7, 135.6, 149.6, 151.8 (C_{Ar}), 161.6 (C=N). IR (KBr, film): 2968, 2928, 1607 (C=N), 1416, 1269, 1173, 945, 810, 704, 623 cm^{-1}. MS (EI): *m*/*z* (%) 192 (M^+, 10), 177 (M^+-CH_3, 8), 105 (29), 88 (33, $SCH_2CH(CH_3)_2^+$), 73 (13), 58 (100), 54 (14). Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.40; H, 6.25; N, 14.29; S, 16.30.

*4.3.10. 4,4-Dimethyl-2-(2-thienyl)-2-thiazoline (**6i**)*

Oil. ^1H NMR δ 1.44 (s, 6H, 2×CH_3), 3.22 (s, 2H, CH_2S), 7.03 (t, 1H, *J*=4.4 Hz, ArH), 7.40 (d, 2H, *J*=4.4 Hz, ArH). ^{13}C NMR δ 27.6 (2×CH_3), 45.9 (SCH_2), 78.8 (*C*–$(CH_3)_2$), 127.5, 129.5, 130.4, 137.6 (C_{Ar}), 157.3 (C=N). IR (KBr, film): 2926, 2854, 1601 (C=N), 1462, 1362, 1261, 1041, 710 cm^{-1}. MS (EI): *m*/*z* (%) 197 (M^+, 35), 182 (M^+-CH_3, 100), 151 (39), 110 (77), 88 ($SCH_2CH(CH_3)_2^+$, 67), 73 (56), 55 (99). Anal. Calcd for $C_9H_{11}NS_2$: C, 54.78; H, 5.62; N, 7.10; S, 32.50. Found: C, 54.89; H, 5.62; N, 7.04; S, 32.07.

*4.3.11. 2-(2-Furyl)-4,4-dimethyl-2-thiazoline (**6j**)*

Oil. ^1H NMR δ 1.44 (s, 6H, 2×CH_3), 3.17 (s, 2H, CH_2S), 6.44 (dd, 1H, *J*=3.5, 1.8 Hz, ArH), 6.84 (dd, 1H, *J*=3.5, 0.9 Hz, ArH), 7.48 (dd, 1H, *J*=1.8, 0.9 Hz, ArH). ^{13}C NMR δ 27.6 (2×CH_3), 45.0 (SCH_2), 78.9 (*C*–$(CH_3)_2$), 111.9, 113.9, 144.8, 148.2 (C_{Ar}), 154.0 (C=N). IR (KBr, film): 2968, 2928, 1611 (C=N), 1475, 1265, 969, 899, 749 cm^{-1}. MS (EI): *m*/*z* (%) 181 (M^+, 34), 166 (M^+-CH_3, 100), 135 (29), 94 (46), 73 (42), 55 (55). Anal. Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73; S, 17.69. Found: C, 59.53; H, 6.11; N, 7.50; S, 18.06.

*4.3.12. 2-Hexyl-4,4-dimethyl-2-thiazoline (**6l**)*

Oil. ^1H NMR δ 0.81 (t, 3H, *J*=6.2 Hz, CH_3CH_2), 1.23–1.28 (br s, 12H, 3×(CH_2), 2×(CH_3)), 1.54 (quint, 6H, *J*=7.1 Hz, CH_2), 2.38 (t, 2H, *J*=8.4 Hz, CH_2C=N), 3.00 (s, 2H, SCH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3CH_2), 22.7 (CH_2), 27.7 (2×*C*H_3), 27.8, 28.8, 31.6, 34.6 (CH_2), 45.4 (SCH_2), 78.2 (*C*–$(CH_3)_2$), 167.8 (C=N). IR (KBr, film): 2924, 2854, 1647 (C=N), 1543, 1462, 1379, 1259 cm^{-1}. MS (EI): *m*/*z* (%) 200 (M^++1, 17), 199 (M^+, 8), 142 (31), 130 (31), 129 (100), 114 (25), 89 (23), 88 (89), 73 (26), 60 (33), 58 (38), 55 (72), 54 (64). Anal. Calcd for $C_{11}H_{21}NS$: C, 66.27; H, 10.62; N, 7.03; S, 16.08. Found: C, 66.69; H, 11.00; N, 7.01; S, 16.11.

