Facile Synthesis of Thiazolidin-4-one Derivatives Incorporating Indole Moiety

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Abstract

Condensation of ethyl 3-formyl-1H-indole-2-carboxylate (**1**) with thiosemicarbazide in ethanol gave ethyl 3-(thiosemicarbazidomethyl)-1H-indole-2-carboxylate (**2**). Treatment of **2** with chloroacetic acid afforded the thiazolidin-4-one derivative **3**. Condensation of **3** with aromatic aldehydes gave the corresponding arylidene derivatives **4a-c**. Cyclization of **4a-c** with hydroxylamine hydrochloride in the presence of sodium acetate yielded thiazolidino[4,5-c]isoxazoline derivatives **5a-c**. The structure of the synthesized compounds were confirmed using elemental and spectroscopic analysis.

1. Introduction

Indole nucleus constitutes a structural unit of several natural alkaloids [1-3] and pharmacologically active molecules [4,5]. Indole-3-carbaldehyde was isolated from the genus *Hyrtios* from the Red-Sea, Egypt [6]. Indole derivatives were reported to possess a wide variety of biological properties *viz.*, anti-inflammatory, [7–9] anticonvulsant, [10] cardiovascular [11] and antibacterial [12]. Herein, we report on the utility of ethyl 3-formyl-1H-indole-2-carboxylate (**1**) in the synthesis of

some indole containing thiazolidine derivatives as potentially active heterocycles.

2. Experimental Section

Melting points were measured on a MEL-TEMPII melting point apparatus and were uncorrected. Microanalyses were performed at the Microanalytical Center, Cairo University. IR spectra were recorded with a Perking Elmer 1430 ratio recording infrared spectrophotometer with CDS data station using KBr Wafer technique. ^{1}H NMR spectra were measured on a Varian Gemini (300 MHz) spectrometer and mass spectra were measured on a GC-MSQP 1000 EX Schimadzu at Cairo University. The purity of the synthesized compounds was checked by TLC on glass coated plates in the laboratory with silica gel GF 254 type, 60 mesh, size 50-250. The spots on the thin layer plates were detected by exposure to iodine vapor. 3-Formyl-1H-indole-2-carboxylate (**1**) and ethyl 3-(thiosemicarbazidomethyl)-1H-indole-2-carboxylate (**2**) were prepared according to a literature method [13].

2.1. Synthesis of ethyl 3-(4-oxo-thiazolidin-2-ylidenehydrazino)methylene-1H-indole-2-carboxylate (3)

A mixture of ethyl 3-(thiosemicarbazidomethyl)-1H-indole-2-carboxylate (**2**) (2.9 g, 10 mmol), chloroacetic acid (0.95 g, 10 mmol) and anhydrous sodium acetate (1.6 g, 20 mmol) in ethanol (60 ml) was heated under reflux for 8 hours on a water bath with continuous stirring. After the reaction was complete, the reaction mixture was poured onto an ice water and the solid precipitate was filtered off and dried. The crude product was finally recrystallized from ethanol to give compound **3** in 87% yield as pale yellow solid. M.p 250 ^{o}C, R_f 0.75 (chloroform/methanol, 9:1); IR (cm^{-1}): 1619 (C=N), 1685 (C=O thiazole), 1708 (C=O ester), 3303 (NH); ^{1}H NMR (DMSO-d$_6$) δ 1.36-1.41 (t, J = 7.24 Hz, 3H, CH_2CH_3), 3.93 (s, 2H, CH_2-thiazole), 4.38-4.46 (q, J = 7.24 Hz, 2H, CH_2CH_3), 7.23-

8.42 (m, 4H, ArH), 9.16 (s, 1H, CH=N), 11.93 (br. s, 1H, NH thiazole), 12.28 (br. s, 1H, NH indole). Anal. Calcd for: $C_{15}H_{14}N_4O_3S$. (M. Wt. 330): C, 54.53; H, 4.27; N 16.96; S, 9.71%. Found: C, 54.39; H, 4.20; N 16.88; S, 9.27 %.

