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-oxothiobutanoic acid anilides was exploited.

Key words: ring closure, heterocycles, cyclizations, thiadiazole, thiadiazine, triazepine

The structure and chemistry of the 1,2,3-thiadiazole system have been under active investigation for years.1–3 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 premature labour and dysmenorrhea.5 The 1,2,3-thiadiazole moiety is crucial for the antibacterial activity of new carbapenems6 as well as for the efficacy of some pesticides.7 The biological activity of 1,2,5-triazepines8 has received less attention than the corresponding benzofused system.

Recently, we have reported9,10 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 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 0.1
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.

![Figure 1](image)

It is also manifested by slight shifts in the relevant bond lengths: C1=S1 is somewhat 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 and Bond Angles for 2a

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond length (pm)</th>
<th>Bond</th>
<th>Bond angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1–C1</td>
<td>168.0(2)</td>
<td>N1–N2–C</td>
<td>124.7(2)</td>
</tr>
<tr>
<td>O1–C3</td>
<td>123.2(3)</td>
<td>C1–N3–C11</td>
<td>133.6(2)</td>
</tr>
<tr>
<td>N1–N2</td>
<td>129.4(3)</td>
<td>N3–C1–C2</td>
<td>113.2(2)</td>
</tr>
<tr>
<td>N1–C5</td>
<td>141.2(3)</td>
<td>N3–C1–S1</td>
<td>124.0(2)</td>
</tr>
<tr>
<td>N2–C2</td>
<td>131.7(3)</td>
<td>C2–C1–S1</td>
<td>122.7(2)</td>
</tr>
<tr>
<td>N3–C1</td>
<td>133.5(3)</td>
<td>N2–C2–C3</td>
<td>110.2(2)</td>
</tr>
<tr>
<td>N3–C11</td>
<td>140.5(3)</td>
<td>N2–C2–C1</td>
<td>127.1(2)</td>
</tr>
<tr>
<td>C1–C2</td>
<td>149.0(3)</td>
<td>C3–C2–C1</td>
<td>122.7(2)</td>
</tr>
<tr>
<td>C2–C3</td>
<td>148.7(3)</td>
<td>O1–C3–C2</td>
<td>122.9(2)</td>
</tr>
<tr>
<td>C3–C4</td>
<td>149.8(4)</td>
<td>C12–C11–N3</td>
<td>126.2(2)</td>
</tr>
</tbody>
</table>

**Table 2** Intramolecular Hydrogen Bonds in 2a

<table>
<thead>
<tr>
<th>D–H–A</th>
<th>D–A (pm)</th>
<th>H–A (pm)</th>
<th>D–H (pm)</th>
<th>Angle D–H–A (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1–H13–S1</td>
<td>292.7(2)</td>
<td>215(4)</td>
<td>92(4)</td>
<td>143(3)</td>
</tr>
<tr>
<td>N3–H10–O1</td>
<td>258.3(2)</td>
<td>182(3)</td>
<td>85(3)</td>
<td>150(3)</td>
</tr>
</tbody>
</table>

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

As an extension of our previous work, 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 H2O2, exclusively produced the 1,2,3-thiadiazole derivatives 5a–c (Scheme 2), which was favoured by intramolecular interaction between the sulphur atom and the nitrogen of the =NNH– fragment. The structure of the 1,2,3-thiadiazoles 5a–c was supported by spectroscopic data and the microanalyses. Both, 1H and 13C 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 =NNH– fragment at δ = 16.8–16.7 and of the –CSNH– fragment at δ = 13.6–13.4 in the 1H NMR spectra, and the signal of the carbon of the C=S group at δ = 184 ppm in the 13C 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.

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 structures 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 13C NMR spectra display the characteristic signals of the C=S group at δ = 180.4–179.6, while signals of NH groups significant for the starting compounds 2a–c are not observed. Probably, as 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 thermodynamically 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, (2Z)-3-oxo-2-phenylhydrazonothiobutanoic acid
anilides 2a–c can be used except for 2c (4-chloroanilide) in reaction with thiophosgene.

