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Synthesis of α-Amino Phosphonates by Three Component Condensation of Carbonyl Compound, Amine, and Dialkyl Phosphite Using Yttria-zirconia Based Lewis Acid Catalyst

S. Ramalingam · Pradeep Kumar

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Abstract An efficient Yttria-zirconia Lewis acid catalyzed one-pot synthesis of α-amino phosphonates by three component coupling reaction of a carbonyl compound amine and dialkyl phosphates is described in good to high yield.

Keywords α-amino phosphonates · Yttria-zirconia based Lewis acid catalyst · Three component coupling

1 Introduction

α-Amino phosphonates, being structural analogs to α-amino acids, have shown considerable potentials as pharmacological agents [1], peptide mimetics [2], enzyme inhibitors [3], and also play an important role in hapten design for antibody generation [4]. Several synthetic methods for α-amino phosphonates have been developed during past two decades [5]. The general method involves the addition of phosphorus nucleophiles to imines, catalyzed by a base or an acid. Lewis acids such as $SnCl_2$, $SnCl_4$ [5a], $BF_3·Et_2O$ [5b], $TiCl_2$ [5c], $TaCl_3$–SiO_2 [5d], montmorillonite clay and $ZrCl_4$ [6], $ZnCl_2$/MgBr [7], have been used earlier. However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and dialkyl phosphite, as the amine and water that exist during imine formation can decompose or deactivate when Lewis acids were used as catalyst [6, 7]. To circumvent the problems associated with these methods, one-pot procedure using lanthanide triflate [8a] and indium trichloride [8b] as catalyst has been developed. $LiClO_4$/LPDE or $LiClO_4$/TMSCl mediated synthesis of α-aminophosphonate are also available [8c]. Recently ionic liquids have also been employed for the synthesis of α-amino phosphonates in moderate yields [9a]. Thus an efficient procedure for the synthesis of α-amino phosphonates from the aldehydes and ketones with aliphatic as well as aromatic amines is highly desirable. In continuation of our ongoing research programme aimed at the application of Yttria-zirconia based Lewis acid catalyst for various organic transformations [10], we have further explored the efficacy of this catalyst for the three component condensation of carbonyl compound, amine and dialkyl phosphite to yield α-amino phosphonates in good to excellent yields and selectivity (Table 1; Scheme 1).

2 Experimental

2.1 Materials and Equipment

All reactions were run under air atmosphere. Chromatographic separations were done using EM SiO_2-60(300–400 mesh) as the stationary phase. The IR spectra were recorded on Perkin–Elmer spectrophotometer 683B or 1605FT-IR and adsorptions are expressed in cm^{-1}. The ^1H and ^{13}C-NMR spectra were recorded on Brucker AC-200, MSL-300, DRX-500 MHz instruments using TMS as the internal standard. Mass spectra were obtained with Finningen MAT mass spectrometer. Elemental analyses were carried out with a carlo Erba CHNS-O analyzer. The diffractogram of X-ray powder diffractometer model D/Max. IIIVC with N-filtered Cu Kα radiation. FTIR spectrum of pyridine adsorbed on the yttrium-based catalyst recorded on a Nicolet 60 SXB FTIR spectrometer. TPD profile

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S. Ramalingam · P. Kumar (✉)
Division of Organic Chemistry, National Chemical Laboratory, Pune 411 008, India
e-mail: pk.tripathi@ncl.res.in

Scheme 1

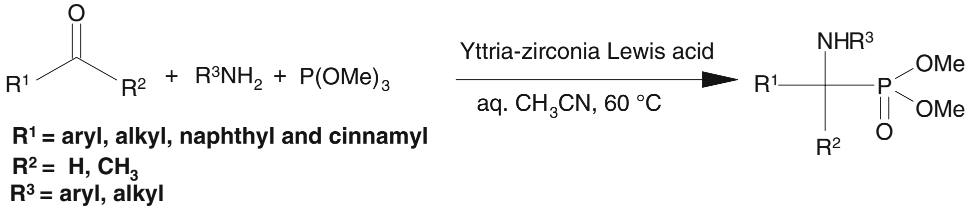
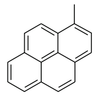
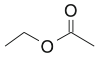
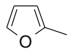
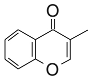
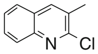
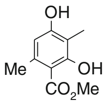


Table 1 One-pot synthesis of α-amino phosphonates catalyzed by yttria-zirconia based Lewis acid catalyst

