Calcium Chloride as an Efficient Lewis Base Catalyst for the One-pot Synthesis of α-Aminophosphonic Esters

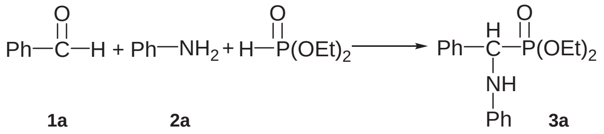
Babak Kaboudin* and Hazegh Zahedi
Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Gava Zang, Zanjan 45195-1159, Iran

(Received February 15, 2008; CL-080176; E-mail: kaboudin@iasbs.ac.ir)

A simple, efficient, and general method has been developed for the one-pot synthesis of α-aminophosphonic esters, under solvent-free conditions, with the use of $CaCl_2$ as a Lewis base catalyst. The esters were obtained under mild conditions and in high yield (80 to 96%) and purity. They were synthesized by the reaction of diethyl phosphite with a mixture of aldehydes and amines, in the presence of $CaCl_2$, and under solvent-free conditions. Major advantages of this protocol are: high yields, inexpensive method, making use of a non-toxic catalyst and finally mild and solvent-free conditions.

α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1] α-Aminophosphonic acids could be used as substitutes for the corresponding α-amino acids in biological systems.[2] Indeed a number of potent antibiotics,[3] enzyme inhibitors,[4] and pharmacological agents[5] are α-aminophosphonic esters or their peptide analogues. α-Aminophosphonic esters are also found as constituents of natural products. Many different methods for the preparation of α-aminoalkylphosphonic esters have been developed so far and the Kabachnik–Fields[6] synthetic method, using an acid or base as catalyst, is the most convenient method. Nucleophilic addition of an amine to a carbonyl compound, followed by reacting with a dialkyl or a diaryl phosphite and resulting an imine, is the key step in the Kabachnik–Fields synthesis of α-aminophosphonic esters. Frequently formation of 1-hydroxyphosphonates or its rearrangement product accompanies the formation of α-aminophosphonic esters.[7] Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3 \cdot Et_2O$, $ZnCl_2$, $MgBr_2$, and $InCl_3$ have been used as catalysts in these transformations.[8] However, these reactions could not be carried out in one-step in a reaction mixture consisting of a carbonyl compound, an amine, and a dialkyl phosphite since the Lewis acids catalysts could be decomposed or deactivated in the presence of amines and water during imine formation. In order to alleviate this problem there has been recently a number of reports about the use of metal triflates[9] and perchlorates[10,11] as catalysts instead of above Lewis acids. However, these new developments also suffer from stoichiometric amounts of reagents such as molecular sieves, $MgSO_4$, etc. Hence, there is still a need to develop a more efficient, practical, and environmentally benign method for the synthesis of α-aminophosphonic esters.

In recent years, there has been considerable interest in developing more economical and environmental-friendly conversion processes. $CaCl_2$ is an inexpensive, and commercially available reagent, and as it has been shown recently, a very good catalyst in organic reactions.[12] In continuation of our interest in developing novel methodologies for the synthesis of organophosphorous compounds,[13] we report here an efficient, practical, environmentally benign, and high yielding method for a three-component, one-pot synthesis of α-aminophosphonic esters using $CaCl_2$ as catalyst.



Scheme 1.

Table 1. Three-component reaction of benzaldehyde (**1a**), aniline (**2a**), and diethyl phosphite using calcium chloride as catalyst

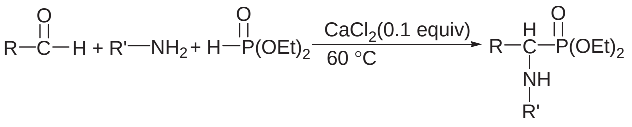
Entry	**1a**:**2a**:DEP:$CaCl_2$	Solvent	Reaction time/h	Yield/%[a,b] **3**
1	1:1:1.2:—	—	24	43
2	1:1:1.2:1	—	2	96
3	1:1:1.2:0.1	—	3	96
4	1:1:1.2:0.1	CH_2Cl_2	24[c]	78
5	1:1:1.2:0.1	CH_3CN	24	91
6	1:1:1.2:0.1	DMSO	24	73
7	1:1:1.2:0.1	DMF	24	73
8	1:1:1.2:0.1	THF	24	78
9	1:1:1.2:0.1	EtOH	24	71
10	1:1:1.2:0.1	MeOH	24	71
11	1:1:1.2:0.1	H_2O	6	92

[a] ^{31}P NMR yields. [b] Reactions carried out at 60 °C. [c] Reflux condition.

