A New Protocol for a One-pot Synthesis of α-Amino Phosphonates by Reaction of Imines Prepared In Situ with Trialkylphosphites

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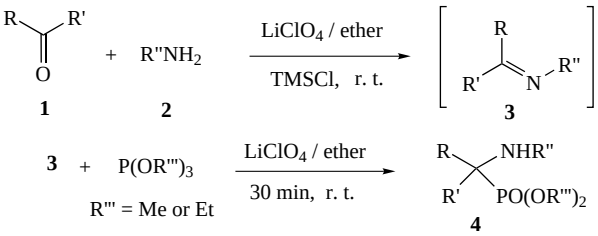
Abstract: Imines prepared in situ by reaction of aldehydes and ketones with primary amines in ethereal solution of $LiClO_4$ react readily at ambient temperature with trialkylphosphite to give high yields of α-amino phosphonates.

Key words: amino phosphonate, imine, trialkylphosphite, lithium perchlorate

α-Amino phosphonates are an important class of compounds since they are considered as structural analogues of the corresponding α-amino acids, and their utilities as enzyme inhibitors, antibiotics, pharmacological agents and many other applications are well documented.[1] Synthesis of α-amino phosphonate has drawn considerable attention over the past few years and a large number of modified conditions,[2–7] as well as the preparation of a three component reaction between triethyl phosphite[8] with a secondary amine and an aldehyde in the presence of a Lewis acid have been reported in the literature. Here we would like to report a one-pot three-component reaction of trialkylphosphite with imines prepared in situ in the presence of trimethylsilyl chloride, TMSCl, in ethereal solution of $LiClO_4$.

During the course of our efforts towards the aminoalkylation of aldehydes mediated by lithium perchlorate in diethyl ether,[9] we found that an imines prepared in situ react very effectively with trimethylphosphite or triethylphosphite as nucleophile to produce α-amino phosphonates. In the present work, we attempted to develop a novel one-pot and fast procedure for the preparation of α-amino phosphonates at ambient temperature. It was found that the reaction of aldehydes or ketones **1** (1 equiv) with an excess of a primary amine **2** (1.25 equiv), forms the imine **3** in the presence of TMSCl in a concentrated ethereal solution of lithium perchlorate.[10] By the addition of trimethylphosphite or triethylphosphite in the same flask, without any further purification of the intermediate imines, α-amino phosphonates **4** were formed in very short time with high yields, (Scheme 1). The reaction can be applied for both enolizable and non-enolizable aldehydes and ketones with a range of substituted starting materials. All transformations were carried out at room temperature in a 5 M ethereal solution of lithium perchlorate in one-pot with a short reaction time (Scheme 1, Table).



Scheme 1

The reactions are clean and the products are obtained in high yield even for the reaction with enolizable aldehyde or ketone, such as isopropyl aldehyde and cyclohexanone. As it was reported before,[10] the yield of the $LiClO_4$-mediated amioalkylation reaction is lower for the enolizable aldehydes due to the formation of enamines as side products. But with this procedure, aminophosphonation of enolizable aldehydes or ketones proceeds with high yields and in short time. In addition, the reaction conditions are mild so that no side products or decomposition of the products are observed.[11,12] To demonstrate the efficiency of lithium perchlorate, a mixture of **1**, **2** and trimethylphosphite were stirred in diethyl ether at ambient temperature for several hours in the absence of lithium perchlorate. After aqueous work-up, in contrast to the above results, no α-amino phosphonate **4** could be detected as the product.

In order to examine the diastereoselectivity in aminophosphonation of aldehyde with the chiral amine, enantiopure (*R*)-1-phenylethylamine, very accessible in both the enantiopure forms, was used**.** Upon addition of trimethylphosphite to the imines prepared in situ by reaction of aldehydes with primary chiral amine, α-amino phosphonates **5** were formed with high yields and with diastereoselectivity (dr) from 70% to more than 80% (Scheme 2). The structure and the ratio of the major and minor diastereomers were determined by ^1H NMR spectra of the crude product and by comparison of the chemical shift and coupling constant of proton attached to the carbon bearing the phosphonate group with similar compound reported in the literature.[6b,7b] Each diasereomers show a doublet with different chemical shift and coupling constant. The upfield doublet was assigned for the major diasereomer

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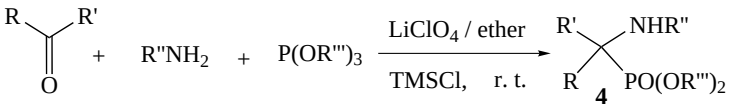
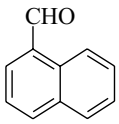
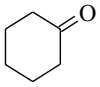
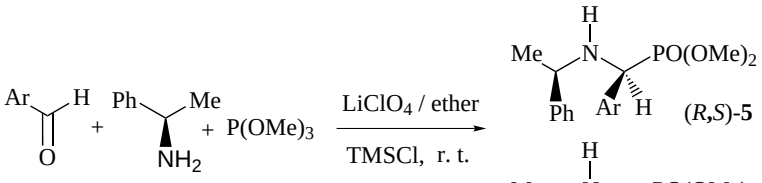
Table Synthesis of α-Amino Phosphonates from Aldehydes and Ketones Mediated by LPDE



