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Aerobic oxidative dehydrogenation of N-heterocycles catalyzed by cobalt porphyrin

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Abstract An efficient catalytic procedure has been developed for the aerobic oxidative dehydrogenation of N-heterocycles by cobalt porphyrin in the absence of any additives. The catalytic system could tolerate various 1,2,3,4-tetrahydroquinoline derivatives and some other N-heterocycles. The corresponding N-heteroaromatics could be obtained in 59~86% yields. The mechanism investigation suggested that the aerobic oxidative dehydrogenation might proceed with imine intermediate through radical paths.

Keywords: N-heterocycles; cobalt porphyrin; oxidative dehydrogenation; no additive

Aromatic heterocycles are common intermediates in pharmaceutical and biological active molecules, and various protocols have been developed to construct these compounds.^[1] Dehydrogenation of N-heterocycles with or without acceptors is an important method to synthesis the corresponding aromatic heterocycles,^[2] and oxidative dehydrogenation has been extensively studied in the field. Obviously, molecular oxygen is a more attractive acceptor in practical application than other oxidant, such as TBHP or other peroxides.^[3] For the transformation, several catalytic systems have been developed, such as carbon nanotubes supported rhodium nanoparticles/tert-butylcatechol,^[4] Nb₂O₅ photocatalytic system,^[5] o-quinone/ Co(salophen),^[6] Ru(OH)_x/Al₂O₃,^[7] intermetallic Pd₃Pb supported on Al₂O₃,^[8] graphite-supported gold nanoparticles,^[9] FeO_x(a)NGr-C,^[10] Co_3O_4 -NGr/C catalyst/K₂CO₃,^[11] Ru/Co₃O₄,^[12] Pd/KOtBu,^[13] Pd(OAc)₂/Zn(OTf)₂,^[14] reduced graphene oxide (rGO),^[15] Pt nanowire catalyst,^[16] graphene oxide/Na₂CO₃^[17] and meso MnO_x.^[18] Although tremendous progress has been made in the research field, most of these catalytic systems were originated from noble metals, or required complicated preparation methods. Developing efficient catalytic system based on readily available materials under ambient conditions is still highly desirable in view of the principles of practical chemistry. Recently, convenient catalytic procedures based on FeCl2^[19] and CuI^[20] have been developed, but DMSO (dimethyl sulfoxide) or DBAD (di-tert-butyl azodicarboxylate) was required as additive. Fe and Co pincers ^[2b, 21] have been found by Jones' group to be effective catalytic system without oxidant, but the specialist ligands were inquired.

Metalloporphyrins, which are typical biomimetic catalysts, have been widely investigated in varied

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reactions and excellent catalytic performance has been observed.^[22] To the best of our knowledge, however, little research has been performed in the aerobic oxidative dehydrogenation of N-heterocycles. In this context, metalloporphyrins were studied as a new catalytic system for the aerobic oxidative dehydrogenation of N-heterocycles without any additives in the present research.

Initially, dehydrogenation of 1,2,3,4-tetrahydroquinoline has been selected as model reaction to investigate various metallotetraphenylporphyrins (MTPPs, M=Co, Cu, Ni and Fe). CoTPP was found to be the most active under the selected conditions, whilst the selectivity of the corresponding quinoline was not high enough for all these MTPPs. Then the reaction solvent was optimized using CoTPP as the catalyst. The results in Table 1 indicate that the reaction was accelerated under the polar solvent, and DMF gave the highest conversion and yield.

	N H	CoTPP, O ₂ 80 °C, 12 h	- ()	N
Entry	Catalyst	Solvent	Conv. ^b /%	Sel. ^b /%
1	CoTPP	DMF	51	57
2	CuTPP	DMF	20	31
3	NiTPP	DMF	<1	<1
4	FeTPP	DMF	18	56
5	CoTPP	dioxane	26	16
6	CoTPP	DMSO	30	22
7	CoTPP	dichloromethane	7	5
8	CoTPP	trifluorotoluene	3	3
9	CoTPP	acetonitrile	2	<1
10	CoTPP	mesitylene	18	13
11	CoTPP	benzonitrile	9	6
12	COTPP	n-vylene	3	2

Table 1 Optimization of the reaction conditions for the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinoline.^a

^a Reaction conditions: 1,2,3,4-tetrahydroquinoline 0.5 mmol, CoTPP 10 mg, solvent 2 mL, 80 °C, 12 h, O₂ atmosphere. ^b Based on the GC analysis.

