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

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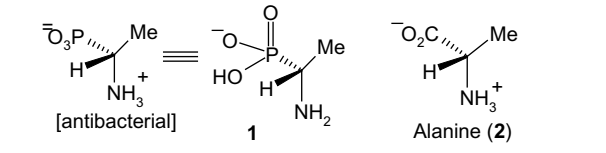
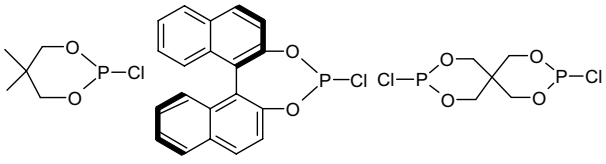
**Abstract**—New α-aminophosphonates of the type $(OCH_2CMe_2CH_2O)P(O)CH(NHCO_2R)(R')$ [**6a–i**, **7a–e**, and **8a–c**] have been synthesized in high yields by a three-component reaction using $(OCH_2CMe_2CH_2O)PCl$ (**3**), benzamide (or urethane or benzyl carbamate), and an aldehyde without using 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.



**3** [δ(P) 145.8] **4** [δ(P) 177.8] **5** [δ(P) 148.1]

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

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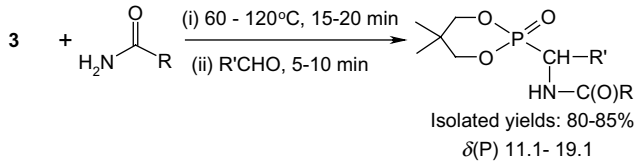



R = Ph; R' = Ph (**6a**), 4-Me-$C_6H_4$ (**6b**), $CHMe_2$ (**6c**), 3-Me-$C_6H_4$ (**6d**), CH=CHPh (**6e**), 9-anthryl (**6f**), 4-Cl-$C_6H_4$ (**6g**), 4-MeO-$C_6H_4$ (**6h**), 1-naphthyl (**6i**)

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.**

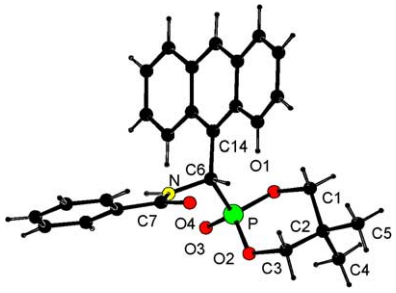
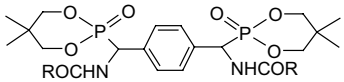



**Figure 1.** Molecular structure of compound **6f** with selected atoms labeled. Selected bond parameters (Å, °): P–O(1) 1.572(3), P–O(2) 1.573(3), P–O(3) 1.459(4), P–C(6) 1.820(5), N–C(6) 1.470(6), N–C(7) 1.348(6), O(1)–P–O(2) 105.45(19). The molecule is a hydrogen bonded dimer through P=O and NH [N–H(N)···O(3′):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

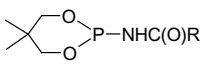
α-aminophosphonates starting from **3** was complete within 30 min. Other features of interest in our synthesis include the following.

(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).



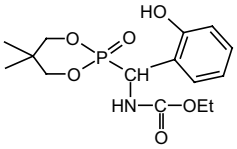

**9** [R = Ph (**a**), OEt (**b**), $OCH_2Ph$ (**c**)]

Yields 80-85%; δ(P) 13.3-13.5

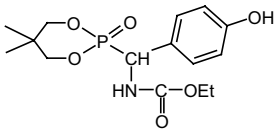



**10**

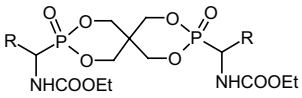
Compounds **14a**–**c** were synthesized in one-pot by the treatment of (*R*)-(+)-($C_{20}H_{12}O_2$)PCl (**4**) with urethane and an aldehyde (Scheme 2). Here a mixture of **4** and



