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Journal of Molecular Catalysis A: Chemical 278 (2007) 38–41
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Iodine-catalyzed coupling of 4-hydroxyproline with isatins: An expeditious synthesis of 3-pyrrolyl indolin-2-ones

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Received 27 June 2007; accepted 7 August 2007
Available online 11 August 2007

Abstract

Molecular iodine is found to catalyze efficiently the coupling of 4-hydroxyproline with isatins under mild conditions to produce 3-(1*H*-pyrrol-1-yl)indolin-2-one and 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-one derivatives in excellent yields in a short reaction time with high selectivity. The use of iodine makes this procedure quite simple, more convenient and cost-effective.

Keywords: Pyrrole; Isatins; Molecular iodine; Indolinone; Quinoxaline

1. Introduction

Pyrrole unit is found in many naturally occurring compounds such as heme, chlorophyll and vitamin B_{12} [1–3]. They are also found in various bioactive drug molecules such as atrovastatin, anti-inflammatants, antitumor agents and immunosuppressants [3–7]. They are very useful intermediates not only for the synthesis of drugs, pigments and pharmaceuticals but also for the development of organic functional materials [8,9]. As a result, a large number of synthetic methods for the preparation of pyrrole derivatives have been reported in the literature [10–13]. Among them, the Paal–Knorr reaction remains one of the most attractive methods for the synthesis of pyrroles [12,13]. However, many of these classical methods often involve the use of expensive reagents, extended reaction times and also generate a mixture of products [8,9]. Since indolinone and quinoxaline systems are useful and important in the field of drugs and pharmaceuticals [14,15], the development of simple, convenient and high-yielding protocols is desirable. Recently, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available catalyst for various organic transformations; affording the corresponding products with high selectivity in excellent yields [16]. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts. Owing to advantages associated with this eco-friendly catalyst, molecular iodine has been explored as a powerful catalyst for various organic transformations [17–22].

2. Results and discussion

In continuation of our interest on the catalytic applications of molecular iodine [23–27] we herein report the first direct and metal catalyst-free synthesis of *N*-substituted pyrroles attached to indole skeleton by the coupling of 4-hydroxyproline with isatins under neutral conditions. Thus, treatment of isatin (**1**) with 4-hydroxyproline (**2**) in the presence of molecular iodine in *tert*-butanol at 70 °C for 55 min gave the corresponding 3-(1*H*-pyrrol-1-yl)indolin-2-one (**3a**) in 90% yield with high selectivity (Scheme 1).

Encouraged by this result, we turned our attention to various isatin derivatives. Interestingly, substituted isatins such as 5-methyl-isatin and 1-benzyl-5-nitro-isatin underwent smooth coupling with 4-hydroxyproline to give the respective 3-(1*H*-pyrrol-1-yl)indolin-2-ones (entries **b** and **c**, Table 1). Like isatin, 7-aza-isatin and its *N*-benzyl and *N*-ethyl derivatives also gave the corresponding 3-pyrrolyl-7-aza-indolinones (entries **d**–**f**, Table 1). Surprisingly, indigo also participated well in this reaction (entry **g**, Table 1). These results prompted us to extend

