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One-pot synthesis of *N*-trimethylsilyloxy-α-amino phosphonates from aldehydes using lithium perchlorate/diethyl ether as a catalyst

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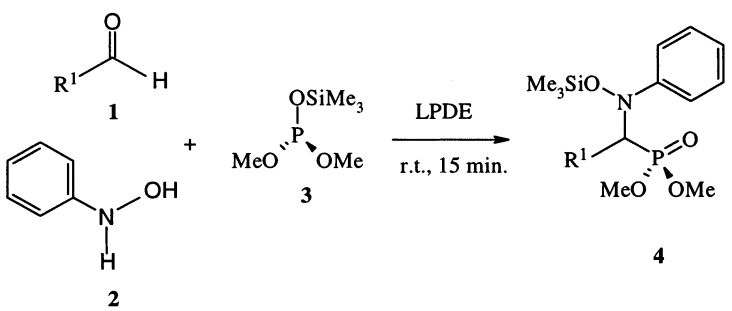
Abstract—A simple and efficent one-pot method was developed to give *N*-trimethylsilyloxy-α-amino phosphonate derivatives from aldehydes+hydroxylamines+dimethyl(trimethylsilyl)phosphonate in lithium perchlorate/diethyl ether solution (LPDE) in high yields. © 2001 Elsevier Science Ltd. All rights reserved.

Phosphonate containing molecules show a wide range of biological activities. Examples include inhibitors of EPSP synthase,[1] HIV protease,[2] renin,[3] PTPases,[4] potent antibiotics,[5] enzyme inhibitors,[6] herbicides[7] and surrogates for α-amino carboxylic acids.[8] Although the chemistry of α-hydroxy phosphonates[9] and α-amino phosphonates[10] has been extensively studied, we were surprised to note, that to our knowledge, only a few syntheses of chiral *N*-hydroxy-α-amino phosphonic acids have been reported in the literature: via the addition of phosphite anions and tris(trimethylsilyl)phosphite to chiral *N*-glycosyl-*C*-aryl-nitrones in the presence of Lewis acids,[11] or a Mitsunobu S_N2-type displacement reaction of the corresponding α-hydroxy phosphonates with *N*-(phenoxycarbonyl)-*O*-*tert*-butyloxycarbonyl hydroxylamine.[12]

We have already reported a general method for one-pot α-aminoalkylation,[13] α-aminocyanation,[14] α-aminophosphonation[15] and α-cyanohydroxylamination[16] of aldehydes in a solution of lithium perchlorate/diethyl ether (LPDE) (5.0 M).[17] This communication reports preliminary results on a new approach for the synthesis of *N*-trimethylsilyloxy-α-amino phosphonates. Although a solution of aldehyde **1**, phenylhydroxylamine **2** and dimethyl(trimethylsilyl)phosphite **3** in diethyl ether remains unchanged after 4 h at room temperature, the reaction in 5 M ethereal $LiClO_4$ solution, followed by hydrolysis, leads to the formation of the *N*-trimethylsilyloxy-α-amino phosphonates **4**, within 15 min, in high yields.[18] *N*-Trimethylsilyloxy-α-amino phosphonates might be transformed further into *N*-hydroxy-α-amino phosphonic acids and into α-amino phosphonic acids.



R¹	Yield 4 (%)
i-Propyl	97
n-Propyl	95
n-Butyl	99
n-Hexyl	90
c-Hexyl	87
Phenyl	90
p-Me*O*-Phenyl	85
2-Furyl	90
3-Pyridyl	95*
trans-PhCH=CH	95

*The isolated yield of *N*-hydroxy-α-aminophosphonate. It is noted that the TMS group was removed after columm chromatography (ethyl acetate: hexane; 1:2) over silica gel.

Scheme 1.

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The *N*-hydroxy-α-amino phosphonic acids and α-amino phosphonic acid analogs of the corresponding amino acids, exert biological activities which have been shown to depend on their absolute configuration.[19] It should be noted that most Lewis acids cannot be used in this reaction since they are decomposed or deactivated by the hydroxylamines and water which exist during nitrone formation.[20] Several examples of the present three component coupling reactions are summarized in Scheme 1.

Not only aromatic, but also aliphatic, heterocyclic and α,β-unsaturated aldehydes reacted smoothly under these conditions.

