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REGULAR ARTICLE

Niobium pentoxide, a recyclable heterogeneous solid surface catalyst for the synthesis of α-amino phosphonates

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Abstract. Niobium pentoxide, a bifunctional solid surface catalyst, has been successfully employed to facilitate the three-component reaction between aldehydes, amines and triethyl phosphite at room temperature under solvent-free conditions to generate α-amino phosphonate in moderate to good yields. The catalyst can be recycled through simple filtration and reused to effect this transformation.

Keywords. α-Amino phosphonates; Bifunctional catalyst; Niobium pentoxide; Kabachnik-fields reaction; Organophosphorus compounds.

1. Introduction

The conventional way of establishing C–C bond involves the use of an electrophilic substrate with Lewis acids and nucleophiles[1]. Construction of C–N and C–P bond in a tandem fashion also facilitated by Lewis acids[2] including $NbCl_5$.[2a] Use of these Lewis acids lead to the generation of effluents, which are not environmentally benign. The heterogeneous Lewis acid catalyst without using an organic solvent is indeed an attractive and respected proposition for organic transformations. Zeolites,[3] metal oxides,[4] modified clay's[5] and others[6] have been utilized as heterogeneous Lewis acid catalysts in several chemical transformations. Recently the niobium pentoxide, a metal oxide, proved to display a Lewis acidic activity in various organic transformations[7]. Due to the presence of polarized Nb-O bond in distorted polyhedron structure of Nb_2O_5 (distorted NbO_6 octahedra and NbO_4 tetrahedra) possess both Brønsted acid sites (surface OH group) and Lewis acidic site (coordinately unsaturated Nb^{5+}). Presence of such bifunctional catalytic sites along with insoluble nature in water and in other organic solvents, the niobium pentoxide would be an ideal choice to use as a solid acid catalyst to activate both carbonyl group and *in situ* generated imine group. While Nb_2O_5 has been successfully utilized for several organic transformations, the use of a bifunctional catalyst in a concomitant formation of C-N and C-P bonds as in Kabachnik-Fields reaction to generate α-amino phosphonates was not explored. α-Amino phosphonates are very important structural motifs isoteric with α-amino acids of biological significance (Figure 1). α-Amino phosphonates are known to display numerous biological activities such as antifungal,[8] antioxidant,[9] antibacterial,[10] antimicrobial,[11] antiviral,[12] anti-inflammatory[13] and anticancer activities.[14] These molecules also act as plant growth regulators[15] as well as an HIV protease inihibitor.[16]

Therefore, numerous synthetic methodologies facilitated by either acids or base have been developed to prepare derivatives of α-amino phosphonic acids.[2,17] Although, there are several catalytic systems developed for α-amino phosphonates synthesis from aldehydes, amines and triethyl phosphites/dialkyl phosphites, the development of recoverable and reusable catalytic system under solvent-free condition will be encouraged. Therefore, the intrinsic solid acid property of Nb_2O_5 encouraged us to examine this

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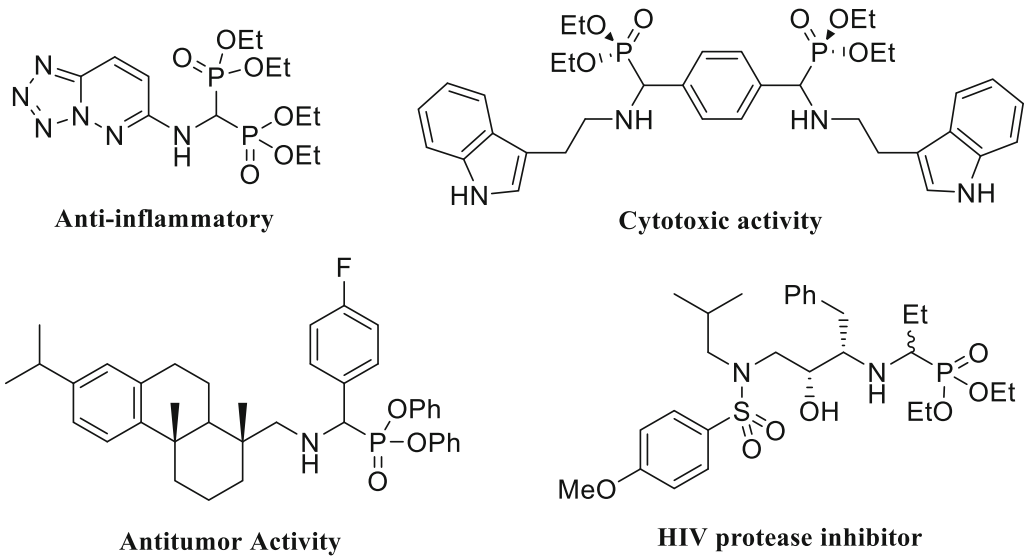


