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Nickel-catalyzed electrochemical Minisci acylation of aromatic *N*-heterocycles with α-keto acids via ligand-to-metal electron transfer pathway

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ABSTRACT

A nickel-catalyzed electrochemical methodology for the Minisci acylation of aromatic electron-deficient heterocycles with α-keto acids has been developed. The reaction is performed in an undivided cell under constant current conditions, featuring broad scope of substrates and avoiding the conventional utilization of silver-based catalysts in conjunction with excess amount of oxidants. Cyclic voltammetric analysis disclosed that a ligand-to-metal electron transfer process may be involved in the generation of the key acyl radicals.

1. Introduction

Minisci reaction refers to a radical substitution process in which a nucleophilic carbon-centered radical reacts with an electron-deficient aromatic heterocycle to assemble a new carbon-carbon bond, thereby providing a complementary avenue to the functionalization of electron-rich aromatics via classical electrophilic Friedel-Crafts reactions [1]. Minisci-type radical reactions are especially useful for the late-stage functionalization of C—H bonds, thus have attracted great attention in pharmaceutical, medicinal chemistry and material sciences [2,3]. To this end, undisputable advances have been made in Minisci alkylation reactions, however, the Minisci acylation reactions are less studied.

Decarboxylative cross-coupling of α-keto acids with heteroaromatics has proven to be one of the powerful and versatile approaches to the Minisci acylation reactions. In 1991, Fontana and co-workers reported for the first time the Ag(I)-catalyzed oxidative decarboxylation of α-keto acids with quinolone, pyrazine, quinoxaline and 4-substituted pyridines, using a combination of $AgNO_3/(NH_4)_2S_2O_8$ to prepare the corresponding mono- and diacyl derivatives [4]. Oh and co-workers have also reported the direct acylation of 2H-indazoles with α-keto acid derivatives [5]. In 2014, the selective C2-monoacylation of pyridine-N-oxides was accomplished by Muthusubramanian et al. using Ag_2CO_3 /$K_2S_2O_8$ as the catalyst and oxidizing reagent [6]. Recently, Wu, Zhao and co-workers have achieved the decarboxylative coupling of pyrazines using $Ag_3PO_4/K_2S_2O_8$ system [7]. In order to replace the expensive sliver-based catalysts, we reported the Fe(II)-catalyzed decarboxylative acylation of *N*-heteroarenes (Scheme 1a) [8]. In addition, visible light-mediated decarboxylative coupling of α-keto acids with *N*-heterocycles has also emerged as a versatile approach to the Minisci acylation reactions (Scheme 1b). For example, Zhang and co-workers reported the acylation of *N*-heterocycles under visible-light irradiation [9]. Later on, Wencel-Delord and co-workers reported a visible-light-induced acylation of *N*-heterocycles with α-keto acids in the presence of $K_2S_2O_8$ as the oxidizing reagent [10]. Recently, Prabhu et al. employed Ir(I) complex as the photocatalyst to synthesize acylated pyridine derivatives [11]. In a word, for the decarboxylative cross-coupling of α-keto acids with *N*-heteroarenes, expensive Ag(I)-based catalysts or Ir (I)-based photocatalysts in conjunction with excess amount of oxidant were generally employed, which is not practical. Therefore, the development of new approaches using cheap metal catalyst, specially under external oxidant-free conditions, are highly desired.

Organic electrosynthesis has emerged as a green and environmentally friendly way to achieve C—H bonds functionalization, and it is revolutionizing the way of organic synthesis [12]. In this context, we have been working on the electrochemical construction of new C—C bonds and C-heteroatom bonds via indirect anodic oxidation using redox mediators, such as halide ions, TEMPO, DDQ

