Iranian Journal of Catalysis 5(2), 2015, 123-127

IRANIAN JOURNAL OF CATALYSIS

Phospho sulfonic acid: an efficient solid acid catalyst for the facile preparation of 1,4-dihydropyridines

Sobhan Rezayati*, Parisa Javanmardi

Department of Chemistry, Payame Noor University, P.O. BOX 19395-4697 Tehran, Iran.

Received 24 May 2014; received in revised form 12 October 2014; accepted 25 October 2014

ABSTRACT

A simple and mild one-pot three-component reaction for the preparation 1,4-dihydropyridines has been developed from various aldehyde substrates, 1,3-dicarbonyl compounds (dimedone) and ammonium acetate (Hantzsch method) in the presence of a catalytic amount of phospho sulfonic acid (PSA) as an efficient and heterogeneous solid acid in EtOH at room temperature. Preparation of PSA is straightforward and handling of the reagent is also easy. The attractive features of this protocol are: (**i**) The elimination of corrosive liquid acids; (**ii**) the use of an inexpensive and relatively non-toxic catalyst, and (**iii**) reusability of the catalyst.

***Keywords**: PO(OSO$_3$H)$_3$, Hantzsch synthesis, Heterogeneous solid acid, Multi-component reactions, Aldehyde.*

1. Introduction

Over the last few years, the use of heterogeneous catalysts has received much attention. The salient features of this kind of catalysts are easily being separated from the reaction products and reused in successive runs. Also, heterogeneous catalyst is more suitable for continuous flow operation than it is for than batch wise processes for large scale industrial synthesis [1-4].

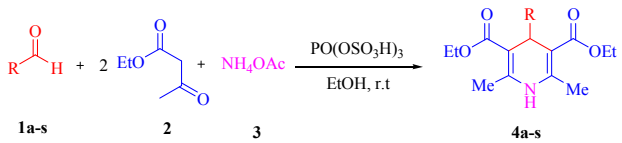
Recent studies have revealed that multicomponent reactions (MCRs) are flexible and convergent reactions. MCRs have attracted the attention of organic and medical chemistry because these compounds have characteristics including the possibility of achieving high synthetic efficiency and reaction design simultaneously and high selectivity, high yielding and friendly environment [5-7].

1,4-Dihydropyridines (1,4-DHPs) and its derivatives are important category of organic compounds, because these compounds have several medicinal characteristics including acting as cerebral anti ischemic agents in the treatment of Alzheimer's disease and as a chemo sensitizer in tumor therapy [8-9].

*Corresponding author email: sobhan.rezayati@yahoo.com
Tel.: +98 91 8343 3771; Fax: +98 84 3333 9303

On the other hand, 1,4-DHP compounds play important roles in medicinal chemistry, for example amlodipine, nifedipine, nicardipine and felodipine, which are the best selling drugs used in the treatment of cardiovascular diseases. [10-12]. 1,4-DHPs are generally synthesized by Hantzsch reaction which involves three component coupling of various aldehydes, β-ketoester and ammonia or ammonium acetate. A number of improved methods have been reported in the literature for this condensation which involve the use of trifluoroethanol [13], I_2 [14], TMSCl–NaI [15], cyanuric chloride [16], $CeCl_3.7H_2O$ [17], $Sc(OTf)_3$ [18], PPh_3 [19] and iodotrimethylsilane (TMSI) [20]. However, these methods suffer from several drawbacks such as long reaction time, high temperature conditions excessive use of an organic solvent, low yield and harsh refluxing conditions.

In this research phospho sulfonic acid was used for the synthesis of 1,4-dihydropyridines derivatives through one-pot three-component reaction at room temperature (Scheme 1).



Scheme 1. The preparation of 1,4-dihydropyridines.

2. Experimental

2.1. General

All reagents were purchased from Aldrich or Merck Fine Chemicals and used without further purification. Products were separated and purified by different chromatographic techniques and identified by the comparison of their IR and NMR with those reported for the authentic samples. ^{1}H NMR spectra were recorded on a Bruker DRX-300 AVANCE spectrometer in $CDCl_3$ as a solvent. Thin-layer chromatography (TLC) was performed on pre-coated aluminum plates (silica gel 60 F254, Merck, Germany). The chromatographic spots on the plates were visualized under UV light and iodine vapor. Melting points were taken on an electrothermal capillary melting point apparatus and are uncorrected.

