Synthesis and characterization of 2,2-disubstituted thiadiazolines

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Abstract

The synthesis of new 1,3,4-thiadiazolines derived from diaryl and aryl-cycloalkyl ketones, via the corresponding thiosemicarbazones, is described.

^{1}H- and ^{13}C-NMR spectra as well as mass spectrometry disclosed the structures of the precursors and heterocyclic derivatives formed. In the case of spirane compounds, the effect of heteroatoms (S, N) on the diastereotopic hydrogens is discussed.

Keywords. Thiadiazolines, ^{1}H-NMR, ^{13}C-NMR, thiosemicarbazones

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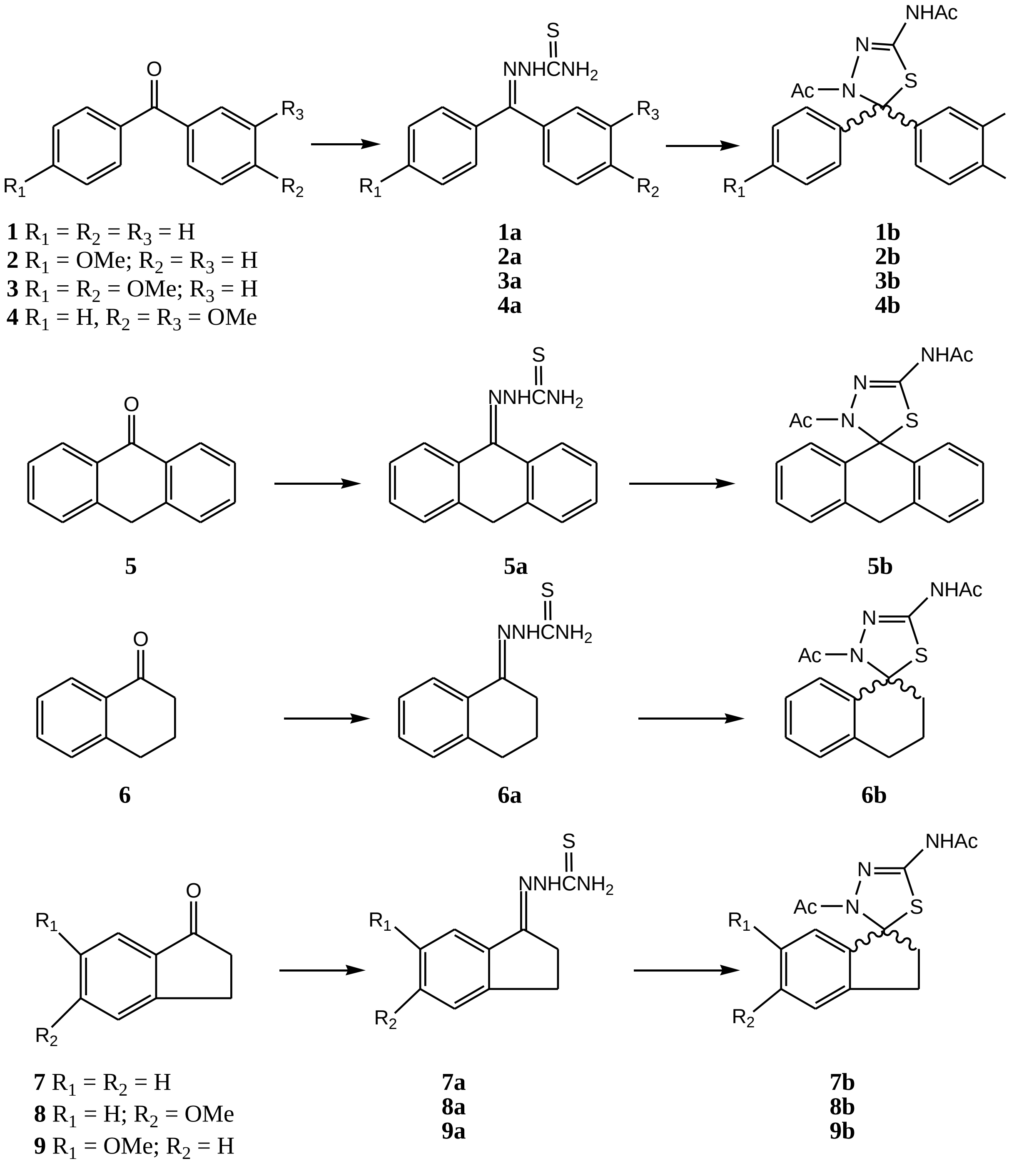
Introduction

Thiadiazoles and their derivatives represent a group of compounds possessing a wide spectrum of biological activity. They exhibit hypoglycemic, antitubercular, antifungal and antibacterial properties.[1-4]

