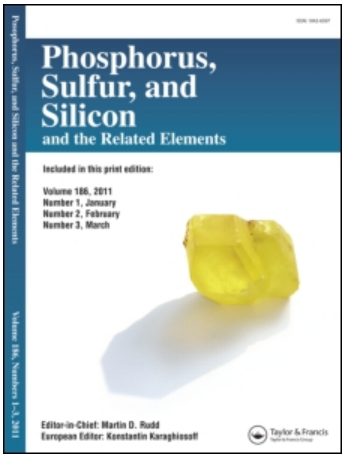

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SYNTHESIS OF 3,5-DISUBSTITUTED-5,6-DIHYDRO- 4H-1,2,5-OXADIAZINE-6-THIONES[1] AND 3,5-DISUBSTITUTED-1,2,4-THIADIAZOLES

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SYNTHESIS OF 3,5-DISUBSTITUTED-5,6-DIHYDRO-4H-1,2,5-OXADIAZINE-6-THIONES[1] AND 3,5-DISUBSTITUTED-1,2,4-THIADIAZOLES

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3,5-Disubstituted-5,6-dihydro-4H-1,2,5-oxadiazine-6-thiones are prepared by the reaction of acetophenone oximes with thiophosgene. The thermal rearrangement of 3-phenyl-5-(*p*-tolyl)-5,6-dihydro-4H-1,2,5-oxadiazine-6-thione yields the corresponding 1,2,5-thiadiazine-6-one. The reaction of 3-substituted-1,2,4-thiadiazoles with various reactants gave 3,4-disubstituted-1,2,4-thiadiazoles.

Key words: 3,5-Disubstituted-5,6-dihydro-4H-1,2,5-oxadiazine-6-thiones, 1,2,5-thiadiazine-6-one, 1,2,4-thiadiazoles.

1,2,4-Oxadiazole-5-thiones as five membered heterocyclic ring system rearrange[2–4] to 1,2,4-thiadiazole-5-ones. The rearrangement occurs either thermally or photolytically. Similar rearrangement can be found in the Schönberg rearrangement of diarylthione carbonates to diarylthiocarbonates[5,6] and in the thermal rearrangement of aryldialkyl thionecarbamates to aryl dialkylthiocarbamates.[7,8] The rearrangements were suggested to proceed through a four-membered[2,6,8–10] or three-membered[11] cyclic transition state or free-radical intermediates.[2,3,12]

In order to investigate thione-thiol rearrangement of six membered heterocyclic ring systems, we decided to synthesize 3,4-disubstituted-5,6-dihydro-4H-1,2,5-oxadiazine-6-thiones.

As starting materials, anilino acetophenone oximes (**1**) were obtained from the oximation of α-amino acetophenones which were synthesized by the reaction of α-bromo acetophenones with primary amines as described in the literature.[13] The (Z) oximes (**1**) were treated with thiophosgene using triethylamine as a base catalyst to give 1,2,5-oxadiazine-6-thiones (**2**) (Scheme I).

^{1}H-NMR spectra of compounds (**2a**) and (**2b**) showed complexity in comparison with the other two thiones (**2c** and **2d**). To clarify this ambiguity ^{1}H-^{1}H COSY and ^{13}C-NMR spectra of compounds (**2a**) and (**2b**) were recorded. The fact that the absence of the singlet related to CH_2 protons between C(3) and N(5) and existence of at least three AB systems revealed a conformational case for these compounds. The interrelationship of these AB systems was observed from the COSY spectra. This situation was also supported by the existence of two peaks corresponding to CH_2 carbons of (**2a**) and (**2b**) at 51 and 52 ppm and two peaks corresponding to C =S carbons at 171 and 169 ppm in the ^{13}C-NMR spectra, respectively.

The rearrangement of 3-phenyl-5-(*p*-tolyl)-5,6-dihydro-4H-1,2,5-oxadiazine-6-thione (**2a**) was carried out in diphenyl ether at 220°C and yielded the corresponding 1,2,5-thiadiazine-6-one (**3a**). The mechanism of the rearrangement, which is shown below (Scheme II), can be considered to proceed through a free radical intermediate.

