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DABCO Catalyzed Efficient Addition of Acetyl Acetone on Isatins Under Neat Condition to Afford 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl) indolin-2-one Derivatives

Pramod B Thakur
Department of Chemistry
Rayat Shikshan Sanstha's, Mahatma Phule Arts, Science & Commerce College, Panvel, Navi Mumbai, Maharashtra
pramod.chem.research@gmail.com

Abstract: *We have demonstrated DABCO catalyzed efficient addition of Acetyl acetone on isatins under neat condition to afford 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one derivatives. The developed method as found applicable for different structurally diverse isatin electrophiles which has tolerated different functional groups in the reaction to afford Aldol addition products with high isolated yields. The use of green organocatalyst DABCO, mild reaction conditions and catalyst-free nature under neat conditions makes the procedure interesting alternative over the previous methods. Moreover the present protocol provides rapid and easy access for functionally diverse 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl) indolin-2-one derivatives, which might be useful for further chemical transformations to prepare a variety of compounds desirable for different applications.*

Keywords: Isatin, Acetyl acetone, DABCO, 3-Hydroxy oxindole, 3-hydroxy-3-((*E*)-2-hydroxy-4-oxopent-2-enyl) indolin-2-one

I. INTRODUCTION

A natural product contains diversely functionalized structural frameworks which possess wide varieties of biochemical properties [1]and function in a highly controlled manner [2], [3]. Consequently, many natural products have explored as a promising leads for drug discovery [4] –[7] Amongst the dome of natural products, 3-hydroxy oxindoles is an alkaloid class of natural product which possess unique structural diversity and biochemical properties [8]–[10] Additionally, this framework is also being used as key intermediates in the complex natural product synthesis. Due to such distinct biochemical properties associated with 3-hydroxy oxindoles, excellent review articles [11]–[16] have been published on this framework. Figure 1 shows the representative examples of natural products and pharmaceutical important molecules possessing 3-hydroxy oxindole structural frameworks.

The aldol reaction [17] is one of the most important C-C bond formation reactions of carbonyl compounds in organic synthesis. In aldol reaction, addition of carbanion based nucleophile to isatin is commonly used approach for the synthesis of 3-substituted 3-hydroxy oxindoles. Among the various nucleophiles, enolizable ketones[18] aldehydes [19] and esters[20]have been explored extensively with isatins to afford 3-hydroxy oxindoles framework. Additionally,1,3-dicarbonyls are well recognized as simple, easily available and versatile starting material in the chemical synthesis for the efficient construction of diversely functionalized complex molecular system [21]Aldol addition of 1,3-diketone to different electrophiles is useful reaction in the chemical transformation. However only two reports are available on the addition of 1,3-diketone like Acetyl acetone on isatins to afford 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one. Both of these reported methods are useful but have few drawbacks like a need of specially designed catalyst, longer reaction time [22] or use of Microwave irradiation [23]. The 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl) indolin-2-one is a structurally diverse framework which have been explored as a useful precursor to prepare a variety of

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compounds [22]. Due to such usefulness of 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one framework, we decided to develop green protocols for the synthesis of this compound. In the context of Green Chemical processes, 1,4-Diazabicyclo[2.2.2]octane (DABCO)has been efficiently used as a green catalyst in different reactions [24-25].

