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Electrochemical Nonacidic N-Nitrosation/N-Nitration of Secondary Amines through a Biradical Coupling Reaction

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Abstract. An acid-free N-nitrosation/nitration of the N-H bonds in secondary amines with $Fe(NO_3)_3{\cdot}9H_2O$ as the nitroso/nitro source through an electrocatalyzed radical coupling reaction was developed. Cyclic aliphatic amines and N-heteroaromatic compounds were N-nitrosated and N-nitrated, respectively, under mild conditions. Control and competition experiments, as well as kinetic studies, demonstrate that N-nitrosation and N-nitration involve two different radical reaction pathways involving $N{\cdot}^+$ and $N{\cdot}$ radicals. Moreover, the electrocatalysis method enables the preferential activation of the N-H bond over the electrode and thus provides high selectivity for specific N atoms. Finally, this strategy exhibits a broad scope and provides a green and straightforward approach to generate useful *N*-nitroso/nitro compounds in good yields.

Keywords: electrochemistry, N-N bond formation; N-nitrosation, N-nitration; radical addition

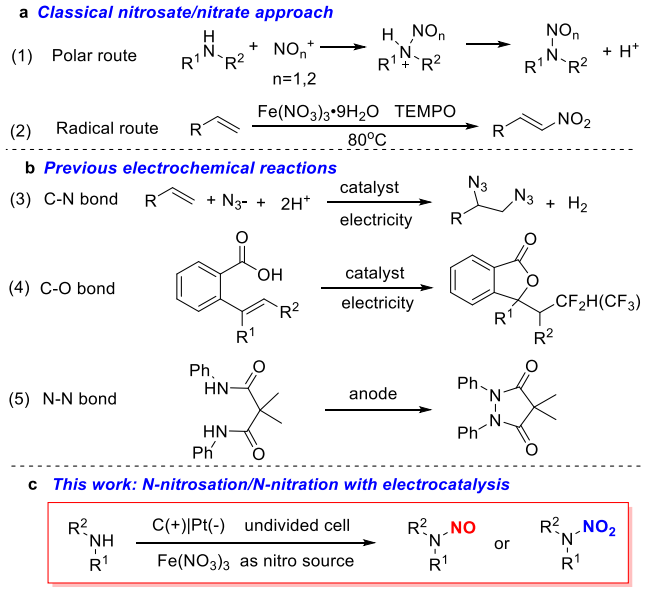
Introduction

N-Nitrosation and N-nitration are the most common strategies to functionalize the N-H group.[1] The products of these reactions can be easily transformed into a variety of diverse functionalities. For example, *N*-nitrosamines (N-NO) are a class of carcinogenic, mutagenic and teratogenic compounds of biological interest and are used as 'trans-nitrosating agents', i.e., NO-donor drugs;[2] *N*-nitramines ($N\text{-}NO_2$) are substances that exist widely in azo dyes and energetic materials.[3] Generally, both N-nitrosation and N-nitration follow the same mechanism. Taking N-nitration as an example, the conventional mechanism involves the in situ generation of nitronium (NO_2^+) ions from NO_3^- under strongly acidic conditions followed by an electron transfer addition (polar addition) step involving reaction with the substrate (Scheme 1a). However, the strongly acidic conditions limit the application of this strategy in complex syntheses, particularly when there is an acid-labile group on the substrate. Recently, other acid-free nitrating agents have been developed, such as nitroalkanes,[4] nitrous esters[5] and nitrogen oxides.[6] However, these agents are not environmentally friendly and can be hazardous to handle. Thus, from the perspective of green chemistry, research on the facile construction of N-N bonds to prepare *N*-nitroso and *N*-nitro compounds is still an important research topic.

The past decade has witnessed a renaissance in electrochemical organic synthesis.[7] Electrochemical reaction conditions can allow the elimination of toxic or hazardous redox reagents with direct redox reactions at an electrode surface, and the unique electronic environment is also helpful for investigating the electron transfer process in radical reactions.[8] In recent years, this green method has led to great success in the area of C-functionalization through metal-induced $C(sp^2)$-H/$C(sp^3)$-H activation to construct C-C,[9] C-N,[10] C-O,[11] C-S[12] and C-X[13] (X = F, Cl, Br, I) bonds (Scheme 1b). However, expanding the application range of electrochemical synthesis to heteroatoms is still rare. Presently, only two types of free radical-induced N-H reactions have been reported: the formation of an azo dye by N-N self-coupling[14] and the formation of a thionyl amine (-S-NH-) group.[15] To the best of our knowledge, the formation of N-N bonds through electrochemical N-nitration/nitrosation is unknown.