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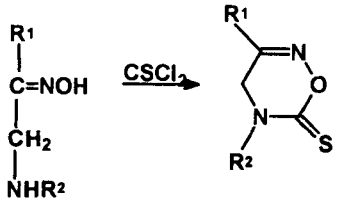
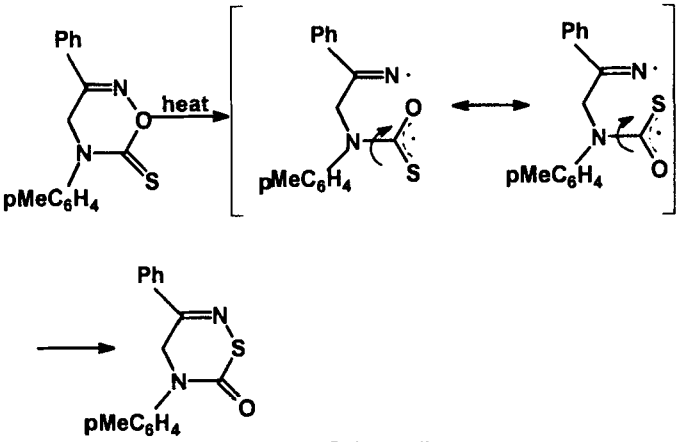


1(Z) 2

	R^1	R^2
a	Ph	p-MeC_6H_4
b	Ph	p-$MeOC_6H_4$
c	p-BrC_6H_4	Ph
d	p-BrC_6H_4	p-MeC_6H_4

Scheme I

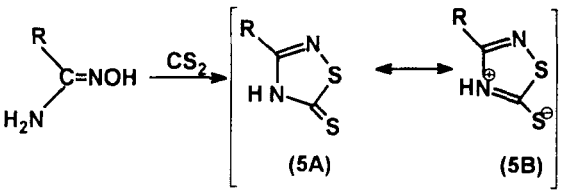


Scheme II

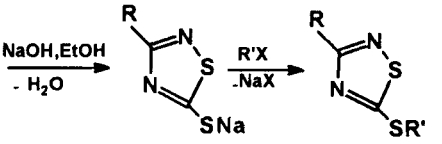
We tried to rearrange compounds (**2b**), (**2c**) and (**2d**) under similar conditions, but we found that they decompose before the rearrangement.

3-Methyl-1,2,4-thiadiazole-5(4H)-thione[14] and 3-phenyl-1,2,4-oxadiazole-5 (4H)-thione[15] were examined and the authors ascribed to the compounds the thione structure from solid state IR measurements. They also suggested the predominance of SH tautomer of the compounds in solution. However, Elguero and co-authors critisized these proposals and taking into account the results on 1,2,4-oxadiazole-5(4H)-ones[16a,17] they suggested[16b] an NH structure to be more likely for the 1,2,4-oxadiazole-5 (4H)-thiones in solution as well as the solid state.

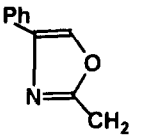
Our solid state IR spectra of 3-phenyl (or *p*-tolyl)-1,2,4-thiadiazole-5(4H)-thiones[4] showed NH absorptions at 3025, and 3000–3010 and C=S absorptions at 1470–1482, 1327–1335 and 1080–1102 cm^{-1}. However, methylation of these compounds in solution gave only S-methyl derivatives rather than N-methyl derivatives. There-



(5)	R
a	Ph
b	p-MeC_6H_4



6 7

(7)	R	R'
a	Ph	2,4-$(NO_2)_2C_6H_3$
b	pMeC_6H_4	2,4-$(NO_2)_2C_6H_3$
c	Ph	p-$MeC_6H_4CH_2$
d	Ph	p-$NO_2C_6H_4CH_2$
e	Ph	p-$BrC_6H_4COCH_2$
f	Ph	

Scheme III

fore, we considered that methylation of 3-substituted-1,2,4-thiadiazole-5(4H)-thiones proceed through the resonance structure (5B) (Scheme III). To generalize this reaction, we have reacted 3-substituted-1,2,4-thiadiazoles with various reactants as shown in Scheme III and obtained 3,5-disubstituted-1,2,4-thiadiazoles in moderate yields (34–60%). In order to be certain for the absence of the other isomer (N-derivative) in the reaction mixture, we checked the crude product by tlc and for each reaction we observed only one product.

