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Polyethylene glycol (PEG-400): a mild and efficient reaction medium for one-pot synthesis of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones

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ABSTRACT

3-(Pyridylmethyl)-3-hydroxy-2-oxindole derivatives were synthesized in high yields under mild, and catalyst-free conditions using polyethylene glycol (PEG-400) as a solvent. The use of low cost PEG-400 makes it simple, convenient, and environmentally benign.

The 3-hydroxyoxindole nucleus is found in various biologically active molecules such as convolutamydines[1] and TMC-95A[2,3] and also exists in various alkaloids such as donaxaridine,[4] dioxibrassinine,[5] welwitindolinone C[6], and 3-hydroxyglucoisatisin (Fig. 1).[7]

These compounds are known to exhibit potent biological and pharmaceutical activities such as anticancer, anti-HIV, antioxidant, and neuroprotective properties.[8] Indeed, a substituent at C-3 position of the oxindole plays a key role in biological activity.[9] Therefore, there is sustained interest in developing simple and efficient methods for the preparation of 3-hydroxyindolin-2-ones. In particular, 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones are attractive intermediates for the synthesis of biologically active compounds.[10] Generally, 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones are prepared by acid catalyzed addition of 2-methylpyridine to isatin.[11–13] Recently, microwave irradiation has also been used to enhance the reaction rates.[14]

In recent years, the use of alternative solvents such as ionic liquids, polyethylene glycol, and super critical fluids has gained importance as green reaction media in view of environmental perception.[15,16] Though water is a safe alternative, it is not always possible to use water as a solvent due to hydrophobic nature of the reactants and the sensitivity of many catalysts to aqueous conditions.[17] In this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable. To the best of our knowledge, there are no reports for the synthesis of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones using PEG-400 as a reaction medium under catalyst-free conditions.

In continuation of our interest on PEG mediated organic transformations,[18] we, herein, report a simple and efficient approach for the synthesis of 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones under catalyst-free conditions using PEG-400 as an eco-friendly and recyclable medium (Scheme 1).

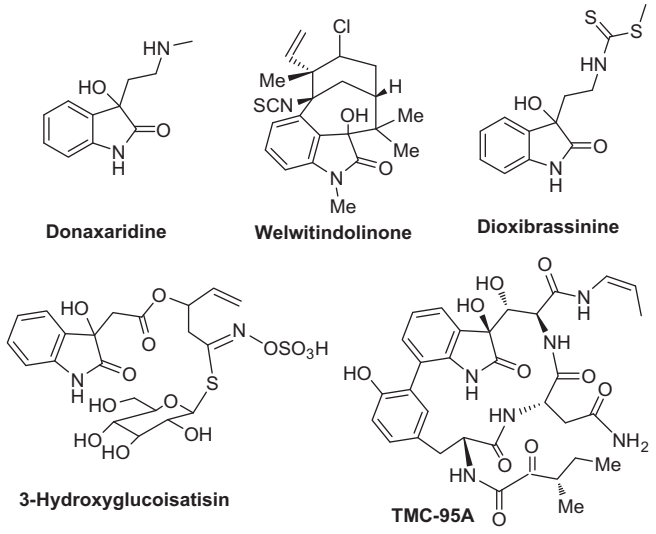

Figure 1. Biologically active 3-hydroxy-2-oxindole derivatives.

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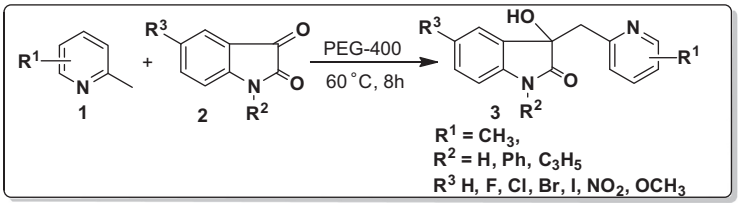


Scheme 1. Preparation of 3-hydroxy-2-oxindoles.

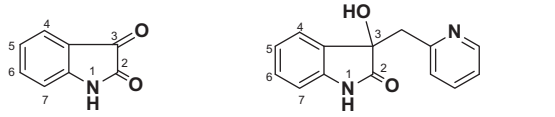


Figure 2. Chemical structure and numbering of isatin and oxindole.

In order to illustrate the products, the structure, and numbering of isatin and oxindole are shown in Figure 2.

