# NOVEL SYNTHESIS OF SUBSTITUTED PYRROLE BOUND TO INDOLINONE VIA MOLECULAR IODINE-CATALYZED REACTION

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**Abstract:** An expeditious synthesis of indolinone bound to pyrrole starting from isatin and 4-hydroxyproline via a molecular iodine-catalyzed reaction is described. A mechanism is postulated that describes the formation of ylide and zwitterion intermediates. It is suggested that iodine can catalyze several spontaneous processes.
**Keywords:** Pyrrole, Indolinone, Molecular Iodine, Catalysis

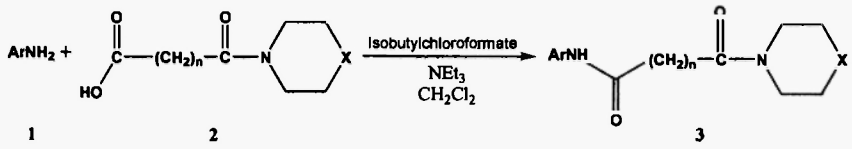
## Introduction

Substituted pyrroles and indoles are important classes of heterocyclic compounds having many medicinal activities.[1] A number of methods for the synthesis of substituted pyrroles are described in the literature.[2] In contrast, synthesis of pyrroles bound to indole systems has not been yet explored. Conjugate addition reactions have been demonstrated for the synthesis of polysubstituted pyrroles.[3] These compounds have also been prepared from transition metal intermediates,[4] by reductive couplings,[5] aza-Wittig reactions,[6] and other multistep operations.[7] However, the Paal-Knorr reaction[8] remains one of the most attractive and simple methods for the synthesis of pyrroles. A clay-mediated[9] reactions and microwave irradiation method[10] have been used for the construction of pyrroles following Paal-Knorr conditions. In this paper, we describe the preparation of pyrroles bound to indolinone via molecular iodine-catalyzed reaction in excellent yield.

## Results

We performed a structure-activity relationship study of various polyaromatic derivatives easily prepared from their corresponding amines in a projected route toward the development of novel anticancer agents.[11] It was demonstrated that modification of the heterocyclic ring is crucial in determining the biological activity of these derivatives (Scheme-1). Based on the anticancer activities of these derivatives, we became interested in the synthesis of pyrroles bound to the polyaromatic amines of different structures.[12] We envision that our work on iodine-catalyzed organic transformations can be used to achieve this goal (Scheme-2).

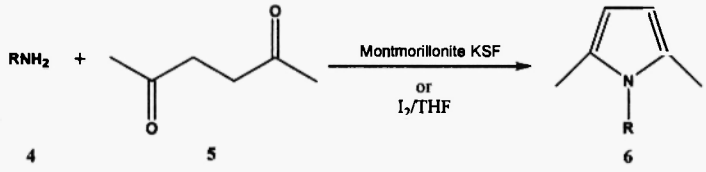
It has been demonstrated that primary amine **4** reacts with hexane-2,4-dione **5** in the presence of iodine or montmorriellonite KSF clay very efficiently to afford *N*,2,5-trisubstituted pyrrole.[12] In this reaction, iodine acts as an acidic catalyst. Realizing the importance of pyrrole-containing compounds, this method has been extended to other keto compounds (Scheme-3).




1 2 3

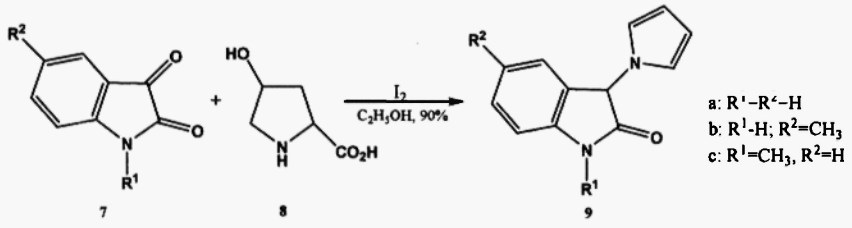
Ar= 6-Chrysenyl, 11-Dibenzofluorenyl, 1-Pyrenyl; n= 1, 2, 3; X= $CH_2$, $NCH_3$

