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A Convenient Procedure for the Oxidative Dehydrogenation of N-Heterocycles Catalyzed by $FeCl_2$/DMSO

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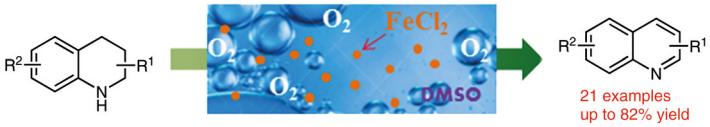

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Abstract A convenient catalytic procedure has been developed for the oxidative dehydrogenations of N-heterocycles. Combining catalytic $FeCl_2$ with DMSO yields a catalyst that promotes the dehydrogenation of tetrahydroquinolines and related heterocycles under 1 bar of O_2, affording the corresponding N-heteroaromatic products in moderate yields.

Key words oxidative dehydrogenation, N-heterocycle, iron catalyst, DMSO, quinolines

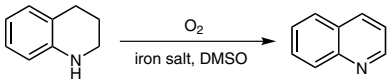
Catalytic dehydrogenation of saturated N-heterocycles provides an easy, atom-economic entry to the corresponding aromatic heterocycles. There are mainly two types of dehydrogenation reaction. One is run under acceptorless conditions, with the hydrogen released as H_2. Catalysts such as iridium–pincer complexes,[1] Cu/Al_2O_3,[2] Cu/TiO_2,[3] hydroxyapatite-bound palladium,[4] and ruthenium–hydride complexes[5] have been explored for the acceptorless dehydrogenation. The other requires the presence of an oxidant such as O_2. This oxidative dehydrogenation has been performed with a number of catalysts, including Ru/Al_2O_3,[6] [Rh_2(caprolactamate)$_4$],[7] Ru/Co_3O_4,[8] $Ru(OH)_x/Al_2O_3$,[9] rhodium nanoparticles supported on multiwalled carbon nanotubes,[10] iron oxides surrounded by nitrogen-doped graphene shells immobilized on carbon (FeO_x@NGr–C),[11] cobalt oxide supported on nitrogen-doped carbon,[12] and *o*-quinone.[13] It is noted that most of the catalytic systems are based on noble metals or require harsh conditions, such as high reaction temperatures, high pressure, and complicated preparation methods.

We have recently reported highly efficient acceptorless dehydrogenation of N-heterocycles with iridicycle catalysts.[14] Prior to this, Fujita and Yamaguchi reported the first example of homogeneous dehydrogenation of tetrahydroquinolines using a [Cp*Ir(2-hydroxypyridine)] catalyst.[15] More recently, Jones et al.[16] reported an iron–pincer catalyst that showed high catalytic activity in the dehydrogenation of N-heterocycles; the same group also found a cobalt–pincer catalyst for the same transformation.[17] Although these catalysts have advanced N-heterocycle dehydrogenation considerably, their performance depends on the use of specialist ligands. Thus, the development of inexpensive and convenient catalytic systems for dehydrogenation is still desirable. Herein we report a simple $FeCl_2$/DMSO system that catalyses efficient oxidative dehydrogenation of N-heterocycles with molecular oxygen as the terminal oxidant. To the best of our knowledge, there appears to be only one report in which an iron salt without ligands, $Fe(NO_3)_3$/TEMPO, was used for the oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline, affording quinoline in a yield of only 27%.[18]

We started the investigation choosing 1,2,3,4-tetrahydroquinoline as a model substrate. Preliminary screening of iron salts showed that various iron compounds, for example, $FeCl_2$, $FeBr_2$, and $Fe(OTf)_3$ (3 mol%), could catalyse the reaction without any ligands under 1 bar of O_2 at 140 °C (Table 1, entries 1–4). $FeCl_2$ led to the highest product yield, which is, however, only moderate. We then varied the solvent and examined the reaction at a reduced temperature (Table 1, entries 5–10). Interestingly, the substrate was fully consumed when DMSO was used as the solvent, although the yield of quinoline was not improved. The higher conversion in DMSO could stem from the solvent acting as an oxidant.[19] Indeed, in the absence of the iron salt, quinoline was obtained in 23% yield (Table 1, entry 11). These results prompted us to reexamine the iron-catalysed dehydrogenation in the presence of DMSO in *p*-xylene. Gratifyingly, when the dehydrogenation was carried out at 110 °C with

