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Solvent-free 조건하에서 $H_3PMo_{12}O_{40}$ 촉매에 의한 Z-Aldoximes의 위치특이적 합성

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Regioselective Synthesis of Z-Aldoximes Catalyzed By $H_3PMo_{12}O_{40}$ under Solvent-Free Conditions

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요 약. Z-aldoximes의 제법을 위한 쉽고 효과적인 이 방법은 solvent-free하에서 $H_3PMo_{12}O_{40}$ 촉매를 사용해서 개선되었다. 이 방법의 큰 이점은 조작의 간편성, 더 작은 촉매량, 선택성, 온화한 반응조건,짧은 반응 시간 그리고 높은 수율이다. 재생된 촉매는 어떤 정제도 없이 다시 사용되어질 수 있다.

주제어: Heteropoly acids, Aldehydes, Z-aldoximes, Solvent-free 조건

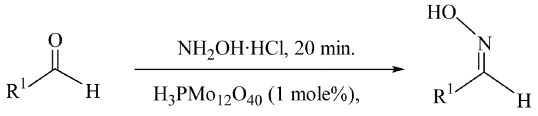
ABSTRACT. A facile and efficient method for the preparation of *Z*-aldoximes is improved by means of $H_3PMo_{12}O_{40}$ catalyst in solvent-free media. The major advantages of this method are: operational simplicity, low catalyst loading, selectivity, mild reaction conditions, short reaction times and excellent yields. The recovered catalyst could be used in new attempts without any purification.

Keywords: Heteropoly Acids, Aldehydes, Z-Aldoximes, Solvent-Free Conditions

INTRODUCTION

Oximes are useful for the isolation, purification and characterization of carbonyl compounds.[1-3] These compounds not only represent a convenient series of derivatives of carbonyl compounds but also may be used as intermediates for the preparation of amides by the Beckmann rearrangement,[4] amines,[5] nitrones,[6] hydroxyiminoyl chlorides,[7] nitriles,[8] nitrile oxides,[7] and chiral α-sulfinyl oximes.[9] The usual method for the preparation of oximes involves treatment of carbonyl compounds with hydroxylamine hydrochloride in a basic aqueous medium with adjustment of pH.[10] Chemical methods for the synthesis of oximes usually give a mixture of the two geometrical isomers (*Z* and *E*), which have different physical properties and biological activities[11] and must be separated by chromatography or recrystallization techniques. In the second step of Beckmann rearrangement mechanism, conversion should take place by the migration of an *anti* group. Whereas, usually the more bulky group has migrates. However, the oxime formation or Beckmann rearrangement reagents also catalyze interconversion of the *Z* and *E* geometrical isomers of oximes.[12] The rate of equilibration of a mixture of *Z* and *E* isomers and the position of the equilibrium is temperature dependent.[12a] Recently, Liu *et al*.,[13] reported that this inter-conversion is also solvent dependent therefore; solvent and temperature control are critical.

A few methods are available of the synthesis of *Z* and *E* isomer of aldoximes.[14-15] In many cases, *E*



Scheme 1.

isomers were obtained from the *Z* forms by either the hydrochloride salt method[16] or by column chromatography.[17] Recently, it has been shown that molecular sieve 3Å[18] and the silicaphos (P_2O_5/SiO_2)[19] can catalyze the stereoselective oxime formation. Thus, there is considerable interest in finding more selective methods for oximes synthesis.

We now report a very simple and efficient method for the selective preparation of *Z*-oximes from aldehydes and hydroxylamine hydrochloride using the $H_3PMo_{12}O_{40}$ (a Heteropolyacid as catalyst) in solvent-free conditions (*Scheme* 1). Heteropolyacids (HPAs) are useful and versatile to a number of transformations because of their redox and superacidic properties.[20] HPAs are promising solid acids to replace environmentally harmful liquid acid catalysts, such as H_2SO_4.[20-21] The keggin-type HPAs, are the most important catalysts, especially $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, and $H_4SiW_{12}O_{40}$.[22] These are easily available, cheap, simply decanted from the reaction mixture and reusable.