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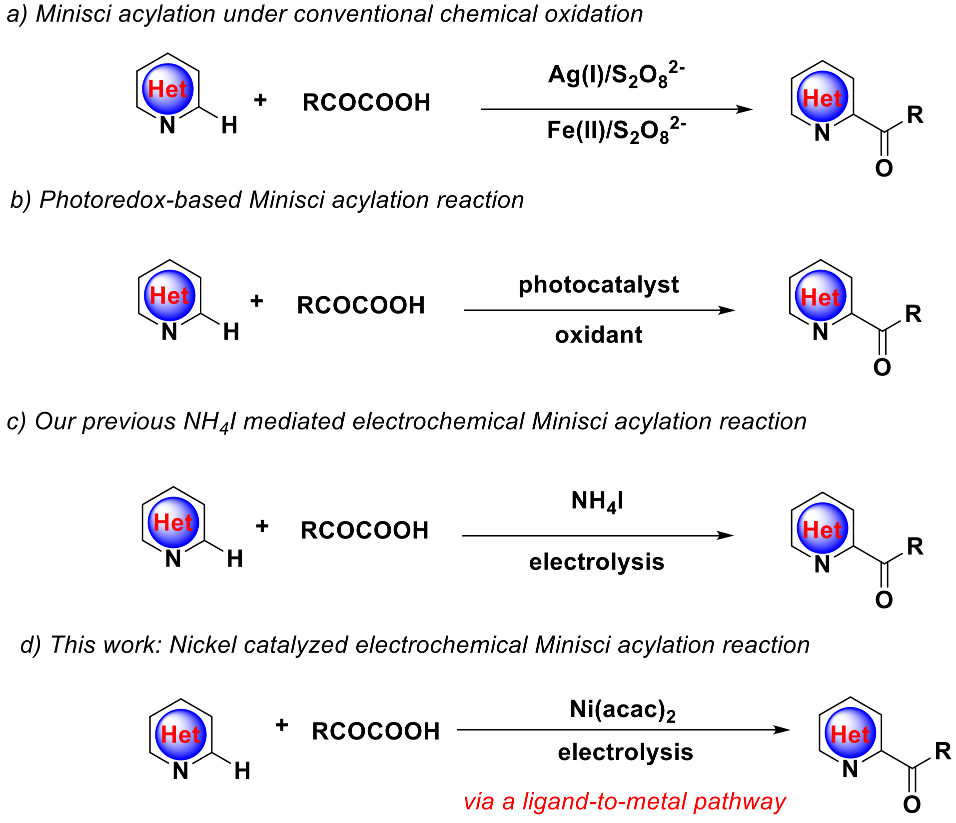

a) Minisci acylation under conventional chemical oxidation

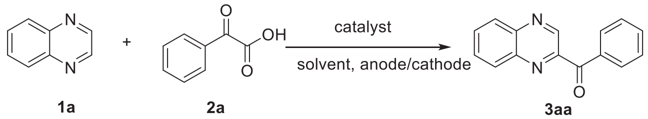
b) Photoredox-based Minisci acylation reaction

c) Our previous NH_4I mediated electrochemical Minisci acylation reaction

d) This work: Nickel catalyzed electrochemical Minisci acylation reaction

Scheme 1. Decarboxylative Minisci-type Acylation reactions of α-keto acids with *N*-heteroarenes.

Table 1
Optimization of Reaction Condition [a].

