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A Novel Route to 1,2,3-Thiadiazole, 1,3,4-Thiadiazine, and 1,2,5-Triazepine Derivatives

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Abstract: New convenient methods for the synthesis of 1,2,3-thiadiazole, 1,3,4-thiadiazine, and 1,2,5-triazepine derivatives are reported. In the heterocyclization process the reactivity of 1-thia-4-aza-1,3-butadiene system of *syn*-2-phenylhydrazono-3-oxo-thiobutanoic acid anilides was exploited.

Key words: ring closure, 1,2,3-thiadiazole, 1,3,4-thiadiazine, 1,2,5-triazepine, 3-oxothiobutanoic acid derivatives

The structure and chemistry of the 1,2,3-thiadiazole system have been under active investigation for years.[1,2,3] Its derivatives are useful in the treatment of hyperproliferative disorders including tumor growth and angiogenesis, and lymphoproliferative symptoms.[4] Moreover, derivatives of this system are applied in the treatment and/or prevention of morbid states mediated by oxytocin, including a premature labour and dysmenorhea.[5] The 1,2,3-thiadiazole moiety is crucial for the antibacterial activity of new carbapenems[6] as well as for the efficacy of some pesticides.[7] The biological activity of 1,2,5-triazepines[8] have received less attention than the corresponding benzofused system.

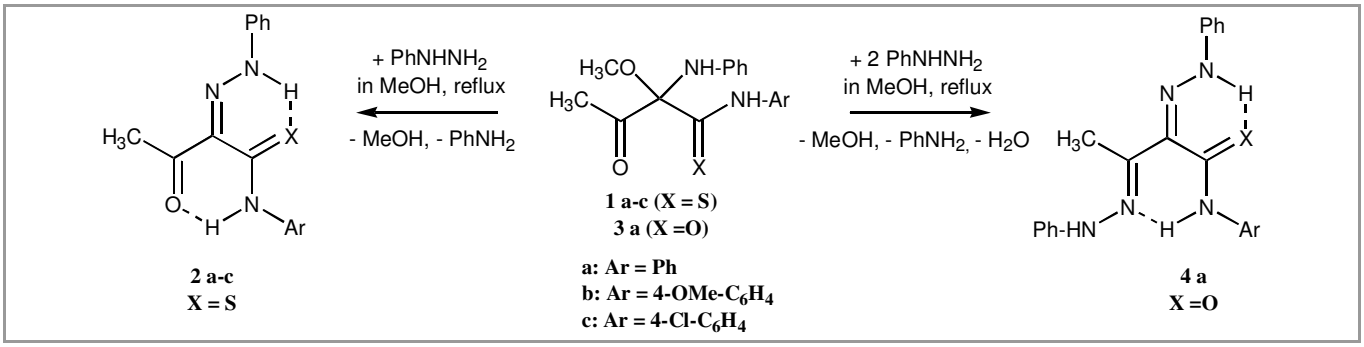
Recently, we have reported[9,10] the synthesis of 1,3- and 1,4-diazines which used the C-2 disubstituted thioanilides of 3-oxobutanoic acid **1** (X=S)[11] in heterocyclization reactions with various diamines. We have found that good leaving groups at C-2 of compound **1** offer an entry to formation of six- and seven-membered rings by treatment with binucleophiles. The reaction includes the initial nucleophilic attack of the nitrogen atoms of aliphatic 1,3- or 1,4-diamines on C-2 of compounds **1**, followed by a novel sigmatropic rearrangement. On the other hand, the reactions of **1** with aliphatic 1,2-diamines lead to 1,4-diazines by ring expansion of the intermediate 1,3-diazines.[12]

In order to develop synthetic applications of thioanilides **1a-c** in closing heterocyclic rings we have transformed them into phenylhydrazones **2a-c** by treatment with phenylhydrazine (Scheme 1). The nucleophilic attack of the amino group of phenylhydrazine took place exclusively on the C-2 position of 2-anilino-2-methoxy-3-oxothiobutanoic acid anilides **1a-c**.

In contrast, the reaction of 2-anilino-2-methoxy-3-oxobutanoic acid anilide **3a** (X=O), under similar conditions, exclusively provided osazone **4a** (Scheme 1).