Three-component reaction system of benzaldehyde (**1a**), aniline (**2a**), and diethyl phosphite was selected as a model for the one-pot synthesis of α-aminophosphonic esters using calcium chloride as catalyst (Scheme 1 and Table 1). In the absence of any catalyst and for 24 h duration, corresponding α-aminophosphonic ester **3a** was obtained with 43% yield (Entry 1).

Addition of an equimolar amount of $CaCl_2$ completed the reaction in 2 h and a quantitatively yield of **3a** was achieved. A catalytic amount of $CaCl_2$ was enough to attain high reaction efficiency (Entry 3, Table 1). The $CaCl_2$-promoted reaction was strongly affected by the solvent (Entries 4–11). The reaction proceeded smoothly in DMSO, while with the use of THF, in which $CaCl_2$ was hardly dissolved, resulted in a moderate yield of **3a**. The homogeneous reaction in MeOH and EtOH gave adduct **3a** in good yield. Although water was surprisingly effective solvent, substrates did not dissolve well in it (Entry 11).

The above results prompted us to use $CaCl_2$ as a catalyst for one-pot synthesis of α-aminophosphonic esters. As shown in Scheme 2 and Table 2, a mixture of aniline (**2a**) and benzaldehyde (**1a**) with diethyl phosphite, in the presence of $CaCl_2$ as catalyst, afforded the desired product **3a** in 90% yield. Other

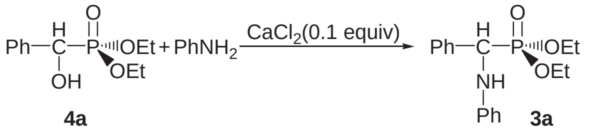


Scheme 2.

Table 2. One-pot synthesis of α-aminophosphonic esters using $CaCl_2$ as catalyst under solvent-free condition

Product	R	R′	Reaction time/h	Yield/%[a]
3a	C_6H_5–	C_6H_5–	3	90
3b	*p*-$CH_3C_6H_4$–	C_6H_5–	3	93
3c	*p*-$(CH_3)_2CHC_6H_4$–	C_6H_5–	2	92
3d	*p*-$CH_3OC_6H_4$–	C_6H_5–	2	90
3e	*p*-$NO_2C_6H_4$–	C_6H_5–	3	96
3f	Ph–CH=CH–	C_6H_5–	3	85
3g	C_6H_5–	*m*-$NO_2C_6H_4$–	3	87
3h	*p*-$CH_3C_6H_4$–	*m*-$NO_2C_6H_4$–	3	94
3i	*p*-$(CH_3)_2CHC_6H_4$–	*m*-$NO_2C_6H_4$–	3	90
3j	*p*-$CH_3OC_6H_4$–	*m*-$NO_2C_6H_4$–	2	83
3k	C_6H_5–	Cyclohexyl	4	80
3l	Ph–CH=CH–	Cyclohexyl	3	88

[a] Yield refers to isolated yield by column chromatography.



Scheme 3.

mixtures of amines and aldehydes also reacted with diethyl phosphite, in the presence of catalytic amounts of $CaCl_2$, to give desired compounds in good yields (Table 2).

Lewis base activity of $CaCl_2$ has recently been reported in literature.[12] We found that LiCl- and NaCl-promoted reactions of **2a** with **1a**, for 8 h, gave **3a** in high yields. However, shortening the reaction time revealed that the rate-accelerating ability of NaCl and LiCl was lower than that of $CaCl_2$ (96% yield of **3a** after 2 h). Interestingly, we also found that Bu_4NCl could be used instead of a metal salt (71% yield of **3a** after 12 h). Chloride ion also accelerated the reaction in the presence of no solvent.

It was detected that 1-hydroxyphosphonates or a product of its rearrangement was not produced in the formation of 1-aminoalkylphosphonates. These results prompted us to examine the conversion of 1-hydroxyalkylphosphonates to 1-aminoalkylphosphonates in the presence of amines, using $CaCl_2$ as catalyst (Scheme 3).[14] Interestingly we found that diethyl 1-hydroxyphenylmethylphosphonate (**4a**) could be converted to diethyl 1-aminophenylmethylphosphonate (**3a**) in the presence of aniline and $CaCl_2$ as catalyst, after 24 h (20% yield, 60 °C, Scheme 3).[15] The reaction yield was increased to 65% with the addition of one equivalent diethyl phosphite to the reaction mixture.

