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Catalytic Aerobic Dehydrogenation of *N*-Heterocycles by *N*-Hydoxyphthalimide

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Abstract. Catalytic methods for the aerobic dehydrogenation of N-heterocycles are reported. In most cases, indoles are accessed efficiently from indolines using catalytic N-hydroxyphthalimide (NHPI) as the sole additive under air. Further studies revealed an improved catalytic system of NHPI and copper for the preparation of other heteroaromatics, for example quinolines.

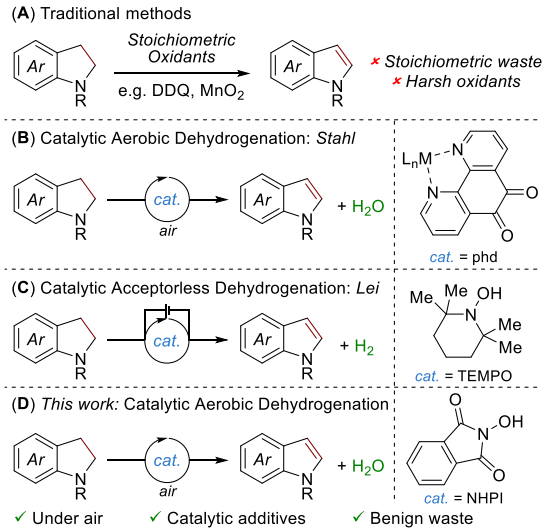
Keywords: Aerobic dehydrogenation; *N*-heterocycles; *N*-hydroxyphthalimide; Indolines; Quinolines

Introduction

The aromatization of saturated heterocycles via dehydrogenation is a fundamental process in organic synthesis.[1] This process has proved particularly useful for the construction of nitrogen-containing heteroaromatics, for example, the dehydrogenation of indolines to indoles has been used numerous times in the total synthesis of complex organic molecules.[2] Accessing heteroaromatics, such as indoles and quinolines, is an important task as they are found in various materials, natural products and bioactive molecules.[3] For instance, indoles and quinolines are amongst the most frequently encountered ring systems in medicine.[4]

In recent years, there have been sustained efforts to replace traditional methods for dehydrogenation that use stoichiometric oxidants, such as DDQ or metal oxides (Scheme 1A), with catalytic alternatives. Catalytic dehydrogenations can be split into two main categories: aerobic dehydrogenation (e.g. Scheme 1B)[5,6] and acceptorless dehydrogenation (e.g. Scheme 1C).[7,8] In aerobic dehydrogenation, O_2 is the terminal oxidant and H_2O is produced as a benign side-product. Acceptorless dehydrogenations are redox-neutral processes that release H_2. Thus, both strategies represent ideals in terms of atom-efficiency. There have been great developments in catalytic aerobic dehydrogenation and catalytic acceptorless dehydrogenation – from early reports using precious transition metals and heterogeneous catalysts, to more recent techniques using electrochemical synthesis and photoredox catalysis. We have highlighted just two of the most recent advances in this area made by the groups of Stahl and Lei. Stahl and co-workers designed novel, bioinspired quinone-based catalytic systems for aerobic dehydrogenation (Scheme 1B).[5m,6a] Alternatively, Lei and co-workers used electrochemistry in the acceptorless dehydrogenation of *N*-heterocycles with TEMPO as an organoelectrocatalyst (Scheme 1C).[8e]

N-hydroxyphthalimide (NHPI) has found widespread use in the radical functionalization of C–H bonds.[9] It is particularly useful for the oxygenation of benzylic C–H bonds.[10] This chemistry also promotes the dehydrogenation/oxidation of alcohols (i.e. C–O bonds) to aldehydes under mild aerobic conditions,[11]



Scheme 1. Methods for the dehydrogenation of indolines.