Figure 1. Biological significance of α-amino phosphonates.

catalyst for the Kabachnik-Fields reaction to generate α-amino phosphonates. In our continued pursuit of employing Lewis acid/Brønsted acid-mediated carbonyl group activation strategy towards C-C[18] and C-heteroatom bond formation,[19] we here in would like to disclose the three-component reaction between aldehyde, amine and triethyl phosphite in the presence of Nb_2O_5 for the synthesis of α-amino phosphonates.

2. Experimental

2.1 *General information*

All reactions were performed in an oven-dried boiling tube and cooled down to room temperature. After reaching room temperature, the boiling tube was charged with reagents and catalyst. HMRS spectra were measured with Agilent-6530 BQ-TOF (ESI-HRMS). The ^1H and ^{13}C NMR spectroscopic data were characterized by a Bruker AVANCE 400 spectrometer. By using TMS as an internal standard all the samples were recorded for NMR spectra data in $CDCl_3$ solvent at room temperature. The chemical shift values are expressed in δ ppm downfield from internal standard TMS. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet), coupling constants in Hertz (Hz) and intensity with integration. Infrared spectra were obtained through Thermo Nicolet iS10 FT-IR Spectrophotometer by using potassium bromide thin films. All the IR data are reported in absorption frequencies (cm^{-1}). Analytical thin-layer chromatographic tests were done on pre-coated Merck silica gel GF_{254} plates. The spots were visualized by short exposure to UV light (254 nm). Column chromatography was performed using Merck silica gel 100-200 mesh. For the synthesis, chemicals such as amines, aldehydes etc. supplied by Aldrich and HiMedia were used as supplied if it was solid. Nb_2O_5 supplied by HiMedia, India was used. The liquid aldehydes were distilled and used. The solvents used for purification were purified by standard procedure. Structures of the previously reported α-amino phosphonates were ascertained by comparing their spectral data such as IR, ^1H NMR and ^{13}C NMR with reported data.

2.2 *General procedure for the synthesis of α-amino phosphonates (3aa–3ra)*

An oven-dried boiling tube was taken out and cooled down to room temperature. After reaching room temperature the tube was charged with a magnetic stir bar, benzaldehyde (1 mmol), aniline (1 mmol), triethyl phosphite (1 mmol) and Nb_2O_5 (106 mg, 40 mol%) catalyst. The tube was covered with septa. Then the mixture was stirred under neat conditions at room temperature. The conversion was monitored by TLC. After all the starting material was consumed, dichloromethane was added to the reaction mixture

and stirred. The dichloromethane was filtered through filter paper. The solvent was evaporated and the reaction mass was purified through silica gel chromatography using ethyl acetate and hexane as eluent. For example, following this procedure, benzaldehyde (106 mg, 1 mmol), aniline (93 mg, 1 mmol), triethyl phosphite (166 mg, 1 mmol) and Nb_2O_5 (0.4 mmol) furnished the crude product mixture. Upon purification through silica gel column chromatography using hexane/ethyl acetate (80:20) as eluent, diethyl (phenyl(phenylamino)methyl)phosphonate (**3aa**) was obtained as a colorless solid (270 mg, 85% yield); M.p. 89 °C, *Lit.*[21] M.p. 90–91; IR (KBr, cm^{-1}): 3295, 2983, 1604, 1497, 1236, 1058, 1018, 966, 752, 697, 573; ^1H ($CDCl_3$, 400 MHz): δ_H 7.49–7.47 (m, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.29–7.28 (m, 1H), 7.13–7.09 (m, 2H), 6.71–6.67 (m, 1H), 6.62–6.56 (m, 2H), 4.91 (brs, 1H), 4.78 (d, $^1J_{P\text{-}H}$ = 24.4 Hz, 1H), 4.16–4.10 (m, 2H), 3.97-3.91 (m, 1H), 3.71–3.65 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H3,4-dimethoxyaniline), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C ($CDCl_3$, 100 MHz): δ_C 146.5, 146.3, 136.0, 135.9, 130.1, 129.2, 128.7, 128.6, 128.4, 128.0, 128.0, 127.7, 127.2, 118.5, 113.9, 63.4, 63.4, 63.3, 56.6, 55.4, 16.6, 16.5, 16.3, 16.2.