Here, acid- and oxidant-free N-nitrosation/N-nitration reactions were performed to form secondary amines by electrochemical methods (Scheme 1c). Cyclic alkyl amines and some azoles can be oxidized at the anode to form nitrogen radicals, while $Fe(NO_3)_3{\cdot}9H_2O$ is the source of the $NO_2{\cdot}$ radical,

referring to previous olefin nitrosation and nitration work.[16] The two radicals form an intimate pair and provide a new pathway for nitrosamine/nitroamine formation.



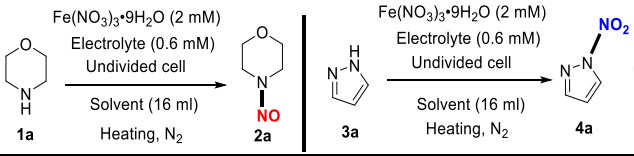
Scheme 1. Reported nitrosate/nitrate approach and electrochemical reactions

Results and Discussion

N-Nitrosation and N-nitration were tested with morpholine (**1a**) and pyrazole (**3a**) as the model substrates, respectively. First, as heating can promote the production of radicals from $Fe(NO_3)_3 \cdot 9H_2O$, we obtained yields of 84% and 62% for **2a** and **4a** at 70 °C, respectively (Table 1, entries 1-3). For the electrolyte test, ^{n}Bu$_4$NClO$_4$ showed a maximum yield of 99% during N-nitrosation; while for N-nitration, ^{n}Bu$_4$NBF$_4$ gave a maximum yield of 62% (Table 1, entries 4-6). For solvent screening, the aprotic solvent CH_3CN outperformed the others, including nonpolar solvents and protic solvents (see SI, Table S1). Electrode materials also play a significant role in catalytic efficiency. The utilization of a Pt plate anode decreased the yield of both reactions more obviously than the replacement of the cathode with a graphite rod or a Ni plate (Table S1), suggesting an anodic oxidation electrochemical process. N-Nitrosation seems to be a facile reaction and is insensitive to voltage changes with yields over 98% (Table 1 entries 8, 9). However, for N-nitration, we found that a stronger current (15 mA) led to **4a** with a higher yield of 66% (Table 1, entry 10), which indicates the higher difficulty for the occurrence of N-nitration. Control experiments demonstrated that no product was obtained without an electric current for either reaction (Table 1, entry 11).

Under the optimal conditions, we further explored the generality of the electrochemical N-nitrosation process (Table 2). Piperidine and its derivatives (**2b-2m**) were effective in this protocol with good isolated yield; nevertheless, 4-aminopiperidine performed sluggishly under the current conditions (**2k**). Biologically active 1,4-dioxa-8-azaspiro[4.5]decane and 2,2,6,6-tetramethylpiperidine were converted to desired products **2n** and **2o** with yields of 83% and 85%, respectively. The X-ray structure of **2n** was obtained and confirmed the structure of the piperidine ring with nitroso substitution.[17] Piperazine can be nitrosated with an outstanding yield of 90% (**2p**), but its derivative 2,6-dimethylpiperazine gave a lower isolated yield of 68% (**2q**). Moreover, when there was a substituent on the nitrogen of piperazine, moderate yields were obtained ranging from 48% to 63% (**2r-2t**). The morpholine derivatives and thiomorpholine, which are similar to morpholine, were also applicable to the system to afford the N-nitrosation products (**2u-2x**). The fused ring compound 1,2,3,4-tetrahydroisoquinoline delivered the target product in 68% yield (**2z**). Pyrrolidine, isoindoline and (*R*)-(-)-3-pyrrolidinol hydrochloride, which were chosen as cyclic alkyl amine-based five-membered rings, were tested and furnished the corresponding products in 88%, 87% and 76% yields, respectively (**2aa-2ac**). The configuration of **2ab** remained unaffected during the electrochemical process. Unfortunately, aromatic secondary amines, such as diphenylamine (**2ad**), do not work in electrochemical nitrosation or nitration reactions.

