A new one-pot synthesis of α-amino phosphonates catalyzed by H$_3$PW$_{12}$O$_{40}$

Akbar Heydari *, Hosein Hamadi, Mehrdad Pourayoubi

Chemistry Department, Tarbiat Modarres University, P.O. Box 14155-4838, Tehran, Iran

Received 16 October 2006; received in revised form 8 November 2006; accepted 8 November 2006
Available online 14 November 2006

In memory of Ahmad Motavasellian

Abstract

A new and highly flexible procedure is described for the synthesis of α-amino phosphonates by in situ generated imines or iminium salts with using dodecatungest phosphoric acid (0.5 mol%) as catalyst in dichloromethane at room temperature in short reaction times (<15 min).

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Keywords: α-Amino phosphonates; Heteropoly acid; Dodecatungest phosphoric acid

1. Introduction

Because of the biological effects and medicinal importance (enzyme inhibitors [1a], HIV protease [1b], antibiotics [1c], herbicides, fungicides, insecticides [1d], plant growth regulators [1e], anti-thrombotic agents [1f], as well as peptidases and proteases) [1g], many procedures for the synthesis of α-amino phosphonate derivatives have been developed during the last two decades [2]. Of the methods, the nucleophilic addition reaction of phosphites with imines is one of the most convenient methods, which is usually promoted by base [3a], protic [3b], or Lewis acids like SnCl$_4$ [3c], BF$_3$ - OEt$_2$ [3d], ZnCl$_2$ and MgBr$_2$ [3e], for this transformation. However, these methods are not devoid of their limitation as many imines are hygroscopic and are not sufficiently stable for isolation. In addition, these reactions cannot be carried out in a one-pot three-component operation from a carbonyl compound an amine and a phosphite, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids [2b]. To overcome some of these problems, recently one-pot three-component procedures have been developed. This conversion can proceed smoothly when using Lewis acids including lanthanide triflate [4a], samarium diiodide [4b], indium(III) chloride [4c], TaCl$_5$ – SiO$_2$ [4d], (bromomethyl)sulphonium bromide [4e], lithium perchlorate [4f], montmorillonite KSF [4g], ZrCl$_4$ [4h], alumina-supported reagents as catalysts [4i], and diethylphosphite and triethylphosphate as phosphorous reagents. However, these catalysts have some drawbacks: for instance, reactions require a long time, and when starting from aliphatic amines, reactions gave noncharacterizable products [5]. In addition, some of these catalysts are either expensive or somewhat difficult to prepare. Even when the desired reactions proceed, because the acids are trapped by the basic nitrogen, the present practice requires an over stoichiometric amounts of the Lewis acids [6]. We focused on the development of highly flexible one-pot way for the synthesis of α-amino Phosphonate in order to overcome the drawbacks described above. For diversity reasons, it was our goal to employ catalyst that is environmentally benign and readily available.

* Corresponding author. Tel.: +98 21 44990106; fax: +98 21 88006544. E-mail address: akbar.heydari@gmx.de (A. Heydari).
2. Results and discussion