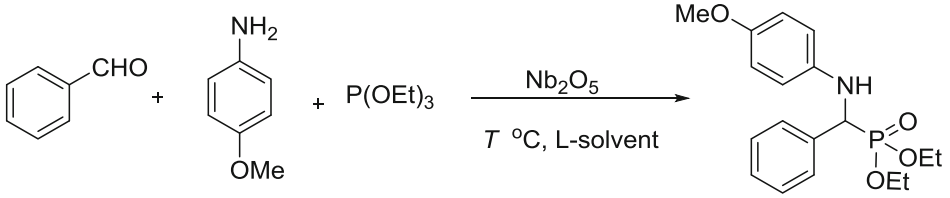
The experimental and characterization details for the compounds **3aa**–**3ra** are given in the supplementary information.

3. Results and Discussion

Due to the water-tolerant Lewis acidic nature of Nb_2O_5, we intend to examine the Kabachnik-Fields reaction between aldehyde **1a**, amine **2b** and triethyl phosphite in the presence of 1 equivalent of Nb_2O_5 in water at elevated temperatures (120 °C, 100 °C and 80 °C). To our delight, the expected α-amino phosphonate **3ab** was obtained albeit in 25%, 32% and 49% yields after 24 h respectively (Table 1, entry **1−3**). The reaction was also performed at room temperature for 36 h to witness the formation of product **3ab** only in 25% yield (Table 1, entry 4).

In the absence of Nb_2O_5, the reaction furnished **3ab** in very trace quantity and indicating the catalytic role played by Nb_2O_5 in this reaction. Quite interestingly, the reaction between aldehyde **1a**, amine **2b** and triethyl phosphite in the presence of Nb_2O_5 (1 equiv.) in dichloromethane at room temperature delivered the expected α-amino phosphonate in 58% yield after 36 h, which is better than water as solvent (Table 1, entry 6). Encouraged by this result, the catalyst loading was reduced from 1 equivalent to 0.5 equivalent and 0.4 equivalent. The results are found to be encouraging (Table 1, entries 7 and 8). With Nb_2O_5 (40 mol%) in dichloromethane as a solvent for 24 h, the α-amino phosphonate **3ab** was obtained in 65%

Table 1. Screening of solvent and temperature in the presence of Nb_2O_5.[a]

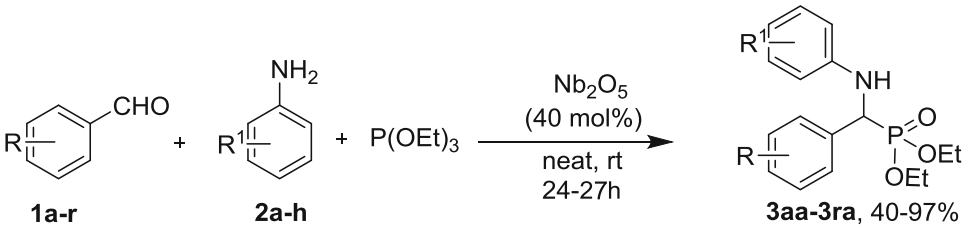


1a **2b** **3ab**

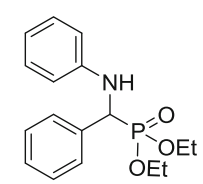
Entry	Solvent	Nb_2O_5 (mmol)	Temperature (°C)	Time (h)	Yield (%)[b]
1	H_2O	1.00	120	24	25
2	H_2O	1.00	100	24	32
3	H_2O	1.00	80	24	49
4	H_2O	1.00	rt	36	25
5	H_2O	–	rt	36	Trace
6	CH_2Cl_2	1.00	rt	36	58
7	CH_2Cl_2	0.50	rt	24	60
8	CH_2Cl_2	0.40	rt	24	65
9[c]	**–**	**0.40**	**rt**	**24**	**97**
10[c]	–	0.30	rt	24	80
11[c]	–	0.25	rt	24	48

[a]Reaction condition: Benzaldehyde **1a** (1.0 mmol), aniline **1b** (1.0 mmol), triethyl phosphite (1.0 mmol) and niobium pentoxide (40 mol%). [b]Isolated yields of pure product. [c]Under solvent-free condition.

