


Proceeding Paper

Electrochemical Synthesis of Imidazopyridine and Benzylidene Malononitrile †

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† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry, 1–15 November 2022; Available online: <https://sciforum.net/event/ecsoc-26>.

Abstract: A one-pot electrochemical synthesis of two medically interesting compounds is presented. 2-Phenylimidazo[1,2-a]pyridine and 2-(4-fluorobenzylidene)malononitrile were prepared using previously used starting materials. The reaction consists of electrochemical methods without adding additional reagents, giving product yields of about 82–90% at 5.0 V, leading to a different approach for synthesizing important organic compounds with efficient route.

Keywords: electrochemical synthesis; one-pot synthesis; imidazopyridine; benzylidene malononitrile



Citation: Deore, N.R.; Pawar, T.J.; Nagare, Y.K.; Patil, S.V.

Electrochemical Synthesis of Imidazopyridine and Benzylidene Malononitrile. *Chem. Proc.* **2022**, *12*, 83. <https://doi.org/10.3390/ecsoc-26-13567>

Academic Editor: Julio A. Seijas

Published: 14 November 2022

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1. Introduction

Electrochemical synthesis is an environmentally friendly method for building complex structures using electricity, avoiding toxic reagents [1] and enabling the construction of bioactive scaffolds using essential chemical bonds. [2] However, successful electrochemical synthesis requires a thorough understanding of the proper selection of parameters such as electrodes, electrochemical cells, media, etc. [3]. Electrochemical synthesis has replaced numerous organic synthesis routes for many years [4]. These modifications are critical to the advancement of modern synthetic chemistry.

Imidazopyridines are a class of drugs that contain many biological activities in their substructure, such as sedatives [5], antipsychotics [6], gastrointestinal agents [7], anti-inflammatory agents [8], cardiovascular agents [9], antineoplastic agents [10], antiviral agents [11], etc. In the last decade, imidazopyridine has been recognized as a medically necessary scaffold, and various ways to synthesize its substructures have been reported. Here, we present a method for the electrochemical synthesis of 2-phenylimidazo[1,2-a] pyridine from pyridine-2-amine and 2-bromo-1-phenylethan-1-one without adding other reagents.

Under similar reaction conditions, we also synthesized 2-(4-fluorobenzylidene) malononitrile using malononitrile and 4-fluorobenzaldehyde with high yields. This method makes it possible to extend the application of electrochemical synthesis.

2. Materials and Method

2.1. Experimental

All chemicals were purchased from Sigma Chemical Co. The reactions were monitored, and the products' purity was checked by thin-layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates with visualization by UV light. Melting points were determined using the "Buchi Melting Point B-545" instrument. Nuclear magnetic resonance (NMR) spectroscopy was recorded using a 400 MHz NMR spectrometer (Bruker). ¹H and ¹³C NMR spectra were recorded in CDCl₃ and calibrated to the solvent resonance as

an internal standard (^1H NMR, CDCl_3 at 7.26 ppm, ^{13}C NMR, CDCl_3 at 77.0 ppm). Column chromatography was performed on silica gel (230–400 mesh) from Acme Chemical Co., Mumbai, India. The chemicals and solvents used were from LR and purified according to the literature's methods.

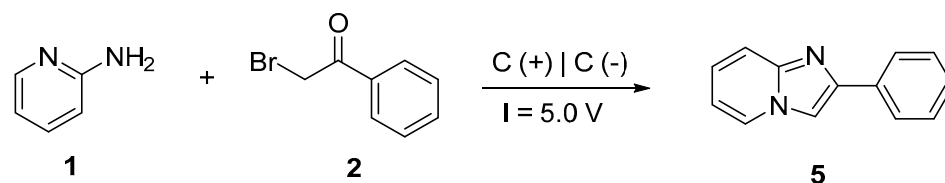
2.2. General Method for Preparation of imidazo[1,2-a]pyridines (1a) by Using Electrochemistry

Unless otherwise stated, all commercially available compounds were used without further preparation. Graphite electrodes were purchased from IKA, and all electrochemical reactions were performed at room temperature using EQUIP-TRONICS model no. EQ -129. A glass slide was placed in a beaker to avoid contact between the two electrodes.

Purification was performed using silica gel column chromatography with a mixture of chloroform and ethyl acetate. A 100 mL dried, reaction vessel was filled with the appropriate 2-amino pyridine (0.94 g, 10 mmol), and phenacyl bromide (1.89 g, 10 mmol) was dissolved in a variable solvent such as acetone, alcohol, THF, or DMF. The electrolysis with constant voltage condition (5.0 V) was carried out using a graphite plate as the anode and a graphite plate as the cathode for two hours by an undivided reaction cell. The reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates under UV light (8:2 to 2:2). The reaction mixture was dried under reduced pressure. The residue was purified by chromatography on silica gel to afford the target product.