**Scheme-1**




4 5 6

**Scheme-2**



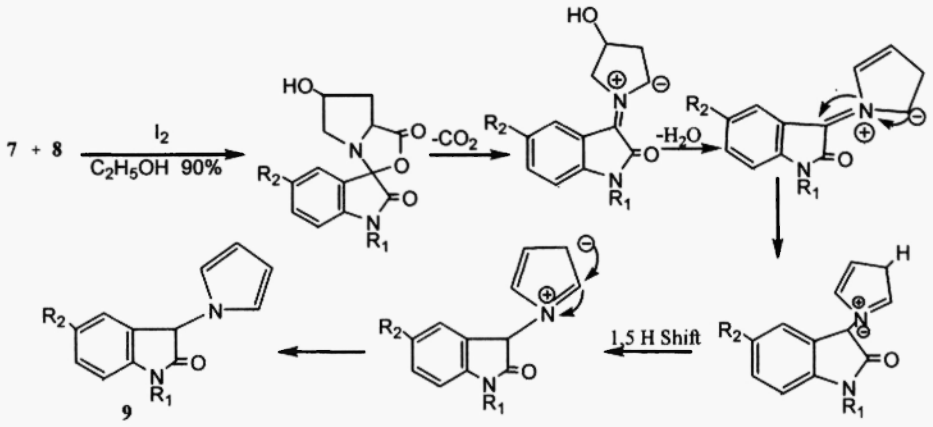

7 8 9

**Scheme-3**

**Discussion**

Isatin derivatives **7** are commercially available. The keto group of these compounds is very reactive. We found that 4-hydroxyproline **8** undergoes a reaction with isatin in the presence of catalytic amount of iodine in tetrahydrofuran or ethanol. The reaction proceeded better in ethanol. The structural analysis of the product indicated that a pyrrole ring is formed at the 3-position of the indole system **9**. However, the reaction did not proceed without iodine. The structure of the product was confirmed by analysis of the $^1$H NMR spectra. The singlet at δ 8.15 indicated the presence of NH-group. This also confirmed that the –NH- group of the indole moiety remains unaltered during this reaction. The presence of 8-aromatic hydrogens was also established from the NMR spectra. The peaks at δ 6.9 and 6.7 clearly indicated the presence of pyrrole moiety. The characteristic peak at δ 5.5 confirmed the presence of a methine hydrogen in compound **9**.

Clay-mediated synthesis of this type of compounds has been reported earlier.[14] However, this type of method is not suitable for a relatively large scale of preparation. In this respects, iodine-catalyzed reaction for the synthesis of compounds **9** is significant since it can be performed on a multigram scale (2-10 g) with excellent yield.




**Scheme-4**

A probable mechanism for this transformation is postulated in Scheme 4. It is based on our strategy on the protection of carbonyl derivatives with bifunctional compounds.[13] The amino and the carboxy group are ideally located to undergo a condensation reaction to the highly reactive keto group of the indolinone moiety in the presence of iodine. On iodine-catalyzed condensation and under a high temperature, this intermediate can be transformed to an azomethine ylide via decarboxylation. Mild acid-induced dehydration at reflux temperature may yield a conjugated product spontaneously. 1,5-Proton shift may then occur to afford a zwitterionic intermediate that can easily isomerize to a stable aromatic product.[14] This indicates the capability of the iodine as an activator in catalyzing several spontaneous processes as described in the present investigation.

## Conclusion

We have demonstrated that two heterocycles, indole and pyrrole, can be fused in a one-step operation using a mild iodine-catalyzed reaction on a relatively large scale. Compounds described herein may demonstrate useful biological activities. We believe that our method can be applied to many other keto compounds.

## Experimental

To isatin (10 mmol), hydroxyproline (10 mmol), and iodine (200 mg) was added ethanol (20 mL) and the mixture was heated under reflux for 1 h. Then the mixture was diluted with water (6 mL), extracted with dichloromethane (2 x 50 mL), and the extract was washed with sodium thiosulfate solution (10%, 50 mL), saturated sodium bicarbonate (50 mL), and dried ($Na_2SO_4$). Pure product (approximately, 90%) was isolated by silica gel column chromatography eluting with ethyl acetate/hexane (30/70).

All solvents and reagents were obtained from commercial sources and used without purification. Reactions were monitored by TLC using pre-coated silica gel aluminum plates containing a fluorescence indicator. $^1$H NMR spectra were recorded at 300 MHz in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra were expressed as wave numbers ($cm^{-1}$).

Compound 9a: mp: 140°C, IR (KBr): 3295, 3190, 1711, 1614, 1482 $cm^{-1}$; $^1$H NMR $\delta$H: 6.51 (1H, s, CH), 6.25 (2H, br s, CH), 6.70 (2H, br s, CH), 6.85-7.34 (4H, m, ArH), 8.87 (1H, br s, NH).

Compound 9b: mp: 161°C, IR (KBr): 3200, 1708, 1619, 1487 $cm^{-1}$; $^1$H NMR $\delta$H: 1.93 (3H, s, $CH_3$), 5.58 (1H, s, CH), 6.25 (2H, t, J = 2.0 Hz, CH), 6.71 (2H, t, J = 2.0 Hz, CH), 6.79-7.31 (4H, m, ArH), 9.09 (1H, br s, NH).

Compound **9c**: mp: 135°C, IR (KBr): 1712, 1606, 1486 $cm^{-1}$; $^1H$ NMR $\delta$H: 3.23 (3H, s, $CH_3$), 5.48 (1H, s, CH), 6.22 (2H, brs, CH), 6.68 (2H, brs, CH), 6.89-7.42 (4H, m, ArH); Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.69; N, 13.19. Found: C, 73.40; H, 5.51; N, 13.00.

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