The use of heteropoly acid (HPA) catalysts has received considerable attention, because of their environmental compatibility, reusability, operational simplicity, greater selectivity, non-toxicity, non-corrosiveness and ease of isolation. Heteropolyacids have been pointed out as versatile green catalysts for a variety of homogenous and heterogenous reactions, and reviwed by many researchers [7], [8], [9] and [10], [11], [12]. In this communication, we wish to report a novel application in several processes [8], Moreover, H3PW12O40 is found to retain its activity even in the presence of a number of organic substrates containing N, S, O, atoms, i.e., amino acids [9], quinoline [10], TTF [11], crown ethers [12]. In this communication, we wish to report a novel and efficient procedure for the synthesis of α-amino phosphonates using non-corrosive and environmentally benign catalyst H3PW12O40. We investigated the reaction between trimethyl phosphate and the in situ generated imine from benzaldehyde and aniline in DCM in the presence of catalytic amount of H3PW12O40 (0.5 mol%) and isolated the benzaldehyde and aniline in DCM in the presence of catalytic amount of H3PW12O40 (0.5 mol%) and isolated the desired amino phosphonate in a 98% yield within 10 min. at room temperature. After this success, several aldehydes, amines (primary and secondary) and trimethyl phosphate were examined in the presence of 0.5% dodecatungstostephosporic acid in DCM. We observed that no reaction occurred when benzaldehyde and aniline was treated with trimethyl phosphate in anhydrous DCM at 40 °C for 5 h. Not only benzaldehyde but also electron deficient aromatic aldehydes react with aromatic as well as aliphatic amines to give the corresponding α-amino phosphonates in high yields. Several sensitive functionalities such as NO2, and CI are unaffected during the reaction. In all cases, the reactions proceeded smoothly at ambient temperature. The reaction conditions are very mild and α-amino phosphonates are exclusively formed without the formation of any undesired side products. In addition this method is even effective with aliphatic aldehydes, which normally produce low yields due to their intrinsic lower reactivity. The present method does not require any additives or promoters to proceed the reaction. The results are summarized in Scheme 1.

3. Conclusion

In summary, the presented studies clearly indicate that the H3PW12O40 (0.5 mol %) catalyzed nucleophilic addition of trimethyl phosphate to in situ generated imines (iminium salts) allows the synthesis of α-amino phosphonates in good to excellent yields. Among various acids [4], H3PW12O40 was found to be more effective than others in terms of yields, reaction time and environmentally benign. Future studies will aim to shed light on the mechanism and scope of this reaction and further application of H3PW12O40 in important carbon–carbon bond-forming reactions.

4. Experimental section

4.1. General procedure: preparation of α-amino phosphonate derivatives

H3PW12O40 (30 mg, 0.01 mmol, 0.5 mol%) was added to a mixture of aldehyde (2 mmol) and amine or amine derivatives (2.2 mmol) in DCM (4 mL) at room temperature. The mixture was stirred at room temperature for 10 min. and then trimethylphosphite was added. After completion of the reaction (~15 min), as indicated by TLC, the reaction mixture was quenched with water and then extracted with CH2Cl2, dried over Na2SO4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethylacetate; 2:1) to afford pure products. Spectral data for selected products, 4e: 1H NMR (500 MHz, CDCl3): δ = 3.51 (d, J = 10.5 Hz, 3H), 3.81 (d, J = 10.6 Hz, 3H), 4.82 (d, J = 24 Hz, 1H), 4.84 (bs, 1H), 6.64 (d, J = 8.0 Hz, 2H), 6.74 (t, J = 7.2 Hz, 1H), 7.1 (t, J = 7.7 Hz, 2H), 7.3 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.5 (d, J = 7.3 Hz, 2H); 13C NMR (125 MHz, CDCl3): δ = 54.1 (d, 3Jp–c = 7.0 Hz, OCH3), 54.2 (3Jp–c = 6.8 Hz, OCH3), 56.2 (d, 1Jp–c = 150 Hz, CH), 68.59 (CH), 114.3 (CH), 119.0 (CH), 128.2 (d, 3Jp–c = 5.8 Hz, CH), 128.4 (d, 3Jp–c = 3.1 Hz, CH), 129.1 (CH), 131.2 (CH), 136.0 (C), 146.6 (d, 2Jp–c = 14.5 Hz, C); 4d: 1H NMR (500 MHz, CDCl3): δ = 3.51 (m, 1H), 3.79 (d, J = 11.8 Hz, 3H), 3.83 (d, J = 10.1 Hz, 3H), 5.2 (d, J = 24 Hz, 1H), 7.3 (d, 2H), 7.5 (t, J = 7.7 Hz, 1H), 7.8 (t, 1H), 8.2 (d, 2H); 13C NMR (22.5 MHz, CDCl3): δ = 56.1 (d, 3Jp–c = 7.0 Hz, OCH3), 56.2 (d, 3Jp–c = 6.8 Hz, OCH3), 57.2 (d, 1Jp–c = 150 Hz, CH), 114.3 (CH), 126.0 (CH), 128.2 (d, 3Jp–c = 5.8 Hz, CH), 128.4 (d, 3Jp–c = 3.1 Hz, CH), 130.1 (CH), 131.2 (C), 140.0 (C), 146.6 (d, 2Jp–c = 14.5 Hz, C); 4j: 1H NMR (90 MHz, CDCl3): δ = 1.0 (t, 6H), 1.02 (d, 6H), 1.95 (m, 1H), 2.5 (dd, 1H), 2.7 (2q, 4H), 3.62 (d, J = 7.0 Hz, 3H), 3.74 (d,
$J = 7.0 \text{ Hz}, 3\text{H})$; $^{13}\text{C NMR (22.5 MHz, CDCl}_3): \delta = 14.8 (\text{CH}_3), 20.66 (d, {^3}J_{p-c} = 2.7 \text{ Hz, CH}_3), 21.21 (d, {^3}J_{p-c} = 11 \text{ Hz, CH}_3), 28.19 (d, {^2}J_{p-c} = 10 \text{ Hz, CH}), 45.72 (d, {^2}J_{p-c} = 1.8 \text{ Hz, CH}_2), 51.5 (t, {^2}J_{p-c} = 7.3 \text{ Hz, OCH}_3), 64.62 (d, {^1}J_{p-c} = 125.9 \text{ Hz, CH})$;

