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Generated via Single-Electron Transfer

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Yu-Xiu Liu

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Dehydrogenation of *N*-Heterocycles by Superoxide Ion Generated via Single-Electron Transfer

Yuan-Qiong Huang, Hong-Jian Song,* Yu-Xiu Liu and Qing-Min Wang*

Abstract: Nitrogen-containing heteroarene motifs are found in a numerous pharmaceuticals, natural products, and synthetic materials. Although several elegant methods for synthesis of these compounds via dehydrogenation of the corresponding saturated heterocycles have been reported, some of the methods are hampered by long reaction times, harsh conditions, and the need for catalysts that are not readily available. Herein, we report a novel method for dehydrogenation of *N*-heterocycles. Specifically, $O_2^{\cdot-}$ generated in situ acts as the oxidant for *N*-heterocycle substrates that are susceptible to oxidation via a hydrogen atom transfer mechanism. This method provides a general, green route to *N*-heteroarenes.

Nitrogen-containing heteroarene motifs, such as carbolines, quinolines, and indoles, are commonly found in pharmaceuticals, natural products, and synthetic materials.^[1–7] Heteroarenes are typically prepared by means of oxidative dehydrogenation reactions of the corresponding saturated heterocycles; these reactions are generally mediated either by a stoichiometric oxidant, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),^[8] 2-iodoxybenzoic acid (IBX),^[9] sulfur,^[10] or SeO_2 ,^[11] or by a catalytic amount of a transition metal (e.g., Cu, Rh, Au, or Pt) in the presence of oxygen (Scheme 1).^[12–15] Recently, elegant syntheses of various heteroarenes have been accomplished by means of catalytic acceptorless dehydrogenation reactions of *N*-heterocycles with catalysis by metals such as iridium, ruthenium and nickel, iron, and cobalt.^[16] These systems show high atom efficiency, but they require either expensive and environmentally unfriendly catalysts or high reaction temperatures. An alternative is to use metal-free frustrated Lewis pairs to catalyze the dehydrogenation of *N*-heterocycles, but this method requires long reaction times and high temperatures (Scheme 1).^[17] Therefore, the development of a simple catalytic system that can be used under ambient conditions is highly desirable.

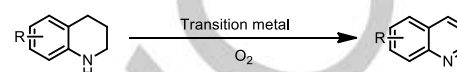
Badu-Tawiah et al.^[18] reported a visible-light-promoted aerobic dehydrogenation reaction of 1,2,3,4-tetrahydroquinolines and suggested that superoxide ion, $O_2^{\cdot-}$, is the active species in the catalytic process. Whereas O_2 is not very reactive with most other molecules, $O_2^{\cdot-}$ is a short-lived species that shows exceptionally high reactivity, particularly as an oxidizing agent and an initiator of radical reactions.^[19, 20] $O_2^{\cdot-}$ can selectively oxidize substrates that are susceptible to oxidation via hydrogen

Oxidative dehydrogenation

Stoichiometric dehydrogenation



Metal-catalyzed oxidative dehydrogenation



Acceptorless dehydrogenation

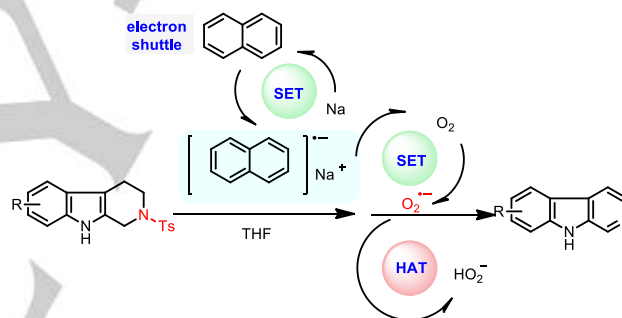
Transition-metal-catalyzed dehydrogenation



