A new entry to synthesis of neocryptolepine related skeletons. An unexpected behavior of 3-acety-2-ethoxyindole and isatins

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**ABSTRACT**

An unexpected and intriguing reaction to the direct construction of indolo[2,3-b]quinoline ring system of neocryptolepine analogues was discovered through simple heating of 3-acetyl-2-ethoxyindole with isatins in 10% aqueous ethanol media with the presence of KOH as the base. The process is very clean and avoids the use of toxic organic solvent, thereby enhancing the greenness of the transformation. Moreover, the newly-synthesized compounds bearing a pendant carboxyl group at the C-11 position of indolo[2,3-b] quinoline skeleton could be potentially applied as useful synthetic building blocks for more complex indolo[2,3-b]quinoline alkaloid derivatives.

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structurally new indolyl substituted quinoline 4-carboxylic acid hybrids. With this idea in mind, we started this study by conducting the reaction of 3-acetyl indole (1, 1.0 equiv) with 5-bromoisatin (2h, 1.5 equiv) in water following our reported method. However, in this case the use of pure water as the medium appeared not so useful herein, and the reaction scarcely proceeded monitored by TLC, presumably due to its less dissolving power. We found that the use of 10% aqueous solution of ethanol circumvented this issue well. However, surprisingly, our proposed Pfitzinger reaction of 1, by taking advantage of the presence of the acetyl group at the 3-position, displayed a different reactivity pattern with 5-bromoisatin (2h) wherein the predicted indolyl substituted quinoline 4-carboxylic acid 3h was not observed and instead, an interesting polycyclic fused indolo[2,3-b]quinoline system 3h bearing a pendant carboxyl group as the major product was formed via an unprecedented pathway as shown in Scheme 2.

The structure of the unexpected product 3h was confirmed unambiguously by its spectral data and X-ray diffraction analysis. The main feature of its 1H NMR spectrum showed no signals attributable to the ethoxyl protons of its precursor 1, along with the presence of a total count of 7 aromatic protons between 7.35 and 8.27 ppm. A single crystal for 3h was obtained by gradual evaporation from ethanol solution at room temperature, and the corresponding ORTEP representation of the structure 3h is shown in Figure 1, which displayed the newly synthesized compound 3h was a linear co-planer tetracyclic fused indolo[2,3-b]quinoline system containing a carboxylic acid substituent at the C-11 carbon along with a bromine substituent at 2 position.

Since the unexpected discovery encountered during our preparations was highly valuable in view of the synthetic and medicinal importance of the tetracyclic fused indolo[2,3-b]quinoline system, we therefore, decided to modulate the reaction to furnish the fused indolo[2,3-b]quinoline products. At this stage, we further investigated the aqueous reaction by varying the amount of EtOH in the EtOH-H2O system or using some phase-transfer catalysts such as BTEAC and TBAB in pure water. We found that no further improvement in the product yield was observed, and the use of 10% aqueous solution of ethanol was most suitable to provide maximum yield. To show the effect of 10% aqueous solution of ethanol, additional experiments using different organic solvents such as EtOH, MeOH, DMF, or MeCN were conducted. However, the 1H NMR spectrum of the reaction mixture showed that no desired product was observed. These attempts suggested to us that 10% aqueous ethanol as the solvent is not only inexpensive and environmentally benign, but also showed its unique superiority over organic solvents in this reaction. Due to the satisfactory yield obtained and in order to retain the simplicity of the procedure, no further optimization in reaction conditions was necessary and the above mentioned condition was chosen for the following work.

Thereafter, the interesting discovery promoted us to further investigate the viability of the transformation. Thus, the reaction was tested with other substituted isatins (2a–g) in a similar fashion. To our delight, analogous reactions occurred with 1, invariably leading to the formation of the corresponding 6-methyl-6H-indolo[2,3-b]quinoline 11-carboxylic acids (3a–g) as expected in the yields ranging 69–78%. The results of this series of experiments are listed in Table 1.

