

# An Efficient, Green Synthesis of Hemiaminals of Isatins using TBAF under Aqueous Reaction Media

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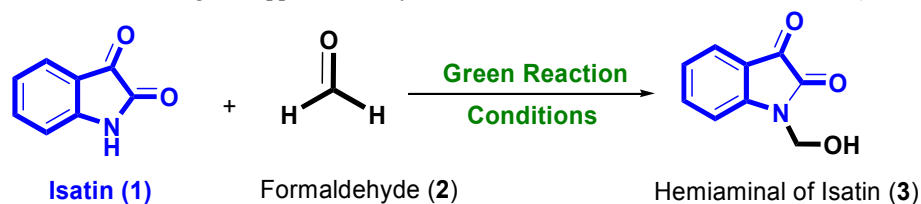
**Abstract:** The synthesis of hemiaminals of isatin derivatives is described by the reaction of isatin with formaldehyde in the presence of TBAF in water at ambient temperature. The procedure is very simple, convenient, and efficient, which provides high yield of product. Additionally the method is applicable for both varieties of substituted isatins derivatives. Moreover, the environmentally benign nature of reaction media makes the procedure attractive alternative over earlier methods.

**Keywords:** Hemianials, Isatin, TBAF, Water, Green Synthesis

## I. INTRODUCTION

Hemiaminal is a chemical compound which has a hydroxyl group and an amine attached to the same carbon atom. It is also known as carbinolamine. The literature shows that, some hemiaminals possess different biological activities such as anti-tumor activity<sup>1</sup>. The hemiaminals isatin derivative showed an improved therapeutic index.<sup>2</sup> In addition to this hemiaminals of indole and related N-heterocycles serve as labile precursor for insitu generation of formaldehyde<sup>3,4</sup> and a self-cleavable linker for drug molecules to improve their bioavailability.<sup>5</sup> Hence, synthesis of hemiaminals of isatin derivatives is desirable. The reported conventional methods used to prepare hemiaminals involve the addition of formaldehyde or paraformaldehyde to the amines under strong basic condition. These methods affords lower to moderate yield (34–70%) even at higher temperature (100 °C).<sup>1,2,6</sup> The deprotection of N-[2-(trimethylsilyl)ethoxy]methylamine (SEMNR<sub>2</sub>) or benzyloxymethylamine (BOM-NR<sub>2</sub>) also afford hemiaminals as byproducts.<sup>7,8</sup> The two step method reported by Hou et al. Include synthesis and reduction of carbamates.<sup>9</sup>

Nowadays the concept of green chemistry is well acknowledged in in industry and academic practices. The international chemical community is trying to alter current working practices and to find greener alternatives. Greener approaches provide transformations that are mild and environmentally benign.<sup>10,11</sup> A green protocol can be considered as a reduction in costs, waste, energy, materials consumption, risks and hazards.<sup>12</sup> As many advantages are associated green synthesis, we envision the green approach for synthesis of hemiaminals of isatin derivatives (**Scheme 1**).



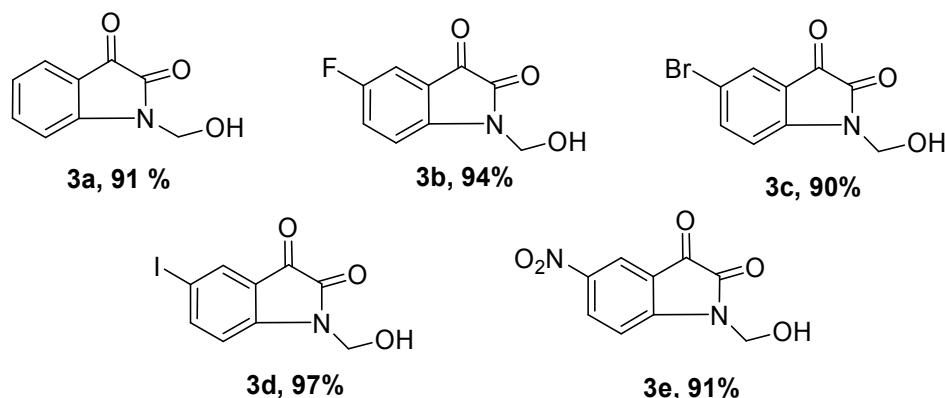
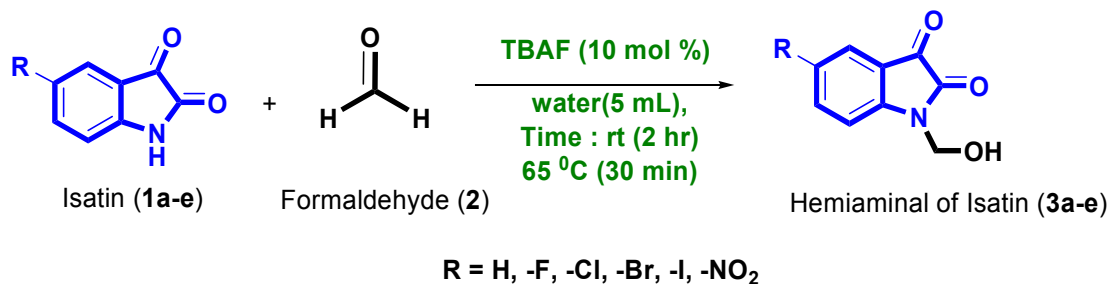
**Scheme 1:** Envisioned green approach for synthesis of hemiaminals of isatin derivatives

