NOVEL ROUTE FOR THE SYNTHESIS OF 3-(PYRROL-1-YL)-INDOLIN-2-ONES IN AQUEOUS MICELLAR MEDIUM

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GRAPHICAL ABSTRACT

Abstract A high-yielding environmentally benign protocol has been developed for the synthesis of 3-(pyrrol-1-yl)-indolin-2-ones from the reaction of isatin and trans-4-hydroxy-L-proline in aqueous micellar medium. The method is operationally simple and more effective than the previous methods in terms of the yield of the products and the reaction time.

Keywords Isatin; micelle; 3-(pyrrol-1-yl)-indolin-2-ones; reactions in water

INTRODUCTION

In recent years, synthetic organic chemists have shown considerable interest in performing organic reactions in water[1–4] because it is abundant in nature, has virtually no cost, and is safest among all available solvents, thus leading to environmentally benign chemical processes.[5,6] The basic problem in performing reactions in water is that many organic compounds are hydrophobic and insoluble in water. The

Received August 1, 2013.
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development that has contributed to some extent to overcome this problem is the introduction of aqueous surfactant solutions in the form of micelles\[7\] as the reaction medium. The solubilization of water-insoluble reactants and products inside the micelles results not only in high concentration within the small volume but also in different orientations of the soluble molecules that influence the reaction mechanism, resulting in remarkable differences in reaction rate as well as selectivity.\[8\]

In recent times, 3-pyrrolyl indolin-2-ones have received much attention because they possess various biological potentials,\[9,10\] and are broadly used in material science.\[11\] The varied biological activities of 3-pyrrolyl indolin-2-one derivatives have attracted the attention of organic chemists, and a number of synthetic methodologies have been developed for this system.\[12–16\] Despite the availability of different methodologies, for the synthesis of 3-pyrrolyl indolin-2-ones derivatives there remains scope for the development of green protocols with greater efficiency and simpler operation, as one of the recent challenges in organic synthesis is the demand for novel green methodologies that afford products of structural complexity in fewer synthetic steps and from simple starting materials. In the present communication we have developed a green protocol for the synthesis of 3-pyrrolyl indolin-2-ones from the reaction of isatin and trans-4-hydroxy-L-proline in aqueous micellar medium using cetyltrimethylammonium bromide (CTAB) as surfactant.

### RESULTS AND DISCUSSION

Our study commenced with the reaction of isatin (1a) and trans-4-hydroxy-L-proline (2) in the absence and presence of various surfactant in water. The results (Table 1) reveal that reactions carried out in the absence of a surfactant were ineffective even up to 24 h (Table 1, entry 1). An encouraging change in the outcome, however, was noticed when 50 mM of CTAB (cmc 0.92 mM\[17\]) was introduced in the system. Carrying out the reaction in water at 80°C for 30 min now ensured its completion (monitored by thin-layer chromatography, TLC) but obtained poor yield (15%) of the product 3a. The structure of the product was determined from NMR, Fourier transform infrared (FTIR), and electrospray ionization (ESI)–mass spectra studies.

To increase the yield of 3a, we then used greater amounts of the surfactant. Use of 60 or 70 mM CTAB indeed improved the product yield. The most striking result (98%) was obtained when the reaction was performed using CTAB at 80 mM concentration (Table 1, entry 5). However, no significant increase in the yield was observed on enhancement of concentration of CTAB beyond 80 mM (Table 1, entries 6 and 7). Also, extension of the reaction time did not improve the yield of the products. After changing to other surface active agents, the reaction yielded only 55% of the product 3a (Table 1, entry 8) with sodium dodecylsulfate (SDS: cmc value 8.1 mM\[18\]) and 85% (Table 1, entry 9) with tetradecyltrimethylammonium bromide (TTAB: cmc value 3.8 mM\[19\]), both at the concentration of 80 mM.

Even the use of a nonionic surfactant like Triton X-114 (cmc 0.28 mM\[20\]) proved less effective than CTAB (Table 1, entry 10). The plausible mechanism for the formation of 3a in aqueous micellar medium is depicted in Scheme 1. In micellar...
Table 1. Effects of the different surfactants on the yield of 3a

| Entry | Surfactant | Concentration (mM) | Yieldb (%) |
|-------|------------|--------------------|------------|
| 1     | None       | —                  | NRc        |
| 2     | CTAB       | 50                 | 15         |
| 3     | CTAB       | 60                 | 35         |
| 4     | CTAB       | 70                 | 75         |
| 5     | CTAB       | 80                 | 98         |
| 6     | CTAB       | 90                 | 98         |
| 7     | CTAB       | 100                | 98         |
| 8     | SDS        | 80                 | 55         |
| 9     | TTAB       | 80                 | 85         |
| 10    | Triton X-114 | 80        | 65         |

aReactions performed using 1a and 2 in water at 80 °C for 30 min.
bYield of isolated pure product.
cNo reaction.

