DOI: 10.1002/cjoc.201100199

$MgCl_2/Et_3N$ Base System as a New Catalyst for the Synthesis of α-Hydroxyphosphonate

Tajbakhsh, Mahmood*,[a] Khaksar, Samad[b] Tafazoli, Zahra[c]
Bekhradnia, Ahmadreza[d]

[a] *Chemistry Department, University of Mazandaran, P. O. Box 453, Babolsar, Iran*
[b] *Chemistry Department, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran*
[c] *Chemistry Department, Payame Noor University, Sari, Iran*
[d] *Pharmaceutical Sciences Research Center, Department of Medicinal Chemistry, Mazandaran University of Medical Sciences, Sari, Iran*

An efficient and simple synthesis of α-hydroxyphosphonates via reaction of aldehydes and ketones with dimethylphosphite in the presence of $MgCl_2/Et_3N$ base system is reported. The use of readily available and easy to handle reagent $MgCl_2/Et_3N$ makes this method simple, convenient, and practical.

Keywords α-hydroxy phosphonates, $MgCl_2/Et_3N$, ketones, nucleophilic addition

Introduction

Over past decades, α-hydroxyphosphonates have received attention both as substrates for the preparation of other α-substituted phosphonates and because of their potential biological activity.[1] α-Hydroxyphosphonates exhibit a wide range of biological activities such as antiviral,[2] antibacterial,[3] antivaccinia,[4] anticancer,[5] pesticides,[6] renin inhibitors,[7] HIV-protease,[8] anti-HIV activities[9] and enzyme inhibitor properties.[10] Much of this activity has been attributed to the relatively inert nature of the C—P bond and to the physical and structural similarity of phosphonic and phosphinic acids to the biologically important phosphate ester and carboxylic acid functional groups.[11] Many α-functionalized phosphonates, such as α-amino,[12] α-keto,[13] α-halo[14] and α-acetoxyphosphonates[15] are prepared from α-hydroxyphosphonates. Recently, numerous activators have been developed for the synthesis of α-hydroxyphosphonates.[16-26] However, these methods often have disadvantages. For example, in the strongly alkaline medium used, α-hydroxy-alkanephosphonic esters are cleaved to regenerate the starting carbonyl compounds.[27] In addition, the yields are not always good and mixtures of products are sometimes obtained. It was found that in many cases which included ketones, the yields were not always good and mixtures of products were sometimes obtained. Hence, there is a need to develop a convenient and environmentally benign method for the synthesis of α-hydroxyphosphonates. The combination of $MgCl_2$ and Et_3N is a considerably stronger base than Et_3N alone. This base system has been used for a variety of base-induced reactions such as condensation,[28] acylation of malonate derivatives,[29] *ortho*-formylation of phenols,[30] Mannich reactions[31] and Dieckman-type cyclizations.[32] As part of our current studies on the development of new catalysts,[33] herein, we report an efficient and environmentally friendly method for the synthesis of α-hydroxyphosphonates catalyzed by $MgCl_2/Et_3N$ base system undr solvent-free conditions (Scheme1).

Experimental

General procedure

A solution of benzaldehyde (0.106 g, 1 mmol), dimethylphosphite (0.136 g, 1.1 mmol) and triethyl amine (0.3 g, 3 mmol) and anhydrous magnesium chloride (0.1 g, 1 mmol) was placed in a round-bottomed flask equipped with a magnetic stirrer and was heated at 50 ℃ for 2 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and the product was extracted three times with 15 mL EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give an oily residue, which was crystallized to give 0.216 g (95%) of dimethyl 1-hydroxy-1-phenylmethylphosphonate as white solid; m.p. 86—87 ℃; IR *v*: 3240 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 3.7 (d, *J*=10.3 Hz, 3H), 3.74 (d, *J*=10.3 Hz, 3H), 4.1 (s, OH), 5.06 (d, *J*=13.2 Hz, 1H), 7.3—7.5 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 53.7

* E-mail: Tajbaksh@umz.ac.ir
Received August 5, 2011; accepted November 9, 2011; published online March 7, 2012.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201100199 or from the author.