*4.3.13. 4,4-Dimethyl-2-nonyl-2-thiazoline (**6m**)*

Oil. ^1H NMR δ 0.82 (t, 3H, *J*=6.8 Hz, *C*H_3CH_2), 1.21–1.29 (m, 18H, 6×(CH_2), 2×(CH_3)), 1.60 (quint, 2H, *J*=7.0 Hz, CH_2), 2.39 (t, 2H, *J*=7.7 Hz, CH_2C=N), 3.01 (s, 2H, SCH_2). ^{13}C NMR δ 14.3 (*C*H_3CH_2), 22.8 (CH_2), 27.7 (2×CH_3), 27.9, 29.2, 29.4, 29.4, 29.6, 32.0, 34.6 (CH_2), 45.4 (SCH_2), 78.2 (*C*–$(CH_3)_2$), 167.8 (C=N). IR (KBr, film): 2926, 2854, 1649 (C=N), 1628, 1541, 1464, 1362, 1259, 895 cm^{-1}. MS (EI): *m*/*z* (%) 241 (M^+, 14), 142 (42), 129 (100), 88 ($SCH_2CH(CH_3)_2^+$, 89), 55 (65). Anal. Calcd for $C_{14}H_{27}NS$: C, 69.65; H, 11.27; N, 5.80; S, 13.28. Found: C, 69.96; H, 11.36; N, 5.63; S, 12.90.

*4.3.14. 1,7-Bis(4,4-dimethyl-4,5-dihydrothiazol-2-yl)heptane (**6n**)*

Oil. ^1H NMR δ 1.32–1.37 (m, 20H, 4×CH_2, 4×CH_3), 1.59 (quint, 4H, *J*=7.5 Hz, 2×CH_2), 2.42 (t, 4H, *J*=7.7 Hz, 2×*C*H_2C=N), 3.05 (s, 4H, 2×SCH_2). ^{13}C NMR δ 27.8 (CH_3), 29.00, 29.05, 29.1, 29.2 34.6 (CH_2), 45.4 (SCH_2), 78.3 (*C*–$(CH_3)_2$), 167.7 (C=N). IR (KBr, film): 2966, 2928, 2856, 1626 (C=N), 1535, 1462, 1360, 1230, 1175, 1084, 955, 885 cm^{-1}. MS (EI): *m*/*z* (%) 326 (M^+, 8), 311 (M^+-CH_3, 100), 239 (50), 223 (46), 198 (65), 142 (40), 129 (95), 88 (88), 55 (76), 54 (49). Anal. Calcd for $C_{17}H_{30}N_2S_2$: C, 62.52; H, 9.26; N, 8.58; S, 19.64. Found: C, 62.45; H, 9.40; N, 8.29; S, 19.45.

