Cyclocondensations of Substituted Thiosemicarbazides with 2-Bromo-1,2-diphenylethan-1-one

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The cyclocondensation of 4-methylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one in ethanol afforded isomeric 2-methylamino-5,6-diphenyl-6*H*-3,4-thiadiazine and 2-hydrazono-3-methyl-4,5-diphenyl-2,3-dihydro-1,3-thiazole. A pyrazole was obtained by cyclocondensation and subsequent desulfurization of the thiadiazine when the reaction was carried out in concentrated hydrochloric acid. A chemical proof of the structures has been provided. The product distribution of the cyclizations strongly depends on the substitution pattern of the starting materials, and the cyclizations of methylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one behaved considerably different from that of the analogous reactions of α-bromoacetophenone.

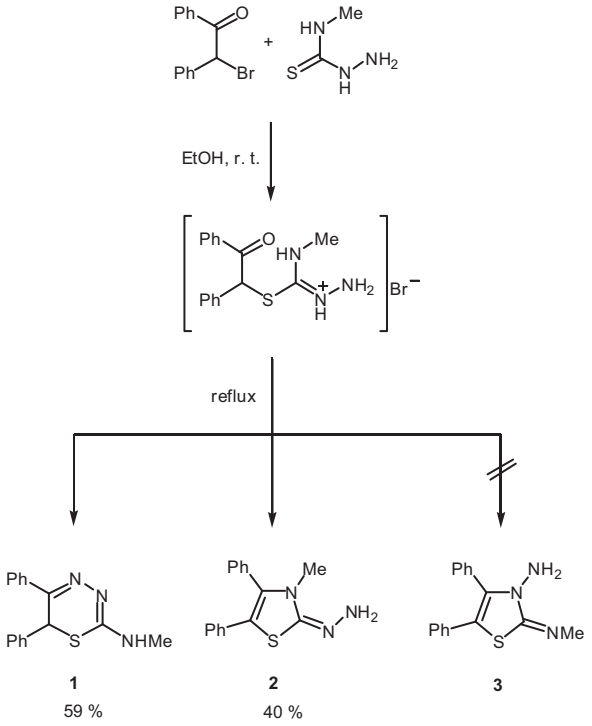
Key words: Cyclizations, Heterocycles, Thiadiazines, Regioselectivity, Thiazoles, Rearrangement

Introduction

1,3,4-Thiadiazines are of considerable biochemical and pharmacological relevance. Many 1,3,4-thiadiazine-2-yl-amine derivatives are important matrix metalloproteinase inhibitors [1, 2]. 2-Alkylimino- and 2-alkyamino-1,3,4-thiadiazines are used as cardiotonic and spasmolytic agents [3 – 8]. 1,3,4-Thiadiazin-2-ones are cardiotonica with calcium sensitizing activity [9 – 11]. 3-Phenylazo-1*H*-4,2,1-thiadiazine is an agent for treating deficient bone growth [12]. 3-Nitrobenzyl-5-aryl-1,3,4-thiadiazin-2-ones and 1,3,4-thiadiazin-2-ones are phosphodiesterase IV inhibitors and can be used for the treatment of tumors and AIDS [13, 14]. 2-Nitrosimino-3,6-dihydro-2*H*-1,3,4-thiadiazines [15], and *N*-morpholinyl-, *N*-thiomorpholinyl- or *N*-piperidinyl-1,3,4-thiadiazines [16] exhibit antithrombotic activities.

Results and Discussion

In continuation of our studies related to the synthesis of 1,3,4-thiadiazines [17 – 27], we have studied the cyclocondensation of 4-methyl- and 4-phenylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one. In principle, the cyclization of 4-alkyl-(aryl)-thiosemicarbazides with α-haloketones can result in the formation of three isomeric products, namely, 2-alkyl(aryl)amino-1,3,4-thiadiazines, 2-hydrazono-3-alkyl(aryl)-2,3-dihydro-1,3-thiazoles and 2-alkyl(aryl)imino-2,3- dihydro-1,3- thiazol-3-amines. The reaction of 4-methylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one in ethanol afforded, *via* unstable, open-chained *S*-(1,2-diphenyl-2-oxoethyl)-isothiosemicarbazide hydrobromide, two isomeric products, *i. e.* 2-methylamino-5,6-diphenyl-6*H*-1,3,4-thiadiazine (**1**) and 2-hydrazono-3-methyl-4,5-diphenyl-2,3-dihydro-1,3-thiazole (**2**) in 59 % and

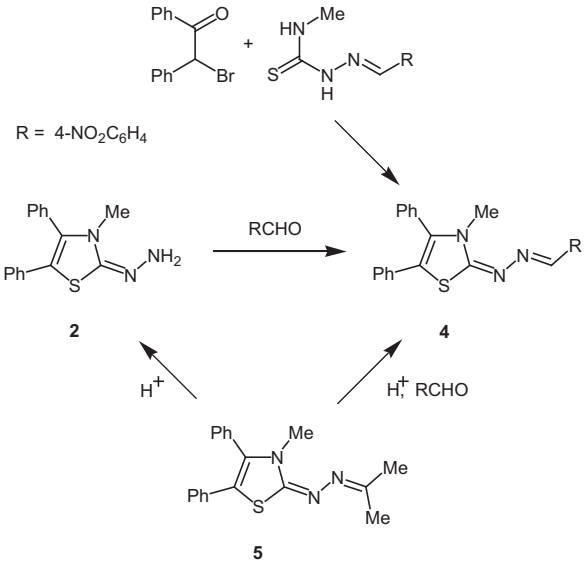


Scheme 1. Synthesis of **1** and **2**.

40 % isolated yields, respectively (Scheme 1). The formation of isomer **3** was not observed.