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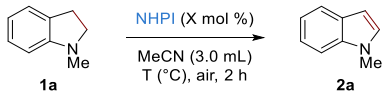
but it has not been applied to the dehydrogenation of C–C bonds. Continuing our interest in the oxidation of heteroaromatic compounds, we questioned whether the radical chemistry of NHPI could be used for the dehydrogenation of saturated *N*-heterocycles.
In this report, we reveal a metal-free aerobic dehydrogenation of indolines to indoles catalyzed by *N*-hydroxyphthalimide (NHPI). A related NHPI/Cu catalyst system is also described, which expands the scope to other heterocycles, for example to gain access to quinolines and benzofurans. The role of NHPI is also unique - whereas benzylic C–H bonds tend to undergo oxygenation to give C–O bonds under aerobic NHPI catalysis, this process leads to dehydrogenated products.

Results and Discussion

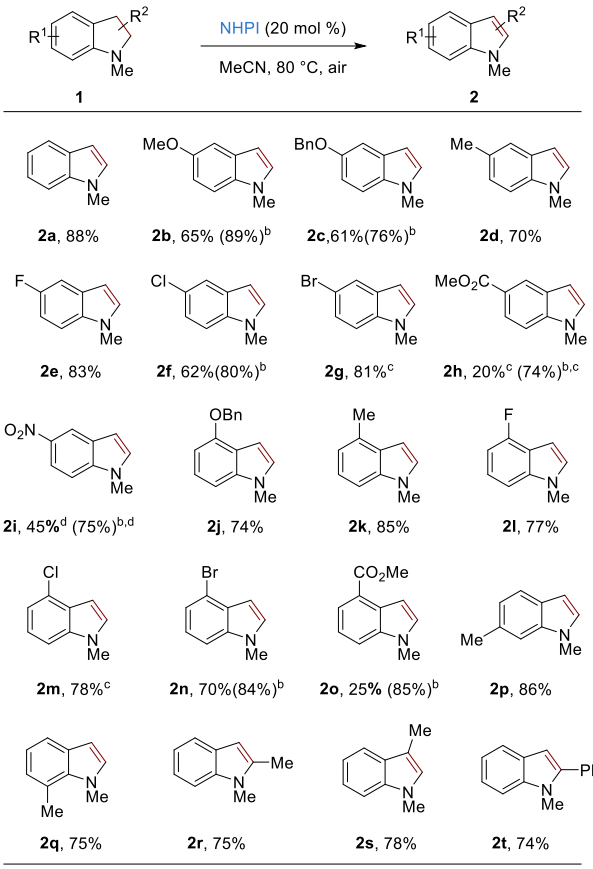
We began by investigating the dehydrogenation of indoline **1a** to indole **2a**.[12] Using *N*-hydroxyphthalimide (NHPI) in acetonitrile, we initially found that a stoichiometric quantity of NHPI was capable of promoting dehydrogenation in 2 h (Table 1, entry 1). Further investigation revealed that the loading of NHPI could be lowered to catalytic amounts (20 mol %) without affecting the efficiency of the reaction (entry 2). This reaction was also performed on a gram-scale to demonstrate robustness and applicability, the recovery of NHPI was 91% in this reaction (entry 3). Decreasing the loading of NHPI further was possible, however, longer reaction times (16 h) were required (entry 4). This represents a

Table 1. Optimization of the catalytic aerobic dehydrogenation of indolines to indoles.[a)]



Entry	NHPI	T (°C)	Yield (%)
1	100 mol %	80	85
2	20 mol %	80	88
3[b]	20 mol %	80	85
4[c]	15 mol %	80	82
5	20 mol %	50	80
6	20 mol %	25	10
7[c]	20 mol %	25	50
8[d]	20 mol %	25	80
9	-	80	0
10[d]	-	80	trace

[a)] Unless otherwise noted, the reactions were performed using 0.2 mmol of **1a** in 3.0 mL of solvent for 2 h. Yields are of pure isolated products. NHPI = *N*-hydroxyphthalimide. [b)] Gram scale (7.8 mmol) reaction. [c)] Reacted for 16 h. [d)] 5 mol % of $Cu(OAc)_2 \cdot H_2O$ was added. [e)] The reaction was performed under N_2.