Compounds **2a-c** can exist appear in two isomeric forms corresponding to (*Z*) or (*E*) configuration of the 1-thia-4-aza-1,3-butadiene system. In solution, spectral data confirm the structure of the molecules of **2a-c** as shown in Scheme 1 as the unique reaction product. X-ray analysis of **2a** was carried out to prove the configuration in the solid state and precisely determine the molecular geometry.[14]

A perspective view of molecule of **2a** with the crystallographic atom numbering is presented in Figure 1. The central framework of the molecule, consisting of heteroatoms (S1, O1, N1..N3) and carbon atoms C1..C4, is quite flat. None of these atoms deviates from the least-squares plane passing through the heteroatoms by more than 0.1Å. This flat configuration is a result of the strong coupling within the 1-thia-4-aza-1,3-butadiene system, as predicted from NMR evidence. The relative position of C1-S1 and C2-N2 double bonds is *Z*. Consequently, the central moiety forms two fused rings, which involve two rather strong hydrogen bonds N1-H13..S1 and N3-H10..O1 (Table 2) enhancing the coupling.



2 a-c
X = S

1 a-c (X = S)
3 a (X =O)

a: Ar = Ph
b: Ar = 4-OMe-C$_6$H$_4$
c: Ar = 4-Cl-C$_6$H$_4$

4 a
X =O

Scheme 1

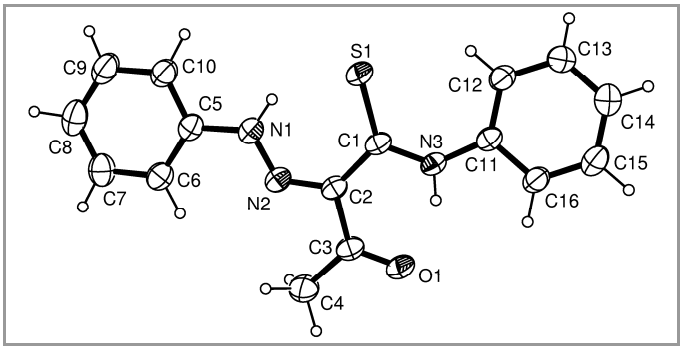


Figure 1

It is also manifested by slight shifts in the relevant bond lengths: C1=S1 is some what shorter, as is N1-N2, whereas C2=N2 is slightly longer than a typical C=N double bond (Table 1). Since all possible hydrogen donors are involved in intramolecular hydrogen bonds, it is no surprise that there are practically no intermolecular close contacts in the crystal. The flat phenyl groups are nearly coplanar with the plane of the 1-thia-4-aza-1,3-butadiene moiety.

Table 1

Selected bond lengths [pm] and bond angles [°] for **2a**			
S1-C1	168.0(2)	∠ N1-N2-C	124.7(2)
O1-C3	123.2(3)	∠ C1-N3-C11	133.6(2)
N1-N2	129.4(3)	∠ N3-C1-C2	113.2(2)
N1-C5	141.2(3)	∠ N3-C1-S1	124.0(2)
N2-C2	131.7(3)	∠ C2-C1-S1	122.7(2)
N3-C1	133.5(3)	∠ N2-C2-C3	110.2(2)
N3-C11	140.5(3)	∠ N2-C2-C1	127.1(2)
C1-C2	149.0(3)	∠ C3-C2-C1	122.7(2)
C2-C3	148.7(3)	∠ O1-C3-C2	122.9(2)
C3-C4	149.8(4)	∠ C12-C11-N3	126.2(2)

