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Direct one-step synthesis of azaheterocyclic phosphonates from diethyl ω-chloro-1-alkynylphosphonates and hydrazines

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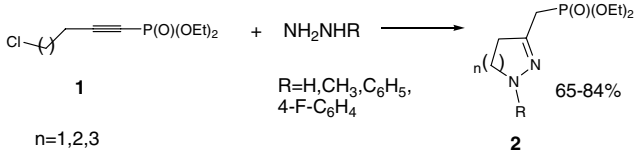
Abstract—Hydrazines react with 4-, 5- and 6-chloro-1-alkynylphosphonates to provide the corresponding azaheterocyclic phosphonates in good yields and purity. The suggested mechanism consists of initial addition to the carbon–carbon triple bond to generate a zwitterionic species in which the amine is situated trans to the lone pair of the anion.

Azacycloalkanes or their subunits occur in diverse natural products and in many drugs. For instance, tetrahydropyridazines display some interesting pharmacological activities. They are antihypertensives,[1] gylocosidase inhibitors,[2] influenza neurimidase inhibitors,[3] γ-aminobutyrate-A-receptor modulators[4] and nonsteroidal progesterone receptor ligands.[5] The phosphorus group is likewise part of many pharmacologically active compounds.[6] However, phosphorylated azacycloalkanes, though potentially possessing significant intrinsic pharmacological activity, are much less common. A major reason for this is apparently their cumbersome synthesis. For instance, 1,4,5,6-tetrahydropyridazin-4-ylphosphonates were obtained by reacting in situ prepared 1,2-diaza-1,3-butadienylphosphonate with alkenes.[7] The difficulty in the latter reaction is the synthesis of the 1,2-diaza-1,3-butadienes. Similarly, 4,5-dihydropyrazoles possess anti-inflammatory and [8] anti-coagulating activities[9] and are KSP inhibitors,[10] while 1,2-diazepines are powerful progesterone antagonists.[11] However, phosphorylated 4,5-dihydropyrazoles and 1,2-diazepines have not been described in the literature. As part of our efforts on developing the chemistry of 1-alkynylphosphonates,[12] we investigated the reaction of diethyl 4-, 5-, and 6-chloro-1-alkynylphosphonates with hydrazines and examined their cyclization products.[13] In this Letter, we report the results of our studies to obtain tetrahydropyridazinylmethylphosphonates, 4,5-dihydropyrazolylmethylphosphonates and 4,5,6,7-tetrahydrodiazepinylmethylphosphonates by reaction of ω-chloro-1-alkynylphosphonates with hydrazines (Scheme 1).

We found that ω-chloro-1-alkynylphosphonates reacted efficiently with hydrazines to produce azacycloalkanes under mild conditions in the absence of metal or other additives. There was no need for prior conversion to iodides or in situ preparation of iodides. The ring size of the azacycloalkanes was dependent on the chain length of the ω-chloro-1-alkynylphosphonate. For instance, five-, six-, and seven-membered ring azacycloalkenylphosphonates were obtained as a result of the reactions between a hydrazine and 4-chloro, 5-chloro, and 6-chloroalkynylphosphonates, respectively (Table 1).[14] Generally, the reactions were carried out at room temperature and were complete within 30 min as determined by GCMS, except for the reactions of phenylhydrazine and 4-fluorophenylhydrazine with 5-chloro-1-pentynylphosphonate, which required heating to 60 °C for 4 h to attain the maximum yield. On the



Scheme 1.

Keywords: Azaheterocyclic phosphonates; Hydrazines; ω-Chloro-1-alkynylphosphonates; Tetrahydropyridazinylmethylphosphonates; 4,5-Dihydropyrazolylmethylphosphonates; 4,5,6,7-Tetrahydrodiazepinylmethylphosphonates.
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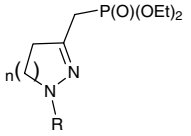
Table 1. Azacycloalkanes, **2**, from reaction of ω-chloro-1-alkynylphosphonates with hydrazines



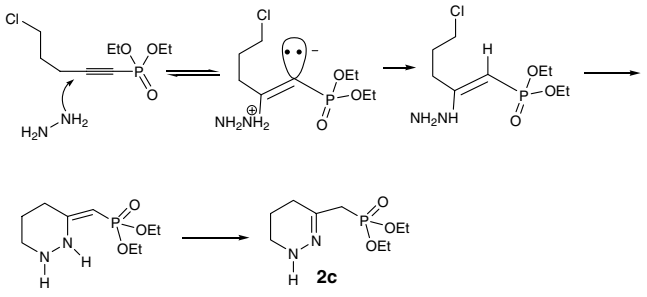
Compound	*n*	R	% Isolated yield (conversion)
2a[a]	1	H	75 (>98)
2b[b]	1	CH_3	84 (>99)
2c[a]	2	H	81 (>99)
2d[a]	2	CH_3	85 (>99)
2e[c]	2	C_6H_5	65 (>99)
2f[c]	2	4-F-C_6H_4	67 (>98)
2g[a]	3	H	78 (>98)
2h[a]	3	CH_3	79 (>99)

[a] Obtained at 25 °C in about 30 min.
[b] Obtained at 0 °C.
[c] Obtained at 60 °C in 4 h.

other hand, in order to avoid the formation of side products, it was necessary to cool the reaction between methylhydrazine and 4-chloro-1-butynylphosphonate to give **2b**, to 0 °C. The products **2a–h** were stable enough to be isolated by column chromatography on silica gel.

