

Synthesis of Spiro Heterocyclic Compounds

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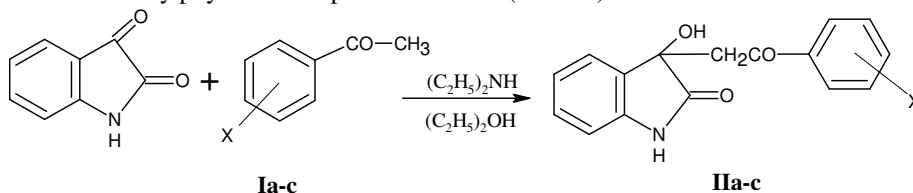
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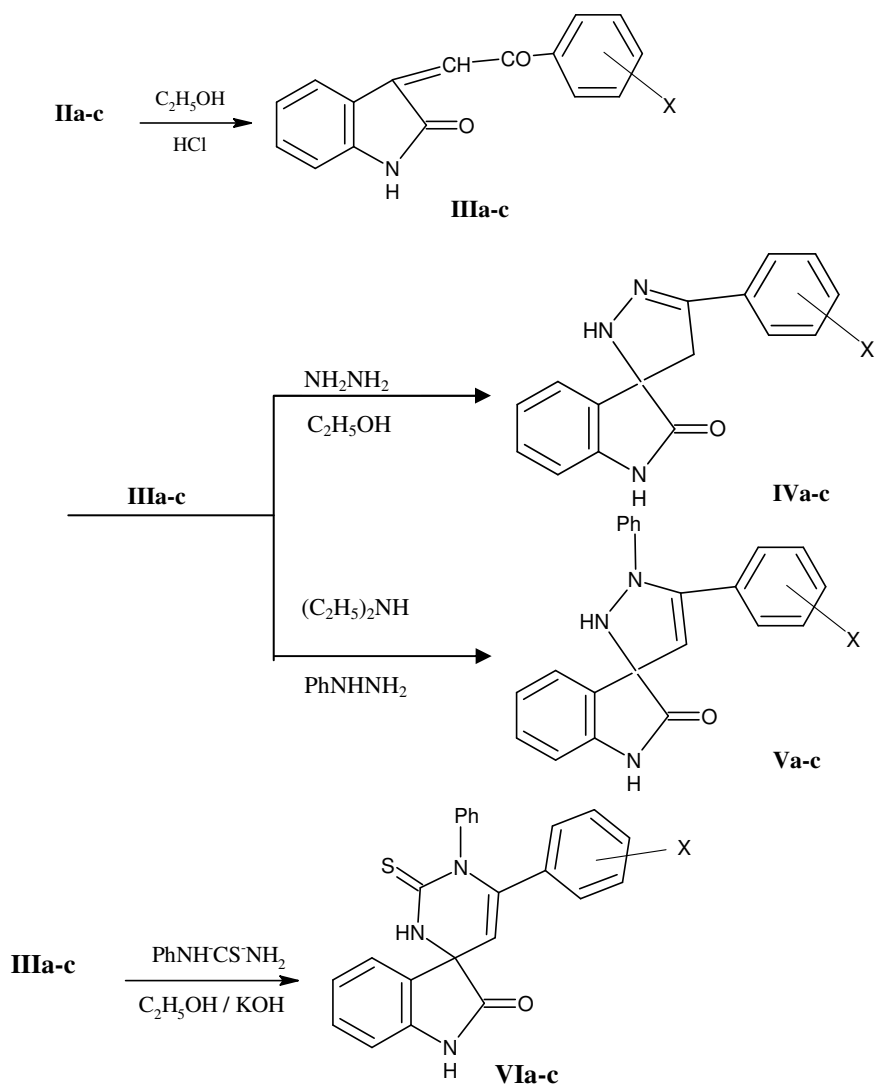
Abstract: Reaction of isatin with acetophenone derivatives gave 3-hydroxy-3-phenacyl oxindole derivatives (**II**), dehydration of (**II**) gave 3-phenacylidene-2-indolinone derivatives (**III**). Condensation of (**III**) with hydrazine hydrate, phenylhydrazine and phenylthiourea afforded new spiro-pyrazolines (**IV & V**) and spiro-pyrimidinethione (**VI**) respectively. The structures of the final products were established by physical and spectral means.

