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# Preparation of 4,7-diphenyl-1,10-phenanthroline-2,9-dicarboxylic acid catalyzed by iron(III)porphyrins with (diacetoxyiodo)benzene

Qi-Di Zhong, Yun-Zhou Xue, Hong Yan *, Xiu-Qing Song, Ru-Gang Zhong

*College of Life Science and Bio-engineering, Beijing University of Technology, Beijing 100124, China*

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ABSTRACT

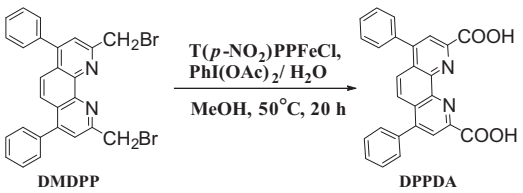
Using iron(III)porphyrins in combination with (diacetoxyiodo)benzene allows for the conversion of 2,9-bis(bromomethyl)-4,7-diphenyl-1,10-phenanthroline into 4,7-diphenyl-1,10-phenanthroline-2,9-dicarboxylic acid. This method provides a cost-effective and environmentally-friendly oxidation procedure using less toxic $PhI(OAc)_2$ and biologically relevant iron(III)porphyrins. The catalytic activity of five kinds of iron-metallated functional porphyrins were investigated using different oxidants, including air, $H_2O_2$, $PhI(OAc)_2$, PhIO and NaClO. Our results showed that the use of T(*p*-$NO_2$)PPFeCl with $PhI(OAc)_2$ as the oxidant in the presence of water displays remarkable activity for the desired oxidation reaction. The generality of this method was examined by synthesizing the carboxylic acids of pyridines and quinolines.



4,7-Diphenyl-1,10-phenanthroline-2,9-dicarboxylic acid (DPPDA) and its derivatives are outstanding sensitizers for Eu(III) ions, which is considered to be a promising candidate for the development of even more powerful enzyme-amplified lanthanide luminescence (EALL) detection schemes.[1] As a result of the vast range of possible applications, the efficient synthesis of DPPDA has remained an important goal in recent years. There have been several previous attempts to prepare DPPDA from 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (DMDPP); however, current synthetic methods have many drawbacks, including low yields from multistep synthetic routes, low product purity, excess use of environmental unfriendly oxidants and long reaction times, often more than 40 h.[2] Therefore, it is desirable to develop a new and efficient method for preparing **DPPDA** with the use of milder reagents, lower toxicity and readily availability materials to produce an efficient yield.

In the past two decades, the biomimetic catalysis of metalloporphyrins under mild conditions has attracted increasing attention.[3] Biomimetic oxygenations using monooxygen donors, such as PhIO, $PhI(OAc)_2$, $H_2O_2$, NaOCl and $KHSO_5$, and catalyzed by metalloporphyrins have been examined under a variety of different reaction conditions.[4] Iron(III)porphyrins have been used as model compounds to mimic the chemistry of cytochrome P-450 enzymes, which are capable of catalyzing a wide range of oxidations, including the hydroxylation of saturated C–H bonds,[5] the oxidation of polycyclic aromatic hydrocarbons[6] and the carboxylation of cyclohexane[7] and *p*-nitrotoluene.[8] The high catalytic activity of this system with various oxidants prompted us to investigate its ability to prepare DPPDA.

In our previous studies, iron(III)porphyrins exhibited high catalytic performance in preparing camphorquinone with molecular oxygen. At the beginning of this work, we attempted to directly prepare camphorquinone from camphor, using iron(III)porphyrins as catalysts with molecular oxygen. Although we succeeded in this goal, the camphorquinone was obtained in very low yields. Continuing our investigation, we found that 3-bromocamphor exhibited excellent activity in these reactions. In addition, the oxidation of bromomethyl moieties catalyzed by iron(III)porphyrins catalysts were more active than methyl substituents under these conditions.[9] We thought that this observation warranted further investigation to better understand the properties of this system. As a part of our ongoing interest in iron(III)porphyrin-catalyzed oxidation reactions that are cost-effective and use less toxic oxidants, the oxidation of DMDPP to DPPDA, catalyzed by chloro-iron tet-




DMDPP DPPDA

**Scheme 1.**

* Corresponding author.
*E-mail address:* hongyan@bjut.edu.cn (H. Yan).

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ra-(*p*-nitrophenyl)porphyrin T(*p*-$NO_2$)PPFeCl in combination with (diacetoxyiodo)benzene, has been developed (Scheme 1). The generality of this catalytic method for the oxidation of bromomethyl groups to carboxylic acids in pyridines and quinolines was also investigated. The catalytic system has been proved to be efficient for the oxidation of bromomethyl moieties in these molecules with high yields under mild conditions.

