Synthesis and Reactivity of 3,4-Dimethyl-4*H*-1,3,4-thiadiazines

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Abstract: 3,4-Dimethyl-4*H*-1,3,4-thiadiazines, novel 8π heterocyclic systems, were prepared by cyclization of α-haloketones with 1,2,4-trialkylthiosemicarbazides. The desulfurization of the products afforded 5-imino-1,2-dimethylpyrazoles by valence isomerization into thia-σ-homopyrazoles.

Key words: cyclizations, heterocycles, sulfur, synthetic methodology, valence isomerization

1,3,4-Thiadiazines are of considerable pharmacological relevance and represent versatile synthetic building blocks.[1] In this context, the desulfurization represents an important feature.[2] Most 1,3,4-thiadiazines reside in their 6*H*-tautomeric form, due to the relative instability of the 8π-electron system of the 4*H*-isomer.[3] The synthesis of 3,4-unsubstituted 4*H*-1,3,4-thiadiazines has been claimed in the early 1950s,[4a] but the structures were later shown to be thiazole rather than thiadiazine isomers.[4b,c] A number of 4-aryl-4*H*-1,3,4-thiadiazines were successfully prepared.[4b–h] Due to the substitution of the nitrogen atom N4, these compounds reside in the 4*H*-tautomeric form. The synthesis of bicyclic derivatives, stabilized by annulation, has also been reported.[5] In an early publication of 1927, the structure of a number of 3-aryl-1,3,4-thiadiazines were drawn in the 4*H*-tautomeric form.[6] However, no spectroscopic evidence was provided. In fact, we and others have shown that simple 3-alkyl-1,3,4-thiadiazines reside as 6*H*-tautomers.[7] In contrast, the 4*H*-tautomeric form is stabilized by the presence of an acetyl or ester group at carbon C6, due to the conjugation of the double bond with the carbonyl group.[8] Herein, we wish to report the synthesis of 3,4-dimethyl-4*H*-1,3,4-thiadiazines. In contrast to 3-methyl-6*H*-1,3,4-thiadiazines (Figure 1), we have found that the desulfurization proceeded very rapidly and allowed a facile synthesis of pharmacologically relevant 5-imino-1,2-dimethylpyrazoles. 4*H*-1,3,4-Thiadiazines (Figure 1) represent interesting building blocks which should have a variety of synthetic and pharmacological applications.

Our starting point was the preparation of the 1,2,4-trialkylthiosemicarbazides **1a,b** by reaction of the corresponding *iso*thiocyanates with *N*,*N*′-dimethylhydrazine.[9a] The cyclization of **1a,b** with α-haloketones **2a**–**d** afforded the 2-imino-3,4-dimethyl-2,3-dihydro-4*H*-1,3,4-thiadiazines **3a**–**g** in good yields (Scheme 1, Table 1).[10] Due to the methyl group attached to nitrogen atom N4, the products reside in the 4*H*-tautomeric form. The isolation of an open-chained intermediate showed that the reaction proceeded by regioselective attack of the sulfur atom of the thiosemicarbazide onto the bromide and subsequent cyclization by attack of the hydrazide onto the carbonyl group. The structure of thiadiazines **3a**–**g** was elucidated by spectroscopy and was independently confirmed by desulfurization experiments (vide infra).

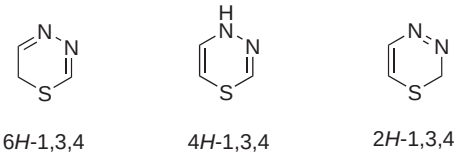
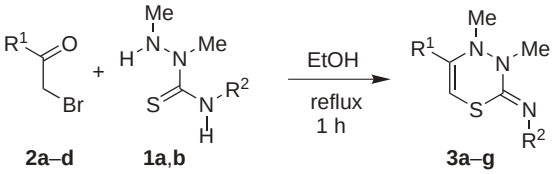