RESULTS AND DISCUSSION

In order to determine the most appropriate reaction conditions and evaluate the catalytic efficiency of $H_3PMo_{12}O_{40}$ catalyst, initially a model study was carried out on the synthesis of benzaldoxime (*Table* 1). Among the tested solvents such as CH_3OH, DMF, CH_3CN, CH_2Cl_2 and solvent-free system, condensation of benzaldehyde and hydroxylamine hydrochloride was more facile and proceeded to gave highest yield, under solvent free conditions (*Table* 1, Entry 6). Interestingly, it was found to be HPA with low loading (1 mole%) is an efficient catalyst and gave exclusively benzaldoxime in 95% yield in 15 min under solvent free conditions. In lower catalyst loading the conversion and isolated yields are decreased (*Table* 1, Entries 11 and 12). However,

Table 1. Synthesis of Bezaldoxime Using $H_3PMo_{12}O_{40}$ Catalyst in the Different Conditions

Entry	Catalyst (mole%)	Reaction conditions	Yield (%)	
			Conversion[a]	Isolated
1	1	CH_2Cl_2, 6 h, reflux	80	59
2	1	CH_3OH, 6 h, reflux	90	65
3	1	CH_3CN, 6 h, reflux	85	65
4	1	DMF, 6 h, reflux	95	85
5	2	Solvent-free, r.t., 10 min.	100	98
6	1	Solvent-free, r.t., 15 min.	100	95
7[b]	1	Solvent-free, r.t., 15 min.	100	94
8[c]	1	Solvent-free, r.t., 20 min.	100	92
9[d]	1	Solvent-free, r.t., 20 min.	95	92
10[e]	1	Solvent-free, r.t., 20 min.	95	90
11	0.50	Solvent-free, r.t., 15 min.	90	81
12	0.25	Solvent-free, r.t., 15 min.	60	42

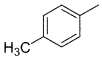
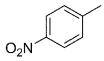
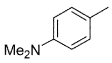
[a]TLC Yields. [b-e]Refer to the recycling of catalyst in new subsequent runs.

oximation of benzaldehyde with hydroxylamine hydrochloride in the absence of catalyst did not occur even under extension of reaction time to one hour, and unreacted benzaldehyde was completely recovered. Furthermore, the use of 1 mole% of catalyst is sufficient to promote the reaction and no other additives are required for this conversion. The HPA catalyst was easily recovered and reused for the next set of oximation reactions without significant decrease in activity even after five runs (*Table* 1, Entries 6-10).

In order to evaluate the generality of the process, various aldehydes were ground with hydroxylamine hydrochloride in the presence of a catalytic amount of the $H_3PMo_{12}O_{40}$ (1 mole%) in solvent-free media. In this approach, corresponding *Z*-aldoximes were obtained in quantitative yield. The general reaction is illustrated according to the *Scheme* 1 and the results have been reported in *Table* 2. All reactions were performed in less than 20 minutes. As shown in the *Table* 2 the reaction of hydroxylamine hydrochloride with different aromatic aldehydes, including those with electron withdrawing and donating substituents in the presence of this catalyst, gave *Z*-aldoximes in high yield and stereoselectivity.

The purity of the products was determined by ^1H NMR and IR spectra, which showed the exclusive

Table 2. Conversion of Aldehydes into *Z*-Aldoximes in the Presence of $H_3PMo_{12}O_{40}$

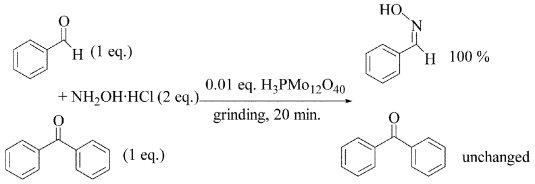
Entry	*Z*-Aldoximes	Yield [a,b]	^{1}H chemical shift of	mp (°C)	
	R[1]	(%)	C(H)=N group	Found	Reported [ref]
1		95	8.15	119	120 [14]
2		94	8.47	89	88-90 [19]
3		90	8.10	71	72 [14]
4		75	8.20	98	100 [14]
5		88	8.20	120	121-3 [23]
6		80	8.10	144	146 [14]
7		85	8.10	138	138 [19]
8		78	8.10	92	94 [19]
9		75	8.10	117	116 [19]

[a]Isolated yield. [b]All the compounds give satisfactory spectral analysis (IR and ^{1}H NMR).

formation of the corresponding *Z*-aldoximes whose structure was confirmed by melting points comparison. In all the ^{1}H-NMR spectra ($CDCl_3$, 25 ºC), the OH group of aldoximes appeared around 8-10 as a broad singlet and in IR spectra the OH and C=N groups were observed around 3200-3500 and 1605-1660 cm^{-1}, respectively. The *Z*-stereochemistry of the products was determined from the ^{1}H-chemical shift[14] of the C(H)=N group which appeared around 8-8.5 as a singlet (*Table* 2).