Keywords: Synthesis, Isatin, Spiropyrzazolines, Spiropyrimidinethione.

Introduction

The reaction of isatin with various compounds have been under intensive studies by many authors¹⁻⁶ and due to the importance of some derivatives, for example, pyrazoline and pyrimidinethione in different biological and industrial aspects^{7,8}, this research work has been initiated to prepare such new molecules. The reaction of isatin with acetophenone derivatives (**I_{a-c}**) was carried out in the presence of diethyl amine as a basic catalyst giving rise to 3-hydroxy-3-phenacyl oxindoles (**II_{a-c}**) in good yields. Dehydration of the above compounds by dilute alcoholic hydrochloric acid gave 3-phenacylidene-2-indolinones (**III_{a-c}**) in quantitative yields. Cyclocondensation of α , β -unsaturated ketones with hydrazine have been previously investigated^{9,10} in which most cases gave pyrazoline. Accordingly the reaction of compound (**III**) with hydrazine, phenylhydrazine were carried out in presence of diethyl amine and gave spiro-pyrazoline (**IV**) and spiro-*N*-phenylpyrazoline (**V**) respectively. On the other hand interaction of (**III**) with phenylthiourea in the presence of alcoholic KOH¹¹ afforded spiro-pyrimidinethione (**VI**), (Scheme 1). The structures of the final products were established by physical and spectral methods (Table 1).





X = H, *p*-Cl, *p*-OCH₃ for a, b, c respectively.

Scheme 1

Experimental

Melting points were measured on Gallen-Kamp apparatus and are uncorrected. I.R. spectra were recorded on a Unicam SP1100 spectrophotometer. ¹H-NMR spectra were recorded in CDCl₃ on a Varian Mercury VX spectrometer at 300 MHz, using TMS as internal reference.

Preparation of 3-hydroxy-3-phenacyl oxindoles (**II_{a-c}**)

A mixture of isatin and substituted acetophenone (0.01 mole of each) was dissolved in ethanol (100 mL) and diethyl amine (1 mL) was added. The mixture was allowed to stand overnight at room temperature, the yellow needles formed were recrystallised from ethanol.

Preparation of 3-phenacylidene -2-indolinones (III_{a-c})

A mixture of 0.01 mole of compound (II_{a-c}), ethanol 25 mL and 50 mL of dilute HCl solution (25%), was allowed to stand overnight, fine orange needles were formed.

Preparation of spiropyrazolines (IV_{a-c} & V_{a-c})

A mixture of 0.01 mole of compound (III_{a-c}) and hydrazine hydrate (50 %) or phenyl hydrazine (0.01 mole) in ethanol (50 mL) and diethyl amine (1 mL) was refluxed for 10-14 hours, then acetic acid (10 ml) was added to the cold solution. The precipitate formed after concentration was filtered and washed with cold ethanol and recrystallised from acetic acid.

Preparation of spiropyrimidinethione (VI_{a-c})

A mixture of 0.01 mole of (III_{a-c}), phenylthiourea (0.02 mol), KOH (2 g), ethanol (60 mL) and water (10 mL) was refluxed for 10-14 hours. The heavy precipitate formed after concentration and cooling was filtered, dried and recrystallised from ethanol.

Table 1. Physical and spectral data of compounds (II_{a-c} – VI_{a-c})

