

SYNTHESIS, OXIDATION AND DEHYDROGENATION OF CYCLIC *N,O*- AND *N,S*-ACETALS. PART 1. TRANSFORMATION OF *N,S*-ACETALS: 3-ACYL-1,3,4-THIADIAZOLINES

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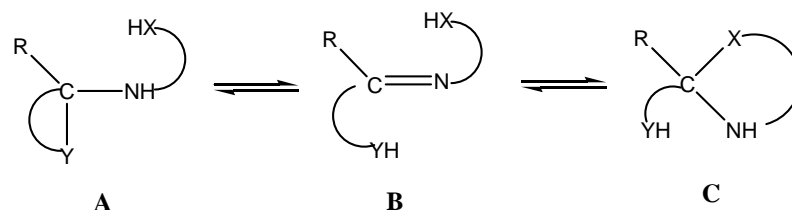
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Abstract – Aldehyde and ketone thiosemicarbazones are synthesized and cyclized into 3-acyl-1,3,4-thiadiazolines under acylating conditions. Reactions of the 2-monosubstituted heterocycles with oxidizing and dehydrogenating agents (KMnO₄ or for the first time with CAN, DDQ, IBDA) lead to the formation of thiadiazoles. CAN oxidation of 2,2-disubstituted 3-acyl-1,3,4-thiadiazolines regenerates the parent ketones efficiently.

INTRODUCTION

The formation of cyclic *N,O*- and *N,S*-acetals can be formally described by addition of an OH or SH group, located in the carbonyl or amino portion of the open-chain molecule, to the C=N bond (Scheme 1). The structure of the cyclic compound formed in this way, and the state of the equilibrium are determined by the electronic, steric and thermodynamic properties of the molecules and the nucleophilicity of the heteroatoms X and Y, respectively.

The ring-chain tautomerism¹ is a very important phenomenon from chemical and biological point of view [glycosylamines, sugar-amino acid condensates, etc.; e.g. to D-galactose thiosemicarbazone an open-chain hydrazone (**B**, Scheme 1) and a pyranose (**A**) structure,² respectively, to the D-glucose derivative a glucosylamine structure (**A**),³ to the ligand of a 1:1 complex of D-glucose thiosemicarbazone with CuCl₂, however, a 2-amino-5-(D-*gluco*-pentahydroxy)pentyl-1,3,4-thiadiazol-5-ine structure (**C**)⁴ have been attributed]. The cyclic or open-chain isomers can be stabilized chemically, e.g. by acetylation,⁵ whereby modifying solubility, biological absorption (membrane and barrier permeability) and activity. Chemical as well as microbial or enzymic deacetylation^{6a-c} (phase 1 metabolism) can lead to (re)cyclization or to regeneration of the original isomerizable compound and the parent acid hydrazide^{6f-h} respectively.



Scheme 1

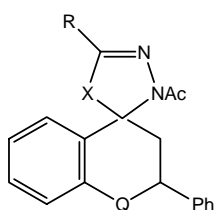
Dehydrogenation of aldehyde cyclic *N,O*- or *N,S*-acetals, the latter is a spontaneous process occasionally, seems to be a versatile and promising alternative route for the synthesis of various 2-substituted 1,3-azoles and 1,3-azines, respectively. – It should also be noted, however, that some dehydrogenation products, e.g. 1,3,4-oxadiazoles⁷ and 1,3,4-thiadiazoles⁸ undergo recyclization with intra- or intermolecular nucleophiles.

The chemistry of 1,3,4-thiadiazol(in)es^{1b,c,e,g,9a,10} as biologically active^{9b,c,11,12} and/or complex-forming^{11p,13} substances is well documented and has been enormously extended if only in view of late ~15 years, as well. 2,5-Disubstituted 1,3,4-thiadiazoles have been synthesized by cyclization of *N,N'*-di(thio)acylhydrazines,¹⁴ by condensing thioacid hydrazides with trichloromethanes,¹⁵ carboxylic acids,¹⁶ iminoesters,¹⁷ or (iso)nitriles^{16d,18} (eventually, however, under vigorous conditions), moreover by treating aldehyde thioacylhydrazones (including thiosemicarbazones) with FeCl_3 ,^{13a,19a-w} $\text{K}_3[\text{Fe}(\text{CN})_6]$,^{19g,20} MnO_2 ,²¹ Br_2/AcOH ,²² or DDQ.²³ On the other hand, DDQ cyclizes 4-substituted thiosemicarbazides into 5-substituted imino- Δ^3 -2,1,3,4-oxathiadiazolines and -2,2-dioxo- Δ^3 -1,2,3,4-dithiadiazolines,²⁴ *N*-benzylidene-2-hydroxyanilines into 2-substituted phenylbenzoxazoles,²⁵ and cleaves tosylhydrazones or oximes to the parent carbonyl compounds.²⁶ In addition, 2,5-disubstituted 1,3,4-thiadiazoles have been prepared, in an uncommon reaction, by treating aldehyde thiosemicarbazones with $\text{NaOAc}/\text{NaBr}/\text{AcOH}$,²⁷ as well as by transforming 1,3,4-oxadiazoles with thiourea^{7d} and 1,2,4,5-tetrazines with sulfur,²⁸ respectively. Of the various 1,3,4-thiadiazole syntheses, for this once, mostly the dehydrocyclization reactions will be considered.

Thioacylhydrazines react with carbonyl compounds to give immediately the corresponding 1,3,4-thiadiazolines^{11d,29} or sometimes their prototrops forms.^{11d,29g} Thiosemicarbazones undergo similar cyclization, mainly in acid medium to form an equilibrium mixture of the open-chain and prototrop cyclic entities.^{11b,e,19m,30} Some aldehyde thiobenzoylhydrazones exist as Δ^2 -thiadiazolines also in solution and are spontaneously dehydrogenated by prolonged heating,^{29c,31} or by oxygen at room temperature,^{19c,x,29d} to afford 1,3,4-thiadiazoles. With respect to the ring-chain tautomerism and the prototropy mentioned above, stabilization of the cyclic form is suitable. Under acylating conditions thioacylhydrazones, including thiosemicarbazones, undergo transformation to 5-substituted 3-acyl-1,3,4-thiadiazolines^{11,14c,32} instead of

N,S-diacyl-thiosemicarbazones as have been suggested previously.^{13a,19 1,33} Dehydrogenation of the 3-acylthiadiazolines by treating with H₂O₂,^{19 1,33c,d} FeCl₃,^{32a,d} or KMnO₄^{21,32d} has been reported to afford 1,3,4-thiadiazoles.