In summary, we have found that 5 M LPDE promotes the direct conversion of aldehydes into *N*-trimethylsilyloxy-α-amino phosphonates. The protocol is simple and potentially leads to versatile *N*-trimethylsilyloxy-α-amino phosphonates. This method has a few noteworthy features: (1) excellent yields can be obtained for aliphatic, aromatic, heteroaromatic and α,β-unsaturated aldehydes, (2) great operational simplicity at ambient temperature and (3) α-aliphatic nitrones are stable under these conditions (it has been reported that nitrones in general are isomerized to isonitrones by light or heat,[21] and aliphatic and alicyclic nitrones are readily dimerized).[22]

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References

1. Sikoski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. *Phosphrus Sulfur Silicon* **1993**, *76*, 115.
2. Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett*. **1989**, *30*, 6625.
3. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett*. **1990**, *31*, 5587.
4. (a) Burke, Jr., T. R.; Barchi, Jr., J. J.; George, C.; Wolf, G.; Shoelson, S. E.; Yan, X. *J. Med. Chem*. **1995**, *38*, 1386; (b) Burke, Jr., T. R.; Kole, H. K.; Roller, P. P. *Biochem. Biophys. Res. Commun*. **1994**, *204*, 129.
5. Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem*. **1998**, *29*, 29.
6. (a) Stowasser, B.; Budt, K.-H.; Jian Gi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett*. **1989**, *30*, 6625; (b) Burke, Jr., T. R.; Barchi, Jr., J. J.; George, C.; Wolf, G.; Shoelson, S. E.; Yan, X. *J. Med. Chem*. **1995**, *38*, 1386.
7. Kafarski, P.; Lejcak, B.; Mastalerz, P. *Beitr. Wirk. Forsh*. **1985**, H25.
8. Yager, K. M.; Taylor, C. M.; Smith, III, A. B. *J. Am. Chem. Soc*. **1994**, *116*, 9377.
9. Wiemer, D. F. *Tetrahedron* **1997**, *55*, 16609.
10. Smith, III, A. B.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc*. **1995**, *117*, 10879 and references therein.
11. (a) Franz, J. E. US Patent 4,084,953; *Chem. Abst*. **1978**, *89*, 109961; (b) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730; (c) Huber, R.; Vasella, A. *Helv. Chim. Acta* **1987**, *70*, 1461; (d) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33.
12. Gouverneur, V.; Lalloz, M.-H. *Tetrahedron Lett*. **1996**, *37*, 6331.
13. Heydari, A.; Ipaktschi, J. *Chem. Ber*. **1994**, *127*, 1761.
14. Heydari, A.; Fatemi, P.; Alizadeh, A.-A. *Tetrahedron Lett*. **1998**, *39*, 3049.
15. Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett*. **1998**, *39*, 5773.
16. Heydari, A.; Larijani, H.; Emami, J.; Karami, B. *Tetrahedron Lett*. **2000**, *41*, 2471.