There are few general routes to obtain 1,3,4-thiadiazolines. Holmberg and Sandström proposed the reaction between an aldehyde or a ketone with substituted thiohydrazides.[5] Taylor *et al.*[6] found that 1,3-dipolar cycloaddition between chlorodiazabutadiene and thiourea rendered 4-amidine-1,3,4-thiadiazolines. However, the preparation of this heterocyclic ring is mostly achieved by heterocyclization of thiosemicarbazones,[7] as reported by Andreae *et al.*[8], Somogyi[9] and Kubota *et al.*[10]

In view of these findings and in a further stage of our work on the synthesis of these heterocycles,[7] here we describe the synthesis of 1,3,4-thiadiazoline derivatives from several ketones (diarylketones, indanones and tetralone) *via* the corresponding thiosemicarbazones, as illustrated in Scheme 1.[11]



1 $R_1 = R_2 = R_3 = H$
2 $R_1 = OMe; R_2 = R_3 = H$
3 $R_1 = R_2 = OMe; R_3 = H$
4 $R_1 = H, R_2 = R_3 = OMe$

1a **2a** **3a** **4a**

1b **2b** **3b** **4b**

5 **5a** **5b**

6 **6a** **6b**

7 $R_1 = R_2 = H$
8 $R_1 = H; R_2 = OMe$
9 $R_1 = OMe; R_2 = H$

7a **8a** **9a**

7b **8b** **9b**

Scheme 1

Results and Discussion

Starting from the corresponding carbonyl compound and using standard methods, a series of thiosemicarbazones were synthesized with almost quantitative yields and characterized by spectroscopy. Table 1 shows the ^{13}C-NMR chemical shifts observed for the latter compounds. These thiosemicarbazones were subjected to ring closure by means of acetylating agents to obtain the corresponding 1,3,4-thiadiazolines with good yields. In the case of compound 5a the ring closure failed in the condition of the general procedure.

Table 1. ^{13}C-NMR chemical shifts (ppm) of thiosemicarbazones 1a- 9a messured at 50 MHz in DMSO-d6

Comp.	C=S	C=N	CH_2 (a)	CH_2 (b)	CH_2 (g)
1a	180.8	154.7	-	-	-
2a	177.8	149.3	-	-	-
3a	177.7	149.4	-	-	-
4a	178.1 / 177.7	149.9 / 149.2	-	-	-
5a	178.1	149.0	-	-	75.8
6a	179.0	147.9	25.9	21.5	29.1
7a	178.7	157.1	28.4	27.3	-
8a	178.5	156.9	28.4	27.6	-
9a	178.5	156.9	27.9	27.5	-

Aromatic carbons: 120.3-141.6 ppm; OCH_3: 55.4-56.1 ppm

Table 2 lists ^{13}C-NMR chemical data of these heterocycles. Ring closure may be observed by a) the disappearance in the ^{13}C-NMR spectrum of the signal at roughly 180 ppm corresponding to the thiocarbonyl; b) the appearance of the signal at *circa* 85 ppm assigned to C-2; and c) the signals of the carbonyl and methyl moieties of the acetyl groups incorporated to the molecule. In spite of the different nature of the substituents at C-2 of the heterocycle, it may be observed in the ^{13}C-NMR spectrum that for all the products this carbon atom signal ranges from 80 to 86 ppm, whereas the C=N signal is around 143 ppm (Table 2). In the case of the spirane heterocycles (6b-9b), in order to assign the carbon atoms corresponding to the alicyclic methylene groups (carbons α, β, γ), shift values observed for the starting ketones, thiosemicarbazones and heterocyclic products were compared. As a result, it was found that the methylene carbon atom (carbon α) vicinal to the chiral center generated during ring closure appears at lower fields. Similar results were observed for the thiadiazoline derived from cyclohexanone.[8]

Table 2. ^{13}C-NMR chemical shifts (ppm) of thiadiazolines 1b-9b, messured at 50 MHz in DMSO-d6

