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Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsrt20

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Majid M. Heravi [a] , Vahideh Zadsirjan [a] , Khadijeh Bakhtiari [a] & Fatemeh F. Bamoharram [b]
[a] Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran
[b] Department of Chemistry, Islamic Azad University -Mashhad Branch, Mashhad, Iran

Accepted author version posted online: 12 Nov 2012.

To cite this article: Majid M. Heravi , Vahideh Zadsirjan , Khadijeh Bakhtiari & Fatemeh F. Bamoharram (2012): One-pot, Three Component Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles Catalyzed by Heteropolyacid, Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry, DOI:10.1080/15533174.2012.740718

To link to this article: http://dx.doi.org/10.1080/15533174.2012.740718

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One-pot, Three Component Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles Catalyzed by Heteropolyacid

Majid M. Heravi,*[1] Vahideh Zadsirjan,[1] Khadijeh Bakhtiari,[1] and Fatemeh F. Bamoharram[2]

[1] Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran

[2] Department of Chemistry, Islamic Azad University -Mashhad Branch, Mashhad, Iran

$H_6[PMo_9V_3O_{40}]$ was used as an efficient catalyst for the preparation of 1-aroyl-2-arylidene hydrazines. 2,5-Disubstituted 1,3,4-oxadiazoles have been synthesized by oxidation of 1-aroyl-2-arylidene hydrazines with CrO_3 in excellent yields.

Keywords 2,5-Disubstituted 1,3,4-oxadiazoles, $H_6[PMo_9V_3O_{40}]$, Vanadium mixed addenda heteropolyacid. Click reaction.

INTRODUCTION

1,3,4-oxadiazoles have emerged as an important class of heterocycles that have attracted significant pharmaceutical and biological properties such as anti-inflammatory, anticonvulsant, analgesic activities,[1] antibacterial[2] and muscle relaxant properties.[3] A wide variety of methods for the preparation of 1,3,4-oxadiazoles have been classified according to starting compounds. The common route for the synthesis of these compounds involves cyclization of diacylhydrazines with a variety of dehydrating reagents.[4-11] They have also been prepared by oxidation of acylhydrazones with different oxidizing agents.[12-14] One-pot synthesis of 1,3,4-oxadiazoles from acid hydrazides and hydrazine with an acid chloride,[15,16] as well as from

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* Corresponding mmh1331@yahoo.com; Tel: 0098-21-88044051; Fax: 0098-21-88041344.

hydrazines with carboxylic acids,[17] have also been reported in the literature. Recently, solid phase syntheses of these compounds under mild conditions were also reported.[18-21]

Heteropolyacids, HPAs, catalyze a wide variety of reactions in homogeneous or heterogeneous (liquid-solid, gas-solid or liquid-liquid biphasic) systems, offering strong options for more efficient and cleaner processing compared to conventional mineral acids.[22-25]

Being stronger acids, heteropoly acids will have significantly higher catalytic activity than conventional catalysts such as mineral acids, mixed-oxides, zeolites etc. In particular, in organic media the molar catalytic activity of heteropoly acid is often 100-1000 times higher than that of H_2SO_4.[24, 25]

The Keggin–type HPAs typically represented by the formula $H_{8-x}[XM_{12}O_{40}]$, when X is the heteroatom (most frequently P^{+5} or Si^{+4}), x is the oxidation state, and M is the addenda atom (usually W^{+6} or Mo^{+6}), are the most important for catalysis.[22-25] They have been widely used as acid and oxidation catalysts for organic synthesis and found several industrial applications.

We have been interested in the synthesis of heterocyclic compounds,[26-28] for several years, and the application of heteropoly anions in organic synthesis,[29-31] Herein, we wish to report the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **(2)** via oxidation of 1-aroyl-2-arylidene hydrazines **(1)** with CrO_3 in very good yields. The efficient route is outlined in Scheme 1. As shown, 1-aroyl-2-arylidene hydrazines **(1)** were obtained from the reaction of aryl hydrazide and various aldehydes in the presence of a catalytic amount of vanadium mixed addenda heteropoly acid. Under these conditions 1-aroyl-2-arylidene hydrazines **(1)** were obtained as sole products.

EXPERIMENTAL

Materials and Methods

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. All products were characterized by spectra and physical data.

Preparation of 1-aroyl-2-arylidene hydrazines (1): General procedure

A mixture of 1mmol aldehyde, 1 mmol acid hydrazide, and $H_6[PMo_9V_3O_{40}]$ (2mol%), in 3 mL acetic acid was refluxed for appropriate time; after completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature. The catalyst was filtered off. The filtrate was successively diluted with 5% $NaHCO_3$ (5 mL) and extracted with diethyl ether (2×5 mL). The combined organic layers then washed with brine (2×5 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the pure product was obtained by recrystallization from the suitable solvent. The products **(1)** were identified by comparison with authentic samples by TLC, ^{1}H NMR and IR spectroscopy.