Table 1. Optimization of the Reaction Conditions [a]



entry	T (°C)	electrolyte	*I* or E_{cell}	**2a** [b] (%)	**4a** [b] (%)
1	r.t.	^{n}Bu$_4$NBF$_4$	12 mA	20	10
2	70	^{n}Bu$_4$NBF$_4$	12 mA	84	62
3	80	^{n}Bu$_4$NBF$_4$	12 mA	79	42
4	70	LiClO$_4$	12 mA	43	17
5	70	^{n}Bu$_4$NPF$_6$	12 mA	95	55
6	70	^{n}Bu$_4$NClO$_4$	12 mA	**99(88)**	36
7	70	^{n}Bu$_4$NBF$_4$	12 mA	74	41
8	70	^{n}Bu$_4$NBF$_4$	3 V	98	--
9	70	^{n}Bu$_4$NBF$_4$	2 V	95	--
10	70	^{n}Bu$_4$NBF$_4$	15 mA	--	**66(54)**
11	70	^{n}Bu$_4$NBF$_4$	0	n.d.	n.d.

[a] Reaction conditions: **1a (3a)** (1 mmol), graphite rod anode, Pt cathode, $Fe(NO_3)_3 \cdot 9H_2O$ (2.0 mmol), electrolyte (0.6 mmol) in 16.0 mL CH_3CN under N_2 for 4(7) h; Undivided cell. [b] Yield determined by gas chromatography. [c] n. d. = not detected.

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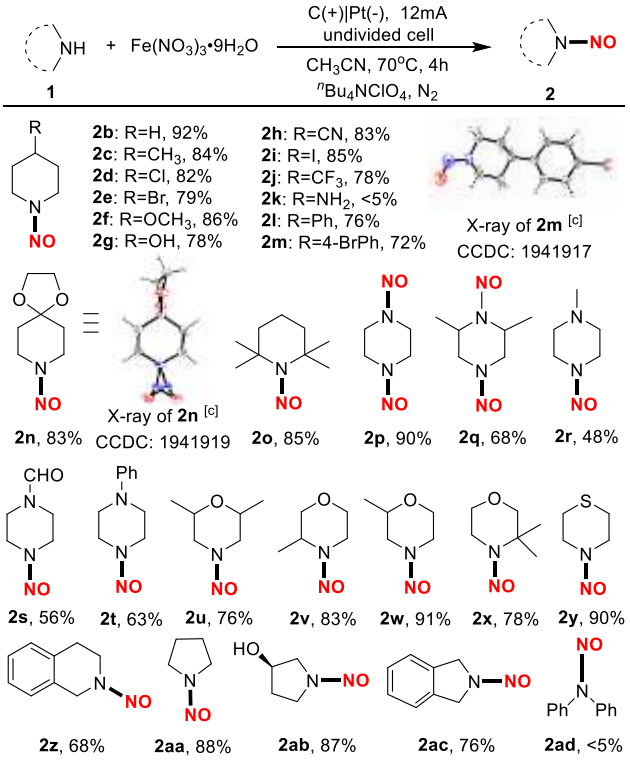
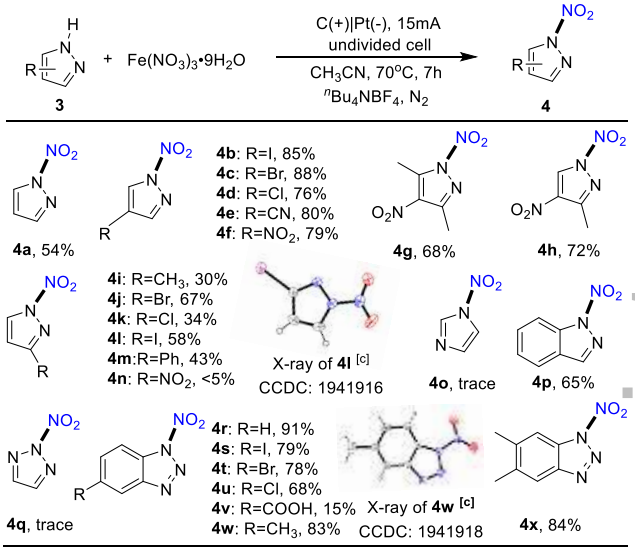
Aliphatic secondary amine and azole compounds underwent different pathways in the electrochemical reaction: the former led to the formation of N-nitrosation products, while the latter underwent an N-nitration reaction. Then, the scope of the electrochemical nitration reaction was also explored (Table 3). Pyrazoles with different functional groups at the 4-position, such as Cl, Br, I, CN and NO_2, successfully gave desired N-nitrated products **4b-4f** in good yields. Notably, the electron-deficient pyrazole with an electron-withdrawing group was more reactive than the others. Polysubstituted pyrazole derivatives also exhibited good reactivity to give products **4g** and **4h** in 68% and 72% yield, respectively. Among these compounds, **4a, 4f, 4h** and **4l** have been reported to be important intermediates for energetic materials. Interestingly, 3-substituted pyrazole is less reactive than 4-substituted pyrazole, and the substrates with electron-withdrawing substituents were nitrated in higher yields (**4i-4k**) than those containing electron-donating substituents (**4h** and **4m**). 3-Nitropyrazole and imidazole were not tolerated to give nitration products **4n** and **4o** in this protocol, which will be discussed in detail in the following section. Indazole was nitrated to desired product **4p** in 65% isolated yield. Next, 1,2,3-triazole (**4q**) was tested but gave almost no product, whereas benzotriazole and its derivatives delivered the target products in outstanding yields (**4r-4u**, **4w** and **4x**).

