Alternative Synthesis of 2,4-Substituted-1,3-thiazines and 2,5-Substituted-thiazole Derivatives

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ABSTRACT

An easy and convenient route for the synthesis of 2,4-substituted thiazine (3–6) and 2,5-substituted thiazole (16) derivatives from phenacetamidines and glycine methyl ester is reported. To the best of our knowledge, this is the first report in which phenacetamidines have been utilized as precursors for thiazine synthesis. The syntheses of novel cyclic fused 1,3-diazabutadienes 13 and 2-aza-1,3-butadiene 17, and iodocyclization of 17 leading to the formation of thiazole 16a are also reported. In this paper a total of twenty novel compounds are reported.

KEY WORDS

Phenacetamidines, 1,3-thiazines, thiazoles, cyclizations.

1. Introduction

Heterocycles containing nitrogen and sulphur atoms, for instance thiazines, display diverse properties such as antifungal,[1] anti-HIV,[2] antipsoratic[3] and antimicrobial[4] activities and thus are of great chemical and pharmaceutical significance.[5–14] Some benzodiazepine substitutes[15] of imidazo[2,1-b]-[1,3] thiazines and pyrimido[2,1-b]-[1,3] thiazines are well known anti-inflammatory agents.[16] Likewise, thiazoles have also been reported to possess an important role in various fields of medicinal and agricultural chemistry. For example, the thiazolium ring present in vitamin B_1 serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids.[17] Some aminothiazole analogues are used as fungicides, inhibit the *in vivo* growth of *Xanthomonas,* and act as an ingredient of herbicides or as schistosomicidal and anthelminitic drugs. Fanetizole is also a derivative of 2-aminothiazole, which is used as an anti-inflammatory agent.[18] Owing to their immense chemical and biological interest, a number of methods have been reported for their synthesis and many of these suffer from disadvantages such as complex experimental procedures[6–8,11–13] and low isolated yields.[19,20]

As part of our ongoing interest in heterocyclic synthesis,[21] we wish to report herein an easy and convenient route for the synthesis of thiazine and thiazole derivatives starting from phenacetamidines and glycine methyl ester, respectively.

2. Results and Discussion

The treatment of phenylacetamidines 1 with potassium *tert*-butoxide (4.2 eq) and carbon disulphide (2.2 eq) and subsequent alkylation with methyl/ethyl iodide (4.0 eq) in THF at 0 °C resulted in the formation of 2-alkylsulphanyl-5-phenyl-4-N-arylamino-[1,3] thiazine-6-thione derivatives **3** in good yields (70–85 %) (Scheme 1). The structures assigned for **3** were based on elemental analysis and spectroscopic data. 2-Methyl-sulphanyl-5-phenyl-4-*p*-tolylamino-[1,3] thiazine-6-thione (**3a**), for example, gave elemental analysis results matching the formula $C_{18}H_{16}N_2S_3$. In the ^{1}H NMR spectrum it shows a characteristic singlet at δ 2.30 ppm for $-CH_3$, a singlet at δ 2.44 ppm for $-SCH_3$ along with multiplets in the aromatic region at δ 7.06–7.59 ppm. A broad singlet at δ 6.56 ppm in the ^{1}H NMR spectrum indicates the presence of a –NH group, which was confirmed further by a D_2O exchange experiment. The structure of the compound was also substantiated by its ^{13}C spectrum, which showed characteristic peaks at δ 14.4 (-SCH_3), 20.8 (-CH_3), 115.7 (=C-CS), 122.2 (CAr), 129.3 (CAr), 129.9 (CAr), 130.2 (CAr), 130.7 (CAr), 132.8 (CAr), 134.2 (C-Ar), 135.3 (-N-C-NH), 159.9 (-NH-C=), 160.6 (-C=N) and 167.3 ppm (-C=S). The presence of a molecular ion peak at m/z 356 (M^+) in its mass spectrum also supports the assigned structure.

However, the same reaction when carried out under the conditions described above but at –78 °C resulted in exclusive formation of thiazines **5** (Scheme 1). These compounds were also characterized on the basis of their spectroscopic data. For example, the compound (2,6-bis-methylsulphanyl-5-phenyl-[1,3] thiazin-4-ylidene)-*p*-tolylamine (**5a**) exhibits a molecular ion peak at m/z 370 (M^+) in its mass spectrum. Its ^{1}H NMR spectrum showed three characteristic singlets at δ 2.28, 2.33 and 2.35 ppm, corresponding to one $-CH_3$ and two $-SCH_3$ groups, respectively, along with multiplets at δ 6.83–7.44 ppm for the nine deshielded aromatic protons. The structure of **5a** was further corroborated by its ^{13}C spectrum, which showed peaks at δ 13.9 (-SCH_3), 16.1 (-SCH_3), 21.0 (-CH_3), 122.2 (CAr), 127.8 (CAr), 128.1 (CAr), 128.3 (CAr), 130.1 (CAr), 130.3 (CAr), 132.4 (CAr), 136.3 (ArC-CH_3), 136.4 (S-C-S), 146.7 (=N-CAr), 150.2 (-S-C=N-) and 164.6 ppm (-N-C=N).

The probable mechanism leading to formation of thiazine derivatives **3** and **5** is outlined in Scheme 2. In this scheme, it is assumed that the treatment of phenacetamidine with base and carbon disulphide leads to the formation of an intermediate **7** which upon its alkylation and tautomerization transforms into an intermediate **8**. The intermediate **8** tautomerizes to another intermediate **9** which, upon intramolecular cyclization by nucleophilic attack of sulphur on the iminic carbon (-C=N), eliminates the alkyl-thiol (-SR^2) moiety resulting in the formation of thiazines **3**.