Oxidants, including $H_2O_2$, NaClO, $PhI(OAc)_2$, $PhI(OAc)_2/H_2O$, PhIO and air, were first tested to determine their effects on the oxidation of DMDPP to DPPDA, catalyzed by T(*p*-$NO_2$)PPFeCl. The reaction time was optimized via TLC monitoring. Our results are summarized in Table 1, below.

Looking at Table 1, it is evident that $PhI(OAc)_2$ was more effective than PhIO, $H_2O_2$, NaClO and air in these oxidation reactions using the conditions, including a reaction time of 20 h at 50 °C. Air exhibited the lowest activity, resulting in an 8% yield. When $H_2O_2$ and NaClO were used instead, the yields of only 37% and 30% could be achieved. It could thus be concluded that the use of the proper oxidant was critical in this catalytic system, and our results indicated that $PhI(OAc)_2$ was the most effective oxidant for this catalytic system. However, while using $PhI(OAc)_2$ as an oxidant we found that water was a necessary agent in this catalytic system. Our results showed that the addition of water to the $PhI(OAc)_2$ system increased the reaction yields from 62% to 85% (entries 3 and 5). However, entry 4 shows that without the addition of water to the system, the yield could still reach 85%, but required a longer reaction time of 30 h. This has been ascribed to the involvement of water in the process of $PhI(OAc)_2$ hydrolysis, which could result in an in situ generation of reactive, non-polymeric PhIO and an increase in the reaction rate.[10] Such a rationale would imply that $PhI(OAc)_2$ hydrolysis was involved in the rate-determining step. This could be further supported by the fact that using PhIO as oxidant exhibited a similarly high activity, giving a yield of 84% (entry 6). Because we found that using $PhI(OAc)_2$ as the oxygen donor in the presence of water led to better oxidation yields compared to PhIO, we continued our studies using this reagent. Furthermore, $PhI(OAc)_2$ is a more stable compound that is soluble in most organic solvents and commercially available.

The catalytic activity of different iron(III)porphyrins in preparing DPPDA was investigated using $PhI(OAc)_2$ in the presence of water.[11] The catalysts employed in our studies were iron(III)porphyrins, having the same ligand, chloro-iron tetraphenylporphyrin (TPPFeCl), but different substituents in the phenyl ring, including TPPFeCl, T(*p*-$OCH_3$)PPFeCl, T(*p*-$CH_3$)PPFeCl, T(*p*-Cl)PPFeCl and T(*p*-$NO_2$)PPFeCl (Fig. 1).[12] Our results are summarized in Table 2.

It is interesting to note the importance of the catalyst in these reactions. Different iron(III)porphyrin catalysts exhibit very different catalytic activities, and little activity was observed in the absence of the iron(III)porphyrins catalysts (Table 2). For example, using $PhI(OAc)_2$ as the oxidant, the reaction using T(*p*-$OCH_3$)PPFeCl as a catalyst resulted in a yield of 53%.

**Table 1**
The effect of oxidants on the preparation of DPPDA catalyzed by T(*p*-$NO_2$)PPFeCl[a]

| Entry | Oxidants | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | $H_2O_2$ | 20 | 37 |
| 2 | NaClO | 20 | 30 |
| 3 | $PhI(OAc)_2$ | 20 | 62 |
| 4 | $PhI(OAc)_2$ | 30 | 85 |
| 5 | $PhI(OAc)_2/H_2O$ | 20 | 85 |
| 6 | PhIO | 20 | 84 |
| 7 | Air | 20 | 8 |

[a] DPPDA (1 mmol), T(*p*-$NO_2$)PPFeCl ($1 \times 10^{-3}$ mmol), air bubbling (1 atm), amount of oxidants was 2.5 mmol, $H_2O$(5 μL), MeOH (20 mL), 50 °C, 20 h.
[b] The yields were obtained after purification via flash chromatography.

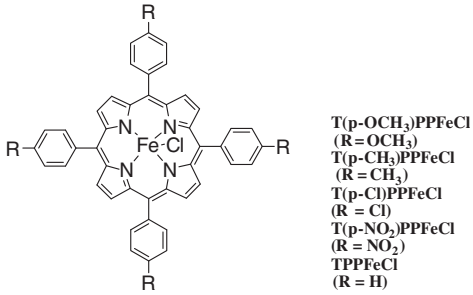



**Figure 1.** The structure of iron(III)porphyrins.

**Table 2**
The effect of iron(III)porphyrin catalysts on the preparation of DPPDA with $PhI(OAc)_2$[a]

| Entry | Catalyst | Yield[b] (%) |
|---|---|---|
| 1 | T(*p*-$OCH_3$)PPFeCl | 53 |
| 2 | T(*p*-$CH_3$)PPFeCl | 56 |
| 3 | T(*p*-Cl)PPFeCl | 83 |
| 4 | T(*p*-$NO_2$)PPFeCl | 85 |
| 5 | TPPFeCl | 57 |
| 6 | — | 7 |

[a] DPPDA (1 mmol), catalyst ($1 \times 10^{-3}$ mmol), $PhI(OAc)_2$ (2.5 mmol), $H_2O$ (5 μL), MeOH (20 mL), 50 °C, 20 h.
[b] The yields were obtained after purification via flash chromatography.