Table 2. Scope of Alkyl Amines for N-Nitrosation [a,b]



[a] **1** (1.0 mmol), $Fe(NO_3)_3·9H_2O$ (2 equiv), $^nBu_4NClO_4$(0.6 mmol), CH_3CN (16 mL) in an undivided cell with C(+) and Pt(-), 70 °C, 12mA, N_2.
[b] Isolated yields.
[c] See reference [17].

Table 3. Scope of N-Heteroaromatic Compounds for N-Nitration [a,b]



[a] **3** (1.0 mmol), $Fe(NO_3)_3·9H_2O$ (2 equiv), $^nBu_4NBF_4$(0.6 mmol), CH_3CN (16 mL) in an undivided cell with C(+) and Pt(-) 70 °C, 15mA, N_2.
[b] Isolated yields.
[c] See reference [17].

Additional experiments for N-nitration/N-nitrosation. To demonstrate the practicality of the current reaction, a gram-scale coupling reaction with **1a** under standard conditions was performed. The desired product **2a** was obtained in 84% yield, which shows great potential for this electrochemical amine nitrosation (Scheme 2a). If the reaction solution, after removal of the products and red iron salt, was directly used without any after-treatment, a yield of 38% **2a** was obtained after being recycled three times (Scheme 2b). The yield increased obviously to 81% when fresh nitroso source $Fe(NO_3)_3·9H_2O$ was added. Inspired by this phenomenon, we tried to add fresh $Fe(NO_3)_3·9H_2O$ (0.5 mmol) after each cycle and found that the yield of **2a** remained over 80% after six recycling cycles.

To gain more insight into the reaction mechanism, several additional experiments were carried out. First, cyclic voltammetry (CV) experiments on both reactants were performed and showed that the oxidation peaks of **1a** and $Fe(NO_3)_3·9H_2O$ were at 1.66 V and 0.98 V, respectively (Scheme 2d). The oxidation peak of the mixture was detected at 1.01 V, near the oxidation peak of $Fe(NO_3)_3·9H_2O$. A control experiment was also conducted at the corresponding anode potential (1.0 V vs SCE) for comparison (Scheme 2c) at a constant anode potential of 1.00 V versus SCE, and desired product **2a** was obtained in 16% yield, which indicated that the oxidation of **1a**