The combined yield of **1** and **2** is nearly quantitative. Product **1** resides in its 6*H*-form as indicated by ^{1}H NMR. It is important to note that the cyclization of 4-methylthiosemicarbazide with α-bromoacetophenone afforded the corresponding thiadiazine along with a small amount (8.5 %) of the hydrazono isomer [28 – 30]. In the cyclization reported herein, where 2-bromo-1,2-diphenyl-ethan-1-one instead of α-bromoacetophenone was employed under otherwise identical conditions, a different result was obtained as the hydrazono isomer **2** was isolated in a considerable amount (40 %). This result suggests that the structure of the electrophile has a strong influence on the product distribution.

The structure of **2** was unambigously confirmed by reaction with 4-nitrobenzaldehyde to give 2-(4-nitrobenzylidenhydrazono)-3-methyl-4,5-diphenyl-2,3-dihydro-1,3-thiazole (**4**) (Scheme 2). This compound proved to be identical with the product obtained from the reaction of 4-nitro-benzaldehyde-4-methylthiosemicarbazone with 2-bromo-1,2-di-

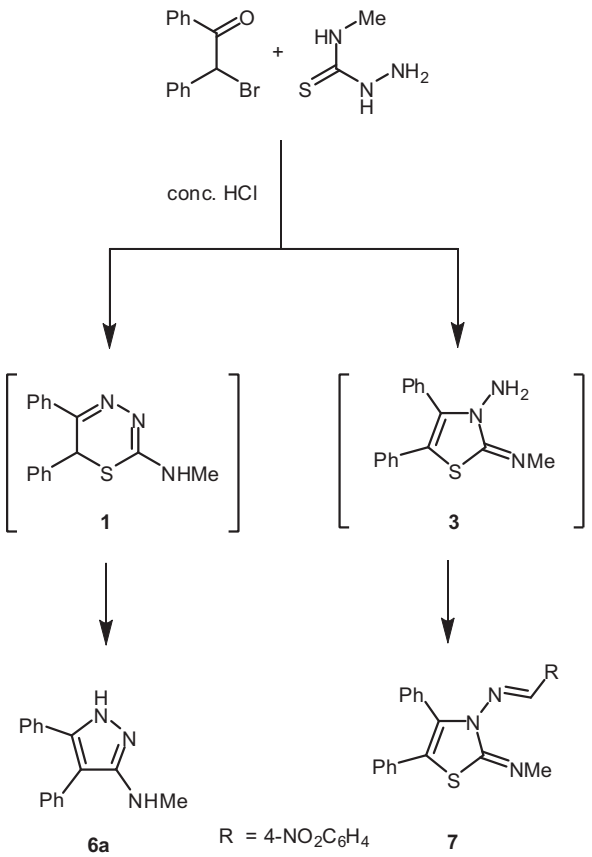


Scheme 2. Chemical proof of the structure of **2**.

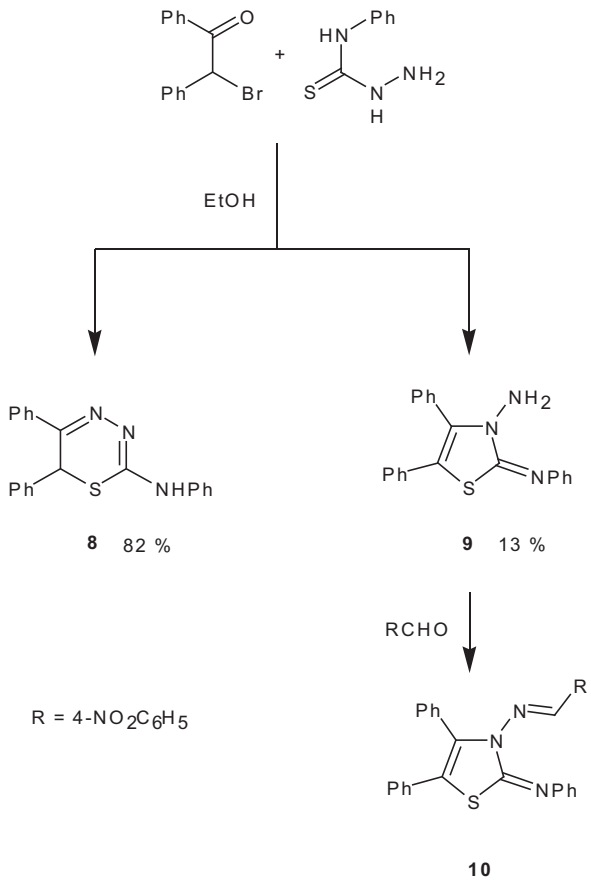
phenylethan-1-one. Besides the direct condensation, product **2** is also formed by acidic steam distillation of 2-isopropylidenehydrazono-3-methyl-4,5-diphenyl-2,3-dihydro-1,3-thiazol (**5**). When the reaction of 4-methylthiosemicarbazone with 2-bromo-1,2-diphenylethan-1-one was carried out in a diluted solution of HCl in ethanol, 1,3,4-thiadiazine **1** was formed as the major product. In contrast to the analogous reaction of α-bromoacetophenone [30], the hydrazono isomer **2** is still formed in 10 % yield. The formation of isomer **3** could not be detected.

The cyclocondensation of 4-methylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one, carried out in concentrated hydrochloric acid, required a long reaction time at elevated temperature. The main product proved to be 1,3,4-thiadiazine **1** which, however, was unstable under these conditions and underwent desulfurization to give pyrazol **6a** (Scheme 3). Heating of the crude product with 4-nitrobenzaldehyde allowed for the isolation of a small amount of the orange compound **7**, which is an isomer of **4** and represents a derivative of 3-amino-4,5-diphenyl-2,3-dihydro-1,3-thiazole **3**.