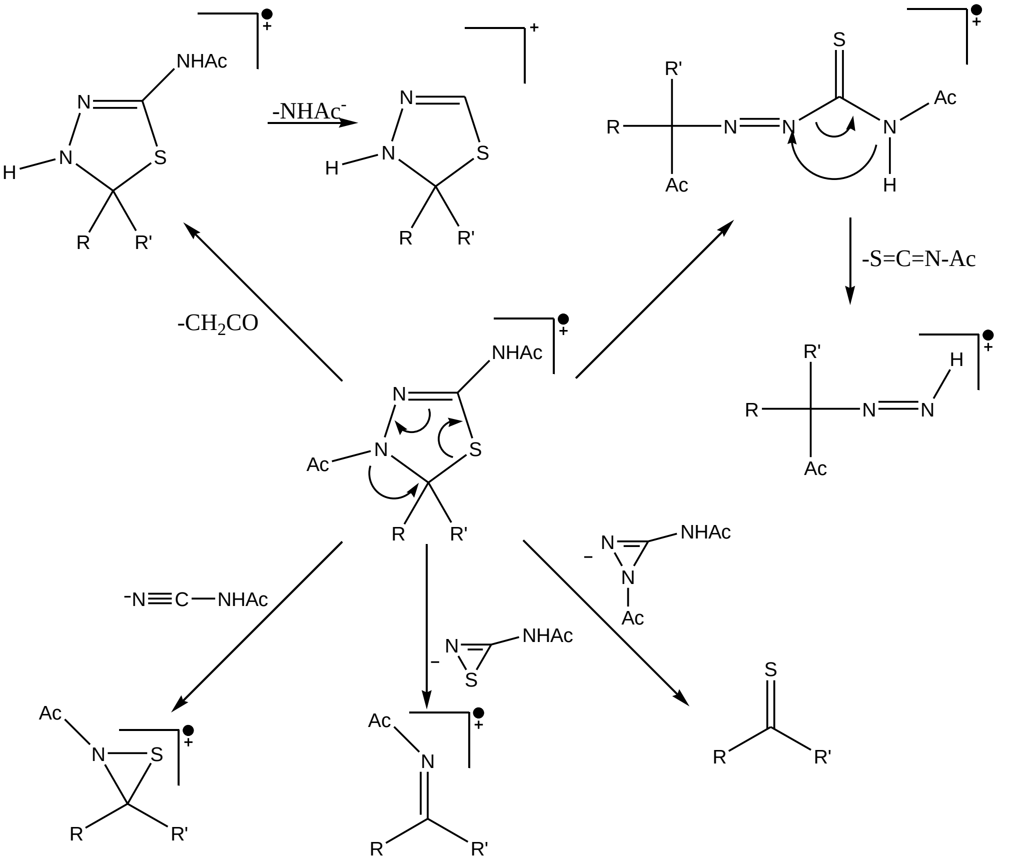
Comp.	C-2	C=N	C=O*	C=O**	CH_3*	CH_3**	CH_2(a)	CH_2(b)	CH_2 (g)
1b	85.6	143.0	170.1	168.1	24.1	22.7	-	-	-
2b	85.3	142.7	169.7	167.6	24.0	22.5	-	-	-
3b	85.4	142.8	169.8	167.8	24.1	22.6	-	-	-
4b	85.7	143.2	170.2	168.1	24.2	22.8	-	-	-
6b	80.6	142.2	169.6	167.3	24.1	22.7	35.8	21.3	28.5
7b	85.0	142.0	169.3	167.2	23.5	22.4	40.7	29.7	-
8b	85.0	142.4	169.4	167.3	23.8	22.6	41.3	30.2	-
9b	85.5	142.5	169.5	167.4	23.8	22.6	41.4	29.0	-

Aromatic carbons: 113.2-142.9 ppm; OCH_3: 55.3-55.4 ppm. *CO and CH_3 of the acetyl group bonded to C-5. **CO and CH_3 of the acetyl group bonded to N-3

Mass spectra of this heterocycle family resemble one another as regards the observed rupture pattern, although the relative abundance and the m/z relationship are characteristic for each compound, in agreement with that observed for similar heterocycles derived from aldehydes.[7] The proposed fragmentation model is presented in Scheme 2.

Since in some of these compounds ring closure generates a chiral center (2b, 4b, 6b-9b) (C-2 in the heterocycle), a racemic mixture is obtained as expected. As a result of this reaction, four aliphatic hydrogen atoms are observed for the indane system in the proton nuclear magnetic resonance spectrum of the compounds (7b-9b) (Figure 1).

In order to assign the four diastereotopic hydrogen atoms unequivocally, and employing thiadiazoline 8b as a model, two-dimensional heteronuclear resonance experiments were carried out (Figure 2). The two protons linked to carbon α of the indane nucleus were thus found to present a 0.6-ppm separation. In contrast, the diastereotopic hydrogen atoms in position β to the chiral center differed by barely 0.2 ppm. The marked difference between the protons linked to carbon α would not only result from the inductive effect exerted by the heteroatoms, but rather due to a spatial effect probably exerted by the acetyl groups.