Concerning the reaction temperature, the conversion increased as the temperature increase, while the selectivity peaked at 110 °C, then began to decline (Figure 1A). The results indicated that an intermediate might form during the dehydrogenation, and the low temperature retarded the transformation of the intermediate to the corresponding product, whilst the high temperature accelerated the over-oxidation of the product to the N-oxide.^[18] After the final optimization of reaction time, a high 88% yield of quinoline was obtained at about 14 h, although the complete conversion of the substrate was reached at about 12 h (Figure 1B). The observation further illustrated that the dehydrogenation proceeded through some intermediate.

With the optimized conditions in hand, the catalytic system was then tested in the dehydrogenation of a variety of 1,2,3,4-tetrahydroquinolin derivatives under analogous reaction conditions (Table 2). The results indicate that substituents at 2-, 3- and 4- sites were well tolerated, and moderate yield of the corresponding dehydrogenation products were obtained (entries 2-4). The relatively decreased yield might be due to the sterie hindrance of methyl group. Comparatively, methyl group locating at aromatic had little effect on the transformation, and 7-methyl substituted substrate gave a high 86% yield (entry 6). 6- methoxyl tetrahydroquinoline gave a lower yield of 60% (entry 8), which might be due to its activation and over-oxidation of the substrate happened. On the other hand, the yield of dehydrogenation varied with different halogen groups at the 6- site, and the bromine group gave the highest yield (entry 10). Although 6- chloro substituted substrate did not afford high yield, good result was obtained when chlorine being located at 8- site (entry 12). Concerning the reaction time needed for the complete conversion of different substrate, it can be concluded that electron-withdrawing substituents reduced the reaction rate. It should be noted that substrate with 2-phenyl underwent dehydrogenation in excellent yield to the desired product (entry 13), which should be due to the activation of the α -C-H bond of benzene. Finally, some multi-substituted 1,2,3,4-tetrahydroquinoline were also investigated in the present catalytic system, and moderate yields of the corresponding products could be obtained (entries 14-16). The prolonging reaction time (15 h) for 2,6-dimethyl-1,2,3,4-tetrahydroquinoline (entry 14), further elucidated the existence of steric effect.



Figure 1. Effect of reaction temperature (A) and reaction time (B) on the reaction. Reaction conditions: 1,2,3,4-tetrahydroquinoline 0.5 mmol, CoTPP 10 mg, DMF 2 mL, O₂ atmosphere, based on the GC analysis. (A) 12 h; (B) 110 °C.

	Entry	Substrate	Product	Time /h	Yield ^b /%	
	1			14	78	
	2	N H		10	75	R
	3	N H		10	67	
	4	N H		11	76	
	5	N N N N N N N N N N N N N N N N N N N		9	69	
	6			11	86	
	7			13	67	
G	8	O N H		10	60	
P	9	F N H	F	12	68	
	10	Br	Br	12	78	
	11	CI	CI	12	59	
	12			15	72	

Table 2 Catalytic dehydrogenation of various N-heterocycles under CoTPP.^a



^a Reaction conditions: substrate 0.5 mmol, CoTPP 10 mg, DMF 2 mL, 110 °C, O₂ atmosphere. ^b Isolated yield. ^c Determined by GC analysis.

Inspired by the smooth catalytic behavior for tetrahydroquinoline derivatives, the catalytic system was then further investigated in the dehydrogenation of other N-heterocycles. Good yield of isoquinoline was obtained in the case of the 1,2,3,4-tetrahydroisoquinoline (entry 17). Dehydrogenation of indoline also gave a 74% yield of indol (entry 18). Quinoxaline and its derivative could also be tolerated in the present catalytic system (entries 19–20). Moreover, dehydrogenation of N-benzylaniline led to moderate yield of the corresponding imine under the reaction conditions (entry 21).

To get insight into the reaction pathway, some controlled experiments have been performed (Table 3). Without catalyst, only trace of the corresponding dehydrogenation product was observed (entry 2), indicating that the catalytic function of CoTPP. When the reaction was performed under N_2 atmosphere, the substrate could transform in a very low conversion, but with an excellent selectivity of the corresponding dehydrogenation product (entry 3). These results might be explained by the fact that, CoTPP could react with substrate, probably get an electron from 1,2,3,4-tetrahydroquinoline to form the product, but the Co cation with lower valence could

not recycle in the absence of oxygen. The high selectivity suggested that the excessive oxygen might accelerate the formation of the N-oxide from the over-oxidation of the product.^[18] The radical scavengers have also been introduced into the reaction system to examine the radical path (entries 4 and 5). Although the BHT (2,6-di-*tert*-butyl-4-methylphenol) and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) had little effect on the conversion of the substrate, the selectivity decreased significantly, indicating the radical intermediate might form in the reaction.

