

# Green, Smooth and Easy Electrochemical Synthesis of *N*-Protected Indole Derivatives

Sarah Fahad Alajmi, Tamer Ezzat Youssef

**Abstract**—Here, we report a simple method for the direct conversion of 6-Nitro-1H-indole into *N*-substituted indoles via electrochemical dehydrogenative reaction with halogenated reagents under strongly basic conditions through N–R bond formation. The *N*-protected indoles have been prepared under moderate and scalable electrolytic conditions. The conduct of the reactions was performed in a simple divided cell under constant current without oxidizing reagents or transition-metal catalysts. The synthesized products have been characterized via UV/Vis spectrophotometry, <sup>1</sup>H-NMR, and FTIR spectroscopy. A possible reaction mechanism is discussed based on the *N*-protective products. This methodology could be applied to the synthesis of various biologically active *N*-substituted indole derivatives.

**Keywords**—Green chemistry, <sup>1</sup>H-indole, NH-containing heteroaromatic, organic electrosynthesis.

## I. INTRODUCTION

INDOLE and their derivatives are an important category of heterocycles; they are used as beneficial intermediates in organic synthesis [1]. Great attention has been concentrated on the synthesis of indole derivatives such as 6-nitroindole derivatives in the last years because they possess advantageous biological activities. They have been prepared previously by traditional methods [2]–[4] and microwave conditions [5]. Through acidic and basic aqueous methanol medium, the synthesis of substituted amino indoles occurs if the electrochemical reduction takes place on 4-, 5-, 6- and 7-nitroindoles [6]. The development of a new and appropriate electrochemical approach for the synthesis of fused indole derivatives has been described previously. In this study, a divided cell equipped with two electrodes, a glassy carbon electrode and a platinum wire, has been used to obtain fused indole derivatives [7]. Nowadays, organic electrosynthesis technique is more commonly used to prepare a series of heterocyclic compounds such as indole derivatives [8], [9]. They have more substantial biological activities and pharmacological properties [10] such as anticancer properties, known as anti-cancer drugs [11] such as anti-lung cancer agent [12], anti-breast cancer agent [13], anti-prostate cancer and anti-bladder cancer agents [14], and anti-proliferative activity against various cancer cell lines [15], in addition to their antibacterial and anti-inflammatory activities

[16]–[18]. They constitute a substantial class of therapeutically agents in medicinal chemistry involving antioxidants [19], [20], and anti-HIV [21]. In a continuation of our previous work [22], we reported the electrochemical reduction of some 2,4-disubstituted pyridines. After a long gap, we report herein the design of an electrochemical reactor and its application in the formation of *n*-protected indole derivatives via the electrochemical synthesis by using a simple divided cell. Besides our own chemistry of indoles, we have begun to examine the chemistry of 6-nitro indoles with introduced groups at *n*-position, e.g., methyl, methoxy, ethyl propanoate, benzensulfonyl, trifluoromethylbenzyl, and benzyl groups.

## II. EXPERIMENTAL

### A. Materials and Reagents

All reagents used were of the highest purity available. 6-Nitro-1H-indole (99.0% purity) were purchased from Sigma-Aldrich while dimethylcarbonate, dimethyl sulfate, ethyl-3-chloropropionate, benzene sulfonyl chloride, 4-trifluoromethyl benzyl bromide, benzyl chloride was purchased from Fluka (99.0% purity). The supporting electrolyte was tetrabutylammonium hexafluorophosphate 99.66% (NBu<sub>4</sub>PF<sub>6</sub>).

### B. Cell and Electrode Design

The controlled-potential organic electrosynthesis experiments were conducted in a divided cell and in constant current of 5 mA and were equipped with two electrodes. They were a graphite electrode (ϕ 6 mm, about 10 mm immersion depth in solution) and a reticulated vitreous carbon foam electrode (10 mm×4 mm×0.2 mm) as the anode and the cathode, respectively.

