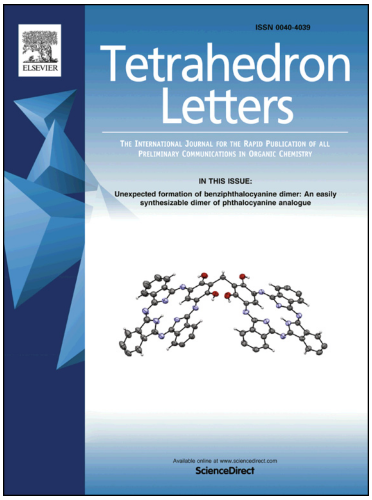

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PII: S0040-4039(17)31108-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.09.003
Reference: TETL 49273

To appear in: *Tetrahedron Letters*

Received Date: 25 July 2017
Revised Date: 30 August 2017
Accepted Date: 1 September 2017

Please cite this article as: Singh, V.K., Dubey, R., Upadhyay, A., Sharma, L.K., Pal Singh, R.K., Electrochemical approach for synthesis of 3-substituted indole derivatives, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.09.003

Graphical Abstract

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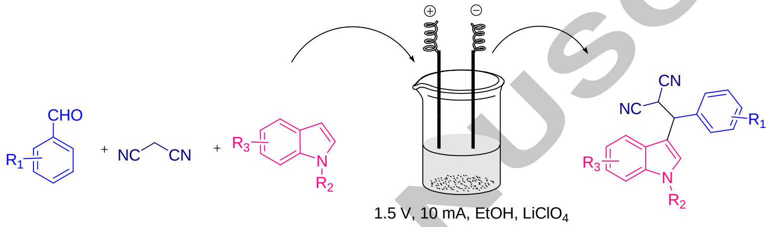

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Electrochemical approach for synthesis of 3-substituted indole derivatives

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Three component reaction,
C-C bond formation
Indole
Nucleophilic addition reaction
Electrochemically induced

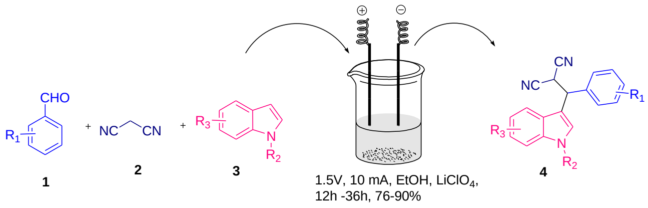
ABSTRACT

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

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.[1] 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. 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.[3] Higher binding affinity to many receptors, huge number of natural and synthetic indole derivatives shows remarkable application in pharmaceutical and medical chemistry.[4] 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.[5] Thus, the success of combinatorial chemistry in drug discovery is considerably dependent on further advances in heterocyclic MCR methodology, and according to current 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.[6, 7] 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.[8] For this reason, synthesis and functionalization of indoles at the C-3 position have been active research area.



R_1 = C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 4-$NO_2C_6H_4$, 3-CNC_6H_4, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-$OCH_3C_6H_4$, 3-$OCH_3C_6H_4$, 4-$CF_3C_6H_4$, $(CH_3)_2CH$
R_2 = H, CH_3
R_3 = H, 5-OMe

Scheme 1. Synthesis of 3-Indoles

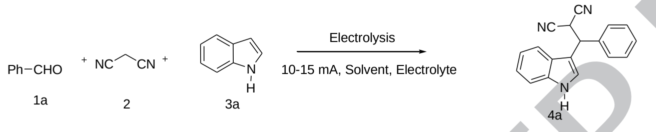
Multicomponent reaction (MCRs) between indoles, aldehydes and malononitrile is a unique type of reaction for the synthesis of 3- substituted indole derivatives. Multicomponent reaction (MCRs) has significant advantages over classical stepwise approaches, multicomponent reaction allowing the formation 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,[9] the development of simple, efficient and environmentally benign approaches for indole 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, electrosynthesis become revolutionized technique for organic synthesis.[10] 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[11], 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 noval 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^2) as anode and iron (5 cm^2) as cathode at room temperature under constant reaction potentia. The progress of the reaction was monitored by TLC using hexane/ethyl acetate mixture.

