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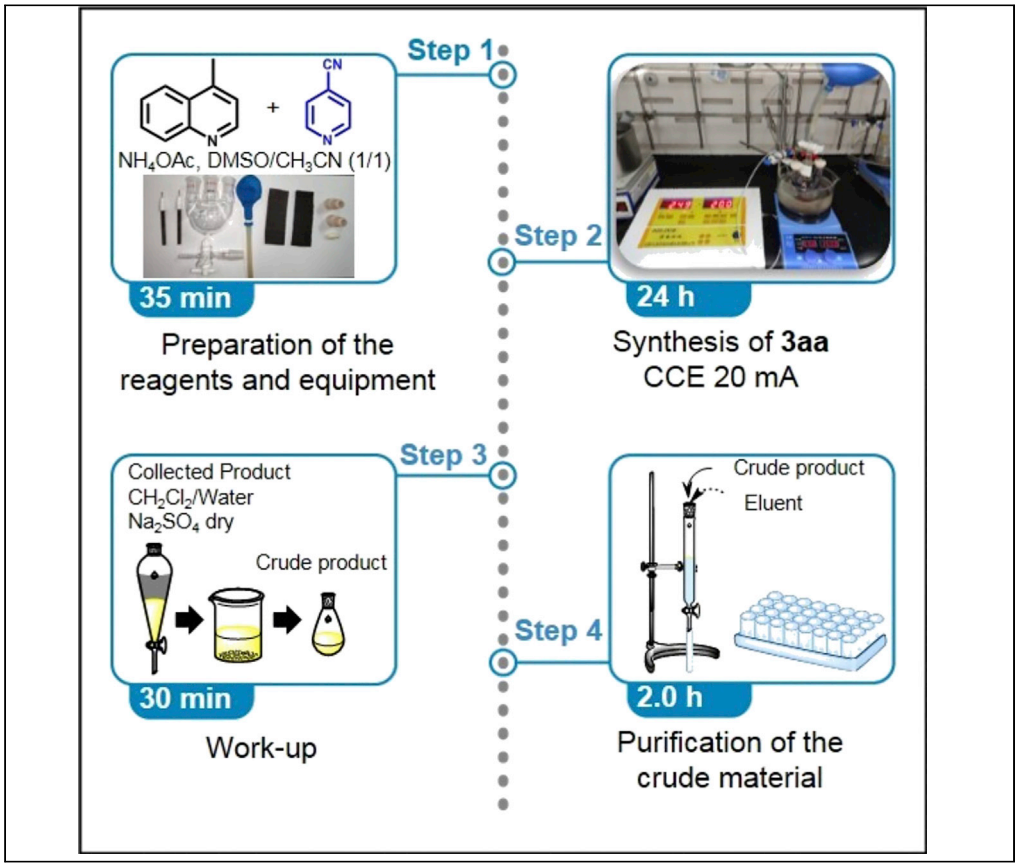
An electrochemical gram-scale protocol for pyridylation of inert N-heterocycles with cyanopyridines



Here, we present a protocol to decyanopyridate inert N-heterocycles access to N-fused heterocycles via the mechanism of dual proton-coupled electron transfer (PCET). We describe a detailed guide to performing an electrochemical gram-scale protocol for decyanopyridation of inert N-heterocycles. The desired pyridylated quinolone is synthesized in a 5.0 mmol scale with a yield of 76%.

Publisher's note: Undertaking any experimental protocol requires adherence to local institutional guidelines for laboratory safety and ethics.

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Highlights

Electrochemical NH_4^+-assisted dual PCET followed by radical cross-coupling

Synthesis of N-fused heterocycles in gram scale

Application of electron-deficient quinolines as radical precursors

The protocol is limited to cyanopyridines

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An electrochemical gram-scale protocol for pyridylation of inert N-heterocycles with cyanopyridines

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SUMMARY

Here, we present a protocol to decyanopyridate inert N-heterocycles access to N-fused heterocycles via the mechanism of dual proton-coupled electron transfer (PCET). We describe a detailed guide to performing an electrochemical gram-scale protocol for decyanopyridation of inert N-heterocycles. The desired pyridylated quinolone is synthesized in a 5.0 mmol scale with a yield of 76%.
The protocol is limited to cyanopyridines.
For complete details on the use and execution of this protocol, please refer to Niu et al. (2022).