[a)] Unless otherwise noted, the reactions were performed using 0.2 mmol of **1** and 0.04 mmol of NHPI in 3.0 mL of MeCN. Yields are of pure isolated products. [b)] 5 mol % of $Cu(OAc)_2 \cdot H_2O$ was added. [c)] The reaction was performed at 100 °C. [d)] The reaction was performed at 120 °C

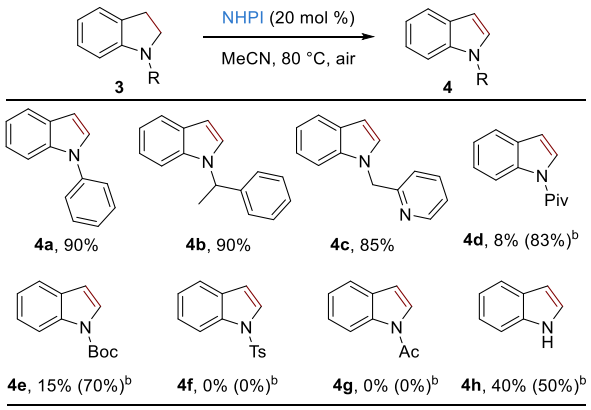
Scheme 2. Scope of the catalytic aerobic dehydrogenation of indolines to indoles.

rare case of transition metal-free aerobic dehydrogenation of heterocycles.[5,6] By experimenting with both the temperature and reaction time (entries 5-7) a respectable yield of 50% was obtained at room temperature (entry 7), though carrying out the reaction with 20 mol % NHPI, at 80 °C for 2 h was considered optimal for the purposes of this investigation (entry 2). Interestingly, the rate and yield of the process were significantly improved when adding catalytic $Cu(OAc)_2 \cdot H_2O$ (5 mol %), to provide an effective method at room temperature (entry 8). The investigation of non-toxic and relatively abundant transition metal catalysts, such as copper, is relatively underdeveloped in this field.[5] Control experiments revealed that the reaction did not occur in the absence of NHPI (entry 9 and 10)
With an efficient dehydrogenation in hand, we explored the versatility of this method by examining the scope of the indoline substrate **1** (Scheme 2). The transition metal-free conditions were applicable to a range of electron-rich (**2b**-**2d**) and electron-deficient (**2e**-**2g**) indolines. We have also demonstrated that, if desired, these yields can be improved by adding

10.1002/adsc.202000767

catalytic amounts of $Cu(OAc)_2 \cdot H_2O$ (5 mol %, **2b**, **2c**, **2f**, **2g**). For indolines bearing strongly electron-withdrawing groups, NHPI alone proved inefficient, however good yields of **2h** and **2i** were achieved upon addition of the copper catalyst and raising the temperature (100-120 °C). Substitution at various positions (C5, **2b-2i**; C4, **2j-2o**, C6, **2p**; C7 **2q**) on the 6-membered ring of the indoline were well tolerated in this reaction. Finally, substitution at the C–C bond that undergoes dehydrogenation (i.e. C2/C3 of the indole product **2**) had little influence on the efficiency of the reaction (**2r**, **2s** and **2t**).

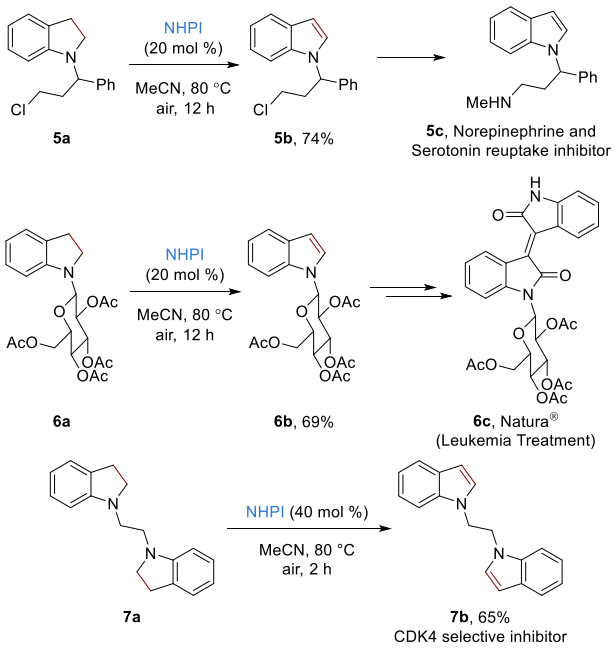
To further show the potential of this reaction in organic synthesis, we investigated the compatibility of other *N*-substituted indolines (Scheme 3). For example, phenyl (**4a**) and benzyl groups (**4b**, **4c**) were well tolerated in the reaction. Pivaloyl and Boc protection was also applicable, though addition of $Cu(OAc)_2 \cdot H_2O$ (5 mol %) was required. Some other indolines bearing removable protecting groups, such as tosyl (**4f**) and acyl (**4g**) groups, were unsuccessful and we only observed recovery of starting material. Finally, free NH-indole (**4h**) was also prepared from the corresponding non-protected indoline in 40% yield. The addition of the copper catalyst gave only a slight improvement in reaction yield in this case.