As an extension of our previous works with spiro[tetrahydroquinoline-4,2'-[1,3,4]thiadiazoline] (**11a**)³⁴ and spiro[flavan-4,2'-[1,3,4]oxa(thia)diazolines] (**11b,c**)^{32h} the analogous thioflavan spirocompounds (**11d,e**) have been synthesized³⁵ and, for obtaining the corresponding thioflaven analogs subjected to transformation with CAN capable³⁶ of dehydrogenating thioflavanone to thioflavone. When treating **11e** with CAN, however, thioflavone formed with degradation of the thiadiazoline moiety.³⁵ Owing to these difficulties, the oxidation and dehydrogenation reactions of 1-thiobenzopyran³⁷ and diazoline rings, respectively, have been separately investigated. In this paper the works aimed at the transformation of 1,3,4-thiadiazolines by oxidizing and dehydrogenating agents are presented.



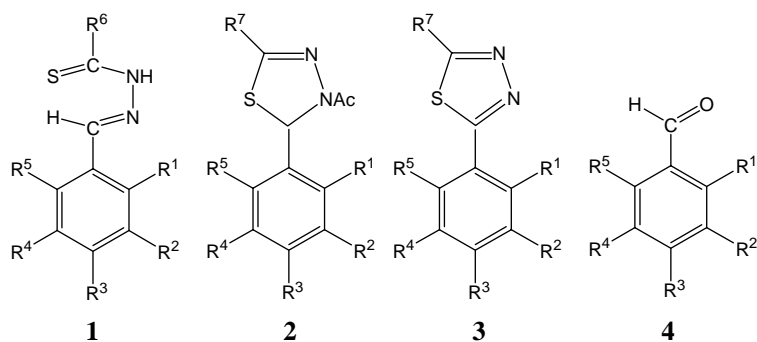
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| | Q | X | R |
|------------|-----|---|--------------------------------|
| 11a | NAc | S | NHAc |
| 11b | O | S | NHAc |
| 11c | O | O | Me |
| 11d | S | O | R ¹ |
| 11e | S | S | NR ² R ³ |

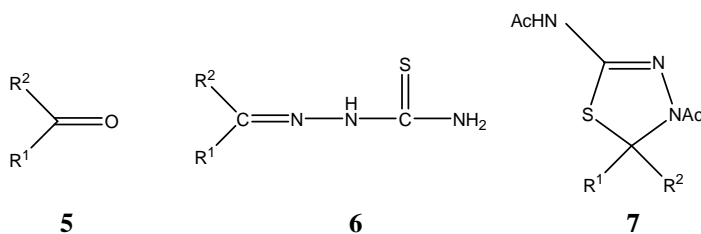
R¹= Me, Ph; R²= H, Ph; R³= Ac

RESULTS AND DISCUSSION

The electronic structure and chemical reactivity of a C=N bond is influenced by the electronic properties of the substituents (see e.g. ref. 38). Thus, thiosemicarbazones of various benzaldehydes diversely substituted as regards the position, number, bulk, electronic properties, and reactivity of the substituents (**1**, see also Table 1) were prepared and, under acetylating conditions (Ac₂O, Ac₂O/pyridine, Ac₂O/ZnCl₂), cyclized into 3-acetyl[1,3,4]thiadiazolines (**2**, Table 2). These compounds are substrates for subsequent reactions with various types of oxidants and dehydrogenating agents of diverse mechanisms of action (see Table 3). For exploring such cyclization reactions, some additional aldehyde and ketone thiosemicarbazones (**6**) were prepared and converted into thiadiazolines (**7**) (see Tables 6,7). The structure of the products was supported by ¹H- and ¹³C NMR spectral data (see Tables 4,5,8).



| | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | R ⁶ | R ⁷ |
|----------|----------------|-----------------|-----------------|----------------|----------------|-----------------|----------------|
| a | H | H | Cl | H | H | NH ₂ | NHAc |
| b | H | H | NO ₂ | H | H | NH ₂ | NHAc |
| c | Cl | H | H | H | Cl | NH ₂ | NHAc |
| d | Cl | H | H | H | Cl | NHPh | NAcPh |
| e | Cl | NO ₂ | H | H | Cl | NH ₂ | NHAc |
| f | H | Cl | Cl | H | H | NH ₂ | NHAc |
| g | H | OMe | OMe | OMe | H | NH ₂ | NHAc |
| h | OMe | H | OMe | H | OMe | NH ₂ | NHAc |



| | R ¹ | R ² |
|----------|--|----------------|
| a | 4-ClC ₆ H ₄ | Me |
| b | 4-BrC ₆ H ₄ | Me |
| c | 2-pyridyl | Me |
| d | 2,4-(HO) ₂ C ₆ H ₃ | Me |
| e | 2,4-(AcO) ₂ C ₆ H ₃ | Me |
| f | Indol-3-yl | H |
| g | 1-(Ac)indol-3-yl | H |

The acetylating agents used (and others e.g. AcCl/Me₂NPh, Ac₂O/Et₃N) are reported, however, also to transform^{2,32h,39,40} thiosemicarbazones into acylhydrazones and diacyhydrazones or *N*-triacetylenehydrazines. On this subject, especially the Ac₂O/ZnCl₂ couple is capable of producing transformations of various types. This agent is known to acetylate thiosemicarbazones at position 4,³⁹ and to cyclize (thio)acylhydrazones into 3-acetyl[1,3,4]oxa(thia)diazolines.⁴¹

Table 1. Preparation and properties of thiosemicarbazones (**1**)

| Product | Reaction components (mmol) | Solvent (mL) | Reaction temp. [°C] ^a (time [h]) | Workup ^b | Yield [%] crude ^c (pure) ^c |
|-----------------------|--|---------------------------|---|---------------------|--|
| 1a | 4a (40) TSC (42) | AcOH (30) | 100 (3) | A | 80 |
| 1b | 4b (20) TSC (30) | AcOH (20) | 100 (2) | A | 90 |
| 1c | 4c (10) TSC (10.5) | MeOH ^f (20) | bp (1.5) | A | 99.5 |
| 1d^h | 4d (10) PTSC (10) | EtOAc (8) | bp (1.5) | A | 95.5 |
| 1e | 4eⁱ (20) TSC (23) | AcOH (20) | 100 (2) | A ^j | 96.4 |
| 1f | 4f (60) TSC (63) | MeOH ^l (75) | bp (3.5) | A | 85 |
| 1g | 4g (20) TSC (21) | MeOH ^o (35) | bp (6) | A | 97 |
| 1h | 4h (20) TSC (21) | MeOH ^o (40) | bp (2.5) | A | 96 (94) |