Figure 1



Scheme 1 Synthesis of 2-imino-3,4-dialkyl-2,3-dihydro-4*H*-1,3,4-thiadiazines **3a**–**g**

Table 1 Products and Yields

3	R^1	R^2	[%][a]	Mp (°C)
A	C_6H_5	Me	70[b]	160–161
B	4-BrC_6H_4	Me	79[b]	186–187
C	4-ClC_6H_4	Me	83[b]	190–192
D	C_6H_5	*i*-Pr	59[b]	164–166
E	4-MeC_6H_4	*i*-Pr	82[b]	123–125
F	4-BrC_6H_4	*i*-Pr	78[c]	131–133
G	4-ClC_6H_4	*i*-Pr	76[c]	155–157

[a] Yields of isolated products.
[b] Hydrobromide.
[c] Free base.

Treatment of 4*H*-1,3,4-thiadiazine **3a** with HBr acid (48%) or HCl acid (concd) afforded the novel 5-imino-1,2-dimethylpyrazole **4** in 40% and 30% yield, respectively (Scheme 2).[11,12] The yield was increased to 53% by use

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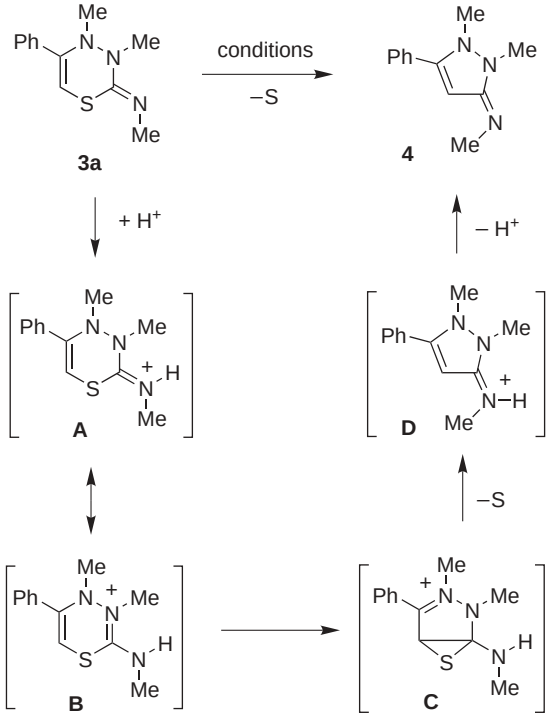
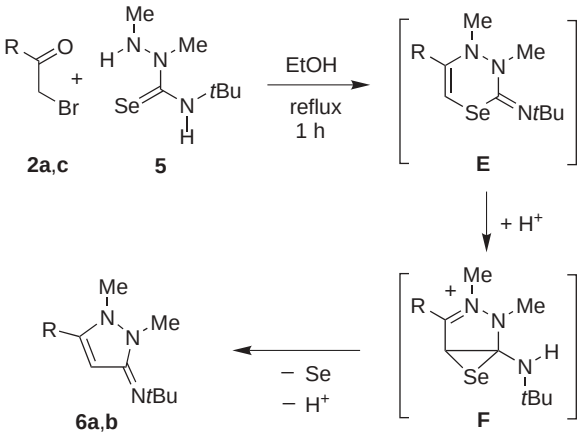
of glacial HOAc. The desulfurization proceeded very rapidly and precipitation of considerable amounts of sulfur was observed already after stirring for a few minutes. A possible mechanism, based on work of Schmidt,[3] is depicted in Scheme 2: Protonation of the amidine moiety afforded intermediate **A** and its mesomeric structure **B**. An 8π valence isomerization afforded the thia-σ-homopyrazole **C**; extrusion of sulfur gave the protonated pyrazole **D** which afforded the product **5a** by deprotonation. The product was isolated as a hydrobromide when hydrobromide acid was used. It was shown by NMR that the hydrobromide exists as a protonated amidine (structure **D**).