a) Unless otherwise noted, the reactions were performed using 0.2 mmol of **3** and 0.04 mmol of NHPI in 3.0 mL of MeCN. Yields are of pure isolated products. b) 5 mol % of $Cu(OAc)_2 \cdot H_2O$ was added.

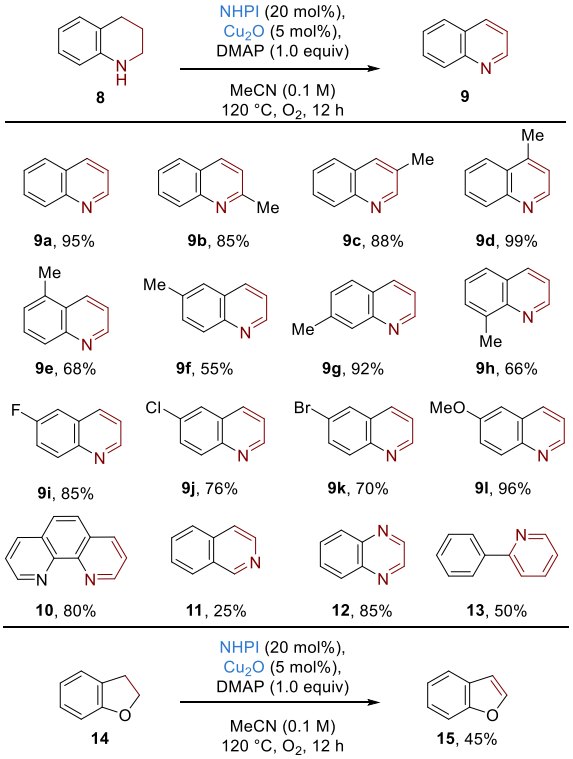
Scheme 3. Scope of *N*-substituted indolines in the catalytic aerobic dehydrogenation to indoles.

We then used this methodology for the synthesis of known drug targets and intermediates (Scheme 4). For example, the benzyl-substituted indoline **5a** was dehydrogenated to give indole **5b**, a precursor of the norepinephrine and serotonin reuptake inhibitor **5c**.[13] The glycosyl substituted indoline **6a** also underwent dehydrogenation to give indole **6b**, an intermediate in the synthesis of the cancer therapeutic **6c**.[14] Finally, we were able to prepare the cyclin dependent kinase 4 (CDK4) selective inhibitor **7b** from the linked diindoline **7a**.[15]



a) The reactions were performed using 0.2 mmol of indolines (**5a**, **6a**, **7a**) and 0.04 mmol of NHPI in 3.0 mL of MeCN. Yields are of pure isolated products.

Scheme 4. Application of the catalytic aerobic dehydrogenation of indolines in the synthesis of biologically active molecules.



a) Unless otherwise noted, the reactions were performed using 0.2 mmol of **8**, 0.04 mmol of NHPI, 0.01 mmol of Cu_2O and 0.2 mmol of DMAP in 2.0 mL of solvent under O_2 atmosphere for 12 h. Yields are of pure isolated products.

Scheme 5. Scope of tetrahydroquinolines in the catalytic aerobic dehydrogenation to quinolines.