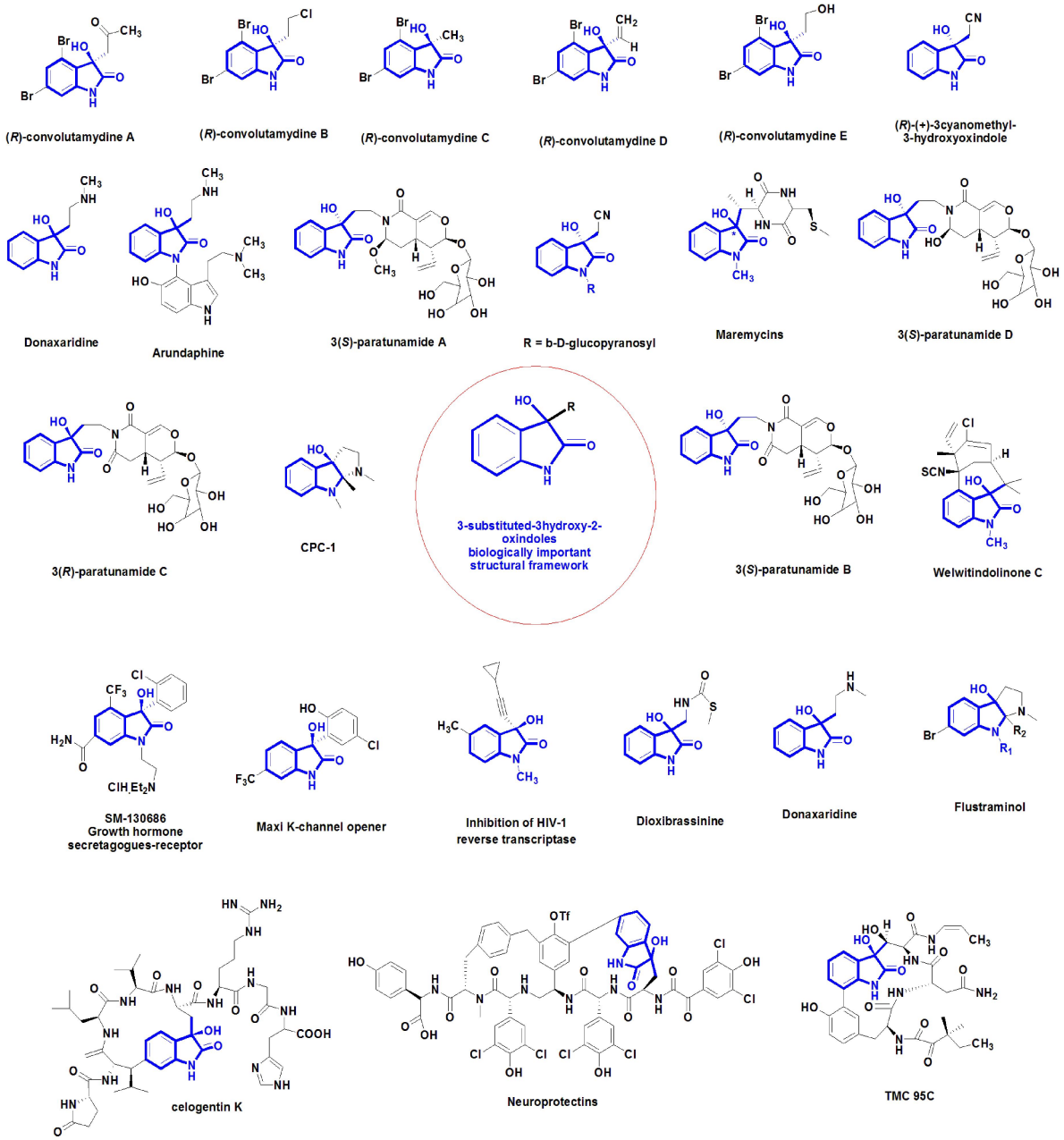

Figure 1: Representative examples of natural products and pharmaceutical important molecules possessing 3-hydroxy oxindole structural frameworks.

In the continuation of our work on green synthesis of 3-hydroxy oxindoles framework[26-32], we decided to explore DABCO for the synthesis of 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one. To the best of our knowledge, DABCO was not used under neat condition to afford 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-ones. In this context, we herein report the DABCO catalyzed efficient addition of Acetyl acetone on isatins under neat condition to afford 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one derivatives.

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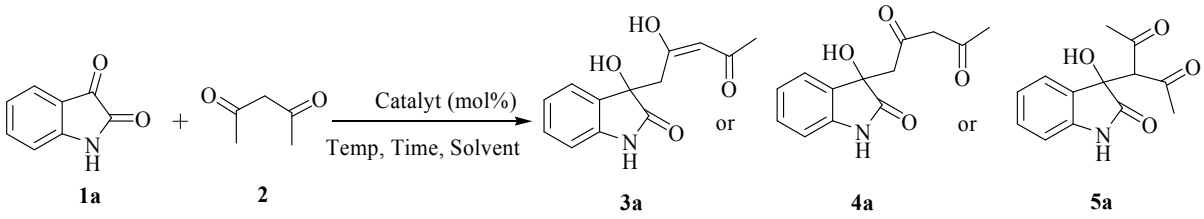
II. Results and Discussions