### C. Instruments

A Stuart SMP30 apparatus was used to determine melting points via open capillary tubes, and they were uncorrected. Thin-layer chromatography (TLC) was used to monitor the progress of all reactions and determine the purity of all compounds performed on aluminum foil sheets, and these sheets were pre-coated by adsorbent material as silica gel 60 F254 with a thickness of 0.20 mm (Merck plates) while the visualization was done via ultraviolet radiation (254 nm). The measurements of <sup>1</sup>H NMR spectra were conducted on NMR spectrometer device (Bruker AVANCE II 300 MHz) and were recorded in deuterated solvent that was dimethyl sulfoxide-*d*<sub>6</sub> (DMSO-*d*<sub>6</sub>) containing tetramethylsilane (TMS). Chemical shifts (δ) were reported in ppm downfield proportional to TMS (δ = 0 ppm); moreover, the peak of the residual proton of the solvent (DMSO-*d*<sub>6</sub>) appeared at δ = 2.53 ppm. Mass

Sarah Fahad Alajmi is with the Department of Chemistry, University College at Nairiyah, Hafr Al Batin University, Nairiyah 31981, Saudi Arabia.

Tamer Ezzat Youssef D is with the department of Chemistry, College of Science, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia (corresponding author, phone: + 966538952007; e-mail: temoustafa@iau.edu.sa).

spectrometric measurements were carried out by the Shimadzu LC-MS/MS 8050 spectrometer operating at 70 eV and were reported in mass/charge (*m/z*). V-Vis spectra measurements were performed on an Agilent 8453 UV-Vis spectrophotometer using dimethyl formamide (DMF). IR spectra were recorded on an FTIR spectrophotometer (Shimadzu, IR Affinity 1, Tokyo). A Vario MICRO cube Elementar (Elemental Analyzer, Germany) was used to conduct the microanalysis for C, H, and N. All spectra were recorded in Imam Abdulrahman Bin Faisal University facilities.

*A. Generic Procedure for the Organic Electrosynthesis of N-Substituted 6-Nitro-1H-Indole Derivatives (3a-g)*

The crude 6-Nitro-1H-indole (5; 0.6 mmol), 2a-f and MeCN (10 mL) were added in a 150 mL divided cell and the mixture was stirred at room temperature. Next,  $\text{NBu}_4\text{PF}_6$  (0.5 mmol) was added and followed by MeCN (5 mL) and  $\text{H}_2\text{O}$  (1 mL). Meanwhile the cell was equipped with a graphite electrode as the anode ( $\phi$  6 mm, about 10 mm immersion depth in solution) and a reticulated vitreous carbon foam electrode as the cathode (10 mm $\times$ 4 mm $\times$ 0.2 mm). The entire mixture was stirred and electrolyzed under a constant current of 5 mA for 20-30 minutes. The MeCN/ $\text{H}_2\text{O}$  was evaporated. Then, the remains of the mixture were washed and extracted with  $\text{CH}_2\text{Cl}_2$  (10 mL  $\times$  3) respectively. The extract was dried over  $\text{Na}_2\text{SO}_4$ , and evaporated. The desired products of 3a-f with high purity were achieved by flash column chromatography on silica gel.

*N*-methyl-6-nitro-1H-indole (3a): Prepared from 2a as a white solid; m.p. 237-240 °C; Rf = 0.9.

IR (KBr):  $\nu$  = 3040  $\text{cm}^{-1}$  (C-H aromatic stretching), 2900  $\text{cm}^{-1}$  ( $\text{CH}_3$  stretching), 4 weak overtone peaks at 2000  $\text{cm}^{-1}$  (mono substituted phenyl), 1590  $\text{cm}^{-1}$  (C=C aromatic stretching), two strong beaks at 1570  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  (N-O stretching), 1360  $\text{cm}^{-1}$  (C-N stretching) 1350  $\text{cm}^{-1}$  ( $\text{CH}_3$  bending), 1330  $\text{cm}^{-1}$  (C-H bending).

$^1\text{H-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 7.33 (1H,H2), 6.41 (1H,H3), 8.31 (1H,H4), 8.17 (1H,H5), 8.85 (1H,H7), 3.69 (3H,N-Me) ppm. UV-Vis (DMF):  $\lambda_{\text{max}}$  (nm): 377, 372, 366 nm. MS (EI): *m/z* = 176.17 ( $\text{M}^+$ ). Elemental analysis:  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$ ; Found C 61.36, H 4.58, N 15.90, Calc. C 61.75, H 5.10, N 16.18.

1-methoxy-6-nitro-1H-indole (3b): Prepared from 2b as a white solid; m.p. 217-218 °C; Rf = 0.7.

