Novel Strategies to the Facile One Pot Synthetic Entry of Pyrimidine Nucleus to the Indolin-2-One Framework

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Abstract

A 'chemistry driven approach' to the synthesis of small molecules of medicinal interest was launched to explore the versatility of 3-benzoylmethyl indolin-2-one (3) (resulted on the reaction of isatin with acetophenone followed by reduction of the obtained enone derivative 2 with $Na_2S_2O_4$) to provide synthetically acceptable protocols to the formation of indolin-2-one analogues substituted on its 3-position with pyrimidine derivatives (7-12) respectively whose structure was unequivocally established from its micro analyses and spectral data.

Key Words: Isatin, indolin-2-one, Oxo-ketenedithioacetals, chalcones, dimethylamino methylene ketones.

Introduction

The search of compound libraries comprising of small molecules, with potential biological activities is a major focus of research in the area of chemical biology and medicinal chemistry. Therefore development of efficient methodologies to access small molecules of medicinal utility are of special interest. Eversince, Waldmann et al[1]. have carried out a quantitative analysis of physiologically active natural products and showed that ones with two or three rings were most often found in active natural products, the interest on the various facets of the chemistry and biology of small molecules have expanded exponentially, thereafter.

The bioactive potential of pyrimidine derivatives have been re-examined with a renewed interest eversince the pyrimidine nucleus has been recognized to belong to the class of 'privileged medicinal scaffold' by virtue of its ability to provide ligands to a number of functionally and structurally discrete biological receptors. The advent of the FDA approved anti-HIV agent 'etravirine'[2] (containing the pyrimidine nucleus as a care structure in its molecule), provided an optimism to the discovery of other chemotherapeutically useful potential agents from other classes of compounds such as the indolin-2-one etc, containing a pyrimidine nucleus in its molecule. To examine the validity of this hypothesis, we considered it of interest to explore the feasibility of the incorporation of a pyrimidine nucleus to the biologically active indolin-2-one system, through synthetically acceptable approaches. We envisioned, that several innovative protocols to the formation of a pyrimidine ring could possibly be developed by exploring the potential of an active methylene function present adjacent to a carbonyl species at 3-position of the indolin-2-one system.

Isatin offers an unprecedented opportunity to a chemist to the synthesis of a wide variety of heterocyclic compounds[3-5]. This is because isatin exists completely in the dicarbonyl form with its 3-carbonyl group being more reactive, than 2-carbonyl group towards nucleophilic reagents. This variation in the reactivity of its two carbonyl groups coupled with the observed, facile opening the ring under the influence of hydroxylic nucleophilic reagents provides additional advantages towards accomplishing the desired synthetic goals using isatins. Besides its versatility in synthesis, the ubiquity of this nucleus in chemical literature is undoubtedly a consequence of the multifarious biological response which its derivatives elicit in combating a variety of body ailments[6].

The importance of the indolin-2-one[7-10], pyrimidine[11] class of heterocyclic scaffolds[12-13] in medicinal chemistry can not be overstated. Their derivatives constitute the most celebrated structural motifs present in a large number of physiologically active molecules including many alkaloids. Chemical literature is replete with examples showing that incorporation of the bioactive pharmacophores in the existing drug molecules sometimes exerts a profound influence on the biological profiles of that molecule. Based on this trend, it was expected that incorporation of the above bioactive pharmacophores on 3-position of indolin-2-one could produce interesting series of compounds with enhanced bioactive potentials, and at the same time could also allow interesting revelations to emerge concerning to the specific structural requirements for the desired bioactivity in this molecule[14]. This speculation turned into the reality when isatin (1) was allowed to react with acetophenone and the resulting enone (2) was reduced[15-16] with $Na_2S_2O_4$ to give the 3-benzoylmethyl substituted derivative of indolin-2-one[17-19] (3). Established literature procedures were applied on (3) to append the following reactive motifs chalcones[20] (4), Oxo-ketenedithioacetals[21] (5), dimethylamino methylene ketones[22] (6) derivatives to generate 7, 8, 9, 10, 11 and 12 by utilizing the synthetic plan[23] depicted in scheme 1,2 and 3.

Experimental Section:

Melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S. ^{1}HNMR spectra were recorded in $CDCl_3$ on Bruker DRX-400 MHz spectrometer using TMS as internal reference and values are expressesd in δ ppm.