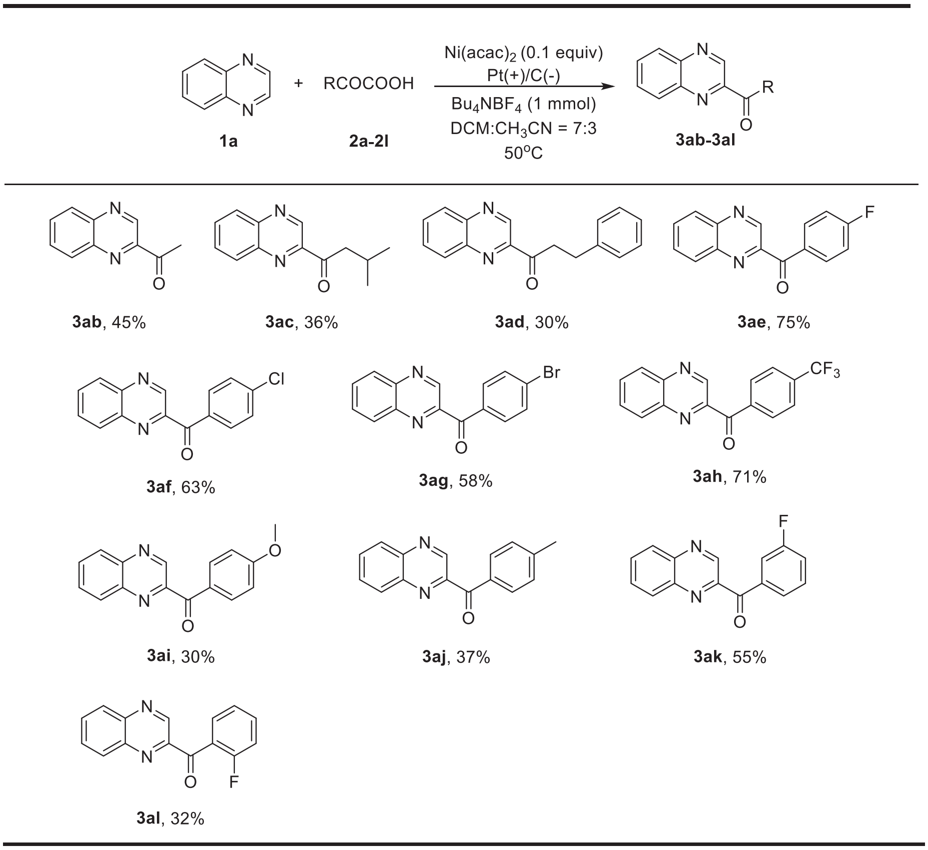


1a **2a** **3aa**

Entry	Catalyst (mol%)	Solvent	Electrolyte	T (°C)	Yield [b](%)
1	$Ni(acac)_2$(10)	CH_3CN	Bu_4NBF_4	20	15
2	$Ni(acac)_2$(10)	DCM	Bu_4NBF_4	20	20
3	$Ni(acac)_2$(10)	DMSO	Bu_4NBF_4	20	0
4	$Ni(acac)_2$(10)	MeOH	Bu_4NBF_4	20	0
5	$Ni(acac)_2$(10)	EtOH	Bu_4NBF_4	20	0
6	$Ni(acac)_2$(10)	DCE	Bu_4NBF_4	20	16
7	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	20	27
8	**$Ni(acac)_2$(10)**	**CH_3CN:DCM (v:v 3:7)**	**Bu_4NBF_4**	**50**	**58**
9	Ni_2SO_4(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	5
10	$NiCl_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	7
11	$Ni(cod)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	17
12	$NiCl_2$.glym(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	20
13	$Ni(acac)_2$(0)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	8
14	$Ni(acac)_2$(5)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	12
15	$Ni(acac)_2$(30)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	45
16[c]	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	13
17[d]	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	46
18	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NPF_6	50	44
19	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Et_4NBF_4	50	37
20[e]	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	36
21[f]	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	5
22[g]	$Ni(acac)_2$(10)	CH_3CN:DCM (v:v 3:7)	Bu_4NBF_4	50	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), 0.1 M supporting electrolyte in 10 mL solvent, undivided cell , current density of 5 mA cm^{-2}, Pt net anode and graphite plate cathode (working area: 3 cm^2).
[b] Isolated yields.
[c] Current density of 3 mA cm^{-2}.
[d] Current density of 10 mA cm^{-2}.
[e] Graphite plate anode and graphite plate cathode (working area: 3 cm^2).
[f] Graphite plate anode and Pt net cathode (working area: 3 cm^2).
[g] No electrolysis.

Table 2
Substrate Scope with α-Keto Acids [a,b.]



3ab, 45% **3ac**, 36% **3ad**, 30% **3ae**, 75%

3af, 63% **3ag**, 58% **3ah**, 71%

3ai, 30% **3aj**, 37% **3ak**, 55%

3al, 32%

[a] Reaction conditions: platinum net anode and graphite plate cathode (working area: 3 cm^2, J = 5 mA/cm^2), **1** (1.0 mmol), **2a** (3.0 mmol)), Bu_4NBF_4 (0.1 M), solvent (7 mL DCM and 3 mL CH_3CN), $Ni(acac)_2$ (0.1 mmol) was added, 50 °C, undivided cell, 4.0 h.