In literatures,^[10,11,18,19] imine was always thought to be the intermediate in the aerobic dehydrogenation of N-heterocycles. To check the possibility in our catalytic system, N-methyl-1,2,3,4-tetrahydroquinoline and 2,2,4,7-tetramethyl-1,2,3,4-tetrahydroquinoline have been introduced into the reaction (Scheme 1). No dehydrogenation could be observed, indicating that imine might be the intermediate. On the other hand, 1,2-dihydroquinoline could not be found in the reaction, confirming that the activation of the C–C was unlikely to occur under the present catalytic system. These obtained results suggested that the presence of nitrogen in the saturated cyclic alkane moiety is necessary to initiate the dehydrogenation by transferring an electron to CoTPP.

Table 3 The results of some controlled experiments.^a

Catalyst, additive						
Entry	Catalyst	Additive	Conv. ^d /%	Sel. ^d /%		
1	CoTPP	-	>99	88		
2	-	-	56	4		
3 ^b	CoTPP	-	24	95		
4	CoTPP	BHT^{c}	95	74		
5	CoTPP	TEMPO ^c	>99	45		

^a Reaction conditions: 1,2,3,4-tetrahydroquinoline 0.5 mmol, catalyst 10 mg, DMF 2 mL, 110 °C. 14 h, O₂ atmosphere. ^b Under the N₂

atmosphere. ^c 2 Equivalent of substrate. ^d Based on the GC analysis.



Scheme 1. The controlled reactions. Reaction conditions: substrate 0.5 mmol, CoTPP 10 mg, DMF 2 mL, 110 °C. 14 h, O₂ atmosphere.

Furthermore, UV-vis was used to monitor the reaction system. To elucidate the result, some controlled experiments have been performed (Figure S1). The UV-vis of CoTPP in DMF exhibited the Soret band at 417

nm and Q bands centered at 531 nm, respectively.^[23] Addition of 1,2,3,4-tetrahydroquinoline had little effect on the spectra of CoTPP solution, while quinoline could significantly increase the intensity without shift of Soret and Q bands. As reported previously,^[24] introduction of *m*-CPBA (3-chloroperbenzoic acid) into CoTPP system generally resulted in the formation of high valent oxocobalt species, and the corresponding absorbance band could be observed at 432 nm in the system, and the Q bands shifted to 516 nm and 547 nm, respectively. The aerobic oxidative dehydrogenation of 1,2,3,4-tetrahydroquinoline was followed by UV-vis spectroscopy as shown in Figure 2. Upon addition of the substrate, no change could be observed for the UV-vis spectra (the two curves with the lowest absorbance in Figure 2), inconsistent with the controlled experiments. As the reaction proceeding, the intensity of the peak between 500 to 550 nm increased, and then decreased at about 15 min (insert graph **a** and **b**). The increasement of the intensity might be due to the formation of quinoline, whilst the reduction might be attributed to the oxidative degradation of CoTPP molecule. With the change of intensity, the Q band shifted from 531 nm to 527 nm, suggesting the transformation of Co(III)TPP to Co(II)TPP.²⁵ Since Co(II)TPP is prone to be oxidized to Co(III)TPP.^[26] the electron accepting reactive species in the dehydrogenation should be the cobalt(III) species. On the other hand, from the variation of the spectra and the controlled experiments, one can conclude that no high-valent metal oxo formed during the reaction.



Figure 2. Time-dependent changes in the visible spectrum of the reaction. Reaction conditions: 1,2,3,4-tetrahydroquinoline 0.5 mmol, CoTPP 10 mg, DMF 2 mL, 110 $^{\circ}$ C, O₂ atmosphere.

On the basis of the obtained and reported results,^[10,18] a possible reaction path for the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinoline by CoTPP has been described in Scheme 2. The reaction started by transferring an electron to Co(III)TPP, and amine radical species formed. The species then underwent α C–H abstraction to produce an imine intermediate with possible formation of H₂O and oxidation of Co(II)TPP to

Co(II)TPP.^[18] The imine species can be in equilibrium with an enamine. After tautomerization, the final dehydrogenation product was then obtained by another dehydrogenation reaction.



Scheme 2. A possible reaction path for the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinoline In summary, a simple and efficient catalytic system for the aerobic oxidative dehydrogenation of N-heterocycles under the catalysis of cobalt porphyrin without any additives has been developed. Various substrates could be tolerated by the present protocol. The mechanism investigation suggested that imine probably was the intermediate and no high valent oxocobalt formed as the active species.

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Supplementary data

Supplementary data (general experimental information, experimental detail, and X-ray data of 1b) associated with this article can be found, in the online version, at doi:0000000.

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