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Cyclic chlorophosphites as scaffolds for the one-pot synthesis of α-aminophosphonates under solvent-free conditions

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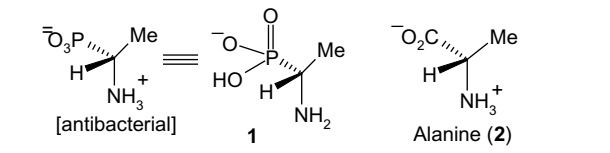
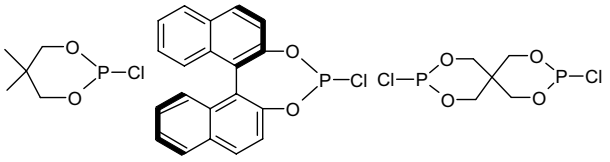
Abstract—New α-aminophosphonates of the type $(OCH_2CMe_2CH_2O)P(O)CH(NHCO_2R)(R')$ [**6a–i**, **7a–e**, and **8a–c**] have been synthesized in high yields by a three-component reaction using $(OCH_2CMe_2CH_2O)PCl$ (**3**), benzamide (or urethane or benzyl carbamate), and an aldehyde without using any catalyst under solvent-free conditions. This route can be readily adapted for bis-aminophosphonates as well as optically active binaphthoxy α-aminophosphonates; it also tolerates the phenolic –OH group as shown by the synthesis of hydroxy functionalized aminophosphonates. Partial hydrolysis of compounds **7a–d** leads to products in which the phosphorinane ring is cleaved first. Compounds $(OCH_2CMe_2CH_2O)P(O)CH[NHC(O)Ph](9\text{-anthryl})$ (**6f**) and optically pure (*R,S*)-(−)-$(C_{20}H_{12}O_2)P(O)CH(NHCO_2Et)(Ph)$ (**14a**) were characterized by X-ray crystallography.

α-Aminophosphonates $(RO)_2P(O)CR'NHR''$ are very often used as precursors to α-aminophosphonic acids (e.g., **1**), which are the phosphorus analogs of α-amino acids (e.g., **2**). As expected from this analogy, aminophosphonic acids have a variety of biological activities that include antibacterial, antiviral, antifungal, pesticidal, enzyme inhibition, and glycine antagonism.[1] As a result and despite the large number of known methods for their preparation, modification of older routes or exploration of new methodologies are still being intensively investigated.[1a,2] In this context, the use of solvent-free conditions is also an aspect worth-studying. Furthermore, although methods utilizing amidoalkylation of P(III)–Cl compounds are well-documented,[1a,3,4] their potential is far less exploited relative to the Kabachnik–Fields reaction. Here we present the utility of $(OCH_2CMe_2CH_2O)PCl$ (**3**)[5] and the analogous cyclic chlorophosphites (*R*)-(+)-$(C_{20}H_{12}O_2)PCl$ (**4**),[6] and $C[(CH_2O)_2PCl]_2$ (**5**)[7] for the synthesis of α-aminophosphonates by amidoalkylation in *one-pot* under *solvent-free* conditions as a viable alternative to other approaches. While precursor **4** provides an opportunity to isolate pure diastereomers, precursor **5** can, in principle, lead to polymeric aminophosphonates on reaction with a dialdehyde.





We report that the reaction of an equimolar mixture of **3** and urethane, benzamide, or benzyl carbamate with an aldehyde under *solvent-free conditions* in *one-pot* smoothly gives the aminophosphonates **6a–i**, **7a–e**, and **8a–c** (Scheme 1) in high yields;[8] this procedure gives far better yields than the one using the analytically pure phosphite $(OCH_2CMe_2CH_2O)P(NHCO_2Et)$ (**10**). The bis-aminophosphonates **9a–c** were obtained analogously in good yields. An X-ray crystal structure has been obtained for **6f** (Fig. 1).[9] The conversion to the

Keywords: Aminophosphonates; Solvent-free conditions; Chlorophosphites; Chiral phosphonates; X-ray structures.
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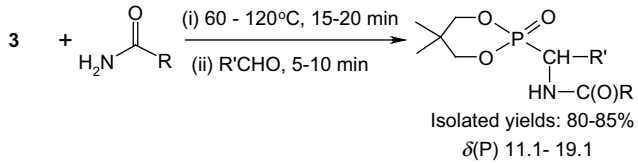


R = Ph; R' = Ph (**6a**), 4-Me-C_6H_4 (**6b**), $CHMe_2$ (**6c**), 3-Me-C_6H_4 (**6d**), CH=CHPh (**6e**), 9-anthryl (**6f**), 4-Cl-C_6H_4 (**6g**), 4-MeO-C_6H_4 (**6h**), 1-naphthyl (**6i**)

R = OEt; R' = Ph (**7a**), 4-Me-C_6H_4 (**7b**), $CHMe_2$ (**7c**), 4-MeO-C_6H_4 (**7d**), 9-anthryl (**7e**)

R = OCH_2Ph; R' = Ph (**8a**), 4-Me-C_6H_4 (**8b**), 4-MeO-C_6H_4 (**8c**)

Scheme 1.

