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ORIGINAL ARTICLE

SYNTHESIS OF INDOLYL IMIDAZOLES USING PEG-400 AS A RECYCLABLE REACTION MEDIUM AT ROOM TEMPERATURE

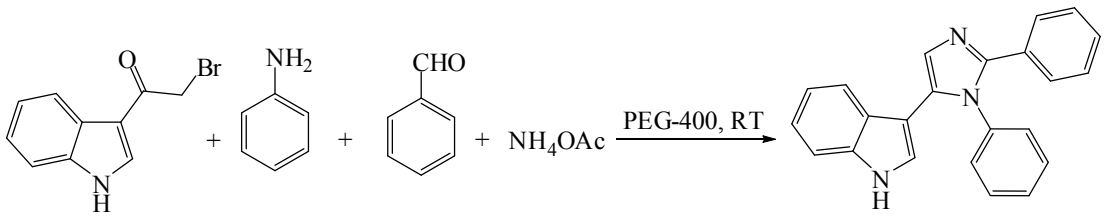
Ashok T. Kadam[1] , Pravin S. Bhale[2*] and Sakharam B. Dongare[3]
[1]Department of Chemistry, Yeshwantrao Chavan Mahavidyalaya, Tuljapur, Dist-Osmanabad, INDIA.
[2]Department of Chemistry, Arts, Science & Commerce College, Naldurg, Dist- Osmanabad, INDIA.
[3]School of Chemical Sciences, Solapur University, Solapur, INDIA.
***Corresponding author:** bhale.ps@gmail.com

ABSTRACT
An efficient and green method for synthesis of imidazole containing indole nucleus has been achieved by the reaction between 3-bromoacetyl indole, aniline, various aldehydes and ammonium acetate using PEG-400 as a recyclable reaction medium at room temperature. The method is simple, efficient and environmental benign. The compounds obtained are in excellent yield with high purity by easy work up.

KEY WORDS: Indolyl-imidazole; 3-bromoacetyl indole; PEG-400.

INTRODUCTION
Compounds containing imidazole ring system have many pharmacological properties and play important roles in biochemical process [1, 2]. Many of the substituted imidazoles are known as inhibitors of p38 MAP kinase, fungicides, herbicides, plant growth regulators and therapeutic agents [3–6]. Owing to the wide range of pharmacological and biological activities, the synthesis of imidazoles has become an important target in current years. There are several methods reported in literature for the synthesis of imidazoles and its derivatives. Generally, triaryl-imidazoles are synthesized by three component cyclocondensation of a 1,2-diketone, a-hydroxyketone or a-ketomonoxime with an aldehyde and ammonium acetate, which comprise the use of microwaves [7,8], ionic liquids [9], europium triflate [10], oxalic acid [11], refluxing in acetic acid [12], silica sulfuric acid [13]. Many of the synthetic protocols for synthesis of imidazoles suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and expensive catalysts. So the development of clean, high-yielding and environmentally friendly approaches is still desirable and much in demand.

Recently, polyethylene glycols (PEGs) are found to be an interesting solvent system for the organic reactions. It is inexpensive, thermally stable, non-volatile, non-toxic and easily degradable, has emerged as reaction medium in organic synthesis [14, 15]. As a part of our ongoing research interest in PEG, in this protocol, we report a simple but effective synthesis of trisubstituted indolyl-imidazoles by one-pot reaction of 3-bromoacetyl indole with variety of aldehydes, anilines, and ammonium acetate using PEG-400 as reaction medium at room temperature (**Scheme 1**).



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

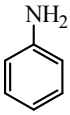
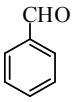
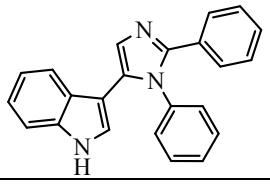
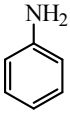
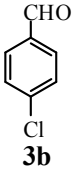
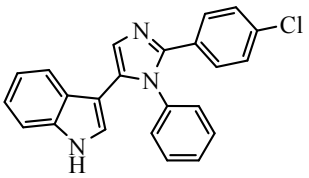
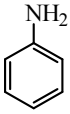
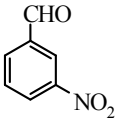
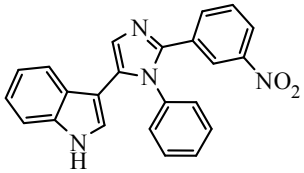
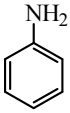
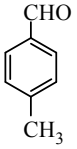
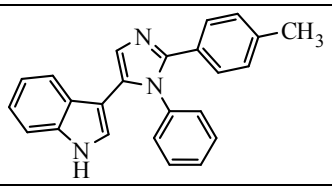
Scheme 1. Synthesis of indolyl imidazole (**5a)**

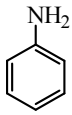
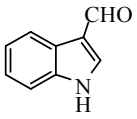
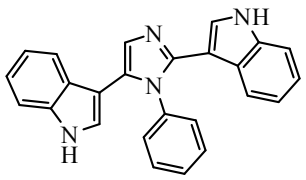
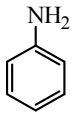
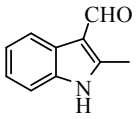
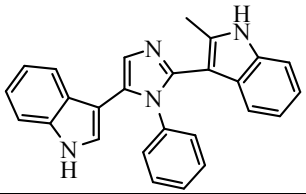
Table 1. Synthesis of indolyl-imidazole 5a in different solvents.

