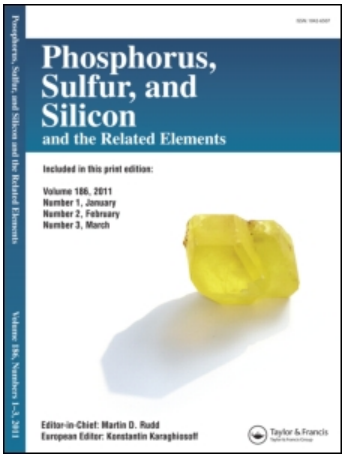

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HETEROCYCLES SYNTHESIS THROUGH REACTIONS OF INDOLIN-2-ONE DERIVATIVES WITH ACTIVE METHYLENE AND AMINO REAGENTS, PART 3, NOVEL AND FACILE ONE-STEP SYNTHESIS OF SPIROTHIOPYRAN-4-YL INDOLIDENE DERIVATIVES

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New spirothiopyran-4-yl indolidene derivatives have been synthesised via a facile one-step method. Structures and reaction mechanisms are also reported and supported by another synthetic route.

Key words: Isatins; malononitrile; cyanothioacetamide; spirothiopyran-4-yl indolidenes; spiropyridin-4-yl indolidenes.

Isatin and its derivatives show marked biological activities such as herbicidal, antibacterial and anticonvulsant properties.[1-3] These interesting biological activities make it desirable to extend our previous syntheses of heterocycles from isatin and its derivatives.[4-8] In this novel synthesis we succeeded in preparing 2,6-diamino-3,5-dicyanospiro[indoline-3,4(1H)thiopyran]-2-one **5a** by the ternary condensation of isatin **1a** with malononitrile and cyanothioacetamide in a molar ratio of 1:1:1 (Method A) in ethanol containing piperidine at room temperature. Structure 5a was confirmed for the reaction product on the basis of analytical and spectral data (cf. Experimental). The single cyano IR absorption band at 2180 cm^{-1} and the ^1H NMR singlet due to the two amino groups at δ 3.34 ppm indicate that the molecule has a plane of symmetry and thus supports the structure of **5a**.

The formation of 5 may be rationalized in terms of the initial condensation of isatin with maloninitrile or cyanothioacetamide affording 2-(oxo-3-indolinylidene)malononitrile **2a** or cyano-(2-oxo-3-indolinylidene)-thioacetamide **3a**, respectively, followed by the addition of the other active methylene reagent to the ylidenic bond in **2a** or **3a** to form an acyclic intermediate **4a** which cyclises to the final isolable product (cf. Chart 1).

Similar treatment of 5-bromoisatin **1b** and 5-methylisatin **1c** with malononitrile and cyanothioacetamide affords the corresponding spirothiopyran-4-yl indolidene derivatives **5b,c** respectively.

Further support of structure **5** and also for the suggested mechanism was achieved by its synthesis via stirring cold ethanolic piperidine solution of **2** and

