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Dehydrogenation of 2-imidazolines with sodium periodate catalyzed by manganese(III) tetraphenylporphyrin

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ABSTRACT

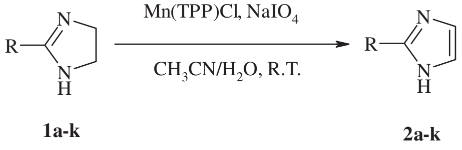
In the present work, dehydrogenation of 2-substituted imidazolines with sodium periodate in the presence of tetraphenylporphyrinatomanganese(III) chloride, [Mn(TPP)Cl], is reported. A wide variety of 2-imidazolines efficiently converted to their corresponding imidazoles by [Mn(TPP)Cl]/$NaIO_4$ catalytic system at room temperature in 1:2, CH_3CN/H_2O mixture. The effect of reaction parameters such as kind of solvent and catalyst amount was also investigated.

Synthetic metalloporphyrins have been known as active catalysts in a wide range of oxidation reactions. These catalysts have attracted much attention because their structures are similar to cytochrome P-450, a natural catalyst which oxidizes foreign organic compounds and metabolizes drugs in our bodies.[1] It was found that when metalloporphyrins are used as catalysts, organic compounds can be oxidized with single oxygen donors such as PhIO, ClO^-, H_2O_2, ROOH or IO_4^-.[2–11] The high efficiency of some of these systems makes them potentially useful for preparative oxidations in organic synthesis.

Oxidation of 2-imidazolines to their corresponding imidazoles is biologically and pharmaceutically very important, since many imidazole derivatives possess antihypertensive, antiinflammatory, antibacterial, and antidiabetic activities.[12] 2-Imidazolines can be easily prepared from nitriles and ethylenediamine.[13] Therefore, dehydrogenation of 2-imidazolines by an oxidizing agent should provide an efficient method for the preparation of imidazole derivatives. Several reagents such as Zn–Al_2O_3,[14] Ni,[15] Se,[16] Pd/C,[17] MnO_2,[18] $BaMnO_4$,[19] DMSO,[20] $KMnO_4$@SiO_2,[21] $KMnO_4$@K10,[22] $KMnO_4$@Al_2O_3,[23] trichloroisocyanuric acid,[24] $KMnO_4$-refluxing dioxane[25] and activated carbon–O_2[26] have been previously reported for this purpose. Some of these reagents suffer from limitations such as low yields of the products, very long reaction times, toxicity, the use of large excess of the reagents, and harsh reaction conditions. Also, some of these reagents are not effective for the oxidation of 2-alkylimidazolines. Therefore, the development of a novel, mild, and efficient method for oxidation of 2-imidazolines to their corresponding imidazoles is of great interest.

Here, the dehydrogenation of 2-substituted imidazolines with sodium periodate in the presence of [Mn(TPP)Cl] in 1:2, CH_3CN/H_2O mixture at room temperature is reported (Scheme 1).

First, the amount of catalyst was optimized in the dehydrogenation of 2-phenyl imidazoline with $NaIO_4$. Different amounts of [Mn(TPP)Cl] was used and the best result was obtained in the presence of 5 mol % of catalyst (Table 1). In order to choose the reaction media, different solvents were checked in the dehydrogenation of 2-phenyl imidazoline with $NaIO_4$. Among the different mixture of acetonitrile, acetone, methanol, ethanol (single phase systems), dichloromethane, chloroform and carbon tetrachloride (two phase systems with n-Bu_4NBr as phase transfer catalyst), the 1:2 mixture



Scheme 1.

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Table 1
Optimization of catalyst amount in the dehydrogenation of 2-phenyl imidazoline with $NaIO_4$[a]

Entry	Catalyst amount (mmol)	Time (h)	Yield[b] (%)
1	0.0125	5	45
2	0.025	5	59
3	0.0375	5	70
4	0.050	5	84
5	0.0625	5	84

[a] Reaction conditions: 2-phenyl imidazoline (1 mmol), catalyst, $NaIO_4$ (2 mmol), CH_3CN (10 mL), H_2O (5 mL).
[b] Isolated yield.