IR (KBr):  $\nu$  = 3040  $\text{cm}^{-1}$  (C-H aromatic stretching), 4 weak overtone peaks at 2000  $\text{cm}^{-1}$  (mono substituted phenyl), 1590  $\text{cm}^{-1}$  (C=C aromatic stretching), Two strong beaks at 1570  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  (N-O stretching), 1360  $\text{cm}^{-1}$  (C-N stretching), 1330  $\text{cm}^{-1}$  (C-H bending), 1070  $\text{cm}^{-1}$  (C-O stretching).

$^1\text{H-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 7.64 (1H,H2), 6.38 (1H,H3), 8.69 (1H,H4), 8.00 (1H,H5), 9.08 (1H,H7), 3.95 (3H,N-OMe) ppm.

UV-Vis (DMF):  $\lambda_{\text{max}}$  (nm): 361, 344, 340 nm. MS (EI): *m/z* = 192.17 ( $\text{M}^+$ ). Elemental analysis:  $\text{C}_9\text{H}_8\text{N}_2\text{O}_3$ ; Found C 56.25, H 4.20, N 14.58. Calc. C 56.66, H 4.50, N 15.33.

Ethyl 3-(6-nitro-1H-indol-1-yl)propanoate (3c): Prepared from 2c as a pale brown solid; m.p. 160-165 °C; Rf = 0.63.

IR (KBr):  $\nu$  = 3040  $\text{cm}^{-1}$  (C-H aromatic stretching), 2900  $\text{cm}^{-1}$  ( $\text{CH}_3$  stretching), 4 weak overtone peaks at 2000  $\text{cm}^{-1}$  (mono substituted phenyl), 1700  $\text{cm}^{-1}$  (C=O stretching), 1600  $\text{cm}^{-1}$  (C-C stretching), 1590  $\text{cm}^{-1}$  (C=C aromatic stretching), Two strong beaks at 1570  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  (N-O stretching), 1360  $\text{cm}^{-1}$  (C-N stretching), 1350  $\text{cm}^{-1}$  ( $\text{CH}_3$  bending), 1330  $\text{cm}^{-1}$  (C-H bending), 1070  $\text{cm}^{-1}$  (C-O stretching).

$^1\text{H-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 7.33 (1H,H2), 6.41 (1H,H3), 8.31 (1H,H4), 8.17 (1H,H5), 8.85 (1H,H7), 4.24 (2H,  $\text{CH}_2$ (a),propanoate), 2.73 (2H, $\text{CH}_2$ (b),propanoate), 4.13 (2H, $\text{CH}_2$ (c),propanoate), 1.29 (3H, $\text{CH}_3$ ,propanoate) ppm.

UV-Vis (DMF):  $\lambda_{\text{max}}$  (nm): 418, 400, 380 nm. MS (EI): *m/z* = 262.26 ( $\text{M}^+$ ). Elemental analysis:  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_4$ ; Found C 59.54, H 5.38, N 10.68, Calc. C 59.90, H 5.78, N 11.47.

1-benzensulfonyl-6-nitro-1H-indole (3d): Prepared from 2d as a dark brown solid; m.p. 190-192 °C; Rf = 0.6.

IR (KBr):  $\nu$  = 3040  $\text{cm}^{-1}$  (C-H aromatic stretching), 4 weak overtone peaks at 2000  $\text{cm}^{-1}$  (mono substituted phenyl), 1590  $\text{cm}^{-1}$  (C=C aromatic stretching), two strong beaks at 1570  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  (N-O stretching), 1360  $\text{cm}^{-1}$  (C-N stretching), 1330  $\text{cm}^{-1}$  (C-H bending), 1325  $\text{cm}^{-1}$  and 1170  $\text{cm}^{-1}$  (S=O stretching).

$^1\text{H-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 7.64 (1H,H2), 6.38 (1H,H3), 8.69 (1H,H4), 8.00 (1H,H5), 9.08 (1H,H7), 7.86 (2H,Ho,benzensulfonyl), 7.62 (2H,Hm,benzensulfonyl), 7.71 (2H,Hp,benzensulfonyl) ppm.

UV-Vis (DMF):  $\lambda_{\text{max}}$  (nm): 332, 327, 320 nm. MS (EI): *m/z* = 302.30 ( $\text{M}^+$ ). Elemental analysis:  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4\text{S}$ ; Found C 55.62, H 3.33, N 9.27. Calc. C 55.84, H 4.20, N 9.77.