Preparation of 3-benzoylmethyledene-indolin-2-one (2).

A mixture containing isatin (13.23 g, 0.09 mmol) and acetophenone (10.80 g, 0.09mmol) in ethanol (500 ml) and diethylamine (9ml) was allowed to stand overnight at room temperature, the yellow needle shaped crystals formed were filtered and washed several times with cold water and dried. The product was taken in ethanol 125 ml and 250 ml dilute HCl solution (25% in ethanol), and allowed to stand overnight, fine orange crystals formed were filtered, washed several times with cold water and dried. The product was recrystallized from ethanol to give **2** (12.32g, 86%); m.p:192-195°C;

Preparation of 3-phenacyl-indolin-2-one (3).

To a mixture of 3-benzoylmethyledene-indolin-2-one (**2**, 1.245g, 0.005mmol) and sodium dithionite (0.870g, .005mmol) in water (6ml), methanol (6ml) and dichloromethane (2ml) was added. The mixture was refluxed for 10hrs. The solvent was evaporated and the resultant compound was recrystallized from ethanol to give **(3)** (0.845g, 73%); m.p: 275-82^{o}C; IR (KBr) cm^{-1} : 1590 [C=C str. ArH], 3090 [C-H str. ArH], 1760 [C=O str.], 3500 [N-H str.], 1210[C-N str]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.95-7.59 [m , 4H, ArH], 7.34-7.89 [m, 5H, ArH], 8.0 [s, 1H, NH], 4.25 [t, 1H, CH], 3.24 [d, 2H, CH_2] ; MS: m/z: 251.28 (36%) ; Anal. Calcd./found for $C_{16}H_{13}NO_2$: C, 76.48/76.52; H, 5.21/5.10 ; N,5.57/5.71.

Preparation of 3-[2'-benzylidene]-phenacyl-indolin-2-one (4).

A mixture of 3-phenacyl-indolin-2-one (**3,** 2.51g, 0.01 mmol), benzaldehyde (1.06g, 0.01 mmol) and fused sodium acetate (0.82 g, 0.01 mmol) in glacial acetic acid was refluxed for 5 hrs. The reaction mixture was cooled and poured in to water. The resulting solid was filtered, washed with water and recrystallised from aq. ethanol to furnish pure (**4).** (1.07 g, yield 65%); m.p:181-83^{o}C; IR (KBr) cm^{-1} : 1500 [C=C str. ArH], 3100 [C-H str. ArH], 1670 [C=O str.], 3340 [N-H str.], 1310[C-N str], 1650[C=C]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52 [m , 4H, ArH], 7.45-7.81 [m, 5H, ArH], 7.14-1.30 [m, 5H,ArH], 8.0 [s, 1H, NH], 4.40 [s, 1H, CH], 6.90 [s, 1H, CH] ; MS: m/z: 339.4 (30%) ; Anal. Calcd./found for $C_{23}H_{17}NO_2$: C, 81.40/81.62; H, 5.05/5.35 ; N,4.13/4.43.

Preparation of 3-[2'-(bis(methylthio)methylene)]-phenacyl-indolin-2-one (5).

A mixture of 3-phenacyl-indolin-2-one (**3,** 1.506g, 0.006mmol) and CS_2 (0.456g, 0.006 mmol) was added to a well stirred and cold suspension of t-BuOK (1.34g, 0.012 mmol) in dry benzene (4.0 ml) and DMF (3.0 ml) and the reaction mixture was allowed to stand at room temperature for 4 hrs. Methyl iodide (2.0 ml, 0.012mol) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 4 hrs at room temperature with occasional shaking and then refluxed on a water bath for 3 hrs. The aqueous portion was extracted with benzene and the combined extracts were washed with water, dried over anhydrous sodium sulphate and the solvent was removed by distillation. The product (**5)** thus obtained was recrystallized from ethanol. (0.859 g, yield 71%); m.p:310-12^{o}C; IR (KBr) cm^{-1} : 3455[NH str], 2910[C-H str ArH], 1600 [C=C ArH], 1640[C=O],1650[C=C str], 1340[C-N str], 800[C-S]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.45-7.81[m, 5H, ArH], 8.0[s, 1H, NH], 4.40[s, 1H, CH], 2.25[s, 3H, CH_3], 2.28[s, 3H, CH_3]; MS: m/z: 355.4 (41%) ; Anal. Calcd./found for $C_{19}H_{17}NO_2S_2$: C, 64.20/6442; H, 4.82/4.69 ; N,3.92/3.76; S,18.04/18.51.