Table 2

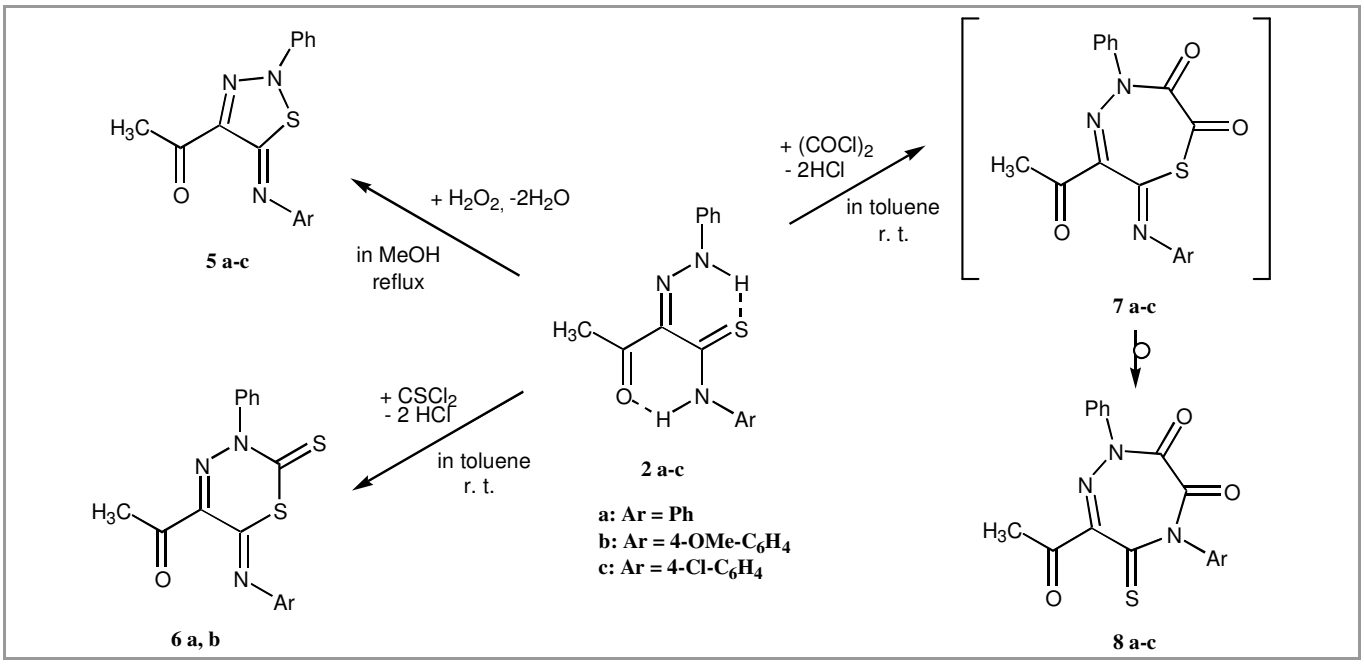
Intramolecular hydrogen bonds in **2a**				
D-H...A	D-A [pm]	H...A [pm]	D...H [pm]	∠D-H...A [°]
N1-H13..S1	292.7(2)	215(4)	92(4)	143(3)
N3-H10..O1	258.3(2)	182(3)	85(3)	150(3)

The (*Z*)-configuration of 1-thia-4-aza-1,3-butadiene system presented in compounds **2a-c**, as well as *syn*-configuration of the hydrazone, incorporate the structural requirements for the construction of heterocyclic rings.

As an extension of our previous work[12,13] we have envisaged that both oxidation and electrophilic attack should take place on the sulfur and nitrogen atoms of compounds **2a-c**.

Oxidative heterocyclisation of hydrazones **2a-c**, by treatment with H_2O_2, exclusively produced the 1,2,3-thiadiazole derivatives **5a-c** (Scheme 2), which was favoured by intramolecular interaction between the sulphur atom and nitrogen of =N–NH– fragment. The structure of the 1,2,3-thiadiazoles **5a-c** were supported by spectroscopic data and the microanalyses. Both, ^{1}H NMR and ^{13}C NMR spectra of derivatives **5a-c** show that the acetyl group and the arylimine groups are substituents. Moreover, signals characteristic for hydrazones **2a-c** have disappeared. They were those of the =N–NH– fragment at δ= 16.8–16.7 ppm and of the –CSNH– fragment at δ=13.6–13.4 ppm in the ^{1}H NMR spectra, and the signal of the carbon of δ C=S group at the 184 ppm in ^{13}C NMR spectra.

The reaction of compounds **2a, b** with thiophosgene led to formation of the six-membered ring of 1,3,4-thiadiazine derivatives **6a, b**.



Scheme 2

Spectral evidences such as NMR, IR, and MS spectra confirm the structure of products **6a, b**. When a 4-chlorophenyl substituent was present in the thioamide moiety of hydrazone **2c**, the expected 1,3,4-thiadiazine derivative **6c** was not isolated. The probably reason is the electron-withdrawing effect of the chlorine atom.

Diacylation of **2a-c** with oxalyl chloride at room temperature in toluene afforded products **8a-c** with high to excellent yields (Scheme 2). The structure of the compounds obtained were established on the basis of spectral evidences. All spectral data confirm that reaction of **2a-c** with oxalyl chloride yielded exclusively the 1,2,5-triazepine derivatives **8a-c** (Scheme 2).

The ^{13}C NMR spectra display the characteristic signals of δ C=S group at the 180.4–179.6 ppm while signals of NH groups remarkable for the starting compounds **2a-c** are not observed. Probably, at the first, step the mechanism of the S- and N-acylation took place with formation of the expected 1,4,5-thiadiazepine derivatives **7a-c** but in a second step the 1,4,5-thiadiazepine system undergoes the Dimroth rearrangement immediately to the thermodynamic more stable 1,2,5-triazepine system.