1-4-trifluoromethylbenzyl-6-nitro-1H-indole (3e): Prepared from 2e as a green brown solid; m.p. 197-200 °C; Rf = 0.5.

IR (KBr):  $\nu$  = 3040  $\text{cm}^{-1}$  (C-H aromatic stretching), 4 weak overtone peaks at 2000  $\text{cm}^{-1}$  (mono substituted phenyl), 1600  $\text{cm}^{-1}$  (C-C stretching), 1590  $\text{cm}^{-1}$  (C=C aromatic stretching), two strong beaks at 1570  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  (N-O stretching), 1360  $\text{cm}^{-1}$  (C-N stretching), 1330  $\text{cm}^{-1}$  (C-H bending), 1000  $\text{cm}^{-1}$  (C-F stretching).

$^1\text{H-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 7.44 (1H,H2), 6.36 (1H,H3), 8.69 (1H,H4), 8.00 (1H,H5), 9.08 (1H,H7), 5.58 (2H, $\text{CH}_2$ , $\text{CF}_3$ benzyl), 7.16 (2H,Ho, $\text{CF}_3$ benzyl), 7.50 (2H,Hm, $\text{CF}_3$ benzyl) ppm.

UV-Vis (DMF):  $\lambda_{\text{max}}$  (nm): 403,399,390 nm. MS (EI): *m/z* = 320.27 ( $\text{M}^+$ ). Elemental analysis:  $\text{C}_{16}\text{H}_{11}\text{N}_2\text{O}_2\text{F}_3$ ; Found C 60.00, H 3.46, N 8.75. Calc. C 60.22, H 4.13, N 8.79.

1-benzyl-6-nitro-1H-indole (3f): Prepared from 2f as a brown solid; m.p. 230-231 °C; Rf = 0.75.

IR (KBr):  $\nu$  = 3040  $\text{cm}^{-1}$  (C-H aromatic stretching), 4 weak overtone peaks at 2000  $\text{cm}^{-1}$  (mono substituted phenyl), 1600  $\text{cm}^{-1}$  (C-C stretching), 1590  $\text{cm}^{-1}$  (C=C aromatic stretching), two strong beaks at 1570  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  (N-O stretching), 1360  $\text{cm}^{-1}$  (C-N stretching), 1330  $\text{cm}^{-1}$  (C-H bending).

$^1\text{H-NMR}$  (126 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  = 7.44 (1H,H2), 6.36 (1H,H3), 8.69 (1H,H4), 8.00 (1H,H5), 9.08 (1H,H7), 5.58 (2H, $\text{CH}_2$ ,benzyl), 7.23 (2H,Ho,benzyl), 7.33 (2H,Hm,benzyl), 7.26 (1H,Hp,benzyl) ppm.

UV-Vis (DMF):  $\lambda_{\text{max}}$  (nm): 336,322,311 nm. MS (EI): *m/z*

= 252.27 ( $M^+$ ). Elemental analysis:  $C_{15}H_{12}N_2O_2$ ; found C 71.42, H 4.79, N 11.10, Calc. C 71.80, H 4.95, N 11.35.

### III. RESULTS AND DISCUSSION

According to our synthetic method, we have prepared a series of *N*-substituted indole derivatives (3a-f) from 6-Nitro-1H-indole (1) in 55-75% overall yield in as shown in Fig. 1. The electrochemical synthesis of *N*-substituted indole derivatives (3a-f) was conducted in a simple divided cell, the applied potential to the working electrode was 2.5 V, and the cell was equipped with a graphite electrode as the anode and a reticulated vitreous carbon as the cathode while  $NBu_4PF_6$  was used as the supporting electrolyte, Fig. 2. As explained previously, the reaction can be carried out in one-pot to provide the desired indole series (3a-f) within 20-30 minutes over one step. For optimal results, stirring can be introduced to increase mass transfer, however, because no laminar flow over the electrode surface is obtained, such setups are not considered hydrodynamic electrodes. In this setup, the maximum *N*-functionalized indole derivatives (3a-f) concentration was reached within the first 20-25 minutes as described in Table I. The course of the reaction was followed up via TLC each 10 minutes. After 30 minutes, the final concentration was already reached. The experiment was repeated and blocking the surface of the electrode was possible.

