Simple Electrochemical Synthesis of Pyrazolo[4,3-c]quinoline Derivatives

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Abstract. Valuable pyrazolo[4,3-c]quinoline derivatives were synthesized efficiently from the easily available 7-Chloro-4-hydrazinoquinoline through electrochemical synthesis under moderate and scalable electrolytic conditions afforded linear hydrazones (3a-g) then the cyclized one (4a-g). The conduct of the reactions was performed in a simple undivided cell under constant current without oxidizing reagents or transition metal catalysts. The synthesized products of the cyclization reaction have been characterized via UV/Vis spectrophotometry, 1H-NMR and FTIR spectroscopy, the understanding of the mechanism of the reaction, the importance of reactant structure to control the rate of the reaction and equilibria in the process is substantial. The applying of this protocol to the effective synthesis of key intermediates for antidiabetic compounds was done.

Keywords: Green chemistry, Quinoline, Heteroaromatic, Organic electrosynthesis

1. Introduction

Organic electrosynthesis (OES) is considered a versatile technique since it is a technique which has environmentally friendly nature; moreover, it is classified as a clean and green procedure. OES method overcomes the conventional processes whether organic synthesis or synthetic via many advantages, such as mild reaction conditions, higher yield, higher products selectivity, easy to control process [1-4]. In recent times, OES has become increasingly popular due to the progress made in the field and development of relevant technology which allows an increasing number of chemical methodologies [5, 6]. Besides the increased safety and improvements in multistep synthesis, advantages such as improved mixing and heat management, energy efficiency, scalability, waste generation, access to a wider range of reaction condition, and reproducibility potential benefit of green chemistry [7].

Nowadays, this technique is more commonly used to prepare a series of heterocyclic compounds such as Imidazoquinolines, benzothiazoles [8-10].

Quinoline and their derivatives are an important category of heterocycles, they used as beneficial dyes and intermediates in organic synthesis. Furthermore, they are used to make rubber and chemicals [11].

They have more substantial biological activities and pharmacological properties such as anticancer [12-14], fungicidal [15], anti-malarial [16], anti-leishmanial [17], antibacterial [18], anticonvulsant [19]. In addition, they possess antitumor activity studies [20].

Great attention has been concentrated on the synthesis of quinoline derivatives such as their hydrazone derivatives in the last years because they are possessed advantageous biological activities. Quinoline hydrazone derivatives used as antimicrobial [21], antifungal agents [22], anti-tubercular [23], anti-tumoral [24], and anti-leishmanial [25], they can be prepared by traditional methods of synthesis from the reaction of arene aldehydes [26, 27], with quinoline hydrazine derivatives.

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In a continuation of our previous work [28], in 1999, Youssef’s group reported the electrochemical reduction of some 2,4-disubstituted pyridines. After a long gap, we report herein for the first time, the design of a novel electrochemical reactor and its application in the cyclic hydrazone formation via the electrochemical reaction of heteroaromatic hydrazines when they react with aromatic aldehydes to give the cyclic heteroaromatic hydrazones, by using an undivided cell.

2. Materials and methods

Materials and reagents
All reagents used were of the highest purity available. 7-Chloro-4-hydrazinoquinoline (99.0% purity) was purchased from Sigma-Aldrich, while benzaldehyde, 4-dimethylaminobenzaldehyde, 2-trifluoromethoxybenzaldehyde, 4-nitrobenzaldehyde, 4-methoxybenzaldehyde, p-tolualdehyde, and 2-chlorobenzaldehyde were purchased from Fluka (99.0% purity). The supporting electrolyte tetrabutylammonium tetrafluoroborate (TBATFB) 99%.

Cell and electrode design
The controlled potential organic electrosynthesis experiments were conducted in an undivided 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 platinum plate electrode (10 mm×10 mm×0.2 mm) as the anode and the cathode, respectively.

Instruments
A Stuart SMP30 apparatus was used to determine melting points via open capillary tubes, and they were uncorrected. Thin-layer chromatography (TLC) was the technique that used to monitor the progress of all reactions and determine the purity of all compounds performed on aluminum foil sheets, and these sheets were precoated 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 1H NMR spectra were conducted on an NMR spectrometer device (Bruker Avance II, 300 MHz) and were recorded in deuterated solvent that was dimethyl sulfoxide-d6 (DMSO-d6) contained in tetramethylsilane (TMS). Chemical shifts (δ) were reported in ppm downfield proportional to tetramethylsilane (TMS, δ = 0 ppm); moreover, the peak of the residual proton of the solvent (DMSO-d6) appeared at δ = 2.53 ppm. The measurements of mass spectrometric were carried out by the Shimadzu LC-MS/MS 8050 spectrometer operating at 70 eV and were reported in mass/charge (m/z). The measurements of UV-Vis spectra 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 facility.