BEFORE YOU BEGIN

A convenient method to construct pyridylated quinolines from abundant precursors is an important synthetic goal for applications in pharmaceuticals, materials, natural product molecules, and organic functional materials (Yadav and Reddy, 2003; Chen et al., 2006; Moser et al., 2008; Misale et al., 2012; Afeli et al., 2013; Felding et al., 2014; Kouznetsov et al., 2017;, 2007; Gil-Martins et al., 2020; Nakao, 2011; Murakami et al., 2017; Wang et al., 2021; Zhou and Jiao, 2021). As a result, Molina and co-workers have disclosed a two-step method synthesis of pyridylated quinolines starting from enamines and pyridine-4-carbonyl chlorides assisted with pyridine and phosphoryl trichloride (Molina et al., 1993). Subsequently, Kouznetsov's group reported that employing $BF_3{\cdot}OEt_2$ as a catalyst has achieved the Kametani reaction to construct pyridylated quinolones (Kouznetsov et al., 2007). However, these traditional methods are limited by the inaccessibility of substrates, harsh reaction conditions, and unsafe conditions. It is considered a straightforward and practical synthetic route for N-fused heterocycles and bidentate nitrogen ligand compounds from the inert N-heterocycles with cyanopyridine derivatives via the mechanism of radical cross-coupling reaction (Proctor and Phipps, 2019; Ma et al., 2017; Ma and Herzon, 2016). However, these electron-deficient pyridine derivatives compounds are difficult to activate due to their inherently negative electrode potential. Our exploring the dual proton-coupled electron transfer (PCET) strategy may provide a promising roadmap for the electrochemical pyridylation of inert N-heterocycles with cyanopyridines (Niu et al., 2022).

In our previous study, we have achieved the C3 pyridylation of quinoxalin-2(1H)-ones with readily available cyanopyridines under electrochemical conditions by employing 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as the protonation reagent (Wen et al., 2021). Nonetheless, the pyridylation of

Table 1. Preparation of clean electrodes and assembly

Cell and electrodes	Specification
three-necked flask (cell)	150.0 mL
carbon rods	φ = 6.0 mm, L = 8.0 cm
carbon felt	2.0 × 4.0 cm^{-2}
stirring bar	2.0 cm

electron-deficient quinolines cannot be realized by adopting the previous protocol (Yang et al., 2022).

Herein, the current protocol describes the first straightforward and practical strategy for the pyridylation of electron-deficient quinolines aided by NH_4^+ in an undivided cell via the dual PCET followed by the radical cross-coupling in mmol scale. For the same experiment performed in batch, please refer to Niu et al. (2022).

Preparation of the reagents and equipment

A complete list of reagents and equipment can be found in the "key resources table".

Preparation of the reagent reservoirs

Timing: 30 min

In this step, cleaning of electrodes and assembly of cells, and reagent reservoirs for the reaction are prepared.

Note: wash the carbon rods and carbon felt with deionized water and ethanol 3 times under sonication, and dried in a forced air drying oven at 70°C.

1. Preparation of electrodes and assembly (Table 1).
   a. Wash the carbon rods and carbon felt with deionized water and ethanol 3 times under sonication, then dry in a forced air drying oven at 70°C.
   b. Assemble carbon rods (Φ = 6 mm, rubber bands tied with carbon felt and wrapped along the long sides) in a 150.0 mL three-necked flask as the anode and cathode, with a distance of 5–6 cm between electrodes (Figure 1B).

   Note: hole-drilled caps are used to secure the electrodes into undivided cell.

   c. Add a stirring bar.

2. Preparation of reaction substrates and seal cells (Table 2).
   a. In the assembled cell add 715.9 mg of 4-methylquinoline (**1a**), 1.561 g of 4-cyanopyridine (**2a**), and 577.5 mg of NH_4OAc.
   b. Seal the three-necked flask with two threaded rubber stoppers and three-way piston. Place the reaction mixture under vacuum *via* an inlet/outlet needle connected to a Nitrogen/vacuum Schlenk manifold. Refill the cell with nitrogen.

   Note: Argon can be used as well to place the reaction under an inert atmosphere.

   c. Repeat the evacuation-refill cycle three times, so that the reaction mixture is under the nitrogen atmosphere.
   d. Add to the cell 50.0 mL of a mixture of 1:1 of dry dimethyl sulfoxide (analytical reagent = AR) and acetonitrile (AR) with a syringe under the nitrogen atmosphere.