*4.3.15. 2-(3-Methylphenyl)-5-phenyl-2-thiazoline (**7b**)*

Oil. ^1H NMR δ 2.42 (s, 3H, CH_3), 4.63 (dd, 1H, J_{gem}=15.8 Hz, *J*=5.7 Hz, NCH_2), 4.79 (dd, 1H, J_{gem}=16.3 Hz, *J*=8.8 Hz, NCH_2), 5.08 (dd, 1H, *J*=8.8, 5.7 Hz, CH), 7.26–7.39 (m, 7H, ArH), 7.70 (dt, 1H, *J*=7.0, 1.8 Hz, ArH), 7.76 (br s, 1H, ArH). ^{13}C NMR δ 21.5 (CH_3), 54.8 (SCH), 73.5 (NCH_2), 126.0, 127.3, 128.0, 128.7, 129.1, 129.2, 132.3, 133.4, 138.6, 142.4 (Ar), 168.1 (C=N). IR (KBr, film): 3028, 2939, 2920, 1601 (C=N), 1583, 1495, 1485, 1454, 1313, 1261, 1022, 999, 789, 696 cm^{-1}. MS (EI): *m*/*z* (%) 254 (M^++1, 6), 253 (M^+, 31), 136 ($C_8H_8S^+$, 68), 135 ($C_7H_5NS^+$, 76), 131 ($C_9H_9N^+$, 100), 103 (18), 91 (49), 77 (26), 65 (21), 51 (15). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53; S, 12.66. Found: C, 75.88; H, 6.03; N, 5.50; S, 12.50.

*4.3.16. 2-(4-Methoxyphenyl)-5-phenyl-2-thiazoline (**7c**)*

Mp 83–84 °C (hexane). ^1H NMR δ 3.84 (s, 3H, OCH_3), 4.58 (dd, 1H, J_{gem}=15.8 Hz, *J*=5.7 Hz, NCH_2), 4.76 (dd, 1H, J_{gem}=15.8 Hz, *J*=8.8 Hz, NCH_2), 5.06 (dd, 1H, *J*=8.8, 5.7 Hz, CH), 6.94 (d, 2H, *J*=8.8 Hz, ArH), 7.27–7.38 (m, 5H, ArH), 7.84 (d, 2H, *J*=8.8 Hz, ArH). ^{13}C NMR δ 54.9 (SCH), 55.6 (OCH_3), 73.3 (NCH_2), 114.1, 126.2, 127.3, 127.9, 129.1, 130.3, 142.4 (Ar), 162.3 (*C*–OCH_3), 167.2 (C=N). IR (KBr, film): 2999, 2937, 1607 (C=N), 1508, 1310, 1254, 1175, 1024, 1013, 849, 768, 702 cm^{-1}. MS (EI): *m*/*z* (%) 270 (M^++1, 8), 269 (M^+, 44), 147 ($C_9H_9NO^+$, 100), 136 ($C_8H_8S^+$, 49), 135 ($C_7H_5NS^+$, 50), 132 (20), 91 (18), 77 (24), 51 (8). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20; S, 11.90. Found: C, 71.22; H, 5.44; N, 4.89; S, 11.76.

*4.3.17. 2-(2-Hydroxy-3-methoxyphenyl)-5-phenyl-2-thiazoline (**7d**)*

Mp 109–111 °C (hexane/CH_2Cl_2). ^1H NMR δ 3.93 (s, 3H, OCH_3), 4.62 (dd, 1H, J_{gem}=15.8 Hz, *J*=5.7 Hz, NCH_2), 4.80 (dd, 1H, J_{gem}=15.8 Hz, *J*=8.8 Hz, NCH_2), 5.03 (dd, 1H, *J*=8.8, 5.7 Hz, CH), 6.82 (t, 1H, *J*=7.9 Hz, ArH), 6.98 (dd, 1H, J_{ortho}=8.4 Hz and J_{meta}=1.3 Hz, Ar–*H*), 7.06 (dd, 1H, J_{ortho}=7.9 Hz and J_{meta}=1.3 Hz, Ar–*H*), 7.26–7.36 (m, 5H, ArH). ^{13}C NMR δ 53.1 (SCHPh), 56.5 (OCH_3), 71.4 (NCH_2), 115.0, 116.6, 118.5, 122.5, 127.3, 128.3, 129.2, 141.3(C_{Ar}), 148.8, 150.0 (C_{Ar}–O), 172.2 (*C*=N). IR (KBr, film): 2939, 2841, 1597 (C=N), 1464, 1256, 1088, 1022, 729, 700 cm^{-1}. MS (EI): *m*/*z* (%) 286 (M^++1, 14), 285 (M^+, 70), 162 (35), 153 (64), 136 ($C_8H_8S^+$, 42), 135 ($C_7H_5NS^+$,

100), 121 (32), 104 (43), 103 (41), 91 (65), 78 (34), 77 (59), 65 (32), 51 (38). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.26; H, 5.38; N, 4.93; S, 11.10.