Table 1: Optimization of reaction conditions[a]



Solvent = MeOH, EtOH, *n*-PrOH, CH_3CN
Electrolyte = $LiClO_4$, NaBr, KBr, Bu_4NClO_4

Entry	Solvent	Potential(V)	Current (mA)	Time (h)	Electrolyte	Yield(%)[b]
1	EtOH	1.4	10	12	$LiClO_4$	85
2	EtOH	1.4	10	36	$LiClO_4$	85
3	EtOH	1.5	10	12	$LiClO_4$	90
4	EtOH	1.7	10	12	$LiClO_4$	85
5	EtOH	1.0	10	12	$LiClO_4$	80
6	EtOH	1.5	5	12	$LiClO_4$	65
7	EtOH	1.5	15	12	$LiClO_4$	65
8	EtOH	1.5	20	12	$LiClO_4$	66
9	EtOH	1.5	10	12	KBr	63
10	EtOH	1.5	10	24	NaBr	65
11	EtOH	1.5	15	12	Bu_4NClO_4	60
12	MeCN	1.5	10	12	$LiClO_4$	65
13	MeOH	1.5	10	12	$LiClO_4$	67
14	*n*-PrOH	1.5	10	12	$LiClO_4$	65

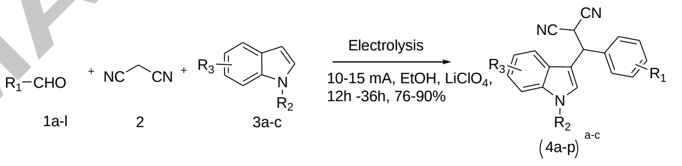
[a] All reactions were run with benzaldehyde **1a** (1.0 mmol), malonotitrile **2** (1.2 mmol), and indole **3a** (1 mmol) various electrolyte (0.5 M), iron cathode (5 cm^2), graphite anode (5 cm^2).) in various solvents (30 mL) in a beaker, for 12-24 h and reaction mixture was monitored by TLC.

[b] Isolated yield of the product **4**

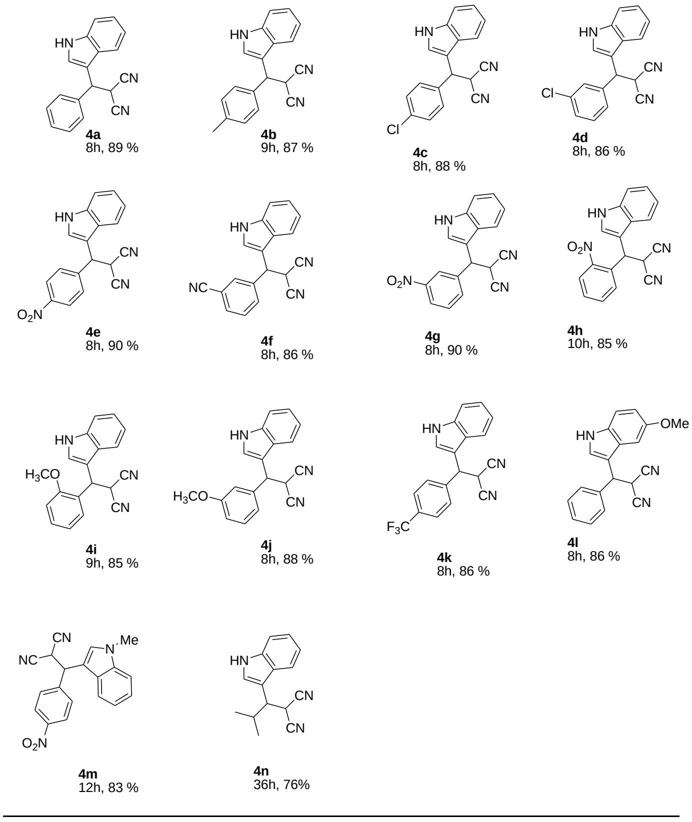
Initially, we selected benzaldehyde (1a) and malononitrile (2) and indole (3a) as the model starting materials to optimize the reaction. Subsequently, the influence of solvents, electrolyte and current density were studied (Table 1 entries 1–14). Reaction mixture was initially at potential 1.4V (Table 1 entry 1), required product was formed with 85% yield, by increasing the potential 1.5V reaction yield increases 90% (Table 1 entry 3), further increase in potential 1.7V decreases the yield (Table 1 entry 4), decrease in the potential 1.0V decrease the yield (Table 1 entry 5). We observed no change in the reaction yield when the reaction time is increased from 12h to 36h (Table 1 entry 2). Current density rendered the best yields with 10 mA cm^{-2} (Table 1 entry 3), whereas lower (5 mA cm^{-2}) (Table 1 entry 5) or higher (20 mA cm^{-2}) (Table 1 entry 6-7) current densities resulted in decreased yield. We attempted similar transformation in various phase transfer catalyst such as $LiClO_4$ (Table 1 entries 1-8, 12-14), KBr (Table 1 entry 9), NaBr (Table 1 entry 10), Bu_4NClO_4 (Table 1 entry 11) among these catalyst $LiClO_4$ (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.