Scheme 2

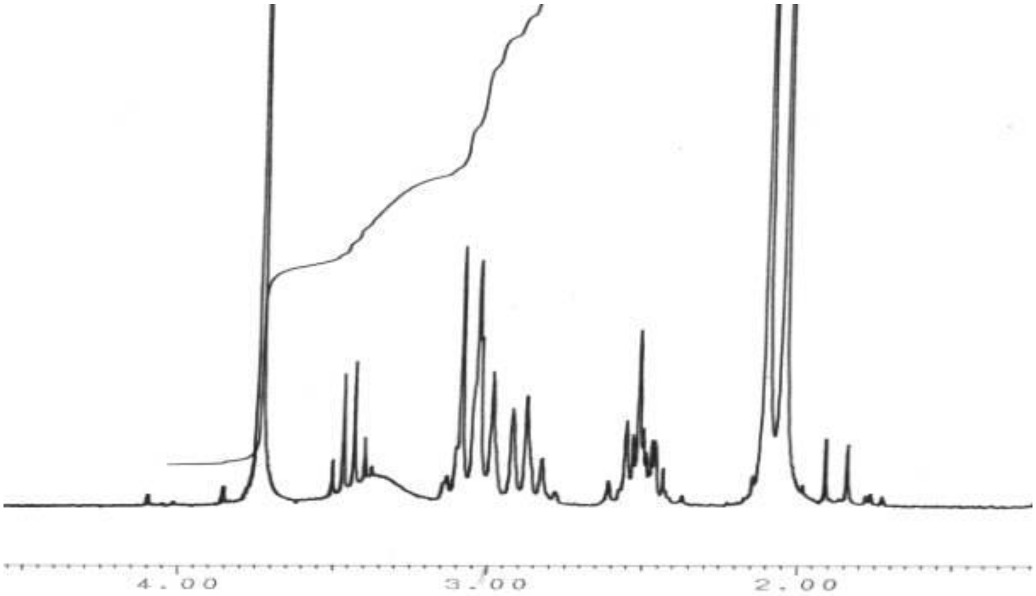


Figure 1

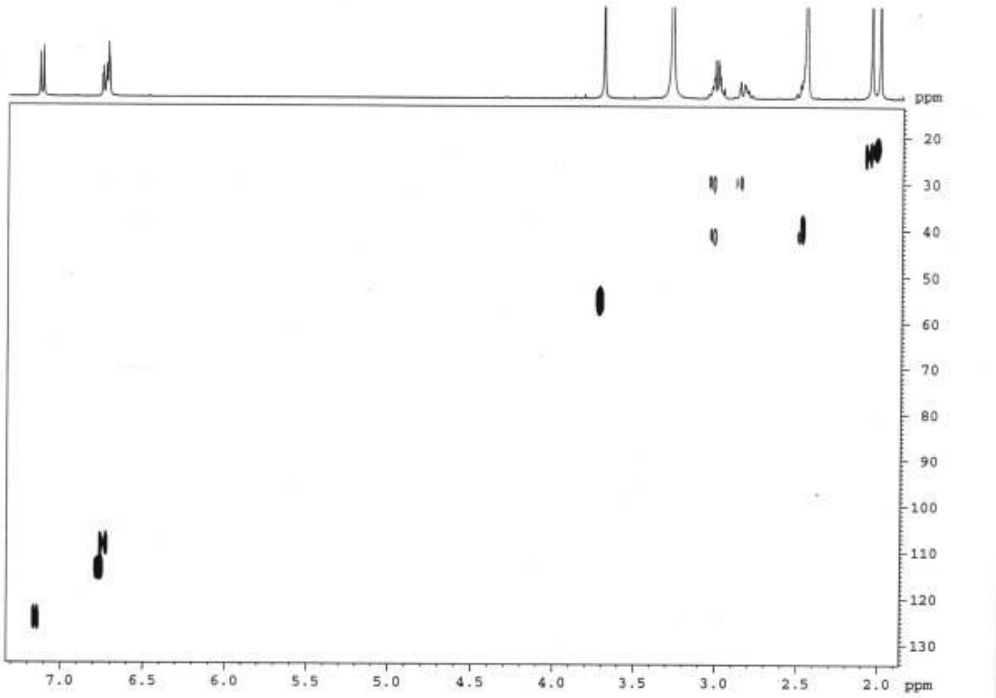


Figure 2

On the basis of this concept, an attempt was made to assign unequivocally the methyl moieties of both acetyl groups, resorting to the nOe effect between the amide proton and the signals of the two methyl moieties. The nOe experiments of compound 8b were the following: a) irradiation of the signal at 11.56 ppm (NH) modified the signal of the methyl group at 2.11 ppm; b) irradiation of the signal corresponding to the methyl group at 2.05 ppm did not modified the NH signal; c) finally irradiation of the signal corresponding to the methyl group at 2.11 ppm modified the NH signal. Thus, nOe was observed between the proton linked to the nitrogen atoms and the least shielded methyl moiety, that is to say, the methyl moiety of the acetamide group linked to C-5 of the heterocycle (Figure 3); therefore, the methyl moiety that appears at a higher field is the one belonging to the acetyl group linked to N-3 of the heterocycle. Considering both acetyl groups, the one located on N-3 of the heterocycle is nearer the indane ring and could present some type of interaction with the hydrogen atoms in position α to the chiral center; however, no NOE effect was observed between the methyl moiety of this acetyl group and the hydrogen atoms belonging to the cyclopentane system. From this evidence it may be concluded that the methyl moiety of this acetyl group is at a considerable distance from the indane ring and possibly oriented outwardly.