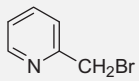
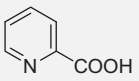
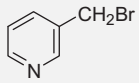
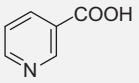
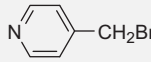
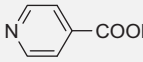
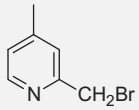
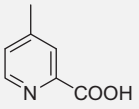
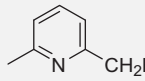
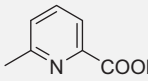
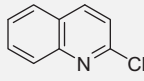
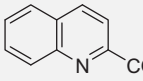
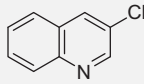
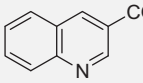
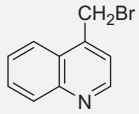
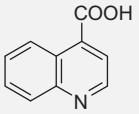
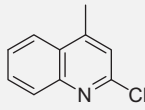
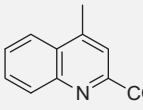
**Table 3**
The effect of solvent and temperature on the preparation of DPPDA, catalyzed by T(*p*-$NO_2$)PPFeCl with $PhI(OAc)_2$ as the oxidant[a]

| Entry | Solvent | *T* (°C) | Yield[b] (%) |
|---|---|---|---|
| 1 | Methanol | 30 | 53 |
| 2 | Methanol | 40 | 72 |
| 3 | Methanol | 50 | 85 |
| 4 | Methanol | 60 | 83 |
| 5 | Ethanol | 50 | 81 |
| 6 | *tert*-Butanol | 50 | 63 |
| 7 | Glycol | 50 | 35 |
| 8 | 1,4-Butanediol | 50 | 24 |
| 9 | Carbon tetrachloride | 50 | 37 |
| 10 | Benzene | 50 | 36 |
| 11 | THF | 50 | 40 |
| 12 | Dioxane | 50 | 45 |

[a] DPPDA (1 mmol), T(*p*-$NO_2$)PPFeCl ($1 \times 10^{-3}$ mmol), $PhI(OAc)_2$ (2.5 mmol), $H_2O$ (5 μL), solvent (20 mL), 50 °C, 20 h.
[b] The yields were obtained after purification via flash chromatography.

The use of TPPFeCl and T(*p*-$CH_3$)PPFeCl as catalysts increased the yield to 57% and 56%, respectively. The use of T(*p*-Cl)PPFeCl resulted in a yield of 83%, and the most effective catalyst in these reactions was T(*p*-$NO_2$)PPFeCl, which produced a yield of 85%. Thus, the order of activity for these iron(III)porphyrin catalysts is as follows: T(*p*-$NO_2$)PPFeCl > T(*p*-Cl)PPFeCl > TPPFeCl > T(*p*-$CH_3$)PPFeCl > T(*p*-$OCH_3$)PPFeCl. Again, the only differences between these catalysts are in the substituents present in the phenyl ring of the porphyrin ligands. Possibly, the catalytic activities could be related to the stability and the low redox potential of the intermediate, high-valence metalloporphyrin that is linked with reactive oxygen species. This difference may be attributed to the generation of the electrophilic, reactive, high-valent oxo-iron cation radical intermediate (Fe(IV)=$O^{+\cdot}$).[6,13] T(*p*-$OCH_3$)PPFeCl has an electron-donating group (*p*-$OCH_3$) present on the phenyl ring, while T(*p*-$NO_2$)PPFeCl and T(*p*-Cl)PPFeCl have electron-withdrawing groups (–$NO_2$ and –Cl). The electron density around the iron ions in the metalloporphyrins decreases with the increase in the

**Table 4**
Carboxylation of substrates catalyzed by T($p$-$NO_2$)PPFeCl[a]

| Entry | Substrate | Product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  | 12 | 89 |
| 2 |  |  | 12 | 85 |
| 3 |  |  | 12 | 87 |
| 4 |  |  | 12 | 81 |
| 5 |  |  | 12 | 84 |
| 6 |  |  | 15 | 84 |
| 7 |  |  | 15 | 87 |
| 8 |  |  | 15 | 83 |
| 9 |  |  | 15 | 86 |