2.3. Gram-Scale Synthesis of 2-phenylimidazo[1,2-a] pyridine 5

A 100 mL beaker was equipped with a graphite plate as an anode and cathode connected to a DC-regulated power supply. A glass slide was placed in the beaker to avoid contact between the two electrodes. To the beaker, 2-amino pyridine (0.94 g, 10 mmol) and phenacyl bromide (1.89 g, 10 mmol) were added and dissolved in various solvents such as acetone, alcohol, ethyl acetate, DMSO, and DMF (Table 1). With stirring, the mixture was electrolyzed under constant voltage conditions (5.0 V) at room temperature. TLC was used to monitor the reaction. The electrodes were washed with ethyl acetate (10 mL) and acetone (10 mL); when the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product 5 (Scheme 1).



Scheme 1. Synthesis of 2-phenylimidazo[1,2-a]pyridine 5.

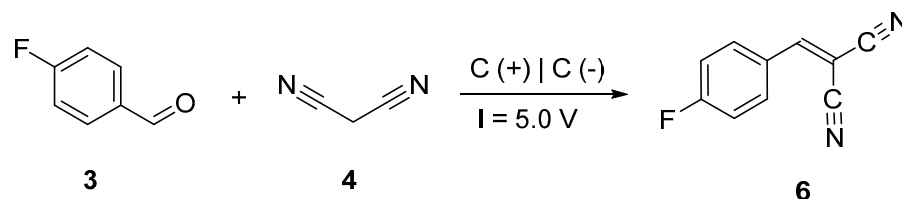
Table 1. Effect of solvent for synthesis for 2-phenylimidazo[1,2-a]pyridine 5.

Entry	Solvent	Time (h)	Yield (%)
1	DMF	1.16	60
2	Ethanol	1.33	65
3	DMSO	2.0	45
4	Ethyl Acetate	0.75	81
5	Acetone	0.5	90

2.4. Gram-Scale Synthesis of 2-(4-fluorobenzylidene)malononitrile 6

Knoevenagel condensation was performed by an electrochemical method. In a 100 mL beaker, a graphite plate was the anode and cathode, and a glass slide was placed in a beaker to avoid contact between the two electrodes. Into the beaker, we added malononitrile (0.266 g) and 4-fluorobenzaldehyde (0.5 mL) dissolved in a variable solvent such as acetone, alcohol, ethyl acetate, and THF (Table 2). With stirring, the mixture was electrolyzed under

constant voltage conditions (5.0 V) at room temperature. TLC was used to monitor the reaction. The electrodes were washed with ethyl acetate (10 mL) and acetone (10 mL); when the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product 6 (Scheme 2).



Scheme 2. Synthesis of 2-(4-fluorobenzylidene) malononitrile 6.

Table 2. Effect of solvent for the synthesis of 2-(4-fluorobenzylidene) malononitrile (6) by using electrochemistry.

Entry	Solvent	Time(h)	Yield(%)
1	THF	1	65
2	Ethanol	1.80	62
3	Ethyl Acetate	1.7	70
4	Acetone	1	82

3. Results and Discussion

3.1. 2-phenylimidazo[1,2-a]pyridine (5) (C₁₃H₁₀N₂)

Yellow solid, m.p 135–139 °C, yield 82%, ¹H NMR (400 MHz, Chloroform-*d*) δ 6.8–6.84 (m, 1H), 7.19–7.26 (m, 1H), 7.61–7.62 (m, 2H), 7.9 (m, 1H), 8.07–8.09 (m, 2H), 8.16–8.14 (m, 1H), 8.24–8.26 (m, 2H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 147.18, 146.25, 132.27, 129.09, 129.09, 127.09, 127.06, 127.06, 126.65, 125.68, 116.74, 111.00, 107.81.

The spectroscopic data matched those that were previously described [1].

3.2. 2-(4-fluorobenzylidene)malononitrile (6) (C₁₀H₅FN₂)

Brown solid, m.p 120–125 °C, yield 90%, ¹H NMR (400 MHz, Chloroform-*d*) δ 7.8 (s, 1H), 6.76–6.71 (m, 2H), 7.2–7.4 (m, 2H).

¹³C NMR (101 MHz, Chloroform-*d*) δ 165.07, 158.7, 134, 128, 117.12, 113.61, 112.58, 81.8.

4. Conclusions

In summary, we succeeded in synthesizing 2-phenylimidazo[1,2-a]pyridine and 2-(4-fluorobenzylidene)malononitrile by electrochemical synthesis without adding any additional reagents. This method is cheaper than conventional organic synthesis and may encourage modern chemists to convert from the use of organic synthesis routes to electrochemical synthesis.

Author Contributions: Conceptualization, S.V.P.; methodology, validation, and execution of chemistry experiments, manuscript preparation, N.R.D.; Formal Analysis, Y.K.N.; Data curation, T.J.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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