(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.

^{1}H NMR and ^{13}C NMR were consistent with the assigned structures and were compared with those reported in the literature.[33d]

Results and Discussion

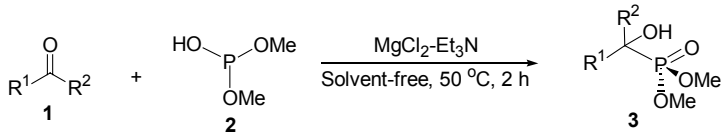
To a suspension of anhydrous $MgCl_2$-Et_3N and benzaldehyde, dimethyl phosphite was added. After stirring for 3 h at 40 ℃, complete conversion of the benzaldehyde to corresponding α-hydroxyphosphonates was obsearved. As shown in the Table 1, aromatic aldehydes and dimethylphosphite in the presence of $MgCl_2$-Et_3N at 50 ℃, gave the target products in good yield, in a typical reaction time of about 1—2 h (Table 1, Entries 1—5).

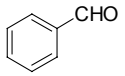
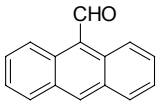
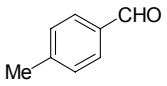
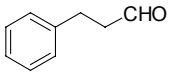
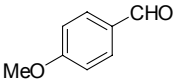
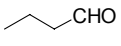
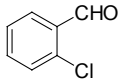
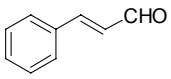
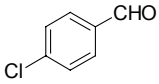
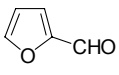
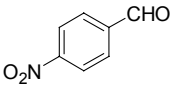
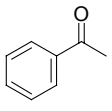
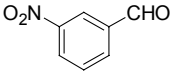
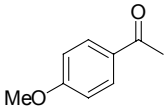
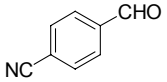
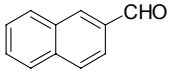
Electron-withdrawing groups in the aromatic rings of the aldehydes make them less reactive and give lower yield in longer reaction time (Table 1, Entries 6—8). Aliphatic aldehydes reacted smoothly with dimethylphosphite under reaction condition and high yields of the corresponding α-hydroxyphosphonates were obtained (Table 1, Entries 11 and 12). 2-Furaldehyde reacted with dimethylphosphite and a high yield of product formed (Table 1, Entry 14). However, in order to find the reactivity of ketones in this reaction, we have carried out this reaction with aromatic and aliphatic ketones and a moderate yield of the corresponding phosphonates were obtained (Table 1, Entries 15—18). Interestingly, α,β-unsaturated aldehyde selectively afforded the corresponding α-hydroxyphosphonate in good yield, with no byproduct formation (Table 1, Entry 13). This reaction has been also performed in different organic solvents which were not effective and only trace amount of products were formed.

Conclusions

In conclusion, we have developed a method for the synthesis of α-hydroxyphosphonates by reacting aldehydes and ketones with dimethylphosphite in the pres-

Table 1 Synthesis of α-hydroxyphosphonates using $MgCl_2$/Et_3N as catalyst



Entry	Aldehyde/Keton	Yield of **3**/%	Entry	Aldehyde/Keton	Yield of **3**/%
1		97	10		96
2		97	11		96
3		96	12		95
4		98	13		90
5		90	14		95
6		90	15		90
7		95	16		85
8		95	17		90
9		92	18		85

ence of $MgCl_2/Et_3N$ base system. The advantages of this procedure are operational simplicity, wide substrate scope, and high yields. In many cases, the products crystallized directly from the reaction mixture in high purity. We believe that this method presents a practical alternative to existing procedures for the synthesis of α-hydroxyphosphonates.