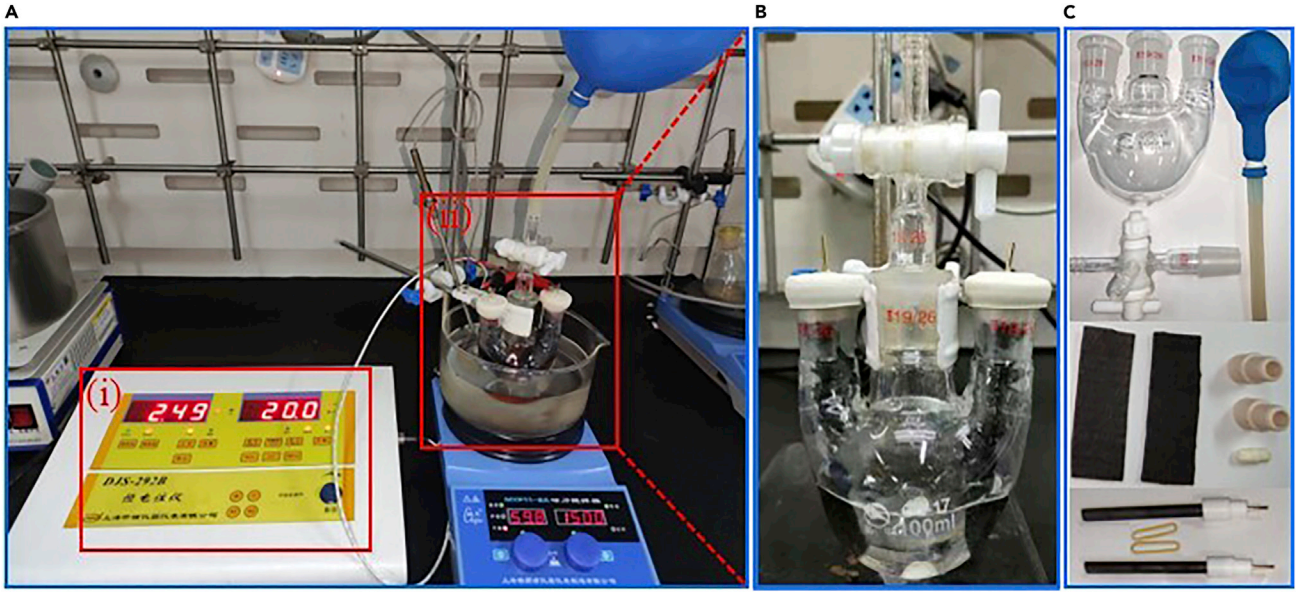


Figure 1. Overview of the electrosynthesis system

(A) DC power DJS-292B system: (i) touch screen interface, (ii) electrochemical reactor.

(B) Zoom in electrochemical reactor.

(C) Zoom in on the required accessories.

e. Place the reagent reservoir under nitrogen *via* an inlet needle. Add an outlet needle and let degas the mixture for 5 min.

f. Finally, open the three-way piston of the nitrogen balloon to prevent the entry of air.

Note: Electrochemically mediated radical reactions usually require an inert atmosphere to avoid the radical species being consumed by oxygen. Anaerobic conditions can be achieved by degassing the solvents before addition to the sealed test tube. Nevertheless, in the present protocol, no degassing and anhydrous treatment of the solvent: controls experiments showed no influence on the outcome of the performed reaction.

DC power DJS-292B and magnetic stirrer set-up

Timing: 5 min

In this step, besides setting up the DC power DJS-292B and magnetic stirrer temperature to perform the reaction under optimal conditions, some key parameters such as current, temperature, and stirring speed are also set.

3. Set up the DC power DJS-292B and magnetic stirrer unit.
   a. Turn on the magnetic stirrer in advance and set the temperature to 60°C, 1500 rpm.
   b. The reactor is placed in a 60°C oil bath.
   c. Correctly connect the positive and negative poles of the DC power DJS-292B and the electrodes on the undivided cell (Figure 1A).

Note: The black electrode clip is the positive electrode, and the red electrode clip is the negative electrode.

d. Select the constant current mode to perform this reaction.

