Available online at www.sciencedirect.com

SCIENCE DIRECT®

ELSEVIER

Bioorganic & Medicinal Chemistry Letters 14 (2004) 6079–6082

Bioorganic & Medicinal Chemistry Letters

Alumina supported potassium permanganate: an efficient reagent for chemoselective dehydrogenation of 2-imidazolines under mild conditions

Mohammad Abdollahi-Alibeik,[a] Iraj Mohammadpoor-Baltork[a,*] and Mohammad Ali Zolfigol[b]

[a] *Department of Chemistry, Isfahan University, Isfahan 81746-73441, Iran*
[b] *Department of Chemistry, Bu-Ali Sina University, Hamadan 65174, Iran*

Received 15 August 2004; revised 18 September 2004; accepted 21 September 2004
Available online 26 October 2004

Abstract—Potassium permanganate supported on alumina was found to be an efficient reagent system for dehydrogenation of 2-imidazolines to imidazoles under mild conditions at room temperature. Selective oxidation of 2-alkylimidazolines in the presence of 2-arylimidazolines was achieved using this reagent system. 2-Imidazolines were also selectively converted to their corresponding imidazoles in the presence of other oxidizable functional groups such as sulfide, ether, aldehyde, acetal and THP ether. The oxidation procedure described here is easy to carry out and does not require strict reaction conditions.

---

1. Introduction

Oxidation is one of the most important classes of organic reactions from the academic, industrial and pharmaceutical points of views. Selective dehydrogenation of 2-imidazolines to their corresponding imidazoles is of importance from both biological and pharmaceutical considerations since many imidazole derivatives possess antiinflammatory, antihypertensive, antibacterial and antidiabetic activities.[1] 2-Imidazolines can be prepared from nitriles and ethylenediamine.[2] Therefore, oxidation of 2-imidazolines by oxidizing agents provides a convenient method for the preparation of imidazoles. Several reagents are available to perform this transformation.[3–12] Unfortunately, the reported reagents suffer from disadvantages such as low yields of the products, very long reaction times, tedious work-up, the use of large excess of the reagents and harsch reaction conditions. Another major drawback of some of the older procedures is their use of reagents, which are either highly toxic or produce serious disposal problems (or both). Consequently, development of novel and mild protocols for the efficient conversion of 2-imidazolines to imidazoles based on readily available safe reagents is still in demand. We now report to the best of our knowledge the first use of alumina supported potassium permanganate for the dehydrogenation of 2-imidazolines to imidazoles.

2. Results and discussion

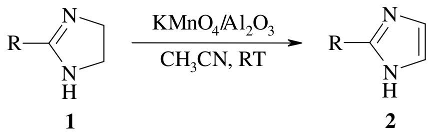
The use of solid supported reagents in synthetic chemistry has become popular due to the altered reactivity, selectivity and convenient product isolation they provide.[13] One of the most striking examples of a change in chemical reactivity and selectivity that has been reported to date is with the well-known oxidant potassium permanganate.[14] Previously, alumina supported potassium permanganate has been used for the oxidative cleavage of enamine double bonds,[15] dehydrogenation of 1,4-cyclohexadienes to aromatics,[16] oxidative cleavage of oximes,[17] oxidation of thiols and sulfides,[18] oxidative deprotection of TMS and THP ethers, ethylene acetals and ketals,[19] oxidation of alcohols,[20] oxidation of urazoles,[21] oxidation of α-hydroxysilanes,[22] oxidation

---

Keywords: Alumina supported potassium permanganate; 2-Imidazolines; Imidazoles; Dehydrogenation.

* Corresponding author. Tel.: +98 311 7932705; fax: +98 311 6689732; e-mail: imbaltork@sci.ui.ac.ir

