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A new one-pot synthesis of α-amino phosphonates catalyzed by $H_3PW_{12}O_{40}$

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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 dodecatungestophosphoric acid (0.5 mol%) as catalyst in dichloromethane at room temperature in short reaction times (<15 min).

Keywords: α-Amino phosphonates; Heteropoly acid; Dodecatungestophosphoric 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], $BF_3 \cdot OEt_2$ [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 lantanide triflate [4a], scandium tris(dodecylsulfate) [4a], samarium diiodide [4b], indium(III) chloride [4c], $TaCl_5$–SiO_2 [4d], (bromodimethyl)sulfonium bromide [4e], lithium perchlorate [4f], montmorillonite KSF [4g], $ZrCl_4$ [4h], alumina-supported reagents as catalysts [4i], and diethylphosphite and triethylphosphite 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 benigin and readily available.

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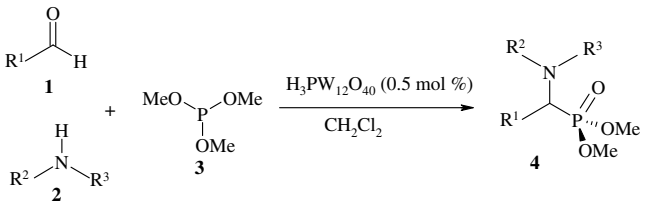
2. Results and discussion

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], 12-Tungstophosphoric acid, the strongest HPA in the Keggin series, have been extensively studied as super acid catalysts for many organic reactions and have found industrial application in several processes [8], Moreover, $H_3PW_{12}O_{40}$ 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 benigin catalyst $H_3PW_{12}O_{40}$. We investigated the reaction between trimethyl phsphite and the *in situ* generated imine from benzaldehyde and aniline in DCM in the presence of catalytic amount of $H_3PW_{12}O_{40}$ (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 phsphite were examined in the presence of 0.5% dodecatungestophosphoric acid in DCM . We observed that no reaction occurred when benzaldehyde and aniline was treated with trimethyl phsphite in anhydrous DCM at 40 °C for 5 h. Not only bezaldehyde but also electron deficient aromatic aldehydes react with aromatic as well as aliphatic amines to give the corresponding α-aminophosphonates in high yields. Several sensitive functionalities such as NO_2, and Cl 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.



	R¹	R²	R³	4%
a	*tert*-Butyl	H	Phenyl	91
b	*n*-Pentyl	H	Phenyl	90
c	Phenyl	H	Phenyl	94
d	4-Cl-Phenyl	H	Phenyl	92
e	4-NO_2-Phenyl	H	Phenyl	90
f	4-Pyridyl	H	Phenyl	90
g	Phenyl	H	Benzyl	92
h	4-CH_3-Phenyl	H	Benzyl	98
i	*2-Furyl*	H	Benzyl	83
j	*i*-Propyl	Ethyl	Ethyl	85
k	*tert*-Bytyl	Ethyl	Ethyl	93
l	Phenyl	Ethyl	Ethyl	89
m	4-Cl-Phenyl	Ethyl	Ethyl	90

Scheme 1.

3. Conclusion

In summary, the presented studies clearly indicate that the $H_3PW_{12}O_{40}$ (0.5 mol %) catalyzed nucleophilic addition of trimethyl phsphite to *in situ* generated imines (iminium salts) allows the synthesis of α-amino phosphonates in good to excellent yields. Among various acids [4], $H_3PW_{12}O_{40}$ was found to be more effective than others in terms of yields, reaction time and environmentally benigin. Future studies will aim to shed light on the mechanism and scope of this reaction and further application of $H_3PW_{12}O_{40}$ in important carbon–carbon bond-forming reactions.

4. Experimental section

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

$H_3PW_{12}O_{40}$ (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 CH_2Cl_2, dried over Na_2SO_4, concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethylacetate; 2:1) to affored pure products. Spectral data for selected products, **4c**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.51$ (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); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 54.1$ (d, $^2J_{p-c} = 7.0$ Hz, OCH_3), 54.2 ($^2J_{p-c} = 6.8$ Hz, OCH_3), 56.2 (d, $^1J_{p-c} = 150$ Hz, CH), 68.59 (CH), 114.3 (CH), 119.0 (CH), 128.2 (d, $^3J_{p-c} = 5.8$ Hz, CH), 128.4 (d, $^3J_{p-c} = 3.1$ Hz, CH), 129.1 (CH), 131.2 (CH), 136.0 (C), 146.6 (d, $^2J_{p-c} = 14.5$ Hz, C); **4d**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.51$ (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, 2H), 7.7 (d, 2H), 7.8 (t, 1H), 8.2 (d, 2H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 56.1$ (d, $^2J_{p-c} = 7.0$ Hz, OCH_3), 56.2 (d, $^2J_{p-c} = 6.8$ Hz, OCH_3), 57.2 (d, $^1J_{p-c} = 150$ Hz, CH), 114.3 (CH), 120.0 (CH), 128.2(d, $^3J_{p-c} = 5.8$ Hz, CH), 128.4 (d, $^3J_{p-c} = 3.1$ Hz, CH), 130.1 (CH), 131.2 (C), 140.0 (C), 146.6 (d, $^2J_{p-c} = 14.5$ Hz, C); **4j** : ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.0$ (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,

$J = 7.0$ Hz, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 14.8$ (CH_3), 20.66 (d, $^3J_{p-c} = 2.7$ Hz, CH_3), 21.21 (d, $^3J_{p-c} = 11$ Hz, CH_3), 28.19 (d, $^2J_{p-c} = 10$ Hz, CH), 45.72 (d, $^2J_{p-c} = 1.8$ Hz, CH_2), 51.5 (t, $^2J_{p-c} = 7.3$ Hz, OCH_3), 64.62 (d, $^1J_{p-c} = 125.9$ Hz, CH); **4l**: ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 1.1$ (t, 6H), 2.35 (m, 2H), 3.0 (m, 2H), 3.65 (d, $^3J_{p-H} = 10.7$ Hz, 3H), 3.92 (d, $^3J_{p-H} = 10.7$ Hz, 3H), 4.25 (d, $^2J_{p-H} = 25.1$ Hz, 1H), 7.4 (m, 5H); ^{13}C NMR (22.5 MHz, $CDCl_3$): $\delta = 12.58$ (s, CH_3), 43.99 (d, $^3J_{p-c} = 8.2$ Hz, CH_2), 51.51 (d, $^2J_{p-c} = 7.3$ Hz, OCH_3), 53.4 (d, $^2J_{p-c} = 6.4$ Hz, OCH_3), 60.97 (d, $^1J_{p-c} = 163.3$ Hz, CH), 127.12 (CH), 127.37 (CH), 129.53 (CH), 129.93 (CH), 132.13 (CH), 132.38 (C).

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