Ring Transformations of 1,2,4-Dithiazoles: Synthesis and Biological Studies of Novel *S*-Heterocycles, and Their Relevant Phosphono Derivatives

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Reactions of 5-phenyl-3(3*H*)-thioxo-1,2,4-dithiazole (**1**) with unsaturated and active phosphonium salts as well as with phosphonates, at r. t. and under the effect of basic catalysis, afforded mainly 1,3,5-dithiazines **5**, **12**, **17a**, **17b**, **23a** or **23b**. Substituted 1,3-dithiol **7** and 1,3-thiazoles **13**, **19a**, **19b**, **22a** and **22b** were isolated as by-products. 1,3,5-Dithiazine products showed pharmacological potency.

Key words: Heterocyclic Disulfides, Vinyl and Allylphosphonium Salts, α-Alkylthiomethylphosphonates, 1,3,5-Dithiazines, 1,3-Thiazoles

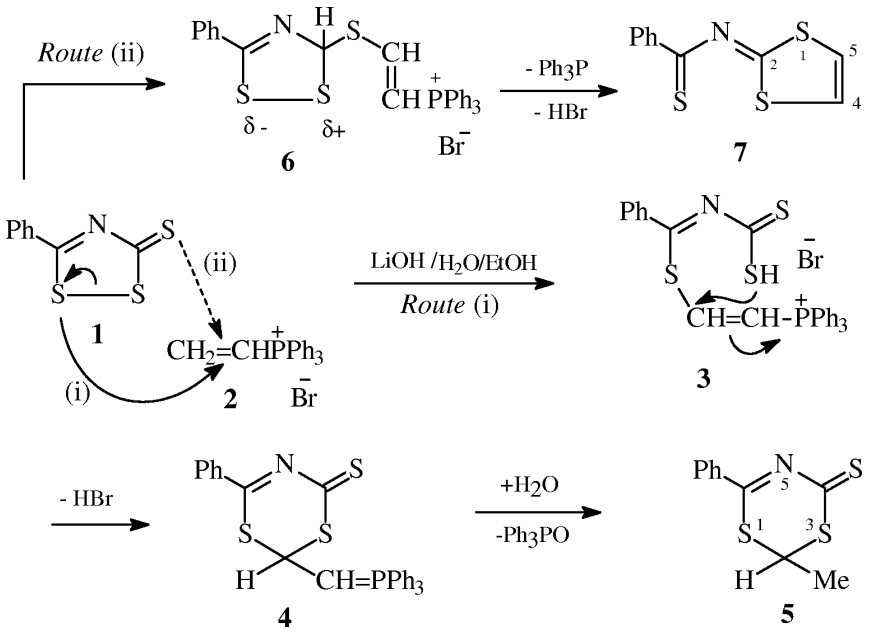
Introduction

Diverse biological and pharmacological activities have been reported for thiazoles, dithiazines and related compounds. For instance, thiazole derivatives are in clinical use [1, 2], and many dithiazines exhibit antiprotozoal, antiviral, bactericidal and fungicidal properties [3], probably by virtue of the presence of the toxophoric (-N=C-S) group. Furthermore, many dithiols and dithiazines are patented as synthetic flavor compounds [4, 5] and in photographic developing by a diffusion transfer process [6]. For these reasons, one of our research programs has centered on the synthesis of dithiols, thiazoles and phosphono-substituted *S*-heterocycles, derived from the reactions of acyclic and cyclic *cis*-disulfides with P^{III} and P^{V} reagents [7]. The work described in this article involves the reactions of 5-phenyl-3(3*H*)-thioxo-1,2,4-dithiazole (**1**) with unsaturated (**2**, **10**) and active phosphonium salts **15a** and **15b** as well as with α-phosphonyl carbanions **20a** and **20b**. The reactions led to the synthesis of new five- and six-membered sulfur heterocycles and their phosphono derivatives.

Results and Discussion

When the 1,2,4-dithiazole **1** was treated with an excess of vinyltriphenylphosphonium bromide (**2**) in a mixture of ethyl alcohol containing aqueous LiOH (0.5 M) or sodium ethanolate at r. t., the reaction was not complete even after two days. Work-up of the product mixture yielded 4-thioxo-1,3,5-dithiazine **5** (42 % yield), and 1,3-dithiol-2-imine **7** (18 % yield) together with unchanged substrate **1** (8 %) (Scheme 1).

Structures **5** and **7** were assigned to the isolated products on the basis of their elemental analyses, IR, ^{1}H and ^{13}C NMR, and mass spectral data. Thus, the ^{1}H NMR spectrum of **5** exhibited the characteristic resonances for the 2-CHMe moiety (δ = 4.27 and 1.31) along with resonances corresponding to the phenyl ring. Its ^{13}C NMR spectrum displayed the dithiazine-carbon resonances at δ = 31.6 (C-2), 143.6 (C-6) and 204.3 (C-4), and the methyl signal at 14.6 ppm. The mass spectrum of **5** confirmed its molecular weight. As expected, initial fragmentation involved the loss of CH_3 and the scission of the ring. On the other hand, the IR spectrum of **7** showed bands in the range 1605 – 1612 (C=C) and strong bands at 1485 and 1425 cm^{-1}, which have been assigned to N-C=S and N=C-S, respectively, in addition to several other bands in the broad region of 1563 – 700 cm^{-1}, which can be attributed to vibrations involving an interaction between the C=S and C-N stretching [8]. In the ^{1}H NMR spectrum of **7** the protons of the dithiol ring appeared as two doublets (J = 5.8 Hz) at δ = 7.76 and 7.82. In its ^{13}C NMR spectrum, signals were displayed at δ = 118.3, 119.7 (C–4 and C-5), 154.6 (C-2) and at 206.4 (C=S). Similar (*N*-thiophenacyl)-1,3-dithiol-2-imines were previously reported for the reaction product of **1** and (alkoxycarbonylmethylene)

