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L-lactic acid catalyzed facile one pot three component solventless synthesis of α-amino phosphonates

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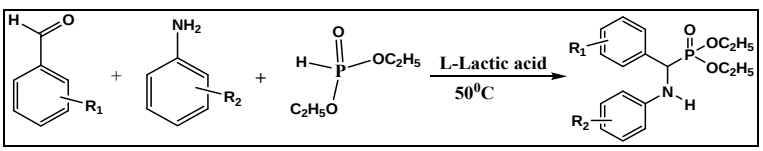
Abstract
One pot three component solventless synthesis of α-aminophosphonate derivatives by reacting substituted aromatic aldehyde, aromatic amine and diethylphosphite at 50 ^{0}C catalyzed by L-lactic acid as an organocatalyst with excellent yield (70-95%) and short reaction time is reported. The structures of synthesized derivatives were characterized and confirmed by FT-IR and ^{1}HNMR data.

Keywords: α-aminophosphonate, L-lactic acid, organocatalyst

Introduction
The active moiety of α-aminophosphonates has vast applicability as antifungal [1], antioxidant, antiviral, anticancer, herbicide [2-5] and antimicrobial [6].
The reported methods for the synthesis of α-aminophosphonates catalyzed by lanthanide triflate [7], samarium diiodide [8], $Cu(OTf)_2$ [9], thiourea [10], Bronsted acid [11], magnesium perchlorate [12], tetramethylguanidine [13], bismuth nitrate pentahydrate [14], silica sulfuric acid [15], Potassium hydrogen sulfate [16], CuO nano powder [17], tartaric acid [18], Cellulose-SO_3H [19], Amberlyst-15 [20], rhodium [21], acidic ionic liquids [22], Triton X-100 [23] and sulfated polyborate [24]. Most of the above reported methods use hazardous catalysts or solvents and take long reaction time. Because of their importance as active biological agents [25], an economic environmentally benign protocol for the synthesis of α-aminophosphonates is desirable.

2. Material and Methods
2.1 Materials
All the reagents, chemicals were purchased from hi-media and were used without further purification. ^{1}H NMR spectra were recorded on 500 MHz Bruker Avance III instrument using $CDCl_3$. The purity of products and reaction progress was checked by TLC on silica gel plates using hexane: ethyl acetate (80:20) solvent system and visualized using iodine vapors and UV radiation.

2.2 Methods
α-Aminophosphonate derivatives were synthesized by taking substituted benzaldehyde (5mmol), substituted aniline (5mmol), diethylphosphite (5mmol) and L-lactic acid (10 mol %) as catalyst in round bottom flask fitted with guard tube (filled with anhydrous $CaCl_2$). The reaction mixture was stirred at 50 ^{0}C (Scheme 1). The progress of reaction was monitored over silica gel TLC plates. After completion of reaction dichloromethane (10ml) was added to the reaction mixture then washed successively with 5% sodium bicarbonate solution (5ml) and brine (5ml). The organic layer was dried over anhydrous sodium sulfate. Dichloromethane was evaporated under reduced pressure. The obtained crude product was recrystallized from chloroform.



Scheme 1: Synthesis of α-Aminophosphonate derivatives

3. Result and Discussion

The reaction was optimized by taking benzaldehyde (5mmol), aniline (5mmol), diethylphosphite (5mmol) with and without catalyst at different temperature (Table 1). First, the reaction was carried out without catalyst at room temperature it took longer time (11hr) affording low yield (50%). By taking the catalyst (L-lactic acid) amount 5 mol% at room temperature the reaction time decreased (7hr) affording higher yield (68%), indicating that catalyst decreases the activation energy of the reaction. With 5 mol% as catalyst amount of reaction time decreased 2 hr at 50 ^{0}C with increased the yield (71%). 10mol% amount of catalyst at room temperature afforded 70% yield by taking reaction time 5.5 hrs, with the same amount (10mol%) catalyst and temperature 50 ^{0}C the reaction was completed within 45 min affording 92% yield. By further increasing catalyst amount (20mol%) did not increase yield (93%) significantly, so optimum conditions for the reaction were established as 10mol% catalyst amount and 50 ^{0}C temperature.