The methylenephosphonate protons in compounds **2** appeared as doublets in the region (δ 2.71–2.90 ppm) corresponding to two hydrogens on C-1 split by phosphorus. Also, the presence of azacycles in compounds **2**, was consistent with the MS molecular weights and fragmentation in addition to consistency of the NMR data.

Mechanistically, the reaction can be rationalized by initial attack of the hydrazine on the carbon–carbon triple bond to give a zwitterionic intermediate in which the amine is situated trans to the lone pair of the anion (and therefore cis to the phosphonate) and enjoys additional stabilization compared to the structure where the amine is situated cis to the lone pair due to the hyperconjugation effects of carbanions.[15] After proton transfer the nitrogen of the hydrazine group attacks the C–Cl bond in an S_N2 fashion to furnish the azaheterocycle rather than the intermediate undergoing C–C cyclization. Isomerization of the *exo*-cyclic double bond completes the mechanism (Scheme 2).



Scheme 2.

In conclusion, a facile method for the synthesis of various azaheterocyclic phosphonates by the reaction of hydrazines and ω-chloro-1-alkynylphosphonates has been described. The products were obtained in good yield and were stable to silica chromatography.

Acknowledgements

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References and notes

1. Le Bourdonnec, B.; Cauvin, C.; Meulon, E.; Yous, S.; Goossens, J.-F.; Durant, F.; Houssin, R.; Jean-Pierre Hénichart, J.-F. *J. Med. Chem.* **2002**, *45*, 4794–4798.
2. Ramana, C. V.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1599–1610.
3. Zhang, L.; Williams, M. A.; Mendel, D. B.; Escarpe, P. A.; Chen, X.; Wang, K.-Y.; Graves, B. J.; Lawton, G.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1751–1756.
4. Rybczynski, P. J.; Combs, D. W.; Jacobs, K.; Shank, R. P.; Dubinsky, B. *J. Med. Chem.* **1999**, *42*, 2403–2408.
5. Combs, D. W.; Reese, K.; Phillips, A. *J. Med. Chem.* **1995**, *38*, 4878–4879.
6. Rye, C. S.; Baell, J. B. *Curr. Med. Chem.* **2005**, *12*, 3127–3141.
7. For a general case see: (a) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 249–257, and references cited therein; Phosphonates: (b) Palacios, F.; Aparicio, D.; Lopez, Y.; Santos, J. M. D.; Alonso, C. *Eur. J. Org. Chem.* **2005**, 1142–1147.
8. (a) Copp, F. C.; Islip, P. J.; Tateson, J. E. *Biochem. Pharmacol.* **1984**, *33*, 339; (b) Frígola, J.; Colombo, A.; Parés, J.; Martínez, L.; Sagarra, R.; Roser, R. *Eur. J. Med. Chem.* **1989**, *24*, 435.
9. Pinto, D. J. P.; Orwat, M. J.; Wang, S.; Fevig, J. M.; Quan, M. L.; Amparo, E.; Cacciola, J.; Rossi, K. A.; Alexander, R. S.; Smallwood, A. M.; Luettgen, J. M.; Liang, L.; Aungst, B. J.; Wright, M. R.; Knabb, R. M.; Wong, P. C.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2001**, *44*, 566.
10. Cox, C. D.; Mariano, B. J.; Coleman, P. J.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Huber, H. E.; Kohl, N. E.; Torrent, M.; Yan, Y.; Kuo, L. C.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2041–2045.
11. Wiethe, R. W.; Stewart, E. L.; Drewry, D. H.; Gray, D. W.; Mehbob, A.; Hoekstra, W. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3777–3779.
12. Al-Quntar, A. A.; Srebnik, M. *J. Organomet. Chem.* **2005**, *690*, 2504–2514.
13. For reactions of ω-halo-1-alkynyl esters and amines, see: (a) David, O.; Fargeau-Bellassoued, M.-C. *Tetrahedron Lett.* **2002**, *43*, 3471–3474; (b) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927–3929; For reactions of ω-iodo-1-alkynylphosphonates and amines, see: (c) Zhu, W.; Dong, D.; Pu, X.; Ma, D. *Org. Lett.* **2005**, *7*, 705–708.
14. Preparation of azaheterophosphonates. Typical procedure for **2a**. To 0.224 g (1 mmol) of 4-chlorobutynylphosphonate in a 25 ml round bottomed flask was added 0.115 g (3 mmol) of hydrazine monohydrate followed by the addition of 0.3 g of 0.4 nm molecular sieves. The reaction was stirred for 4 h at 25 °C, then worked up with 10%

