Pyridine 2,6-Dicarboxylic Acid as a Bifunctional Organocatalyst for Hydrophosphonylation of Aldehydes and Ketones in Water

Fatemeh Jahani,[a] Behi Zamenian,[a] Samad Khaksar,[b] Mahmood Tajbakhsh*[a]

[a] Department of Chemistry, University of Mazandaran, P.O. Box 453, Babolsar, Iran

[b] Chemistry Department, Islamic Azad University, Ayatollah Amoli Branch, P.O. Box 678, Amol, Iran
Fax +98(112)5342350; E-mail: tajbaksh@umz.ac.ir

Received 10 May 2010; revised 18 May 2010

Abstract: A novel organocatalytic, direct synthesis of α-hydroxy phosphonates via reaction of aldehydes and ketones with trimethylphosphite in the presence of catalytic amounts of pyridine 2,6-dicarboxylic acid in water is reported. The method is simple, cost-effective and environmentally benign.

Key words: α-hydroxy phosphonates, organocatalyst, pyridine 2,6-dicarboxylic acid, nucleophilic addition, water

There has been a recent resurgence of interest in the development of organocatalytic reactions.[1] Catalysis with simple organic molecules can provide an attractive alternative to organometallic catalysis, particularly in situations where residual metals or ligands compromise the purity or end-use of the product.[2] Organocatalysts have afforded important advantages in organic synthesis, for instance they are, in general, operationally simple, nontoxic, less corrosive, environmentally compatible, reusable, inexpensive, simple to isolate, and can be applied with less demanding reaction conditions (such as rigorously anhydrous or anaerobic conditions).[3] Recently, organocatalyzed reactions in water have received much attention.[4] The use of water as a reaction medium has gained considerable interest in organic synthesis due to its many advantages from economical, environmental, and safety standpoints.[5] Reactions in water can facilitate access to different reactivity and selectivity patterns compared with those observed in common organic solvents due to the unique physical and chemical properties of this solvent.[6] It is a weak electrolyte at room temperature but dissociates to a greater extent on increasing the temperature, resulting in higher concentrations of H_3O^+ and HO^- under neutral conditions that can catalyze chemical reactions.[7]

α-Hydroxy phosphonates and the corresponding phosphonic acids display a wide spectrum of biological activity,[8] and α-hydroxy phosphonic acid derivatives have been shown to be very important inhibitors of important medicinal enzymes such as renin[9] or human immunodeficiency protease and polymerase.[10] Many of these compounds have attracted attention because of their antibacterial, antivirus, antibiotic, and pesticidal activities,[11] and some hydroxy phosphonates possessing potent antitumor activity are used for the treatment of cancer.[12] Furthermore, many α-functionalized phosphonates, such as α-amino,[13] α-keto,[14] α-halo,[15] and α-acetoxy phosphonates[16] are prepared from α-hydroxy phosphonates.

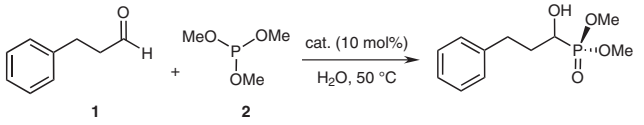
The synthesis of α-hydroxy phosphonates has been investigated in the presence of Lewis acids and bases,[17,18] alumina and cesium fluorides,[19] potassium fluoride on alumina,[20] Al-Li-BINOL complex (ALB),[21] chiral Al^{III} complex,[22] lithium perchlorate in diethyl ether,[23] guanidine hydrochloride,[24] quaternary ammonium hydroxide ion-exchange resin,[25] titanium alkoxides,[26] aluminum (salen) complex,[27] L-proline,[28] L-prolinamide,[29] HCl,[30] and oxalic acid.[31] However, despite satisfactory results, some of the reported procedures required the use of hazardous organic solvents, costly and toxic catalysts or create byproducts and salt wastes that are not desirable from a green chemistry point of view. It was found that in many cases involving ketones, the yields were not always good and mixtures of products were sometimes obtained due to the low reactivity of ketones, retro-hydrophosphonylation reactions,[32] phospha-Brook rearrangements[33] and other competing processes.[34]