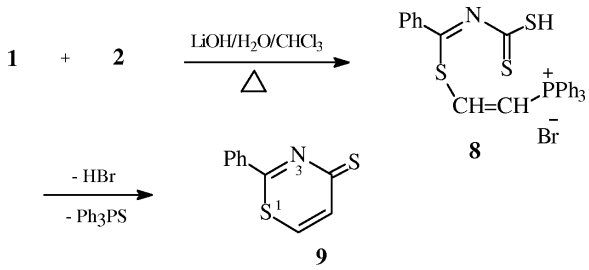


Scheme 1.

triphenylphosphorane [7f] and for the reaction product of **1** with dimethyl acetylenedicarboxylate [9].

A mechanism that accounts for the formation of **5** and **7** is outlined in Scheme 1. Obviously, the striking difference between vinylphosphonium salts and analogous ammonium salts is the ease with which the C=C bond of the former reacts with nucleophiles [10]. Thus, the initial Michael addition of **1** to **2** leads to the formation of both intermediates **3** and **6**. Cyclization of **3** with extrusion of HBr gives the phosphorane **4**, which by hydrolysis yields dithiazine **5** with concomitant elimination of triphenylphosphane oxide. The feasibility of insertion of a carbanion between two sulfur atoms is well known [7a, 7b, 11, 12]. Nevertheless, intermediate **6** undergoes cyclization to yield the dithiol **7** with elimination of hydrogen bromide and triphenylphosphane. The latter step arises because of the enhanced ability of the S-S linkage to be disrupted due to the effect of the alkaline medium.

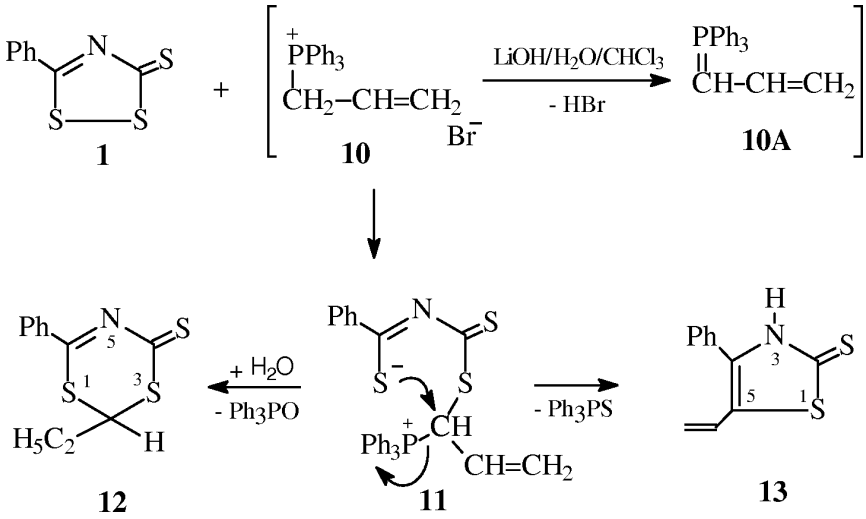
When the reaction between the dithiol **1** and **2** was carried out in refluxing chloroform (or EtOH) containing aq. LiOH (0.5 M) for 8 h, 2-phenyl-4(*4H*)-thioxo-1,3-thiazine (**9**) was the reaction product (67 % yield) (Scheme 2). Compound **9** was the only isolable adduct regardless of the ratio of the reactants employed. The identity of **9** is inferred from its analytical and spectral properties (see Experimental Section). Following the initial Michael addition product **8**, a substitution reac-



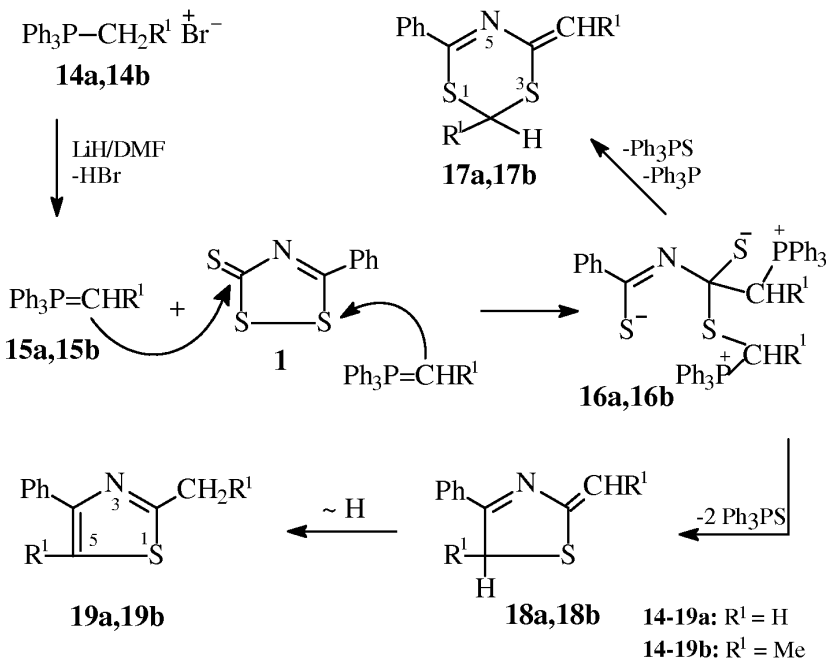
Scheme 2.

tion took place leading to the thione **9**, accompanied by elimination of HBr and Ph_3PS.