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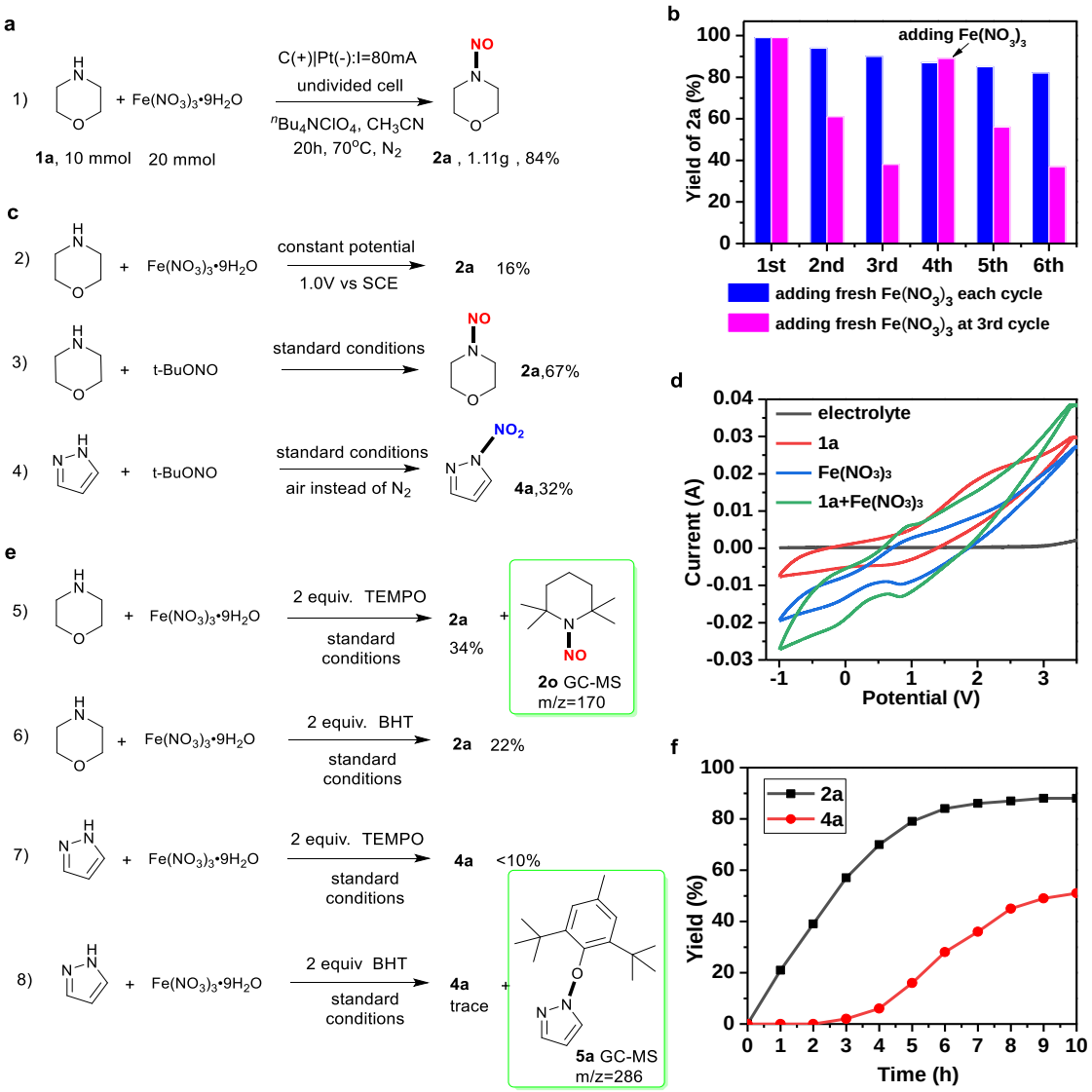
on the anode was essential to facilitate the reaction. When ^{t}BuONO was employed as the source of NO· and NO_2· radicals to react with morpholine and pyrazole instead of $Fe(NO_3)_3 \cdot 9H_2O$, 67% yield of **2a** and 32% yield of **3a** were obtained, respectively, which indicate that both reactions remained unaffected and that the metal ion may not participate in the reaction.