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.09.070



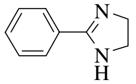
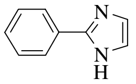
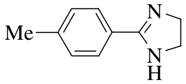
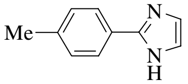
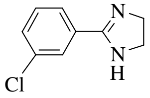
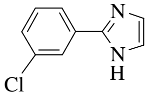
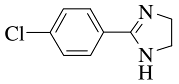
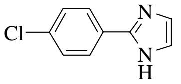
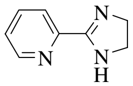
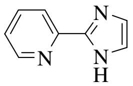
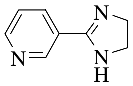
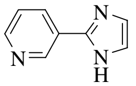
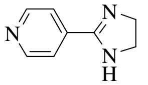
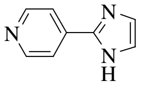
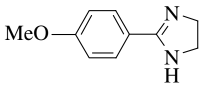
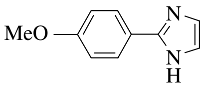
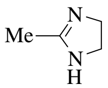
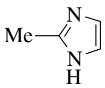
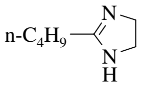
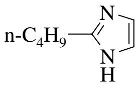
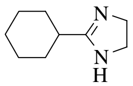
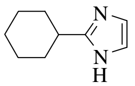
Scheme 1.

of α-hydroxyphosphonates[23] and deprotection of thioacetals.[24] Along this line, we found that potassium permanganate supported on alumina is able to oxidize 2-imidazolines to imidazoles efficiently (Scheme 1).

Our objectives in undertaking this work were: (a) to overcome the drawbacks of some of the reported methods such as tedious work-up and safety problems; (b) to achieve rapid reaction rates, higher yields and milder reaction conditions; (c) to develop an efficient method for the chemoselective oxidation of 2-imidazolines to imidazoles using a cheap commercially available reagent.

The applicability of $KMnO_4/Al_2O_3$ system was then examined using 2-aryl- and 2-alkylimidazolines. The reaction conditions, specified in Table 1, were optimized and it was found that different types of 2-arylimidazol-

Table 1. Dehydrogenation of 2-imidazolines to imidazoles with $KMnO_4/Al_2O_3$ in CH_3CN at room temperature

Substrate (**1**)	Product[a] (**2**)	$KMnO_4$/imidazoline[b,c]	Time (h)	Yield[d] (%)
 (**1a**)	 (**2a**)	3	1.75	85
 (**1b**)	 (**2b**)	3	1.3	82
 (**1c**)	 (**2c**)	3	2	78
 (**1d**)	 (**2d**)	3	2	90
 (**1e**)	 (**2e**)	3	1.25	75
 (**1f**)	 (**2f**)	3	1.3	80
 (**1g**)	 (**2g**)	3	1.3	95
 (**1h**)	 (**2h**)	3	1.25	77
 (**1i**)	 (**2i**)	1.3	0.25	92
 (**1j**)	 (**2j**)	1.3	0.25	90
 (**1k**)	 (**2k**)	1.6	0.35	90

[a] All products were characterized by comparison of their physical and spectral data with those of authentic samples.[8–10,25]

[b] Molar ratio.

[c] 700 mg of Al_2O_3 per mmol of 2-imidazoline was used.

[d] Isolated yields.

ines can be oxidized to their corresponding imidazoles in high yield in acetonitrile at room temperature (entries **1a**–**h**). Oxidation of 2-alkylimidazolines to their corresponding imidazoles is also of great interest, since 2-alkylimidazoles are used as intermediates for the synthesis of valuable nitroimidazole drugs.[10] The results show that 2-alkylimidazolines were also converted to their imidazoles in excellent yields using this reagent system (**1i**–**k**). It is noteworthy that the oxidation of 2-alkylimidazolines by this method is much faster than those of 2-arylimidazolines. Moreover, in comparison with 2-arylimidazolines, the oxidation of 2-alkylimidazolines can proceed effectively with lower amounts of $KMnO_4$ (1.3–1.6 equiv). In order to show the necessity of alumina in this transformation, the oxidation of 2-phenylimidazole (**1a**) was investigated with potassium permanganate alone in acetonitrile at room temperature. Under this condition, only 20% of 2-phenylimidazole (**2a**) was obtained from the reaction mixture after 2 h.