Preparation of 3-[2'-(dimethyl amino) methyledene]-phenacyl-indolin-2-one (6).

A mixture of 3-phenacyl-indolin-2-one (**3,** 3.765g, 0.015mmol) was dissolved in N,N-dimethylformamide dimethyl acetal (15.0 ml), and the solution was heated under reflux for 24 hrs and concentrated. The residue was triturated with hexane, filtered, and washed with hexane to give **(6)** as a brown powder. (1.859 g, yield 78%); m.p:294-96^{o}C; IR (KBr) cm^{-1} : 1550 [C=C str. ArH], 2095 [C-H str. ArH], 1620 [C=C str.], 1240 [C-N str.], 1795 [C=O str.], 3300 [N-H str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52 [m , 4H, ArH], 7.45-7.81 [m, 5H, ArH], 8.0 [s, 1H, NH], 4.40 [s, 1H, CH], 6.32 [s, 1H, CH], 2.45 [s, 3H, CH_3], 2.47 [s,3H, CH_3]; MS: m/z: 306.4 (28%) ; Anal. Calcd./found for $C_{19}H_{18}N_2O_2$: C, 74.49/74.22; H, 5.92/5.61; N,9.14/9.44.

Preparation of 3-(1,2-dihydro-2-oxo-4,6-diphenylpyrimidin-5yl)indolin-2-one (7).

A mixture of 3-[2'-benzylidene]-phenacyl-indolin-2-one (**4**, 0.678g, 0.002mmol), urea (0.12g, 0.002mmol) and 0.1g NaOH in 25ml of 80% dil. ethanol was refluxed for 5-6 hrs, then concentrated and cooled, the precipitate of **(7)** was filtered off and recrystallized from DMF/water to give (0.589g, yield 70%); m.p. 185-86^{0}C; IR (KBr) cm^{-1} : 3080[C-H str. ArH], 1540[C=C str. ArH], 1720[C=O str.], 3490[N-H str.], 1210[C=N str.], 1080[C-N str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.3-7.6[m, 5H, ArH], 7.04-7.30[m, 5H, ArH], 8.0[s, 1H, NH], 8.0[s, 1H, NH], 4.40[s, 1H, CH]; MS: m/z: 379.41 (32%) ; Anal. Calcd./found for $C_{24}H_{17}N_3O_2$: C, 75.97/75.65; H, 4.52/4.81; N,11.08/11.36.

Preparation of 3-(1,2-dihydro-4,6-diphenyl-2-thioxopyrimidin-5yl)indolin-2-one (8)

A mixture of 3-[2'-benzylidene]-phenacyl-indolin-2-one (**4**, 0.678g, 0.002mmol), thiourea (0.152g, 0.002mmol) and 0.1g NaOH in 25ml of 80% dil. ethanol was refluxed for 4-5 hrs, then concentrated and cooled, the precipitate of **(8)** was filtered off and recrystallized from DMF/water to give with chloroform to give (0.625g, yield 75%); m.p. 214-15^{0}C; IR (KBr) cm^{-1} : 3000[C-H str. ArH], 1590[C=C str. ArH], 1680[C=O str.], 3380[N-H str.], 1260[C=N str.], 1320[C-N str.], 800[C-S str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.3-7.6[m, 5H, ArH], 7.04-7.30[m, 5H, ArH], 8.0[s, 1H, NH], 2.0[s, 1H, NH], 4.40[s, 1H, CH]; MS: m/z: 395.48 (38%) ; Anal. Calcd./found for $C_{24}H_{17}N_3OS$: C, 72.89/72.42; H, 4.33/4.62; N,10.63/10.98.

Preparation of 3-(1,2-dihydro-6-(methylthio)-2-oxo-4-phenylpyrimidin-5yl)indolin-2-one (9).