Preparation of 2,5-disubstituted 1,3,4-oxadiazoles: General procedure

A mixture of 1mmol 1-aroyl-2-arylidene hydrazines **(1)** and 1mmol CrO_3 was refluxed in acetic acid for appropriate time. After completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature. The catalyst was filtered off. The filtrate was successively diluted with 5% $NaHCO_3$ (5 mL) and extracted with diethyl ether (2×5 mL). The combined organic layers then washed with brine (2×5 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the pure product was obtained by recrystallization from EtOH. The products (1) were identified by comparison with authentic samples by TLC, ^{1}H NMR and IR spectroscopy.

One-pot preparation of 2,5-disubstituted 1,3,4-oxadiazoles: General procedure

A mixture of aldehyde (1mmol), acid hydrazide (1 mmol), and $H_6[PMo_9V_3O_{40}]$ (2mol%), in acetic acid (3 mL) was refluxed for appropriate time; after forming of 1-aroyl-2-arylidene hydrazines **(1)** as intermediate, which was monitored by TLC, CrO_3 was added to the mixture and refluxed in the same condition. Upon completion of the reaction the mixture was cooled to room temperature. The catalyst and oxidant were filtered off. The filtrate was successively diluted with 5% $NaHCO_3$ (5 mL) and extracted with diethyl ether (2×5 mL). The combined organic layers then washed with brine (2×5 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the pure product was obtained by recrystallization from the suitable solvent. The products **(2)** were identified by comparison with authentic samples by TLC, ^{1}H NMR and IR spectroscopy.

RESULT AND DISCUSSION

At first, the synthesis of 1,3,4-oxadiazoles was investigated through a two-step pathway. For optimization of the reaction conditions, the reaction of $PhCONHNH_2$ (1mmol) with benzaldehyde (1mmol) in different solvents under reflux conditions in the presence of a catalytic amount of vanadium mixed addenda heteropolyacid was studied (Scheme 1, Step 1). The results are summarized in Table 1. Acetic acid was found to be a good solvent for this reaction. In this stage, 1-aroyl-2-arylidene hydrazines **(1)** were obtained in very good yields in the presence of $H_6[PMo_9V_3O_{40}]$ as catalyst.

To show the merits of our catalyst, the above reaction was also carried out in the absence of $H_6[PMo_9V_3O_{40}]$. As can be seen in Table 1, no product was obtained even after long time reaction.

These products were known and characterized by comparison of their spectral and physical data with those already reported. The results are shown in Table 2.

One of the important factors affecting the oxidation capacity of polyanions is the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied orbital (LUMO). It should be noted that all of the HOMOs and LUMOs of the polyoxoanions have very high energy levels (3.0-9.0 and 6.0-12.0 eV, respectively) because of their large negative charges. It is well known that these highly charged heteropolyanions do not exist in the gas phase and that the external field generated by the solvent and the counterions is crucial to stabilize them. Keep in mind that the heteropolyanions are easily reducible chemical species, and thus the energy of the LUMO must be sufficiently low to accept the incoming electron in catalytic reactions. The solvent molecules in dilute solutions stabilize these anions and place these molecular orbitals at the appropriate level. Moreover, the metal substitution may modify the energy and composition of the LUMO and thus also the redox properties of the cluster.[32]

Subsequently, compound **(1)** underwent oxidative cyclization using CrO_3 under reflux condition. (Scheme 1, Step 2) 2,5-Disubstituted 1,3,4-oxadiazoles were obtained in high yields within 3-7h.

Then, we decided to carry out the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles in a one-pot manner without isolation of compound **(1)** as intermediate. For this purpose, at the end of step 1 which monitored by TLC, CrO_3 was added to the mixture and refluxed in the same condition for the appropriate time. After completion of the reaction the products were isolated and identified by comparison of their spectra and physical data with those reported in the literature.

In order to show the general applicability of the protocol, we have applied this catalytic system for the preparation of a variety of 2,5-disubstituted 1,3,4-oxadiazoles from different hydrazides and aldehyde derivatives in acetic acid. We found that the reaction proceeds very efficiently with benzaldehyde and electron-withdrawing and electron-donating substituted benzaldehydes. The results are summarized in Table 3.

In conclusion, we have found an efficient route for the synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles in very good yields in the presence of $H_6[PMo_9V_3O_{40}]$ as catalyst and CrO_3 as oxidant.