Table 1: Optimization of reaction condition

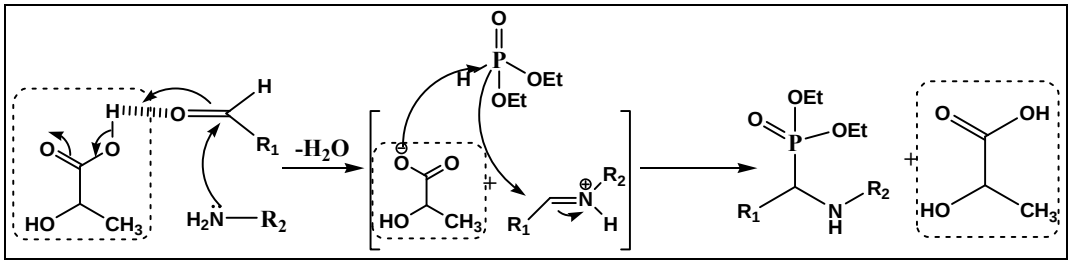
SI. No.	Catalyst amount (mol %)	Reaction condition	Time	Yield
1.	0	Room temp	11hr	50
2.	5	Room temp	7hr	68
3.	5	50 ^{0}C	2hr	71
4.	10	Room temp	5.5hr	70
5.	10	50 ^{0}C	45min	92
6.	20	Room temp	5hr	72
7.	20	50 ^{0}C	40min	93

The various derivatives of α-aminophosphonate were synthesized based on the above method. The melting point, yield%, color and completion time of reaction for the different derivatives are given in Table 2. A perusal of Table 2 clearly indicates that the different derivatives of benzaldehyde and derivative of aniline having electron withdrawing group or electron donating group afford good to excellent yield (80-95%).

Table 2: Synthesis of α-aminophosphonate derivatives

SI. No.	Compound name	Yield%	Time (hr)	Melting Point (^{0}C)	Color
1	Diethyl[1-phenyl-1-(4-methylphenylamino)]-methylphosphonate	80	0.75	84	Light orange
2	Diethyl[1-(4-methoxyphenyl)-1-(4-methylphenylamino)]-methylphosphonate	85	1.3	112	Light yellow
3	Diethyl[1-(4-flouorophenyl-1-(4-methylphenylamino)]-methylphosphonate	90	2.5	86	Light brown
4	Diethyl[1-(4-methoxyphenyl-1-phenylamino)]-methylphosphonate	84	2	115	Light yellow
5	Diethyl[1-(3-methoxyphenyl-1-(4-methylphenylamino)]-methylphosphonate	90	1.3	118	Light orange
6	Diethyl[1-(4-chlorophenyl)-1-(4-methylphenylamino)]-methylphosphonate	92	0.91	110	yellow
7	Diethyl[1-(4-methylphenyl)-1-(4-methylphenylamino)]-methylphosphonate	80	3	72	Light yellow
8	Diethyl[1-(2,5-methoxyphenyl)-1-(4-methylphenylamino)]-methylphosphonate	90	1.5	87	Light brown
9	Diethyl[1-(2,5-methoxyphenyl-1-phenylamino)]-methylphosphonate	78	2.5	82	Light green
10	Diethyl[1-(4-nitrophenyl)-1-phenylamino)]-methylphosphonate	84	2	88	yellow
11	Diethyl[1-(2-chlorophenyl)-1-phenylamino)]-methylphosphonate	95	2.5	113	white
12	Diethyl[1-(3-methoxyphenyl-1-phenylamino)]-methylphosphonate	90	3	114	white

The variously reported lewis acids are used for the synthesis of α-aminophosphonates but the reaction could not be carried out efficiently because water formed during imine formation can decompose or deactivate lewis acid [26]. In addition, some of the catalyst are expensive and are difficult to prepare. L-lactic acid is easily available, nonhygroscopic, stable and easy to handle. A plausible mechanism for the reaction catalyzed by L-lactic acid is proposed (Scheme 2). L-lactic acid interacts with CO group of benzaldehyde via hydrogen bonding thus activating it by increasing the electrophilicity of CO group. The resulting intermediate further activated by lactic acid facilitates the removal of a water molecule to get the final product.