A mixture of 3-[2'-(bis(methylthio)methylene)]-phenacyl-indolin-2-one (**5**, 0.710g, 0.002mmol), urea (0.12g, 0.002mmol) and sodium ethoxide (0.14g, 0.002mmol) and the reaction mixture was refluxed for 13-15 hrs. The solvent was removed by distillation and residue was treated with glacial acetic acid (4-5

ml just enough to dissolved sodium salt of the pyrimidine) and refluxed for 15 minutes. The reaction mixture was poured on crushed ice and precipitate **(9)** obtained was purified by crystallization with chloroform to give (0.621g, yield 68%); m.p. 214-215^{0}C; IR (KBr) cm^{-1} : 3100[C-H str. ArH], 1590[C=C str. ArH], 1670[C=O str.], 3440[N-H str.], 1100[C=N str.], 1320[C-N str.], 750[C-S str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.3-7.6[m, 5H, ArH], 8.0[s, 1H, NH], 8.0[s, 1H, NH], 4.40[s, 1H, CH], 2.25[s, 3H, CH_3]; MS: m/z: 349.41 (28%) ; Anal. Calcd./found for $C_{19}H_{15}N_3O_2S$: C, 65.31/65.66; H, 4.33/4.63; N,12.03/12.46.

Preparation of 3-(1,2-dihydro-6-(methylthio)-4-phenyl-2-thioxopyrimidin-5yl)indolin-2-one (10)

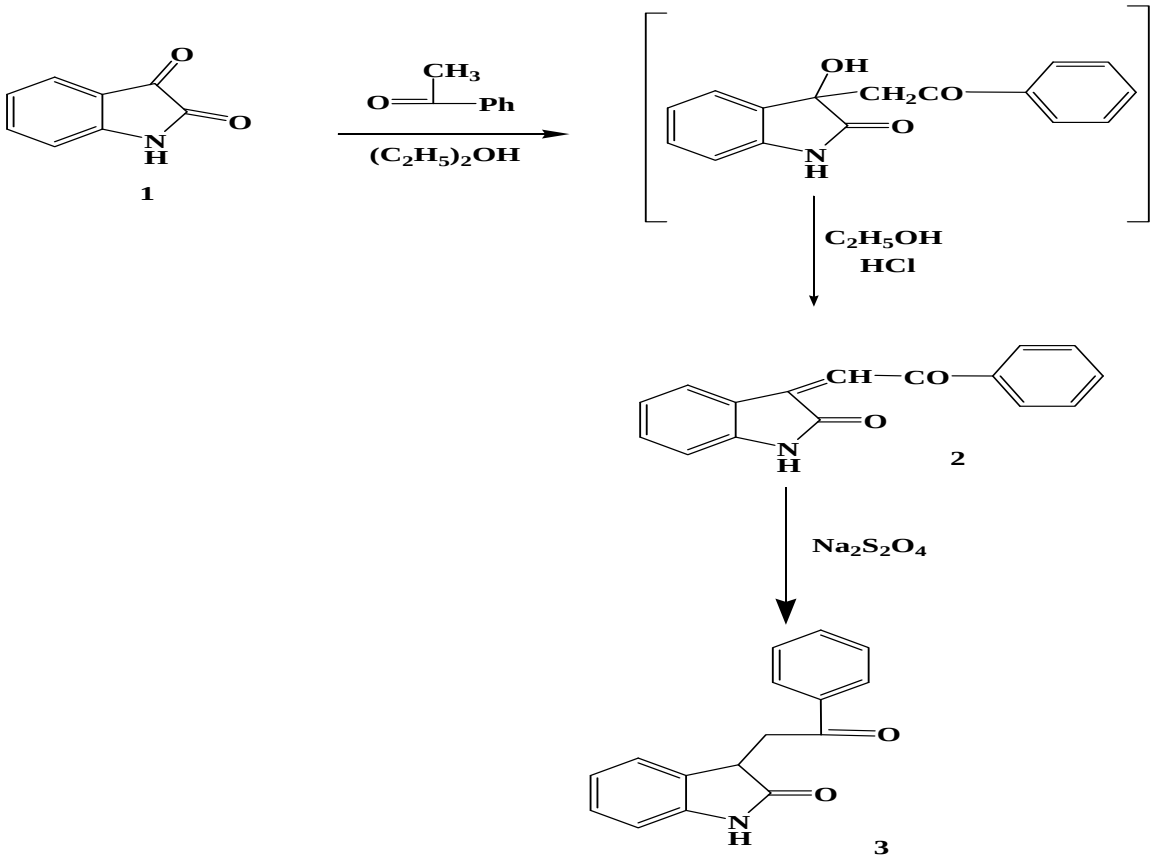
A mixture of 3-[2'-(bis(methylthio)methylene)]-phenacyl-indolin-2-one (**5**, 0.710g, 0.002mmol), thiourea (0.152g, 0.002mmol) and sodium ethoxide (0.14g, 0.002mmol) and the reaction mixture was refluxed for 10-14 hrs. The solvent was removed by distillation and residue was treated with glacial acetic acid (4-5 ml just enough to dissolved sodium salt of the pyrimidine) and refluxed for 15 minutes. The reaction mixture was poured on crushed ice and precipitate **(10)** obtained was purified by crystallization with chloroform to give (0.566g, yield 66%); m.p. 198-200^{0}C; IR (KBr) cm^{-1} : 3090[C-H str. ArH], 1600[C=C str. ArH], 1790[C=O str.], 3500[N-H str.], 1200[C=N str.], 1320[C-N str.], 700[C-S str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.3-7.6[m, 5H, ArH], 8.0[s, 1H, NH], 2.0[s, 1H, NH], 4.40[s, 1H, CH], 2.25[s, 3H, CH_3]; MS: m/z: 365.47 (30%) ; Anal. Calcd./found for $C_{19}H_{15}N_3OS_2$: C, 62.44/62.71; H, 4.14/4.40; N,11.50/11.80.