Frustrated Lewis pair

Visible-light-promoted dehydrogenation

This work: superoxide ion oxidative dehydrogenation



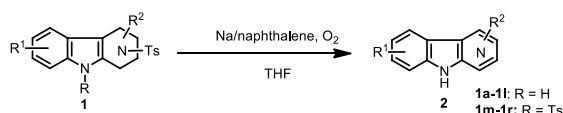
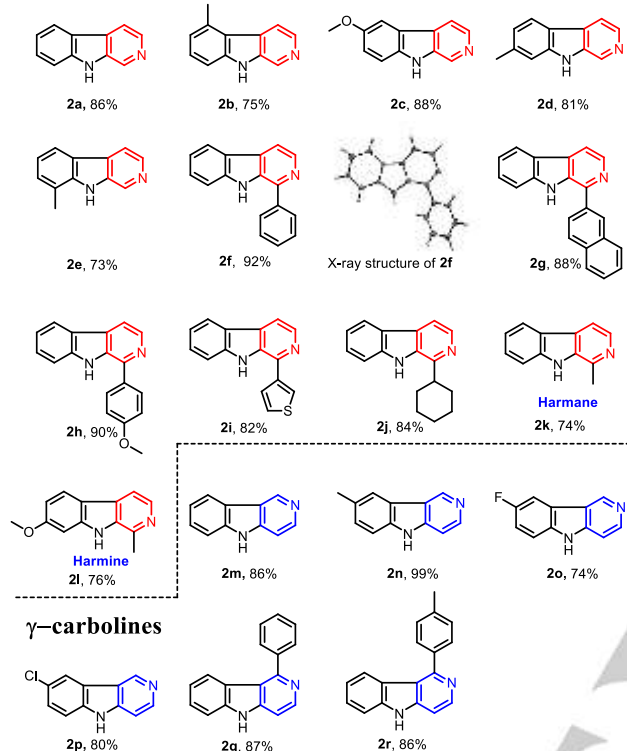
Scheme 1. Dehydrogenation Reactions for the Synthesis of *N*-Heteroarenes.

atom transfer.^[21] Many methods are available for $O_2^{\cdot-}$ generation, including various biological methods, peroxide decomposition, and electrochemical, chemical, photochemical, photocatalytic, and singlet-oxygen one-electron reduction reactions.^[22] However, because all the reported methods for preparation of $O_2^{\cdot-}$ are complicated and require the use of superoxide, which is dangerous to handle,^[23] conducting experiments that focus specifically on the generation of $O_2^{\cdot-}$ and its subsequent reactions is difficult. Therefore, a general, efficient method for the generation of $O_2^{\cdot-}$ would be highly desirable.

Aromatic hydrocarbons are known to act as electron shuttles, and direct reduction of aromatic hydrocarbons by alkali metals generates strong one-electron donors.^[24] In previous work, we observed that small amounts of carbolines were generated during the removal of *N*-tosyl groups from tetrahydro- β -carbolines with Na/naphthalene under Ar. We hypothesized that the carbolines were generated when Na/naphthalene transferred an electron to O_2 , present in a small amount in the reaction system, to generate $O_2^{\cdot-}$, which subsequently reacted with the tetrahydro- β -carbolines. To test our hypothesis, we carried out the reaction under O_2 instead of Ar and found that β -carbolines could be obtained as the sole products. In the present study, we explored the substrate scope of this reaction.

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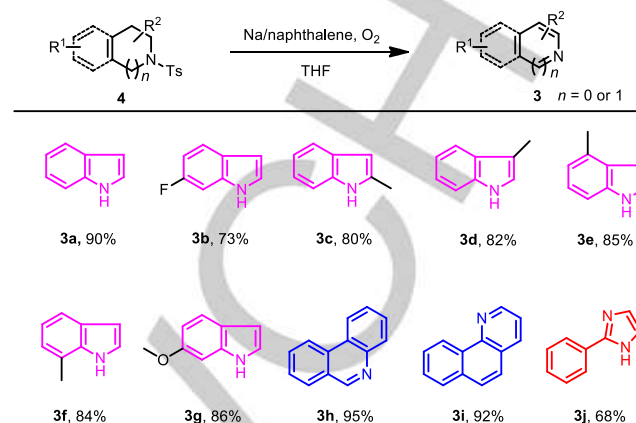
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 **β -carbolines**

Scheme 2. Desulfonation and Dehydrogenation of Tetrahydrocarbolines. [a] Isolated yields are given. Reactions were conducted with **1** (1 equiv) in the presence of freshly prepared Na/naphthalene (10 equiv) in tetrahydrofuran (THF) (substrate concentration = 0.01 mol/L) at -78 °C for 2 h. Then an oxygen ball was inserted into the reaction mixture, which was held at room temperature for 20–40 h.