Table 1. Preparation and properties of thiosemicarbazones (**1**) (continued)

| Product | Mp [°C] (solvent) | Lit. mp [°C] (solvent) | Formula (mol. mass) | Analysis found (calcd) | | |
|-----------------------|--|------------------------------------|--|------------------------|----------------|-------------------------------|
| | | | | C | H | N |
| 1a | 215 ^d | 220 ^e (aq.EtOH) | C ₈ H ₈ N ₃ ClS (213.7) | | | |
| 1b | 243 ^d | 255 ^e (95% EtOH) | C ₈ H ₈ N ₄ O ₂ S (224.2) | | | |
| 1c | 237 ^d | 236–237 ^g (EtOH) | C ₈ H ₇ N ₃ Cl ₂ S (248.1) | | | |
| 1d^h | 208–209 ^d | | C ₁₄ H ₁₁ N ₃ Cl ₂ S (324.2) | 52.07 (51.86) | 3.49 (3.42) | 13.08 ^h (12.96) |
| 1e | 229–230 ^d 234–235 (MeOH) | | C ₈ H ₆ N ₄ O ₂ Cl ₂ S (293.1) | 33.28 (32.78) | 2.51 (2.06) | 18.93 ^k (19.11) |
| 1f | 214–215 ^{d,m} 216 (MeOH) | 194–195 (EtOH) ⁿ | C ₈ H ₇ N ₃ Cl ₂ S (248.1) | 38.94 (38.72) | 2.86 (2.84) | 16.87 (16.94) |
| 1g | 206–207 ^d 209–210 (EtOH) | 216–217 ^p (DMF/EtOH) | C ₁₁ H ₁₅ N ₃ O ₃ S (269.3) | 49.33 (49.05) | 5.60 (5.61) | 15.70 ^q (15.60) |
| 1h | 160–162 (DMF/H ₂ O) | | C ₁₁ H ₁₅ N ₃ O ₃ S (269.3) | 49.22 (49.05) | 5.71 (5.61) | 15.68 ^r (15.60) |

TSC = thiosemicarbazide, PTSC = 4-phenyl-3-thiosemicarbazide. ^a Bath if not bp. ^b For general operations of processing the reaction mixtures see EXPERIMENTAL. ^c Without workup of the mother liquors. ^d Crude product. ^e Corrected, ref. 53. ^f Containing 0.5 mL AcOH. ^g Ref. 54. ^h Cl 21.98 (21.87), S 10.05 (9.89). The same product was obtained in 71% yield when treating 2,6-dichlorobenzaldehyde hydrazone (1mmol) with PhNCS (1.1 mmol) in boiling EtOAc (2 mL) for 1.5 h; mp 206–208 °C (from pyridine with addition of water). ⁱ Ref. 55. ^j Previously water (10 mL) was added. ^k Cl 24.04 (24.19), S 11.01 (10.94). ^l Containing 3 mL AcOH. ^m TLC [PhH/EtOAc (1:2)] homogeneous. ⁿ Ref. 19b. ^o Containing 1 mL AcOH. ^p Ref. 56; ref. 57 : mp 215–216 °C. ^q S 11.87 (11.91). ^r S 11.66 (11.91).

By heating above the melting point, 5-acetamido-3-acetyl-2-(4-nitrophenyl)-1,3,4-thiadiazoline (**2b**) was dehydrogenated to thiadiazole (**3b**) in 88% yield (see EXPERIMENTAL). Hitherto thermolysis of 2,5-disubstituted 3-nitroso-1,3,4-thiadiazolines^{19m} and of a spiro- Δ^3 -1,3,4-thiadiazoline with C—O bond cleavage to give a 2-substituted 1,3,4-thiadiazole have been reported.⁴² Also dehydrogenation of ketone cyclic *N,S*-acetals with concomitant reductive C—C bond cleavage resulting in the formation of benzothiazole⁴³ and 1,3,4-thiadiazole^{19d,44} derivatives, respectively, has been observed perviously. Moreover, when treating a carbohydrate aldehyde thiosemicarbazone with Ac₂O/pyridine, in addition to the expected formation of the corresponding 2-substituted 5-acetamido-3-acetyl-1,3,4-thiadiazoline the

Table 2. Preparation and properties of 1,3,4-thiadiazolines (**2**)

| Product | Substrate (mmol) | Agents (mmol) | Reaction temp. [°C] ^a (time [h]) | Workup ^b | Yield[%] crude (pure) ^c |
|-----------|--------------------|---|---|---------------------|-------------------------------------|
| 2a | 1a (20) | Ac ₂ O (233) | bp (2) | C, D, A | 90 ^e |
| 2b | 1b (9) | Ac ₂ O (53) | bp (0.5) | B | 98 ^f |
| 2c | 1c (40) | Ac ₂ O (530) | bp (1) | A | 95 |
| | 1c (4) | Ac ₂ O (106) ZnCl ₂ (11) | 55 (5) | A | 95 |
| 2d | 1d (6) | Ac ₂ O (106) py ¹ (124) | 23 (24) | B | 97 (80) |
| 2e | 1e (63) | Ac ₂ O (1060) | bp (0.75) | A | 96 (88) |
| 2f | 1f (16) | Ac ₂ O (212) | bp (2) | A | 85 (70) |
| 2g | 1g (22) | Ac ₂ O (159) | bp (0.5) | C, E | 99 (86) |
| 2h | 1h (1.9) | Ac ₂ O (27) | bp (2) | B | 69 (27) |

Table 2. Preparation and properties of 1,3,4-thiadiazolines (**2**) (continued)

| Product | Mp [°C] (solvent) | Lit. mp [°C] (solvent) | Formula (mol. mass) | Analysis found (calcd) | | |
|-----------|--|--------------------------------|--|---------------------------|----------------|-------------------------------|
| | | | | C | H | N |
| 2a | 247 ^d (EtOH) | 229–233 ^e (EtOH) | C ₁₂ H ₁₂ N ₃ O ₂ ClS (297.8) | | | |
| 2b | 227 ^d 230 (EtOH) | 210–211 ^f (EtOH) | C ₁₂ H ₁₂ N ₄ O ₄ S (308.3) | 46.89 (46.74) | 3.92 (3.92) | 18.16 ^g (18.17) |
| 2c | 203 ^d 236–237 (DMSO/H ₂ O) ^h 235–236 ^d 203–204 (DMSO/H ₂ O) ^h | | C ₁₂ H ₁₁ N ₃ O ₂ Cl ₂ S (332.2) | 43.88 (43.38) | 3.54 (3.34) | 12.34 ⁱ (12.65) |
| 2d | 183 (EtOAc/heptane) | | C ₁₈ H ₁₅ N ₃ O ₂ Cl ₂ S (408.3) | 53.12 (52.95) | 3.70 (3.70) | 10.34 ^j (10.29) |
| 2e | 266–267 ^d 271–272 (Ac ₂ O) | | C ₁₂ H ₁₀ N ₄ O ₄ Cl ₂ S (377.2) | 38.42 (38.21) | 2.70 (2.67) | 14.90 ^k (14.85) |
| 2f | 202–204 ^d 203 (EtOH ^l /heptane) | | C ₁₂ H ₁₁ N ₃ O ₂ Cl ₂ S (332.2) | 43.56 (43.38) | 3.40 (3.34) | 12.68 ^m (12.65) |
| 2g | 164 ^{d,n} 166–167 (MEK) ^o | | C ₁₅ H ₁₉ N ₃ O ₅ S (353.4) | 51.03 (50.98) | 5.63 (5.42) | 12.18 ^p (11.89) |
| 2h | 218–219 (CHCl ₃ /EtOAc) | | C ₁₅ H ₁₉ N ₃ O ₅ S (353.4) | 51.15 (50.98) | 5.50 (5.42) | 12.07 ^q (11.89) |