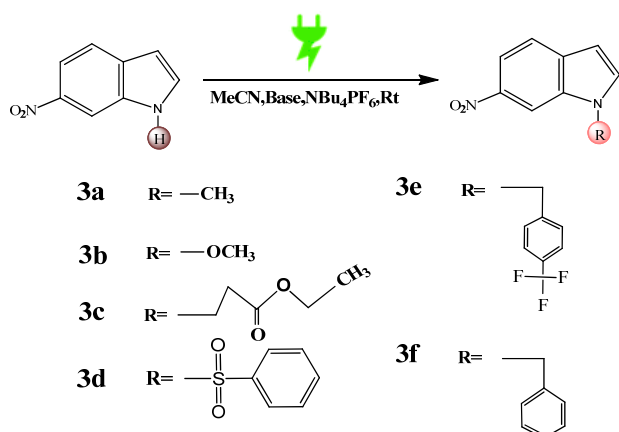


Fig. 1 General scope for the synthesis of *N*-substituted 6-nitro-1H-indole derivatives (3a-f)

In this study, the substrate scope with respect to indoles was also investigated. We reported the room temperature electrochemical synthesis of a range of *N*-functionalized indoles (*N*-R; R = a series of functional groups, such as methyl, methoxy, ethyl propanoate, benzenesulfonyl, trifluoromethylbenzyl, and benzyl groups) (Fig. 3). Alkylation of indole N-H requires bases such as sodium carbonate or potassium hydroxide, alkylation of indoles could be easily achieved without catalyst by employing an appropriate alkylating agent.

Dimethylcarbonate was used as a selective mono *N*-methylation reagent to convert 6-Nitro-1H-indole (1) into the

corresponding *N*-Methyl-6-nitro-1H-indole derivative (3a). However, the synthetic procedures for the direct mono *N*-methylation of 1H-indole failed when using classical methylation reagents, such as methyl iodide.



Fig. 2 The controlled-potential organic electrosynthesis cell design

The conversion of mono *N*-methoxylation of 6-Nitro-1H-indole (1) into the corresponding *N*-Methoxyl-6-nitro-1H-indole derivative (3b) is successfully achieved by utilizing dimethyl sulfate as the methylation reagent.

The above convenient reagents toward methylation or methoxylation at room temperatures enable the formation of corresponding product 3a-f with absence of catalyst and highly selectivity. Excess amounts of methylation or methoxylation reagents are applied without any problems (Fig. 3).

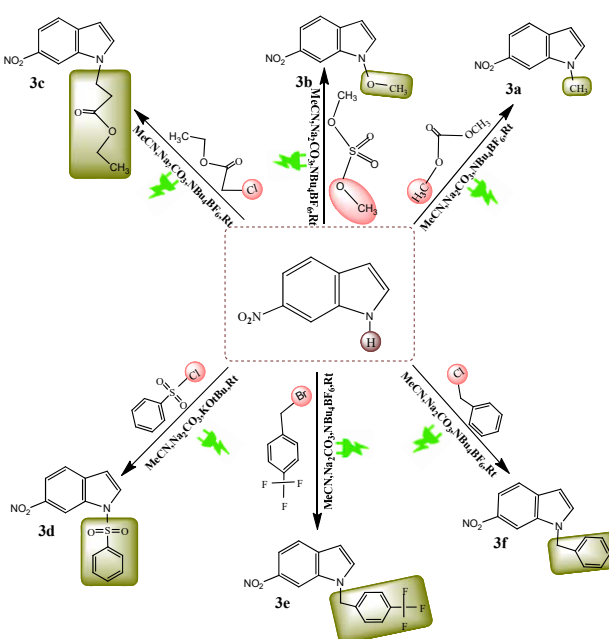


Fig. 3 Pathways for the synthesis of *N*-substituted 6-nitro-1H-indole derivatives (3a-g)

Under similar reaction conditions, *N*-benzylation of basic NH-indole heterocycles provided a series of *N*-benzylation derivatives 3e and 3f in 55% and 69% yields, respectively. On

the other hand, we examined the reaction of 6-nitro-1H-indole (1) with benzene sulfonyl chloride (2d) in the presence of KOtBu in MeCN at room temperature and isolated product 3d in 59% yield (Fig. 3). Success attempt to convert 1 to 3c by the reaction with ethyl-3-chloropropionate (2c) in 65% yield is described.