2.2. Preparation of phospho sulfonic acid

A 100 ml suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through adsorbing solution (water) and alkali trap. Diammonium hydrogen phosphate (4 g, 30 mmol) was charged into the flask and chlorosulfonic acid (10.48g, ca. 6 mL, 90 mmol) in CH_2Cl_2 (10 mL) was added drop wise over a period of 45-60 min under N_2 gas and at room temperature. After completion of the addition, the mixture was shaken for 2 h, while the residual HCl was eliminated by suction. Then the mixture was washed with CH_2Cl_2 (2×5 mL) to remove the unreacted chlorosulfonic acid [21].

2.3. General procedure for the preparation of 1,4-dihydropyridines

A mixture of various aldehyde **1a-s** (2 mmol), dimedone **2** (4 mmol), ammonium acetate **3** (3 mmol) in the presence of catalytic amount PSA (0.05 g) was stirred in ethanol (5 ml) at room temperature. The progress of the eaction was monitored by TLC (*n*-Hexane:EtOAc 4:1). After completion of the reaction, the ethanol was evaporated under vacuum and the crude product extracted by dichloromethane. The solvent was removed by simple evaporation. The precipitate was collected and recrystallized from EtOH/H_2O to give 1,4-dihydropyridines **4a-s** in good to high yields.

Selected spectral data

*Ethyl 4-chloro-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**Table 3, Entry 2**):*

^{1}HNMR (300 MHz, $CDCl_3$): δ= 1.11-1.16 (t, *J* = 7.1 Hz, 6H, $2CH_3$ at C-3 and C-5), 2.19 (s, 6H, $2CH_3$ at C-2 and C-6), 3.96-4.05 (m, *J* = 8.51 Hz, 4H, $2CH_2$, diastereotopic protons), 4.89 (s, 1H, CH), 6.30 (s br, 1H, NH), 7.06-7.15 (m, 2H, Ar-H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$): δ= 14.27, 19.31, 39.24, 59.85, 103.50, 127.92, 129.36, 131.66, 144.56, 145.45, 167.68 ppm.

*Ethyl 4-(2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**Table 3, Entry 13**):*

^{1}HNMR (300 MHz, $CDCl_3$): δ= 1.14-1.19 (t, *J* = 7.1 Hz, 6H, $2CH_3$ at C-3 and C-5), 2.21 (s, 6H, 2 CH_3 at C-2 and C-6), 4.04-4.09 (q, *J* = 7.2 Hz, 4H, $2CH_2$ diastereotopic protons), 5.11 (s, 1H, CH), 6.29 (s br, 1H, NH), 7.10-7.11 (m, 3H, Ar-H) ppm. ^{13}CNMR (75 MHz, $CDCl_3$): δ= 14.31, 19.29, 33.38, 59.28, 100.41, 104.39, 110.0, 140.78, 145.51, 158.76, 167.65 ppm.

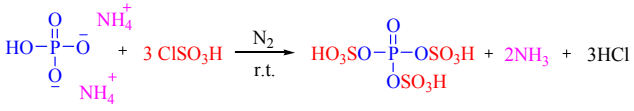
3. Results and discussion

Phospho sulfonic acid was easily prepared in one step by the simple mixing of diammonium hydrogen phosphate and chlorosulfonic acid in CH_2Cl_2 at room temperature (Scheme 2) [21]. This reaction is simple and facile because the by-products of the reaction are HCl and NH_3 gases, which are immediately evolved from the reaction vessel.

In recent years, researchers have become more and more interested to apply the heterogeneous solid acids in organic reactions, which have many advantages such as unable polarity, high efficiency and selectivity, high thermal stability, immiscibility with a number of organic solvents, insignificant vapor pressure and ease of recyclability [22-28]. In a typical experimental procedure we wish to report on synthesis of 1,4-dihydropyridines through one-pot three-component reaction using various aldehyde substrates, dimedone and ammonium acetate in presence of PSA to excellent yields (Scheme 1).