General procedure for the organic electrosynthesis of 7-chloro-1H-pyrazolo[4,3-c]quinoline derivatives (4a-g)

The crude 7-chloro-4-hydrazinoquinolines (5; 0.6 mmol), aldehydes 2a-g and MeCN (10 mL) were added in a 150 mL undivided cell; moreover, this mixture was stirred at room temperature or heated until TLC showed that condensation was done. Next, Tetrabutylammonium tetrafluoroborate (TBATFB) (0.5 mmol) was added and followed by MeCN (5 mL) and H2O (1 mL). Meanwhile, the cell was equipped with a graphite electrode as the anode (ϕ 6 mm, about 10 mm immersion depth in solution) and a platinum plate electrode as the cathode (10 mm×10 mm×0.2 mm). The entire mixture was stirred and electrolyzed under a constant current of 10 mA for 20-30 min. The reaction mixture was transported to a single-necked flask after the reaction was finished; therefore, the MeCN was removed by rotary evaporation. Then, the remains of the mixture were washed and extracted with water and CH2Cl2 (10 mL x 3), respectively. The organics were combined, dehydrated over Na2SO4, and concentrated.
obtaining of the desired products 4a-g with high purity was achieved by flash column chromatography on silica gel.

7-chloro-3-phenyl-1H-pyrazolo[4,3-c]quinoline (4a)
Prepared from 2a as a pale green solid; m.p. 224-234°C; Rf = 0.7; IR (KBr): v= 3400 cm⁻¹ (N-H stretching), 3000 cm⁻¹ (C-H aromatic stretching), weak overtone peaks at 2000 cm⁻¹ (Mono substituted phenyl), 1600 cm⁻¹ (C=N stretching), 1450 cm⁻¹ (C=C aromatic stretching), 1350 cm⁻¹ (C-H bending), 1200 cm⁻¹ (C-N stretching), 1100 cm⁻¹ (C=C-H bending). Two strong bands at 750 and 690 cm⁻¹ (Mono substituted), 550 cm⁻¹ (C-Cl stretching);¹H-NMR (126 MHz, DMSO-d⁶): δ= 8.47 (1H, 2), 7.91 (2H, 5&6), 7.82 (1H;8), 7.70 (1H;6), 7.51 (1H;7), 7.23 (1H;3) ppm. UV–Vis (DMF): λmax (nm): 373, 368, 361 nm. MS (EI): m/z = 279.72 (M⁺). Elemental analysis: C₁₆H₁₅N₃Cl; Found C 67.20, H 3.10, N 14.12, Calc. C 68.70, H 3.60, N 15.02.

7-chloro-3-(p-tolyl)-1H-pyrazolo[4,3-c]quinoline (4b)
Prepared from 2b as a brown solid; m.p. 210-212°C; Rf = 0.9; IR (KBr): v= 3416 cm⁻¹ (N-H stretching), 3010 cm⁻¹ (C-H aromatic stretching), 2900 cm⁻¹ (CH₃ stretching), 4 weak overtone peaks at 2000 cm⁻¹ (mono substituted phenyl), 1610 cm⁻¹ (C=N stretching), 1460 cm⁻¹ (C=C aromatic stretching), 1360 cm⁻¹ (C-H bending), 1230 cm⁻¹ (C-N stretching), 1156 cm⁻¹ (C-C stretching), 1116 cm⁻¹ (C=C-H (bending). One strong band at 813 cm⁻¹ (para-di-substituted), 554 cm⁻¹ (C-Cl stretching);¹H-NMR (126 MHz, DMSO-d⁶): δ= 8.36 (1H, 2), 7.81 (2H, 5&6), 7.67 (1H;8), 7.54 (1H;6), 7.30 (1H;m), 2.34 (3H;ppm. UV–Vis (DMF): λmax (nm): 375, 370, 363 nm. MS (EI): m/z = 293.75 (M⁺). Elemental analysis: C₁₇H₁₂N₃Cl; Found C 69.98, H 3.90, N 13.90, Calc. C 69.51, H 4.12, N 14.30.