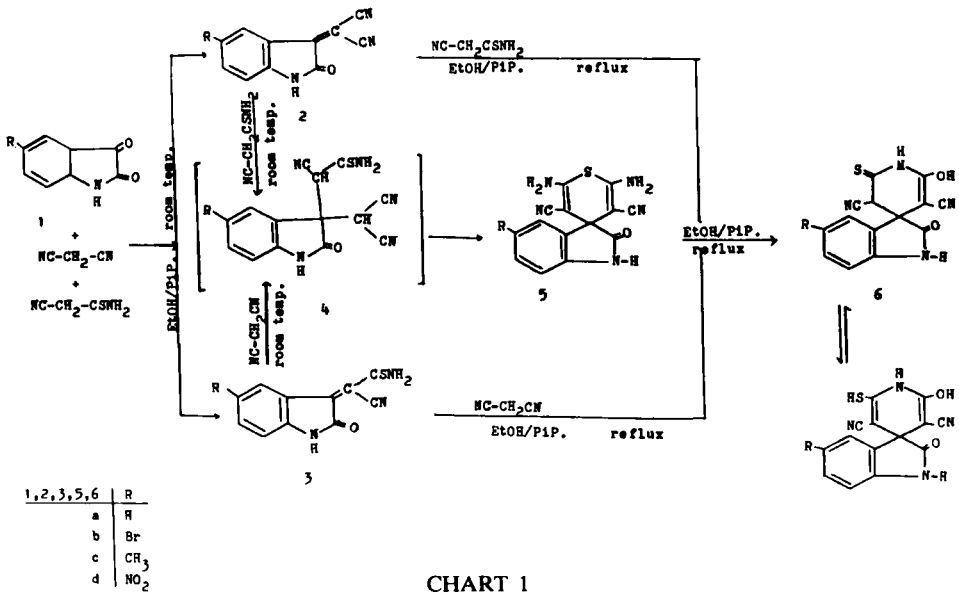

CHART 1

cyanothioacetamide and also by stirring cold ethanolic piperidine solution of **3** and malononitrile at room temperature (cf. Chart 1).

In contrast to the behavior of **2a** toward cyanothioacetamide and **3a** toward malononitrile in cold ethanolic piperidine solution, compound **2a** reacts with cyanothioacetamide and compound **3a** with malononitrile in refluxing ethanolic piperidine solution to yield 3,5-dicyano-1,2-dihydro-6-hydroxy-2-thioxospiro[indoline-3,4(1H)-pyridine]-2-one **6a**. The absence of an SH band at 2600 cm^{-1} which revealed the existence of compound **6a** as the thione tautomer ((cf. Experimental).

The formation of **6a** is rationalized in terms of the initial formation of **5a** which is the kinetically controlled reaction product, followed by its rearrangement via ring opening and recyclization to the thermodynamically controlled reaction product **6a** (cf. Chart 2).

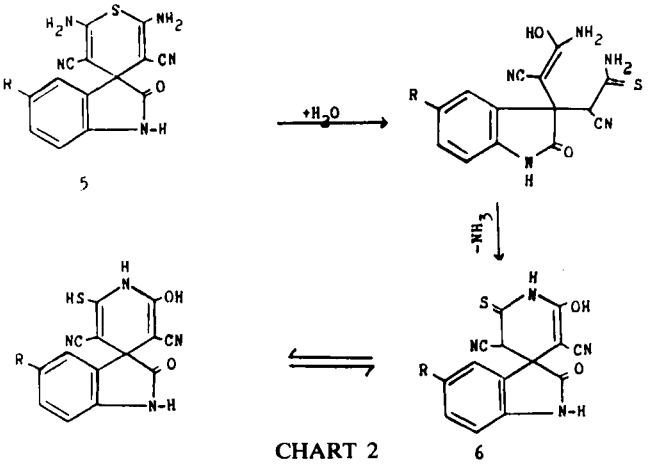

CHART 2

Further support for the suggested mechanism was achieved by synthesis of **6a** by refluxing an aqueous ethanolic piperidine solution of **5a**.

Similarly, **6b,c** were synthesised by the previous two methods (cf. Experimental).

Stirring cold ethanolic piperidine solution of equimolar amounts of 5-nitroisatin **1d**, malononitrile and cyanothioacetamide at room temperature affords 3,5-dicyano-1,2-dihydro-6-hydroxy-5-nitro-2-thioxospiro[indoline-3,4(1H)pyridine]-2-one **6d**. Also treatment of **2d** with cyanothioacetamide under the previous conditions affords **6d**.