^a Bath if not bp. ^b For general operation of processing the reaction mixtures see EXPERIMENTAL. ^c Without workup of the mother liquors. ^d Crude product. ^e Ref. 32a, d, yield 68%. ^f Ref. 32a, d, yield 57%. ^g S 10.67 (10.40). ^h From hot DMSO solution with addition of water. When recrystallized from AcOH/H₂O or DMF/H₂O **2c** contains some AcOH and DMF, respectively, as a solvate. ⁱ Cl 21.05 (21.35), S 9.73 (9.65); before the analysis **2c** was kept at 100 °C/0.1 Torr over P₄O₁₀. EI-MS: *m/z* (%) [M⁺] 333 (8) and 331 (11), [2,6–Cl₂C₆H₃–C≡S⁺] 189 (6). ^j Cl 17.37 (17.37), S 7.88 (7.85). ^k Cl 18.93 (18.80), S 8.65 (8.50). ^l Anhydrous. ^m Cl 21.28 (21.35), S 9.86 (9.65). ⁿ When workup (A) was done (yield 81%). ^o 2-butanone (methyl ethyl ketone). ^p S 9.39 (9.07); EI-MS: *m/z* (%) [M⁺] 353 (21). ^q EI-MS: *m/z* (%) [M⁺] 353 (22).

dehydrogenated analog thiadiazole was also formed.^{19w} For the pyrolysis of aldehyde thiosemicarbazones to give, among others, 5-substituted 2-amino-1,3,4-thiadiazoles⁴⁵ a free radical mechanism has been suggested.⁴⁶

Besides the oxidant KMnO₄ used^{21,32d} previously for the dehydrogenation of 2,5-disubstituted 3-acyl-1,3,4-thiadiazolines, also the one-electron acceptor CAN was efficiently applied for such transformations now for the first time. This method is more ready and, with more simple processing, often affords almost pure crude products in better yields in comparison with the KMnO₄ oxidation (see Table 3). Also the dehydrogenation power of the charge-transfer complex forming DDQ and the hypervalent iodine oxidant IBDA were tested and found to be effective (transformations **2b**→**3b** and **2a**→**3a**, Table 3).

It should be noted, however, that while IBDA has been reported⁴⁷ to transform aldehyde acylhydrazones into 1,3,4-oxadiazoles at room temperature within 2 minutes,^{47a} it dehydrogenated 5-acetamido-3-acetyl-1,3,4-thiadiazoline (**2a**) into thiadiazole (**3a**), devoid of a deprotonable *N*-iminoamide or an intermediary endocyclic secondary amine moiety, much more slowly. The transformation of the 5-acetamido (**2**) entities can be suggested to start with loss of the AcNH proton and then the electron rich heterocycle joins with the endocyclic nitrogen to the hypervalent iodine reaction centre. In consonance with this mechanistic hypothesis, while a treatment with IBDA in methanol solution dehydrogenated 5-acetamido thiadiazoline (**2c**) at room temperature almost completely [TLC, CHCl₃/MeOH (95:5)] during 3 days, under the same conditions the 5-acetanilido analog (**2d**) resisted transformation [TLC, CHCl₃/MeOH (95:5)] after 4 days,

Table 3. Preparation and properties of thiadiazoles (**3**)^a

| Product | Substrate (mmol) | Agent (mmol) | Solvent (mL) | Reaction temp. [°C] (time [h] ^{b,c}) | Workup ^d | Yield[%] crude (pure) |
|-----------|--------------------|-----------------------------|-------------------------------------|--|---------------------|-----------------------|
| 3a | 2a (0.5) | KMnO ₄ (1.85) | AcOH(10) H ₂ O (3) | < 20 (1.5; 3) | F, C, E | 70 |
| | 2a (0.5) | CAN ^h (0.967) | MeCN(10) H ₂ O (1) | 23 (0.33; 0.75) | G, A | 94.5 |
| | 2a (0.5) | IBDA ⁱ (0.55) | MeOH (15) | 23 (2; 36) | A | 93 |
| 3b | 2b (2) | KMnO ₄ (5) | AcOH (20) H ₂ O (3) | < 20 (1; 1.5) | F, G, A | 81 |
| | 2b (1) | CAN (2.08) | MeCN (10) H ₂ O (3) | 23 (0.15; 0.1) | G, A | 98.5 |
| | 2b (0.5) | DDQ ^o (0.6) | PhH (5) | bp (6) | A, K | 85 |
| 3c | 2c (1) | KMnO ₄ (2.5) | AcOH (10) H ₂ O (3) | < 20 (1.5; 1) | F, G, A | 77.5 |
| | 2c (1) | CAN (1.7) | MeCN (10) H ₂ O (1) | 23 (0.13; 0.5) | G, A | 84 |
| 3d | 2d (1.5) | CAN (2.63) | MeCN (30) H ₂ O (1.5) | 23 (0.2; 0.33) | G, A | 97 (88) |
| 3e | 2e (1) | KMnO ₄ (2.5) | AcOH (12) H ₂ O (2) | < 20 (1.2; 1.5) | F, G, A | 84 |
| 3g | 2g (2) | KMnO ₄ (5) | AcOH (15) H ₂ O (3) | < 20 (1; 2) | F, G, A | 35 (31) |
| | 2g (1) | CAN (2.03) | MeCN (5) H ₂ O (1.5) | 23 (0.6; 0.17) | G, A | 64 (52) |

Table 3. Preparation and properties of thiadiazoles (**3**)^a (continued)

| Product | Mp [°C] (solvent) | Lit. mp [°C] (solvent) | Formula (mol. mass) | Analysis found (calcd) | | |
|-----------|--------------------------------------|--------------------------------|---|---------------------------|--------|--------------------|
| | | | | C | H | N |
| 3a | 330 ^{e,f} | 322–324 (EtOH) ^g | C ₁₀ H ₈ N ₃ OClS (253.7) | 47.31 | 3.18 | 16.65 |
| | 331 ^{e,f} | | | (47.34) | (3.18) | (16.56) |
| | 335(CHCl ₃) ^f | | | | | |
| 3b | 333 ^{e,f} | | | | | |
| | >360 ^e | | C ₁₀ H ₈ N ₄ O ₃ S (264.3) | 45.19 | 3.00 | 20.89 ^j |
| | >360 (DMSO/H ₂ O) | | | (45.45) | (3.05) | (21.20) |
| | >360 ^e | | | | | |
| 3c | >370 ^e | | | | | |
| | 258–259 ^e | | C ₁₀ H ₇ N ₃ OCl ₂ S (288.2) | 42.02 | 2.74 | 14.67 ^k |
| | 260 (EtOH) | | | (41.68) | (2.45) | (14.58) |
| 3d | 258 ^e | | | | | |
| | 259 (CHCl ₃ /EtOAc) | | | | | |
| 3d | 208 ^e | | C ₁₆ H ₁₁ N ₃ OCl ₂ S (364.3) | 52.66 | 2.95 | 11.42 ^l |
| | 208(CHCl ₃ /EtOAc) | | | (52.75) | (3.04) | (11.54) |
| 3e | 298 ^e | | C ₁₀ H ₆ N ₄ O ₃ Cl ₂ S (333.2) | 35.90 | 1.90 | 16.88 |
| | 298 (DMF/H ₂ O) | | | (36.05) | (1.82) | (16.82) |
| 3g | 253–254 ^e | 251 ^m | C ₁₃ H ₁₅ N ₃ O ₄ S (309.3) | 50.87 | 5.09 | 13.54 ⁿ |
| | 255 (AcOH/H ₂ O) | (EtOH) | | (50.47) | (4.89) | (13.58) |
| | 255 (AcOH/H ₂ O) | | | | | |