The high efficiency of the proposed facile syntheses can be explained by the unique (*Z*)-configuration of the 1-thia-4-aza-1,3-butadiene system presented in hydrazones **2a-c**, which was confirmed by X-ray analysis. Hydrazones **2a-c** are, therefore, excellent building-blocks for constructing heterocyclic systems of 1,2,3-thiadiazole, 1,3,4-thiadiazine, and 1,2,5-triazepine. In all syntheses described, (2*Z*)-3-oxo-2-phenylhydrazonothiobutanoic acid anilides **2a-c** can be used except of **2c** (4-chloroanilide) in reaction with thiophosgene.

General procedure for the preparation of **(2*Z*)-3-oxo-2-phenylhydrazonothiobutanoic acid anilides 2**: 30 mmol of the corresponding 2-anilino-2-methoxy-3-oxothiobutanoic acid anilide **1** and 30 mmol (3.24 g) of phenylhydrazine were heated in presence of the catalytic amount of 4-methylsulphonic acid in 50 mL of methanol under reflux for 1h. Cooling the mixture yielded orange crystals, which were purified by crystallization from ethanol.

Procedure for the preparation of **2,3-bisphenyl-hydrazonobutanoic acid anilide 4a**: 3.4 mmol (1.00g) of the corresponding 2-anilino-2-methoxy-3-oxobutanoic acid anilide **3a** and 6.8 mmol (0.74 g) of phenylhydrazine were heated in presence of the catalytic amount of 4-methylsulphonic acid in 10 mL of methanol under reflux for 2h. Cooling the mixture yielded yellow crystals, which were crystallized from ethanol.

General procedure for the preparation of **2,5-dihydro-1,2,3-thiadiazole** derivatives **5**: 2 mmol of the corresponding hydrazone **2** were dissolved in 10 mL of methanol and 6 mmol of hydrogen peroxide in 30% water solution (0.68 g) were added. The mixture was heated under reflux for 2h and the solvent was evaporated. The brownish residue was purified twice by rotatory chromatography (SiO_2, $CHCl_3$:methanol, 20:1, then 30:1) to give a red powder, which was crystallized from methanol.

General procedure for the preparation of **2-thioxo-3,6-dihydro-2*H*-1,3,4-thiadiazine** derivatives **6**: 1.47 mmol of the corresponding hydrazone **2** was dissolved in 10 mL of toluene at r.t. and 0.17 g (1.47 mmol) of $CSCl_2$ were added. The solution was stirred for 24h. Yellow crystals of the product were separated and crystallized from toluene.

General procedure for the preparation of **4-thioxo-4,5-dihydro-1*H*-1,2,5-triazepin-6,7-dione** derivatives **8**: 1 mmol of the corresponding hydrazone **2** was dissolved in 5 mL of toluene at r.t. and 1 mmol (0.13 g) of oxalyl chloride was added to the stirred solution. Red or orange crystals of the products were filtered off under reduced pressure after 10 minutes and purified by crystallization from toluene.

Physical data: Melting points were determined on an electrothermal IA9000 digital melting point apparatus and are uncorrected. The IR spectra were obtained on a Bruker IFS 48 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker AMX 500 NMR spectrometer at room temperature. Chemical shifts are given in ppm.

Spectral data for compounds **1a-c** and **3a** are described in our previous work[11].

Yields are given for pure products.

(2Z)-3-oxo-2-phenylhydrazonothiobutanoic acid anilide (2a): $C_{16}H_{15}N_3OS$; MW 297.4; orange needles; yield 7.85 g (88%); mp 103–104 °C; (% C, H, N): calcd: 64.62, 5.08, 14.13; found: 64.56, 4.96, 14.05; IR (KBr): ν(cm^{-1}) = 1662, 1532, 1462, 1284, 1105; ^1H NMR ($CDCl_3$): δ (ppm) = 16.76 (s, 1H, NNH), 13.53 (s, 1H, CONH), 7.60–7.20 (m, 10H, 2 × phenyl), 2.64 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 201.3 (C=O), 184.4 (C=S), 141.6 (C=N), 137.6, 129.7, 128.9, 127.1, 126.2, 125.9, 125.0, 116.6 (2 × phenyl), 27.1 (CH_3); MS (EI): *m/z* (%) = 297 (55) M^+, 254 (7) M^+–CH_3CO^+, 205 (38) M^+–C_6H_6N, 173 (27) M^+–C_6H_6N–S, 136 (11) PhNHCS, 105 (22) PhNN, 93 (83) C_6H_7N, 77 (100) Ph, 43 (72) CH_3CO^+.