EXPERIMENTAL

NMR spectra ($CDCl_3$ as solvent) were recorded on a Varian Gemini (^1H, 200 MHz; ^{13}C, 5O MHz) and Bruker Spectrospin (^1H, 250 MHz) instruments. IR spectra were recorded on Perkin-Elmer 177 and 881 models spectrophotometers (KBr and $CDCl_3$). Mass spectra were run at 70 eV by direct inlet on a Carlo Erba QMD 1000 instrument. Elemental analyses were performed by a Perkin-Elmer 240 C analyzer. Silica Gel (Fluka or Merck) were used for thin layer and column chromatography.

3-Phenyl-5-(p-tolyl)-5,6-dihydro-4H-1,2,5-oxadiazine-6-thione (**2a**). To a solution of (Z)-anilino acetophenone oxime (**1a**) (0.518 g, 2.28 mmol) and triethylamine (0.462 g, 4.57 mmol) in tetrahydrofuran 125 ml) cooled with an ice-salt mixture, thiophosgene (0.263 g, 2.29 mmol) in tetrahydrofuran (5 ml) was added dropwise. Reaction mixture was stirred overnight at room temperature. The precipitate (triethylamine hydrochloride) was removed and the solvent was evaporated under reduced pressure. The residual oily matter was subjected to flash column chromatography (eluant, chloroform-benzene, 5:1, R_f: 0.39) and crystallized from benzene-petroleum ether to give (**2a**) (0.410 g, 63%). m.p. 213–214°C. ^{1}H-NMR: δ 7.83–7.78 (m, 4 aromatic H), 7.54–7.45 (m, 5 aromatic H), 6.13 (d, J = 9.73 Hz, 1H) and 5.49 (d, J = 9.56 Hz, 1H) (AB system), 5.62 (m, broad, 1H), 4.93 (d, J = 16.5 Hz, 1H) and 4.31 (d, J = 16.5 Hz, 1H) (AB system), 4.80 (m, 1H) and 1.93 (s, 3H). ^{13}C-NMR: δ 171.80, 169.09, 133.42, 132.90, 131.54, 129.41, 128.53, 125.01, 116.44, 52.75, 51.81, 22.11, IR: 1665, 1445, 1275, 1150 cm^{-1}; m/z 282 (17%, M$^+$). Anal. Calcd. for $C_{16}H_{14}N_2OS$: C, 68.06; H, 4.99; N, 9.92. Found: C, 67.55; H, 4.95; N, 9.61.

3-Phenyl-5-(p-methoxyphenyl)-5,6-dihydro-4H-1,2,5-oxadiazine-6-thione (**2b**). To a solution of (Z)-methoxyanilino acetophenone oxime (**1b**) (6.0 g, 23 mmol) and triethylamine (5.05 g, 50 mmol) in tetrahydrofuran (50 ml), thiophosgene (2.6 g, 23 mmol) in tetrahydrofuran (5 ml) was added dropwise under cooling with an ice-salt mixture. The reaction mixture was stirred overnight at room temperature. The white precipitate was removed and solvent was evaporated under vacuo. The remaining dark coloured oily matter was subjected to flash column chromatography (eluant, chloroform-benzene, 3:1, R_f: 0.32) and crystallized from benzene to give (**2b**) (4.5 g, 66%). m.p. 194–195°C: ^{1}H-NMR: δ 7.83–7.36 (m, 6 H), 6.13 and 6.07 (d, J = 2.20 Hz, 2H) (AB system), 5.57 (broad d, J = 9.85 Hz, 1H), 5.02 and 4.32 (d, J = 13.74 Hz, 2H) (AB system), 4.83 and 4.80 (d, J = 2.20 Hz, 1H) (AB system), 3.64 (s, 3H). ^{13}C-NMR: δ 170.86, 168.96, 154.16, 132.45, 130.97, 128.91, 128.29, 128.04, 126.98, 125.29, 95.31, 87.91, 54.74, 52.55, 52.27; IR: 1690, 1455, 1285, and 1170 cm^{-1}; m/z 298 (49%, M$^+$). Anal. Calcd. for $C_{16}H_{10}N_2O_2S$: C, 64.41; H, 4.72; N, 9.38. Found: C, 64.66; H, 4.74; N, 9.11.