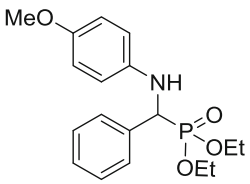
Table 2. Synthesis of α-amino phosphonate derivatives



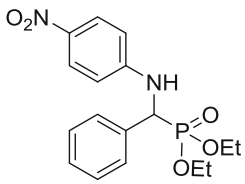
1a-r **2a-h** **3aa-3ra**, 40-97%



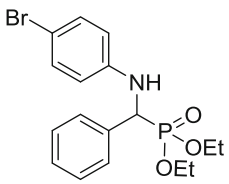
3aa, 24h, 85%



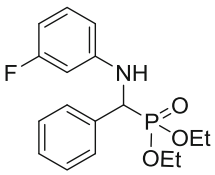
3ab, 24h, 97%



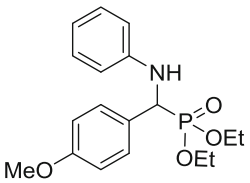
3ae, 24h, 66%



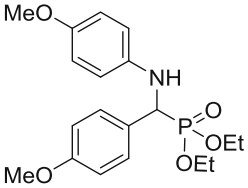
3af, 24h, 87%



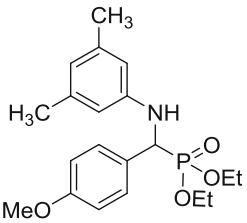
3ah, 24h, 71%



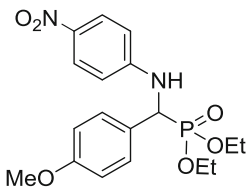
3ba, 24h, 89%



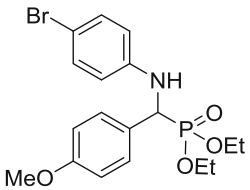
3bb, 24h, 71%



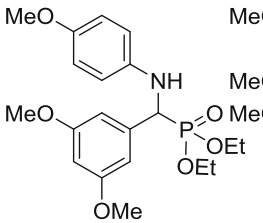
3bc, 25h, 82%



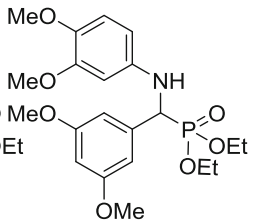
3be, 24h, 66%



