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Graphical Abstract





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Sulfated polyborate catalyzed Kabachnik-Fields reaction: An efficient and ecofriendly protocol for synthesis of α -amino phosphonates

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ABSTRACT

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anti-viral agent (Fig. 1).

Solvent free The Kabachnik–Fields reaction is a multi-component organic tri reaction forming an α -amino phosphonates from aldehydes, tau amines, and dialkyl phosphites.¹ Recently, the synthesis of α amino phosphonates has attracted much attention in synthetic an organic chemistry as well as in medicinal chemistry due to their significant biological activities and structural analogy to α -amino lik acids.²⁻⁵ α -Amino phosphonates has diverse applications such as antibiotics,⁶ antithrombotics,⁷ inhibitors of HIV protease,⁸ and ba peptidases,⁹ anti-cancer agents,¹⁰ antitubercular,¹¹ fungicides, en herbicide and insecticide,¹² α -Amino phosphonates have been used as for the synthesis of valuable actives such as alafosfalin; an antibacterial agent,⁶ glyphosate; a herbicide,¹³ and dufulin; an



Fig. 1 Biologically active molecules.

An efficient, and environmentally benign protocol for a three-component Kabachnik-Fields reaction of aldehydes, amines, and diethyl phosphite catalyzed by sulfated polyborate has been described to afford α -amino phosphonates under solvent-free reaction conditions. The major advantages of the present method are high yields, short reaction time, simple work-up procedure, inexpensive, eco-friendly and reusable catalyst and solvent-free reaction conditions and tolerance towards various functional groups present in the substrates.

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triflates/magnesium sulfate^{,37} magnesium dodecylsulphate,³⁸ tartaric acid,³⁹ sulfamic acid,⁴⁰ silica sulfuric acid,⁴¹ xanthan sulfuric acid,⁴² sulfated zirconia,⁴³ TfOH/C,⁴⁴ [H-DABCO]Cl,⁴⁵ and so on.

However, these methods suffer from various shortcomings like unsatisfactory yields, longer reaction time, extractive product isolation with toxic organic solvents, use of expensive, metalbased, toxic/corrosive catalysts, which limits their use due to environmental issues. Therefore, the development of a safe, environmentally benign, mild, efficient, and high yielding rapid reaction procedure using cost effective and recyclable catalyst would be valuable.

Pursuit of convenient and practical catalytic methods for the current interest in organic synthesis and commercial process; recently we have introduced sulfated polyborate catalyst and demonstrated its efficiency for catalyzing the Biginelli reaction.⁴⁶ Its mild acidity, ease of preparation, reusability, and eco-friendliness have encouraged us to investigate its potential to catalyze many other useful reactions. Therefore, in continuation of our previous study, in this paper, we explored the application of sulfated polyborate catalyst as a rapid and efficient protocol for the synthesis of α -amino phosphonates *via* Kabachnik-Fields reaction of aldehydes, amines and diethyl phosphite under solvent free condition (Scheme 1).

Literature revealed that boric acid catalyzes many important organic transformations at temperature above 100 °C.⁴⁷ Boric acid dehydrates above 100 °C and converts to its polymeric forms, which presumably is the active species catalyzing the reaction.⁴⁸⁻⁴⁹ Dehydrative polymerization of boric acid liberates water molecules which may hamper the progress of the reactions.

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Scheme 1. Schematic representation of sulfated polyborate catalyzed Kabachnik Fields reaction.

This inspired us to develop a polymeric boric acid catalyst with mild Bronsted acidity. To accomplish this boric acid was dehydrated at 200 °C to convert it into its polymeric Lewis acid form and then sulfonated to introduce a mild Bronsted acid character. Boron is an electron deficient element and electron withdrawing effect of adjacent sulfate enhances its Lewis acidity, hence it has both Lewis as well as Bronsted acid characters (Scheme 1).

For initial screening, the study was structured to investigate the suitability of sulfated polyborate as a catalyst at different reaction conditions. For the preliminary experiment, a mixture of benzaldehyde; a model substrate, aniline, and diethyl phosphite were used (Scheme 2). The results are summarized in Table 1.