$41l$: $^1\text{H NMR (90 MHz, CDCl}_3): d = 1.1 (t, 6\text{H}), 2.35 (m, 2\text{H}), 3.0 (m, 2\text{H}), 3.65 (d, {^3}J_{p-H} = 10.7 \text{ Hz, 3H}), 3.92 (d, {^3}J_{p-H} = 10.7 \text{ Hz, 3H}), 4.25 (d, {^2}J_{p-H} = 25.1 \text{ Hz, 1H}), 7.4 (m, 5\text{H})$;

$13\text{C NMR (22.5 MHz, CDCl}_3): \delta = 12.58 (s, \text{CH}_3), 43.99 (d, {^3}J_{p-c} = 8.2 \text{ Hz, CH}_2), 51.51 (d, {^2}J_{p-c} = 7.3 \text{ Hz, OCH}_3), 53.4 (d, {^2}J_{p-c} = 6.4 \text{ Hz, OCH}_3), 60.97 (d, {^1}J_{p-c} = 163.3 \text{ Hz, CH}), 127.12 (\text{CH}), 127.37 (\text{CH}), 129.53 (\text{CH}), 129.93 (\text{CH}), 132.13 (\text{CH}), 132.38 (\text{C})$.

Acknowledgement

Research supported by the National Research Council of I. R. Iran as a National Research project under the number 984.

References

(d) L. Maier, H. Spoerri, Phosphorus, Sulfur, Silicon Relat. Elem. 61 (1991) 69;

(b) T. Yokomatsu, Y. Yoshida, S. Shibuya, J. Org. Chem. 59 (1994) 7938;

(c) S. Laschat, H. Kunz, Synthesis (1992) 90;
(d) H.-J. Ha, G.-S. Nam, Synth. Commun. 22 (1992) 1143;

(c) B.C. Ranu, A. Hajra, J. Jana, Org. Lett. 1 (1999) 1141;
(g) J.S. Yadav, B.V.S. Reddy, C. Madan, Synlett (2001) 1131;
(i) B. Kaboudin, R. Nazari, Tetrahedron Lett. 42 (2001) 8211, although this approach is statisfactory for reactions with aromatic aldehydes and the amino phosphonates from aliphatic aldehydes are obtained in moderate yields.


I.V. Kozhennikov/Phosphorylation by Polyoxometalates, vol. 2, Wiley, Chichester, 2002;

I.V. Kozhenikov, Synthesis (2001) 1141;