Entry	R	R′	R″	R‴	Product	Yield
1	Ph	H	Ph	Me	**4a**	98
2	Ph	H	Ph	Et	**4b**	98
3	*p*-Cl-Ph	H	Ph	Me	**4c**	98
4	*p*-Cl-Ph	H	Ph	Et	**4d**	97
5	PhCH=CH	H	Ph	Me	**4e**	93
6	PhCH=CH	H	Ph	Et	**4f**	95
7	*m*-NO_2-Ph	H	Ph	Me	**4g**	98
8	*m*-NO_2-Ph	H	Ph	Et	**4h**	98
9	Me_2CH	H	Ph	Me	**4i**	85
10	Me_2CH	H	Ph	Et	**4j**	85
11	*p*-OMe-Ph	H	Ph	Me	**4k**	85
12	*p*-OMe-Ph	H	Ph	Et	**4l**	85
13			Ph	Me	**4m**	97
14			Ph	Et	**4n**	97
15	Ph	H	*p*-Br-Ph	Me	**4o**	97
16	Ph	H	*n*-Bu	Me	**4p**	95
17	Ph	H	*n*-Bu	Et	**4r**	94
18	*p*-Cl-Ph	H	*n*-Bu	Me	**4s**	94
19	*m*-NO_2-Ph	H	*n*-Bu	Me	**4t**	96
20			Ph	Me	**4u**	90
21			Ph	Et	**4v**	88



Ar	Yield(%)	dr
Ph	95	75/25
p-Cl-Ph	97	78/22
m-NO_2-Ph	96	80/20
PhCH=CH	93	70/30

Scheme 2

(*R*,*S*)-**5** and the downfield doublet was assigned for the minor diastereomer (*R*,*R*)-**5**.

In summary, we have reported that in situ prepared imines in a concentrated ethereal solution of lithium perchlorate can react with trimethylphosphite or triethylphosphite in excellent yields. The procedure for the reaction is mild and operationally simple. With enantiopure (*R*)-1-phenylethylamine, a mixture of two diastereomers formed with dr from 70% to 80%.

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References

(1) (a) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (b) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845. (c) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.

(2) Kudzin, Z. H.; Lyzwa, P.; Luczak, J.; Andrijewski, G. *Synthesis* **1997**, 44.

(3) Yadav, J. S.; Reddy, B. V. S.; Madan, C. *Synlett* **2001**, 1131.

(4) Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, Ch. *Tetrahedron Lett.* **2001**, *42*, 5561.

(5) Yadav, J. S.; Reddy, B. V. S.; Sarita Raj, K.; Bhaskar Reddy, K.; Prasad, A. R. *Synthesis* **2001**, 2277.

(6) (a) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141. (b) Qian, C.; Huang, T. J. *Org. Chem.* **1998**, *63*, 4125.

(7) (a) Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211. (b) Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett.* **1998**, *39*, 6729.

(8) (a) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669. (b) Lee, S.-G.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, 1698.

(9) (a) Naimi-Jamal, M. R.; Mojtahedi, M. M.; Ipaktschi, J.; Saidi, M. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3709. (b) Saidi, M. R.; Azizi, N.; Zali-Boinee, H. *Tetrahedron* **2001**, *57*, 6829. (c) Saidi, M. R.; Azizi, N.; Naimi-Jamal, M. R. *Tetrahedron Lett.* **2001**, *42*, 8111. (d) Mojtahedi, M. M.; Saidi, M. R.; Shirzi, J. S.; Bolourtchian, M. *Synth. Commun.* **2001**, *31*, 3587.

(10) Naimi-Jamal, M. R.; Ipaktschi, J.; Saidi, M. R. *Eur. J. Org. Chem.* **2000**, 1735.

(11) **General Procedure for the Preparation of α-Amino Phosphonates 4.** The aldehyde (2 mmol)and 4 mL of 5 M $LiClO_4$ in diethyl ether were placed in a 50 mL flask under argon and stirred for 5 min. Then a primary amine (3.0 mmol) and TMSCl (2.0 mmol) were added via a syringe. After 10 min, trimethyl-phosphite or triethyl-phosphite (2.5 mmol) was added and the mixture was stirred at r.t. for about 15 min. Then water (20 mL) and CH_2Cl_2 (20 mL) were added. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed. Almost pure crude product obtained. Further purification was carried out by column chromatography on basic alumina eluting with petroleum ether/EtOAc, if needed. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) and comparison with those reported in the literature. **Caution:** Although we did not have any accident while using $LiClO_4$, it is advisable to dry lithium perchlorate in a fume hood using a suitable lab-shield.