However, at –78 °C, the intermediate **9**, probably being more stable, undergoes further alkylation to form an intermediate 10

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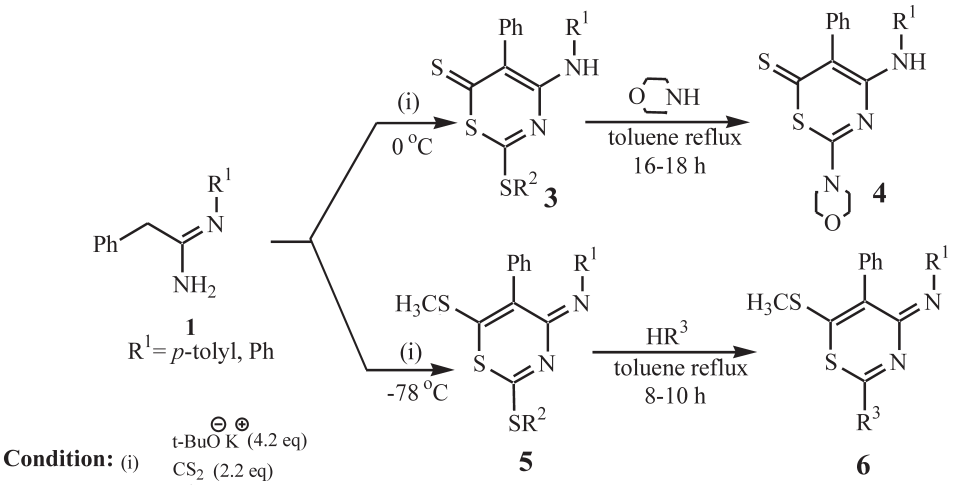


No.	R^1	R^2
3a	*p*-tolyl	CH_3
3b	Ph	CH_3
3c	*p*-tolyl	C_2H_5
3d	Ph	C_2H_5
4a	*p*-tolyl	-
4b	Ph	-
5a	*p*-tolyl	CH_3
5b	Ph	CH_3

No.	R^1	R^3
6a	*p*-tolyl	-N O
6b	*p*-tolyl	-N(Me_2)
6c	*p*-tolyl	-NH-Ph
6d	Ph	-N O
6e	Ph	-N(Me_2)
6f	Ph	-NH-Ph

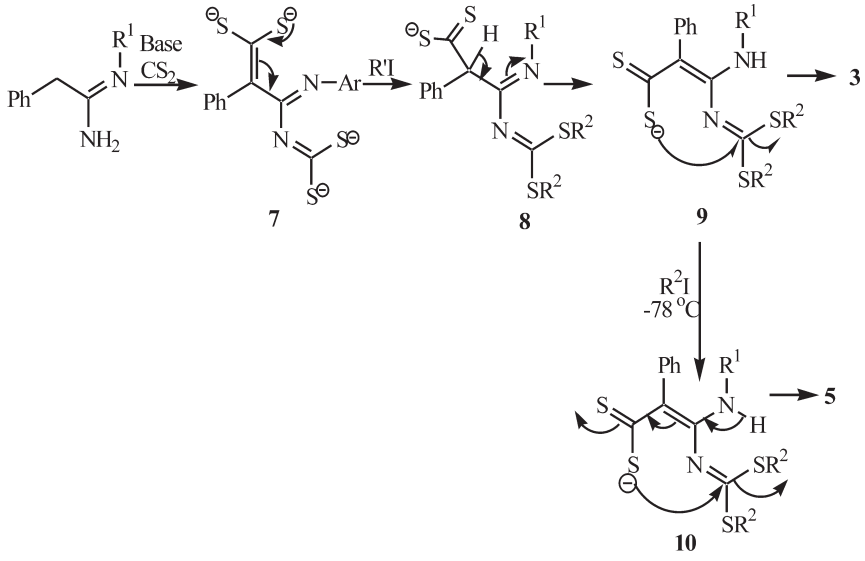
Scheme 1

which undergoes ring closure with removal of the alkyl thiol moiety to form thiazines **5**.

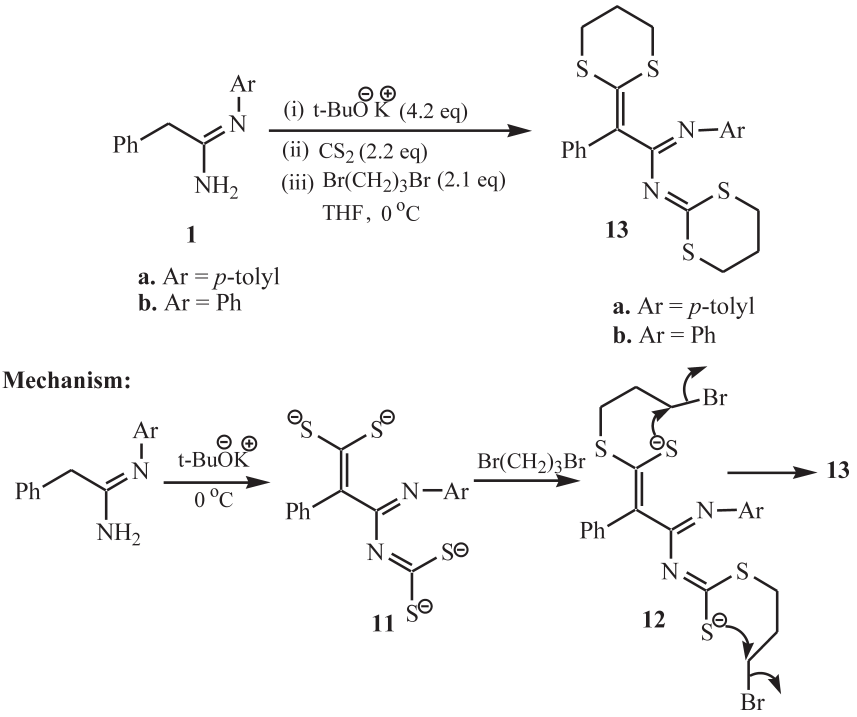
The thioalkyl (-SR^2) group attached to the C=N bond of thiazines **5** was replaced by aniline and some secondary amines (morpholine and dimethylamine) in refluxing toluene to obtain the corresponding imino-thiazines **6** (Scheme 1). Similarly, the thioalkyl group of 3 was also replaced by morpholine in toluene reflux (16–18 h) to obtain the corresponding morpholine substituted thiazines **4** (Scheme 1).

However, the treatment of phenacetamidines under similar conditions, as discussed for **3**, after alkylation with 1,3-dibromopropane (2.1 eq) led to the formation of cross-conjugated systems **13** (Scheme 3). A plausible mechanistic pathway for this reaction, depicted in Scheme 3, probably involves the initial formation of an intermediate **11** which upon alkylation transforms into an intermediate **12**. The intermediate **12** undergoes intramolecular cyclization by nucleophilic attack of sulphur on the alkyl halide carbon (-CH_2Br), being more facile and approachable, than on iminic carbon (-C=N), leading to the formation of compound **13**.