First of all, the effect of catalyst loading on the condensation reaction between benzaldehyde, dimedone and ammonium acetate under solvent-free conditions was studied (Table 1). As shown in Table 1, the use of 0.05 g of catalyst under solvent-free conditions resulted in the highest yield in 80 min (Table 1, Entry 4). Also, the reaction was examined in different solvents such as, chloroform, water, n-hexane and etc. (Table 2). Among all these solvents, ethanol (Table 2, Entry 5) was found to be the best solvent of choice which not only afforded the product in 97% yield, but also with higher reaction rate (30 min).

We next examined a wide variety of aldehydes to establish the scope of this catalytic transformation. As shown in Table 3, the reaction rate and the yields are depending on electron donating/withdrawing effect of the groups on the benzene ring in benzaldehyde.



Scheme 2. Preparation of phospho sulfonic acid.

Table 1. Optimization of amount of catalyst-loading in the model reaction.[a]

Entry	Catalyst (g)	Time (min)	Yield (%)[b]
1	None	400	Trace
2	0.01	180	51
3	0.03	140	66
4	0.05	80	83
5	0.07	95	79
6	0.10	110	71

[a]Model reaction: Benzaldehyde (2 mmol), dimedone (4 mmol) and ammonium acetate (3 mmol) in presence PSA at room temperature under solvent-free condition.
[a]Yield of isolated products.

Table 2. Solvent effect on the reaction of benzaldehyde, dimedone and ammonium acetate catalyzed by PSA.

Entry	Solvent[a]	Time (min)	Yield (%)[b]
1	H_2O	200	38
2	CH_2Cl_2	200	<21
3	CH_3Cl	200	66
4	*n*-Hexane	240	Trace
5	EtOH	30	97

[a]Reaction was carried out in 5 mL of solvents at room temperature.
[b]Yield of isolated products.

Table 3. PSA Catalyzed Synthesis of 1,4- dihydropyridine derivatives through Hantzsch Reaction.

Entry	Aldehyde	Time (min)	Yield (%)[a]	m.p. (°C)		Ref.
				Found	Reported	
1	Benzaldehyde	30	97	154-156	155.3-158.3	[29]
2	4-Chlorobenzaldehyde	30	95	147-149	149.5-151	[29]
3	Terephthalaldehyde	30	88	290-292	289-293	[29]
4	4-Bromobenzaldehyde	25	96	164-165	165.5-166.5	[29]
5	4-Fuorobenzaldehyde	35	89	148-149	149-150.5	[29]
6	3-Nitrobenzaldehyde	75	85	159-161	160-161	[29]
7	Isobutyraldehyde	85	81	98	97-99	[29]
8	3,4-Dimethoxybenzaldehyde	35	85	130-131	132-133	[29]
9	2-Butenal	90	82	Viscous oil	-	-
10	3-(4-Methoxyphenyl)acrylaldehyde	25	94	142-143	-	-
11	4-Hydroxy-3-methoxybenzaldehyde	60	89	129	129	[30]
12	4-Methoxybenzaldehyde	35	92	137-138	140	[30]
13	Furfural	50	88	160-162	163	[31]
14	Cinnamaldehyde	30	91	146-148	147	[31]
15	4-Nitrobenzaldehyde	25	95	124-126	126	[31]
16	4-Hydroxybenzaldehyde	35	86	230-231	230-232	[32]
17	Picolinaldehyde	60	86	193-195	192-194	[33]
18	4-Methylbenzaldehyde	20	95	136	135-137	[34]
19	2-(Thiophen-2-yl)benzaldehyde	45	91	169-170	171-173	[35]

[a]Yield of isolated products.

Aryl aldehydes containing electron-donating substituent gave excellent yields of the products in a shorter reaction time. The time of reactions was within 20-90 min, and good to excellent yields of 1,4-dihydropyridines were obtained. Reusability of the catalyst is one of the main advantages of our method. For the reaction of benzaldehyde with 1,3-dicarbonyl compounds and ammonium acetate (Table 2, Entry 1), dichloromethane (2×5 ml) was poured in cooled reaction mixtures until solid crude product was dissolved. Then, the PSA as catalyst was isolated from the reaction mixture by simple filtration and could be reused again after washing by dichloromethane. Good yield was observed when PSA was reused even after six times recycling (Yield varied from 87 to 897%).