Scheme 2 Desulfurization of **3a**. *Reaction conditions*: Reflux, 1 h, HBr (48%), HCl (concd) or glacial HOAc, 30–53% yield

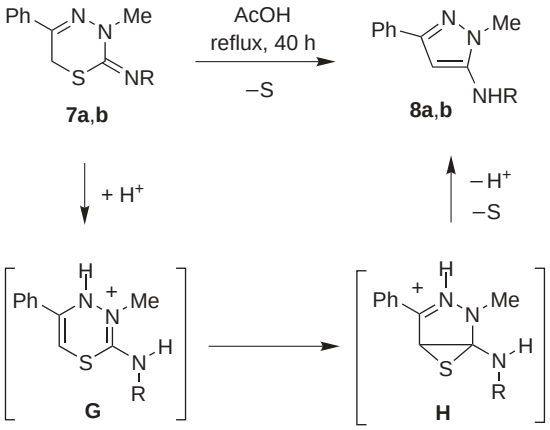
The synthesis and desulfurization of a 4*H*-1,3,4-selenadiazine was next studied (Scheme 3). The reaction of selenosemicarbazide **5**[9b] with α-phenacylbromides **2a** and **2c** directly afforded the 5-imino-1,2-dimethylpyrazoles **6a** and **6b** in 54% and 62% yield, respectively. The reaction proceeded by formation of the 4*H*-1,3,4-selenadiazine **E** which underwent a valence isomerization into the selena-σ-homopyrazole **F**. The latter underwent a rapid extrusion of selenium.

We have earlier reported that the desulfurization of the 6-unsubstituted 3-methyl-6*H*-1,3,4-thiadiazine **7a** was studied (Scheme 4).[7a] This experiment is included herein for reasons of comparison. Treatment of **7a** and of novel **7b** with glacial HOAc afforded the pyrazoles **8a** and **8b** in 41% and 81% yield. In contrast to the rapid desulfurization of 4*H*-1,3,4-thiadiazines **3**, a much longer reaction time (40 h) was required to achieve a complete desulfurization. A possible mechanism is depicted in Scheme 4:



Scheme 3 Cyclization of selenosemicarbazide **5** with -phenacylbromides **2a,c** (**6a**: R = C_6H_5, 54%, **6b**: R = 4′-ClC_6H_4, 62%)

Protonation of the amidine moiety and an acid catalyzed prototropic shift afforded the 8π system **G** which underwent a valence isomerization to give the thia-σ-homopyrazole **H**. Desulfurization and deprotonation afforded the final product.



Scheme 4 Desulfurization of **7a,b** (**8a**: R = Me, 41%, **8b**: *i*-Pr, 81%)

The results outline above can be explained as follows: the extrusion of sulfur from thiadiazines **3** and **7** proceeded by a valence isomerization and required the formation of a thermodynamically unfavourable 8π electron intermediate. The rapid desulfurization of 4*H*-1,3,4-thiadiazines **3** can be explained by the fact that the 8π intermediate **B** is readily available by simple protonation of the amidine moiety; the C(5)=C(6) double bond was already present in the starting material. In contrast, the desulfurization of the 6*H*-1,3,4-thiadiazines **7** required the formation of the C(5)=C(6) double bond (intermediate **G**). In case of the selena-analogous system, the 4*H*-1,3,4-selenadiazine was detected only in the form of intermediate **F**.

