Chemistry of Heterocyclic Compounds, Vol. 44, No. 7, 2008

METAL-FREE OXIDATIVE DEHYDROGENATION OF IMIDAZOLINES AND PYRAZOLINES USING SILICA-ADSORBED PEROXYMONOSULFATE UNDER APROTIC AND ALMOST NEUTRAL CONDITIONS

H. Adibi[1], A. R. Hajipour[2,3], and H. Jafari[4]

Oxidative dehydrogenation of 1,3,5-trisubstituted pyrazolines and 2-substituted imidazolines to their corresponding pyrazoles and imidazoles is carried out effectively by treatment with benzyltriphenylphosphonium peroxymonosulfate as an oxidant silica-adsorbed under aprotic and almost neutral conditions.

Keywords: imidazoles, peroxymonosulfate, pyrazoles, silica, oxidative dehydrogenation.

1,3,5-Trisubstituted pyrazolines are important five-membered heterocyclic compounds, which can be easily prepared from phenylhydrazine and chalcone derivatives [1-3], and their oxidative dehydrogenation provides the corresponding pyrazoles, which are known to possess diverse biological activities, including anti-inflammatory, antiarrhythmic, antidiabetic, and antibacterial activities [1-3]. For the oxidative aromatization of pyrazolines various methods have been reported employing reagents such as $Pb(OAc)_4$ [4], MnO_2 [5], $KMnO_4$ [6], $Zr(NO_3)_4$ [7], iodobenzene diacetate [8], $AgNO_3$ [9], Pd/C in acetic acid [10], activated carbon [11], N-hydroxyphthalimide (NHPI)/$Co(OAc)_2/O_2$ [12], 4-(*p*-chlorophenyl)-1,2,4-triazole-3,5-dione [13], cobalt soap of fatty acids [14], mercury or lead oxide [15], HIO_3 or I_2O_5 [16], trichloroisocyanuric acid [17], clay-supported $Cu(NO_3)_2 \cdot 3H_2O$ (claycop)/ ultrasound [18], *p*-chloranil [19], and DDQ [20]. However, many of these methods suffer from disadvantages such as the use of expensive transition metal oxidants and reagents, which are highly toxic, produce by-products that either destroy the sensitive pyrazoles or are difficult to remove, and the use of acidic media and tedious work-up.

2-Imidazolines can be prepared from nitriles and ethylenediamine [21, 22].

Selective dehydrogenation of 2-imidazolines to their corresponding imidazoles is of importance from both biological and pharmaceutical considerations since many imidazole derivatives possess anti-inflammatory, antihypertensive, antibacterial, and antidiabetic activities [23-25]. Several reagents are available to perform this transformation including $KMnO_4/Al_2O_3$ [26], DMSO [27], Pd/C [28], Swern oxidation [29], trichloro-

[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah 67145-1673, IR Iran; e-mail: hadibi@kums.ac.ir. [2]Pharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran. [3]Department of Pharmacology, University of Wisconsin, Medical School, Madison, Wisconsin 53706-1532, USA. [4]Islamic Azad University, Sanandaj Branch, Sanandaj, IR Iran. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 1003-1008, June, 2008. Original article submitted February 24, 2008.

 0009-3122/08/4407-0802

isocyanuric acid [30], $KMnO_4/SiO_2$ [31], $KMnO_4$ [32], Zn/Al_2O_3 [33], Ni [34], Se [35], MnO_2 [36], and $BaMnO_4$ [37]. These reagents suffer from limitations such as low yields of the products, very long reaction times, toxicity of transition metal oxidants, the use of large excess of the reagents, and harsh reaction conditions. Therefore, we decided to introduce a new reagent to overcome these limitations.

Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is an inexpensive, water-soluble, and stable oxidizing reagent that is commercially available. However, this reagent is insoluble in organic solvents and buffering is needed due to its acidity [38–40]. Recently, we reported benzyltriphenylphosphonium peroxymonosulfate (BTPPMS) as a mild, inexpensive, and efficient reagent in organic transformations [41–44]. Over the last two decades, the use of solid supports has become popular due to their characteristic properties such as enhanced selectivity and reactivity, straightforward work-up procedure, milder reaction conditions, and associated ease of manipulation [45]. Following our continued interest in BTPPMS [41–44] and in the course of our studies on the dehydro- genation of organic compounds [43], we herein report metal-free oxidative dehydrogenation of 1,3,5-tri-substituted pyrazolines **1** and 2-substituted imidazolines **3** to their corresponding pyrazoles **2** and imidazoles **4** employing BTPPMS as an oxidant silica-adsorbed as the supporting agent under non-aqueous and almost neutral conditions. To the best of our knowledge, this is the first example of BTPPMS-mediated metal-free dehydrogenation of pyrazolines and imidazolines.

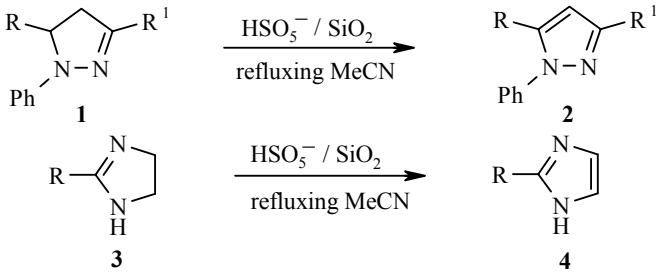
We first examined the reaction of 1,3,5-trisubstituted pyrazolines **1** using BTPPMS as the oxidant. During the course of the screening of a variety of reaction conditions such as solvent, time, reaction temperature, and the amount of the oxidant, we found that the use of silica as a supporting agent was essential for the efficient conversion of 1,3,5-trisubstituted pyrazolines **1** to pyrazoles **2**. That is, the treatment of 1,3,5-triphenyl- pyrazoline **1a** as a model compound (1 mmol) with BTPPMS (2 mmol) silica-adsorbed (0.5 g per mmol of pyrazoline) as an inexpensive and readily available supporting agent in refluxing acetonitrile for 5 h afforded 1,3,5-triphenylpyrazole **2a** in 76% yield. The oxidation of compound **1a** was investigated with BTPPMS alone in refluxing acetonitrile and only 30% of compound **2a** was obtained from the reaction mixture after 5 h. The reactions in MeCN, which turned out to be one of the best choices in our previously organic transformations [41–44], produced the corresponding pyrazoles **2** by simple filtration and evaporation of the solvent in good to moderate yields. The results and reaction conditions are exemplified in Table 1. Having successfully achieved the aromatization of pyrazolines, we applied this method to the oxidative aromatization of 2-substituted imidazolines **3** to imidazoles **4**. As shown in Table 1, the treatment of 2-substituted imidazolines **3** according to the above mentioned-procedure led to the formation of the corresponding imidazoles **4** in refluxing acetonitrile in good yields.

Oxidation of 2-alkylimidazolines to the corresponding imidazoles was achieved by this oxidation system (Table 1, **3g–i**), since 2-alkylimidazoles are used as intermediates for the synthesis of valuable nitroimidazole drugs [32]. Some of the reported reagents such as DMSO [27] and Pd/C [28] were not effective for dehydrogenation of 2-alkylimidazolines.

The actual role of BTPPMS and silica is not clear to us; however, according to a plausible mechanism suggested in our previously reported literature for BTPPMS-oxidized aromatization of 1,4-dihydropyridines to pyridines [43], we propose a possible mechanism for BTPPMS-mediated oxidative dehydrogenation of pyrazolines according to a radical pathway upon homolytic cleavage of O–O bond in peroxymonosulfate anion ($^{-}O_3S–O–OH$). It is believed that the presence of silica increases the decomposition rate of peroxymonosulfate anion to form a hydroxyl radical and a sulfate radical anion.

Presumably the oxidation of pyrazoline **I** is initiated by a single electron transfer on the nitrogen of pyrazoline **I** to the hydroxyl radical that produces hydroxide anion and a radical cation **II**, which subsequently loses a proton to generate the radical **III** and water. The radical **III** transfers an electron to the sulfate radical anion to form the cation **IV** and sulfate anion, subsequently resulting in the aromatized pyrazoline(s) **V** and hydrogen sulfate anion. The suggested mechanism for BTPPMS-mediated oxidative dehydrogenation of imidazolines is similar to that of pyrazolines.