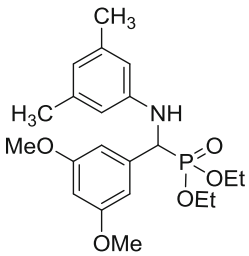
3bf, 25h, 76%



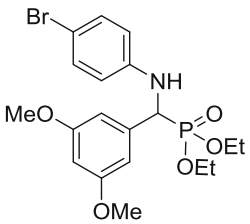
3cb, 24h, 80%



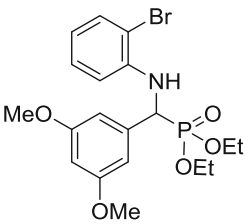
3cd, 24h, 74%



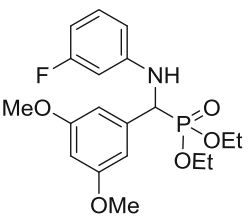
3cc, 24h, 70%



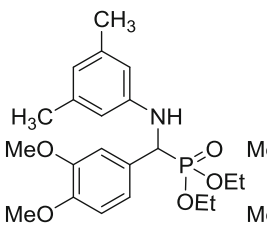
3cf, 25h, 85%



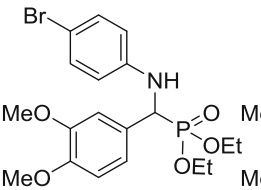
3cg, 24h, 58%



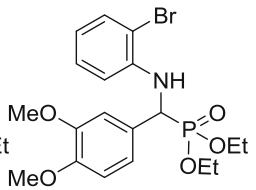
3ch, 25h, 64%



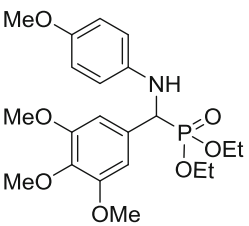
3dc, 24h, 75%



3df, 26h, 75%

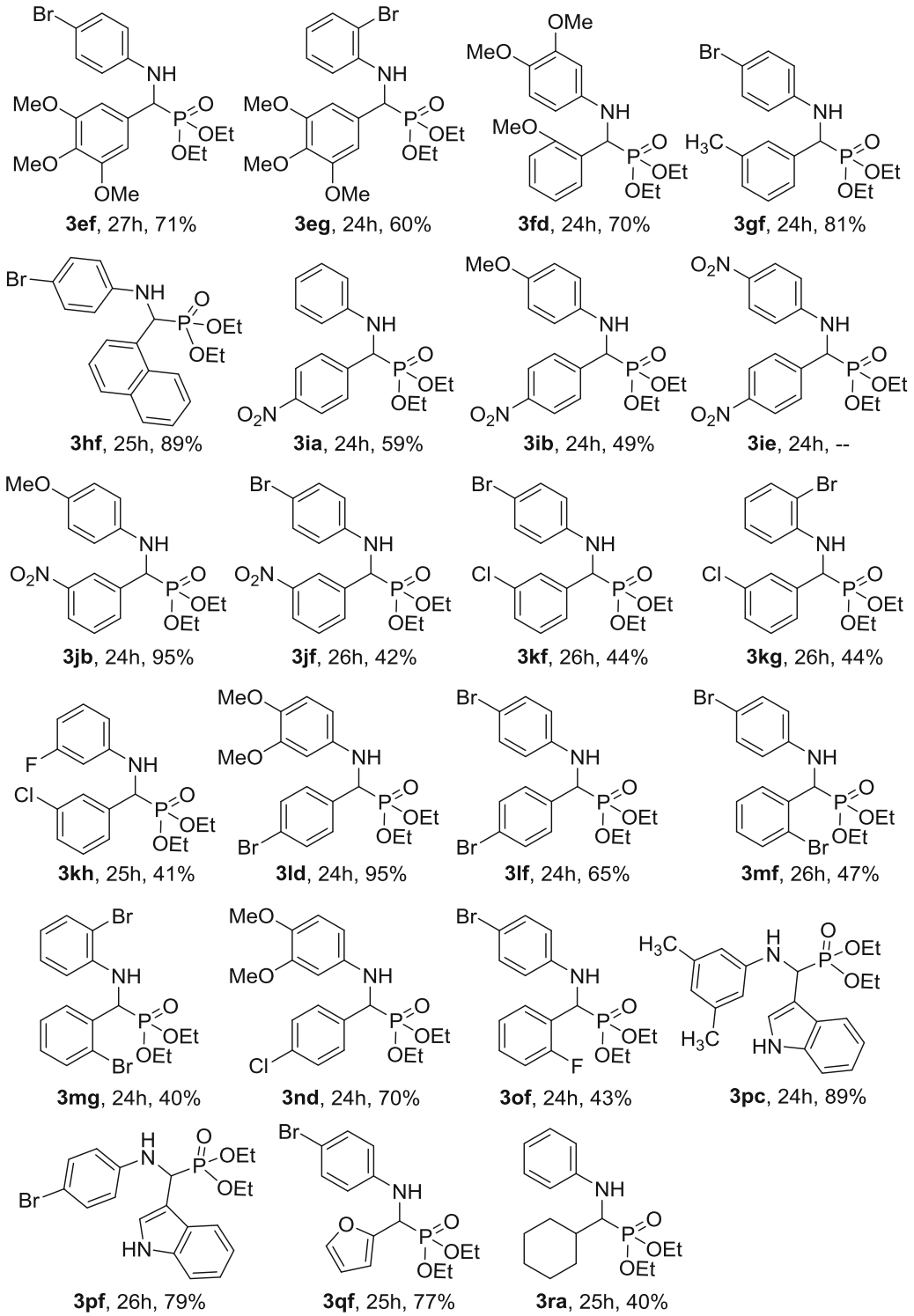


3dg, 25h, 55%



3eb, 24h, 69%

Table 2. (contd)



[a]Reaction condition: Benzaldehyde (1.0 mmol), aniline (1.0 mmol), triethyl phosphite (1.0 mmol)
[b]Yields are of isolated products