Preparation of 3-(2-methyl-4-phenylpyrimidin-5yl)indolin-2-one (11)

A mixture of sodium ethoxide (0.14g, 0.002mmol), ethanol (10-15 ml) and acetamidine hydrochloride was added and the reaction mixture was stirred for 15-20 minutes. 3-[2'-(dimethyl amino) methyledene]-phenacyl-indolin-2-one (**6,** 0.612g, 0.002mmol) was added and the reaction mixture was refluxed for 18-20 hrs. The solvent was distilled under red. Pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with H_2O, dried over anhydrous sodium sulphate and distilled off to give crude pyrimidine, which was purified by crystallisation to give (0.545g, yield 70%); m.p. 193-195^{0}C; IR (KBr) cm^{-1} : 3060[C-H str. ArH], 1560[C=C str. ArH], 1680[C=O str.], 3450[N-H str.], 1190[C=N str.], 1180[C-N str.], 2960[C-H alkanes]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.22-7.48[m, 5H, ArH], 8.0[s, 1H, NH], 5.0[s, 1H, CH], 8.14[s, 1H, CH], 2.35[s, 3H, CH_3]; MS: m/z: 301.34 (33%) ; Anal. Calcd./found for $C_{19}H_{15}N_3O$: C, 75.73/75.45; H, 5.02/5.36; N,13.94/13.62.

Preparation of 3-(2-amino-4-phenylpyrimidin-5yl)indolin-2-one (12)

A mixture of 3-[2'-(dimethyl amino) methyledene]-phenacyl-indolin-2-one (**6,** 0.918g, 0.003mmol) in ethanol (250 ml) were added guanidine nitrate (0.366g, 0.003mmol) and sodium acetate (0.216g, 0.003mmol) and the solution was refluxed for 48 hrs. Reaction mixture was filtered and extracted with chloroform and washed with water to give (0.853g, yield 75%); m.p. 182-185^{0}C; IR (KBr) cm^{-1} : 3040[C-H str. ArH], 1580[C=C str. ArH], 1710[C=O str.], 3410[N-H str.], 1220[C=N str.], 1280[C-N str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52[m, 4H, ArH], 7.22-7.48[m, 5H, ArH], 8.0[s, 1H, NH], 5.0[s, 1H, CH], 7.98[s, 1H, CH], 4.0[s, 2H, NH_2]; MS: m/z: 302.33 (38%) ; Anal. Calcd./found for $C_{18}H_{14}N_4O$: C, 71.51/71.75; H, 4.67/4.89; N,18.53/18.89.



