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A general synthesis of ethyl 4-aminophenyl and ethyl 4-[amino(hydroxyimino)methyl]phenyl phosphonates

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Abstract—Diethyl phosphonates were conveniently converted into ethyl 4-aminophenyl and ethyl 4-[amino(hydroxyimino)methyl]phenyl phosphonates as potentially useful intermediates for the preparation of functionalized phenyl phosphonates.

Organophosphorus(V) derivatives like phosphonates, phosphinates or phosphonamidates, find great utility as transition-state analog enzyme inhibitors. Phosphonate (mono)ester containing molecules include potent inhibitors of many proteases and other enzymes.[1] In the last decade, the synthesis of complex phosphonate esters as haptens for the generation of catalytic antibodies has become very important.[2] Generally, mixed phosphonate esters are synthesized through phosphonochloridates, obtained either from phosphonate diesters with phosphorus pentachloride,[3,4] from phosphonate monoesters with thionyl or oxalyl chloride,[1a,4] or from phosphinate esters with carbon tetrachloride.[5] They have also been prepared from phosphonate monoesters using BOP-Cl,[6] BOP and PyBOP[7] reagents, and by modified Mitsunobu reactions.[8] Landry has synthesized mixed phosphonic diesters from phosphonic dichlorides with tetrazole as the catalyst.[9]

During the course of our investigations aimed at developing new serine protease inhibitors, we became interested in synthesizing mixed alkyl phenyl phosphonates with a functionalized phenyl moiety. Many phenyl phosphonate ester derivatives synthesized to date contain a substituted phenyl ring. Nitrophenyl and carboxyphenyl monophosphonates were reported to inhibit serine β-lactamase,[10] while alkyl 4-nitrophenyl[11,12] and di(4-nitrophenyl)[12] phosphonates were active as inhibitors of lipase. Furthermore, di(4-nitrophenyl) phosphonates were also used as activated intermediates for the DBU-catalyzed transesterification by various alcohols.[13] α-Aminoalkyl phosphonate di(chlorophenyl) esters were prepared as inhibitors of serine proteases,[14] while di(2-methylphenyl) and di(2-methoxyphenyl) phosphonates were developed as prodrugs of fosmidomycin derivative FR900098.[15] A series of diaryl phosphonates with different substituents on the phenyl rings (hydroxyl, methoxy, acylamino, sulfonylamino, ureyl, methoxycarbonyl, and alkylaminocarbonyl) were synthesized to develop irreversible dipeptidyl peptidase(IV) inhibitors.[16]

Although a variety of phenyl phosphonates with substituted phenyl rings have already been described,[10–16] no synthesis of aminophenyl and [amino(imino)methyl]-phenyl phosphonate ester derivatives has been reported in the literature. We wanted to synthesize ethyl 4-aminophenyl and ethyl 4-[amino(hydroxyimino)-methyl]phenyl phosphonates, a new type of substituted phenyl phosphonate derivatives that allow facile further derivatization of the phenyl substituent. Aromatic amines are widely used as intermediates in the preparation of important chemicals such as pharmaceuticals, dyes, and agrochemicals.[17] Some benzamines are active as serine protease inhibitors, for example 4-aminophenyl based thrombin inhibitors.[18] The benzamidoxime motif on the other hand is an important constituent of ribonucleotide reductase inhibitors with antitumor activity[19] and NO donors[20] with antithrombotic and antihypertensive activities.[21] The amidoxime group can serve as a prodrug functionality for an amidino group[22] and the amidoxime prodrug strategy has been used for improved oral bioavailability for