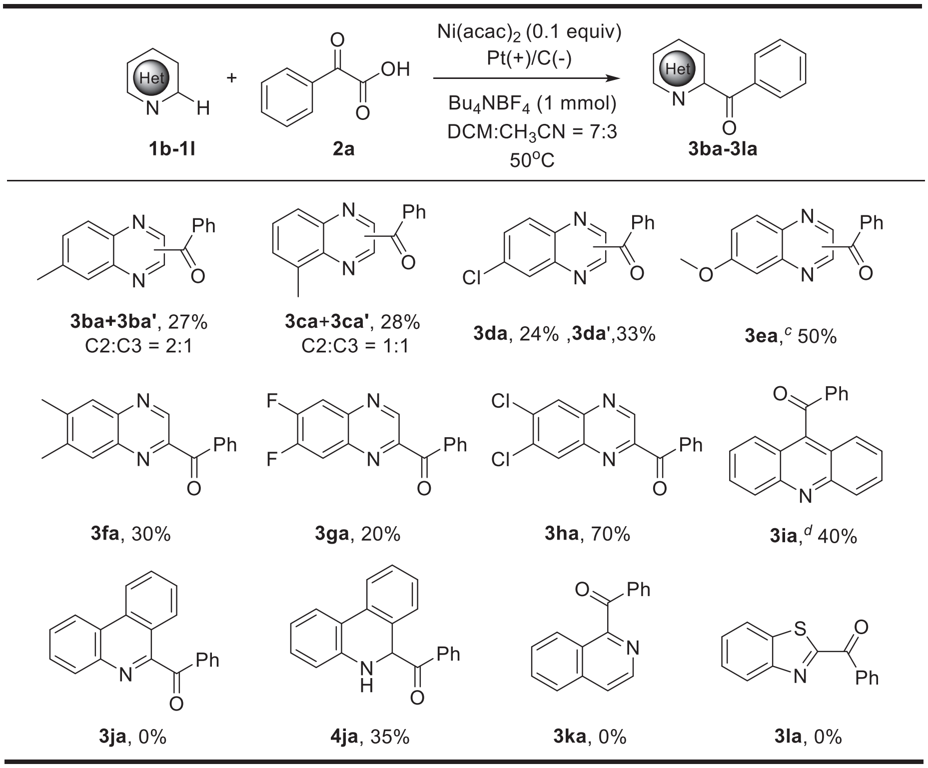
[b] Isolated yield.

and triarylimidazole [13]. For example, we have recently achieved the NH_4I-mediated Minisci acylation reaction of aromatic *N*-heterocycles with α-keto acids (Scheme 1c) [14]. Herein, we reported for the first time a Ni(II)-catalyzed electrochemical Minisci acylation reaction of electron-deficient *N*-heteroarenes with α-keto acids (Scheme 1d). The chemistry is performed in an undivided cell under galvanostatic conditions, avoiding the utilization of Ag(I)-based catalyst and excess chemical oxidants. Distinct from conventional Ni-catalyzed decarboxylative cross-coupling reactions wherein Ni-catalysts work as a radical capturer [15], this Ni-catalyzed electrochemical Minisci acylation may involve a ligand-to-metal electron transfer process to generate the key acyl radicals.