The effect of the catalyst loading on time and yields of the reaction was assessed (Table 1, entries 2-5). In absence of a catalyst, the reaction proceeded at 90 °C and took longer reaction time with a lower yield (Table 1, entry 1). An increase in the catalyst loading increased the product yield with significate reduction in the reaction time was observed (Table 1, entries 2-5). The catalyst loading beyond 5 wt % was not advantageous (Table 1, entries 4 and 5). Hence, 5 wt % catalyst loading was chosen for further study.

Temperature played an important role for Kabachnik-Fields reaction. The temperature effect was examined at ambient, 50 °C, 70 °C, and 90 °C under solvent free condition using sulfated



Scheme 2. Kabachnik-Fields reaction of benzaldehyde, aniline and diethyl phosphite.

Table 1		
Results	of optimization	studies

Entry	Catalyst	Solvent	Temperature	Time	Yield ^a
	(wt %)		(°C)	(min)	(%)
1.	0	solvent free	90	360	51
2.	1	solvent free	90	30	88
3.	2.5	solvent free	90	15	94
4.	5	solvent free	90	5	98
5.	7.5	solvent free	90	5	98
6.	5	solvent free	rt	60	88
7.	5	solvent free	50	30	93
8.	5	solvent free	70	15	97
9.	5	EtOH	reflux	30	91
10.	5	ACN	reflux	30	90
11.	5	THF	reflux	30	88
12.	5	water	90	30	Traces
13.	5	toluene	90	30	81
14.	5	DMF	90	30	94

^a Isolated yield.

Table 2

Efficiency of sulfated polyborate in comparison with literature reported
catalysts for the Kabachnik-Fields reaction

Entry	Catalyst	Condition	Time	Yield ^a	Ref.
	-		(min)	(%)	
1.	Sulfated	solvent free/	5	98	This
	polyborate	90 °C			work
2.	[H-DABCO]Cl	MeOH/rt	10	96	45
3.	Polyboric acid	solvent free/	45	96	-
		90 °C			
4.	Sulfamic acid	solvent free/rt	60	94	40
5.	Xanthan sulfuric	solvent free/	60	-93	42
	acid	60 °C			
6.	Tartaric acid	solvent free/	120	83	39
		50°C			
7.	Zirconocene	ACN/rt	150	96	22
	bis(perfluorobuta				
	nesulfonate)				
8.	TfOH/C	solvent free/rt	180	97	44
9.	Silica sulfuric	ACN /rt	300	87	41
	acid				
10.	Sulfated zirconia	ACN/rt	480	95	43
11.	Trifluoro acetic	solvent free/rt	1440	96	32
	acid				

^a Isolated yield.

polyborate (Table 1, entry 4 and 6-8). The reaction proceeded at room temperature but took longer time with a relatively lower yield (Table 1, entry 6). An increase in the temperature to 90 °C resulted in significantly increased product yield in shorter reaction time (Table 1, entries 4). Therefore, 90 °C was chosen as optimum temperature for the reaction.

The effect of various solvents on time and yield of the reaction was ascertained (Table 1, entries 9-14). None of the solvents have shown advantage over solvent free condition. Hence, the solvent free condition was regarded as best for the cost and environmental acceptability.

Various catalysts are reported for the synthesis of α -amino phosphonates *via* Kabachnik-Fields reaction. Herein, in comparison with other acid catalysts sulfated polyborate catalyst showed an advantage with respect to reaction conditions, workup procedure, time and yields (Table 2, entry 1-11).