Entry	Solvent [a]	Temp. (°C)	Time (hr)	Yield (%)[b]
1	PEG-200	30	5	70
2	PEG-400	30	4	90
3	PEG-600	30	5	88
4	PEG-800	30	6	85
5	Ethanol	30	8	45
6	Acetonitrile	30	8	40

[a]Solvent volume used 5 ml. [b]Isolated yields.

Table 2. Synthesis of indolyl imidazoles

Entry	Aniline	Aldehyde	Product	Time (h)	Yield (%)[a]
5a		 **3a**		4.0	90
5b		 **3b**		4.0	88
5c		 **3c**		4.5	89
5d		 **3d**		4.0	87

5e		 **3e**		5.0	83
5f		 **3f**		5.0	85

[a]Isolated yields.

MATERIALS AND METHODS

Experimental

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. All the solvents were dried and distilled before use. The IR spectra of synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide. The 1H NMR were recorded in $CDCl_3$ or DMSO-d_6 using NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Reactions were monitored using thin layer chromatography (TLC) carried out on Merck silica gel 60 F254 precoated aluminium plates. The visualization was achieved under UV light or staining with I_2. Chromatographic separations were achieved on silica gel columns (Merck, 60–120 mesh) using gradient of hexane/ethyl acetate as eluent.

General procedure for the synthesis of indolyl-imidazole

A mixture of 3-bromoacetyl indole **1** (1 mmol), aniline **2** (1 mmol), various aldehyde **(3a-f)** (1 mmol) and ammonium acetate **4** (2 mmol) were taken in PEG-400 (5 ml) and stirred at room temperature for the appropriate time as mentioned in Table 2. After completion of the reaction (monitored by TLC), the reaction mass was poured into cold water. The solid imidazole product was filtered, washed with water and dried. The resulting product was purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane) to afford pure product**.**

Spectral data of representative compound:

3-(1,2-diphenyl-1H-imidazol-5-yl)-1H-indole (5a): Yellow Solid, IR (KBr): 3250, 3045, 1610, 1590, 1250 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.35(s, 1H, NH), 8.50(s, 1H), 8.24(d, 2H), 8.14(d, 1H), 7.65(s, 1H), 7.58-7.30(m, 10H), 7.00(t, 1H); LCMS(ESI): m/z 336.15(M+1); Anal. calcd. for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53; Found: C, 82.34; H, 5.12; N, 12.52%

RESULTS AND DISCUSSION

In the initial studies, the reaction of 3-bromoacetyl indole **1** (1 mmol), aniline **2** (1 mmol), benzaldehyde **3** (1 mmol) and ammonium acetate **4** (4 mmol) was performed in different solvents without any added catalyst to synthesize the compound **5a**. It was observed that among the tested solvents (**Table 1**, entry **2**), the reaction in PEG-400 was more facile and proceeded to give best yield (90%) when the reaction mixture was stirred at room temperature for 4 hr. Moreover, there are many potential advantages of replacing organic solvents with PEG-400. So PEG-400 is used as the optimal reaction medium for the reaction.

In order to evaluate the generality of this process, we studied the reaction of 3-bromoacetyl indole **1** with aniline **2**, various aldehyde **3a-f** and ammonium acetate **4** in PEG-400 as reaction medium at room temperature. Aromatic aldehyde were bearing electron withdrawing groups (such as

nitro, chloro) or electron releasing groups (such as methyl), smoothly converted to corresponding imidazole derivatives in excellent yields. The results were illustrated in **Tables 2**. In the present procedure, PEG-400 not only acts as a phase transfer catalyst but also as a clean solvent by significantly enhancing the intramolecular cyclization. Moreover, PEG-400 is a recyclable reaction medium. In the reaction for synthesis of **5a**, we recycled PEG-400 for three times and the reaction proceeded cleanly with good yields (86%, 83%, and 81%) although a little weight loss of PEG-400 was observed during recycle study due to mechanical loss. After workup of the reaction, the filtrate was extracted with ethyl acetate, then the aqueous layer was concentrated in vacuum and the crude PEG-400 was recovered. Further studies to develop the new clean environmentally benign reagent towards the synthesis of biologically active compounds are in progress.

CONCLUSION

In summary, this protocol describes a simple and convenient method for the one-pot, four component synthesis of indolyl imidazoles in PEG-400 at room temperature. Present methodology offers very attractive features such as excellent yields, simple reaction conditions and easy work up. Moreover, the use of PEG-400 as recyclable reaction medium makes this process a green synthesis.

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