A well known general method[16] was chosen to confirm the *Z*-aldoxime configuration. *Z*-Aromatic aldoximes are known to convert readily to their *E*-isomers especially in dilute acid condition. We have examined such a conversion in the cases of *Z*-*p*-chlorobenzaldoxime and *Z*-*p*-nitrobenzaldoxime. Complete conversion was occurred on standing in the presence of 15 mole% of hydrochloric acid in aqueous ethanol. These *Z*-aldoximes by melting points, 144 ºC and 98 ºC, were converted to the corresponding *E*-aldoximes by melting points 107ºC and 120 ºC, respectively. Thus, the *E*-aldoximes structures were confirmed by melting points comparison with literature.[14,16] By comparison of ^{1}H NMR of these isomers, we have observed that the C(H) =N signal in 8.20 and 8.36 have disappeared in the *Z*-aldoximes and the new signal for *E*-aldoximes appeared in 7.30 and 7.60 ppm, respectively. TLC examination showed that the *Z*-aldoxime gave only one spot which had a lower R_f value than the *E*-aldoxime. Also, we only detected and isolated the *Z*-aromatic aldoximes according to TLC examination and melting point comparison.

Of greater significance, we found that, whereas all of the preparation of the oximes in the presence of Lewis or Brönsted acids require an acidic work up, the HPA work up is a simple washing the mixture by inert solvent. However, the effects of hydrochloric acid[16] or solvent[13] for interconversion of *Z* and *E* isomers are ruled out for our solvent-free procedure. We suggested that the regioselective formation of *Z*-aldoximes attributed to the bulky super



Scheme 2.

acid behavior of HPA catalyst.

When the reaction was carried out using aliphatic aldehydes such as octanal and phenylacetaldehyde, the conversion is low and a mixture of *E* and *Z* isomers was obtained. However, ketones such as benzophenone, acetophenone and cyclohexanone did not afford the corresponding oximes under these conditions. In order to show chemoselectivity of the presented reagent, a mixture of one equivalent of aldehyde and one equivalent of ketone was treated with two equivalents of hydroxylamine hydrochloride in the presence of a catalytic $H_3PMo_{12}O_{40}$ at room temperature for 20 min. Only the aldehyde was selectively converted to the corresponding oxime and ketones did not react at all (*Scheme* 2). Therefore this methodology could be used selectively for the preparation of aldoximes of compounds that contain both aldehyde and ketone functional groups.

In conclusion, the reported procedure is an easy and novel method for the preparation of aldoximes in solvent-free media. In addition, this catalyst affords various aldoximes in a shorter reaction time (20 min), in good to excellent yields (85-95%), and high stereoselectivities (*Z*-isomers). Also, catalyst loading is low (1 mole%) and easily isolated from reaction mixture and can be reused for several times.

EXPERIMENTAL SECTION

Starting materials were obtained from Fluka (Buchs, Switzerland) Company. Products are known compounds and were characterized by comparison of their spectral data (IR and ^{1}H NMR) and physical properties with those reported in the literature.[14,19,23] IR spectra were recorded on a Shimadzu 470 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 100 and 500 MHz instruments using tetramethylsilane (TMS) as an internal standard. Progresses of the reactions were followed by TLC using silica gel Polygrams SIL G/UV 254 Sheets. All melting points recorded are uncorrected open capillary measurements. All yields refer to isolated products.