^a For general method of preparation see EXPERIMENTAL. ^b Input. ^c Additional reaction time. ^d For general operations of processing the reaction mixtures see EXPERIMENTAL. ^e Crude product. ^f Volatile near the melting point. ^g Ref. 58. ^h Ceric ammonium nitrate. ⁱ Iodobenzene diacetate: PhI(OAc)₂. ^j S 12.50 (12.13). ^k Cl 24.44 (24.61), S 11.50 (11.13). ^l Cl 19.56 (19.47), S 9.08 (8.80). ^m Ref. 59. ⁿ S 10.69 (10.37). ^o 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

and only scarcely traces of the thiadiazole (**3d**) could be detected. Similar to the dehydrogenations **2**→**3**, treatment of the 2-monosubstituted fused Δ^4 -thiadiazoline (**8**) with KMnO₄, or more advantageously with CAN, led to the formation of the thiadiazolylbenzoic acid derivative (**9**) (see EXPERIMENTAL). However, treatment of the dialdehyde derivative bithiadiazoline **10a** with KMnO₄, CAN or PhI(OAc)₂ (IBDA) did not afford the corresponding 5,5'-diacetamido-2,2'-bi[1,3,4]thiadiazole as expected, but instead 2-acetamido[1,3,4]thiadiazole *via* cleavage of the C(2)—C(2') bond. Although CAN oxidation of 2,2'-disubstituted 3-acetyl[1,3,4]thiadiazolines was found³⁵ to regenerate the carbonyl group of the parent ketone (see also INTRODUCTION), treatment of the 1,2- keto aldehyde derivative

Table 4. Characteristic ^1H NMR spectral data^a of thiosemicarbazones (**1**), thiadiazolines (**2**), and thiadiazoles (**3**)

| Compound | δ [ppm] | | | |
|-----------|-----------------------|-------------------|-------------------|--|
| | NH/OH | CH=N | S-CH(Ar)-N | CH ₃ |
| 1a | | 8.02 ^b | | |
| 1b | | 8.11 ^b | | |
| 1c | 11.77 8.42 7.46 | 8.32 | | |
| 1d | 12.19 | 8.43 | | |
| 1e | 11.86 8.47 7.62 | 8.30 | | |
| 1g | 11.84 8.39 8.25 | 8.11 | | 3.96 ^c 3.81 |
| 1h | 11.32 8.14 7.26 | 8.41 | | 3.96 3.94 ^c |
| 2a | | | 6.82 ^b | |
| 2b | 11.86 | | 6.98 ^b | 2.27 2.08 |
| 2c | 12.50 | | 7.30 | 2.14 2.07 |
| 2d | | | 7.37 ^d | 1.92 1.75 |
| 2e | 12.06 | | 7.53 | 2.29 2.23 |
| 2f | 11.81 | | 6.81 | 2.20 2.05 |
| 2g | 12.19 | | 6.92 | 3.89 ^{c,e} 3.78 ^e 2.37 2.18 |
| 2h | 11.59 | | 7.05 | 3.76 ^f |
| 3a | 12.69 | | | 2.22 |
| 3b | 12.84 | | | 2.25 |
| 3c | 12.90 | | | 2.37 |
| 3d | | | | ^g 2.13 |
| 3e | 12.93 | | | 2.36 |
| 3g | | | | 4.03 ^{c,e} 3.87 ^e 2.35 ^g 2.68 ^h |

^a 200 MHz, for solutions in [DMSO- d_6] if not otherwise stated *before* the columns. ^b Ref. 32a, for **2b** δ = 6.95. ^c 6 H. ^d Presumably; superimposed on the signals of aromatic hydrogens. ^e OMe. ^f 9 H; 3 MeO. ^g For solutions in CDCl₃. ^h 360 MHz.

bithiadiazoline (**10b**) with CAN did not provide 5-acetamido-2-acetyl[1,3,4]thiadiazole but 5-acetamido-2-methyl[1,3,4]thiadiazole likewise with C(2)—C(2') bond cleavage (see EXPERIMENTAL).

CAN oxidation has been reported to transform thiocarboxamides into their oxygen analogs^{48a,b} and/or into 1,2,4-thiadiazoles.^{48a} Quite recently C—C bond cleavages of radical cations, obtained by photolysis of C-4 analog cyclic *N,S*-acetals 2-substituted benzothiazolines, have been thoroughly investigated.^{48c}

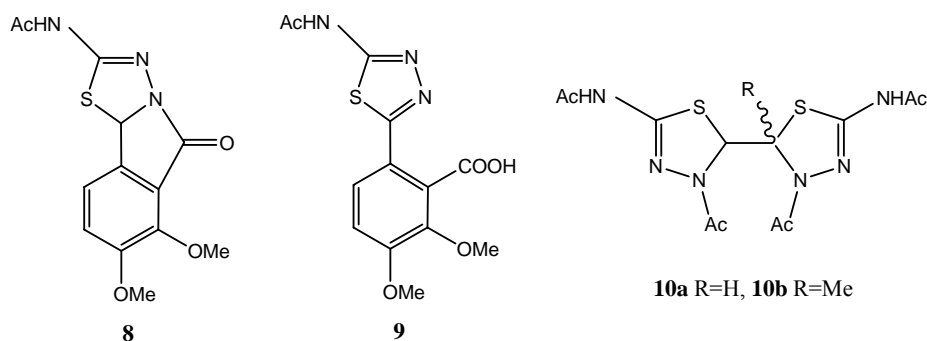


Table 5. Characteristic 50 MHz ¹³C NMR spectral data of thiadiazolines (**2**) for solutions in [DMSO-d₆]

| Compound | δ [ppm] | | | |
|-----------|---------|------------------------|------------|-----------------|
| | C=O | S-C(R ⁷)=N | S-C(Ar)H-N | CH ₃ |
| 2c | 169.56 | | 63.34 | 22.35 |
| | 167.43 | | | 21.62 |
| 2d | 170.38 | 148.07 | 65.66 | 23.26 |
| | 168.87 | | | 21.23 |
| 2f | 169.40 | 145.82 | 64.68 | 22.40 |
| | 167.55 | | | 21.67 |