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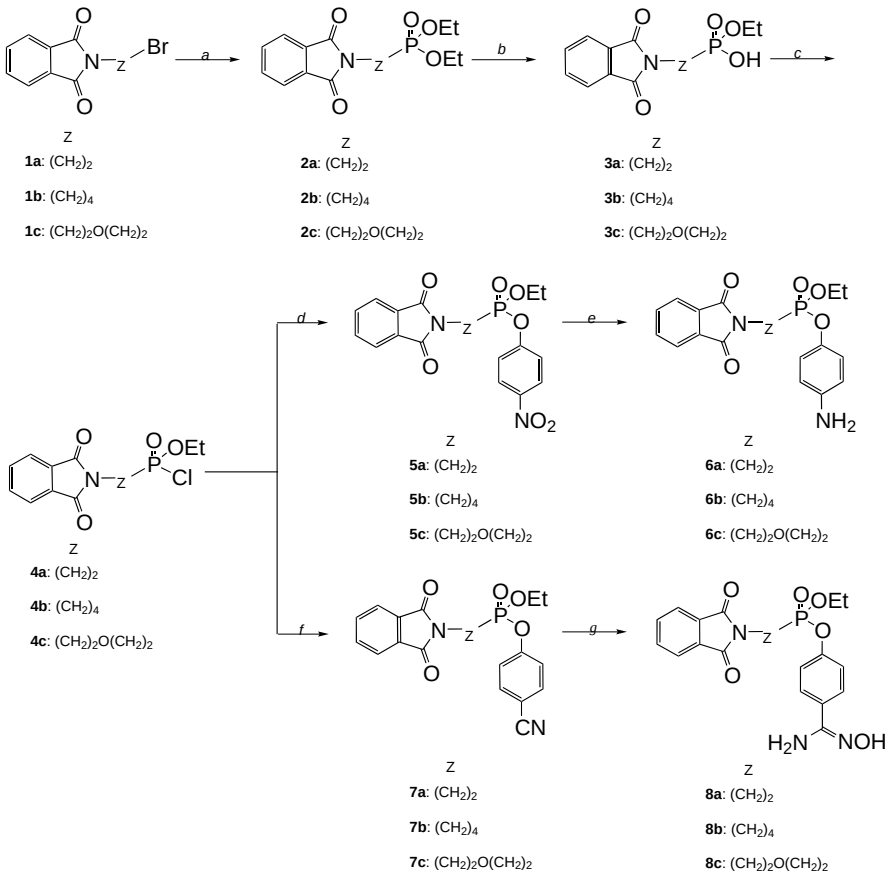
fibrinogen antagonists,[23] pentamidine[22,24] and other anti-*Pneumocystis carinii* pneumonia agents.[22,25] From the synthetic point of view, amidoxime derivatives have been employed as key intermediates for the synthesis of a wide variety of valuable compounds, such as 4,5-dihydro-1,2,4-oxadiazoles,[26,27] 2-oxo-1,2,3,5-oxathiadiazole derivatives,[27] oxadiazolone[28,29] and the thiadiazolone ring.[27,29]

We started the synthesis with the preparation of the known diethyl alkylphosphonates **2a**–**b**[30,31] and a novel diethyl 2-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-ethoxy] ethylphosphonate **2c** from the appropriate bromides **1a**–**c**,[32] using the Arbuzov reaction with neat triethyl phosphite (Scheme 1). After selective cleavage of *C*-substituted phosphonic acid diesters **2a**–**c** with sodium azide[35] to the corresponding monoesters **3a**–**c**, the latter were reacted with 2 equiv. of oxalyl chloride in the presence of 0.1 equiv. of DMF for the formation of the key intermediate phosphonochloridates **4a**–**c**.[4] Following the precedent of Buono and co-workers,[12] the crude chloridates were then reacted with sodium 4-nitrophenolate to form ethyl 4-nitrophenyl phosphonates **5a**–**c**. As an extension of the method, the aromatic nitro compounds were hydrogenated over 10% Pd/C at normal pressure to afford the desired ethyl 4-aminophenyl phosphonates **6a**–**c** in satisfactory yields.

Similarly, ethyl 4-cyanophenyl phosphonates **7a**–**c** were obtained after the reaction of phosphonochloridates **4a**–**c** with sodium 4-cyanophenolate. Finally, the reaction of the aromatic nitriles **7a**–**c** with hydroxylamine[36] in absolute ethanol gave novel organophosphorus(V) derivatives of benzamidoximes **8a**–**c**.[37] Both ethyl 4-nitrophenyl phosphonates **5a**–**c** and ethyl 4-cyanophenyl phosphonates **7a**–**c** are activated phosphonate species and we were unable to purify them by silica-gel column chromatography. Due to their instability, crude activated phosphonates were used immediately in the next reaction steps.