(2Z)-3-oxo-2-phenylhydrazonothiobutanoic acid (4-methoxy) anilide (2b): $C_{17}H_{17}N_3O_2S$; MW 327.4; orange needles; yield 7.30 g (76%); mp 109–110 °C; (% C, H, N): calcd: 62.37, 5.23, 12.83; found: 62.19, 5.20, 12.90; IR (KBr): ν(cm^{-1}) = 1652, 1459, 1277, 1105; ^1H NMR ($CDCl_3$): δ (ppm) = 16.73 (s, 1H, NNH), 13.38 (s, 1H, CONH), 7.52–6.94 (m, 9H, phenyl and methoxyphenyl), 3.84 (s, 3H, OCH_3), 2.63 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 201.2 (C=O), 184.1 (C=S), 141.6 (C=N), 158.3, 130.5, 129.6, 126.3, 126.2, 125.7, 116.5, 114.1 (phenyl and methoxyphenyl), 55.4 (OCH_3), 27.0 (CH_3); MS (EI): *m/z* (%) = 327 (100) M^+, 284 (8) M^+–CH_3CO^+, 235 (25) M^+–C_6H_6N, 203 (29) M^+–C_6H_6N–S, 166 (9) MeO-PhNCS, 134 (59) MeO-PhNC, 107 (9) MeO-Ph 105 (12) PhNN, 92 (55) C_6H_6N, 77 (62) Ph, 43 (43) CH_3CO^+.

(2Z)-3-oxo-2-phenylhydrazonothiobutanoic acid (4-chloro) anilide (2c): $C_{16}H_{14}ClN_3OS$; MW 331.8; orange needles; yield 8.76 g (88%); mp 132–133 °C; (% C, H, N): calcd: 57.92, 4.25, 12.66; found: 57.75, 4.28, 12.62; IR (KBr): ν(cm^{-1}) = 1650, 1533, 1457, 1284, 1093; ^1H NMR ($CDCl_3$): δ (ppm) = 16.73 (s, 1H, NNH), 13.58 (s, 1H, CONH), 7.58–7.21 (m, 9H, phenyl and chlorophenyl), 2.63 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 201.3 (C=O), 184.5 (C=S), 141.5 (C=N), 136.0, 132.3, 129.6, 129.0, 126.1, 126.1, 126.0, 116.6 (phenyl and chlorophenyl), 27.0 (CH_3); MS (EI): *m/z* (%) = 331 (87) M^+, 298 (17) M^+–HS, 288 (6) M^+–CH_3CO^+, 239 (20) M^+–C_6H_6N, 207 (19) M^+–C_6H_6N–S, 138 (37) Cl-PhNC, 111 (24) Cl-Ph 105 (24) PhNN, 93 (100) C_6H_7N, 77 (96) Ph, 43 (71) CH_3CO^+.

2,3-bisphenylhydrazonobutanoic acid anilide (4a): MW 371.4; yellow needles; yield 0.81 g (65%); mp 172–174 °C; (% C, H, N): calcd: 71.14, 5.70, 18.86; found: 70.80, 5.71, 18.74; IR (KBr): ν(cm^{-1}) = 3331, 3205, 3168, 1640, 1513, 1240; ^{1}H NMR ($CDCl_3$): δ (ppm) = 13.95 (s, 1H, C-2 NNH), 12.07 (s, 1H, CONH), 7.40 (s, 1H, C-3 NNH), 7.68–6.95 (m, 15H, 3 × phenyl), 2.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 163.3 (C=O), 146.4, 144.5 (2 × C=N), 143.3, 137.7, 129.6, 129.4, 129.1, 125.6, 124.6, 122.6, 121.0, 120.9, 114.3, 113.5 (3 × phenyl), 11.5 (CH_3); MS (EI): *m/z* (%) = 371 (46) M^+, 278 (96) M^+–$PhNH_2$, 105 (14) PhNN, 93 (100) $PhNH_2$.