Scheme 1. Plausible mechanism for the formation of 3a.
media where the reactants 1a and 2 are in very close proximity, so thus a condensation reaction took place between the amino group of 2 to the carbonyl group of 1a, forming an iminium ion as intermediate A, which can readily decarboxylate to give intermediate B, perhaps via an eight-membered ring in which the hydrogen of the -COOH group becomes the hydrogen of the enol -OH at the C2,C3 position. Next, the intermediate B dehydrates to give intermediate C. Finally, the intermediate C tautomerizes to give the most stable product 3a to enjoy aromatic character. These compounds in acetonitrile exhibited fluorescence at room temperature upon excitation at 290 nm with emission maximum \( \lambda_{\text{em}} \) in the range of 360–371 nm and the calculated quantum yield (QY) in the range of 0.12–0.16.

To establish the generality and scope of this new methodology under the optimized conditions (80 mM CTAB, 80 °C, 30 min), we used various derivatives of isatin. The yields obtained were excellent and the results are summarized in Table 2.

Table 2. Yields of 3-(pyrrol-1-yl)-indolin-2-ones 3a–j from the reaction of variously substituted isatins 1a–j and trans-4-hydroxy-L-proline 2 in aqueous micellar medium

| Entry | Isatin 1 | 3-(Pyrrol-1-yl)-indolin-2-ones 3<sub>a–j</sub> | Yield<sup>b</sup> (%) | \( \lambda_{\text{ex}} \) at 290 nm | \( \lambda_{\text{em}} \) (QY) |
|-------|----------|---------------------------------|-----------------|---------------------------------|-----------------|
| 1     | 1a       | 3a (1a,3a:R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = R<sup>5</sup> = H) | 98              | 360 (0.12)                      |                 |
| 2     | 1b       | 3b (1b,3b:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H, R<sup>3</sup> = I) | 96              | 364 (0.14)                      |                 |
| 3     | 1c       | 3c (1c,3c:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H, R<sup>3</sup> = F) | 98              | 367 (0.15)                      |                 |
| 4     | 1d       | 3d (1d,3d:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H, R<sup>3</sup> = Cl) | 95              | 366 (0.14)                      |                 |
| 5     | 1e       | 3e (1e,3e:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H, R<sup>3</sup> = Br) | 98              | 370 (0.16)                      |                 |
| 6     | 1f       | 3f (1f,3f:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H, R<sup>3</sup> = Me) | 96              | 365 (0.12)                      |                 |
| 7     | 1g       | 3g (1g,3g:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = H, R<sup>3</sup> = NO<sub>2</sub>) | 95              | 368 (0.16)                      |                 |
| 8     | 1h       | 3h (1h,3h:R<sup>1</sup> = R<sup>2</sup> = R<sup>4</sup> = H, R<sup>3</sup> = R<sup>5</sup> = Me) | 98              | 371 (0.15)                      |                 |
| 9     | 1i       | 3i (1i,3i:R<sup>1</sup> = R<sup>3</sup> = R<sup>4</sup> = H, R<sup>2</sup> = R<sup>5</sup> = Cl) | 96              | 369 (0.16)                      |                 |
| 10    | 1j       | 3j (1i,3i:R<sup>1</sup> = Bn, R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = R<sup>5</sup> = H) | 98              | 365 (0.13)                      |                 |

<sup>a</sup>Reaction conditions: isatin (1 mmol), trans-4-hydroxy-L-proline (1 mmol), water (50 ml), CTAB (4 mmol), 30 min at 80 °C.

<sup>b</sup>Yield of isolated pure products.
CONCLUSION

In summary, we have developed a simple, efficient, single-step method for the synthesis of 3-(pyrrol-1-yl)-indolin-2-ones in aqueous micellar medium. These molecules present a privileged core from a biological point of view. Also, we report here that the reaction of isatin and trans-4-hydroxy-L-prolin in the presence of CTAB is a high-yielding environmentally benign protocol. Efforts to expand the scope of the method in combination with its application to the synthesis of biologically active molecules are ongoing in our laboratory.

EXPERIMENTAL

IR spectra were recorded on a Jasco FTIR instrument (model 410) in KBr pellets. ESI-MS (positive) was conducted using a LC-ESI-Q-TOF micromass spectrometer. $^1$H and $^{13}$C NMR spectra were taken on a Bruker 300-MHz DPX spectrometer at 300 and 74.99 MHz respectively, with tetramethylsilane (TMS) as internal standard, and the chemical shifts are reported in $\delta$ units. Fluorescence spectra were obtained using a Hitachi F-2500 instrument.

A mixture of isatin derivative (1.0 mmol), trans-4-hydroxy-L-proline (0.131 g, 1 mmol), and CTAB (4 mmol) in water (50 mL) was stirred at 80°C for 30 min. After completion of the reaction (monitored by TLC), the contents were filtered and the residue was washed thoroughly with water until free from CTAB. Finally, the residue was crystallized from a chloroform–petroleum ether mixture to afford the desired products in excellent yields. The characterizations of the products were accomplished by spectroscopic analysis ($^1$H, $^{13}$C NMR, FTIR, and ESI-mass) and also by comparison of the data reported in the literature.

FUNDING

This research work was supported by Council of Scientific and Industrial Research (CSIR) and West Bengal State Council of Technical Education (WBSCTE), India.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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