7-chloro-3-(4-methoxyphenyl)-1H-pyrazolo[4,3-c]quinoline (4c)
Prepared from 2c as a pale brown solid; m.p. 175-195°C; Rf = 0.76; IR (KBr): v= 3423 cm⁻¹ (N-H stretching), 3011 cm⁻¹ (C-H aromatic stretching), 2930 cm⁻¹ (CH₃ stretching), 4 weak overtone peaks at 2000 cm⁻¹ (mono substituted phenyl), 1605 cm⁻¹ (C=N stretching), 1454 cm⁻¹ (C=C aromatic stretching), 1352 cm⁻¹ (C-H bending), 1253 cm⁻¹ (C-O stretching), 1210 cm⁻¹ (C-N stretching), 1070 cm⁻¹ (C=C-H (bending), One strong band at 825 cm⁻¹ (para-di-substituted), 559 cm⁻¹ (C-Cl stretching);¹H-NMR (126 MHz, DMSO-d⁶): δ= 7.85 (1H;2), 7.76 (2H, 5&6), 7.60 (1H;8), 7.35 (1H;6), 7.04 (1H;m), 3.81 (3H;ppm. UV–Vis (DMF): λmax (nm): 379, 375, 366 nm. MS (EI): m/z = 309.75 (M⁺). Elemental analysis: C₁₅H₁₁N₃ClO; Found C 65.01, H 3.90, N 12.97, Calc. 65.52, H 4.12, N 13.57.

7-chloro-3-(p,N,N-dimethylphenyl)-1H-pyrazolo[4,3-c]quinoline (4d)
Prepared from 2d as a red-brown solid; m.p. 180-183°C; Rf = 0.5; IR (KBr): v=3424 cm⁻¹ (N-H stretching), 3013 cm⁻¹ (C-H aromatic stretching), 2911 cm⁻¹ (CH₃ stretching), 4 weak overtone peaks at 2015 cm⁻¹ (mono substituted phenyl), 1667 cm⁻¹ (C=N stretching), 1453 cm⁻¹ (C=C aromatic stretching), 1359 cm⁻¹ (C-H bending), 1260 cm⁻¹ (C-N stretching), 1054 cm⁻¹ (C=C-H (bending). One strong band at 807 cm⁻¹ (para-di-substituted), 554 cm⁻¹ (C-Cl stretching);¹H-NMR (126 MHz, DMSO-d⁶): δ= 7.80 (1H;2), 7.61 (2H, 5&6), 7.50 (1H;8), 7.27 (1H;6), 6.77 (1H;m), 2.97 (6H;p) ppm. UV–Vis (DMF): λmax (nm): 392, 378, 367 nm. MS (EI): m/z = 322.79 (M⁺). Elemental analysis: C₁₈H₁₅N₃ClO; Found C 67.54, H 4.01, N 16.80, Calc. C 66.98, H 4.68, N 17.36.

7-chloro-3-(4-nitrophenyl)-1H-pyrazolo[4,3-c]quinoline (4e)
Prepared from 2e as a pale brown solid; m.p. 200-210°C; Rf = 0.7; IR (KBr): v= 3433 cm⁻¹ (N-H stretching), 3020 cm⁻¹ (C-H aromatic stretching), 4 weak overtone peaks at 2000 cm⁻¹ (mono substituted phenyl), 1622 cm⁻¹ (C=N stretching), 1559 cm⁻¹ (N=O stretching), 1456 cm⁻¹ (C=C aromatic stretching), 1355 cm⁻¹ (C-H bending), 1210 cm⁻¹ (C-N stretching), 1120 cm⁻¹ (C=C-H bending). One strong band at 800 cm⁻¹ (para-di-substituted), 553 cm⁻¹ (C=Cl stretching);¹H-NMR (126 MHz, DMSO-d⁶): δ=8.40 (1H;2), 8.29 (2H, 5&6), 8.05 (1H;8), 8.02 (1H;6), 7.58 (1H;m) ppm. UV–Vis (DMF): λmax (nm):
405,387,367 nm. MS (EI): m/z = 324.72 (M+). Elemental analysis: C_{16}H_{9}N_{4}ClO_{2}; Found C 58.93, H 2.02, N 17.83, Calc. C 59.18, H 2.79, N 17.25.