As shown in Table 1, in most cases, no significant difference in the reaction outcome was observed for the electronic nature of the substituents on these examined isatins. Moreover, functional substituents, such as F, Cl, and Br, were compatible under the reaction conditions, which could be further transformed into other functionalities. To the best of our knowledge, no examples of such heterocyclic structures have been reported in the literature so far.

Mechanistically, the exact details of how the one-step reactions proceed still remain unclear and elusive. Taking into consideration the entire outcome, a tentative explanation is given as shown in Scheme 3 using isatin as an example. Isatin was firstly transformed into 2-(2-aminophenyl)-2-oxoacetate under the action of KOH, which was presumably underwent the condensation reaction with 3-acetyl-2-ethoxyl indole to afford the fused indolo[2,3-b][1]benzazocine-5-carboxylate (1). This might be followed by the base mediated tautomerization to give the enol form II. Subsequently, we hypothesized the resulting II might have the intramolecular

Scheme 2. Unexpected reaction between 3-acetyl-2-ethoxyl-N-methylindole and 5-bromoisatin.
electrocyclic reaction by invoking the help of ambient light, because such \( \alpha, \beta \)-unsaturated carbonyl moiety in II is very easily photoexcited, leading to the generation of the transient reactive intermediate III. In addition, we speculated that the substituent of II may also have a positive influence on the rate of the thermal pericyclic reaction. The inherent ring strain present in the formed polycyclic-fused system III rendered it amenable to strain-releasing reaction at the refluxing temperature, resulting in the cleavage of the cyclobutanone ring. Thus, the unexpected indolo[2,3-b]quinoline moiety might be obtained via a tandem electrocyclic reaction/thermal ring cleavage sequence.

Considering the ambient light irradiation might involve in the reaction, we further designed two parallel experiments under the tungsten light irradiation and dark condition, respectively, in order to gain some insight with regard to the possible reaction mechanism. Based on the experimental results we found that the use of tungsten light irradiation indeed resulted in an increase in the reaction yield, and a 5% improvement in yield of 3a was achieved when we placed a 100 Watt tungsten bulb 5 cm from the flask. Moreover, the time required for the formation of the product was also comparatively reduced to half of its original cost. On the other hand, upon the same reaction was conducted under dark conditions, the reaction did not proceed satisfactorily, and the reaction mixture showed a combination of starting materials and numerous products, in which the desired product was detected only in negligible amount that did not warrant isolation. Such results may adequately support our hypothesis that ambient light might play a role in the rate and the product.

Although these attempts have been made, the present explanation is still in its infancy, and difficulties are encountered in the isolation of reactive intermediates, since they are present in very low concentrations in the reaction mixture and usually react further during isolation. Further research to explore its reaction mechanism represents an intriguing goal that we are currently contemplating, and now the investigations concerning the detailed mechanistic studies by capturing the key intermediate and providing adequate proof-of-concept are ongoing in our laboratory.

In summary, a new, simple, and environmentally safe procedure for the synthesis of 6-methyl-6H-indolo[2,3-b]quinoline-11-carboxylic acids through the unexpected reaction of 3-acetyl-2-ethoxyindole with isatins has been described. This method, that combined the synthetic efficiency of one-pot consecutive process in a single synthetic operation with the environmental benefits of the reaction medium, could be considered as an excellent strategy for the construction of the interesting indolo[2,3-b]quinoline framework. Moreover, taking into account the presence of carboxyl functional group on the indolo[2,3-b]quinoline ring, these molecules could be potentially applied as useful synthetic building blocks for the development of more complex indolo[2,3-b]quinoline alkaloid derivatives. Work is currently ongoing to extend its scope by exploring its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield/( % ^{a} )</th>
<th>mp/( ^{\circ} )C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>77</td>
<td>279–281</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>74</td>
<td>289–290</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>78</td>
<td>298–299</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>71</td>
<td>292–293</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>69</td>
<td>&gt;300</td>
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<td>6</td>
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<td>72</td>
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<tr>
<td>7</td>
<td>3g</td>
<td>70</td>
<td>&gt;300</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>74</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

\( ^{a} \) Reaction conditions: substrate 1, isatin 2 (1.5 equiv), KOH (14 equiv).

\( ^{b} \) Isolated yields.
Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.019.

References and notes