Competition and radical-trapping experiments were conducted to clarify whether the nitrosation and nitration reactions involved a similar radical process (Schemes 2e and 2f). A radical inhibition experiment with either 2 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,4-di-tert-butyl-4-methylphenol (BHT) significantly hindered the N-nitrosation and N-nitration reactions, therefore suggesting a radical pathway. In addition, the radical species were captured (see details in GC-MS results in Fig. S4 and Fig. S5). TEMPO captured the NO· radical in the morpholine nitrosation to form the stable N- nitroso product TEMP-NO **2o**, and BHT captured the pyrazole radical in the pyrazole nitration to form BHT-pyrazole **5a**. Interestingly, neither TEMPO nor BHT could capture the free radical intermediate of morpholine, indicating that morpholine may form a different radical cation $[H\text{-}N\cdot]^{+}$ rather than the [N·] radical. Therefore, a competition experiment was performed in which both morpholine and pyrazole existed in a reactor. If the reactions for N-nitrosation and N-nitration undergo the same pathway, two products will be observed at any time in a certain ratio depending on the activity of the substrates. However, it was found that the nitration process was inhibited until nitrosation was almost complete (after 5 h). Thus, N-nitrosation and N-nitration under the current could be biradical coupling reactions that involve a radical cation and radical intermediates, respectively.



Scheme 2. Extra experiments for N-nitration/N-nitrosation. (a) Gram-scale experiment of **1a**. (b) Recycle of reaction solution of **1a**. (c) Control experiments for N-nitration/N-nitrosation. (d) CV curves of reagents in morpholine nitrosation. (e) Radical trapping experiments under standard conditions. (f) Competitive reaction of **2a** and **4a** under standard conditions.

Theoretical simulation and mechanistic study. We have chosen piperidine and pyrazole as the representative cyclic alkyl amine and N-heteroaromatic compound for the DFT-based spin population analysis and atom charge simulation. As shown in Figure 1a and 1b, the N atom in piperidine shows weak electropositivity (positive atom charge), so it is more prone to exist in the form of a radical cation $[H\text{-}N\cdot]^+$.[14b,15] For this type of $[H\text{-}N\cdot]^+$ intermediate of aliphatic compounds, the single electron spin density is mainly distributed on the N radical cation with a spin population of 0.9, where the p orbital contribution is 0.8; in other words, the single electron mainly occupies the unbonded p orbital. Further transition states in which NO· or NO_2· radicals attack the $[H\text{-}N\cdot]^+$ intermediate were found, and their reaction kinetic constants were calculated with KiSTheIP.[18] The reaction rate of NO· is much higher than that of NO_2·; therefore, only nitrosation of cyclic alkyl amines will occur, and the nitration product will not be obtained (Figure 2a).

The N-heteroaromatic compound pyrazole, where N1/N2 is not electropositive (negative atom charge), is generally beneficial for the formation of N radicals, which is consistent with the results of the previously captured BHT-pyrazole complex. Moreover, there is no transition state in the reaction with NO· and NO_2· radicals, so the rate-determining step affecting the overall reaction is the generation of the radicals, after which the N-heteroaromatic compound reacts with the NO_2 radical spontaneously (Figure 2b). The calculations showed that the energy of *N*-nitropyrazole is much lower than that of *N*-nitrosopyrazole, which means that *N*-nitropyrazole is much more stable than *N*-nitrosopyrazole and that the nitration pathway would more easily occur.

