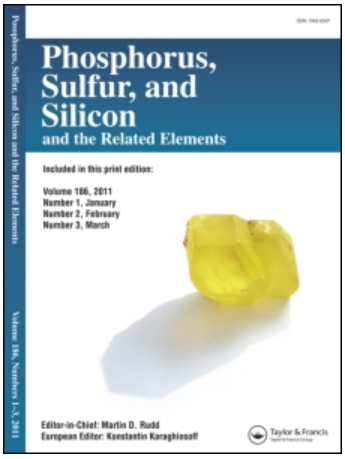

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Synthesis of Some 3-Substituted 1,2-Dihydroindoles

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The reaction of 4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazone-1,3-thiazin-6-methyl carboxylate ***2*** *with hydrazine hydrate in methanol gave 4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazone-1,3-thiazin-6-carbonylhydrazine* ***3****. Furthermore, the reaction of* ***3*** *with carbon disulfide and then hydrazine hydrate afforded 3-[6-(4-amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4-oxo-1,3 - thiazin- 2- yl] hydrazone-1,3-dihydroindol-2-one* ***5****. the latest reacted with DMAD to give {6-hydroxy-3-[4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazone-1,3-thiazin-6-yl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-ylidene}methoxycarbonylmethylene* ***6****.*

Keywords 1,3-Thiazine; dimethyl acetylenedicarboxylate (DMAD); isatin-3-thiosemicarbazone; triazolo[3,4-*b*]-1,3,4-thiadiazine

INTRODUCTION

Isatin (1*H*-indole-2,3-dione) is an endogenous indole present in mammalian tissues and fluids.[1] It has shown wide variety of biological such as CNS[2] and antiviral activity.[3] Schiff base, imines of Isatin and its derivatives were reported to show a wide variety of biological activities such as antibacterial,[4] antifungal,[5] antiviral,[6] anti-HIV,[7] and anticonvulsant[8] activities. Triazoles and condensed triazole systems were reported to possess diverse types of biological activities., including antifungal, antibacterial, antiparasitic, hypocholesteremic, hypotensive, and anti-inflammatory properties.[9–11] In continuation of our work on the synthesis of heterocyclic systems containing nitrogen and sulfur,[12] we describe here the synthesis of new 1,2-dihydroindole derivatives with thiazine and triazolo[3,4-*b*]-1,3,4-thiadiazine nucleus.

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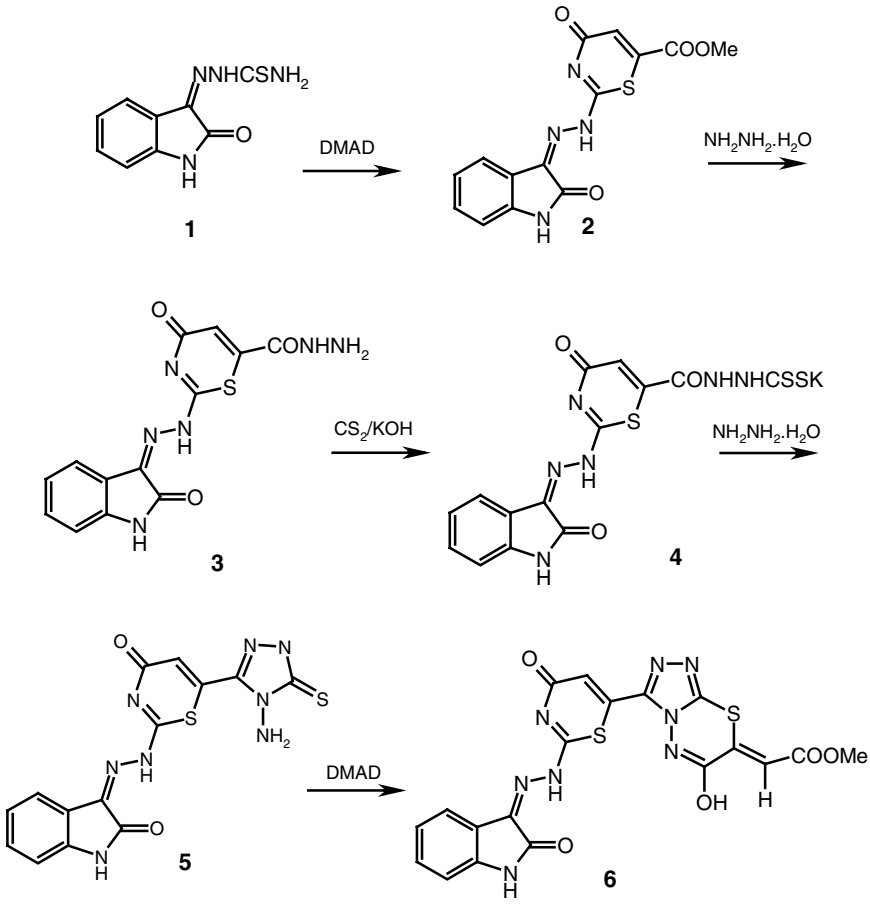
RESULTS AND DISCUSSION