2.2. Synthesis of ethyl 3-(5-arylidene-4-oxo-thiazolidin-2-ylidenehydrazino)- methylene-1H-indole-2-carboxylates 4a-c.

To a mixture of ethyl 3-(4-oxo-thiazolidin-2-ylidenehydrazino)methylene-1H-indole-2-carboxylate (**3**) (3.3 g, 10 mmol) and the appropriate aromatic aldehyde (10 mmol) in acetic acid (40 ml), anhydrous sodium acetate (1.6 g, 20 mmol) were added. The reaction mixture was refluxed for 4 hours, then left to cool to room temperature. The reaction mixture was then poured onto crushed ice and the precipitated solid was filtered, washed with water and recrystallized from DMF-ethanol to yield the corresponding 5-arylidene-4-oxothiazolidene derivatives **4a-c**.

4a: Yield (82%), yellow solid, m.p 215 ^oC, R_f 0.65 (chloroform/methanol, 9:1), IR (KBr) ν cm^{-1}: 1629 (C=N), 1685 (C=O thiazole), 1724 (C=O ester), 3305 (NH); ^1H NMR (DMSO-d_6) δ 1.36-1.41 (t, 3H, $CH_2\mathit{CH_3}$), 4.41-4.47(q, 2H, $\mathit{CH_2}CH_3$), 6.30 (s, 1H, Ar-CH=C), 7.24-8.63 (m, 8H, ArH), 9.16 (s, 1H, CH=N), 10.63 (s, 1H, NH-thiazole), 11.98 (s, 1H, NH-indole). Anal. Calcd for: $C_{22}H_{17}ClN_4O_3S$ (M.wt. 452): C, 58.34; H, 3.78; N, 12.37; S, 7.08%. Found: C, 58.25; H, 3.73; N, 12.29; S, 7.01 %.

4b: (78%) yellow powder, m.p 215 ^oC, R_f 0.84 (chloroform/methanol, 9:1); IR (KBr) ν cm^{-1}: 1631 (C=N), 1685 (C=O thiazole), 1704 (C=O ester), 3303 (NH). ^1H NMR (DMSO-d_6) δ 1.31-1.38 (t, 3H, $CH_2\mathit{CH_3}$), 4.35-4.42 (q, 2H, $\mathit{CH_2}CH_3$), 6.28 (s, 1H, Ar-CH=), 7.37-8.72 (m, 8H, ArH), 9.12 (s, 1H, CH=N), 10.54 (s, 1H, NH thiazole), 12.07 (s, 1H, NH-indole). MS: *m/z* (%) 463 (M^+, 7.58), 446 (7.42), 416 (3.01), 375 (4), 330 (19.72), 214 (28.11), 185 (100), 179 (64.84), 128 (25.8), 114 (18), 89 (64.36), 63 (19.36), 51 (24).

Anal. Calcd for: $C_{22}H_{17}N_5S$ (M. Wt. 463): C, 57.01; H, 3.70; N, 15.11; S, 6.92%. Found: C, 56.94; H, 3.61; N, 15.02; S, 6.84%.

4c: (72%) yellow solid, m.p 235 ^oC; IR (KBr) ν cm^{-1}: 1632 (C=N), 1694 (C=O thiazole), 1709 (C=O ester), 3340 (NH); ^1H NMR (DMSO-d_6) δ 1.28-1.35 (t, 3H, CH_2CH_3), 3.78 (s, 3H, CH_3O), 4.40-4.47 (q, 2H, CH_2CH_3), 6.38 (s, 1H, Ar-CH=), 6.90-7.82 (m, 8H, ArH), 9.18 (s, 1H, CH=N), 10.83 (s, 1H, NH-thiazole), 11.87 (s, 1H, NH-indole). Anal. Calcd for: $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49; S, 7.15%. Found: C, 16.53; H, 4.40; N, 12.42; S, 7.09%.