2. Results and discussion

We commenced our studies by choosing quinoxaline (**1a**) and phenylglyoxylic acid (**2a**) as the model substrates to optimize the reaction conditions. As shown in Table 1, when constant current electrolysis (CCE) of **1a** and **2a** was performed in an undivided cell with a platinum net as the anode and a graphite plate as the cathode at a constant current of 5 mA cm^{-2} with $Ni(acac)_2$ (10 mol%) as the catalyst and CH_3CN as the solvent at room temperature, the desired product **3aa** was isolated in 15% yield (entry 1). Encouraged by this result, solvent screening was then performed and it was observed that the yield of **3aa** increased to 27% when a mixture of CH_3CN and DCM (v:v = 3:7) was used as the solvent (entries 2–7). When the reaction was carried out at 50 °C, the yield of **3aa** improved to 58% (entry 8). Further catalyst screening disclosed that Ni_2SO_4, $NiCl_2$, $Ni(cod)_2$ and $NiCl_2$glym were not suitable for the acylation reaction (entries 9–12). In addition, decreasing the loading of catalyst $Ni(acac)_2$ to 5 mol% or increasing to 30 mol% resulted in inferior results (entries 14 and 15). Besides, it was observed that **3aa** was afforded in 13% or 46% yields when the CCE was carried out at 3 mA/cm^2 or 10 mA/cm^2 (entries 16 and 17). Further screening of the supporting electrolytes indicated that Bu_4NBF_4 was superior since **3aa** was obtained in lower yield when *n*-Bu_4NPF_6 or Et_4NBF_4 were employed as the supporting electrolytes (entries 18 and 19). Finally, we turned our attention to the evaluation of electrode materials. When a graphite plate, instead of a Pt net, was used as the anode, **3aa** was obtained in 36% yield (entry 20). Conversely, only 5% yield of **3aa** was afforded when Pt net was used as the cathode and graphite plate as the anode. Notably, **3aa** was afforded in only 8% yield or less when the reaction was performed in the absence of the catalyst $Ni(acac)_2$ (entry 13) and electricity (entry 22), which indicates that $Ni(acac)_2$ and electricity played an essential role for the Minisci acylation reaction. At this stage of our investigation, we concluded that the optimal conditions call for using 10 mol% of $Ni(acac)_2$ as the redox

Table 3
Substrate Scope with *N*-Heteroarene [a,b.]



3ba+3ba', 27% C2:C3 = 2:1

3ca+3ca', 28% C2:C3 = 1:1

3da, 24% ,**3da'**,33%

3ea,[c] 50%

3fa, 30%

3ga, 20%

3ha, 70%

3ia,[d] 40%

3ja, 0%

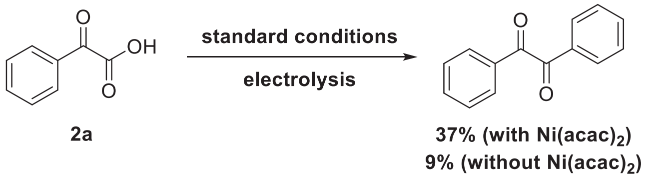
4ja, 35%

3ka, 0%

3la, 0%

[a] Reaction conditions: platinum net anode and graphite plate cathode (working area: 3 cm^2, $J = 5$ mA/cm^2), **1** (1.0 mmol), **2a** (3.0 mmol), Bu$_4$NBF$_4$ (1 mmol), solvent (DCM 7 mL and CH$_3$CN 3 mL), Ni(acac)$_2$ (0.1 mmol), 50 °C, undivided cell, 4.0 h.

[b] Isolated yield. [c] 16 h. [d] 20 h.



Scheme 2. Control experiments.

catalyst and Bu$_4$NBF$_4$ in the mixed solution of CH$_3$CN with DCM as the supporting electrolyte. The reaction prefers performing in an undivided cell equipped with Pt net anode and graphite plate cathode at 5 mA/cm^2 current density (see Table 1, entry 8).

With the optimal reaction conditions in hand, we then studied the scope and the generality of the protocol by examining reactions of quinoxaline **1a** with a variety of α-keto acids **2**. As shown in Table 2, it was observed that the aliphatic α-keto acids proceeded smoothly with **1a** under the standard conditions to give the corresponding Minisci acylation products. For example, when aliphatic α-keto acids **2b**, **2c** and **2d** were subjected to react with **1a**, the corresponding **3ab**, **3ac** and **3ad** were afforded in 45%, 36% and 30% yields, respectively. Moderate to good yields of Minisci acylated products were obtained in the cases of aromatic α-keto acids. It seems that the electron-withdrawing groups, such as F, Cl, Br and CF$_3$, gave higher yields than that of electron-donating groups MeO and Me, when these groups were appended at the *para*-position of the benzene ring. For example, CF$_3$-substituted **3ah** was obtained in 71% yield, whereas methyl-substituted **3aj** was delivered in 37% yield. In addition, it was observed that lower yields of products were obtained when the substituted group was located at the *ortho*- or *meta*- positions. For example, **3ak** and **3al** were afforded in 55% and 32% yields, respectively, whereas the analogous **3ae** was obtained in 75% yield.

