**A convenient procedure for the oxidative dehydrogenation of N‑heterocycles catalyzed by FeCl2/DMSO**

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Abstract A convenient catalytic procedure has been developed for the oxidative dehydrogenations of N-heterocycles. Combining catalytic FeCl2 with DMSO yields a catalyst that promotes the dehydrogenation of tetrahydroquinolines and related heterocycles under 1 bar of O2, affording the corresponding N-heteroaromatics 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 reactions. One is run under acceptorless conditions, with the hydrogen released as H2. Catalysts such as Ir-pincer complexes,1 Cu/Al2O3,2 Cu/TiO2,3 hydroxyapatite-bound Pd,4 and Ru-hydride complexes5 have been explored for the acceptorless dehydrogenation. The other requires the presence of an oxidant such as O2. This oxidative dehydrogenation has been performed with a number of catalysts, including Ru/Al2O3,6 [Rh2(caprolactamate)4],7 Ru/Co3O4,8 Ru(OH)x/Al2O3,9 rhodium nanoparticles supported on multiwalled carbon nanotubes,10 iron oxides surrounded by nitrogen-doped-graphene shells immobilized on carbon (FeOx@NGr−C),11 cobalt oxide supported on nitrogen-doped carbon,12 and *ο*-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 which 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 FeCl2/DMSO system that catalyzes 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(NO3)3/TEMPO, was attempted 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, e.g. FeCl2, FeBr2 and Fe(OTf)3 (3 mol %), could catalyze the reaction without any ligands under 1 bar of O2 at 140 °C (Table 1, entries 1-4). FeCl2 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 yield 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, entries 11). These results prompted us to reexamine the iron-catalyzed dehydrogenation in the presence of DMSO in *p*-xylene. Delightfully, when the dehydrogenation was carried out at 110 °C with 0.8 equivalent of DMSO added, quinoline was isolated in a higher yield of 65% (Table 1, entry 19), indicating a synergistic effect between FeCl2 and DMSO in the reaction.

Table 1 Optimization of conditions for the dehydrogenation of 1,2,3,4-tetrahydroquinoline



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Entry | Iron salt | solvent | DMSO (equiv.) | Temperature (°C) | Yield (%) |
| 1 | FeCl2 | p-xylene | 0 | 140 | 45 |
| 2 | FeBr2 | p-xylene | 0 | 140 | 26 |
| 3 | Fe(BF4)2 | p-xylene | 0 | 140 | 8 |
| 4 | Fe(OTf)3 | p-xylene | 0 | 140 | 23 |
| 5 | FeCl2 | Acetonitrile | 0 | 100 | 25 |
| 6 | FeCl2 | Ethyl acetate | 0 | 100 | 12 |
| 7 | FeCl2 | THF | 0 | 100 | trace |
| 8 | FeCl2 | DMF | 0 | 100 | 13 |
| 9 | FeCl2 | DMSO | - | 100 | 42 |
| 10 | FeCl2 | p-xylene | 0 | 100 | 24 |
| 11 | - | DMSO | - | 100 | 23 |
| 12 | FeCl2 | p-xylene | 3 | 100 | 41 |
| 13 | FeCl2 | p-xylene | 1.5 | 100 | 48 |
| 14 | FeCl2 | p-xylene | 0.8 | 100 | 52 |
| 15 | FeCl2 | p-xylene | 0.3 | 100 | 46 |
| 16 | FeCl2 | p-xylene | 0.15 | 100 | 13 |
| 17 | FeCl2 | p-xylene | 0.8 | 80 | 32 |
| 18 | FeCl2 | p-xylene | 0.8 | 90 | 42 |
| 19 | FeCl2 | p-xylene | 0.8 | 110 | 65 |

Reaction conditions: 1,2,3,4-tetrahydroquinoline 0.5 mmol, amount of catalyst 3%, reaction time 24 h, under 1 bar O2 atmosphere, solvent 1 mL. Isolated yields are given.