Table 2. Preparation of reaction substrates and seal cells

Chemical	Final concentration	Amount
4-methylquinoline (**1a**)	14.3 mg/mL	715.9 mg
4-cyanopyridine (**2a**)	31.2 mg/mL	1.561 g
NH_4OAc	11.55 mg/mL	577.5 mg
Dimethyl sulfoxide (AR)	n/a	25.0 mL
Acetonitrile (AR)	n/a	25.0 mL

e. Set the current of the DC power DJS-292B to 20 mA.
f. The setting method has been explained in detail later.

4. Touch screen interface and instructions.
   a. Turn on the power.
   The setting steps are as follows:
   b. Select constant current mode (button **D**).

   Note: If you want to use the constant voltage mode, please select button **C**, and add the corresponding reference electrode in the cell, the other settings are the same as the constant current mode.

   c. Select button **E** to turn on the work light, then you will find that lights **1–3** are all brightened.
   d. Press and hold buttons **I** (cell) and **K** (load) at the same time to eliminate light **1** and set it to cell mode (energize lights **2–3**).
   e. Select the current range as 200 mA (Figure 2, black box, button **L**).
   f. Adjust the current via button **M** so that the current window B displays 20 mA.

   Note: The constant voltage mode is also to adjust the voltage through the button **M**, and the voltage window **A** will display the voltage you desire.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
4-Methylquinoline	Adamas	CAS: 491-35-0
4-Cyanopyridine	Macklin	CAS: 100-48-1
NH_4OAc	Adamas	CAS: 631-61-8
Dimethyl sulfoxide (AR)	Adamas	CAS: 67-68-5
Acetonitrile (AR)	Greagent	CAS: 75-05-8
Deuterated chloroform	Aladdin (D, 99.8%) + TMS(0.03%)	CAS: 865-49-6
Na_2SO_4	Adamas	CAS: 7757-82-6
Other		
DC power	Shanghai Xinrui DJS-292B	Cat#1806039
Magnetic stirrer	MYP11-2A	N/A
Stir bar (2.0 cm)	N/A	N/A
Three-necked flask (150.0 mL)	Beijing Xinweier Glass Instrument Co., Ltd.	N/A
Carbon rods (φ: 6 mm)	Xuzhou Xinke Instrument and Meter Co. LTD	N/A
Carbon felt (thickness: 2 mm, 2 × 4 cm^{-1})	Xuzhou Xinke Instrument and Meter Co. LTD	N/A
5.0 mL syringe	Dongbei Medicine	N/A
Thin-layer chromatography using TLC-Plates 0.25 mm	Shanxi Nuotai	N/A
Silica gel for chromatography, 200–300 mesh	Shanxi Nuotai	N/A

(*Continued on next page*)

Continued

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Bruker Avance III (500 MHZ) spectrometer	Bruker	N/A
Chromatography columns (24 cm of silica, Ø of the column= 5.0 cm)	Beijing Xinweier Glass Instrument Co., Ltd.	N/A
Nitrogen /vacuum Schlenk manifold.	N/A	N/A
Round bottom flasks (100 mL)	Beijing Xinweier Glass Instrument Co., Ltd.	N/A

STEP-BY-STEP METHOD DETAILS

Part 1: Synthesis of 4-methyl-2-(pyridin-4-yl)quinolone (3aa)

Timing: 24 h

In this part, the synthesis of 4-methyl-2-(pyridin-4-yl)quinoline **3aa** (Scheme 1) has been accomplished in a one-compartment electrochemical cell.

1. Set up and run the reaction (Figure 1) (troubleshooting 1, 2, 3, and 4).
   a. Clean the electrodes and assemble the cell (for details see Table 1, 1a, 1b).
   b. Add the corresponding raw materials and place the mixture under inert atmosphere (for details see Table 2).
   c. Place the reaction vial in an oil bath and connect it to a DC power source.
   d. Power on set DC power parameters (details see Figure 2).
   e. Run the reaction for 24 h under a temperature of 60°C.
   f. Upon reaction completion monitored by TLC (PE/EA = 2/1), disconnect DC power and cool to ambient temperature.