In general, all the reactions were clean affording the 3-hydroxy-2-oxindole derivatives in good yields under the above conditions (Table 1). The substituent had shown some effect on conversion. For instance, 5-methoxyisatin gave the desired product in high yield in short reaction time (entries d, e, and q, Table 1) compared to electron-deficient counterparts. Halogen substituted isatins

Table 1
PEG mediated synthesis of 3-hydroxy-2-oxindoles via the condensation of isatins with alkyl pyridines

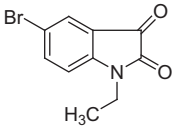
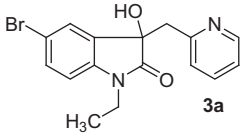
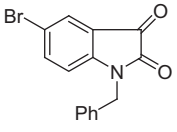
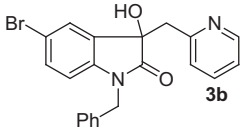
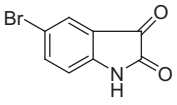
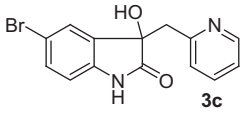
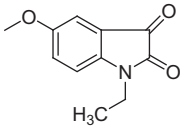
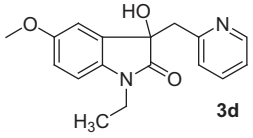
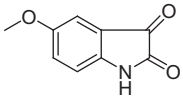
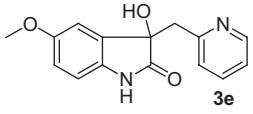
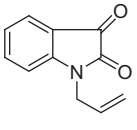
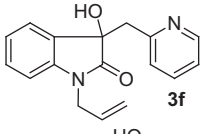
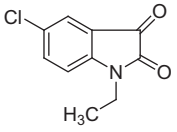
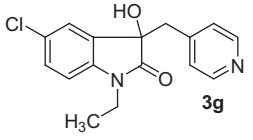
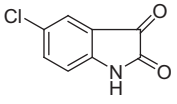
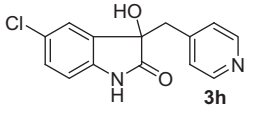
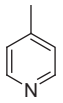
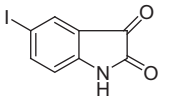
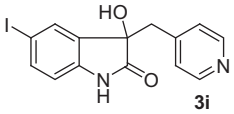
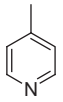
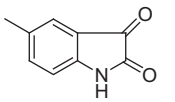
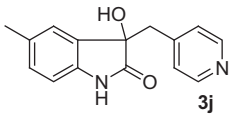
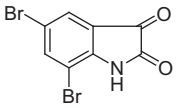
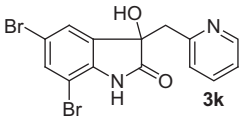
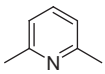
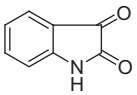
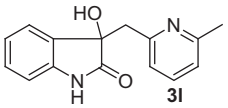
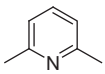
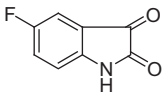
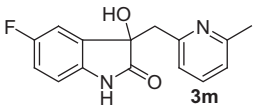
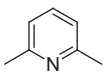
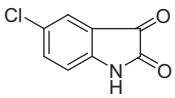
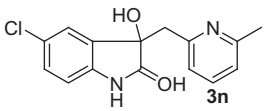
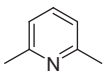
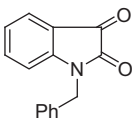
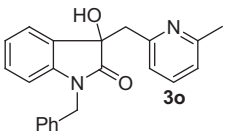
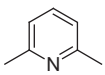
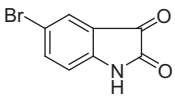
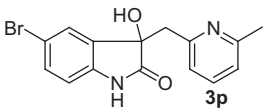
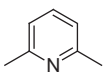
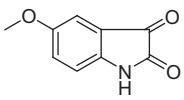
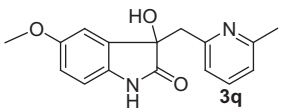
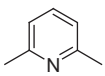
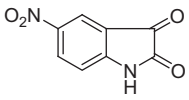
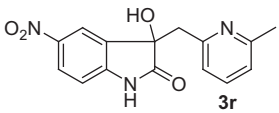
Entry	Methylpyridine (**1**)	Isatin (**2**)	Product (**3**)[a]	Time (h)	Yield (%)[b]
a			 **3a**	6.0	75
b			 **3b**	7.0	70
c			 **3c**	5.0	79
d			 **3d**	4.0	83
e			 **3e**	3.0	85
f			 **3f**	5.0	80
g			 **3g**	7.0	77
h			 **3h**	6.0	80