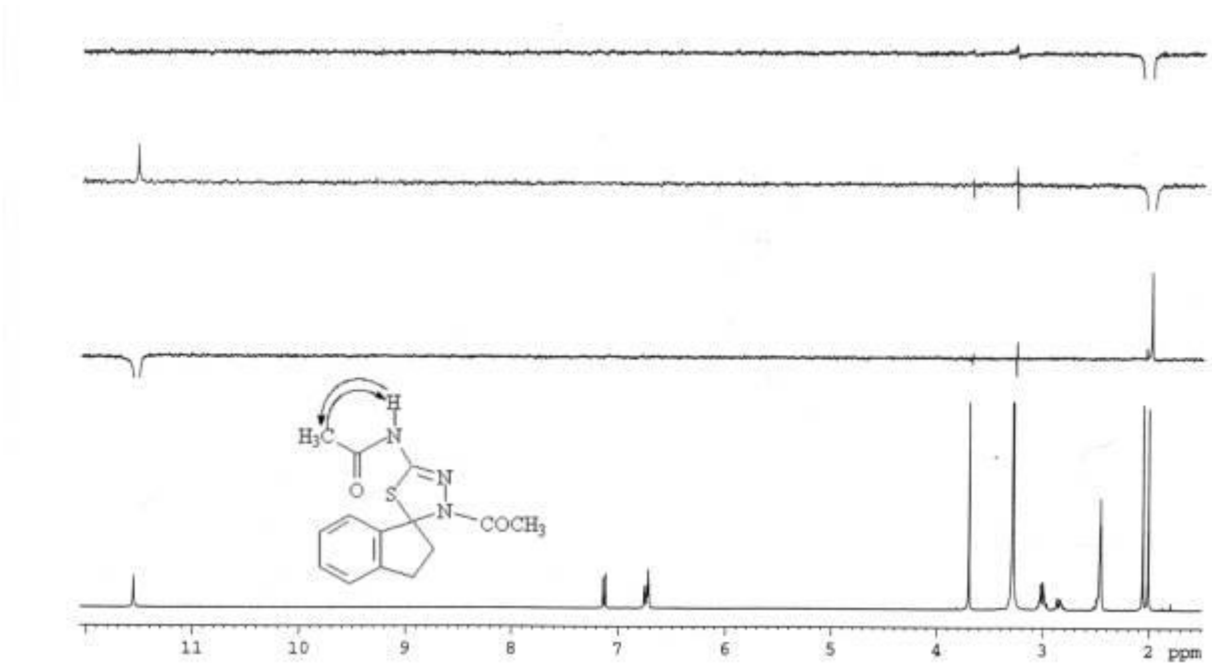


Figure 3

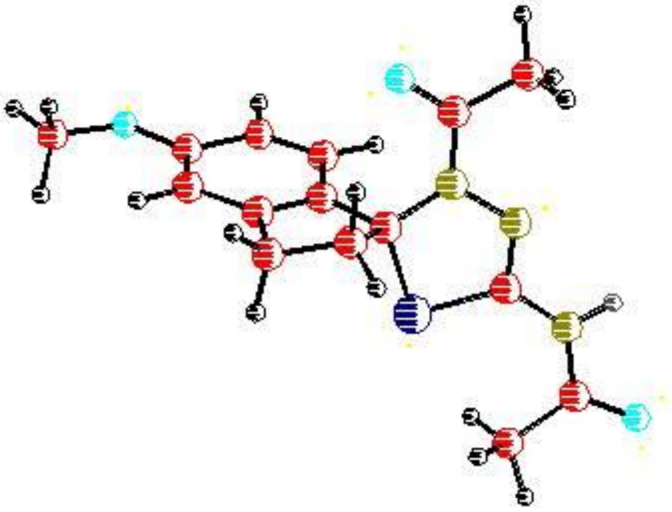


Figure 4

This hypothesis is supported by the results obtained by modeling the corresponding structure using PCMODEL software, in which the acetyl group is observed to adopt an orientation towards the outside of the cycle. This orientation would leave one of the hydrogen atoms located on C-α of the cycle within the carbonyl anisotropy area. From this assumption it may be inferred that the hydrogen atom located on C-α vicinal to the nitrogen atom is the least shielded one (Figure 4).