(12) Selected spectral data. **4a**: IR (KBr): 3304 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.48 (d, 3 H, *J* = 6.1 Hz), 3.78 (d, 3 H, *J* = 10.7 Hz), 4.50 (br s, 1H, NH), 4.83 (d, 1 H, *J* = 24.3), 6.61–6.72 (m, 3 H), 7.28–7.50 (m, 7 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 53.68 (d, $^2J_{PC}$ = 6.6 Hz), 54.2 (d, $^2J_{PC}$ = 7.6 Hz), 55.6 (d, $^1J_{PC}$ = 150.6 Hz), 114.2, 119.2, 123.4, 129.0, 129.8 (d, J_{PC} = 4.5 Hz), 130.2, 135.9 (d, J_{PC} = 2.5 Hz), 146.4 (d, J_{PC} = 14.7 Hz). **4c**: IR (KBr): 3314 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.55 (d, 3 H, *J* = 10.6 Hz), 3.78 (d, 3 H, *J* = 10.7), 4.83 (d, 1 H, *J* = 24.6 Hz), 4.85 (br s, 1 H, NH), 6.62–7.46 (m, 9 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 53.70 (d, $^2J_{PC}$ = 6.6 Hz), 54.2 (d, $^2J_{PC}$ = 6.0 Hz) 55.02 (d, $^1J_{PC}$ = 154 Hz), 114.0, 119.1, 129.0, 129.6 (d, J_{PC} = 8.1), 129.9, 130.2, 134.2 (d, J_{PC} = 3.9 Hz), 146.4 (d, J_{PC} = 15.0 Hz). **4g**: IR (KBr): 3325 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.64 (d, 3 H, *J* = 10.7 Hz), 3.83 (3 H, *J* = 10.7 Hz), 4.99 (d, 1 H, *J* = 25.0 Hz), 5.12 (br s, 1 H, NH), 6.62–6.73 (m, 3 H), 7.11–7.13 (m, 2 H), 7.88–8.40 (m, 4 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 54.1 (d, $^2J_{PC}$ = 6.8 Hz), 54.6 (d, $^2J_{PC}$ = 5.9 Hz), 54.8 (d, $^1J_{PC}$ = 155.0 Hz), 114.2 (d, J_{PC} = 11.2 Hz), 119.3 (d, J_{PC} = 11.4 Hz), 123.2, 129.7 (d, J_{PC} = 4.5 Hz), 130.0 (d, J_{PC} = 11.2 Hz), 134.3 (d, J_{PC} = 3.9 Hz), 139.9, 145.9 (d, J_{PC} = 13.8 Hz), 148.9 (d, J_{PC} = 2.5 Hz). **4n**: IR (KBr): 3300 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.77 (t, 3 H, *J* = 6.9 Hz), 1.37 (t, 3 H, *J* = 7.0 Hz), 3.26 (m, 1 H), 3.79 (m, 1 H), 4.26 (m, 2 H), 5.01 (br s, 1 H, NH), 5.75 (d, 1 H, *J* = 24.1 Hz), 6.63–6.70 (m, 3 H), 7.06–7.09 (m, 2 H), 7.45–7.93 (m, 6 H), 8.33–8.35 (m, 1 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.3 (d, $^3J_{PC}$ = 2.3 Hz) 17.0 (d, $^3J_{PC}$ = 5.8 Hz), 51.8 (d, $^1J_{PC}$ = 151 Hz), 63.6 (d, $^2J_{PC}$ = 6.5 Hz), 63.9 (d, $^2J_{PC}$ = 5.8 Hz), 113.9, 114.1, 118.6, 123.4 (d, J_{PC} = 6.6 Hz), 126.2, 126.2, 126.7, 128.8, 129.0, 129.4, 129.6 (d, J_{PC} = 10.6 Hz), 132.0 (d, J_{PC} = 5.0) 134.3, 146.6 (d, J_{PC} = 14.5 Hz). **4u**: IR (KBr): 3320 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.13-2.13 (m, 10 H), 3.45(br s, NH), 3.54 (d, 6 H, *J* = 10.2 Hz), 6.66–7.05 (m, 5 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 20.2 (d, J_{PC} = 10.5 Hz), 25.6, 30.5, 53.3 (d, J_{PC} = 7.7 Hz), 58.1 (d, J_{PC} = 159.0 Hz), 118.6 (d, J_{PC} = 10.5 Hz), 119.6 (d, J_{PC} = 13.2 Hz), 129.0 (d, J_{PC} = 6.7 Hz), 146.1.