Table 1 (*continued*)

Entry	Methylpyridine (**1**)	Isatin (**2**)	Product (**3**)[a]	Time (h)	Yield (%)[b]
i			 **3i**	6.0	82
j			 **3j**	5.0	78
k			 **3k**	7.0	75
l			 **3l**	5.0	82
m			 **3m**	6.0	78
n			 **3n**	6.0	82
o			 **3o**	5.0	75
p			 **3p**	6.0	80
q			 **3q**	4.0	85
r			 **3r**	8.0	60

[a] Reaction conditions: isatin (1 mmol), methylpyridine (3 mmol), PEG (5 ml), 60 °C.
[b] Isolated yield.

afforded products reasonably in good yields (entries a–c, g–i, k, m, n, and p, Table 1). However, 5-nitroisatin afforded the product in a relatively low yield (entry r, Table 1). The reaction was also successful with 4-methylpyridine (entries g–j, Table 1). Next, we attempted the coupling of isatins with 2,6-dimethylpyridine. Interestingly, mono-aldol reaction was observed in case of 2,6-dimethylpyridine. No bis-adduct was isolated under the present reaction conditions (entries l–r, Table 1). The structures of all the products were determined from their spectral (IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS) data and also by direct comparison with authentic samples.[14] The scope of this process was illustrated with respect to various isatins and alkylpyridines (Table 1). In order to assess the efficiency of PEG-400, the reaction of 2,6-dimethylpyridine with isatin was also carried out in polar solvents such as DMF, DMSO, NMP, and ethyleneglycol. Of these solvents, PEG-400 was found to be superior to provide the corresponding product **3l** and the results are presented in Table 2.

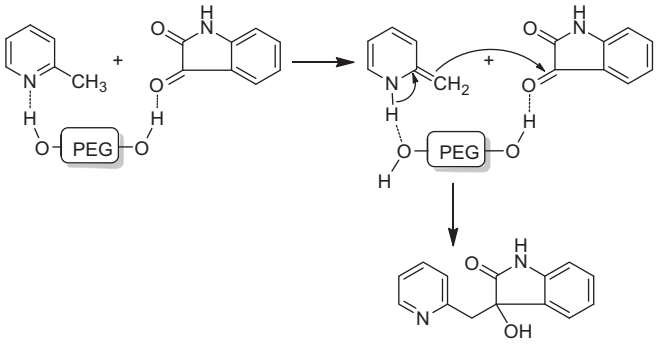
The generality of this reaction was investigated and the results are presented in Table 1. As seen in Table 1, a variety of isatins underwent smooth condensation with alkyl pyridines in PEG-400 at 60 °C to provide a diversified 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-ones (Table 1)[19].

A plausible reaction mechanism is depicted in Scheme 2. PEG-400 activates both picoline and isatin by protonation. Subsequent attack of the methylene group on isatin gave the desired 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-one derivative (Scheme 2).

In conclusion, we have developed an efficient approach for the synthesis of various 3-hydroxy-3-(pyridin-2-ylmethyl)indolin-2-one derivatives using PEG-400 without the need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction

Table 2
Comparison of solvents in the synthesis of **31**

Entry	Solvent	Amount (mL)	Time (h)	Yield (%)
1	DMF	5	12	58
2	DMSO	5	10	60
3	NMP	5	10	57
4	Ethyeleglycol	5	10	65



Scheme 2. A plausible reaction pathway.

medium, operational simplicity, and high yields are the advantages of this protocol.

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References and notes

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19. *Typical procedure for the synthesis of 3-hydroxy-3-(6-methylpyridin-2-yl)methyl)indolin-2-one derivative:* a mixture of isatin (147 mg, 1 mmol) and 2,6-dimethylpyridine (321 mg, 3 mmol) was taken in 5 mL polyethylene glycol-400. The resulting mixture was allowed to stir at 60 °C for 5.0 h. After completion of the reaction, as monitored by TLC, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel using ethyl acetate:hexane mixture (3:7) as eluent to yield (208 mg 82%) the desired product **3l**.