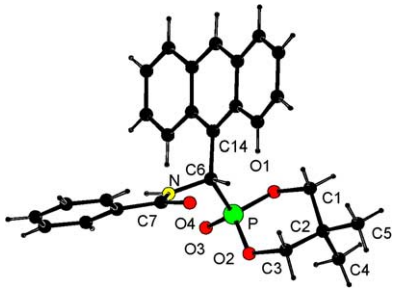
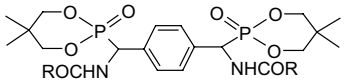


Figure 1. Molecular structure of compound **6f** with selected atoms labeled. Selected bond parameters (Å, °): P–O(1) 1.572(3), P–O(2) 1.573(3), P–O(3) 1.459(4), P–C(6) 1.820(5), N–C(6) 1.470(6), N–C(7) 1.348(6), O(1)–P–O(2) 105.45(19). The molecule is a hydrogen bonded dimer through P=O and NH [N–H(N)···O(3′): 0.90(5) Å, 2.26(5) Å, 3.141(6) Å, 165(4)°].

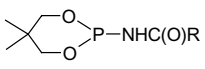
α-aminophosphonates starting from **3** was complete within 30 min. Other features of interest in our synthesis include the following.

(i) The aminophosphonates **6**–**8** are also formed directly by sequential addition of the diol, urethane/benzamide/benzyl carbamate, and an aldehyde to PCl_3 (^{31}P NMR; >80% yield).
(ii) The reaction tolerates the phenolic –OH as shown by the preparation of compounds **11**–**12** (the P(III) intermediate does not react with the phenolic –OH).[10]
(iii) Extension of this route using the bis-chlorophosphite **5** affords the bisaminophosphonates **13** and possibly polymeric **I** (insoluble).



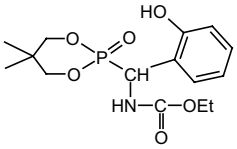
9 [R = Ph (**a**), OEt (**b**), OCH_2Ph (**c**)]

Yields 80-85%; δ(P) 13.3-13.5

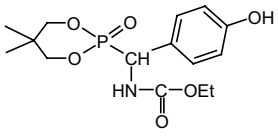


10

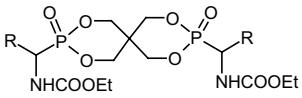
Compounds **14a**–**c** were synthesized in one-pot by the treatment of (*R*)-(+)-($C_{20}H_{12}O_2$)PCl (**4**) with urethane and an aldehyde (Scheme 2). Here a mixture of **4** and



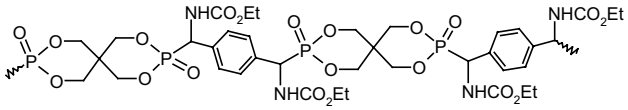
11 [δ(P) 16.4]



12 [δ(P) 16.8]



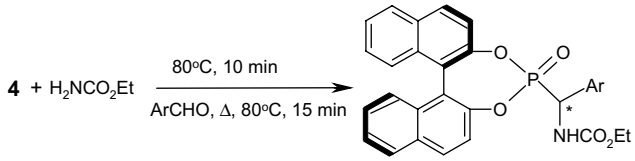
13 [R = C_6H_4-4-OMe (δ(P) 18.9, 19.2)]



urethane was heated at 80 °C for 10 min followed by cooling to afford a white solid [δ(P) same as that of **4**]; addition of aldehyde to this solid followed by heating at 80 °C for 15 min yielded the α-aminophosphonates **14a**–**c**. The ^{31}P NMR spectra of the reaction mixtures showed two peaks at δ ~30.0 and ~29.0 (ratio 3:2) indicating the formation of two diastereomers in each case. The diastereomer corresponding to δ(P) ~29.0 was isolated in a pure state in all cases by column chromatography. The pure diastereomer of **14a** was characterized by X-ray crystallography (Fig. 2). The configuration of the isolated α-aminophosphonate **14a** is (*R*,*S*). The chiral center at the alpha carbon C(21) attached to the phosphorus atom has the *S* configuration whereas the configuration of the 1,1′-binaphthoxy ring is *R*; the configurations of **14b**–**c** are also likely to be the same. The specific rotations of **14a**–**c** are given in Table 1.