7-chloro-3-(2-chlorophenyl)-1H-pyrazolo[4,3-c]quinoline (4f)
Prepared from 2f as a green brown solid; m.p. 184-213°C; Rf = 0.95; IR (KBr): ν= 3434 cm⁻¹ (N-H stretching), 3011 cm⁻¹ (C-H aromatic stretching), 4 weak overtone peaks at 2078 cm⁻¹ (mono substituted phenyl), 1602 cm⁻¹ (C=N stretching), 1453 cm⁻¹ (C=C aromatic stretching), 1352 cm⁻¹ (C-H bending), 1220 cm⁻¹ (C-N stretching), 1130 cm⁻¹ (C=C-H bending). One strong band at 756 cm⁻¹ (ortho-di-substituted), 555 cm⁻¹ (C-Cl stretching);¹H-NMR (126 MHz, DMSO-d₆): δ = 8.38 (1H; 2), 8.16 (2H; 5&6), 7.86 (1H;8), 7.49 (1H;m), 7.37 (1H;p) ppm. UV–Vis (DMF): λ max (nm): 371, 366, 360 nm. MS (EI): m/z = 314.17 (M+). Elemental analysis: C_{16}H_{9}N_{3}ClO; found C 60.13, H 2.12, N 12.92, Calc. C 61.17, H 2.89, N 13.37.

7-chloro-3-(2-(trifluoromethoxy)phenyl)-1H-pyrazolo[4,3-c]quinoline (4g)
Prepared from 2g as a yellow-green solid; m.p. 150-232°C; Rf = 0.86; IR (KBr): ν= 3411 cm⁻¹ (N-H stretching), 3023 cm⁻¹ (C-H aromatic stretching), 4 weak overtone peaks at 2033 cm⁻¹ (mono substituted phenyl), 1645 cm⁻¹ (C=N stretching), 1452 cm⁻¹ (C=C aromatic stretching), 1352 cm⁻¹ (C-H bending), 1267 cm⁻¹ (C-O stretching), 1204 cm⁻¹ (C-N stretching), 1153 cm⁻¹ (C-F stretching), 1180 cm⁻¹ (C=C-H bending). One strong band at 756 cm⁻¹ (ortho-di-substituted), 552 cm⁻¹ (C-Cl stretching);¹H-NMR (126 MHz, DMSO-d₆): δ = 8.38 (1H;2), 8.19 (2H; 5&6), 7.87 (1H;8), 7.48 (1H;m), 7.39 (1H;p) ppm. UV–Vis (DMF): λ max (nm): 381, 364, 360 nm. MS (EI): m/z = 363.72 (M+). Elemental analysis: C_{17}H_{9}N_{3}ClF_{3}O, found C 55.90, H 2.11 N 11.30, Calc. C 56.14, H 2.49, N 11.55.

3. Results and discussions
The electrochemical synthesis of hydrazone derivatives (4a-g) through dehydrogenative cyclization was conducted in an undivided cell, and the cell was equipped with a graphite electrode as the anode and a platinum plate electrode as the cathode while Tetrabutylammonium tetrafluoroborate (TBATFB) was used as the supporting electrolyte. The electrochemical reactions proceed without oxidizing reagents or transition metal catalysts (Figure 1).

As explained previously, the reaction can be carried out in two steps to provide the desired cyclic hydrazones (4a-g) within 20-30 min with 40-84% yields. The first step is chemical condensation of
linear hydrazones 7-chloro-4-quinolinylhydrazones derivatives (3a-g) and the second step is the electrochemical cyclization (4a-g) in Scheme 1. All linear hydrazones 7-chloro-4-quinolinylhydrazones derivatives formed during all the reactions did not interfere with the cyclization reaction.

Scheme 1. General scope for the synthesis of cyclic hydrazones (4a-g)

The substrate scope for the synthesis of cyclic hydrazones (4a-g) was then explored Scheme 1. First, the benzene ring of aldehydes (2a-g) at the para-position could be substituted with electron donating groups such as methyl (2b), methoxy (2c), dimethyl amine (2d) and with electron-withdrawing substituents such as nitro (2e). Second, substituted groups at the ortho-position such as chloro (2f) and trifluoro methoxy (2g) have been used.

The efficiency of the reaction of the electron-deficient substrates was decreased due to the possibility of the difficulty in cyclizing the electrophilic C-radical onto the N-phenyl ring.

Hydrazones bearing methyl (2b), methoxy (2c), and dimethyl amine (2d) groups reacted in a smooth way to afford the desirable cyclic products in higher yields (70-84%) but, the reaction of nitro-derived hydrazone (2e) afforded 4e in lower yield (40 %) Scheme 2.

Scheme 2. Pathways for the synthesis of pyrazolo[4,3-c]quinoline derivatives
Our experiments were carried out in the undivided cell, and the applied potential to the working electrode was 2.5 V. The electrodes were placed in an undivided cell as close to each other as possible to reduce cell resistance. Platinum electrode selected as the working electrode since it has been proven that it has a good activity toward the organic electrosynthesis [29]. The reaction proceeded at the cathode graphite.