When **1** was refluxed with an equimolar amount of allyltriphenylphosphonium bromide (**10**) in $CHCl_3$ containing aq. LiOH (0.5 M), dithiazine-4-thione **12** and thiazol-2-thione **13** were isolated in 44 and 21 % yield (Scheme 3). The product **13** had infrared bands at 3358 and 1608 cm^{-1} attributed to the NH and exocyclic olefin. In the ^1H NMR spectrum of **13** the exocyclic vinyl protons give signals at δ = 5.22, 5.64 and 6.47 ppm (*AMX* pattern). The presence of the vinyl moiety was attested to the signals at δ = 109.4 ($CH{=}CH_2$), 125.7 ($CH{=}CH_2$) and at 141.4 (C-5) in the ^{13}C NMR spectrum of **13**. According to Scheme 3, an initial nucleophilic addition of the carbanion center in **10A** at the S-S-linkage leads to the formation of the zwitterion **11**, which subsequently could fol-



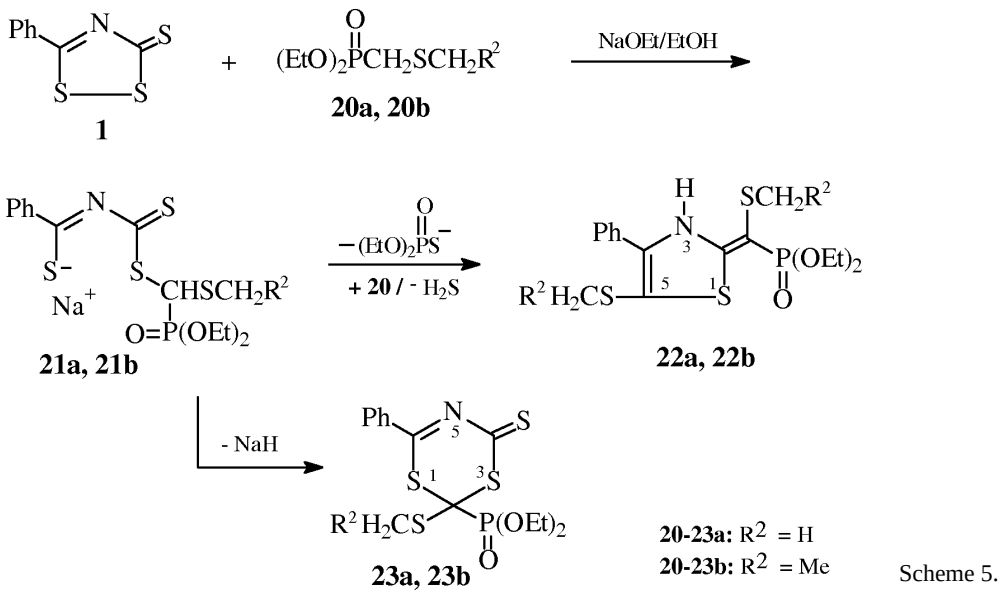
Scheme 3.



Scheme 4.

low two different pathways: i) cyclization and addition of a molecule of water yields **12** and Ph_3PO, as it is discussed in Scheme 1; ii) extrusion of triphenylphosphane sulfide from the intermediate **11** affords **13**.

In a systematic study, the reaction of the thione **1** with reactive ylides **15a** and **15b** was studied. When **1** was treated with two molar equivalents of methylidenetriphenylphosphorane (**15a**), prepared *in situ* from the corresponding phosphonium bromide **14a**, in dimethylformamide solution containing excess LiH, the reaction proceeded smoothly at r. t. with stirring for 8 h. Chromatographic separation of the product mixture afforded the substituted dithiazine **17a** (48 % yield) and the thiazole derivative **19a** (23 %). In a similar fashion, compound **1** reacted with ethylidenetriphenylphosphorane (**15b**), prepared *in situ* from its bromide salt, to give **17b** (42 % yield) and **19b** (25 % yield) (Scheme 4). Structures **17** and **19** were derived from elemental analyses and spectroscopic data. The IR spectrum of **19a** indicates the absence of an



Scheme 5.

S-S-linkage, since a sharp and strong band assigned [9] to the *cis*-disulfide stretching vibration at 1225 cm^{-1} in the IR spectrum of **1** was absent in the IR spectra of **19a** and **19b**. On the other hand, they showed bands in the range 1600 – 1610 (C=C) and at ≈ 1420 cm^{-1} assigned to the N=C-S moiety. The appearance of two signals in the ^{1}H NMR spectrum of **19b** at δ = 0.97 (t) and 1.54 (s), assignable to 2-CH_2CH_3 and 5-CH_3 groups (^{13}C NMR: δ = 12.8 and 16.4 ppm), excludes the formation of the alternative ylidene structure **18**.

