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A Green, Efficient Protocol for Synthesis of a 3-Pyranyl Indole Derivatives by Using Ionic Liquid Under Reflux Condition

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Abstract

A green and efficient method was described for one pot synthesis of 3-pyranyl indole derivatives by reaction of 3-cyano acetyl indole, aromatic aldehydes and malanonitrile in an aqueous media under reflux by using [Hmim]HSO_4 as a green catalyst. Simple and easy work process, use of green catalyst, green solvent, short reaction time and excellent yields of the products are the advantages of this method.

Keywords: *3-cyano acetyl indole, aromatic aldehydes, malanonitrile, ionic liquid.*

1. Introduction

In recent years 3-substituted indole and pyranyl ring containing hetrocycles having structural and biological importance made them attractive moieties in organic synthesis, drug discovery and medicinal chemistry. In synthesis of such heterocyclic compounds, multicomponent reactions (MCR's) plays an important role. The major advantages of multicomponent reactions are high atom-economy, operational simplicity, high selectivity, due to substantial minimization of waste, time, labor and cost [1-4].

Heterocycles containing 4H-pyrane moiety have important biological, pharmacological activities and used in wide range of therapeutic areas [5-7]. 3-Substituted indole moieties also play an important role in the synthesis of biologically active compounds. 3-Substituted indole moieties shows various pharmacological activities such as anticancer, antitumor, hypoglycemic, antiinflammatory, analgesic and antipyretic activities [8-10]. Because of pharmaceutical importance of 4H-pyrane and 3-substituted indole compounds, herein, we have developed an green an efficient protocol for the synthesis of 3-pyrane indole derivatives by using [Hmim]HSO_4 catalyst in an aqueous media at reflux condition(Fig. 1).

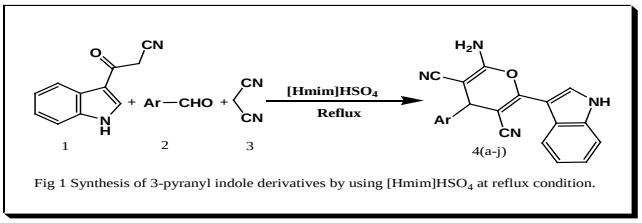


Fig 1 Synthesis of 3-pyranyl indole derivatives by using [Hmim]HSO_4 at reflux condition.

2. Experimental

2.1 General

Melting points were measured in open glass capillaries on a Veego melting-point apparatus and were uncorrected. ^{1}H NMR was recorded at room temperature on a Bruker Avance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in $CDCl_3$ using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instrument. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. Compounds were characterized by IR and ^{1}H NMR spectroscopy.

2.2 General procedure for synthesis of 3-pyranyl indole derivatives.

A mixture of an benzaldehyde (1 mmol), malononitrile (1.2 mmol) and 3-cyanoacetyl indole (1 mmol) was refluxed with [Hmim]HSO_4 (20 mol %) in 5ml water for 25 minutes. The progress of the reaction was monitored on TLC. After completion of reaction, the reaction mixture was cooled to room temperature and the solid product was collected by filtration, washed with distilled water (5 ml x 5). The crude reaction product was collected and further purified by column chromatography (8:2 system of Pet

ether:Ethyl acetate as eluent). The filtrate so obtained was concentrated under reduced pressure to recover ionic liquid which could be reused in subsequent experiments.

3.3 Spectral data for selected compound

1]2-Amino-6-(1H-indol-3-yl)-4-(naphthalen-1-yl)4H-pyran-3,5-dicarbonitrile (Table 3, entry 10):IR (KBr): 3433, 3243, 2112, 1608, 1512, 771, 733 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): d 5.18 (s, 1H, -CH),7.11 (t, 1H, J = 6.75 Hz, Ar-H), 7.27 (t, 1H, J = 7.45 Hz, Ar-H), 7.19 (s, 2H, $–NH_2$), 7.38–7.46 (m, 5H, Ar-H), 7.79–7.88 (m, 3H, Ar-H), 8.17 (d, 1H, J = 7.15 Hz, Ar-H), 8.28 (d, 1H, J = 7.45 Hz, Ar-H), 12.07 (br s, 1H, –NH), MS (EI): m/z 388.42 [M+].

3. Results and discussion

Recently, the use of ionic liquids as a green catalyst, solvent found applications in number of organic reactions. Here we developed the use of ionic liquids as a green catalyst in an aqueous median under reflux conditions for one pot multicomponent synthesis of 3-pyranyl indole derivatives.

In order to check the generality of the reaction, the effect of solvent on the reaction was studied at reflux condition with model reaction of benzaldehyde, malononitrile and 3-cyanoacetyl indole by using $[Hmim]HSO_4$ (for 20 mol%) . The best results were obtained for aqueous media as shown in Table 1.

Table 1. Synthesis of 3-pyranyl indole derivative using different solvents.

Entry	**Solvent used**	**Time in Minutes**	**Yield (%)**
1	Chloroform	30	76
2	Ethanol	30	84
3	Acetonitrile	25	82
4	Water	25	94
5	Solvent free	25	81

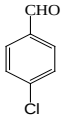
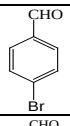
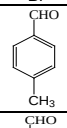
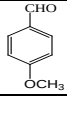
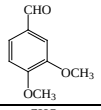
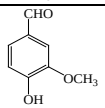
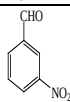
However the scope of the reactions were studied with different substituted aldehyde derivatives. The reaction undergo very smoothly with both electron withdrawing and electron donating substituents. The results are summarized in Table 3.

The reuse of the catalyst is a major factor in a new synthetic green procedure. The ionic liquid can be reused after simple distillation to remove water and remaining ionic liquids was dried under vacuum and reuse for further reactions. To test this, a series of three consecutive runs for the reaction with catalyst were carried out. The results, however, demonstrated no significant change in the activity of the catalyst. The catalyst could be reused for fourth times without significant decrease in catalytic activity (Table 2).

Table 2. Reuse IL for the synthesis 3-pyranyl indole derivatives.

Cycle	Fresh	First	Second	Third
Yield (%)	94	91	88	81

Table 3: Synthesis of 3-pyranyl indole derivatives by using $[Hmim]HSO_4$ at reflux condition in an aqueous media.

Entry	Aldehydes	Products	Time (Min)	[a]Yield (%)
1		**4a**	25	94
2		**4b**	28	88
3		**4c**	28	90
4		**4d**	25	90
5		**4e**	37	87
6		**4f**	40	85
7		**4g**	35	85
8		**4h**	40	86
9		**4i**	30	87
10		**4j**	30	88

[a]Yields refer to the pure isolated product

4. Conclusions

In conclusion here we describe a highly efficient and environmentally benign process for the synthesis of 3-pyran indole derivatives under reflux condition by using ionic liquid in an aqueous media. This method offers several advantages such as catalyst reusability, high yield of product, short reaction time, simple work-up procedure and easy isolation.

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