Table 6. Preparation and properties of thiosemicarbazones (**6**)

| Product | Reaction components (mmol) | Solvent (mL) | Reaction temp. [°C] ^a (time [h]) | Workup ^b | Yield[%] crude ^c (pure) ^c |
|-----------|----------------------------|-------------------------------------|---|---------------------|---|
| 6a | 5a (30) | EtOH ^{d,e} (200) | bp (22) | C, H | 99.5 (69) |
| | TSC (60) | | | | |
| 6b | 5b (30) | EtOH ^{d,e} (200) | bp (20) | I, C | ~ 100 (76) |
| | TSC (60) | | | | |
| 6c | 5c (60) | H ₂ O ^j (500) | bp (3) | A ^k | 98 (92) |
| | TSC (72) | | | | |
| 6d | 5d (30) | EtOH ^{d,e} (300) | bp (44) | C, J | 90 |
| | TSC (60) | | | | |
| 6f | 5f (10) | MeOH ^q (25) | bp (4) | A | 95 (71) |
| | TSC (15) | | | | |

Table 6. Preparation and properties of thiosemicarbazones (**6**) (continued)

| Product | Mp [°C] (solvent) | Lit. mp [°C] (solvent) | Formula (mol. mass) | Analysis found (calcd) | | |
|-----------|---|--|---|---------------------------|----------------|-------------------------------|
| | | | | C | H | N |
| 6a | 190 ^f 198 (EtOH) | 202 ^g (EtOH) | C ₉ H ₁₀ N ₃ ClS (227.7) | 47.34 (47.47) | 4.27 (4.43) | 18.63 ^h (18.45) |
| 6b | 195 ^f 199–200 (80% EtOH) | 204 ⁱ (aq. H ₂ O) | C ₉ H ₁₀ N ₃ BrS (272.2) | 39.58 (39.71) | 3.65 (3.70) | 15.52 (15.44) |
| 6c | 161–162 ^f 162 (H ₂ O) ^l | 161 ^m (EtOH) | C ₈ H ₁₀ N ₄ S (194.3) | 49.92 (49.46) | 5.36 (5.19) | 28.94 ⁿ (28.84) |
| 6d | 220 ^f 221 (EtOH) | 222 ^o (EtOH) | C ₉ H ₁₁ N ₃ O ₂ S (225.3) | 48.29 (47.98) | 5.08 (4.92) | 18.97 ^p (18.65) |
| 6f | 221 ^f 221 (MEE/H ₂ O) ^r | 226–227 ^s (50% EtOH) | C ₁₀ H ₁₀ N ₄ S (218.3) | 55.36 (55.02) | 4.65 (4.62) | 25.76 (25.67) |

TSC = thiosemicarbazide. ^a Bath if not bp. ^b For general operations of processing the reaction mixtures see EXPERIMENTAL. ^c Without workup of the mother liquors. ^d Commercial anhydrous. ^e In the presence of cc. HCl (1.5 mL). ^f Crude product. ^g Ref. 60; 86 °C (sic!; EtOH), ref. 61. ^h Cl 15.90 (15.57), S 14.25 (14.08). ⁱ Ref. 60; 201–202 °C (MeOH), ref. 1g; 202–203 °C (corr., 40–60% EtOH), ref. 53. ^j To a hot solution of TSC in water containing 4.8 mL AcOH was added **5c**. ^k The mother liquor was concentrated and the residue was crystallized from water. ^l The product was dried at 100 °C/0.1 Torr over P₄O₁₀. ^m Ref. 62; 158–160 °C (EtOH), ref. 63; 158–160 °C (MeOH), ref. 64; 195 °C (H₂O), ref. 65. ⁿ S 16.95 (16.51). ^o Ref. 66; 212–215 °C (corr.; 40–60% EtOH), ref. 53. ^p S 14.41 (14.23). ^q Containing 0.5 mL AcOH. ^r 2-Methoxyethyl ether with addition of water to the hot solution. ^s Ref. 67; 230–232 °C (MeOH), ref. 68; 265 °C, ref. 57; 208 °C (MeOH or EtOH), ref. 69.

Table 7. Preparation and properties of thiadiazolines (**7**)

| Product | Substrate (mmol) | Agents (mmol) | Reaction temp. [°C] ^a (time [h]) | Workup ^b | Yield[%] crude (pure) ^c |
|-----------|---------------------|---|---|---------------------|--|
| 7a | 6a (15) | Ac ₂ O (212) py ^d (247) | 100 (5) | C, D | 93 (70) |
| 7b | 6b (30) | Ac ₂ O (424) py ^d (247) | 100 (5) | C, E | 100 (84) |
| 7c | 6c (25) | Ac ₂ O (530) py ^d (124) | 100 (5.5) | C, D | 81 (75) |
| 7e | 6d (67) | Ac ₂ O (1060) py ^d (927) | 100 (5.5) | C, E | (83) |
| 7g | 6f (18) | Ac ₂ O (318) py ^d (247) | 100 (4) | C, E | 91 (58) |

Table 7. Preparation and properties of thiadiazolines (**7**) (continued)

| Product | Mp [°C] (solvent) | Formula (mol. mass) | Analysis found (calcd) | | |
|-----------|---|--|---------------------------|----------------|-------------------------------|
| | | | C | H | N |
| 7a | 214–216 ^e 220–221 (CHCl ₃ /EtOAc) | C ₁₃ H ₁₄ N ₃ O ₂ ClS (311.8) | 49.94 (50.08) | 4.58 (4.53) | 13.45 ^f (13.48) |
| 7b | 218–219 (CHCl ₃ /EtOAc) | C ₁₃ H ₁₄ N ₃ O ₂ BrS (356.2) | 43.63 (43.83) | 4.05 (3.96) | 11.76 ^g (11.79) |
| 7c | 219 ^e 220 (ME/H ₂ O) ^h | C ₁₂ H ₁₄ N ₄ O ₂ S (278.3) | 52.06 (51.78) | 5.09 (5.07) | 20.11 ⁱ (20.13) |
| 7e | 189 (CHCl ₃ /EtOAc) | C ₁₇ H ₁₉ N ₃ O ₆ S (393.4) | 51.96 (51.90) | 5.09 (4.87) | 10.42 ^j (10.68) |
| 7g | 165–166 (EtOH) ^k | C ₁₆ H ₁₆ N ₄ O ₃ S (344.4) | 55.65 (55.80) | 4.82 (4.68) | 16.37 ^l (16.27) |

^a Bath if not bp. ^b For general operations of processing the reaction mixtures see EXPERIMENTAL. ^c Without workup of the mother liquors. ^d Anhydrous. ^e Crude product. ^f Cl 11.73 (11.37), S 10.58 (10.28). ^g Br 23.13 (22.43), S 9.20 (9.00).