In conclusion, in all reactions reported in this paper, the cleavage of Et–O–P bond was not detected and the conversion of substrates to their corresponding α-aminophosphonic esters was clean. It was revealed that $CaCl_2$ could be an effective Lewis base catalyst for one-pot synthesis of α-aminophosphonic esters. We also found that α-hydroxyphosphonate could be converted to α-aminophosphonic esters in the presence of aniline and $CaCl_2$ as catalyst. All NMR data could be assigned and they were in good agreement with the characteristic products.[16]

The Institute for Advanced Studies in Basic Sciences (IASBS) is thanked for supporting this work.

References and Notes

1 a) J. Hiratake, J. Oda, *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211. b) K. A. Schug, W. Lindner. *Chem. Rev.* **2005**, *105*, 67. c) K. Moonen, I. Laureyn, C. V. Stevens, *Chem. Rev.* **2004**, *104*, 6177.

2 P. P. Giannousis, P. A. Bartlett, *J. Med. Chem.* **1987**, *30*, 1603.

3 F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29.

4 M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.* **1989**, *32*, 1652.

5 C. H. Hassal, in *Antibiotics*, ed. by F. E. Hahn, Springer Verlag, Berlin, **1983**, Vol VI, p. 1.

6 M. Horiguchi, M. Kandatsu, *Nature* **1959**, *184*, 901.

7 a) V. P. Kukhar, H. R. Hudson, in *Aminophosphonic and Aminophosphinic Acids*, John Wiley & Sons, Chichester, **2000**. b) B. Kaboudin, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1749. c) E. K. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528.

8 J. Lewkowski, *J. Organomet. Chem.* **2003**, *681*, 225.

9 a) B. C. Ranu, A. Hajra, U. Jana, *Org. Lett.* **1999**, *1*, 1141, and references cited their. b) M. M. Kabachnik, T. N. Ternovskaya, E. V. Zobnina, I. P. Beletskaya, *Russ. J. Org. Chem.* **2002**, *38*, 504.

10 a) R. Ghosh, S. Maiti, A. Chakraborty, D. K. Maiti, *J. Mol. Catal. A: Chem.* **2004**, *210*, 53. b) H. Firouzabadi, N. Iranpoor, S. Sobhani, *Synthesis* **2004**, 2692.

11 S. Bhagat, A. K. Chakraborti, *J. Org. Chem.* **2007**, *72*, 1263.

12 K. Miura, T. Nakagawa, A. Hosomi, *J. Am. Chem. Soc.* **2002**, *124*, 536.

13 a) B. Kaboudin, *Chem. Lett.* **2001**, 880. b) B. Kaboudin, *Tetrahedron Lett.* **2002**, *43*, 8713. c) B. Kaboudin, R. Nazari, *Tetrahedron Lett.* **2001**, *42*, 8211. d) B. Kaboudin, A. Rahmani, *Synthesis* **2003**, 2705. e) B. Kaboudin, F. Saadati, *Synthesis* **2004**, 1249. f) B. Kaboudin, A. Rahmani, *Org. Prep. Proced. Int.* **2004**, *36*, 82. g) B. Kaboudin, K. Moradi, *Tetrahedron Lett.* **2005**, *46*, 2989. h) B. Kaboudin, H. Haghighat, *Tetrahedron Lett.* **2005**, *46*, 7955. i) B. Kaboudin, H. Haghighat, T. Yokomatsu, *J. Org. Chem.* **2006**, *71*, 6604. j) B. Kaboudin, M. Karimi, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5324. k) B. Kaboudin, F. Farjadian, *Beilstein J. Org. Chem.* **2006**, *2*, 4. l) B. Kaboudin, K. Moradi, *Tetrahedron Lett.* **2005**, *46*, 2989. m) T. Yamagishi, T. Kusano, B. Kaboudin, T. Yokomatsu, C. Sakuma, S. Shibuya, *Tetrahedron* **2003**, *59*, 767. n) B. Kaboudin, K. Moradi, *Synthesis* **2006**, 2339. o) B. Kaboudin, E. Jafari, *Synthesis* **2006**, 3063. p) B. Kaboudin, M. Sorbiun, *Tetrahedron Lett.* **2007**, *48*, 9015.

14 1-Hydroxyphosphonates synthesized using known methods: A. R. Sardarian, B. Kaboudin, *Synth. Commun.* **1997**, *27*, 543.

15 B. Kaboudin, *Tetrahedron Lett.* **2003**, *44*, 1051.

16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) April 12, 2008; doi:10.1246/cl.2008.540