As an extension of the above methodology, a solution of glycine methyl ester **14** in DMF, when treated with carbon



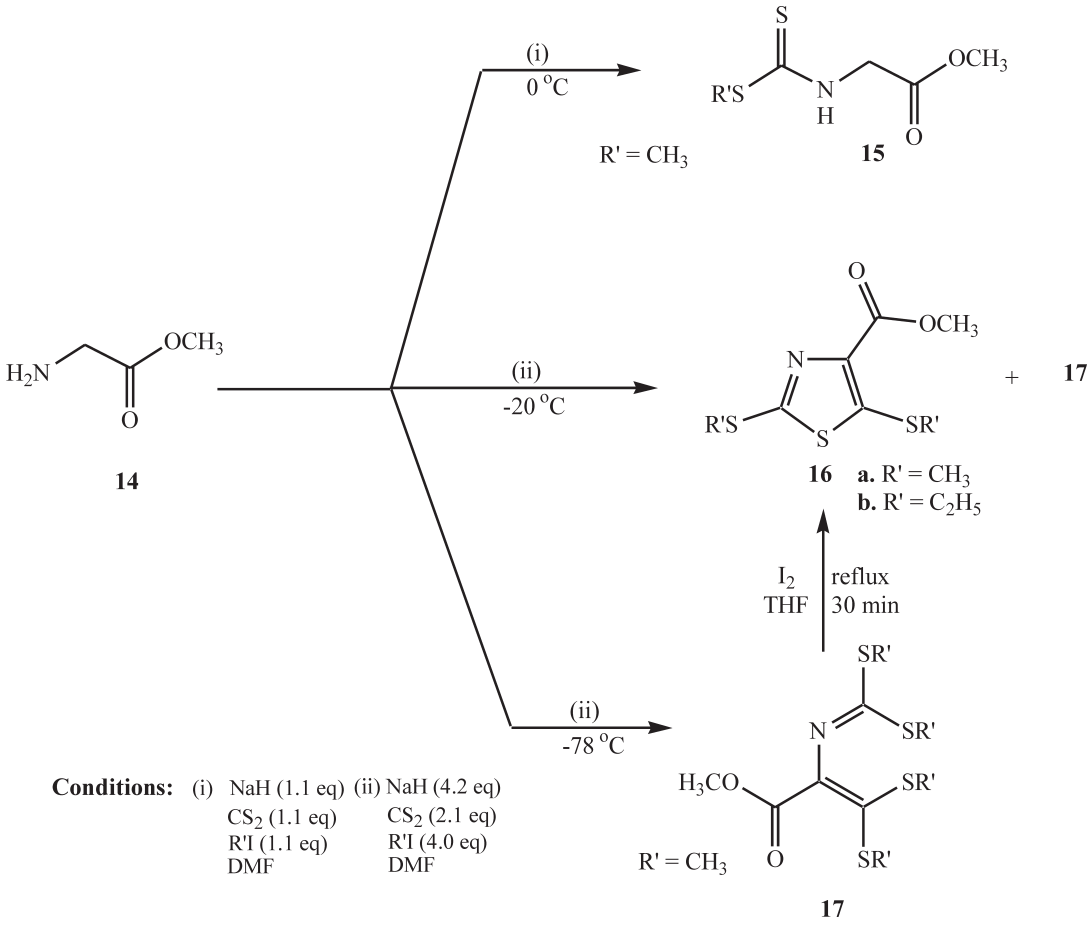
Scheme 2



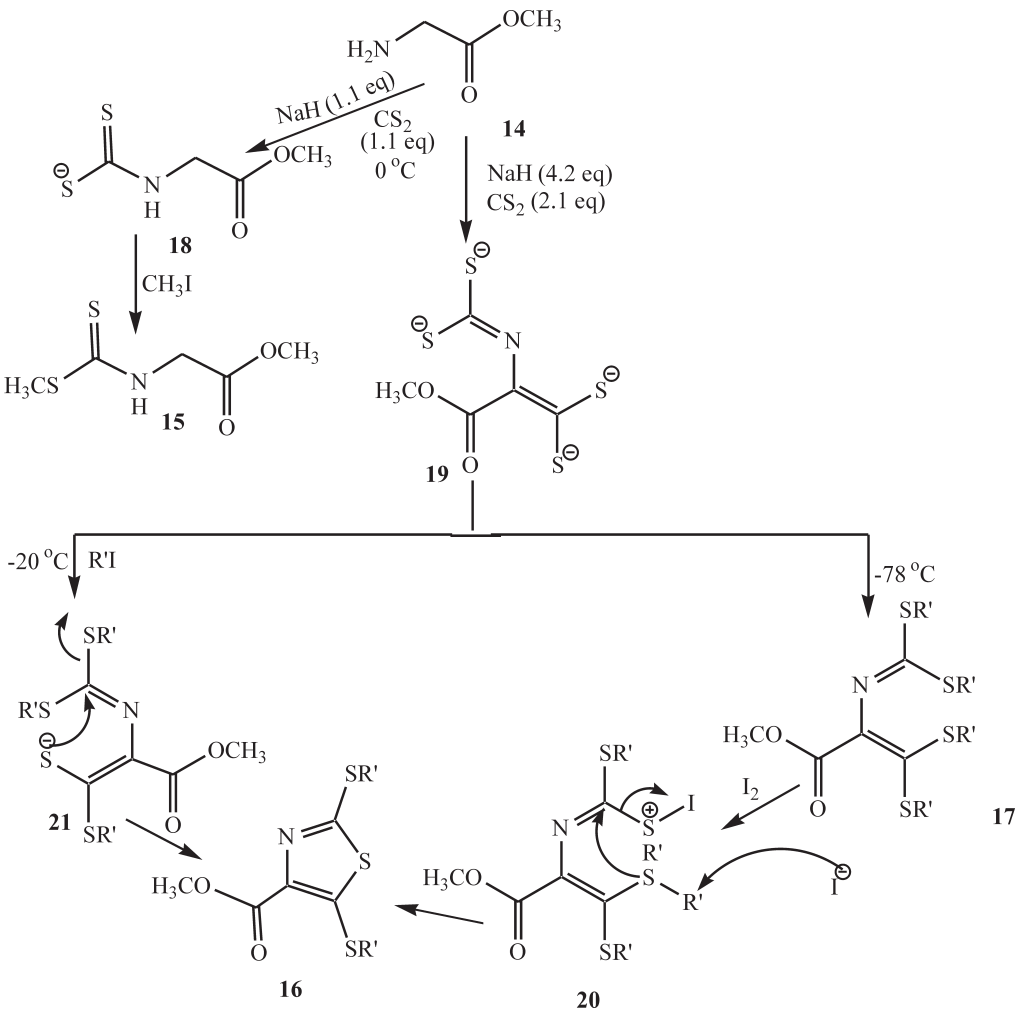
Scheme 3

disulphide (1.1 eq) in the presence of sodium hydride (1.1 eq) followed by alkylation with methyl iodide at 0 °C resulted in a compound, characterized as methylsulphanylthiocarbonyl-aminoacetic acid methyl ester **15** on the basis of spectral and analytical data (Scheme 4).