The cyclocondensation of 4-phenylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one afforded 2-phenylamino-5,6-diphenyl-6*H*-1,3,4-thiadiazine hydrobromide (**8**) which crystallized as the major product (Scheme 4). The solution contains 2- phenylimino-



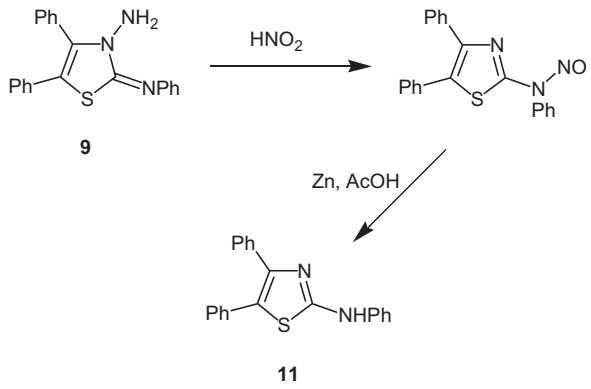
Scheme 3. Cyclocondensation in concentrated hydrochloric acid.



Scheme 4. Cyclocondensation of 4-phenylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one.

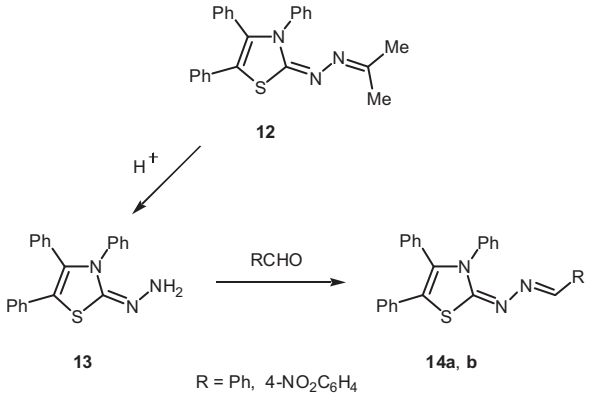
4,5- diphenyl- 2,3- dihydro- 1,3- thiazol- 3- amine (**9**) which was reacted with 4-nitrobenzaldehyde to give 2-phenylimino-3-(4-nitrobenzylidenamino)-2,3-dihydro-1,3-thiazole (**10**).

The reaction of the 2-phenylimide **9** with nitrous acid resulted in deamination and nitrosylation (Scheme 5). The attempt to transform this product into the corresponding hydrazine derivative by treatment with zinc in glacial acetic acid failed and resulted in the cleavage of the nitrosyl group to give known 2-phenylamino-4,5-diphenyl-1,3-thiazole (**11**) [29].

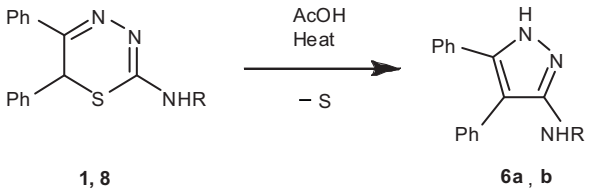


Scheme 5. Nitrosylation and reduction of **9**.

The third isomer of this series, 2-hydrazono-3,4,5-triphenyl-2,3-dihydro-1,3-thiazole (**13**), is not available by direct cyclocondensation. However, it can be obtained in good yield *via* the 2-isopropylidene-hydrazono derivative **12** (Scheme 6). Compound **12** is a weak base which is stable in a 2 M aqueous solution of HCl. The addition of conc. hydrochloric acid resulted in the formation of a soluble hydrobromide which underwent hydrolysis to give hydrazono derivative **13**. The acetone formed has to be removed from the equilibrium by steam distillation. The reaction of **13** with benzaldehyde or 4-nitrobenzaldehyde afforded



Scheme 6. Transformation of **12** into **13** and **14**.



Scheme 7. Desulfurization of **1** and **8**.

Table 1. Kinetic parameters for the desulfurization of **1** and **8** to pyrazoles **6a**, **b** in glacial acetic acid.

		R	E_A (kJ mol^{-1}) ln k_0	$k_{80\,°C}$ (s^{-1})	$t_{1/2}$ (min)
1	**6a**	Me	95.2 24.3	$2.95 \cdot 10^{-4}$	39.1
8	**6b**	Ph	69.5 18.1	$3.81 \cdot 10^{-3}$	3

the corresponding benzylidene-hydrazono derivatives **14a**, **b**.

The reaction of 4-phenylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one in conc. hydrochloric acid-EtOH (1 : 1) only proceeded at elevated temperature and afforded 3-phenylamino-4,5-diphenylpyrazole (**6b**) by desulfurization of 1,3,4-thiadiazine **8**. The phenylimide isomer was only formed in 0.6% yield. While the reaction of 4-phenylthiosemicarbazide with 2-bromo-1,2-diphenylethan-1-one in ethanol proceeds similarly to the analogous reaction of bromoacetophenone [31], the reaction proceeds differently in hydrochloric acid. This can be explained by the strong influence of the substitution pattern of the thiadiazine on the stability towards acid. To shed further light on this observation, we compared the rate of desulfurization of 1,3,4-thiadiazines **1** and **8** (to give pyrazoles **6a**, **b**) by heating in glacial acetic acid (Scheme 7, Table 1). The kinetic data reveal that 2-phenylamino-5,6-diphenylthiadiazine **8** is much more prone towards desulfurization than the corresponding 2-methylamino derivative **1**.

Experimental Section

*2-Methylamino-5,6-diphenyl-6H-1,3,4-thiadiazine (**1**)*

Method A: 4-Methylthiosemicarbazide (2.1 g, 20 mmol) was dissolved in hot EtOH (20 mL) and conc. HCl (5 mL). 2-Bromo-1,2-diphenylethan-1-one was added to this mixture in portions, and the mixture was refluxed for 5 min. Subsequently, the mixture was diluted with H_2O (500 mL) and filtered after addition of active carbon. The free base was obtained from the filtrate by addition of a conc. solution of NH_3. The crude product contains **2**. Fractional crystallization from benzene yielded **1** (3.4 g, 60.5%); colorless lamella; m. p. 125 °C and **2** (0.56 g, 10%).