To summarize, we report here an expeditious synthesis of hitherto unknown ethyl 4-aminophenyl and ethyl 4-[amino(hydroxyimino)methyl]phenyl phosphonates. In the crucial synthetic steps, ethyl 4-nitrophenyl phosphonates **5a**–**c** were reduced to ethyl 4-aminophenyl phosphonates **6a**–**c** by catalytic hydrogenation, and ethyl 4-cyanophenyl phosphonates **7a**–**c** were converted to the corresponding benzamidoximes **8a**–**c** with hydroxylamine. The resulting functionalized phenyl phosphonates are valuable intermediates for further derivatization of the phenyl substituent. Furthermore, they represent an interesting type of mixed phosphonate derivative with possible applications in the development of new serine protease inhibitors.



Scheme 1. (a) $P(OEt)_3$, reflux, 16 h (56–77%); (b) NaN_3, DMF, 100°C, 16 h (59–69%); (c) $(COCl)_2$, DMF, CH_2Cl_2, 0°C, 0.5 h, then rt, 1.5 h; (d) sodium *p*-nitrophenolate, THF, CH_2Cl_2, −15°C, 0.5 h, then rt, 16 h (44–50%, three steps); (e) H_2, Pd/C, MeOH, rt, 1.5–6 h (85%); (f) sodium *p*-cyanophenolate, THF, CH_2Cl_2, −15°C, 0.5 h, then rt, 16 h (40–51%, three steps); (g) NH_2OH, abs. EtOH, rt, 16 h, then 80°C, 4 h (60–96%).