To study the generality and scope, optimized reaction conditions⁵⁴ were applied to various aldehydes. All the aromatic, heterocyclic and alicyclic aldehyde variants reacted well and afforded higher yields of the corresponding α -amino phosphonates in shorter reaction time (Table 3, entry 1-16). Various electron donating or electron withdrawing substituents at the ortho, meta and para position of aromatic aldehydes have been examined. The nature of substitutions on aromatic aldehydes has no significant effect on the reaction time and yields (Table 3, entries 2-12). The protocol was also extended to heterocyclic and alicyclic aldehyde variants, resulted in corresponding a-amino phosphonates in shorter reaction time with good yields (Table 3, entries 13-16). Further the substrate scope was evaluated for various aromatic amines and benzyl amine, which also resulted in higher yields of the corresponding α -amino phosphonates in shorter reaction time. Various electron donating or electron withdrawing substituents at the para position of aromatic amines have been examined. The nature of substitutions on aromatic amines has no significant effect on the reaction time and yields (Table 3, entries 17-21). This protocol tolerated a variety of substituents on aromatic aldehydes and amines, whereas, found to be unsuitable for aliphatic aldehydes and amines.

The reusability of the catalyst in the model reaction of benzaldehyde, aniline and diethyl phosphite under solvent free

Table 3

Substrate scope for the Kabachnik-Fields reaction using sulfated polyborate catalyst

$H_2N^{-R_2}$		Sulfated Polyborate	н	HN^{R_2}	
C R ₁) + OEt P−OEt U	Solvent free, 90 °C	R ₁	P U OEt	
Entry	Aldehydes (R ₁)	Amines (R ₂)	Time (min)	Yield ^a (%)	
1.	0	NH ₂	5	98	
2.		NH ₂	10	94	
3.		D NH ₂	10	95	
4.		D NH ₂	5	95	
5.		NH ₂	10	93	
6.	O ₂ N	0 NH2	10	94	
7.		O NH ₂	5	94	
8.		NH ₂	10	92	
9.		NH ₂	10	94	
10.		NH ₂	10	95	
11.		NH ₂	10	94	
12.			10	93	
13.		NH ₂	10	93	
14.	0	NH ₂	10	95	
15.	N O	NH ₂	10	90	
16.	0	NH ₂	5	95	
17.	0	NH ₂	10	97	
18.	0	NH ₂	10	95	
19.	0		10	93	
20.	0	NH ₂	10	97	



conditions at 90 °C was evaluated. After completion of each reaction cycle, water was added and the product was filtered off. The filtrate was evaporated in vacuum rotary evaporator to recover the catalyst quantitatively. The recovered catalyst was recycled for four times with no significant loss in a catalytic activity (Fig. 2).

The plausible mechanism of the Kabachnik-Fields reaction catalyzed by sulfated polyborate is as depicted in Fig. 3. A nucleophilic attack of aniline on sulfated polyborate activated aldehydes results in formation of imine intermediate^{50,51} followed by a nucleophilic attack of phosphite on sulfated polyborate activated imine leads to the formation of α -amino phosphonates.5

Conclusion

In conclusion, the present procedure is a rapid, efficient and eco-friendly protocol for Kabachnik-Fields reaction of various aldehydes, amines, and diethyl phosphite under optimized conditions. Mild reaction conditions, easy of workup procedure, shorter reaction time, high yields, and recyclability of the catalyst are the key features of this procedure. Moreover, this protocol has the ability to tolerate a wide variety of substituents along with enhanced product purity which promises economical as well as ecological rewards.



Fig. 3. The plausible mechanism of the Kabachnik-Fields reaction catalyzed by sulfated polyborate.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/00.0000/