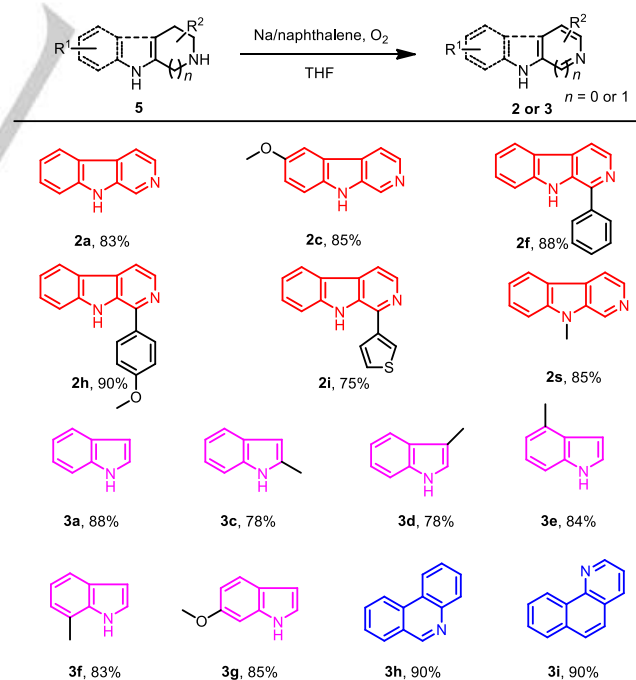
We began by investigating reactions of *N*-tosyl-tetrahydro- β -carbolines bearing a substituent at the 5-, 6-, 7-, or 8-position of the benzene ring (Scheme 2). We found that the corresponding desulfonated and dehydrogenation products (β -carbolines) could be obtained in >70% yields (**2a–2e**). We then carried out reactions of substrates with an aromatic or aliphatic substituent on the tetrahydropyridine ring. Substrates with phenyl, naphthalen-2-yl, 4-methoxyphenyl, thiophen-3-yl, and cyclohexyl substituents afforded corresponding β -carbolines **2f–2j** in >80% yields. The structure of **2f** was confirmed by X-ray diffraction analysis.^[25] In addition, we successfully used this reaction to obtain the alkaloid natural products harmine (**2k**) and harmine (**2l**) in 76% and 74% yields, respectively. Next, we evaluated the reactions of 2,5-ditosyl-tetrahydro- γ -carbolinesubstrates (**1m–1r**). An unsubstituted substrate and a substrate with a 6-methyl substituent provided corresponding γ -carbolines **2m** and **2n**, respectively, in good yields. Substrates with 6-F and 6-Cl substituents provided good to excellent yields of **2o** and **2p**, respectively, and the halogen atoms can be expected to be useful handles for further elaboration of the molecules via cross-

coupling reactions. Phenyl-substituted product **2q** and 4-methylphenyl-substituted product **2r** were obtained in >80% yields.



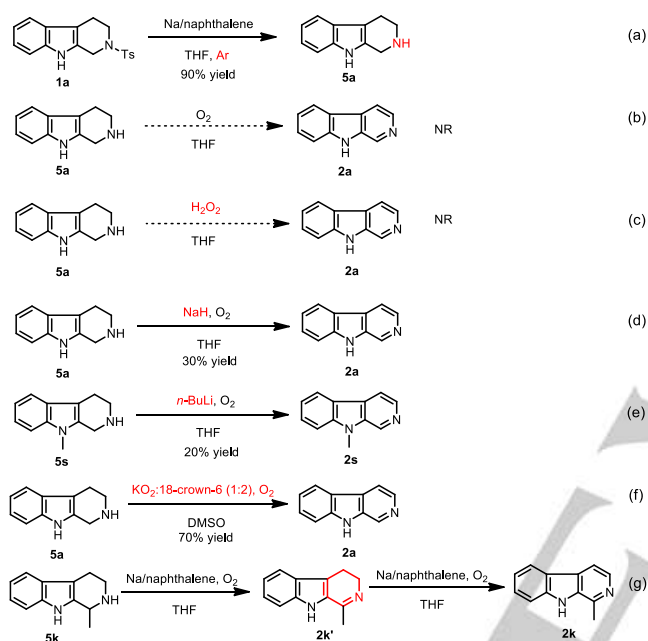
Scheme 3. Desulfonation and Dehydrogenation of Indolines and other Nitrogen-Containing Heterocycles. [a] Isolated yields are given.

We next sought to expand the substrate scope of the reaction by applying it to various indolines, as well as to dihydrophenanthridine, tetrahydrobenzo[*h*]quinoline, and an imidazolidine (Scheme 3). Specifically, *N*-tosyl-indolines **4a–4g** smoothly afforded the corresponding indoles (**3a–3g**) in good to excellent yields (73–90%). Phenanthridine (**3h**, 95%), benzo[*h*]quinoline (**3i**, 92%), and imidazole **3j** (68%) could also be obtained by means of this method.