The sparingly water-soluble α-aminophosphonic acids **15a**–**e** were readily obtained from aminophosphonates by treating **6a**–**e** with concd HCl followed by passing ethylene oxide into the mixture (Scheme 3); similarly compounds **7a**–**c** were hydrolyzed to **15a**–**c**. The ^1H NMR spectra (D_2O/KOH) of these compounds showed a characteristic doublet at δ ~3.0 (^2J(P–H) = 15.5 Hz) for the P–C*H* proton. The ^{31}P NMR spectra showed a single peak at δ ~18.0 as expected for aminophosphonic acids.[11]

Partial hydrolysis is an aspect on which not much information is available in the literature. Under base catalyzed conditions we were able to isolate compounds **16a**–**c** and **17a**–**c** in which the dioxaphosphorinane ring was partly cleaved; while in **16a**–**c** the urethane residue



Ar = Ph (**14a**)
4-MeO-C_6H_4 (**14b**)
9-anthryl (**14c**)

Scheme 2.

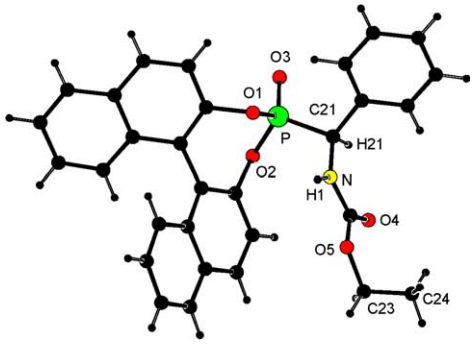


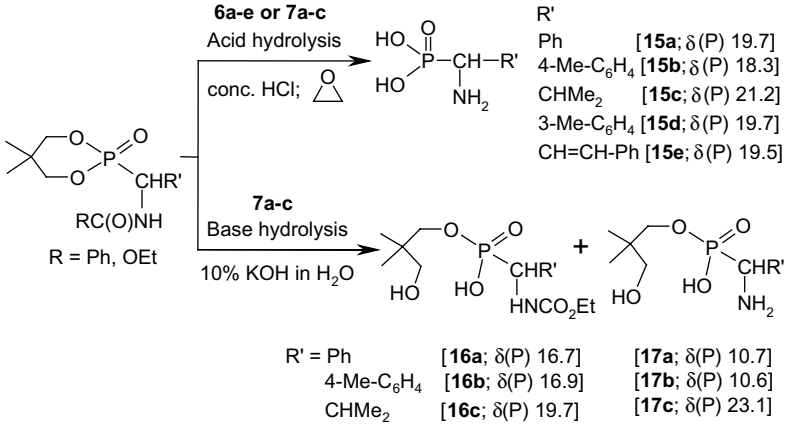
Figure 2. Molecular structure of (*R*,*S*)-(−)-**14a**; only selected atoms are labeled. Selected bond parameters (Å, °): P–O(1) 1.591(2), P–O(2) 1.595(2), P–O(3) 1.448(4), P–C(21) 1.813(2), N(1)–C(21) 1.449(3), N(1)–C(22) 1.353(3), O(1)–P–O(2) 103.90(9). The molecule is a hydrogen bonded *chain* through C=O and NH (cf. structure **6f**): N(1)–H(N1)···O(4′) 0.87(3) Å, 2.03(3) Å, 2.893(3) Å, 173(2)°.

Table 1. Data on optically pure α-aminophosphonates **14a–c**

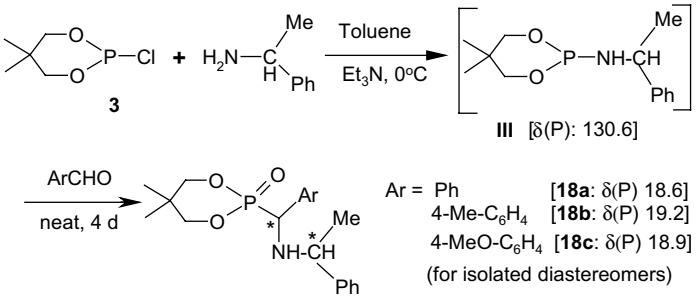
Compd	Mixture δ(P)	Total yield (%)	Pure diastereomer	
			δ(P)	$[\alpha]_D$ ($CHCl_3$, 25 °C)
14a	29.5, 30.1	70	29.5	−285 (*c* 0.4)
14b	29.9, 30.4	90	29.9	−307 (*c* 0.4)
14c	31.5, 32.9	90	31.5	−260 (*c* 0.4)

was retained, in **17a–c** it was also cleaved. These two products could be readily separated in a spectroscopically pure state (>95%) by utilizing the difference in their solubilities. Thus a new category of aminophosphonic monoesters has been prepared.