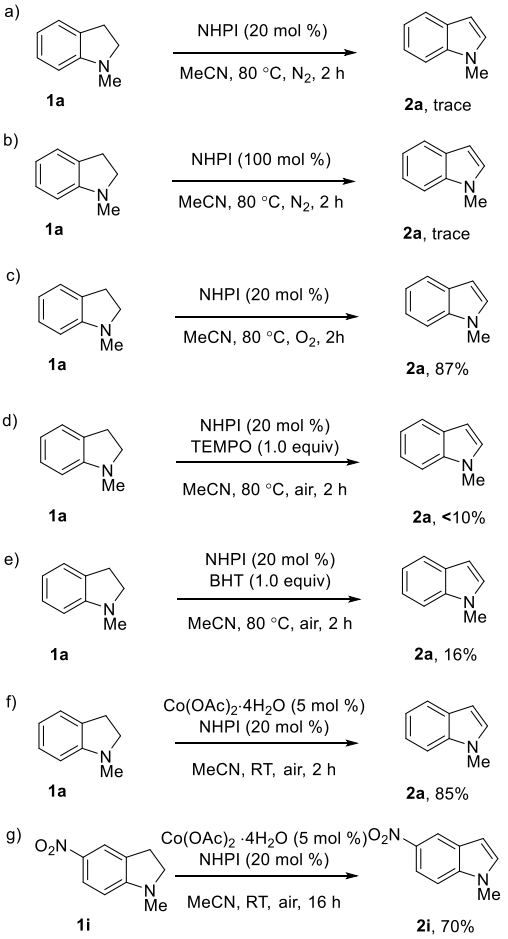
Having developed an efficient catalytic dehydrogenation of indolines, we then looked to expand this process to incorporate other heterocycles. Our conditions were initially insufficient when applied to the synthesis of quinoline **9a**. However, further optimization revealed that a combination of NHPI (20 mol %), Cu_2O (5 mol %) and DMAP under an atmosphere of oxygen gave high yields of dehydrogenation (scheme 5).[12] This procedure proved applicable to substitution at every position of the tetrahydroquinoline (**9b**-**9h**), and both electron-withdrawing (**9i**-**9k**) and electron-donating (**9l**) substituents were well tolerated. This method of dehydrogenation was also used to prepare other aromatic *N*-heterocycles, such as phenanthroline **10**, isoquinoline **11**, quinoxaline **12**, and pyridine **13**. Access to benzofuran **15** from 2,3-dihydrobezofuran **14** was also possible.

Some control reactions have been set up to understand the mechanism (Scheme 6). Under an inert (N_2) atmosphere only a trace of product was obtained (a), even when using a stoichiometric amount of NHPI (b); reactivity was turned back on under an oxygen atmosphere (c). These show that oxygen is essential for the transformation, suggesting the conversion of NHPI to an active species, (PINO). The use of radical traps (e.g. 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) significantly decreased reactivity suggesting a radical mechanism (d and e). The addition of copper to the reaction allows the process to run efficiently at lower temperatures (Table 1, entry 8). We suggest that copper promotes the formation of PINO from NHPI. Cobalt salts are also commonly used to promote the formation of PINO,[16] and, like copper, they also promoted the reaction (f). The oxidation of 5-nitro-1-methylindoline (**1i**) could also be promoted by the use of cobalt salt (g), which is similar to the reaction using Cu salt (Scheme 2, **2i**). Finally, the formation of H_2O_2 was detected under mild conditions by ^1H NMR spectrum.[17]

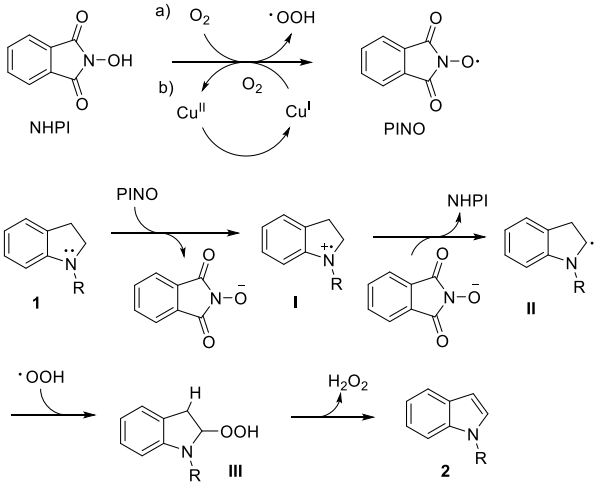
A putative mechanism for this reaction is presented in Scheme 7. First of all, oxygen promotes the conversion of NHPI to PINO (path a).[18] The addition of a copper catalyst can aid this process (path b).[19] PINO can then undergo single electron transfer (SET) with the indoline to give the radical cation **I** and the anion of NHPI.[10] Deprotonation then leads to **II** and regenerates NHPI. The trapping of radical **II** with ·OOH leads to intermediate **III**,[21] which gives to the desired product **2** upon expulsion of H_2O_2.[11,17]

