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Electrochemical Synthesis of Imidazopyridine and Benzylidene Malononitrile †

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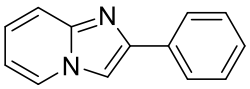
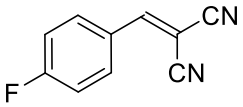
Abstract: A one-pot electrochemical synthesis of two medically targeted, well-known compounds is presented. 2-phenylimidazo[1,2-a] pyridine and 2-(4-flurobenzylidene)malononitrile were prepared using previously used starting materials. The reaction consists of electrochemical methods without adding additional reagents, which deliver the products with about 82–90% yield at 5.0 V, leading to a different approach to synthesizing important organic moieties with efficient pathways.



2-phenylimidazo[1,2-*a*]pyridine



2-(4-fluorobenzylidene)malononitrile

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

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1. Introduction

Electrochemical synthesis is an environment-friendly method for constructing complex structures using electricity by avoiding toxic reagents,[1] allowing essential chemical bonds to build bioactive skeletons.[2] However, a successful electrochemical synthesis requires a precise understanding of the proper selection of parameters, such as electrodes, electrochemical cells, the media, etc.[3] Electrochemical synthesis has been replacing numerous organic synthetic pathways for many years. These modifications are critical for the advancement of modern synthetic chemistry.

Imidazopyridine is a class of drugs that contain many biological activities in its substructure, such as sedatives,[4] antipsychotics,[5] gastrointestinal,[6] anti-inflammatories,[7] cardiovascular,[8] antineoplastic,[9] Antiviral,[10] etc. Over the past decade, Imidazopyridine has been recognized as a medically necessary skeleton, and various pathways have been reported to synthesize its substructures. Here, we present an electrochemical synthesis of 2-phenylimidazo[1,2-a] pyridine from pyridin-2-amine and 2-bromo-1-phenylethan-1-one without adding other reagents.

Using a similar reaction condition, we also synthesized 2-(4-fluorobenzylidene) malononitrile by using malononitrile and 4-fluorobenzaldehyde with high yields. This methodology allows to explore the expanding application of electrochemical synthesis.

2. Materials and Method

2.1. Experimental

Chemicals were purchased from Sigma Chemical Co. Reactions were monitored, and the purity of the products 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 on the apparatus, "Buchi Melting Point B-545". Nuclear magnetic resonance (NMR) spectroscopy was recorded on a 400 MHz-NMR Spectrometer (Bruker). ^{1}H and ^{13}C NMR spectra were recorded in CDCl3 and calibrated to the solvent resonance as internal standard (^{1}H NMR, CDCl3 at 7.26 ppm, ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Column chromatography was performed on silica gel (230–400 mesh) supplied by Acme Chemical Co. The chemicals and solvents used were of LR grade and were purified as per literature methods.

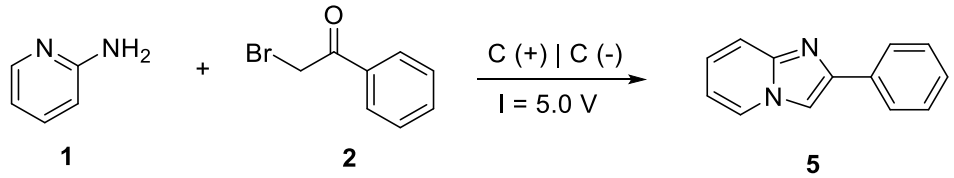
2.2. General Method for Preparation of Imidazo[1,2-a]pyridines (1a) by Using Electrochemistry

Unless otherwise stated, all commercially available compounds were used as received without further purification. Graphite electrodes were purchased from IKA, and all electrochemical reactions were performed at room temperature using EQUIP-TRONICS Model No. EQ-129. In a beaker, to avoid contact between two Electrodes, Glass Slide is placed.

Purification on silica gel column chromatography using a mixture of Chloroform and Ethyl acetate. A dried undivided reaction cell charged with appropriate 2-Amino pyridine (0.94 g, 10 mmol), phenacyl bromide (1.89 g, 10 mmol) dissolved in a Variable Solvents such as Acetone, Alcohol, THF, DMF in Beaker. The reaction mixture was electrolyzed using a graphite plate as the anode and Cathode at Constant Voltage Condition (I = 5.0 V) under an atmosphere at room temperature. Electrolysis with a 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 through an undivided reaction. Reactions under standard conditions were standardized 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.

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

A 100 mL beaker was equipped with a graphite plate as the anode and a graphite plate as the cathode, which was connected to a DC regulated power supply. In a beaker to avoid contact between two electrodes, a glass slide is placed. To the beaker, 2-Amino pyridine (0.94 gm, 10 mmol), phenacyl bromide (1.89 gm, 10 mmol) was added and dissolved in various solvents such as acetone, alcohol, ethyl acetate, DMSO & DMF. The mixture was electrolyzed under constant Volt conditions (5.0 V) under atmosphere at room temperature while stirring. The reaction was monitored by TLC. Electrodes were washed with ethyl acetate (10 mL) & acetone (10 mL); when the reaction was finished, the solvent was removed under reduced pressure.



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

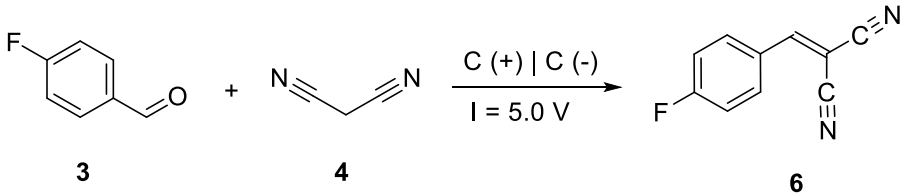
Table 1. Effect of solvent for synthesis for 2-phenylimidazo[1,2-a]pyridine **5**.

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**

A 100 mL beaker was equipped with a graphite plate as the anode and a graphite plate as the cathode, which was connected to a DC-regulated power supply. In a beaker to avoid contact between two electrodes, a glass Slide is placed. To the beaker, we added malononitrile (0.266 g) & 4-flurobenzaldehyde (0.5 mL) dissolved in a variable solvent such as acetone, alcohol, ethyl acetate, THF. Knovengel Condensation is done by electrochemical method. While stirring, the mixture was electrolyzed under constant volt conditions (5.0 V) under the atmosphere at room temperature. The reaction was monitored by TLC. Electrodes were washed with ethyl acetate (10 mL) & acetone (10 mL); when the reaction was finished, the solvent was removed under reduced pressure.



3 **4** **6**

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

Table 2. Effect of solvent for synthesis of 2-(4-flurobenzylidene) malonitrile (**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***) (*$C_{13}H_{10}N_2$*)*

Yellow solid, m.p 135–139 °C, yield 82%, ^{1}H NMR (400 MHz, Chloroform) 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). ^{13}C NMR (100 MHz, Chloroform) 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 match with those previously described [11].

*3.2. 2-(4-Flurobenzylidene)malononitrile (***6***) (*$C_{10}H_5FN_2$*)*

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

^{13}C NMR (100 MHz, Chloroform) δ 165.07, 158.7, 134, 128, 117.12, 113.61, 112.58, 81.8.

4. Conclusions

In conclusion, we have successfully synthesized 2-phenylimidazo[1,2-a] pyridine and 2-(4-flurobenzylidene)malononitrile via electrochemical synthesis without adding any additional reagent. This method is cheaper than regular organic synthesis and can motivate modern chemists to modify the organic synthesis pathways to electrochemical synthesis.

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Conflicts of Interest:

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