The aminophosphite **10** does not appear to be formed when **3** is heated with urethane or benzamide; the ^{31}P NMR spectra in the absence of the aldehyde showed a resonance at the position expected for **3** [δ(P) 145.8]. Upon addition of *p*-tolualdehyde to [**3**+urethane] in C_6D_6, there was no evidence for the formation of the amidophosphite ($OCH_2CMe_2CH_2O$)$PNHCO_2Et$ [**10**]; instead the product **7b** was formed *quantitatively within 5 min*. In a blank reaction of urethane with an aldehyde under these conditions, there was no evidence for the formation of the imine (TLC). For this reason, we prepared **10** [δ(P) 106.2; supporting information and X-ray structure are available] and reacted it with *p*-tolualdehyde under the same conditions; the reaction was sluggish under these conditions and only ~15% of the product **7b** was formed [the rest was mostly starting material (62%), α-hydroxy phosphonate and ($OCH_2CMe_2CH_2O$)P(O)H (**II**)]. These observations suggest that this reaction does not occur through the intermediacy of **10**. However, the α-aminophosphonates **18a–c** could be readily prepared in reasonable yields from the reaction of the crude α-methylbenzylamino compound ($OCH_2CMe_2CH_2O$)P[NHCH(Me)(Ph)] [**III**; δ(P) 130.6; from the 1:1:1 reaction of the amine (racemic or chiral) with **3** and Et_3N in toluene followed by filtration and removal of solvent] with aromatic aldehydes (Scheme 4).[12]



Scheme 3.



Scheme 4.

For the formation of **6a–i**, **7a–e**, and **8a–c**, one possible pathway is the in situ generation of the imine $EtO_2CN{=}CHAr$, with **3** acting as a dehydrating agent;[4b] the resulting phosphite **II** could then react with the imine. However, since the reaction of phosphites with imines is generally sluggish, there is a possibility that the HCl present may act as an activating agent. Also, since direct formation of α-substituted phosphonates $(RO)_2P(O)CH(X)Ar$ from the corresponding phosphites $(RO)_2PX$ and ArCHO is possible,[4c,13] mechanistic aspects of the formation of compounds **6–8** and **14** need to be probed further, in particular with respect to the role of acid (HCl) or amine hydrochloride.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.080. An ORTEP drawing with selected bond parameters for **10**, CIF files for compounds **6f**, **10**, and **14a** and further experimental data and figures of the ^{31}P NMR spectra are included.