Compd. No	M. p, °C	Yield, %	IR, ν / Cm^{-1}	¹ H NMR, δ / ppm
II _a	127-9	65	1630(CO); 1705(CO) 3410(NH); 3500(OH)	3.7(s,2H,CH ₂); 6.0(b,1H,OH) 7.6(m,9H,Ar-H); 10.1(s,1H,NH)
II _b	184-6	76	1640(CO); 1685(CO) 3400(NH); 3440(OH)	3.5(s,2H,CH ₂); 5.7(s,1H,OH) 7.8(m,8H,Ar-H); 10.2(s,1H,NH)
II _c	187-9	72	1650(CO); 1710(CO) 1100(O-C); 3420(NH) 3500(OH)	3.3(s,2H,CH ₂); 4.6(s,3H,OCH ₃) 5.9(s,1H,OH); 7.4(m,8H,Ar-H) 10.0(s,1H,NH)
III _a	194-6	86	1590(C=C); 1630(CO) 1690(CO); 3400(NH)	7.6(s,1H,CH); 7.8(m,9H,Ar-H) 10.8(s,1H,NH)
III _b	182-5	80	1580(C=C); 1620(CO) 1675(CO); 3400(NH)	7.5(s,1H,CH); 7.7(m,8H,Ar-H) 10.6(s,1H,NH)
III _c	192-4	87	1580(C=C); 1640(CO) 1690(CO); 3400(NH)	4.6(s,3H,OCH ₃); 7.5(s,1H,CH) 7.8(m,8H,Ar-H); 10.4(s,1H,NH)
IV _a	262-4	56	1240(C-N); 1625(C=N) 1695(CO); 3300(NH)	3.8(s,2H,CH ₂); 7.7(m,9H,Ar-H) 10.1(s,2H,2NH)
IV _b	222-3	52	1250(C-N); 1620(C=N) 1690(CO); 3400(NH)	3.6(s,2H,CH ₂); 7.8(m,8H,Ar-H) 10.1(s,2H,2NH)
IV _c	226-7	55	1240(C-N); 1630(C=N) 1690(CO); 3340(NH)	3.8(s,2H,CH ₂); 4.4(s,3H,OCH ₃); 7.7(m,8H,Ar-H); 10.2(s,2H,2NH)
V _a	210-2	56	1240(C-N); 1600(C=C) 1700(CO); 3400(NH)	6.6(s,1H,CH); 8.0(m,14H,Ar-H) 10.0(s,2H,2NH)
V _b	164-6	60	1250(C-N); 1605(C=C) 1690(CO); 3390(NH)	6.7(s,1H,CH); 7.9(m,13H,Ar-H) 10.1(s,2H,2NH)
V _c	212-3	55	1245(C-N); 1590(C=C) 1695(CO); 3400(NH)	6.5(s,1H,CH); 4.4(s,3H,OCH ₃) 8.0(m,13H,Ar-H); 10.0(s,2H,2NH)
VI _a	146-9	60	1240(CS); 1605(C=C) 1695(CO); 3400(NH)	6.9(s,1H,CH); 8.0(m,13H,Ar-H) 10.0(s,2H,2NH)
VI _b	245-7	57	1250(CS); 1580(C=C) 1695(CO); 3360(NH)	6.8(s,1H,CH); 7.9(m,13H,Ar-H) 10.1(s,2H,2NH)
VI _c	183-5	50	1240(CS); 1590(C=C) 1695(CO); 3400(NH)	6.6(s,1H,CH); 4.6(s,3H,OCH ₃) 8.1(m,13H,Ar-H); 10.1(s,2H,2NH)

Results and Discussion

The first step in this synthesis involve crossed aldol condensation between the acetophenone or its derivatives (**I**_{a-c}) with the isatin in basic medium to give the aldol products, 3-hydroxy-3-phenacyloxindoles (**II**_{a-c}) which then dehydrated easily by using dilute alcoholic hydrochloric acid, to yield the expected α , β -unsaturated carbonyl compounds, 3-phenacylidene-2-indolinones (**III**_{a-c}). Nucleophilic Michael addition of hydrazine or phenyl hydrazine or phenylthiourea to the above compounds leads to the formation of spiro-5-(-3-indolyl-2-one)-3-phenylpyrazoline, spiro-5-(-3-indolyl-2-one)-2, 3-diphenylpyrazolin-3-ene, and spiro-6-(-3-indolyl-2-one)-3, 4-diphenylpyrimidinethione, (**IV**_{a-c}; **V**_{a-c}; **VI**_{a-c}) respectively. The structures of these products were established by physical and spectral methods.

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