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(10) **Typical Procedure for the Synthesis of 2-Alkylamino-3,4-dimethyl-5-aryl-2,3-dihydro-4*H*-1,3,4-thiadiazines (3)**. An EtOH solution (20 mL) of 1,2-dimethyl-4-*iso*-propylthiosemicarbazide (**1a**) (1.47 g, 10.0 mmol) or of 1,2,4-trimethylthiosemicarbazide (**1b**) (1.19 g 10.0 mmol) and of the corresponding phenacyl bromide **2** (10.0 mmol) was refluxed for 1 h. After cooling to 20 °C, Et_2O was added to give a colourless precipitate. The latter was isolated by filtration and recrystallized from EtOH–Et_2O with addition of HBr. **3a**: Yield: 2.20 g (70%); colourless lamella (EtOH–Et_2O); mp 160–161 °C. IR (KBr): 705 (m), 712 (m), 781 (m), 820 (m), 970 (m), 1030 (m), 1170 (m), 1311 (s), 1410 (m), 1460 (s), 1499 (s), 1610 (s), 2995 (m), 3110 (m), 3225 (s) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ =3.22 (br s, 1 H, NH^+), 3.36 (d, 3 H, $NHMe^+$), 3.75 (s, 3 H, NMe) 4.18 (s, 3 H, NMe), 6.26 (s, 1 H, 6-H), 7.32–7.66 (m, 5 H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.14 (NMe), 32.52 (NMe), 43.99 (NMe), 121.78 (6-C), 124.38 (CH, Ar), 128.65 (CH, Ar), 129.90 (CH, Ar), 130.92 (Ar), 150.58 (5-C), 152.50 (2-C). MS (EI, 70 eV): *m*/*z* = 234 (17) [M^+], 233 (11), 231 (9), 220 (31), 218 (43), 202 (23), 201 (29), 187 (48), 186 (16), 118 (23), 96 (92), 94 (100). Anal. Calcd for $C_{12}H_{16}N_3BrS$ (314.25): C, 45.87; H, 5.13; N, 13.37. Found: C, 45.79; H, 4.56; N, 13.08. All products gave satisfactory spectroscopic and analytical data.

(11) **1,2-Dimethyl-3-phenyl-5-methyliminopyrazoline-hydrate hydrobromide (4)**. *Method A*: A solution of **3a** (3.14 g, 10.0 mmol) in HBr acid (15 mL, 48%) was refluxed for 1 h. After refluxing for 4–5 min sulfur started to precipiate. The solvent was evaporated under reduced pressure. The residue was recrystallized from EtOH–Et_2O to give **4** as colourless lamella (1.20 g, 40%), mp 168 °C. The compound crystallized as a hydrate and hydrobromide. The water could not be completely removed in vacuo over P_4O_{10} (140 °C). *Method B:* A solution of **3a** (3.14 g, 10.0 mmol) in HCl acid (15 mL, concentrated) was refluxed for 1 h. The work up was carried out as described for method A. Yield: 0.90 g, 30%. *Method C:* A solution of **3a** (3.14 g, 10.0 mmol) in glacial HOAc (10 mL) was refluxed 1 h. The mixture was poured into Et_2O (150 mL). A colourless precipitate was formed. The latter was filtered off and recrystallized from EtOH–Et_2O to give **4** as a colourless solid (1.60 g, 53%). IR (KBr): 780 (s), 805 (m), 812 (m), 924 (w), 989 (w), 1045 (m), 1082 (m), 1203 (w), 1295 (m) 1302 (m), 1430 (s), 1480 (s), 1496 (m), 1542 (m), 1645 (s), 2920 (m), 2951 (m), 3098 (s), 3225 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.78 (br s, 1 H, NH^+), 2.99–3.01 (d, 3 H, $NHMe^+$), 3.71–3.78 (d, 3 H, $NHMe^+$), 4.24 (s, 3 H, NMe), 5.74 (s, 1 H, 4-H), 7.45–7.59 (s, 5 H, ArH), 8.40 (br s, 1 H, NH^+). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.31 (NMe), 34.74 (NMe), 35.11 (NMe), 89.53 (CH, Hetar), 126.89 (CH, Ar), 128.8 (CH, Ar), 129.49 (CH, Ar), 131.34 (Ar), 152.10 (3-C), 153.72 (5-C). MS (EI, 70 eV): *m*/*z* = 234 (4) [M^+], 219 (4), 201 (11), 188 (100), 172 (10), 145 (16), 102 (48). Anal. Calcd for $C_{12}H_{18}N_3O$ (300.20): C, 48.01; H, 6.04; N, 13.98. Found: C, 48.20; H, 6.20; N, 13.98.

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