17. Concentrated homegeneous solutions of lithium perchlorate in diethyl ether (1–5 M) induce a variety of synthetically interesting transformations: (a) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59; (b) Waldmann, H. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1306; (c) Ipaktschi, J.; Heydari, A. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 313; (d) Ipaktschi, J.; Heydari, A. *Chem. Ber*. **1992**, *125*, 1513; (e) Ipaktschi, J.; Heydari, A. *Chem. Ber*. **1993**, *126*, 1905; (f) Grieco, P. A.; Beck, J. P. *Tetrahedron Lett*. **1993**, *34*, 7367; (g) Wustrow, D. J.; Smith, III, W. J.; Wise, L. D. *Tetrahedron Lett*. **1994**, *35*, 61; (h) Ipaktschi, J.; Heydari, A.; Kalinowski, H.-O. *Chem. Ber*. **1994**, *127*, 905; (i) Asano, J.; Ryu, Y.; Chiba, K.; Tada, M. *J. Chem. Res. (S)* **1995**, 124; (j) Sudha, R.; Maloia Narashimhan, K.; Geetha Saraswathy, V.; Sankararaman, S. *J. Org. Chem*. **1996**, *61*, 1877; (k) Ipaktschi, J.; Eckert, T. *Chem. Ber*. **1995**, *128*, 1171; Jenner, G.; Ben Salem, R. *Tetrahedron* **1997**, *53*, 4637; (l) Zarghi, A.; Naimi-Jamal, M. R.; Webb, S. A.; Balalaie, S.; Saidi, M. R.; Ipaktschi, J. *Eur. J. Org. Chem*. **1998**, 197; (m) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 1539; (n) Sudha, R.; Sankaraman, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, *4*, 383.
18. **Typical experimental procedure**: To a mixture of aldehyde (2 mmol) in 5 M LPDE (4 ml) was added hydroxylamine (2.2 mmol) at room temperature. The mixture was stirred for 2 min and dimethyl(trimethylsilyl)phosphite (2.2 mmol) was added. The mixture was stirred for 15 min then water was added and the product was extracted with CH_2Cl_2. The organic phase was collected, dried (Na_2SO_4) and evaporated to afford the crude product. The product was purified by flash chromatography (hexane–ethyl acetate). ^1H, ^{13}C NMR, IR and MS spectra were entirely consistent with the assigned structures. Selected data as follow: **4** ($R^1 = i$-propyl): oil ^1H NMR (500 MHz, $CDCl_3$): δ 7.2 (m, 2H, Ar-H), 7.0 (m, 2H, Ar-H), 6.8 (m, 1H, Ar-H), 3.61 (d, $J_{P\text{-}H} = 10$ Hz, 3H, OCH_3), 3.47 (d, $J_{P\text{-}H} = 10$ Hz, 3H, OCH_3), 3.31 (dd, $^3J_{p\text{-}H} = 13.5$ Hz, $J_{H\text{-}H} = 10$ Hz, 1H, H1), 3.24 (m, 1H, H2), 1.21 (d, $J_{H\text{-}H} = 6.5$ Hz, 3H, H3), 1.12 (d, $J_{H\text{-}H} = 6.5$ Hz, 3H, H3) 0.14 (s, 9H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6 (C-Ar), 128.4 (CH-Ar), 121.8 (CH-Ar), 116.6 (CH-Ar), 75.7 (d, $^2J_{P\text{-}C} = 135$ Hz, C1), 52.6 (d, $^3J_{P\text{-}C} = 6.7$ Hz, OCH_3), 51.64 (d, $^3J_{P\text{-}C} = 6.7$ Hz, OCH_3), 28.6 (d, $^3J_{P\text{-}C} = 5.7$ Hz, CH), 22.9 (d, $^3J_{P\text{-}C} = 13.7$ Hz, CH_3), 20.6 (s, CH_3), 0.4 (CH_3): **4** ($R^1 = n$-propyl): oil ^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 2H, Ar-H), 7.07 (m, 2H, Ar-H), 6.92 (m, 1H, Ar-H),

