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SYNTHESIS OF NOVEL BENZOPYRANO-1,2,3-SELENADIAZOLE AND SPIRO[BENZO PYRANO]-1,3,4-THIADIAZOLINE ERIVATIVES

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ABSTRACT

A facile and high yielding synthetic protocol of new selenadiazole and thiadiazoline derivatives incorporating bezopyran moiety from readily available starting materials was described. Reaction of 2,2-dimethyl and 2,2-spiro-cyclohexyl dihydrobenzopyranones **1a,b** with semicarbazide hydrochloride and thiosemicarbazide afforded the corresponding semicarbazones **2a,b** and thiosemicarbazones derivatives **3a,b**, respectively. Furthermore, cyclization of semicarbazones **2a,b** *via* oxidation using selenium dioxide gave benzopyranoselenadiazoles derivatives **4a,b**. Also, spirobenzopyrano-1,3,4-thiadidazolines **5a,b** were synthesized by refluxing of thiosemicarbazones **3a,b** in acetic anhydride. The chemical structure of all the newly synthesized compounds were established using the elemental analysis as well as different spectral techniques

Keywords: Benzopyranone, Chromeno-1,2,3-selenadiazole, 1,3,4-Thiadiazoline

INTRODUCTION

Substituted benzopyran-4-ones are common among natural products and they have been used to prepare various heterocyclic ring systems. For instance, 6-hydroxy-2,2-dimethyl-2,3-dihydro benzopyran-4-one (**1a**) which was previously isolated from *Calea cuneifolia* DC and *Gynura elliplia* possesses anti-platelt aggregation activity [**Loureneo**

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T.O. *et al.*, (1981) & Lin W.-T. *et al.*, (2000)]. Heterocyclic systems with 1,2,3-selenadiazole and 1,3,4-thiadiazoline ring systems are well known. Alkyl or aryl aldehyde and ketone semicarbazones can be converted into 1,2,3-selenadiazoles by oxidation with selenium dioxide **[Lalezari and Shafiee, (1969)]**. The construction of 1,3,4-thiadiazoline ring is mostly achieved by heterocyclization of thiosemicarbazones by acylation with acid anhydrides or acid chlorides **[Kubota S. *et al.*, (1980)]**.

In continuation of our studies in the chemistrty of chromones **[Atta S.M.Sh. *et al.*, (2010) & El-Desoky S.I. *et al.*, (1997) & Abdel-Rahman A.H. *et al.*, (2005)]**, we report herein the synthesis of 1,2,3-selena and 1,3,4- (thia)diazoles incorporated bezopyranone scaffold.

EXPERIMENTAL

General:

All melting points are uncorrected and were recorded on an open glass capillaries using a Gallenkamp apparatus. Infrared spectra (IR) were recorded (KBr), (υ cm-1) on a Mattson 5000 FTIR Spectrophotometer at Micro analytical Center, Faculty of Science, Mansoura University. The ^{1}H-NMR spectra were run on Bruker AC 300 MHz Spectrophotometer at Faculty of Science, Cairo University and ^{13}C-NMR spectra were recorded on JOEL 500 MHz at National Research Center (NRC. Egypt) using TMS as an internal reference and $CDCl_3$ and DMSO-d_6 as solvents and chemical shift (δ) values are recorded in ppm. The mass spectra (EI) were run at 70 eV with JEOL JMS600 equipment. Elemental analyses (C, H and N) were carried out at the Microanalytical Center at Cairo University, Egypt. The results were found to be in good agreement with the calculated values. Follow-up of the reactions was made by thin layer chromatography (TLC) on Silica gel pre-coated aluminum sheets (type 60 F254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ_{254} nm.

Synthesis:

General procedure for the synthesis of benzo-pyranones 1a,b

Equimolar amounts of 2,5-dihydroxyacetophenone (1.52 g, 10 mmol) and ketone derivatives (10 mmol) namely: acetone and hexanone in ethanol containing a catalytic amount of pyrrolidine (1 mL) were

allowed to react together. The reaction mixture was refluxed for 15 h (TLC control). The solvent was evaporated under reduced pressure and dried well. The obtained residual syrup was purified with column chromatography using (petroleum ether / ethyl acetate) as eluent to give compounds **1a,b**.

6-Hydroxy-2,2-dimethyl-2,3-dihydrobenzopyran-4-one (1a).

Yield (1.48 g, 77%); yellow needles; m.p. 140-141°C; [petroleum ether / ethyl acetate 4:1]. Melting point and spectral data were in complete agreement with the published data **[Tripathi A.K. *et al.*, (2009)]**.