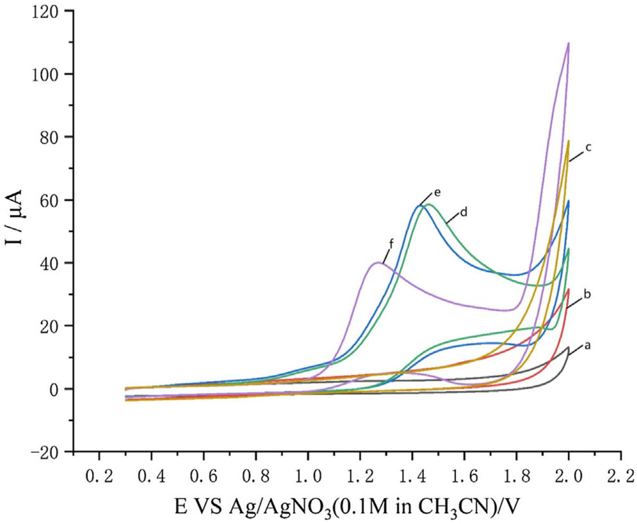
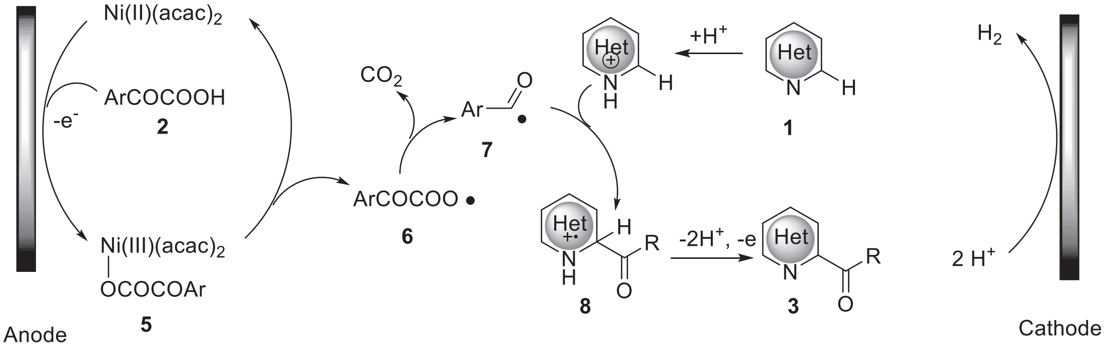


Fig. 1. Cyclic voltammograms of related compounds in 0.1 M LiClO$_4$/CH$_3$CN using glass carbon working electrode, Pt wire, and Ag/AgNO$_3$ (0.1 M in CH$_3$CN) as counter and reference electrode at 100 mV/s scan rate: (a) background, (b) Quinoxaline (5.0 mmol/L), (c) PhCOCOOH (5.0 mmol/L), (d) Ni(acac)$_2$ (2.0 mmol/L), (e) Ni(acac)$_2$ (2.0 mmol/L) and Quinoxaline (5.0 mmol/L), (f) Ni(acac)$_2$ (2.0 mmol/L) and PhCOCOOH (5.0 mmol/L).



Scheme 3. A proposed mechanism for the nickel-catalyzed electrochemical Minisci acylation.