*4.3.18. 2-(2-Naphthyl)-5-phenyl-2-thiazoline (**7e**)*

Mp 66–67 °C (hexane). ^{1}H NMR δ 4.68 (dd, 1H, J_{gem}=15.8 Hz, J=5.7 Hz, NCH_2), 4.85 (dd, 1H, J_{gem}=15.8 Hz, J=8.8 Hz, NCH_2), 5.14 (dd, 1H, J=8.8, 5.7 Hz, CH), 7.26–7.41 (m, 5H, ArH), 7.50–7.59 (m, 2H, ArH), 7.86–7.93 (m, 3H, ArH), 8.06 (dd, 1H, J=8.8, 1.8 Hz, ArH), 8.32 (d, 1H, J=1.3 Hz, ArH). ^{13}C NMR δ 54.9 (SCHPh), 73.4 (NCH_2), 125.0, 126.9, 127.3, 127.8, 128.0, 128.1, 128.5, 129.1, 129.8, 133.1, 135.1, 142.2 (Ar_r), 168.3 (C=N). IR (KBr, film): 3059, 3028, 1607 (C=N), 1495, 1454, 1311, 1186, 1013, 928, 860, 822, 750, 698, 474 cm^{-1}. MS (EI): m/z (%) 290 (M^++1, 10), 289 (M^+, 44), 167 ($C_{12}H_9N^+$, 100), 153 (26) 136 ($C_8H_8S^+$, 56), 135 ($C_7H_5NS^+$, 55), 127 (45), 121 (18), 91 (21), 77 (23), 51 (11). Anal. Calcd for $C_{19}H_{15}NS$: C, 78.86; H, 5.22; N, 4.84; S, 11.08. Found: C, 78.56; H, 5.44; N, 4.87; S, 11.02.

*4.3.19. 2-(4-Chlorophenyl)-5-phenyl-2-thiazoline (**7f**)*

Mp 76–78 °C. ^{1}H NMR δ 4.60 (dd, 1H, J_{gem}=16.3 Hz, J=5.7 Hz, NCH_2), 4.78 (dd, 1H, J_{gem}=16.3 Hz, J=8.8 Hz, NCH_2), 5.10 (dd, 1H, J=8.8, 5.7 Hz, CH), 7.26–7.43 (m, 7H, ArH), 7.82 (d, 2H, J=8.4 Hz, ArH). ^{13}C NMR δ 55.3 (SCHPh), 73.4 (NCH_2), 127.3, 128.1, 129.0, 129.1, 129.9, 131.9, 137.6, 142.0 (Ar), 166.8 (C=N). IR (KBr, film): 3063, 3030, 1599 (C=N), 1487, 1452, 1398, 1229, 1092, 1011, 972, 930, 831, 698 cm^{-1}. MS (EI): m/z (%) 275 (^{37}Cl–M^+, 17), 274 (8), 273 (^{35}Cl–M^+, 44), 151 ($C_8H_6ClN^+$, 100), 136 ($C_8H_8S^+$, 79), 135 ($C_7H_5NS^+$, 84), 121 (18), 91 (23), 77 (22), 51 (13). Anal. Calcd for $C_{15}H_{12}ClNS$: C, 65.80; H, 4.42; N, 5.12; S, 11.71. Found: C, 66.22; H, 4.69; N, 5.07; S, 11.47.