aqueous NaOH solution. After extraction with CH_2Cl_2 (20 ml), the product was separated on a silica gel column (97% CH_2Cl_2–3% methanol), and was analyzed by GCMS, elemental analysis, and NMR spectroscopy. Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, 6H, $J_{HH} = 7.2$ Hz), 2.61 (dt, 2H, $J_{HH} = 9.6$ Hz, $J_{PH} = 4.2$ Hz), 2.90 (d, 2H, $J_{HP} = 21.9$ Hz), 3.25 (t, 2H, $J_{HH} = 9.6$ Hz), 3.98 (q, 4H, $J_{HH} = 7.2$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 26.98; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.0 (d, $^3J_{PC} = 5.6$ Hz), 28.6 (d, $^1J_{PC} = 140.1$ Hz), 35.1 (d, $^3J_{PC} = 1.7$ Hz), 47.5, 62.0 (d, $^2J_{PC} = 6.6$ Hz), 148.0 (d, $^2J_{PC} = 10.3$ Hz); MS(EI): *m*/*z* (%) 220 (4.2), 219 (11.7), 191 (6.4), 163 (20.5), 145 (14.3), 109 (24.9), 95 (46.5), 81 (100), 65 (10.5), 28 (64.8); Anal. Calcd for $C_8H_{17}N_2O_3P$: C, 43.63; H, 7.78; N, 12.72; P, 14.07. Found: C, 43.52; H, 7.66; N, 12.81; P, 14.28. Compound **2c**: Identical procedure as for **2a**, except that 0.238 g (1 mmol) of 5-chloro-1-pentynylphosphate was used. ^{1}H NMR (300 MHz, CD_3OD): δ 1.32 (t, 6H, $J_{HH} = 7.2$ Hz), 1.90 (m, 2H), 2.29 (m, 2H), 2.76 (d, 2H, $J_{HP} = 21.9$ Hz), 2.97 (br t, 2H, $J_{HH} = 5.4$ Hz), 4.07–4.17 (m, 4H); ^{31}P NMR (121 MHz, CD_3OD): δ 27.55; ^{13}C NMR (75.5 MHz, CD_3OD): δ 15.6 (d, $^3J_{PC} = 6.0$ Hz), 19.6, 25.6 (d, $^3J_{PC} = 2.0$ Hz), 34.7 (d, $^1J_{PC} = 137.5$ Hz), 41.3, 62.5 (d, $^2J_{PC} = 6.6$ Hz), 142.0 (d, $^2J_{PC} = 10.0$ Hz); MS(EI): *m*/*z* (%) 234(51.0), 206 (17.6), 178 (22.5), 150 (34.3), 125 (23.5), 97 (100), 81 (24.5), 57 (21.6), 41 (16.6), 29 (25.5); Anal. Calcd for $C_9H_{19}N_2O_3P$: C, 46.15; H, 8.18; N, 11.96; P, 13.22. Found: C, 45.98; H, 8.29; N, 11.90; P, 13.41. Compound **2g**: Identical procedure as for **2a**, except that 0.252 g (1 mmol) of 6-chloro-1-hexynylphosphonate was used. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, 6H, $J_{HH} = 6.9$ Hz), 1.45 (m, 2H), 1.71 (m, 2H), 2.48 (broad t, 2H), 2.83 (d, 2H, $J_{HP} = 22.2$ Hz), 2.89 (broad t, 2H, $J_{HH} = 5.4$ Hz), 4.11 (dq, 4H, $J_{HH} = 6.9$ Hz, $J_{PH} = 0.3$ Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 26.29; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.3 (d, $^3J_{PC} = 6.0$ Hz), 22.0, 31.1, 34.2, 37.8 (d, $^1J_{PC} = 136.4$ Hz), 50.1 (d, $^3J_{PC} = 4.0$ Hz), 62.0 (d, $^2J_{PC} = 6.6$ Hz), 155.9 (d, $^2J_{PC} = 10.0$ Hz); MS(EI): *m*/*z* (%) 248 (30.9), 230 (11.8), 219 (20.1), 191 (12.6), 163 (18.6), 125 (51.9), 111 (62.1), 81 (100), 65 (26.6), 41 (55.8), 29 (61.2); Anal. Calcd. for $C_{10}H_{21}N_2O_3P$: C, 48.38; H, 8.53; N, 11.28; P, 12.48. Found: C, 48.44; H, 8.61; N, 11.19; P, 12.43.

15. Epiotis, N. D.; Cherry, W.; Shaik, S.; Yates, R. L.; Bernardi, F. Structural Theory of Organic Chemistry. In *Topics in Current Chemistry*; Springer: Berlin, 1977; Vol. 70, pp 1–242.