Acknowledgment

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

References

[1] Kim, D. Y.; Wiemer, D. F. *Tetrahedron Lett.* **2003**, *44*, 2803.
[2] Neyts, J.; De Clercq, E. *Antimicrob. Agents Chemother.* **1997**, *41*, 2754.
[3] Fleisch, H. *Endocr. Rev.* **1998**, *19*, 80.
[4] Snoeck, R.; Holy, A.; Dewolf-Peeters, C.; Van Den Oord, J.; De Clercq, E.; Andrei, G. *Antimicrob. Agents Chemother.* **2002**, *46*, 3356.
[5] Lee, M. V.; Fong, E. M.; Singer, F. R.; Guenett, R. S. *Cancer Res.* **2001**, *61*, 2602.
[6] Kafarski, P.; Lejczak, B. *J. Mol. Catal. B*: *Enzym.* **2004**, *29*, 99.
[7] Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, E. W. Jr. *J. Med. Chem.* **1995**, *38*, 4557.
[8] Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.
[9] Zheng, X.; Nair, V. *Tetrahedron* **1999**, *55*, 11803.
[10] Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591.
[11] Fields, S. C. *Tetrahedron* **1999**, *55*, 12237.
[12] Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051.
[13] Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 6720.
[14] Eymery, F.; Lorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 2671.
[15] Firouzabadi, H.; Iranpoor, N.; Sobhani, S.; Amoozgar, Z. *Synthesis* **2004**, 1771.
[16] Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.***1978**, *100*, 3467.
[17] Texier-Boullet, F.; Foucaud, A. *Synthesis* **1982**, 916.
[18] Texier-Boullet, F.; Lequitte, M. *Tetrahedron Lett.* **1986**, *27*, 3515.
[19] Heydari, A.; Arefi, A.; Khaksar, S.; Tajbakhsh, M. *Catal. Commun.* **2006**, *7*, 98.
[20] Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978.
[21] Dodda, R.; Zhao, C. G. *Org. Lett.* **2006**, *8*, 4911.
[22] Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1779.
[23] Tajbakhsh, M.; Heydari, A.; Khalilzadeh, M. A.; Lakouraj, M. M.; Zamenian, B.; Khaksar, S. *Synlett* **2007**, 2347.
[24] Chen, W.; Hui, Y.; Zhou, X.; Jiang, J.; Cai, Y.; Liu, X.; Lin, L.; Feng, X. *Tetrahedron Lett.* **2010**, *51*, 4175.
[25] Zhou, X.; Liu, Y.; Chang, L.; Zhao, J.; Shang, D.; Liu, X.; Lin, L.; Feng, X. *Adv. Synth. Catal.* **2009**, *351*, 2567.
[26] Cai, Z. H.; Du, G. F.; He, L.; Gu, C. Z.; Dai, B. *Synthesis* **2011**, 2073.
[27] Kharasch, M. S.; Mosher, R. A.; Bengelsdorf, I. S. *J. Org. Chem.* **1960**, *25*, 1000.
[28] Zhang, M.; Zhang, A.-Q.; Huang, Y.-X. *Chin. J. Org. Chem.* **2005**, *25*, 1133.
[29] (a) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622; (b) Rathke, M. W.; Nowak, M. A. *Synth. Commun.* **1985**, *15*, 1039.
[30] (a) Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258; (b) Hansen, T. V.; Skattebøl, L. *Org. Synth.* **2005**, *82*, 64.
[31] Anwar, H. F.; Skattebøl, L.; Hansen, T. V. *Tetrahedron* **2007**, *63*, 9997.
[32] Tamai, S.; Ushirogochi, H.; Sano, S.; Nogao, Y. *Chem. Lett.* **1995**, 295.
[33] (a) Asghari, S.; Tajbakhsh, M.; Jafarzadeh, B. K.; Khaksar, S. *Chin. Chem. Lett.* **2011**, *22*, 127; (b) Tajbakhsh, M.; Khaksar, S.; Zamenian, B.; Jahani, F. *Synthesis* **2010**, 3315; (c) Jahani, F.; Tajbakhsh, M.; Golchoubian, H.; Khaksar, S. *Tetrahedron Lett.* **2011**, *52*, 1260; (d) Vahdat, S. M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, S. M.; Khaksar, S. *Tetrahedron Lett.* **2008**, *49*, 6501.

(Pan, B.; Qin, X.)