Table 2
The effect of solvent on the dehydrogenation of 2-phenyl imidazoline with $NaIO_4$ catalyzed by [Mn(TPP)Cl][a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	CH_3CN/H_2O (1:1)	5	73
2	CH_3CN/H_2O (2:1)	5	51
3	CH_3CN/H_2O (1:2)	5	84
4	CH_3COCH_3/H_2O (1:1)	5	70
5	CH_3OH/H_2O (1:1)	5	62
6	CH_3CH_2OH/H_2O (1:1)	5	48
7	$CHCl_3/H_2O$ (1:1)	5	22
8	CH_2Cl_2/H_2O (1:1)	5	29
9	CCl_4/H_2O (1:1)	5	10

[a] Reaction conditions: 2-phenyl imidazoline (1 mmol), [Mn(TPP)Cl] (5 mol %), $NaIO_4$ (2 mmol), solvent.
[b] Isolated yield.

of acetonitrile: water was chosen as the reaction medium, because the higher catalytic activity was observed (Table 2). The higher catalytic activity in acetonitrile/water mixture is attributed to polarity of solvent and solubility of $NaIO_4$ in this medium. The reaction of 2-phenyl imidazoline with $NaIO_4$ was also performed in the presence *tetrakis*(*p*-nitrophenyl)porphyrinatomanganese(III) chloride, [Mn(TNO_2PP)Cl], octabromotetraphenylporphyrinatomanganese(III) chloride, [Mn(Br_8TPP)Cl] and *tetrakis*(2,6-dichlorophenyl)porphyrinatomanganese(III) chloride, [Mn(TDCPP)Cl]. The results show that [Mn(TPP)Cl] is more efficient than the others (Table 3). It is known that introducing the electron-withdrawing substituents on the prophyrin ring, decreases the catalytic activity of metalloporphyrins in the oxidation reactions.

Under the optimized conditions, a wide range of 2-aryl-2-imidazolines were dehydrogenated to their corresponding imidazoles with $NaIO_4$ in good to excellent yields (Table 4, entries **1a**–**i**)[27]. Some of the reported reagents such as DMSO[20] and Pd/C[20] were not effective for dehydrogenation of 2-alkylimidazolines. Thus, efficient oxidation of 2-alkylimidazolines to their imidazoles by [Mn(TPP)Cl]/$NaIO_4$ catalytic system is an interesting feature of the presented method (entries **1j**–**k**).

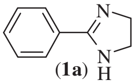
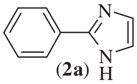
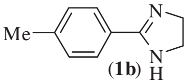
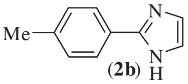
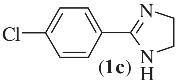
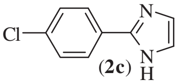
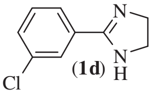
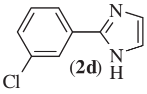
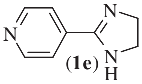
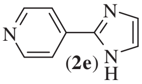
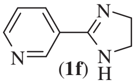
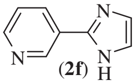
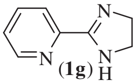
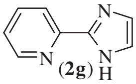
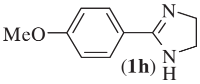
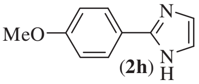
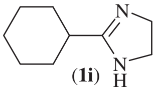
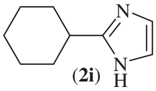
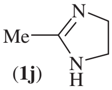
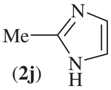
The results showed that in the absence of catalyst only 5–10% of imidazoles were produced.

Table 3
Investigation of catalytic activity of different metalloporphyrins on the dehydrogenation of 2-phenyl imidazoline with $NaIO_4$[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	[Mn(TPP)Cl]	5	84
2	[Mn(Br_8TPP)Cl]	5	73
3	[Mn(TDCPP)Cl]	5	48
4	[Mn(TNO_2PP)Cl]	5	36

[a] Reaction conditions: 2-phenyl imidazoline (1 mmol), catalyst (5 mol %), $NaIO_4$ (2 mmol), CH_3CN (10 mL), H_2O (5 mL).
[b] Isolated yield.

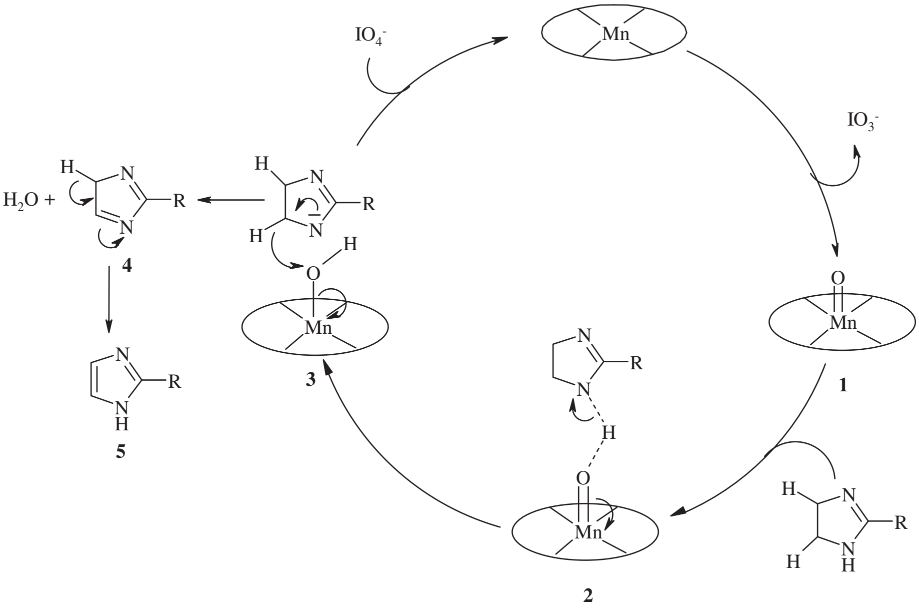
Table 4
Dehydrogenation of 2-imidazolines with $NaIO_4$ catalyzed by **[**Mn(TPP)Cl**]**[a]