3.66 (ddd, $^3J_{P\text{-}H}=18.9$ Hz, $J_{H\text{-}H}=10.9$, 3.2 Hz, 1H, H1), 3.61 (d, $^3J_{P\text{-}C}=10$ Hz, 3H, OCH_3), 3.54 (d, $^3J_{P\text{-}H}=10$ Hz, 3H, OCH_3), 1.9 (m, 1H), 1.7 (m, 2H), 1.5 (m, 1H), 1.0 (t, $J_{H\text{-}H}=8$ Hz, 3H, CH_3), 0.11 (s, 9H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9 (C-Ar), 128.7 (CH-Ar), 122.9 (CH-Ar), 118.1 (CH-Ar), 69.1 (d, $^2J_{P\text{-}C}=136$ Hz, C1), 52.5 (d, $^3J_{P\text{-}C}=6.2$ Hz, OCH_3), 52.3 (d, $^3J_{P\text{-}C}=6.5$ Hz, OCH_3), 31.0 (d, $^3J_{P\text{-}C}=3.3$ Hz, CH_2), 21.1 (d, $^3J_{P\text{-}C}=13$ Hz, CH_2), 14.1 (s, CH_3), 0.2 (s, CH_3): **4** ($R^1=c$-Hexyl): oil ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.2 (m, 2H, Ar-H), 7.0 (m, 2H, Ar-H), 6.9 (m, 1H, Ar-H), 3.64 (d, $^3J_{P\text{-}H}=11$ Hz, 3H, OCH_3), 3.49 (d, $^3J_{P\text{-}H}=11$ Hz, 3H, OCH_3), 3.44 (dd, $^3J_{P\text{-}H}=19.2$ Hz, $J_{H\text{-}H}=11$ Hz, 1H, H1), 2.3 (m, 1H), 2.1 (m, 1H), 2.0 (m, 1H), 1.8 (m, 2H), 1.7 (m, 1H), 1.3 (m, 3H), 1.1 (m, 2H), 0.17 (s, 9H, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.1 (C-Ar), 128.7 (CH-Ar), 122.1 (CH-Ar), 116.9 (CH-Ar), 74.9 (d, $^2J_{P\text{-}C}=134$ Hz, C1), 52.6 (d, $^3J_{P\text{-}C}=6.6$ Hz, OCH_3), 51.6 (d, $^3J_{P\text{-}C}=6.7$ Hz, OCH_3), 37.8 (d, $^3J_{P\text{-}C}=5.6$ Hz, CH), 33.0 (d, $J_{P\text{-}C}=13$ Hz, CH_2), 30.9 (s, CH_2), 27.0 (s, CH_2), 26.7 (s, CH_2), 26.5 (s, CH_2), 0.4 (s, CH_3); **4** ($R^1=3$-pyridyl): after hydrolysis the crude product was a mixture of silylated and desilylated (87:13). The TMS group was removed after flash chromatography. Oil ^{1}H NMR (500 MHz, acetone-d_6): δ 8.7 (s, 1H, Ar-H), 8.4 (m, 1H, Ar-H), 8.1 (m, 1H, Ar-H), 7.3 (m, 1H, Ar-H), 7.2 (m, 4H, Ar-H), 6.9 (m, 1H, Ar-H), 5.4 (d, $^2J_{P\text{-}H}=24$ Hz, 1H, H1), 3.8 (d, $^3J_{P\text{-}H}=10$ Hz, 3H, OCH_3), 3.6 (d, $^3J_{P\text{-}H}=10$ Hz, 3H, OCH_3), 3.0 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.2 (C-Ar), 152.4 (C-Ar), 151.8 (CH-Ar), 151.7 (CH-Ar), 149.6 (CH-Ar), 138.7 (CH-Ar), 138.6 (CH-Ar), 131.4 (CH-Ar), 124.0 (CH-Ar), 121.5 (CH-Ar), 116.5 (CH-Ar), 64.6 (d, $^2J_{P\text{-}C}=157$ Hz, C1), 53.8 (OCH_3), 53.7 (OCH_3); **4** (R = PhCH=CH): mp = 126°C ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.3 (m, 9H, Ar-H), 7.0 (m, 1H, Ar-H), 6.5 (m, 2H, vinyl-H), 4.7 (dd, $^3J_{P\text{-}H}=23$ Hz, $J_{H\text{-}H}=8$ Hz, 1H, H1), 3.88 (d, $^3J_{P\text{-}H}=10$ Hz, 3H, OCH_3), 3.86 (d, $^3J_{P\text{-}H}=10$ Hz, 3H, OCH_3), 0.1 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.0 (C-Ar), 136.7 (CH-Ar), 129.6 (CH-Ar), 129.2 (CH-Ar), 129.0 (CH-Ar), 128.5 (CH-Ar), 127.2 (CH-Ar), 122.8 (CH-Ar), 119.7 (CH-vinylic), 117.5 (CH-vinylic), 68.7 (d, $^3J_{P\text{-}C}=164$ Hz, CH, C1), 54.5 (d, $^3J_{P\text{-}C}=6.6$ Hz, OCH_3), 54.0 (d, $^3J_{P\text{-}C}=7.0$ Hz, OCH_3), 0.4 (s, CH_3).

19. (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Haga, S.; Sugi, H.; Tanigawa, K.; Suski, Y.; Fukawa, K.; Irino, O.; Saita, O.; Yamabe, S. *Heterocycles* **1981**, *16*, 1205; (b) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. M.; Holmes, S. W.; Lambert, R. W.; Lioyd, W. J.; Nisbet, L. J.; Ringrose, P. S. *Nature (London)* **1978**, *272*, 56.
20. Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett*. **1997**, 1039.
21. (a) Smith, L. J. *Chem. Rev*. **1938**, *23*, 193; (b) Hamer, J.; Macaluso, A. *Chem. Rev*. **1964**, *29*, 473; (c) Delpierre, G. R.; Lamchen, M. *Q. Rev*. **1965**, *19*, 329.
22. (a) Thesting, J.; Mayer, H. *Chem. Ber*. **1958**, *89*, 2157; (b) Brown, R. F. C.; Clark, V. M.; Todd, Sir, A. *Proc. Chem. Soc*. **1957**, 97.