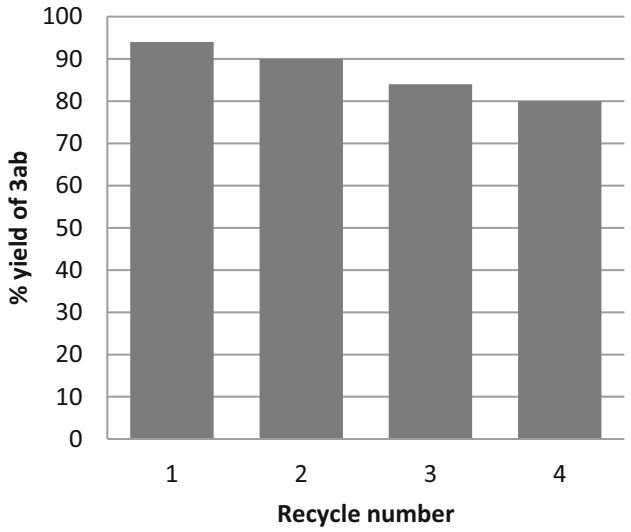


Figure 2. Reusability of Nb_2O_5 catalyst for the preparation of α-amino phosphonate 3ab.

yield. The enhanced yield in non-aqueous condition intrigued us to examine the reaction in the absence of solvent. Accordingly, the reaction was carried out between aldehyde **1a**, amine **2b** and triethyl phosphite in the presence of Nb_2O_5 (40 mol%) under neat condition at room temperature. Under this reaction condition, the product **3ab** was obtained in 97%, an excellent yield, after 24 h (Table 1, entry 9). Further reduction in catalyst load did not show any fruitful result (Table 1, entries 10−11).

Based on these optimized conditions, we investigated the scope of substrates bearing electron-donating/electron-withdrawing groups or without substituents over various aromatic or heteroaromatic aldehydes as well as aryl amines. These results are summarized in Table 2. The desired products were obtained in poor to excellent yield depending on the substituents on both aldehyde and amine (Table 2: entries **3aa** to **3ra**, 40-97%). When benzaldehyde **1a** reacted with various electronically different substituents containing anilines the products are obtained in moderate to excellent yields (Table 2, entries **3aa**−**3ah**). More nucleophilic aniline **2b** due to the presence of electron-donating methoxy group furnished the α-amino phosphonate in excellent yield, compared to the poor nucleophilic aniline **2e** (Table 2, entry **3aa**−**3ae**). Electron donating groups containing aldehydes **2b-2f** with aniline of varying nucleophilicity delivered the expected product in moderate to excellent yields (Table 2, entries **3ba-3gf**). The presence of electron-donating groups in benzaldehydes reduces the electrophilicity of carbonyl carbon as well as the imine carbon formed in this multi-component reaction and hence the yield of α-amino phosphonate obtained from **1b**−**1 g** are slightly lower compared to the products obtained from benzaldehyde **1a** (Table 2 compare entries **3aa**−**3ah** and **3ba**−**3gf**). Whereas the α-amino phosphonate **3hf** obtained in good yield when naphthaldehyde **1 h** and 4−bromoaniline **2f** reacted with triethyl phosphite (Table 2, entry **3hf**). The electron-withdrawing nitro group containing benzaldehydes **1i**−**1j** furnished the corresponding α-amino phosphonates in very poor to excellent yield