TABLE 1. Oxidative dehydrogenation of 1,3,5-trisubstituted pyrazolines **1** and 2-substituted imidazolines **3** using BTPPMS/silica* under aprotic conditions*[2]



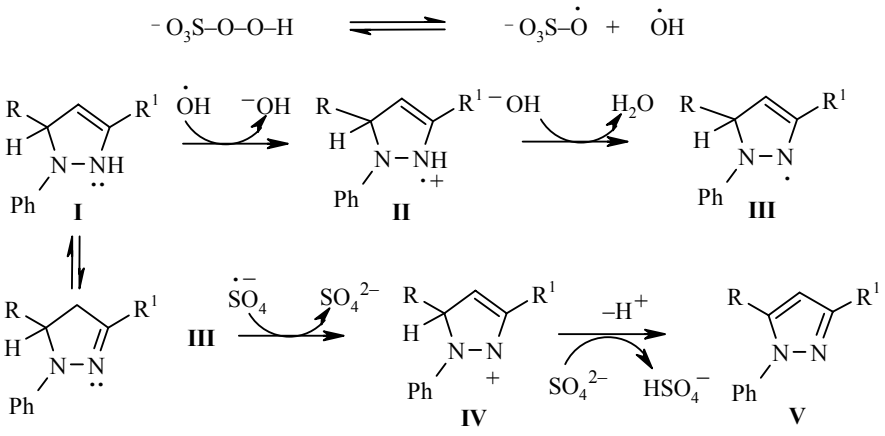
Substrate	R	R^1	Time, h	Yield, %*[3]
1a	Ph	Ph	5	76
1b	Ph	*p*-$O_2NC_6H_4$	6.5	70
1c	Ph	*p*-$MeOC_6H_4$	4.5	65
1d	Ph	*m*-ClC_6H_4	3.5	68
1e	2-Naphthyl	*p*-ClC_6H_4	8	66
1f	2-Naphthyl	*m*-MeC_6H_4	7	69
1g	*p*-MeC_6H_4	2-Furyl	6	70
1h	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	6	72
1i	*p*-$MeOC_6H_4$	Ph	5	62
1j	*p*-MeC_6H_4	*m*-MeC_6H_4	4.5	60
3a	Ph		5	81
3b	*p*-$MeOC_6H_4$		3	80
3c	2-Py		2.5	78
3d	*p*-ClC_6H_4		6	75
3e	*m*-ClC_6H_4		5	82
3f	*p*-MeC_6H_4		4.5	75
3g	Me		0.6	70
3h	Ph		1	72
3i	*n*-Bu		1.2	78

* Molar ratio: BTPPMS–imidazoline (2:1 and 0.5 g silica per mmol of pyrazoline (for **1a–j**) and imidazoline (for **3a–i)** was used).
*[2] Confirmed by comparison with authentic samples [2].
*[3] Yield of isolated pure product after purification.

In conclusion, we have disclosed a facile and environmentally benign oxidative aromatization process to convert 1,3,5-trisubstituted pyrazolines and 2-substituted imidazolines to the corresponding pyrazoles and imidazoles using silica-adsorbed BTPPMS as an interesting alternative to liquid and transition metal oxidants. The advantages of the present reaction are the elimination of metals and toxic reagents, operational simplicity, and easy work-up. Extension of this procedure to other substrates is under way in our laboratory.

EXPERIMENTAL

The products were characterized by comparing their spectral and physical data with those of authentic samples reported in the literature [4-20, 26-37]. The reagent BTPPMS was prepared according to our previously reported procedures [41–44]. 1,3,5-Trisubstituted pyrazolines **1** were synthesized according to the reported procedure [13]. 2-Substituted imidazolines **3** were synthesized according to the reported procedure [21, 22].