Treatment of 14 with carbon disulphide (2.1 eq) in the presence of sodium hydride (4.2 eq) at –20 °C and subsequent alkylation with methyl/ethyl iodide (4.0 eq) resulted in a mixture consisting predominantly of thiazoles 2,5-bis-methyl/ethylsulphanyl-thiazole-4-carboxylic acid methyl ester **16** (62–68 %) and



Scheme 4



Scheme 5

1,1,4,4-tetramethylsulphanyl-3-methoxycarbonyl-2-aza-1,3-butadiene **17**. Interestingly, the same reaction carried out at –78 °C under the conditions described above led to the exclusive formation of **17** (Scheme 4). The compound **17** could also be easily converted to thiazole 16a by activation with I_2 in refluxing THF (Scheme 4). The observed single step and one pot conversion of **14** to **16** is a significant improvement over the earlier reported conversion of glycine ethyl ester to thiazoles[22] in overall yields of approximately 10 %. A plausible mechanistic pathway for the formation of these compounds under varying reaction conditions is depicted in Scheme 5.

The formation of **15** could be explained by the initial formation of an intermediate **18**, generated by the treatment of glycine methyl ester **14** with CS_2 using NaH, followed by methylation with methyl iodide at 0 °C. The formation of **16** was thought to involve the initial formation of an intermediate **19** obtained by treatment of **14** with carbon disulphide (2.1 eq) using NaH (4.2 eq), which upon alkylation with methyl/ethyl iodide (4.0 eq) was transformed to another intermediate **21**. The intermediate **21** upon elimination of a –SR group by the nucleophilic attack of sulphur anion leads to the thiazoles **16** (Scheme 5). The exclusive formation of **17** could be explained by the more favoured alkylation at low temperature (–78 °C) compared with higher temperature (0 °C), where intramolecular attack by S^- on the imino carbon also competes with the alkylation. The synthesis of **16a** from **17** may be explained by the initial iodination of a $–SCH_3$ group attached to C-1 leading to the formation of an intermediate **20**. This intermediate **20** on cyclization accompanied by elimination of $–CH_3SI$ and R′I yields thiazole **16a** (Scheme 5).

Conclusions

An easy and efficient method for the synthesis of 1,3-thiazine derivatives has been developed. To the best of our knowledge, this is the first report in which phenacetamidines have been utilized as precursors for thiazine synthesis. An easy access to the synthesis of thiazoles from glycine methyl ester and novel 2-azadiene **17** has also been reported.

3. Experimental

3.1. General

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (Mumbai, India) and are uncorrected. IR spectra were recorded on a Shimadzu (Shanghai, China) FTIR-8400S spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Bruker (Geldermalsen, Netherlands) AC-E 200 (200 MHz) spectrometers using TMS as internal standard. ^{13}C NMR spectra were also recorded on Bruker AC-E 200 (50.4 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on a Shimadzu (Shanghai, China) GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on a Heraus CHN-O-Rapid Elemental Analyzer (Hanau, Germany). Phenacetamidines were prepared according to the reported procedure.[23]

3.2. General Procedure for the Synthesis of 1,3-Thiazines (3, 5 and 13)

To a suspension of potassium t-butoxide (42 mmol) in THF (30 mL) at 0 °C was added a solution of phenacetamidine **1** (10 mmol) in THF (10 mL) and stirred for 10 min followed by the addition of carbon disulphide (22 mmol). After stirring for 5 min at the same temperature, alkyl halide (40 mmol) (methyl/ethyl iodide for **3**/1,3-dibromopropane for **13**) was added to the reaction mixture and stirring continued for 30 min. On completion (monitiored by TLC), the reaction mixture was washed with excess water (100 mL) and extracted using chloroform. The crude product obtained after removal of the solvent under reduced pressure was purified by silica gel column chromatography. The compound, thus isolated, was recrystallized using a hexane:ethyl acetate (10:1) mixture. The same reaction when carried out under the conditions described above at –78 °C resulted in exclusive formation of thiazines **5.**

2-Methylsulphanyl-5-phenyl-4-p-tolylamino-[1,3] thiazine-6-thione (**3a**)

From the reaction of **1a** with carbon disulphide and methyl iodide; eluent ethyl acetate:hexane mixture (5:95, R_f = 0.74); yield 67 %; yellow crystalline solid, m.p. 161–163 °C; δ_H (300 MHz, $CDCl_3$): 2.30 (s, 3H, -CH_3), 2.44 (s, 3H, -SCH_3), 6.56 (bs, 1H, -NH), 7.06 (d, *J* 8.2 Hz, 2H, ArH), 7.34–7.36 (m, 4H, ArH), 7.54–7.59 ppm (m, 3H, ArH); δ_C (75 MHz, $CDCl_3$): 14.4 (-SCH_3), 20.8 (-CH_3), 115.7, 122.2, 129.3, 129.9, 130.2, 130.7, 132.8, 134.2, 135.3, 159.9, 160.6, 167.3 ppm; ν_{max} ($CHCl_3$): 1580, 1529, 1440 cm^{-1}; m/z: 356 (M^+). Found: C, 60.75; H, 4.47, N, 7.83 %. Calc. for $C_{18}H_{16}N_2S_3$ (356); C, 60.64; H, 4.52, N, 7.86 %).

2-Methylsulphanyl-5-phenyl-4-phenylamino-[1,3] thiazine-6-thione (**3b**)

From the reaction of **1b** with carbon disulphide and methyl iodide; eluent ethyl acetate:hexane mixture (6:94, R_f = 0.72); yield 65 %; light yellow crystalline solid; m.p. 145–147 °C; δ_H (300 MHz, $CDCl_3$): 2.45 (s, 3H, -SCH_3), 6.54 (bs, 1H, -NH), 6.99–7.24 (m, 6H, ArH), 7.26–7.38 ppm (m, 4H, ArH); δ_C (75 MHz, $CDCl_3$): 14.4 (-SCH_3), 114.9, 116.5, 121.8, 124.5, 129.8, 130.6, 133.4, 134.3, 135.3, 159.7, 160.3, 167.2 ppm; ν_{max} ($CHCl_3$): 1581, 1532, 1437 cm^{-1}; m/z: 342 (M^+). Found: C, 59.72; H, 4.07; N, 8.23 %. Calc. for $C_{17}H_{14}N_2S_3$ (342); C, 59.61; H, 4.12; N, 8.18 %).