Scheme 2: Plausible mechanism for the synthesis of α-aminophosphonates

3.1 Spectral Analysis

Diethyl[1-(4-methoxyphenyl)-1-(4-methylphenyl amino)]-methylphosphonate: FTIR(KBr): 3320, 1231, 1106, 780 cm^{-1}, ^{1}HNMR ($CDCl_3$, 500MHz): 1.16(3H, t, J=7 Hz, P-O-CH_2-CH_3), 1.31(3H, t, J=7 Hz, P-O-CH_2-CH_3), 2.20 (3H, s, Ar-Me), 3.69-3.75(2H, m, P-O-CH_2-CH_3), 3.79 (3H, s, O-CH_3), 3.91-3.99(2H, m, P-O-CH_2-CH_3), 4.72(1H, d, $^3J_{H\text{-}N\text{-}CH}$, 24Hz, CH), 4.8(1H, br s, N-H), 6.53-7.41(8H, m, Ar-H).

Diethyl[1-(4-flouorophenyl)-1-(4-methylphenyl amino)]-methylphosphonate: FTIR(KBr): 3240, 1311, 1089, 784 cm^{-1}, ^{1}HNMR ($CDCl_3$, 500MHz): 1.17(3H, t, J=7 Hz, P-O-CH_2-CH_3), 1.31(3H, t, J=7 Hz, P-O-CH_2-CH_3), 2.21 (3H, s, Ar-Me), 3.74-3.82(2H, m, P-O-CH_2-CH_3), 3.96-3.99(2H, m, P-O-CH_2-CH_3), 4.77(1H, d, $^3J_{H\text{-}N\text{-}CH}$, 24Hz, CH), 4.8(1H, br s, N-H), 6.51-7.47(8H, m, Ar-H).

Diethyl[1-(4-chlorophenyl)-1-(4-methylphenyl amino)]-methylphosphonate: FTIR(KBr): 3370, 1267, 1090, 783 cm^{-1}, ^{1}HNMR ($CDCl_3$, 500MHz): 1.19(3H, t, J=7 Hz, P-O-CH_2-CH_3), 3H, t, J=7 Hz, P-O-CH_2-CH_3), 2.21(3H, s, Ar-Me), 3.77-3.80(2H, m, P-O-CH_2-CH_3), 3.97-4.00(2H, m, P-O-CH_2-CH_3), 4.76(1H, d, $^3J_{H\text{-}N\text{-}CH}$, 24Hz, CH), 4.8(1H, br s, N-H), 6.50-7.47(8H, m, Ar-H).

