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A green approach for efficient synthesis of *N*-substituted pyrroles in ionic liquid under microwave irradiation

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ABSTRACT

A rapid synthesis of *N*-substituted pyrroles has been described by the reaction of 4-hydroxyproline with isatins in ionic liquid under microwave irradiation. The recovered ionic liquid was reused for six cycles. The reaction proceeds without addition of any acid promoter

Pyrroles are important heterocyclic compounds displaying remarkable pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antitumoural, and antioxidant activities.[1] The pyrrole moiety is found in many naturally occurring compounds such as heme, chlorophyll, and vitamin B_{12}.[2] Pyrroles are also present in various bioactive drug molecules such as atrovastatin, anti-inflammatory and antitumor agents, and immunosuppressants.[3] Quinoxaline[4] derivatives are important classes of nitrogen-containing heterocycles which are useful intermediates in organic synthesis. In view of their high significance, many methodologies have been developed for the construction of the pyrrole skeleton.[5] Among them, the Paal–Knorr[6] synthesis remains the most useful preparative method for generating pyrroles. In recent years, a variety of reagents such as K10 clay,[7] bismuth nitrate,[8] $Dy(OTf)_3$,[9] PMA/SiO_2,[10] β-CD,[11] under reflux conditions have been utilized for the synthesis of *N*-substituted pyrroles. Many of these procedures involve the use of expensive reagents, metal triflates, extended reaction times and produce a huge amount of toxic waste. So it is desirable to discover ecofriendly procedures for the synthesis of pyrrole derivatives. Recently, ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible vapor pressure and recyclability.[12] Among various ionic liquids, 1-butyl-3-methylimidazoliumtetrafluoroborate ($[Bmim]BF_4$) has been used in the synthesis of vicinal diamines,[13] one-pot syntheses of 2*H*-indazolo[2,1-*b*]-phthalazine-triones,[14] and hydrative cyclization of 1,6-diynes.[15] It has been proven recently that microwave heating improves the preparative efficiency and reduces the reaction time for several organic transformations.[16] Our interest in the development of new methodologies[17] in the area of green chemistry[18] prompted us to synthesize *N*-substituted pyrroles in ionic liquid in conjugation with microwave irradiation (Scheme 1).

Our initial effort was focused on the conventional thermal heating reaction of 5-bromoisatin (entry 3) with 4-hydroxyproline in 2 ml of $[Bmim]BF_4$. The reaction remained incomplete even after heating the reaction mixture at 110 °C for 24 h. Considering the recent advances of microwave irradiation for rapid reactions, we carried out the same reaction in the microwave. Surprisingly, the reaction was completed in 10 min with complete conversion of 5-bromoisatin. This success encouraged us to extend this method to a wide range of isatins (entries 1–10). The microwave reactions were performed in a CEM[19] discover model microwave apparatus. Having optimized conditions[20] for the rapid synthesis of these pyrrole derivatives, various 5-substituted isatins and 1-substituted isatins were condensed with 4-hydroxyproline to afford the corresponding 3-(1*H*-pyrrol-1-yl)indolin-2-ones (entries 1–10) in good to excellent yields (Table 1). It was also observed that (ethylideneamino)-2,3-dihydroindene-1-ones underwent condensation with 4-hydroxyproline under similar conditions to produce the corresponding 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-ones in good yield (Table 1, entries 11 and 12). It is worthy to mention that there is no byproduct formation in the reaction. The formation of the desired products may be explained by the formation of an azomethine ylide via decarboxylation and subsequent 1,5-proton shift to give the more stable zwitterion, which can easily transform to the more stable product to gain aromatic character

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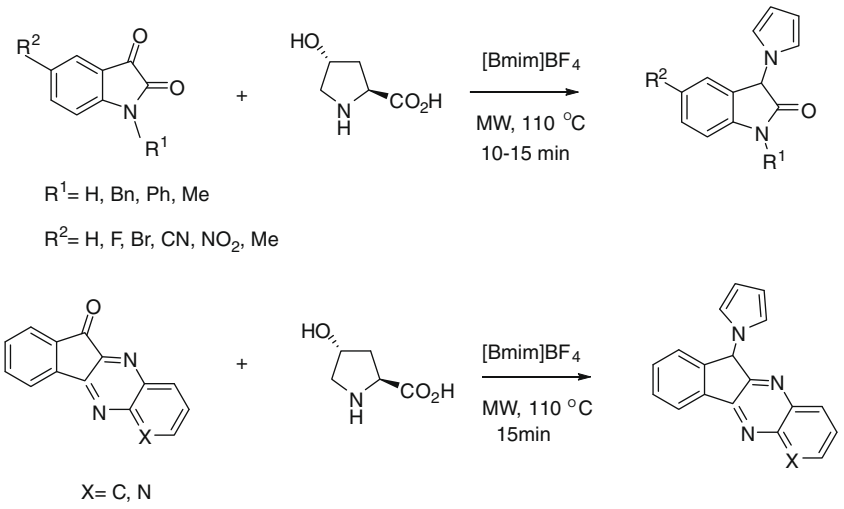


Scheme 1.