0.8 equivalents of DMSO added, quinoline was isolated in a higher yield of 65% (Table 1, entry 19), indicating a synergistic effect between $FeCl_2$ and DMSO in the reaction.

Table 1 Optimization of Conditions for the Dehydrogenation of 1,2,3,4-Tetrahydroquinoline[a]



Entry	Iron salt	Solvent	DMSO (equiv)	Temp (°C)	Yield (%)[b]
1	$FeCl_2$	*p*-xylene	0	140	45
2	$FeBr_2$	*p*-xylene	0	140	26
3	$Fe(BF_4)_2$	*p*-xylene	0	140	8
4	$Fe(OTf)_3$	*p*-xylene	0	140	23
5	$FeCl_2$	MeCN	0	100	25
6	$FeCl_2$	EtOAc	0	100	12
7	$FeCl_2$	THF	0	100	trace
8	$FeCl_2$	DMF	0	100	13
9	$FeCl_2$	DMSO	–	100	42
10	$FeCl_2$	*p*-xylene	0	100	24
11	–	DMSO	–	100	23
12	$FeCl_2$	*p*-xylene	3	100	41
13	$FeCl_2$	*p*-xylene	1.5	100	48
14	$FeCl_2$	*p*-xylene	0.8	100	52
15	$FeCl_2$	*p*-xylene	0.3	100	46
16	$FeCl_2$	*p*-xylene	0.15	100	13
17	$FeCl_2$	*p*-xylene	0.8	80	32
18	$FeCl_2$	*p*-xylene	0.8	90	42
19	$FeCl_2$	*p*-xylene	0.8	110	65

[a] Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), amount of catalyst (3 mol%), 24 h, under 1 bar O_2 atmosphere, solvent (1 mL).
[b] Isolated yields are given.

Using the optimized $FeCl_2$/DMSO catalyst system (Table 1, entry 19), various derivatives of 1,2,3,4-tetrahydroquinoline were dehydrogenated under a balloon pressure of O_2. As shown in Table 2, substituents at the 2, 3 or 4 positions were well tolerated, with 2-methylquinoline, 3-methylquinoline, and 4-methylquinoline being produced in 65%, 82%, and 75% yields, respectively (Table 2, entries 2–4). Quinolines with a substituent on the aromatic ring were also obtained in comparable yields (Table 2, entries 7–13). In addition, a 2,5,7-trisubstituted substrate was tested, and the desired product was obtained in good yield (Table 2, entry 5). From the reaction time needed for different substrates, it can be observed that electron-withdrawing groups tend to deactivate the substrate (Table 2, entries 8–12), although the effect varies and is not dramatic under the conditions used. The 8-chloro-substituted tetrahydroquinoline necessitated a much longer time, presumably a reflection of both electronic and steric effects (Table 2, entry 13). However, installing a phenyl moiety at the 2 position confers a much higher reactivity on the substrate, which was fully reacted in 8 h (Table 2, entry 14). This is likely due to the sp^3 C–H bond being made weaker by the phenyl ring, indicating that electronic effects may play a more important role than steric hindrance in the oxidative dehydrogenation reaction.

