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ORIGINAL ARTICLE

GREEN APPROACH FOR SYNTHESIS OF INDOLYL IMIDAZOLE

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ABSTRACT
An efficient and green method for synthesis of 2-aminoimidazole containing indole nucleus has been achieved by the reaction between 2-bromo-1-(1H-indol-3-yl)-ethanone and guanidine hydrochloride using PEG-400 as a recyclable reaction medium. Simple experimental procedure, mild reaction conditions are the important features of the present method.

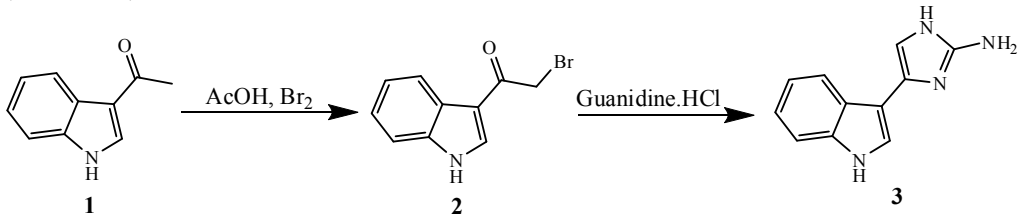
KEYWORDS: *2-aminoimidazole, 2-bromo-1-(1H-indol-3-yl)-ethanone, indolyl imidazole*.

INTRODUCTION
Azoles constitute immensely important members of the aromatic heterocycles family due to their presence in a myriad of bioactive natural products as privileged pharmacophores. These compounds attracts particular attention in methodology design for its utility as a synthetic building block and widespread occurrence in target structures, such as functional materials and biologically-relevant compounds [1-3]. In recent years, the high therapeutic properties of the imidazole related drugs have been attracting the attention of medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Medicinal properties of imidazole containing compounds include anticancer [4], antimicrobial [5-6] and antioxidant [7]. It is known that clinically useful drugs such as miconazole, econazole and oxiconazole having imidazole moiety exhibit strong antifungal activity.

Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including anticancer [8], antioxidant [9], anti-rheumatoid and anti-HIV [10, 11] and also play a vital role in the immune system [12]. Many indole derivatives are considered as the most potent scavenger of free radicals [12].

Polyethylene glycol (PEG) a biologically acceptable polymer used extensively in drug delivery and in bio conjugates as tool for diagnostics has hitherto not been widely used as a solvent medium but has been used as a support for various transformations [13].

It was envisaged that the two pharmacophores if linked together would generate novel molecular templates which are likely to exhibit interesting biological properties. We were designed and synthesized indolyl imidazoles using PEG-400 as reaction medium under mild conditions (**Scheme 1**).



Scheme 1. Reagents and conditions: (**a**) Acetic acid, Br_2; (**b**) Guanidine. HCl, PEG- 400, RT.

RESULTS AND DISCUSSION

In the initial studies, the reaction of 3-bromoacetyl indole **2** (1 mmol) and guanidine hydrochloride (1 mmol) was performed in different PEGs without any catalyst to synthesize the compound **3**. 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 2 h. Same reaction was also performed in PEG-600 (**Table 1**, entry **3**) and PEG-800 (**Table 1**, entry **4**), comparable yields of **3** were obtained after 3 h. Results of table 1 shows the model reaction proceeds smoothly in PEG-400 at room temperature. 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 the reaction for synthesis of **3**, we recycled PEG-400 for three times and the reaction proceeded cleanly with good yields (90%, 87%, and 82%), 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 and then the aqueous layer was concentrated under vacuum and to get the recovery of PEG-400.

Table 1. Synthesis of 3 in different PEG.

Entry	Solvent[a]	Temp. (^oC)	Time (h)	Yield (%)[b]
1	PEG-200	30	4	78
2	PEG-400	30	2	90
3	PEG-600	30	3	85
4	PEG-800	30	4	82

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

Experimental Section

Synthesis of 2-bromo-1-(1H-indol-3-yl)-ethanone (Compound 2):

Indole **1** (1 mmol) was taken in acetic acid and bromine (1.5 mmol) was added to the indole solution below 20^{o}C for 30 min and stirred at room temperature for 1h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on crushed ice and stirred. The solid product was filtered, washed with water and dried. The crude product obtained was sufficiently pure and used further without purification.

Synthesis of 4-(1H-indol-3-yl)-1H-imidazol-2-amine (Compound 3):

A mixture of 3-bromoacetyl indole **2** (1 mmol) and guanidine hydrochloride (2 mmol) was taken in PEG-400 (5 ml) and stirred at room temperature for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured on crushed ice and stirred. The solid product was filtered, washed with water and dried. The crude product was recrystallized with appropriate solvent to obtain the indolyl imidazole **3**

Spectral data of representative compound 3:

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.0-8.1 (m, 4H), 7.51(d, 1H), 7.18(s, 2H), 8.6 (s, 1H), 12.4 (s, 1H), 13.4 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 105.0, 111.1, 119.8, 119.9, 121.7, 124.4, 124.8, 128.4, 136.6, 140.1, 150; LCMS (ESI): *m/z* 199.2 ($M+H^+$).

CONCLUSIONS

In conclusion, we have developed a novel, efficient and eco-friendly route for the synthesis of 2-aminoimidazole containing indole nucleus using PEG-400 as a recyclable reaction medium. This medium rendered this procedure attractive and environmentally benign. In addition to its efficiency and simplicity, this method provided high yields of desired products in short reaction time.

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