Scheme-1

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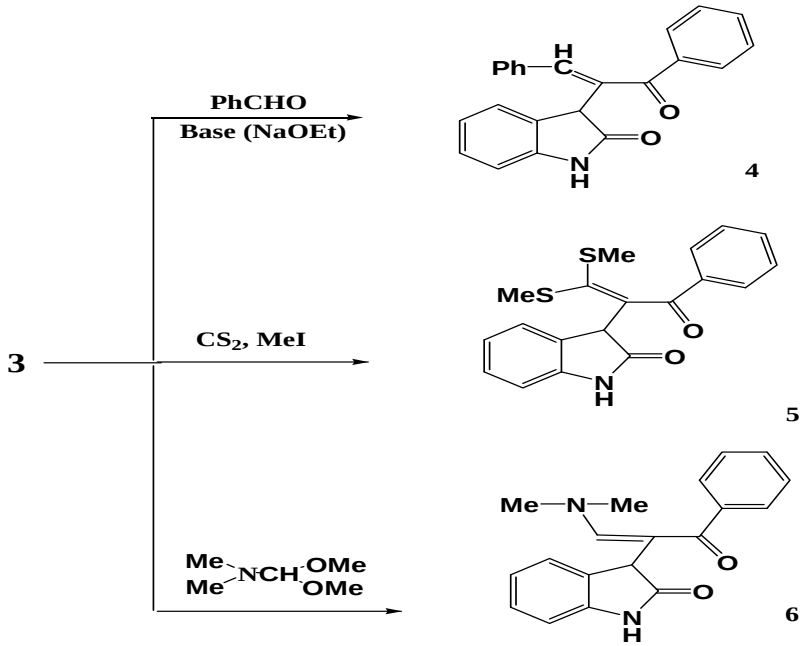
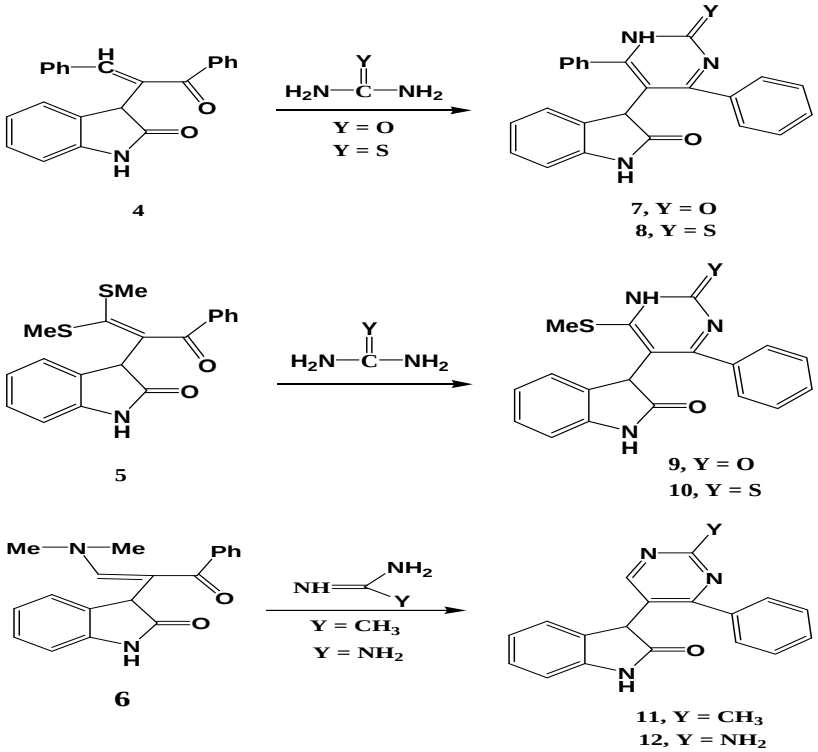
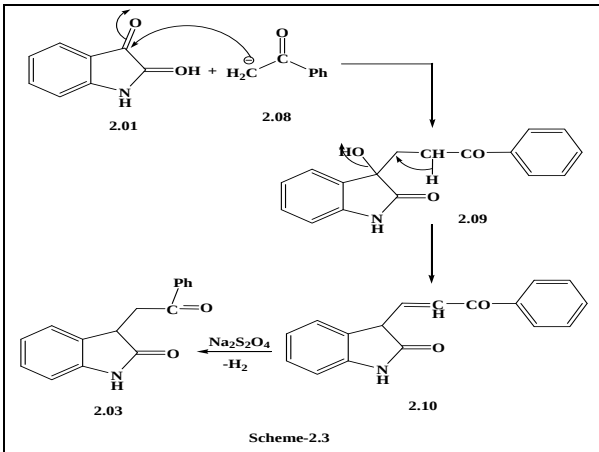