Recently, aqueous reaction medium has gained importance as an essential component of the development of sustainable chemistry.<sup>13,14</sup> not only because water is the most abundant, cheapest, and environmentally friendly solvent but also because water exhibits unique reactivity and selectivity, compared to organic solvents. Likewise, tetrabutylammonium fluoride (TBAF) has emerged as a versatile green reagent for fluoride-assisted reactions,<sup>15</sup> deprotection of silyl groups,<sup>16</sup> desilylation,<sup>17</sup> and fluorination.<sup>18</sup> Moreover, it has also been widely used for a variety of

base-catalyzed reactions such as alkylation, elimination, Michael addition, and aldol condensation.<sup>19</sup> In continuation of our work<sup>20</sup> on exploration of isatins in different reactions, we envisioned the direct synthesis of hemiaminals of isatin derivatives with formaldehyde might readily proceed with TBAF in water under certain appropriate reaction conditions.<sup>21</sup> Herein, we wish to report the synthesis of hemiaminals of indole and isatin derivatives utilizing TBAF in water as reusable reaction media at ambient temperature.

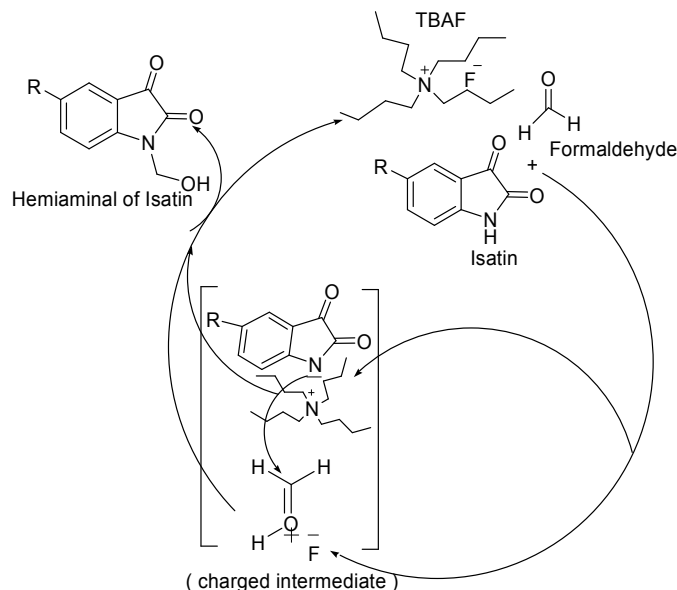
## II. RESULTS AND DISCUSSIONS

Earlier we have explored<sup>22</sup> that 10 mol% TBAF can be effectively utilized for the synthesis of hemiaminal of indoles by the reaction of indole (1 mmol) with formaldehyde (1 ml, 37% aqueous solution) in water (5 ml) at rt/ 65°C. With this rationale, we decided to test the reaction of 5-Iodoisatin (1 mmol) with formaldehyde (1 ml, 37% aqueous solution) in the presence of 10 mmol% TBAF in water (5 ml) at room temperature. We were surprised to observe that, the reaction worked very well under this condition to afford 97% isolated yield of the desired hemiaminal of 5-Iodoisatin in 2 hr reaction time. When the same reaction was conducted at 65 °C, the reaction time was reduced to 30 minute without compromising the yield of the reaction. With this reaction conditions in our hand, we decided to test the scope of this with different substituted isatins to get respective hemiaminals. Various substituted isatins with different electronic group at various positions reacted successfully to afford the desired products **3a – 3e** in excellent yields (90-97%) as shown in **Scheme 2**.