Entry	*R*[1]	*R*[2]	*R*[3]	Time (h)	Yield[a,b] (%)	M.P. (°C)
1	Ph	H	Ph	2	99	181–183
2	Ph	H	$PhCH_2$	3	86	171–172
3	Ph	H	n-C_3H_7	4	95	168–169
4	4-OMe–C_6H_4	H	Ph	3	95	184–185
5	4-Cl–C_6H_4	H	4-OMe–C_6H_4	7	82	155–158
6	4-OMe–C_6H_4	H	4-OMe–C_6H_4	4	98	184–185
7	4-Me–C_6H_4	H	Ph	7	79	174–175
8	Ph–CH=CH–(trans)	H	Ph	4	98	Brown oil
9	2-OH–C_6H_4	H	4-Cl–C_6H_4	9	77	Brown oil
10	2-Me-6-OMe–C_6H_3	H	$PhCH_2$	5	55	162–163
11	2-Cl–C_6H_4	H	$PhCH_2$	11	93	165–167
12	3-OMe–C_6H_4	H	2,6(Me)$_2$–C_6H_3	10	89	173–175
13	3,4,5-(OMe)$_3$–C_6H_2	H	4-OMe–C_6H_4	3	89	191–194
14	4-NO_2–C_6H_4	H	Ph	6	87	201–203
15	4-N(Me)$_2$–C_6H_4	H	$PhCH_2$	7	84	218–220
16	2-OH-3-OMe–C_6H_3	H	2-Cl-3-F–C_6H_3	9	99	189–190
17	3,4,-(OMe)$_2$–C_6H_3	H	2-NO_2-4-OMe–C_6H_3	9	98	198–200
18	1-Napthyl	H	2,6-(Me)$_2$-C_6H_3	6	75	Pale green oil
19		H	$PhCH_2$	5	98	Dark brown oil
20	Ph	CH_3	$PhCH_2$	5	48	Brown oil
21		CH_3	Ph	5	45	Pale yellow oil
22	Me_2CH	H	$PhCH_2$	7	88	Dark brown oil
23		H	4-OMe–C_6H_4	3	83	Brown oil
24		H	$PhCH_2$	6	99	154–155
25		H	Ph	12	75	224–226
26		H	$PhCH_2$	6	42	167–169

[a] Isolated yield after column chromatography

[b] Products were characterised by spectroscopy methods (IR, ^{1}H NMR and Mass)

(ammonia) of the yttrium-based catalyst was recorded on a Sorbstar apparatus. Determination of specific surface area was carried out by BET (Brunner–Emmett–Teller) N_2 adsorbtion using a Omnisorp 100CX apparatus. Solvents were purified and dried by standard procedures before use according to reported procedure [11] and distilled prior to use. Petroleum ether refers to the fraction collected in boiling range 60–80 °C.

The catalyst was prepared and characterized in following manner and it was calcined at 573 K before use.

2.2 Synthesis of Catalyst

The catalyst was prepared by mixing aqueous solutions of yttrium nitrate and zirconyl nitrate in the mole ratio 16:84, to which aqueous ammonia (28%) was added under vigorous stirring until a pH of 8.5 was achieved and precipitate was formed. Washing with deionized water, drying at 110 °C for 24 h, treating with sulfuric acid (4 M), drying at 120 °C and subsequent programmed calcinations at 500 °C for 3 h at a heating rate of 2 °C min^{-1} resulted in a highly acidic material. The chemical composition of the final catalyst (determined by XRF technique) was found to be 82.6 mol% Zr, 15.6 mol% Y and 1.8 mol% S. The physicochemical characterization of the catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption techniques.

2.3 Characterization of the Catalyst

The physicochemical characterization of catalyst was carried out by titration, temperature programmed desorption (TPD), scanning electron microscopy (SEM) and N_2 adsorption technique. The X-ray powder diffraction profile of the catalyst shows the formation of a cubic phase (Fig. 1). The IR spectra of pyridine adsorbsed on the catalyst show absorption band at 1,640, 1,605, 1,577, 1,542, 1,490 and 1,444 cm^{-1} (Fig. 2). The strong absorption bands at 1,605 and at 1,444 cm^{-1} indicate the presence of coordinated pyridine at the Lewis acid sites of the catalyst.