2-Ethylsulphanyl-5-phenyl-4-p-tolylamino-[1,3] thiazine-6-thione (**3c**)

From the reaction of **1a** with carbon disulphide and ethyl iodide; eluent **e**thyl acetate:hexane mixture (5:95, R_f = 0.75); yield 66 %; yellow crystalline solid; m.p. 175–176 °C; δ_H (300 MHz, $CDCl_3$): 1.33 (t, *J* 7.4 Hz, 3H, -S-C-CH_3), 2.30 (s, 3H, -CH_3), 2.99 (q, *J* 7.4 Hz, 2H, -SCH_2), 6.59 (bs, 1H, -NH), 7.09 (d, *J* 8.2 Hz, 2H, ArH), 7.32–7.36 (m, 5H, ArH), 7.55–7.61 ppm (m, 2H, ArH); δ_C (75 MHz, $CDCl_3$): 14.0 (-S-C-CH_3), 20.8 (-CH_3), 25.9 (-SCH_2), 115.9, 122.2, 129.3, 129.8, 130.1, 130.7, 133.0, 134.2, 135.2, 159.8, 160.0, 167.2 ppm; ν_{max} ($CHCl_3$): 2972, 2923, 1583, 1531, 1440, 1215 cm^{-1}; m/z: 370 (M^+). Found: C, 61.77; H, 4.58; N, 7.63 %. Calc. for $C_{19}H_{18}N_2S_3$ (370); C, 61.58; H, 4.90; N, 7.56 %).

2-Ethylsulphanyl-5-phenyl-4-phenylamino-[1,3] thiazine-6-thione (**3d**)

From the reaction of **1b** with carbon disulphide and ethyl iodide; eluent **e**thyl acetate:hexane mixture (6:94, R_f = 0.71); yield 59 %; pale white solid; m.p. 166-168 °C; δ_H (300 MHz, $CDCl_3$): 1.32 (t, *J* 7.4 Hz, 3H, -S-C-CH_3), 2.98 (q, *J* 7.4 Hz, 2H, -SCH_2), 6.58 (bs, 1H, -NH), 7.10–7.33 (m, 6H, ArH), 7.36–7.48 ppm (m, 4H, ArH); δ_C (75 MHz, $CDCl_3$): 14.1 (-S-C-CH_3), 26.1 (-SCH_2), 115.7, 121.4, 126.8, 129.6, 130.3, 130.9, 132.9, 134.5, 135.8, 158.4, 161.1, 167.1 ppm; ν_{max} ($CHCl_3$): 2924, 1584, 1502, 1441, 1215 cm^{-1}; m/z: 356 (M^+). Found: C, 60.77; H, 4.45; N, 7.78 %. Calc. for $C_{18}H_{16}N_2S_3$ (356); C, 60.64; H, 4.52; N, 7.86 %).

(2,6-Bis-methylsulphanyl-5-phenyl-[1,3] thiazin-4-ylidene)-p-tolylamine (**5a**)

From the reaction of **1a** with carbon disulphide and methyl iodide; eluent **e**thyl acetate:hexane mixture (8:92, R_f = 0.68); yield 69 %; yellow crystalline solid; m.p. 136-137 °C; δ_H (300 MHz, $CDCl_3$): 2.28 (s, 3H, -CH_3), 2.33 (s, 3H, -SCH_3), 2.35 (s, 3H, -SCH_3), 6.83 (d, *J* 8.1 Hz, 2H, ArH), 7.02 (d, *J* 8.1 Hz, 2H, ArH), 7.31–7.44 ppm (m, 5H, ArH); δ_C (75 MHz, $CDCl_3$): 13.9 (-SCH_3), 16.1 (-SCH_3), 21.0 (-CH_3), 122.2, 127.8, 128.1, 128.3, 130.1, 130.3, 132.4, 136.3, 136.4, 146.7, 150.2, 164.6 ppm; ν_{max} ($CHCl_3$): 1571, 1552, 1523, 1440 cm^{-1}; m/z: 370 (M^+). Found: C, 61.69; H, 4.86; N, 7.63 %. Calc. for $C_{19}H_{18}N_2S_3$ (370); C, 61.58; H, 4.90; N, 7.56 %).

(2,6-Bis-methylsulphanyl-5-phenyl-[1,3] thiazin-4-ylidene)-phenylamine (**5b**)

From the reaction of **1b** with carbon disulphide and methyl iodide; eluent **e**thyl acetate:hexane mixture (10:90, R_f = 0.70); yield 59 %; yellow solid; m.p. 157–158 °C; δ_H (300 MHz, $CDCl_3$): 2.29 (s, 3H, -SCH_3), 2.36 (s, 3H, -SCH_3), 6.99–7.28 (m, 6H, ArH), 7.31–7.42 ppm (m, 4H, ArH); δ_C (75 MHz, $CDCl_3$): 13.8 (-SCH_3), 16.1 (-SCH_3), 120.8, 126.7, 127.3, 128.2, 129.9, 131.1, 132.5, 135.9, 136.5, 144.9, 150.1, 164.5 ppm; ν_{max} ($CHCl_3$): 1570, 1551, 1440 cm^{-1}; m/z: 356 (M^+). Found: C, 60.79; H, 4.58; N, 7.73 %. Calc. for $C_{18}H_{16}N_2S_3$ (356); C, 60.64; H, 4.52; N, 7.86 %).

2,N-Bis-[1,3] dithian-2-ylidene-2-phenyl-N'-p-tolyl-acetamidine (**13a**)

From the reaction of **1a** with carbon disulphide and 1,3-dibromopropane; eluent ethyl acetate:hexane mixture (12:88, R_f = 0.71); yield 51 %; light yellow solid; m.p. 122–123 °C; δ_H (300 MHz, $CDCl_3$): 1.93 (q, *J* 6.6 Hz, 2H, -CH_2), 2.12 (q, *J* 6.6 Hz, 2H, -CH_2), 2.27 (s, 3H, -CH_3), 2.76 [(t, *J* 6.6 Hz, 4H, -$SCH_2)_2$], 2.92 [(t, *J* 6.6 Hz, 4H, -$SCH_2)_2$], 6.97 (d, *J* 8.2 Hz, 2H, ArH), 7.02 (d, *J* 8.2 Hz, 2H, ArH), 7.25–7.33 ppm (m 5H, ArH); δ_C (75 MHz, $CDCl_3$): 20.9 (-CH_3), 21.8, 23.9, 29.3, 29.8, 122.0, 127.5, 127.7, 128.6, 128.9, 130.3, 132.9, 138.1, 145.2, 147.4, 156.6, 166.1 ppm; ν_{max} ($CHCl_3$): 1580, 1500, 1298 cm^{-1}; m/z: 456 (M^+). Found: C, 60.58; H, 5.42; N, 6.02 %. Calc. for $C_{23}H_{24}N_2S_4$ (456); C, 60.49; H, 5.30; N, 6.13 %).