Conclusion

In conclusion, we have developed a catalytic aerobic dehydrogenation of *N*-heterocycles. In many cases, the conversion of indolines to indoles is possible under air using catalytic NHPI as the sole additive. For more challenging substrates, and to expand the scope to other heterocycles, a catalyst system of NHPI and copper was developed. The process displays good functional group compatibility and can be used in the synthesis of bioactive compounds. Studies to delineate this unique reactivity of NHPI are ongoing in our laboratories.



Scheme 6. Control reactions.



Scheme 7. Putative reaction mechanism.

Experimental Section

General information

All reagents and solvents were purchased from commercial suppliers and used without further purification. All the reactions were carried out without any precautions to exclude air and moisture. Reactions were monitored by thin-layer chromatography (TLC) on silica gel GF-254 pre-coated glass plates. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm. ^{1}H NMR spectra, recorded at 400 MHz, are referenced to the residual solvent peak at 7.26 ppm ($CDCl_3$). ^{13}C NMR spectra, recorded at 101 MHz, are referenced to the residual solvent peak at 77.0 ppm ($CDCl_3$).

Representative procedure for the dehydrogenation of indolines, 1a (Scheme 2): To a 20 mL vial, **1a** (26.6 mg, 0.20 mmol) and *N*-hydroxyphthalimide (6.6 mg, 0.04 mmol) were dissolved in MeCN (3.0 mL). The vial was sealed and reaction mixture was stirred at 80 °C for 2 h. After that time, the reaction mixture was cooled down to room temperature, and the reaction solvent was evaporated under vacuum. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc = 20/1) to afford the 1-methyl-1H-indole (**2a**) as a light yellow liquid (23.1 mg, 88% yield).

Representative procedure for the dehydrogenation of tetrahydroquinolines, 8a (Scheme 5):

To a 20 mL vial, **8a** (25.8 mg, 0.20 mmol), Cu_2O (1.4 mg, 0.01 mmol), 4-dimethylaminopyridine (24.4 mg, 1 equiv) and *N*-hydroxyphthalimide (6.6 mg, 0.04 mmol) were dissolved in MeCN (2.0 mL). The reaction mixture was bubbled with O_2 for 20 minutes and quickly sealed. The reaction was then stirred at 120 °C for 12 h. After that time, the reaction mixture was evaporated under vacuum. The crude residue was purified by flash column chromatography (petroleum ether/EtOAc = 20/1) to afford the quinoline (**9a**) as a colorless liquid (24.1 mg, 95% yield).

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FULL PAPER

Catalytic Aerobic Dehydrogenation of *N*-Heterocycles by *N*-Hydoxyphthalimide

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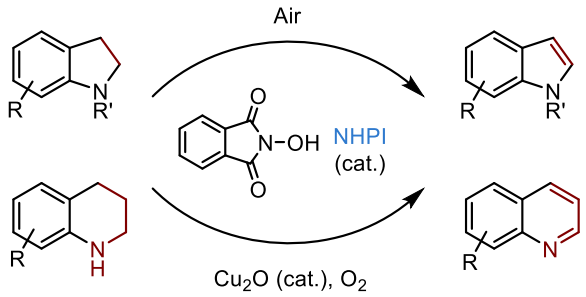

A mild and efficient aerobic dehydrogenation of *N*-heterocycles is reported using catalytic *N*-hydroxyphthalimide (NHPI).