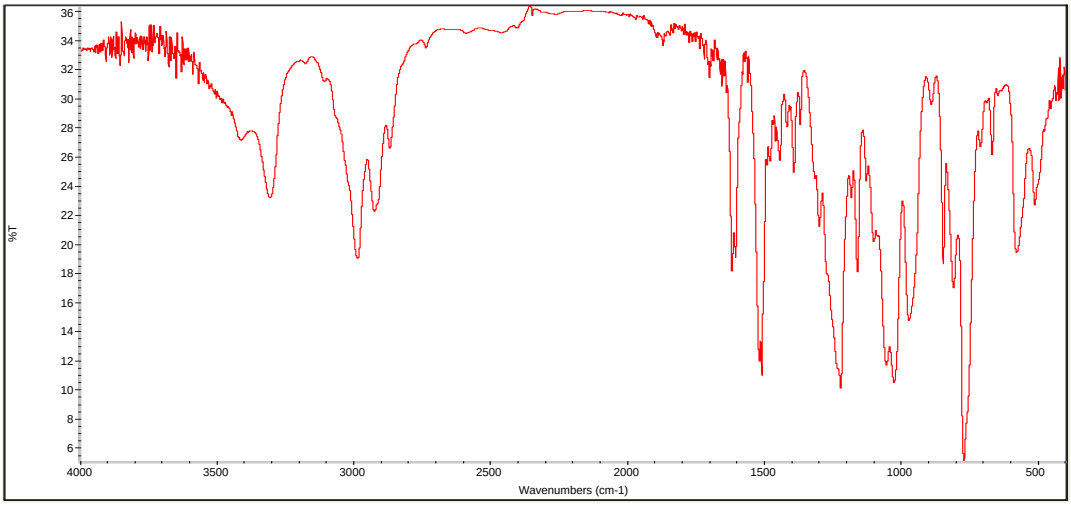


Fig 1: IR spectra of diethyl [1-(4-methoxyphenyl)-1-(4-methlphenylamino)]- methylphosphonate

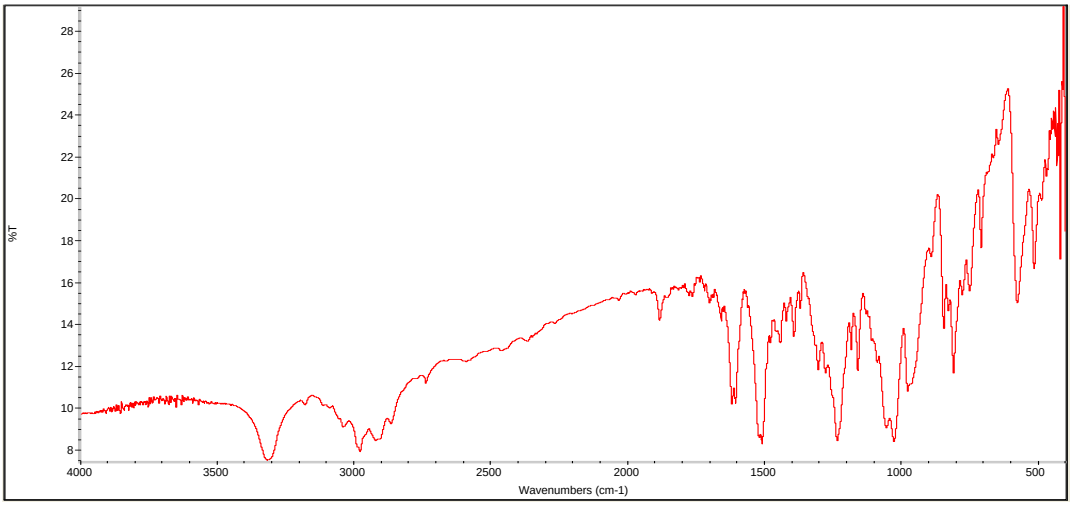


Fig 2: IR spectra of diethyl[1-(4-flouorophenyl)-1-(4-methylphenylamino)]-methylphosphonate