Table 2

Substrate scope for the preparation of 3 substituted indoles

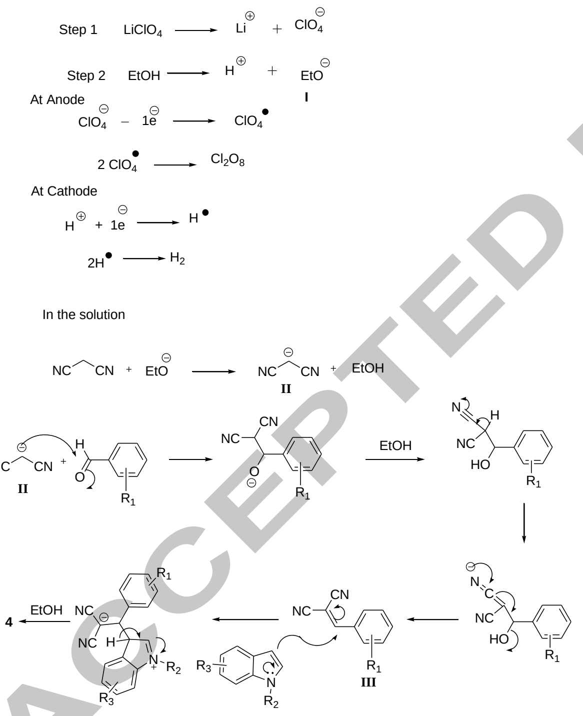


R_1 = C_6H_5 (1a), 4-$CH_3C_6H_4$ (1b), 4-ClC_6H_4 (1c), 3-ClC_6H_4 (1d), 4-$NO_2C_6H_4$ (1e), 3-CNC_6H_4 (1f), 3-$NO_2C_6H_4$ (1g), 2-$NO_2C_6H_4$ (1h), 2-$OCH_3C_6H_4$ (1i), 3-$OCH_3C_6H_4$ (1j), 4-$CF_3C_6H_4$ (1k), $(CH_3)_2CH$ (1l)
R_2 = H, R_3 = H (3a)
R_2 = CH_3, R_3 = H (3b)
R_2 = H, R_3 = 5-OMe (3c)



[a] For experimental procedure, see supporting information.
[b] All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.[8]
[c] Yields of isolated pure compounds 4a.

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 aldehydes bearing electron withdrawing substituents seemed to be beneficial for the electrolysis, and the steric hindrance seemed to have few effects on the results (Table 2, entries 4h-i). Aliphatic aldehydes, such as pivalaldehyde (Table 2, entry 4n) also formed the desired products in 76% yield, though it takes longer time 36h to complete the reaction . To extend the scope of the methodology, two other kinds of indoles were tested. 5-Methoxy indole reacted well with various aldehydes and malononitrile to give the corresponding product with 86% yield (Table 2, entry 4l). Meanwhile, N-methyl indole gave slightly lower yields, around 83% (Table 2, entry 4m).



Scheme 2. A plausible mechanism for the formation 3-indole

We anticipated that anion of malononitrile II act as intermediates, which are directly generated at the anode by reaction of malononitrile and in situ generation ethoxide ion in ethanol solvent. Knoevenagel condensation of aldehyde with malononitrile anion takes place in the solution with the elimination of water and formation of the corresponding intermediate 2-arylidene malononitrile **III** with in 3 min with 95% yield. Michael addition of indole to the adduct **III** furnishes the desired product **4** in the 90 % yield, though the Michael addition reaction is takes place in 12 h.

In conclusion, we are demonstrating here an environmentally friendly, electrochemical reaction protocol for the synthesis of 3-substituted indoles. These reactions were conducted using inexpensive graphite and iron plate electrodes in a beaker open to air (Sheme 1) and $LiClO_4$ was used as the supporting electrolyte. The reaction procedure was simple, efficient and the reaction conditions were mild.

Acknowledgments

We sincerely thank SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra. Vinay K. Singh is grateful to UGC, New Delhi, for the award of a DS Kothari postdoctoral fellowship award No. F.4-2/2006 (BSR)/CH/14-15/0020 and Rahul Dubey, A. Upadhyay thanks UGC for financial support.

Supplementary data

Supplementary data (detailed experimental procedures,product characterization, and NMR spectra of the products) associated with this article can be found,in the online version,at http://

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Highlights of the paper

1. C–C bond formation reaction is a very important transformation in organic chemistry.
2. 3 substituted indoles are biologically active moieties.
3. Reaction is catalyzed by electricity.
4. Green solvent is used as reaction medium.