Since the reaction proceeds rapidly and selectively under relatively mild condition using green catalyst in a one pot reaction, giving covalently link components of oxadiazoles, it can be considered as a click reaction.

Acknowledgments

MMH is thankful to the Iran National Science Foundation for partial financial support.

REFRENCES

1. Palaska, E., Sahin, G., Kelicen, P., Tugbadurlu, N., and Altinok, G. *IL Farmaco*, **2002**, 57, 101-107.
2. Angelini, I., Angelini, L., and Sparaco, F. *Brit. Pat.* 1.161.801, 1966/1969, *Chem Abstr*, **1969**, 71, 112937.

3. Yale, H.L., and Losee, K.A**.** 2-Amino-5-substituted 1,3,4-oxadiazoles and 5-imino-2-substituted Δ^2-1,3,4-oxadiazolines. A Group of novel muscle relaxants. *J. Med. Chem.*, **1966**, 9, 478-483.
4. Kerr, V.N., Ott, D.G., and Hayes, F.N. Quaternary salt formation of substituted oxazoles and thiazoles. *J. Am. Chem. Soc*., **1960**, 82, 186-189.
5. Al-Talib, M., Tastoush, H., and Odeh, N.A. A convenient synthesis of alkyl and aryl substituted bis-1,3,4-oxadiazoles. *Synth. Commun*., **1990**, 20, 1811-1817.
6. Carlsen, P.H.J., and Jorgensen, K.B. Synthesis of unsymmetrically substituted 4H-1,2,4-triazoles. *J. Heterocycl. Chem*., **1994**, 31, 805-807.
7. Klinsberg, E. Synthesis of carboxylic acid hydrazides and s-triazoles of the anthraquinone series. *J. Am. Chem. Soc*., **1958**, 80, 5786-5789.
8. Liras, S., Allen, M.P., and Segelstein, B.E.A. A mild method for the preparation of 1,3,4-oxadiazoles: Triflic anhydride promoted cyclization of diacylhydrazines. *Synth. Commun*., **2000**, 30, 437-443.
9. Brown, P., Best, D.J., Broom, N.J.P., Cassels, R., Bhanlon, P.J., Mitchell, T.J., sborne, N.F., and Wilson, J.M. The chemistry of Pseudomonic Acid. 18. Heterocyclic replacement of the α,β-unsaturated ester: Synthesis, molecular modeling, and antibacterial activity. *J. Med. Chem*., **1997**, 40, 2563-2570.
10. Tully, W.R., Gardner, C.R., Gillespie, R.J., and Westwood, R. 2-(oxadiazolyl)- and 2-(thiazolyl)imidazo[1,2-a]pyrimidines as agonists and inverse agonists at benzodiazepine receptors. *J. Med. Chem*., **1991**, 34, 2060-2067.

11. Short, F.W., and Long, L.N. Synthesis of 5-aryl-2-oxazolepropionic acids and analogs. Antiinflammatory agents. *J. Heterocycl. Chem.*, **1969**, 6, 707-712.
12. Balachandran, K.S., and George, M.V. Oxidation with metal oxides-VI: Oxidation of benzoylhydrazones of aldehydes, ketones and 1,2-diketones with nickel peroxide. *Tetrahedron*, **1973**, 29, 2119-2128.
13. Chiba, T., and Okimoto, M. Electrooxidative cyclization of N-acylhydrazones of aldehydes and ketones to Δ^3-1,3,4-oxadiazolines and 1,3,4-oxadiazoles. *J. Org. Chem.*, **1992**, 57, 1375-1379.
14. Yang, R., and Dai, L. Hypervalent iodine oxidation of N-acylhydrazones and N-phenylsemicarbazone: an efficient method for the synthesis of derivatives of 1,3,4-oxadiazoles and Δ^3-1,3,4-oxadiazolines. *J. Org. Chem.*, **1993**, 58, 3381-3383.
15. Tandon, V.K., and Chhor, R.B. An Efficient one pot synthesis of 1,3,4-oxadiazoles. *Synth. Commun.*, **2001**, 31, 1727-1732.
16. Mashraqui, S.H., Ghadigaonkar, Sh.G., and Kenny, R.S. An expeditious and convenient one pot synthesis of 2,5-disubstituted-1,3,4-oxadiazoles. *Synth. Commun.*, **2003**, 33, 2541-2545.
17. Bentiss, F., Lagrenee, M., and Barbry, D. Rapid synthesis of 2,5-disubstituted 1,3,4-oxadiazoles under microwave irradiation. *Synth. Commun.*, **2001**, 31, 935-938.
18. Brown, B.J., Clemens, I.R., and Neesom, J.K. Diisopropylcarbodiimide: A novel reagent for the synthesis of 1,3,4-oxadiazoles on solid-phase. *Synlett*, **2000,** 131-133.
19. Brain, C.T., and Brunton, Sh.A. Synthesis of 1,3,4-oxadiazoles using polymer supported reagents. *Synlett*, **2001**, 382-384.