According to Scheme 4, initial nucleophilic attack by the carbanion center in the ylides **15a** (or **15b**) at a ring sulfur atom in **1** followed by an addition of a second phosphorane species at the thiocarbonyl carbon atom resulted in the formation of the intermediate **16a** (or **16b**). Further thio-olefination and elimination of triphenylphosphane sulfide from **16** can lead to the formation of the dithiazoles **17a**, **17b** or of thiazoles **19a** and **19b**.

The above four reactions illustrate the dissimilarities between the behavior of unsaturated and active phosphonium salts with 1,2-dithiol **1** and the previously reported [7f] behavior of resonance-stabilized ylides towards the same substrate **1**. In the latter case, it was possible to isolate the symmetric dimeric form of **1** along with the thiazole or dithiol derivatives from the reactions of **1** with ylides of the type (Ph_3P=CHCOR′, R′ = OMe, OEt, Ph, Me). On the other hand, dithiazines derived from an insertion reaction at the S-S-linkage in **1** were the common major products in the present study (Schemes 1, 3 and 4).

Next, the reaction of the 1,2-disulfide **1** with diethyl (α-alkylthiomethyl)phosphonates **20a** and **20b** was investigated with regard to the synthesis of new phosphonate derivatives. It is conceivable that a molecular modification of thiazole or dithiazole rings by introducing an organophosphorus functionality enhances the potential biological activity. Treatment of **1** with a threefold excess of **20a** (or **20b**) in an alcoholic sodium ethoxide solution at r. t. yielded the phosphonates **22a** (27 % yield) and **23a** (40 % yield), or **22b** and **23b** in 23 % and 43 % yields, respectively (Scheme 5). Elemental analyses and spectral data substantiated the structures of **22** and **23**. The NMR spectra of **22a** (δ_p = 18.93 ppm) showed a sharp singlet of the NH proton at δ = 9.75. The two thiomethyl groups gave one doublet (J_{HP} = 4.5 Hz) at 2.16 and a singlet at 2.23 ppm. The two thiomethyl carbon signals in the ^{13}C NMR spectrum appeared at δ = 13.4 and 15.6 while the C-P carbon atom gave a doublet (J_{CP} = 184.7 Hz) at 96.8 ppm. In the IR spectrum of **22a**, the NH- and P-O-C moieties gave rise to absorptions at 3365 and 1132 cm^{-1} while the exocyclic C=C gave a strong sharp band at 1628 cm^{-1}. The foregoing results confirm the vinylphosphonate structure **22** and rule out the alternative enaminophosphonate.

The mechanism outlined in Scheme 5 includes a similar initial thiophilic addition of the phosphonyl carbanions **20** to **1** leading to the intermediates **21**,

which can react further on two different pathways: i) intramolecular cyclization, as previously discussed, affords **23**; ii) further condensation [7a, 7b, 13] of **21** with a second species of **20a** (or **20b**) and internal Wittig-Horner reaction gives rise to the olefin **22** with concomitant elimination of H_2S and a thiophosphonate moiety.

Pharmacological Evaluation

The dithiazoles **5**, **12**, **17a**, **17b**, **23a** and **23b** were screened against various types of fungi including *Candida albicans*, *Asperigillus fumigatus* and *Cryptococcus neoformans* by adopting food poisoning technique. Compounds **5** and **12** are moderately active against *As. fumigatus* and *Cr. neoformans* at the 455 μg/mL concentration level, while compounds **23a**, and **23b** are more active against the same fungi at the same dose level. Compounds **23a** and **5** registered 100 % spore germination inhibition in *Candida albicans*. Compounds **12** and **23b** have shown 100 % inhibition in the same fungi at 600 μg/mL. Compounds **17a** and **17b** showed only feeble activity.

Compounds **5**, **12**, **23a** and **23b** exhibited also reasonable activity against one or the other type of bacteria: *B. subtilis*, *B. cereus* and *Esch. coli*. Phosphorylated dithiazoles **23a** and **23b** showed the highest inhibitory effect against all the tested organisms.

In conclusion, compounds **23a** and **23b**, on the basis of our results, could be considered as lead molecules to be modified in order to improve the antimicrobial activity.

Experimental Section

Melting points are uncorrected. The IR spectra were recorded on a Perkin Elmer 317 Grating IR spectrophotometer, using KBr. The ^{1}H and ^{13}C NMR spectra were measured on a Joel E.C.A-500 MHz instrument using $SiMe_4$ as an internal reference. The ^{31}P NMR spectra were recorded with the same instrument, relative to external H_3PO_4 (85 %). The mass spectra were performed on a Joel JMS-A X 500 spectrometer. Solvents were dried by standard techniques. The substrate 5-phenyl-3*H*-1,2,4-dithiazole-3-thione (**1**) was prepared according to the reported method [9].

