HETEROCYCLES, Vol. 75, No. 3, 2008, pp. 669 - 673. © The Japan Institute of Heterocyclic Chemistry
Received, 21st October, 2007, Accepted, 3rd December, 2007, Published online, 7th December, 2007. COM-07-11248

# SILICA SULFURIC ACID-ACTIVATED POLY-1,3-DICHLORO-5-METHYL-5-(4'-VINYLPHENYL)HYDANTOIN (PDCVH) AS AN EFFECTIVE REAGENT FOR OXIDATION OF 1,3,5-TRISUBSTITUTED 2-PYRAZOLINES BOTH UNDER MICROWAVE IRRADIATION AND THERMAL CONDITIONS

**Davood Azarifar,* Behrooz Maleki, and Mehrnaz Setayeshnazar**

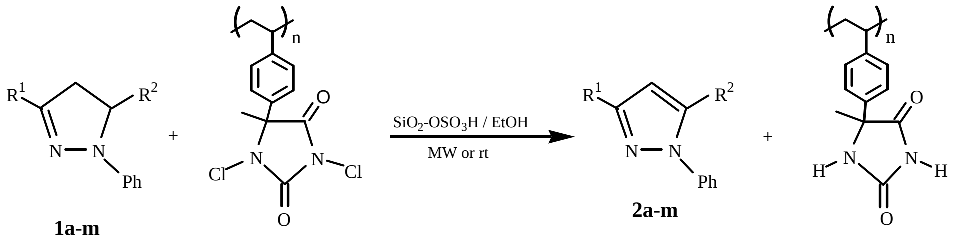
Faculty of Chemistry, Bu-Ali Sina University, Zip Code 65178, Hamedan, Iran
*Corresponding author; Fax: +98(811)8257407; E-mail: azarifar@basu.ac.ir

**Abstract** – Oxidation of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles to the corresponding pyrazoles has been achieved by utilizing silica sulfuric acid-activated poly-1,3-dichloro-5-methyl-5(4'-vinylphenyl)hydantoin in EtOH under both microwave irradiation and conventional thermal conditions at room temperature with good yields.

Pyrazole derivatives, amongst five-membered heterocycles, are interesting heterocyclic compounds since they show a wide range of pharmacological properties including anti-inflammatory,[1] anti-cancer,[2] anti-bacterial,[3] anti-viral,[4] anti-diabetic,[5] anti-microbial, and anti-fungal activities.[6] Some pyrazoles display agrochemical properties (i.e., herbicidal and soil fungicidal activity) and have applications as pesticides and insecticides.[7] 1,3,5-Trisubstituted pyrazoles can be easily obtained by oxidation of their corresponding pyrazolines produced by cyclization of chalcones with arylhydrazines.[8] There is an obvious demand for oxidation of pyrazolines to pyrazoles due to their importance both as pharmacological targets and synthetic intermediates. A number of methods have been previously reported on the oxidation of pyrazolines using a variety of oxidants including $Zr(NO_3)_4$,[9] carbon-activated oxygen,[10] Pd/C/AcOH,[11] Co(II)/$O_2$,[12] iodobenzene diacetate,[13] $Pb(OAc)_4$,[14] $MnO_2$,[15] $KMnO_4$,[16] $Ag(NO_3)_2$,[17] HgO,[18] *N*-hydroxyphthalimide (NHPI)[19] and $I_2O_5$/KBr.[20] However, many suffer from certain drawbacks such as the use of expensive reagents, longer reaction times, low yields of products and toxicity of certain elements embodied in these reagents. These limitations necessitate further demand for new environmentally benign and easily accessible reagents for conversion of 2-pyrazolines to pyrazoles.

In this article, as part of our ongoing efforts to develop more robust methods for oxidative aromatization of various heterocycles including pyrazolines,[21] we describe the use of silica-sulfuric acid-activated poly-1,3-dichloro-5-methyl-5(4’-vinylphenyl)hydantoin (PDCVH) as a new and efficient system for aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles, under microwave irradiation.

In this approach, we have observed that the coupling of microwave irradiation with the use of PDCVH,[22] activated by silica sulfuric acid, provides smooth conversion of 2-pyrazolines (**1a-m**) to 2-pyrazoles (**2a-m**) in EtOH with special attributes such as enhanced reaction rates, higher yields of products and improved ease of manipulation (Scheme **1**). The reactions were conducted under microwave irradiation as well as conventional thermal heating. The results (summarized in Table **1**) display the superiority of microwave irradiation to thermal heating in providing enhanced reaction rates and improved yields.