TABLE I  
THE REACTION YIELDS OF N-SUBSTITUTED 6-NITRO-1H-INDOLE  
DERIVATIVES (3A-F) FORMATION

Entry	R= substituent	Time	Yield (%)	MP (C°)
3a	methyl	20 min	75%	237-240
3b	methoxy	22 min	71%	217-218
3c	ethyl propanoate	25 min	65%	160-165
3d	benzensulfonyl	27 min	59%	190-192
3e	trifluoromethylbenzyl	30 min	55%	197-200
3f	benzyl	23 min	69%	230-231

For further investigation of the resulted *N*-functionalized indole derivatives (3a-f), the measurements of UV-VIS spectroscopy were performed on the products and were recorded in DMF, Fig. 4. UV spectra showed an absorption band at 332-403 nm in all *N*-functionalized derivatives spectra.

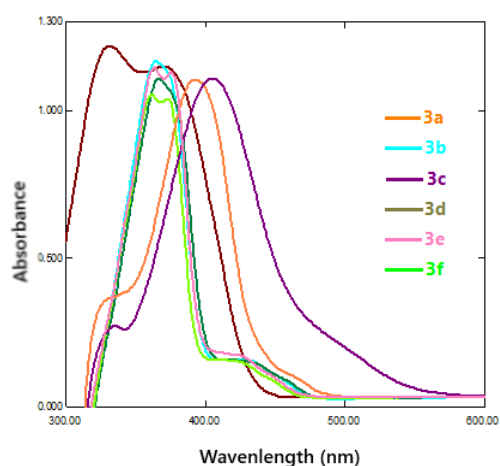


Fig. 4 UV absorption spectra for (3a-f) recorded in DMF.

For further verification, FT-IR spectra measurements were performed on the *N*-functionalized derivatives (3a-f) and were recorded in a spectral range among 4000 and 400  $\text{cm}^{-1}$ . The IR spectra did not display the band at 3410  $\text{cm}^{-1}$  attributed to the NH stretching vibration. The noticed vibrations in the region 3040  $\text{cm}^{-1}$  were specified to aromatic CH stretching; in addition, the band of phenyl ring was observed at 2030  $\text{cm}^{-1}$ . The C=C aromatic stretching was observed at 1590  $\text{cm}^{-1}$ . The band at 1350  $\text{cm}^{-1}$  can be assigned to CH bending. The noticed vibrations in the region 1060–1110  $\text{cm}^{-1}$  were assigned to C=C-H bending. In the IR spectra of all *N*-functionalized derivatives (3a-f), we observed the apparition of strong band at 1360  $\text{cm}^{-1}$  and it was assigned to the stretching vibration of (C-N stretching).

#### IV. MECHANISM

To clear the reaction mechanism for the formation of 3c, 2c was treated with KOtBu in MeCN at room temperature in the presence of ethyl-3-chloropropionate resulting in the formation of 3c 65% yield. Therefore, we can propose the following possible mechanism as shown in Fig. 5. In the following step, efforts were made to verify the reaction mechanism. Because of previous results and reports, [23] a possible mechanism of the electrochemical synthesis of Ethyl 3-(6-nitro-1H-indol-1-yl)propanoate (3c) was suggested as an example (Fig. 5). The structural features and new mechanism have been covered by this work to speed up the reaction.

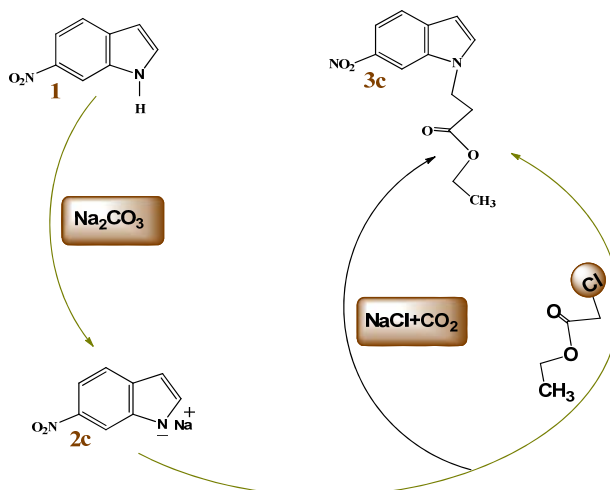


Fig. 5 Proposed mechanism for electrochemical *N*-functionalized derivative (3c)