Recently, Feng et al.[35] found that titanium isopropoxide [Ti(O-*i*-Pr)$_4$] can catalyze the hydrophosphonylation of ketones successfully. This method was suitable for a wide range of substrates, and especially for functionalized ketones. However, realizing the fact that metal-free organocatalysis has drawn considerable interest from chemists in recent years and that metal-free homogeneous catalysis is advantageous for designing suitable drugs that are free of any metal content, it would be desirable to develop the hydrophosphonylation of ketones using metal-free Lewis acid catalysts.[36] Due to the problems mentioned above and because of recent intense attention on environmentally benign protocols, the search for new and efficient catalysts that are able to promote organic reactions under green conditions is of interest for the production of α-hydroxy phosphonates. In this regard, and in connection with our previous work,[37] we report here the synthesis of α-hydroxy phosphonate derivatives in the presence of a catalytic amount of pyridine 2,6-dicarboxylic acid (PDA) in aqueous media. The catalyst can either be recovered or, after separation of the product, the remaining aqueous layer can be used directly in subsequent reactions. In our first experiments, we examined the reaction of 3-phenylpropionaldehyde and trimethylphosphite in aqueous media by

SYNTHESIS 2010, No. 19, pp 3315–3318
Advanced online publication: 22.07.2010
DOI: 10.1055/s-0030-1257866; Art ID: Z12210SS

using different catalysts such as MgO nanoparticles, cellulose sulfuric acid, $H_3PW_{12}O_{40}$ (PW), silica sulfuric acid, sulfamic acid, and PDA. The results are collected in Table 1.

Table 1 Hydrophosphonylation of **1** and **2** Using 10 mol% Catalyst



1 2

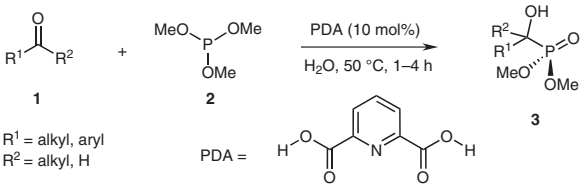
Entry	Catalyst	Time (h)	Yield (%)[a]
1	sulfamic acid	4	70
2	silica sulfuric acid	3	70
3	cellulose sulfuric acid	2	60
4	$H_3PW_{12}O_{40}$	2.5	75
5	MgO nanoparticle	2	50
6	pyridine 2,6-dicarboxylic acid	1.5	95

[a] Yield of isolated product.

Solid acid catalysts such as sulfamic acid, cellulose sulfuric acid, heteropoly acid, and silica sulfuric acid gave moderate yields of the corresponding α-hydroxy phosphonates (entries 1–4). The use of MgO nanoparticles was also examined whereby a low yield of product was obtained (entry 5). PDA very efficiently gave an excellent yield of the corresponding dimethyl 1-hydroxy-3-phenyl-2-propylphosphonate in a shorter reaction time (entry 6). This might be due to the solubility of PDA in water, which could accelerate the carbonyl activation. Therefore, to explore the potential of PDA catalyst for this reaction we carried out a more detailed study on the use of PDA. To the best of our knowledge, there is only one report on the application of PDA as a Brønsted acidic organocatalyst.[38] In respect to the mechanism, we assume that the catalyst generates a hydronium ion in water that activates the carbonyl group, which consequently undergoes nucleophilic attack by trimethylphosphite. In the absence of catalyst, when benzaldehyde was treated with trimethylphosphite only a low yield (<40%) of dimethyl 1-hydroxy-1-phenylmethylphosphonate was obtained. Lowering the catalyst loading from 10 to 5 mol% significantly reduced the yield, and increasing the temperature did not result in any improvement. Consequently, 10 mol% PDA was used in subsequent experiments. Having these data in hand, we have applied this reaction to a range of aldehydes and ketones; the results are summarized in Table 2.

As shown in the Table 2, the reaction of aromatic aldehydes and trimethylphosphite in the presence of PDA in water at 50 °C, gave the target products in good yields in a typical reaction time of 1–4 hours (Table 2, entries 1–5). Electron-withdrawing groups on the aromatic rings of the aldehydes make them less reactive, leading to lower yields and requiring longer reaction times (Table 2, entries 6–8). Aliphatic aldehydes reacted smoothly with trimethylphosphite under convenient reaction conditions to give high yields of the corresponding α-hydroxy phosphonates (Table 2, entries 9 and 10). 2-Furaldehyde reacted with trimethylphosphite to give a lower yield of the expected product (Table 2, entry 12).