**Scheme 1**

It is interesting to know that, the reagent PDCVH can only affect the conversion of pyrazolines to pyrazoles if a suitable promoter is used in the reaction either under microwave irradiation or thermal conditions. Several acids including AcOH, TsOH and silica-sulfuric acid have been examined to activate the reagent to release $Cl^+$ cation. It is noticed that, silica-sulfuric acid appears as the most effective activator providing highest yields and least reaction times. In addition, when the reactions are allowed to run in the absence of PDCVH with using solely silica-sulfuric acid in the reaction mixture, no oxidation of pyrazolines is resulted. This evidence substantiates the role of PDCVH as the main species acting as oxidant, and any involvement of silica sulfuric acid as the oxidant is ruled out. According to the experimental results shown in Table **1**, more efficient conversion of 2-pyrazolines occurs under microwave irradiation in EtOH to yield the corresponding pyrazoles in shorter reaction times and higher yields (78-98%) when compared with the yields obtained under thermal conditions at room temperature (68-90%). The actual role of PDCVH is not clear at this time. However, a plausible explanation is that PDCVH might act as a source for $Cl^+$, which in turn activates silica sulfuric acid for further reaction with pyrazolines.

In conclusion, we have developed a new and mild procedure for oxidation of 2-pyrazolines to 2-pyrazoles utilizing poly-1,3-dichloro-5-methyl-5(4'-vinylphenyl)hydantoin (PDCVH) as a cheap, non-toxic and easily recoverable reagent which operates both under microwave irradiation and conventional thermal conditions at rt.

**Table 1** Oxidative aromatization of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles (1 mmole) (**1a-j**) with silica sulfuric acid-activated poly-1,3-dichloro-5-methyl-5(4’-vinylphenyl)hydantoin (PDCVH) in EtOH under both microwave irradiation and thermal conditions at rt.[a]

| Substrate | Product[b] | $R^1$ | $R^2$ | Time (min) | Yield (%)[c] | Mp (°C) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Found | Reported[9,21] |
| **1a** | **2a** | Ph | Ph | 60 (1.5) | 82 (82) | 140-141 | 139-140 |
| **1b** | **2b** | Ph | 4-MeOC$_6$H$_4$ | 60 (1) | 70 (88) | 79-81 | 78-80 |
| **1c** | **2c** | Ph | 4-NO$_2$C$_6$H$_4$ | 150 (2) | 84 (90) | 139-142 | 142-143 |
| **1d** | **2d** | Ph | 4-ClC$_6$H$_4$ | 120 (2) | 78 (92) | 114-115 | 114-115 |
| **1e** | **2e** | 4-MeOC$_6$H$_4$ | Ph | 60 (1) | 86 (98) | 80-82 | 77-79 |
| **1f** | **2f** | 2-naphthyl | 4-ClC$_6$H$_4$ | 180 (2) | 72 (86) | 131-133 | 130-133 |
| **1g** | **2g** | 2-naphthyl | 2-ClC$_6$H$_4$ | 165 (2) | 70 (80) | 72-74 | 67-70 |
| **1h** | **2h** | 2-naphthyl | 2-MeC$_6$H$_4$ | 60 (1) | 82 (85) | 152-154 | 148-150 |
| **1i** | **2i** | Ph | 4-BrC$_6$H$_4$ | 150 (1.5) | 72 (85) | 127-129 | 126-128 |
| **1j** | **2j** | Ph | 3-ClC$_6$H$_4$ | 120 (2) | 68 (82) | 92-94 | 93-95 |
| **1k** | **2k** | 4-MeOC$_6$H$_4$ | 2-ClC$_6$H$_4$ | 150 (2) | 85 (96) | 70-72 | 66-68 |
| **1l** | **2l** | 4-MeC$_6$H$_4$ | 3-MeC$_6$H$_4$ | 120 (2) | 68 (78) | 100-102 | 95-98 |
| **1m** | **2m** | 4-MeC$_6$H$_4$ | 2-Furyl | 150 (2) | 86 (96) | 92-94 | 93-95 |

[a]The reaction data obtained under microwave irradiation are given in parentheses. [b]All the isolated products were characterized on the basis of their physical properties and IR, $^1$H NMR and $^{13}$C NMR spectral analysis and by direct comparison with authentic materials. [c]Isolated yields.