6-Hydroxy-2,2-pentamethylene-2,3-dihydrobenzopyran-4-one (1b)

Yield (2.13 g, 92%); yellow crystals; m.p. 116°C; [petroleum ether / ethyl acetate 4:1]. Melting point and spectral data were in complete agreement with the published data **[Tripathi A.K. *et al.*, (2009)]**.

General procedure for the synthesis of semicarbazones 2a,b

A solution of **1a,b** (10 mmol), semicarbazide hydrochloride (2.23 g, 20 mmol), dry sodium acetate (2 g) in dry ethanol (20 mL) and a catalytic amount of glacial acetic acid (1 mL) was refluxed with stirring for 5 h (TLC control). The reaction mixture was poured onto crushed ice after cooling. The formed precipitate was filtered off, washed with water, dried and recrystallized from ethanol to give compounds **2a,b**.

6-Hydroxy-2,2-dimethyl-2,3-dihydrobenzopyran-4-one semicarbazone (2a).

Yield (1.82, 73%); yellow crystals; m.p. 212-214°C; Melting point and spectral data were in complete agreement with the published data **[Quilico A. *et al.*, (1950)]**.

6-Hydroxy-2,2-pentamethylene-2,3-dihydrobenzopyran-4-one semicarbazone (2b)

Yield (2.60 g, 90%); pale yellow crystals; m.p. 188-190°C; IR (KBr): ν/cm^{-1} = 3467, 3349-3261 (OH, NH, NH_2), 1673 (C=O, amide), 1573 (Ar); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.20-1.80 (m, 10H, 5 CH_2) 2.65 (s, 2H, H-3), 6.39 (s, 2H, NH_2, exchangeable with D_2O), 6.64-6.67 (m, 2H, H-7 and H-8), 7.36 (d, 1H, H-5, J= 2.10 Hz), 8.80 (s, broad, 1H, NH, exchangeable with D_2O), 9.36 (s, 1H, OH, exchangeable with D_2O).

Anal. Calcd. for $C_{15}H_{19}N_3O_3$ (289.33): C, 62.27; H, 6.62; N, 14.52%. Found: C, 62.47; H, 6.81; N, 14.73%.

General procedure for the synthesis of thiosemicarbazones 3a,b

A mixture of chromanones **1a,b** (10 mmol), thiosemicarbazide (1 g, 11 mmol) in dry ethanol (25 mL) and a catalytic amount of conc. HCl (1 mL) was refluxed with stirring for 3-5 h (TLC control). The reaction mixture was cooled, poured onto crushed ice (100 g) thereafter; stirring was continued for 1 h. The formed precipitate was filtered off, washed well with cold water, dried and recrystallized from ethanol to give compounds **3a,b**.

6-Hydroxy-2,2-dimethyl-2,3-dihydrobenzopyran-4-one thiosemicarbazone (3a)

Yield (1.86 g, 70%); yellow crystals; m.p. 238-239°C; IR (KBr): ν/cm^{-1} = 3426, 3351, 3270 (OH, NH, NH_2), 1606 (C=N), 1197 (C=S); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.27 (s, 6H, 2 CH_3), 2.81 (s, 2H, H-3), 6.63 (d, 1H, H-8, J= 9 Hz), 6.74 (dd, 1H, H-7, J= 2.70, 9Hz), 7.49 (d, 1H, H-5, J= 2.70Hz), 7.86 (s, 1H, NH_2, exchangeable wtih D_2O), 8.24 (s, 1H, NH_2, exchangeable wtih D_2O), 8.90 (s, 1H, NH, exchangeable wtih D_2O), 10.22 (s, 1H, OH, exchangeable wtih D_2O). Anal. Calcd. for $C_{12}H_{15}N_3O_2S$ (265.33): C, 54.32; H, 5.70; N, 15.84; S, 12.08%. Found: C, 54.50; H, 5.88; N, 15.57; S, 12.27%.

6-Hydroxy-2,2-pentamethylene-2,3-dihydrobenzopyran-4-one thiosemicarbazone (3b)

Yield (2.44 g, 80%); yellow crystals; m.p. 122°C; IR (KBr): ν/cm^{-1} = 3422, 3298-3200 (OH, NH, NH_2), 1589 (C=N), 1208 (C=S); ^{1}H-NMR($CDCl_3$) δ (ppm): 1.34-1.97 (m, 10H, 5CH_2), 2.56 (s, 2H, H-3), 6.45 (s, broad, 3H, NH, NH_2, exchangeable with D_2O), 6.80 (d, 1H, H-8), 7.25 (dd, 1H, H-7), 7.35 (d, 1H, H-5), 8.77(s, broad, 1H, OH, exchangeable with D_2O). Anal. Calcd. for $C_{15}H_{19}N_3O_2S$ (305.4): C, 58.99; H, 6.27; N, 13.76; S, 10.50%. Found: C, 58.71; H, 6.41; N, 13.90; S, 10.69%.