*4.3.20. 2-(4-Bromophenyl)-5-phenyl-2-thiazoline (**7g**)*

Mp 88–89 °C (hexane). ^{1}H NMR δ 4.60 (dd, 1H, J_{gem}=16.3 Hz, J=5.7 Hz, NCH_2), 4.77 (dd, 1H, J_{gem}=16.3 Hz, J=8.8 Hz, NCH_2), 5.10 (dd, 1H, J=8.8, 5.7 Hz, CH), 7.26–7.36 (m, 5H, ArH), 7.56 (d, 2H, J=8.8 Hz, ArH), 7.74 (d, 2H, J=8.4 Hz, ArH). ^{13}C NMR δ 55.3 (SCHPh), 73.5 (NCH_2), 126.0, 127.3, 128.1, 129.1, 130.1, 132.0, 132.4, 142.0 (Ar), 166.8 (C=N). IR (KBr, film): 1599 (C=N), 1583, 1481, 1452, 1393, 1223, 1068, 926, 825, 754, 694, 594 cm^{-1}. MS (EI): m/z (%) 319 (^{81}Br–M^+, 17), 317 (^{79}Br–M^+, 18), 197 (56), 195 (57), 136 ($C_8H_8S^+$, 100), 135 ($C_7H_5NS^+$, 91), 121 (20), 103 (22), 102 (21), 91 (32), 77 (Ph^+, 29), 51 (18). Anal. Calcd for $C_{15}H_{12}BrNS$: C, 56.61; H, 3.80; N, 4.40; S, 10.08. Found: C, 56.78; H, 3.45; N, 4.55; S, 9.90.

*4.3.21. 5-Phenyl-2-(3-pyridyl)-2-thiazoline (**7h**)*

Mp 132–133 °C (hexane/AcOEt). ^{1}H NMR δ 7.26–7.43 (m, 4H, ArH), 7.63 (d, 2H, J=7.0 Hz, ArH), 7.77 (dt, 1H, J=7.9, 1.3 Hz, ArH), 8.07 (s, 1H, NCH), 8.18 (d, 1H, J=7.9 Hz, ArH), 8.61 (d, 1H, J=4.4 Hz, ArH). ^{13}C NMR δ 119.6, 124.5, 127.0, 128.7, 129.2, 131.8, 137.2 (Ar), 139.8 (NCH), 141.9, 149.7, 151.8 (Ar), 168.2 (C=N). IR (KBr, film): 1581 (C=N), 1470, 1446, 1421, 1001, 785, 756, 690 cm^{-1}. MS (EI): m/z (%) 239 (M^++1, 15), 238 (M^+, 87), 134 ($C_8H_6S^+$, 100), 135 (11), 108 (8), 102 (8), 90 (18), 89 (23), 78 (13), 77 (14), 51 (15). Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76; S, 13.46. Found: C, 70.54; H, 4.11; N, 11.98; S, 13.60.

*4.3.22. 2-Hexyl-5-phenyl-2-thiazoline (**7l**)*

Oil. ^{1}H NMR δ 0.90 (t, 3H, J=6.6 Hz, CH_3), 1.29–1.42 (m, 6H, 3×CH_2), 1.70 (sex, 2H, J=7.5 Hz, CH_2), 2.57 (tt, 2H, J=7.5, 1.6 Hz, CH_2CN), 4.35 (ddt, 1H, J_{gem}=15.4 Hz, J=5.7, 1.3 Hz, NCH_2C), 4.54 (ddt, 1H, J_{gem}=15.4 Hz, J=8.8, 1.8 Hz, NCH_2), 4.94 (dd, 1H, J=8.8, 5.7 Hz, NCH_2CH), 7.22–7.34 (m, 5H, ArH). ^{13}C NMR δ 14.2 (CH_3), 22.7, 27.7, 29.0, 31.7, 34.6 (CH_2), 55.0 (SCH), 72.9 (NCH_2), 127.2, 127.8, 129.0, 142.6 (Ar), 171.5 (C=N). IR (KBr, film): 2954, 2928, 2856, 1649, 1632 (C=N), 1541, 1493, 1454, 972, 760, 698 cm^{-1}. MS (EI): m/z (%) 248 (M^++1, 4), 247 (M^+, 20), 177 (100), 136 ($C_8H_8S^+$, 37), 135 ($C_7H_5NS^+$, 96), 124 (19), 104 (38), 103 (22), 91 (30), 77 (Ph^+, 22), 55 (11). Anal. Calcd for $C_{15}H_{21}NS$: C, 72.82; H, 8.56; N, 5.66; S, 12.96. Found: C, 72.43; H, 9.03; N, 5.39; S, 12.77.