^h 2-Methoxyethanol, with addition of water. ⁱ S 11.53 (11.52). ^j S 8.24 (8.15). ^k Commercial anhydrous. ^l The product was dried at 100 °C/0.1 Torr over P₄O₁₀; S 9.62 (9.31); EI-MS: *m/z* (%) [M⁺] 344 (3), 302 (5). Treatment with boiling Ac₂O for 4 h has been reported (ref. 70) to transform **6f** into **7f** [C₁₄H₁₄N₄O₂S (302.3), the diacetyl analog of **7g**, with free indole NH].

Table 8. Characteristic 200 MHz ¹H- and 50 MHz ¹³C NMR spectral data^a of thiadiazolines (**7**)

| Compound | δ [ppm] | | | | |
|-----------------------|--------------------|-----------------|----------------------------------|------------------|--------------------|
| | ¹ H | | ¹³ C | | |
| | NH | CH ₃ | C=O | C-2 ^b | CH ₃ |
| 7a | ^c 10.93 | 2.33 | ^c 169.19 | 78.24 | 26.25 |
| | | 2.24 | 168.06 | | 23.29 |
| | | 2.05 | | | 22.21 |
| 7b | 10.29 | 2.33 | 169.25 ^d | 79.11 | 26.57 |
| | | 2.30 | | | 23.64 |
| | | 1.84 | | | 22.49 |
| 7c | ^e 11.67 | 2.30 | ^e 169.30 | 79.67 | 25.87 |
| | | 2.20 | 167.99 | | 23.37 |
| | | 2.02 | | | 22.31 |
| 7e | 10.88 | 2.30 | 170.00 | 75.60 | 27.95 |
| | | 2.24 | 168.89 | | 23.15 |
| | | 2.22 | 168.35 | | 22.23 |
| | | 2.18 | 168.02 | | 20.86 |
| 7g^f | | 1.76 | | | 20.75 |
| | ^e 11.11 | 2.15 | ^e 169.25 ^d | 60.88 | 22.61 ^d |
| | | 2.09 | 167.12 | | 21.96 |
| | | 2.06 | | | |

^a For solutions in CDCl₃ if not otherwise stated *before* the first column.

^b C-2 of the thiadiazoline ring. ^c For solution in CDCl₃ + [DMSO-d₆]. ^d 2 C.

^e For solution in [DMSO-d₆]. ^f The signal of S-CHR-N is superimposed on those of the indole hydrogens at $\delta = 7.49$ –6.97.

EXPERIMENTAL

Melting points (uncorrected): Kofler block. Solutions were concentrated under reduced pressure in a rotary evaporator (< 50 °C, bath). TLC: Kieselgel 60 F₂₅₄ (Merck, Alurolle). IR (KBr disks): Perkin-Elmer 16 PC-FT and Perkin-Elmer 283 B spectrophotometers. 200 MHz ¹H- and 50 MHz ¹³C NMR: Bruker WP 200 SY, 360 MHz ¹H- and 90 MHz ¹³C NMR: Bruker AM 360 spectrometers; for recording the ¹³C spectra, *J*-echo techniques were used. MS: VG-7035 GC/MS/DS instrument (ion current 0.1 mA, direct insertion technique, 70 eV).

General Operations of Processing the Reaction Mixtures (see Tables 1–3,6,7) (A) The product was filtered off in the cold. (B) The cold reaction mixture was poured into ice and water. (C) The reaction mixture was concentrated. (D) The cold residue was triturated with a small amount of anhydrous EtOH and kept at room temperature for 0.5–1 h, then hexane was added. (E) The cold residue was triturated with ice/water. (F) Under ice/water cooling, to the stirred reaction mixture was added 30% H₂O₂ in small portions until discoloration was complete. (G) The mixture was diluted with 2–3-fold volume of water. (H) To about a quarter. (I) The hot solution was filtered. (J) The residue was extracted with water on a steam bath to remove unreacted thiosemicarbazide. (K) The solid was stirred with aq. NaHCO₃ to leave the crude product undissolved.

General Procedure for KMnO₄ Oxidation (see Table 3) With a slight modification of the literature method^{32d,71} to a stirred and cooled suspension of the finely powdered substrate in 99% AcOH were added finely powdered KMnO₄ in small portions, and water in 3–4 portions. For processing the reactions mixtures see the indications in Table 3 and the General Operations (see above).

General Procedure for CAN Oxidation (see Table 3)

To a stirred suspension/solution of the powdered substrate in MeCN were added CAN in small portions (the proper time intervals being indicated by the change of color) and water in 3–4 portions. For processing the reaction mixtures see the indications in Table 3 and the General Operations (above).

Thermal Dehydrogenation of 3-Acetylthiadiazoline (2b) to Thiadiazole (3b). Thiadiazoline (**2b**) (1.3290 g, 4.31 mmol; mp 228.5 °C) was kept at 245–260 °C (bath) for 30 min (after temporary sparkling the melt resolidified; loss of weight 0.3000 g, i.e. 69.6 mg/mmol). The cold residue was triturated with 2-PrOH to give crude (1.0013 g, 87.9%) or recrystallized **3b** (0.4578 g, 40.2%), mp > 365 °C (from DMSO). The product kept at 100 °C/0.5 Torr over P₄O₁₀ for 8 h was identical in all respects [mp, TLC, IR(KBr) and ¹H NMR (DMSO-d₆) spectrum] with that obtained by KMnO₄, CAN or DDQ dehydrogenations (see Table 3).

6-(5-Acetamido-1,3,4-thiadiazol-2-yl)-2,3-dimethoxybenzoic Acid (9).

Procedure A. To a stirred suspension of the finely powdered thiadiazoline lactam⁴⁹ (**8**) (9.219 g, 30 mmol) in AcOH (225 mL) was added powdered KMnO₄ (11.850 g, 75 mmol) in small portions during 25 min at 15–16 °C. The mixture was stirred for 10 min then H₂O (37 mL) was added in portions during 20 min. The mixture was stirred at 11–13 °C for an additional 100 min, then under further cooling ~30% H₂O₂ (~5.5 mL) was added in small portions until the decomposition of the excess KMnO₄ was complete and the colorless solution was concentrated. The solid residue was extracted with aq. NaHCO₃ (3.60 g, ~43 mmol in 50 mL H₂O) at 50–55 °C and filtered. The filtrate was acidified with concd HCl to Congo Red and kept at 5 °C for 2–3 h to obtain crude (2.672 g, 27.5%) or recrystallized **9** (2.115 g, 21.8%), mp 269 °C (from AcOH). *Anal.* Calcd for C₁₃H₁₃N₃O₅S: C 48.29; H 4.05; N 13.00; S 9.92. Found: C 48.26; H 4.24; N 12.98; S 10.00. IR (cm⁻¹): 3161, 2938, 2786, 1730, 1702, 1596, 1552. ¹H NMR (200 MHz, DMSO-d₆): δ 12.61 (s, 1 H, exchangeable with D₂O, NH), 7.55 and 7.23 (each d, 1 H, *J* = 8 Hz, 2 H, H–Ar), 3.91 and 3.78 (each s, 3 H; 2 MeO), 2.21 (s, 3 H, Ac).