#### V. CONCLUSION

We report herein a simple process for *N*-methylation or methoxylation of various indole compounds. We have developed an efficient electrochemical synthesis for N-R bond formation by the straightforward dehydrogenative in a simple divided cell. This methodology is simple, selective, and inexpensive. The understanding of the reaction and the improvement of the outcome of the transformation are necessary to avoid the degradation of the formed intermediates, and that is for further verification in the mechanism. This electrochemical process provides access to N-fused heterocycles in straightforward and clean way. Since the electrochemical construction of aromatic heterocycles represents a major part of drugs, it deserves more attention.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## REFERENCES

- [1] L. Wang, Y. Chen, and J. Xiao, "Alkylideneindoleninium ions and alkylideneindolenines: key intermediates for the asymmetric synthesis of 3-indolyl derivatives," *Asian J. Org. Chem.*, vol. 3, no.10, pp.1036-1052, Oct. 2014.
- [2] J. Bergman, and P. Sand, "Synthesis of indoles via ring closure of 2-alkylnitroaniline derivatives," *Tetrahedron*, vol. 46, no.17, pp. 6085-6112, Jan. 1990.
- [3] S. A. Yamashkin, and M. A. Yurovskaya, "Synthesis of nitro-and aminoindoles," *Chem Heterocycl Compd*, vol. 35, no.12, pp. 1426-1432, Dec. 1999.
- [4] K. Yamada, F. Yamada, T. Shiraishi, S. Tomioka, and M. Somei, "Nucleophilic substitution reaction in indole chemistry: 1-methoxy-6-nitroindole-3-carbaldehyde as a versatile building block for 2, 3, 6-trisubstituted indoles," *Heterocycles*, vol. 77, no. 2, pp. 971-982, Jan. 2009.
- [5] S. Sampaioles, S. Gabrielli, R. Ballini, and A. Palmieri, "Two-step synthesis of polysubstituted 6-nitroindoles under flow chemical and microwave conditions," *Adv. Synth. Catal.*, vol. 359, no. 19, pp. 3407-3413, Oct. 2017.
- [6] I. Marcotte, A. Lemire, and J. Lessard, *The Synthesis of Substituted Aminoindoles by Chemical and Electrochemical Reduction of Nitroindoles in Novel Trends in Electroorganic Synthesis*. Tokyo: Springer, 1998, (pp. 329-332).
- [7] C. C. Zeng, F. J. Liu, D. W. Ping, L. M. Hu, Y. L. Cai, and R. G. Zhong, "One-pot electrochemical synthesis of fused indole derivatives containing active hydroxyl groups in aqueous medium," *J. Org. Chem.*, vol. 74, no. 16, pp. 6386-6389, Aug. 2009.
- [8] J. Wu, Y. Dou, R. Guillot, C. Kouklovsky, and G. Vincent, "Electrochemical dearomative 2, 3-difunctionalization of indoles," *J. Am. Chem. Soc.*, vol. 141, no. 7, pp. 2832-2837, Jan. 2019.
- [9] D. I. Bugaenko, A.V. Karchava, and M. A. Yurovskaya, "Synthesis of indoles: recent advances," *Russ. Chem. Rev.*, vol. 88, no. 2, pp. 99-159, Feb. 2019.
- [10] D. Kumar, N. Kumar, S. Kumar, T. Singh, and C.P. Singh, "Synthesis of pharmacologically active 2-phenyl sulpha/substituted indoles," *Int. J. Eng. Sci. Technol.*, vol. 2, no. 7, pp. 2553-2557, July 2010.
- [11] S. Dadashpour, and S. Emami, "Indole in the target-based design of anticancer agents: a versatile scaffold with diverse mechanisms," *Eur. J. Med. Chem.*, vol. 150, pp. 9-29, Apr. 2018.
- [12] J. Dhuguru, and R. Skouta, "Role of indole scaffolds as pharmacophores in the development of anti-lung cancer agents," *Molecules*, vol. 25, no. 7, p. 1615, Jan. 2020.