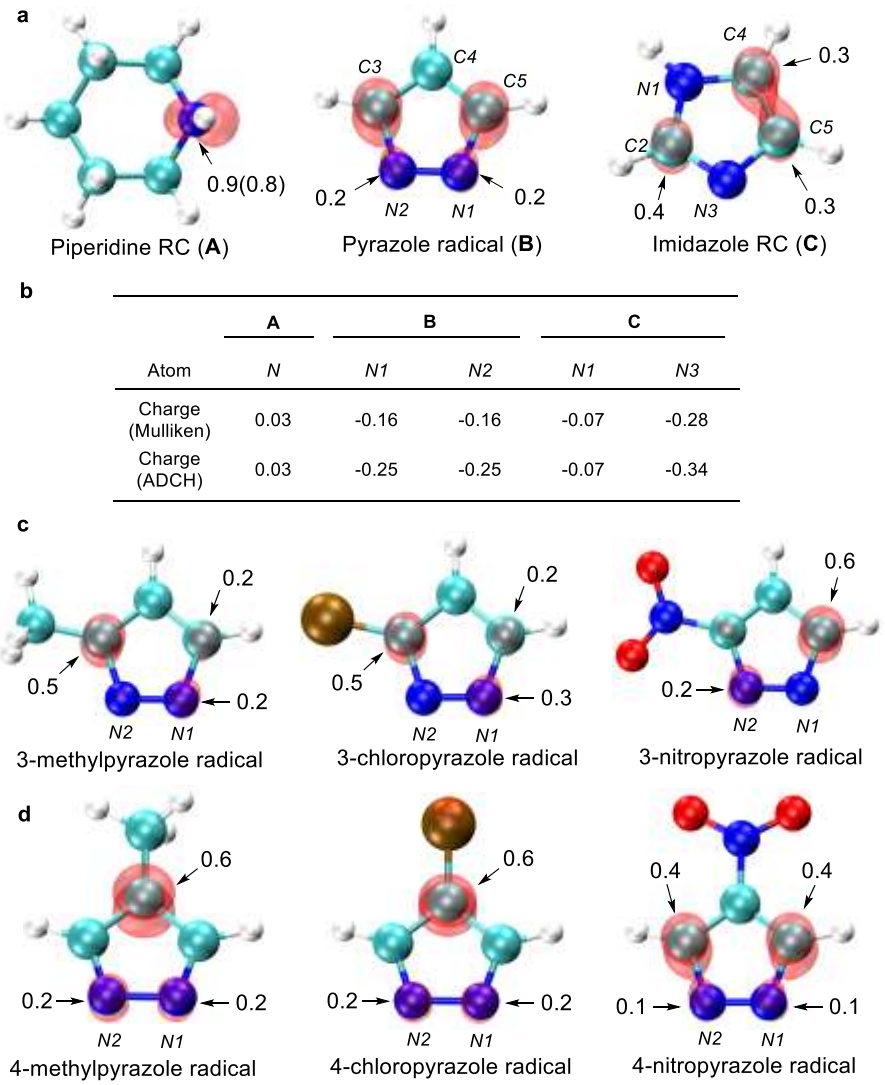


Figure. 1 Atom charge and electron spin population and secondary amines

The substitution effect on pyrazole nitration was further studied. As shown in Figure 1c and 1d, the introduction of an electron donor, halogen or electron-withdrawing substituent at the 4-position had a slight influence on N1/N2. However, substitution at the 3-position led to a different result. The introduction of an electron donor or halogen here causes the spin population of N2 to be close to 0, indicating that a single electron will appear only at the N1 site and thus affect the yield because the possibility of the reduction reaction is lower than that of the 4-substituted pyrazole derivatives. In contrast, the introduction of an electron-withdrawing NO_2 group at the 3-position reduces the spin population of N1 to 0, so nitration at this position rarely occurs with only 5% yield accordingly. The consistency between the experimental and calculated results shows that the pyrazole radical is indeed the intermediate and that its formation is the rate-determining step of the reaction.

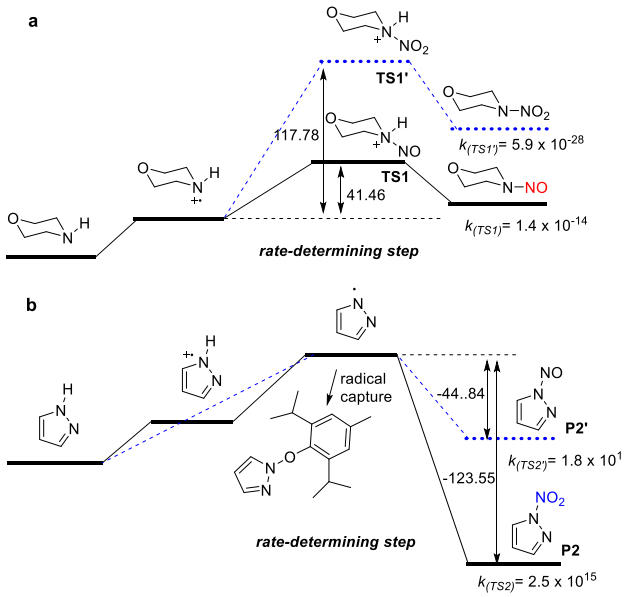
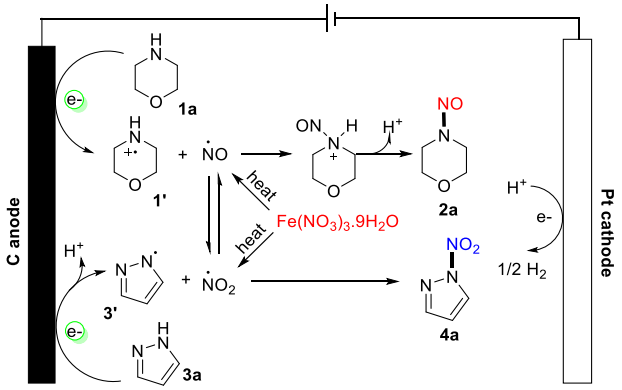


