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Note

Synthesis of 3-methyl/2,3-dimethyl/ 2,3-dimethoxy 6,7,8,9-tetrahydro-spiro[benzo [7]annulene-5,3′-[1,2,4]triazolidine]-5′-thione

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3-Methyl/2,3-dimethyl/2,3-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo [7] annulen-5-ylidene hydrazine-1-carbothioamides **2a-c** obtained by the condensation of benzocycloheptene-5-ones **1a-c** with thiosemicarbazide, on reaction with hydrogen peroxide in chloroform or acetic anhydride in acetic acid yield new 1,2,4–triazolidine-5′-thiones **3a-c**. These compounds have been characterized by analytical and spectral methods.

Keywords: Benzocycloheptene-5-ones, carbothioamides, spirothiones, hydrogen peroxide, acetic anhydride

1,2,4-Triazolidine-5′-thiones have been reported in the literature[1-4] for their pharmacological properties. 1,2,4-Triazolidine-5′-ones were normally obtained from carbothioamides by oxidative cyclization with hydrogen peroxide[5] or aluminum oxide[6]. In view of these observations and in continuation of our work in the synthesis of biologically active hetero cycles[7-10], we report herein the synthesis of new 1,2,4-triazolidine-5′-thiones **3** from carbothioamides **2**.

Results and Discussion

3-Methyl/2,3-dimethyl/2,3-dimethoxy-6,7,8,9-tetrahydro benzocycloheptene-5-ones **1a-c** reacted with thiosemicarbazide in ethanol containing a catalytic amount of conc. HCl, to give the 3-methyl/2,3-dimethyl/2,3-dimethoxy 6,7,8,9-tetrahydro-5*H*-benzo [7] annulen-5-ylidene) hydrazine-1-carbothioamides **2a-c** (Scheme I). These carbothioamides were characterized by their analytical and spectral data. IR spectrum of **2a** (taken as a representative example) showed absorption peaks at 3419, 3245, 3142 and 1192 cm^{-1} attributed to NH, NH_2 and C=S functional groups respectively.

On oxidative cyclization with hydrogen peroxide in chloroform at RT for 3 h (Method A) or acetic anhydride in acetic acid under reflux conditions for 12 h (method B) carbothioamides **2a-c** afforded 3-methyl/2,3-dimethyl/2,3-dimethoxy- 6,7,8,9-tetrahydrospiro [benzo [7] annulene-5,3′-[1,2,4] triazolidine]-5′-thiones **3a-c** (Scheme I) as light gray crystalline solids.

Oxidative cyclization of carbothioamides **2a-c** with hydrogen peroxide at RT gave better yields in comparison to acetic anhydride under reflux conditions. The IR, mass spectral fragmentation pattern and ^1H NMR spectral data gave strong substantiation for the structures **3a-c**. The IR spectrum exhibited the characteristic absorption bands at 3315 cm^{-1} for N-H and 1170 cm^{-1} for C=S respectively. The mass spectrum of **3a** (taken as representative example) had the molecular ion $C_{13}H_{17}N_3S$ at *m/z* 247, consistent with the molecular formula. The ^1H NMR spectrum had signals for 4 methylene group protons between δ 1.7 and 2.9. Besides these signals, the aromatic protons appeared as a multiplet at δ 7.00-7.70 and N-H protons nearer to the seven membered ring appeared at δ 5.75.

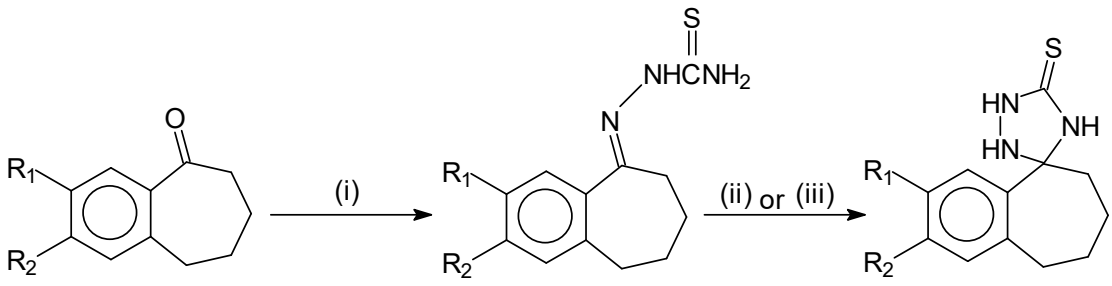
Experimental Section

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1605 FT-IR instrument. ^1H NMR was recorded in $CDCl_3$ on a Bruker NMR spectrometer at 400 MHz with TMS as internal standard. Mass spectra were recorded on a VG Micromass 7070H mass spectrometer. TLC was run on silica gel G coated plates using iodine vapor as visualizing agent.

General procedure for the synthesis of carbothioamides

A mixture of 3-methyl-6,7,8,9-tetrahydrobenzo-cyclohepten-5-one **1a** (1.0 mmol), thiosemicarbazide (1.0 mmol) and 0.4 mL of conc. HCl in absolute ethanol (10.0 mL) was stirred at RT for 3 h. It was poured into ice-cooled water. The solid thus obtained was filtered, dried and purified by recrystallization from ethanol to furnish **2a**.

(*E*)-2-(3-Methyl-6,7,8,9-tetrahydro-5*H*-benzo [7] annulen-5-ylidene) hydrazine-1-carbothioamide, 2a: Yield 0.230 g, 93%. m.p. 176-78°C. IR (KBr): 3419, 3245, 3142 (NH & NH_2), 1192 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.70-1.85 (4H, m, 7 & 8-CH_2), 2.40 (3H, s, 3-CH_3), 2.52-2.62 (2H, t, 6-CH_2), 2.68-2.75 (2H, t, 9-CH_2), 6.90-7.00 (1H, d, 1-CH), 7.0-7.15 (1H, d, 2-CH), and 7.20 (1H, s, 4-CH). Anal. Found: C, 63.07; H, 6.80; N, 16.83. $C_{13}H_{17}N_3S$ requires: C, 63.15; H, 6.88; N, 17.00%.