General procedure for the Synthesis of selenadiazoles 4a,b

A solution of compounds **2a,b** (5 mmol) in glacial acetic acid (15 mL) was warmed at 60°C with stirring then selenium dioxide (0.55 g, 5 mmol) was added portionwise during a period of 30 min and stirring was continued for further 10 h (TLC control). After completion of the

reaction, the reaction mixture was filtered to remove the deposited selenium. The filtrate was poured onto crushed ice and the obtained solid was filtered off, washed thoroughly with cold water, sodium carbonate solution and water. The obtained product after drying was purified with column chromatography using (petroleum ether / ethyl acetate) as eluent to give compounds **4a,b**.

8-Hydroxy-4,4-dimethylbenzopyrano[4,3-d](1,2,3)selenadiazole (4a)

Yield (1.04 g, 74%); yellowish brown crystals; m.p. 168-170°C; [petroleum ether / ethyl acetate 7:3]; IR (KBr): ν/cm^{-1} = 3500-3250 (OH, broad), 1502 (N=N); ^{1}H-NMR($CDCl_3$) δ (ppm): 1.77 (s, 6H, $2CH_3$), 5.35 (s, broad, 1H, OH, exchangeable with D_2O), 6.83 (dd, 1H, H-7, J= 2.70, 8.70 Hz), 6.87 (d, 1H, H-6, J= 8.70 Hz), 7.79 (d, 1H, H-9, J= 2.70 Hz); ^{13}C-NMR($CDCl_3$) δ (ppm): 30.39, 80.05, 111.58, 117.46, 118.52, 145.82, 151.09, 153.71, 159.60. Anal. Calcd. for $C_{11}H_{10}N_2O_2Se$ (281.17): C, 46.99; H, 3.58; N, 9.96%. Found: C, 46.72; H, 3.80; N, 9.76%.

8-Hydroxy-4,4-pentamethylene benzopyrano[4,3-d](1,2,3) selenadiazole (4b)

Yield (1.17g, 73%); yellow crystals; m.p. 184°C; [petroleum ether / ethyl acetate 7:3]; IR (KBr): ν/cm^{-1} = 3378 (OH, free), 3530-3210 (OH, broad, bonded), 1500 (N=N); ^{1}H-NMR(DMSO-d_6) δ (ppm): 1.38-2.20 (m, 10H, 5 CH_2), 6.74 (d, 1H, H-7, J= 7.80 Hz), 6.93 (d, 1H, H-6, J= 8.70 Hz), 7.44 (s, 1H, H-9), 9.34 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd. for $C_{14}H_{14}N_2O_2Se$ (321.23): C, 52.35; H, 4.39; N, 8.72%. Found: C, 52.10; H, 4.21; N, 8.42%.

General procedure for the synthesis of thiadiazolines 5a,b

A mixture of 3a-d (10 mmol) in freshly distilled acetic anhydride (20 mL) was heated on water bath (90oC) for 5-20 h (TLC control). After completion of the reaction, the reaction mixture was poured onto crushed ice with vigorous stirring. The formed precipitate was filtered off, washed with water, dried and purified by column chromatography using petroleum ether/ ethyl acetate as eluent to give compounds **5a,b**.

6-Acetoxy-4′-acetyl-2′-acetylamido-2,2-dimethylspirochroman-4,5′-Δ^2-1,3,4-thiadiazoline (5a)

Yield (3.08g, 70%); pale brown crystals; m.p. 144°C; [petroleum ether/ ethyl acetate 4:6]; IR (KBr): ν/cm^{-1} = 3218 (NH), 1758 (CH_3-COO), 1702, 1680 (CH_3CON, two groups), 1621 (C=N). ^{1}H-

NMR($CDCl_3$) δ (ppm): 1.34 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.00 (s, 3H, $\underline{CH_3}$-COO-), 2.236 (s, 3H, $\underline{CH_3}$-CON), 2.243 (s, 3H, $\underline{CH_3}$-CON), 2.43 (d, 1H, H_a-3, J_{gem}= 13.80 Hz), 3.42 (d, 1H, H_b-3, J_{gem}= 13.80 Hz), 6.73 (d, 1H, H-8, J= 8.70 Hz), 6.89 (dd, 1H, H-7, J=3, 8.70 Hz), 7.13 (d, 1H, H-5, J= 3 Hz), 9.64 (s, br., 1H, NH, exchangeable with D_2O). Anal. Calcd. for $C_{18}H_{21}N_3O_5S$ (391.44): C, 55.23; H, 5.41; N, 10.73; S, 8.19%. Found, 55.43; H, 5.21; N, 10.53; S, 8.00%.