In the context of Green chemistry, we begin our work with testing of the reaction of isatin electrophile with acetyl acetone in the presence of green organocatalyst DABCO. Firstly we treated 1 mmol isatin (**1a**) with stirred solution of 1.5 mmol Acetyl acetone (**2**) in 0.5 ml of Ethyl acetate in the presence of 10 mol% of catalyst DABCO (Table 1, entry 1). However, the formation of expected γ-addition enol product **3a** was not observed even after stirring the reaction mixture up to 24 hr. In contrast, the γ-addition keto product **4a**was formedwith11% yield (Table 1, entry 1). Even after increasing the catalyst amount to 20 mol % the desired product **3a** was not obtained, but the increase in yield of **4a** was observed (Table 1, entry 2). Our objective was to synthesize 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one by reaction of isatin (**1a**) and acetyl acetone (**2**). So, we decided to explore the reaction of isatin (**1a**) and acetyl acetone (**2**) under different reaction conditions. In this regard, we assume that, as Acetyl acetone is a liquid compound it make works as a reactant as well as medium in this reaction. Hence, next, we tested the reaction of 1 mmol isatin (**1a**) and 1.5 mmol Acetyl acetone (**2**) under a neat conditionin the absence of catalyst (Table 1, entry 3). In this case we observed the formation of any compound even after stretching the reaction time up to 24 hr (Table 1, entry 3). However, when we added 10 mol % DABCO in the reaction of 1 mmol isatin (**1a**) and 1.5 mmol Acetyl acetone (**2**) under neat condition, we obtain the 56% yield of desired product **3a** (Table 1, entry 4). Encouraged by the above results, next we increased the catalyst amount to 15 mol% to check its effect on reaction (Table 1, entry 5). We were happy to see that significant improvement in the yield of the desired product **3a**.The further increase in the yield up to 89 % of the desired product **3a** was observed with 20 mol% DABCO (Table 1, entry 6). When we tested the reaction of 1 mmol isatin (**1a**) and 1.5 mmol Acetyl acetone (**2**) under a neat condition in the presence of 30 mol % of catalysts, the 91 % yield of the desired product **3a** was obtained after 8 hr of reaction time (Table 1, entry 7). However a further increase in the catalyst amount did not result in to significant improvement in the reaction efficiency (Table 1, entry 8). Hence, we have selected the use of 30 mol% DABCO in the reaction of 1 mmol isatin (**1a**) and 1.5 mmol Acetyl acetone (**2**) under a neat condition as an optimized reaction condition to afford the desired product desired product **3a** (Table 1, entry 7).



1a **2** **3a** **4a** **5a**

Scheme 1: Optimization of Reaction Condition

Table 1: Optimization of Reaction Condition[a]

Entry	Solvent (ml)	Temperature	Catalyst (mol %)	Time (hr)	Yield[b](%) 3a/4a/5a
1	Ethyl acetate (0.5)	RT (28 °C)	DABCO (10 mol%)	24	00/11/00
2	Ethyl acetate (0.5)	RT (28 °C)	DABCO (20 mol %)	24	00/23/00
3	*Neat*	RT (28 °C)	—	24	00/00/00
4.	*Neat*	RT (28 °C)	DABCO (10 mol %)	24	56/00/00
5.	*Neat*	RT (28 °C)	DABCO (15 mol %)	24	72/00/00
6.	*Neat*	RT (28 °C)	DABCO (20 mol %)	24	89/00/00
7.	***Neat***	**RT (28 °C)**	**DABCO (30 mol %)**	**08**	**91/00/00**
8.	*Neat*	RT (28 °C)	DABCO (40 mol %)	08	92/00/00

[a]Reaction Condition: Isatin **1a** (1mmol) was reacted Acetyl acetone 2 (1.5 mmol)under different conditions.[b]By ^{1}H NMR analysis of crude products.