Experimental Section

General Procedures. Melting points were measured on a Unimelt apparatus and are uncorrected. IR spectra were measured as mull with a Nicolet IRFT spectrophotometer. Standard ^1H and ^{13}C NMR spectra were recorded with a Bruker AC200 instrument at 200 MHz and 50 MHz, respectively in d_6-dimethyl sulfoxide; chemical shifts are in parts per milliom (ppm) downfield from tetramethylsilane. Heteronuclear correlation spectroscopy and NOE experiment were determined in a Bruker 400-MHz. Mass spectra were performed in a Shimadzu QP-5000 by electron impact ionization and high-resolution mass spectra (HRMS) in a ZAB-SEQ4F. Thin layer chromatography (tlc) was performed with Silica Gel G (Merck, Darmstadt) with benzene: ethyl acetate (2:3), as eluent.

General Procedure I

Synthesis of thiosemicarbazone.

Title compound was prepared from the equimolecular quantity of ketone and thiosemicarbazide dissolved in 50 mL of ethanol and several drops of H_2SO_4 (concd). The mixture was heated at reflux monitoring the reaction using tlc. Evaporation under reduced pressure gave the corresponding thiosemicarbazone.

4-Methoxybenzophenone thiosemicarbazone (2a). Compound 2a was obtained from 4-methoxybenzophenone by general procedure I. This compound was recrystallized from ethanol (yield 76%); m.p. 178-180 ºC. IR: ν_{max} 3409, 3340, 3245, and 3150 (NH), 1606 (“$CSNH_2$” I), and 1472 cm^{-1}(“$CSNH_2$” II). ^1H-NMR: 3.88 (3H, s, OCH_3); 6.91 - 7.64 (9H, several signals, ArH); 8.27, 8.32, 8.53 (3H, NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd. 285.0936; found 285.0939.

4,4'-Dimethoxybenzophenone thiosemicarbazone (3a). Compound 3a was obtained from 4,4'-dimethoxybenzophenone by general procedure I. This compound was recrystallized from ethanol (yield 95%); m.p. 172-174 ºC. IR: $_{\nu max}$ 3410, 3335, 3250, and 3170 (NH), 1610 (“$CSNH_2$” I), and 1481 cm^{-1} (“$CSNH_2$” II). ^1H-NMR: 3.79 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 6.91-7.62 (8H, several signals, ArH); 8.21, 8.41, 8.47 (3H, NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd.315.1041; found 315.1042.

***syn and anti* 3,4-Dimethoxybenzophenone thiosemicarbazone (4a).** Compound 4a was obtained, as a *syn* and *anti* mixture, from 3,4-dimethoxybenzophenone[12] by general procedure I. This compound was recrystallized from ethanol (yield 91%); m.p. 220-222 ºC. IR: $_{\nu max}$ 3385, 3350, 3240, and 3160 (NH), 1617 and 1570 (“$CSNH_2$” I), and 1510 and 1480 cm^{-1} (“$CSNH_2$” II). ^1H-NMR: 3.77, 3.83, 3.87 (s, OCH_3); 6.65 - 7.71 (several signals, ArH); 8.28, 8.52, 8.58 (NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd. 315.1041; found 315.1043.

Anthrone thiosemicarbazone (5a). Compound 5a was obtained from anthrone by general procedure I. This compound was recrystallized from ethanol (yield 30 %); m.p.177-178 ºC. IR: $_{\nu max}$ 3410, 3345, 3250, and 3150 (NH), 1620 and 1571 (“$CSNH_2$” I), and 1515 and 1482 cm^{-1}

(“$CSNH_2$” II). ^{1}H NMR: 4.48 (2H, s, CH_2); 7.44-8.25 (11H, several signals, PhH, NH and NH_2). ^{13}C- N: see Table 1. HRMS calcd. 267.0830; found 267.0833.

3,4-Dihydronaphtalen-1(2*H*)one thiosemicarbazone (6a). Compound 6a was obtained from 2,3,4-trihydronaphtalen-1-one by general procedure I. This compound was recrystallized from ethanol (yield 91%); m.p. 202-204 ºC. IR: $_{\text{νmax}}$ 3411, 3314, 3145, and 3050 (NH), 1601 and 1496 (“$CSNH_2$” I), and 1481 cm^{-1} (“$CSNH_2$” II). ^{1}H-NMR: 1.82 (2H, dt, CH_2); 2.70 (2H, t, CH_2); 2.74 (2H, t, CH_2); 7.16 -8.30 (4H, several signals, ArH); 7.97, 10.08 (3H, NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd. 219.0830; found 219.0833.