## EXPERIMENTAL

IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained using 90 MHz JEOL FT NMR spectrometer. Microwave-assisted reactions were conducted in a commercial Black & Decker model MX30PG1000 watt microwave oven. 4,5-Dihydro-1*H*-pyrazoles were all prepared according to our previously reported procedure.[8] Poly-1,3-dichloro-5-methyl-5(4’-vinylphenyl)hydantoin was provided by Halosource Company in USA. 2-Pyrazoles were characterized on the basis of their melting points and IR, $^1$H NMR, and $^{13}$C NMR spectral analysis and compared with the reported data.[9,21]

### Aromatization of 1,3,5-trisubstituted pyrazolines with silica sulfuric acid-activated PDCVH; General Procedure:

Poly-1,3-dichloro-5-methyl-5(4’-vinylphenyl)hydantoin (0.45g) and silica-sulfuric acid (0.45g) were added to a flask containing 1,3,5-trisubstituted 2-pyrazolines **(1a-m)** (1mmol) dissolved in EtOH (5 mL). The reaction mixture was stirred at rt for the time given in table **1**. After the complete conversion of the substrate as indicated by TLC analysis, the reaction mixture was quenched with aqueous $NaHCO_3$ solution (5%) and extracted with $Et_2O$ (10 mL). Then organic layer was dried over anhydrous $Na_2SO_4$ and concentrated to leave the crude products **(2a-m)** which were purified by recrystallization from EtOH (96%). In a separate set of experiments, these reactions were all repeated under microwave irradiation condition in an alumina bath using a MX30PG1000 watt microwave oven.

## ACKNOWLEDGEMENT

This project was financially supported by the Research Council of Bu-Ali Sina University (Hamedan, Iran). We wish to thank the Vanson Halosource Company in USA for generous dedication of PDCVH reagent.

## REFERENCES

1. S. Rapposelli, A. Lapucci, F. Minutolo, E. Orlandini, G. Ortore, M. Pinza, and A. Balsamo, *Farmaco*, 2004, **59**, 25.
2. K. D. Shin, M.-Y. Lee, D.-S. Shin, S. Lee, K.-H. Son, S. Koh, Y.-K. Paik, B.-M. Kwon, and D. C. Han, *J. Biol. Chem.*, 2005, **280**, 41439.
3. P. Cali, L. Naerum, S. Mukhija, and A. Hjelmencrantz, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5997.
4. M. Sechi, L. Sannia, F. Carta, M. Palomba, R. Dallocchio, A. Dessi, M. Derudas, Z. Zawahir, and N. Neamati, *Antiviral Chem. Chemother*., 2005, **16**, 41.
5. B. Cottineau, P. Toto, C. Marot, A. Pipaud, and J. Chenault, *Bioorg. Med. Chem. Lett*., 2002, **12**, 2105.
6. F. Al-Omran and A. A. El-Khair, *J. Heterocycl. Chem.*, 2004, **41**, 327.
7. (a) Y. Li, H.-Q. Zhang, J. Liu, X.-P. Yang, and Z.-J. Liu, *J. Agric. Food Chem.*, 2006, **54**, 3636; (b) T. L. Siddall, D. G. Ouse, Z. L. Benko, G. M. Garvin, J. L. Jackson, J. M. McQuiston, M. J. Ricks, T. D. Thibault, J. A. Turner, J. C. VanHeertum, and M. R. Weimer, *Pest Manage. Sci.*, 2002, **58**, 1175.
8. (a) D. Azarifar and M. Shaebanzadeh, *Molecules*, 2002, **7**, 885. (b) D. Azarifar and H. Ghasemnejad, *Molecules,* 2003, **8**, 642. (c) D. Azarifar and B. Maleki, *J. Heterocycl. Chem*., 2005, **42**, 157.
9. G. Sabitha, G. S. K. Kumar Reddy, Ch. S. Reddy, N. Fatima, and J. S. Yadav, *Synthesis*, 2003, 1267.
10. N. Nakamichi, Y. Kawashita, and M. Hayashi, *Synthesis*, 2004, 1015.
11. N. Nakamichi, Y. Kawashita, and M. Hayashi, *Org. Lett.*, 2002, **4**, 3955.
12. J. N. Shah and C. K. Shah, *J. Org. Chem.*, 1978, **43**, 1266.
13. S. P. Singh, D. Kumar, O. Prakash, and R. P. Kapoor, *Synth. Commun*., 1997, **27**, 2683.
14. W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc.*, *Chem. Commun*., 1966, 1536.
15. I. Bhatnagar and M. V. George, *Tetrahedron*, 1968, **24**, 1293.
16. L. I. Smith and K. L. Howard, *J. Am. Chem. Soc.*, 1943, **65**, 159.
17. R. P. Dodwadmath and T. S. Wheeler, *Proc. Ind. Acad. Sci.*, 1935, **2A**, 438.
18. K. Auwers and P. Heimke, *Liebigs Ann*., 1927, **458**, 186.
19. B. Han, Z. Liu, Q. Liu, L. Yang, Z. Li-Liu, and W. Yu, *Tetrahedron*, 2006, **62**, 2492.
20. F. L. Chai, Y. Zhao, O. Sheng, and Z.-O. Liu, *Tetrahedron Lett.*, 2006, **47**, 9283.
21. (a) D. Azarifar, M. A. Zolfigol, and B. Maleki, *Bull. Korean Chem. Soc.*, 2004, **25**, 23. (b) D. Azarifar, M. A. Zolfigol, and B. Maleki, *Synthesis*, 2004, 1744. (c) R. Ghorbani-Vaghei, D. Azarifar, and B. Maleki, *Bull. Korean Chem. Soc.*, 2004, **25**, 953. (d) R. Ghorbani-Vaghei, D. Azarifar, A.