SCHEME - 2

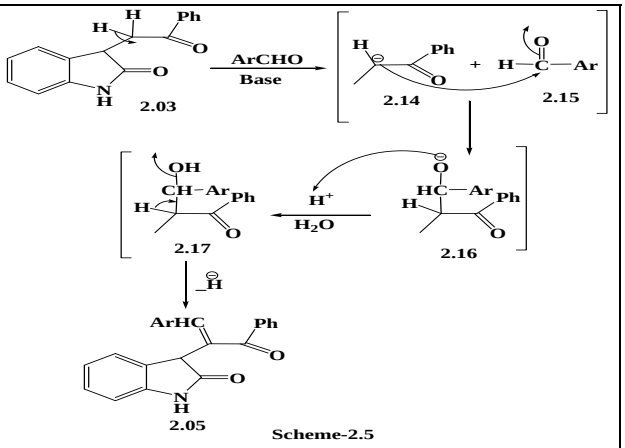


Scheme-3

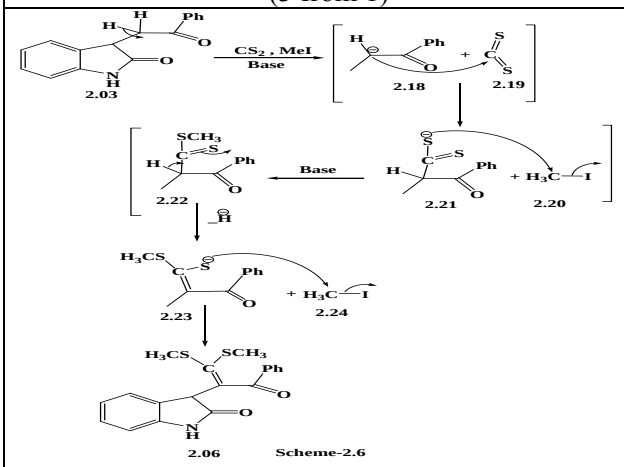
Mechanism of formation of compounds 3-12.



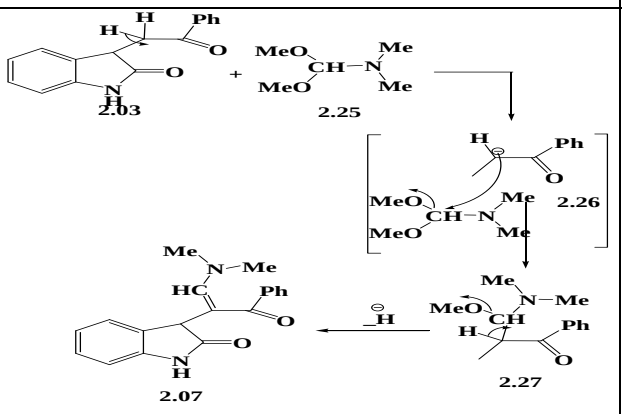
a) Formation of 3- phenacyl indolin-2-one (3 from 1)



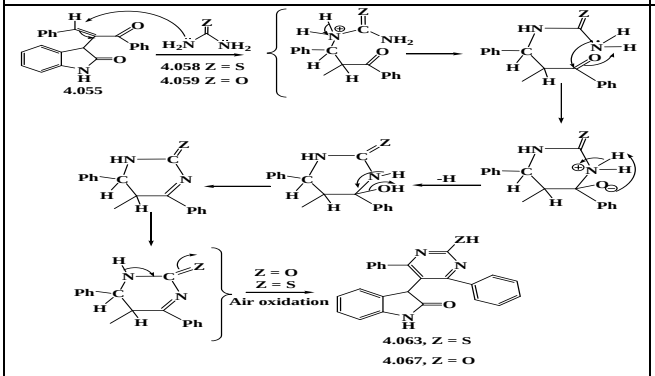
b) Mechanism of formation of compound 4 from 3.



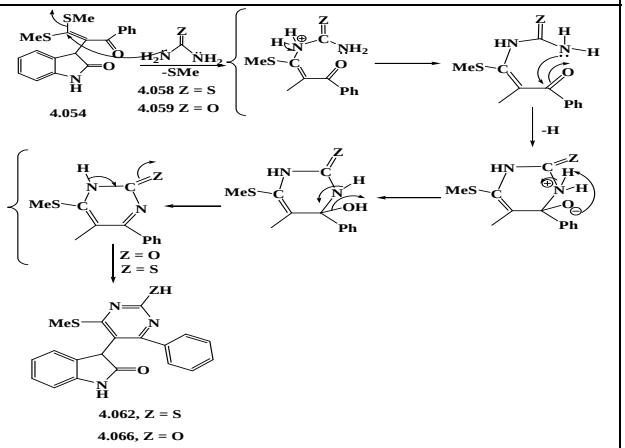
c) Mechanism of formation of compound 5 from 3.