Method B: A mixture of thiosemicarbazide (2.1 g 20 mmol) and 2-bromo-1,2-diphenylethan-1-one in EtOH (20 mL) was stirred with cooling in cold H_2O for 1 h. A precipitate formed which was separated, washed with EtOH – EtO_2 (1 : 1) and dissolved in EtOH (40 mL) and conc. HCl (5 mL). The mixture was refluxed for 10 min. Subsequently, the solution was neutralized by a solution of NH_3 and cautiously diluted with H_2O (100 mL). The colorless crystals formed were filtered off. Yield: 5.0 g (89%); colorless lamella (benzene); m. p. 125 °C. Addition of NH_3 to the filtrate gave **2** (0.5 g, 9%).

Method C: From the filtrate of **2** (*Method A*) by addition of a solution of NH_3 and H_2O. Yield: 3.4 g (61%); colorless lamella (benzene); m. p. 125 °C. – IR (KBr, cm^{-1}): $\tilde{\nu} = 572$ (m), 694 (s), 728 (m), 764 (m), 973 (m), 1060 (m), 1169 (m), 1262 (m), 1354 (m), 1400 (s), 1441 (m), 1514 (s), 1538 (s), 1639 (m), 2941 (m), 3031 (m), 3262 (m), 3416 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.98$ (s, 3H, Me), 5.30 (s, 1H, 6-CH), 5.70 (s, br, 1H, NH), 7.22–7.84 (m, 10H, ArH). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 39.26$ (Me), 126.48, 127.30, 128.32, 128.61, 128.79, 128.96, 129.57, 129.83, 135.83, 136.15, 147.26. – MS (EI, 70 eV): $m/z(\%) = 281(4)$ $[M]^+$, 252 (52), 207 (3), 154 (4), 104 (2), 82 (11), 28 (100). – Anal. for $C_{16}H_{15}N_3S$ (281.38): calcd. C 68.30, H 5.37, N 14.93; found C 68.31, H 5.39, N, 14.95.

*3-Methyl-4,5-diphenyl-thiazolone-(2)-hydrazone (**2**)*

Hydrobromide: 4-Methylthiosemicarbazide (2.1 g, 20 mmol) and 2-bromo-1,2-diphenylethan-1-one (5.5 g, 20 mmol) in EtOH (20 mL) was stirred for 15 min at 20 °C, and the mixture was refluxed for 5 min. After cooling, the crystalline precipitate was filtered off. Yield: 2.9 g **2**·HBr (40%); colorless needles (EtOH); m. p. 180 °C. The work

up of the filtrate followed the procedure as given for **1**. – IR (KBr, cm^{-1}): $\tilde{\nu} = 507$ (w), 697 (m), 762 (m), 782 (m), 938 (m), 1084 (m), 1100 (w), 1356 (s), 1420 (m), 1443 (m), 1493 (m),1565 (s), 1642 (s), 3058 (m), 3173 (m), 3299 (s), 3427 (m). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 3.12$ (s, 3H, Me) 4.52 (s, br, 2H, NH_2) 6.99–7.54 (m, 10H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 30.84$ (C, Me), 108.74 (C-5), 126.86 (CH, Ar), 127.70 (CH, Ar), 128.00 (CH, Ar), 128.78 (CH, Ar), 128.90 (CH, Ar), 129.13 (CH, Ar), 129.39 (Ar), 130.58 (Ar), 131.42 (C-4), 136.47 (C-2). – MS (EI, 70 eV): $m/z(\%) = 281$ (100) $[M]^+$, 266 (8), 225 (4), 178 (16), 118 (7), 103 (8), 77 (8), 52 (4), 28 (29). – Anal. for $C_{16}H_{16}N_3SBr$ (362.29): calcd. C 53.04, H 4.45 N 11.60; found C 53.24, H 4.78 N, 11.20.

Free base (Method A): The free base of **2** was obtained quantitatively from a hot EtOH solution of the hydrobromide by addition of conc. NH_3. Yield: 3.32 g (100 %); yellow needles (EtOH); m. p. 178 °C.

Method B: **5** (3.21 g, 10 mmol) in EtOH (30 mL) and 2 M HCl (5 mL) was subjected to steam distillation for 30 min. The distillation residue was filtered to remove impurities. NH_3 solution was added to the filtrate and a precipitate formed. Yield: 2.5 g (89 %).

Method C: From the mother liquor of **1** (*Method A*), yield: 0.56 g (10 %). – IR (KBr, cm^{-1}): $\tilde{\nu} = 508$ (w), 697 (m), 725 (m), 761 (m), 938 (w), 1083 (m), 1099 (m), 1356 (s), 1420 (m), 1443 (m), 1493 (m), 1565 (s), 1590 (s), 1642 (s), 3173 (w), 3299 (m), 3427 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.08$ (s, 3H, Me) 4.40 (s, br, 2H, NH_2) 6.97–7.44 (m, 10H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 32.14$ (C, Me), 108.74 (C-5), 126.06 (CH, Ar), 126.79 (CH, Ar), 128.29 (CH, Ar), 129.08 (CH, Ar), 129.28 (CH, Ar), 130.16 (CH, Ar), 130.72 (Ar), 132.70 (Ar), 135.79 (C-4), 156.30 (C-2). – MS (EI, 70 eV): $m/z(\%) = 281$ (100) $[M]^+$, 266 (8), 225 (4), 178 (16), 118 (7), 103 (8), 77 (8), 52 (4), 28 (29). – Anal. for $C_{16}H_{15}N_3S_1$ (281.38): calcd. C 68.30, H 5.37, N 14.93; found C 68.32, H 5.40, N 14.95.