The reaction of benzaldehyde, dimedone with ammonium acetate has been compared with several catalysts in literature (Table 4). The important features of this procedure are, short period of conversion and excellent yields, simplicity of reaction, easy synthesis of catalyst and simple work-up, in comparison with other existing methods.

4. Conclusions

In summary, PSA as highly efficient and reusable catalyst has been prepared and utilized for the synthesis of Hantzsch 1,4-dihydropyridines via one-pot three-component reaction of ethyl acetoacetate with a wide range of aromatic aldehydes, ethyl acetoacetate and ammonium acetate in ethanol. The important features of this procedure are the availability of the starting materials, eco-friendly conditions, a clean work-up, short reaction times and good to high yields. In addition, the catalyst can be recycled after a simple work-up, and used at least six times in the reactions without substantial reduction in its catalytic activity.

Acknowledgments

We wish to express our thanks to Payame Noor University of Ilam, Iran, for partially supporting this work

References

[1] E. Kolvari, N. Koukabi, M.M. Hosseini, J. Mol. Catal. A: Chem. 397 (2015)68-75.
[2] M. Hosseini-Sarvari, Z. Razmi, Appl. Surf. Sci. 324 (2015) 265-274.
[3] K. Wilson, J.H. Clark, Pure Appl. Chem. 72 (2000) 1313-1319.
[4] A. Davoodnia, A. Tavakoli-Nishaburi, N. Tavakoli-Hoseini, Bull. Korean Chem. Soc. 32 (2011) 635-638.
[5] P. Slobbe, E. Ruijter, R.V.A. Orru, Med. Chem. Commun. 3 (2012) 1189-1218.
[6] A. Dömling, I. Ugi. Chem. Intl. Ed. 39 (2000) 3168-3210.
[7] S. Pednekar, R. Bhalerao, N. Ghadge, J. Chem. Sci. 125 (2013) 615–621.
[8] M. Suarez, Y. Verdecia, B. Illescas, R. Martinez-Alvarez, A. Avarez, E. Ochoa, C. Seoane, N. Kayali, N. Martin, Tetrahedron 59 (2003) 9179-9186.
[9] A. Zarghi, H. Sadeghi, A. Fassihi, F.M. Aizi, A. Shafiee, Il Farmaco. 58 (2003) 1077-1081.
[10] M.E. Ortiz, L.J. Nunez-Vergara, J.A. Sequella, Pharm. Res. 20 (2003) 292-296.

Table 4. Comparison of the results of PSA with those of other catalysts reported in the literature in the synthesis of 1,4-dihydropyridines.

Entry	Catalyst	Time (h)	Yield (%)[a]	Ref.
1	$AlCl_3$	24	48	[18]
2	$Yb(OTf)_3$	5	85	[18]
3	L-Proline	6	92	[36]
4	Ionic liquid	8 min	95	[37]
5	Silica sulfuric acid	15 min	98	[38]
6	$Bi(NO)_3.5H_2O$	1 min	99	[39]
7	Fe_3O_4 MNPs	5 min	94	[40]
8	Alumina sulfuric acid	5	87	[41]
9	[EMIM]OAc	35	96	[42]
10	This work	30 min	97	-

[a]Yield of isolated products.