Oxidative aromatization of 1,3,5-triphenylpyrazoline 1a to 1,3,5-triphenylpyrazole 2a (Typical procedure). BTPPMS (0.932 g, 2 mmol) and silica (0.5 g) were shaken together by a mini-shaker (vortex) until a fine homogeneous powder was obtained. To a solution of 1,3,5-triphenylpyrazoline **1a** (1 mmol) in MeCN (10 ml), silica-adsorbed BTPPMS (1.432 g, 2 mmol) was added and the mixture was stirred under reflux for 5 h. The progress of the reaction was monitored by TLC (eluent EtOAc–cyclohexane, 2:8). The mixture was cooled to room temperature and then filtered off, and the solid material was washed with MeCN (10 ml). The filtrate was evaporated and the resulting crude material was purified by chromatography on silica gel (eluent acetone/petroleum ether, 1:5) to afford the pure 1,3,5-triphenylpyrazole **2a** as a pale yellow solid in 76% yield, mp 133-135ºC (mp 133-134ºC [13]).

Oxidative aromatization of 2-phenylimidazoline 3a to 2-phenylimidazole 4a (Typical procedure). A mixture of silica-adsorbed BTPPMS (1.432 g, 2 mmol) and 2-phenylimidazole **3a** (1 mmol) in MeCN (10 ml) was heated under reflux conditions. After disappearance of the starting imidazoline monitored by TLC using EtOAc–cyclohexane, 2:8, the mixture was cooled to room temperature and then filtered off through a sintered glass funnel, and the solid material was washed with MeCN (2×10 ml). The combined organic layer was evaporated and the crude product was purified by column chromatography on silica gel (eluent acetone–petroleum ether, 1:5) to afford the pure 2-phenylimidazole **4a** in 81% yield as revealed from TLC and ^{1}H NMR analysis, mp 141-144ºC (mp 140-142ºC [31]).

We gratefully acknowledge the Kermanshah University of Medical Sciences Research Council for financial support.

REFERENCES

1. E. Takabata, R. Kodama, Y. Tanaka, R. Dohmori, H. Tachizawa, and T. Naito, *Chem. Pharm. Bull.*, **16**, 1900 (1979).
2. S. S. Parmar, B. R. Pandey, C. Dwivedi, and R. D. Harbison, *J. Pharm. Sci.*, **63**, 1152 (1974).
3. N. Soni, K. Pande, R. Kalsi, T. K. Gupta, S. S. Parmer, and J. P. Barthwal, *Res. Commun. Mol. Pathol. Pharmacol.*, **56**, 129 (1987).
4. W. A. F. Goldstone and R. O. C. Norman, *J. Chem. Soc., Chem. Commun.*, 1536 (1966).
5. I. Bhatnagar and M. V. George, *Tetrahedron*, **24**, 1293 (1968).
6. L. I. Smith and K. L. Howard, *J. Am. Chem. Soc.*, **65**, 159 (1943).
7. G. Sabitha, G. S. Reddy, C. S. Reddy, N. Fatima, and J. S. Yadav, *Synthesis*, 1267 (2003).

