EXPLORATION OF NEWER POSSIBILITIES TO THE SYNTHESIS OF SMALL MOLECULES OF MEDICINAL INTEREST FROM ISATIN

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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 isoxazole (**5)**, pyrazole (**6)**, pyridine (**7)**, pyrido pyrimidine (**8,9)** and quinoline carboxylic acid derivatives **10** resepectively. In a related reaction the Beckmann rearrangement of the oxime of **3**, with acid and with TCT + DMF allowed the formation of the amide **13** which underwent cyclocondensation with NH_4OAc in AcOH to give the corresponding pyrrolo-indole derivative **15** whose structure was unequivocally established from its micro analyses and spectral data.

KEY WORDS: Isatin, indolin-2-one, Pfitzinger reaction, Beckmann rearrangement.

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.

Isatin offers an unprecedented opportunity to a chemist to the synthesis of a wide variety of heterocyclic compounds[2-4]. 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[5]. Recent discovery of promising anti-HIV activity of its imino isatin Mannich's base derivativs has stimulated further interest in compounds derived from isatin[6], with yet another perspective.

The importance of the indolin-2-one[7], isoxazole[8], pyrazole[9],pyridine[10], pyrimidine[11], quinoline[12], pyrrolo indole[13] class of heterocyclic scaffolds 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.

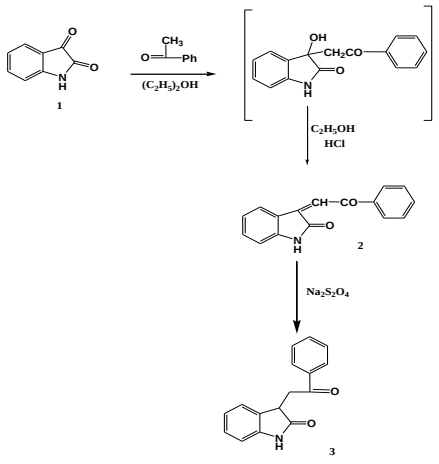
RESULTS AND DISCUSSION

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 oxo enolic ether derivative **4**. 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 ethyl formate yielded the desired oxo enolic ether derivative **4**. The versatility of **4** was exploited in reactions with the indicated bidentate nucleophiles to allow the formation of **5,6,7,8** and **9** respectively (Scheme 1 and 2).

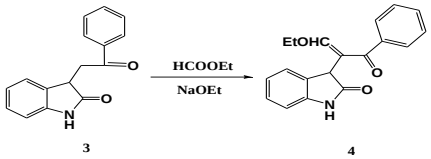
The intermediate **4** reacted smoothly with hydroxylamine hydrochloride and hydrazine hydrate to give the corresponding isoxazole[17] and pyrazole[18] derivatives **5** and **6** respectively. A similar reaction of **4** with malononitrile[19] and ammonium acetate yielded the corresponding pyridine ring incorporated derivative **7**. The adjacent amino and nitrile functions of **7** when allowed to undergo reactions with urea[19] and thiourea[20] formed the pyrido pyrimidine derivatives **8** and **9** respectively.

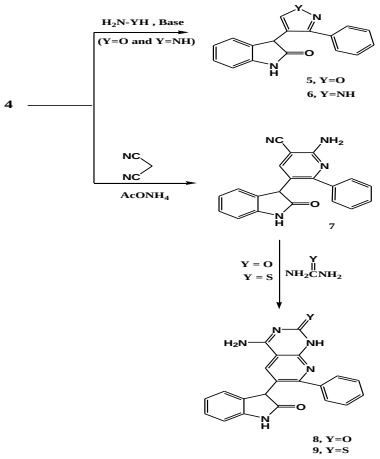
The potentiality of **3** to undergo Pfitzinger reaction[21] with isatin was explored to provide an easy access to the corresponding quinoline-4-carboxylic acid substituted derivative **10**. The ketoxime **11** which resulted from **3** through the base catalyzed condensation with $NH_2OH.HCl$ was assigned configuration **11** (wherein the OH group was shown to exist in an 'anti' position to Ph), on the basis of its acid catalyzed[22] conventional and an organocatalyst (formed from 2,4,6-trichloro-1,3,5-triazine (TCT) + DMF) catalyzed[23] Beckmann rearrangement, followed by heterocyclocondensation of the resulting amide **13** with NH_4OAc in AcOH to yield the 2-phenylamino substituted pyrrolo-indole derivative **15**. If the oxime had the configuration **12**, the Beckmann rearrangement of this should have resulted the amide **14** and a cyclocondensation product **16** (on its reaction with NH_4OAc in AcOH) (Scheme-3). The most diagnostic evidence which ruled out the possibility of formation of **16** and supported the formation of **15** was provided by the ^{1}HNMR spectrum of **15** which displayed no peak for CH_2

protons (existed in **16** in between the indole nucleus and the pyrimidine nitrogen). This result was in full agreement to the traditional Beckmann rearrangement of the ketoximes of aryl alkyl ketones[24] in which it was generally observed that it was the aryl group that preferentially migrated to form the N-aryl substituted amides.