6-Acetoxy-4′-acetyl-2′-acetylamido-2,2-pentamethylenespirochroman-4,5′-Δ^2-1,3,4-thiadiazoline (5b)

Yield: (4.09g, 95%); colorless crystals; m.p. 130°C; [petroleum ether/ ethyl acetate 4:6]; IR (KBr): ν/cm^{-1}= 3224 (NH), 1756 (CH_3COO), 1706, 1650 (CH_3CON, two groups), 1621 (C=N). ^{1}H-NMR($CDCl_3$) δ (ppm): 1.20-1.90 (m, 10H, $5CH_2$), 2.01 (s, 3H, $\underline{CH_3}COO$), 2.22 (s, 3H, $\underline{CH_3}CON$), 2.23 (s, 3H, $\underline{CH_3}CON$), 2.48 (d, 1H, H_a-3, J_{gem}= 14.10 Hz), 3.30 (d, 1H, H_b-3, J_{gem}= 14.10 Hz), 6.78 (d, 1H, H-8, J= 8.70 Hz), 6.90 (dd, 1H, H-7, J= 2.70, 8.70 Hz), 7.09 (d, 1H, H-5, J= 2.70 Hz), 9.44 (s, 1H, NH, exchangeable with D_2O); ^{13}C-NMR($CDCl_3$) δ (ppm): 21.26, 21.50, 22.85, 24.32, 25.45, 32.65, 38.11, 45.30, 74.83, 75.86, 118.43, 120.03, 123.11, 125.38, 144.32, 145.52, 150.34, 168.95, 169.61, 170.21. Anal. Calcd. for $C_{21}H_{25}N_3O_5S$ (431.51): C, 58.45; H, 5.84; N, 9.74; S, 7.43%. Found: C, 58.25; H, 5.74; N, 9.93, S, 7.33%.

RESULTS AND DISCUSSION

Refluxing of 2,5-dihydroxyacetophenone with acetone and cyclohexanone in the presence of catalytic amount of pyrrolidine [**Kabbe and Widdig, (1982)**] gave a quantitative yield of the naturally occurring 2,2-dimethyl-2,3-dihydrobenzopyran-4-one (**1a**) and the structurally related derivative **1b** (**Scheme 1**). The melting points and spectral data of **1a,b** are in agreement with the reported data (**Tripathi A.K. *et al.*, (2009)**]. Treatment of **1a,b** with semicarbazide hydrochloride and thiosemicarbazide led to the formation of the corresponding semicarbazones **2a,b** and thiosemicarbazones **3a,b**, respectively (**Scheme 1**).

On the other hand, heating of compounds **2a,b** with equimolar amounts of selenium dioxide gave chromenoselenadiazole derivatives **4a,b**, respectively. Moreover, reaction of thiosemicabazone derivatives