Scheme 4. Dehydrogenation of Nitrogen-Containing Heteroarenes. [a] Isolated yields are given.

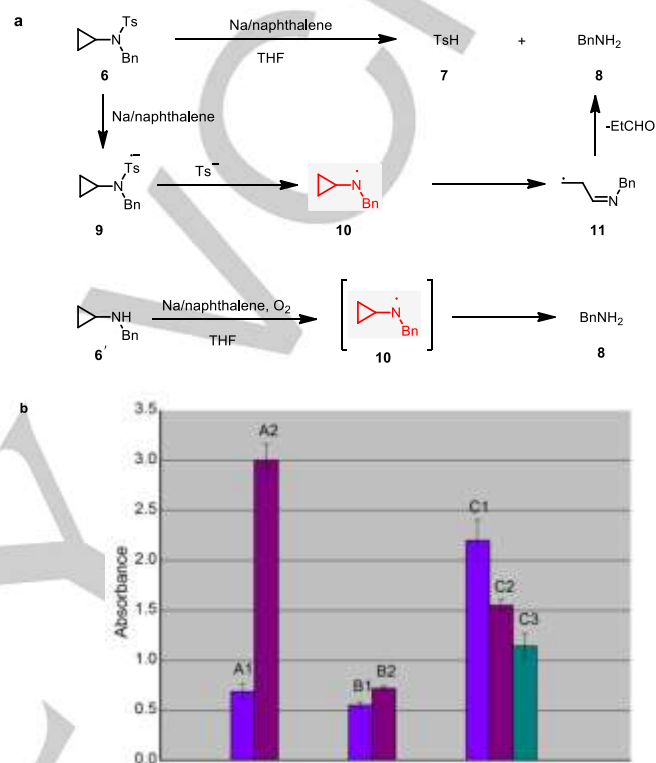
We suspected that this method would be applicable to unprotected *N*-heterocyclic substrates **5**, and we were delighted to find that dehydrogenation of such substrates did indeed proceed smoothly, albeit in slightly lower yields than those obtained with the *N*-tosyl substrates (Scheme 4). Specifically, tetrahydro- β -carbolines with a substituent on either the benzene ring or the tetrahydropyridine ring afforded the corresponding aromatic compounds in good yields. 9-Methyl- β -carboline (**2s**) was obtained in 85% yield. Similarly, substituted indoles, as well as phenanthridine and benzo[*h*]quinolone, could be obtained via direct dehydrogenation of the corresponding unprotected saturated heterocycles.



Scheme 5. Control Experiments.

With the goal of expanding the scope of the method and investigating additional applications of it, we performed preliminary studies aimed at elucidating the reaction mechanism (Scheme 5). When O_2 was replaced with Ar, reaction of **1a** under the standard conditions resulted in reductive cleavage of the S–N bond to afford **5a** in 90% yield (Scheme 5a). This result indicates that O_2 was essential for the dehydrogenation reaction. Reaction of **5a** under O_2 but in the absence of Na/naphthalene did not afford the desired aromatic product (**2a**), which indicates that Na/naphthalene was also necessary (Scheme 5b). Addition of H_2O_2 to a solution of **5a** in freshly distilled THF failed to afford **2a**; this experiment excludes the possibility that H_2O_2 acted as the oxidant for the dehydrogenation process (Scheme 5c). **2a** can be obtained in about 30% yield when the sodium adduct of **5a**, which was synthesized by reaction with NaH, reacted with O_2 (Scheme 5d). **2s** can also be obtained in about 20% yield when **5s** reacted with *n*-BuLi under O_2 (Scheme 5e). **2a** can be obtained in 70% yield when **5a** reacted with KO_2 (KO_2 :18-crown-6 = 1:2) in the presence of O_2 (Scheme 5f). It needs to be emphasized that no **2a** was obtained when **3a** reacted with KO_2

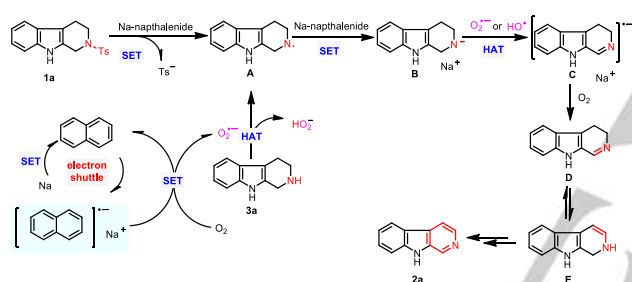
in the absence of O_2 . Partially dehydrogenated product **2k'** was obtained when the reaction time was halved, and **2k'** underwent complete dehydrogenation to afford aromatic product **2k** in excellent yield (92%) under the standard reaction conditions (Scheme 5g). This finding suggests that **2k'** was generated more readily than **2k** and that **2k** was indeed derived from partially dehydrogenated compound **2k'**.