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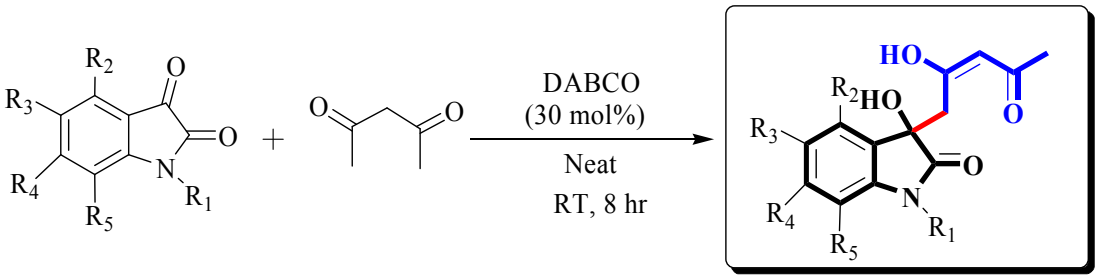
With this established condition in our hand, we have tested the substrate scope of this reaction with different isatin electrophiles and Acetyl acetone nucleophiles and the results are summarized in **Table 2**. We screened Acetyl acetone **2** with different substituted isatins **1**(**a-h**) under standard reaction conditionas given in **Table 2**andshown in **Scheme 2**. It was observed that all the screened 5-halogen substituted isatins **1**(**b-d**) reacted smoothly with Acetyl acetone to afford desired products **3**(**b-d**)in good yields (**Table 2**, entry 2-4). The 5-nitro isatin was also reacted efficiently under optimized reaction condition (**Table 2**, entry 5). Further, we have also screened few di-substituted isatins in this reaction which were found equally efficient (**Table 2**, entry 6-7). The *N*-substituted isatin like *N*-Phenyl isatin was also tested in this reaction which have afforded 81% isolated yield of the desired product (**Table 2**, entry 8). It was delighted to found that the optimized reaction condition worked well on all the structurally varied isatins with Acetyl acetone to provide the diversely functionalized 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one scaffolds within very short period of time under neat reaction condition with 30 mol% DABCO with very good yields.

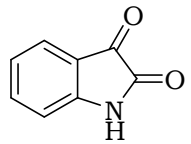
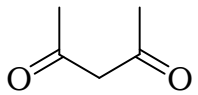
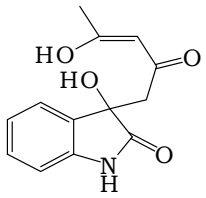
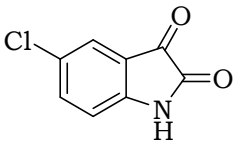
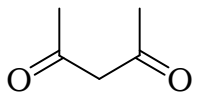
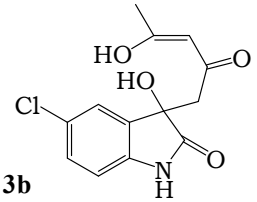
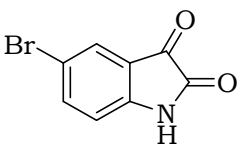
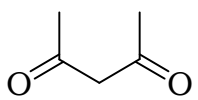
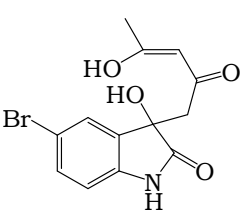


1a-f **2a** **3a-3f**
88-92% Isolated Yields

R_1 = Phenyl, R_2 = -H, -Cl, Me, R_3 = -H, -Cl, -Br, -I, NO_2, R_4 = -H, Me, R_5 = -H, -Cl

Scheme 2: Synthesis of 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one scaffolds under optimized reaction conditions.

Table 2: Substrate scope of reaction of acetyl acetone with isatins under optimized reaction conditions[a]

Entry	Isatin 1(a-f)	Acetyl acetone 2	Product 3(a-f)	Time	Isolated Yield
1.	 **1a**	 **2**	 **3a**	**8 Hr**	**89 %**
2.	 **1b**	 **2**	 **3b**	**8 Hr**	**90 %**
3.	 **1c**	 **2**	 **3c**	**8 Hr**	**90 %**