Table 2 Synthesis of α-Hydroxy Phosphonates from Various Aldehydes and Ketones



Entry	R^1	R^2	Time (h)	Yield[a] (%)[(Ref.)]
1	Ph	H	1.30	95[26]
2	4-MeC_6H_4-	H	2	87[21]
3	4-$MeOC_6H_4$-	H	2	91[21]
4	2-ClC_6H_4-	H	3	94[27]
5	4-ClC_6H_4-	H	4	80[27]
6	4-$NO_2C_6H_4$-	H	3	60[27]
7	3-$NO_2C_6H_4$-	H	2.50	85[23]
8	4-CNC_6H_4-	H	3	65[37]
9	$PhCH_2CH_2$-	H	1.50	95[27]
10	*n*-Pr-	H	2	92[24]
11	PhCH=CH-	H	2	85[27]
12	2-Furyl	H	2	60[24]
13	Ph	Me	3	80[35]
14	4-$MeOC_6H_4$-	Me	3	83[35]
15	-$(CH_2)_5$-	–	2	75[35]
16	-$(CH_2)_4$-	–	2.40	80[35]

[a] All the products are known compounds and were characterized by their IR and ^1H NMR spectra and by comparison with authentic samples. All yields refer to isolated products.

In order to determine the reactivity of ketones, the reaction was carried out with aromatic and aliphatic ketones, and a moderate yield of the corresponding phosphonates were obtained (Table 2, entries 13 and 16). Interestingly, the α,β-unsaturated aldehyde selectively afforded the corresponding α-hydroxy phosphonates in good yield, with no byproduct formation (Table 2, entry 11). This reaction was also performed in a range of organic solvents, however, none of the solvents were found to be effective and only trace amounts of products were formed. Clearly, water, which leads to fast conversion and high yields of the desired product, stands out as the solvent of choice. We also examined the use of a range of solvents for the work-up process and found that dichloromethane was optimal

due to the poor solubility of PDA in this solvent. The advantages of using an organocatalyst would clearly be higher if the catalyst could be efficiently recovered and reused. Thus, the reusability of the catalyst was examined by treating 3-phenylpropionaldehyde and trimethylphosphite in the presence of 10 mol% of the catalyst in aqueous media for three consecutive runs. The reactions proceeded smoothly with minimum variation in the yield of the product, as shown in the Table 3.

Table 3 Reusability of the PDA Catalyst

Entry	Number of recycle	Time (min)	Yield (%)[a]
1	fresh	90	95
2	1	90	92
3	2	100	90

[a] Yield of isolated product.

In summary, we have developed a method for the synthesis of α-hydroxy phosphonates by reacting aldehydes and ketones with trimethylphosphite in the presence of a catalytic amount of PDA as a novel organocatalyst in aqueous media. The simple experimental procedure, application of an inexpensive catalyst, short reaction times and high yields are the notable advantages of the protocol. In many cases the products crystallize directly out of the reaction mixture.

^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz Bruker spectrometer in $CDCl_3$ and DMSO using $SiMe_4$ as an internal standard. Chemical shifts are reported in ppm. The coupling constants (*J* values) are reported in Hz. Reactions were monitored by TLC (Merck) or GC. Evaporation of solvents was performed at reduced pressure, using a rotary evaporator. Melting points were measured using the capillary tube method with a Bamstead Electrothermal 9200 apparatus. IR spectra were recorded from KBr disks on a Bruker Tensor 27 FT-IR spectrophotometer. All solvents and reagents were purchased from Aldrich or Merck with high-grade quality and used without any purification.

Dimethyl 1-Hydroxy-1-phenylmethylphosphonate; Typical Procedure

A solution of benzaldehyde (0.106 g, 1 mmol), trimethylphosphite (0.136 g, 1.1 mmol) and pyridine 2,6-dicarboxylic acid (0.0167 g, 0.1 mmol) in H_2O (2 mL) was placed in a round-bottomed flask equipped with a magnetic stirrer and heated at 50 °C for 1.5 h. After completion of the reaction as indicated by TLC, the mixture was cooled to r.t. and the product was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give an oily residue that crystallized to give the title compound.