3-(p-Bromophenyl)-5-phenyl-5,6-dihydro-4H-1,2,5-oxadiazine-6-thione (**2c**). To a solution of (Z)-anilino *p*-bromoacetophenone oxime (**1c**) (0.60 g, 1.97 mmol) and triethylamine (0.397 g, 3.92 mmol) in tetrahydrofuran (10 ml) cooled by an ice-salt mixture, thiophosgene (0.225 g, 1.98 mmol) in tetrahydrofuran (5 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature. The precipitate was filtered off and solvent was evaporated under reduced pressure. The residual oily matter was extracted with acetone (3 × 50 ml). Acetone extract was subjected to flash column chromatography (eluant, benzene-chloroform, 5:1, Rf: 0.64) to yield (**2c**) (0.240 g, 35%). m.p. 143–145°C. ^{1}H-NMR: δ 7.92–7.07 (m, 9H), 5.25 (s, 2H); IR 1662, 1474, 1268 and 1189 cm^{-1}; m/z 347 (27%, M+).

3-(p-Bromophenyl)-5-(p-tolyl)-5,6-dihydro-4H-1,2,5-oxadiazine-6-thione (**2d**). To a solution of (Z)-*p*-toluidino *p*-bromoacetophenone oxime (**1d**) (0.200 g, 0.60 mmol) and triethylamine (0.126 g, 1.24 mmol) in chloroform (10 ml) cooled by an ice-salt mixture, thiophosgene (0.072 g, 0.62 mmol) in chloroform (5 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent remaining oily matter was extracted with acetone (3 × 50 ml). The precipitate was removed and extract was subjected to flash column chromatography (eluant, benzene, R_f = 0.34) and crystallized from benzene-petroleum ether to give (**2d**) (0.12 g, 55%). m.p. 173–174°C; IR 1670, 1490, 1298 and 1182 cm^{-1}; ^{1}H-NMR: δ 7.90 (m, 2H), 7.65 (m, 2H), 7.06 (m, 2H), 6.70 (m, 2H), 5.28 (s, 2H), 2.37 (s, 3H); m/z 361 (48%, M$^+$).

3-Phenyl-5-(p-tolyl)-5,6-dihydro-4H-1,2,5-thiadiazine-6-one (**3a**). Compound (**2a**) (50 mg, 0.177 mmol) was heated in diphenyl ether at 220°C for 4 h. The reaction mixture was extracted with acetone (3 × 10 ml). Acetone extract was subjected to thin layer chromatography (eluant, dichloromethane-benzene, 7:1, R_f: 0.62) to yield (**3a**) (17 mg, 34%) as light yellow oil. IR: 1675, 1601, 1488, 1449, 1332, 1223, 1178 cm^{-1}; ^{1}H-NMR: δ 8.03 (m, 2H), 7.53 (m, 5H), 7.03 (d, J = 8.63 Hz, 1H), 6.69 (d, J = 8.22 Hz, 1H), 5.34 (s, 2H), 2.36 (s, 3H); m/z 283 (27%, M$^+$).

3-Phenyl-1,2,4-thiadiazole-5 (4H)-thione (**5**). *General procedure*: KOH (5.16 g, 92.12 mmol) in ethanol (60 ml) was added to benzamidoxime (12.53 g, 92.12 mmol) in ethanol (60 ml). To this solution CS_2 (7 g, 92.12 mmol) in ethanol (15 ml) was added dropwise and the solution was refluxed for 6 h. The solvent was evaporated under reduced pressure and the yellow residue was dissolved in 5% solution of KOH. The solution was neutralized with 5% HCl. The resulting precipitate was filtered, dried over P_2O_5 under vacuo, and recrystallized from acetic acid, yielding compound (**5a**) (3.04 g, 24%); m.p. 158–159°C (lit.[4] 161–162°C).

3-(p-Tolyl)-1,2,4-thiadiazole-5(4H)-thione (**5b**), recrystallized from benzene-light petroleum (60–80°C) (1:1); m.p. 164–165°C (lit.[4] 165°C).