2.3. Synthesis of 3-(3,3a-dihydro-3-arylisoxazolo[3,4-d]thiazol-5(6H)-ylidene)-hydrazino)methylene-1H-indole-2-carboxylates 5a-c.

A solution of sodium acetate (1 g, 12 mmol) in acetic acid (5 ml) was added to a mixture of compounds **4a-c** (12 mmol) and hydroxylamine hydrochloride (0.84 g, 12 mmol) in absolute ethanol. The reaction mixture was refluxed for 10 hours then left to cool to room temperature. Excess solvent was distilled off under reduced pressure and the residue was treated with water. The solid obtained was filtered off, dried and then recrystallized from ethanol to give the corresponding isoxazolo[3,4-d]thiazole derivatives **5a-c**.

5a: Yellowish brown solid, (61%), m.p 195 ^oC, R_f 0.65 (chloroform/methanol, 9:1). IR (KBr) ν cm^{-1}: 1642 (C=N), 1758 (C=O ester), 3362 (NH); ^1H NMR (DMSO-d_6) δ 1.35-1.44 (t, 3H, CH_2CH_3), 1.62 (d, 1H, *CH*-S, *J* = 6 Hz), 1.76 (d, 1H, *CH*-O, *J* = 6 Hz), 4.37-4.44 (q, 2H, CH_2CH_3), 7.30-8.52 (m, 8H, ArH), 9.01 (s, H, CH=N), 11.23 (s, 1H, NH), 11.23 (s, 1H, NH-thiazolidine), 12.04 (s, 1H, NH-indole); MS: *m/z* (%) 467 (M^+, 6.25), 441 (18.5), 383 (7.38), 327 (32.3), 204 (80.9), 187 (96.6), 163 (17.8), 129 (26). Anal. Calcd for: $C_{22}H_{18}ClN_5O_3S$ (M. Wt. 467): C, 56.47; H, 3.88; N, 14.97; S, 6.85%. Found: C, 56.38; H, 3.81; N, 14.82; S, 6.80%.

5b: Pale brown solid, m.p 225 ^{o}C, IR (KBr) ν cm^{-1}: 1617 (C=N), 1772 (C=O ester), 3311 (NH), ^{1}H NMR (DMSO-d_6) δ 1.33-1.40 (t, 3H, CH_2CH_3), 1.59 (d, 1H, CH-S, *J* = 6 Hz), 1.70 (d, 1H, *CH*-O, *J* = 6 Hz), 4.42-4.49 (q, 2H, CH_2CH_3), 7.41-8.27 (m, 8H, Ar), 9.14 (s, 1H, CH=N), 11.19 (s, 1H, NH-thiazolidine), 12.01 (s, 1H, NH-indole); MS: *m/z* (%) 478 (M^{+}, 7.14%), 452 (33.6), 395 (45.3), 340 (11.1), 245 (23.8), 181 (82). Anal. Calcd for: $C_{22}H_{18}ClN_6O_5S$: C, 55.52; H, 3.79; N, 17.56; S, 6.70%. Found: C, 55.09; H, 3.79; N, 17.56; S, 7.60%.

5c: Pale brown solid, yield (76%), m.p 225 °C, IR (KBr) ν cm^{-1}: 1632 (C=N), 1718 (C=O ester), 3240 (NH). ^{1}H NMR (DMSO-d_6) δ 1.34-1.40 (t, 3H, CH_2CH_3), 1.65 (d, 1H, CH-S, *J* = 6 Hz), 1.78 (d, 1H, CH-O, *J* = 6 Hz), 3.79 (S, 3H, CH_3-O), 4.35-4.41 (q, 2H, CH_2CH_3), 7.14-8.86 (m, 8H, ArH), 8.86 (s, 1H, CH=N), 11.11 (s, 1H, NH thiazolidinone), 11.95 (s, 1H, NH indole); MS: *m/z* (%) 463 (M^{+}, 10.5), 437 (31.7), 379 (5.3), 327 (19.7), 204 (72), 97 (70), 89 (30). Anal. Calcd for: $C_{23}H_{21}N_5O_4S$ (M. wt. 463) C, 59.60; H, 4.57; N, 15.11; S, 6.92%. Found: C, 59.52; H, 4.49; N, 15.01; S, 6.84%.