To further explore the potential of the protocol, the reactions of phenylglyoxylic acid **2a** with a variety of quinoxalines **1** were also investigated, and the results are summarized in Table 3. It was observed that most of the quinoxalines tolerated the reaction conditions. Notably, for non-symmetric quinoxalines (**1b**-**1d**), there are two α-C-Hs to the nitrogen atom, therefore a mixture of regioisomers was afforded. In the cases of disubstituted substrates, **1f-1h**, the desired products **3fa-3ha** were isolated in 20%-70% yields. Other aromatic heterocycles were also tested. As shown in Table 3, when acridine, **1i**, was used as the substrate, the corresponding **3ia** was afforded in a 40% yield. Unexpectedly, when phenanthridine **1j** was used as a substrate to react with **2a** under the standard conditions, direct addition product **4ja** was generated and isolated in 35% yield, without further conversion to **3ja**. In addition, the cross-coupling reactions of isoquinoline (**1k**) and benzothiazole (**1l**) with **2a** did not take place, instead, benzil from the homo-coupling of benzoyl radical was isolated in 32% and 15% yields, respectively.

To understand the mechanism for the nickel-catalyzed electrochemical Minisci acylation reaction of *N*-heteroarenes, control experiments were performed. As shown in Scheme 2, when **2a** itself was subjected to electrolysis under the standard conditions, benzil was isolated in 37% yield, whereas, only 9% yield of benzil was afforded in the absence of Ni(acac)$_2$. In addition, the formation of benzil was observed in the reaction of **1k** and **1l** with **2a** (Table 3). These results indicate that acyl radical is the key intermediate and Ni(acac)$_2$ is able to promote its formation via decarboxylation of phenylglyoxylic acid.

Cyclic voltammetric analysis was also performed to understand the mechanism. As shown in Fig. 1, the starting substrates, quinoxaline **1a** (curve b) and phenylglyoxylic acid **2a** (curve c), are not oxidized up to 2.0 V, whereas Ni(acac)$_2$ exhibits an oxidation peak at 1.46 V (*vs.* Ag/AgNO$_3$ in 0.1 M CH$_3$CN) (curve d). These results disclose that Ni(acac)$_2$ is easier to be oxidized than **1a** and **2a**. It is worth noting that the oxidation peak potential of Ni(acac)$_2$ shifted negatively by 0.19 V in the presence of **2a** (curve f), whereas a slight shift was observed in the presence of **1a** (curve e). These results indicate that complexation between Ni(acac)$_2$ and **2a** may occur to form a **2a**-bound complex which rendered easier the oxidation of Ni(II) to Ni(III) [16]. To further demonstrate the interaction between Ni(acac)$_2$ and **2a**, the decarboxylative coupling of **1a** with **2a** was electrolyzed at the controlled potential of 1.3 V, and the corresponding product **3aa** was obtained in 42% yield.

Based on these control experiments and cyclic voltammetric examination, a possible mechanism for the nickel-catalyzed electrochemical Minisci acylation reaction is proposed. As shown in Scheme 3, the anodic oxidation of Ni(acac)$_2$ in the presence of α-keto carboxylic acid generates complex **5**, which undergoes ligand-to-metal electron transfer giving radical **6**, along with the regeneration of Ni(acac)$_2$. The radical **6** is very unstable, followed by loss of CO$_2$ to give acyl radical **7**, which then undergoes radical addition with protonated *N*-heteroarenes to afford adduct **8**. After further oxidation and deprotonation, the Minisci acylated products **3** are finally afforded. Simultaneously, the cathodic reduction of proton offers hydrogen.

3. Conclusion

In summary, we have developed an efficient Ni-catalyzed electrochemical Minisci acylation reaction via decarboxylative cross-coupling of *N*-heteroarenes with α-keto acids. The protocol proceeded in an undivided cell under constant current conditions, thereby avoiding the utilization of a combination of silver-based catalysts with oxidants. Control experiments and cyclic voltammetric analysis disclosed that a ligand-to-metal electron transfer process may be involved in the generation of the key acyl radicals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2019.10.030.