Khazaei, and B. Maleki, *Phosphorus, Sulfur and Silicon*, 2004, **179**, 1877. (e) R. Ghorbani-Vaghei, D. Azarifar, and B. Maleki, *J. Chin. Chem. Soc*., 2004, **51**, 1373. (f) D. Azarifar, E. Nadimi, R. Ghorbani-Vaghei, and B. Maleki, *Mendeleev Commun*., 2006, 329. (g) D. Azarifar and B. Maleki, *Heterocycles*, 2005, **65**, 865. (h) M. A. Zolfigol, D. Azarifar, and B. Maleki, *Tetrahedron Lett.*, 2004, **45**, 2181. (i) D. Azarifar and B. Maleki, *J. Chin. Chem. Soc*., 2005, **52**, 1215. (j) D. Azarifar and A. Gharshasebi, *Heterocycles*, 2006, **68**, 1209. (k) D. Azarifar and B. Maleki, *Synth. Commun*., 2005, **35**, 2581. (l) M. A. Zolfigol, D. Azarifar, I. Mohammadpour-Baltork, S. Mallakpour, A. Forghaniha, B. Maleki, and M. Abdollahi-Alibeik, *Tetrahedron Lett.*, 2006, **47**, 833. (m) D. Azarifar and B. Maleki, *Synth. Commun*., 2005, **35**, 2581.

22. (a) A. Akdag, T. Webb, and S. D. Worley, *Tetrahedron Lett.*, 2006, **47**, 3509. (b) G. Sun and S. D. Worley, *Chem. Oxid*., 1997, 134. (c) G. Sun, W. B. Wheatly, and S. D. Worley, *Ind. Eng. Chem. Res.*, 1994, **33**, 168. (d) Y. Chen, S. D. Worley, J. Kim, C.-I. Wei, T.-Y. Chen, J. I. Santiago, J. F. Williams, and G. Sun, *Ind. Eng. Chem. Res.*, 2003, **42**, 280. (e) Y. Chen, S. D. Worley, J. Kim, C.-I. Wei, T.-Y. Chen, J. Suess, H. Kawai, and J. F. Williams, *Ind. Eng. Chem. Res.*, 2003, **42**, 5715.

23. (a) M. A. Zolfigol, G. Chehardoli, and S. Mallakpour, *Synth. Commun*., 2003, **33**, 833. (b) R. Ghorbani-Vaghei, *Tetrahedron Lett.*, 2003, **44**, 7529. (c) M. A. Zolfigol, *Tetrahedron*, 2001, **57**, 9509.