*Reaction of 1,2-dithiol **1** with vinyltriphenylphosphonium bromide (**2**)*

*Method a: In ethanol at r. t.; preparation of compounds **5** and **7***

To a stirred solution of **1** (0.8 g, 3.8 mmol) and **2** (1.55 g, 4.2 mmol) in ethanol (30 mL) a freshly prepared aqueous LiOH solution (0.5 M) (15 mL) (or NaOEt) was added and the mixture was stirred at r. t. for 2 days (TLC). The product mixture was concentrated, and then poured onto H_2O (50 mL), acidified with conc. HCl and then extracted with $CHCl_3$ (2 × 100 mL). The combined organic extracts were washed with H_2O (50 mL), dried and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (Kieselgel 60, particle size 0.2 – 0.5 mm; E. Merck, Darmstadt) using *n*-hexane/AcOEt as eluents. *n*-Hexane elution afforded colorless needles, m. p. 80 °C, identified as triphenylphosphane; and *n*-hexane/AcOEt (up to 7 : 3, v/v) yielded colorless crystals of triphenylphosphane oxide, m. p. 156 °C.

n-Hexane/AcOEt (up to 8 : 2, v/v) afforded red crystals of unchanged substrate **1**, 64 mg (8 % yield), m. p. 138 – 140 °C (from EtOH) (lit. [9]: m. p. 140 °C).

n-Hexane/AcOEt (up to 1 : 1, v/v) gave 161 mg (18 % yield) of colorless crystals of *N*-(thiophenacyl)-1,3-dithiol-2-imine (**7**), m. p. 146 – 148 °C (from CH_2Cl_2). – IR: ν = 1605 – 1612 (C=C, dithiol and aromatic), 1485 (N-C=S), 1425 (-N=C-S-) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 7.41, 7.52 (2× d, J_{HH} = 8.1 Hz, 2 × 2 H, H-Ph), 7.76, 7.82 (2× d, J = 5.8 Hz, 2 × 1 H, H-dithiol), 8.18 (m, 1 H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 118.3, 119.7 (dithiol, C-4, C-5), 126.3, 128.6, 131.2, 133.9 (C-arom.), 154.6 (C=N, exocycl.), 206.4 (C=S). – MS: *m/z* (%) = 237 (29) [M$^+$], 205 (100), 102 (77), 77 (31). – $C_{10}H_7NS_3$ (237.37): calcd. C 50.60, H 2.97, N 5.90, S 40.53; found C 50.64, H 2.93, N 5.85, S 40.57.

n-Hexane/AcOEt (up to 4 : 6, v/v) afforded 362 mg (42 % yield) of straw-yellow crystals of 2-methyl-6-phenyl-4H-1,3,5-dithiazine-4-thione (**5**), m. p. 161 – 163 °C (from acetone). – IR: ν = 1480 (N-C=S), 1424 (N=C-S) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (d, J = 7.4 Hz, 3 H, 2-Me), 4.27 (q, J = 7.4 Hz, 1 H, 2-H), 7.40, 7.53 (2× d, J = 8.2 Hz, 2 × 2 H, H-Ph), 8.16 (m, 1 H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 14.6 (2-Me), 31.6 (C-2), 125.9, 127.3, 131.6, 133.7 (C-arom.), 143.6 (C-6), 204.3 (C-4). – MS: *m/z* (%) = 239 (26) [M$^+$], 238 (44), 224 (16), 150 (100), 77 (21). – $C_{10}H_9NS_3$ (239.4): calcd. C 50.17, H 3.79, N 5.85, S 40.18; found C 50.22, H 3.76, N 5.91, S 40.12.

*Method b: In boiling chloroform; preparation of compound **9***

The above reaction of **1** and **2** was repeated under reflux for 8 h in $CHCl_3$ (or EtOH) that contained aq. LiOH (0.5 M), using the same amounts, whereby the procedure and the work-up were the same. The residue was chromatographed to give **9** along with triphenylphosphane sulfide.

*2-Phenyl-4(4H)-thioxo-1,3-thiazine (**9**)* was eluted (*n*-hexane/AcOEt 8 : 2, v/v) as colorless crystals (520 mg, 67 % yield), m. p. 123 – 125 °C (from cyclohexane). – IR: ν = 1482 (N-C=S), 1422 (N=C-S) cm^{-1}. – ^{1}H NMR ($CDCl_3$):

δ = 6.84 (d, J = 4.5 Hz, 1 H, 5-H), 7.13 (d, J = 4.5 Hz, 1 H, 6-H), 7.42, 7.55 (2× d, J = 8.2 Hz, 2 × 2 H, H-Ph), 8.18 (m, 1 H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 116.6 (C-5), 124.8 (C-6), 125.9, 127.6, 130.7, 133.2 (C-arom.), 153.1 (C-2), 198.8 (C-4). – MS: *m/z* (%) = 205 (100) [M^+], 179 (28), 135 (53), 77 (22). – $C_{10}H_7NS_2$ (205.3): calcd. C 58.5, H 3.44, N 6.82, S 31.24; found C 58.57, H 3.45, N 6.74, S 31.29.

*Reaction of **1** with allyltriphenylphosphonium bromide (**10**); preparation of compounds **12** and **13***: A solution of **1** (0.8 g, 3.8 mmol) and **10** (1.61 g, 4.2 mmol) in $CHCl_3$ (40 mL) was treated with aq. LiOH solution (0.5 M) (15 mL). The reaction mixture was heated under reflux for 5 h and worked up as described for the reaction of **1** with **2**. Column chromatography gave compounds **12** and **13**, respectively.