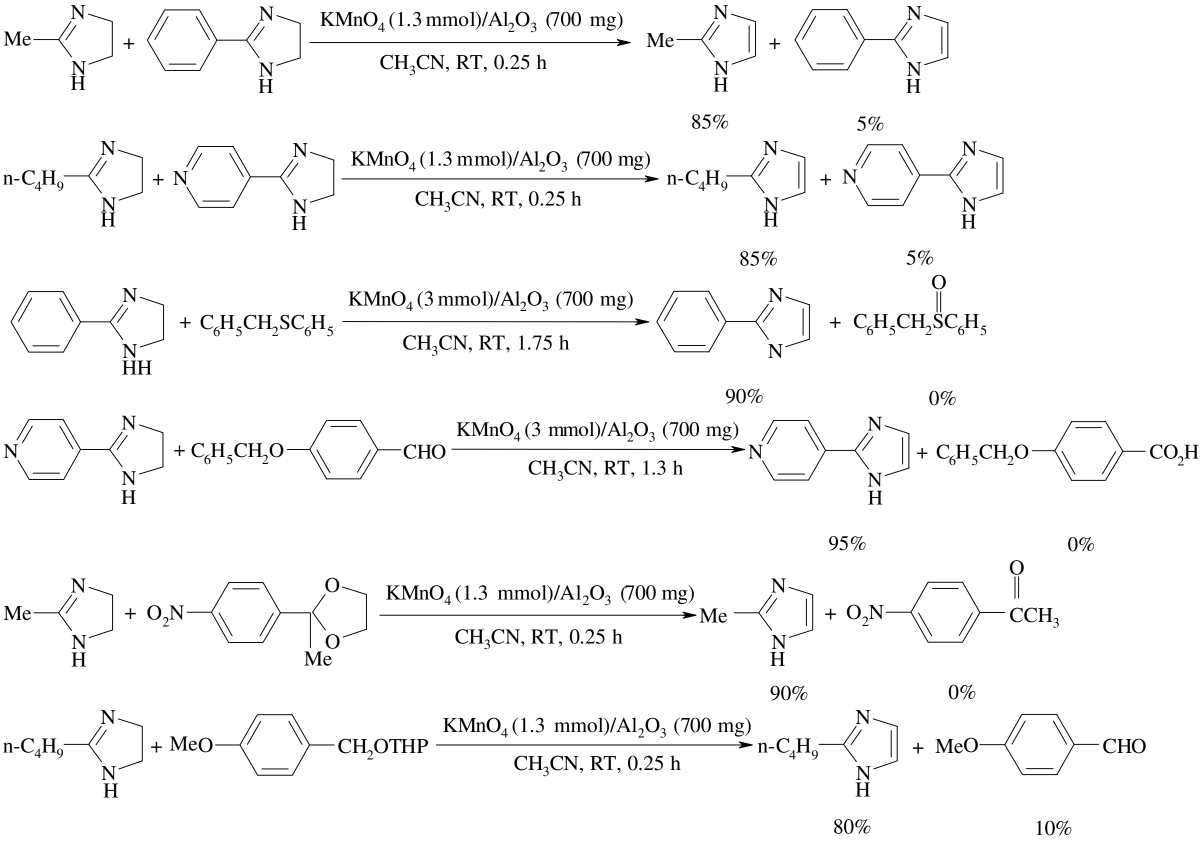
There are several advantages associated with this procedure. This method offers a simple, general and efficient route for converting 2-imidazolines to the corresponding imidazoles under very mild conditions. The selectivity of this procedure is remarkable. As evident from the results presented in Scheme 2, oxidation of 2-alkylimidazolines can be achieved selectively in the presence of 2-arylimidazolines. Chemoselective oxidation of 2-imidazolines to the corresponding imidazoles was also performed in the presence of a variety of functional groups including sulfide, ether, aldehyde, acetal and THP ether; these functional groups have been effectively oxidized using $KMnO_4/Al_2O_3$ system.[18,19] To the best of our knowledge this is the first report of selective oxidation of 2-alkylimidazolines in the presence of 2-arylimidazolines and other above-mentioned oxidizable functional groups.

3. Conclusion

The results presented on this paper demonstrated that $KMnO_4/Al_2O_3$ can be used for the efficient oxidation of 2-imidazolines to their corresponding imidazoles. In addition, this method offers several advantages including high yields, short reaction times, easy work-up, very mild reaction conditions and excellent chemoselectivity, which make it ideal for the use in the oxidation of 2-imdazolines.

4. Experimental

2-Imidazolines were prepared according to the described procedure.[2b] Melting points were determined using a Stuart Scientific apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^1H NMR spectra were recorded in DMSO-d_6 solvent on a Bruker 500 MHz using TMS as an internal standard.



Scheme 2.

4.1. General procedure for oxidation of 2-imidazolines to imidazoles

Potassium permanganate and alumina were ground together in a mortar until a fine homogeneous powder was obtained.