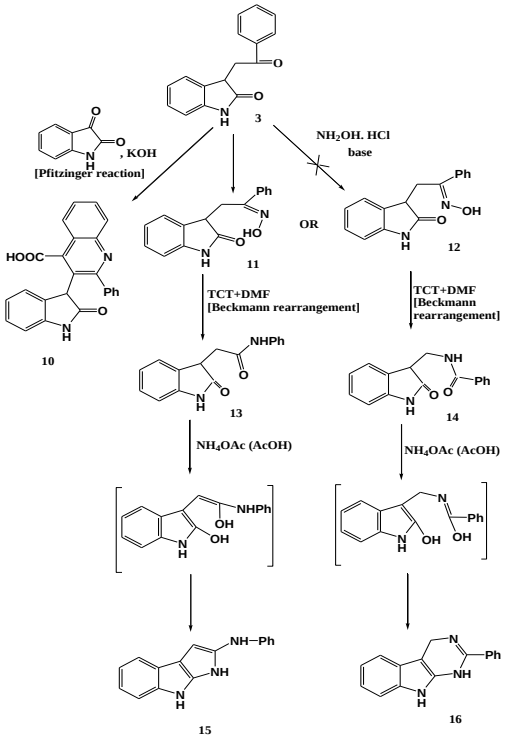


Scheme-1





Scheme-2

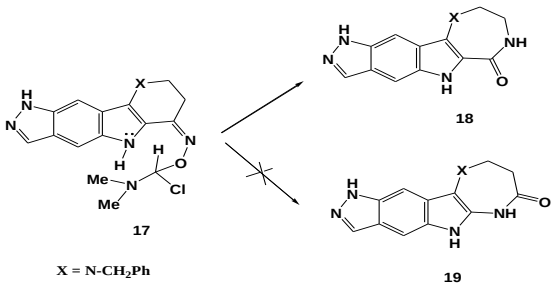


Scheme-3

Though most ketoximes undergo Beckmann rearrangement generally with acidic reagents[25] to form the corresponding amides in one stroke by undergoing the cleavage of carbon-carbon bond followed by the formation of carbon-nitrogen bond, but the reaction generally requires a high temperature and strongly acidic and dehydrating media. Under these conditions the reaction usually leads to the large amount of by-products and precludes its application to acid sensitive substrates. This required alternate non-acidic variants to be developed for this rearrangement. On such variant which found application, employed the ionic liquid[26] at room temperature. Subsequently, a very mild procedure was developed that used the organic catalyst[29] derived from TCT + DMF that allowed almost the quantitative conversion of a ketoxime into the corresponding amide to occur at room temperature. The procedure involved a room temperature reaction of the DMF solution of 1 mol. equiv. of the ketoxime with the complex formed from the inexpensive TCT and DMF. Application of this reagent on the rearrangement of ketoxime **11** yielded the amide **13** in a high yield and purity (Scheme 3).

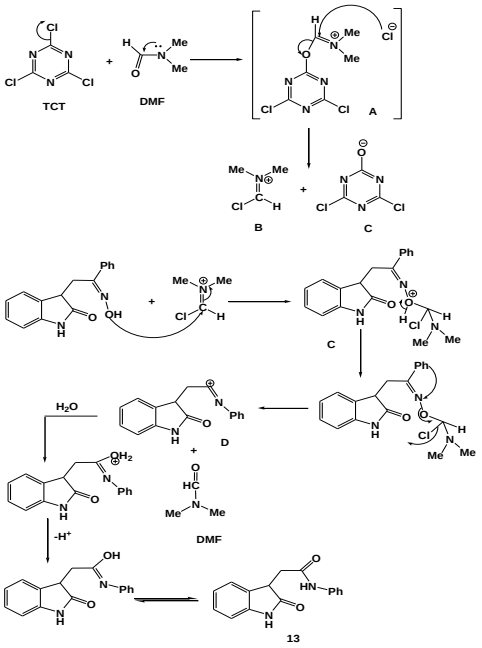
In an another related substrate **17** in which the oxime function existed in a close proximity to the indole nitrogen in a pyrazolo condensed oxo-carbazole species, we have recently demonstrated[27] that its TCT + DMF catalyzed rearrangement led to the exclusive formation of

the regioisomer **18** (and not **19**). This result firmly established the versatility of this reagent in rearrangement reactions, in exclusively forming of one product in these reactions (Scheme-4).