*2-Ethyl-6-phenyl-1,3-5-dithiazine-4(4H)-thione (**12**)* was obtained (*n*-hexane/AcOEt 5 : 5, v/v) as pale yellow crystals (422 mg, 44 % yield), m. p. 149 – 151 °C (from MeCN). – IR: ν = 1477 (N-C=S), 1425 (N=C-S) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.6 Hz, 3 H, 2-CH_2*Me*), 2.74 (q, J = 7.6 Hz, 2 H, 2-CH_2), 4.43 (t, ill-defined, 1 H, 2-H), 7.38, 7.52 (2× d, J = 6.5 Hz, 2 × 2 H, H-Ph), 8.14 (m, 1 H, H-Ph). – ^{13}C NMR ([D_6]DMSO): δ = 13.4 (2-CH_2*Me*), 23.6 (2-CH_2), 29.8 (C-2), 125.2, 126.8, 131.1, 133.6 (C-arom.), 148.3 (C-6), 209.2 (C-4). – MS: *m/z* (%) = 253 (22) [M^+], 252 (41), 223 (13), 150 (100), 77 (24). – $C_{11}H_{11}NS_3$ (253.4): calcd. C 52.14, H 4.38, N 5.53, S 37.96; found C 52.21, H 4.34, N 5.47, S 38.00.

*4-Phenyl-5-vinyl-2(2H)-thioxo-1,3-thiazole (**13**)* was obtained after chromatography (*n*-hexane/AcOEt 3 : 7, v/v) as yellow crystals (175 mg, 21 % yield), m. p. 168 – 170 °C (from acetone). – IR: ν = 3358 (NH), 1608 (C=C, exocycl.) cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 5.22 (2d, $J_{b,c}$ = 16.8, $J_{b,a}$ = 2.4 Hz, 1 H, H^b), 5.64 (2d, $J_{a,c}$ = 10.4, $J_{a,b}$ = 2.4 Hz, 1 H, H^a), 6.47 (2d, $J_{c,a}$ = 16.8, $J_{c,b}$ = 10.4 Hz, 1 H, H^c), 7.40, 7.52 (2× d, J = 6.6 Hz, 2 × 2 H, H-Ph), 8.14 (m, 1 H, H-Ph), 9.76 (s, 1 H, NH). – ^{13}C NMR ([D_6]DMSO): δ = 109.40 (5-CH=*C*H_2), 125.7 (5-CH), 124.8, 126.4, 129.8, 131.5, 133.2, (C-arom.), 141.4 (C-5), 149.8 (C-4), 194.6 (C=S). – MS: *m/z* (%) = 219 (17) [M^+], 218 (23), 198 (100), 122 (66), 77 (23). – $C_{11}H_9NS_2$ (219.3): calcd. C 60.24, H 4.14, N 6.39, S 29.24; found C 60.27, H 4.09, N 6.46, S 29.20.

No reaction was observed in a parallel experiment when the reactants (**1**+**10**) were mixed at ambient temperature, even after 48 h.

*Reaction of **1** with reactive ylides **15a** and **15b**; preparation of compounds **17a**, **17b**, **19a** and **19b***: A solution of methyltriphenylphosphonium bromide (**14a**) (2.7 g, 7.7 mmol) or ethyltriphenylphosphonium bromide (**14b**) (2.8 g, 7.7 mmol) in DMF (40 mL) was added dropwise to a slurry of a LiH dispersion (60 % in paraffin oil) (200 mg) in DMF (15 mL). The reaction mixture was stirred at r. t. until all hydrogen evolution had ceased, and **1** (0.8 g, 3.8 mmol) was introduced all at once. The reaction mixture was stirred at r. t. for further ∼ 8 h (TLC). The product mixture was concentrated to 10 mL, diluted with dist. H_2O (30 mL), acidified with conc. HCl, and then extracted with two portions (100 mL) of ethyl acetate. The AcOEt extracts were combined, back-washed with H_2O (100 mL), dried, and the solvents were evaporated to dryness. The residue was chromatographed on silica gel to afford compounds **17a** and **19a** or **17b** and **19b**.

*2-Methyl-4-phenylthiazole (**19a**)* was obtained (*n*-hexane/AcOEt 8 : 2, v/v) as yellow needles (155 mg, 23 % yield), m. p. 153 – 155 °C (MeCN). – IR: ν = 1600 – 1610 (C=C), 1422 (N=C-S) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 3 H, 2-Me), 7.11 (s, 1 H, 5-H), 7.38, 7.47 (2× d, J = 6.7 Hz, 2 × 2 H, H-Ph), 8.09 (m, 1 H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 18.2 (2-Me), 118.6 (C-5), 124.8, 126.4, 129.3, 130.7, 133.3 (C-arom.), 158.6 (C-2). – MS: *m/z* (%) = 175 (100) [M^+], 116 (48), 77 (27). – $C_{10}H_9NS$ (175.26): calcd. C 68.53, H 5.18, N 7.99, S 18.30; found C 68.58, H 5.12, N 7.92, S 18.36.

*6-Phenyl-4H-4-methylidene-1,3,5-dithiazine (**17a**)* was obtained (*n*-hexane/AcOEt 1 : 1, v/v) as orange crystals (376 mg, 48 % yield), m. p. 182 – 184 °C (EtOH). – IR: ν = 1622 (4-C=C) cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 2.72 (s, 2 H, 2-H_2), 5.74 [s, 2 H, 4-(=CH_2)], 7.44, 7.62 (2× d, J = 7.8 Hz, 2 × 2 H, H-Ph), 7.98 (m, 1 H, H-Ph). – ^{13}C NMR ([D_6]DMSO): δ = 29.6 (C-2), 109.4 [4-(=CH_2)], 124.7, 126.2, 129.5, 131.8, 133.4 (C-arom.), 141.6 (C-6), 146.6 (C-4). – MS: *m/z* (%) = 207 (13) [M^+], 189 (31), 135 (100, $C_6H_5CNS^+$), 77 (19). – $C_{10}H_9NS_2$ (207.3): calcd. C 57.93, H 4.38, N 6.76, S 30.93; found C 57.99, H 4.36, N 6.85, S 30.96.