Table 2 Scope of the Oxidative Dehydrogenation of N-Heterocycles under $FeCl_2$/DMSO[a]

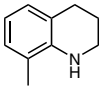
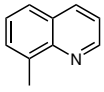
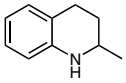
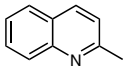
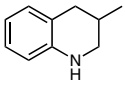
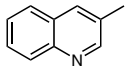
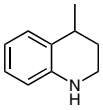
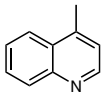
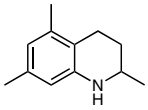
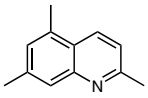
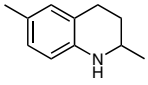
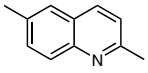
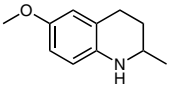
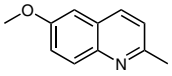
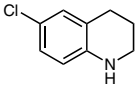
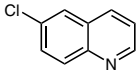
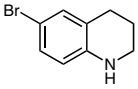
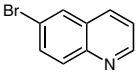
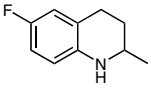
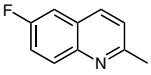
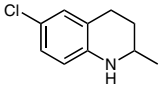
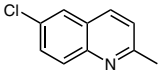
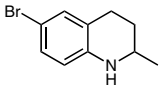
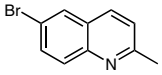
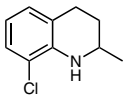
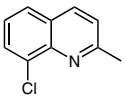
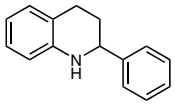
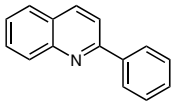
Entry	Substrate	Product[20]	Time h)	Yield (%)[b]
1			24	70
2			24	65
3			24	82
4			24	75
5			24	54
6			24	73
7			24	59
8			28	71
9			26	71
10			24	52
11			24	76

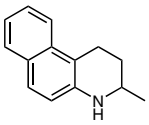
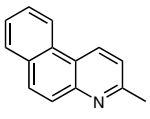
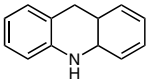
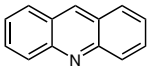
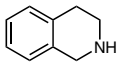
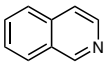
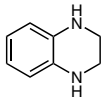
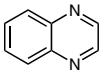
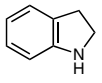
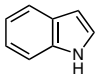
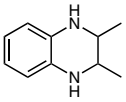
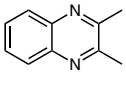
Table 2 (continued)

Entry	Substrate	Product[20]	Time h)	Yield (%)[b]
12			30	81
13			40	64
14			8	80

[a] Reaction conditions: substrate (0.5 mmol), $FeCl_2$ (3 mol%), DMSO (0.4 mmol), 110 °C, under O_2 atmosphere, *p*-xylene (1 mL).
[b] Isolated yields are given.

The high reactivity of the tetrahydroquinoline derivatives encouraged us to explore the $FeCl_2$/DMSO catalytic system for the dehydrogenation of other N-containing compounds. As shown in Table 3, apart from quinoline derivatives, quinoxaline, acridine, quinoxaline, isoquinoline, and indole were also generated in 41–79% yield under the optimized reaction conditions (Table 3). Although most of the yields are lower than those in previous reports,[6,7,12] some substrates, such as acridine and quinoxaline, afforded the target products in comparable yields with those obtained with FeO_x@NGr–C.[11]

Table 3 Oxidative Dehydrogenation of Other N-Containing Compounds under $FeCl_2$/DMSO[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			24	41
2			20	79
3			24	47
4			26	46
5			34	61
6			24	75

[a] Reaction conditions: substrate (0.5 mmol), $FeCl_2$ (3 mol%), DMSO (0.4 mmol), 110 °C, under O_2 atmosphere, *p*-xylene (1 mL).
[b] Isolated yields are given.