It previously has been reported that 4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazone-1,3-thiazin-6-methylcarboxylate **2** was obtained when isatin-3-thiosemicarbazone **1** is stirred with DMAD (dimethyl acetylenedicarboxylate) in hot methanol for a short time.[13] The reaction of **2** with hydrazine hydrate in methanol afforded 4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene)hydrazone-1,3-thiazin-6-carbonylhydrazine **3**. The IR spectra of **3** exhibited the absorption band of NH_2 at 3294 cm^{-1}. The ^1H NMR spectra showed two broad lines δ 8.05 and 8.22 ppm arising from NH_2 and NH, respectively. The OMe was not observed in the ^1H and ^{13}C NMR spectra of compound **3**. These assigned for exchange of OMe with NH_2-NH_2 and are in agreement with carbonylhydrazine in compound **3**.

Carbon disulfide was then added to a solution of potassium hydroxide/ethanol and **3** to give potassium N-{2-[4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene) hydrazone-1,3-thiazin-6-yl] carbonyl}hydrazinecarbodithiolate **4**. A suspension of **4** and hydrazine hydrate in water refluxed while stirring to give 3-[6-(4-amino-5-thioxo–4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4-oxo-1,3-thiazin-2-yl]hydrazone-1, 3-dihydroindol-2-one **5**. The structure of compound **5** was deduced from its elemental analyses and its IR, ^1H and ^{13}C NMR spectra. The ^1H NMR of compound **5** exhibited two broad lines δ 11.17 and 12.90 ppm arising from NH protons along with a broad signal from NH_2 protons at about δ 1.27 ppm. The condensation of C=S and NH_2 functions of compound **5** with DMAD in methanol gave {6-hydroxy-3-[4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene) hydrazone-1, 3-thiazin-6-yl]-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-7- ylidene}methoxycarbonylmethylene **6** (Scheme 1). The IR spectra of **6** exhibited a broad vibration bond of OH in the region 3407 cm^{-1}. The ^1H NMR spectra exhibited a fairly broad singlet for the OH group at δ 4.41 ppm, a sharp singlet for the OMe group at δ 3.77 ppm and one exomethylene proton (C=CH) in the region δ 7.15 ppm. We can assume that in the reaction of **5** with DMAD, sulfur and nitrogen nucleophiles add to the activated triple bonds (by Michael type addition) and COOMe under cyclocondensation reaction to give fused heterocyclic compound **6**.

In conclusion, a general and convenient synthesis of functionalized C=S and NH2 has been developed using nucleophilic reaction. The main advantages of these reactions are mild reaction conditions and high yields. The new compounds could be of interest in pharmacology, biology, and as building blocks for cyclocondensates 1–11.



SCHEME 1

EXPERIMENTAL

The melting points were obtained using an Electrothermal IA 9100 Digital melting point apparatus. The IR spectra were recorded on a Bruker IFS-88 instrument (the samples as KBr disks for the range 4000–400 cm^{-1}). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer (^{1}H, 300.134 MHz; ^{13}C, 75.469 MHz) using TMS as internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The C, H, N analyses were performed by the microanalytical service of the N.I.O.C. Research Institute of Petroleum Industry.

4-Oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene) hydrazone-1,3 -thiazin- 6-carbonylhydrazine 3

A mixture of **2** (3.30 g, 10 mmol) and hydrazine hydrate (0.85 mL, 15 mmol, 85%) in 40 mL of methanol was heated at reflux for 4 h. The methanol, water, and excess hydrazine hydrate were removed in vacuo, and the residual solid recrystallized from ethanol. Yield 88%, m.p. 142–143°C; MS: *m/z* 330 (M^+); FT-IR: NH_2 3294, CO 1715, 1695 cm^{-1}; ^1H NMR (DMSO-d_6)δ 6.59 (s, 1H, C=CH), 6.82 (d, J = 7.5 Hz, 1H, Ar-H), 6.98 (m, 1H, Ar-H), 7.13 (br, 1H, NH), 7.30 (m, 1H, Ar-H), 7.59 (d, J = 7.5 Hz, 1H, Ar-H), 8.05 (br, 2H, NH_2), 8.22 (br, 1H, NH), 10.63 (s, 1H, NH). ^{13}C NMR (DMSO-d_6)δ 101.5 (=CH), 116.6 (C-Ar), 121.0 (C-Ar), 123.4 (C-Ar), 126.4 (C-Ar), 128.2 (C-Ar), 143.5 (C-NH), 148.0 (C=N), 148.8 (=C), 153.7 (C=N), 162.6 (C=O), 162.9 (C=O), 165.3 (C=O). *Anal*. calcd. for $C_{13}H_{10}N_6O_3S$: C, 47.27; H, 3.03; N, 25.45. Found: C, 47.25; H, 3.02; N, 25.49.