1a, b, c **2a, b, c** **3a, b, c**

a : $R_1 = H$, $R_2 = CH_3$

b : $R_1 = R_2 = CH_3$

c : $R_1 = R_2 = OCH_3$

Reagents: (i) Thiosemicarbazide, conc. HCl & EtOH; (ii) $H_2O_2/CHCl_3$; (iii) Ac_2O/AcOH

Scheme I

(*E*)-2-(2,3-Dimethyl-6,7,8,9-tetrahydro-5*H*-benzo [7] annulen-5-ylidene) hydrazine-1-carbothioamide, 2b: Yield 95%. m.p. 180-82°C. IR (KBr): 3416, 3200, 3142 (NH & NH_2), 1168 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.60-1.80 (4H, m, 7 & 8-CH_2), 2.25 (6H, s, 2 & 3-CH_3), 2.65-2.80 (4H, m, 6 & 9-CH_2), 6.80 (1H, s, 1-CH), and 7.22 (1H, s, 4-CH). Anal. Found: C, 64.26; H, 7.20; N, 15.98. $C_{14}H_{19}N_3S$ requires: C, 64.36; H, 7.27; N, 16.09%.

(*E*)-2-(2,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo [7] annulen-5-ylidene) hydrazine-1-carbothioamide, 2c: Yield 95%. m.p. 158-59°C. IR (KBr): 3203, 3245, 3429 (NH & NH_2), 1181 (C=S) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.60-1.80 (4H, m, 7 & 8-CH_2), 2.65-2.80 (4H, m, 6 & 9-CH_2), 3.9 (6H, s, 2,3-di methoxy), 6.80 (1H, s, 1-CH), and 7.0 (1H, s, 4-CH); MS: *m/z* (M^+) 294. Anal. Found: C, 57.30; H, 6.45; N, 14.31. $C_{14}H_{19}N_3O_2S$ requires: C, 57.33; H, 6.48; N, 14.32%.

General procedure for the synthesis of 3-methyl/ 2,3-dimethyl/2,3-dimethoxy-6,7,8,9-tetrahydrospiro [benzo [7]annulene-5,3′-[1,2,4]triazolidine]-5′-thione

Method A: A solution of **2a**[11] (1 mmol) in chloroform (8 mL) was treated with excess hydrogen peroxide (30%, 4 mL) and stirred for 3 h at RT. After completion of reaction, the organic layer was separated and dried over anhydrous sodium sulphate. The crude product thus obtained was purified by preparative TLC using 10% ethyl acetate and hexane, which gave the product **3a** in 74% yield.

Method B: The mixture of **2a** (1 mmol), acetic anhydride (0.3 mL) and acetic acid (1mL) were heated under reflux for 12 h. After completion of the reaction, the mixture was poured into ice-cooled water, extracted with chloroform, washed with water and dried. The crude product thus obtained was purified by preparative TLC using 10% ethyl acetate and hexane which gave the same product **3a** in51% yield.

3-Methyl-6,7,8,9-tetrahydrospiro[benzo[7]annulene -5,3′-[1,2,4]triazolidine]-5′-thione, 3a: Yield 74%. m.p.104-106°C. ^1H NMR ($CDCl_3$): δ 1.75-1.90 (4H, m, 7, 8-CH_2), 2.35 (3H, s, 3-CH_3), 2.68-2.78 (2H, t, 6-CH_2), 2.88-2.98 (2H, t, 9-CH_2), 7.05-7.10 (1H, d, 1-CH), 7.18-7.27 (1H, d, 2-CH), 7.53 (1H, s, 4-CH); MS: *m/z* 247 (M^+). Anal. Found: C, 63.07; H, 6.80; N, 16.93. $C_{13}H_{17}N_3S$ requires: C, 63.15; H, 6.88; N, 17.00%.

2,3-Dimethyl-6,7,8,9-tetrahydrospiro[benzo[7] annulene-5,3′-[1,2,4]triazolidine]-5′-thione,3b: Yield 70%. m.p. 97-98°C. ^1H NMR ($CDCl_3$): δ 1.75-1.90 (4H, m, 7, 8-CH_2), 2.28 (6H, s, 2,3-CH_3), 2.65-2.75 (2H, t, 9-CH_2), 2.80-2.90 (2H, t, 6-CH_2), 6.98 (1H, s, 1-CH), 7.53 (1H, s, 4-CH); MS: *m/z* 261 (M^+). Anal. Found: C, 64.30; H, 7.17; N, 15.98. $C_{14}H_{19}N_3S$ requires: C, 64.36; H, 7.27; N, 16.09%.

2,3-Dimethoxy-6,7,8,9-tetrahydrospiro[benzo [7] annulene-5,3′-[1,2,4]triazolidine]-5′-thione, 3c: Yield 64%. m.p.112-14°C. ^1H NMR ($CDCl_3$): δ 1.75-1.80 (4H, m, 7, 8-CH_2), 3.8 (6H, s, 2,3-OCH_3), 2.65-2.75 (2H, t,

9-CH_2), 2.80-2.90 (2H, t, 6-CH_2), 6.68 (1H, s, 1-CH), 7.23 (1H , s, 4-CH); MS: *m/z* 293 (M^+). Anal. Found: C, 57.30; H, 6.40; N, 14.29. $C_{14}H_{19}N_3SO_2$ requires: C, 57.33; H, 6.48; N, 14.33%.

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