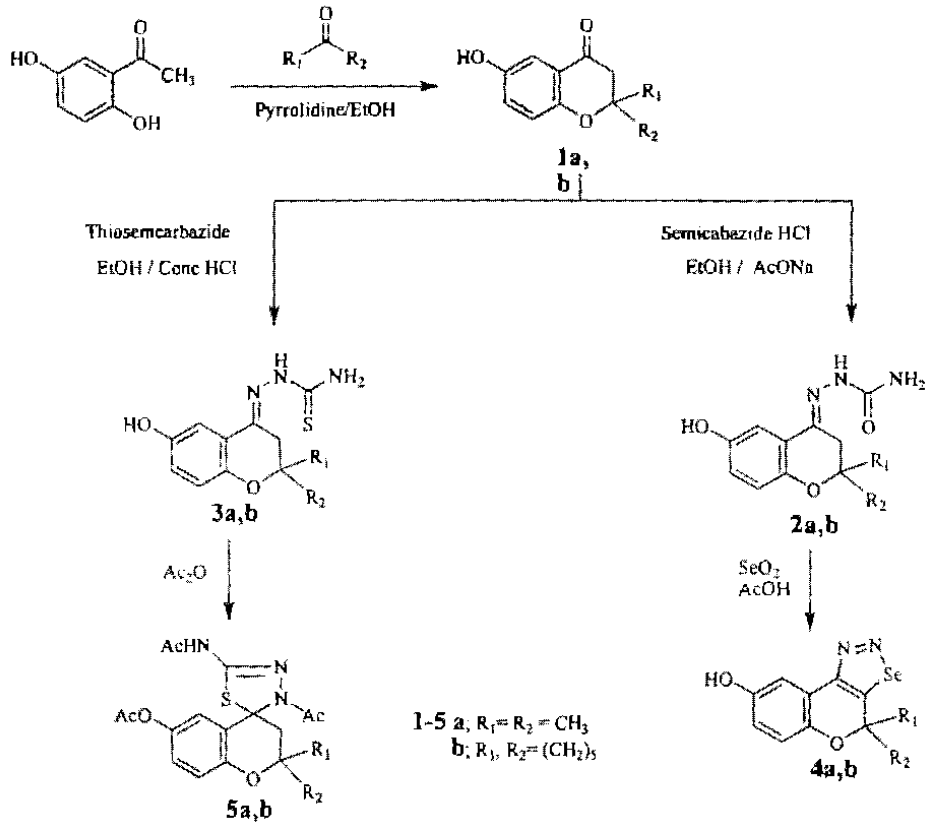
3a,b with acetic anhydride afforded the corresponding spirochroman-4,5'-Δ^2-1,3,4-thiadiazoline derivatives **5a,b** in very good yields (**Scheme 1**).

< Scheme 1 >

All of the synthesized compounds were established on the basis of analytical and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS). The ^{1}H-NMR spectrum of **2b** revealed the aromatic and methylene protons, in addition to protons of NH_2, NH and OH which are exchangeable with D_2O at δ 6.39, 8.80 and 9.36, respectively. Additionally, the ^{1}H-NMR spectra of **4a,b** revealed the absence of methylene protons of the chroman ring, in addition to the exchangeable protons except hydroxyl group proton (*C.f.* Experimental Section).

As a result of the diastereotopic nature of methylene protons related to the chroman ring of thiadiazoline derivatives **5a,b**, they appeared in the ^{1}H-NMR spectra at two different chemical shifts with coupling constant 13.80-14.10 Hz. This marked difference between the chemical shifts not only results from the inductive effect exerted by the heteroatoms, but also due to a spatial effect probably exerted by the acetyl groups.

Moreover, the ^{13}C-NMR spectrum of **5b** confirmed the ring closure by the appearance of a signal at *circa* 75.86 ppm assigned to C-2 in thiadiazoline ring, and signals of carbonyl moieties incorporated in the molecule at δ = 168.95, 169.61 and 170.21 ppm.



Scheme 1: Synthesis of chromenoselenadiazoles **4a,b** and spirochroman-4,5′-Δ^2 1,3,4-thiadiazolines **5a,b**

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تشـــــــيد بعض مشتقات
البنزوبيرانو-٣،٢،١-ســـــيلينـاديازول و ســـــــبايرو[بنزوبيرانو]-٤،٣،١-ثيـاديازولين الجديدة

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أحتوى هذا البحـث علـى شـرح لطـرق جديـدة وبـسيطة لتـشييد مركبـات الســـيلينـاديازول وأيضا الثياديازولين المتلاحمة مع مشتقات البنزوبيران من مـواد اوليـة متداولـة وسـهلة التحـضير. عنـدما يتفاعـل ٢،٢-ثنـائي ميثيـل-٢،٢-ســـــبايرو سيكلوهكســـــيل دأى هيدروبنزوبيرانون **1a,b** مع الســـــيمي كاربازيد هيدروكلوريـد والثيوســـــيميكاربازيد تتكون مشتقات الـســـــيميكاربازون والثيوســـــــيميكاربازون المقابلة زيادة على ذلك، عنـد حولقـة الـســـــيميكاربازون **2a,b** مـن خـلال عمليـة الأكـســـــدة بإســـتخدام ثنـــائي أوكـــسيد الـســـــيلينيوم تتكـــون مـــشتقات البنزوبيرانوســـيلينـاديازول **4a,b** .أيضـــا مشتقات ســـــبايرو[بنزوبيرانـو]-٤،٣،١-ثياديازولين **5a,b** امكن تحضيرها بتسخين الثيوســـــــيميكاربازون **3a,b** فـي حمـض الخليك اللامائي. تم إثبات التركيب الكيميائي للنواتج الجديدة بالتحليل العنصرى الدقيق وأيضاً بالطرق الطيفية المختلفة.