3-[6-(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-4-oxo-1,3-thiazin-2-yl]hydrazone-1,3-dihydroindol-2- one 5

Carbon disulfide (0.85 mL, 14 mmol) was added dropwise to an ice-cold solution of potassium hydroxide (0.84 g, 15 mmol) and **3** (2.97 g, 9 mmol) in 30 mL absolute ethanol. The mixture was stirred at room temperature for 14 h. Dry ether 40 mL was then added and the separated solid was filtered and washed with ether (2 × 5 mL). The product **4** obtained in nearly quantitative yields was employed in the next reaction without further purification. A suspension of **4** (about 2.70 g, 8 mmol) and hydrazine hydrate (0.91 mL, 16 mmol, 85%) in 20 mL of water refluxed while stirring for 4 h. Hydrogen sulfide was evolved. On dilution with 100 mL of cold water and acidification with concentrated HCl, the solid was precipitated. The product was filtered, washed with water, and recrystallized from ethanol. Yield 81%, m.p. > 300°C; MS: *m/z* 386 (M^+); FT-IR: NH_2 3223, CO 1699 cm^{-1}; ^1H NMR (DMSO-d_6)δ 1.27 (s, 2H, NH_2), 5.83 (s, 1H, C=CH), 6.93 (d, J = 8.0 Hz, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 7.30 (m, 1H, Ar-H), 7.51 (d, J = 7.5 Hz, 1H, Ar-H), 11.17 (s, 1H, NH), 12.90 (s, 1H, NH), 14.03 (s, 1H, NH). ^{13}C NMR (DMSO-d_6)δ 102.1 (C=CH), 118.9 (C-Ar), 121.7 (C-Ar), 122.6 (C-Ar), 124.6 (C-Ar), 127.3 (C-Ar), 141.3 (C-NH), 145.2 (C=N), 148.5 (C=CH), 150.5 (C=N), 152.3 (C=S), 156.2 (C=O), 158.2 (C=N), 166.5 (C=O). *Anal*. calcd. for $C_{14}H_{10}N_8O_2S_2$: C, 43.52; H, 2.59; N, 29.02. Found: C, 43.57; H, 2.55; N, 29.06.

{6-Hydroxy-3-[4-oxo-2-(2-oxo-1,2-dihydroindol-3-ylidene) hydrazone-1,3-thiazin-6-yl]-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-ylidene}methoxycarbonylmethylene 6

A solution of **5** (3.86 g, 10 mmol) and DMAD (1.42 g, 10 mmol) in 40 mL of MeOH was heated at reflux for 2 h. The solution was cooled, and the crystals that formed were separated. Yield 73%, m.p. 285–286°C; MS: *m/z* 496 (M^+); FT-IR: OH 3407, CO 1734 cm^{-1}; ^1H NMR (DMSO-d_6)δ 3.77 (s, 3H, OMe), 4.41 (s, 1H, OH), 6.91 (s, 1H, C=CH), 6.94 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.08 (m, 1H, Ar-H), 7.15 (s, 1H, C=CH), 7.25 (m, 1H, Ar-H), 7.33 (d, $J = 7.5$ Hz, 1H, Ar-H), 8.31 (br, 1H, NH), 10.75 (br, 1H, NH). ^{13}C NMR (DMSO-d_6)δ 52.2 (OMe), 100.7 (=CH), 117.9 (=CH exomethylene), 118.6 (C-Ar), 121.2 (C-Ar), 121.6 (C-Ar), 123.5 (C-Ar), 128.5 (C-Ar), 140.3 (NH-C), 143.3 (C=N), 144.3 (C=N), 145.5 (=C), 146.5 (C=N), 151.2 (=C exomethylene), 153.8 (C=N), 154.5 (HN-C=O indole), 156.7 (N=C-OH), 166.0 (C=O), 166.5 (CO_2). *Anal*. calcd. for $C_{19}H_{12}N_8O_5S_2$: C, 45.97; H, 2.42; N, 22.58. Found: C, 45.93; H, 2.38; N, 22.61.

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