References and notes

- 1. E.K. Fields, J. Am. Chem. Soc. 74 (1952) 1528-1531.
- M.C. Allen, W. Fuhrer, B. Tuck, R. Wade, J.M. Wood, J. Med. Chem. 32 (1989) 1652–1661.
- 3. P.P. Giannousis, P.A. Bartlett, J. Med. Chem. 30 (1987) 1603–1609.
- 4. P.A. Bartlett, W.B. Kezer, J. Am. Chem. Soc. 106 (1984) 4282–4283.
- H. Kleszczynska, J. Sarapuk, Cell. Mol. Biol. Lett. 6 (2001) 83–92.
 F.R. Atherton, C.H. Hassall, R.W. Lambert, J. Med. Chem. 29 (1986) 29–40.
- 7. J.H. Meyer, P.A. Bartlett, J. Am. Chem. Soc. 120 (1998) 4600-4609.
- D. Hendlin, E.O. Stapley, M. Jackson, H. Wallick, A.K. Miller, F.J. Wolf, T.W. Miller, L. Chaiet, F.M. Kahan, E.L. Foltz, Science. 166 (1969) 122–123.
- D. Miller, S. Hammond, T.H. Bugg, J. Chem. Soc. Perkin Trans. 1 (1998) 131–142.
- 10. P. Kafarski, B. Lejczak, Curr. Med. Chem. 1 (2001) 301-312.
- S.A.R. Mulla, M.Y. Pathan, S.S. Chavan, S.P. Gample, D. Sarkar, RSC Adv. 4 (2014) 7666–7672.
- L. Maier, H. Spörri, Phosphorus. Sulfur. Silicon Relat. Elem. 61 (1991) 69–75.
- 13. S.O. Duke, S.B. Powles, Pest Manag. Sci. 64 (2008) 319-325.
- 14. Z. Chen, M. Zeng, B. Song, C. Hou, D. Hu, X. Li, Z. Wang, H. Fan, L. Bi, J. Liu, PLoS One 7 (2012) 37944.
- 15. B.C. Ranu, A. Hajra, U. Jana, Org. Lett. 1 (1999) 1141-1143.
- Z. Rezaei, H. Firouzabadi, N. Iranpoor, A. Ghaderi, M.R. Jafari, A.A. Jafari, H.R. Zare, Eur. J. Med. Chem. 44 (2009) 4266–4275.
- 17. M.R. Saidi, N. Azizi, Synlett (2002) 1347–1349.
- J.S. Yadav, B.V.S. Reddy, K.S. Raj, K.B. Reddy, A.R. Prasad, Synthesis (Stuttg). (2001) 2277–2280.
- S. Bhagat, A.K. Chakraborti, J. Org. Chem. 73 (2008) 6029–6032.
 A.A. Jafari, M. Nazarpour, M. Abdollahi-Alibeik, Heteroat. Chem. 21
- (2010) 397–403.
- 21. A.K. Bhattacharya, T. Kaur, Synlett (2007) 745-748.
- 22. N. Li, X. Wang, R. Qiu, X. Xu, J. Chen, X. Zhang, S. Chen, S. Yin, Catal. Commun. 43 (2014) 184–187.
- S. Kumar, S.C. Taneja, M.S. Hundal, K.K. Kapoor, Tetrahedron Lett. 49 (2008) 2208–2212.
- S. Chandrasekhar, S.J. Prakash, V. Jagadeshwar, C. Narsihmulu, Tetrahedron Lett. 42 (2001) 5561–5563.
- 25. M. Hosseini-Sarvari, Tetrahedron 64 (2008) 5459-5466.
- X.C. Li, S.S. Gong, D.Y. Zeng, Y.H. You, Q. Sun, Tetrahedron Lett. 57 (2016) 1782–1785.
- 27. F. Xu, Y. Luo, J. Wu, Q. Shen, H. Chen, Heteroat. Chem. 17 (2006) 389–392.
- 28. H.J. Ha, G.S. Nam, Synth. Commun. 22 (1992) 1143-1148.
- H. Firouzabadi, N. Iranpoor, S. Sobhani, Synthesis (Stuttg). (2004) 2692–2696.
- 30. S. Bhagat, A.K. Chakraborti, J. Org. Chem. 72 (2007) 1263–1270.
- S.G. Lakoud, M. Merabet-Khelassi, L. Aribi-Zouioueche, Res. Chem. Intermed. 42 (2016) 4403–4415.
- 32. T. Akiyama, M. Sanada, K. Fuchibe, Synlett (2003) 1463-1464.
- S. Sobhani, E. Safaei, M. Asadi, F. Jalili, J. Organomet. Chem. 693 (2008) 3313–3317.
- 34. B. Kaboudin, M. Sorbiun, Tetrahedron Lett. 48 (2007) 9015–9017.
- M. Tajbakhsh, A. Heydari, H. Alinezhad, M. Ghanei, S. Khaksar, Synthesis (Stuttg). (2008) 352–354.
- 36. A.K. Bhattacharya, K.C. Rana, Tetrahedron Lett. 49 (2008) 2598-2601.
- 37. C. Qian, T. Huang, J. Org. Chem. 63 (1998) 4125–4128.
- 38. K. Ando, T. Egami, Heteroat. Chem. 22 (2011) 358-362.
- 39. N. Gangwar, V.K. Kasana, Synth. Commun. 41 (2011) 2800–2804.
- S.D. Mitragotri, D.M. Pore, U. V. Desai, P.P. Wadgaonkar, Catal. Commun. 9 (2008) 1822–1826.
- M.T. Maghsoodlou, S.M.H. Khorassani, N. Hazeri, M. Rostamizadeh, S.S. Sajadikhah, Z. Shahkarami, N. Maleki, Heteroat. Chem. 20 (2009) 316–318.
- G. Sun, J. Hou, J. Dou, J. Lu, Y. Hou, T. Xue, Z. Zhang, J. Chinese Chem. Soc. 57 (2010) 1315–1320.
- 43. Y. Prashanthi, N. Bhasker, A. Kavita, R. Srinivas, B.V.S. Reddy, Der