2,N-Bis-[1,3] dithian-2-ylidene-2-phenyl-N'-p-tolyl-acetamidine (**13b**)

From the reaction of **1b** with carbon disulphide and 1,3-dibromopropane; eluent **e**thyl acetate:hexane mixture (10:90, R_f = 0.65); yield 55 %; light yellow solid; m.p. 137–138 °C; δ_H (300 MHz, $CDCl_3$): 1.94 (q, *J* 6.6 Hz, 2H, -CH_2), 2.11 (q, *J* 6.6 Hz, 2H, -CH_2), 2.72 [t, *J* 6.6 Hz, 4H, (-$SCH_2)_2$], 2.91 [t, *J* 6.6 Hz, 4H, (-$SCH_2)_2$], 6.93–7.37 ppm (m, 10H, ArH); δ_C (75 MHz, $CDCl_3$): 21.7, 23.5, 28.6, 29.6, 121.5, 125.6, 127.6, 128.5, 129.5, 131.5, 133.2, 137.6, 142.9, 147.3, 155.9, 166.2 ppm; ν_{max} ($CHCl_3$): 1582, 1500, 1298 cm^{-1}; m/z: 442 (M^+). Found: C, 59.59; H, 4.97; N, 6.41 %. Calc. for $C_{22}H_{22}N_2S_4$ (442); C, 59.69; H, 5.01; N, 6.33%).

3.3. General Procedure for the Synthesis of Substituted Thiazines 4 and 6

For synthesis of **4**, a solution of thiazine **3** (10 mmol) in toluene was refluxed along with morpholine (11 mmol) for 16–18 h. The completion of the reaction was monitored by TLC. After comple-

tion of the reaction, the solvent was evaporated under reduced pressure and the crude product was purified through silica gel column chromatography. The compounds thus obtained were recrystallized using hexane:ethyl acetate (10:1) mixture.

For the synthesis of **6**, a solution of thiazine **5** (10 mmol) and primary/secondary amine (11 mmol) in toluene was refluxed under a constant supply of ice-cooled water in a condenser, for a period of 8–10 h. After completion (monitored by TLC), the solvent was evaporated under reduced pressure and the crude compounds were recrystallized using ethyl acetate:hexane (5:1) mixture.

2-Morpholin-4-yl-5-phenyl-4-p-tolylamino-[1,3] thiazine-6-thione (**4a**)

From the reaction of **3a** with morpholine; eluent **e**thyl acetate: hexane mixture (6:94, R_f = 0.69); yield 62 %; yellow solid; m.p. 164–165 °C; δ_H (300 MHz, $CDCl_3$): 2.31 (s, 3H, -CH_3), 3.56–3.61 (m, 4H, H_2C-N-CH_2), 3.62–3.66 (m, 4H, H_2C-O-CH_2), 6.58 (bs, 1H, -NH), 6.84 (d, *J* 7.9 Hz, 2H, ArH), 6.99 (d, *J* 7.9 Hz, 2H, ArH), 7.19–7.42 ppm (m, 5H, ArH); δ_C (75 MHz, $CDCl_3$): 21.1 (-CH_3), 45.6 (-C-N-C-), 66.2 (-C-O-C-), 120.1, 121.9, 129.2, 130.5, 131.2, 131.6, 132.8, 134.5, 137.3, 158.7 161.5, 167.4 ppm; ν_{max} ($CHCl_3$): 2923, 1528, 1445, 1330, 1216, 1110 cm^{-1}; m/z: 395 (M^+). Found: C, 63.89; H, 5.39; N, 10.59 %. Calc. for $C_{21}H_{21}N_3OS_2$ (395); C, 63.77; H, 5.35; N, 10.62 %).

2-Morpholin-4-yl-5-phenyl-4-phenylamino-[1,3] thiazine-6-thione (**4b**)

From the reaction of **3b** with morpholine; eluent ethyl acetate: hexane mixture (8:92, R_f = 0.70); yield 67 %; yellow solid; m.p. 171–173 °C; δ_H (300 MHz, $CDCl_3$): 3.55–3.60 (m, 4H, H_2C-N-CH_2), 3.62–3.67 (m, 4H, H_2C-O-CH_2), 6.59 (bs, 1H, -NH), 6.89–7.15 (m, 6H, ArH), 7.19–7.46 ppm (m, 4H, ArH); δ_C (75 MHz, $CDCl_3$): 45.5 (-C-N-C-), 66.3 (-C-O-C-), 120.2, 122.1, 128.2, 130.3, 131.8, 132.0, 132.8, 134.7, 138.1, 157.9 161.7, 167.3 ppm; ν_{max} ($CHCl_3$): 2919, 1529, 1442, 1388, 1226 cm^{-1}; m/z: 381 (M^+). Found: C, 63.09; H, 5.11; N, 11.05 %. Calc. for $C_{20}H_{19}N_3OS_2$ (381); C, 62.96; H, 5.02; N, 11.01 %).

(6-Methylsulphanyl-2-morpholin-4-yl-5-phenyl-[1,3] thiazin-4-ylidene)-p-tolylamine (**6a**)

From the reaction of **5a** with morpholine; eluent **e**thyl acetate: hexane mixture (5:95, R_f = 0.66); yield 71 %; yellow crystalline solid; m.p. 141–142 °C; δ_H (300 MHz, $CDCl_3$): 2.28 (s, 3H, -CH_3), 2.33 (s, 3H, -SCH_3), 3.57-3.60 (m, 4H, H_2C-N-CH_2), 3.67–3.69 (m, 4H, H_2C-O-CH_2), 6.80 (d, *J* 8.0 Hz, 2H, ArH), 6.97 (d, *J* 8.0 Hz, 2H, ArH), 7.26–7.46 ppm (m, 5H, ArH); δ_C (75 MHz, $CDCl_3$): 16.6 (-SCH_3), 20.9 (-CH_3), 45.7 (-C-N-C-), 66.2 (-C-O-C-), 122.2, 127.5, 127.9, 128.2, 130.1, 131.5, 132.0, 136.3, 136.5, 147.2, 153.1, 155.1 ppm; ν_{max} ($CHCl_3$): 1585, 1560, 1527, 1442 cm^{-1}; m/z: 409 (M^+). Found: C, 64.69; H, 5.59; N, 10.29 %. Calc. for $C_{22}H_{23}N_3OS_2$ (409); C, 64.52; H, 5.66; N, 10.26 %).