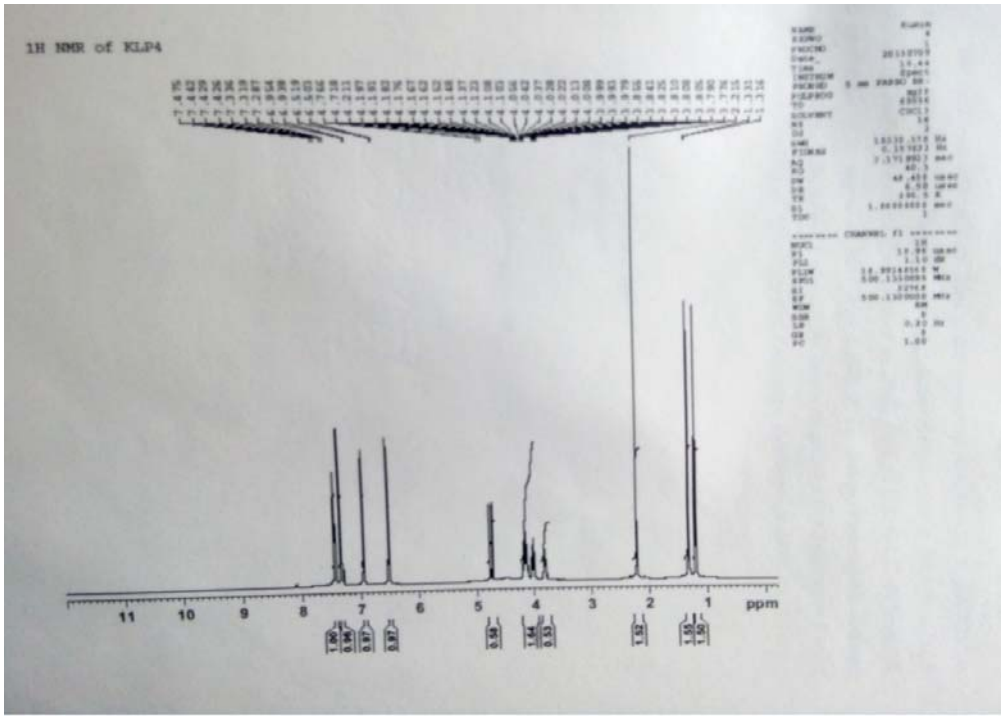


Fig 3: 1HNMR spectra of diethyl[1-(4-chlorophenyl)-1-(4-methyl phenylamino)]-methyl phosphonates

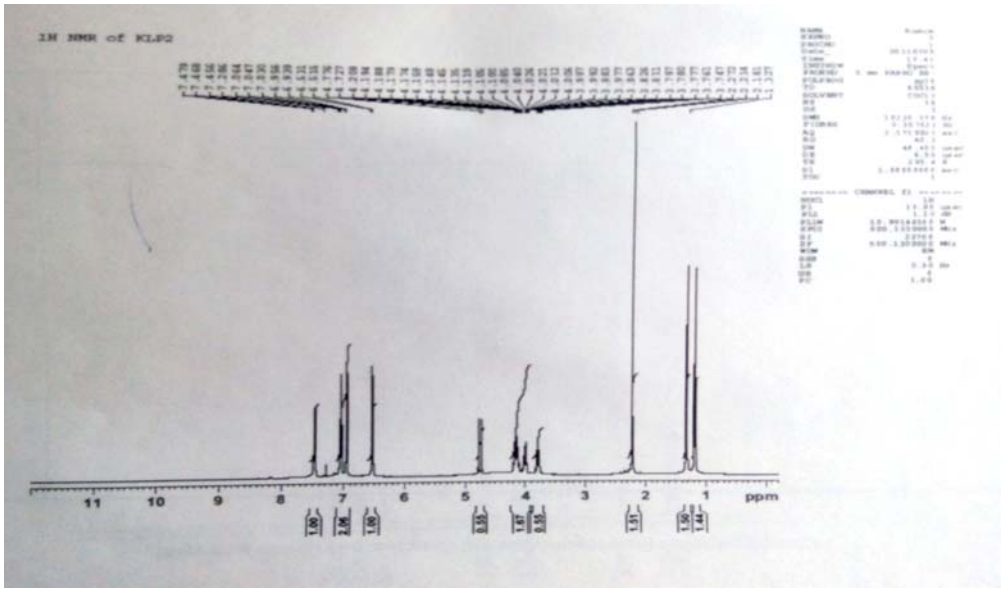


Fig 4: 1HNMR spectra of diethyl[1-(4-flourophenyl)-1-(4-methyl phenylamino)]-methyl phosphonates