Using the optimized FeCl2/DMSO catalyst system (Table 1, entry 19), various derivatives of 1,2,3,4-tetrahydroquinoline were dehydrogenated under a balloon pressure of O2. As shown in Table 2, substituents at the 2, 3 or 4 positions were well tolerated, with 2-methylquinoline, 3-methylquinoline and 4-methylquinoline produced in 65%, 82% and 75% yield, 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-cholor-substituted tetrahydroquinoline necessitated a much longer time, presumably a reflection of both electronic and steric effect (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 (entry 14). This is likely due to the sp3 C-H bond being made weaker by the phenyl ring, indicating that the electric effect may play a more important role than steric hindrance in the oxidative dehydrogenation reaction.

The high reactivity of the tetrahydroquinoline derivatives encouraged us to explore the FeCl2/DMSO catalytic system for the dehydrogenation of other N-containing compounds. As shown in Table 3, apart from quinoline derivatives, quinoxaline,

Table 2 Scope of the oxidative dehydrogenation of N-heterocycles under FeCl2/DMSO

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | Substrate | Product20 | Time (h) | Yield (%) |
| 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 |
| 12 |  |  | 30 | 81 |
| 13 |  |  | 40 | 64 |
| 14 |  |  | 8 | 80 |

Reaction conditions: substrate 0.5 mmol, FeCl2 3%, DMSO 0.4 mmol, temperature 110 °C, reaction time 24 h, under O2 atmosphere, p-xylene 1 mL. Isolated yields are given.

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 FeOx@NGr−C.11

Table 3 Oxidative dehydrogenation of other N-containing compounds under FeCl2/DMSO

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

Reaction conditions: substrate 0.5 mmol, FeCl2 3%, DMSO 0.4 mmol, reaction temperature 110 °C, under O2 atmosphere, p-xylene 1 mL. Isolated yields are given.

To gain some insight into the mechanism of the FeCl2/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 O2, the reaction could not happen (Table 4, entries 4). This is in contrast with the Iridicycle-catalyzed dehydrogenation we reported recently,14 where no oxidant is needed, with the hydrogen released as H2. 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 | Conversion (%) | Yield (%) |
| 1 | FeCl2/DMSO | - | 100 | 65 |
| 2 | FeCl2/DMSO | TEMPO b | 66 | 45 |
| 3 | FeCl2/DMSO | BHT b | 100 | 69 |
| 4 | FeCl2/DMSO c  | - | 0 | 0 |

a Reaction conditions: 1,2,3,4-tetrahydroquinoline 0.5 mmol, FeCl2 3%, DMSO 0.4 mmol, reaction temperature 110 °C, under O2 atmosphere, p-xylene 1 mL. Isolated yields are given.

b 1.0 mmol.

c Without O2.

According to the literature14 and our results, a possible reaction pathway for the oxidative dehydrogenation of N-heterocycles under FeCl2/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.



Scheme 1 A possible pathway for the oxidative dehydrogenation of tetrahydroquinolines catalyzed by FeCl2/DMSO where M may be Fe2+ or H+.

In summary, we have developed a convenient protocol for the oxidative dehydrogenation of N-heterocycles, which centers on the use of FeCl2 and sub-catalytic 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 FeCl2 and DMSO act in concert to promote it.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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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), FeCl2 (1.9 mg, 1.5x10-2 mmol), DMSO (31.2 mg, 0.4 mmol) and p-xylene (1 mL). The reaction mixture was stirred at 110 ℃ 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/ethyl acetate = 10/1) to give the corresponding product 8-methylquinoline in 70% yield.

**8-Methylquinoline**

Colorless oil, 1H NMR (400 MHz, CDCl3) 8.93 (m, 1H), 8.10 (m, 1H), 7.64 (d, J = 4.0 Hz, 1H), 7.54 (m, 1H), 7.43 – 7.35 (m, 2H) 2.82 (s, 3H). 13C NMR (100 MHz, CDCl3) 149.2, 147.3, 137.1, 136.3, 129.6, 128.3, 126.3, 125.9, 120.8, 18.2. HRMS calcd for (C10H9N+H+): 144.0813; found: 144.0813.