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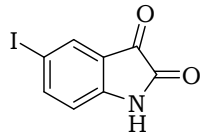
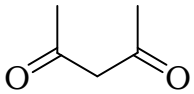
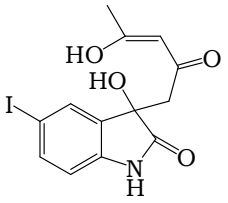
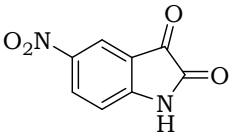
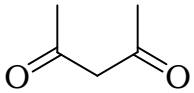
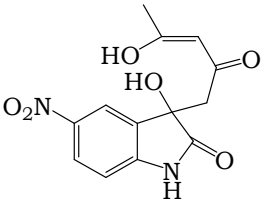
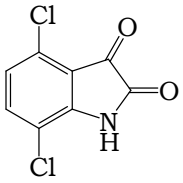
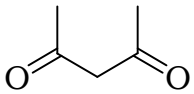
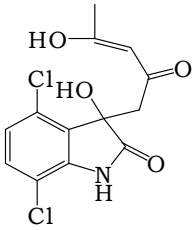
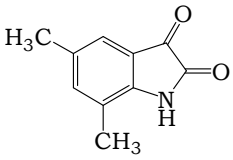
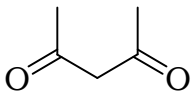
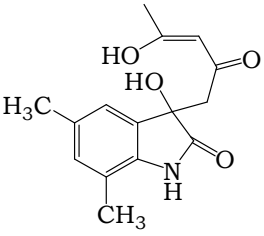
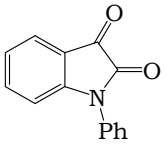
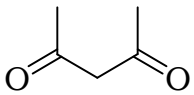
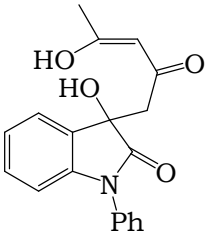
4.	 **1d**	 **2**	 **3d**	**8 Hr**	**91 %**
5.	 **1e**	 **2**	 **3e**	**8 Hr**	**92 %**
6.	 **1f**	 **2**	 **3f**	**8 Hr**	**91 %**
7.	 **1g**	 **2**	 **3g**	**8 Hr**	**88 %**
8.	 **1h**	 **2**	 **3h**	**8 Hr**	**89 %**

[a] Reaction condition: Isatin **1a-f** (1 mmol) with Acetyl acetone**2** (1.5 mmol) in the presence of 30 mol% DABCO under neat condition.

III. Experimental

General procedure for synthesis of 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl) indolin-2-one derivatives:

To the stirred solution of Acetyl acetone (1.5 mmol) and 30 mol % DABCO in the round bottom flask, Isatin (**1a-f**) was added. The resulting reaction mixture was stirred for stipulated time and progress of the reaction was continuously monitored through TLC. After completion of the reaction as indicated by TLC, the reaction, excess of acetyl acetone was evaporated and the resulting mixture was washed with 20 ml cold water to afford crude products. The obtained

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crude products were further purified by short column chromatography (hexane/AcOEt, 1:4-1:1 as eluent) to afford the desired product **(3a-f)**.

Characterization data of 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one, (3a, entry 1, Table 2)

Yield	: 89 %, Time, 8hr
mp	: White solid, mp 132-134 $^{\circ}$C
IR (KBr)	: 3301, 1708, 1617, 1476, 1422, 1330, 1209, 1171, 1050, 774, 656 cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$ + DMSO d_6)	: δ 9.98 (br s, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 5.52 (s, 1H), 2.94 (d, *J* = 3.9 Hz, 2H), 1.97 (s, 3H) ppm
^{13}C NMR (75 MHz, $CDCl_3$ + DMSO d_6)	: δ 189.35, 188.91, 177.67, 141.01, 129.58, 128.35, 123.30, 120.83, 109.08, 100.45, 73.33, 45.02, 23.45 ppm
Mass (ESI)	: *m/z* 248 $[M+H]^+$
HRMS	: calcd. for $C_{13}H_{14}O_4N$ $[M+H]^+$ = 248.09228, found 248.09162.

IV. Conclusion

In conclusion, we have demonstrated practically green, efficient and rapid DABCO catalyzed efficient addition of Acetyl acetone on isatins under neat condition to afford 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one derivatives by using simple, cheap and readily available materials. The method is applicable for different structurally diverse isatins to afford desired products with high isolated yields. Moreover the developed method was found to be efficient, which have tolerated different functional groups in this reaction. The neat reaction condition, efficient green catalyst DABCO, mild reaction conditions and environmentally begin nature makes the procedure interesting alternative over the previous methods. The present protocol provides rapid and easy access for functionally diverse 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl) indolin-2-one derivatives. These molecular frameworks 3-hydroxy-3-((E)-2-hydroxy-4-oxopent-2-enyl)indolin-2-one having diverse functionality which might be useful for further chemical transformations to prepare a library of derivatives desirable for a variety of applications.

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