2-Dimethylamino-6-methylsulphanyl-5-phenyl-[1,3] thiazin-4-ylidene)-p-tolylamine (**6b**)

From the reaction of **5a** with dimethylamine; eluent **e**thyl acetate:hexane mixture (7:93, R_f = 0.65); yield 62 %; reddish yellow solid; m.p. 182–184 °C; δ_H (300 MHz, $CDCl_3$): 2.29 (s, 3H, -CH_3), 2.35 (s, 3H, -SCH_3), 2.92 (s, 6H, -N (CH_3)$_2$), 6.83 (d, *J* 8.2 Hz, 2H, ArH), 6.97 (d, *J* 8.2 Hz, 2H, ArH), 7.19–7.47 ppm (m, 5H, ArH); δ_C (75 MHz, $CDCl_3$): 16.5 (-SCH_3), 21.0 (-CH_3), 39.9 [-N (CH_3)$_2$], 117.3, 122.3, 124.9, 127.5, 130.9, 133.1, 134.8, 135.4, 136.5, 144.8, 153.2, 155.1 ppm; ν_{max} ($CHCl_3$): 1588, 1408, 1330, 1114 cm^{-1}; m/z: 367 (M^+). Found: C, 65.52; H, 5.71; N, 11.52 %. Calc. for $C_{20}H_{21}N_3S_2$ (367); C, 65.36; H, 5.76; N, 11.43 %).

6-Methylsulphanyl-5-phenyl-2-phenylamino-[1,3] thiazin-4-ylidene)-p-tolylamine (**6c**)

From the reaction of **5a** with aniline; eluent **e**thyl acetate:hexane mixture (6:94, R_f = 0.70); yield 71 %; pale yellow solid; m.p. 129–131 °C; δ_H (300 MHz, $CDCl_3$): 2.31 (s, 3H, -CH_3), 2.39 (s, 3H, -SCH_3), 6.35 (bs, 1H, -NH), 6.99–7.12 (m, 4H, ArH), 7.15–7.28 (m, 5H, ArH), 7.30–7.69 ppm (m, 5H, ArH); δ_C (75 MHz, $CDCl_3$): 16.3 (-SCH_3), 21.0 (-CH_3), 120.8, 121.1, 122.4, 123.8, 125.1, 127.2, 129.4, 131.3, 133.4, 134.6, 135.1, 136.2, 137.3, 144.5, 153.4, 155.3 ppm; ν_{max} ($CHCl_3$): 1598, 1571, 1527, 1485, 1330 cm^{-1}; m/z: 415 (M^+). Found: C, 69.52; H, 5.13; N, 10.14 %. Calc. for $C_{24}H_{21}N_3S_2$ (415); C, 69.36; H, 5.09; N, 10.11%).

(6-Methylsulphanyl-2-morpholin-4-yl-5-phenyl-[1, 3] thiazin-4-ylidene)-phenylamine (**6d**)

From the reaction of **5b** with morpholine; eluent ethyl acetate: hexane mixture (5:95, R_f = 0.64); yield 67 %; light yellow solid; m.p. 151–152 °C; δ_H (300 MHz, $CDCl_3$): 2.34 (s, 3H, -SCH_3), 3.55–3.58 (m, 4H, H_2C-N-CH_2), 3.63–3.68 (m, 4H, H_2C-O-CH_2), 6.78–7.19 (m, 5H, ArH), 7.23–7.46 ppm (m, 5H, ArH); δ_C (75 MHz, $CDCl_3$): 16.4 (-SCH_3), 45.6 (-C-N-C-), 66.2 (-C-O-C-), 119.2, 121.5, 125.3, 127.3, 130.1, 131.8, 132.6, 135.9, 136.8, 146.8, 152.9, 155.2 ppm; ν_{max} ($CHCl_3$): 1583, 1559, 1527, 1442 cm^{-1}; m/z: 395 (M^+). Found: C, 63.69; H, 5.52; N, 10.59 %. Calc. for $C_{21}H_{21}N_3OS_2$ (395); C, 63.77; H, 5.35; N, 10.62 %).

2-Dimethylamino-6-methylsulphanyl-5-phenyl-[1,3] thiazin-4-ylidene)-phenylamine (**6e**)

From the reaction of **5b** with dimethylamine; eluent **e**thyl acetate:hexane mixture (8:92, R_f = 0.66); **y**ield 67 %; reddish crystalline solid; m.p. 178–179 °C; δ_H (300 MHz, $CDCl_3$): 2.35 (s, 3H, -SCH_3), 2.91 (s, 6H, -N (CH_3)$_2$, 6.88–7.15 (m, 7H, ArH), 7.21–7.38 ppm (m, 3H, ArH); δ_C (75 MHz, $CDCl_3$): 16.5 (-SCH_3), 40.1[(-N (CH_3)$_2$], 115.2, 121.3, 125.4, 126.3, 131.2, 132.6, 133.1, 135.4, 136.1, 144.7, 151.8, 154.9 ppm; ν_{max} ($CHCl_3$): 1589, 1485, 1407, 1330 cm^{-1}; m/z: 353 (M^+). Found: C, 64.68; H, 5.46; N, 11.79 %. Calc. for $C_{19}H_{19}N_3S_2$ (353); C, 64.55; H, 5.42; N, 11.89 %).

6-Methylsulphanyl-5-phenyl-2-phenylamino-[1,3] thiazin-4-ylidene)-phenylamine (**6f**)

From the reaction of **5b** with aniline; eluent ethyl acetate:hexane mixture (5:95, R_f = 0.78); yield 62 %; light yellow solid; m.p. 154–155 °C; δ_H (300 MHz, $CDCl_3$): 2.38 (s, 3H, -SCH_3), 6.38 (bs, 1H, -NH), 6.88–7.21 (m, 6H, ArH), 7.23–7.52 ppm (m, 9H, ArH); δ_C (75 MHz, $CDCl_3$): 16.5 (-SCH_3), 120.7, 121.2, 122.4, 123.7, 125.2, 127.1, 129.4, 130.9, 134.1, 134.7, 135.5, 135.9, 137.1, 145.1, 153.1, 155.2 ppm; ν_{max} ($CHCl_3$): 1596, 1527, 1485, 1408, 1330 cm^{-1}; m/z: 401 (M^+). Found: C, 68.91; H, 4.69; N, 10.41 %. Calc. for $C_{23}H_{19}N_3S_2$ (401); C, 68.80; H, 4.77; N, 10.46 %).