References and notes

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5. Stirring PCl_3 with 2,2-dimethyl-1,3-propanediol (neat, 8 h) followed by distillation under low vacuum affords **3** in 80–85% yields. For earlier preparations, see: (a) Zwierzak, A. *Can. J. Chem.* **1967**, *45*, 2501; (b) Stec, W.; Zwierzak, A. *Can. J. Chem.* **1967**, *45*, 2513; (c) Muthiah, C.; Praveen Kumar, K.; Aruna Mani, C.; Kumara Swamy, K. C. *J. Org. Chem.* **2000**, *65*, 3733.
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8. Compound **6f**: Benzamide (1.36 g, 11.3 mmol) was added to freshly distilled **3** (1.91 g, 11.3 mmol) and the mixture heated at 130 °C under nitrogen with continuous swirling to afford a homogeneous liquid (15–20 min). This was cooled (25 °C) to give a solid, 9-anthraldehyde (2.33 g, 11.3 mmol) was added in one portion and the mixture shaken vigorously. A slightly exothermic reaction occurred and a viscous liquid was formed in 3 min (mostly the required compound). This was dissolved in dichloromethane–toluene (1:1; 10 mL) mixture and the solvent was allowed to evaporate in open air to give crystalline **6f**. Yield: 4.41 g (85%). Mp: 276–278 °C, IR (cm^{-1}): 3337, 1649, 1514, 1271, 1057. ^1H NMR (200 MHz, $CDCl_3$): δ 0.81, 1.03 (2s, 6H, $2CH_3$), 3.34 and 3.70 (2t, ^3J(P–H) ~ ^2J(H–H) = 10.3 Hz, 2H, OCH_AH_B), 4.21 (~d, ^2J(H–H) = 10.7 Hz, 2H, OCH_2), 7.36–8.50 (m, 15H, Ar–*H* + P–C*H*) 8.85 (m, 1H, N*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1, 21.5 ($2CH_3$), 32.4 (d, ^3J(P–C) = 6.2 Hz, CMe_2), 45.6 (d, ^1J(P–C) = 148.4 Hz, P–*C*H), 76.4 (d, ^2J(P–C) = 5.9 Hz, OCH_2) 125.0, 126.8, 127.2, 128.5, 129.5, 129.7, 131.8, 133.5,167.0. ^{31}P NMR (81 MHz, $CDCl_3$): δ 16.9. Anal. Calcd for $C_{27}H_{26}NO_4P$: C, 70.57; H, 5.70; N, 3.04. Found: C, 70.45; H, 5.68; N, 3.01.
Compound **14a**: To *R*-(+)-**4** (1.44 g, 4.1 mmol) was added urethane (0.36 g, 4.1 mmol) and the mixture heated at 80 °C under nitrogen with continuous swirling to yield a homogeneous liquid (ca. 10 min). Upon cooling to 25 °C, this became a solid mass. Benzaldehyde (0.43 g, 4.1 mmol, 0.4 mL) was added in one portion and the mixture heated at 80 °C under nitrogen for 15 min to give a viscous liquid that solidified upon cooling. A ^{31}P NMR examination revealed that this solid was a mixture of diastereomers of **14a** (δ 30.1 (65%) and 29.5 (35%)). One of these was separated in pure form by column chromatography using hexane–ethyl acetate (3:1). Yield: 1.4 g (70%). Yield (single diastereomer): 0.20 g (10%): Mp: 230–232 °C. IR (cm^{-1}): 3275, 1682, 1510, 1300, 1224, 1072, 964. ^1H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, ^3J(H–H) = 7.2 Hz, 3H, CH_2CH_3), 4.03 (q, ^3J(H–H) = 7.2 Hz, 2H, OCH_2CH_3), 5.40 (m, 2H, P–C*H* + N*H*), 6.96–8.05 (m, 16H, Ar–*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 53.1 (d, ^1J(P–

C) = 150.5 Hz, P–*C*H), 61.6 (O*C*H_2), 120.1, 121.1, 126.0, 126.8, 127.0, 127.3, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0, 129.1, 130.8, 131.4, 131.6, 132.4, 145.2, 145.3, 148.2, 148.3, 155.3, 155.4. ^{31}P NMR (81 MHz, $CDCl_3$): δ 29.5. Anal. Calcd for $C_{30}H_{24}NO_5P$: C, 70.72; H, 4.74; N, 2.74. Found: C, 70.76; H, 4.71; N, 2.75.

Single crystal X-ray data were collected on Enraf-Nonius MACH3 (compound **6f**) or Bruker AXS SMART (compound **14a**) diffractometer [Mo K_α (λ = 0.71073 Å)]. The structures were solved and refined by standard methods.[9] *Crystal data for* **6f**: $C_{27}H_{26}NO_4P$, M = 459.46, monoclinic, space group $P2_1/n$, a = 10.307(2), b = 10.630(3), c = 21.018(6), β = 97.818(2), V = 2281.3(10) Å^3, Z = 4. Data/restraints/parameters: 4007/0/305. R indices ($I > 2\sigma(I)$): $R1$ = 0.0620, $wR2$ = 0.1793. CCDC no. 262907. *Crystal data for* **14a**: $C_{30}H_{24}NO_5P$, M = 509.47, monoclinic, space group $P2_1$, a = 10.873(1), b=8.952(1), c = 13.387(1), β = 104.621(10), V = 1260.7(2) Å^3, Z = 2. Data/restraints/parameters: 5840/1/342. R indices ($I > 2\sigma(I)$): $R1$ = 0.0491, $wR2$ = 0.1286. CCDC no. 262909.

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10. If ($OCH_2CMe_2CH_2O$)PNHC(O)R was an intermediate, the phenolic OH may have replaced the NHC(O)R group. See: Satish Kumar, N.; Kumaraswamy, S.; Said, M. A.; Kumara Swamy, K. C. *Org. Process Res. Dev.* **2003**, *7*, 925.
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12. The reaction mixture showed two signals in the aminophosphonate region in ^{31}P NMR [δ 17.5–19.2; ratio ~3:1] whether chiral or racemic amine was used. The downfield isomer (major resonance) was isolated. The products obtained starting with the chiral amine showed optical rotation {$[\alpha]_D$ ($CHCl_3$, 25 °C: −31 to −35, *c* 1)}, but no further attempt was made to assign the configuration.
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