Table 1
Synthesis of *N*-substituted pyrroles using ionic liquid [Bmim]BF_4

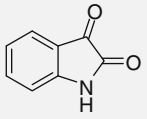
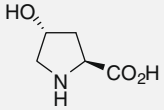
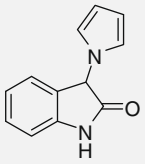
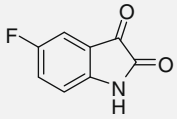
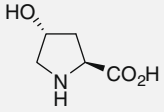
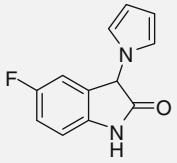
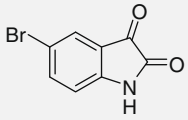
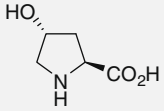
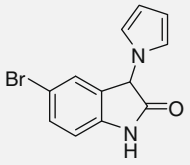
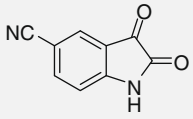
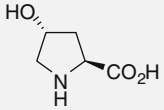
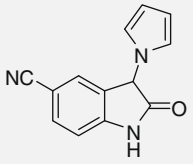
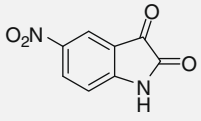
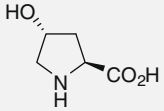
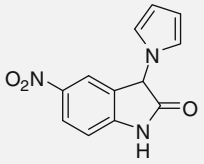
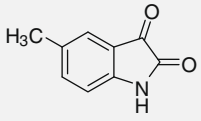
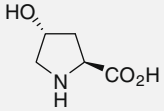
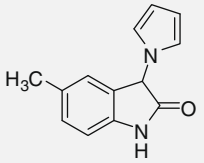
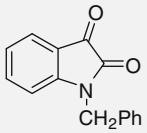
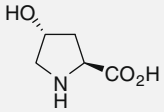
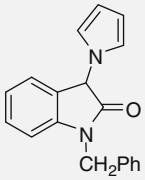
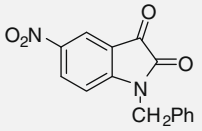
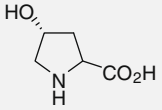
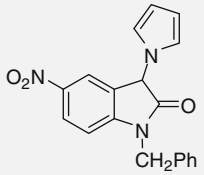
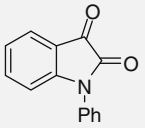
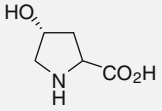
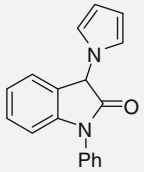
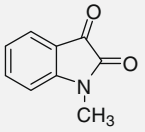
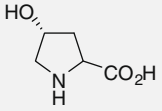
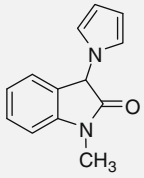
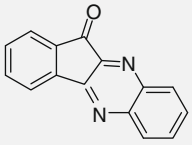
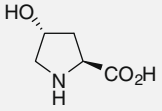
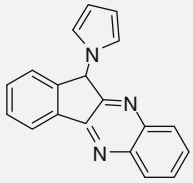
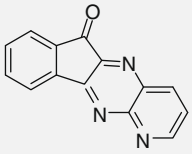
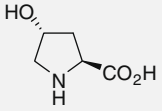
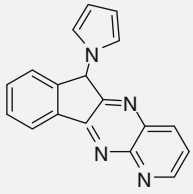
Entry	Isatin	4-Hydroxy proline	Product[a]	Time (min)	Yield[b] (%)
1				10	93
2				10	96
3				10	95
4				15	93
5				15	92
6				10	97
7				10	94

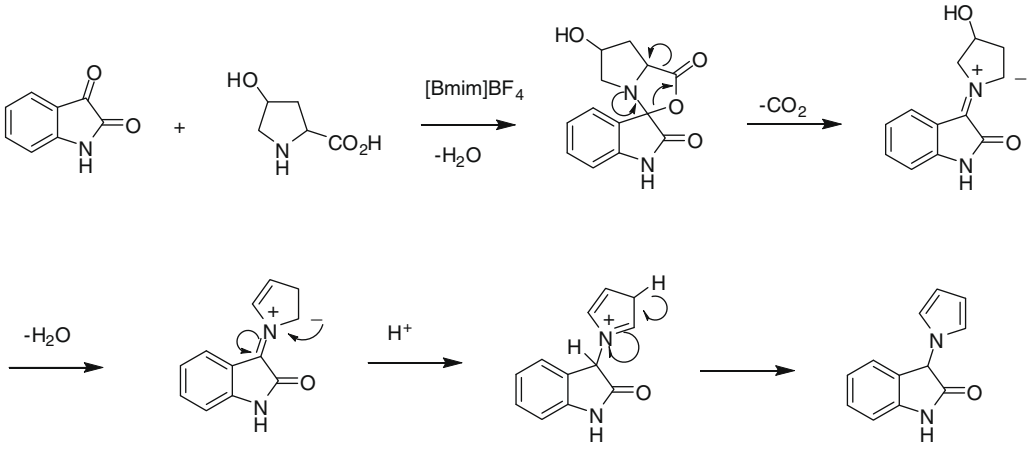
Table 1 (*continued*)