General Procedure for Preparation of *Z*-Aldoximes

In a typical reaction, a mixture of the aldehyde (2 mmol), hydroxylamine hydrochloride (4 mmol) and $H_3PMo_{12}O_{40}$·$21H_2O$ (0.02 mmol, 44 mg) was grounded thoroughly in a mortar for 15-20 minutes. Usually an immediate color change was observed. The completion of the reaction was monitored by TLC examination (CH_2Cl_2/CH_3OH, 9:1). After the completion of the reaction (20 min.), the mixture was washed with CH_2Cl_2 and filtered to remove the catalyst. The resulting solution was extracted with saturated sodium hydrogen bicarbonate solution (10 cm^3) and H_2O (2×10 cm^3). The organic layer dried over $CaCl_2$ and evaporated under vacuum to give the aldoximes in high purity (based on TLC, ^{1}H NMR, and IR). The structures of the products were confirmed by the melting points and ^{1}H NMR comparisons.[14,19,23]

^{1}H NMR data of products(100 MHz, $CDCl_3$, 25 °C):

Compounds **1**: δ 10.15 (bs, 1H, =NOH), 8.20 (s, 1H, CH=N), 7.30-7.60 (m, 5H, ArH). **2** (500 MHz, $CDCl_3$, 25 °C): δ 8.82 (bs, 1H, =NOH), 8.47 (s, 1H, CH=N), 7.64 (dd, 1H, ArH, J=7.6, 1.5 Hz), 7.35 (dt, 1H, ArH, J=7.7, 1.5 Hz), 6.96 (t, 1H, ArH, J= 7.5 Hz), 6.92 (d, 1H, ArH, J=8.3 Hz), 3.89 (s, 3H, CH_3). **3**: δ 8.10 (s, 1H, CH=N), 8.05 (bs, 1H, =NOH), 7.47 (d, 2H, ArH, J=8.0 Hz), 7.20 (d, 2H, ArH, J=8.0 Hz), 2.37 (s, 3H, CH_3). **4**: δ 10.20 (bs, 1H, =NOH), 8.36 (s, 1H, CH=N), 8.00-8.45 (m, 3H, ArH), 7.75 (d, 1H, ArH, J=8.0 Hz). **5**: δ 10.15 (bs, 1H, =NOH), 8.43 (d, 1H, ArH, J=2 Hz), 8.23 (dd, 1H, ArH, J=8.0, 1.5 Hz), 8.15 (s, 1H, CH=N), 7.90 (dd, 1H, ArH, J=8.0, 1.5 Hz), 7.55 (t, 1H, ArH, J=8.0 Hz). **6**: δ 9.98 (bs, 1H, =NOH), 8.20 (s, 1H, CH=N), 7.35-7.60 (m, 4H, ArH). **7**: δ 9.75 (bs, 1H, =NOH), 8.10 (s, 1H, CH=N), 7.75 (d, 2H, ArH, J=8.0 Hz), 6.65 (d, 2H, ArH, J=8.0 Hz), 3.0 (s, 6H, CH_3). **8** δ 8.20 (s, 1H, CH=N), 7.55 (d, 2H, ArH, J=8.5 Hz), 6.90

(d, 2H, ArH, J=8.5 Hz), 5.75 (bs, 2H, =NOH and ArOH). **9**: δ 9.85 (bs, 1H, =NOH), 8.10 (s, 1H, CH=N), 7.30-7.50 (m, 2H, ArH), 7.0 (d, 1H, ArH, J=8.0 Hz), 6.33 (bs, 1H, ArOH), 3.96 (s, 3H, CH_3).

Conversion of the *Z*-Aldoximes to the *E*-Isomers

To a solution of *Z*-aldoxime (5 mmol) in 70% aqueous ethanol (40 cm^3) was added 1 M hydrochloric acid (0.75 cm^3, 15 mole%). After standing one week at room temperature, saturated aqueous sodium bicarbonate solution (2.5 cm^3) was added and the ethanol was removed under vacuum. The crude product was recrystallized from ethanol and water to give the *E*-aldoxime in high purity.

***E-p*-Chlorobenzaldoxime:** 95% yield, mp=107 °C (lit.[16] 100-105 °C) ^{1}H NMR (100 MHz, $CDCl_3$, 25 °C: δ 10.40 (bs, 1H, =NOH), 8.00 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.30 (s, 1H, CH=N).

***E-p*-Nitrobenzaloxime:** 90% yield, mp=120 °C (lit.[14] 120 °C) ^{1}H NMR (100 MHz, $CDCl_3$, 25 °C): δ 10.60 (bs, 1H, =NOH), 8.00-8.40 (m, 4H, ArH), 7.55(s, 1H, CH=N).