Scheme-4

The formation of **13** from **11** could be rationalized by the mechanism shown in (scheme-5). It is assumed that the reaction proceeds through the formation of species B (from TCT + DMF) which interacts with the oxime **11** to form C, simultaneous migration of the phenyl group followed by the loss of the DMF fragment, from C, generates the species D and the usual workup produces the rearranged product **13**.



Scheme-5

Mechanism for the TCT + DMF catalyzed Beckmann rearrangement of 11 to 13

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.

P**reparation of 3-benzoylmethyledene-indolin-2-one (2).**

A mixture containing isatin (13.23 g, 0.09 mol) and acetophenone (10.80 g, 0.09 mol) 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;

P**reparation of 3-phenacyl-indolin-2-one (3).**

To a mixture of 3-benzoylmethyledene-indolin-2-one (2) (1.245g, .005mol) and sodium dithionite (0.870g, .005mol) in water (6ml), methanol (6ml) and dichloromethane (2ml) was added. The mixture was refluxed for 10h. The solvent was evaporated and the resultant compound was recrystallized from ethanol to give (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.]; ^{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 (30%) ; 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.

P**reparation of 3-[2'-ethoxymethyledene]-phenacyl-indolin-2-one (4).**

To a mixture of 3-phenacyl-indolin-2-one **3** (7.53 g, 0.03 mol) in dry benzene (10 ml), sodium methoxide (0.5 g) in dry benzene (25 ml) at 0°C, a solution of ethyl formate (l.2 ml) in dry benzene (12.5 ml) was added. The mixture was stirred for 6h at room temperature and allowed to stand overnight. It was then diluted with cold water and extracted with ether. The solvent was evaporated and the resultant product was recrystallized from ethanol to give **4**, (5.02 g, 68%); m.p: 194-198^{o}C; IR (KBr) cm^{-1} : 1580 [C=C str. ArH], 3100 [C-H str. ArH], 1020 [C-N str.], 1690 [C=O str.], 3450 [N-H str.],[C-O-C str.], 2960 [C-H str., CH_3] [C-C 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], 6.74 [s. 1H, CH], 4.00 [q, 2H, CH_2], 1.22 [t, 3H, CH_3] ; MS: m/z: 307.34 (32%) ; Anal. Calcd./found for $C_{19}H_{17}NO_3$: C, 74.25/74.49; H, 5.58/5.36 ; N,4.56/4.71.

Preparation of 3-phenyl-4-[-2'-oxo-3'-indolinyl]-isoxazole (5).

Hydroxylamine hydrochloride (2.78 g, 0.04mol) was added to sodium methoxide (3.24 g, 0.06 mol) in absolute methanol (30.0 ml) and stirred for l0 min. To this mixture **4,** (1.23 g, 0.04 mol) was added and it was refluxed for 8 h. Most of the methanol was evaporated under reduced pressure and the mixture was poured into ice cold water. The solid separated was filtered washed with diethyl ether and dried. Recrystallization from ethanol gave **5** (1.01 g, yield 62%); m.p. l71-75ºC; IR (KBr) cm^{-1} : 1600 [C=C str. ArH], 3080 [C-H str. ArH], 3400 [N-H str.], 1560 [C=N str.], 1670 [C=O str.], 1260 [C-O str.], 900 [C-O-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], 5.00 [s, 1H, CH], 7.12 [s, 1H, CH] ; MS: m/z: 276.29 (25%) ; Anal. Calcd./found for $C_{17}H_{12}N_2O_2$: C, 73.90/73.78; H, 4.38/4.15 ; N,10.14/10.28.

Preparation of 3-phenyl-4-[-2'-oxo-3'-indolinyl]-pyrazole (6).

A mixture of **5**, (1.23 g, 0.04 mol) and hydrazine hydrate (5.0ml) was heated under reflux for 12-14h, in ethanol (250ml) then cooled and the residual material was filtered off and recrystallized from DMF/water to give **6**, (0.98 g, yield 78%); m.p.169-71°C; IR (KBr) cm^{-1} : 1500 [C=C str. ArH], 3045 [C-H str. ArH], 1550 [C=N str.], 1020 [C-N str.], 1710 [C=O str.], 3500 [N-H 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], 5.00 [s, 1H, CH], 7.33 [s, 1H, CH], 13.7 [s, 1H, NH]; MS: m/z: 275.3 (28%) ; Anal. Calcd./found for $C_{17}H_{13}N_3O$: C, 74.17/74.32; H, 4.76/4.91; N,15.26/15.44.