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References

1. (a) Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengeler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B., III. *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190; (b) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359–1472 and references cited therein.
2. (a) Lerner, R. A.; Benkovic, S. J.; Schultz, P. G. *Science* **1991**, *252*, 659–667; (b) Hirschmann, R.; Smith, A. B., III.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237; (c) Smithrud, D. B.; Benkovic, P. A.; Benkovic, S. J.; Taylor, C. M.; Yager, K. M.; Witherington, J.; Philips, B. W.; Sprengeler, P. A.; Smith, A. B., III.; Hirschmann, R. *J. Am. Chem. Soc.* **1997**, *119*, 278–282; (d) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281–1301.
3. Yamauchi, K.; Kinoshita, M.; Imoto, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2528–2531.
4. Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7616–7624.
5. Sampson, N. S.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500–4503.
6. Morgan, B. P.; Scholtz, J. M.; Ballinger, M. D.; Zipkin, I. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 297–307.
7. Campagne, J.-M.; Coste, J.; Jouin, P. *J. Org. Chem.* **1995**, *60*, 5214–5223.
8. (a) Campbell, D. A. *J. Org. Chem.* **1992**, *57*, 6331–6335; (b) Campbell, D. A.; Bermak, J. C. *J. Org. Chem.* **1994**, *59*, 658–660.
9. Zhao, K.; Landry, D. W. *Tetrahedron* **1993**, *49*, 363–368.
10. (a) Rahil, J.; Pratt, R. F. *Biochemistry* **1992**, *31*, 5869–5878; (b) Li, N. X.; Rahil, J.; Wright, M. E.; Pratt, R. F. *Bioorg. Med. Chem.* **1997**, *5*, 1783–1788.
11. (a) Mannesse, M. L. M.; Boots, J.-W. P.; Dijkman, R.; Slotboom, A. J.; van der Hijden, H. T. W. V.; Egmond, M. R.; Verheij, H. M.; de Haas, G. H. *Biochim. Biophys. Acta* **1995**, *1259*, 56–64; (b) Stadler, P.; Zandonella, G.; Haalck, L.; Spener, F.; Hermetter, A.; Paltauf, F. *Biochim. Biophys. Acta* **1996**, *1304*, 229–244; (c) Deussen, H.-J.; Danielsen, S.; Breinholt, J.; Borchert, T. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2027–2031.
12. Marguet, F.; Cudrey, C.; Verger, R.; Buono, G. *Biochim. Biophys. Acta* **1994**, *1210*, 157–166.
13. Tawfik, D. S.; Eshhar, Z.; Bentolila, A.; Green, B. S. *Synthesis* **1993**, 968–972.
14. (a) Boduszek, B.; Brown, A. D.; Powers, J. C. *J. Enzym. Inhib.* **1994**, *8*, 147–158; (b) Boduszek, B.; Oleksyszyn, J.; Kam, C.-M.; Selzler, J.; Smith, R. E.; Powers, J. C. *J. Med. Chem.* **1994**, *37*, 3969–3976.
15. Reichenberg, A.; Wiesner, J.; Weidemeyer, C.; Dreiseidler, E.; Sanderbrand, S.; Altincicek, B.; Beck, E.; Schlitzer, M.; Jomaa, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 833–835.
16. Belyaev, A.; Zhang, X. M.; Augustyns, K.; Lambeir, A.-M.; De Meester, I.; Vedernikova, I.; Scharpé, S.; Haemers, A. *J. Med. Chem.* **1999**, *42*, 1041–1052.
17. Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035–2052.
18. Rewinkel, J. B. M.; Adang, A. E. P. *Curr. Pharm. Design* **1999**, *5*, 1043–1075.
19. Grusch, M.; Fritzer-Szekeres, M.; Fuhrmann, G.; Rosenberger, G.; Luxbacher, C.; Elford, H. L.; Smid, K.; Peters, G. J.; Szekeres, T.; Krupitza, G. *Exp. Hematol.* **2001**, *29*, 623–632.
20. (a) Jousserandot, A.; Boucher, J.-L.; Henry, Y.; Niklaus, B.; Clement, B.; Mansuy, D. *Biochemistry* **1998**, *37*, 17179–17191; (b) Sennequier, N.; Boucher, J.-L.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1995**, *36*, 6059–6062.
21. Rehse, K.; Brehme, F. *Arch. Pharm.* **1998**, *331*, 375–379.
22. (a) Hauptmann, J.; Paintz, M.; Kaiser, B.; Richter, M. *Pharmazie* **1988**, *43*, 559–560; (b) Clement, B.; Immel, M.; Terlinden, R.; Wingen, F. J. *Arch. Pharm.* **1992**, *325*, 61–62; (c) Boykin, D. W.; Kumar, A.; Hall, J. E.; Bender, B. C.; Tidwell, R. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3017–3020; (d) Hall, J. E.; Kerrigan, J. E.; Ramachandran, K.; Bender, B. C.; Stanko, J. P.; Jones, S. K.; Patrick, D. A.; Tidwell, R. R. *Antimicrob. Agents Ch.* **1998**, *42*, 666–674; (e) Clement, B.; Lomb, R.; Möller, W. *J. Biol. Chem.* **1997**, *272*, 19615–19620.
23. (a) Weller, T.; Alig, L.; Beresini, M.; Blackburn, B.; Bunting, S.; Hadvary, P.; Muller, M. H.; Knopp, D.; Levet-Trafit, B.; Lipari, M. T.; Modi, N. B.; Muller, M.; Refino, C. J.; Schmitt, M.; Schönholzer, P.; Weiss, S.; Steiner, B. *J. Med. Chem.* **1996**, *39*, 3139–3147; (b) Eldred, C. D.; Evans, B.; Hindley, S.; Judkins, B. D.; Kelly, H. A.; Kitchin, J.; Lumley, P.; Porter, B.; Ross, B. C.; Smith, K. J.; Taylor, N. R.; Wheatcroft, J. R. *J. Med. Chem.* **1994**, *37*, 3882–3885.
24. Clement, B.; Raether, W. *Arzneimittel-Forsch.* **1985**, *35*, 1009–1014.
25. Patrick, D. A.; Hall, J. E.; Bender, B. C.; McCurdy, D. R.; Wilson, W. D.; Tanious, F. A.; Saha, S.; Tidwell, R. R. *Eur. J. Med. Chem.* **1999**, *34*, 575–583.
26. (a) Lessel, J.; Herfs, G. *Pharmazie* **2000**, *55*, 22–26; (b) Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco, J. A., Jr. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 209–212.
27. Kohara, Y.; Kubo, K.; Imamiya, E.; Wada, T.; Inada, Y.; Naka, T. *J. Med. Chem.* **1996**, *39*, 5228–5235.
28. Bolton, R. E.; Coote, S. J.; Finch, H.; Lowdon, A.; Pegg, N.; Vinader, M. V. *Tetrahedron Lett.* **1995**, *36*, 4471–4474.
29. Kitamura, S.; Fukushi, H.; Miyawaki, T.; Kawamura, M.; Terashita, Z.; Naka, T. *Chem. Pharm. Bull.* **2001**, *49*, 268–277.
30. Yamauchi, K.; Ohtsuki, S.; Kinoshita, M. *J. Org. Chem.* **1984**, *49*, 1158–1163.
31. Urleb, U.; Gobec, S.; Prelog, D. *Lett. Pept. Sci.* **1995**, *2*, 193–197.
32. While bromides **1a**–**b** are commercially available, we synthesized compound **1c** from the known alcohol 2-[2-(2-hydroxyethoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione[33] in 88% yield, using CBr_4 and PPh_3 according to the procedure reported previously.[34]