*4.3.23. 2-Nonyl-5-phenyl-2-thiazoline (**7m**)*

Oil. ^{1}H NMR δ 0.90 (t, 3H, J=6.8 Hz, CH_3), 1.29–1.42 (m, 12H, 6×CH_2), 1.71 (sex, 2H, J=7.9 Hz, CH_2), 2.57 (tt, 2H, J=7.7, 1.3 Hz, CH_2CN), 4.36 (ddt, 1H, J_{gem}=15.6 Hz, J=5.5, 1.3 Hz, NCH_2), 4.54 (ddt, 1H, J_{gem}=15.6 Hz, J=9.0, 1.3 Hz, NCH_2), 4.94 (dd, 1H, J=9.0, 5.5 Hz, CH), 7.22–7.34 (m, 5H, ArH). ^{13}C NMR δ 14.3 (CH_3), 22.9, 29.4, 29.5, 29.5, 29.7, 32.1, 34.6 (CH_2), 55.1 (SCH), 73.0 (NCH_2), 127.2, 127.8, 129.0, 142.6 (Ar), 171.3 (C=N). IR (KBr, film): 2926, 2854, 1649 (C=N), 1632, 1543, 1493, 1454, 997, 760, 698 cm^{-1}. MS (EI): m/z (%) 289 (M^+, 11), 177 (100), 172 (37), 136 ($C_8H_8S^+$, 46), 135 ($C_7H_5NS^+$, 87), 104 (53), 103 (34), 91 (45), 77 (Ph^+, 31), 57 (28), 55 (46). Anal. Calcd for $C_{18}H_{27}NS$: C, 74.68; H, 9.40; N, 4.84; S, 11.08. Found: C, 74.47; H, 9.55; N, 4.67; S, 10.82.

*4.3.24. 1,7-Bis(5-phenyl-4,5-dihydrothiazol-2-yl)heptane (**7n**)*

Oil. ^{1}H NMR δ 1.40 (br s, 6H, 3×CH_2), 1.70 (br s, 4H, 2×CH_2), 2.56 (br t, 4H, J=7.5 Hz, 2×CH_2CN), 4.35 (dd, 2H, J_{gem}=15.4 Hz, J=5.3 Hz, 2×NCH_2), 4.54 (dd, 2H, J_{gem}=15.4 Hz, J=8.8 Hz, 2×NCH_2), 4.94 (dd, 2H, J=8.8 and 5.7 Hz, 2×CH), 7.29 (br s, 10H, ArH). ^{13}C NMR δ 27.6, 29.1, 29.2, 34.5 (CH_2), 55.1 (SCH), 72.9 (NCH_2), 127.2, 127.8, 129.0, 142.6 (Ar), 171.3 (C=N). IR (KBr, film): 2928, 2854, 1647 (C=N), 1543, 1493, 1452, 1215, 760, 698 cm^{-1}. MS (EI): m/z (%) 423 (M^++1, 1), 305 (10), 271 (10), 174 (16), 134 (22), 123 (100), 120 (87), 119 (79), 118 (32), 104 (22), 102 (19), 91 (11). Anal. Calcd for $C_{25}H_{30}N_2S_2$: C, 71.04; H, 7.15; N, 6.63; S, 15.17. Found: C, 70.97; H, 7.43; N, 6.51; S, 15.02.

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Supplementary data

^{1}H NMR spectra for all no previously synthesized compounds are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.027.

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