On the other hand 2,6-diamino-3,5-dicyano-5-nitrospiro[indoline-3,4(1H)thiopyran]-2-one **5d** was synthesised by warming an equimolar amount of **2d** with cyanothioacetamide in ethanol or dioxane in the absence of piperidine. Also stirring cold ethanolic piperidine solution of **5d** at room temperature gave **6d**.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded with KBr wafers on Shimadzu-408 spectrophotometer, the ^{1}H NMR spectra in DMSO-d6 at 90 MHz with a Varian EM-390 spectrometer with Me4Si as internal standard and chemical shifts expressed as δ values. Microanalytical data were obtained from the microanalytical data unit at Cairo University. Compounds 2 and 3 were prepared following the literature procedures.[9-11]

Synthesis of **5a–c**

Method A. A suspension of equimolar amounts (0.01 mol) of **1a–c**, malononitrile and cyanothioacetamide in ethanol (70 ml) and a catalytic amount of piperidine was stirred at room temperature for 2 h. The solid product was collected by filtration.

Method B. A suspension of equimolar amounts (0.01 mol) of **2a–c** and/or **3a–c** was treated with 0.01 mol of cyanothioacetamide and/or malono-nitrile and a catalytic amount of piperidine and stirred at room temperature for 2 h. The solid product was collected and crystallized from the proper solvent.

2,6-Diamino-3,5-dicyanospiro[indoline-3,4(1H)-thiopyran]-2-one **5a**; yield 80% (method A) and 70% (method B), m.p. 200°C (ethanol-dioxane), colourless crystals. IR: 3400, 3300, 3210 (NH_2, NH), 2180 (CN) and 1700 cm^{-1} (CO). ^{1}H NMR: δ = 3.34 (*s*, 4H, $2NH_2$), 6.7–7.2 (*m*, 4H, aromatic protons) and 10.4 (*s*, 1H, NH). Found: C, 57.10; H, 3.00; N, 23.50; S, 10. 80%, Calc. for $C_{14}H_9N_5OS$: C, 56.95; H, 3.05; N, 23.73; S, 10.85%. 5-Bromo-2,6-diamino-3,5-dicyanospiro[indoline-3,4(1H)-thiopyran]-2-one **5b**; yield 85% (method A) and 72% (method B), m.p. 190–192°C (ethanol), colourless crystals. IR: 3360, 3330, 3250, 3200 (NH_2, NH), 2200 (CN), 1715 cm^{-1} (CO). ^{1}H NMR: δ = 3.4 (*s*, 4H, $2NH_2$), 6.5–7.1 (*m*, 3H, aromatic protons) and 10.4 (*s*, 1H, NH). Found: C, 45.00; H, 2.30; Br, 21.2; S, 8.50%, Calc. for $C_{14}H_8BrN_5OS$: C, 44.90; H, 2.10; Br, 21.39; S, 8.55%.

2,6-Diamino-3,5-dicyano-5-methylspiro[indoline-3,4(1H)-thiopyran]-2-one **5c**; yield 80% (method A) and 60% (method B), m.p. 205–207°C (ethanol), colourless crystals. IR: 3350, 3330, 3262, 3210 (NH_2, NH), 2200 (CN), and 1708 cm ^{1}((CO). Found: C, 58.40; H, 3.60; N, 22.80; S, 10.30%, Calc. for $C_{15}H_{11}N_5OS$: C, 58.25; H, 3.55; N, 22.65; S, 10.35%.

Synthesis of **6a-c**

Method A. To a suspension of an equimolar amount (0.01 mol) of 2 and/or 3 in ethanol (70 ml) was added (0.01 mol) of cyanothioacetamide and/or malononitrile and a catalytic amount of piperidine. The reaction mixture was refluxed for 2h and then evaporated in vacuo. The residue was triturated with water and acidified with acetic acid. The solid so formed was collected by filtration.

Method B. A suspension of **5a–c** (1.0 g) in ethanol (20 ml) and 4 drops of piperidine was refluxed for 2 h. The reaction mixture was treated as in method A.