For optimal results, stirring can be introduced to increase mass transfer, however, since no laminar flow over the electrode surface is obtained, such setups are not considered hydrodynamic electrodes.

In this setup, the maximum cyclic hydrazones (4a-g) concentration was reached within the first 20 min as described in (Table 1). The course of the reaction was followed up via TLC each ten minutes. After 30 min, the final concentration was already reached. The experiment was repeated and blocking the surface of the electrode was possible.

For further investigation of the resulted cyclic hydrazones (4a-g), the measurements of UV-VIS spectroscopy were performed on the products and were recorded in DMF Figure 2. UV spectra show an absorption band at (361-366) nm in all aldehyde's spectra.

| Entry | Substituents | Reaction Time | Yield (%) | MP (°C) |
|-------|--------------|---------------|-----------|---------|
| 4a    | R_1= R_2= R_3= R_4=R_5=H | 25 min | 68% | 224-234 |
| 4b    | R_3=CH_3; R_1= R_2= R_4=R_5=H | 25min | 70% | 210-212 |
| 4c    | R_3=OCH_3; R_1= R_2= R_4=R_5=H | 20 min | 80% | 175-195 |
| 4d    | R_3= N(CH_3)_2; R_1= R_2= R_4=R_5=H | 20 min | 84% | 180-183 |
| 4e    | R_3=NO_2; R_1= R_2= R_4=R_5=H | 30 min | 45% | 200-210 |
| 4f    | R_3=Cl; R_1= R_2= R_4=R_5=H | 25 min | 67% | 184-193 |
| 4g    | R_3= OCF_3; R_1= R_2= R_4=R_5=H | 30 min | 64% | 150-232 |

Figure 2. UV absorption spectra for cyclic hydrazone derivatives (4a-g) recorded in DMF

For further verification, the measurements of FT-IR spectra were performed on the cyclic hydrazone derivatives (4a-g) and were recorded in a spectral range between 4000 and 400 cm\(^{-1}\). The IR spectra displayed a strong band at 3400 cm\(^{-1}\) attributed to the NH stretching vibration. The noticed vibrations in the region 3000 cm\(^{-1}\) were specified to aromatic CH stretching; in addition, the band of phenyl ring was observed at 2000 cm\(^{-1}\). The C=C aromatic stretching was observed at 1450 cm\(^{-1}\). The band at 1350 cm\(^{-1}\)
can be assigned to CH bending, whereas the band at 1200 cm\textsuperscript{-1} was observed to C-N stretching. The noticed vibrations in the region 1050–1100 cm\textsuperscript{-1} were assigned to C=C-H bending. In the IR spectra of all cyclic hydrazone derivatives (4a-g), we observed the apparition of a strong band at 1600 cm\textsuperscript{-1} and it was assigned to the stretching vibration of C=N.

**Mechanism**

In the following step, efforts were made to verify the reaction mechanism. Because of previous results and reports [2], a possible mechanism of the electrochemical synthesis of hydrazones through the dehydrogenative cyclization of the linear hydrazones 7-chloro-4-quinolinyldihydrazone derivatives was suggested via using the reaction of hydrazine; 7-chloro-3-phenyl-1H-pyrazolo[4,3-c]quinoline (4a) as an example Scheme 3. The structural features and new mechanism have been covered by this work to speed up the reaction. Although the synthesis of hydrazone was a direct condensation Scheme 1, the reaction was not reversible in aqueous media.

![Scheme 3. Proposed mechanism for electrochemical dehydrogenative cyclization](image)

**4. Conclusions**

In conclusion, we have developed an efficient electrochemical system for cyclic hydrazone (4a-g) formation of the linear hydrazones 7-chloro-4-quinolinyldihydrazone derivatives (3a-g) by the straightforward dehydrogenative in a simple undivided cell. The electroosynthetic pathway of the cyclic hydrazone formation reaction of hydrazine with aromatic aldehydes has been investigated. 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 fused heterocycles in a straightforward and clean way. Since the electrochemical construction of aromatic heterocycles represents a major part of drugs, it deserves more attention.
Acknowledgments: This work was realized in a close collaboration with the laboratory of Prof. Dr. Tamer Ezzat: Director of Renewable and Sustainable Research Unit-Basic and Applied Scientific Research Center; Imam Abdulrahman Bin Faisal University, Saudi Arabia.

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Manuscript received: 06.11.2020