To gain some insight into the mechanism of the $FeCl_2$/DMSO-catalyzed dehydrogenation of N-heterocycles, the oxidation of 1,2,3,4-tetrahydroquinoline in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were investigated. Table 4 (entries 2 and 3) shows that TEMPO suppressed the reaction to some extent, whilst BHT had little effect, indicating that radicals may be involved at some stages of the reaction. Control experiments showed that, without O_2, the reaction did not happen (Table 4, entries 4). This is in contrast with the iridicycle-catalysed dehydrogenation we reported recently,[14] where no oxidant is needed, with the hydrogen being released as H_2. Thus, the reaction in question is oxidative in nature, with the hydrogen being turned into water. In a further experiment, *N*-methylquinoline was used as the substrate. However, no dehydrogenation product could be detected, indicating that the presence of the N–H proton is critical for the dehydrogenation to proceed.[12]

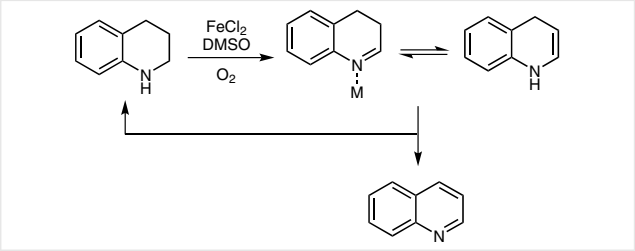
Table 4 Further Experiments for the Dehydrogenation of 1,2,3,4-Tetrahydroquinoline[a]

Entry	Catalyst	Additive	Conv. (%)	Yield (%)
1	$FeCl_2$/DMSO	–	100	65
2	$FeCl_2$/DMSO	TEMPO[b]	66	45
3	$FeCl_2$/DMSO	BHT[b]	100	69
4	$FeCl_2$/DMSO[c]	–	0	0

[a] Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), $FeCl_2$ (3 mol%), DMSO (0.4 mmol), reaction temperature 110 °C, 24 h, under O_2 atmosphere, *p*-xylene (1 mL). Isolated yields are given.
[b] 1.0 mmol.
[c] Without O_2.

According to the literature[14] and our results, a possible reaction pathway for the oxidative dehydrogenation of N-heterocycles under $FeCl_2$/DMSO is proposed and shown in Scheme 1. Oxidative dehydrogenation of the tetrahydroquinoline, which may start from single electron transfer from the nitrogen to the iron, affords an imine or iminium intermediate in equilibrium with an enamine. The activated imine is then reduced by the electron-rich enamine, furnishing the starting substrate and quinoline.

In summary, we have developed a convenient protocol for the oxidative dehydrogenation of N-heterocycles that centres on the use of $FeCl_2$ and substoichiometric DMSO. Various substituted 1,2,3,4-tetrahydroquinolines and some other N-containing compounds have been examined, giving the desired products in moderate yields. Oxygen is indispensible for the dehydrogenation and it appears that $FeCl_2$ and DMSO act in concert to promote it.



Scheme 1 A possible pathway for the oxidative dehydrogenation of tetrahydroquinolines catalyzed by $FeCl_2$/DMSO where M may be Fe^{2+} or H^+

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561613.

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(20) **Typical Procedure**
To a Schlenk tube equipped with a magnetic stir bar were added 8-methyl-1,2,3,4-tetrohydroquinoline (0.50 mmol), $FeCl_2$ (1.9 mg, $1.5\cdot10^{-2}$ mmol), DMSO (31.2 mg, 0.4 mmol), and *p*-xylene (1 mL). The reaction mixture was stirred at 110 °C under an oxygen atmosphere using a balloon and monitored by TLC. After the reaction, the mixture was cooled to room temperature and purified using flash chromatography (hexane–EtOAc, 10:1) to give the corresponding product 8-methylquinoline in 70% yield.
8-Methylquinoline
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (m, 1 H), 8.10 (m, 1 H), 7.64 (d, *J* = 4.0 Hz, 1 H), 7.54 (m, 1 H), 7.43–7.35 (m, 2 H) 2.82 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 147.3, 137.1, 136.3, 129.6, 128.3, 126.3, 125.9, 120.8, 18.2. HRMS: *m/z* calcd for $[C_{10}H_9N + H^+]$: 144.0813; found: 144.0813.