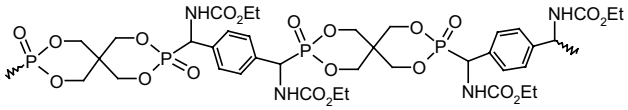

**11** [δ(P) 16.4]




**12** [δ(P) 16.8]



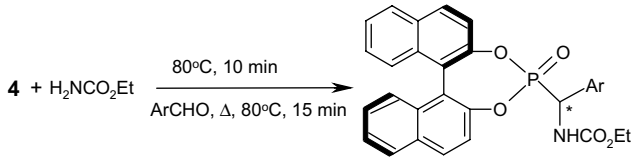

**13** [R = $C_6H_4$-4-OMe (δ(P) 18.9, 19.2)]




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.**

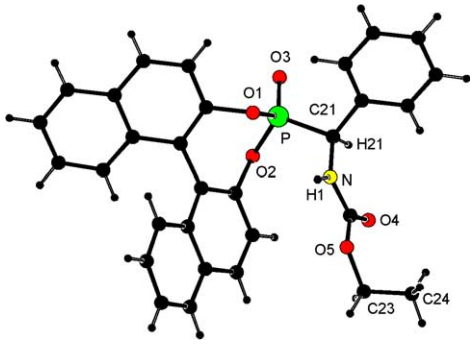


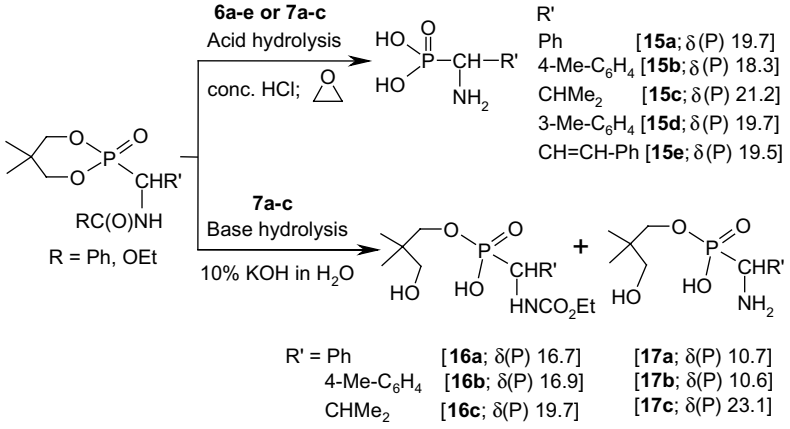

**Figure 2.** Molecular structure of (*R*,*S*)-(−)-**14a**; only selected atoms are labeled. Selected bond parameters (Å, °): P–O(1) 1.591(2), P–O(2) 1.595(2), P–O(3) 1.448(4), P–C(21) 1.813(2), N(1)–C(21) 1.449(3), N(1)–C(22) 1.353(3), O(1)–P–O(2) 103.90(9). The molecule is a hydrogen bonded *chain* 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**

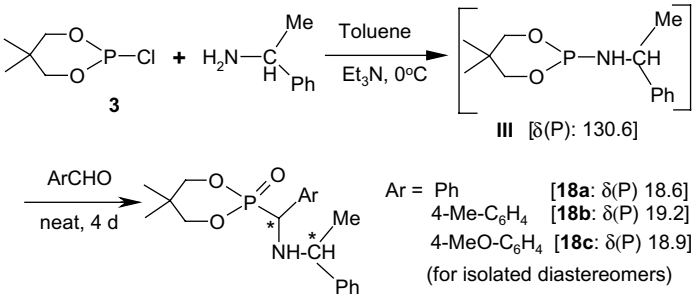
| Compd | Mixture $\delta$(P) | Total yield (%) | Pure diastereomer | |
|---|---|---|---|---|
| | | | $\delta$(P) | $[\alpha]_D$ ($CHCl_3$, 25 °C) |
| **14a** | 29.5, 30.1 | 70 | 29.5 | −285 (*c* 0.4) |
| **14b** | 29.9, 30.4 | 90 | 29.9 | −307 (*c* 0.4) |
| **14c** | 31.5, 32.9 | 90 | 31.5 | −260 (*c*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

We thank (i) Department of Science and Technology (DST), New Delhi for financial support, (ii) DST (New Delhi) for Single Crystal Diffractometer facilities, and (iii) The UPE program under UGC (New Delhi) for equipment, and (iv) CSIR for a fellowship to K.S.K.

## 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.

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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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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** ($\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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 $K_\alpha$ ($\lambda$ = 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), $\beta$ = 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), $\beta$ = 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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12. The reaction mixture showed two signals in the aminophosphonate region in $^{31}$P NMR [$\delta$ 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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