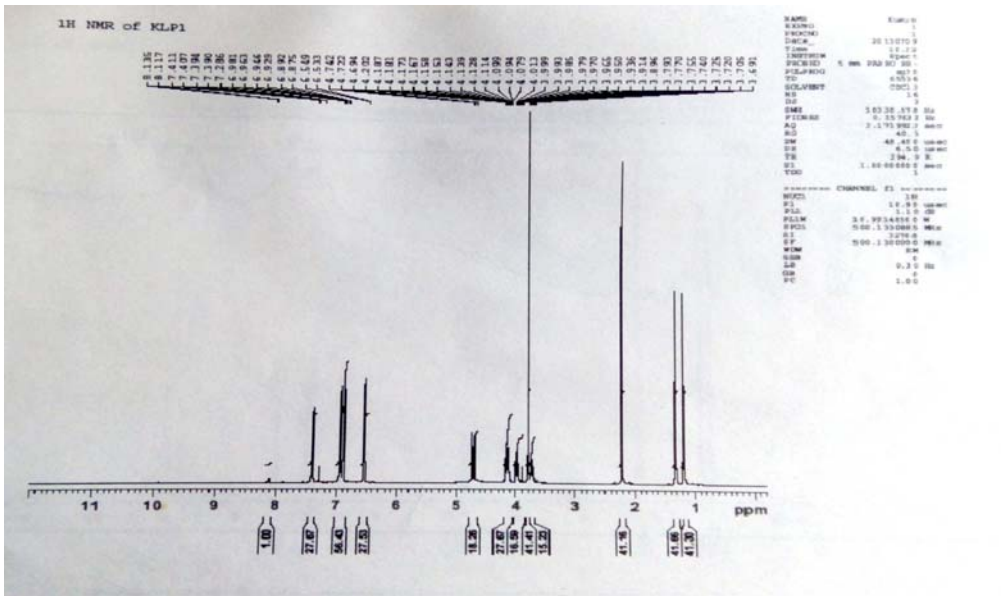


Fig 5: 1HNMR spectra of diethyl[1-(4-methoxy phenyl)-1-(4-methyl phenylamino)]-methyl phosphonates

4. Conclusion

L-lactic acid was found to be a cheaper environmentally benign catalyst for the synthesis of α-aminophosphonates affording good to excellent yield and simple reaction conditions.

5. Acknowledgement

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6. Reference

1. Rezaei Z, Khabnadideh S, Zomorodian K, Pakshir K, Nadali S, Mohtashami N *et al*. Design, synthesis and antifungal activity of new α-aminophosphonates. Int J Med Chem. 2011. DOI: 10.1155/2011/678101.
2. Onita N, Sisu I, Penescu M, Purcarea VL, Kurunczi L. Synthesis, characterization and biological activity of some α-aminophosphonates. Farmacia. 2010; 58:531-545.
3. Ramana KV, Rasheed S, Sekhar KC, Adam S, Raju CN. One-pot and catalyst-free synthesis of novel α-aminophosphonates under microwave irradiation and their biological activity. Der Pharmacia Lettre. 2012, 456-463.
4. Prasad GS, Rao GN. Synthesis of biologically active α-aminophosphonates. J Mod Med Chem. 2013; 1:49-60.
5. Reddy GS, Rao KUM, Sundar CS, Sudha SS, Haritha B, Swapna S *et al*. Neat synthesis and antioxidant activity of α-aminophosphonates. Arab J Chem. 2014; 7:833-838.
6. Rezaei Z, Khabnadideh S, Ghasemi Y, Fadaei M, Karimi Z. Design and one-pot synthesis of new α-aminophosphonates and antimicrobial activity. J Pharm Negative Results. 2011; 2:78-86.
7. Lee S, Park JH, Kang J, Lee JK. Lanthanide triflate catalyzed three component synthesis of alpha amino phosphonates in ionic liquids: A catalyst reactivity and reusability study. Chem Commun. 2001; 7:1698-1689.