3-Phenyl-5-(2,4-dinitrophenylthio)-1,2,4-thiadiazole (**7a**). *General procedure*: 3-Phenyl-1,2,4-thiadiazole-5 (4H)-thione (0.38 g, 2 mmole) was dissolved in ethanol and aqueous solution of NaOH (0.08 g, 2 mmole) was added. The solution was refluxed for 30 min and 2,4-dinitrochlorobenzene (0.4 g, 2 mmole) in ethanol (15 ml) was added dropwise. The colour of the solution changed to yellow. The reaction mixture was refluxed for 1.5 h on a water bath. Solvent was evaporated under reduced pressure. The residue was washed with water, extracted with chloroform and dried with calcium chloride. The solvent was evaporated and remaining solid was recrystallized from benzene-light petroleum (40–60°C) (1:1) to give compound (**7a**) (0.42 g, 60%); m.p. 133–134°C, IR (KBr) 1575 (C=N), 1510 and 1330 cm^{-1} (NO_2); ^{1}H-NMR ($CDCl_3$) δ 7.47–7.62 (m, 3 aromatic H), 7.87 (d, 1 aromatic H), 8.03–8.48 (m, 3 aromatic H). Found: C, 46.98; H, 2.06; N, 15.57, Calcd. for $C_{14}H_8N_4S_2O_4$: C, 46.66; H, 2.23; N, 15.54.

Analytical and spectroscopic data of compounds (**7b–f**) are given below.

3-(p-Tolyl)-5-(2,4-dinitrophenylthio)-1,2,4-thiadiazole (**7b**), recrystallized from benzene-light petroleum (40–60°C) (1:1) (0.48 g, 44%); m.p. 163–164°C, IR (KBr) 1585 (C=N), 1515 and 1335 cm^{-1} (NO_2); ^{1}H-NMR ($CDCl_3$) δ 2.45 (s, 3, CH_3), 7.3 (m, 2 aromatic H), 7.87 (d, 1 aromatic H), 8.17 (m, 2 aromatic H), 8.32 and 8.42 (2d, 1 aromatic H) and 9.1 (d, 1 aromatic H). Found: C, 48.45; H, 2.74; N, 14.81, Calcd. for $C_{15}H_{10}N_4O_4S_2$: C, 48.12; H, 2.69; N, 14.96).

3-Phenyl-5-(p-methylbenzylthio)-1,2,4-thiadiazole (**7c**), recrystallized from light petroleum (40–60°C) (0.26 g, 58%); m.p. 155–156°C, IR (KBr) 1500 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, 3, CH_3), 4.50 (s, 2, CH_2), 7.01–7.50 (m, 7 aromatic H) and 8.20–8.40 (m, 2 aromatic H). Found: C, 64.67; H, 4.65; N, 9.30, Calcd. for $C_{16}H_{14}N_2S_2$: C, 64.40; H, 4.72; N, 9.38.

3-Phenyl-5-(p-nitrobenzylthio)-1,2,4-thiadiazole (**7d**), recrystallized from light petroleum (40–60°C) (0.19 g, 38%); m.p. 81–82°C, IR (KBr) 1590 (C=N), 1505 cm^{-1} (NO_2); ^{1}H-NMR ($CDCl_3$) δ 4.67 (s, 2, CH_2), 7.35–7.72 (m, 5 aromatic H) and 8.07–8.32 (m, 4 aromatic H). Found: C, 55.04; H, 3.02; N, 12.53. Calcd. for $C_{15}H_{11}N_3O_2S_2$: C, 54.70; H, 3.36; N, 12.75.

3-Phenyl-5-(p-bromophenacylthio)-1,2,4-thiadiazole (**7e**), recrystallized from light petroleum (40–60°C) (0.27 g, 34%); m.p. 109–110°C, IR (KBr) 1660 (C=O), 1578 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ 4.82 (s, 2, CH_2) and 7.30–8.12 (m, 9 aromatic H). Found: C, 48.79; H, 2.55; N, 7.56, Calcd. for $C_{16}H_{11}N_2OS_2Br$: C, 49.11; H, 2.83; N, 7.15.

3-Phenyl-5-(3-phenyl-1,2,4-oxadiazolyl)-1,2,4-thiadiazole (**7f**), recrystallized from light petroleum (40–60°C) (0.205 g, 34%); m.p. 104–105°C, IR (KBr) 1580 (cm^{-1}) (C=N); ^{1}H-NMR ($CDCl_3$) δ 4.80 (s, 2, CH_2), 7.37–7.57 (m, 6 aromatic H) and 8.00–8.32 (m, 4 aromatic H). Found: C, 58.22; H, 3.36; N, 15.63. Calcd. for $C_{17}H_{12}N_4OS_2$: C, 57.94; H, 3.43; N, 15.89.

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