[11] R. Budriesi, A. Bisi, P. Ioan, A. Rampa, S. Gobbi, F. Belluti, L. Piazzi, P. Valenti, A. Chiarini, Bioorg. Med. Chem. 13 (2005) 3423-3430.
[12] R. Miri, K. Javidnia, H. Sarkarzadeh, B. Hemmateenejad, Bioog. Med. Chem. 14 (2006) 4842-4849.
[13] A. Heydari, S. Khaksar, M. Tajbakhsh, H.R. Bijanzadeh, J. Fluorine Chem. 130 (2009) 609-614.
[14] S. Ko, M.N.V. Sastry, C. Lin, C.F. Yao, Tetrahedron Lett. 46 (2005) 5771-5774.
[15] G. Sabitha, G.S.K.K. Reddy, C.H.S Reddy, J.S. Yadav, Tetrahedron Lett. 44 (2003) 4129-4113.
[16] G.V.M. Sharma, K.L. Reddy, P.S. Lakshmi, P.R. Krishna, Synthesis 1 (2006) 55-58.
[17] G. Sabitha, K. Arundhathi, K. Sudhakar, B.S. Sastry, J.S. Yadav, Synth. Commun. 39 (2009) 2843-2851.
[18] J.L. Donelson, R.A. Gibbs, S.K. De, J. Mol. Catal. A: Chem. 256 (2006) 309-311.
[19] A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, Tetrahedron Lett. 50 (2009) 5248-5250.
[20] G. Sabitha, G.S.K. Kumar Reddy, Ch.Srinivas Reddy, J.S. Yadav, Tetrahedron Lett. 44(2003) 4129–4131.
[21] A.R Kiasat, A. Mouradzadegun, S.J. Saghanezhad, J. Serb. Chem. Soc. 78 (2013) 469–476.
[22] S. Sajjadifar, S. Rezayati, Chem. Pap. 68 (2014) 531-539.
[23] A.R. Kiasat, M. Fallah-Mehrjardi, J. Braz. Chem. Soc. 19 (2008) 1595-1599.
[24] R. Hajinasiri, S. Rezayati, Z. Naturforsch. 68B (2013) 818–822.
[25] D. Zareyee, M. Serehneh, J. Mol. Catal. A: Chem. 391 (2014) 88–91.
[26] D. Zareyee, P. Alizadeh, M.S. Ghandali, M.A. Khalilzadeh, Chem. Pap. 67 (2013) 713-721.
[27] M. Dabiri, S.C. Azimi, A. Bazgir, Chem. Pap. 62 (2008) 522–526.
[28] B. Karimi, D. Zareyee, Org. Lett. 10 (2008) 3989-3992.
[29] A. Ghorbani-Choghamarani, M.A. Zolfigol, M. Hajjami, H. Goudarziafshar, M. Nikoorazm, S. Yousefi, B. Tahmasbi, J. Braz. Chem. Soc. 22 (2011) 525-531.
[30] M. Anniyappam, D. Muralidharan, P.T. Perumal, Synth. Commun. 32 (2002) 659–663.
[31] J.S. Yadav, B.V. Subba Reddy, P. Thirupati, Synth. Commun. 31 (2001) 425–430.
[32] A. Debache, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, Synlett 4 (2008) 509–512.
[33] F. Tamaddon, Z. Razmi, A.A. Jafari, Tetrahedron Lett. 51 (2010) 1187–1189.
[34] A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, Tetrahedron Lett. 50 (2009) 5248–5250.
[35] J.J.V. Eynde, F. Delfosse, A. Mayence, Y.V. Haverbeke, Tetrahedron 51 (1995) 6511-6516.
[36] N.N. Karade, V.H. Budhewara, S.V. Shindeb, W.N. Jadhav, Lett. Org. Chem. 4 (2007) 16-19.
[37] J.P. Nirmal, P.V. Dadhaniya, M.P. Patel, R.G. Patel, Indian J. Chem. 49 (2010) 587-592.
[38] E. Kolvari, M.A. Zolfigol, N. Koukabi, B. Shirmardi-shaghasemi, Chem. Pap. 65 (2011) 898-902.
[39] D. Bandyopadhyay, S. Maldonado, B.K. Banik, Molecules 17 (2012) 2643-2662.
[40] F. Farzaneh, E. Zamanifar, L.J. Foruzin, M. Ghandi, J. Sci. I. R. Iran. 23 (2012) 313-318.
[41] M. Arslan, C. Faydali, M. Zengin, M. Kucuk, H. Demirhan, Turk. J. Chem. 33 (2009) 769-774.
[42] B. Palakshi Reddy, K. Rajesh, V. Vijayakumar. J. Chin. Chem. Soc. 58 (2011) 384-388.