In a round-bottomed flask (100 mL), a solution of 2-imidazoline (2 mmol) in CH_3CN (40 mL) was prepared. Potassium permanganate (2.6–6 mmol) and alumina (1.4 g) were added and the mixture was stirred at room temperature for the appropriate time according to Table 1. The progress of the reaction was monitored by TLC (eluent: EtOAc/MeOH: 4:1). Ethanol (1 mL) was added to reduce excess oxidant. The mixture was filtered and the solid material was washed with CH_3CN (20 mL). The filtrate was evaporated and the resulting crude material was purified by column chromatography on alumina to afford the pure imidazole in 75–95% yields (Table 1).

Acknowledgements

We are grateful to the Isfahan University Research Council for partial support of this work.

References and notes

1. (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.
2. (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.
3. Dockner, T.; Frank, A. *Ger. Offen* **1979**, 2,729,017.
4. Kyrudes, L. P.; Zienty, F. B.; Steahly, G. W.; Morrill, H. L. *J. Org. Chem.* **1947**, 577.
5. Klem, R. E.; Skinner, H. F.; Walba, H.; Isensee, R. W. *J. Heterocycl. Chem.* **1970**, 403.
6. Amemiya, Y.; Miller, D. D.; Hsu, F. L. *Synth. Commun.* **1990**, *20*, 2483.
7. Martin, P. K.; Matthews, H. R.; Rapoport, H.; Thyagarajan, G. *J. Org. Chem.* **1968**, 3758.
8. Hughey, J. L., IV; Knapp, S.; Schudar, H. *Synthesis* **1980**, 489.
9. Anastassiadou, M.; Baziard-Mouysset, G.; Payard, M. *Synthesis* **2000**, 1814.
10. Campos, M. E.; Jimenez, R.; Martinez, F.; Salgado, H. *Heterocycles* **1995**, *40*, 841.
11. Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077.
12. Chou, C.-H.; Chu, L.-T.; Chiu, S.-J.; Lee, C.-F.; She, Y.-T. *Tetrahedron* **2004**, *60*, 6581.
13. (a) *Solid Supports and Catalysis in Organic Synthesis*; Smith, K., Ed.; Prentice Hall: New York, 1992; (b) Laszlo, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 7, p 839.
14. Lee, D. G. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995.
15. Harris, C. E.; Chrisman, W.; Bickford, S. A.; Lee, L. E.; Torreblanca, A. E.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 981.
16. McBride, C. M.; Chrisman, W.; Harris, C. E.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 45.
17. Chrisman, W.; Blankinship, M. J.; Taylor, B.; Harris, C. E. *Tetrahedron Lett.* **2001**, *42*, 4775.
18. (a) Shaabani, A.; Lee, D. G. *Tetrahedron Lett.* **2001**, *42*, 5833; (b) Hajipour, A. R.; Mallakpour, S. E.; Adibi, H. *Sulfur Lett.* **2002**, *25*, 155.
19. Hajipour, A. R.; Mallakpour, S. E.; Mohammadpoor-Baltork, I.; backnezhad, H. *Synth. Commun.* **2002**, *32*, 771.
20. Hajipour, A. R.; Mallakpour, S. E.; Imanzadeh, G. *Chem. Lett.* **1999**, 99.
21. Hajipour, A. R.; Mallakpour, S. E.; Zolfigol, M. A.; Adibi, H. *Indian J. Chem.* **2002**, *41B*, 2425.
22. Patrocinio, A. F.; Moran, P. J. S. *Synth. Commun.* **2001**, *31*, 2457.
23. Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 477.
24. Hajipour, A. R.; Mallakpour, S. E.; Mohammadpoor-Baltork, I.; Adibi, H.; Ruoho, A. E. *Sulfur Lett.* **2003**, *26*, 77.
25. (a) Baldwin, J. J.; Lumma, P. K.; Novello, F. C.; Ponticello, G. S.; Sprague, J. M. *J. Med. Chem.* **1977**, *20*, 1189; (b) Miller, R. D.; Lee, V. Y.; Moylan, C. R. *Chem. Mater.* **1994**, *6*, 1023; (c) Schubert, H.; Hofmann, S. *J. Prak. Chem.* (*Leipzig*) **1958**, *7*, 119.