33. Korošec, E.; Poljšak, D.; Urleb, U. *Arch. Pharm.* **1992**, *325*, 251–252.
34. Nair, S. A.; Lee, B. Y.; Hangauer, D. G. *Synthesis* **1995**, 810–814.
35. Holý, A. *Synthesis* **1998**, 381–385.
36. Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. *Synth. Commun.* **1996**, *26*, 4351–4367.
37. A typical procedure for preparing compounds **8a–c** is as follows: ethyl phosphonate **3b** (2.254 g, 7.24 mmol) was dissolved in CH_2Cl_2 (50 mL) and the mixture was cooled to 0°C. DMF (56 μL, 0.724 mmol) was added, followed by dropwise addition of oxalyl chloride (1.26 ml, 14.48 mmol). The reaction was stirred at 0°C for 30 min, and then allowed to warm to rt and stirred for 1.5 h. The reaction mixture was then concentrated in vacuo and the resulting phosphonochloridate **4b** immediately reacted with sodium 4-cyanophenolate, which was prepared in the following way. 4-Cyanophenol (0.826 g, 7.24 mmol), dissolved in dry THF (4–6 mL), was added dropwise to a mixture of sodium hydride (0.217 g, 7.24 mmol) in dry THF (3–5 mL). After 1 h, the reaction mixture was cooled to −15°C and a solution of phosphonochloridate **4b** in CH_2Cl_2 was slowly added dropwise. The reaction was stirred for 30 min, then allowed to warm to rt and stirred overnight. The solvent was removed in vacuo, diluted with EtOAc, filtered, washed with 10% K_2CO_3 (3×20 mL) and brine (2×20 mL), dried (anh. Na_2SO_4) and concentrated to afford 1.188 g (40%, three steps) of the desired product, 4-cyanophenyl ethyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butylphosphonate **7b**. The latter (1.188 g, 2.88 mmol) was immediately dissolved in absolute ethanol (15 mL). Hydroxylamine (0.206 g, 6.24 mmol) was added, the reaction mixture was stirred overnight at rt, and then heated under reflux for 4 h. The solution was cooled, the solvents removed in vacuo and the residue purified by silica-gel column chromatography (eluent EtOAc/MeOH (30/1)) to give 4-[amino(hydroxyimino)methyl]phenyl ethyl 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butylphosphonate **8b** (yield: 60%); IR (KBr): 3345, 2931, 1768, 1706, 1644, 1514, 1397, 1207, 1115, 1037, 928, 719, 530 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, $J=7.00$ Hz, 3H, P-O-CH_2-C$\underline{H}_3$), 1.70–2.06 (m, 6H, N-CH_2 C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-P), 3.72 (t, $J=6.79$ Hz, 2H, N-C$\underline{H}_2$-CH_2-), 4.07–4.29 (m, 2H, P-O-C$\underline{H}_2$-CH_3), 4.89 (broad s, 2H, C(NOH)N$\underline{H}_2$), 7.26 (d, $J=7.53$ Hz, 2H, Ar-$\underline{H}$), 7.61 (d, $J=9.04$ Hz, 2H, Ar-$\underline{H}$), 7.71–7.74 (m, 2H, Pht-$\underline{H}$), 7.84–7.87 (m, 2H, Pht-$\underline{H}$) ppm; ^{31}P NMR (121 MHz $CDCl_3$): δ 30.01 ppm; MS (FAB): m/z 446 $(M+H)^+$; Anal. calcd for $C_{21}H_{24}N_3O_6P$: C, 56.63; H, 5.43; N, 9.43. Found: C, 56.31; H, 5.54; N, 9.07; mp: 138–142°C.