*2-Ethyl-5-methyl-4-phenylthiazole (**19b**)* was obtained (*n*-hexane/AcOEt 8 : 2, v/v) as yellow needles (192 mg, 25 % yield), m. p. 196 – 198 °C (EtOH). – IR: ν = 1600 – 1610 (C=C), 1420 (N=C-S) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.97 (t, J = 6.8 Hz, 3 H, 2-CH_2*Me*), 1.54 (s, 3 H, 5-Me), 3.67 (q, J = 6.8 Hz, 2 H, 2-CH_2), 7.39, 7.49 (2× d, J = 8.1 Hz, 2 × 2 H, H-Ph), 8.12 (m, 1 H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 12.8 (2-CH_2*Me*), 16.4 (5-Me), 124.6, 125.3, 126.8, 129.2, 133.4, 133.8 (C-Ph, and C-5), 140.2 (C-6), 148.4 (C-2). – MS: *m/z* (%) = 203 (100) [M^+], 188 (72), 173 (76), 129 (29), 77 (24). – $C_{12}H_{13}NS$ (203.3): calcd. C 70.89, H 6.45, N 6.89, S 15.77; found C 70.83, H 6.47, N 6.96, S 15.82.

*2-Methyl-6-phenyl-4(4H)-ethylidene-1,3,5-dithiazine (**17b**)* was obtained (*n*-hexane/AcOEt 1 : 1, v/v) as orange prisms (374 mg, 42 % yield), m. p. 195 – 197 °C ($CHCl_3$). – IR: ν = 1628 (4- C=C) cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 1.37 (d, J = 7.6 Hz, 3 H, 2-Me), 1.86 (d, J = 6.6 Hz, 3 H, 4-(=CH)*Me*), 4.16 (q, J = 7.6 Hz, 1 H, 2-CH), 5.86 (q, J = 6.6 Hz, 1 H, 4-CH), 7.46, 7.67 (2× d, J = 8.1 Hz, 2 × 2 H, H-Ph), 7.96 (m, 1 H, H-Ph). – ^{13}C NMR

[D_6](DMSO): δ = 13.7, 16.6 (2× Me), 31.7 (C-2), 124.4, 125.6, 126.8, 129.3, 131.8 (C-Ph), 141.2 (C-6), 148.2 (C-4). – MS: *m/z* (%) = 235 (17) [M^+], 220 (21), 207 (37), 135 (100), 77 (22). – $C_{12}H_{13}NS_2$ (235.4): calcd. C 61.23, H 5.57, N 5.95, S 27.25; found C 61.31, H 5.63, N 6.01, S 27.31.

*Reaction of **1** with α-phosphonyl reagents **20a** and **20b**; preparation of phosphonates **22a**, **22b**, **23a** and **23b***: A solution of NaOEt prepared from Na (1.0 g, 4.2 mmol) in EtOH (15 mL) was added to a stirred solution of **20a** (or **20b**) (14 mmol) in EtOH (15 mL) at −10 °C. Stirring was continued for 20 min and a solution of **1** (0.8 g, 3.8 mmol) in EtOH (10 mL) was then added at −10 °C. After stirring for an additional hour at 0 °C and for further 6 h (TLC control) at r. t., the solution was concentrated to half of the volume *in vacuo* and then poured onto ice, extracted with $CHCl_3$, dried and evaporated. The residue was purified by column chromatography to give **22a** and **23a** (or **22b** and **23b**).

*Diethyl (6-phenyl-2-methylthio-4-thioxo-1,3,5-dithiazin-2-yl)phosphonate (**23a**)* was obtained as straw-yellow crystals (617 mg, 40 % yield), m. p. 122 – 124 °C (from cyclohexane). – IR: ν = 1487, 1422 (N-C=S) and (N=C-S), 1256 (P=O), 1083 (P-O-C) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.09, 1.14 (2dt, J_{HH} = 7.4, J_{HP} = 4.8 Hz, 2 × 3 H, 2× OCH_2*Me*), 2.31 (d, 3H, J_{HP} = 4.8 Hz, SMe), 3.85, 4.02 (2× q, J = 10.6 Hz, 2 × 2 H, 2× OCH_2), 7.47, 7.72 (2× d, J = 8.2 Hz, 2 × 2 H, H-Ph), 8.04 (m, 1 H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 13.8 (SMe), 17.4, 18.6 (2× OCH_2*Me*), 37.3 (C-2), 61.4, 62.72 (2× OCH_2), 124.2, 125.6, 128.7, 129.3, 133.1 (C-arom.), 151.3 (C-6), 204.8 (C-4). – ^{31}P NMR ($CDCl_3$): δ = 19.83. – MS: *m/z* (%) = 407 (16) [M^+], 406 (25), 359 (17), 211 (100), 196 (68), 137 (44‘, $P(O)(OEt)_2$, 135 (23). – $C_{14}H_{18}NO_3PS_4$ (407.55): calcd. C 41.26, H 4.45, N 3.44, P 7.60, S 31.47; found C 41.22, H 4.37, N 3.32, P 7.54, S 31.51.

