



## Electrochemical approach for synthesis of 3-substituted indole derivatives



Vinay K. Singh, Rahul Dubey, Abhishek Upadhyay, Laxmi Kant Sharma, Rana Krishna Pal Singh\*

Electrochemical Laboratory of Green Synthesis, Department of Chemistry, University of Allahabad, Allahabad 211002, India

### ARTICLE INFO

#### Article history:

Received 25 July 2017

Revised 30 August 2017

Accepted 1 September 2017

Available online 6 September 2017

#### Keywords:

Three component reaction

C–C bond formation

Indole

Nucleophilic addition reaction

Electrochemically induced

### ABSTRACT

An efficient and economical method was developed for synthesis of 3-substituted indole by using electrochemically induced condensation of various aldehyde, indole and malononitrile.

© 2017 Published by Elsevier Ltd.

### Introduction

Multi-component reactions (MCRs) are novel synthetic methodologies for the preparation of compound libraries which is pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry.<sup>1</sup> These reactions are offering many advantages, as they allow the simple operation by which organic structures with impressive molecular complexity can be assembled into target molecules with high variability, atom efficiency, high reaction yield.<sup>2</sup> Moreover, this strategy has proved to be a particularly valuable and efficient methodology in the section of synthetic chemistry. Indole structural motif represents a 'privileged scaffold' in drug discovery.<sup>3</sup> Higher binding affinity to many receptors, huge number of natural and synthetic indole derivatives shows remarkable application in pharmaceutical and medical chemistry.<sup>4</sup> Therefore indole scaffolds have achieved a prominent position as these structures are known for their importance in the development of new compounds of pharmaceutical interest.

In recent years, the synthesis of combinatorial small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.<sup>1</sup> Thus, the success of combinatorial chemistry in drug discovery is considerably dependent on further advances in heterocyclic MCR methodology, and according to cur-

rent synthetic requirements, ecologically pure multicomponent procedures are particularly welcome. In this context, electroorganic synthesis has recognized as one of the methodologies that can fulfill several important criteria that are needed if society has to develop environmentally compatible processes. It can be used to replace toxic or dangerous oxidizing or reducing reagents, reduce energy consumption, and can be used for the *in situ* production of unstable and hazardous reagents.

Since 3-substituted indole derivatives have been widely found in biologically active compounds, and natural products.<sup>5,6</sup>

Synthetic chemist shows special interest for synthesis of 3-substituted indoles, because they are key synthons in planning the synthesis of therapeutic agents which exhibit diverse pharmaceutical activities.<sup>4,7</sup> For this reason, synthesis and functionalization of indoles at the C-3 position have been active research area.

Multicomponent reaction (MCRs) between indoles, aldehydes and malononitrile is a unique type of reaction for the synthesis of 3-substituted indole derivatives. Multicomponent reaction (MCRs) has significant advantages over classical stepwise approaches, multicomponent reaction allowing the formation of several bonds and the construction of molecule from simple precursors in a single synthetic operation without isolation of intermediates, results in maximization of yields and reduction of waste. Despite several methods present in the literature for the synthesis of substituted indoles,<sup>8</sup> the development of simple, efficient and environmentally benign approaches for indole

\* Corresponding author.

E-mail address: [rkp.singh@rediffmail.com](mailto:rkp.singh@rediffmail.com) (R.K.P. Singh).

derivatives is highly desirable. In consideration of importance of the multicomponent reaction, there still remains a necessity to develop new environmentally friendly methodology for the preparation of potential medicinal scaffolds. So we wish report the synthesis of 3-substituted indoles via three-component reaction of indole, aldehyde and malononitrile in ethanol at room temperature, using electron as an inexpensive and environmentally benign catalyst.

Over the past 3 decades, the due to extensive research on electrochemistry of organic compound, electrochemistry become revolutionized technique for organic synthesis.<sup>9</sup> Electrochemistry has become an attractive alternative to conventional methods in organic synthesis, since only electricity is applied which might even originate from renewable resources, and therefore no reagent waste is produced.

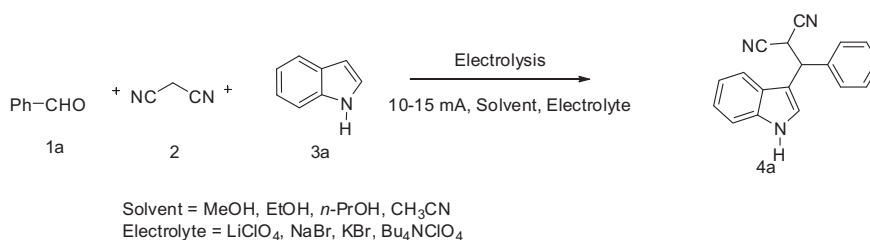
In the course of our research on the development of efficient methods for the synthesis of bioactive heterocycles,<sup>10</sup> herein we have introduced electricity as green reagent for synthesis of 3-substituted indoles analogues.