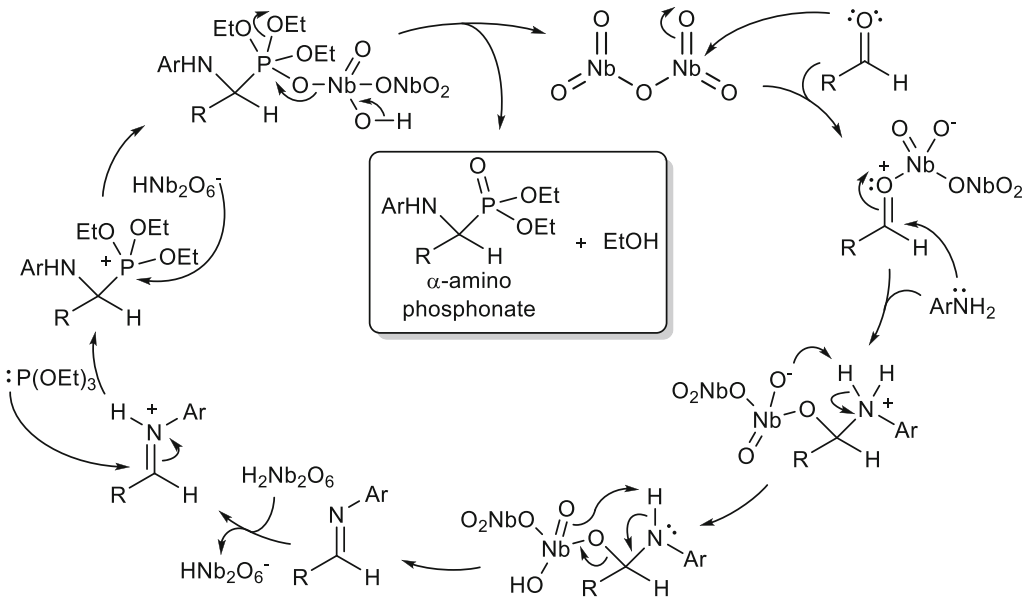


Figure 3. Plausible mechanism for the formation of α-amino phosphonate.

depending on the anilines used (Table 2, entries **3ia−3jf**). 4−Nitrobenzaldehyde furnished a complex mixture of products with 4−nitroaniline and this may be due to the poor complexing ability of aldehyde with Nb_2O_5 as well as poor nucleophilicity of 4−nitroaniline (Table 2, entry **3ie**). On the other hand, 3−nitrobenzaldehyde **1j** with more nucleophilic aniline, p−anisidine **2b,** in the presence of Nb_2O_5 furnished the corresponding α-amino phosphonate **3ab** in excellent yield (Table 2, entry **3jb**). Whereas, the reaction of 3-nitrobenzaldhyde with 4−bromoaniline in presence of Nb_2O_5 and triethyl phosphite, the α-amino phosphonate was obtained in moderate yield (Table 2, entry **3jf**).

The halogen-substituted benzaldehydes **2k-2o** upon reaction with anilines in the presence of Nb_2O_5 and triethyl phosphite, the respective α-amino phosphonates were obtained in moderate to good yields (Table 2, entries **3kf−3of**). Interestingly, the electron-rich nucleophile, 3,4-dimethoxyaniline **2d** with 4-bromobenzaldehyde furnished the corresponding α-amino phosphonate in excellent yield (Table 2, entry **3ld**). Heterocyclic carboxaldehyde also underwent this reaction smoothly to deliver the α-amino phosphonates, **3pc-3pf** and **3ql** in 89%, 79% and 77% yields, respectively. Aliphatic aldehyde too furnished the α-amino phosphonate in 40% yield (Table 2, entry **3ra**).

It is noteworthy that the niobium pentoxide, a heterogeneous solid surface catalyst, is failed to dissolve in any solvents. Since it is insoluble in any solvent, the catalyst can be readily recovered by filtration and reused for the next cycle (Figure 2). Therefore, the recovered catalysts Nb_2O_5 reused after drying at 120 °C for 1 h. The product **3ab** was obtained in 94% yield. Second and third cycle furnished the α-amino phosphonate in 90% and 84% yields respectively. The fourth cycle furnished the α-amino phosphonate *albeit* in 80% yields. This indicates that the catalytic activity is indeed retained for further uses (Figure 2).

Based on the results obtained thus far we propose a plausible catalytic cycle for the formation of α-amino phosphonate from aldehyde, primary amine, triethyl phosphate in presence of Nb_2O_5. Due to the presence of Lewis acidic nature, the Nb_2O_5 coordinates with oxygen [7] in aldehyde to facilitate the formation of imine with primary amine. The hydrated niobium pentoxide ($H_2Nb_2O_6$) generated along with imine formation may then activate the aldimine by protonation and then make aldimine to react with triethyl phosphite to generate α-amino phosphonate as shown in the catalytic cycle (Figure 3).

4. Conclusions

In conclusion, we carried out successfully the Kabachinik-Fields reaction with an equimolar ratio of aldehydes, amines and triethyl phosphite using heterogeneous solid surface niobium pentoxide in substoichiometric quantity, which enables the direct access to the functionalized α-amino phosphonates. The condensation process involves the solvent-free condition at room temperature to produce α-amino phosphonates in moderate to excellent yields. Since the catalyst is insoluble in organic solvents, the catalyst can be recovered by simple filtration and reused for further catalytic cycle.

Supplementary Information (SI)

Details related to experimental data, references and 1H 285 NMR and 13C NMR spectra are available at https://www.ias.ac.in/chemsci.

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