4-acetyl-2-phenyl-5-phenylimino-2,5-dihydro-1,2,3-thiadiazole (5a): $C_{16}H_{13}N_3OS$; MW 295.4; dark orange powder; yield 0.37 g (63%); mp 107–108 °C; (% C, H, N): calcd: 65.06, 4.44, 14.23; found: 65.17, 4.51, 14.37; IR (KBr): ν(cm^{-1}) = 1690, 1580, 1436, 1304, 1064; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.43–7.09 (m, 10H, 2 × phenyl), 2.73 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 190.4 (C=O), 158.0 (N=C–S), 154.9 (C=N), 142.1, 141.2, 130.0, 129.7, 126.5, 125.6, 119.1, 117.9 (2 × phenyl), 29.0 (CH_3); MS (EI): *m/z* (%) = 295 (84) M^+, 190 (3) M^+–PhNN, 135 (18) PhNCS, 123 (13) PhNS, 91 (5) C_6H_5N, 77 (11) Ph, 43 (5) CH_3CO^+.

4-acetyl-2-phenyl-5-(4-methoxy)phenylimino-2,5-dihydro-1,2,3-thiadiazole (5b): $C_{17}H_{15}N_3O_2S$; MW 325.4; orange powder; yield 0.34 g (52%); mp 113–114 °C; (% C, H, N): calcd: 62.75, 4.65, 12.91; found: 62.51, 4.70, 12.78; IR (KBr): ν(cm^{-1}) = 1696, 1590, 1478, 1276, 1103; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.46–6.94 (m, 9H, phenyl and methoxyphenyl), 3.83 (s, 3H, OCH_3) 2.72 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 190.5 (C=O), 156.7 (N=C–S), 147.9 (C=N), 157.4, 142.3, 141.4, 129.7, 126.3, 120.6, 117.9, 115.0 (phenyl and methoxyphenyl), 55.4 (OCH_3), 29.0 (CH_3); MS (EI): *m/z* (%) = 325 (100) M^+, 123 (21) PhNS, 107 (5) MeO-Ph, 43 (20) CH_3CO^+.

4-acetyl-2-phenyl-5-(4-chloro)phenylimino-2,5-dihydro-1,2,3-thiadiazole (5c): $C_{16}H_{12}ClN_3OS$; MW 329.8; orange powder; yield 0.27 g (42%); mp 130–131 °C; (% C, H, N): calcd: 58.27, 3.67, 12.74; found: 58.42, 3.68, 12.70; IR (KBr): ν(cm^{-1}) = 1698, 1571, 1473, 1277, 1092; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.44–7.03 (m, 9H, phenyl and chlorophenyl), 2.73 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 190.3 (C=O), 158.5 (N=C–S), 153.2 (C=N), 142.1, 141.1, 130.7, 130.1, 129.8, 126.7, 120.6, 118.0 (phenyl and chlorophenyl), 29.0 (CH_3); MS (EI): *m/z* (%) = 329 (47) M^+, 123 (23) PhNS, 111 (11) Cl-Ph, 43 (27) CH_3CO^+.

5-acetyl-3-phenyl-6-phenylimino-2-thioxo-3,6-dihydro-2*H*-1,3,4-thiadiazine (6a): $C_{17}H_{13}N_3OS_2$; MW 339.4; yellow needles; yield 0.36 g (73%); mp 214–215 °C; (% C, H, N): calcd: 60.16, 3.86, 12.38; found: 60.13, 4.02, 12.45; IR (KBr): ν(cm^{-1}) = 1718, 1558, 1453, 1334, 1079; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.53–6.97 (m, 10H, 2 × phenyl), 2.58 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 194.6 (C=O), 184,2 (C=S), 147.0 (N=C–S), 143.4 (C=N), 144.6, 144.2, 129.6, 129.4, 129.2, 126.9, 126.9, 119.6 (2 × phenyl), 28.8 (CH_3); MS (EI): *m/z* (%) = 339 (32) M^+, 296 (12) M^+–CH_3CO^+, 236 (80) M^+–PhNC, 135 (10) PhNCS.

5-acetyl-6-(4-methoxy)phenylimino-3-phenyl-2-thioxo-3,6-dihydro-2*H*-1,3,4-thiadiazine (6b): $C_{18}H_{15}N_3O_2S_2$; MW 369.5; yellow needles; yield 0.16 g (30%); mp 160–161 °C; (% C, H, N): calcd: 58.52, 4.09, 11.37; found: 58.51, 4.17, 11.72; IR (KBr): ν(cm^{-1}) = 1716, 1329, 1077; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.52–6.94 (m, 9H, phenyl and methoxyphenyl), 3.84 (s, 3H, OCH_3), 2.56 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 195.0 (C=O), 184.1 (C=S), 145.1 (N=C–S), 143.5 (C=N), 158.8, 144.8, 139.7, 129.4, 126.9, 122.5, 115.8, 114.6 (phenyl and methoxyphenyl), 55.5 (OCH_3), 28.9 (CH_3); MS (EI): *m/z* (%) =369 (92) M^+, 326 (39) M^+–CH_3CO^+, 236 (100) M^+–MeO-PhNC, 165 (39) MeO-PhNCS, 43 (37) CH_3CO^+.