8. Xu F, Luo Y, Deng M, Shen Q. One pot synthesis of α-amino phosphonated using samarium diiodide as a catalyst precursor. J Org Chem. 2003, 4728-4730.
9. Kobzyashi S, Kiyaohara H, Nakamura Y, Matsubara R. Catalytic Asymmetric Synthesis of α-Amino Phosphonates Using Enantioselective Carbon-Carbon Bond-Forming Reactions. J Am Chem Soc. 2004; 126:6558-6559.
10. Joly GD, Jacobsen EN. Thiourea-Catalyzed Enantioselective Hydrophosphonylation of Imines: Practical Access to Enantiomerically Enriched α-Amino Phosphonic Acids. J Am Chem Soc. 2004; 126:4102-4103.
11. Akiyama T, Morita H, Itoh J, Fuchibe K. Chiral Brønsted Acid Catalyzed Enantioselective Hydrophosphonylation of Imines: Asymmetric Synthesis of α-Amino Phosphonates. Org Lett. 2005; 7:2583-2585.
12. Bhagat S, Chakraborti AK. An Extremely Efficient Three-Component Reaction of Aldehydes/Ketones, Amines, and Phosphites (Kabachnik-Fields Reaction) for the Synthesis of α-Aminophosphonates Catalyzed by Magnesium Perchlorate. J Org Chem. 2006; 72:1263-1270.
13. Reddy MVN, Kumar BS, Balakrishna A, Reddy CS, Nayak SK, Reddy CD. One-pot synthesis of novel α-amino phosphonates using tetramethylguanidine as a catalyst. Arkivoc (xv). 2007, 246-254.
14. Bhattacharya AK, Kaur T. An efficient one pot synthesis of α-amino phosphonates catalyzed by bismuth nitrate pentahydrate. Syn Letters. 2007; 5:745-748.
15. Maghsoodlou MT, Khorassani SMH, Hazeri N, Rostamizadeh M, Sajadikhah SS, Shahkarami Z *et al*. An Efficient Synthesis of α-Amino Phosphonates Using Silica Sulfuric Acid as a Heterogeneous Catalyst. Heteroatom Chem. 2009; 20:316-318.
16. Thirumurugan P, Nandakumar A, Priya NS, Muralidaran D, Perumal PT. KHSO4-mediated synthesis of α-amino phosphonates under a neat condition and their 31P NMR chemical shift assignments. Tetrahedron Lett. 2010; 51:5708-5712.
17. Karmakar B, Paul S, Banerji J. A highly efficient, one pot synthesis of α-aminophosphonates over CuO nanopowder. Arkivoc (ii). 2011, 161-171.
18. Gangwar N, Kasana V. Tartaric Acid–Catalyzed Synthesis of α-Aminophosphonates Under Solvent-Free Conditions. Synth Commun. 2011; 41:2800-2804.
19. Kumar KS, Krishna BS, Reddy CB, Reddy MVN, Reddy CS. Solvent-free synthesis of a-aminophosphonates: Cellulose-SO3H as an efficient catalyst. Arab J Chem. 2012. DOI: 10.1016/j.arabjc.2012.09.009
20. Reddy GS, Rao KUM, Sundar CS, Sudha SS, Haritha B, Swapna S *et al*. Neat synthesis and antioxidant activity of α-aminophosphonates. Arab J Chem. 2013. DOI: 10.1016/j.arabjc.2013.01.004
21. Lefevre N, Brayer JL, Folleas B, Dares S. Chiral α-amino phosphonates via rhodium-catalyzed asymmetric 1,4-addition reactions. Org Lett. 2013; 15:4274-4276.
22. Ying A, Liu S, Yang J, Hu H. Synthesis of α-amino phosphonates under a neat condition catalyzed by multiple-acidic ionic liquids. Ind Eng Chem Res. 2014. DOI: 10.1021/ie5025062
23. Reddy NB, Sundar CS, Rani CR, Rao KUM, Nayak SK, Reddy CS. Triton X-100 catalyzed synthesis of α-aminophosphonates. Arab J Chem. 2016; 9:S685.
24. Khatri CK, Satalkar VB, Chaturbuj GU. Sulfated polyborate catalyzed Kabachnik-Fields reaction: An efficient and ecofriendly protocol for synthesis of α-amino phosphonates. Tetrahedron Lett. 2017. DOI: 10.1016/j.tetlet.2017.01.022.
25. Naydenova ED, Todorov PT, Troev KD. Recent synthesis of aminophosphonic acids as potential biological importance. Amino Acids. 2010; 38:23-30.
26. Zon J. Enantioselective synthesis of α-amino propargyl phosphonates. Pol J Chem. 1981; 55:643-646.