Preparation of 5-[2'-oxo-3'-indolinyl]-6-phenyl-2-amino-pyridine-3-carbonitrile (7).

A mixture of 3-[2'-ethoxymethyledene]-phenacyl-indolin-2-one **4,** (3.07g, 0.01mol), malononitrile (0.66g, 0.01mol) and ammonium acetate (6.2g, 0.08mol) in ethanol (25ml) was refluxed on a water bath for 8h, cooled and poured on the crushed ice with constant stirring. The solid mass thus obtained was washed with water and recrystallized from ethanol to give **7.** (2.08g, yield 80%); m.p.198-02°C; IR (KBr) cm^{-1} : 1560 [C=C str. ArH], 3000 [C-H str. ArH], 1560 [C=N str.], 1340 [C-N str.], 1700 [C=O str.], 3300 [N-H str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.04 [m , 4H, ArH], 7.28-7.99 [m, 5H, ArH], 8.0 [s, 1H, NH], 5.00 [s, 1H, CH],

7.82 [s, 1H, CH], 4.00 [s, 2H, NH_2]; MS: m/z: 326.35 (29%) ; Anal. Calcd./found for $C_{20}H_{14}N_4O$: C, 73.61/73.84; H, 4.32/4.62; N,17.17/17.39.

Preparation of 2-phenyl-3-(2'-oxo-3'-indolinyl)-pyrido[5,6-b]-5-amino-7-hydroxy-pyrimidine (8)

A mixture of **7,** (1.63g, 0.005mol) and urea (0.300g, 0.005mol) was heated on an oil bath at 120^{o}C for 4h with constant stirring. The temperature was raised to 180^{o}C and finally the mixture was heated at 220^{o}C for 2h. On cooling the product solidified, which was recrystallized from DMF-EtOH mixture (1:2) to give **8** (0.89g, yield 61%); m.p. 220-21^{0}C; IR (KBr) cm^{-1} : 1580 [C=C str. ArH], 3065 [C-H str. ArH], 1550 [C=N str.], 1300 [C-N str.], 1670 [C=O str.], 3400 [N-H str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.25 [m , 4H, ArH], 7.28-7.99 [m, 5H, ArH], 8.0 [s, 1H, NH], 5.00 [s, 1H, CH], 7.74 [s, 1H, CH], 8.00 [s, 1H, CH], 2.0 [s, 2H NH_2] ; MS: m/z: 369.38 (33%) ; Anal. Calcd./found for $C_{21}H_{15}N_5O_2$: C, 68.28/68.39; H, 4.09/4.21; N,18.96/18.68.

Preparation of 2-phenyl-3-(2'-oxo-3'-indolinyl)-pyrido[5,6-b]-5-amino-7-mercapto-pyrimidine (9)

A mixture of **7,** (1.63g, 0.005mol) and thiourea (0.380g, 0.005mol) was heated on an oil bath at 120^{o}C for 4h with constant stirring. The temperature was raised to 180^{o}C and finally the mixture was heated at 220^{o}C for 2h. On cooling the product solidified, which was recrystallized from DMF-EtOH mixture (1:2) to give **9.** (1.12g, yield 75%); m.p. 231-34^{o}C; IR (KBr) cm^{-1} : 1600 [C=C str. ArH], 3010 [C-H str. ArH], 1540 [C=N str.], 1050 [C-N str.], 1710 [C=O str.], 3340 [N-H str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52 [m , 4H, ArH], 7.28-7.99 [m, 5H, ArH], 8.0 [s, 1H, NH], 5.00 [s, 1H, CH], 7.74 [s, 1H, CH], 8.00 [s, 1H, NH], 2.0 [s, 2H, NH_2] ; MS: m/z: 385.44 (26%) ; Anal. Calcd./found for $C_{21}H_{15}N_5OS$: C, 65.44/65.58; H, 3.92/3.81; N,18.17/18.34; S, 8.32/8.12.

Preparation of 2-phenyl-3-(2'-oxo-3'-indolinyl)-quinoline-4-carboxylic acid (10).