Mps were determined on an electrothermal IA9000 digital mp apparatus and are uncorrected. The IR spectra were obtained on a Bruker IFS 48 spectrometer. 1H and 13C NMR spectra were recorded with a Bruker AMX 500 NMR spectrometer at r.t. 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 Anilides 2; General Procedure
The corresponding 2-anilino-2-methoxy-3-oxothiobutanoic acid anilide 1 (30 mmol) and phenylhydrazine (30 mmol, 3.24 g) were heated in the presence of a catalytic amount of 4-methylsulphonic acid in MeOH (50 mL) under reflux for 1 h. Cooling the mixture yielded orange crystals, which were purified by crystallization from EtOH.

2,3-Bisphenylhydrazonobutanoic Acid Anilide 4a
The corresponding 2-anilino-2-methoxy-3-oxobutanoic acid anilide 3a (3.4 mmol, 1.00 g) and phenylhydrazine (6.8 mmol, 0.74 g) were heated in presence of a catalytic amount of 4-methylsulphonic acid in MeOH (10 mL) under reflux for 2 h. Cooling the mixture yielded yellow crystals, which were crystallized from EtOH.

2,5-Dihydro-1,2,3-thiadiazole Derivatives 5; General Procedure
The corresponding hydrazone 2 (2 mmol) was dissolved in MeOH (10 mL) and hydrogen peroxide (30%; 6 mmol) solution in H2O (0.68 g) was added. The mixture was heated under reflux for 2 h and the solvent was evaporated. The brownish residue was purified twice by rotary chromatography (SiO2; CHCl3–MeOH, 20:1, then 30:1) to give a red powder, which was crystallized from MeOH.

2-Thioxo-3,6-dihydro-2H-1,3,4-thiadiazine Derivatives 6; General Procedure
The corresponding hydrazone 2 (1.47 mmol) was dissolved in toluene (10 mL) at r.t. and CSCl2 (0.17 g, 1.47 mmol) was added. The solution was stirred for 24 h. Yellow crystals of the product were separated and crystallized from toluene.

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

(2Z)-3-Oxo-2-phenylhydrazonothiobutanoic Acid Anilide (2a)
Yield: 7.85 g (88%); orange needles; mp 103–104 °C.
IR (KBr): 1662, 1532, 1462, 1284, 1105 cm–1.
1H NMR (CDCl3): δ = 16.76 (s, 1 H, NNH), 13.53 (s, 1 H, CONH), 7.60–7.20 (m, 10 H, 2 Ph), 2.64 (s, 3 H, CH3).
13C NMR (CDCl3): δ = 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 Ph), 27.1 (CH3).
MS (EI): m/z (%) = 297 (55, M+), 254 (7, M+ – CH3CO+), 205 (38, M+ – C6H6N), 173 (27, M+ – C3H3N – S), 136 (11, PhNHCS), 105 (22, PhNN), 93 (83, C3H4N2), 77 (100, Ph), 43 (72, CH2CO+).
Anal. Calcd for C16H15N3OS: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.56; H, 4.96; N, 14.05.

X-Ray Crystal Structure of 2a
Compound 2a with formula C16H15N3OS 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)°, V = 3016.2(3) Å3, Z = 8. A total of 2697 independent reflections [R(int) = 0.0213] were collected on a sample (size 0.35 × 0.3 × 0.2 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 F2 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 eÅ⁻³, respectively.

(2Z)-3-Oxo-2-phenylhydrazonothiobutanoic Acid (4-Methoxy) Anilide (2b)
Yield: 7.30 g (76%); orange needles; mp 109–110 °C.
IR (KBr): 1696, 1590, 1478, 1276, 1103 cm⁻¹.

1H NMR (CDCl₃): δ = 7.43–7.09 (m, 10 H, 2 Ph), 2.73 (s, 3 H, CH₃).

13C NMR (CDCl₃): δ = 163.3 (C=O), 72.5, 72.5, 155.3, 155.3, 129.4, 129.4, 126.9, 126.9, 119.6, 119.6, 113.5 (Ph), 113.5 (Ph).

MS (EI): m/z (%) = 325 (100, M⁺), 290 (54, M⁺ – CH₃), 239 (30, M⁺ – Ph), 207 (19, M⁺ – Ph – CH₃), 135 (10, PhNCS), 123 (21, PhNS), 111 (11, C₁₇H₁₇CO⁺), 105 (9, Ph). Anal. Calcd for C₁₇H₁₃N₃OS: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.17; H, 4.51; N, 14.37.

4-Acetyl-2-phenyl-5-(4-methoxy)phenylimino-2,5-dihydro-1,2,3-thiadiazole (5b)
Yield: 0.34 g (52%); orange powder; mp 113–114 °C.
IR (KBr): 1696, 1590, 1478, 1276, 1103 cm⁻¹.