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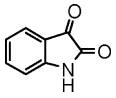
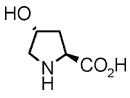
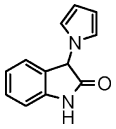
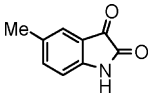
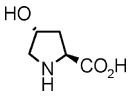
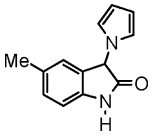
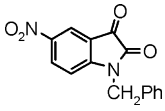
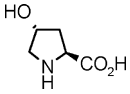
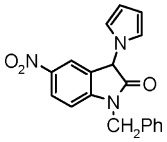
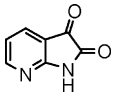
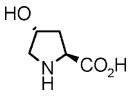
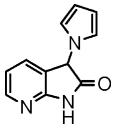
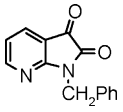
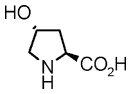
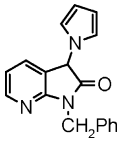
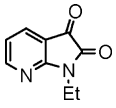
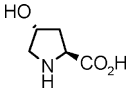
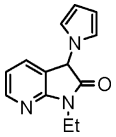
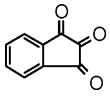
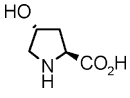
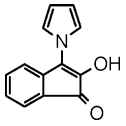
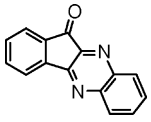
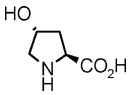
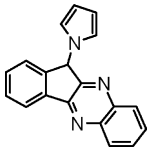
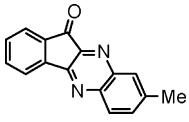
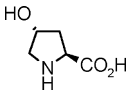
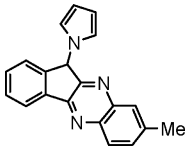
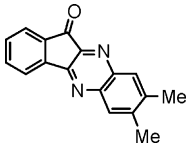
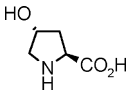
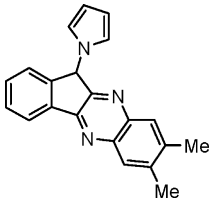
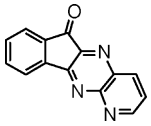
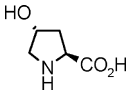
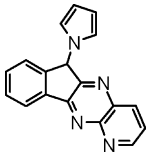
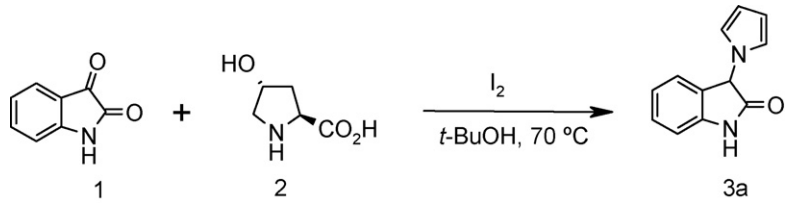
doi:10.1016/j.molcata.2007.08.005

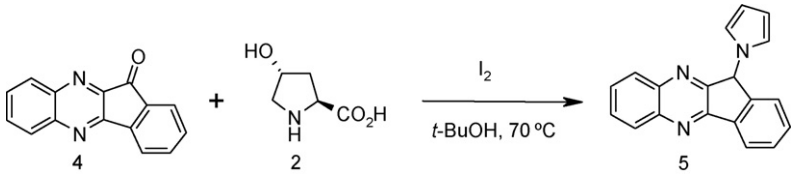
Table 1
Preparation of 3-(1*H*-pyrrol-1-yl)indolin-2-ones and 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline

Entry	Substrate	4-Hydroxyproline	Product[a]	Time (min)	Yield (%)[b]
a				55	90
b				60	92
c				160	80
d				70	78
e				75	82
f				65	77
g				165	60
h				200	75
i				180	77
j				135	85
k				260	79

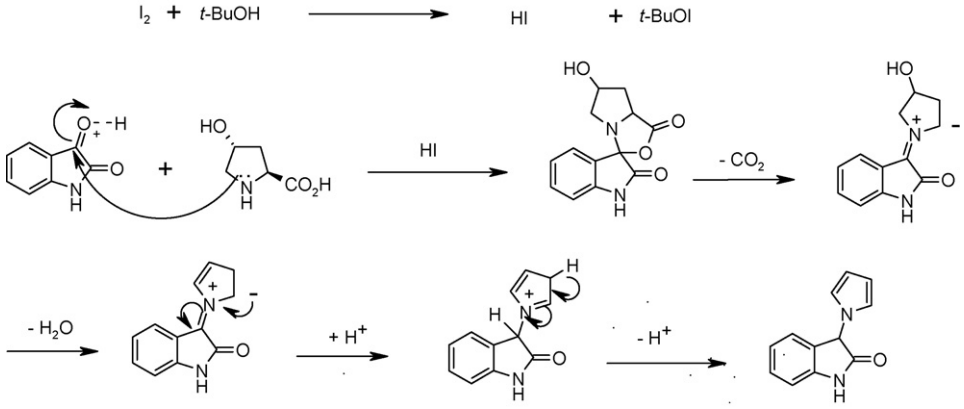
[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 1.