3.4. Procedure for the Synthesis of 15, 16 and 17 from Glycine Methyl Ester 14

To a suspension of NaH (11 mmol) in DMF (40 mL) at 0 °C was added a solution of glycine methyl ester **(**10 mmol) in DMF (10 mL) and stirred for 5 min, followed by addition of carbon disulphide (11 mmol). After stirring for an additional 10 min at the same temperature, methyl iodide (10 mmol) was added to the reaction mixture and the stirring continued for 30 min. On completion, the reaction mixture was washed with an excess of water (100 mL) and extracted using toluene. The crude product

obtained after removal of the solvent under reduced pressure was purified using silica gel column chromatography. The solid compound **(15)** thus obtained was recrystallized from hexane:ethyl acetate (5:1) mixture. For the synthesis of compounds **16** and **17**, the same procedure as described above was used using NaH (42 mmol), carbon disulphide (21 mmol), methyl/ethyl iodide (40 mmol) for **16** and methyl iodide (40 mmol) for **17** keeping the reaction temperature at –20 °C and –78 °C, respectively. The solid compounds were further recrystallized using hexane:ethyl acetate (5:1) mixture.

For **16a**, a solution of **17** (10 mmol) and iodine (10 mmol) was refluxed in tetrahydrofuran (50 mL) for a period of 30 min. The completion of reaction was monitored by TLC and the crude product obtained after removal of the solvent was purified using silica gel column chromatography. The solid compound was further recrystallized using hexane:ethyl acetate (8:1) mixture.

Methylsulphanylthiocarbonylaminoacetic acid ethyl ester (**15**)

From the reaction of glycine methyl ester **14** with CS_2 and methyl iodide at 0 °C; eluent ethyl acetate:hexane mixture (4:96, R_f = 0.80); **y**ield 76 %; light brown solid; m.p. 109–110 °C; δ_H (300 MHz, $CDCl_3$): 2.57 (s, 3H, SCH_3), 3.75 (s, 3H, -OCH_3), 4.42 ppm (s, 2H, -CH_2); δ_C (75 MHz, $CDCl_3$): 17.5 (-SCH_3), 42.5 (-CH_2), 52.2 (-OCH_3), 163.5, 198.9 ppm; ν_{max} ($CHCl_3$): 1688, 1478, 1332 cm^{-1}; m/z: 179 (M^+). Found: C, 33.88; H, 4.88; N, 7.67 %. Calc. for $C_5H_9NO_2S_2$ (179); C, 33.50; H, 5.06; N, 7.81 %).

2,5-Bis-methylsulphanyl-thiazole-4-carboxylic acid methyl ester (**16a**)

From the reaction of glycine methyl ester **14** with CS_2 and methyl iodide at –20 °C; eluent ethyl acetate:hexane mixture (20:80, R_f = 0.41); yield 68 %; pale white solid; m.p. 85–86 °C; δ_H (300 MHz, $CDCl_3$): 2.56 (s, 3H, -SCH_3), 2.68 (s, 3H, -SCH_3), 3.91 ppm (s, 3H, -OCH_3); δ_C (75 MHz, $CDCl_3$): 17.0 (-SCH_3), 20.1 (-SCH_3), 52.2 (-OCH_3), 138.2, 148.6, 161.7, 162.2 ppm; ν_{max} ($CHCl_3$): 1687, 1482, 1328, 1054 cm^{-1}; m/z: 235 (M^+). Found: C, 36.01; H, 3.92; N, 5.88 %. Calc. for $C_7H_9NO_2S_3$ (235); C, 35.72; H, 3.85; N, 5.95 %).

2,5-Bis-ethylsulphanyl-thiazole-4-carboxylic acid methyl ester (**16b**)

From the reaction of glycine methyl ester **14** with CS_2 and ethyl iodide at –20 °C; eluent **e**thyl acetate:hexane mixture (25:75, R_f = 0.40); yield 62 %; colourless solid; m.p. 95–96 °C; δ_H (300 MHz, $CDCl_3$): 1.29 [t, *J* 7.5 Hz, 6H, 2x (-S-C-CH_3)], 2.99 [q, *J* 7.5 Hz, 4H, 2x (-SCH_2)], 3.90 ppm (s, 3H, -OCH_3); δ_C (75 MHz, $CDCl_3$): 14.1 [2x (-S-C-CH_3)], 25.9 [2x (-S-CH_2)], 54.2 (-OCH_3), 138.5, 148.3, 162.2, 163.1 ppm; ν_{max} ($CHCl_3$): 1688, 1330, 1054 cm^{-1}; m/z: 263 (M^+). Found: C, 40.97; H, 4.88; N, 5.40 %. Calc. for $C_9H_{13}NO_2S_3$ (263); C, 41.04; H, 4.97; N, 5.32 %).

1,1,4,4-Tetramethylsulphanyl-3-methoxycarbonyl-2-aza-1,3-butadiene (**17**)

From the reaction of glycine methyl ester **14** with CS_2 and methyl iodide at –78 °C; eluent ethyl acetate:hexane mixture (40:60, R_f = 0.36); yield 72 %; light yellow solid; m.p. 75–76 °C; δ_H (300 MHz, $CDCl_3$): 2.30 (s, 3H, -SCH_3), 2.32 (s, 3H, -SCH_3), 2.52 (s, 6H, 2x-SCH_3), 3.75 ppm (s, 3H, -OCH_3); δ_C (75 MHz, $CDCl_3$): 14.8 (-SCH_3), 15.7 (-SCH_3), 18.0 (2x-SCH_3), 51.3 (-OCH_3), 128.7, 139.5, 162.6, 166.0 ppm; ν_{max} ($CHCl_3$): 1698, 1481, 1039, 785 cm^{-1}; m/z: 297 (M^+). Found: C, 36.44; H, 4.94; N, 4.82 %. Calc. for $C_9H_{15}NO_2S_4$ (297); C, 36.34; H, 5.08; N, 4.71 %).

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