1H NMR (CDCl₃): δ = 7.46–6.94 (m, 9 H, Ph, MeOPh), 3.83 (s, 3 H, OCH₃), 2.63 (s, 3 H, CH₃).

13C NMR (CDCl₃): δ = 190.5 (C=O), 156.7 (N=CS), 147.9 (C=N), 157.4, 142.3, 141.4, 129.7, 126.3, 126.0, 117.9, 115.0 (Ph, MeOPh), 55.4 (OCH₃), 29.0 (CH₂).

MS (EI): m/z (%) = 325 (100, M⁺), 123 (21, PhNS), 105 (7, MeOPh), 43 (20, CH₃CO⁺).

Anal. Calcd for C₁₇H₁₇N₃O₃S: C, 67.52; H, 4.65; N, 12.91. Found: C, 67.51; H, 4.70; N, 12.78.

5-Acetyl-3-phenyl-6-phenylimino-2-thioxo-3,6-dihydro-1H-1,3,4-thiadiazine (6a)
Yield: 0.36 g (73%); yellow needles; mp 214–215 °C.
IR (KBr): 1718, 1558, 1453, 1334, 1079 cm⁻¹.

1H NMR (CDCl₃): δ = 7.53–6.97 (m, 10 H, 2 Ph), 2.58 (s, 3 H, CH₃).

13C NMR (CDCl₃): δ = 194.6 (C=O), 184.2 (C=O), 147.0 (N=CS), 143.4 (C=N), 144.6, 144.2, 129.6, 129.4, 129.2, 126.9, 119.6 (2 Ph), 28.8 (CH₂).

MS (EI): m/z (%) = 339 (32, M⁺), 296 (12, M⁺ – CH₃CO⁺), 236 (80, M⁺ – PhNCS), 135 (10, PhNS).

Anal. Calcd for C₁₇H₁₃N₃O₃S: C, 60.16; H, 3.86; N, 12.38. Found: C, 60.13; H, 4.02; N, 12.45.

5-Acetyl-6-(4-methoxy)phenylimino-2-thioxo-3,6-dihydro-1H-1,3,4-thiadiazine (6b)
Yield: 0.16 g (30%); yellow needles; mp 160–161 °C.
IR (KBr): 1716, 1329, 1077 cm⁻¹.

1H NMR (CDCl₃): δ = 7.52–6.94 (m, 9 H, Ph, MeOPh), 3.84 (s, 3 H, OCH₃), 2.56 (s, 3 H, CH₃).

13C NMR (CDCl₃): δ = 195.0 (C=O), 184.1 (C=O), 145.1 (N=CS), 143.5 (C=N), 158.8, 144.8, 139.7, 129.4, 126.9, 122.5, 115.8, 114.6 (Ph, MeOPh), 55.5 (OCH₃), 28.9 (CH₂).

MS (EI): m/z (%) = 369 (92, M⁺), 326 (39, M⁺ – CH₃CO⁺), 236 (100, M⁺ – MeOPhNC), 165 (39, MeOPhNCS), 43 (37, CH₃CO⁺).
3-Acetyl-1,5-diphenyl-4-thioxo-4,5-dihydro-1H,1,2,5-triazepin-6,7-dione (8a)
Yield: 0.34g (97%); red plates; mp 211–212 °C.
IR (KBr): 1717, 1698, 1650, 1458, 1124 cm–1.
Yield: 0.25 g (65%); light red plates; mp 220–221 °C.

3-Acetyl-1,5-diphenyl-4-thioxo-4,5-dihydro-1H,1,2,5-triazepin-6,7-dione (8b)
Yield: 0.33 g (86%); orange needles; mp 229–230 °C.

3-Acetyl-5-(4-chloro)phenyl-1-phenyl-4-thioxo-4,5-dihydro-1H,1,2,5-triazepin-6,7-dione (8c)
Yield: 0.34 g (97%); red plates; mp 211–212 °C.

3-Acetyl-5-(4-methoxy)phenyl-1-phenyl-4-thioxo-4,5-dihydro-1H,1,2,5-triazepin-6,7-dione (8d)
Yield: 0.25 g (65%); light red plates; mp 220–221 °C.

References

(14) Compound 2a crystallizes in the monoclinic system. See experimental for details of X-ray structure determination. The structural data have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 209483.