8. S. P. Singh, D. Kumar, O. Prakash, and R. P. Kapoor, *Synth*. *Commun*., **27**, 2683 (1997).
9. R. P. Dodwadmath and T. S. Wheeler, *Proc*. *Ind. Acad*. *Sci*., **2A**, 438 (1935).
10. N. Nakamichi, Y. Kawashita, and M. Hayashi, *Org*. *Lett*., **4**, 3955 (2002).
11. N. Nakamichi, Y. Kawashita, and M. Hayashi, *Synthesis*, 1015 (2004).
12. B. Han, Z. Liu, Q. Liu, L. Yang, Z.-L. Liu, and W. Yu, *Tetrahedron*, **62**, 2492 (2006).
13. M. A. Zolfigol, D. Azarifar, S. Mallakpour, I. Mohammadpoor-Baltork, A. Forghaniha, B. Maleki, and M. Abdollahi-Alibeik, *Tetrahedron Lett*., **47**, 833 (2006).
14. J. N. Shah and C. K. Shah, *J. Org. Chem*., **43**, 1266 (1978).
15. K. Auwers and P. Hemke, *Lieb. Ann*. *Chem*., **458**, 186 (1927).
16. L. Chai, Y. Zhao, Q. Sheng, and Z-Q. Liu, *Tetrahedron Lett*., **47**, 9283 (2006).
17. M. A. Zolfigol, D. Azarifar, and M. Maleki, *Tetrahedron Lett*., **45**, 2181 (2004).
18. S. Mallouk, K. Bougrin, H. Doua, R. Benhida, and M. Soufiaoui, *Tetrahedron Lett*., **45**, 4143 (2004).
19. R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).
20. D. Walker and J. D. Hiebert, *Chem. Rev*., **67**, 153 (1967).
21. G. Levesque, J.-C. Gressier, and M. Proust, *Synthesis*, 963 (1981).
22. I. Mohammadpoor-Baltork and M. Abdollahi-Alibeik, *Bull. Korean Chem. Soc*., **24**, 1354 (2003).
23. M. R. Grimmett, in: K. T. Potts (editor), *Comprehensive Heterocyclic Chemistry*; Pergamon: Oxford, 1984, Vol. 4, p. 345.
24. J. G. Lambardino and E. H. Wiseman, *J. Med. Chem*., **17**, 1182 (1974).
25. H. G. Kim, J. K. Lee, J. T. Lee, and C. S. Lee, *Bull. Korean Chem. Soc*., **21**, 345 (2000).
26. M. Abdollahi-Alibeik, I. Mohammadpoor-Baltork, and M. A. Zolfigol, *Bioorg. Med. Chem. Lett*., **14**, 6079 (2004).
27. M. Anastassiadou, G. Baziard-Mouysset, and M. Payard, *Synthesis*, 1814 (2000).
28. Y. Amemiya, D. D. Miller, and F. L. Hsu, *Synth. Commun*., **20**, 2483 (1990).
29. D. H. Huh, H. Ryu, and Y. G. Kim, *Tetrahedron,* **60**, 9857 (2004).
30. I. Mohammadpoor-Baltork, M. A. Zolfigol, and M. Abdollahi-Alibeik, *Synlett,* 2803 (2004).
31. I. Mohammadpoor-Baltork, M. A. Zolfigol, and M. Abdollahi-Alibeik, *Tetrahedron Lett*., **45**, 8687 (2004).
32. M. E. Campos, R. Jimenez, F. Martinez, and H. Salgado, *Heterocycles*, **40**, 841 (1995).
33. T. Dockner and A. Frank, Ger. Offen. 2,729,017 (1979), *Chem. Abstr*., 204100 (1979).
34. L. P. Kyrides, F. B. Zienty, G. W. Steahly, and H. L. Morrill, *J. Org. Chem*., **12**, 577 (1947).
35. R. E. Klem, H. F. Skinner, H. Walba, and R. W. Isensee, *J. Heterocycl. Chem*., **7**, 403 (1970).
36. P. K. Martin, H. R. Matthews, H. Rapoport, and G. Thyagarajan, *J. Org. Chem*., **33**, 3758 (1968).
37. J. L. Hughey, S. Knapp, and H. Schudar, *Synthesis*, 489 (1980).
38. A. R. Hajipour, *Indian J. Chem.,* **36B**, 1069 (1997).
39. A. R. Hajipour and N. Mahboubkhah, *Org. Prep. Proced. Int*., **31**, 112 (1999).
40. B. Meunier, *New J. Chem*., **16**, 203 (1992).
41. A. R. Hajipour, S. E. Mallakpour, and H. Adibi, *J. Org*. *Chem*., **67**, 8666 (2002).
42. A. R. Hajipour and H. Adibi, *J. Chem*. *Res*., *Synop*., 274 (2004).
43. H. Adibi and A. R. Hajipour, *Bioorg. Med. Chem. Lett*., **17**, 1008 (2007).
44. H. Adibi and A. R. Hajipour, M. Hashemi, *Tetrahedron Lett*., **48**, 1255 (2007).
45. J. H. Clark, in *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH: Weinheim (1994).