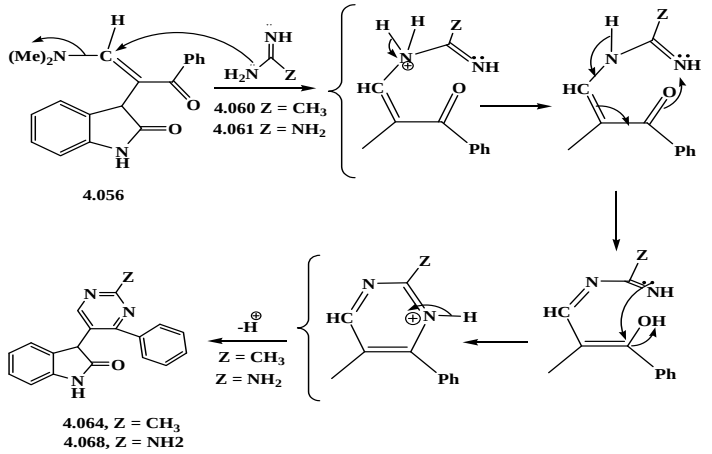
d) Mechanism of formation of compound 6 from 3.



e) Mechanism of formation of compound 7,8 from 4



f) Mechanism of formation of compound 9,10 from 5



g) Mechanism of formation of compound 11,12 from 6.

Result and Discussion:

Eversince, the potential of isatin has been recognized in the literature[2-4] in providing an unprecedented opportunity to a chemist in synthesis, it has remained in the mainstay as the evergreen synthan in the synthesis of a wide variety of six and seven membered heterocyclic rings. In order that our synthetic plan depicted in scheme-1 using isatin could succeed to form the indicated heterocyclic rings on to the indolin-2-one system, it had required the synthesis to proceed through the formation of the 3-benzoylmethyl indolin-2-one (3) from isatin (1), followed by its subsequent conversion to corresponding chalcones (4), Oxo-ketenedithioacetals (5), dimethylamino methylene ketones (6) derivatives. The key intermediate (3) was formed on allowing the reaction of isatin (1) to take place with acetophenone under the conditions of Claisen Schmidt condensation[14] followed by reduction[15-16] of the enone (2), with $Na_2S_2O_4$. A base catalyzed condensation of (3) with (i) with aromatic aldehydes in presences of base, (ii) with CS_2 and CH_3I in presence of NaOEt, (iii) with commercial N,N-dimethyl formamide dimethylacetal yielded the desired chalcones, Oxo-ketenedithioacetals and dimethylamino methylene ketones respectively. The versatility of (4,5,6) was exploited in reactions with the indicated bidentate nucleophiles to allow the formation of (7,8,9,10,11,12) respectively (Scheme 1,2 and 3).

The intermediate 4 and 5 reacted smoothly with urea and thiourea to give the corresponding pyrimidine derivatives 7,8,9 and 10 respectively. A similar reaction of 6 reacts with acetamidine and guanidine yielded the corresponding pyrimidine ring incorporated derivatives 11 and 12 in good yield respectively (Scheme-3). All the synthesized compounds gave satisfactory results of their elemental analysis, IR, ^{1}HNMR and MS spectral data which were found to be consistent to the assigned structures.

Conclusion: Two noteworthy features are apparent from our study projected on the synthesis of small molecules of medicinal interest from isatin. Firstly, ‘a chemistry driven approach to biologically active

pharmacophores' allowed the development of drug like molecules, on the incorporation of bioactive heterocyclic scaffolds having proven record of biological potential as pyrimidine, on to the indolin-2-one system. This study was undertaken on this premise that the presence of each scaffold in tandem, with a different mechanism of action could allow to form materials possibly with new pharmacological profiles with action strengthening effects and toxicity lowering effects. Secondly, the study established that the chalcones, Oxo-ketenedithioacetals, dimethylamino methylene ketones, provided a better option to the conventional base catalyzed reactions and forming the cyclized products in high yield and purity.

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