Procedure B. To a stirred suspension of the powdered thiadiazoline lactam⁴⁹ (**8**) (0.0768 g, 0.25 mmol) in MeCN (4 mL) were added water (0.8 mL) and CAN (0.291 g, 0.531 mmol) in small portions during 30 min at rt. The mixture was concentrated and the residue triturated with water to furnish crude (0.0652 g, 80.7%) or recrystallized **9** (0.040 g, 49.5%), mp 265–267 °C (from AcOH with addition of water), identical [TLC, 20 mL CHCl₃/MeOH (7:3) + 6 drops of AcOH, as well as IR(KBr) spectrum] with the product obtained in procedure A.

5,5'-Diacetamido-3,3'-diacetyl-2,2'-bi[1,3,4]thiadiazoline (10a). A mixture of glyoxal bis(thiosemicarbazone)⁵⁰ (10.00 g, 48.95 mmol), Ac₂O (50 mL) and anhydrous pyridine (20 mL) was boiled with stirring for 1 h and then cooled to give a crude product (12.39 g, 68%), mp > 365 °C. The mother liquor was poured into ice/water to afford a second crop (1.300 g, 7.1%). For analysis a sample (2.00 g) was recrystallized from DMF (23 mL) with addition of warm water (50 mL) to give the pure title compound (1.665 g). *Anal.* Calcd for C₁₂H₁₆N₆O₄S₂: C 38.70; H 4.33; N 22.57. Found: C 38.82; H 4.40; N 22.62. ¹H NMR (100 MHz at 330 K, DMSO-d₆) HMDSO as the internal standard: δ 11.73 (br s, 1 H, exchangeable with CD₃COOD, NH), 6.47 and 6.32 (2 s, ³/₄ and ¹/₄ H, S–CHR–N), 2.28 (s, 3 H, Ac), 2.22 (s, 3 H, Ac).

Oxidative Transformation of the Bithiadiazoline (10a) into 2-Acetamido[1,3,4]thiadiazole.

Procedure A. To a stirred suspension of powdered **10a** (0.372 g, 1 mmol, 2 “mmol” of the heteroring) in AcOH (20 mL) were added powdered KMnO₄ (0.790 g, 5 mmol) and water (1 + 1 mL) at rt during 1 h. The reaction mixture was stirred for an additional 2 h then processed (see General Procedure as well as General Operations C, E, G) to give crude (0.090 g, 62.8%) or recrystallized (0.055 g, 38.4%)

2-acetamido[1,3,4]thiadiazole, mp 269 °C (from water), ref. 51: 268 °C (from water), ref. 19i: mp 267–268 °C (from AcOH). ¹H NMR (DMSO-d₆): δ 12.26 (s, 1 H, NH), 9.27 (s, 1 H, 5-H), 2.31 (s, 3 H, Ac).

Procedure B. To a stirred mixture of powdered **10a** (0.9311 g, 2.5 mmol, 5 “mmol” of the heteroring) in MeCN (60 mL) and water (12 mL) was added CAN (6.439 g, 11.51 mmol, 98%) during 30 min at rt. The reaction mixture was saturated with Na₂SO₄ and thoroughly extracted with CHCl₃. The CHCl₃ solution was washed with aq. NaHCO₃ and water, dried (MgSO₄) and then concentrated. The residue was crystallized from EtOAc to give crude (0.2161 g, 60.4%) or recrystallized (0.1273 g, 39.1%) 2-acetamido[1,3,4]thiadiazole, mp 272 °C (from EtOAc; near the mp it volatilizes). MS: *m/z* [M⁺] 143(28), [M⁺ – Me] 128(7), [M⁺ – N₂: 2-acetamidothiirene] 115(30), [M⁺ – CH₂CO: 2-aminothiadiazole] 101(100), [M⁺ – CH₂CO – HCN: 3-aminothiazirene] 74(28), [M⁺ – CH₂CO – H₂NCN: thiazirene] 59(9), [HC≡S⁺] 45(45), in accordance with the known⁵² fragmentation pattern of 2-(acyl)amino[1,3,4]thiadiazoles.

Procedure C. To a stirred suspension of powdered **10a** (1.117 g, 3 mmol, 6 “mmol” of the heteroring) in MeOH (160 mL) was added powdered IBDA (2.241 g, 6.818 mmol, 98%) at rt during 10 min. The mixture was stirred for 5 d (the oxidant was consumed: KI/starch paper), filtered and concentrated. The residue was extracted with CHCl₃ (~350 mL) and the solution washed with aq. NaHCO₃ and water, dried (MgSO₄), treated with fuller’s earth and charcoal, and then concentrated. The residue was boiled in EtOAc (30 mL) to give the TLC-homogeneous pure title thiadiazole (0.3595 g, 83.7%, calcd for 3 mmol), mp 272–273 °C.

Degradation of 5,5’-Diacetamido-3,3’-diacetyl-2’-methyl-2,2’-bi[1,3,4]thiadiazoline (10b) to 2-Acetamido-5-methyl-1,3,4-thiadiazole. To a stirred suspension of the powdered bithiadiazoline (**10b**)^{41f} (0.773 g, 2 mmol, 4 “mmol” of the heteroring) in MeCN (50 mL) and water (10 mL) was added CAN (4.984 g, 8.91 mmol, 98%) during 30 min. The mixture was neutralized with NaHCO₃ and concentrated. The residue was extracted several times with hot CHCl₃. The combined CHCl₃ solution was washed with water, dried (MgSO₄) and then concentrated. The residue was crystallized from EtOAc to give homogeneous [TLC, CHCl₃/MeOH (95:5)] 2-acetamido-5-methyl-1,3,4-thiadiazole (0.131 g, 41.7%), mp 294–296 °C, ref. 44c: 293 °C (from aq. NaOH with addition of HCl), ref. 51: 292 °C (from water). IR (cm⁻¹): 3170, 3040, 2914, 2796, 1696, 1570. MS: *m/z* [M⁺] 157(18), [M⁺ – Me] 142(15), [M⁺ – CH₂=CO] 115(85), [2-aminothiadiazole?] 101(8), [M⁺ – CH₂=CO – MeCN = 3-aminothiazirene] 74(45), [thiazirene and/or Me–C≡S⁺] 59(25); 56(22), [Me–C≡O⁺] 43(100), in accordance with the known⁵² fragmentation pattern of 2-amino-1,3,4-thiadiazoles. C₅H₇N₃OS (157.2).

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