Pharma Chemica. 5 (2013) 288-293.

- A.A. Jafari, S. Amini, F. Tamaddon, J. Iran. Chem. Soc. 10 (2013) 677– 684.
 - 45. Y.Q. Yu, D.Z. Xu, Synthesis (Stuttg). 47 (2015) 1869–1876.
 - C.K. Khatri, D.S. Rekunge, G.U. Chaturbhuj, New J. Chem. (2016); doi:10.1039/C6NJ03120J.
 - A. Shahrisa, S. Esmati, M.G. Nazari, J. Chem. Sci. 124 (2012) 927–931.
 S. Chandrasekhar, K. Gopalaiah, Tetrahedron Lett. 43 (2002) 2455–
 - 2457.
 O. Sivrikaya, A.I. Arol, Open Miner. Process. J. 3 (2010) 25-35.
 - 50. M. Yamanaka, T. Hirata, J. Org. Chem. 74 (2009) 3266–3271.
 - 51. J. Tang, L. Wang, W. Wang, L. Zhang, S. Wu, D. Mao, J. Fluor. Chem. 132 (2011) 102–106.
 - H. Ghafuri, A. Rashidizadeh, H.R.E. Zand, RSC Adv. 6 (2016) 16046– 16054.
 - 53. Preparation of Sulfated polyborate: Boric acid was heated in a petri dish at 200 °C for 4 h to convert it to the polyboric acid; resultant glassy solid was ground into fine powder. Polyboric acid powder (5 g) was suspended in chloroform (20 ml) in 250 ml round bottom flask, chlorosulfonic acid (4.23 ml) was added dropwise over a period of 30 minutes at room temperature. The mixture was further stirred for 120 min. The reaction was quenched by ethanol (10 ml). Residual HCl gas was flushed with nitrogen, the solid was filtered, washed several times with chloroform. Finally, solid sulfated polyborate was dried at 100 °C in hot air oven till constant weight.
 - 54. General procedure for the synthesis of α -amino phosphonates: To a mixture of aldehyde, (2.0 mmol), amine (2.0 mmol), and diethyl phosphite (2.2 mmol), was added sulfated polyborate (5 wt %). The reaction was stirred at 90 °C in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and quenched by water; solid precipitated was filtered at vacuum pump, washed with water (3 X 5 mL), and dried under vacuum to afford the pure products.

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Highlights:

- Solvent free, efficient, rapid • and environmentally benign Kabachnik-Fields reaction.
- High yields, short reaction time and simple • work-up procedure.
- Recyclable catalyst with no significant loss ٠ in activity.
- Method tolerates a variety of functional • groups with wide substrate scope.