Yield: 0.216 g (95%); white solid; mp 86–87 °C.

IR: 3240 (OH) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.7 (d, *J* = 10.3 Hz, 3 H), 3.74 (d, *J* = 10.3 Hz, 3 H), 4.1 (s, OH), 5.06 (d, *J* = 13.2 Hz, 1 H), 7.3–7.5 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.7 (d, *J* = 7.5 Hz), 54.0 (d, *J* = 6.7 Hz), 70.6 (d, *J* = 158.4 Hz), 126.9, 128.1, 128.2 (d, *J* = 2.5 Hz), 136.2.

Catalyst Recycling

To investigate the reusability of the catalyst, after completion of the reaction, the product was extracted with CH_2Cl_2 (3 × 15 mL) and the aqueous layer was evaporated under reduced pressure to give PDA, which was then washed with cool H_2O (2 × 2 mL) and Et_2O (2 × 2 mL), successively, and dried at 100 °C for 1 h. The recovered catalyst was reused consecutively three times with a minimum variation in the yield of the product. Alternatively, after extraction of the product with CH_2Cl_2 (3 × 15 mL), the aqueous layer can be used directly for subsequent runs.

Acknowledgment

Financial support for this work from the Research Council of the University of Mazandaran is gratefully acknowledged.

References

(1) For reviews see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. (b) List, B. *Tetrahedron* **2002**, *58*, 5573. (c) Duthaler, R. O. *Angew. Chem. Int. Ed.* **2003**, *42*, 975. (d) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *116*, 5248. (e) List, B. *Chem. Commun.* **2006**, 819. (f) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (g) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (h) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (i) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (j) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

(2) (a) Csihony, S.; Beaudette, T. T.; Sentman, C. A.; Nyce, W. G.; Waymouth, M. R.; Hedrickb, L. J. *Adv. Synth. Catal.* **2004**, *346*, 1081. (b) Barbas, C. F. III *Angew. Chem. Int. Ed.* **2008**, *47*, 42. (c) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (d) Bengoa, E. G.; Linden, A.; López, R.; Mendiola, I. M.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955. (e) Wittkopp, A.; Schreiner, P. R. *Eur. J. Org. Chem.* **2003**, 407. (f) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5442. (g) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Córdova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4507. (h) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4504. (i) Maerten, E.; Carbrera, S.; Kjaersgaard, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 8893.

(3) Xu, D. Q.; Wang, L. P.; Luo, S. P.; Wang, Y. F.; Zhang, S.; Xu, Z. Y. *Eur. J. Org. Chem.* **2008**, 1049.

(4) (a) Mosse, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577. (b) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (c) Zhao, J. F.; He, L.; Jiang, J.; Tang, Z.; Cun, L. F.; Gong, L. Z. *Tetrahedron Lett.* **2008**, *49*, 3372.

(5) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095.

(6) Lindstrom, U. M.; Andersson, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 548.

(7) Hailes, H. C. *Org. Process Res. Dev.* **2007**, *11*, 114.

(8) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591.

(9) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587.