Scheme 2.



Scheme 3.

this methodology to 11*H*-indeno[1,2-*b*]quinoxalin-11-ones. Interestingly, several indeno[1,2-*b*]quinoxalin-11-ones underwent smooth coupling 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 high yields (entries **h**–**k**, Scheme 2, Table 1).

The structure of the product was determined by ^{1}H NMR and also by comparison with authentic samples. In all cases, the reactions proceeded rapidly under mild conditions. The reactions were clean and the products were obtained in high yields. However, no reaction was observed in the absence of iodine even after a long reaction time (24 h). The formation of the products may be explained by the formation of azomethine lade via decarboxylation and a subsequent 1,5-proton shift to generate the more stable zwitterion as shown in Scheme 3.

Among various solvents such as methanol, ethanol and isopropanol tested, *t*-BuOH was found to give the best results. Other reagents such as LiI, KI and NaI failed to produce the desired product. The scope and generality of this process is illustrated with respect to various isatins and indeno[1,2-*b*]quinoxalin-11-one derivatives and the results are presented in Table 1.

3. Conclusion

In summary, molecular iodine is proved to be a useful and novel catalyst for the preparation of 3-(1*H*-pyrrol-1-yl)indolin-2-ones in high yields in short reaction times. The use of inexpensive and readily available molecular iodine has made this procedure simple, convenient and practical. In addition to its simplicity, efficiency and milder reaction conditions, this method provides a rapid access for 3-(1*H*-pyrrol-1-yl)indolin-2-one and 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-one derivatives.

4. Experimental

4.1. General remarks

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Varian-unity 300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for synthesis of 3-pyrrolyl indolin-2-ones: A mixture of 4-hydroxyproline (1 mmol), isatin (1 mmol) and I_2 (0.1 mmol) in *tert*-butanol (5 mL) was stirred at 70 °C for a specified time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (2× 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) gave pure 3-(1*H*-pyrrol-1-yl)indolin-2-one. The products thus obtained were characterized by IR, NMR spectroscopy. The characterization data was found to be consistent with authentic samples.

(3f) 1-Ethyl-3(1*H* pyrrol-1-yl)-1*H*-pyrrol[2,3-*b*]pyridin-2-[3*H*]-one: Solid, mp 135–138 °C, IR (KBr): (υ_{max}): 2923, 2853, 1728, 1595, 1460, 1352, 1231, 1097, 782 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.25 (d, $J = 7.3$ Hz, 1H), 7.50 (d, $J = 7.3$ Hz, 1H), 7.00 (m, 1H), 6.60 (d, $J = 2.2$ Hz, 2H), 6.20 (t, $J = 2.2$ Hz, 2H), 5.45 (s, 1H), 3.85 (q, 2H, $J = 7.0$ Hz), 0.90 (t, 3H, $J = 7.0$ Hz). LC–MS: *m/z*: 250 $(M + Na)^+$ **(3g) 2-Hydroxy-3-(1*H*-pyrrol-1-yl)-1*H*-inden-1-one**: Semi-solid, IR (KBr): (υ_{max}): 3412, 2922, 2852, 1747, 1710, 1587, 1251, 1147, 1019, 850, 738, 648 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.20–8.10 (m, 2H), 7.95–7.89 (m, 2H), 6.90 (d, $J = 1.8$ Hz, 2H), 6.20 (t, $J = 1.7$ Hz, 2H), 3.82 (br, s, 1H). LC–MS: *m/z*: 212 $(M + 1)^+$ **(3i) 8-Methyl-11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxaline**: Solid, mp 191–193 °C, IR (KBr): (υ_{max}): 2922, 2852, 1743, 1631, 1462, 1335, 1258, 1090, 1036, 876, 726 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.22 (d, $J = 7.5$ Hz, 1H), 7.90–7.81 (m, 2H), 7.62–7.51 (m, 4H), 6.67 (t, $J = 1.6$ Hz, 2H), 6.18 (t, $J = 1.5$ Hz, 2H), 6.15 (s, 1H), 260 (s, 3H). LC–MS: *m/z*: 298 $(M + 1)^+$.

Acknowledgment

RJ and UVSR thank CSIR, New Delhi for the award of fellowship.

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