*4-Nitrobenzaldehyde-[(3-methyl-4,5-diphenyl-1,3-thiazolon-(2)]-azine (**4**)*

Method A: A mixture of **2** (2.81 g, 10 mmol) and 4-nitrobenzaldehyde (1.51 g, 10 mmol) in EtOH (30 mL) was refluxed briefly. Yield: 4.06 g (98 %); red needles (ethyl acetate); m. p. 198 °C.

Method B: A mixture of 4-nitrobenzaldehyde-4-methylthiosemicarbazone (2.38 g, 10 mmol) and 2-bromo-1,2-diphenylethan-1-one (2.75 g, 10 mmol) in EtOH (100 mL) was refluxed for 2 h. After cooling, the mixture was neutralized with NH_3. Yield: 3.52 g, 85 %); red needles (ethyl acetate); m. p. 198 °C.

Method C: A mixture of **5** (3.21 g, 10 mmol) and 4-nitrobenzaldehyde (1.51 g, 10 mmol) in EtOH (100 mL) and HCl (1 mL) was refluxed 2 h. Yield: 3.23 g, (78 %); red needles (ethyl acetate); m. p. 198 °C. – IR (KBr, cm^{-1}): $\tilde{\nu} = 694$ (m), 841 (m), 924 (m), 1018 (m), 1065 (s), 1106 (m), 1334 (s), 1420 (m), 1507 (s), 1588 (s). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 3.41$ (s, 3H, Me), 7.04–8.30 (m, 14H, ArH), 8.45 (s, 1H, CH). – MS (EI, 70 eV): $m/z(\%) = 415$ (2) $[M]^+$, 226 (2), 178 (2), 148 (2), 122 (3), 102 (4), 56 (3), 43 (9), 32 (32), 28 (100). – Anal. for $C_{23}H_{18}N_4O_2S$ (414.48): calcd. C 66.65, H 4.38, N 13.52; found C 66.38, H 4.40, N 13.53.

*Acetone-[3-methyl-4,5-diphenyl-thiazolon-(2)]-azine (**5**)*

A mixture of acetone-4-methylthiosemicarbazone (2.9 g, 20 mmol) and 2-bromo-1,2-diphenylethan-1-one (5.5 g, 20 mmol) in acetone (20 mL) was refluxed for 2 h. After cooling, the solution was neutralized with NH_3. Yield: 5.6 g (87 %); yellow lamella (EtOH); m. p. 126 °C. – IR (KBr, cm^{-1}): $\tilde{\nu} = 701$ (m), 744 (m), 792 (m), 1065 (w), 1251 (w), 1345 (m), 1357 (m), 1420 (m), 1494 (w), 1557 (s), 1625 (s), 2910 (w), 3024 (w), 3432 (w). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.08$ (s, 3H, Me) 2.10 (s, 3H, Me) 3.19 (s, 3H, Me) 6.99–7.44 (m, 10H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 17.90$ (Me), 24.93 (Me), 32.62 (Me, N-3, Hetar), 112.03 (C-5), 126.53 (CH, ArH), 127.07 (CH, ArH), 128.34 (CH, ArH), 129.09 (CH, Ar), 129.38 (CH, Ar), 130.31 (CH, ArH), 130.37 (Ar), 132.18 (Ar), 135.17 (N=C), 157.55 (C-5), 163.62 (C-2). – MS (EI, 70 eV): $m/z(\%) = 321$ (100) $[M]^+$, 265 (17), 250 (6), 225 (9), 178 (17), 118 (28), 77 (10), 36 (24), 28 (16). – Anal. for $C_{19}H_{19}N_3S$ (321.44): calcd. C 70.99, H 5.96, N 13.07: found C 70.91, H 5.92, N 13.08.

*3-Methylamino-4,5-diphenyl-pyrazole (**6a**)*

Method A: **1** (2.81 g, 10 mmol) in glacial acetic acid (20 mL) was refluxed for 30 min. After cooling, the solution was filtered to remove sulfur. Concentrated hydrochloric acid (1 mL) was added to the filtrate. The solution was diluted with H_2O (200 mL). After addition of active carbon, the mixture was heated, and the hot solution was filtered. On basification with NH_3, a precipitate was obtained. Yield: 2.3 g (92.5 %); colorless lamella (EtOH); m. p. 176 °C.

Method B: A mixture of 4-methylthiosemicarbazide (2.1 g, 20 mmol) in conc. hydrochloric acid (15 mL) and EtOH 10 mL) was heated under reflux, and 2-bromo-1,2-diphenylethan-1-one (2.75 g, 10 mmol) was added. The solution was refluxed for 2 h and then diluted with H_2O (200 mL). Active carbon was added to the solution, the latter was heated briefly, and the hot solution was filtered. The mixture was neutralized by addition of a aqueous NH_3 solution. A crystalline precipitate was separated. Yield: 3.2 g (64 %). The mother solution was worked up accordingly to give **7** (0.37 g, 4.5 %; m. p. 173 °C. – IR (KBr, cm^{-1}): $\tilde{\nu} = 698$

(s), 735 (m), 771 (s), 1413 (w), 1441 (w), 1488 (m), 1532 (s), 1601 (m), 2952 (m), 3054 (m), 3244 (s), 3404 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.73$ (s, 3H, Me), 7.16–7.33 (m, 10H, ArH), 12.01 (s, br, 1H, NH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 30.59$ (Me), 125.66, 127.20, 127.52, 128.29, 128.43, 129.27, 133.38. – MS (EI, 70 eV): $m/z(\%) = 249$ (42) $[M]^+$, 248 (13) 173 (4), 104 (16), 77 (3), 44 (18), 32 (19), 28 (100). – Anal. for $C_{16}H_{15}N_3$ (249.31): calcd. C 77.08, H 6.06, N 16.86; found C 77.09, H 6.08, N, 16.91.