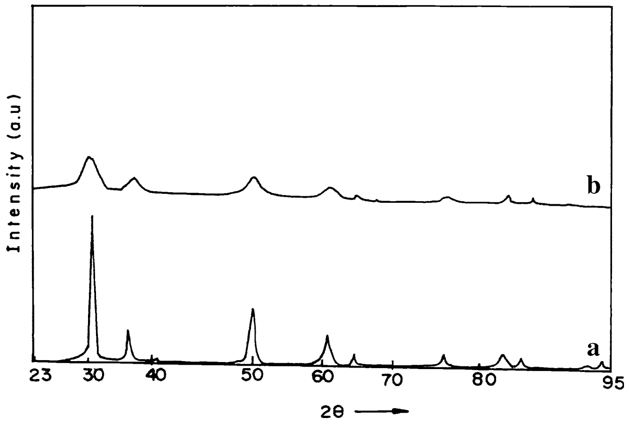


Fig. 1 X-ray powder diffraction pattern of the yttrium based catalyst prior to (a) and after (b) sulfation. The diffraction was recorded on Rigaku diffractometer, model D/Max IIIVC, with Ni-filtered $Ca_{2\alpha}$ radiation 1 = intensity (arbitrary units)

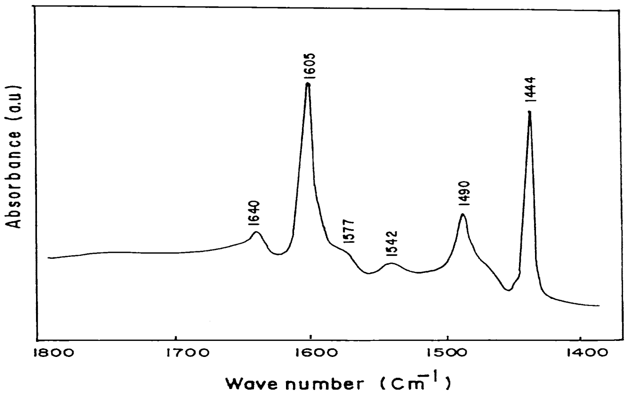


Fig. 2 FTIR spectrum of pyridine adsorbed on the yttrium based catalyst, recored on a Nicolet 60 SXB FTIR spectrometer A = absorption (arbitrary units)

The weak absorption at 1,542 cm^{-1} attributed to pyridinium ion [12] indicates the presence of a few Brönsted acid sites. The potentiometric titration of the acid sites with *n*-butylamine in non-aqueous medium (Fig. 3) shows the influence of yttrium in enhancing the number of acid sites [13]. The amount of *n*-butylamine consumed was 7.7 mol equiv g^{-1} for the yttrium-based catalyst compared to 5.8 mol equiv g^{-1} for the yttrium free catalyst. The presence of very strong acid sites in the catalyst is indicated by the peak maxima at 530 °C in the TPD profile (Fig. 4) [14]. The scanning electron mocrograph of sample shows the presence of uniform-sized (around 0.3 µm) particles (Fig. 5). The surface area of the sample determined by the BET (Brunner–Emmett–Teller) method was 150 $\mathrm{m}^2\ \mathrm{g}^{-1}$. The lattice defects caused by the incorporation of yttrium in the Zr^{4+} sites appear to enhance the number and strength of the Lewis acid sites of the catalyst.

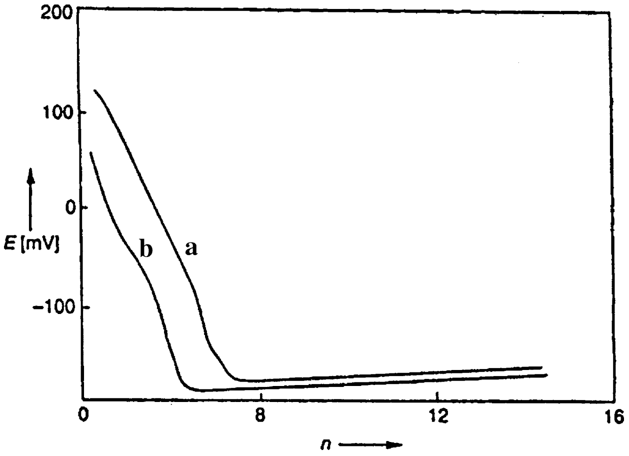


Fig. 3 Potentiometric titration curve of the sulfated catalyst with yttrium (curve a) and without yttrium (curve b) in acetonitrile. For details see Ref. [7]. n = number molar equivalent of *n*-butylamine per gram