Row	Imidazoline	Imidazole[b]	Time (h)	Yield[c] (%)
1	 (1a)	 (2a)	5	84
2	 (1b)	 (2b)	5	73
3	 (1c)	 (2c)	5	77
4	 (1d)	 (2d)	5	75
5	 (1e)	 (2e)	5	92
6	 (1f)	 (2f)	5	86
7	 (1g)	 (2g)	5	81
8	 (1h)	 (2h)	5	72
9	 (1i)	 (2i)	5	95
10	 (1j)	 (2j)	5	92

[a] Reaction conditions: 2-imidazoline (1 mmol), [Mn(TPP)Cl] (5 mol %), $NaIO_4$ (2 mmol), CH_3CN (10 mL), H_2O (5 mL).
[b] All products are known and were identified by comparison of their spectral data with those reported in the literature.[21–24]
[c] Isolated yield.

The exact mechanism of the reaction is not clear at present. However, a plausible explanation is that the catalyst is first transformed to the corresponding oxo compound **1** by the oxidant. The oxo compound reacts with imidazoline to afford **2** which in turns converted to **3** by proton transfer. The intermediate **3** is converted to **4** by elimination of water and releases the catalyst for the next catalytic cycle. The intermediate **4** is finally converted to the desired product **5** by hydrogen shift (Scheme 2). It seems that the stabilization of **3** by resonance and also by electron-withdrawing character of R group are good indications for the proposed mechanism. These explanations are also supported by the results in Table 4 in which imidazolines bearing electron-withdrawing groups (entries 5–7) were more reactive in these transformations. The possibility of radical mechanism was also investigated. In this manner, a radical scavenger such as acryl amide was added to the reaction mixture. The results showed that the reaction was preceded as in the absence of acryl amide. These results showed that the reaction has no radical nature.

In order to show the effectiveness of the presented method in the dehydrogenation of imidazolines, the obtained results were compared with some of those reported systems. The results showed that this catalytic system is a mild and efficient system for oxidation of imidazolines (Table 5).



Scheme 2.

Table 5
Comparison of the obtained results in the dehydrogenation of 2-phenylimidazoline with some of those reported in the literature

Entry	Reagent	Conditions	Time (h)	Yield (%)	Ref.
1	$BaMnO_4$	Reflux	24	96	19
2	DMSO	120 °C	48	51	20
3	Pd/C (10%)	Reflux	40	75	17
4	TCCA/DBu	−15 °C	3 min	93	24
5	$KMnO_4$/dioxane	Reflux	16	40	25
6	O_2/activated carbon	120 °C	24	84	26
7	[Mn(TPP)Cl]/ $NaIO_4$	rt	5	84	Present method

In conclusion, an efficient method has been reported for the dehydrogenation of imidazolines to imidazoles with $NaIO_4$ using [Mn(TPP)Cl] as catalyst. In addition, this method offers several advantages including high yields, easy work-up, applicability for both 2-aryl and 2-alkylimidazolines, and mild reaction conditions which make it ideal for the use in the oxidation of 2-imdazolines.