3. Results And Discussion

Treatment of ethyl 3-formyl-1H-indole-2-carboxylate (**1**) with thiosemicarbazide in ethanol at reflux temperature gave 3-(thiosemicarbazidomethyl)-1H-indole-2-carboxylate (**2**), according to the reported procedure [13]. Reaction of compound **2** with chloroacetic acid in refluxing ethanol in the presence of anhydrous sodium acetate resulted in the formation of ethyl 3-(4-oxo-thiazolidin-2-ylidenehydrazino)-methylene-1H-indole-2-carboxylate (**3**) as shown in the Scheme. The structure of the obtained product **3** was established on the basis of its elemental analysis and spectral data. For example, its IR spectrum displayed absorption bands at 1685, 1708 and 3303 cm^{-1} corresponding to thiazole C=O, ester C=O, and NH functions, respectively. The structure of the reaction product **3** was further supported by ^{1}H-NMR spectrum

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exhibiting singlet signals at δ 12.28 (NH indole), 11.93 (NH thiazole), 9.16 (C*H*=N) and 3.92 (CH_2 thiazole), respectively, in addition to the ester-ethyl protons which appeared as a triplet and a quartet signals at δ 1.39 (CH_3) and 4.42 (CH_2), respectively, with *J* value 7.24 Hz.

Condensation of **3** with aromatic aldehydes in acetic acid at refluxing temperature in the presence of sodium acetate furnished, in each case, only one isolable product identified as the 5-arylidene-4-oxothiazolidene derivatives **4a-c**. Structure of the isolated products **4a-c** were substantiated from their elemental and spectral analyses. The ^{1}H-NMR spectrum of compound **4a**, taken as a typical example of the series, revealed the absence of the singlet signal at δ 3.92 due to thiazole-5-CH_2, and showed new singlet signals at δ 3.78 and 6.38 due to the *p*-OCH_3 protons and the thizoliden-5- C=C*H*-Ar, respectively, in addition to the ester-ethyl protons at δ 1.32 and 4.44.

5-Benzylidene-4-oxothiazolidene derivative **4a** underwent cyclocondensation reaction when treated with hydroxylamine hydrochloride in the presence of sodium acetate at reflux condition to afford only one product assigned 3-(3,3a-dihydro-3-phenylisoxazolo[3,4-d]thiazol-5(6H)-ylidene)hydrazino)methylene-1H-indole-2-carboxylate (**5a**) as shown in the Scheme. The structure of compound **5a** was confirmed from its elemental analysis and spectral data as described in the experimental section. Similarly, compounds **4b,c** reacted with hydroxylamine hydrochloride under the same experimental conditions to give the corresponding isoxazolo[3,4-d]thiazole derivatives **5b,c**.