In present work we here in report a catalyst free three component reaction in which we indole or *N*-methyl indole or substituted indole, aldehyde or substituted aldehyde and malononitrile react to form the novel 3-substituted indole. We initiated our studies of three-component reaction using aldehyde (1 mmol), malononitrile (1 mmol), and indole (1 mmol), lithium perchlorate (0.5 M) was used as an electrolyte and ethanol (30 mL) as solvent. The electrochemical synthesis was carried out in an undivided cell equipped with graphite rods (5 cm<sup>2</sup>) as anode and iron (5 cm<sup>2</sup>) as cathode at room temperature under constant reaction potential. The progress of the reaction was monitored by TLC using hexane/ethyl acetate mixture.

Initially, we selected benzaldehyde (1a) and malononitrile (2) and indole (3a) as the model starting materials to optimize the reaction. Subsequently, the influence of solvents, electrolyte and current density were studied (Table 1 entries 1–14). Reaction mixture was initially at potential 1.4 V (Table 1 entry 1), required product was formed with 85% yield, by increasing the potential 1.5 V reaction yield increases 90% (Table 1 entry 3), further increase in potential 1.7 V decreases the yield (Table 1 entry 4), decrease in the potential 1.0 V decrease the yield (Table 1 entry 5). We observed no change in the reaction yield when the reaction time is increased from 12 h to 36 h (Table 1 entry 2). Current density rendered the best yields with 10 mA cm<sup>-2</sup> (Table 1 entry 3), whereas lower (5 mA cm<sup>-2</sup>) (Table 1 entry 5) or higher (20 mA cm<sup>-2</sup>) (Table 1 entry 6–7) current densities resulted in decreased yield. We attempted similar transformation in various phase transfer catalyst such as LiClO<sub>4</sub> (Table 1 entries 1–8, 12–14), KBr (Table 1 entry 9), NaBr (Table 1 entry 10), Bu<sub>4</sub>NClO<sub>4</sub> (Table 1 entry 11) among these catalyst LiClO<sub>4</sub> (Table 1 entry 3) is found to be best in terms of yield. Performing the electrolysis in various solvent such as EtOH (Table 1 entries 1–11), MeOH (Table 1 entry 12), MeCN (Table 1 entry 13) and *n*-PrOH (Table 1 entry 14) reaction proceeded in all these solvents, among these solvent we found that EtOH (Table 1 entry 3) is found to be best in terms of yield.

With the optimized electrolysis parameters in hand, we applied the method to a range of substrates in order to elucidate the scope of the reaction (Table 2). We were pleased to find that reaction works with wide range of aromatic aldehydes (Table 2, entries 1a–k), aliphatic aldehyde (Table 2, entries 1l), various types of indoles, viz., indole (Table 2, entry 3a), *N*-methyl indole (Table 2, entry 3b), and 5-methoxy indole (Table 2, entry 3c). Aromatic

**Table 1**  
Optimization of reaction conditions.<sup>a</sup>



Entry	Solvent	Potential (V)	Current (mA)	Time (h)	Electrolyte	Yield (%) <sup>b</sup>
1	EtOH	1.4	10	12	LiClO <sub>4</sub>	85
2	EtOH	1.4	10	36	LiClO <sub>4</sub>	85
3	EtOH	1.5	10	12	LiClO <sub>4</sub>	90
4	EtOH	1.7	10	12	LiClO <sub>4</sub>	85
5	EtOH	1.0	10	12	LiClO <sub>4</sub>	80
6	EtOH	1.5	5	12	LiClO <sub>4</sub>	65
7	EtOH	1.5	15	12	LiClO <sub>4</sub>	65
8	EtOH	1.5	20	12	LiClO <sub>4</sub>	66
9	EtOH	1.5	10	12	KBr	63
10	EtOH	1.5	10	24	NaBr	65
11	EtOH	1.5	15	12	Bu <sub>4</sub> NClO <sub>4</sub>	60
12	MeCN	1.5	10	12	LiClO <sub>4</sub>	65
13	MeOH	1.5	10	12	LiClO <sub>4</sub>	67
14	<i>n</i> -PrOH	1.5	10	12	LiClO <sub>4</sub>	65

<sup>a</sup> All reactions were run with benzaldehyde **1a** (1.0 mmol), malononitrile **2** (1.2 mmol), and indole **3a** (1 mmol) various electrolyte (0.5 M), iron cathode (5 cm<sup>2</sup>), graphite anode (5 cm<sup>2</sup>) in various solvents (30 mL) in a beaker, for 12–24 h and reaction mixture was monitored by TLC.

<sup>b</sup> Isolated yield of the product **4**.

Download English Version:

<https://daneshyari.com/en/article/5264007>

Download Persian Version:

<https://daneshyari.com/article/5264007>

[Daneshyari.com](https://daneshyari.com)