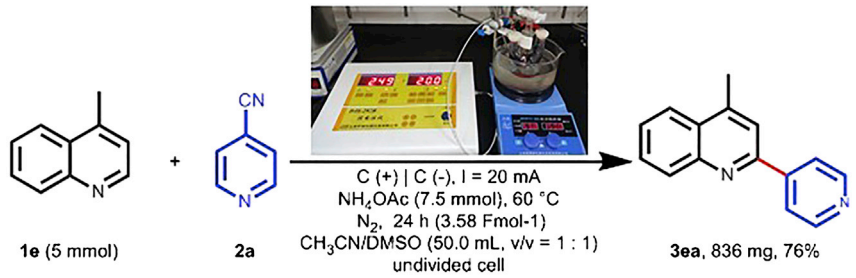
Part 2: Purification of the crude material

Timing: 2.5 h, step 2: 30 min, steps 3–9: 2.0 h

This section completes the purification of the product **3aa**.

2. Extraction to remove DMSO (30 min).
   a. Transfer the reaction solution into a 250 mL separatory funnel, and then add 30.0 mL of deionized water and 30.0 mL of CH_2Cl_2.
   b. Shake the separatory funnel vigorously, and let the aqueous phase separate from the organic one.

Figure 2. DC power DJS-292B touch screen interface
The function of each button has been described (A–M).



Scheme 1. General scheme of the reaction

c. Three vigorous extractions with water and CH_2Cl_2 to remove DMSO (approximately 30 min) (troubleshooting 5).

Note: This step must remove as much DMSO as possible while minimizing the loss of the organic phase to avoid product loss.

3. Transfer the organic phase into a 200 mL beaker.
4. Collect the organic layers, dry with Na_2SO_4, gently shaken the beaker, and filter in a 100 mL round bottom flask.
5. Discard the aqueous phase in the appropriate waste container.
6. Remove the solvent by rotatory evaporation (40°C, 90 rpm).
7. Add to the concentrated crude 2.0 mL of dichloromethane and 200 mg of silica. Gently swirl the flask and evaporate the solvent under vacuum (40°C, 60 rpm).
8. Purify the crude product by flash column chromatography (24 cm of silica, Ø of the column= 5.0 cm) using a 3:1 (by volume) mixture of petroleum ether (PE) /ethyl acetate (EA) (~ 1000 mL).
9. Collect the combined fractions containing pure product and concentrate under reduced pressure to yield the desired product (troubleshooting 5).

EXPECTED OUTCOMES

4-methyl-2-(pyridin-4-yl)quinolone **3aa** appears as a yellow oil obtained in 76% yield.

Analytical data

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 6.0 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 4.6 Hz, 2H), 8.01 (d, J = 8.3 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.59 (t, J = 7.6 Hz, 1H), 2.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 150.4, 148.0, 146.8, 145.5, 130.5, 129.7, 127.8, 126.9, 123.7, 121.6, 119.2, 19.0.

LIMITATIONS

The protocol is limited to cyanopyridines.

TROUBLESHOOTING

Problem 1

Step 1a: Carbon rods and carbon felt must be thoroughly cleaned and dried.

Potential solution

Wash the carbon rods and carbon felt with deionized water and ethanol 3 times under sonication, and the final washing with ethanol facilitated rapid drying.

Problem 2

Step 1a: The small contact area of the carbon rods results in a long reaction time.

Potential solution

An effective method is to wrap the carbon felt around the carbon rod, which can increase the contact area between the electrode and the reaction solution and improve the reaction efficiency.

Problem 3

Step 1a: The positive and negative poles of the DC power supply and the electrodes on the reactor cannot be wrongly connected.

Potential solution

Check that the positive pole of the DC power supply DJS-292B is the black electrode clip, the negative pole is the large red pole clip, and the reference electrode is the smaller red pole clip.

Problem 4

Step 1e: Rapid agitation in an electrochemical cell may cause a short circuit of the electrodes and interrupt the reaction.

Potential solution

An appropriate distance should be maintained between the positive and negative electrodes when assembling the electrochemical cell and should be checked and adjusted in time during the reaction process.

Problem 5

Step 9: Yield is lower than expected.

Potential solution

Product may be lost during extraction. This step must remove as much DMSO as possible while minimizing the loss of the organic phase.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Jiangwei Wen (wenjy@qfnu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

All data reported in this paper will be shared by the lead contact upon request.

This paper does not report the original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

N.C., Y.J., and W.J. conceived the project and designed the experiments. Y.J. and W.J. wrote the manuscript. N.C., J.W., and X.J. performed and analyzed experiments. L.B. performed theoretical calculations in Niu et al. (2022). All the authors discussed the results of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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