*3-Anilino-4,5-diphenyl-pyrazole (**6b**)*

Method A: A mixture of **8** (3.43 g, 10 mmol) with glacial acetic acid (50 mL) was refluxed for 10 min. The solution was filtered and diluted with H_2O (200 mL). The precipitate was filtered rapidly using vacuum. Yield: 3.08 g (99 %); colorless needles (benzene); m. p. 182 °C.

Method B: 4-Phenylthiosemicarbazide (1.67 g, 10 mmol) in EtOH (20 mL) and conc. HCl (20 mL) was heated under reflux, and 2-bromo-1,2-diphenylethan-1-one (2.75 g, 10 mmol) was added. The solution was refluxed for 1 h, and the hot solution was filtered. The mixture was allowed to settle at −10 °C (refrigerator). The resultant precipitate was suspended in EtOH (10 mL), an aqueous NH_3 solution was added, and the solution was diluted with H_2O (100 mL). Yield: 1.7 g (55 %), colorless needles (benzene); m. p. 182 °C. The mother solution was worked up accordingly to give **10**. – IR (KBr, cm^{-1}): $\tilde{\nu} = 696$ (s), 749 (s), 769 (m), 1016 (w), 1240 (m), 1312 (m), 1442 (m),1463 (m), 1497 (s), 1537 (s), 1572 (m), 1602 (s), 3031 (m), 3056 (m), 3189 (m), 3426 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.88$ (s, br, 1H, NH), 6.87 (s, br, 1H, NH) 7.30–7.42 (m, 15H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 114.47$, 117.68, 126.32, 127.31, 127.81, 128.35, 128.48, 129.59, 132.50. MS (EI, 70 eV): $m/z(\%) = 311$, (100) $[M]^+$, 218 (5), 207 (2), 178 (4), 155 (2), 104 (3), 77 (7), 28 (16). – Anal. for $C_{21}H_{17}N_3$ (311.38): calcd. C 81.00, H 5.50, N 13.49; found C 81.04, H 5.53, N 13.51.

*2-Anilino-5,6-diphenyl-1,3,4-thiadiazine (**8**)*

Hydrobromide: A solution of 4-phenylthiosemicarbazide (13.75 g, 50 mmol) and 2-bromo-1,2-diphenylethan-1-one (13.75 g, 50 mmol) in EtOH (70 mL) was stirred for 20 min with cooling by cold H_2O. The product was isolated by cooling of the mixture and filtration of the precipitate. Yield: 17.4 g (82 %); yellow prisms; m. p. 164 °C. Partial desulfurization of **8**·HBr occured during the recrystallization. – IR (KBr, cm^{-1}): 574 (w), 637 (w), 693 (m), 763 (m), 1225 (w), 1329 (m), 1383 (m), 1449 (m), 1494 (s), 1538 (s), 1571 (s), 1602 (s), 2774 (m), 2912 (m), 2979 8m), 3161 (m), 3410 (m). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 5.35$ (s, 1H, 6-CH) 6.95–7.72 (m, 15H, ArH) 8.72 (s, br, 2H, NH_2). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 115.43$, 116.62, 126.59, 126.69, 127.47, 127.62, 128.15, 128.48, 128.67, 129.68, 129.71, 131.14, 131.96, 144.35, 146.49. – MS (EI, 70 eV): $m/z(\%) = 343$ (13) $[M]^+$, 311 (100), 310 (25), 256 (3), 192 (6), 179 (9), 178 (10), 160 8(5), 105 (6), 82 (20), 80 (21), 77 (12), 65 (19), 32 (14), 28 (49). – Anal. for $C_{21}H_{18}BrN_3S$ (424.36): calcd. C 59.44, H 4.28 N 9.40; found C 59.54, H 4.31, N 9.92.

Free base: The hydrobromide was dissolved in EtOH and an aqueous NH_3 solution was carefully added. Purification of **8** (4.2 g, 10 mmol) was performed by mild heating in pyridine and addition of EtOH to give a precipitate. Yield: 2.74 g (80 %); colorless prisms (pyridine- EtOH); m. p. 207 °C. – IR (KBr, cm^{-1}): $\tilde{\nu} = 563$ (m), 637 (m), 694 (s), 720 (m), 767 (s), 852 (m), 914 (m), 1005 (m), 1074 (w), 1142 (m), 1176 (m), 1205 (m), 1281 (m), 1310 (m), 1447 (m), 1495 (s), 1578 (s), 2914 (s), 3064 (m), 3179 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.30$ (s, 1H, 6-CH) 6.99–7.76 (m, 15H, ArH) 8.70 (s, br, 2H, NH_2). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 120.54$, 122.53, 123.78, 126.01, 126.69, 127.26, 127.84, 128.06, 128.17, 128.52, 128.76, 129.46, 135.54, 137.64, 149.51. – MS (EI, 70 eV): $m/z(\%) = 343$ (47) $[M]^+$, 311 (3), 207 (4), 179 (31), 178 (22), 151 (4), 91 84), 77 (10), 43 (7), 32 (19), 28 (100). – Anal. for $C_{21}H_{17}N_3S$ (343.45): calcd. C 73.44, H 4.99, N 12.23; found C 73.50, H 5.02, N 12.35.