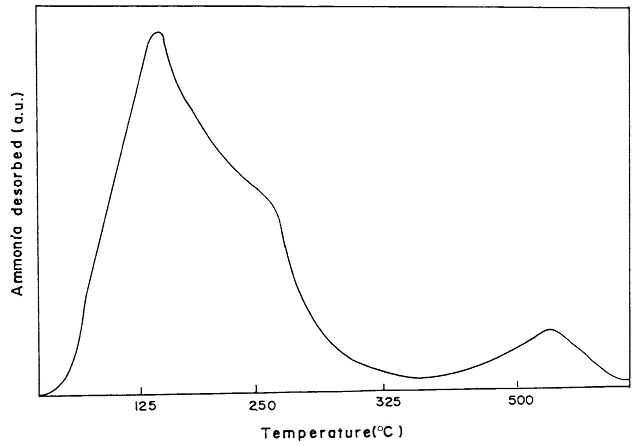


Fig. 4 TPD profile (ammonia) of the yttrium-based catalyst, recorded on a Sorbstar apparatus, Institutes of Isotopes, Hungary, with He as the carried gas, a flow rate of 50 mL min^{-1}, and a heating rate of 10 K min^{-1} from room temperature to 625 °C. NH_3 = Amount of ammonia desorbed(arbitrary units)

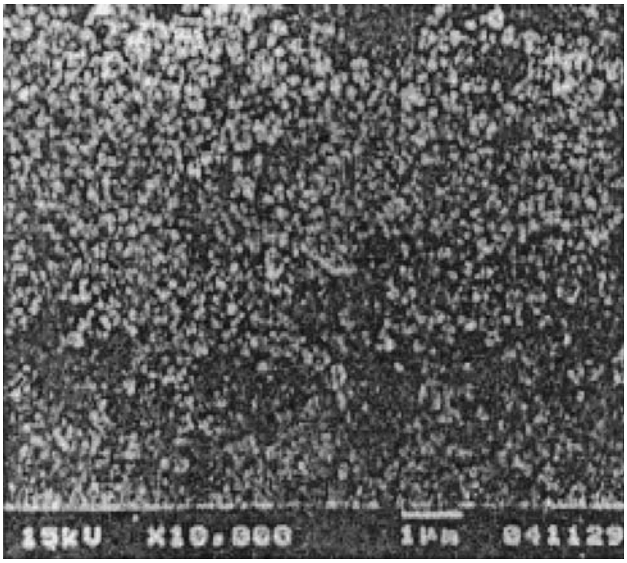


Fig. 5 Scanning electron micrograph of the catalyst

2.4 General Experimental Procedure for the Synthesis of α-amino phosphonates Using Yttria-zirconia Lewis Acid Catalyst

A slurry of carbonyl compound (1 mmol), amine (1 mmol) and dialkyl phosphite (1 mmol) with yttria-zirconia catalyst (10 mol%) in 5% aqueous acetonitrile (5 mL) was stirred at 60 °C for the indicated time (Table 1). The progress of reaction was monitored by TLC. After completion, the reaction mixture was filtered in hot condition and poured into cold water and extracted with CH_2Cl_2 (3 × 50 mL); washed (brine), dried (Na_2SO_4) and concentrated to afford the crude product which was purified by silica gel column chromatography using petroleum ether: ethyl acetate (7:3) as eluent to give the pure product which was fully characterized by spectroscopic data.

3 Results and Discussion

In a typical experimental procedure, a mixture of a carbonyl compound (1 mmol), an amine (1 mmol) and dialkyl phosphite (1 mmol) was added to a slurry of yttria-zirconia (10 mol%) in 5 mL of aqueous acetonitrile (5%) and heated at 60 °C for the indicated length of time (Table 1) to afford the corresponding α-amino phosphonates in good to excellent yield. A wide range of structurally varied carbonyl compounds were subjected to this procedure and converted into the corresponding α-amino phosphonates in high yields. Aromatic, heteroaromatic and aliphatic aldehydes react with aromatic as well as aliphatic amines and dimethylphosphite to form the corresponding α-amino phosphonates. This procedure equally worked well for the conversion of aromatics ketones into α-amino phosphonates. As it is seen from the Table 1 (entry 24), in the presence of both aldehyde and ketone functionalities, aldehyde reacted faster and gave exclusively one product. We also succeeded in the reaction of β-keto esters with dimethylphosphite which led to the corresponding α-amino phosphonates. No difficulty was encountered with the reaction of conjugated aldehydes (entry 8 and 24). The presence of electron withdrawing or electron donating substituents on aromatic rings does not make any difference in the course of reaction. Several sensitive functionalities such as OH, OMe, NO_2, Cl, F and C=C bond were unaffected under the present reaction conditions. The reactions were in general very fast, clean, no side product has been isolated. The notable advantages of this procedure are (i) operational simplicity and requirement of no additives (ii) heterogeneous catalysis with easy workup and recyclability of the catalyst.