3,5-Dicyano-1,2-dihydro-6-hydroxy-2-thioxospiro[indoline-3,4(1H)-pyridine]-2-one **6a**; yield 60% (method A) and 50% (method B), m.p. >300°C (DMF/H_2O), brown crystals. IR: 3500–3390, 3150 (OH, NH), 2180 (CN) and 1700 cm^{-1} (CO). ^{1}H NMR: δ = 5.5 (*s*, 1H, pyridine H-3), 6.5–7.2 (*m*, 4H, aromatic protons), 8.0 (*s*, 1H, OH) and 10.1 (*s*, 1H, NH). Found: C, 56.60; H, 2.70; N, 18.60; S, 10.70%, Calc. for $C_{14}H_8N_4O_2S$: C, 56.67; H, 2.70; N, 18.90; S, 10.80%.

5-Bromo-3,5-dicyano-1,2-dihydro-6-hydroxy-2-thioxospiro[indoline-3,4(1H)-pyridine]-2-one **6b**; yield 55% (method A) and 65% (method B), m.p. >300°C (DMF/H_2O), brown crystals. IR: 3500–3300 (OH, NH), 2190 (CN) and 1710 cm^{-1} (CO). Found: C, 45.10; H, 1.80; Br, 21.50%, Calc. for $C_{14}H_7BrN_4O_2S$: C, 44.80; H, 1.86; Br, 21.33%.

3,5-Dicyano-1,2-dihydro-6-hydroxy-5-methyl-2-thioxospiro[indoline-3,4(1H)-pyridine]-2-one **6c**; yield 55% (method A) and 50% (method B), m.p. >300°C (DMF/H_2O), brown crystals. ^1H NMR: δ = 2.2 (s, 3H, CH_3), 5.6 (*s*, 1H, pyridine H-3), 6.7–7.0 (*m*, 3H, aromatic protons), 8.2 (*s*, 1H, OH), and 9.9 (*s*, 1H, NH). Found: C, 58.20; H, 3.30; S, 10.50%, Calc. for $C_{15}H_{10}N_4O_2S$: C, 58.06; H, 3.20; S, 10.30%.

Synthesis of **5d**

Method A. A suspension of equimolar amounts (0.01 mol) of 1d, malono-nitrile and cyanothioacetamide in ethanol or dioxane (50 ml) was warmed for 15 min. The reaction mixture was then left to cool and the solid formed collected by filtration.

Method B. A suspension of equimolar amounts (0.01 mol) of 2d and cyanothioacetamide in ethanol or dioxane (50 ml) was warmed for 15 min. The reaction mixture was treated as in method A.

2,6-Diamino-3,5-dicyano-5-nitrospiro[indoline-3,4(1H)-thiopyran]-2-one **5d**; yield 90% (method A and B), m.p. 255°C (dioxane), colourless crystals. IR: 3350, 3200 (NH_2, NH), 2190 (CN) and 1720 cm^{-1} (CO). Found: C, 49.50; H, 2.10; N, 24.70; S, 9.60%, Calc. for $C_{14}H_8N_6O_3S$: C, 49.40; H, 2.35; N, 24.70; S, 9.40%.

Synthesis of **6d**

Method A. A suspension of equimolar amounts (0.01 mol) of **1d**, malononitrile and cyanothioacetamide in ethanol (50 ml) and a catalytic amount of piperidine was stirred at room temperature for 2 h.The solid product was collected by filtration.

Method B. A suspension of **5d** (1.0 g) in ethanol (20 ml) and 4 drops of piperidine was stirred for 2 h at room temperature. The reaction mixture was treated as in method A.

3,5-Dicyano-1,2-dihydro-6-hydroxy-5-nitro-2-thioxospiro[indoline-3,4(1H)-pyridine]-2-one **6d**; yield 55% (method A and B), m.p. >300 °C (DMF/H_2O), brown crystals. IR: 3430–3200 (OH, NH), 2200 (CN) and 1705 cm^{-1} ((CO). Found: C, 49.10; H, 2.00; N, 20.50; S, 9.50%, Calc. for $C_{14}H_7N_5O_4S$::C, 49.26; H, 2.05; N, 20.50; S, 9.33%.

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