3-acetyl-1,5-diphenyl-4-thioxo-4,5-dihydro-1*H*-1,2,5-triazepin-6,7-dione (8a): $C_{18}H_{13}N_3O_3S$; MW 351.4; red plates; yield 0.34g (97%); mp 211–212 °C; (% C, H, N): calcd: 61.53, 3.73, 11.96; found: 61.56, 3.82, 11.80; IR (KBr): ν(cm^{-1}) = 1717, 1698, 1650, 1458, 1124; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.70–7.33 (m, 10H,2 × phenyl), 1.87 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 198.4 (C=O), 180.4 (C=S), 156.1, 152.4 (COCO), 143.2 (C=N), 137.5, 135.2, 132.2, 131.2, 130.3, 129.5, 128.6, 123.0 (2 × phenyl), 31.8 (CH_3); MS (EI): *m/z* (%) = 351 (8) M^+, 323 (8) M^+–CO, 295 (100) M^+–2 × CO, 218 (19) M^+–Ph, 135 (8) PhNCS, 91 (15) C_6H_5N, 77 (61) Ph, 43 (18) CH_3CO^+.

3-acetyl-5-(4-methoxy)phenyl-1-phenyl-4-thioxo-4,5-dihydro-1*H*-1,2,5-triazepin-6,7-dione (8b): $C_{19}H_{15}N_3O_4S$; MW 381.4; orange needles; yield 0.33 g (86%); mp 229–230 °C; (% C, H, N): calcd: 59.83, 3.96, 11.02; found: 59.97, 3.91, 11.01; IR (KBr): ν(cm^{-1}) = 1736, 1702, 1130; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.71–7.01 (m, 9H, phenyl and methoxyphenyl), 3.88 (s, 3H, OCH_3), 1.90 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 198.3 (C=O), 180.2 (C=S), 156.1, 152.2 (COCO), 143.2 (C=N), 161.3, 137.4, 131.9, 129.7, 129.2, 127.2, 122.8, 115.2 (phenyl and methoxyphenyl), 55.7 (OCH_3), 31.7 (CH_3); MS (EI): *m/z* (%) = 381 (11) M^+, 353 (13) M^+–CO, 325 (100) M^+–2 × CO, 107 (18) MeO-Ph, 105 (10) PhNN, 77 (71) Ph, 43 (33) CH_3CO^+.

3-acetyl-5-(4-chloro)phenyl-1-phenyl-4-thioxo-4,5-dihydro-1*H*-1,2,5-triazepin-6,7-dione (8c): $C_{18}H_{12}ClN_3O_3S$; MW 385.8; light red plates; yield 0.25 g (65%); mp 220–221 °C; (% C, H, N): calcd: 56.04, 3.14, 10.89; found: 56.00, 3.19, 10.65; IR (KBr): ν(cm^{-1}) = 1735, 1698, 1650, 1132; ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.69–7.28 (m, 9H, phenyl and chlorophenyl), 1.95 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ (ppm) = 198.0 (C=O), 179.6 (C=S), 155.6, 152.1 (COCO), 142.6 (C=N), 137.2, 137.2, 133.3, 132.0, 130.3, 129.5, 129.2, 122.8 (phenyl and chlorophenyl), 31.6 (CH_3); MS (EI): *m/z* (%) = 385 (6) M^+, 357 (6) M^+–CO, 329 (100) M^+–2 × CO, 111 (18) Cl-Ph, 105 (8) PhNN, 77 (73) Ph, 43 (36) CH_3CO^+.

References

(1) (a) Cyrański, M. K.; Krygowski, T. M.; Katritzky, A. R.; von Schleyer, P. *J. Org. Chem.* **2002**, *67*, 1333. (b) Glossman-Mitnik, D. *THEOCHEM* **2001**, *549*, 285.

(2) (a) Shafiee, A.; Jalilian, A. R.; Rezaei, M. *J. Heterocycl. Chem.* **2000**, *37*, 1325. (b) Naidu, A. V.; Dave, M. A. *Asian. J. Chem.* **2000**, 687.