20. Brain, C.T., Paul, J.M., Loong, Y., and Oakley, P.J. Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using polymer-supported Burgess reagent under microwave conditions. *Tetrahedron Lett*., **1999**, 40, 3275-3278.
21. Wipf, P., and Venkatraman, S. An improved protocol for azole synthesis with PEG-supported Burgess reagent. *Tetrahedron Lett*., **1996**, 37, 4659-4662.
22. Izumi, Y., Urabe, K., and Onaka, M. *Zeolite Clay and heteropoly acid in organic Reactions,* Kodansha/VCH, Tokyo. **1992**.
23. Misono, M. Unique acid catalysis of heteropoly compounds (heteropolyoxometalates) in the solid state. *Chem. Commun*., **2001**, 1141-1152.
24. Kozhevnikov, I.V. Catalysis by heteropoly acids and multicomponent polyoxometalates in liquid-phase reactions. *Chem. Rev*., **1998**, 98, 171-198.
25. Kozhevnikov, I.V. *Catalysts for fine chemicals, in: Catalysis by Polyoxometalates,* vol 2, Wiely, Chichester. **2002**.
26. Heravi, M.M., Rahimzadeh, M., Bakavoli, M., and Ghassemzadeh, M. Pd–Cu catalyzed heterocyclization during Sonogashira coupling: synthesis of 3-benzylthiazolo[3,2-a]benzimidazole. *Tetrahedron Lett*., **2004**, 45, 5747-5749.
27. Heravi, M.M., Rahimzadeh, M., Bakavoli, M., and Ghassemzadeh, M. Regioselective synthesis of 6-benzylthiazolo[3,2-b]1,2,4-triazoles during Sonogashira coupling. *Tetrahedron Lett*., **2005**, 46, 1607-1610.
28. Heravi, M.M., Tajbakhsh, M., Ahmadi, A.N., and Mohajerani, B. Zeolites efficient and eco-friendly catalysts for the synthesis of benzimidazoles. *Monatsh. Chem*., **2006**, 137, 175-179.

29. Heravi, M.M., Bakhtiari, K., and Bamoharram, F.F. An efficient and chemoselective synthesis of acylals from aromatic aldehydes and their regeneration, catalyzed by 12-molybdophosphoric acid. *Catal. Commun.*, **2006**, 7, 499-501.
30. Heravi, M.M., Bakhtiari, K., and Bamoharram, F.F. 12-Molybdophosphoric acid: A recyclable catalyst for the synthesis of Biginelli-type 3,4-dihydropyrimidine-2(1*H*)-ones. *Catal. Commun.*, **2006**, 7, 373-376.
31. Bamoharram, F.F., Heravi, M.M., Roshani, M., Jahangir, M., and Gharib, A. Preyssler catalyst, $[NaP_5W_{30}O_{110}]^{14-}$: A green, efficient and reusable catalyst for esterification of salicylic acid with aliphatic and benzylic alcohols. *Applied Catal. A*: *Gen.*, **2006,** 302, 42-47.
32. Wang, J., Hu, Ch., Jiana, M., Zhang, J. and Li, G. Catalytic oxidation performance of the α-Keggin-type vanadium-substituted heteropolymolybdates: A density functional theory study on $[PV_nMo_{12-n}O_{40}]^{(3+n)-}$ (n = 0–3). *J. Catal.*, **2006**, 240, 23–30.
33. Grekov, A.P., and Kulakova, L.N.Zh. *Obshch. Khim.*, **1959**, 29, 3054, *Chem Abstr*, **1960**, 54, 13108g.
34. Rao, V.S., and Chandra Sekhar, K.V.G. Iodobenzene diacetate mediated solid state synthesis of heterocyclyl 1,3,4-oxadiazoles. *Synth. Commun.*, **2004**, 34, 2153-2157.

35. Gilbert, E.C. The molecular rearrangment of some new unsymmetrical hydrazines. *J. Am. Chem. Soc.*, **1927**, 49, 286-292.
36. Rostamizadeh, S., and Housaini, S.A. G. Microwave assisted synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. *Tetrahedron Lett.*, **2004**, 45, 8753-8756.
37. Dabiri, M., Salehi, P., Baghbanzadeh, M., and Bahramnejad, M. A facile procedure for the one-pot synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles. *Tetrahedron Lett.*, **2006**, 47, 6983-6986.