*2-Phenylimino-3-amino-4,5-diphenyl-2,3-dihydro-1,3-thiazole (**9**)*

The filtrate of **8** was neutralized with NH_3 and a precipitate was formed. Yield: 2.0 g (13 %); yellow needles (EtOH); m. p. 162 °C. – IR (KBr, cm^{-1}): $\tilde{\nu} = 694$ (s), 725 (w), 765 (m), 913 (m), 1203 (w), 1291 (w), 1446 (m), 1492 (m), 1517 (w), 1576 (s), 2919 (w), 3059 (w), 3433 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.56$ (s, br, 2H, NH_2) 6.99–7.76 (m, 15H, ArH). – ^{13}C NMR (50 MHz, [D$_6$]DMSO): $\delta = 105.66$ (C-5), 120.96 (CH, Ar), 122.59 (CH, Ar), 126.78 (CH, Ar), 127.50 (CH, Ar), 128.12 (CH, Ar), 128.42 (CH, Ar), 128.68 (CH, Ar), 129.35 (CH, Ar), 130.45 (Ar), 130.61 (Ar, CH), 131.95 (Ar), 136.18 (Ar), 150.56 (C-4), 156.07 (C-2). – MS (EI, 70 eV): $m/z(\%) = 343$ (100) $[M]^+$, 328 (40), 327 (11), 251 (11), 223 (9), 211 (4), 210 (21), 179 (16) 178 (30), 165 (24), 121 (15), 77 (33), 28 (20). – Anal. for $C_{21}H_{17}N_3S$ (343.45): calcd. C 73.44, H 4.99, N 12.23; found C 73.30, H 5.01, N 12.33.

*3-[(4-Nitrobenzylideneamino)-4,5-diphenyl-1,3-thiazolon-(2)]phenylimide (**10**)*

Method A: A mixture of **9** (343 mg, 1 mmol) and 4-nitrobenzaldehyde (151 mg, 1 mmol) in EtOH (10 mL) was refluxed for 15 min. Yield: 460 mg (97 %); orange needles (ethyl acetate); m. p. 193 °C.

Method B: The mother liquor of the recrystallization of **6b** (*Method B*) and 4-nitrobenzaldehyde (10 mg, 0.066 mmol) were refluxed briefly to give a precipitate. Yield: 28.6 mg (0.6 %). – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 509 (w), 568 (w), 694 (m), 752 (m), 753 (m), 838 (m), 1108 (w), 1188 (m), 1267 (m), 1341 (s), 1446 (w), 1493 (m), 1516 (s), 1582 (s), 1606 (s), 1630 (m), 3435 (m). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.15 – 8.27 (m, 19H, ArH), 8.87 (s, 1H CH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 123.63 (CH, Ar), 125.5 (CH, Ar), 126.0 (CH, Ar), 128.02 (CH, Ar), 128.37, 138.86, 140.07, 140.45, 147.65 (C-4), 176.50 (C-2). – MS (EI, 70 eV): m/z(%) = 476 (14) $[M]^+$, 328 (100), 300 (35), 207 (19), 165 (42), 150 (56), 93 (62), 51 (20), 28 (28). – Anal. for $C_{28}H_{20}N_4O_2S$ (476.56): calcd. C 70.57, H 4.23, N 11.76; found C 70.58, H 4.25, N 11.81.

*Acetone-[3,4,5-triphenyl-thiazolon-(2)]-azine (**12**)*

A mixture of acetone-4-methylthiosemicarbazone (20.7 g, 100 mmol) and 2-bromo-1,2-diphenylethan-1-one (27.5 g, 10 mmol) in acetone (100 mL) was refluxed for 2 h. A precipitate formed. Yield: 35.3 g (92 %); grey bright needles (ethyl acetate); m. p. 205 °C. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 591 (w), 694 (s), 734 (m), 764 (m), 801 (w), 817 (w), 1028 (w), 1078 (m), 1261 (m), 1344 (s), 1443 (m), 1492 (s), 1559 (s), 1594 (s), 1628 (s), 3053 (w). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (s, 3H, Me), 2.02 (s, 3H, Me), 7.03 – 7.26 (m, 15H, ArH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 17.50 (Me), 23.70 (Me), 113.0 (C-5), 126.51 (CH, Ar), 126.94 (CH, Ar), 127.26 (CH, Ar), 127.77 (CH, Ar), 127.91 (CH, Ar), 128.11 (CH, Ar), 128.49 (CH, Ar), 130.23 (CH, Ar), 131.92 (Ar), 135.12 (Ar), 137.47 (C-4), 158.27 (N=C), 163.82 (C-2). – MS (EI, 70 eV): m/z(%) = 383 (100) $[M]^+$, 328 (7), 327 (20), 326 (6), 210 (12), 180 (30), 178 (12), 165 (12), 77 (20), 44 (6), 28 (22). – Anal. for $C_{24}H_{21}N_3S$ (383.51): calcd. C 75.1, H 5.52 N 10.96; found C 75.20, H, 5.61, N 10.91.

*3,4,5-Triphenyl-thiazolone-(2)-hydrazone (**13**)*

Compound **12** (11.4 g, 30 mmol) in hydrochloric acid (18 %, 150 mL) was subjected to steam distillation for 1 h. The distillation residue was filtered. After cooling an oil precipitated which, on basification with a NH_3 solution, gave the free base as a solid. Yield: 9.8 g (95 %); yellow prisms (pyridine); m. p. 210 °C. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 590 (w), 695 (m), 725 (m), 757 (m), 1074 (m), 1232 (m), 1353 (s), 1401 (m), 1446 (m), 1493 (s), 1564 (m), 1593 (m), 1642 (s), 3180 (m), 3299 (m), 3428 (m). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, br, 2H, NH_2) 7.14 – 7.24 (m, 15H, ArH). – ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 110.40 (C-5), 126.55 (CH, Ar), 127.17 (CH, Ar), 127.29 (CH, Ar), 127.29 (CH, Ar), 128.26 (CH, Ar), 128.35 (CH, Ar), 128.42 (CH, Ar), 128.50 (CH, Ar), 129.22 (CH, Ar), 130.40 (CH, Ar), 130.65 (Ar), 132.55 (Ar), 135.18 (Ar), 137.99 (C-4), 156.00 (C-2). – MS (EI, 70 eV): m/z(%) = 343 (100) $[M]^+$, 334 (15), 333 (14), 318 (13), 317 (66), 257 (20), 256 (51), 198 (10), 197 (83), 180 (18), 165 (22), 151 (30), 121 (20), 119 (16), 114 (13), 91 (50), 77 (35), 28 (56). – Anal. for $C_{21}H_{17}N_3S$ (343.45): calcd. C 73.44, H 4.99, N 12.23; found C 73.46, H 5.01, N 12.28.