Scheme 6. (a) Reaction of radical clock substrate **6** and **6'**. (b) Extinction at λ_{530} nm. [a] A1: Na/naphthalene in THF; A2: Na/naphthalene and O_2 in THF; B1 and B2: blank experiments; C1–C3: aqueous solutions of $NaNO_2$ (1, 0.5, and 0.2 mmol/L, respectively). For detailed experimental procedures, see Supporting Information.

Benzylamine **8** was detected when radical clock substrate **6** was allowed to react with Na/naphthalene (Scheme 6a). This transformation proceeded via the formation of aminyl radical **10**.^[26] Rapid opening of the cyclopropane ring of **10** afforded imine **11**, which then underwent quenching and hydrolysis to afford **8**.^[27] Benzylamine **8** also could be detected when substrate **6'** reacted under the standard reaction conditions (Scheme 6a). It is known that $O_2^{\cdot-}$ can be generated by means of monovalent reduction of O_2 (typically $E = -0.75$ V vs. SCE).^[28,29] We carried out an ultraviolet spectrophotometry experiment to determine whether $O_2^{\cdot-}$ was produced in the system containing O_2 and Na/naphthalene (which has a reduction potential of approximately -2.5 V vs NHE).^[30] This experiment clearly indicated that $O_2^{\cdot-}$ was indeed produced in the Na/naphthalene and O_2 system (Scheme 6b).

On the basis of the results of the above-described experiments and in consideration of previously proposed mechanisms,^[31, 32] we suggest that $O_2^{\cdot-}$ generation and subsequent desulfonation and dehydrogenation of the *N*-heterocycle substrates proceed via the mechanism outlined in Scheme 7, with substrate **1a** as an example. Specifically, reductive cleavage of the *N*-tosyl group with Na/naphthalene via single-electron transfer affords amine radical **A**, which can abstract a hydrogen atom from the solvent to form **3a**. In addition to cleaving the S–N bond, naphthalene acts as an electron shuttle, delivering a single electron to O_2 to generate $O_2^{\cdot-}$, which reacts with **3a** to generate $HO_2^{\cdot-}$ and aminyl radical **A** via hydrogen atom transfer. Aminyl radical (**A**) gets immediately reduced with Na-naphthalenide that is present in large excess. The Na-amide **B** formed has a highly activated alpha C–H bond. Hence, the superoxide radical anion generated upon SET reduction of O_2 with Na-naphthalenide or the hydroxyl radical formed by reduction of in situ generated hydroperoxide abstracts that activated H-atom to get a radical anion **C** that is readily oxidized by air to give **D**. Rearomatization is then easily achieved via H-abstraction either by air or the superoxide radical anion or the hydroxyl radical.



Scheme 7. Plausible Reaction Mechanism.

In summary, we have developed a novel method for dehydrogenation of *N*-heterocycles. Specifically, reductive electron transfer from Na/naphthalene to O_2 generates $O_2^{\cdot-}$, which oxidizes the *N*-heterocycles via a hydrogen atom transfer mechanism. We anticipate that this general, green dehydrogenation method will find further applications for the synthesis of other *N*-heterocycles.

Acknowledgements

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Keywords: dehydrogenation • nitrogen heterocycles • redox chemistry • single-electron transfer • superoxide ion

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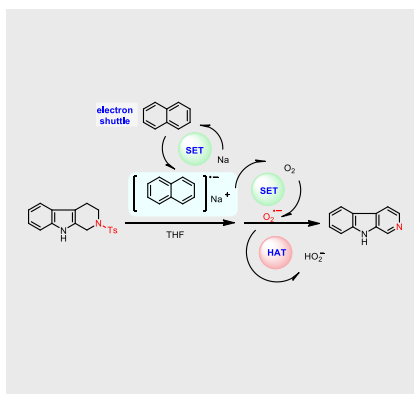
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Yu-Xiu Liu and Qing-Min Wang*

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Dehydrogenation of *N*-Heterocycles
by Superoxide Ion Generated via
Single-Electron Transfer

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