(3) (a) Abramov, M. A.; Dehaen, W.; D'hooge, B.; Petrov, M. L.; Smeet, S.; Toppet, S.; Voets, M. *Tetrahedron* **2000**, *56*, 3933. (b) Hameurlaine, A.; Abramov, M. A.; Dehaen, W. *Tetrahedron Lett.* **2002**, *43*, 1015.

(4) Zhang, Z.; Yan, J.; Leung, D.; Wang, S.; Costello, P. C.; Sanghera, J. U.S. US 6420400 **2002**, Appl. 545237 **2002**; *Chem. Abstr.* **2002**, *137*, 93758p.

(5) Schwarz, M.; Page, P.; Pomel, V.; Quattropani, A.; Thomas, R. J. PCT Int. Appl. WO 02102799 **2002**, EP Appl. 2001/113632 **2001**; *Chem. Abstr.* **2003**, *138*, 55968v.

(6) (a) Shin, K. J.; Koo, K. D.; Yoo, K. H.; Kang, Y. K.; Park, W. S.; Kim, D. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2397. (b) Yamamoto, H.; Terasawa, T.; Nakamura, A.; Kawabata, K.; Takasugi H.; Tanaka H.; Matsumoto, S.; Matsumoto, Y.; Tawara, S. *Bioorgan. Med. Chem.* **2001**, *9*, 465.

(7) (a) Fujii, K.; Hatano, K.; Yoshida, J. Jpn. Kokai Tokkyo Koho JP 2001 335570 **2001**, Appl. 2000/157103 **2000**; *Chem. Abstr.* **2002**, *136*, 20074g. (b) Lindell, S.; Dickhaut, J.; Jakobi, H.; Tiebes, J.; Jans, D.; Thoenessen, M.-T.; Waibel, J. M. Eur. Pat. Appl. EP 1236727 **2002**, EP Appl. 2001/105017 **2001**; *Chem. Abstr.* **2002**, *137*, 201314b. (c) Uchikurohashi, T.; Tashima, T.; Yamamoto, Y.; Otsuka, T.;

Yamaguchi, R.; Imano, T.; Jpn. Kokai Tokkyo Koho JP 2002 114612 **2002**, Appl. 2002/307632 **2000**, *Chem. Abstr.* **2002**, *136*, 305521n.

(8) (a) Shibamoto, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, *11*, 3233. (b) Bianchi, M.; Butti, A.; Rossi, S. *Tetrahedron* **1974**, *30*, 2765.

(9) Zaleska, B.; Bazanek, T.; Socha, R.; Karelus, M.; Grochowski, J.; Serda, P. *J. Org. Chem.* **2002**, *67*, 4526.

(10) Zaleska, B.; Socha, R. *Monatsh. Chem.* **2000**, *131*, 1151.

(11) Zaleska, B.; Socha, R.; Ciechanowicz-Rutkowska, M.; Pilati, T. *Monatsh. Chem.* **2000**, *131*, 1158.

(12) Zaleska, B.; Socha, R.; Grochowski, J.; Serda, P.; Szneler, E. *J. Org. Chem.* **2003**, *68*, 2334.

(13) Zaleska, B.; Cież, D.; Haas, A.; *Synth. Commun.* **1996**, *26*, 4165.

(14) Compound **2a** with formula $C_{16}H_{15}N_3OS$ crystallizes in the monoclinic system, space group C2/c, with unit cell parameters a=27.250(1), b=7.1912(4), c=15.392(1) Å, β=90.028(3)º, V=3016.2(3)Å^3, Z=8. A total of 2697 independent reflections (R(int) = 0.0213) were collected on a sample (size 0.35x0.3x0.2 mm) using a KappaCCD diffractometer and MoKα radiation. The structure was solved by direct methods and refined by the full-matrix least squares method on F^2 using the SHELX97 program system. All hydrogen atoms were located on a difference Fourier map of electron density. Final R indices for I>2σ(I) were equal R1 = 0.0588, wR2 = 0.1484, and R1 = 0.0788, wR2 = 0.1741 for all data. The extinction coefficient was refined and converged to 0.055(6). The final difference Fourier map of electron density was featureless with the largest peak and hole at 0.280 and -0.251 e.Å^{-3}, respectively. The structural data have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 209483.

A Novel Route to 1,2,3-Thiadiazole, 1,3,4-Thiadiazine, and 1,2,5-Triazepine Derivatives