A mixture of isatin (1.47g, 10mmol) and 3-phenacyl-2-indolinones **(3)** (2.51g, 10mmol) in 50% aqueous EtOH (10 ml) containing KOH (0.55g) was heated under reflux for 20 h and then diluted with 50% aqueous EtOH to obtain a homogeneous mixture. This was filtered and acidified with AcOH, and the product settled was collected, washed with 30% aqueous EtOH, and recrystallized from MeOH to give **10,** (1.12g, yield 78%), m.p.288-91 ˚C; IR (KBr) cm^{-1} : 1575 [C=C str. ArH], 3030 [C-H str. ArH], 1540 [C=N str.], 1030 [C-N str.], 1670 [C=O str.],

3350 [N-H str.], 2500 [O-H str.], 1260 [C-O str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.88-7.52 [m , 4H, ArH], 7.28-7.99 [m, 5H, ArH], 7.82-9.08 [m, 4H, ArH], 8.0 [s, 1H, NH], 5.00 [s, 1H, CH], 11.0 [s, 1H, O-H], ; MS: m/z: 380.4 (30%) ; Anal. Calcd./found for $C_{24}H_{16}N_2O_3$: C, 75.78/75.63; H, 4.24/4.35; N,7.36/7.12.

Preparation of 2-(2-oxo-indolin-3-yl)-N-phenyl acetamide (13)

(11a) Preparation of ketoxime (11)

3-Phenacyl-indolin-2-one **3, (**0.753g, .003mol**),** hydroxylamine hydrochloride (0.207g, .003mol) and 0.5g of sodium hydroxide (pellet form) in 5ml rectified spirit and 3ml water was mixed with shaking. As the reaction became too vigorous the flask was cooled in running tap water. The mixture was refluxed for 20 min cooled and poured the content into (5ml) of water. Filtered the precipitated oxime at the pump, washed and recrystallized with methanol to give ketoxime **11** (0.38g, yield 72%); m.p.248-49 ˚C;

(11b) Preparation of 2-(2-oxo-indolin-3-yl)-N-phenyl acetamide (13)

2,4,6-Trichloro-[1,3,5] triazine (1.84g, 0.01mol) was added to DMF (2 ml), maintained at 25ºC. After formation of white solid was complete, (the reaction was monitored (by TLC) until complete disappearance of TCT), then ketoxime of 3-phenacyl-indolin-2-one **3,** (2.66g, 0.01mol) in DMF (15 ml) was added. After the addition, the mixture was stirred at room temperature, monitored (by TLC) until completion of reaction (20 h). Water (20 ml) was added and the residue obtained was filtered washed with 15 ml of a saturated solution of Na_2CO_3. The organic layer was dried over the sodium sulphate. Evaporation of solvent gave **13** (2.43g, yield 81%); m.p. 270-72ºC; IR (KBr) cm^{-1} : 1560 [C=C str. ArH], 3065 [C-H str. ArH], 1670 [C=O str.], 3400 [N-H str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 6.95-7.59 [m , 4H, ArH], 7.00-7.64 [m, 5H, ArH], 8.0 [s, 1H, NH], 3.99 [t, 1H, CH], 2.92 [d, 2H, CH], 8.00 [s, 1H, NH] ; MS: m/z: 266.29 (36%) ; Anal. Calcd./found for $C_{16}H_{14}N_2O_2$: C, 72.16/72.39; H, 5.30/5.61; N,10.52/10.86.

Preparation of 2-phenylamino-[4,5-b]-indolo-pyrrole (15)

A mixture of **11,** (0.25g, 0.01mol) ammonium acetate (0.08g, 0.01mol) in acetic acid 10.0 ml was refluxed for 9-10 h, cooled and poured the content of the flask into cold water.

Filtered the precipitate at the pump, washed and recrystallized with ethyl acetate to give **15** (0.22g, yield 82%); m.p 240-244ºC; IR (KBr) cm^{-1} : 1560 [C=C str. ArH], 3000 [C-H str. ArH], 1547 [C=N str.], 1045 [C-N str.], 3300 [N-H str.]; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 7.1-7.5 [m , 4H, ArH], 6.62-7.01 [m, 5H, ArH], 3.5 [d, 1H, CH], 5.8 [d, 1H, CH], 4.0 [s, 1H NH], 2.0 [s, 1H, NH], ; MS: m/z: 247.29 (32%) ; Anal. Calcd./found for $C_{16}H_{13}N_3$: C, 77.71/77.62; H, 5.30/5.44; N,16.99/16.74.

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 several bioactive heterocyclic scaffolds having proven record of biological potential such as isoxazole, pyrazole, pyridine, pyrido pyrimidine, quinoline, pyrrolo indole etc, 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 Beckmann rearrangement of ketoximes with organocatalyst derived from TCT + DMF provided a better option to the conventional acid catalyzed rearrangements in allowing the reaction to take place under mild conditions and in forming the rearranged products in high yield and purity.

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