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REFERENCES

1. Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 2nd Ed. Wiley, New York, U. S. A.,1999; p 24.
2. Hajipour, A. R.; Khoee, S.; Ruoho, A. E. *Org. Prep. Proced. Int.* **2003**, *35*, 527.
3. Eshghi, H.; Hassankhani, A. *Org. Prep. Proced. Int.* **2005**, *37*, 575.
4. (a) Donaruma, L. G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1; (b) Eshghi, H.; Gordi, Z. *Synth. Commun.* **2003**, *33*, 2971; (c) Eshghi, H.; Hassankhani, A. *J. Korean Chem. Soc.* **2007**, *51*, 361.
5. Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2005**, *52*, 109.
6. (a) Smith, P. A.; Robertson, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 1197; (b) Bucher, E. *J. Org. Chem.* **1967**, *32*, 261; (c) Schoenewaldt, E. F.; Kinnel, R. B.; Davis, P. *J. Org. Chem.* **1968**, *33*, 4270.
7. (a) Chiang, Y. H. *J. Org. Chem.* **1971**, *36*, 2146; (b) Liu, K. C.; Shelton, B. R.; How, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
8. Eshghi, H.; Gordi, Z. *Phosphorus, Sulfur, Silicon* **2005**, *180*, 619.
9. Hajipour, A. R.; Mahboubghan, N. *J. Chem. Res. (S)* **1998**, 122.
10. Finar, I. J.; Lord, G. H. *J. Chem. Soc*. **1957**, 3314.
11. (a) Burakevich, J. V.; Lore, A. M.; Volpp, G. P. *J. Org. Chem*. **1971**, *36*, 1; (b) Brandt, U.; Von Jagow, G. *FEBS Lett.* **1991**, *287*, 215; (c) Tecie, H.; Lauffer, D. J.; Mirzadegan, T.; Moos, W. H.; Moreland, D. W.; Pavia, M. R.; Schwarz, R. D.; Davis, R. E. *Life Sci.* **1993**, *52*, 505.
12. (a) Smith, P.A. S.; Antoniades, E. P. *Tetrahedron* **1960**, *9,* 210; (b) Kusama, H.; Yamashita, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68,* 373; (c) Narasaka, K.; Kusama, H.; Yamashita Y.; Sato, H. *Chem. Lett.* **1993**, 489; (d) Uno, T.; Gong, B.; Schultz, P. G. *J. Am. Chem. Soc.* **1994**, *116,* 1145.
13. Xu, W.; Wang, J.; Liu, C.; Chen, C.-L. *J. Chin. Chem. Soc.* **2004**, *51,* 1259.
14. Sharghi, H.; Sarvari, M. H. *Synlett* **2001**, 99.
15. Zvilichovsky G.; Heller, L. *Synthesis* **1972**, 563.
16. Hauser, C. R.; Hoffenberg, D. S.; *J. Org. Chem.* **1955**, *20,* 1491.
17. Vogel, A. I. *Text Book of Practical Organic Chemistry*, 4th Ed. Longman, London, 1971; p 1113.
18. Bigdeli, M. A.; Alavi Nikje, M. M.; Jafari, S.; Heravi, M. M. *J. Chem. Research (S)* **2002**, 20.
19. Eshghi, H.; Gordi, Z. *Phosphorus, Sulfur, Silicon* **2005**, *180*, 1553.
20. (a) Alizadeh,M. H., Eshtiagh-Hosseini, H.; Khoshnavazi, R. *J. Mol. Struct*. **2004**, *688*, 33; (b) Alizadeh, M. H.; Razavi, H.; Mohammadi Zonoz, F.; Mohammadi, M. R. *Polyhedron* **2003**, *22*, 933; (c) Alizadeh, M. H.; Harmalker, S. P.; Jeanenin, Y.; Martin-Frere, J.; Pope, M. T. *J. Am. Chem. Soc.* **1985**, *107*, 2662; (d) Alizadeh, M. H.; Razavi, H.; Bamoharram, F. F.; Daneshvar, K. *J. Mol. Catal. A* **2003**, *206*, 89; (e) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98,* 171.
21. Okuhara, T.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113.
22. (a) Moffat, J. B. *Metal-Oxygen Clusters: The Surface and Catalytic Properties of Heteropoly Oxometalates*, Kluwer, New York, 2001; (b) Firozabadi, H. Jafari, A. A. *J. Iran. Chem. Soc.* **2005**, *2*, 85.
23. Dalton, D. R.; Foley, H. G. *J. Org. Chem.* **1973**, *38*, 4200.