Indan-1-one thiosemicarbazone (7a). Compound 7a was obtained from indan-1-one by general procedure I. This compound was recrystallized from ethanol (yield 61%); m.p.175-177ºC. IR: $_{\text{νmax}}$ 3395, 3253, 3171, and 3048 (NH), 1602 (“$CSNH_2$” I), and 1485 cm^{-1} (“$CSNH_2$” II). ^{1}H-NMR: 2.88 (2H, m, CH_2); 3.07 (2H, m, CH_2); 7.34 -7.87 (4H, several signals, ArH); 7.90, 8.17, 10.21 (3H, NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd. 205.0674; found 205.0674.

5-Methoxyindan-1-one thiosemicarbazone (8a). Compound 8a was obtained from 5-methoxyindan-1-one by general procedure I. This compound was recrystallized from ethanol (yield 76%); m.p. 179-180 ºC. IR: $_{\text{νmax}}$ 3400, 3275, 3181, and 3041 (NH), 1602 and 1526 (“$CSNH_2$” I), and 1457 cm^{-1} (“$CSNH_2$” II). ^{1}H NMR: 2.82 (2H, m, CH_2); 3.04 (2H, m, CH_2); 3.80 (3H, s, OCH_3); 6.85 -7.80 (3H, several signals, ArH); 7.82, 8.07, 10.08 (3H, NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd. 235.0779; found 235.0780.

6-Methoxyindan-1-one thiosemicarbazone (9a). Compound 9a was obtained from 6-methoxyindan-1-one by general procedure I. This compound was recrystallized from ethanol (yield 35%); m.p. 217-219 C. IR: $_{\text{νmax}}$ 3398, 3254, 3158, and 3050 (NH), 1603 (“$CSNH_2$” I), and 1481 cm^{-1} (“$CSNH_2$” II). ^{1}H NMR: 1.87-1.89 (4H, m, CH_2); 3.79 (3H, s, OCH_3); 6.92 -7.48 (3H, several signals, ArH); 8.03, 8.18, 10.18 (3H, NH_2 and NH). ^{13}C- NMR: see Table 1. HRMS calcd. 235.0779; found 235.0780.

General procedure II

Synthesis of 5-acetamido-3-*N*-acetyl-2,2-disubstituted-1,3,4-thiadiazoline.

Thiosemicarbazone was dissolved in pyridine and acetic anhydride and the mixture was heated at 100 °C during 1h with magnetic stirring. The crude product was purified by flash chromatography using benzene: ethyl acetate (3:2).

5-Acetamido-3-*N*-acetyl-2,2-diphenyl-1,3,4-thiadiazoline (1b)

Compound 1b was obtained from benzophenone thiosemicarbazone (1a) [13] by general procedure II. This compound was recrystallized from ethanol (yield 54%); m.p.183-186 ºC. IR: $_{\text{νmax}}$ 3215 (NH), 1694 (exo Amide I), 1637 (endo Amide I), 1610 (C=N), and 1504 cm^{-1} (Amide II). ^{1}H NMR: 2.03 (3H, s, CH_3); 2.20 (3H, s, CH_3); 7.37 (10H, m, PhH); 11.67 (1H, s, NH) ^{13}C- NMR: see Table 2. HRMS calcd. 339.1041; found 339.1041

5-Acetamido-3-*N*-acetyl-2-(4´-methoxyphenyl) - 2-phenyl-1,3,4-thiadiazoline (2b). Compound 2b was obtained from 4-methoxybenzophenone thiosemicarbazone (2a) by general procedure II.

This compound was recrystallized from ethanol (yield 92%); m.p. 85-87 ºC. IR: $_{\nu max}$ 3219 (NH), 1696 (exo Amide I), 1640 (endo Amide I), 1615 (C=N), and 1510 cm^{-1} (Amide II). ^{1}H-NMR: 2.06 (3H, s, CH_3); 2.22 (3H, s, CH_3); 3.78 (3H, s, OCH_3); 6.90 - 7.40 (9H, several signals, ArH); 11.71 (1H, s, NH). ^{13}C- NMR: see Table 2. HRMS calcd. 369.1147; found 369.1136.

5-Acetamido-3-*N*-acetyl-2,2-bis(4´-methoxyphenyl)-1,3,4-thiadiazoline (3b). Compound 3b was obtained from 4,4'-dimethoxybenzophenone thiosemicarbazone (3a) by general procedure II. This compound was recrystallized from ethanol (yield 90%); m.p. 99-101 ºC. IR: $_{\nu max}$ 3215 (NH), 1689 (exo Amide I), 1638 (endo Amide I), 1610 (C=N), and 1512 cm^{-1} (Amide II). ^{1}H NMR: 2.09 (3H, s, CH_3); 2.18 (3H, s, CH_3); 3.77 (6H, 2 s, OCH_3); 6.91 (4H, d, *J* = 8.7 Hz, ArH); 7.31 (4H, d, *J* = 8.7 Hz, ArH); 11.61 (1H, s, NH). ^{13}C- NMR: see Table 2. HRMS calcd. 399.1253; found 399.1255.