Figure. 2 (a) Reaction route and kinetic constant for morphline nitrosation. (b) Reaction route and kinetic constant for pyrazole nitration.

Based on our experimental facts and related reports, a possible biradical reaction mechanism for the electrochemical N-nitrosation/N-nitration process has been proposed (Scheme 3). First, morpholine and pyrazole were oxidized to their respective nitrogen radical cation **1'** and nitrogen radical **3'** in the anode via a single electron transfer process. Furthermore, the nitroso radical and nitro radical could be generated by heating with NO_3^- formed from $Fe(NO_3)_3 \cdot 9H_2O$. Then, the nitroso radical reacts with the nitrogen radical cation **1'** to afford the cross-coupling product **2a**, and the nitro radical reacts with nitrogen radical **3'** to afford the cross-coupling product **4a**. Correspondingly, the cathodic reduction of proton-hydrogen leads to the formation of hydrogen gas.



Scheme 3. Proposed Mechanism

Conclusion

In conclusion, we have developed a direct and selective N-nitrosation/N-nitration process of secondary amines via the coupling of amine radicals with nitro radicals under acid- and oxidant-free electrochemical conditions. A wide range of cyclic alkyl amines and N-heteroaromatic compounds can be transformed into the target products under a mild environment. Benefiting from the biradical mechanism, *C*-nitrosated/nitrated byproducts were avoided with high and unique selectivity for N-H activation. The operational ease, broad functional group tolerance and scalability of this reaction make it suitable for adoption in both academic and industrial settings. This work opens a new avenue for the use of electrochemistry in organic synthesis and offers new scaffolds for N-H functionalization.

Experimental Section

General procedure for the electrocatalyzed nitrosation of secondary amines with ferric nitrate: In an oven-dried undivided three-necked bottle (25 mL) equipped with a stirrer, secondary amines (1.0 mmol) and $^nBu_4NClO_4$ (205 mg, 0.6 mmol) were added. The bottle equipped with a graphite rod (Φ = 6 mm) as the anode and platinum electrodes as the cathode was then charged with nitrogen. Under the protection of N_2, CH_3CN (16 mL) was injected into the tubes via a syringe. The reaction mixture was stirred and electrolyzed at a constant current of 12 mA at 70 °C for 4-8 h. When the reaction was finished, the mixture was washed with water and extracted with diethyl ether (10 mL × 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. The pure product was obtained by flash column chromatography on silica gel.

General procedure for the electrocatalyzed nitration of azoles with ferric nitrate: In an oven-dried undivided three-necked bottle (25 mL) equipped with a stirrer, azoles (1.0 mmol) and $^nBu_4NBF_4$ (200 mg, 0.6 mmol) were

added. The bottle–equipped with a graphite rod (Φ = 6 mm) as the anode and platinum electrode (1.0 cm × 1.0 cm × 0.2 mm) as the cathode was then charged with nitrogen. Under the protection of N_2, CH_3CN (16 mL) was injected into the tubes via syringes. The reaction mixture was stirred and electrolyzed at a constant current of 12 mA at 70 °C for 7-10 h. When the reaction was finished, the reaction mixture was washed with water and extracted with diethyl ether (10 mL × 3). The organic layers were combined, dried over Na_2SO_4, and concentrated. The pure product was obtained by flash column chromatography on silica gel.

Acknowledgments

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FULL PAPER

Electrochemical nonacidic N-nitrosation/N-nitration of secondary amines through bi-radical coupling reaction

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