(10) (a) Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. (b) Szymanska, A.; Szymczak, M.; Boryski, J.; Stawinski, J.; Kraszewski, A.; Collu, G.; Sanna, G.; Giliberti, G.; Loddo, R.; La Colla, P. *Bioorg. Med. Chem.* **2006**, *14*, 1924.
(11) (a) Snoeck, R.; Holy, A.; Dewolf-Peeters, C.; Van Den Oord, J.; De Clercq, E.; Andrei, G. *Antimicrob. Agents Chemother.* **2002**, *46*, 3356. (b) Hammerschmidt, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 341. (c) Jennings, L. J.; Macchia, M.; Parkin, A. *J. Chem. Soc., Perkin Trans.* **1992**, *1*, 2197. (d) Sikorski, J. A.; Miller, M. J.; Braccoli, D. S.; Cleary, D. J.; Corey, S. D.; Font, K. J.; Gruys, K. J.; Han, C. Y.; Lin, K.-C.; Pansegrau, P. D.; Ream, J. E.; Shnur, D.; Shah, A.; Walker, M. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *76*, 115.
(12) Peters, M. L.; Leonard, M.; Licata, A. A. *Cleveland Clinic J. Med.* **2001**, *68*, 945.
(13) Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051.
(14) Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 6720.
(15) Eymery, F.; Lorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 2671.
(16) Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Amoozgar, Z. *Synthesis* **2004**, 1771.
(17) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467.
(18) Nakanishi, K.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron* **2008**, *64*, 6415.
(19) Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 916.
(20) Texier-Boullet, F.; Lequitte, M. *Tetrahedron Lett.* **1986**, *27*, 3515.
(21) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926.
(22) Gou, S.; Zhou, X.; Wang, J.; Liu, X.; Feng, X. *Tetrahedron* **2008**, *64*, 2864.
(23) Azizi, N.; Saidi, M. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1255.
(24) Heydari, A.; Arefi, A.; Khaksar, S.; Tajbakhsh, M. *Catal. Commun.* **2006**, *7*, 982.
(25) Alexander, C. W.; Albiniak, P. A.; Gibson, L. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *167*, 205.
(26) Rowe, B. J.; Spilling, C. D. *Tetrahedron: Asymmetry* **2001**, *12*, 1701.
(27) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978.
(28) Samanta, S.; Zhao, C. G. *J. Am. Chem. Soc.* **2006**, *128*, 7442.
(29) Dodda, R.; Zhao, C. G. *Org. Lett.* **2006**, *8*, 4911.
(30) Goldeman, W.; Soroka, M. *Synthesis* **2006**, 3019.
(31) Vahdat, M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, M.; Khaksar, S. *Tetrahedron Lett.* **2008**, *49*, 6501.
(32) (a) Kharasch, M. S.; Mosher, R. A.; Bengelsdorf, I. S. *J. Org. Chem.* **1960**, *25*, 1000. (b) Sekine, M.; Nakajima, M.; Kume, A.; Hashizume, A.; Hata, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 224. (c) Oehler, E.; El-Badawi, M.; Zbiral, E. *Chem. Ber.* **1985**, *118*, 4099. (d) Gancarz, R.; Gancarz, I.; Walkowiak, U. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *104*, 45. (e) Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron* **1998**, *54*, 12233.
(33) (a) Timmler, H.; Kurz, J. *Chem. Ber.* **1971**, *104*, 3740. (b) Hammerschmidt, F.; Schneyder, E.; Zbiral, E. *Chem. Ber.* **1980**, *113*, 3891. (c) Arbuzov, B. A.; Fuzhenkova, A. V.; Banderova, N. A. *Zh. Obshch. Khim.* **1986**, *56*, 1691. (d) Hammerschmidt, F. *Monatsh. Chem.* **1993**, *124*, 1063. (e) El Kaïm, L.; Gaultier, L.; Grimaud, L.; Dos Santos, A. *Synlett* **2005**, 2335.
(34) (a) Demir, A. S.; Reis, O.; Igdir, A. C.; Esiringue, I.; Eymur, S. *J. Org. Chem.* **2005**, *70*, 10584. (b) Demir, A. S.; Eymur, S. *J. Org. Chem.* **2007**, *72*, 8527. (c) Demir, A. S.; Esiringu, I.; Gollu, M.; Reis, O. *J. Org. Chem.* **2009**, *74*, 2197.
(35) Zhou, X.; Liu, Y.; Chang, L.; Zhao, J.; Shang, D.; Liu, X.; Lin, L.; Feng, X. *Adv. Synth. Catal.* **2009**, *16*, 2567.
(36) Prakash, G. K. S.; Panja, C.; Do, C.; Mathew, T.; Olah, G. A. *Synlett* **2007**, 2395.
(37) Tajbakhsh, M.; Heydari, A.; Khalilzadeh, M. A.; Lakouraj, M. M.; Zamenian, B.; Khaksar, S. *Synlett* **2007**, 2347.
(38) Zhou, W.; Xu, L. W.; Yang, L.; Zhao, P. Q.; Xia, C. G. *J. Mol. Catal. A: Chem.* **2006**, *249*, 129.