**Scheme 2:** Synthesis of hemiaminal of different substituted isatins

A possible mechanism for the formation of hemiaminals of isatin is shown in the scheme 3. We presume that TBAF react with both isatin and formaldehyde to give two charged intermediate species. This two intermediate species react quickly with each other to furnish the required product. We assume that because of such dual activation of both nucleophile (isatin) and electrophile (formaldehyde) by TBAF, reaction proceed faster to give high yields of hemiaminals with the regeneration of TBAF (**Scheme 3**).



**Scheme 3:** Plausible mechanistic pathway of formation of hemiaminal of isatins

### III. EXPERIMENTAL

#### 3.1 General Procedure for Synthesis of Hemiaminal of Isatins

Isatin (1 mmol) and formaldehyde (1ml, 37 % aqueous solution) were combined with 5 ml water in a closed round bottomed flask equipped with a stir bar. Tetrabutylammonium fluoride (10 mol %) was added to above reaction mixture. Reaction was allowed to stir vigorously at room temperature for 2 hr (or at 65 °C for 30 min). After complete conversion as indicated by TLC, the reaction mixture was extracted with 1:1 ethyl acetate:Hexane (3 x 6 ml). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. The resulting crude product was further purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate:hexane, 1:3-1:2 solvent system) to afford the pure hemiaminals of isatin derivative.

#### 3.2 Spectral Data for Selected Compounds

**5-fluoro-1-(hydroxymethyl)indoline-2,3-dione (3b)** : red solid, mp 122-124 °C; <sup>1</sup>H NMR (300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 7.44-7.23 (m,3H), 6.33 (t, *J* = 6.8 Hz, 1H [for OH]), 5.11 (d, *J* = 6.8 Hz,2H); <sup>13</sup>C NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>SO ) : δ 183.01,160.55, 157.41, 157.29, 146.49, 124.86, 124.54, 117.82, 117.73, 113.21, 113.13, 111.50, 111.18, 63.24; IR (KBr) ν = 3395.59, 2933.09, 2863.47, 1734.50, 1612.08, 1333.27, 1046.39, 749.44 cm<sup>-1</sup>. MS (ESI) *m/z* 218 (M+ Na)<sup>+</sup>.

**1-(hydroxymethyl)-5-iodoindoline-2,3-dione (3d)** : Orange solid, mp 265-268 °C; <sup>1</sup>H NMR (300 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 7.89 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.83 (d, *J* = 1.5 Hz, 1H), 7.06 (dd, *J* = 1.5, 8.3 Hz, 1H), 6.29-6.19 (m, 1H [for OH]), 5.13 (d, *J* = 7.4 Hz,2H); <sup>13</sup>C NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>SO ) : δ 184.51,165.52, 141.29, 138.62, 133.31, 130.68, 113.11, 84.61, 66.39; IR (KBr) ν = 3385.69, 2923.19, 2853.57, 1724.60, 1602.18, 1323.37, 1036.49, 831.76 cm<sup>-1</sup>. MS (ESI) *m/z* 326 (M+ Na)<sup>+</sup>.

### IV. CONCLUSION

In conclusion, we have developed a novel, highly efficient, procedure for the synthesis of hemiaminal of isatin derivatives by using TBAF in water as green reaction media. This method is bestowed with merits like simple, mild, high yield, cost effectiveness, and environmentally benign nature. The reaction system can be successfully applied to a variety of substituted Isatins to give respective hemiaminals in good to excellent yield.

**ACKNOWLEDGMENT:**

The authors Pramod B. Thakur and Rupashri K. Kadu thankful to Hon. Principal, Dr. Ganesh A. Thakur for their support & encouragement and providing a research facility at Rayat Shikshan Sanstha's, Mahatma Phule Arts, Science & Commerce College, Panvel, District-Raigad, Navi Mumbai, Maharashtra.

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