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References and notes

1. Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
2. (a) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786; (b) Meunier, B. *Bull. Soc. Chim. Fr.* **1986**, *4*, 578.
3. (a) Sugimoto, H.; Tung, H. C.; Sawyer, D. T. *J. Am. Chem. Soc.* **1988**, *110*, 2465; (b) Mansuy, D. *Pure Appl. Chem.* **1987**, *59*, 579; (c) Mansuy, D.; Battioni, P.; Battioni, J. P. *Eur. J. Biochem.* **1989**, *184*, 267.
4. Bortolini, O.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1967.
5. Amatsu, H.; Miyamoto, T. K.; Sasaki, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3193.
6. Hirao, T.; Ohno, M.; Ohshiro, Y. *Tetrahedron Lett.* **1990**, *31*, 6039.
7. Tsuchiya, S.; Seno, M. *Chem. Lett.* **1989**, 263.
8. Ledon, H. J.; Durbut; Varescon, F. *J. Am. Chem. Soc.* **1981**, *103*, 3601.
9. Traylor, T. G.; Fann, W. P.; Bandyopadhyay, D. *J. Am. Chem. Soc.* **1989**, *111*, 8009.
10. Mohajer, D.; Tangestaninejad, S. *Tetrahedron Lett.* **1994**, *35*, 945.
11. Mohajer, D.; Tangestaninejad, S. *J. Chem. Soc., Chem. Commun.* **1993**, 240.
12. (a) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 4, p 345; (b) Lambardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182; (c) Kim, H. G.; Lee, J. K.; Lee, J. T.; Lee, C. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 345.
13. (a) Levesque, G.; Gressier, J.-C.; Proust, M. *Synthesis* **1981**, 963; (b) Mohammadpoor-Baltork, I.; Abdollahi-Alibeik, M. *Bull. Korean Chem. Soc.* **2003**, *24*, 1354.
14. Dockner, T.; Frank, A. Ger. Offen. 2,729,017, 1979; *Chem. Abstr.* **1979**, 204100.
15. Kyrides, L. P.; Zienty, F. B.; Steahly, G. W.; Morrill, H. L. *J. Org. Chem.* **1947**, *12*, 577.
16. Klem, R. E.; Skinner, H. F.; Walba, H.; Isensee, R. W. *J. Heterocycl. Chem.* **1970**, *7*, 403.
17. Amemiya, Y.; Miller, D. D.; Hsu, F. L. *Synth. Commun.* **1990**, *20*, 2483.
18. Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. *J. Org. Chem.* **1968**, *33*, 3758.
19. Hughey, J. L., IV; Knapp, S.; Schudar, H. *Synthesis* **1980**, 489.
20. Anastassiadou, M.; Baziard-Mouysset, G.; Payard, M. *Synthesis* **2000**, 1814.
21. Mohammadpoor-Baltork, I.; Zolfigol, M. A.; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2004**, *45*, 8687.
22. Mohammadpoor-Baltork, I.; Abdollahi-Alibeik, M. *Can. J. Chem.* **2005**, *83*, 110.
23. Abdollahi-Alibeik, M.; Mohammadpoor-Baltork, I.; Zolfigol, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6079.
24. Mohammadpoor-Baltork, I.; Zolfigol, M. A.; Abdollahi-Alibeik, M. *Synlett* **2004**, 2803.
25. Campos, M. E.; Jimenez, R.; Martinez, F.; Salgado, H. *Heterocycles* **1995**, *40*, 841.
26. Haneda, S.; Okui, A.; Ueba, C.; Hayashi, M. *Tetrahedron* **2007**, *63*, 2414.
27. All materials were purchased from Merck. Tetraphenylporphyrins was prepared and metallated according to reported procedures.[28–31] All 2-substituted imidazolines were synthesized by the reported procedures.[13b,32] ^1H NMR spectra were recorded on a Bruker–Avance AQS 400 MHz. TLC monitored all reactions and all yields refer to isolated products.
General procedure for dehydrogenation of imidazolines with $NaIO_4$ catalyzed by [Mn(TPP)Cl]: All of the reactions were carried out at room temperature under air in a 25 mL flask equipped with a magnetic stirrer bar. A solution of $NaIO_4$ (2 mmol) in H_2O (10 mL) was added to a mixture of 2-imidazolines (1 mmol), [Mn(TPP)Cl] (0.05 mmol) in CH_3CN (5 mL). The progress of reaction was monitored by TLC (eluent: EtOAc/MeOH 4:1). After the reaction was completed, water (30 mL) was added and the corresponding imidazoles were extracted with CH_2Cl_2 (2 × 20 mL). The imidazole derivatives were obtained after evaporation of solvent. IR and ^1H NMR spectral data confirmed the identities of the products.
28. Adler, A. D.; Long, F. R.; Finarellii, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
29. Bhyrappa, P.; Krishnan, V. *Inorg. Chem.* **1991**, *30*, 239.
30. Bettelheim, A.; White, B. A.; Raybuck, S. A.; Murray, R. W. *Inorg. Chem.* **1987**, *26*, 1009.
31. Rebelo, S. L. H.; Pereira, M. M.; Simões, M. M. Q.; Graça, M.; Neves, P. M. S.; Cavaleiro, J. A. S. *J. Catal.* **2005**, *234*, 76.
32. Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Kargar, H. *Tetrahedron Lett.* **2006**, *47*, 2129.