Entry	Isatin	4-Hydroxy proline	Product[a]	Time (min)	Yield[b] (%)
8				10	95
9				15	93
10				10	96
11				15	93
12				15	94

[a] All products were identified by IR, NMR, mass spectroscopy and elemental analysis.
[b] Yields of products isolated after column chromatography.

(Scheme 2). After completion of the reaction (entry 3), the reaction mixture was extracted with ether (two or three times) and the residual ionic liquid was dried at 80 °C under vacuum and reused for six cycles. We have observed consistent yield (95%) for four cycles and there was gradual decrease in yields (87% and 79%) for 5th and 6th cycles, respectively. Thus the present method provides an useful alternative over conventional methods for the same transformation, since our method can avoid the use organic solvents and metallic reagents, moreover it reduces the reaction time significantly.

In conclusion, we have demonstrated a rapid, efficient and ecofriendly method for the synthesis of 3-(1*H*-pyrrol-1-yl)indolin-2-ones and 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-ones by the condensation of 4-hydroxyproline with substituted



Scheme 2.

isatins and (ethyldeneamino)-2,3-dihydroindene-1-ones by using an ionic liquid. Rapid reactions, operational simplicity, high yields, and reusability of ionic liquids are notable features of the present protocol.

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20. *General procedure for the synthesis of N-substituted pyrroles*: Isatin (1 mmol), 4-hydroxyproline(1 mmol) and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF4) (2 ml) were placed in a 10 ml crimp-sealed thick walled glass tube equipped with a pressure sensor and magnetic stirrer. The reaction tube was placed inside the cavity of a CEM Discover benchmate, operated at 110 °C (temperature monitored by built-in infrared sensor), power 150 W and pressure 25–30 psi for 10–15 min. After completion of the reaction, the reaction mixture brought to room temperature and extracted with ether (2 × 5 ml). The organic layer was washed with brine solution and dried over Na_2SO_4. The combined organic layers were evaporated and purified through column (30% ethyl acetate/petroleum ethers). The products (solids) were recrystallized from appropriate solvents. The residual ionic liquid was dried under vacuum at 80 °C for 4 h and reused for subsequent cycles. The products were characterized by IR, NMR and mass spectroscopy. The spectral data of all compounds are in accordance with those reported in literature. The data for some selected compounds are given below. *3-(1H-Pyrrol-1-yl)indolin-2-one (entry 1)*: Solid. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 5.46 (s, 1H), 6.17 (t, 2H, J = 2.2 Hz), 6.63 (t, 2H, J = 2.2 Hz), 6.85–7.09 (m, 2H), 7.20–7.33 (m, 2H), 9.5 (br s, 1H). IR (KBr) ν = 3306, 3194, 1717, 1618, 1466 cm^{-1}. EIMS: *m/z* 198 (M^+). *5-Nitro-3-(1H-pyrrol-1-yl)indolin-2-one (entry 5)*: Solid. Mp 135–136 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 5.60 (s, 1H), 6.25 (s, 2H), 6.66 (s, 2H), 6.97 (d, 1H, J = 8.5 Hz), 8.09–8.29 (m, 2H), 9.50 (br s, 1H). IR (KBr) ν = 3292, 2925, 1738, 1625, 1524, 1481, 1338 cm^{-1}. EIMS: *m/z* 243 (M^+). *(6E,9Z)-N1-(1-(1H-pyrrol-1-yl)-1H-inden-2(3H)-ylidene)-N2-ethylidenebenzene-1,2-diamine (entry 11)*: Solid. Mp 180–181 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 6.19 (s, 1H), 6.22 (t, 2H, J = 2.2 Hz), 6.73 (t, 2H, J = 2.2 Hz), 7.49–7.74 (m, 5H), 8.04–8.26 (m, 3H). IR (KBr) ν = 3092, 2924, 1479 cm^{-1}. EIMS: *m/z* 283 (M^+). *6-(1H-1-Pyrroyl)-6H-indeno-[1,2-b]-pyrido[3,2-e]pyrazine (entry 12)*: Solid. Mp: 150–153 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 6.15 (s, 1H), 6.18 (t, 2H, J = 1.5 Hz), 6.67 (t, 2H, J = 1.5 Hz), 7.47–7.52 (m, 1H), 7.61–7.70 (m, 4H), 8.38 (m, 1H), 9.12 (s, 1H). IR (KBr) ν = 2959, 2927, 2854, 1725, 1577, 1283, 1076, 787 cm^{-1} LC–MS: *m/z* 285 (M^++1).