4 Recyclability of the Catalyst

In order to evaluate the reusability and leaching of the catalyst in aqueous acetonitrile, experiments were carried out by simple condensation of benzaldehyde, aniline and dimethylphosphite, in aqueous acetonitrile (5%). The first, second and third cycles of the experiments gave yields such as 99, 95 and 82% of desired product with 100% conversion. After the third cycle the catalyst needed reactivation by calcinations at 573 K. The experiment which was carried out with 20% water in acetonitrile gave 90% yield with the reaction time of 5 h. While reusing catalyst which was recovered from the experiment with 20% of water in acetonitrile, it gave only 10% of the desired product with recovery of starting material as major compound even after 24 h of reaction time. But after reactivation by calcination at 573 K, the same catalyst which is recovered from 20% water in acetonitrile gave 90% of the desired product with the conversion of 100%. It is concluded from the above experiments that less proportion of water (5%) is favorable for the recovery of catalyst retaining its original activity. The addition of excess of water could be disturbing the Lewis acidity by collapsing the acid sites of the catalyst. The recycling of the catalyst showed that there was no leaching of the metal as there was no drop in the conversion rate in the subsequent recycling reactions.

5 Conclusion

In summary, the present procedure using Yttria-zirconia Lewis acid provides an efficient heterogeneous catalysis in the one-pot synthesis of α-amino phosphonates from the reaction of a to carbonyl compound, amine and dialkylphosphites. We believe, our procedure will find important applications in the synthesis of α-amino phosphonates in a practical way as an alternative existing methodologies.

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References

1. Baylis EK, Campbell CD, Dingwall JG (1984) J Chem Soc Perkin Trans I 29:2845
2. Kafarski P, Lejczak B (1991) Phosphorus Sulfur Silicon Relat Elem 63:1993
3. Allen MC, Fuhrer W, Tuck B, Wade R, Wood JM (1989) J Med Chem 32:1652
4. Hirschmann R, Smith AB III, Taylor CM, Benkovic PA, Taylor SD, Yager KM, Sprengler PA, Venkovic SJ (1994) Sciences 265:234
5. (a) Kukhar VP, Solodenko VA (1987) Russ Chem Rev 56:859; (b) Losachat S, Kunz H (1992) Synthesis 90; (c) Yokomatsu T, Yoshida Y, Shibuya S (1994) J Org Chem 59:7930; (d) Chandrasekhar S, Prakash SJ, Jagadeshwar V, Narsihmulu Ch (2001) Tetrahedron Lett 42:1698
6. Yadav JS, Reddy BVS, Sarita Raj K, Bhaskar Reddy K (2001) Synthesis 2277
7. Zon J (1981) Pol J Chem 55:643
8. (a) Qian C, Huang T (1998) J Org Chem 63:4125; (b) Ranu BC, Hajra A, Jana U (1999) Org Lett 1:1141; (c) Najmedin A, Mohammad RS (2003) Tetrahedron 29:5329
9. (a) Yadav JS, Reddy BVS, Sreedhar P (2002) Green Chem 4; (b) Ranu BC, Hajra A (2002) Green Chem 4:551
10. (a) Keshava Raja A, Hegde VR, Pandey B, Ramaswamy AV, Kumar P, Ravindranathan T (1995) Angew Chem Int Ed Engl 34:2143. U.S. Patent 1999, 5932752; (b) Kumar P, Pandey RK (2000) Synlett 251; (c) Kumar P, Pandey RK, Bodas MS, Dongare MK (2001) Synlett 206; (d) Kumar P, Pandey RK, Bodas MS, Dagade SP, Dongare MK, Ramaswamy AV (2002) J Mol Catal A Chem 187:207; (e) Pandey RK, Dagade SP, Upadhyay RK, Dongare MK, Kumar P (2002) Arkivoc VII:28
11. Furniss BS, Hannaford AJ, Rogeres V, Smith PWG, Tatchell AR (eds) (1978) Vogel' text book of practical organic chemistry, 4th edn. ELBS/Longman, London
12. Mizuno N, Fujii H, Igarashi H, Misono M (1992) J Am Chem Soc 114:7151
13. Cid R, Pecchi G (1985) Appl Catal 14:15
14. Verhaak MJFM, Van Dillen AJ, Geus JW (1993) Appl Catal 105:251