5-Acetamido-3-*N*-acetyl-2-(3´,4´-dimethoxyphenyl)- 2-phenyl-1,3,4-thiadiazoline (4b). Compound 4b was obtained from 3, 4-dimethopxybenzophenone thiosemicarbazone (4a) by general procedure II. This compound was purified by chromatography to afford a syrup (yield 82%). IR: $_{\nu max}$ 3212 (NH), 1692 (exo Amide I), 1636 (endo Amide I), 1608 (C=N), and 1508 cm^{-1} (Amide II). ^{1}H-NMR: 2.03 (3H, s, CH_3); 2.20 (3H, s, CH_3); 3.66 (3H, s, OCH_3); 3.77 (3H, s, OCH_3); 6.92-6.99 (3H, m, ArH); 7.31-7.39 (5H, m, PhH). ^{13}C-NMR: see Table 2 HRMS calcd. 399.1253; found 399.1253

Spiro[5-acetamido-3-*N*-acetyl-2,1´-(1´,2´,3´,4´-tetrahydronaphtalen-)]-1,3,4-thiadiazoline (6b). Compound 6b was obtained from 2,3,4-trihydronaphtalen-1-one thiosemicarbazone (6a) by general procedure II. This compound was recrystallized from ethanol (yield 50%); m.p. 199-200 ºC. IR: $_{\nu max}$ 3214 (NH), 1695 (exo Amide I), 1645 (endo Amide I), 1608 (C=N), and 1496 cm^{-1} (Amide II). ^{1}H-NMR: 1.73-1.93 (1H, m, C*H*H); 2.03 (3H, s, CH_3); 2.17-2.30 (2H, m, CH_2); 2.18 (3H, s, CH_3); 2.89-3.04 (1H, m, C*H*H); 7.05-7-16 (4H, m, ArH); 11.55 (1H, s, NH). ^{13}C-NMR: see Table 2. HRMS calcd. 303.1041; found 303.1042.

Spiro[5-acetamido-3-*N*-acetyl-2,1´-indane]-1,3,4-thiadiazoline (7b). Compound 7b was obtained from indan-1-one thiosemicarbazone (7a) by general procedure II. This compound was recrystallized from ethanol (yield 76%); m.p.179-180 ºC. IR: $_{\nu max}$ 3220 (NH), 1695 (exo Amide I), 1640 (endo Amide I), 1608 (C=N), and 1491 cm^{-1} (Amide II). ^{1}H-NMR: 2.06 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.88-3.13 (4H , m, $2CH_2$), 7.33-7.70 (4H, m, ArH) and 11.58 (1H, s, NH). ^{13}C-NMR: see Table 2. HRMS calcd. 289.0885; found 289.0883

Spiro[5-acetamido-3-*N*-acetyl-2,1´-(5′-methoxyindan)]-1,3,4-thiadiazoline (8b). Compound 8b was obtained from 5-methoxyindan-1-one thiosemicarbazone (8a) by general procedure II. This compound was recrystallized from ethanol (yield 76%); m.p. 179-180 ºC. IR: $_{\nu max}$ 3223 (NH), 1693 (exo Amide I), 1638 (endo Amide I), 1610 (C=N), and 1490 cm^{-1} (Amide II). ^{1}H-NMR: 2.05 (3H, s, CH_3); 2.11 (3H, s, CH_3); 2.52 (1H, m, CH_2); 2.79-3.14 (3H, m, CH_2); 3.74 (3H, s, OCH_3); 6.76-7.20 (3H, several signals, ArH) and 11.56 (1H, s, NH). ^{13}C-NMR: see Table 2. HRMS calcd. 319.0991; found 319.0986.

Spiro[5-acetamido-3-*N*-acetyl -2,1´-(6'-methoxyindan)]-1,3,4-thiadiazoline (9b). Compound 9b was obtained from 6-methoxyindan-1-one thiosemicarbazone (9a) by general procedure II. This compound was recrystallized from ethanol (yield 93%); m.p.164-168 ºC.

IR: $_{\nu max}$ 3225 (NH), 1698 (exo Amide I), 1640 (endo Amide I), 1612 (C=N), and 1495 cm^{-1} (Amide II). ^{1}H-NMR: 2.07 (3H, s, CH_3); 2.03 (3H, s, CH_3); 2.22-3.10 (4H , m, 2 CH_2); 3.66 (3H, s, OCH_3); 6.70-7.29 (3H, several signals, ArH) and 11.52 (1H, s, NH). ^{13}C-NMR: see Table 2. HRMS calcd. 319.0991; found 319.0995.

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