*2-Benzylidenehydrazono-3,4,5-triphenyl-2,3-dihydro-1,3-thiazole (**14a**)*

A mixture of **13** (3.43 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol) in EtOH (20 mL) was refluxed briefly to give a precipitate. Yield: 4.09 g (95 %); yellow needles (PrOH); m. p. 207 °C. – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 514 (w), 593 (w), 694 (m), 732 (w), 756 (m), 1023 (w), 1336 (m), 1360 (w), 1447 (w), 1491 (s), 1525 (s), 1574 (m), 1611 (m), 3027, (w), 3433m). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 – 7.75 (m, 20H, ArH), 8.30 (s, 1H, CH). – ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 114.34 (CH, Ar), 126.88 (CH, Ar), 127.19 (CH, Ar), 127.54 (CH, Ar), 127.64 (CH, Ar), 127.82 (CH, Ar), 127.98 (CH, Ar), 128.29 (CH, Ar), 128.48 (CH, Ar), 128.56 (CH, Ar), 128.79 (CH, Ar), 129.41 (CH, Ar), 130.02 (Ar), 130.68 (CH, Ar), 131.68 (Ar), 135.02 (Ar), 135.13 (Ar), 137.14 (C-4), 151.53 (HC=N), 167.70 (C-2). – MS (EI, 70 eV): m/z(%) = 432 (37) $[M]^+$, 314 (4), 178 (3), 77 (9), 44 (6), 32 (21), 28 (100). – Anal. for $C_{28}H_{21}N_3S$ (431.56): calcd. C 77.93, H 4.90, N 9.74; found C 77.95, H 4.92, N, 9.93.

*4-Nitrobenzaldehyde-[3,4,5-triphenyl-thiazolone-(2)]-azine (**14b**)*

Method A: A mixture of **13** (3.43 g, 10 mmol) and 4-nitrobenzaldehyde (1.51 g, 10 mmol) in EtOH (30 mL) was refluxed briefly. Yield: 4.57 g (96 %); red lamella (dioxane-EtOH); m. p. 222 °C.

Method B: A mixture of 4-nitrobenzaldehyde-4-phenylthiosemicarbazone (3.0 g, 10 mmol) and 2-bromo-1,2-diphenylethan-1-one (2.75 g, 10 mmol) in EtOH (100 mL) was refluxed for 2 h. Yield: 4.05 g, 85 %); red lamella (dioxane- EtOH); m. p. 222 °C.

Method C: A mixture of **12** (3.83 g, 10 mmol) and 4-nitrobenzaldehyde (1.51 g, 10 mmol) in EtOH (100 mL) and HCl (1 mL) was refluxed 2 h. Yield: 3.57 g, (75 %). – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 513 (w), 595 (m), 695 (s), 735 (m), 755 (m), 830 (m), 848 (m), 873 (m), 1026 (m), 1047 (s), 1106 (m), 1175 (w), 1335 (s), 1482 (s), 1497 (s), 1590 (s), 3062 (w), 3434 (m). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.11 – 7.95 (m, 15H, ArH), 8.30 (s, 1H, CH). – ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 115.31 (C-5), 123.94 (CH – Ar), 127.46 (CH, Ar), 127.61 (CH, Ar), 128.23 (CH, Ar), 128.32 (CH, Ar), 128.57 (CH, Ar), 128.75 (CH, Ar), 128.95 (CH, Ar), 129.04 (CH, Ar), 129.76 (Ar), 130.75 (CH, Ar), 131.36 (Ar), 135.45 (Ar), 136.93 (Ar), 141.42

(Ar), 147.27 (C-4), 149.00 (N=CH), 169.69 (C-2). – MS (EI, 70 eV): $m/z(\%) = 476$ (100) $[M]^+$, 447 (4), 314 (4), 312 (3), 210 (1), 178 (6), 77 (4), 28 (4). – Anal. for $C_{28}H_{20}N_4O_2S$ (476.55): calcd. C 70.57, H 4.73, N 11.76; found C 70.50, H 4.21, 11.82.

4-Nitrobenzaldehyde-4-phenylthiosemicarbazone

IR (KBr, cm^{-1}): $\tilde{\nu} = 508$ (w), 693 (m), 748 (m), 843 (m), 1091 (m), 1107 (m), 1192 (s), 1262 (s), 1340 (s), 1448 (m), 1516 (s), 1541 (s), 1580 (m), 1598 (m), 2989 (m), 3139 (m), 3340 (m). – ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta =$ 7.21 – 7.56 (m, 9H, ArH), 8.27 (s, 1H, CH), 10.33 (s, br, 1H, NH), 12.10 (s, br, 1H, NH). – MS (EI, 70 eV): $m/z(\%) = 300$ (51) $[M]^+$, 207 (26), 176 (26), 150 (48), 149 (18), 148 (18), 136 (19), 135 (30), 119 (17), 118 (16), 104 (14), 103 (31), 93 (100), 92 (20), 91 (12), 89 (16), 77 (62), 51, 76 (42), 75 (20), 66 (31), 64 (19), 51 (27), 50 (26), 32 (22), (27), 28 (83). – Anal. $C_{14}H_{12}N_4O_2S$ (300.34): calcd. C 55.99, H 4.03, N 18.65; found C 55.90, H 4.05, N 18.70.

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