- [13] C. N. Marconett, S. N. Sundar, K. M. Poindexter, T. R. Stueve, L. F. Bjeldanes, and G. L. Firestone, "Indole-3-carbinol triggers AhR-dependent ERalpha protein degradation in breast cancer cells disrupting an ERalpha-GATA3 transcriptional cross-regulatory loop," *Mol. Biol. Cell*, vol. 21, no. 7, pp. 1166-1177, Feb. 2010.
- [14] Y. M. Jeong, H. Li, S. Y. Kim, W. J. Park, H. Y. Yun, K. J. Baek, N. S. Kwon, J. H. Jeong, S. C. Myung, and D. S. Kim, "Photo-activated 5-hydroxyindole-3-acetic acid induces apoptosis of prostate and bladder cancer cells," *J PHOTOCH PHOTOBIO B*, vol. 103, no. 1, pp. 50-56, Apr. 2011.
- [15] B. Dulla, E. Sailaja, U. R. CH, M. Aeluri, A. M. Kalle, S. Bhavani, D. Rambabu, M. B. Rao, and M. Pal, "Synthesis of indole based novel small molecules and their in vitro anti-proliferative effects on various cancer cell lines," *Tetrahedron Lett.*, vol. 55, no. 4, pp. 921-926, Jan. 2014.
- [16] S. Muralikrishna, P. Raveendreddy, L. K. Ravindranath, S. Harikrishna, and P. A. Raju, "Synthesis characterization and anti-inflammatory activity of indole derivatives bearing-4-oxazetidinone," *J Chem Pharm Res*, vol. 5, no. 10, pp. 280-288, Jan. 2013.
- [17] S. Sarva, J. S. Harinath, S. P. Sthanikam, S. Ethiraj, M. Vaithiyalingam, and S. R. Cirandur "Synthesis, antibacterial and anti-inflammatory activity of bis (indolyl) methanes," *Chin. Chem. Lett.*, vol. 27, no. 1, pp. 16-20, Jan. 2016.
- [18] T. MahamadAlli Shaikh, and H. Debebe, "Synthesis and evaluation of antimicrobial activities of novel N-substituted indole derivatives," *J. Chem.*, vol. 2020, no. 5, pp. 1-159, Apr. 2020.
- [19] S. Sützen, *Antioxidant Activities of Synthetic Indole Derivatives and Possible Activity Mechanisms in Bioactive Heterocycles V*. Berlin: Springer, 2007, pp. 145-178.
- [20] M. S. Estevão, L. C. Carvalho, D. Ribeiro, D. Couto, M. Freitas, A. Gomes, L. M. Ferreira, E. Fernandes, and M. M. Marques, "Antioxidant activity of unexplored indole derivatives: synthesis and screening," *Eur. J. Med. Chem.*, vol. 45, no. 11, pp. 4869-4878, Nov. 2010.
- [21] H. Xu, M. Lv, "Developments of indoles as anti-HIV-1 inhibitors," *Curr. Pharm. Des.*, vol. 15, no. 18, pp. 2120-2148, Jun. 2009.
- [22] A. Attia, O. I. Abd El-Salam, T. E. Youssef, "Electron and hydrogen transfer reductions of some 2, 4-disubstituted pyridines," *Indian J Hetero Chem*, vol. 8, no. 4, pp. 325-328, Apr. 1999.
- [23] S. T. Gadge, A. Mishra, A. L. Gajengi, N. V. Shahi, and B. M. Bhanage, "Magnesium oxide as heterogeneous and recyclable base for the N-methylation of indole and O-methylation of phenol using dimethyl carbonate as a green methylating agent," *RSC Adv.*, vol. 4, no. 91, pp. 50271-50276, Oct. 2014.



**Professor Tamer Ezzat** was born in Egypt. He received the Ph.D. degree in materials science from Eberhard Karls University of Tübingen, Germany in 2004. He worked as a CHAIR PROFESSOR and as a DIRECTOR of Renewable and Sustainable Energy Unit of the Basic and Applied Scientific Research Center from year 2018-till now. He worked at Leibniz Universität Hannover, Germany as a visiting assistant professor in 2007-2011, at the King Abdulaziz University (KAU) as an academic professor in 2012, and then at Imam Abdulrahman Bin Faisal University (IAU), kingdom of Saudi Arabia in 2017. Prof. Youssef received numerous prestigious scientific research publishing awards, particularly in 2011 award conferred by the National Research Centre, 2013, 2014 and 2019 awards of KAU& IAU, kingdom of Saudi Arabia. In addition to his home field in Chemical Industries Research Division.