تخليق مشتقات ثيازوليدين -4-اون متحده بجزئ اندول

حسين احمد حسين
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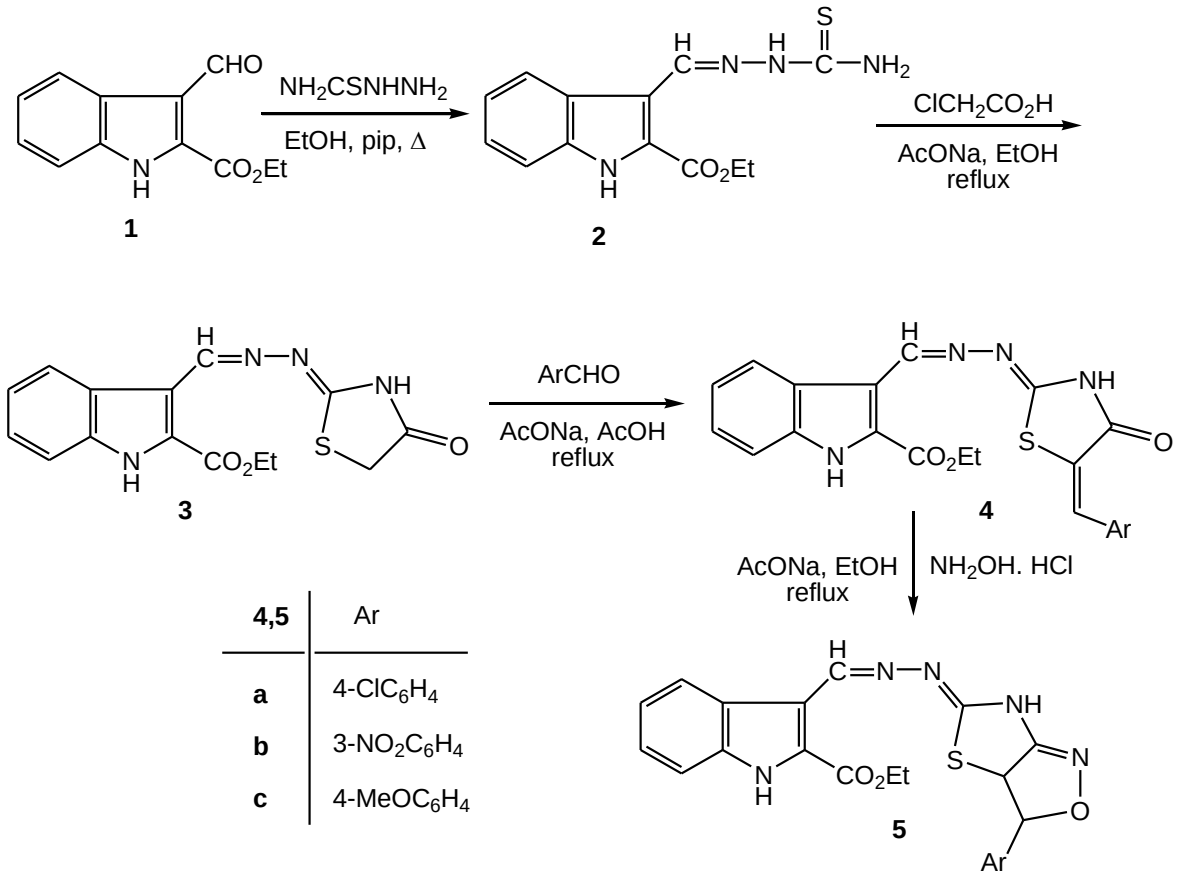
الملخص

تكاثف ايثايل -3-فورمويل-H 1 – اندول 2- كربوكسيلات مع ثيوسيمي كاربازيد في الايثانول أعطى ايثيل – (ثيوسيمي كاربازيدو ميثيل) – H1 – اندول -2 – كربوكسيلات مركب (2) .معاملة المركب(2) بحمض كلور حمض الخليك اعطى مشتق ثيازوليدين – 4 – اون مركب(3) . تكاثف المركب (3) مع الدهيدات اروماتيه

اعطى مشتقات الاريليدين المقابله (4a-c). حولقة المركبات (4a-c) بواسطة هيدروكسيل أمين هيدروكلوريد في وجود خلات صوديوم انتج مشتقات (4,5-c) أيزواوكسالين (5a-c) .

تم اثبات التراكيب الكيميائية للمركبات المحضرة باستخدام التحاليل العنصرية والطيفية



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