References

[1] For reviews on Minisci reactions, see (a) S. J. P, Rupert, J. P. Robert, Angew. Chem. Int. Ed. 10.1002/anie.201900977; (b) J.Tauber; D. Imbri, T. Opatz, Molecules. 19 (2014) 16190-16222; (c) F. Minisci, A. Citterio, C. Giordano, Accounts Chem. Res. 16 (1983) 27-32; (d) M. Tojino, N. Otsuka, T. Fukuyama, H. Matsubara, I. Ryu, J. Am. Chem. Soc. 128 (2006) 7712-7713; e) C. H. Schiesser, U. Wille, H. Matsubara, I. Ryu, Accounts Chem. Res. 40 (2007) 303-313; (f) L. N. Guo, H. Wang, X. H. Duan, Org. Biomol. Chem. 14 (2016) 7380-7391; (g) F. Penteado, E. F. Lopes, D. Alves, G. Perin, R. G. Jacob, E. J. Lenardão, Chem. Rev. 119 (2019) 7113-7278.
[2] M.A.J. Duncton, Med. Chem. Commun. 2 (2011) 1135–1161.
[3] (a) K.H.C. Baser, J. Nat. Prod. 45 (1982) 704–706;
(b) S. Al-Khalil, P.L. Schiff, J. Nat. Prod. 48 (1985) 989–991.
[4] F. Fontana, F. Minisci, M.C.N. Barbosa, E. Vismara, J. Org. Chem. 56 (1991) 2866–3286.
[5] G. Bogonda, H.Y. Kim, K. Oh, Org. Lett. 20 (2018) 2711–2715.
[6] R. Suresh, R.S. Kumaran, V. Senthilkumar, S. Muthusubramanian, RSC Adv. 4 (2014) 31685–31688.

[7] Y. Li, M. Lai, Z.Y. Wu, M.Q. Zhao, M.Y. Zhang, ChemistrySelect 3 (2018) 5588–5592.

[8] X.Z. Wang, C.C. Zeng, Tetrahedron 75 (2019) 1425–1430.

[9] X.Y. Zhang, W.Z. Weng, H. Yang, H. Liang, B. Zhang, Org. Lett. 20 (2018) 4686–4690.

[10] L. Guillemard, F. Colobert, J. Wencel-Delord, Adv. Synth. Catal. 360 (2018) 4184–4190.

[11] S. Manna, K.R. Prabhu, J. Org. Chem. 84 (2019) 5067–5077.

[12] (a) R. Francke, R.D. Little, Chem. Soc. Rev. 43 (2014) 2492–2521;
(b) Y.Y. Jiang, K. Xu, C.C. Zeng, Chem. Rev. 118 (2018) 4485–4540;
(c) A. Shrestha, M. Lee, A.L. Dunn, M.S. Sanford, Org. Lett. 20 (2018) 204–207;
(d) N. Sauermann, T.H. Meyer, C. Tian, L. Ackermann, J. Am. Chem. Soc. 139 (2017) 18452–18455.

[13] (a) Y.Y. Jiang, G.Y. Dou, K. Xu, C.C. Zeng, Org. Chem. Front. 5 (2018) 2573–2577;
(b) C. Li, C.C. Zeng, L.M. Hu, F.L. Yang, S.J. Yoo, R.D. Little, Electrochim. Acta 14 (2013) 560–566;
(c) L.S. Kang, H.L. Xiao, C.C. Zeng, L.M. Hu, R.D. Little, J. Electroanal. Chem. 767 (2016) 13–17;
(d) C.C. Zeng, N.T. Zhang, C.M. Lam, R.D. Little, Org. Lett. 145 (2012) 1314–1317.

[14] Q.Q. Wang, K. Xu, Y.Y. Jiang, Y.G. Liu, B.G. Sun, C.C. Zeng, Org. Lett. 19 (2017) 5517–5520.

[15] (a) Z.J. Wan, J.Y. Wang, J. Luo, Tetrahedron Lett. 60 (2019) 613–616;
(b) A.P. Honeycutt, J.M. Hoover, ACS Catal. 7 (2017) 4597–4601;
(c) N.A. Till, R.T. Smith, D.W.C. MacMillan, J. Am. Chem. Soc. 140 (2018) 5701–5705;
(d) K. Yang, C. Zhang, P. Wang, Y. Zhang, H. Ge, Chem. Eur. J. 20 (2014) 7241–7244.

[16] K.Y. Ye, G. Pombar, N. Fu, G.S. Sauer, I. Keresztes, S. Lin, J. Am. Chem. Soc. 140 (2018) 2438–2441.