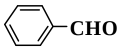
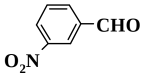
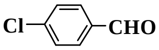
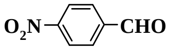
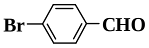
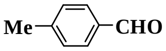
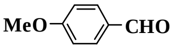
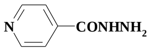
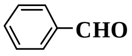
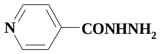
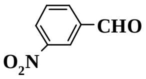
TABLE 1.

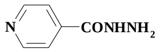
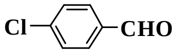
Synthesis of 1-aroyl-2-arylidene hydrazines **(1)** at different conditions

Entry	**Catalysis**	**Solvent**	**Time (h)**	**Yield (%)**
1	$H_5[PMo_{10}V_2O_{40}]$ (2 mol%)	CH_3COOH	2.15	60
2	$H_6[PMo_9V_3O_{40}]$ (2 mol%)	C_2H_5OH	2	49
3	$H_6[PMo_9V_3O_{40}]$ (2 mol%)	$PhCH_3$	2.5	42
4	$H_6[PMo_9V_3O_{40}]$ (2 mol%)	CH_3COOH	1.15	94
5	$H_6[PMo_9V_3O_{40}]$ (2 mol%)	Ac_2O	1.45	70
6	-	CH_3COOH	24	Trace
7	-	$PhCH_3$	24	Trace
8	-	C_2H_5OH	24	-

TABLE 2.

Synthesis of 1-aroyl-2-arylidene hydrazines **(1)**

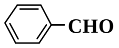
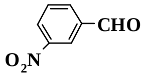
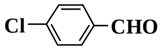
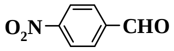
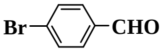
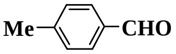
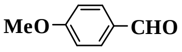
Entry	**Hydrazide**	**aldehyde**	**Time (min)**	**Yield (%)[a]**	**m.p. (°C) Found**	**Reported**
1	**$PhCONHNH_2$**		75	89	202	203-205[37]
2	**$PhCONHNH_2$**		80	88	187	188 [37]
3	**$PhCONHNH_2$**		85	88	219	218-220 [35]
4	**$PhCONHNH_2$**		80	91	239	240-242 [35]
5	**$PhCONHNH_2$**		76	90	224	225 [36]
6	**$PhCONHNH_2$**		74	89	216	217 [35]
7	**$PhCONHNH_2$**		80	88	146	145 [35]
8	**$PhCONHNH_2$**	**CH_3CHO**	75	87	225	224 [36]
9			77	91	160	159[34]
10			75	90	268	267[34]

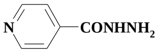
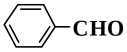
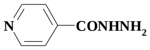
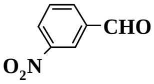
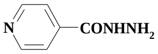
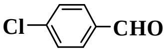
11			80	91	211	210 [34]

a) Yields refer to isolated products.

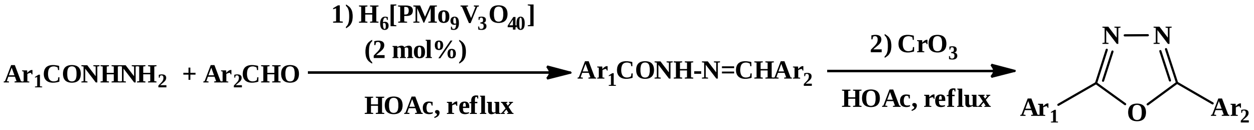
TABLE 3.

Synthesis of 2,5- disubstituted 1,3,4- oxadiazoles in a one-pot reaction

Entry	Hydrazide	aldehyde	Time (h)	Yield (%)^a	m.p. (^{o}C) Found	Reported
1	$PhCONHNH_2$		6	89	139	139-140 [14]
2	$PhCONHNH_2$		6.5	90	145	143-146 [14]
3	$PhCONHNH_2$		5	89	161	160-162 [14]
4	$PhCONHNH_2$		7	90	203	202-204 [14]
5	$PhCONHNH_2$		4.5	88	166	167[33]
6	$PhCONHNH_2$		3.5	87	147	145-146 [14]
7	$PhCONHNH_2$		3	88	149	149-151[14]
8	$PhCONHNH_2$	CH_3CHO	4	87	68	67 [36]

9			6	90	152	153 [34]
10			5	89	120	125 [34]
11			4	91	170	168-170 [34]

a) Yields refer to isolated products.



(1)

(2)

SCHEME 1.