*Diethyl 1-(4-phenyl-5-thiomethyl-1,3-thiazolyl-2-ylidene) -1-methylthio-methane-phosphonate (**22a**)* was obtained (*n*-hexane/$CHCl_3$ 1 : 1, v/v) as fine yellow needles (412 mg, 27 % yield), m. p. 142 – 144 °C (MeCN). – IR: ν = 3365 (NH), 1628 (2-C=C), 1262 (P=O), 1132 (P-O-C) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.11, 1.15 (2× dt, J_{HH} = 7.4, J_{HP} = 4.8 Hz, 2 × 3 H, 2× OCH_2*Me*), 2.16 (d, J_{HP} = 4.5 Hz, 3 H, SMe), 2.23 (s, 3 H, 5-SMe), 3.88, 4.02 (2× q, J = 10.8 Hz, 2 × 2 H, 2× OCH_2), 7.48, 7.75 (2× d, J = 8.2 Hz, 2 × 2 H, H-Ph), 8.09 (m, 1 H, H-Ph), 9.75 (s (br), 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 13.4, 15.6 (2× SCH_2Me), 18.3, 18.8 (2× OCH_2*Me*), 61.7, 62.7 (2× OCH_2), 96.8 (d, J = 184.7 Hz, =C-P), 124.2, 124.8, 126.4, 129.1, 132.6 (C-Ph), 138.8 (C-5), 141.6 (C-4), 151.3 (2-C=C). – ^{31}P NMR ($CDCl_3$): δ = 18.93. – MS: *m/z* (%) = 403 (21) [M^+], 402 (30), 355 (17), 308 (46), 228 (100), 137 (36), 131 (68). – $C_{16}H_{22}NO_3PS_3$ (403.5): calcd. C 47.62, H 5.49, N 3.47, P 7.68, S 23.84; found C 47.68, H 5.46, N 3.55, P 7.73, S 23.81.

*Diethyl (6-phenyl-2-ethylthio-4-thioxo-1,3,5-dithiazin-2-yl)phosphonate (**23b**)* was obtained (*n*-hexane/$CHCl_3$ 2 : 8, v/v) as straw-yellow crystals (687 mg, 43 % yield), m. p. 133 – 135 °C (from cyclohexane). – IR: ν = 1484, 1428 (C=S) and (N=C), 1248 (P=O), 1100 (P-O-C) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.98, 1.12 (3× t (m), 3 x 3 H, 2× OCH_2*Me* and SCH_2*Me*), 3.73 (q, J_{HP} = 4.6 Hz, 2 H, SCH_2), 3.98, 4.07 (2q, J = 10.8 Hz, 2× OCH_2), 7.47, 7.76 (2× d, J = 8.3 Hz, 2 × 2 H, H-Ph), 8.04 (m, 1H, H-Ph). – ^{13}C NMR ($CDCl_3$): δ = 12.6 (S CH_2CH_3), 18.63 (O CH_2CH_3), 35.2 (SCH_2), 38.8 (C-2), 61.73 (OCH_2), 124.6, 125.7, 126.8, 129.2, 131.6 (C-Ph), 150.6 (C-6), 209.3 (C=S). – ^{31}P NMR ($CDCl_3$): δ = 18.67. – MS: *m/z* (%) = 421 (14) [M^+], 420 (23), 359 (28), 211 (100), 196 (72), 137 (40), 135 (23). – $C_{15}H_{20}NO_3PS_4$), (421.6): calcd. C 42.74, H 4.78, N 3.32, P 7.35, S 30.42; found C 42.62, H 4.8, N 3,45, P 7.41, S 30.25.

*Diethyl 1-(4-phenyl-5-ethylthio-1,3-thiazolyl-2-ylidene)-1-ethylthio-methane- phosphonate (**22b**)* was obtained (*n*-hexane/$CHCl_3$ 3 : 8, v/v) as yellow needles (376 mg, 23 % yield), m. p. 148 – 150 °C ($CHCl_3$/diethylether 1 : 1, v/v). – IR: ν = 3355 (NH) 1618 (C=C), 1258 (P=O), 1110 (P-O-C) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.96 – 1.18 (4× t (m), 4 × 3H, 2SMe and 2OCCH_3), 3.88, 4.23 (4q (m), 4×2 H, 2× SCH_2 and 2× OCH_2), 7.48, 7.76 (2d, J = 8.2 Hz, 2 × 2 H, H-Ph), 8.03 (m, 1 H, H-Ph), 9.62 (s (br), 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 13.7, 14.6, 15.9 (2× SCH_2*Me* and 2× OCH_2*Me*), 28.8, 29.4 (2× SCH_2), 60.6, 61.4 (2× OCH_2), 101.3 (d, J = 174.6 Hz, =C-P), 124.6, 125.3, 127.4, 129.2, 133.3 (C-Ph), 138.4 (C-5), 148.5 (C-4), 153.2 (2-C=C). – ^{31}P NMR ($CDCl_3$): δ = 19.63. – MS: *m/z* (%) = 431 (18) [M^+], 430 (26), 369 (16), 308 (44), 242 (100), 145 (77), 137 (28). – $C_{18}H_{26}NO_3PS_3$ (431.6): calcd. C 50.09, H 6.07, N 3.25, P 7.18, S 22.29; found C 50.15, H 6.11, N 3.18, P 7.22, S 22.23.

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