[a] Substrate (1 mmol), T($p$-$NO_2$)PPFeCl ($1 \times 10^{-3}$ mmol), PhI(OAc)$_2$ (2.5 mmol), $H_2O$ (5 μL), MeOH (20 mL), 50 °C.
[b] The yields were obtained after purification via flash chromatography.

electron-withdrawing groups. In addition, this decrease is proportionate to the electron-withdrawing abilities of the substituents from $p$-$OCH_3$ to $p$-$NO_2$. This effect would lead to the enhancement of the iron(III)/iron(II) reduction potential, and because of this, iron(III) could be easily reduced to iron(II), aiding in the completion of the full catalytic cycle.[14]

The effect of the solvents and reaction temperature on the oxidation of DMDPP using T($p$-$NO_2$)PPFeCl as a catalyst was also investigated. The results are summarized in Table 3.

These results indicate that the choice of solvent strongly influences the result of the reaction (Table 3, entries 3, 5–12). By using solvents with strong polarity, such as glycol and 1,4-butanediol, and solvents with weak polarity, such as carbon tetrachloride and benzene, T($p$-$NO_2$)PPFeCl exhibited a relatively low activity for the oxidation of DMDPP to DPPDA. However, solvents with medium polarity, including methanol, ethanol and *tert*-butanol, showed high activities in the reaction, resulting in yields of 63–85%. In particular, using methanol as the solvent resulted in the highest yield, 85%. Notably, raising the reaction temperature from 30 to 50 °C also increased the yield. The yield was highest when the reaction was performed at 50 °C (entries 1–3). Higher temperatures normally result in faster oxidation reactions, but more side reactions as well, and these side reactions can reduce the overall yield. In these experiments, the yield declined when the temperature was higher than 50 °C, meaning that the formation of side products was enhanced more than the formation of DPPDA (entry 4).

After establishing the optimal conditions for the oxidation of DMDPP to DPPDA, the scope of this catalytic system was investigated. Because of their similarity to DPPDA, carboxylic acids of pyridines and quinolines were chosen to investigate the effectiveness of the iron(III)porphyrin catalytic system. The carboxylic acids of pyridines and quinolines have previously been prepared from the corresponding methyl pyridines and methyl quinolines using different oxidants, including $NO_2$, $SeO_2$, $TiO_2$, $V_2O_5$, $Fe_2O_3$, $Cr_2O_3$, $HNO_3$, $H_2SO_4$,[15] under severe reaction conditions that often require high reaction temperatures and pressures.[16] Therefore, our mild and effective catalytic system provides an attractive new method for preparing carboxylic acids of pyridines and quinolines. Our results are summarized in Table 4.

Inspecting these results, the bromomethyl pyridines and bromomethyl quinolines were converted to their corresponding carboxylic acids (entries 1–9) in high yields (81–89%) and with good selectivities. Moreover, the position of the bromomethyl group on the pyridine (entries 1–3) and quinoline rings (entries 6–8) appears to have little effect on the reaction yields, which were all above 80%. Compared to the oxidation of DMDPP to DPPDA, the oxidation of bromomethyl pyridines and bromomethyl quinolines required shorter reaction times, 12 and 15 h, respectively. When both bromomethyl and methyl groups were present in the pyridine and quinoline rings (entries 5, 6, and 10), the carboxylation reaction expressed higher selectivity for the bromomethyl group.

In summary, iron(III)porphyrins have proved to be an excellent catalyst for the oxidation of DMDPP to DPPDA using Ph(OAc)$_2$ in the presence of water. The main parameters that affected the reaction yield were investigated and optimal conditions were established. In addition, various bromomethyl substituents of pyridines and quinolines could also be successfully oxidized to their corresponding carboxylic acids using this method, resulting in reactions with better yields with fewer toxic reagents, lower temperatures, and generally milder reaction conditions than those used in many previous methods.

## Acknowledgments

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11. In a 50 mL round-bottom flask, reagents were added in the following order: 2,9-bis(bromomethyl)-4,7-diphenyl-1,10 phenanthroline (1 mmol), MeOH (20 mL), iron(III)porphyrin ($1 \times 10^{-3}$ mmol), $H_2O$ (5 μL) and PhI(OAc)$_2$ (2.5 mmol) to achieve the desired ratio. The reaction mixtures were stirred thoroughly at 50 °C for 20 h. The products were separated and purified by flash column chromatography (silica gel, eluting agent: acetic ester/petroleum ether = 1:1).

12. The meso-tetraphenylporphyrin (TPP) was prepared according to the known procedure, see: Alder, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476. Metalloporphyrins were prepared according to the work of Wang et al.[8]..
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